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Enantiomeric Natural Products: Occurrence and Biogenesis**

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Abstract

In Nature, chiral natural products are usually produced in optically pure form; however, on occasion Nature is known to produce enantiomerically opposite metabolites. These enantiomeric natural products can arise in Nature from a single species, or from different genera and/or species. Extensive research has been carried out over the years in an attempt to understand the biogenesis of naturally occurring enantiomers, however, many fascinating puzzles and stereochemical anomalies still remain.

1. Introduction

Terrestrial and marine plants, animals, fungi, and bacteria (among others) are known to produce a multitude of secondary metabolites, often referred to as "natural products."[1] Contrary to the required production of primary metabolites in order to sustain life, organisms can generally survive without the production of secondary metabolites; however, these metabolites often aid in the reproductive and/or defensive efforts of the species that produce them.[2,3] From a medicinal standpoint, many natural products also provide a rich source of bioactive agents, such as antitumoral, antibacterial, anti-insecticidal, anthelmintic, antinematodal, immunosuppressives, among other clinically relevant activities which have been widely exploited for both synthetic and semi-synthetic drug discovery and development efforts.[4,5]

In the vast majority of cases, chiral natural products are produced in Nature in optically pure form, where only one enantiomer is biosynthesized in the producing organism.[1,6] For example, only the biologically active (−)-isomer of morphine is produced by Nature, specifically by the opium poppy plant *Papaver somniferum*.[7] On the other hand, the production and isolation of enantiomeric metabolites is known, but in a relative sense to the overall abundance of secondary metabolites, remains a rare occurrence. These enantiomerically opposite metabolites can be produced by different genera or species, where one enantiomer is isolated from one species while the other enantiomer is isolated from a different species or genera; or both enantiomers may be produced and isolated as either a racemic or scalemic mixture (where one enantiomer predominates) from a single species.[6a]

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Efforts to elucidate the biosynthetic pathway of bioactive natural products have been an area of intense research for over seventy-five years to both organic chemists and biologists.[2,4] However, the biogenesis of enantiomeric metabolites is generally not well understood. This is due in part to the fact that oftentimes one enantiomer always predominates over the other in Nature, as is the case with (−)-nicotine,[8] and in many other instances, the other natural enantiomer may be discovered years or decades later. As a result, the biosynthesis of the major and sometimes more bioactive enantiomer is well-studied, while the biosynthesis of the minor enantiomer remains unknown.

This Review is intended to provide an overview of the occurrence of well-known enantiomeric natural products produced in Nature, and to present a discussion, when applicable, of how these rare enantiomerically opposite metabolites arise biosynthetically. Due to the overwhelming number of known secondary metabolites, and the often overlooked reporting of the optical rotation, or CD spectra of like substances obtained from different sources, not all enantiomeric natural products have been identified. Furthermore, despite decades of research, not all of the biosynthetic pathways for the formation of enantiomeric natural products are fully understood; therefore, biogenetic discussions will focus on those metabolites where substantial and relevant biosynthetic research has been carried out. The present review is organized into classes of secondary metabolites based on their main biosynthetic derivations: terpenes (isoprene), phenylpropanoids (shikimic acid), polyketides (acetate), and alkaloids (amino acids). In many cases, these partitions are superficial since oftentimes, many natural products are of mixed biosynthetic origins (for example, the terpenoid alkaloids or mixed polyketide-nonribosomal peptide metabolites).

2. Terpenes

The terpenes are a large group of structurally diverse natural products numbering well over 30,000 compounds.[9,10] Typically isolated from a wide variety of plant species, these secondary metabolites display myriad biological activities ranging from pollinator attractants and chemical defenses for plants to essential oils and anti-cancer drugs for human clinical use.[10] All terpenoids are constructed from the head-to-tail condensation of repeating C_5 isoprene units and are further subdivided into families based on the number of isoprenoid residues. The monoterpenes (C_{10}) are the smallest structural type, followed by the sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), triterpenes (C_{30}), tetraterpenes (C_{40}), and polyterpenes ($>C_{40}$).

Enantiomeric terpenoids are (in a relative sense) rather common; however, they are generally limited to monoterpenes, sesquiterpenes, and on the rare occasion, diterpenes. Currently, (+)- and (−)-wistarin are the only examples to date of enantiomeric sesterterpenes (Figure 1), and the biosynthetic formation of these enantiomers is yet to be investigated.[11] Extensive research has been put forth toward determining the biosynthesis of enantiomeric monoterpenes, and while the biosynthesis of sesquiterpenes and diterpenes is understood, there are several unanswered questions about the formation of enantiomerically opposite secondary metabolites.

2.1-Monoterpenes

The C_{10} monoterpene family of secondary metabolites are mainly isolated from higher plants and make up the flavor and aroma components of many essential oils of herbs, spices, citrus, and conifers.[12] The biosynthesis of monoterpenes has been thoroughly investigated via isotope studies with enzyme preparations and the isolation of cDNAs encoding monoterpene synthases;[13] however not all of the biosynthetic routes leading to the monoterpenes are fully understood.

Over the years, considerable attention has been placed specifically on the stereochemistry and mechanism of the cyclization reactions.[10,14,13a,15] Decades of research have established that monoterpene synthases are responsible for the formation of acyclic, monocyclic, and bicyclic monoterpenes, and that each synthase is capable of generating multiple products at the same active site. Since the co-occurrence of both monoterpene enantiomers in the same species is fairly common, interest has focused on determining how these enantiomers arise biosynthetically. With the isolation and characterization of numerous cyclases from *Salvia, Mentha, Tanacetum, Foeniculum, Pinus*, and *Citrus* species, including (+)-limonene synthase from *Mentha piperita* (peppermint), (−)-limonene synthase from *Carum carvi* L. (caraway seeds), and (+)- and (−)-α-pinene synthases from *Salvia officinalis* (sage), it was determined that monoterpene enantiomers can arise independently via stereochemically distinct routes; however, not all monoterpene synthases are completely stereospecific, as observed in the (−)-limonene synthase isolated from caraway seeds (discussed below).[10,13a]

The sizeable amount of research that has been carried out on the monoterpenes has led to the formation of a widely accepted mechanism for the monoterpene cyclization reaction (Scheme 1).[10,13a] To start, GPP stereoselectively binds in the active site as either a right-handed or left-handed helical conformer. GPP then undergoes ionization and isomerization to afford either (3*R*)- or (3*S*)-linalyl diphosphate (LPP), respectively. The enzyme-bound (3*R*)- or (3*S*)-LPP then undergoes a second ionization that initiates the C6-C1 cyclization to afford the α-terpinyl cation in either the (4*R*)- or (4*S*)-form, respectively. From this universal monocyclic intermediate a plethora of mechanisms (further electrophilic cyclization, hydride shifts, or Wagner-Meerwein rearrangements) are possible for the formation of the various monoterpene skeletons, which is finally terminated by deprotonation or nucleophilic capture.

As shown in Table 1, many of the chiral monoterpenes are produced in both enantiomeric forms, often by the same plant species. Additionally, many of the enantiomeric monoterpenes display unique biological activity, oftentimes with each enantiomer exhibiting distinct biological properties. Efforts to elucidate the biosynthetic formation of enantiomeric monoterpenes have been greatly aided by the isolation and characterization of several monoterpene synthases. Discussed below are three well-studied enantiomeric monoterpene biosyntheses (limonene, carvone, and α-pinene) for which distinct stereospecific enzymes have been identified that catalyze the cyclization of GPP to the corresponding monoterpene olefins of opposite configurations.

2.1.1-Limonene and Carvone—Limonene is a widely distributed cyclic monoterpene and is a common precursor to the *p*-menthane family of natural products, as well as to the known monoterpene carvone. Both limonene and carvone are unique from a bioactivity perspective, in that each enantiomer exhibits a distint scent. Perhaps the most well known example of this is that (+)-carvone smells of caraway, while the enantiomer produces a spearmint odor.[16a]

The two limonene enantiomers known to occur in Nature are produced as either a single enantiomer or as a mixture of enantiomers, depending on the species. Limonene is derived from GPP, and through cell-free extracts and enzyme preparations two distinct limonene cyclases (synthases) have been identified from several species.[4,15d,17–24] As shown in Scheme 2, when tritium-labeled GPP was reacted with limonene synthase isolated from *Mentha piperita* (peppermint) and *Mentha spicata* (spearmint), (−)-^{3}H-limonene was obtained.[17] On the other hand, a soluble limonene cyclase preparation was obtained from *Citrus sinensis* (Valencia oranges), which when reacted with tritium labeled GPP, enantiomerically pure (+)-limonene was obtained.[18] Likewise, when tritium-labeled GPP

was reacted with a limonene synthase isolated from *Carum carvi* L. (caraway seeds), a 98:2 mixture of (+)- and (−)-limonene was observed, thus indicating that the limonene synthase from caraway seeds favors formation of (+)-limonene.[24]

Carvone is also a cyclic monoterpene in which both enantiomers have been isolated. Through precursor incorporation studies and enzyme preparations, limonene has been established as a biosynthetic precursor to carvone.[17a,23,25] Two sets of enantioselective enzymes responsible for the conversion of (+)- or (−)-limonene to (+)- or (−)-carvone, respectively, have been isolated and characterized. As shown in Scheme 3, (−)-limonene-6-hydroxylase and (−)-*trans*-carveol dehydrogenase have been identified in *Mentha spicata* (spearmint), which catalyze the enantioselective conversion of (−)-limonene to (−)-*trans*-carveol to (−)-carvone.[25] While these enzymes are highly stereospecific, the corresponding enantiomeric enzymes found in *Carum carvi* L. were not completely stereo- or substrate-specific. Both (+)- and (−)-limonene served as substrates for (+)-limonene-6-hydroxylase, and when (+)-limonene was reacted with the enzyme, only 97% if the expected (+)-*trans*-carveol was isolated. The other 3% was made up of a mixture of (−)-*trans*-carveol and (−)-*cis*-carveol. These unexpected metabolites also displayed significant enzyme activity with (+)-*trans*-carveol dehydrogenase.

2.1.2-Pinene—α-Pinene and β-pinene are widely distributed bicyclic monoterpenes and serve as the major constituents in the volatile oil from *Salvia officinalis* (common sage).[18,35] Both enantiomers of α-pinene are natural products and can co-occur with either enantiomer predominanting. Contrary to this, β-pinene is almost always isolated as the optically pure (−)-isoform. The isolation of the (+)-β-pinene isomer is known, albeit the production of this metabolite is rare.[30,31,33] Biosynthetic studies carried out by Croteau and co-workers in the 1980s revealed that two enantiomeric pinene cyclases exist within *Salvia officinalis*, (+)-pinene cyclase (cyclase I) and (−)-pinene cyclase (cyclase II).[42] Croteau demonstrated that when ^{3}H-GPP was reacted with each individual cyclase, the corresponding α-pinene enantiomers were formed (Scheme 4). In addition, (−)-β-pinene was formed from the reaction with cyclase II, whereas (+)-β-pinene was not detected from either cyclase reaction. From these reactions, minor amounts of (+)- and (−)-camphene and limonene were also formed as scalemic mixtures, (80% (+)-camphene isomer and 55% (−)-limonene isomer).[35,42,43]

2.2-Sesquiterpenes

The sesquiterpenes make up a diverse group of acyclic and cyclic C_{15} terpenes isolated from a wide variety of plant, fungal, bacterial, marine and insect species. Like the monoterpenes, sesquiterpenes are often found as components of essential oils, such as vetiver oil and cubeb oil, and display a wide range of pharmacological activity.[44,45] Unfortunately, in most instances, the optical rotation of the sesquiterpenes is not reported, and as such, critical information regarding biological activity remains unknown.

Over the past two decades numerous sesquiterpene synthases have been isolated and characterized, including 5-epiaristolochene,[46] epiubenol,[47] pentalene,[48] germacrene C,[49] γ-humulene,[49] and δ-selinene,[50] and the mechanisms of these enzymes have also been investigated;[11,45,51] however, the biosynthetic formation of enantiomeric sesquiterpenes has, for the most part, remained obscure. Recently, König et al. isolated and characterized two enantioselective germacrene D synthases from *S. canadensis*.[44,45] The presence of these two cyclases within *S. canadensis* helps to explain the production of both enantiomers of germacrene D within the species, as well as support the possibility that the biosynthetic pathway of other enantiomeric sesquiterpenes arise from multiple enantioselective enzymes within different species of the same genera.

Most sesquiterpenes are chiral, and some members of this family of natural products have been found to be produced in both enantiomeric forms.[44] Generally, enantiomeric sesquiterpenes are produced by different species within the same genera as shown in Table 2; however, there are notable exceptions, such as the isolation of both enantiomers of germacrene D from *Solidago canadensis* and *S. altissima*.[45,52] Another unique example is the isolation of both enantiomers of furodysinin from *Dysidea herbaceae*. The (+)-isoform was isolated from *D. herbaceae* collected from Australia,[53] whereas the (−)-isoform is produced by the same species collected in Fiji.[54] Another observable trend in the isolation of enantiomeric sesquiterpenes is that terrestrial and marine sources have sometimes been observed to produce opposite enantiomers. An example of this is seen in the isolation of several sesquiterpenes from the soft coral *Sinularia mayi*. Seven of the major metabolites isolated from *S. mayi* were the opposite enantiomers of the more common forms found in terrestrial sources.[55] This is most likely a common occurrence, however, the stereochemical investigation of marine sesquiterpenoids is frequently disregarded.[56]

2.3-Diterpenes

Diterpenes are isolated from numerous plants and fungi and are generally found in resins and essential oils. The structurally diverse family of diterpenes contains a C_{20} skeleton and is derived from the condensation of three equivalents of IPP with DMAPP to afford the acyclic geranylgeranyl diphosphate (GGPP) precursor.[10]

Similar to the monoterpenes and sesquiterpenes, enantiomeric diterpenes have been isolated, although their occurrence is rather rare (Table 3). The production of both enantiomers of various diterpenes can occur within the same species, or more commonly, within different species of the same genera. Unfortunately, biosynthetic studies on the formation of enantiomeric diterpenes have not been reported. Additionally, no biological activity has been reported for any of the individual diterpene enantiomers. As observed with the sesquiterpenes, optical rotation is generally not reported upon isolation of the diterpenes, and therefore, information concerning the occurance and biological activity of enantiomeric diterpenes is lacking.

3. Phenylpropanoids

Phenylpropanoids are found in numerous plant species and contribute greatly to plant defenses, structure, pigments, and reproduction.[85] Derived from the shikimate pathway, the phenylpropanoids are a class of natural products comprised of a vast array of diverse secondary metabolites formed from L-phenylalanine and/or L-tyrosine.[3] Lignins, lignans, flavonoids, coumarins, quinones, stilbenes, catechin, aurones and neoflavonoids are just a few of the many different types of phenylpropanoids derived from the enzymatic conversion of phenylalanine to the key intermediate *p*-coumaroyl-CoA, by way of the general phenylpropanoid pathway.[86]

3.1-Lignans

Lignans are phenylpropanoid dimers linked by the central C8 carbons of two phenylpropane units and make up an abundant class of phenylpropanoids.[87,88] Lignans are isolated from a wide range of plant species, specifically trees, and are believed to help prevent heart rot in trees.[88] They also display a plethora of biological activity, such as antitumor, antimitotic, and antiviral properties.[89] Some of the lignans produced early in the biosynthetic pathway also serve as lead compounds in the development of new drugs for the use in cancer therapies, such as the well-known podophyllotoxin-derived semisynthetic drug, etoposide.[89,90]

Enantiomerically, lignans can occur as mixtures of enantiomers with various enantiomeric compositions dependent upon the specific plant species. One extensively examined type of lignan is the early 9(9′) oxygenated lignans (pinoresinol, lariciresinol, secoisolariciresinol, and matairesinol). These lignans exists as either enantiomerically pure compounds, or as enantiomeric mixtures with various enantiomeric constitution.[91] As shown in Table 4, several trends are noticeable about these naturally occurring lignans: furofuran and furan lignans have never been isolated in optically pure form, while all dibenzylbutyrolactone lignans analyzed by chiral HPLC have been found to be optically pure. Furthermore, the predominant enantiomer of furofuran, furan, and dibenzylbutane lignans vary with plant species.[91] The optical rotation of the enantiomerically pure dibenzylbutyrolactone lignans were also found to vary between plant species.[92]

Like all phenylpropanoids, the lignans are derived via the cinnamate pathway. The biosynthetic pathway of 9(9′) oxygenated lignans is one of the more well-studied lignan pathways. The first five steps of this pathway have been extensively investigated and most of the enzymes responsible for the transformations and enantiomeric diversity seen in these types of lignans have been isolated and characterized. To date, several enantioselective lignan producing enzymes have been isolated and characterized. As shown in Scheme 5, the 9(9′) oxygenated lignans are formed by enantioselective dimerization of two coniferyl alcohol residues via an oxidase in the presences of a dirigent protein to afford pinoresinol in enantiomeric excess. The dirigent protein aids in controlling the stereospecificity of the bimolecular phenoxy radical coupling reactions of the two coniferyl alcohol units.[93]

Next, pinoresinol is stereoselectively reduced to lariciresinol, which is subsequently reduced stereospecifically to secoisolariciresinol via pinoresinol/lariciresinol reductase. Two isoforms of this enzyme have been isolated, each displaying opposite enantioselectivity (Scheme 6).

(+)-Pinoresinol/(+)-lariciresinol reductase has been isolated from *Forsythia intermedia* and *Thuja plicata*, whereas the (−)-pinoresinol/(−)-lariciresinol reductase was isolated from *Thuja plicata*.[94,95] Through incorporation studies it was determined that (+)-pinoresinol/lariciresinol reductases converts (+)-pinoresinol into (−)-secoisolariciresinol, and the opposite reductase converts (−)-pinoresinol into (+)-secoisolariciresinol.[95]

The final enzymatic conversion of secoisolariciresinol into enantiomerically pure matairesinol is not yet fully understood. (−)-Matairesinol is biosynthetically formed in various plant species (i.e. *Forsythia intermedia*, *Arctium lappa*, *Thuja occidentalis*, etc.); however, in Thymelaeaceae plants (*Wikstroemia sikokiana* and *Daphne odora*) the optically pure dextrorotatory enantiomer of matairesinol is produced. From *Forsythia intermedia*, secoisolariciresinol dehydrogenase was isolated and found to catalyze the enantioselective conversion of (−)-secoisolariciresinol into (−)-matairesinol (Scheme 7).[96] Secoisolariciresinol dehydrogenase preparation was also obtained from *Daphne odora* and *Daphne genkwa*, both known producers of the (+)-enantiomer of matairesinol; however, the in vitro reactions with enzyme preparation of both *Daphne* species resulted in the preferential formation of (−)-matairesinol.[97] To date, the biosynthesis of (+)-matairesinol remains unknown.

3.2-Flavonoids

Flavonoids make up a large, diverse family of aromatic secondary metabolites that are largely noted by the red, blue, and purple pigments found in plants.[111] Due to their colorful pigmentation, flavonoids are believed to act as an aid in plant reproduction by recruiting pollinators and seed dispersers. More recently, flavonoids have become an area of interest due to their association with the health benefits of wine, chocolate, fruits, and vegetables.

