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Natural Enantiomers

Enantiomeric Natural Products: Occurrence and Biogenesis

*Jennifer M. Finefield, David H. Sherman, Martin Kreitman, and Robert M. Williams**

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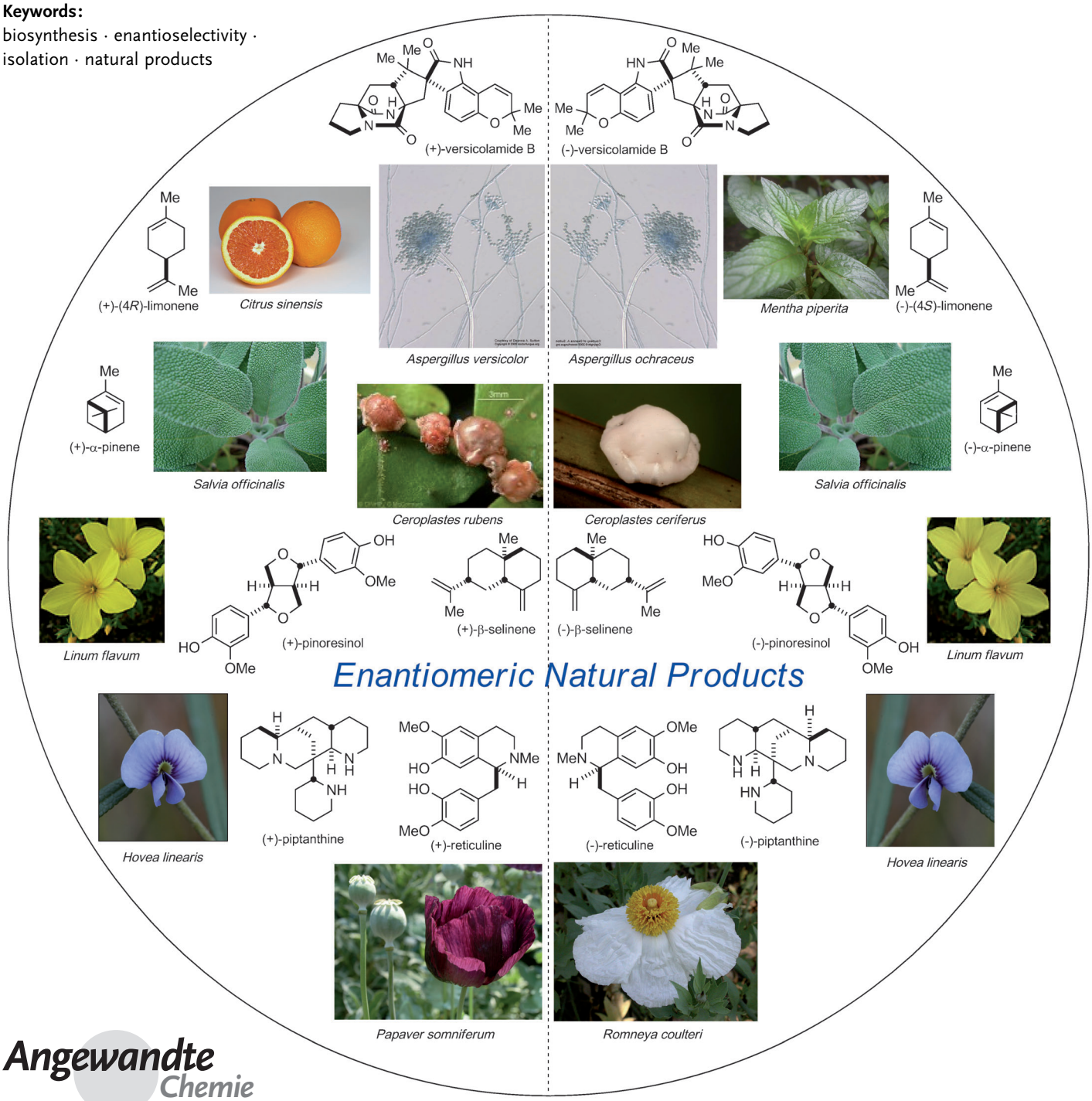
biosynthesis · enantioselectivity · isolation · natural products



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In nature, chiral natural products are usually produced in optically pure form—however, occasionally both enantiomers are formed. These enantiomeric natural products can arise 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.

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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] In contrast to the required production of primary metabolites 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 antitumor, antibacterial, anti-insecticidal, anthelmintic, antinematodal, immunosuppressives, as well as other clinically relevant activities, which have been widely exploited for both synthetic and semisynthetic drug discovery and development efforts.[4,5]

In the vast majority of cases, chiral natural products are produced in nature in optically pure form, with only one enantiomer 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 remains a rare occurrence relative to the overall abundance of secondary metabolites. These enantiomerically opposite metabolites can be produced by different genera or species, with one enantiomer being isolated from one species and the other enantiomer from a different species or genera. Sometimes both enantiomers may also be produced and isolated as either a racemic or scalemic mixture (where one enantiomer predominates) from a single species.[6a]

Efforts to elucidate the biosynthetic pathway of bioactive natural products have been an area of intense research for over 75 years for 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 often 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. As a consequence of the overwhelming number of known secondary metabolites, and the often overlooked reporting of the optical rotation or CD spectra of similar substances obtained from different sources, not all the 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. This Review is organized into classes of secondary metabolites on the basis of their main biosynthetic derivations: terpenes (isoprene), phenylpropanoids (shikimic acid), polyketides (acetate), and alkaloids (amino acids). In many cases, these partitions are superficial since many natural products are often 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 of 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 anticancer drugs for human clinical use.[10]

[*] J. M. Finefield, Prof. Dr. R. M. Williams
Department of Chemistry, Colorado State University
Fort Collins, CO 80523 (USA)
Prof. Dr. D. H. Sherman
Life Sciences Institute and Departments of Medicinal Chemistry
Microbiology & Immunology, and Chemistry
University of Michigan
Ann Arbor, MI 48109 (USA)
Prof. Dr. M. Kreitman
Department of Ecology and Evolution, University of Chicago
1101 East 57th Street, Chicago, IL 60637 (USA)
Prof. Dr. R. M. Williams
The University of Colorado Cancer Center
Aurora, CO 80045 (USA)
E-mail: rmw@lamar.colostate.edu
Homepage: http://rwindigo1.chm.colostate.edu/

All terpenoids are constructed from the head-to-tail condensation of repeating C_5 isoprene units and are further subdivided into families on the basis of 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 rare occasions, 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.

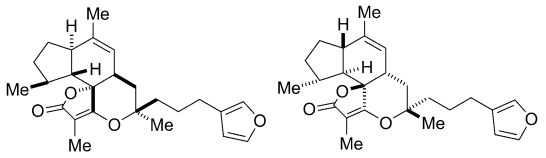


Figure 1. (+)- and (−)-wistarin, the only known enantiomeric sesterterpenes.

2.1. Monoterpenes

Compounds from 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 by 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.[10,13a,14,15] 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 by stereochemically distinct routes. However, not all monoterpene synthases are completely stereospecific, as observed in the (−)-limonene synthase isolated from caraway seeds (see Section 2.1.1).[10,13a]

The sizeable amount of research that has been carried out on the monoterpenes has led to the formation of a widely

Robert M. Williams received a BA (Chemistry, 1975) from Syracuse University (E.-i. Negishi) and a PhD (1979) at MIT (W. H. Rastetter), and carried out postdoctoral research at Harvard (1979–80; R. B. Woodward/Y. Kishi). He joined Colorado State University in 1980 and became University Distinguished Professor in 2002. His awards include the ACS Cope Scholars Award (2002) and the ACS Ernest Guenther Award in the Chemistry of Natural Products (2011). His research program concerns the synthesis, biosynthesis, and chemical biology of biomedically significant natural products.

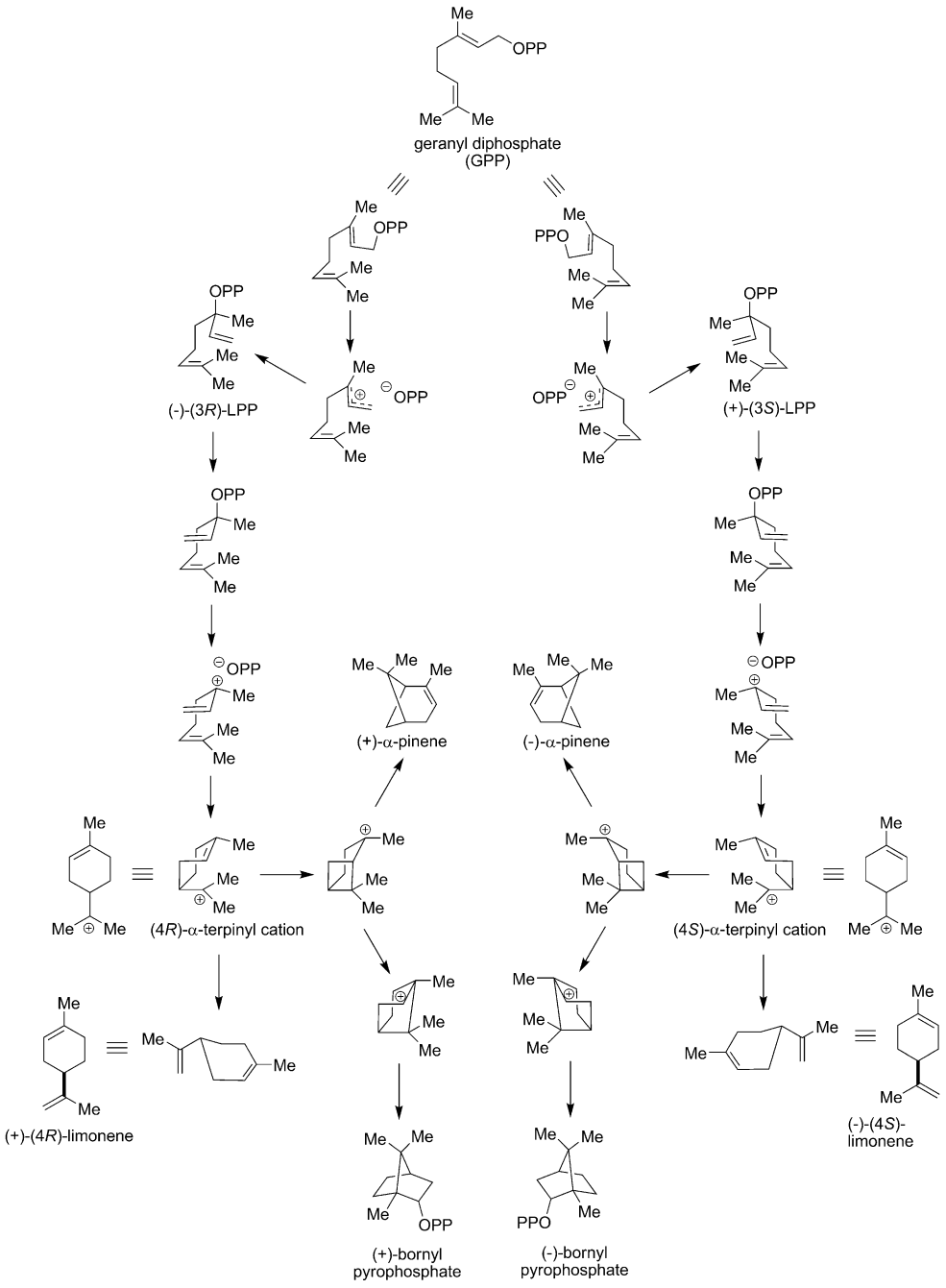
Jennifer M. Finefield graduated from Illinois State University in 2004 with a BS in Chemistry. She received her PhD in 2011 from Colorado State University under the guidance of R. M. Williams for work focusing on elucidating the biosynthesis of reverse prenylated indole secondary metabolites from Aspergillus versicolor. She is currently working on the synthesis of a novel HDAC inhibitor in the same research group.

