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Natural products containing 'decalin' motif in microorganisms

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Microorganisms are well-known producers of a wide variety of bioactive compounds that are utilized not only for their primary metabolism but also for other purposes such as defense, detoxification, or communication with other micro- and macro-organisms. Natural products containing a 'decalin ring' occur often in microorganisms. They exhibit diverse and remarkable biological activities, including antifungal, antibacterial, anticancer and immunosuppressive activities, to name a few. This review surveys the natural decalin-type compounds that have been isolated from microorganisms, with emphasis on both chemical and biological implications. Total syntheses of some important decalin moiety-containing natural products are also highlighted.

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- 1 Introduction
- 2 Structural classification
- 3 Polyketide decalin
 - 3.1 Monacolins
 - 3.2 Monacolin derivatives
 - 3.3 Side chains with a 3-oxopropanol or its derivative
 - 3.4 Side chains with a pentadienoic acid
 - 3.5 Decalins with oxygenated diene/triene/tetraene side chains
 - 3.6 Pyrone derivatives
 - 3.7 Macrolides
 - 3.8 Pyrrolidine-2-one
 - 3.9 4-Hydroxy-2-pyridone alkaloids
 - 3.10 Spirotetronates
 - 3.11 Pyrrolizidines
 - 3.12 Others
- 4 Isoprenoid decalin
- 5 Conclusions
- 6 Acknowledgements
- 7 References

1 Introduction

The 'decalin' motif is found in an array of secondary metabolites produced by microorganisms, mainly fungi and actinomycetes. It is usually correlated with highly multifunctionalized or architecturally complex groups, thereby demonstrating surprising structural and functional diversity. Their intricate structures and diverse biological activities have attracted researchers around the world to investigate their biosynthesis, chemical synthesis, and the various facets of the functionalized decalin skeleton.¹⁻³

The decalin scaffold is primarily biosynthesized by microorganisms based on two biosynthetic derivations, isoprenoids (mevalonate) and polyketides (acetate). Isoprenoid-derived decalins typically belong to natural sesquiterpenoids and diterpenoids, and have been thoroughly covered in a series of reports by Fraga⁴ and Hanson.^{5,6} However, there is a dearth of comprehensive reviews on polyketide decalin-derived secondary metabolites, either about their isolation and biological activities, or related syntheses. Furthermore, no critical observation about the differences or similarities of these decalin moiety-containing compounds from a microbial origin has been reported.

The polyketide decalin skeleton in some fungal or bacterial secondary metabolites is proposed to be biosynthesized by an enzymatic intramolecular Diels–Alder (IMDA) cycloaddition.^{1,7} However, only five potential or possible Diels–Alderase enzymes have been purified until now,^{7,8} of which lovastatin nonaketide synthase (LovB) and solanapyrone synthase (SPS) are proposed to be related to the decalin formation of lovastatin and solanapyrone A.^{9,10} It should be noted that the non-enzymatic catalytic synthesis of decalin in biological systems is also

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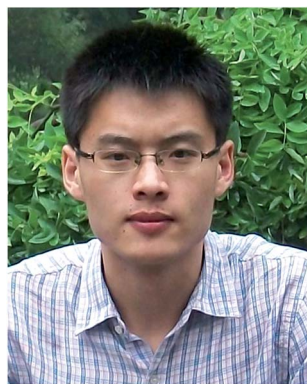


possible, as suggested in a biomimetic total synthesis of the decalin compound (\pm)-UCS1025A.¹¹ Based on the IMDA reaction of a substrate,⁹ all possible cyclization types to decalin are shown in Scheme 1. There are four comprehensive reviews on the syntheses of *trans*- or *cis*-decalins mainly in isoprenoids (mevalonate)-derived natural products.^{3,12–14} However, to the best of our knowledge, reviews compiling different facets of the polyketide decalin have not been reported.

Therefore, given the present gaps in a comprehensive elaboration of the ‘decalin’ system and considering their intriguing structural and biological features, the target of this review is to provide an informative overview of the topic that can serve as a point of reference for an understanding of the functions and applications of decalin.

2 Structural classification

Decalin, as a ring system or scaffold, can be greatly modified by many functional groups, such as a side chain, or diverse moieties. The side chains are usually substituted by many functional groups such as hydroxyl, carboxyl, or C=C and C=O



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Souvik Kusari received bachelor and master degrees in Biotechnology from Bangalore University, India. He then earned a doctorate in Natural Sciences from INFU, TU Dortmund, Germany in 2010. After working as a scientist in the same institute for over two years, he became a visiting researcher at the Department of Plant Sciences, University of Oxford, UK for a year in 2013. He is also a

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double bonds. Many other moieties such as small lactone ring, pyrone, tetramic acid, unusual sugars, pyridone, tetrionic acid, or pyrrolizidine act as diverse moieties, and are usually found in this type of compound. With the occurrence and interaction of these functional units in structures, a complex macrocycle or polycycle that is often fused with the decalin ring, is formed in microbial secondary metabolites. In this manuscript, those secondary metabolites are mainly classified according to the proposed biosynthesis of the decalin moiety-containing compounds: polyketide or isoprenoid biosynthetic derivations. The compounds with polyketide or isoprenoid decalin motifs are further classified according to the features of the remaining side chain or diverse moieties.

3 Polyketide decalin

Fungi and bacteria are the major microbial resources that produce the decalin moiety-containing secondary metabolites with a broad spectrum of biological activities. Most of these compounds have a polyketidic decalin scaffold. Frequently, they are highly functionalized through the substitution of methyl, hydroxyl, or C=C and C=O double bonds on the decalin skeleton, or through a three-, five-, or seven-membered side chain with carboxyls (or its ester), several double bonds, or *via* ring formation. Furthermore, a pyrone moiety connected to a poly-substituted decalin nucleus by a carbon-carbon bond contributes to an important class of polyketide natural products. In addition, the pyrrolidine-2-one moieties such as tetramic acids and the 4-hydroxy-2-pyridone group are important functionalized units found in many polyketide decalin natural products. The promising biosynthetic potential of fungi is also elaborated here with several examples of macrocyclic or polycyclic compounds.

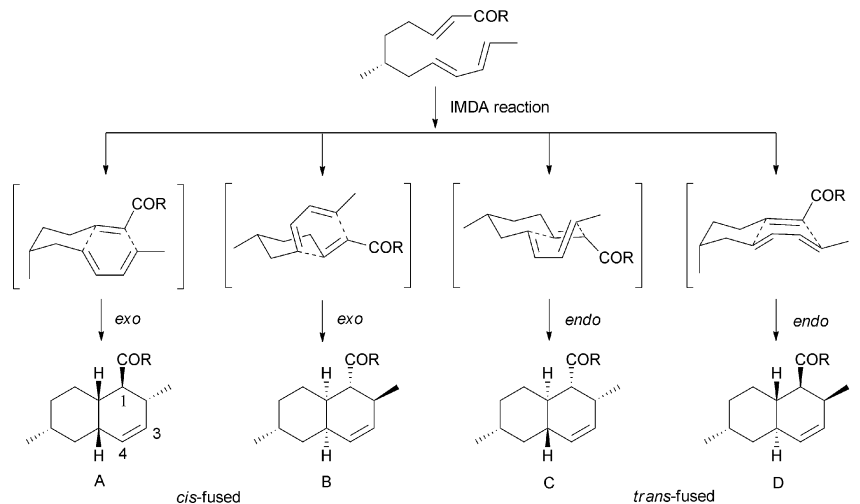
The biosynthesis of secondary metabolites with a polyketide decalin system is attributed to single or mixed biosynthetic pathways. Specifically, these compounds are proposed to be



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and Head of INFU, TU Dortmund, Germany. He is involved in various projects dealing with natural product drug discovery from plants and endophytes, structural identification of unknown xenobiotics and their metabolites, metabolism of pesticides in the environment, and veterinary drugs.





Scheme 1 The IMDA reaction to decalin.

assembled by a linear polyketide unit, which are then cyclized by an enzymatic or non-enzymatic IMDA cycloaddition to form the decalin scaffold.^{1,7} Prior to or after cyclization, many functionalized substituted groups are joined to the above polyketide skeletons which undergo some inter- or intra-molecular reactions to form the complete structure. Amino acids or other unusual units are also occasionally integrated into such a polyketide system to form diverse structures with intriguing structural features.

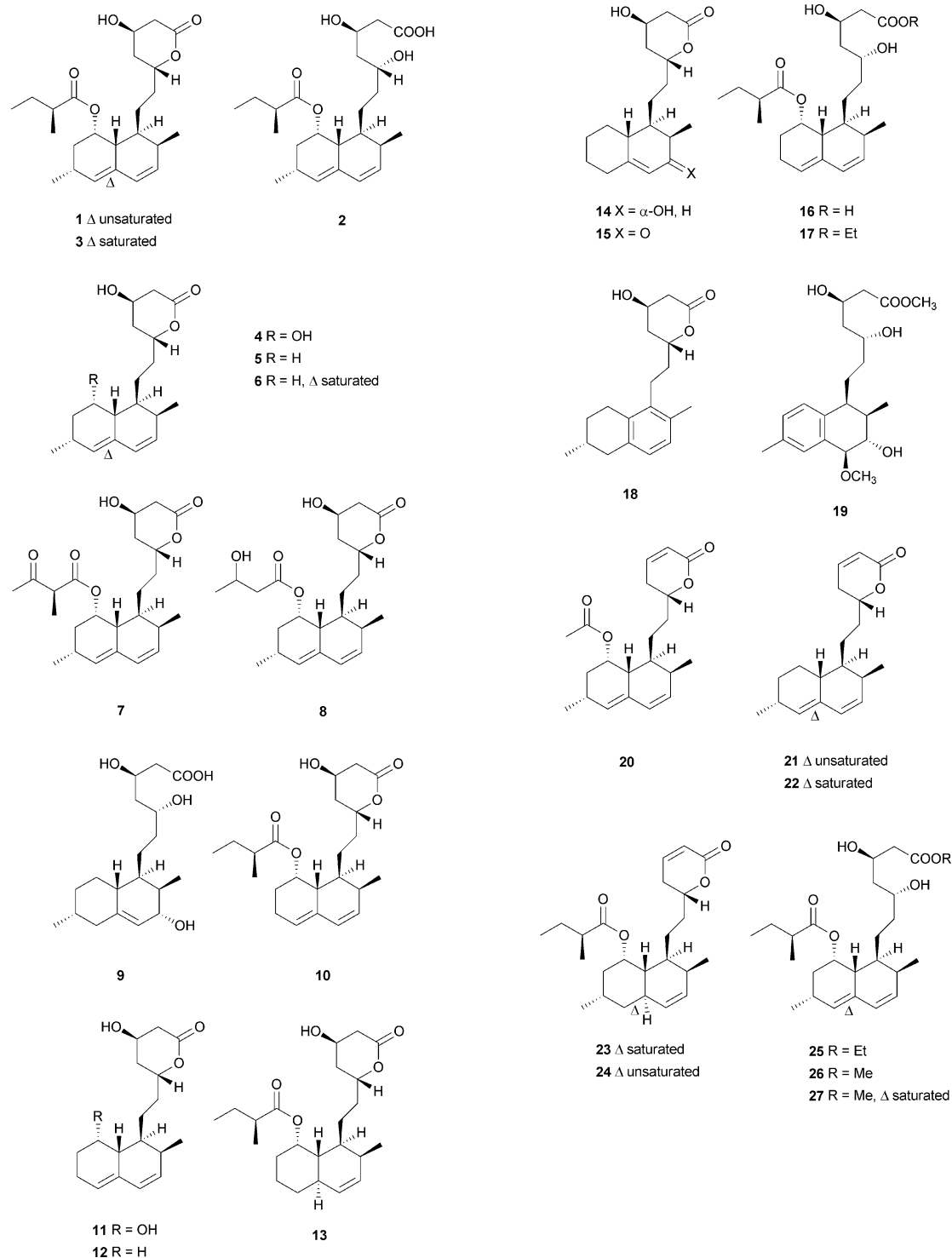
3.1 Monacolins

Monacolins are produced by microorganisms, and show a remarkable inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase that catalyzes the key step in cholesterol biosynthesis.¹⁵ Lovastatin (**1**), a cyclic nonaketide acylated by a diketide, and its semisynthetic derivative simvastatin act as potent inhibitors of HMG-CoA reductase and are widely prescribed in the treatment of hypercholesterolemia.¹⁶ Potent monacolin-type inhibitors of HMG-CoA reductase have been isolated from several fungal strains, mainly *Monascus ruber*, *Aspergillus terreus*, and *Penicillium citrinum*. They share a HMG-like moiety which is linked to the rigid and hydrophobic decalin system, and occupy a portion of the binding site of HMG-CoA, thus blocking access of this substrate (HMG-CoA) to the active site when these potent decalin-type inhibitors are bound.¹⁵ Until now, about 27 monacolins have been isolated and identified from fungal resources. The decalin skeleton is most likely formed *via* a biological Diels–Alder reaction by polyketide synthase (PKS) enzymes, as suggested earlier for lovastatin nonaketide synthase (LovB).⁹ This kind of compound is often isolated as an inactive lactone or active hydroxy-acid form. In this review, we will use the word “acid” to describe some lactone-opened monacolins for easy readability.

