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**Aromatic Abietane Diterpenoids: Their Biological Activity
and Synthesis**

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REVIEW

Aromatic Abietane Diterpenoids: Their Biological Activity and Synthesis

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In this study, the biological properties of natural abietane-type diterpenoids with an aromatic C ring are reviewed. An overview of the synthetic studies of this group of abietanes, including dehydroabietic acid, callitrisic acid and ferruginol, is presented. The review contains about 160 references.

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1 Introduction

Abietanes are a family of naturally occurring diterpenoids that have been isolated from a variety of terrestrial plant sources. These compounds exhibit a wide variety of interesting biological activities, which has generated significant interest from the medicinal and pharmacological communities. In this review, attention is focused on diterpenoids characterised by cyclic structures having the abietane (**I**, C₂₀) (Fig. 1) carbon framework and an aromatic ring C.

Abietanes having the characteristic carbon skeleton **I** (Fig. 1), exemplified by the resin acid abietic acid (**1**), have been reviewed up to 1991 and listed in the Dictionary of Terpenoids.¹ During the last three decades, many new members of this family of natural products have been isolated and described in several specific reviews on naturally occurring diterpenoids by Professor Hanson.² The biological activities of natural abietane acids and their derivatives have been reviewed up to 1992.³ A number of reviews that cover various aspects of diterpenoids have appeared: "Oxygenated di- and tricyclic diterpenoids of southern hemisphere conifers",⁴ "Biological activity of diterpenoids isolated from Anatolian Lamiaceae plants",⁵ "Bioactive diterpenoids of Salvia species",⁶ "Constituents from Salvia species and their biological activities",⁷ The biological activities of synthetic derivatives of abietanes possessing an aromatic C-ring have been also reviewed.⁸ However, the biological activity of natural abietane diterpenoids does not seem to have been the focus of a review. We now provide coverage of past and recent advances in the field (biological activity upon isolation) which have been reported in the literature from late 1980s up to August 2014.

A number of synthetic studies of aromatic abietane diterpenoids have appeared since the first isolations in the late 1930s. These have

included the syntheses from other natural products, and total syntheses. Most of the synthetic studies toward aromatic abietane diterpenoids have been focused on the synthesis of dehydroabietic acid (**2**) and ferruginol (**3**) (Fig. 1). The interesting molecular structures and biological properties of related congeners have led to a number of additional synthetic studies toward their preparation. An overview of these synthetic studies is presented.

2 Structure, occurrence and biological activity

The semisystematic naming and numbering of this family of diterpenoids was introduced in 1969, by Burgstahler,⁹ following the synthesis of fichtelite, a fossil resin hydrocarbon, from abietic acid (7,13-abietadien-18-oic acid, **1**). Thus, in accordance with the IUPAC recommendations the saturated hydrocarbon **I**, named 'abietane', was chosen as the fundamental parent structure with the numbering pattern as depicted in Figure 1.

Aromatic abietanes comprised the largest group of components of naturally occurring abietanes. They are characterised by an aromatic ring C and a different degree of oxygenation at several positions. The first known members of this group of terpenoids are dehydroabietic acid¹⁰ (**2**) and ferruginol¹¹ (**3**) which were discovered more than seventy years ago. Both structures were assigned based on chemical data. Dehydroabietic acid (**2**) was initially obtained from chemical studies starting from abietic acid, later, it was found in resin or extracts of conifers.¹² Ferruginol (**3**) was firstly isolated in 1939 from the resin of the Miro tree (*Podocarpus ferrugineus*), endemic to New Zealand.¹¹

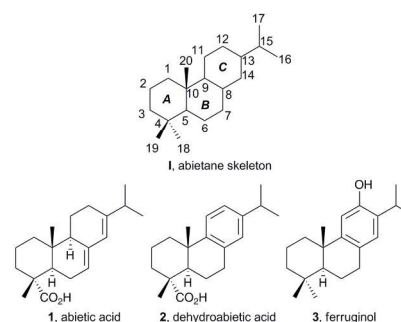
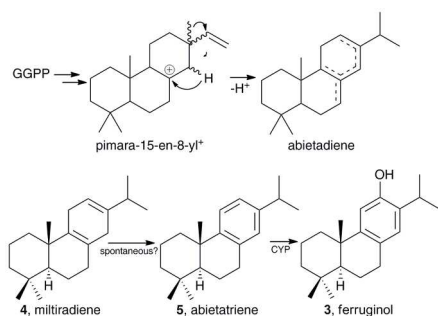


Figure 1. Abietane numbering system and abietic acid (**1**).

Aromatic abietanes are compounds that possess a core skeleton of 20 carbons. They are biosynthesised by two different pathways, the mevalonic acid pathway or the deoxyxylulose phosphate pathway and involve a sequential pair of cyclisation and/or rearrangement reactions of geranylgeranyl diphosphate (GGPP) (Scheme 1).¹³ This most often results in the production of an olefin, such as miltiradiene (**4**), which contains a planar cyclohexa-1,4-diene ring that is poised for aromatisation, and recently was shown to be the precursor of the phenolic diterpenoid ferruginol (**3**) *via* labelling studies.¹⁴ Miltiradiene (**4**) requires further elaboration to produce bioactive natural products, particularly the incorporation of oxygen catalysed by cytochromes P450 enzymes (CYP). These heme thiolate mono-oxygenases also catalyse more complex reactions, including aromatisation. In the case of ferruginol (**3**), recent studies suggest that a specific cytochrome P450 enzyme, simply hydroxylates the aromatic intermediate abietatriene (**5**) (Scheme 1).¹⁵ While the conversion of **4** to **5** does occur spontaneously, it seems likely that this aromatisation reaction is enzymatically catalysed in planta, although the relevant enzyme is yet to be determined. Diterpene synthases/cyclases catalysing some of the possible cyclisation and/or rearrangement reactions have been identified, though many remain unknown.



Scheme 1. Biosynthesis of ferruginol (**3**).

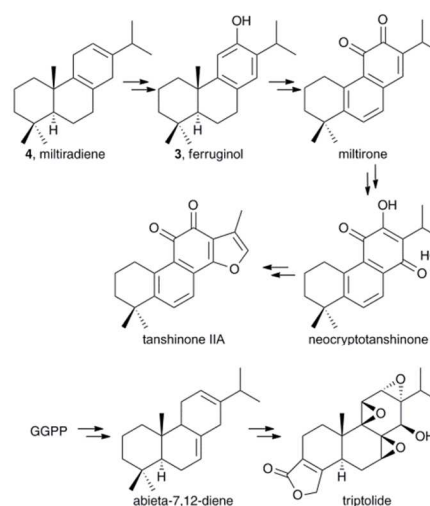
The main source of abietanes is colophony, the distillation residue of pine resins. In addition, abietanes are components of extracts or resins from many other conifers belonging to the families *Araucariaceae*, *Cupressaceae*, *Phyllocladaceae*, *Pinaceae*, and *Podocarpaceae*. They also occur in several Angiosperm species and, particularly in the families *Asteraceae*, *Celastraceae*, *Hydrocharitaceae*, and *Lamiaceae*. Some abietanes have also been isolated from fungal species.

To date, there are around two hundred known compounds belonging to this group of natural products, commonly known as dehydroabietic derivatives (dehydroabietanes). Generally, aromatic abietanes are not functionalised on A-ring carbons. Most of them present a different degree of oxidation in their B- and C-ring carbons. The number and positions of double bonds varies from three (abietatrienes) to four (abietatetraenes) and are mainly located on ring C. Given the variety of chemical structures, derived from dehydroabietic acid, found in the aromatic abietane group, we can classify them according to the number of double bonds and type of carbocyclic framework. Thus, we have divided most of them into three main groups: compounds having three double bonds and a tricyclic ring system (tricyclic abietatrienes), compounds having three double bonds and a lactone ring (abietatriene lactones), and compounds having four double bonds (abietatetraenes).

Most of these compounds play a key role as eco-physiological mediators (chemical defense) and are of interest for potential applications as therapeutic agents. In fact, the aromatic abietanes have displayed a wide spectrum of interesting biological properties (see Tables 1-3) including antimicrobial, antileishmanial, antiplasmodial, antifungal, antitumour, cytotoxicity, antiviral,

antiulcer, cardiovascular, antioxidant as well as anti-inflammatory activity.

In addition to the abietanes possessing an aromatic C-ring, a number of co-occurring metabolites have also been found, such as quinonoid tanshinones and related compounds. These are highly oxidised metabolites with significant biological properties whose biosynthetic formation is under investigation. For example, Peters et al. have proposed an hypothetical pathway in which miltiradiene (**4**) and ferruginol (**3**) are precursors of tanshinones (Scheme 2).¹⁶ It is possible that this biogenetic connection between quinonoid metabolites and their phenol precursors could also be involved in the observed biological properties. Thus, phenolic compounds could be metabolised to further oxidised metabolites responsible of the biological activity. Another abietane-related diterpenoid which possess important pharmacological properties and probably a common biosynthetic origin is triptolide (Scheme 2). Despite the close relationship between both groups of metabolites, only aromatic C-ring abietanes have been considered in this review. Also, the tanshinones and triptolide have been reviewed specifically quite recently.¹⁷



Scheme 2. Proposed biosynthetic pathway to tanshinones and probable biosynthetic origin of triptolide.

2.1 Tricyclic abietatrienes

The first group of aromatic abietanes is formally derived from the naturally occurring tricyclic hydrocarbon abietatriene (**5**) (Scheme 1), which was first isolated in the early 70s from *Podocarpus ferrugineus* and *Thujopsis dolabrata*.¹⁸ Carboxylic acids are representative of this group, of which the earliest example is the biologically active dehydroabietic acid (**2**, DHA) (Fig. 1), which possess an acid group at C-18. DHA (**2**) is commercially available and can be obtained by disproportionation of rosin or abietic acid.¹⁹

Dehydroabietic acid (**2**) displays not only antiulcer and antimicrobial properties but also antitumour and anti-inflammatory effects (Table 1). Antimicrobial effects of DHA (**2**) have been studied, specifically against methicillin resistant strains of *Staphylococcus aureus*.²⁰ It also showed activity against other gram-positive organisms such as *Salmonella* sp., *Bacillus subtilis* and *E. coli*. Recently, a study reported on the activity of DHA (**2**) against bacterial biofilms infections of *S. aureus*, which demonstrated not only its ability to prevent bacterial colonisation, but also to the inhibition of existing biofilms.²¹ Compound **2** exhibited strong inhibitory effects against the Epstein-Barr virus early antigen (EBV-EA) activation induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) and was selected to examine effects on *in vivo* two-stage

mouse skin carcinogenesis. It exhibited high activity in this antitumour-promoting test.²² In addition, DHA (**2**) has displayed anti-inflammatory activity by inhibiting 5-lipoxygenase-mediated leukotriene (LTB₄) formation,²³ suppressing the production of pro-inflammatory mediators such as monocyte chemoattractant protein (MCP)-1, and tumor necrosis factor (TNF)- α in stimulated macrophages and in the co-culture of macrophages and adipocytes.²⁴ This latter study also described the inhibition of nitric oxide (NO) production by DHA (**2**), which was reported by other researchers as well (IC₅₀ = 98.9 μ M).²⁵ Kawada et al. have reported in relation with the inhibition of pro-inflammatory cytokines that DHA (**2**) is useful for treating obesity-related diseases.²⁶ The allergenic and anti-allergic properties of acid components of resins has been studied in depth and are controversial.³ For example, 7-oxydehydroabietic acid (**6**) (Fig. 2) and 15-hydroperoxydehydroabietic acid (**7**) have shown contact allergenic properties.²⁷

Potential antitumour-promoting abietanes (**8-10**) (Fig. 2), including DHA (**2**), were isolated from the stem bark of *Picea glehni*.²⁸ They showed potent inhibitory effects on EBV-EA activation induced by the tumour promoter TPA (100% inhibition of induction at 1000 mol ratio/TPA, about 70-80% inhibition at 500 mol ratio/TPA, and about 25-40% inhibition at 100 mol ratio/TPA), being more potent than β -carotene.

