

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/225055775>

ChemInform Abstract: Xanthones from Fungi, Lichens, and Bacteria: The Natural Products and Their Synthesis

ARTICLE *in* CHEMICAL REVIEWS · MAY 2012

Impact Factor: 46.57 · DOI: 10.1021/cr100446h · Source: PubMed

CITATIONS

70

READS

111

2 AUTHORS:



Kye-Simeon Masters

Queensland University of Technology

42 PUBLICATIONS 258 CITATIONS

[SEE PROFILE](#)



Stefan Bräse

Karlsruhe Institute of Technology

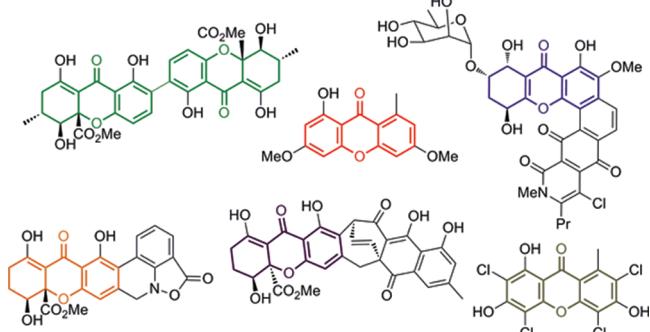
657 PUBLICATIONS 10,070 CITATIONS

[SEE PROFILE](#)

Xanthones from Fungi, Lichens, and Bacteria: The Natural Products and Their Synthesis

Kye-Simeon Masters*,† and Stefan Bräse*,†,‡

[†]Institute for Organic Chemistry, Karlsruhe Institute of Technology (KIT), Fritz-Haber-Weg 6 D-76131, Karlsruhe, Germany

[‡]Institute for Toxicology and Genetics, Karlsruhe Institute of Technology, 76344 Eggenstein-Leopoldshafen, Germany


CONTENTS

1. Introduction	3718
1.1. Existing Review Literature	3718
1.2. Xanthone Synthesis	3719
2. Monomers	3720
2.1. Monomers 1: Xanthones	3720
Arthothelin	3720
Asemone and Derivatives	3720
Asperxanthone	3720
Austocystins	3721
Bikaverin	3721
Chaetoxanthones	3721
Chodatin and Demethylchodatin	3722
Conioxanthone A	3722
1,8-Dihydroxy-3,6-dimethoxyxanthone	3722
6,8-Dihydroxy-3-methylxanthone-1-carboxylic acid	3722
Erythromnone	3722
Emericellin	3722
Globosuxanthones	3722
Griseoxanthone C	3723
8-Hydroxy-1-methoxycarbonyl-6-methylxanthone	3723
1-Hydroxy-6-methyl-8-hydroxymethylxanthone	3723
Lichexanthones, Norlichexanthone, and Derivatives	3723
Occurrence and Biosynthetic Relationships	3723
Synthesis	3726
Isolation and Structural Determination	3729
Biosynthesis	3729
Bioactivity	3730
Synthesis	3730
2.2. Monomers 2: Dihydroxanthones	3735
Globosuxanthone A	3735
Nidulalin A	3735
2.3. Monomers 3: Tetrahydroxanthones	3736
Blennolides	3736
Dihydroglobosuxanthone	3739
Diversonol	3739
Diversonolic Esters	3740
Globosuxanthone B	3741
2.4. Monomers 4: Hexahydroxanthones	3741
Applanatins	3741
Isocochlioquinones	3742
Monodictysins	3742
3. Dimers and Heterodimers	3742
3.1. Dimers and Heterodimers 1: Xanthones	3742
Acremoxanthones	3742
Cervinomycins	3743
FD-594	3743
IB-00208	3744
Lysolipins	3744
Vinaxanthones	3745
Xanthofulvin	3746
Xantholipin	3746
3.2. Dimers and Heterodimers 2: Dihydroxanthones	3747
Citreamicins	3747
3.3. Dimers and Heterodimers 3: Tetrahydroxanthones	3747
Actinoplanones	3747
Albofungins	3748
Ascherxanthone	3748
Beticolins	3749
Isolation and Structural Determination	3749
Structure and Biosynthesis	3750
Biological Properties	3752
Synthesis	3754
Isolation and Structural Determination	3755
Structure	3758
Bioactivity	3758
Synthesis	3759
4. Conclusions	3769
Author Information	3769
Corresponding Author	3769
Notes	3769
Biographies	3769
Acknowledgments	3769
Dedication	3769
References	3769

Received: December 22, 2010

Published: May 22, 2012

1. INTRODUCTION

Many fungi, lichens, and bacteria produce xanthones (derivatives of 9H-xanthen-9-one, “xanthone” from the Greek “xanthos”, for “yellow”) as secondary metabolites. Xanthones are typically polysubstituted and occur as either fully aromatized, dihydro-, tetrahydro-, or, more rarely, hexahydro-derivatives. This family of compounds appeals to medicinal chemists because of their pronounced biological activity within a notably broad spectrum of disease states, a result of their interaction with a correspondingly diverse range of target biomolecules. This has led to the description of xanthones as “privileged structures”.¹ Historically, the total synthesis of the natural products has mostly been limited to fully aromatized targets. Syntheses of the more challenging partially saturated xanthones have less frequently been reported, although the development in recent times of novel and reliable methods for the construction of the (polysubstituted) unsaturated xanthone core holds promise for future endeavors. In particular, the fascinating structural and biological properties of xanthone dimers and heterodimers may excite the synthetic or natural product chemist.

In 1961 Roberts submitted a comprehensive review in which he described the 16 naturally occurring xanthones identified to that date, of which 5 were of fungal or lichenoid origin.² Since that time the number of naturally occurring xanthone compounds known has increased 100-fold.³ Xanthones are to be found in nature as the metabolites of many different species within the plant, fungal, and bacterial kingdoms; they have even been isolated from fossil fuels, possibly suggesting considerable stability of the xanthone core.⁴ Many reviews on xanthones have been published in the time between, and although the majority have focused on xanthones from plants,^{2,3,5–17} xanthones from fungi (which result from biosynthetically distinct pathways) are also prevalent in the primary literature. For this reason, alongside the fascinating structural, biochemical, and medicinal qualities that they possess, this review attempts to address the existing omission in the secondary literature and will focus on the natural occurrence of xanthones from fungi, lichens, and bacteria, alongside selected syntheses directed at these natural product targets.

The xanthone family may be split into the following categories based upon their structural characteristics: first into xanthone monomers (sections 2.1–2.4) and dimers/heterodimers (sections 3.1–3.3), and further into four subclasses based upon the level of oxidation of the xanthone C-ring: fully aromatic-, dihydro-, tetrahydro-, and hexahydro-xanthone derivatives (e.g., 1, 2/3, 4/5, and 6, respectively; see Figure 1). Nonetheless, biosynthetically related xanthones of differing categories can be occasionally found together within the same species (for example, globosuxanthones A, B, C, and D; see compounds 240, 336, 56, and 57, respectively, isolated from *Chaetomium globosum* Ames). The numbering of the xanthone nucleus is in accordance with IUPAC recommendations and is devised according to the mixed biosynthetic origins of these carbons in plants (see Scheme 1).

Xanthone biosynthesis occurs by distinct pathways in fungi compared to those in plants. In the former the xanthone unit is wholly derived from a polyketide species (8, Scheme 1). Even at the time of Roberts’ review it was suggested that the xanthone nucleus may be of “polyacetic acid” origin.^{2,5} In 1953, Birch and Donovan had suggested this pathway, which utilizes the head-to-tail linkage of acetate units, to explain the

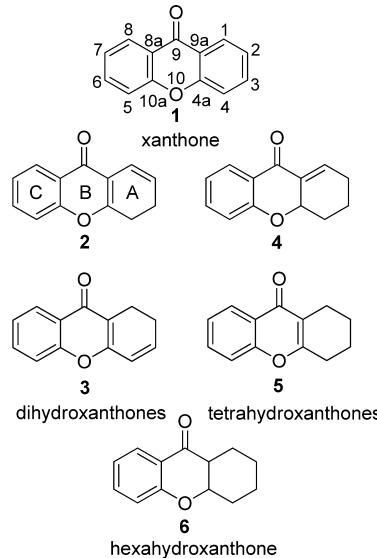


Figure 1. Xanthones.

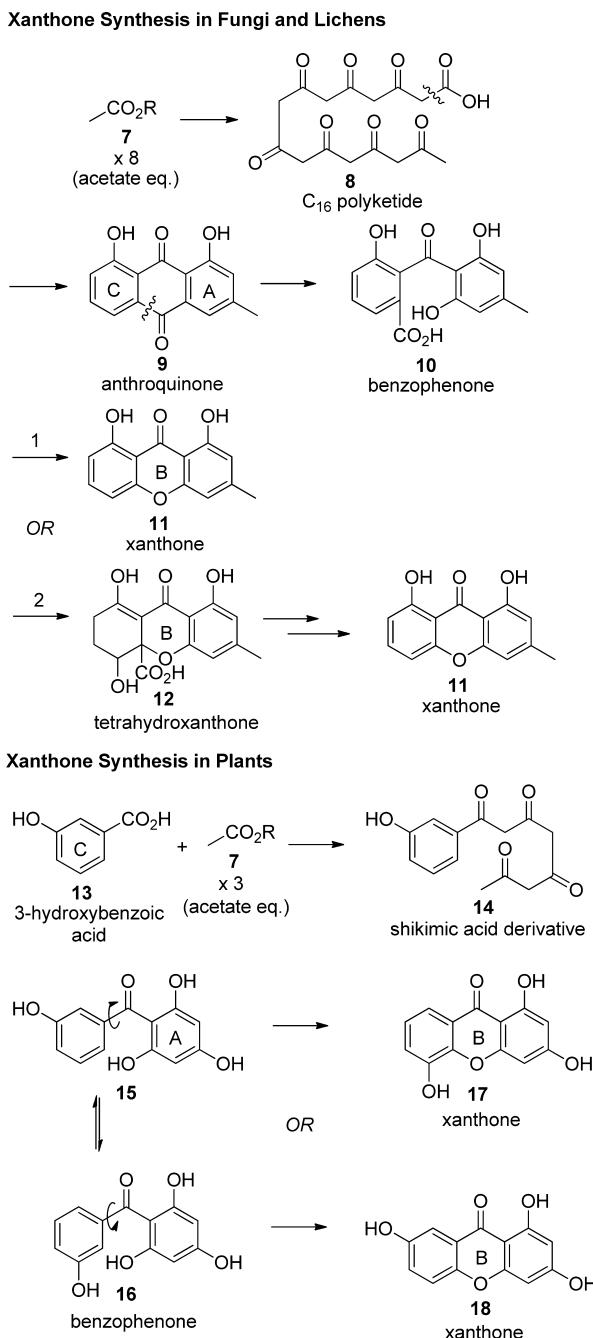
generation of structures associated with many phenolic natural products.¹⁸ A polyacetate unit, 8 (Scheme 1), is cyclized to form an anthroquinone, 9, followed by oxidative cleavage. The following biosynthetic pathways are dependent on the producing organism: xanthones (e.g., 11) may form via cyclization directly from a benzophenone intermediate (10 to 11, pathway 1). Alternatively, it has been proposed that in some cases the fully aromatic species may result by elimination from, or allylic rearrangement of, polyhydrogenated intermediate xanthones (10 to 12 to 11, pathway 2).¹⁹

In higher plants, the xanthone nucleus is of mixed biosynthetic origin, with the A-ring (carbons 1–4) being acetate-derived whereas the shikimic acid pathway^{9,10,20–23} gives rise to the C-ring (i.e., carbons 5–8, 1, Figure 1).²⁴ A typical pathway for the biosynthesis of plants is also shown in Scheme 1; in this example, from studies of xanthone synthesis in *Gentiana lutea*,²⁵ 3-hydroxybenzoic acid (13, Scheme 1, derived from phenylalanine) is coupled with three acetate equivalents to polyketide 14. Aromatization of the side-chain leads again to a freely rotating benzophenone intermediate, 15/16, which undergoes divergent oxidative phenolic coupling to give two different products, the 1,3,7-trihydroxyxanthone (17) and the 1,3,5-trihydroxyxanthone (18). In at least some species of plants, this cyclization is catalyzed by xanthone synthase, a membrane-bound enzyme associated with cytochrome P₄₅₀, a process requiring oxygen and NADPH.²⁶

1.1. Existing Review Literature

A recent review from the Bräse group described the chemistry and biology of mycotoxins, many of which are in possession of a xanthone core or xanthone component of a grosser structure.²⁷ A review from Peres, Nagem, and de Oliveira in 2000 described tetra-oxygenated naturally occurring xanthones, of which 232 were of plant origin and only 3 were of fungal and lichen origin [those being 5- and 6-methoxysterigmatocystin (149 and 150, Figure 30) and a xanthone from *Diplochistes* sp., 1,8-dihydroxy-3,6-dimethoxyxanthone, 51, Figure 10].¹¹ Another review from Peres and Nagem in 1997 described 127 trioxygenated xanthones, of which 55 were of fungal or lichen origin.¹⁷ Additionally, a recent review from Sousa and Pinto focused on methods for the synthesis of xanthones.²⁸

Scheme 1. Xanthone Biosynthesis Pathways in Fungi and Plants



A review from Gottlieb in 1968 described 7 fungal xanthones among near 70 in total,⁹ whereas a review from Carpenter et al. in 1969 described 82 xanthones from plants.⁸ A further review from Sultanbawa in 1980 dealt exclusively with xanthones from tropical plants, particularly Guttiferae and Gentianaceae,¹² the former of which was updated in 1989 by Bennett and Lee.¹⁴ Mandel and co-workers published an additional review in 1992 on xanthones from plants.¹⁵ Pinto and Sousa described in 2003 the xantholignoids, derived from a xanthone and cinnamyl component.¹³ Peres and Nagem also reported in 1997 on penta-oxygenated, hexa-oxygenated, and dimeric xanthones, which included actinoplanones (403–409, Figure 64) and compounds from *Penicillium glabrum*.⁶ A review from Brahmachari and co-workers in 2004 described many plant-

derived xanthone species that had to date been isolated in *Swertia* species, from the family Gentianaceae.¹⁶

A 2005 issue of *Current Medicinal Chemistry* was devoted to the xanthone nucleus, derivatives, natural products, and the spectral and biological properties thereof.^{7,13,29–31,36} Pinto, Sousa, and Nascimento reviewed the ever-expanding array of biological activities of xanthones, which includes pharmacological effects in the cardiovascular, renal, hepatic, neuronal, and immune systems, as well as antitumor,^{32–34} antiviral, antibacterial, antifungal, antimalarial,³⁵ antitubercular, antiplatelet, antithrombotic, antimutagenic, antioxidant, antihepatotoxic, antileukemic, antiulcer, anti-inflammatory, anthelmintic, and anticoccidial activities.⁷ Another report from Silva and Pinto focused on the typical characteristics of xanthones in nuclear magnetic resonance spectroscopy, as well as the applicability of 1D and 2D techniques to the study of the xanthone skeleton.²⁹ A review from Gales and Damas focused on single-crystal X-ray studies of the xanthone-containing species that had been studied by that technique to date, the number being only 50 crystal structures from 47 differing xanthones, somewhat low given the number identified at that time, and the fact that xanthones are (unsurprisingly) essential planar in the solid state (sometimes with small deviations due to substituent effects).³⁰ Also in the issue of *Current Medicinal Chemistry* was a review on xanthone-core containing antimalarial compounds from Riscoe and co-workers, detailing in particular the discovery process and application of xanthones in synergy with other antimalarial drugs.³⁶ In terms of the mechanism of action, it is thought that complexation of 4,5-dihydroxanthones with heme inhibits the aggregation of this biomolecule.^{37–39} A review from Vieira and Kijjoa described recent findings (reports from the literature in the period from January 2000 to December 2004) on the subject of naturally occurring xanthones.³¹ A review from El-Seedi and co-workers in 2009 focused on the most recently isolated xanthones (2005–2008) of both plant and fungal origin,²⁴ and last, a review was published in 2010 by the same authors on the subject of both recent elucidations of xanthone biosynthesis and the findings (period 2001–2008) with respect to xanthone bioactivities.⁴⁰ Among the newly reported activities were gastro-protective effects, antiatherosclerotic activity, inhibition of hypotension, cardioprotection, inhibition of cholinesterase, α -glucosidase and COX activity, and immunosuppression.

1.2. Xanthone Synthesis

The first total synthesis of a naturally occurring xanthone was that of euxanthone by Ullmann and Panchaud in 1906.⁴¹ One hundred years later, Sousa and Pinto summarized the most common methods that had been developed in that time for the synthesis of aromatic xanthones.²⁸ Of importance among these is the Michael and Kostenecki synthesis,^{42,43} which involves refluxing a phenol, an α -hydroxybenzoic acid, and acetic anhydride, although these substrates have in later times been coupled using Lewis acids via an in situ generated acid chloride.⁴⁴ Related are syntheses making use of either Friedel–Crafts coupling then nucleophilic ring-closing,⁴⁵ or a less common alternative from equivalent substrates that involves Ullmann coupling followed by ring-closure.⁴⁶ Additionally, syntheses utilizing Photo-Fries⁴⁷ or Smiles⁴⁸ rearrangement from a diaryl ester substrate are known, and the Tanase method⁴⁹ by way of xanthenes and the Muller method⁵⁰ by way of benzoquinones have proven popular. Other syntheses making use of ketimines,⁵¹ thioxanthonedioxides,⁵² and

biomimetic Claisen cyclization of polyketides⁵³ are known. The protection and deprotection of phenolic moieties in various positions on the xanthone core has also been examined.²⁸

Some novel methodologies for the synthesis of aromatic xanthones published very recently involve the CO addition of carboxylic acids to benzene derivatives,⁵⁴ the CAN-mediated oxidative cyclization of 2-hydroxy-2',5'-dimethoxybenzophenones,⁵⁵ an unusual base-promoted dimerization of 3-(1-alkynal)chromones to form 2-alkynyl xanthones,⁵⁶ and the oxidation of xanthenes with C–H activation utilizing a chromium(III) superoxo complex.⁵⁷ While the number of methodologies for the synthesis of hydroxanthones are far fewer in number, an effective and general one-step methodology for the synthesis of the partially reduced xanthone core has been developed via domino oxa-Michael aldol reaction of salicylaldehyde derivatives and cyclohexenones.^{1,58–64}

2. MONOMERS

2.1. Monomers 1: Xanthones

The majority of xanthones reported from fungi, bacteria, and lichens, and particularly those reported relatively early on, have a monomeric and fully aromatized structure. These include arthothelin, asemone, asperxanthone, austocystins, bikaverin, chaetoxanthones, chodatin, conioxanthone A, erythrommone, emericillin, globosuxanthones C and D, griseoxanthone C, lichexanthones and norlichexanthones, *Microsphaeropsis* xanthones, mycoxanthone, *Phoma* and *Phomopsis* xanthones, pinselin and pinselic acid, sterigmatocystins, tajixanthone, thiomelin, thiophanic acid, thiophanic acid, thuringione, umbilicaxanthones, vinetorin, varixanthone, vertixanthone, and *Wardomyces* and *Xylaria* xanthones.

Arthothelin. Santesson reported observing this compound in the mass-spectral analysis of the lichen *Leconora reuteri*.⁶⁵ Arthothelin (2,4,5-trichloronorlichexanthone, **19**, Figure 2) has

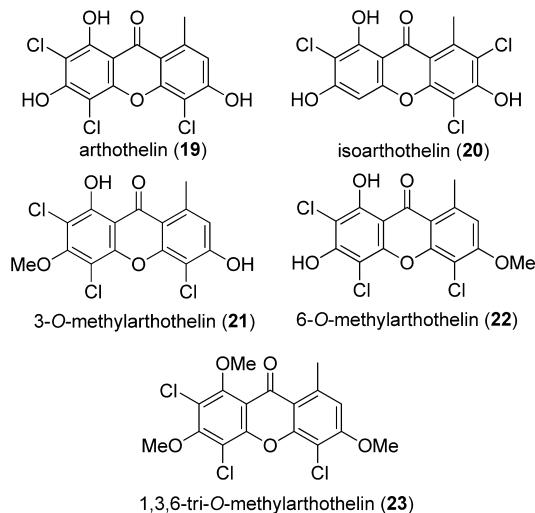


Figure 2. Arthothelin xanthones.

also been isolated from *Arthothelium pacificum*,⁶⁶ *Buellia* sp.,⁶⁷ *Dimelaena cf. australiensis*,⁶⁸ *Lecanora andrewii*,⁶⁹ *L. broccha*,⁷⁰ *L. bolanderi*,⁶⁹ *L. sulphurata*,⁶⁸ *L. flavidopallens*,⁶⁹ *L. flavopallescens*,⁷¹ *L. ingae*,⁶⁹ *L. pruinosa*,⁶⁹ *L. pinguis*,⁶⁶ *L. straminea*,⁶⁶ *Lecidella asema*,⁶⁷ *L. meiococca*,⁶⁸ *L. quema*,⁶⁶ *L. subalpicida*,⁶⁷ *L. vorax*,⁶⁸ *Melanaria melanospora*,⁶⁹ *Micarea austroternaria*,⁷¹ *M. isabellina*,⁶⁸ *Pertusaria* sp.,⁷² *P. pycnothelia*,⁶⁸ and *Tapellaria*

epiphylla (Müll. Arg.) R. Sant.⁷³ Closely related species are isoarthothelin (**20**, from *Buellia* sp.,^{43,67,74} *Lecanora broccha*,^{70,67} *Lecidella asema*,⁶⁸ *L. meiococca*,⁶⁸ *L. vorax*,⁶⁸ *L. subalpicida*,⁶⁷ *Sporopodium phyllocharis* (Mont.) Mass.,⁷³ and 3-O-methylarthothelin (**21**, from *D. australiensis*⁶⁸ and *Dimelaena* sp.⁷⁵).

In 1990 Elix and Bennett reported the isolation of two new arthothelin derivatives from the lichen *Dimelaena cf. australiensis* sp., alongside several other compounds and the known xanthone, 2,4,5-trichlorolichexanthone (**74**, Figure 19).⁷⁶ They were 6-O-methylarthothelin (**22**, also isolated from *Micarea isabellina*)⁶⁸ and 1,3,6-tri-O-methylarthothelin (**23**, from *Dimelaena* sp.,⁷⁶ and *D. australiensis*).⁶⁸) The structures were determined using chromatographic and spectral techniques; that of the former was confirmed by demethylation with boron tribromide, giving arthothelin (**19**). The structure of the latter was confirmed by the treatment of **19** with excess dimethyl sulfate, giving a trimethylated product, identical with **23**. The authors further isolated two minor xanthones from the same species but were unable to attribute structures.⁷⁶ In the same year, Elix and co-workers reported the synthesis and therefore structural confirmation of isoarthothelin utilizing a Friedel–Crafts pathway,⁷⁴ which allowed them to correct previous reports of the occurrence of this compound in *Lecanora sulphurata* and *L. flavo-pallescens*.^{69,77,78}

Asemone and Derivatives. Asemone (**24**, Figure 3, from *Buellia* sp.,⁶⁷ *Lecanora broccha*,^{68,67} *Lecidella asema*,⁶⁷ *L.*

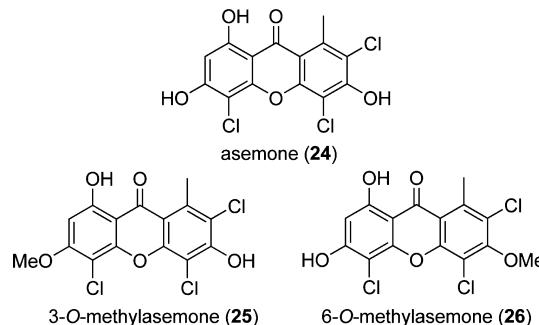


Figure 3. Asemone xanthones.

subalpicida,⁶⁷ *Micarea isabellina*,^{68,71,79} *M. austroternaria*,⁶⁷ *Pertusaria pycnothelia*,⁶⁸ and *Micarea austroternaria* var. *isabellina*⁷¹), a norlichexanthone derivative, was first reported by Sundholm in 1978. The related compounds 3-O-methylasemone (**25**, from *Buellia* sp.,⁶⁷ *Lecanora asema*,⁶⁷ *L. broccha*,^{68,70} *L. capistrata*,^{69,67} *L. buelliastrum* (Müll. Arg.),^{80,81} *Lecidella meiococca*,⁶⁸ *L. subalpica*,⁶⁷ *L. vorax*,⁶⁷ and 6-O-methylasemone (**26**, from *Pertusaria pycnothelia*)⁶⁸ have also been isolated; the former was also synthesized by Sundholm.⁸²

Asperxanthone. Asperxanthone (Figure 4), was isolated alongside a biphenyl compound from the cultures of a marine-derived *Aspergillus* species (culture MF-93) by Ouyang and co-workers.⁸³ The compound is structurally related to the

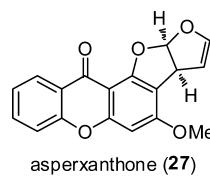


Figure 4. Asperxanthone.

difuranoxanthones in the sterigmatocystin series but differs in that the connection of the oxygen of the xanthone to form the first of the furan rings is at a position *ortho*- rather than *para*- to the xanthone ketone. This compound was identified using 2D NMR techniques and FAB-MS (fast atom bombardment mass spectrometry) and was shown to be inhibitory against the tobacco mosaic virus.

Austocystins. Austocystins A–F (28–33, Figure 5) were first described in 1974 after they were isolated by Steyn and

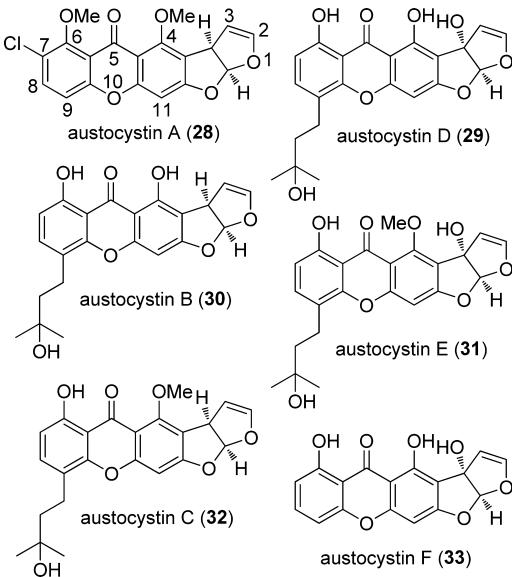


Figure 5. Austocystins A–F.

Vleggaar from *Aspergillus ustus*, alongside the known mycotoxins versicolorin C and averufin.⁸⁴ The authors used NMR (benzene-induced solvent-shifts, nuclear Overhauser effects (NOEs)) and chemical derivatization/degradation to determine the structure of austocystin A, then inferred the others from this structure based on the comparisons of spectral data.

Bikaverin. In 1957 Nakamura and co-workers isolated bikaverin (34, Figure 6), a deep-red colored compound, from

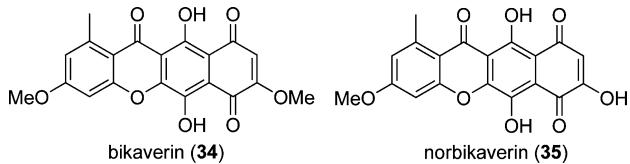
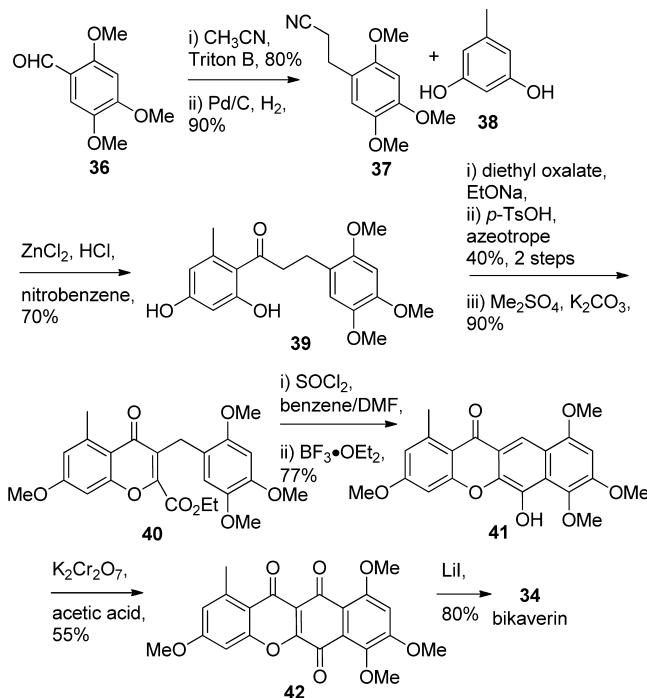


Figure 6. Bikaverin and norbikaverin.

Gibberella fujikori.⁸⁵ Bikaverin was later reisolated from the same source,^{86,87} and the structure determined^{87,88} and confirmed by a single-crystal X-ray study.⁸⁹ The compound has also been isolated from *Fusarium oxysporum*,⁹⁰ *Fusarium* sp. *lycopersici*, and *Mycogone jaapai*⁹¹ and is known to have a vacuolation effect in fungi,⁸⁸ to have a specific antiprotozoal activity against *Leishmania brasiliensis*,⁹² and to be cytotoxic to various tumor cell types.^{93,94}

In 1976 Barton et al. reported their synthesis of bikaverin (34, Scheme 2),⁹⁵ beginning with the condensation of aldehyde 36 with acetonitrile to form, after subsequent hydrogenation, the arylpropionitrile 37, which was used to acylate orcinol (38). Subsequent formation of the chromene ring of 40 was achieved

Scheme 2. Barton's bikaverin synthesis



in three steps, followed by conversion to an acid chloride and Friedel-Crafts cyclization, giving the xanthone intermediate 41, which was oxidized and demethylated to the natural product.

Other full^{14–16,94,96–101} and partial^{102,103} syntheses of bikaverin have been reported. Vining and co-workers have reported on the biosynthesis of this compound, finding it to be formed from a single polyketide species.¹⁰⁴

Chaetoxanthones. Chaetoxanthones A–C (43–45, Figure 7) were isolated from the marine-derived fungus *Chaetomium*

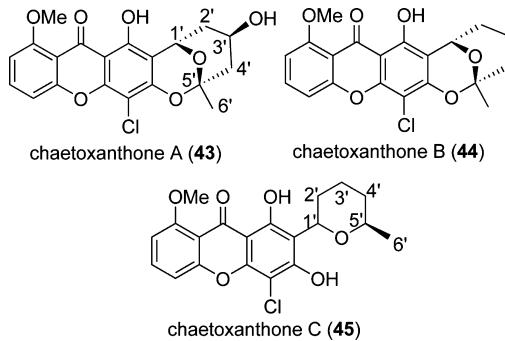


Figure 7. Chaetoxanthones A–C.

sp. and reported by König and co-workers in 2008.¹⁰⁵ The absolute configuration of these compounds was determined with circular dichroism (CD) spectra, NOE studies, and a modified Mosher's method. The first two of these novel xanthones have a rare dioxane/tetrahydropyran bicyclic fused with the xanthone nucleus (see also the xanthone biosynthetic precursor averufin, 156, Scheme 7), whereas 45 is a chlorinated xanthone substituted with a tetrahydropyran component. The authors propose a probable biosynthetic pathway for these compounds involving internal ketalisation of a side-chain. Chaetoxanthones A–C were tested for antiprotozoal use;

chaetoxanthone B was found to be active against *Plasmodium falciparum* in the midmicromolar range, whereas C was active in low micromolar range against *Trypanosoma cruzi*, the causative organism of Chaga's disease.¹⁰⁵

Chodatin and Demethylchodatin. Chodatin (structure unknown) and demethylchodatin (**46**, Figure 8) were isolated

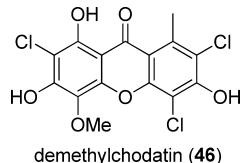


Figure 8. Demethylchodatin.

from *Lecidella chodati* (Samp.) Knopf and Leuckert and *L. dimelaenophila* by Knopf in 1990.¹⁰⁶ The structure of the latter was resolved by Elix et al. with X-ray crystallographic analysis of the triacetate derivative, which was isolated from *Lecanora pachysoma*,¹⁰⁷ but it appears that the structure (i.e., methylation position) of chodatin ($C_{16}H_{11}Cl_3O_6$) itself remains presently unresolved (presumably it is methylated at the more commonly observed 3- or 6-position). These two species have also been found in *Lecanora tropica* Zahlbr.,¹⁰⁸ *L. immersa* ssp. *ramboldii* Lumbsch,^{108,109} and *L. pachysoma* Ryan and Poelt.¹¹⁰

Conioxanthone A. Conioxanthone A (**47**, Figure 9) has been isolated alongside the structurally related microxanthone

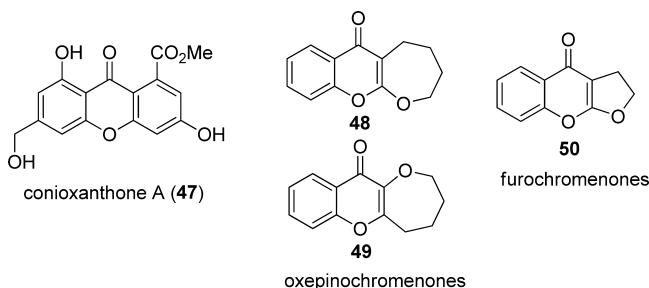


Figure 9. Conioxanthone A; also shown are the (oxidatively derived) ring-expanded oxepinochromenone and furochromenone frameworks.

