Natural Sesquiterpenoids, Diterpenoids, Sesterterpenoids, and Triterpenoids with Intriguing Structures from 2017 to 2022

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Abstract

This review covers the isolation, structural determination, plausible biosynthetic pathways, and biological activities of 166 natural terpenoids including 57 sesquiterpenoids, 65 diterpenoids, 15 sesterterpenoids, and 29 triterpenoids from January 2017 to December 2022.

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Sesquiterpenoids | Diterpenoids | Sesterterpenoids | Triterpenoids | Structural scaffolds | Biosynthetic pathways
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Contents

1. Introduction

Terpenoids, widely distributed in plants and fungi, are a large and diverse class of secondary metabolites both in terms of their overall number and the range of structural scaffolds. Structurally, terpenoids are defined as a group of natural products (NPs) composed of the simple "C_5" units, called isoprene units. Thus, terpen-

Fig. 1. Classification of the terpenoids.

oids can be classified based on the number of isoprene units, mainly including monoterpenoids (C_{10}), sesquiterpenoids (C_{15}), diterpenoids (C_{20}), sesterterpenoids (C_{25}), and triterpenoids (C_{30}). Biosynthetically, it is demonstrated that the origins of the isoprene units are isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), generated by the MVA (mevalonate) or MEP

(methylerythritol phosphate) pathways. Both IPP and DMAPP can be converted into hemiterpenes, and under the catalyzation of enzymes, they can be condensed into geranyl diphosphate (GPP), farnesy diphosphate (FPP), Geranylgeranyl diphosphate (GGPP), and Geranylfarnesyl diphosphate (GFPP) and further derived into monoterpenes, sesquiterpenoids, diterpenoids, sesterterpenoids, and triterpenoids (Fig. 1).[1] Moreover, the rich structural variation of terpenoids led to their diverse bioactivities as well,[2-7] represented by the notable antimalarial activity of artemisinin and antitumor activity of taxol.

This review will not comprehensively exhibit all terpenoids in recent years, and it only focuses on representative natural terpenoids (C_{15}-C_{30}), with intriguing skeletons and bioactivities, from 2017 to 2022. We hope this review will provide a wide horizon for all the scholars who are interested in terpenoids.

2. Sesquiterpenoids

As one of the largest classes and the most frequently reported terpenoids, sesquiterpenoids, derived from FPP, have attracted increasing attention from organic chemists and pharmacologists due to their diverse carbon skeletons as exemplified by various ring systems and polymer architectures and extensive biological activities including neuroprotective, anti-inflammatory, and antimicrobial effects.[8-15]

Fig. 2 . Classification of the sesquiterpenoids.

To date, many types of sesquiterpenoids with different carbon skeletons have been reported, namely, germacrane, humulane, bisabolane, eudesmane, cedrane, guaiane, etc (Fig. 2).[1] Based on this classification by biosynthetic pathways, a series of intriguing new sesquiterpenoids will be introduced herein.

2.1. Cedrane

The genus *Illicium* is a rich source of sesquiterpenoids, such as seco-prezizaane, acorane, allo-cedrane, etc, and some of them have been reported to exhibit diverse biological activities including antimicrobial, antiviral, and neurotrophic effects.[16-20] Chromatography of extracts of*Illicium simonsii* and *Illicium henryi* afforded two new caged sesquiterpenoids illisimonin A (**1**) and illihenin A (**2**), respectively.[21, 22] **1** possesses a unique 5/5/5/5/5 pentacyclic scaffold featuring a caged 2-oxatricyclo[3,3,0,$1^{4,7}$]nonane ring system fused to a five-membered carbocyclic ring and a five-membered lactone ring.**2** represents a class of novel 5/7/6 tricyclic sesquiterpenoids featuring a caged tricyclo[6.2.2.$0^{1,5}$]dodecane skeleton. Furthermore, their structures have been determined by spectroscopic analyses, ECD calculations, and single-crystal X-ray diffraction. Additionally, the plausible biosynthetic of their skeletons are both via a 5/6/6 tricarbocyclic allo-cedrane framework involved in the Wagner-Meerwein (W-M) rearrangement as shown in Fig. 3.

Fig. 3. Proposed biosynthetic pathways for **1** and**2** .

2.2. Cuparene

A chemical study on the extract of the fungus *Coprinopsis cinerea*has afforded two new skeletal sesquiterpenoids, which have been named hitoyols A and B (**3** and **4**).[23] *C. cinerea* from the genus *Coprinopsis* (Hitoyotake, in Japanese) plays an important role in model basidiomycete, and *Coprinopsis* sp. are rich sources of cuparene-type sesquiterpenoids.[24-26] Structurally, hitoyol A (**3**), as an unprecedented norsesquiterpenoid, possesses an*exo* -tricyclo[5.2.1.$0^{2,6}$]decane core. The novel skeletal sesquiterpenoid hitoyol B (**4**), containing 4-cyclopentene-1,3-dione, has displayed antimalarial activity with an IC_{50} of 59 μ M. Moreover, **3** and**4** are possibly biosynthesized through decarboxylation-induced cyclization of lagopodin B, a known cuparene-type sesquiterpenoid (Fig. 4).

