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Recent advancements in the chemistry of Diels–Alder reaction for total synthesis of natural products: a comprehensive review (2020–2023)

Anitesh Rana,[†] Anupam Mishra  [†] and Satish K. Awasthi  ^{*}

Despite being discovered nearly a century ago, the Diels–Alder (DA) reaction remains a crucial tool in the total synthesis of natural products. It accommodates a broad range of building blocks with varying complexity and levels of derivatization, allowing the formation of six-membered rings with precise stereochemistry. This, in turn, simplifies the synthesis of core structures found in many natural products. In recent years, modifications to the traditional Diels–Alder reaction have expanded its scope. These modifications include the inverse electron demand Diels–Alder reaction, dehydro Diels–Alder reaction, hetero-Diels–Alder reaction, photoenolization Diels–Alder reaction, asymmetric Diels–Alder reaction, and domino Diels–Alder reaction have been employed to extend the scope of this process in the synthesis of natural products. This review discusses the application of the Diels–Alder reaction in the total synthesis of natural products from 2020 to 2023, along with select methodologies that are inspired by or can be used to synthesize natural products.

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Chemical Biology Laboratory, Department of Chemistry, University of Delhi, Delhi 110007, India. E-mail: Satishpna@gmail.com

[†] Contributed equally.

1. Introduction

Natural products are renowned for their remarkable structural diversity and complexity, and have played a pivotal role in



Anitesh Rana

organocatalysis, organometallic catalysis, photocatalysis, electrocatalysis and in microdroplet chemistry.

Anitesh Rana, born in Paschim Bardhaman, West Bengal, completed Bachelor's degree in Chemistry from Visva-Bharati University in 2021. Later, he took admission in University of Delhi and received his Master's degree with specialization in Organic Chemistry in 2023. He qualified the CSIR-UGC NET DECEMBER 2023 with JRF (AIR 29) and GATE 2024 with AIR 146. His research interest is in organic synthesis, catalysis like



Anupam Mishra

Technology (DST), supporting his studies from graduation through post-graduation. Subsequently, he was awarded the prestigious INSPIRE fellowship by DST for his postdoctoral research. Additionally, he achieved an impressive All India Rank (AIR) 47 in the Council of Scientific & Industrial Research (CSIR) NET JRF Fellowship examination. He has many publications in reputed international journals with filled one international patent. His research interests include advanced synthetic methods, medicinal chemistry, heterocyclic chemistry, heterogeneous catalysis, peptide chemistry and drug discovery.

Dr Anupam Mishra completed his BSc at the University of Delhi in India, 2015. Later, in 2017, he finished his postgraduate studies at the Chemistry Department, University of Lucknow in India. He received his PhD degree from the Department of Chemistry, University of Delhi under the guidance of Professor S. K. Awasthi. Dr Anupam Mishra was a recipient of the INSPIRE (SHE) scholarship from the Department of Science and



Scheme 1 The reaction discovered by Diels and Alder in 1928.⁷

advancing chemical biology and driving the discovery of new pharmacophores for drug development.^{1–4} The abundance of heteroatom substituents and stereocenters in natural products enhances their selective binding affinity for specific biological targets, often surpassing that of synthetic compounds.⁵ Additionally, the diverse functional groups in these natural products enhance their cell permeability, positioning them as promising candidates for drug discovery.⁶ Nevertheless, natural sources are unable to sustainably supply these compounds in their native or modified forms to meet rising demand. As a result, total synthesis has become a viable alternative for producing bioactive natural products and their analogues, utilizing scalable techniques such as diverted organic synthesis (DOS) and

function-directed synthesis (FDS). Diels–Alder reactions are among the most efficient methods for the total synthesis of natural products, particularly due to the polycyclic structures present in many natural compounds.

In 1928, Otto Diels and Kurt Alder⁷ developed an extraordinary method for diene synthesis, named Diels–Alder reaction (Scheme 1). A conjugated diene **1** and a dienophile **2** are involved in this reaction, which is a through [4+2] cycloaddition reaction that forms a six-membered ring having up to four stereogenic centres. Since it follows a concerted reaction path, the Diels–Alder reaction affords high stereospecificity. The stereochemistry of the product, formed by cycloaddition reaction between electron-rich 4 π and electron-poor 2 π system, was explained by FMO theory.^{8,9} In case of thermally allowed Diels–Alder reaction between 1,3-butadiene derivatives and ethylene there is a primary interaction and a secondary interaction.^{10–12} The secondary interaction produced a kinetic *endo* product in major amount than the thermodynamically stable *exo* product.¹³ In 1990, Hondrogiannis *et al.*¹⁴ explained the *endo* selectivity by illustrating an example where *endo* product formed in 9 : 1 ratio (Fig. 1).¹⁴

Generally, the Diels–Alder reactions (DARs) were done under thermal conditions, but were accelerated by using Lewis acid catalysis, which was done by Yates and Eaton in 1960.¹⁵

Moreover, in 2004, Tririya and Zanger¹⁶ reported that the Diels–Alder reaction can proceed at room temperature in quantitative yield by making the diene **7** more electron rich or the dienophile **2** more electron deficient (Fig. 2).¹⁶ Different kinds of substrates can participate in a Diels–Alder reaction. Due to the high versatility and huge applications of Diels–Alder reactions, the Nobel Prize in Chemistry was awarded to Otto Diels and Kurt Alder in 1950.

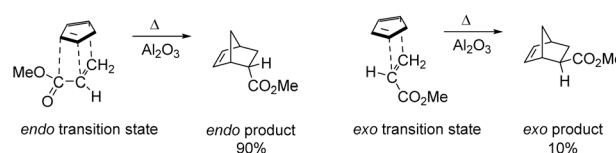
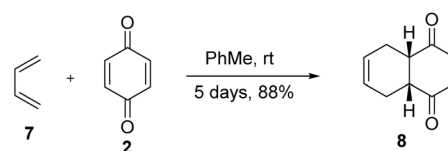
The use of Diels–Alder reactions in total synthesis was not taken up until Woodward *et al.* reported the total synthesis of cortisone, cholesterol in 1952 followed by reserpine in 1956, all of which involved the Diels–Alder reaction.^{17,18} These two total syntheses of natural products have opened a new avenue in total synthesis using Diels–Alder reactions (DARs) and proven effective in constructing various natural products and complex architectures.



Satish K. Awasthi

Dr Satish Kumar Awasthi earned his DPhil from Allahabad University, UP, India, in 1991. Following this, he received a National Research Associateship from the DBT, Government of India, and conducted research at the Molecular Biophysics Unit at IISc, Bangalore. His career is decorated with numerous prestigious awards, such as the TIT-UNICEF Fellowship Award in Tokyo, Japan; the INSA Visiting Scientist Award in Germany; the

ICMR-Biomedical Young Scientist Award at the University of Copenhagen, Denmark; and the Commonwealth Academic Fellowship Award at the Royal Veterinary College, University of London, UK. Currently, Prof. S. K. Awasthi is senior Professor and the Head of the Department of Chemistry at the University of Delhi. His research spans various areas, including the antisense properties of peptide nucleic acids (PNAs), the design and synthesis of small molecules for antibacterial and antimalarial studies, X-ray analysis of small molecules, and heterogeneous catalysis. For more detailed information, please visit (<http://www.du.ac.in/filead-min/DU/faculty/PDF/3023.pdf>).

Fig. 1 The orbital interactions between the diene and dienophile.¹⁵Fig. 2 Tririya and Zanger's work in 2004.¹⁶

Previous studies have emphasized the diverse applications of Diels–Alder reactions. Bhat *et al.*¹⁹ highlighted advancements in the inverse electron demand Diels–Alder reaction, particularly its role in the total synthesis of bioactive natural products over a thirteen-year period (2011 to 2023). Similarly, Kalesse *et al.*²⁰ (2022) presented a review focusing on the applications of the Diels–Alder reaction in natural product synthesis from 2017 to 2020. Their review also explored methodologies inspired by or applicable to natural product synthesis, encompassing intermolecular, intramolecular, hetero, dehydro, inverse electron demand hetero, and aza-Diels–Alder reactions. These approaches have been instrumental in the total synthesis of various polycyclic natural products with significant biological activities, including anti-tumor, antioxidant, anti-malarial, anti-cancer, anti-microbial, and anti-inflammatory properties.^{19–23}

In this review, we aim to spotlight key Diels–Alder reactions reported in the literature between 2020 and 2023 that offer new strategies and approaches for the total synthesis of natural products using normal Diels–Alder (DA) reaction, Intramolecular Diels–Alder (IMDA) reaction, Dehydro Diels–Alder (DDA) reaction, Hetero-Diels–Alder (HDA) reaction, Photo-enolization Diels–Alder (PEDA) reaction, Inverse Electron Demand and Hetero-Diels–Alder (IEDDA) reaction.

In this study, we present the total synthesis of approximately 80 natural products utilizing Diels–Alder reactions, featuring key scaffolds such as *para*-hydroquinone (*p*-HQ), azulene phthalimides, tetrahydrocarbazoles, tetra and tri cyclic cores, spirocyclohexanes, terpinen-4-ol, fused pyridines, 6/6/5-fused tricyclic terpenoids, aryldihydronaphthalenes, spirocyclic cores, *cis*-decalins, spiroimines, aryl naphthalene lignans, tetrahydroquinolines, 6-azaindoles, tricyclic tetrahydropyrans, chromenones, tetracyclic isochromans, tetrahydrochromeno[4,3-*b*]quinolines, and *cis*-hydroindoles, which are commonly found in pharmacologically active compounds.²⁴ Furthermore, where applicable, we discuss key structural features and biological activity characteristics of the bioactive natural products. This review thus summarizes recent advancements in the chemistry of Diels–Alder reactions for total synthesis from 2020 to 2023.

2. Normal Diels–Alder (DA) reaction

2.1. Mulberry Diels–Alder type adducts (MDAA) kuwanons G and H synthesis

MDAAs are a group of rare natural polyphenols found in mulberry trees, possessing promising several biological properties like anti-inflammation, anti-bacterial, anti-virus, anti-oxidation, and anti-phlogistic activities.^{25–29} Kuwanons G **15** and H **16** fall in the 4th type of MDAA *i.e.* dehydroprenyl flavonoid type. Moreover, kuwanons G **15** and H **16** can be potent multitargeted agents for Alzheimer's disease. These two bioactive MDAAs were totally first synthesized by Luo *et al.*³⁰ in 2021 (Scheme 2). These can be derived from simple [4+2] cycloaddition of chalcone dienophiles **11** and dehydroprenylphenol dienes **14**.



Scheme 2 Diels–Alder reaction between **11** and **14** in the total synthesis of kuwanon G **15** and kuwanon H **16**.³⁰

2.2. Total synthesis of tetrodotoxin

Tetrodotoxin (**20**) a well-known natural product found in puffer fish has immense biological properties. It is also known as sodium channel blocker and used to relieve the headache associated with heroin withdrawal. It contains a cyclic guanidine, hemiaminal and *ortho*-ester moieties making this molecule unique. Murakami *et al.*³¹ took **17** and siloxydiene **18** as Diels–Alder substrate for the formation of *cis*-fused 5/5/6-tricyclic compound **19** in a quantitative yield (Scheme 3). At first, the alkyne moiety was transformed to an amine group **19b** through a Curtius rearrangement reaction in four steps. Murakami *et al.* also transforms alkyne moiety to a nitrile group **19c** by CuI, TMSN₃ and then Hofmann rearrangement to give the amine **19b** in two more steps. Subsequently, cyclic guanidine moiety was constructed followed by cyclic hemiacetal group. The resulted compound was further converted to the target molecule tetrodotoxin **20** in several steps.³¹

2.3. Synthesis of *para*-hydroquinone (*p*-HQ) motif and total synthesis of (±)-indanostatin

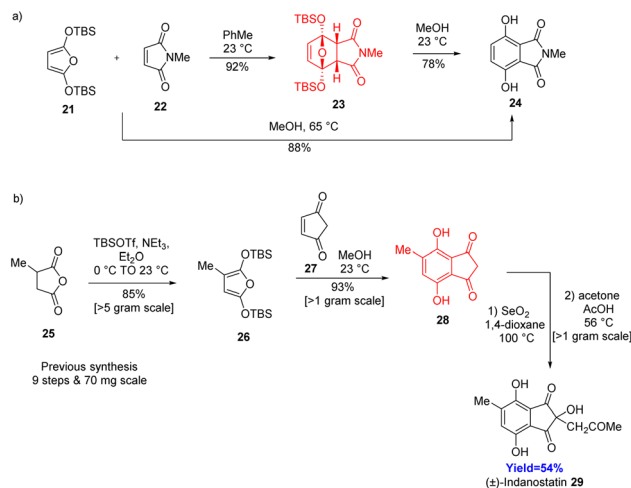
Many natural products, potential drug molecules composed of *p*-hydroquinone (*p*-HQ) **17** core structure. Among them, indanostatin, a natural product found in *Streptomyces* sp. which exhibits neuroprotective activity.³² Dissanayake *et al.*³² have taken 2,5-difunctionalized furans as bisketene equivalent **21**,



Scheme 3 Total synthesis of tetrodotoxin **20**.³¹



Review



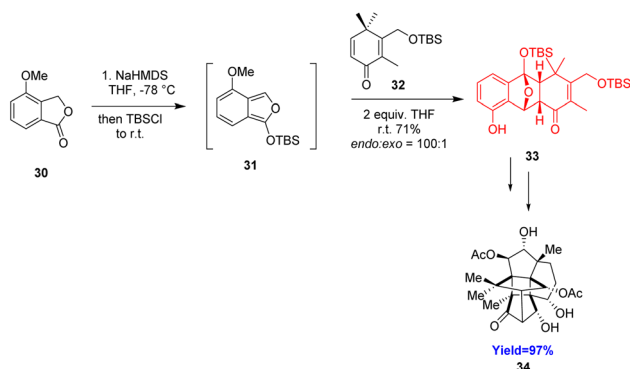
Scheme 4 (a) Diels-Alder reaction of furan **21** and *N*-methylmaleimide (**22**) in two ways to form *p*-HQs. (b) Gram scale synthesis of (±)-indanostatin **29**.³²

which form *p*-HQs via D-A/ring-opening/tautomerization sequence (Scheme 4a).³² The ring opening and tautomerization step can be done by simply stirring the compound in MeOH. Moreover, by performing the Diels-Alder reaction in MeOH, Dissanayake and the co-workers formed *p*-HQ in a one pot Diels-Alder/ring opening/tautomerization cascade. Same methodology was also applied in natural product synthesis, where methylfuran was opted as diene **26**, 1,3-cyclopentenedione **27** as dienophile and produced (±)-indanostatin **29** in only three steps (Scheme 4b).³²

2.4. Total synthesis of canataxpropellane

Canataxpropellane, a taxane skeleton, belongs to the taxane diterpene family which were isolated from plants of the genus *Taxus*. Anti-cancer³³ drugs such as Taxol and Taxotere also belong to this family.