(**120**, Figure 23) and several oxepinochromenones and a furochromenone (ring-expanded and -contracted xanthone derivatives, of the general frameworks **48–50**, respectively) from the endolichenic fungus *Coniochaeta* sp. by Che and co-workers.¹¹¹

1,8-Dihydroxy-3,6-dimethoxyxanthone. 1,8-Dihydroxy-3,6-dimethoxyxanthone (**51**, Figure 10) was isolated from the genus *Diploschistes* s. lat. and structurally characterized by Elix et al., who also used an unambiguous synthetic procedure to obtain this compound and make a direct confirmation of the structure.¹¹²

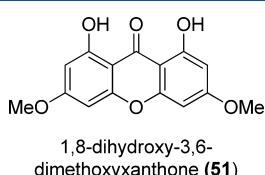


Figure 10. 1,8-Dihydroxy-3,6-dimethoxyxanthone.

6,8-Dihydroxy-3-methylxanthone-1-carboxylic acid. The title xanthone (**52**, Figure 11) was reported by Li and



Figure 11. 6,8-Dihydroxy-3-methylxanthone-1-carboxylic acid.

co-workers in 2010 after its isolation alongside four known compounds from *Penicillium oxalicum*, and structural determination with the use of spectroscopic methods including 1D and 2D NMR experiments.¹¹³

Erythrommone. Erythrommone (**53**, Figure 12), which is an unusually acylated lichen-derived xanthone based upon the

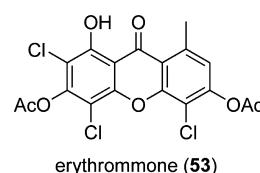


Figure 12. Erythrommone.

norlichexanthone skeleton, was reported by Huneck and Follmann¹¹⁴ and Huneck and Höfle⁷² after isolation from *Haematomma erythromma*.

Emericellin. Emericellin (aka variecoxanthone B,¹¹⁵ **54**, Figure 13) and the anthraquinone emodin were isolated from

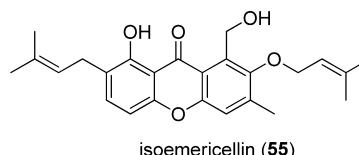
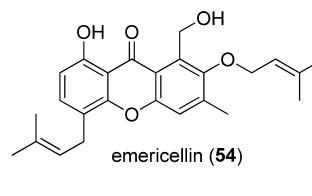
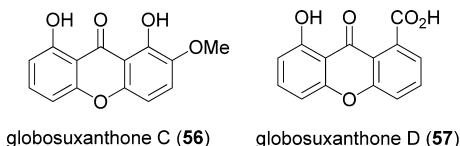


Figure 13. Emericellin and isoemericellin.

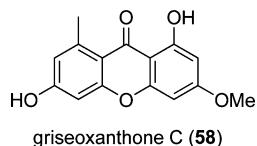
Aspergillus nidulans in 1975 by Ishida and co-workers.¹¹⁶ The structurally related compound isoemericellin (**55**, Figure 9) was isolated from a sponge-derived fungus *Emericella variecolor* (an anamorph of *Aspergillus variecolor*) alongside shamixanthone (**185**, Figure 33) and several non-xanthone species by Bringmann and co-workers.¹¹⁷

Globosuxanthones. Globosuxanthones C and D (**56** and **57**, Figure 14) were isolated from the fungal strain *Chaetomium globosum* Ames, alongside a related dihydro-xanthone (Globosuxanthone A, **240**, Figure 46) and a related tetrahydro-xanthone (Globosuxanthone B, **336**, Figure 52), 2-hydroxyvertixanthone, and some known anthraquinones, from the rhizosphere of the Sonoran desert plant the "Christmas cactus", *Opuntia leptocaulis* DC. The extracts from this microorganism were determined to be cytotoxic against multiple human cancer

**Figure 14.** Globosuxanthone C and D.

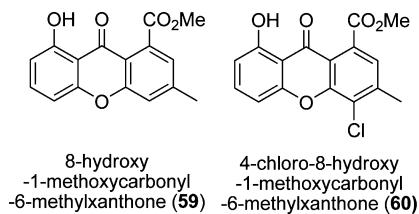
cell lines; Globosuxanthone A was found to be particularly effective (240, Figure 46).¹¹⁸

Griseoxanthone C. In 1961, McMasters et al. reported the isolation of a compound from *Penicillium patulum*, which they identified as 1,3,6-trihydroxy-8-methylxanthone and named griseoxanthone C (58, Figure 15).¹¹⁹ Griseoxanthone C was

**Figure 15.** Griseoxanthone C.

isolated from *Penicillium patulum* by Rhodes and co-workers at Glaxo Laboratories.¹²⁰ They confirmed the structure identified as 358 through comparison of a methylated derivative with lichexanthone (62, Figure 18) and a 6-methyl isomer obtained by Grover, Shah, and Shah in their seminal xanthone synthetic work.¹²¹ Griseoxanthone C is an intermediate in the biosynthesis of aflatoxins, which are significant environmental toxins, produced by various fungi, infecting plants such as peanuts and cereals under the correct conditions.¹²² This compound was found by Broadbent and co-workers to possess antimicrobial activity against *Clostridium welchii* at low concentrations (MIC = 25 ppm).¹²³ Elix and Crook also isolated griseoxanthone C from the lichen *Lecanora vinetorum*,⁶⁸ and it was synthesized by Jayalakshmi et al. in 1974.¹²⁴

8-Hydroxy-1-methoxycarbonyl-6-methylxanthone. The xanthone 8-hydroxy-1-methoxycarbonyl-3-methylxanthone (59, Figure 16) was first reported in 1986 by Kachi and Sassa

**Figure 16.** Xanthones from *Chalara* sp.

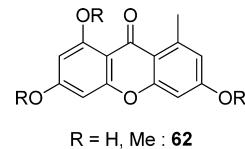
after isolation from the economically significant fungus *Monotinia fructicola*,¹²⁵ which effects stone-fruit trees (peaches, pears, etc.). It was later isolated again from *Guanomyces polythrix*, and the structure was confirmed using X-ray crystallography.¹²⁶ This same xanthone and its novel 4-chloro derivative (60) were isolated from the endophytic fungi *Chalara* sp. by Zeeck and co-workers in 2008.¹²⁷

1-Hydroxy-6-methyl-8-hydroxymethylxanthone. 1-Hydroxy-6-methyl-8-hydroxymethylxanthone (61, Figure 17) was isolated from *Cyathus intermedius*, a rare bird's nest fungus, by Ayer and Taylor.¹²⁸ The authors note that hydroxymethyl-substituted xanthones are normally isolated from plant-derived xanthones.

**Figure 17.** 1-Hydroxy-6-methyl-8-hydroxymethylxanthone.

Lichexanthones, Norlichexanthone, and Derivatives.

Many of the lichenoid xanthones have the typical oxygenation pattern shown below (62, Figure 18), which may be further

**Figure 18.**

chlorinated at selected aryl methane positions. Lichexanthone (63, Figure 19), the first xanthone isolated from lichens, was first identified in *Parmelia formosa*^{129,130} and *Parmelia* sp.¹³¹ The synthesis was performed as a confirmation of structure from both orsellinic acid and phloroglucinol,^{129,130} and then from everninic acid and phloroglucinol.¹²¹

Occurrence and Biosynthetic Relationships. 2,7-Dichlorolichexanthone (70, Figure 19), thought to be a typical fungal-derived metabolite, was isolated from samples of the lichen *Lecanora dispersa*. However, when the fungal species is cultured in the absence of the alga, the xanthone production is no longer triggered or enabled, and other secondary metabolites are instead isolated (i.e., depsidones such as pannarin, and related compounds).¹³²

After some initial problems with identification of lichen-derived xanthones (in particular, frequent confusion between isomers),^{21,67} lichen-derived xanthones have been quite thoroughly studied, and conclusions have been drawn about the interrelation of these species. They come in the form of two different basic skeletons: those derived from the norlichexanthone skeleton (with a methyl group in the 8-position, for example lichexanthone and derivatives, Figure 14), and those derived from a biosynthetically distinct pathway that gives the ravenelin skeleton (with the methyl group in the 3-position; see ravenelin, 139, Figure 29). It has been suggested for lichen xanthones that the single linear polyketide chain undergoes ring-closure, possibly through a benzophenone intermediate, to give the common oxygen-substitution pattern of lichexanthone and norlichexanthone.^{68,133,69,78} From this point of departure, the compounds differ in the position and extent of substitution (hydroxylation, methylation of these hydroxyl groups, and chlorination).⁶⁸ Elix and Crook proposed that the site-selective chlorination and methylation processes that follow involve discrete enzymes, which can thus be mapped systematically.⁶⁸ The taxonomic evaluation and phylogenetic assembly of these organisms has become more possible due to careful study and the testing of proposed biosynthetic sequences. The chemical analysis of several species of lichen was reported in 1992 by Elix and Crook and revealed the presence of xanthones (particularly chloroxanthones) in 40 species of lichen, including 13 new species.⁶⁸ The co-occurrence of multiple xanthones within one species usually follows a logical sequence of chlorination and methylation steps. For example, the presence of 2,4,5-

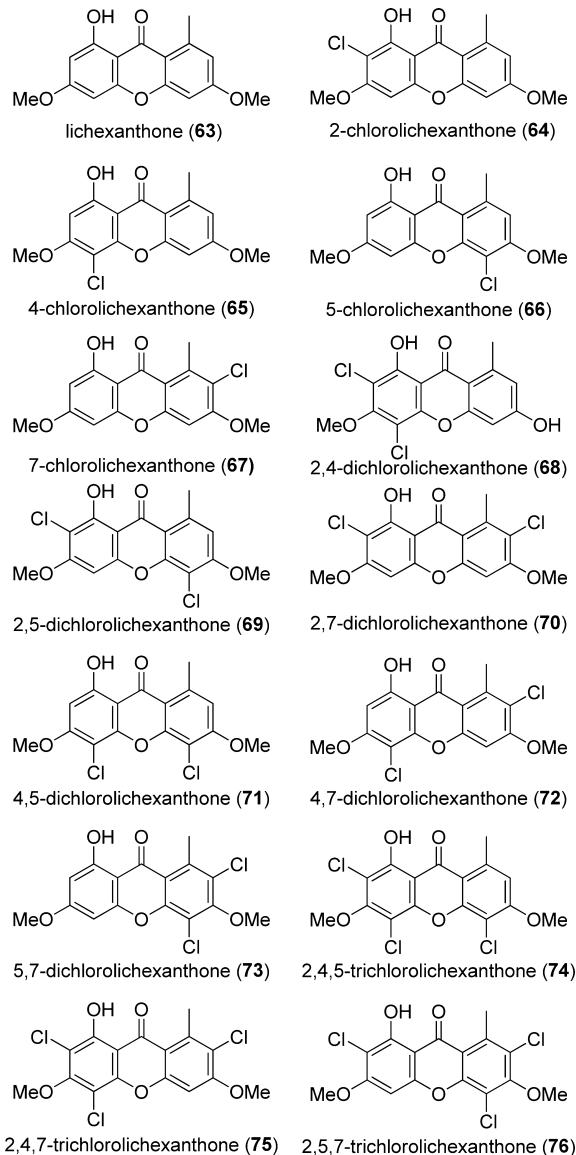


Figure 19. Lichexanthone and derivatives.

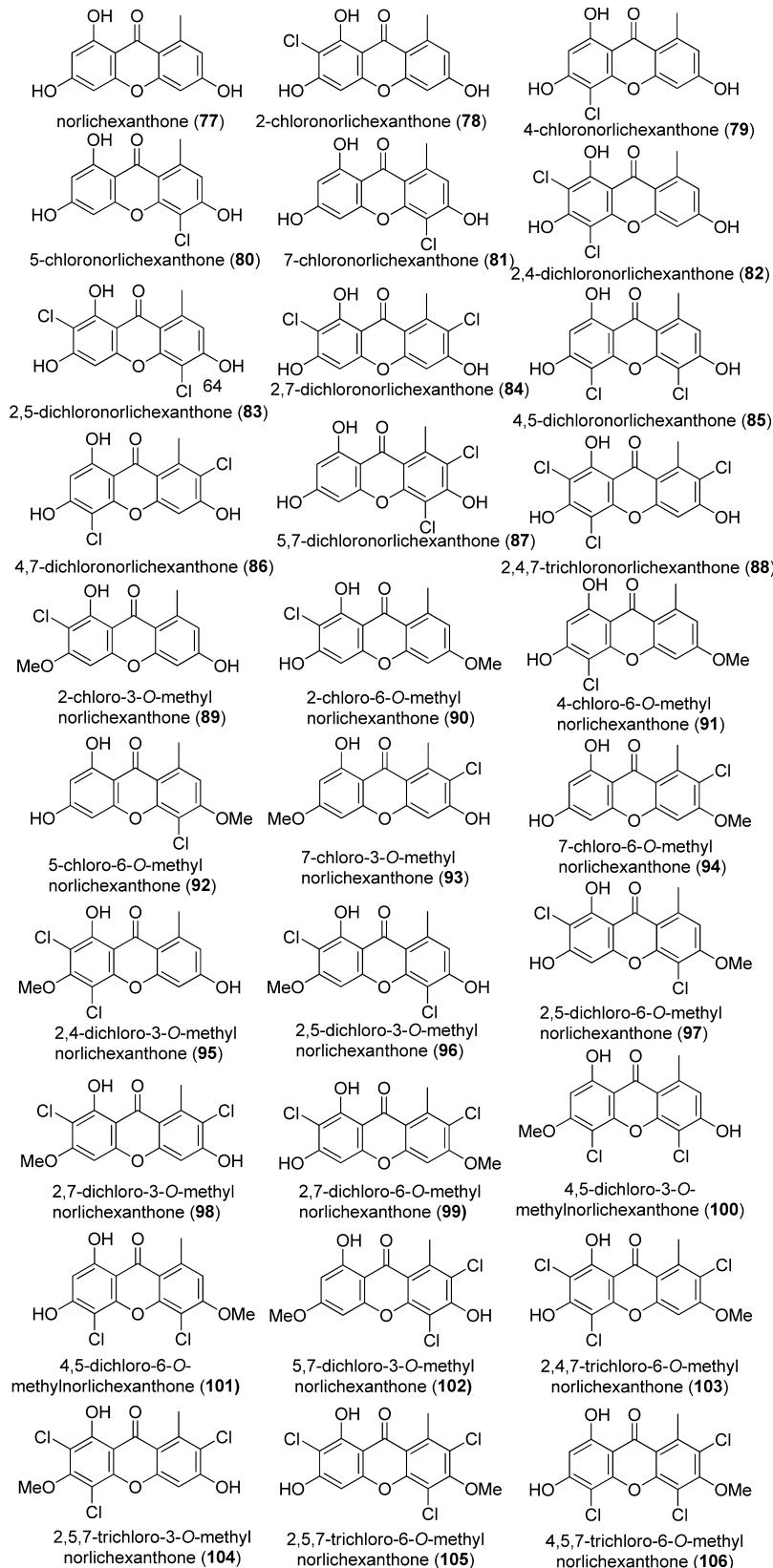
trichlorinated xanthone would suggest the co-occurrence of likely precursors with elements of the same substitution pattern: The 2,4-dichloro, 2,5-dichloro, and 4,5-dichloro derivatives would also be expected to occur, but not the xanthones containing a 7-chlorination (resulting from regioselective enzymatic chlorination processes).⁶⁷ This analysis is a culmination of the considerable work from the Elix group on the isolation, structural elucidation, organic synthesis, biosynthesis, and taxonomic determination of xanthones from lichen sources.

Lichexanthone (**62**, Figure 18) was initially identified from the lichens *Parmelia formosa*¹³⁰ and *Parmelia* sp.¹³¹ and has been since identified in many more lichen species, for example, *Athcoleista djalonensis*,¹³⁴ *Pertusaria* sp.,⁶⁹ *P. sulphurata*,¹³⁵ *Pyxine consocians* Vainio,¹³⁶ and *P. berteriana*.¹³⁷ The synthesis of this molecule was performed as a confirmation of structure from orsellinic acid and phloroglucinol,^{129,130} and then from everninic acid and phloroglucinol.¹²¹ In 1993, Feige and co-workers described the development of a standardized high-performance liquid chromatography (HPLC) assay for the identification of many lichen-derived natural products, with

particular mention of 55 xanthones and 1 xanthone-containing compound (secalonic acid B, **449**, Figure 74).¹³⁸

The lichexanthone derivatives identified so far include 2-chlorolichexanthone (**64**, from *Lecanora* sp. and *Pertusaria cicatricosa*,⁶⁸ and *P. sulphurata*¹³⁵), 4-chlorolichexanthone (**65**, synthesized by Elix, Sargeant, and co-workers, see later), 5-chlorolichexanthone (**66** from *Lecanora contractula*),⁶⁸ 7-chlorolichexanthone (**67**), 2,4-dichlorolichexanthone (**68**, *Dimelaena cf. australiensis*, *Pertusaria cicatricosa*,⁶⁸ and *Pertusaria* sp.,⁷²), 2,5-dichlorolichexanthone (**69**, from *Dimelaena cf. australiensis*,⁶⁸ *Pertusaria cicatricosa*,⁶⁸ and *Pertusaria* sp.,⁷²), 2,7-dichlorolichexanthone (**70** from *Lecanora behringii*,⁶⁸ *L. salina*,⁶⁸ *L. populicola*,⁶⁸ *Lecanora* sp.,⁶⁸ and *L. dispersa*⁶⁸), 4,5-dichlorolichexanthone (**71**, also known as coronatone, *Dimelaena cf. australiensis*, abd *Pertusaria cicatricosa*,⁶⁸ 4,7-dichlorolichexanthone (**72**, synthesized by Elix and co-workers, see later), 5,7-dichlorolichexanthone (**73**, synthesized by Elix and co-workers, see later), 2,4,5-trichlorolichexanthone (**74**, from *Dimelaena cf. australiensis*,⁶⁸ *Dimelaena* sp.,⁴⁷⁶ *Pertusaria cicatricosa*,⁶⁸ and *Pertusaria* sp.,⁷²), 2,4,7-trichlorolichexanthone (**75** from *Lecanora straminea*⁶⁶), and 2,5,7-trichlorolichexanthone (**76**, from *Dimelaena cf. australiensis* and *Lecanora broccha*⁶⁸).

Other lichen natural products of the norlichexanthone type (**77**, Figure 20) have been reported. They are norlichexanthone (**77**, from *Lecanora reuteri*¹³⁹ and *L. straminea*¹⁴⁰) and derivatives 2-chloronorlichexanthone (**78**, from *Lecanora populicola*, *Lecanora salina*, *Lecanora* sp., and *Lecidella vorax*),⁶⁸ 4-chloronorlichexanthone (**79**), 5-chloronorlichexanthone (**80**), 7-chloronorlichexanthone (**81**, from *Lecanora populicola*, *Lecanora* sp.),⁶⁸ 2,4-dichloronorlichexanthone (**82**, from *Buellia* sp.,⁶⁷ *Lecanora broccha*,⁶⁷ *L. straminea*,⁶ *Lecidella vorax*,⁶⁸ *L. asema*,⁶⁷ and *L. subalpica*⁶⁷), 2,5-dichloronorlichexanthone (**83**, from *Lecanora broccha*, *Lecidella meiococca*, *Lecidella vorax*,⁶⁸ *L. asema*,⁶⁷ *L. subalpica*,⁶⁷ and *Buellia* sp.,⁶⁷), 2,7-dichloronorlichexanthone (**84**, from *Buellia* sp.,⁶⁷ *Lecanora andrewii*,⁶⁹ *L. behringii*,⁶⁸ *L. broccha*,^{67,68} *L. ingae*,⁶⁹ *L. populicola*,⁶⁸ *L. pruinosa*,⁶⁹ *L. salina*,⁶⁸ *Lecanora* sp.,⁶⁸ *L. straminea*,¹⁴¹ *L. sulphurata*,⁶⁹ *Lecidella asema*,⁶⁷ *L. meiococca*,⁶⁹ *L. subalpica*,⁶⁷ *Lopadium* species *L. foliicola* (Fée), R. Sant.,⁷³ and *L. fuscum* (Müll. Arg.),⁷³ *L. nymanii* R. Sant.,⁷³ and *L. phyllogenum*⁷³), *Melanaria melanospora*,⁶⁹ 4,5-dichloronorlichexanthone (**85**, from *Buellia* sp.,⁶⁷ *Lecanora straminea*,⁸² *Lecidella vorax*,⁶⁷ *Lecidella asema*,⁶⁷ *L. subalpica*,⁶⁷ *L. flavo-pallescens*,⁷¹ *Micarea isabellina*,⁶⁸ *M. austroternaria*,⁷¹ and *Pertusaria pycnothelia*⁶⁸), 4,7-dichloronorlichexanthone (**86**, from *Buellia* sp.,⁶⁷ *Lecanora broccha*,⁶⁷ *Lecidella meiococca*,⁶⁷ *L. asema*,⁶⁷ and *L. subalpida*⁶⁷), 5,7-dichloronorlichexanthone (**87**, from *Lecanora broccha*,⁶⁸ *L. asema*,⁶⁷ *Lecidella vorax*,⁶⁸ *L. subalpida*,⁶⁷ and *Buellia* sp.,⁶⁷), 2,4,5-trichloronorlichexanthone (also known as arthothelin, **19**, Figure 2, from *Dimelaena cf. australiensis*,⁶⁸ *Pertusaria cicatricosa*,⁶⁸ *L. flavo-pallescens*,⁷¹ and *L. reuteri*¹³⁹), 2,4,7-trichloronorlichexanthone (**88**, from *Lecanora sulphurata*,⁶⁸ *L. flavo-pallescens*,⁹ and *L. reuteri*¹³⁹), 2-chloro-3-O-methylnorlichexanthone (**89**, isolated and synthesized by Elix and co-workers¹⁴⁶), 2-chloro-6-O-methylnorlichexanthone (**90**, from *Lecanora salina*,⁶⁸ *Pertusaria cicatricosa*,⁶⁸ and *P. sulphurata*¹³⁵), 4-chloro-6-O-methylnorlichexanthone (**91**, from *Pertusaria sulphurata*¹³⁵), 5-chloro-6-O-methylnorlichexanthone (**92**, from *Lecanora contractula*),⁶⁸ 7-chloro-3-O-methylnorlichexanthone (**93**, reported by Sundholm⁸²), 7-chloro-6-O-methylnorlichexanthone (**94**, from *Lecanora populicola*, *L. salina*, and *Lecanora* sp.),⁶⁸ 2,5-

**Figure 20.** Norlichexanthone and derivatives.

dichloro-3-O-methylnorlichexanthone (**95**, from *L. behringii*, *L. contractula*, *L. populicola*, and *L. salina*),¹⁴² 2,5-dichloro-6-O-methylnorlichexanthone (**96**, from *Dimelaena* sp.,⁷⁵ *Dimelaena* cf. *australiensis*,⁷⁶ *Lecanora contractula*, and *Pertusaria cicatrica*),⁶⁸

cosa),⁶⁸ 2,7-dichloro-3-O-methylnorlichexanthone (**98**, from *Lecanora behringii*, *L. salina*, and *Lecanora* sp.),⁶⁸ 2,7-dichloro-6-O-methylnorlichexanthone (**99**, from *Lecanora behringii*, *L. salina*, *L. populicola*, and *Lecanora* sp.),⁶⁸ 4,5-dichloro-3-O-

methylnorlichexanthone (**100**), 4,5-dichloro-6-O-methylnorlichexanthone (**101**, from *Dimelaena cf. australiensis*),^{68,76} 5,7-dichloro-3-O-methylnorlichexanthone (**102**, from *Buellia* sp.,⁶⁷ *Lecanora broccha*,^{67,68,70} *L. vinetorum*, *Lecidella meiococca*, *L. vorax*,⁶⁸ *L. asema*,⁶⁷ and *L. subalpica*⁶⁷), 2,4,7-trichloro-6-O-methylnorlichexanthone (**103**, isolated and synthesized by Elix and co-workers¹⁴⁶), 2,5,7-trichloro-3-O-methylnorlichexanthone (**104**, from *Buellia* sp.,⁶⁷ *Lecanora broccha*,^{67,68,70} *L. capistrata*,⁶⁹ *Lecidella asema*,⁶⁷ *L. meiococca*,⁶⁸ *L. vorax*,⁶⁸ *L. subalpica*,⁶⁷ and *Sporopodium phyllocharis* var. *flavescens*⁷³), 2,5,7-trichloro-6-O-methylnorlichexanthone (**105**, isolated and synthesized by Elix and co-workers¹⁴⁶), and 4,5,7-trichloro-6-O-methylnorlichexanthone (**106**, from *Pertusaria pycnothelia* var. *A*⁷³).

Elix and Crook also analyzed the following compounds (included in other parts of this review) by HPLC:⁶⁸ arthothelin and isoarthothelin (**19** and **20**, see Figure 2), 6-O-methylarthothelin (**22**, Figure 2), 3-O-methylasemone (**22**, Figure 3), 6-O-methylasemone (**23**, Figure 3), demethylchodatin (**46**, Figure 8), 1,8-dihydroxy-3,6-dimethoxyxanthone (**51**, Figure 10), thiophanic acid (**211**, Figure 36), 8-O-methylthiomelin (**203**, Figure 34), 4-dechlorothiomelin (**212**, Figure 34), thuringione (**202**, Figure 37), vinetorin (**230**, Figure 41), thiomelin (**199**, Figure 34), 1,3,6-tri-O-methylarthothelin (**23**, Figure 2), 6-O-methylthiophanic acid (**208**, Figure 34), and 3-O-methylthiophanic acid (**209**, chodatin, structure unknown). Santesson also developed a reliable thin-layer chromatography (TLC) method for the study of various lichen-derived natural products, including five xanthones,^{5,143} and a more recent paper from Yoshimura and co-workers describes the analysis of eight lichen-derived xanthones by the use of HPLC and photodiode-array detection.^{9,144}

Elix and Crook have re-examined the specimen of *Lecanora contractulata* and found that it in fact contained 2,5-dichloro-6-O-methylnorlichexanthone (**97**), alongside lesser amounts of 5-chloro-6-O-methylnorlichexanthone (**95**) and 5-chlorolichexanthone (**66**, Figure 19), whereas Santesson had originally suggested the major constituent to be 2,5-dichloro-3-O-methylnorlichexanthone¹⁴⁵ (**94**, later corrected to 2,7-dichloro-3-O-methylnorlichexanthone, **98**, by Sundholm).⁸²

Synthesis. In 1978 Sundholm described the synthesis of several chlorinated lichen xanthones using the condensation of benzyl-protected phloroglucinol carboxylic acids with benzyl-protected orcinol derivatives.⁸² After removal of the protecting groups from the resulting benzophenones, spontaneous cyclization occurred in most cases to give the corresponding xanthones: 2-chloronorlichexanthone (**78**, Figure 20), griseoxanthone B (**58**, Figure 15), 7-chlorolichexanthone (**67**, Figure 19), and 2,7-dichlorolichexanthone (**70**). In 1978, Elix and co-workers described the isolation from *Pertusaria sulphurata* of three novel xanthones alongside the known xanthones lichexanthone (**63**, Figure 19) and thiophanic acid (**211**, Figure 36), all of which were unambiguously synthesized using an Ullmann coupling to form biphenyl ether intermediates, followed by ring-closing on an *ortho*-carboxyl group to deliver the targets.¹³⁵ The newly discovered xanthones were 2-chloro-1,3-dihydroxy-6-methoxy-8-methylxanthone (**107**, Figure 21), 2-chloro-1-hydroxy-3,6-dimethoxy-8-methylxanthone (**108**, Figure 21), and 4-chloro-1,3-dihydroxy-6-methoxy-8-methylxanthone (**109**).

In 1992 Elix and co-workers reported the unambiguous synthesis¹⁴⁶ of 17 newly isolated⁶⁸ chlorinated derivatives of (nor)lichexanthone and thiophanic acid via a condensation of

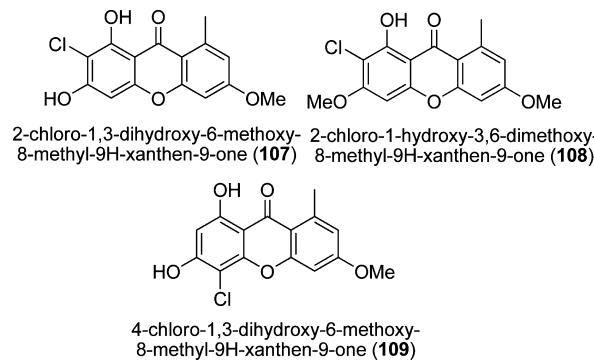
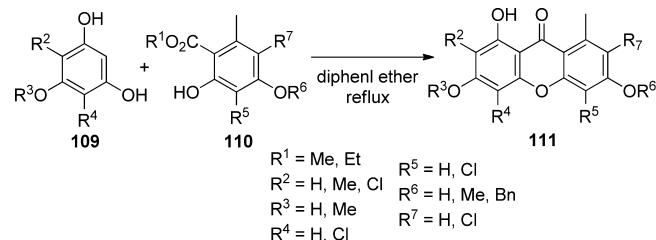


Figure 21. Lichen xanthones, isolated and synthesized by Elix et al.

an appropriately substituted phloroglucinol (**109**, Scheme 3) and an alkyl orsellinate (**110**);¹⁴⁶ the method has been

Scheme 3. Elix Synthesis of Xanthones



developed by Patolia and Trivedi¹⁴⁷ and is itself a variant of the method established by Grover, Shah, and Shah.¹²¹ 7-Chloro-6-O-methylnorlichexanthone (**94**, Figure 20), 2-chloro-3-O-methylnorlichexanthone (**89**), 5-chlorolichexanthone (**66**, Figure 19), 7-chlorolichexanthone (**67**), 2,7-dichloro-6-O-methylnorlichexanthone (**99**, Figure 20), 2,4-dichloro-3-O-methylnorlichexanthone (**95**), 2,7-dichloro-3-O-methylnorlichexanthone (**77**), 4,7-dichlorolichexanthone (**72**), 5,7-dichlorolichexanthone (**73**), 2,4,7-trichloro-6-O-methylnorlichexanthone (**103**), 2,5,7-trichloro-6-O-methylnorlichexanthone (**105**), 2,4,7-trichlorolichexanthone (**75**), 2,5,7-trichlorolichexanthone (**76**), 3-O-methylthiophanic acid (**208**, Figure 35), and 3,6-di-O-methylthiophanic acid (**210**) were all prepared. These syntheses were an extension of their previous synthetic work with related xanthone derivatives.^{76,78} 2,4,7-Trichloronorlichexanthone (**88**) and 4,5,7-trichloronorlichexanthone (asemenone, **24**, Figure 3) were synthesized by the Smiles rearrangement of the appropriate depside to the biphenyl ether, followed by treatment of the raw product with trifluoroacetic anhydride.^{9,20,71,148}

In 1980 Sargent co-workers reported the unambiguous synthesis of some chlorinated fungal xanthones¹⁴⁹ by way of cyclization of 2,2-dihydroxy- or 2-hydroxy-2-methoxy-benzophenones to 5-chloronorlichexanthone (**80**, Figure 20), vinetorin (**209**, Figure 41), and four more naturally occurring lichen xanthones, 5-chloro-6-hydroxy-1,3-dimethoxy-8-methylxanthone (**112**, Figure 22, isolated from *Pertusaria aleinata* by Huneck and Höfle),^{7,72} 4,5-dichloro-1,3,6-trihydroxy-8-methylxanthone (**113**, isolated from *Lecanora straminea* by Santesson),¹⁴⁰ 4,5-dichloro-1-hydroxy-3,6-dimethoxy-8-methylxanthone (**114**, isolated from *Buellia glazioniana*, the structure of which was reassigned by Sundholm¹⁵⁰ and confirmed by this synthetic work), and 2,4,5-trichloro-1-hydroxy-3,6-dimethoxy-8-methylxanthone (**115**, also from *Pertusaria aleinata*).^{7,72}

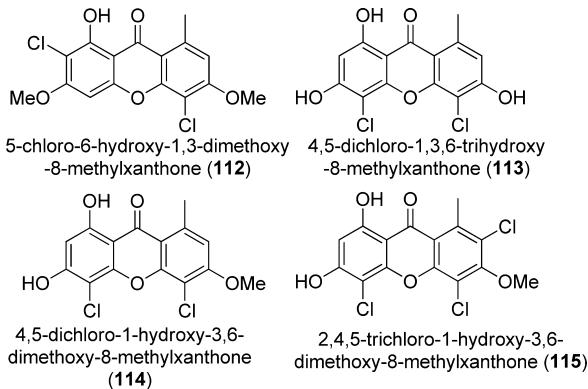
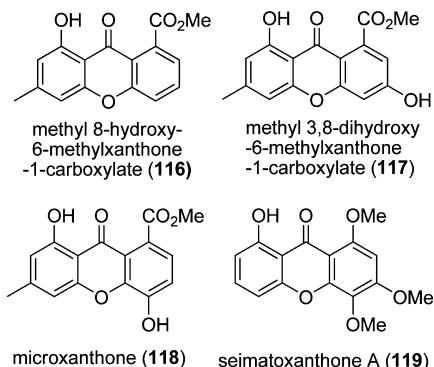


Figure 22. Lichen xanthones, synthesized by Sargent et al.