David H. Sherman obtained a BA from UC Santa Cruz (1978), a PhD from Columbia (1981) with G. Stork, and carried out postdoctoral research at Yale (1981–82) and MIT (1982–84) with H. Eisen. He is currently the Hans W. Vahlteich Professor of Medicinal Chemistry, Professor of Chemistry, and Professor of Microbiology and Immunology at the University of Michigan. His awards include the ACS Cope Scholar Award (2009) and the SIM Charles Thom Award. His research concerns molecular genetic, biochemical, and bioorganic chemical studies of microbial natural product biosynthesis.

Martin Kreitman received a BS in Biology (Stony Brook University, 1975), an MS in Zoology (University of Florida, 1977), and a PhD in Population Genetics (Harvard, 1983) with R. Lewontin. He is currently a Professor at the University of Chicago. His awards include the 1991 MacArthur Fellows Program and became a Fellow of the American Academy of Arts and Sciences (2010). His research centers on understanding evolutionary forces governing molecular variation and evolution.

accepted mechanism for the monoterpene cyclization reaction (Scheme 1).[10,13a] To start, geranyl diphosphate (GPP) binds stereoselectively 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). 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. 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, with a final deprotonation or nucleophilic capture terminating the sequence.

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 activities, 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.



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

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 distinct scent. Perhaps the most well-known example of this is that (+)-carvone smells of caraway, while its 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, treatment of tritium-labeled GPP with limonene synthase isolated from *Mentha piperita* (peppermint) and *Mentha spicata* (spearmint) generated (−)-

Table 1: Occurrence and biological activity of enantiomeric monoterpenes.

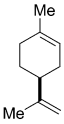
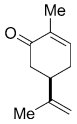
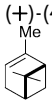
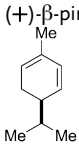
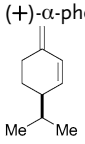
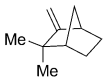
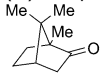
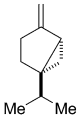
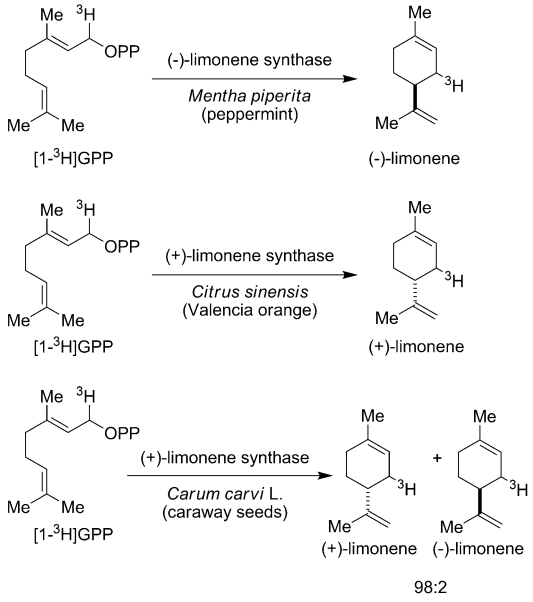
Monoterpene	Species	Biological activity
 (−)-(4*S*)-limonene	*Mentha piperita* (peppermint),[17] *Mentha spicata* (spearmint),[17] *Mentha pulegium* (European pennyroyal),[17] *Perilla frutescens* (Chinese basil),[18,19] *Perilla citriodora*,[26] *Abies grandis* (grand fir),[20] *Anethum graveolens* 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]	
 (−)-β-phellandrene	*Pinus contorta*,[36] *Pinus sylvestris*,[29] *Angelica archangelica* L.,[31] *Juniperus* spp. (Juniper evergreen),[9] *Pinus* spp. (pine)[9]	
(+)-β-phellandrene	*Anethum graveolens* L.,[27] *Angelica archangelica* L.,[31] *Bupleurum fruticosum* (Shrubby Hare's Ear),[9] *Juniperus* spp.[9]	
 (−)-camphene	*Salvia officinalis*,[37] *Picea abies*,[29] *Pinus sylvestris*,[29] *Angelica archangelica* L.[31]	
(+)-camphene	*Salvia officinalis*,[37] *Picea abies*,[29] *Pinus sylvestris*,[29] *Angelica archangelica* L.[31]	
 (−)-camphor	*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	*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]

Table 1: (Continued)

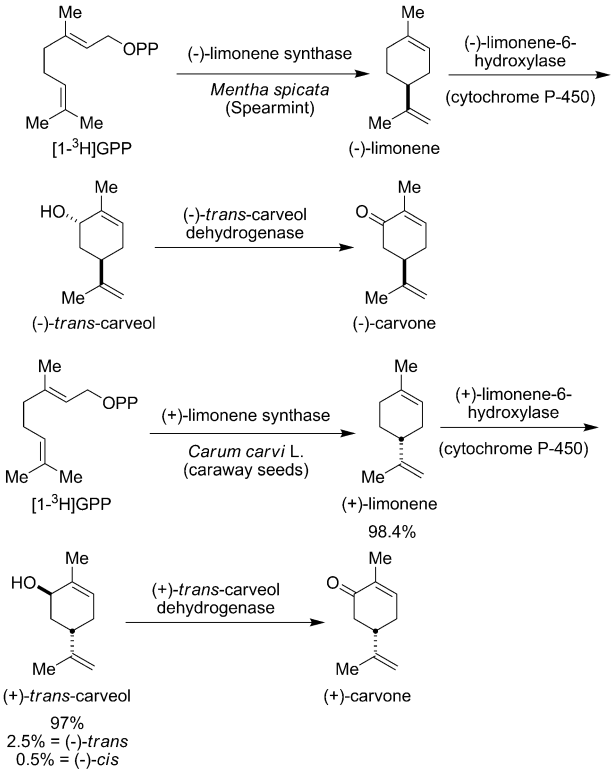
Monoterpene	Species	Biological activity
 (−)-borneol	*Thuja orientalis* (Chinese Arborvitae),[38] *Thuja standishii* (Japanese Thuja),[38] *Pinus sylvestris*[29]	camphoraceous odor with woody undertones[16b]
(+)-borneol	*Picea sitchensis*,[38] *Chamaecyparis lawsoniana*,[38] *Pinus sylvestris*,[29] *Salvia officinalis*[38]	camphoraceous odor with earthy-peppery undertones[16b]
 (−)-sabinene	*Pinus sylvestris*,[29] *Angelica archangelica* L.[31]	
(+)-sabinene	*Pinus sylvestris*,[29] *Salvia officinalis*,[41] *Angelica archangelica* L.[31]	



Scheme 2. Enantioselective biogenesis of limonene.

[^{3}H]limonene.[17] On the other hand, a soluble limonene cyclase preparation was obtained from *Citrus sinensis* (Valencia oranges), which when treated with tritium-labeled GPP afforded enantiomerically pure (+)-limonene.[18] Likewise, when tritium-labeled GPP was treated 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]

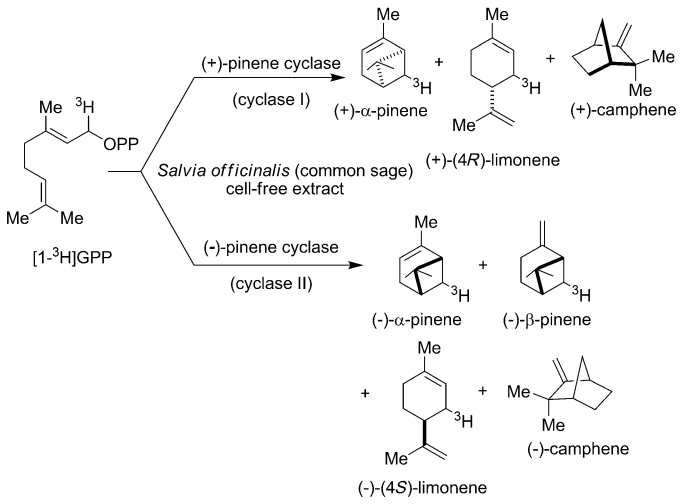
Carvone is also a cyclic monoterpene, of which both enantiomers have been isolated. Through precursor incorporation studies and enzyme preparations, limonene has been established as a biosynthetic precursor to carvone.[17a,23,25] Two sets of enantioselective enzymes responsible for the conversion of (+)- or (−)-limonene into (+)- 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 into (−)-*trans*-carveol and finally into (−)-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 treated with the enzyme, only 97% of the expected (+)-*trans*-carveol was isolated. The other 3% was made up of a mixture of (−)-*trans*-carveol and (−)-*cis*-carveol. Finally, carveol dehydrogenase displays moderate substrate specificity, as evident by the conversion of not only (+)-*trans*-carveol into (+)-carvone, but also (−)-*cis*-carveol into (−)-carvone.[23]



Scheme 3. Enantiomeric biosynthesis of carvone.

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 predominating. In contrast, β-pinene is almost always isolated as the optically pure (−) isoform. The (+)-β-pinene isomer is also known, although the production of this metabolite is rare.[30,31,33] Biosynthetic studies carried out by Gambliel and Croteau in the 1980s revealed that the two enantiomeric pinene cyclases (+)-pinene cyclase (cyclase I) and (−)-pinene cyclase (cyclase II) exist within *Salvia officinalis*.[42] Croteau and co-workers demonstrated that when [^{3}H]GPP was treated 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. Minor amounts of (+)- and (−)-camphene and limonene were also formed as scalemic mixtures from these reactions (80% (+)-camphene isomer and 55% (−)-limonene isomer).[35,42,43]



Scheme 4. Enantioselective pinene cyclases.

