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Diterpenoids of terrestrial origin

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Covering January to December 2015. Previous review; *Nat. Prod. Rep.*, 2015, 32, 1654–1663.
This review covers the isolation and chemistry of diterpenoids from terrestrial as opposed to marine sources and includes labdanes, clerodanes, abietanes, pimaranes, kauranes, cembranes and their cyclization products. There are 214 references.

1 Introduction

This report covering the period January to December, 2015, follows the pattern of its predecessors[1,2] and includes the identification and chemistry of diterpenoids of terrestrial as opposed to marine origin. The latter are covered in the articles on marine natural products.[3] Traditional Chinese medicines have continued to be a treasure trove of novel diterpenoids. Many of these warrant a further examination of their structure–biological activity relationships in order to identify the pharmacophores. There are a number of diterpenoids that are sufficiently abundant to provide suitable starting materials for partial synthesis. Several studies in this context have been reported during the year including work on the abietane diterpenoids. This has been reviewed.[4,5]

Advances in the synthesis of multi-functionalized decalins,[6] the bicyclo[3,2,1]-octane system of the *ent*-kauranoids,[7,8] the atisane diterpenoids,[9] the neodolastanes,[10] the pseudopterosin aglycones,[11] and vinigrol,[12] together with the use of dehydrogenation to access diterpenoid degradation products that are found in the environment,[13] have all been reviewed. Other articles on the diterpenoid composition of *Pinus sibirica*[14] and various aspects of the diterpene biosynthetic synthases including their genetics, have appeared.[15,16] Genetic studies have led to the identification of diterpene gene clusters[17] and of silent pathways that can be activated to produce diterpenoids.[18]

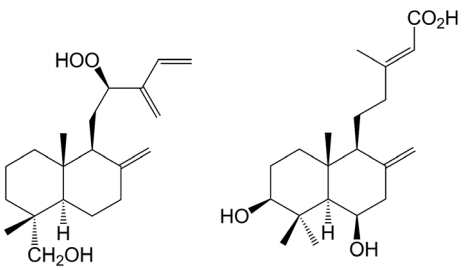
2 Acyclic and related diterpenoids

The syntheses of C-8, C-9 and C-10 deuteriated geranylgeraniols have been reported.[19]

3 Bicyclic diterpenoids

3.1 Labdanes

Labdanolic acids have been identified as biomarkers for the botanical origin of French ambers[20] whilst copalic acid and its relatives have been associated[21] with the biological activity of the resins from *Copaifera* species. The lanceolatanols, including some rare hydroperoxides such as the 12-hydroperoxide **1**, have been isolated[22] from the Chinese fir, *Cunninghamia lanceolata* (Cupressaceae) which is grown in plantations for timber production. The lanceolatins A–G (*e.g.* A, **2**) are a group of labdanes and abietanes which were obtained[23] from *Cephalotaxus lanceolata* (Cephalotaxaceae). Some of the abietanes described in this paper were formulated without comment, as a dienone tautomer of a phenol.



1 2

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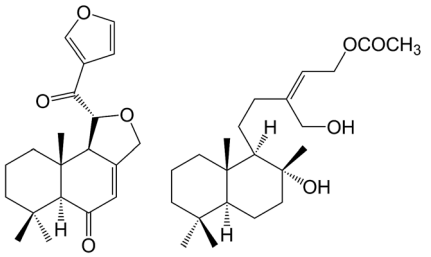
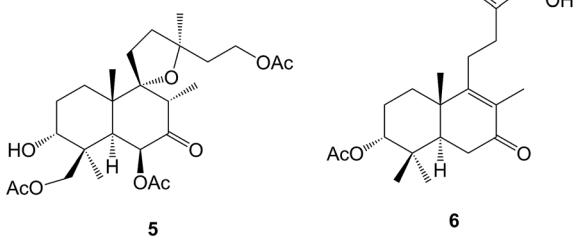
A number of the labdanes which have been found in members of the Zingiberaceae, *e.g. Alpinia japonica*,[24] *Curcuma longa*[25] and *Hedychium longipetalum*[26] such as the hedylongnoids A–C (*e.g.* A, **3**), inhibit the production of nitric oxide. The paraguhenryisins A–D (*e.g.* C, **4**) which were isolated[27] from the capitate glandula trichomes of *Paragutzlaffi henryi* (Acanthaceae), have phytotoxic properties and may provide a defensive measure against other invasive plants. The absolute configuration at C-14 of the labdanes from *Physalis nicandroides* (Solanaceae) has been established.[28]