Interestingly, lichexanthone (**63**, Figure 19) has also been found in a number of plant sources, for example, from the bark of *Xanthoxylum microcarpum* and *X. valens*,¹⁵¹ and from *Minquartia guianensis* Aubl., a plant used by traditional healers and as a fish poison in eastern Ecuador.¹⁵² Lichexanthone (**63**, Figure 19), norlichexanthone (**77**, Figure 20), and several derivatives were found to be weakly active against *Mycobacterium tuberculosis*,¹⁵³ another study found a similar result for lichexanthone against *M. aureus*.¹⁵⁴ Lichexanthone was also found to exhibit sperm mobility enhancing activity.¹³⁶

Microsphaeropsis Xanthones. Krohn and co-workers isolated three xanthones from *Microsphaeropsis* sp.¹⁹ They are methyl 8-hydroxy-6-methylxanthone-1-carboxylate (**116**, Figure 23), methyl 3,8-dihydroxy-6-methylxanthone-1-carboxylate (**117**), and the novel species microxanthone (**118**). Of biosynthetic interest, the authors also isolated the anthraquinones emodin and citreorosein. These compounds were demonstrated to be xanthone precursors and ring-expanded xanthones (i.e., oxepino[2,3-*b*]chromones; see **48** and **49**, Figure 9), which they named microsphaeropsones. In the same publication, the authors reported finding another, trimethoxylated, xanthone, from *Seimatosporium* sp. (internal strain 8883), taken from a halotolerant plant species. The authors named this last species seimatoxanthone A (**119**).

Figure 23. Xanthones from *Microsphaeropsis* sp. (**116–118**), and seimatoxanthone A (**119**).

(**117**), and the novel species microxanthone (**118**). Of biosynthetic interest, the authors also isolated the anthraquinones emodin and citreorosein. These compounds were demonstrated to be xanthone precursors and ring-expanded xanthones (i.e., oxepino[2,3-*b*]chromones; see **48** and **49**, Figure 9), which they named microsphaeropsones. In the same publication, the authors reported finding another, trimethoxylated, xanthone, from *Seimatosporium* sp. (internal strain 8883), taken from a halotolerant plant species. The authors named this last species seimatoxanthone A (**119**).

Mycoxanthone. Assante and co-workers reported in 1979 the novel structures of mycoxanthone (**120**, Figure 24) and the related mycochromone (not shown), from screening the genus *Mycosphaerella rosigena*, a fungus causing the leaf-spot disease of rose plants. The authors deduced the structures from chemical degradation processes alongside the use of various spectro-

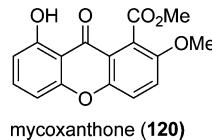
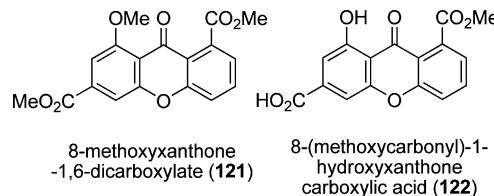


Figure 24. Mycoxanthone.

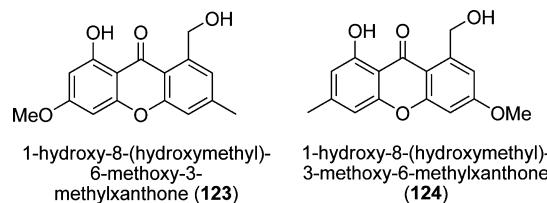
scopic techniques. *Mycosphaerella* is related to the genus *Cercospora*, from which beticolins were isolated (see section 3.3).¹⁵⁵

Penicillium sp. ZZF 32#. Lin and co-workers reported the isolation of two novel xanthones after their isolation from a cultivated *Penicillium* species, ZZF 32#, and identified them as methyl 8-methoxyxanthone-1,6-dicarboxylate (**121**, Figure 25)

Figure 25. Xanthones from *Penicillium* sp. ZZF 32#.

and 8-(methoxycarbonyl)-1-hydroxyxanthonecarboxylic acid (**122**). These compounds were found to be inactive in terms of cytotoxicity, but the latter was found to exhibit modest antifungal activity against *Fusarium oxysporum* f. sp. *cubense*.¹⁵⁶

Phoma sp. SK3RW1M Xanthones. Lin and co-workers reported the discovery of two new xanthones from an epiphytic fungus, *Phoma* sp., itself isolated from the roots of the mangrove species *Avicennia marina* (Forsk.) Vierh.¹⁵⁷ The two species, 1-hydroxy-8-(hydroxymethyl)-6-methoxy-3-methylxanthone (**123**, Figure 26) and 1-hydroxy-8-(hydroxymethyl)-3-

Figure 26. Xanthones from *Phoma* sp. SK3RW1M.

methoxy-6-methylxanthone (**124**), were isolated with repeated column chromatography, and the structures determined aided by 1D and 2D NMR techniques, as well as a crystal structure of **123**. The authors have tested these compounds for activity against KB and KBv200 cells and found them to be inactive.¹⁵⁸

Phomopsis-ZH19 Xanthones. Huang and co-workers reported in 2010 on the isolation and characterization of two new xanthones from the mangrove endophytic fungus ZH19, collected from the leaves of *Avicennia marina* in the South China Sea.¹⁵⁹ The compounds were 1,7-dihydroxy-2-methoxy-3-(3-methylbut-2-enyl)xanthone (**125**, Figure 27) and 1-hydroxy-4,7-dimethoxy-6-(3-oxobutyl)xanthone (**126**). The compounds were identified with a variety of spectral techniques and tested in cytotoxicity assays against KB cells with IC₅₀ values of 20 and 35 μmol/mL and KB cells (KBv200) with IC₅₀ values of 30 and 41 μmol/mL, respectively.

Pinselin and Pinselic Acid. Pinselin and pinselic acid (**127** and **128**, Figure 28) were first isolated from cultured *Penicillium*

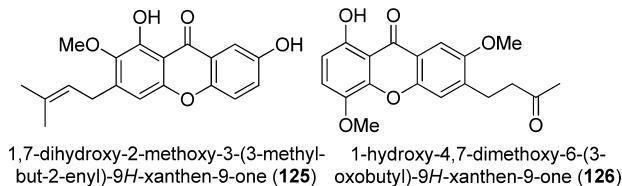
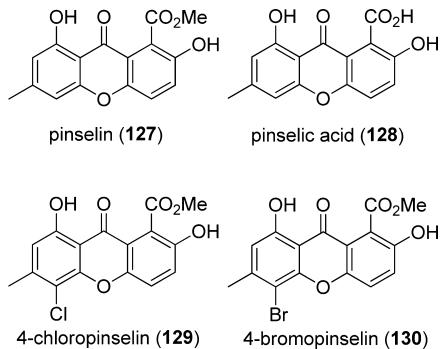
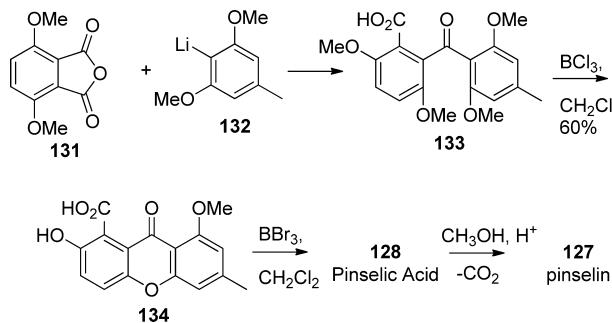
Figure 27. Xanthones from *Phomopsis* sp. ZH19.

Figure 28. Pinselin, pinselic acid, and 4-chloro- and 4-bromo-pinselin.

amarum and were originally identified by chemical degradation processes.¹⁶⁰ In a rarely occurring event, pinselin was also isolated from the plant *Cassia occidentalis*,¹⁶¹ although it was originally misidentified as 1,7-dihydroxy-5-methoxycarbonyl-3-methylxanthone and later corrected to be identical with pinselin.¹⁶² 4-Bromo- and 4-chloropinselin (129 and 130) have been isolated from *Monilinia fructicola* by Kachi and co-workers in 1986;¹²⁵ the latter compound was also isolated alongside some ring-expanded lactones by Suzuki and co-workers in 1989.⁴⁷²

An unambiguous synthesis of these compounds was reported in 1979 by Tam and co-workers (Scheme 4), making use of a

Scheme 4. Tam and Co-workers's Synthesis of Pinselin



nucleophilic addition and demethylation, followed by cyclization of the resulting diphenol 133.¹⁶³ The monomethyl ether was demethylated to pinselic acid (128, Scheme 5), which was further decarboxylated under acidic conditions to pinselin (127).

In 1985 Whalley and co-workers reported the synthesis of pinselin by a Lewis acid-mediated furan-ring-opening/pyranone-ring-closing of bromide 136, followed by oxidation of this alcohol, α -bromination, and aromatization with base to give pinselin (127).^{165,166}

Ravenelin. Ravenelin (139, Figure 29) was reported by Raistrick, Robinson, and White in 1936 after being isolated from both *Helminthosporium ravenelii* (aka *Drechslera ravenelii*)

Scheme 5. Whalley and Co-workers's Synthesis of Pinselin

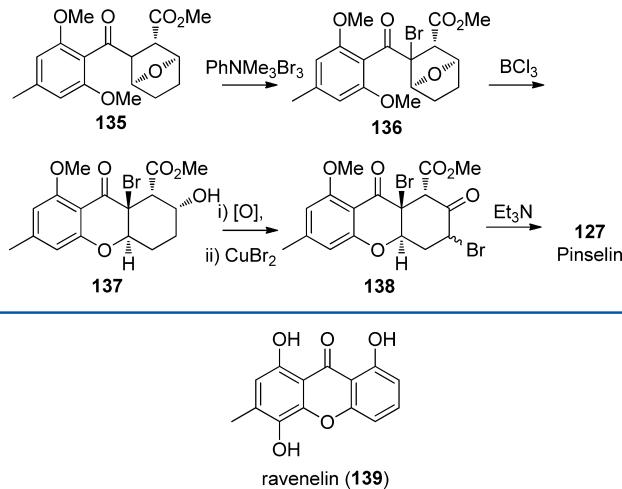
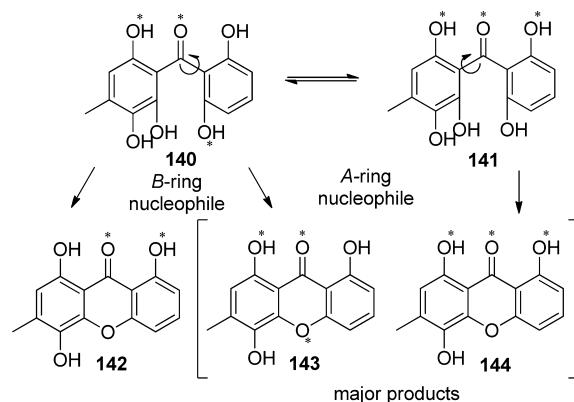


Figure 29. Ravenelin.

and *Helminthosporium turicum*.¹⁶⁷ A synthesis of this species was reported in 1944 by Mull and Nord,¹⁶⁸ and a second was reported in 1956.¹⁶⁹

In 1975 Birch and co-workers published a conclusive investigation of ravenelin biosynthesis involving the use of [1^{-14}C]- and [2^{-14}C]-acetate and -malonate feeding experiments, followed by degradation studies of the resulting enriched ravenelin. They also performed [1^{-13}C]- and [2^{-13}C]-acetate feeding experiments, followed by ^{13}C NMR analysis, with the combined studies showing that ravenelin, like bikaverin,¹⁰⁴ is derived from a single polyketide (C_{16}) precursor.¹⁷⁰ The authors furthermore found that the biosynthetic pathway must contain intermediates in the form of an anthraquinone or anthrone, followed by a freely rotating benzophenone, as evidenced by ^{14}C and ^{13}C labeling in the xanthone product.¹⁷⁰ Later work by Vederas and co-workers used the incorporation of ^{18}O into ravenelin and subsequent detection by isotopic shifts in the ^{13}C NMR spectrum to support the conclusions of Birch and to differentiate between two possible modes of addition—elimination ring-closure of the o,o -dihydroxybenzophenone intermediate (140 or 141, Scheme 6), showing that the predominant modes were leading to labeled species 143 and 144, meaning that the oxygen of the A-ring (nonmethylated) acts as the nucleophile upon the B-ring, and not vice versa. This labeled oxygen is thus preserved in the

Scheme 6. Ravenelin Biosynthesis



product (Scheme 6), providing the first insight into the role of each ring in the biosynthesis of xanthones.¹⁷¹

Sterigmatocystin and Derivatives. The optically active fungal metabolite sterigmatocystin (**146**, Figure 30) was first

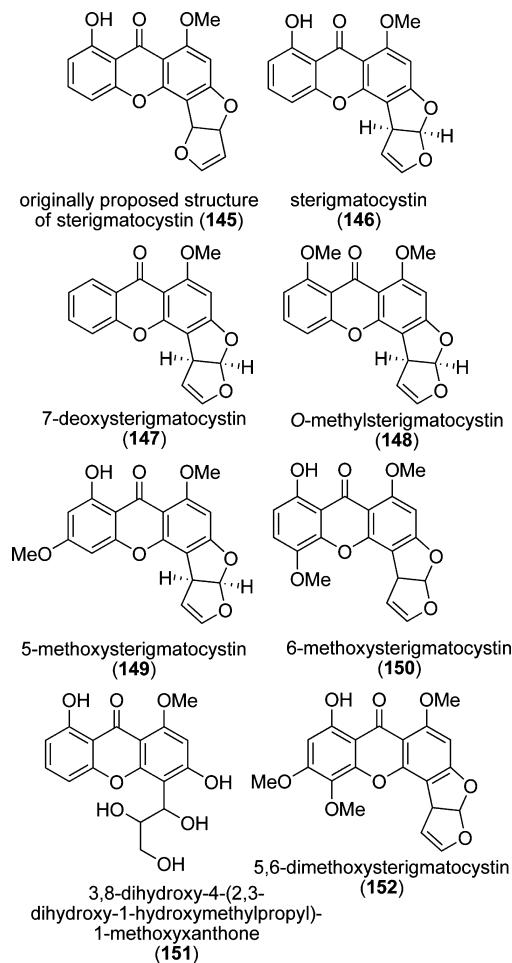


Figure 30. Sterigmatocystin and derivatives (stereochemistry shown, where known).

isolated (but not structurally defined) from *Aspergillus versicolor* by Abou-Zeid in 1953, and has been subsequently isolated a number of times from this species,^{172–175} the related *A. parasiticus*,¹⁷⁶ and *A. multicolor*,¹⁷⁷ and both *Emericella venezuelensis*¹⁷⁸ and *Emericella astellata*¹⁷⁹ (both of which also produced aflatoxins).

Isolation and Structural Determination. The structure of sterigmatocystin was originally determined² by a combination of spectral techniques and chemical degradation.^{180–182} Bullock and co-workers reported in 1962 the characterization of isosterigmatocystin, formed by reaction of sterigmatocystin with base, and the reassignment of the previously reported structure (**145**, Figure 30) to the correct structure, **146**,¹⁸³ which constituted the first known natural dihydrofurobenzofuran ring system. Such a structural motif was later also found in the aflatoxins and other carcinogenic products from microorganisms. The same group reported in 1963 the isolation of 6-methoxysterigmatocystin (**150**, Figure 30) after isolating it and a related anthraquinone (but not sterigmatocystin) from a mutant variety of *Aspergillus versicolor*.¹⁸⁴ Holker and Kagal reported the isolation of 5-methoxysterigmatocystin (**149**) from a mutant strain of *Aspergillus versicolor*, produced by

irradiation of wild strain spores, in 1968.¹⁸⁵ Small amounts of 5,6-dimethoxysterigmatocystin were reported alongside sterigmatocystin by Hatsuda and co-workers from *A. multicolor*.¹⁷⁷ In 1977 Hamasaki and co-workers reported the structure of 5,6-dimethoxysterigmatocystin (**152**), which they isolated from *Aspergillus multicolor* Sappa, having also isolated sterigmatocystin and averufin from the same extracts. The structure of **151** was determined based on chemical degradation and NMR studies and was finally confirmed with single-crystal X-ray studies of the monoacetate.¹⁸⁶

In 2007 Lin and co-workers reported the structure of dihydrosterigmatocystin and secosterigmatocystin (**153** and **154**, Figure 31), which they isolated from the South Chinese

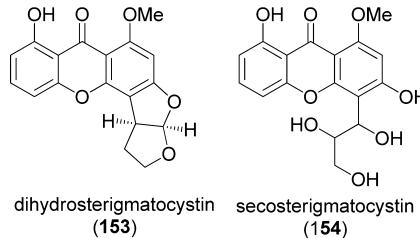
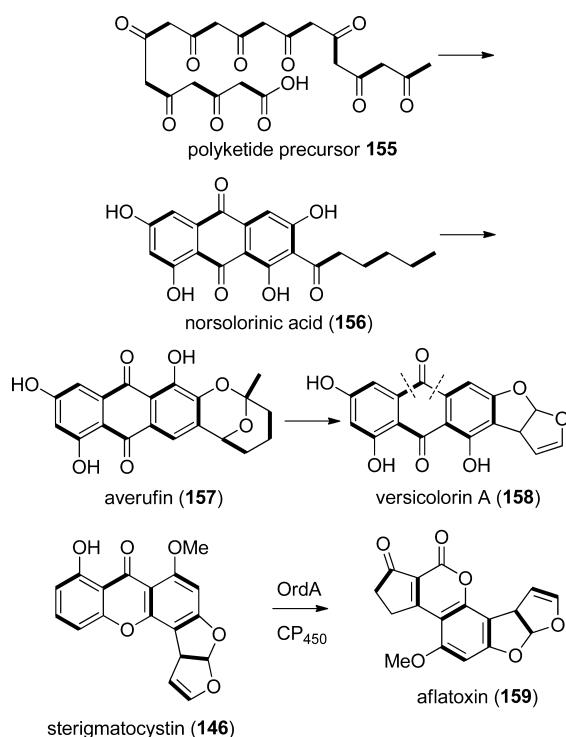


Figure 31. New xanthones from mangrove fungus derived from *Kandelia candel*.

Sea mangrove fungus ZSUH-36.¹⁸⁷ These compounds were isolated alongside two anthraquinones and the two known xanthones, sterigmatocystin and 5-methoxysterigmatocystin (**146** and **149**, to which they are related, see Figure 30), and the structures were determined from NMR data and liquid chromatography–mass spectrometry (LCMS) experiments.¹⁸⁷ Also in 2007 Lin and co-workers reported three xanthones: sterigmatocystin, dihydrosterigmatocystin, and secosterigmatocystin (**146**, Figure 30, **153**, and **154**, Figure 31), which they isolated from an endophytic mangrove fungus of *Kandelia candel* (isolate 1850).¹⁸⁸ The structures were determined with NMR data and LCMS experiments, and biological testing showed a weak cytotoxic activity of sterigmatocystin against two tumor cell lines with values in the midmicromolar range.¹⁸⁸

Biosynthesis. Sterigmatocystin is both a carcinogenic hepatotoxin and a biosynthetic precursor to the important mycotoxin aflatoxin, and as such the biosynthetic pathway leading to it has been extensively studied.^{189–191} It is supposed to begin with a single C₂₀ polyketide unit, which is folded by a single mode to form averufin and then sterigmatocystin.¹⁹² The authors provided evidence to support the identity of this compound through the synthesis of a common product from it and a derivative of dihydrosterigmatocystin (**153**, Figure 31). O-Methylsterigmatocystin (**148**, Figure 30) was reported in 1968 by Burkhardt and Forgacs after being isolated from a highly toxic aflatoxin-containing strain of *Aspergillus flavus* (cycad strain II) and the structure confirmation by synthesis from sterigmatocystin.¹⁹³ In 1984 Maes and Steyn reported 3,8-dihydroxy-4-(2,3-dihydroxy-1-hydroxymethylpropyl)-1-methoxyxanthone (**151**, Figure 30), an open-chain isomer of the difuran component of the sterigmatocystins, after isolating it from *Bipolaris sorokiniana*. This species also contained isolable amounts of the anthraquinones averufin (**157**, Scheme 7), versicolorin C, versiconol, versiconol acetate, and sterigmatocystin (**146**).¹⁹¹ The isolation of all these compounds alongside each other provides evidence to support the proposed acetate/polymalonate pathway to polyhydroxylated anthraquinones,

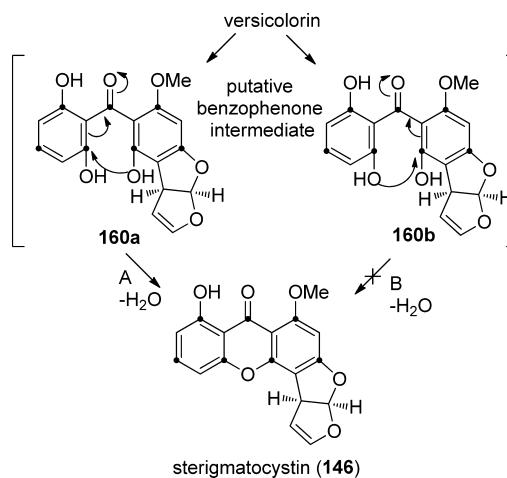
Scheme 7. Suggested Pathway for Sterigmatocystin Biosynthesis^{23–25,28,34}



followed by cyclization/condensation to xanthones by oxidative cleavage, and then to coumarins (i.e., aflatoxins) through rearrangement. Such a sequence had already been suggested for the ergochromes (see section 3.3)¹⁹⁴ and ravenelin (139, Figure 25).¹⁹⁵ In 2002 Glover and co-workers reported the isolation of 7-deoxysterigmatocystin (147, Figure 30) alongside two nonxanthone products from *Humicola fuscoatra*, a mycoparasitic fungi that invades other fungi.¹⁹⁶

The final steps of conversion to aflatoxin seem to be catalyzed by a single cytochrome-P₄₅₀ oxidative cleavage of the aromatic ring with an epoxide intermediate, O-demethylation, dehydration, decarboxylation, and finally rearrangement to give aflatoxin (159, Scheme 7);¹⁸⁹ the pathway also involves an intermediate reductive step.¹⁹⁰ Further to previous studies on the ¹³C spectrum of sterigmatocystin,^{197,199} Nakashima and Vedera reported in 1982 the use of spin-echo resolution technique in the ¹³C NMR analysis of sterigmatocystin (146) derived from *Aspergillus versicolor* grown in the presence of ¹³C-labeled sodium acetate.¹⁹⁸ In a previous study, ¹³C incorporation suggested that the intermediate (benzophenone) between versicolorin A (anthraquinone) and sterigmatocystin (xanthone) is unsymmetrical, as the resulting pattern of ¹³C incorporation is unscrambled.¹⁹⁹ Of two possible modes of oxo-Michael addition to form the xanthone ring of sterigmatocystin (146, via path A or B, Scheme 8), the authors determined that the cyclization occurs only from path A, i.e., nucleophilic attack of the hydroxy group of a benzophenone intermediate derived from oxidative ring-cleavage of versicolorin A.²⁰⁰ A study from Zamir and Hufford on the intermediates in aflatoxin biosynthesis was carried out using kinetic pulse-labeling, beginning with feeding of radioactive acetate to a culture broth of *A. versicolor*. The various intermediates could be radiotrapped (with TLC analysis) so as to follow their order of appearance in the *A. versicolor* cultures. As expected, averufin and norsolonic acid

Scheme 8. Nakashima and Vedera's Observations with Respect to the Mode of Xanthone Formation in Sterigmatocystin



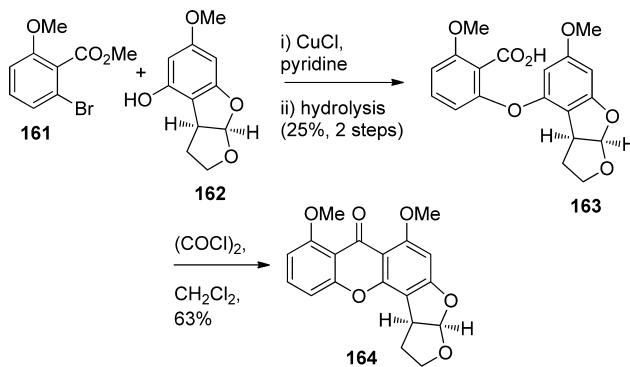
appeared first, followed by versicolorin A, aflatoxins, and sterigmatocystin, a finding which led the authors to speculate that perhaps sterigmatocystin is the result of a branched biosynthetic pathway, rather than necessarily an aflatoxin precursor.

Bioactivity. Sterigmatocystin has been found to be an inhibitor of the growth of transplanted leukemias P-388 and L1210 in mice.²⁰¹ Interestingly, sterigmatocystin has also been isolated from an *Aspergillus fumigatus* strain that was itself derived from surgically removed human lung samples²⁰² and can be collected from the air in various environments that are high in organic-matter-derived dust, such as composting plants,²⁰³ and from *Aspergillus versicolor* samples collected from household carpet dust,²⁰⁴ highlighting the significant nature of this environmental toxin to humans.

Synthesis. In 1969 Rance and Roberts reported the synthesis of dihydro-O-methylsterigmatocystin,²⁰⁵ utilizing a variant of the Ullmann reaction, under which the dihydrafuranobenzofuran bicyclic moiety was stable, and a following condensation reaction of an acid chloride intermediate to install the xanthone ring of 164 (Scheme 9).

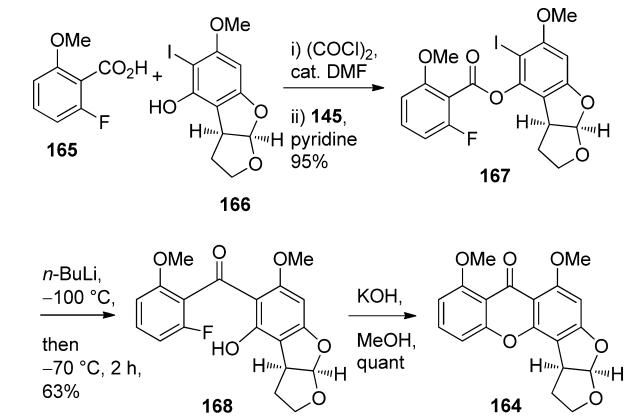
Horne and Rodrigo further reported in 1990 the synthesis of dihydro-O-methylsterigmatocystin²⁰⁶ (148, Figure 30) utilizing an iodide intermediate, 166, which they had developed in an earlier synthesis of aflatoxin B₂,²⁰⁷ as part of an investigation for

Scheme 9. Rance and Robert's Synthesis of Dihydro-O-methylsterigmatocystin



a general method to the synthesis of substituted xanthones. The key conversions are an esterification, anionic Fries rearrangement, and base-mediated cyclization of a phenol upon an aryl fluoride to deliver the xanthone core of **164** (Scheme 10).

Scheme 10. Horne and Rodrigo's Synthesis of Dihydro-*O*-methylsterigmatocystin



Having found that standard methods of xanthone synthesis were not applicable to the synthesis of sterigmatocystin species of their interest, Casillas and Townsend synthesized *O*-methylsterigmatocystin (**148**, Figure 30) in 18 steps utilizing a new methodology (Scheme 11). The synthesis involved a modified Houben–Hoesch reaction as the key step with *N*-alkylnitrilium salt, in conjunction with the effective, if unusual, protection of a carbonyl group as an alkene (i.e., via addition of *n*-butyllithium and elimination of H₂O).²⁰⁸ The facile removal of the butenyl group was then effected with *meta*-chloroperbenzoic acid.

In a subsequent paper, the Townsend group utilized a very similar synthetic sequence with a (protected) 3-hydroxyarene variant of nitrile **169** in order to access the related 11-hydroxy-*O*-methylsterigmatocystin (a putative biosynthetic intermediate, not shown).¹⁸⁹ Further to the interest of these authors to the biosynthesis of these significant environmental carcinogens,²⁰⁹ this compound was used as an enzymatic substrate to support a proposed biosynthetic sequence leading to aflatoxin B₁. In this sequence, cytochrome P₄₅₀ catalyzes a series of oxidative transformations from anthraquinone to xanthone to coumarin; the xanthone intermediates are demonstrated to involve first *O*-methylsterigmatocystin and then 11-hydroxy *O*-methylsterigmatocystin, both of which were converted by the OrdA cytochrome P₄₅₀ of *Aspergillus parasiticus*.¹⁸⁹

In a later report, Henry and Townsend investigated the order of the reductive and oxidative steps of the synthesis of demethylsterigmatocystin, a key intermediate in the aflatoxin biosynthetic pathway.¹⁹⁰ Toward this end, they synthesized sterigmatocystin analogues **181**–**184** (Figure 32). It was found that the “bent” isomers (with the oxygen *ortho*- to the carbon framework of the difuran ring) spontaneously isomerized to the more stable “linear” species over a period of two weeks in acidic conditions (catalyzed by silica gel), thus providing another example of the facile nature of the oxa-Michael and retro-oxa-Michael reactions. They found that an unusual sequence of oxidation–reduction–oxidation was involved in the biosynthetic conversion of versicolorin A to demethylsterigmatocystin.¹⁹⁰

Scheme 11. Casillas and Townsend's Synthesis of *O*-Methylsterigmatocystin

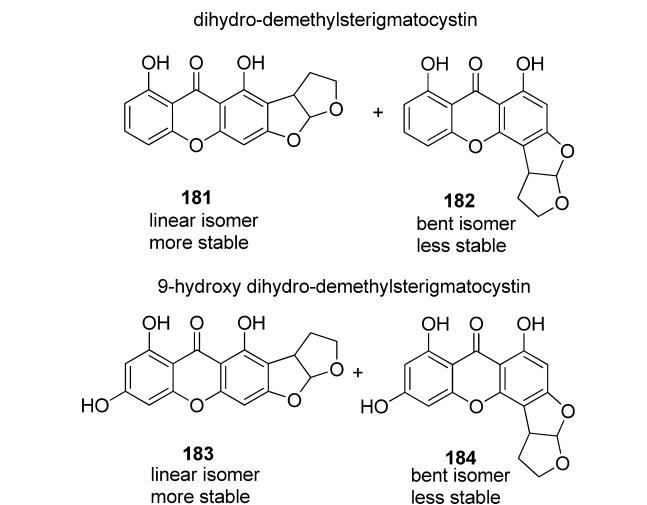
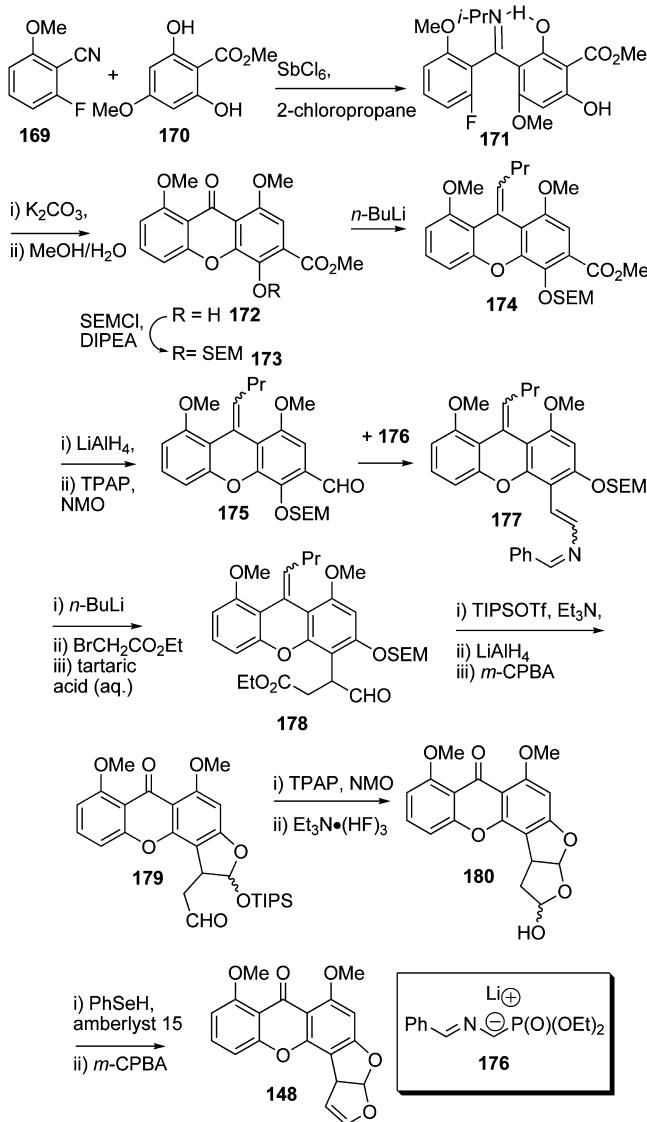


Figure 32. Sterigmatocystin derivatives used by Townsend and co-workers to investigate the biosynthesis of aflatoxins.

