Naturally Occurring Diterpenoid Dimers: Source, Biosynthesis, Chemistry and Bioactivities

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Key words
- diterpenoid dimers
- structure
- source
- biosynthesis
- synthesis
- bioactivities

Abstract

Diterpenoid dimers are rare in nature and mainly found in higher plants including the families Acanthaceae, Annonaceae, Asteraceae, Calceolariaceae, Chrysobalanaceae, Cupressaceae, Euphorbiaceae, Fabaceae, Lamiaceae, Liliaceae, Meliaceae, Rhizophoraceae, Taxaceae, Velloziaceae, and Zingiberaceae. In addition, a few diterpenoid dimers have been also reported from fungi (Psathyrellaceae), liverworts (Scapaniaceae), and a gorgonian (Gorgoniidae). They feature a wide variety of structures due to different core skeletons, linkage patterns, substituents, and configurations. Accordingly, diterpenoid dimers exhibit a broad range of bioactivities, including cytotoxic, anti-inflammatory, antimicrobial, antimalarial, and antifouling properties, which have attracted more and more research interests in the past decades. This review with 176 metabolites from 109 references provides a comprehensive and up-to-date overview of the source, biosynthesis, structure, synthesis, and bioactivities of diterpenoid dimers.

Abbreviations

DGAT:	diacylglycerol *O*-acyltransferase
ECD:	electronic circular dichroism
LPS:	lipopolysaccharide
NO:	nitric oxide
TRAIL:	tumor necrosis factor-related apoptosis-inducing ligand

Introduction

Diterpenoids are a structurally diverse class of natural products, consisting of four isoprene units to form a 20-carbon backbone. Based on their core structures, diterpenoids can be classified into linear, macrocyclic, bicyclic, tricyclic, tetracyclic and pentacyclic types [1]. Naturally occurring diterpenoids are always found in a polyoxygenated form: i) with hydroxyl groups, which are often esterified by aliphatic or aromatic acids, or etherified by alcohols; ii) with formyl and carbonyl groups, which have often reacted with hydroxyl groups to form hemiacetal or acetal moieties; or iii) with carboxyl groups, which often form esters or lactones through reaction with alcohols. Moreover some diterpenoids have been found with opened and rearranged ring structures. Diterpenoids exhibit various biological activities such as cytotoxic, anti-microbial, and anti-inflammatory properties, and have been identified as active principles in some traditional medicines [2, 3]. Due to their structural diversity and broad bioactivities, diterpenoids have attracted increasing research attentions, resulting in the identification of a growing number of compounds. Some of these compounds have been proven to be clinically effective. Taxol, for example, is an unusual diterpenoid discovered from Taxus brevifolia (Taxaceae), which inhibits the normal breakdown of microtubules during cell division, and is widely used in therapy against ovarian, breast, and lung cancer [4]. Salvinorin A, a diterpenoid isolated from Salvia divinorum, has psychoactive effects on humans, and has been used as an analgesic [5, 6].

Diterpenoid dimers are a rather uncommon subclass of diterpenoids, which are composed of two 20-carbon diterpenoid units linked through one or two C–C bond, ester bond, ether bond or a ring moiety. On the basis of a literature search in various databases, including Google Scholar, SciFinder, Web of Science, and Scopus, using "diterpenoid dimer" or "tetraterpenoid" as key words, 176 naturally occurring diterpenoid dimers were retrieved, with various bioactivities including cyto-

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toxic, anti-inflammatory, antimicrobial, antimalarial, and antifouling activities (**Table 1**). Due to their structural complexity and the wide range of bioactivities, naturally occurring diterpenoid dimers have attracted more and more research interests in the past decades. Furthermore, the development of purification and structural elucidation methods, especially preparative HPLC and high resolution NMR, makes it now possible to identify compounds at trace amounts. Chiral HPLC dramatically accelerated the isolation of stereoisomers, especially those with complex structures like diterpenoid dimers [7–9]. In recent years, ECD calculations have been widely used to determine the absolute configurations of diterpenoid dimers [7,9–11]. According to our literature review, around 31 publications related to diterpenoid dimers were found before 2000, and this number has increased to 88 in January 2016. However, up to now, no systematical review was carried out on this particular group of diterpenoids. The present review describes the biosynthesis, occurrence and structures of diterpenoid dimers identified up to date, summarizes their bioactivities, gives examples of total synthesis, and explores some research perspectives on diterpenoid dimers.

Biosynthesis

The biosynthesis of diterpenoids has been widely investigated and involves different modes of cyclization of geranylgeranyl diphosphate (GGPP) [12]. To date, four different classes of synthases have been cloned with their functional proteins sequenced, including casbene synthase, *ent*-copalyl diphosphate synthase, taxadiene synthase, and abietadiene synthase. In contrast, the biosynthesis of diterpenoid dimers, especially the identification and characterization of the key dimerization processes, has been seldom studied. There are different ways in which diterpenoid dimers can be linked, including a rotatable or atropisomeric C–C bond, an ether C–O–C linkage, an ester bond, or a ring formed through homo- or hetero-Diels-Alder reaction. The incorporation of a malonic acid unit to form a diester linkage is observed in the diterpenoid dimers from the families Calceolariaceae and Asteraceae. Most of diterpenoid dimers arise as a result of a Diels-Alder condensation of two monomeric moieties. Yue and colleagues [7] proposed that aphadilactones A–D were formed from two molecules of nemoralisin-type diterpenoid through enzyme-catalyzed Diels-Alder reaction. Later, the total synthesis of these compounds using Diels-Alder cyclization further supported this hypothesis [13]. Until now some progresses have been achieved in the identification of natural Diels–Alderase [14]. Ichihara and colleagues [15,16] isolated and purified an enzyme from *Alternaria solani* that catalyzes the [4 + 2] cycloaddition of prosolanapyrone III to the *exo* adduct solanapyrone A and *endo* adduct solanapyrone D. This enzyme was the first Diels-Alderase reported. In 2000, a study carried out by Vederas's group [17] identified a lovastatin nonaketide synthase, which catalyzes intramolecular Diels-Alder *endo* closure of (*E,E,E*)-(*R*)-6-methyl-dodecatri-2,8,10-enoic acid *N*-acetylcysteamine thioester to a bicyclic system. In a later study, Tanaka's group [18] reported for the first time the 1.70 Å resolution crystal structure of a natural Diels-Alderase, fungal macrophomate synthase, in complex with pyruvate. The authors also determined the active site of the enzyme as large and hydrophobic, with amino acid residues that can form hydrogen-bonds to the substrate 2-pyrone. Additionally, several artificial Diels-Alderases have been generated to catalyze different reactions [19–21]. However, to the best of our knowledge, no Diels-Alderase catalyzing the formation of diterpenoid dimers has been characterized.

Another common dimerization way in the diterpenoid dimers is through a C–C linkage. Some studies [22,23] propose that this kind of linage is formed through Michael addition or aldol condensation. The formation of an ether bond and a dioxane ring is believed to occur through hemiacetal and acetal reactions. Despite many plausible biosynthetic pathways have been proposed, the nature and extent of enzymes involvement in the formation of diterpenoid dimers remain unclear. There has been no direct observation of enzymatic dimerization of the monomer units. The biosynthesis of diterpenoid dimers is worth further investigation as this promising progress has just started.

Occurrence

Diterpenoid dimers are rare in nature, and they have been discovered in eighteen families of higher plants, fungi, liverworts and a gorgonian so far. The majority of diterpenoid dimers have been reported from higher plants including the families Acanthaceae (*Andrographis*), Annonaceae (*Annona* and *Xylopia*), Asteraceae (*Baccharis*), Calceolariaceae (*Calceolaria*), Chrysobalanaceae (*Parinari*) Cupressaceae (*Calocedrus, Chamaecyparis, Cryptomeria, Cunninghamia, Juniperus*, and *Taiwania*), Euphorbiaceae (*Croton, Euphorbia*, and *Neoboutonia*), Fabaceae (*Caesalpinia, Cylicodiscus*, and *Erythrophleum*), Lamiaceae (*Ballota, Clerodendrum, Isodon, Plectranthus, Premna, Salvia*, and *Teucrium*), Liliaceae (*Fritillaria*), Meliaceae (*Aphanamixis*), Rhizophoraceae (*Ceriop*), Taxaceae (*Taxus* and *Torreya*), Velloziaceae (*Vellozia*), and Zingiberaceae (*Alpinia*). They are widely distributed throughout the plants from roots, barks, stems, bulbs, leaves, seeds to fruits (**Table 1**). Some diterpenoid dimers were found in fungi [Psathyrellaceae (*Coprinus*)], liverworts [Scapaniaceae (*Scapania*)] and a gorgonian [Gorgoniidae (*Antillogorgia*)].

Diterpenoid Dimers from Plants

Family Acanthaceae

As part of a search for cell differentiation inducers on mouse myeloid leukemia (M1), the aerial parts of *Andrographis paniculata* were chemically investigated and four labdanoid dimers, namely bisandrographolides A–D (**1**–**4**) (**Fig. 1**), were isolated [24]. All these compounds were deduced to be dimers linked via a C–C single bond between C-12 and C-15′ of andrographolide derivatives but the respective configurations at C-12 and C-15′ of these compounds remained undetermined. Bisandrographolides A–C showed potent phagocytic and growth-inhibitory activities against M1 cells, while bisandrographolide D showed no induction of phagocytosis, but exhibited growth-inhibitory effects.

Family Annonaceae

Thirteen diterpenoid dimers have been isolated from plants of the family Annonaceae but only from the genera *Xylopia* and *Annona* (**Fig. 2**).

Acutifloric acid (**5**) was isolated from the stem barks of *X. acutiflora* [25], and was identified as a dimer resulting from a Diels-Alder condensation between 15-oxo-kaur-16-en-19-oic and labda-8(17),13,15-trien-19-oic. Phytochemical studies of the green fruits of *X. amazonica* and stem barks and leaves of *X. frutescens* resulted in the identification of amazonins B and A (**6, 10**) and

Table 1 Naturally occurring diterpenoid dimers[a].

No.	Name	Molecular formula	Source	Part	Ref.
Plants					
Acanthaceae					
1	bisandrographolide A	$C_{40}H_{56}O_8$	*Andrographis paniculata*	aerial parts	[24]
2	bisandrographolide B	$C_{40}H_{56}O_8$	*Andrographis paniculata*	aerial parts	[24]
3	bisandrographolide C	$C_{40}H_{56}O_8$	*Andrographis paniculata*	aerial parts	[24]
4	bisandrographolide D	$C_{41}H_{60}O_9$	*Andrographis paniculata*	aerial parts	[24]
Annonaceae					
5	acutifloric acid	$C_{40}H_{60}O_3$	*Xylopia acutiflora*	stem barks	[25]
6	amazonin B	$C_{41}H_{60}O_5$	*Xylopia amazonica*	fruits	[26]
7	frutoic acid	$C_{40}H_{60}O_4$	*Xylopia frutescens*	stem barks	[27]
8	emarginatine D	$C_{42}H_{62}O_5$	*Xylopia emarginata*	stem barks	[26]
9	emarginatine A	$C_{42}H_{62}O_5$	*Xylopia emarginata*	branches	[28]
10	amazonin A	$C_{41}H_{60}O_5$	*Xylopia amazonica*	fruits	[26]
11	emarginatine C	$C_{42}H_{62}O_5$	*Xylopia emarginata*	stem barks	[26]
12	emarginatine B	$C_{42}H_{62}O_5$	*Xylopia emarginata*	branches	[28]
13	*ent*-methylisoozate dimer	$C_{42}H_{64}O_4$	*Xylopia aromatic*	stem barks	[29]
14	*ent*-13′-nor-13′-oxomethylisoozate dimer	$C_{41}H_{62}O_5$	*Xylopia aromatic*	stem barks	[29]
15	*ent*-13-epoximethylisoozate dimer	$C_{42}H_{64}O_5$	*Xylopia aromatic*	stem barks	[29]
16	annonebinide A	$C_{40}H_{64}O_3$	*Annona glabra*	stem barks	[30]
17	annoglabayin	$C_{38}H_{62}$	*Annona glabra*	fruits	[31]
Asteraceae					
18	bacchalejin 1	$C_{43}H_{60}O_6$	*Baccharis lejia*	aerial parts	[32]
19	bacchalejin 2	$C_{43}H_{60}O_7$	*Baccharis lejia*	aerial parts	[32]
20	bacchalejin 3	$C_{45}H_{62}O_8$	*Baccharis lejia*	aerial parts	[32]
21	bacchalejin 4	$C_{47}H_{64}O_{10}$	*Baccharis lejia*	aerial parts	[32]
Calceolariaceae					
22	foliosate	$C_{43}H_{64}O_4$	*Calceolaria foliosa*	aerial parts	[33]
23	glandulosate	$C_{43}H_{64}O_4$	*Calceolaria glandulosa*	aerial parts	[34]
24	lepidate	$C_{43}H_{66}O_5$	*Calceolaria lepida*	aerial parts	[35]
25	polifosate	$C_{43}H_{64}O_4$	*Calceolaria polifolia*	aerial parts	[36]
26	petiolate	$C_{43}H_{64}O_4$	*Calceolaria petioalaris*	aerial parts	[37]
27	bis-[*ent*-9-epi-labda-8(17),(12Z),14-trien-19-yl] malonate	$C_{43}H_{64}O_4$	*Calceolaria densifolia*	aerial parts	[38]
Chrysobalanaceae					
28	15-oxozoapatlin-13α-yl-10′α,16′α-dihydroxy-9′α-methyl-20′-nor-kauran-19′-oic acid γ-lactone-17′-aote	$C_{40}H_{52}O_8$	*Parinari campestris*	leaves	[39]
Cupressaceae					
29	6-(abieta-6′,8′,11′,13′-tetraenyl-12′-oxy)-7-methoxyabieta-8,11,13-trien-12-ol	$C_{41}H_{58}O_3$	*Chamaecyparis obtusa*	barks	[40]
30	sugikurojin B	$C_{41}H_{58}O_3$	*Cryptomeria japonica*	heartwood	[41]
31	formosadimer A	$C_{41}H_{58}O_3$	*Calocedrus macrolepis*	barks	[42]
32	formosadimer B	$C_{46}H_{68}O_4$	*Calocedrus macrolepis*	barks	[42]
33	formosadimer C	$C_{48}H_{70}O_5$	*Calocedrus macrolepis*	barks	[42]
34	calocedimer C	$C_{40}H_{56}O_3$	*Calocedrus macrolepis*	barks	[43]
35	calocedimer D	$C_{44}H_{60}O_5$	*Calocedrus macrolepis*	barks	[43]
36	formosaninol	$C_{40}H_{56}O_4$	*Juniperus formosana*	heartwood	[44]
37	formosanin	$C_{42}H_{60}O_4$	*Juniperus formosana*	heartwood	[44]
38	sugikurojin C	$C_{40}H_{56}O_4$	*Cryptomeria japonica*	heartwood	[41]
39	obtusanol A	$C_{40}H_{56}O_4$	*Chamaecyparis obtusa*	heartwood	[45]
40	obtusanol B	$C_{40}H_{54}O_5$	*Chamaecyparis obtusa*	heartwood	[45]
41	bicunningine A	$C_{40}H_{50}O_4$	*Cunninghamia lanceolata*	barks	[46]
42	bicunningine B	$C_{40}H_{52}O_4$	*Cunninghamia lanceolata*	barks	[46]
43	taiwaniadduct B	$C_{40}H_{56}O_6$	*Taiwania crypomerioides*	leaves	[47]
44	taiwaniadduct C	$C_{40}H_{56}O_6$	*Taiwania crypomerioides*	leaves	[47]
45	taiwaniadduct D	$C_{40}H_{56}O_6$	*Taiwania crypomerioides*	leaves	[47]
46	taiwaniadduct E	$C_{40}H_{56}O_6$	*Taiwania crypomerioides*	leaves	[47]
47	taiwaniadduct F	$C_{40}H_{56}O_6$	*Taiwania crypomerioides*	leaves	[48]
48	taiwaniadduct G	$C_{40}H_{56}O_7$	*Taiwania crypomerioides*	leaves	[48]
49	taiwaniadduct H	$C_{39}H_{56}O_6$	*Taiwania crypomerioides*	leaves	[48]
50	taiwaniadduct I	$C_{39}H_{54}O_6$	*Taiwania crypomerioides*	leaves	[48]

