Diterpenoids of terrestrial origin

Article (Accepted Version)

Hanson, James R, Nichols, Tyler, Mukhrish, Yousef and Bagley, Mark C (2019) Diterpenoids of terrestrial origin. Natural Product Reports. ISSN 0265-0568

This version is available from Sussex Research Online: http://sro.sussex.ac.uk/id/eprint/85467/

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher’s version. Please see the URL above for details on accessing the published version.

Copyright and reuse:
Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.
Graphical Abstract

Diterpenoids of Terrestrial Origin

James R. Hanson, Tyler Nichols, Yousef Mukhrish and Mark C Bagley

This review covers the isolation and chemistry of diterpenoids from terrestrial sources from 2017.
Diterpenoids of terrestrial origin
James R. Hanson, Tyler Nichols, Yousef Mukhrish and Mark C. Bagley

Received


This review covers the isolation and chemistry of diterpenoids from terrestrial as opposed to marine sources and includes labdanes, clerodanes, abietanes, pimaranes, kauranes, cembrenes and their cyclization products. There are 228 references.
1 Introduction

This report, which covers the period between January and December 2017, follows the pattern of its predecessors by describing the isolation and chemistry of novel diterpenoids of terrestrial origin. Marine natural products are covered in a separate article.

The investigation of plants that play a role in traditional folk medicine has continued to yield novel diterpenoids. Reviews have appeared of diterpenes as lead molecules against neglected tropical diseases, as potential anti-cancer agents, as anti-bacterial agents, and as more general pharmaceutical agents. In studies of this kind it is important to consider not just the natural products that are present at the time of harvest but also any changes, e.g. autoxidation of phenols to form quinones, that may have occurred by the time that the plant is used in a medicinal context. Secondly although it is well-established that there can be seasonal and regional variations in natural product content and the time and place of harvesting of a plant is normally recorded, the relationship of this to the use of the plant in folk medicine needs to be considered in the context of attributing the role of novel diterpenoids. Plant material obtained from local markets may have a less well-defined provenance. The potential for synergistic interactions is also a feature which needs consideration particularly where multiple compounds are isolated. A number of phytochemical reviews have appeared including bioactive diterpenoids from the Celastraceae, the structural diversity of Pieris diterpenoids, and on the constituents of the Brazilian medicinal plant, Echinodorus grandiflorus.

2 Acyclic and related diterpenoids

The nemoralisin diterpenoids of Aphanamixis (Meliaceae) species have continued to attract interest in the light of their biological activity. Aphapolin A (1) which was
obtained\textsuperscript{10} from \textit{Aphanamixis polystachya}, contains an unusual 4,5-bicyclic system which may arise by a 2+2 cycloaddition of a co-constituent \textit{2}. The sauruchinenols (e.g. \textit{A}, \textit{3}) from \textit{Saururus chinensis}\textsuperscript{11} exert an anti-inflammatory action by inhibiting NO production. A number of degraded carotenoids, e.g. solanerioside A from \textit{Solanum erianthum} have been described as diterpenoids.\textsuperscript{12}

3 Bicyclic diterpenoids

3.1 Labdanes

Over half of the known diterpenoids belong to the labdane-related group in which the initial cyclization of geranylgeranyl diphosphate involves a type II diterpene cyclase to form a bicyclic intermediate prior to further transformation. The presence of the associated biosynthetic genes in an \textit{Aspergillus} species has been examined.\textsuperscript{13} A significant number of labdane diterpenoids possess anti-inflammatory activity by inhibiting NF-\textit{κ}B activity, NO production or arachidonic acid metabolism. This has been reviewed.\textsuperscript{14}

The use of roots of \textit{Coleus forskohlii} has a long history in Ayurvedic medicine. In recent years the constituent, forskolin, has become a popular herbal remedy for the treatment of cardiovascular disease, high blood pressure and as a weight-loss supplement. The genes responsible for its biosynthesis have been incorporated\textsuperscript{15} into the yeast \textit{Saccharomyces cerevisiae} to produce forskolin. A number of forskolin isoxazole derivatives have been synthesized.\textsuperscript{16} The anti-cancer activity of andrographolide has continued to attract attention. This has been reviewed\textsuperscript{17} and further analogues have been synthesized.\textsuperscript{18}

