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COMPREHENSIVE REVIEW

Cross-coupling reactions towards the synthesis of natural products

Shaheera Tabassum[1] · Ameer Fawad Zahoor[1] · Sajjad Ahmad[2] · Razia Noreen[3] · Samreen Gul Khan[1] · Hamad Ahmad[4]

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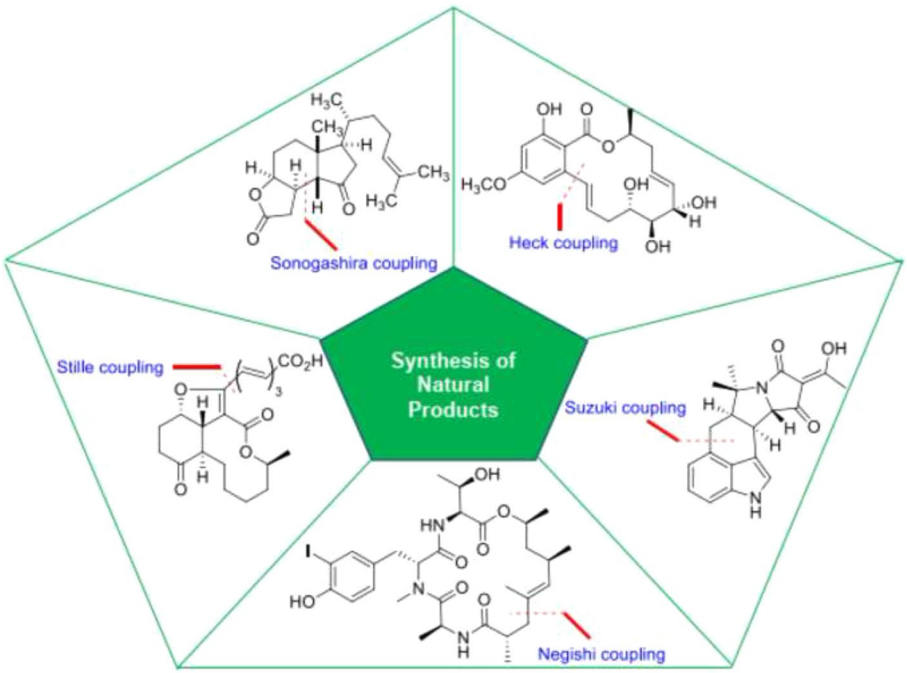
Abstract

Cross-coupling reactions are powerful synthetic tools for the formation of remarkable building blocks of many naturally occurring molecules, polymers and biologically active compounds. These reactions have brought potent transformations in chemical and pharmaceutical disciplines. In this review, we have focused on the use of cross-coupling reactions such as Suzuki, Negishi, Heck, Sonogashira and Stille in the total synthesis of some natural products of recent years (2016–2020). A short introduction of mentioned cross-coupling reactions along with highlighted aspects of natural products has been stated in separate sections. Additionally, few examples of natural products via incorporation of more than one type of cross-coupling reaction have also been added to demonstrate the importance of these reactions in organic synthesis.

Graphic abstract



Keywords Cross-coupling · *C*–*C* bond · Natural products · Terpenoids · Alkaloids

✉ Ameer Fawad Zahoor
fawad.zahoor@gcuf.edu.pk; fawad.zahoor@gmail.com

Extended author information available on the last page of the article

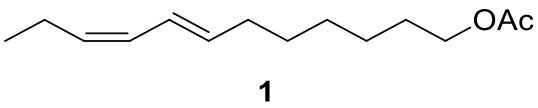


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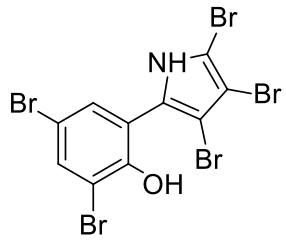
Fig. 1 Structure of sex pheromone **1**



Pentabromopseudilin (**2**)

Fig. 2 Structure of pentabromopseudilin **2**

Introduction

Reactions assembling the carbon–carbon bonds in organic compounds constitute a pillar of strength to organic synthesis. Particularly, the designing of natural products framework demands a rapid and selective construction of carbon skeleton [1, 2]. Cross-coupling reactions have gathered much attention of researchers from the past few decades because of simple, general and mild synthetic approaches involving the use of highly active ligands and transition metal complexes. These protocols are involved in the accomplishment of simple to complex carbon skeletons such as functional materials, synthetic fragments, bioactive compounds, natural products and agrochemicals [3, 4]. One of the prominent cross-coupling reactions is palladium catalyzed *C–C* bond forming reactions that give interesting properties to the final chains of molecules [5–8]. In 2010, Nobel Prize award for palladium-catalyzed cross-coupling reactions [4] had fastened its roots in chemical synthesis and their enabling characteristics make them a center of interest in multiple domains.

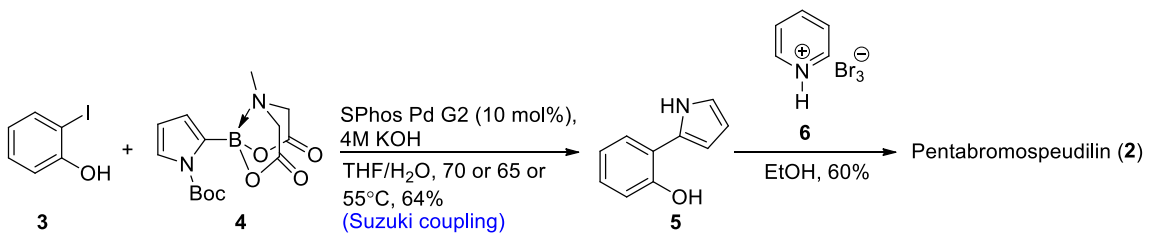
Tamura and Kochi [9] reported the first iron-catalyzed cross-coupling reaction and then as the time passed, many new strategies including Suzuki [10], Heck [11], Sonogashira [12], Negishi [13], Stille [14], Cadiot–Chodkiewicz [15], Castro–Stephens [16], Hiyama [17], Fukuyama [18], Liebeskind–Srogl [19] and Kumada reactions [20], etc., were developed for framing the structures of organic compounds and the scope of cross-coupling reactions became a key topic for the investigators. Keeping in view the recent advances and extensive applications of cross-coupling reactions, several reviews on novel synthetic methodologies have been reported [21–23].

Owing to unique chemical features and biological potential, many of the natural products are used as core part of valuable drugs [24]. Herein, we have emphasized the role of cross-coupling reactions in the total synthesis of some natural products. Natural products are briefly introduced and categorized into alkaloids, terpenoids, steroids, polyketides, macrolides, lignans, alkamides and lactones classes.

Review of literature

Suzuki cross-coupling reaction

Palladium-catalyzed Suzuki cross-coupling reaction (Suzuki–Miyaura coupling) is a widely known method to couple organoboranes/boronic acids with organic halides/triflates under basic conditions to form *C–C* bonds [25]. Non-toxicity and stability, accessibility of organoboron compounds/boronic acids, their incorporation into organometallic compounds and simple workup techniques add additional features to the armory of Suzuki cross-coupling. This cross-coupling endures many functional groups and the stereochemistry of coupling reagents is retained in the resulting biaryls [26]. It is one of the well-built tool to furnish biaryl moiety which displays vast applications in pharmaceuticals and material science [27]. The first natural product synthesis via Suzuki coupling was disclosed by Rossi [28] in 1981 which involved the preparation of sex pheromone **1** in 21.6% overall yield (Fig. 1).



Scheme 1 Synthesis of pentabromopseudilin **2**

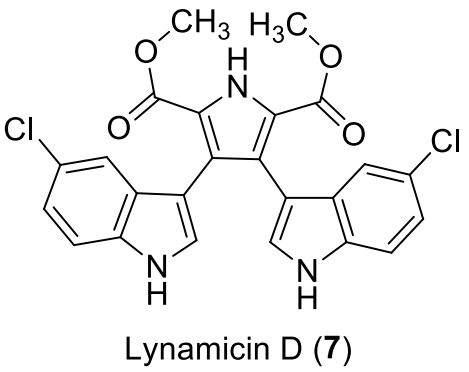


Fig. 3 Structure of lynamicin D **7**

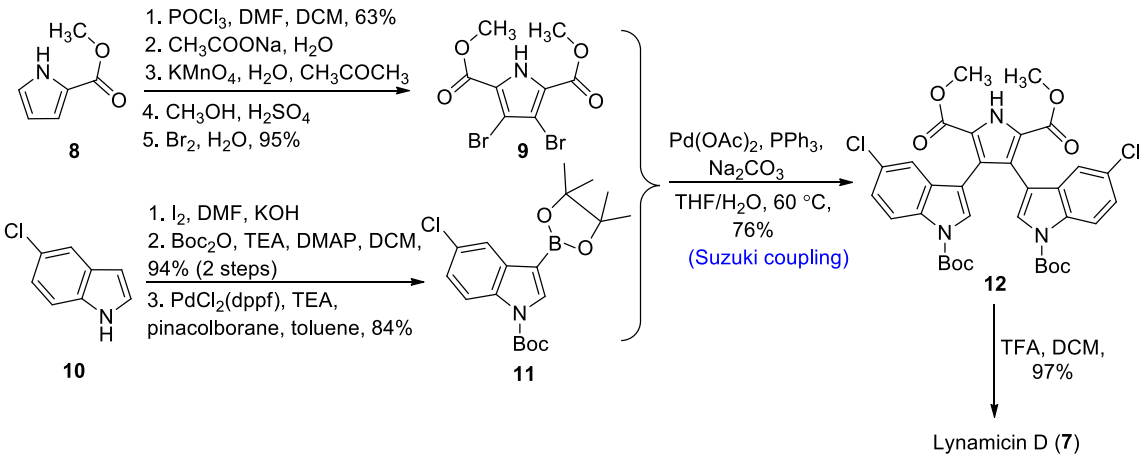
Synthesis of alkaloids

Pentabromopseudilin **2** is a polyhalogenated bicyclic alkaloid [29] which was firstly isolated from *Pseudomonas bromoutilis* (1996) and later from *Alteromonas luteoviolaceus*, *Chromobacteria* and *Pseudoalteromonas* sp (Fig. 2). Biological activities such as antifungal, anti-tumour and antibiotic are associated with this polybrominated natural product. It acts as inhibitor against human lipoxygenases, myosin and exhibits the potential to act against MRSA with IC_{50} value of 0.1 µM [30].

Kum et al. [31] carried out the synthesis of an anti-MRSA and myosin-inhibiting natural product **2** with 38% overall yield through two steps by using Suzuki coupling protocol (Scheme 1). Synthesis was started from the coupling of phenol **3** with *N*-methyliminodiacetic acid (MIDA) boronate **4** and conditions were optimized to achieve the best results. The use of 10 mol% Buchwald 2nd generation precatalyst (Sphos Pd G2) along with 4 M KOH (base) in tetrahydrofuran (THF)/H_2O led to the formation of compound **5** which was treated with pyridinium tribromide **6** to shape the core of pentabromopseudilin **2** in 60% yield. The synthesized compounds **2** and **5** were evaluated for biological potential against *Staphylococcus epidermidis*; however among them, compound **2** showed clear zones of inhibition at 50 and 5 µM.

Marine environment provides a number of valuable natural products with potential of anticancer, antibiotic and therapeutic activities. Among them, actinobacteria are of vital importance as these are the sources of market valued chemical substances. Lynamicin D **7** is a chlorinated bisindole pyrrole alkaloid which has been obtained from marine actinomycetes such as SCSIO 03,032 and NPS12745 (Fig. 3). This compound has the capability to act against drug-resistant pathogens (*Staphylococcus aureus* and *Enterococcus faecium*) [32, 33].

The first total synthesis of lynamicin D **7** was reported by Sigala et al. [34] which involved Suzuki coupling of dicarboxylate **9** with boronate **11** (Scheme 2). In this regard, pyrrole **8** was subjected to $POCl_3$ (63% yield) and CH_3COONa and resulting product was oxidized (using $KMnO_4$) followed by Fischer esterification (with CH_3OH, H_2SO_4) and bromination (using Br_2, 95%) provided indole-based dibromo dicarboxylate derivative **9**. While boronate **11** was obtained from indole **10** by employing iodination followed by protection with Boc group (94% yield, 2 steps) and then treatment with pinacolborane in the presence of $PdCl_2$(dppf) (84% yield). Suzuki coupling of synthesized fragments **9** and **11** in the presence of $Pd(OAc)_2$, triphenylphosphine (PPh_3), Na_2CO_3 in THF/H_2O mixture at 60 °C produced bisindole pyrrole **12** in good yield (76%) which on treatment with trifluoroacetic acid (TFA) afforded the acquired product **7** in an excellent yield (97%). Biological activity of lynamicin D **7** was also studied which revealed that it had a minor effect on cell viability, but it could regulate splicing of pre-mRNAs as it alters the levels of kinase (SRPK1).



Scheme 2 Synthesis of lynamicin D **7**

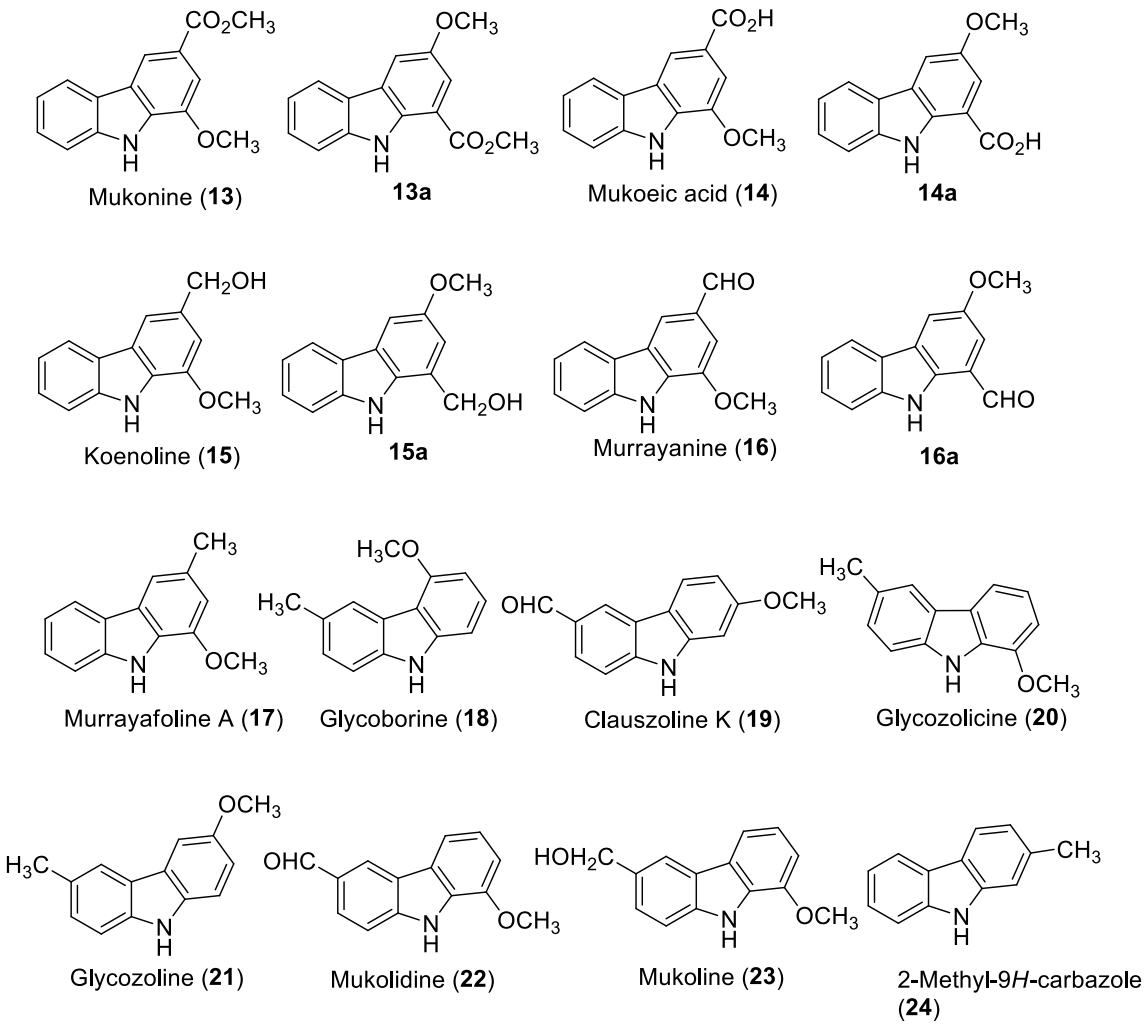
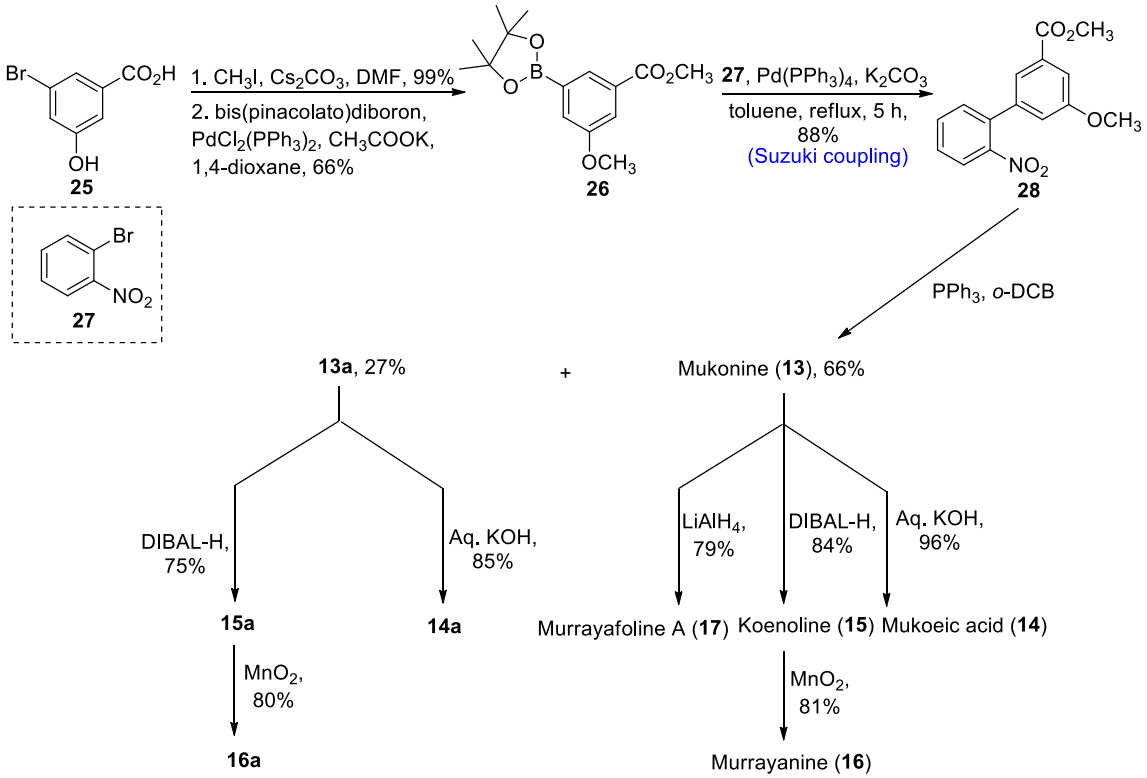


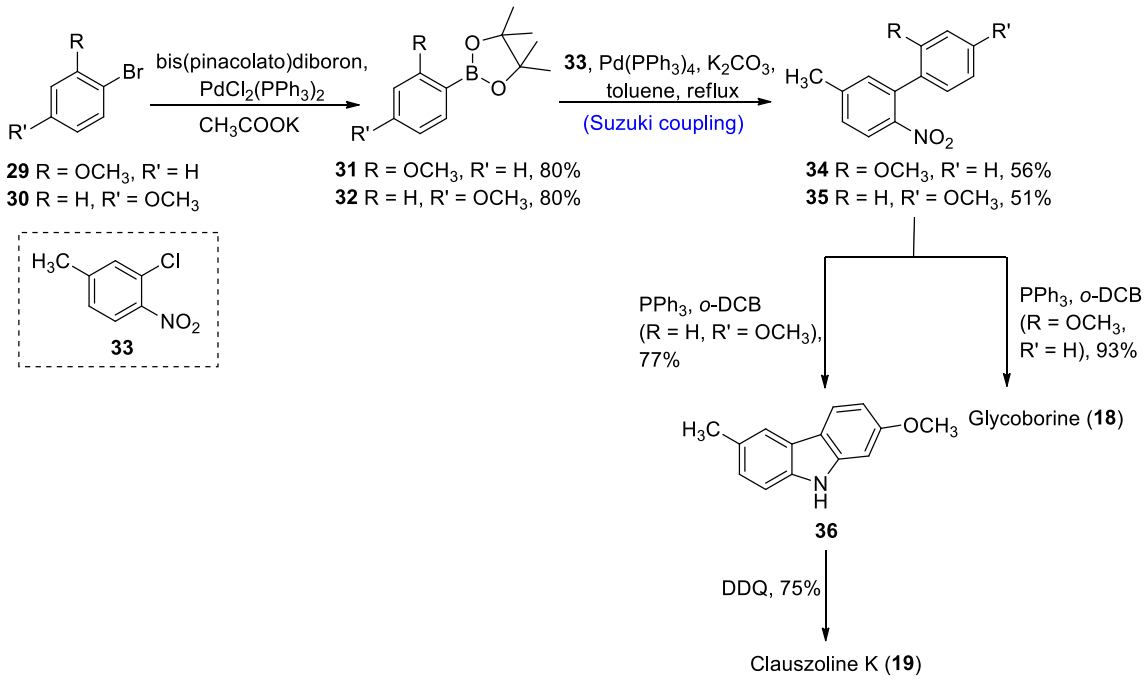
Fig. 4 Structures of carbazole alkaloids **13–24**

Carbazole alkaloids bearing pyrrole ring constitute a major class of natural products and their source of extraction includes various plant species including bacteria and fungi. From the last few decades, extensive work has been carried out on carbazole compounds due to their versatile chemical characteristics and biological potentials such as anti-HIV, anti-malarial, anti-tumour, anti-TB, etc. [35] Some of the biologically important carbazole alkaloids **13–24** are listed in Fig. 4.

