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Part 1: Occurrence of Racemic Natural Products and Their Biological Activities

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Abstract

Normally, natural products are optically active compound that exist as a single enantiomer owing to biosynthesis by enzymatic catalysis. However, many natural products have been isolated as racemic mixtures comprising both enantiomers. This review provides information on some racemic natural products isolated from bioresources. The biological activities of racemic natural products are also discussed.

Keywords: Natural Products, Racemic mixture, Racemate, Biological activity

Introduction

The stereochemistry of organic compounds is important for drug development. The importance of chiral configuration is exemplified by the drug thalidomide (Figure 1), which has been used to treat morning sickness in pregnant women.[1] In the past, thalidomide was sold as a racemic mixture of both *R*- and *S*-enantiomers, but the drug was banned due to causing birth defects in children. Further research showed that only the *R*-isomer was therapeutically active (Figure 1) and responsible for health benefits to patients, while the *S*-isomer was toxic and responsible for the negative effects. Furthermore, the *S*-isomer of thalidomide was found to be inactive, showing no therapeutic effect on patients. Another classic example of the importance of stereochemistry is ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), which acts through inhibition of cyclooxygenase, an enzyme responsible for the biosynthesis of prostanoids, thromboxane, and prostaglandins. *S*-Ibuprofen can inhibit cyclooxygenase, while *R*-ibuprofen cannot. Studies have shown that *S*- and *R*-ibuprofens have different metabolic profiles, but that *R*-ibuprofen can be metabolically converted into *S*-ibuprofen.[2] Unlike thalidomide, neither enantiomer of ibuprofen has any substantial negative effect, allowing ibuprofen to be used as a racemic mixture. These examples underscore the importance of stereochemistry in organic compounds.

In the past, many chemists have considered natural products to be optically active, existing as only a single enantiomer, owing to their biosynthesis by enzymes in living organisms. As enzymes are chiral molecules, the natural products produced by enzymatic catalysis should, in theory, comprise a single enantiomer. Natural products in racemate form can be derived from optically active

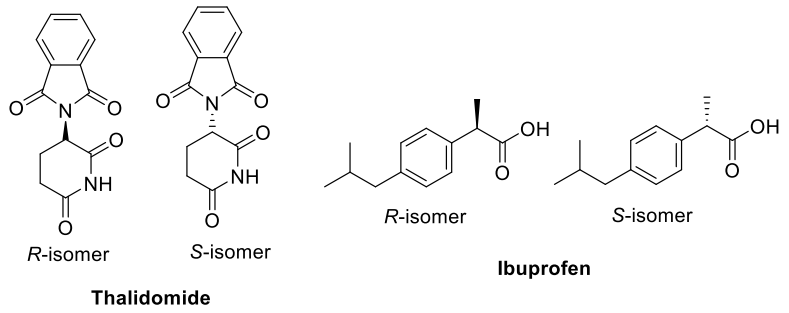

Figure 1: Structures of the two enantiomers (R- and S-isomers) of drugs thalidomide and ibuprofen.

single-enantiomer natural products through racemization. This hypothesis is supported by the reported synthesis of alkaloid sinoracutine, which underwent racemization.[3] Racemic mixtures of natural products can result from nonenzymatic reactions, which do not involve enzymatic catalysis and afford achiral precursors (containing both enantiomers). Examples of nonenzymatic reactions include electrocyclizations and cycloadditions.[4–9] In 2012, a review of the occurrence and biogenesis of enantiomeric natural products was published by Finefield and coworkers.[10] Furthermore, the separation and absolute configuration assignment of enantiomeric natural products was recently published by Batista and coworkers.[11] The present review provides information on some racemic natural products isolated from natural sources. For high-performance liquid chromatography (HPLC) as an advanced separation technology, new chiral materials can be used as stationary phases in HPLC columns, known as "chiral columns". Individual enantiomers in a racemic mixture of natural products can be separated by chiral columns, with the absolute configuration of each enantiomer established by calculating electronic circular dichroism (ECD) spectra and/or quantum chemical predictions of ^{13}C NMR chemical shifts.

Occurrence of Racemic Natural Products in Plants

Tetracyclic compounds racemosol (**1**) and 10-*O*-demethylracemosol (**2**) were first isolated from the plants *Bauhinia racemosa* and *Bauhinia rufescens* (Figure 2). X-ray analysis suggested that both compounds **1** and **2** existed as mixtures of two enantiomers (*R*- and *S*-isomers).[12,13] Later, compounds **1** and **2** were isolated from the roots of a Thai medicinal plant, *B. malabarica*, locally known in Thai as "Siaw Yai".[14] The specific optical rotation of racemosol (**1**) was close to zero, implying that it was a racemate. Furthermore, bibenzyl derivatives preracemosols A (**3**) and B (**4**), which are possible biogenetic precursors of racemosol (**1**) and 10-*O*-demethylracemosol (**2**), were isolated from *B. malabarica* (Figure 2). Hostettmann and coworkers proposed that the tetracyclic core structure of racemosol (**1**) and its derivative (**2**) was constructed from bibenzyl intermediates.[12] The isolation of bibenzyl derivatives **3** and **4** within the same plant fully supported this hypothesis. As shown in Figure 2, preracemosols A (**3**) and B (**4**) have been proposed as potential biogenetic precursors of compound **2**. Methyl transfer by a methyltransferase enzyme, such as *S*-adenosyl methionine (SAM), leads to the formation of racemosol (**1**) (Figure 2). The key step in this synthesis is formation of the tetracyclic ring system in compound **2** from its tricyclic precursor (for example, **4**) (Figure 2), which generates a new stereogenic center. However, compound **2** is a racemate. Metabolites **1**–**4** exhibit antimalarial activities with EC_{50} values of 0.9–18.0 μg/mL.

