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Steglich esterification: A versatile synthetic approach toward the synthesis of natural products, their analogues/derivatives

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A B S T R A C T

The exploitation of natural products and their analogues in the field of pharmacology has been regarded as of great importance. It can be attributed to the fact that these scaffolds exhibit diverse chemical properties, distinct biological activities and zenith specificity in their biochemical processes, enabling them to act as favorable structures for lead compounds. The synthesis of natural products has been a crafty and hard-to-achieve task. Steglich esterification reaction has played a significant role in that area. It is a mild and efficient technique for constructing ester linkages. This technique involves the establishment of ester moiety via a carbodiimide-based condensation of a carboxylic acid with an alcohol, thiol or an amine catalyzed by dimethyl aminopyridine (DMAP). Specifically, labile reagents with multiple reactive sites are esterified efficiently with the classical and modified Steglich esterification conditions, which accounts for their synthetic utility. This review encloses the performance of the Steglich esterification reaction in forging the ester linkage for executing the total synthesis of natural products and their derivatives since 2018.

1. Introduction

Ester linkages are omnipresent in nature, constructed by the condensation of a carboxylic acid and an alcohol in the presence of acid catalysts or coupling agents. It falls under the category of oleochemicals, which is defined as nature-acquired chemicals. The ester moiety can be detected in numerous biological compounds except in proteins (functional biopolymers) and DNA/RNA (information storing) because of their lability towards hydrolysis. The esters have been employed for a number of synthetic applications as well. To mention a few esterification products having vast applications in modern life, including biofuels (biodiesel), varnishes, paints, solvents (ethyl acetate/methyl acetate), coatings, plastics, pesticides, herbicides, fungicides and in pharmaceutical industries. The most frequent utilization of esters is found in food preservatives, flavorings, perfume additives and fragrances in cosmetics and soaps [1–4].

Esterification reaction is generally performed in three ways i.e., either by reaction of acid anhydride and alcohol, alcohol and acid chloride or alcohol and carboxylic acid. The ester linkage can be introduced via a number of methodologies including; Yamaguchi esterification based on alcoholysis of heterogeneous anhydride; Mitsunobu coupling assisted by triphenylphosphines; Baeyer–Villiger oxidation comprising of NADPH-mediated carbonyl conversion to lactones; Corey– Nicolaou reaction to convert hydroxy acids into lactones; Trost, based on Ru chemistry; Fischer esterification involving acid catalysts and Steglich esterification comprising of coupling agents [5–10]. All these esterification methodologies employ different activating reagents and reaction conditions. The appropriate

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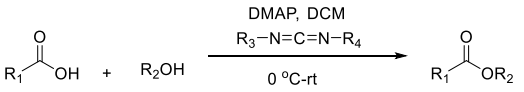
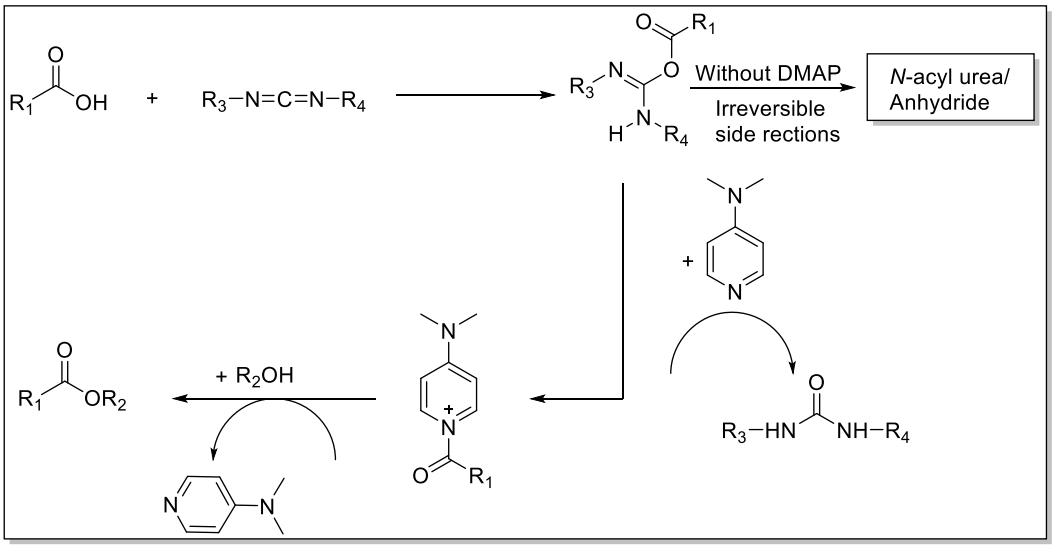


Where
R_1, R_2 = alkyl, aryl
For DCC: R_3 = R_4 = cyclohexyl
DIC: R_3 = R_4 = *iso*-Propyl
EDC: R_3 = ethyl
R_4 = 3-dimethylamino propyl

Scheme 1. General Steglich esterification reaction.



Scheme 2. Reaction mechanism of Steglich esterification.

selection of the esterification technique requires understanding the transformation sustainability of starting materials towards required linkage under provided conditions.

Among these above-mentioned techniques, the Steglich esterification reaction is an efficient method to convert acid and alcohol into esters under neutral and mild conditions. It was developed by Steglich and Neises in 1978 [11]. The reaction conditions employed for this reaction include coupling agents i.e., *N*, *N*′-dicyclohexylcarbodiimide (DCC), *N*, *N*′-diisopropylcarbodimide (DIC) and *N*-ethyl-*N*'- (3-dimethylaminopropyl) carbodiimide (EDC) with or without the catalytic amount of dimethyl aminopyridine (DMAP) in a suitable solvent (Scheme 1) [11]. The general Steglich esterification reaction is presented as follows.

The general mechanism of Steglich esterification is represented as.

The first step involves the reaction between carbodiimide and carboxylic acid mediated by ion pair interaction giving off *O*-acyl urea as an intermediate. This intermediate then transfers the acyl group to dimethyl aminopyridine (DMAP) which reacts with an alcohol to give corresponding esters. DMAP acts as an active reagent to transfer the acyl group. Without DMAP or active reagents for acyl transfer, irreversible reactions occur generating side products i.e., *N*-acyl urea or possible anhydrides leading towards poor or diminished yields of desired products (Scheme 2) [12].

Due to their biological significance, the Steglich esterification reaction has been extremely advantageous in synthesizing natural products [13–15]. The derivatives and analogues of natural products have also been synthesized via Steglich esterification, possessing striking medicinal properties i.e., anticancerous, antimicrobial, antiviral and antiinflammatory etc. [16–18]. Fig. 1 contains the structures and biological significance of some important natural compounds and derivatives of natural compounds ((−)-Herdmanine D **1**, Gallinamide A **2**, Betulin derivative **3**, Leoligin **4**) [19–22].

This review aims to provide the significance of Steglich esterification in the synthesis of natural products and their derivatives reported since 2018.

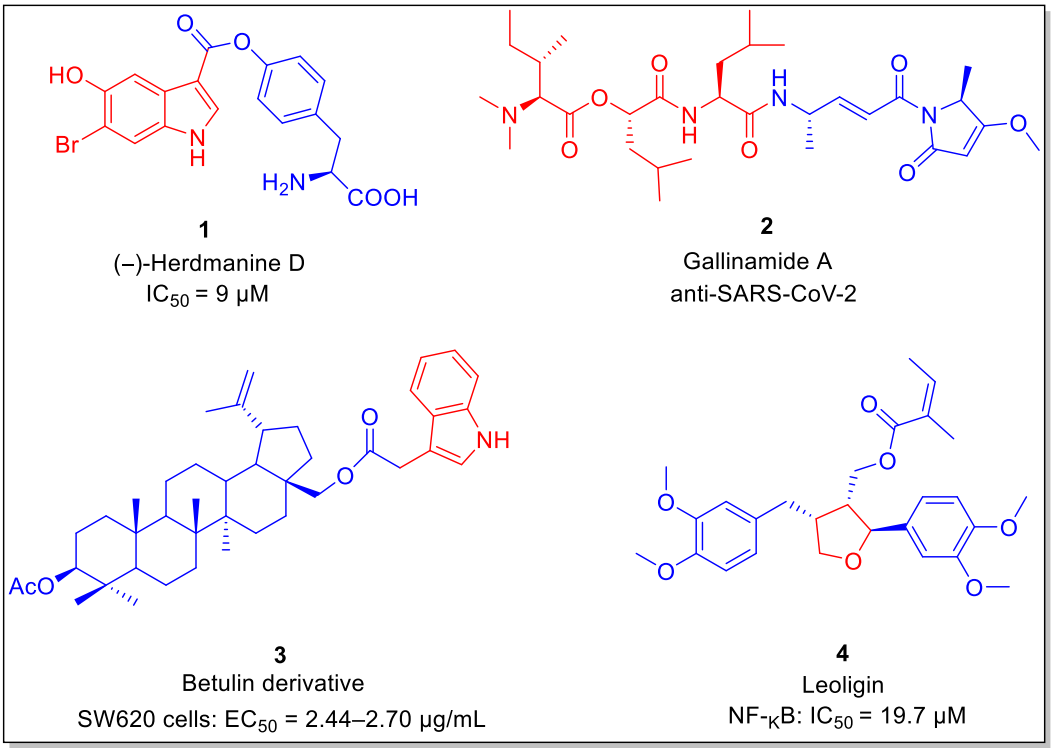


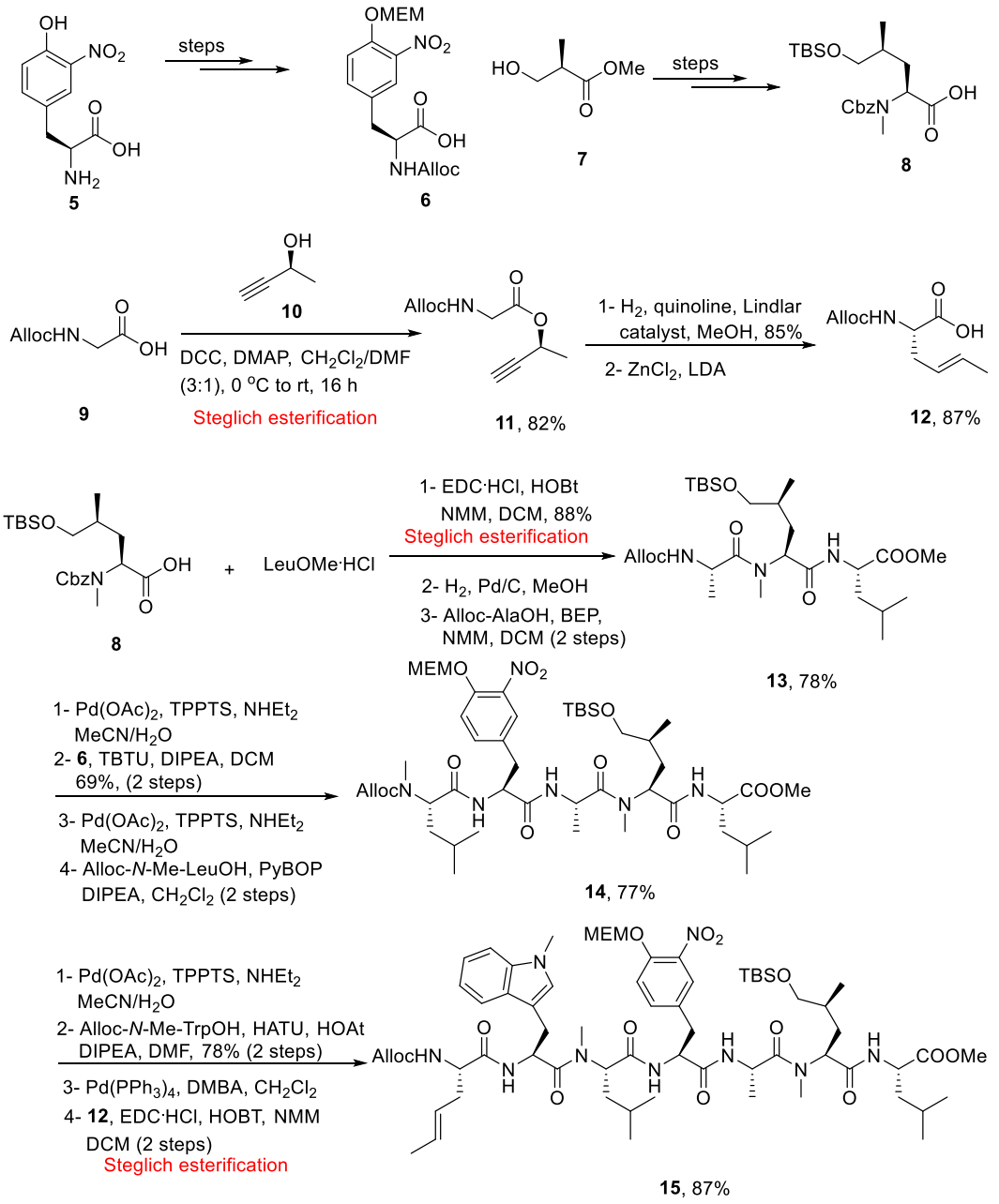
Fig. 1. Structures of some biologically active compounds ((−)-Herdmanine D **1**, Gallinamide A **2**, Betulin derivative **3**, Leoligin **4**).

2. Literature review

2.1. Peptide-based natural product synthesis

Natural products containing peptides and cyclotides are important because of their medicinal and pharmacological significance [23,24]. The increased resistance of bacterial strains against antibiotics has prompted researchers towards a number of trials to get their hands on novel biologically active antibacterial compounds. Ilamycin and its derivatives were obtained from *Streptomyces insulates* (A-165-Z1) and were found active against *Mycobacterium phlei* and *Mycobacterium* 607 [25,26]. Greve et al., in 2022, proposed the total synthesis of Ilamycin and its derivatives by employing asymmetric hydrogenation, Claisen rearrangement and Steglich esterification as key steps [27]. The synthesis commenced from commercially available nitrotyrosine **5** which was converted to amino acid building block **6** over a few steps. Further, commercially available (*R*)-Roche ester **7** was employed to obtain required *N*-methylated-hydroxyleucine **8** over a few steps. Further, Alloc-protected glycine **9** underwent modified Steglich protocol to produce compound **11** in the presence of *N*, *N*′-dicyclohexylcarbodiimide (DCC), dimethyl aminopyridine (DMAP), compound **10** and a solvent ratio of DCM/DMF. In the next step, Lindlar hydrogenation was employed mediated by Lindlar catalyst followed by Claisen rearrangement in the presence of zinc chloride and lithium diisopropylamide (LDA) to obtain amino acid **12** in 87 % yield. The synthesis of linear peptide started with the coupling of synthesized hydroxyleucine derivative **8** with Leu-OMe followed by deprotection of Cbz-protecting group along with Alloc-Ala-OH coupling to furnish 78 % of tripeptide **13**. The next step involved Pd-catalyzed Alloc removal with TPPTS ligand along with nitrotyrosine followed by TBTU/DIPEA-assisted activation of **6** and coupling with *N*-MeLeu to obtain 77 % of compound **14**. Further, 87 % of linear heptapeptide **15** was obtained by ring-closing reaction along with Alloc-protecting group cleavage. The heptapeptide **15** was converted to aldehyde **16** over a few steps. The aldehyde **16** was transformed to hemiaminal **17** via oxidation in 40 % yield and carboxylic acid **18** in 39 % yield via Pinnick conditions of sodium chlorate, sodium hydrogen phosphate and 2-methyl-2-butene as presented in Scheme 4. The synthesized derivatives were evaluated against bacterial strains, among which the derivative with hemiaminal structure was found to exhibit an excellent MIC activity of 50 nM against *M. tuberculosis* and 0.26 nM against *M. marinum* and *M. smegmatis* (Schemes 3 and 4).

Marine organisms have been a great source of bioactive compounds including cyanobacteria as part of this family. *Hormoscilla* sp. is a green filamentous cyanobacteria which produces anaenamide natural products obtained from the reef system of Anae Island in Guam [28]. Brumley et al. in 2020, have proposed the total synthesis of anaenamides A, B and biosynthetic intermediate anaenoic acid [24]. The synthesis was initiated from compound **19** which produced compound **20** over a few steps. The next step involved the Steglich esterification between compound **20** and compound **21** in the presence of DCC, DMAP and DCM at 0 °C to rt followed by deprotection in the presence of Pd/C in ethanol to forge anaenoic acid **22** in 48 % yield over 2 steps. Further, the anaenoic acid was reacted with

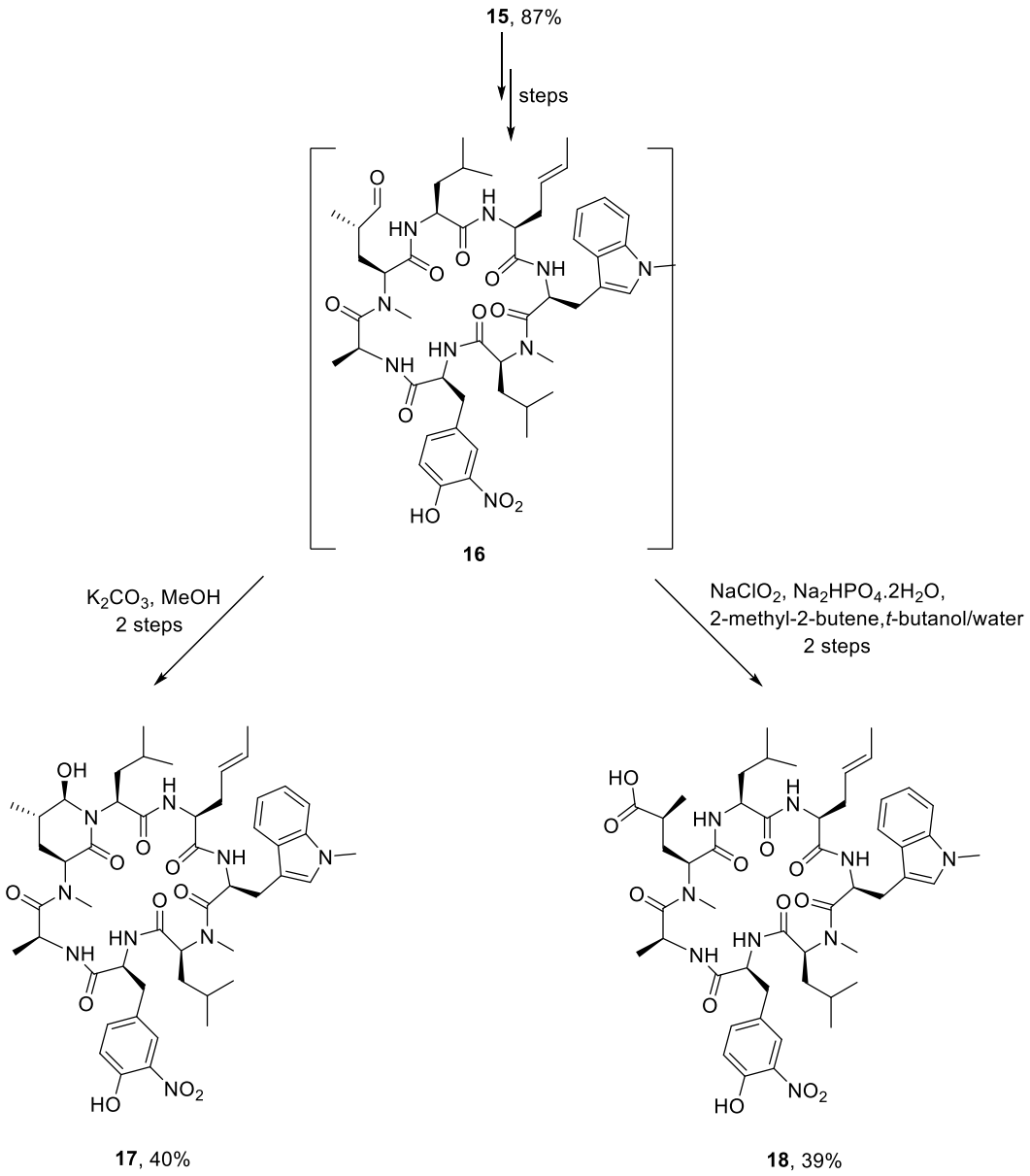


Scheme 3. Synthesis of compound **15**.

compounds **23** and **25** to construct anaenamide A **24** and B **26** respectively, each in 53 % yield. The synthesized compounds were evaluated against HCT116 cancer cells and exhibited moderate cytotoxicity (Scheme 5).

2.2. *Lactam-based natural product synthesis*

Dysoxylum species has a folklore background due to its usage in malarial treatment in old Chinese times and production of anticancerous agents, Hangkonoides [29]. One of the members of dysoxylum, *Dysoxylum hongkongense* produces biologically active dysoxylactam A [30]. In 2020, Reddy et al. provided the total synthesis of dysoxylactam A in 17 linear steps with Steglich esterification, ring-closing metathesis and iterative aldol reactions as key steps to give a 9.5 % overall yield of the desired product [31]. The synthesis was actualized from dibutyl boron triflate-mediated aldol reaction of Evans propionate **27** and 4-pentene-1-al **28** to give 89 % aldol product **29**. The aldol product **29** was transformed into polypropionate fragment **30** over a few steps. The EDCl-mediated

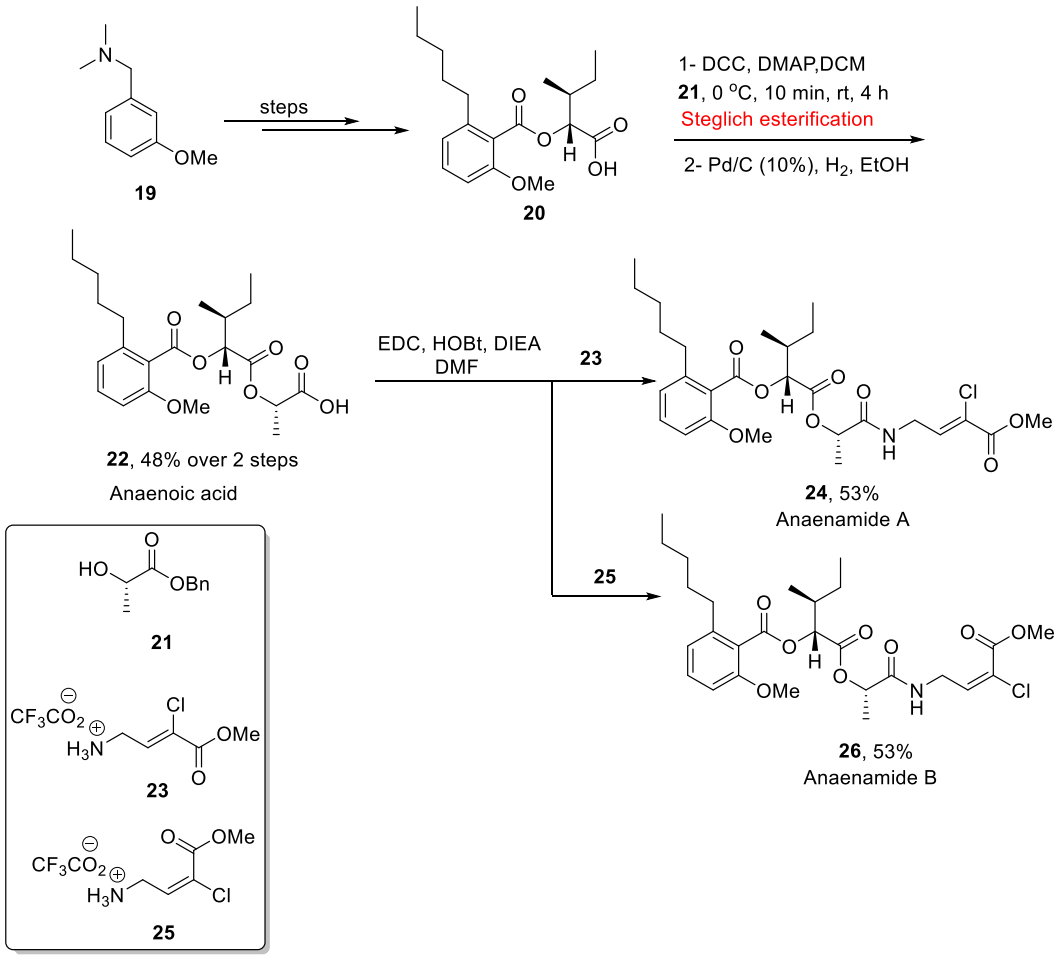


Scheme 4. Synthesis of compounds **17** and **18**.

Steglich esterification was employed as a next step in the presence of *N*-Boc-*L*-valine followed by treatment with 5-hexenoic acid and Hunig's base in the presence of HATU to give 79 % of bis-olefin amides **31**. The macrolactam ring was completed with the final step of ring-closing metathesis in the presence of Grubbs II catalyst and subsequent hydrogenation to furnish dysoxylactam A **32** in 72 % yield over 2 steps (Scheme 6).

2.3. Antibiotic-based natural product synthesis

Among antibiotics, β-lactam antibiotics are considered more significant. Cephalosporin is one of the β-lactam antibiotics which exhibit good potential as an antibacterial agent. Woodward et al. proposed a scheme for the total synthesis of cephalosporin C in 2021 [32]. The synthesis commenced from compound **34** which was converted to β-lactam **35** over a few steps. The next step involved coupling of compounds **35** with **36** followed by the functionalization of β-lactam ring by employing the Michael reaction to give compound **37**. It was followed by Steglich esterification with **38** which took place in the presence of DCC and pyridine to furnish compound **39**. The obtained compound **39** underwent a series of deprotection steps assisted with acetic acid to furnish cephalosporin C **40** (Scheme 7).



