RSC Advances



View Article Online

View Journal | View Issue

REVIEW

Check for updates

Cite this: RSC Adv., 2025, 15, 8121

Corey–Fuchs reaction enabled synthesis of natural products: a review

Rabia Ashraf,^a Ameer Fawad Zahoor, ^b*^a Samreen Gul Khan,^a Muhammad Jawwad Saif, ^b Syed Makhdoom Hussain,^c Syed Ali Raza Nagvi,^a Bushra Parveen,^a Kulsoom Ghulam Ali,^a Asim Mansha^a and Ahmad Irfan^d

Natural products can be derived from a vast array of animals, plants and microorganisms and are generally characterized by a wide spectrum of bioactive properties such as anti-viral, anti-cancer, anti-inflammatory and anti-bacterial properties. Synthesis of natural products is of paramount importance in various fields including medicine, biotechnology and agriculture. The Corey-Fuchs reaction, also known as the Ramirez Corey-Fuchs reaction, is a pivotal organic transformation and plays a significant role in the synthesis of intricate natural products and their analogues. This review article highlights the development of the Corey-Fuchs reaction in recent years towards the synthesis of complex natural products including polyketides, alkaloids, terpenoids and peptides.

Received 26th January 2025 Accepted 6th March 2025

DOI: 10.1039/d5ra00619h

rsc li/rsc-advances

Introduction 1.

The Corey-Fuchs reaction was established by Nobel laureate E. J. Corey and his colleague P. L. Fuchs in 1972.¹ It is a pioneering transformation in organic synthesis involving the construction of a terminal alkyne via one carbon homologation of aldehyde. The reaction protocol includes a two steps methodology entailing the formation of α, α -dibromoalkene from an aldehyde followed by its conversion to a terminal alkyne under the assistance of a strong base (Scheme 1). The general reaction mechanism involves the formation of phosphorus vlide 8 from the reaction of triphenylphosphine and carbon tetrabromide, succeeded by its treatment with aldehyde 1 to furnish dibromoolefin 2. In the next step, the lithium halogen exchange process and elimination lead to the synthesis of desired alkyne 3 (Scheme 2).²

Terminal alkynes constitute a primary class of organic substances that have gained considerable acclaim since the turn of the century due to their diverse utilization and applications in multiple fields. Over 400 naturally occurring substances possessing terminal alkyne as a building block, have been characterized by a range of biological active properties including anti-viral, anti-cancer, anti-microbial, anti-malarial and anti-inflammatory³ properties. Moreover, alkynes

synthesized through Corey-Fuchs reaction, act as key intermediates in the assembly of various other natural products, such as macrolides,⁴ δ-lactone,⁵ alkaloids,⁶ unsaturated fatty acids,⁷ polyketides8 and terpenoids9 etc.

A well-utilized strategy for the construction of alkynes is the one-carbon homologation of carbonyl compounds. Building on Corey's pioneering studies in this field,¹⁰ numerous methodologies including Ramirez Corey-Fuchs reaction, Colvin rearrangement,11 Ohira-Bestmann reaction12 and Seyferth-Gilbert homologation11 have been come forth in the literature. Corey-Fuchs reaction is often found as an optimal method for the alkyne synthesis owing to mild reaction conditions, wide substrate scope and high yields over other phosphorous-catalyst based reactions.13 Ohira-Bestman reagent (dimethyl 1-diazo-2oxopropylphosphonate) (termed as Seyferth-Gilbert homologation) was widely employed for the synthesis of terminal alkynes, however, these types of reagents are relatively expensive, precarious and also have limited applications for the preparation of acetylenic group starting from aldehydes.14 Moreover, Corey-Fuchs procedure allows for the preparation of enantiomerically pure products in contrast to Ohira-Bestmann reaction protocol as it is incompatible due to the racemization of the product.15



Scheme 1 General reaction of Corey-Fuchs protocol.

^aDepartment of Chemistry, Government College University Faisalabad, Faisalabad, 38000, Pakistan. E-mail: fawad.zahoor@gcuf.edu.pk

^bDepartment of Applied Chemistry, Government College University Faisalabad, Faisalabad, 38000, Pakistan

^cDepartment of Zoology, Government College University Faisalabad, Faisalabad, 38000, Pakistan

^dDepartment of Chemistry, College of Science, King Khalid University, P. O. Box 9004, Abha, 61413, Saudi Arabia



Scheme 2 General mechanism for Corey–Fuchs reaction involving the synthesis of terminal alkyne.

Various organic reactions are employed to carry out the total synthesis of naturally occurring compounds and other intricate biologically active heterocyclic functionalities.16-19 Surplus literature regarding the construction of several sophisticated natural products and other intricate organic compounds involving the Corey-Fuchs reaction as a main step, has been reported yet.²⁰⁻²³ Natural products have been the backbone of various biological active and potential lead compounds and their total synthesis has witnessed a pronounced advancement in recent years.²⁴ In this perspective, Lee et al., in 2014, demonstrated the total synthesis of (+)-Violapyrone C employing Corey-Fuchs reaction. (+)-Violapyrone C 14 is featured with high cytotoxic activity against six human tumor cell lines.²⁵ Similarly, in the same year, Sengoku and coworkers described the total synthesis of Kendomycin 15 utilizing the Corey-Fuchs reaction conditions.²⁶ This natural product not only exhibit strong anti-tumor activity against human call lines but also show excellent anti-bacterial properties against Gram positive and negative bacteria. In 2015, Huang et al. devised the total synthesis of 6-epi-Aculeatin D 16 via Corey-Fuchs alkyne synthesis, which showcases strong anti-malarial activity with IC₅₀ value of 0.18-3 µM against P. falciparum (Fig. 1).²⁷

The Corey-Fuchs reaction has endured notable breakthrough in the recent past and the need for a thorough and



Fig. 1 Structure of some biological important natural products having Corey–Fuchs reaction as main step in total synthesis.

state-of-the-art review on this topic has gained great prominence. The most recent comprehensive review on this topic dates back to 2015, emphasizing the need for a contemporary assessment of its scope and applications.²⁸ This manuscript intends to provide a latest (2016 to date) update on the cuttingedge development, showcasing the versatility and potential of this invaluable reaction in natural product synthesis.

2. Review of literature

2.1. Synthesis of polyketide-based natural products

2.1.1. Chatenaytrienin-4 synthesis. Acetogenin membranacin is a naturally occurring polyketide which belongs to a large group of fatty acid type compounds called annonaceous acetogenins. These natural products are characterized by a number of biological active properties such as pesticidal, cytotoxic, anti-malarial, anti-feedant, immunosuppressive and most likely, anti-tumor properties.²⁹ Adrian and Stark³⁰ in 2016, described modified strategy for the efficient stereodivergent construction of straight chain 1,5,9, n-polyenes and employed this for the first total synthesis of chatenaytrienin-4 24, which is the hypothetical biosynthetic forerunner of membranacin 25. The total synthesis commenced from the unexpensive 1-dodecyne 17 which was subjected to subsequent allylation to yield 18 followed by hydroboration to form bis-homopropargylic alcohol 19 in 70% yield. Next, the alcohol 19 was subjected to PCC/silica mediated oxidation in DCM to furnish aldehyde compound 20 (86%), followed by Corey-Fuchs alkyne synthesis reaction under the presence of CBr3 and PPh3 to furnish a dibromo compound 21 in conjugation with its lithiation and allylation in the presence of TBAI to furnish enediyne 22 in 80% yield. Further, enediyne 22 was subjected to chemoselective hydroboration in the presence of 9-BBN-dimer to deliver alcohol 23 in 63% yield. Carboxylic compound 24 was synthesized from 23 in a few steps followed by its treatment with hydroxy butanolide 25 in the presence of DMAP, ensued by Fries rearrangement and successive selective hydrogenation to deliver compound 26 (90%). Further, the hydroxyl group was protected under the presence of Tf2O followed by Lindlar's catalyst mediated reduction and then Pd-mediated reduction to finally achieve chatenaytrienin-4 27 (51% over 2 steps) in overall 6% yield in 15 linear steps (Scheme 3).

2.1.2. Tetrangulol synthesis. Tetrangulol 35 is a naturally occurring quinone, which belongs to the group of angucyclines. This group of compounds exhibit a wide range of biological properties such as anti-cancer and anti-bacterial activities.³¹ Tetrangulol 35 was synthesized for the first time by Brown & Thomson in 1976.³² Since then, a number of synthetic methods have been reported on the synthesis of biological active tetrangulol.³³ Owing to high medicinal properties, Ngwira³⁴ *et al.*, in 2016 reported the synthesis of tetrangulol by employing Suzuki–Miyaura coupling reaction & Corey–Fuchs alkyne synthesis as key synthetic steps. The total synthesis initiated *via* generation of substituted benzaldehyde **30** which is a key precursor, from commercially available 1,5-dihydroxynaph-thalene **29** over few steps. Next, the compound **31** was subjected to reductive methylation followed by its reaction with *n*-BuLi





Scheme 3 Total synthesis of chatenaytrienin-4 27 by Adrian and Stark.

and triisopropylborate to furnish boronic acid 32 (96%). The synthesized acid 32 underwent Suzuki–Miyaura coupling reaction in the presence of Pd(PPh₃)₄ to access 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde 33 in 80% yield. Compound 33 was then subjected to Corey–Fuchs reaction under the presence of CBr₄ and PPh₃ to furnish dibromoalkene 34 in conjugation with *n*-BuLi to form desired alkyne compound 35 in 88% yield. In the next step, formation of a mixture of tetracyclic product 36 (61%) and 37 (23%) took

place when compound **35** was reacted in the presence of $PtCl_2$ and PhMe. Both the products were separated *via* chromatography and compound **36** were further subjected to CAN oxidation followed by its treatment with boron tribromide to afford desired tetrangulol **38** in 97% yield (Scheme 4).