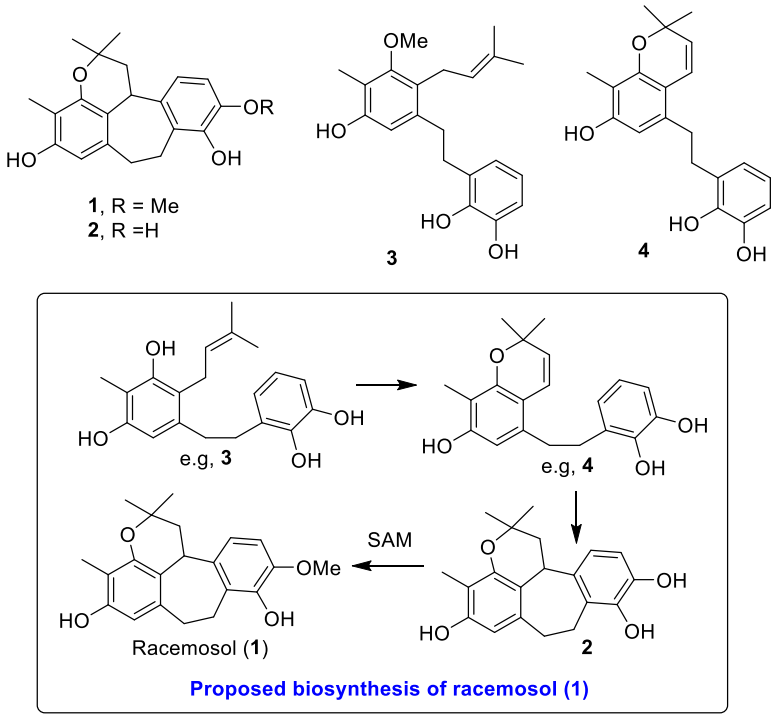

Figure 2: Structures of compounds **1**–**4**, and the proposed biosynthetic pathway of racemosol (**1**) and 10-*O*-demethylracemosol (**2**).

Racemic mixtures of racemosol (**1**) and its derivative (**2**) have shown cytotoxic activities against KB and BC cancer cell lines, with EC_{50} values of 3.6–15.0 □g/mL.[14] Both racemosol (**1**) and compound **2** showed potent *in vitro* anti-inflammatory activity, and were found to be inhibitors of cyclooxygenase (COX) enzymes COX-1 and COX-2.[15] The inhibition of COX enzymes is a drug mechanism for treating inflammation and pain, such as with NSAIDs. The total synthesis of racemosol (**1**) and 10-*O*-demethylracemosol (**2**) has been achieved by researchers in Thailand.[16]

The presence of two enantiomers in caged xanthones pruniflorone T (**5**), cochinchinone C (**6**), and pruniflorone U (**7**) was confirmed by the specific optical rotation being close to zero (Figure 3). These caged xanthones were isolated from the roots of Thai medicinal plant *Cratoxylum formosum* ssp. *Pruniflorum*, known in Thai as "Tiow Kon".[17] X-ray crystallographic analysis showed the presence of two enantiomers in pruniflorone T (**5**), cochinchinone C (**6**), and pruniflorone U (**7**). Chiral HPLC analysis indicated that the ratios of the (+)/(−)-enantiomers of compounds **5**, **6**, and **7** were 1.0:1.1, 1.0:1.9, and 1.1:1.0, respectively. Cochinchinone C (**6**) exhibited cytotoxic activity against the MCF-7 cancer cell line, with an IC_{50} value of 0.36 μg/mL, while pruniflorones T (**5**) and U (**7**) were inactive, with IC_{50} values of 5 μg/mL. However, a mixture (1:1 ratio) of compounds **5** and **7** showed significantly enhanced cytotoxic activity, with an IC_{50} value of 0.11 μg/mL. This demonstrates the synergistic effect of natural products in herbal medicines. Pure compounds or single compounds in traditional herbal medicine might not show certain biological activities, but will show activity in the presence of other compounds. Therefore, some herbal medicinal plants should be used as a crude extract or partially purified fraction for medication.

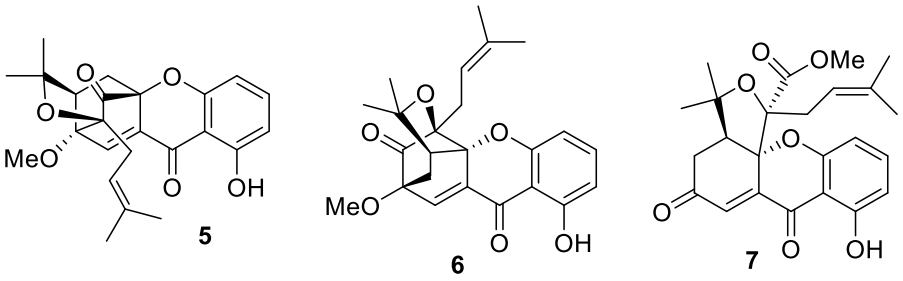

Figure 3: Structures of pruniflorone T (**5**), cochinchinone C (**6**), and pruniflorone U (**7**).