Essery and co-workers have developed some derivatives of 5-methoxysterigmatocystin for the purpose of testing as antitumor agents.²¹⁰ They found that the double bond of the furan system is necessary for the antitumor activity of these compounds.

Tajixanthones. The tajixanthone family includes the titular compound and the highly structurally related species shamixanthone, variecoxanthone, and their derivatives (**185–195**, Figure 33). Shamixanthone was isolated alongside three other structurally nonresolved optically active species by Kamal and co-workers in 1970 from *Aspergillus variecolor*,²¹¹ followed shortly by tajixanthone.²¹² Tajixanthone and shamixanthone (**186** and **185**, Figure 33) were reisolated in 1974 by Holker and co-workers,²¹³ who redetermined their structures (as shown in Figure 33), including absolute configuration, based upon the detailed analyses of ¹H- and ¹³C NMR spectra, chemical degradation, and a Horeau asymmetric synthesis.²¹⁴ Further members of this family include variecoxanthones A–C (**187–189**, Figure 33), which were isolated in a following study²¹⁵ of a variant strain of *Aspergillus variecolor* by the same group.

Additional xanthone species (**190–195**, Figure 33) were reported to be present in minor amounts, and the structures were determined (save the absolute stereochemistry of **194**).²¹⁵ Variecoxanthones were also isolated from *Emericella dentata*,²¹⁶ and the related cycloisoemericillin (**195**, Figure 33) was isolated from *Emericella striata*.²¹⁷ Pornpakakul and co-workers⁴⁷³ reported in 2006 the isolation of shamixanthone (**185**), 14-methoxy-tajixanthone-25-acetate (**193**), tajixanthone (**186**), and tajixanthone monohydrate (**191**), which they subsequently tested in comparison with doxorubicin against several cancer cell lines, including gastric, colon, breast, lung, and human hepatocarcinoma. Among these, tajixanthone hydrate (**191**) showed the most widespread activity against all the cell lines tested.

The members of this family are interestingly constructed from a combination of polyketide (xanthone) and terpenoid-derived carbon units; the latter is biosynthetically derived from an O-prenyl group, which has not undergone cyclization for the variecoxanthones. Holker and co-workers have proposed a stereospecific “ene reaction” to explain the *trans*-relationship of substituents on the dihydropyran ring of tajixanthone and shamixanthone.¹¹⁵ The biosynthetic pathway to these species was originally proposed based upon ¹³C and ²H feeding experiments as originating from an octaketide xanthone precursor, which is converted to a 1,8-dihydroxy anthrone (chrysophyl anthrone), which after oxidative cleavage is subsequently cyclized and derivatized and then C- and O-prenylated by dimethylallylpyrophosphate.²¹⁸ Additionally, a report from Simpson and co-workers described feeding experiments with ¹⁸O molecular oxygen, which led to tajixanthone incorporating oxygen at all positions of the molecule save the C13 ketone (which is acetate derived) and that the oxygens at C1 and C10 were labeled with half the relative amount of ¹⁸O in comparison with the other O₂-derived oxygens. This observation is consistent with one of these oxygens being O₂-derived and the other one being acetate-derived, and thus supports the intermediacy of a symmetrical (2,6-dihydroxy)benzophenone in the biosynthesis of the xanthone ring,²¹⁹ subsequently cyclized with an oxa-Michael type process,²²⁰ which occurs exclusively at the C-ring rather than A-ring. The preceding ring cleavage is of the Baeyer–Villiger type.²²¹ In 1992 Simpson and co-workers gave a comprehensive account of the literature on these compounds

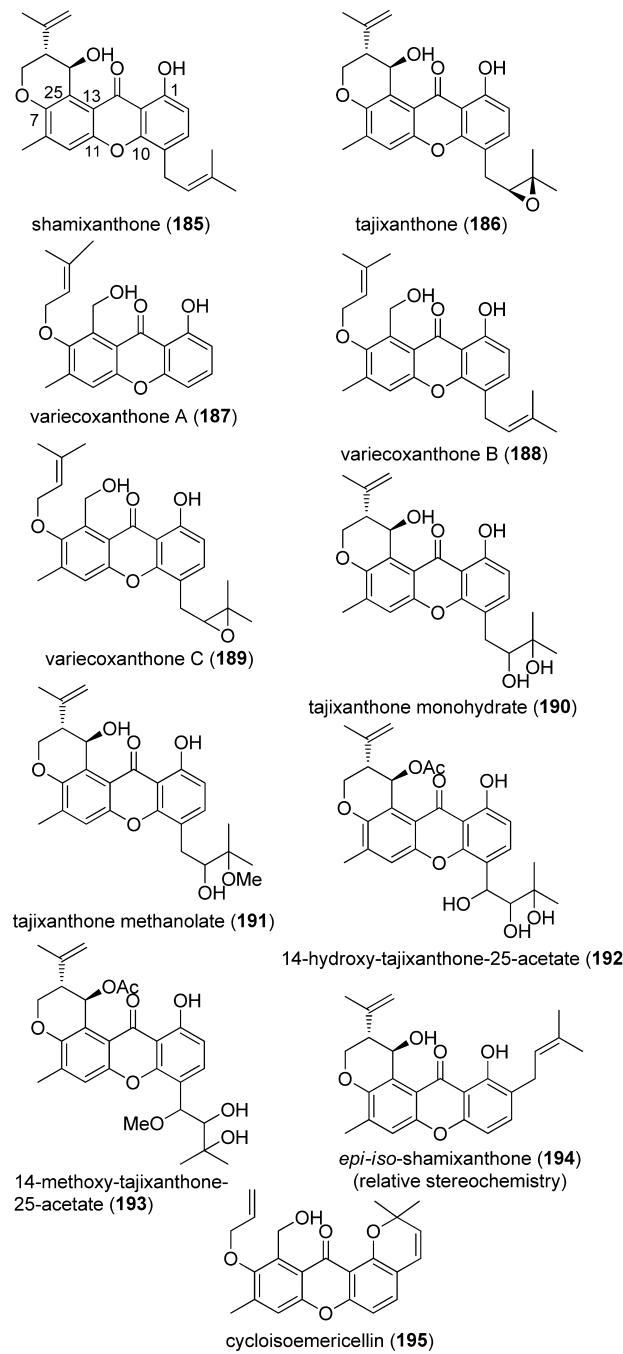
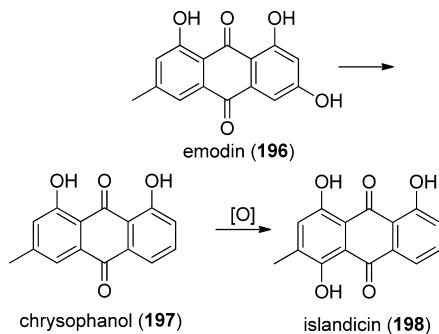


Figure 33. Tajixanthone and shamixanthone; variecoxanthones A, B, and C; and minor metabolites tajixanthone hydrate, methanolate, 14-hydroxytajixanthone-25-acetate, 14-methoxytajixanthone-25-acetate, and *epi*-*iso*-shamixanthone.²¹⁵

and proposed an overall biosynthetic pathway for the tajixanthone family.^{222,223} The authors also fed the *A. variecolor* culture broth directly with a proposed intermediate in the biosynthetic pathway, being synthetically derived methyl-²H₃- and 3-¹⁴C-chrysophanol. The tajixanthone produced was devoid of proton signals in the ¹H NMR, save those for the aromatic methyl at C24, showing that an anthraquinone is the substrate for the synthesis of the xanthone product. The overall pathway is thus proposed to include the anthraquinones emodin, then chrysophanol, then islandicin (**196–198**, Scheme 12). Holker and co-workers also synthesized shamixanthone by

the epoxidation of tajixanthone with triphenylphosphine selenide and trifluoroacetic acid.²¹³

Scheme 12. Tajixanthone Biosynthesis Passes through Three Anthraquinones²²²



Thiomelin and Derivatives. Thiomelin (199, Figure 34) was first described as a lichen pigment from *Rinodina thiomela*

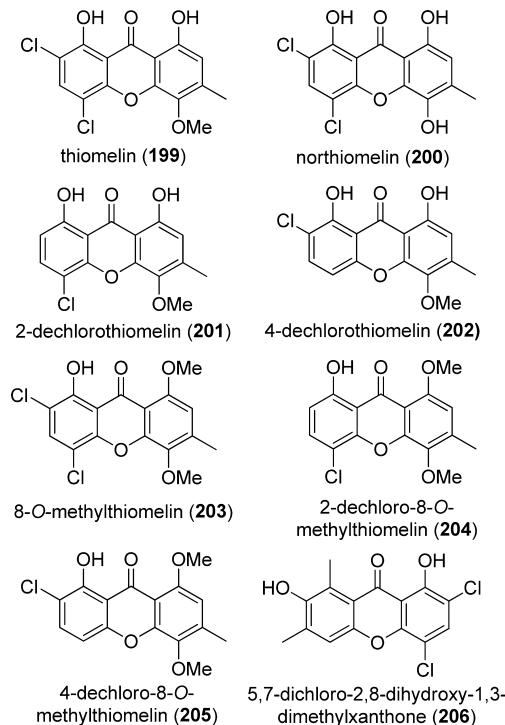


Figure 34. Thiomelin and related species.

(Nyl.) Müll. Arg. and then *R. Lepida* (Nyl.) by Leuckert and Mayrhofer in 1984.²²⁴ It is structurally related to ravenelin (139, Figure 29, with the methyl substituted in the *para*-(3/6), rather than *ortho*-(8) position to the benzophenone carbonyl). Northiomelin (200) has also been reported, from *Rinodina thiomela*.²²⁵ Elix and co-workers reported the isolation and structural elucidation of thiomelin (199, Figure 34) in 1987, following the use of X-ray crystallographic analysis of the diacetate derivative;²²⁵ Elix et al. later reported a synthesis of thiomelin.²²⁶ The structures of several co-occurring xanthone species were determined based on this structure and the comparison of spectral data.

Elix and co-workers reported the isolation and synthesis of several xanthone compounds from the lichen *Rinodinia*

thiomela: 2-dechloro-8-O-methylthiomelin (204),²²⁵ 4-dechloro-8-O-methylthiomelin (205), 4-dechlorothiomelin (202), and northiomelin (200).²²⁷ The compounds 5,7-dichloro-2,8-dihydroxy-1,3-dimethylxanthone (206) and 2-dechlorothiomelin (201, from *Rinodina thiomela*) were also synthesized, with these latter two having been isolated from nature for the first time.²²⁷

Thiophanic Acid. Thiophanic acid was isolated from *Lecanora rupicola* (L.) Zahlbr. and reported by Hesse as early as 1898.²²⁸ This xanthone was reisolated in 1937 by Kennedy and co-workers²²⁹ and in 1966 by Huneck, and characterized for the first time through a combination of NMR, UV, and other spectral methods, confirming the structure shown (207, Figure 35).²³⁰ Elix and co-workers also isolated this species

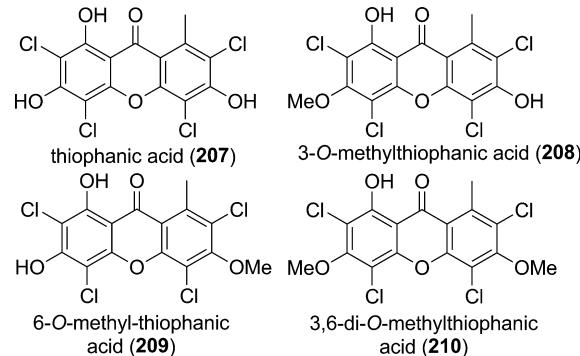


Figure 35. Thiophanic acid and derivatives.

from an Australian *Dimelaena* lichen.⁷⁶ Thiophanic acid has also been isolated from *Lecanora bolanderi*,⁶⁹ *L. flavo-pallescens*,^{69,71} *L. rupicola*,²³⁰ *L. straminea*,²³¹ *L. sulpharata*,^{68,69,71} *Lecidella meiococca*, *L. vorax*, *Micarea isabellina*,⁶⁸ *M. austroternaria*,²³¹ *Pertusaria pycnothelia*,⁶⁸ *Dimelaena cf. australiensis*,⁶⁸ 3-O-methylthiophanic acid (208, from *Lecidella meiococca*),⁶⁸ and 6-O-methylthiophanic acid (209, from *Micarea isabellina*).⁶⁸

A synthesis of this compound was reported by Neelakantan and co-workers,²³² followed shortly by Ollis and co-workers,²³³ and then another from Neelakantan.²³⁴ Recently, this compound was isolated from *Leconora iseana* (*Lecanora broccha* Räs)⁷⁰ alongside several other xanthones [norlichexanthone (77, Figure 20), 4-chlorolichexanthone (65, Figure 19), 2,4-dichlorolichexanthone (68, Figure 19), 4,5-dichloronorlichexanthone (85, Figure 20), 4,5-dichlorolichexanthone (71, Figure 19), and arthothelin (10, Figure 2)] and several dibenzofuran compounds.²³⁵

Thiophanic Acid. The isolation of thiophanic acid (211, Figure 36) alongside thiophanic acid (207, Figure 35) from *Lecanora rupicola* (L.) Zahlbr. was also reported by Hesse in 1898²³⁶ and by Huneck in 1966 from *L. rupicola* (L.) Zahlbr. *L. novnovomexicana*, *L. quearnea*, *Pertusaria hymenea*, and *P. lutescens*.²³⁰ It has also been isolated from *Pertusaria flavicans* by Santesson and Wachtmeister,²³⁷ *Hypogymnia enteromorpha*

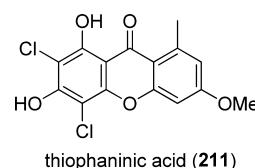


Figure 36. Thiophanic acid.

by Shibamoto and Bernhard,²³⁸ *Lecidella asema*, *L. subalpica*, and *Buellia* sp. by Elix and co-workers,¹³⁸ and also in a subgroup of *Pertusaria* species, along with other chlorinated xanthones.²³⁹ This compound was further isolated from *Buellia* sp. and *Dimelaena* sp.⁷⁵ and *P. sulphurata*.¹³⁵

Thuringione. Thuringione (**212**, Figure 37) was isolated from *Lecidea carpathica* by Santesson and Huneck,^{240,241} from

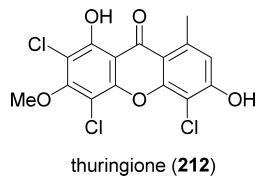


Figure 37. Thuringione.

Pertusaria sp. by Huneck and Höfle,⁷² from *L. pinguis* and *L. carpathica* by Santesson,⁶⁶ and from *Tapellaria epiphylla* (Müll. Arg.) R. Sant. by Santesson.⁷³

1,3,5,6-Tetrahydroxy-8-methylxanthone. A novel hydroxylated xanthone (**213**, Figure 38) was isolated alongside three

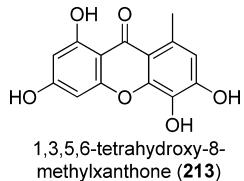


Figure 38. 1,3,5,6-Tetrahydroxy-8-methylxanthone.

new *p*-terphenyl derivatives, candidusins, from *Penicillium raistrickii* by Gloer and co-workers.²⁴² This xanthone produced inhibitory zones in a disk-assay against both *Staphylococcus aureus* and *Bacillus subtilis*.

Umbilicaxanthosides A and B and Acylated Derivatives. Two new prenylated xanthone glycosides, umbilicaxanthosides A and B (**214** and **215**, Figure 39), were described by Řezanaka

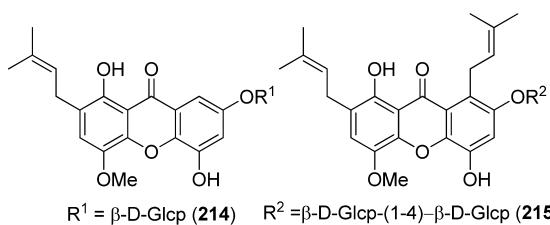


Figure 39. Umbilicaxanthosides A and B.

and co-workers in 2003 after their isolation and structural elucidation via a variety of spectral techniques, from a lichen native to the Urals *Umbilicaria proboscidea* (aka *Gyrophora proboscidea*).²⁴³ Glycosylated xanthones are relatively rarely isolated from fungi and lichens, with other examples being FD-594 (**370**, Figure 58) and hirtusneanoside A (**496**, Figure 76).

In a second publication in 2003, Řezanaka and Dembitsky reported the discovery and identification of 14 distinct acylated xanthone-O-glycosides (**216**–**229**, Figure 40) from the crude extracts of *Umbilicaria proboscidea*, the structures of which were determined with LC-UV diode ray detection, LC-APCI-MS (APCI, atmospheric pressure chemical ionization) methods, UV, MS, and NMR spectroscopy (including HMQC

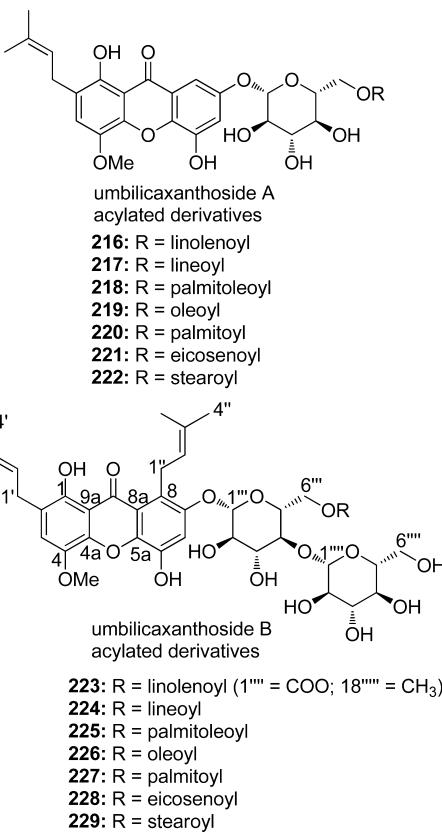


Figure 40. Acylated umbilicaxanthosides A and B.

(heteronuclear multiple quantum correlation) to determine details of the glycosidic linkages).²⁴⁴ These compounds are rather unusual, given the infrequent occurrence of acylated glycoside xanthones from fungi and lichens.

Vinetorin. Vinetorin (**230**, Figure 41) was isolated from *Lecanora vinetorum* by Poelt and Huneck²⁴⁵ and later

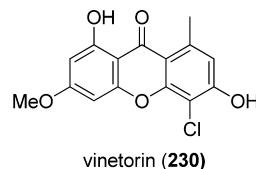


Figure 41. Vinetorin.

structurally redefined by Huneck and Höfle⁷² and Sundholm.²⁴⁶ The reassigned structure was confirmed by the unambiguous synthesis performed by Sargent and co-workers.¹⁴⁹ This compound has also been isolated from *Pertusaria* sp.⁷²

Varixanthone. Barrero and co-workers reported in 2002 the isolation of varixanthone (**210**, Figure), alongside tajixanthone hydrate (**231**, Figure 42) and several nonxanthone products, from a marine-derived strain of *Emericella variecolor* (a fungus which is the “perfect state” of *Aspergillus variecolor*).²⁴⁷ Varixanthone was structurally elucidated using a variety of spectral techniques, as well as the absolute configuration, which was determined by hydrolysis of **231** to tajixanthone (**186**, Figure 33) and measurement of the optical rotation. This compound was found to be inactive in cytotoxicity tests against several cell lines, including human lung and colon carcinoma; however, it was active against Gram-positive and -negative

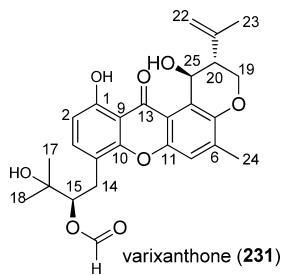


Figure 42. Varixanthone.

bacteria, including *E. coli*, *Proteus* sp., *B. subtilis*, and *S. aureus* at lower concentration than the structurally related compounds terrein, shamixanthone, and tajixanthone hydrate.²⁴⁷

Vertixanthone. In 1989 Ayer and co-workers reported the structure of two new xanthones, vertixanthone and hydroxyvertixanthone (232 and 233, Figure 43) after isolating them

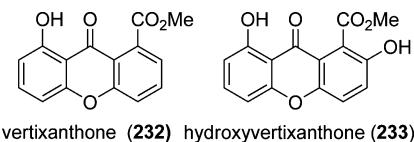
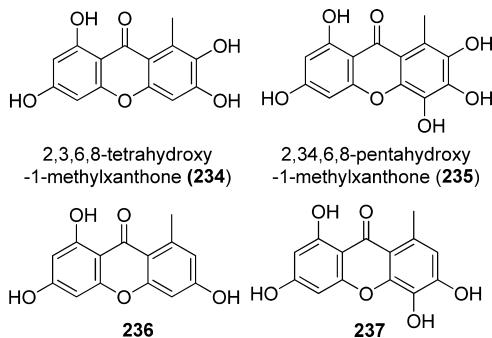


Figure 43. Vertixanthone and hydroxyvertixanthone.

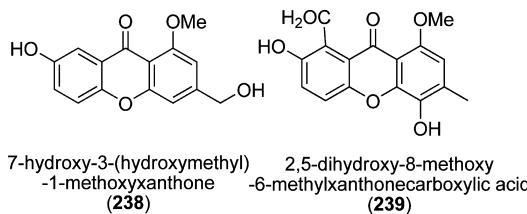
from the cultures of a fungus, *Leptographium wageneri* (aka *Verticiladiella wageneri*), causative agent of the black-root disease in Douglas pine and other conifers.²⁴⁸ These compounds were demonstrated to cause inhibition of water transport in pine seedlings.

Wardomyces Xanthones. König and co-workers isolated two new and two previously known xanthones (234–237, Figure 44) from *Wardomyces anomalous* after the crude extract of

Figure 44. Xanthones from *Wardomyces anomalous*.

this marine fungus had shown inhibition of HIV-1 reverse transcriptase and p56¹ tyrosine kinase, as well as antimicrobial activity against *Microbotryum violaceum* and *Eurotium repens*.²⁴⁹ The structure of the two new xanthones, 2,3,6,8-tetrahydroxy-1-methylxanthone (234) and 2,3,4,6,8-pentahydroxy-1-methylxanthone (235), was determined using HMBC (heteronuclear multiple-bond correlation) correlations to determine the substitution pattern.²⁴⁹ The compounds were also demonstrated to have considerable antioxidant properties.

Xylaria sp. FRR 5657 Xanthones. Two novel xanthones were isolated from cultures of the endophytic fungus, *Xylaria* FRR 5657, and identified by Davis and Pierens in 2006.²⁵⁰ They are 7-hydroxy-3-(hydroxymethyl)-1-methoxyxanthone (238, Figure 45) and 2,5-dihydroxy-8-methoxy-6-methylxanthone carboxylic acid (239).

Figure 45. Xanthones from *Xylaria* sp. FRR 5657.

thonecarboxylic acid (239). These compounds were inactive in a brine-shrimp assay and assays against a diversity of microorganisms, including *Bacillus megaterium*, *Escherichia coli*, *Microbotryum vioaceum*, and *Chlorella fusca*.

2.2. Monomers 2: Dihydroxanthones

Relatively few dihydroxanthone monomers have been identified from fungi, bacteria, and lichens; however, important compounds of this type include globosuxanthone and nidulalin A.

Globosuxanthone A. Globosuxanthone A (240, Figure 46) was reported in 2006 by Gunatilaka and co-workers.²⁵¹

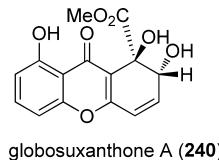


Figure 46. Globosuxanthone A.

Interestingly, it was found alongside some variably saturated xanthones: see section 2.3 for globosuxanthone B (336, Figure 47) and section 2.1 for globosuxanthones C and D (56 and 57, Figure 14). The structure of this compound was determined using NMR techniques and single-crystal X-ray diffraction studies. Globosuxanthone A was found to inhibit the proliferation and survival of tumor cells even after the drug had been washed out. In an in vivo model the application to Lewis lung tumor cell inoculated mice of a single intraperitoneal dosage (20 mg/kg) resulted in a mean 50% reduction in tumor volume after three weeks, as compared to DMSO-treated mice.²⁵¹

Krohn and co-workers determined the absolute configuration of this compound, which they isolated alongside other xanthones (vertixanthone and 2-hydroxyvertixanthone; see section 2.1), from *Microdiplodia* sp.²⁵² Using a novel method, the quantum-mechanical calculation of the theoretical CD spectrum with Cartesian-coordinate data from the X-ray structure allowed the configuration to be calculated and then compared with experimentally acquired data, giving an excellent match.¹²³ Such an approach should in theory be extendable to the determination of absolute configuration for other examples where both the solid-state structure and CD spectrum in the solid state (determined, for example, with a KCl disk) are known.

Nidulalin A. The dihydroxanthone nidulalin A (220, Figure 47) was reported by Kawai and co-workers in 1994 after being isolated from *Emericella nidulans*.²⁵³ In 1997 Tsuji and co-workers reported the reisolation of nidulalin A and the related derivatives F390B and F390C (241 and 242) from *Penicillium* sp.²⁵⁴ These compounds were shown to have potent antitumor (colon 26 murine adenocarcinoma) activities as a result of their

effects on DNA topoisomerase II,²⁵⁵ which are responsible for regulating the DNA topology and by this regulating the key aspects of replication, translation, and transcription.

In 1998 Fujimoto and co-workers reported the isolation (alongside the known xanthones emodin and 1,7-dihydroxy-3-methylxanthone) of a novel nidulalin derivative, 1,9a-dihydro derivative of nidulalin A (243, Figure 47) from the ascomycete

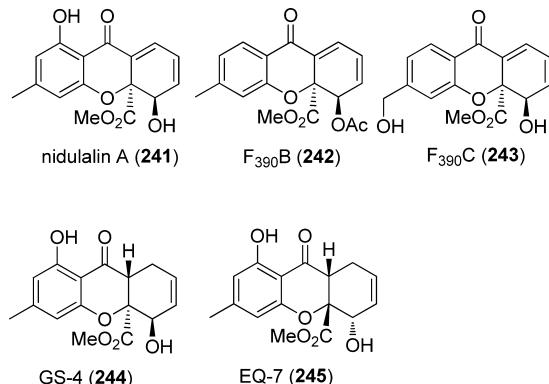


Figure 47. Nidulalin and related xanthones.

Anixiella micropertusa.²⁵⁶ The authors also reported the isolation of this same compound in 2006, denoting it as GS-4 (244, Figure 47), this time alongside nidulalin A (241) from the ascomycete *Gelasinospora santi-florii*, and a related novel compound from *Emericella quadrilineata*, (4S,4aR,9aR)-4a-carbomethoxy-1,4,4a,9a-tetrahydro-4,8-dihydro-6-methylxanthone (245), which they denoted EQ-7.²⁵⁷ The configurations of GS-4 and EQ-7 were determined based on the modified Mosher method upon the (R)- and (S)-(trifluoromethyl)-phenylacetate ester derivatives at the cyclohexyl alcohol moiety of EQ-7 (and inferred for GS-4).

In 1999 Tsuji and co-workers investigated the synthesis of esterase-stable amide analogues of the methyl ester of nidulalin A, starting from the natural product itself. These compounds were stable to hydrolysis in the present of endogenous murine plasma esterases and showed variable toxicity as well as increases or decreases in activity against Topo I and II as compared to nidulalin A.²⁵⁵

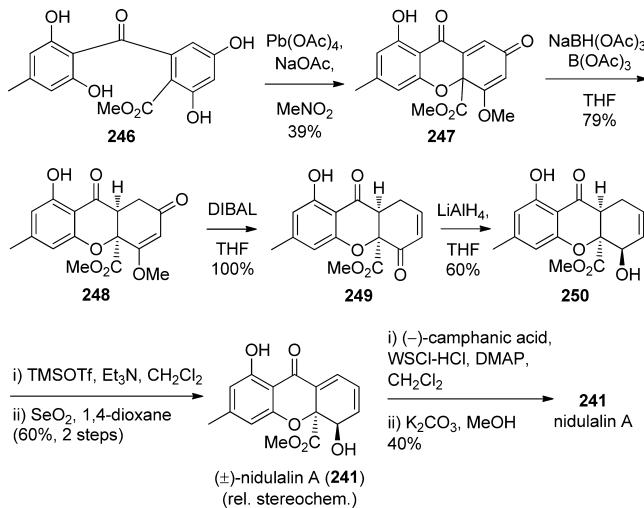
In 2009 Hosokawa and co-workers reported the synthesis of nidulalin A (and *ent*-nidulalin A, not shown) from the benzophenone 246, (Scheme 13), which was cyclized under oxidative conditions to xanthone 247.²⁵⁸ This was followed by a sequence of three reductions that delivered cyclohexanol 250, which was then converted to racemic nidulalin A in two steps. Conversion to the camphanic esters diastereomers, then separation and hydrolysis of these, gave nidulalin A and its unnatural enantiomer. This synthesis confirmed the absolute stereochemistry previously proposed using spectroscopic methods.

2.3. Monomers 3: Tetrahydroxanthones

Tetrahydroxanthones from fungi, bacteria, and lichens include the blennolides, dihydroglobosuxanthone, diversonol and the diversonolic esters, and globosuxanthone B.²⁵⁹ Tetrahydroxanthones are the monomeric components of interesting mycotoxins such as the beticolins and the secalonic acids (see section 3.3).