2.2. Sesquiterpenes

The sesquiterpenes make up a diverse group of acyclic and cyclic C_{15} terpenes that are isolated from a wide variety of plant, fungal, bacterial, marine, and insect species. Similar to 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 activities.[44,45] Unfortunately, in most cases, the optical rotation of the sesquiterpenes is not reported, and thus critical information regarding their 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 and co-workers isolated and characterized two enantioselective germacrene D synthases from *Solidago 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 arises 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] In general, enantiomeric sesquiterpenes are produced by different species within the same genera (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 is 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 isopentenyl pyrophosphate (IPP) with dimethylallyl pyrophosphate (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 occurrence and biological activity of enantiomeric diterpenes is lacking.

Table 2: Enantiomeric sesquiterpenes.

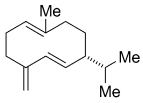
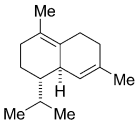
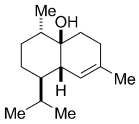
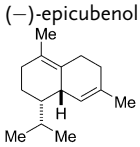
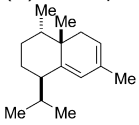
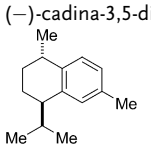
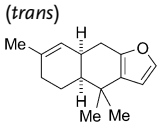
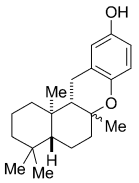
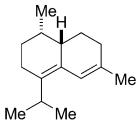
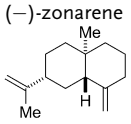
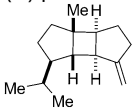
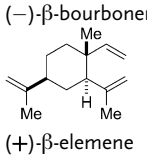
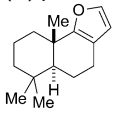
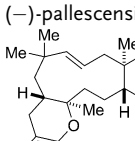
Sesquiterpene	Species	Biological activity
 (+)-germacrene D	*Ceroplastes rubens* (scale insect),[57] *Dendropanax trifidus* M. (ivy tree),[58] *Sinularia mayi* (soft coral),[55] *Preissia quadrata* (liverwort),[59] *Solidago altissima* (late goldenrod),[52] *Solidago canadensis* (Canada goldenrod),[60] *Podocarpus spicatus* (black pine),[61] *Zingiber officinale* (ginger)[60]	
(−)-germacrene D	*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]	
 (+)-δ-cadinene	*Araucaria bidwillii*,[63] *Carum carvi* L.,[64] *Gossypium arboreum* (tree cotton),[60] *Gossypium hirsutum* (upland cotton),[60] *Mentha piperata*[9]	
(−)-δ-cadinene	*Ceroplastes ceriferus*,[57] *Sinularia mayi*,[55] *Araucaria araucana* (monkey-puzzle tree),[63] *Araucaria bidwillii*,[63] *Carum carvi L.*,[64] *Heteroscyphus planus*[65]	
 (+)-epicubenol	*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	Cubeb oil,[69] *Juniperus rigida*,[67] *Cedrus atlantica* (Atlas cedar)[9]	
 (+)-δ-amorphene	*Leptospermum scoparium* (tea tree)[70]	
(−)-δ-amorphene	*Vetiveria zizanioides* (L. Nash ex Small) (vetiver oil)[71]	
 (+)-cadina-3,5-diene	*Conocephalum conicum* (scented liverwort)[70]	
(−)-cadina-3,5-diene	*Leptospermum scoparium*,[70] *Piper cubeba* oil[70]	
 (+)-calamenene (*trans*)	*Ceroplastes ceriferus*,[57] *Conocephalum conicum*[70]	
(−)-calamenene (*trans*)	*Leptospermum scoparium*,[70] *Piper cubeba* (tailed pepper)[70]	
 (+)-furodysinin	*Dysidea* sp. (marine sponge),[72] *Dysidea herbaceae* (marine sponge, Australia)[53]	
(−)-furodysinin	*Dysidea herbaceae* (marine sponge, Fiji),[54] *Dysidea tupha*,[73] *Ceratosoma trilobatum* (sea slug)[74]	feeding deterrent,[74] ichthyotoxic[74]
 (+)-chromazonarol	*Disidea pallescens* (Black Sea sponge)[75]	
(−)-chromazonarol	*Dictyopteris undulata* (brown algae)[76]	antimicrobial[77]

Table 2: (Continued)

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

3. Phenylpropanoids

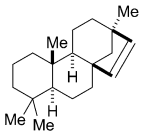
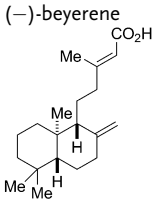
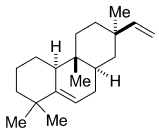
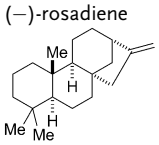
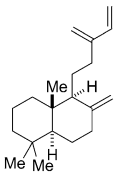
Phenylpropanoids are found in numerous plant species and contribute greatly to plant defenses, structure, pigments, and reproduction.[85] Derived from the shikimate pathway, the phenylpropanoids are a class of natural products comprised of a vast array of diverse secondary metabolites formed from L-phenylalanine 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 into 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 carbon atoms 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 activities, 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 use in cancer therapies, such as the well-known podophyllotoxin-derived semisynthetic drug etoposide.[89,90]

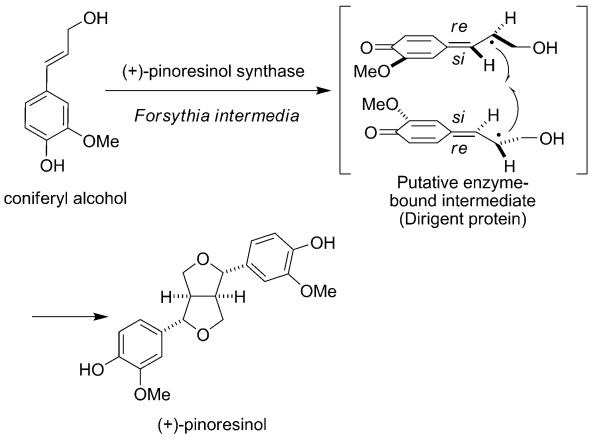
Lignans can occur as mixtures of enantiomers with various enantiomeric compositions, depending on the specific plant species. One extensively examined type of lignan is the early 9(9′)-oxygenated lignans (pinoresinol, lariciresinol, secoisolariciresinol, and matairesinol). These lignans exists as either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

Table 3: Diterpenes.

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

optical rotation of the enantiomerically pure dibenzylbutyrolactone lignans were also found to vary between plant species.[92]

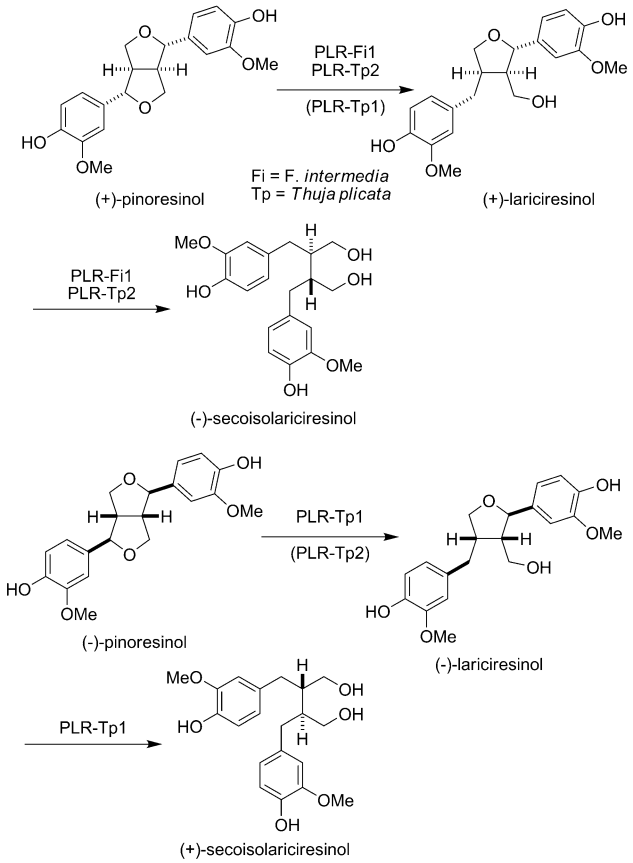
Like all phenylpropanoids, the lignans are derived through the cinnamate pathway. The biosynthetic pathway of 9(9′)-oxygenated lignans is one of the most well-studied lignan pathways. The first five steps of this pathway have been investigated extensively and most of the enzymes responsible for the transformations 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 the enantioselective dimerization of two coniferyl alcohol residues by an oxidase in the presence of a dirigent protein to afford pinoresinol in an enantiomeric excess. The dirigent protein aids in controlling the stereospecificity of the bimolecular phenoxy radical coupling reactions of the two coniferyl



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

alcohol units.[93] Next, pinoresinol is stereoselectively reduced to lariciresinol, which is subsequently reduced stereospecifically to secoisolariciresinol by 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] It was determined through incorporation studies that (+)-pinoresinol/lariciresinol reductases



Scheme 6. Enantioselective conversion of pinoresinol into secoisolariciresinol by pinoresinol/lariciresinol reductase (PLR).

Table 4: Enantiomeric lignans.