Racemic mixtures of dimeric styrylpyrones velutinindimers B (**8**) and C (**9**) (Figure 4), were isolated from the leaves of a Thai medicinal plant *Miliusa velutina*, known in Thai as "Khang Hua Mou".[18] Both compounds **8** and **9** showed specific rotation values close to zero, and X-ray crystallographic analysis showed that both natural products existed as racemic mixtures. Furthermore, a symmetrical cyclobutane dimer, velutinindimer A (**10**), together with its possible precursor, yangonin (**11**), were also isolated from *M. velutina*. Both velutinindimers B (**8**) and C (**9**) are unsymmetrical cyclobutane dimers possibly derived from yangonin (**11**). The cyclobutane dimers isolated from *M. velutina* are possibly derived from the (2+2) cycloaddition of yangonin (**11**). Kanokmedhakul and coworkers proved that cyclobutane dimers **8**–**10** were not artifacts obtained during extraction and isolation, because they were not obtained after stirring yangonin (**11**) in silica gel for one week.[18] Therefore, dimers **8**–**10** are natural products produced by the plant *M. velutina*, exhibiting antimalarial activity with IC_{50} values of 5.4–6.4 μM, but not displaying cytotoxic activity against KB, MCF-7, NCI-H187, and Vero cell lines.[18]

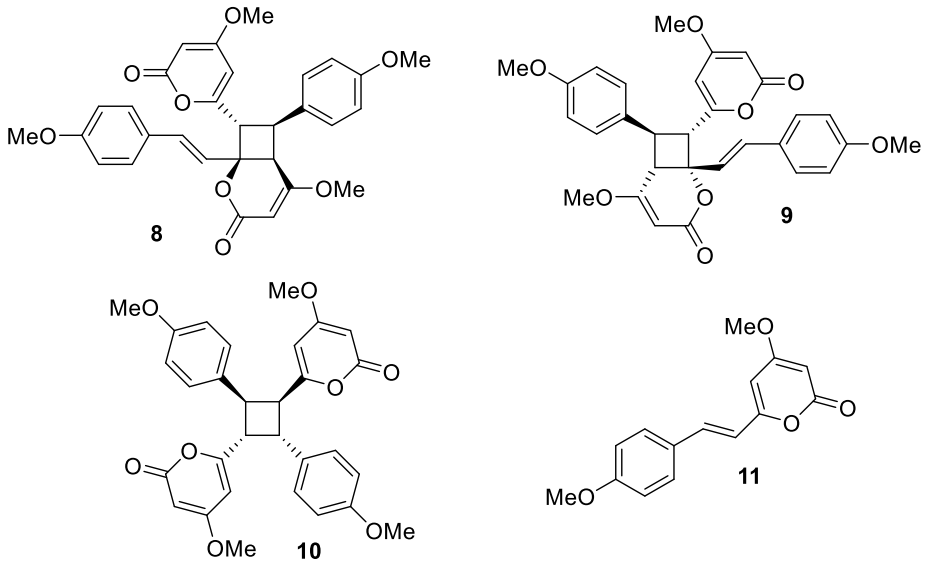

Figure 4: Structures of velutinindimers B (**8**), C (**9**), and A (**10**), and yangonin (**11**).

A racemic mixture of isoflavanone mucunone A (**12**) (Figure 5) was isolated from Thai medicinal plant *Mucuna pruriens*, known in Thai as "Tum Yae" or "Mha Mooy".[19] The optical rotation of **12** was close to zero, while the resulting Cotton effect in the CD spectrum was negligible, suggesting that **12** was a racemate.[19] Mucunone A (**12**) exhibited □-glucosidase inhibitory activity with an IC_{50} value of 58.43 μM, and weak cytotoxic activity against A549 and HuCCA-1 cancer cell lines with IC_{50} values of 53.1 and 73.2 μM, respectively. The inhibition of □-glucosidase is a drug-design mechanism for the treatment of diabetes. Mucunone A (**12**) inhibited □-glucosidase with an IC_{50} value of 58.43 μM, while the standard drug, acarbose, had an IC_{50} value of 7.96 μM. Therefore, mucunone A (**12**) was 7.3-times less active than acarbose.[19] Racemic mixtures of two isopropenyl-dihydrofuranoisoflavones, lachnoisoflavones A (**13**) and B (**14**) (Figure 5), were isolated from Cameroonian medicinal plant *Crotalaria lachnophora*.[20] Both compounds **13** and **14** had a specific optical rotation of 0.002, which is close to zero, while the CD spectra also suggested that they existed as racemic mixtures. Lachnoisoflavones A (**13**) and B (**14**) exhibited moderate antibacterial activity against *Escherichia coli* and *Klebsiella pneumoniae*.[20] Equol (**15**), an isoflavandiol found in humans and animals, is produced from the metabolism of daidzein (**16**) (Figure 5), an isoflavone found in soybeans. Daidzein (**16**) from soybeans is converted into equol (**15**) by bacterial flora in the intestines of humans and animals. Normally, the (*S*)-isomer of equol (**15**) is found in humans and animals, and is a potent ligand for estrogen receptor beta. Fecal bacteria were found to produce only the *S*-isomer of equol (**15**) from soy isoflavone daidzein (**16**).[21] However, enzyme dihydrodaidzein racemase in a lactic acid bacterium, *Lactococcus* sp. strain 20-92, was able to transform both *R*- and *S*-dihydrodaidzeins, intermediates for the synthesis of equol (**15**), into a racemic mixture.[22] Interestingly, a mixture of the two enantiomers of equol (**15**) inhibited bone loss in ovariectomized mice,[23] while the inhibitory effect of the *S*-isomer of equol (**15**) against bone fragility was better than that of the racemic mixture.[24]