cont.

Table 1 *Continued*

No.	Name	Molecular formula	Source	Part	Ref.
Euphorbiaceae					
51	crotoeurin A	$C_{38}H_{36}O_{10}$	*Croton euryphyllus*	twigs and leaves	[49]
52	crotonkinensin C	$C_{40}H_{62}O_8$	*Croton tonkinensis*	leaves	[50]
53	crotonkinensin D	$C_{44}H_{66}O_{10}$	*Croton tonkinensis*	leaves	[50]
54	yuexiandajisu D	$C_{38}H_{48}O_4$	*Euphorbia ebracteolata*	roots	[51]
55	langduin C	$C_{40}H_{50}O_{10}$	*Euphorbia fischeriana*	roots	[52]
56	bisyinshanic acid A	$C_{40}H_{56}O_6$	*Euphorbia yinshanica*	roots	[53]
57	bisyinshanic acid B	$C_{40}H_{58}O_5$	*Euphorbia yinshanica*	roots	[53]
58	neoboutomannin	$C_{32}H_{26}O_6$	*Neoboutonia mannii*	barks	[54]
Fabaceae					
59	cyclodione	$C_{40}H_{56}O_4$	*Cylicodiscus gabunensis*	barks	[55]
60	erythrophlesin A	$C_{41}H_{58}O_{10}$	*Erythrophleum succirubrum*	leaves	[56]
61	erythrophlesin B	$C_{43}H_{60}O_{12}$	*Erythrophleum succirubrum*	leaves	[56]
62	erythrophlesin C	$C_{43}H_{63}NO_{10}$	*Erythrophleum succirubrum*	leaves	[56]
63	erythrophlesin D	$C_{45}H_{65}NO_{12}$	*Erythrophleum succirubrum*	leaves	[56]
64	erythrophlesin E	$C_{44}H_{63}NO_{12}$	*Erythrophleum fordii*	leaves	[57]
65	erythrophlesin F	$C_{42}H_{61}NO_{10}$	*Erythrophleum fordii*	leaves	[57]
66	erythrophlesin G	$C_{44}H_{63}NO_{12}$	*Erythrophleum fordii*	leaves	[57]
67	erythrophlesin H	$C_{45}H_{65}NO_{10}$	*Erythrophleum fordii*	barks	[58]
68	erythrophlesin I	$C_{45}H_{65}NO_{11}$	*Erythrophleum fordii*	barks	[58]
69	caesanine D	$C_{42}H_{55}NO_7$	*Caesalpinia sappan*	seeds	[11]
Lamiaceae					
70	persianone	$C_{40}H_{56}O_6$	*Ballota aucheri*	aerial parts	[60]
71	inermes A	$C_{52}H_{74}O_{19}$	*Clerodendrum inerme*	leaves	[61]
72	inermes B	$C_{53}H_{76}O_{20}$	*Clerodendrum inerme*	leaves	[61]
73	trichotomone	$C_{40}H_{48}O_9$	*Clerodendrum trichotomum*	roots	[10]
74	maoecrystal M	$C_{48}H_{64}O_{16}$	*Isodon eriocalyx*	leaves	[62]
75	bistenuifolin L	$C_{52}H_{68}O_{18}$	*Isodon tenuifolius*	aerial parts	[64]
76	bistenuifolin M	$C_{50}H_{66}O_{16}$	*Isodon tenuifolius*	aerial parts	[64]
77	bisjaponin A	$C_{40}H_{52}O_{12}$	*Isodon japonicus*	aerial parts	[65]
78	bisjaponin B	$C_{40}H_{54}O_{12}$	*Isodon japonicus*	aerial parts	[65]
79	lushanrubescensin J	$C_{40}H_{52}O_{12}$	*Isodon rubescens*	leaves	[66]
80	bisrubescensin C	$C_{40}H_{56}O_{12}$	*Isodon rubescens*	leaves	[67]
81	biexcisusin B	$C_{48}H_{68}O_{14}$	*Isodon excisus*	aerial parts	[68]
82	biexcisusin C	$C_{48}H_{68}O_{16}$	*Isodon excisus*	aerial parts	[68]
83	biexcisusin D	$C_{48}H_{66}O_{16}$	*Isodon excisus*	aerial parts	[68]
84	biexcisusin E	$C_{48}H_{66}O_{16}$	*Isodon excisus*	aerial parts	[68]
85	bistenuifolin A	$C_{52}H_{68}O_{18}$	*Isodon tenuifolius*	aerial parts	[64]
86	bistenuifolin B	$C_{52}H_{68}O_{18}$	*Isodon tenuifolius*	aerial parts	[64]
87	bistenuifolin C	$C_{48}H_{64}O_{16}$	*Isodon tenuifolius*	aerial parts	[64]
88	bistenuifolin D	$C_{50}H_{66}O_{16}$	*Isodon tenuifolius*	aerial parts	[64]
89	bistenuifolin E	$C_{48}H_{62}O_{15}$	*Isodon tenuifolius*	aerial parts	[64]
90	bistenuifolin F	$C_{48}H_{68}O_{16}$	*Isodon tenuifolius*	aerial parts	[64]
91	xindongnin M	$C_{48}H_{70}O_{15}$	*Isodon rubescens*	leaves	[69]
92	xindongnin N	$C_{48}H_{68}O_{15}$	*Isodon rubescens*	leaves	[69]
93	xindongnin O	$C_{48}H_{68}O_{15}$	*Isodon rubescens*	leaves	[69]
94	bisrubescensin B	$C_{40}H_{58}O_{13}$	*Isodon rubescens*	leaves	[67]
95	biexcisusin A	$C_{48}H_{70}O_{16}$	*Isodon excisus*	aerial parts	[68]
96	bispseurata F	$C_{44}H_{60}O_{14}$	*Isodon pharicus*	aerial parts	[23]
97	bistenuifolin G	$C_{48}H_{66}O_{17}$	*Isodon tenuifolius*	aerial parts	[64]
98	bistenuifolin H	$C_{49}H_{68}O_{17}$	*Isodon tenuifolius*	aerial parts	[64]
99	bistenuifolin I	$C_{49}H_{68}O_{17}$	*Isodon tenuifolius*	aerial parts	[64]
100	bistenuifolin J	$C_{45}H_{64}O_{15}$	*Isodon tenuifolius*	aerial parts	[64]
101	bistenuifolin K	$C_{47}H_{66}O_{16}$	*Isodon tenuifolius*	aerial parts	[64]
102	bisrubescensin A	$C_{43}H_{60}O_{13}$	*Isodon rubescens*	leaves	[67]
103	rubescensin M	$C_{40}H_{58}O_9$	*Isodon rubescens*	leaves	[70]
104	hebeiabinin E	$C_{40}H_{60}O_{11}$	*Isodon rubescens*	leaves	[71]
105	hebeiabinin F	$C_{40}H_{56}O_9$	*Isodon rubescens*	leaves	[71]
106	hispidanin A	$C_{42}H_{56}O_6$	*Isodon hispida*	rhizomes	[72]
107	hispidanin B	$C_{42}H_{56}O_6$	*Isodon hispida*	rhizomes	[72]
108	hispidanin C	$C_{42}H_{56}O_7$	*Isodon hispida*	rhizomes	[72]
109	hispidanin D	$C_{42}H_{56}O_7$	*Isodon hispida*	rhizomes	[72]
110	grandidone A	$C_{40}H_{48}O_9$	*Plectranthus grandidentatus*	whole plants	[73]

cont.