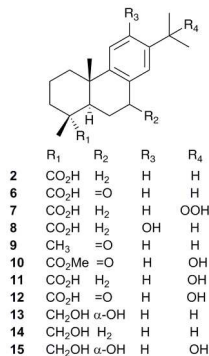


Figure 2. Dehydroabietic acid (**2**) related metabolites.

Other metabolites related to DHA (**2**), compounds **11-14**, have been isolated along with DHA (**2**) and compound **8** from the aerial parts of *Abies georgei* (Pinaceae), which occurs exclusively in China.²⁹ Compounds **2**, **8**, **11** and **12** showed anti-inflammatory effects against LPS-induced NO production in macrophages, while compounds **13** and **14** exhibited potent antiproliferation activities against LoVo tumor cells (IC₅₀ = 9.2 μ g/mL). Pomiferin A (dehydroabietinol, **14**) was also isolated from *Juniperus brevifolia* (Cupressaceae) leaves and displayed considerable antiproliferative activity against cancer cell lines, namely HeLa, A-549 and MCF-7, as well as antimicrobial activity against *B. cereus* (MIC 2.5-5 μ g/mL).³⁰ Abieta-8,11,13-triene-7 α ,15,18-triol **15** (Fig. 2) was isolated from the cones of *Larix kaempferi* (Pinaceae) and showed inhibitory effects on EBV-EA activation in a primary screening for antitumor promoters.³¹

Ferruginol (abieta-8,11,13-triene-12-ol) (**3**) (Fig. 1 and Fig. 3) is the simplest phenolic abietane diterpenoid. This abietane occurs in plants belonging to the Podocarpaceae, Cupressaceae, Lamiaceae and Verbenaceae families among others.¹ This diterpene has attracted much attention since it has exhibited important bioactivities, such as antimicrobial,³² mitocidal,³³ cardioactive,³⁴ antioxidative,³⁵ antileishmanial and nematocidal.³⁶ Also, it was reported that ferruginol (**3**) displays a gastroprotective effect in animal models of induced gastric lesions. Furthermore, the diterpene accelerates the gastric ulcer healing process after subchronic ulcer

induction in animals.³⁷ These effects have been related with the ability of ferruginol (**3**) to increase the gastric prostaglandin content *in vitro*, a stimulating effect on cell proliferation and the antioxidant properties of the compound.

Ferruginol (**3**) showed strong inhibitory effects on EBV-EA activation in a primary screening for antitumor promoters.³⁸ Recently, it has shown antitumor activity against prostate cancer by inducing apoptosis,³⁹ cytotoxicity against human pancreatic tumor cell lines,⁴⁰ cytotoxicity and apoptotic effectiveness against leukemic K562 and HL-60 cancer cells,⁴¹ as well as anti-inflammatory activity.⁴² Several reports on antimalarial activity have also been described. In 2003, a report revealed that ferruginol (**3**) displayed significant (IC₅₀ < 1 μ g/mL) *in vitro* antiplasmodial activity against a chloroquine-resistant (K1) and -sensitive (D10) strain of *Plasmodium falciparum*, and low cytotoxicity (SI > 65) against two mammalian cell lines (CHO and HepG2). It was found that **3** did not modify the erythrocyte shape, which in combination with the cytotoxicity results, indicates selective antiplasmodial activity.⁴³ In 2006 there was another report in which antimalarial activity was described using the D6 (chloroquine-sensitive) clone of *Plasmodium falciparum*. Strong antimalarial activity was shown by an IC₅₀ of 1.95 μ g/mL.⁴⁴ In 2008, Muhammad and co-workers reported antimalarial activity against D6 (chloroquine-sensitive, IC₅₀ = 4.2 μ g/mL) and W2 (chloroquine-resistant, IC₅₀ = 3.5 μ g/mL) strains of *P. falciparum* for ferruginol (**3**), and no cytotoxic activity against Vero cells at a concentration of 4.76 μ g/mL.³⁶ Recently, an additional report confirmed significant antimalarial activity showing moderate selectivity index against K1 strain (chloroquine-resistant, IC₅₀ = 0.9 μ M, SI = 15.6 (in L6 cells)).⁴⁵

Ferruginol (**3**) isolated from the roots of the herb *Craniolaria annua* (Martyniaceae) showed trypanocidal activity against trypanomastigote and epimastigote forms of *Trypanosoma cruzi*, though it also showed cytotoxic effects against fibroblastic Vero cells.⁴⁶ This phenolic compound also possess potent antiviral properties against severe acute respiratory syndrome coronavirus (SARS-CoV) (EC₅₀ = 1.39 μ M, SI = 58.0 (in Vero E6 cells)),⁴⁷ and it has been demonstrated that specifically inhibits SARS-CoV protease (3CL^{pro}) which plays a pivotal role in processing viral polyproteins and controlling replicase complex activity (IC₅₀ = 49.6 μ M).⁴⁸ In addition, ferruginol (**3**) inhibits several enzymes which are targets for several diseases such glycogen phosphorylase (55% at 100 μ M),⁴⁹ cholesterolacyltransferase (IC₅₀ = 2.0 μ g/mL),⁵⁰ and cholinesterase (IC₅₀ = 10.5 μ M).⁵¹

Other common phenolic metabolites related to ferruginol (**3**) are hinokiol (abieta-8,11,13-triene-3 β ,12-diol) (**16**) and sugiol (12-hydroxyabieta-8,11,13-trien-7-one) (**17**) (Fig. 3). The crystal structures of both hinokiol (**16**) and sugiol (**17**) have been reported.^{52,53} A sample of hinokiol (**16**) isolated from *Plectranthus strigosus* (Lamiaceae) revealed antioxidant activity,⁵⁴ while another sample isolated from the wood of *Cunninghamia konishii* (Cupressaceae) exhibited significant concentration-dependent inhibition of nitric oxide (NO) production in macrophages (IC₅₀ = 7.9 μ g/mL).⁵⁵ Sugiol (**17**) isolated from the tree *Juniperus polycarpus* (Cupressaceae) exhibited antimalarial activity against the D6 (IC₅₀ = 472 ng/mL) and W2 (IC₅₀ = 409 ng/mL) clones of *Plasmodium falciparum*.⁵⁶ A sample of sugiol (**17**) was obtained from the conifer *Cryptomeria japonica* (Taxodiaceae) known as "sugi" in Japanese and was shown to possess potent anti-inflammatory and hepatoprotective activities.⁵⁷ *In vitro* cytotoxic activity of sugiol (**17**) against human pancreatic (MIA PaCa-2, IC₅₀ = 17.9 μ M) and melanoma (MV-3, IC₅₀ = 34.1 μ M) tumour cells has been reported,⁵⁸ as well as antitumour promoting activity against EBV-EA activation.³⁸ In addition, sugiol (**17**) is a potent inhibitor of xanthine oxidase activity with an IC₅₀ of 6.8 μ M and inhibits ROS

formation.⁵⁹ Antimicrobial activity against antibiotic resistant bacteria of sugiol (**17**) has been described,⁶⁰ as well as activity against gram-negative bacteria and *Candida albicans*.⁶¹ This was also exhibited by the abietane **18** (Fig. 3) isolated from the leaves of *Salvia albocaerulea* (Lamiaceae).⁶¹

A sugiol-related abietane, 6 α -hydroxysugiol (**19**), was isolated from stem bark of *Thuja standishii* (Cupressaceae) along with phenolic abietane **20** (Fig. 3). Compound **19** showed strong inhibitory effect on EBV-EA induction while compound **20** showed moderate activity.⁶²

Bioactivity-guided fractionation of *Salvia hypargeia* (Lamiaceae) yielded demethylcryptojaponol (**21**) (Fig. 3) which was active against A2780 human ovarian cancer cells with an IC₅₀ value of 1.2 μ g/mL.⁶³ 1-Oxoferruginol (**22**) (Fig. 3) was isolated from the roots of *Salvia viridis* (Lamiaceae) along with ferruginol (**3**) and sugiol (**17**) and showed antimicrobial activity.⁶⁴ 20-Hydroxyferruginol (**23**) (Fig. 3) was found in the methanol extract of the dried cones of *Sequoia sempervirens* (Cupressaceae) along with 6 α -hydroxysugiol (**19**). Both compounds strongly inhibited colon, lung, and breast tumours and oncogene transformed cells with GI₅₀ 2-5 μ g/mL.⁶⁵ Known 18-methylesterferruginol (**24**) and a dimethoxyacetal related to ferruginol, 18-dimethoxyferruginol (**25**) (Fig. 3), were isolated from the ethanolic extracts of *Torreya nucifera* (Taxaceae). Both compounds showed potent antioxidant activities. In addition, compound **24** inhibited nitric oxide production and inducible nitric oxide synthase expression in lipopolysaccharide-stimulated RAW264.7 cells.⁶⁶ 2 β -Acetoxylferruginol (**26**) (Fig. 3) was discovered from the bark of *Prumnopitys andina* (Podocarpaceae) and had antibacterial activity at 8 μ g/mL against two effluxing strains of *Staphylococcus aureus* but it was inactive against a methicillin-resistant (MRSA) clinical isolate.⁶⁷

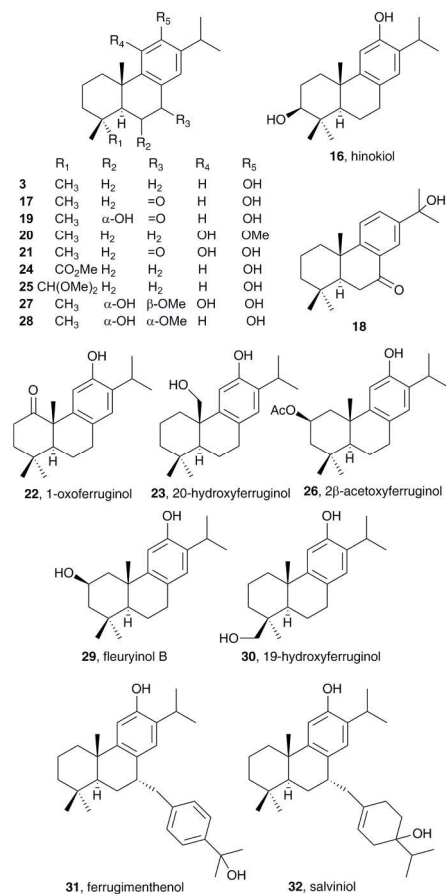


Figure 3. Ferruginol (**3**) and related metabolites.

Taxodistines A (**27**) and B (**28**) (Fig. 3) have been isolated by the guidance of inhibitory effect of tubulin polymerisation from the fruits of *Taxodium distichum* (Taxodiaceae).⁶⁸ Both showed cytotoxicity against murine lymphoma P388 cells at IC₅₀ 0.43 and 6.5 μ g/mL, respectively. Fleuryinol B (**29**) and 19-hydroxyferruginol (**30**) (Fig. 3) were isolated from the twigs and leaves of *Podocarpus fleuryi* (Podocarpaceae).⁶⁹ Both compounds exhibited moderate cytotoxic activity.

Recently, two rare abietane diterpenoids possessing a ferruginol-menthol coupled skeleton have been discovered. Ferrugimenthonol (**31**) and salvinol (**32**) (Fig. 3) were isolated from the bark of *Calocedrus macrolepis* (Cupressaceae) and from the ethanol extract of giant salvinia (*Salvinia molesta*, Salviniaceae), respectively.^{70,71} Both compounds exhibited significant cytotoxic activity.