Canataxpropellane, a very complex natural product having heptacyclic carbon framework with two propellanes[3.3.2]propellane and [4.4.2]propellane simultaneously. Schneider *et al.*³⁴ completed the total synthesis of (–)-canataxpropellane **34** in 26 steps from simple and easily accessible compounds. The starting material lactone **30** formed the diene **31** which underwent Diels-



Scheme 5 Racemic synthesis of canataxpropellane **34**.³⁴



Scheme 6 Enantiomeric synthesis of canataxpropellane **34**.³⁴

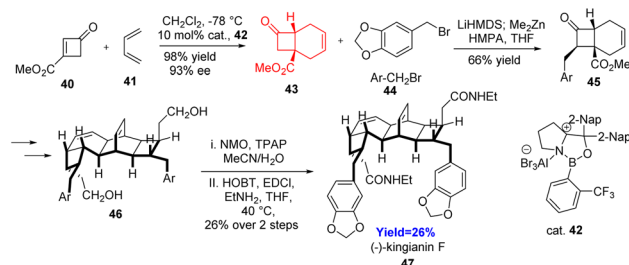
Alder reaction with dienophile **32** and showed excellent diastereoselectivity (*endo*:*exo* = 100:1) in racemic synthesis (Scheme 5).³⁴ In enantioselective synthesis (Scheme 6)³⁴ of this compound, a chiral silyl group TADDOL catalyst **39** was used where the diastereoselectivity (*endo*:*exo* = 1.5:1) was moderate. But the advantage is that the products can be readily separated by column chromatography. The Diels-Alder reaction and the *ortho*-alkene-arene photocycloaddition sequence formed the core structure of canataxpropellane which was further converted to the target molecule canataxpropellane in several steps.³⁴

2.5. Total synthesis of kingianin F

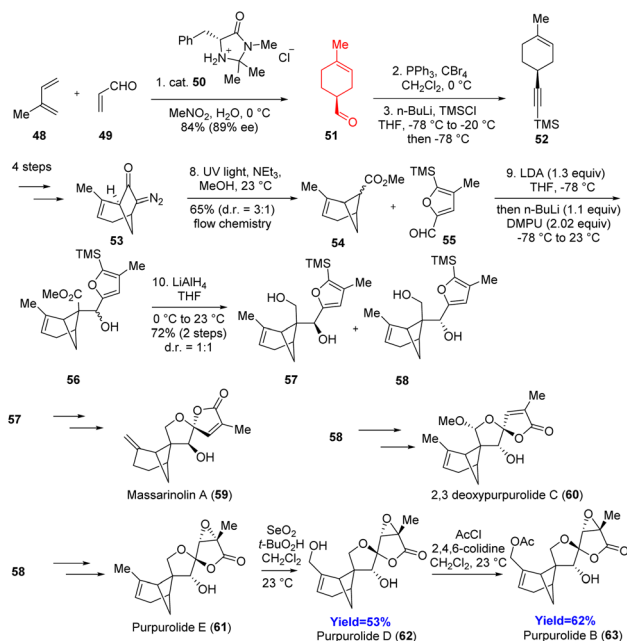
Yan and co-workers³⁵ in 2021 developed a method where cyclobutenone acts as a reactive dienophile and further used this method in the total synthesis of kingianin F **47**. Kingianins A–N, having significant binding affinity for the protein Bcl-X_L,³⁶ belongs to a family of bicyclo[4.2.0]octadiene dimers. These bicyclo[4.2.0]octane motifs are present in several natural products. Yan *et al.* synthesised bicyclo[4.2.0]octane motifs **43** using Diels-Alder reaction between highly reactive cyclobutenone having better stability and diene **41** (Scheme 7). Their work performed best when they have used 3-(methoxycarbonyl)cyclobutenone **40** in the presence of chiral oxaborolidinium ions (COBI) **42**. The formation of bicyclo[4.2.0]octane scaffold is the key step in the total synthesis of kingianin F **47**. After forming this scaffold, kingianin F was generated in 12 steps only.³⁵

2.6. Total syntheses of massarinolin A, purpurolides B, D, E; 2,3-deoxypurpurolide C and structural revision of massarinolin A

Massarinolin A, purpurolides belong to the bioactive bergamotane sesquiterpenes. These compounds have a complex ring



Scheme 7 Total synthesis of kingianin F (**47**).³⁵

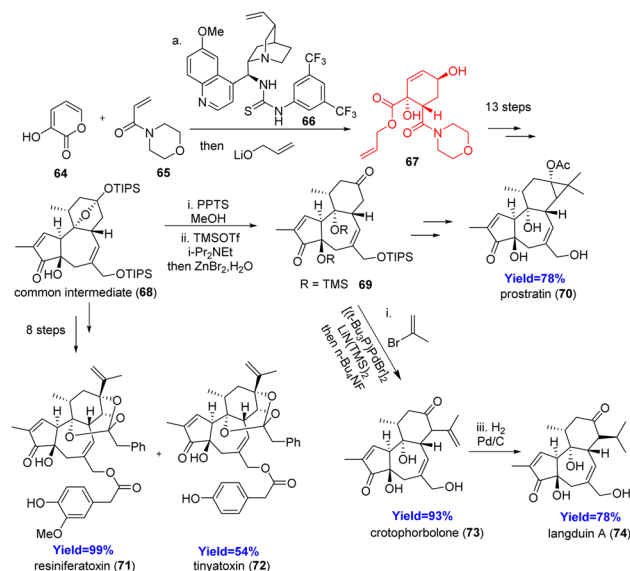


Scheme 8 Total Syntheses of massarinolin A, purpurolides B, D, E; 2,3-deoxypurpurolide C.³⁷

system consisting of a bicyclo[3.1.1]heptane, oxaspiro[3.4]octane, and dioxaspiro[4.4]nonane (oxaspirolactone). Massarinolin A shows activity against Gram-positive bacteria whereas purpurolides D, E, and F showed significant inhibitory activity against anti-obesity drug target pancreatic lipase. Wang and co-workers³⁷ started with a Diels–Alder reaction with chiral amine catalyst, and the adduct **51** underwent Corey–Fuchs homologation to form **52** (Scheme 8).³⁷ Flow photochemical Wolff rearrangement of **53** had been used to produce the key intermediate **54**. Aldol reaction with 1.3 equiv. of LDA followed by reduction produced the precursors **57** and **58** of these natural products. Photochemical oxidative furan cyclization with tetraphenylporphyrin as catalyst formed the oxaspirolactone moiety in separable mixture form. For the purpurolides, similar procedure has been done and in both the cases mixture has been produced where the *trans*-product is thermodynamically more stable. That *trans*-product was converted to the massarinolin A **59**, and purpurolides D, E and B **61–63**. Consequently, Wang *et al.* demonstrated that massarinolin A is also a *trans* compound.³⁷

2.7. Unified total syntheses of diterpenoids rhamnofolane, tiglane, and daphnane

Rhamnofolane, tiglane and daphnane are three families of diterpenoids which have closely related biosynthetic origins. Various biological activities like anti-viral, anti-cancer, analgesic, immunomodulatory, neuro-trophic, and tumor promotional activities are observed by these families of diterpenoids.³⁸ They have same 5/7/6-*trans* fused ring system only differing in the substitutions at the C13, C14 positions. Hirose and the co-workers³⁹ synthesised crotophorbolone/ langduin A, prostratin, and resiniferatoxin/tinyatoxin which



Scheme 9 Total syntheses of rhamnofolane, tiglane, and daphnane diterpenoids.³⁹

belong to the rhamnofolane, tiglane, and daphnane families, respectively. They have prepared a common intermediate which diverged into the targets. At first an asymmetric Diels–Alder reaction was done between **64** and **65** using a quinine derived catalyst **66** to prepare the six membered ring (Scheme 9). The resulting adduct **67** converted to the common intermediate **68** in thirteen steps. After forming the common intermediate **68**, the C13 cyclic acetal was converted to C13 ketone in two steps for the functionalization of C14 position. The formed product **69** could be converted to prostratin **70** and crotophorbolone **73** which on hydrogenation produced langduin A **74**. Resiniferatoxin **71** and tinyatoxin **72** was synthesized from the common intermediate **68**.³⁹

2.8. Synthesis of spirocyclic core of 13-desmethyl spirolide C

13-Desmethyl spirolide C having [7,6]spirocyclic imine moiety has the potential to work against Alzheimer's disease. Earl and co-workers⁴⁰ developed an economical, robust way to synthesize spirocyclic core through a key aza-Claisen rearrangement and *exo*-selective Diels–Alder reaction. At first aza-Claisen precursor amide was prepared from (S)-(–)- α -methylbenzylamine **75** and then the amide was converted to enantiopure lactam dienophile **76** (Scheme 10). The lactam dienophile reacted with the diene **77** (containing benzoyl protected side chain) and produced the spirocyclic fragment **78**, **79** with complete *exo*-selectivity.⁴⁰



Scheme 10 Synthesis of spirocyclic core of 13-desmethyl spirolide C.⁴⁰

Scheme 11 Synthesis of azulene cross-conjugated phthalimides.⁴¹

2.9. Synthesis of azulene cross-conjugated phthalimides

Phthalimides and their derivatives are largely found in bioactive compounds and can also be used as organic electronics and organic semiconductors. Shoji *et al.*⁴¹ coupled azulene-2-aminofurans **81** and maleimide derivatives **82** via an *endo*-selective Diels–Alder reaction. At first, [4+2] cycloaddition took place to form the bridged hemi-aminals **82**, and then electron donation of the germinal amino group helped to cleave the bridged C–O bond (Scheme 11). After the ring opening isomerization, tautomerization and rearomatization the azulene cross-conjugated phthalimide **83** have been produced.⁴¹

2.10. Total synthesis of senepodine F

Senepodine F, containing a decahydroquinoline ring (AB) and a quinolizidine ring (CD) connected by a methylene tether, isolated from *lycopodium* plants. Some *lycopodium* alkaloids are known for acetylcholinesterase inhibition. This is the first time ever senepodine F has been synthesized which is done by Nakashima *et al.*⁴² The decahydroquinoline ring (AB) was constructed via asymmetric Diels–Alder reaction between 5-nitro-2,3-dihydropyridone derivative **84** and a $\alpha,\beta,\gamma,\delta$ -unsaturated aldehyde **85** followed by denitration/isomerization (Scheme 12).

Scheme 12 Total synthesis of senepodine F (**93**).⁴²

After preparing the C ring, from 2-oxazolidinone substituted pyridine derivative **89**, it was coupled with AB ring **88**. Noyori asymmetric reduction and intramolecular S_N² cyclization formed the D ring and at last senepodine F **93**.⁴²

2.11. Total syntheses of rhodomollins A and B

Rhodomollins A and B have a complex structure having five rings (ABCDE) connected with each other. Zhao *et al.* have developed first ever total syntheses of rhodomollins A and B, two graynoids having oxa-bicyclo[3.2.1] core (BC ring). According to their retrosynthetic analysis, Zhao and co-workers⁴³ commenced the total synthesis by constructing A and DE ring separately. Diels–Alder reaction was needed during the preparation of DE ring between a diene **95** and methyl vinyl ketone **96** in the presence of 2,6-lutidine as buffer and BHT as an anti-oxidant (Scheme 13). The A and DE ring was merged by Stille coupling and the coupled product converted to rhodomollins **101**, **102** in more than 10 steps through lithium–halogen exchange/Williamson ether synthesis and Payne–Meinwald rearrangement.⁴³

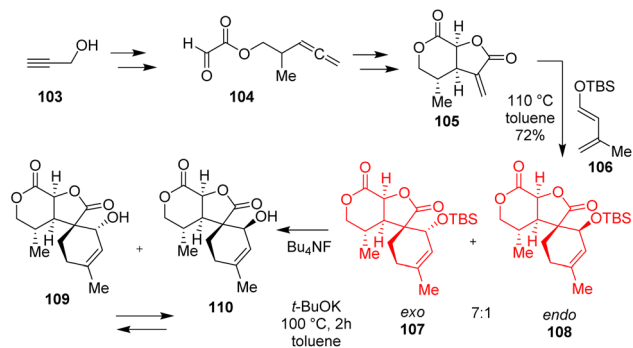
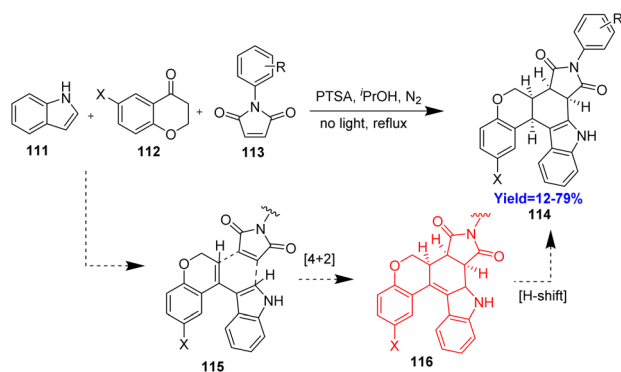
2.12. Synthesis of tricyclic core of cyclocalopin A

Several mushrooms such as *Boletus calopus*, *Caloboletus radi-cans* are the source of cyclocalopin family. Cyclocalopin A, comprised of a fused and spiro-ring, showed free radical scavenging activity as well as anti-cancer activities.⁴⁴ Yu *et al.*⁴⁵ based on their retrosynthesis began to prepare allenyl glyoxylate **104** from **103** through Fischer esterification (Scheme 14). The allenyl glyoxylate **104** on two [2+2+1] cyclocarbonylation constructed the dienophile α -methylene bis- γ,δ -lactone **105**. The Diels–Alder reaction, performed at 110 °C for 15 h in toluene, produced the major component **107** with *exo*-selectivity and minor component **108** with *endo*-selectivity. In the equilibrium-separation process the *exo*-product **109** was interconvertible to the *endo* one **110** and the tricyclic core of cyclocalopin A was formed.⁴⁵

2.13. Synthesis of tetrahydrocarbazole motif via vinylindole

Tetrahydrocarbazole motifs are largely found in natural products and bioactive molecules.⁴⁶ Moreover, they are found to be a precursor or an intermediate in the formation of various complex natural products. Noland and Abzhbarov⁴⁷ had developed a one pot three component reaction for the synthesis

Scheme 13 Total syntheses of rhodomollins A (**101**) and B (**102**).⁴³

Scheme 14 Synthesis of tricyclic core of cyclocalopin A.⁴⁵Scheme 15 Synthesis of tetrahydrocarbazole motif (114) via vinylindole (115).⁴⁷

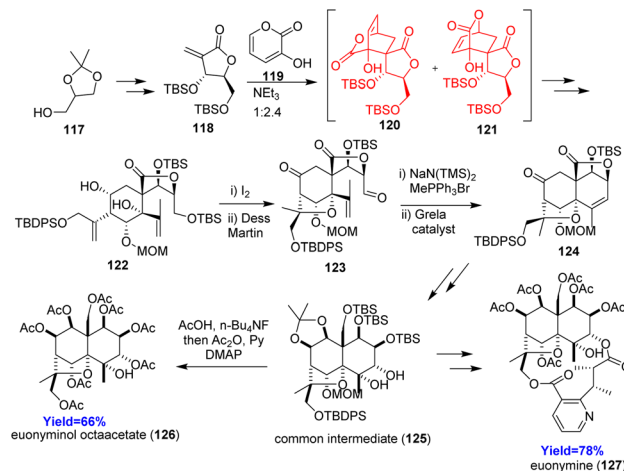
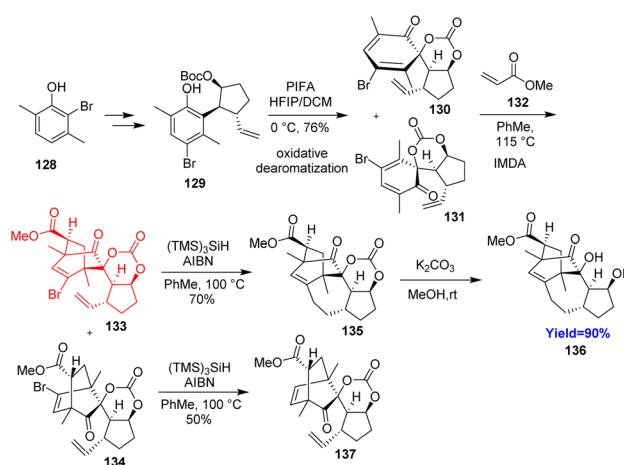
of tetrahydrocarbazole (Scheme 15). They have taken indole **111**, 1-tetralone **112**, *N*-phenylmaleimide **113** in a pot where the indole **111** and 1-tetralone **112** reacted to form a vinylindole **115** *in situ*. Then vinylindole **115** and *N*-phenylmaleimide **113** underwent normal Diels–Alder reaction to generate the tetrahydrocarbazole motif **114**.⁴⁷

