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Peculiarities of meroterpenoids and their bioproduction

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Abstract

Meroterpenoids are a class of terpenoid-containing hybrid natural products with impressive structural architectures and remarkable pharmacological activities. Remarkable advances in enzymology and synthetic biology have greatly contributed to the elucidation of the molecular basis for their biosynthesis. Here, we review structurally unique meroterpenoids catalyzed by novel enzymes and unusual enzymatic reactions over the period of last five years. We also discuss recent progress on the biomimetic synthesis of chrome meroterpenoids and synthetic biology driven biomanufacturing of tropolone sesquiterpenoids, merochlorins, and plant-derived meroterpenoid cannabinoids. In particular, we focus on the novel enzymes involved in the biosynthesis of polyketide-terpenoids, nonribosomal peptide-terpenoids, terpenoid alkaloids, and meroterpenoid with unique structures. The biological activities of these meroterpenoids are also discussed. The information reviewed here might provide useful clues and lay the foundation for developing new meroterpenoid-derived drugs.

Key points

- *Meroterpenoids possess intriguing structural features and relevant biological activities.*
- *Novel enzymes are involved in the biosynthesis of meroterpenoids with unique structures.*
- *Biomimetic synthesis and synthetic biology enable the construction and manufacturing of complex meroterpenoids.*

Keywords

Meroterpenoids, Biomimetic synthesis, Biomanufacturing, Synthetic biology

Introduction

Meroterpenoids are a class of hybrid natural products containing terpenoid and nonterpenoid moieties, and the prefix of "mero-" is derived from the Greek word *merus* meaning "part, partial, or fragment" (Geris and Simpson 2009; Matsuda et al. 2016). Meroterpenoids are a large class of secondary metabolites derived from a wide range of organisms, including bacteria, fungi, plants, and animals, with diverse structural features and a broad range of biological activities (Geris and Simpson 2009). In particular, fungi are fascinating producers of several meroterpenoid-type drugs or leads, such as immunosuppressant mycophenolic acid (Sintchak et al. 1996), antimicrobial fumagillin (McCowen et al. 1951), acyl-coenzyme A:cholesterol acyltransferase (ACAT) inhibitor pyripyropene A (Tomoda et al. 1994), and antibiotic ascofuranone (Minagawa et al. 1996) (**Fig. S1**). In recent year, significant efforts have been devoted to studying the mechanisms of meroterpenoid biosynthesis, and many enzymes responsible for their chemical transformation have been characterized, inspiring the discovery of new fungal meroterpenoids.

Meroterpenoid biosynthesis has been well-documented in the literature (Barra and Abe 2020; Matsuda and Abe 2016; Matsuda et al. 2016; Murray et al. 2020). Along with the exploration of new habitats, low-cost and high-efficient genome sequencing, bioinformatics methods, and synthetic biology, many new meroterpenoids and corresponding enzymes have been investigated (Gozari et al. 2020; Li et al. 2020c; Schotte et al. 2020). This review focuses

on the novel enzyme-mediated biosynthesis of meroterpenoids and unique structures of this class that have been discovered in the last five years. The biological activities of these meroterpenoids, the biomimetic synthesis of chromane meroterpenoids, and the biomanufacturing of meroterpenoids by synthetic biology are also reviewed.

Diversity, biosynthesis, and pharmaceutical potentials of meroterpenoids

Based on their biosynthetic origins, meroterpenoids have been divided into two major groups: polyketide-terpenoids and non-polyketide-terpenoids. Non-polyketide terpenoids are further subdivided into three classes: nonribosomal peptide (NRPS)-terpenoids, terpenoid alkaloids, and meroterpenoid with unique structures. The structures and novel enzymes involved in their biosynthesis are summarized in **Table 1**, **Figure 1**, and **4**.

Polyketide-terpenoids

Polyketide-terpenoids are a large group of meroterpenoids. The polyketide portion of the molecules is predominantly assembled by polyketide synthase (PKS) using precursors such as orsellinic acid, 3-methylorsellinic acid (3-MOA), 5-methylorsellinic acid (5-MOA), and 3,5-dimethylorsellinic acid (DMOA) (Geris and Simpson 2009; Matsuda and Abe 2016). However, enzymes other than PKS have recently been reported to produce some unique chemical structures (**Fig. 1**).

Novofumigatonin (**5**) was isolated from *A. novofumigatus* and contained an unprecedented scaffold bearing an unusual ortho-ester moiety, which was found to be a DMOA-derived fungal meroterpenoid. A mechanistic investigation revealed an intriguing non-heme iron-dependent endoperoxide isomerase NvfE that can catalyze the ortho-ester formation. NvfE was believed to be the first reported enzyme with isomerase activity due to a loss of its αKG-binding ability (Matsuda et al. 2018) (**Fig. S2**).

Emeridone F (**6**) and anditomin (**7**) are both 3,5-DMOA derived meroterpenoids with a characteristic bridged-ring system. A biosynthetic study of anditomin in *Emericella variecolor* NBRC 32302 showed that the non-heme iron-dependent dioxygenase AndA was involved in the formation of the bridged-ring via a novel skeletal reconstruction (Matsuda et al. 2014); this reaction mechanism was in contrast to the previously proposed Diels−Alder reaction. Two α-ketoglutarate (αKG)-dependent dioxygenases SptF and SptN were also found to be involved with increasing structural complexity in late-stage biosynthesis to form emeridone F and other analogues (**Fig. 2a**) (Bai et al. 2020).

Terretonin (**8**) is a DMOA-derived meroterpenoid, possessing a unique tetracyclic 6/6/6/6 core skeleton. This polyketide-sesquiterpene hybrid compound was first isolated from *Aspergillus terreus* NPPL6273 in 1979, and the gene cluster *trt* and biosynthesis pathway have been recently characterized (Guo et al. 2012; Matsuda et al. 2012; Springer et al. 1979). Cytochrome P450 Trt6 and a novel isomerase Trt14 were found to be involved in the successive oxidations and unprecedented rearrangement, respectively, leading to the D-ring expansion (**Fig. 2b**) (Matsuda et al. 2015). The crystallographic analysis of Trt14 provided structural insights into the molecular architecture and diversification of this novel enzyme (Mori et al. 2017).

Berkeleyacetals are heavily oxidized DMOA-derived meroterpenoids isolated from *P. rubrum* Stoll, a microorganism obtained from metal-sulfate-rich water (Stierle et al. 2007).

These types of compounds possess a unique and congested pentacyclic ring skeleton. Berkeleyacetals display inhibitory activity against matrix metalloproteinase-3 (MMP-3) and caspase-1 with IC_{50} values in the micromolar or millimolar range (Stierle and Stierle 2014). Genome mining revealed a distinctive gene cluster *ber* in the chromosome of the *Neosartorya glabra* strain. Chemical analysis of extracts from the mutant strain *Ng*-OE:*berA* by overexpressing the regulator gene *berA* led to the isolation of a new berkeleyacetal derivative berkeleyacetal D (**9**) (Zhang et al. 2018a).

Chevalone E (**10**) was isolated from an undescribed marine derived fungus *Aspergillus similanensis* KUFA 0013. It demonstrated synergistic effects with oxacillin against the methicillin-resistant *Staphylococcus aureus* (MRSA) strain with an MIC value of 64 μg/mL and a fractional inhibitory concentration (FIC) index less than 0.188 (Prompanya et al. 2014). The biosynthetic gene cluster (BGC) *cle* was identified by targeted genome mining of an endophytic fungus *A. versicolor* 0312 (Wang et al. 2019a). Interestingly, two cytochrome P450 monooxygenases (Cle2 and Cle4) can derivatize chevalone E into new analogues containing a five-membered lactone ring (**Fig. S3**).

Arthripenoid A (**11**), a 6/6/6/6-tetracyclic ring system from *Arthrinium* sp., has shown antimicrobial, cytotoxic, and immunosuppressive activities (Han et al. 2020; Long et al. 2019; Zhang et al. 2018b). *Atn* cluster consisting of highly reducing polyketide synthase (HR-PKS), non-reducing polyketide synthase (NR-PKS), prenyltransferase, and terpenoid cyclase was found to be involved in the biosynthesis of arthripenoids. These compounds and the related *ccq* cluster were also identified from the fungus *Bipolaris sorokiniana*, which showed high sequence similarity with genes of the *atn* cluster (Han et al. 2020). It has been reported that the assembly of the hexaketide backbone required both HR-PKS and NR-PKS, and the divergent stereochemistry of the polyketide side chain resulted from the reduction of the polyketide backbone (Han et al. 2020).