Table 1 *Continued*

No.	Name	Molecular formula	Source	Part	Ref.
111	premnalatifolin A	$C_{40}H_{50}O_6$	*Premna latifolia*	stem barks	[74]
112	obtusinone D	$C_{40}H_{52}O_6$	*Premna obtusifolia*	roots	[75]
113	obtusinone E	$C_{40}H_{52}O_6$	*Premna obtusifolia*	roots	[75]
114	hongencaotone	$C_{40}H_{50}O_5$	*Salvia prionitis*	roots	[76]
115	bisprioterone A	$C_{40}H_{48}O_4$	*Salvia prionitis*	roots	[77]
116	bisprioterone B	$C_{39}H_{46}O_5$	*Salvia prionitis*	roots	[77]
117	bisprioterone C	$C_{38}H_{42}O_6$	*Salvia prionitis*	roots	[77]
118	rosmanoyl carnosate	$C_{40}H_{48}O_7$	*Salvia canariensis*	flowers	[78]
119	salviwardin A	$C_{40}H_{54}O_4$	*Salvia wardii*	roots	[79]
120	salviwardin B	$C_{40}H_{52}O_4$	*Salvia wardii*	roots	[79]
121	salvialeriafone	$C_{39}H_{48}O_7$	*Salvia leriaefolia*	whole plants	[80]
122	salvialeriicone	$C_{40}H_{50}O_6$	*Salvia leriaefolia*	whole plants	[83]
123	broussonetone A	$C_{40}H_{60}O_4$	*Salvia broussonetii*	roots	[84]
124	broussonetone B	$C_{40}H_{60}O_4$	*Salvia broussonetii*	roots	[84]
125	epirosmanol ester of 12-*O*-methyl carnosic acid	$C_{41}H_{54}O_8$	*Salvia officinalis*	stems and leaves	[85]
126	–	$C_{40}H_{50}O_7$	*Salvia wagneriana*	aerial parts	[86]
127	–	$C_{40}H_{42}O_9$	*Salvia wagneriana*	aerial parts	[86]
128	biteuvisone A	$C_{40}H_{52}O_8$	*Teucrium viscidum*	whole plants	[87]
129	biteuvisone B	$C_{40}H_{52}O_8$	*Teucrium viscidum*	whole plants	[87]
Liliaceae					
130	fritillebin A	$C_{42}H_{66}O_5$	*Fritillaria ebeiensis*	bulbs	[88]
131	fritillebin B	$C_{44}H_{68}O_7$	*Fritillaria ebeiensis*	bulbs	[88]
132	fritillebin C	$C_{40}H_{64}O_3$	*Fritillaria ebeiensis*	bulbs	[89]
133	fritillebin D	$C_{40}H_{64}O_3$	*Fritillaria ebeiensis*	bulbs	[89]
134	fritillebinide A	$C_{40}H_{64}O_2$	*Fritillaria ebeiensis*	bulbs	[22]
135	fritillebinide B	$C_{42}H_{66}O_4$	*Fritillaria ebeiensis*	bulbs	[90]
136	fritillebinide C	$C_{42}H_{66}O_4$	*Fritillaria ebeiensis*	bulbs	[91]
137	fritillebinide D	$C_{44}H_{68}O_6$	*Fritillaria ebeiensis*	bulbs	[92]
138	fritillebinide E	$C_{44}H_{68}O_6$	*Fritillaria ebeiensis*	bulbs	[92]
Meliaceae					
139	aphadilactone A	$C_{40}H_{52}O_8$	*Aphanamixis grandifolia*	leaves	[7]
140	aphadilactone B	$C_{40}H_{52}O_8$	*Aphanamixis grandifolia*	leaves	[7]
141	aphadilactone C	$C_{40}H_{52}O_8$	*Aphanamixis grandifolia*	leaves	[7]
142	aphadilactone D	$C_{40}H_{52}O_8$	*Aphanamixis grandifolia*	leaves	[7]
143	aphanamene C	$C_{40}H_{54}O_8$	*Aphanamixis grandifolia*	root barks	[8]
144	aphanamene D	$C_{40}H_{54}O_8$	*Aphanamixis grandifolia*	root barks	[8]
145	aphanamene E	$C_{40}H_{54}O_8$	*Aphanamixis grandifolia*	root barks	[8]
146	aphanamene F	$C_{40}H_{54}O_8$	*Aphanamixis grandifolia*	root barks	[8]
147	aphanamene K	$C_{40}H_{52}O_8$	*Aphanamixis grandifolia*	root barks	[8]
148	aphanamene L	$C_{40}H_{52}O_8$	*Aphanamixis grandifolia*	root barks	[8]
149	aphanamene M	$C_{40}H_{52}O_8$	*Aphanamixis grandifolia*	root barks	[8]
150	aphanamene N	$C_{40}H_{52}O_8$	*Aphanamixis grandifolia*	root barks	[8]
151	aphanamene G	$C_{40}H_{54}O_8$	*Aphanamixis grandifolia*	root barks	[8]
152	aphanamene H	$C_{40}H_{54}O_8$	*Aphanamixis grandifolia*	root barks	[8]
153	aphanamene I	$C_{40}H_{54}O_8$	*Aphanamixis grandifolia*	root barks	[8]
154	aphanamene J	$C_{40}H_{54}O_8$	*Aphanamixis grandifolia*	root barks	[8]
155	aphanamene O	$C_{40}H_{52}O_8$	*Aphanamixis grandifolia*	root barks	[8]
156	aphanamene P	$C_{40}H_{52}O_8$	*Aphanamixis grandifolia*	root barks	[8]
157	aphanamene B	$C_{40}H_{52}O_8$	*Aphanamixis grandifolia*	root barks	[95]
158	aphanamene A	$C_{40}H_{54}O_7$	*Aphanamixis grandifolia*	root barks	[95]
159	aphadilactone I	$C_{40}H_{54}O_7$	*Aphanamixis grandifolia*	leaves	[9]
160	aphadilactone E	$C_{40}H_{52}O_8$	*Aphanamixis grandifolia*	leaves	[9]
161	aphadilactone F	$C_{40}H_{52}O_8$	*Aphanamixis grandifolia*	leaves	[9]
162	aphadilactone G	$C_{40}H_{52}O_8$	*Aphanamixis grandifolia*	leaves	[9]
Rhizophoraceae					
163	tagalsin I	$C_{40}H_{60}O_2$	*Ceriop tagal*	stems and twigs	[96]
164	tagalsin J	$C_{40}H_{58}O_3$	*Ceriop tagal*	stems and twigs	[96]
165	tagalsin L	$C_{40}H_{60}O_3$	*Ceriop tagal*	roots	[97]
166	tagalsin M	$C_{40}H_{58}O_2$	*Ceriop tagal*	roots	[97]
167	tagalsin N	$C_{40}H_{58}O_2$	*Ceriop tagal*	roots	[97]
168	8(14)-enyl-pimar-2′(3′)-en-4′(18′)-en-15′(16′)-en-dolabr-16,15,2′,3′-oxoan-16-one	$C_{40}H_{58}O_2$	*Ceriop tagal*	roots	[98]

cont.

Table 1 *Continued*

No.	Name	Molecular formula	Source	Part	Ref.
Taxaceae					
169	grandione	$C_{40}H_{56}O_6$	*Torreya grandis*	stems	[99]
170	diabietane ether	$C_{41}H_{60}O_5$	*Taxus cuspidata*	needles	[100]
Velloziaceae					
171	bismagdalenic acid	$C_{40}H_{60}O_4$	*Vellozia magdalenae*	whole plants	[101]
Zingiberaceae					
172	pahangensin C	$C_{40}H_{58}O_6$	*Alpinia pahangensis*	rhizomes	[102]
Fungi, liverworts and gorgonian					
Psathyrellaceae					
173	radianspene M	$C_{40}H_{50}O_6$	*Coprinus radians*	fruiting body	[103]
Scapaniaceae					
174	scapaundulin A	$C_{32}H_{48}O_6$	*Scapania undulata*	whole plants	[104]
175	scapaundulin B	$C_{40}H_{64}O_6$	*Scapania undulata*	whole plants	[104]
Gorgoniidae					
176	bisersolanolide	$C_{40}H_{48}O_{10}$	*Pseudopterogorgia bipinnata*	whole animals	[105]

[a]The diterpenoid dimers are grouped according to biological sources. For plants, families and genera are listed in alphabetical order.

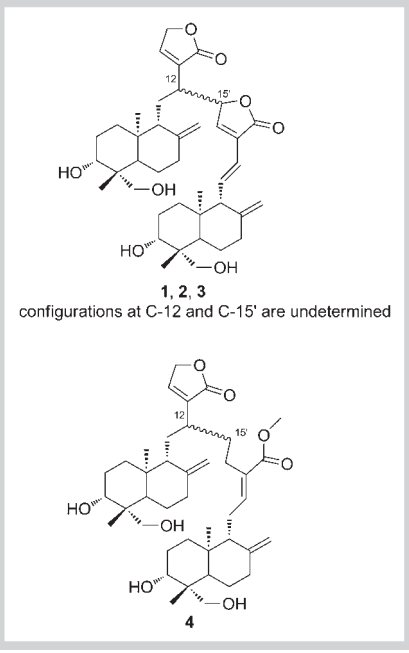

Fig. 1 Diterpenoid dimers from the family Acanthaceae.

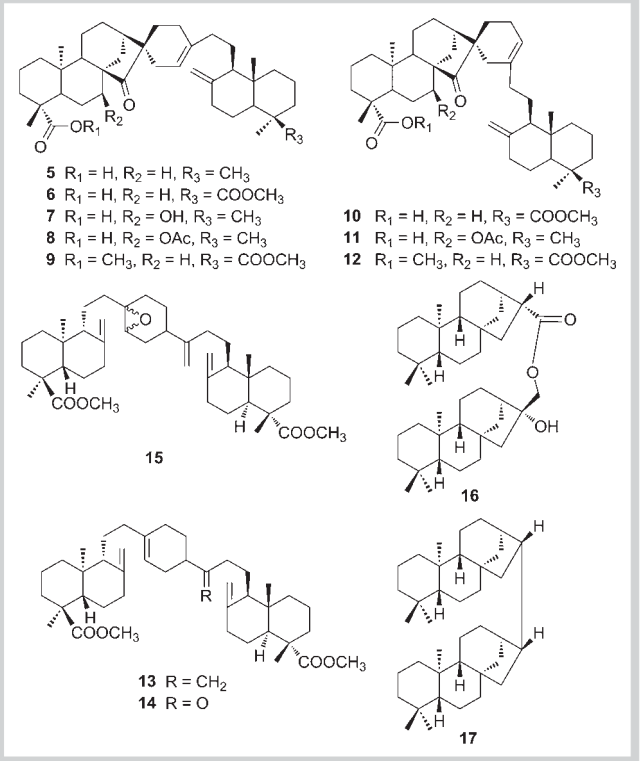

Fig. 2 Diterpenoid dimers from the family Annonaceae.

frutoic acid (**7**), respectively [26,27]. In other studies, emarginatines A–D (**8, 9, 11, 12**) were isolated from the branches and stem barks of *X. emarginata* [26,28]. These dimers are composed of kauranoid and labdanoid units, and could be considered as taxonomic markers of the genus *Xylopia*. Three diterpenoid dimers linked through a six-membered ring via a Diels-Alder condensation of two labdanoid units, namely *ent*-methylisoozate dimer (**13**), *ent*-13′-nor-13′-oxomethylisoozate dimer (**14**) and *ent*-13-epoximethylisoozate dimer (**15**), were isolated from the stem barks of *X. aromatica* [29]. They were the first labdanoid dimers identified from the family Annonaceae.

Annonebinide A (**16**) was identified from the stems of *A. glabra* and determined to be a dimer with two *ent*-kauranoid units linked via an ester bond between C-17 and C-17′ [30]. Annoglabayin (**17**), a kauranoid dimer, was isolated from *A. glabra* with its structure determined on the basis of spectroscopic analysis [31]. Annoglabayin has a unique C–C linkage between two nor-*ent*-kauranoid units.

Family Asteraceae

Four clerodanoid dimers linked via a C-18 malonate ester, baccharalejins 1–4 (**18**–**21**) (**Fig. 3**), were reported from the aerial parts of *Baccharis lejia* [32]. These compounds represent the first and the only examples of diterpenoid dimers from the family Asteraceae.

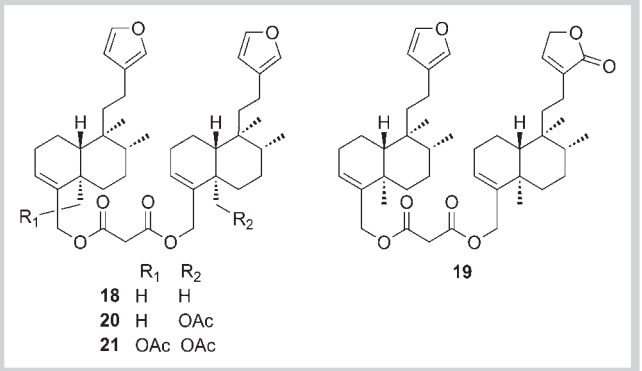

Fig. 3 Diterpenoid dimers from the family Asteraceae.

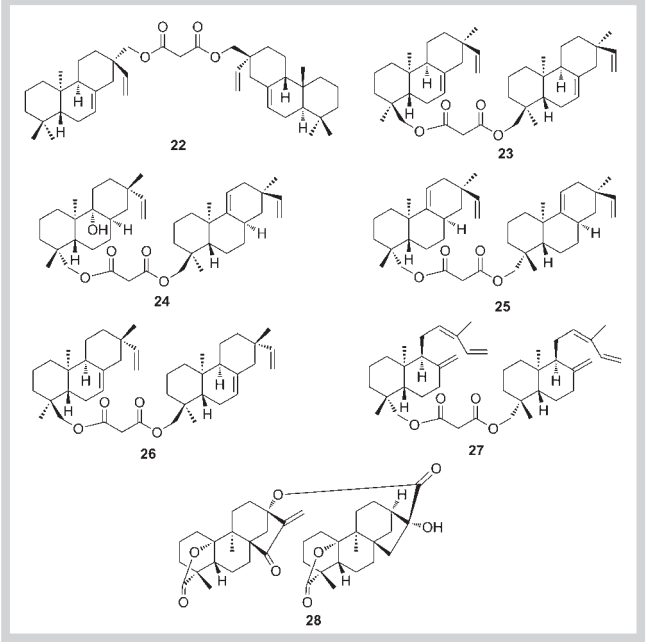

Fig. 4 Diterpenoid dimers from the families Calceolariaceae and Chrysobalanaceae.

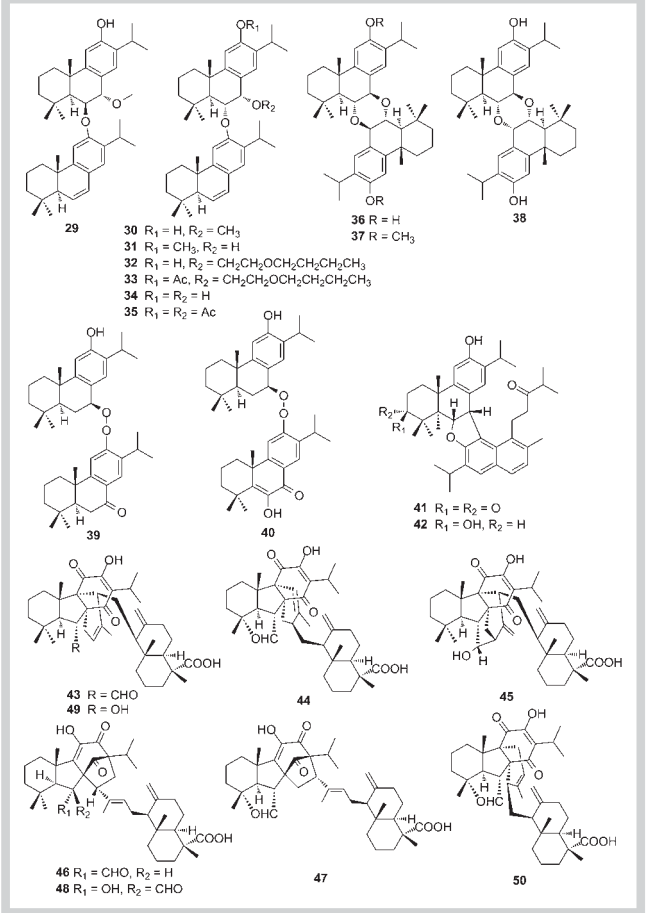

Fig. 5 Diterpenoid dimers from the family Cupressaceae.

