NPR

REVIEW

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Cite this: Nat. Prod. Rep., 2014, 31, 1175

Natural products containing 'decalin' motif in microorganisms

Gang Li,† Souvik Kusari†* and Michael Spiteller*

Covering: up to February 2014

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.

Received 19th March 2014

DOI: 10.1039/c4np00031e

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Institute of Environmental Research (INFU), Department of Chemistry and Chemical Biology, Chair of Environmental Chemistry and Analytical Chemistry, TU Dortmund, Otto-Hahn-Str.6, 44221 Dortmund, Germany. E-mail: souvik.kusari@infu.tu-dortmund.de; m.spiteller@infu.tu-dortmund.de; Fax: +49-231-755-4084; +49-231-755-4085; Tel: +49-231-755-4086; +49-231-755-4080

† These authors contributed equally to this work.

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 multi-functionalized 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 Fraga[4] 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 possible, as suggested in a biomimetic total synthesis of the decalin compound (±)-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 double bonds. Many other moieties such as small lactone ring, pyrone, tetramic acid, unusual sugars, pyridone, tetronic 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

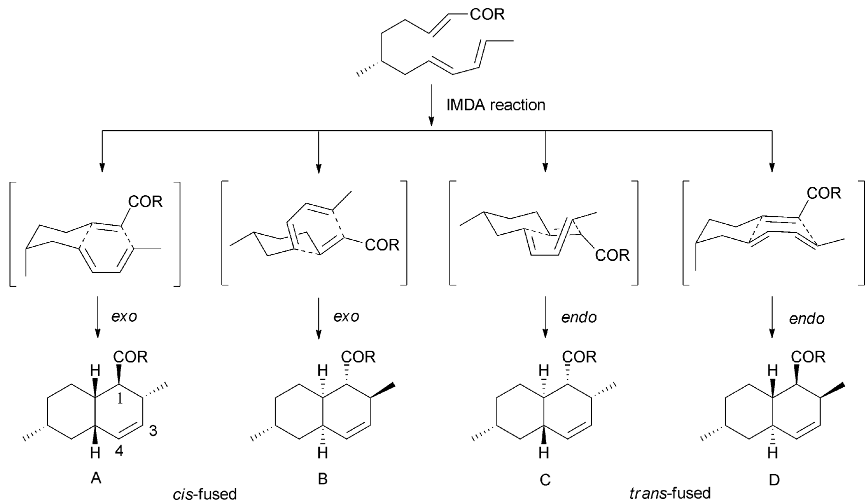
Fungi and bacteria are the major microbial resources that produce the decalin moiety-containing secondary metabolites with a broad spectrum of biological activities. Most of these compounds have a polyketidic decalin scaffold. Frequently, they are highly functionalized through the substitution of methyl, 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

Gang Li received his B.Sc. degree (2009) at Shandong University of Traditional Chinese Medicine and M.Sc. degree (2012) under the supervision of Prof. Hong-Xiang Lou from Shandong University, China. He is presently working at INFU, TU Dortmund, Germany for his doctorate with a fellowship from the China Scholarship Council (CSC). His research focuses on bioactive secondary metabolites from endophytic fungi.

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 visiting lecturer at the University of Yaoundé 1, Cameroon, Africa since 2012 within the scope of the DAAD "Welcome to Africa" initiative. His research interests include characterization of fungal and bacterial endophytes to evaluate their diversity, chemical ecology and biosynthetic pathways.

Michael Spiteller received his Diploma in Chemistry (1976) from the Georg-August-Universität in Göttingen, Germany where he earned a doctorate in Chemistry in 1979. After Habilitation in Soil Science, he joined the Institute for Metabolism and Environmental Fate, Bayer Corp., Germany for 8 years as a Group Leader. He then joined the University of Kassel as a full Professor and is now Professor 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.



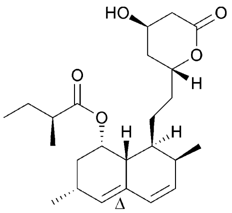
Scheme 1 The IMDA reaction to decalin.

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.

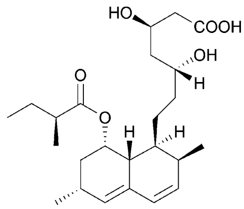
3.1 Monacolins

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 Tang[16] 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 3α-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 μg kg^{-1} in 50% inhibitory dose compared to a 50% inhibitory dose of 290 μg kg^{-1} for the sodium salt of **10**.[19] In 1981, Lam *et al.*



1 Δ unsaturated
3 Δ saturated



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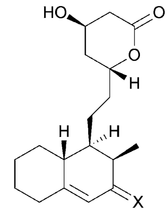
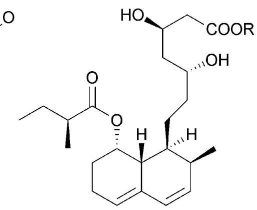
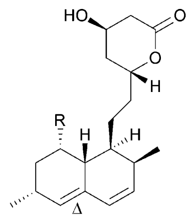


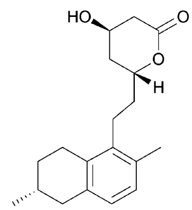
14 X = α-OH, H
15 X = O



16 R = H
17 R = Et



4 R = OH
5 R = H
6 R = H, Δ saturated



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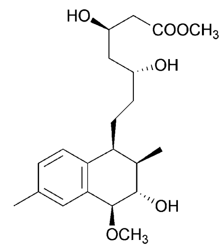

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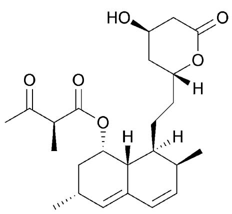

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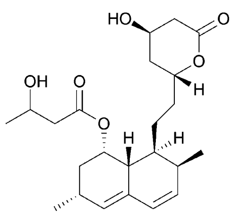

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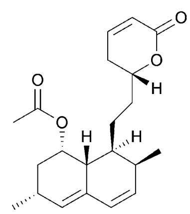

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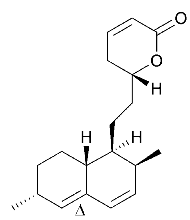
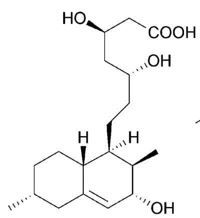


21 Δ unsaturated
22 Δ saturated



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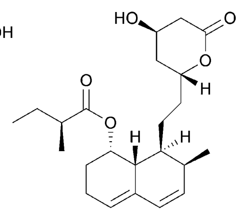

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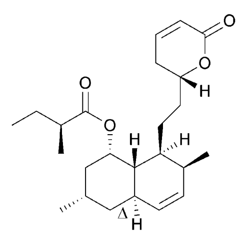
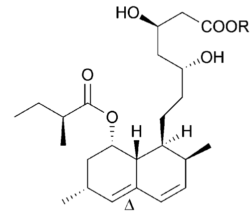
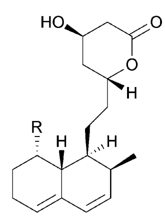


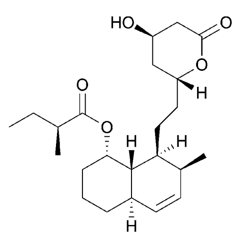
23 Δ saturated
24 Δ unsaturated



25 R = Et
26 R = Me
27 R = Me, Δ saturated

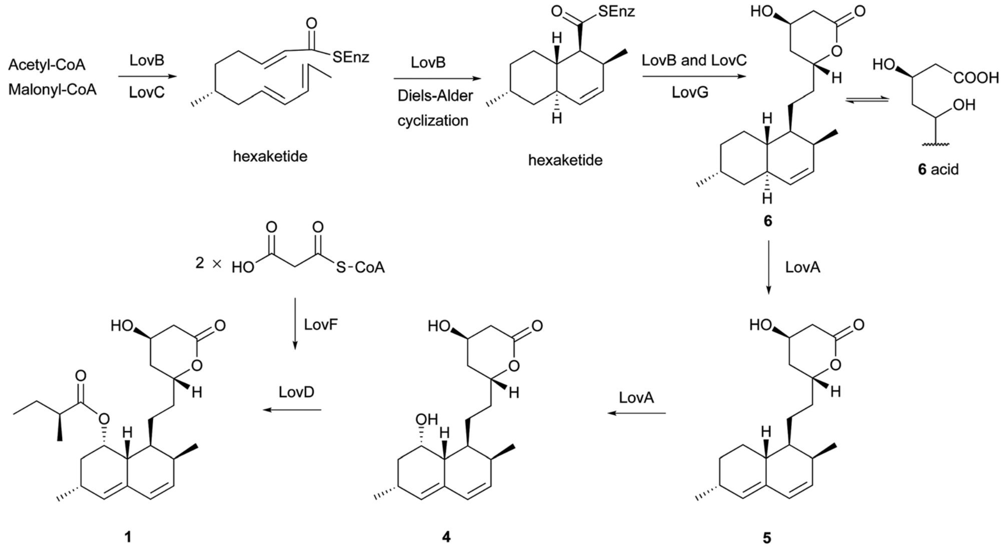


11 R = OH
12 R = H



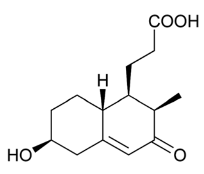
13

discovered 4a,5-dihydrocompactin (**13**) from the fungus *P. citrinum*.[31] 3α-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-didydro-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]



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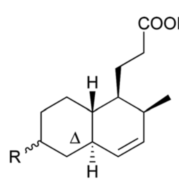
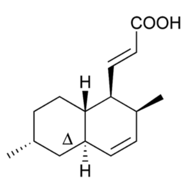
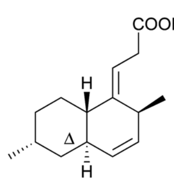


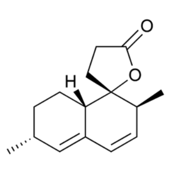
29 R = β-OH
30 R = α-Me
31 R = α-Me, Δ unsaturated



32 Δ saturated
34 Δ unsaturated



33 Δ saturated
35 Δ unsaturated



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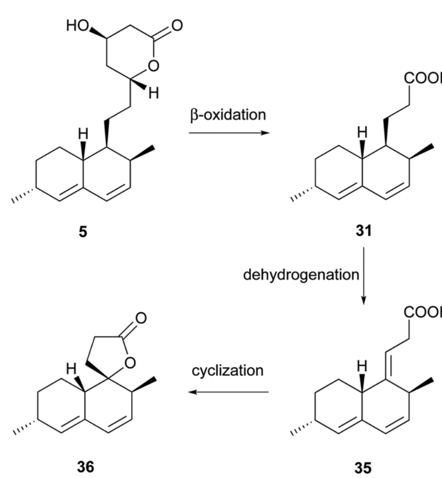
3.2 Monacolin derivatives

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 polyfunctionalized *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]

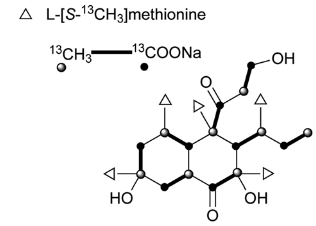
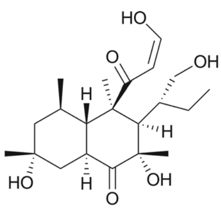


Fig. 1 Biosynthetic origins of carbons in **40**.



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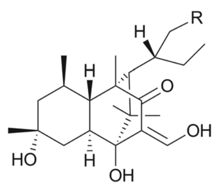
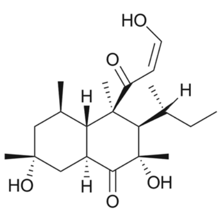


38 R = OH
39 R = H



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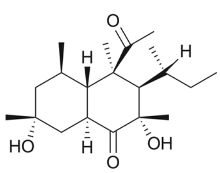

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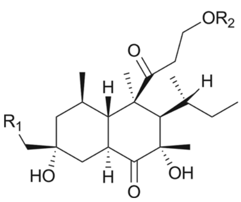
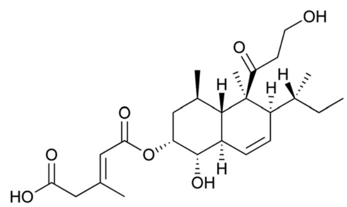


40 R_1 = H, R_2 = H
42 R_1 = OH, R_2 = H
44 R_1 = H, R_2 = Ac

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



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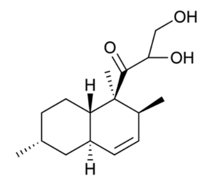

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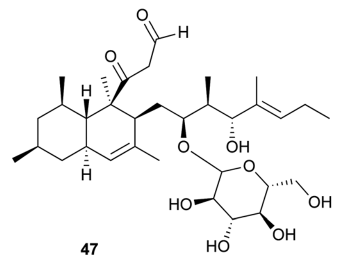

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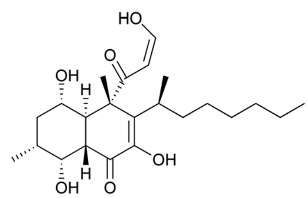

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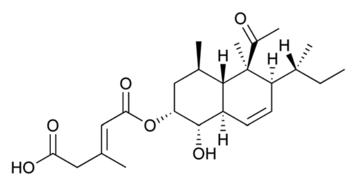

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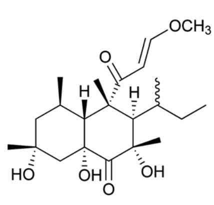

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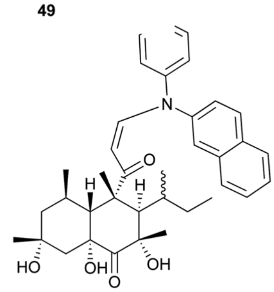

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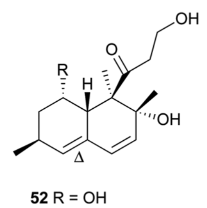
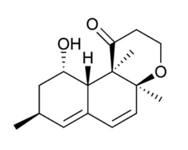


52 R = OH
53 R = OH, Δ saturated
55 R = H, Δ saturated



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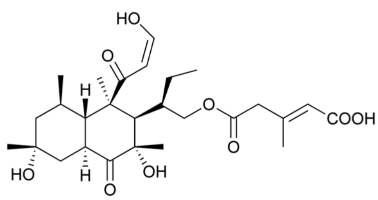
Another polyketide, deoxynortrichoharzin (**49**) was obtained from the saltwater culture of *Paecilomyces* cf. *javanica* isolated from the marine sponge *Jaspis* cf. *coriacea*, which did not show any cytotoxic activity against solid tumor cells in culture.[51] Two betaenone derivatives, 10-hydroxy-18-methoxybetaenone (**50**) and 10-hydroxy-18-*N*-2-naphtyl-*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 IC_{50} values of 36.0, 11.5, and 10.5 μM, 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 $COCH_2CH_2OH$ 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 μM. 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,



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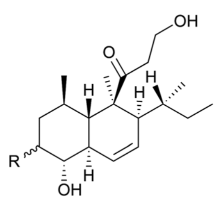
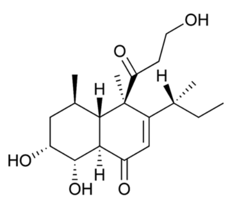


57 R = α-OH
58 R = β-OH



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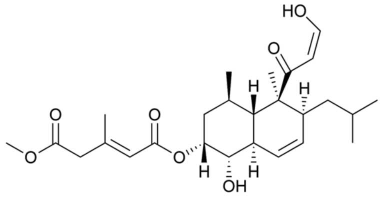

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and the murine L1210 leukemia cell lines with IC_{50} values ranging from 41 to 55 mM.