Labdanes are widespread and an increasing number of labdane glycosides have been reported some of which possess an ecological role. Thus blakielloside, which is a ribofuranoside of labda-7,14-dien-13(\textit{S})-ol, has been found\textsuperscript{19} in the foliar exudates of the rare high-altitude plant, \textit{Blakiella bartsiifolia} (Asteraceae) where it exerts a phytotoxic activity against other plants in a competitive rocky environment. The grindelic acid esters from \textit{Grindelia chiloensis} (Asteraceae), one of the 'gum weeds', have anti-fungal activity
against the plant pathogen, *Botrytis cinerea*. 

Labdanes are common constituents of spices from the Zingiberaceae where some of the aldehydes contribute to the 'hot' taste. The elettarins A and B are tetranorlabdanes which were isolated from the spice *Elettaria cardamomum* and the galangalditerpenes A-C (e.g. A, 4) possessed melanogenesis inhibitory activity and were obtained from the fruit of *Alpinia galanga*. Other labdanes have been found in the rhizomes of *Curcuma amada*. 

Labdanes are common constituents of the medicinal plants from the Lamiaceae. The modification of the side chain with the formation of a furan, a butenolide or a lactol, are common structural features. The possibility that some of the methoxy and ethoxy acetals that have been reported are artefacts, arising from the use of methanol or ethanol during isolation and chromatography, needs to be considered. There have been a number of investigations of *Leonurus japonicus*. The leojapones A-C and leojaponicin are novel constituents which have been described. Other labdanes that have been isolated include the loxocalyxins D and E from *Loxocalyx urticifolius*, a plant which is used in traditional Chinese medicine to treat rheumatism, the cinereanoids C and D from *Roylea cinerea* and a norlabdane from *Salvia sahendica*. Further investigation of *Vitex trifolia* (Verbenaceae), the three-leaved chaste tree which is widely used around the Pacific as a medicinal plant (Man Jing Zi in traditional Chinese medicine), afforded the vitextrifloxides and the unusual 2-cyanopyrrole, vitepyrroloid A (5). Other labdane glycosides which have been isolated include the ent-labdane glucosides microtropiosides G-I from *Microtropis japonica* (Celestraceae) and phocantosides A and B from *Pholidota cantonensis*. Labdanes have also been obtained from the conifers *Araucaria bidwillii*, *Pinus kwangtungensis*, and *Pinus thunbergii* as well as from a Tahitian *Jungermannia* species of liverwort.

The availability of (−)-sclareol has continued to make it an attractive starting material for synthesis and it has been used in a formal synthesis of (+)-subersic acid. The total synthesis of natural fregenedadiol from chiral pool precursors has been reported.
3.2 Halimanes and clerodanes

Further studies on *Croton crassi folius* (Euphorbiaceae), the roots of which have been widely used in folk medicine in China and Thailand, have yielded halimanes including the crassifolins A-C\(^3\) which showed activity against hepatocellular carcinoma, penduliflorosin\(^4\) and the crassins A-H including the unusual cyclization product crassin D (6).\(^1\)

Interest in the neoclerodane \(\kappa\)-opioid receptor agonist salvinorin A and its potential therapeutic role, has continued.\(^2\),\(^3\) An analogue in which the 2-acetate had been replaced by a spirobutyrolactone, was a powerful \(\kappa\)-opioid agonist with enhanced stability.\(^4\)
Structural simplification with synthetic analogues has been examined.\(^5\) Other relatives derived from columbin have been prepared.\(^6\) The synthesis of 20-nor-salvinorin A has been described.\(^7\) The screening and genetic characterization of 40 *Salvia* species for the potential production of salvinorin A has been investigated.\(^8\) Enzymatic aspects of the early stages in its biosynthesis have been examined.\(^9\),\(^10\) Other medicinal properties of *Salvia* species include those of antibacterial and hypoglycemic activity. Investigation of the Mexican species *Salvia chamaedryoides*\(^11\) and *Salvia circinata* (syn. *Salvia amarissima*),\(^12\) which is used in folk medicine to treat diabetes, has yielded 7 and amarisolide which inhibit \(\alpha\)-glucosidases. The tiliifolins A-E obtained\(^13\) from *Salvia tiliifolia* exhibit neurotrophic activity and include some unusual structures (e.g. A, 8) in which ring B has been modified. The anti-feedant activity of the neo-clerodanes from *Scutellaria altissima* against the Colorado potato beetle larvae has been investigated.\(^14\) The scutebatas U-W\(^15\) and scubatines A-F\(^16\) have been obtained from further studies of *Scutellaria barbata*. Some of the scutellapenes A-F (e.g. A, 9) isolated\(^17\) from *Scutellaria formosana* inhibit LPS-induced NO production.