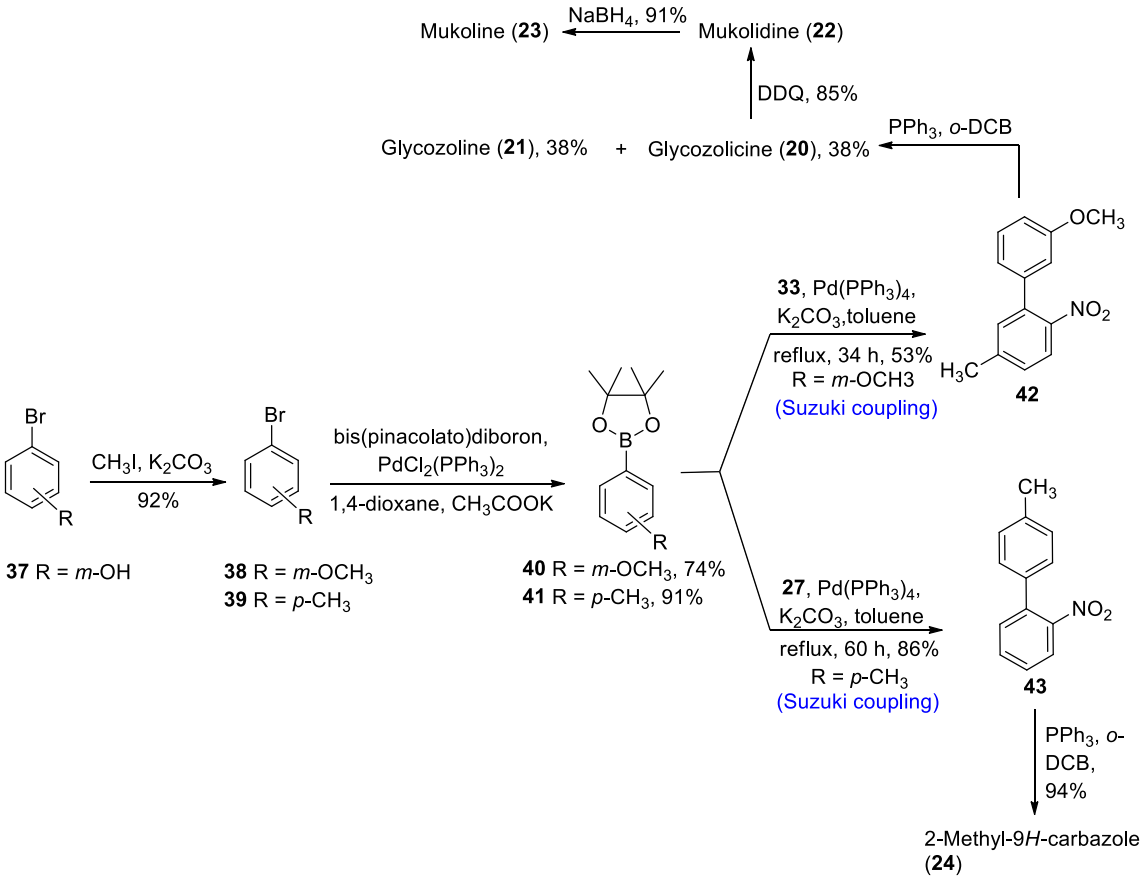
A convenient strategy for the total synthesis of carbazole alkaloids **13–24** was reported by Bhatthula et al. [36] with moderate to excellent yields (27–96%). The synthetic route involved Suzuki cross-coupling and Cadogan reductive cyclization as vital steps. Synthesis of mukonine **13** was started from benzoic acid **25** which underwent esterification (with CH_3I, Cs_2CO_3, 99%) followed by addition of bis(pinacolato diboron) to give compound **26** in 66% yield. Coupling of compound **26** with *o*-nitrobenzene **27** using $Pd(PPh_3)_4$ and K_2CO_3 in refluxing toluene in 5 h gave the coupled product **28** in 88% yield. Later, compound **28** in the presence of PPh_3 and *o*-dichlorobenzene (*o*-DCB) experienced Cadogan reductive cyclization to furnish the desired natural product **13** (66%) along with its regioisomer **13a** (27%). Reduction of compound **13** with diisobutylaluminium hydride (DIBAL-H) and $LiAlH_4$ afforded koenoline **15** and murrayafoline A **17**, respectively, while oxidation of compound **15** with MnO_2 gave murrayanine **16** in 81% yield. Saponification of compound **13** (using aq. KOH) produced mukoeic acid **14** in 96% yield. Carbazole **13a** provided regioisomers **14a**, **15a** and **16a** under saponification, reduction and oxidation conditions, respectively (Scheme 3). Synthesis of glycoborine **18** and clauszoline K **19** was achieved in 93% and 75% yield using compound **31/32** and 2-cholro-4-methyl-1-nitrobenzene **33** as Suzuki coupling partners (Scheme 4). Treatment of compound **41** (obtained from 4-bromotoluene **39**) with *o*-nitrobenzene **27** in the presence of $Pd(PPh_3)_4$ gave biphenyl **43** in 86% yield which was cyclized (using PPh_3, *o*-DCB) to obtain



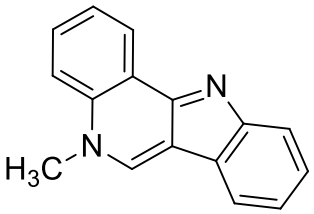
Scheme 3 Synthesis of carbazole alkaloids **13–17**



Scheme 4 Synthesis of carbazole alkaloids **18** and **19**



Scheme 5 Synthesis of carbazole alkaloids **20**–**24**



Isocrytolepine (**44**)

Fig. 5 Structure of isocrytolepine **44**

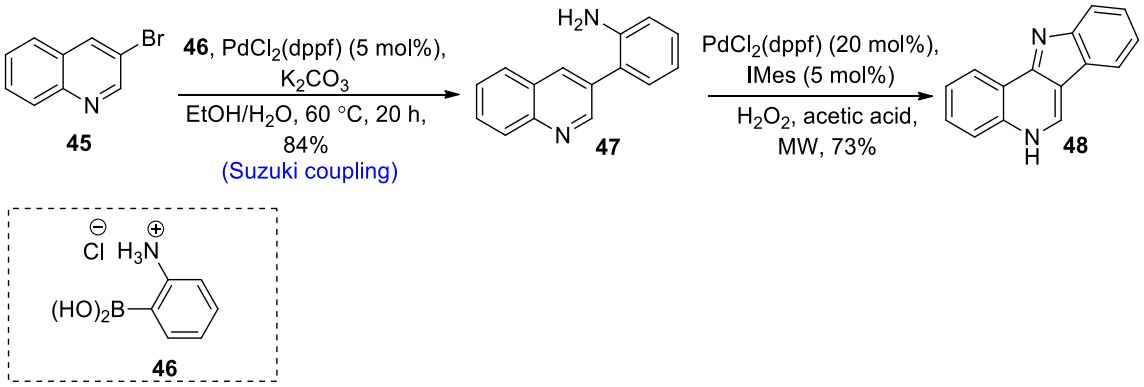
2-methyl-9*H*-carbazole **24** (94%). Moreover, the use of 3-bromophenol **37** as starting material and 2-cholro-4-methyl-1-nitrobenzene **33** (for Suzuki coupling) framed the structures of glycozolicine **20** (38%), glycozoline **21** (38%), mukolidine **22** (85%) and mokuline **23** (91%) (Scheme 5).

Isocrytolepine **44** (obtained from *Cryptolepis sanguinolenta*) is an indoloquinoline alkaloid reported independently by Pousset et al. [37] and Sharaf et al. [38] in 1995 (Fig. 5). It consists of tetracyclic skeleton based on angularly fused indolo[3,2-*c*]quinoline ring with wide range of biological activities such as antiplasmodial, antimicotic, antihyperglycemic, antimuscarinic and antibacterial, etc. [39].

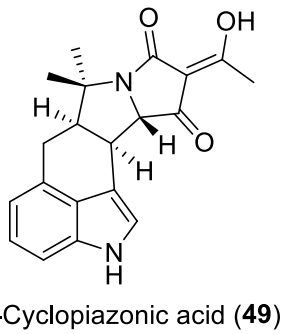
Håheim et al. [40] presented the synthesis of tetracyclic core **48** of isocrytolepine **44** (Scheme 6). Suzuki coupling was employed between 3-bromoquinoline **45** and boronic acid **46** in the presence of $PdCl_2$(dppf) (5 mol%), K_2CO_3 in EtOH/H_2O at 60 °C for 20 h to give compound **47** in 84% yield. The latter compound **47** was cyclized using $PdCl_2$(dppf) (20 mol%) as catalyst and 1,3-bis(2,4,6-trimethylphenyl)-imidazolium (IMes) (5 mol%) as ligand to produce regiospecific compound **48** in good yield (73%).

α-Cyclopiazonic acid **49** is a member of prenylated alkaloids possessing the potential to inhibit calcium-ATPase enzyme in sarcoendoplasmic reticulum due to its toxic nature (Fig. 6). For the first time, it was obtained from fungus *Penicillium cyclopium* [41].

A shortest synthetic pathway for the preparation of α-cyclopiazonic acid **49** involving seven steps was reported by Shi et al. [42] (Scheme 7). Synthesis was commenced from palladium-catalyzed coupling of 4-bromoindole **50** with *t*-prenylboronate **51** using $Pd(PPh_3)_4$, NaOH in toluene/H_2O at 90 °C to form regioisomer **52** in 91% yield.



Scheme 6 Synthesis of tetracyclic motif **48** of isocrytolepine **44**



α-Cyclopiazonic acid (**49**)

Fig. 6 Structure of α-cyclopiazonic acid **49**

Vilsmeier–Haack formylation (with $POCl_3$, dimethylformamide (DMF), aq. KOH, 75%) and *N*-tosylation (with TsCl, 53%) produced aldehyde **53** which on reaction with compound **54** in the presence of LiHMDS yielded indole derivative **55** (78%). It was then subjected to [3 + 2] annulation by employing Tf_2NH (50% yield) to achieve diastereomeric mixture of three tetracycles. Only small amount of one diastereomer was separated and was treated with excess of Mg (50% yield) to give mixture of diastereomeric amines (**56a**:**b**:**c** = 1:0.3:0.7) from which the amine **56a** was successfully separated. It was converted to the target product **49** in 59% yield on treatment with diketene **57** in dichloromethane (DCM) and *t*-BuOK.

Synthesis of polyketides

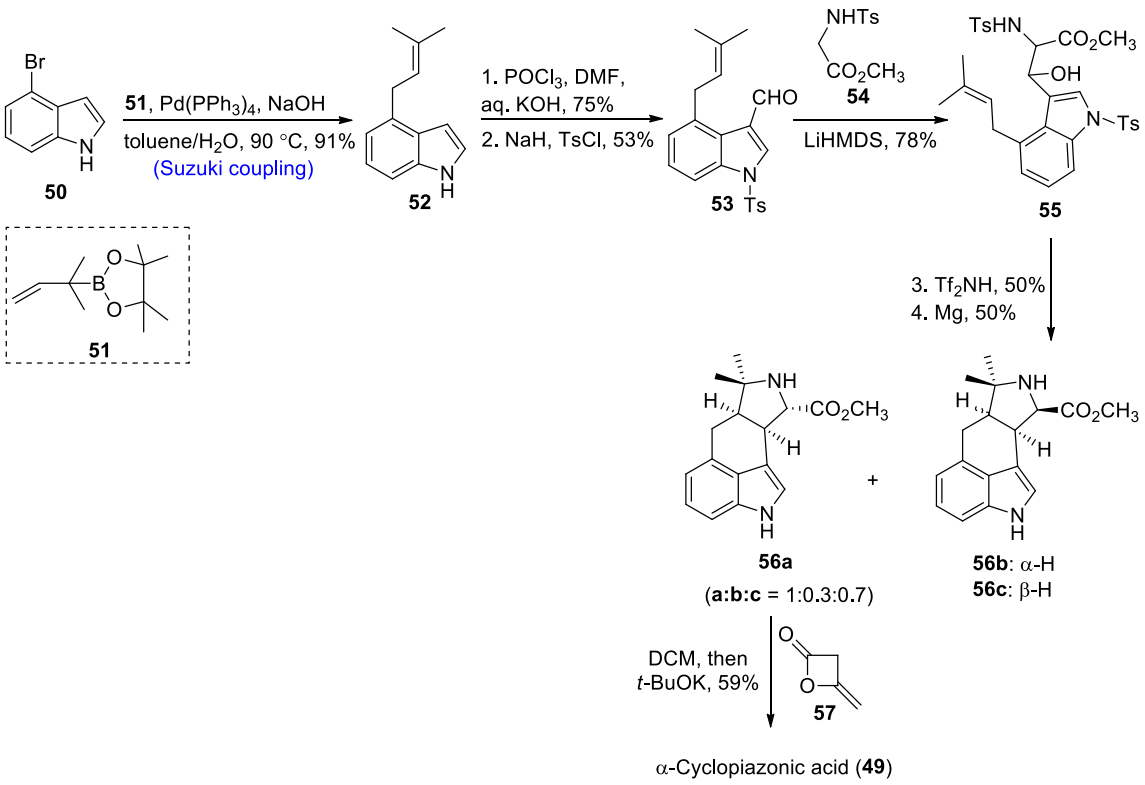
Anthracyclines account for a medically prime class of aromatic polyketides and demonstrate anti-cancer potential. Their structure contains aglycone chromophore attached with one or more deoxysugars. Nogalamycin **58** (extracted from *Streptomyces nogalater*) possesses antibacterial and anticancer potential, whereas its semisynthetic derivative, menogaril **59** exhibits anticancer properties. These compounds are naturally occurring polyketides (Fig. 7) [43].

The synthesis of anthracyclines **58** and **59** was achieved by Peng and VanNieuwenhze [44] via implementation of Suzuki cross-coupling protocol for the preparation of the DFT-ring system **65** (Scheme 8). In this regard, enol triflate **60** and D-ring precursor **61** in the presence of $PdCl_2$(dppf) and KOH in toluene at room temperature produced coupled product **62** in 69% yield. Then, compound **62** on subsequent primary alcoholic group protection (with TBSCl, 88%) followed by Staudinger reduction (using PPh_3, H_2O/THF) provided amine which was further protected with 2-naphthylsulfonyl group. In the following step, addition of formic acid selectively cleaved the primary TBS group to produce compound **63** (88% over 3 steps) which on treatment with $PySO_3$ followed by the addition of $HC(OCH_3)_3$ accomplished dimethyl acetal **64** in an excellent yield (95% over 2 steps). Epoxidation of alkene **64** was carried out with *m*-chloroperoxybenzoic acid (*m*-CPBA, 57%) which was reduced (using $LiAlH_4$, 59%) and cyclized in acidic conditions (3 M HCl, acetic acid) to afford DFT-ring system **65** in 77% yield.

Synthesis of terpenoids

The presence of tricarbocyclic core is a peculiarity of naturally occurring diterpenoid hamigerans. Furthermore, hamigerans possess three or four stereogenic centers arranged in adjacent positions around *cis* bicyclic core [45]. (−)-Hamigeran B **66** with magnificent anti-viral property was first isolated from *Hamigera tarangaensis* (a sponge) in 2000 (Fig. 8) [46].

Total synthesis of (−)-hamigeran B **66** was disclosed by Kuwata et al. [47] over 17 steps via Suzuki cross-coupling of (*R*)-triflate **68** (obtained from a cyclic ketone **67**) with compound **69** using $PdCl_2$(dppf)·DCM, K_2CO_3 in dimethyl sulfoxide (DMSO) at 80 °C (Scheme 9). The coupling product (*R*)-**70** (68%) was obtained as a mixture of two rotamers which was divulged through ^1H NMR interpretations. Further, the treatment of (*R*)-**70** with SmI_2 for reductive



Scheme 7 Synthesis of α-cyclopiazonic acid **49**

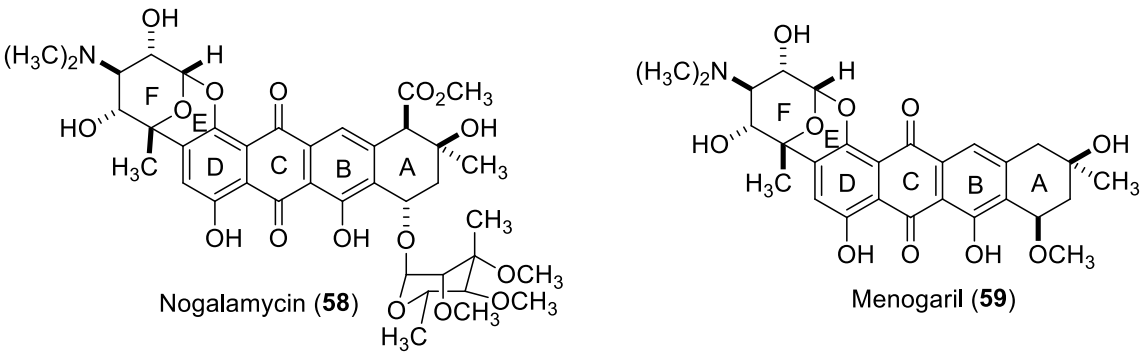
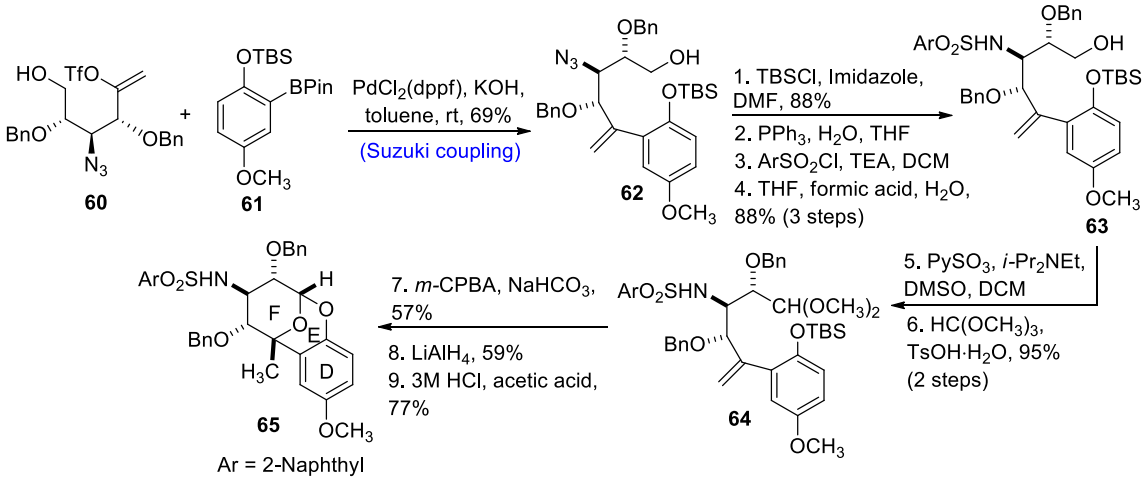


Fig. 7 Structures of nogalamycin **58** and menogaril **59**

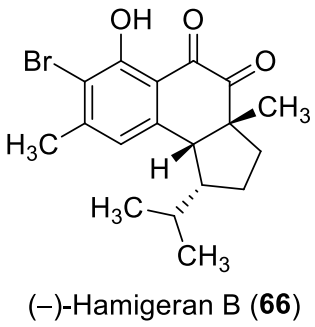
coupling of two aldehydes resulted in two diastereomers **71a** (51%) and **71b** (49%). The stereochemistry of the target product **66** was maintained during the synthetic route and was obtained over several steps from diastereomer **71a**.

Magnolia officinalis var. *biloba* is a commonly used Chinese medicine. Its active ingredient known as terpenoid quinone is also named as magterpenoid C **72**. It is famous for the remedy of phlegm, dyspepsia and abdominal distension (Fig. 9) [48].

The first total synthesis of magterpenoid C **72** by using Suzuki coupling and silica-gel accelerated [4 + 2] cycloaddition protocols was explained by Kumar et al. [49] (Scheme 10). Hydroquinone and 4-allyl anisole gave 2-bromo-1,4-dimethoxy-benzene **73** and compound **74**, respectively, which were subjected to Suzuki coupling in the presence of $Pd(PPh_3)_4$, Na_2CO_3 in refluxing dimethoxyethane (DME)/H_2O for 6 h to give intermediate **75** in 60% yield. In the next step, oxidative demethylation of compound **75** was done using phenyliodine bis(trifluoroacetate) (PIFA) in acetonitrile/water mixture to access quinone **76** (62%). Quinone **76** was subjected to reduction (with $NaBH_4$, 99%) followed by the addition of $AlCl_3$ for demethylation (50% yield) and $NaIO_4$ to furnish the desired quinone **77** in 95% yield. Final framework of terpenoid **72** (67% over 2 steps)



Scheme 8 Synthesis of DFT- ring **65** of nogalamycin **58** and menogaril **59**



(−)-Hamigeran B (**66**)

Fig. 8 Structure of (−)-hamigeran B **66**

was achieved in a regioselective manner by the combination of quinone **77** with β-myrcene **78** in the presence of SiO_2-gel and MnO_2 for [4 + 2] cycloaddition and subsequent aromatization.

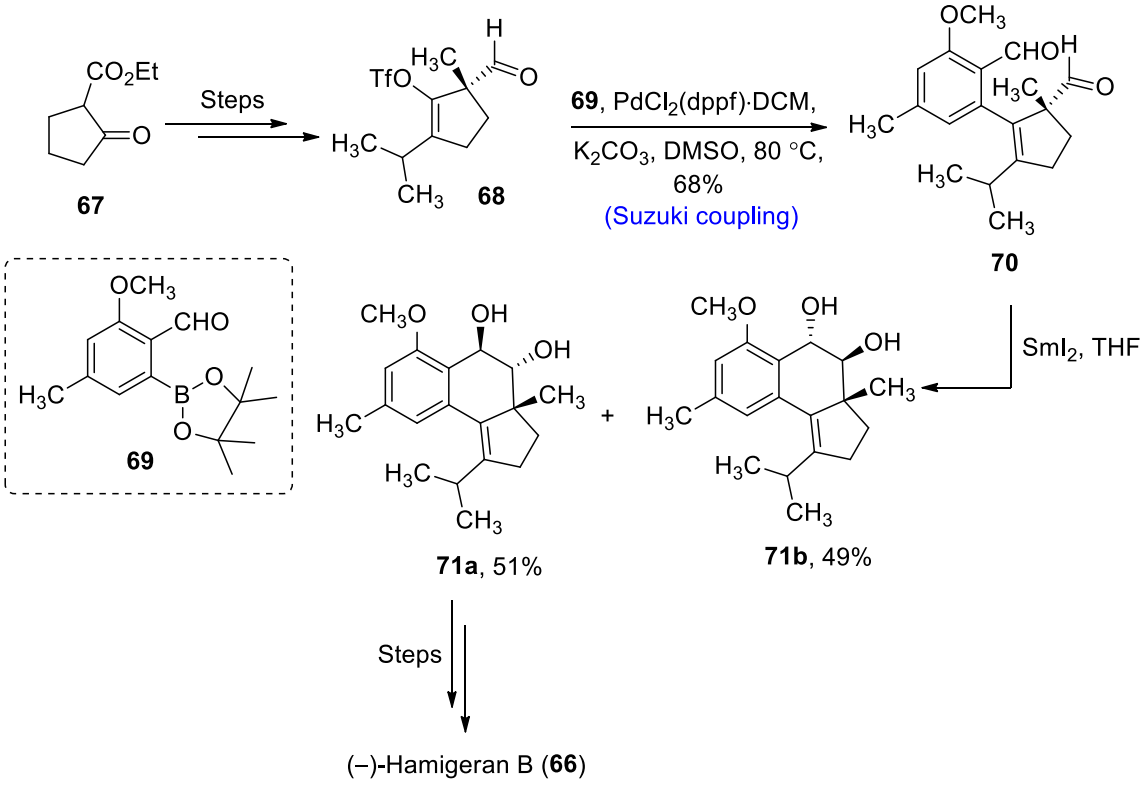
Miscellaneous

Insects constitute a major portion of animals on earth. Although a number of peptides and proteins have been isolated from various insect species from past few years however, their biologically activity has been less investigated. *Aspongopus chinensis* Dallas, found in China, is used as traditional medicine as well as food. Investigation revealed that it exhibits pronounced biological activities such as anticancer, analgesic and angiogenesis, etc. Proliferation of neural stem cells is also associated with this insect species. Aspongpyrazine A **79** is a pyrazine obtained from insect A. *chinensis* (Fig. 10) [50].

Bendre et al. [51] reported an efficient, simple and environmental friendly biological route for the preparation of palladium nanoparticles (PdNPs) using palladium chloride and oxytoxin (a harmone). These PdNPs were then applied in the Suzuki cross-coupling for the synthesis of aspongpyrazine A **79** with 86.4% overall yield (Scheme 11). Readily available 2-bromo-6-methylpyrazine **80** was subjected to Suzuki coupling with boronic acid **81** over PdNPs and K_2CO_3 in DMF/H_2O at 100 °C to obtain compound **82** in 90% yield. The latter compound **82** underwent deprotection with 47% HBr and aliquat© 336 (catalyst) to afford final skeleton of aspongpyrazine A **79** in 96% yield.

Kehokorin A **83** and kehokorin B **84** contain dibenzofuran core in their structures and have been extracted from field-collected sample of fruit bodies of Trichiaceae (*Trichia favoginea* var. *persimilis*) (Fig. 11). Biological evaluation of these compounds showed that kehokorin A **83** possesses cytotoxicity potential against HeLa cell line which was attributed to the presence of rhamnose unit [52].

Fujiwara et al. [53] implemented Suzuki cross-coupling approach twice in the total synthesis of kehokorin A **83** and kehokorin B **84**. In their work, phenol **85** was transformed into bromo-phenol derivative **86** (95%) on treatment with *N*-bromosuccinimide (NBS) in the presence diisopropylamine (*i*-Pr_2NH) followed by the addition of $TMSCHN_2$ (trimethylsilyldiazomethane) for methylation of phenolic hydroxyl group. In the next step, compound **86** was coupled with boronic acid **87** to access biaryl compound **88** in 94% yield under the conditions of $Pd_2(dba)_3$, SPhos and K_3PO_4 in toluene at 105 °C which over three steps provided dibenzofuran core **89**. Compound **89** produced was further transformed into compound **90** which again underwent Suzuki coupling with boronic acid **91** under similar conditions to give *p*-terphenyl dibenzofuran **92** in 55% yield (Scheme 12). The benzyl group of the dibenzofuran **92** was cleaved by using H_2, Pd/C to obtain compound **93** which on treatment (with K_2CO_3, BuOH, 1,4-dioxane) furnished kehokorin B **84** (70%), whereas on incorporation of imidate **94** (using TMSOTf) followed by the addition of K_2CO_3,



Scheme 9 Synthesis of (−)-hamigeran B **66**

BuOH, 1,4-dioxane and H_2, Pd/C for hydrogenolysis produced kehokorin A **83** (48%) (Scheme 13).

11,12-Dihydro-3-hydroxyretinol **95** has been collected from *Laurencia nipponica* (red alga) at Muroran, Hokkaido in Japan. It possesses moderate antifouling property in 5–10 μg/cm^2 against the larvae of *Amphibalanus amphitrite* (Fig. 12) [54].