Chrodrimanin A (**12**) isolated from *Penicillium verruculosum* TPU1311 displayed potent inhibitory activity against protein tyrosine phosphatase 1B (PTP1B) with an IC_{50} value of 8.5 μM (Yamazaki et al. 2015). The search for genes encoding a PKS, a farnesyltransferase, an epoxidase, and a terpene cyclase led to the discovery of the *cdm* cluster (Bai et al. 2018). A heterologous reconstitution study in fungus *A. oryzae* identified CdmE as the first PKS that catalyzed the formation of 6-hydroxymellein without the aid of dehydratase and ketoreductase enzymes (**Fig. S4**) (Abdel-Hameed et al. 2016; Bai et al. 2018; Zaehle et al. 2014).

Eupenifeldin (**13**) possesses a unique pentacyclic skeleton and was first isolated from *Eupenicillium brefeldianum* in 1993 as an antitumor agent (Mayerl et al. 1993). It showed anthelmintic, anti-malarial, antifungal, and anti-glioma activities (Ayers et al. 2008; Bunyapaiboonsri et al. 2008; Zhai et al. 2019). This tropolone-sesquiterpenoid with a unique 11-membered macrocycle was proposed to be derived from tropolone *O*-quinone methides and 10-hydroxyhumulene via hetero-Diels–Alder reactions. Chemical investigation of *Phoma* sp. (CGMCC10481) also lead to the discovery of eupenifeldin and a rearranged congener phomanolide A (Zhai et al. 2019), and the eupenifeldin BGC (*eupf*) was identified and partially validated. A NR-PKS EupfA, a FAD-dependent monooxygenase EupfB, an αKG-dependent dioxygenase EupfC, and a short-chain dehydrogenase EupfE were identified as the enzymes responsible for tropolone (stipitol) formation. The terpene cyclase EupfG and cytochrome P450 monooxygenase EupfD were found to catalyze the formation of 1*E*, 4*E*, 8*Z*-humulenol (Chen

et al. 2019). Notably, EupfF was biochemically characterized and found to be the first fungal intermolecular hetero-Diels−Alderase to generate tropolone *O*-quinone methide (**Fig. 3**).

Xenovulene A (**14**), a novel gamma-aminobutyric acid (GABA)-benzodiazepine receptor binding compound, was first isolated from *Acremonium strictum* (Ainsworth et al. 1995). It strongly inhibited the binding of flunitrazepam in an *in vitro* assay with an IC_{50} value of 40 nM. Structurally, xenovulene A consists of one humulene sesquiterpene and one rearranged polyketide-derived subunit. Genomic sequence analysis and targeted knockout (KO) experiments were used to elucidate the gene cluster responsible for the biosynthesis of xenovulene A. Heterologous reconstruction of the biosynthetic pathway in *A. oryzae* allowed for the determination of each biosynthetic step (Schor et al. 2018). Three types of highly unusual enzymes involved in the biosynthesis of xenovulene A were characterized: a putative hetero-Diels–Alderase AsR5, two enzymes AsL4 and AsL6 that catalyze oxidative-ring contractions, and terpene cyclase AsL6 (**Fig. S5**). The biosynthetic pathway proposed in Schor's study agreed with previous isotopic labelling studies (Raggatt et al. 1997; Schor et al. 2018).

Fumagillin (**15**), isolated from *A. fumigatus*, showed numerous biological activities, such as anti-microsporidial, anti-angiogenic, anti-parasitic, and anti-microbial activity (Arico-Muendel et al. 2009; Didier et al. 2006; Picoul et al. 2003; Sin et al. 1997). Structurally, this compound consists of decatetraenedioic acid connected to a cyclohexane-containing terpenoid by an ester bond (Han et al. 2020; Lin et al. 2013). *β*-trans-bergamotene synthase Fma-TC was discovered as the first membrane-bound terpene cyclase involved in the production of the sesquiterpene moiety. Intriguingly, a multifunctional cytochrome P450 monooxygenase Fma-P450 was shown to be involved in the multistep transformation, including hydroxylation, bicyclic ring-opening, and two epoxidations (Lin et al. 2014) (**Fig. S6**).

NRPS-terpenoids

NRPS terpenoids belong to the class of non-polyketide meroterpenes and they are generated by NRPS and terpene cyclase (TC). There have only been a few examples identified, including flavunoidine (**16**), aculene A (**17**), ergokonin A (**18**), and proversilin C (**19**) (**Fig. 4a**) (Lee et al. 2019; Li et al. 2020b; Yee et al. 2019).

Genome mining has been used to identify several NRPS/TC hybrid clusters in *Aspergillus*, *Penicillium*, *Cordyceps*, and *Apiospora* (Yee et al. 2019). The new metabolite flavunoidine (**16**), an alkaloidal terpenoid with a characteristic tetracyclic cage structure, was detected and isolated from the heterologous host *A. nidulans* expressing the NRPS/TC *flv* cluster (Yee et al. 2019). The tetracyclic core of flavunoidine is produced by TC FlvE and P450 FlvD, and connected to dimethylcadaverine by the second TC FlvF via an axial C−N bond. The NRPS FlvI further acylates the terpenoid core with dimethylpipecolate (**Fig. S7**). This is the first report of a genome mining strategy used to exploit the secondary metabolites of NRPS-terpenoids from fungi.

Aculenes (**17**), a novel class of norsesquiterpenes (C14), are produced by *A. aculeatus* (Petersen et al. 2014). Structurally, aculenes consist of a proline residue and a fourteen-carbon moiety that was proposed to originate from demethylation of a sesquiterpene (Petersen et al. 2014). Genome sequence analysis of *A. aculeatus* ATCC16872 predicted a candidate gene cluster *ane* responsible for the biosynthesis of aculenes. The detailed biosynthetic pathway of aculenes was characterized and verified through genetic inactivation and heterologous

reconstitution in *Saccharomyces cerevisiae* and *A. oryzae*. Specifically, three cytochrome P450 enzymes AneF, AneD, and AneG were revealed to be involved in the stepwise demethylation process to form the nordaucane (C14) structure (**Fig. S8**) (Lee et al. 2019).

Ergokonin A (**18**), isolated from *Trichoderma* sp., exhibits antifungal activity against *Candida* and most of the filamentous fungi species (Augustiniak et al. 1991; Vicente et al. 2001). Five new drimane-type sesquiterpenoids featuring an *N*-acetyl-*β*-phenylalanine moiety (one example proversilin C **19**) were isolated from the endophytic fungus *A. versicolor* F210. Proversilin C showed moderate cytotoxic activity against human tumor HL-60 cells with an IC_{50} value of 7.3 μM (Li et al. 2020b).

Terpenoid alkaloids

Terpenoid alkaloids are constructed from a meroterpenoid and an alkaloid moiety. Several examples have recently been reported, along with their biosynthetic pathways (**Fig. 4b**).

Oxalicines, isolated from *P. oxalicum*, are a rare class of hexacyclic alkaloidal meroterpene with a unique pyridinyl-*α*-pyrone polyketide moiety and a diterpenoid moiety connected through an asymmetric spiro carbon (Ubillas et al. 1989; Yaegashi et al. 2015). The *olc* gene cluster was identified from *P. canescens* and the biosynthesis of 15-deoxyoxalicine B (**20**) and its biosynthetic pathway were proposed. Seven additional metabolites were also characterized from gene deletion strains (Yaegashi et al. 2015).

Terreuspyridine (**21**) was the first DMOA derived meroterpenoid alkaloid possessing an unprecedented pyridine-fused tetracyclic 6/6/6/6 skeleton. It was isolated from the soil-derived strain *A. terreus* collected from Penguin Island in Antarctic. The tetracyclic architecture was proposed to be generated by the fusion of a glutamate and a DMOA-type meroterpenoid. Terreuspyridine displayed moderate inhibitory effects against butyrylcholinesterase (BChE) with an IC_{50} value of 16.4 μM. Further molecular docking revealed that terreuspyridine fit well in the binding pocket of BChE (Li et al. 2020a).