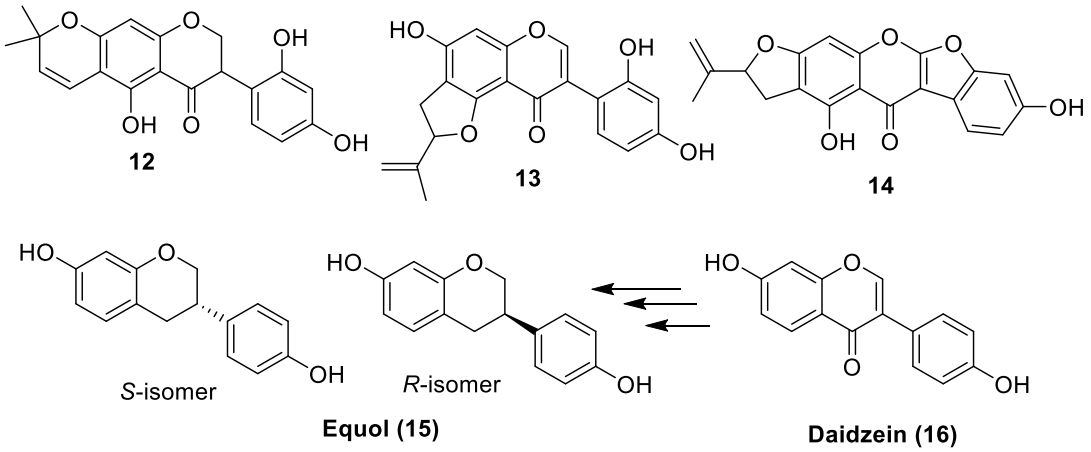

Figure 5: Structures of mucunone A (**12**), lachnoisoflavones A (**13**) and B (**14**), equol (**15**), and daidzein (**16**).

Gaudichaudianic acid (**17**) is a prenylated chromene isolated from the plant *Piper gaudichaudianum* as a racemic mixture (Figure 6).[25] Gaudichaudianic acid (**17**) was found to exhibit potent trypanocidal activity against the Y-strain of *Trypanosoma cruzi*, and the two enantiomers of compound **17** were separated by chiral HPLC. (+)-(*S*)-**17** exhibited better trypanocidal activity than the corresponding (−)-(*R*)-isomer. Furthermore, the mixture of both enantiomers showed a synergistic effect, exhibiting better trypanocidal activity than the individual enantiomers.[25] Previously, gaudichaudianic acid (**17**) was isolated from Piper species as the (+)-(*S*)-isomer, and exhibited antifungal activity against *Cladosporium cladosporioides* and *C. sphaerospermum*.[26] The biosynthesis of (+)-(*S*)-**17** was investigated in leaves of *P. gaudichaudianum* by feeding with [1-^{13}C]-D-glucose as precursor.[27] Leaves of *P. gaudichaudianum* were administrated with a solution of [1-^{13}C]-D-glucose in water at 25 °C, incubated for 72 h, and the labeling pattern in gaudichaudianic acid was analyzed by ^{13}C NMR spectroscopy.

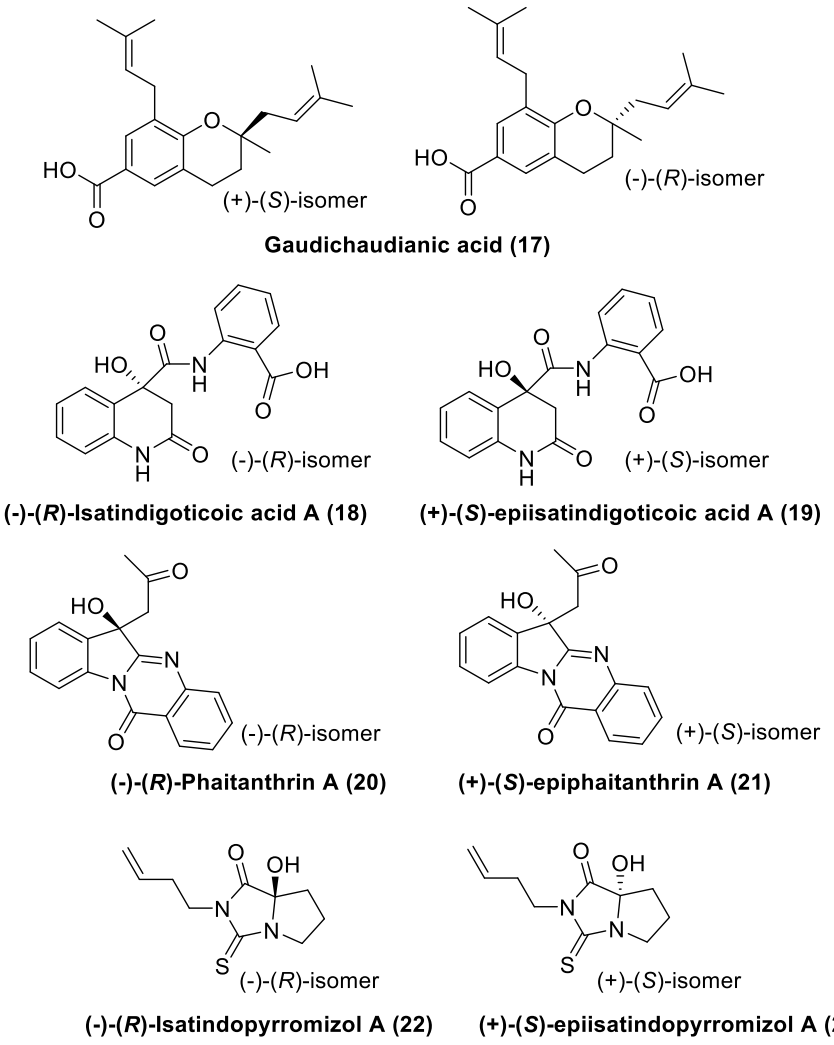

Figure 6: Structures of gaudichaudianic acid (**17**), (−)-(*R*)-isatindigoticoic acid A (**18**), (+)-(*S*)-epiisatindigoticoic acid A (**19**), (−)-(*R*)-phaitanthrin A (**20**), (+)-(*S*)-epiphaitanthrin A (**21**), (−)-(*R*)-isatindopyrromizol A (**22**), and (+)-(*S*)-epiisatindopyrromizol A (**23**).