Rivas et al. [55] reported the stereocontrolled synthesis of (*R*)-11,12-dihydro-3-hydroxyretinol **95** with 73% yield via Suzuki cross-coupling of enantiopure alkenyl iodide **99** with pinacolboranedienoate **98** (Scheme 14). Compound **98** was obtained when methyl geranoate **96** with 2-propenylboronate **97** was coupled with second generation Grubbs' catalyst in 48% yield. In the following step, Suzuki coupling in the presence of 7 mol% $Pd(PPh_3)_4$ and 10% aq. TlOH in THF at 25 °C in 2 h gave all-*trans*-tetraenoate **100** (71%) which on reduction with DIBAL-H yielded the desired product **95**.

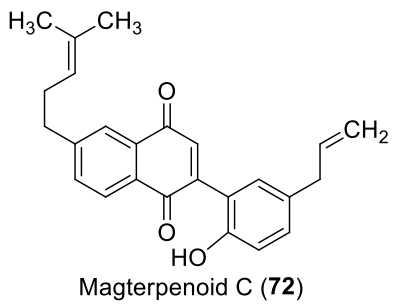
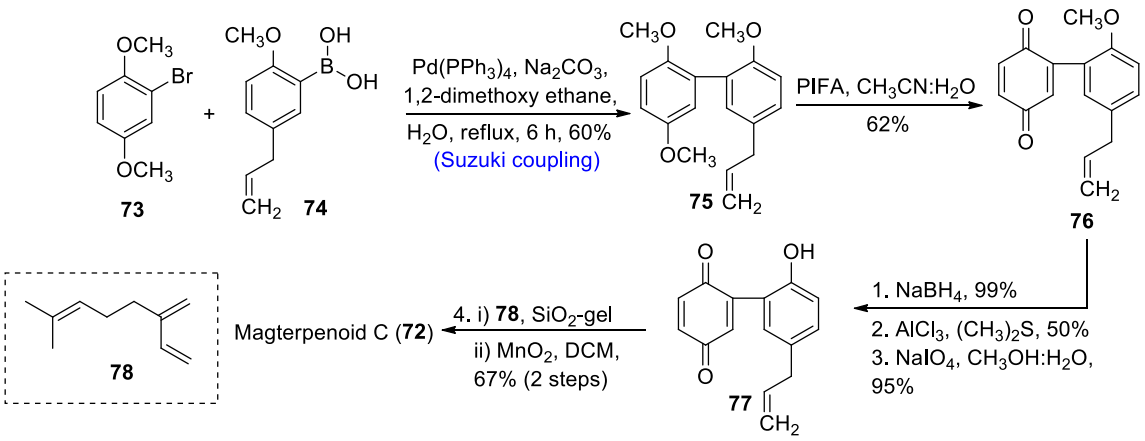


Fig. 9 Structure of magterpenoid C **72**

Bradykinin binding inhibitor, a metabolite termed as L-755,807 **101** (non-peptide natural product) was isolated from *Microsphaeropsis* sp. It acted as ^{3}H-bradykinin binding inhibitor with IC_{50} of 71 μM (Fig. 13) [56].

A convergent synthetic route for the total synthesis of L-755–807 **101** and its stereoisomers via Suzuki coupling and *E*-selective HWE (Horner-Wadsworth-Emmons) protocol was presented by Tanaka et al. [57]. (*R*)(−)-3-Hydroxy-2-methylpropionate **102** gave (*R*,*R*)-vinyl bromide **103** over several steps. Then, (*R*,*R*)-**103** was treated with boronic acid **104** by loading $Pd(PPh_3)_4$, TlOEt in THF/H_2O to accomplish (*R*,*R*)-triene alcohol **105** in 65% yield which on oxidation (with MnO_2) provided (*R*,*R*)-triene aldehyde **106** in 79% yield (Scheme 15). Moreover, amide **107** was converted to phosphonate **108** on treatment with *n*-BuLi and dimethoxy methyl phosphonate which was further assembled with already synthesized fragment **106** under HWE reaction conditions (*t*-BuOK in 1 M THF) to form compound **109** in 65% yield. Deprotection of TES group of compound **109** using 3HF·TEA followed by the addition of AZADOL for oxidation afforded the target skeleton of L-755,807 **101** in 63%



Scheme 10 Synthesis of magterpenoid C **72**

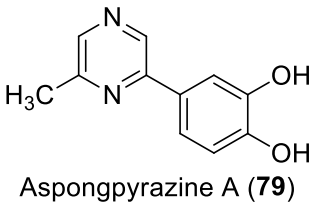
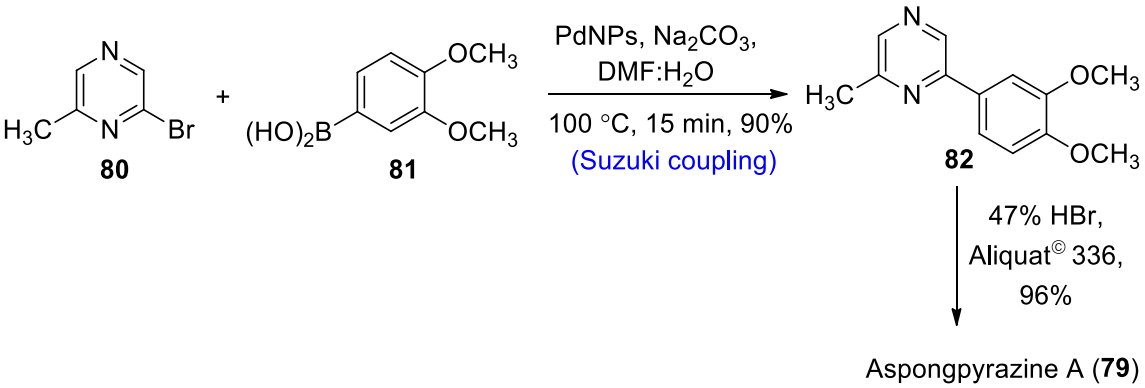


Fig. 10 Structure of aspongpyrazine A **79**

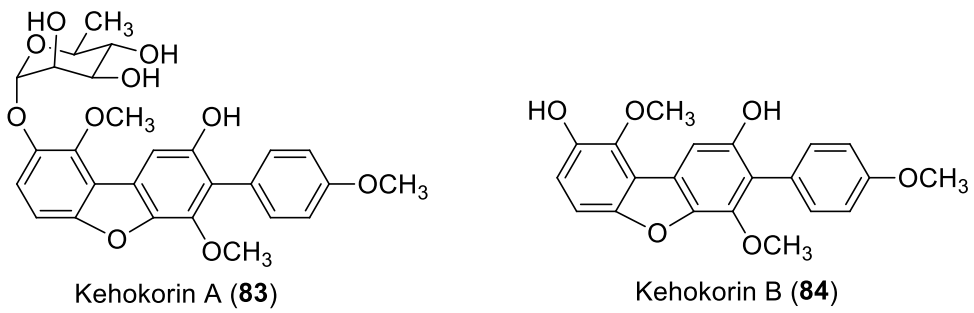
yield (Scheme 16). Additionally, structure–activity relationship (SAR) for L- 755,807 **101** and its isomers was studied for the first time and it was observed that the prepared compounds showed potent Aβ aggregation inhibitory activity (IC_{50} values 5–21 μM).

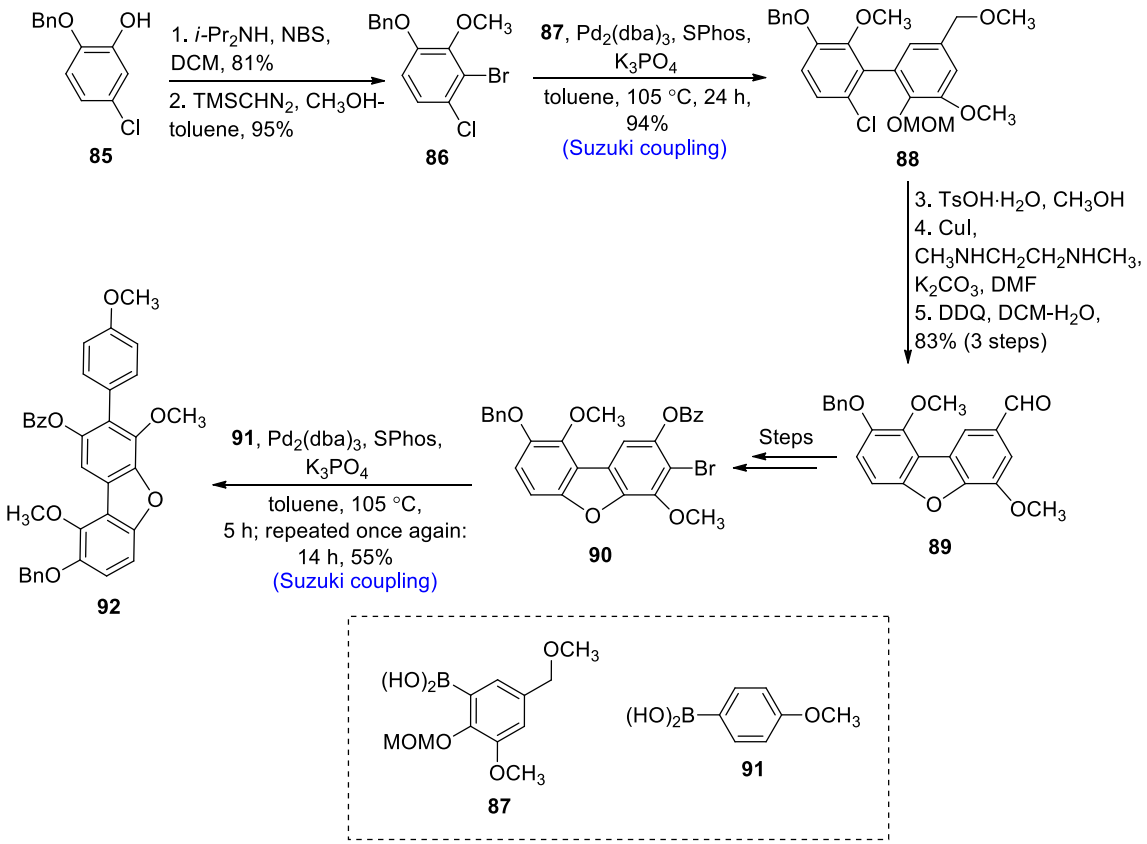
Anithiactins A-C (**110**–**112**) are modified phenylthiazole derivatives and have been extracted from *Streptomyces* sp. These compounds displayed moderate acetylcholinesterase inhibitory activity with no cytotoxicity [58]. Later on,



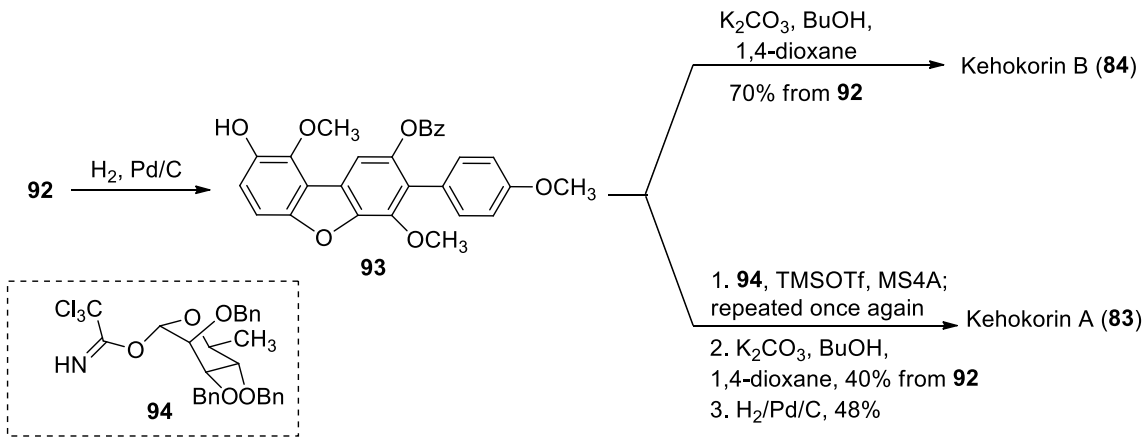
Scheme 11 Synthesis of aspongpyrazine A **79**

Fig. 11 Structures of kehokorin A **83** and kehokorin B **84**





Scheme 12 Synthesis of *p*-terphenyl dibenzofuran **92**



Scheme 13 Completion of the total synthesis of kehokorin A **83** and kehokorin B **84**

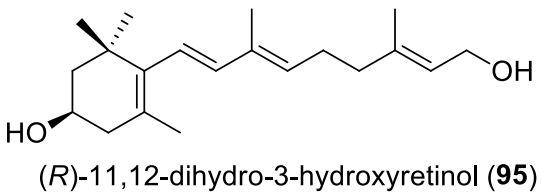
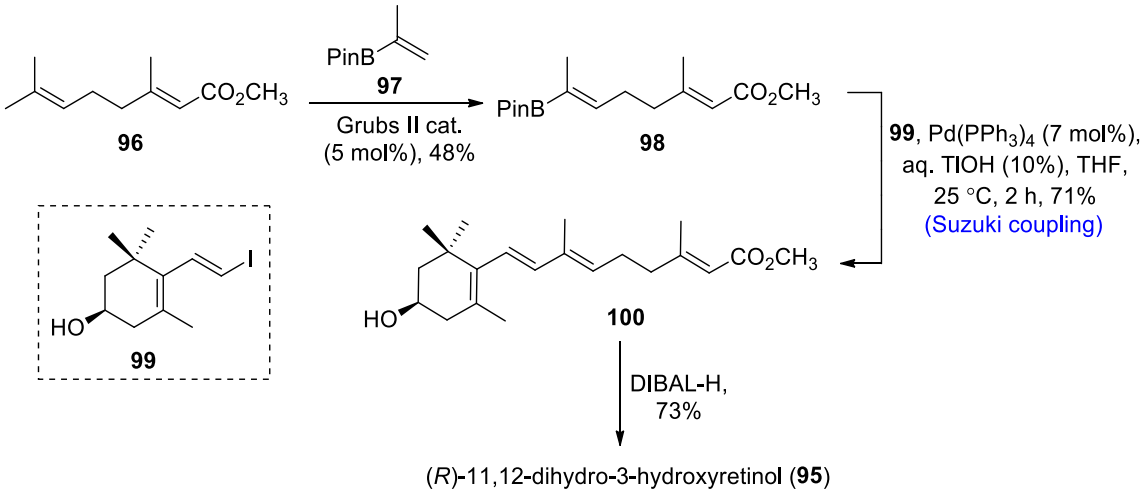


Fig. 12 Structure of (*R*)-11,12-dihydro-3-hydroxyretinol **95**

thiasporine A **113** was extracted from *Actinomycetospora chlora* in addition to anithiactins A and C (Fig. 14) [59].

Vaaland et al. [60] designed the synthetic route for four title natural products **110**–**113** by employing Suzuki coupling as main step (Scheme 17). The starting substrates i.e. boronic acid hydrochloride **46** and thiazole bearing carboxylate **114** were coupled in the presence of 15 mol%



Scheme 14 Synthesis of (*R*)-11,12-dihydro-3-hydroxyretinol **95**

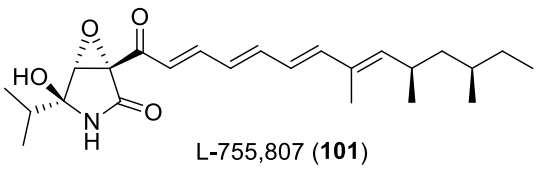
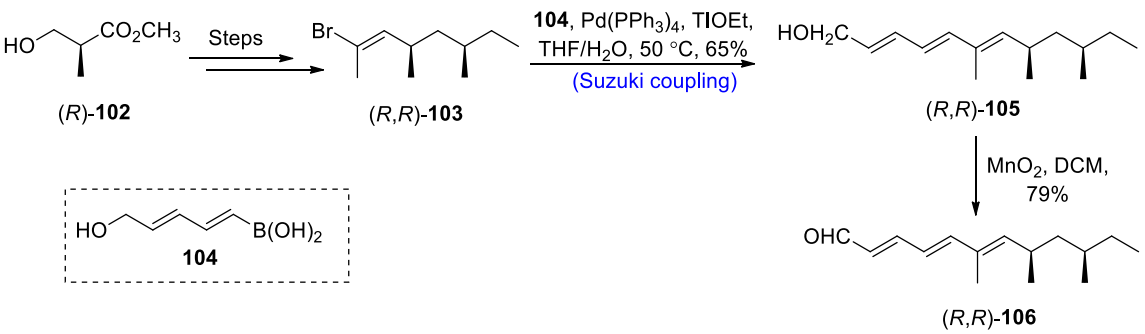


Fig. 13 Structure of L-755,807 **101**

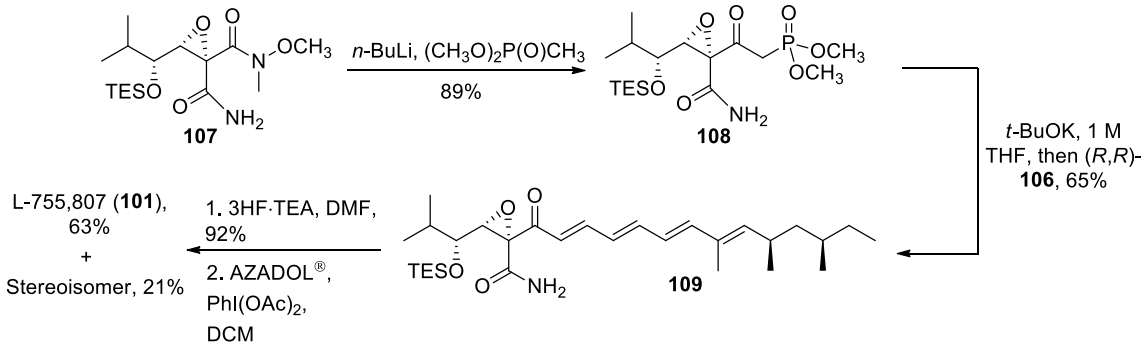
Pd_2dba_3, 43 mol% XPhos and CsF in refluxing dioxane for 17 h to form a common intermediate **115** in 64% yield. Furthermore, protocols such as hydrolysis (using aq. NaOH, CH_3OH) and aminolysis (using 4 M NH_3, CH_3OH) were implemented to obtain the structures of desired naturally occurring thiazole derivatives **110**–**113** in moderate to excellent yields (57–95%).

Fumimycin **116** (obtained from *Aspergillus fumisynnematus*) is an unusual metabolite bearing interesting alanine motif connected to a phenyl moiety at the α-carbon (Fig. 15). It showed peptide deformylase inhibitory potential with IC_{50} of 4.1 µM in addition to antibacterial activity [61].

Zaghouani et al. [62] gave a concise total synthesis of (±)-fumimycin **116** in 11.6% overall yield based on 7 steps by employing Suzuki coupling approach (Scheme 18). For this purpose, pyruvic acid **117** and phenol **118** underwent esterification using *N*,*N*'-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) followed by intramolecular aza-Friedel–Crafts cyclization (using Cbz-NH_2, 15 mol% TfOH) and regioselective chlorination (with *N*-chlorosuccinimide (NCS), 5 mol% Palau'Chlor) to give chlorobenzofuranone **119** in 76% yield. Decorated styrene **121** with complete *E*-selectivity in 73% yield was obtained by coupling of chlorobenzofuranone **119** with boronate **120** by using $Pd(OAc)_2$ (catalyst), SPhos (ligand), K_3PO_4 (base) in THF/H_2O at 60 °C. The synthesis of natural product **116** was achieved in 42% yield (over 3 steps) when styrene derivative **121** underwent Cbz-deprotection (with $Pd(OAc)_2$/Et_3SiH, trimethylamine (TEA)) followed by



Scheme 15 Synthesis of (*R*,*R*)-triene aldehyde **106**



Scheme 16 Completion of synthesis of L-755,807 **101**

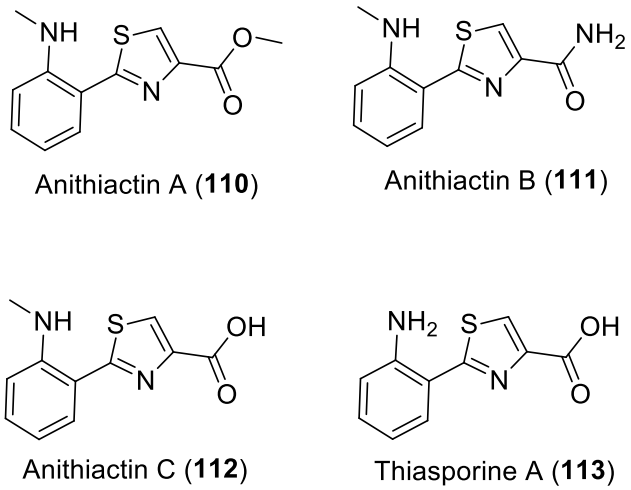


Fig. 14 Structures of anithiactin A **110**, anithiactin B **111**, anithiactin C **112** and thiasporine A **113**

fumaryl coupling (using fumaryl chloride) and hydrolysis (with silica/H_2O).

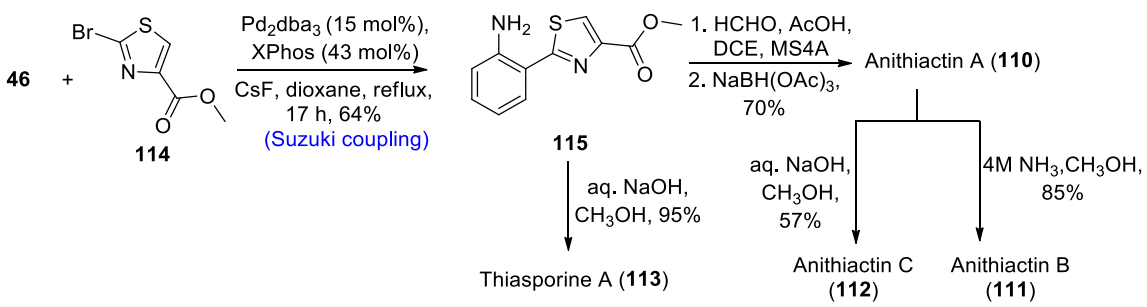
Sonogashira cross-coupling reaction

Numerous natural products contain alkynes as a fundamental component in their structure and Sonogashira cross-coupling is a vital approach to incorporate alkynes in the skeleton of a wide range of natural products [63]. This reaction includes coupling of a terminal alkyne with vinyl/aryl halide in the presence of palladium catalyst and copper additive as a co-catalyst. Under certain circumstances, copper additives may be harmful to reaction results for some substrates. To solve such kind of problems, copper-free Sonogashira coupling has also been discovered [64, 65]. Furthermore, Sonogahira coupling is employed for the building of bioactive compounds and electronic materials [66].

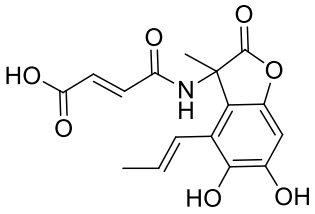
Synthesis of alkaloids

(±)-Aspergilline A **122** (extracted from *Aspergillus versicolor*) is a cyclopiazonic acid derived alkaloid with a rigid and highly oxygenated hexacyclic skeleton which is based on indole, tetrahydrofuran and tetramic acid moieties (Fig. 16). This natural product shows inhibitory activity against tobacco mosaic virus and moderate cytotoxicity in various human cell lines [67].

Nakhla and Wood [68] described the total synthesis of (±)-aspergilline A **122** in 16 steps by employing Sonogashira coupling in addition to various protocols such as oxidation, cyclization, [3 + 2] cycloaddition and Aldol reaction (Scheme 19). The synthesis was commenced from

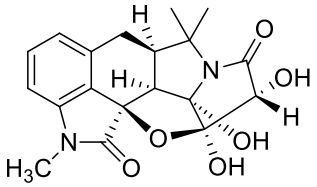


Scheme 17 Synthesis of thiazole derivatives **110**–**113**



(±)-Fumimycin (**116**)

Fig. 15 Structure of (±)-fumimycin **116**



(±)-Aspergilline A (**122**)

Fig. 16 Structure of (±)-aspergilline A **122**

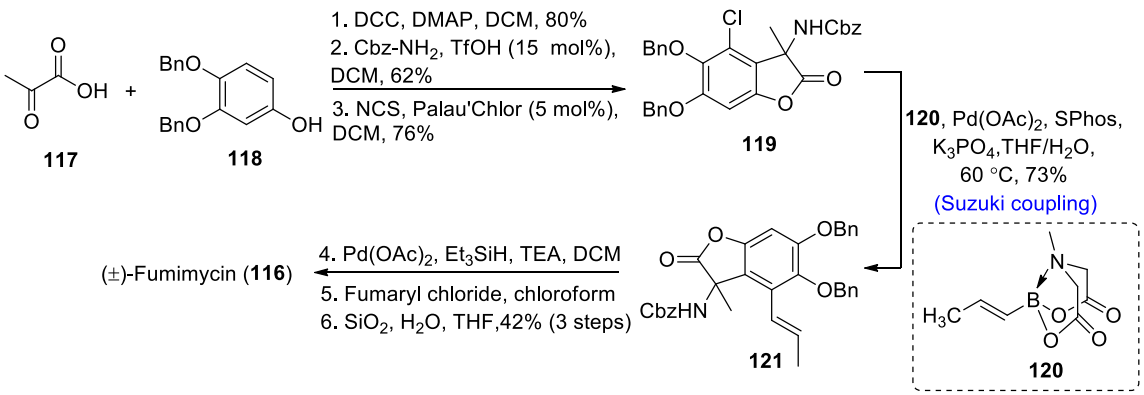
N-methylation of readily available bromoisatin 1**23** to obtain *N*-methylated product **124** (using CH_3I and K_2CO_3) in good yield (94%) which on coupling with propargyl amine **125** in the presence of 4 mol% $Pd(PPh_3)_4$, 8 mol% CuI, Cs_2CO_3 and *i*-Pr_2NEt (Hünig's base) in toluene at 85 °C gave isatin **126** in 72% yield. Aldol substrate **128** was prepared in 69% yield from acid chloride **127** by premixing it with *i*-Pr_2NEt followed by the addition of isatin **126**, Raney Ni and DMP. The compound **128** was further converted into (±)-aspergilline A **122** over several steps.