Lovastatin (**1**) (also called monacolin K or mevinolin) was first isolated in 1979 as an active inhibitor of HMG-CoA reductase (Endo reported **1** as monacolin K isolated from *M. ruber* in 1979;^{17,18} Alberts *et al.*, isolated and reported the same

compound as mevinolin isolated from *A. terreus*¹⁹). The lovastatin biosynthetic gene cluster was first identified in 1999 by the groups of Vederas and Hutchinson. After this work, more attention was paid towards identification of the complete biosynthetic pathway leading to **1**. Recently, the group of Tang¹⁶ briefly summarized important findings and recent advances on the investigation of the lovastatin (**1**) biosynthesis,^{9,20–23} and proposed that LovG from the lovastatin (**1**) gene cluster is responsible for the LovB protein (lovastatin nonaketide synthase, LNKS) turnover and release of dihydromonacolin L (**6**) (Scheme 2). From the cultures of *A. terreus*, in addition to **1**, its lactone-opened form, lovastatin acid (**2**) (designated as mevinolinic acid) was obtained.¹⁹ Another lovastatin analog, 4a,5-dihydromevinolin (**3**), a potent hypocholesterolemic agent, was isolated from this fungus.²⁴ Two metabolites related to **1** were isolated from *M. ruber* and designated as monacolins J (**4**) and L (**5**) by Endo *et al.*²⁵ From a mutant strain of *M. ruber*, dihydromonacolin L (**6**) and monacolin X (**7**) were further discovered.²⁶ Endo and co-workers also isolated a β -hydroxybutyryl ester of **4**, named monacolin M (**8**).²⁷ A hydrolysis derivative of **6**, identified as 3 α -hydroxy-3,5-dihydromonacolin L (**9**), was found to be produced by *A. terreus*.²⁸ Compactin (**10**) was first isolated from *Penicillium brevicompactum* in 1976 by Brown *et al.* as an antifungal metabolite.²⁹ In the same year, **10** (designated ML-236B) was also isolated as a hypercholesterolemic agent from cultures of the fungus *P. citrinum*.³⁰ ML-236A (**11**) and ML-236C (**12**) were further isolated from this fungus. Of the three compounds, **10** was most active in inhibiting cholesterol synthesis to 50% of control at a concentration of 26 nM, compared to 280 nM for **12** and 590 nM for **11**.³⁰ However, the sodium acid of **1** was found to be more than twice as active as the sodium acid of **10** as an inhibitor of HMG-CoA reductase, with respective K_i values of 0.64 nM and 1.4 nM.¹⁹ As also shown in an acute assay for rats, the orally administered sodium salt of **1** inhibited cholesterol biosynthesis at a concentration of 46 $\mu\text{g kg}^{-1}$ in 50% inhibitory dose compared to a 50% inhibitory dose of 290 $\mu\text{g kg}^{-1}$ for the sodium salt of **10**.¹⁹ In 1981, Lam *et al.*

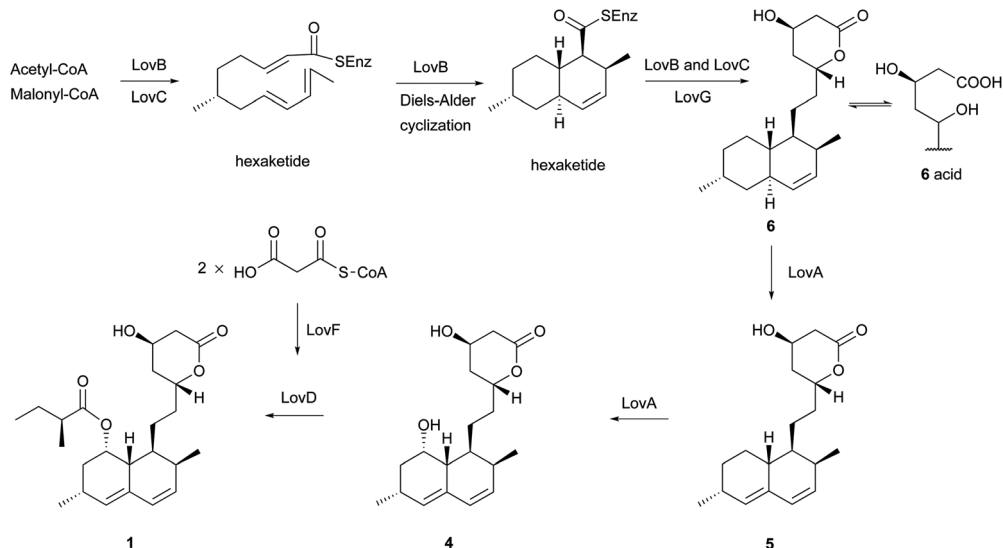




discovered 4a,5-dihydrocompactin (**13**) from the fungus *P. citrinum*.³¹ 3 α -Hydroxy-3,5-dihydro-ML-236C (**14**) was isolated as a white amorphous solid, in its sodium salt form, from

Paecilomyces viridis.³² Compound **14** along with 3,5-dihydro-3-oxo-ML-236C (**15**), compactin acid (**16**), and the ethyl ester of compactin (**17**) were isolated and identified from *Eupenicillium*





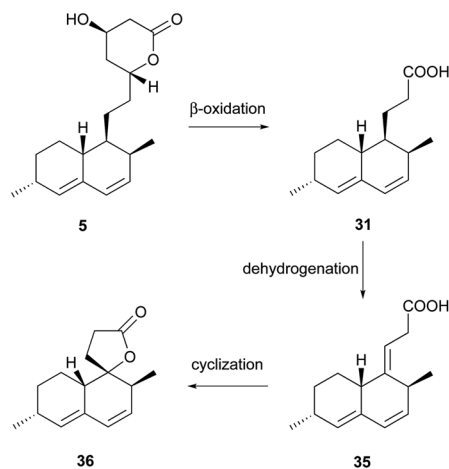
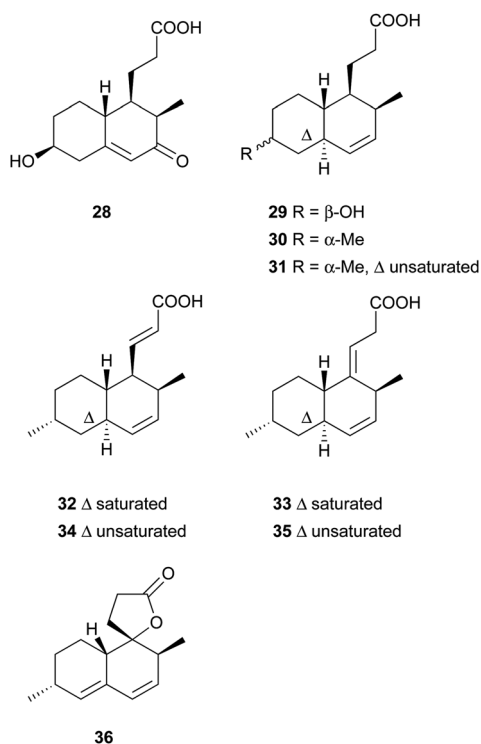
Scheme 2 The proposed biosynthetic pathway for 1.

javanicum.³³ Monacophenyl (**18**) and aromonacolin A (**19**), two unusual aromatic monacolin analogs, were isolated from *Monascus purpureus*-fermented rice (red yeast rice).^{34,35} In the course of further investigation using red yeast rice, five cytotoxic dehydromonacolins, namely dehydromonacolin N (**20**), dehydromonacolin L (**21**), α,β -dehydrodihydromonacolin L (**22**), α,β -dehydrodihydromonacolin K (**23**), and dehydromonacolin K (**24**), together with the ethyl ester of **1** (**25**), the methyl ester of **1** acid (**26**) and the methyl ester of **3** (**27**) were isolated and characterized.³⁶

3.2 Monacolin derivatives

Simple decalin derivatives are usually found in monacolin-producing fungi. From the biosynthetic point of view, they are presumed to be formed by β -oxidation or/and dehydrogenation of monacolins.³⁷

Antifungal activity-guided fractionation led to the isolation of the two decalin derivatives, eujavanoic acids A (**28**) and B (**29**) from *E. javanicum*.³³ A heptaketide (**30**) and a decalin derivative, monascusic acid A (**31**) were isolated from red yeast rice fermented by *M. purpureus*.³⁸ Further chemical investigation using red yeast rice provided five new decalin derivatives, monascusic acids B–E (**32–35**) and monascusic lactone A (**36**).³⁷ **30–34** showed the immunosuppressive effect on human T cell proliferation in a dose-dependent manner from 10 to 100 μM .³⁷ Compound **36**, the first reported naturally-occurring decalin derivative possessing a spiro lactone at the C-1 position, is biosynthetically related to monacolin L (Scheme 3).



Scheme 3 The proposed biosynthesis of 36.



3.3 Side chains with a 3-oxopropanol or its derivative

The skeleton of these compounds could have the same construction pattern from some acetate units *via* a polyketide pathway, and like lovastatin (**1**) biosynthesis, an intramolecular Diels–Alder reaction seems to be responsible for their decalin scaffold formation. They share a highly substituted *trans*-decalin, which is modified by methyls, hydroxyl, double bond and side chain groups or moieties. More importantly, the side chain with a β -ketoaldehyde seems to be crucial for some biological activities.

Stemphyloxin I (**37**) and II (**38**), two nonspecific phytotoxic ferric ion chelates, were isolated from the plant pathogenic fungus *Stemphylium botryosum*.^{39–41} They are highly functionalized *trans*-decalin derivatives and exhibited high toxicity towards tomato and eggplant. The presence of β -ketoaldehyde functional group appears to be crucial for both toxicity and chelation of iron.⁴² Six phytotoxins, betaenones A–F (**39–44**), have been isolated from the cultures of *Phoma betae*, a fungus causing leaf spot disease of sugar beet.^{43,44} The biosynthesis of **40** involving an intramolecular Diels–Alder reaction was studied using feeding experiments (Fig. 1).^{45,46}

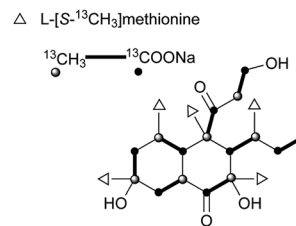
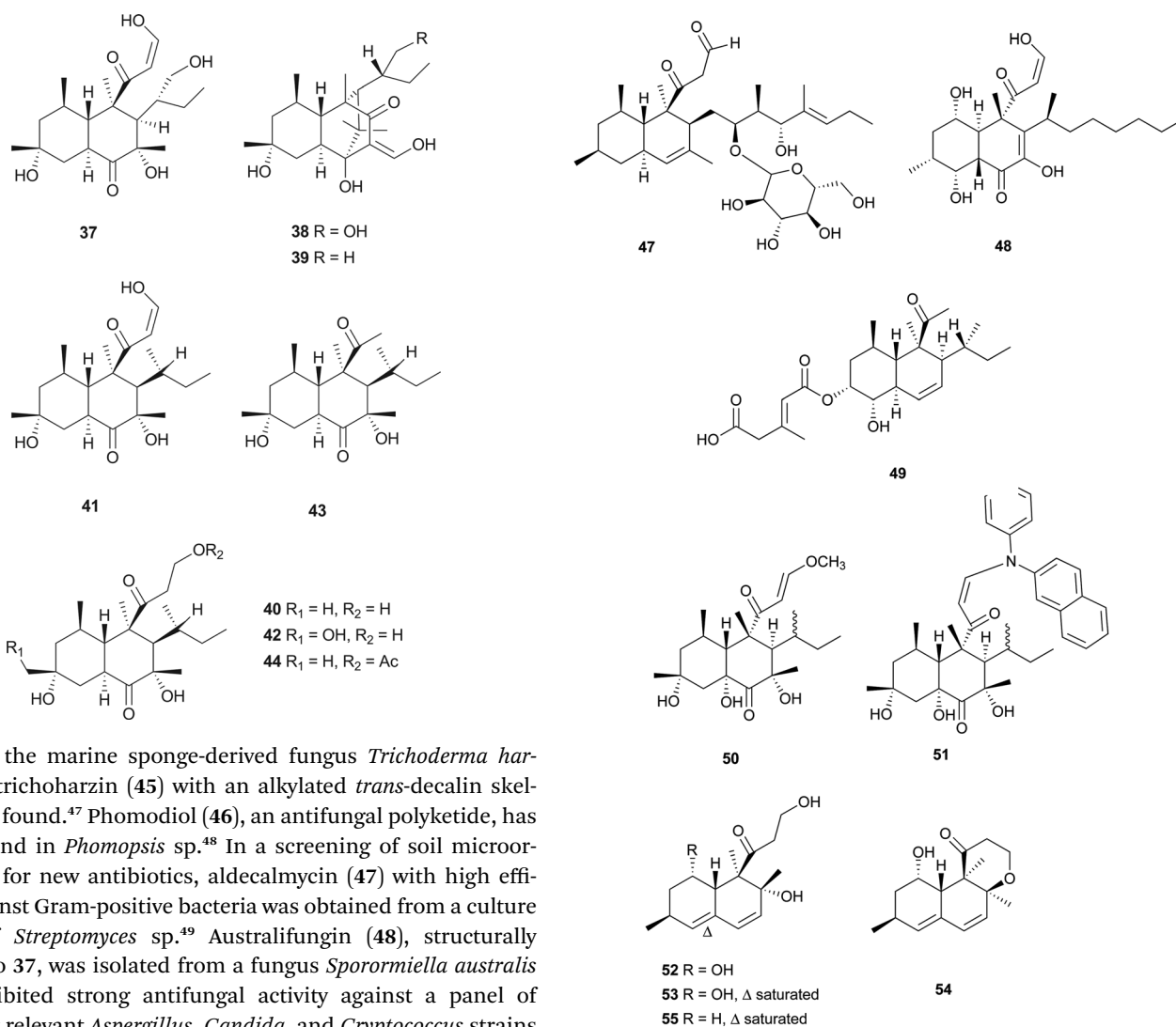


Fig. 1 Biosynthetic origins of carbons in **40**.

with minimum inhibitory concentration (MIC) values ranging from 0.015 to 1.0 $\mu\text{g mL}^{-1}$.⁵⁰ It was also the first reported non-sphingosine-based inhibitor of sphingolipid biosynthesis.



From the marine sponge-derived fungus *Trichoderma harzianum*, trichoharzin (**45**) with an alkylated *trans*-decalin skeleton was found.⁴⁷ Phomodiol (**46**), an antifungal polyketide, has been found in *Phomopsis* sp.⁴⁸ In a screening of soil microorganisms for new antibiotics, aldecalmycin (**47**) with high efficacy against Gram-positive bacteria was obtained from a culture broth of *Streptomyces* sp.⁴⁹ Australifungin (**48**), structurally related to **37**, was isolated from a fungus *Sporormiella australis* and exhibited strong antifungal activity against a panel of clinically relevant *Aspergillus*, *Candida*, and *Cryptococcus* strains



Another polyketide, deoxynortrichoharzin (**49**) was obtained from the saltwater culture of *Paecilomyces* cf. *javanica* isolated from the marine sponge *Jaspis* cf. *coriacea*, which did not show any cytotoxic activity against solid tumor cells in culture.⁵¹ Two betaenone derivatives, 10-hydroxy-18-methoxybetaenone (**50**) and 10-hydroxy-18-*N*-2-naphthyl-*N*-phenylaminobetaenone (**51**) were produced by an undescribed fungus of the genus *Microsphaeropsis* isolated from the Mediterranean sponge *Aplysina aerophoba*.⁵² Derivative **50** showed inhibitory activity against PKC- ϵ , CDK4, and EGF receptor tyrosine kinases, with IC₅₀ values of 36.0, 11.5, and 10.5 μ M, respectively, whereas **51** did not. Decumbenones A (**52**) and B (**53**), together with versiol (**54**) were isolated from the fungus, *Penicillium decumbens*.⁵³ Only one of them, compound **52**, inhibited melanization in *Magnaporthe grisea*, the rice blast pathogen, suggesting the importance of the structural units of the diene and COCH₂CH₂OH for its inhibition efficacy.

Aspermytin A (**55**), a heptaketide with a *trans*-decalin framework, was reported from a cultured marine fungus, *Aspergillus* sp., inhabiting the mussel *Mytilus edulis*.⁵⁴ It induced significant neurite outgrowth in rat pheochromocytoma (PC-12) cells at concentration of 50 μ M. FR225654 (**56**), a novel gluconeogenesis inhibitor was isolated from the culture of *Phoma* sp.⁵⁵ Eujavanicols A–C (**57–59**) were purified from an antifungal-active fraction of *E. javanicum*, but showed no antifungal activity.⁵⁶ More recently, Tandyukisin (**60**), a novel decalin derivative with an enolic β -ketoaldehyde, was produced by a marine sponge-derived fungus, *T. harzianum*.⁵⁷ It exhibited moderate cytotoxic activity against the murine P388 leukemia, the human HL-60 leukemia,

and the murine L1210 leukemia cell lines with IC₅₀ values ranging from 41 to 55 mM.