Amongst other neo-clerodanes which have been isolated from the Lamiaceae are the fatimanols A-E and fatimanone from *Teucrium yemense*\(^18\) and the A-noraldehyde, 16-hydroxypentandralactone (10) from *Vitex cofassus*.\(^19\) Crolaevinoid G (11) from *Croton*
laevigatus (Euphorbiaceae) has an unusual cyclopropane ring which may be formed by a C-8 carbanion displacing an 11,12-epoxide.\textsuperscript{60} ent-15-Norcleroda-3,12-diene has been identified in a Dominican amber.\textsuperscript{61} Polystachyne G which was isolated\textsuperscript{62} along with a C-15 epimer from Salvia polystachya was assigned the cis A/B configuration which is less-common amongst the constituents of Salvia species. Other cis-clerodanes which have been isolated include forsythidin A from the fruits of Forsythia suspensa (Oleaceae),\textsuperscript{63} the corymbulosins D-H from the bark of Laetia corymbulosa (Salicaceae),\textsuperscript{64} borapetoside E from Tinospora crispa (Menispermaceae),\textsuperscript{65} tinosinenosides A-C from the stems of Tinospora sinensis\textsuperscript{66} and the dimeric cis-clerodane glycosides, bistinospinosides A and B, from the roots of Tinospora sagittata.\textsuperscript{67}

4 Tricyclic diterpenoids

4.1 Abietanes

The podocarpane, commiphorane F (12), has been isolated\textsuperscript{68} from commiphora resin (Commiphora myrrha, Burseraceae). A study of the constituents of Jatropha multifida, in the context of their thioredoxin reductase activity, led\textsuperscript{69} to the isolation of jatromulone A. The 17-norabietane nagiol A (13) has been isolated from Podocarpus nagi (Podocarpaceae).\textsuperscript{70} Further studies on Podocarpus nagi include investigations into the cytotoxic activity of the nagilactones (e.g. 2-oxonagilactone A, 14) in which ring C has been cleaved.\textsuperscript{71} The anti-inflammatory action of abietane constituents (e.g. 16-hydroxylambertic acid, 15) from Podocarpus nagi has been examined.\textsuperscript{72} More abietanes have been found in other Abies species including from branches and leaves from Abies faxoniana\textsuperscript{73} and cones from Abies numidica.\textsuperscript{74} More highly oxidized abietanes in which ring C has been modified have been isolated from members of the Lamiaceae and their biological activity has been assessed. These include sageone (16) from Salvia apiana\textsuperscript{75} and the icetexane ballotiquinone (17), with a
seven-membered ring B, which was isolated\textsuperscript{76} from the aerial parts of Mexican \textit{Salvia ballotiflora}. Further examination of the roots of \textit{Salvia miltiorrhiza} (Danshen) afforded the salmiltiorins A-F (e.g. A, \textsuperscript{18}) and a number of acetone condensation products (e.g. \textsuperscript{19}).\textsuperscript{77} It is worth noting that acetone was used in the chromatographic purification. A number of \textit{ortho}-benzoquinones such as \textsuperscript{20}, which may be related, were also isolated. Oxazole-containing diterpenoids, such as salvianan A (\textsuperscript{21}) were obtained from cell cultures of \textit{Salvia miltiorrhiza} and shown to be inhibitors of HIV transcriptase.\textsuperscript{78} The anhydride ganxincastanate A (\textsuperscript{22}) was obtained from \textit{Salvia przewalskii}.\textsuperscript{79,80} The ring C cleavage product, salprzelactone which was also obtained from this plant, has now been synthesized.\textsuperscript{81} The plebeins C-F, plebein C of which contains an unusual \textit{lα},11-ether, were obtained\textsuperscript{82} from \textit{Salvia plebeian} whilst prattinin A was obtained\textsuperscript{83} from \textit{Salvia prattii}. Ring A has been cleaved in the cytotoxic compound, sahandinone (\textsuperscript{23}), from \textit{Salvia rhytidea}.\textsuperscript{84} Further \textit{para}-benzoquinones related to royleanone have been found\textsuperscript{85} in \textit{Plectranthus punctatus} and displayed antimicrobial properties. The sideritins A and B were isolated\textsuperscript{86} from \textit{Sideritis montana}. Sideritin B (\textsuperscript{24}) has a 9,13-epidioxide and these epidioxides, which could be formed from the corresponding homoannular abietadienes, may act as the progenitors of further oxidation and rearrangement products amongst this series of diterpenoids. Root cultures of \textit{Nepeta teydea} afforded\textsuperscript{87} some abietanes including teydeadione (\textsuperscript{25}) with insect anti-feeding activity.