Similarly, a number of phenolic abietanes, compounds **33-44** (Fig. 4) have been isolated. For example, phenol **33** was isolated from the aerial material of *Plectranthus elegans* (Lamiaceae) and inhibited the growth of Gram-positive bacteria and the germination of spores of *Cladosporium cucumerinum*.⁷² This activity against fungal and bacterial species suggests its role in the chemical defence of the plant. Another species of the same genus, *Plectranthus nummularius* (Lamiaceae), yielded the diterpenoid plectranthol B (**34**) (Fig. 4) which showed antioxidant properties scavenging the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical more effectively than α -tocopherol.⁷³ Examination of the bark components of *Cryptomeria japonica* (Taxodiaceae) led to the isolation of cryptojaponol derivative **35**, which showed moderate cytotoxic activity against HL-60 tumour cells (IC₅₀ = 28.0 μ M).⁷⁴ Another abietane, such as inuroyleanol (**36**), has been isolated from *Salvia barrelieri* and showed free radical scavenging and lipid peroxidation inhibition activity.⁷⁵ The fortunins A-D (*e. g.* **37**) (Fig. 4) were found among the constituents of *Cryptomeria fortunei* (Taxodiaceae).⁷⁶ Fortunin C (**37**) showed weak inhibitory activity on HL-60 cells. Cryptojaponol derivative **38** was isolated from the heartwood of *Cryptomeria japonica* (Taxodiaceae) showed potent antiviral properties against severe acute respiratory syndrome coronavirus (SARS-CoV) (EC₅₀ = 1.15 μ M, SI = 111.0 (in Vero E6 cells)).⁴⁷ The hydroquinone

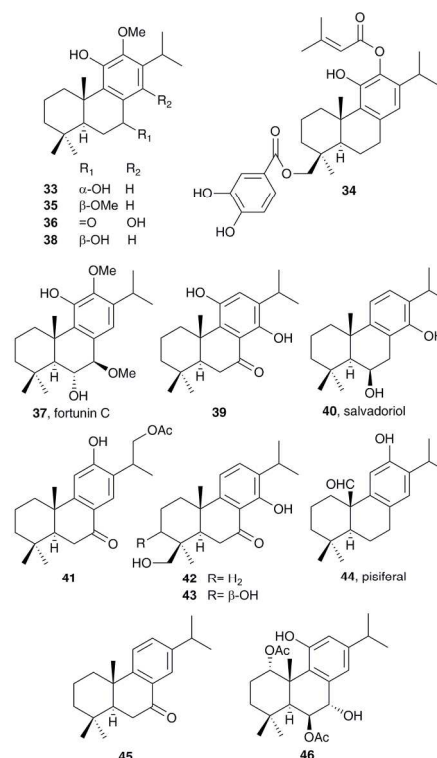


Figure 4. Abietatrienes **33-46**.

derivative **39** was isolated from the hexane extract of *Hyptis martiusii* (Lamiaceae) and displayed cytotoxic activity on several tumour cell lines.⁷⁷ The potent anti-tumour promoting activity of salvadoriol (**40**) which was obtained from the plant, *Crossopetalum uragoga* (Celastraceae), has been described.⁷⁸ The Chinese medicinal plant *Isodon lophanthoides* var. *graciliflorus* (Lamiaceae) yielded 16-acetoxysugiol (**41**) and the C-19-functionalised abietane (**42**) (Fig. 4).⁷⁹ Both compounds demonstrated potent cytotoxicity on A549, MCF-7 and HeLa tumour cells with the IC₅₀ values ranging from 1.79 to 15.92 μM. The screening for immunosuppressive components of the Chinese medicinal plant *Tripterygium wilfordii* (Celastraceae) led to the isolation of triptobenzene J (**43**) among other potent terpenoid inhibitors of cytokine production on lipopolysaccharide-stimulated human peripheral mononuclear cells.⁸⁰ Pisiferic acid (**44**) and abietanone **45** (Fig. 4) have been isolated from the stem bark of *Fraxinus sieboldiana* (Oleaceae).⁸¹ Pisiferic acid (**44**) showed inhibitory activity against the release of β-glucuronidase in rat polymorphonuclear leukocytes induced by platelet-activating factor with 65.9% inhibition at 10 μM, while compound **45** was active against H5N1 influenza virus with an IC₅₀ value of 4.8 μM. Another phenolic abietane, euroabienol (**46**) (Fig. 4), was isolated from the plant *Lycopus europaeus* (Lamiaceae) and showed a broad spectrum of activity against 15 strains of bacteria and six fungal strains.⁸²

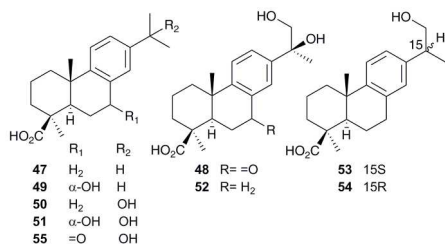


Figure 5. Callitrisic acid (**47**) and related metabolites.

Dehydroabietic acid (**2**) possesses an equatorial carboxylic group (C-18) while in other natural congeners the carboxylic group adopts the axial configuration (C-19) as in 4-epidehydroabietic acid or callitrisic acid (**47**) (Fig. 5). Callitrisic acid (**47**) is a diterpenoid acid contained in the resins of several *Callitris* species (Cupressaceae) (Australian sandarac resin). It was simultaneously reported as a new natural product by Gough,⁸³ and Carman and Deeth.⁸⁴ This acid also occurs in plants of the genus *Juniperus* and *Calceolaria* and it has also been found in the genus *Illicium*. Recently, a series of related acids to callitrisic acid having a C-19 carboxylic group have been isolated. For example, the jiadifenoic acids A-I (e. g. D, **48**) (Fig. 5) along with callitrisic acid (**47**), 7α-hydroxycallitrisic acid (**49**) and angustanoic acid F (**50**) were isolated from the roots of *Illicium jiadifengpi* (Illiciaceae).⁸⁵ All these acids demonstrated important antiviral activity against Coxsackie virus B. Similarly, investigation of the constituents of the stems of *Illicium jiadifengpi* yielded abietane acid **51** which exhibited reasonable activity against Coxsackie virus B3 with an IC₅₀ value of 21.9 μM, and selective index value of 45.6.⁸⁶ Examination of the constituents of the twigs and leaves of *Illicium majus* (Illiciaceae) led to the isolation of the majusanic acids A-D (e. g. B, **52**) (Fig. 5) along with callitrisic acid (**47**).⁸⁷ Majusanic acid B (**52**) exhibited significant anti-inflammatory activity with IC₅₀ value of 0.26 μM, while callitrisic acid (**47**) showed good anti-inflammatory activity with an IC₅₀ value of 2.60 μM. The roots of *Illicium majus* were also investigated and resulted in the isolation of majusanic acids E (**53**) and F (**54**) (Fig. 5) along with callitrisic acid (**47**), and majusanic acids B (**52**) and D (**55**).⁸⁸ These abietane acids displayed antiviral activity against the Coxsackie B3 virus, with IC₅₀ values of 3.3–51.7 μM.

Another abietane acid with demonstrated biological activity is pisiferic acid (**56**) (Fig. 6). This acid possesses the carboxylic group at C-20 and a hydroxy group at C-12 like ferruginol. Pisiferic acid (**56**) is a constituent of *Chamaecyparis pisifera* (Cupressaceae) and has also been found in some *Salvia* species.

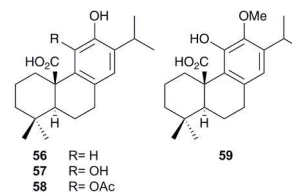


Figure 6. Pisiferic acid (**56**) and related metabolites.

This abietane acid has shown antifungal activity against the rice blast fungus,⁸⁹ antibacterial activity against Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* and Gram-negative bacteria,⁹⁰ as well as cytotoxic activity against HeLa tumour cells.⁸⁹ Pisiferic acid (**56**) inhibits predominantly DNA synthesis in HeLa cells as compared with RNA and protein synthesis. It showed inhibitory activity on HeLa DNA polymerase α and inhibitory activity is about 1/20 of aphidicolin.⁹¹ Recently, it has been reported that pisiferic acid induces apoptosis in HL60 tumour cells.⁹²

Carnosic acid (CA, **57**) (Fig. 6), a derivative of pisiferic acid, also possesses a C-20 carboxylic acid. It is found in the popular Lamiaceae herbs, sage (*Salvia officinalis*) and rosemary (*Rosmarinus officinalis*). Carnosic acid (**57**) contains a o-diphenol structure which undergoes oxidation easily and provides potent antioxidant activity.⁹³ A number of biological activities have been studied on CA. For example, the inhibitory effects of CA on HIV-1 protease (IC₉₀ = 0.08 μg/mL) and HIV-1 virus replication (IC₉₀ = 0.32 μg/mL) have been reported.⁹⁴ CA also inhibited both A- and B- type human respiratory syncytial virus (hRSV) replication, while it did not affect the replication of influenza A virus. CA not only reduced viral RNA synthesis (IC₅₀ = 6.51 μg/mL in A549 cells and IC₅₀ = 6.71 μg/mL in HEP-2 cells), it also inhibited the initial infection of hRSV.⁹⁵ The antibacterial and resistance modifying activity of rosemary constituents (CA) has been demonstrated.⁹⁶ CA also promotes the synthesis of nerve growth factor in T98G human glioblastoma cells, which makes CA a potential compound for the treatment of Alzheimer disease.⁹⁷ CA significantly inhibited collagen-, arachidonic acid-, U46619- and thrombin-induced washed rabbit platelet aggregation in a concentration-dependent manner, with IC₅₀ values of 39.0, 34.0, 29.0 and 48.0 μM, respectively. Accordingly, serotonin secretion and arachidonic acid liberation were also inhibited.⁹⁸ CA protects neurons from oxidative stress and excitotoxicity. It increases the level of reduced glutathione *in vivo*, and protects the brain against middle cerebral artery ischemia/reperfusion.⁹⁹ This research suggests that CA may represent a new type of neuroprotective agent. Rosemary extracts that are rich in CA have potential use as a preventive treatment against metabolic disorders, since they limit weight gain, and improves plasma lipid and glucose levels in a high-fat diet mouse model.¹⁰⁰ CA has also shown potential antiatherosclerosis effects by studying inhibition of monocyte chemoattractant protein-1 (MCP-1) and matrix metalloproteinase-9 (MMP-9), as well as cell migration.¹⁰¹ CA exerts its antiadipogenic effect in a multifactorial manner by interfering with mitotic clonal expansion, altering the ratio of the different transcription factors and blocking their expression.¹⁰² An investigation showed that CA strongly suppressed the production of inflammatory mediators such as interleukin IL-6, IL-8 and MCP-1.¹⁰³ In this study, CA also arrested the growth of dermatitis-inducing Gram-positive and Gram-negative microorganism such *Propionibacterium acnes*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.

Carnosic acid (CA, **57**) has also been reported to possess antitumour activities. For example, CA potently inhibits proliferation of ER-negative human breast cancer cells, induces G1 cell cycle arrest, and exhibits synergy with turmeric/curcumin.¹⁰⁴ CA induced antiproliferative effects on androgen-independent human prostate cancer PC-3 cells in a concentration- and time-dependent manner, which was due to apoptotic induction as evident from flow-cytometry, DNA laddering and TUNEL assay.¹⁰⁵ In addition, CA induced apoptosis in another androgen refractory prostate cancer DU145 cells. Thus, it was concluded that CA may have the potential for use in the prevention and/or treatment of prostate cancer. A study describing the antitumour action of CA on three human colon cancer cell lines (Caco-2, LoVo and HT29) has been reported.¹⁰⁶ This investigation found that CA reduces cell viability by inducing apoptosis Caco-2 cell line, and inhibits cell migration ability. In addition, CA inhibited cyclooxygenase COX-2, at mRNA and protein levels.