Trichothecrotocins A (**5**) and B (**6**) are two new trichothecene derivatives, which have been obtained from the potato endophytic fungus *Trichothecium crotocinigenum* .[27] Biosynthetically, trichothecenes have been demonstrated to be derived from an important precursor trichodiene, also originated from cuparene-skeleton similar to**3** and **4** . Moreover, one of the most critical steps of the proposed biosynthetic pathway for**5** would be the formation of a new carbon-carbon bond between C-9 and C-12 (Fig. 4).[28-30] In addition,**5** and **6** exhibit antiphytopathogenic activities with MIC values of 16-32 μ g/mL.

Fig. 4. Proposed biosynthetic pathways for**3** -**6** .

2.3. Humulane

Higher fungi (mushroom) are undoubtedly an important source of sesquiterpenoids.[13] In the past decade, many interesting secondary metabolites of higher fungi have been reported by Liu's group, such as trefolane A from culture of the mushroom *Tremella foliacea* and conosilane A from culture of the mushroom *Conocybe siliginea* .[31, 32] In this study, a novel skeletal sesquiterpenoid antroalbocin A (**7**), possessing a bridged tricyclic system, has been obtained from the higher fungus *Antrodiella albocinnamomea* , a white-rot fungus belonging to the Basidiomycota (widely distributed in northeast China).[33] **7** , an antibacterial sesquiterpenoid, was found to inhibit*Staphylococcus aureus* with an MIC value of 169μ M,[34] and its structure has been confirmed by single crystal X-ray diffraction. Furthermore, the key steps of the plausible biosynthetic pathway derived from humulane would involve a cyclization of humulene building a backbone of triquinane-type sesquiterpene and the formation of new C-C bond between C-8 and C-9 (Fig. 5).

The endophytic Fungus *Phomopsis* sp. TJ507A, isolated from the medicinal plant *Phyllanthus glaucus* , has provided a naturally occurring 2,3-*seco* -protoilludane-type sesquiterpenoid, named phomophyllin A (**8**).[35] One new cage-like cerapicane derivative, cerrenin A (**9**), and two new isohirsutane derivatives, cerrenins B and C (**10** and **11**), have been obtained from the broth extract of *Cerrena* sp. A593.[36] Three pairs of enantiomeric sesquiterpenoids, ([?])-syringanoid A (**12a** and **12b**) and (±)-pinnatanoids A (**13a** and**13b**) and B (**14a** and **14b**) have been isolated from the peeled stems of *Syringa pinnatifolia* .[37] **12** -**14**represent unprecedented 5/4/6 tricyclic backbone and a rare 6/7 bicyclic backbone, respectively, and their cardiomyocyte-protective and anti-inflammatory activities were evaluated. In addition, plausible biosynthetic pathways for **7** and **12** -**14** have been proposed (Fig. 5).

Fig. 5. Proposed biosynthetic pathways for **7** and**12** -**14** .

2.4. Germacrane

The traditional Chinese medicine *Anisodus tanguticus* , usually used for promoting blood circulation, contain four novle norsesquiterpenoids anisotanols A-D (**15** -**18**) with a congested tricyclic 6/3/5 ring system, which have been assumed to be biosynthesized by W-M 1,4-hydride shift and cyclization of germacane-type carbon skeleton (Fig. 6).[38]Another unusual germacrane derivative tomenphantadenine (**19**), with an adenine-substituted unit, has been isolated from the whole plant of *Elephantopus tomentosus* L, and **19** showed potent antibacterial activity against the gram-positive *Staphylococcusaureus* .[39]

Four rearranged sesquiterpenoids eugenunilones C-F (**20** -**23**), possibly originated from the carbon skeleton of germacrane, have been isolated from the fruits of *Eugenia uniflora* ,[40] an evergreen shrub native to South

America.[41-43] Structurally, eugenunilones C and D (**20** and **21**) possess new skeletons assembled on caged tricyclo[4.3.1.$0^{3,7}$]decane and bicyclo[3.2.1]octane scaffolds, respectively, while eugenunilones E and F (**22** and **23**) possess a rare tricyclo[4.4.0.$0^{2,10}$]decane ring system.

Fig. 6. Proposed biosynthetic pathway for**15 -18.**

2.5. Eudesmane

Spiroalanfurantones A-D (**24 -27**) have been isolated from the roots of *Inula helenium* ,[44] which has been reported to be one of the most important source of sesquiterpene lactones, such as guaianolide, eudesmanolide, germacranolide, etc.[45-49] Structurally, spiroalanfurantones A-D (**24 -27**), four eudesmanolide-furan sesquiterpene adducts, have an unprecedented pentacyclic 6/6/5/5/5 skeleton. Moreover, their structures have been confirmed by spectroscopic data analysis and single-crystal X-ray diffraction analysis. Biogenetically, [4 + 2] cycloaddition between eudesmane and furan would be a key step to construct the carbon skeleton in the proposed biogenetic pathway of**24 -27** (Fig. 7). Additional, **24 -25**showed inhibition activity of nitric oxide production in lipopolysaccharide-induced RAW264.7 macrophages with IC_{50} values of 17.3 and 9.5 μ M, respectively.