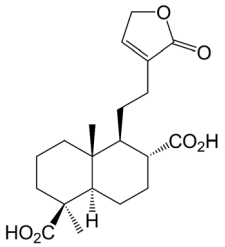
3 **4**

Labdane glycosides have been reported[29] as constituents of *Diplopterygium rufopilosum* (Gleicheniaceae) whilst examination of the seeds and leaves of *Colophospermum mopane* [Fabaceae (Leguminosae)][30] and *Leonotis leonurus* (Lamiaceae)[31] has yielded some further labdanes and clerodanes. Continued examination of *Leonurus japonicus* gave leojaponin D[32] whilst the macranthins (*e.g.* A, **5**) were anti-inflammatory labdanes which were obtained[33] from *L. macranthus*. Further studies on white horehound (*Marrubium vulgare*, Lamiaceae) afforded[34] 12(*S*)-hydroxymarrubiin. The structure **6** has been assigned[35] to cinereanoid A which was isolated from *Roylea cinerea* (Lamiaceae) whilst the vitexolides A–E were similar anti-bacterial γ-hydroxy-αβ-unsaturated 15→16-lactones which were obtained[36] from *Vitex vestita* (Lamiaceae).



5 **6**

Isodon species (Lamiaceae) are renowned for the tetracyclic diterpenoid constituents of their leaves. However examination of the roots of *I. adenantha* afforded[37] the labdanes, adenanthic acids A and B (*e.g.* A, **7**) and the adenanthosides A–C whilst two other labdanes were obtained[38] from *I. yuennanensis*.



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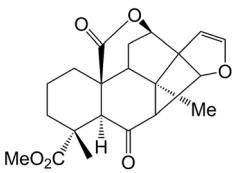
A large number of labdanes have been detected in Chinese liverworts including the haplomintrins (*e.g.* A, **8**) from *Haplomitrium minioides*[39] in which a cyclobutane ring has been formed by the possible photochemical addition of a side-chain furan across the double bond of a 7,8-en-6-one. Other examples of labdanes which have been isolated include the ptychantins P and R from *Ptychanthus striatus*[40] and the scapairrins A–Q from *Scapania irrigua*.[41]



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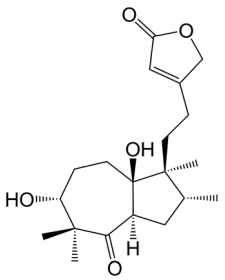
Various methods for the recovery of useful compounds from *Stevia rebaudiana* (Asteraceae) have been reviewed.[42] The fermentation of *S. rebaudiana* with the yeast *Saccharomyces cerevisiae* has led[43] to the formation of some modified sterebins arising from the selective epoxidation and hydration of the 14,15-double bond. Examination of the Taiwanese shrub, *Callicarpa randaiensis* (Verbenaceae) in the search for anti-inflammatory agents afforded[44] the randainins A–D. As an alternative to the biosynthesis suggested in the original paper, their structures (*e.g.* A, **9**) may arise by the oxidative cleavage of a 5,10-double bond of a halimane followed by aldol condensations of the 5,10-diketone to form the *trans* 7/5 and 5/7 ring systems of these diterpenoids.



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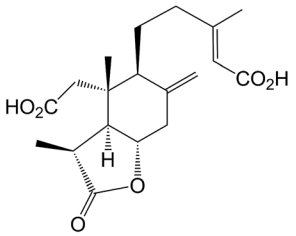
The cleavage of ring A has been encountered in a number of diterpenoids including labdanes. A 3-nor-2,3-secolabdane structure **10** has been assigned[45] to penioxalicin which was obtained from the fungus, *Penicillium oxalicum* and to paecilomycine A from an insect pathogenic fungus, *Paecilomyces* sp.[46] Further examination[47] of the stems of the highly poisonous mangrove plant, *Excoecaria agallocha* (Euphorbiaceae) gave

excolide **11** in a study which also led to a revision of the structure of rhizophorin A. The structure of the spiro-ketal, leonuketal **12** obtained[48] from *Leonurus japonicus*, may be derived by a retro-Prins cleavage of the 8 : 9-bond in a 7,9-dihydroxylabdane followed by a cyclization involving the 3-hydroxyl group, the 9-ketone and C-15.



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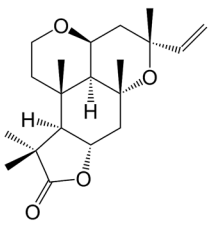

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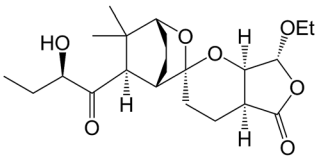

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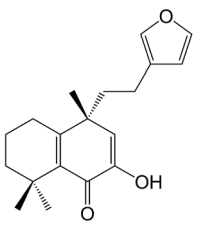
Derivatives of the readily available labdanes such as polyalthic acid[49] and copalic acid[50] have been evaluated for the treatment of various diseases. The merosesquiterpenes, neopterosiquinones A and B have been synthesized[51] from *trans*-communic acid. The anti-fungal activity of sclareol[52] and some derivatives[53] has been examined. Sclareol has been used[54] as the starting material for the synthesis of the sesterterpenes, luffarin L and 16-epiluffarin and for a biomimetic synthesis of two salmahyrtisanes.[55] Work has continued[56–58] to prepare derivatives of andrographolide in order to study structure–biological activity relationships. The enzyme systems responsible for the biosynthesis of 13(*R*)-manoyl oxide have been transferred[59] from Sitka spruce to a cyanobacterium, *Synechocystis* sp.