Cyclopiamide A **129** (obtained from *Penicillium cyclopium*) and speradine E **130** (obtained from *Aspergillus oryzae*) are *N*-methyl-2-oxindoles [69] having structural resemblance to alkaloid **122**. However, speradine E **130** consists of an additional β-dicarbonyl motif than cyclopiamide A **129** (Fig. 17).

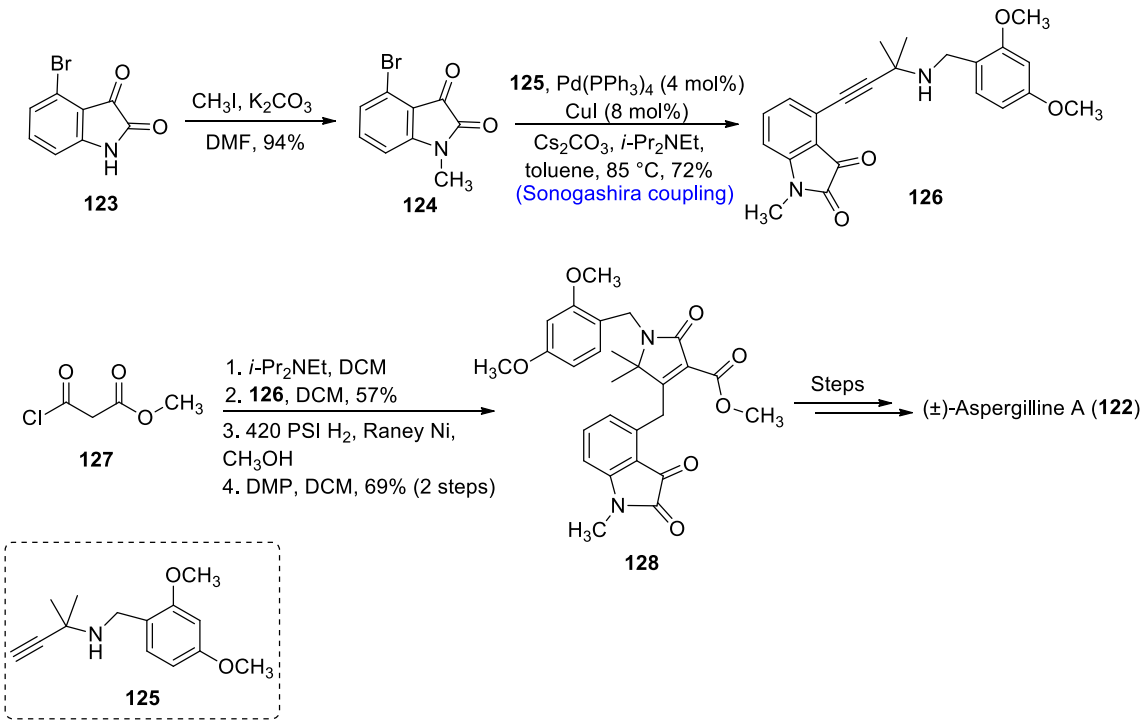
The preparation of cyclopiamide A **129** and speradine E **130** was described by Nakhla et al. [70] via a unified approach (Scheme 20). Isatin **126** (obtained from Sonogashira coupling) was advanced to pyrrolinone **132** (45%) by treating allyl malonyl chloride **131** with *i*-Pr_2NEt followed by the addition of isatin **126**. The compound **132** was treated with sodium hydride to get tetracycle **133** in 25% yield which in the presence of 1.2 mol% $Pd(PPh_3)_4$ and morpholine underwent decarboalkoxylation and dehydrative aromatization and the addition of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) furnished cyclopiamide A **129** in 93% yield. The framework of speradine E **130** was obtained in 54% yield from the reaction of methyl malonyl fluoride **134** with alkaloid **129**.

(+)-Anatoxin-a **135** and (+)-homoanatoxin-a **136** are natural alkaloids possessing distinctive structural features and strong biological properties that have made them a theme of considerable research work in synthetic and pharmacological studies (Fig. 18). These are extremely neurotoxic compounds generated during surface-water blooms by benthic and planktonic cyanobacteria. These compounds may prompt asphyxiation, respiratory paralysis and ultimately death as they function as neuromuscular blocking agents [71–74].

Addante-Moya et al. [75] reported an easy and systematic synthetic methodology for the construction of natural and unnatural enantiomers of anatoxin-a **135** and homoanatoxin-a **136** by utilizing ring opening reaction, cyclization, Sonogashira coupling and chemo- and regioselective hydration as key steps. 9-Oxabicyclo[6.1.0]non-4-ene **137** and chiral α-methylbenzylamine **138** reacted under microwave irradiation in methanol to give a mixture of diastereoisomeric amino-alcohols (-)-**139** and (+)-**140** in 34% and 34.2% yields, respectively (Scheme 21). Azabicyclo ketone (-)-**141** required for the accomplishment of natural enantiomers (+)-anatoxin-a **135** and (+)-homoanatoxin-a **136** was prepared from (-)-**139** over several steps. Enol triflate (+)-**142** produced from azabicyclo ketone (-)-**141**



Scheme 18 Synthesis of (±)-fumimycin **116**



Scheme 19 Synthesis of (±)-aspergilline A **122**

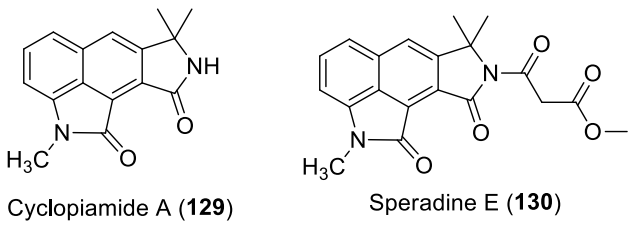
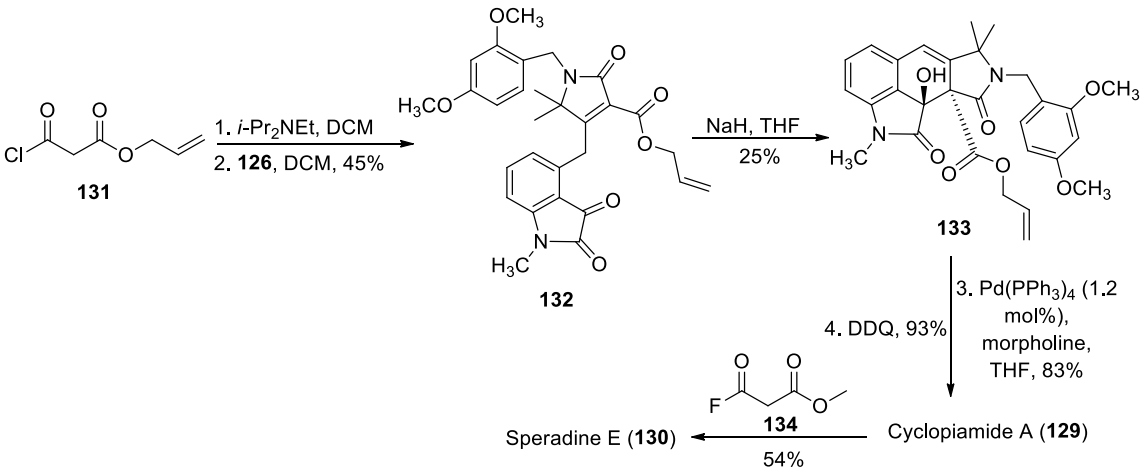


Fig. 17 Structures of cyclopiamide A **129** and speradine E **130**

(using potassium bis(trimethylsilyl)amide (KHMDS) and Comins' reagent) was coupled with trimethylsilyl enyne (for anatoxin-a) and propyne (for homoanatoxin-a) by loading $PdCl_2(PPh_2)_2$, CuI, TEA in DMF at room temperature to give corresponding compounds (-)-**143** (86%) and (-)-**144** (75%), respectively. Next, trimethylsilyl group of compound (-)-**143** was unmasked using K_2CO_3 in methanol followed by triple bond hydration (using HgO, boron trifluoride etherate,



Scheme 20 Synthesis of cyclopiamide A **129** and speradine E **130**

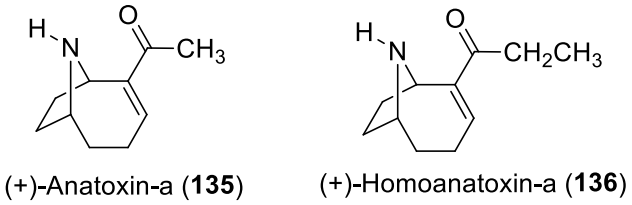
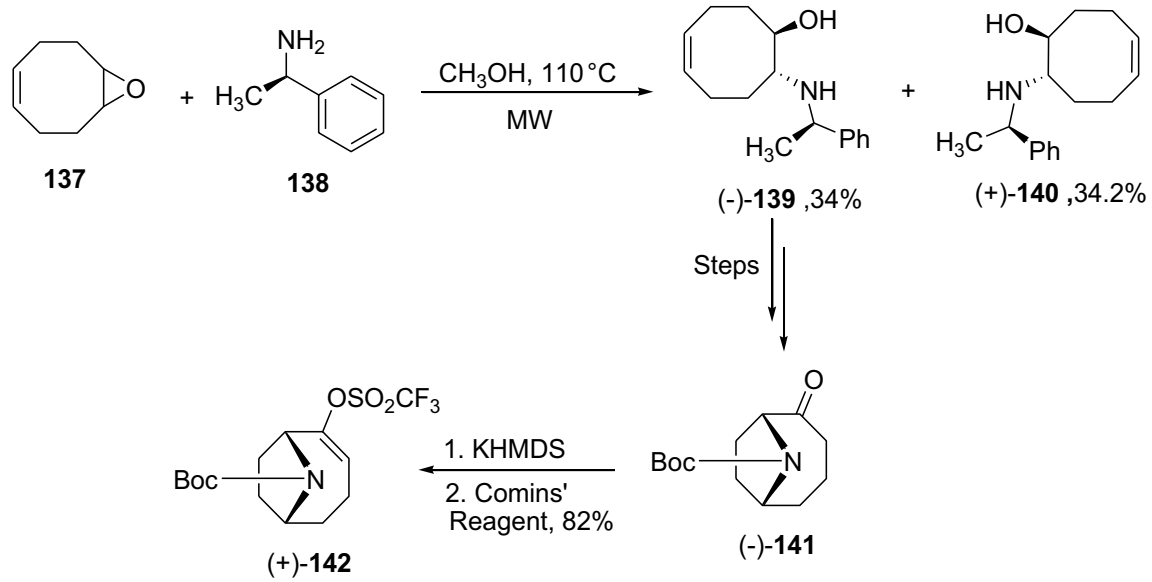
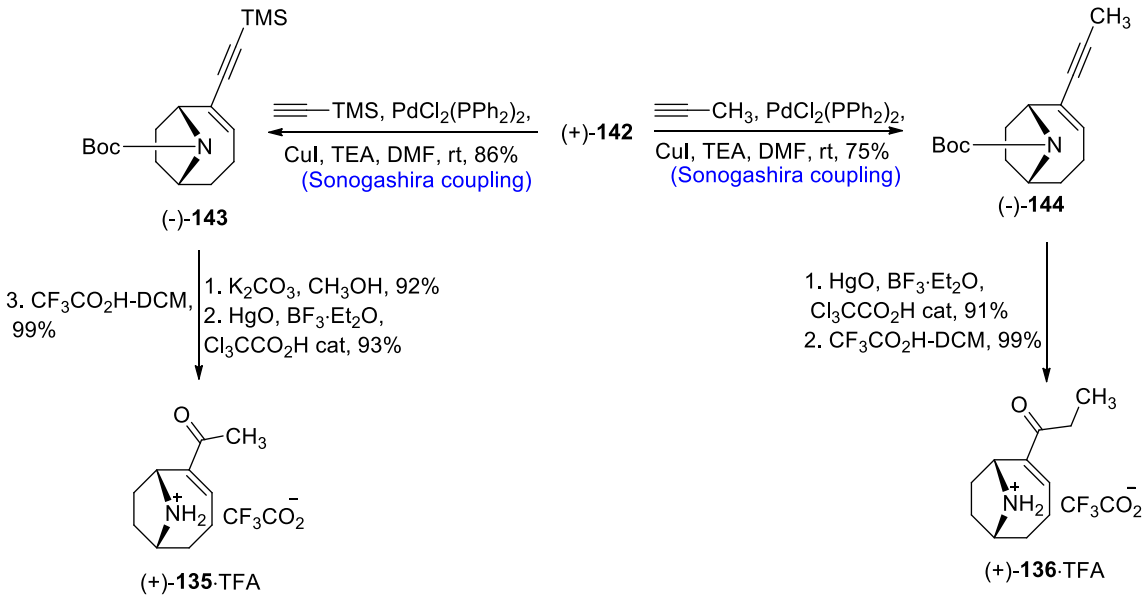


Fig. 18 Structures of (+)-anatoxin-a **135** and (+)-homoanatoxin-a **136**

trichloroacetic acid). The addition of trifluoroacetic acid cleaved Boc group and afforded trifluoroacetate salt of (+)-**135** in 99% yield. The final structure of homoanatoxin-a (+)-**136** was also achieved in 99% yield by using the similar conditions for the triple bond hydration and Boc deprotection (Scheme 22).



Scheme 21 Preparation of enol triflate (+)-**142**



Scheme 22 Synthesis of (+)-anatoxin-a **135** and (+)-homoanatoxin-a **136**

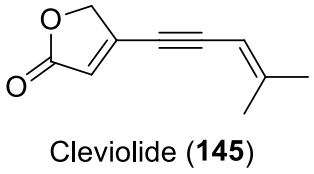


Fig. 19 Structure of cleviolide **145**

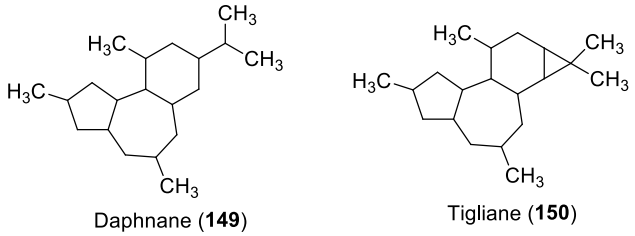


Fig. 20 Structures of daphnane **149** and tigliane **150**

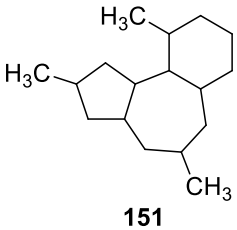
Synthesis of terpenoids

Cleviolide **145** is a first monoterpene isolated from *Senecio clevelandii* by Bohlmann et al. [76] It is reported as a precursor of two monoterpenes named *cis*-dihydrocleviolide (obtained from *S. clevelandii*) and *trans*-dihydrocleviolide (obtained from *Psathyrella scobinacea*) (Fig. 19) [77].

The three-step preparation of natural acetylenic monoterpene cleviolide **145** was described by Cheval et al. [78] in 40% overall yield via Sonogashira coupling (Scheme 23). Nosylate **146** bearing 2,5-dihydrofuran-2-one is a component of various natural products and has been utilized for the synthesis of cleviolide **145**. Nosylate **146** and 4-methylpentyn-3-ol **147** were reacted in the presence of $PdCl_2(PPh_3)_2$ as catalyst, CuI as co-catalyst and *i*-Pr_2NEt as base in acetonitrile to produce compound **148** in 67% yield. Treatment of compound **148** with diphosphorous pentaoxide in benzene gave the desired natural product cleviolide **145** in good yield (81%). Vinyl nosylates could be efficient coupling partners for Sonogashira coupling approach either in the presence of Cu or Ag salts and *p*-nitro substituted nosylate allowed this cross-coupling to be done at room temperature.

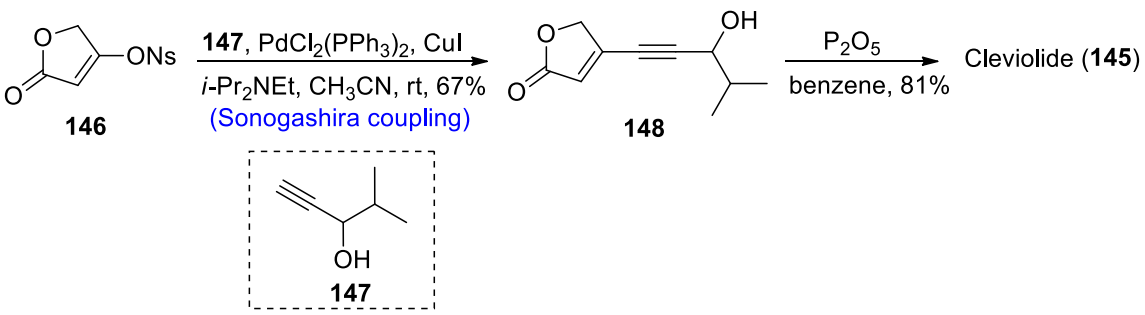
Over the years, natural products have been considered as valuable compounds in synthetic as well as therapeutic industry owing to the diversity in their chemical structures and biological capabilities. They are obtained from various species. In this regard, daphnane **149** and tigliane **150** have been extracted from *thymelaeaceae* and *euphorbiaceae* (Fig. 20). Daphnane and tigliane are structurally complex naturally occurring diterpenes comprising of [5–7-6] tricyclic carbon framework and these natural compounds are

Fig. 21 Common tricyclic core **151** of daphnane **149** and tigliane **150**

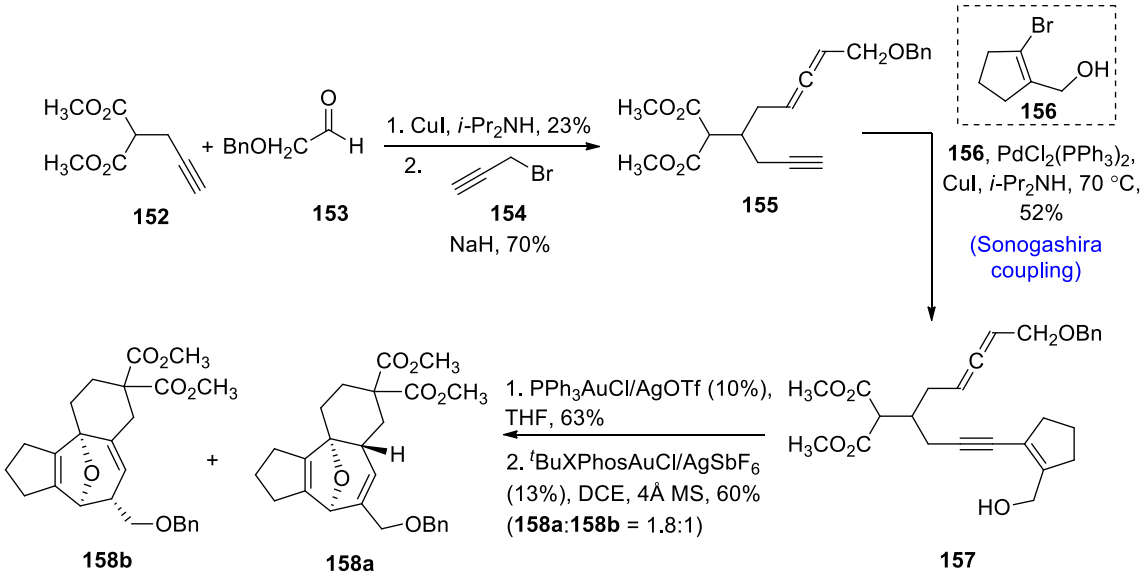


of great importance due to their antimalarial, antimicrobial, anti-HIV and neurotrophic properties [79, 80].

Dai et al. [81] reported a concise synthesis of common tricyclic carbon core **151** (Fig. 21) of daphnane and tigliane via Sonogashira coupling followed by gold catalyzed furan preparation and furan/allene [4 + 3] cycloaddition (Scheme 24). Synthesis was commenced from the reaction of aldehyde **153** with compound **152** in the presence of CuI and *i*-Pr_2NH followed by the addition of bromo moiety **154** and sodium hydride to produce fragment **155** in 70% yield. In the following step, allene **157** was obtained by the combination of compound **155** with fragment **156** (obtained from cyclopentanone) in the presence of palladium catalyst [$PdCl_2(PPh_3)_2$], CuI and *i*-Pr_2NH at 70 °C. The gold catalysis (with 10% $PPh_3AuCl/AgOTf$) followed by [4 + 3] cycloaddition (with 13% $^tBuXPhosAuCl/AgSbF_6$) of substrate **157** produced the target skeleton of diterpenes **158a** and **158b** in acceptable ratio (1.8:1). It was concluded that gold-catalyzed [4 + 3] cycloaddition could be used for the



Scheme 23 Synthesis of cleviolide **145**



Scheme 24 Synthesis of common tricyclic carbon core of daphnane and tigliane

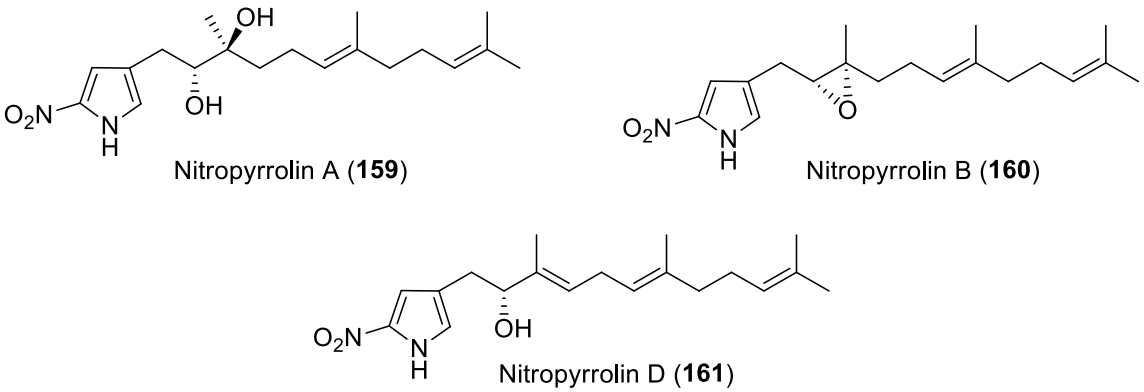
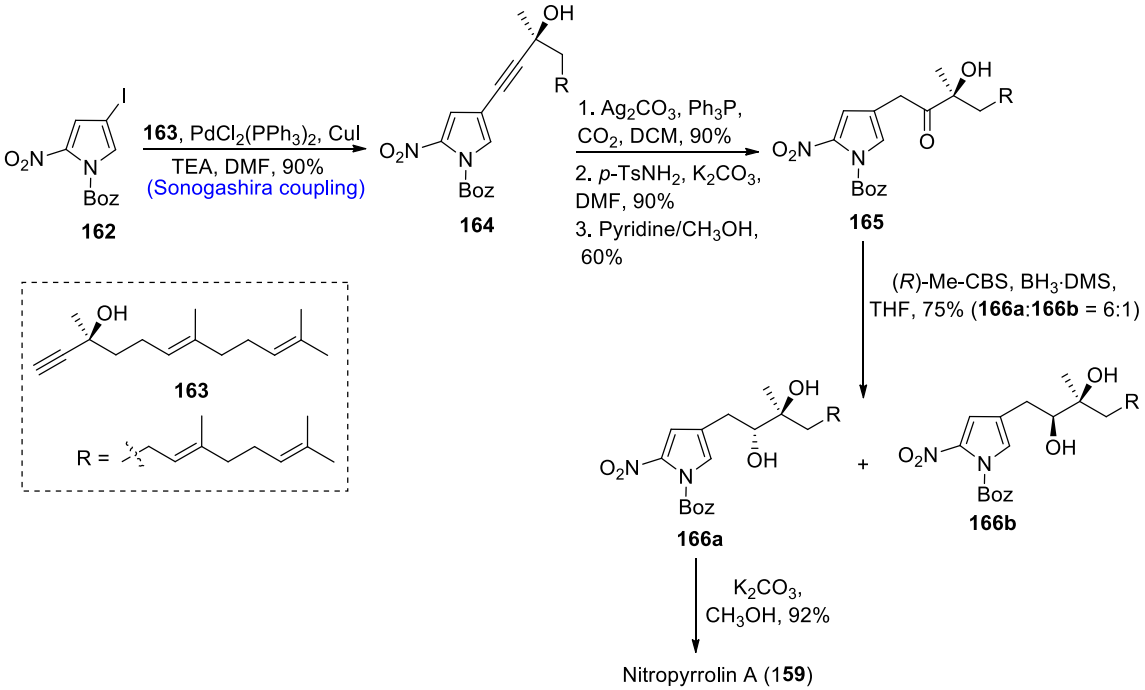