2.14. Total synthesis of euonymine and euonyminol octaacetate

Euonymine and euonyminol octaacetate, members of dihydro- β -agarofuran family, shows anti-HIV and P-glycoprotein inhibitory effects.⁴⁸ Wang and co-workers⁴⁸ constructed euonymine and euonyminol octaacetate in 29 and 24 steps respectively from (*R*)-glycerol acetonide **117** (Scheme 16). These two compounds have ABC ring, where the B ring was prepared through Morita–Baylis–Hillman reaction followed by Diels–Alder reaction. The Diels–Alder adducts **120**, **121** converted to **122**, which upon iodo etherification produced the C-ring **123** and the A-ring **124** was formed by ring-closing olefin metathesis. After forming the core ABC ring, the common intermediate **125** was formed which can form euonyminol octaacetate **126** in 1 step and euonymine **127** in several steps.⁴⁸

2.15. Synthesis of tetracyclic core of calyciphylline N

Calyciphylline N, belongs to the daphniphyllum alkaloids, possess a unique bicyclo[2.2.2]octane core, dihydropyrrole, and

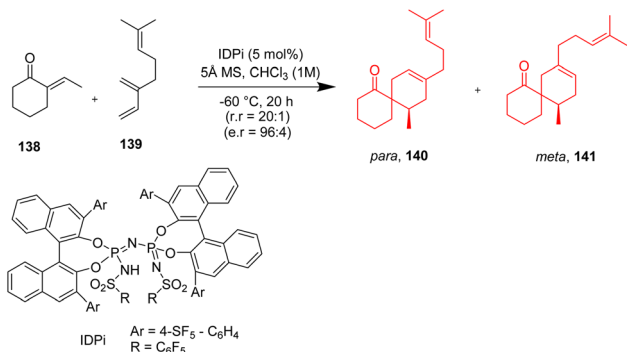
Scheme 16 Total synthesis of euonymine (**127**) and euonyminol octaacetate (**126**).⁴⁸Scheme 17 Synthesis of tetracyclic core of calyciphylline N (**136**).⁴⁹

a tricyclic dodecahydrocyclopenta[*cd*]azulene. Yumeng Lv and co-workers⁴⁹ started from *p*-xylene to **128** which converted to the key intermediate **129** (Scheme 17). The bicyclo[2.2.2]octane motif present in **133** and **134** was prepared by the usual oxidative dearomatization/intermolecular Diels–Alder reaction cascade. At last intramolecular radical cyclization of **133** constructed the [6.6.7.5] tetracyclic core of calyciphylline N **136** via **135** while **134** produced uncyclized **137**.⁴⁹

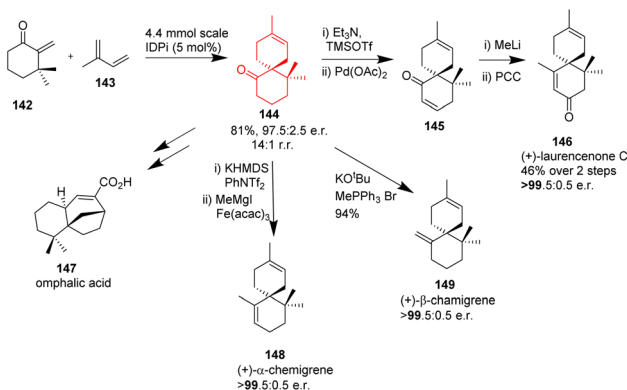
2.16. Total synthesis of some spirocyclane containing natural products

Enantioselective synthesis of spirocyclanes maintaining the step-economic and atom economic route remains an interesting problem to the chemists. The skeletons of spiro[4.5]decane and spiro[5.5]undecane skeletons have attracted the chemists, since several biologically active sesquiterpenoids comprise these. Catalytic enantioselective spirocyclization Diels–Alder reactions between *exo*-enones and dienes are unprecedented. Strongly acidic and confined





Scheme 18 Enantioselective intermolecular Diels-Alder reaction to form spirocyclophanes (140, 141).⁵⁰



Scheme 19 Total syntheses of various spirocycle containing natural products.⁵⁰

imidodiphosphorimidate (IDPi) catalyst is used to catalyse these reactions. It was proposed by Santanu Ghosh⁵⁰ and his coworkers that these acids may also be used to protonate such *exo*-enone. Thus Ghosh *et al.*⁵⁰ have showed an effective intermolecular Diels-Alder reaction of diversely substituted *exo*-enones 138 with various dienes 139 that is enantioselective and catalyzed by Brønsted acid, which aids in the synthesis of enantiopure spirocarbocyclic scaffolds 140, 141 of bioactive sesquiterpene natural products (Scheme 18).⁵⁰ Excellent yield, enantio and regioselectivities are obtained because the regio and stereochemical outcomes are controlled by the high acidity and confined chiral microenvironment of the IDPi catalyst.

These reactions were applicable in forming various natural products like (+)- β -chamigrene 149, (+)- α -chamigrene 148, omphalic acid 147, and (+)-laurencenone C 146 from a common intermediate 144 (Scheme 19).⁵⁰

2.17. Total synthesis of atrachinenin A and B

Atrachinenin A and B were isolated from the rhizomes of Chinese medicinal plant *Atractylodes chinensis*. French *et al.*⁵¹ commenced the total synthesis with geranylation of 4-methoxy-2-methylphenol 150 followed by oxidation and it led to quinone 151 (Scheme 20). The quinone 151 underwent Diels-Alder reaction with *E*- β -ocimene 152 to give four possible *endo*



Scheme 20 Total synthesis of atrachinenin A (161) and B (159).⁵¹

products. The desired product 155 was purified and produced 157 on [3+2] cycloaddition. 157 on aerobic oxidation in DMSO produced atrachinenin B 159 which on reduction gave atrachinenin A 161.⁵¹

2.18. Synthesis of terpinen-4-ol

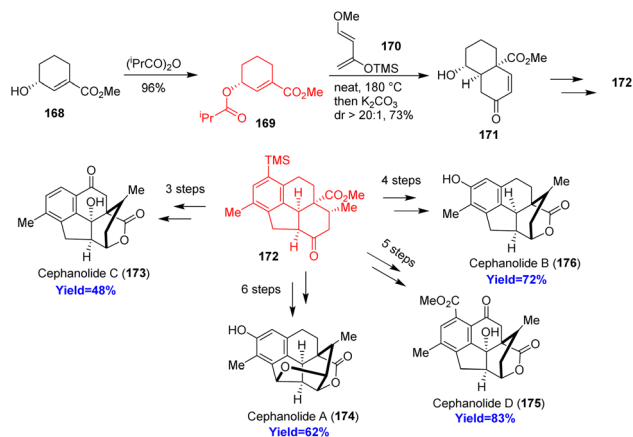
Naturally occurring monocyclic cyclohexene containing monoterpenes are important chiral building blocks for the synthesis of bioactive compounds, medicines, and agrochemicals. In the synthesis of commercial herbicide cinmethylin, a key intermediate terpinen-4-ol 162, also a naturally occurring monoterpene. Retrosynthetic disconnection of 162 showed that it can be made from isoprene unit 163 (Scheme 21a).⁵² Mendoza *et al.*⁵² in 2022, reported Y-catalysed asymmetric DAR of α -acyloxy enones 166 with diene 165 to form the terpinen-4-ol 162 (Scheme 21b). Generally these reactions have good enantio, diastereo, as well as regioselectivity.⁵²

2.19. Total synthesis of cephanolides A-D

Cephalotane-type diterpenoids cephanolides A-D, isolated from *Cephalotaxus sinensis*, have 6/6/6/5 tetracyclic core with a bridged δ -lactone. According to the retrosynthetic analysis, Qing *et al.*⁵³ began the synthesis with alcohol 168 which on acylation formed the dienophile 169 (Scheme 22). This dienophile 169 and Danishefsky's diene 170 on Diels-Alder reaction produced 171



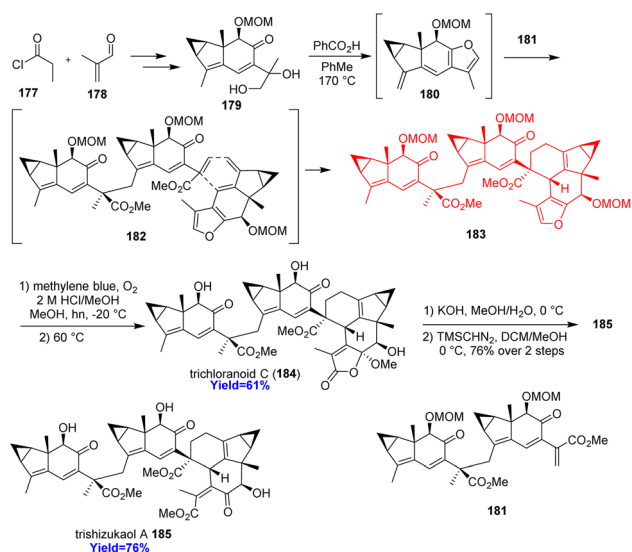
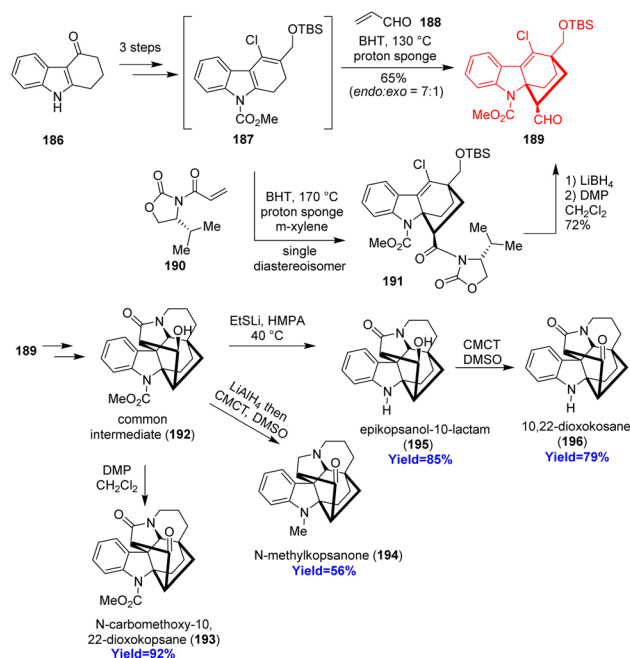
Scheme 21 (a) Retrosynthetic disconnection of terpinen-4-ol (162), (b) Y-catalysed asymmetric DAR to construct (162).⁵²

Scheme 22 Total synthesis of cephanolides A–D.⁵³

with high diastereoselectivity ($dr = 20 : 1$). The cycloadduct **171** was converted to common intermediate **172** through a palladium catalyzed [2+2] cycloaddition. The common intermediate (**172**) synthesized cephanolide A **174** in 6 steps and other cephanolides **173**, **175**, **176** in 4–5 steps.⁵³

2.20. Total synthesis of trichloranoid C and trishizukaol A

Trichloranoid C and trishizukaol A are two oligomeric lindenane sesquiterpenoids from *Chloranthus* genus having several biological properties.⁵⁴ Wang *et al.*⁵⁵ commenced the total synthesis by assembling propionyl chloride **177** and methacrolein **178** (Scheme 23). The substrates were converted to **179** in ten steps which produced the diene **180** in presence of benzoic acid in toluene. The Diels–Alder adduct **183**, produced by diene **180** and dienophile **181**, underwent dearomatization of furan and formed lactone sequentially. Deprotection of that lactone produced trichloranoid C **184** which in two steps formed trishizukaol A **185**.⁵⁵

Scheme 23 Total synthesis of trichloranoid C (**184**) and trishizukaol A (**185**).⁵⁵Scheme 24 Total synthesis of four kopsane alkaloids (**193**, **194**, **195**, **196**).⁵⁶

2.21. Total synthesis of four kopsane alkaloids

Kopsane-type alkaloids are indole alkaloids having a complex heptacyclic skeleton. Qin and co-workers⁵⁶ reported the total synthesis of 22-dioxokopsane, 10,22-dioxokopsane, epikopsanol-10-lactam, *N*-carbomethoxy-10 and *N*-methylkopsanone. According to the retrosynthetic analysis, commercially available tetrahydrocarbazolone **186** was used to prepare the Diels–Alder substrate **187** *via* Vilsmeier–Haack reaction (Scheme 24). The diene **187** along with acrolein dienophile **188** underwent Diels–Alder reaction to construct the bicyclo[2.2.2]octane motif **189**. Besides, the cycloadduct **189** has been synthesized *via* an enantioselective way also. The common intermediate **192** having the heptacyclic skeleton was prepared in total 16 steps and was converted to the targeted natural products.⁵⁶

2.22. Total syntheses of sarbracholide and shizukaol B

Lindenane sesquiterpenoid oligomers are generally dimers or trimers coupled head-to-head or head-to-back from lindenane monomer. Huang and co-workers⁵⁷ have chosen most abundant [4+2] head to back type oligomers sarbracholide and shizukaol B for their total synthesis because of their excellent biological activities. Sarbracholide is the most potent anti-malarial agent (1000 times more than artemisinin) while shizukaol B showed excellent anti-malarial and anti-HIV-1 activities.^{58–61} Total synthesis started with (+)-verbenone **197** and formed the common intermediate **198** which can form the dienophiles **199**, **200** of sarbracholide and shizukaol B respectively (Scheme 25). Then the dienophile was reacted with the common diene **201** of natural lindenane oligomers to form the desired sarbracholide **202** and shizukaol B **203**.⁵⁷





Scheme 25 Total syntheses of sarbracholide (202) and shizukaol B (203).⁵⁷

2.23. Total synthesis of artatrovireno A

Sesquiterpenoid artatrovireno A, found in traditional Chinese medicinal plant *Artemisia*, isolated from *Artemisia atrovirens*. Artatrovireno A showed its potential for preparing anti-hepatoma drug and exhibited cytotoxicity against human hepatoma cell lines.⁶² Lavernhe *et al.*⁶³ started the total synthesis with a Diels–Alder reaction between diene isoprene **204** and dienophile **205** in the presence of oxazaborolidine catalyst **206** (Scheme 26). The cycloadduct **207** formed with excellent regio, diastereo and enantioselectivity transformed to the final product artatrovireno A **208** through several steps.⁶³

2.24. Synthesis of spiroimine fragment of portimines A and B

Though spiroimines are toxins produced by dinoflagellates, they have huge biological activities like anti-HIV, anti-cancer



Scheme 26 Total synthesis of artatrovireno A (208).⁶³

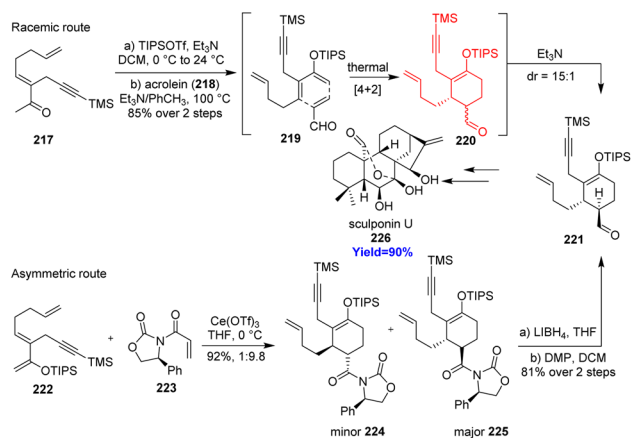


Scheme 27 Synthesis of spiroimine fragment **214** of portimines A (**215**) and B (**216**).⁶⁶

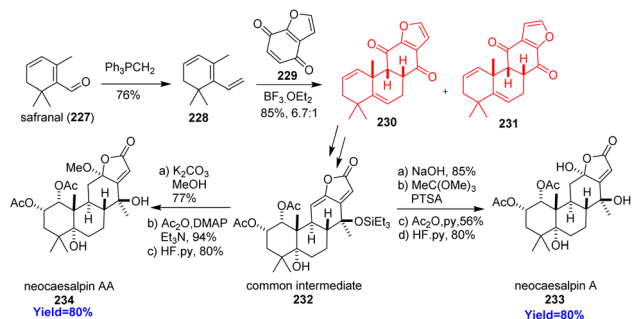
and anti-fouling activities.^{64,65} Portimines A and B belong to the rare [5,6]-spiroimine system. However, there are few examples of portimines total synthesis, Ding *et al.*⁶⁶ decided to develop portimine fragment spirocyclic lactam, which could be the common intermediate for the portimines (Scheme 27). Synthesis began with a Diels–Alder reaction between bromodiene **209** and a dienophile **210** produced *in situ*. The cycloadduct **211** again cyclized *in situ* and formed lactone **212** which upon reduction, lactonization produced the key intermediate **213**. The key intermediate **213** produced the desired spirocyclic lactams **214** in few steps.⁶⁶