3.2 Halimanes and clerodanes

18-Hydroxy-*ent*-halima-1(10),13(*E*)-dien-15-oic acid has been isolated[60] from *Hymenaea stigonocarpa* (Fabaceae) whilst investigations of the anti-microbial activity of *Vellozia kolbekii* (Velloziaceae) afforded[61] 15,16-dihydroxy-*ent*-halima-1(10)-ene. The halimane structure **13** has been assigned[62] to isoleojaponin from *Leonurus japonicus*.



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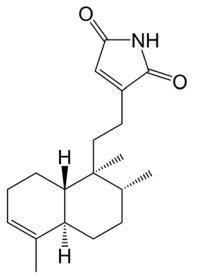
The clerodane pyrrole **14** was amongst[63] the anti-plasmodial constituents of *Polyalthia longifolia* var[n].*pendula* (Annonaceae), the bark of which is used in West African folk medicine for the treatment of malaria. 2β-Acetoxyhardwickiic acid and a number of other clerodanes were anti-bacterial constituents of *Salvia adenophora* (Lamiaceae)[64] and *S. buchananii.*[65] Further structural modifications of salvinorin have been made[66] including some 2-alkyl-2-methoxymethyl ethers in order to examine its structure–activity relationships as a selective κ-opioid receptor agonist. *ent*-2β,18,19-Trihydroxycleroda-3,13-dien-15,16-olide has been obtained[67] from *Crassocephalum bauchiense* (Asteraceae) which is a herb that is used in Cameroon folk medicine. The dichrocephnoids A–E (*e.g.* A, **15**) which possess anti-HIV integrase activity, were isolated[68] from *Dichrocephala benthamii* (Asteraceae). Further examination of the Chinese medicinal herb, *Scutellaria barbata* (Lamiaceae) has led to the isolation of



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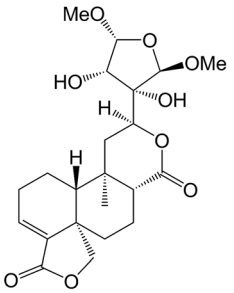

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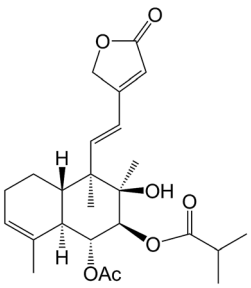

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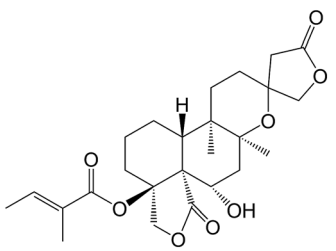

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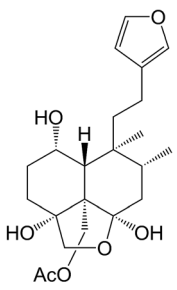

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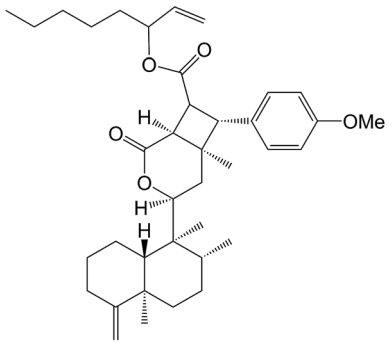

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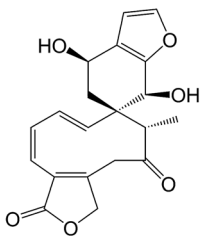

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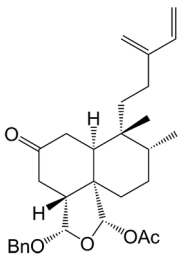
the anti-viral scutolides A–L (*e.g.* A, **16**)[69] and the scutebatins A–C[70] which inhibit NO production. The scutefolides (*e.g.* A, **17**) were obtained[71] from *S. coleifolia* whilst the teufruintins A–G (*e.g.* A, **18**) were obtained[72] from the aerial parts of the herb, *Teucrium fruticans* (Lamiaceae) which had been cultivated in China. Examination of *Isodon scoparius* (Lamiaceae) afforded[73] the scopariusicides A **19** and B which were unusual cyclobutane derivatives which were formed by the cycloaddition of an ester of 4-hydroxycinnamic acid to the clerodane side chain. The unusual spirocyclic ring system **20** which may be derived from a clerodane, has been assigned[74] to teotihuacanin, which was obtained from the Mexican plant, *Salvia amarissima*. It has shown activity against multi-drug resistance in cancer cells.