Fig. 22 Structures of nitropyrrolins A, B, D (**159**–**161**)

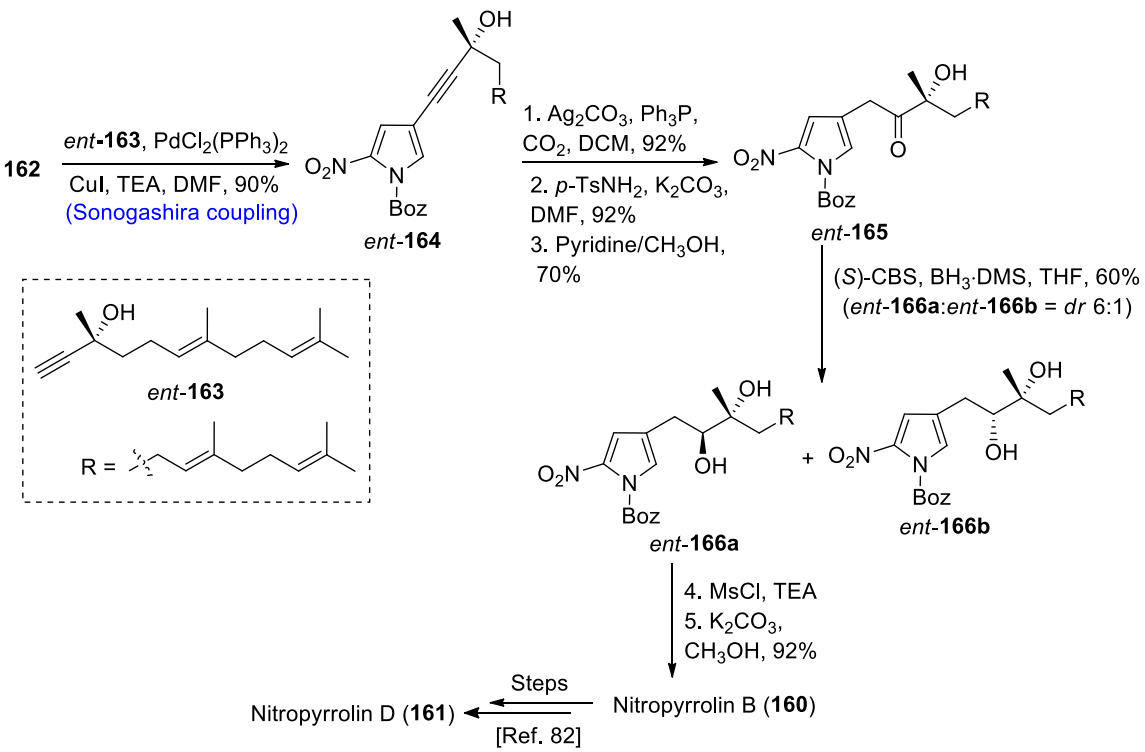
accomplishment of complex oxa-bridged polycyclic frameworks of natural products in a stereoselective way.

Fenical and co-workers in 2010 isolated secondary metabolites, nitropyrrolins A-E from CNQ-509 strain. Nitropyrrolin A **159**, nitropyrrolin B **160** and nitropyrrolin D **161** (hybrid isoprenoid natural products) showed cytotoxic activity toward human colon cancer cells with IC_{50} values 31.1 µM, 31.0 µM and 5.7 µM, respectively (Fig. 22) [82, 83].

Ding et al. [84] outlined a synthetic methodology for the synthesis of nitropyrrolins A, B, D via Sonogashira coupling approach for substituted pyrrole formation. This approach further involves carboxylative cyclization, sulfonylcarbamate preparation and deprotection protocol for the formation of hydroxyl ketone. The synthesis was commenced with the coupling of *N*-Boc protected iodide **162** with alkyne **163** using $PdCl_2(PPh_3)_2$, CuI, TEA in DMF to furnish pyrrole substrate **164** in 90% yield. Pyrrole **164** was subjected to carboxylative cyclization by using silver carbonate, PPh_3 in DCM to afford desired carbonate which was then treated with *p*-$TsNH_2$ and K_2CO_3 in DMF followed by refluxing in pyridine/CH_3OH afforded the required hydroxyl ketone **165** (60% yield). Next step involved the diastereoselective reduction of ketone **165** through Corey–Bakshi–Shibata reduction approach (using (*R*)-Me-CBS and BH_3·DMS) to give diols **166a** and **166b** with good diastereoselectivity (6:1). The final structure of natural product **159** was achieved in 92% yield by deprotection of Boz group of diol **166a** with aqueous K_2CO_3 in methanol (Scheme 25). Similarly, the skeleton of nitropyrrolin B **160** was constructed in 60% overall yield from *N*-Boz protected iodide **162** by employing Sonogashira coupling with *ent*-**163** in the presence of $PdCl_2(PPh_3)_2$ and diastereoselective reduction (with CBS) of *ent*-**165**



Scheme 25 Synthesis of nitropyrrolin A **159**



Scheme 26 Synthesis of nitropyrrolin B and D (**160**, **161**)

to furnish *ent*-**166a** which was subjected to one-pot epoxidation and mesylation (using MsCl, TEA) followed by deprotection of *N*-Boz group under mild conditions yielded nitropyrrolin B **160** in 92% yield. It was further transformed to nitropyrrolin D **161** as previously reported by Morimoto and coworkers [82] (Scheme 26).

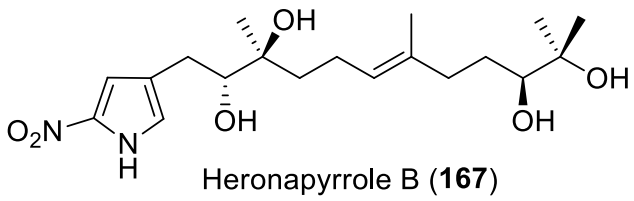
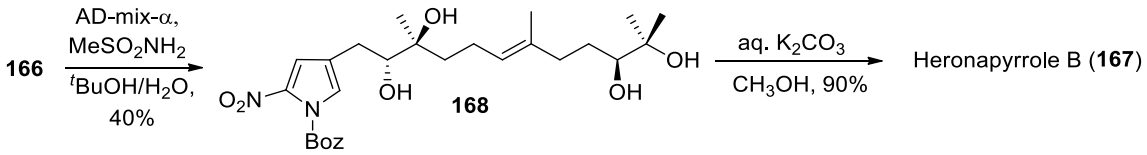


Fig. 23 Structure of heronapyrrole B **167**

antibacterial activity against Gram-positive bacteria (*S. aureus*, *B. subtilis*) (Fig. 23) [87].

The synthesis of nitropyrrolin A **159** and heronapyrrole B **167** through Sonogashira coupling was reported by Ding et al. [88] (Scheme 27). Heronapyrrole B **167** was accomplished in 90% yield by treating compound **166** (prepared from iodide **162**) with AD-mix-α, $MeSO_2NH_2$ in *tert*-butanol/water mixture followed by deprotection of Boz group with aq. K_2CO_3 in methanol.



Scheme 27 Synthesis of heronapyrrole B **167**

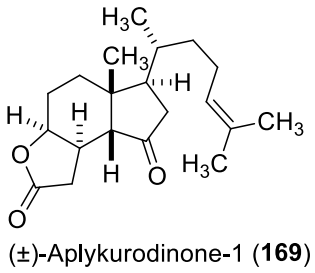
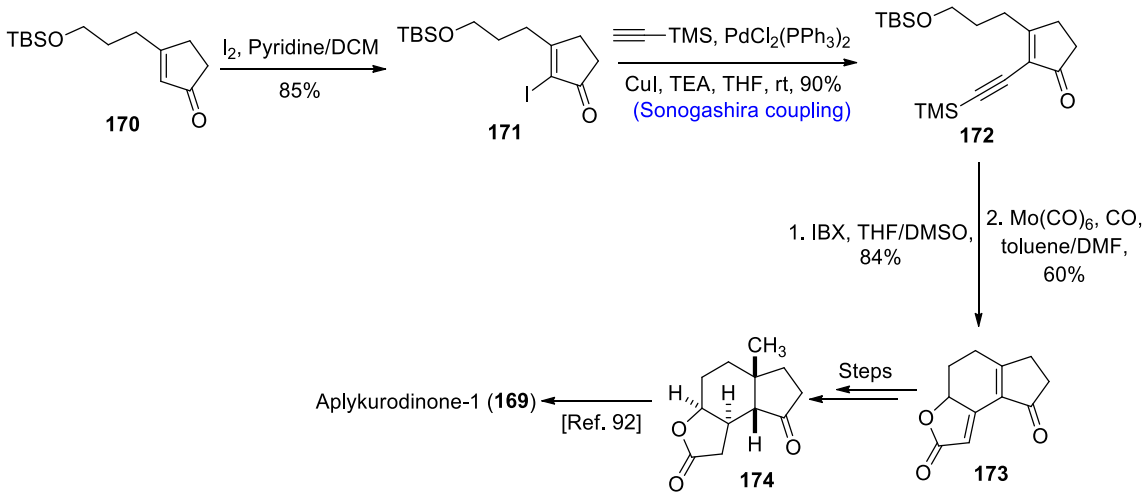


Fig. 24 Structure of (±)-aplykurodinone-1 **169**

Synthesis of steroids

Among all the categories of natural products, steroids have played a vital role in evoking latest ideas in total synthesis. A significant amount of knowledge has been added to organic chemistry in the context of tracking suggestions for the assembly of fragments to form steroids. Evidently, this curiosity continues to present day. Aplykurodine obtained from mollusks represents a class of most degraded steroids and (±)-aplykurodinone-1 **169** (extracted from *Synphonota geographica*) belongs to this family of natural products. Its



Scheme 28 Synthesis of aplykurodinone-1 **169**

Heronapyrrole B **167** is a secondary metabolite obtained from CMB-M0423 strain of *Streptomyces* sp. by Capon research group [85, 86]. This natural product shows

skeleton consists of a *cis*-fused ring with epimeric C_8, an unsaturated side chain [89] and six contiguous stereocenters (Fig. 24) [90].

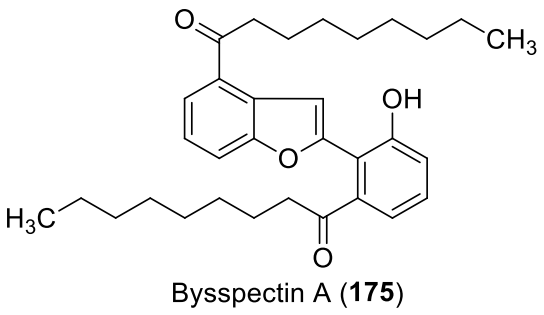


Fig. 25 Structure of bysspectin A **175**

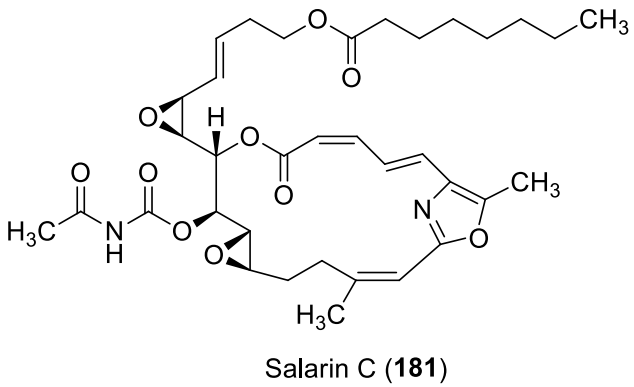


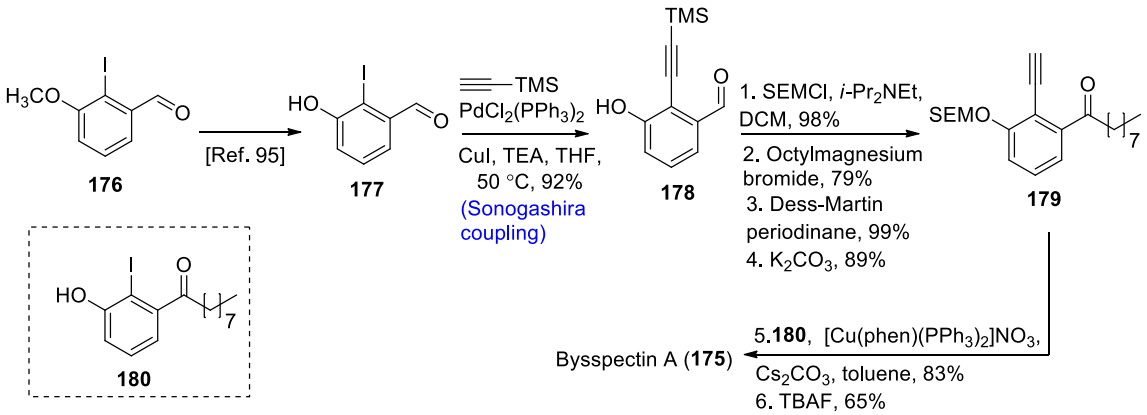
Fig. 26 Structure of salarin C **181**

Tao et al. [91] reported a highly efficient formal synthesis of (±)-aplykurodinone-1 **169** via one pot hetero-Pauson–Khand reaction (*h*-PKR), desilylation and Sonogashira coupling as key steps (Scheme 28). *h*-PKR has rare applications in the formation of natural products; however it is known as a convenient method to shape butenolides and α,β-unsaturated lactams. The synthesis was commenced with the iodination of enone **170** (using iodine, pyridine in DCM) to afford vinyl halide **171** in good yield (85%). Then, vinyl iodide **171** underwent Sonogashira coupling with TMS-acetylene in the presence of $PdCl_2(PPh_3)_2$, CuI, TEA as base in THF at room temperature to give 2-alkynyl-2-cyclopentanone **172** (90% yield). The compound **172** was treated with 2-iodobenzoic acid (IBX) in DMSO/THF for TBS deprotection followed by the addition of $Mo(CO)_6$, CO in toluene/DMF to perform one pot cycloaddition and desilylation to produce tricyclic compound **173** in 60% yield. The formal synthesis of (±)-aplykurodinone-1 **169** was achieved by converting tricyclic compound into required enone **174** (20% overall yield) over several steps. The final framework of natural product **169** with high stereoselectivity was established through Micheal addition [92] of enone **174**.

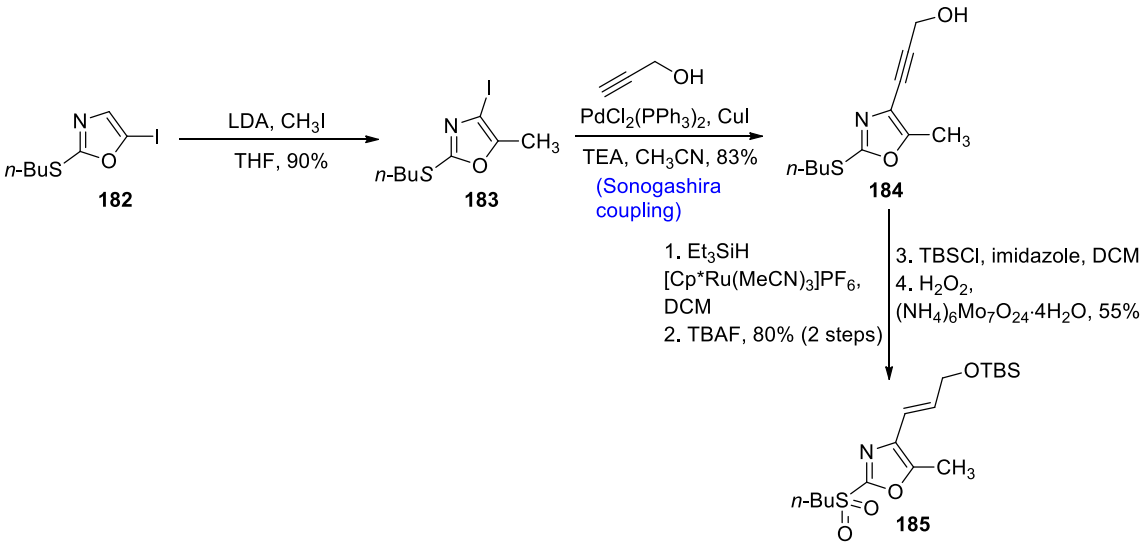
Synthesis of polyketides

Bysspectin A **175** is a polyketide-derived octaketide dimer isolated from endophytic fungus (*Byssochlamys spectabilis*) and consists of a unique carbon skeleton based on two hydrophobic ketone chains and 2-phenylbenzofuran motif (Fig. 25). It acts as an inhibitor against hCE2 (human carboxylesterase) owing to its hydrophobic nature [93].

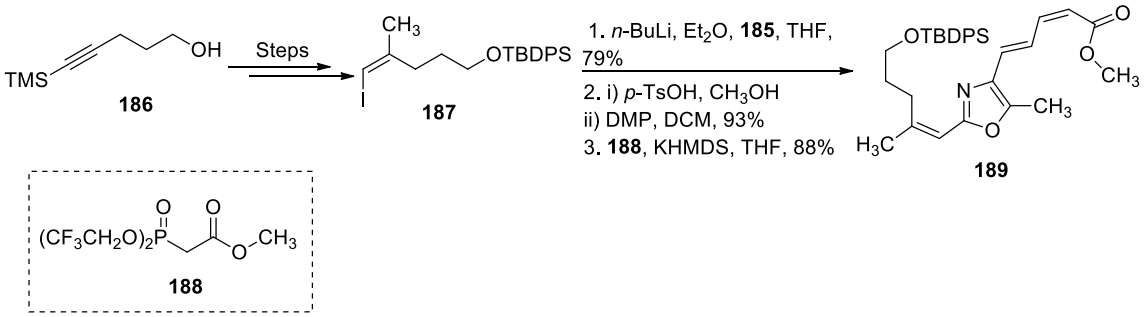
Yang et al. [94] designed the synthetic strategy for bysspectin A **175** for the first time and utilized copper catalyzed domino Sonogashira cyclization to obtain the targeted product with 7.7% overall yield (Scheme 29). In order to complete the synthesis, compound **177** was obtained from **176** [95] and was further converted into compound **178** in 92% yield via Sonogashira coupling using trimethylsilyl acetylene, $PdCl_2(PPh_3)_2$, CuI, TEA in THF at 50 °C. Phenolic hydroxyl group of compound **178** was protected (using SEMCl, *i*-Pr_2NEt) followed by the addition of octylmagnesium bromide, Dess–Martin periodinane (DMP) and potassium carbonate to form terminal alkyne **179** in good yield (89%). Then, domino Sonogashira cyclization was done between terminal alkyne **179** and fragment **180**



Scheme 29 Synthesis of bysspectin A **175**



Scheme 30 Synthesis of trisubstituted *n*-butanesulfonyloxazole **185**



Scheme 31 Synthesis of partial section **189** of salarin C

in the presence of $[Cu(phen)(PPh_3)_2]NO_3$, Cs_2CO_3 in toluene to obtain benzofuran ring in 83% yield. Deprotection of SEM group with *tetra*-*n*-butylammonium fluoride (TBAF) afforded the required product **175** in 65% yield.

Synthesis of macrolides

Salarins are marine macrolides extracted from Madagascan sponge (*Facaplysinopsis* sp.) comprising of 17-membered lactone set with a trisubstituted oxazole or a trisacylamine core. Salarin C **181** (a nitrogenous macrolide) isolated by Kashman and coworkers belongs to this class and acts as antiproliferative agent (Fig. 26) [96, 97].

Schäckermann and Lindel [98] reported the synthesis of eastern portion **189** of salarin C **181** by employing halogen dance reaction to join the trisubstituted oxazole ring. In the first step, methylation of oxazole **182** was done with CH_3I to furnish trisubstituted oxazole **183** in 90% yield which in the next step was coupled with propargyl alcohol in the presence of $PdCl_2(PPh_3)_2$, CuI, TEA in acetonitrile

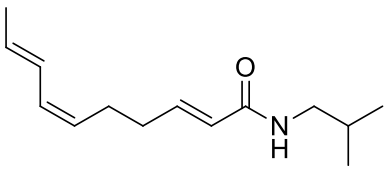
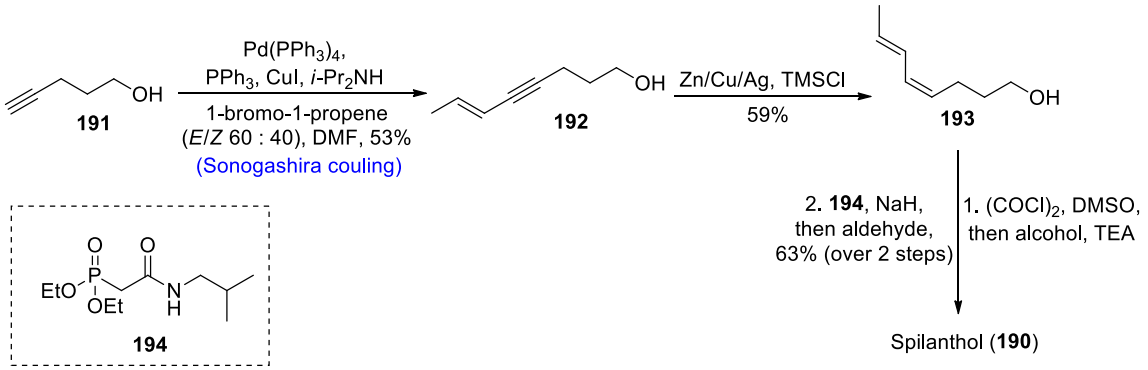


Fig. 27 Structure of spilanthol **190**

to give compound **184** in 83% yield. Hydrosilylation of compound **184** with Et_3SiH $[Cp^*Ru(MeCN)_3]PF_6]$ and desilylation with TBAF was performed to get allylic alcohol. Trisubstituted *n*-butanesulfonyloxazole **185** was prepared from allylic alcohol by *O*-silylation (TBSCl, imidazole) followed by oxidation (H_2O_2, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$) (Scheme 30). Then, trisubstituted *n*-butanesulfonyloxazole **185** was coupled with (*Z*)-iodoalkene **187** (prepared from TMS-protected alkyne **186**) in the presence of *n*-BuLi followed by the addition of *p*-TsOH in methanol and DMP in



Scheme 32 Synthesis of spilanthol **190**

DCM to form unsaturated aldehyde in good yield (93%). Phosphonate **188** was used for the Still Gennari olefination of aldehyde (using KHMDS in THF) to accomplish the partial segment **189** (bisalkenyloxazole) of salarin C **181** in 88% yield (Scheme 31). Additionally, photooxidation of bisalkenyloxazole was carried out by using singlet oxygen which supported Kashman's hypothesis of conversion of salarin C to salarin A.

Synthesis of alkamides

Alkamides are secondary metabolites obtained from various plant families and constitute a well-defined class of natural compounds in which peptide bonding connects unsaturated fatty acids with different amino acids. Tingling and pungent effects are the characteristic features of this class. Spilanthol (affinin) **190** is a familiar bioactive alkamide which has been extracted from plants of Asteraceae family and it also produces numbing, tingling, pungency and mouth-watering effects. According to scientific research, it exhibits a variety of biological activities such as antimicrobial, antimutagenic and insecticidal, etc. (Fig. 27) [99].

Alonso et al. [100] reported the synthesis of spilanthol **190** in five steps via Sonogashira coupling, *Z*-selective alkyne semi-reduction and HWE as main steps (Scheme 32). During the connection of double bonds, control of alkene geometry was maintained in the synthetic route. The first step in synthetic strategy involved the Sonogashira coupling of alcohol **191** with 1-bromo-1-propene in the presence of $Pd(PPh_3)_4$, PPh_3, CuI, diisopropanolamine (DIPA) in DMF to afford the compound **192** (53%) which was further transformed to a diene **193** (59% yield) by using Zn/Cu/Ag in the presence of TMSCl through *Z*-selective alkyne semi-reduction. Later, alcohol **193** underwent Swern oxidation followed by the addition of phosphonoacetamide **194** to crude aldehyde to accomplish the synthesis of **190** in 63% yield. Moreover, it was found that spilanthol could be an advantageous contemporary anesthetic in medical field.