Family Calceolariaceae

In the family Calceolariaceae, six diterpenoid dimers have been identified, all of which were from the genus *Calceolaria* (**Fig. 4**). They are linked through C-17, C-18 or C-19 by a malonic acid unit. Three dimers composed of two isopimarane-type units, foliosate (**22**), glandulosate (**23**), and lepidate (**24**), were isolated from the aerial parts of *C. foliosa, C. glandulosa*, and *C. lepida*, respectively [33–35]. Additionally, polifosate (**25**) and petiolate (**26**) were identified from *C. polifolia* and *C. petioalaris*, respectively, which are composed of two pimarane-type units [36, 37]. Interestingly, bis-[*ent*-9-epi-labda-8(17),(12Z),14-trien-19-yl] malonate (**27**), a dimer composed of two labdane-type units, was also isolated from *C. densifolia* [38].

Family Chrysobalanaceae

A kauranoid dimer, 15-oxozoapatlin-13α-yl-10′α,16′α-dihydroxy-9′α-methyl-20′-nor-kauran-19′-oic acid γ-lactone-17′-aote (**28**) (**Fig. 4**), was isolated from the leaves of *Parinari campestris* and identified on the basis of 2D NMR and ESI-MS [39]. It is the only diterpenoid dimer reported from the family Chrysobalanaceae.

Family Cupressaceae

Plants from the family Cupressaceae are rich in abietane-type diterpenoids [3]. At present, twenty-two diterpenoid dimers have been identified from this family (**Fig. 5**). Among them, fourteen compounds possess two abietane-type units, and eight others are composed of an abietane-type unit and a labdane-type unit.

A dimer, 6-(abieta-6′,8′,11′,13′-tetraenyl-12′-oxy)-7-methoxyabieta-8,11,13-trien-12-ol (**29**), was isolated from the stem barks of *Chamaecyparis obtusa* [40]. It is composed of two abietanoid units linked via an ether bridge between C-6 and C-12′. In a phytochemical investigation of the black heartwood of *Cryptomeria japonica*, sugikurojin B (**30**) was identified as a dimer of 6,7-dihydroxyferruginol and 6,7-dehydroferruginol with a 6-*O*-12′ linkage [41]. In chemical studies of the barks of *Calocedrus macrolepis*, five abietanoid dimers with the same linkage pattern as sugikurojin B were isolated, including formosadimers A–C (**31**–**33**) [42] and calocedimers C and D (**34, 35**) [43]. Formosaninol (**36**) and formosanin (**37**) were isolated from the heartwood of *Juniperus formosana* [44]. The structure of formosaninol was deduced to be a dimeric ferruginol with 6-*O*-7′ and 7-*O*-6′ linkages on the basis of spectroscopic analysis and chemical evidences. Formosanin was a dimethyl ether of formosaninol. Sugikurojin C (**38**) was a dimeric ferruginol with the same planar structure as formosaninol, which was isolated from the black heartwood of *Cryptomeria japonica* [41]. The only difference between the two com-

pounds is the configuration at C-7′. Two diterpenoid dimers, namely obtusanols A and B (**39, 40**), were isolated from the heartwood of *Chamaecyparis obtusa*, and characterized by spectroscopic means and chemical degradation [45]. Obtusanols A and B have a rare peroxide bond linking two abietanoid units between C-7 and C-12′. In another study, bicunningines A and B (**41, 42**) were isolated from *Cunninghamia lanceolata* [46]. Their structures were elucidated by spectroscopic measurements. Their absolute configurations were determined by quantum chemical TDDFT (time-dependent density functional theory) ECD calculations, chemical transformations and Mosher's method. They were the first diterpenoid dimers reported to contain a 2,3-dihydrofuran ring fusing an abietanoid and a 4,5-seco-abietanoid.

Taiwaniadducts B–J (**43**–**50**) were isolated from the leaves of *Taiwania crypomerioides* and identified as dimers composed of an abietanoid unit and a labdanoid unit [47, 48]. Taiwaniadducts B, C, H and I were presumably derived from a [4 + 2] Diels-Alder reaction of the labdane trans-ozic acid and different taiwaniaquinones; while taiwaniadducts E–G appeared to result from the corresponding [5 + 2] Diels-Alder reaction. Taiwaniadducts B–J are the only naturally occurring heterodimers formed by abietanoid and labdanoid units, and could be considered as taxonomic markers of the species *T. crypomerioides*. They have attracted strong synthetic interest due to their structural complexity.

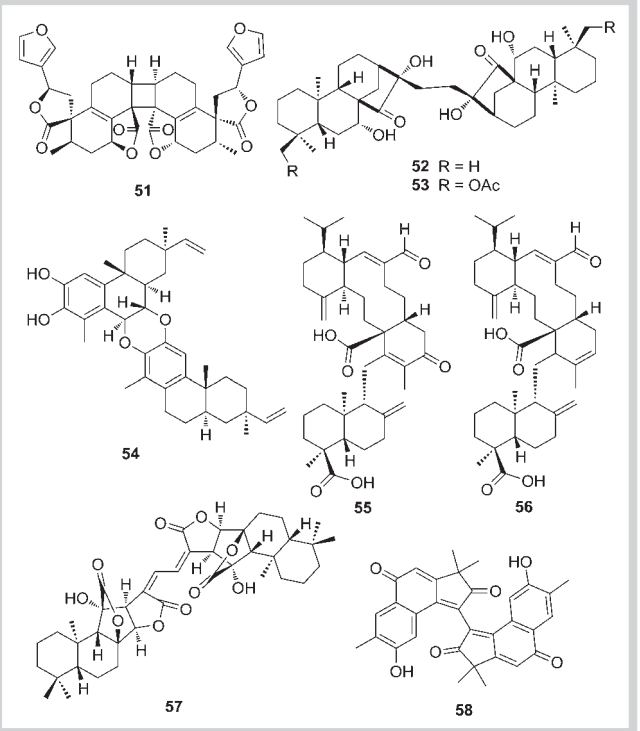

Fig. 6 Diterpenoid dimers from the family Euphorbiaceae.

Family Euphorbiaceae

Plants from the family Euphorbiaceae are rich in sesquiterpenoids and diterpenoids. At present, eight diterpenoid dimers have been isolated from this family (**Fig. 6**).

In a chemical study of the twigs and leaves of *Croton euryphyllus*, a nor-clerodanoid dimer, namely crotoeurin A (**51**), was isolated, which contains a unique cyclobutane ring formed via [2 + 2] cycloaddition [49]. The structure was elucidated by spectroscopic analysis and the configuration was confirmed by single crystal X-ray diffraction. Crotoeurin A represents the first nor-clerodanoid dimer with a cyclobutane ring and is of particular significance for the biosynthesis of clerodane-type diterpenoids. Crotoeurin A exhibited neurite outgrowth-promoting activity on nerve growth factor-mediated PC12 cells at a concentration of 10 µM. During a screening program for cytotoxic compounds, two symmetric *ent*-kauranoid dimers with connectivity at C-17, namely crotonkinensins C and D (**52, 53**), were isolated from the leaves of the Vietnamese endemic medicinal plant *C. tonkinensis* [50]. *ent*-Kauranoid diterpenoids are rarely found from the genus Croton, and these two compounds are the first examples from this genus. Crotonkinensin D showed potent cytotoxic activity against MCF-7, tamoxifen-resistant MCF-7 and adriamycin-resistant MCF-7 breast cancer cell lines, with IC_{50} values of 9.4 ± 1.7, 2.6 ± 0.9, and 18.9 ± 0.6 µM, respectively.

In another study, yuexiandajisu D (**54**), an 18-nor-rosane-type diterpenoid dimer, was isolated from the roots of *Euphorbia ebracteolata* [51]. It is the first and to date the only example of 18-nor-rosane-type diterpenoid dimer isolated from the family Euphorbiaceae. Yuexiandajisu D showed weak cytotoxic activity against HCT-8 and Bel-7402 cancer cell lines, with IC_{50} values of 2.66 and 3.76 mM, respectively. Langduin C (**55**) was isolated from the roots of *E. fischeriana* and its structure was established by spectroscopic data and single crystal X-ray diffraction analysis [52]. Langduin C is a symmetrical diterpenoid dimer with a five-membered C ring instead of the normal six-membered C ring found in the *ent*-abietane-type diterpenoids. It is the first diterpenoid dimer from the genus *Euphobia*. This dimer is probably derived from jolkinolide B, a major *ent*-abietane-type diterpenoid of this plant, by successive oxidative cleavage of ring C and D, rearrangement, lactonization, and dimerization. Two diterpenoid dimers with a bismagdalenic acid skeleton, namely bisyinshanic acids A and B (**56, 57**), were isolated from the roots of *E. yinshanica* [53]. Their structures were elucidated on the basis of spectroscopic evidences.

Neoboutomannin (**58**), a degraded diterpenoid dimer, was isolated from the stem barks of *Neoboutonia mannii* [54]. Neoboutomannin was active against *Enterococcus faecalis, Staphylococcus aureus, Proteus mirabilis*, and three *Candida* species, *C. albicans, C. tropicalis* and *C. parapsilosis*.

Family Fabaceae

At present, eleven diterpenoid dimers with a cassane-type skeleton have been identified from plants of the family Fabaceae (**Fig. 7**).

A chemical investigation of the stem barks of *Cylicodiscus gabunensis* resulted in the identification of the cassanoid dimer cyclodione (**59**) [55]. Cyclodione was proposed to be formed through a [4 + 2] Diels-Alder reaction between two cassanoid units.

Nine diterpenoid dimers were isolated from plants of the genus *Erythrophleum*. They possess an unsymmetrical dimeric structure with two cassanoid units linked through an ester bond at C-16 and C-3′ [56–58]. These compounds could be considered as taxonomic markers of this genus. TRAIL is a promising agent for new anticancer therapy as it can induce apoptosis in a variety of cancer cells but not in normal cells [59]. Bioassay-guided fractionation of the extract of *E. succirubrum* for TRAIL resistance-overcoming activity led to the isolation of four cassanoid dimers, namely erythrophlesins A–D (**60**–**63**) [56]. These four compounds are the first examples of cassanoid dimers linked via an ester

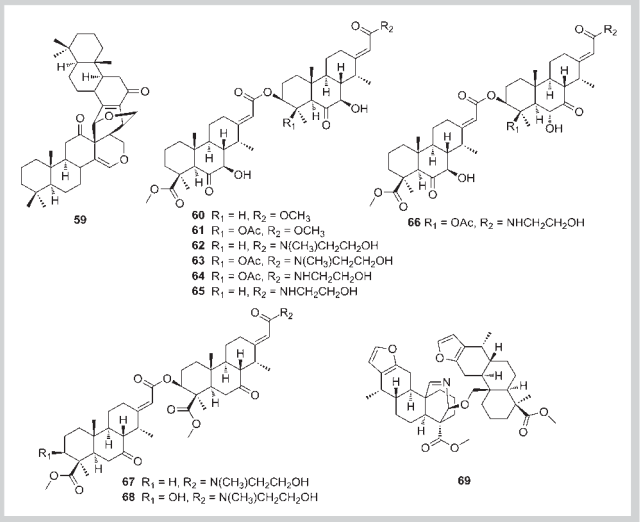

Fig. 7 Diterpenoid dimers from the family Fabaceae.

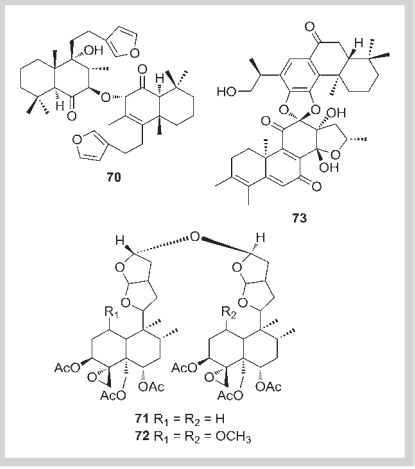

Fig. 8 Diterpenoid dimers from the genera *Ballota* and *Clerodendrum* (Lamiaceae).

bond, which are rarely found in nature. Moreover, erythrophlesins C and D possess an amide moiety, which is seldom found in naturally occurring diterpenoids. Erythrophlesins A–C exhibited significant TRAIL resistance-overcoming activity in human gastric adenocarcinoma cells. A detailed phytochemical investigation of the leaves of *E. fordii* resulted in the isolation of three cassanoid dimers, namely erythrophlesins E–G (**64**–**66**), all of which were found to contain an amide group [57]. Their structures were determined by extensive 1D and 2D NMR analyses and ESIMS. Cytotoxic activity of these compounds was evaluated against HCT-8, Bel-7402, BGC-823, A549, and A2780 human cancer cell lines in an MTT assay. All three compounds exhibited significant cytotoxic activity (IC_{50} < 10 µM) against these cells. Cytotoxic activity-guided fractionation of *E. fordii* led to the isolation of two cassanoid amide dimers, namely erythrophlesins H and I (**67, 68**) [58]. An MTT assay confirmed that erythrophlesin H had significant cytotoxic effect toward the human prostate cancer PC-3 cell line, with an IC_{50} value of 12.5 µM.