The antimicrobial activity of carnosic acid related compounds, such as 11-acetoxy-carnosic acid (**58**), isolated from *Salvia* species, and 12-methoxycarnosic acid (**59**), isolated from *Dauphinea breviflora* (Lamiaceae) has been described. Compound **58** showed considerable antibiotic activity against Gram-positive microorganism, *Staphylococcus aureus* and *Bacillus subtilis*.¹⁰⁷ Compound **59** also inhibited the growth of these organisms, including *Streptomyces scabies* with MIC values of 1.0, 20.0 and 1.0 µg/mL, respectively.¹⁰⁸ A study on the structure-antimicrobial activity relationships of abietatriene diterpenoids from *Salvia* species has been reported.¹⁰⁹ It concluded that the free catechol group is essential for antimicrobial activity against Gram-positive bacteria. The compounds in which the catechol group had been oxidised to a quinone exhibited enhanced activity.

Finally, the activation by compound **59** of the nuclear receptor peroxisome proliferator-activated receptor PPAR γ , which is potential therapeutic target for many obesity-related disorders such as type 2 diabetes, atherosclerosis, and the metabolic syndrome, has been reported.¹¹⁰

Table 1. Biological activity found in compounds 2-59.

Compound	Biological activity	Ref.
Dehydroabietic acid, 2	Antitumor	3
	Antimicrobial	20,21
	Antitumor	22,28
	Anti-inflammatory	23-25,29
	Improves diabetes and hyperlipidemia	26
7-Oxydehydroabietic acid, 6		
15-Hydroperoxy-dehydroabietic acid, 7	Contact allergen	27
12-Hydroxydehydroabietic acid, 8	Antitumor	28
	Anti-inflammatory	29
Abieta-8,11,13-trien-7-one, 9		
Methyl 15-hydroxy-7-oxo-dehydroabietate, 10	Antitumor	28
15-Hydroxydehydroabietic acid, 11		
15-Hydroxy-7-oxo-dehydroabietic acid, 12	Anti-inflammatory	29
8,11,13-abietatriene-7 α ,18-diol, 13	Antitumor	29
Pomiferin A (dehydroabietinol), 14	Antitumor	29,30
	Antimicrobial	30
Abieta-8,11,13-triene-7 α ,15,18-triol, 15	Antitumor	31
Ferruginol, 3	Antimicrobial	32

	Cytotoxicity	32b
	Mitocidal	33
	Cardioactive	34
	Antioxidative	35
	Antileishmanial and nematocidal	36
	Antitumor	37
	Antitumor	38-41
	Antimalarial	36,43-45
	Anti-inflammatory	42
	Trypanocidal	46
	Anti-SARS	47,48
	Glycogen phosphorylase inhibition	49
	Cholesterolacyltransferase inhibition	50
	Cholinesterase inhibition	51
	Hinokiol, 16	Antioxidative
Anti-inflammatory		55
Sugiol, 17	Antimalarial	56
	Anti-inflammatory and hepatoprotective	57
	Cytotoxicity	58
	Xanthine oxidase inhibition	59
	Antitumor	38
	Antimicrobial	60,61
	15-Hydroxy-7-oxoabieta-8,11,13-triene, 18	Antimicrobial
6 α -Hydroxysugiol, 19	Antitumor	62,65
12-Methoxyabieta-8,11,13-trien-11-ol, 20	Antitumor	62
Demethylcryptojaponol, 21	Cytotoxicity	63
1-Oxoferruginol, 22	Antimicrobial	64
20-Hydroxyferruginol, 23	Antitumor	65
18-Methyl esterferruginol, 24	Antioxidative	66
	Anti-inflammatory	
18-Dimethoxyferruginol, 25	Antioxidative	66
2 β -Acetoxyferruginol, 26	Antimicrobial	67
Taxodistine A, 27	Cytotoxicity	68
Taxodistine B, 28	Cytotoxicity	
	Inhibition of tubulin polymerisation	68
Fleuryinol B, 29	Cytotoxicity	69
19-Hydroxyferruginol, 30	Cytotoxicity	69
Ferrugimthenol, 31	Cytotoxicity	70
Salviniol, 32	Cytotoxicity	71
12-Methoxyabieta-8,11,13-trien-7 α ,11-diol, 33	Antibacterial and antifungal	72
12-O-(3-methyl-2-butenoyl)-19-O-(3,4-dihydroxybenzoyl)-11-hydroxyabieta-8,11,13-triene, 34	Antioxidative	73
7 β -Methoxydeoxo-cryptojaponol, 35	Antitumor	74
Inuroleanol, 36	Antioxidant	75
Fortunin C, 37	Antitumor	76
7 β -Hydroxydeoxy-cryptojaponol, 38	Anti-SARS	47
11,14-Dihydroxy-8,11,13-abietatrien-7-one, 39	Cytotoxicity	77
Salvadoriol, 40	Antitumor	78
16-Acetoxyugiol, 41	Cytotoxicity	79
Abieta-8,11,13-triene-14,19-	Cytotoxicity	79

diol, 42		
Triptobenzene J, 43	Immunosuppressive	80
Pisiferal, 44	β -glucuronidase inhibition	81
7-Dehydroabietanone, 45	Antiviral	81
Euroabienol, 46	Antimicrobial	82
Callitrisic acid, 47	Antiviral	85,88
	Anti-inflammatory	87
Jiadifenolic acid D, 48	Antiviral	85
7 α -Hydroxycallitrisic acid, 49	Antiviral	85
Angustanoic acid F, 50	Antiviral	85
4-Epi-7 α ,15-dihydroxy-dehydroabietic acid, 51	Antiviral	86
Majusanic acid B, 52	Anti-inflammatory	87
Majusanic acid E, 53	Antiviral	88
Majusanic acid F, 54	Antiviral	88
Majusanic acid D, 55	Antiviral	88
Pisiferic acid, 56	Antifungal	89
	Antibacterial	90
	Antitumour	91,92
Carnosic acid, 57	Antioxidant	93,126
	Anti-HIV	94
	Antiviral	95
	Antibacterial	96,103,112,113
	Anti-Alzheimer disease	97
	Antiplatelet	98
	Neuroprotective	99
	Improves diabetes and hyperlipidemia	100
	Antiatherosclerosis	101
	Antiadipogenic	102
	Anti-inflammatory	103,114,115
	Antitumour	104-107
Antiangiogenic	124,125	
11-Acetyoxycarnosic acid, 58	Antimicrobial	107
12-Methoxycarnosic acid, 59	Antimicrobial	108
	Antidiabetic	110

2.2 Abietatrien 20-7 lactones

The abietatriene lactones are a group of compounds which possess an oxygen-containing ring which predominantly is in the form of lactones (i.e. abietatrien-20,7-olides). This group of abietanes are exemplified by carnosol (CS, **60**) (11,12-dihydroxy-8,11,13-20,7-olide) (Fig. 7), one of the main constituents of sage (*Salvia officinalis*) (Lamiaceae) and rosemary (*Rosmarinus officinalis*) (Lamiaceae) and constitutes an oxidation product of carnosic acid (CA, **57**), the other principal constituent of these plants. This is why many times both compounds have been studied together.

Carnosol (**60**) (Fig. 7) possesses an aromatic C ring, carbon C-20 is a keto group, and carbons C-11 and C-12 are hydroxy groups. This abietane has displayed several biological activities (see Table 2). Among them, CS has demonstrated antioxidant and anti-HIV (IC₅₀= 8.0 μ M) properties.¹¹¹ The antimicrobial activity of CS against oral pathogens responsible for initiating dental caries such as *Streptococcus mutans*, *S. sobrinus*, *S. mitis*, *S. sanguinis*, and *Enterococcus faecalis* has been described.¹¹² The minimum inhibitory concentration (MIC) values ranged between 35.0 and 100.0 μ g/mL. Carnosic acid (CA, **57**) also showed similar values. Another study on antimicrobial activity of CS reported that this abietane is the effective compound of a crude extract from sage leaves that reduces the MICs of aminoglycosides against vancomycin-resistant enterococci (VRE).¹¹³ Carnosic acid (CA, **57**) showed similar activity. The pharmacological basis for the anti-

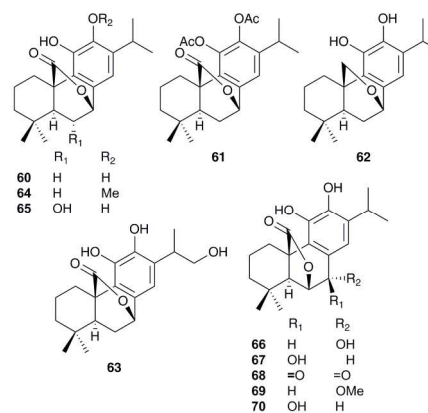


Figure 7. Carnosol (**60**) and related metabolites.

inflammatory properties reported for CS- and CA-containing extracts has been studied. Thus, it was found that: (i) CS and CA inhibit the formation of pro-inflammatory leukotrienes in intact human polymorphonuclear leukocytes (PMNL) (IC₅₀= 7.0 μ M [CS], 15-20 μ M [CA], respectively), as well as purified recombinant 5-lipoxygenase (IC₅₀= 0.1 μ M [CS], 1.0 μ M [CA], respectively), (ii) both CS and CA potently antagonise intracellular Ca²⁺ mobilisation induced by a chemotactic stimulus, and (iii) CS and CA attenuate formation of reactive oxygen species and the secretion of human leukocyte elastase.¹¹⁴ The anti-inflammatory properties of CS and CA have also been studied *in vivo*. Pretreatment with CS and CA, inhibited phorbol 12-myristate 13-acetate (PMA)-induced ear inflammation in mice with an EC₅₀ of 10.7 μ g/cm² and 10.2 μ g/cm², respectively.¹¹⁵ In addition, this study showed that CS and CA differentially regulate the expression of inflammation-associated genes.

The antitumor activities of CS (**60**) have been reviewed.¹¹⁶ For example, it has been demonstrated that CS can prevent DNA damage and tumor formation in the rat mammary gland, and, thus, has potential for use as a breast cancer chemopreventive agent.¹¹⁷ CS also induces apoptosis and down regulation of Bcl-2 in B-lineage leukemia cells.¹¹⁸ Antitumour activities of CS on human prostate cancer PC3 cells (IC₅₀= 34 μ M at 72 h) and ovarian cancer A2780 cells have also been reported.^{119,120} The potent anti-tumour promoting activity of CS and carnosol diacetate (**61**) (Fig. 7) isolated from the plant *Crossopetalum uragoga* (Celastraceae), has been described.⁷⁸ This study demonstrated that CS possess a remarkable chemopreventive effect in an *in vivo* two-stage carcinogenesis model. A phytochemical study carried out on the aerial parts of *Salvia pachyphylla* and *S. clevealandii* (Lamiaceae) led to the isolation of CS (**60**), 20-deoxycarnosol (**62**) and 16-hydroxycarnosol (**63**). These diterpenoids were the most active compounds when evaluated *in vitro* for cytotoxicity on five cell lines, including A2780 ovarian cancer, SW1573 non-small-cell lung cancer, WiDr colon cancer, T-47D breast cancer, and HBL-100 breast cancer.¹²¹ The growth inhibition 50% values (GI₅₀) were in the range 3.6-35.0 μ M, with the A2780 and HBL-100 cell lines being the most sensitive, with GI₅₀ values in the range 3.6-5.4 μ M. The results obtained against the breast cancer cells suggest that these compounds may have a mechanism of action independent of the estrogen receptor (ER). T-47D cells are ER positive, while HBL-100 cells lack this receptor and are ER negative. However, another study demonstrated that CS delays chemotherapy-induced DNA fragmentation and morphological changes associated with apoptosis in leukemia cells, which may decrease the effectiveness of some standard chemotherapy treatments used for leukemia.¹²² Carnosol (CS, **60**) has also been identified as a possible active constituent for the gastroprotective effect of aqueous alcoholic extract of *Salvia officinalis*.¹²³ CS has been investigated for antiangiogenic activity,

which is related with lower risk of neurodegenerative diseases. In this study, however, carnosic acid (**57**) was more potent than CS suppressing angiogenesis in a *ex vivo* model.¹²⁴ This biological activity could be related to the antioxidant properties of both compounds and contributes to the chemopreventive, antitumour and antimetastatic activities of rosemary extracts.¹²⁵