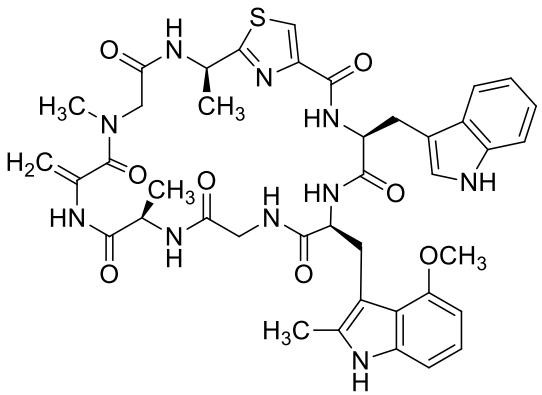


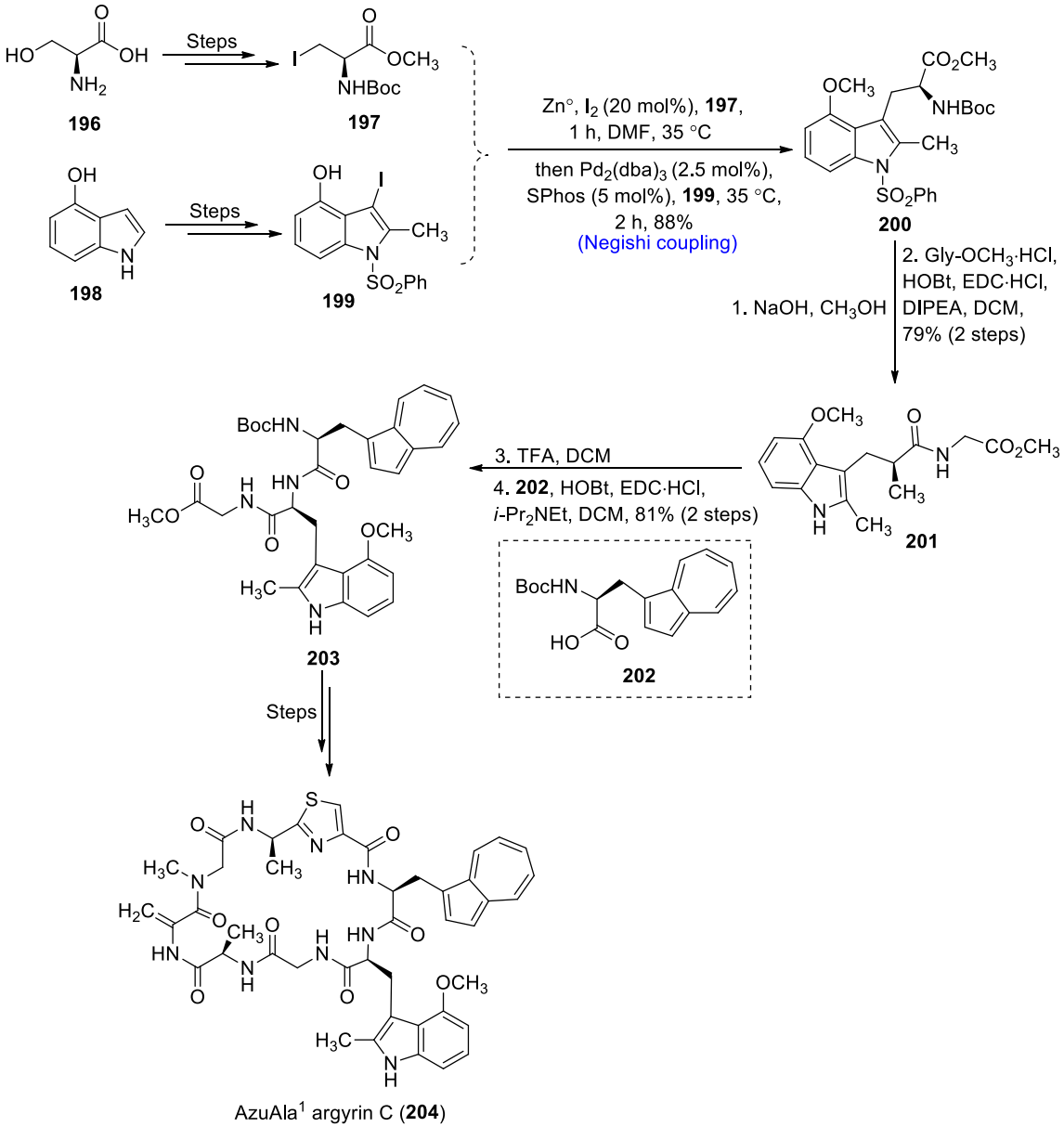
Fig. 28 Structure of argyrin C **195**

Negishi cross-coupling reaction

After the revelation of palladium catalyzed Negishi coupling of aryl/vinyl chlorides by Fu and co-workers [101], a significant success has been made in developing new catalytic methodologies related to this approach. It involves the use of organozinc reagent as a coupling partner and immensely utilized to compose natural products [102]. It implies mild reaction conditions with advantage of low toxicity of readily available organozinc substrates and their fast transmetalation to palladium. In some cases, other metal catalyst systems containing nickel, iron, copper or cobalt are also used instead of palladium-based catalyst [103, 104].

Synthesis of macrocycles

Argyrins are macrocyclic natural products which have been isolated from myxobacteria in 2002 by Sasse et al. These are



Scheme 33 Synthesis of AzuAla[1] argyrin C **204**

known as heptapeptides based on thiazole heterocycle and tryptophan amino acid. Biological interpretation showed that these compounds act as cytotoxic and immunosuppressant agents, etc. (Fig. 28) [105, 106].

For the first time, Stempel et al. [107] carried out an efficient and short synthesis of AzuAla[1] argyrin C **204** in a stereocontrolled manner by incorporating Negishi coupling reaction (Scheme 33). By keeping in consideration to track and detect bioactive compounds by using non-invasive probes, β-(1-azulenyl)-L alanine (termed as AzuAla[1], unnatural deep blue amino acid) was prepared with fluorescent/photophysical features and then utilized it for the preparation of natural product **204**. Iodoalanine **197** (obtained from alanine **196**) was converted into organozinc reagent by using zinc and 20 mol% iodine that underwent Negishi coupling with *C*3-iodinated compound **199** (prepared from indole **198**) in the presence of 2.5 mol% $Pd_2(dba)_3$ as catalyst and 5 mol% SPhos as ligand at 35 °C to give compound **200** in 88% yield. Compound **200** was saponified (sodium hydroxide, methanol) with subsequent benzenesulfonyl group cleavage and addition of glycine methyl ester to produce dipeptide **201** in good yield (79%). Next, the dipeptide **201** was fused with fragment **202** to give tripeptide unit **203** (81% yield) which over several steps gave Azuala[1] argyrin

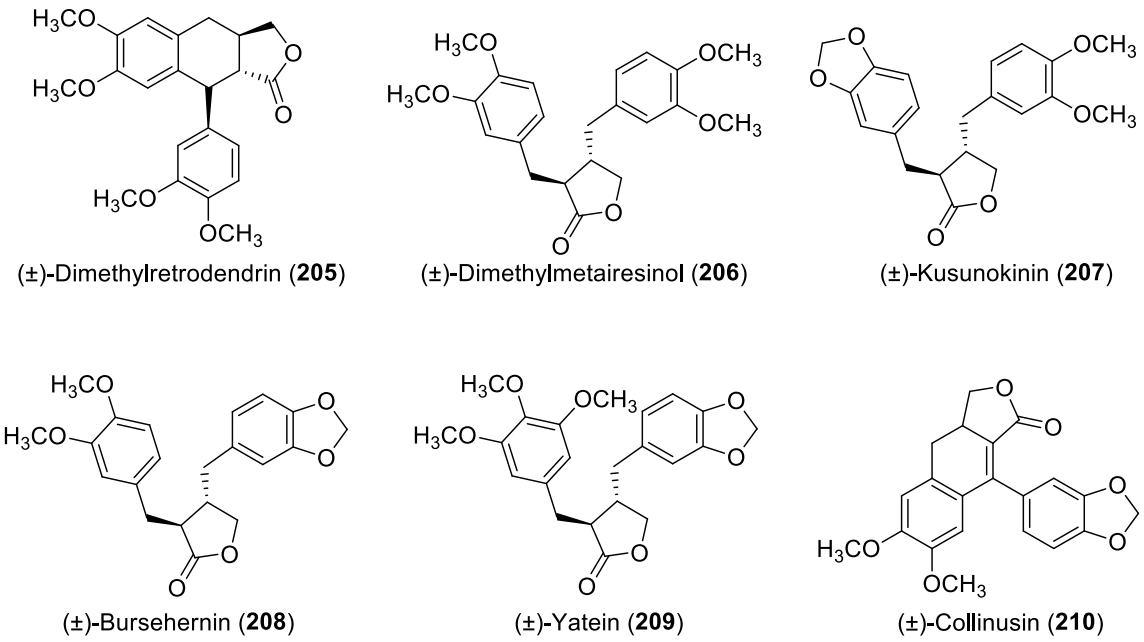
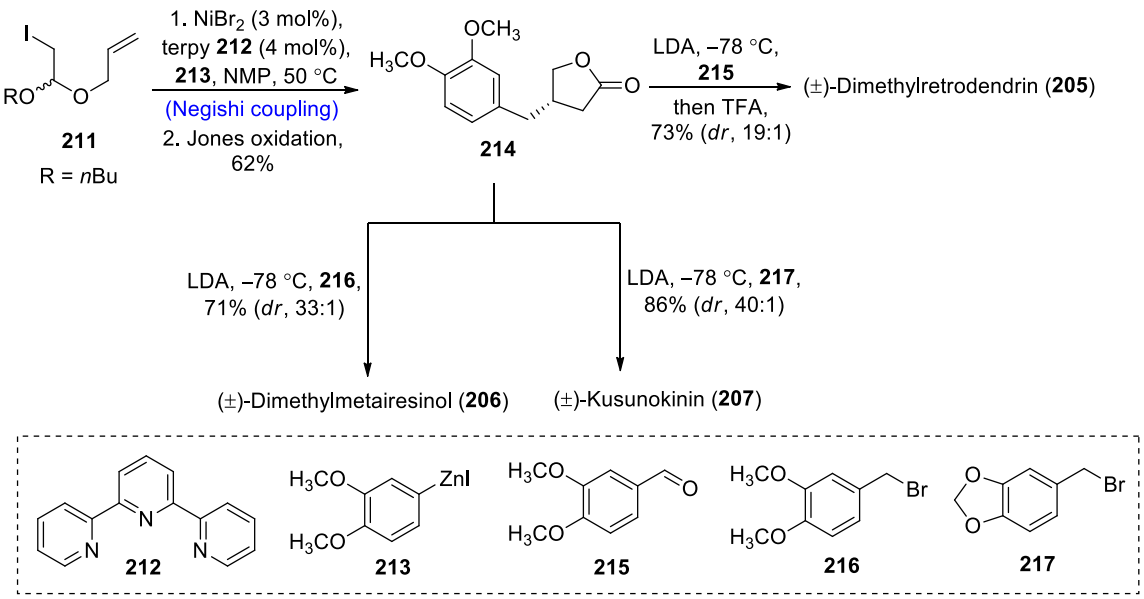


Fig. 29 Structures of lignan natural products (**205**–**210**)



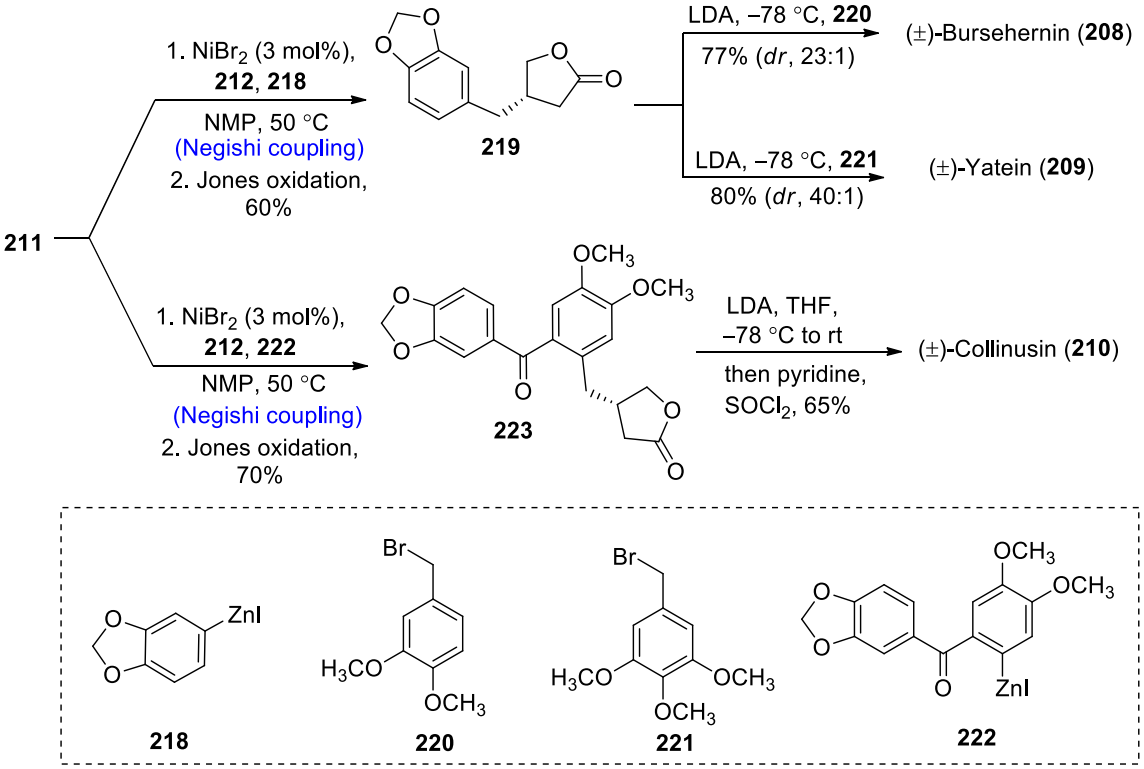
Scheme 34 Synthesis of (±)-dimethylretrodendrin **205**, (±)-dimethylmetairesinol **206**, (±)-kusunokinin **207**

C **204**. Nevertheless, it was the first synthetic approach to introduce fluorophore group such as AzuAla[1] in complex natural product.

Synthesis of lignans

Lignan natural products; (±)-dimethylretrodendrin **205**, (±)-dimethylmetairesinol **206**, (±)-kusunokinin **207**, (±)-bursehernin **208**, (±)-yatein **209**, (±)-collinusin **210** bearing dibenzylbutyrolactone and aryltetralin cores are associated with anti-tumour, anti-viral, fungicidal, antibiotic and anti-HIV activities (Fig. 29) [108, 109].

KC et al. [110] reported regioselective dicarbofunctionalization of unactivated olefins via Ni-catalyzed tandem cyclization/Negishi cross-coupling and implemented this methodology to construct the skeletons of six lignan



Scheme 35 Synthesis of (±)-bursehernin **208**, (±)-yatein **209**, (±)-collinusin **210**

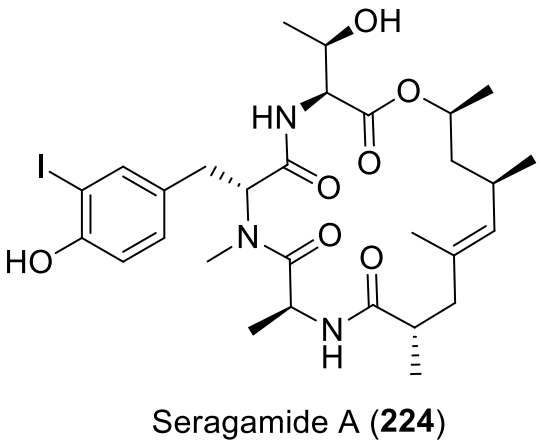


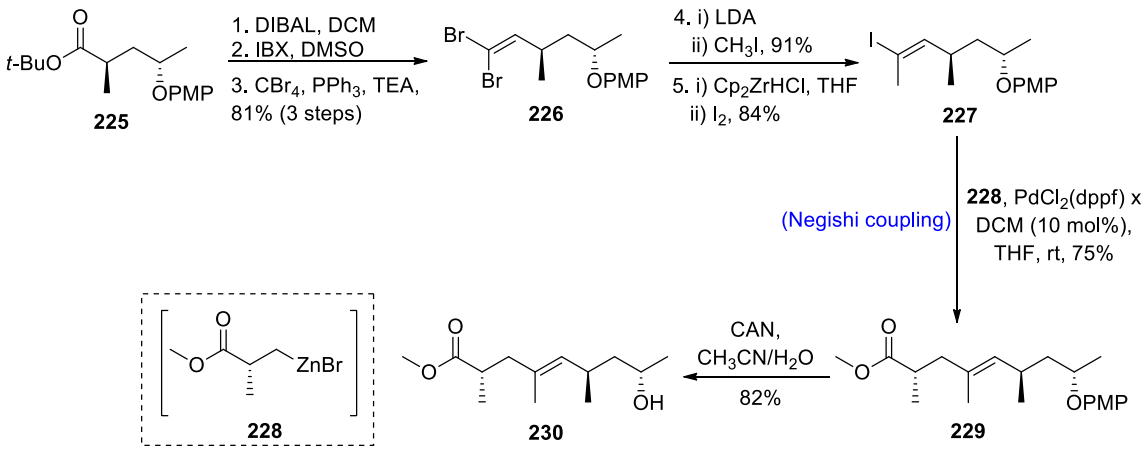
Fig. 30 Structure of seragamide A **224**

natural products (**205**–**210**) in good yields (65–86%) and diastereoselectivities (*dr*, 19:1–40:1). For this purpose, organozinc reagent **213** and substrate **211** were coupled in the presence of $NiBr_2$, terpy **212** in *N*-methyl-2-pyrrolidone (NMP) at 50 °C followed by Jones oxidation to produce lactone **214** in 62% yield. Lactone **214** on treatment with fragments **215**, **216** and **217** after subjection to lithium diisopropylamide (LDA) gave natural products **205** (73%), **206** (71%) and **207** (86%), respectively (Scheme 34). The same procedure was repeated for the accomplishment of remaining lignans **208**–**210** by employing different organozinc reagents **218** and **222** (Scheme 35).

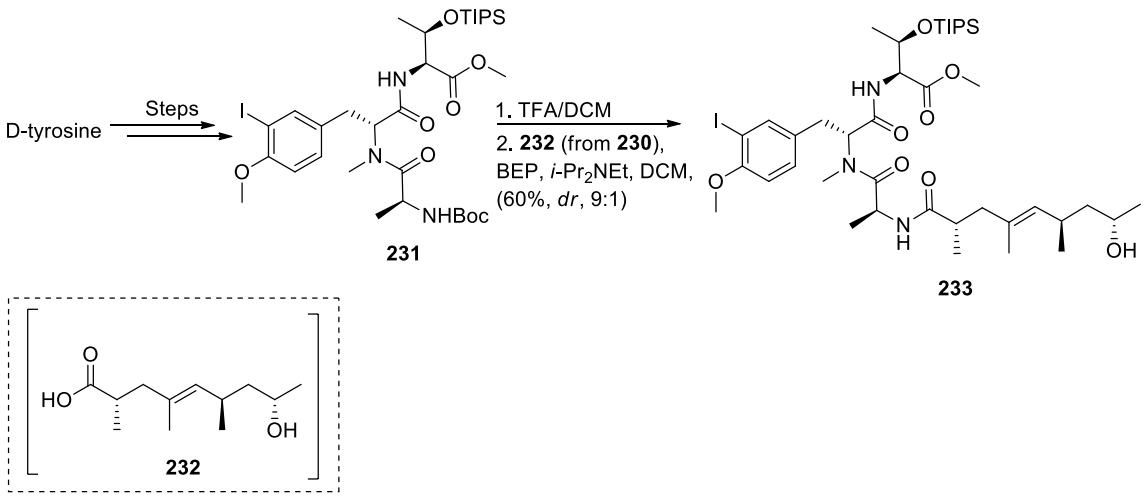
Synthesis of polyketides

Seragamide A **224** was isolated from *Suberites japonicas* (Okinawan sponge) as a cytotoxic metabolite having peptide motif. It plays a vital role in the polymerization of G-actin and stabilizes F-actin filaments (Fig. 30) [111].

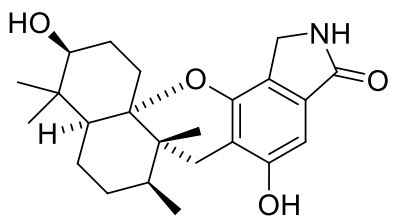
Lang and Lindel [112] disclosed the synthesis of polyketide Sect. **230** of seragamide A **224** via Negishi coupling reaction. *tert*-Butyl ester **225** (obtained from enantiomerically pure (*R*)-propylene oxide) was subjected to reduction (DIBAL-H) followed by oxidation and Corey-Fuchs reaction (CBr_4, PPh_3, TEA) to access dibromoalkene **226** (81%). Then, the compound **226** was treated with LDA followed by methylation (using CH_3I) and hydrozirconation/iodination (with Cp_2ZrHCl and I_2) to get (*E*)-olefin **227** in 84% yield with perfect stereo- and regioselectivity. Olefin **227** was coupled with organozinc homoenolate **228** (prepared from β-bromopropionic acid ester) in the presence of $PdCl_2$(dppf) x DCM at room temperature to produce compound **229** in 75% yield which on subjection with ceric ammonium nitrate (CAN) afforded polyketide portion **230** (82%) (Scheme 36).



Scheme 36 Synthesis of polyketide section **230** of seragamide A **224**



Scheme 37 Synthesis of tripeptide-polyketide **233** of seragamide A **224**



Stachyflin (**234**)

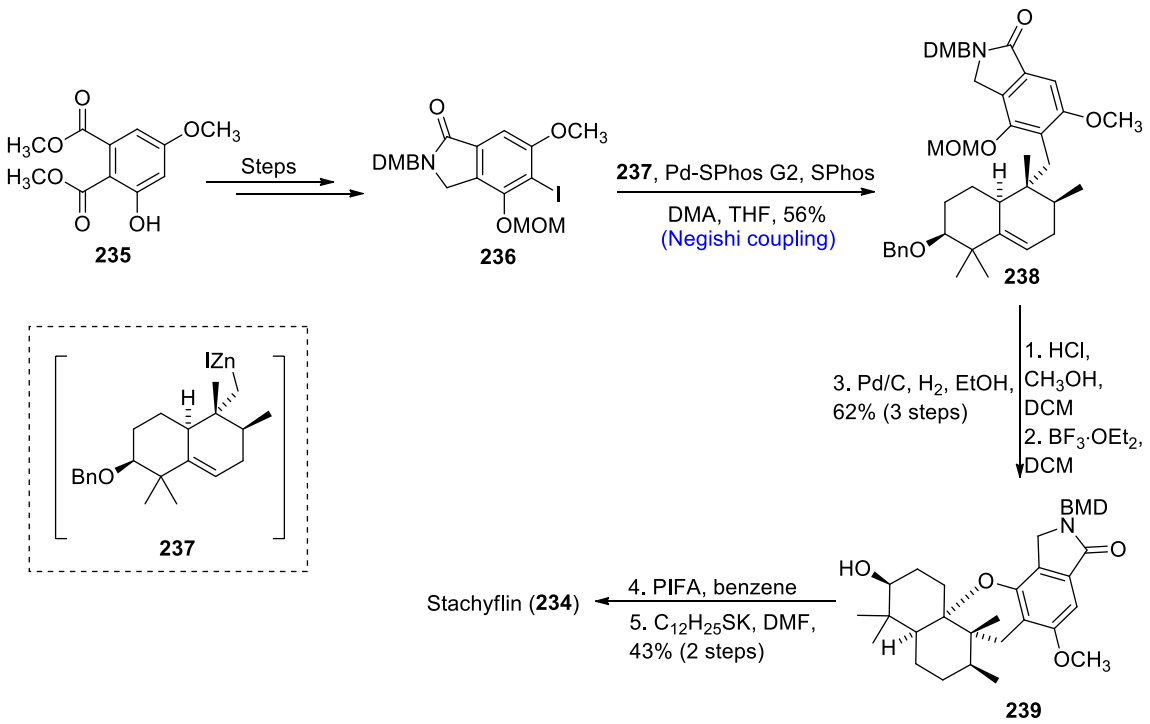
Fig. 31 Structure of stachyflin **234**

Further, tripeptide Sect. **231** of seragamide **224** was synthesized by using D-tyrosine as starting material that was converted to tripeptide **231** over several steps which in the presence of TFA/DCM followed by the addition of BEP, *i*-Pr_2NEt in DCM was fused with polyketide unit **232** (from **230**) to give pepetide-polyketide **233** (60%) with higher diastereoselectivity (*dr*, 9:1) than tripeptide fragment **231** (*dr*, 4:1) (Scheme 37).