Artemilavanolides A (**28**) and B (**29**), two new rearranged eudesmane-type sesquiterpenoids with an unprecedented 6-oxabicyclo[3.2.1]octane system, have been obtained from aerial parts of *Artemisia lavandulaefolia* .[50] Atralanols A and B (**30** and **31**),[51] derived from eudesmane derivativies, possess a rare spiro [4,4] skeleton, and a plausible biosynthetic pathway for **30** and **31** has been given in Fig. 7.

Fig. 7. Proposed biosynthetic pathways for**24 -27** and **30 -31.**

2.6. Guaiane

The genus *Artemisia* is famous because of artemisinin, an amorphane sesquiterpenoid obtained from *Artemisia annua*exhibiting notable antimalarial activity.[52-55]Two novel cage-like sesquiterpenoids artatrovirenols A and B (**32** and **33**), have been found from the plant*Artemisia atrovirens* .[56] Structurally, artatrovirenols A and B (**32** and **33**) possess a 5/5/6/5/5-pentacyclic and a 5/5/6/5-tetracyclic system with an unprecedented tetracyclo[5.3.1.$1^{4,11}$.$0^{1,5}$]dodecane scaffold, respectively, as demonstrated by X-ray crystallography definitely. Additionally, a plausible biosynthetic pathway has been proposed from a guaiane derivative via the key intramolecular Diels-Alder cycloaddition (Fig. 8).

Daphnenoids A-C (**34 -36**) are three novel rearranged guaiane-type sesquiterpenoids which have been isolated from the herb of*Daphne penicillata* by molecular networking strategies.[57] Daphnenoid A (**34**) possesses a unique caged tetracyclo[5.3.2.$0^{1,6}$.$0^{4,11}$]dodecane scaffold by unexpected cyclizations of C-1/C-11 and C-2/C-14 in hypothetical biogenetic pathway (Fig. 8). Daphnenoids B and C (**35** and **36**) represent the first natural sesquiterpenoids with unique 5/5 spirocyclic system. Moreover, they showed potential inhibitory activities on the production of NO against LPS-induced BV2 microglial cells.

Fig. 8. Proposed biosynthetic pathways for**32 -36** .

2.7. Miscellaneous sesquiterpenoids

Curcumanes A (**37**) and B (**38**) are two novel bicyclic sesquiterpenoids with significant vasorelaxant activity, which have been isolated from *Curcuma longa* ,[58] a traditional Chinese medicine for promoting blood circulation.[59] Structurally, **37** and **38** possess unprecedented skeletons with a dicyclo[3.2.1]octane and a dicyclo[3.3.1]nonane moiety, respectively. Biosynthetically, the cyclization from C-1" to C-1' and C-1" to C-5 of a bisabolane derivative, respectively, are key steps in the proposed biogenetic pathways of **37** and **38**(Fig. 9), respectively.

A pair of caged norsesquiterpenoidal enantiomers (±)-preuisolactone A (±**39**), featuring an unprecedented tricyclo[4.4.$0^{1,6}$.$0^{2,8}$]decane carbon scaffold determined by X-ray crystallography, have been found from the plant endophytic fungus *preussia isomera* .[60-62] A plausible biosynthetic pathway for (+-)-**39** has been

proposed (Fig. 9). In addition, (+-)-**39** exhibited remarkable antibacterial activity against *Micrococcus luteus* with an MIC value of 10.2 μ M.

Fig. 9. Proposed biosynthetic pathways for**37** -**39** .

2.8. Sesquiterpenoid polymers

A novel dimeric guaianolide xylopiana A (**40**), possessing an unprecedented pentacyclo[5.2.1.$0^{1,2}$.$0^{4,5'}$.$0^{5,4'}$]decane-3,2'-dione core, has been found from the leaves of *Xylopia vielana* , which is one of the main sources of guaiane-type sesquiterpenoid dimers.[63] Furthermore, the case-shaped skeleton of xylopiana A (**40**) is possibly biosynthesized through Diels-Alder cycloaddition of two monomeric guaiane intermediates and then underwent an intramolecular [2 + 2] cycloaddition of a guaianoid dimer (Fig. 10). Some other dimeric guaianolides, hedyorienoid A (**41**), vlasoulamine A (**42**), heliaquanoids A-E (**43** -**47**), and artematrovirenolides A-D (**48** -**51**), have been isolated from four plants including*Hedyosmum orientale* , *Vladimiria souliei* , *Inula helianthus-aquatica* , and *Artemisia atrovirens* , respectively.[64-67] Structurally, **41**possesses an unprecedented heterodimeric structure with two different classes of sesquiterpenoids furnished by forming an unusual 1,3-dioxolane ring. **42** , an unprecedented sesquiterpene lactone dimer featuring a fully hydrogenated pyrrolo[2,1,5-cd]indolizine core, has exhibited neuroprotective activity. **43** represents the first *exo* -2,4-linked Diels-Alder adduct between a pseudoguaianolide dienophile and a guaianolide diene.**48** -**51** are four novel hetero-dimeric [4 + 2] Diels–Alder adducts dimerized from a rotundane-type unit and a guaiane-type monomer.

Fig. 10. Proposed biosynthetic pathway for **40** .