The antioxidant activity of chemical components of sage (*Salvia officinalis*) (Lamiaceae) has been established by several methods. Thus, a new diterpenoid, 12-O-methyl carnosol (**64**) (Fig. 7), was isolated from the leaves of sage, together with 11 abietane diterpenoids.¹²⁶ Among them, carnosic acid (**57**), carnosol (**60**), isorosmanol (**65**), and the abietatriene-20,6-olides rosmanol (**66**), epirosmanol (**67**) and galdosol (**68**) exhibited remarkably potent activity which was comparable to that of α -tocopherol. Galdosol (**68**) (Fig. 7) was also isolated along with 7-methoxyrosmanol (**69**) by benzodiazepine receptor binding assay-guided fractionation of the methanol extract of sage.¹²⁷ 7-Methoxyrosmanol exhibited an IC_{50} value of 7.2 μ M while galdosol (**68**) showed the strongest binding activity to the benzodiazepine receptor with an IC_{50} value of 0.8 μ M. Finally, deoxyepirosmanol derivative **70**, isolated from the stem bark of *Fraxinus sieboldiana* (Oleaceae), exhibited selective cytotoxic activity against lung (A549) cancer cell line (IC_{50} = 6.0 μ M).⁸¹

Table 2. Biological activity found in compounds **60-70**.

Compound	Biological activity	Ref.
Carnosol, 60	Antioxidant	111,126
	Anti-HIV	111
	Antimicrobial	112,113
	Anti-inflammatory	114,115
	Antitumour	78,117-121
	Decreases effectiveness of chemotherapy for leukemia	122
	Gastroprotective	123
	Antiangiogenic	124,125
Carnosol diacetate, 61	Antitumour	78
20-Deoxocarnosol, 62	Antitumour	121
16-Hydroxycarnosol, 63	Antitumour	121
12-O-methyl carnosol, 64	Antioxidant	126
Isorosmanol, 65		
Rosmanol, 66		
Epirosmanol, 67		
Galdosol, 68	Antioxidant	126
	Benzodiazepine-receptor affinity	127
7 α -methoxyrosmanol, 69	Benzodiazepine-receptor affinity	127
7 β ,12-dihydroxyabieta-8,11,13-trien-20,6-olide, 70	Cytotoxicity	81

2.3 Abietatetraenes

The abietatetraenes are a group of compounds which possess a fourth double bond which can be located at different positions, as for example in 5,6-dehydro derivatives (**71-80**) (Fig. 8), 6,7-dehydro derivatives (**81** and **82**) (Fig. 9), and 15,16-dehydro derivatives (**83-87**) (Fig. 9).

Among the 5,6-dehydro derivatives are coleon C (**71**) and coleon U (**72**) and related compounds. These metabolites are common in plants of the genus *Coleus* (synonym *Plectranthus*) and have displayed several biological activities. For example, coleon C (6,11,12,14,16-pentahydroxyabieta-5,8,11,13-tetraen-7-one, **71**) isolated from *Coleus forskohlii* (Lamiaceae) was investigated for its antitumour activity on eight tumour cell lines (95-D, A375, HeLa, A431, MKN45, BEL7402, LoVo and HL60).¹²⁸ The results indicated that the melanoma A375 cell line was the most sensitive of all the cell lines and there was induction to apoptosis. In the acute

toxicity studies on mice, the median lethal dose (LD_{50}) of coleon C (**71**) was 1496 \pm 150 mg/kg. In the model of Lewis lung carcinoma, the average tumour weight in groups injected with 80 mg/kg coleon C (**71**) decreased by 48.9 \pm 14.3% compared with that of the control. These results indicate that this molecule could effectively inhibit tumour cell proliferation and growth by inducing apoptosis with low toxicity.

The antiproliferative activity of coleon U (**72**) which was isolated from *Plectranthus grandidentatus* (Lamiaceae) has been described.¹²⁹ Coleon U (**72**) has also been examined for antimicrobial activity. The MIC values were 0.98 μ g/mL for methicillin-resistant *Staphylococcus aureus* (MRSA) clinical strain and 31.25 μ g/mL for vancomycin-resistant *Enterococcus faecalis* (VRE) clinical strain.¹³⁰ A sample of coleon U (**72**) isolated from *Plectranthus forsteri* (Lamiaceae) showed antimicrobial activity against *Bacillus subtilis* (MIC: 3.13 μ g/mL) and *Pseudomonas syringae* (MIC: 6.25 μ g/mL), and moderate antifungal activity against *Cladosporium herbarum* (MIC: 200 μ g/mL).¹³¹ The cytotoxic activity of coleon U 11-acetate (**73**) (Fig. 8) isolated from the Chinese medicinal plant *Coleus xanthanthus* (Lamiaceae) (leukemia K562 cells, IC_{50} = 2.2 μ g/mL) has been described.¹³² Bioactivity-guided fractionation of *Salvia hypargeia* (Lamiaceae) yielded 14-deoxycoleon U (=) (**74**) (Fig. 8) which was active against A2780 human ovarian cancer cells with an IC_{50} value of 3.9 μ g/mL.⁶³ Examination of giant salvinia (*Salvinia molesta*, Salviniaceae), one of the most noxious invasive species in the world, has led to the isolation of 14-deoxycoleon U (**74**) and montbretol (**75**).⁷¹ Both compounds showed significant cytotoxicity against several cancer cell lines, including human exocrine pancreatic (PANC-1, BxPC-3), non-small lung (A459), prostate (PC-3), breast (MDA-MB-231) and leukemia (HL-60). The GI_{50} were between 8.39 and 37.28 μ M. A sample of 6-hydroxysalvinolone (14-deoxycoleon U, **74**) isolated from *Salvia leriifolia* (Lamiaceae) exhibited potent antiproliferative activity against prostate cancer cells (PC-3, IC_{50} = 3.9 μ M) and cervical cancer cells (HeLa, IC_{50} = 8.0 μ M).¹³³ This compound also inhibited α -chymotrypsin, a protease enzyme that catalyses the breakdown of polypeptide and proteins (IC_{50} = 188.8 μ M). A sample of the same compound (14-deoxycoleon U, **74**)

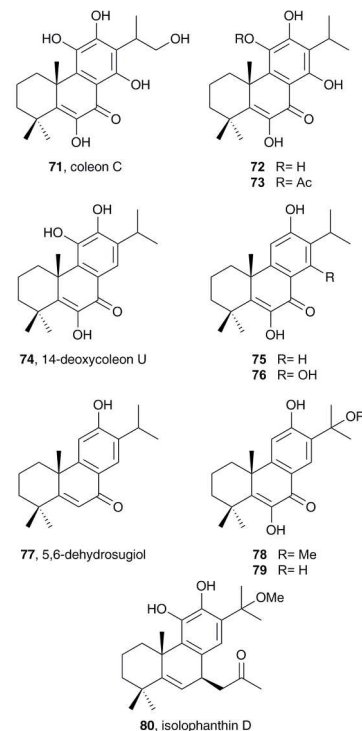


Figure 8. Abietatetraenes **71-80**.

isolated from the roots and twigs of *Premna obtusifolia* (Verbenaceae) showed significant antibacterial activities against *Bacillus subtilis*, *Streptococcus aureus*, *Enterococcus faecalis*, MRSA, VRE, *Salmonella typhi*, and *Shigella sonnei* (MIC 2.34-4.68 µg/mL) as well as anti-inflammatory activity (inhibition of NO production, IC₅₀ = 6.1 µM).¹³⁴ Another sample of 14-deoxycoleon U (**74**) isolated from *Taxodium distichum* (Taxodiaceae) was highly active against two wood decay fungi, *Trametes versicolor* and *Fomitopsis palustris*.¹³⁵ Fractionation of the stem bark of *Cryptomeria japonica* (Taxodiaceae) led to the isolation of 6-hydroxy-5,6-dehydrosugiol (montbretol, **75**). This compound exhibited potent androgen receptor antagonist in metastatic prostate cancer. It induces apoptosis and its oral administration at 0.5 and 2.5 mg/kg once daily for 24 days to androgen-responsive prostate cancer xenografted mice suppressed tumour growth by 22% and 39%, respectively.¹³⁶ *Craniolaria annua* (Martyniaceae) is a herb that grows in American tropical areas which is used in traditional medicine. Examination of this plant has led to the isolation of montbretol derivative **76** (Fig. 8) which showed trypanocidal activity against trypomastigote (IC₅₀ = 25 µM) and epimastigote (IC₅₀ = 69 µM) forms of *Trypanosoma cruzi*.⁴⁶ The study of the bark components of *Cryptomeria japonica* (Taxodiaceae) yielded 5,6-dehydrosugiol (**77**), which showed moderate cytotoxic activity against HL-60 tumour cells (IC₅₀ = 52.4 µM).⁷⁴ From the Chinese medicinal plant *Isodon lophanthoides* var. *graciliflorus* (Lamiaceae), graciliflorin E (**78**) and its precursor (**79**) (Fig. 8) were isolated.⁷⁹ Both compounds demonstrated moderate cytotoxicity on A549, MCF-7 and HeLa tumour cells with the IC₅₀ values ranging from 20.61 to 52.67 µM. The well known plant in folk medicine in South China *Isodon lophanthoides* var. *gerardianus* (Lamiaceae), which is used as a tea or herbal drug to prevent and cure hepatitis has been chemically studied. A number of abietanes have been isolated in this research leading to the isolation of isolophanthins A-D (e. g. D, **80**) (Fig. 8). Compound **80** displayed significant activity against hepatitis B virus (IC₅₀ < 0.02 mM, SI > 3.0).¹³⁷

Another subgroup of abietatetraenes are 6,7-dehydroabietanes exemplified by 6,7-dehydroferruginol (**81**) and compound **82** (Fig. 9). 6,7-Dehydroferruginol (**81**) isolated from *Taiwania cryptomerioides* (Cupressaceae) has shown antioxidant^{35b} activity as well as moderate cytotoxic⁷⁴ activity. Abietatetraene **82** was isolated from the heartwood of *Juniperus formosana* (Cupressaceae). It has demonstrated potent antiviral properties against severe acute respiratory syndrome coronavirus (SARS-CoV) (EC₅₀ = 1.57 µM, SI = 193 (in Vero E6 cells)).⁴⁷

Finally, the last group of aromatic abietanes are common in *Illicium* (Illiciaceae) species and are exemplified by 8,11,13,15-abietatetraene **83** (Fig. 9), which was isolated from *Illicium minwanense*.¹³⁸ However, an examination of this molecule did not show neurite outgrowth promoting activity. Angustanoic acid E (**84**) has been found in the roots of *Illicium jiadifengpi* and in the twigs

and leaves of *Illicium majus*.^{85,87} It has exhibited important antiviral properties against Coxsackie B virus as well as good anti-inflammatory activity (IC₅₀ = 2.47 µM). Jiadifenoic acids B (**85**) and C (**86**) (Fig. 9) were also isolated from *Illicium jiadifengpi* and were the most potent inhibitors found against Coxsackie virus B2, B3, B4 and B6 (IC₅₀ = 2.67-23.21 µM, SI = 10.74-55.89).⁸⁵ Chinese eaglewood, the resinous wood from the tree *Aquilaria sinensis* (Thymelaeaceae), is as crude drug used as a traditional sedative, analgesic and digestive medicine in China. Further examination via bioassay-guided fractionation through the *in vitro* inhibition of serotonin and norepinephrine reuptake in rat brain synaptosomes gave 10 new abietane diterpenoids, the aquilarabietic acids A-J (e. g. H, **87**) (Fig. 9). Compound **87** remarkably exhibited antidepressant activity at 10 µM.¹³⁹

Table 3. Biological activity found in compounds **71-87**.