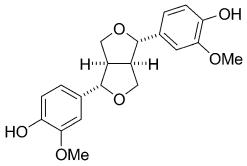
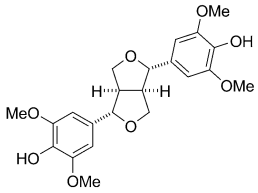
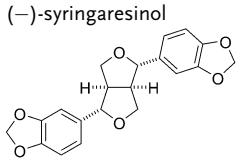
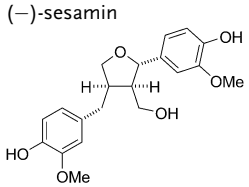
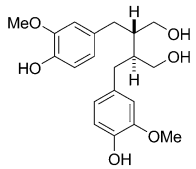
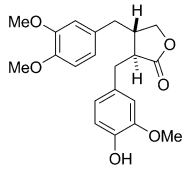
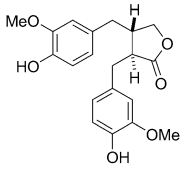
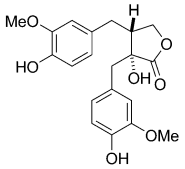
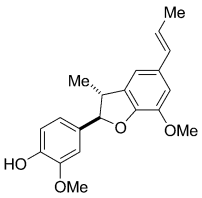
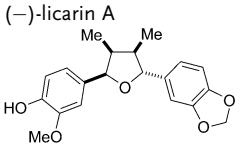
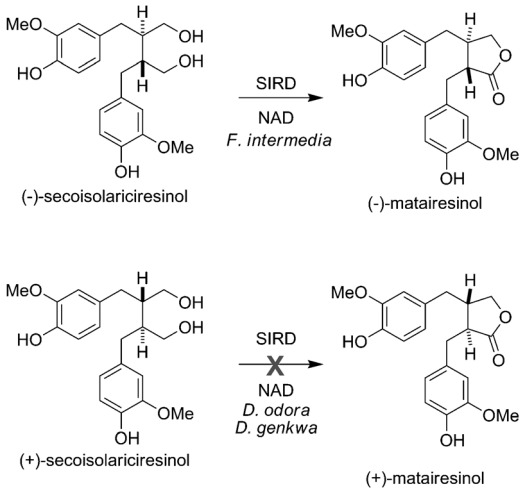
Lignans	Species	Biological activity
 (+)-pinoresinol (−)-pinoresinol	*Forsythia koreana* (Korean flowering plant, 82% *ee*),[91] *Linum flavum* var. *compactum* (dwarf golden flax, 65% *ee*),[91] *Larix leptolepis* (Japanese larch, 92% *ee*),[91,92] *Wikstroemia viridiflora*,[92] *Stellera chamaejasme* (Tibetan flowers),[92] *Forsythia suspensa* (Asian flowering plant),[92] *Forsythia* spp.,[92] *Fraxinus* spp.,[92] *Helianthus annuus* (common sunflower)[98] *Wikstroemia sikokiana* (deciduous shrub, 74% *ee*),[91] *Daphne odora* (winter Daphne, 95% *ee*),[91] *Daphne genkwa* (92% *ee*),[91] *Daphne tangutica*,[92] *Zanthoxylum ailanthoides* (Japanese prickly ash),[92] *Zanthoxylum kellermanii*,[92] *Senecio scandens* (wild daisy)[99]	phytotoxic[98] antioxidant[99]
 (+)-syringaresinol (−)-syringaresinol	*Wikstroemia elliptica*,[92] *Daphne tangutica*,[92] *Passerina vulgaris*,[92] *Dirca occidentalis* (western leatherwood)[93] *Daphne tangutica*,[92] *Zanthoxylum acanthopodium*,[92] *Daphne genkwa*[100]	anticancer[100]
 (+)-sesamin (−)-sesamin	*Zanthoxylum acanthapodium*,[92] *Zanthoxylum valens*,[92] *Zanthoxylum setulosum*[92] *Zanthoxylum piperitum* (Japanese pepper tree)[92]	antihypertensive[101]
 (+)-lariciresinol (−)-lariciresinol	*Forsythia koreana* (35% *ee*),[91] *Linum flavum* var. *compactum* (70% *ee*),[91] *Wikstroemia elliptica*,[92] *Larix leptolepis*,[92] *Abies sachalinensis* (Sakhalin fir),[92] *Araucaria angustifolia*[92] *Wikstroemia sikokiana* (39% *ee*),[92] *Daphne odora* (89% *ee*),[92] *Daphne genkwa* (88% *ee*),[92] *Wikstroemia elliptica*,[93] *Daphne tangutica*,[93] *Dirca occidentalis*[93]	phytotoxic (inhibits lettuce germination)[102] phytotoxic (inhibits root growth of Italian ryegrass)[102]
 (+)-secoisolariciresinol (−)-secoisolariciresinol	*Arctium lappa* (burdock, petiole) (81% *ee*),[91] *Phyllanthus* sp. (98% *ee*),[91] *Daphne odora* (>99% *ee*),[91] *Daphne genkwa* (97% *ee*)[91] *Arctium lappa* (seeds) (65% *ee*),[91] *Forsythia koreana* (>99% *ee*),[91] *Forsythia intermedia* (>99% *ee*),[91] *Wikstroemia sikokiana* (45% *ee*),[91] *Zanthoxylum ailanthoides*,[92] *Larix leptolepis*,[92] *Larix decidua* (European larch),[92] *Araucaria angustifolia*,[92] *Podocarpus spicatus*[92]	antioxidant[103] antioxidant[103]
 (+)-arctigenin (−)-arctigenin	*Wikstroemia indica*,[92] *Daphne genkwa*[100] *Arctium lappa* (seeds) (>99% *ee*),[91] *Forsythia koreana* (>99% *ee*),[91] *Forsythia intermedia* (>99% *ee*),[91] *Trachelospermum asiaticum* var. *intermedium* (yellow star jasmine),[92] *Centaurea pamphylica*[104]	anticancer[100] antitumoral,[105] anticancer,[105] antioxidant[104]

Table 4: (Continued)

Lignans	Species	Biological activity
	*Wikstroemia sikokiana* (>99% *ee*),[91] *Daphne odora* (>99% *ee*),[91] *Daphne genkwa* (>99% *ee*),[91] *Centaurea pamphylica*[104]	
(+)-matairesinol		
(−)-matairesinol	*Arctium lappa* (seeds) (>99% *ee*),[91] *Forsythia koreana* (>99% *ee*),[91] *Forsythia intermedia* (>99% *ee*),[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% *ee*)[91]	antioxidant[104]
	*Wikstroemia viridiflora*,[92] *Wikstroemia foetida*,[92] *Wikstroemia sikokiana* (>99% *ee*),[91] *Wikstroemia indica*,[92] *Daphne odora*,[92] *Passerina vulgaris*[92]	anticancer[106]
(+)-wikstromol		
(−)-wikstromol	*Thuja occidentalis* (>99% *ee*),[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]	
	*Schisandra* sp.[110]	
(+)-chicanine		
(−)-chicanine	*Leucas aspera*[108]	antioxidant[108b]

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 formed biosynthetically in various plant species (i.e. *Forsythia intermedia*, *Arctium lappa*, *Thuja occidentalis*); however, the optically pure dextrorotatory enantiomer of matairesinol is produced in Thymelaeaceae plants (*Wikstroemia sikokiana* and *Daphne odora*). Secoisolariciresinol dehydrogenase was isolated from *Forsythia intermedia* 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.



Scheme 7. (−)-Matairesinol biosynthesis by secoisolariciresinol dehydrogenase (SIRD). NAD = nicotinamide adenine dinucleotide.

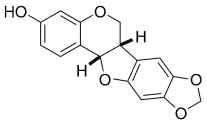
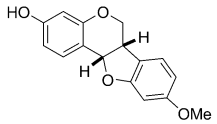
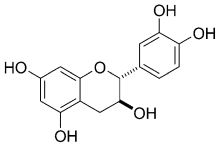
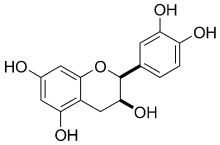
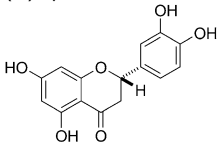
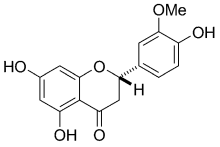
3.2. Flavonoids

Flavonoids make up a large, diverse family of aromatic secondary metabolites that are largely characterized by the red, blue, and purple pigments found in plants.[111] As a consequence of 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 because of their association with the health benefits of wine, chocolate, fruits, and vegetables.

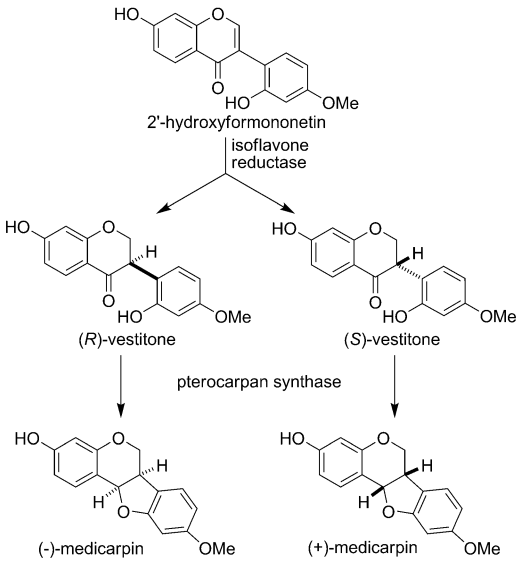
As shown in Table 5, the enantiomeric flavonoids occur mostly within three structural groups of flavonoids: the flavanones, flavonols, and isoflavonoids. Elucidation of the flavonoid biosynthetic pathway has been an area of growing research, with much of the attention recently being directed at the molecular 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 bio-

Table 5: Enantiomeric flavonoids.

Flavonoid	Species	Biological activity
	*Dalbergia spruceana* (Amazon rosewood),[114] *Dalbergia stevensonii* (Honduras rosewood),[114] *Sophora 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]	
	*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]	

chemical techniques and confirmed by gene cloning and expression experiments.[112,113] As shown in Scheme 8, the advanced achiral precursor 2′-hydroxyformononetin is converted into (*R*)-vestitone by isoflavone reductase, which subsequently reacts with pterocarpan synthase to yield (−)-medicarpin in alfalfa.[112] In contrast to what is known regarding the biosynthesis of (−)-medicarpin, there are several unanswered questions concerning the biosynthesis of (+)-medicarpin in peanuts. Surprisingly, the isoflavone reductase in peanuts produces the same (*R*)-vestitone intermediate generated in alfalfa. This compound has the opposite substrate and product stereospecificity necessary for the pterocarpan synthase, thus indicating the possibility of an epimerase in peanuts.



Scheme 8. Biosynthesis of the medicarpin enantiomers.[112]

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

Table 6: Enantiomeric coumarins.

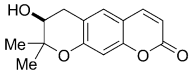
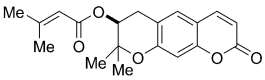
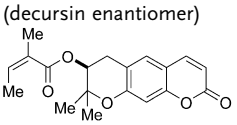
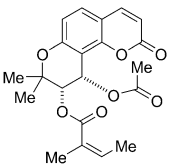
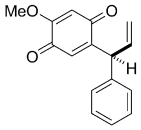
Coumarins	Species	Biological activity
 (+)-decursinol	*Angelica gigas* (aerial),[128] *Angelica gigas* Nakai (roots)[129]	anticancer,[130] antihelicobacterpyloric,[131] antinociceptive,[132] inhibitor of acetyl cholinesterase[133]
(−)-aegelinol (decursinol enantiomer)	*Angelica gigas* (aerial),[128] *Aegle marmelos*,[134] *Ferulago campestris* (aegelinol benzolate),[135] *Eryngium campestre* (benzoyl aegelinol)[136]	antibacterial[135]
 (*S*)-decursin	*Angelica gigas* (roots),[137] *Angelica gigas* (aerial),[128] *Angelica sinensis* (female ginseng),[138] *Angelica acutiloba*[136]	antibacterial,[137] sedative[137]
(*R*)-grandivittin (decursin enantiomer)	*Ferulago campestris*,[135] *Eryngium campestre*[136]	
 (*S*)-agasyllin	*Angelica gigas* (aerial),[128] *Angelica gigas* (roots),[137] *Angelica sinensis*,[138] *Angelica acutiloba*[138]	antibacterial[137]
(*R*)-agasyllin	*Angelica gigas* (aerial),[128] *Ferulago campestris*,[135] *Eryngium campestre*[136]	antibacterial,[135] antihelicobacterpyloric[135]
 (+)-praeruptorin A	*Peucedanum praeruptorum* Dunn.[139]	reduces blood pressure[139]
(−)-praeruptorin A	*Peucedanum praeruptorum* Dunn.[139]	reduces blood pressure[139]

Table 7: Neoflavonoid enantiomers.