2.1.3. Synthesis of C16–C28 fragment of hemicalide. Hemicalide is a naturally occurring compound, fits into the class of polyketides.³⁵ It is extracted from marine sponge *Hemimycale* sp. in the south pacific and featured with potent **RSC** Advances



Scheme 4 Total synthesis of tetrangulol 38 by Ngwira and coworkers.

cytotoxic properties. Hemicalide exhibit excellent growth inhibitory potential against human cancer cell lines with IC_{50} values in picomolar, processing *via* tubulin targeting antimitotic mechanism.^{36,37} In this regard, MacGregor³⁶ *et al.*, in 2016 synthesized the advanced C16–C28 fragment 47 of the hemicalide **48** with restructured 18,19-*syn* geometry. The synthesis commenced with the formation of alkyne compound **40** (94%) under the Corey–Fuchs reaction followed by hydrozirconation and iodination in conjugation with subsequent 2,3dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) induced ether cleavage and oxidation to furnish (*Z*)-vinyl iodide **41** (80%). In the next step, vinyl iodide **41** were subjected to aldol addition reaction with PMB ether 42 under the conditions of ((–)-Ipc₂BCl, Et₃N) to generate a *syn* adduct 43 in 70% yield with exclusive diastereoselectivity. Next, subsequent formation of TBS ether and enolate addition in the presence of EtOAc and LDA led to the formation of ester 44 (97%), which was further subjected to TBS ether cleavage and induced lactonization in conjugation with elimination to furnish α -lactone 45 in 83% yield. Next, aldehyde compound 46 was achieved in 4 steps including *syn*-dihydroxylation and TES ether generation in the presence of TESOTf and 2,6-lutidine followed by PMB ether cleavage in DDQ and Dess–Martin periodinane (DMP) mediated oxidation. In the next step, Horner–Wadsworth Emmons olefination in the



presence $(MeO)_2P(O)CH_2COMe \& Ba(OH)_2$ and Stryker reduction under the conditions of $[Ph_3PCuH]_6$ and PhMe subsequently led towards the synthesis of completed C16–C28 points

fragments 47 in 67% yield (Scheme 5). 2.1.4. Actinoallolide synthesis. Actinoallolides belong to the class of 12 or 14-membered macrolides, derived from culture medium of *Actinoallomurus fulvus* MK10-036.³⁸ These compounds showcase a number of activities, such as *in vitro* anti trypanosomal potential against *Trypanosoma brucei brucei* GUTat 3.1 strain which is a bioweapon of Nagana disease in animals, *Trypanosoma brucei rhodesiense* which is a bioweapon of African *Trypanosomiasis* and *Trypanosoma cruzi Tulahun* strain which cause Chagas disease.³⁸ Actinoallolide A **61** possessed most of the potent activities such as *anti*-trypanosomal activity against *T. b. rhodesiense* STIB900 strain and also exhibit cytotoxic properties against MRC-5 cell lines and MIC; >10 μg per paper disk against Gram-negative and Gram-positive bacteria.38 Since macrolides depict a variety of biological activities, actinoallolides are first naturally occurring macrolides possessing anti-trypanosomal properties. In 2016, Ohista³⁹ et al., reported the construction of the key intermediate (+)-60 towards the convergent total synthesis of 61. The synthesis commenced from the synthesis of right part (-)-54 of the compound (+)-60. For this purpose, the compound 49 was transformed into asymmetric alcohol 50 (78%) via protection of hydroxyl group in the presence of MsCl, DMAP and pyridine followed by its treatment with cesium acetate under the presence of 18-crown-6, in conjugation with DIBAL-H mediated reduction. Next, alcohol 50 was subjected to acetalization followed by ozonolysis to furnish aldehyde compound 51 (79%) which was further reacted under the Corey-Fuchs reaction conditions to furnish alkyne 52. Next, PMP acetal ring opening furnished ketone 53 in 4 steps. The hydrozirconation of compound 53 followed by TIPS protection of hydroxyl group

RSC Advances

finally furnished first precursor (-)-54 (97%) for the synthesis of intermediate (+)-60. Next, the other coupling partners *i.e.*, *E*-vinyl stannane (+)-56 and alkyne compound (+)-58 were also synthesized from commercially available mono-methyl hydroquinone 55 and methyl-3-hydroxy methyl propanoate 57 respectively over a few steps. Next, the construction of main carbon skeleton of the key intermediate (+)-**60** was obtained from above synthesized precursors *i.e.*, (–)-**54** and (+)-**58**. As cross coupling reactions facilitate the robust synthesis of C–C and C–heteroatom bonds, accelerating the synthesis of coupled products.^{40,41} For this purpose, compound (+)-**58** was subjected to Negishi cross coupling with (–)-**54** to generate coupling



Scheme 6 Total synthesis of key intermediate of the actinoallolide A (+)-60 by Ohista and coworkers.

product **59** (59%). In the next step, the compound **59** underwent hydrozirconation followed by Stille coupling with (+)-**56** to finally furnish (+)-**60** in 28% yield (Scheme 6).

2.1.5. Orevactaene and epipyrone synthesis. Orevactaene 74 and epipyrone A 76 are significant naturally occurring scaffolds, comprised of 4-hydroxy-2-pyrone core structure.⁴² Both compounds were extracted from Epicoccum purpurascens strains and featured with a number of biological actives properties such as orevactaene depicts HIV-1 inhibitory and telomerase inhibitory properties.42 Whereas epipyrone A showcase potential against the influenza A virus and also act as a strong fungicide.43 Owing to the unique structural and biological properties, Preindl⁴⁴ et al., in 2017 devised total synthesis of these intriguing moieties via a number of key steps such as Corey-Fuchs reaction, two alkyne cycloisomerization reaction and Stille coupling. The total synthesis began with the generation of first precursor 63 from commercially available p-arabinose 62 over a few steps. In the next step, alcohol 64 was transformed into propargyl alcohol 65 (51% over 3 steps) via subsequent oxidation and Corey-Fuchs reaction in conjugation with the treatment of resulting alkyne with paraformaldehyde. Compound 65 was then reacted with ethyl trifluoropyruvate 66 followed by hydroboration in the presence of the oxyboran succeeded by subsequent oxidation in the presence of trimethylamine N-oxide and Suzuki-type crosscoupling with 1-iodopropyne under the conditions of Pd catalysis furnished compound 67 (57% over 3 steps). Further, compound 67 was reacted with PhMe₂SiLi to form silyl compound 68 (90%) which was converted to compound 69 over 4 steps yielding 89%. In the next step, commercially available epichlorohydrin 70 was subjected to alkylation under the presence of sodium acetylide in basic conditions followed by stannylcupration in conjugation with oxidation to yield 71. Next, Wittig olefination, reduction, oxidation and bora-Wittig reaction subsequently delivered heterodimetalated tetraene 73 (84%). Next, compound 73 was subjected to Stille coupling with compound 69 in the presence of Pd catalysis followed by Suzuki coupling reaction with compound 63 that resulted in formation of core structure of orevactaene. Next, deprotection using TSAF ultimately furnished desired 74. Apipyrone A 76 was also synthesized in the same manner from galactopyranosyl fluoride 75 over a few steps (Scheme 7).

2.1.6. (-)-Dactylolide synthesis. (-)-Dactylolide 85 is a naturally occurring compound fits into the class of cytotoxic macrolides, derived from Dactylospongia sp. of Vanuatu sponge.45 In 2018, Tanaka46 et al., published the convergent total synthesis of (-)-dectylolide 85, centered around the interand intramolecular allylation strategies. The synthesis commenced with the generation of key reactant 80 from known alcohol 77 via protection in the presence of MOMCl/iPr₂NEt/ DMAP succeeded by the DIBAL-H mediated reduction. Next, treated it with CBr₄ and PPh₃ to furnish dibromoalkene 78 via Corey-Fuchs reaction in conjugation with its reaction in the presence of *n*-BuLi and then ethyl chloroformate to generate ester compound 79 (88%). Precursor 80 was afforded from compound 79 over a few steps. Next, the other reacting partner 82 was also generated over a few steps from a known alcohol 81. Both the reacting partners 80 & 82 in hand, the total synthesis of (–)-dactylolide **85** was performed under various reaction conditions. First, both the reactants *i.e.*, **80** & **82** were reacted *via* Mukaiyama aldol condensation in the presence of CMPI followed by its reduction with DIBAL-H in conjugation with treatment with (CH₂ClCO)₂O, pyridine and DMAP to afford α acetoxy ether **83**. Next, compound **83** was subjected to react with ZnBr₂.OEt₂ and MS5A succeeded by its reaction with TMSBr/ TBAI in conjugation with MnO₂ *via* oxidation (73% over 2 steps) and then Pinnick oxidation to access seco-acid **84** (99%). The compound **84** was subjected to react with MNBA and DMAP succeeded by its deprotection using TBAF in conjugation with Dess-Martin oxidation to synthesize (–)-dactylolide **85** in 88% yield (Scheme 8).

2.1.7. Synthesis of polyketide fragment of seragamide. Seragamides are naturally occurring compounds featured with excellent cytotoxic properties.47 These compounds were isolated from marine sponge Suberites japonicus.48 Lang and Lindel49 in 2019, described the total synthesis of the polyketide fragment of the Seragamide employing Corey-Fuchs reaction as a main step. The synthesis involved nine overall steps with 21% yield. The total synthesis commenced from the preparation of organozinc homoenolate 87 which was utilized as Negishi coupling partner, from the treatment of β -bromopropionic acid **86** in the presence of manganese bromide, copper chloride and di ethyl zinc. Next, tert-butyl ester 89 was synthesized from tert-butyl propionate 88 over a few steps. Compound 89 was then reduced in the presence of DIBAL followed by DMAP-catalyzed oxidation to obtain aldehyde 90. In the next step, aldehyde 90 was subjected to Corey-Fuchs reaction under the presence of carbon tetrabromide and triphenyl phosphine to form dibromoalkene 91 succeeded by its reaction with LDA and then methyl iodide to form internal alkyne 92 in 91% yield (over 2 steps). Next, compound 92 underwent subsequent hydrozirconation and iodination under the presence of Schwartz reagent and iodine to form (E)-olefin 93 in 84% yield (over 2 steps) with exclusive regio- and stereoselectivity. Compound 93 underwent Negishi coupling with homoenolate 87 under the presence of palladium catalysis in DCM to furnish protected nonenoic acid 94 in 85% yield. In the final step, PMP deprotection of 94 in the presence of CAN afforded fragment 95 in 82% yield. Next, tripeptide 97 was subjected to BEP-catalyzed reaction with compound 96 (synthesized from polyketide section 95 via saponification), to form peptidepolyketide open chain compound 98 in 60% yield (over 2 steps) with 9:1 ratio of diastereoselectivity. This open chain peptidepolyketide compound 98 was further transformed into natural product seragamide A 99 over few steps (Scheme 9).

2.1.8. (–)-Enigmazole A and (–)-15-O-methylenigmazole synthesis. (–)-Enigmazole A **110** and its natural chemical analog (–)-15-O-methylenigmazole **114** fits into the family of phosphomacrolides derived from marine sponge *Cinachyrella enigmatica* of New Guinean Papua.⁵⁰ These naturally occurring compounds are featured by 18-membered macro-lactone possessing biological active properties. (–)-Enigmazole A **110** exhibit cytotoxic activity against the NCl 60 cell line, with a GI₅₀ value of 1.7 μ M.⁵¹ In 2020, Sakurai⁵² *et al.*, reported the total synthesis of (–)-enigmazole A **110** and (–)-15-O-methyl-enigmazole **114** by employing a number of key reaction



Scheme 7 Total synthesis of putative orevactaene 74 & epipyron A 76 by Preindl and coworkers.

procedures and Corey–Fuchs alkyne synthesis reaction is one of them. The total synthesis commenced with protection of homoallylic alcohol **100** to generate TBS protected ether **101** (97%), which on oxidative cleavage, furnished aldehyde compound **102**. The aldehyde **102** underwent two steps Corey–Fuchs reaction to access alkyne **104** in 94% yield in the presence



Scheme 8 Total synthesis of (–)-dactylolide 85 by Tanaka and coworkers.

of standard Corey–Fuchs conditions. Next, alkyne **104** was deprotected in the presence of *n*-BuLi followed by acetylide trapping with acetaldehyde succeeded by benzoyl chloride/ pyridine mediated acylation and then TBAF catalyzed deprotection generated compound **105** (92% over 2 steps). In the next step, compound **105** was made to react with the synthesized carboxylic acid **106** in the presence of 3,4,6-Cl₃C₆H₂COCl, Et₃N and DMAP (Yamaguchi conditions) to furnish ester compound **107**. Finally, (–)-enigmazole A **108** was synthesized from ester **107** over a few steps. The total synthesis of (–)-15-*O*-methyl-enigmazole **109** was also accessible from ester compound **107**, which was transformed into natural product **109** over a few synthetic steps (Scheme 10).