2.25. Total synthesis of sculponin U

Sculponin U, an *ent*-kaurane-type diterpenoid, isolated from *Isodon sculponeatus*. This family of diterpenoids showed anti-tumor, anti-bacterial properties.⁶⁷ Cao *et al.*⁶⁸ started the total synthesis with a Diels–Alder reaction between a silyl enolate diene and acrolein dienophile **218** forming the middle six-membered ring of sculponin U **226** (Scheme 28). Epimeric mixture of cycloadduct **220** was formed *in situ* which in presence of triethylamine produced a thermodynamically stable compound **221** with 15:1 dr. Finally, racemic synthesis of sculponin U **226** was done from compound **221**. Cao and co-



Scheme 28 Total synthesis of sculponin U (226).⁶⁸

Scheme 29 Total synthesis of neocaesalpin A (233), AA (234).⁷¹

workers also showed the asymmetric way to synthesize sculpopin U by preparing enantiopure form of compound 221 through Diels–Alder reaction.⁶⁸

2.26. Total synthesis of neocaesalpin A and AA

Neocaesalpin A, AA, K all belongs to the cassane-type diterpenoids having anti-malarial, anti-viral, anti-inflammatory, anti-tumor, anti-oxidant properties.^{69,70} The first cassane-type diterpenoid neocaesalpin A isolated from *Caesalpinia bonduc*. Papidocha *et al.*⁷¹ commenced the total synthesis with safranal 227 which produced the Diels–Alder precursor triene 228 (Scheme 29). The triene 228 and furanoquinone 229 produced the desired cycloadduct 230 with its regioisomer 231 in 6.7 : 1 ratio. The cycloadduct 230 converted to the intermediate 232 which formed neocaesalpin A 233 in four steps and neocaesalpin AA 234 in 3 steps. At last, Papidocha and co-workers mentioned that neocaesalpin AA and neocaesalpin K might be the same natural product.⁷¹

3. Intramolecular Diels–Alder (IMDA) reaction

3.1. Synthesis of fused pyridine motif and total synthesis of lycopodium alkaloids

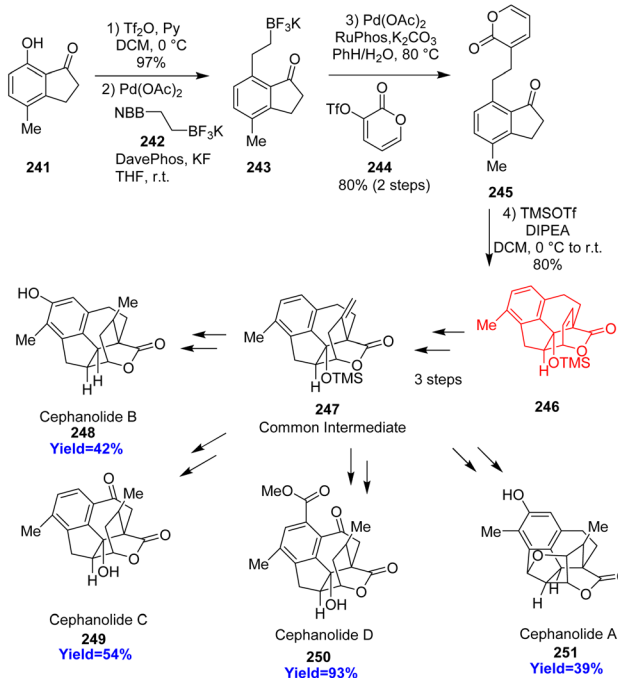
Pyrindane moiety (pyridine unit fused to a cyclopentane ring) has gained recent attention for its occurrence in bioactive natural products and drugs like rasagiline, ipidacrine, carinatine A, (+)-lycopoladine A, pyridinohopane, cimicifugadine and (–)-lycopoloserramine. K. H. Sim *et al.*⁷² have reported the total synthesis of lycopoladine A and lycopoloserramine R by constructing the fused pyrindane moiety. Lycopoladine A and lycopoloserramine R, a member of *Lycopodium* alkaloid family, showed biological activities and they are anticipated to treat Alzheimer's disease to improve memory loss.⁷³ Lycopoloserramine R consists of four asymmetric centers, 5/6 *cis* fused ring and a pyridone ring whereas lycopoladine A possesses a pyridyl-fused hydrindanone core. K. H. Sim *et al.*⁷² used 3,5-dibromo-2-pyrone 235 as substrate which undergoes Stille coupling with 236 to produce 2-pyrone having a chiral branched allylic silyl ether group 237 (Scheme 30). The product 237 underwent intramolecular Diels–Alder (IMDA) reaction with very high π -facial- and endoselectivities in a tandem fashion. The resulting

Scheme 30 Stille coupling between (235) and (236) accompanied with IMDA reaction produced (238) which further can be converted to the lycopoladine A (239) and (–)-lycopoloserramine R (240).⁷²

cycloadduct 238 was transformed into the (+)-lycopoladine A 239 and (–)-lycopoloserramine R 240 in several steps.⁷²

3.2. Total synthesis of the (±)-cephanolides A–D

Cephanolides A–D belong to the cephalotaxus norditerpenoids family, which have shown a broad range of activity like anti-viral, anti-tumor, anti-neoplastic properties and can also control plant growth inhibition.^{74–76} These substances cytotoxic activity against human cancer cell lines relies upon the ring A. Haider *et al.*⁷⁷ commenced the total synthesis with 7-hydroxy-4-methylindanone 241, which underwent Suzuki cross coupling reacting with BF_3K -ethylene-9BBN 242 (Scheme 31). The formed product 243 reacted with pyrone triflate 244 and 245 underwent intramolecular Diels–Alder cycloaddition. The *endo* Diels–Alder adduct 246 was transformed to the common intermediate 247.

Scheme 31 Total synthesis of cephanolide congeners (248–251).⁷⁷

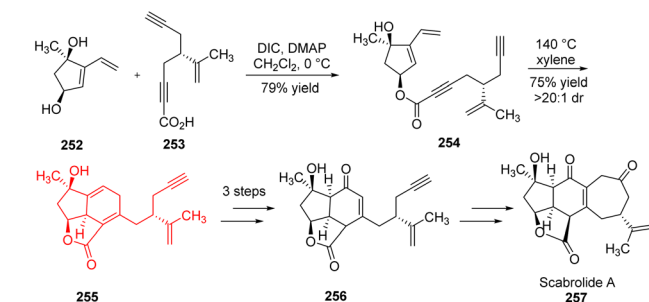
Finding a common, versatile intermediate **247** that could be used for the preparation of all the cephanolide congeners like cephanolide A **251**, cephanolide B **248**, cephanolide C **249**, and cephanolide D **250** was the goal.⁷⁷

3.3. Total synthesis of (–)-scabrolide A

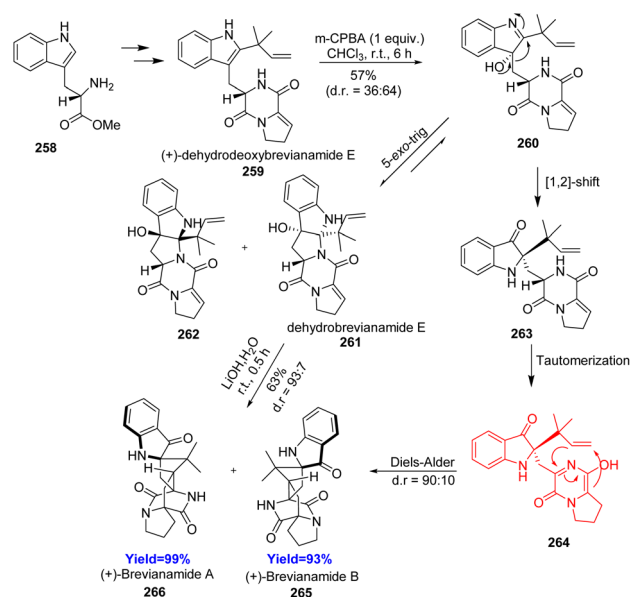
Scabrolide A belongs to the family of polycyclic furanobutenolide derived norcembranoid diterpenoids and shows anti-inflammatory properties. Hafeman and co-workers⁷⁸ reported the first ever total synthesis of any member of polycyclic furanobutenolide derived norcembranoid diterpenoid family. They have developed a retrosynthetic route of scabrolide A, and commenced its total synthesis. Using it they have prepared two chiral compound dihydroxyvinylcyclopentene **252** and ynoic acid **253** as substrates which underwent esterification to introduce all the carbon atoms of the natural product (Scheme 32). Compound **254** formed **255** through intramolecular Diels–Alder reaction which in turn formed the key intermediate enone **256** in 3 steps. The enone underwent several transformations to form scabrolide A **257**.⁷⁸

3.4. Total synthesis of brevianamide A

Brevianamides A was isolated from the fungus *Penicillium brevicompactum*, and one of the first known bicycle[2.2.2]diazaoctane alkaloids. Insecticidal brevianamides fall in the group of dioxopiperazine type structures of bicyclo[2.2.2]diazaoctane alkaloids. Godfrey *et al.*⁷⁹ reported the chemical synthesis of (+)-brevianamide A in seven steps from commercially available L-tryptophan methyl ester **258** (Scheme 33). This starting material formed the biosynthetic precursor (+)-dehydrodeoxybrevianamide E **259**. At first, diastereoselective epoxidation of the indole moiety of **259** followed by intramolecular epoxide-opening, which produced mixture of diastereomeric dehydrobrevianamide E **261** and **262**. The mixture gave (+)-brevianamide A **266** and (+)-brevianamide B **265** through a complex cyclization-cascade when exposed to LiOH in water for 30 minutes. The cascade involved retro-5-*exo*-trig/[1,2]-alkyl shift/Diels–Alder reaction where the retro-5-*exo*-trig cyclization opened up the pyrrolidine ring for [1,2]-alkyl shift. The alkyl shift placed the diene and the dienophile in close proximity though the dienophile was formed in the next step *via* tautomerization. At last, intramolecular diastereoselective [4+2] cycloaddition of **264** led to target molecule.⁷⁹



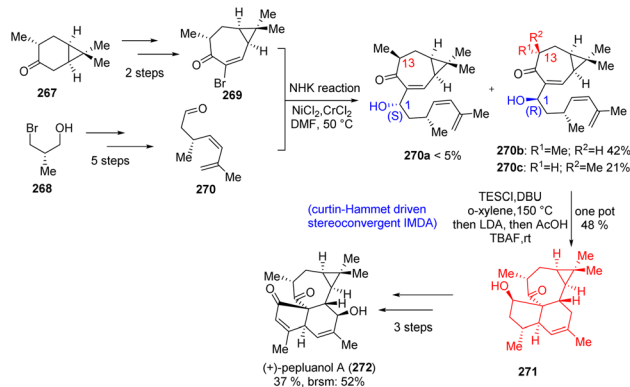
Scheme 32 Total synthesis of scabrolide A (**257**).⁷⁸



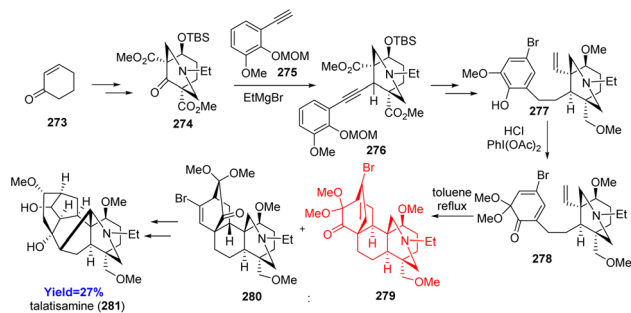
Scheme 33 Total synthesis of brevianamide (**265** and **266**).⁷⁹

3.5. Total synthesis of pepluanol A

Pepluanol A, belongs to the family of *Euphorbia* diterpenes and isolated from *Euphorbia* plants, which behave as medicinal plants. These diterpenes had anti-viral, anti-tumor, cytotoxic and multidrug-resistance-reversing (MDR) properties.^{80–82} Yuan *et al.*⁸³ had produced bromocycloheptenone **269** and an aldehyde **270** from commercially available compounds (Scheme 34). These two compounds formed the Diels–Alder precursor **270** through Nozaki–Hiyama–Kishi (NHK) reaction. The NHK reaction produced three different diastereoisomers (**270a**, **b**, **c**) differing in the absolute configuration of C₁ and epimerization of methyl group at C₁₃ position. After so many experiments, the experimental results suggest that Curtin–Hammett like situation arise in the Diels–Alder reaction. The C₁₃ α -epimer **270b** failed to undergo the DAR contrast to the C₁₃ β -isomer **270c**. From DFT calculation they have shown that the DA adduct formed from C₁₃ β -isomer is less stable than the DA adduct formed from C₁₃ α -isomer. After the DAR, the inversion of C₁₃ stereocenter from β to α had been done using strong base LDA



Scheme 34 Total synthesis of pepluanol A (**272**).⁴³

Scheme 35 Total synthesis of talatisamin (281).⁸⁴

followed by quenching with acetic acid. Oxidation of the C₁-OH of 271 followed by Saegusa-Ito oxidation and allylic oxidation led to the natural product (+)-pepluanol 272.⁸³

3.6. Total synthesis of talatisamin

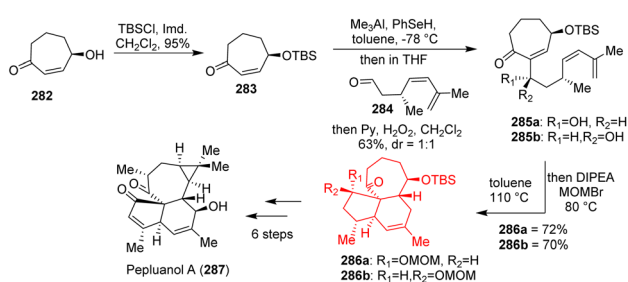
Talatisamin, a member of C₁₉ diterpenoid family, isolated from *Aconitum* species displays anti-arrhythmic activities and K⁺ channel inhibitory.⁸⁴ Talatisamin composed of six fused rings (ABCDEF) with 12 contiguous stereocenters. Kamakura and coworkers⁸⁴ have synthesized talatisamin in 33 steps from cyclohexenone 273. Cyclohexenone 273 was converted to azabicyclo 274 (AE ring) and coupled with aromatic D ring 275 to form 276 (Scheme 35). It went oxidative dearomatization of D ring followed by intramolecular Diels-Alder reaction of 278 to form 279 which can be transformed to talatisamin 281 in 9 steps.⁸⁴

3.7. Total synthesis of pepluanol

Yuan *et al.*⁸⁵ have developed *Euphorbia* diterpenoid pepluanol in only 11 steps from 1,3 cycloheptadiene. These natural products could be used as herbal folk medicine because of their anti-tumor, cytotoxic, anti-viral, anti-inflammatory properties.^{80–82} The total synthesis started with 282 to form 283 which on Morita-Baylis-Hillman reaction with an aldehyde 284 produced the Diels-Alder precursor 285 (Scheme 36). The intramolecular Diels-Alder reaction was conducted overnight at 110 °C in *o*-xylene successfully. The cycloadducts 286 were converted to pepluanol 287 in 6 steps.⁸⁵

3.8. Total synthesis of havellockate

Havellockate, a furanobutenolide-derived cembranoid and isolated from *Sinularia granosa*, has a unique spiro-fused β-

Scheme 36 Total synthesis of pepluanol (287).⁸⁵Scheme 37 Total synthesis of havellockate (295).⁸⁶