Neoflavonoid	Species	Biological activity
 (*S*)-methoxydalbergione	*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]	
(*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]

Guttiferae, the Leguminosae, the Rubiaceae, the Passifloraceae, the Polypodiaceae, and the Compositae families.

4-Methoxydalbergione is an open-chained neoflavonoid that contains a stereogenic center at the C7-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, and the biogenesis of enantiomeric neoflavonoids is thus unknown.

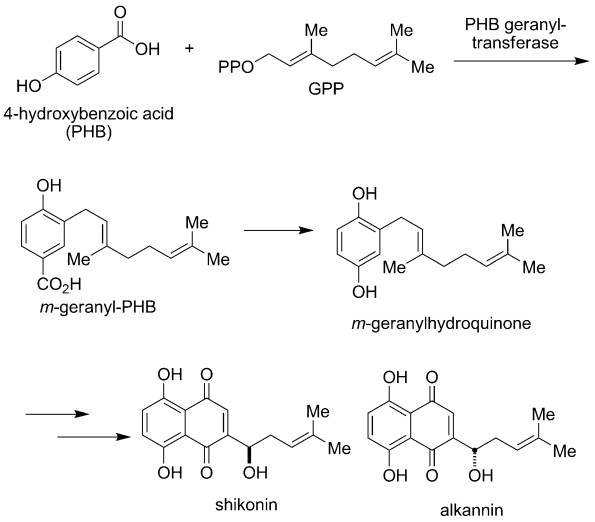
3.5. Quinones

Through numerous feeding experiments, it has been determined that quinones are also derived from phenylalanine, which is converted into the known intermediate *p*-hydroxybenzoic acid (PHB).[151] Subsequent prenylation at the C3-position affords *m*-geranyl-*p*-hydroxybenzoic acid, which is further converted into 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 activities, including anti-inflammatory, antitumor, and antimicrobial activity. A more in depth review of the chemistry and biology of alkannin, shikonin, and their quinone derivatives can be found in the review by Nicolaou and co-workers.[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 of plants. Polyketides also display important medicinal activity, such as antibiotic, anticancer, and immunosuppressant properties.

There are several examples of enantiomeric polyketides biosynthesized in the plant kingdom (Table 9); however, little 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.



Scheme 9. Proposed biosynthesis of shikonin and alkannin.

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 homologues, homononactic acid and/or bishomonanactic acid (Figure 2).[155,156] Of the five known homologues (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 highly 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 dimer.[156] Recently, the biosynthetic research on 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

Table 8: Natural quinone enantiomers.[a]

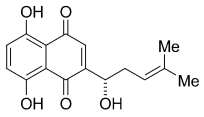
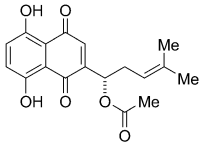
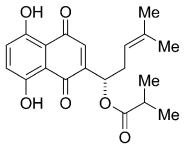
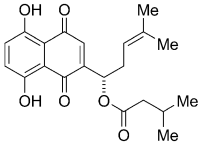
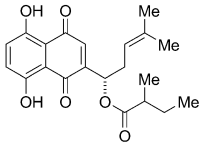
Quinone	Species	Biological activity
 alkannin shikonin (alkannin enantiomer)	*Alkanna tinctoria* (Alkanet), *Arnebia hispidissima*, *Arnebia nobilis*, *Arnebia tinctoria*, *Macrotomia cephalotes*, *Macrotomia euchroma* (Syrian Alkanet), *Onosma echioides*, *Onosma paniculata*, *Plagiobotrys arizonicus* *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* (bluebur), *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*	wound healing, anti-inflammatory, antibacterial, inhibition of topoisomerase-I, antithrombotic antitumor, antiamebic, antipyretic and analgesic, antifungal, antibacterial, wound healing, chemopreventive, anti-inflammatory, 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 acetylshikonin	*Alkanna tinctoria*, *Arnebia euchroma*, *Arnebia hispidissima*, *Arnebia nobilis*, *Macrotomia cephalotes* *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*	antimicrobial, inhibition of topoisomerase-I, antithrombotic, antitumor
 isobutyrlalkannin isobutyrylshikonin	*Alkanna tinctoria* *Cynoglossum officinale*, *Echium vulgare*, *Eritrichium sichotenze*, *Lappula consanguinea*, *Lappula echinata*, *Lithospermum arvense*, *Lithospermum erythrorhizon*, *Macrotomia euchroma*, *Mertensia maritima*	
 isovalerylalkannin isovalerylshikonin	*Alkanna tinctoria*, *Arnebia hispidissima*, *Arnebia tinctoria*, *Macrotomia cephalotes*, *Onosma heterophylla* *Arnebia decumbens*, *Cynoglossum officinale*, *Echium vulgare*, *Lappula consanguinea*, *Lappula echinata*, *Lithospermum arvense*, *Lithospermum erythrorhizon*, *Macrotomia euchroma*	inhibition of topoisomerase-I
 α-methylbutyrylalkannin α-methylbutyrylshikonin	*Alkanna tinctoria*, *Macrotomia cephalotes* *Cynoglossum officinale*, *Echium vulgare*, *Eritrichium incanum*, *Eritrichium sichotenze*, *Lappula consanguinea*, *Lappula echinata*, *Lappula erythrorhizon*, *Mertensia maritima*	antimicrobial antimicrobial

Table 8: (Continued)

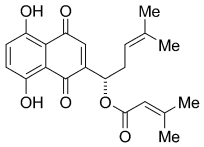
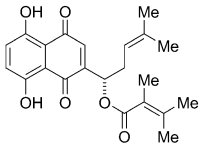
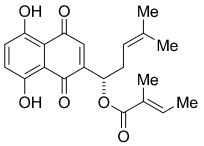
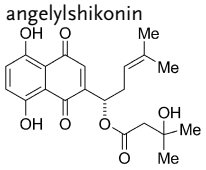
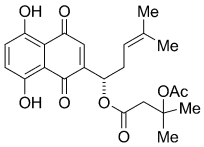
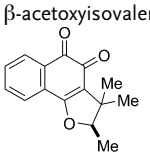
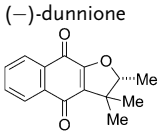
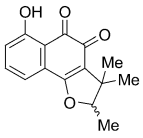
Quinone	Species	Biological activity
	*Alkanna tinctoria*, *Arnebia euchroma*, *Arnebia gutatta*, *Arnebia nobilis*, *Lithospermum erythrorhizon*, *Macrotomia cephalotes*, *Onosma heterophylla*, *Onosma hookeri*, *Onosma paniculata*	inhibition of topoisomerase-I and anticancer, antimicrobial, antithrombotic, anti-inflammatory
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 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]	
	*Streptocarpus dunni*[152]	
(+)-α-dunnione (−)-α-dunnione	*Streptocarpus dunni*[152]	

Table 8: (Continued)

Quinone	Species	Biological activity
 (±)-8-hydroxydunnione	*Streptocarpus dunni*[152]	

[a] For species and biological activity that do not have a reference, please see the Review by Nicolau and co-workers (Ref. [151]).

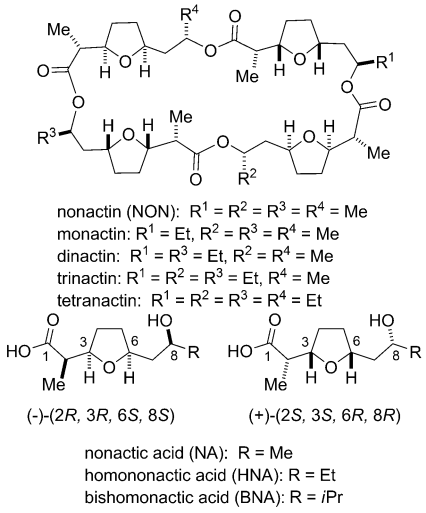


Figure 2. Nactins and the monomeric units that make up the macrotetrolide antibiotics.

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 the research groups of 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 enantiocomplementary pathways of nonactic acid.

Opposite stereospecific reductions of **2** would result in the generation of enantiomeric precursors **3** and **4**. Studies 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 incorporated enantioselectively into nonactin via the respective (+)- and (−)-nonactate precursors.[173b] 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 homologues 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 C3 and C15 stereogenic centers, thus these metabolites can be grouped into one of two categories: dihydrogranaticin (DHGRA), which display the 3*R*,15*S* configuration, or actinorhodin (ACT), which display the 3*S*,15*R* configuration (Figure 3).[177,178]