Dysivillosins are the first examples of polyketide-terpene-pyridine hybrid molecules from the marine sponge *Dysidea villosa*, and dysivillosin A (**22**) showed anti-allergic activity. Specifically, it significantly inhibited the activation of the Syk/PLCγ1 signaling pathway, which subsequently resulted in the inhibition of degranulation and the downregulation of LTB4 and IL-4 production in mast cells (Jiao et al. 2017).

Frondoplysin A and B, two unusual terpene-alkaloid metabolites, were isolated from the marine sponge *D. frondosa*. Frondoplysin A (**23**) showed strong *in vitro* inhibitory activity against protein-tyrosine phosphatase 1B (PTP1B) with an IC_{50} value of 0.39 μM and *in vivo* antioxidant activity in transgenic zebrafish with no cytotoxicity observed at 64 μM (Jiao et al. 2019).

Teleocidin B (**24**) is a unique indole alkaloid isolated from *S. mediocidicus* and a potent protein kinase C activator (Fujiki et al. 1984; Takashima and Sakai 1960). Teleocidin B consists of an indolactam and a monoterpenoid moiety. Intriguingly, TleD was characterized as the first methyltransferase capable of triggering terpene cyclization (Awakawa et al. 2014). Use of recombinant TleD in *in vitro* enzyme reactions suggested that a cation generated by methylation initiated the cyclization of the geranyl moiety. The sequence analysis and crystal structure of TleD provided support for the cation stabilization mechanism (Awakawa et al. 2014; Yu et al. 2016) (**Fig. S9**).

Xiamycin A (**25**), a pentacyclic indolosesquiterpenoid, was isolated from an endophytic *Streptomyces* sp. GT2002/150 and a marine-derived *Streptomyces* sp. SCSIO 02999 (Ding et al. 2010; Li et al. 2012). A bioactivity screening showed that xiamycin A exhibited selective activity against HIV. The *xia* cluster harbouring 18 genes was proposed to be involved in the biosynthesis of xiamycin A. Notably, the novel oxidative cyclization function of the flavin-dependent indole oxygenase XiaI was utilized *in vitro* to convert indosespene to xiamycin A (Li et al. 2012). Intriguingly, XiaI also showed substrate flexibility and could recognize several surrogate substrates to generate indole terpene analogues (Li et al. 2015) (**Fig. S10**).

Twenty four chartarlactams (one example **26**) were isolated from the sponge *Niphates recondite*-associated fungus *Stachybotrys chartarum* (Li et al. 2014). Phenylspirodrimane-type metabolites were only isolated from the genus *Stachybotrys* and could be used as a chemotaxonomic marker. Some of these compounds exhibited antihyperlipidemic effects on HepG2 cells, such as inhibition of intracellular triglyceride (TG) levels and reduction of total cholesterol (TC), but the mechanism of antihyperlipidemic activity remains unknown. The same group reported four new phenylspirodrimane-type dimers in 2020, which showed antibacterial (MIC: 4−16 μg/mL) and antiviral activities (Liu et al. 2020).

Meroterpenoid with unique structures

The alkyne group is a biologically active moiety found in many NPs and widely used in chemical biology research. However, the genetic basis and biosynthesis of the alkyne is poorly understood. Biscognienyne B (**27**), featuring a rare acetylenic isoprene moiety, was isolated from an endolichenic fungus *Biscogniauxia* sp. (**Fig. 4c**) (Zhao et al. 2017). Recently, whole genome sequencing has been performed and the *bis* gene cluster has been identified. Heterologous expression, feeding experiments, and *in vitro* assays were used to characterize the biosynthetic pathway. Specifically, an novel cytochrome P450-dependent BisI was shown to be involved in alkynylation of the prenyl chain (Lv et al. 2020) (**Fig. S11**).

Alternarin A (**28**) was isolated from *Alternaria* sp. ZH-15 and is characterized by a thioglycerate moiety and an unusual cyclopentenone. It showed inhibitory activity on neuronal excitability, indicating alternarin A can act as a potential neuroactive agent with antiepileptic effects (Wang et al. 2020). Avinosol (**29**), the first natural product constituting a meroterpenoid-nucleoside conjugate, was isolated from the marine sponge *Dysidea* sp. Avinosol had an IC_{50} value of ~50 μg/mL in an anti-invasion assay against two human tumor cell lines, MDA-MB-231 breast cancer cells and LS174T colon carcinoma cells (Diaz-Marrero et al. 2006).

Production of meroterpenoids by bio-inspired methods and synthetic biology

Natural products and their derivatives have long contributed to the discovery of new drugs (Newman and Cragg 2016). However, the difficulty in obtaining natural products, a result of their complicated structure and normally comprehensive stereochemistry, has hindered pharmaceutical research into natural products (Wolfender and Queiroz 2012). Therefore, new efficient approaches for constructing the complex structure of natural products are crucial for future natural product drug discovery. Considerable efforts have been made to take advantage of the biogenesis properties of natural products for their production, including biomimetic

synthesis and biomanufacturing by enzymatic reactions or in model organisms. In this section, we outline recent progress in obtaining meroterpenoids via these two approaches.

Biomimetic synthesis of meroterpenoids

Sir Robert Robinson's organic synthesis of alkaloid tropinone a century ago (Robinson 1917) inspired a new focus on biomimetic synthesis, a process by which synthetic reactions are catalyzed by enzymatic transformations of an established biosynthetic pathway of natural products (de la Torre and Sierra 2004). Many successful examples have been developed in the area of biomimetic synthesis in the last two decades, especially in studies of the biosynthetic mechanisms and organic reaction mechanisms of natural products (Baunach et al. 2015). Currently, the biosynthetic pathway of a large array of meroterpenoids have been completely or partially elucidated, which provide templates for researchers to design biomimetic synthesis pathways. To the best of our knowledge, the biomimetic synthesis of meroterpenoids has yet to be reported. The majority of studies reported on this topic focused on the biomimetic synthesis of chromane meroterpenoids. Several studies focusing on FPP–3,5-DMOA-derived meroterpenoids and other type of meroterpenoids are also summarized in this section.

Chromane meroterpenoids showed a wide range of bioactivities and share a common characteristic feature, a benzopyran/chromane-fused terpenoid unit (**Fig. 5a**). The formation of chromanes is typically generated by the hetero Diels–Alder reaction between *O*-quinone methide and an appropriate olefin (Brulíková et al. 2016; Heravi et al. 2015) (**Fig. 5b**). [4 + 2]-cycloadditions have been increasingly discovered and have introduced highly diversified structures to natural products (Jeon et al. 2017). The Diels–Alder reactions are regards as a [4 + 2]-cycloaddition. A large number of biosynthetic pathways have been hypothesized to involve a Diels–Alder reaction, and several Diels–Alderases have been investigated (Hashimoto and Kuzuyama 2016; Oikawa 2016), but identification and characterization of putative Diels–Alderases and their applications still face large challenges (Kim et al. 2012). Therefore, biomimetic reactions of these [4 + 2]-cycloadditions can serve as an efficient tool to aid in the elucidation of biosynthetic pathways or as an alternative strategy to accomplish these reactions.

Psidium guajava has been used in African and Asian traditional medicine and has been reported to produce a series of bioactive natural products including meroterpenoids (Gutiérrez et al. 2008; Qin et al. 2017). Several meroterpenoids isolated from this plant have been successfully biomimetically synthesized and are presented in **Fig. 5a**. Lee group (Lawrence et al. 2010) developed a short biomimetic synthesis of the chromane meroterpenoids, guajadial (**33**) and psidial A, through an aqueous three-component coupling reaction between caryophyllene **34**, benzaldehyde **35**, and diformylphloroglucinol **36** (**Fig. 6a**). This method precisely controlled the stereochemistry of the hetero Diels–Alder reaction by using caryophyllene **34** (Collado et al. 1998) and the reaction was successfully conducted in water, which might be the promising solvent for other *O*-quinone methide reactions.

Recently, Maiti group established the first total biomimetic synthesis of chromane meroterpenoids, including guadial B (**30**) and C, guapsidial A (**31**), and psiguajadial D (Dethe et al. 2018). They developed a highly efficient hetero Diels–Alder strategy for the total synthesis of these four benzopyran products from commercially available phloroglucinol. The reaction required 3 steps to produce guadial B **30** and C with 18.4% and 16.8% overall yields, respectively, while both guapsidial A and psiguajadial D were obtained with a 13.6% yield.