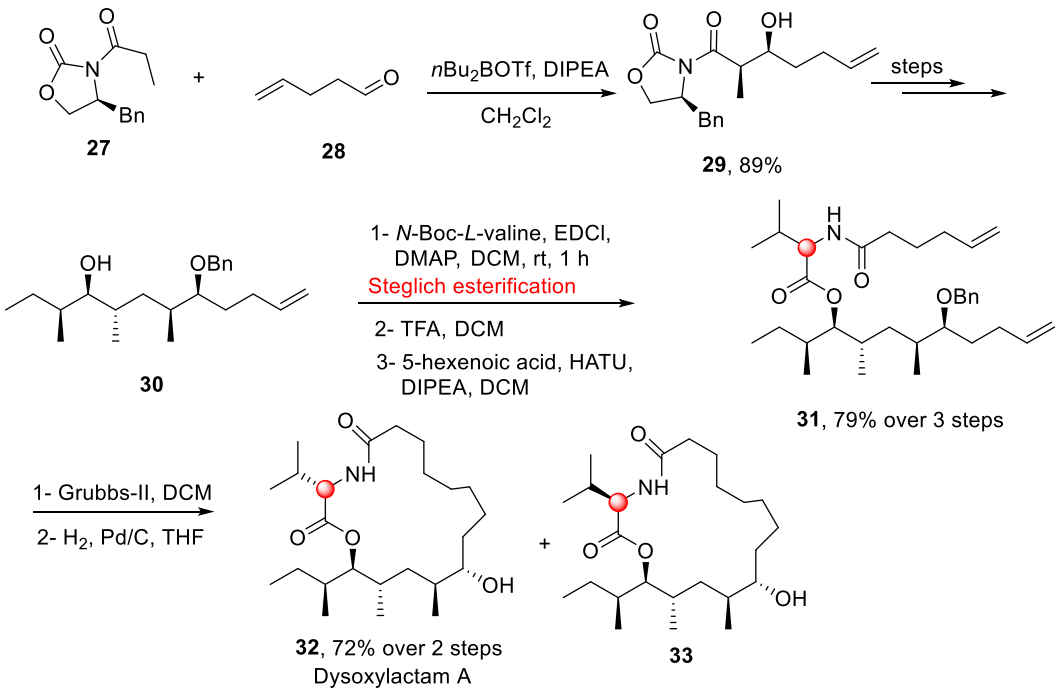
Scheme 5. Total synthesis of anaenamides A **24** and B **26**.

Laterocidines and brevicidine are obtained from *Brevibacillus laterosporus* strains [33]. These are found to be potent antibiotics against ESKAPE family of bacterial strains with considerable MIC values. Laboratory synthesis is preferred to avoid the laborious fermentation process for the acquisition of these products. Ayed et al. provided the total synthesis of laterocidines and brevicidine in 2021 [34]. For the total synthesis of laterocidine, Fmoc-Asp-OAll **41** was employed as a commencing reagent. The Fmoc-Asp-OAll was loaded with a rink amide resin in the presence of BOP/DIPEA to provide **42**. In the next step, allyl ester cleavage was performed with palladium tetrakis triphenylphosphine and $PhSiH_3$ followed by macrolactamization assisted with BOP/DIPEA to give macrocyclic product **43**. The next step was Steglich esterification, for which DIC and DMAP were employed to obtain the desired esterified product **44** with Alloc-Gly-OH. The required laterocidine **45** was obtained from compound **44** over a few steps in 2 % overall yield (Scheme 8).

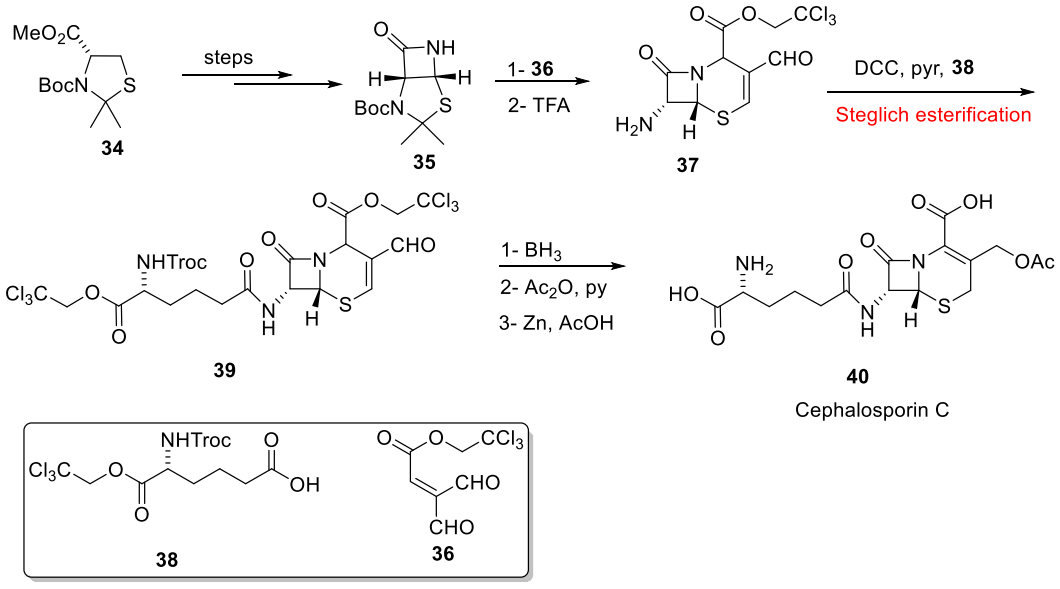
In 2023, Ayed et al. employed a similar strategy to synthesize another member of laterocidine family, named as relacidine A. The structure of relacidine A **46** is presented in Fig. 2 [35].

2.4. Terpenoid-based natural product synthesis

Terpenoids exist in the form of mono, di or triterpenoid, meroterpenoid, indole terpenoids and various others [36]. A meroterpenoid consists of phenolic and quinone moieties combined with sesquiterpene i.e., yahazunol. Yahazunol and natural products related to it consist of meroterpenoid skeleton. These are naturally occurring compounds extracted from *Dictyopteris undulata* and *Dysidea* genus, occurring as sponges [37,38]. (−)-Yahazunol demonstrated antimicrobial activity and (+)-yahazunol exhibited anticancerous activity against some human cancer cell lines i.e., A-549 and MDA-MB-231 [39]. Some of yahazunol related natural products i.e., isozonarol, zonarol, isozonarone and zonarone also showed significant biological activity such as antifungal towards *Rhizoctonia solani*, *Sclerotinia sclerotiorum* and *Phytophthora cinnamomic* [40]. In 2018, Zhang et al. provided the total synthesis of (+)-yahazunol and relevant natural products by employing (−)-sclareol **47** as an inexpensive and commercially available starting material [41]. The first step involved oxidative degradation of (−)-sclareol **47** into 8-*O*-acetylhomodrimanic acid **48** in 42 % yield. Next, the Steglich esterification was employed to obtain thiohydroxamic ester **50** from 8-*O*-acetylhomodrimanic acid **48** and

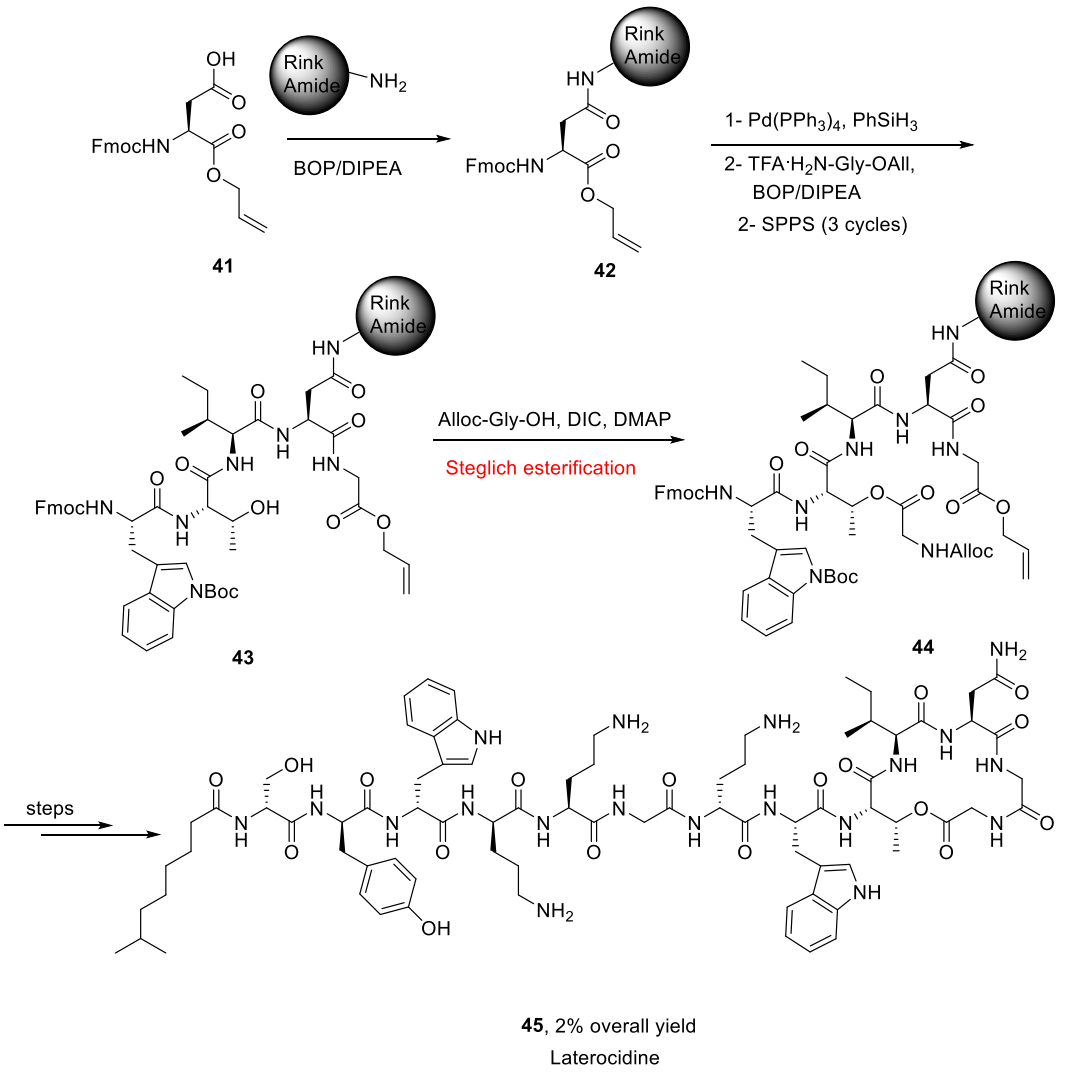


Scheme 6. Total synthesis of dysoxylactam A **32**.



Scheme 7. Total synthesis of cephalosporin C **40**.

2-mercaptopyridine *N*-oxide **49** in the presence of EDC and DMAP. Over a few steps, (+)-8-*O*-acetylyahazunol **51** was obtained over a few steps which was subjected to $LiAlH_4$-mediated hydrolysis to give (+)-yahazunol **52** in 93 % yield. Treatment of (+)-yahazunol **52** with MnO_2 furnished 83 % of (+)-yahazunone **53**. Exo- and endo-cyclic olefins **54a** and **54b** (86 %) were obtained by $SOCl_2/Et_3N$ based oxidation. Further, (−)-zonarol (**55a**) and (−)-isozonarol (**55b**) were obtained in a combined yield of 50 % by reduction of (−)-zonarone **54a** and (−)-isozonarone **54b** in the presence of sodium dithionite and DCM. Lastly, (+)-yahazunol **52** was also converted to 94 % of (+)-chromazonarol **56** in the presence of trifluoro acetic acid and DCM. The synthesized compounds were subjected to antifungal screening which proved (+)-yahazunone **53** and (+)-chromazonarol **56** as potent antifungal agents with EC_{50} values of 28.7 and 24.1 μM respectively (Scheme 9).



Scheme 8. Synthesis of laterocidine **45**.

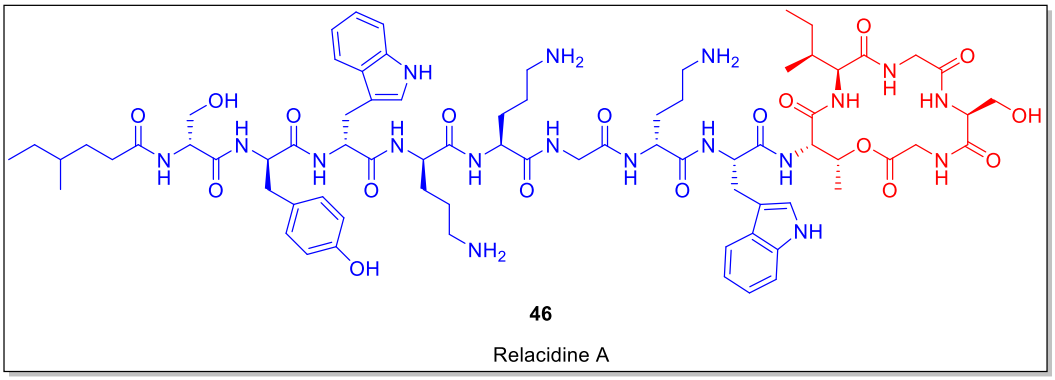
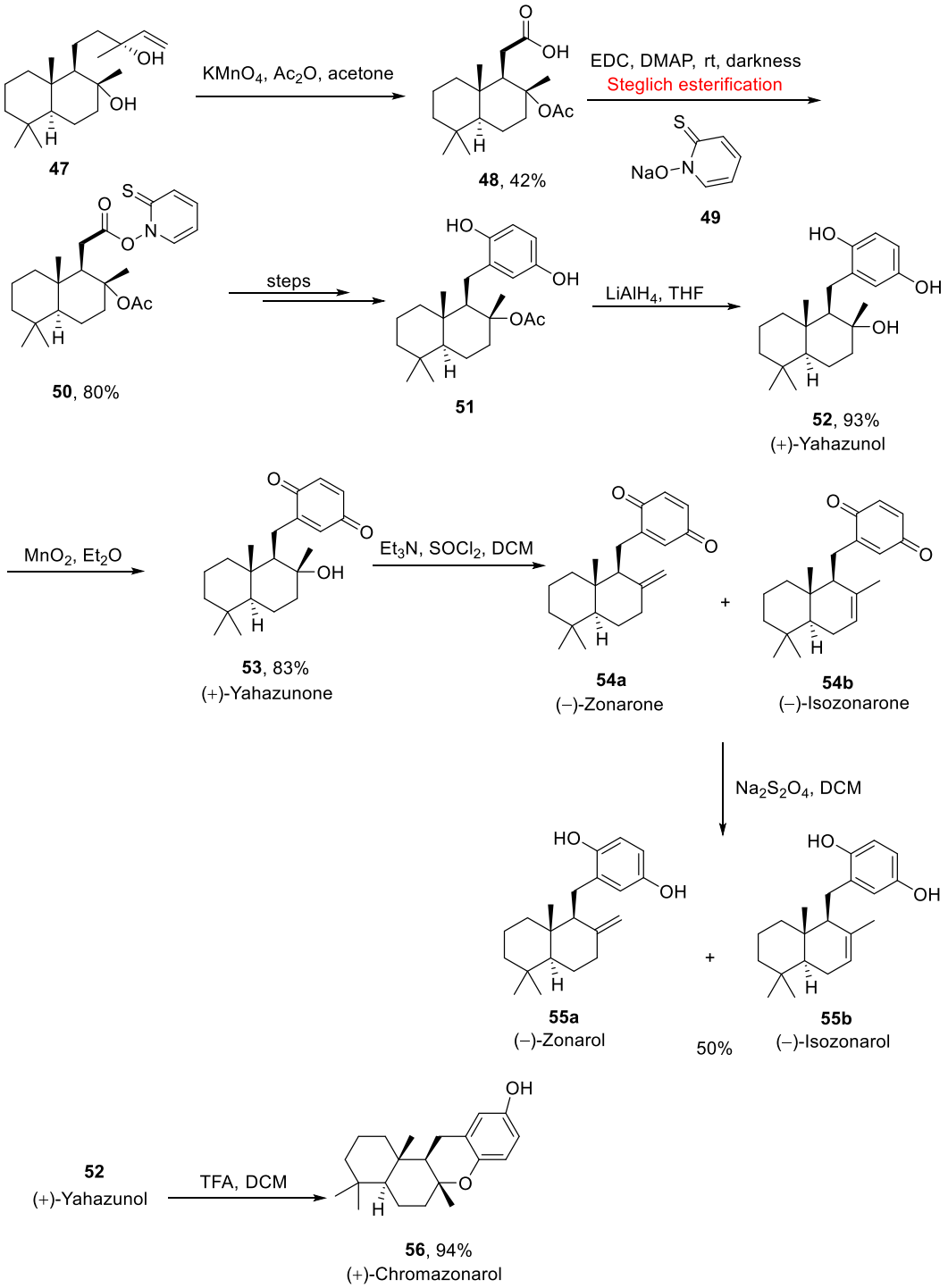
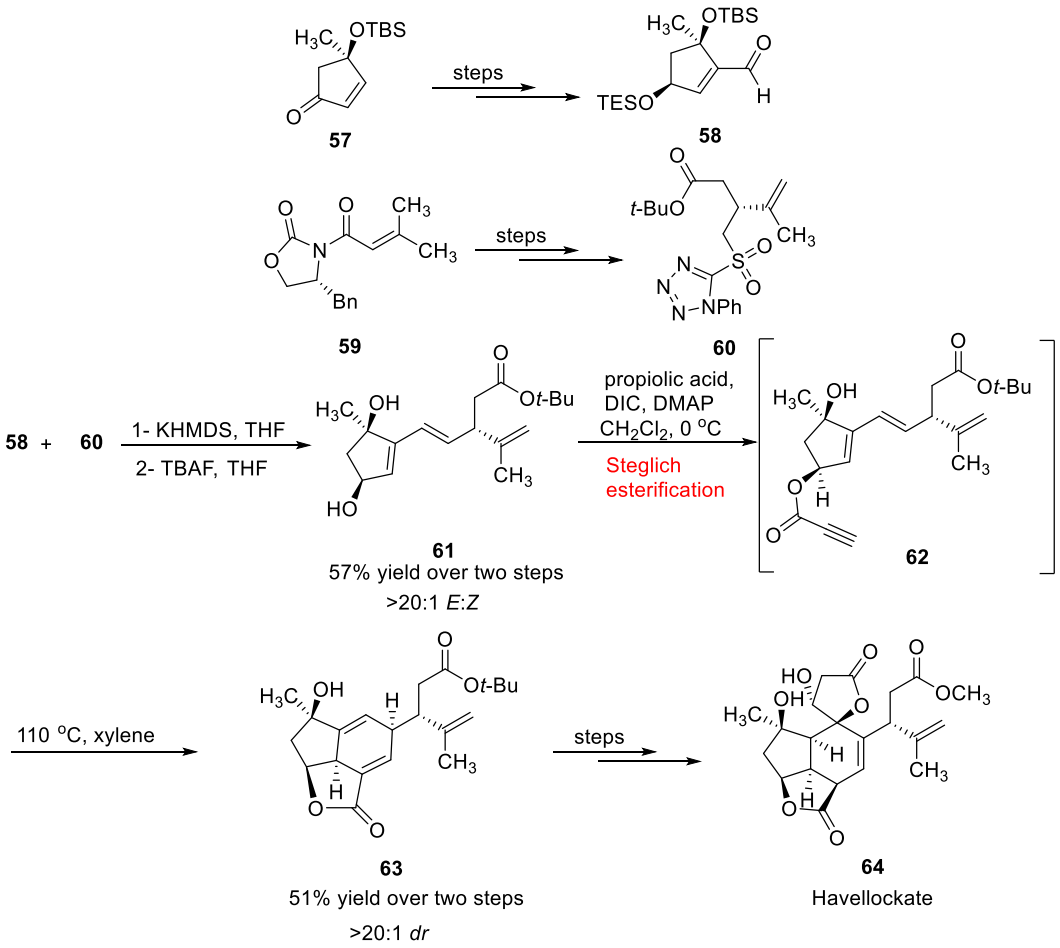


Fig. 2. Structure of relacidine A **46**.



Scheme 9. Synthesis of (+)-yahazunol **52** and related analogues.

Cembranoid is a family of furanobutenolide-derived polycyclic diterpenoid. The total synthesis of four members of this family have been achieved. Havellockate is a member of this family obtained from *Sinularia granosa* in 1998 [42]. Hafemen et al., in 2022 aimed at total synthesis of havellockate by engaging Julia−Kocienski olefination, propiolic acid mediated esterification, Zn-mediated Barbier allylation, Cu-catalyzed aerobic oxidation and Steglich esterification as key steps [43]. The synthesis commenced with the acquisition of aldehyde **58** from enone **57** and sulfone **60** from acyl oxazolidinone **59** over a few steps. These two fragments were made to couple via Julia−Kocienski olefination in the presence of KHMDS in THF followed by desilylation to forge a diol **61** with >20:1 *E*:*Z* selectivity



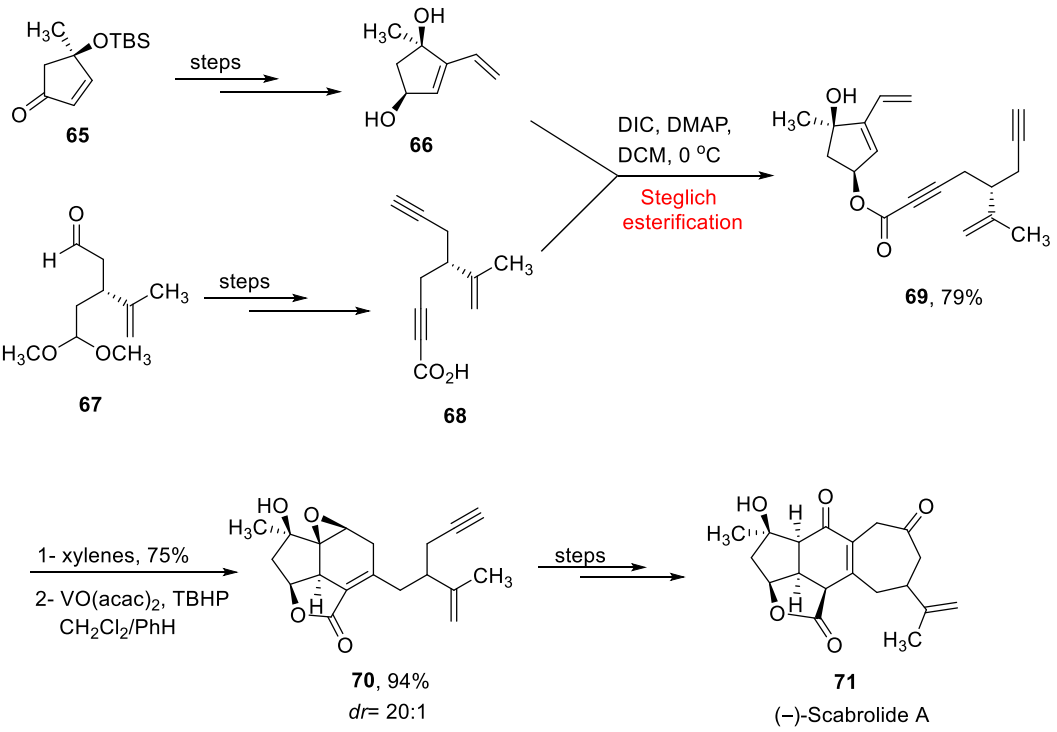
Scheme 10. Total synthesis of havellockate **64**.

in 57 % yield over two steps. Steglich esterification has opted for the next step in the presence of propiolic acid, DIC and DMAP in DCM to furnish an ester **62**. The ester **62** was subjected to heating in xylene to provide Diels-Alder product **63** by [4 + 2] cycloaddition in 51 % yield over two steps having *dr* > 20:1 which leads to the final product havellockate **64**, over a couple of steps (Scheme 10).

(−)-Scabrolide A is a furanobutenolide-derived diterpenoid obtained from soft corals of *Sinularia* [44]. In 2020, Hafeman et al. disclosed its first total synthesis by employing enone-olefin reactions, Diels-Alder reaction and Steglich esterification [45]. The synthesis was commenced from enone **65** which was converted to dihydroxy vinyl cyclopentene **66** and a dialdehyde **67** which was converted to ynoic acid **68**. The next step involved Steglich esterification between dihydroxy vinyl cyclopentene **66** and ynoic acid **68** in the presence of DIC, DMAP and DCM to give ester **69** in 79 % yield. The Diels-Alder reaction was employed as a next step, followed by vanadium-mediated epoxidation to give epoxide **70** in 94 % yield. The epoxide **70** was transformed to (−)-scabrolide A **71** over a few steps. In 2023, Hafeman et al. provided an account of all the approaches and key advancements employed to accomplish the synthesis of scabrolide A and its related natural product, inferring this class to be a relevant and substantial research area (Scheme 11) [46].