A novel lindenane sesquiterpene dimer spirolindemer A (**52**) and a trimer spirolindemer B (**53**),[68]equipped with oxaspiro[4.5]decane unit, have been discovered from the medicinal plant *Chloranthus henryi* . **52** showed anti-inflammatory activity by inhibiting the expression of iNOS and COX-2. Chromatography of extracts of plant *Chloranthus fortunei*and *Chloranthus holostegius* afforded the two novel skeletal lindenane sesquiterpene dimers fortunoid A (**54**) and chlotrichene A (**55**), respectively.[69, 70] **54** , the rearranged lindenane dimer, showed moderate antimalarial activities, and **55** , featuring a unique 3/5/6/6/6/6/5/3-fused octacyclic skeleton, possesses a new type of spirocarboncyclic dimeric framework formed by *endo* -Diels-Alder reaction. In addition, a possible biosynthetic pathway for **54**would involve in an intermolecular Diels-Alder cycloaddition by an unidentified [4 + 2] cyclase and oxidative cleavage of the Δ^4 double bond.

A novel cadinane sesquiterpene dimer commiphoratone A (**56**),[71] containing a saddle shape skeleton with a unique 6/6/5/5/6/6 heptacyclic architecture, has been isolated from the plant *Resina Commiphora* , a Chinese medicine for the treatment of blood stagnation. **56** showed significant retardation of lipid metabolism in a concentration-dependent manner. Another compound arteannoide A (**57**),[72]an unusual cadinane dimer featuring a rare fused 6,8-dioxabicyclo[3.2.l]octan-7-one ring system, has also been isolated from the traditional Chinese medicine plant *Artemisia annua* L. Moreover, a plausible biosynthetic pathway for **57** , involving in aldol and Michael addition reactions, has been proposed in Fig. 11.

Fig. 11. Proposed biosynthetic pathway for **57** .

3. Diterpenoids

Diterpenoids (C_{20}), consisted of four basic isoprene units, are an important group of natural terpenoids with structural diversity, ranking only second to sesquiterpenoids. Biosynthetically, diterpenoids arise from GGPP, which is formed by addition of an IPP to FPP under the catalysis of diterpene synthase. Structurally, they have mainly cyclic carbon skeleton especially tri- and tetracyclic ring systems.[73]The main carbon skeletons and their transformation between each other have been shown in Fig. 12. Importantly, compounds of this family show diverse biological activities, including anti-tumor, anti-renal fibrosis, antimicrobial, and neurotrophic effects.[74-77]In the following pages, diterpenoids (abietane, kaurene, cembrane, etc.) with diverse skeletal types will be introduce

Fig. 12. Classification of the diterpenoids.

3.1. Abietane

The abietane diterpenoids are the main components of conifers oleoresins, which play crucial roles in plant to resist pests and pathogens. Abietane diterpenoids isolated in recent years can be divided into five subclasses, namely, classical abietanes, rearranged abietanes,[78] aromatic abietanes,[79] abietane lactones,[80] and abietane dimers.

In previous studies, more than 90 diterpenoids belonging to abietane have been reported from the genus *Isodon* .[81] During ongoing investigation on *Isodon rugosiformis* , rugosiformisin A, a skeleton-rearranged abietane-type diterpenoid with potent NO inhibitory activity, has been obtained (**58**).[82] The stereochemistry of **58** has been determined using single-crystal X-ray diffraction analysis.

Officinalins A (**59**) and B (**60**),[83] which are a pair of unique C_{23} terpenoid epimers possessing an unprecedented tetracyclic 6/7/5/5 carbon skeleton with a tetracycline[9.6.0.$0^{3,8}$.$0^{12,16}$]heptadecane core, have been isolated from the leaves of *Salvia officinalis* . Another rearranged abietane diterpenoid, salviyunnanone A (**61**),[84] has been isolated from *Salvia yunnanensis* . **61** possesses an unprecedented 7/5/6/3 fused ring system comprising an unusual 9,11-epoxy moiety. Recently, a series of highly oxidized abietane diterpenoids with potent inhibitory activity against cancer cells were identified from *Euphorbia fischeriana* .[85]

A unique abietane diterpenoid dimer, fischdiabietane A (**62**),[86] possessing 2-oxaspiro[4.5]decane-1-one and 2-oxabicyclo[3.2.2]nonane framework, has been isolated from *Euphorbia fischeriana* . The absolute configuration of **62** has been determined by single-crystal X-ray diffraction analysis. **62** has induced apoptosis in T47D cells through the activation of caspase-3 and the degradation of poly (ADP-ribose) polymerase.

3.2. Ent-kaurane

The simplest *ent* -kaurane diterpenoid, *ent* -kaurane (**63**),[87] was identified from the genus *Agathis* in 1961. The plant is locally called *kauri pine* , therefore the diterpenoid with negative optical rotation was called *ent* -kaurane. Up to now, more than 1000 *ent* -kaurane diterpenoids have been isolated,[88] and most of them are derived from the genus *Isodon* .[89]

Maoeriocalysin A (**64**),[90] a novel rearranged *ent* -kaurane diterpenoid with an unprecedented 4,5-*seco* -3,5-cyclo-7,20-epoxy-*ent* -kaurane skeleton, have been isolated from *Isodon eriocalyx* . Another highly rearranged and dual-bridged spiro *ent* -kaurane diterpenoid crokonoid A (**65**) has been isolated from *Croton kongensis* .[91] **65** has displayed strong cytotoxicity against HL-60 and A-549 cell lines. Pierisketolide A (**66**) and pierisketones B and C (**67** and **68**), three diterpenoids with an unusual A-*homo* -B-*nor* -*ent* -kaurane carbon skeleton, have been obtained from the roots of *Pieris formosa* .[92] **66** exhibited an analgesic effect with a 45% writhe inhibition rate at a dose of 10.0 mg/kg.