3.4 Side chains with a pentadienoic acid

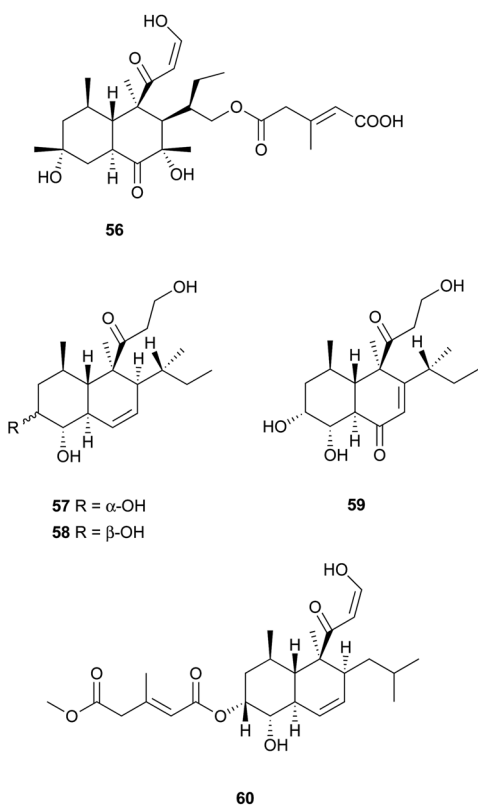
Most of these carboxylic acids have been detected in the cultures of *Penicillium* species, and possess a penta-2,4-dienoic acid unit connected to a *trans*-decalin, showing a plethora of interesting activities. A few *cis*-decalin skeletons can also be found, which seems to play an important role for their relevant biological activities.

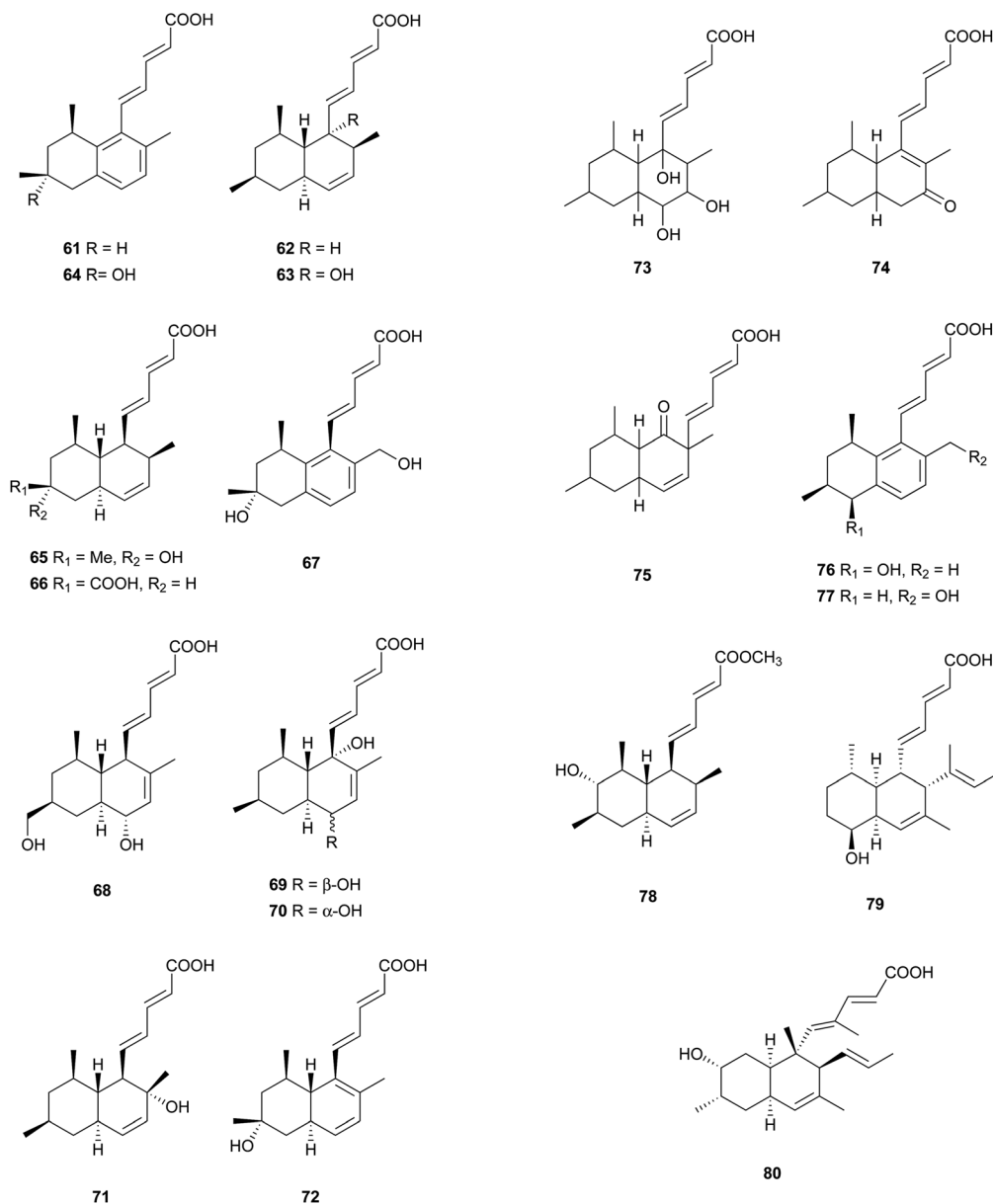
Tanzawaic acids A–D (**61–64**) from *Penicillium citrinum*,⁵⁸ tanzawaic acids E (**65**) and F (**66**) from a marine-derived strain of *Penicillium steckii*,⁵⁹ tanzawaic acids G (**67**) and H (**68**) from an endophytic fungus *P. citrinum*,⁶⁰ and tanzawaic acids I–L (**69–72**) from a soil derived *Penicillium* sp.⁶¹ are representative *trans*-decalin pentadienoic acids. Among metabolites **61–64**, only **62** significantly inhibited superoxide anion production in human neutrophils (IC₅₀ = 26 μ g mL⁻¹).⁵⁸ Acids **67** and **68** exhibited no cytotoxicity on the growth of the L5178Y mouse lymphoma cell line (IC₅₀ > 10 μ M) and no antimicrobial activity against *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Escherichia coli* at a concentration of 64 μ g mL⁻¹.⁶⁰ Compounds **61**, **65**, and **71** showed inhibition of the conidial germination in the rice blast fungus *Magnaporthe oryzae* at concentrations of around 25 μ g mL⁻¹.⁶¹ Ōmura and co-workers reported five anticoccidial agents: hynapenes A–C (**73–75**), from a soil-inhabiting *Penicillium* sp. that were effective against monensin-resistant *Eimeria tenella*,⁶² and arohynapenes A (**76**) and B (**77**) from a water-inhabiting *Penicillium* sp.⁶³ Bioassay-guided fractionation led to the isolation of coprophilin (**78**), a *trans*-decalin-pentanoic acid methyl ester from an unidentified fungus.⁶⁴ **78**, as an anti-coccidial agent, inhibited the growth of *E. tenella* with an MIC value of 1.5 μ M, compared to that of 123 μ M for **73**, 34.7 μ M for **74** and **75**, 35 μ M for **76**, and 7.0 μ M for **77**.^{62,63} Phomopsidin (**79**) with a *cis*-decalin core, was obtained from *Phomopsis* sp., and is a new inhibitor of the assembly of microtubule proteins at an IC₅₀ of 5.7 μ M.⁶⁵ Using ¹³C-labeled precursors, **79** was proposed to be a trimethylated nonaketide (Fig. 2).⁶⁶ Biological tests for many structurally related compounds **61–64** suggested that the *cis*-decalin structure of **79** is important for the anti-microtubule activity.⁶⁶ In antisense-based screening strategies, pannomycin (**80**) was isolated from *Geomyces pannorum*.⁶⁷ It exhibited weak antibacterial activity.

3.5 Decalins with oxygenated diene/triene/tetraene side chains

These kinds of decalin derivatives are highly methylated and oxygenated polyketides, and typically have a 6-, 7-, or 9-membered side chain similar to pentadienoic acids.

A weakly antifungal polyketide, fusarielin A (**81**), and three biosynthetically related fusarielins B–D (**82–84**), were isolated from *Fusarium* sp.⁶⁸ Dehydrochlorofusarielin B (**85**) is a mild antibacterial compound isolated from the marine-derived fungus *Aspergillus* sp.⁶⁹ In addition, **81** and **82** were also isolated from this fungus and demonstrated weak antibacterial activity. ICM0301A–H (**86–93**) were inhibitors of angiogenesis in human





umbilical vein endothelial cells (HUVECs) with IC_{50} values of 2.2–9.3 $\mu\text{g mL}^{-1}$.⁷⁰ Six fungal-derived polyketides, cladobotic acids A–F (**94–99**), were isolated from a *Cladobotryum* species from New Zealand.⁷¹ All of them showed modest growth

inhibition against the murine P388 leukemia cell line with IC_{50} values of 6.6, 27.8, 19.4, 24.9, 1.4, and 15.6 μM , respectively, and were even active against *Bacillus subtilis* and *Candida albicans*. Furthermore, compound **98** was active against *Trichophyton mentagrophytes* and *Cladosporium resinae*. Feeding experiments with ^{13}C -labeled precursors disclosed their polyketide biosynthesis from 11 intact C_2 units (Fig. 3).^{69,71} Antifungal bioassay-guided isolation yielded two new *cis*-decalin derivatives, **100** and **101**, from an endophytic *Penicillium* sp. isolated from the inner bark of the Pacific yew tree, *Taxus brevifolia*.⁷² Both were selectively active against the plant pathogen *Sclerotinia sclerotiorum* (17 mm zone at 1.1×10^{-4} $\mu\text{mol/disk}$ for **100**; 16 mm zone at 3.4×10^{-4} $\mu\text{mol/disk}$ for **101**). In a screening program for potent compounds inducing osteoblast differentiation in C3H10T1/2 cells, decalpenic acid (**102**) bearing a tetraenoic acid side chain

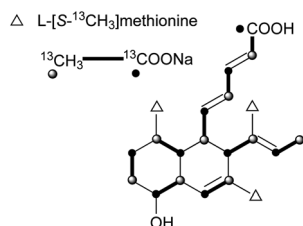
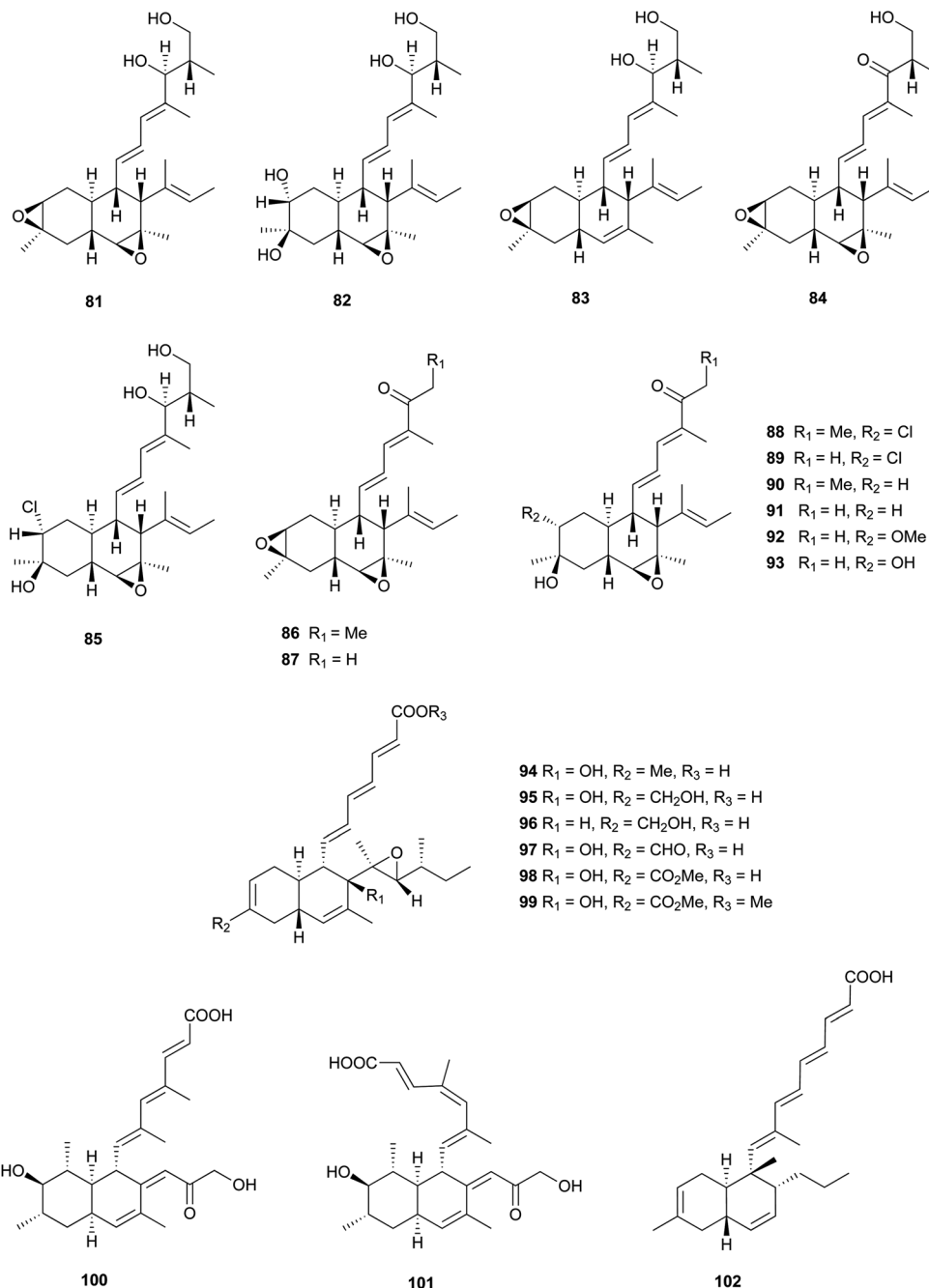


Fig. 2 Biosynthetic origins of carbons in **79**.





was isolated from *Penicillium verrucosum*.⁷³ Through activation of retinoic acid receptor γ , it induces early osteoblastic markers in pluripotent mesenchymal cells.⁷⁴

3.6 Pyrone derivatives

Pyrone derivatives are formed when the pyrone ring is substituted by the methoxyl, aldehyde, hydroxymethyl, amino or ethanolamide group and connected to the decalin framework directly *via* carbon–carbon bond. Most of these decalin derivatives possess the *cis*-decalin system. The modified decalin motif with two types of relative configurations has been proposed to

be formed *via* a biological intramolecular Diels–Alder reaction to give *exo* or *endo* products.^{75,76}