Compound	Biological activity	Ref.
Coleon C, 71	Antitumour	128
Coleon U, 72	Antitumour	129
	Antimicrobial	130,131
	Antifungal	131
Coleon U 11-acetate, 73	Cytotoxicity	132
14-Deoxycoleon U, 74	Cytotoxicity	63,71 133
	α-Chymotrypsin inhibition	133
	Antimicrobial	134
	Anti-inflammatory	134
	Antifungal	135
	Montbretol, 75	Cytotoxicity
Antitumour		136
6,12,14-Trihydroxyabieta-5,8,11,13-tetraen-7-one, 76	Trypanocidal	46
5,6-Dehydrosugiol, 77	Cytotoxicity	74
Graciliflorin E, 78	Cytotoxicity	79
6,12,15-Trihydroxyabieta-5,8,11,13-tetraen-7-one, 79	Cytotoxicity	79
Isolophanthins D, 80	Antiviral	137
6,7-Dehydroferruginol, 81	Antioxidant	35b
	Cytotoxicity	71
3β,12-Diacetoxyabieta-6,8,11,13-tetraene, 82	Antiviral	47
Angustanoic acid E, 84	Antiviral	85
	Anti-inflammatory	87
Jiadifenoic acid B, 85	Antiviral	85
Jiadifenoic acid C, 86	Antiviral	85
Aquilarabietic acid H, 87	Antidepressant	139

3 Structure-activity relationships

Some structure-activity features can be identified for the most studied biological properties (antimicrobial, antiviral and antitumour) of naturally occurring aromatic abietanes.

For example, it is found that either a carboxylic acid (DHA, **2**) or a hydroxymethyl group (pomiferin A, **14**) at the C-18 position provides the dehydroabietane skeleton with antimicrobial activity. Likewise, this biological property is observed in phenolic compounds with a hydroxyl group at C-12, such as ferruginol (**3**) and some congeners, including sugiol (**17**) with a carbonyl group at C-7. The presence of a carboxylic group at C-20, as in carnosic acid (**57**) and related compounds, also delivers molecules with antimicrobial properties. This activity is also displayed by catechol-containing molecules such as carnosol (**60**) and certain coleons.

A common structural characteristic in most of the antiviral aromatic abietanes is a carboxylic acid at C-19, exemplified by callitrisic acid (**47**), majusanic acids, and some jiadifenoic acids,

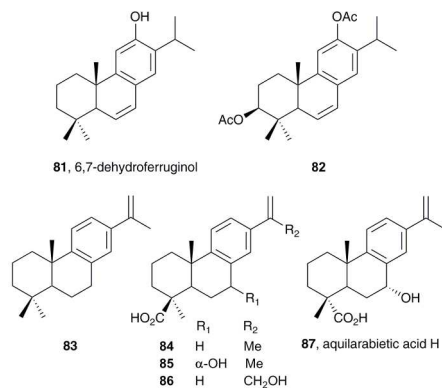


Figure 9. Abietatetraenes **81-87**.

including compounds with a functionalised isopropyl group with either hydroxyl groups or a double bond.

With respect to the structural requirements for antitumour activity, some key elements are a carboxylic group (DHA, **2**; **8**) or a hydroxymethyl group (**13-15**) at the C-18 position. Likewise, phenolic compounds with a hydroxyl group at C-12, such as ferruginol (**3**) and some congeners, including sugiols **17**, **19** and **41** with a carbonyl group at C-7. The presence of a carboxylic group at C-20 along with a hydroxyl group at C-12, as in pisiferic acid (**56**) orarnosic acid (**57**) and related compounds, also delivers molecules with antitumour properties. This property is also displayed by catechol-containing molecules such asarnosol (**60**) and its congeners, and certain coleons with the additional diosphenol moiety in the B ring.

4 Synthetic studies overview

A number of syntheses of aromatic abietane diterpenoids have appeared since the first isolations in the late 1930s. The earliest synthesis example, in 1938, addressed the synthesis of dehydroabietic acid (**2**, DHA) and was a semisynthetic route from abietic acid (**1**). The first total synthesis was carried out in 1939 and dealt with racemic 4-epidehydroabietic acid (**47**, callitrisic acid) (Fig. 5) before its isolation from natural sources. From the mid-1950s until 1979, several racemic total syntheses were developed. In 1979, the first enantioselective total synthesis of (+)-ferruginol (**3**) was reported by a Japanese research group. Only recently, in 2014, the enantioselective total synthesis of DHA (**2**) has been described by the Corey's research group at Harvard. An overview of the synthetic studies of this group of abietanes is presented below. Thus, some partial syntheses will be described from other natural products (semisynthesis), and finally several key total syntheses.

Several naturally occurring compounds have been used as enantiomerically pure starting materials for the synthesis of bioactive abietanes. Some are commercially available as for example, abietic acid (**1**), dehydroabietic acid (**2**), podocarpic acid (**88**), and sclareol (**89**) (Fig. 10). Other are obtained directly from natural sources as for example, abieta-8,11,13-triene (**5**), callitrisic acid (**47**) and pisiferic acid (**56**) (Fig. 10). These starting materials are converted into versatile tricyclic intermediates having the characteristic ABC-ring system of abietanes, which are subjected to functionalisation to obtain the desired products.

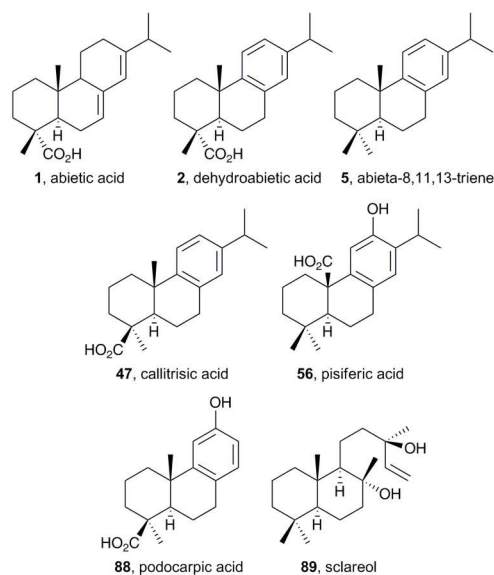
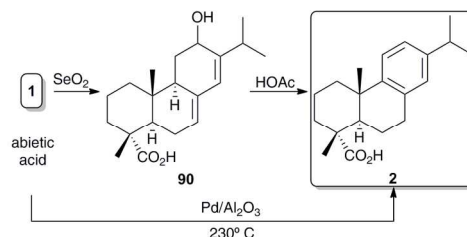


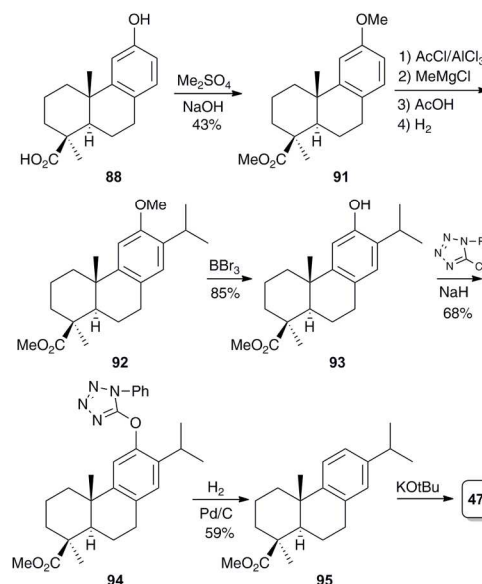
Figure 10. Starting materials for the semisynthetic studies.

In 1938, Fieser and Campbell reported the first synthesis of DHA (**2**).¹⁰ It happened before this naturally occurring diterpenoid was isolated from natural sources. The synthesis started from abietic acid (**1**) which was converted into 12-hydroxyabietic acid (**90**) by treatment with SeO_2 (Scheme 3). Heating of **90** at reflux in HOAc gave DHA (**2**). Simultaneous studies by Littmann described the preparation of DHA (**2**) and its corresponding methyl ester directly from abietic acid (**1**) (Scheme 3). This simplified method consisted of the disproportionation of abietic acid (**1**) over a palladium catalyst.¹⁴⁰



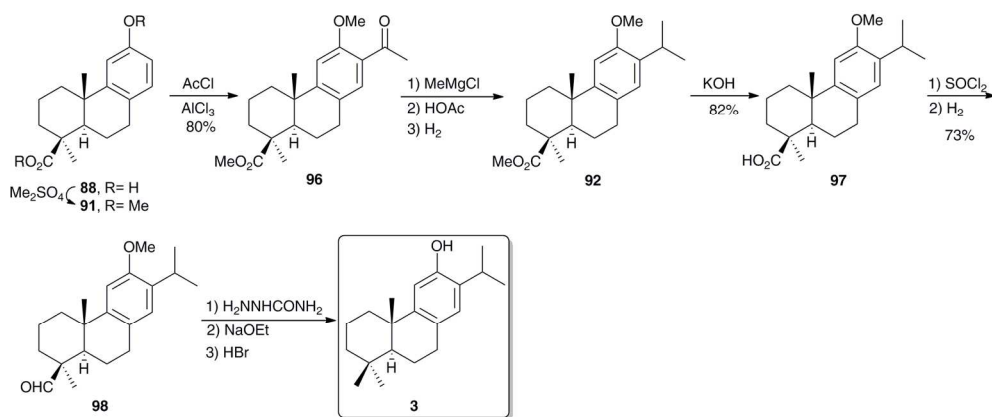
Scheme 3. Fieser's and Littmann's syntheses of DHA (**2**).

Huffman described the synthesis of 4-epidehydroabietic acid (**47**, callitrisic acid) (Scheme 4) from podocarpic acid (**88**).¹⁴¹ Thus, podocarpic acid (**88**) was treated with dimethyl sulfate and base to give methoxy-ester **91** which was converted into methyl 12-methoxyabieta-8,11,13-trien-19-oate **92** by Friedel-Crafts acetylation, reaction with methylmagnesium chloride followed by dehydration and catalytic hydrogenation. Then, cleavage of the methoxy group with BBr_3 gave methyl 12-hydroxyabieta-8,11,13-trien-19-oate **93**, which was treated with NaH and 1-phenyl-5-chlorotetrazole to afford phenyltetrazolyl ether **94**. The hydrogenolysis of **94** proceeded smoothly under mild conditions to give methyl 4-epidehydroabieta-8,11,13-trien-19-oate (**95**, methyl callitrisate), which was hydrolysed with KOtBu to afford 4-epidehydroabietic acid (**47**, callitrisic acid).



Scheme 4. Huffman's synthesis of 4-epidehydroabietic acid (**47**).