A number of new *cis*-clerodanes have been isolated including linarenone A from *Linaria japonica* (Plantaginaceae),[75] the crotocurins A–C from *Croton europhyllus* (Euphorbiaceae)[76] and the graveopenes A–J (*e.g.* A, **21**) from *Casearia graveolens* (Flacourtiaceae).[77] The latter were shown to stimulate NGF-mediated neurite out-growth which is of interest in the context of neuron degeneration in Alzheimer's disease. The related caseagrewifolins were obtained[78] from *C. grewifolia*. Further examination of *Tinospora sagittata* (Menispermaceae) gave[79] tinosporin A and B.



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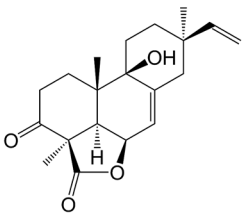
4 Tricyclic diterpenoids

4.1 Pimaranes

The arabinofuranoside of isopimara-7,15-dien-19-ol has been identified[80] amongst the anti-fungal constituents of *Sagittaria latifolia* (Alismataceae). A series of isopimaranes known as the kaempulchraols A–I have been obtained[81–83] from the rhizomes of *Kaempferia pulchra* (Zingiberaceae). Some constituents of the roots of *Oryza sativa* (rice) including momilactone D **22** have been shown[84] to inhibit the production of NO. Further studies[85–87] on the tubers of the Nigerian herbal medicine *Icacina trichantha* (Icacinaceae) have revealed the presence of more 9β-H-pimaranes and some aromatic 17-norpimaranes, the icacinlactones A–H (*e.g.* A, **23**). The xylabisboeins A and B were anti-bacterial pimarane 14,16-ethers which were isolated[88] from an endophytic *Xylaria* sp. obtained from the leaves of *Bisboeckiera microcephala*. Isopimaranes (*e.g.* **24**) were amongst[89] the anti-inflammatory constituents of *Dysoxylum gotadhora*. A group of 16-norditerpenoids have been obtained[90] from the aerial parts of *Flickingeria fimbriata* (Orchidaceae) whilst some pentahydroxypimaranes were isolated[91] from *Aerva lanata* (Amaranthaceae), a plant which is used in Ayurvedic medicine. The dienone **25** and the corresponding 11,14-α- and β-epidioxides and diols were isolated[92] from the stems of *Croton insularis* which was found in the Australian rain forest. A group of rosanes, *e.g.* stachyrosane I **26** have been reported[93–95] as constituents of *Stachys parviflora* (Lamiaceae).



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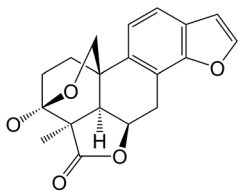

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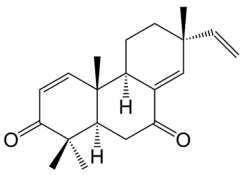

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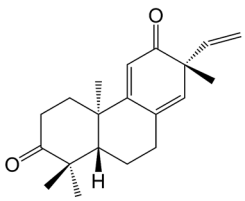

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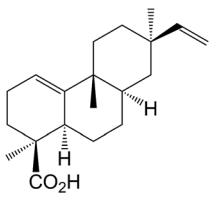

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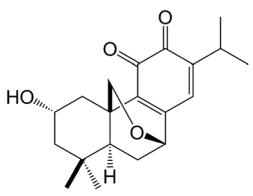
4.2 Abietanes

The intervention of quinone methides in the anti-oxidant activity of the phenolic diterpenoids ferruginol[96] and carnosic acid[97] has been described. The anti-fungal activity of some abietic acid esters in the context of their use as wood preservatives[98] and the anti-viral activity of podocarpic acid derivatives[99] have been examined. The action of a visible light LED on the *N*-chlorosulfonamide of dehydroabietylamine afforded[100] a 6α-chloro compound. Dehydroabietic acid has been shown[101] to regulate liver glucose levels which may be linked to the use of *Abies balsamea* in a folk medicine treatment for type 2 diabetes. The brevistylumsides A and B, obtained from *Illicium brevistylus* have been identified[102] as glycosides of dehydroabietic acid. The structure **27** has been assigned[103] to the *o*-quinone teuvisone which was obtained from *Teucrium viscidum*. The dimeric biteuvisones A and B arose by addition of the corresponding *o*-catechol across the 8,9-bond.