(+)-Darwinolide is a diterpenoid extracted from marine sources. This natural product express activity against biofilm phase of methicillin-resistant *S. aureus*. In 2019, Siemon and co-workers proposed the total synthesis of (+)-darwinolide by forging Steglich esterification, an aldol fragment coupling, Ireland-Claisen rearrangement, ring-closing metathesis and organocatalytic meso-desymmetrization as key steps [47]. The total synthesis was begotten with Steglich esterification between **72** and compound **73** in the presence of 10 mol% of DMAP, DCC and dichloromethane accompanied with Ireland-Claisen rearrangement in the presence of LiHMDS to give carboxylic acid **74** in 70 % yield with diastereomeric ratio of 14:1. The carboxylic acid functionality was converted to aldehyde **77** through a two-step sequence to give 70 % of product. Furthermore, the compound **78** was converted to compound **79** over a few steps. Aldol reaction of compound **79** with aldehyde **77** in the presence of NaHMDS accompanied by 5 steps gave compound **80** in 50 % yield. In the next step, ring-closing metathesis was performed to obtain 54 % of compound **82**. Over a series of steps, the target compound (+)-darwinolide **84** was furnished in 18 % yield (Scheme 12).

Kauranes are plant-based diterpenes possessing a number of pharmacological properties i.e., antibacterial, antiinflammatory and



Scheme 11. Total synthesis of (−)-scabrolide A **71**.

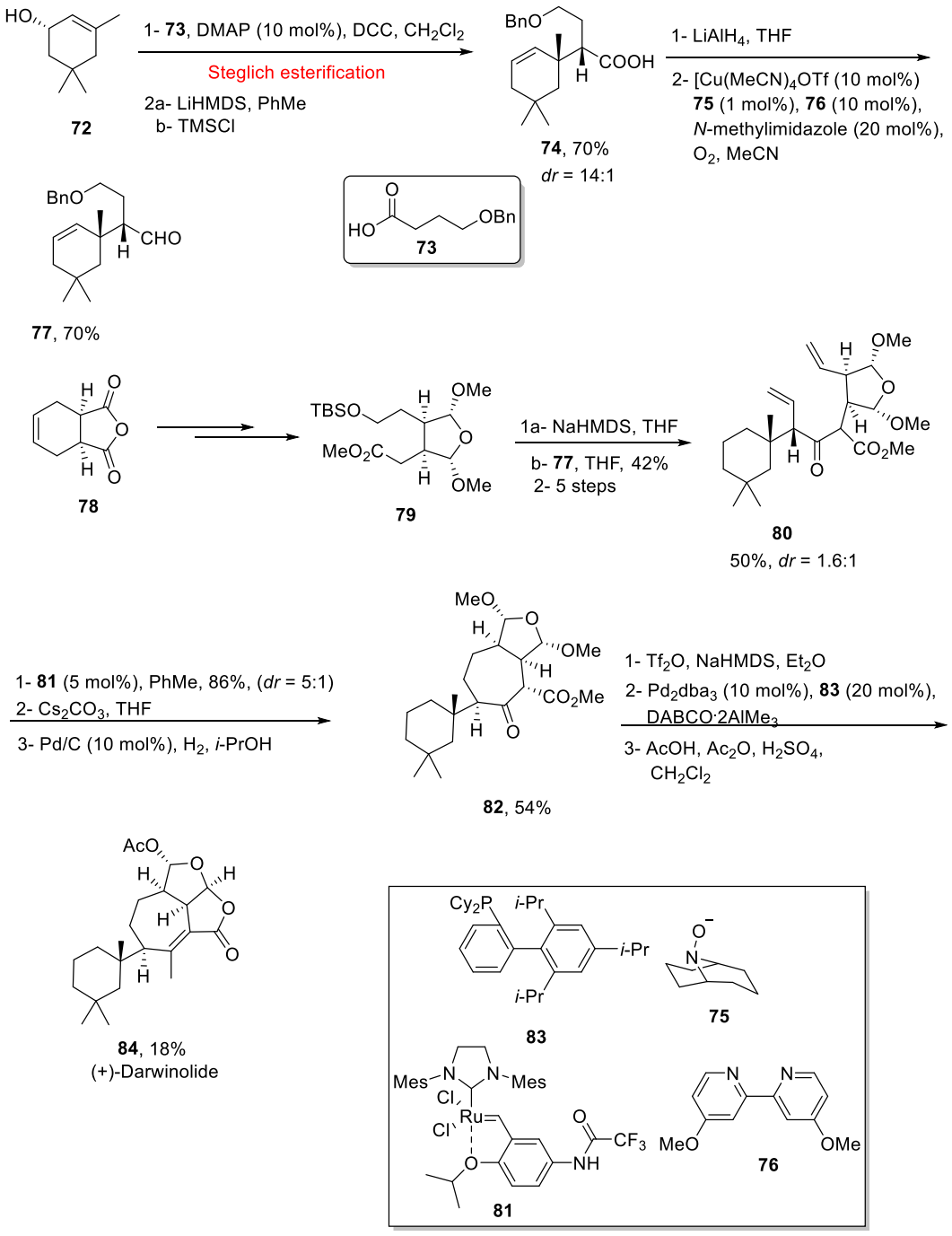
anticancerous. These are also considered active agents against leishmaniasis which is a group of zoonotic and anthroponotic diseases caused by 20 protozoan parasite species of the genus *Leishmania*. The database of around 360 kauranes was generated and studied by structure-based and ligand-based analysis to identify bioactive kauranes. Among these, only 7 kauranes were found potentially active. Out of these seven kauranes, two are ranked best and are obtained from *Wedelia chinensis* [48]. In 2021, Herrera-Acevedo et al. reported the synthesis of these biologically active kauranes [49]. For the synthesis of these kauranes, commercially available precursors were envisaged from *Xylopia frutescens*, which produced kaurane-type diterpenoids. These kaurane-type diterpenoids were utilized as synthetic precursors. The synthesis was materialized from (*R*)-(−)-carvone **85** which underwent chemoselective monohydroxylation in the presence of Cu–Al Ox and *tert*-butoxide followed by selective hydrogenation in the presence of Wilkinsin's catalyst to forge 2-oxo-menth-6-en-5*β*-ol **86** in 91 % yield. For the next step, Steglich esterification was actualized to obtain ester adduct **88** with coupling of compounds **86** and **87** in 79 % yield. A selective 1,2-reduction was employed to obtain 2β-hydroxy-menth-6-en-5*β*-yl *ent*-kaurenoate **89** in the presence of sodium borohydride and cerium chloride in 82 % yield (Scheme 13).

Further, 2 kauranes (**92**, **93**) and their derivatives (**92a**, **93a**) were envisioned by esterification of cinnamic acid derivatives **90a** and **90b** with compound **91a** and **92b** in 78–79 % yield. The synthesized kauranes were evaluated for their potential against *Lm*PTR1 enzyme inhibition which provided **89** and **93** most potent leishmaniasis inhibitor with IC_{50} value of 10 μM against *L. major* (Scheme 14). [49].

2.5. Dihydropyrone-based natural product synthesis

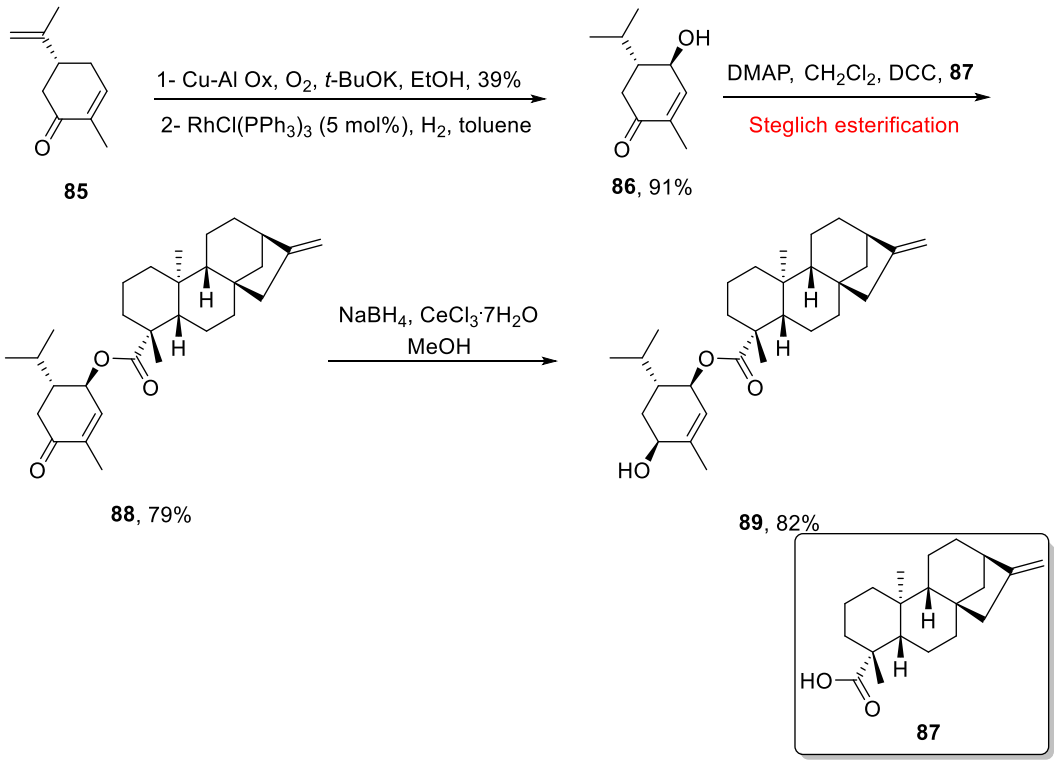
Brevipolide M belongs to pyrone-based natural compounds which have been found to exhibit numerous biological activities. In 2022, Liu et al. aimed at total synthesis of Brevipolide M by employing ring-closing metathesis, Wittig olefination and Steglich esterification in 17.8 % overall yield in 13 linear steps [50]. The synthesis was actualized from D-mannofuranose diacetonide **94** which was transformed to compound **95** over a few steps. The compound **95** was esterified via Steglich conditions in the presence of (*E*)-4-methoxy cinnamic acid, DMAP, DIC and anhydrous DCM to give ester **96** in 81 % yield. The next step involved acetyl chloride-mediated isopropylidene removal to give 95 % of diol **97**. The diol underwent another Steglich reaction with vinyl acetic acid, DIC, DMAP and DCM to give 61 % of ester **98**. Finally, Brevipolide M **99** was obtained by ring-closing metathesis followed by DBU-assisted isomerization (Scheme 15).

Pyrone diterpenes are biologically active natural compounds obtained from fungal strains [51]. Merchant et al. utilized radical-based inter- and intramolecular chemistry to provide access to the pyrone diterpenes, a class of natural products, in 2018 [52]. By employing the electrochemically mediated oxidative radical polycyclization and radical decarboxylative cross couplings, four natural products i.e., higginsianin A, subglutinols A/B and sesquicillin A have been synthesized. The synthesis of higginsianin A commenced from polyene **100** which underwent Mn-assisted radical polycyclization in the presence of $Cu(sal)_2$, potassium acetate,

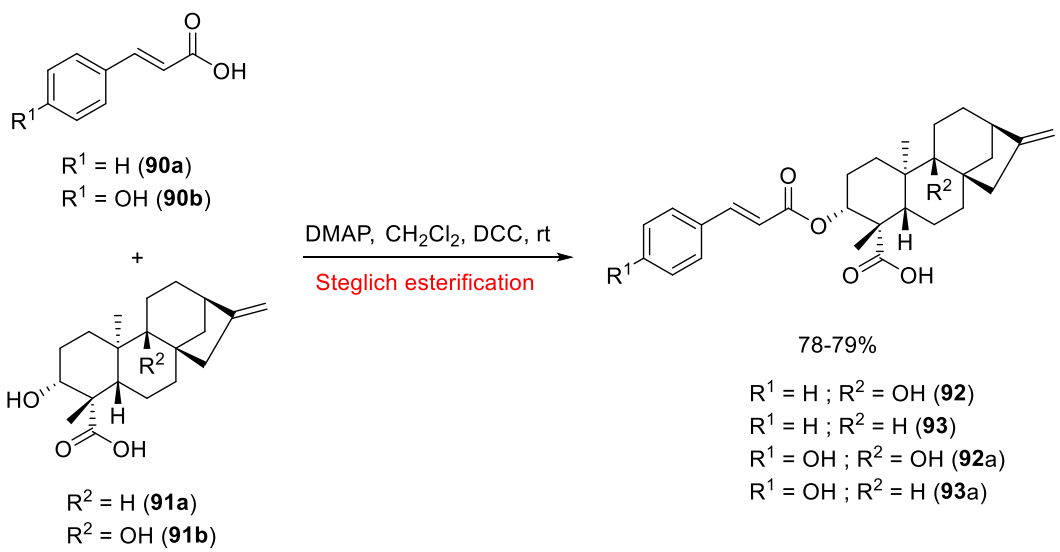


Scheme 12. Synthesis of (+)-darwinolide **84**.

acetic acid and ethyl acetate followed by diastereoselective H-PHOX-mediated Tsuji-allylation to give compound **101**. Next, compound **101** was treated with L-selectride along with V-directed Sharpless epoxidation to produce a diastereomeric mixture of **102a** and **102b** in 1.2:1 *dr*. The next step involved esterification by employing TPAP/NMO and DIC/MeOH-mediated Steglich esterification method followed by allylic oxidation and TESOTf-assisted quenching along with hydroboration in the presence of BH_3 and hydrolysis to provide a mixture of epimers **103** in 1.3:1 diastereomeric ratio. The acid **103** was converted to higginsianin A **104** over a few steps (Scheme 16). The divergent synthesis protocol employed by Merchant et al. was also utilized for the synthesis of a few other pyrone diterpenes named as subglutinol B **105**, subglutinol A **106** and sesquicillin A **107** as presented in Fig. 3.



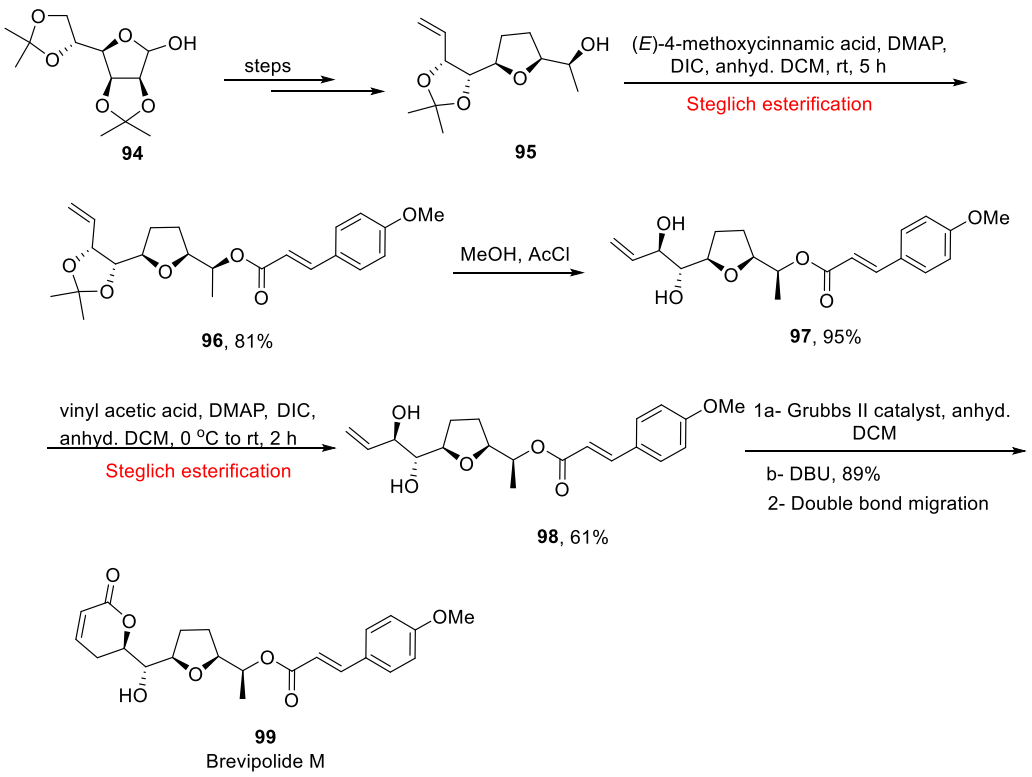
Scheme 13. Synthesis of diterpenoid ester adduct **89**.



Scheme 14. Synthesis of diterpenoid ester adducts.

2.6. Lactone-based natural product synthesis

(+)-Longirabdiol, (−)-longirabdolactone, and (−)-effusin are ent-kaurane diterpenoids obtained from *Isodon* genus [53]. These are structurally diverse and biologically active natural products exhibiting potent potential as antiinflammatory, antibacterial and anti-neoplastic properties [53]. Zhang et al. have furnished the first total synthesis of these ent-kauranes by materializing tandem decarboxylative alkenylation, Giese reaction, Steglich reaction and vinyl radical cyclization as key steps in 2019 [54]. The synthesis was commenced from ethyl 2-cyclohexanonecarboxylate **108** which is commercially available as *rac*-20 and provided compound **109**



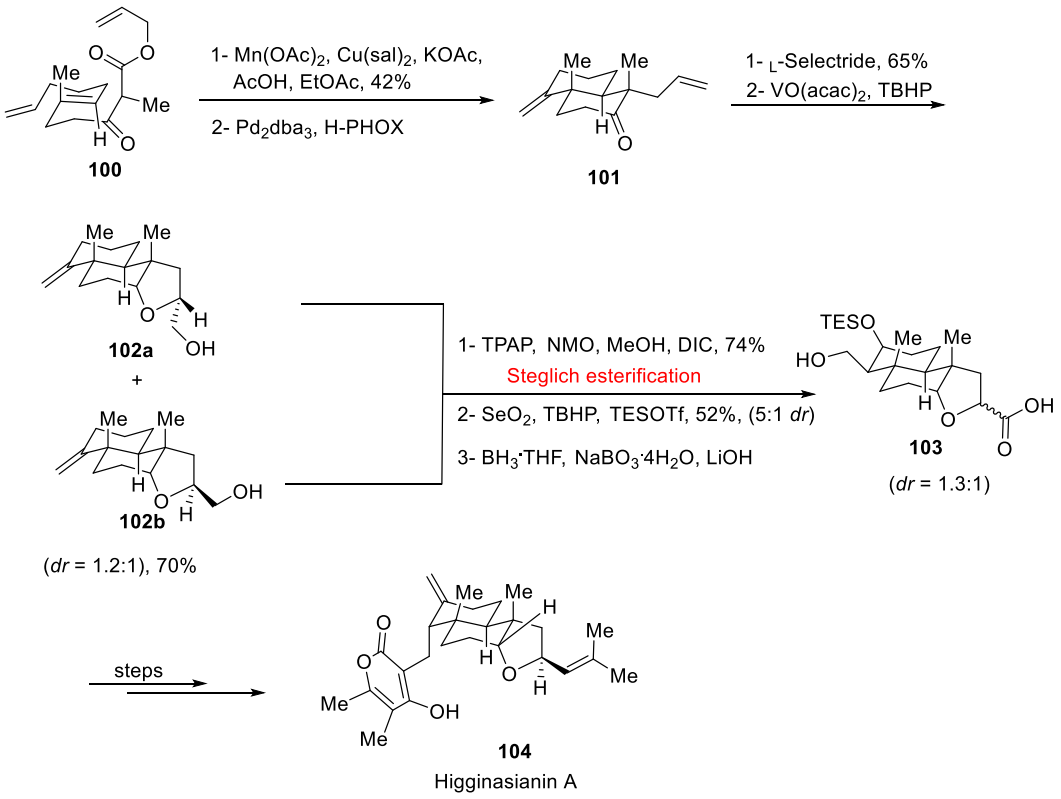
Scheme 15. Synthesis of brevipolide M **99**.

over a few steps. The compound **109** underwent the Steglich esterification in the presence of DIC, DMAP and *N*-hydroxyphthalimide (NHPI) to provide ester **110** in 88 % yield over 2 steps. After optimization of radical alkenylation or cyclization step, the ester **110** was converted to γ-lactone **114** in the presence of 7 mol% $CuCl_2$, 7 mol% of **111**, 7 mol% of **112** and 3 equivalents of **113** in 60 % yield. The γ-lactone **114** was transformed to (+)-longirabdiol **115** over a few steps which underwent DMP-mediated oxidation to furnish (−)-longirabdolactone **116** in 76 % yield. Next, (+)-longirabdiol **115** was being proceeded through the Steglich esterification accompanying Dess-Martin oxidation to establish (−)- effusin **117** in 65 % yield (Scheme 17).

Berkeleylactone A is a potent antibiotic, obtained from co-culturing of *Penicillium camembertii* and *Penicillium fuscum* [55]. In 2019, Ferko et al. provided the total synthesis of berkeleylactone A by employing ring closing metathesis, Steglich esterification, sulfa-Michael addition and chemoselective reduction to achieve target compound in 9.5 % overall yield consisting of 10 steps [56]. The synthesis was initiated by weinreb amide **118** which underwent addition with cyclohexenyl magnesium bromide **119** followed by reduction with borane dimethylsulfide in the presence of 10 mol% catalyst (*R*)-2-methyl-CBS-oxazaborolidine along with TBS-mediated hydroxyl group protection to give 93 % of compound **120**. The next step involved *N*-bromosuccinimide-assisted Achmatowicz oxidation together with pyridine catalyzed isomerization of double bond to give 69 % of aldehyde **121**. Further, the aldehyde **121** underwent oxidation with sodium chlorite and amylene followed by Steglich esterification with alcohol **122** in the presence of DCC and DMAP to provide compound **123** in 67 % yield. Next, compound **124** was obtained in 89 % yield by Grubbs–II–mediated ring closing metathesis followed by TBS deprotection with TFA. Further, Potassium (*R*)-oxirane-carboxylate **125** was employed to give acid **126** in 85 % yield by epoxide opening reaction in the presence of sodium hydride followed by triethyl silane. The last step involved two-step coupling of compounds **124** and acid **126** to furnish target compound berkeleylactone A **127** in 92 % yield with high diastereoselectivity of >20:1. The synthesized compound was screened for antibacterial activity and exhibited potency against *S. aureus* MB17 (Scheme 18).

The synthesis of some new berkeleylactones have also been provided by Schriefer et al. in 2023 [57]. The synthesis was initiated from halide **128** and epoxide **129** which were transformed into protected alcohol **130**. The alcohol **130** underwent Steglich esterification in the presence of EDC·HCl, DMAP and dichloromethane to acquire quantitative yield of **132**. Berkeleylactone E **133** and K **134** were obtained from ester **132** by TFA-mediated deprotection. Further, compound **130** underwent TBDPSP-assisted protection of OH group and deprotection of MOM group to get ether **134**. Next, Steglich esterification was employed in the presence of carboxylic acid **131** catalyzed with EDC·HCl along with hydrogenation to obtain macrolide **135** in 98 % yield over 2 steps. Berkeleylactone M **136** was obtained from macrolide **135** by TBAF global deprotection in 66 % yield and Berkeley—lactone O **137** was obtained in 57 % yield. The article also covers the synthesis of some other berkeleylactones by employing a similar strategy (Scheme 19).

(-)-Cleistenolide is a naturally occurring α,β-unsaturated δ-lactone derived from *Cleistochlamys kirkii* [58]. The (-)-cleistenolide and its analogues possess antiproliferative potential against a number of human cancer cell lines [59]. The purpose of analogue synthesis of



Scheme 16. Synthesis of higginasianin A **104**.