2.1.9. Metacridamide B synthesis. Metacridamide B **120** fits into the class of macrolides, extracted for the first time from conidia of the entomopathogenic fungus *M. acridum* By Krasnoff *et al.*, in 2012.⁵³ It is a 17 membered macrocyclic secondary metabolite featuring biological active property *i.e.*, anticytotoxicity with IC_{50} of 18.2 mM against HepG2/C3A.⁵³ Due to its unique structural architecture with remarkable biological potential, researchers explore various synthetic pathways towards its total synthesis.⁵⁴ In this regard, Sharma and coworkers⁵⁵ in 2021 documented the total synthesis of metacridamide B in overall 27 steps. The key methodological steps involved Yamaguchi macrolactonization, Corey–Fuchs alkyne synthesis, Ru-catalyzed alkyne functionalization, Stille coupling





ΟН

MnBr₂, CuCl,

Et₂Zn, DMPU, 75%

^tBuC

Corey-Fuchs Reaction

91

93

CAN, MeCN/H2O, 82%

B

Β̈́r

MeO₂C

ŌPMP

1) LDA

2) Mel, THF (91% over two steps)

THF, 85%

89

ŌPMP

ŌPMP

ZnBr

87, Pd(dppF)Cl₂, DCM,

polyketide section of seragamide 95

OTIPS

0

98

Ĥ

LiOH, H₂O/MeOH

95

1) DIBAL, DCM, 80%

2) IBX, DMSO, rt, 89%

ŌPMP

ŌН

92

ŌΗ

87

and Micalizio coupling. The total synthesis was proceeded with the synthesis of a key intermediate 111. The alkyne moiety 111 (79%) was accomplished from primary alcohol 110 in two reaction steps including DMP oxidation and Corey-Fuchs alkyne synthesis reaction in the presence of TPP, CBr₄ in conjugation with the use of *n*-BuLi. The synthesis of the second reactant aldehyde compound 114 was accomplished over few steps starting from an alkyne 112 and aldehyde compound 113. Next, both reacting entities in hands, coupling of 111 & 114 took place to yield enantiopure secondary alcohol 115 (80%) in three steps involving reaction with n-BuLi, DMP oxidation and asymmetric reduction in the presence of (S)-CBS catalysis. Secondary alcohol



Scheme 10 Total synthesis of (–)-enigmazole A 108 & (–)-15-O-methylenigmazole 109 by Sakurai and coworkers.

115 was subjected to regioselective functionalization under the presence of Bu_3SnH and ruthenium catalyst followed by its treatment with NIS in conjugation with Stille coupling in the presence of CuTC, Pd[PPh₃]₄ and [Ph₂PO₂][NBu₄] to afford compound **116** in 84% yield. Further, protection of free hydroxyl with TBS group took place followed by selective deprotection in the presence of CSA (catalyst). Next, DMP oxidation was followed by Pinnick oxidation to furnish intermediate **117** in 77% yield over 2 steps. Intermediate **117** was further treated with L-

phenylalanine methyl ester **118** under the presence of 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) followed by PMB deprotection with DDQ to form alcohol compound **119** in 94% yield. In the final step, compound **119** was subjected to ester hydrolysis in the presence of Me₃SnOH succeeded by Yamaguchi macrolactonization to generate TBS protected metacridamide B which on HF-pyridine catalyzed silyl deprotection gave metacridamide B **120** in 50% yield over 2 steps (Scheme 11).



Scheme 11 Total synthesis of metacridamide B 120 by Sharma and coworkers.

2.1.10. Veramycin A, NFAT-133 & TM-123 synthesis. Veramycins along with their chemical analogues NFAT-133 and TM-123 are well known polyketides, were derived from culture broth of *Streptomyces* sp. from Sanofi microbial strain. These natural

products showcased an enhanced baseline deoxy glucose uptake in a tailored L6 rat skeletal muscle cell line.⁵⁶ In 2022, Dardić⁵⁷ *et al.*, reported a detailed total synthesis of α -pyrone featured veramycin A **135** and its congeners NFAT-133 **126** and

TM-123 132. The synthesis was commenced with the formation of Weinreb amide intermediate 123 (95%) from (S)-aldehyde 121 in two steps involving the aldol addition with benzyl-3propionyloxazolidinone 122 in the presence of Bu₂BOTf and NEt₃ followed by oxazolidinone cleavage. Next, compound 123 was coupled with pinacol boronate 124 via Suzuki coupling in the presence of XPhos Pd G4 (as catalyst) to afford 125 in 96% yield. Compound 125 was efficiently converted to NFAT-133 126 in two steps entailing the formation of methyl ketone in the presence of Grignard reagent in conjugation with deprotection of TBS group in 25% overall yield. Next, to accomplish the synthesis of veramycin A 135 and TM-123 132, the intermediate 125 was converted into aldehyde 127 (97% yield) via TBS protection of hydroxyl group, succeeded by reduction in the presence of DIBAL-H. The prepared aldehyde 127 underwent two step Corey-Fuchs reaction in the presence of CBr₄, PPh₃, and NEt₃ to yield dibromoalkene **128** followed by its treatment with butyl lithium and methyl chloroformate to furnish propiolic acid methyl ester 129 in 76% yield. Next, the ester 129 was reacted with t-butyl ester 88 & TMSE protected ester 132 to furnish cyclized intermediates 130 (84% yield) and 133 (94% yield) correspondingly under the Claisen reaction conditions. These cyclized precursors were then transformed into their corresponding pyrones i.e., veramycin A 134 and TM-123 131 in the presence of (SPhos)AuNTf2 (gold catalyst) and MeNO2/AcOH followed by deprotection of alcohols (in 16% and 12% overall yield respectively) (Scheme 12).

2.1.11. (\pm) -Parvistilbine B & (\pm) -stemenone B synthesis. (\pm) -Parvistilbine B 149 and (\pm) -stemenone B 148 are naturally occurring compounds that fit into the class of polyketides and extracted from the Stemona parviflora and Stemona tuberosa respectively, exhibiting profound historical roots in Chinese phytomedicines.58 Parvistilbine B was extracted from the same room which exhibit excellent nematocidal activity while (\pm) -stemenone B has anti-inflammatory potential with IC₅₀ value of 2.97 µM.59 In 2022, Kozlowski60 et al., first proposed a new dearomative oxidation strategy for the construction of para-quinol moiety which is the core structure of both abovementioned natural compounds, then performed the total synthesis of these compounds. The main steps involving the total synthesis were Corey-Fuchs alkyne synthesis and Sonogashira-hydrogenation. The total synthesis began with the synthesis of alkyne precursors 137 and 140 from commercially available o-anisaldehyde 135 and p-hydroxy-2-anisaldehyde 136 respectively via Corey-Fuchs reaction. Next, the second coupling partner 144 was synthesized from dimethyl resorcinol 141 which was subjected to debromination to synthesize 142 (99%) succeeded by subsequent methylation and debromination to achieve 143 in 99% yield. Next, the compound 143 was subjected to Li-halogen exchange reaction and selective deprotection to furnish compound 144 with 55% yield. All the coupling partners 137, 140 & 144 in hand, Sonogashira coupling of 144 with 137 and 140 led to the formation of compounds 145 (51%) and 146 (45%) respectively, followed by hydrogenation-debenzylation and photo-catalytic dearomatization strategy to construct (\pm)-stemenone B 147 (86% over 2 steps) and (\pm) -parvistilbine B 148 (90% over 2 steps) respectively (Scheme 13).

2.1.12. Aigialomycin D synthesis. Aigialomycin D 160 is a fungal polyketide, derived from the marine mangrove fungus Aigialus parvus BCC 5311. This is a 14 membered resorcyclic acid lactone, featuring a number of bioactive properties including anti-malarial activity (IC₅₀: 6.6 μ g mL⁻¹ for *P. falciparum*) and cytotoxicity in human cell lines (IC₅₀: 3.0 & 18 μ g mL⁻¹ in KB and BC-1 cells respectively).⁶¹ Total synthesis of aigialomycin D was disclosed for the first time in 2004 by Danishefsky and coworkers in 18 steps and with 8% overall yield.⁶² In continuation of exploring the new ways towards the total synthesis of bioactive natural products, Sudhakar⁶³ et al., in 2024 published the total synthesis of aigialomycin D 160. The key reactions in synthetic approach entailed Corey-Fuchs alkyne synthesis, Yamaguchi esterification and ring closing metathesis. The synthesis was initiated with epoxide 149, which was subjected to ring opening reaction with homoallyl magnesium bromides under the conditions of dry ether to generate an alcohol.64 The synthesized alcohol on reaction with BnBr and NaH furnished benzyl ether 150 in 86% yield. Next, benzyl ether 150 was transformed into diol under the acidic medium (70% aq. acetic acid) which on reaction with BzCl and Et₃N got converted to monobezoate 151 in 81% yield. On treatment with TBSCl and imidazole, a TBS protected product was furnished which subjected debenzoylation in the presence of K₂CO₃ followed by Swern oxidation to form respective aldehyde 152. Aldehyde 152 underwent Corey-Fuchs reaction in the presence of CBr₄ and PPh₃ to access corresponding alkyne 153 in 77% yield. On treatment with n-BuLi, resulting acetylenic anion reacted with (S)-propylene oxide followed by its reaction with red-Al to give intermediate 154 in 74% yield. In the next step, the synthesis of another key precursor 157 took place from 2,4dimethoxybenzoic acid 155, which was converted into aldehyde compound 156 in 2 steps including the synthesis of amide in the presence of thionyl chloride and its conversion to aldehyde 156 in the presence of *n*-BuLi and DMF. Next, Wittig olefination of aldehyde 156 consequently led to the formation of styrene derivative which on hydrolysis gave 157 in 82% yield. The prepared intermediate 157 subjected to Yamaguchi reaction to form an anhydride which on further condensation with above synthesized intermediate 154 in the presence of DMAP delivered ester 159 in 72% yield. Finally, the ester 159 transformed into aigialomycin D 160 (74% & 2.67% overall yield) in two steps entailing the reaction of 159 with Grubb's 2nd generation catalyst in conjugation with deprotection step in the presence of AlI₃ in benzene (Scheme 14).

2.2. Synthesis of alkaloid-based natural products

2.2.1. Synthesis of C22–C40 fragment of azaspiracids. Alkaloids are a diverse class of naturally products, comprise of millions of biologically active compounds.⁶⁵ Azaspiracids are naturally occurring compounds fits into the category of lipophilic algal toxins (originally alkaloids), extracted from the dinoflagellates *A. spinosum* and *A. poporum*.⁶⁶ These azaspiracids are responsible for various biological responses in higher animals as its consumption by human through shellfish may cause diarrhetic shellfish poisoning.⁶⁷ Having intricate



Scheme 12 Total synthesis of veramycin A 134, NFAT-133 126 & TM-123 131 by Dardić and coworkers.

structural features along with bioactive properties, synthesis of these compounds has gained much interest. In this regard, Zhang⁶⁸ *et al.* in 2016 demonstrated the total synthesis of C22–C40 region **173** of the azaspiracids utilizing Corey–Fuchs reaction, Nozaki–Hiyama–Kishi coupling and intramolecular-hetero-Michael addition reaction as main steps. The total synthesis commenced from the synthesis of TMS alkyne fragment **166** involving the anti-aldol reaction of (*S*)-lactate ketone

161 with easily available aldehyde **162** in the presence of c-Hex₂BCl to access β -hydroxy ketone **163**. Next, compound **163** was first protected and then reduction of keto-ester took place with the assistance of lithium borohydride to furnish **164** (78%) followed by sodium periodate mediated oxidative cleavage to furnish aldehyde compound **165**. Next, the synthesis of TMS protected alkyne **166** (81%) was took place utilizing the Corey-Fuchs reaction followed by the silyl protection. Next,



Scheme 13 Total synthesis of (±)-parvistilbine B 148 & (±)-stemenone B 147 by Kozlowski and coworkers.

deprotection of the TBS group led the synthesis of compound **167** (90%), followed by its conversion to epimeric acetal **168** in the presence of DDQ in DCM. Epimeric acetal **168** underwent DIBAL-H mediated reduction followed by the Parikh–Doering oxidation to achieve compound **169** in 95% yield. Next, compound **170** was treated in the presence of NIS and AgOTf in DMF to prepare iodo-alkyne followed by Nozaki–Hiyama–Kishi coupling with **169** to furnish propargylic alcohol **171** in 95% yield. Next, acyclic intermediate **172** was generated over a few steps. The acyclic intermediate **172** underwent ring closing reaction over a few steps to finally generate C22–C40 fragment **173** of the naturally occurring azaspiracids (Scheme 15).