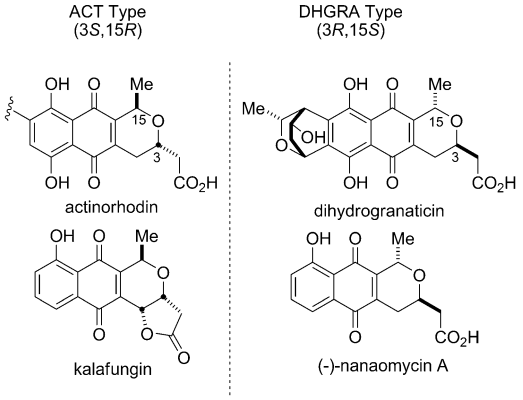
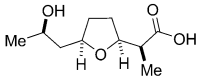
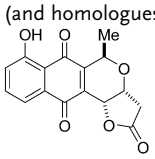
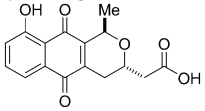
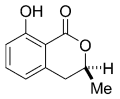
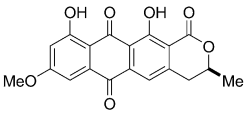
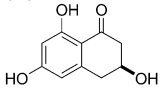
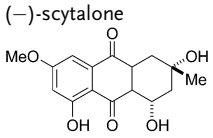
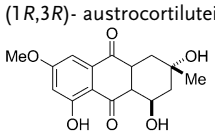
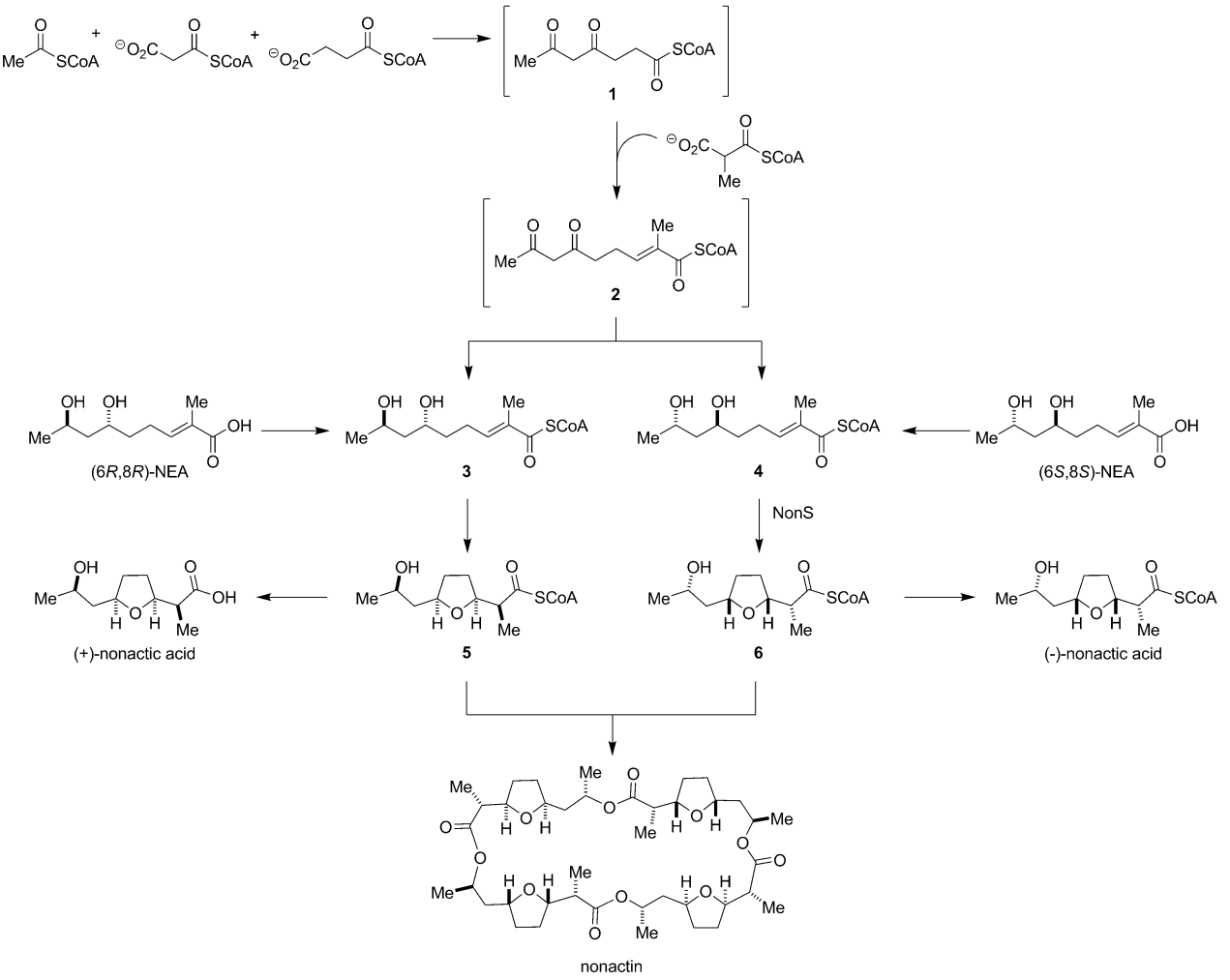


Figure 3. Structural diversity of the BIQ antibiotics.

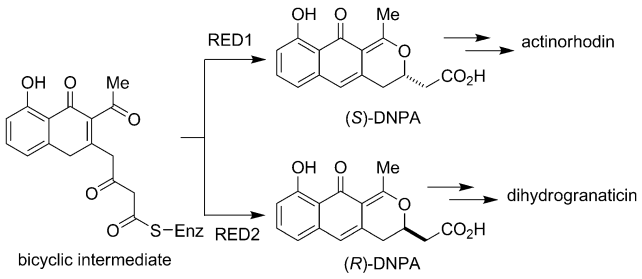
The formation of enantiomerically opposite stereocenters in the ACT and DHGRA families has led to the isolation of early stage enantiomeric intermediates from different sources. Analysis of the numerous gene clusters (*act*, *kal*, *nnm*, *gra*, etc.) that have been identified led to the identification of two enantioselective ketoreductases. As shown in Scheme 11, RED1/2 stereospecifically reduces the carbonyl functionality in the bicyclic intermediate, thereby setting the C3 configuration.[178] In ACT biosynthesis, the *S* configuration is established by *act*-VI-ORF1 (RED1),[179] whereas the *R* configuration is established in dihydrogranaticin (DHGRA) biosynthesis by the completely unrelated *gra*-ORF6 ketoreductase RED2.[177,180] These two enzymes show a remarkable difference in their substrate specificities as well as in their three-dimensional structures and catalytic mechanisms; however, both recognize the same substrate motif of the bicyclic intermediate.[178a] Subsequent cyclization and reduction of this intermediate results in the formation of the respective

Table 9: Enantiomeric polyketides.

Polyketide	Species	Biological activity
		
(+)-nonactic acid (and homologues)	*Streptomyces griseus* (bacteria),[155] *Streptomyces* spec. JA 5909-1[156]	
(−)-nonactic acid (and homologues)	*Streptomyces griseus*,[155] *Streptomyces* spec. JA 5909-1[156]	
		
kalafungin	*Streptomyces tanashiensis* strain Kala,[157] *Streptomyces coelicolor* A3(2)[158]	antibiotic[159]
nanaomycin D (kalafungin enantiomer)	*Streptomyces rosa* var. *notoensis* OS3966[160]	antibiotic[160]
		
(+)-nanaomycin A	*Nocardia* sp. (bacteria)[161]	antibiotic[161]
(−)-nanaomycin A	*Streptomyces rosa* var. *notoensis* OS3966[162]	antibiotic,[162] antifungal,[162] antimycoplasma activity[162]
		
(+)-mellein	*Cercospora taiwanensis*,[163] *Fusarium larvarum*,[163] *Grignardia laricina*,[163] *Gyrostroma missouriense* (fungus),[163] *Helicascus kanaloanus* (marine fungus),[164] unidentified fungus[163]	
(−)-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]
		
(+)-dermolactone	*Dermocybe kula* (fungus)[166]	major orange-red fungal pigment[166]
(−)-dermolactone	*Dermocybe kula*[166]	minor orange-red fungal pigment[166]
		
(+)-scytalone	*Verticillium dahliae* (fungus),[167] *Phialophora lagerbergii* (fungus),[168] *Scytalidium* sp.[169]	
(−)-scytalone	*Phialophora lagerbergii*,[168] *Scytalidium* sp.[169]	
		
(1*S*,3*S*)-austrocortilutein	*Dermocybe splendida* (splendid red skinhead, fungus)[170]	antibiotic,[171] fungal pigment (yellow)[172]
(1*R*,3*R*)- austrocortilutein	*Dermocybe* sp. WAT 20934[172]	
		
(1*S*,3*R*)- austrocortilutein	*Dermocybe splendida*,[170] *Dermocybe* sp. WAT 20934,[172] *Dermocybe* sp. WAT 21568[172]	antibiotic,[171] fungal pigment (yellow-*D. splendida*)[172]
(1*R*,3*S*)- austrocortilutein	*Dermocybe* sp. WAT 21567,[172] *Dermocybe* sp. WAT 20934[172]	



Scheme 10. Proposed stereocomplimentary pathways for the biogenesis of (+)- and (−)-nonactic acid.[155i] NEA = 2-methyl-6,8-dihydroxynon-(2*E*)-enoic acid.



Scheme 11. Proposed enantioselective biosynthetic pathways of actinorhodin and dihydrogranaticin. (RED1/2 = stereospecific C3 reductase).

enantiomeric intermediates (*S*)-DNPA and (*R*)-DNPA. The advanced BIQ natural products, such as actinorhodin and DHGRA, are derived from these chiral intermediates.

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 that the 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, or 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 with 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 activities, including, but not limited to, antitumor, anti-inflammatory, insecticidal, and antiparasitic activity. 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 and common or closely related microorganisms, 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.

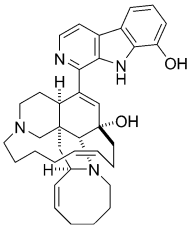
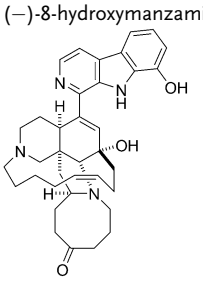
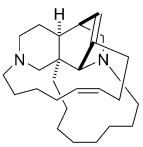
Within this class of alkaloids, the isolation of both enantiomers of 8-hydroxymanzamine A, manzamine F, and keramaphidin B have been reported, along with the enantiomeric congeners, ircinal A and B as well as ircinol A and B.[183] Interestingly, ircinols A and B are enantiomeric congeners of the alcoholic 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, and 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 groups of alkaloid secondary metabolites.[193] Biogenetically, this class of alka-

Table 10: Enantiomeric manzamine alkaloids.