As shown in Table 5, the enantiomeric flavonoids occur mostly within three structural groups of flavonoids: the flavanones, flavonols, and isoflavonoids. Elucidation of the flavonoid biosynthetic pathway has been an area of growing research, with much of the attention recently being directed at the molecular genetics of the pathway.[71,86,111] Many of the enzymes responsible for the biosynthesis of the different subgroups of flavonoids have been isolated and characterized; however, the biosynthesis of enantiomeric flavonoids remains largely unresolved.

The biosynthesis of enantiomeric medicarpin has been investigated in both *Medicago sativa* L. (alfalfa) and *Arachis hypogea* (peanut), which are known producers of (−)- and (+)-medicarpin, respectively. The complete biosynthetic pathway of (−)-medicarpin has been determined by biochemical techniques and confirmed by gene cloning and expression experiments.[112,113] As shown in Scheme 8, the advanced achiral precursor 2′-hydroxyformononetin is converted to (*R*)-vestitone via isoflavone reductase, which subsequently reacts with pterocarpan synthase to yield (−)-medicarpin in alfalfa.[112] Contrary to what is known regarding the biosynthesis of (−)-medicarpin, there are several unanswered questions concerning the biosynthesis of (+)-medicarpin in peanut. Surprisingly, peanut isoflavone reductase in peanuts produces the same (*R*)-vestitone intermediate produced in alfalfa. This compound has the opposite substrate and product stereospecificity necessary for the pterocarpan synthase, thus indicating the possibility of an epimerase in peanut.

3.3-Coumarins

Coumarins are generally produced by higher plants and are also derived from the general phenylpropanoid pathway. Coumarins play an important role for plants by acting as a defense against phytopathogens.[124] They also display myriad bioactivities for human therapeutics, including antibiotics, anticoagulants, and analgesic properties.[125] Unlike the lignans and flavonoids, the formation of enantiomeric coumarins is not as common (Table 6), and therefore the biosynthesis of these enantiomeric secondary metabolites has not been investigated.

3.4-Neoflavonoids

The neoflavonoids are a group of secondary metabolites containing a C_6-C_3-C_6 skeleton and are closely related both structurally and biogenetically to the flavonoids, isoflavonoids, coumarins and quinones.[3,126] The neoflavonoids are found in a wide variety of plant families, including the Guttiferae, the Leguminosae, the Rubiaceae, the Passifloraceae, the Polypodiaceae, and the Compositae.

4-Methoxydalbergione is an open-chained neoflavonoid that contains a stereogenic center at the C-7 position, and is naturally produced as the (*R*)- or (*S*)-isoform from various species of the genera *Dalbergia*.[127] As shown in Table 7, the occurrence of enantiomeric open-chain neoflavonoids in Nature is limited; therefore, the biogenesis of enantiomeric neoflavonoids is unknown.

3.5-Quinones

Through numerous feeding experiments, it has been determined that quinones are also derived from phenylalanine, which is converted to the known intermediate *p*-hydroxybenzoic acid (PHB).[151] Subsequent prenylation at the C3 position affords *m*-geranyl-*p*-hydroxybenzoic acid, which is further converted to a key intermediate (geranylhydroquinone) in the biosynthesis of enantiomeric shikonin and alkannin (Scheme 9). Currently, the early steps in the biosynthesis of shikonin and alkannin are far more understood than the later steps. As shown in Table 8, these enantiomeric quinones and their

derivatives display a plethora of biological activity, including anti-inflammatory, antitumor, and antimicrobial activity. For a more in depth review of the chemistry and biology of alkannin, shikonin, and their quinone derivatives, please refer to the review by Nicolaou et al.[151]

4. Polyketides

Derived from acetate, polyketides represent a structurally diverse family of secondary metabolites produced by a wide variety of plants, fungi, bacteria, and insects.[3,154] The exact role of polyketides in producing organisms is not known, however, it appears as though several serve as either chemical defense agents or aid in the growth and development for plants. Polyketides also display important medicinal activity, such as antibiotic, anticancer and immunosuppressant properties.

There are several examples of enantiomeric polyketides biosynthesized throughout the plant kingdom (Table 9), however, not much is known about the enantioselective biosynthesis of many of these secondary metabolites. To date, extensive research has been carried out at an enzymatic level on the enantiomeric formation of macrotetrolide antibiotics (nactins) and benzylisochromanequinone antibiotics.

4.1-Macrotetrolides

The macrotetrolide antibiotics (nactins) are mainly produced by *Streptomyces* species and are biosynthetically formed from four monomeric units of nonactic acid (NA) or its homologs, homononactic acid and/or bishomonanactic acid (Figure 2).[155,156] Of the five known homologs (nonactin, monactic, dinactin, trinactin, and tetranactin), biosynthetic studies mostly focus on nonactin, a 32-membered macrocycle composed of two alternating units of (+)-nonactic acid and (−)-nonactic acid, which in turn makes nonactin achiral.[155,156,173–175]

The biosynthesis of nonactin has been well-studied through in vivo feeding esperiments with ^{13}C-, ^{2}H-, and ^{18}O- labeled precursors[173] and by the isolation of both nonactic acid enantiomers and its dimmer.[156] Recently, the biosynthetic research of nonactin has centered around the isolation and characterization of the genes and enzymes responsible for the biosynthesis of both enantiomers of nonactic acid.[155i] The biosynthesis of both NA enantiomers resulted in the proposal that the enantiomeric polyketide intermediates arise from a pair of enantiospecific pathways. The proposed biogenesis of the macrotetrolides, is supported through both feeding and enzymatic studies, which were carried out individually by Robinson, Priestley, and Shen.[155i,173–175] As shown in Scheme 10, the nactins are derived from malonyl-CoA, succinyl-CoA, and acetyl-CoA, which results in the formation of proposed intermediate **1**. Biosynthetic studies performed by Robinson and co-workers using ^{14}C-labeled compounds established that propionate also serves as a primary metabolic precursor, which most likely results in the formation of the proposed achiral intermediate **2**.[173] Since **2** is achiral, it can serve as a common precursor to both nonactic acid enantiocomplementary pathways.

Opposite stereospecific reductions of **2** would result in the generation of enantiomeric precursors, **3** and **4**. Work carried out by Robinson and Spavold confirmed that the acyclic intermediates **3** and **4**, as well as (6*R*,8*R*)- and (6*S*, 8*S*)-2-methyl-6,8-dihydroxynon-2*E*-enoic acids (NEA), were enantioselectively incorporated into nonactin via the respective (+)- and (−)-nonactate precursors.[173] However, the details of the conversion of the primary metabolites into **3** and **4** are still relatively unknown. Shen and co-workers garnered additional support for enantioelective pathways through enzymatic studies with NonS.[155i] They demonstrated that *nonS* governs only the enantioselective formation of (−)-NA and its

homologus in *S. griseus*, however, the enzyme responsible for the biosynthesis of (+)-NA remains elusive.

4.2-Benzoisochromanequinones

Kalafungin, actinorhodin, medermycin, dihydrogranaticin and nanaomycin are all antifungal and antimycoplasmal antibiotics that possess a benzoisochromanequinone (BIQ) skeleton and are produced by various *Streptomyces* species.[176] Structurally, the BIQs all show a *trans* configuration in respect of the C-3 and C-15 chiral centers, thus these metabolites can be grouped into one of two categories: dihydrogranaticin (DHGRA), which displays the (3*R*, 15*S*) configuration; or actinorhodin (ACT), which display the (3*S*,15*R*) stereochemistry (Figure 3).[177,178]

With the formation of enantiomerically opposite stereocenters in the ACT and DHGRA families, early stage enantiomeric intermediates have been isolated from different sources. Upon analysis of the numerous gene clusters (*act, kal, nnm, gra,* etc.) that have been identified, two enantioselective ketoreductases were identified; and as shown in Scheme 11, from a bicyclic intermediate, RED1/2 stereospecifically reduces the carbonyl functionality, which sets the C-3 stereochemistry.[178] In the ACT biosynthesis, the (*S*)-configuration is established via *act*-VI-ORF1 (RED1),[179] whereas the (*R*)-configuration is established in the dihydrogranaticin (DHGRA) biosynthesis by a completely unrelated *gra*-ORF6 ketoreductase, RED2.[177,180] These two enzymes show a remarkable difference in their substrate specificities as well as in the three-dimensional structures and catalytic mechanisms; however, both recognize the same substrate motif of the bicyclic intermediate.[178a] From this intermediate, subsequent cyclization and reduction results in the formation of the respective enantiomeric intermediates (*S*)-DNPA and (*R*)-DNPA. From these chiral intermediates, the advanced BIQ natural products, such as actinorhodin and DHGRA are derived.

5. Alkaloids

Alkaloids make up a vast and structurally diverse group of nitrogenous metabolites that are isolated from plants, bacteria, fungi, and animals.[3] This family of natural products can be further classified into subgroups, which are based on the handful of α-amino acids alkaloids are derived from, mainly lysine, ornithine, phenylalanine, tyrosine and tryptophan. In addition to these primary building blocks, mevalonate and acetate also serve as important starting points in the biosynthesis of alkaloids.

Pharmacologically, alkaloids display myriad bioactivities and are often used as medications, as recreational drugs, or in entheogenic rituals.[181] Morphine, caffeine, and psilocin (a mushroom hallucinogen) are common and well-known bioactive examples of alkaloids. Several lesser-known alkaloids are also biologically active and display anticancer, antibacterial, anthelmintic, anti-inflammatory activity.[182]

The occurrence of enantiomeric alkaloids in Nature is known, however, they are generally produced and isolated as racemic or scalemic mixtures. As observed in the lignans, many of the advanced alkaloid metabolites are produced in optically pure form, but the metabolites produced in the early stages of alkaloid biosynthesis are often isolated as enantiomeric mixtures. Select examples of these enantiomeric alkaloids are discussed below.

5.1-Manzamine Alkaloids

The manzamines are a growing class of β-carboline-containing cytotoxic marine sponge alkaloids that display an unusual polycyclic diamine system.[183] These natural products were first identified in the late 1980s and were found to have a diverse range of biological

activity, including, but not limited to, antitumor, anti-inflammatory, insecticidal, and antiparasitic. Several of these natural products also display promising anti-infective activity against malaria and Mtb.[183]

The diversity in the location (Okinawa, the Philippines, Indonesia, the Red Sea, Italy, South Africa, and Papua New Guinea) and genera of sponges (*Amphimedon* sp. and *Acanthostrongylophora*) responsible for the production of manzamine alkaloids is widely believed to be a result of a symbiotic relationship between these sponges with common or closely related microorganism(s), which may account for the generation of manzamine enantiomers.[183] To date, only a few enantiomeric manzamine natural products have been isolated (Table 10) and the biosynthetic formation of these enantiomeric metabolites is currently under investigation.

Within this class of alkaloids, the isolation of both enantiomers of 8-hydroxymanzamine A, manzamine F, and keramaphidin B have been reported, along with the enantiomeric congers, ircinal A and B and ircinol A and B.[183] Interestingly, ircinols A and B are enantiomeric congeners of the alcoholic forms of ircinal A and B, respectively, and they also represent the first manzamine alkaloids to possess the opposite absolute configuration to that of manzamines A and B.[184] As shown in Figure 4, one enantiomer of keramaphidin B, ircinals A and B, and manzamines A and B all belong to one configurational series, while the other enantiomer of keramaphidin B and ircinols A and B, ingenamine, ingamine A contain the opposite absolute configuration, and thus make up a second enantiomeric series.

Since it is likely that sponge-associated microbes produce the manzamines, efforts to elucidate the biosynthetic pathway of these unique compounds is limited.[183] The identification of bacterial isolates from a manzamine producing sponge, as well as culturing the bacteria responsible for these transformations are limiting factors to completely understanding the biosynthesis of the manzamines. However, following the identification, isolation, and screening of numerous microbes from manzamine producing sponges, the biotransformation of both 8-hydroxymanzamine A to manzamine A[185] and *ent*-8-hydroxymanzamine A to the known metabolite *ent*-12,34-oxamazamine F[186] have been successfully carried out (Scheme 12).

5.2-Indole Alkaloids

Indole alkaloids are natural products derived from tryptophan and make up one of the largest group of alkaloid secondary metabolites.[193] Biogenetically, this class of alkaloids can be divided into two structural categories, isoprenoid containing natural products and non-isoprenoid containing alkaloids. The latter group is comprised of simple indole derivatives, simple derivatives of β-carboline, and pyrroloindole alkaloids.[194] The isoprenoid alkaloids contain terpenoid structural elements derived from dimethylallyl pyrophosphate (DMAPP) and/or isopentenyl pyrophosphate (IPP).[195] The formation of enantiomeric indole alkaloids has been documented within the various subdivisions of the more complex isoprenoid alkaloids as outlined below.

5.2.1-Terpenoid Indole Alkaloids—Terpenoid alkaloids are often found in plant species belonging to the Apocynaceae, Loganiaceae, Rubiaceae, and Nyssaceae families.[196] Madagascar periwinkle (*Catharanthus roseus*), from the family *Apocynaceae*, is known to produce over one hundred structurally diverse terpenoid indole alkaloids; and elucidation of the terpenoid indole alkaloid biosynthetic pathway in *Catharanthus roseus* has been extensively studied. More than twenty enzymatic steps have been identified in this intricate biosynthetic pathway, which leads from the primary metabolites to the structurally complex antineoplastic agent, vinblastine. As is the case for many secondary metabolites, the advanced late stage intermediates, such as vinblastine and vincristine, are produced and

isolated as a single enantiomer, whereas the early stage metabolites are sometimes produced as scalemic mixtures. As shown in Table 11, these enantiomeric metabolites oftentimes occur in separate species as a single enantiomer. While the overall biosynthesis of terpenoid indole alkaloids is fairly well understood, the biogenesis of enantiomeric metabolites is not currently known.

5.2.2-Reverse Prenylated Indole Alkaloids—The unique and diverse family of reverse prenylated indole alkaloids containing a bicyclo[2.2.2]diazaoctane ring system has been the subject of extensive research due to their complex molecular structure and wide array of biological activity.[203] Members of this family have been isolated from both marine and terrestrial sources, most notably from the genera *Aspergillus* and *Penicillium*, and have been reported to display insecticidal, anthelmintic, calmodulin-inhibitory, antibacterial and antitumor properties. The recent identification of enantiomeric metabolites from related *Aspergillus* species has sparked interest in elucidating the biosynthetic pathway of the stephacidin and notoamide family of reverse prenylated indole alkaloids.

In 2009, Tsukamoto and co-workers isolated the known natural product (+)-stephacidin A[204] from marine-derived *Aspergillus* sp. MF297-2, along with several new metabolites later named the notoamides.[205] Shortly following the isolation of the stephacidins and notoamides from *Aspergillus* sp. MF297-2, Gloer and co-workers isolated the corresponding enantiomers from the terrestrial-derived fungus *Aspergillus versicolor* NRRL 35600.[206] These enantiomeric alkaloids (Table 12) are hypothesized to arise via a biosynthetic Diels-Alder reaction, which implies that each *Aspergillus* species possesses enantiomerically distinct Diels-Alderases. Furthermore, each fungal culture must also possess enantiomerically distinct oxidases responsible for the face-selective pinacol-type rearrangement to form the *spiro*-oxindole moiety observed in notoamide B and versicolamide B. Thus, Williams and co-workers proposed that the stephacidin and notoamide family shared a common biosynthetic pathway and that the enantiomeric formation of these alkaloids was due to a key enantiodivergent step in an otherwise common biogenetic pathway.[203] This work was further aided through the identification and characterization of the *Aspergillus* sp. MF297-2 and the *Aspergillus versicolor* NRRL35600 genome clusters,[207] as well as parallel precursor incorporation studies with both fungal cultures.[208]

Based on results from genome mining and tracer studies, a biosynthetic pathway has been proposed.[207,208] As shown in Scheme 13, starting with the proposed pivotal intermediate notoamide S,[209] the pathway branches into at least two possible directions. Formation of the pyranoindole to yield notoamide E results in the biosynthesis of notoamide C, 3-*epi*-notoamide C, and notoamide D[208a,b] via the proposed enzyme NotB. However, notoamide S could also undergo a 2-electron oxidation by either NotD or NotH to give the achiral azadiene, which acts as the enantio-diverging point in the biosynthesis. The achiral azadiene can undergo a stereoselective [4+2] cycloaddition to yield either (+)-notoamide T in *Aspergillus* sp. MF297-2 or (−)-notoamide T in *Aspergillus versicolor*. From these putative intermediates, cyclization to form the pyranoindole ring system would furnish the enantiomeric pair of stephacidin A, respectively. Through precursor incorporation studies of ^{13}C-labeled (±)-stephacidin A with both *A. versicolor* and *Aspergillus* sp. MF297-2, it was ascertained that face-selective oxidative enzymes (currently presumed to be flavo-enzymes) are present in both fungal cultures as evident by the enantioselective conversion of stephacidin A into notoamide B.[208c] Specifically in *A. versicolor* NRRL 35600, this oxidase is responsible for the biosynthetic conversion of (−)-stephacidin A into (+)-notoamide B, while a stereochemically complementary oxidase in the marine-derived *Aspergillus* sp. MF297-2 converts (+)-stephacidin A into (−)-notoamide B.

It is significant that in each of these respective oxidation reactions of the 2,3-disubstituted indole moiety of stephacidin A, the oxidation must occur from distinct enantiotopic faces of the indole ring system and we presently doubt that this is accomplished by identical enzymes. More precisely, the oxidation of (+)-stephacidin A into (−)-notoamide B, must occur exclusively from the pro-*R* face of the indole in *Aspergillus* sp. MF297-2 and the oxidation of (−)-stephacidin A into (+)-notoamide B in *Aspergillus versicolor*, must occur exclusively from the pro-*S* face of the indole. To date, the diastereomeric oxindoles that would result from a putatively non-face-selective oxidation have not been detected. Of further intrigue, was the observation that *Aspergillus* sp. MF297-2 produces (−)-versicolamide B and that *Aspergillus versicolor* produces the enantiomer, (+)-versicolamide B. The putative precursor to versicolamide B, C6-epi-stephacidin A, has not yet been detected as a natural metabolite but its existence in each fungus is anticipated. Synthetic samples of this substance have been prepared and are under interrogation.

In an effort to understand the enzymatic basis for the biosynthesis of enantiomeric alkaloid natural products, we have pursued total genome sequencing and mining of the stephacidin/notaomide pathways from two fungal strains. The marine *Aspergillus* sp. MF297-2 strain generates (−)-notoamide B, whereas the terrestrial *Aspergillus versicolor* strain generates enantiomeric (+)-notoamide B, with the key chiral determinant hypothesized to reside within the presumed intramolecular Diels-Alderase enzyme. We have found the molecular architecture (e.g. gene placement and directionality of transcription) of these pathways to be remarkably similar with >70% identity of nucleotide sequences across the 35 kb gene clusters. The corresponding high level of amino acid sequence similarity suggests that subtle active site sequence variation plays a critical role in controlling chirality, and in accommodating the corresponding enantiomeric substrates for downstream assembly and tailoring reactions.