Blennolides. In 2008 the long-anticipated but never-before-detected monomeric components of the secalonic acids

Scheme 13. Synthesis of Nidulalin



(blennolides, or hemisecalonic acids, 251–256, Figure 48) were isolated from an endophytic *Blennoria* sp., alongside

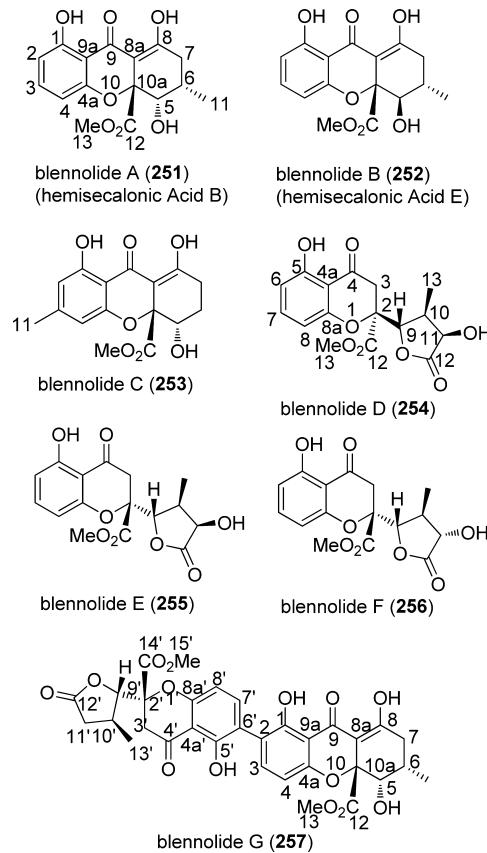


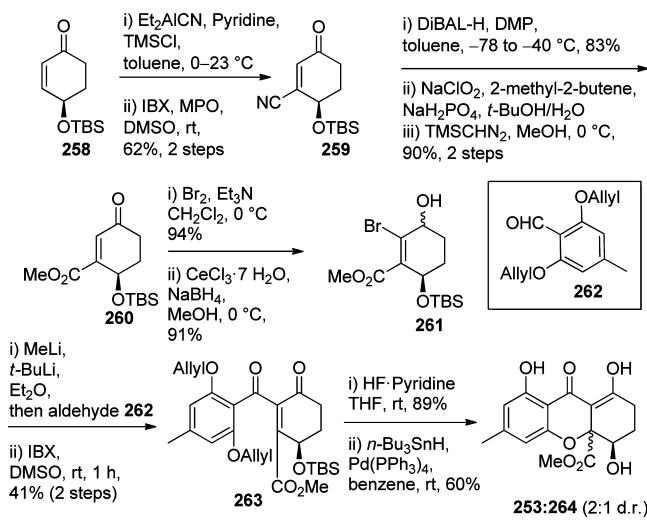
Figure 48. Blennolides A–G.

secalonic acid B (449, Figure 74) and several other biosynthetically related isolates, and named blennolides A–G (251–257).²⁶⁰ The structure of blennolide A, the monomeric unit of secalonic acid B, was further confirmed using single-crystal X-ray analysis; blennolide B is the monomeric unit of secalonic acid D. The configurations of all these compounds were ascertained using CD spectra to determine the absolute stereochemistry of the C10a positions as R and then the

other stereocenters on the basis of relative stereochemistry (except blennolide D, which is C10aS-configured). Dihydrobenzopyranones 256 to 257 seem to be derived from 251 and 252 by rearrangement of the tetrahydroxanthone ring to a γ -lactone in a similar manner to that reported for the heterodimer xanthoquinodin A₃ (582, Figure 90); in the case of 254, an inversion of the C10a stereocenter appears to have taken place during this process. Dimer 257 is composed of a blennolide A and 11-deoxyblennolide F monomers and is, like ergoxanthin, a member of the ergochrome family rearranged to incorporate a γ -lactone. Interestingly, a compound had already been assigned the structure now ascribed to blennolide C (253) (see entry for β -diversonolic ester).²⁶¹

In 2008 Nicolaou and Li reported the synthesis of blennolide C (253, Scheme 14), alongside the synthesis of diversonol and

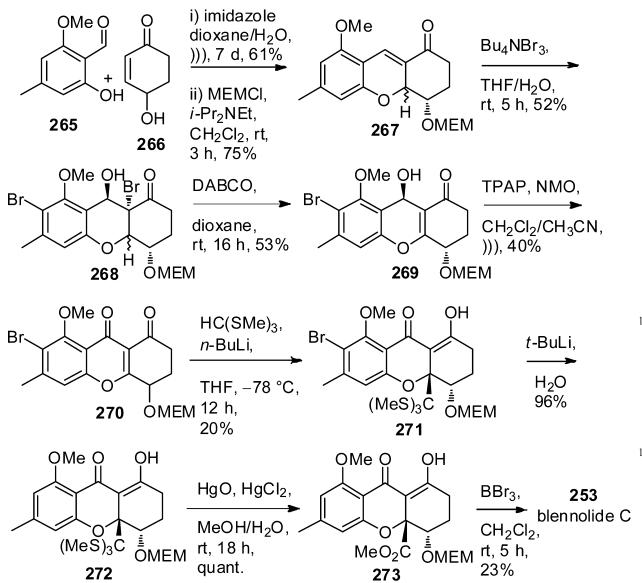
Scheme 14. Nicolaou and Li's Synthesis of Blennolide C



the diversonolic esters through a commonly applicable methodology.²⁶² The synthetic sequence involved manipulation of a silyl-protected 4-hydroxycyclohex-2-enone (258) through several steps to the 2-bromo-3-carboxymethyl ester 261 and then reaction of this species with the aldehyde 262 to form intermediate benzophenone 263. This species was first desilylated, then deallylated; the second deprotection was followed by an in situ cyclization of the phenolic intermediate to give blennolide C (253) and the diastereomer 264 in approximately 2:1 diastereomeric ratio after 11 steps from cyclohexenone 258.²⁶²

Also in 2008, Gérard and Bräse reported the synthesis of blennolide C and some analogues,²⁶³ confirming the suggestion made by Krohn that this compound had the structure formerly assigned to β -diversonolic ester. In common with the group's synthesis of diversonol (Scheme 13), the ABC-ring tricyclic xanthone was constructed in a single step via an efficient domino oxa-Michael-aldo reaction^{158–64,264} from a substituted salicylic aldehyde 237 (Scheme 15) and 4-hydroxycyclohexenone (266), the latter of which can be accessed enantioselectively and efficiently constructed using a synthesis developed within the group.²⁶⁵ Use of the weak base imidazole delivered the tricycle in 61% yield as a 1.5:1 ratio of diastereomers. Hydroxyl protection and bromohydration gave the bromide 268, elimination of HBr from which enabled the completion of the tetrahydroxanthone core.

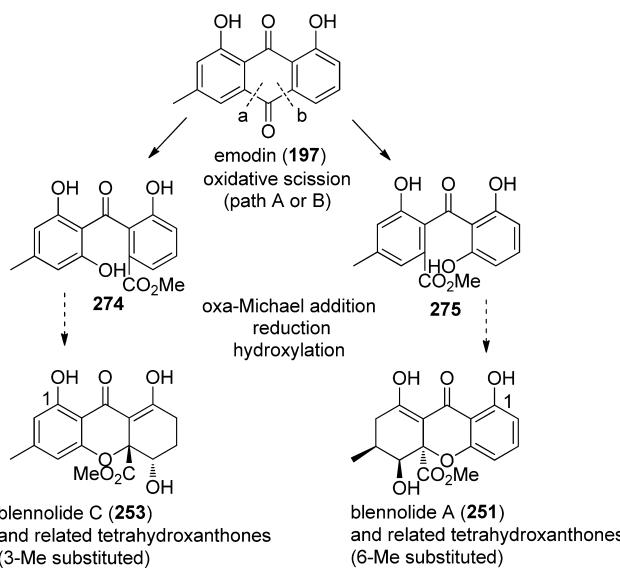
Scheme 15. Gérard and Bräse's Synthesis of Blennolide C



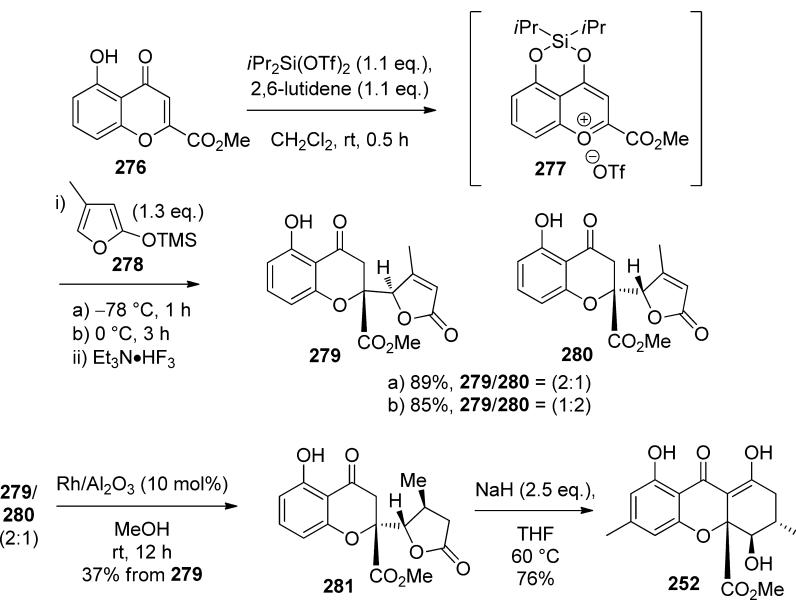
Michael addition to this enone was performed using the Gabbut method,²⁶⁶ whereby lithiated trimethylorthomethanethioate is added *trans* to the OMEM group. The following steps included debromination, conversion to the methyl ester, and demethylation to provide blennolide C in nine steps from 4-hydroxycyclohex-2-one (266). The authors point out that this monomeric unit is found in the dimeric compounds eumitriol A1, neosartorin, xanthonol, xanthoquinodins, and beticolins (see section 3.3).²⁶³

In their investigations of the blennolides, König and co-workers had described that pathway divergence in the formation of xanthones (Scheme 16), which can even occur via both pathways at once within the same fungus, is a result of the asymmetric nature of cleavage of the anthraquinone precursor¹⁹ to yield benzophenone intermediates 274 or 275. As a result in this case, the methyl group can ultimately reside on either the reduced ring, or the nonreduced ring, allowing the

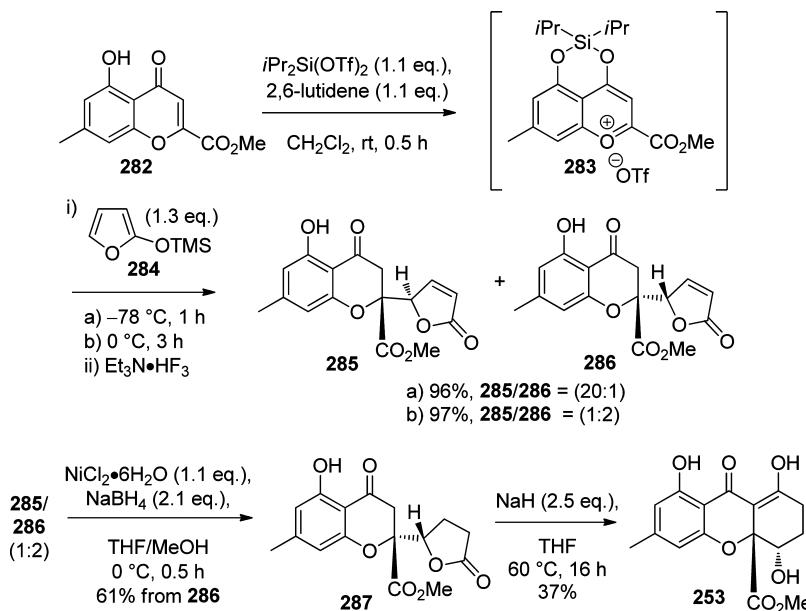
Scheme 16. Biosynthetic Diversity in the Tetrahydroxanthones²⁶⁷



Scheme 17. Porco's Synthesis of Blennolide B



Scheme 18. Porco's Synthesis of Blennolide C



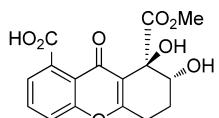
fungus to create a more diverse array of biochemical agents. Interestingly, Krohn and co-workers have observed that both pathways can operate within a single xanthone-producing organism, for example, to give rise to blennolide A and C (253 and 251, Scheme 16).¹⁹ The resulting xanthone structures are isomeric; one is methylated on the aryl position and the other is methylated on the tetrahydroxanthone ring. In the former case (hetero-)dimers can be made through oxidative coupling at the benzylic position (beticolins and xanthoquinodins; see section 3.3).

Recently, Porco and co-workers described a novel retro-biomimetic synthetic strategy to access the tetrahydroxanthone core, utilizing the vinylogous addition of siloxyfurans to benzopyryliums, reduction of the lactenone products, and intramolecular Dieckmann cyclization as the key steps.²⁶⁸ They utilized this strategy to diastereoselectively synthesize racemic blennolides B and C (Schemes 17 and 18, respectively). An

expedient synthesis of blennolide B was achieved by first conversion of chromene 276 to the benzopyrylium salt intermediate, which was reacted with 4-methyl-2-trimethylsiloxy furan (278, Scheme 17) prior to deprotection; variation in temperature of the addition step gave differing diastereoselectivities, likely due to epimerization of the initial product at higher temperatures. Lactenone 279 was reduced with rhodium on aluminum oxide in methanol to give lactone 281; the Dieckmann condensation then provided blennolide B (252).

In the synthesis of blennolide C (253, Scheme 18), the sequence commenced from methyl-substituted chromenone 282 with 2-trimethylsiloxy furan (284), followed by deprotection to the chromones 285 and 286; this time the contrast in selectivities at different temperatures was even stronger. The lactenone was reduced with nickel chloride hexahydrate and sodium borohydride to lactone 287; Dieckmann condensation followed again to deliver blennolide C (253).

Dihydroglobosuxanthone. Krohn and co-workers reported in 2009 the isolation of 3,4-dihydroglobosuxanthone A (288, Figure 49)¹⁹ as a result of their reinvestigation of

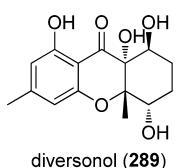


3,4-dihydroglobosuxanthone (288)

Figure 49. 3,4-Dihydroglobosuxanthone A.

Microdiplodia sp. As with the diversonolic esters (A and B, 329 and 330, Figure 51), this species has the methyl ester located at the C1 position, rather than the usual C4a position, as with the remaining monomeric and dimeric members of the tetrahydroxanthone family. This compound was demonstrated to have strong antibacterial activity against *Escherichia coli*, *Bacillus megaterium*, and *Chlorella fusca*.

Diversonol. In 1978 Turner reported the isolation of several fungal metabolites, including a compound from the phenolic fraction of cultured *Penicillium diversum* that he subsequently named diversonol (289, Figure 50).²⁶⁹ It was not



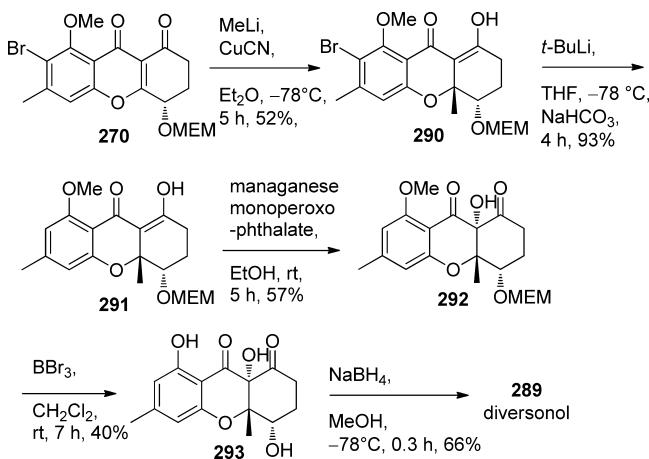
diversonol (289)

Figure 50. Diversonol.

made clear in the initial publication if diversonol was a racemate or, if not, what was the absolute configuration. A reference was made in this initial publication to X-ray crystallographic data that was to be reported later, but it evidently did not come to light.

This compound was selected as a target by the Bräse group in their ongoing studies on the synthesis of the secalonic acids and related natural products,^{1,58–64} and the successful racemic synthesis was reported in 2006.²⁷⁰ The synthesis began with the synthetic intermediate 270 (Scheme 19), in common with the group's synthesis of blennolide C (see Scheme 11). Enone substrate 270 was doubly activated for diastereoselective

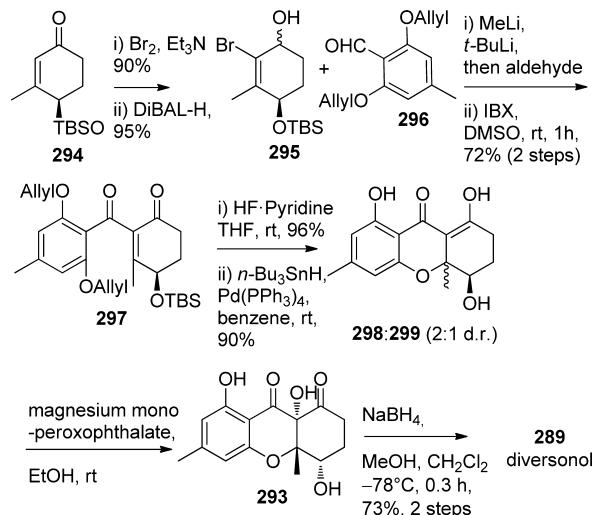
Scheme 19. Bräse's Synthesis of Diversonol



Michael addition of methylcyano cuprate to afford 290. Debromination and diastereoselective oxidation with manganese monoperoxo-phthalate gave alcohol 292, which was deprotected and finally reduced to give the polyhydroxylated core and thus racemic diversonol (289, Figure 50) in 10 steps from 4-hydroxycyclohexen-2-one 266.

In 2008 Nicolaou and Li reported their synthesis of diversonol (Scheme 20).²⁶² The synthesis involved the

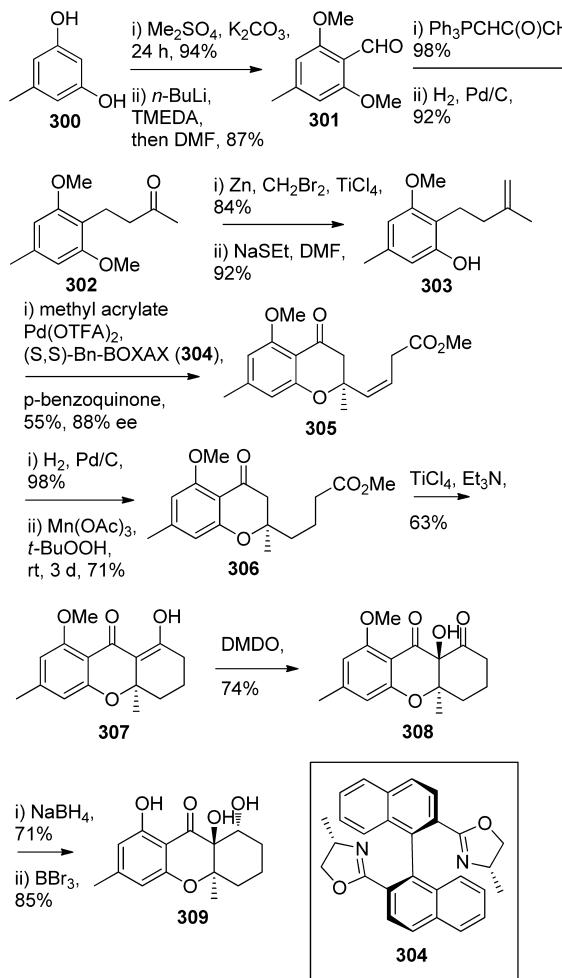
Scheme 20. Nicolaou's Synthesis of Diversonol



nucleophilic addition of a lithiated cyclohexene species derived from bromide 295 with allyl-protected aldehyde 296, followed by oxidation, desilylation, deallylation, and spontaneous xanthone ring-closure of the intermediate phenol (not shown). As in the Bräse synthesis, the enol moiety is oxidized and the C-ring ketone is reduced with NaBH₄ to generate diversonol in eight steps from cyclohexenone 294.

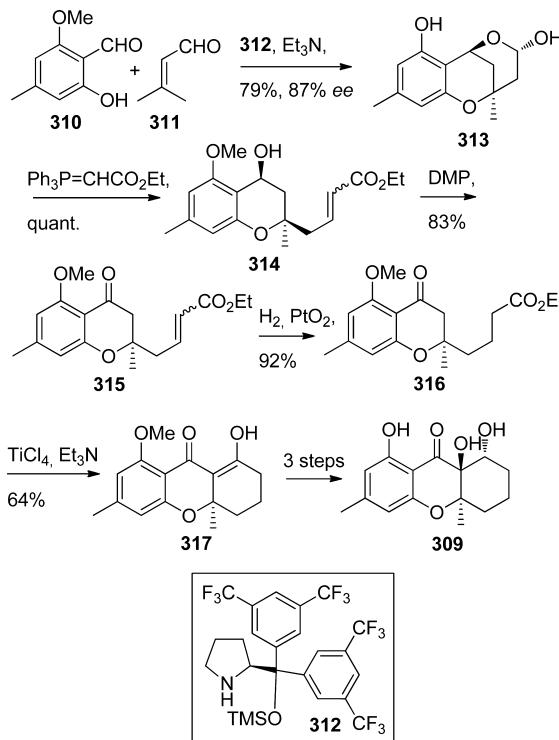
In 2008 Tietze and co-workers reported on their stereoselective synthesis of 4-dehydroxydiversonol utilizing pathways involving both Pd-catalyzed domino-Wacker–Heck and domino-Wacker–carbonylation reactions.²⁷¹ The shortest and highest yielding sequence was as follows: dimethylation and *ortho*-lithiation-directed formylation of orcinol (300, Scheme 21), followed by Wittig olefination, Lombardo methylation, and monomethyl cleavage with sodium ethanethiolate to give the domino-Wacker–Heck substrate 303. This was reacted with methyl acrylate in the presence of Pd ditriflate and (*S,S*)-Bn-BOXAX ligand (304) alongside *p*-benzoquinone (as a catalyst reoxidant), giving chromane 305 in 55% yield and 88% enantiomeric excess (ee). The same compound was synthesized by a complementary three-step sequence involving an enantioselective domino-Wacker–carbonylation process, which gave chromane 305 in 96% ee (not shown). This species was reduced and oxidized to a chromanone before intramolecular acylation with TiCl₄ and Et₃N (the use of strong bases led to poor conversions) to give the xanthone tricycle 307. This species was *trans*-selectively oxidized with DMDO (dimethyl-dioxirane), reduced at the C-ring ketone, and demethylated to give (*S*)-(–)-4-dehydroxydiversonol (309), the relative confirmation of which was confirmed by single-crystal X-ray crystallography.²⁷¹

Volz, Bröhmer, Nieger, and Bräse also reported a synthesis of 4-dehydroxydiversonol (309) the following year.²⁷² The reaction sequence involved an enantioselective domino-oxa-

Scheme 21. Tietze's Synthesis of 4-Dehydroxydiversonol

Michael–aldol reaction mediated by the organocatalyst **312** (Scheme 22), followed by a Wittig ring-opening reaction to ester **275**, which was reduced to give ester **316**, treatment of which with a similar sequence to the Tietze synthesis delivered 4-dehydroxydiversonol (**309**).

Bröhmer, Bourcet, Nieger, and Bräse reported another synthesis of diversonol in 2011; this time the synthesis was enantioselective (Scheme 23) and allowed the synthetic confirmation of absolute configuration of diversonol,²⁷³ which had previously been inferred by Krohn and co-workers. The synthetic strategy had been executed contemporaneously to that of Porco and co-workers, also using a “retro-biomimetic” approach, whereby the putative products of further secondary metabolism of xanthones, chromone lactones (e.g., blennolides D–F, 251–257, Figure 48), were synthetically converted via Dieckmann cyclization to form the xanthone nucleus. A domino reaction between salicylaldehyde **310** and 3-methylcrotonaldehyde (**311**) catalyzed by Jørgensen’s catalyst gave enantioselective access to tricyclic lactol **273** in 67% yield and 83% ee. Dehydration and 1,2-cis-dihydroxylation of **318** gave the two diastereomeric diols **319** and **320**; the former (major) of the tricyclic lactol was used in the synthesis of *ent*-lachnone C. Conversion of minor diol **320** through the aldehyde tautomer (not shown) with a Wittig reaction gave α,β -unsaturated ester **321**, which was hydrogenated and with two consecutive acid-catalyzed and one reductive step converted to

Scheme 22. Volz, Bröhmer, Nieger, and Bräse's Synthesis of 4-Dehydroxydiversonol

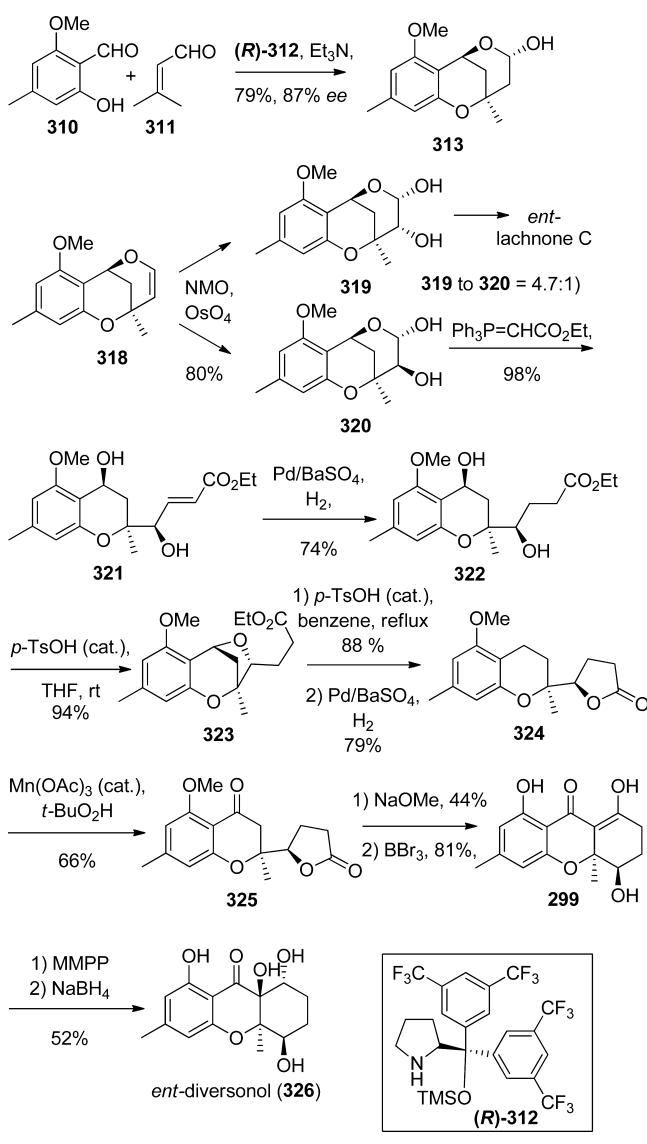
chroman lactone **324**. Oxidation to chromone **325** and Dieckmann cyclization gave the xanthone framework.

The final steps involved demethylation with boron tribromide and then a sequence of oxidation and reduction steps taken directly from the Nicolaou racemic synthesis,²⁶² delivering the unnatural isomer of diversonol, with a perfectly complementary circular dichroism (CD) spectrum to that supplied by Krohn and workers for the natural product.²⁷⁴ Hence, natural diversonol is the enantiomer of the product **326** shown in Scheme 23, namely, that of *SS,5aS,8S,8aR* in configuration. Further in this study, the chromone lactones lachnone C and *epi*-lachnone C (not shown) were also synthesized enantioselectively for the first time, utilizing common synthetic intermediates.

Diversonolic Esters. In 1983 Holker, O’Brien, and Simpson reported the diversonolic esters (**329**, **330**, Figure S1, originally proposed structures shown as **327** and **328**), which they had also isolated from *Penicillium diversum*, alongside lichexanthone (**63**, Figure 18) and several other known compounds.²⁶¹ The authors originally undertook analysis based upon methylation, proton NMR analysis, ferric chelate effects, and other spectroscopic techniques, which led these scientists to attribute the structures as **327** and **328**, which appear reminiscent of hemisecalonic acids (ergochrome monomers) but are in fact incorrect.

Twenty-five years later, the synthesis of the diversonolic esters was reported by Nicolaou and Li (Scheme 24), along with the synthesis of blennolide C and diversonol (see entries above).²⁶² In a twist of good fortune, the use of MOM-protecting (MOM, methoxymethyl) groups as an alternative to allyl groups (see diversonol synthesis) and oxidative conditions resulted in the synthesis of compounds **329** and **330** through nucleophilic attack of the phenolic group either on the enone in an oxa-Michael addition or on the ketone, followed by loss and

Scheme 23. Volz, Bröhmer, and Bräse's Synthesis of 4-Dehydroxydiversonol



then readdition of water. As a result of their synthesis of these two compounds, which had identical spectroscopic characteristics to those originally reported for the diversonolic esters, the

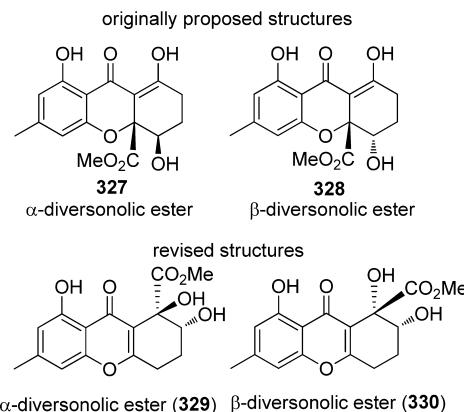
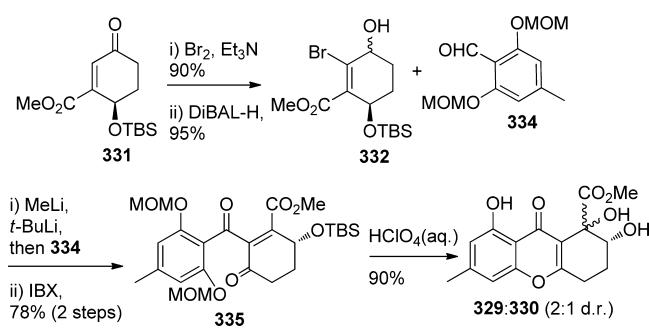


Figure 51. Diversonolic esters.

Scheme 24. Nicolaou's Synthesis of α - and β -Diversonol Esters



structures of 327 and 328 were revised to 329 and 330, respectively (see Figure 51).²⁶²

Globosuxanthone B. Globosuxanthone B (336, Figure 52) is a tetrahydroxanthone that was isolated from the *Chaetomium*

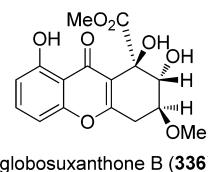


Figure 52. Globosuxanthone B.

globosum Ames, alongside a related dihydroxanthone (globosuxanthone A, 240, Figure 46) and two xanthones (globosuxanthone C and D, 56 and 57, Figure 14).¹¹⁸ The configuration at C1–3 was determined by ¹H NMR and the configuration of globosuxanthone A, which was determined with single-crystal X-ray diffraction.

2.4. Monomers 4: Hexahydroxanthones

Hexahydroxanthone derivatives have been identified in nature from fungal, bacterial, or lichenoid sources. These include applanatins, isocochlioquinones, and monodictyins.

Applanatins. Wang, Dong, and Liu reported the structure of two new hexahydroxanthones, applanatins A and B, and one known hexahydroxanthone, ganoderma aldehyde (337, 338, and 339, respectively, Figure 53) after isolating these species alongside ganodermic acids A, B, D, and G, from *Ganoderma applanatum*. This fungus has long been used as a traditional medicine in China, Japan, and Korea. The structures of 337 and 338 were determined spectroscopically, and the structure of ganoderma aldehyde (339) was revised based on NMR data.²⁷⁵

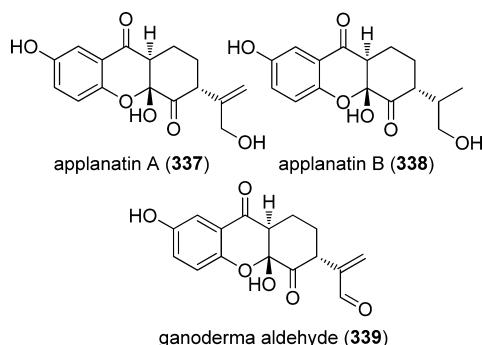


Figure 53. Applanatin A and B and ganoderma aldehyde.