The formation of di-methylallyl- and geranyl-derived moieties in the biosynthesis of gaudichaudianic acid (**17**) might involve both mevalonic acid and 2-*C*-methyl-D-erythritol-4-phosphate pathways.[27] Three pairs of alkaloid enantiomers, (–)-(*R*)-isatindigoticoic acid A (**18**), (+)-(*S*)-epiisatindi-goticoic acid A (**19**),(–)-(*R*)-phaitanthrin A (**20**), (+)-(*S*)-epiphaitanthrin A (**21**), (–)-(*R*)-isatindopyr-romizol A (**22**), and (+)-(*S*)-epiisatindo-pyrromizol A (**23**), were isolated from the roots of *Isatis indigotica* (Figure 6).[28] The pair of (–)-(*R*)-isatindigoticoic acid A (**18**) and (+)-(*S*)-epiisatindigoticoic acid A (**19**) was a scalemic mixture with a 3:2 ratio, while the pairs of compounds **20** and **21** and of compounds **22** and **23** were racemic mixtures with 1:1 ratios.[28] The enantiomers of compounds **18**–**23** were successfully separat-ed by chiral HPLC, and the absolute configurations of each enantiomer were determined from calculated ECD spectra.[28] Although the root of *I. indigotica* is used as an ingredient in "Ban Lan Gen" (herbal formulation known as Radix Isatidis), a traditional Chinese medicine for the treatment of influenza and infection diseases, alkaloids **18**–**23** did not show biological activity in preliminary assays.[28]

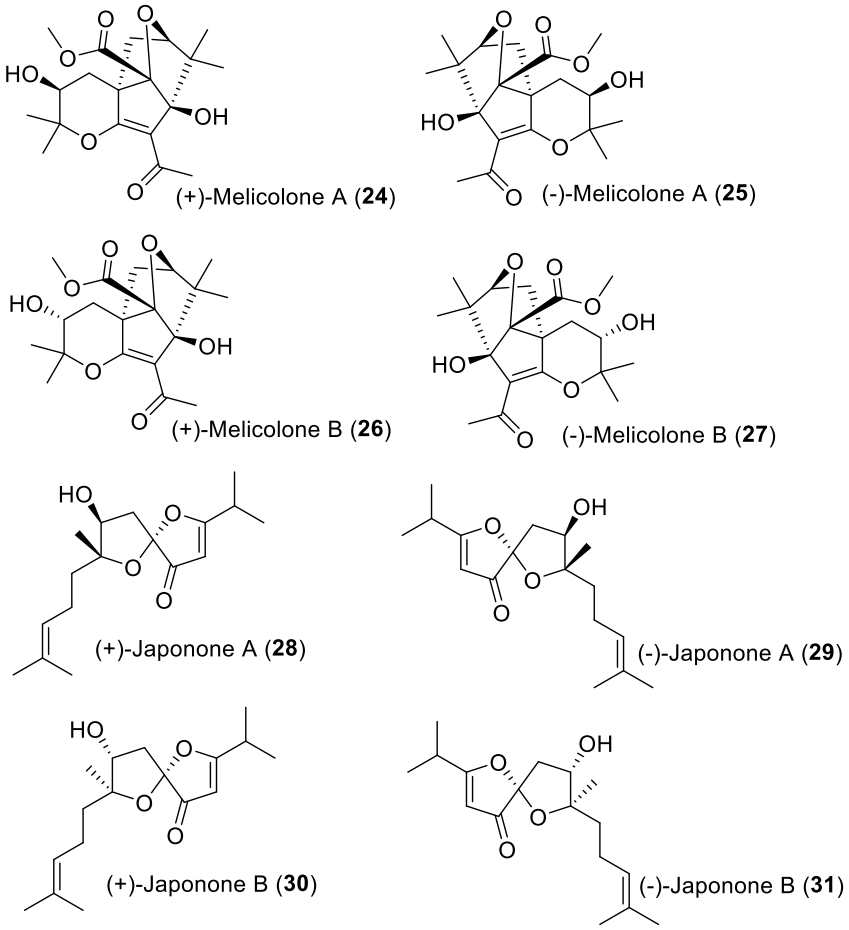

Figure 7: Structures of (+)-melicolone A (**24**), (–)-melicolone A (**25**), (+)-melicolone B (**26**), (–)-melicolone B (**27**), (+)-japonone A (**28**), (–)-japonone A (**29**), (+)-japonone B (**30**), and (–)-japonone B (**31**).

Two pairs of rearranged prenylated acetophenone epimers, (+)/(−)-melicolone A (**24**/**25**) and (+)/(–)-melicolone B (**26**/**27**) (Figure 7), were isolated from the plant *Melicope ptelefolia*.[29] These rearranged prenylated acetophenones (**24**–**27**) contained an unusual 9-oxatricyclo[3.2.1.1^{3,8}] nonane core. The structures and absolute configurations of (−)-melicolone A (**25**) and (+)-melicolone B (**26**) were established by X-ray crystallographic analysis. Compounds **24**–**27** showed protective effects against high-glucose-induced oxidative stress in human umbilical vein endothelial cells, indicating that they might help prevent diabetic endothelial dysfunction and related complications.[29] Two pairs of enantiomers of 1,6-dioxaspiro[4.4] non-2-en-4-ones, namely (+)/(−)-japonone A (**28**/**29**) and (+)/(−)-japonone B (**30**/**31**) (Figure 7), were isolated from *Hypericum japonicum*, a herb used in traditional Chinese medicine.[30] Japonones A and B possess an unusual 5,5-spiroketal core, and their racemic mixtures were separated by chiral HPLC. The absolute configurations of compounds **28**–**31** were established using calculated ECD spectra, the modified Mosher's method, and quantum chemical predictions of ^{13}C NMR chemical shifts.[30] Compounds **28**–**31** were assessed for inhibitory activity against Kaposi's sarcoma-associated herpesvirus, with (+)-japonone A (**28**) showing inhibitory activity.[30]