Solanapyrones A–E (**103–107**), the phytotoxins, were isolated from the fungus *Alternaria solani* which causes early blight disease in tomato and potato plants.^{77–79} Phytotoxin **103** was reported to be an inhibitor of DNA polymerase β and γ , with IC₅₀ values of 30 and 37 μ M, respectively.⁷⁸ The biosynthetic pathway for **103** was investigated by feeding experiments and gene expression studies (Scheme 4).^{10,76,79} The decalin scaffold of **106** and **107** was first synthesized by a domino Michael reaction (Scheme 5).⁸⁰ In order to complete the total synthesis of **103** and **104**, Lygo *et al.* reported an



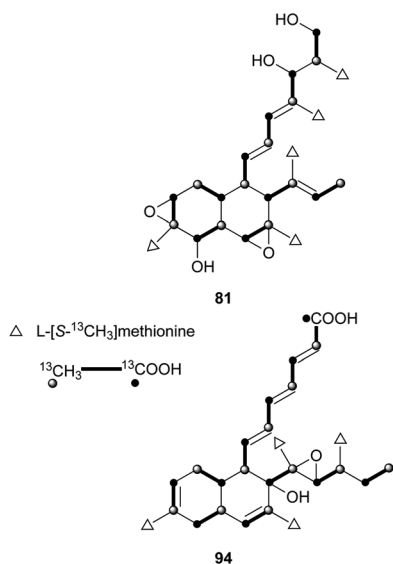
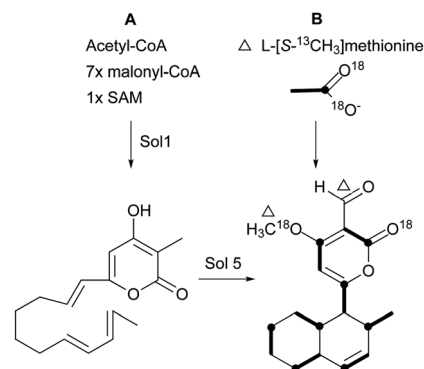
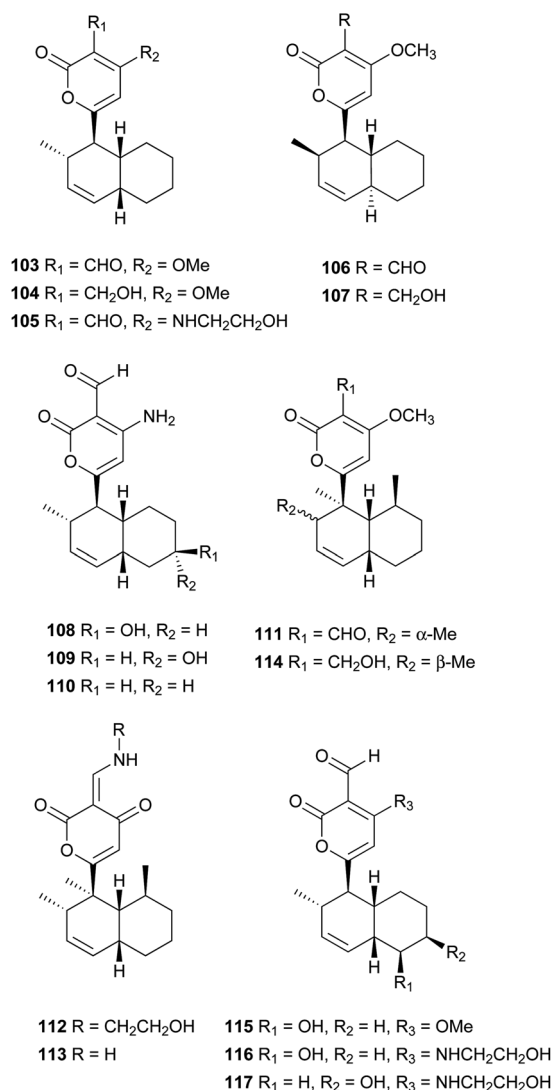


Fig. 3 Biosynthesis of **81** and **94** on the basis of the data from feeding experiments.

optimized IMDA cycloaddition to the decalin fragment (Scheme 6).⁸¹ MacMillan and co-workers developed a new powerful organocatalytic IMDA reaction protocol to achieve the asymmetric synthesis of **106** (Scheme 7).⁸² Chemical investigation of an unidentified filamentous marine fungus led to the isolation of new phytotoxic compounds, solanapyrones E–G (**108–110**) and the known compound **105**.⁸³ Compound **108**, with a *cis*-decalin unit, has the same compound name as the *trans*-decalin derivative **107**. Solanapyrones J–M (**111–114**), new solanapyrone analogues with modest antifungal and antibacterial activities, were obtained from an unidentified fungicolous fungus.⁸⁴ Nigrosporapyrones A–C (**115–117**) were isolated from the marine-derived fungus *Nigrospora*.⁸⁵ Compound **115** exhibited a weak antibacterial activity with an MIC value of 128 $\mu\text{g mL}^{-1}$.

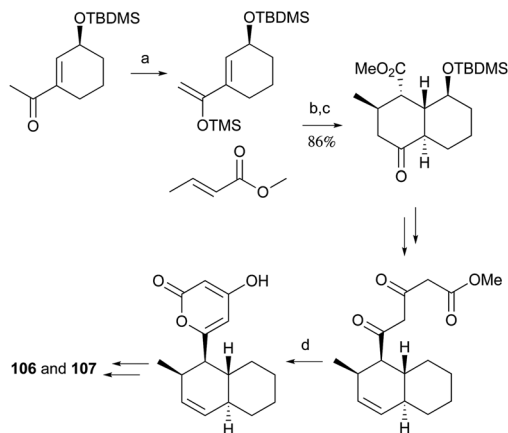
3.7 Macrolides

Nodusmicin (**118**) and nargenicin (**119**) represent a class of macrolide antibiotics that were isolated from *Saccharopolyspora hirsuta* by Whaley *et al.* in 1980⁸⁶ and from *Nocardia argentinensis* by Celmer *et al.* in the same year, respectively.⁸⁷ They possess a ten-membered lactone ring fused to an oxygen-bridged *cis*-decalin system. The acetylated products, 18-*O*-acetylnodusmicin (**120**) and 18-*O*-acetylnargenicin (**121**), were also isolated and identified from *N. argentinensis*.⁸⁸ A more complex analog, coloradocin (**122**) (luminamicin) with an additional 14-membered macrolactone containing an enol ether in conjugation with an unsaturated cyclic anhydride functionality, was found from the actinomycete strains, *Actinoplanes coloradoensis* and *Nocardioides* sp.⁸⁹ Compound **122** showed selective activity against anaerobic and microaerophilic bacteria whereas compounds **118** and **119** inhibited some aerobic bacteria, thereby suggesting the importance of the additive macrocyclic moiety.⁹⁰ The biosynthetic origin of this family was investigated

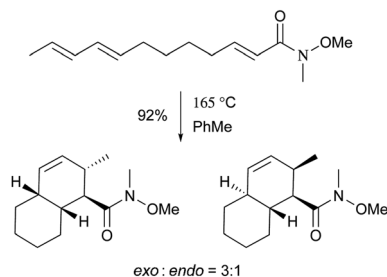


Scheme 4 (A) The prosolanapyrone synthase (PSS) encoded by Sol1 catalyzes octaketide prosolanapyrone formation and then a flavin-dependent oxidase (solanapyrone synthase, SPS) encoded by Sol5 catalyzes Diels–Alder cyclization to form **103**. (B) Incorporation of labeled acetate and methionine into **103**.

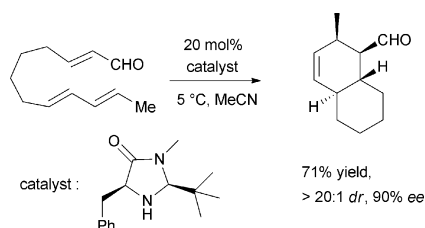




Scheme 5 The first total syntheses of **106** and **107**: the domino Michael reaction to decalone and the general biosynthetic strategy of pyrone. (a) LDA, TMSCl, 93%; (b) MeLi, methyl crotonate, HMPA, THF; (c) MeONa, MeOH; (d) DBU, benzene, 93%.



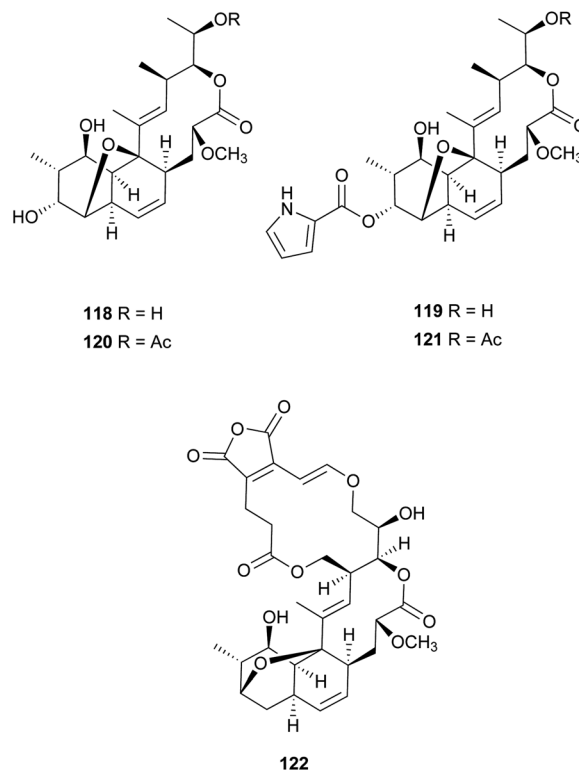
Scheme 6 The exo-selective thermal Diels–Alder reaction used for the total syntheses of **103** and **104**.



Scheme 7 MacMillan's effective organocatalytic IMDA reaction to the decalin scaffold in the total synthesis of **106**.

through feeding experiments, as shown for compound **122** in Fig. 4.^{88,91} Compared with the assembly of a polyketide chain in compounds **118**–**121**, **122** also involves an acetate and a succinate unit incorporated into the additional 14-membered macrolactone.

In a broad screening program for active secondary metabolites produced by myxobacteria, *Sorangium cellulosum* was found to produce a novel polyketide, chlorotonil A (**123**), with a unique *gem*-dichloro-1,3-dione functionality in a 14-membered macrolide ring fused to an unsaturated *trans*-decalin.⁹² The total synthesis of **123** was reported by Rahn and Kalesse in the same year.⁹³ The decalin system was prepared by



a highly stereoselective halogen (bromine)-directed Diels–Alder reaction over standard Diels–Alder routes (Scheme 8). More recently, antibacterial activity-guided fractionation yielded the antibiotic anthracimycin (**124**) from a *Streptomyces* species isolated from near-shore marine sediments by the group of Fenical.⁹⁴ It exhibited significant inhibition of Gram-positive pathogens such as *Bacillus anthracis* and clinically-relevant methicillin-resistant *S. aureus* (MRSA) with MIC values of 0.031 and 0.06 $\mu\text{g mL}^{-1}$, respectively. The semi-synthetic derivative, dichloro-anthracimycin has similar activity against Gram-positive pathogenic bacteria as **124**, but is active against Gram-negative pathogens. However, **124** lacked activity against Gram-negative pathogens or was weakly active against them. The biosynthesis of compounds **123** and **124** could be proposed *via* a polyketide pathway with 11 acetate units.

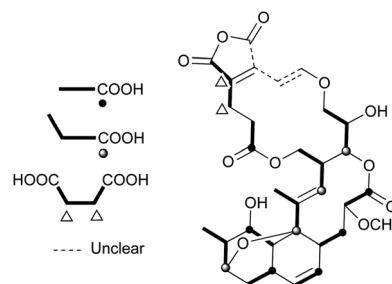
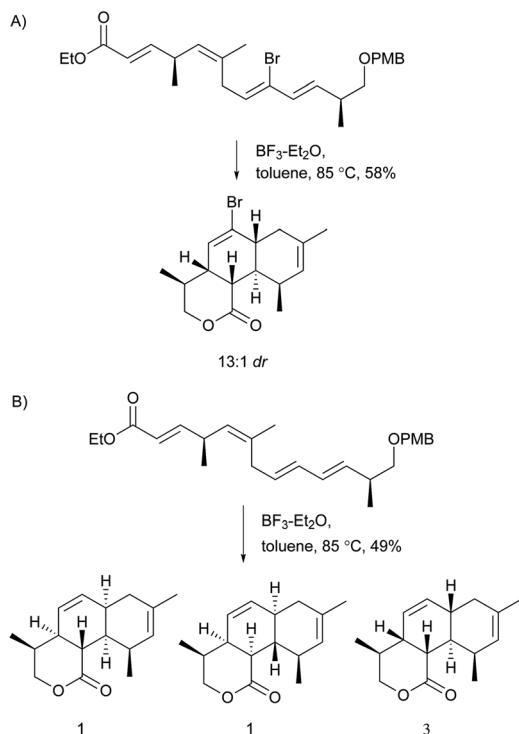
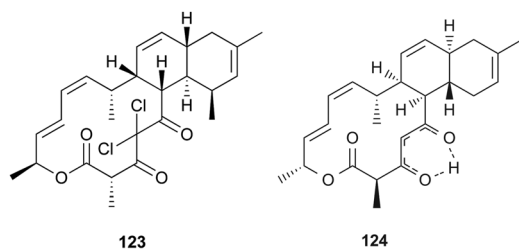


Fig. 4 Biosynthetic origin of **122** on the basis of the data from feeding experiments.





Scheme 8 Synthesis of the decalin system in compound **123**. A) Highly stereoselective halogen (bromine)-directed Diels–Alder reaction. B) The same reaction condition without bromine substituent.