Isocochlioquinones. Isocochlioquinones, xanthone isomers of the food-crop associated mycotoxins, cochlioquinones,²⁷⁶ are of mixed biosynthetic origin, with the addition of a farnesyl-unit and methionine-derived methyl groups.²⁷⁷ Isocochlioquinones A and C (340 and 341, Figure S4) were

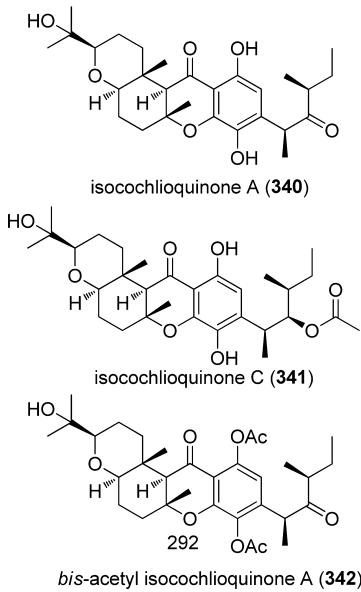


Figure 54. Isocochlioquinones A and C and bisacetyl isocochlioquinone A.

isolated from *Bipolaris cynodontis* cynA²⁷⁸ and the culture broth of *Bipolaris bicolor* EI-1,²⁷⁹ as well as from *Bipolaris oryzae*.²⁷⁶ These compounds were also isolated from a fungus *Drechslera dematioidea*, which inhabits the marine red alga *Liagora viscida*.²⁷⁷ Isocochlioquinone A and its bisacetyl derivative (240 and 342, respectively, Figure 54) were both isolated from *Drechslera dematioidea* after a study into the fungi associated with nest-building bees. In this environment, the antifungal properties of these compounds may have a protective function for the bee colony.²⁸⁰

Both isocochlioquinones A and C inhibit the growth of *Plasmodium falciparum* (IC_{50} 's < 5 μ g/mL). Cochlioquinones have antiangiogenic and chemokine-receptor (CCRS) antagonist properties, and isocochlioquinone A and bisacetyl isocochlioquinone A (290 and 292) were found to have cytotoxicity against HeLa and KB cells in the low micromolar and midmicromolar ranges, respectively.

Monodictysins. The hexahydroxanthone-derived monodictysins A–C (343–345, Figure 55) were isolated alongside monodictyxanthone (346) from *Monodictys putrenidis*, a fungus that lives in the inner tissue of green algae, and reported in 2007 by König and co-workers.²⁶⁷ Monodictysin B (344) was also reported as being isolated from the *Leptosphaeria* sp. fungus in 2010.²⁸¹ Unlike the majority of dimeric xanthones (for example, the secalonic acids and their monomeric units, the blennolides), which have carboxymethyl substituents at C10a, the monodictysins have methyl substituents at the C5a position. Additionally, monodictysin A instead has a methyl group at C3 rather than C6, as found in monodictysins B and C, indicating an alternative oxidative cleavage in their biosynthesis. The relative configuration of monodictysin A was determined by X-ray crystal structure analysis and with NOE experiments for B and C. A comparison of the CD

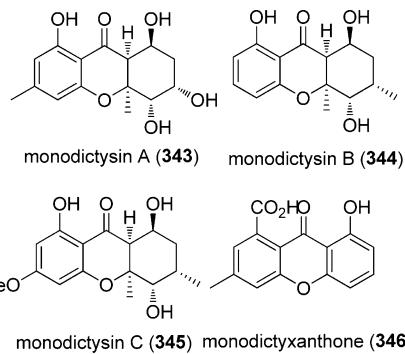


Figure 55. Monodictysins A–C.

spectra was made with time-dependent density functional theory (TDDFT) calculations.

In terms of bioactivity, monodictysin B was shown to inhibit cytochrome P₄₅₀ 1A with an IC_{50} value of 3.0 μ M. Both B and C were shown to effect the induction of NAD(P)H:quinone reductase (QR) in Hepa cells. The modulation of enzymes such as these is important in metabolism, and thereby excretion, of carcinogens and is frequently investigated for chemopreventive agents.²⁶⁷

3. DIMERS AND HETERODIMERS

3.1. Dimers and Heterodimers 1: Xanthones

Xanthone dimers and heterodimers possess increasingly complex and interesting structures and in many cases have very specific and selective biological properties. They include the acremoxanthones, cervinomycins, FD594, IB-00208, lysolipins, vinaxanthones, xanthofulvin, and xantholipin.

Acremoxanthones. Acremoxanthones A and B (347 and 348, Figure 56) were reported by the Isaka group in 2009 after

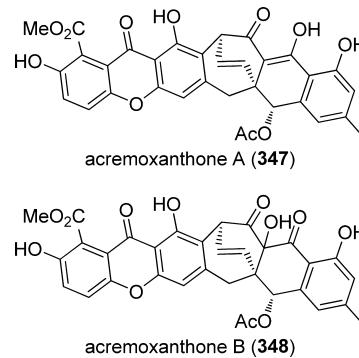


Figure 56. Acremoxanthones.²⁸²

being isolated alongside biosynthetically related products from an airborne fungus.²⁸² The authors suggest that these compounds are formed by a xanthone (elminthosporine) to anthraquinone (pinselin) coupling, resulting in a xanthroquinodine species of the type represented by beticolins, xanthoquinodins, and chrysophanol (see later). Mass spectral data and ¹³C NMR data indicated a nonsymmetrical structure of the formula C₃₃H₂₄O₁₁. The further analysis of the structure with 2D NMR experiments such as COSY, HMBC, and NOESY data further indicated that the C11' and H10 have a *syn*-facial relationship. The relative configurations of 347 and 348 were also determined using this NOESY data; 9a-OH and H-10 occupy pseudoaxial positions.

It was found that both of the acremoxanthones are in possession of antibacterial activity (against *Staphylococcus aureus* and *Bacillus cereus*), antifungal activity (acremoxanthone A showed activity against *Candida albicans*), and antiplasmodial activity (acremoxanthone B showed activity against *Plasmodium falciparum*), as well as activity against four cancer lines (KB, BC, NCI-H187, and Vero cell lines with IC₅₀ values from 0.87 to 14 µg/mL).²⁸²

Cervinomycins. Cervinomycins A₁ and A₂ were isolated from *Streptomyces cervinus* sp. nov. by Ōmura and co-workers in 1982²⁸³ and determined to be potent antibiotics, particularly against aerobic bacteria.²⁸⁴ In 1986 they reported the structure of these (see Figure 57) after determination with numerous spectral techniques.²⁸⁵

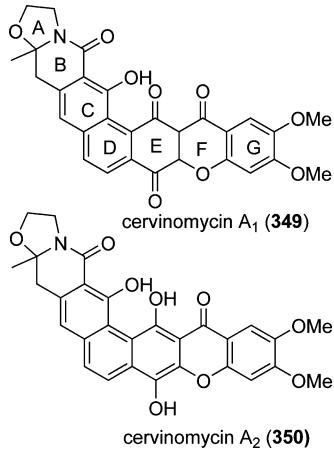
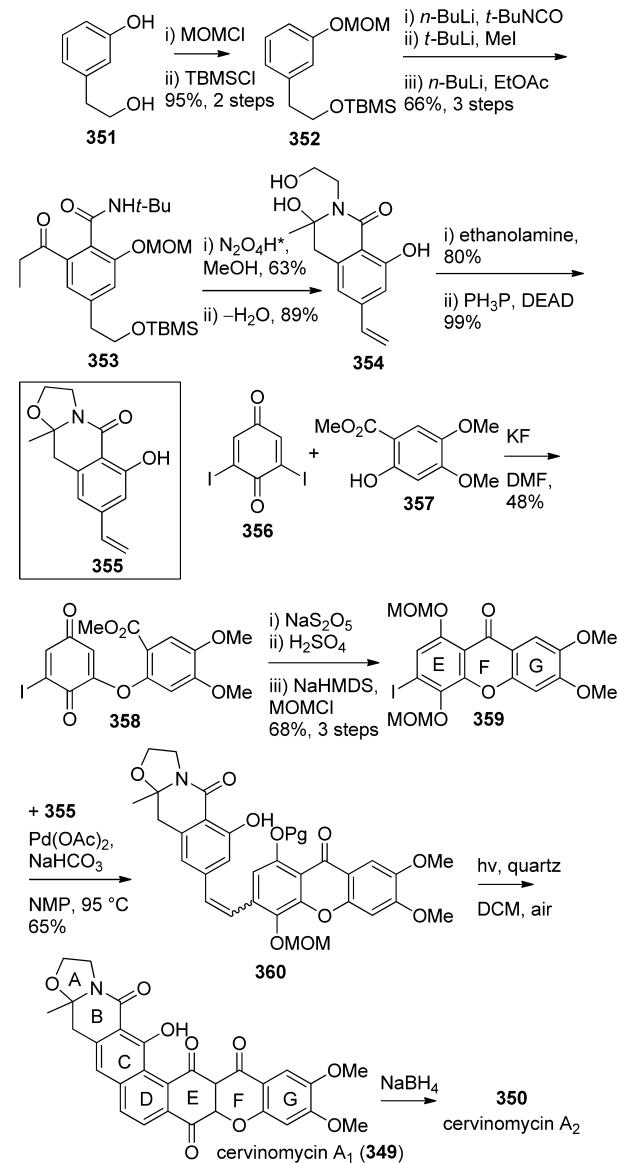


Figure 57. Cervinomycins A₁ and A₂.

In 1989 Kelly and co-workers reported a synthesis of cervinomycins A₁ and A₂ (349 and 350, Figure 57).²⁸⁶ The construction of the ABC-ring component began with three successive selective lithiation reactions from protected phenol 352 (Scheme 25) and reaction with electrophiles to give amide 353, which was cyclized and dehydrated to isoquinoline 354. Reaction with ethanalamine gave tricyclic alkene 355. The EFG-ring component was constructed with an addition–elimination of phenol 357 onto iodide 356, followed by reduction of the quinone and acid-promoted cyclization of the resulting diaryl ether to give the xanthone core 359, which was MOM-protected prior to Heck-coupling with the ABC-ring. Finally, the mixture of E- and Z-alkenes was irradiated with a mercury lamp in DCM under air, conditions which simultaneously deprotected the MOM groups and brought about cyclization to give racemic cervinomycin A₁ (349), which could in turn be reduced with NaBH₄ to cervinomycin A₂ (350).

In 1988 Mehta and co-workers published a synthesis of cervinomycins A₁ and A₂,²⁸⁷ and in 1994 they published a follow-up to their studies on the subject,²⁸⁸ related to their 1991 publication on the synthesis of cervinomycin A₁-trimethyl ether and cervinomycin A₂-methyl ether.²⁸⁹ The synthesis began with construction of the EFG-ring xanthone moiety 363 (Scheme 26) through a series of steps involving Friedel–Crafts acylation and base-mediated cyclization of the resulting benzophenone to construct the xanthone core. This was brominated and then converted to a Wittig salt for reaction with the C-ring component aldehyde 365, which was accessed from an aryl methyl species in one step, utilizing an

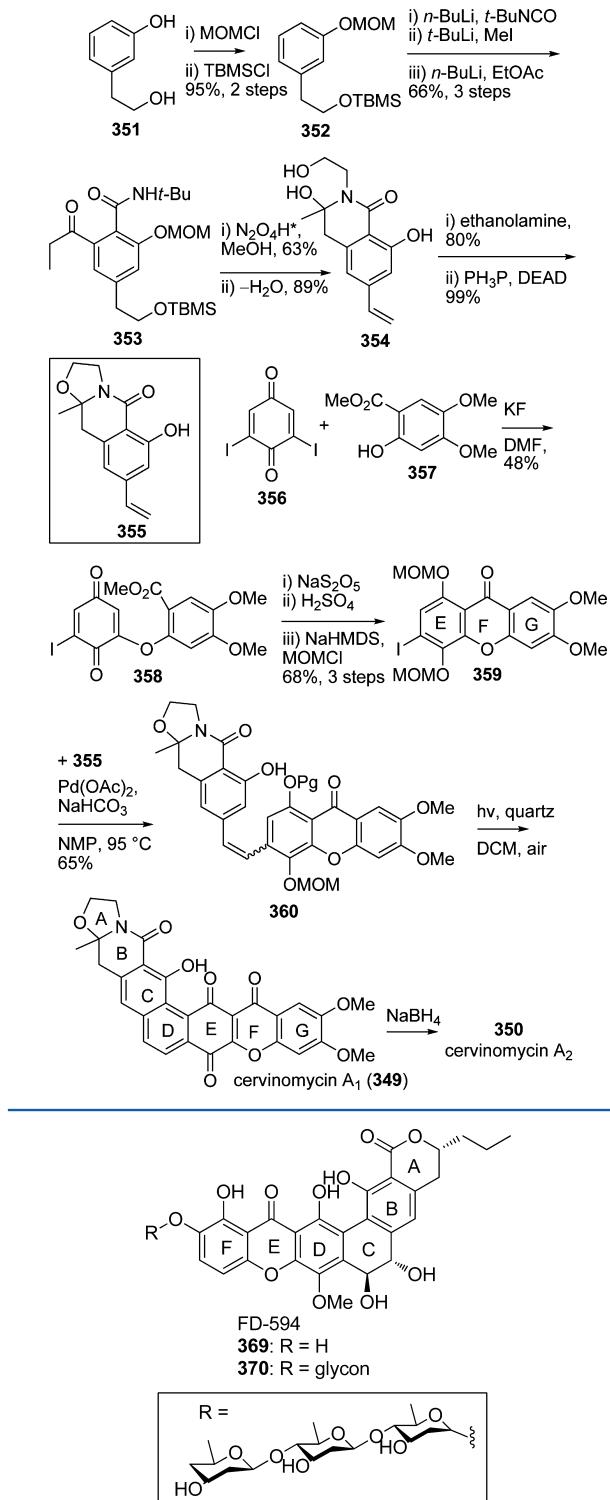
Scheme 25. Kelly's Synthesis of Cervinomycins A₁ and A₂



intermediate benzyl bromide species. The key coupling step again involved a photochemical electrocyclization to build the D-ring, this time after a crown-ether (PTC)-mediated Wittig reaction was used to couple the C- and EFG-ring components. The AB-ring system was then installed in a single reaction with 2-aminoethanol, and the resulting mixture of double-bond isomers was cyclized with a mercury lamp in the presence of iodine as oxidant. Deprotection and literature steps gave formal access to cervinomycins A₁ and A₂.²⁸⁹

Yadav published in 1993 an account of his synthesis of cervinomycins A₁ and A₂, a topic of particular interest due to the potential use of cervinomycin acetate derivatives as chemotherapeutic agents.²⁹⁰ He also made use of key ester-condensation steps to construct the xanthone core. The synthesis of cervinomycin A₁ was achieved in 19 steps, including reduction of cervinomycin A₂ with NaBH₄ as the final transformation.

FD-594. The glycosylated naphthoxyxanthone FD-594 (370, Figure 58) is a cytotoxic antibiotic isolated by Eguchi, Kakinuma, and co-workers from *Streptomyces* sp., TA-0256.^{291,292} An interesting property of this compound noted

Scheme 26. Mehta's Synthesis of Cervinomycins A₁ and A₂**Figure 58.** FD-594.

during its structural determination was the solvent-dependent atropisomerism that it displays, giving essentially opposite CD spectra in chloroform and methanol.²⁹³ The conformation of the C-ring appears to be at the root of this atropisomerism, with the two hydroxyl groups here adopting an equatorial relationship in chloroform, and diaxial relationship in methanol or water. Such atropisomerism had not previously been described for a natural product. The biological properties of FD-594 were

also noteworthy; the compounds have moderate activity against several cancer cell lines and also antibiotic activity against several Gram-positive species of bacteria.²⁹¹

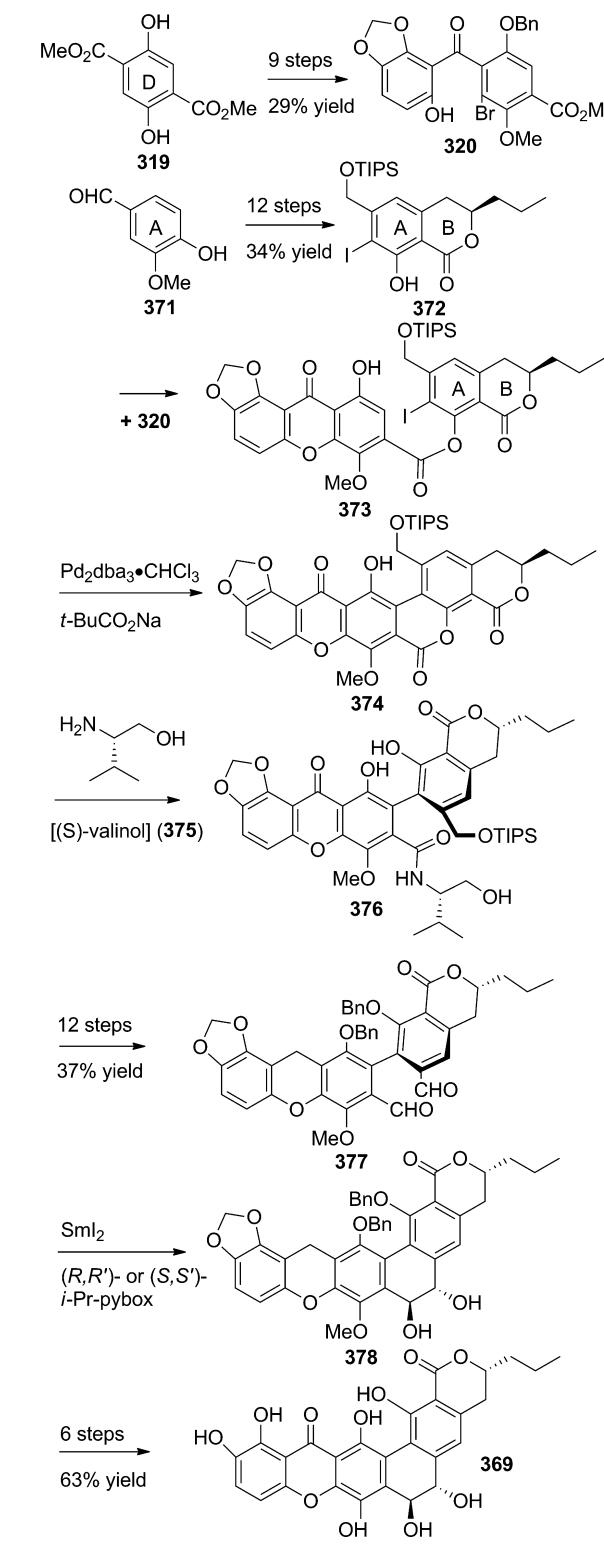
In 2009 Suzuki and co-workers reported the synthesis of the FD-594 aglycon (369, Figure 58),²⁹⁴ work which had been preceded with an interesting study on solvent-dependent chemoselectivity in the base-mediated cyclization of *ortho*-hydroxy benzophenones to form xanthones.²⁹⁵ Other key steps included intermolecular esterification and then direct arylation reactions, as well as a Bringmann-type asymmetric cleavage with a chiral-pool nucleophile, (*S*)-valinol (375, Scheme 27), to give axially chiral biaryl 376, a dialdehyde derivative of which, 377, could later be cyclized to give diol 378 in a chirality-transfer sequence.

IB-00208. IB-00208 (379, Figure 59) was isolated alongside several known compounds from the mycelial cake of cultures of *Actinomadura* sp., a marine-derived actinomycete bacteria (strain BL-42-PO13-046).²⁹⁶ The structure was proposed to be a γ -pyrone containing glycoside from data including spectral analysis, coupling constants around the glycoside unit, and 2D NMR experiments (COSY, HMBC, and NOESY). The compound was active in terms of both bactericidal and cytotoxic effects,²⁹⁷ particularly against Gram-positive bacteria, with MIC values determined against *Staphylococcus aureus* (1.4 nM), *Bacillus subtilis* (1.4 nM), and *Micrococcus luteus* (0.09 nM). The compound also possessed strong cytotoxicity against P388D1, A-549, HT-29, and SK-MEL-28 cells, all of which with an MIC at a concentration of 1 nM.

Lysolipins. Lysolipins X and I (380 and 381, respectively, with 380 being the hydrate of 381, Scheme 28) were isolated from *Streptomyces violaceoniger* strain Tü 96 by Drautz, Keller-Schierlein, and Zähner in 1975.²⁹⁸ Lysolipins are polycyclic xanthone-containing species that have antibiotic properties due to their inhibition of cell-wall biosynthesis; lysolipins are active against both Gram-positive and Gram-negative bacteria.²⁹⁸ They were the second group of examples of the “xanthone antibiotic” family of compounds to be discovered after albofungins, in which the xanthone ring is inverted and the N-NCH₃ group of albofungins is replaced by a hydrazino group (see albofungins, later). This family, which also includes cervinomycins, simaomicin, and several others (see sections 3.2 and 3.3) have in common a dimeric structural motif containing a xanthone ring bound with an isoquinoline ring. They are the largest subgroup of polyketides to be assembled by a type-2 polyketide synthase.²⁹⁹ Lysolipin X (actually a dihydroxanthone) is easily converted to lysolipin I (i.e., 380 and 381, Scheme 28) through the action of UV light or heat. In 1977 a crystal structure of the triacetate of lysolipin I was produced, confirming the structure.³⁰⁰

In 1994 Rohr and co-workers reported on biosynthetic studies of these lysolipins, finding that lysolipins X and I were derived from a polyketide pathway with 12 malonate units³⁰¹ as well as molecular oxygen and a C₁ unit from methionine. The authors propose the biosynthetic pathway to begin with a Baeyer–Villiger type oxidation, followed by formation of the xanthone core with either a decarbonylative ring-opening then closing or a hydrolysis and then oxa-Michael addition reaction with decarboxylation/reduction.³⁰¹ An ¹⁸O₂ feeding experiment with subsequent detection of isotopic incorporation using a ¹³C–¹⁸O shift method allowed determination of the total number and location of 9 of the 12 oxygen atoms in lysolipin X that are derived from molecular oxygen, including both oxygens of the xanthone core.³⁰¹ This result is surprising given that a

Scheme 27. Suzuki's Synthesis of FD-594



study on the structurally related citreamicin α species (see section 3.2)³⁰² determined that the xanthone oxygens of this molecule are derived from the polyketide building material. With this discrepancy, the diversity of xanthone biosynthetic pathways is thus highlighted, whereby deoxygenation, then aromatization, then reoxygenation of the framework appears to have occurred in the biosynthesis of lysolipin.³⁰¹ Duthaler

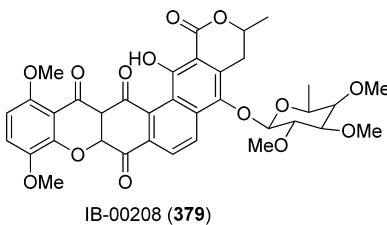
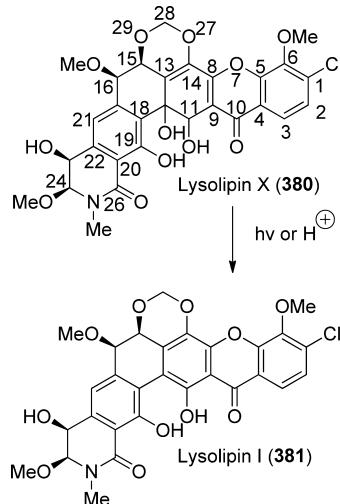


Figure 59. IB-00208.

Scheme 28. Lysolipins X and I



reported in three parts investigations into the synthesis of lysolipin I.^{303–305}

Vinaxanthones. Vinaxanthone (382, Figure 60) was isolated from *Penicillium vinaceum* of soil origin by Yokose and Seto in 1991 after being identified as a novel phospholipase C (PLC) inhibitor in the low- to midmicromolar range.³⁰⁶ PLC is the enzyme that hydrolyses phosphatidylinositol biphosphate (PIP) in the cellular membrane. Inhibitors of this PLC are therefore of interest, as they are involved in the signal transduction cascade and pathways effecting cell proliferation. Encountering difficulty in the structural elucidation process due to both the low solubility and highly substituted nature of 382, the authors used a barrage of NMR techniques including 2D-INADEQUATE and selective 1D-INADEQUATE experiments to solve the structure.

Vinaxanthone (382) was subsequently isolated alongside three novel xanthones (383–385, Figure 60) in 1994 by Wrigley and co-workers from *Penicillium galabrum* and identified as an effective CD4-binder. CD4 is a protein involved in many immune responses and is known as the cellular receptor for HIV.³⁰⁷ The compounds were identified based upon mass spectral data and multiple 2D NMR experiments, particularly the use of ROESY as an alternative to NOESY. The authors propose that these polyketide-derived products result from dimerization of a C_{14} -polyketide related to the polivione, also a metabolite of *P. galabrum*. In 2003 vinaxanthone was again isolated by Kumagai and co-workers and shown to have semaphorin inhibitor activity.³⁰⁸ Semaphorinins are a group of endogenous molecules that inhibit axonal growth of specific cells in the nervous system. Inhibitors of the binding of Sema3A to its receptor may be of interest for the purpose of studying neuronal growth and regeneration, for example, in the damaged nervous system.³⁰⁹

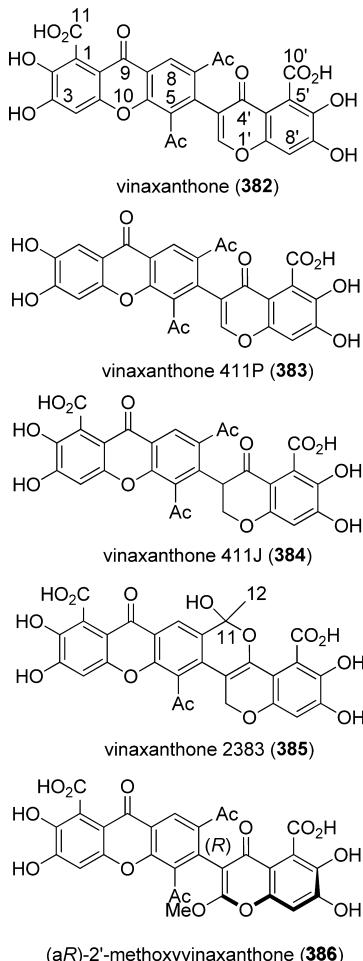


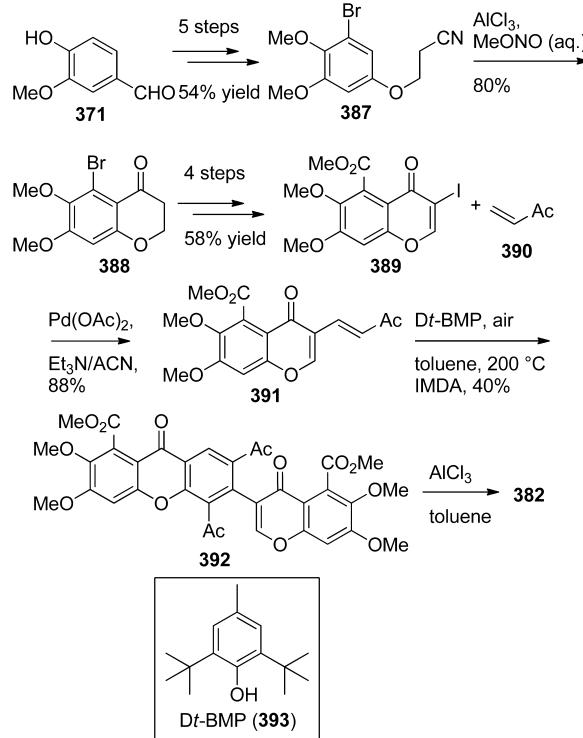
Figure 60. Vinaxanthone (382),³⁰⁶ vinaxanthone species 383, 384, and 385,³⁰⁷ and (aR)-2'-methoxyvinaxanthone 386 (absolute stereochemistry shown).³¹⁰

In 2008 Řezanaka and co-workers reported the isolation and characterization (including determination of absolute configuration) of (aR)-2'-methoxyvinaxanthone (386, Figure 60), isolated from *Penicillium vinaceum*.³¹⁰ Computational chiroptical methods were used to conformationally define this compound as the R (or M) atropisomer, due to negligible free rotation at room temperature around the biaryl bond linking the xanthone and chromone components (calculated free energy required is 103.5 KJ/mol). The compound showed no antibacterial or antifungal activity with standard tests but was positive in both sea-urchin and crown gall tumor (potato disk) tests.³¹⁰

The total synthesis of vinaxanthone (328, Scheme 29) has been achieved by Tatsuta and co-workers in 2007 starting from vanillin (371).³⁰⁹ A sequence of 13 steps yielded the natural product, including a key intermolecular Diels–Alder (IMDA) reaction to link the xanthone and chromone components, constructing the xanthone C-ring in the process. Interestingly, this IMDA was greatly assisted in terms of selectivity by the addition of Dt-BMP (393), without which the product distribution lay in favor of elimination and aromatization products; the authors suggest that this species acts as an electron acceptor by way of the corresponding quinone, whereas the addition of standard oxidants had no such effect.

Xanthofulvin. Xanthofulvin was first isolated by Masubuchi and co-workers⁴⁷⁴ from a *Eupenicillium* strain and found to be a

Scheme 29. Tatsuta's Vinaxanthone Synthesis



chitin synthase II inhibitor ($IC_{50} = 2.2 \mu\text{M}$). Kimura and co-workers have reported the isolation of SM-216289 or xanthofulvin (394, Figure 61) alongside the known tautomer,



Figure 61. Xanthofulvin or SM-216289.

vinaxanthone (382, Figure 60), from cultures of *Penicillium* sp. SPF-3059.³¹¹ The authors demonstrated that xanthofulvin is also a semaphoring inhibitor (see vinaxanthone, previously); Sema3A was inhibited at low levels, with an IC_{50} of 0.16 μM .³¹¹

Xantholipin. Xantholipin (395) is structurally related to albofungin, lysolipin, and the actinoplanes (see sections 3.2 and 3.3). Terui and co-workers reported in 2003 the structure of xantholipin (Figure 62), which they isolated from the cultures of soil-sample derived *Streptomyces* sp. during a screening program to identify inhibitors of a heat shock protein (HSP47).³¹² The authors determined the structure with the use of spectral techniques and chemical derivatization and determined the absolute configuration with a modified Mosher's method. The compound inhibited HSP47 with an IC_{50} of 0.20 mM, inhibited collagen production, and demonstrated cytostatic activity with an IC_{50} of 80 nM.

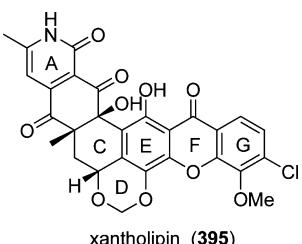


Figure 62. Xantholipin.

3.2. Dimers and Heterodimers 2: Dihydroxanthones

Dihydroxanthone dimers are limited to the citreamicins and lysolipin X (Scheme 21; see section 3.1).

Citreamicins. Citreamicins (396–402, Figure 63, originally designated LL-E19085 antibiotics)³¹³ are again members of the polycyclic antibiotic family that includes cervinomycins, lysolipin, albofungins, and simaomicin. They were originally isolated from *Micromonospora citrea*, and the structures, due to

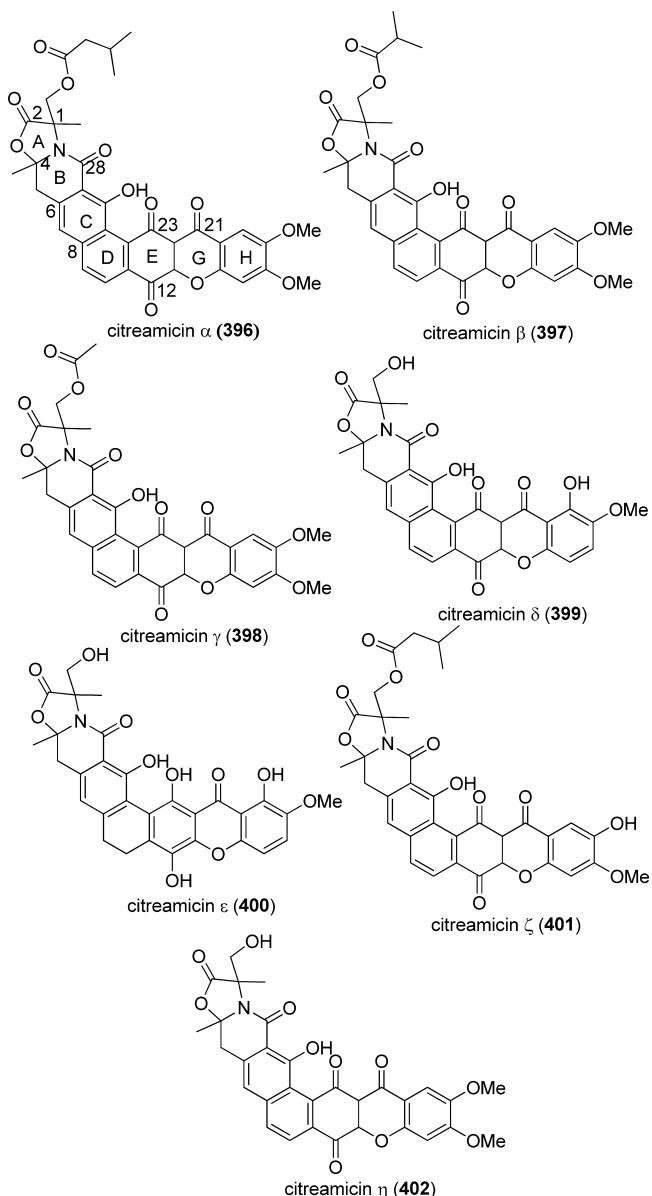


Figure 63. Citreamicins.

the lack of protonation of the skeleton, were determined with the assistance of high-resolution fast atom bombardment mass spectrometry (HRFAB-MS) and a specific NMR technique, CSCMLR (carbon detected long-range heteronuclear correlation experiment). They are active as agents against Gram-positive (aerobic and anaerobic) bacteria,^{313,314} importantly including methicillin-resistant *Staphylococcus aureus* (MRSA). From the various species, citreamycin α (396) was the most abundant and citreamycin η (402) was determined to be the most active, with *in vitro* MIC values of $<0.015 \mu\text{g/mL}$.³¹⁴

A 1990 paper from Carter and co-workers elucidated the biosynthetic processes involved in the construction of citreamicins.³¹⁴ Working on the assumption that the compounds were assembled from the enzymatic manipulation of a single polyketide precursor, as the authors had previously established for the related species simaomicin (see below), 1^{-13}C - and 2^{-13}C -enriched fermentation broths of *M. citrea* were made, and ^{13}C NMR analysis of citreamycin A confirmed the polyketide pathway. Additionally, the feeding of ^{13}C -methionine to the culture resulted in enrichment of the ^{13}C content of both methoxy groups and confirmed S-adenosyl methionine as the methylation agent. ^{13}C and $^{18}\text{O}_2$ acetate feeding experiments showed that the oxygens at 4, 15, 17, 21, 26, and 28 are derived from acetate, whereas positions 12 and 18 are isotopically enriched upon exposure of the broth to $^{18}\text{O}_2$. Additionally, citreamycin has been tested by the agar-dilution method against 313 isolates of *Staphylococci* and 116 strains of *Streptococci* by Qadri and co-workers,³¹⁵ who found that MICs for the former group were typically in the range 0.12–4.0 $\mu\text{g/mL}$, activities that are comparatively far greater than those of ampicillin, augmentin, cephalothin, and erythromycin but equal or less than that of vancomycin.