A large number of \textit{ent}-kauranoid diterpenoids have been isolated from \textit{Isodon} (Lamiaceae) species. A common oxygenation pattern of these includes carbonyl groups at C-7 and C-15. A retro-Claisen reaction particularly with neighbouring group participation from a hydroxyl group at C-14, can result in the cleavage of ring D and the formation of an \textit{ent}-abietane. This has recently been exemplified\textsuperscript{88} by the isolation of serrin K (\textsuperscript{26}) from \textit{Isodon serra}.

The thunder-god vine \textit{Tripterygium wilfordii} (Celastraceae) has been widely used in traditional Chinese medicine and is the source of the abietane triepoxide triptolide (\textsuperscript{27}), a derivative of which, minnelide, is in phase II clinical trials for the treatment of pancreatic cancer. The tripterycosides A-C are related abietane glycosides which have been
obtained from the roots of this plant. Root cultures have been developed from *Tripterygium regelii* for the sustainable biosynthesis of triptolide. The genes that code for some steps in the biosynthesis have been identified and a biosynthetic pathway involving known metabolites has been proposed. 90,91

Further abietanes have been obtained from a Chinese 'plum-yew' *Cephalotaxus lanceolata* and from the bark of the Japanese cedar (sugi) *Cryptomeria japonica* (Cupressaceae). 93,94 These include new C35 'sesquiterpenoids' in which the diterpenoid ferruginol is linked at C-7 with a sesquiterpene such as cadinol or cryptomeridiol. Two dimeric abietane diterpenoids, the taxodikaloids A and B which were isolated from *Taxodium ascendens* (Cupressaceae), are linked through an oxazoline ring which is also attached to ring B.

Eupractenoid A (28) from *Euphorbia ebracteolata*, is a heterodimeric diterpenoid comprising an abietane lactone and a rosane unit. 97 Further examination of another member of the Euphorbiaceae, *Euphorbia fischeriana*, which has been used in traditional Chinese medicine as 'Lang-du' to treat tuberculosis and various cancers, has yielded a novel ent-abietan 11α,17-dihydroxyhelioscopolinide E and some further ent-abietanes known as the fischeriaabietanes A–E. 99 The crotonlaevigatones A–G (e.g. A, 29) are cytotoxic abietanes which have been obtained from twigs and leaves of *Croton laevigatus* (Euphorbiaceae). Evaluation of the roots of *Trigonostemon reidioides* (Euphorbiaceae) for their anti-mycobacterial activity afforded the trigonoreidons A–E (e.g. A, 30) in which ring B has undergone ring-expansion to form a seven-membered ring.