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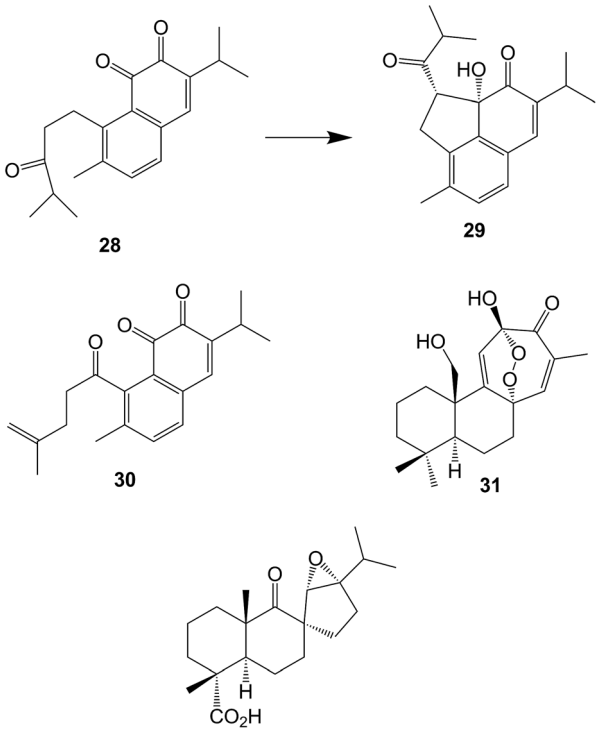
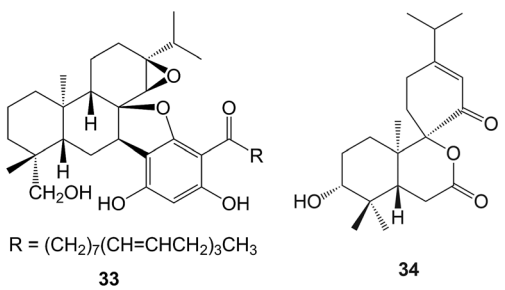
Further examples of diterpenoids in which ring A has been cleaved have been isolated from *Salvia* species. Thus salviaprione **29** was isolated[104] as a racemate from *S. prionitis*. It may be formed by the cyclization of salvisyrianone **28.** 1-Ketoethiopinone

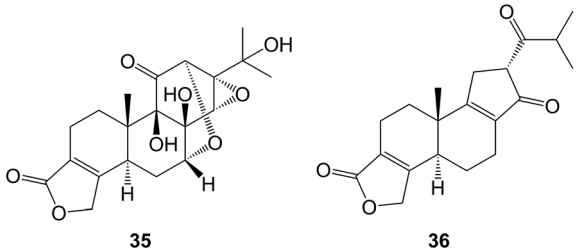
30 was obtained[105] from the roots of *S. sahendica*. The diacetate of dihydroethiopinone inhibits the growth of breast cancer cells. The roots of *S. grandifolia* yielded[106] the grandifolias A–F (*e.g.* A, **31**). These include some modified abietanes arising from the cleavage of ring C. The quinone, caryopterone A possesses a methylcyclopropane ring in place of the isopropyl group of the abietanes. It was isolated[107] from the roots of *Caryopteris mongolica* (Lamiaceae). Some of the abietanes from this plant showed[108] cholinesterase inhibitory activity. The macrophypenes A–E, obtained[109] from *Callicarpa macrophylla* (Verbenaceae) included some rearranged abietanes (*e.g.* A, **32**).



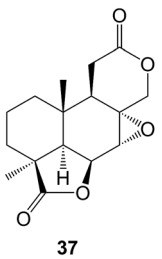
The constituents of the genus *Chloranthus* have been reviewed.[110] *ent*-Abietanes have been obtained[111] from *C. henryi* whilst the chlorabietols A–C isolated[112] from *C. oldhamii* included an unusual phloroglucinol-abietane adduct (A, **33**). Rings B and C have been cleaved in the formation of various sessilifols A–N (*e.g.* C, **34**) obtained[113] from *C. sessilifolius*.



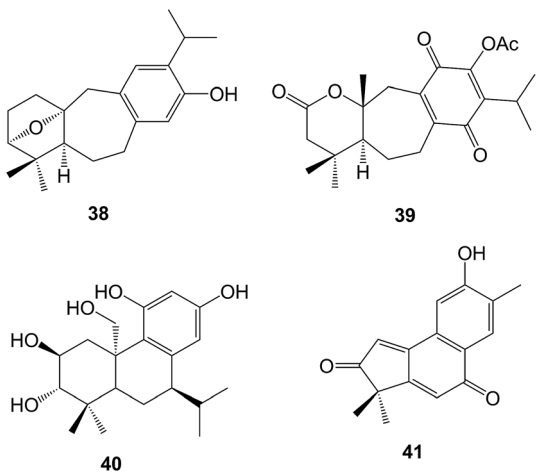
Further studies on the traditional Chinese medicine *Tripterygium wilfordii* (Celastraceae) have afforded more highly oxidized 18(4→3)-*abeo*-abietanoid derivatives including the triptergulides A and B (*e.g.* B, **35**),[114] the wilfordosides A and B,[115] and the tripterlides A–F (*e.g.* A, **36**)[116] in which ring C has also undergone rearrangement. A range of abietanes, pimaranes and kauranes have been isolated[117] from *T. hypoglaucom*.