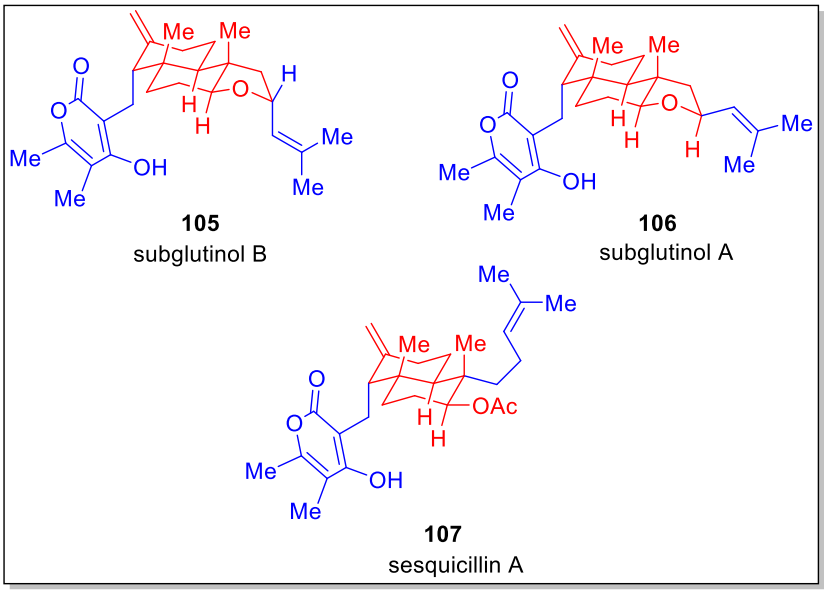
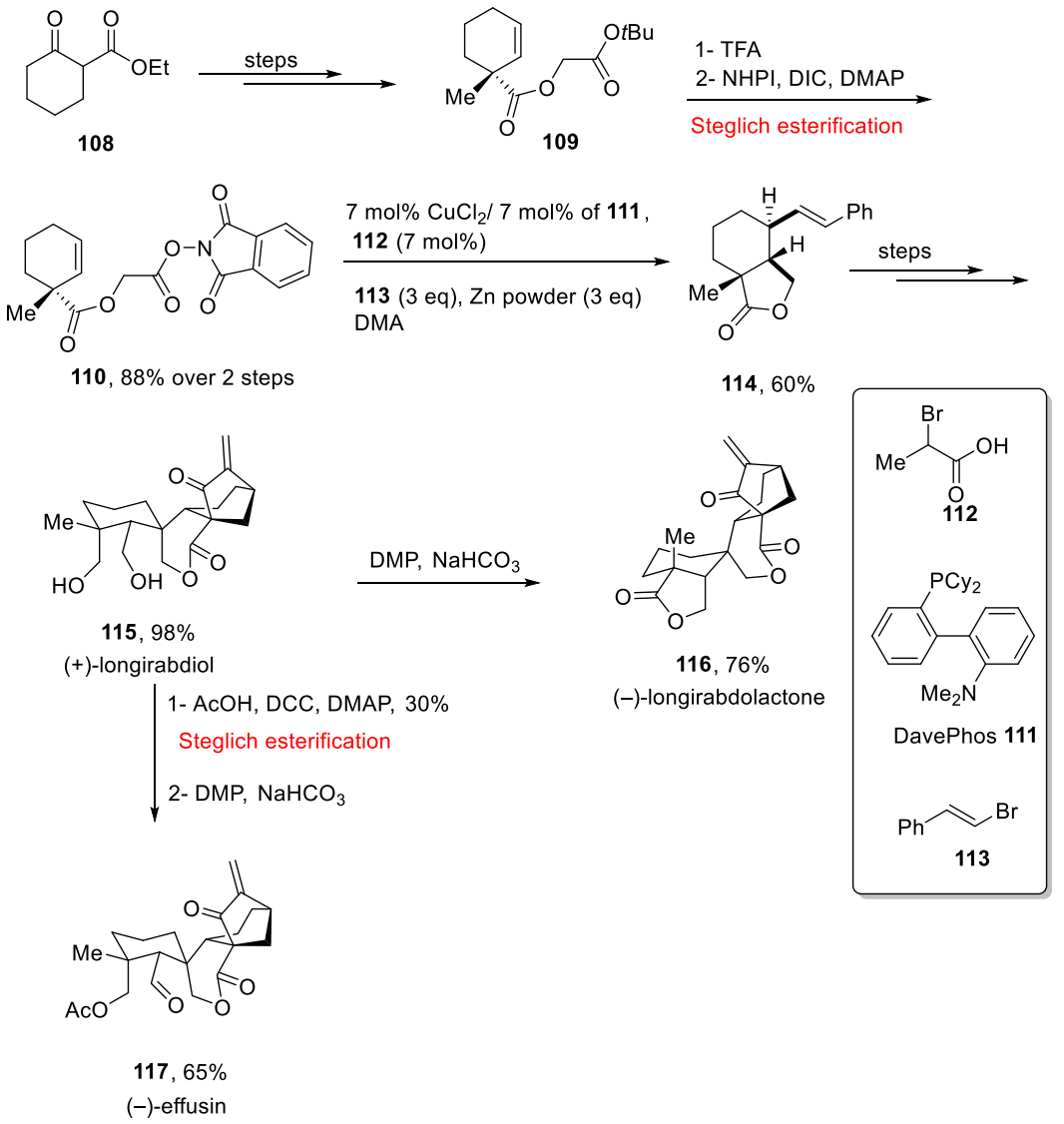


Fig. 3. Structures of pyrone diterpenes subglutinol B **105**, subglutinol A **106** and sesquicillin A **107**.

natural products is to enhance their potential as antiproliferative agents which is achieved by introducing a number of functionalities. The synthesis of (-)-cleistenolide analogues was reported by Benedekovic et al. in 2021 which commenced from triol **138** [60]. The triol **138** was converted to secondary alcohol **139** over a few steps. The secondary alcohol **139** was made to couple with carboxylic acid **140** under Steglich conditions of DCC and DMAP to facilitate ester **141** in 88 % yield. The synthesized esters **141** were acylated in the

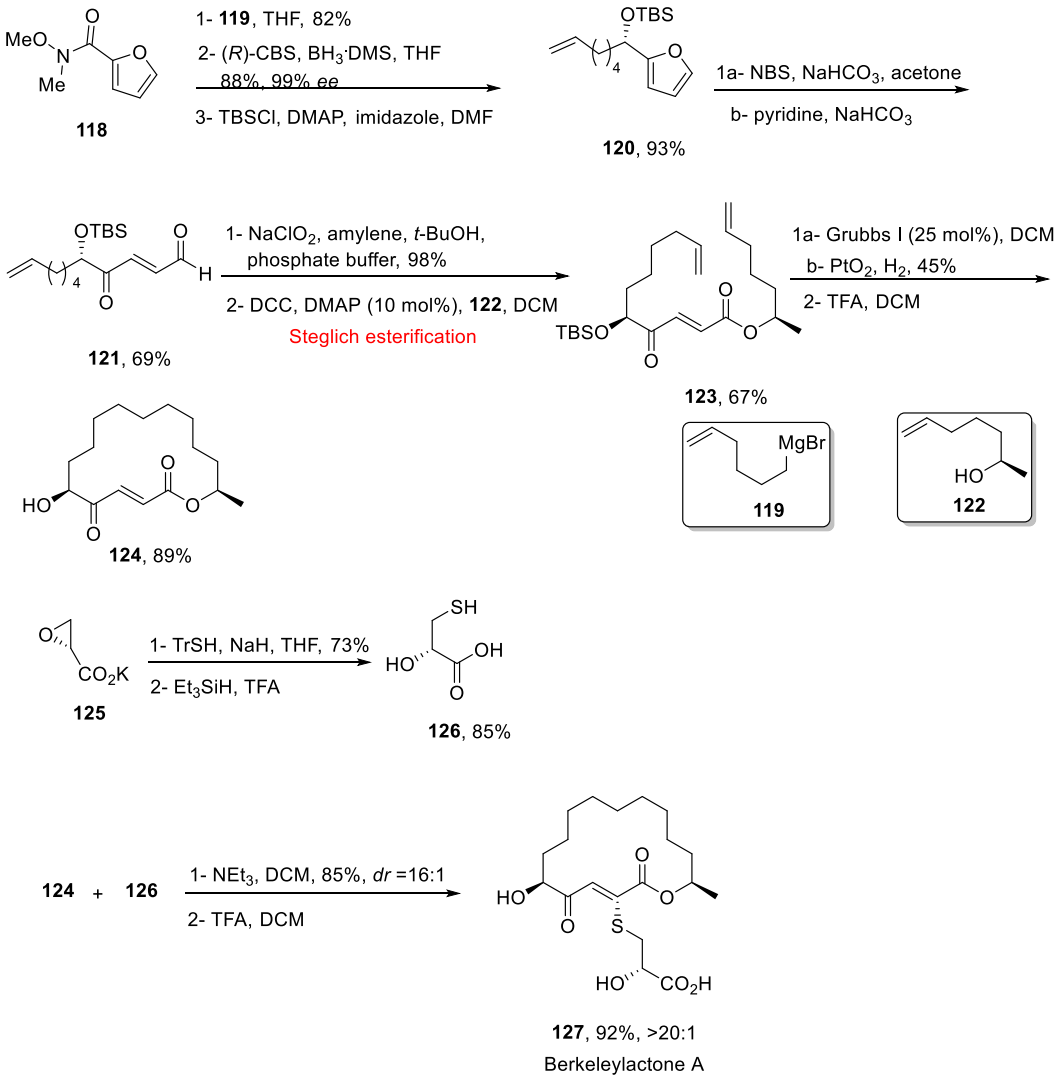


Scheme 17. Synthesis of (+)-longirabdiol **115**, (−)-longirabdolactone **116**, and (−)- effusin **117**.

presence of acetic anhydride and ferric chloride to afford mono-*O*-acetylated derivative **142** in 95 % yield. For the synthesis of di-*O*-acetylated derivatives, acetyl bromide with zinc triflate as a catalyst were employed along with cinnamic acid derivative, acetic anhydride and ferric chloride to furnish the target analogue **143** in 63 % yield. By employing different acid derivatives, a number of analogues can be synthesized. The synthesized analogues were studied for antiproliferative activities against seven human cancer cell lines in comparison with cleistenolide. The best activity was exhibited by flouro-cinnamic acid derivative against HeLa cell lines with IC_{50} value of 0.04 μM (Scheme 20).

2.7. Chromanone-based natural product synthesis

Violacin A and its analogues are naturally occurring chromanones obtained from fermentation broth of *Equus burchelli* [61]. These are effective antiinflammatory agents and have been analyzed by antiinflammatory mechanism. The inhibitory effects of these compounds have been estimated by using Raw 264.7 macrophage of lipopolysaccharide (LPS). The synthesis of violacin and its analogues have been provided by Liu et al. in 2019 [62]. The key steps for achieving the synthesis involve Baker-Venkatamaran rearrangement promoted by NaH, regioselective etherification and Friedel-Crafts acylation. The construction of violacin skeleton was actualized from commercially available orcinol **144** which provided 2,4-dihydroxy-6-methyl-acetophenone **145**. Next, etherification of dihydric phenol **146** was achieved by treating it with acetic acid and BF_3OEt_2 to achieve compound **147**. Further, compound **147** underwent *O*-benzylation with potassium carbonate, benzyl chloride and sodium iodide to obtain compound **148**. Compound **148**

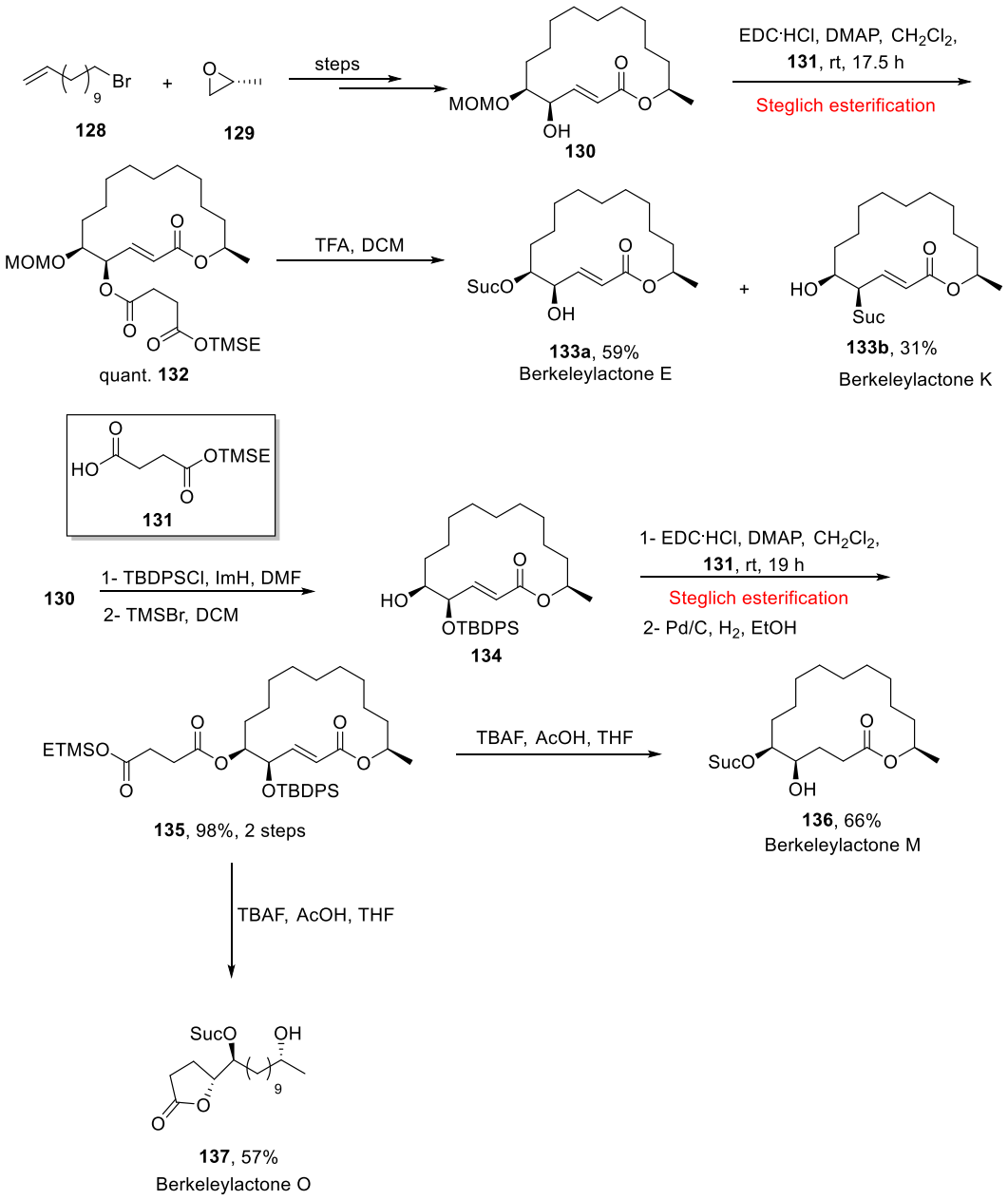


Scheme 18. Synthesis of berkeleylactone A **127**.

underwent the Steglich esterification with ketone **145** in the presence of DCC, DMAP and DCM to give compound **149**. The ester underwent cyclization with sodium hydride along with deprotection by employing soft Lewis acid $PdCl_2(CH_3CN)_2$ in acetone accompanying the hydrogenolysis in the presence of Pd–C and hydrogen gas to furnish the target compound violacin A **150**. Furthermore, the compound **152** was synthesized from dihydric phenol **151** by treating it with an alkyl halide, sodium iodide and potassium carbonate accompanied by the Steglich esterification and NaH-mediated cyclization to get **152** in 92 % yield. Next, compound **152** was treated with K_2CO_3 in methanol to obtain **153** in 75 % yield. The compound **152** gave 82 % of analogue **154** by trimethylsilyl treatment and 92 % of analogue **155** was obtained by treatment with $PdCl_2(CH_3CN)_2$ in acetone. The same strategy was employed to synthesize various other analogues as well. The synthesized analogues were subjected to analyze the production of NO in macrophages. Some of the synthesized compounds exhibited potent anti-inflammatory activity, even better than violacin A (Scheme 21).

2.8. Alkaloid-based natural product synthesis

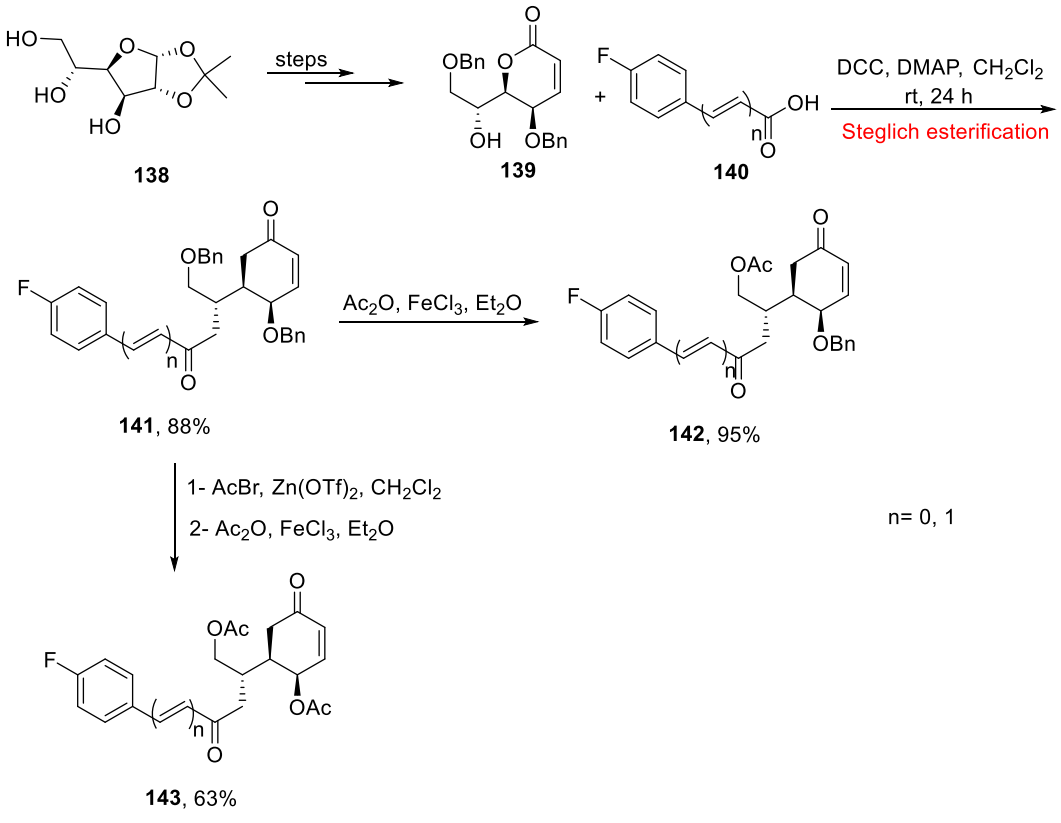
Rauvolfia serpentina is a flower that belongs to *Apocynaceae* family. It is a potent source of a drug, named reserpine, which is used for hypertension treatment. Owing to its medicinal properties, many research groups have undertaken this structure to accomplish its total synthesis. Its first total synthesis was achieved by Woodward and co-workers, in 2022, by forging Meerwein– Ponndorf–Verley reduction, Jones oxidation, Bischler–Napieralski reaction and Steglich esterification as key steps [63]. The reaction of quinone **156** and diene **157** comprised the first step to provide compound **158** in 27 % yield. Over a few steps, the compound **158** was converted to (**159**) which underwent the Steglich esterification in the presence of DCC, PvOH and pyridine to provide esterified product **160** in 50 %



Scheme 19. Synthesis of different berkeleylactones.

yield. The next step involved coupling with 3,4,5-trimethoxybenzoyl chloride **161** in the presence of sodium methoxide in methanol to furnish target compound (±)-reserpine **162** in 45 % yield (Scheme 22).

Schwarzinicines A and B are isolated from *Ficus schwarzii*. These are 1,4-diarylbutanoid–phenethylamine alkaloids attributed with ethnopharmacological and vasorelaxant properties [64]. Lee et al. provided the total synthesis of schwarzinicines A and B by employing Claisen condensation and reductive amination to envisage the core skeleton of target compounds with overall yield of 9.1 % and 3.5 % respectively [65]. The synthesis commenced from commercially available (3,4-dimethoxyphenyl) propionic acid **163** which underwent Steglich esterification with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) in the presence of DMAP and DCM to yield 82 % of esterified product **164**. Further, the Claisen condensation of 3,4-dimethoxyphenyl) acetonitrile **165** and ester **164** in the presence of organolithium reagent followed by nitrile hydrolysis in acetic acid with subsequent reductive amination in the presence of $NaBH(OAc)_3$ with 3,4-dimethoxyphenethylamine **166** to forge schwarzinicines A **167** in 79 % yield. Schwarzinicines B **168** was obtained by N-methylation with MeI from **167** in 38 % yield. The synthesized alkaloids underwent for evaluation of vasorelaxant effects on phenylephrine-precontracted aortic rings of rat and exhibited EC_{50} value in the range of 1.19–2.98 μM (Scheme 23).



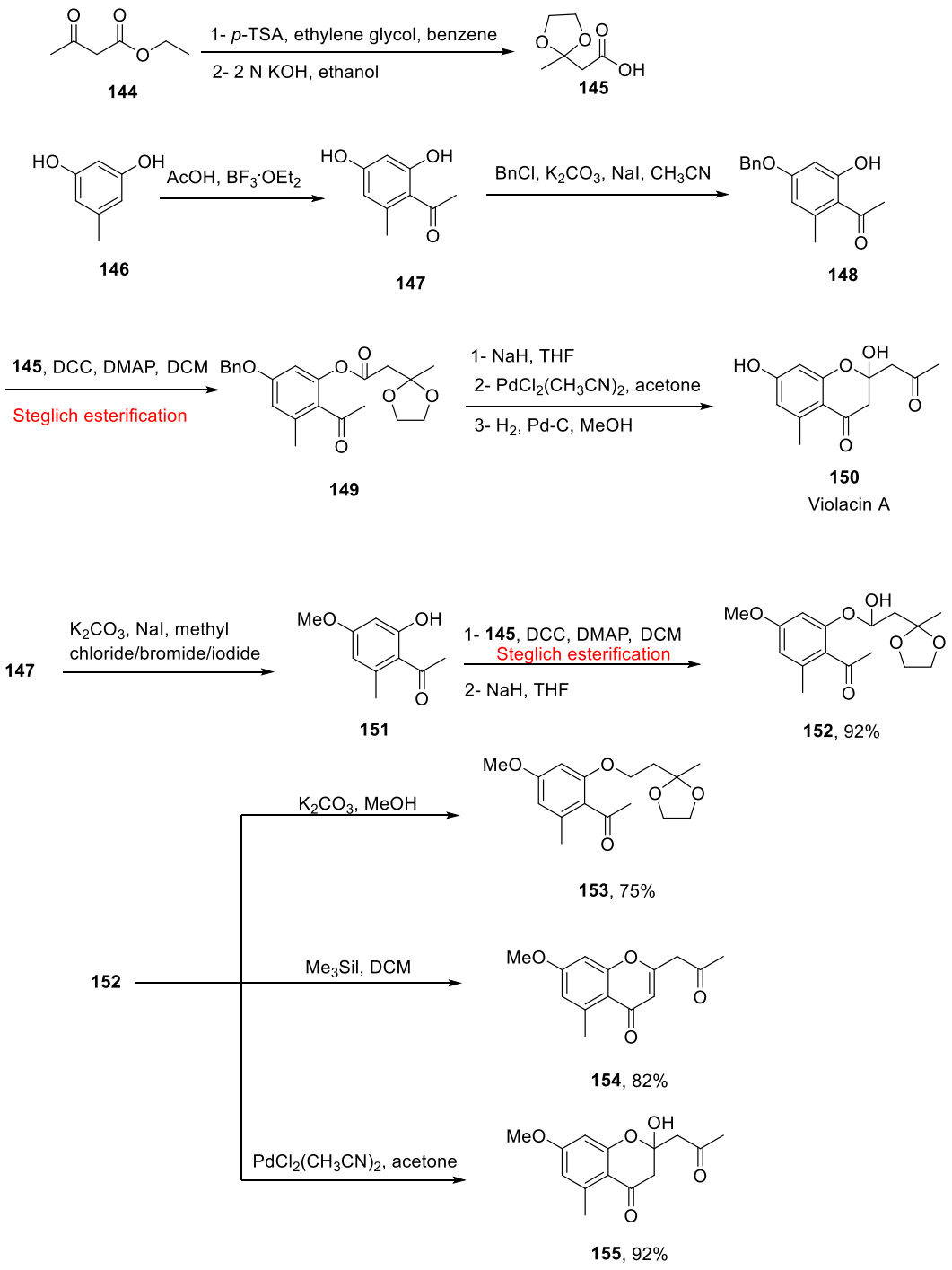
Scheme 20. Synthesis of (-)-cleistenolide analogues.

A *cis*-fused decahydroquinoline (DHQ) containing marine alkaloids, known as lepadins, are obtained from flatworms and tunicates [66]. Lepadins exhibit a wide range of biological activities such as lepadins A and B are anticancerous, lepadin B is active against receptor blocking of neuronal nicotinic acetylcholine, lepadins D-F exhibit antimalarial activity and lepadin I inhibit the action of butyrylcholine esterase. The significance of lepadins has led towards strivings on achieving the total synthesis of DHQ core [67,68]. In 2021, Ma et al. provided the synthetic methodology comprised of five steps to achieve the DHQ core by intramolecular [3 + 2] cycloaddition and aza-Achmatowicz rearrangement [69]. The synthesis was initiated by furfuryl amide **169** which furnished DHQ core structure **170** over a few steps. The next step involved one carbon homologation by Wittig reaction in the presence of $Ph_3PCH_2OCH_3Cl$ and NaHMDS along with subsequent hydrolysis with trichloroacetic acid to produce a mixture of diastereomeric products (5*S*)-**171a** and (5*R*)-**171b** in 1:1.9 ratio with a combined yield of 72 %. The next step involved Julia− Kocienski olefination in the presence of NaHMDS and tetrazole sulfone **172** with subsequent hydrolysis to give alcohol **173**. The *ent*-lepadin I **175** was obtained in 34 % yield by employing the Steglich esterification with acid **174** followed by deprotection in the presence of TFA. Next, phosphonate-mediated olefination was utilized to give **177a** and **177b**. The lepadin B **178** was obtained from **177a** by TBAF-assisted deprotection in 96 % yield. The **177a** was converted to lepadin A **180** in 70 % yield over two steps by deprotection and BF_3OEt_2 treatment. Further, **177b** underwent TBAF-mediated acylation with **179** to give 47 % of lepadin C **181** (Scheme 24).

The structures of lepadin D **184**, lepadin E **183** and lepadin H **182** are presented in Fig. 4, whose synthesis was also achieved from **139a** by employing Julia−Kocienski olefination, Pd-catalyzed hydrogenation, Mitsunobu reaction and cesium acetate-mediated mesylate substitution (Fig. 4).