2.2.2. Tetradecapentaenoic acid synthesis. Tetradecapentaenoic acids, a class of poly-unsaturated fatty acid amides





Scheme 14 Total synthesis of aigialomycin D 160 by Sudhakar and coworkers.

present in many tropical plant species such as *Z. bungeanum*, *Z. piperitum* and *Z. ailanthoi*.⁶⁹ Until now, more than 50 compounds of poly-unsaturated fatty acids have been extracted from Zanthoxylum plant species displaying remarkable bioactivities. Amides of these fatty acids depict *anti*-helmintic, antioxidant, apoptotic and anti-proliferative potential. Tetradecapentaenoic acid amide derivative **178** also termed as sanshool derivative, extracted from *Zanthoxylum bungeanum*.⁷⁰ Sanshool derivatives exhibit promising biological active properties as they act as power activator for cell apoptosis and also depict anticancer properties⁷¹ as cancer continues to pose as a causative agent for death worldwide.⁷² In 2019, Kolodiazhna & Kolodiazhnyi⁷³ demonstrated the total synthesis of sanshool derivative **178** *via* employing Corey–Fuchs reaction as the key step. The total synthesis commenced with the reaction of known

unsaturated aldehyde **174** in the presence of dibromomethylene phosphorane (generated *via* reaction of CBr_4 and PPh_3) to furnish dibromoalkene **175**. Next, dibromoalkene **175** was treated with *n*-BuLi to form terminal alkyne **176** followed by its reaction with oxalyl dichloride in conjugation with triphenyl phosphine to form unsaturated ester compound **177**. In the final step, desired tetradecapentaenoic acid amide **178** was obtained, upon treatment of ester compound **177** with *n*-BuLi (Scheme **16**).

Same group of scientists⁷⁴ also represented the stereoselective synthesis of tetradecapentaenoic acid derivatives *i.e.*, **178** & **186**. The key steps in the synthesis involved Wittig reaction, Ramirez–Corey–Fuchs reaction and Trost–Kazmaier rearrangement. The synthesis began with the synthesis of sorbaldehyde **180** from hexadienol **179** *via* Parikh–Doering



Scheme 15 Total synthesis of C22–C40 fragment 173 of azaspiracids by Zhang and coworkers.

oxidation in the presence of pyridine sulfur trioxide complex. Next step involved the synthesis of second reactant *i.e.*, phosphonium salt **182** which was generated from aldehyde compound **181** in two steps. The above synthesized compound **180** underwent Wittig olefination reaction with phosphonium compound followed by lithium aluminum hydride mediated reduction to generate alcohol **184**. Next, Parikh–Doering oxidation of alcohol **184** generated aldehyde compound **174** which was subjected to two steps Corey–Fuchs reaction in the presence of CBr_4 , PPh_3 to form dibromoalkene **175** and then *n*-BuLi in conjugation with methyl chloroformate to furnish alkyne compound **185**. Next, amides **178** and **186** were synthesized from compound **185** over a few steps (Scheme 17).

2.2.3. (–)-Chelonin A synthesis. (–)-Chelonin A 196 having 2,6-disubstituted morpholine core structure, was first extracted from the marine sponge *Chelonaplysilla* sp. in 1991.⁷⁵ This







Scheme 17 Total synthesis of tetradecapentaenoic acid derivatives 178 & 186 by Kolodiazhna & Kolodiazhnyi.

compound showcased good anti-microbial potential against *B. subtilis* and also depicted 60% inhibition of phorbol myristate acetate triggered inflammation in the host animals.⁷⁵ Hitherto, four total syntheses of chelonin A and an asymmetric synthesis of (+)-chelonin A (unnatural enantiomer) have been reported to date.^{76–79} Thus, Gunawana⁸⁰ *et al.*, in 2023 described the asymmetric total synthesis of (–)-chelonin A by employing various reaction processes *i.e.*, Corey–Fuchs, 1,3-addition of rhodium carbenoid, and annulation reaction. The first step for the total synthesis of (–)-chelonin included the synthesis of two starting substrates *i.e.*, bromohydrin (–)-**188** and triazole precursor **194**. In this regard, α -bromoketone **187** was converted to

enantioenriched bromohydrin (–)-**188** in the presence of Noyori catalyst **189** and HCO₂H/HCO₂K to furnish target product (–)-**188** in 87% yield with exceptional enantiomeric excess (>80% ee). In the next step, indole-3-carbaldehyde **190** was subjected to *N*-tosylation, followed by Corey–Fuchs reaction to synthesize terminal alkyne **193** in 62% yield. For this purpose, the protected aldehyde **191** (synthesized *via N*-tosylation) was treated under the conditions of CBr₄ and PPh₃ to generate gemdibromo alkene **193** followed by its reaction with *n*-BuLi to form alkyne **193**. In the next step, alkyne **193** was then transformed into triazole **195** (75%) when treated with TsN₃ under the catalytic conditions of Cu thiophene carboxylate (CuTc). The

synthesized substrates *i.e.*, triazole **194** and (–)-bromohydrin **188** were both subjected to the Rh_2OcT_4 catalyzed reaction followed by cyclization reaction in the presence of $CH_3CN \&$ Cs_2CO_3 succeeded by its treatment with a mixture of trifluoroacetic acid and triethylsilane to generate the diastereoselective *syn*-compound **195** in 77% yield. In the last step, deprotection of protected morpholine **195** took place in the presence of Na naphthalenide to finally deliver enantioselective (–)-chelonin A **196** in 52% yield (Scheme 18).

2.2.4. Schwarzinicines A–D synthesis. Schwarzinicines A–D, chemically referred as 1,4-diarylbutanoidphenethylamine derivatives are naturally occurring alkaloids, isolated from *Ficus schwarzii*.⁸¹ These natural products are attributed to vaso-relaxant, anti-diarrheal, anti-ulcer and anti-inflammatory

properties.⁴² Annapurna⁸³ *et al.*, in 2024 accomplished the total synthesis of these Schwarzinicines A–D compounds by employing Corey–Fuchs, Henry and Eschweiler–Clarke reactions. The synthesis began with the formation of 2-arylace-taldehyde **198** from veratraldehyde **197** in two steps *via* Wittig reaction and ether cleavage protocol in the presence of MeOCH₂PPh₃Cl, 'BuOK and HCl. Alongside, phenyl acetylene **200** (90%) was synthesized *via* Corey–Fuchs reaction from veratraldehyde **197** in two steps under the conditions of CBr₄, PPh₃, *n*-BuLi. Next, phenyl acetylene **200** and 2-arylacetaldehyde **198** underwent coupling reaction in the presence of *n*-BuLi to furnish alkynol **201** (85%) followed by the reduction of triple bond and subsequent oxidation in the presence of Dess–Martin periodinane to access diaryl ketone **202** in 90% yield. In the next



Scheme 18 Total synthesis of (–)-chelonin A 196 by Gunawana and coworkers.



Scheme 19 Total synthesis of schwarzinicines A–D 208–211 by Annapurna and coworkers.

step, 2-arylethanamines **205**, **206**, **207** were synthesized from veratraldehyde **197**, piperonal **203** and 3-methoxy-4,5-methylenedioxybenzaldehyde **204** respectively in the presence of CH_3NO_2 , NH_4OAc , AcOH and $LiAlH_4$ in two steps. The synthesized 2-arylethanamines *i.e.*, **205**, **206** & **207** were reacted with diaryl ketone **202** in the presence of titanium(IV) isopropoxide and NaBH₄ to furnish schwarzinicines A **208** (82%), schwarzinicines C **210** (84%) and Schwarzinicines D **209** (86%) respectively. Finally, schwarzinicines A **208** was converted into

schwarzinicines B **211** *via* Eschweiler–Clarke methylation providing 78% yield (Scheme 19).

2.3. Synthesis of polyunsaturated lipid-based natural products

2.3.1. Xestospongenyne synthesis. Xestospongenyne is a marine brominated naturally occurring compound which belongs to the class of polyunsaturated lipids.⁸⁴ It is considered as strong anti-obesity agent with exclusive pancreatic lipase



Scheme 20 Total synthesis of xestospongenyne 218 by Gong and coworkers.

inhibition potential with $IC_{50} = 0.61 \,\mu$ M. Owing to the significant importance as potent pancreatic lipase inhibitor, the total synthesis of xestospongenyne attain much interest in organic synthesis.85 In the regard, Gong and coworkers86 in 2016, represented first total synthesis of xestospongenyne 218 in 13% overall yield. There were three key steps involved in the total synthesis of xestospongenyne 218 including Corey-Fuchs reaction, Cadiot-Choskiewicz cross-coupling and Sonogashira coupling. The total synthesis initiated with the synthesis of vinyl iodide 213 by the treatment of commercially available compound hept-6-yn-1-ol 212 with DIBAL-H in the presence of iodine. Further, the compound 213 was reacted in the presence of ethynyl trimethyl silane under the catalytic dichlorobis(triphenylphosphine)palladium in Et₃N followed by Swern's oxidation to furnish envnal compound 214 (87%). In the next step, compound 214 was transformed into silvlated envne 215 (85%) via Corev-Fuchs reaction under the conditions of tetra-bromomethane and triphenylphosphine in conjugation with butyl lithium in THF. Next, the alkyne compound 215 was subjected to CadiotChoskiewicz cross-coupling with methyl 10-bromodec-9-ynoate **216** in the presence of hydroxylamine hydrochloride and copper chloride to furnish enyne ester **217** (55%). In the final step, subsequent potassium carbonate-mediated deprotection and Sonogashira coupling with dibromoethane under the presence of tetrakis(triphenylphosphine)palladium consequently gave xestospongenyne **218** in 53% yield (Scheme 20).