5.3-Quinolizidine (Lupine) Alkaloids

Quinolizidine alkaloids, often referred to as lupine (or lupin) alkaloids, are secondary metabolites found in a wide variety of leguminous plant and tree species.[211] There are over 550 known quinolizidine alkaloids, with many of these secondary metabolites occurring in the subfamily Papilionoideae of the *Fabaceae*. They are especially abundant in the tribes Genisteae, Sophoreae and Thermopsideae. Biologically, the lupine alkaloids have been implicated in plant-herbivore interactions with many of these alkaloids displaying toxic and/or teratogenic properties to livestock.[212]

The first reported isolations of the lupine alkaloids revealed that in many cases both enantiomers of a given alkaloid occur in Nature;[213] however, after further examination, many of the proposed racemates were found to actually occur as optically pure isoforms.[214] This review will only focus on select major enantiomeric lupine metabolites that are known to occur in Nature. Several of these metabolites are shown in Table 13, along with a limited listing of the respective sources of isolation.

Unfortunately, biosynthetic studies of enantiomeric lupine alkaloids are rather limited. Independently, Spenser, Robins, and Wink demonstrated that the quinolizidine alkaloids are biosynthesized from lysine via a symmetrical cadaverine intermediate. Enzymatically, a lysine decarboxylase that converts lysine into cadaverine was isolated from lupine cell cultures and intact plants; however, late stage biosynthetic conversions remain elusive.[222] Through feeding studies using labeled precursors, both lysine and cadaverine have been shown to incorporate into (−)-sparteine, (+)-sparteine, and (+)-lupanine (Scheme 14).[223]

5.4-Piperidine and Pyridine Alkaloids

Both piperidine and pyridine alkaloids are secondary metabolites containing a 6-membered heterocyclic ring system with a nitrogen containing nucleus, in which this heterocycle is saturated in piperidine alkaloids and unsaturated in pyridine alkaloids. Simple piperidine and pyridine natural products are generally associated with toxic alkaloids, as observed in one of the most well known examples of a pyridine alkaloid, nicotine.[8] Similarly, several piperidine alkaloids are known poisons produced by poison hemlock, *Conium maculatum*.[224] Many of the piperidine and pyridine alkaloids are known teratogenic agents,[225] and the ingestion of plants that produce these natural products by pregnant livestock can result in newborns with multiple congenital contractures and/or cleft palates.[226] As shown in Table 14, enantiomeric metabolites of these alkaloids are particularly rare, but those that are known are produced by a variety of plant sources. Several of these metabolites, such as ammodendrine, are produced as a nearly racemic mixture by a single species, whereas other metabolites occur as partial racemates.[6b] For example, the *S*- or (−)-isoform of nicotine generally makes up more than 95% of the natural product produced by tobacco.[8]

While significant effort has been put forth towards elucidating the biosynthetic pathway of these metabolites,[8,227] the enantiomeric biogenesis of the piperidine and pyridine alkaloids has not been investigated. As observed with nicotine, biosynthetic studies have focused on the biogenesis of the major enantiomer, (−)-nicotine, and as such, there are currently no known explanations for the formation of (+)-nicotine. Furthermore, the characterization of enzymes responsible for the biosynthesis of piperidine and pyridine alkaloids, such as coniine, demonstrate a high substrate- and stereo-specificity, and therefore, the biosynthesis of only one enantiomer is known.[182] To date, no enantiomerically opposite enzymes responsible for the biosynthesis of pyridine or piperidine alkaloids have been identified.

5.5-Benzylisoquinoline Alkaloids

Benzylisoquinoline alkaloids (BIA) are a structurally diverse group of nitrogen-containing plant secondary metabolites, consisting of more than 2,500 defined structures found mostly in five plant families: the *Papaveraceae, Fumariaceae, Ranunculaceae, Berberidaceae*, and *Menispermaceae*.[196c,231] Structurally, the benzylisoquinoline natural products can be further divided into numerous groups, such as the aporphines, phthalideisoquinolines, morphinans, protoberberines, and pavines.[232] Benzylisoquinoline alkaloids are widely known to be produced by opium poppy (*Papaver somniferum*), and are well known for their wide range of biological activity and pharmaceutical importance, including: morphine and codeine, two well-known analgesics; papaverine, a muscle relaxant; noscapine, an antitumor agent; and sanguinarine, an antibiotic.[231b,233] The biosynthesis of benzylisoquinoline alkaloids has been thoroughly studied, and as such most of the biogenesis is understood at an enzymatic level.[196c,231–233] Furthermore, as shown in Table 15, the occurrence of enantiomeric benzylisoquinolines is known, however the biosynthetic formation of all these enantiomers is not fully understood.

Biosynthetically, benzylisoquinoline alkaloids are all derived from L-tyrosine along a basic benzylisoquinoline pathway.[232,233] As shown in Scheme 15, the first committed step in the BIA biosynthesis is the asymmetric Pictet-Spengler condensation of tyrosine derived dopamine and *para*-hydroxyphenylacetaldehyde (4-HPAA) via norcoclaurine synthase (NCS) to yield optically pure (*S*)-norcoclaurine.[231] Through four enzymatic transformations (*S*)-norcoclaurine is converted to optically pure (*S*)-reticuline. This intermediate serves as a vital branching point to the various benzylisoquinoline alkaloids, many of which display the same stereochemistry as (*S*)-reticuline; however, the promorphinan and morphinan subgroup of BIAs contain the opposite (*R*)

stereochemistry.[232] These alkaloids are derived from (*R*)-reticuline, which arises from the inversion of stereochemistry of (*S*)-reticuline by way of oxidation and reduction via 1,2-dehydroreticuline synthase (DRS) and 1,2-dehydroreticuline reductase (DRR), respectively.[235]

Early on, the biogenesis of some of the (*R*)-configured benzylisoquinoline alkaloids had been proposed to arise via (*R*)-reticuline; however, tracer incorporation studies have shown that this is not the case.[236] Based on the lack of incorporation of (*R*)-reticuline into the more advanced (*R*)-configured BIAs, it has been suggested that the formation of the (*R*)-series of metabolites arise from a stereochemical inversion of the (*S*)-enantiomer via enzymatic oxidation and reduction. Similar to the formation of enantiomeric reticuline, other BIA enantiomers, such as (*R*)- and (*S*)-canadine are formed from an inversion of stereochemistry. In the case of enantiomeric canadine, (*S*)-canadine is first oxidized by (*S*)-tetrahydroxyprotoberberine oxidase (STOX) to form berberine, which is subsequently reduced by berberine reductase to yield (*R*)-canadine (Scheme 16).[236,237]

Unfortunately, substantial information is lacking in understanding the biosynthesis of all of the enantiomeric BIAs. As seen in the elucidation of the enantiomeric nicotine biosynthetic pathway, the biogenesis of only one enantiomer of the BIA natural products is understood, as is the case with (*S*)-scoulerine and (+)-salutaridine.[233] To date, no enantiomerically opposite enzymes in the biosynthesis of the benzylisoquinoline alkaloids have been isolated.

6. Summary and Outlook

As demonstrated in this Review, the formation of enantiomeric natural products by Nature is not as uncommon as one might have initially expected. While the number of enantiomeric natural products that have been discovered to date represent a small fraction (less than 1%) of the biospheres' metabolome, it is clear that biogenetic mechanisms to create distinct enantiomers are widely expressed. Many puzzles and stereochemical anomalies remain and provide for a fertile area of future inquiry and discovery. A substantial body of research has been carried out over the years to attempt to understand the biogenesis of some enantiomeric metabolites, but our level of understanding remains in its' infancy.

The points at which an enantiodivergence may occur in a biosynthetic pathway vary. For example, in the terpene cyclases (pinene, limonene, see Scheme 2), a simple precursor, such as geranyl diphosphate, can give rise to the two enantiomeric forms in the first committed step of the pathway. In other instances, the enantiodivergent step occurs deeper into the pathway, as appears to be the case with the stephacidins and notoamides. With recent advances in whole genome sequencing, proteomics, metabolomics and genome mining, significant leaps in unraveling many of these intriguing biosynthetic pathways are expected to accelerate. In many instances, enantiomeric metabolites arise from two distinct enzymes that function in an enantiodivergent and distinct mechanistic manifold, such as the (+)- and (−)-limonene synthases. On the other hand, the accumulation of both enantiomers from a single enzyme may be due in part to a lack of enzyme substrate- and stereo-specificity, which was observed in the biosynthesis of (+)-carvone via (+)-limonene-6-hydroxylase and (+)-*trans*-carveol dehydrogenase. In several examples, the biosynthetic formation of one enantiomer is understood at an enzymatic level, while the biogenesis of the minor enantiomer remains unknown. Furthermore, the enantioselective catabolism of an initially produced racemic metabolite, remains an additionally valid paradigm that has been little investigated. As more and more natural metabolites are discovered, despite the recent, severe cutback in research funding for natural products isolation and structural elucidation, it is almost a certainty, that additional families of enantiomeric natural substances will be discovered. The myriad of genetic and biochemical mechanisms controlling and leading to

the phenotypic expression of enantiomeric natural substances will continue to tantalize the imagination. The impact of next-generation sequencing and bioinformatic tools to mine natural product biosynthetic genes, and assemble pathways from diverse microbial and plant species will have an enormous impact on future investigations. Moreover, the continued development of molecular tools to engineer gene-disruption mutants, and for heterologous expression will enable new insights into the details of natural product assembly and functional group elaboration. Moreover, the ability to clone, overexpress and purify biosynthetic enzymes from diverse microbial and plant species will allow *in vitro* studies of the metabolic pathway components with natural and unnatural substrates. These powerful approaches will provide access to even more chemical diversity from which exciting biological activities and potential drug leads might be identified.

Finally, the genetic mechanisms resulting in the formation of enantiomeric natural products has yet to be analyzed from an evolutionary molecular genetics perspective.[238] Focusing on molecular evolution, key questions remain about the mechanism(s) by which an enzyme making one enantiomeric form evolves to produce the enantiomeric form. Does the process, for example, require a gene duplication event, where one of the paralogs can be freed from selective constraints, thus allowing it to evolve by genetic drift to acquire multiple substitutions? Or, alternatively, can a single ortholog evolve this ability independently from different ancestral forms of an enzymatic function? Based on the examples covered here in this review, it appears that both may occur. A related question in cases where the two stereoselective enzymes have evolved from a common ancestor is, what is the ancestral state - an enzyme that produces a (partially) racemic mixture or an enzyme that produces one pure enantiomer? It is interesting to note that instances in which an enzyme produces both enantiomers are known, and also cases in which one enantiomer is produced in great excess over the other. Can the latter be thought of as an example of an intermediate state in the evolution of an enzyme from a nonselective form to a purely selective form? This provocative question merits thought and investigation because of course for evolution to proceed from one form of the enzyme to the other (i.e., from a (−)-producing form to a (+)-producing form), if it does not happen in a single mutation (say a single amino acid substitution in an active site) but rather through a transition requiring multiple amino acid changes, then all of the intermediate states have to be both possible functionally and also not be deleterious to the producing organism. Thus, the ancestral state and the number of changes in a protein required for the transition from one antipodal product to the other are fundamental questions that have been little, if at all studied. Another equally interesting question concerns the adaptive significance of these stereoselective transitions and this field is probably wide open. Phylogenetic and bioinformatic analysis of enantiomeric enzymes holds the promise of revealing mechanistic signatures of their functional evolution, including the roles of gene duplication, exon shuffling, natural selection, and genetic drift. What is particular tantalizing about enzymes that generate opposite enantiomers of a particular structure, is the ability to study many independent instances of this evolutionary process, a rare opportunity in molecular evolution. Such investigation has the potential of revealing generalities about the evolution of protein structure/function for this subtlest of possible change in natural product chemistry.

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Biographies

Robert M. Williams received a B.A. (Chemistry, 1975) from Syracuse University (Ei-ichi Negishi), the Ph.D. (1979) at MIT (W.H. Rastetter) and was a post-doc at Harvard (1979–80; R.B. Woodward/Yoshito Kishi). He joined Colorado State University in 1980 and named University Distinguished Professor in 2002. Significant awards include the ACS Cope Scholars Award (2002) and the ACS Ernest Guenther Award in the Chemistry of Natural Products (2011). His interdisciplinary research program (>280 publications) at the chemistry-biology interface concerns the synthesis, biosynthesis and the chemical biology of biomedically significant natural products.

Jennifer M. Finefield graduated from Illinois State University in 2004 with a B.S. in Chemistry. She received her Ph.D. in 2011 from Colorado State University under the guidance of Professor Robert M. Williams, wherein her work focused on elucidating the biosynthesis of reverse prenylated indole secondary metabolites from *Aspergillus versicolor.* She is currently working on the synthesis of a novel HDAC inhibitor as a post-doc for Professor Robert M. Williams at Colorado State University.

David H. Sherman is the Hans W. Vahlteich Professor of Medicinal Chemistry, Professor of Chemistry, and Professor of Microbiology & Immunology at the University of Michigan. He obtained a B.A. from UC Santa Cruz (1978), the Ph.D. from Columbia (1981) and was a post-doc at Yale (1981–82) and MIT (1982–84). Dr. Sherman's research concerns molecular genetic, biochemical and bioorganic chemical studies of microbial natural product biosynthesis. His lab employs pathway engineering, synthetic biology and chemoenzymatic synthesis to harness the tremendous metabolic capabilities of diverse bacteria, fungi and unculturable microbial symbionts.

Martin Kreitman, Ph.D. is a Professor at the University of Chicago. He received a B.S. in Biology (Stony Brook University, 1975), the M.S. in Zoology (University of Florida, 1977), and a Ph.D. in Population Genetics (Harvard, 1983). Significant awards include the 1991 MacArthur Fellows Program and became a Fellow of the American Academy of Arts and Sciences (2010). His research interests center on understanding evolutionary forces governing molecular variation and evolution. His lab is currently investigating the functional and evolutionary biology of eukaryotic *cis*-regulatory sequences and is developing models of complex human genetic diseases.

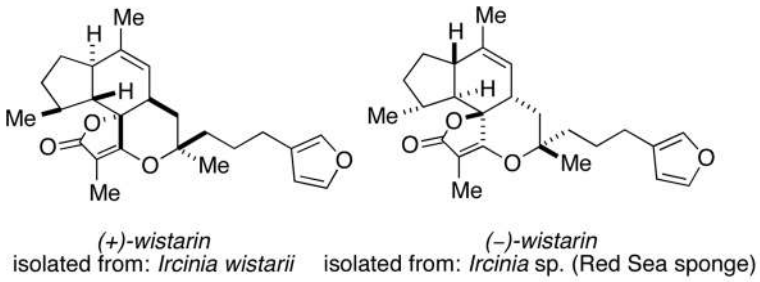


Figure 1.
(+)- and (−)-wistarin; the only known enantiomeric sesterterpenes.

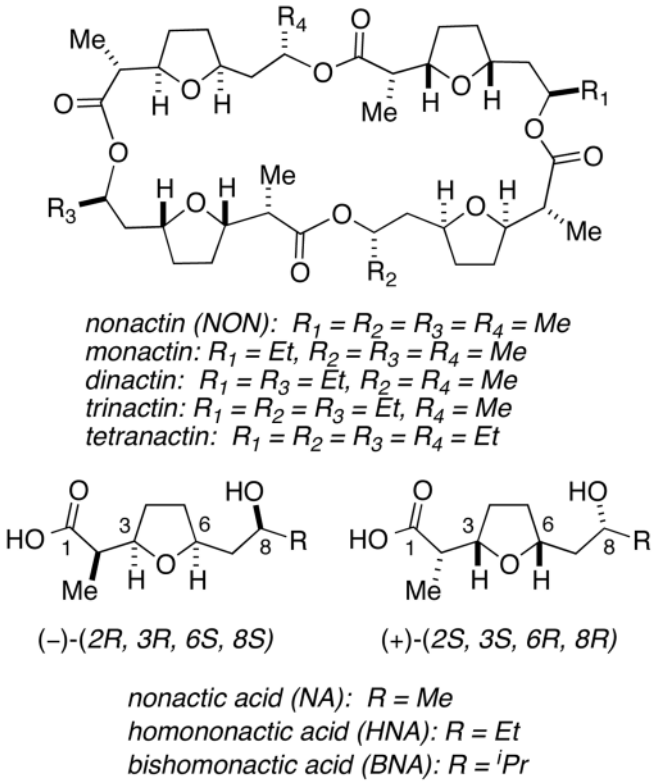


Figure 2.
Nactins and the monomeric units that make up the macrotetrolide antibiotics.

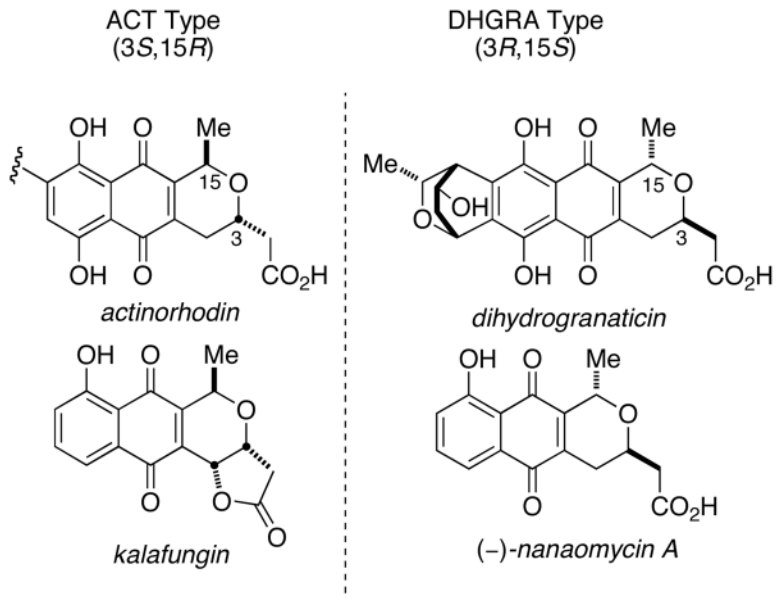


Figure 3.
Structural diversity of the BIQ antibiotics.