2.9. Macrolide-based natural product synthesis

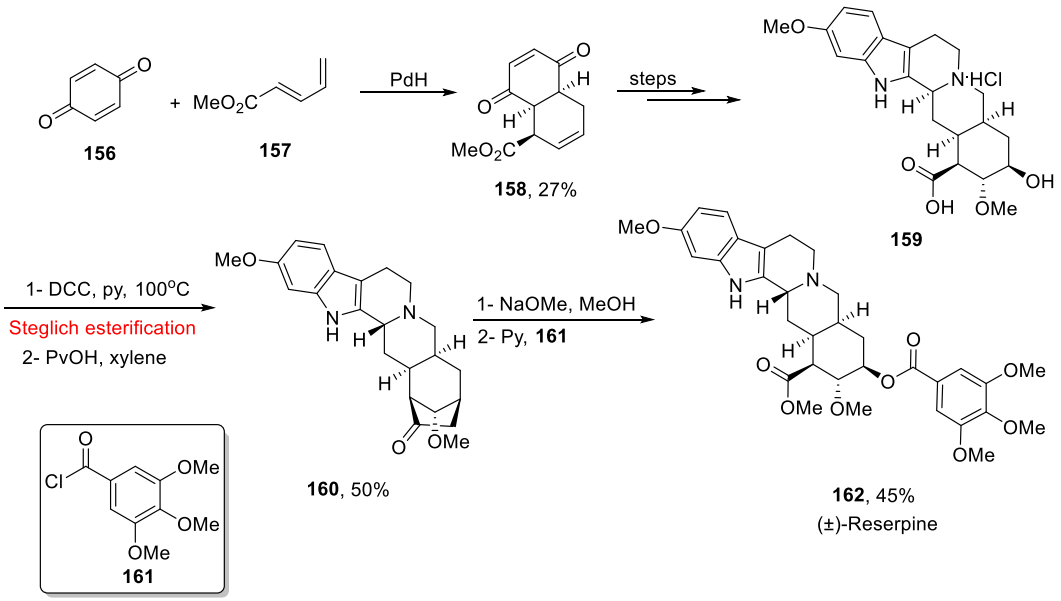
Macrocyclic scaffolds are omnipresent in naturally occurring compounds [70] whose synthesis can be achieved by employing ring-closing metathesis and Steglich esterification [71,72]. Thiacladospolide is a sulfur containing natural product obtained from marine sources. These are biologically important as they act against plant pathogen named *Colletotrichum glecosporioides* with 1–2 μg/ml MIC value and gram-negative and gram-positive bacteria [73]. The total synthesis of thiocladospolide A and its C2-epimer was designed by Swami et al. in 2022 [74]. They employed sulfa-michael addition, ring-closing metathesis and Steglich esterification reaction as key steps to achieve 12 % overall yield in straightforward nine steps. The synthesis commenced from TBS protection of *cis*-but-2-ene-1,4-diol **185** followed by Swern oxidation in the presence of $(COCl)_2$, DMSO and triethylamine to furnish secondary alcohol **187** in 83 % yield over 2 steps. TBS deprotection of alcohol **187** in the presence of TBAF followed by Jones oxidation in acetone



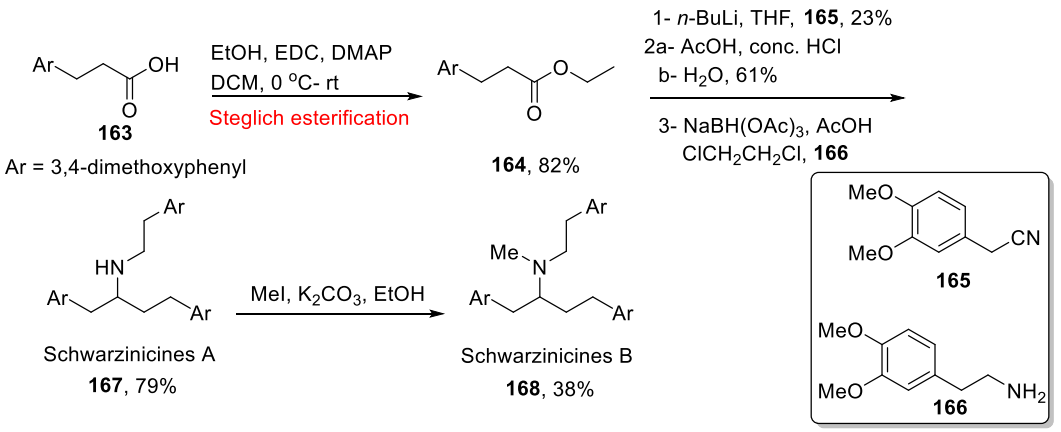
Scheme 21. Synthesis of violacin A **150** and its analogues.

provided 74 % of acid **188**. The Steglich esterification of acid **188** with a known alcohol **187** in the presence of DCC, DMAP and dichloromethane furnished compound **190**. Further, L-serine **191** was converted to alcohol **192** over a few steps. Finally, a Sulfa-Michael addition was proceeded between the compound **190** and alcohol **192** in the presence of triethylamine in DCM followed by Grubbs-II mediated ring-closing metathesis along with hydrogenation forging the final compounds thiocladospolide A **193** and its C2-epimer **193a** in 76 % and 78 % respective yields (Scheme 25).

The total synthesis of a queen specific compound has been reported by Machara et al., in 2018 [75]. This compound is specifically present in the bodies of *Silvestritermes minutus* that regulate a number of female body functions i.e., fertility signals to nestmates and



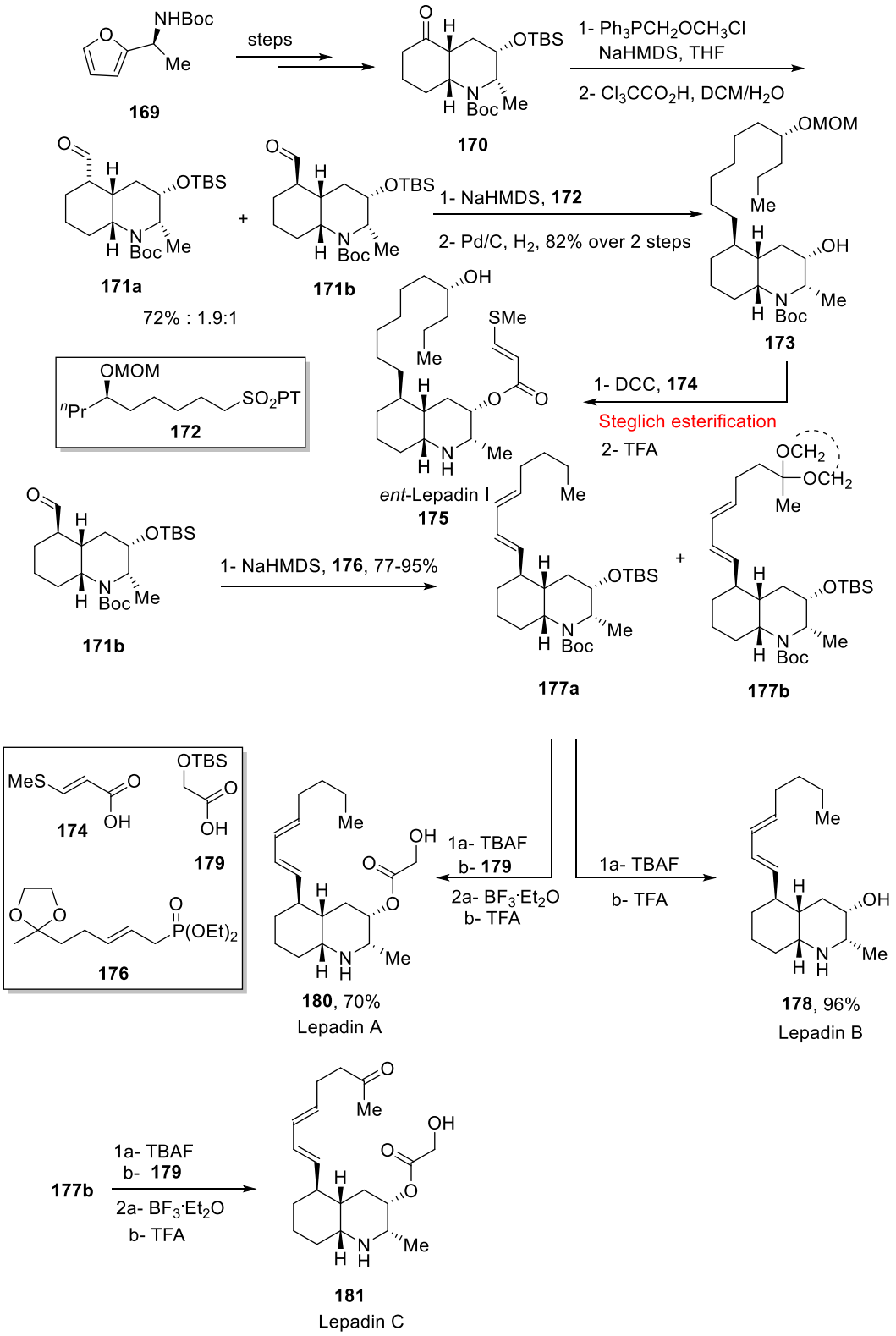
Scheme 22. Synthesis of (±)-reserpine **162**.



Scheme 23. Synthesis of schwarzinicines A **167** and B **168**.

supporting the dominance of reproduction etc. [76]. The synthesis begets with the (*S*)-glycidyl tosylate **194**, an optically pure substance, which underwent allyl magnesium bromide-mediated epoxide opening with Li_2CuCl_4 in a catalytic amount along with Grignard reaction in the presence of butyl magnesium bromide and copper catalyst to give 78 % of secondary alcohol **195**. Next, the Steglich esterification reaction was utilized with alcohol **195** in the presence of DCC, DMAP and hex-5-enoic acid followed by synthesis of macrolide in the presence of HG-II catalyst to furnish mixture of 3-*E* **196** and 4-*Z* **197** macrolides in 41 % yield. Furthermore, the synthesis of 6-*E* and 7-*Z* macrolides also commenced from (*S*)-glycidyl tosylate **194** which underwent butyl magnesium bromide-mediated epoxide opening with Li_2CuCl_4 in a catalytic amount along with Grignard reaction in the presence of allyl magnesium bromide and copper catalyst to give 40 % of secondary alcohol **198**. The Steglich protocol in the presence of DCC, DMAP and hex-5-enoic acid along with HG-II mediated metathesis and morpholinoethyl isocyanide-mediated quenching was employed with alcohol **166** to give target compounds **199** and **200**. The synthesized compounds were characterized by CIMS fragmentation and FTIR spectra (Scheme 26).

Nonenolide is a ten-membered macrolide, also known as decanolide, obtained from *Cordyceps militaries* BCC2816, which is an entomopathogenic fungus [77]. Nonenolide has been proven to be a potent antimalarial agent against *Plasmodium falciparum* K1, a multidrug-resistant bacterium. Sudina et al. proposed the total synthesis of nonenolide in 10.4 % overall yield constituting 12 linear steps by employing MacMillan α-hydroxylation, the Steglich esterification and ring-closing metathesis in 2018 [78]. The synthesis commenced from the construction of fragment **202** and **204** from **201** and **203** over a few steps. Next, the fragment **202** and **204** were coupled via the Steglich esterification mediated by DCC and DMAP to obtain 84 % of ester **205**. Further, lactone ring of nonenolide was



Scheme 24. Synthesis of lepadin A **180**, B **178**, and C **181**.

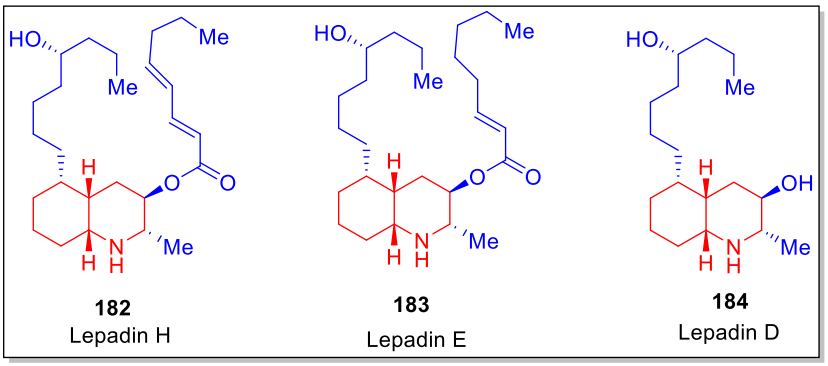
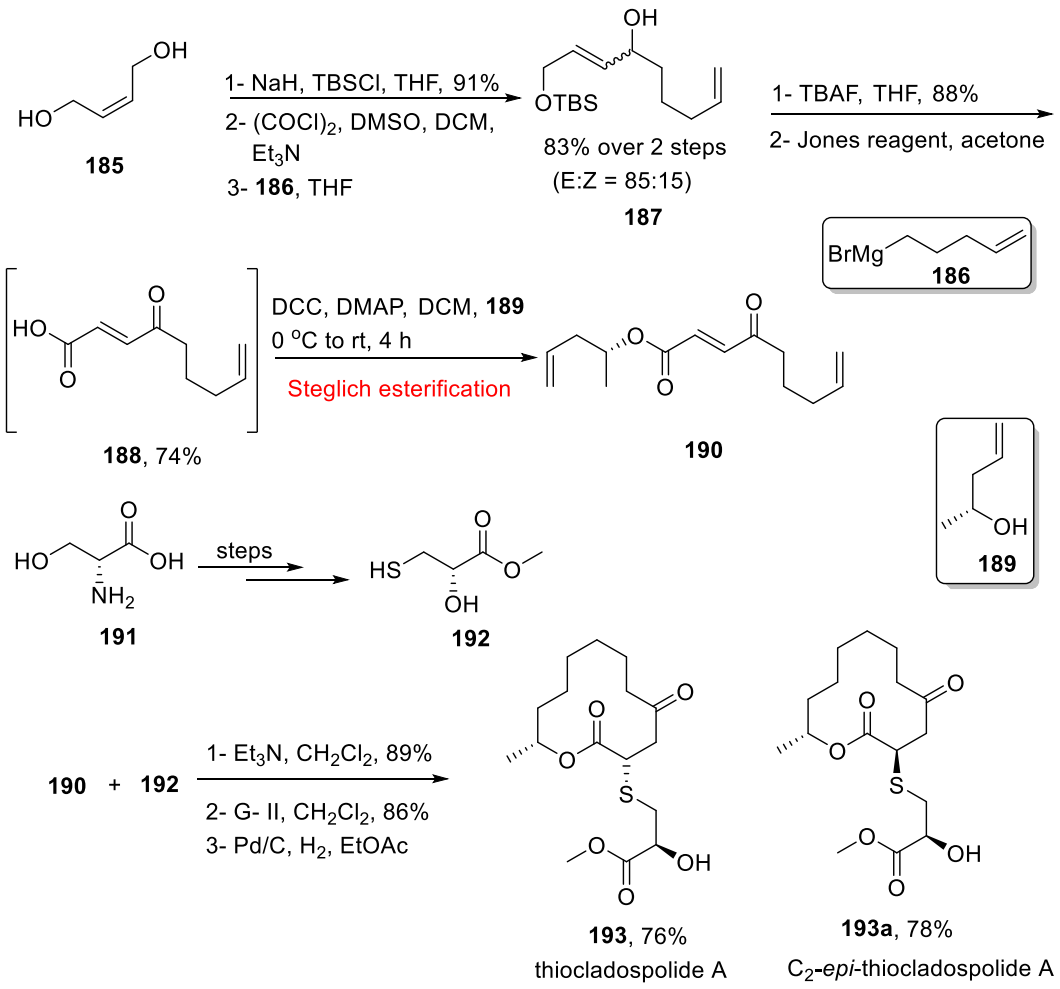


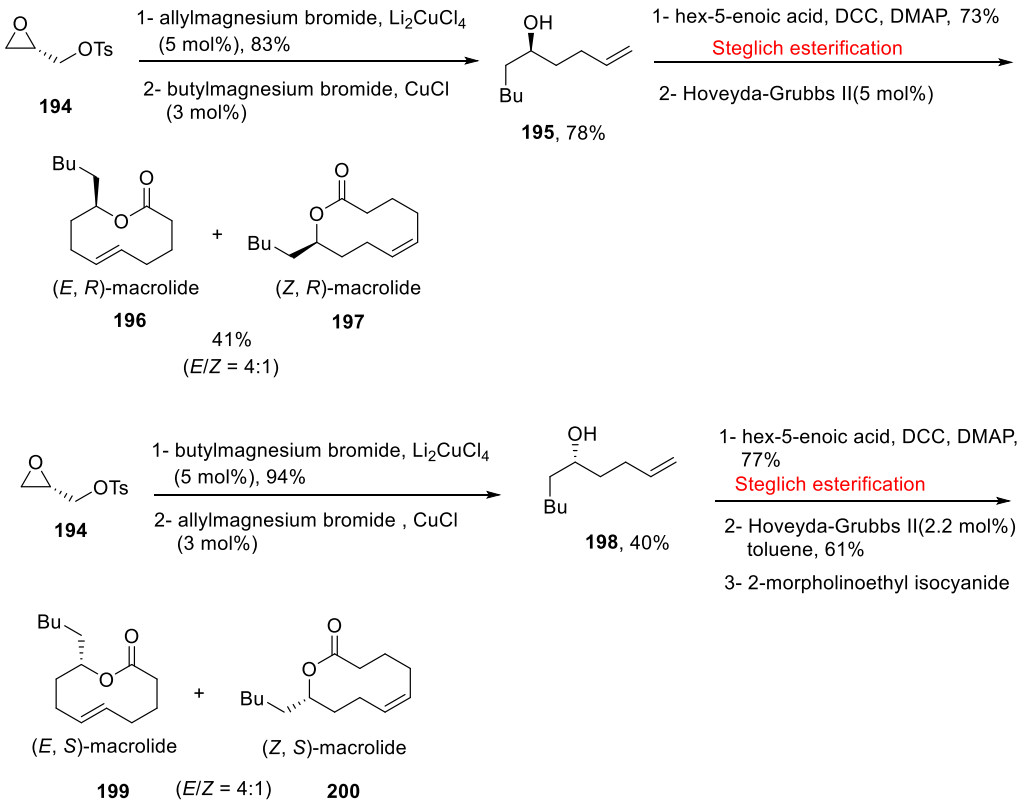
Fig. 4. Structures of lepadin H **182**, E **183** and D **184**.



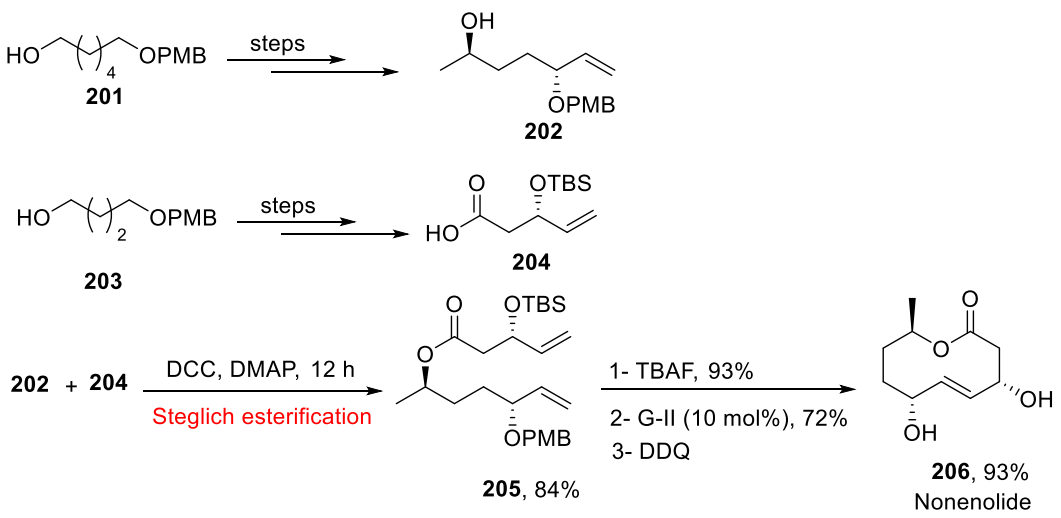
Scheme 25. Synthesis of thiocladospolide A **193** and its C2-epimer **193a**.

constructed by TBAF-mediated silyl group deprotection along with ring-closing metathesis with Grubbs catalyst followed by DDQ-based PMB group removal to furnish 93 % of nonenolide **206** (Scheme 27).

Oxacyclododecindione, 14-deoxyoxacyclododecindione and 13-hydroxy isomer are twelve-membered macrolactones. *Exserohilum rostratum* is a fungal source of these secondary metabolites [79]. The oxacyclododecindiones are exceptionally good antiinflammatory agents and can prove to be a scaffold in the field of pharmacology [80]. But, exhaustive procedure and low yield of fermentation make

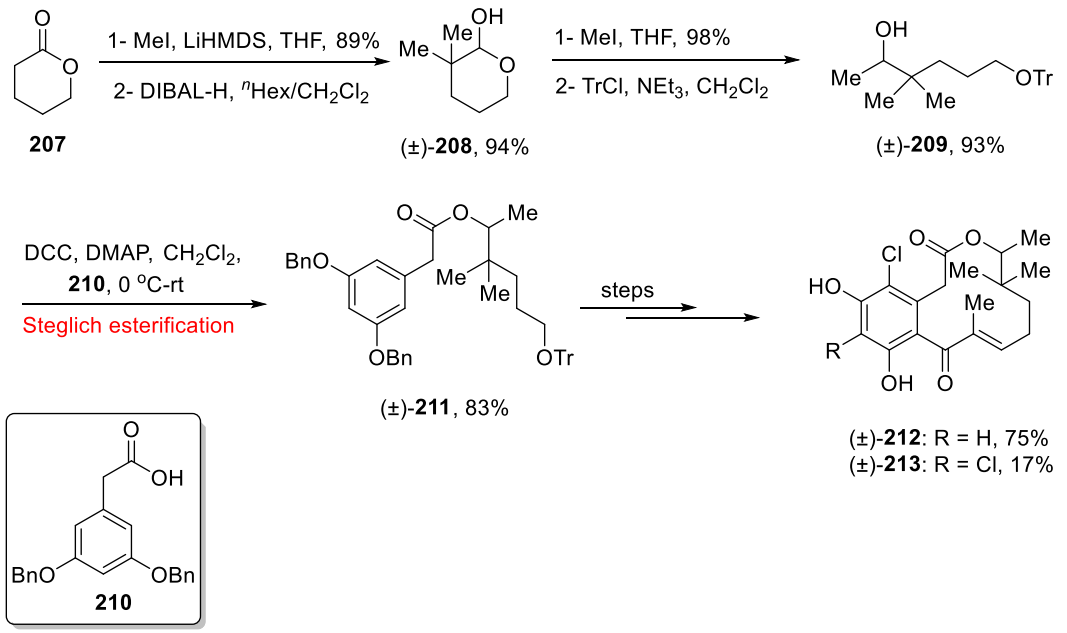


Scheme 26. Synthesis of macrolides **196**, **197**, **199** and **200**.

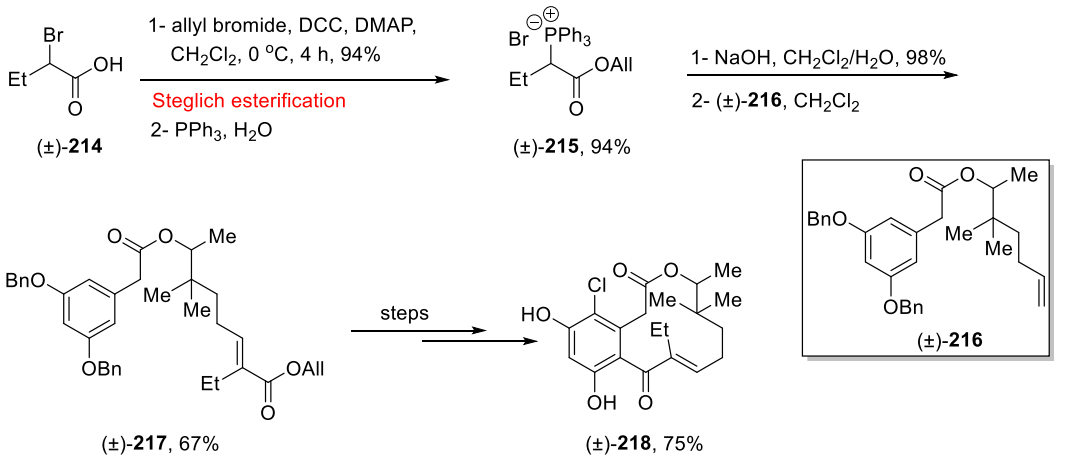


Scheme 27. Synthesis of nonenolide **206**.

it less applicable for medicinal field. To provide a back-up for this problem, seven new analogues of oxacyclododecindione-type macrolactones have been synthesized and evaluated for their antiinflammatory activities. Weber et al. forged the synthesis of seven new analogues of oxacyclododecindione-type macrolactones in 2020 [81]. The synthesis was actualized from *δ*-valerolactone **207** which gave 94 % of lactol **(±)-208** via double methylation in the presence of methyl iodide followed by subsequent reduction with DIBAL-H. Trityl-protected alcohol **(±)-209** was obtained from lactol **(±)-208** by ring-opening in the presence of a methyl lithium reagent. The next step involved selective Steglich esterification of secondary alcohol **(±)-209** in the presence of DCC, DMAP, acid **210**



Scheme 28. Synthesis of oxacyclododecindione-type macrolactones **(±)-212** and **(±)-213**.