Examination of the anti-proliferative constituents of Ethiopean *Podocarpus falcatus* led[118] to the isolation of 16-hydroxynagilactone F and a revision of the stereochemistry of 2α-hydroxynagilactone F to the 2β-epimer. The botryosphaerins G and H (*e.g.* G, **37**) which were obtained[119] from a *Botryosphaeria* endophyte of *Huperzia serrata*, have a *seco* ring C structure or they may be tetranorlabdanes.

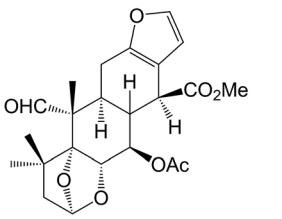


Some further icetexanes have been isolated[120] from *Perovskia atriplicifoiia* (Lamiaceae). The hispidanols A and B (*e.g.* B, **38**) were sempervirane relatives which were obtained[121] from the rhizomes of *Isodon hispida*. The roots of *Pygmacopremna herbacea* (Verbenaceae), which have been used in Ayurvedic medicine as an anti-inflammatory agent, yielded a quinone which was assigned[122] the somewhat unusual structure **39** in which ring B has been expanded but the C-20 methyl group has been retained. Another unusual structure **40** involving a curious biosynthesis, has been assigned[123] to plebeianiol A which was obtained from *Salvia plebeia*. Neoboutomannin A **41** isolated[124] from the West African *Neoboutonia macrocalyx* (Euphorbiaceae) may be a degraded abietane.



4.3 Cassanes

Cassane diterpenoids are characteristic constituents of the Caesalpiniaceae. Further examination of *Caesalpinia bonducella* has yielded[125] the bonducellpins H–P whilst *C. crista* afforded[126] the phangininoxys D and E. The echinalides H–U were obtained[127] from *C. echinata*. Many of these compounds have been shown to possess anti-inflammatory and anti-oxidative properties. The cassanes from several studies[128–130] of *C. minax* have been examined in this context. These included the caesalmins I–M[128] and a *seco* ring A compound neocaesalminin A **42**.[130] The caesalsappanins A–L (*e.g.* A, **43**) which were isolated[131] from *C. sappan*, have been studied for their anti-malarial and anti-proliferative activity. Other cassanes have been isolated from *Erythrophleum suaveolens*[132] and *Swartzia simplex*.[133] The activation by epigenetic mining of a silent biosynthetic pathway in the fungus *Calcarisporium arbuscula* led to the isolation[18] of arbusculic acid A **44**. A new phytoalexin phytocassane F **45** has been identified[134] in rice leaves that had been subjected to UV radiation.



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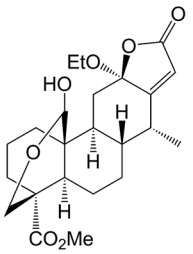

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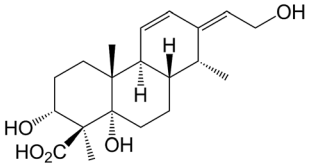

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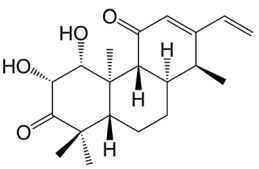

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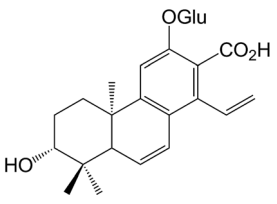
The cleistanthanes phyllanembloids A–F (*e.g.* A, **46**) have been obtained[135] from the roots of *Phyllanthus emblica* which are used in Chinese traditional medicine.



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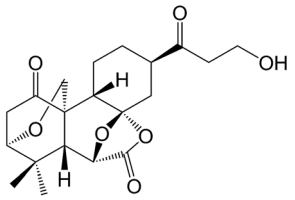
5 Tetracyclic diterpenoids

The *ent*-kauranes which have been obtained[136] from the fruits of *Annona glabra* (Annonaceae) as part of a study of their anti-inflammatory activity, include 7β,16α,17-trihydroxy-*ent*-kauran-19-oic acid. 4β,16α,17,19-Tetrahydroxy-18-nor-*ent*-kaurane has been isolated[137] from *Wedelia trilobata* (Asteraceae) whilst some *ent*-kaurenoic acid glycosides have been found[138] in *Ageratina cylindrica* (Asteraceae). It has been estimated that over a thousand diterpenoids, many of which possess interesting biological activity, have been detected in *Isodon* (Lamiaceae) species. Further examples include the neolaxiflorins I–Y[139] and the unusual laxiflorol A **47**[140] from *I. eriocalyx* var^{n}.*laxiflora*. Extraction of *I. excisoides*,[141] *I. parvifolius*[142] and *I. scoparius*[143] provided other examples. The 7,20-azakaurenes, kaurines A and B (*e.g.* A, **48**) were isolated[144] from *I. rubescens* together with a compound containing an unusual 17-succinimide moiety. Xerophilusin B has been shown[145] to induce cell cycle arrest and apoptosis in esophageal squamosus cell carcinoma. The total synthesis of maoecrystal V has been described.[146]



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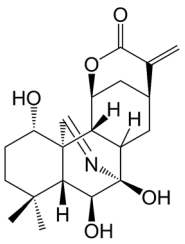

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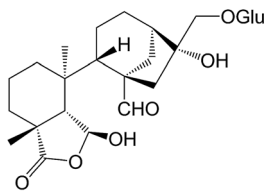
The helikaurolides A–D which were obtained from *Helianthus annuus* var^{n}.*arianna*, have been assigned[147] structures based on a combination of a sesquiterpene lactone (helivypolide L) and an *ent*-kauranoic acid.