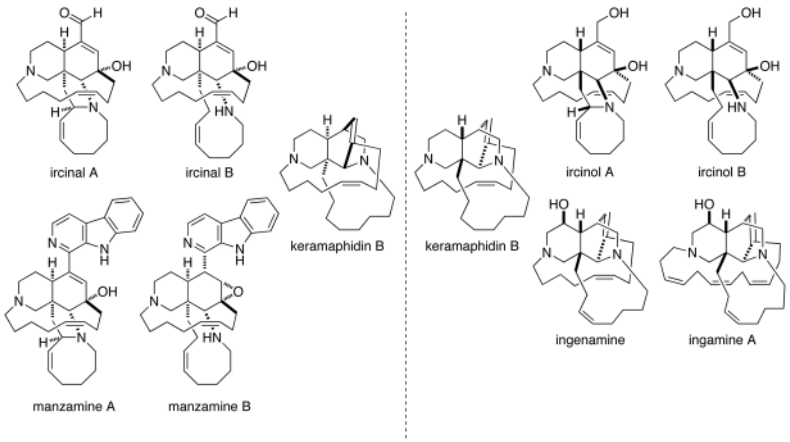
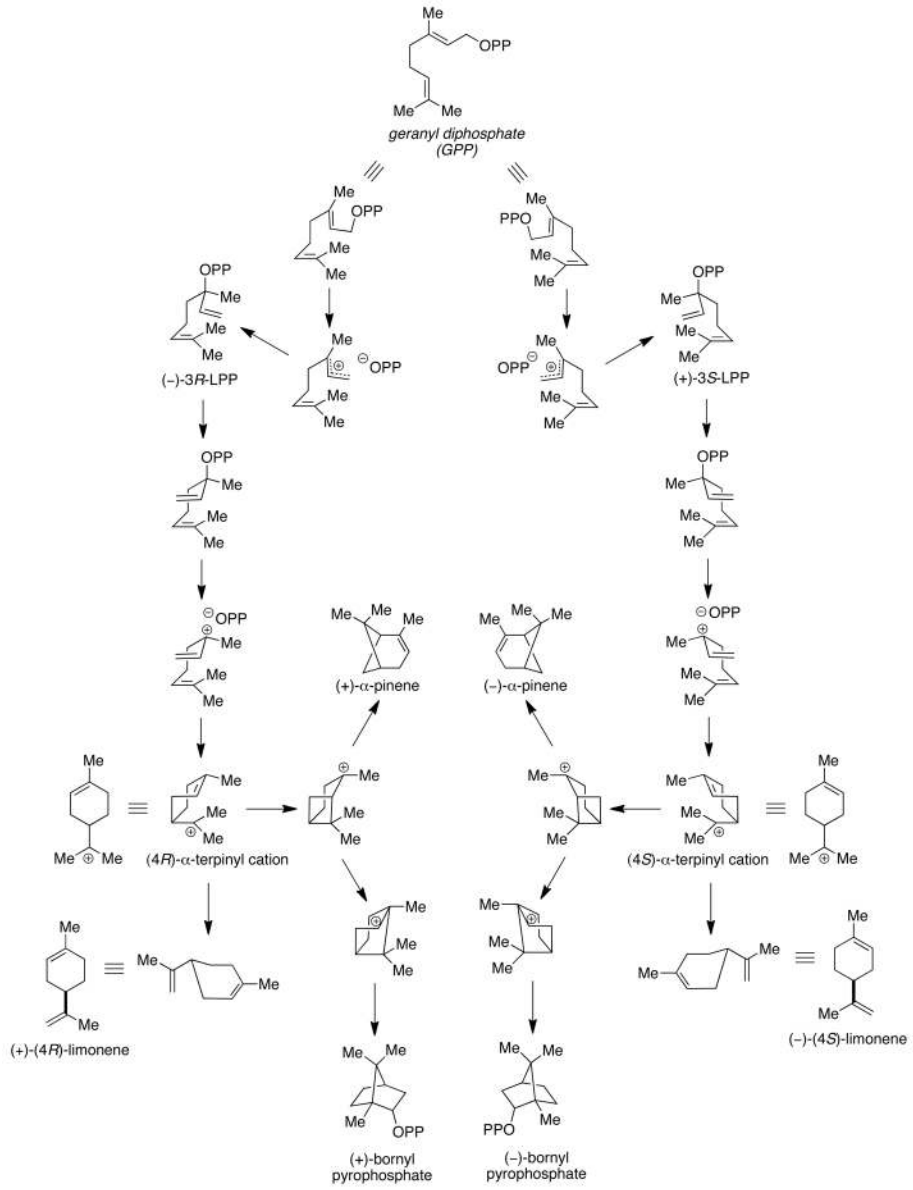
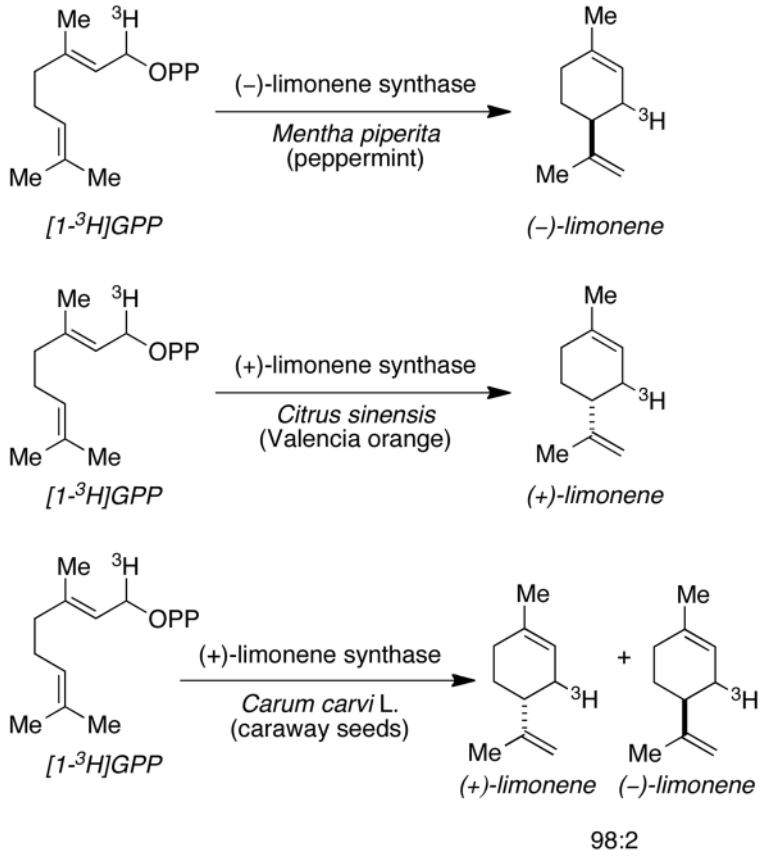


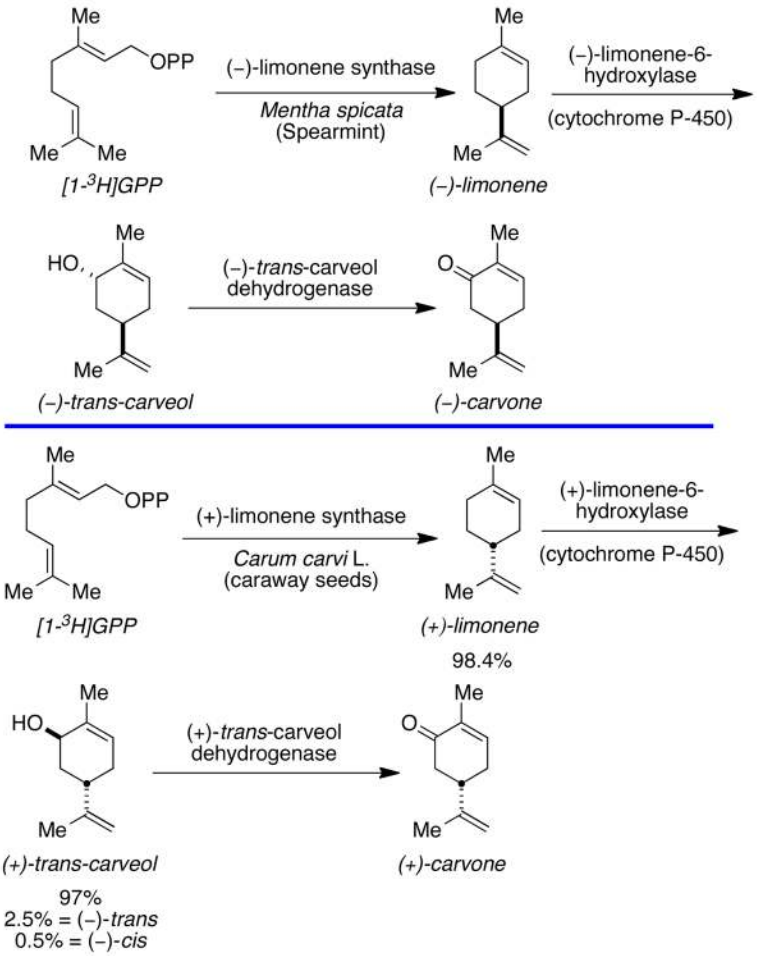
Figure 4.
The two enantiomeric series of manzamine alkaloids.



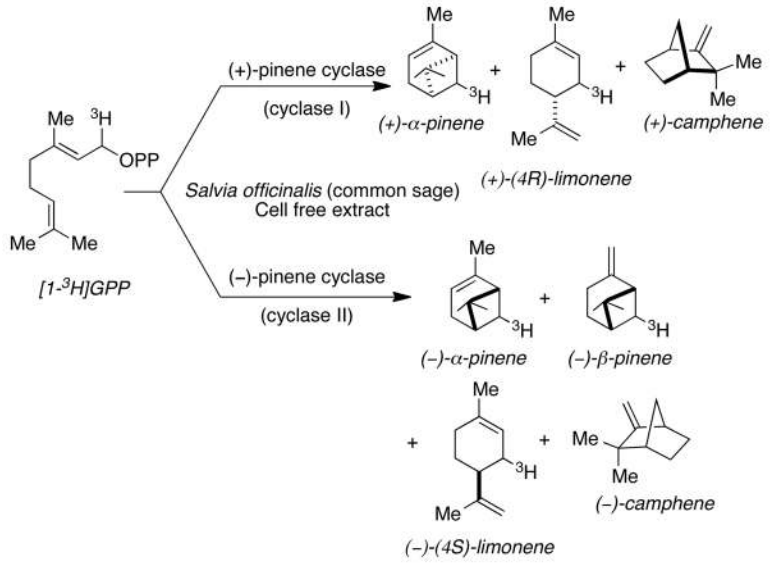
Scheme 1.
Enantiomeric biogenesis of select monoterpenes.[15a]



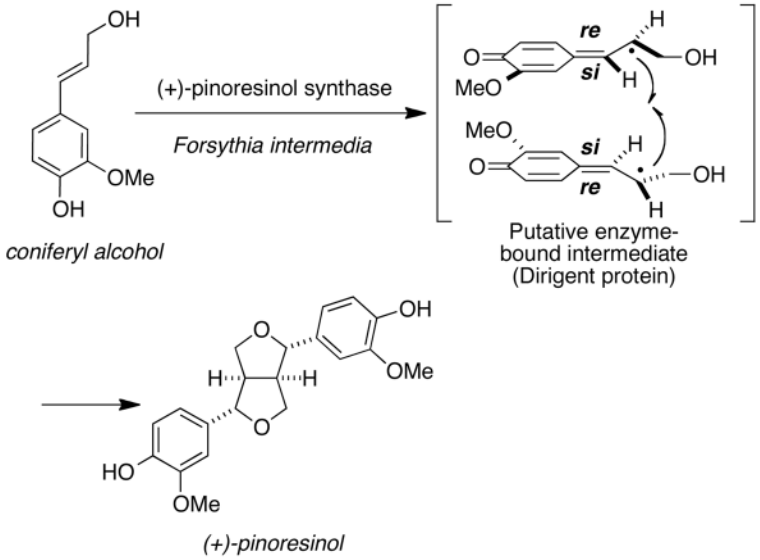
Scheme 1.
Enantioselective biogenesis of limonene.



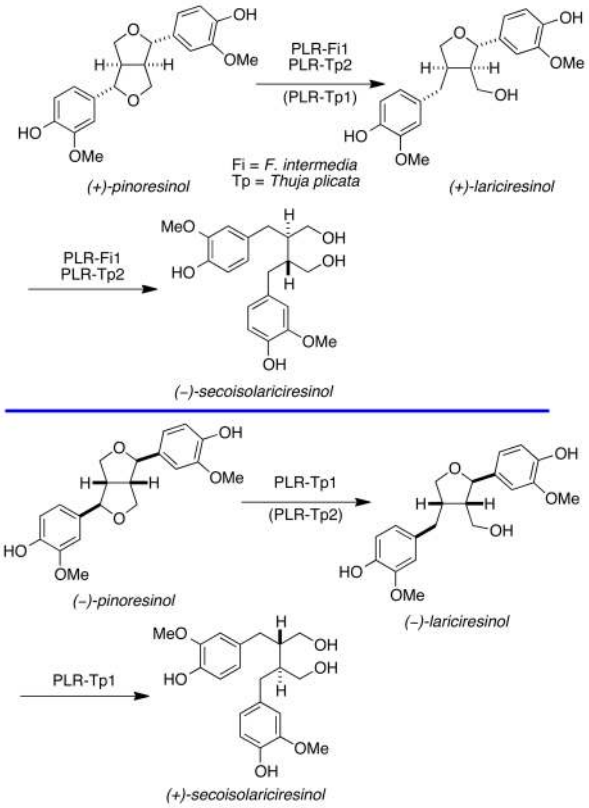
Scheme 3.
Enantiomeric carvone biosynthesis.



Scheme 4.
Enantioselective pinene cyclases.

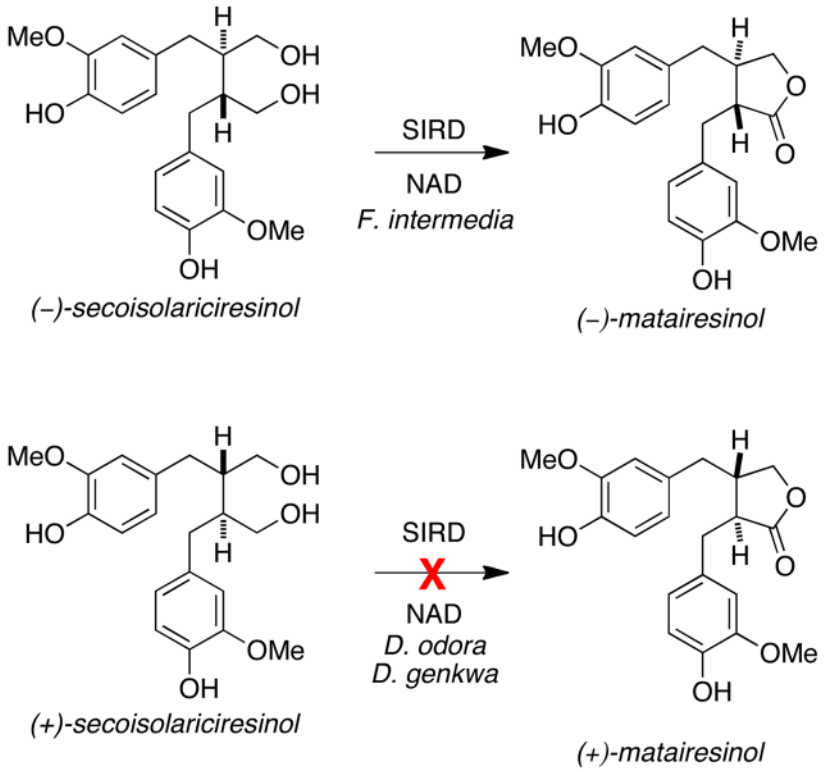


Scheme 5.
Enantioselective biosynthesis of (+)-pinoresinol.

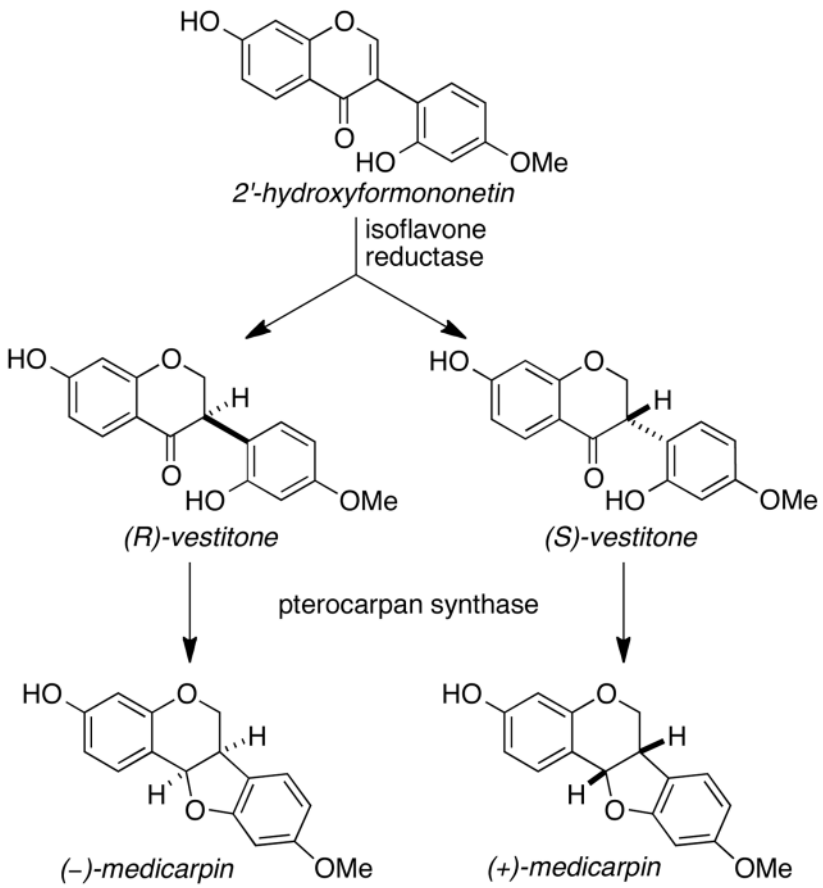


Scheme 6.

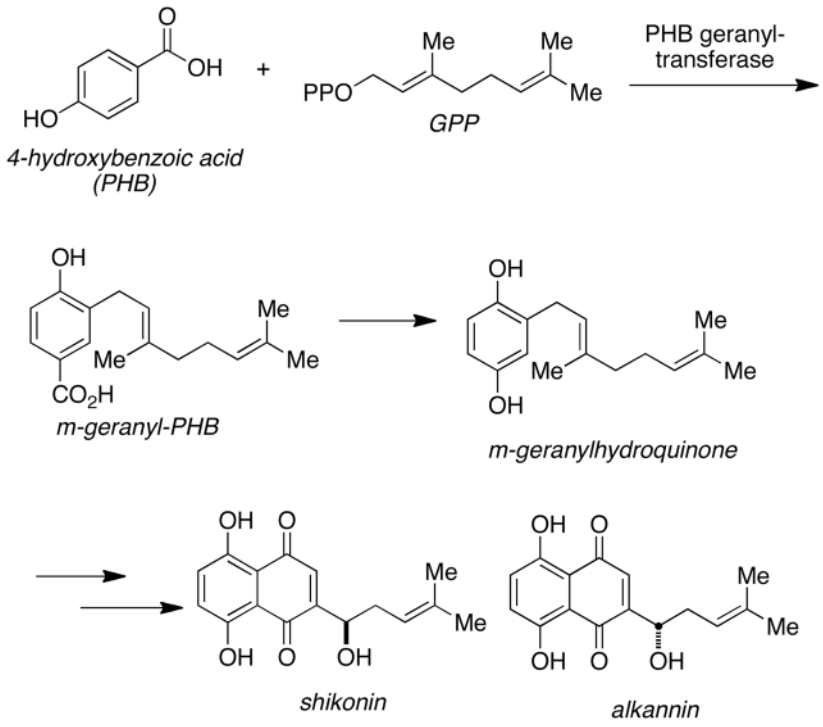
Enantioselective conversion of pinoresinol to secoisolariciresinol via pinoresinol/lariciresinol reductase (PLR).