In a recent study, a cassanoid dimer, namely caesanine D (**69**), was isolated from the seeds of *Caesalpinia sappan* [11]. Caesanine D represents the first example of a cassanoid dimer where the subunits are linked via an ether bond. Interestingly, one of the diterpene units of this compound possesses a cassane-type skeleton with an unusual N bridge between C-19/C-20. The structure was determined by various spectroscopic methods and ECD calculation.

Family Lamiaceae

Plants of the family Lamiaceae contributed a significant number of diterpenoid dimers. At present, 60 diterpenoid dimers have been isolated and structurally characterized. Most are homodimers, composed of two diterpenoids units with the same core skeleton. Twenty-nine kaurane-type diterpenoid dimers were reported from the genus Isodon, and could be considered as taxonomic markers of this genus; sixteen abeitane-type diterpenoid dimers were identified from the genera *Salvia, Clerodendrum, Plectranthus*, and *Teucrium*; four clerodane-type diterpenoid dimers were found from the genera *Salvia* and *Clerodendrum*; three icetexane-type diterpenoid dimers were from the genus *Premna*; and one labdane-type dimer was from the genus *Ballota*. Besides, some are rare heterodimers, consisting of two units belonging to different types of diterpenoids. Four dimers composed of a totarene-type unit and a labdane-type unit, as well as three dimers containing an abietane-type unit and a kaurane-type unit were isolated from the genus Isodon.

***Ballota* genus.** A study on the chemical constituents of *B. aucheri* led to the isolation of persianone (**70**) (**Fig. 8**), a dimer composed of two labdane-type units linked through an ether bond at C-7 [60]. The structure of persianone was elucidated by high field NMR spectroscopy, including NOE difference experiments, and chemical transformations.

***Clerodendrum* genus.** Two compounds, namely inermes A and B (**71, 72**) (**Fig. 8**), were isolated from *C. inerme* [61]. On the basis of comprehensive spectroscopic analysis, both compounds were elucidated to contain two clerodane units linked through an ether bridge at C-15. Interestingly, a hexahydrofurofuran ring was found in each clerodane unit. The isolation and structural elucidation of trichotomone (**73**) (**Fig. 8**) was reported from the roots of the medicinal ornamental plant *C. trichotomum* [10]. This compound is a rare phenolic ketal derivative consisting of a regular abietanoid and a rearranged abietanoid derivative in a 17 (15 → 16),18(4 → 3)-diabeo-abietane framework. The structure was elucidated by extensive spectroscopic methods. The absolute configuration was defined by comparison of experimental and calculated ECD spectra. Trichotomone exhibited significant *in vitro* cytotoxicity against several human cancer cell lines (A549, Jurkat, BGC-823, and 293 T WT) with IC_{50} values ranging from 7.51 to 19.38 µM.

***Isodon* genus.** Besides lots of diterpenoid monomers, the genus *Isodon* is also a major source of diterpenoid dimers with a considerable structural diversity. At present, 36 dimers have been isolated from this genus, most of which possess a kaurane-type core skeleton (**Fig. 9**–**11**).

Maoecrystal M (**74**) (**Fig. 9**), the first example of naturally occurring *ent*-kaurane-type dimer, was isolated from *I. eriocalyx* [62]. By means of ^{1}H-^{1}H COSY and ROESY, as well as chemical transformation, the structure of maoecrystal M was determined to be a symmetric dimer of an *ent*-kaurane diterpenoid connected at 16R, 16′R through a cyclobutane ring. The four-membered ring was proposed to be formed by condensation between the olefinic bond in the *α,β*-unsaturated ketone group of the monomer diterpenoid, probably through a [2 + 2] cycloaddition [63]. In a chemical study of *I. tenuifolius*, bistenuifolins L and M (**75** and **76**) (**Fig. 9**) were isolated and found to possess the

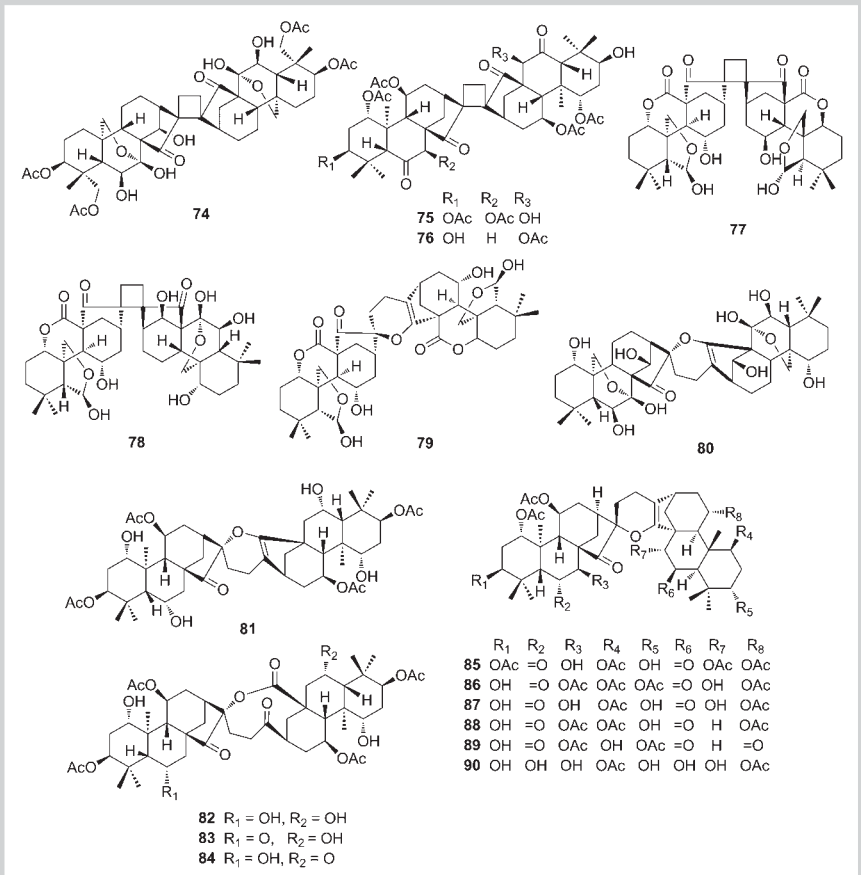

Fig. 9 Diterpenoid dimers from the genus *Isodon* (Lamiaceae) – part I.

same skeleton as maoecrystal M [64]. In 2008, another two *ent*-kaurane-type dimers connected with a four-membered carbon ring, namely bisjaponins A and B (**77** and **78**) (**Fig. 9**), were isolated from the aerial parts of *I. japonicus* [65]. These two compounds contain a 6,7-seco-6,20-epoxy-*ent*-kaurane fragment.

An asymmetric *ent*-kauranoid dimer, namely lushanrubescensin J (**79**) (**Fig. 9**), was isolated from *I. rubescens* var. *lushanensis* [66]. Its structure was established by spectroscopic evidences and single crystal X-ray diffraction. It is the first *ent*-kauranoid dimer found to possess a dihydropyran ring resulting from a [4 + 2] cycloaddition between the *α,β*-unsaturated ketone group of one diterpenoid and the olefinic bond of another diterpenoid. Interestingly, this compound contains a 6,7-seco-6,20-epoxy-*ent*-kaurane monomer. Lushanrubescensin J exhibited potent inhibitory activity against K562 cells with an IC_{50} value of 0.93 µg/mL. Bisrubescensin C (**80**) (**Fig. 9**), an *ent*-kauranoid dimer with the same linkage pattern as lushanrubescensin J, was isolated from *I. rubescens* [67]. Four *ent*-kauranoid dimers, namely biexcisusins B–E (**81**–**84**) (**Fig. 9**), were reported from *I. excisus* [68]. Their structures which are closely related to bisrubescensin C were established on the basis of detailed spectroscopic analyses. Biexcisusins C–E possess an unprecedented linkage through a nine-membered lactone ring between two *ent*-kaurane-type subunits. The lactone ring was proposed to arise through oxidative cleavage of the double bond of the dihydropyran ring in biexcisusin B. In a chemical study of *I. tenuifolius*, six *ent*-kauranoid dimers, namely bistenuifolins A–F (**85**–**90**) (**Fig. 9**), were identified and found to be linked by a dihydropyran ring [64]. The structures of these compounds were established via spectroscopic analysis. The absolute configurations of bistenuifolins A and D were defined by single crystal X-ray diffraction. Bistenuifolin B exhibited significant cytotoxicity against several human cancer cell lines, including HL-60, SMMC-7721, MCF-7, and SW-480, with IC_{50} values ranging from 4.0 to 9.9 µM.

Three asymmetric dimers, namely xindongnins M–O (**91**–**93**) (**Fig. 10**), have been isolated from *I. rubescens* var. *rubescens* [69]. They represent the first examples of *ent*-kauranoid dimers with a rare linkage through a single C–C bond between two units. Their structures were characterized by spectroscopic methods including 2D NMR analyses. The relative configuration of xindongnin M was determined by single crystal X-ray diffraction. *ent*-Kauranoids isolated from the genus *Isodon* normally have *α,β*-unsaturated ketone groups. The [4 + 2] cycloaddition between the *α,β*-unsaturated ketone of one diterpene unit and the olefinic bond of the second unit might yield a dihydropyran ring. In a further step, hydrolysis and rearrangement at the dihydropyran ring could produce the single C–C bond linkage. Two other *ent*-kauranoid dimers, namely bisrubescensin B (**94**) and biexcisusin A (**95**) (**Fig. 10**), connected with a single C–C bond linkage, were isolated from *I. rubescens* [67] and *I. excisus* [68], respectively. The co-occurrence of dimers with a single C–C bond linkage (bisrubescensin B and biexcisusin A) and congeners with a dihydropyran ring (bisrubescensin C and biexcisusin B) in the same plant further supports the above proposed biosynthetic pathway. A phytochemical investigation of *I. pharicus* led to the isolation of an asymmetric dimer, namely bispseurata F (**96**) (**Fig. 10**), which is the first and the only example of *ent*-kauranoid dimer connected by direct linkage of C-17 with C-11′ [23]. A Michael addition reaction is proposed to be the key step in the biosynthesis of bispseurata F. The dimerization of this type of di-

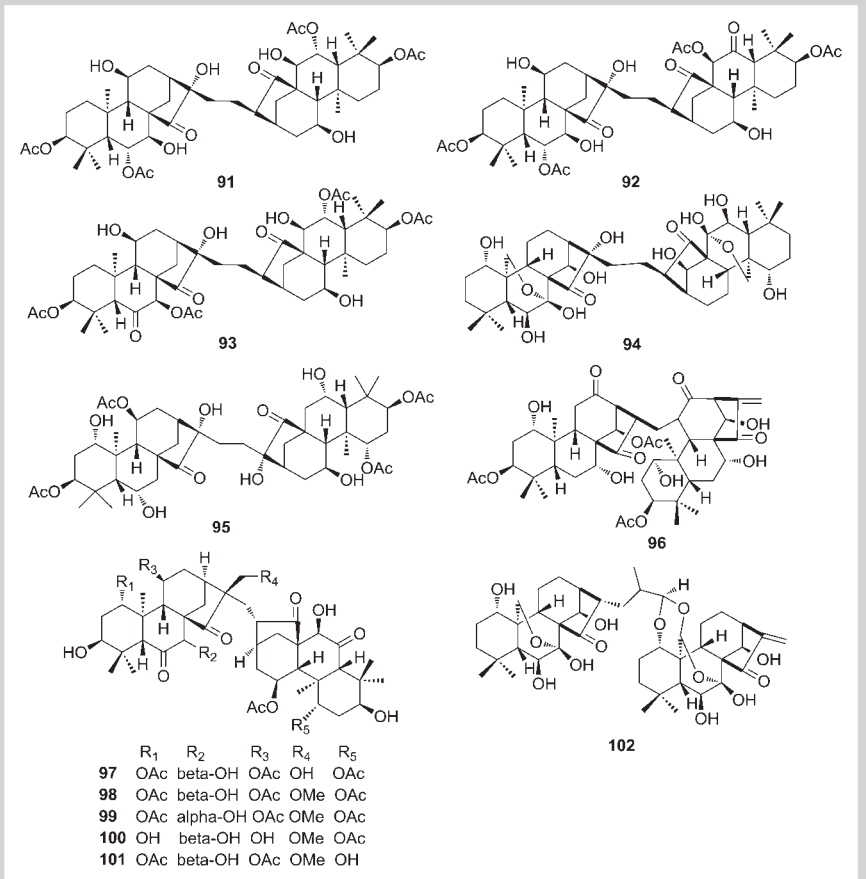

Fig. 10 Diterpenoid dimers from the genus *Isodon* (Lamiaceae) – part II.

terpenoid dimers is worth further studies. Five *ent*-kauranoid dimers linked by a unique C-16 to C-17′ single bond, namely bistenuifolins G–K (**97**–**101**) (**Fig. 10**), were identified from *I. tenuifolius* [64]. Bisrubescensin A (**102**) (**Fig. 10**) is an *ent*-kauranoid dimer from *I. rubescens* and contains an unprecedented C_{23} *ent*-kaurane unit [67].