The steviol glycosides from *Stevisa rebaudiana* have continued to attract attention particularly in the food industry. The relationship between the conformation of rebaudioside A in solution and its sweetness[148] and molecular modeling studies of the docking of rebaudioside A with the human sweet taste receptor[149] have been reported. Dereplication of the NMR profiles of mixed steviol glycosides[150] and the application of new separation techniques[151] have been described. 15α-Hydroxyrebaudioside M has been isolated[152] from *S. rebaudiana*. The ready availability of isosteviol from the acid-hydrolysis of the mixed glycosides from *S. rebaudiana* has led to its use as the starting material for a number of studies.[153–156] The X-ray crystal structure of a dimeric isosteviol sulfite has been described.[157]

The prinsosides A–C which were isolated[158] from *Prinsepia utilis* (Rosaceae) included the *seco*-ring B *ent*-kaurane (C, **49**). Two glycosides, ranunculosides A and B that were isolated[159] from *Ranunculus muricatus* (Ranunculaceae), were described as *ent*-kaurane glycosides but were drawn with an *ent*-phyllocladene structure **50**.



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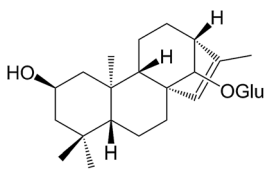

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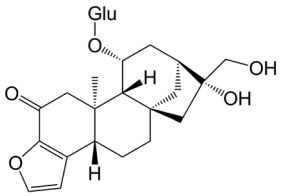
Cafestol has been shown[160] to stimulate insulin production and it has been suggested that cafestol may contribute to the effect of coffee on reducing type 2 diabetes. The known furanokaurane, mozambioside **51** has been identified[161] as a bitter tasting glycoside that is specific to *Coffea arabica* as opposed to

C. robusta. The tricalysins A–H that were found[162] in *Tricalysia fruticosa* (Rubiaceae), have been shown to be cafestol relatives and to have anti-inflammatory properties. The frutilactones A and B (*e.g.* A, **52**) were 2,3-*seco*-cafestol relatives that were isolated[163] from the same plant.



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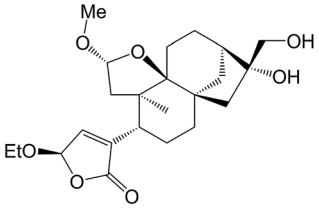

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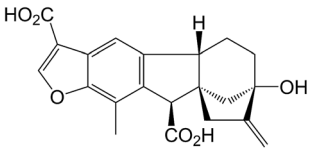
The gastroprotective activity of some derivatives of 18-hydroxybeyerenes has been described.[164] 2β,12β-Dihydroxygibberellin A_{12} has been isolated[165] from the leaves of *Scheffiera sessiliflora* (Araliaceae) in a surprisingly high amount for a gibberellin. The synthesis of pharbinilic acid **53** starting from gibberellic acid has been described.[166] This is an allogibberic acid relative which had been obtained from Morning Glory (*Pharbitis nil*).



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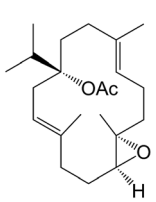
Further grayane diterpenoids have been obtained from the leaves of *Rhododendron micranthum* (Ericaceae)[167] and *R. molle*[168] both of which are used in Chinese traditional medicine. The total synthesis of atisane diterpenoids has been reported.[169] The biological activity of scopadulciol has been examined.[170]

6 Macrocyclic diterpenoids and their cyclization products

Diterpenoids with the cembrane skeleton have been found in various resins. Thus the resin of the North American *Bursera microphylla* (Burseraceae) afforded[171] microphyllanin **54** whilst the frankincense from *Boswellia carterii* (Burseraceae) yielded[172] a further group of cembranoids including the boscartins. The regioselective oxidation of the tobacco component, β-cembranediol at C-9 and C-10 using cytochrome P_{450} variants has been studied.[173] Some casbanes, *e.g.* pekinenin G **55** have been isolated[174] from *Euphorbia pekinensis*. A relative, sapidisin A was obtained[175] from *Sapium discolor* (Euphorbiaceae).