2.3.2. (5*Z*,9*Z*)-Eicosa-5,9-dienoic acid synthesis. (5*Z*,9*Z*)-Eicosa-5,9-dienoic acid 220 falls under the category of (5*Z*,9*Z*)-dienoic fatty acids which belongs to the class of non-methylene interrupted, very long chain fatty acids (VLCFA), mostly found in microorganisms, marine invertebrates and in some higher plants.⁸⁷ As these fatty acids are amidst the primitive and simplest I and II α inhibitors known so far and hence considered for the development of new antitumor agents.^{88,89} Owing to these properties, researchers are eager to develop new strategies towards the total synthesis of these structurally important natural products. In this prospective, Adrian and Stark⁹⁰ in 2016, demonstrated the total synthesis of topoisomerase



Scheme 21 Total synthesis of (5Z,9Z)-eicosa-5,9-dienoic acid 220 by Adrian and Stark.

inhibitor, (5*Z*,9*Z*)-eicosa-5,9-dienoic acid **220**, which is a potent human antitumor agent. The main steps towards the total synthesis involved Corey–Fuchs reaction, Lindlar reduction, TPAP-mediated oxidation of alcohol, and Arndt Eistert homologation. The synthesis commenced with precursor **17**, which was converted to compound **23** (provided in Scheme 3). Further, Lindlar catalyst-mediated reduction of alkyne **23** resulted in (Z,Z)-alcohol **219** in 92% yield followed by TPAP/NMO·H₂O catalyzed direct oxidation that led towards the efficient total synthesis of natural (5Z,9Z)-eicosa-5,9-dienoic acid **220**. The straightforward total synthesis of compound **220** was achieved in 10 steps and with 20% overall yield (Scheme 21).



Scheme 22 Total synthesis of resolvin D4 232a and its 17(R)-hydroxy-epimer 232b by Nshimiyimana and coworkers.



Scheme 23 Total synthesis of (–)-gummiferol 242a & (+)-gummiferol 242b by Sarabia and coworkers.



Scheme 24 Total synthesis of atractylodinol 248 by Kraus and coworkers.

2.3.3. Resolvin D4 and its 17(R)-hydroxy-epimer synthesis. Resolvin D4 and its 17(R)-hydroxy-epimer are lipid based biosynthetic natural compounds derived from docosahexaenoic acid. These compounds have many biological active properties such as anti-inflammatory and pro resolution property which enhanced the activity of human macrophages.⁹¹ In this context, Nshimiyimana92 et al., in 2023 disclosed a convergent, stereocontrolled total synthesis of resolvin D4 232a and its epimer 17(R)-resolvin D4 232b. The synthesis was initiated by the generation of propargyl bromide 222 from D-erythrose 221 in multiple steps. The other key intermediates i.e., 229 & 230 was synthesized via a number of reaction protocols. In this regard, 1butyne 223 was reacted with chiral glycidol 224 in the presence of boron trifluoride etherate followed by silvlation in conjugation with mild deprotection to generate isomers of intermediate 225 (87-89%) in weak acidic medium. Next, Lindlar hydrogenation of 225 succeeded by Dess-Martin oxidation generated aldehyde 226 which on Wittig olefination with (triphenylphosphoranylidene)acetaldehyde 227 delivered elongated enol 228 (228a in 75% & 228b in 72% yield). This enol was converted to terminal alkyne 229 via two steps Corey-Fuchs alkyne synthesis reaction in the presence of CBr₄ and PPh₃ in CH₂Cl₂ in conjugation with dehydrohalogenation using LDA in tetrahydrofuran (THF). To generate second isomer *i.e.*, 230, protection of 229 with less bulky silvl group was achieved which assisted in uniform desilylation in final step of the synthesis of AT-resolvin

D4 232b. In the next step, the reactions between 222 & 229 and 222 & 230 were took place *via* copper-catalyzed coupling to form bis-acetylenic moieties followed by Lindlar catalyzed selective reduction to generate silyl ethers 231 & 233 respectively. Next, desilylation in the presence of TBAF succeeded by its reaction with diazomethane and alkaline hydrolysis in the presence of LiOH furnished resolvin D4 232a and its 17(R)-hydroxy-epimer 232b (Scheme 22).

2.4. Synthesis of polyacetylene-based natural products

2.4.1. (–)-Gummiferol synthesis. (–)-Gummiferol 242a is a naturally occurring polyacetylene compound extracted from *Adenia gummifera* by Wall *et al.*, in 1995.⁹³. (–)-Gummiferol 242a is characterized by excellent cytotoxic activities as it shows potential against P388 murine leukemia with ED_{50} values of 0.03 µg mL⁻¹ and against U373 human glioma cell lines with the ED_{50} value 0.05 µg mL⁻¹.⁹⁴ Regarding the promising anticancer properties, the synthesis of different enantiomeric gummiferol is crucial in organic synthesis. In 2016, Sarabia and coworkers⁹⁵ designed the total synthesis of natural and nonnatural gummiferol utilizing the novel asymmetric approach of epoxide construction. The two epoxide rings, installed on natural product were formed *via* novel asymmetric sulfonium salts. The total synthesis commenced with the oxidation of commercially available alcohol 234 in the presence of PCC and



Scheme 25 Total synthesis of distaminolyne A 258 by Dumpala and coworkers.

sodium acetoacetate to form an aldehyde compound 235 followed by its reaction under the influence of sulfonium salt 236a in basic conditions to access epoxy amide 237 (54%). Compound 237 were efficiently converted to diepoxy compound 238 (95%) *via* Red-Al induced reduction followed by its reaction with novel sulfonium salt 236a. Subsequent reduction and Corey–Fuchs reaction delivered dibromo compound 239 in 40% yield. Next, the treatment of 239 with TBAF and coupling with dialkyne compound 240 in the presence of NH₂OH·HCl and CuCl followed by acetylation that led to the synthesis of compound 241 (51%). Finally, compound 241 was subjected to silyl deprotection in the presence of HF·Py to furnish natural (–)-gummiferol 242a in overall 10% yield with 10 steps. Unnatural (+)-gummiferol 242b was also obtained *via* same

synthetic protocol with the assistance of sulfonium salt **236b** (Scheme 23).

2.4.2. Atractylodinol synthesis. Atractylodinol 248 is an unsaturated natural product extracted from the rhizomes of *Atractylodes lancea*. *A. lancea* and known for its activity against porcine reproductive and respiratory syndrome virus (*anti*-PRRSV) potency with IC_{50} values of 7.9 µmol $L^{-1.96}$ It was utilized as traditional Chinese and Japanese drug against various diseases including night blindness, influenza, rheumatic and digestive disorders.⁹⁷ Owing to various biological activities, Kraus⁹⁸ *et al.*, in 2016, reported the total synthesis of atractylodinol 248 *via* utilizing a number of key synthetic procedure *i.e.*, Corey–Fuchs alkyne synthesis, Dess–Martin oxidation of alcohol and Wittig reaction. The total synthesis



Scheme 26 Total synthesis of petrosiol B 268 & petrosiol D 269 by Geng and coworkers.

began with the known two step Corey–Fuchs reaction in which 3-(2-furyl)acrolein **243** was transformed into terminal alkyne **244** (86% overall yield) under the presence of carbon tetrabromide and triphenylphosphine in DCM. Next, terminal alkyne **244** was coupled with 3-iodopropargyl alcohol **245** in the presence of copper chloride, sodium hydroxide in butyl amine to furnish compound **246**, which was subjected to Dess–Martin oxidation in conjugation with Wittig reaction in the presence of phosphorane to form ester **247**. In the final step, reduction using DIBAL led to the synthesis of final natural product atractylodinol **248** in 88% yield (Scheme 24).

2.4.3. Distaminolyne A synthesis. Distaminolyne A **258** is a first naturally occurring compound, featuring diacetylene 1amino 2-alcohol core structure. It was extracted from the New Zealand ascidian *Pseudodistoma opacum* exhibiting antimicrobial activity against several bacterial species such as *E. coli, S. aureus* and *M. tuberculosis.*⁹⁹ As *M. tuberculosis* remains a global health threat with unprecedented levels, spurring the need for effective inhibitors.^{100,101} Owing to potential biological property, Dumpala¹⁰² *et al.*, in 2017 proposed the total synthesis of distaminolyne A **258** utilizing a number of key synthetic steps. These steps including Corey–Fuchs reaction, Cadiot– Chodkiewicz coupling and Witting olefination reaction. The total synthesis started with the formation of bromoalkynes analogue **251** in two steps involving the reaction of commercially available 4-pentyn-1-ol **249** under the presence of PMB-OH and amberlyst-15 to form PMB ether 250 (90%) followed by its conversion to bromoalkyne 251 (80%) in the presence of Nbromosuccinimide (NBS) and AgNO₃ (as catalyst). Next, the second coupling partner 256 of Cadiot-Chodkiewicz reaction was synthesized. For this purpose, 9-dacene-1-ol 252 was transformed into compound 253 over few steps. Next, compound 253 was subjected to p-anisyl group deprotection in the presence of DDQ to furnish alcohol 254 in 89% yield followed by DMP catalyzed oxidation to form Corey-Fuchs reaction precursor. Subsequent reaction with CBr₄ and triphenyl phosphine (TPP) yielded dibromide compound 255 (86%) succeeded by its treatment with n-BuLi in THF to afford alkyne 256 in 90% yield. Having the both coupling partners in hand, Cadiot-Chodkiewicz coupling of 251 & 256 led to the synthesis of diacetylene-1-amino-2-alcohol 257 (84%) under the influence of copper catalysis. Next, the desired natural product 258 was synthesized from compound 257 over few steps (Scheme 25).

2.4.4. Petrosiol B & D synthesis. Polyacetylenes are a large group of naturally occurring compounds featured with multitudinous double and triple bonds.⁸⁴ Petrosiol B & D fits into the class of these polyacetylene natural products extracted from marine sponge named *Petrosia strongylata*. These types of compounds are emphasized by various medicinal properties including neuritogenic, anti-inflammatory, antiviral, antitumor and anti-microbial.¹⁰³ Taking into account the significant potentials of these type of natural products Geng¹⁰⁴ *et al.*, in



Scheme 27 Total synthesis of Waihoensene 279 by Lee and coworkers

2019 devised the total synthesis of petrosiol B **268** & D **269**, reporting for the first time the total synthesis of petrosiol B **268** with 13 steps in 10% overall yield. The trajectory of the total synthesis involved Ohira–Bestmann homologation, Corey– Fuchs alkynes synthesis and Cadiot–Chodkiewicz reaction as key steps. The total synthesis commenced from unexpensive isopropylidene- α -D-mannofuranose **259** which was subjected to Ohira–Bestmann homologation in conjugation with its treatment with K₂CO₃ and MOM protection to furnish terminal alkyne **260** (93%). The synthesized alkyne **260** was then subjected to alkylation with bromide compound **261** under the influence of HMPA and butyl lithium followed by its hydrogenation in the presence of ethyl acetate and methanol to furnish compound **262** in 94% yield. Next, *cis*-olefin **263** was obtained from compound **263** over few steps. The regioselective cleavage of isopropylidene region of the compound **263** under the presence of periodic acid in conjugation with Corey–Fuchs reaction in assistance of CBr_4 and PPh_3 led to the formation of dibromoalkene **264** in 51% yield. The synthesized dibromoalkene **264** underwent sodium hydride catalyzed dehydrobromination to furnish mono-bromoalkyne compound **265**. In the next step, compound **265** was subjected to Cadiot–Chodkiewicz coupling reaction with propargyl alcohol **266** in the presence of copper chloride, hydroxylamine, butylamine and diethyl ether to access diynes compound **267** in 68% yield. In the last step, the deprotection of terminal isopropylidene group of **267** in the presence of 3 N HCl led to the synthesis of natural product *i.e.*, petrosiol B **268** in 97% yield. The other natural product *i.e.*, petrosiol D **269** (98%) was also synthesized from the same precursor **259** over a few steps (Scheme 26).



Scheme 28 Route leading towards the total synthesis of shagene A 289 by Bai and coworkers.