3.4 Side chains with a pentanedienoic acid

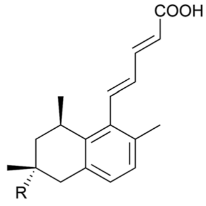
Most of these carboxylic acids have been detected in the cultures of *Penicillium* species, and possess a penta-2,4-dienoic acid unit connected to a *trans*-decalin, showing a plethora of interesting activities. A few *cis*-decalin skeletons can also be found, which seems to play an important role for 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 pentanedienoic acids. Among metabolites **61–64**, only **62** significantly inhibited superoxide anion production in human neutrophils ($IC_{50} = 26$ μg mL^{-1}).[58] Acids **67** and **68** exhibited no cytotoxicity on the growth of the L5178Y mouse lymphoma cell line ($IC_{50} > 10$ μM) and no antimicrobial activity against *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Escherichia coli* at a concentration of 64 μg 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 μg 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*-decalinpentanoic acid methyl ester from an unidentified fungus.[64] **78**, as a anticoccidial agent, inhibited the growth of *E. tenella* with an MIC value of 1.5 μM, compared to that of 123 μM for **73**, 34.7 μM for **74** and **75**, 35 μM for **76**, and 7.0 μM 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 IC_{50} of 5.7 μM.[65] Using ^{13}C-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 pentanedienoic acids.

A weakly antifungal polyketide, fusarielin A (**81**), and three biosynthetically related fusarielins B–D (**82–84**), were isolated from *Fusarium* sp.[68] Dehydroxychlorofusarielin 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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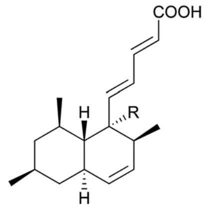
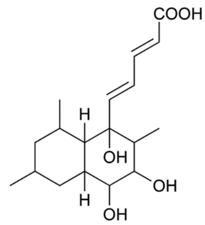
64 R= OH


62 R = H
63 R = OH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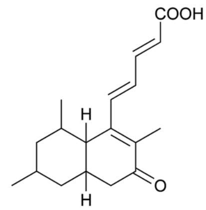
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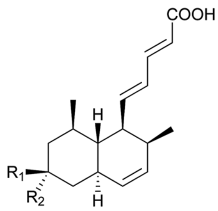
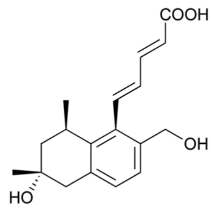

65 R_1 = Me, R_2 = OH
66 R_1 = COOH, R_2 = H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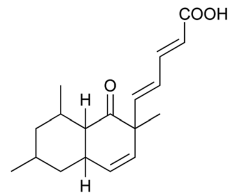
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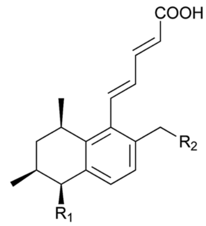
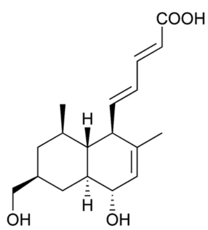

76 R_1 = OH, R_2 = H
77 R_1 = H, R_2 = OH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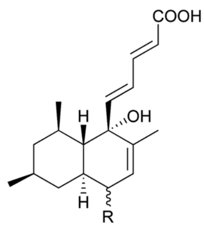
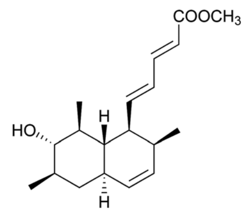

69 R = β-OH
70 R = α-OH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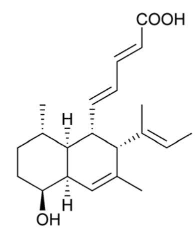
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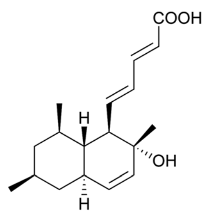
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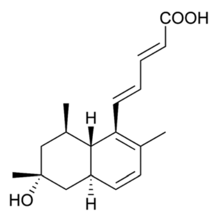
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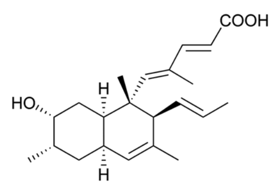
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umbilical vein endothelial cells (HUVECs) with IC_{50} values of 2.2–9.3 μg mL^{-1}.[70] Six fungal-derived polyketides, cladobotric acids A–F (**94–99**), were isolated from a *Cladobotryum* species from New Zealand.[71] All of them showed modest 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} μmol/disk for **100**; 16 mm zone at 3.4×10^{-4} μmol/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

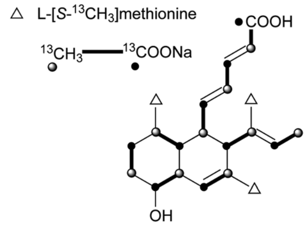
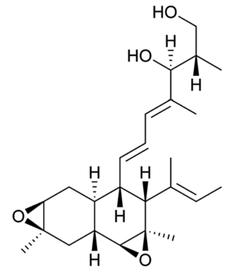


Fig. 2 Biosynthetic origins of carbons in 79.



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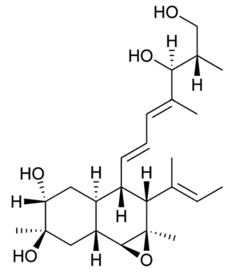

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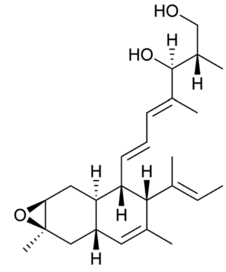

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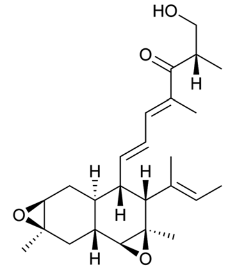

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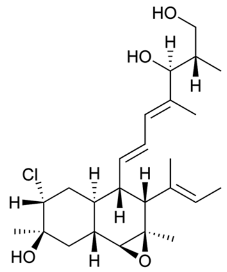

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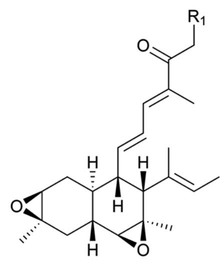
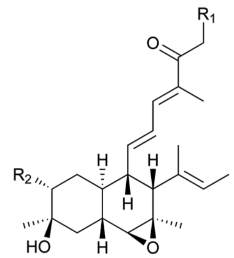
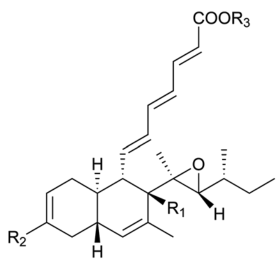


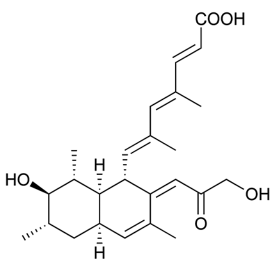
86 R_1 = Me
87 R_1 = H



88 R_1 = Me, R_2 = Cl
89 R_1 = H, R_2 = Cl
90 R_1 = Me, R_2 = H
91 R_1 = H, R_2 = H
92 R_1 = H, R_2 = OMe
93 R_1 = H, R_2 = OH



94 R_1 = OH, R_2 = Me, R_3 = H
95 R_1 = OH, R_2 = CH_2OH, R_3 = H
96 R_1 = H, R_2 = CH_2OH, R_3 = H
97 R_1 = OH, R_2 = CHO, R_3 = H
98 R_1 = OH, R_2 = CO_2Me, R_3 = H
99 R_1 = OH, R_2 = CO_2Me, R_3 = Me



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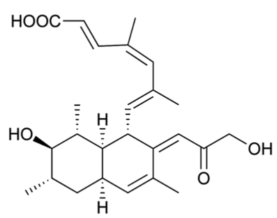

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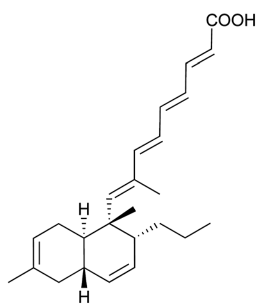


102

was isolated from *Penicillium verruculosum*.[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 IC_{50} values of 30 and 37 μM, 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

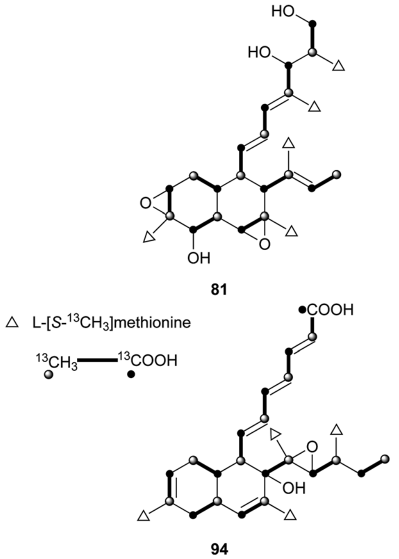
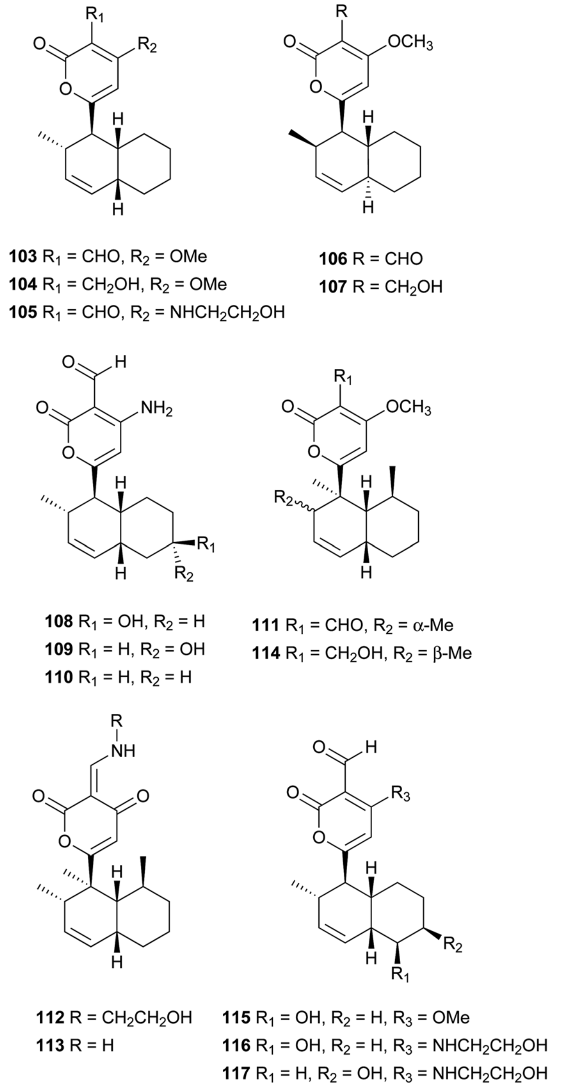


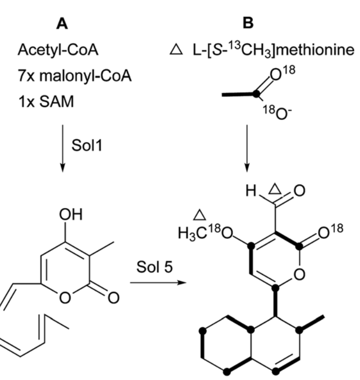
Fig. 3 Biosynthesis of **81** and **94** on the basis of the data from feeding experiments.

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 μg mL^{-1}.