Xie and co-workers isolated a unique chromane meroterpenoid dimer psiguajdianone (**32**) from *P. guajava* (Ning et al. 2019). This caryophyllene-derived meroterpenoid dimer contained two monomers coupled by a C–C bond with two vicinal quaternary carbons and ten chiral centers. The authors successfully established a biomimetic strategy including Knoevenagel condensation/hetero Diels–Alder reactions and radical dimerization (**Fig. 6b**). In addition, five new synthetic intermediates were characterized and demonstrated to be natural products with anti-inflammatory activities that were present in the original plant.

Through a similar strategy, Wang and co-workers (Hou et al. 2020) achieved biomimetic synthesis of meroterpenoids, baefrutones, baeckenons, and frutescones isolated from the leaves of *Baeckea frutescens* (Hou et al. 2017a; Hou et al. 2017b; Hou et al. 2018). By utlizing Michael addition, oxidative [4 + 2] cyclo-addition, and the water-promoted Diels–Alder click reaction, the authors accomplished the total synthesis of baefrutones, baeckenon B, and frutescones in less than 10 steps with yields in the range of 72–83%.

The biomimetic synthesis of another type of chromane meroterpenoids, austalides, was accomplished by Barrent's group (Ma et al. 2019). The austalides are a diverse group of meroterpenoid natural product possessing a *trans*,*transoid*,*cis*-fused ring system, which were isolated from *Aspergillus* sp. and *Penicillium* sp. (Wang et al. 2019b; Zhou et al. 2011). These products showed a broad spectrum of bioactivity including cytotoxic and antibacterial properties. Based on the revised plausible biosynthetic pathway (Dillen et al. 1989) and previously well-developed sequential polyketide aromatization and polyene cyclization platform (**Fig. 6c**) (Ma et al. 2018), the authors applied the polyketide aromatization of a *trans*,*trans*-farnesol-derived β,δ-diketodioxinone to synthesize the terpene β-resorcylate **37**. This intermediate then functioned as the start substrate for further successful formation of epoxide **38**, which served as the important intermediate for further titanium(III)-mediated reductive radical cyclization to give the drimene core. The subsequent phenylselenonium ion-induced diastereoselective cyclization of the drimane to furnish the final austalides **39**–**41** is shown in **Fig. 6c**.

The unique chemistry of the hetero Diels–Alder reaction in the formation of chromene meroterpenoids continues to challenge researchers. In 2020, a few additional studies on the biomimetic synthesis of chromene meroterpenoids have been reported. Zhao and co-workers (Shao et al. 2020) presented a divergent synthetic approach to six ganoderma meroterpenoids, which were isolated from the fruiting bodies of the medicinal mushroom *Ganoderma cochlear* (Peng et al. 2015; Peng et al. 2014). This approach involved a two-phase strategy: a rapid construction of a common planar tricyclic phenol intermediate **42** (**Fig. 7**) by an intramolecular hetero Diels–Alder reaction and Stahl-type oxidative aromatization, and highly selective transformations that accomplished the oxygen bridge and fully substituted stereogenic centers of the molecule to produce **43**–**48** (**Fig. 7**).

Bruceol **49** is a pentacyclic chromene meroterpenoid and was first isolated from the Australian plant *Philotheca brucei* in 1963 (Duffield et al. 1963). Although its biosynthesis was proposed in review articles (Beaudry et al. 2005; Ghisalberti 1998), George and co-workers (Day et al. 2019) carried out a comprehensive synthesis of bruceol family compounds from a key intermediate protobruceol-I **50**. Key steps involved an intramolecular hetero Diels–Alder reaction for both bruceol (**Fig. 8a**) and isobrucel, a photochemical [2 + 2] cycloaddition for eriobrucinol, and a Claisen/Cope/Diels–Alder cascade reaction for prenylated bruceol.

A biomimetic route of farnesyl pyrophosphate (FPP) and 3,5-DMOA-derived meroterpenoid scaffolds was first developed by Powers and co-workers (Powers et al. 2019). Inspired by the biosynthesis of DMOA-derived meroterpenoids reported by Abe group (Matsuda and Abe 2016), the authors started from the preparation of the key dearomatized substrate **51** from DMOA derivatives **52** and an appropriate farnesyl electrophile **53**, followed by chemical polycyclization to form the complex natural and non-natural meroterpenenoid library (**Fig. 8b**). The authors developed a C5-selective alkylative dearomatization of substrate **51**, which is the most difficult part in this biomimetic approach. A dearomatization-driven polycyclization (DDP) for generating unique tetracyclic DMOA-derived meroterpenoids could provide a valuable strategy for the synthesis of other meroterpenoids.

Aside from the typical biomimetic synthesis of meroterpenoids described above, researchers have also spent efforts in developing new strategies for construction of new meroterpenoid derivatives according to their biosynthetic properties. Kikuchi *et al*. proposed "diversity-enhanced extracts" (Kikuchi et al. 2016; Kikuchi et al. 2014), a combination of natural product chemistry and diversity-oriented synthesis, which successfully led to the construction of a meroterpenoid-like library containing 25 compounds with diverse structural scaffolds based on the diversity-enhanced extracts of classic medicinal plants. Based on the observation that phenolic meroterpenoids normally possess a cyclic ether moiety fused with a benzene or pyrone ring (**Fig. S12a**), the authors designed similar cyclic ether moieties to produce meroterpenoid-like compounds in diversity-enhanced extracts. Firstly, they prepared the mixtures of ether solutions, i.e. phenyl ethers and pyronyl ethers. Secondly, traditional medicinal plants containing rich sources of sesquiterpenoids, *Cyperus rotundus*, *Curcuma zedoaria*, *C. longa*, and *Atractylodes japonica*, were chosen for preparation of the terpenoid-rich extracts. The etherification of the chemically reduced extracts with the ethers was carried out and led to the identification of 25 new meroterpenenoids (**Fig. S12b**), some of which showed promising anti-osteoporotic and anti-lymphoma/leukemia activities (Kikuchi et al. 2019). This study revealed an efficient strategy for producing chemical libraries based on biosynthetic logic.

The elucidation or speculation of natural product biosynthetic pathways can significantly inspire the development of novel cascade reactions for biomimetic synthesis. These reactions can provide the required quantity of natural products or produce new derivative libraries for aiding natural product drug discovery. Currently, only a few types of meroterpenoids, the majority of which are chromene-type meroterpenoids, have been successfully obtained by biomimetic synthesis. More studies on biomimetic synthesis for the other type of meroterpenoids will provide useful approach for understanding chemical reactions and product acquisition.

Biomanufacturing of meroterpenoids by synthetic biology approaches

There are several meroterpenoid compounds that have been successfully biosynthesized in heterologous systems, as discussed in the first section of this review article. In this section, we focus on the expression of meroterpenoids in heterologous hosts for the purpose of producing new bioactive analogues or higher yields of production.

Aspergillus oryzae is a well-established host for the expression of fungal biosynthetic gene clusters (Itoh et al. 2010; Kahlert et al. 2020; Matsuda et al. 2014). Tropolone sesquiterpenoids are a family of fungal meroterpenoids with significant bioactivities (El-Elimat et al. 2019).

They share the common structure of a core 11-membered macrocycle (derived from humulene), one or two dihydropyran rings, and polyketide-derived tropolones (Chen et al. 2019). Tropolone sesquiterpenoids are of significant interest due to a unique intermolecular hetero Diels–Alder reaction between humulene and tropolones that is responsible for their core skeleton structures. Cox and co-workers performed heterologous reconstruction of the entire biosynthetic pathway of tropolone sesquiterpenoid xenovulenes in *A. oryzae* and produced a variety of xenovulene derivatives on a multi-milligram scale (Schor et al. 2018). Based on this accomplishment, Cox group (Schotte et al. 2020) further developed a synthetic biology driven biosynthesis by recombination of the genes from three tropolone sesquiterpenoids biosynthetic gene clusters (pycnidione **54**, xenovulene B **55**, and eupenifeldin **13**) in *A. oryzae*. This approached resulted in a series of unnatural tropolone sesquiterpenoids (**Fig. 9**). This rational design of the reconstituted pathway successfully expanded the chemical space of target natural products.