Occurrence of Racemic Natural Products in Microorganisms

Fungi and bacteria are rich microorganism sources of bioactive compounds. Racemic mixtures of natural compounds are also produced by microorganisms. The recent discovery of fungal metabolite preuisolactone A as a racemic mixture has received much research attention. A pair of norsesquiterpene enantiomers, (+)-preuisolactone A (**32**) and (−)-preuisolactone A (**33**) (Figure 8), was isolated from endophytic fungus *Preussia isomera*, which was isolated from herbal plant *Panax notoginseng*.[31] Endophytic fungi or fungal endophytes are microfungi found inside plant tissues, and have a mutualistic relationship with plants, meaning that they share certain benefits with each other.[32] (+)-Preuisolactone A (**32**) and (−)-preuisolactone A (**33**) have a unique chemical structure, with seven adjacent stereocenters and an unprecedented tricyclo[4.4.0^{1,6}.0^{2,8}]decane carbon skeleton.[31] The biosynthetic origin of both compounds **32** and **33** is proposed to be the terpenoid pathway, starting from farnesyl pyrophosphate (Figure 8).[31] Tricyclic intermediate A is derived from farnesyl pyrophosphate. Intermediate A undergoes rearrangement and oxidation to form bicyclic intermediate B. An Aldol reaction of intermediate B forms tricyclic intermediate C, which then undergoes two key reactions, oxidation and esterification, to generate intermediates D and E, respectively (Figure 8). Intermediate E undergoes oxidation to form intermediate F, with the loss of one carbon through a decarboxylation reaction leading to the formation of intermediate G. Preuisolactone A is finally formed after double-bond migration, oxidation, and methylation of intermediate G (Figure 8).[31] The racemic mixture of (+)-preuisolactone A (**32**) and (−)-preuisolactone A (**33**) was evaluated for antifungal and antibacterial activities, and showed antibacterial activity against *Micrococcus luteus* and *Bacillus megaterium* with MIC values of 10.2 and 163.4 μM, respectively. The racemate of compounds **32** and **33** also exhibited antifungal activity against *Alternaria alternata* (MIC value, 163.4 μM), but did not show cytotoxic activity against some cancer cell lines at a concentration of 100 μM, such as A549, Huh7, MGC803, HCT116, and LN229 cell lines.[31]

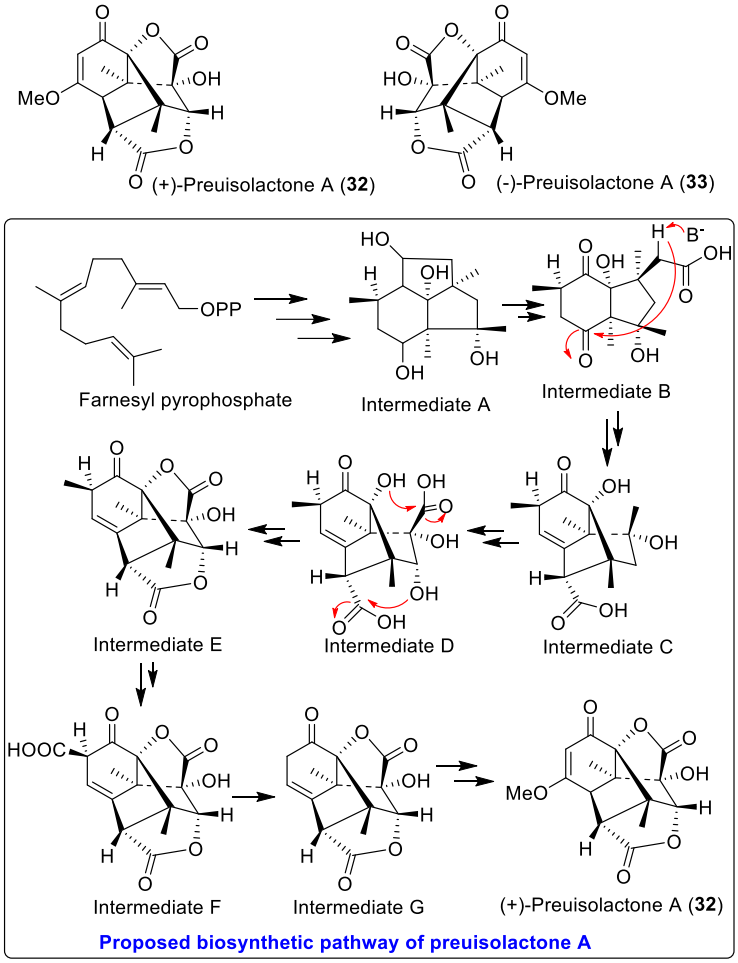

Figure 8: Structures of (+)-preuisolactone A (**32**) and (–)-preuisolactone A (**33**), and the proposed biosynthetic pathway of preuisolactone A *via* the terpenoid pathway (adapted from ref. 31).