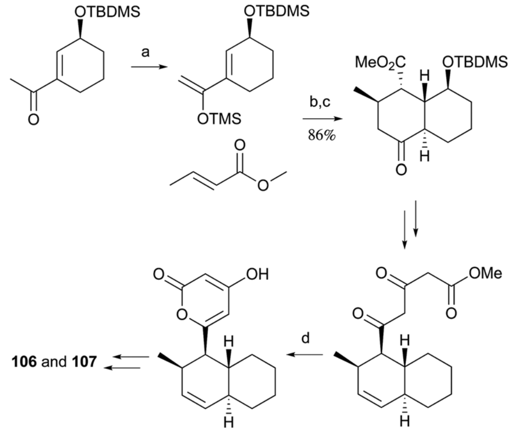


3.7 Macrolides

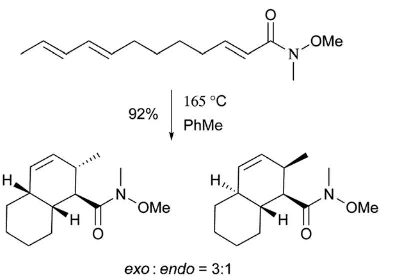
Nodusmicin (**118**) and nargenicin (**119**) represent a class of macrolide antibiotics that were isolated from *Saccharopolyspora hirsuta* by Whaley *et al.* in 1980[86] and from *Nocardia argentinensis* by Celmer *et al.* in the same year, respectively.[87] They possess a ten-membered lactone ring 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



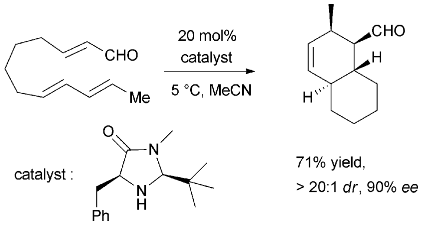
Scheme 4 (A) The prosolanapyrone synthase (PSS) encoded by Sol1 catalyzes octaketide prosolanpyrone formation and then a flavin-dependent oxidase (solanapyrone synthase, SPS) encoded by Sol5 catalyzes Diels–Alder cyclization to form **103**. (B) Incorporation of labeled acetate and methionine into **103**.



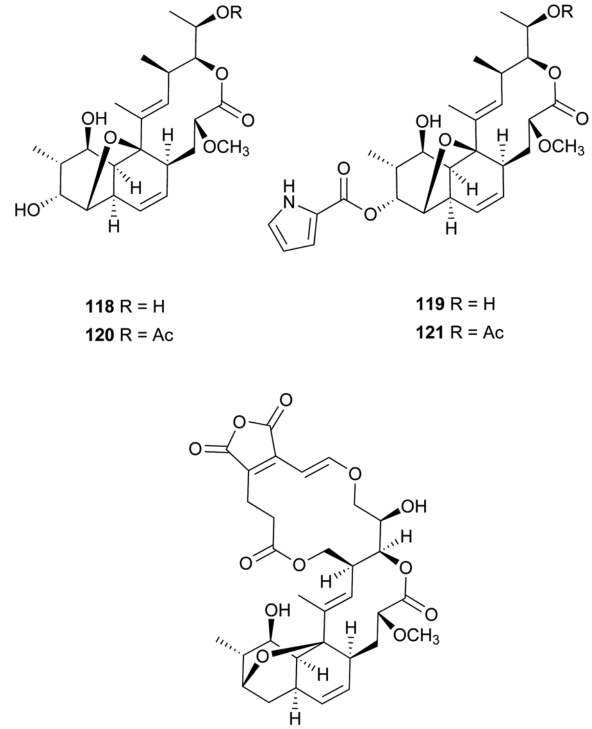
Scheme 5 The first total syntheses of **106** and **107**: the domino Michael reaction to decalone and the general biosynthetic strategy of pyrone. (a) LDA, TMSCl, 93%; (b) MeLi, methyl crotonate, HMPA, THF; (c) MeONa, MeOH; (d) DBU, benzene, 93%.



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**.



118 R = H
120 R = Ac

119 R = H
121 R = Ac

122

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 μg 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.

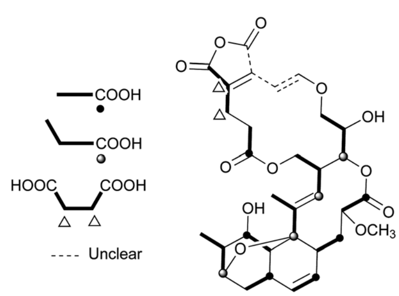
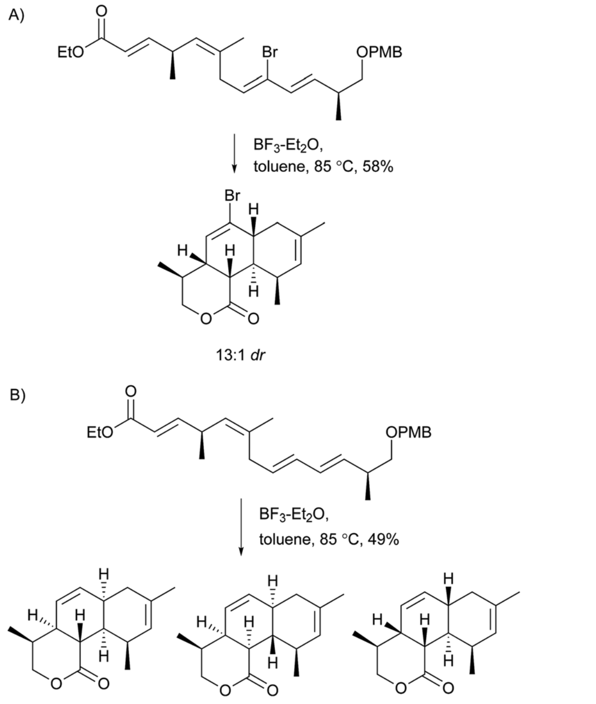


Fig. 4 Biosynthetic origin of **122** on the basis of the data from feeding experiments.



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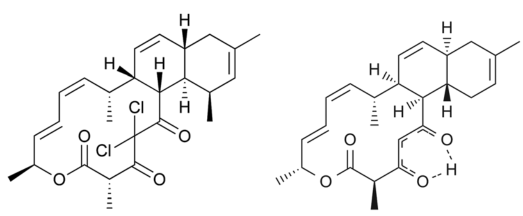
Scheme 8 Synthesis of the decalin system in compound **123**. A) Highly stereoselective halogen (bromine)-directed Diels–Alder reaction. B) The same reaction condition without bromine substituent.

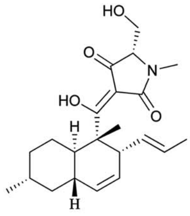


123 124

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 C_{14}, C_{16}, C_{18} 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 IC_{50} 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 *Tripterygium 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] Ophiosetin (**132**) was isolated from the mycopathogenic fungus *Elaphocordyceps ophioglossoides*.[113] Co-culture of the fungus *Fusarium pallidoroseum* with the bacterium *Saccharopolyspora erythraea* afforded *N*-demethylophiosetin (**133**) and pallidorosetins A and B (**134**, **135**), along with compounds **125** and **132**.[114] Compound **125** exhibited a GI_{50} 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 antibacterial agent against *S. aureus* and *Haemophilus influenzae*.[116] CJ-17,572 (**138**) and CJ-21,058 (**139**) were isolated from *Pezicula*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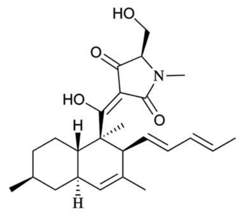
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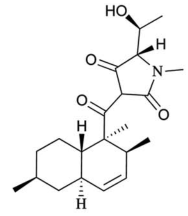
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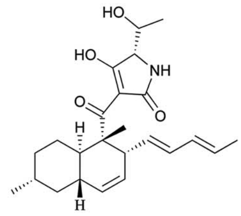
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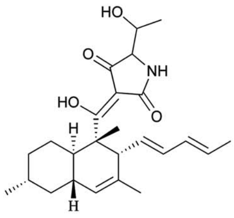
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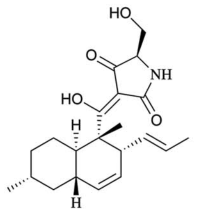
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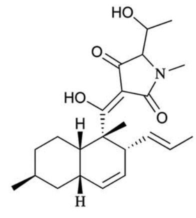
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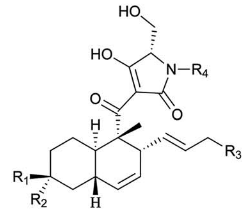
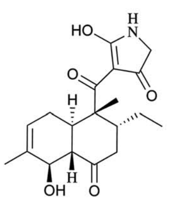

132 R_1 = H, R_2 = CH_2OH, R_3 = H, R_4 = Me
133 R_1 = H, R_2 = CH_2OH, R_3 = H, R_4 = H
134 R_1 = OH, R_2 = Me, R_3 = H, R_4 = Me
135 R_1 = H, R_2 = CH_2OH, R_3 = OH, R_4 = Me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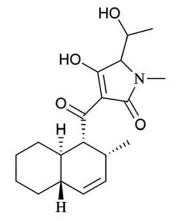
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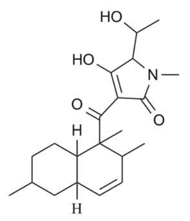
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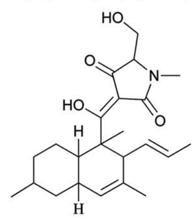
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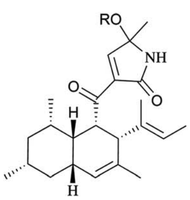
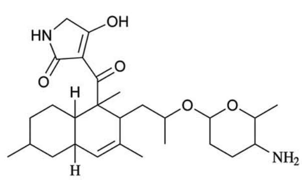

140 R = $CH_2CH_2CH_2CH_3$
141 R = Me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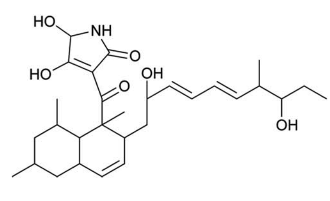
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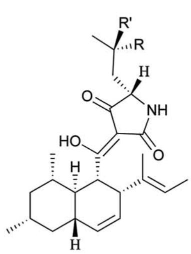
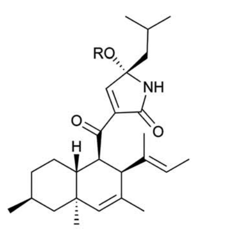
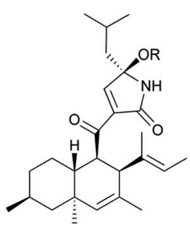
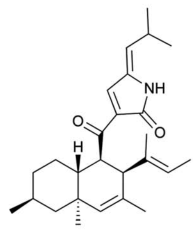

144 R = COOH, R' = OH
145 R = OH, R' = COOH


146 R = H
148 R = Me


147 R = H
149 R = Me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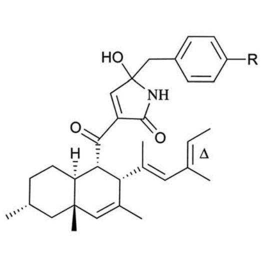
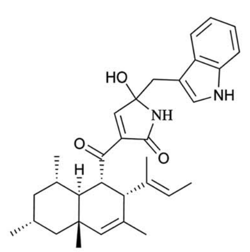

151 R = H
152 R = OH, Δ saturated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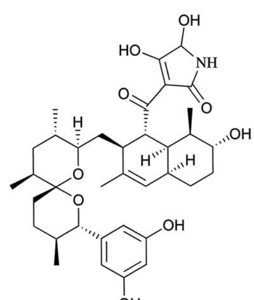
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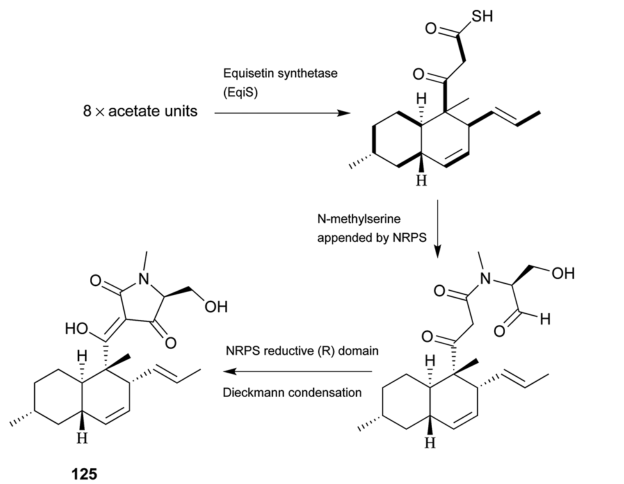


Scheme 9 The biosynthetic origin of **125**. Bold bonds in the polyketide portion represent ^{13}C-labelled acetate units. The timing of N-methylation is unclear.

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 albulus*,[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-1494α (**152**),[125] two phenylalanine-derived tetramic

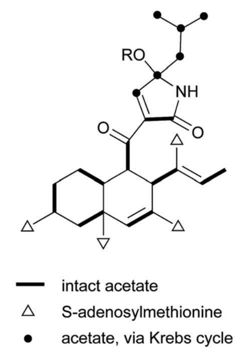
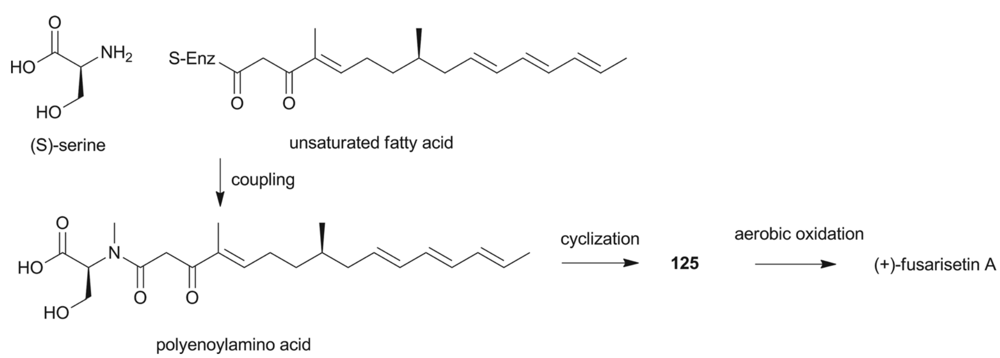
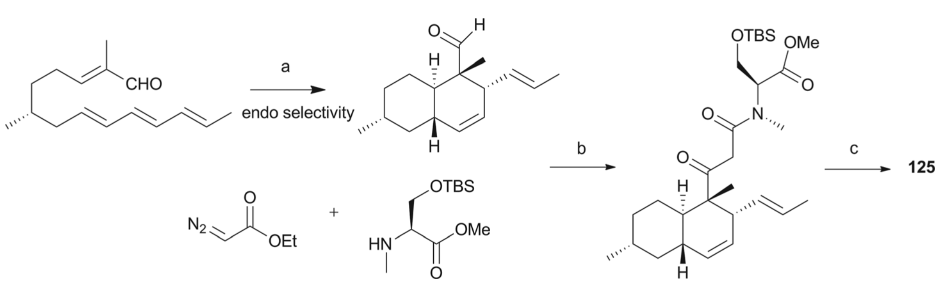


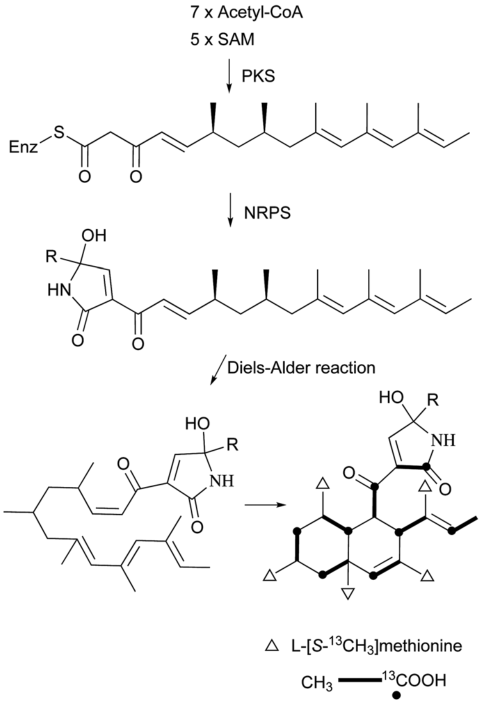
Fig. 5 Biosynthetic origin of myceliothermophins A-D (**146–149**).