Merochlorins A and B consist of polyketidic and isoprenic units and are produced by the marine bacterium *Streptomyces* sp. strain CNH-189, and theyfeature unique ring systems, bicyclo-[3.2.1]octadione and 6-5-5-fused tricycle, respectively (Kaysser et al. 2012; Sakoulas et al. 2012). Moore and co-worker (Teufel et al. 2014) constructed a four-enzyme system, including a type III polyketide synthase, a prenyl diphosphate synthase, an aromatic prenyltransferase, and a vanadium-dependent haloperoxide, to synthesize merochlorin A and isomeric merochlorin B (**Fig. S13**). This study presents the first example of total enzymatic synthesis of meroterpenoids and describes a compact pathway involving four enzymes and the common metabolites DMAPP, GPP, and malonyl CoA.

Renata group (Li et al. 2020c) developed a hybrid strategy, combining the unparalleled site selectivity of enzymatic hydroxylation with the radical-based transformations, to generate eight C3-oxidized meroterpenoids through 7–12 steps from commercial materials. Both α-pyrone meroterpenoids (Sunazuka and Ōmura 2005) and diterpene meroterpenoids (Macias et al. 2014) possess a common C3-oxidized unit: C3-oxidized drimane for the former and C3-oxidized *ent*-isocopalane for the latter. The previously reported synthesis of C3-oxidized meroterpenoids was limited due to the slow rates of dihydroxylation, variable levels of regio- and enantio-selectivity, varying degrees of success in the biomimetic cyclization step, and inefficient ring construction (Nagamitsu et al. 1995; Smith III et al. 1996). Alternately, the report by Renata group presents a combined strategy based on site-selective oxidation of a simple drimane or isocopalane-like framework, both of which are available in the form of sclareolide and sclareol, the common feedstocks in the perfume industry (**Fig. S14**).

Reconstruction of plant-derived natural products into microbial cell factories is valuable for the production of suitable quantities of pharmaceutically relevant compound. However, this approach faces challenges due to the limited knowledge of applicable biosynthetic pathways (Cravens et al. 2019). Cannabinoids, a class of plant-derived meroterpenoids, were isolated from *Cannabis sativa* and applied to many therapeutic uses, including the relief of chemotherapy-derived nausea and anorexia, and symptomatic mitigation of multiple sclerosis (Appendino et al. 2011). Recently reported studies revealed that cannabinoids show potential in the treatment of some psychological conditions, such as depression and psychotic disorders (García-Gutiérrez et al. 2020). However, although there are more than 100 known cannabinoids reported in addition to the main product tetrahydrocannabinolic acid (THC) (Carvalho et al.

2017), the majority of the other analogous could only be obtained in low amounts and their pharmacological profile has not been extensively determined. Exploration of synthesis for cannabinoids in heterologous hosts via synthetic biology would provide an attractive mode of production.

Stehle and co-workers comprehensively summarized recent advances in cannabinoid biosynthesis in heterologous hosts (Carvalho et al. 2017). The biosynthesis of cannabinoids is divided into three parts according to their structural features: GPP supply for the formation of terpenoid unit; synthesis of the polyketide unit olivetolic acid (OA); and the formation of GPP and OA (**Fig. S15**). The synthesis of OA starts with the short-chain fatty acid, hexanoic acid, the production of which was considered the challenging step in the biosynthesis of cannabinoids. Choosing suitable host organisms for production of heterologous metabolites is critical. Currently, five host organisms have been evaluated for the expression of cannabinoids, including *Escherichia coli*, *Saccharomyces cerevisiae*, *Komagataella phaffii* (*Pichia postoris*), *Kluyveromyces marxianus*, and *Yarrowia lipolytica*. The most efficient hexanoic acid formation was found in *K. marxianus*, as reported by Cheon *et al*., with a production of up to 142 mgL^{-1} (Cheon et al. 2014). *S. cerevisiae* is a model and excellent host organism for isoprenoid production (Nevoigt 2008), and the optimization of the engineering approach could be adapted to improve the GPP supply for cannabinoid biosynthesis. Identifying the metabolic bottlenecks associated with OA and cannabigerolic acid (CBGA) in the tetrahydrocannabinolic acid (THCA) biosynthetic pathway is crucial for improvement of the yeast chassis for sufficient precursor (acetyl-CoA), energy (ATP), and NADH delivery (Thomas et al. 2020). Notably, a recent study revealed the complete biosynthesis of cannabinoids from the simple sugar galactose in yeast by Keasling and co-workers (Luo et al. 2019). The MVA pathway was engineered to provide a high flux of GPP supply and combined a multi-organism-derived hexanoyl-CoA biosynthetic pathway.

Terpenoids are the largest family of natural products. These compounds derive from the elongation of different units of 5-carbon building blocks (i.e. IPP and DMAPP), cyclization catalyzed by terpene cyclases (TCs), and post-modification enzymes. The cyclization patterns observed can be incredibly diverse, which contribute to the vast diverse skeleton of terpenoids core structure (Schmidt-Dannert 2014). Future work on the synthetic biology driven biomanufacturing of meroterpenoids should consider both tuning the biosynthetic pathway and precursor metabolism flux for high yield production.

Future perspectives

Meroterpenoids are found to be distributed in a wide range of organisms, including microbes, plants, and animials. According to the chemical complexity of the terpene unit and non-terpene unit (PKS, NRPS, etc.), meroterpenoids possess intriguing structural diversity and potential for various therapeutical applications. Our summary on the recent studies of meroterpenoids reveals that the intriguing reactions performed by multifunctional enzymes can lead to the production of meroterpenoids with novel molecular architectures.

Future work on meroterpenoids should focus on the following aspects. Firstly, the genomic data for thousands of organisms have been uploaded to public databases and the genome sequencing cost has steadily decreased. Genome mining will become an efficient approach for new meroterpenoids discovery. Since the phylogenetic realationship of enzymes

was found to relate to the substrate specificity and catalytical chemistry, meroterpnoid cyclase (non-canonical terpene cyclase) could serve as the probe for mining unique meroterpnoids (Barra and Abe 2020; Mitsuhashi et al. 2020). Secondly, more attention and efforts are required in the biomanufacturing of plant-derived meroterpnoids in microbial cell factories, namely by reconstructing a combined biosynthetic pathways via synthetic biology. The successful use of synthetic biology and metabolic engineering for the production of semi-synthetic artemisinin has demonstrated the incredible potential of the approach (Ro et al. 2006). Finally, rational design and engineering of metabolic pathways has enabled the production of new meroterpenoids. This could be carried out by tailoring enzyme incorporation, exogenous substrate feeding, and combinatorial biosynthesis. Combinatorial biosynthesis has been demonstrated to infinitely expand the chemical diversity of meroterpenoids, exemplified by the production of 22 decalin-containing diterpenoid pyrones in *A. oryzae* through reconstitution of five native pathways, one shunt pathway, and four extended pathways derived from five fungal genera (Tsukada et al. 2020). The future outlook is an integrated platform combining genome mining, synthetic biology, metabolic engineering, and many others that can be applied for the production of meroterpenoids.

Author contributions

Y.F. and R.Q. conceived and designed research. J.H., L.J., and X.L. wrote the manuscript. Y.F., X.L., R.Q., and L.Z. reviewed and revised the manuscript. All authors read and approved the manuscript.

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Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest

The authors declare that they have no conflicts of interest.