After the discoveries of (+)-preuisolactone A (**32**) and (–)-preuisolactone A (**33**) by Abe and coworkers in 2019,[31] the biomimetic synthesis of preuisolactone A was achieved by Trauner and coworkers in the same year.[33] Abe and coworkers proposed the biosynthesis of preuisolactone A through the terpenoid pathway starting from farnesyl pyrophosphate (Figure 8).[31] However, Trauner and coworkers proposed an alternative biosynthetic pathway for preuisolactone A *via* the polyketide pathway, starting from the oxidative dimerization of catechol (**34**) with pyrogallol (**35**) (Figure 9).[33] Intermediates *o*-quinone (**36**) and hydroxy-*o*-quinone (**37**), derived from the oxidation of corresponding substrates **34** and **35**, undergo a (5+2) cycloaddition to give tricyclic intermediate **38**. Water attacks at the carbonyl bridge of **38**, followed by rearrangement *via* a retro-Dieckmann fragmentation, yielding bicyclic intermediate **39** bearing a 6/7 ring system. Intermediate **39** then undergoes a vinylogous aldol addition to give intermediate **40**, which then undergoes oxidative lactonization, affording intermediate **41**. The oxidation of intermediate **41** forms intermediate **42**, which then undergoes benzylic acid rearrangement to give intermediate **43**. Finally, the ring-contraction of intermediate **43** affords preuisolactone A (Figure 9).[33]

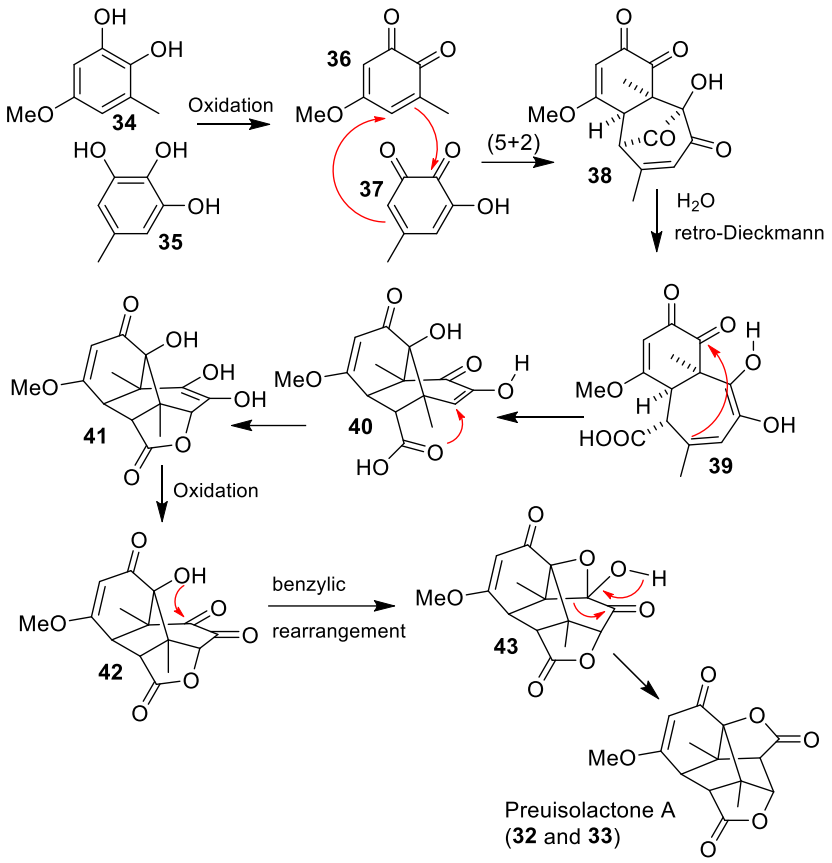

Figure 9: Alternative biosynthesis of preuisolactone A (**32** and **33**) *via* a polyketide pathway proposed by Trauner and coworkers (adapted from ref. 33).

Trauner and coworkers confirmed the proposed biosynthetic pathway (Figure 9) through the biomimetic synthesis of preuisolactone A, starting with the Dakin oxidation of resorcinol ether **44** to give catechol derivative **34**.[33] In the presence of potassium ferricyanide, $K_3Fe(CN)_6$, catechol derivative **34** reacted with pyrogallol (**35**) to give a mixture of compound **40** and hemiketal **45**, which were interconverting isomers (Figure 9). Acetal **45** was crystallizable, and its structure was readily confirmed by X-ray analysis.[33] Oxidation of compound **40** using Koser's reagent, hydroxyl (tosyloxy)iodobenzene, provided compound **46**, which was transformed into compound **42**. However, compound **42** was not isolated, perhaps because it underwent the proposed benzilic acid rearrangement during the workup process with an aqueous phosphate buffer, furnishing compound **43** and preuisolactone A in 57% overall yield from the mixture of compound **40** and acetal **45**[33] (Figure 9). Interestingly, the biomimetic synthesis of preuisolactone A with seven chiral centers in its molecule involved only three steps,[33] which is considered a short and efficient synthesis for a natural product with such a complex structure. Normally, the synthesis of natural products with seven adjacent stereocenters, such as preuisolactone A, requires many more steps.