The roscotanes A–D and roscoranes A–D are a group of abietanes and pimaranes which have been isolated from *Kaempferia roscoeana* (Zingiberaceae), a plant which is used in Thai cuisine as a spice. The nepetaefolins A–J which were isolated from *Caryopteris nepetaefolia* (Verbenaceae) include nepetaefolin A (31) which was elucidated as 11β-hydroxy-14-oxochinanol-19-oic acid. This was accompanied by epimeric 9,13-epidioxyabiet-8(14)-enes (e.g. nepetaefolin B, 32). Their rearrangement via a spiranic intermediate may afford the chinane skeleton.
Kwangpene A (33) from Callicarpa kwangtungensis (Verbenaceae) has been assigned a rare 9,10-seco-abietane structure. This was also accompanied by a 9,13-epidioxide, the fission of which could afford the 9,10-ether. Further abietanes, callicapoic acids M3, M4 and M5, have been isolated from Callicarpa macrophylla.

The synthesis of aromatic podocarpanes and tanshinones together with the modification of ring A of the tanshinones by substitution at C-1 and of ring C by the Diels-Alder cycloaddition of alkynes to 13,14-ortho-quinones followed by photodecarbonylation, has been described. The availability of dehydroabietic acid and of some tanshinones has also provided useful starting materials for biological activity studies. These have included the preparation of dehydroabietic acid-based arylhydrazones as potential anti-cancer agents, dehydroabietylamine derivatives as acetylcholinesterase inhibitors, tanshinone metal chelates as butyrylcholinesterase inhibitors, and abietane derivatives as anti-bacterial, anti-protozoal and anti-cancer agents.

### 4.2 Pimaranes, cassanes and related diterpenoids

Biosynthetic studies on phytoalexins involving ent-cassadiene and syn-pimaradiene precursors have been reported. The callicarpes M1-M3 (e.g. M1, 34) from Callicarpa macrophylla have been shown to exert their anti-inflammatory activity through the inhibition of NO production. The absolute stereochemistry of callicarpene M3 has been established by experimental and theoretical electronic circular dichroism and vibrational circular dichroism. The fungus Aspergillus candidus is a source of sphaeropsidin A in sufficient quantity to enable analogues to be prepared to assess their anti-cancer activity. The botrysin A-F metabolites of the fungus Botrysphaeria laricina include 3β,14α-dihydroxyisopimara-8,15-dien-1-one, botrysin A (35). In continuation of previous work on Boesenbergia pandurata (Zingiberaceae), the boesenberols I-K have been shown to overcome resistance to some anti-cancer agents. The lyonivalosides are a group of isopimarane glycosides which have been isolated from the twigs and leaves of Lyonia ovalifolia (Ericaceae).

Work has continued on Siegesbeckia pubescens (Asteraceae) which is used in traditional
Chinese medicine for the treatment of arthritis. This has led to the isolation\textsuperscript{127} of the strobols A and B (e.g. strobol A, \textbf{36}) in which the seven-membered ring C may arise by migration of the C(13):C(14) bond to C(15), together with the siegesides A-E which are \textit{ent}-pimarane glycosides.\textsuperscript{128} Other isopimarane rearrangement products which have been isolated include euonymusisopimaric acid A (\textbf{37}) from the stems of \textit{Euonymus oblongifolius} (Celastraceae),\textsuperscript{129} and libertellenone L (\textbf{38}) which was amongst the metabolites of the lichen-associated fungus \textit{Apiospora montagnei}.\textsuperscript{130} The latter may arise by cleavage of ring B and rotation about the C(9):C(10) bond. Euphominoid A (\textbf{39}), which was one of thirteen \textit{ent}-rosanes isolated\textsuperscript{131} from \textit{Euphorbia milii} (Euphorbiaceae), inhibited the growth of the Epstein-Barr virus. Rosololactone isolated from the endophytic fungus \textit{Trichothecium roseum} has been shown\textsuperscript{132} to induce apoptosis in human cervical cancer. The tagalenes G-I are further dolabrane diterpenes that have been isolated\textsuperscript{133} from the Chinese mangrove plant, \textit{Ceriops tagal} (Rhizophoraceae), which is used in the treatment of malaria.