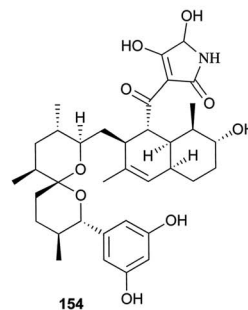
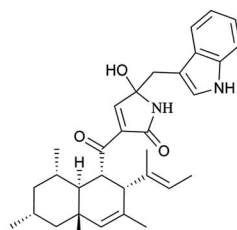
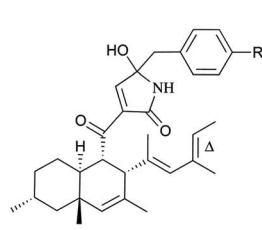
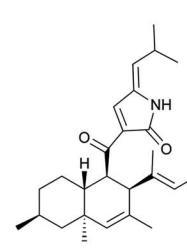
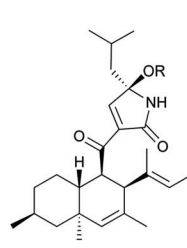
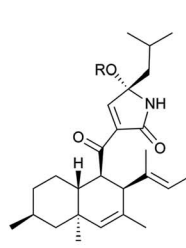
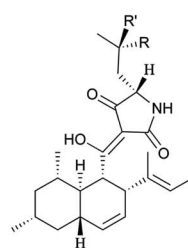
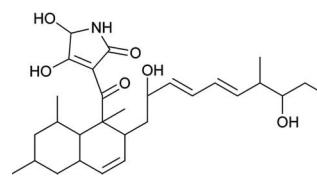
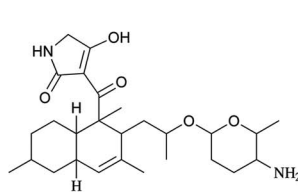
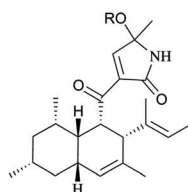
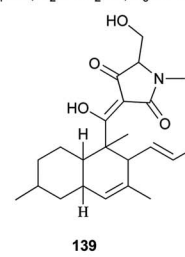
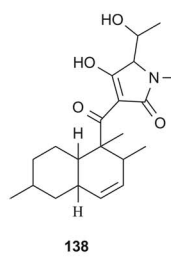
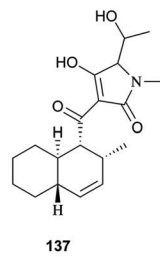
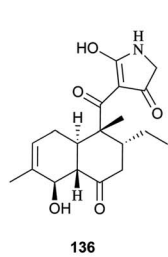
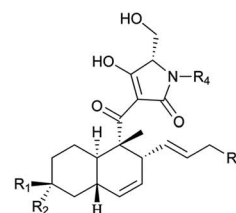
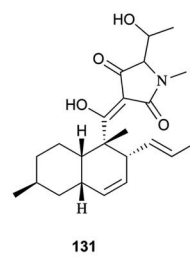
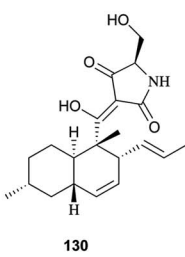
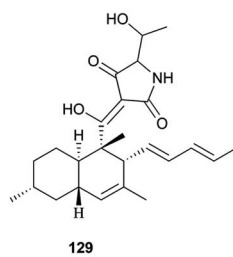
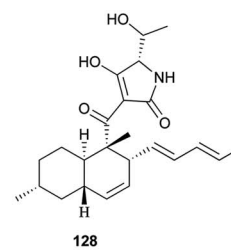
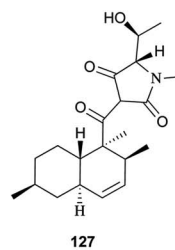
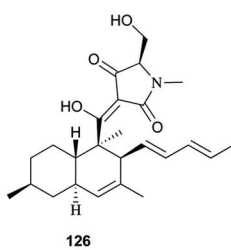
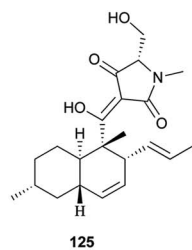
3.8 Pyrrolidine-2-one

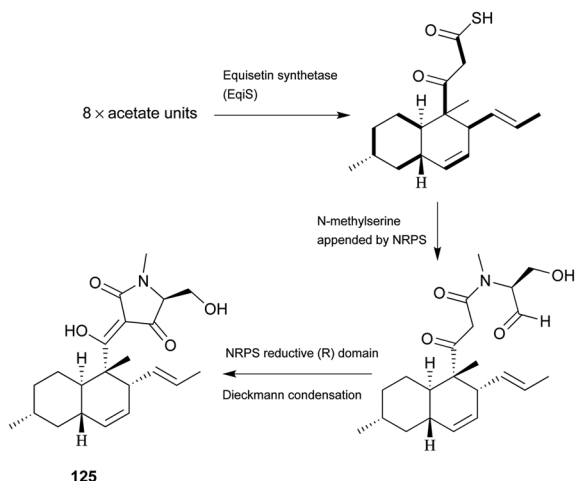
Pyrrolidine-2-one, an important biologically active moiety, is often found in fungal metabolites arising from the mixed PKS-nonribosomal peptide synthetase (NRPS) pathway and has been reported in several reviews.^{95–97} However, to the best of our knowledge, there is a dearth of information on pyrrolidine-2-one metabolites. Here, we highlight all those compounds that preferentially cooperate with a decalin system. Decalin-type pyrrolidine-2-one derivatives are comprised of two important biosynthetic units. The first one is a linear C₁₄, C₁₆, C₁₈ or more C_n-fragment(s) with several methyl substituents. This linear polyketide unit is then cyclized by a biological intramolecular Diels–Alder cycloaddition to form the decalin scaffold. The second one is comprised of amino acids serine, threonine, leucine, phenylalanine, tyrosine or tryptophan-derived heterocyclic ring (pyrrolidine-2-one) joined to the decalin system. Typically, as a character of this family, this ring is tetramic acid that may also undergo a series of tautomeric shifts to form its

derivatives, for example, having a reduced carbonyl carbon. Unfortunately, the exact ‘timing’ of *N*-methylation for this kind of compound remains unclear. These compounds have significant inhibitory activities against Gram-positive bacteria.

Equisetin (**125**), showing considerable biological activity in an array of assays and inhibiting HIV-1 integrase,⁹⁶ was first isolated in 1974 from *Fusarium equiseti* by Burmeister *et al.*^{98,99} It comprises a substituted decalin system bearing a quaternary stereogenic center and an *N*-methylserine-derived heterocycle, tetramic acid. The proposed biosynthesis of **125** catalyzed by a PKS/NRPS hybrid is shown in Scheme 9.^{100–102} The total synthesis has already been reported by the groups of Danishefsky,¹⁰³ Shishido,¹⁰⁴ and Dixon.¹⁰⁵ More recently, Gao and co-workers reported synthetic studies of **125** and the biosynthetically related (+)-fusarisetin A based on the proposed biosynthetic hypothesis (Scheme 10).¹⁰⁶ A cyclization sequence involving an intermolecular Diels–Alder reaction followed by a Dieckmann cyclization yielded **125** (Scheme 11). Compound **125** and a new enantiomer, phomasetin (**126**), were isolated from *Fusarium heterosporum* and *Phoma* sp., respectively.¹⁰⁷ They are almost equally active in inhibiting recombinant integrase enzyme *in vitro* with IC₅₀ values of 7–20 μM. Cryptocin (**127**), showing activity against a wide variety of plant pathogenic fungi (MIC of 0.78–1.56 μg mL⁻¹) but not against human pathogenic fungi, was isolated from an endophytic fungus *Cryptosporiopsis cf. quercina* arising from the stems of *Tripterogium wilfordii*.¹⁰⁸ Two endophytic *Alternaria* species produce another antibiotic called altersetin (**128**).¹⁰⁹ It significantly inhibited several pathogenic Gram-positive bacteria with MIC values of no more than 1 μg mL⁻¹, but has no or much less effect on Gram-negative bacteria and pathogenic yeast. Similarly, *Coniochaeta ellipsoidea* produces a tetramic acid, coniosetin (**129**), with strong efficacy against Gram-positive bacteria and sensitive against resistant microbial pathogens, especially the multi-drug-resistant *S. aureus* at a concentration of 0.3 μg mL⁻¹.¹¹⁰ From the co-culture of *T. harzianum* and *Catharanthus roseus*, an equisetin derivative without the *N*-methyl, named trichosetin (**130**), was isolated.¹¹¹ Interestingly, this compound was not detected in the individual cultures. Cissetin (**131**) with a *cis*-decalin ring fusion exhibited similar antibiotic activities as those of compounds **125** and **130** containing a different *trans*-decalin system, suggesting the possible biological function of tetramic acid.¹¹² Ophioisetin (**132**) was isolated from the mycopathogenic fungus *Elaphocordyceps ophioglossoides*.¹¹³ Co-culture of the fungus *Fusarium pallidroseum* with the bacterium *Saccharopolyspora erythraea* afforded *N*-demethylphioisetin (**133**) and pallidrossetins A and B (**134**, **135**), along with compounds **125** and **132**.¹¹⁴ Compound **125** exhibited a GI₅₀ of 144 nM against the leukemia cell line CCRF-CEM. Following a histone deacetylase (HDAC)-based yeast screening method, streptosetin A (**136**) was purified and found to show weak inhibitory activity against yeast Sir2p and human SIRT1 and SIRT2.¹¹⁵ The structure of compound **136** was confirmed by X-ray crystal structure analysis and CD theoretical calculation. In an antibiotic screening program, methiosetin (**137**) was discovered as a modest anti-bacterial agent against *S. aureus* and *Haemophilus influenzae*.¹¹⁶ CJ-17,572 (**138**) and CJ-21,058 (**139**) were isolated from *Pezizula*







Scheme 9 The biosynthetic origin of **125**. Bold bonds in the polyketide portion represent ^{13}C -labelled acetate units. The timing of N-methylation is unclear.

sp. and an unidentified fungus, respectively.^{117,118} Two structurally unusual tetramic acids, ascosalipyrrolidinones A (**140**) and B (**141**), were obtained from an endophytic fungus, *Ascochyta salicorniae* isolated from the green alga *Ulva* sp.¹¹⁹ The antimicrobial, anti-algal, nematicidal, antiplasmodial, anti-trypanosomal and cytotoxic properties as well as brine shrimp lethality of **141** were assessed. BU-4514N (**142**) with significant NGF-mimic activity and antibacterial efficacy against Gram-positive bacteria, and delaminomycin A (**143**), a novel

extracellular matrix receptor antagonist, have been isolated from the fermentation broth of *Microtetraspora* sp.¹²⁰ and *Streptomyces albus*,¹²¹ respectively. Sch 210971 (**144**) and its epimer, Sch 210972 (**145**), showed potent inhibitory activity (IC_{50} of 1.2 μM and 79 nM, respectively) in the chemokine receptor CCR-5 *in vitro* binding assay, indicating an interesting structure-activity relationship of the relative configuration at tetramic acid.¹²² Myceliothermophins A–E (**146–150**) (Fig. 5) (see Supporting Information of ref. 123) are the decalin polyketides containing tetramic acid moieties which were isolated from a fungus *Myceliophthora thermophila*.¹²³ Only compounds **146**, **148**, and **150** exhibited inhibitions against four cancer cell lines, A549, Hep3B, MCF-7, and HepG2, indicating the importance of the relative configuration of tetramic acids. Oteromycin (**151**)¹²⁴ and ZG-1494 α (**152**),¹²⁵ two phenylalanine-derived tetramic

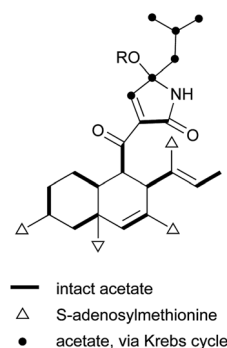
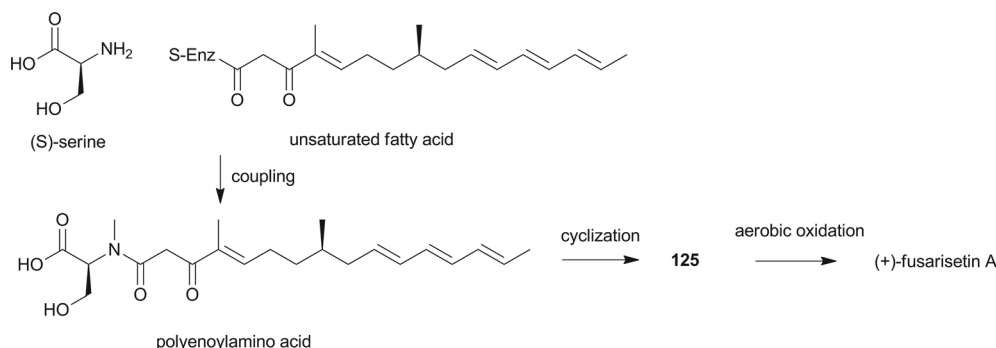
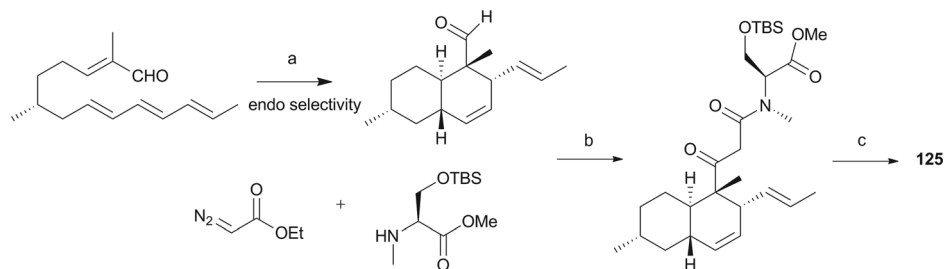


Fig. 5 Biosynthetic origin of myceliothermophins A–D (**146–149**).

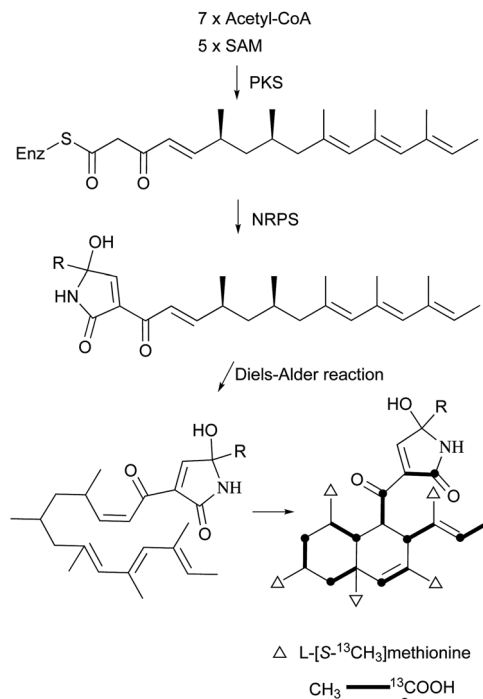


Scheme 10 Biosynthetic hypothesis for the total syntheses of **125** and (+)-fusarisetin A.



Scheme 11 Key construction of decalin ring system and the preparation of **125**. (a) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, -78°C , CH_2Cl_2 , 20 min; (b) 0°C , 1.5 h; then (S)-serine derivative, DMAP, toluene, 118°C , 18 h; (c) NaOMe, MeOH, 25°C , 2 h, 72%, d.r. = 3 : 1 (at C3); then HF, CH_3CN , 25°C , 2 h, 95%.