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

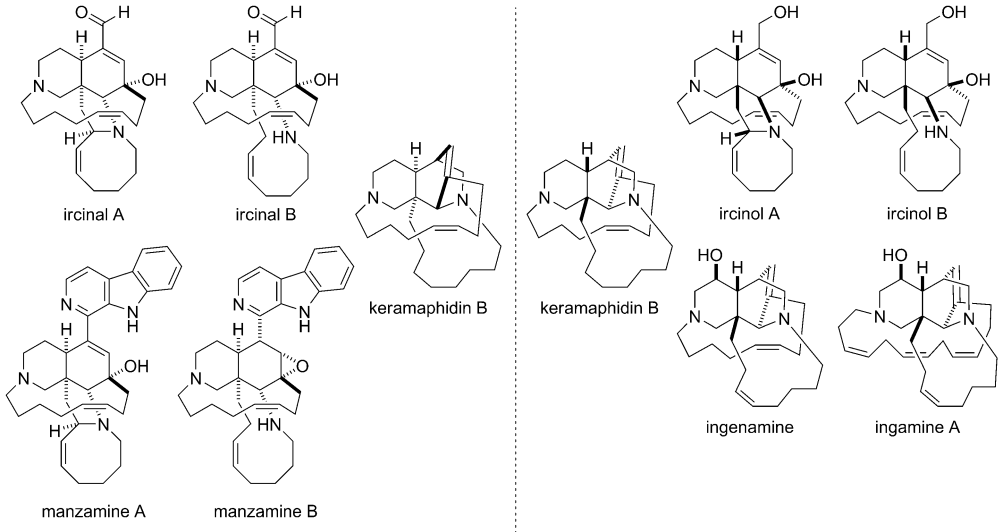
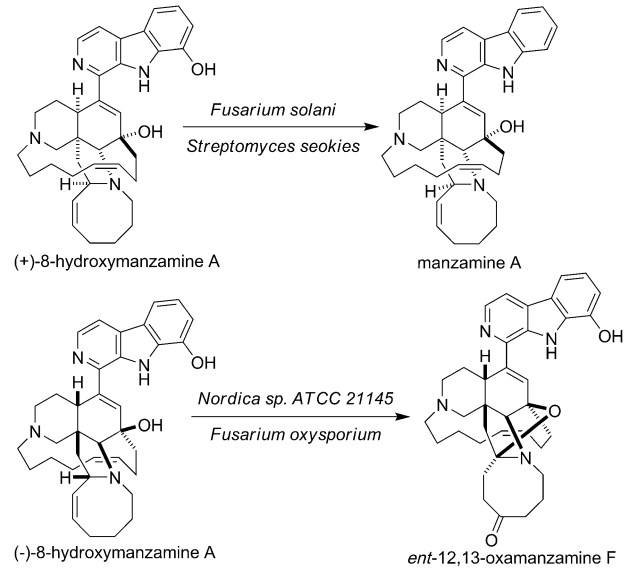


Figure 4. The two enantiomeric series of manzamine alkaloids.



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

loids 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 DMAPP and/or IPP.[195] The formation of enantiomeric indole alkaloids has been documented within the various subdivisions of the more complex isoprenoid alkaloids, as outlined in Section 5.2.1 and 5.2.2.

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 100 structurally diverse terpenoid indole alkaloids. Elucidation of the terpenoid indole alkaloid biosynthetic pathway in *Catharanthus roseus* has been extensively studied. More than 20 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 of 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 often 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 because of their complex molecular structures and wide array of biological activities.[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 by 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-

Table 11: Enantiomeric indole alkaloid metabolites.[a]

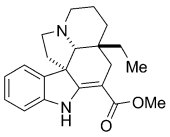
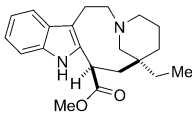
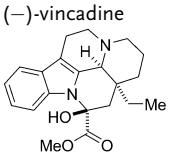
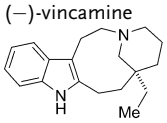
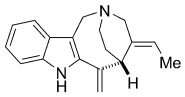
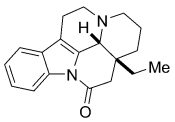
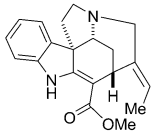
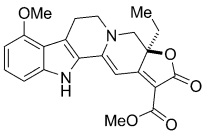
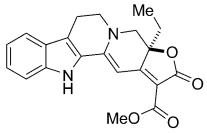
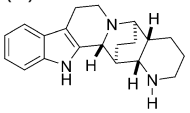
Indole alkaloid	Species	Biological activity
	*Amsonia tabernaemontana* (Eastern bluestar),[197] *Amsonia angustifolia*, *Rhazya stricta*, *Tabernaemontana riedelii*, *Vinca difformis* (intermediate periwinkle), *Macoubea guianensis*[198]	
(+)-vincadifformine		
(−)-vincadifformine	*Vinca minor* (dwarf 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		
(−)-apparicine	*Aspidosperma olivaceum*, other *Aspidosperma* spp., *Catharanthus ovalis* (rosy periwinkle), *Catharanthus roseus* (Madagascar periwinkle), *Pandaca ochrascens*, *Pandaca eusepala*, *Ervatamia heyneana*, *Tabernaemontana cumminsii*, *Schizzygia caffaeoides*	anticancer, antibacterial, antiviral
	*Hunteria eburnea*, *Amsonia tabernaemontana*, *Vinca minor*	
(+)-eburnamonine		
(−)-eburnamonine	*Vinca minor*	stimulates muscle activity
	*Picralima nitida*	
(+)-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]	

Table 11: (Continued)

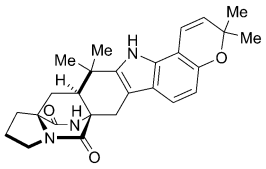
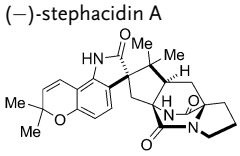
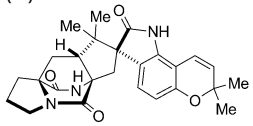
Indole alkaloid	Species	Biological activity
 (+)-mitralactonine	*Mitragyna speciosa*[201]	
(−)-mitralactonine	*Mitragyna speciosa*[201]	
 (±)-nitrarine	*Nitraria schoberi* (nitre bush)[193, 202]	

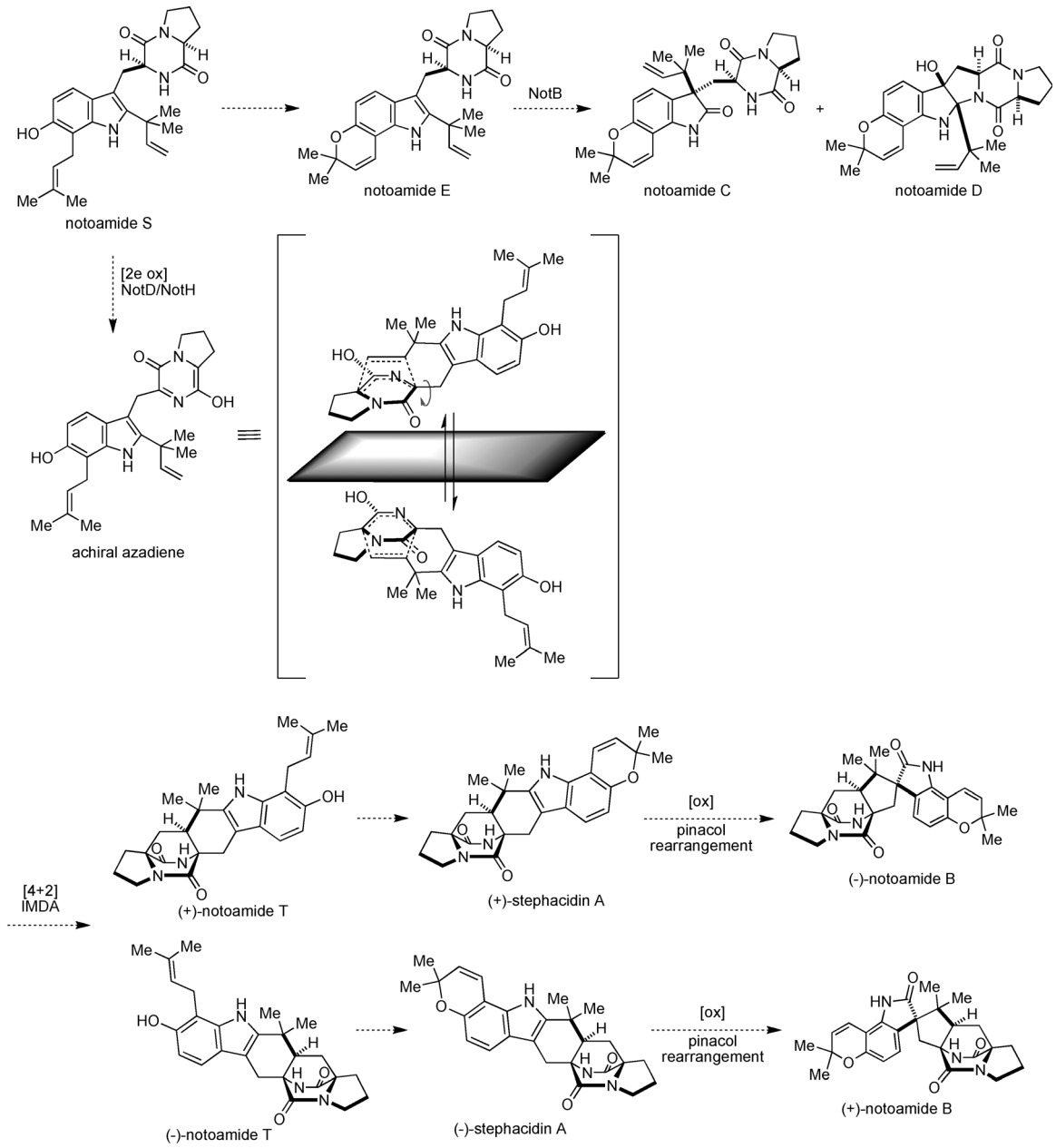
[a] For species and biological activity that do not have a reference, see the *Dictionary of Alkaloids* (Ref. [193]).

selective pinacol-type rearrangement to form the spirooxindole 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 study was further aided by the identification and characterization of the *Aspergillus* sp. MF297-2 and the *Aspergillus versicolor* NRRL35600 gene clusters,[207] as well as parallel precursor incorporation studies with both fungal cultures.[208]

A biosynthetic pathway has been proposed on the basis of results from genome mining and tracer studies.[207,208] As shown in Scheme 13, the pathway branches into at least two possible directions from the proposed pivotal intermediate notoamide S.[209] Formation of the pyranoindole to yield notoamide E results in the biosynthesis of notoamide C, 3-*epi*-notoamide C, and notoamide D[208a,b] by the proposed enzyme NotB. However, notoamide S could also undergo a two-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. It was ascertained through precursor incorporation studies of ^{13}C-labeled (±)-stephacidin A with both *A. versicolor* and *Aspergillus* sp. MF297-2 that face-selective oxidative enzymes (currently presumed to be flavoenzymes) are present in both fungal cultures, as evident by the enantioselective conversion of stephacidin A into notoamide B.[208c] In *A. versicolor* NRRL 35600, this oxidase is responsible for the biosynthetic conversion of (−)-stephacidin A into (+)-notoamide B, while a stereochemically

Table 12: Enantiomeric reverse prenylated indole alkaloids.

Reverse prenylated indole alkaloid	Species	Biological activity
 (+)-stephacidin A	*Aspergillus* sp. MF297-2 (fungus),[205] *Aspergillus ochraceus* (fungus)[204]	anticancer[204]
(−)-stephacidin A	*Aspergillus versicolor* (fungus)[206]	
 (+)-notoamide B	*Aspergillus versicolor*[206]	
(−)-notoamide B	*Aspergillus* sp. MF297-2[205]	
 (+)-versicolamide B	*Aspergillus versicolor*[206]	
(−)-versicolamide B	*Aspergillus* sp. MF297-2[210]	



Scheme 13. Putative enantiodivergent biosynthesis of stephacidin A and the notoamides. IMDA = intramolecular Diels–Alder reaction.

complementary oxidase in the marine-derived *Aspergillus* sp. MF297-2 converts (+)-stephacidin A into (−)-notoamide B.