The synthesis of ferruginol (**3**) has been studied extensively. This bioactive phenol has attracted much attention from synthetic chemists and a number of synthetic routes have been described. The first synthesis of ferruginol (**3**) was carried out in 1942 by Campbell



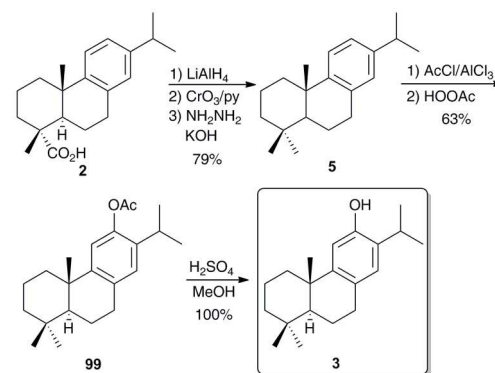
Scheme 5. Campbell's and Todd's synthesis of ferruginol (3).

and Todd from podocarpic acid (88) (Scheme 5).¹⁴² Podocarpic acid (88) was methylated with dimethyl sulfate followed by Friedel-Crafts acetylation to give methyl ketone 96. The treatment of 96 with methyl magnesium chloride followed by dehydration and hydrogenation led to the compound 92 containing the isopropyl group typical of abietanes. Hydrolysis of the ester group in 92 with KOH gave acid 97 which was subjected to chlorination and Rosenmund reduction to give aldehyde 98. Formation of the semicarbazone of 98 and reduction with excess sodium ethoxide followed by treatment with hydrobromic acid afforded ferruginol (3).

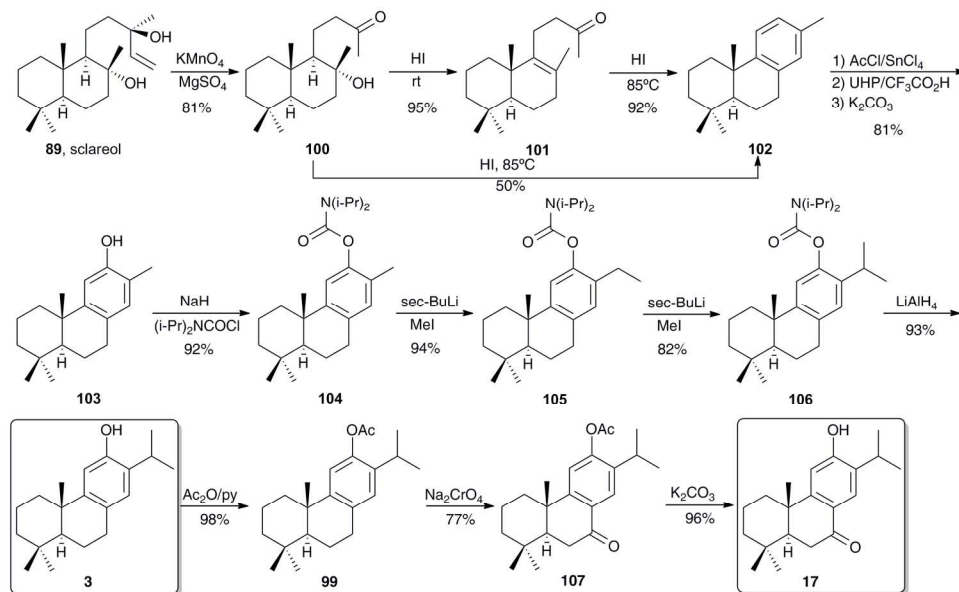
Almost forty years later, Oishi and Akita described another synthesis of ferruginol (3) via dehydroabietane 5, which was prepared from dehydroabiatic acid (2) (Scheme 6).¹⁴³ Firstly, the carboxyl group in 2 is converted into a methyl group by reduction, oxidation to the aldehyde and modified Wolff-Kishner reduction in 79% overall yield. Then, Friedel-Crafts acetylation of 5 followed by Baeyer-Villiger oxidation with HOOAc gave 12-acetoxy compound 99, and this was hydrolyzed with conc. H₂SO₄ in MeOH to give ferruginol (3) in 63% overall yield.

In 2010, Marcos et al. described the synthesis of ferruginol (3) and sugiol (17) from sclareol (89) using as key step the side chain

lithiation of a dinorditerpene precursor (Scheme 7).¹⁴⁴ Thus, sclareol was transformed into methylketone 100 by treatment with KMnO₄ and MgSO₄. The podocarpene derivative 102 can be directly obtained in a 50% yield from 100 by treatment with HI and heating at 85°C, but the transformation could be achieved in a better yield in



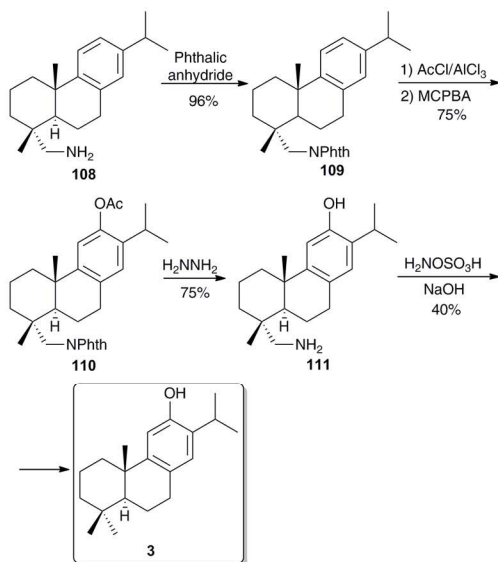
Scheme 6. Oishi's synthesis of ferruginol (3).



Scheme 7. Marcos' syntheses of ferruginol (3) and sugiol (17).

two steps. The treatment of **100** with HI at room temperature gave compound **101** in nearly quantitative yield, which on heating at 85°C with HI led to the podocarpane **102** in an excellent yield. The introduction of the hydroxyl group at C-12 followed the classical Friedel-Crafts acetylation followed by Baeyer-Villiger oxidation and hydrolysis to give phenol **103**. Compound **103** was converted into the carbamoyloxy derivative **104** since the carbamoyl was the chosen group for directing the side chain lithiation. Compound **104** was treated with a big excess of *sec*-BuLi at -78°C and the lithiated species were made to react with an electrophile as MeI to give norditerpenoid **105**. The same process was repeated on **105** to complete the abietane carbon skeleton giving compound **106**, which was reduced with LiAlH₄ to afford ferruginol (**3**). Acetylation of **3** with Ac₂O gave the acetyl derivative **99**, which by oxidation with Na₂CrO₄ led to ketone **107**. Finally, hydrolysis of **107** with K₂CO₃ gave sugiol (**17**).

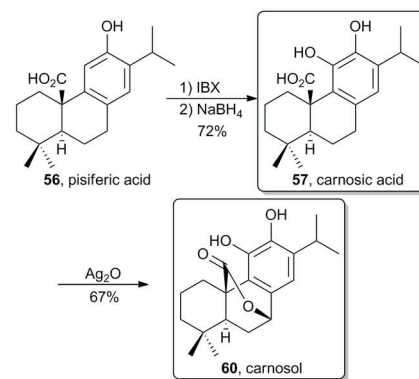
Recently, González and Pérez-Guaita reported a short synthesis of ferruginol (**3**) from commercially available (+)-dehydroabietylamine (**108**) (Scheme 8), which is not a natural product but derived from industrial rosin amine.¹⁴⁵ In order to prepare ferruginol (**3**) from **108**, the introduction of a hydroxyl group at C-12 and deamination were required. Thus, classical sequence of Friedel-Crafts acetylation followed by Baeyer-Villiger oxidation on phthaloyl protected dehydroabietylamine, compound **109**, led to phthaloyl-acetate **110** in high yield. Simultaneous cleavage of the acetate and phthaloyl groups in **110** was carried out by treatment with hydrazine leading to amino-phenol **111**. This was reductively deaminated upon treatment with hydroxylamine-O-sulfonic acid (HOS) in aqueous basic media to give ferruginol (**3**) in gram scale, though in moderate yield.



Scheme 8. González's synthesis of ferruginol (**3**).

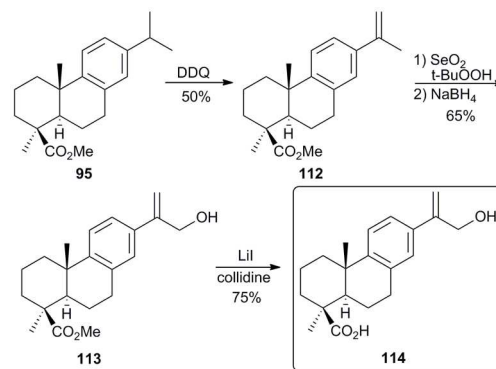
Simultaneous studies by Tada et al. reported the synthesis of bioactive carnosic acid (**57**) and carnosol (**60**) from natural pisiferic acid (**56**) (Scheme 9).¹⁴⁶ Thus, the oxidation of **56** to introduce a hydroxyl group at C-11 was carried out with several reagents. The best results were found after treatment of **56** with 2-iodoxy-benzoic acid (IBX) giving an unstable ortho-quinone which was reduced with NaBH₄ to carnosic acid (**57**). Benzylic oxidation of **57** with Ag₂O gave desired carnosol (**60**) with *in situ* lactonisation.

González et al. have just reported the synthesis of the antiviral diterpenoid jiadifenoic acid C (**114**) from callitrisic acid (**47**) isolated from sandarac resin (Scheme 10).¹⁴⁷ Callitrisic acid (**47**) was used as



Scheme 9. Tada's synthesis of carnosic acid (**57**) and carnosol (**60**).

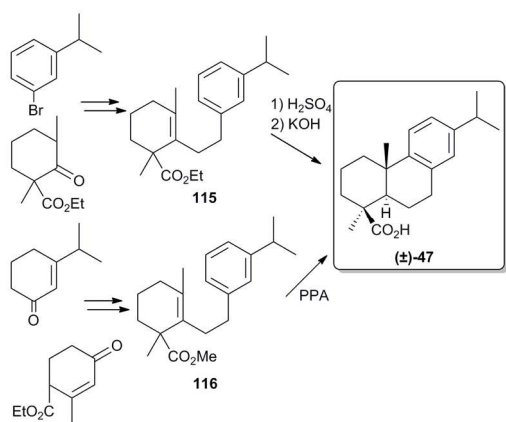
its methyl ester (**95**, methyl callitrisate) which was converted into tetraene **112** by treatment with DDQ. Allylic C-17 oxygenation with catalytic SeO₂ and *t*-BuOOH as co-oxidant gave, after treatment with NaBH₄, alcohol **113**. Ester hydrolysis of **113** with LiI in collidine afforded jiadifenoic acid C (**114**) in 22% overall yield from methyl callitrisate (**95**).



Scheme 10. González's synthesis of jiadifenoic acid C (**114**).

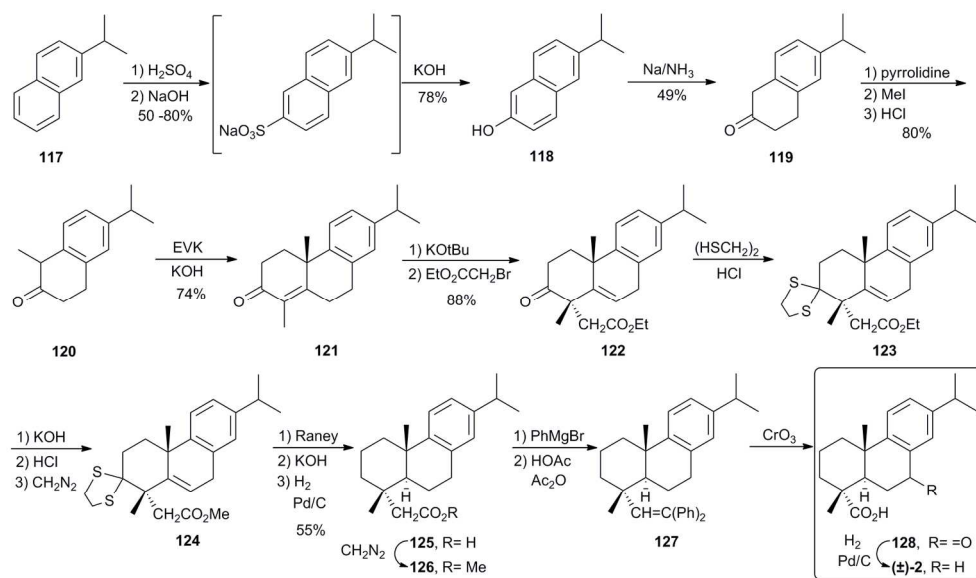
As mentioned previously, most of the studies directed toward the total synthesis of aromatic abietane diterpenoids are racemic, including the synthesis of resin acids (\pm)-DHA (**2**), (\pm)-callitrisic acid (**47**), as well as the synthesis of (\pm)-ferruginol (**3**) and some of its congeners. The first enantioselective total synthesis of an aromatic abietane diterpenoid occurred in 1979, when (+)-ferruginol (**3**) was obtained by a Japanese research group. Since then, several enantioselective total syntheses of this terpenoid have been achieved, including the synthesis of its enantiomer. Only recently, in 2014, the enantioselective total synthesis of DHA (**2**) has been described by the Corey's research group at Harvard.