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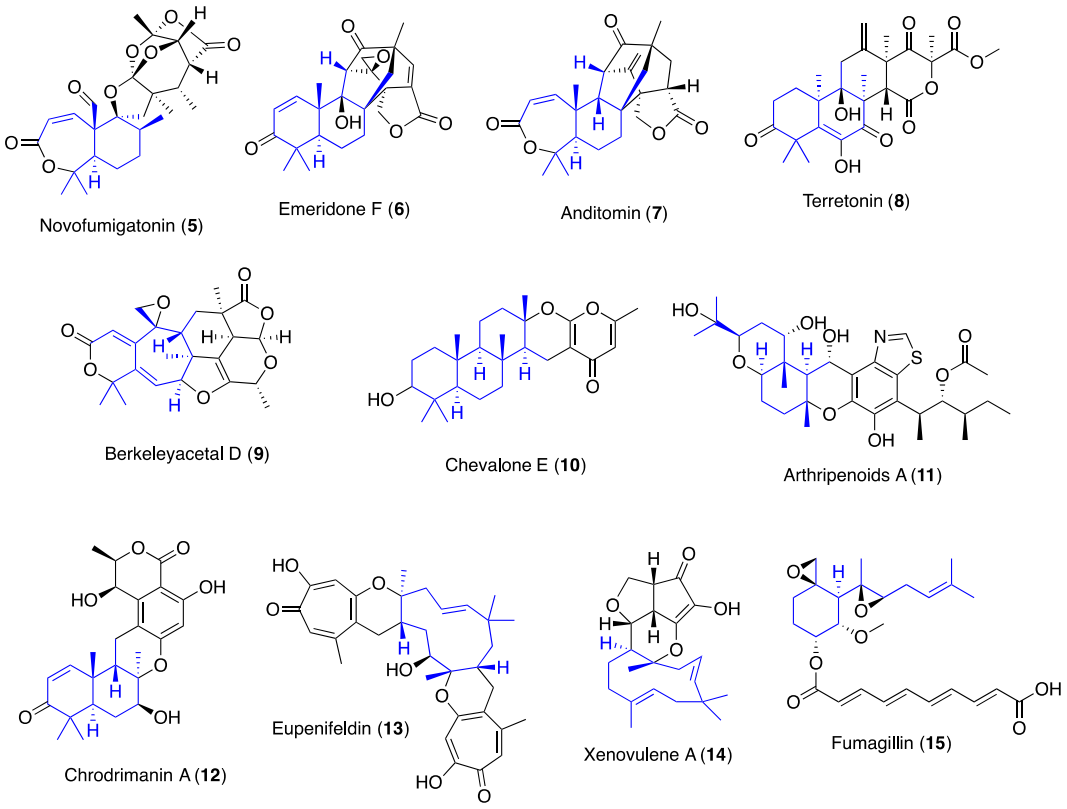


Fig. 1 Structures of polyketide-terpenoid hybrid natural products (NPs) **5–15** (terpenoid moieties in blue)