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) $BF_3 \cdot Et_2O$, −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.

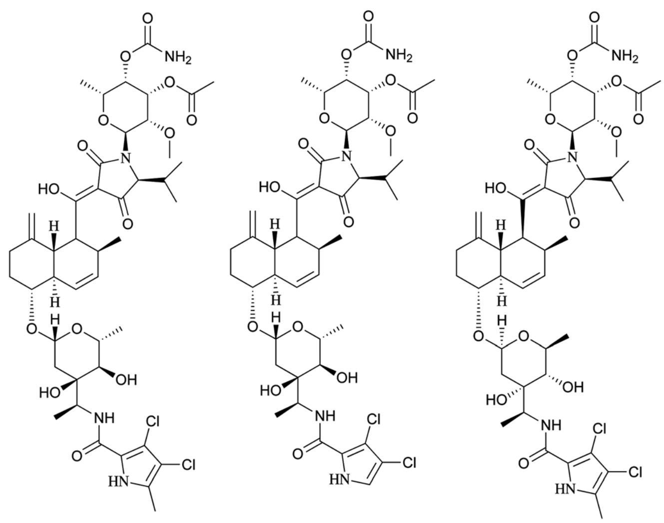
acids, were isolated from an unidentified fungus and *Penicillium rubrum*, respectively. Compound **151** was reported to be a novel antagonist of endothelin receptor while **152** was an inhibitor of platelet-activating factor acetyltransferase. An endophytic fungus, *Codinaeopsis gonytrichoides*, produced an antimalarial compound that is active against *Plasmodium falciparum* with an IC_{50} 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 IC_{50} 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}.

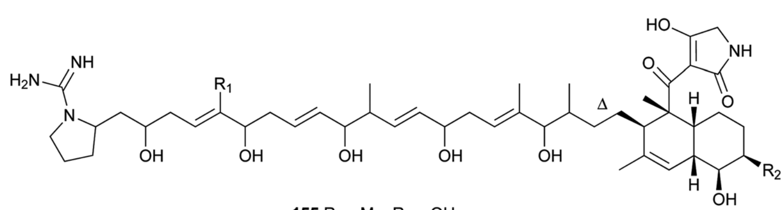
Recently, three novel broad-spectrum antibiotics (**160–162**) active against Gram-positive bacteria by inhibiting DNA gyrase and bacterial topoisomerase IV were reported.[131–133] They consist of a *trans*-decalin, tetramic acid, two unusual sugars, and dichloropyrrole carboxylic acid. Kibdelomycin (**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



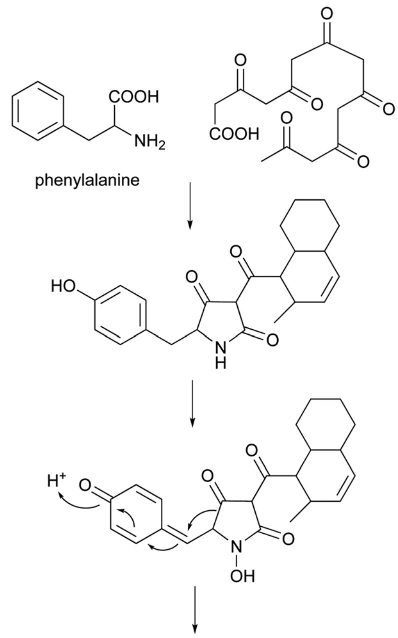
160 161 162



155 R_1 = Me, R_2 = OH
156 R_1 = H, R_2 = OH
157 R_1 = Me, R_2 = H, Δ unsaturated
158 R_1 = H, R_2 = H
159 R_1 = Me, R_2 = 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 μg mL^{-1}) and was cytotoxic against HeLa S3 cells (IC_{50} of 3.4 μg 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



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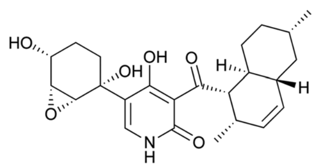
Scheme 13 The proposed biogenesis of **164**.



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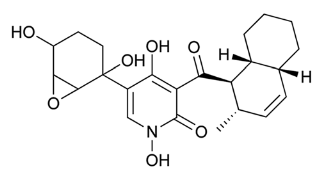

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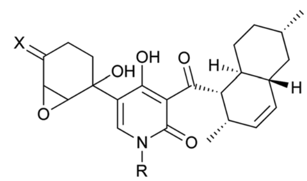
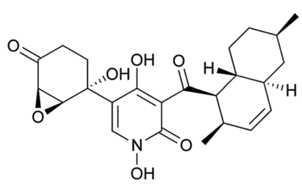


165 R = H, X = O
166 R = OH, X = OH, H



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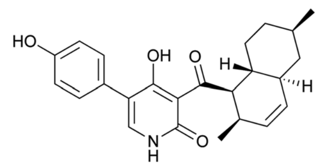

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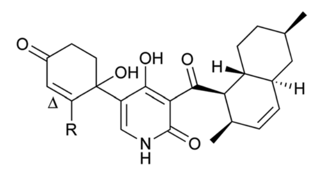
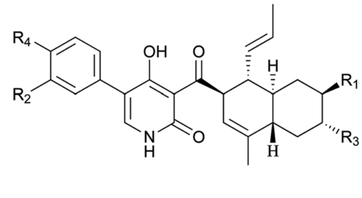
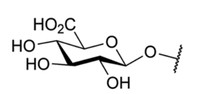


169 R = H
170 R = OH, Δ saturated



171 R_1 = Me, R_2 = H, R_3 = H, R_4 = OH
172 R_1 = CH_2OH, R_2 = H, R_3 = H, R_4 = OH
173 R_1 = COOH, R_2 = H, R_3 = H, R_4 = OH
174 R_1 = CH_2OAc, R_2 = H, R_3 = H, R_4 = OH
175 R_1 = CH_2OH, R_2 = OH, R_3 = H, R_4 = OH
176 R_1 = CH_2OAc, R_2 = OH, R_3 = H, R_4 = OH
177 R_1 = CH_2OH, R_2 = H, R_3 = OH, R_4 = OH
178 R_1 = CH_2OH, R_2 = OX, R_3 = H, R_4 = OH
179 R_1 = Me, R_2 = H, R_3 = H, R_4 = X

X =


azole-resistant *C. albicans* with an MIC value of 3.1 μg 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 bc_1 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

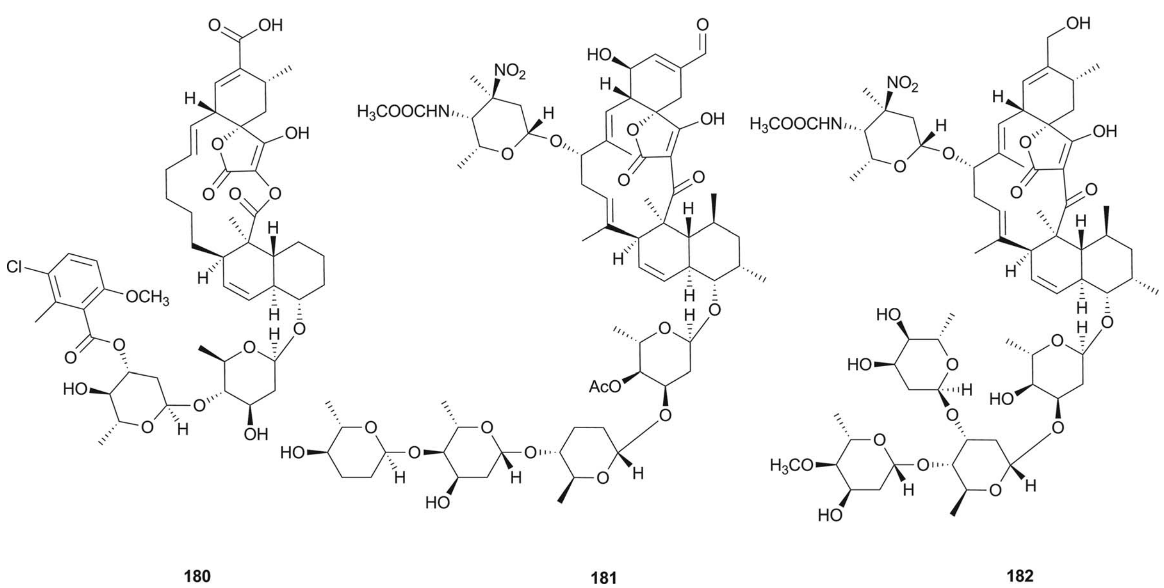
Spirotetronates, the macrolide natural products consist of a *trans*-decalin system, a spiro ring between a cyclohexene and a tetronic acid, several similar or dissimilar deoxysugars and/or a multi-substituted benzene or pyrrole.

Chlorothricin (**180**), the first reported member of spirotetronate 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]

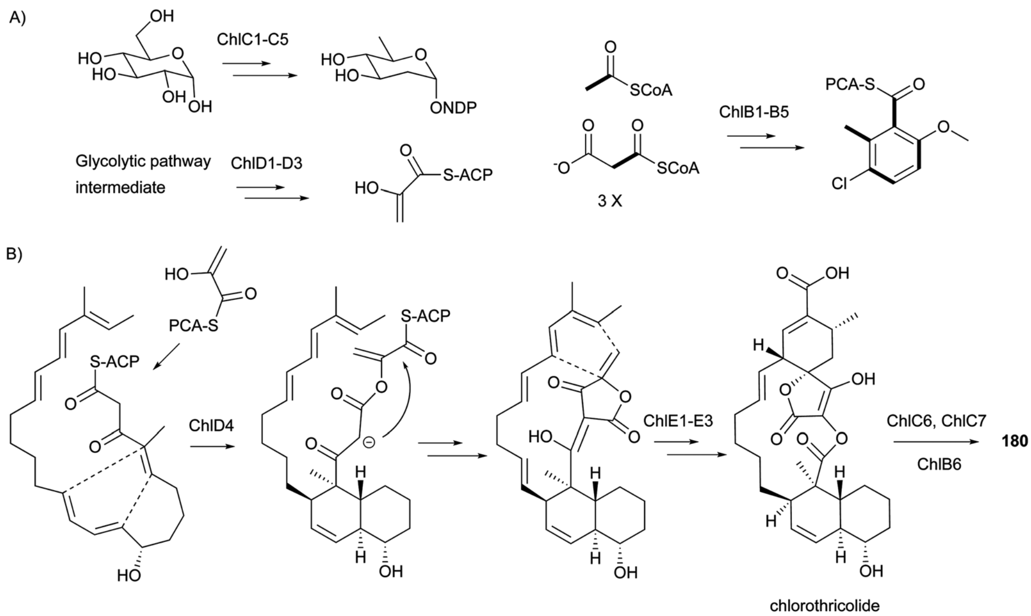
Compounds **180–182** are well-known members of more than 60 spirotetronate-type compounds, and exhibit antibacterial activities against Gram-positive bacteria and show selective antitumor activities.[151] Other biological activities are increasingly being revealed. Compound **180** has been shown to inhibit the biosynthesis of cholesterol from mevalonate with an IC_{50} 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 spirotetronate 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.