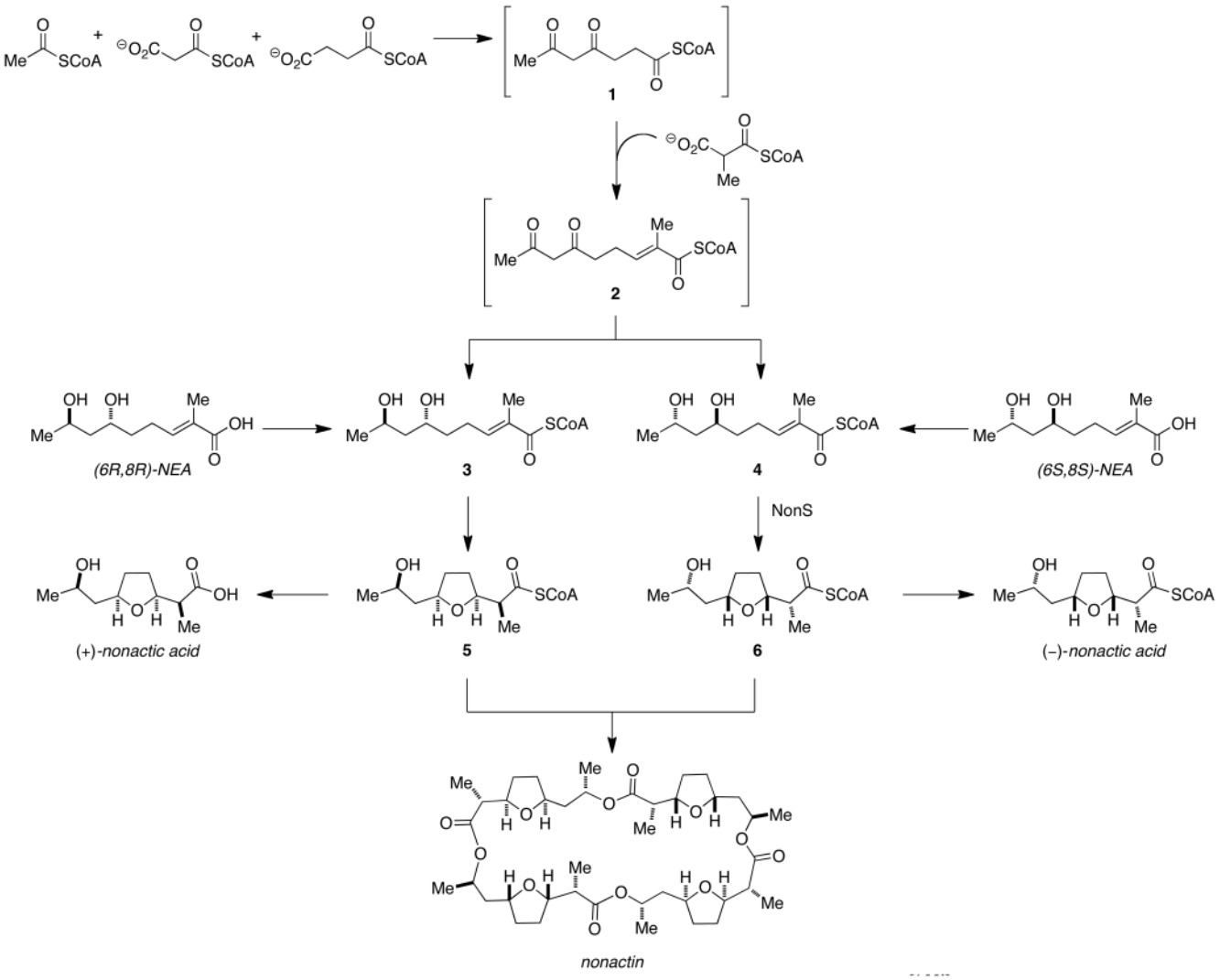
Scheme 7.
(−)-Matairesinol biosynthesis via secoisolariciresinol dehydrogenase (SIRD).



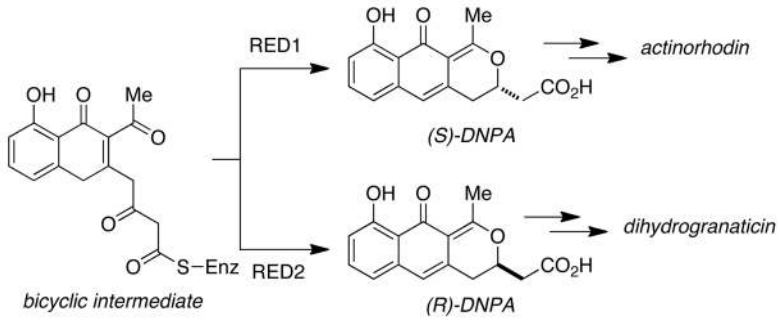
Scheme 8.
Enantiomeric medicarpin biosynthesis.[112]



Scheme 9.
Proposed biosynthesis of shikonin and alkannin.

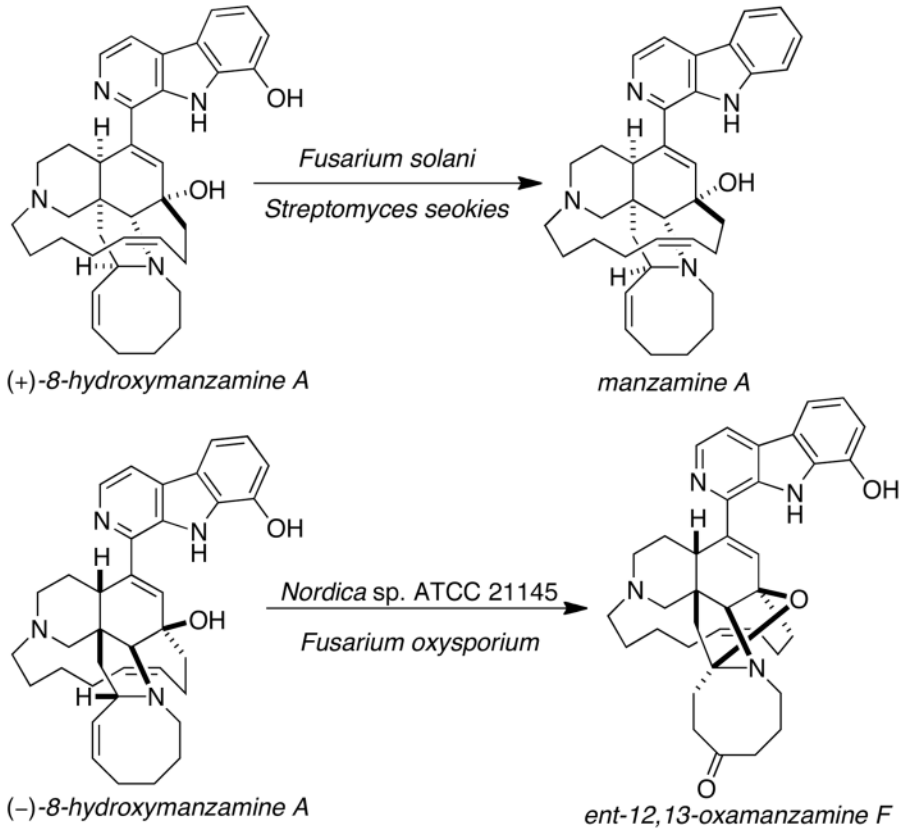


Scheme 10.
Proposed enantiocomplimentary pathways for the biogenesis of (+)- and (−)-nonactic acid.[155i]

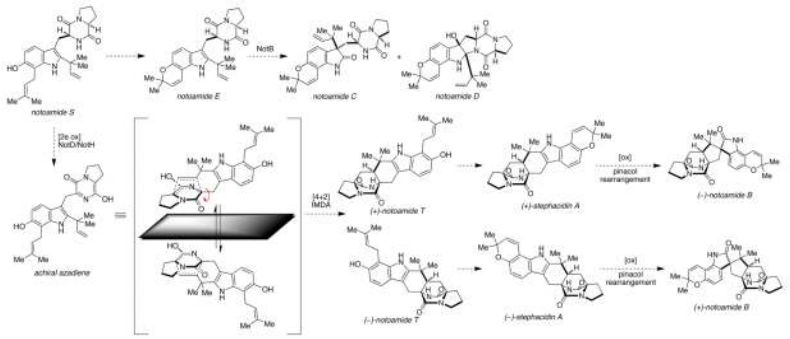


Scheme 11.

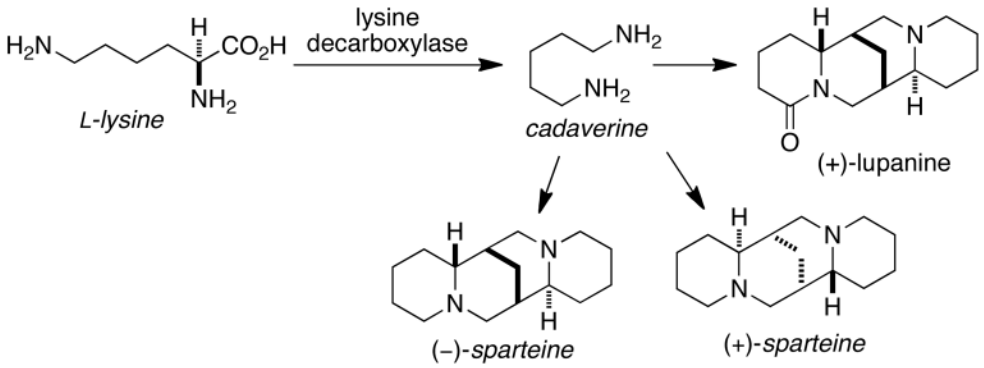
Proposed enantioselective biosynthetic pathways of actinorhodin and dihydrogranaticin. (RED1/2 = stereospecific C-3 reductase)



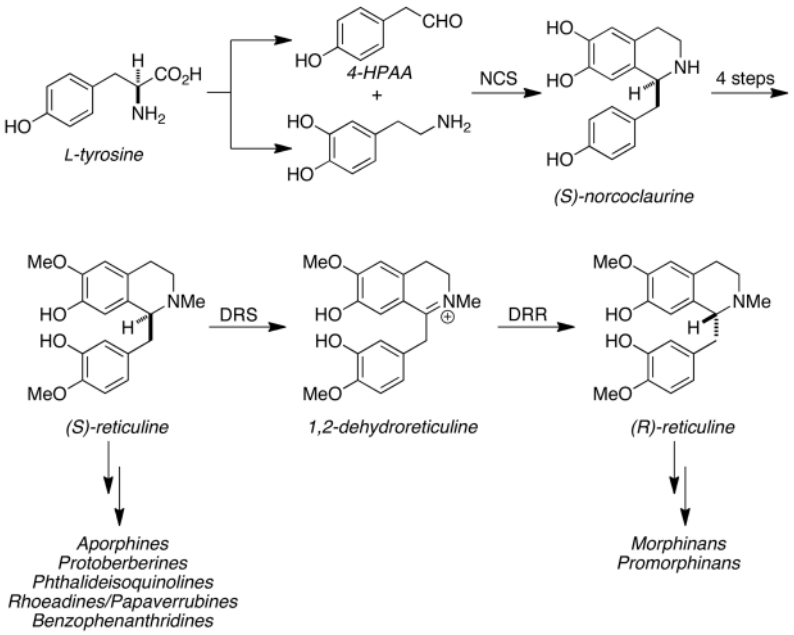
Scheme 12.
Biocataytic conversion of enantiomeric 8-hydroxymanzamine A.



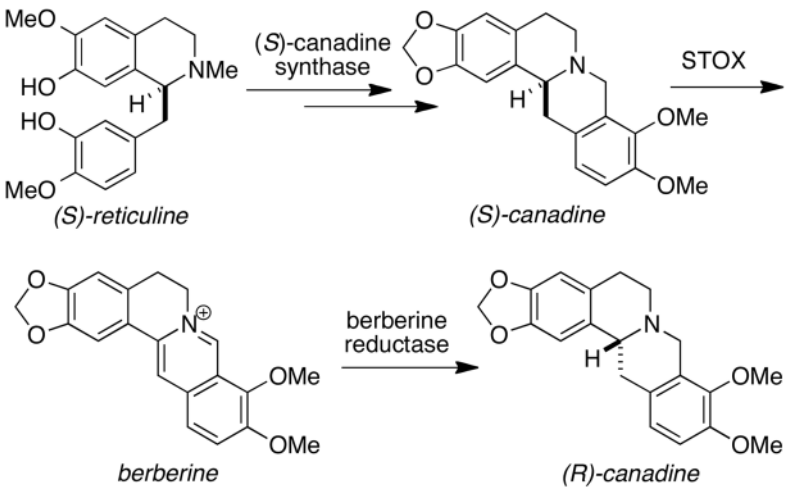
Scheme 13.
Putative enantio-divergent biosynthesis of stephacidin A and the notoamides.



Scheme 14.
Biogenesis of (−)-sparteine.



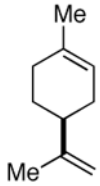
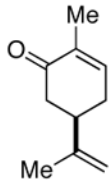
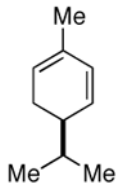
Scheme 15.
Early stages of the benzylisoquinoline alkaloid biogenesis.



Scheme 16.
Biosynthesis of enantiomeric canadine.

Table 1

Occurrence and biological activity of enantiomeric monoterpenes.

Monoterpene	Species	Biological Activity
 (−)-(4*S*)-limonene	*Mentha piperita* (peppermint),[17] *Mentha spicata* (spearmint),[17] *Mentha pulegium* (European pennyroyal),[17] *Perilla frutescens* (Chinese basil),[18,19] *Perilla citriodora*,[26] *Abies grandis* (grand fir),[20] *Anethum graveolens* L. (dill),[27] *Semiardistomis puncticollis* (carabid beetle),[28] *Mentha cardiaca* (Scotch spearmint),[21] *Salvia officinalis* (sage),[18] *Pinus sylvestris* (Scots pine),[29] pine needle oil,[9] *Oleum cinae*,[9] *Pistacia vera* L. (pistachio),[30] *Angelica archangelica* L. (wild celery)[31]	Turpentine odor[16a] Lemon odor[16b]
(+)-(4*R*)-limonene	*Mentha piperita*,[17] *Mentha spicata*,[17] *Schizonepeta tenuifolia* (Japanese catnip),[22] *Citrus unshiu* (mandarin orange),[21] *Anethum graveolens* L.,[27] *Carum carvi* L. (caraway fruit),[23] *Ardistomis schaumii* (carabid beetle),[28] *Mentha cardiaca*,[21] *Salvia officinalis*,[18] *Pinus sylvestris*,[29] *Citrus limon* (lemon),[24] *Citrus sinensis* (Valencia orange),[18] oil of orange rind,[9] dill oil,[9] oil of cumin, neroli, bergamot caraway and lemon (*Citrus, Antethum, Juniperus, Peucedanum* spp.),[9] *Oleum cinae*,[9] *Pistacia vera* L.,[30] *Angelica archangelica* L.[31]	Orange odor[16b] Shows insecticidal properties[9]
 (−)-(4*R*)-carvone	*Mentha spicata*,[32] *Mentha cardiaca*,[21] *Tanacetum balsamita* (balsam herb)[16]	Spearmint odor[16a]
(+)-(4*S*)-carvone	*Anethum graveolens* L.,[27] *Carum carvi* L.[23]	Caraway odor[16a]
 (−)-α-pinene	*Abies grandis*,[20] *Pinus contorta*(lodgepole pine),[33] *Pinus taeda* (loblolly pine),[34] *Salvia officinalis*,[18,35] *Pinus sylvestris*,[29] *Pistacia vera* L.,[30] *Angelica archangelica* L.,[31] *Eucalyptus* spp.[9]	Pine odor[16a]
(+)-α-pinene	*Pinus contorta*,[33] *Pinus taeda*,[34] *Salvia officinalis*,[18,35] *Pinus sylvestris*,[29] *Pistacia vera* L.,[30] *Angelica archangelica* L.,[31] *Eucalyptus* spp.[9]	Pine odor[16a]
 (−)-β-pinene	*Abies grandis*,[20] *Pinus contorta*,[33] *Pinus taeda*,[34] *Salvia officinalis*,[18,35] *Pinus sylvestris*,[29] *Citrus limon*, [24] *Pistacia vera* L.,[30] *Angelica archangelica* L.[31]	
(+)-β-pinene	*Pinus contorta*,[33] *Pistacia vera* L.,[30] *Angelica archangelica* L.[31]	
 (−)-α-phellandrene	*Pinus contorta*[36]	
(+)-α-phellandrene	*Anethum graveolens* L.[27]	

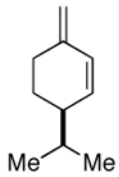
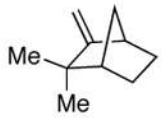
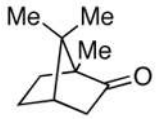
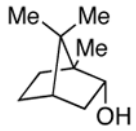
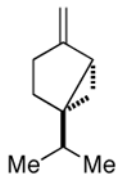
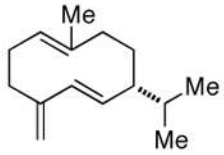
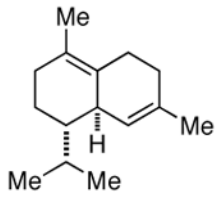
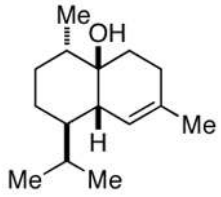
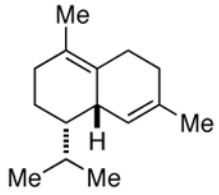
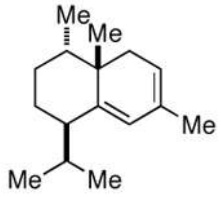
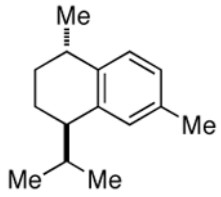
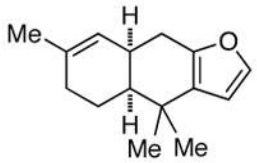
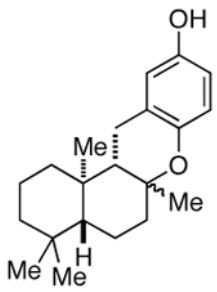
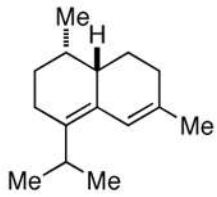
Monoterpene	Species	Biological Activity
	*Pinus contorta*,[36] *Pinus sylvestris*,[29] *Angelica archangelica* L.,[31] *Juniperus* spp. (Juniper evergreen),[9] *Pinus* spp. (pine)[9]	
(−)-β-phellandrene		
(+)-β-phellandrene	*Anethum graveolens* L.,[27] *Angelica archangelica* L.,[31] *Bupleurum fruticosum* (Shrubby Hare's Ear),[9] *Juniperus* spp.[9]	
	*Salvia officinalis*,[37] *Picea abies*,[29] *Pinus sylvestris*,[29] *Angelica archangelica* L.[31]	
(−)-camphene		
(+)-camphene	*Salvia officinalis*,[37] *Picea abies*,[29] *Pinus sylvestris*,[29] *Angelica archangelica* L.[31]	
	*Picea pungens* glauca (Colorado blue spruce),[38] *Salvia officinalis*,[38] *Picea mariana* nana (dwarf black spruce),[38] *Thuja occidentalis* (Northern Whitecedar),[38] *Pinus sylvestris*,[38] *Tanacetum vulgare* L. (tansy),[39] *Chrysanthemum parthenium* L. (feverfew),[40] *Artemisia cana* L. (silver sagebrush),[40] *Chrysanthemum balsamita* L. (costmary),[40] *Matricaria parthenium* (wild camomile),[9] *Chrysanthemum sinense* (mum),[9] *Chrysanthemum indicum* (mum)[9]	Camphoraceous odor[16a]
(−)-camphor		
(+)-camphor	*Picea mariana* nana,[38] *Picea albertiana* conica (dwarf white spruce),[38] *Picea sitchensis* (Sitka spruce),[38] *Artemesia californica* (coastal sagebrush),[38] *Chamaecyparis lawsoniana* (Lawson's cypress),[38] *Pinus sylvestris*,[38] *Salvia officinalis*,[38] *Salvia leucophylla* L. (San Luis purple sage),[40] *Chrysanthemum sinese*,[9] *Chrysanthemum indicum*,[9] *Cinnamomum camphora* (camphor tree)[9]	Camphoraceous odor[16a] Analeptic[9] Respiratory stimulant[9] Topical analgesic[9] Antipruritic[9] Antirheumatic[9]
	*Thuja orientalis* (Chinese Arborvitae),[38] *Thuja standishii* (Japanese Thuja),[38] *Pinus sylvestris*[29]	Camphoraceous odor with woody undertones[16b]
(−)-borneol		
(+)-borneol	*Picea sitchensis*,[38] *Chamaecyparis lawsoniana*,[38] *Pinus sylvestris*,[29] *Salvia officinalis*[38]	Camphoraceous odor with earthy-peppery undertones[16b]
	*Pinus sylvestris*,[29] *Angelica archangelica* L.[31]	
(−)-sabinene		
(+)-sabinene	*Pinus sylvestris*,[29] *Salvia officinalis*,[41] *Angelica archangelica* L.[31]	

Table 2

Enantiomeric sesquiterpenes.