Scheme 12 Proposed biosynthesis of **153** and the labeling patterns observed in feeding experiments.

acids, were isolated from an unidentified fungus and *Penicillium rubrum*, respectively. Compound **151** was reported to be a novel antagonist of endothelin receptor while **152** was an inhibitor of platelet-activating factor acetyltransferase. An endophytic fungus, *Codinaeopsis gonytrichoides*, produced an antimalarial compound that is active against *Plasmodium falciparum* with an IC₅₀ of 4.7 μM.¹²⁶ This metabolite, with its unusual heterocyclic unit linking indole and decalin fragments, was named codinaeopsin (**153**) and was proposed to be biosynthesized by the PKS-NRPS hybrid involving an IMDA-like addition (Scheme 12).¹²⁶ A hexacyclic secondary metabolite, integramycin (**154**) isolated from *Actinoplanes* sp., exhibited an IC₅₀ value of 4 μM against HIV-1 integrase.¹²⁷

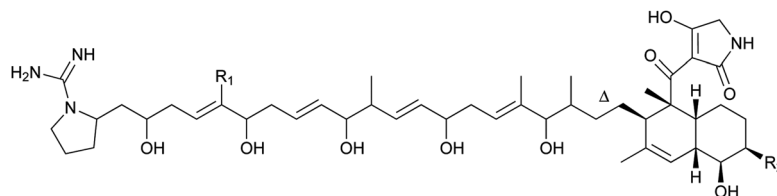
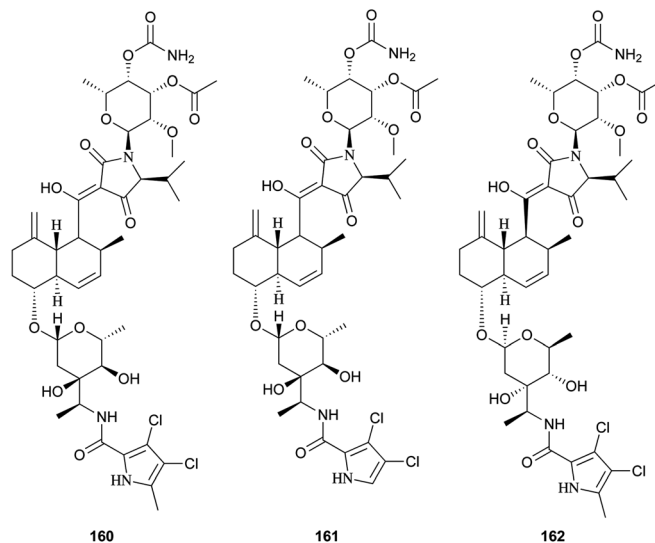
Lydicamycin (**155**) with a long side chain proved to be a potent antibiotic against Gram-positive bacteria such as *B. subtilis* and *S. aureus* with MIC values of 1.5 and 6.2 μg mL⁻¹, respectively.^{128,129} It was isolated from the culture broth of an

actinomycete, *Streptomyces lydicus*. From another actinomycete, *Streptomyces platensis*, four novel congeners, TPU-0037-A-D (**156–159**), were obtained.¹³⁰ They also exhibited inhibition of some Gram-positive bacteria with MIC values of 1.56–12.5 μg mL⁻¹.

Recently, three novel broad-spectrum antibiotics (**160–162**) active against Gram-positive bacteria by inhibiting DNA gyrase and bacterial topoisomerase IV were reported.^{131–133} They consist of a *trans*-decalin, tetramic acid, two unusual sugars, and dichloropyrrole carboxylic acid. Kibdelomycin (**160**) and its demethylated congener kibdelomycin A (**161**) were isolated from a previously undescribed strain of *Kibdelosporangium* by Singh and co-workers.¹³¹ Compound **160** also demonstrated potent and selective activity against toxigenic *Clostridium difficile*.¹³² Amycolamicin (**162**) (AMM) was obtained from the culture broth of the soil actinomycete, *Amycolatopsis* sp.¹³³

3.9 4-Hydroxy-2-pyridone alkaloids

4-Hydroxy-2-pyridone alkaloids have attracted much attention in the scientific community owing to their diverse biological activities.¹³⁴ A review focusing only on their structures and synthetic approaches has been published.¹³⁴ Here, we mainly pay attention to the biological activities and biosynthesis of

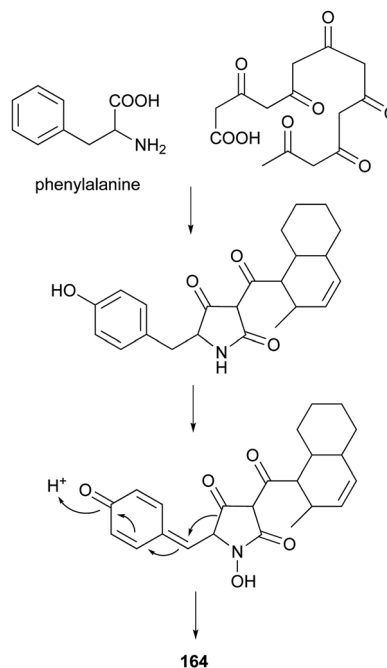


- 155** R₁ = Me, R₂ = OH
156 R₁ = H, R₂ = OH
157 R₁ = Me, R₂ = H, Δ unsaturated
158 R₁ = H, R₂ = H
159 R₁ = Me, R₂ = H

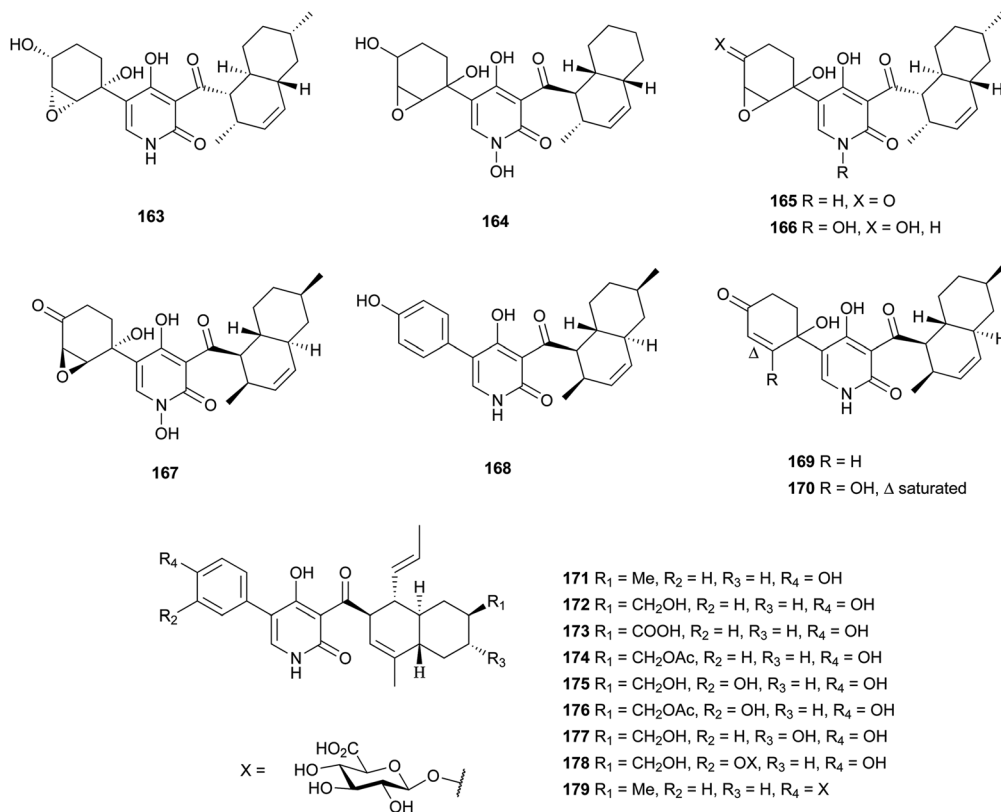


4-hydroxy-2-pyridone alkaloids with a decalin scaffold, and include some recent discoveries. Their biosynthesis is related to that of polyketide tetramic acid, phenylalanine-derived heterocyclic ring (*vide supra*, Section 3.8). In their biosynthesis, the key rearrangement of the tetramic acid ring eventually results in the construction of the 4-hydroxy-2-pyridone.

Chemical investigation of an EtOAc extract from the coprophilous fungus *Apiospora montagnei* led to the isolation of an antifungal metabolite named apiosporamide (**163**).¹³⁵ Fischerin (**164**) was isolated from an ascomycete, *Neosartorya fischeri*. It was toxic to mice, causing lethal peritonitis.¹³⁶ The biogenetic pathway of **164** related to tetramic acid has been studied (Scheme 13). This kind of biosynthesis related to tetramic acid derivatives was also supported by the group of Hertweck in their discovery of a silent PKS-NRPS hybrid gene cluster and the resulting new pyridine metabolites.¹³⁷ YM-215343 (**165**), isolated from *Phoma* sp., showed antifungal activities against the pathogenic fungi *C. albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus* (MIC values of 2–16 $\mu\text{g mL}^{-1}$) and was cytotoxic against HeLa S3 cells (IC_{50} of 3.4 $\mu\text{g mL}^{-1}$).¹³⁸ An insect-associated fungus tentatively identified as *Cytospora*, was found to produce a cholesteryl ester transfer protein inhibitor **166** (IC_{50} of 40 μM).¹³⁹ More recently, four new members of this family, didymellamides A–D (**167–170**) were isolated from the marine-derived fungus *Stagonosporopsis cucurbitacearum* growing on the surface of an unidentified sponge.¹⁴⁰ Compound **167** showed antifungal activity against



Scheme 13 The proposed biogenesis of **164**.



azole-resistant *C. albicans* with an MIC value of $3.1 \mu\text{g mL}^{-1}$.¹⁴⁰ The antifungal antibiotic, ilicicolin H (**171**), was first isolated in 1971 from the imperfect fungus *Cylindrocladium ilicicola* harboring the dead leaf of beech (*Fagus* sp.).¹⁴¹ It was found to inhibit the yeast cytochrome bc₁ complex by interacting with the Qn site of the complex.¹⁴² Using feeding experiments conducted with different labeled acetates and phenylalanine, biosynthesis of **171** was investigated and found to be similar to **164**.¹⁴³ Singh *et al.* worked on the biotransformation of compound **171** using *Actinoplanes* sp. and *Streptomyces* sp., and found eight new oxidized products **172–179**.¹⁴⁴ The predominant modification was selective oxidation of the methyl group on the decalin ring. Only compound **171** had significant antifungal activity against *C. albicans* with an MIC value of 8 ng mL^{-1} . The total syntheses of compounds **163**, **165**, and **171** have been summarized in a recent review.¹³⁴

3.10 Spirotetronates

Spirotetronates, the macrolide natural products consist of a *trans*-decalin system, a spiro ring between a cyclohexene and a tetronic acid, several similar or dissimilar deoxysugars and/or a multi-substituted benzene or pyrrole.

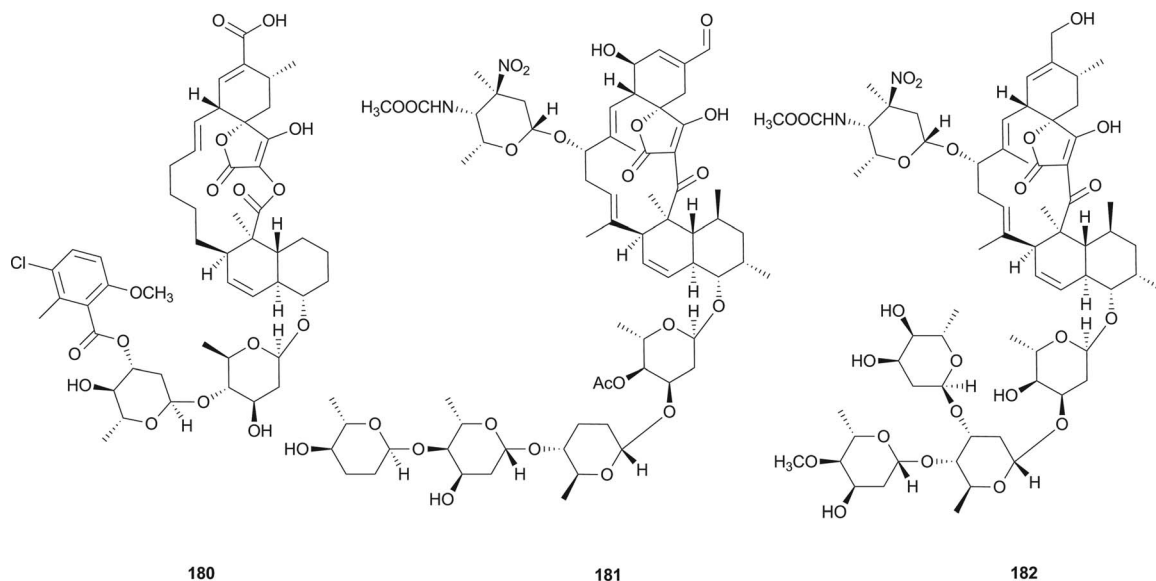
Chlorothricin (**180**), the first reported member of spiro-tetronate family, was isolated from an actinomycete *Streptomyces antibioticus* in 1969 by Keller-Schierlein *et al.*¹⁴⁵ Tetrocarcin A (**181**) was isolated in 1979 from the bacterium *Micromonospora chalcea* by Tomita *et al.*¹⁴⁶ and was found to be identical to antlermicin A (also isolated from *M. chalcea*).¹⁴⁷ Waitz *et al.* isolated kijanimicin (**182**) (or Sch 25663) in 1981 from a complex of antibiotics produced by a previously undescribed species of *Actinomadura*, *A. kijaniata*.¹⁴⁸ Its structure was investigated and confirmed by Mallams *et al.* in the same year.^{149,150}

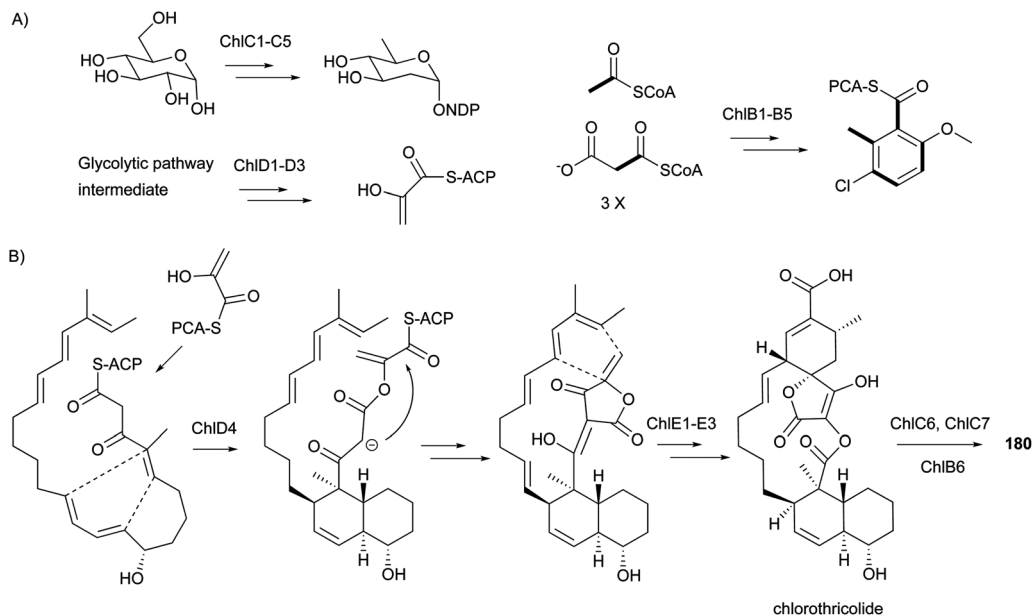
Compounds **180–182** are well-known members of more than 60 spiro-tetronate-type compounds, and exhibit antibacterial activities against Gram-positive bacteria and show selective antitumor

activities.¹⁵¹ Other biological activities are increasingly being revealed. Compound **180** has been shown to inhibit the biosynthesis of cholesterol from mevalonate with an IC₅₀ value of 0.1 mM,¹⁵² and further inhibited pyruvate carboxylases purified from vertebrate sources not owing to the occupancy of the acyl-CoA site.¹⁵³ Metabolite **181** has been proven to be an efficient inducer of apoptosis,¹⁵⁴ showing selective inhibition against the mitochondrial functions of Bcl-2 to suppress its anti-apoptotic function in Bcl-2-overexpressing cells,¹⁵⁵ mediating apoptosis *via* endoplasmic reticulum stress preferentially in B-chronic lymphocytic leukemia cells,¹⁵⁶ and inactivating the PI3-kinase pathway to directly induce apoptosis of human breast cancer cells.¹⁵⁷