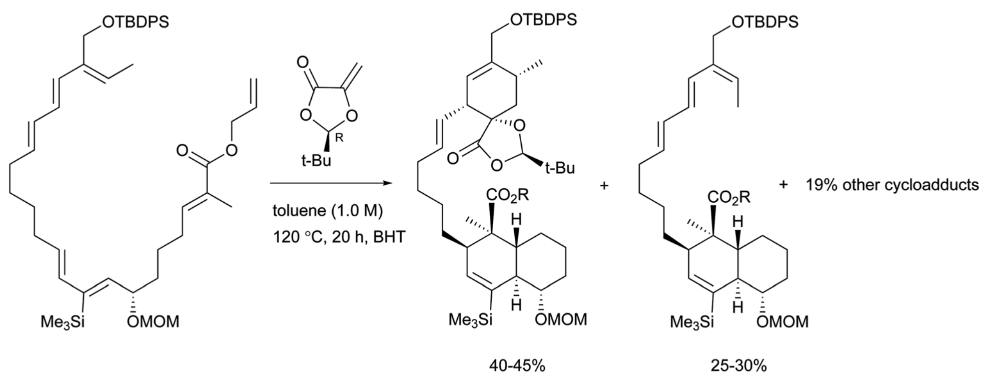
To the best of our knowledge, total syntheses of compounds **180–182** have not yet been reported, even though many syntheses for their aglycones have been achieved and many preparations of the functional intermediates have been accomplished.[162–168] Enantioselective synthesis of (−)-chlorothricolide, 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



180 **181** **182**



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



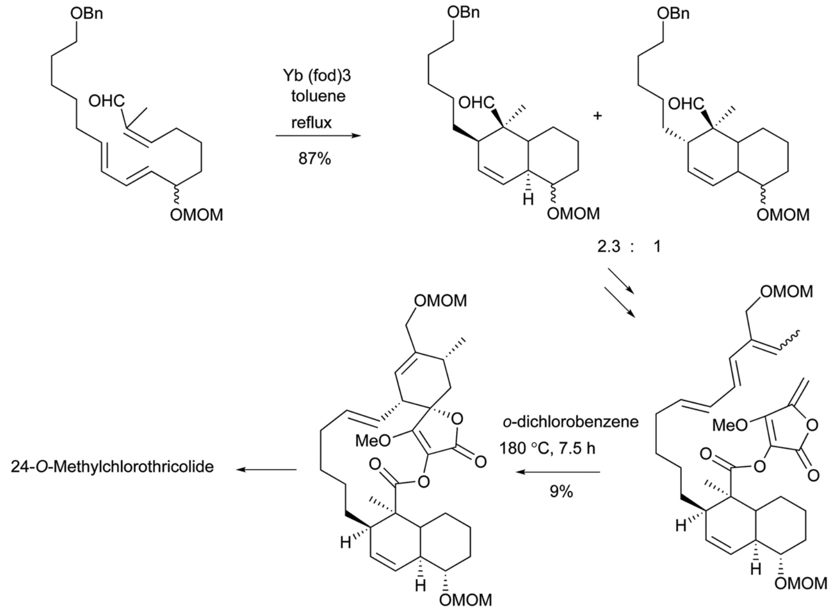
Scheme 15 Roush's key Diels–Alder reactions in the enantioselective total synthesis of (-)-chlorothricolide.

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]

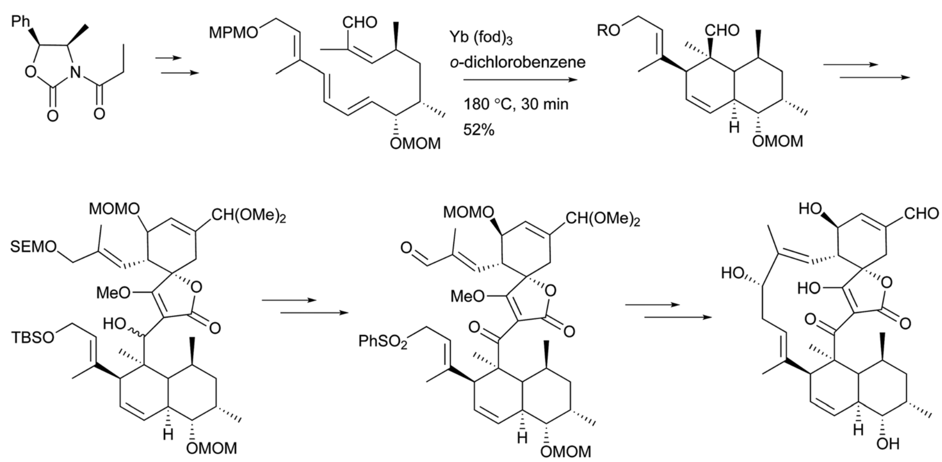
3.11 Pyrrolizidines

UCS1025-A (**183**) and -B (**184**), possessing the unprecedented furopyrrolizin-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 furopyrrolizidine fragment and used a powerful enantioselective organocatalytic intramolecular Diels–Alder reaction to obtain the required decalin.[82] The remarkable BEt_3-mediated reaction allowed direct coupling of the furopyrrolizidine fragment and the



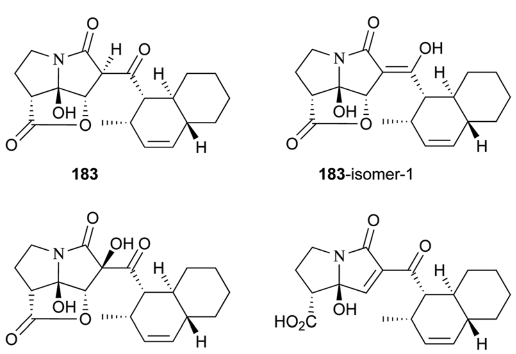
Scheme 16 Yoshii's IMDA approach to the synthesis of racemic 24-*O*-methylchlorothricolide.



Scheme 17 Yoshii's synthesis of the aglycone of **181**, tetronolide.

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

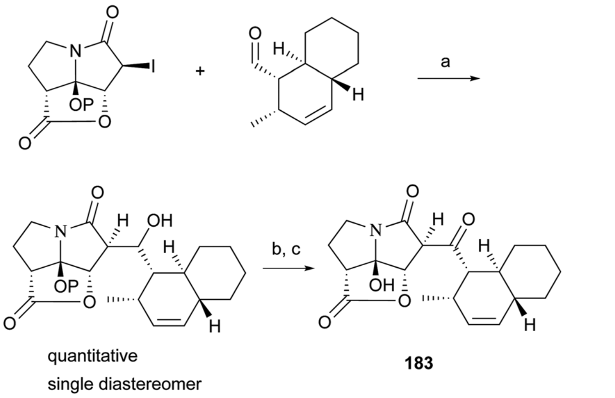
A biomimetic total synthesis of (±)-UCS1025A involving seven linear steps was accomplished by Hoye *et al.*



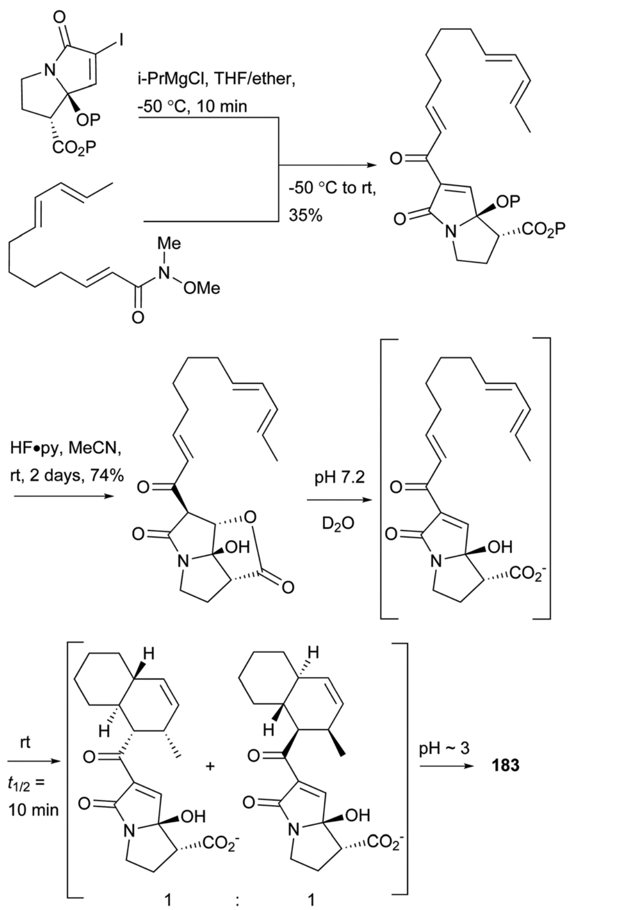
183 **183**-isomer-1 **184** **183**-isomer-2

(Scheme 19).[11] The interesting automatic cyclization of a long chain in phosphate buffer (pH 7.2, D_2O) 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 Hoye *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



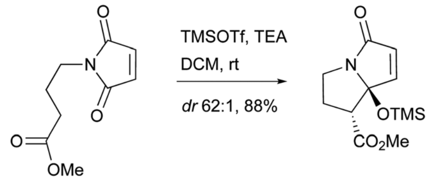
Scheme 18 Danishefsky's coupling protocol for the synthesis of **183**. (a) BEt_3, toluene, −78 °C, P = TBS; (b) TBAF, THF, 85%; (c) Dess–Martin periodinane, CH_2Cl_2, 84%.



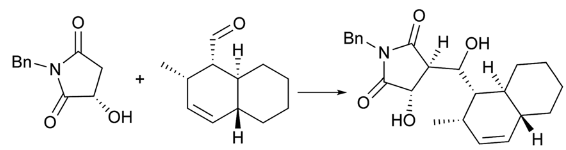
Scheme 19 Hoye's biomimetic total synthesis of **183**.

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

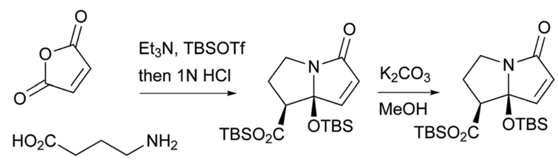
A stereoselective total synthesis of compound **183** was performed by Kan and co-workers, involving an intramolecular Diels–Alder reaction to the decalin skeleton, an intramolecular Staudinger/aza-Wittig reaction to the eight-membered lactam, the stereoselective construction of a labile



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



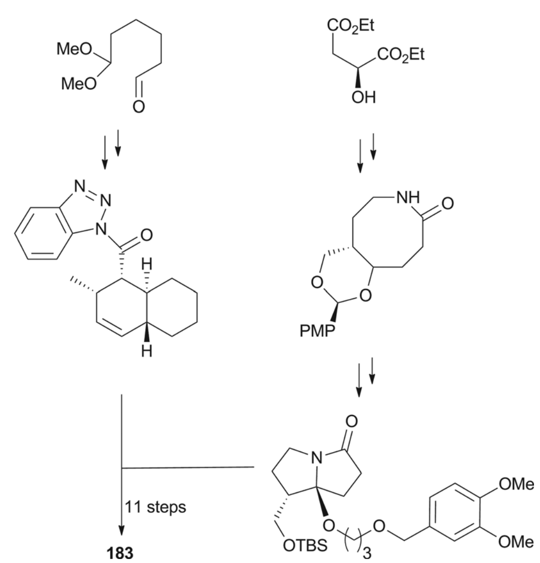
Scheme 21 Christmann's aldol coupling involved in the synthesis of an analogue of **183**. Condition: NaHMDS, THF, 0 °C, then decalin substance, −78 °C, 3.5 h, 55%.



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

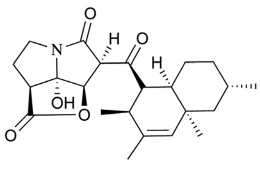
hemiaminal moiety to assess the pyrrolizidinone skeleton, and the condensation of decalin and the pyrrolizidinone system (Scheme 23).[2]

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 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]



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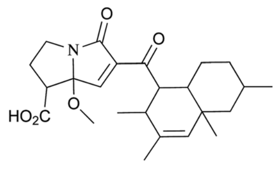

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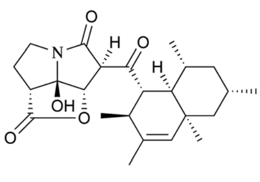

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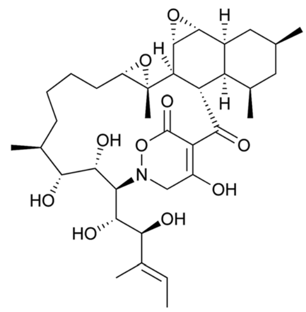
3.12 Others

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 μg 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 ^{13}C-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] Nahuoic acid A (**191**), the first known selective SAM-competitive inhibitor of SETD8 (IC_{50} of 6.5 ± 0.5 μM), 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, satosporins 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 dihydrotetrodecamycin (**195**) were obtained from the broth of *Streptomyces nashvillensis*.[184]



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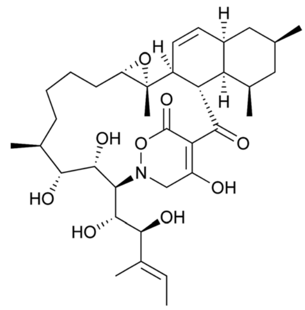

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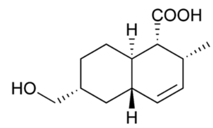

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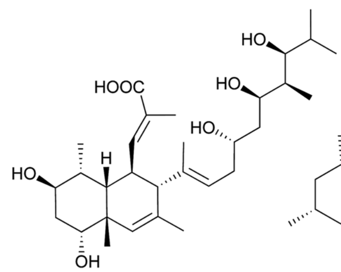

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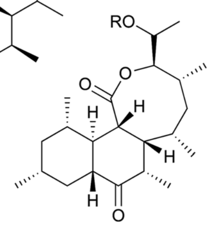
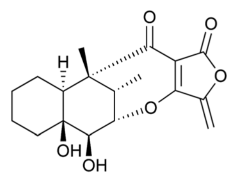


192 R = β-D-Glu(1 to 3)-β-D-Glu
193 R = β-D-Glu



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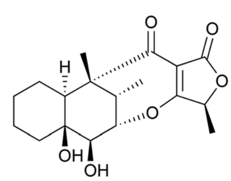

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4 Isoprenoid decalin

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 bicyclofarnesane-type sesquiterpenes according to the

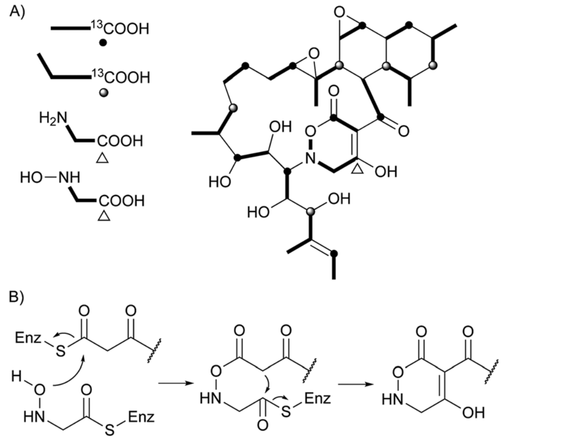
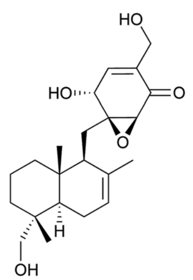