Sesquiterpene	Species	Biological Activity
	*Ceroplastes rubens* (scale insect),[57] *Dendropanax trifidus* M. (ivy tree),[58] *Sinularia mayi* (soft coral),[55] *Preissia quadrata* (liverwort),[59] *Solidago altissima* (late goldenrod),[52] *Solidago canadensis* (Canada goldenrod),[60] *Podocarpus spicatus* (black pine),[61] *Zingiber officinale* (ginger)[60]	
(+)-germacrene D		
(−)-germacrene D	*Ceroplastes ceriferus* (scale insect),[57] *Solidago altissima*,[52] *Solidago canadensis*,[60] *Pogostemon cablin* (patchouli),[60,62] *Pseudotsuga japonica* (Japanese Douglas-fir),[9] *Araucaria bidwillii* (bunya pine),[63] *Vitis vinifera* (common grape vine),[60] *Populus trichocarpa* x *deltoides* (California poplar)[60]	
	*Araucaria bidwillii*,[63] *Carum carvi* L.,[64] *Gossypium arboreum* (tree cotton),[60] *Gossypium hirsutum* (upland cotton),[60] *Mentha piperata*[9]	
(+)-δ-cadinene		
(−)-δ-cadinene	*Ceroplastes ceriferus*,[57] *Sinularia mayi*,[55] *Araucaria araucana* (Monkey-puzzle tree),[63] *Araucaria bidwillii*,[63] *Carum carvi L.*,[64] *Heteroscyphus planus*[65]	
	*Streptomyces* sp. LL-B7 (bacteria),[66] *Heteroscyphus planus*,[65] *Scapania undulata* (liverwort),[64] *Juniperus rigida* (temple juniper),[67] *Streptomyces* sp. B-7 (bacteria)[68]	
(+)-epicubenol		
(−)-epicubenol	Cubeb oil,[69] *Juniperus rigida*,[67] *Cedrus atlantica* (Atlas Cedar)[9]	
	*Leptospermum scoparium* (Tea tree)[70]	
(+)-δ-amorphene		
(−)-δ-amorphene	*Vetiveria zizanioides (L.)* Nash ex Small (vetiver oil)[71]	

Sesquiterpene	Species	Biological Activity
	*Conocephalum conicum* (scented liverwort)[70]	
(+)-cadina-3,5-diene		
(−)-cadina-3,5-diene	*Leptospermum scoparium*,[70] *Piper cubeba* oil[70]	
	*Ceroplastes ceriferus*,[57] *Conocephalum conicum*[70]	
(+)-calamenene (*trans*)		
(−)-calamenene (*trans*)	*Leptospermum scoparium*,[70] *Piper cubeba* (tailed pepper)[70]	
	*Dysidea* sp. (marine sponge),[72] *Dysidea herbaceae* (marine sponge, Australia)[53]	
(+)-furodysinin		
(−)-furodysinin	*Dysidea herbaceae* (marine sponge, Fiji),[54] *Dysidea tupha*,[73] *Ceratosoma trilobatum* (Sea Slug)[74]	Feeding deterent,[74] Ichthyotoxic[74]
	*Disidea pallescens* (Black Sea sponge)[75]	
(+)-chromazonarol		
(−)-chromazonarol	*Dictyopteris undulata* (brown algae)[76]	Antimicrobial[77]
	*Dictyopteris zonarioides* (brown seaweed),[64,78] *Conocephalum conicum*[70]	
(+)-zonarene		

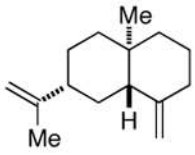
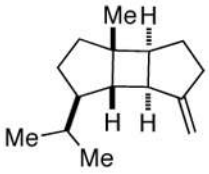
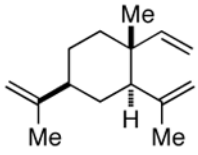
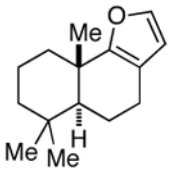
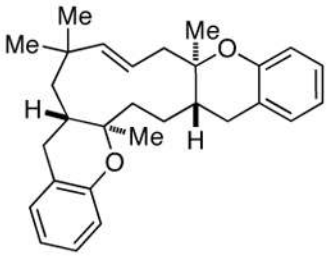
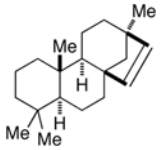
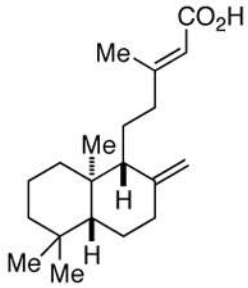
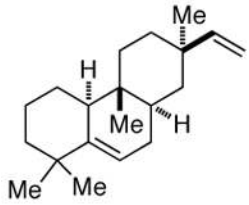
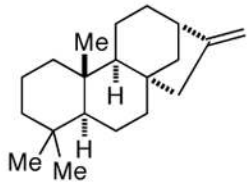
Sesquiterpene	Species	Biological Activity
(−)-zonarene	*Dictyopteris zonarioides*,[64,78] *Leptospermum scoparium*,[70] *Piper cubeba*[70]	
	*Ceroplastes rubens*[57]	
(+)-β-selinene		
(−)-β-selinene	*Ceroplastes ceriferus*[57]	
	*Ceroplastes rubens*[57]	
(+)-β-bourbonene		
(−)-β-bourbonene	*Ceroplastes ceriferus*[57]	
	*Ceroplastes ceriferus*[57]	
(+)-β-elemene		
(−)-β-elemene	*Ceroplastes rubens*[57]	
	*Disidea pallescens*[79]	
(+)-pallescensin A		
(−)-pallescensin A	*Doriopsilla areolata* (sea slug)[80]	
	*Uvaria lucida* spp. *lucida* (African shrub)[81]	
(±)-lucidene		

Table 3

Diterpenes.

Diterpene	Species
	*Dacrydium intermedium* (mountain pine),[82] *Araucaria araucana*[63]
(+)-beyerene	
(−)-beyerene	*Podocarpus spicatus*[61]
	*Eperua purpurea* (Wapa tree),[83] *Oxystigma oxyphyllum* (African tree)[84]
(±)-labda-8(20),13-diene-15-oic acid	
	*Podocarpus spicatus*[61]
(+)-rosadiene	
(−)-rosadiene	*Dacrydium intermedium*[82]
	*Podocarpus spicatus*[61]
(+)-16-kaurene	
(−)-16-kaurene	*Dacrydium intermedium* T. Kirk,[82] *Araucaria bidwillii*,[63] *Araucaria araucana*,[63] *Araucaria heterophylla*[63]

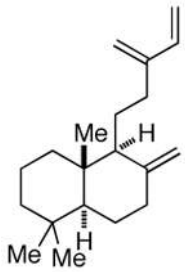
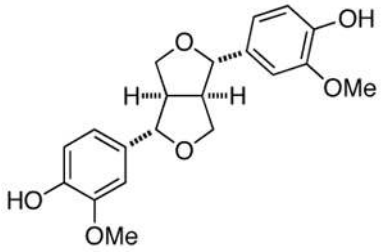
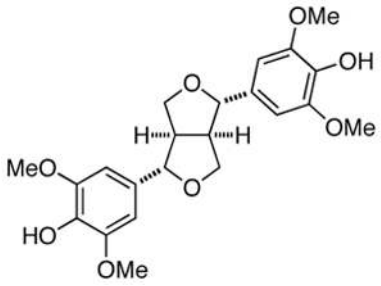
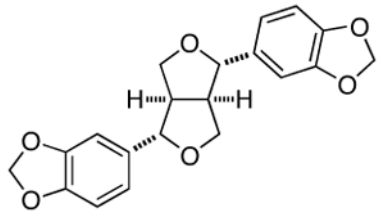
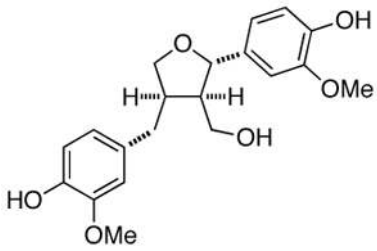
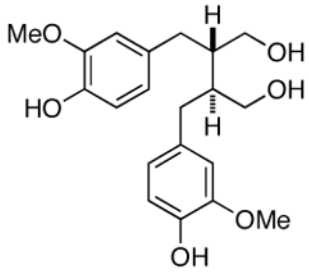
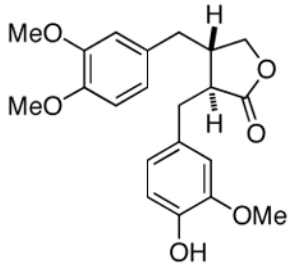
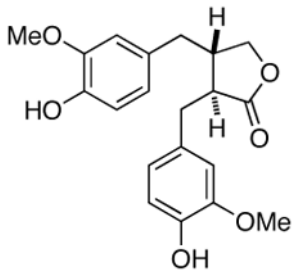
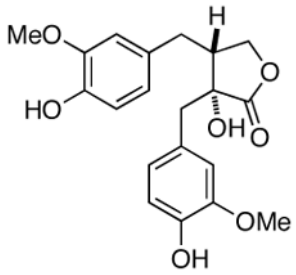
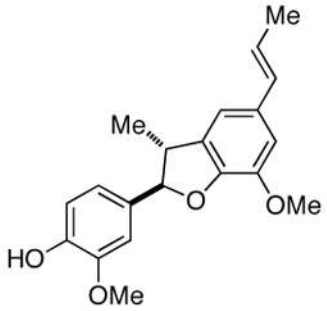
Diterpene	Species
	*Dacrydium intermedium*,[82] *Araucaria bidwillii*,[63] *Araucaria heterophylla*[63]
(+)-sclarene	
(−)-sclarene	*Podocarpus spicatus*,[61] *Dacrydium intermedium*,[82] *Araucaria araucana*,[63] *Araucaria heterophylla*[63]

Table 4

Enantiomeric lignans.

Lignans	Species	Biological Activity
 (+)-pinoresinol	*Forsythia koreana* (Korean flowering plant, 82% e.e),[91] *Linum flavum* var. *compactum* (Dwarf Golden Flax, 65% e.e.),[91] *Larix leptolepis* (Japanese Larch, 92% e.e.),[91,92] *Wikstroemia viridiflora*,[92] *Stellera chamaejasme* (Tibetan Flowers),[92] *Forsythia suspensa* (Asian flowering plant),[92] *Forsythia* spp.,[92] *Fraxinus* spp.,[92] *Helianthus annuus* (common sunflower)[98]	Phytotoxic[98]
(−)-pinoresinol	*Wikstroemia sikokiana* (deciduous shrub, 74% e.e.),[91] *Daphne odora* (Winter Daphne, 95% e.e.),[91] *Daphne genkwa* (92% e.e.),[91] *Daphne tangutica*,[92] *Zanthoxylum ailanthoides* (Japanese Prickly-ash),[92] *Zanthoxylum kellermanii*,[92] *Senecio scandens* (wild daisy)[99]	Antioxidant[99]
 (+)-syringaresinol	*Wikstroemia elliptica*,[92] *Daphne tangutica*,[92] *Passerina vulgaris*,[92] *Dirca occidentalis* (Western Leatherwood)[93]	
(−)-syringaresinol	*Daphne tangutica*,[92] *Zanthoxylum acanthopodium*,[92] *Daphne genkwa*[100]	Anticancer[100]
 (+)-sesamin	*Zanthoxylum acanthapodium*,[92] *Zanthoxylum valens*,[92] *Zanthoxylum setulosum*[92]	Antihypertensive[101]
(−)-sesamin	*Zanthoxylum piperitum* (Japanese Pepper tree)[92]	

Lignans	Species	Biological Activity
 (+)-lariciresinol	*Forsythia koreana* (35% e.e.),[91] *Linum flavum* var. *compactum* (70% e.e.),[91] *Wikstroemia elliptica*,[92] *Larix leptolepis*,[92] *Abies sachalinensis* (Sakhalin fir),[92] *Araucaria angustifolia*[92]	Phytotoxic (Inhibits lettuce germination)[102]
(−)-lariciresinol	*Wikstroemia sikokiana* (39% e.e.),[92] *Daphne odora* (89% e.e.),[92] *Daphne genkwa* (88% e.e.),[92] *Wikstroemia elliptica*,[93] *Daphne tangutica*,[93] *Dirca occidentalis*[93]	Phytotoxic (Inhibits root growth of Italian ryegrass)[102]
 (+)-secoisolariciresinol	*Arctium lappa* (Burdock, petiole) (81% e.e.),[91] *Phyllanthus* sp. (98% e.e.),[91] *Daphne odora* (>99% e.e.),[91] *Daphne genkwa* (97% e.e.)[91]	Antioxidant[103]
(−)-secoisolariciresinol	*Arctium lappa* (seeds) (65% e.e.),[91] *Forsythia koreana* (>99% e.e.),[91] *Forsythia intermedia* (>99% e.e.),[91] *Wikstroemia sikokiana* (45% e.e.),[91] *Zanthoxylum ailanthoides*,[92] *Larix leptolepis*,[92] *Larix decidua* (European larch),[92] *Araucaria angustifolia*,[92] *Podocarpus spicatus*[92]	Antioxidant[103]
 (+)-arctigenin	*Wikstroemia indica*,[92] *Daphne genkwa*[100]	Anticancer[100]
(−)-arctigenin	*Arctium lappa* (seeds) (>99% e.e.),[91] *Forsythia koreana* (>99% e.e.),[91] *Forsythia intermedia* (>99% e.e.),[91] *Trachelospermum asiaticum* var. *intermedium* (Yellow Star-jasmine),[92] *Centaurea pamphylica*[104]	Antitumoral,[105] Anticancer,[105] Antioxidant[104]

Lignans	Species	Biological Activity
	*Wikstroemia sikokiana* (>99% e.e.),[91] *Daphne odora* (>99% e.e.),[91] *Daphne genkwa* (>99% e.e.),[91] *Centaurea pamphylica*[104]	
(+)-matairesinol		
(−)-matairesinol	*Arctium lappa* (seeds) (>99% e.e.),[91] *Forsythia koreana* (>99% e.e.),[91] *Forsythia intermedia* (>99% e.e.),[91] *Stellera chamaejasme*,[92] *Forsythia* spp.,[92] *Trachelospermum asiaticum* var. *intermedium*,[92] *Zanthoxylum kellermanii*,[92] *Picea excelsa* (Norway spruce),[92] *Tsuga mertensiana* (Mountain Hemlock),[92] *Thuja occidentalis* (>99% e.e.)[91]	Antioxidant[104]
	*Wikstroemia viridiflora*,[92] *Wikstroemia foetida*,[92] *Wikstroemia sikokiana* (>99% e.e.),[91] *Wikstroemia indica*,[92] *Daphne odora*,[92] *Passerina vulgaris*[92]	Anticancer[106]
(+)-wikstromol		
(−)-wikstromol	*Thuja occidentalis* (>99% e.e.),[91] *Trachelospermum asiaticum* var. *intermedium*,[92] *Trachelospermum axillare*[92]	Anticancer[107]
	*Leucas aspera* (Common Leucas),[108] *Machilus thunbergii* (Japanese bay tree)[109]	Neuroprotective[109]
(+)-licarin A		
(−)-licarin A	*Leucas aspera*[108]	

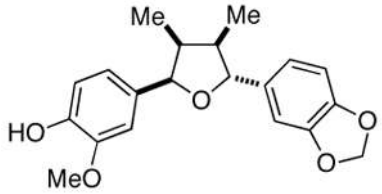
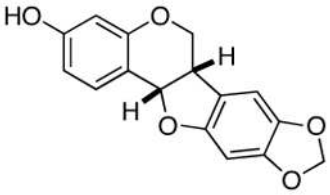
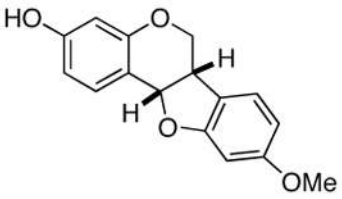
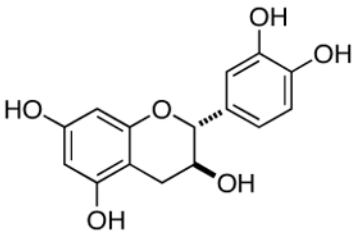
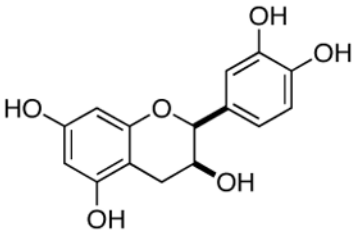
Lignans	Species	Biological Activity
	*Schisandra* sp.[110]	
(+)-chicanine		
(−)-chicanine	*Leucas aspera*[108]	Antioxidant[108b]

Table 5

Enantiomeric flavonoids.