Synthesis of terpenoids

Stachyflin **234** possessing *cis*-fused rings and an ethereal bond is a terpenoid and shows anti-influenza A virus activity with EC_{50} value of 0.003 µM. Its biological potential and structural features have made it a fascinating molecule in synthetic chemistry (Fig. 31) [113].

Haut et al. [114] and Wildermuth et al. [115] independently reported a total synthesis of (+)-stachyflin **234** through sp^2-sp^3 Negishi cross-coupling reaction of isoindolinone **236** with dehydrodecalin **237** in the presence of Pd-SPhos G2 catalyst, SPhos ligand and dimethylacetamide



Scheme 38 Synthesis of stachyflin **234**

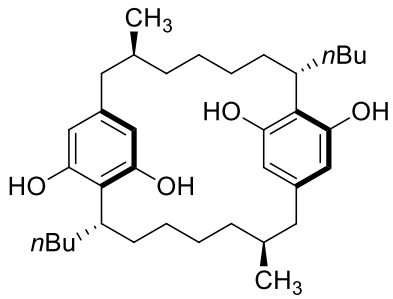


Fig. 32 Structure of (−)-cylindrocyclophane F **240**

(DMA) base in THF to furnish compound **238** in 56% yield (Scheme 38). Cleavage of MOM-ether group (with HCl), cationic cyclization (with $BF_3{\cdot}OEt_2$) and hydrogenation (with H_2, Pd/C) gave *cis*-fused decalin **239** (62% over 3 steps) which on treatment with PIFA in benzene and demethylation by potassium *n*-dodecanthiolate provided required (+)-stachyflin **234** (43% over 2 steps).

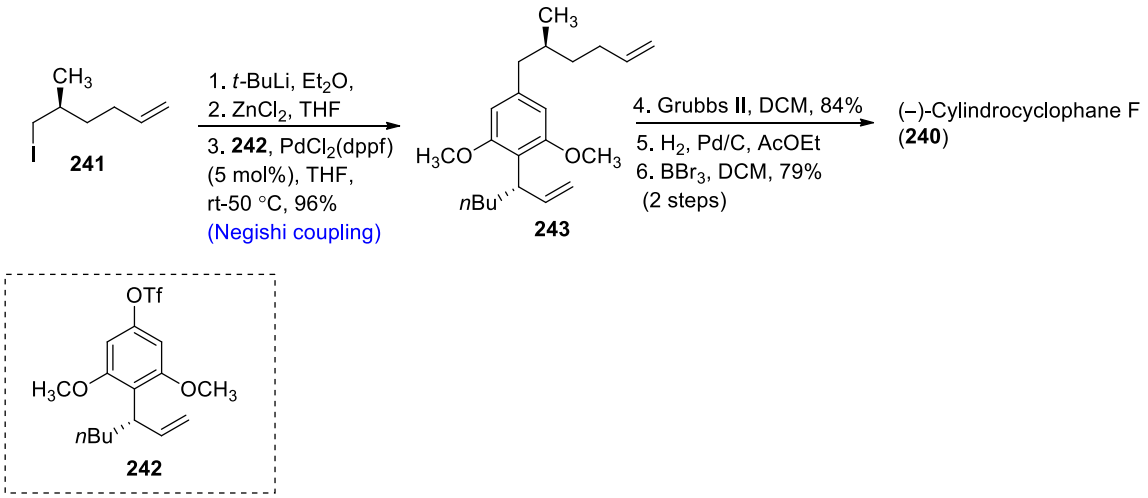
Miscellaneous

In 1990, first naturally occurring paracyclophanes were extracted from blue-green algae and contained 22-membered cyclic infrastructure exhibiting cytotoxic potential against tumor cell lines (KB and LoVo) with IC_{50} value 2–10 µg/mL. (−)-Cylindrocyclophane F **240** belongs to these types of natural products (Fig. 32) [116–118].

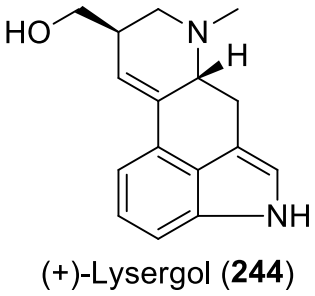
Berthold and Breit [119] reported a short and convergent route for the preparation of (−)-cylindrocyclophane F **240** using Pd-catalyzed Negishi coupling and cross olefin metathesis protocol (Scheme 39). Compound **241** (obtained from L-(+)-lactic acid precursor) underwent iodine lithium exchange (*t*-BuLi, Et_2O) followed by transmetalation ($ZnCl_2$, THF) and Negishi cross-coupling reaction with triflate **242**. As a result, diene **243** was obtained in 96% yield with 5 mol% $PdCl_2$(dppf) loading in THF. Next step involved olefin cross metathesis using Grubbs II followed by hydrogenation (H_2, Pd/C, AcOEt) and deprotection (BBr_3, DCM) to obtain targeted (−)-cylindrocyclophane F **240**.

Heck cross-coupling reaction

Heck cross-coupling reaction includes the coupling of aryl iodide/bromide/chloride, triflates, mesylates, tosylates and diazonium salts with olefins to accomplish aryl-substituted alkenes. This methodology has been extended to the coupling of alkenyl compounds with olefins [120]. This interesting strategy finds its applications in the formation of medicinally important analogues, polymers and natural products. Some known examples are the synthesis of retinoid x receptor antagonist and diazepinylbenzoic acid via Heck coupling [121].



Scheme 39 Synthesis of (−)-cylindrocyclophane F **240**



(+)-Lysergol (**244**)

Fig. 33 Structure of (+)-lysergol **244**

Synthesis of alkaloids

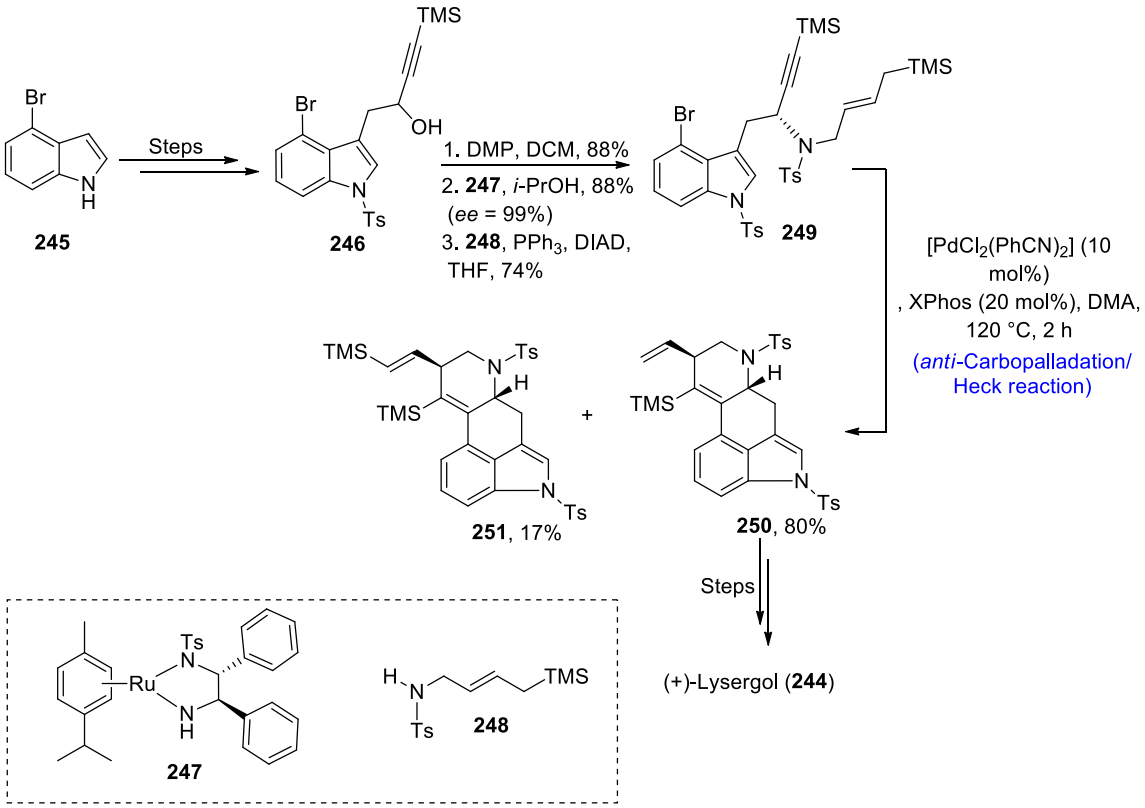
Ergot alkaloids are a source of indole alkaloids exhibiting a wide spectrum of biological activities such as antiprolactin and anti-Parkinson's activity. These are obtained from *Claviceps pupurea* (fungus) which grows on rye and other grains. (+)-Lysergol **244** is an indole alkaloid belonging to this attractive family of natural products (Fig. 33) [122].

Milde et al. [123] used *anti*-carbopalladation/Heck reaction to achieve the enantioselective synthesis of (+)-lysergol **244** in 12 steps and with 13% overall yield (Scheme 40). 2-Bromoindole **245** was used as starting precursor to obtain alcohol **246** over several steps. Racemic alcohol **246** was converted to required domino precursor **249** on treatment with DMP followed by enantioselective reduction (using Noyori's catalyst **247**) and Mitsunobu reaction (using sulfonamide **248**). Next step involved *anti*-carbopalladation/Heck reaction by the addition of 10 mol% $[PdCl_2(PhCN)_2]$ as catalyst, 20 mol% XPhos as ligand in DMA at 120 °C for 2 h to form two rings of target product **250** in a stereospecific manner in 80% yield along with side product **251** (17%). Proceeding from compound **250**, the final structure of (+)-lysergol **244** was accomplished over several steps.

Lycorine-type alkaloids are derived from plants and show antimitotic, antiviral and antineoplastic activities, etc. (±)-γ-Lycorane **252** is not associated with any significant pharmaceutical property; however, it has become a popular molecule in the aspect of describing the potential of new synthetic techniques for the combination of fragments in lycorine-type alkaloids (Fig. 34) [124].

Monaco et al. [125] reported the synthesis of (±)-γ-lycorane **252** via Heck cyclization reaction (Scheme 41). Firstly, compound **254** was prepared in 87% yield by treating piperonylamine **253** with bromine in acetic acid followed by the addition of cyclohexanone, diacetoxyacetyl chloride and boron trifluoride diethyl etherate. Next, compound **254** was cyclized in the presence of $PdCl_2(PPh_3)_2$ in DMF to afford pentacyclic motif **255** in 74% yield. The required product **252** (85%) was formed by the hydrogenation of double bonds of compound **255** by using H-Cube hydrogenation flow reactor, 10% palladium on charcoal in ethanol/ethyl acetate mixture and then followed by its reduction with $LiAlH_4$.

Tuberculosis (TB) is an infectious disease and needs to be treated with effective drugs. Advent of new drugs with low toxicity, high potency, good interaction and novel mechanism of action remains a challenge for the cure of tuberculosis. However, natural resources serve best in producing molecules with unique chemical and biological attributes. 3,4-Diarylpyrrole alkaloids are suitable example of captivating bioactive metabolites obtained from marine species. Denigrin A **256** and denigrin B **257** (extracted from *Dendrilla nigra*) with potent antitubercular activity belongs to this category of natural products (Fig. 35) [126].



Scheme 40 Synthesis of (+)-lysergol **244**

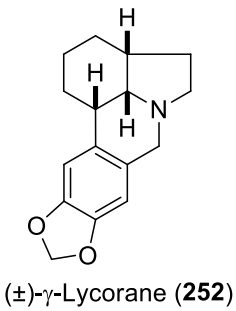
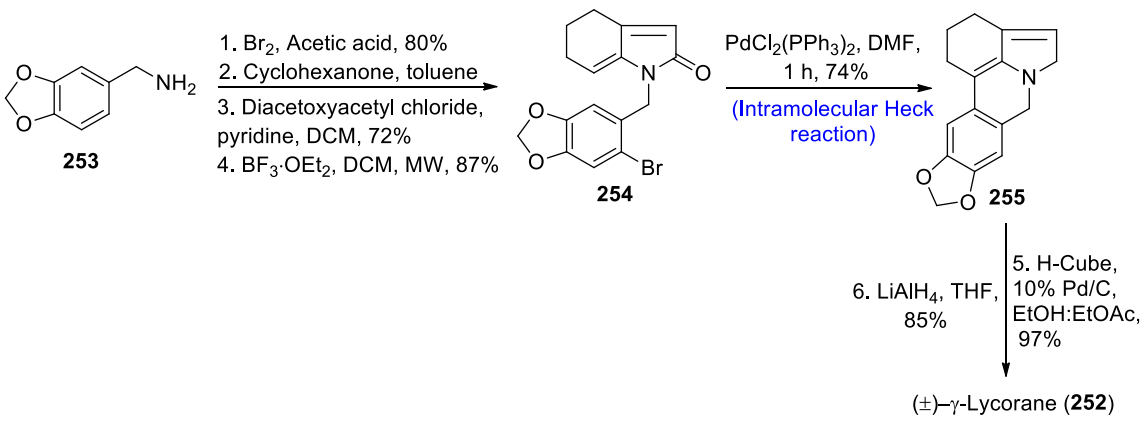


Fig. 34 Structure of (±)-γ-lycorane **252**

Karak et al. [127] reported the first synthesis of denigrin A and B (**256**, **257**) with 62% and 31% overall yields based on three and five steps, respectively, via Heck reaction as a key step (Scheme 42). The starting substrates; maleic anhydride **258** and diaryliodonium tosylate **259** were coupled through Heck reaction ($Pd(OAc)_2$, sodium acetate in acetonitrile) to produce monoarylated **260** and diarylated compound **261** (69%, 4:96). To obtain denigrin A **256** (97%), compound **261** was reacted with *p*-methoxyphenethylamine



Scheme 41 Synthesis of (±)-γ-lycorane **252**

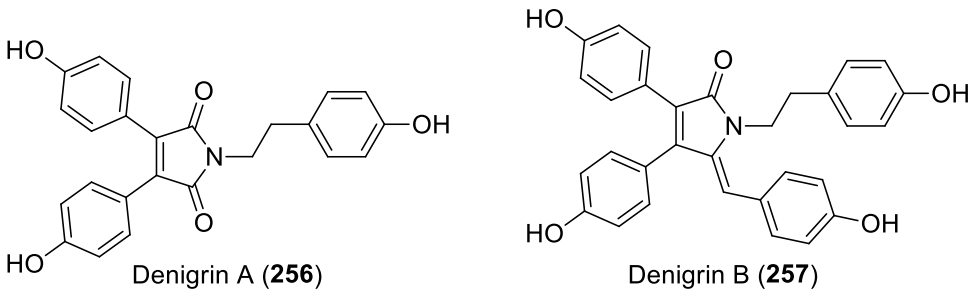
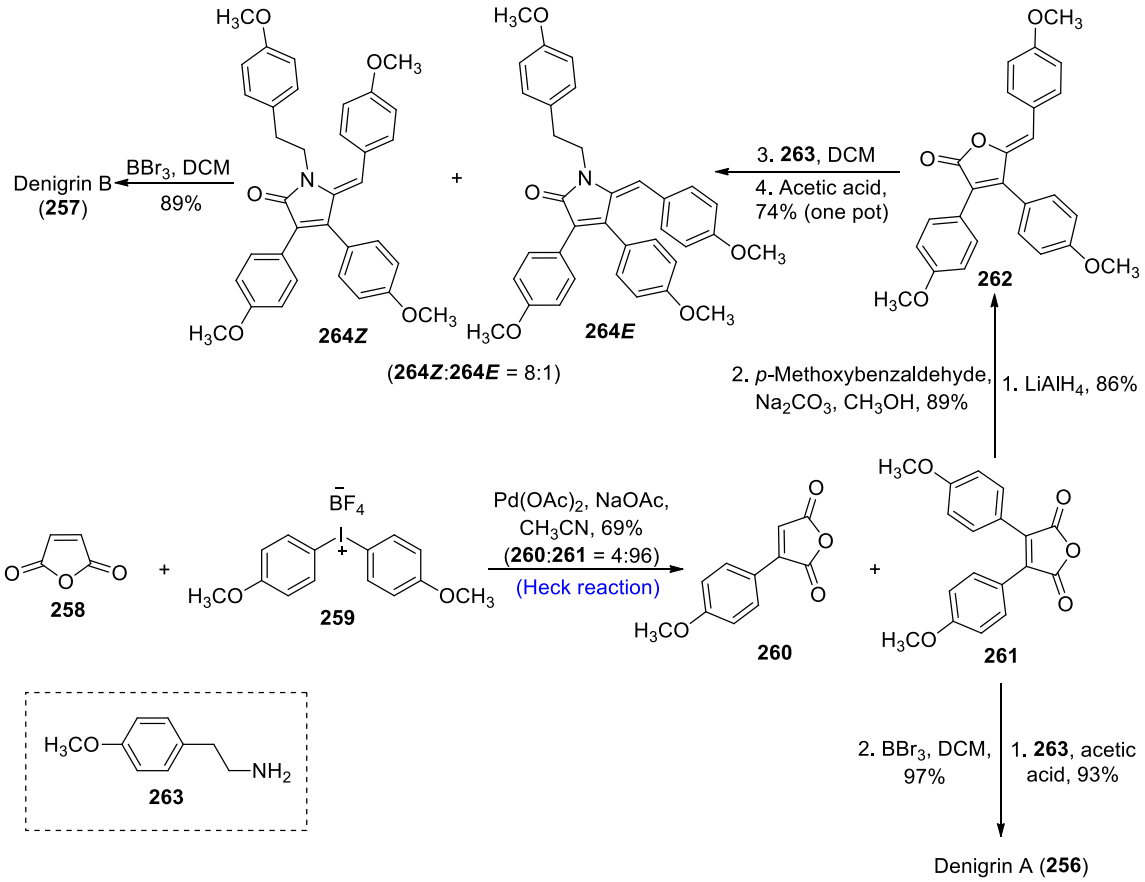


Fig. 35 Structures of denigrin A **256** and denigrin B **257**



Scheme 42 Synthesis of denigrin A and B (**256**, **257**)

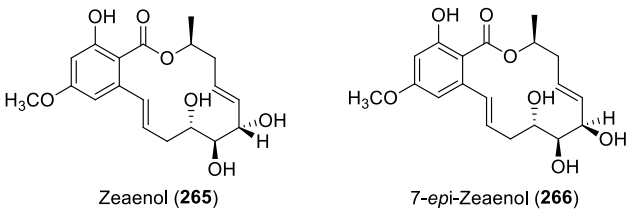
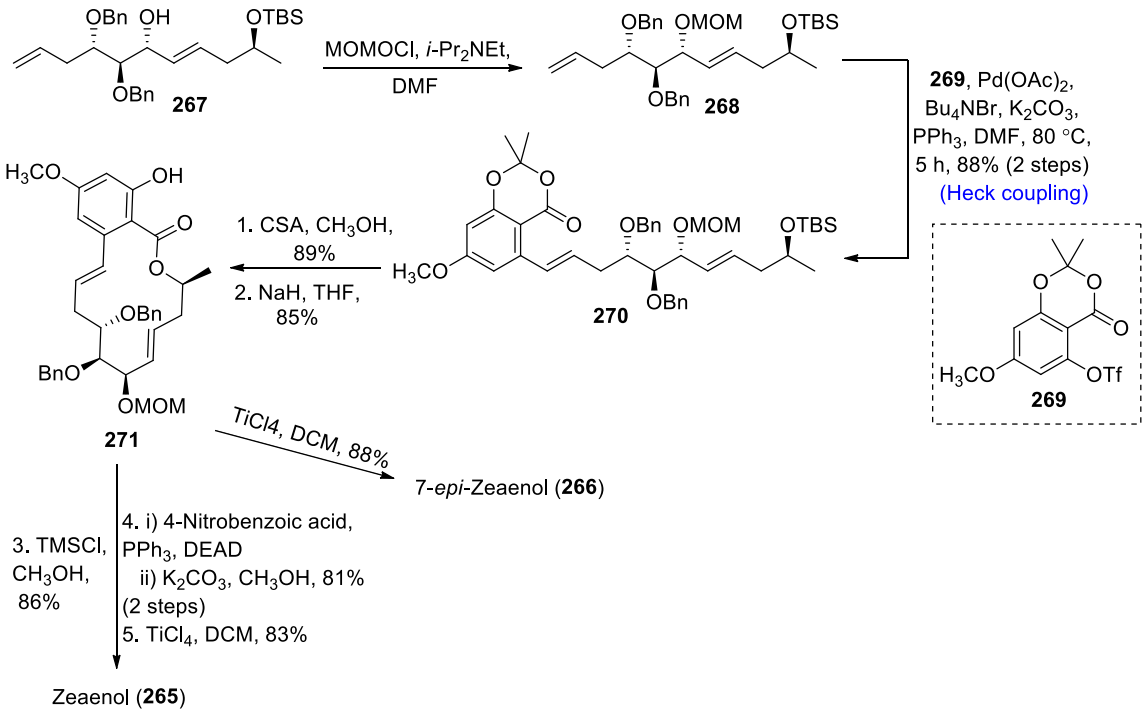


Fig. 36 Structures of zeaenol **265** and 7-*epi*-zeaenol **266**

263 in acetic acid followed by the addition of BBr_3 in DCM. On the other hand, treatment of diarylated compound **261** with $LiAlH_4$ and *p*-methoxybenzaldehyde provided *Z*-isomer **262** as sole product in 89% yield. Later, compound **262** was reacted with fragment **263** in acetic acid to yield *Z*-benzylidene-diarylpyrrol-2(5*H*)-one **264Z** and **264E** through one-pot reaction. The cleavage of methyl ether groups of **264Z** with BBr_3 afforded denigrin B **257** in 89% yield.



Scheme 43 Synthesis of resorcyclic acid lactones **265** and **266**

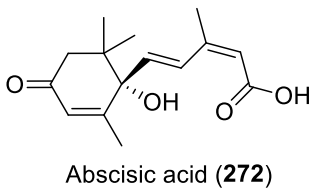
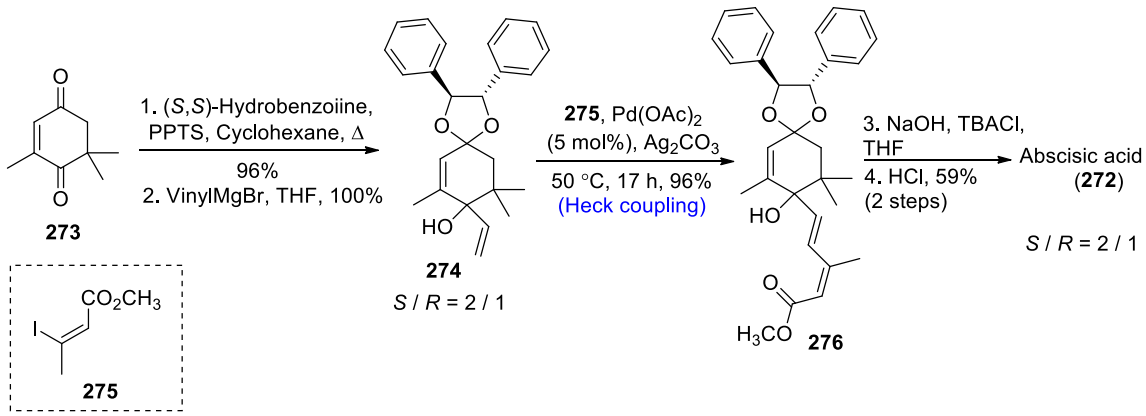


Fig. 37 Structure of abscisic acid **272**

Synthesis of lactones

Zeaenol **265** and 7-*epi*-zeaenol **266** extracted from a filamentous fungi belongs to resorcyclic acid lactones. Such compounds are known for cytotoxic potential having anticancer potential against human tumor cell line with same IC_{50} act as NF-κB inhibitor. (Fig. 36) [128].