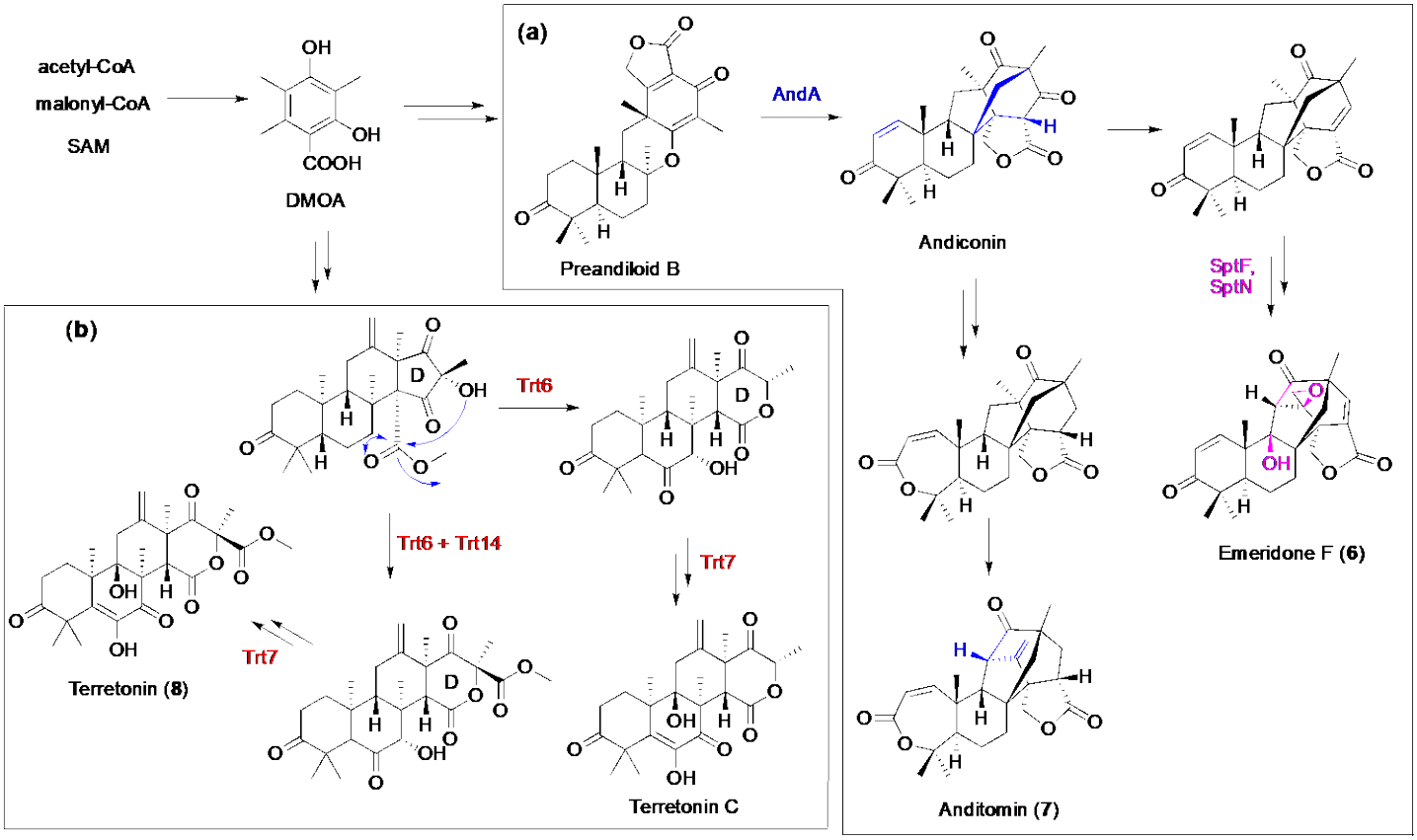


Fig. 2 Biosynthetic pathway of DMOA-derived meroterpenoids **6–8**

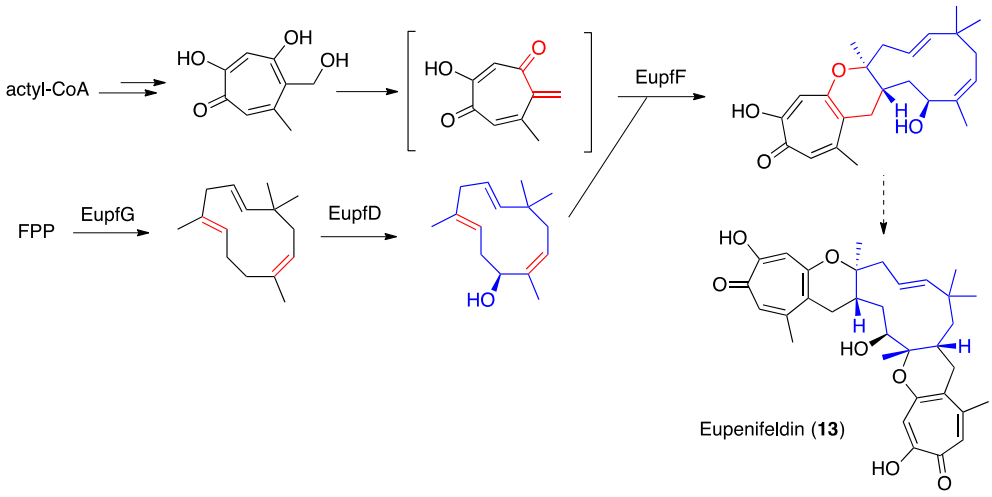


Fig. 3 Proposed biosynthetic pathway of eupenifeldin **13**

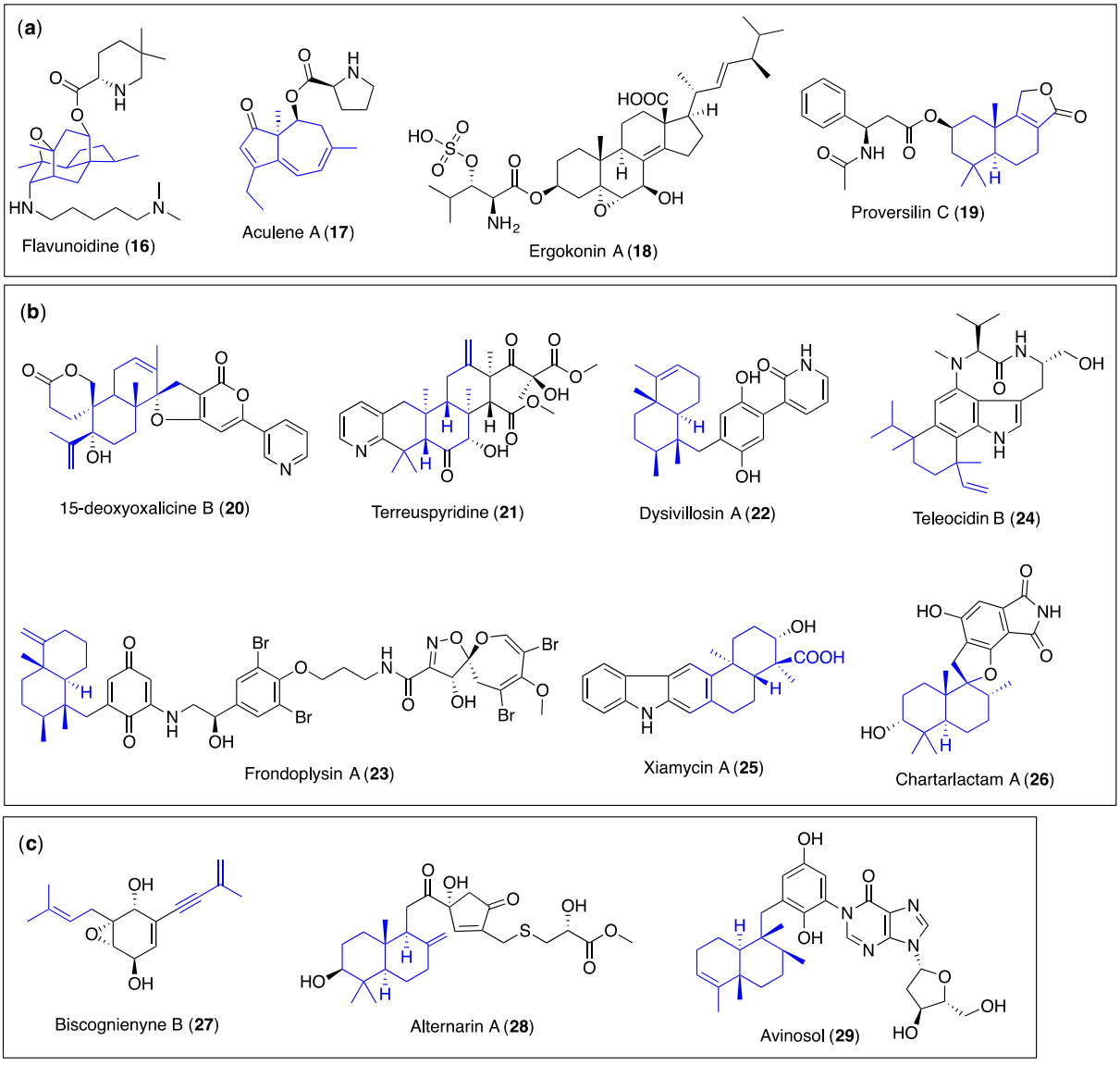


Fig. 4 Structures of NRPS-terpenoids **16**–**19** (**a**), meroterpenoid alkaloids **20**–**26** (**b**), and meroterpenoids with unique structures (**c**)

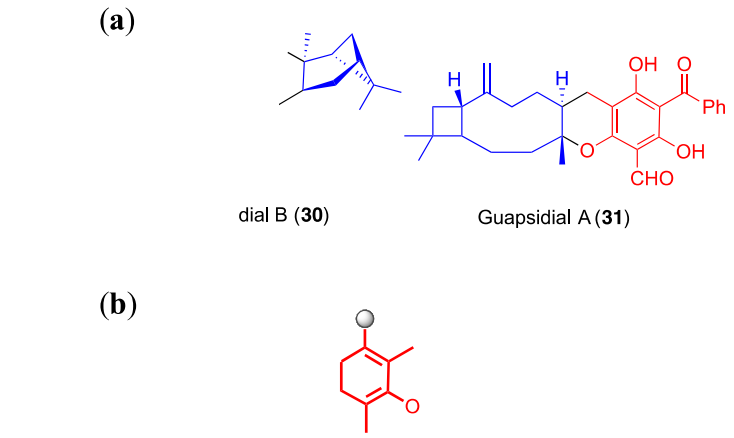


Fig. 5 Representative chromane meroterpenoids for biomimetic synthesis (chromane unit in red and terpene unit in blue) (**a**) and the biosynthetic logic of the hetero Diels–Alder reaction (**b**)

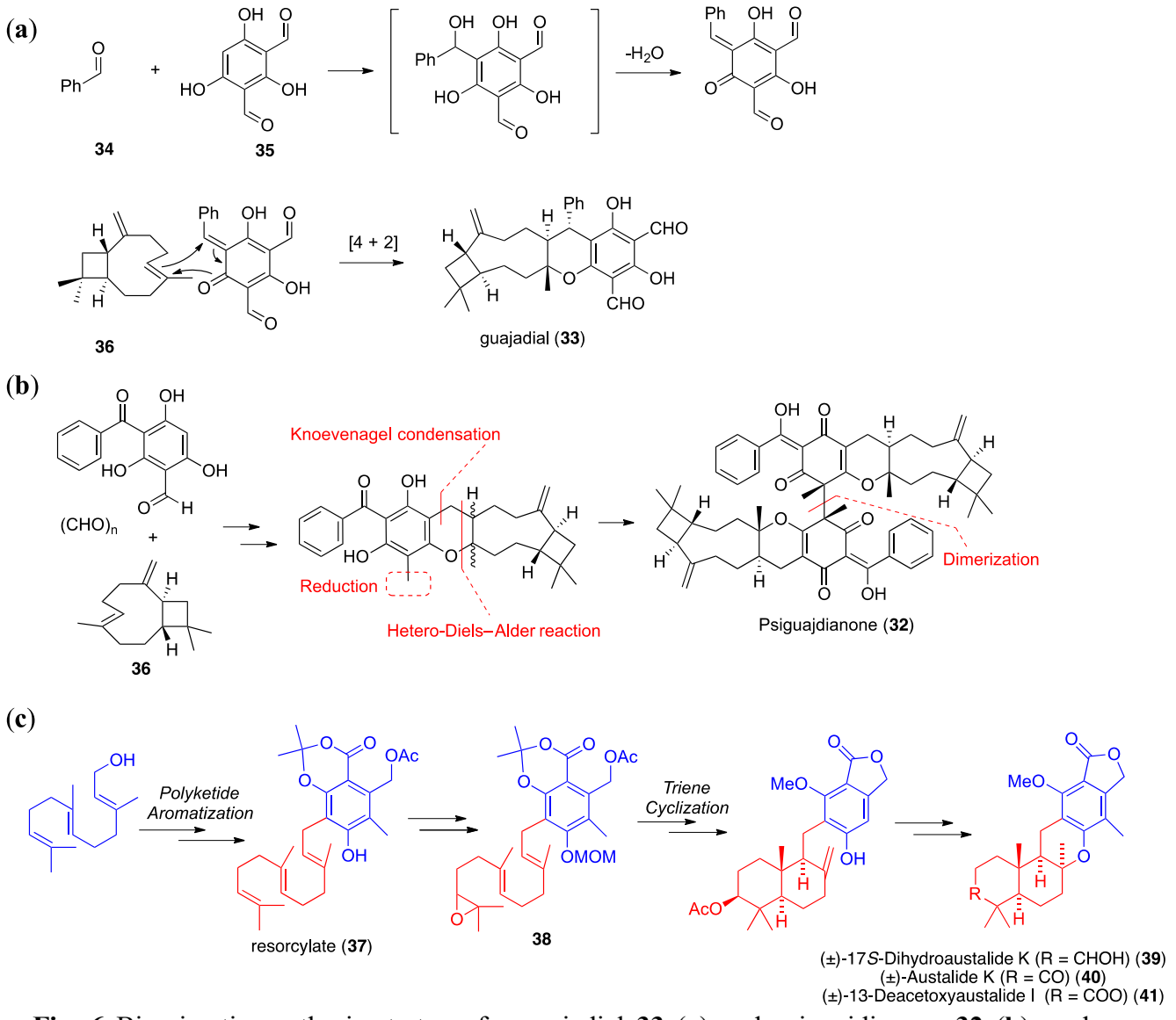


Fig. 6 Biomimetic synthesis strategy for guajadial **33** (**a**) and psiguajdianone **32** (**b**), and austalides (**c**)