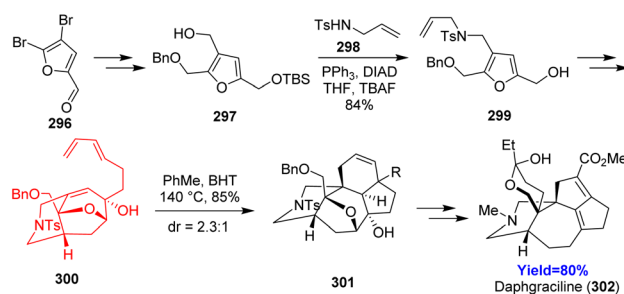
hydroxybutanolide ring. Hafeman and co-workers⁸⁶ began to prepare aldehyde 290 and sulfone 291 from enone 288 and acyl oxazolidinone 289 respectively (Scheme 37). Julia-Kocienski olefination product 292 of aldehyde 290 and sulfone 291 produced the Diels-Alder precursor 293 on Steglich esterification. The [5-5-6] framework of havellockate was constructed through the intramolecular Diels-Alder reaction of 293 and converted to the targeted compound havellockate 295.⁸⁶

3.9. Total synthesis of daphgraciline

Li *et al.*⁸⁷ reported the synthesis of daphgraciline, a *Daphniophyllum* yuzurine-type alkaloid comprising of [6-7-5-5-6] pentacyclic core, unique azabicyclo[4.3.1] system and a spiro tetrahydropyran ring. Based on the retrosynthesis, Mitsunobu reaction was performed between 297 (prepared from commercially available 296) and 298 (Scheme 38). The Mitsunobu product 299 was converted to the Diels-Alder substrate 300 through a [5+2] cycloaddition forming the azabicyclo[4.3.1] system. The desired mixture of diastereomers 301 was obtained in the intramolecular Diels-Alder reaction which was converted to daphgraciline (302).⁸⁷

3.10. Total synthesis of erectones A, B and hyperelodione D

Franov and co-workers⁸⁸ reported bioinspired total synthesis of erectones A, B and hyperelodione D which belong to the polycyclic polyprenylated acylphloroglucinols family of natural

Scheme 38 Total synthesis of daphgraciline (302).⁸⁷

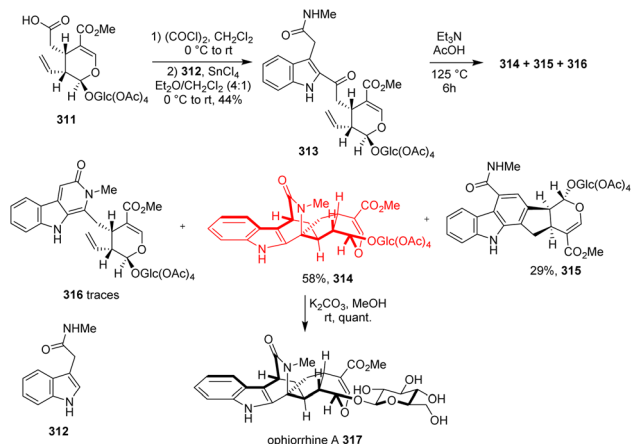


Scheme 39 Total synthesis of erectones A (307), B (308) and hyperelodione D (310).⁸⁸

products. Moreover, the structure of hyperelodione D was revised since the NMR spectra of the proposed structure and natural structure not matched. The synthesis commenced with the preparation of common intermediate erectquione A 304 from 2,4,6-trihydroxybenzaldehyde 303 (Scheme 39). Erectquione A 304 then formed erectones A 307, B 308 and hyperelodione D 310 *via* Diels-Alder cascade with *E*-β-ocimene 305 and *E,E*-α-farnesene 306 respectively.⁸⁸

3.11. Bioinspired total synthesis of ophiorrhine A

Indole alkaloids ophiorrhine A, isolated from *Ophiorrhiza japonica*, exhibits immunosuppressive activity. Cao *et al.*⁸⁹ synthesized this natural product from the acid of secologanin aglycon ethyl ether 311 which converted to its acid chloride form (Scheme 40). Friedel-Crafts type reaction with amide 312 formed 2-(2-acyl-3-indolyl)-acetamide 313 and it was aimed to convert to the key indolopyridone 316. Rather 316 was found in traces amount because transient 316 underwent intramolecular Diels-Alder cycloaddition to construct spirocyclic azabicyclo [2.2.2]octanone 314. On methanolysis of acetates of glucose moiety produced ophiorrhine A 317.⁸⁹



Scheme 40 Bioinspired total synthesis of ophiorrhine A (317).⁸⁹

3.12. Total synthesis of yonarolide

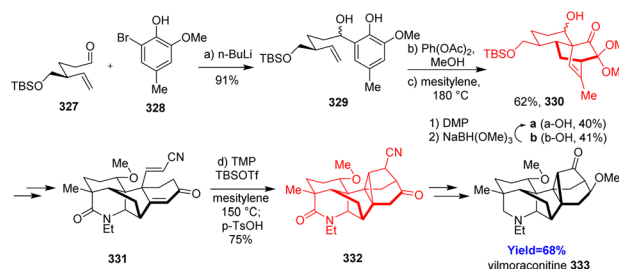
Scabrolide A and yonarolide, belong to the polycyclic furanobutenolide derived norcembranoids, were isolated from soft corals *Simularia*. Hafeman and co-workers⁹⁰ have showed the challenges they faced during the synthesis and how they overcame those challenges. (*R*)-Carvone 318, the starting material of this synthesis, was converted to ynoic acid 319 which then underwent esterification with diol 320 to form Diels-Alder substrate 321 (Scheme 41). Intramolecular Diels-Alder adduct 322 on epoxidation/reductive epoxide opening formed a diol which was oxidized selectively to produce 323. The major steps involved during the last several transformations were [2+2] photocycloaddition, Tamao-Fleming oxidation and Grieco elimination to reach scabrolide A 325 and yonarolide 326.⁹⁰

3.13. Total synthesis of vilmoraconitine

Vilmoraconitine, a C₁₉-diterpenoid alkaloid, isolated from medicinal plant *Aconitum*. These natural products exhibit analgesic, anti-inflammatory and cardioactive effects.^{91–93} Jiu-jian Ji and co-workers⁹⁴ commenced the total synthesis with aldehyde 327 and bromide 328 according to their retrosynthetic analysis (Scheme 42). The phenol adduct 329 underwent oxidative dearomatization followed by Diels-Alder when treated with Ph(OAc)₂ in methanol. Though a pair of separable diastereoisomers 330a, b has been produced, the undesired one 330b was recycled to the desired one 330a effectively. Another Diels-



Scheme 41 Total synthesis of scabrolide A (325) and yonarolide (326).⁹⁰



Scheme 42 Total synthesis of vilmoraconitine (333).⁹⁴

Alder reaction was required in the last stage of this total synthesis to form **332** from **331**.⁹⁴

3.14. Total synthesis of lancilactone C

Lancilactone C, found in the stems and roots of *Kadsura lancilimba*, a Chinese folk medicine used for the anti-HIV activity.⁹⁵ Kuroiwa *et al.*⁹⁶ developed the total synthesis of lancilactone C for the very first time and commenced with Wieland–Miescher ketone **334**. After forming the proposed structure of lancilactone C and comparing with the NMR data, the proposed structure was revised. The total synthesis of the revised structure also started with Wieland–Miescher ketone **334** and converted to the Diels–Alder precursor **335** which underwent intramolecular Diels–Alder reaction (Scheme 43). The Diels–Alder adduct **336** on oxidation with DDQ produced benzene ring in **336**.⁹⁶

3.15. Total synthesis of zygadenine

Zygadenine natural products belong to the cevanine subgroup of *Veratrum* genus of plants having medicinal properties. They can be used for the treatment of injuries, pain, hypertension *etc.* Guo and co-workers⁹⁷ began their synthesis according to their retrosynthetic analysis. Substrates acid **338** and Hajos–Parrish ketone **339** formed the diene **340** and the dienophile **341** part respectively which upon coupling produced the Diels–Alder precursor (Scheme 44). Since the precursor had both the diene and dienophile counterpart it underwent intramolecular Diels–Alder reaction. The adduct **342** was converted to the target molecule zygadenine **343** in more than 20 steps.⁹⁷



Scheme 43 Total synthesis of lancilactone C (**337**).⁹⁶



Scheme 44 Total synthesis of zygadenine (**343**).⁹⁷

3.16. Total syntheses of cinchona alkaloids

Quinine, quinidine, cinchonine, cinchonidine being the members of cinchona alkaloids are famous for their anti-malarial activities.⁹⁸ Though there are several synthetic routes to cinchona alkaloids, preparing quincorine and quincoridine (precursors of cinchona alkaloids) remains difficult and lengthy. Lei Li and co-workers⁹⁹ hence *de novo* synthesized these two alcohols through a key intramolecular Diels–Alder reaction. Two known compounds **344** and **345** initiated the synthesis and the formed product **346** was oxidized before intramolecular cycloaddition (Scheme 45). Then the cycloadduct **348** was converted to quincorine **349** and quincoridine **350** in 8 steps. Next, the cinchona alkaloids **358**–**361** have been produced using metallaphotoredox-catalyzed deoxygenative arylation based on Macmillan's recent methodology.⁹⁹

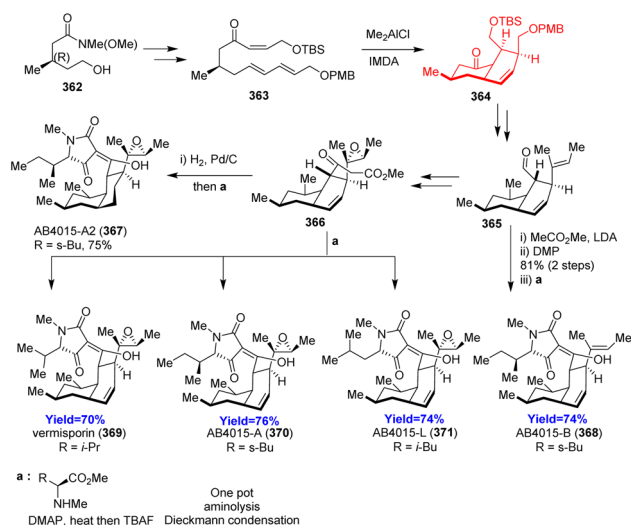
3.17. Total syntheses of tetramic acid bearing *cis*-decalin natural products

Dong *et al.*¹⁰⁰ developed an alternative strategy for the synthesis of AB4015-A2 and four antibiotics vermispurin, PF1052/AB4015-A, AB4015-B, AB4015-L. These natural products work excellently against Gram-positive bacteria and anaerobic bacteria and being isolated from fungi. Dong and co-workers followed their retrosynthetic analysis and commenced with Weinreb amide **362** as starting material (Scheme 46). The amide on Mitsunobu reaction, oxidation followed by Julia olefination produced triene intramolecular Diels–Alder precursor **363**. All these anti-biotics **367**–**371** were formed through a one pot aminolysis/Dieckmann condensation cascade in the presence of L-amino acid derivatives.¹⁰⁰



Scheme 45 Total syntheses of cinchona alkaloids (**358**–**361**).⁹⁹





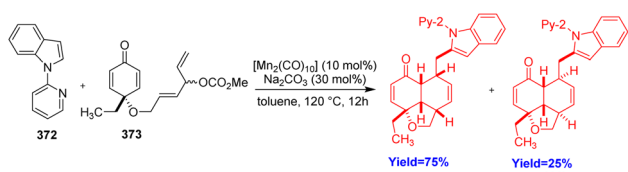
Scheme 46 Total syntheses of tetramic acid bearing *cis*-decalin natural products.¹⁰⁰

3.18. Synthesis of 6/6/5-fused tricyclic terpene scaffold

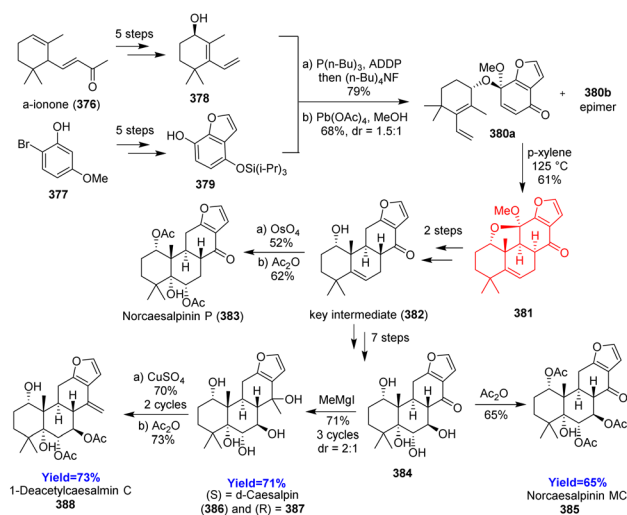
6/6/5-Fused tricyclic scaffold is a central core of many complex natural products like nagilactones, azadirachtin, endiandric acid A and marrubin. Parammal and co-workers¹⁰¹ opened a new way to construct this type of scaffold through manganese catalyzed C–H activation. 2-Pyridinyl indole 372 and cyclohexadienone 373 were taken as substrate in the presence of $[\text{Mn}_2(\text{CO})_{10}]$ catalyst and Na_2CO_3 additive in toluene (Scheme 47). C–H dienylation of 2-pyridinyl indole produced an intermediate which underwent intramolecular Diels–Alder reaction to give the 6/6/5-fused tricyclic scaffold 374, 375.¹⁰¹

3.19. Total syntheses of cassane furanoditerpenoids

Bulthaupt and co-workers¹⁰² reported first ever total syntheses of norcaesalpin MC, δ -caesalpin, 1-deacetylcaesalmin C, and norcaesalpin P. Based on their retrosynthetic path, synthesis commenced with the preparation of the (*R*)-diene 378 from α -ionone 376 and phenol 379 from 377 (Scheme 48). After preparing, both 378, 379 were coupled using Tsunoda's modification of Mitsunobu reaction followed by desilylation and oxidative dearomatization to produce the Diels–Alder precursor 380a, b as diastereomeric mixture. The mixture was heated in *p*-xylene to form single diastereomeric Diels–Alder adduct 381 which then led to the key intermediate 382 and further modifications produced the above-mentioned natural products.¹⁰²



Scheme 47 Synthesis of 6/6/5-fused tricyclic terpene scaffold.¹⁰¹



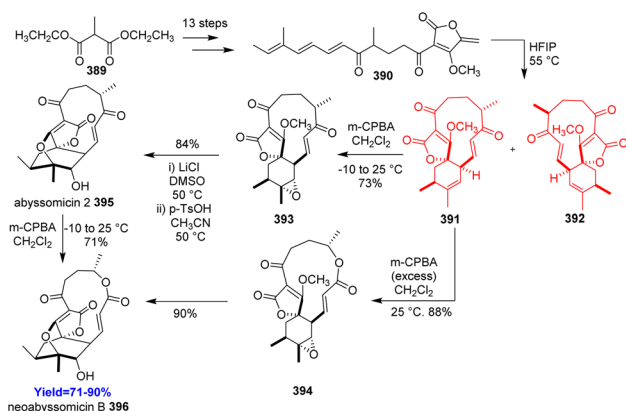
Scheme 48 Total syntheses of cassane furanoditerpenoids.¹⁰²

3.20. Total synthesis of abyssomicin 2 and neoabyssomicin B

Abyssomicin 2, belongs to the subclass of class I spirotrionate polyketides, showed its anti-microbial activity against Gram-positive bacteria.¹⁰³ Since, a bio-inspired approach *via* an intramolecular Diels–Alder reaction was successful for the construction of key intermediate of abyssomicin C, Canko *et al.*¹⁰⁴ used that approach too here. Synthesis started with commercially available diethyl 2-methylmalonate 389 and aimed to form the Diels–Alder precursor diketone 390 (Scheme 49). It took 13 steps to form the diketone 390 which then underwent intramolecular Diels–Alder reaction in the HFIP solvent. Both abyssomicin 2 395 and neoabyssomicin B 396 was formed from one of the Diels–Alder adduct isomer in 2 to 3 steps.¹⁰⁴

3.21. Total synthesis of atropurpuran

Atropurpuran, belongs to the arcutate-type diterpenoid, isolated from roots of *Aconitum hemslayanum*. One of its structural



Scheme 49 Total synthesis of abyssomicin 2 (395) and neoabyssomicin B (396).⁵⁸

Scheme 50 Total synthesis of atropurpuran (**401**).¹⁰⁵

feature is that it contains two contiguous bicyclo[2.2.2]octane motifs, which is usually synthesized by oxidative dearomatization-intramolecular Diels–Alder reaction. Jing Xu and co-workers¹⁰⁵ decided to begin the synthesis from readily available 5-methoxytetralone **397** which produced **398** through ring closing enyne metathesis (RCEM) (Scheme 50). **398** underwent double-oxidative dearomatization (RDOD) to form dienone **399** the Diels–Alder precursor. The diol **400** formed from intramolecular Diels–Alder reaction of dienone **399** converted to the target molecule atropurpuran **401** in few steps.¹⁰⁵

4. Dehydro Diels–Alder (DDA) reaction

4.1. Total synthesis of aspidosperma alkaloids using didehydro Diels–Alder reaction

A class of monoterpene indole alkaloids are called aspidosperma alkaloids. Techniques based on a common intermediate are likely the most effective strategies used in total synthesis. For the synthesis of aspidosperma natural products, Cain *et al.*¹⁰⁶ reported a common intermediate method through a didehydro Diels–Alder reaction between **403** and **404** in which *N*-Boc tryptamine **402** is the starting material for cascade reactions leading to the common intermediate **406** (Scheme 51a).¹⁰⁶

Scheme 51 (a) Construction of the common intermediate **406**.¹⁰⁶ (b) Aspidosperma alkaloids formed from **406**.¹⁰⁶

Additionally, they showed how useful this cascade technique was in the synthesis of that common intermediate **406** into (±)-aspidospermidine **409**, (±)-aspidofractinine **407**, (±)-limaspermidine **408**, and (±)-vincadifformine **410** (Scheme 51b).