2.5. Synthesis of terpene-based natural products

2.5.1. Waihoensene synthesis. Waihoensene **279** is a naturally occurring tetracyclic diterpene, derived from New Zealand podocarp, *Podocarpus totara* var. *waihoensis* by Weavers *et al.*, in 1997.¹⁰⁵ Waihoensene has intriguing architectural features as it is decorated with four contiguous quaternary carbons and thus also recognized as structurally challenging compound for total synthesis. In 2017, Lee¹⁰⁶ and coworkers reported the total of Waihoensene for the first time from commercially available

reagents. The total synthesis commenced from a racemic keto ester 270 which was subjected to Lombardo–Takai olefination in the presence of Zn, TiCl₄ and CH₂I₂ followed by lithium aluminum hydride (LAH) mediated reduction to furnish alcohol 271 (91%). Next, Swern's oxidation of compound 271 in conjugation with Horner Wadsworth–Emmons reaction yielded α , β unsaturated ester 272 (93%). Selective reduction of compound 272 employing magnesium and then partial reduction using DIBAL generated aldehyde 273 in 97% yield. Aldehyde 273 was



Scheme 29 Total synthesis of houttuynoid B 301 by Kerl and coworkers.



transformed into propargylic alcohol 274 (91%) utilizing Corey-Fuchs reaction conditions in conjugation with hydroxymethylation. Next, tetracyclic product 275 was accessed from compound 274 over a few steps. Compound 275 was further subjected to dihydroxylation in the presence of OsO_4 succeeded by selective tosylation using TsCl to furnish compound 276 (39%). In the next step, the formation of enone 277 was achieved *via* elimination reaction in the presence of DBU followed by PDC mediated oxidation. Reaction of enone compound 277 with cyanocopper and boron trifluoride etherate in conjugation with LiHMDS and methyl iodide furnished methyl substituted compound 278 in 75% yield. In the final step, employing Petasis reagent (Cp_2TiMe_2) in toluene, natural product Waihoensene 279 was achieved in 32% yield (Scheme 27).

2.5.2. Synthesis of key intermediate of shagene A. Shagene A 289 is a tricyclic sesquiterpenoid, extracted for the first time from soft corals of Scotia Sea by baker group in 2014.107 Shagene A showcase high toxicity against parasite Leishmania donovani (IC₅₀ = 5 μ M), which is a causative agent for serious visceral leishmaniasis.¹⁰⁸ In 2024, Bai⁹ et al., demonstrated an efficient route leading towards the total synthesis of Shagene A 289 by employing ring closing cascade reaction of dienyne 286 constructed via Corey-Fuchs reaction, into 5/6 membered bicyclic compound. The ring closing metathesis was succeeded by the formation of diazoacetate 287 which was considered hypothetical key intermediate for the total synthesis of shagene A 289. The total synthesis was initiated with hydroxyl group protection of ester 280 in conjunction with hydrolysis followed by installation of chiral auxiliary 281 in the presence of DCC and DMAP to furnish amide 282 in

86% yield. Next, 282 was subjected to the subsequent aldol reaction by reacting it with acrolein followed by hydroxyl group protection with TBS and reductive cleavage of previously installed chiral auxiliaries in the presence of DIBAL-H to access compound 283 (in 86% yield). The conversion of aldehyde 283 to alkyne 285 took place by Corey-Fuchs reaction utilizing PPh₃ and CBr₄ and then *n*-BuLi and alkyl iodide over 2 steps reaction (resulting in 96% yield). The internal alkyne 285 was then subjected to selective deprotection of TBDPS followed by oxidation in the presence of DMP to form an aldehyde in 87% yield. Further, next step proceeded with the treatment of aldehyde with Grignard reagent via nucleophilic addition to generate two diastereomers 286a (53%) and 286b (31%). Both the isomers were transformed to the cyclic compound 287 over a few steps. The compound 286a was subjected to ring closing cascade reaction to deliver cyclic compound 287 (in 28% yield) catalyzed by Grubbs 2nd catalyst, 2-bromoacetic acid, DCC DMAP and N,N'-ditosylhydrazine (for the installation of diazo group) over three steps. Compound 286b was also transformed into compound 287 over several reaction steps. It was first reacted with Grubb's 2nd catalyst followed by its treatment with MnO₂ and then sodium borohydride and CeCl₃·7H₂O. Next, its treatment with bromoacetic acid, DCC DMAP and N,N'-ditosylhydrazine led to the synthesis of 287 in 28%. The target compound 289 was assumed to achieve over few steps from compound 288. Several reaction conditions were applied for the efficient conversion of the intermediate 287 to 3-membered ring compound 288 via cyclopropanation reaction but the starting material was decomposed (Scheme 28).

2.6. Synthesis of flavonoid-based natural products

2.6.1. Houttuynoid synthesis. Houttuynoid 301 is a naturally occurring flavonoid glycoside that belongs to the family of *Sauruaceae* and extracted from Chinese *Houttuynia cordata* by Yao *et al.*, in 2012.¹⁰⁹ It is considered as strong antiviral flavonoid having various viral inhibition properties such as inhibition of herpes simplex virus (with IC_{50} values of 57.7 μ M).¹⁰⁹ Owing to the importance of development of new antiviral agents, Kerl and coworkers¹¹⁰ in 2016 reported for the first the total synthesis of houttuynoid B 301 in overall 9 linear steps with 11% yield. The key steps involving the total synthesis include Corey–Fuchs alkyne synthesis reaction, Sonogashira coupling and Baker–Venkataraman rearrangement. The

synthesis commenced from the unexpensive decanal **290** which was subjected to Corey–Fuchs reaction under the presence of carbon tetrabromide and triphenyl phosphine in conjugation with *n*-butyl lithium to furnish terminal alkyne **291** (70%). Next, alkyne **291** underwent Sonogashira coupling reaction with iodophenol **292** in the presence of Pd(PPh₃)₂Cl₂, CuI and trie-thylamine to furnish **293** (51%) which was then rearranged to a benzofuran moiety. In the next step, the aldehydic functionality on **293** underwent Pinnick oxidation in the presence of NaH₂PO₄, NaClO₂ and 2-methyl-2-butene2 **294** to furnish carboxylic framework **295** in 71% yield. Further, to achieve HOBT activated ester **296** (87%), the carboxylic compound **295** was reacted with 1-hydroxybenzotriazole (HOBT) and ethyl-3-(3-dimethylaminopropyl)-carbodiimide in CH₂Cl₂. On the other



Scheme 31 Total synthesis of haliclamide 315 by Gahalawat and coworkers.

side, the second precursor **298** was synthesized from commercially available chrysin **297** over a few steps. Having both the reaction partners *i.e.*, **296** & **298** in hand, HOBT activated ester **296** was made to react with **298** in the presence of sodium hydride in THF to form arylester **299** (76%). Next, chromenone **300** (57%) was accessed from arylester **299** *via* Baker–Venkataraman rearrangement under the presence of K₂CO₃ and TBAB in toluene. Finally, the desired natural product houttuynoid B **301** was synthesized by deprotection of chromenone **300** under the presence of sodium methoxide in toluene with 99% yield (Scheme 29).

2.7. Synthesis of polyphenol-based natural products

2.7.1. Nepetoidin B synthesis. Nepetoidin B 306 belongs to the class of phenolic compounds existing in two isomeric forms *i.e.*, (Z, E)- and (E, E). It is extracted from *P. frutescens*,¹¹¹ *P.*

forsteri¹¹² and S. miltiorrhiza¹¹³ and depicting remarkable bioactive properties including anti-viral, anti-fungal and antioxidant properties.114 It is also used for the production of nitric oxide and the inhibition of xanthine oxidase. Nepetoidin B was synthesized for the first time in 2018 by Timokhin and coworkers in 17% overall yield.¹¹⁵ Due to the ongoing research on the synthesis of bioactive phenolic compounds, Yao¹¹⁶ et al., in 2020 developed a three steps synthesis of nepetoidin B with an overall 52% yield. The key steps involved Corey-Fuchs alkyne synthesis reaction, Ru-catalyzed anti-Markovnikov addition and demethylation. The synthesis commenced from the commercially available 3,4-dimethoxybenzaldehyde 197 which underwent Corey-Fuchs reaction to form respective terminal alkyne 302 (95%). Next, the alkyne 302 was subjected to anti-Markovnikov addition with 3,4-dimethoxycinnamic acid 303 under the presence of Ru-catalyst 304 to afford tetramethylated



Scheme 32 Total synthesis of fusaramin 328 by Kimishima and coworkers.

nepetoidin B **305** in 90% yield. Subsequent demethylation of compound **305** in the presence of Me₃SiI and pyridine afforded the mixture of (Z, E)/(E, E) isomers of nepetoidin B **306** with 2; 8 : 1 ratio and 61% yield (Scheme 30).

2.8. Synthesis of peptide-based natural products

2.8.1. Haliclamide synthesis. Haliclamide 315 is a naturally occurring compound, extracted from the marine sponge Haliclona sp. of Vanuatu island by Randazzo et al., in 2001.117 Haliclamide exhibited excellent in vitro anti-tumor properties against human lung carcinoma cell line. The first total synthesis of haliclamide was also done by the same group at the time of its extraction. Due to its significant anti-tumor properties, the total synthesis of haliclamide has gained much interest of synthetic chemists. In this perspective, Gahalawat¹¹⁸ et al., in 2016 published the total synthesis of haliclamide 315 employing MacMillan cross aldol reaction, Corey-Fuchs alkyne synthesis, Yamaguchi-Hirao Reaction, Steglich esterification reaction and macro-lactamization reaction as key steps. The total synthesis began with the commercially available ethylene glycol 307, which was subjected to MacMillan cross aldol strategy in the presence of L-proline followed by NaBH₄-mediated reduction to furnish 1,3-diol 308 (85%). Next, compound 308 was easily transformed into monobenzylated derivative 309 (91%) via treating it with K₂CO₃ and BnBr followed by subsequent silvl deprotection, NaIO₄ catalyzed oxidation and Corey-Fuchs alkyne synthesis reaction under the presence of carbon tetrabromide and phosphine triphenyl to furnish acetylene moiety 310 in 90% yield. Next, compound 310 was subjected to Yamaguchi-Hirao alkylation protocol with glycidol silyl ether 229b under the presence of boron trifluoride diethyl etherate to access homopropargylic alcohol 311 in 88% yield. Compound 311 was then transformed into compound 312 over a few steps. Next, LiOH mediated saponification of compound 312 took place succeeded by Steglich esterification reaction with alcohol 313 under the presence of DCC and DMAP to form compound 314 (89%). Next, subsequent Cbz deprotection, hydrogenation and HATU mediated macro-lactamization finally furnished haliclamide 315 in 71% yield (Scheme 31).