Cassane diterpenoids are often found in the Leguminosae. Further examples include the erythrofordins T and U and the erythroformines A and B which are 16-\textit{N}-methylethanolamine relatives that were isolated from the bark of \textit{Erythrophleum fordii},\textsuperscript{134} the furanocassane sucupiranins A-L from the seeds of \textit{Bowdichia virgilioides},\textsuperscript{135} the caesmimosins A-F from \textit{Caesalpinia mimosoides},\textsuperscript{136} and the caesalsappans G-I from \textit{Caesalpinia sappan}.\textsuperscript{137} A number of these compounds are the ethoxy or methoxy ethers of lactols and the possibility of artefact formation should be considered when ethanol or methanol have been used in the extraction.

Caesalsappanin R (\textbf{40}) from \textit{Caesalpinia sappan} possessed an unusual C(9),C(20) nitrogen bridge.\textsuperscript{138} Lactone formation in the photo-oxidation of the furan ring of 6\textbeta-acetoxyvouacapane has been examined.\textsuperscript{139} The cleavage of ring A of a cleistanthane has been encountered in the constituents of \textit{Trigonostemon howii} which were examined\textsuperscript{40} for their NO inhibitory activity. The unusual structure which was assigned to the phyllanes A and B (e.g. A, \textbf{41}) isolated from the roots of \textit{Phyllanthus acidus} may arise by further cyclization of a rearranged cleistanthane in which ring A has been cleaved.\textsuperscript{141}
5 Tetracyclic diterpenoids

The chemistry and biological activity of the ent-kaurene diterpenoids has been reviewed. The zinc complexes of ent-kaur-16-en-19-oic acid and the corresponding beyerenoic acid have been characterized and the application of ent-kaur-16-en-19-oic acid in controlling the anthracnose disease of bean plants has been reported. Interest has continued in the use of Stevia glycosides as sweeteners with the identification of rebaudiosides T and U from Stevia rebaudiana and the development of enzymatic methods to determine stevioside content. The anti-diabetic properties of cafestol from coffee have been examined. The tumour-inhibitory properties of the acetonide of ent-kaur-2-one-16β,17-diol, obtained from the leaves of the Chinese raspberry Rubus corchorifolius, and of ent-3-oxokaurane-16β,17-diol, from the traditional Chinese medicine Euphorbia fischeriana, have been reported. Further ent-kaurenes have been obtained from Euphorbia stracheyi Boiss. Whilst the decoxenes A-F which were isolated from Gochnatia decoras (Asteraceae) exert their anti-inflammatory activity by the inhibition of NO production, the leontopics which are glycosides of 13-hydroxyatractyligenin obtained from Leontopodium leontopodioides (Asteraceae), appear to act by inhibiting cyclooxygenase. ent-Kaurenes are very common constituents of the Asteraceae and further examples have been obtained from Ligularia fischeri, Mikania micrantha, Siegesbeckia pubescens, Wedelia chinensis, and Wedelia prostrata. Mannic acid from Diospyros mannii (Ebenaceae) is an ent-kaurene dimer related to xylopic acid whilst other ent-kaurenes and their glycosides have been obtained from Pteris ensiformis and Pteris multifida. The genus Isodon (Lamiaceae) is widespread in Asia and a number of its members are important biologically-active components of traditional Chinese medicines. Over 1200 mostly ent-kaurenoind and their ring B cleaved products, have been isolated from these herbs and a thorough up-date review covering their isolation, biological activity and synthesis over the period 2005–2016 has appeared. Recent reports of novel
Diterpenoids include constituents of *Isodon japonicus*, *Isodon phyllostachys*, *Isodon rubescens*, and *Isodon scoparius*. Many of these compounds containing a 15-oxo-16-ene moiety exhibit tumour-inhibitory activity and their chemistry has been investigated in this context. Their structural complexity has presented a synthetic challenge with syntheses of lungshengenin D, pharicin A and pseurata C being reported.