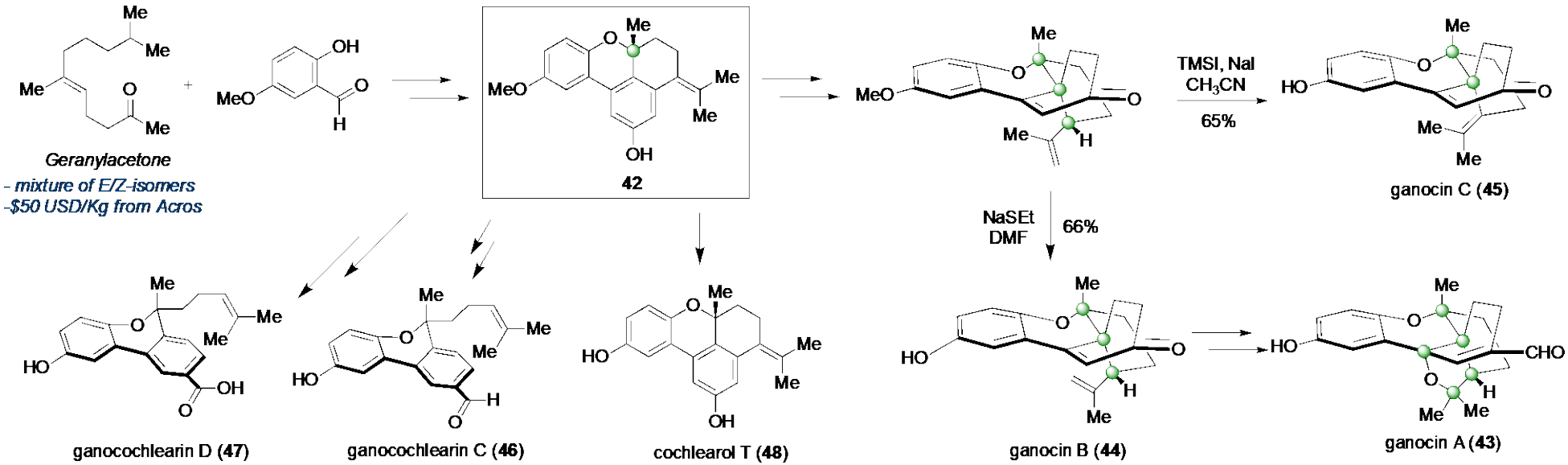


Fig. 7 The synthesis of ganoderma meroterpenoids **43**–**48**

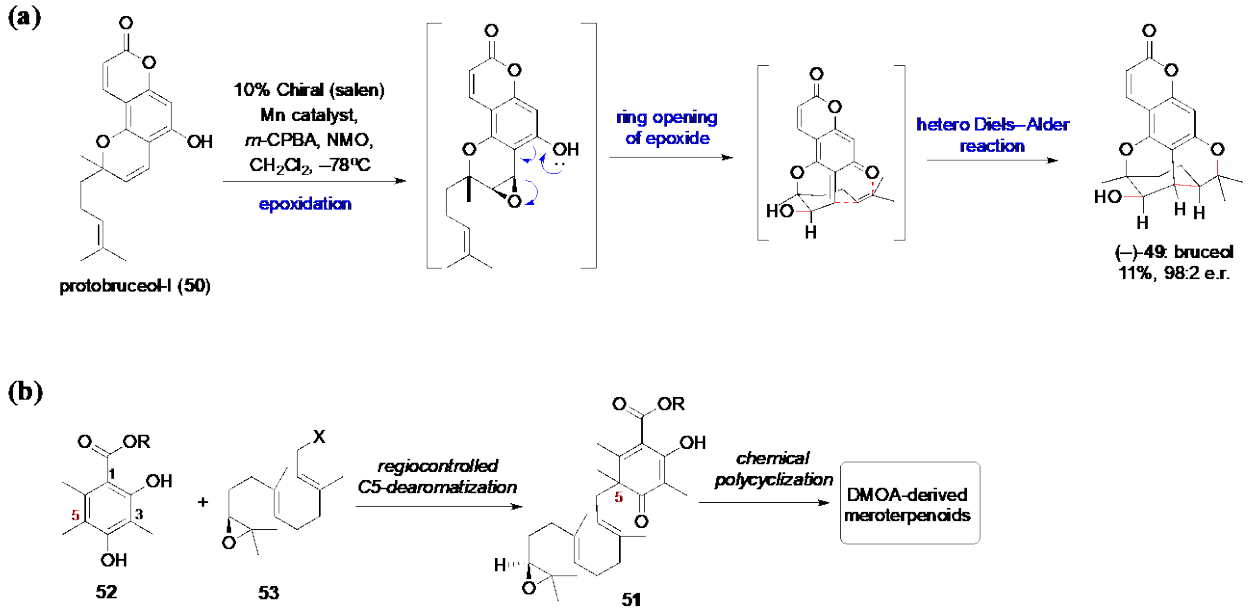
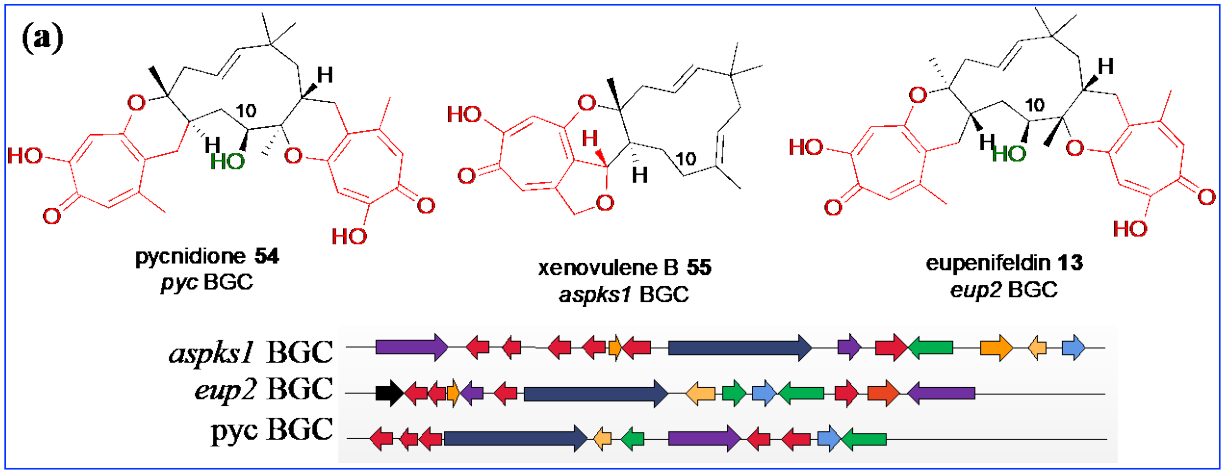


Fig. 8 The total biomimetic synthesis of bruceol **49** (**a**) and approach to access DMOA-derived meroterpenoids (**b**)



(b)

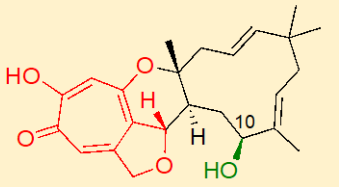
Expt		Xen. B	Xen. A	1	2	3	4	5	6	7	8	9
Gene	Func.											
aspks	PKS	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
asL1	FMN	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
asL3	NHI	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
asR2	P450	▯	▯	▯	▯	▯						
asR5	hDA	▯	▯	▯	▯	▯	▯	▯				
asR6	Hum	▯	▯	▯	▯	▯	▯	▯				
asL4	RC		▯		▯							
asL6	RC		▯		▯							
pycR1	hDA											▯
pycR6	Hum											▯
eupL4	SDR						▯	▯		▯	▯	
eupR1	hDA								▯	▯	▯	
eupR3	Hum								▯	▯	▯	
eupR5	RC					▯					▯	
eupR6	P450			▯	▯			▯			▯	
Products		-	-	*	-	-	*	*	-	-	-	*

* New compounds

Recombination of BGC

A. oryzae

(c)



New tropolone sesquiterpenoids

Fig. 9 Recombination of tropolone sesquiterpenoids BGCs for new analogous. (**a**) Three tropolones and their correlated BGCs. (**b**) Recombination of tropolone BGCs. (**c**) Heterologous expression in *A. oryzae* and generation of new tropolones.