Fig. 6 Biosynthetic investigation for **188**. (A) Incorporation of ^{13}C-labeled precursors into **188**. (B) Proposed biosynthetic pathway for tetrahydrooxazine ring.

classification in earlier reviews.[4–6] Cadinane sesquiterpenes have demonstrated highly selective and notable nematicidal 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



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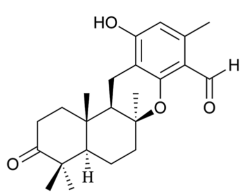

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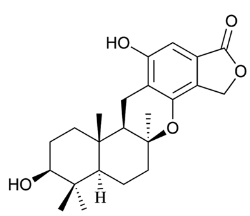

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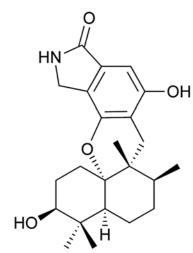

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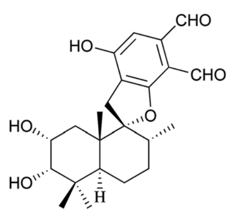

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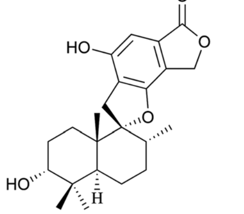

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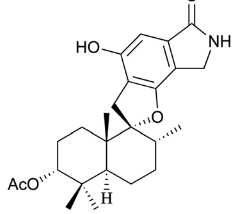

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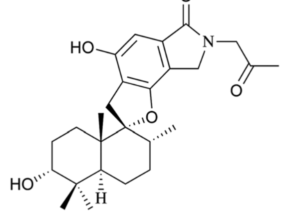

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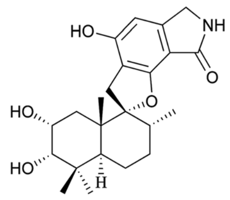

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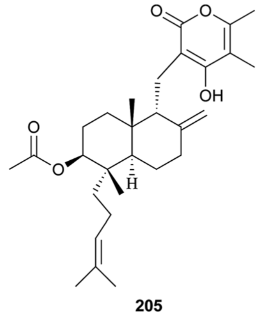

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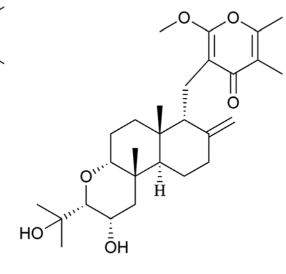

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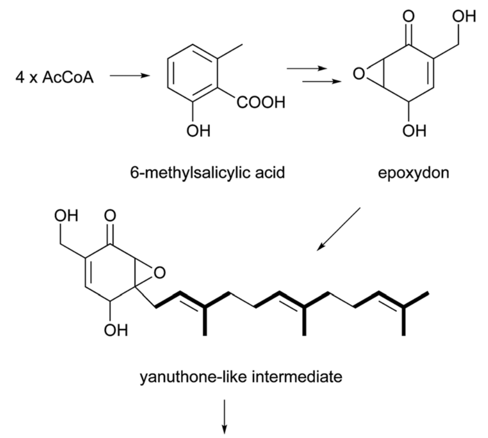

Scheme 24 The proposed biosynthesis for **196**.

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 monacolins 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.

6 Acknowledgements

G.L. gratefully acknowledges the China Scholarship Council (CSC) for a doctoral fellowship. S.K. was a Visiting Researcher at the Department of Plant Sciences, University of Oxford, South Parks Road, Oxford OX1 3RB, UK, during preparation of the manuscript (Apr 2013 to Mar 2014). S.K. gratefully acknowledges Dr Gail M. Preston for hosting and TU Dortmund for supporting his stay at the University of Oxford. The authors are grateful to Prof. Michael Müller of the University of Freiburg, Germany for valuable comments and suggestions.

7 References

1 E. M. Stocking and R. M. Williams, *Angew. Chem., Int. Ed.*, 2003, **42**, 3078–3115.
2 K. Uchida, T. Ogawa, Y. Yasuda, H. Mimura, T. Fujimoto, T. Fukuyama, T. Wakimoto, T. Asakawa, Y. Hamashima and T. Kan, *Angew. Chem., Int. Ed.*, 2012, **51**, 12850–12853.
3 V. Singh, S. R. Iyer and S. Pal, *Tetrahedron*, 2005, **61**, 9197–9231.
4 B. M. Fraga, *Nat. Prod. Rep.*, 2013, **30**, 1226–1264.
5 J. R. Hanson, *Nat. Prod. Rep.*, 2009, **26**, 1156–1171.
6 J. R. Hanson, *Nat. Prod. Rep.*, 2013, **30**, 1346–1356.
7 W. L. Kelly, *Org. Biomol. Chem.*, 2008, **6**, 4483–4493.
8 H. J. Kim, M. W. Ruszczycky, S.-h. Choi, Y.-n. Liu and H.-w. Liu, *Nature*, 2011, **473**, 109–112.
9 K. Auclair, A. Sutherland, J. Kennedy, D. J. Witter, J. P. Van den Heever, C. R. Hutchinson and J. C. Vederas, *J. Am. Chem. Soc.*, 2000, **122**, 11519–11520.
10 K. Kasahara, T. Miyamoto, T. Fujimoto, H. Oguri, T. Tokiwano, H. Oikawa, Y. Ebizuka and I. Fujii, *ChemBioChem*, 2010, **11**, 1245–1252.
11 T. R. Hoye and V. Dvornikovs, *J. Am. Chem. Soc.*, 2006, **128**, 2550–2551.
12 M. A. Varner and R. B. Grossman, *Tetrahedron*, 1999, **55**, 13867–13886.
13 T. Tokoroyama, *Synthesis*, 2000, 611–633.
14 H. Akita, *Heterocycles*, 2013, **87**, 1625–1658.
15 E. S. Istvan and J. Deisenhofer, *Science*, 2001, **292**, 1160–1164.
16 W. Xu, Y.-H. Chooi, J. W. Choi, S. Li, J. C. Vederas, N. A. Da Silva and Y. Tang, *Angew. Chem., Int. Ed.*, 2013, **52**, 6472–6475.
17 A. Endo, *J. Antibiot.*, 1979, **32**, 852–854.
18 A. Endo, *J. Antibiot.*, 1980, **33**, 334–336.
19 A. W. Alberts, J. Chen, G. Kuron, V. Hunt, J. Huff, C. Hoffman, J. Rothrock, M. Lopez, H. Joshua, E. Harris, A. Patchett, R. Monaghan, S. Currie, E. Stapley, G. Albers-Schonberg, O. Hensens, J. Hirshfield, K. Hoogsteen, J. Liesch and J. Springer, *Proc. Natl. Acad. Sci. U. S. A.*, 1980, **77**, 3957–3961.
20 J. Kennedy, K. Auclair, S. G. Kendrew, C. Park, J. C. Vederas and C. R. Hutchinson, *Science*, 1999, **284**, 1368–1372.
21 X. Xie, M. J. Meehan, W. Xu, P. C. Dorrestein and Y. Tang, *J. Am. Chem. Soc.*, 2009, **131**, 8388–8389.
22 J. Barriuso, D. T. Nguyen, J. W.-H. Li, J. N. Roberts, G. MacNevin, J. L. Chaytor, S. L. Marcus, J. C. Vederas and D.-K. Ro, *J. Am. Chem. Soc.*, 2011, **133**, 8078–8081.
23 B. D. Ames, C. Nguyen, J. Bruegger, P. Smith, W. Xu, S. Ma, E. Wong, S. Wong, X. Xie, J. W.-H. Li, J. C. Vederas, Y. Tang and S.-C. Tsai, *Proc. Natl. Acad. Sci. U. S. A.*, 2012, **109**, 11144–11149.
24 G. Albers-Schönberg, H. Joshua, M. B. Lopez, O. D. Hensens, J. P. Springer, J. Chen, S. Ostrove,

C. H. Hoffman, A. W. Alberts and A. A. Patchett, *J. Antibiot.*, 1981, **34**, 507–512.
25 A. Endo, K. Hasumi and S. Negishi, *J. Antibiot.*, 1985, **38**, 420–422.
26 A. Endo, K. Hasumi, T. Nakamura, M. Kunishima and M. Masuda, *J. Antibiot.*, 1985, **38**, 321–327.
27 A. Endo, D. Komagata and H. Shimada, *J. Antibiot.*, 1986, **39**, 1670–1673.
28 L. R. Treiber, R. A. Reamer, C. S. Rooney and H. G. Ramjit, *J. Antibiot.*, 1989, **42**, 30–36.
29 A. G. Brown, T. C. Smale, T. J. King, R. Hasenkamp and R. H. Thompson, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1165–1170.
30 A. Endo, M. Kuroda and Y. Tsujita, *J. Antibiot.*, 1976, **29**, 1346–1348.
31 Y. K. Tony Lam, V. P. Gullo, R. T. Goegelman, D. Jorn, L. Huang, C. DeRiso, R. L. Monaghan and I. Putter, *J. Antibiot.*, 1981, **34**, 614–616.
32 S. Murakawa, K. Sakai and A. Endo, *J. Antibiot.*, 1994, **47**, 108–109.
33 S. Okamoto, T. Hosoe, T. Itabashi, K. Nozawa, K. Okada, G. M. de C. Takaki, M. Chikamori, T. Yaguchi, K. Fukushima, M. Miyaji and K. Kawai, *J. Nat. Prod.*, 2004, **67**, 1580–1583.
34 M.-T. Liu, J.-J. Li, X.-Y. Shang, S. Li, L.-L. Li, N. Luan and Z.-L. Jin, *Magn. Reson. Chem.*, 2011, **49**, 129–131.
35 M.-T. Liu, N. Luan, J.-J. Li, X. Huang, Y.-F. Wang, A.-L. Wang and X.-Y. Shang, *Magn. Reson. Chem.*, 2012, **50**, 709–712.
36 L. Zhu, L.-F. Yau, J.-G. Lu, G.-Y. Zhu, J.-R. Wang, Q.-B. Han, W.-L. Hsiao and Z.-H. Jiang, *J. Agric. Food Chem.*, 2012, **60**, 934–939.
37 L. Zhu, J.-G. Lu, T. Li, G.-Y. Zhu, Q.-B. Han, W.-L. Hsiao, L. Liu and Z.-H. Jiang, *J. Nat. Prod.*, 2012, **75**, 567–571.
38 Y.-T. Zhang, Y. Wang, X.-T. Zhang, D.-L. Wu, X.-Q. Zhang and W.-C. Ye, *J. Asian Nat. Prod. Res.*, 2009, **11**, 792–795.
39 I. Barash, G. Pupkin, D. Netzer and Y. Kashman, *Plant Physiol.*, 1982, **69**, 23–27.
40 I. Barash, S. Manulis, Y. Kashman, J. P. Springer, M. H. M. Chen, J. Clardy and G. A. Strobel, *Science*, 1983, **220**, 1065–1066.
41 S. Manulis, Y. Kashman, D. Netzert and I. Barash, *Phytochemistry*, 1984, **23**, 2193–2198.
42 I. Barash and S. Manulis, in *Iron, Siderophores, and Plant Diseases*, Springer 1986, 117, pp. 273–281.
43 A. Ichihara, H. Oikawa, K. Hayashi, S. Sakamura, A. Furusaki and T. Matsumoto, *J. Am. Chem. Soc.*, 1983, **105**, 2907–2908.
44 A. Ichihara, H. Oikawa, M. Hashimoto, S. Sakamura, T. Haraguchi and H. Nagano, *Agric. Biol. Chem.*, 1983, **47**, 2965–2967.
45 H. Oikawa, A. Ichihara and S. Sakamura, *J. Chem. Soc., Chem. Commun.*, 1984, 814–815.
46 H. Oikawa, A. Ichihara and S. Sakamura, *J. Chem. Soc., Chem. Commun.*, 1988, 600–602.
47 M. Kobayashi, H. Uehara, K. Matsunami, S. Aoki and I. Kitagawa, *Tetrahedron Lett.*, 1993, **34**, 7925–7928.
48 W. S. Horn, R. E. Schwartz, M. S. J. Simmonds and W. M. Blaney, *Tetrahedron Lett.*, 1994, **35**, 6037–6040.
49 R. Sawa, Y. Takahashi, S. Itoh, K. Shimanaka, N. Kinoshita, Y. Homma, M. Hamada, T. Sawa, H. Naganawa and T. Takeuchi, *J. Antibiot.*, 1994, **47**, 1266–1272.
50 O. D. Hensens, G. L. Helms, E. T. T. Jones and G. H. Harris, *J. Org. Chem.*, 1995, **60**, 1772–1776.
51 L. Rahbæk, S. Sperry, J. E. Piper and P. Crews, *J. Nat. Prod.*, 1998, **61**, 1571–1573.
52 G. Brauers, R. A. Edrada, R. Ebel, P. Proksch, V. Wray, A. Berg, U. Gräfe, C. Schächtele, F. Totzke, G. Finkenzeller, D. Marme, J. Kraus, M. Münchbach, M. Michel, G. Bringmann and K. Schaumann, *J. Nat. Prod.*, 2000, **63**, 739–745.
53 Y. Fujii, M. Asahara, M. Ichinoe and H. Nakajima, *Phytochemistry*, 2002, **60**, 703–708.
54 S. Tsukamoto, S. Miura, Y. Yamashita and T. Ohta, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 417–420.
55 Y. Ohtsu, S. Yoshimura, T. Kinoshita, S. Takase and H. Nakajima, *J. Antibiot.*, 2005, **58**, 479–482.
56 S. Nakadate, K. Nozawa, H. Horie, Y. Fujii, M. Nagai, T. Hosoe, K. Kawai, T. Yaguchi and K. Fukushima, *J. Nat. Prod.*, 2007, **70**, 1510–1512.
57 T. Yamada, Y. Mizutani, Y. Umebayashi, N. Inno, M. Kawashima, T. Kikuchi and R. Tanaka, *Tetrahedron Lett.*, 2014, **55**, 662–664.
58 M. Kuramoto, K. Yamada, M. Shikano, K. Yazawa, H. Arimoto, T. Okamura and D. Uemura, *Chem. Lett.*, 1997, 885–886.
59 J. Malmstrøm, C. Christophersen and J. C. Frisvad, *Phytochemistry*, 2000, **54**, 301–309.
60 M. El-Neketi, W. Ebrahim, W. Lin, S. Gedara, F. Badria, H.-E. A. Saad, D. Lai and P. Proksch, *J. Nat. Prod.*, 2013, **76**, 1099–1104.
61 L. P. Sandjo, E. Thines, T. Opatz and A. Schüffler, *Beilstein J. Org. Chem.*, 2014, **10**, 251–258.
62 N. Tabata, H. Tomoda, R. Masuma, K. Haneda, Y. Iwai and S. Ōmura, *J. Antibiot.*, 1993, **46**, 1849–1853.
63 R. Masuma, N. Tabata, H. Tomoda, K. Haneda, Y. Iwai and S. Ōmura, *J. Antibiot.*, 1994, **47**, 46–53.
64 J. G. Ondeyka, R. A. Giacobbe, G. F. Bills, C. Cuadrillero, D. Schmatz, M. A. Goetz, D. L. Zink and S. B. Singh, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 3439–3442.
65 M. Namikoshi, H. Kobayashi, T. Yoshimoto and T. Hosoya, *J. Antibiot.*, 1997, **50**, 890–892.
66 H. Kobayashi, S. Meguro, T. Yoshimoto and M. Namikoshi, *Tetrahedron*, 2003, **59**, 455–459.
67 C. A. Parish, M. de la Cruz, S. K. Smith, D. Zink, J. Baxter, S. Tucker-Samaras, J. Collado, G. Platas, G. Bills, M. T. Díez, F. Vicente, F. Peláez and K. Wilson, *J. Nat. Prod.*, 2009, **72**, 59–62.
68 H. Kobayashi, R. Sunaga, K. Furihata, N. Morisaki and S. Iwasaki, *J. Antibiot.*, 1995, **48**, 42–52.
69 H. P. Nguyen, D. Zhang, U. Lee, J. S. Kang, H. D. Choi and B. W. Son, *J. Nat. Prod.*, 2007, **70**, 1188–1190.
70 H. Kumagai, T. Someno, K. Dobashi, K. Isshiki, M. Ishizuka and D. Ikeda, *J. Antibiot.*, 2004, **57**, 97–103.