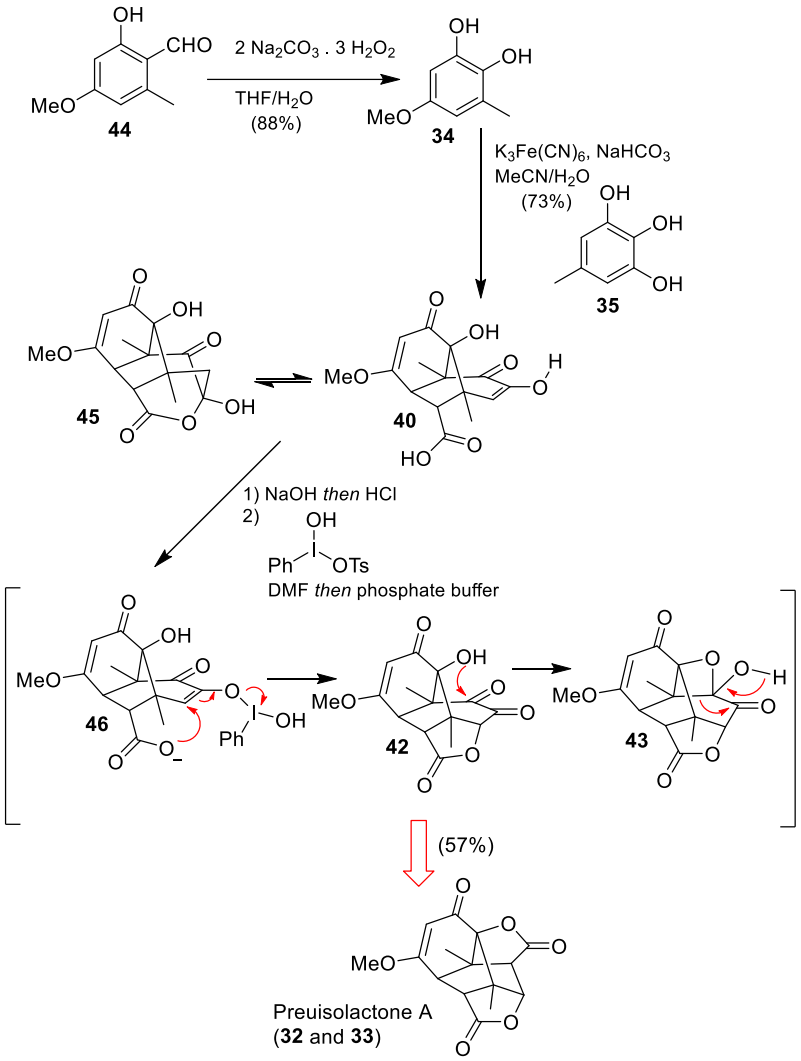

Figure 10: Biomimetic synthesis of preuisolactone A by Trauner and coworkers (adapted from ref. 33).

Racemic mixtures of butenolide derivatives have been isolated from coral-associated fungus *Aspergillus terreus*, including four pairs of enantiomers of (–)/(+)-asperteretone A (**47**/**48**), (–)/(+)-asperteretone B (**49**/**50**), (–)/(+)-asperteretone C (**51**/**52**), (–)/(+)-asperteretone D (**53**/**54**), and a racemic mixture of asperteretone E (**55**) (Figure 11).[34] Chiral HPLC was used to separate the racemic mixtures of (±)-asperteretones A–D (**47**–**54**), but failed to separate the racemic mixture of asperteretone E (**55**). The absolute configurations of individual enantiomers of asperteretones A–D (**47**–**54**) were established by experimental and calculated ECD analysis. Isolated compounds **47**–**55** were evaluated for their a-glucosidase inhibitory activity, which is one mechanism for the design of antidiabetes drugs, showing IC_{50} values ranging from 15.7±1.1 to 53.1±1.4 μM.[34] Notably, compounds **47**–**55** were more potent than antidiabetes drug acarbose (IC_{50} = 154.7±8.1 μM), which was used as the positive control. All enantiomers of asperteretones A–D (**47**–**54**) inhibited a-glucosidase with similar IC_{50} values, suggesting that the chiral center configuration did not affect the ⍰-glucosidase inhibitory activity.

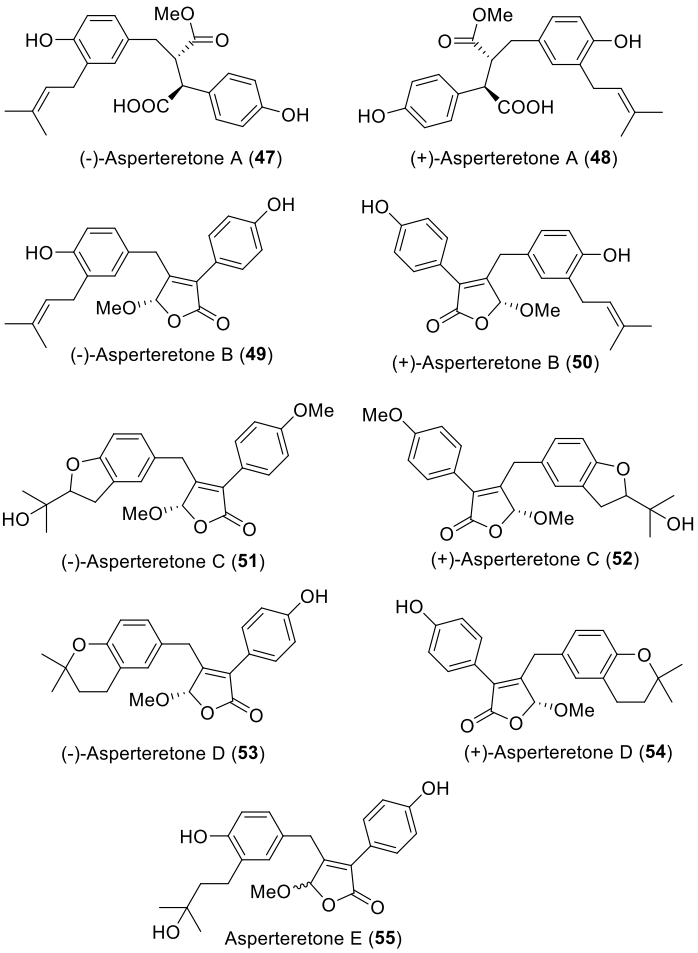

Figure 11: Structures of (–)-asperteretone A (**47**), (+)-asperteretone A (**48**), (–)-asperteretone B (**49**), (+)-asperteretone B (**50**), (–)-asperteretone C (**51**), (+)-asperteretone C (**52**), (–)-asperteretone D (**53**), (+)-asperteretone D (**54**), and a racemic mixture of asperteretone E (**55**).

In summary, the occurrence of racemic mixtures of natural products is commonly found in nature, with a number of natural products existing as racemates recently isolated from living organisms. Some natural racemates have unique structural features and exhibit interesting pharmacological activities.

Acknowledgments

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