Flavonoid	Species	Biological Activity
	*Dalbergia spruceana* (Amazon rosewood),[114] *Dalbergia stevensonii* (Honduras rosewood),[114] *ophora japonica* (Pagoda Tree)[114]	Antimicrobial[115] Phytoalexin[115]
(+)-maackiain		
(−)-maackiain	*Dalbergia stevensonii*,[114] *Sophora japonica*,[115] *Trifolium pratense* L. (red clover),[116] *Pisum sativum* L. (garden pea)[116]	Antimicrobial[115] Phytoalexin[115]
	*Dalbergia decipularis* Rizz. et Matt. (Tulipwood),[114] *Dalbergia riparia*,[114] *Dalbergia variabilis*,[114] *Machaerium kuhlmannii* Hoehne,[114] *Machaerium nictitans*,[114] *Machaerium vestitum*,[114] *Arachis hypogea* (peanut),[117] *Sophora japonica*[115]	Antimicrobial[115] Phytoalexin[115]
(+)-medicarpin		
(−)-medicarpin	*Dalbergia stevensonii*,[114] *Trigonella foenum-graecum* (Fenugreek),[115] *Medicago sativa* (alfalfa)[118]	Antimicrobial[115] Phytoalexin[115]
	*Acacia mearnsii* (Black Wattle),[119] *Acacia decurrens* (Green Wattle),[119] *Acacia dealbata* (Silver Wattle),[119] *Acacia pycnantha* (Golden Wattle),[119] *Chamaerops humilis* (Mediterranean Dwarf Palm),[109] *Phoenix canariensis* (Canary Island Date Palm),[120] *Butia capitata* (Jelly Palm),[120] *Howea forsteriana* (Thatch Palm),[120]	
(+)-catechin		
(−)-catechin	*Chamaebatia foliolosa* Benth (mountain misery), [121] chocolate[122]	
	*Chamaerops humilis*,[120] *Livistona chinensis* (Fountain Palm)[120]	
(+)-epicatechin		
(−)-epicatechin	*Acacia dealbata*,[119] *Acacia pycnantha*[119]	

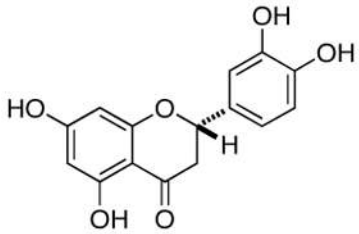
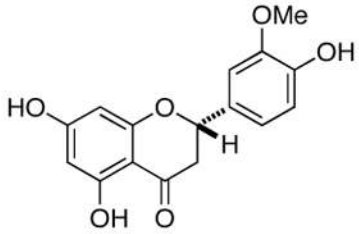
Flavonoid	Species	Biological Activity
	*Arachis hypogaea* (peanut hulls),[123] *Hemizonia increscens* (grassland tarweed)[123]	
(+)-eriodictyol		
(−)-eriodictyol	*Arachis hypogaea*,[123] *Hemizonia increscens*,[123] *Thymus vulgaris*[123]	
	*Eriodictyon glutinosum* (Mountain Balm)[123]	
(+)-homoeriodictyol		
(−)-homoeriodictyol	*Eriodictyon glutinosum*[123]	

Table 6

Enantiomeric coumarins

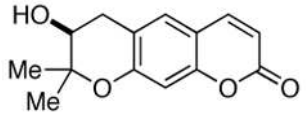
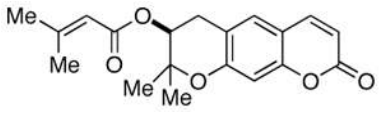
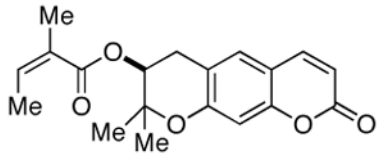
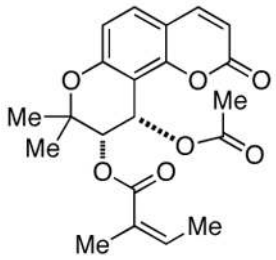
Coumarins	Species	Biological Activity
	*Angelica gigas* (aerial),[128] *Angelica gigas* Nakai (roots)[129]	Anticancer,[130] Antihelicobacterpyloric,[131] Antinociceptive,[132] Inhibitor of acetyl cholinesterase[133]
(+)-decursinol		
(−)-aegelinol (decursinol enantiomer)	*Angelica gigas* (aerial),[128] *Aegle marmelos*,[134] *Ferulago campestris* (aegelinol benzolate),[135] *Eryngium campestre* (benzoyl aegelinol)[136]	Antibacterial[135]
	*Angelica gigas* (roots),[137] *Angelica gigas* (aerial),[128] *Angelica sinensis* (female ginseng),[138] *Angelica acutiloba*[136]	Antibacterial,[137] Sedative[137]
(*S*)-decursin		
(*R*)-grandivittin (decursin enantiomer)	*Ferulago campestris*,[135] *Eryngium campestre*[136]	
	*Angelica gigas* (aerial),[128] *Angelica gigas* (roots),[137] *Angelica sinensis*,[138] *Angelica acutiloba*[138]	Antibacterial[137]
(*S*)-agasyllin		
(*R*)-agasyllin	*Angelica gigas* (aerial),[128] *Ferulago campestris*,[135] *Eryngium campestre*[136]	Antibacterial,[135] Antihelicobacterpyloric[135]
	*Peucedanum praeruptorum* Dunn.[139]	Reduces blood pressure[139]
(+)-praeruptorin A		
(−)-praeruptorin A	*Peucedanum praeruptorum* Dunn.[139]	Reduces blood pressure[139]

Table 7

Neoflavonoid enantiomers.

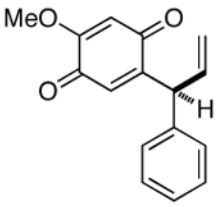
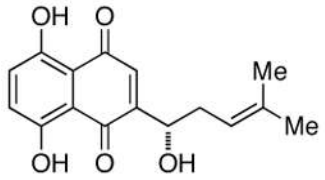
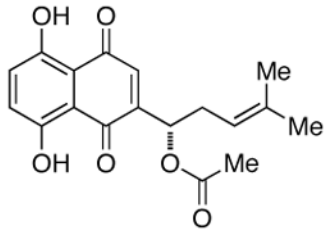
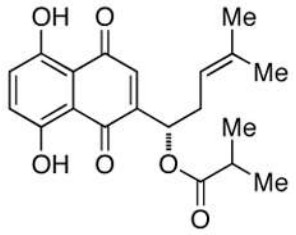
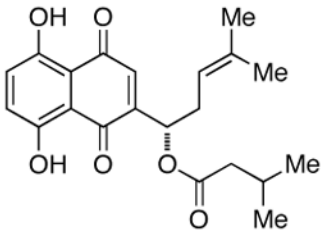
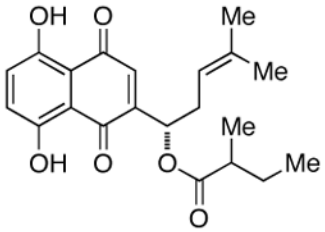
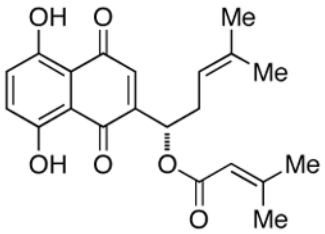
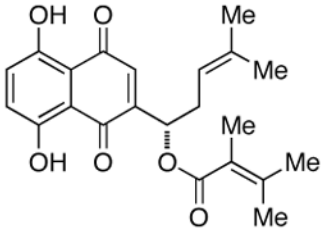
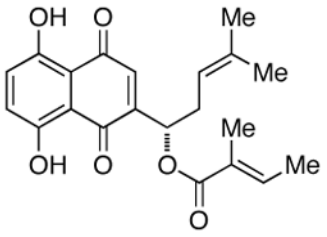
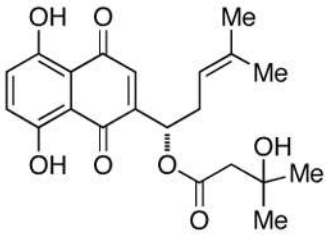
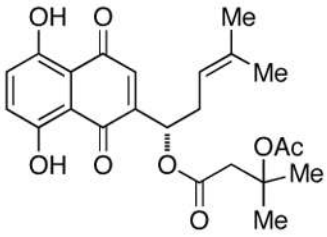
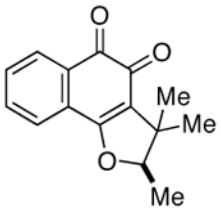
Neoflavonoid	Species	Biological Activity
	*Dalbergia violacea*,[127] *Dalbergia baroni* Baker (Madagascar Rosewood),[140] *Dalbergia cultrate* (Khamphi Rosewood),[141] *Dalbergia melanoxylon* (African Blackwood),[142] *Dalbergia inundata*,[143] *Dalbergia nitidula*,[144] *Dalbergia miscolobium*[145]	
(*S*)-methoxydalbergione		
(*R*)-methoxydalbergione	*Dalbergia niger* Fr. Allem. (Bahia Rosewood),[127] *Dalbergia latifolia* Roxb. (Indian Rosewood),[127c,146] *Dalbergia parviflora*,[147] *Dalbergia cochinchinensis* (Thiland Rosewood),[148] *Dalbergia retusa* (Cocobolo)[149]	Antiplasmodial[150]

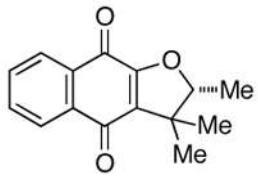
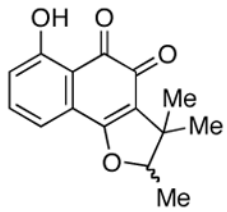
Table 8

Quinone natural enantiomers[a]

Quinone	Species	Biological Activity
 alkannin	*Alkanna tinctoria* (Alkanet), *Arnebia hispidissima, Arnebia nobilis, Arnebia tinctoria, Macrotomia cephalotes, Macrotomia euchroma* (Syrian Alkanet), *Onosma echioides, Onosma paniculata, Plagiobotrys arizonicus*	Wound healing, Antiinflammatory, Antibacterial, Inhibition of topoisomerase-I, Antithrombotic
shikonin (alkannin enantiomer)	*Arnebia euchroma, Arnebia hispidissima, Arnebia guttata, Arnebia tibetiana, Cynoglossum officinale* (Gypsyflower), *Echium lycopsis, Echium rubrum, Echium vulgare* (Blueweed), *Eritrichium incanum, Eritrichium sichotenze, Jatropha glandulifera, Lappula consanguinea, Lappula echinata* (Blue-bur), *Lithospermum erythrorhizon* (Purple Gromwell), *Lithospermum officinale* (European Stoneseed), *Macrotomia echioides, Macrotomia ugamensis, Macrotomia euchroma, Mertensia maritima* (Sea Lungwort), *Onosma caucasicum, Onosma conferitum, Onosma hookeri, Onosma livanovii, Onosma polyphyllum, Onosma tauricum, Onosma sericium, Onosma setosum, Onosma visianii, Onosma zerizaminium*	Antitumor, Antiamebic, Antipyretic and analgesic, Antifungal, Antibacterial, Wound healing, Chemopreventive, Antiinflammatory, Inhibition of topoisomerase-II, Inhibition of microsomal monooxygenase, Stimulation of peroxidase, Protection from uv-radiation, Inhibition of testosterone-α-reductase, Induction and secretion of nerve growth factors
 acetylalkannin	*Alkanna tinctoria, Arnebia euchroma, Arnebia hispidissima, Arnebia nobilis, Macrotomia cephalotes*	Antimicrobial, inhibition of topoisomerase-I, Antithrombotic, Antitumor
acetylshikonin	*Arnebia decumbens, Arnebia euchroma, Arnebia guttata, Cynglossum officinale, Echium vulgare, Eritrichium incanum, Eritrichium sichotenze, Jatropha glandulifera, Lappula consanguinea, Lappul echinata, Lithospermum arvense* (Field Gromwell), *Lithospermum erythrorhizon, Mertensia maritima, Onosma confertum, Onosma hookeri, Onosma paniculatum*	
 isobutyrlalkannin	*Alkanna tinctoria*	
isobutyrylshikonin	*Cynoglossum officinale, Echium vulgare, Eritrichium sichotenze, Lappula consanguinea, Lappula echinata, Lithospermum arvense, Lithospermum erythrorhizon, Macrotomia euchroma, Mertensia maritima*	

Quinone	Species	Biological Activity
	*Alkanna tinctoria, Arnebia hispidissima, Arnebia tinctoria, Macrotomia cephalotes, Onosma heterophylla*	Inhibition of topoisomerase-I
isovalerylalkannin		
isovalerylshikonin	*Arnebia decumbens, Cynoglossum officinale, Echium vulgare, Lappula consanguinea, Lappula echinata, Lithospermum arvense, Lithospermum erythrorhizon, Macrotomia euchroma*	
	*Alkanna tinctoria, Macrotomia cephalotes*	Antimicrobial
α-methylbutyrylalkannin		
α-methylbutyrylshikonin	*Cynoglossum officinale, Echium vulgare, Eritrichium incanum, Eritrichium sichotenze, Lappula consanguinea, Lappula echinata, Lappula erythrorhizon, Mertensia maritima*	Antimicrobial
	*Alkanna tinctoria, Arnebia euchroma, Arnebia gutatta, Arnebia nobilis, Lithospermum erythrorhizon, Macrotomia cephalotes, Onosma heterophylla, Onosma hookeri, Onosma paniculata*	Inhibition of topoisomerase-I and anticancer, Antimicrobial, Antithrombotic, Antiinflammatory
β,β-dimethylacrylalkannin		
β,β-dimethylacrylshikonin	*Alkanna hirsutissima, Arnebia euchroma, Arnebia guttata, Arnebia tibetiana, Cynoglossum officinale, Echium vulgare, Eritrichium incanum, Eritrichium sichotenze, Jatropha glandulifera, Lappula consanguinea, Lappula echinata, Echium* spp., *Lithospermum erythrorhizon, Macrotomia ugamensis, Mertensia maritima, Moltkiopsis ciliata, Onosma confertum, Onosma paniculatum, Onosma hookeri, Onosma zerizaminum*	
	*Arnebia densiflora*	Antimicrobial
teracrylalkannin		

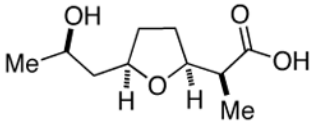
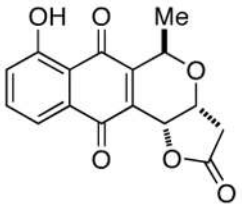
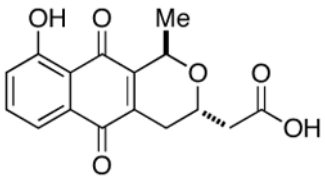
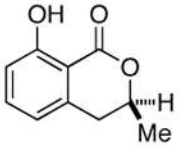
Quinone	Species	Biological Activity
teracrylshikonin	*Arnebia euchroma, Arnebia guttata, Lithospermum erythrorhizon, Lithospermum euchromum*	Antimicrobial
	*Alkanna tinctoria*	
angelylalkannin		
angelylshikonin	*Alkanna hirsutissima*	
	*Arnebia euchroma, Arnebia hispidissima, Macrotomia cephalotes*	Antimicrobial
β-hydroxyisovalerylalkannin		
β-hydroxyisovalerylshikonin	*Arnebia euchroma, Arnebia guttata, Lithospermum arvense, Lithospermum erythrorhizon, Lithospermum euchromum*	Antimicrobial
	*Alkanna tinctoria, Arnebia euchroma, Moltkiopsis ciliata, Onosma heterophylla*	Antimicrobial
β-acetoxyisovalerylalkannin		
β-acetoxyisovalerylshikonin	*Macrotomia euchroma*	
	*Streptocarpus dunnii* (Cape Primrose),[152] *Calceolaria integrifolia*[153]	
(+)-dunnione		
(−)-dunnione	*Streptocarpus dunnii*,[152] *Calceolaria integrifolia*[153]	

Quinone	Species	Biological Activity
 (+)-α-dunnione	*Streptocarpus dunnii*[152]	
(−)-α-dunnione	*Streptocarpus dunnii*[152]	
 (±)-8-hydroxydunnione	*Streptocarpus dunnii*[152]	

[a] For species and biological activity that do not have a reference, please refer to the Review by Nicolau et al. (reference 151)

Table 9

Enantiomeric polyketides.

Polyketide	Species	Biological Activity
	*Streptomyces griseus* (bacteria),[155] *Streptomyces* spec. JA 5909-1[156]	
(+)-nonactic acid (and homologues)		
(−)-nonactic acid (and homologues)	*Streptomyces griseus*,[155] *Streptomyces* spec. JA 5909-1[156]	
	*Streptomyces tanashiensis* strain Kala,[157] *Streptomyces coelicolor* A3(2)[158]	Antibiotic[159]
kalafungin		
nanaomycin D (kalafungin enantiomer)	*Streptomyces rosa* var. *notoensis* OS3966[160]	Antibiotic[160]
	*Nocardia* sp. (bacteria)[161]	Antibiotic[161]
(+)-nanaomycin A		
(−)-nanaomycin A	*Streptomyces rosa* var. *notoensis* OS3966[162]	Antibiotic, [162] Antifungal, [162] Antimycoplasma activity[162]
	*Cercospora taiwanensis*,[163] *Fusarium larvarum*,[163] *Grignardia laricina*,[163] *Gyrostroma missouriense* (fungus),[163] *Helicascus kanaloanus* (marine fungus),[164] unidentified fungus[163]	
(+)-mellein		
(−)-mellein	*Aspergillus melleus* (fungus),[163] *Aspergillus ochraceus* (fungus),[163] *Aspergillus oniki* (fungus),[163] *Camponotus* spp.,[163] *Cornitermes* spp.,[163] *Grapholithia molesta* (Oriental Fruit Moth),[163] *Hypoxylon* spp.,[163] *Lasiodiplodia theobromae* (fungus),[163] *Marasmiellus ramealis* (Twig Parachute Mushroom),[163] *Pestalotia ramulosa* (fungus),[163] *Rhytidoponera metallica* (Green-head Ant),[163] *Septoria nodorum* (fungus)[163]	Hepatitis C Inhibitor,[165a] Antibacterial,[165b] Antiviral, [165b] Phytotoxic[165b]

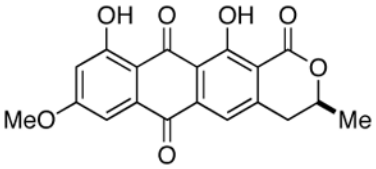
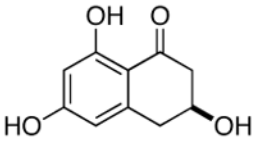
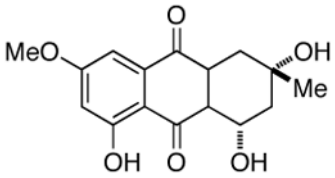
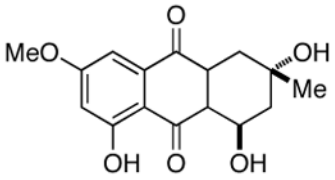
Polyketide	Species	Biological Activity
	*Dermocybe kula* (fungus)[166]	Major orange-red fungal pigment[166]
(+)-dermolactone		
(−)-dermolactone	*Dermocybe kula*[166]	Minor orange-red fungal pigment[166]
	*Verticillium dahliae* (fungus),[167] *Phialophora lagerbergii* (fungus),[168] *Scytalidium* sp.[169]	
(+)-scytalone		
(−)-scytalone	*Phialophora lagerbergii*,[168] *Scytalidium* sp. [169]	
	*Dermocybe splendida* (Splendid Red Skinhead, fungus)[170]	Antibiotic,[171] Fungal pigment (yellow)[172]
(1*S*,3*S*)-austrocortilutein		
(1*R*,3*R*)- austrocortilutein	*Dermocybe* sp. WAT 20934[172]	
	*Dermocybe splendida*,[170] *Dermocybe* sp. WAT 20934,[172] *Dermocybe* sp. WAT 21568[172]	Antibiotic,[171] Fungal pigment (yellow-*D. splendida*)[172]
(1*S*,3*R*)- austrocortilutein		
(1*R*,3*S*)- austrocortilutein	*Dermocybe* sp. WAT 21567,[172] *Dermocybe* sp. WAT 20934[172]	

Table 10

Enantiomeric manzamine alkaloids.