Rubescensin M (**103**) (**Fig. 11**) was isolated from *I. rubescens* [70]. By detailed spectroscopic analysis, it was deduced to be a dimer linked by an oxygen bridge between C-18 of an abietanoid and C-20′ of a kauranoid. Abietane-type diterpenoids are very rare in the genus *Isodon*, and rubescensin M is the first heterodimer from this genus. In a chemical study of *I. rubescens*, hebeiabinins E and F (**104, 105**) (**Fig. 11**) were identified with the same linkage pattern as rubescensin M [71]. Hebeiabinin F showed significant inhibitory activity against A549 and HT-29 cells with IC_{50} values of 0.91 and 1.81 µM, respectively.

Hispidanins A–D (**106**–**109**) (**Fig. 11**) are four unprecedented heterodimers formed by the bonding of totarane-type and labdane-type diterpenoids. They were obtained from the rhizomes of *I. hispida* [72]. Their structures were elucidated by extensive spectroscopic analyses, and the structure of hispidanin A was further confirmed by single crystal X-ray diffraction. Totarane-type diterpenoids are rarely found in nature. Hispidanins A–D are the first and the only naturally occurring heterodimers composed of a labdane-type and a totarane-type diterpenoid. The biosynthetic pathway of hispidanins A–D was proposed to involve an intermolecular Diels-Alder reaction between totarane-type and labdane-type derivatives. Hispidanin B showed significant cytotoxicity against tumor cell lines SGC7901, SMMC7721, and K562, with IC_{50} values of 10.7, 9.8, and 13.7 µM, respectively.

***Plectranthus* genus.** An abietanoid dimer linked by a ketal, namely grandidone A (**110**) (**Fig. 12**), was isolated from *P. grandidentatus* [73]. This compound showed slight antiproliferative activity against five human cancer cell lines MCF-7, NCI-H460, SF-268, TK-10, and UACC-62, with GI_{50} values of 9.6 ± 1.8, 19.2 ± 3.1, 25.8 ± 4.0, 40.9 ± 3.7, and 35.7 ± 1.5 µM, respectively.

***Premna* genus.** Premnalatifolin A (**111**) (**Fig. 12**), a unique icetexanoid dimer, was isolated from the stem barks of the Indian medicinal plant *P. latifolia* [74]. Its structure and relative configuration were elucidated on the basis of detailed spectroscopic analyses, including HRESIMS and 2D NMR spectra. This compound is composed of two icetexanoid units linked via an ether bridge. The formation of premnalatifolin A was proposed to follow a radical reaction. A phenoxyl radical of one subunit reacted with a phenyl radical of the other subunit to result in the ether bridge. Premnalatifolin A displayed potent cytotoxicity against HT-29 and MCF-7 cell lines with IC_{50} values of 12.15 and 1.11 µg/mL, respectively. In 2013, two icetexanoid dimers, namely obtusinones D and E (**112** and **113**) (**Fig. 12**), were isolated from the roots of *P. obtusifolia*, and were suggested to be formed via a hetero-Diels-Alder type dimerization reaction [75]. Obtusinone D represents the first example of a linearly fused icetexanoid dimer, whereas obtusinone E is an angularly fused icetexanoid dimer. The structures of obtusinones D and E were elucidated on the basis of 1D and 2D NMR spectroscopic analyses. Icetexanoid dimers could be considered as taxonomic markers of the genus *Premna*.

***Salvia* genus.** Fourteen diterpenoid dimers have been isolated from the genus *Salvia*, including twelve abietane-type dimers and two clerodane-type dimers (**Fig. 13**). Abietanoid dimers

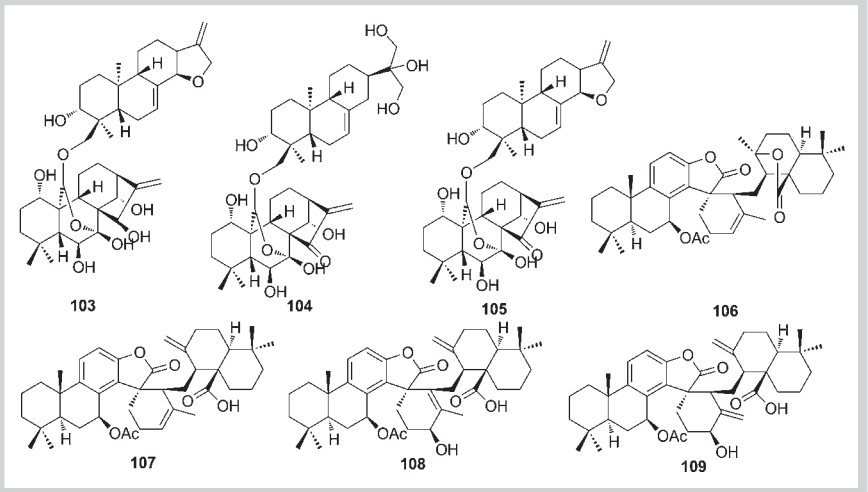

Fig. 11 Diterpenoid dimers from the genus *Isodon* (Lamiaceae) – part III.

from the genus *Salvia* are linked via C–C single bond, ether bridge, dioxane ring, or ketal moiety.

The abietanoid dimer hongencaotone (**114**) was isolated from the roots of *S. prionitis* and its structure was determined by spectroscopic data interpretation and X-ray analysis [76]. From the same species, three further abietanoid dimers, namely bisprioterones A–C (**115**–**117**), were identified by Zhang and his colleagues [77]. Bisprioterone A possesses two 4,5-seco abietanoid subunits linked via a C–C single bond at C-14 and C-1′. In bisprioterone B the subunits are connected via a C–C single bond between C-14 of an abietanoid subunit and C-1′ of a 4,5-seco abietanoid subunit. Bisprioterone C possesses an ether bridge linked between C-12 of an abietanoid subunit and C-1′ of an 11,12-seco abietanoid subunit. Their structures were characterized by analysis of 1D and 2D NMR spectroscopic data. The structure of bisprioterone A was further confirmed by single crystal X-ray diffraction. In contrast to their monomers these diterpenoid dimers did not exhibit obvious cytostatic, antiphlogistic, or antibacterial activities. The disappearance of some functional groups during the dimerization process might account for the decrease of the bioactivities.

In 1987, rosmanoyl carnosate (**118**), a dimer composed of two abietanoid units linked via an ether bond between C-7 and C-20′, was isolated from the flowers of *S. canariensis* [78]. It was the first ether-linked diterpenoid dimer identified from the genus *Salvia*. Two other dimers, namely salviwardins A and B (**119** and **120**), were isolated from the roots of *S. wardii* [79]. In both compounds, two abietanoid subunits are connected via a dioxane ring. Salvialeriafone (**121**), a diterpene-norditerpene conjugate, was isolated from *S. leriaefolia* and its structure was determined by spectroscopic data analysis [80]. Salvialeriafone which contains a spiro-dihydrofuran moiety attached to ring C of the norditerpenoid unit is the first example of norditerpene-diterpene conjugated abietanoid dimer. The probable origin of the spiro-dihydrofuran group is proposed to be through a nucleophilic addition/substitution between the 1,6,12-trihydroxy derivative of sibiriquinone B [81] and the 6-deoxo analogue of 14-hydroxytaxodion [82]. This compound exhibited antiproliferative activity against HeLa cells with an IC_{50} value of 10.91 μM. Salvialeriicone (**122**), isolated from *S. leriifolia*, is an abietanoid dimer connected via a dihydropyran ring [83]. The structure was determined using mass spectrometry and NMR spectroscopy. In a chemical study of *S. broussonetii*, two abietanoid dimers, namely broussonetones A and B (**123, 124**), were isolated [84]. Their structures were determined based on spectroscopic data and confirmed by X-ray analysis. These dimers could be formed by a [4 + 2] cycloaddition of two molecules of 13*β*-hydroxyabieta-8(14),9(11)-dien-12-one. Broussonetones A and B are the first non-phenolic or quinonic abietanoid dimers to be isolated from natural sources. In a study aimed to the identification of nuclear peroxisome proliferator-activated receptor (PPAR)-γ activators from *S. officinalis*, the epirosmanol ester of 12-*O*-methyl carnosic acid (**125**), was identified. This compound contains two abietanoid subunits linked by an ester bond [85]. As the only example of abietanoid dimer resulting from the formation of an ester bond, it was considered as an artefact formed during extraction and isolation. This was further supported by the fact that this compound was not detectable in the crude extract by HPLC analysis.

From the aerial parts of *S. wagneriana*, two clerodanoid dimers (**126** and **127**) were obtained with their structures established by 1D- and 2D-NMR spectroscopic analyses [86]. They are the on-

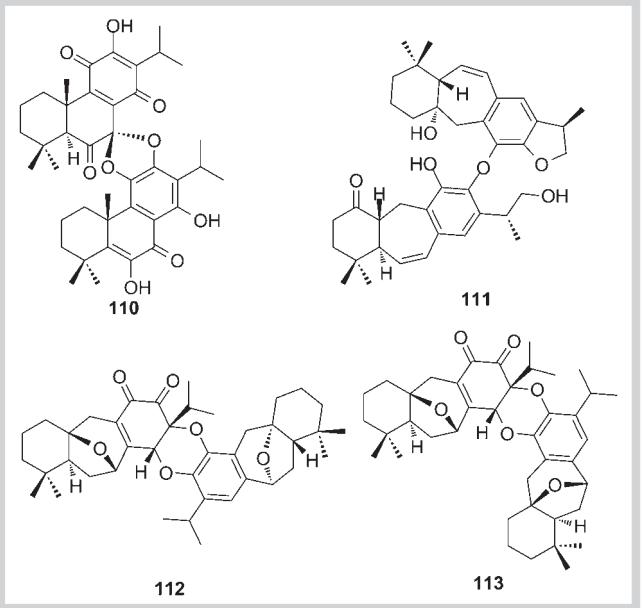

Fig. 12 Diterpenoid dimers from the genera *Plectranthus* and *Premna* (Lamiaceae).

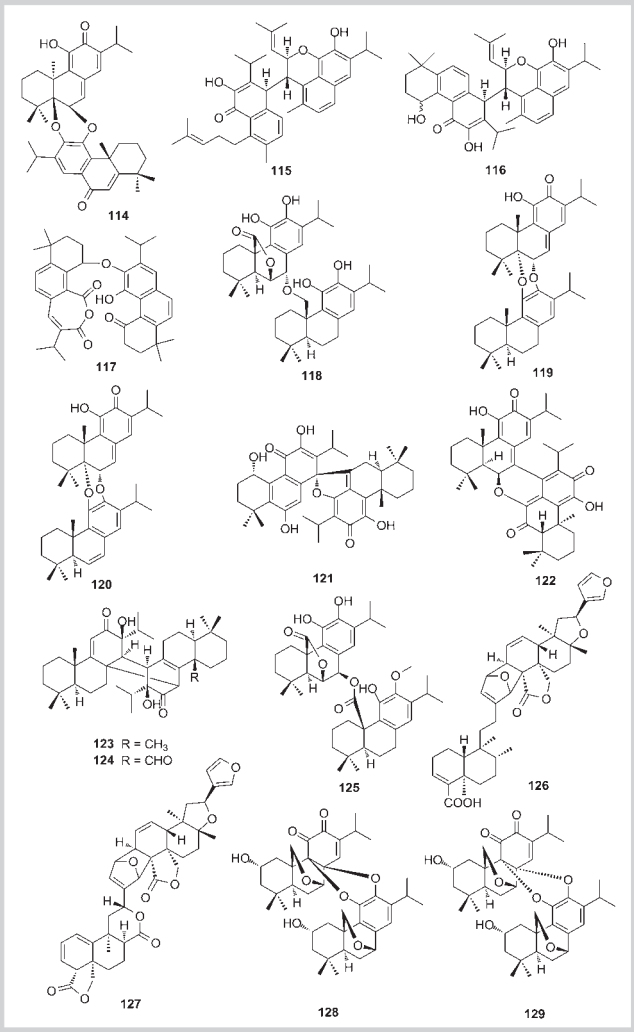

Fig. 13 Diterpenoid dimers from the genera *Salvia* and *Teucrium* (Lamiaceae).

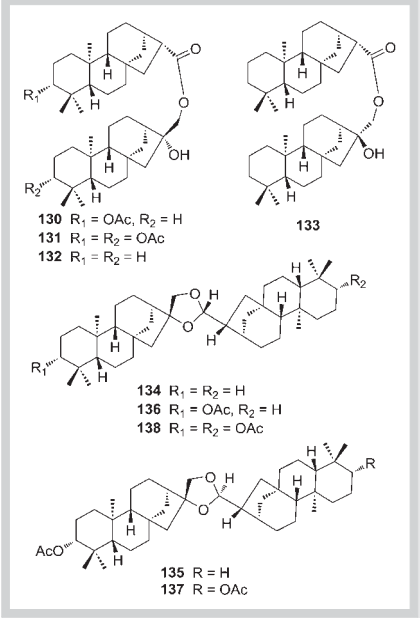

Fig. 14 Diterpenoid dimers from the genera *Teucrium* and *Plectranthus* (Lamiaceae).

ly clerodane-type diterpenoid dimers reported from the genus *Salvia*.

***Teucrium* genus.** A pair of dimeric abietanoid stereoisomers connected via a dioxane ring, namely biteuvisones A and B (**128** and **129**) (◉ **Fig. 13**), were isolated from *T. viscidum* [87]. These two compounds are proposed to be formed through a hetero-Diels-Alder reaction of the o-quinone of teuvisone.