71 M. I. Mitova, G. Lang, J. W. Blunt, N. J. Cummings, A. L. J. Cole, W. T. Robinson and M. H. G. Munro, *J. Org. Chem.*, 2006, **71**, 492–497.
72 D. B. Stierle, A. A. Stierle and B. K. Ganser, *J. Nat. Prod.*, 1999, **62**, 1147–1150.
73 S. Sakamoto, F. Kojima, M. Igarashi, R. Sawa, M. Umekita, Y. Kubota, K. Nakae, S. Yamaguchi, H. Adachi, Y. Nishimura and Y. Akamatsu, *J. Antibiot.*, 2010, **63**, 703–708.
74 S. Sakamoto, F. Kojima, I. Momose, M. Kawada, H. Adachi and Y. Nishimura, *Biochem. Biophys. Res. Commun.*, 2012, **422**, 751–757.
75 H. Oikawa, T. Yokota, A. Ichihara and S. Sakamura, *J. Chem. Soc., Chem. Commun.*, 1989, 1284–1285.
76 H. Oikawa, Y. Suzuki, A. Naya, K. Katayama and A. Ichihara, *J. Am. Chem. Soc.*, 1994, **116**, 3605–3606.
77 A. Ichihara, H. Tazaki and S. Sakamura, *Tetrahedron Lett.*, 1983, **24**, 5373–5376.
78 Y. Mizushina, S. Kamisuki, N. Kasai, N. Shimazaki, M. Takemura, H. Asahara, S. Linn, S. Yoshida, A. Matsukage, O. Koiwai, F. Sugawara, H. Yoshida and K. Sakaguchi, *J. Biol. Chem.*, 2002, **277**, 630–638.
79 H. Oikawa, T. Yokota, C. Sakano, Y. Suzuki, A. Naya and A. Ichihara, *Biosci., Biotechnol., Biochem.*, 1998, **62**, 2016–2022.
80 H. Hagiwara, K. Kobayashi, S. Miya, T. Hoshi, T. Suzuki, M. Ando, T. Okamoto, M. Kobayashi, I. Yamamoto, S. Ohtsubo, M. Kato and H. Uda, *J. Org. Chem.*, 2002, **67**, 5969–5976.
81 B. Lygo, M. Bhatia, J. W. B. Cooke and D. J. Hirst, *Tetrahedron Lett.*, 2003, **44**, 2529–2532.
82 R. M. Wilson, W. S. Jen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 11616–11617.
83 K. M. Jenkins, S. G. Toske, P. R. Jensen and W. Fenical, *Phytochemistry*, 1998, **49**, 2299–2304.
84 L. E. Schmidt, J. B. Gloer and D. T. Wicklow, *J. Nat. Prod.*, 2007, **70**, 1317–1320.
85 K. Trisuwan, V. Rukachaisirikul, Y. Sukpondma, S. Preedanon, S. Phongpaichit and J. Sakayaroj, *Phytochemistry*, 2009, **70**, 554–557.
86 H. A. Whaley, C. G. Chidester, S. A. Mizsak and R. J. Wnuk, *Tetrahedron Lett.*, 1980, **21**, 3659–3662.
87 W. D. Celmer, G. N. Chmurny, C. E. Moppett, R. S. Ware, P. C. Watts and E. B. Whipple, *J. Am. Chem. Soc.*, 1980, **102**, 4203–4209.
88 W. C. Snyder and K. L. Rinehart, Jr, *J. Am. Chem. Soc.*, 1984, **106**, 787–789.
89 R. R. Rasmussen, M. H. Scherr, D. N. Whittern, A. M. Buko and J. B. McAlpine, *J. Antibiot.*, 1987, **40**, 1383–1393.
90 H. Gouda, T. Sunazuka, H. Ui, M. Handa, Y. Sakoh, Y. Iwai, S. Hirono and S. Ōmura, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 18286–18291.
91 J. B. McAlpine, L. A. Mitscher, M. Jackson, R. R. Rasmussen, D. V. Velde and E. Veliz, *Tetrahedron*, 1996, **52**, 10327–10334.
92 K. Gerth, H. Steinmetz, G. Höfle and R. Jansen, *Angew. Chem., Int. Ed.*, 2008, **47**, 600–602.
93 N. Rahn and M. Kalesse, *Angew. Chem., Int. Ed.*, 2008, **47**, 597–599.
94 K. H. Jang, S.-J. Nam, J. B. Locke, C. A. Kauffman, D. S. Beatty, L. A. Paul and W. Fenical, *Angew. Chem., Int. Ed.*, 2013, **52**, 7822–7824.
95 B. J. Royles, *Chem. Rev.*, 1995, **95**, 1981–2001.
96 R. Schobert and A. Schlenk, *Bioorg. Med. Chem.*, 2008, **16**, 4203–4221.
97 B. Nay, N. Riache and L. Evanno, *Nat. Prod. Rep.*, 2009, **26**, 1044–1062.
98 H. R. Burmeister, G. A. Bennett, R. F. Vesonder and C. W. Hesseltine, *Antimicrob. Agents Chemother.*, 1974, **5**, 634–639.
99 R. F. Vesonder, L. W. Tjarks, W. K. Rohwedder, H. R. Burmeister and J. A. Laugal, *J. Antibiot.*, 1979, **32**, 759–761.
100 E. C. Marfori, T. Bamba, S. Kajiyama, E. Fukusaki and A. Kobayashi, *Tetrahedron*, 2002, **58**, 6655–6658.
101 D. Boettger and C. Hertweck, *ChemBioChem*, 2013, **14**, 28–42.
102 J. W. Sims and E. W. Schmidt, *J. Am. Chem. Soc.*, 2008, **130**, 11149–11155.
103 E. Turos, J. E. Audia and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1989, **111**, 8231–8236.
104 K. Yuki, M. Shindo and K. Shishido, *Tetrahedron Lett.*, 2001, **42**, 2517–2519.
105 L. T. Burke, D. J. Dixon, S. V. Ley and F. Rodríguez, *Org. Biomol. Chem.*, 2005, **3**, 274–280.
106 J. Yin, L. Kong, C. Wang, Y. Shi, S. Cai and S. Gao, *Chem.-Eur. J.*, 2013, **19**, 13040–13046.
107 S. B. Singh, D. L. Zink, M. A. Goetz, A. W. Dombrowski, J. D. Polishook and D. J. Hazuda, *Tetrahedron Lett.*, 1998, **39**, 2243–2246.
108 J. Y. Li, G. Strobel, J. Harper, E. Lobkovsky and J. Clardy, *Org. Lett.*, 2000, **2**, 767–770.
109 V. Hellwig, T. Grothe, A. Mayer-Bartschmid, R. Endermann, F.-U. Geschke, T. Henkel and M. Stadler, *J. Antibiot.*, 2002, **55**, 881–892.
110 M. P. Segeth, A. Bonnefoy, M. Brönstrup, M. Knauf, D. Schummer, L. Toti, L. Vértesy, M.-C. Wetzel-Raynal, J. Wink and G. Seibert, *J. Antibiot.*, 2003, **56**, 114–122.
111 E. C. Marfori, S. Kajiyama, E. Fukusaki and A. Kobayashi, *Z. Naturforsch.*, 2002, **57c**, 465–470.
112 C. Boros, A. Dix, B. Katz, Y. Vasina and C. Pearce, *J. Antibiot.*, 2003, **56**, 862–865.
113 S. P. Putri, H. Kinoshita, F. Ihara, Y. Igarashi and T. Nihira, *J. Antibiot.*, 2010, **63**, 195–198.
114 J. Whitt, S. M. Shipley, D. J. Newman and K. M. Zuck, *J. Nat. Prod.*, 2014, **77**, 173–177.
115 T. Amagata, J. Xiao, Y.-P. Chen, N. Holsopple, A. G. Oliver, T. Gokey, A. B. Guliaev and K. Minoura, *J. Nat. Prod.*, 2012, **75**, 2193–2199.
116 K. Herath, H. Jayasuriya, D. L. Zink, J. Sigmund, F. Vicente, M. de la Cruz, A. Basilio, G. F. Bills, J. D. Polishook, R. Donald, J. Phillips, M. Goetz and S. B. Singh, *J. Nat. Prod.*, 2012, **75**, 420–424.