It is significant that the oxidation must occur from distinct enantiotopic faces of the indole ring system in each of these respective oxidation reactions of the 2,3-disubstituted indole moiety of stephacidin A, and we currently 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 investigation.

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/notoamide pathways from two fungal strains. The marine *Aspergillus* sp. MF297-2 strain generates (−)-notoamide B, whereas the terrestrial *Aspergillus versicolor* strain

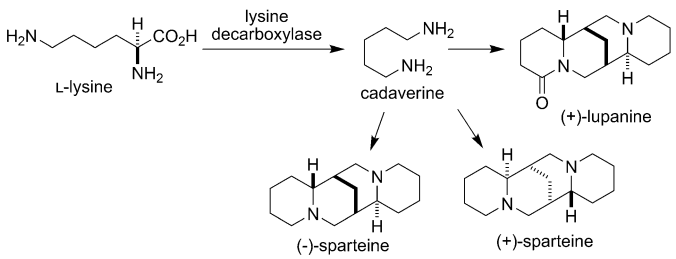
generates the enantiomer (+)-notoamide B. The key chiral determinant is hypothesized to reside within the presumed intramolecular Diels–Alderase enzyme. We have found the molecular architecture (e.g. gene placement and directionality of transcription) of these pathways to be remarkably similar, with >70% identity of nucleotide sequences across the 35 kb gene clusters. The corresponding high level of amino acid sequence similarity suggests that subtle variation in the active-site sequence plays a critical role in controlling the 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 families 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, the research groups of Spenser, Robins, and Wink demonstrated that the quinolizidine alkaloids are biosynthesized from lysine via a symmetrical cadaverine intermediate. 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]



Scheme 14. Biogenesis of (−)-sparteine.

5.4. Piperidine and Pyridine Alkaloids

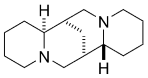
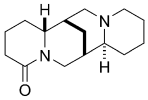
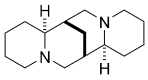
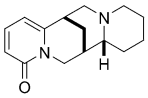
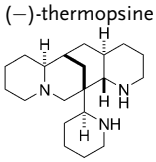
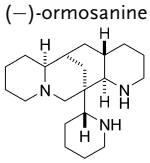
Both piperidine and pyridine alkaloids are secondary metabolites containing a six-membered heterocyclic ring system with a nitrogen-containing nucleus, in which this heterocycle is saturated in piperidine alkaloids and unsaturated in pyridine alkaloids. Simple piperidine and pyridine natural products 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 the 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 found with nicotine, biosynthetic studies have focused on the biogenesis of the major enantiomer, in this case (−)-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 stereospecificity, and thus 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 2500 defined structures and are 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. This group of alkaloids include 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,

Table 13: Lupine alkaloid enantiomers.[a]

Lupine alkaloid	Species	Biological activity
 (+)-sparteine (−)-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
	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 (−)-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
	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*	
(−)-ormosanine	*Podopetalum ormondii*, *Ormosia semicastrata*, *Ormosia jamaicensis*, *Piptanthus nanus*	
 (+)-piptanthine	*Hovea linearis*, *Templetonia retusa* (cockies tounge), *Ormosia semicastrata*, *Ammopiptanthus mongolicus*	
(−)-piptanthine	*Hovea linearis*, *Templetonia retusa*, *Ormosia semicastrata, Ammopiptanthus mongolicus*, *Piptanthus nanus*	

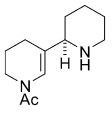
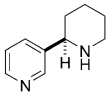
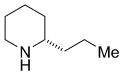
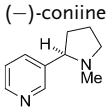
[a] For species and biological activity that do not have a reference, see the *Dictionary of Alkaloids* (Ref. [193]).

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.

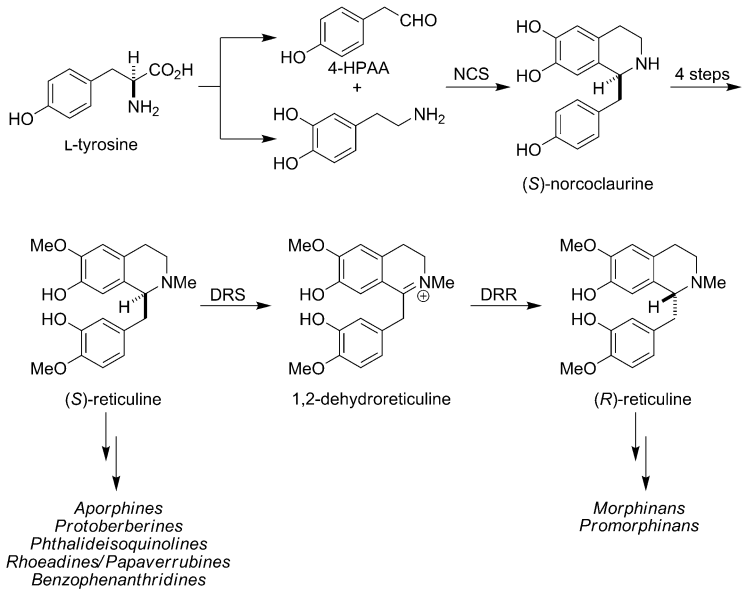
Biosynthetically, benzylisoquinoline alkaloids are all derived from L-tyrosine along a basic benzylisoquinoline pathway.[232,233] As shown in Scheme 15, the first committed step in the BIA biosynthesis is the asymmetric Pictet–Spengler condensation of tyrosine-derived dopamine and *para*-hydroxyphenylacetaldehyde (4-HPAA) in the presence of norcoclaurine synthase (NCS) to yield optically pure (*S*)-norcoclaurine.[231] (*S*)-norcoclaurine is converted into optically pure (*S*)-reticuline through four enzymatic transformations. This intermediate serves as a vital branching point to the various benzylisoquinoline alkaloids, many of which display the same configuration as (*S*)-reticuline; however, the promorphinan and morphinan subgroup of BIAs contain the opposite (*R*) configuration.[232] These alkaloids are derived from (*R*)-reticuline, which arises from the inversion of the configuration of (*S*)-reticuline by way of oxidation and reduction with 1,2-dehydroreticuline synthase (DRS) and 1,2-dehydroreticuline reductase (DRR).[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 by 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 configuration. In the case of

Table 14: Enantiomeric piperidine and pyridine alkaloids.[a]

Piperidine and pyridine alkaloid	Species	Biological activity
 (+)-ammodendrine	*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	*Ammodendron conollyi*, *Ammodendron* spp., *Sophora franchetiana*, *Sophora tomentosa*,[228] *Coelidium fourcadei*, *Lupinus formosus*,[225a,b] *Castilleja miniata* (giant red Indian paintbrush)[225a]	teratogen[225]
 (+)-anabasine	*Nicotiana glauca* (wild tobacco),[225d] *Aphaenogaster subterranea* (ant),[229] *Aphaenogaster miamiana* (ant)[229]	teratogen[225d]
(−)-anabasine	*Nicotiana glauca*,[225d] *Anabasis aphylla*,[230] *Aphaenogaster subterranea*,[229] *Aphaenogaster miamiana*,[229] *Messor sanctus* (ant)[229]	teratogen[225d]
 (+)-coniine	*Conium maculatum* (poison hemlock)[225c]	toxic to livestock[225c]
(−)-coniine	*Conium maculatum*[225c]	toxic to livestock[225c]
 (+)-nicotine	*Nicotiana tabacum* (cultivated tobacco)	weakly binds to nicotinic acetylcholine receptors[8]
(−)-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, see the *Dictionary of Alkaloids* (Ref. [193]).



Scheme 15. Early stages in the benzylisoquinoline alkaloid biogenesis.

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]

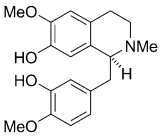
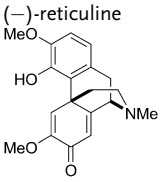
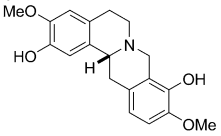
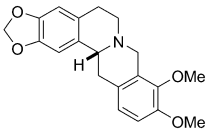
Unfortunately, substantial information is lacking on the biosynthesis of all of the enantiomeric BIAs. As seen in the elucidation of the enantiomeric nicotine biosynthetic pathway, the biogenesis of only one enantiomer of the BIA natural products is understood, as is the case with (*S*)-scoulerine and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

6. Summary and Outlook

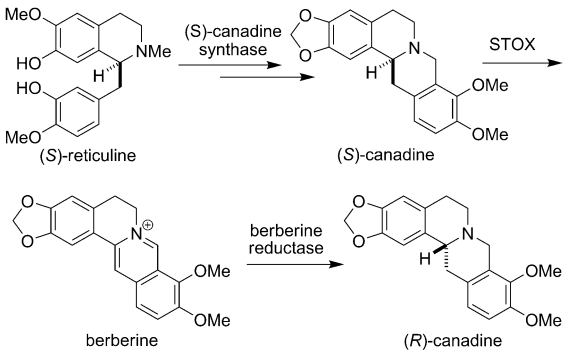
As demonstrated in this Review, the formation of enantiomeric natural products by nature is not as uncommon as one might have initially expected. While the number of enantiomeric natural products that have been discovered to date represent a small fraction (less than 1%) of the biosphere's metabolome, it is clear that biogenetic mechanisms to create distinct enantiomers are widely expressed. Many puzzles and stereochemical anomalies remain and provide 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 of the 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 precur-

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, see the *Dictionary of Alkaloids* (Ref. [193]).



Scheme 16. Biosynthesis of enantiomeric canadine.

sor, 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 later in 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 cases, 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 generation of both enantiomers from a single enzyme may be due in part to a lack of enzyme substrate- and stereospecificity, which was observed in the biosynthesis of (+)-carvone by (+)-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 the isolation and structural elucidation of natural products, 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 provide 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] In this regard, 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 paralogues can be freed from selective constraints, thus allowing it to evolve by genetic drift to acquire multiple substitutions? Or, alternatively, can a single orthologue 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, if evolution does not proceed from one form of the enzyme to the other (i.e., from a (−)-producing form to a (+)-producing form) in a single mutation (e.g 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 cases of this evolutionary process—a rare opportunity in molecular evolution. Such an investigation has the potential of revealing generalities about the evolution of protein structure/function for this subtlest of possible changes in natural product chemistry.

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