In 2008 Mocek and co-workers reported the discovery of the related quinone/2,3-dihydro-dihydroquinone species citreamicins δ and ϵ (398 and 399, Figure 63), which were isolated from the EtOAc extract of a *Streptomyces vinaceus* fermentation following screening in the search for compounds that may be able to solve the problems associated with increased microbial resistance, using multidrug-resistant *Staphylococcus aureus* as a model.³¹⁶ The authors solved the structures for 398 and 399 based on mass spectrometry and NMR spectroscopy and further found MIC values as low as 0.06 $\mu\text{g/mL}$ against several Gram-positive strains of bacteria. Also noteworthy in terms of cytotoxicity was that human hepatocellular liver carcinoma cell line (HepG2) cells were 90% inhibited in growth (CC_{90}) following the application of 2.4 and 1.0 $\mu\text{g/mL}$ for 398 and 399, respectively, and normal human dermal fibroblasts (NHDF) cells at CC_{90} of 0.3 and 0.1 $\mu\text{g/mL}$ for 398 and 399, respectively.³¹⁶

3.3. Dimers and Heterodimers 3: Tetrahydroxanthones

Arguably the most structurally and biologically interesting (as well as synthetically challenging) xanthones from fungi are to be found in an always-growing group of tetrahydroxanthone dimers and heterodimers. Those known include actinoplanones, albofungins, ascherxanthone, beticolins, chrysanthone, dicerandrol, ergochromes (secalonic acids, ergochrysin, and ergoxanthines), eumitrins, hirtusneanoside, microsphaerins, neosartorin, parnafungins, phomoxanthones, rugulotrosins, Sch 42137, Sch 54445, xanthonol, and xanthoquinodins.

Actinoplanones. The actinoplanones (403–409, Figure 64) were isolated from *Actinoplanes* sp. in 1988 by Kobayashi and co-workers from the culture broth of a soil-derived

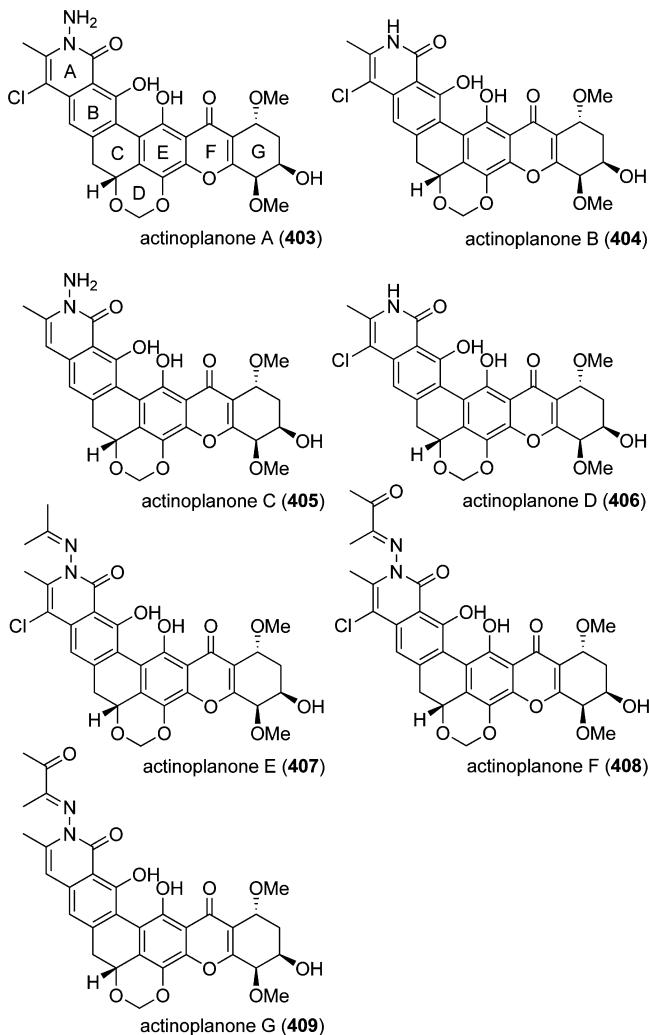


Figure 64. Actinoplanones A–G.

Actinoplates sp. R-304.³¹⁷ The species were identified in conjunction with their cytotoxicity against HeLa cells, which was extraordinarily high (actinoplanone A having an IC₅₀ of 0.04 ng/mL); this was the first report of such cytotoxic activity from the polycyclic antibiotic class of compounds (also including albofungins, lysolipin, cervinomycins, etc.).

The structures, including the relative configuration, were established using 2D heteronuclear correlation NMR experiments, comparison to the structure of known species (albofungin and chloroalbofungin, 410 and 411, Figure 65) and the absolute configuration at the G-ring was determined with circular dichroism (CD) spectra and the NMR analysis of chiral derivatives, in the form of α -methoxy- α -(trifluoromethyl)acetic acid ((R)-(+)-MTPA) esters.³¹⁷

A Japanese team found the remaining actinoplanones C to G (405 to 409, Figure 59) and reported them in a follow-up publication the same year.³¹⁸ Actinoplanones were shown to exhibit cytotoxic activities in the same order as those for actinoplanone A. Actinoplanone A, B and F were tested against 21 bacterial species, and found to be most effective against Gram-positive species, in particular *Staphylococcus aureus*, *Bacillus subtilis*, and *Micrococcus luteus*. The compounds further showed a strong antifungal activity against many bacteria and the rice blast fungus, *Pyricularia oryzae*, with IC₅₀ values ranging from 0.0016 to 0.16 μ g/mL. Actinoplanone A was

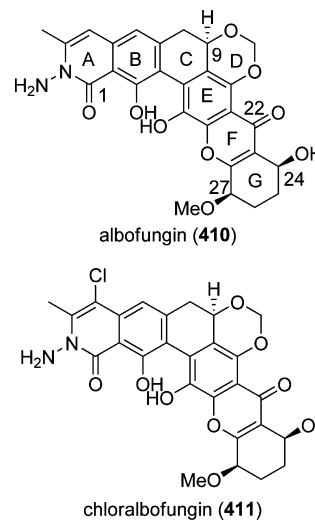


Figure 65. Albofungin (absolute stereochemistry shown) and chloroalbofungin.

further tested against nine tumor cell lines, and found to show consistently strong activity, which may be related to the inhibitory effects of actinoplanones on DNA synthesis. Finally, actinoplanone A could be converted to E and F upon condensation of acetone or 2,3-butadione in the presence of catalytic acetic acid.³¹⁸

Albofungins. Albofungin (also known as kanchanomycin, BA-180265, 410, Figure 65) was reported in 1972 by Gurevich and co-workers after isolation from *Actinomyces albus* var. *fungatus*.³¹⁹ The compound contains the xanthone nucleus linked in a heterodimer with an isoquinoline ring (see other polycyclic antibiotics) and an unusual hydrazino moiety at the 2-position.

A second study by the same authors described the determination of the absolute configuration of 410 (particularly at C9, C24, and C27) by CD spectra for the natural product, as well as those of selective chemical derivatization and decomposition products.³²⁰

Ascherxanthone. The symmetrical dimeric structure of ascherxanthone A (411, Figure 66) was reported in 2005 after being isolated from *Aschersonia* sp., an entomopathogenic fungus collected on a Homoptera-scale insect.³²¹ The relative configuration around C5, C6, and C10a was determined using

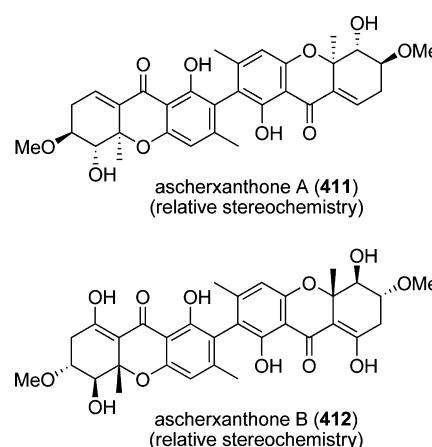


Figure 66. Ascherxanthones.

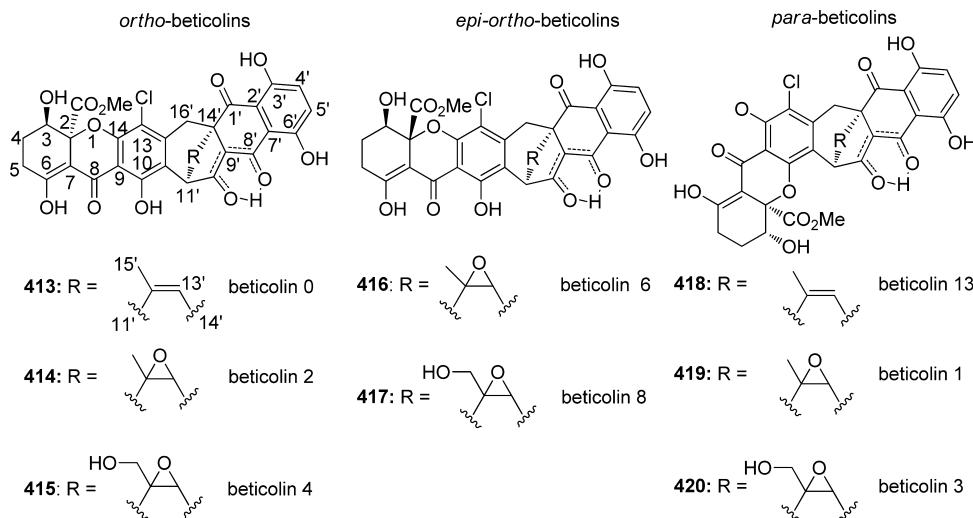


Figure 67. Beticolins. Numbering shown for the *ortho*-beticolins is retained in the corresponding *para*-species according to the original position.

¹H NMR and NOESY experiments. Like diversonol (see section 2.3), this compound has methyl substituents in the 4a positions; however, the absence of a hydroxy group at C8 and C8' is rather unique among this family of natural products. The compound exhibited strong activity against *Plasmodium falciparum* ($IC_{50} = 0.20 \mu\text{g/mL}$) and Vero cells ($IC_{50} = 0.80 \mu\text{g/mL}$) and activity against three cancer cell lines (IC_{50} values in the range from 0.16 to 1.7 $\mu\text{g/mL}$).³²¹

In 2009 Chutrakal and co-workers reported the large-scale isolation of a new compound related to ascherxanthone A from *Aschersonia luteola* BCC 8774, albeit with hydroxyl groups in the place of the alkenyl hydrogen substituent of 411.³²² The compound was isolated after in vitro screening of antifungal substances and exhibited significant toxicity ($IC_{90} = 0.95 \mu\text{M}$) against a virulent strain of the rice blast fungus, *Magnaporthe grisea*. Subsequently, preliminary in vivo tests were also carried out by the team. The use of NOESY and other NMR techniques confirmed that the compound possessed the same relative configuration as 411 and was named ascherxanthone B (412, Figure 66).

Beticolins. The beticolins (ascertained structures shown, b0, 2, 4, 6, 8, 13, 1, and 3, 413–420, respectively, Figure 67) are a fascinating family of closely related nonhost-specific mycotoxins produced by several strains of *Cercospora beticola* Sacc., a fungus responsible for Cercosporiose, the leaf-spot disease of sugar beet (*Beta vulgaris* L.).^{323–326} They are additionally produced by at least one strain of *C. bertoreae*.³²⁶ Toxins from this fungus have been studied extensively because of their significant damage to this economically important crop. They include a red perylenequinone pigment, cercosporin,³²⁷ which can affect the peroxidation of membrane lipids. Schlosser isolated from the same strain a bright yellow substance with both phytotoxic and antibiotic activity,³²⁸ originally referred to as first the “gelbe Fraktion”³²⁹ and then as CBT (*Cercospora beticola* toxin).³²⁸ CBT is a polyphenolic complexing agent of Fe^{3+} , Cu^{2+} , Zn^{2+} , Mn^{2+} , or Mg^{2+} ions.^{324,325,328} The chemical identity of CBT is not, as was suggested by one team in the 1970s, a mixture of fatty acids and cercosporin³²⁹ but rather a group of closely related compounds now named beticolins.

Twenty beticolins have been distinguished to date (designated b0–b19 according to their R_f in TLC analysis),³³⁰ and structures of eight have been established (413–420, Figure

67). The isolation and structural elucidation of these compounds constitutes merely a part of the many publications on the subject of the beticolins (>30 to date).³³¹

Isolation and Structural Determination. The first structural elucidations of the beticolins were reported independently by two groups in 1992. A collaboration of French researchers reported the structure of beticolin 2 (b2, 414, Figure 67) from X-ray diffraction studies,³³² as a heterodimer comprising a xanthone and an anthraquinone component. A structure for b1 was suggested based on a best-fit model from the analysis of MS, ¹H, and ¹³C data. This compound was initially reported as being cyclized on the *ortho*-hydroxyl position relative to chlorine (not shown) but was later structurally revised by the researchers involved to the *para*-hydroxyl-cyclized species shown (419, Figure 67).³³³ Very soon afterward a report came from an American group that had isolated two compounds and determined their structures by single-crystal X-ray diffraction (cebetin B) and comparison by other spectral techniques (cebetin A). The former of these corresponds to the stable,³³⁴ electronically neutral beticolin dimagnesium complex of beticolin 1, which has a 2-fold axis of symmetry $[\text{b}]_2\text{Mg}_2$ (Figure 69).³³⁵ These researchers found that the dimagnesium dimer cebetin B could also be produced by *C. beticola* isolated from soybean roots and cultured in vitro.³³⁶

Independent work by Assante et al. soon confirmed the structure of cebetin CBT1 with independent single-crystal X-ray studies on the purified compound,³³¹ which showed it to be equivalent to cebetin B (421, Figure 69), i.e., a dimagnesium dimer of b1 (419, Figure 67).³³⁴ Chemical derivatization (acetylation), ¹³C labeling, and biological testing of this complex were also performed.

Another report from the French group gave spectroscopic details and proposed structures for two more beticolins, b3 and b4 (again, b3 was later determined by the same researchers to be an *ortho*- rather than *para*-cyclized species,³³³ see also 420 and 415, Figure 67).³³⁷ In 1994, the structures of two minor components from *C. beticola* were detailed. These were *epi*-*ortho*-beticolins 6 and 8 (416 and 417, respectively; see Figure 67), which also inhibit plasma membrane H^+ -ATPase.³³⁸ Another report followed in 1995 from Blein et al. detailing the single-crystal X-ray structures of b2 and b4, which were

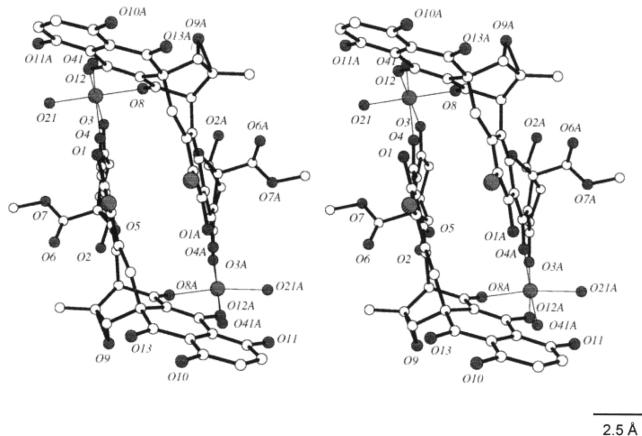


Figure 68. Beticolin crystal structure. Adapted with permission from Goudet, C. et al. *Biophys. J.* **1999**, *77*, 3052.³⁴¹

shown to have a “V-shaped” conformation about the central bridged cycloheptene ring (in the solid state). The phenolic protons were strongly intramolecularly H-bonded with neighboring keto groups.³³⁹ The authors suggest that the final stage in the biosynthesis of the beticolins and related xanthoquinodins is the heterodimerization to form the bridged cycloheptene. Milat and Blein published a description of the purification of several individual beticolins from CBT—beticolins 0, 1, 2, 3, 4, and 7—and described the TLC and both quantitative and qualitative HPLC analysis of these compounds. They note that b2 (an *ortho*-beticolin) was by far the most prevalent beticolin in an 11-day old culture of *Cercospora beticola*.³⁴⁰

In 1994 the original team that reported the structures of beticolins 1 and 3 revised these, changing the original structure of b1 and b3 from an *epi*-*ortho*-species (**419**, Figure 67) to the *para*-species (**420**).³³³ They detailed the conversion of beticolin 1 to cebetin B in 95% yield in the presence of magnesium carbonate in acetone with sonication and revealed that cebetin A and b1 are in fact composed of the same compound. Beticolin 2 could be converted to cebetin B (albeit in low yield) under these conditions; the authors proposed a retro-oxa-Michael/recyclization isomerization pathway.³³³ The suggested spontaneous cyclization under basic conditions may explain why Jalal et al.³³⁵ and Arnone et al.³³¹ did not find b2 in their extracts.

Another report from the French collaboration in 1996 reported the isolation and structural elucidation of b0. This species has a trisubstituted olefinic moiety in place of the 2-methylepoxy/2-hydroxymethylepoxy moieties previously observed on the bicyclo[3.2.2]nonane ring, and is thus the putative precursor to the other beticolins, through presumed enzymatic oxidation and the observed isomerization processes.³⁴² The authors transformed b0 to b2 through regio- and stereoselective epoxidation in high yield (*m*CPBA, CHCl₃, room temperature, 6 days, 92%).³⁴²

Prangé and co-workers reported single-crystal X-ray data confirming the previously proposed structures of b1 (i.e., cebetin A)³³⁵ and b3,³³³ allowing the determination of the structure of b13, a *para*-isomer of b0 (see structures **419**, **420**, and **413**, respectively).³⁴³ To acquire material for the X-ray study of these hitherto difficult-to-crystallize compounds, the *para*-beticolins³⁴² were crystallized using a specially developed vapor-diffusion technique.³⁴³ They were found to be unstable

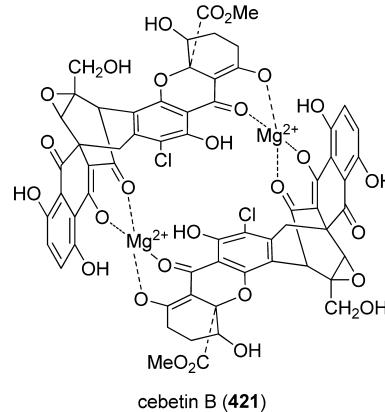
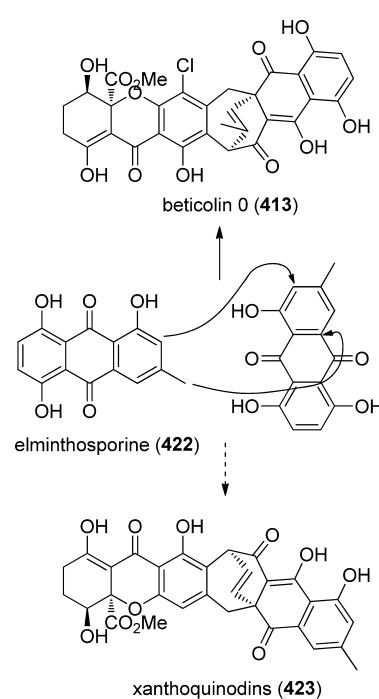


Figure 69. Cebetin B (b1 dimagnesium dimer).^{7,330}

in solution (light, heat); this contrasts with the stable Mg²⁺ dimers. Ducrot published a summary of spectroscopic chemical behavior of the beticolins in 2001, including NOEs and chemical methods for distinguishing between the *ortho*- and *para*-cyclized species.³³⁰

Structure and Biosynthesis. This family of compounds was unique when first discovered, as other previously described xanthones and anthraquinones were symmetrical or pseudo-symmetrical structures, composed of two equivalent components.³³⁵ The beticolins (Figure 67) have polycyclic skeletons that incorporate both a monochlorinated xanthone and a tetrahydrogenated anthraquinone, both of which result from acetogenic pathways. Biosynthetically, the beticolins result from the head-to-head addition of two elminthosporine subunits. The structurally related xanthoquinodins can be seen as a head-to-tail coupling of the same (Scheme 30),³³⁰ albeit without a chloride substituent, which appears to endow the beticolins with relatively high degree of stability in terms of their

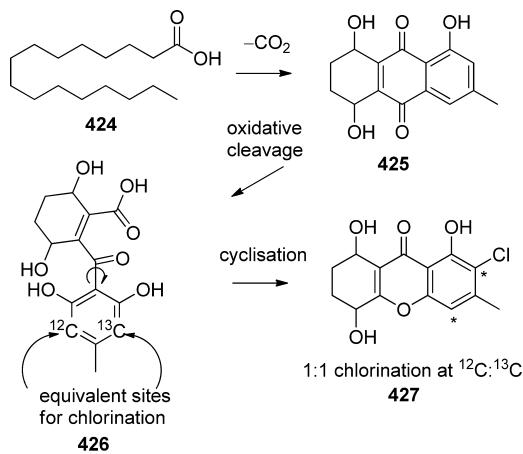
Scheme 30. Pathways from Elminthosporines to Beticolin 0 and Xanthoquinodins³³⁰



xanthone ring system. It must follow that there is initially reduction then oxidative cleavage of one molecule of anthraquinone (elminthosporin), and then recyclization to xanthone.

The ^{13}C labeling suggested that each of the xanthone and anthraquinone components are derived from octaketides following decarboxylation. The beticolins are thus formed from a combination of tetrahydroxanthone and tetrahydroanthraquinone (reduced elminthosporine) precursors. Other fungal xanthones are also themselves produced by anthraquinones, for example, α - and β -diversonolic esters,²⁶¹ by first oxidative cleavage of a C14–C15 bond, followed by rotation around the C8–C9 bond, and then recyclization via Michael addition of the phenolate moiety to the intermediate enone

Scheme 31. Beticolin Biosynthesis and Evidence for a Freely Rotating Benzophenone Intermediate **426**³³¹



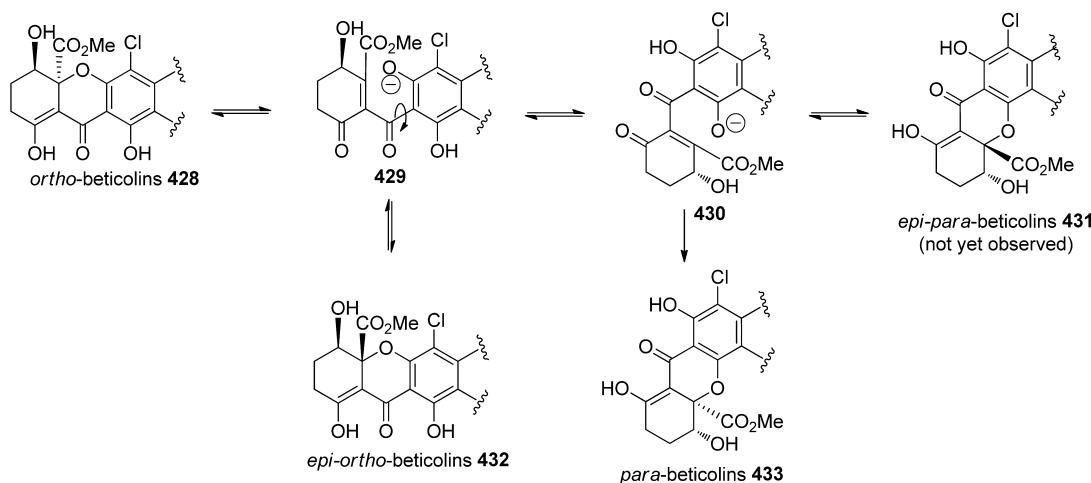
(see Scheme 31). Arnone et al. observed that incorporation of ^{13}C -labeled acetate results in a 50:50 $^{12}\text{C}/^{13}\text{C}$ chlorination ratio. Chlorination of a symmetrical benzophenone intermediate **426**, from which cyclization can take place on either of two chemically equivalent phenolic groups, provides for the randomization of attachment of the chlorine atom in **427**. The authors suggest that this process probably takes place

during the coupling of the hexahydroxanthone moiety to the second molecule of elminthosporin.³³⁰

The beticolins identified thus far are structurally differentiated in three aspects: (a) the variable attachment within the tetrahydroxanthone component gives rise to an isomeric distinction of *ortho*- and *para*-species with respect to the position of attachment of the oxygen linker in the xanthone ring relative to the chlorine substituent (Figure 1); (b) the identity of the C₃ "R" unit, which links C11' and C12' in the central bicyclo[3.2.2]nonene: methylethene, 2-methyloxirane, or (2-hydroxy)methyloxirane (linked in a 1,2-manner); and (c) the relative stereochemistry of the methylcarboxylate at C2 and the hydroxyl at C3. The *cis*-variants are designated *ortho*-beticolins, while those where the two substituents are *trans* are *epi-ortho*-beticolins. Corresponding *epi-para*-beticolins have not been observed to date.

The *ortho*-isomers are known to convert to the more-stable *para*-isomers under basic conditions (Scheme 32). Treatment of (*ortho*)-b2 with MgCO₃ gave the (*para*)-beticolin Mg₂ dimer cebetin B by way of b1 through a retro-oxa-Michael-addition and recyclization from the *para*-hydroxyl, confirming this isomerization route between the beticolins.³³⁰ b2 could be converted more efficiently through application of K₂CO₃ in acetone to *para*-beticolin 1 (**419**, 80%), alongside a minor amount of *epi-ortho*-beticolin 6 (**416**, 10%); the latter could also be converted into beticolin 1, showing that the *para*-compound does indeed represent the thermodynamically or kinetically most stable species of the three.³³⁸ Similar results were obtained for the conversion of *ortho*-beticolin 4 to *para*-beticolin 3 and *epi-ortho*-beticolin 8.³³⁸ The authors further point out that the relative stereochemistry at the carbomethoxy and hydroxyl substituents of ring A can be determined by the coupling of H3/H4 protons.³³⁸ Similar conversion of b0 to b13 has been reported in polar solvents. Almost certainly this interconversion is the origin of the (b) class of betolin diversity; the *ortho*-beticolins are initially formed and then converted to the more stable *para*-beticolins.³⁴³ Sonication of *para*-beticolin 1 with MgCO₃ in acetone gave complete conversion to the stable and biologically potent [beticolin 1]₂Mg₂ species.³³⁰ Neither *ortho*-beticolins nor *epi-ortho*-beticolins dimerize under such conditions; the former instead slowly convert to the thermodynamically favored *para*-beticolins.³⁴² Ducrot suggests this to take place by a base-

Scheme 32. Interconversion of Beticolins



promoted retro-Michael addition and recyclization of the resulting phenolate to form *para*-, *ortho*-, and *epi*-*ortho* variants of the initial beticolin.³³⁰ It is possible that the chlorine has a stabilizing effect, suppressing the retro-oxa-Michael initiated interconversion, by decreasing the acidity of the proton of the C-6 enol (Scheme 32), making the beticolins less prone to interconversion than related xanthoquinodins (which isomerize readily under neutral conditions). The chlorine may also be responsible for favoring *para*-beticolin formation, as it would reduce the nucleophilicity of the *ortho*-phenolic moiety.³³⁰

The optically active molecules (absolute stereochemistry determined by X-ray crystal studies) contain a bicyclo[3.2.2]-nonane ring system, which itself contains a methyl-substituted alkene bridge, or one of two oxidized derivatives of it (either 1-methyl epoxide or 1-methylhydroxy epoxide).

The phenolic OH protons are involved in strong hydrogen bonds to a neighboring keto group. *ortho*-Beticolins are roughly V-shaped in the crystal structure,³³⁹ whereas *para*-beticolins have two planes linked in a perpendicular relationship, allowing two molecules to complex $2 \times \text{Mg}$ ions in a head-to-tail coupled open-ended cubelike structure.³⁴³ In the absence of magnesium ions, the *para*-beticolins nevertheless form dimers, this time using hydrogen bonding; however, this latter dimer lacks the 2-fold access of symmetry associated with B_2Mg_2 dimers due to the dissymmetry required for hydrogen bonding.³⁴³

In the original crystal structure, the two halves of cebetin B ($[\text{beticolin } 1]_2\text{Mg}_2$) were observed to have a roughly perpendicular arrangement (78° angle).³³⁵ The absolute configuration was determined to be 10*a*S, 5S, 2'R, 3'R, 4'S, and 4'a3S.³³⁵ Of these centers, only the stereochemistry at C2 varies between beticolins (*ortho*-, *epi*-*ortho*-, and *para*-). Circular dichroism has been used to confirm that *ortho*- and *para*-beticolins are identical in terms of absolute configurations, with the exception of the C2 center.³⁴³

Biological Properties. There appear to be multiple, diverse cytotoxic effects of the beticolin family, the mechanistic revelation of which makes these compounds even more intriguing. Schröder found CBT, at the time a beticolin mixture of unknown composition, to possess both phytotoxic and antibiotic activity.³²⁸ Cebetins A and B (beticolin 1 monomer and Mg^{2+} -chelated dimer) were demonstrated to kill sugar beet cells at concentrations of 1 ppm. This activity was dependent on the presence of light, suggesting that they are photoactivated phytotoxins.³³⁵

For some time, studies with respect to beticolin-induced disruption of membrane integrity and potential were published, sometimes suggesting contrary modes of action. Macri et al. showed that K^+ uptake, H^+ extrusion, K^+ -activated ATPase, and transmembrane polarization of tissues of three different plants were all deleteriously effected by CBT. They ascribed these effects to nonspecific membrane alterations.³⁴⁴ Electrolytes (such as ions, amino acids, and even larger molecules, i.e., β -cyanin) were lost from plant cell discs after the application of CBT, and roots treated with CBT displayed inhibited K^+ uptake. K^+ -ATPase activity of plasmalemma-enriched membrane fractions was also strongly inhibited. These researchers later showed that CBT inhibits the proton-gradient in corn root segments³⁴⁵ and in pea-cell microsomes. The results supported the hypothesis that these effects are due to CBT acting with a primary effect as an inhibitor of plasmalemma or tonoplast ATPase proton pump.³⁴⁶ Blein et al. showed that CBT inhibits the vanadate-sensitive ATP-dependent H^+ -transport and, thus,

maintenance of the proton-gradient through corn root microsomes; this effect was demonstrated to increase with higher pH.³⁴⁷ Taken together, these effects can be explained either by the direct effect on the membrane transporter(s) or by indirect effect due to damage/compromise of the membrane or decreased energy supply to the plasma-membrane ATPase (i.e., direct inhibition or inhibition through proton permeability).³⁴⁷

The polyphenolic nature of beticolins is probably responsible for the display of a seemingly unrelated O_2^- scavenging ability, demonstrated for b1, which is more effective in this respect than classic scavengers such as T-iron and vitamin E.³⁴⁸ They additionally have an antiproliferative effect on mammalian cells through the modulation of a step in steroid biosynthesis pathway. Both b1 and b2 were also shown to inhibit the proliferation of both ras-transformed rat adrenocortical cells and mouse adrenal tumor cells at IC_{50} values in the submicromolar range. The production of 11β -hydroxysteroids was also strongly and specifically inhibited.³⁴⁹ The authors also showed that, in these animal cells, the beticolins accumulated in the cytoplasmic organelles rather than in plasma and nucleic membranes.³⁴⁹

The biological effects of beticolins include inhibition of plasma membrane H^+ -ATPase,^{350,347} interfering with the electrochemical gradient across the membrane.³⁵¹ This transmembrane potential normally enables nutrient uptake and storage. It follows that the toxins have been demonstrated to induce a loss of vital solutes from plant cells.³⁴⁴ Another report investigating the action of beticolin–magnesium complexes with the plasma membrane H^+ -ATPase was published in 1996 by Gomès et al. It detailed that $\text{Mg}_2\text{H}_2\text{B}_2$, which can form at plant-cell levels of Mg^{2+} (being ~ 0.4 mM), is the dominant form in the inhibition of this enzyme.³⁵² Vacuolar H^+ -PPase is also inhibited by b1. H^+ -ATPases hydrolyze ATP and move protons to the outside of the cell; the resulting proton gradient enables proton-coupled symporters and antiporters in the membrane to import vital nutrients and solutes. Beticolin 2 (b2) was found to form the neutral dimagnesium dimer less readily than b1 and was also found to be less inhibitory than b1.³⁵² Fluorescent cyanine dye was used to determine the effect of b1 and b2 on transmembrane potential, which was partially abolished in a similar manner by both.³⁵¹ Thus, the majority of beticolin toxicity seems to be a result of destruction of this transmembrane potential and secondary effects associated with it.