117 Y. Sugie, K. A. Dekker, T. Inagaki, Y.-J. Kim, T. Sakakibara, S. Sakemi, A. Sugiura, L. Brennan, J. Duignan, J. A. Sutcliffe and Y. Kojima, *J. Antibiot.*, 2002, **55**, 19–24.
118 Y. Sugie, S. Inagaki, Y. Kato, H. Nishida, C.-H. Pang, T. Saito, S. Sakemi, F. Dib-Hajj, J. P. Mueller, J. Sutcliffe and Y. Kojima, *J. Antibiot.*, 2002, **55**, 25–29.
119 C. Osterhage, R. Kaminsky, G. M. König and A. D. Wright, *J. Org. Chem.*, 2000, **65**, 6412–6417.
120 S. Toda, S. Yamamoto, O. Tenmyo, T. Tsuno, T. Hasegawa, M. Rosser, M. Oka, Y. Sawada, M. Konishi and T. Oki, *J. Antibiot.*, 1993, **46**, 875–883.
121 M. Ueno, T. Someno, R. Sawa, H. Iinuma, H. Naganawa, M. Ishizuka and T. Takeuchi, *J. Antibiot.*, 1993, **46**, 979–984.
122 S.-W. Yang, R. Mierzwa, J. Terracciano, M. Patel, V. Gullo, N. Wagner, B. Baroudy, M. Puar, T.-M. Chan, A. T. McPhail and M. Chu, *J. Nat. Prod.*, 2006, **69**, 1025–1028.
123 Y.-L. Yang, C.-P. Lu, M.-Y. Chen, K.-Y. Chen, Y.-C. Wu and S.-H. Wu, *Chem.-Eur. J.*, 2007, **13**, 6985–6991.
124 S. B. Singh, M. A. Goetz, E. T. Jones, G. F. Bills, R. A. Giacobbe, L. Herranz, S. Stevens-Miles and D. L. Williams, Jr, *J. Org. Chem.*, 1995, **60**, 7040–7042.
125 R. R. West, J. Van Ness, A.-M. Varming, B. Rassing, S. Biggs, S. Gasper, P. A. Mckernan and J. Piggott, *J. Antibiot.*, 1996, **49**, 967–973.
126 R. Kontnik and J. Clardy, *Org. Lett.*, 2008, **10**, 4149–4151.
127 S. B. Singh, D. L. Zink, B. Heimbach, O. Genilloud, A. Teran, K. C. Silverman, R. B. Lingham, P. Felock and D. J. Hazuda, *Org. Lett.*, 2002, **4**, 1123–1126.
128 Y. Hayakawa, N. Kanamaru, A. Shimazu and H. Seto, *J. Antibiot.*, 1991, **44**, 282–287.
129 Y. Hayakawa, N. Kanamaru, N. Morisaki, H. Seto and K. Furihata, *Tetrahedron Lett.*, 1991, **32**, 213–216.
130 T. Furumai, K. Eto, T. Sasaki, H. Higuchi, H. Onaka, N. Saito, T. Fujita, H. Naoki and Y. Igarashi, *J. Antibiot.*, 2002, **55**, 873–880.
131 J. W. Phillips, M. A. Goetz, S. K. Smith, D. L. Zink, J. Polishook, R. Onishi, S. Salowe, J. Wiltsie, J. Allocco, J. Sigmund, K. Dorso, S. Lee, S. Skwish, M. de la Cruz, J. Martín, F. Vicente, O. Genilloud, J. Lu, R. E. Painter, K. Young, K. Overbye, R. G. K. Donald and S. B. Singh, *Chem. Biol.*, 2011, **18**, 955–965.
132 S. B. Singh, M. A. Goetz, S. K. Smith, D. L. Zink, J. Polishook, R. Onishi, S. Salowe, J. Wiltsie, J. Allocco, J. Sigmund, K. Dorso, M. de la Cruz, J. Martín, F. Vicente, O. Genilloud, R. G. K. Donald and J. W. Phillips, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 7127–7130.
133 R. Sawa, Y. Takahashi, H. Hashizume, K. Sasaki, Y. Ishizaki, M. Umekita, M. Hatano, H. Abe, T. Watanabe, N. Kinoshita, Y. Homma, C. Hayashi, K. Inoue, S. Ohba, T. Masuda, M. Arakawa, Y. Kobayashi, M. Hamada, M. Igarashi, H. Adachi, Y. Nishimura and Y. Akamatsu, *Chem.-Eur. J.*, 2012, **18**, 15772–15781.
134 H. J. Jessen and K. Gademann, *Nat. Prod. Rep.*, 2010, **27**, 1168–1185.
135 A. A. Alfatafta, J. B. Gloer, J. A. Scott and D. Malloch, *J. Nat. Prod.*, 1994, **57**, 1696–1702.
136 H. Fujimoto, M. Ikeda, K. Yamamoto and M. Yamazaki, *J. Nat. Prod.*, 1993, **56**, 1268–1275.
137 S. Bergmann, J. Schümann, K. Scherlach, C. Lange, A. A. Brakhage and C. Hertweck, *Nat. Chem. Biol.*, 2007, **3**, 213–217.
138 M. Shibazaki, M. Taniguchi, T. Yokoi, K. Nagai, M. Watanabe, K. Suzuki and T. Yamamoto, *J. Antibiot.*, 2004, **57**, 379–382.
139 J. C. Lee, S. J. Coval and J. Clardy, *J. Antibiot.*, 1996, **49**, 693–696.
140 A. Haga, H. Tamoto, M. Ishino, E. Kimura, T. Sugita, K. Kinoshita, K. Takahashi, M. Shiro and K. Koyama, *J. Nat. Prod.*, 2013, **76**, 750–754.
141 S. Hayakawa, H. Minato and K. Katagiri, *J. Antibiot.*, 1971, **24**, 653–654.
142 E. B. Gutierrez-Cirlos, T. Merbitz-Zahradnik and B. L. Trumpower, *J. Biol. Chem.*, 2004, **279**, 8708–8714.
143 M. Tanabe and S. Urano, *Tetrahedron*, 1983, **39**, 3569–3574.
144 S. B. Singh, X. Li and T. Chen, *Tetrahedron Lett.*, 2011, **52**, 6190–6191.
145 W. Keller-Schierlein, R. Muntwyler, W. Pache and H. Zähner, *Helv. Chim. Acta*, 1969, **52**, 127–142.
146 F. Tomita, T. Tamaoki, K. Shirahata, M. Kasai, M. Morimoto, S. Ohkubo, K. Mineura and S. Ishii, *J. Antibiot.*, 1980, **33**, 668–670.
147 K. Kobinata, M. Uramoto, T. Mizuno and K. Isono, *J. Antibiot.*, 1980, **33**, 244–246.
148 J. A. Waitz, A. Horan, M. Kalyanpur, B. K. Lee, D. Loebenberg, J. A. Marquez, G. Miller and M. G. Patel, *J. Antibiot.*, 1981, **34**, 1101–1106.
149 A. K. Mallams, M. S. Puar and R. R. Rossman, *J. Am. Chem. Soc.*, 1981, **103**, 3938–3940.
150 A. K. Mallams, M. S. Puar, R. R. Rossman, A. T. McPhail and R. D. Macfarlane, *J. Am. Chem. Soc.*, 1981, **103**, 3940–3943.
151 H. Zhang, J. A. White-Phillip, C. E. Melançon, H.-j. Kwon, W.-l. Yu and H.-w. Liu, *J. Am. Chem. Soc.*, 2007, **129**, 14670–14683.
152 A. Kawashima, Y. Nakamura, Y. Ohta, T. Akama, M. Yamagishi and K. Hanada, *J. Antibiot.*, 1992, **45**, 207–212.
153 P. W. Schindler and M. C. Scrutton, *Eur. J. Biochem.*, 1975, **55**, 543–553.
154 I. Tinhofer, G. Anether, M. Senfter, K. Pfaller, D. Bernhard, M. Hara and R. Greil, *FASEB J.*, 2002, **16**, 1295–1297.
155 T. Nakashima, M. Miura and M. Hara, *Cancer Res.*, 2000, **60**, 1229–1235.
156 G. Anether, I. Tinhofer, M. Senfter and R. Greil, *Blood*, 2003, **101**, 4561–4568.
157 H. Nakajima, K. Sakaguchi, I. Fujiwara, M. Mizuta, M. Tsuruga, J. Magae and N. Mizuta, *Biochem. Biophys. Res. Commun.*, 2007, **356**, 260–265.
158 X.-Y. Jia, Z.-H. Tian, L. Shao, X.-D. Qu, Q.-F. Zhao, J. Tang, G.-L. Tang and W. Liu, *Chem. Biol.*, 2006, **13**, 575–585.
159 J. Fang, Y. Zhang, L. Huang, X. Jia, Q. Zhang, X. Zhang, G. Tang and W. Liu, *J. Bacteriol.*, 2008, **190**, 6014–6025.
160 J. J. Lee, J. P. Lee, P. J. Keller, C. E. Cottrell, C.-J. Chang, H. Zähner and H. G. Floss, *J. Antibiot.*, 1986, **39**, 1123–1134.

161 Y. Sun, H. Hong, F. Gillies, J. B. Spencer and P. F. Leadlay, *ChemBioChem*, 2008, **9**, 150–156.
162 W. R. Roush and R. J. Sciotti, *J. Am. Chem. Soc.*, 1994, **116**, 6457–6458.
163 W. R. Roush and R. J. Sciotti, *J. Am. Chem. Soc.*, 1998, **120**, 7411–7419.
164 K. Takeda, Y. Igarashi, K. Okazaki, E. Yoshii and K. Yamaguchi, *J. Org. Chem.*, 1990, **55**, 3431–3434.
165 K. Takeda, H. Kato, H. Sasahara and E. Yoshii, *J. Chem. Soc., Chem. Commun.*, 1986, 1197–1198.
166 K. Takeda, E. Kawanishi, H. Nakamura and E. Yoshii, *Tetrahedron Lett.*, 1991, **32**, 4925–4928.
167 R. K. Boeckman, Jr., P. Shao, S. T. Wrobleski, D. J. Boehmler, G. R. Heintzelman and A. J. Barbosa, *J. Am. Chem. Soc.*, 2006, **128**, 10572–10588.
168 W. R. Roush, C. Limberakis, R. K. Kunz and D. A. Barda, *Org. Lett.*, 2002, **4**, 1543–1546.
169 D. Niu and T. R. Hoye, *Org. Lett.*, 2012, **14**, 828–831.
170 R. Nakai, H. Ogawa, A. Asai, K. Ando, T. Agatsuma, S. Matsumiya, S. Akinaga, Y. Yamashita and T. Mizukami, *J. Antibiot.*, 2000, **53**, 294–296.
171 T. Agatsuma, T. Akama, S. Nara, S. Matsumiya, R. Nakai, H. Ogawa, S. Otaki, S. Ikeda, Y. Saitoh and Y. Kanda, *Org. Lett.*, 2002, **4**, 4387–4390.
172 T. H. Lambert and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2006, **128**, 426–427.
173 T. R. Hoye, V. Dvornikovs and E. Sizova, *Org. Lett.*, 2006, **8**, 5191–5194.
174 R. M. de Figueiredo, M. Voith, R. Fröhlich and M. Christmann, *Synlett.*, 2007, **3**, 391–394.
175 R. M. de Figueiredo, R. Fröhlich and M. Christmann, *Angew. Chem., Int. Ed.*, 2007, **46**, 2883–2886.
176 Y. Sugie, H. Hirai, H. Kachi-Tonai, Y.-J. Kim, Y. Kojima, Y. Shiomi, A. Sugiura, Y. Suzuki, N. Yoshikawa, L. Brennan, J. Duignan, L. H. Huang, J. Sutcliffe and N. Kojima, *J. Antibiot.*, 2001, **54**, 917–925.
177 T. Nogawa, M. Kawatani, M. Uramoto, A. Okano, H. Aono, Y. Futamura, H. Koshino, S. Takahashi and H. Osada, *J. Antibiot.*, 2013, **66**, 621–623.
178 Y. Futamura, M. Kawatani, M. Muroi, H. Aono, T. Nogawa and H. Osada, *ChemBioChem*, 2013, **14**, 2456–2463.
179 Y. Igarashi, Y. Kim, Y. In, T. Ishida, Y. Kan, T. Fujita, T. Iwashita, H. Tabata, H. Onaka and T. Furumai, *Org. Lett.*, 2010, **12**, 3402–3405.
180 Y. Kim, Y. In, T. Ishida, H. Onaka and Y. Igarashi, *Org. Lett.*, 2013, **15**, 3514–3517.
181 C. Klemke, S. Kehraus, A. D. Wright and G. M. König, *J. Nat. Prod.*, 2004, **67**, 1058–1063.
182 D. E. Williams, D. S. Dalisay, F. Li, J. Amphlett, W. Maneerat, M. A. G. Chavez, Y. A. Wang, T. Matainaho, W. Yu, P. J. Brown, C. H. Arrowsmith, M. Vedadi and R. J. Andersen, *Org. Lett.*, 2013, **15**, 414–417.
183 J. C. Arens, F. Berrué, J. K. Pearson and R. G. Kerr, *Org. Lett.*, 2013, **15**, 3864–3867.
184 T. Tsuchida, H. Iinuma, C. Nishida, N. Kinoshita, T. Sawa, M. Hamada and T. Takeuchi, *J. Antibiot.*, 1995, **48**, 1104–1109.
185 F. Hiramatsu, T. Murayama, T. Koseki, K. Okada and Y. Shiono, *Helv. Chim. Acta*, 2008, **91**, 1595–1603.
186 F. Hiramatsu, T. Murayama, T. Koseki and Y. Shiono, *Phytochemistry*, 2007, **68**, 1267–1271.
187 M. Clericuzio, R. Negri, M. Cossi, G. Gilardoni, D. Gozzini and G. Vidari, *Phytochemistry*, 2013, **93**, 192–198.
188 Y. Shiono, F. Hiramatsu, T. Murayama, T. Koseki, T. Funakoshi, K. Ueda and H. Yasuda, *Z. Naturforsch*, 2007, **62b**, 1585–1589.
189 G.-H. Li, M. Duan, Z.-F. Yu, L. Li, J.-Y. Dong, X.-B. Wang, J.-W. Guo, R. Huang, M. Wang and K.-Q. Zhang, *Phytochemistry*, 2008, **69**, 1439–1445.
190 G. Wu, A. Lin, Q. Gu, T. Zhu and D. Li, *Mar. Drugs*, 2013, **11**, 1399–1408.
191 H. Oh, P. R. Jensen, B. T. Murphy, C. Fiorilla, J. F. Sullivan, T. Ramsey and W. Fenical, *J. Nat. Prod.*, 2010, **73**, 998–1001.
192 M. Isaka, P. Chinthanom, T. Boonruangprapa, N. Rungjindamai and U. Pinruan, *J. Nat. Prod.*, 2010, **73**, 683–687.
193 S. B. Singh, D. Zink, J. Polishook, D. Valentino, A. Shafiee, K. Silverman, P. Felock, A. Teran, D. Vilella, D. J. Hazuda and R. B. Lingham, *Tetrahedron Lett.*, 1999, **40**, 8775–8779.
194 I. E. Mohamed, H. Gross, A. Pontius, S. Kehraus, A. Krick, G. Kelter, A. Maier, H.-H. Fiebig and G. M. König, *Org. Lett.*, 2009, **11**, 5014–5017.
195 C. Hemtasin, S. Kanokmedhakul, K. Kanokmedhakul, C. Hahnvajanawong, K. Soytong, S. Prabpai and P. Kongsaeree, *J. Nat. Prod.*, 2011, **74**, 609–613.
196 K. Minagawa, S. Kouzuki, J. Yoshimoto, Y. Kawamura, H. Tani, T. Iwata, Y. Terui, H. Nakai, S. Yagi, N. Hattori, T. Fujiwara and T. Kamigauchi, *J. Antibiot.*, 2002, **55**, 155–164.
197 H. Kaise, M. Shinohara, W. Miyazaki, T. Izawa, Y. Nakano, M. Sugawara, K. Sugiura and K. Sasaki, *J. Chem. Soc., Chem. Commun.*, 1979, 726–727.
198 B. B. Jarvis, J. Salemme and A. Morais, *Nat. Toxins*, 1995, **3**, 10–16.
199 X. Ma, L. Li, T. Zhu, M. Ba, G. Li, Q. Gu, Y. Guo and D. Li, *J. Nat. Prod.*, 2013, **76**, 2298–2306.
200 K. Sakai, K. Watanabe, K. Masuda, M. Tsuji, K. Hasumi and A. Endo, *J. Antibiot.*, 1995, **48**, 447–456.
201 R. Uchida, R. Imasato, Y. Yamaguchi, R. Masuma, K. Shiomi, H. Tomoda and S. Ōmura, *J. Antibiot.*, 2005, **58**, 397–404.
202 S. B. Singh, D. L. Zink, A. W. Dombrowski, G. Dezeny, G. F. Bills, J. P. Felix, R. S. Slaughter and M. A. Goetz, *Org. Lett.*, 2001, **3**, 247–250.
203 W. Wilk, H. Waldmann and M. Kaiser, *Bioorg. Med. Chem.*, 2009, **17**, 2304–2309.