2.9. Miscellaneous natural products

2.9.1. Fusaramin synthesis. Fusaramin 328 is a naturally occurring potent antimitochondrial compound obtained from agar broth of *Fusarium* sp. FKI-7550.¹¹⁹ This compound shows excellent anti-fungal activities against plant disease-causing fungi. Thus, in 2024, Kimishima¹²⁰ *et al.*, envisioned the total synthesis of Fusaramin 328 and enabled the elucidation of its stereochemical structure. The total synthesis commenced with the formation of vinyl iodide 319 (37% yield) from gem-dibromo alkene 316 *via* sequential Corey–Fuchs, methylation and Schwartz hydrozirconation reaction in the presence of *n*-BuLi, MeI, DIBAL-H, Cp₂ZrCl₂ and I₂. Next, phenylalanine derivative 320 was condensed with Meldrum's acid followed by the ketene formation and attack of the Boc-amine group to access tetramic acid fragment 321 with 62% yield. The next step involved treatment of asymmetric silyl protected alcohol 322 under the

conditions of PPh₃, I₂ and imidazole (Appel conditions) in DCM to afford alkyl iodo compound **323**. This reaction was followed by the generation of an intermediate **324** *via* lithium–halogen exchange in the presence of *n*-BuLi which was then quenched with *B*-methoxy-9-BBN. The intermediate **324** underwent Suzuki–Miyaura coupling reaction with **319**, followed by silyl deprotection in the presence of TBAF to deliver chiral alcohol **325** in 79% yield. Further, two steps oxidation of the compound **325** took place to form carboxylic acid compound **326** (76%) which was reacted with **321** to form Boc protected fusaramin **327**. Finally, the deprotection of **327** in the presence of TFA, TBAF and AcOH led to the synthesis of desired product **328** with 82% yield (Scheme 32).

3. Conclusion

In conclusion, this manuscript summarizes the significance of Corey–Fuchs reaction in the total synthesis of various biologically important natural products as a key step. The protocol facilitates the direct and efficient pathway to alkynes from aldehydes and has been the area of extensive research and development. This review covers the total synthesis of various natural products *i.e.*, polyketides, alkaloids, peptides and polyacetylene-based natural products utilizing the Corey–Fuchs reaction as one of the significant steps. Current breakthroughs and modifications of the reaction have further broadened its viability and practicality, and is expected to remain a corner-stone in the synthesis of complex compounds for the foresee-able future.

Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Authors are thankful to the facilities provided by Government College University Faisalabad, Pakistan. A. Irfan extends his appreciation to the Deanship of Research and Graduate Studies at King Khalid University for funding this work through Large Groups Research Project under grant number (RGP2/172/45).

References

- 1 N. Desai, N. McKelvie and F. Ramirez, J. Am. Chem. Soc., 1962, 84, 1745–1747.
- 2 F. Pandolfi, I. Chiarotto and M. Feroci, *Beilstein J. Org. Chem.*, 2018, 14, 891–899.
- 3 H. Okumura, N. I. Prakoso, T. Morozumi and T. Umezawa, *Org. Lett.*, 2024, **26**, 9817–9821.

- 4 A. K. Ghosh and Y. Wang, *Tetrahedron Lett.*, 2000, **41**, 4705–4708.
- 5 S. Das, S. Paul, K. K. Mandal, A. Anoop and S. Nanda, *J. Org. Chem.*, 2024, **89**, 15764–15776.
- 6 Y. Garg, S. Gahalawat and S. K. Pandey, *RSC Adv.*, 2015, 5, 38846–38850.
- 7 M. G. Jakobsen, A. Vik and T. V. Hansen, *Tetrahedron Lett.*, 2014, 55, 2842–2844.
- 8 H. F. Sneddon, M. J. Gaunt and S. V. Ley, *Org. Lett.*, 2003, 5, 1147–1150.
- 9 M. Bai, X. Wang and Q. Li, Tetrahedron, 2024, 154, 133846.
- 10 E. Corey and P. Fuchs, *Tetrahedron Lett.*, 1972, 13, 3769-3772.
- 11 D. Habrant, V. Rauhala and A. M. Koskinen, *Chem. Soc. Rev.*, 2010, **39**, 2007–2017.
- 12 M. Dhameja and J. Pandey, Asian J. Org. Chem., 2018, 7, 1502–1523.
- 13 F. Eymery, B. Iorga and P. Savignac, *Synthesis*, 2000, **2000**, 185–213.
- 14 Y. Thummala, G. V. Karunakar and V. R. Doddi, *Adv. Synth. Catal.*, 2019, **361**, 611–616.
- 15 W. Doherty, N. Adler, A. Knox, D. Nolan, J. McGouran, A. P. Nikalje, D. Lokwani, A. Sarkate and P. Evans, *Eur. J. Org Chem.*, 2017, **2017**, 175–185.
- 16 S. Kumar, M.-T. Ho and Y.-T. Tao, *Org. Lett.*, 2016, **18**, 200–203.
- 17 A. Irfan, S. Faisal, S. Ahmad, S. A. Al-Hussain, S. Javed, A. F. Zahoor, B. Parveen and M. E. Zaki, *pharmaceuticals*, 2023, 16, 344.
- 18 S. Faiz, A. F. Zahoor, N. Rasool, M. Yousaf, A. Mansha, M. Zia-Ul-Haq and H. Z. Jaafar, *Molecules*, 2015, 20, 14699–14745.
- 19 P. J. Parsons, C. S. Penkett and A. J. Shell, *Chem. Rev.*, 1996, **96**, 195–206.
- 20 Y. Bai, X. Shen, Y. Li and M. Dai, *J. Am. Chem. Soc.*, 2016, **138**, 10838–10841.
- 21 D. L. Boger, S. Ichikawa and W. Zhong, J. Am. Chem. Soc., 2001, **123**, 4161–4167.
- 22 H. Johansson and D. S. Pedersen, *Eur. J. Org Chem.*, 2012, 2012, 4267–4281.
- 23 M. Yao, W. Yang, J. Li, C. Huang, J. Fang, S. Qin, S. Liu and X. Yang, *Chin. J. Chem.*, 2024, **42**, 1509–1514.
- 24 A. Mushtaq, A. F. Zahoor, M. Bilal, S. M. Hussain, M. Irfan, R. Akhtar, A. Irfan, K. Kotwica-Mojzych and M. Mojzych, *Molecules*, 2023, 28, 2722.
- 25 J. S. Lee, J. Shin, H. J. Shin, H. S. Lee, Y. J. Lee, H. S. Lee and H. Won, *Eur. J. Org Chem.*, 2014, **2014**, 4472–4476.
- 26 T. Sengoku, S. Xu, K. Ogura, Y. Emori, K. Kitada, D. Uemura and H. Arimoto, *Angew. Chem.*, 2014, **126**, 4297–4300.
- 27 S. Huang, S. Chen, G. Wang, J. Zhang, L. Tang, G. Du and X. Wang, *Synthesis*, 2015, 47, 1303–1308.
- 28 M. M Heravi, S. Asadi, N. Nazari and B. Malekzadeh Lashkariani, *Curr. Org. Chem.*, 2015, **19**, 2196–2219.
- 29 N. Li, Z. Shi, Y. Tang, J. Chen and X. Li, *Beilstein J. Org. Chem.*, 2008, 4, 48.
- 30 J. Adrian and C. B. Stark, J. Org. Chem., 2016, 81, 8175-8186.

- 31 K. Krohn and J. Rohr, *Bioorganic Chemistry Deoxysugars*, *Polyketides and Related Classes: Synthesis, Biosynthesis, Enzymes*, 2008, pp. 127–195.
- 32 P. M. Brown and R. H. Thomson, *J. Chem. Soc., Perkin Trans.* 1, 1976, 997–1000.
- 33 D.-S. Hsu and J.-Y. Huang, J. Org. Chem., 2012, 77, 2659–2666.
- 34 K. J. Ngwira, A. L. Rousseau, M. M. Johnson and C. B. de Koning, *Eur. J. Org Chem.*, 2017, 2017, 1479–1488.
- 35 S. M. Dalby and I. Paterson, *Curr. Opin. Drug Discovery Dev.*, 2010, **13**, 777–794.
- 36 C. I. MacGregor, B. Y. Han, J. M. Goodman and I. Paterson, *Chem. Commun.*, 2016, **52**, 4632–4635.
- 37 K.-H. Altmann and J. Gertsch, *Nat. Prod. Rep.*, 2007, 24, 327– 357.
- 38 Y. Inahashi, M. Iwatsuki, A. Ishiyama, A. Matsumoto,
 T. Hirose, J. Oshita, T. Sunazuka, W. Panbangred,
 Y. Takahashi and M. Kaiser, *Org. Lett.*, 2015, 17, 864–867.
- 39 J. Oshita, Y. Noguchi, A. Watanabe, G. Sennari, S. Sato,
 T. Hirose, D. Oikawa, Y. Inahashi, M. Iwatsuki and
 A. Ishiyama, *Tetrahedron Lett.*, 2016, 57, 357–360.
- 40 F. Doraghi, L. Rezainia, M. H. Morshedsolouk, H. Navid, B. Larijani and M. Mahdavi, *RSC Adv.*, 2025, **15**, 1134–1151.
- 41 R. Akhtar, A. F. Zahoor, M. Irfan, T. H. Bokhari and A. ul Haq, *Chem. Pap.*, 2022, **76**, 7275–7293.
- 42 Y.-Z. Shu, Q. Ye, H. Li, K. F. Kadow, R. A. Hussain, S. Huang, D. R. Gustavson, S. E. Lowe, L.-P. Chang and D. M. Pirnik, *Bioorg. Med. Chem. Lett.*, 1997, 7, 2295–2298.
- 43 J. Peng, J. Jiao, J. Li, W. Wang, Q. Gu, T. Zhu and D. Li, *Bioorg. Med. Chem. Lett.*, 2012, 22, 3188–3190.
- 44 J. Preindl, S. Schulthoff, C. Wirtz, J. Lingnau and A. Fürstner, *Angew. Chem., Int. Ed.*, 2017, **56**, 7525–7530.
- 45 A. Cutignano, I. Bruno, G. Bifulco, A. Casapullo, C. Debitus,
 L. Gomez-Paloma and R. Riccio, *Eur. J. Org Chem.*, 2001, 2001, 775–778.
- 46 T. Tanaka, Y. Murai, T. Kishi, H. Takamura and I. Kadota, *Tetrahedron Lett.*, 2018, **59**, 763–766.
- 47 C. Tanaka, J. Tanaka, R. F. Bolland, G. Marriott and T. Higa, *Tetrahedron*, 2006, 62, 3536–3542.
- 48 H. D. Arndt, S. Rizzo, C. Nöcker, V. N. Wakchaure, L. G. Milroy, V. Bieker, A. Calderon, T. T. Tran, S. Brand and L. Dehmelt, *Chem.-Eur. J.*, 2015, 21, 5311–5316.
- 49 J. H. Lang and T. Lindel, *Beilstein J. Org. Chem.*, 2019, **15**, 577–583.
- 50 N. Oku, K. Takada, R. W. Fuller, J. A. Wilson, M. L. Peach, L. K. Pannell, J. B. McMahon and K. R. Gustafson, *J. Am. Chem. Soc.*, 2010, **132**, 10278–10285.
- 51 C. K. Skepper, T. Quach and T. F. Molinski, *J. Am. Chem. Soc.*, 2010, **132**, 10286–10292.
- 52 K. Sakurai, K. Sakamoto, M. Sasaki and H. Fuwa, *Chem.-Asian J.*, 2020, **15**, 3494–3502.
- 53 S. B. Krasnoff, U. Englich, P. G. Miller, M. L. Shuler, R. P. Glahn, B. G. Donzelli and D. M. Gibson, *J. Nat. Prod.*, 2012, **75**, 175–180.
- 54 M. Yoshida, Y. Okoshi and H. Kigoshi, *Chem. Commun.*, 2023, **59**, 9880–9883.