4.2. Intramolecular DDA reaction in arylidihydronaphthalene synthesis

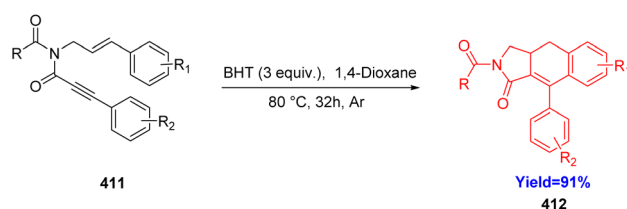
Although numerous methods are available for synthesizing arylidihydronaphthalene skeletons, [4+2] annulation reactions and didehydro Diels–Alder (DDDA) reactions of styrene–ynes are commonly acknowledged as particularly promising and effective strategies for their formation. These skeletons are essential components in various natural products and functional materials and can also serve as valuable precursors for synthesizing aryltetrahydronaphthalenes and arylnaphthalenes. Chen *et al.*¹⁰⁷ in 2022, solved various previous drawbacks and performed intramolecular DDDA reaction of styrene–ynes **411** under metal and catalyst free conditions with high chemoselectivity to produce arylidihydronaphthalene **412** (Scheme 52).¹⁰⁷

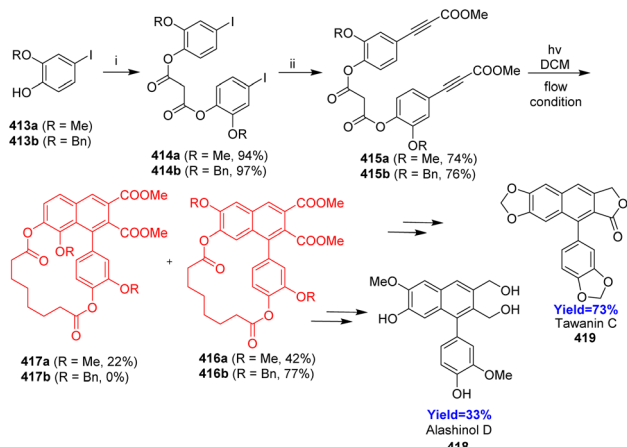
Chen and co-workers¹⁰⁷ have used 2,6-di-*tert*-butyl-4-methylphenol (BHT) as the antioxidant in 1,4-dioxane solvent. Further, with the increase of the reaction time to 32 h, the product yield also increased to 91% yield. In absence of BHT, but in presence of air or argon atmosphere the reaction yield was 88% and 89% yield respectively. Hence it is clear that addition of BHT is essential for the increase of yield of the product.

4.3. Photo-dehydro-DA reaction in total synthesis of arylnaphthalene lignans (ANLs)

Lignans, a large class of natural products distributed in different type of plants, belong to the large family of phenylpropanoids and consist of two C6 C3 units. Consequently, most lignans exhibit a C18 skeletons. Arylnaphthalene lignans (ANL) are wide spread secondary metabolites and exhibit a variety of biological properties like cytotoxicity, anti-microbial and anti-viral activity.¹⁰⁸

Though various methods of total syntheses of ANLs are available, the PDDA reactions are the most convenient and straightforward way to synthesize arylnaphthalenes. Wessig and his co-workers¹⁰⁹ in 2022, reported the PDDA reaction (*i.e.* the light-induced [4+2] cycloaddition between two arylacetylenes), as a key step in total syntheses of ANLs. They have approached through the intramolecular systems of 3-(hydroxyaryl)propionic esters where the aryl propiolates were tethered by a linker unit to synthesize ANLs *via* a PDDA reaction. Suberic acid, chosen as

Scheme 52 Synthesis of arylidihydronaphthalene.¹⁰⁷



Scheme 53 Total synthesis of alashinol D **418**, taiwanin C **419** (i) suberic acid, DIC, DMAP, DCM; (ii) methyl propiolate, Pd(PPh₃)₂Cl₂, Cul, K₂CO₃, THF.¹⁰⁹

a tethering unit because it can be easily introduced and removed, has suitable length to facilitate the reaction and has no desirable influence on photo radiation.

In the total synthesis of lignans like alashinol D **418**, taiwanin C **419**, they have taken 4-iodocatechols **413a**, **b** having protected at 2 position formed iodophenyl suberates **414a**, **b** through steglich esterification with suberic acid (Scheme 53). On Sonogashira coupling, methylpropiolates **415a**, **b** were formed, which underwent PDDA reaction under flow condition resulting the formation of **416a** and **417a** in 2 : 1 ratio but when Bn group was used **416b** formed exclusively. Further, **416a**, **b** were used for the synthesis of ANLs like alashinol D **418**, taiwanin C **419**.¹⁰⁹

5. Hetero-Diels–Alder (HDA) reaction

5.1. Aza Diels–Alder reaction in total synthesis of matrine alkaloids

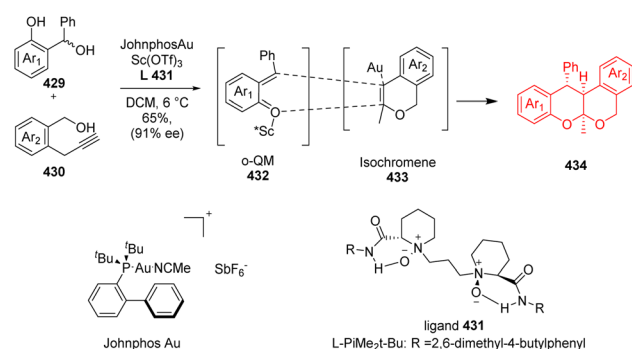
Plants of the Sophora family are used in traditional medicine in Asia, South America and Australasia. Most of the known biologically active ingredients belong to the matrine alkaloid family. Matrines have anti-cancer effects by inhibiting the proliferation and inducing apoptosis of various cancer cell lines, have been used for the clinical treatment of hepatitis B and has antiviral activity.^{110–112} Starting material methyl hex-5-enoate **420** was converted to the Diels–Alder substrate **421** in 5 steps (Scheme 54). The first hetero intramolecular Diels–Alder reaction was observed in **422** to produce **423** which paved the way for the second one through **424**. The tetracyclic core in **425** was thus generated using two intramolecular HDA reaction reported by Magann *et al.*¹¹³ On hydrogenation mixture of three matrine natural products **426–428**.¹¹³

5.2. Oxa–Diels–Alder reaction in tetracyclic isochroman synthesis

Tetracyclic isochromans, one type of polyketide oligomers, are distributed in wide range of bioactive molecules and natural



Scheme 54 Aza Diels–Alder reaction in total synthesis of matrine alkaloids (**426–428**).¹¹³



Scheme 55 Construction of the isochroman motif **434**.¹¹⁴

products. But, a general and stereoselective approach for the formation of the structure remains challenging due to their inherent instability and complex stereochemistry of polyketide.

Herein (Scheme 55), Lin *et al.*¹¹⁴ synthesized polyketide oligomer using a combination of Au(I) catalyst and a chiral Sc(III) Lewis acid catalyst. The isochromene **433** and *ortho*-quinone-methide **432** are *in situ* generated from readily available α -propargyl benzyl alcohols (**430**) and 2-(hydroxymethyl) phenols (**429**) under mild conditions (Scheme 55). Isochromene **433** and *ortho*-quinonemethide **432** underwent oxo Diels–Alder reaction forming the tetracyclic isochroman **434**.¹¹⁴

5.3. Divergent synthesis of chromenones by domino Knoevenagel-hetero–“Diels–Alder” (DKHDA) reaction

Many natural products like flavonoids, alkaloids, anthocyanins contain chromene core. The chromene derivatives exhibit anti-oxidant, anti-microbial, anti-cancer, molluscicidal properties.^{115–118} The DKHDA reaction has huge applications in the formation of synthetic drugs, natural products. Suri *et al.*¹¹⁹ synthesized chromenone derivatives **439** through a three-component reaction involving 1,3 dicarbonyl **435**, aldehydes/ ketones **436**, and alkenes **437**/alkynes **438** (Scheme 56).¹¹⁹ With no appreciable decrease in the catalytic activity, the catalyst could be employed for up to five consecutive catalytic cycles. Since, the reaction was performed under solvent free condition with a non-toxic, low cost, widely available silica catalyst, which was magnetically recoverable, reusable; this is considered as greener approach.¹¹⁹





Scheme 56 Synthesis of chromenons by solvent free, silica catalysed three component DKHDA reaction.⁶⁵

5.4. Ball-milling synthesis of tetrahydroquinolines

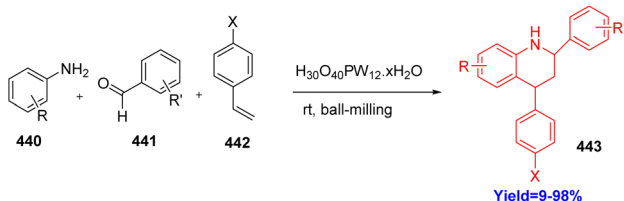
Tetrahydroquinolines are important scaffolds in various natural products. They show several pharmacological activities like excellent anti-thrombotic efficiencies in rabbit thrombosis. Though there are many ways to construct tetrahydroquinolines, Diels–Alder reaction remains the most efficient and successful route. Wang *et al.*¹²⁰ have chosen phosphotungstic acid as a catalyst in this reaction because it can be used as a phase transfer catalyst as well as green catalyst. Moreover, they have taken various anilines **440**, alkenes **442**, benzaldehydes **441** and performed solvent free (ball milling method) one pot three component Diels–Alder reaction at room temperature successfully to produce tetrahydroquinolines **443** with wide range of substrate scopes (Scheme 57).¹²⁰

5.5. Total synthesis of stereochemically diverse isomers of spirooliganins

Spirooliganins, isolated from *Illicium oligandrum*, exhibit potent activity against coxsackievirus B3 (CVB3). Wang *et al.*¹²¹ have developed the total synthesis of a library of stereoisomers of spirooliganins *via* 17 steps reaction procedure. Commercially available methyl 3,3-dimethylpent-4-enoate **444** was the precursor of this total synthesis which was converted to **445** (Scheme 58). **445** and isoprene unit **446** was irradiated with 365 nm UV light which underwent Diels–Alder reaction to give a pairs of trans-fused regioisomers **447**, **448**. Both the regioisomers **447**, **448** again underwent hetero-Diels–Alder cycloaddition with formaldehyde and 1,3-cyclohexanedione **449** to construct the cyclic core. The spirooliganins **450–453** have been produced from it through several conversions and finally Wang *et al.* constructed 16 diastereomers, 16 regioisomers of spirooliganin.¹²¹

5.6. Bioinspired total synthesis of pyritide A2

Natural product pyritide A2 belongs to the family of ribosomally synthesized and post-translationally modified peptides (RiPPs). This pyridine containing macrocyclic peptide pyritide A2 was



Scheme 57 Ball-milling synthesis of tetrahydroquinolines.¹²⁰



Scheme 58 Total synthesis of stereochemically diverse isomers of spirooliganins.¹²¹



Scheme 59 Bioinspired total synthesis of pyritide A2 (460).¹²²

identified from *Micromonospora rosaria* genome. Hooper *et al.*¹²² commenced the synthesis with the coupling of arginine derivative **454** and a phosphonium salt **455** followed by oxidative cleavage of C=P bond to form the tricarbonyl **457** (Scheme 59). The tricarbonyl was converted to the triazine **458** which on aza-Diels–Alder reaction by a solvent swap and addition of norbornadiene produced the pyridine core in **459** and at last pyritide A2 **460**.¹²²

5.7. Bio-inspired formal total synthesis of bisabosqual A

Bisabosqual A was isolated from the culture broth of *Stachybotrys* sp. RF-7260 obtained from decaying tree leaves. A unique 6/



Scheme 60 Bio-inspired formal total synthesis of bisabosqual A.^{123,124}

Review

6/5/6 ring system is the feature of bisabosqual A. Though there are several examples present to synthesize bisabosquals, there isn't any example of bio-inspired synthesis of bisabosquals. Xuanxuan Du and co-workers¹²³ took this challenge and analysed bio-inspired retrosynthesis. Oxa [3+3] annulation started the synthesis which followed by retro-6 π -electrocyclization and intramolecular hetero-Diels–Alder reaction in presence of Lewis acid (Scheme 60). The adduct **465** was converted to an alkenyl ketone **466** which could form bisabosqual A following the procedure of Parker's group.^{123,124}

5.8. Total synthesis of penostatin A and C

The penostatin family of natural products, isolated from *Penicillium* sp. OUPS-79 and *Penicillium* sp. CPCC 401423, exhibited cytotoxicity against cultured P388 cells. Penostatins A–C inhibited enzyme protein tyrosine phosphatase 1B (PTP1B), moreover penostatin C showed most inhibitory action and cytotoxicity against several other tumor cells. Jia *et al.*¹²⁵ have taken an ester **467** prepared from L-ascorbic acid as substrate which transformed to a dienophile **469** in two steps (Scheme 61). The Diels–Alder adduct **470** formed with high chemo, regio and stereoselectivity was converted to another Diels–Alder precursor **471**. A key intramolecular hetero-Diels–Alder reaction of the precursor **471** constructed the B and C ring of **472** which on elimination gave the common intermediate **473**. One of its major advantage is in all these 19 and 20 steps synthesis, 13 steps could be conducted without column chromatography.¹²⁵

5.9. Total syntheses of phlegghenrines A and C

Lycopodium alkaloids phlegghenrines A and C have same [6-6-7-6] tetracyclic scaffold where bicyclo[3.2.2]nonane being the central core and two aza heterocycles are fused in left and right side. Shi *et al.*¹²⁶ utilized three Diels–Alder reactions in their 19 and 18 steps total synthesis of phlegghenrines A and C respectively starting from cyclopentenone **476** and Danishefsky's diene **477** (Scheme 62). The Diels–Alder adduct **478** then chemoselectively



Scheme 62 Total syntheses of phlegghenrines A (**486**) and C (**487**).¹²⁶

protected and again underwent Diels–Alder reaction with dienophile nitro ethylene **480**. The adduct **481** converted to last hetero-Diels–Alder precursor **482** and reacted with 1,1-dimethoxyethylene **483** which can further form the final phlegghenrines **486**, **487** in 3 to 4 steps.¹²⁶

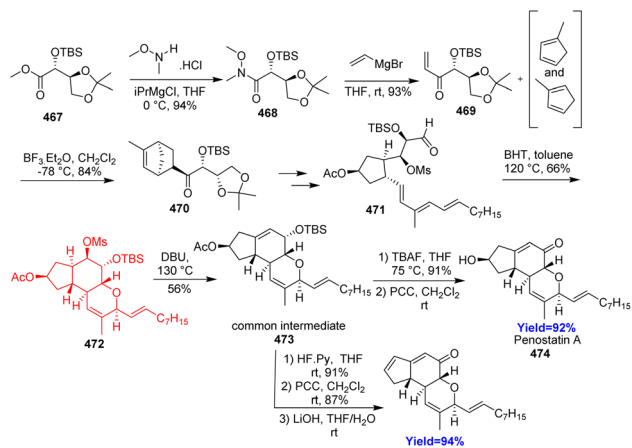
5.10. Synthesis of 6-azaindoles and total synthesis of marinoquinoline A

Marinoquinolines possess potent inhibitory effect on enzyme acetylcholine esterase and weak anti-bacterial, anti-fungal, anti-malarial activities and cytotoxic properties.¹²⁷

Osano *et al.*¹²⁸ developed intramolecular Diels–Alder oxazole (IMDAO) of allenyl oxazole **488** to form 6-azaindole **491** (Scheme 63), the core structure of marinoquinoline A.