Grayannotoxane diterpenoids with a 5/7/6/5 ring system are derived from the *ent* -kaurane, and their tetracyclic skeleton is formed by the rearrangement of the kaurane A/B ring system to a 5,7-ring system.[93, 94]

In recent years, Yao's group has reported a serious of grayanane diterpenoids from the traditional Chinese medicine *Rhododendron mole* . Rhodomollacetals A-C (**69** -**71**),[95] three novel diterpenoids with an unprecedented 2,3:5,6-di-*seco* -grayanane carbon skeleton, have been isolated in 2017. The absolute configurations of **69** and **70** have been assigned by single-crystal X-ray crystallography, and **69** -**71** show moderate PTP1B inhibitory activities. Rhodomollanol A (**72**) also has been reported in 2017,[96] which possesses a unique 3/5/7/5/5/5 hexacyclic ring system featuring a rare 7-oxabicyclo[4.2.1]nonane core decorated with three cyclopentane units, and **72** exhibited moderate PTP1B inhibitory activity. Furthermore, two highly modified grayanane diterpenoids, mollebenzylanols A (**73**) and B (**74**),[97] have been identified, and the key steps of plausible biosynthetic pathway would involve in an enzymatic W-M rearrangement and two retro-aldol reactions as shown in Fig. 13. Three highly functionalized 5,6-*seco* -grayanane diterpenoids mollactones A–C (**75** –**77**) have been reported in 2020,[98] and these compounds exhibited significant PTP1B inhibitory activity. In 2021, epoxymicranthol G (**78**)[99] has been obtained from *Rhododendron micranthum* , which is a 5,9-epoxygrayanane diterpenoid expressed potent analgesic activity. The structure-activity relationship for the analgesic effects of 5,9-epoxygrayanane diterpenoids has been discussed, and the 3β -OH, 10α -OH, 14α

-OH, and 16α -OH may be the activating groups to the analgesic activity of 5,9-epoxygrayanane diterpenoids. Bismollether A (**79**), a dimeric grayanane diterpenoid with a caged structrue has been isolated in 2022,[100] and it exhibits significant analgesic activities. An unprecedented 5/6/6/5 tetracyclic grayanane-derived diterpenoid rhomollone A (**80**) has been obtained from flowers of*Rhododendron molle.* [101]

Fig. 13. Proposed biosynthetic pathway for**73** -**74** .

3.3. Cembrane

Cembranolides, with a 14-membered macrocyclic skeleton, are the precursors of casbane, tigliane, and related diterpenoids.[102] (±)-Mangelonoids A and B (**81** –**84**),[103] two pairs of enantiomers featuring an unprecedented bicyclo[9.3.1]pentadecane core and a bridgehead double bond, have been isolated from *Croton mangelong* . **81** exhibited NF-κ B inhibition with an IC_{50} value of 7.27 ± 1.30 μ M. A novel cembranoid, sarcomililate A (**85**),[104] possessing a previously undescribed tricyclo[11.3.0.$0^{2,16}$]hexadecane scaffold, has been isolated from *Sarcophyton mililatensis* . Populusene A (**86**) is a cembrane-type diterpenoid possessing an unprecedented carbon skeleton,[105]western blotting analysis has confirmed that **86** significantly inhibits LPS-induced activation of NF-$\varkappa$B in RAW264.7 cells. Sinudenoid A (**87**),[106] a new furanobutenolide-derived C_{19}-norcembranoid diterpene, has been isolated from the soft coral *Sinularia densa* . Recently, several casbane-type diterpenoids have been reported,[107-112] and sinunanolobatone A (**88**) from *Sinularia nanolobata* ,[107] featuring an unprecedented casbane related carbon framework, showed significant inhibitory activity against lipopolysaccharide (LPS) induced inflammation.

3.4. Pimarane

Pimarane, a type of tricyclic diterpenoids, generally obtained from plants and fungi but seldom from other biological resources.[113, 114] Pimarane could be further classified into pimarane, isopimrane, *ent* -pimarane, and*ent* -isopimrane based on differed stereochemistry. Seven new diterpenoids (**89** –**95**) have been isolated from the tuber of *Icacina oliviformis* .[115]Oliviformislactones A (**89**) and B **(90**) are the first examples of rearranged 3,4-*seco* -pimarane possessing a 6/6/5/5 tetracyclic ring system; secopimaranlactone A (**91**) and secocleistanthone A (**92**) are the first examples of 3,4-*seco* -pimarane and 3,4-*seco* -cleistanthane type diterpenoids, respectively, which have been obtained from the Icacinaceae family. Chromatographic purification of *Premna fulva*extracts led to one undescribed isopimarane-type diterpenoid, named premnafulvol A (**93**),[116] and the plausible biotransformation pathway of **93** has been proposed (Fig. 14). Glabresides A-C (**94** -**96**),[117] three undescribed*ent* -pimarane diterpenoid dimers, have been isolated from*Sigesbeckia glabrescens* . **96** exhibited the most potent inhibition activity on nitric oxide (NO) production induced by LPS in BV2 microglia compared with the other two compounds. **96** also increased the protein expression level of heme oxygenase-1 (HO-1), and suppressed inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) in LPS-stimulated BV2 cells.