Family Liliaceae

Nine diperpenoid dimers were isolated from the bulbs of *Fritillaria ebeiensis* (Liliaceae). They contain two *ent*-kauranoid units linked through an ester bond or a dioxolane ring (◉ **Fig. 14**). In 1995, Wu and colleagues [88] found two compounds, namely fritillebins A and B (**130, 131**), which possess an *ent*-kauranoid dimer skeleton linked via an ester bond between C-17 and C-17′. These compounds are the first diterpenoid dimers identified from the family Liliaceae. Later, the same group [89] reported other two dimers, namely fritillebins C and D (**132, 133**), from the same plant. These two dimers share the same core skeleton as fritillebin A. An acetal diterpenoid dimer with *ent*-kauranoid skeleton, namely fritillebinide A (**134**), was isolated from the bulbs of *F. ebeiensis* [22]. The structure of fritillebinide A was elucidated by spectroscopic analysis and chemical synthesis. It represents the first *ent*-kauranoid dimer possessing a dioxolane ring formed by aldol condensation. In subsequent studies, two pairs of further *ent*-kauranoid dimers containing a dioxolane ring, namely fritillebinides B and C (**135, 136**) and fritillebinides D and E (**137, 138**), were isolated from the same plant [90–92]. Fritillebinides B and D have a R configuration at C-17′ while fritillebinides C and E have a S configuration at this position.

Family Meliaceae

Diterpenoids are not widely found in plants of the family Meliaceae. In fact, *Aphanamixis grandifolia* is the only source of diterpenoid dimers in this family, which has contributed 25 congeners in recent years (◉ **Fig. 15**). *A. grandifolia* is an arbor tree mainly distributed in the tropical and subtropical areas of Asia [93]. Its leaves and roots are used as folk medicine in China to treat rheumatism and alleviate pain [94]. As part of a search for new DGAT inhibitors, the ethanolic extract of *A. grandifolia* was found to exhibit significant inhibition against DGAT-1. Bioassay-guided isolation resulted in identification of four diastereoisomers possessing an unprecedented carbon skeleton, namely aphadilactones A–D (**139**–**142**) [7]. Their structures and absolute configurations were determined by a combination of spectroscopic data, chemical degradation, partial synthesis, experimental CD spectra and ECD calculations. Aphadilactones A–D were proposed to be formed from two molecules of nemoralisin-type diterpenoid through an enzyme-catalyzed [4 + 2] cycloaddition reaction, which leads to a cyclohexene ring with a 2,2-dimethylfuran-3(2 H)-one ring and the substituents attached at the para-position [7]. According to further biological evaluation, aphadilactone C is a potent DGAT-1 inhibitor (IC_{50} = 0.46 ± 0.09 µM) with marginal activity against DGAT-2 (IC_{50} > 100 µM). In addition, these compounds have weak antimalarial activity with IC_{50} values ranging from 120 to 190 µM. In a later study, eight diterpenoid dimers with the same skeleton as aphadilactone A, namely aphanamenes C–F and K–M (**143**–**150**), were isolated from the root barks of *A. grandifolia* [8]. In this study, other six diterpenoid dimers with a 2,2-dimethylfuran-3(2 H)-one ring and two substituents attached at the meso-position, namely aphanamenes G–J, O and P

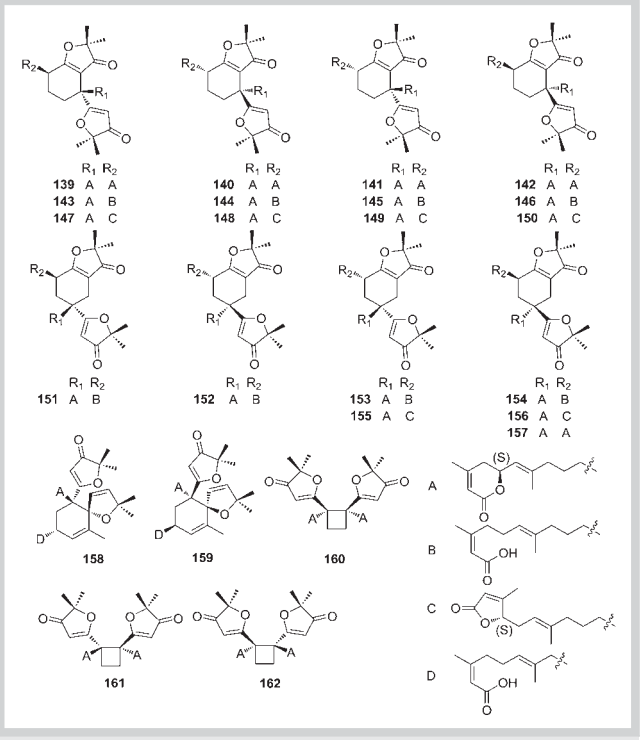

Fig. 15 Diterpenoid dimers from the family Meliaceae.

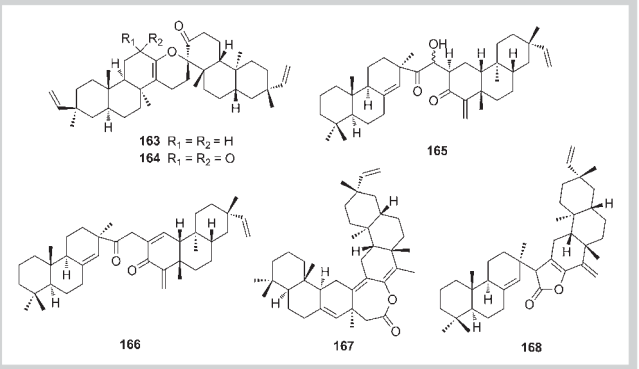

Fig. 16 Diterpenoid dimers from the family Rhizophoraceae.

(**151**–**156**), were identified [8]. The structures of these compounds were elucidated by spectroscopic analysis, and their absolute configurations were determined using the CD exciton chirality method. As shown in a further study, these compounds exhibited significant inhibition of LPS-induced NO production in RAW264.7 macrophages, with IC_{50} values ranging from 7.75 to 19.31 µM. The isolation and structural elucidation of aphanamene B (**157**) was reported as part of an investigation of *A. grandifolia* [95]. This compound shares the same skeleton with aphanamene G. Aphanamene A (**158**) was also reported in this study and found to possess a spiro 2,2-dimethyl dihydroxyfuran ring on the cyclohexene ring [95]. It was proposed to be formed through a different [4 + 2] cycloaddition reaction. Both structures were elucidated by spectroscopic analysis, and the absolute configuration of aphanamene A was determined by ECD calculations. These two compounds inhibited LPS-induced NO production in RAW264.7 cells with IC_{50} values of 9.72 and 7.98 µM, respectively. Recently, a chemical investigation into the minor constituents of *A. grandifolia* yielded one diterpenoid dimer, namely aphadilactone I (**159**), which was found to be a diastereoisomer of aphanamene A [9]. Besides, three diastereomeric diterpenoid dimers, namely aphadilactones E–G (**160**–**162**), were also isolated from this species and found to contain a new carbon skeleton incorporating a 1,1,2,2-tetrasubstituted cyclobutane moiety. Their structures and absolute configurations were fully established by comprehensive spectroscopic data analysis and ECD calculations. It was proposed that aphadilactones E–G were formed through a [2 + 2] cycloaddition reaction in a head-to-head and tail-to-tail way. Aphadilactones E and F exhibited remarkable antimalarial activity with IC_{50} values of 1.03 ± 0.13 and 2.86 ± 0.47 µM, respectively. These dimers could be considered as taxonomic markers of the species *A. grandifolia*.

Family Rhizophoraceae

The occurrence of diterpenoid dimers in the family Rhizophoraceae was only reported from the mangrove plant *Ceriop tagal*. At present, six dolabrane-type dimers have been isolated (**Fig. 16**). By means of extensive spectroscopic analysis and single crystal X-ray diffraction, two dolabrane-type dimers, namely tagalsins I (**163**) and J (**164**), were identified. They represent the first examples of diterpenoid dimers from the family Rhizophoraceae [96]. In later studies, four dimers, namely tagalsins L–N (**165**–**167**) and 8(14)-enyl-pimar-2′(3′)-en-4′(18′)-en-15′(16′)-endolabr-16,15,2′,3′-oxoan-16-one (**168**), were isolated from the roots of *C. tagal* [97,98]. 8(14)-enyl-pimar-2′(3′)-en-4′(18′)-en-15′(16′)-endolabr-16,15,2′,3′-oxoan-16-one exhibited antifouling activity against cyprid larvae (*Balanus albicostatus*) of the barnacle without significant toxicity. Dolabrane-type dimers could be considered as taxonomic markers of the species *C. tagal*. The stem barks of *Xylopia acutiflora* yielded a dimeric diterpene derived via Diels-Alder condensation of kaurene and labdane monomers. The structure of the dimer, which has been given the trivial name acutifloric acid, was assigned on the basis of detailed spectroscopic analysis.

Family Taxaceae

The isolation and structure elucidation of grandione (**169**) (**Fig. 17**) was reported in the course of an investigation of Chinese specimens of *Torreya grandis* [99]. Grandione is formed by two icetexanoid units linked via a hetero-Diels-Alder dimerization reaction and shares the same skeleton as obtusinone D (**112**). Grandione represents the first and the only example of a linearly fused icetexanoid dimer from the family Taxaceae. Diabietane ether (**170**) (**Fig. 17**), an abietanoid dimer connected by an ether linkage, was isolated from the needles of *Taxus cuspidata* [100].

Family Velloziaceae

An unusual bis-diterpenoid diacid, bismagdalenic acid (**171**) (**Fig. 17**), was isolated from the hexane extract of the Brazilian plant *Vellozia magdalenae* [101]. Bismagdalenic acid is a dimer formed via a Diels-Alder condensation of magdalenic acid and a regular labdane diterpenoid, cis-ozic acid. This is the first report of the isolation of diterpenoid dimer from the family Velloziaceae.

Family Zingiberaceae

The rhizomes of Alpinia pahangensis yielded the labdanoid dimer pahangensin C (**172**) (**Fig. 17**) [102]. This dimer is formed via an ester bond between C-15 and C-15′. The structure of pahangensin C was elucidated by spectroscopic methods including 1D and 2D NMR and LCMS-IT (ion trap)-TOF analyses. It is the only diterpenoid dimer reported from the family Zingiberaceae.

Diterpenoid Dimers from Fungi, Liverworts and Gorgonian

A few diterpenoid dimers have been reported from sources other than plants, including fungi, liverworts and a gorgonian. These groups of organisms could be potential sources of novel diterpenoid dimers with promising biological activities and are worth further investigation in the future.

Fungi (family Psathyrellaceae)

Radianspene M (**173**) (**Fig. 18**), a guanacastane-type diterpenoid dimer, was isolated from a fermentation of the M65 strain of the higher fungus *Coprinus radians* [103]. This is the first report of a diterpenoid dimer from fungi and provides new opportunities to investigate the dimerization mechanisms of diterpenoids as fungi are much easier to be manipulated in the laboratory through cultivation than plants.

Liverworts (family Scapaniaceae)

Two labdanoid dimers, namely scapaundulins A and B (**174** and **175**) (**Fig. 18**), were isolated from the diethyl ether extract of the Japanese liverworts *Scapania undulata* [104]. Their structures were characterized by spectroscopic techniques, especially 2D NMR and mass spectrometry. Two identical labdanoid units are connected via ester linkages in scapaundulin A, or hemiacetal linkages in scapaundulin B, from C-8 of one subunit to C-11 of the other subunit. The structures of scapaundulins possess a C_2 axis of symmetry.

Gorgonian (family Gorgoniidae)

A chemical study of the hexane extract of the Caribbean gorgonian *Antillogorgia bipinnata* collected in San Andre's Island, Colombia, led to the isolation of an unprecedented heptacyclic diterpenoid dimer, namely bisersolanolide (**176**) (**Fig. 18**) [105]. The structure of this secondary metabolite was established by spectroscopic studies including 2D NMR, IR, UV, and accurate mass measurements, and was further confirmed by synthesis. Bisersolanolide is the first diterpenoid dimer found to contain two cembranoid units. The generation of the 2,3-dihydro-4H-pyran ring is proposed to occur via a Diels-Alder coupling of two units of gersolane diterpenoids.

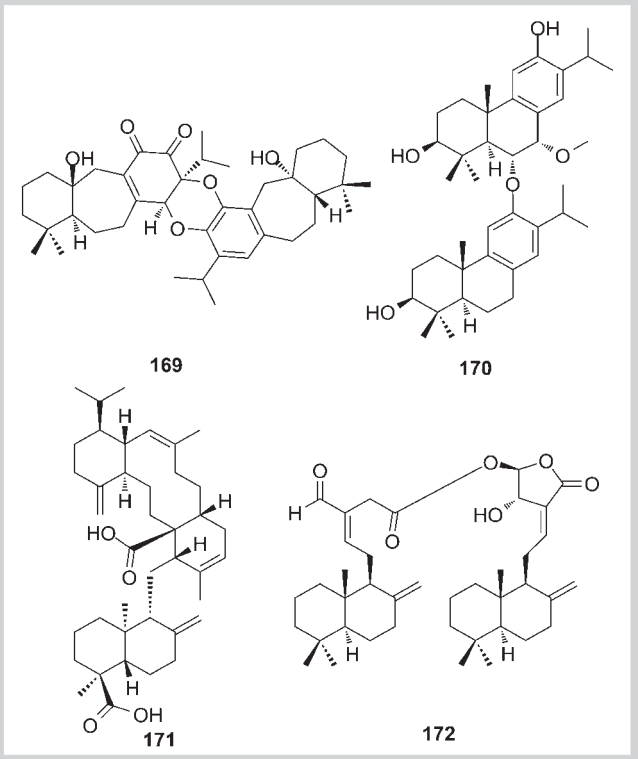

Fig. 17 Diterpenoid dimers from the families Taxaceae, Velloziaceae and Zingiberaceae.