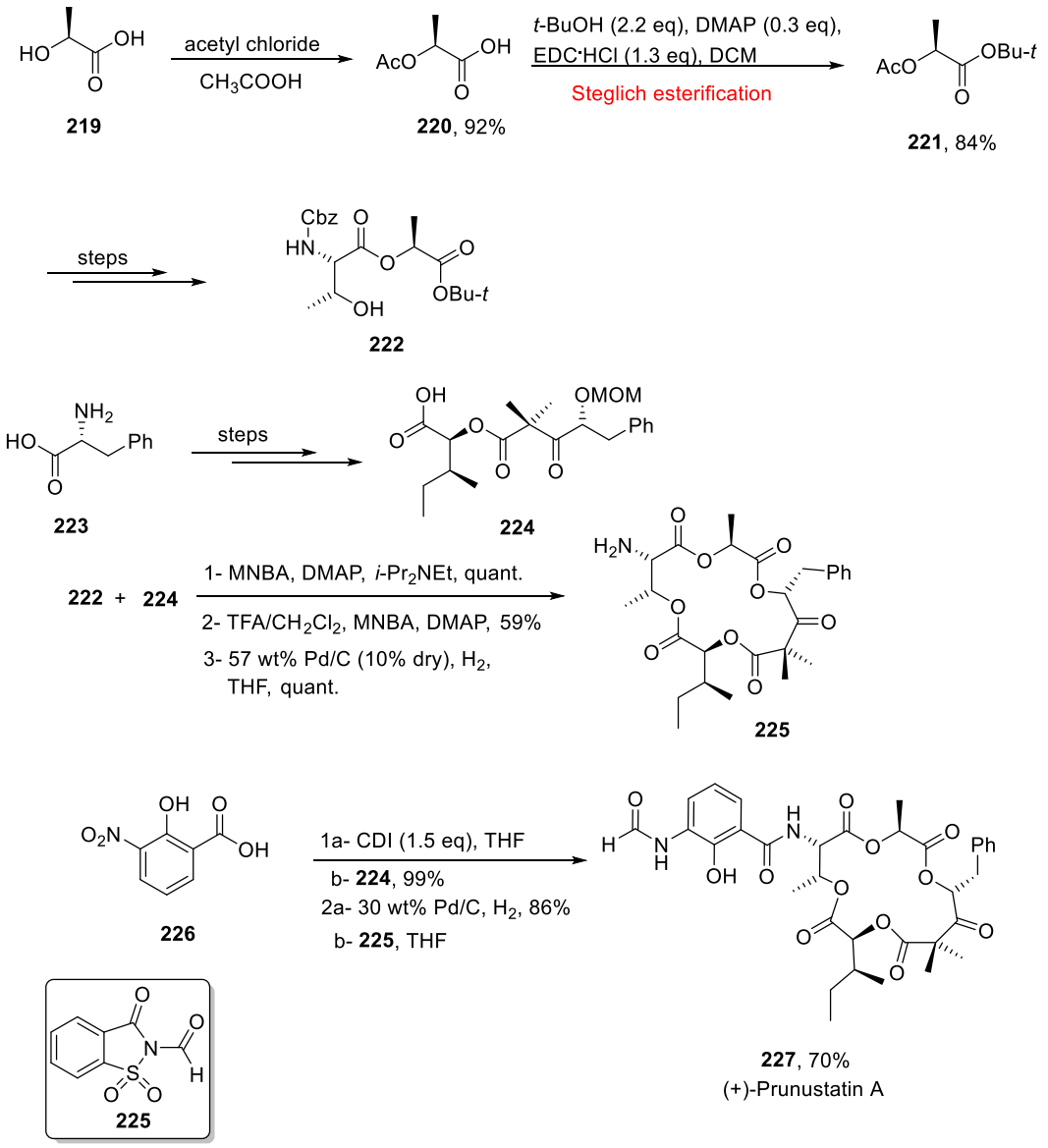


Scheme 29. Synthesis of oxacyclododecindione-type macrolactone **(±)-218**.

and DCM to give ester **(±)-211** in 83 % yield. The analogues **(±)-212** and **(±)-213** were obtained from ester **(±)-211** over a few steps (Scheme 28).

Furthermore, the synthesis of analogue **(±)-218** commenced from 2-bromobutyric acid **(±)-214** which underwent the Steglich esterification in the presence of allyl bromide and DCC followed by treatment with triphenylphosphine to give salt **(±)-215** in 94 % yield. The next step involved deprotonation of salt **(±)-215** together with Wittig olefination in the presence of aldehyde **(±)-216** to provide 67 % of unsaturated ester **(±)-217**. The analogue **(±)-218** was obtained from unsaturated ester **(±)-217** over a few steps (Scheme 29). In 2023, Seipp et al. disclosed a stereoselective synthesis of (13*R*,14*S*,15*R*)-13-hydroxy-14-deoxyoxacyclododecindione by employing Steglich esterification and confirmed its structure by analytical techniques [82].

Isolated from a soil sample of a volcanic island, (+)-prunustatin is an anticancer agent produced by *Streptomyces violaceoniger* specie. It exhibits anticancerous activity by downregulation of molecular chaperone, GRP78, that helps tumors to survive against chemotherapy [83]. Chojnacka et al. (2018) provided the total synthesis of (+)-prunustatin by employing Steglich esterification, MNBA Shiina couplings, organoboron-mediated prenylation and carbonyldiimidazole-based coupling [84]. The synthesis commenced by L-lactic acid **219** which underwent acetylation in the presence of acyl halide and acetic acid to give compound **220** in 92 % yield. Next, modified Steglich esterification was employed to protect tertiary butyl group mediated by EDCl, DMAP and DCM to provide 84 % of ester **221**. Further, the northern fragment **222** was synthesized from ester **221** over a few steps. The southern fragment **224** was

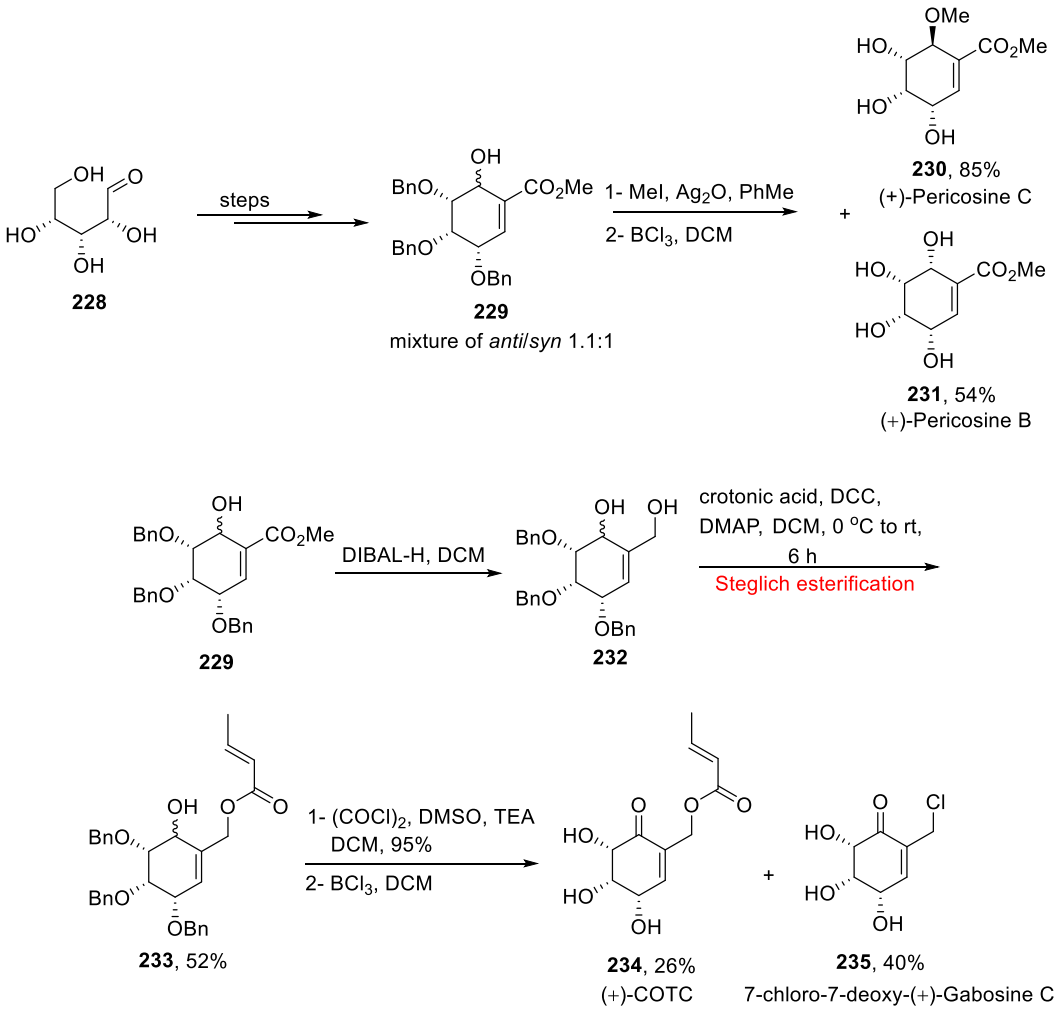


Scheme 30. Synthesis of (+)-prunustatin A **227**.

prepared from D-phenylalanine **223** over a few steps. A MNBA-mediated Shiina coupling was employed for coupling the northern fragment **222** and southern fragment **224** followed by MOM and *t*-butyl group deprotection in the presence of TFA and Cbz removal to provide a quantitative yield of macrocycle **225**. Next, 3-nitrosalicylic acid **226** in an unprotected form, activated by CDI followed by coupling with macrocycle **225** along with reduction of nitro group mediated by 30 wt% Pd/C and Cossy's protocol based on *N*-formyl saccharin to furnish (+)-prunustatin A **(+)-227** in 70 % yield (Scheme 30).

2.10. Carbasugar-based natural product synthesis

Carbasugars are a subclass of carbohydrates having a minor difference of ring oxygen replaced with a methylene group and thus being more stable than carbohydrates. Pericosines (A-E) and Gabosines are carbasugars obtained from a fungus *Perconia byssoides* (OUPS–N133) and culture broth of *Streptomyces filipensis* respectively [85,86]. These compounds are considered significant in medicinal field owing to their applications. Bidus et al. provided the total synthesis of these carbasugars in 2020 [87]. The synthesis begun from D-ribose **228** which was converted to **229** over a few steps. Next, the *anti*-**229** was consumed by employing mild conditions of MeI and Ag_2O and recovered *syn*-**229** was methylated followed by deprotection in the presence of BCl_3 in DCM to achieve 85 % of (+)-Pericosine C **230** and 54 % of (+)-Pericosine B **231**. Further, carbocyclic intermediate **229** was employed for the synthesis of COTC **234** and 7-chloro-analogue of (+)-Gabosine C **235**. For that purpose, carbocyclic intermediate **229** was first reduced with DIBAL-H to



Scheme 31. Synthesis of (+)-Pericosine C **230** and (+)-Pericosine B **231**, (+)-COTC **234** and 7- chloro-7-deoxy-(+)-gabosine C **235**.

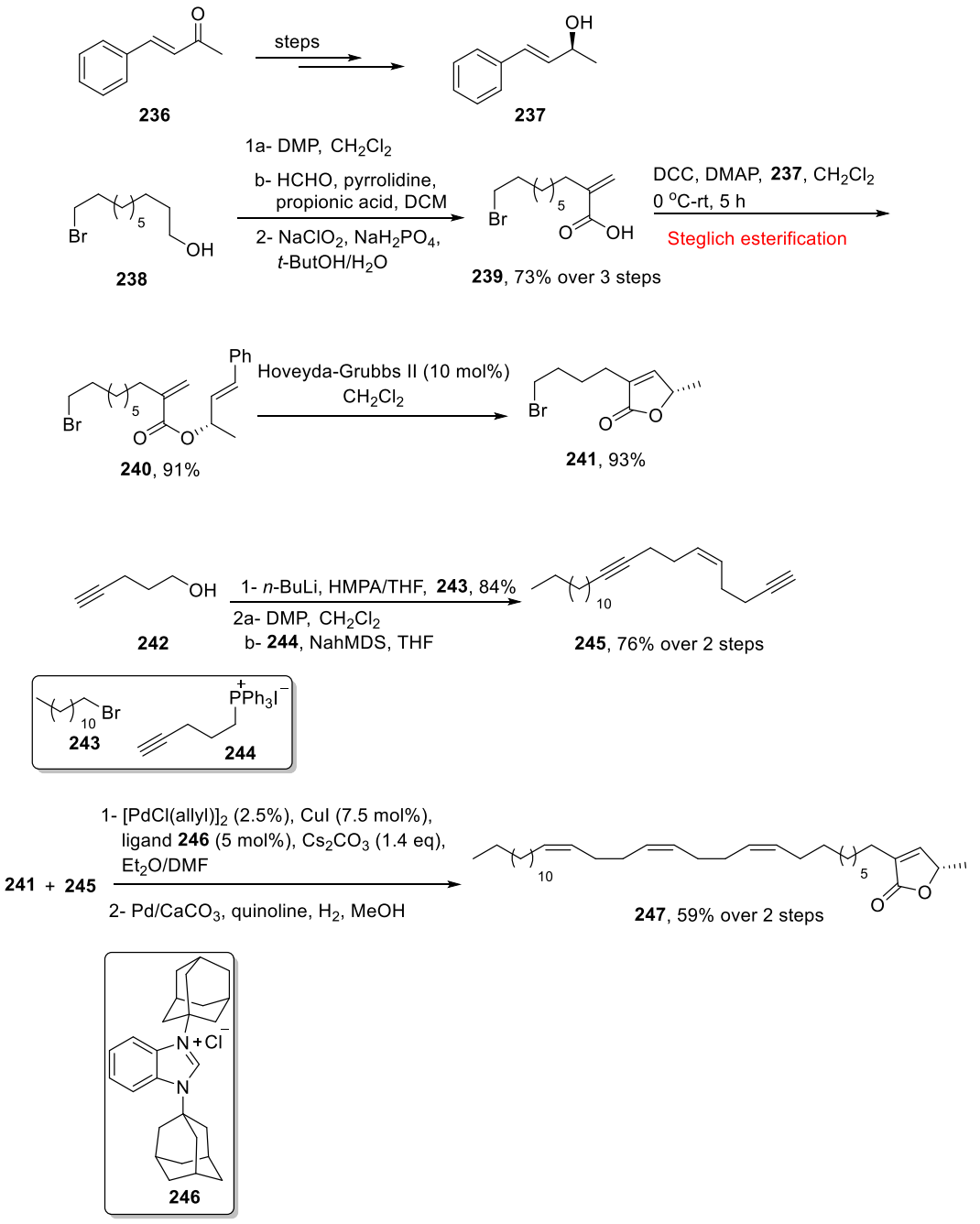
obtain mixture of **232**. In the next step, Steglich esterification was employed for esterification of **232** in the presence of crotonic acid, DCC and DMAP to obtain 52 % of ester **233** with 9 % of the unreacted substrate. Finally, 26 % of (+)-COTC **234** and 40 % of 7-chloro-7-deoxy-(+)-gabosine C **235** were obtained by Swern oxidation followed by deprotection with BCl_3 in DCM (Scheme 31).

2.11. Fatty acid-based natural product synthesis

Chatenaytrienin-2 is annonaceous acetogenins, obtained from *Annonaceae* family, which exhibits growth inhibitory and anti-cancerous effects [88]. In 2019, Kunkalkar et al. executed the total synthesis of chatenaytrienin-2**247** by implementation of Sonogashira cross coupling reaction and ring closing metathesis to achieve 36.5 % overall yield of final product [89]. The total synthesis started off from Styryl methyl ketone **236** which underwent a few steps to give alcohol **237**. The bromo decanol **238** was subjected to DMP-mediated oxidation along with Mannich reaction together with Pinnick oxidation to give 73 % of α-methelenic acid **239**. Next, the Steglich esterification was performed with alcohol **237** and α-methelenic acid **239** in the presence of DCC, DMAP and DCM to give 91 % of ester **240**. Further, Hoveyda-Grubbs-assisted ring closing metathesis was carried out to yield 93 % of the cyclic product **241**. The next step involved the synthesis of ene-diyne fragment **245** in 76 % yield by alkylation of compound **242** with the help of 1-bromododecane **243** followed by DMP-interceded oxidation and treatment with Wittig salt **244**. The final step involved coupling of compounds **241** and ene-diyne **245** in the presence of 5 mol% of ligand **246** and 2.5 mol% of $[PdCl(allyl)]_2$ catalyst, CuI and cesium carbonate followed by Lindlar reduction to furnish target compound chatenaytrienin-2**247** in 59 % yield over two steps (Scheme 32).

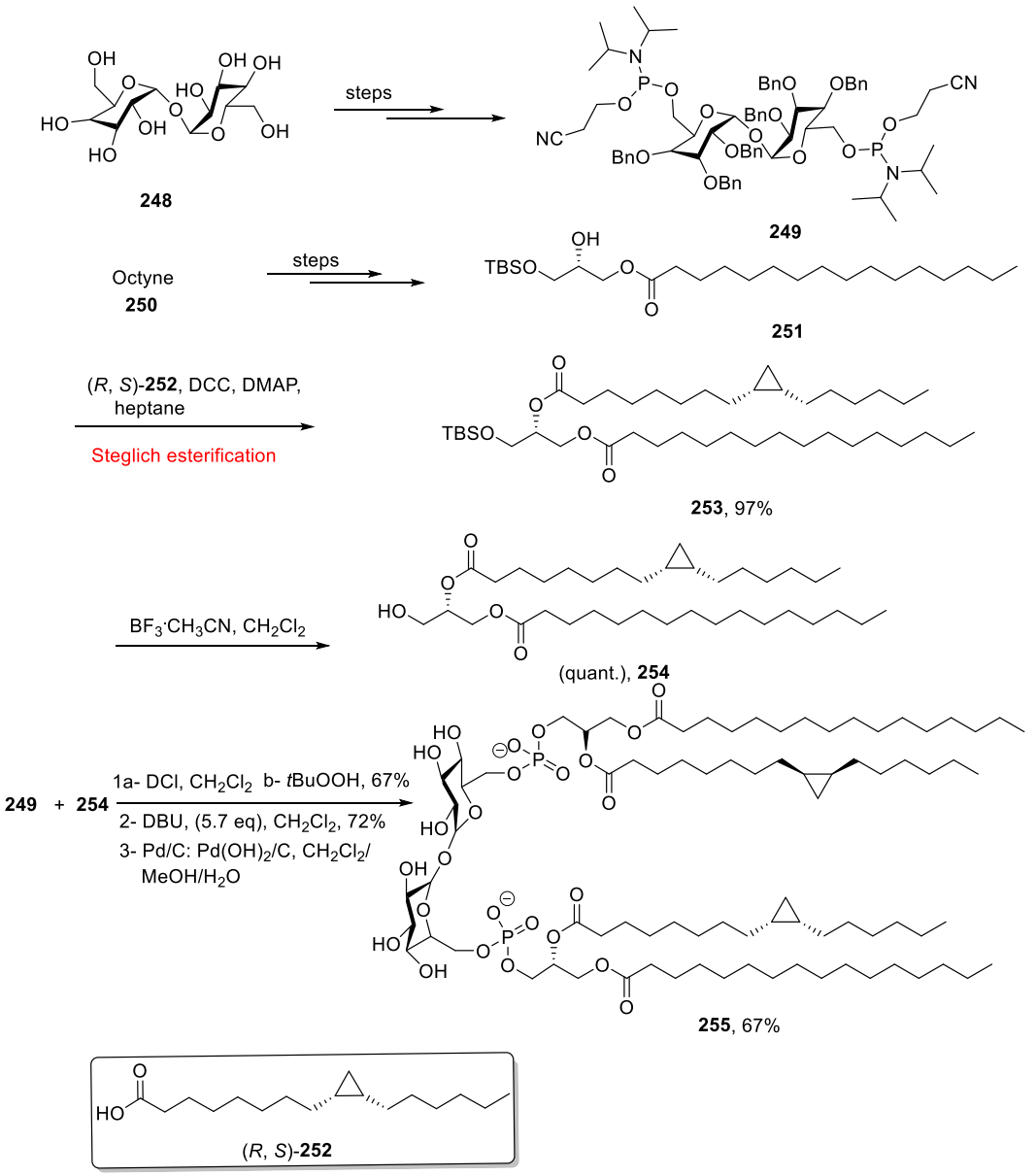
2.12. Glycolipid-based natural product synthesis

An immunity booster glycolipid, diphosphatidyltrehalose (diPT), is obtained from a fever-causing *Salmonella Typhi* gram-negative



Scheme 32. Synthesis of chatenaytrienin-2**247**.

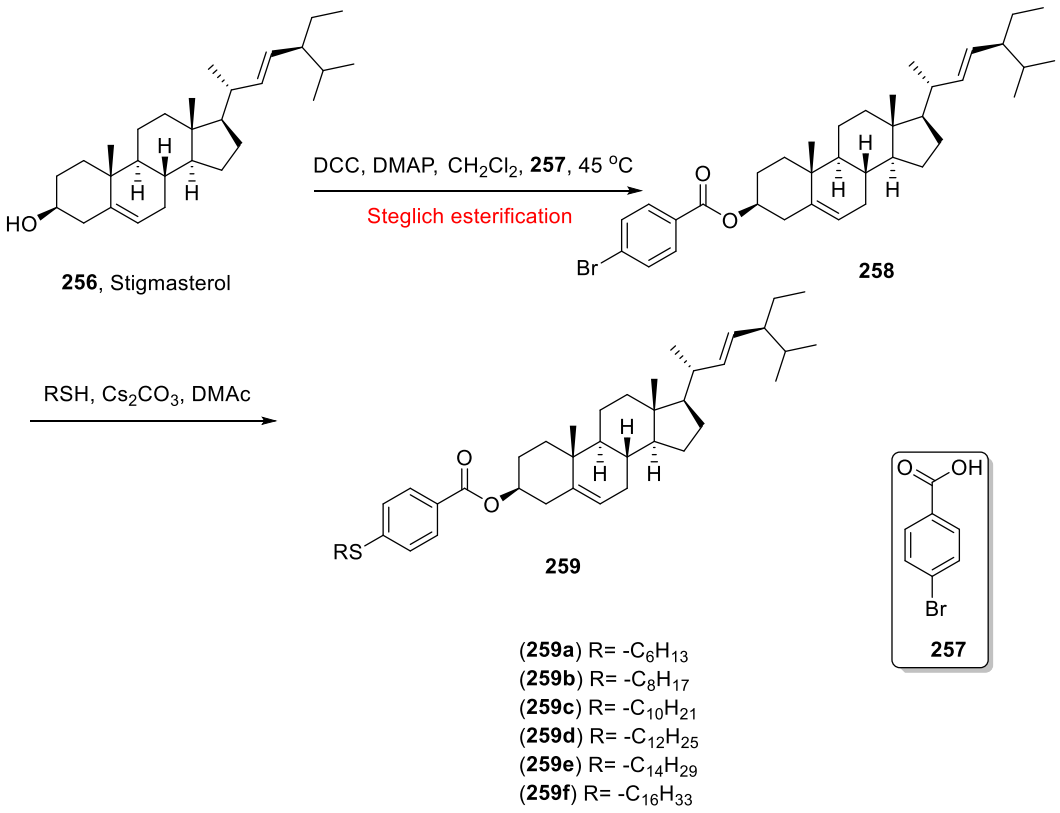
bacterium [90]. Mishra et al. proposed total synthesis of diphosphatidyltrehalose (diPT) in 2019 [91]. The synthesis started from α, α-trehalose **248** which was converted to bisphosphoramidite **249** over a few steps in good yield. Next, acyl glycerol **251** was synthesized over a few steps from octyne **250**. A Steglich protocol with (*R*, *S*)-**252** was employed in the presence of DCC, DMAP and DCM to give diglyceride **253** in 97 % yield. The intermediate **254** was obtained in quantitative yield by $BF_3{\cdot}CH_3CN$-mediated deprotection of diglyceride **253**. Subsequently, coupling of intermediate **254** and bisphosphoramidite **249** was performed in the presence of DCI in DCM followed by clean deprotection with DBU along with hydrogenolysis in the presence of Pd/C and $Pd(OH)_2/C$ (2:3) in a CH_2Cl_2/MeOH/water mixture furnished target compound diPT **255** in 67 % yield (Scheme 33).



Scheme 33. Synthesis of glycolipid **255**.

2.13. Sterol-based natural product synthesis

Steroids are a peremptory class of naturally occurring organic compounds possessing a wide range of biological properties. These steroids are also known as mesogens because of their occurrence as liquid crystals. The liquid crystals exhibit a number of applications in different fields [92]. Bhat et al. proposed the synthesis of target compounds by employing Steglich esterification as a key step in 2020 [93]. The first step involved coupling of Stigmasterol **256** with 4-bromo benzoic acid **257** via Steglich esterification in the presence of DCC, DMAP and dichloromethane to obtain sterol 4-bromo benzoates **258**. The mercapto alkanes were nucleophilically substituted with sterol 4-bromo benzoates **258** to realize 4-mercapto alkyl benzoate **259**. Just like the synthesis of Stigmasterol mesogens, Cholesterol and Ergosterol mesogens were also synthesized by employing same strategy. The synthesized mesogens were subjected for mesomorphic studies which revealed that stigmasterol and ergosterol derivatives (**259a-259f**) were smectogenic. Further the cholesterol derivatives exhibited cholesteric, smectic and blue phase with brief temperature range. The studies further revealed that replacement of sulfur with oxygen in cholesterol derivatives provides a low clearing temperature (Scheme 34).