Open Access Article. Published on 17 March 2025. Downloaded on 26/07/2025 11:45:33 PM.
Provento: This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

This article is licensed under a Creative Com

- 55 A. Sharma, S. Athe, P. Ramesh, K. Vishali and S. Ghosh, *Tetrahedron Lett.*, 2021, **82**, 153374.
- 56 W. Zhou, H. A. Alharbi, E. Hummingbird, A. T. Keatinge-Clay and T. Mahmud, *ACS Chem. Biol.*, 2022, **17**, 2039–2045.
- 57 D. Dardić, N. Böhringer, A. Plaza, F. Zubeil, J. Pohl, S. Sommer, L. Padva, J. Becker, M. A. Patras and M.-K. Bill, Org. Chem. Front., 2022, 9, 1604–1615.
- 58 S.-Z. Huang, F.-D. Kong, G. Chen, X.-H. Cai, L.-M. Zhou, Q.-Y. Ma, Q. Wang, W.-L. Mei, H.-F. Dai and Y.-X. Zhao, *Phytochemistry*, 2019, **159**, 208–215.
- 59 L. Fang, X.-Q. Song, T.-T. He, K.-K. Zhu, J.-H. Yu, J.-T. Song, J. Zhou and H. Zhang, *Fitoterapia*, 2018, **129**, 150–153.
- 60 M. C. Carson, B. J. Orzolek and M. C. Kozlowski, *Org. Lett.*, 2022, 24, 7250–7254.
- 61 S. DGS, V. R. R. Ch, T. Syed, G. Sridhar and S. R. Alapati, *Synth. Commun.*, 2024, 1–7.
- 62 X. Geng and S. J. Danishefsky, Org. Lett., 2004, 6, 413-416.
- 63 D. Sudhakar, V. R. R. Ch, T. Syed, G. Sridhar and S. R. Alapati, *Synth. Commun.*, 2024, **54**, 992–998.
- 64 S. Faiz and A. F. Zahoor, Mol. Diversity, 2016, 20, 969-987.
- 65 S. Munawar, A. F. Zahoor, S. Ali, S. Javed, M. Irfan, A. Irfan, K. Kotwica-Mojzych and M. Mojzych, *Molecules*, 2022, 27, 6953.
- 66 U. Tillmann, M. Elbrächter, B. Krock, U. John and A. Cembella, *Eur. J. Phycol.*, 2009, 44, 63–79.
- 67 E. Ito, M. Satake, K. Ofuji, N. Kurita, T. McMahon, K. James and T. Yasumoto, *Toxicon*, 2000, **38**, 917–930.
- 68 Z. Zhang, Y. Chen, D. Adu-Ampratwum, A. A. Okumu, N. T. Kenton and C. J. Forsyth, *Org. Lett.*, 2016, 18, 1824– 1827.
- 69 M. Bader, T. D. Stark, C. Dawid, S. Lösch and T. Hofmann, *J. Agric. Food Chem.*, 2014, **62**, 2479–2488.
- 70 K. Aoki, Y. Igarashi, H. Nishimura, I. Morishita and K. Usui, *Tetrahedron Lett.*, 2012, **53**, 6000–6003.
- 71 C. Mugnaini and F. Corelli, Synthesis, 2016, 48, 2085–2092.
- 72 A. Irfan, S. Faiz, A. Rasul, R. Zafar, A. F. Zahoor, K. Kotwica-Mojzych and M. Mojzych, *Molecules*, 2022, 27, 1023.
- 73 A. Kolodiazhna and O. Kolodiazhnyi, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2019, **194**, 275–276.
- 74 A. Kolodyazhnaya and O. Kolodyazhny, *Russ. J. Gen. Chem.*, 2019, **89**, 1998–2004.
- 75 S. C. Bobzin and D. J. Faulkner, *J. Org. Chem.*, 1991, 56, 4403-4407.
- 76 K. Nakagawa, Heterocycles, 1995, 41, 5.
- 77 S. J. Gharpure, D. Anuradha, J. V. Prasad and P. Srinivasa Rao, *Eur. J. Org Chem.*, 2015, **2015**, 86–90.
- 78 M. Borah, U. Borthakur and A. K. Saikia, J. Org. Chem., 2017, 82, 1330–1339.
- 79 Y. Wang, W.-Y. Zhang and S.-L. You, J. Am. Chem. Soc., 2019, 141, 2228–2232.
- 80 N. Gunawan, M. J. Nutt, A. C. Bissember, J. A. Smith and S. G. Stewart, *Synlett*, 2023, 34, 1524–1528.
- 81 P. Krishnan, F.-K. Lee, V. A. Yap, Y.-Y. Low, T.-S. Kam, K.-T. Yong, K.-N. Ting and K.-H. Lim, *J. Nat. Prod.*, 2020, 83, 152–158.

- 82 Y. Y. Mak, B. J. Loong, P. Millns, C. C. Bauer, R. S. Bon, Y. Mbaki, F. K. Lee, K. H. Lim, C. Kong and S. M. Then, *Phytother. Res.*, 2022, **36**, 2952–2963.
- 83 K. Annapurna and A. V. Narsaiah, *Tetrahedron*, 2024, 155, 133909.
- 84 Z.-F. Zhou, M. Menna, Y.-S. Cai and Y.-W. Guo, *Chem. Rev.*, 2015, **115**, 1543–1596.
- 85 M. Smietana, E. Benedetti, C. Bressy and S. Arseniyadis, *Efficiency in Natural Product Total Synthesis*, 2018, 319–344.
- 86 J.-X. Gong, H.-Y. Wang, L.-G. Yao, X.-W. Li and Y.-W. Guo, Synlett, 2016, 27, 391–394.
- 87 C. Djerassi and W. K. Lam, Acc. Chem. Res., 1991, 24, 69-75.
- 88 K. Suzuki, F. Shono, H. Kai, T. Uno and M. Uyeda, *J. Enzyme Inhib.*, 2000, 15, 357–366.
- 89 N. M. Carballeira, N. Montano, R. Alvarez-Velilla, C. F. Prada, R. M. Reguera and R. Balaña-Fouce, *Mar. Drugs*, 2013, 11, 3661–3675.
- 90 J. Adrian and C. B. Stark, Eur. J. Org Chem., 2016, 2016, 4607–4610.
- 91 R. Nshimiyimana, T. F. Lam, S. Aggarwal, C. N. Serhan and N. A. Petasis, *RSC Adv.*, 2022, **12**, 11613–11618.
- 92 R. Nshimiyimana, S. J. Glynn, C. N. Serhan and N. A. Petasis, *Org. Biomol. Chem.*, 2023, **21**, 1667–1673.
- 93 F. Fullas, D. M. Brown, M. C. Wani, M. R. Wall, T. E. Chagwedera, N. R. Farnsworth, J. M. Pezzuto and A. D. Kinghorn, *J. Nat. Prod.*, 1995, **58**, 1625–1628.
- 94 H. Takamura, H. Wada, N. Lu and I. Kadota, *Org. Lett.*, 2011, **13**, 3644–3647.
- 95 C. Garcia-Ruiz, I. Cheng-Sanchez and F. Sarabia, *Synthesis*, 2016, **48**, 1655–1662.
- 96 W.-g. Li, F.-y. Dai, Y.-x. Cheng, G.-f. Yin, J.-l. Bi and D.-p. Li, *Chem. Res. Chin. Univ.*, 2013, **29**, 290–293.
- 97 Y. Nishikawa, I. Yasuda, Y. Watanabe and T. Seto, *Yakugaku Zasshi*, 1976, **96**, 1322–1326.
- 98 G. A. Kraus, P. Dong, Y. Qu, A. Evans and S. Carpenter, *Tetrahedron Lett.*, 2016, **57**, 5185–5187.
- 99 J. Wang, A. N. Pearce, S. T. Chan, R. B. Taylor, M. J. Page,
 A. Valentin, M.-L. Bourguet-Kondracki, J. P. Dalton,
 S. Wiles and B. R. Copp, *J. Nat. Prod.*, 2016, **79**, 607–610.
- 100 A. Irfan, S. Faisal, A. F. Zahoor, R. Noreen, S. A. Al-Hussain,B. Tuzun, R. Javaid, A. A. Elhenawy, M. E. Zaki andS. Ahmad, *Pharmaceuticals*, 2023, 16, 829.
- 101 A. F. Zahoor, M. Yousaf, R. Siddique, S. Ahmad, S. A. R. Naqvi and S. M. A. Rizvi, *Synth. Commun.*, 2017, 47, 1021–1039.
- 102 M. Dumpala, S. Theegala and R. K. Palakodety, *Tetrahedron Lett.*, 2017, **58**, 1273–1275.
- 103 R. Negri, Fitoterapia, 2015, 106, 92-109.
- 104 J. Geng, Q. Ren, C. Chang, X. Xie, J. Liu and Y. Du, *RSC Adv.*, 2019, **9**, 10253–10263.
- 105 D. B. Clarke, S. F. Hinkley and R. T. Weavers, *Tetrahedron Lett.*, 1997, **38**, 4297–4300.
- 106 H. Lee, T. Kang and H. Y. Lee, Angew. Chem., 2017, 129, 8366-8369.
- 107 J. L. von Salm, N. G. Wilson, B. A. Vesely, D. E. Kyle, J. Cuce and B. J. Baker, *Org. Lett.*, 2014, **16**, 2630–2633.

- Review
- 108 World Health Organization, *Fourth WHO report on neglected* tropical diseases, World Health Organization, Geneva, 2017.
- 109 S.-D. Chen, H. Gao, Q.-C. Zhu, Y.-Q. Wang, T. Li, Z.-Q. Mu, H.-L. Wu, T. Peng and X.-S. Yao, *Org. Lett.*, 2012, 14, 1772– 1775.
- 110 T. Kerl, F. Berger and H. G. Schmalz, *Chem.-Eur. J.*, 2016, **22**, 2935–2938.
- 111 T. Nakanishi, M. Nishi, A. Inada, H. Obata, N. Tanabe, S. Abe and M. Wakashiro, *Chem. Pharm. Bull.*, 1990, 38, 1772–1774.
- 112 R. Kubínová, E. Švajdlenka, K. Schneiderová, Z. Hanáková,
 S. Dall'Acqua and O. Farsa, *Biochem. Syst. Ecol.*, 2013, 49, 39–42.
- 113 X. Wu, H. Gao, W. Sun, J. Yu, H. Hu, Q. Xu and X. Chen, *Phytother. Res.*, 2017, **31**, 1072–1077.

- 114 R. J. Grayer, M. R. Eckert, N. C. Veitch, G. C. Kite, P. D. Marin, T. Kokubun, M. S. Simmonds and A. J. Paton, *Phytochemistry*, 2003, 64, 519–528.
- 115 V. Timokhin, M. Regner, Y. Tsuji, J. Grabber and J. Ralph, *Synlett*, 2018, **29**, 1229–1231.
- 116 M. Yao, J. Zhang, S. Yang and H. Xiong, *ARKIVOC*, 2020, 2020, 52–59.
- 117 A. Randazzo, C. Debitus and L. Gomez-Paloma, *Tetrahedron*, 2001, **57**, 4443–4446.
- 118 S. Gahalawat and S. K. Pandey, Org. Biomol. Chem., 2016, 14, 9287–9293.
- 119 K. Sakai, Y. Unten, M. Iwatsuki, H. Matsuo, W. Fukasawa, T. Hirose, T. Chinen, K. Nonaka, T. Nakashima and T. Sunazuka, *J. Antibiot.*, 2019, **72**, 645–652.
- 120 A. Kimishima, D. Hagimoto, M. Honsho, K. Sakai, S. Honma, S.-i. Fuji, M. Iwatsuki, T. Tokiwa, K. Nonaka and T. Chinen, *Org. Lett.*, 2024, **26**, 597–601.