Diterpenoids with a 5:7:6:5 grayane carbon skeleton which is derived from *ent*-kaurene, are typical biologically-active constituents of *Rhododendron* and *Pieris* (Ericaceae) species. A further example, 42, with a 9(11)-ene has been isolated from *Rhododendron brachycarpum*. Examination of *Rhododendron molle* has afforded some compounds with a modification of this carbon skeleton including rhodomollanol A (43) and the rhodomollacetals A-C (e.g. A, 44) which are 2,3:5,6-di-seco-grayananes. The dimeric grayananes birhodomolleins A-C were also obtained from the flowers of this member of the Ericaceae family. The seco-grayananes from *Pieris japonica* and *Pieris formosa* have insecticidal activity. These include a 3,4-seco-grayanane pieristoxinlactone A (45) and pierisketolide A (46). The latter may arise by rearrangement of an *ent*-kaurene 5,6-epoxide.

The mechanism of action of the gibberellin plant growth hormones and the development of biosynthetically-patterned plant growth regulators based on the ring-contraction step in gibberellin biosynthesis, have been reviewed. Further studies on the effect of GA-13315 (methyl 13-chloro-3,15-dioxogibberellate) on the proliferation and apoptosis of cancers have been reported. The biotransformation of *ent*-15α-hydroxy-16-kauren-19-oic acid by *Fusarium proliferatum* has provided a new allelopathic agent.

Routes for the synthesis of the atisane carbon skeleton have been reviewed. A novel enantio- and stereoselective route to the atisane carbon skeleton has been developed. An *ent*-atisane 16,17-acetonide has been reported as a novel constituent of *Euphorbia wallichii* although acetone was used in the extraction. Aromaticane I (47), an atisane which was isolated from *Curcuma aromatica* and aleuritopsis A, a beyerene from
*Aleuritopteris argentea* have been assigned the unusual steroid-like A/B configuration rather than the much more common ent-configuration. Inflatin G (48) is a further aphidicin derivative which was isolated\(^\text{190}\) from the fungus, *Tolypocladium inflatum*.

6 Macrocyclic diterpenoids and their cyclization products

Examination of the leaves and twigs of *Macaranga deheiculata* (Euphorbiaceae) has afforded\(^\text{191}\) a series of C-20 oxygenated cembranoids named the deheiculatins A–L (e.g. A, 49). Launine O is a cembranoid which was isolated\(^\text{192}\) from *Croton laui* (Euphorbiaceae). The production of taxol by microbiological methods has continued with investigations\(^\text{193}\) into its formation in a strain of *Aspergillus niger*. Examination of different cultivars of the Himalayan yew, *Taxus wallichiana*, has yielded\(^\text{194-196}\) further taxanes including taxiwallinine\(^\text{196}\) and the wallitaxanes A–H,\(^\text{194,195}\) some of which showed α-glucosidase inhibitory activity.

Investigations into the constituents of the Euphorbiaceae and Thymelaceae has continued to yield novel jatrophanes, lathyranes, tiglianes and ingenanes and their structural relatives. Studies of *Euphorbia helioscopia* afforded the euphoscopoids A–C\(^\text{197}\) and the heliosterpenoids A and B (e.g. A, 50)\(^\text{198}\) which possess a novel 5:6:4:6 ring system. This may be derived by cyclization of a jatrophane in which the four-membered ring was formed by a 2+2 cyodoaddition. Gaditanone (51) is a similar compound, in which the carbon skeleton was named gaditanane, and was obtained\(^\text{199}\) from *Euphorbia gadinata*. The relationship to jatrophanes was established by a chemical correlation. Other jatrophanes were obtained\(^\text{200}\) from *Euphorbia semiperfoliata* whilst some premyrisinanes, myrsinanes and tiglianes, some of which showed activity against the Chikungunya virus, were isolated\(^\text{201}\) from *Euphorbia pithyusa*. Further pepluanes have been isolated\(^\text{202}\) from the invasive species *Euphorbia peplus* where they were found in latex which is exuded by specialized lacticifer cells that have a defensive role. Euphoractine relatives have been isolated\(^\text{203}\) from *Euphorbia soongarica* whilst some tiglianes in which ring B has been cleaved (e.g. euphordraculoate A, 52) were obtained from *Euphorbia dracunculoides*\(^\text{204}\) and *Jatropha dioica*.\(^\text{205}\) Examination of the Kenyan folk medicine, *Croton dichogamus*...
gave\textsuperscript{206} crotodichogamoins A and B which have a crotolane skeleton (e.g. A, \textsuperscript{53}). More phorbol esters have been isolated from Croton tiglium\textsuperscript{207} and Aquilaria malaccensis.\textsuperscript{208} Further investigations of the daphnanes from Trigonostemon chinensis and Trigonostemon thyroides have been reported.\textsuperscript{209,210} The absolute configuration of the jatropholones from Jatropha dioica has been established.\textsuperscript{211} The potential of jolkinol D derivatives to overcome multi-drug resistance in cancer has been explored.\textsuperscript{212} Syntheses of resiniferatoxin\textsuperscript{213} and pepluanol A\textsuperscript{214} have been reported as well as a convenient method for 20-[\textsuperscript{18}O]-labelling ingenol.\textsuperscript{215}