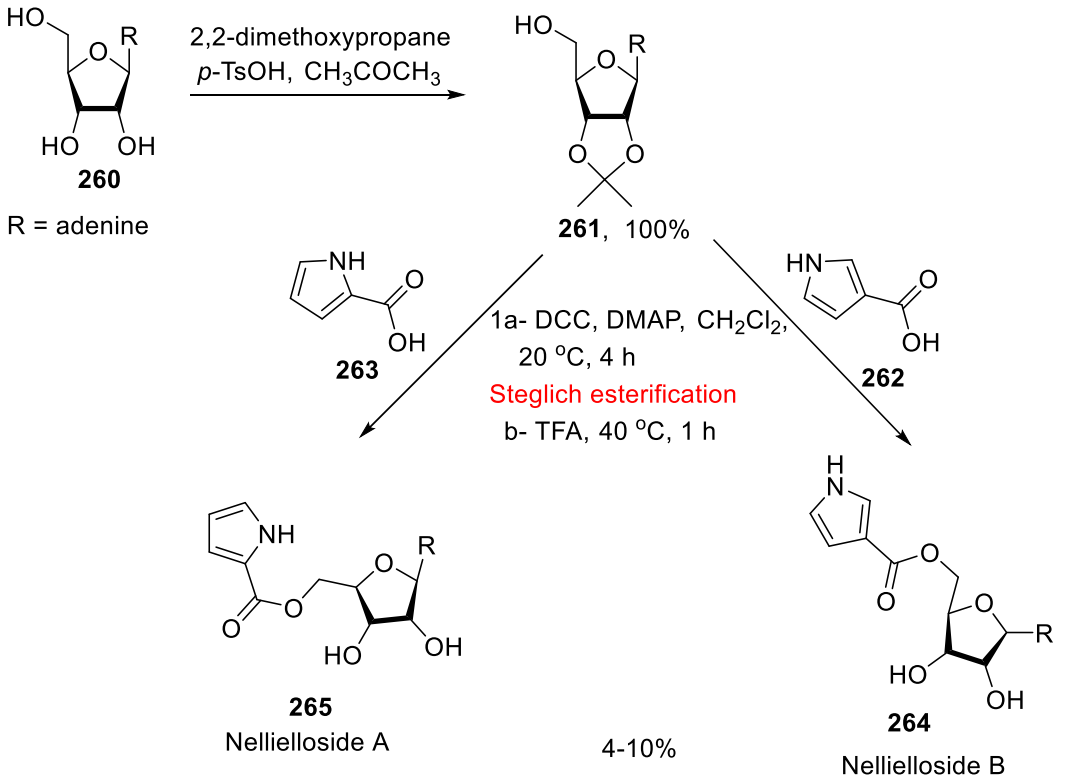
Scheme 34. Synthesis of Stigmasterol mesogens.

2.13.1. Miscellanous

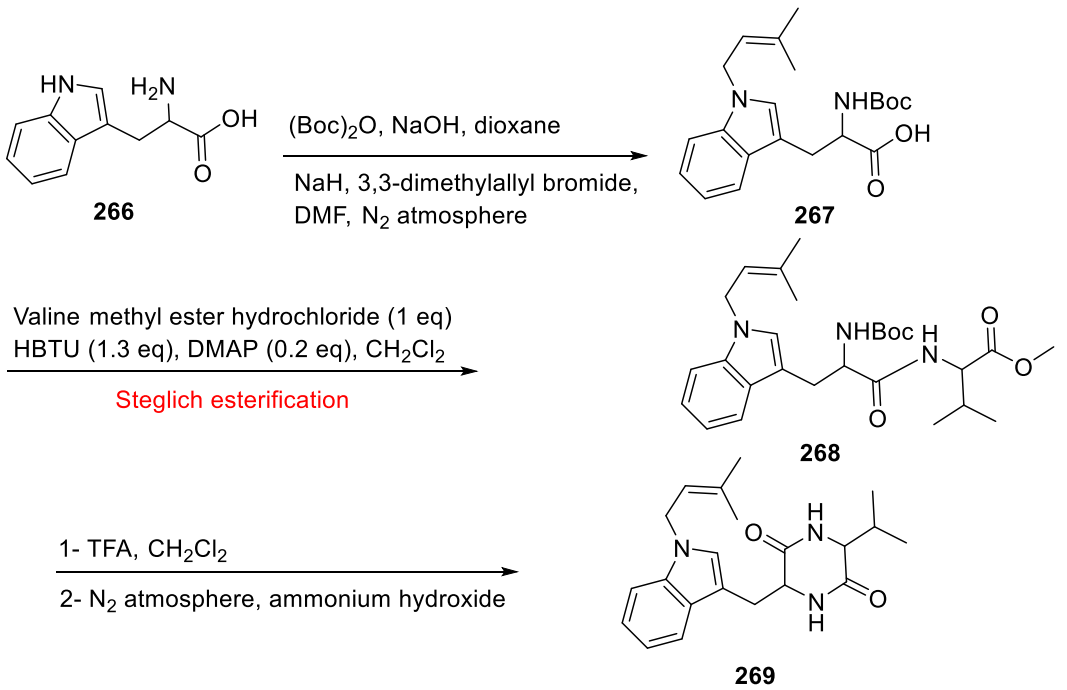
Nelliella nelliiformis is a Pacific bryozoan, known for the source of secondary metabolites nelliellosides A and B. These bioactive natural compounds belong to nucleoside family which have been recognized as potent antibacterial, antiviral and anticancerous drugs [94]. Bracegirdle et al. reported the synthesis of nelliellosides A and B by utilizing the Steglich esterification in 2019 [95]. The synthesis commenced from adenosine **260** which underwent OH group protection in the presence of 2,2-dimethoxypropane, *p*-TsOH and acetic acid to give compound **261**. The next step involved the Steglich esterification with pyrrole-2-carboxylic acid **263** and pyrrole-3-carboxylic acid **262** in the presence of DCC, DMAP and DCM accompanied by deprotection to give nelliellosides A **265** and nelliellosides B **264**. To synthesize the derivatives of hypoxanthine and guanine nucleoside, an exact similar strategy was employed (Scheme 35).

The (indole-*N*-isoprenyl)-tryptophan-valine diketopiperazine is a natural product possessing antifungal properties which was obtained from *Ascomycota* phylum. This natural product exhibits a variety of medicinal properties depending upon amino acid derivative attached to it i.e., tryptophan causes it to be herbicide and insecticide active in addition to antiviral, anticancerous and antioxidant [96]. In 2019, Bai et al. reported its first total synthesis along with the synthesis of stereoisomers [97]. The synthesis was initiated from tryptophan **266**, which underwent NH protection in the presence of $(Boc)_2$ to give intermediate **267**. The next step involved condensation reaction with valine methyl ester via the Steglich protocol to provide compound **268**. Next, Boc deprotection was being performed in the presence of TFA in dichloromethane followed by cyclization in the presence of ammonium hydroxide to furnish target compound **269**. Depending upon the configuration of starting compound, configuration of final compound is obtained. On a similar note, four stereoisomers of target compound were also obtained by employing an analogous pathway as employed for its total synthesis. The synthesized compounds exhibited a broad spectrum of antifungal properties with a rate of 15 % at 50 mg/L (Scheme 36).

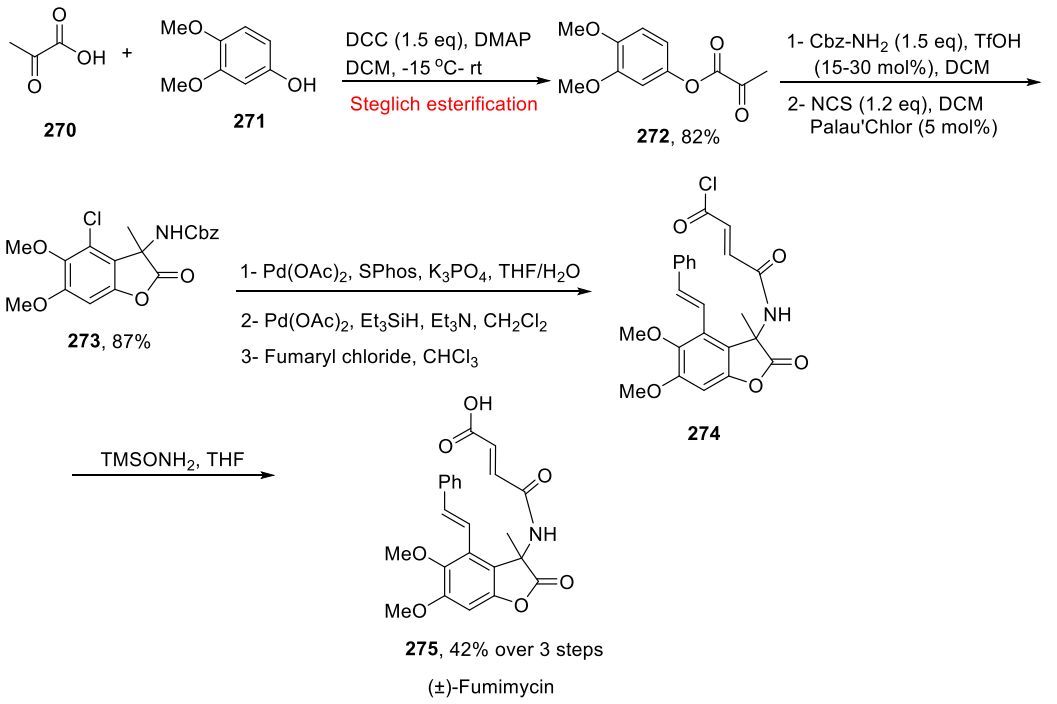
In 2019, Zaghouani et al. provided a total synthesis scheme to obtain 11.6 % overall yield of (±)-fumimycin in concise seven steps [98]. The key steps of this synthesis were Steglich esterification, intramolecular aza Friedel–Crafts reaction, regioselective chlorination and Suzuki-Miyaura cross coupling reaction. The synthesis commenced from Steglich esterification of 3,4-dimethoxy phenyl **271** and pyruvic acid **270** in the presence of 1.5 equivalents of DCC, DMAP and dichloromethane to give 82 % of pyruvate **272**. The next step involved intramolecular aza Friedel–Crafts reaction followed by regioselective chlorination in the presence of 5 mol% of Palau' Chlor catalyst to furnish 87 % of product **273**. The Suzuki-Miyaura cross coupling reaction was employed for next step along with Cbz deprotection and fumaryl coupling to forge **274**. The final step involved the hydrolysis to furnish target compound (±)-fumimycin **275** in 42 % yield. By altering the substitution of starting compounds, the analogues of (±)-fumimycin can also be obtained with the same



Scheme 35. Synthesis of derivatives of nellielloside A **265** and B **264**.



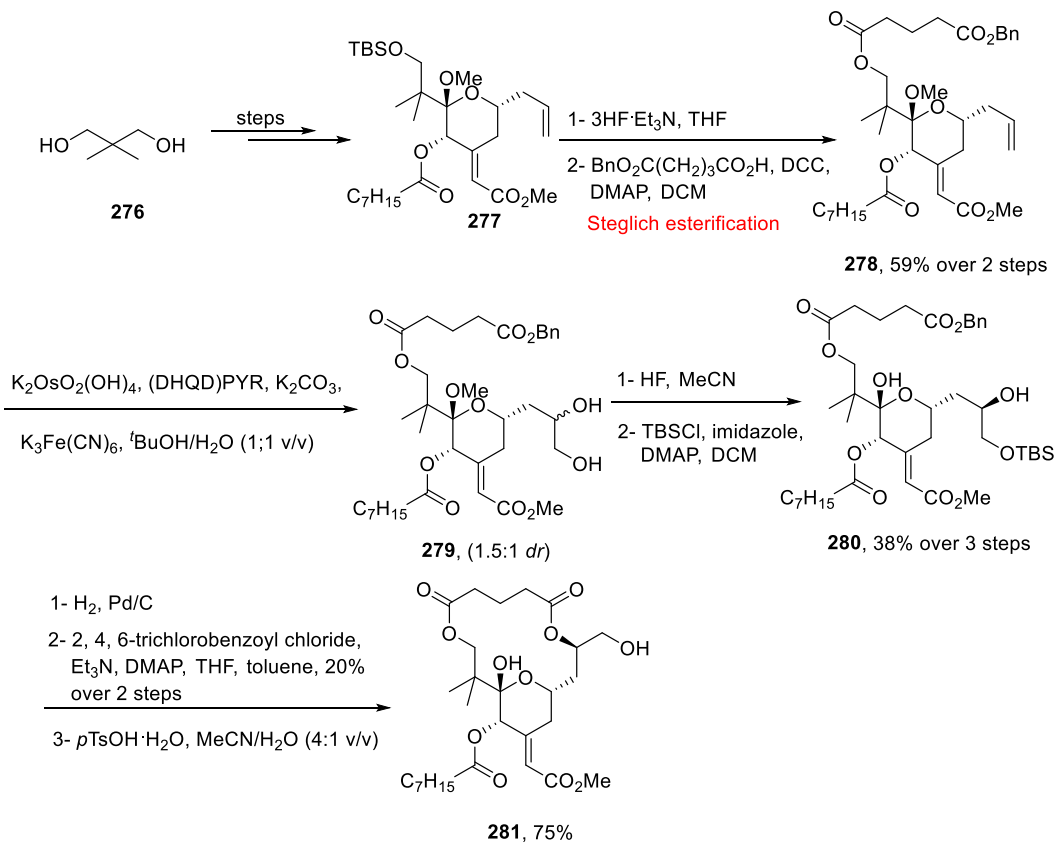
Scheme 36. Synthesis of diketopiprazine **269**.



270 **271** **272**, 82% **273**, 87% **274** **275**, 42% over 3 steps

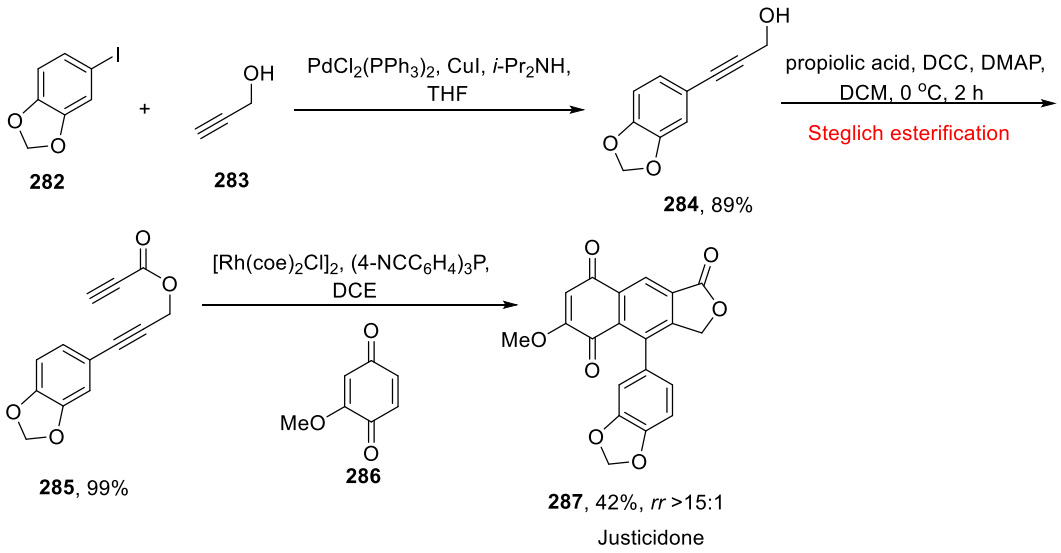
(±)-Fumimycin

Scheme 37. Synthesis of (±)-fumimycin **275**.



276 **277** **278**, 59% over 2 steps **279**, (1.5:1 *dr*) **280**, 38% over 3 steps **281**, 75%

Scheme 38. Synthesis of bryostatin analogue **281.**



Scheme 39. Synthesis of justicidone **287**.

scheme (Scheme 37).

Bryostatin is a natural product obtained from a marine source named, *Bugula Neritina*. It is known for its pharmacological and medicinal properties and has undergone for trials for a number of diseases like ischemic stroke, Niemann-Pick, multiple sclerosis, fragile X disorder and Charcot-Marie-Tooth syndrome. Due to its indispensable potential in medicinal field, researchers have approached this compound to achieve its total synthesis. But they have achieved only the synthesis of bryostatin analogues so far which behave similar to bryostatin and are more active biologically. The synthesis of bryostatin analogue, reported by Wender et al. in 2020, commenced from neopentyl glycol **276** which was converted to compound **277** over a few steps [99]. Next, the compound **277** underwent deprotection followed by Steglich esterification with monobenzyl glutarate in the presence of DCC and DMAP to give ester **278**. The next step included Sharpless asymmetric dihydroxylation to introduce a diastereoselective mixture of diols **279** with a 1.5:1 diastereomeric ratio. Further, mixtures of diastereomers were separated by treating the mixture with aq. HF in acetonitrile followed by hydroxyl group protection with TBSCl in the presence of DMAP and DCM to obtain **280** in 38 % yield over three steps. Further, the compound **280** underwent hydrogenolysis followed by Yamguchi lactonization with 2,4,6-trichlorobenzoyl chloride in the presence of triethylamine and DMAP along with deprotection of silyl group to furnish bryostatin analogue **281** in 75 % yield (Scheme 38).

In 2020, Wood et al. aimed at [2 + 2+2] cycloaddition of benzoquinones and diynes catalyzed by rhodium and exemplified it with a short total synthesis of justicidone [100]. The synthesis was initialized with a Sonogashira coupling of aryl iodide **282** and propargyl alcohol **283** to give 89 % of compound **284**. Further, the Steglich esterification of compound **284** with propiolic acid in the presence of DCC, DMAP and dichloromethane furnished ester **285** in 99 % yield. The final step involved Rh-catalyzed optimized protocol to provide target compound **287** in 42 % yield (Scheme 39).

3. Conclusion

The synthesis of natural products which include alkaloids, peptides, lactams, terpenoids, chromanones, macrolides, glycolipids, pyrones, fatty acids and carbasugars has been a tedious task since the advancement of synthetic chemistry. A number of key steps and procedures play vital part in achieving this task. Steglich reaction is one of those procedures. To conclude, this review article has provided an efficacious role of the Steglich reaction towards the total synthesis of simple to complex natural products. The key points of this reaction are mild reaction conditions, best yields, facile procedure for esterification of complex compounds with difficult separation procedures, requiring further research to be done in that area. The synthesis of representative classes of natural products with necessary conditions has been mentioned in this article. This review will prove to be helpful for the selection of Steglich esterification conditions to achieve the total synthesis of natural products and synthetically important compounds.

Data availability statement

Data included in the article and referenced in article. No data associated with this study has been deposited into a publicly available repository.

CRediT authorship contribution statement

Saba Munawar: Writing - original draft, Investigation. **Ameer Fawad Zahoor:** Supervision, Project administration,

Conceptualization. **Syed Makhdoom Hussain:** Methodology, Investigation. **Sajjad Ahmad:** Resources, Methodology, Investigation. **Asim Mansha:** Resources, Methodology, Investigation. **Bushra Parveen:** Resources, Methodology, Investigation. **Kulsoom Ghulam Ali:** Resources, Methodology, Investigation. **Ahmad Irfan:** Resources, Investigation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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List of Abbreviations used

DMAP	Dimethyl aminopyridine
DCC	N, N′-dicyclohexylcarbodiimide
DIC	N, N′-diisopropylcarbodimide
EDC	N-ethyl-N'- (3-dimethylaminopropyl) carbodiimide
LDA	Lithium diisopropylamide
MIC	Minimum inhibitory concentration
HATU	Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
DIPEA	N, N-Diisopropylethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
DCM	Dichloromethane
LiAlH4	Lithium Aluminium Hydride
DCI	Dicyanoimidazole
DBU	Diazabicyclo Undec Ene
p-TsOH	p-Toluenesulfonic acid
Boc	tert-butyloxycarbonyl
NCS	N-Chlorosuccinimide
TBSCl	tert-Butyldimethysilyl chloride
DiPT	Diphosphatidyltrehalose
MNBA	2-Methyl-6-nitrobenzoic anhydride
CDI	1,1′-Carbonyldiimidazole
TBAF	Tetra-n-butylammonium fluoride
TPAP	Tetra-n-propyl Ammonium Perruthenate
NMO	N-Methylmorpholine-N-Oxide
TESOTf	Triethylsilyl trifluoromethanesulfonate
KHMDS	Potassium bis(trimethylsilyl)amide

References

[1] Y.J. Zhou, N.A. Buijs, Z. Zhu, J. Qin, V. Siewers, J. Nielsen, Production of fatty acid-derived oleochemicals and biofuels by synthetic yeast cell factories, Nat. Commun. 7 (2016) 1–9, https://doi.org/10.1038/ncomms11709.
[2] G. Groeneveld, S. Kuijer, M.D. Puit, Preparation of cyanoacrylate derivatives and comparison of dual action cyanoacrylate formulations, Sci. Justice 54 (2014) 42–48, https://doi.org/10.1016/j.scijus.2013.09.002.
[3] Y.J. Shin, J. Shin, H. Jang, H. Son, Y. Kwon, Decursinol chloroacrylates useful as fungicides, Appl. Bio. Chem. 65 (2022) 53–61, https://doi.org/10.1186/s13765-022-00720-y.
[4] A.G.A. Sá, A. C. de Meneses, P. H. H. de Araújo, D. de Oliveira, A review on enzymatic synthesis of aromatic esters used as flavor ingredients for food, cosmetics and pharmaceuticals industries, Trends Food Sci. Technol. 69 (2017) 95–105, https://doi.org/10.1016/j.tifs.2017.09.004.
[5] M.S. Dekić, E.S. Selimović, New natural products from Asphodelus albus MILL, Essential Oil. Chem. Biodiversity 18 (2021) 1–8, https://doi.org/10.1002/cbdv.202100103.
[6] S. Majhi, Applications of Yamaguchi method to esterification and macrolactonization in total synthesis of bioactive natural products, ChemistrySelect 6 (2021) 4178–4206, https://doi.org/10.1002/slct.202100206.
[7] S. Munawar, A.F. Zahoor, S. Ali, S. Javed, M. Irfan, A. Irfan, K. Kotwica-Mojzych, M. Mojzych, Mitsunobu reaction: a powerful tool for the synthesis of natural products: a review, Molecules 27 (2022) 1–67, https://doi.org/10.3390/molecules27206953.
[8] M.J.L.J. Fürst, A. Gran-Scheuch, F.S. Aalbers, M.W. Fraaije, Baeyer−Villiger monooxygenases: tunable oxidative biocatalysts, ACS Catal. 9 (2019) 11207–11241, https://doi.org/10.1021/acscatal.9b03396.
[9] J.J. Li, Corey–nicolaou macrolactonization, in: Name Reactions, Springer, Cham, 2014, pp. 178–179, https://doi.org/10.1007/978-3-319-03979-4_73.

[10] Z. Khan, F. Javed, Z. Shamair, A. Hafeez, T. Fazal, A. Aslam, W.B. Zimmerman, F. Rehman, Current developments in esterification reaction: a review on process and parameters, J. Ind. Eng. Chem. 103 (2021) 80–101, https://doi.org/10.1016/j.jiec.2021.07.018.

[11] B. Neises, W. Steglich, Simple method for the esterification of carboxylic acids, Angew. Chem., Int. Ed. Engl. 17 (1978) 522–524, https://doi.org/10.1002/anie.197805221.

[12] M. Tsakos, E.S. Schaffert, L.L. Clement, N.L. Villadsen, T.B. Poulsen, Ester coupling reactions – an enduring challenge in the chemical synthesis of bioactive natural products, Nat. Prod. Rep. 32 (2015) 605–632, https://doi.org/10.1039/c4np00106k.

[13] S. Saha, S.S. Auddy, S. Chatterjee, P. Sen, R.K. Goswami, Late-stage functionalization: total synthesis of beauveamide A and its congeners and their anticancer activities, Org. Lett. 24 (2022) 7113–7117, https://doi.org/10.1021/acs.orglett.2c02699.

[14] S. Scheeff, S. Rivière, J. Ruiz, S. Dedenbach, D. Menche, Modular total synthesis of iso-archazolids and archazologs, J. Org. Chem. 86 (2021) 10190–10223, https://doi.org/10.1021/acs.joc.1c00946.

[15] M. Liniger, C.M. Neuhaus, K.H. Altmann, Ring-closing metathesis approaches towards the total synthesis of rhizoxins, Molecules 25 (2020) 4527, https://doi.org/10.3390/molecules25194527.

[16] E.V. Nurieva, N.A. Zefirov, N.S. Temnyakova, S.A. Kuznetsov, O.N. Zefirova, C(7)-Derivatives of colchicine with guanosine and biphenyl moieties: molecular modeling, synthesis, and tubulin clustering effect in cancer cells, Russ. Chem. Bull. 69 (2020) 2222—2227, https://doi.org/10.1007/s11172-020-3025-y.

[17] A. Kiefer, C.D. Bader, J. Held, A. Esser, J. Rybniker, M. Empting, R. Müller, U. Kazmier, Synthesis of new cyclomarin derivatives and their biological evaluation towards Mycobacterium tuberculosis and Plasmodium falciparum, Chem. Eur J. 25 (2019) 8894–8902, https://doi.org/10.1002/chem.201901640.

[18] A.C. Karagöz, C. Reiter, E.J. Seo, L. Gruber, F. Hahn, M. Leidenberger, V. Klein, F. Hampel, O. Friedrich, M. Marschall, B. Kappes, T. Efferth, S.B. Tsogoeva, Access to new highly potent antileukemia, antiviral and antimalarial agents via hybridization of natural products (homo)egonol, thymoquinone and artemisinin, Bioorg. Med. Chem. 26 (2018) 3610–3618, https://doi.org/10.1016/j.bmc.2018.05.041.

[19] P. Sharma, N. Sharma, G. Kashyap, S. Bhagat, First total synthesis of the marine-derived antiinflammatory natural product (–)-Herdmanine D through a Steglich esterification, Synlett 33 (2022) 62–65, https://doi.org/10.1055/a-1672-3000.

[20] T. Linder, E. Papaplioura, D. Ogurlu, S. Geyrhofer, S. Hummelbrunner, D. Schachner, A.G. Atanasov, M.D. Mihovilovic, V.M. Dirsch, M. Schnürch, Investigation of Leoligin derivatives as NF-κB inhibitory agents, Biomedicines 10 (2022) 62–76, https://doi.org/10.3390/biomedicines10010062.