If alkyne is present in place of allenes, the alkyne–allene isomerization take place to form the allene followed by IMDAO.

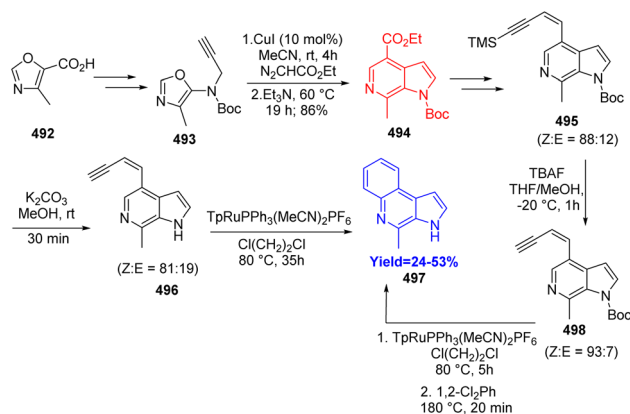
After forming the substituted aza-indole, marinoquinoline A **497** was synthesized by Osano *et al.* in the following pathway (Scheme 64). Starting from compound **492**, intermediates **495**, **496** were prepared by several transformations. Both from **495**



Scheme 61 Total synthesis of penostatin A (**474**) and C (**475**).¹²⁵



Scheme 63 IMDAO reaction of allenyl oxazole (**488**) formed 6-azaindole (**491**).

Scheme 64 Total synthesis of marinoquinoline A (497).¹²⁸

and **496**, pyrroloquinoline marinoquinoline A **497** was prepared however, the yields get doubled when the starting substrate was choosed **495**.¹²⁸

6. Photoenolization Diels–Alder (PEDA) reaction

6.1. Total synthesis of aglacin A, B, and E

Podophyllotoxin exhibits different kinds of biological activities, such as anti-cancer, insecticidal, anti-fungal, anti-viral, anti-inflammatory, neurotoxic, immunosuppressive activities.^{129–131} Aglacin A, B, E are biologically related natural products to podophyllotoxin. These compounds belong to the aryltetralin cyclic ether lignans. They consist of tetracyclic fused ring containing aryltetralin ring (A–B), two oxygenated aromatic rings (A, D), γ -lactone ring (C), and consecutive four chiral centres in B

Scheme 65 Total synthesis of aglacin A (504), B (505), and E (503).¹³²

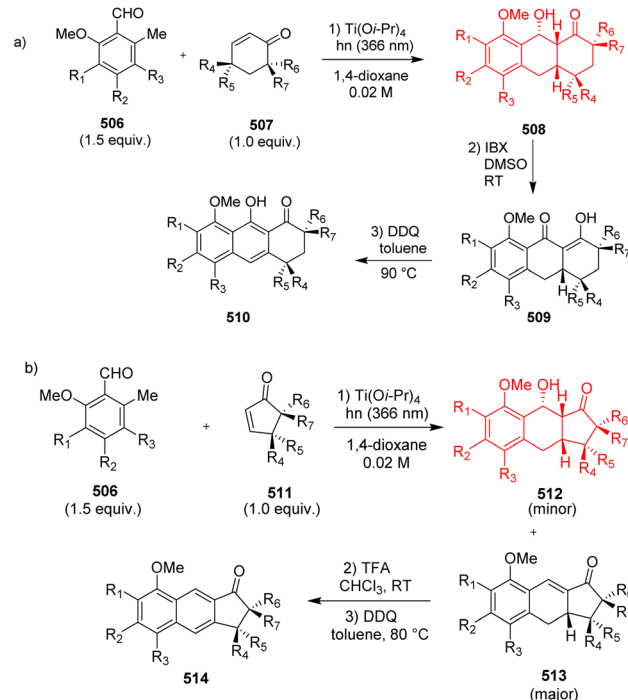
ring. Xu *et al.*¹³² proposed two pathways to construct the core skeleton of lignans through PEDA reaction in the retrosynthetic analysis. When Xu and co-workers performed choosen two pathways, only the B pathway gave better results. Total synthesis commenced with asymmetric photoenolization Diels–Alder reaction between **499** and α -bromolactone **500**. The cycloadduct **502** was converted to aglacin E **503** in 12 steps which then can be converted to aglacin A **504** by intermolecular Mitsunobu reaction and to aglacin B **505** through reductive dehydroxylation (Scheme 65).¹³²

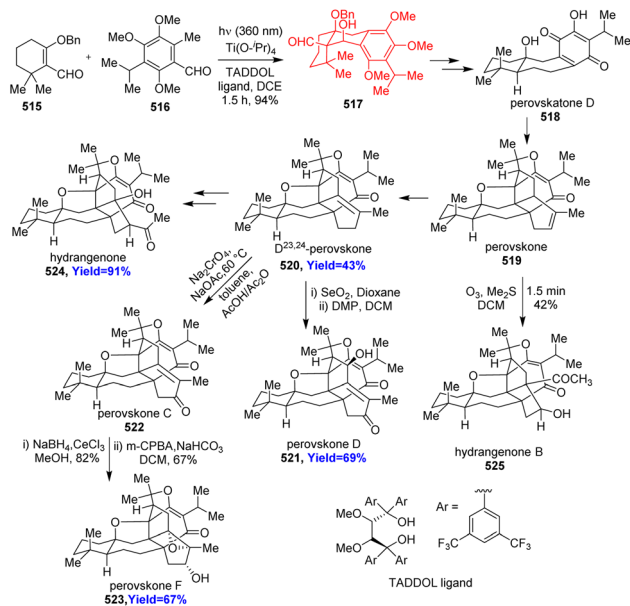
6.2. Synthesis of naphthol and naphthalene core

Many natural products such as garveatins A–D, exiguaquinol contain the naphthol and naphthalene core. These natural products show anti-microbial, anti-bacterial activities.¹³³ Diels–Alder reactions or PEDA reactions play important role in constructing the naphthol and naphthalene scaffolds. Lu *et al.*¹³³ have used sterically hindered dienophiles like α,α -disubstituted, γ,γ -disubstituted or $\alpha,\alpha,\gamma,\gamma$ -tetrasubstituted cyclohexenones **507** and cyclopentenones **511** having a quaternary center adjacent to the enone. The product **510** synthesized from cyclohexenone dienophiles generated the core of garveatin A–D, whereas the product **514** synthesized from cyclopentenone dienophile formed the core of exiguaquinol (Scheme 66).¹³³

6.3. Total synthesis of perovskones, hydrangenone, hydrangenone B

Triterpenoids perovskones and hydrangenones were isolated from *Salvia* medicinal plants. Biological activities like anti-

Scheme 66 (a) PEDA reaction with cyclohexenone dienophile (**507**), (b) PEDA reaction with cyclopentenone dienophile (**511**).¹³³



Scheme 67 Total synthesis of perovskones (519–523), hydrangenone (524), hydrangenone B (525).¹³⁴

tumor, anti-plasmodial activities were shown by these complex natural products.¹³⁴ Yang and co-workers¹³⁴ commenced the total synthesis with asymmetric photoenolization/Diels-Alder reaction between 515 and 516 in the presence of a TADDOL type ligand and $\text{Ti}(\text{O}^i\text{Pr})_4$ (Scheme 67). The Diels-Alder adduct 517 was converted to perovskatonone D (518), which is biosynthetic precursor of perovskones and hydrangenones. Perovskatonone D (518) treated with *trans*- α -ocimene, $\text{Eu}(\text{fod})_3$ and the product underwent intramolecular Diels-Alder reaction. After some tandem process $\Delta^{23,24}$ -perovskone 520 produced through perovskone 519. The latter led to the hydrangenone B 525 while the former led to other perovskones 521–523 and hydrangenone 524.¹³⁴

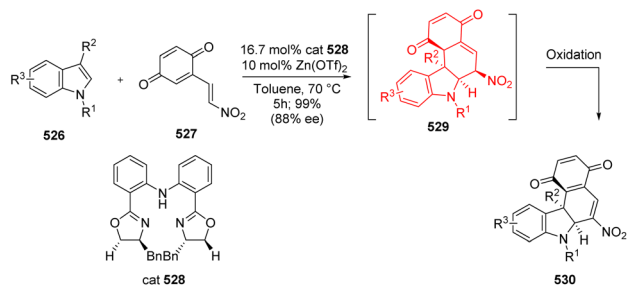
7. Inverse electron demand Diels-Alder (IEDDA) reaction

7.1. Synthesis of chiral [2,3]-fused indolines

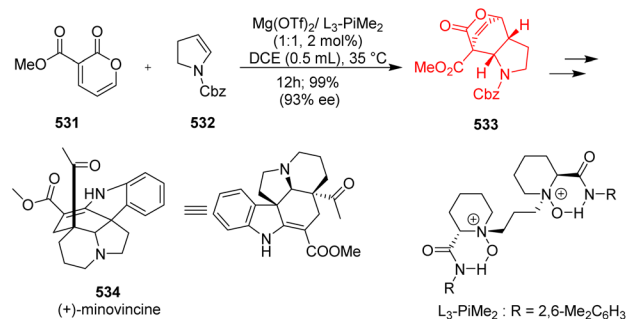
[2,3]-Fused indolines are core structure of many naturally occurring alkaloids having medicinal properties. Zhao *et al.*¹³⁵ developed chiral [2,3]-fused indoline derivatives 530 by an enantioselective dearomatization IEDDA reaction (Scheme 68).¹³⁵ Zhao and co-workers¹³⁵ started this chiral bisoxazoline/zinc-catalyst-complex mediated reaction with 2-(2-nitrovinyl)-1,4-benzoquinone 527 (diene) and a highly substituted indole 526.

7.2. Construction of *cis*-hydroindole scaffolds and total synthesis of minovincine

cis-Hydroindole scaffold is present in many natural products like minovincine, kopsinine, vindolinine, aeruginosin, pharmaceuticals like anti-hypertensive drug perindopril.^{136,137} Zhang



Scheme 68 IEDDA reaction to form the [2,3]-fused indoline scaffold.¹³⁵



Scheme 69 IEDDA reaction of 2-pyrone 531 with enamine 532 in total synthesis of (+)-minovincine (534).¹³⁸

*et al.*¹³⁸ had started with 3-carbomethoxy-2-pyrone 531 and cyclic enamine 532 as substrates (Scheme 69). This reaction showed wide substrate scope, and also compatible with acyclic enamines. The chiral ligand coordinated with $\text{Mg}(\text{OTf})_2$ in a tetradentate manner to form an octahedral structure. 2-Pyrone coordinated with its two carbonyl groups of ester to the Lewis acid catalyst and lowered the LUMO level to accelerate the IEDDA reaction. The bulky amide group of the ligand causes steric hindrance, so cyclic enamine prefers to attack the Si-face of 2-pyrone to produce *endo*-adduct with excellent stereo-selectivity. The DA adduct 533 was transformed to form the natural product (+)-minovincine 534.¹³⁸

7.3. Total syntheses of cephanolides A and B

Cephanolides belong to the *Cephalotaxus* diterpenoids class of natural products, isolated from *Cephalotaxaceae* plants. These well-known natural products have important biological activities especially potent anti-tumor activity.¹³⁹ Cephanolide B has same pentacyclic core like cephanolide A but there is an extra tetrahydrofuran ring in cephanolide A. Lu and co-workers¹⁴⁰ disclosed a Cu catalyzed asymmetric IEDDA reaction with an electron deficient 2-pyrone 535 and indene 536 which produced hexahydrofluorenyl bridged-lactone scaffold 538 (Scheme 70). This scaffold 538 is common for the cephanolides A–D and could serve as an ideal precursor for natural product synthesis. 538 was converted to the common intermediate 539 and completed the total syntheses of cephanolides A 540 and B 541 in 13 and 14 steps more respectively.¹⁴⁰



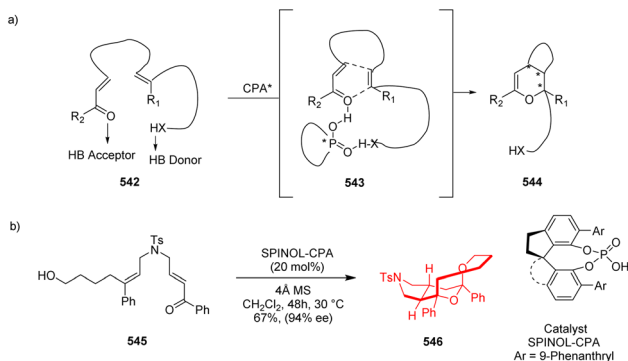
Scheme 70 IEDDA reaction of 2-pyrone 535 with indane 536 in the total synthesis of cephanolide A (540), and cephanolide B (541).¹⁴⁰

7.4. H-Bonding mediated intramolecular IEDHDA reaction to access tricyclic tetrahydropyran derivatives

Jin *et al.*¹⁴¹ had recently developed a method to produce tricyclic tetrahydropyran derivative by intramolecular IEDHDA reaction between neutral alkene and α,β -unsaturated ketones or aldehydes. It was the first example where a simple α,β -unsaturated ketone or aldehyde has been used with neutral alkene in intramolecular IEDHDA. The non-activated alkenes could be cyclized with α,β -unsaturated ketones or aldehydes with chiral phosphoric acid through double H-bonding (Scheme 71a). Substrate 545 had a hydroxyl hydrogen bonding donor group and an α,β -unsaturated arylketone as hydrogen bond acceptor. Catalyzed by SPINOL-CPA ligand, those two moieties in 545 came in close proximity and performed the cycloaddition reaction (Scheme 71b). Z-Configured substrate didn't perform in this reaction.¹⁴¹

7.5. Synthesis of *cis*-decalin derivatives and total synthesis of 4-aminophen-11-ol and *cis*-crotonin

cis-Decalin cores are present in various bioactive natural products and drugs. Si *et al.*¹⁴² have reported the formation of *cis*-



Scheme 71 (a) IEDHDA reaction *via* dual hydrogen bonding interaction, (b) formation of tricyclic tetrahydropyran derivatives *via* intramolecular IEDHDA reaction of 545.¹⁴¹