7 Miscellaneous diterpenoids

Studies on the genetics of cyathane biosynthesis in the fungus Hericium erinaceum have led\textsuperscript{216} to the discovery of the genes that code for a new family of diterpene cyclases. The damasterpenes I-IV (e.g. damasterpene I, \textsuperscript{54}) were obtained\textsuperscript{217} from the seeds of Nigella damascena (Ranunculaceae) which are used as a spice. The fusicoccane skeleton has been assigned\textsuperscript{218} to a metabolite 14-hydroxycyclooctatrin (\textsuperscript{55}) of Streptomyces violascens. Further cephalotanes which have been isolated\textsuperscript{219} include 20-oxohainanolidol (\textsuperscript{56}) from Cephalotaxus fortunei and the cephanolides A-J from Cephalotaxus sinensis.\textsuperscript{220} The vulgarisins (e.g. B, \textsuperscript{57}) which were obtained\textsuperscript{221} from Prunella vulgaris (Lamiaceae) have an unusual 5:6:4:5 carbon skeleton.

Harzianone biosynthesis using labelled mevalonates has been investigated\textsuperscript{222} in Trichoderma species and its microbial oxidation by a Bacillus species has been examined.\textsuperscript{223,224} Isoryanodane structures have been assigned to perseaindicol (\textsuperscript{58}) and secoperseanol which were obtained\textsuperscript{225} from Persea indica (Lauraceae) and the structure of cinnacassiol E has been revised. A related cage structure has been proposed\textsuperscript{226} for the cinnamomols from the traditional Chinese medicine, Cinnamomum cassia. A series of amides with moderate anti-malarial activity has been synthesized from 3,7,8-trihydroxyserrulat-14-en-19-oic acid\textsuperscript{227} whilst serrulat-14-ene-7,8,18-triol has been identified\textsuperscript{228} in an Australian bees' wax.
8 References


2017, **117**, 147-153.


2017, 58, 1822-1825.


134 M. T. Ha, M. H. Tran, T. T. Phuong, J. A. Kim, M. H. Woo, J. S. Choi, S. Lee, J.


159 H. M. F. Feusso, C. M. Akak, M. F. Tala, A. G. B. Azebaze, J. C. Vardamides and H.


**Figures**

![Aphapolin A (1)](aphapolinA.png)

![Sauruchinenol A (3)](sauruchinenolA.png)
galangalditerpene A (4)

vitepyrroloid A (5)

crassin D (6)

tiliifolin A (8)
scutellapene A (9)

16-hydroxypentandralactone (10)

crolaevinoid G (11)

commiphorane F (12)
nagiol A (13)

2-oxonagilactone A (14)
16-hydroxylambertic acid (15)

sageone (16)

ballotiquinone (17)

salmiltiorin A (18)

19

20

salvianan A (21)
botryosphin A (35)

strobol A (36)

euonymus isopimaric acid A (37)

libertettenone L (38)

euphominoid A (39)

caesalsappanin R (40)

phyllane A (41)
rhodomollanol A (43)

rhodomollacetal A (44)

pieristoxinlactone A (45)

pierisketolide A (46)

aromaticane I (47)

inflatin G (48)
deheiculatin A (49)

heliosterpenoid (50)

gadilanone (51)
euphordraculoate A (52)
crotodichogamoin A (53)
damasterpene I (54)
55

20-oxohainanolidol (56)

vulgarisin B (57)

perseaindicol (58)