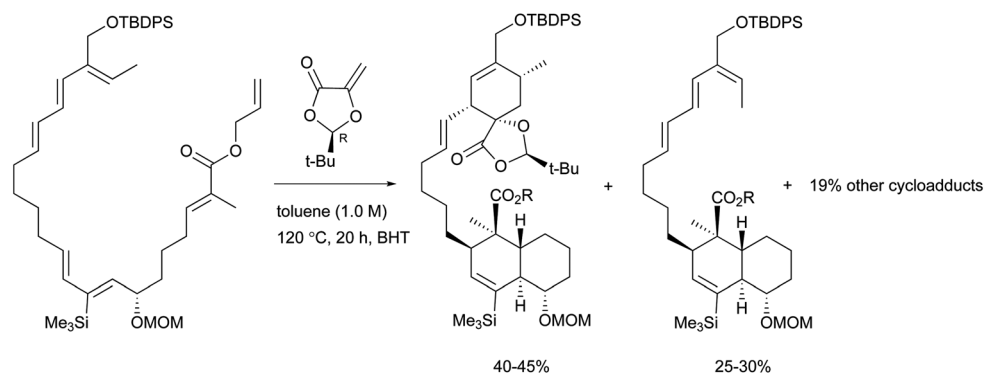
The biosynthetic gene clusters for compounds **180–182** were reported in 2006,¹⁵⁸ 2008,¹⁵⁹ and 2007,¹⁵¹ respectively. During the same period, the proposed biosynthetic pathways for the representative **180** (Scheme 14), **181**, and **182** were also reported. It is notable that their biosynthesis involves two [4 + 2] Diels–Alder cycloadditions resulting in the formation of the *trans*-decalin and the spiro-fusion ring systems. However, it is still unclear whether these two Diels–Alder reactions are performed enzymatically or non-enzymatically. The above results indicate the common biosynthetic route for spiro-tetronate antibiotics to include: (1) formation of the polyketide linear chain; (2) incorporation of a glycerol-derived three-carbon unit;^{160,161} (3) involvement of two [4 + 2] Diels–Alder cycloadditions resulting from either enzymatic or non-enzymatic processes; and (4) modification of the aglycone cores by some moieties, such as various deoxysugars.

To the best of our knowledge, total syntheses of compounds **180–182** have not yet been reported, even though many syntheses for their aglycones have been achieved and many preparations of the functional intermediates have been accomplished.^{162–168} Enantioselective synthesis of (–)-chlorothricolide, the aglycone of **180**, was achieved in 1994 by Roush and Sciotti (Scheme 15).^{162,163} Prior to this work, the group of Yoshii reported the chemical synthesis of racemic





Scheme 14 Biosynthetic study on spirotetronate antibiotics. (A) Proposed biosynthesis for deoxysugar olivose, 3-carbon unit enoylpyruvate, and 2-methoxy-5-chloro-6-methylsalicylic acid. (B) Proposed two [4 + 2] IMDA cycloadditions in the biosynthesis of **180**.



Scheme 15 Roush's key Diels–Alder reactions in the enantioselective total synthesis of (-)-chlorothricolide.

24-*O*-methylchlorothricolide (Scheme 16).¹⁶⁴ Both syntheses involved Diels–Alder cyclizations to construct the spirotetronate structure and decalin motif of the aglycones. The aglycon of compound **181**, tetronolide, was first synthesized by the group of Yoshii in 1991.^{165,166} Two key steps, the aldol coupling of spirotetronate and a Diels–Alder product decalin system and the internal cyclization, were involved in the construction of the macro-ring as shown in Scheme 17.^{165,166} A tandem ketene-trapping [4 + 2] cycloaddition strategy for the total synthesis of (+)-tetronolide was also described.¹⁶⁷ The synthetic methods of the functional fragments of spirotetronates involving the intermolecular Diels–Alder reaction can be increasingly found in many reports.^{168,169}

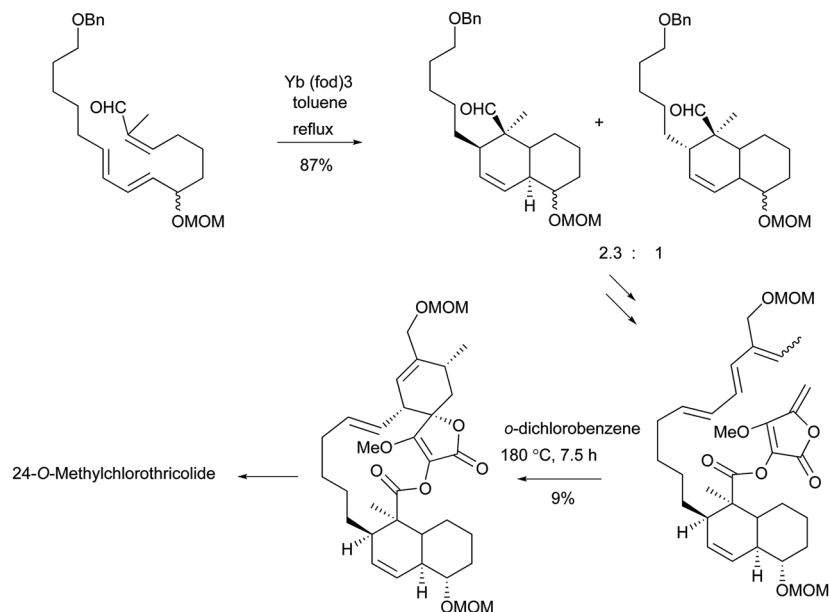
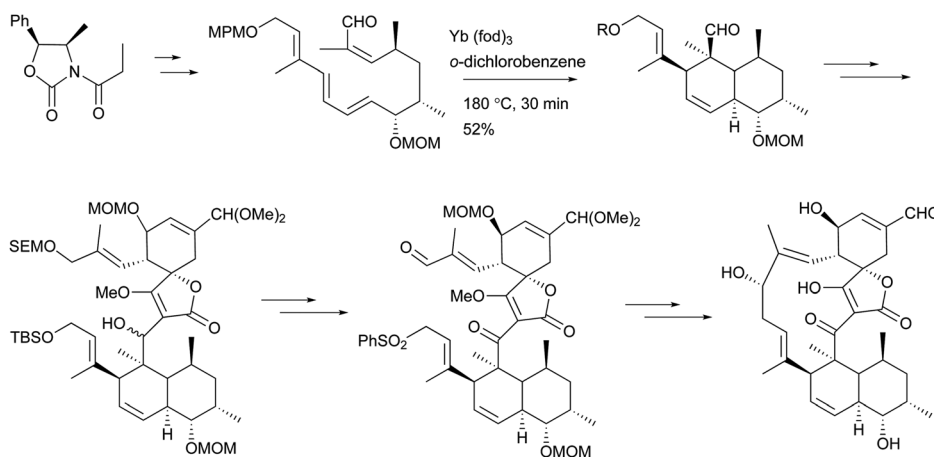
3.11 Pyrrolizidines

UCS1025-A (**183**) and -B (**184**), possessing the unprecedented furopyrrrolizin-2,6-dione system, were isolated in 2000 from the

broth of the fungus *Acremonium* sp.¹⁷⁰ Their structural elucidations were achieved by spectral data and X-ray crystallographic analysis,¹⁷¹ indicating two more tautomeric isomers in UCS1025A. Compared with compound **184**, **183** exhibited significant inhibitory activities against the Gram-positive bacteria *S. aureus*, *B. subtilis* and *Enterococcus hirae*, and Gram-negative bacterium *Proteus vulgaris* with the MIC values ranging from 1.3 to 5.2 μg mL⁻¹. Moreover, they possessed weak anti-proliferative activities against human tumor cell lines ACHN, A431, MCF-7, and T24.

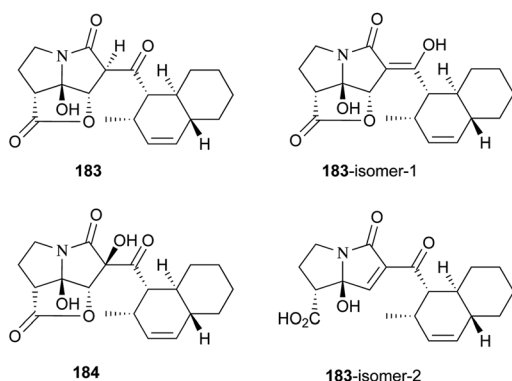
The total synthesis of compound **183** has been accomplished by four groups worldwide.² The first synthesis of **183** was reported by Lambert and Danishefsky,¹⁷² who achieved asymmetric access to the furopyrrrolizidine fragment and used a powerful enantioselective organocatalytic intramolecular Diels–Alder reaction to obtain the required decalin.⁸² The remarkable BEt₃-mediated reaction allowed direct coupling of the furopyrrrolizidine fragment and the



Scheme 16 Yoshii's IMDA approach to the synthesis of racemic 24-*O*-methylchlorothricolide.Scheme 17 Yoshii's synthesis of the aglycone of **181**, tetronolide.

decalin aldehyde to provide the full skeleton of **183** (Scheme 18).¹⁷²

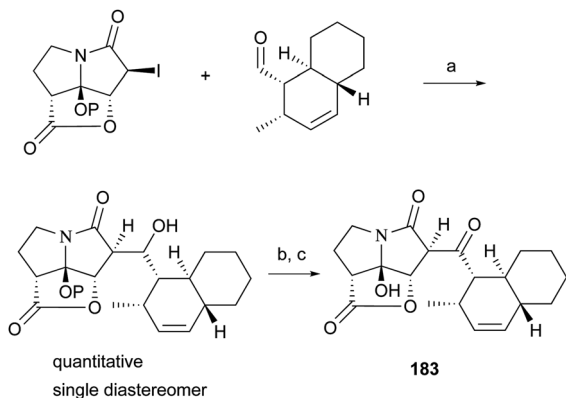
A biomimetic total synthesis of (\pm)-UCS1025A involving seven linear steps was accomplished by Hoyer *et al.*



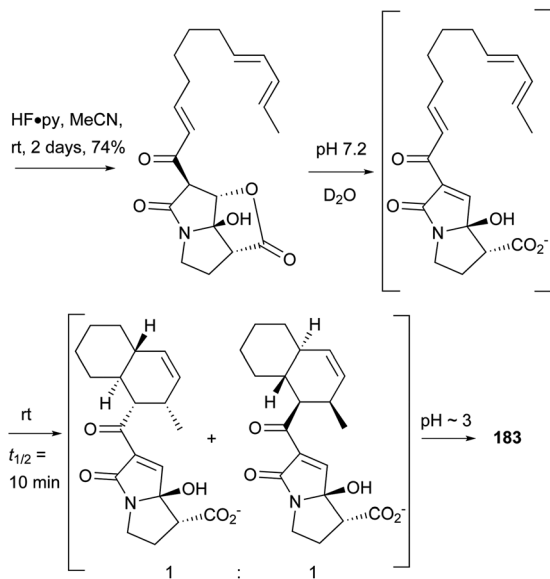
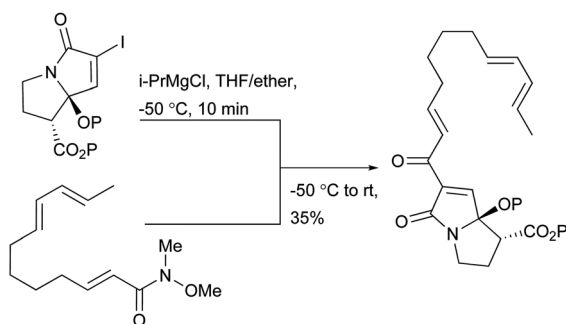
(Scheme 19).¹¹ The interesting automatic cyclization of a long chain in phosphate buffer (pH 7.2, D₂O) to the decalin system indicated a possible non-enzymatic biosynthetic event *in vivo*. Furthermore, an effective trialkylsilyl triflate (TMSOTf)-mediated cyclization of ester-imide to pyrrolizidine was reported by Hoyer *et al.* (Scheme 20).¹⁷³

The group of Christmann synthesized a simplified analogue of compound **183** using an aldol coupling approach (Scheme 21).¹⁷⁴ They performed an improved MacMillan organocatalytic Diels–Alder reaction to obtain the concise *trans*-decalin moiety with an enantiomeric excess (*ee*) of 99%. For the pyrrolizidine fragment of compound **183**, compared to Danishefsky's synthesis in nine steps,¹⁷² the group of Christmann showed its two-step enantioselective synthesis (Scheme 22).¹⁷⁵ The conditions can also be applied to the commercially available maleimide and some substituted maleimidic acids. An enantioselective lactonization and the trituration enrichment at

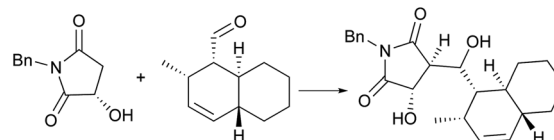




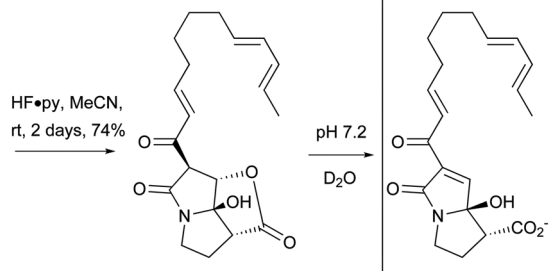
Scheme 18 Danishefsky's coupling protocol for the synthesis of **183**. (a) BEt_3 , toluene, -78°C , $\text{P} = \text{TBS}$; (b) TBAF, THF, 85%; (c) Dess–Martin periodinane, CH_2Cl_2 , 84%.



Scheme 20 Hoye's silylative Dieckmann-like cyclization to pyrrolizidine fragment.



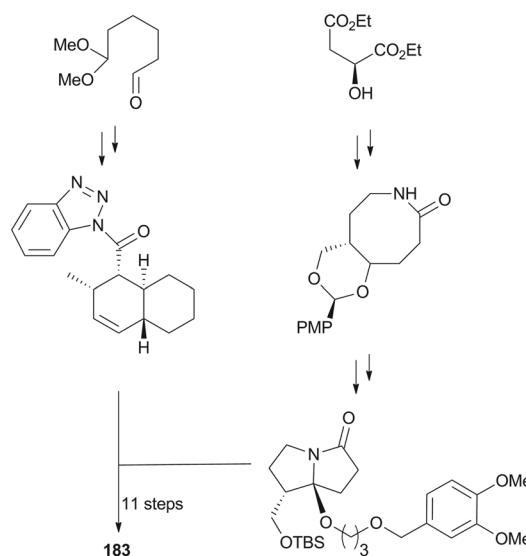
Scheme 21 Christmann's aldol coupling involved in the synthesis of an analogue of **183**. Condition: NaHMDS, THF, 0°C , then decalin substance, -78°C , 3.5 h, 55%.