Fig. 14. Proposed biosynthetic pathway for **93** .

3.5. Fusicoccane

In recent years, Zhang's group has reported a serious of fusicoccane diterpenoids with unexpected carbon skeleton from the genus*Alternaria* and *Talaromyces* . Alterbrassicene A (**97**),[118] a fusicoccane diterpenoid bearing an unprecedented 5/9/4-fused carbocyclic skeleton, has been characterized from *Alternaria brassicicola* . **97** is the first fusicoccane derivative acting as a potent IKKβ inhibitor in the NF-κ B signaling pathway. Alterbrassicicene A (**98**),[119] a fusicoccane diterpenoid with a degradatived framework, has been also obtained from *A. brassicicola* . **98** reprents the first fusicoccane-derived diterpenoid functioning as a potent PPAR-γ agonist (EC_{50} = 744.1 nM). A plausible biosynthetic pathway for**98** has been proposed and involved in a series of cyclizations and rearrangement by the function of enzymes (Fig. 15). Alterbrassinoids A-D (**99** -**102**),[120] the first examples of fusicoccane dimers furnished by forming an undescribed C-12-C-18' bond, have been isolated from the same fungus. Talaronoids A–D (**103** -**106**), four diterpenoids with an unexpected tricyclic 5/8/6 carbon skeleton, have been isolated from*Talaromyces stipitatus* . Talaromynoid A (**107**),[121] the first fusicoccane diterpenoid bearing an unexpected 5/7/5 tricyclic ring system, have been

obtained from the endophytic fungus *Talaromyces* sp. DC-26.

Fig. 15. Proposed biosynthetic pathway for **98** .

3.6. Jatrophane

Jatrophane diterpenoids possess a bicyclo[10.3.0]pentadecane skeleton, and occur exclusively in the *Euphorbiaceae*family.[3, 122] Heliojatrones A and B (**108** and **109**), two jatrophane-derived diterpenoids with an unprecedented *trans* -bicyclo[8.3.0]tridecane core, have been isolated from the whole plants of *Euphorbia helioscopia* . **109** showed significant Pglycoprotein inhibitory activity. Euphopias A-C (**110** -**112**), three rearranged jatrophane-type diterpenoids with unexpected carbon skeleton, have been isolated from *Euphorbia helioscopia* . **111** could ameliorate mitochondria damage, thereby interrupting NLRP3 inflammasome activation. Euphohelioscoids A (**113**) and B (**114**), diterpenoids with rearranged 9(10-11)-*abeo* -10,12-cyclojatrophane skeleton and the first (15*S*)-jatrophane have been isolated from*Euphorbia helioscopia* .[123] Yin's group has studied *Euphorbia* plants a lot, and they have identified a serious of highly modified jatrophane diterpenoids, such as euphorhelipanes A (**115**) and B (**116**) from the whole plants of *Euphorbia helioscopia* ,[124]jatrofolianes A (**117**) and B (**118**) from *Jatropha gossypiifolia* ,[125] euphohyrisnoids A (**119**) and B (**120**) from the seeds of *Euphorbia lathyris* ,[7] and euphylonoids A (**121**) and B (**122**) from *Euphorbia hylonoma* .[126] **115** and **116**showed a triglyceride-lowering effect in oleic-acid-stimulated HuH7 cells, and **122** significantly inhibited early adipogenesis in 3T3-L1 adipocytes via activating AMP-activated protein kinase signaling.

4. Sesterterpenoids

Sesterterpenoids are a small group of terpenoids containing 25 carbons, which are derived from the linear precursor GFPP. Sesterterpenoids have been isolated from many kinds of organisms such as plants, fungi, and marine sponge, with a great diversity of structures and skeletons and broad biological functions. A review has introduced the structures and bioactivities of marine sesterterpenoids since 2013 until 2017;[127] another review has summarized the distribution, chemistry, biological activities, biosynthesis and evolution of plant sesterterpenoids since 1969 until 2021.[128] In this contribution, some typical sesterterpenoids with unprecedented carbon skeletons will be introduced, including their chemical structures and biological activities.