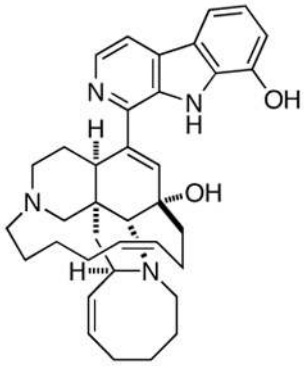
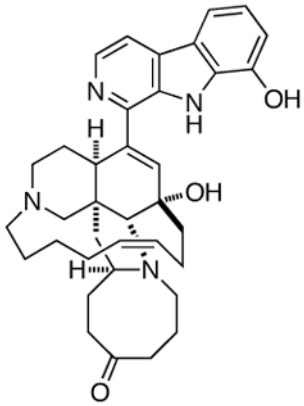
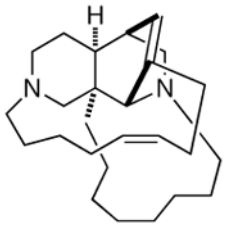
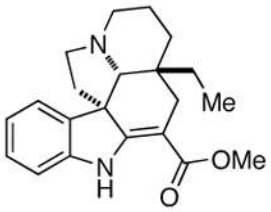
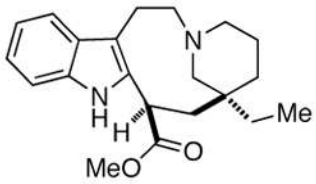
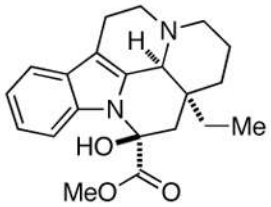
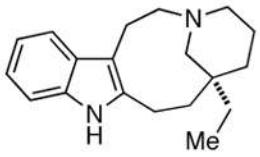
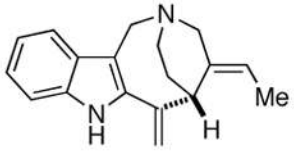
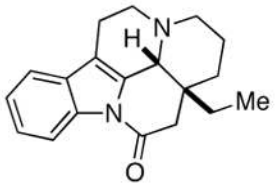
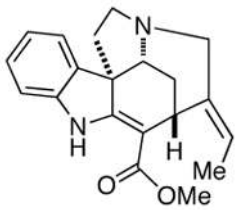
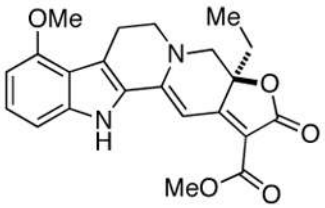
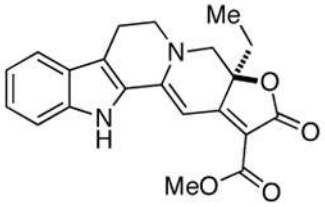
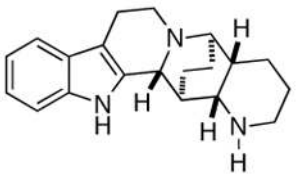
Manzamine	Species	Biological Activity
	Indonesian sponge *Pachypellina* sp.,[187] Okinawan sponge *Xestospongia* sp.,[188] Okinawan sponge *Amphimedon* sp.[188]	Anticancer[183]
(+)-8-hydroxymanzamine A		
(−)-8-hydroxymanzamine A	Unidentified Indo-Pacific sponge (family *Petrosiidae*, order *Haplosclerida*)[189]	Anticancer,[183] Antimalarial[183]
	*Xestospongia* sp.[190]	Antimicrobial,[183] Anticancer[183]
(+)-manzamine F		
(−)-manzamine F	Unidentified Indo-Pacific sponge (family *Petrosiidae*, order *Haplosclerida*)[189]	Activity against *Mycobacterium tuberculosis*[183]
	*Amphimedon* sp.,[191] *Xestospongia ingens* [optically active, $[\alpha]_D$ +29.8° (c 1.1; MeOH)][192]	Anticancer[183]
(±) keramaphidin B		

Table 11

Enantiomeric indole alkaloid metabolites.[a]

Indole Alkaloid	Species	Biological Activity
	*Amsonia tabernaemontana* (Eastern Bluestar),[197] *Amsonia angustifolia, Rhazya stricta, Tabernaemontana riedelii, Vinca difformis* (Intermediate Periwinkle), *Macoubea guianensis*[198]	
(+)-vincadifformine		
(−)-vincadifformine	*Vinca minor* (Dwarf Periwinkle), *Vinca difformis, Rhazya stricta, Tabernaemontana riedelii, Macoubea guianensis*[198]	
	*Vinca minor, Amsonia tabernaemontana, Amsonia angustifolia, Macoubea guianensis*[198]	
(+)-vincadine		
(−)-vincadine	*Amsonia tabernaemontana, Amsonia angustifolia, Macoubea guianensis*	
	*Vinca minor, Vinca major* (Blue Periwinkle), *Vinca erecta, Vinca difformis, Tabernaemontana rigida*	Antihypertensive
(+)-vincamine		
(−)-vincamine	*Tabernaemontana rigida*	
	*Vinca erecta, Pleiocarpa tubicina, Pleiocarpa pycnantha* var. *pycnantha, Stemmadenia donnell-smithii*	
(+)-quebrachamine		
(−)-quebrachamine	*Aspidosperma quebracho-blanco* (South American tree), *Aspidosperma chakensis*, other *Aspidosperma* spp., *Gonioma kamassi, Hunteria elliotii, Rhazya stricta*	
	*Aspidosperma dasycarpon*	
(+)-apparicine		

Indole Alkaloid	Species	Biological Activity
(−)-appariciné  	*Aspidosperma olivaceum*, other *Aspidosperma* spp., *Catharanthus ovalis* (Rosy Periwinkle), *Catharanthus roseus* (Madagascar Periwinkle), *Pandaca ochrascens, Pandaca eusepala, Ervatamia heyneana, Tabernaemontana cumminsii, Schizzygia caffaeoides* *Hunteria eburnea, Amsonia tabernaemontana, Vinca minor*	Anticancer, Antibacterial, Antiviral
(+)-eburnamonine		
(−)-eburnamonine  	*Vinca minor* *Picralima nitida*	Stimulates muscle activity
(+)-akuammicine		
(−)-akuammicine  	*Picralima nitida, Alstonia scholaris* (Blackboard tree), other *Alstonia* spp., several *Vinca* spp., *Rauwolfia volkensii, Hunteria congolana, Catharanthus microphyllus, Cabucala erythrocarpa, Pandaca ochrascens, Catharanthus roseus*[199] *Mitragyna speciosa* (Kratom)[200]	
(+)-9-methoxymitralactonine		
(−)-9-methoxymitralactonine	*Mitragyna speciosa*[200]	
 	*Mitragyna speciosa*[201]	
(+)-mitralactonine		
(−)-mitralactonine	*Mitragyna speciosa*[201]	

Indole Alkaloid	Species	Biological Activity
 (±)-nitrarine	*Nitraria schoberi* (Nitre Bush)[193,202]	

[a]For species and biological activity that do not have a reference, please refer to the *Dictionary of Alkaloids* (reference 193)

Table 12

Enantiomeric reverse prenylated indole alkaloids.

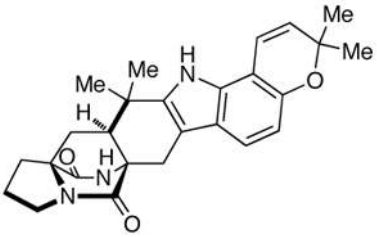
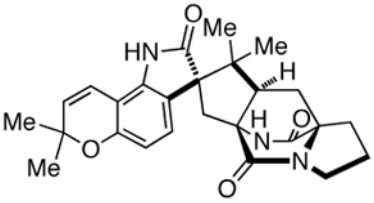
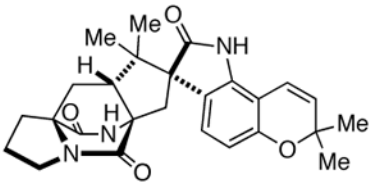
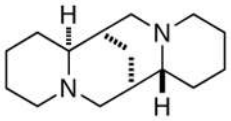
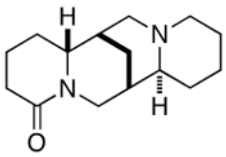
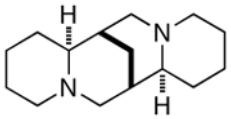
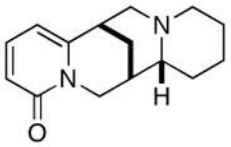
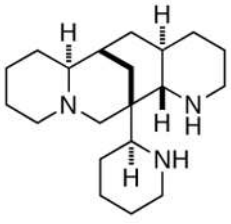
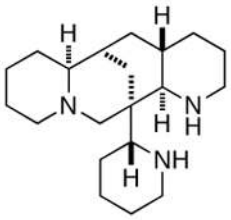
Reverse Prenylated Indole Alkaloid	Species	Biological Activity
	*Aspergillus* sp. MF297-2 (fungus),[205] *Aspergillus ochraceus* (fungus) [204]	Anticancer[204]
(+)-stephacidin A		
(−)-stephacidin A	*Aspergillus versicolor* (fungus) [206]	
	*Aspergillus versicolor*[206]	
(+)-notoamide B		
(−)-notoamide B	*Aspergillus* sp. MF297-2[205]	
	*Aspergillus versicolor*[206]	
(+)-versicolamide B		
(−)-versicolamide B	*Aspergillus* sp. MF297-2[210]	

Table 13

Lupine alkaloid enantiomers.[a]

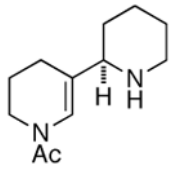
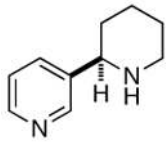
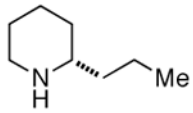
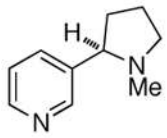
Lupine Alkaloid	Species	Biological Activity
 (+)-sparteine	*Cytisus caucasicus*, *Lupinus pusillus* (Rusty Lupine), *Genista monosperma* (Bridal Broom), *Pelargonium acutifolia, Pelargonium longifolia, Sophora pachycarpa, Ammodendron* spp., *Baptisia* spp. *Chamaecytisus proliferus, Adenocarpus hispanicus, Hovea linearis* (Common Hovea),[214] *Lygos raetam* var. *sarcocarpa*,[215] *Lupinus albus* (White Lupine),[216] *Genista lydia* (Hardy Dwarf Broom)[217]	Highly toxic
(−)-sparteine	*Cytisus scoparius* (Scotch Broom), *Lupinus* spp., *Adenocarpus* spp., *Piptanthus nanus, Sarothamnus* spp., *Chamaecytisus proliferus, Corothamnus rectipilosus*,[215] *Chamaecytisus austriacus*,[216] *Genista lydia*[217]	Oxytoxic, Antiarrhythmic
 (+)-lupanine	*Lupinus albus, Lupinus termis, Podalyria buxifolia, Virgilia capensis, Cytisus scoparius*, other *Cytisus* spp., *Cadia purpurea, Ammopiptanthus mongolicus, Thermopsis chinensis* (Chinese Bush Pea), *Leontice* spp., *Genista* spp., *Templetonia* spp. *Chamaespartium sagittale*,[215] *Corothamnus rectipilosus*,[215] *Genista rumelica*,[215] *Genista sessilifolia*,[215] *Chamaecytisus austriacus*,[216] *Genista lydia*[217]	Toxic to livestock
(−)-lupanine	*Lupinus albus, Lupinus termis, Podalyria buxifolia, Virgilia capensis, Lupinus pusillus, Lupinus macounii, Baptisia versicolor, Podalyria calyptrata* (Water Blossom Pea), *Ammodendron* spp., *Leontice smirnovii, Leontice eversmannii, Lygos raetam* var. *sarcocarpa*,[215] *Genista lydia*,[217] *Clathrotropis glaucophylla*[218]	Toxic to livestock
 (+)-β-isosparteine	*Lupinus* spp.,[211a] *Lupinus pusillus*[219]	
(−)-β-isosparteine	*Lupinus pusillus*,[211a,220] *Lupinus sericeus* (Silky Lupine),[221] *Lupinus argenteus stenophyllus* (Silvery Lupine), *Lupinus solosericeus, Sophora secundiflora* (Texas Mountain Laurel)	
 (+)-thermopsine	*Lupinus caudatus* (Tailcup Lupine), *Lupinus corymbosus*	
(−)-thermopsine	*Thermopsis lanceolata* (Golden Banner), *Thermopsis rhombifolia* (Buffalo Bean), *Sophora secundiflora*	
 (+)-ormosanine	*Ormosia panamensis* (Coronil), *Piptanthus nanus*	

Lupine Alkaloid	Species	Biological Activity
(−)-ormosanine	*Podopetalum ormondii, Ormosia semicastrata, Ormosia jamaicensis, Piptanthus nanus*	
	*Hovea linearis, Templetonia retusa* (Cockies Tounge), *Ormosia semicastrata, Ammopiptanthus mongolicus*	
(+)-piptanthine		
(−)-piptanthine	*Hovea linearis, Templetonia retusa, Ormosia semicastrata, Ammopiptanthus mongolicus, Piptanthus nanus*	

[a]For species and biological activity that do not have a reference, please refer to the *Dictionary of Alkaloids* (reference 193)

Table 14

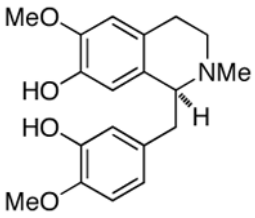
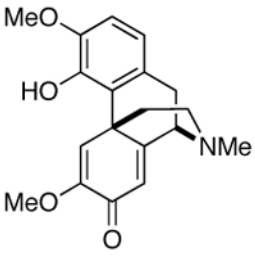
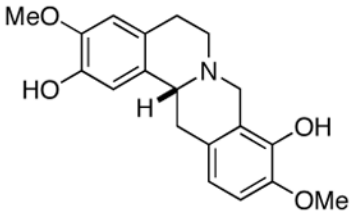
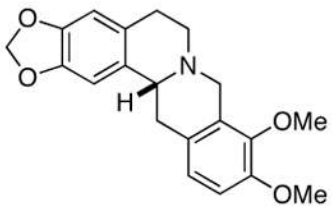
Enantiomeric piperidine and pyridine alkaloids.[a]

Piperidine and Pyridine Alkaloid	Species	Biological Activity
	*Genista sphaerocarpa, Ammodendron conollyi, Ammodendron* spp., *Sophora franchetiana, Sophora tomentosa* (Yellow Necklace Pod),[228] *Coelidium fourcadei, Lupinus formosus* (Summer Lupine),[225a–b] *Lupinus varius,*[225a] *Lupinus hirsutus*[225a]	Teratogen[225]
(+)-ammodendrine		
(−)-ammodendrine	*Ammodendron conollyi, Ammodendron* spp., *Sophora franchetiana, Sophora tomentosa,*[228] *Coelidium fourcadei, Lupinus formosus,*[225a–b] *Castilleja miniata* (Giant Red Indian Paintbrush)[225a]	Teratogen[225]
	*Nicotiana glauca* (wild tobacco),[225d] *Aphaenogaster subterranea* (ant),[229] *Aphaenogaster miamiana* (ant)[229]	Teratogen[225d]
(+)-anabasine		
(−)-anabasine	*Nicotiana glauca,*[225d] *Anabasis aphylla,*[230] *Aphaenogaster subterranea,*[229] *Aphaenogaster miamiana,*[229] *Messor sanctus* (ant)[229]	Teratogen[225d]
	*Conium maculatum* (poison hemlock)[225c]	Toxic to livestock[225c]
(+)-coniine		
(−)-coniine	*Conium maculatum*[225c]	Toxic to livestock[225c]
	*Nicotiana tabacum* (cultivated tobacco)	Weakly binds to nicotinic acetylcholine receptors[8]
(+)-nicotine		
(−)-nicotine	*Nicotiana tabacum*, other *Nicotiana* spp., *Asclepias syriaca* (Common Milkweed), *Lycopodium* spp., *Equisetum arvense* (Field Horsetail), *Sedum acre* (Golden Stonecrop)	Incredibly reactive at nicotinic acetylcholine receptors[8]

[a]For species and biological activity that do not have a reference, please refer to the *Dictionary of Alkaloids* (reference 183)

Table 15

Enantiomeric benzylisoquinoline alkaloid secondary metabolites.[a]

Benzylisoquinoline Alkaloid	Species	Biological Activity
	*Annona reticulata* (Wild-sweetsop), *Phylica rogersii, Papaver somniferum* (Opium Poppy)	
(+)-reticuline		
(−)-reticuline	*Romneya coulteri* var. *trichocalyx* (Coulter's Matilija Poppy)	
	*Croton salutaris, Croton balsamifera, Papaver* spp., *Glaucium* spp.	Antitumor
(+)-salutaridine		
(−)-sinoacutine (salutaridine enantiomer)	*Sinomenium acutum, Corydalis* spp., *Gacium* spp., *Nandina* spp., *Croton salutaris, Stephania yunnanensis*[234]	
	*Corydalis tuberosa, Corydalis cava*	
(+)-scoulerine		
(−)-scoulerine	Many *Corydalis* spp., *Erythrina orientalis, Bocconia frutescens* (Tree Poppy), *Glaucium* spp., *Eschscholzia lobbii* (Frying Pans), *Fumaria officinalis* (Common Fumitory)	Antiemetic and Antitussive activity
	*Corydalis tuberosa*	Analgesic, Hypotensive
(+)-canadine		
(−)-canadine	*Hydrastis canadensis* (Goldenseal), several *Corydalis* spp.	Analgesic, Hypotensive

[a]For species and biological activity that do not have a reference, please refer to the *Dictionary of Alkaloids* (reference 193)