Scheme 22 Christmann's two-step synthesis of the pyrrolizidine fragment.

hemiaminal moiety to assess the pyrrolizidinone skeleton, and the condensation of decalin and the pyrrolizidinone system (Scheme 23).²

Two new pyrrolizidinone antibiotics closely related to **183** and **184**, CJ-16,264 (**185**) and CJ-16,367 (**186**), were isolated from an unidentified soil fungus CL39457.¹⁷⁶ Recently, a



Scheme 19 Hoye's biomimetic total synthesis of **183**.

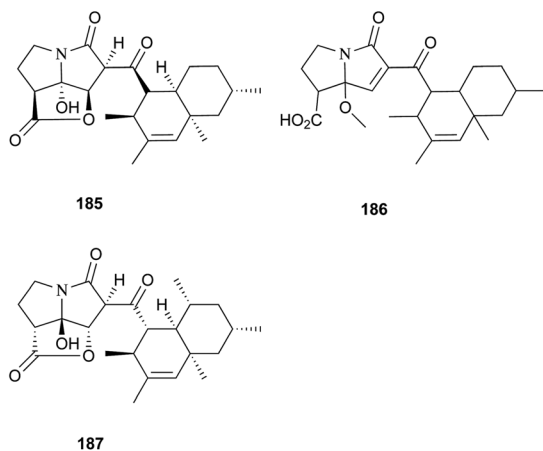
a high eutectic ee for the pyrrolizidine fragment were also reported.

A stereoselective total synthesis of compound **183** was performed by Kan and co-workers, involving an intramolecular Diels–Alder reaction to the decalin skeleton, an intramolecular Staudinger/aza-Wittig reaction to the eight-membered lactam, the stereoselective construction of a labile

Scheme 23 Kan's stereo-controlled total synthetic method of **183**.

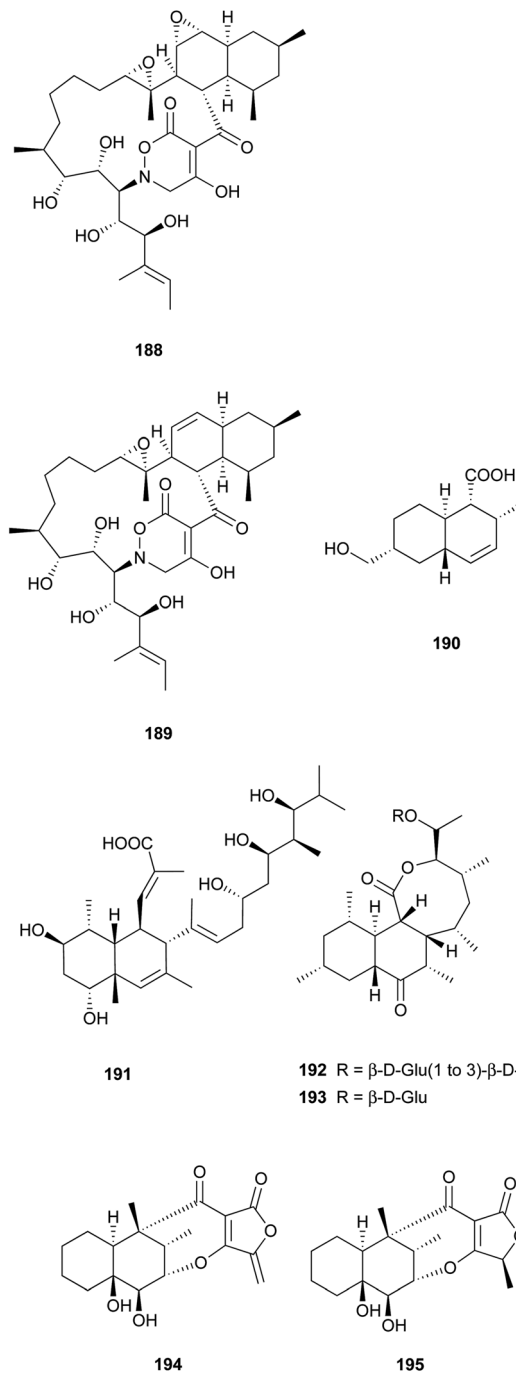


novel proteasome inhibitor, pyrrolizilactone (**187**), was discovered from an uncharacterized fungus,¹⁷⁷ and inhibited the trypsin-linked activity of the proteasome.¹⁷⁸ All these pyrrolizidine antibiotics could be biogenetically related to tetramic acid derivatives. Specifically, apart from a common polyketide precursor and an amino acid (glycine) as suggested in tetramic acid biosynthesis, an unknown C₄ unit could be involved in the construction of these pyrrolizidine antibiotics.¹⁷¹



3.12 Others

Two unprecedented polycyclic polyketides, alchivemycins A (**188**) and B (**189**), were isolated from a plant-derived actinomycete *Streptomyces* sp.^{179,180} Their structures were confirmed by X-ray crystal structure analysis along with chemical and spectroscopic methods. They showed a selective antimicrobial activity against *Micrococcus luteus* with MIC values of 0.03 and 0.004 $\mu\text{g mL}^{-1}$, respectively without inhibitory effects on *B. subtilis*, *E. coli*, or *C. albicans*. Furthermore, they exhibited potency in inhibiting murine colon carcinoma 26-L5 cell invasion (IC_{50} of 0.34 and 1.9 μM , respectively) without showing any cytotoxic effects. The unprecedented heterocyclic ring system, 2*H*-tetrahydro-4,6-dioxo-1,2-oxazine, was proposed to be biosynthesized *via* a similar PKS-NRPS pathway as that of tetramic acid.¹⁸⁰ This hypothesis was further investigated by feeding ¹³C-labeled precursors (Fig. 6). Apiosporic acid (**190**) is a polyketide-derived compound from a marine fungus *A. montagnei* isolated from the inner tissue of the North Sea alga *Polysiphonia violacea*.¹⁸¹ Nahuic acid A (**191**), the first known selective SAM-competitive inhibitor of SETD8 (IC_{50} of $6.5 \pm 0.5 \mu\text{M}$), was produced by a *Streptomyces* sp. isolated from a tropical marine sediment.¹⁸² The actinomycete *Kitasatospora griseola* was known to produce two unprecedented glucosylated polyketides, satsosporins A **192** and B **193**.¹⁸³ Their absolute configurations were confirmed using TDDFT/CD calculations and chemical derivatization methods. Two novel antimicrobial agents, tetrodecamycin (**194**) and dihydro-tetrodecamycin (**195**) were obtained from the broth of *Streptomyces nashvillensis*.¹⁸⁴



4 Isoprenoid decalin

The isolation and structures of natural sesquiterpenoids, diterpenoids, or marine natural products containing isoprenoid-derived decalin have been covered in a series of reports.⁴⁻⁶ Therefore, in this manuscript, we only highlight the important features of isoprenoid-derived decalin secondary metabolites isolated from microorganisms (mainly fungi). Almost always, these isoprenoid decalin-derived compounds of microbial origin belong to sesquiterpenes mainly including cadinane-, eremophilane- and bicycloparnesane-type sesquiterpenes according to the



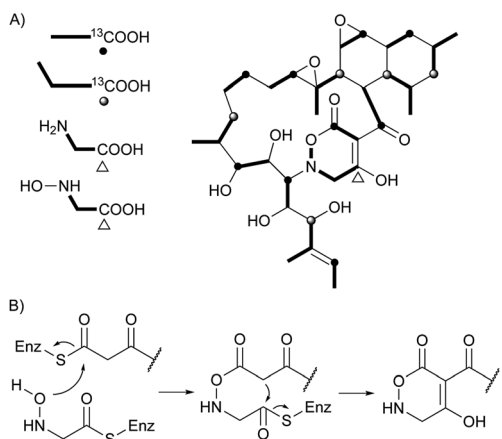


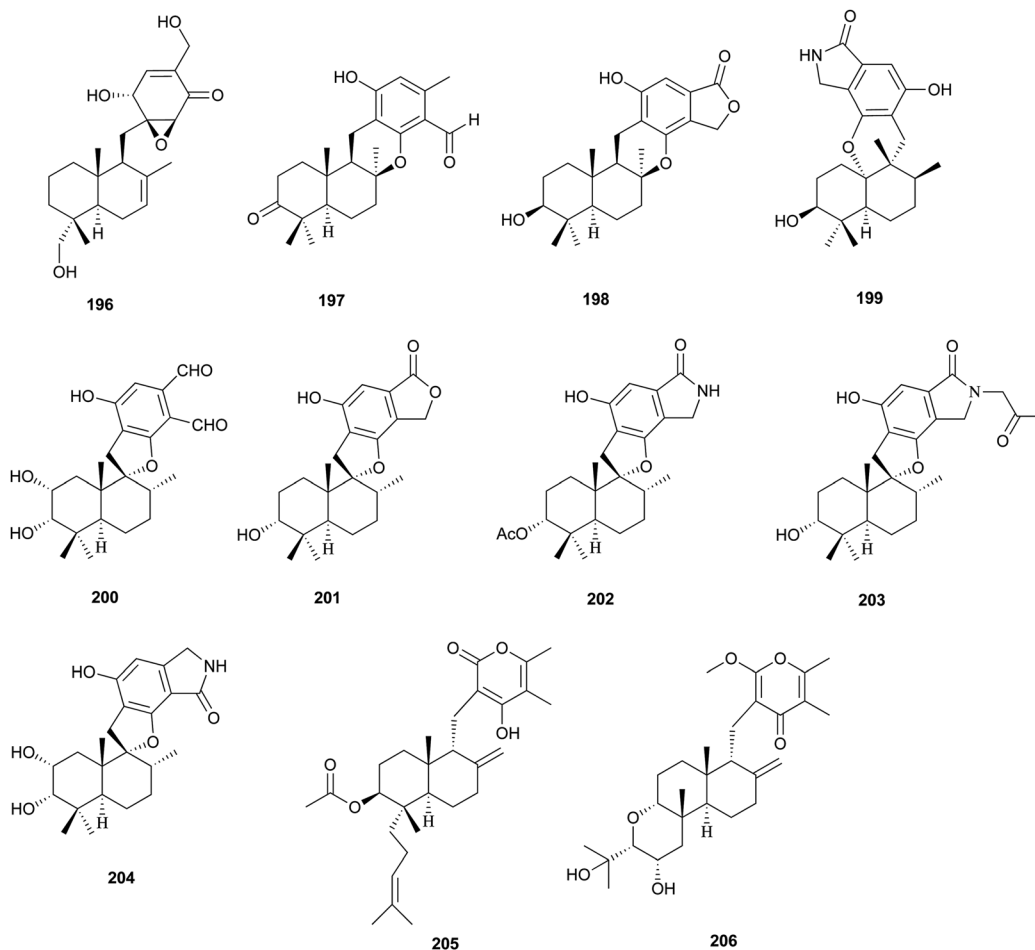
Fig. 6 Biosynthetic investigation for **188**. (A) Incorporation of ^{13}C -labeled precursors into **188**. (B) Proposed biosynthetic pathway for tetrahydrooxazine ring.

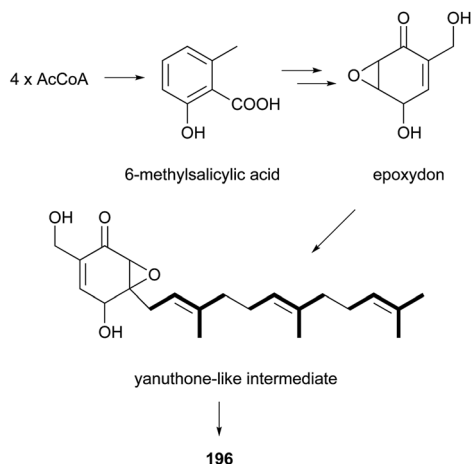
classification in earlier reviews.^{4–6} Cadinane sesquiterpenes have demonstrated highly selective and notable nematocidal activities, but have remained largely inactive in antimicrobial and cytotoxic assays.^{185–189} Eremophilane

sesquiterpenes, typically isolated from fungi of the genera *Xylaria* and *Penicillium* exhibit diverse biological properties, such as cytotoxic,^{190,191} antimicrobial,¹⁹² and inhibition of HIV integrase.¹⁹³ More importantly, most of the bicyclofarnesane-type sesquiterpenes are composed of an isoprenoid-derived decalin ring system linked to a polyketide ring unit with some substituted functionalized groups such as an amino acid. The typical diverse structures of this family are the compounds **196**,¹⁹⁴ **197**,¹⁹⁵ **198**,¹⁹⁵ **199**,¹⁹⁶ **200**,¹⁹⁷ **201**,¹⁹⁸ **202**,¹⁹⁸ **203**,¹⁹⁹ and **204**.²⁰⁰ The proposed biosynthesis of compound **196** is shown in Scheme 24 (see Supporting Information of ref. 194). Similarly, a coupling between a polyketide-derived pyranone or pyrone and a diterpene (decalin part) contribute to the structural diversity of the diterpenes **205**²⁰¹ and **206**.^{202,203}

5 Conclusions

A number of bioactive microbial secondary metabolites with the decalin scaffold are increasingly being discovered. Herein, we present a comprehensive review on nearly 200 polyketide decalin secondary metabolites and 11 representative sesquiterpenoids and diterpenoids with the decalin system. The structural diversity of decalin-derived microbial natural





Scheme 24 The proposed biosynthesis for 196.

products is a consequence of the large manifold of fungal or bacterial species, and also a result of the biosynthetic capability of these fascinating producers to assemble decalin compounds in single or mixed biosynthetic pathways. Furthermore, they display diverse and remarkable biological activities.

More importantly, nearly all the polyketide decalin-derived compounds we have discussed in this manuscript have a double bond between C3 and C4 (sometimes oxygenated), suggesting an enzymatic or non-enzymatic IMDA cycloaddition to form the decalin scaffold. Moreover, all the decalin-containing secondary metabolites presented here seem to be assembled by a linear polyketide or isoprenoid unit, which then cyclize to the decalin scaffold followed by incorporation of functionalized substituted groups. This suggests that the biosynthetic pathways of many of these compounds are extremely related, as exemplified in this review. Specifically, the decalin cyclization type *endo-trans*-fused one (C or D) is the most common, even though two other fused classes are dominant in some classifications, such as the pyrone derivatives (*exo-cis*-fused, A) and macrolides (*exo-cis*-fused, B). This phenomenon may be the result of a steric or enzymatic effect. Lastly, compounds with the decalin system conjoining different functionalized moieties such as lactones in monacolin and tetramic acids often have different biological activities. Therefore, these intriguing similarities or differences prove helpful in elucidating their biosynthesis and might provide a scientific handle for aiding biomimetic total synthesis. Finally, the decalin scaffold is more likely to serve as the rigid or basic template for construction of the whole structure.

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