Pre-leucosceptroid (**123**) and isopre-leucosceptroid (**124**) are intriguing monocarbocyclic sesterterpenoids.**123** has been identified from the leaves of *Leucosceptrum canum* , while its isomer **124** has been isolated from the excrement of *Nacna malachitis* larvae, a specialist insect feeding on *L. canum* . Extensive spectroscopic analysis and quantum chemical calculations have confirmed their absolute configurations.[129]

A pair of enantiomeric bicyclic sesterterpenoids, (±)-hippolide J (**125** and **126**), have been isolated from the marine sponge *Hippospongia lachne* collected from the South China Sea.[130] Both of them showed potent antifungal activity against three strains of hospital-acquired pathogenic fungi,*Candida albicans* SC5314, *Candida glabrata* 537, and*Trichophyton rubrum* Cmccftla, with MIC_{50} values of 0.125-0.25 μ g/mL.[130]

Two unique tricyclic sesterterpenoids linderasesterterpenoids A (**127**) and B (**128**), with an unprecedented 7-cyclohexyldecahy-droazulene carbon skeleton, have been separated from the root of *Lindera glauca* .[131]**127** and **128** showed good inhibitory activities against LPS-induced NO production in RAW 264.7 cells with IC_{50}values of 18.9 and 16.2 μ M, respectively, as compared to the positive control (indomethacin, IC_{50} = 30.9μ M).[131] Gentianelloids A (**129**) and B (**130**), a pair of sesterterpenoid epimers, possessing an unusual 10,11-*seco* -gentianellane skeleton, have been obtained from the traditional Uighur medicine *Gentianella turkestanorum* . Their structures including absolute configurations have been determined by extensive spectroscopic and single-crystal X-ray diffraction analyses. Moreover, the plausible biosynthetic origins of their skeletons are both via the tetracyclic precursor nitidasin, which must be derived from GFPP via cyclization and oxidation reactions (Fig. 16).[132]

Eurysoloids A (**131**) and B (**132**), two novel diastereomeric sesterterpenoids possessing a pentacyclic 5/6/5/10/5 framework with an unusual macrocyclic ether system, have been reported from *Eurysolen gra-*

cilis Prain, and their absolute configurations have been assigned by single-crystal X-ray diffraction and DP4$^+$analyses.[133]Peniroquesines A-C (**133** -**135**), possessing an 5/6/5/6/5 fused pentacyclic ring system, identified based on NMR spectroscopy, MS, Mosher's method, and single-crystal X-ray crystallography, have been isolated from the fungus *Penicillium roqueforti*YJ-14.[134] Additionally, compounds **133**and **134** showed a potent inhibitory effect on nitric oxide production in LPS-activated RAW264.7 macrophages with IC_{50} values of 16.13 ± 1.61 and 11.74 ± 0.26 μ M, respectively, making them more potent than the positive control (L-NMMA, IC_{50} = 42.24 ± 0.68 μ M). Biosynthetically, a plausible cyclization mechanism to yield the scaffold of**133** -**135** via a series of W-M rearrangement and alkyl shift has been proposed (Fig. 16).[134]

Fig. 16. Proposed biosynthetic pathways for**129** -**130** and **133** -**137** .

Niduterpenoids A (**136**) and B (**137**), isolated from*Aspergillus nidulans* , represent the first examples of sesterterpenoids with a highly congested hexacyclic 5/5/5/5/3/5 carbon skeleton. Their structures have been determined via a combination of spectroscopic data and single-crystal X-ray diffraction analyses.[135] Compounds **136** and**137** are estrogen receptorα inhibitors, and **136** abolished 17-estradiol induced human breast tumor cell proliferation in a dose-dependent manner (IC_{50} = 11.42 ± 0.85 μ M). Furthermore, a plausible biosynthetic pathway for **136** and **137** has been proposed and involved in a series of cyclization and W-M hydride and alkyl shift reactions (Fig. 16).[135]

5. Triterpenoids

Triterpenes are a class of terpenoids with 30 carbons in the basic parent nucleus. They exist in plants in free form or as glycosides, and have various biochemical activities. Among them, three systematic reviews have covered the published data on triterpenoids isolated from all organisms from 2013 to 2015.[136-138] In recent years, many triterpenoids have been reported with unusual tetracyclic,[139-144]pentacyclic,[140, 145-149] and a few tricyclic ring systems.[150-153] Among them, a series of dimers bearing different scaffold have been designed and synthesized, and their anti-HCV entry activities have also been evaluated.[154]

Belamchinenin A (**138**), an unprecedented 6/5/6 fused tricyclic triterpenoid with a novel carbon skeleton, has been isolated from the rhizomes of *Belamcanda chinensis* .[151] The absolute configuration of tricyclic nucleus system has been unequivocally assigned by ECD calculation. In addition, **138**exhibits cytotoxicity against NCI-H1650, HepG2, BGC 823, HCT-116, and MCF-7 cells with IC_{50} values of 2.48, 2.55, 4.47, 2.29, and 2.85 μ M, respectively.[151]Nototronesides A-C (**139** -**141**), three triterpenoid saponins with a 6/6/9 fused tricyclic tetranordammarane carbon skeleton, have been isolated from the leaves of *Panax notoginseng* .[152]Moreover, **140** showed a moderate neuroprotective effect on serum deficiency-induced cellular damage.[152]

Fig. 17. Proposed biosynthetic pathway for **142** .