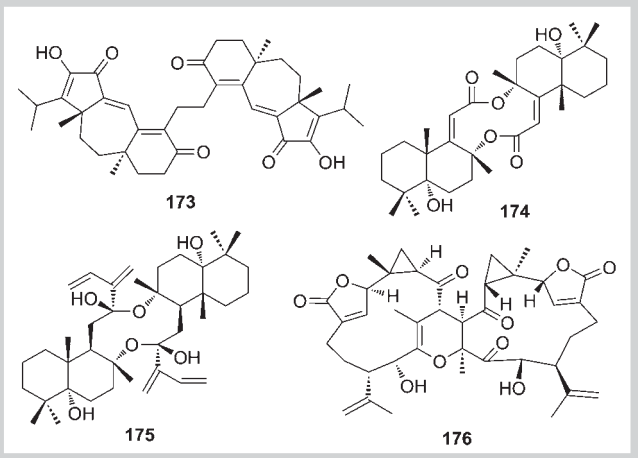

Fig. 18 Diterpenoid dimers from the families Psathyrellaceae, Scapaniaceae and Gorgoniidae.

Synthesis

Due to their high structural diversity and their biological activities, diterpenoids have attracted remarkable attention from a synthetic perspective. In contrast, only few successful total syntheses of diterpenoid dimers have been reported.

Synthesis of grandione

Grandione (**169**) is a unique icetexanoid dimer. In 2005, Kurihara's group [106] first reported the partial synthesis of grandione from demethylsalvicanol via the solid state hetero-Diels-Alder type dimerization reaction. Three years later, Majetich's group [107] reported the total synthesis of (+)-grandione from benzyl bromide (**177**) and 6,6-dimethyl-1,3-cyclohexadione (**178**). The authors developed a two-step process to convert the achiral enone **179** into the 5*S* alkene **180** (**Fig. 19**). Next, the authors took advantage of Kelecom's approach to convert alkene **180** into

alcohol **181** [108]. The epoxidation of the C-1, C-10-trisubstituted double bond occurred from the *β*-face of **180**, and the subsequent opening of this epoxide with LAH introduced a *β*-oriented tertiary alcohol at C-10 (**Fig. 19**). To avoid the solid state hetero-Diels-Alder reaction, the authors carried out the cycloaddition in water at 50 °C overnight, which produced (+)-grandione in good yield (**Fig. 19**).

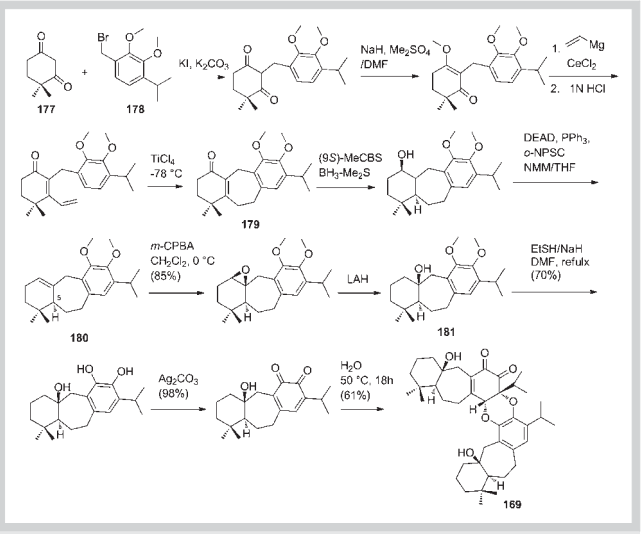

Fig. 19 Majetich's synthesis of (+)-grandione.

Synthesis of aphadilactones

Shortly after the isolation of aphadilactones A–D (**139**–**142**), a study on the total synthesis of these diterpenoid dimers was reported [13]. A proposed biosynthetic pathway of aphadilactones was put forward by Yue's group, in which the *S*-dienelactone **184** (**Fig. 20**) served as a common biosynthetic precursor to these dimers [7]. The diastereomeric aphadilactones A–D were obtained in comparable amounts from the natural source, strongly suggesting that the final [4 + 2] dimerization was a non-enzymatically catalyzed process. The total syntheses of aphadilactones A–D were accomplished in eleven steps starting from the commercially available 1-methoxy-3-methylbuta-1,2-diene (**182**) and but-2-y-nal (**183**) (**Fig. 20**). The *S*-dienelactone **184** reacted with BHT (butylated hydroxytoluene) in toluene at 170 °C for 17 hours to form aphadilactones A–D (approx. 1 : 1 : 1 : 1) through the bioinspired [4 + 2] dimerization/1,3 *σ*-hydrogen migration (**Fig. 20**).

Synthesis of taiwaniadduts

A few members of taiwaniaquinoids, namely taiwaniadducts A–J, possess a characteristic Diels-Alder cycloadduct scaffold. In 2014, Li's group [109] carried out the first total synthesis of taiwaniadducts B–D, which took advantage of an Iridium-catalyzed asymmetric polyene cyclization in the synthesis of the two key fragments, namely taiwaniaquinone F (**185**) and methyl trans-ozitate (**186**). Then, the dimerization reaction was carried out with Er $(fod)_3$ under neat conditions and elevated temperature to produce the cycloadduct **187** (52% yield) and its regioisomer **188** (21% yield) but no other positional or diastereomeric isomers (**Fig. 21**). The site selectivity toward the C-8 olefin over the C-12 olefin may be attributable to the bulky isopropyl and the electron-donating methoxyl that make the latter olefin a worse dienophile. The facial selectivity may arise from the steric effect of the axial C-20 methyl group. Both cycloadducts were subjected to a three-step sequence of oxidation to furnish taiwaniadducts B and C. Me_2AlCl-mediated carbonyl-ene reaction formed taiwaniadduct D (91% yield) (**Fig. 21**).

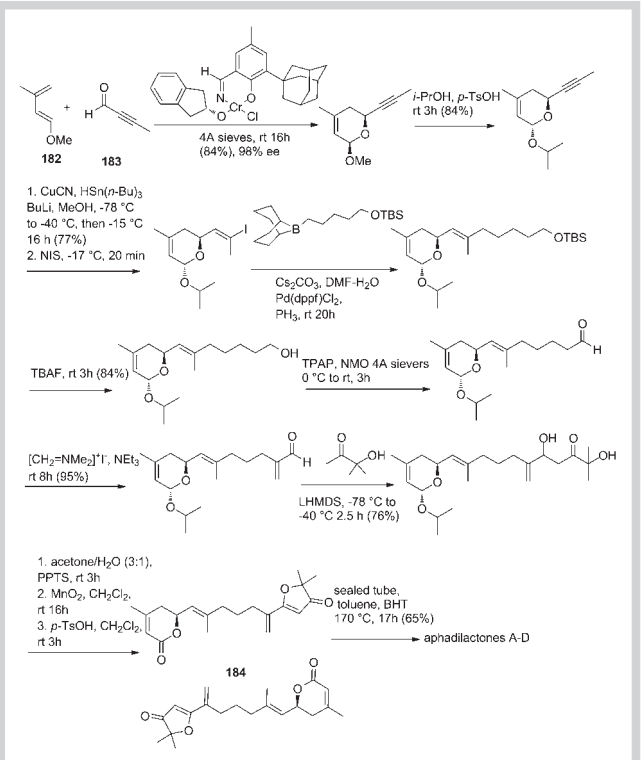

Fig. 20 Nan's synthesis of aphadilactones A–D (**139**–**142**).

Conclusions

As illustrated in this review, naturally occurring diterpenoid dimers have become an important research area in the field of natural products. There have been around 90 publications focusing on chemistry of diterpenoid dimers during the period covered by this review (1981 to January 2016). Up-to-date, 176 diterpenoid dimers have been described, most of which are from higher plants. As shown in **Table 1**, the family Lamiaceae contributes the greatest number of diterpenoid dimers (60 compounds), and the families Meliaceae (23 compounds) and Cupressaceae (22 compounds) have also afforded numerous compounds. In contrast, only a few examples of diterpenoid dimers have been isolated from fungi, liverworts or marine animals, which might be due to the limited availability of these natural resources. These organisms are believed to be promising materials for identifying novel diterpenoid dimers and eventually developing lead compounds.

There is a great structural diversity of diterpenoid dimers. As highlighted in this review, diterpenoid dimers can be classified into one of the following skeletons: kaurane-type, abietane-type, nemorallisin-type, labdane-type, clerodane-type, cassane-type, dolabrane-type, pimarane-type, icetexane-type, guanacastane-type, cembrane-type, rosane-type, or a combination of two from the above structural types. With 44 compounds the kaurane-type

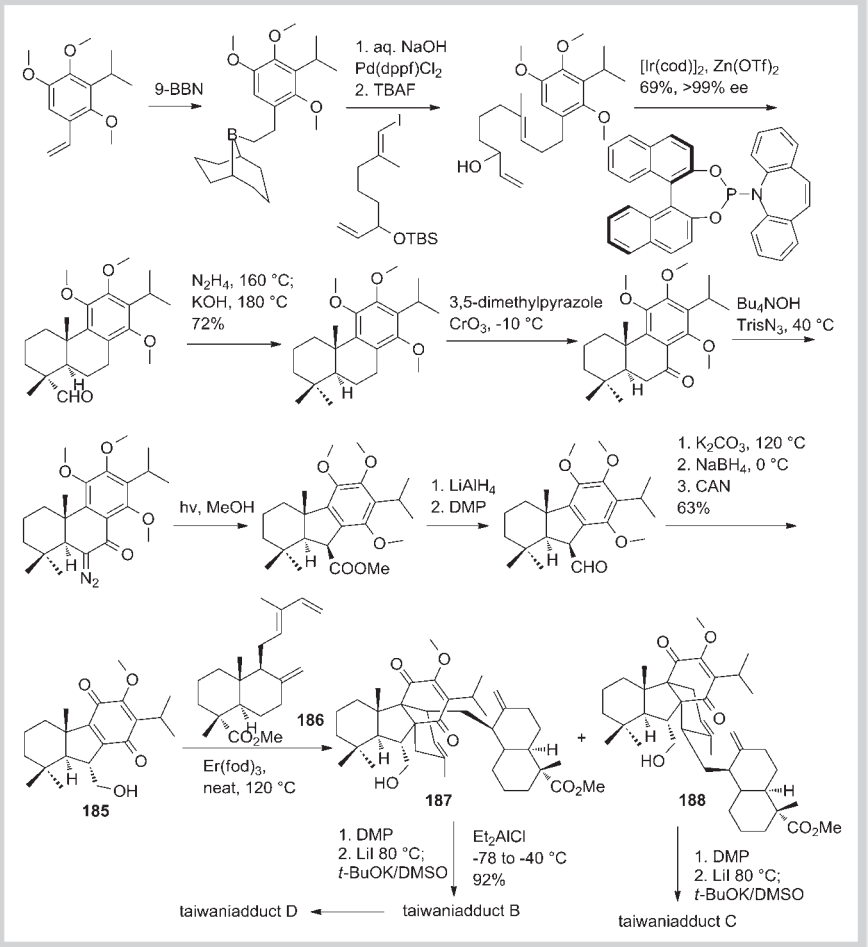

Fig. 21 Li's synthesis of taiwaniadducts B–D (**43**–**45**).

dimers contribute the greatest proportion. Most of the diterpenoid dimers are homodimers formed by two units of the same skeleton. Only 23 compounds are heterodimers containing two units of different skeletons. Three dimers composed of abietane-type and kaurane-type units, and four dimers composed of totarane-type and labdane-type units have been identified from plants of the family Lamiaceae. Besides, eight dimers with abietane-type and labdane-type units, and eight compounds with kaurane-type and labdane-type units have been found from plants of the families Cupressaceae and Annonaceae, respectively.

The linkages of diterpenoid dimers include single C–C bonds, ether bonds, ester bonds and ring moieties. Enzyme-catalyzed Diels-Alder cycloaddition reaction is proposed to be a major mechanism involved in the synthesis of diterpenoid dimers. In addition enzyme-mediated Michael addition or aldol condensation is also proposed to form C–C linkages in diterpenoid dimers. At present, there is no direct evidence confirming the proposed biosynthetic pathways of diterpenoid dimers and the putative natural Diels-Alderase still remains unknown. Increased efforts should be made in the future to elucidate the key enzymes and individual steps of the biosynthetic pathway of diterpenoid dimers.

Diterpenoid dimers have been reported with various bioactivities, including cytotoxic, anti-inflammatory, anti-microbial, anti-malarial, and anti-fouling effects. However, all these studies were carried out in in vitro assays. No *in vivo* animal studies or clinical trials have been conducted to evaluate the therapeutic effects of diterpenoid dimers. Moreover, due to low amounts, most diterpenoid dimers have never been biologically tested. Further investigations should be performed in the future.

The studies summarized in this review confirm the potential of diterpenoid dimers for the discovery of novel pharmaceutical agents. It is hoped that chemists, pharmacologists and biologists will intensify research efforts on these complex secondary metabolites as a potential source of novel bioactive lead compounds.

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Conflict of Interest

The authors declare no competing financial interest.

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