The first total synthesis of a diterpene resin acid, (\pm)-callitrisic acid (**47**), was reported by Haworth and Barker as early as 1939 (Scheme 11).¹⁴⁸ Interestingly, it occurred 28 years before the natural product was isolated.⁸⁴ The synthesis exploited the Bogert-Cook reaction on a cyclohexene **115** which is appropriately substituted with a phenylethylene moiety. Cyclohexene **115** was obtained from 3-bromocumene and 2,6-dimethylcyclohexanone-2-carboxylate. Cyclisation of **115** with HOAc-H₂SO₄ gave a tricyclic ester, which was hydrolysed with KOH to give (\pm)-**4**. In 1963, the same strategy was used by Sharma et al. using polyphosphoric acid (PPA) for the key cyclisation step on the cyclohexene **116**, which was prepared from 3-isopropylcyclohexenone and 4-carbomethoxy-3-methyl-2-cyclohexen-1-one (Scheme 11).¹⁴⁹



Scheme 11. Haworth's and Sharma's syntheses of callitricic acid (47).

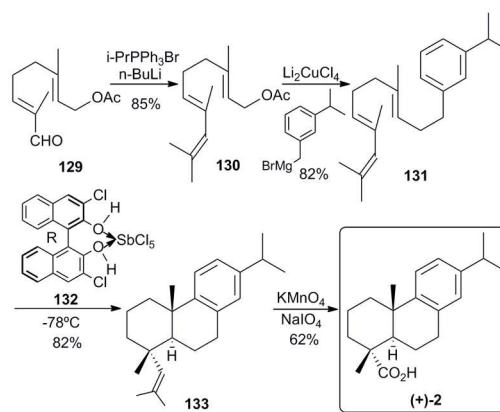
The first total synthesis of (±)-dehydroabietic acid (2) was reported in 1956 by Stork and Schulenberg, starting from 2-isopropyl-naphthalene 117 via phenanthrone 121 (Scheme 12).¹⁵⁰ The key step was the alkylation of 246 with ethyl bromoacetate which defined the stereochemistry of the C-4 center. Thus, sulfonation 2-isopropyl-naphthalene 117 gave a sodium sulfonate salt which was not purified and was directly converted into 6-isopropyl-2-naphthol 118 by fusion with KOH. Birch reduction of naphthol 118 gave 6-isopropyl-2-tetralone 119, which was alkylated via pyrrolidine enamine with MeI to afford methyl ketone 120. Ring annelation of tetralone 120 with ethyl vinyl ketone (EVK) in the presence of aqueous methanolic KOH afforded tricyclic enone 121. Enone 121 was alkylated by treatment with KOtBu and EtO₂CCH₂Br to the desired keto ester 122. Conversion of 122 into its thioketal 123 was accomplished by treatment with HSCH₂CH₂SH in the presence of anhydrous HCl. Then, thioketal 123 was converted into its methyl ester 124 by saponification and esterification with CH₂N₂. Desulfurisation with Raney nickel followed by ester hydrolysis and hydrogenation with Pd-C in HOAc afforded homodehydroabietic acid 125, which was converted into its corresponding methyl ester, compound 126, with CH₂N₂. Barbier-Wieland degradation of the ester 126, via the diphenylcarbinol and diphenylethylene 127 with chromic acid, gave 7-oxo-dehydroabietic acid 128, which was converted into (±)-dehydroabietic acid (2) by hydrogenation on Pd-C. This synthesis was a milestone in diterpene



Scheme 12. Stork's and Schulenberg's synthesis of dehydroabietic acid (2).

chemistry.

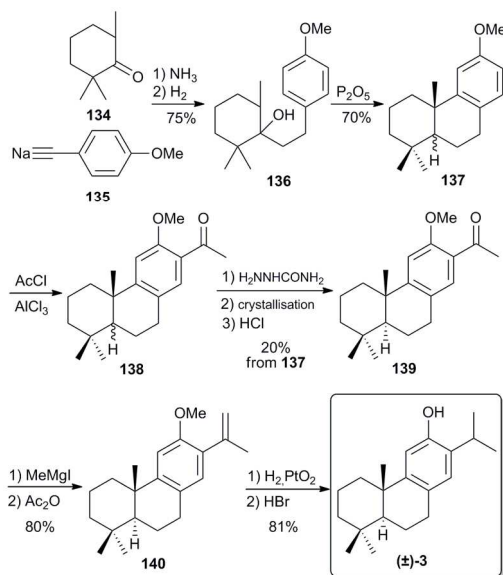
Very recently, Corey et al. reported a very short enantioselective synthesis of (+)-dehydroabietic acid (2) starting from a derivative of geranyl acetate, compound 129, using as key step an enantioselective cationic polycyclisation with *o,o'*-dichloro-R-BINOL (132) complex with SbCl₅ (Scheme 13).¹⁵¹ Compound 129 was converted into olefin 130 by Wittig reaction. Coupling of 130 with *m*-isopropylbenzylmagnesium bromide by Copper catalysis (Li₂CuCl₄) gave the cyclisation precursor 131. This substrate underwent smooth cyclisation with the complex 132-SbCl₅ to the required tricyclic product 133 with high enantioselectivity (91% ee) and high yield (82%). Subsequent degradation of the olefin 133 with KMnO₄ and NaIO₄ afforded (+)-dehydroabietic acid (2).



Scheme 13. Corey's enantioselective synthesis of dehydroabietic acid (2).

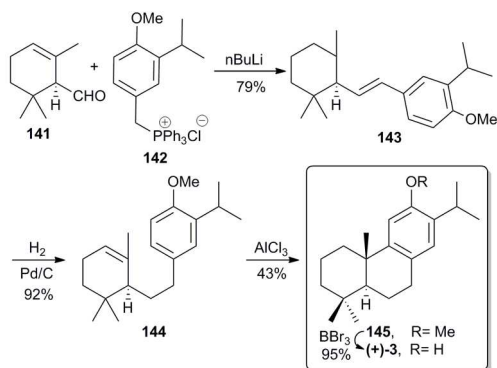
Synthetic efforts directed toward ferruginol (3) have employed various permutations of the order in which the three rings are assembled. The earliest approach by King et al., 1957, utilised the Bogert-Cook ring-closure (Scheme 14), as in the synthesis of callitricic acid (47) (Scheme 10), but suffered from a lack of stereoselectivity in the A/B ring fusion. However, this synthesis represented the first established synthesis of the racemic form of a naturally occurring tricyclic diterpene.¹⁵² The synthesis started with the preparation of cyclisation precursor 136 by reaction of 2,2,6-trimethylcyclohexanone 134 and sodium *p*-methoxyphenylacetylde 135 in liquid ammonia followed by hydrogenation with a palladium

catalyst. Cyclisation of **136** with phosphoric oxide (P_2O_5) gave a mixture of cis- and trans-isomers (**137**) in the A/B ring juncture. This mixture was subjected to Friedel-Crafts acetylation with AcCl and $AlCl_3$ to give a mixture of ketones **138**, which were separated by fractional crystallisation of the corresponding semicarbazones. Regeneration of the ketone by hydrolysis with HCl gave pure trans-isomer **139** in 20% overall yield from mixture **137**. Reaction of pure isomer **139** with MeMgI gave a tertiary alcohol, which was dehydrated with Ac_2O to the isopropenyl derivative **140**. This was hydrogenated with Adams (PtO_2) catalyst and then demethylated with HBr to give (\pm)-ferruginol (**3**).



Scheme 14. King's synthesis of ferruginol (**3**).

The first total synthesis of (+)-ferruginol (**3**) was achieved by Matsumoto and Usui in 1979 (Scheme 15).¹⁵³ They started the synthesis from (-)- α -cyclocitral (**141**), which was subjected to Wittig reaction with (3-isopropyl-4-methoxybenzyl) triphenylphosphonium chloride **142**. The resulting trans alkene **143** was submitted to partial catalytic hydrogenation to afford cyclisation precursor **144**. Treatment of **144** with anhydrous $AlCl_3$ gave a mixture of two tricyclic compounds. The chromatographic purification of the mixture afforded ferruginyl methyl ether (**145**) and its cis-isomer in a ratio of 1:1. Demethylation of **145** with BBr_3 gave (+)-ferruginol (**3**).



Scheme 15. Matsumoto's enantioselective synthesis of ferruginol (**3**).

5 Future directions

As illustrated in this review, nature is an abundant source of novel chemotypes and pharmacophores. However, only a small number of the different species of higher plants have been systematically investigated for the presence of bioactive compounds. Further research with different species to those species presented herein will surely provide new insights in phytochemistry and the discovery of biological properties on novel abietanes and known compounds. It would be interesting to study different biological properties to those studied upon isolation due to the wide range of activities observed. This could lead to the identification of promising lead compounds.

For the synthetic chemistry community, one important challenge is the development of efficient enantioselective routes. This task is still in its infancy. Known Friedel-Crafts methods have been used, but other cyclisation reactions could be explored as per example radical chemistry. Novel semisynthetic studies could also be developed with available abietanes and related compounds such as podocarpic acid (**88**).¹⁵⁴ The chemistry of the latter has been intensively studied and provides a good reference for the aromatic substitution reactions on ring C. Selective functionalisation of the isopropyl group in the dehydroabietane skeleton has recently been achieved.¹⁵⁵ This could lead to the synthesis of a number of abietanes functionalised at the isopropyl group. As mentioned above, the development of enantioselective approaches is important as an organic synthesis achievement itself, but also from the medicinal chemistry point of view, since it has been demonstrated that some unnatural enantiomeric abietanes possess enhanced bioactivity (i. e., (-)-ferruginol).¹⁵⁶

The biological activities of synthetic derivatives of aromatic abietanes have been reviewed.⁸ In particular, the biological activities of dehydroabietic acid (**2**), ferruginol (**3**), carnosic acid (**57**) and dehydroabietylamine (**108**) derivatives are described in that review. From that study, it can be deduced that little work has been done to modify both the C-18 position and ring C and/or B. Most of the studies, have been carried out with modification at C-18. It would be interesting to modulate the properties of derivatives modifying B and/or C ring, as well as C-18 and/or C-20 (in the case of carnosic acid derivatives). Therefore, there are still interesting modifications to be explored.

Last, it is possible than in the future this field will move in the direction of chimeric drugs and analogues. The first attempts are promising.¹⁵⁷

6 Conclusions

The scientific investigations of the aromatic abietane group of diterpenoids has been an active field during the last two decades producing a high number of publications on isolation and structural characterisation of its members, including many preliminary biological studies. The work listed in this review justifies the potential for discovery of novel pharmaceutical agents and biological probes in this area of research. The availability of several natural terpenoids in large amounts, such as abietic acid, dehydroabietic acid and podocarpic acid has allowed several semisynthetic studies. For over 50 years, abietane diterpenoids have been synthesised by Friedel-Crafts cyclisations, but the synthetic studies are still a minor fraction of the investigations in the area. It is hoped that the synthetic community will be attracted by these diterpenoids in order to allow further studies and also obtain novel bioactive lead compounds.

7 Acknowledgments

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