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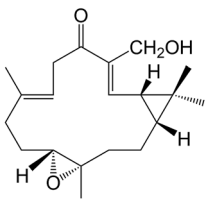

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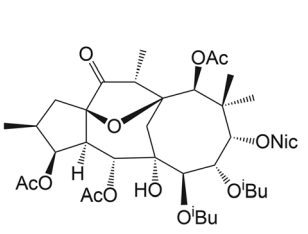
Preparative methods have been described[176] for the isolation of paclitaxel (taxol®) and of further taxanes from *Taxus chinensis* (*T. wallichiana* var^{n}.*mairei*).[177] The modification of the structure of ring D-*seco*-taxanes in the context of microtubule interactions has been examined.[178] Further synthetic studies directed at paclitaxel continue to be reported.[179]

A large number of esters of jatrophanes, lathyranes, myrsinanes, daphnanes, tiglianes and ingenanes have been isolated, particularly from members of the Euphorbiaceae and Thymelaeaceae. Care must be taken in the separation of these compounds to avoid conditions that may lead to acyl migration and transesterification. The juxtaposition and consequent interactions between functional groups provide ample opportunities for these reactions in this closely related series of compounds and indeed may contribute to their biological activity. Molecular modeling and advanced NMR methods have been used in locating esters in the jatrophanes of *Euphorbia amydaloides*.[180] Some cytotoxic lathyranes including lathyranlactone and jatrocurcusenone A have been isolated[181] from *Jatropha curcas* cv. *nigroviens rugosus* whilst further jatrophane and myrsinane esters have been obtained from *E. connata*,[182] *E. dracunculoides*,[183–185] *E. exigua*.[186] *E. osyridea*,[187] *E. prolifera*,[188] and *E. wallichii*.[189] A 12,17-cyclojatrophane, euphowelwitschine A **56** was isolated[190] from *E. weiwitschii*. Venenatin **57** which had been obtained from *Excoecaria venenta* (Euphorbiaceae), showed[191] inhibitory effects on human leukaemia cells. Further daphnane esters have been isolated from *Trigonostemon xyphophylloides* (Euphorbiaceae),[192] *Daphne genkwa* (Thymelaeaceae),[193] *Gnidia polycephela* (Thymelaeaceae),[194] and *Stellera chamaejasme* (Thymelaeaceae)[195] whilst some more tigliane (phorbol) esters with cytotoxic and anti-viral activity were obtained from *Croton tiglium* (Euphorbiaceae),[196,197] *Daphne aurantica*,[198] and *Stillingia lineata* (Euphorbiaceae).[199] The anti-viral activity of these compounds (e.g. **58**) against the chikungunya virus was examined. The evaluation of epoxylathyrol derivatives in combating multi-drug resistance[200] and the anti-viral activity of a number of phorbol and ingenol esters[201] has been reported. Some synthetic studies directed towards jatrophanes have been described.[202]



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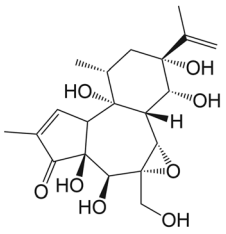

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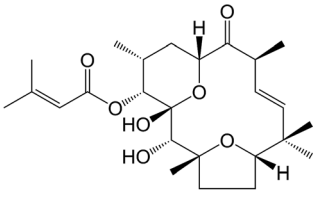

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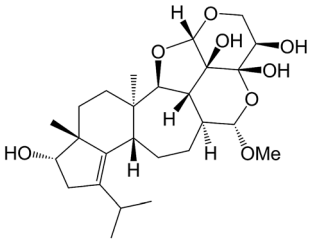
7 Miscellaneous diterpenoids

The synthesis of the 5,6,7-ring system of the mulinane diterpenoids has been achieved.[203] A number of new cyathane diterpenoids have been isolated including the striatoids A–F (*e.g.* A, **59**) from the basidiomycetes, *Cyathus striatus*,[204] and from *C. africanus*[205] and *Hericium erinaceus*.[206] The total synthesis of the guanacastepenes N and O,[207] dolestatrienol,[208] and the trichoaurantiolides C and D[209] have been reported. Further derivatives of pleuromutilin have been prepared[210] in the context of their potential anti-tubercular activity.



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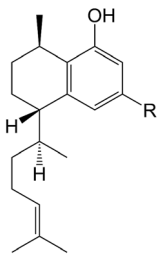
Dehydrovibsanin G has been isolated[211] from *Viburnum odoratissimum* and a total synthesis of vibsanin which unambiguously defines its stereochemistry has been reported.[212] 8-Hydroxyserrulat-14-en-19-oic acid **60** (R = CO_2H) which was isolated from the Australian medicinal plant, *Eremophila neglecta* (Scrophulariaceae) has been shown[213] to break-up and disperse bacterial biofilms with the potential for use in wound management. A number of modified serrulatanes have been synthesized[214] from leubethanol **60** (R = Me) and examined for activity against *Mycobacterium tuberculosis*.



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