Doda et al. [129] disclosed the asymmetric synthesis of zeaenol **265** and 7-*epi*-zeaenol **266** in 7 and 9 steps with 32% and 21% overall yield, respectively, by employing Heck reaction as fundamental step (Scheme 43). In this regard, *trans* allyl alcohol **267** obtained from D-mannitol was



Scheme 44 Synthesis of abscisic acid **272**

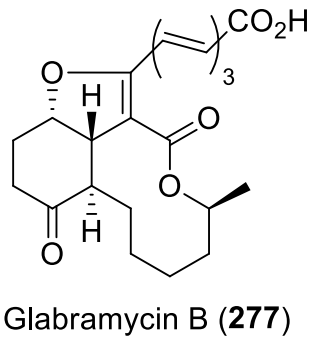


Fig. 38 Structure of glabramycin B **277**

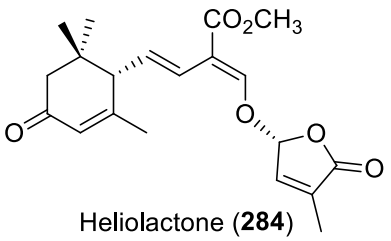


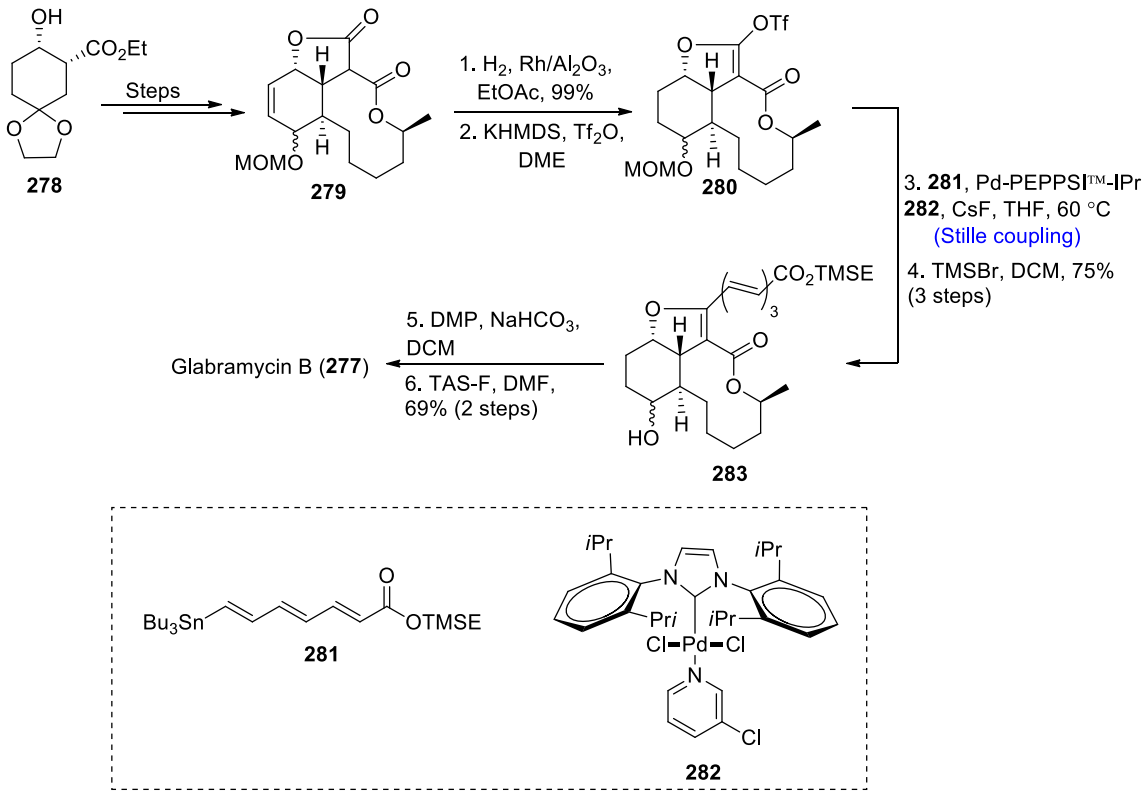
Fig. 39 Structure of heliolactone **284**

protected with MOM group to give compound **268** which underwent coupling with aromatic triflate **269** in the presence of $Pd(OAc)_2$, PPh_3, Bu_4NBr, K_2CO_3 in DMF at 80 °C for 5 h to provide *trans* olefin **270** in 88% yield over 2 steps. Deprotection of compound **270** with camphorsulfonic acid (CSA) and macrolactonization (using sodium hydride) gave macrolactone **271** in good yield (85%) which on treatment with $TiCl_4$ produced desired 7-*epi*-zeaenol **266** in 88% yield. Moreover, subjection of macrolactone **271** with TMSCl, 4-nitrobenzoic acid, potassium carbonate and $TiCl_4$ furnished zeaenol **265** in 83% yield.

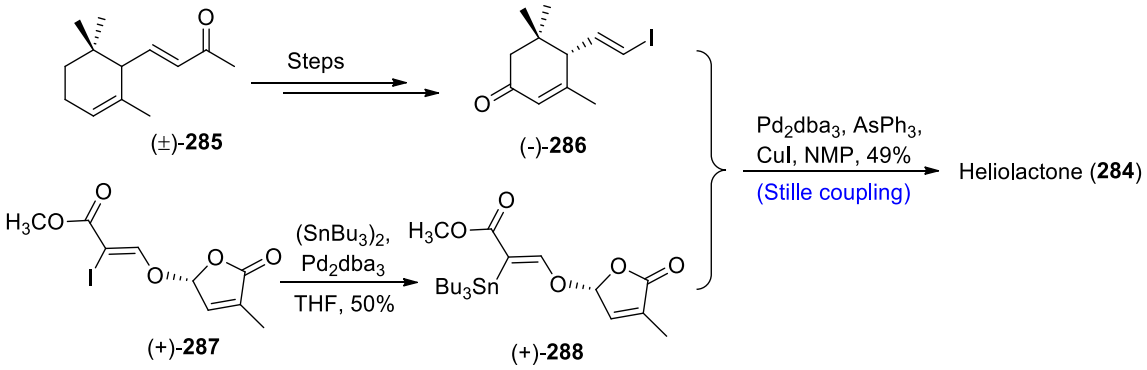
Miscellaneous

Abscisic acid **272** isolated in 1960s is a plant hormone. It plays an important role in growth of plants from different aspects including seed development, germination and alteration to abiotic environmental stress (Fig. 37) [130].

Dumonteil et al. [131] reported an environment friendly synthesis of abscisic acid **272** via Heck reaction in ligand and solvent free conditions with 54% yield (Scheme 44). In order to proceed, diketone **273** was reacted with (*S*,*S*)-hydrobenzoin and pyridinium *p*-toluenesulfonate (PPTS) in cyclohexane followed by the loading of vinylmagnesium bromide in THF to give compound **274** in quantitative



Scheme 45 Synthesis of glabramycin B **277**



Scheme 46 Synthesis of heliolactone **284**

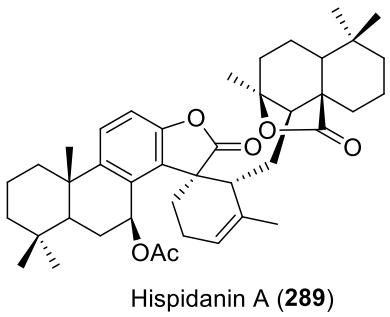


Fig. 40 Structure of hispidanin A **289**

yield. Heck coupling of compound **274** with *Z*-enoate **275** in the presence of 5 mol% $Pd(OAc)_2$ and silver carbonate at 50 °C for 17 h delivered (*E*/*Z*)-diene **276** in 96% yield which on saponification using NaOH and TBACl followed by acidic treatment (with HCl) yielded the *S*-enantiomeric enriched **272** (59% over 2 steps).

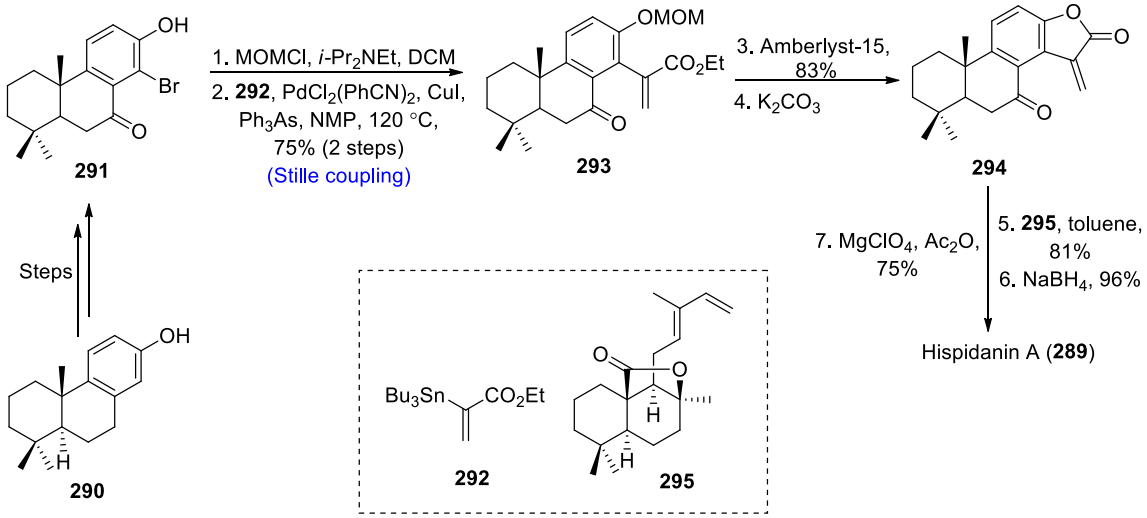
Stille cross-coupling reaction

Stille cross-coupling reaction represents the coupling of organostannanes with organic halides/triflates usually in the presence of palladium catalyst to connect carbon–carbon bonds in a variety of compounds. It finds enormous use in the preparation of precursors of drugs, for instance valsartan and imatinib C and in the formulation of electronic materials such as transistors and photovoltaic cells [132, 133].

Synthesis of lactones

Glabramycin B **277** was isolated through an antisense screening method from fermentation broth of *Neosartorya glabra* by Singh and co-workers in 2009 (Fig. 38). It exhibited antibacterial activity [134].

Yamamoto et al. [135] reported an enantioselective synthesis of glabramycin B **277** through Stille coupling as one of the main step and corrected its relative configuration

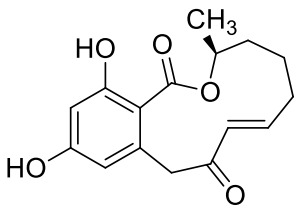


Scheme 47 Synthesis of hispidanin A **289**

(Scheme 45). Compound **278** was used as starting material to produce tricyclic core **279** over several steps and was converted to vinyl triflate **280** on hydrogenation using H_2, Rh/Al_2O_3 in ethyl acetoacetate followed by the addition of KHMDS and Tf_2O in DME. Later, vinyl triflate **280** and trienylstannane **281** were coupled in the presence of Pd-PEPPSI-IPr **282**, CsF in THF at 60 °C and cleavage of MOM group with TMSBr produced compound **283** in good yield (75% over 3 steps). The final skeleton of glabramycin B **277** was obtained by oxidation (with DMP) and deprotection (with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F)).

Heliolactone **284**, a non-sesquiterpene lactone stimulates the germination of root parasitic weeds which causes harmful effects on many crops (Fig. 39). It has been investigated that production of heliolactone increased in the presence of water while lowered in the presence of phosphorous and nitrogen supplements [136].

Woo and McErlean [137] reported enantioselective total synthesis of heliolactone **284** by using Stille coupling and confirmed the stereochemical nature (Scheme 46). α-Ionone **285** and chiral iodide **287** gave enantiomers **286** and **288**, respectively, which were coupled in the presence of Pd_2dba_3, $AsPh_3$, CuI in NMP to obtain target product **284** in 49% yield.



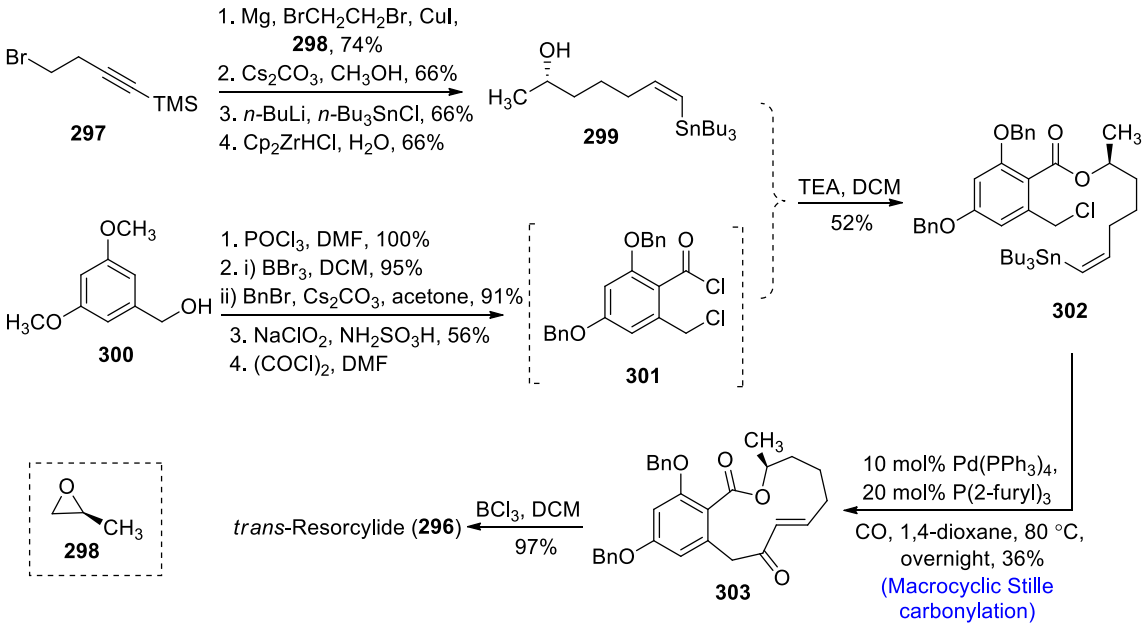
trans-Resorcylide (**296**)

Fig. 41 Structure of *trans*-resorcylide **296**

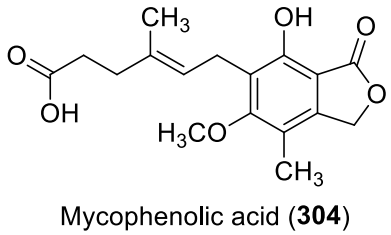
Synthesis of terpenoids

Plant of East Asia of genus *Isodon* is used as traditional medicine for the treatment of different infections including respiratory, cancer and inflammation problems in China. Mainly, its aerial parts such as stems and leaves are used for this purpose and some species of *Isodon* bears swollen rhizomes which also exhibit medicinal value. Hispidanin A-D are asymmetric dimeric diterpenoids which have been obtained from rizhomes of *Isodon* (Fig. 40) [138].

Deng et al. [139] reported the asymmetric total synthesis of hispidanin A **289** via Stille coupling approach (Scheme 47). Compound **290** produced **291** over 3 steps, masking of phenol of tricyclic compound **291** (using MOMCl) and coupling with substrate **292** in the presence of palladium catalyst $PdCl_2(PhCN)_2$, CuI, Ph_3As in NMP at 120 °C furnished compound **293** in 75% yield (2 steps). The compound **293** upon deprotection (with Amberlyst-15) followed by base promoted lactonization (with K_2CO_3) gave dienophile **294**. Diels–Alder cycloaddition was conducted between fragment **294** and diene **295** (obtained from an epoxide) in toluene followed by addition of $NaBH_4$ and $MgClO_4$, acetic anhydride to produce diterpenoid **289** in 75% yield.



Scheme 48 Synthesis of *trans*-resorcylide **296**



Mycophenolic acid (**304**)

Fig. 42 Structure of mycophenolic acid **304**

Synthesis of macrolides

The resorcyclic macrolides account for important family of natural products containing β-resorcylate motif and macrocyclic lactone core. *trans*-Resorcylide **296** with a distinctive structure acts as plant growth inhibitor and is an influential template from synthetic point of view (Fig. 41) [140, 141].

Luo et al. [142] prepared *trans*-resorcylide **296** via Stille carbonylation protocol (Scheme 48). In this regard, bromide **297** reacted with magnesium metal, CuI and epoxide **298** for regioselective ring opening to form alcohol which was transformed to *cis*-vinylstannane **299** (66%). It involved the treatment with cesium carbonate, subsequent formation of terminal alkyne (using *n*-BuLi, *n*-Bu_3SnCl) and stereoselective reduction of alkyne bond (using Cp_2ZrHCl). Compound **301** was shaped from starting material **300** over 4 steps. Fragments **299** and **301** gave Stille carbonylative precursor **302** in 52% yield with TEA in DCM. In the following step, **302** was reacted in the presence of 10 mol% $Pd(PPh_3)_4$, 20 mol% P(2-furyl)$_3$ and CO in dioxane to furnished macrocyclic product **303** in 36% yield. The addition of BCl_3 produced the required structure of *trans*-resorcyclide **296** in an excellent yield (97%).

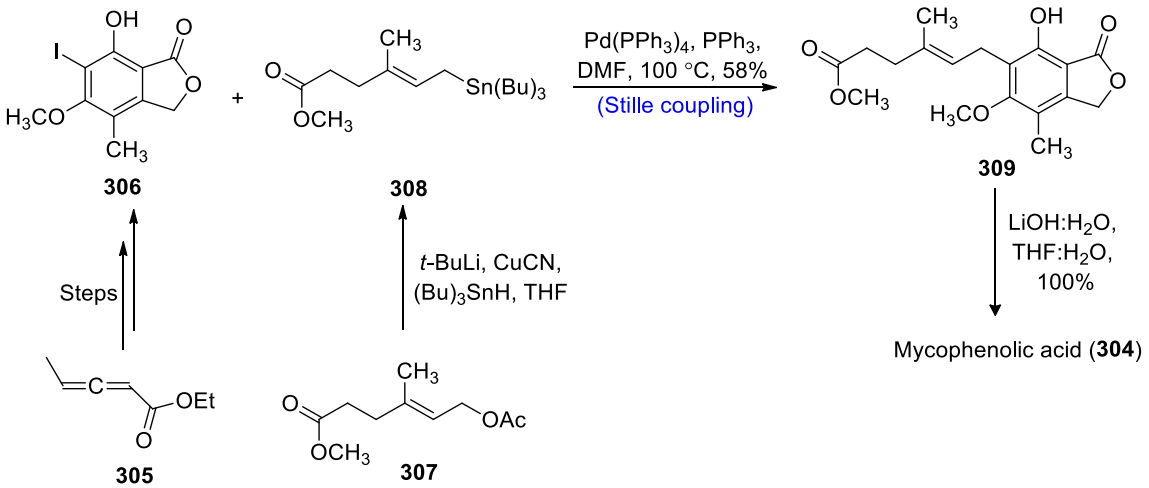
Miscellaneous

Mycophenolic acid **304** isolated from *Penicillium fungus* is associated with a variety of biological properties including antifungal, antibacterial, antiviral, anticancer and acts as immunosuppressive agent, etc. The presence of arene bearing six substituents make it an interesting molecule in synthetic chemistry (Fig. 42). Halle et al. [143] reported a short synthesis of mycophenolc acid **304** (quantitative yield) via Stille coupling of compound **306** (prepared from ethyl allenoate **305**) with stannane **308** (obtained from acetate **307**) in the presence of $Pd(PPh_3)_4$, PPh_3 in DMF at 100 °C followed by hydrolysis using LiOH/H_2O mixture (Scheme 49).

Schisandrene **310** (Suzuki and Stille coupling) [144], hemigeran C **311** and hemigeran D **312** (Negishi and Heck coupling) [145], patellazole B **313**, raputimonoindole A **314** (Suzuki and Heck coupling) [146, 147] and diptoindonesin G **315** (Suzuki and Sonogashira coupling) [148] are examples of natural products incorporating more than one type of cross-coupling reactions to connect their synthons (Fig. 43).

Conclusion

In summary, cross-coupling reactions have made immense progress in shaping structurally diverse natural products. We have explored the synthesis of natural products via Suzuki, Negishi, Heck, Sonogashira and Stille cross-coupling



Mycophenolic acid (**304**)

Scheme 49 Synthesis of mycophenolic acid **304**

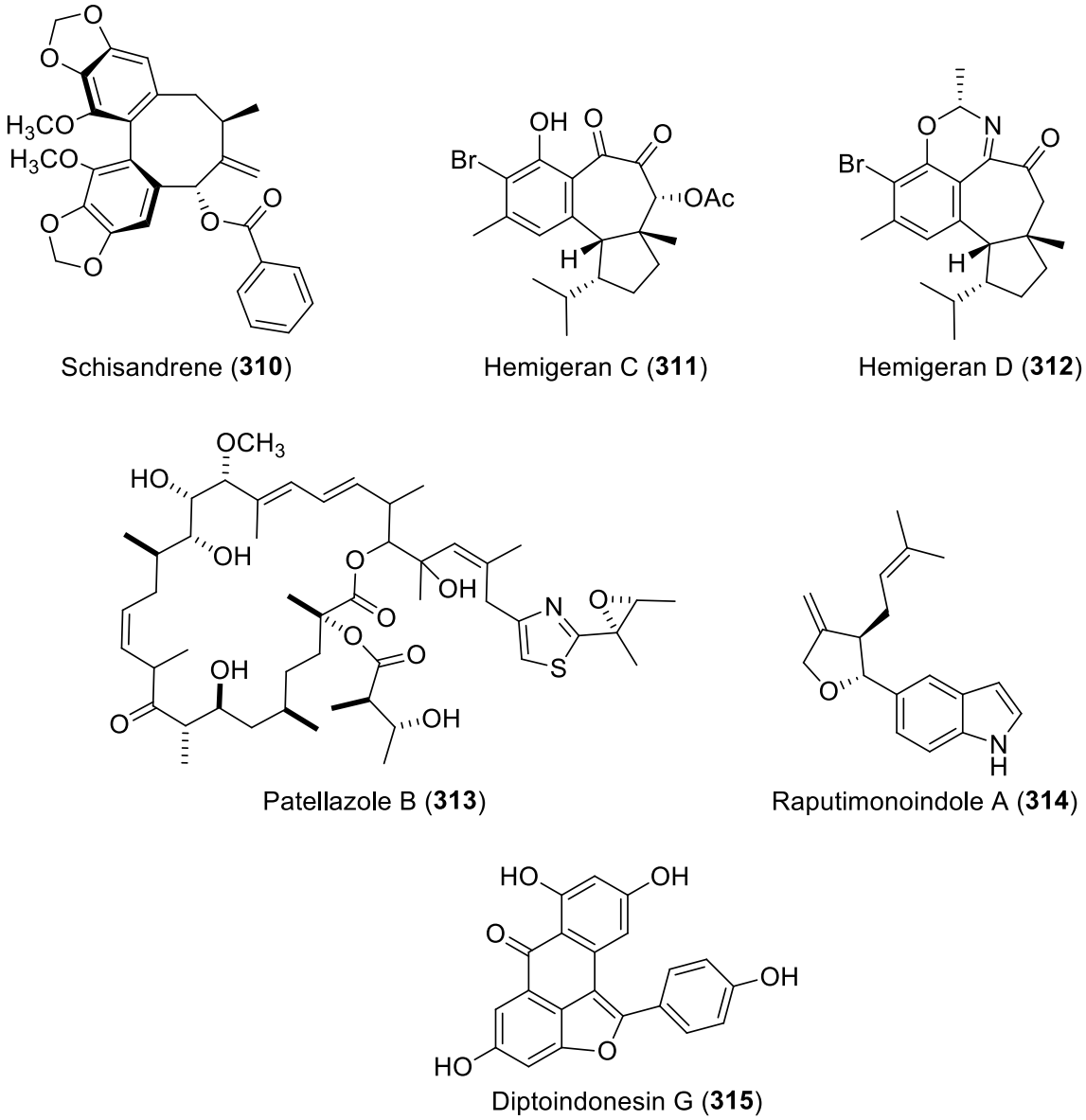


Fig. 43 Structures of natural products (**310**–**315**) illustrating the role of more than one type of cross-coupling in the synthesis

reactions to recognize the benefits of these strategies in synthetic as well as pharmaceutical sectors. The interesting features of these reactions have played role in the production of diastereoselective, stereoselective, regioselective and enantioselective fragments of naturally occurring molecules with moderate to good yields. Mostly palladium-based catalysts including $Pd(PPh_3)_4$, $Pd(OAc)_2$, $PdCl_2(PPh_2)_2$, $PdCl_2(dppf)$ and $Pd_2(dba)_3$ with various combination of ligands, bases and solvents have been used in this respect. Furthermore, the important biological activities of natural compounds such as anticancer, antiviral, antituberculosis, hCE2 inhibitor, ATPase inhibitor, etc. add supremacy to the entire constructed framework. However, this review would serve as a parameter to attract the attention of chemists towards the applications of cross-coupling reactions to make more adorable advancements with no shortcomings.

Acknowledgements The authors are thankful to Government College University, Faisalabad to carry out this work.

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Authors and Affiliations

Shaheera Tabassum[1] · Ameer Fawad Zahoor[1] · Sajjad Ahmad[2] · Razia Noreen[3] · Samreen Gul Khan[1] · Hamad Ahmad[4]

[1] Department of Chemistry, Government College University Faisalabad, Faisalabad 38000, Pakistan

[2] Department of Chemistry, University of Engineering and Technology, Lahore, Faisalabad Campus, Faisalabad 38000, Pakistan

[3] Department of Biochemistry, Government College University Faisalabad, Faisalabad 38000, Pakistan

[4] Department of Chemistry, University of Management and Technology, Lahore, Pakistan