[21] Z. Rzepka, E. Bębenek, E. Chrobak, D. Wrześniok, Synthesis and anticancer activity of indole-functionalized derivatives of Betulin, Pharmaceutics 14 (2022) 2372–2388, https://doi.org/10.3390/pharmaceutics14112372.

[22] A.H. Tang, R.J. Payne, Second generation synthesis of the antiinfective natural product gallinamide A, Tetrahedron (2023), https://doi.org/10.1016/j.tet.2023.133445.

[23] A. Rahmadani, M.A. Masruhim, L. Rijai, A.T. Hidayat, U. Supratman, R. Maharani, Total synthesis of cyclohexadepsipeptides exumolides A and B, Tetrahedron 83 (2021) 1–5, https://doi.org/10.1016/j.tet.2021.131987.

[24] D.A. Brumley, S.P. Gunasekera, Q.Y. Chen, V.J. Paul, H. Luesch, Discovery, total synthesis, and sar of anaenamides A and B: anticancer cyanobacterial depsipeptides with a chlorinated pharmacophore, Org. Lett. 22 (2020) 4235–4239, https://doi.org/10.1021/acs.orglett.0c01281.

[25] Y. Nakayama, T. Takita, H. Ozawa, H. Umezawa, K. Tahara, Studies on ilamycin, J. Antibiot. 15 (1962) 49–50, https://doi.org/10.11554/antibioticsa.15.1_49.

[26] T. Takita, K. Ohi, K. Maeda, Y. Okami, H. Umezawa, New antibiotics, ilamycins, J. Antibiot. 15 (1962) 46–48, https://doi.org/10.11554/antibioticsa.15.1_46.

[27] J. Greve, A. Mogk, U. Kazmaier, Total synthesis and biological evaluation of modified illamycin derivatives, Mar. Drugs 20 (2022) 632, https://doi.org/10.3390/md20100632.

[28] D. Brumley, K.A. Spencer, S.P. Gunasekera, T. Sauvage, J. Biggs, V.J. Paul, H. Luesch, Isolation and characterization of anaephenes A−C, alkylphenols from a filamentous cyanobacterium (hormoscilla sp., oscillatoriales), J. Nat. Prod. 81 (12) (2018) 2716−−2721, https://doi.org/10.1021/acs.jnatprod.8b00650.

[29] M.L. Han, J.X. Zhao, H.C. Liu, G. Ni, J. Ding, S.P. Yang, J.M. Yue, Limonoids and Triterpenoids from *Dysoxylum mollissimum* var. *glaberrimum*, J. Nat. Prod. 78 (2015) 754–761, https://doi.org/10.1021/np500967k.

[30] C.P. Liu, C.Y. Xie, J.X. Zhao, K.L. Ji, X.X. Lei, H. Sun, L.G. Lou, J.M. Yue, A. Dysoxylactam, A macrocyclolipopeptide reverses P-Glycoprotein-Mediated multidrug resistance in cancer cells, J. Am. Chem. Soc. 141 (2019) 6812–6816, https://doi.org/10.1021/jacs.9b02259.

[31] R.B. Reddy, B. Yu, Total synthesis of macrocyclic dysoxylactam, A. Chem. Asian J. 15 (2020) 2467–2469, https://doi.org/10.1002/asia.202000482.

[32] R.B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, H. Vorbruggen, Total synthesis of cephalosporin C, J. Am. Chem. Soc. 88 (1996) 852–853, https://doi.org/10.1021/ja00956a051.

[33] Y.X. Li, Z. Zhong, W.P. Zhang, P.Y. Qian, Discovery of cationic nonribosomal peptides as Gram-negative antibiotics through global genome mining, Nat. Commun. 9 (2018) 3273, https://doi.org/10.1038/s41467-018-05781-6.

[34] K.A. Ayed, R. Ballantine, Z. Zhong, Y.X. Li, S.A. Cochraneb, N.I. Martina, Total Synthesis of the brevicidine and laterocidine family of lipopeptide antibiotics, Chem. Sci. 13 (2021) 3563–3570, https://doi.org/10.26434/chemrxiv.13660949.v1.

[35] K.A. Ayed, D.Z. Losada, N.V. Machushynets, B. Terlouw, S.S. Elsayed, J. Schill, V. Trebosc, M. Pieren, M.H. Medema, G.P.v. Wezel, N.I. Martin, Total synthesis and structure assignment of the relacidine lipopeptide antibiotics and preparation of analogues with enhanced stability, ACS Infect. Dis. 9 (4) (2023) 739–748, https://doi.org/10.1021/acsinfecdis.3c00043.

[36] N. Hauser, M.A. Imhof, S.S. Eichenberger, T. Kündig, E.M. Carreira, Total synthesis of shearinines D and G: a convergent approach to indole diterpenoids, Angew. Chem., Int. Ed. 134 (2022), e202112838, https://doi.org/10.1002/anie.202112838.

[37] M. Ochi, H. Kotsuki, K. Muraoka, T. Tokoroyama, The structure of yahazunol, a new sesquiterpene-substituted hydroquinone from the Brown seaweed Dictyopteris undulata okamura, Bull. Chem. Soc. Jpn. 52 (1979) 629–630, https://doi.org/10.1246/bcsj.52.629.

[38] E. Perez-Garcia, E. Zubıa, M.J. Ortega, J.L. Carballo, Merosesquiterpenes from two sponges of the genus *Dysidea*, J. Nat. Prod. 68 (2005) 653–658, https://doi.org/10.1021/np040237z.

[39] P. Djura, D.B. Stierle, B. Sullivan, D.J. Faulkner, Some metabolites of the marine sponges Smenospongia aurea and Smenospongia (.ident.Polyfibrospongia) echina, J. Org. Chem. 45 (1980) 1435–1441, https://doi.org/10.1021/jo01296a019.

[40] K. Kurata, K. Taniguchi, M. Suzuki, Cyclozonarone, a sesquiterpene-substituted benzoquinone derivative from the brown alga *Dictyopteris undulata*, Phytochemistry (Elsevier) 41 (1996) 749–752, https://doi.org/10.1016/0031-9422(95)00651-6.

[41] S. Zhang, X. Wang, J. Hao, D. Li, R. Csuk, S. Li, Expediently scalable synthesis and antifungal exploration of (+)-Yahazunol and related meroterpenoids, J. Nat. Prod. 81 (2018) 2010–2017, https://doi.org/10.1021/acs.jnatprod.8b00310.

[42] A.S.R. Anjaneyulu, M.J.R.V. Venugopal, P. Sarada, J. Clardy, E. Havellockate Lobkovsky, A novel seco and spiro lactone diterpenoid from the Indian ocean soft coral Sinularia granosa, Tetrahedron Lett. 39 (1998) 139–142, https://doi.org/10.1016/S0040-4039(97)10470-1.

[43] N.J. Hafeman, M. Chan, T.J. Fulton, E.J. Alexy, S.A. Loskot, S.C. Virgil, B.M. Stoltz, Asymmetric total synthesis of havellockate, J. Am. Chem. Soc. 144 (2022) 20232–20236, https://doi.org/10.1021/jacs.2c09583.

[44] Y. Li, G. Pattenden, Novel macrocyclic and polycyclic norcembranoid diterpenes from Sinularia species of soft coral: structural relationships and biosynthetic speculations, Nat. Prod. Rep. 28 (2011) 429–440, https://doi.org/10.1039/C0NP00029A.

[45] N.J. Hafeman, S.A. Loskot, C.E. Reimann, B.P. Pritchett, S.C. Virgil, B.M. Stoltz, The total synthesis of (–)-Scabrolide A, J. Am. Chem. Soc. 142 (19) (2020) 8585–8590, https://doi.org/10.1021/jacs.0c02513.

[46] N.J. Hafeman, S.A. Loskot, C.E. Reimann, B.P. Pritchett, S.C. Virgil, B.M. Stoltz, Total synthesis of (−)-scabrolide A and (−)-yonarolide, Chem. Sci. 14 (2023) 4745–4758, https://doi.org/10.1039/d3sc00651d.

[47] T. Siemon, S. Steinhauer, Synthesis of (+)-Darwinolide, Angew. Chem. Int. Ed. 114 (2019), https://doi.org/10.1002/anie.201813142.

[48] M. Sarwar, Y.-X. Xia, Z.-M. Liang, S.W. Tsang, H.-J. Zhang, Mechanistic pathways and molecular targets of plant-derived anticancer ent-kaurane diterpenes, Biomolecules 10 (2020) 144, https://doi.org/10.3390/biom10010144.

[49] C. Herrera-Acevedo, A. Flores-Gaspar, L. Scotti, F.J.B. Mendonça-Junior, M.T. Scotti, E. Coy-Barrera, Identification of kaurane-type diterpenes as inhibitors of leishmania pteridine reductase I, Molecules 26 (2021) 3076–3099, https://doi.org/10.3390/molecules26113076.

[50] Y. Liu, Z. Zhao, C. Hu, C. Zhao, J. Liu, Y. Du, Chiron approach for the total synthesis of brevipolide M, Synlett 33 (2022) 478–482, https://doi.org/10.1055/a-1730-9857.

[51] R. Uchida, R. Imasato, Y. Yamaguchi, R. Masuma, K. Shiomi, H. Tomoda, S. Omura, New insecticidal antibiotics, hydroxyfungerins A and B, produced by *metarhizium* sp. FKI-1079, J. Antibiot. 58 (2005) 804, https://doi.org/10.1038/ja.2005.107.

[52] R.R. Merchant, K.M. Oberg, Y. Lin, A.J.E. Novak, J. Felding, P.S. Baran, Divergent synthesis of pyrone diterpenes via radical cross coupling, J. Am. Chem. Soc. 140 (2018) 7462–7465, https://doi.org/10.1021/jacs.8b04891.

[53] H.D. Sun, S.X. Huang, Q.B. Han, Diterpenoids from Isodon species and their biological activities, Nat. Prod. Rep. 23 (2006) 673–698, https://doi.org/10.1039/B604174D.

[54] J. Zhang, Z. Li, J. Zhuo, Y. Cui, T. Han, C. Li, A tandem decarboxylative cyclization/alkenylation strategy for the total syntheses of (+)-Longirabdiol, (−)-Longirabdolactone, and (−)- effusin, J. Am. Chem. Soc. 141 (2019) 8372–8380, https://doi.org/10.1021/jacs.9b03978.

[55] A.A. Stierle, D.B. Stierle, D. Decato, N.D. Priestley, J.B. Alverson, J. Hoody, K. McGrath, D. Klepacki, The berkeleylactones, antibiotic macrolides from fungal coculture, J. Nat. Prod. 80 (2017) 1150–1160, https://doi.org/10.1021/acs.jnatprod.7b00133.

[56] B. Ferko, M. Zeman, M. Formica, S. Veselý, J. Doháošová, J. Moncol, P. Olejníková, D. Berkes, P. Jakubec, D.J. Dixon, O. Caletkova, Total synthesis of berkeleylactone A, J. Org. Chem. (2019) 1–9, https://doi.org/10.1021/acs.joc.9b00850.

[57] M.G. Schriefer, R. Schobert, Divergent synthesis of six recent berkeleylactones, J. Nat. Prod. 86 (2023) 423–428, https://doi.org/10.1021/acs.jnatprod.3c00053.

[58] S. Samwel, S.J.M. Mdachi, M.H.H. Nkunya, B.N. Irungu, M.J. Moshi, B. Moulton, B.S. Luisi, Nat. Prod. Commun. A novel antiplasmodial 3′,5′-diformylchalcone and other constituents of Friesodielsia obovata 2 (2007) 737–741, https://doi.org/10.1177/1934578X0700200706.

[59] G. Benedeković, M. Popsavin, I. Kovačević, V. Kojić, M. Rodić, V. Popsavin, Synthesis, antiproliferative activity and SAR analysis of (−)-cleistenolide and analogues, Eur. J. Med. Chem. 202 (2020), 112597, https://doi.org/10.1016/j.ejmech.2020.112597.

[60] G. Benedeković, M. Popsavin, I. Kovačević, V. Kojić, J. Kesić, S. Farkas, V. Popsavin, Design, synthesis and cytotoxic activity of new 6-O-aroyl (-)-cleistenolide derivatives, Tetrahedron 96 (2021), 132385, https://doi.org/10.1016/j.tet.2021.132385.

[61] J. Ma, B. Cao, X. Chen, M. Xu, X. Bi, P. Guan, Y. Jiang, J. Xu, L. Han, X. Huang, A. Violacin, A new chromanone produced by Streptomyces violaceoruber and its antiinflammatory activity, Bioorg. Med. Chem. Lett. 5 (2018) 947–951, https://doi.org/10.1016/j.bmcl.2018.01.051.

[62] Q. Liu, Y. Mu, Q. An, J. Xun, J. Ma, W. Wu, M. Xu, J. Xu, L. Han, X. Huang, Total synthesis and antiinflammatory evaluation of violacin A and its analogues, Bioorg. Chem. (2019), https://doi.org/10.1016/j.bioorg.2019.103420.

[63] R.B. Woodward, F.E. Bader, H. Bickel, A.J. Frey, R.W. Kierstead, The total synthesis of (±)-Reserpine, J. Am. Chem. Soc. 78 (1956) 2023–2025, https://doi.org/10.1016/0040-4020(58)88022-9.

[64] P. Krishnan, F.K. Lee, V.A. Yap, Y.Y. Low, T.S. Kam, K.T. Yong, K.N. Ting, K.H. Lim, A.-G. Schwarzinicines, 1,4-diarylbutanoid-phenethylamine conjugates from the leaves of Ficus schwarzii, J. Nat. Prod. 83 (1) (2020) 152–158, https://doi.org/10.1021/acs.jnatprod.9b01160.

[65] F.K. Lee, P. Krishnan, A. Muhamad, Y.Y. Low, T.S. Kam, K.N. Ting, K.H. Lim, Concise synthesis of the vasorelaxant alkaloids schwarzinicines A and B, Nat. Prod. Res. (2021), https://doi.org/10.1080/14786419.2021.1903005.

[66] B. Steffan, Lepadin A, a decahydroquinoline alkaloid from the tunicate clavelina-lepadiformis, Tetrahedron 47 (1991) 8729–8732, https://doi.org/10.1016/S0040-4020(01)96194-0.

[67] J. Kubanek, D.E. Williams, E.D. Desilva, T. Allen, R.J. Andersen, Cytotoxic alkaloids from the flatworm prostheceraeus-villatus and its tunicate prey clavelina-lepadiformis, Tetrahedron Lett. 36 (1995) 6189–6192, https://doi.org/10.1016/0040-4039(95)01246-E.

[68] H. Tsuneki, Y.R. You, N. Toyooka, T. Sasaoka, H. Nemoto, J.A. Dani, I. Kimura, Marine alkaloids (−)-Pictamine and (−)-Lepadin B block neuronal nicotinic acetylcholine receptors, Biol. Pharm. Bull. 28 (2005) 611–614, https://doi.org/10.1248/bpb.28.611.

[69] F. Ma, C. He, E. Wang, R. Tong, Collective asymmetric total syntheses of marine decahydroquinoline alkaloid lepadins A−E, H, and ent-I, Org. Lett. 23 (2021) 6583–6588, https://doi.org/10.1021/acs.orglett.1c02435.

[70] N.R. Gade, J. Iqbal, Natural product inspired topology directed synthesis of hybrid macrocyclic compounds: a simple approach to natural product analogues, ChemistrySelect 3 (2018) 6262–6266, https://doi.org/10.1002/slct.201801117.

[71] T.M. Brütsch, E. Cotter, D.L. Agell, M.R. Horcajo, C. Davies, B. Pfeiffer, S. Pagani, S. Berardozzi, J.F. Díaz, J.H. Miller, K.H. Altmann, Synthesis and structure-activity relationship studies of C(13)-desmethylene-(−)-zampanolide analogs, Chem (2023) 1–24, https://doi.org/10.26434/chemrxiv-2023-mfxxz-v2.

[72] .

[73] F.Z. Zhang, X.M. Li, S.Q. Yang, L.H. Meng, B.G. Wang, A.-D. Thiocladospolides, 12-Membered macrolides from the mangrove-derived endophytic fungus cladosporium cladosporioides MA-299 and structure revision of pandangolide 3, J. Nat. Prod. 82 (2019) 1535, https://doi.org/10.1021/acs.jnatprod.8b01091.

[74] P. Swami, M. Mali, B. Dhulshette, S. Ghosh, Total synthesis of thiocladospolide A and its C2-epimer, Synth. Met. 54 (2022) 683–688, https://doi.org/10.1055/a-1652-3714.

[75] A. Machara, J. Křivánek, K. Dolejšová, J. Havlíčková, L. Bednárová, R. Hanus, P. Majer, P. Kyjaková, Identification and enantiodivergent synthesis of (5Z,9S)-Tetradec-5- en-9-olide, a queen-specific volatile of the termite Silvestritermes minutus, J. Nat. Prod. 81 (2018) 2266–2274, https://doi.org/10.1021/acs.jnatprod.8b00632.

[76] R. Fougeyrollas, J. Křivánek, V. Roy, K. Dolejšová, S. Frechault, Y. Roisin, R. Hanus, D. Sillam-Dussès, Asexual queen succession in termites, Mol. Ecol. 26 (2017) 3295–3308, https://doi.org/10.1111/mec.14095.

[77] V. Rukachaisirikul, S. Pramjit, C. Pakawatchai, M. Isaka, S. Supothina, 10-Membered macrolides from the insect pathogenic fungus Cordyceps militaris BCC 2816, J. Nat. Prod. 67 (2004) 1953–1955, https://doi.org/10.1021/np0401415.

[78] P.R. Sudina, D.R. Motati, A. Seema, Stereocontrolled total synthesis of nonenolide, J. Nat. Prod. 81 (2018) 1399–1404, https://doi.org/10.1021/acs.jnatprod.8b00001.

[79] P.-C. Lin, Y.-Z. Wu, T.-W. Bao, Y.-N. Wang, X.-Y. Shang, S. Lin, A new cytotoxic 12-membered macrolactone from the endophytic fungus *Exserohilum rostratum* LPC-001, J. Asian Nat. Prod. Res. 20 (2018) 1093–1100, https://doi.org/10.1080/10286020.2018.1518322.

[80] J. Richter, L.P. Sandjo, J.C. Liermann, T. Opatz, G. Erkel, 4-Dechloro-14-Deoxy-Oxacyclododecindione and 14-deoxy-oxacylododecindione, two inhibitors of inducible connective tissue growth factor expression from the imperfect fungus *Exserohilum rostratum*, Bioorg. Med. Chem. 23 (2015) 556–563, https://doi.org/10.1016/j.bmc.2014.12.004.

[81] C. Weber, N. Vierengel, T. Walter, T. Behrendt, T. Lucas, G. Erkel, T. Opatz, Total synthesis and biological evaluation of seven new AntiInflammatory oxacyclododecindione-type macrolactones, Org. Biomol. Chem. 18 (2020) 5906–5917, https://doi.org/10.1039/D0OB00958J.

[82] K. Seipp, J. Groß, A.M. Kiefer, G. Erkel, T. Opatz, Total synthesis and biological evaluation of the AntiInflammatory (13R,14S,15R)-13-Hydroxy-14-deoxyoxacyclododecindione, J. Nat. Prod. 86 (2023) 924–938, https://doi.org/10.1021/acs.jnatprod.2c01145.

[83] S. Thomas, N. Sharma, R. Gonzalez, P.-W. Pao, F.M. Hofman, T.C. Chen, S.G. Louie, M.C. Pirrung, A.H. Schönthal, Repositioning of verrucosidin, a purported inhibitor of chaperone protein GRP78, as an inhibitor of mitochondrial electron transport chain complex I, PLoS One 8 (2013) 1–14, https://doi.org/10.1371/journal.pone.0065695.

[84] M.W. Chojnacka, R.A. Batey, Total synthesis of (+)-Prunustatin A: utility of organotrifluoroborate-mediated prenylation and Shiina MNBA esterification and macrolactonization to avoid a competing Thorpe−Ingold effect accelerated transesterification, Org. Lett. 20 (2018) 5671–5675, https://doi.org/10.1021/acs.orglett.8b02396.

[85] A. Numata, M. Iritani, T. Yamada, K. Minoura, E. Matsumura, T. Yamori, T. Tsuruo, Novel antitumor metabolites produced by a fungal strain from a sea hare, Tetrahedron Lett. 38 (1997) 8215–8218, https://doi.org/10.1016/S0040-4039(97)10198-8.

[86] K. Tatsuta, T. Tsuchiya, N. Mikami, S. Umezawa, H. Umezawa, H. Naganawa, KD16-U1, A new metabolite of Streptomyces: isolation and structural studies, J. Antibiot. 27 (1974) 579–586, https://doi.org/10.7164/antibiotics.27.579.

[87] N. Biduś, P. Banachowicz, S. Buda, Application of a tandem seleno-michael/aldol reaction in the total syntheses of (þ)-Pericosine B, (þ)-Pericosine C, (þ)-COTC and 7- chloro-analogue of (þ)-Gabosine C, Tetrahedron 76 (2020) 1–8, https://doi.org/10.1016/j.tet.2020.131397.

[88] N.H. Oberlies, V.L. Croy, M.L. Harrison, J.L. McLaughlin, The annonaceous acetogenin bullatacin is cytotoxic against multidrug-resistant human mammary adenocarcinoma cells, Cancer Lett. 115 (1997) 73, https://doi.org/10.1016/S0304-3835(97)04716-2.
[89] R.A. Kunkalkar, R.A. Fernandes, A protecting-group-free total synthesis of chatenaytrienin-2, J. Org. Chem. (2019) 1–7, https://doi.org/10.1021/acs.joc.9b01952.
[90] P. Reinink, J. Buter, V.K. Mishra, E. Ishikawa, T.-Y. Cheng, P.T.J. Willemsen, S. Porwollik, P.J. Brennan, E. Heinz, J.A. Mayfield, G. Dougan, C.A. van Els, V. Cerundolo, G. Napolitani, S. Yamasaki, A.J. Minnaard, M. McClelland, D.B. Moody, I. Van Rhijn, Discovery of trehalose phospholipids reveals functional convergence with mycobacteria, J. Exp. Med. 216 (2019) 757–771, https://doi.org/10.1084/jem.20181812.
[91] V.K. Mishra, J. Buter, M.S. Blevins, M.D. Witte, I.V. Rhijn, D.B. Moody, J.S. Brodbelt, A.J. Minnaard, Total synthesis of an immunogenic trehalose phospholipid from Salmonella Typhi and elucidation of its sn-regiochemistry by mass spectrometry, Org. Lett. 21 (2019) 5126–5131, https://doi.org/10.1021/acs.orglett.9b01725.
[92] B. Bahadur, M. Tilton, Liquid crystals – applications and uses, J. Soc. Inf. Disp. 63 (1994) 1–2, https://doi.org/10.1889/1.1984911.
[93] S.V. Bhat, K. Swamynathan, S. Kumar, Synthesis and mesomorphic characterization of novel liquid crystals derived from bioactive natural sterols, J. Mole. Liquids. 326 (2021), 115216, https://doi.org/10.1016/j.molliq.2020.115216.
[94] J. Shelton, X. Lu, J.A. Hollenbaugh, J.H. Cho, F. Amblard, R.F. Schinazi, Metabolism, biochemical actions, and chemical synthesis of anticancer nucleosides, nucleotides, and base analogs, Chem. Rev. 116 (2016), 14379, https://doi.org/10.1021/acs.chemrev.6b00209.
[95] J. Bracegirdle, D.P. Gordon, J.E. Harvey, R.A. Keyzers, Kinase-inhibitory nucleoside derivatives from the pacific bryozoan *Nelliella nelliiformis*, J. Nat. Prod. 83 (2020) 547–551, https://doi.org/10.1021/acs.jnatprod.9b01231.
[96] Y.-M. Ma, X.-A. Liang, Y. Kong, B. Jia, Structural diversity and biological activities of indole diketopiperazine alkaloids from fungi, J. Agric. Food Chem. 64 (2016) 6659–6671, https://doi.org/10.1021/acs.jafc.6b01772.
[97] H. Bai, P. Cui, C. Zang, S. Li, Enantioselective total synthesis, divergent optimization and preliminary biological evaluation of (indole-*N*-alkyl)-Diketopiperazines, Bioorg. Med. Chem. Lett. 29 (2019), 126718, https://doi.org/10.1016/j.bmcl.2019.126718.
[98] M. Zaghouani, L.A.K. Bögeholz, E. Mercier, W. Wintermeyer, S.P. Roche, Total synthesis of (±)-Fumimycin and analogues for biological evaluation as peptide deformylase inhibitors, Tetrahedron 75 (2019) 3216–3230, https://doi.org/10.1016/j.tet.2019.03.037.
[99] P.A. Wender, J.L. Sloane, Q.H. Luu-Nguyen, Y. Ogawa, A.J. Shimizu, S.M. Ryckbosch, J.H. Tyler, C. Hardman, Unlocking the drug potential of the bryostatin family: recent advances in product synthesis and biomedical applications, J. Org. Chem. 85 (2020) 15116–15128, https://doi.org/10.1021/acs.joc.0c01988.
[100] J.M. Wood, E.N. Juńior, S. da, J.F. Bower, Rh-catalyzed [2 + 2 + 2] cycloadditions with benzoquinones: de novo access to naphthoquinones for lignan and type II polyketide synthesis, Org. Lett. 22 (2019) 265–269, https://doi.org/10.1021/acs.orglett.9b04266.