Ganolearic acid A (**142**), a hexanorlanostane triterpenoid with a 3/5/6/5 fused tetracyclic skeleton from *Ganoderma cochlear* , has been found using a LC-UV/MS screening approach.[155] The stereochemical structure has been established by spectroscopic data, ^{13}C NMR and ECD calculations, and then a plausible biosynthetic pathway for**142** has been given (Fig. 17).[155]Alismanin A (**143**), a novel protostane-type triterpenoid with a C_{34} skeleton, has been isolated from the rhizomes of*Alisma orientale* .[156] Its structure has been determined by a combination of HRESIMS, 2D NMR spectra, ECD calculation. **143** displayed significant agonistic effects on pregnane X receptor at a concentration of 10 nM.[156] Colqueleganoids A (**144**) and B (**145**), with the first methyl-30 incorporated 6/6/6/6 tetracyclic carbon skeleton, have been isolated from the root of *Colquhounia elegans* .[157]Interestingly, **144** and **145** showed significant immunostimulatory effects and enhanced the production of cytokines TNF-α and IL-6 in the RAW 264.7 cells stimulated with LPS.[157]

Applanoids A-E (**146** -**150**) represent the first example of*Ganoderma* triterpenoids with 6/6/5/6/5 pentacyclic system and the formation of the ether ring between C-15 and C-20 involves Michael addition reaction.[158] Among of them,**146** , **147** , and **148** could significantly activate human pregnane X receptor (hPXR), and molecular docking revealed that they were docked well into the ligand binding domain by

the establishment of hydrogen bonds and van der Waals effects.[158] Irpexolidal (**151**), a triterpenoid with an unprecedented 6/5/6/5/6/5 fused polycyclic skeletal system carbon skeleton, has been isolated from the fruiting bodies of the medicinal fungus *Irpex lacteus* .[159] The structure of **151** has been established by ECD calculation, and DP4$^+$probability based on GIAO NMR chemical shift calculations.[159]

Belamchinanes A-D (**152 -155**), four triterpenoids with an unprecedented 4/6/6/6/5 pentacyclic system, have been isolated from the seeds of *Belamcanda chinensis* .[160] Biological studies reveal that they have dose-dependently protect age-related renal fibrosis in*vitro* . In addition, a key step of plausible biosynthetic pathway would involve in Michael addition reaction of the 3,4-*seco*fernane (Fig. 18).[160] Alstoscholarinoids A (**156**) and B (**157**), representing new subtypes of pentacyclic triterpenoids, with unique 6/6/6/7/5 and 6/6/5/6/6/6 ring systems have been isolated from *Alstonia scholaris* .[161] Their absolute structures have been established by single-crystal X-ray diffraction, and ECD calculations. Surprisingly, both compounds exhibited potent antihyperuricemic bioactivity in *vitro* and in*vivo* .[161]

Fig. 18. Proposed biosynthetic pathway for**152 -155**

Schincalactones A (**158**) and B (**159**), featuring a unique 5/5/6/11/3 fused schinortriterpenoids with a 13-membered carbon ring system, have been obtained from *Schisandra incarnata* .[162] The absolute configuration of**158** has been confirmed by single-crystal X-ray diffraction, and then a plausible biosynthetic pathway for **158** and **159**via 8,9-oxidative cleavage has been given (Fig. 19). Moreover, schilancidilactone C (**160**), representing the first 3-norlancischiartane with unusual configurational inversions occurring at C-1 and C-10 compared to the reported schindilactones A-C, has been isolated from *Schisandra lancifolia* .[163, 164]

Dichagelinoids A-E (**161 -165**) have been isolated and characterized by solid data from *Dichapetalum gelonioides* .[165] Particularly,**161 -163** showed significant cytotoxic activities against A549 and HL-60 cells with IC_{50} values ranging from 1.00 to 1.35 μ M and 0.38 to 4.23μ M, respectively.[165]

Phainanolide A (**166**), a highly modified triterpenoid incorporating an unprecedented 6/9/6 heterotricyclic system in the down-left and a highly oxygenated 5,5-spirocyclic ketal lactone motif in the up-right, has been isolated from *Phyllanthus hainanensis* .[166] Particularly, **166**exhibited potent activity against HL-60 cell lines with IC_{50} values of 0.079 $\pm$ 0.037 μ M, compared to that of the positive control (Adriamycin, IC_{50} = 0.073 $\pm$ 0.015 μ M).[166]

Fig. 19. Proposed biosynthetic pathway for **158** and

159

6. Challenge and prospect

Natural products (NPs) have been increasingly attracting attention from various fields due to their structural diversity and biological activities.[13] The skeletal types of NPs are closely related to their biological evolution. As the evolution progresses, organisms must continuously change their biosynthetic pathways to adapt the change in the various environment or resist external threats, which result in changes in the skeletal types of NPs. This relationship between NPs structure and evolution makes NPs an important area in the fields of chemistry and biology.[167]

The discovery of new carbon skeletons in NPs is often accompanied by the discovery of new biological activities. For example, the famous sesquiterpenoid artemisinin and diterpenoid taxol show notable antimalarial and antitumor activities respectively, which highlights the significance of the discovery of novel skeletal NPs and their potential impact on the development of new drugs.

However, the quantity of novel skeletal NPs is generally limited, makeing it difficult to evaluate the biological activities of novel skeleton compounds,[168] which might limit the potential of NPs or hinder the development of new drugs based on these compounds. Therefore, these challenges may inspire strong interests among organic chemists, biologists, and pharmacologists. As terpenoids are one of the largest classes of NPs, this review focuses on 166 natural terpenoids with intriging structures from 2017-2022, including the isolation,

structural determination, plausible biosynthetic pathways, and biological activities. Hopefully, this review would provide a new perspective for the scholars who are interested in NPs.

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