Scheme 72 (a) IEDDA reaction to construct *cis*-decalin motif in 549, (b) total synthesis of 4-amorphen-11-ol (553), (c) total synthesis of *cis*-crotonin (558).¹⁴²

decalin core by an ytterbium-catalyzed asymmetric IEDDA. They also showed the potential of their synthesis by providing enantioselective total synthesis of 4-amorphen-11-ol and *cis*-crotonin. 4-Amorphen-11-ol is one type of sesquiterpene natural products of the *Fabiana imbricate* medicinal plant and crotonins belong to the clerodane diterpenes. Si and co-workers performed inverse-electron-demand Diels–Alder reaction between 3-carboalkoxyl-2-pyrone 547 and silyl cyclohexadienol ether 548 in the presence of Yb(OTf)₃/BINOL (Scheme 72a). Moreover, enantioselective total synthesis of 4-amorphen-11-ol 553 (Scheme 72b) and *cis*-crotonin 558 (Scheme 72c) was done *via* this reaction.¹⁴²

7.6. Total synthesis of lissodendoric acid A

Lissodendoric acid A, isolated from marine sponge *Lissodendoryx florida*, belongs to the manzamine family of alkaloids. The structural feature of lissodendoric acid A is it holds an azadecalin scaffold and 14-membered macrocycle. During the total synthesis, Ippoliti *et al.*¹⁴³ had trapped a cyclic allene intermediate which is very rare also in a Diels–Alder reaction. The two Diels–Alder precursor pyrone 561 and silylbromide 562 (cyclic allene precursor) were synthesized from commercially available carboxylic acid 559 and bromotriflate 560 respectively (Scheme 73). The inverse electron demand Diels–Alder reaction was successfully done in the presence of CsF, Bu₄NBr at −20 °C to construct the azadecalin core. The cycloadduct 564 completed the total synthesis of lissodendoric acid A 565 in 5 steps.¹⁴³



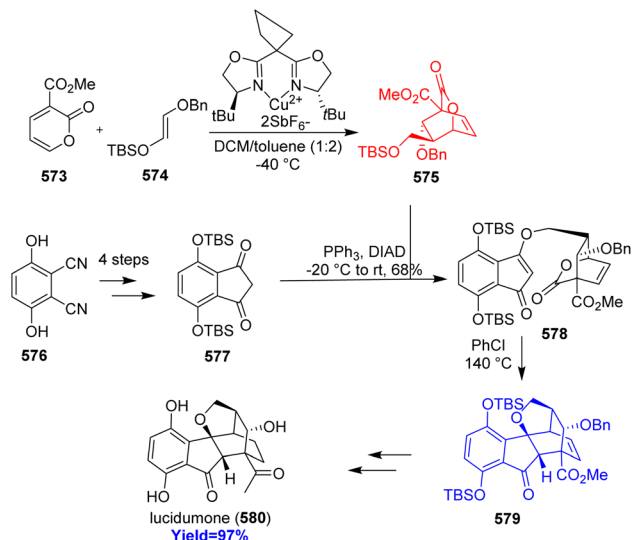
Scheme 73 Total synthesis of lissodendoric acid A (565).¹⁴³

7.7. Synthesis of *cis*-decalin motifs

Since, *cis*-decalin motifs are hugely found in natural products and in bioactive compounds it gains much attention from chemists. Si and co-workers¹⁴⁴ had developed a unique way to construct the *cis*-decalins through multi-step synthesis. Birch reduction of **566** to **567** merged with inverse-electron-demand Diels–Alder reaction between **567** and **568** in presence of $\text{Cu}(\text{OTf})_2$ catalyst, a bis(oxazoline) ligand provided the *cis*-decalins **570** (Scheme 74). This reaction produced a wide range of polysubstituted *cis*-decalins, key intermediate **572** to several triterpene and had led to the concise total synthesis of occidantalol (**571**).¹⁴⁴

7.8. Concise total synthesis of lucidumone

Lucidumone, extracted from *Ganoderma lucidum*, inhibited COX-2, showed anti-inflammatory activity and has a very complex structure with bicyclo[2.2.2]scaffold. Huang and co-workers¹⁴⁵ synthesized this complex lucidumone natural product through a retro-[4+2]/intramolecular Diels–Alder cascade. Inverse-electron-demand Diels–Alder reaction between 2-pyrone **573** and acyclic enol ether **574** formed a lactone **575** which then combined with indanedione **577** prepared from readily available dicyanodihydroquinone **576** (Scheme 75). The product **578** then underwent retro-[4+2]/IMDA cascade to form **579** and finally converted to lucidumone **580** in few steps.¹⁴⁵

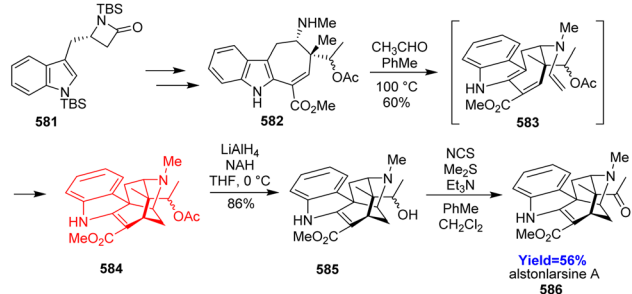
Scheme 74 Synthesis of *cis*-decalin motifs.¹⁴⁴Scheme 75 Concise total synthesis of lucidumone (**580**).¹⁴⁵

7.9. Total synthesis of alstonlarsine A

9-Azatricyclo[4.3.1.0^{3,8}] decane motif fused with indoline ring is a unique feature of alstonlarsine A which was isolated from *Alstonia scholaris*. Alstonlarsine A is known for its Drak2 inhibitory activity which in turn a promising drug target for autoimmune diseases.¹⁴⁶ Based on their retrosynthetic analysis, Ferjancic *et al.*¹⁴⁷ commenced with homotryptophan β -lactam **581** (Scheme 76). The β -lactam **581** was converted to the key intermediate **582** through intramolecular Horner–Wadsworth–Emmons reaction to form the cycloheptane ring. Amine **582** formed enamine **583** when heated with acetaldehyde and the enamine **583** underwent inverse-electron-demand dearomative Diels–Alder reaction to form **584**. This domino sequence followed by selective deprotection of acetate group and Corey–Kim oxidation completed the total synthesis of alstonlarsine A **586**.¹⁴⁷

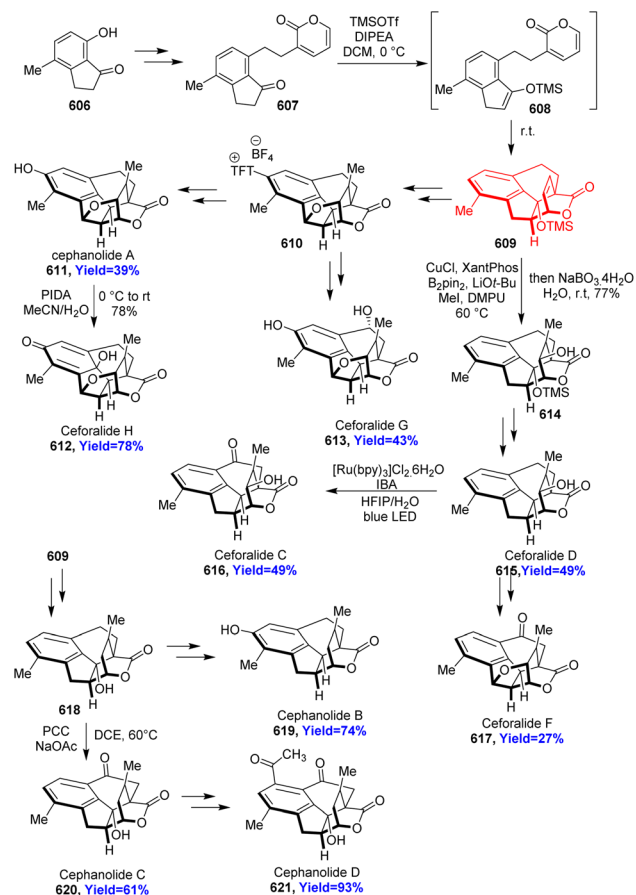
7.10. Collective syntheses of illudalane sesquiterpenoids

Polysubstituted benzene rings are commonly found in illudalane sesquiterpenoids. Though there are several strategies to form benzene rings, Park and co-workers¹⁴⁸ took a different approach through inverse-electron demand Diels–Alder

Scheme 76 Total synthesis of alstonlarsine A (**586**).¹⁴⁷



Scheme 77 Collective syntheses of illudalane sesquiterpenoids (a) synthesis of riparol B, granulactone, echinolactone A, radulactone (b) synthesis of alcyopterosins.¹⁴⁸



Scheme 78 Total syntheses of cephanolides and ceforalides.¹⁴⁹

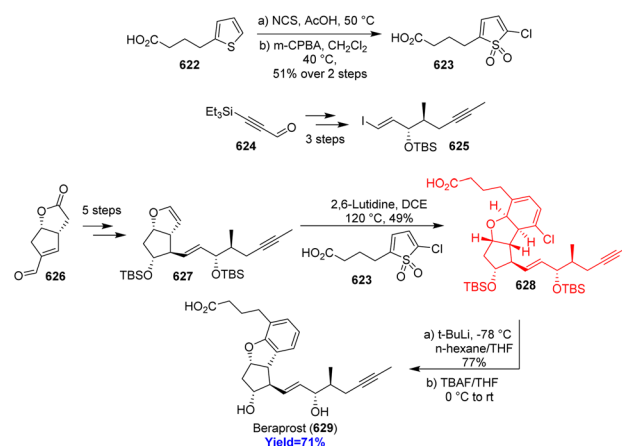
cycloaddition/retro-cycloaddition with SO_2 extrusion. The diene 2,3-fused bicyclic thiophene *S,S*-dioxide **589** was synthesized from 3,3-dimethylcyclopentanone **587** and underwent Diels–Alder reaction with dienophile furan **590** to construct the core of illudalane benzenoid **592** (Scheme 77a). This cycloadduct **592** then could be converted to few illudalane sesquiterpenoids **593–596** consecutively.¹⁴⁸ Alcyopterosins O, A, B, C, H were also synthesized through similar kind of reactions only by changing the reaction components (Scheme 77b).¹⁴⁸

7.11. Total syntheses of cephanolides and ceforalides

Cephanolides and ceforalides, both belong to the *Cephalotaxus* diterpenoids, were isolated from *Cephalotaxus sinensis* and seeds of *Cephalotaxus fortune* respectively. Sennari and co-workers¹⁴⁹ commenced the total synthesis with hydroxyindanone **606** and converted it to the Diels–Alder precursor **607** through repetitive cross-coupling (Scheme 78). The intramolecular inverse-electron demand Diels–Alder reaction produced the desired product **609** successfully with high yield and finally synthesized cephanolide A **611** via **610**. **610** synthesized ceforalide G **613** while cephanolide A **611** formed ceforalide H **612**. Moreover **609** was converted to **618** which formed cephanolides B–D **619–621** in few steps and to **614** which formed ceforalide D **615**, C **616** and F **617**.¹⁴⁹

7.12. Total synthesis of beraprost

Antiplatelet drug beraprost, a less cytotoxic prostacyclin analogue, used for the treatment of pulmonary arterial hypertension (PAH) and can be taken orally. Wang *et al.*¹⁵⁰ based on their retrosynthesis commenced the synthesis from commercially available thiophene **622** and ynol **624** to form the



Scheme 79 Total synthesis of beraprost (**629**).¹⁵⁰



Scheme 80 Total synthesis of pedrolide (638) through key Diels-Alder cascade.¹⁵¹

upper sidechain **623** and lower sidechain **625** of beraprost respectively (Scheme 79). After forming the sidechains, enalactone **626** was converted to Diels-Alder precursor **627** in 5 steps. The precursor **627** and the upper sidechain containing thiophene 1,1-dioxide **623** on inverse-electron demand Diels-Alder reaction produced chlorocyclohexadiene **628** which then aromatized with *t*-BuLi and converted to beraprost **629** on deprotection with TBAF.¹⁵⁰

7.13. Total synthesis of pedrolide

Pedrolide, a tigliane derived diterpenoid, isolated from *Euphorbia pedroi*. Highly oxidized carane fragment and a bicyclo [2.2.1]heptane (pedrolane scaffold) made it highly congested. Fadel and co-workers¹⁵¹ developed the first ever total synthesis of pedrolide with 4-methoxyphenol **630** as substrate (Scheme 80). A key Diels-Alder cascade was observed in constructing the bicycloheptane motif from **631** to **633**. The cascade involves inverse-electron-demand Diels-Alder → retro-Diels-Alder → retro-Diels-Alder → intramolecular Diels-Alder reaction of **631** led to the bicycloheptane **633** successfully. Finally, the total synthesis of pedrolide **638** was completed in 20 steps with 45% yield.¹⁵¹

8. Inverse electron demand hetero-Diels-Alder reaction

8.1. Total synthesis of (–)-strictosidine

MIAs (monoterpene indole alkaloids), are a large class of natural products possessing valuable pharmacological activities, derived from a single biosynthetic precursor strictosidine. Quinine, an anti-malarial drug; strychnine, a potent toxin; and vinblastine, a frontline anti-cancer drug are three most well-known members of MIA family.^{152–154} Anthony and co-workers¹⁵⁵ synthesised strictosidine to access MIAs and their derivatives. They have taken a vinylogous ester **639** to produce enol ether **640** (Scheme 81). This enol ether **640** acted as a dienophile when reacted with a cyclopentenone (diene) **641** in hexafluoroisopropanol at 50 °C for 16 h. Among the four stereoisomeric transition states during this IEHDAR, the major product **642** was dictated by the orientation of the adjacent



Scheme 81 Total synthesis of (–)-strictosidine (645).¹⁵⁵

reactive olefin. The Diels-Alder adduct **642** was converted to secologanin **643** which produced strictosidine **645** using enzyme strictosidine synthase.¹⁵⁵

8.2. Synthesis of tetrahydrochromeno[4,3-*b*]quinolines using Povarov reaction

Tetrahydrochromeno[4,3-*b*]quinolines (THCQs) having tetrahydroquinoline scaffolds exhibit anti-bacterial, anti-cancer, anti-inflammatory properties including progesterone receptor modulation.^{156–158} Géraldine Masson¹⁵⁹ and her colleagues reported that the Povarov reaction, specifically the intramolecular inverse-electron-demand aza-Diels-Alder (IEDADA) reaction, is one of the most straightforward methods to construct two fused rings in a single step. They have approached through 3-(4-hydroxyphenyl)acrylate **646** and primary anilines **647** formed the azadiene precursor **650**. This precursor then underwent the Povarov reaction in the presence of a bulky chiral phosphoric acid **648**, as illustrated in Scheme 82. Without any purification step diverse type of complex tetracyclic heterocycles **649** were produced with high yields and excellent diastereo, enantioselectivity. The two OH groups in the two substrates are crucial for the stereogenic outcome of the reaction.¹⁵⁹



Scheme 82 Synthesis of tetrahydrochromeno[4,3-*b*]quinolines using Povarov reaction.¹⁵⁹

9. Conclusions

The review highlights and points out the key steps of the total synthesis involving DARs. The applications of these DARs lead to the formation of many natural product core skeleton and other motifs of bioactive compounds. Though Diels–Alder reaction was discovered in 1928, its developments and applications are still in the focus area of researches ongoing all over the world. Over the past few decades, the total synthesis of natural products has grown enormously and the role of Diels–Alder reactions in the total synthesis is unprecedented. The newer methodologies have demonstrated their high synthetic value by utilising many adaptations and variants as was highlighted by the numerous instances provided in this review.

Due to the effectiveness, adaptability, and scope of DAR, its use in the assembly of complex molecules is likely to be secured for a very long time. There are so many natural products which are undiscovered till now but will discover in the recent times. Those syntheses will probably require various types of DAR as a key step. So, the synthetic chemists must require this reaction in future as a tool for the total syntheses and will be keen to contribute to the longevity of DAR.

Data availability

No data was used for the research described in the article.

Author contributions

Anitesh Rana and Anupam Mishra contributed equally in this review article; Satish K. Awasthi: supervision editing and reviewing.

Conflicts of interest

There are no conflicts to declare.

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