Research then focused on determining whether the effects of beticolins were specific (target protein) or nonspecific. A report from Simon-Plas, Blein, and co-workers detailed the inhibition of corn-root-derived plant plasma membrane by b1 at micromolar (a purified component of CBT) concentrations.³⁵⁰ The authors also found that the effect of b1 on the dynamics of formation of H^+ -ATPase-phosphorylated intermediate (active form) were starkly different between purified/solubilized form (no effect) and the enzyme when incorporated into liposomes (strong inhibition). This indicates that the inhibition is dependent on the lipid environment of the enzyme (i.e., the membrane). The authors asserted that these factors suggest that H^+ -ATPase is a direct target for beticolin 1 (specific mode of action) and that the kinetics of inhibition and phosphorylation of this enzyme are linked. They further suggest that this inhibition is due to interaction of b1 with a hydrophobic domain of the enzyme near the lipid bilayer and then effects a

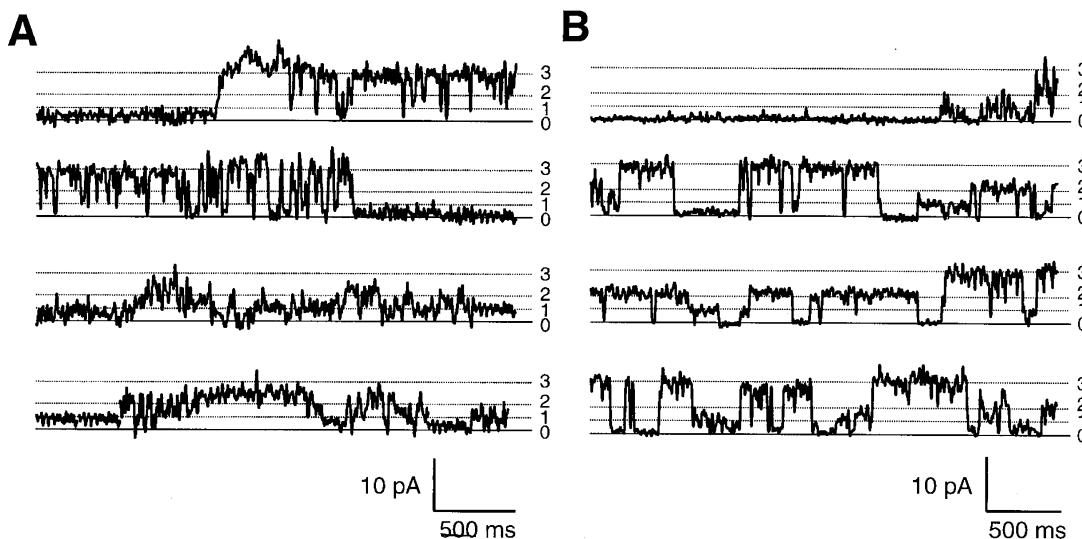


Figure 70. Ion channel traces across planar lipid bilayers, measured by patch-clamp technique, after addition of 10 μM solutions of (A) b3 (420) or (B) b4 (415) in the presence of free Mg^{2+} . Levels 1, 2, and 3 represent discrete current amplitude levels (1-, 2-, and 4-fold activity). Adapted with permission from Goudet, C. et al. *Mol. PlantMicrobe Interact.* 2000, 13, 203.³⁵⁹

conformational change, which decreases the efficacy of the H^+ -ATPase activity.³⁵⁰

To test the theory that beticins and CBT may have enhanced complex formation with magnesium, Mikes, Blein, and co-workers investigated pH-dependent deprotonation (of the keto-enol and one of the phenolic moieties) and found that the $\text{Mg}_2\text{H}_2\text{B}_2$ is the dominant form at physiological pH.³⁵³ Further details of the interaction of the beticins and their magnesium complexes with membranes were detailed in a following report: using fluorimetric techniques, the authors determined that beticin 1 (a *para*-beticolin) associates with liposomes 3-fold more than beticin 2 (an *ortho*-beticolin).³⁵⁴ Increasing pH dramatically increases the partition coefficient of both beticins, as did addition of magnesium salts to liposomes. The latter result shows that the dimeric salts have a higher affinity for nonpolar environment of the membrane than do the monomers.³⁵⁴

A further study confirmed that the species most active in blocking the activity of this ATPase is the dimeric neutral complex $\text{Mg}_2\text{H}_2\text{B}_2$ (initially given the name cebetin B when the structure was determined).³⁵⁵ For cebetin B in the crystal form, the Mg coordinates the xanthone β -keto-enolate moieties of one (deprotonated) molecule and the anthraquinone β -keto-enolate of the other. This dimer is the dominant form at the physiological pH range when Mg^{2+} is present, although beticins have been observed to form less strongly associated dimer pairs in the absence of Mg^{2+} . Beticin also blocks the activity of some other proteins that require Mg^{2+} as a cosubstrate.³⁵² As stated before, b2 (an *ortho*-beticolin) has been demonstrated to have a V-shaped conformation in the crystalline form,³³⁹ which is possibly the three-dimensional basis for higher-order intermolecular stacking of the beticin units to form ion-pore structures.

A report from Gomès et al. in 1996 detailed a comparative study into whether b1 interferes equally with a C-terminal truncated plasma-membrane H^+ -ATPase versus the wild-type enzyme demonstrated that the IC_{50} was similar, showing that the autoinhibitory domain of the C-terminal is not the site targeted by b1.³⁵⁵ The authors again give the view that beticin toxins are likely to bind to the protein at a hydrophobic

transmembrane location of the enzyme in order to effect its inhibitory activity.³⁵⁵ Another report from these groups that same year detailed investigations of the effect of b1 on corn-root plasma membrane H^+ -ATPase at different purification levels.³⁵⁶ The purified proton pump was inhibited at IC_{50} values of $\sim 1.5 \mu\text{M}$, and effects of b1 and CBT were shown to be similar. A relationship was determined by fluorimetric studies that showed IC_{50} and liposomal partition coefficient to be related (i.e., greater interaction with lipid bilayers correlates with greater toxin efficacy).³⁵⁶

Interestingly, the *ortho*-beticins 0, 2, and 4 were shown to be effective at lower IC_{50} values than the *para*-beticins 1 and 3. The latter have been previously observed to have a higher partition coefficient ($\log P$) in lipid bilayers.³⁵⁴ This observation was rationalized by the authors, who suggest that the trapping of the more membrane-soluble *para*-forms reduces the amount of free molecule to interact with the H^+ -ATPase. In results that seem at odds with later reports,^{357–361} the authors claim that b1 was unable to disrupt a pre-established proton gradient across liposomal membranes at μM concentrations, meaning that the reduction in ATPase activity could not result from a membrane-permeabilization effect. The authors thus conclude that the inhibition of phosphohydrolytic activity created by beticin toxins is the result of a direct action on the enzyme (specific mode of action).³⁵⁶

In an exciting development, Thibaud and co-workers reported in 1998 that b0 was able to assemble at cytotoxic levels and in the presence of Mg^{2+} ions into multimeric, nonspecific transmembrane channels through the lipid bilayer, with multiple conductance states, as determined via patch-clamp techniques (i.e., nonspecific mode of action; see Figure 70).³⁵⁷ Both *Arabidopsis* and *Xenopus* cell membranes demonstrated increased membrane conductance in the presence of b0 in a Mg^{2+} -dependent manner. That the effect was not due to endogenous properties of those membranes was exhibited by the recreation of these results with synthetic planar-lipid bilayers; instead, the increase in membrane conductance is due to the formation of nonselective channels. These were permeable to Cl^- , K^+ , Na^+ , and Ca^{2+} ; the latter is of potentially great importance, as it may lead to scrambling of

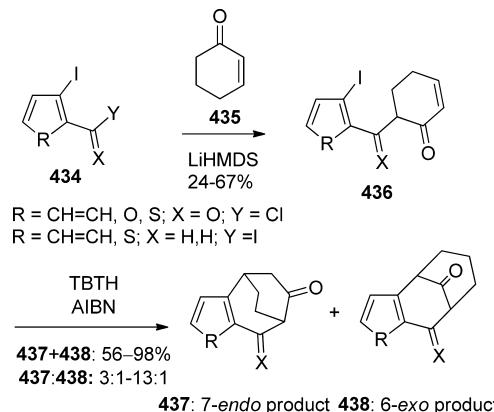
intracellular processes.³⁵⁷ The formation of such channels from nonpeptide compounds is fascinating and extremely rare, but has been observed for another molecule.³⁶⁰ When protein-free lipid bilayers were studied in the absence of Mg²⁺, discrete current transitions were observed, similar to the function of individual ion channels. Upon the addition of MgCl₂, macroscopic currents were recorded; the addition of EDTA (strong Mg²⁺ chelator) reversed this current and returned the single-channel current. Ca²⁺ was unable to produce such a macroscopic current. Because the length of the b0 molecule is ~17 Å,³⁴³ a multimer of dimers may be responsible for the channel formation across the 30 Å thick lipid bilayer. That the Mg²⁺ ion promotes formation of such a multimeric structure is supported by the clearly dosage-dependent conductance response curve.³⁵⁷

In a follow-up publication, b3 was demonstrated to form voltage-independent ion channels with multiple conductance levels, each increasing level double that of the last.³⁵⁸ The authors suggestion that this is due to a cluster structure opening, rather than the alternative of different structures coexisting in the lipid bilayer, was supported by the independence of pore size and selectivity with respect to conductance level. The authors suggest a 3D structure for the pore, as formed from X-ray crystal structures of *para*-beticolins b1³³⁵ and b3,³⁴³ to be a twisted rectangle/trapezoid, open at opposite ends, which several could arrange together to form a channel through the membrane with a maximum pore size of 7.5 Å (see also Figures 68 and 69).³⁵⁸

A final paper detailed a comparative study of *ortho*-beticolins b0, b2, and b4 and *para*-beticolins b1, b3, and b13, all of which formed multiple-conductance-level ion channels in planar-lipid bilayers.³⁵⁹ Interestingly, ion channels composed of the *para*-beticolins give 20–30% higher conductance levels than the corresponding *ortho*-isomers. The nature of the R groups in the pore center also influences the conductance, with the 2-methyloxirane species outperforming the 2-(hydroxy)-methyloxirane and methylethene species. There was little difference in selectivity between the three forms, all being cation-selective.³⁶⁰ This channel formation is likely involved in the biological activity of the compounds, presumably through the associated disruption of cellular ion gradients, and the associated effect of causing membrane depolarization.^{344–347,352} This may be the (nonspecific) mechanism by which they inhibit the plasma membrane H⁺-ATPase. It also may be the mechanism by which cellular levels of amino acids and other valuable solutes are depleted upon exposure to the toxins, as glucose and even sucrose may travel through the poorly selective channels.³⁵⁸ Thus, evidence has been presented in support of both the specific (direct enzyme target) and nonspecific (ion channel assembly) mechanisms of membrane depolarization, although the latter now seems irrefutable.

Synthesis. To date, there have not been published any whole or partial syntheses of any member of the beticolin family. Beticolin 2 (Figure 67) was found by HPLC to be the beticolin most prevalent in the crude mycelial extract, indicating a degree of stability *in vivo* and through the extraction process.³⁴⁰ Duffault and Tellier have detailed a nucleophilic substitution/7-*endo*-trig radical cyclization pathway to species containing the bicyclo[3.2.2]nonene core (437, Scheme 33).³⁶² Yields in the nucleophilic addition step were poor to fair, something the authors ascribe to necessary use of crude acid chlorides and the instability of the di-iodo substrates. However, the following cyclizations gave moderate to excellent yields, and

Scheme 33. Radical Synthesis of Bicyclo[3.3.2]nonenes³⁶²



the selectivity between the desired pathway to 437 and a competing 6-*exo* product, 438, was generally good.³⁶²

The beticolins are the first reported members of a new class of heterodimer compounds constituted of xanthone and anthraquinone components: xanthraquinones.³⁴³ These now also include acremoxanthones, chrysoxanthone, JBIR-97-99, and the xanthoquinodins (see later).

Chrysoxanthone. Anke and co-workers isolated and identified chrysoxanthone (439, Figure 71), from the

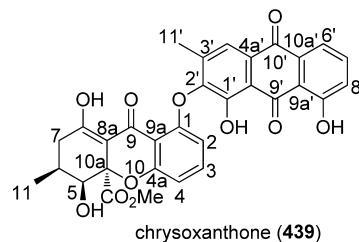


Figure 71. Chrysoxanthone.

ascomycete IBWF11-95A, and identified it as a heterodimer of ergochrome B (or blennolide A; see 250), and anthraquinone. It is thus a relatively new member of the xanthraquinone family (alongside the acremoxanthones, beticolins, and xanthoquinodins).³⁶³ The characterization and determination of relative configuration was carried out with a variety of 1D and 2D NMR techniques, and the CD spectrum was in accordance with data from blennolide A, giving the absolute structure in Figure 71. The linkage of a xanthone by diaryl ether is specific to this molecule. The synthesis of an ether linkage between two xanthenes has been recently reported by Sahin, Nieger, and Bräse.⁶³ Chrysoxanthone displayed antibacterial and antifungal properties against several species, which can be related to the properties of its individual components.

Dicerandrols. The dicerandrols A–C (440–442, Figure 72) were isolated from *Phomopsis longifolia*, an endophytic fungus found to be growing on the endangered Floridian mint species *Dicerandra frutescens*.³⁶⁴ The structures were determined using NMR experiments in combination with a positive FeCl₃ experiment, which is indicative of a *para*-unsubstituted phenol (meaning here that the dimer must be commonly 2,2'-linked). The relative configuration of these was determined to be the same as for secalonic acids B and E (see later). These species had antimicrobial activities against *Bacillus subtilis* and *Staph-*

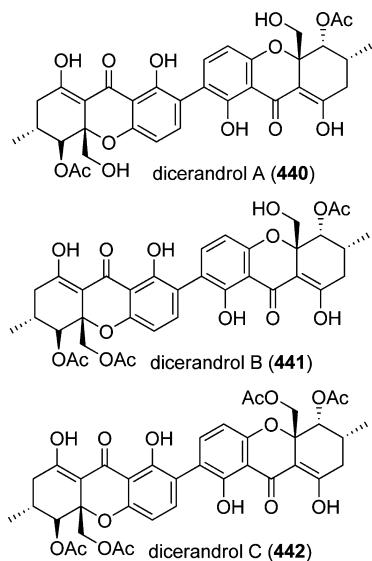


Figure 72. Dicerandrols A–C.

yloccoccus aureus, which were correlated to their extent of acylation (i.e., C > B > A); however, dicerandrol B had the best activity across two cancer cell lines, HCT-116 and A549 (colon and lung tumor, respectively).³⁶⁴

Ergochromes. “Ergochromes” is a collective name for a group of compounds including secalonic acids and the closely related ergoflavins, ergochrysins, and chrysergonic acid, all of which can be described as “ergochrome dimers”. The secalonic acids are homodimers of two esters; the ergochrysins are heterodimers of one lactone and one ester, whereas the ergoflavins are homodimers of the lactone species.⁴⁰⁴ They are a relatively widespread group of symmetrical or semisymmetrical dimeric xanthone mycotoxins, first reported as a single compound of the formula $C_{14}H_{14}O_6$ by Kraft in 1906 after isolation from *Claviceps purpurea*.³⁶⁵ The mixture of toxins produced by this fungus were responsible for the toxicity and debilitating effects of the famous cereal-contamination epidemics known as ergotism or “St. Anthony’s Fire” in middle-ages Europe. Bergmann in 1932 detailed the isolation of ergochrysin³⁶⁷ and ergoflavin³⁶⁶ from *C. purpurea* extracts and identified them as dimers with the formula $C_{28}H_{28}O_{12}$.³⁶⁷ A number of papers followed in the 1950s to 1970s, over which time more secalonic acids were isolated and structurally elucidated. In addition, various members of the family have been isolated from other fungi, including *Aspergillus ochraceus* (SAA = secalonic acid A),³⁶⁸ *Aspergillus aculeatus* (SAB, SAD, SAF),^{369,370} *Aspergillus japonicus* (SAF),³⁷¹ *Penicillium oxalicum* (SAD),³⁷² *Phoma terrestris* (SAA, SAE),^{373,374} *Pyrenophaeta terrestris* (SAA, SAE, SAG),³⁷⁵ *Paecilomyces* sp. (SAD),³⁷⁶ and, of course, *C. purpurea* (SAA, SAB, SAC).^{377–382} Secalonic acids have also been found in lichens, including *Diploicia canescens* (SAB, SAD, SAF),³⁸³ *Physiconia distorta* (SAA),³⁸⁴ *Parmelia entothelechroa* (SAA),³⁸⁵ *Pseudoparmelia hypomiltha* (SAA),³⁸⁶ *Cetraria ornata* (SAA),³⁸⁷ *Gliocladium* sp. T31 (SAD),³⁸⁸ *Penicillium atramentosum* (SAA),³⁸⁹ and *P. chrysogenum* and *P. confertum* (both SAD and SAF).³⁹⁰

Isolation and Structural Determination. Because of the early time at which they were isolated, modern spectral methods were not available to facilitate the (nontrivial) structural elucidation of the ergochromes, and early reports on these compounds frequently contain structural errors.

Ergochrysin was first isolated by Freeborn in 1912.³⁹¹ In 1931 Barger and co-workers also isolated ergochrysin,³⁹² as did Bergmann in 1932,³⁹³ although initially secalonic acid and ergochrysin were assumed to have the same identity. Whalley and co-workers reported that pigments, comprising 1–2% of the mass of *C. purpurea*, contain ergoflavin, which they identified as a dilactone dimer with the formula $C_{30}H_{26}O_{14}$, after it was originally reported as a monomer, $C_{15}H_{14}O_7$.³⁹⁴ In 1952 Stoll, Renz, and Brack isolated a new compound, chrysergonic acid, with the formula $C_{32}H_{30–32}O_{14}$.³⁹⁵

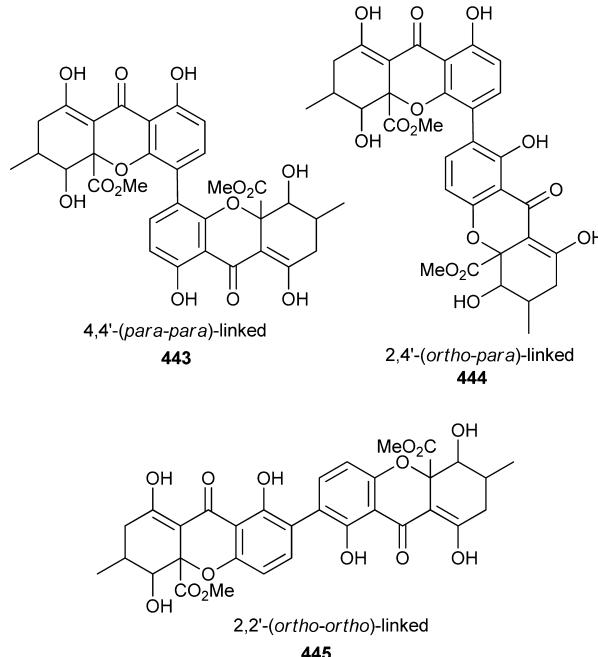
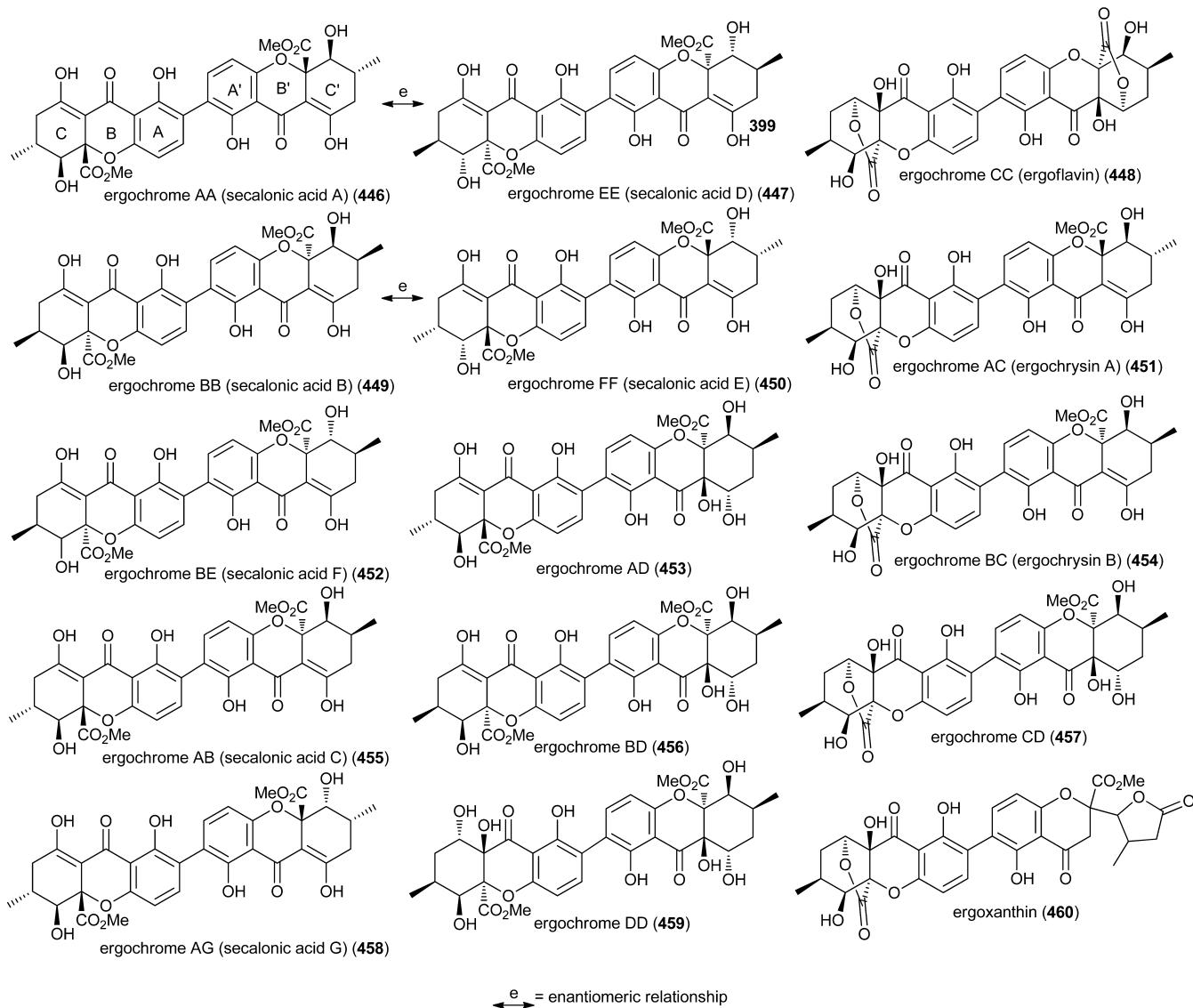


Figure 73. Secalonic acids: proposed 4,4'-, 2,4'-, or 2,2'-linked structures.

Franck and co-workers originally proposed a structure of a secalonic acid as a dimeric, diphenolic compound connected in a 4,4' fashion (i.e., *para-para* to the phenolic moieties, 443, Figure 73).³⁷⁷ A 1962 paper from his group detailed the isolation and the attempted chemical identification of secalonic acid/ergochrysin through selective chemical degradation and derivatization pathways.³⁷⁸ In 1963, Franck and Baumann published a paper detailing having determined that the bichromonyl product of alkaline degradation is either a *para-para*, *para-ortho*, or *ortho-ortho* linked bichromyl species.³⁷⁹ The authors chose the former option, based upon the negative Gibbs reaction test, which is normally positive for aromatic species containing a proton *para* to the phenolic moiety. They then report the synthesis of related substituted bichromonys through *para*-selective iodination and Ullmann coupling.³⁷⁹ The following year, Franck and Gottschalk detailed the isolation of a secalonic acid diastereomer, this time named secalonic acid B (449, Figure 74).³⁸⁰ Suggestions were made on the structure of secalonic acids A and B, including stereochemistry, based on the generation of *R*(−)-configured methyl succinic acid from ozone decomposition of secalonic acid; however, the connection between the two monomers was still thought to be *para-para* (4,4') at this stage.³⁸¹

DeMayo, Aberhart, and co-workers reported in 1965 on the isolation in crystalline form of six compounds from a Portuguese ergot drug.³⁸² In contrast to earlier re-

**Figure 74.** Ergochromes.

ports,^{380,382,396} these authors found that all compounds gave a positive Gibbs test, possibly indicating the presence of a free *para*-position to the phenolic moiety and, thus, a 2,2'-linkage.³⁸² These compounds proved to be secalonic acid B (449, Figure 74), secalonic acid C (455), ergochrysin A (451), ergochrysin B (454), ergoflavin (448), and a novel compound that the authors named ergoxanthin (460). The authors submitted a report the following year on the constitution of the latter compound.³⁹⁷ They determined through chemical derivatization, degradation, and spectroscopic techniques that the structure contained both γ -butyrolactone and dihydrochromone moieties. They suggest that this ergoxanthin may be derived from ergochrysin A or B (451 or 454) by oxidative cleavage between the two ketones and subsequent lactonization.

Franck and Baumann reported ergochromes AD, BD, CD, and DD (453, 456, 457, and 459, respectively, Figure 74).³⁹⁸ In the same year they described the absolute configuration of secalonic acids A, B, and C, as determined by a variety of techniques including CD and NMR spectra and chemical degradation studies. The first two of these compounds were still incorrectly ascribed 4,4'-linkages.³⁹⁹

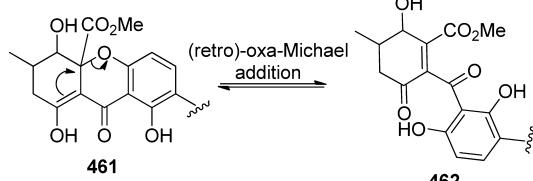
Whalley and co-workers initially isolated ergoflavin (448, Figure 74) from the complex mixture of ergot pigments and defined it as a tetraphenolic dimer with the formula $C_{30}H_{26}O_{14}$ after performing chemical degradation studies that gave *ortho*-*ortho*-linked biphenyls.⁴⁰⁰ The group then later followed this publication with details of the structure of ergoflavin⁴⁰¹ and then followed with details of the stereochemistry of these species, including the oxidation of ergoflavin to yield (*R*)-(-)-methylsuccinic acid. This information enabled the assignment of other stereocenters based on relative configuration.⁴⁰² Robertson and co-workers reported at the same time on the structures of ergochrysin A, secalonic acid A, and secalonic acid B (449), using single-crystal X-ray analysis,⁴⁰³ chemical degradation, and spectroscopic methods, and claimed that all have the "linear" or *ortho*-*ortho*-linked structure.^{396,404} The authors discuss possible biosynthetic routes to the ergot pigments, starting with an acetate- or malonate-derived quinone, which can be oxidatively coupled to form the observed dimers. They also note that ergochrysin is converted to an isomer, isoergochrysin A, upon exposure to pyridine.⁴⁰⁴ Ergochrysin A (451, Figure 67) is converted to (\pm)-methylsuccinic acid by $KMnO_4$ oxidation, meaning the two halves of

the dimer must be oppositely configured at the methyl substituent. A retro-oxa-Michael addition is invoked in this paper to explain the observed generation of benzophenone derivative from ergochrysin A. Finally, the authors conclude that secalonic acids A and B are *para*-*para*-linked dimers with a diastereomeric relationship and that ergochrysin A and ergoflavin are *ortho*-*ortho*-linked dimers.⁴⁰⁴

Franck and co-workers in 1965 reported a more comprehensive analysis of the ergochrome constituents of *C. purpurea*; this time a total of 10 dimers were isolated. In addition to the already known secalonic acids A (446, Figure 62) and B (449) and ergoflavin (448), a new homodimer was identified, which the authors named "ergochrome DD" (459), as well as the remaining six heterodimers possible with the combination of one subunit of each of those four species (A, B, C, and D subunits; see Figure 62), the majority of which they identified as 2,2'-(*ortho*-*ortho*)-linked.⁴⁰⁵ The ergochromes are thus diastereomeric at positions 6,6', 5,5', 10, and 10'. The absolute stereochemistry at these centers was determined based upon the isolation of (*R*)-methylsuccinic acid and the observed relative chemistry of the ring with respect to the methyl at C-6.⁴⁰⁵ The authors also showed that the "D" unit of ergochromes could be converted to the lactone "C" units in acidic solvents (e.g., acetic acid).⁴⁰⁵

Franck and Baumann reported the structure of ergochrysins A and B in 1966, this time determined by extensive spectroscopic analysis. Each of these species is a heterodimer, with ergochrysin A being ergochrome AC and ergochrysin B being ergochrome BC.⁴⁰⁶ Different relative peak heights for the two compounds in the mass spectrum for the molecular ion and a peak corresponding to $[M - CO_2Me]^+$ reveal that ergochrysin A loses this fragment more readily than ergochrysin B. Another paper from Franck et al. in 1968 investigated the biosynthesis of the ergochrome class of compounds with 1-¹⁴C, 2-¹⁴C, and 1-³H sodium acetate feeding of several *Claviceps* species.⁴⁰⁷ The results indicated that the species are acetate-derived and that an anthraquinone intermediate is involved in the biosynthetic pathway, which proceeds to the ergochromes with oxidative ring-opening and subsequent oxa-Michael addition (see Schemes 27 and 29). The authors exposed radioactive shikimic acid to the *Claviceps* cultures, but this material was not fed into the ergochrome species isolated at the end,⁴⁰⁷ which is due to the contrasting xanthone biosynthesis pathways in fungi to those found in plants (which use shikimic acid as a biosynthetic precursor).⁴⁰⁸

Scheme 34. Retro-oxa-Michael Ring-Opening⁴⁰⁴

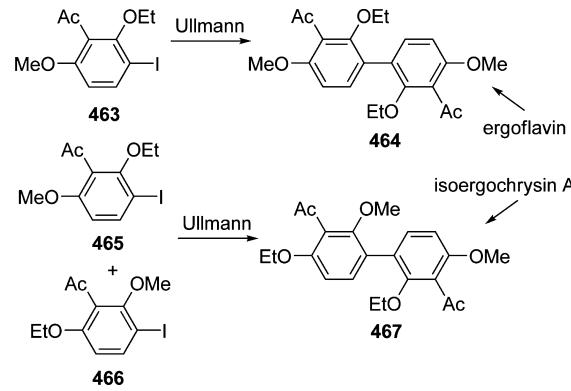


Steyn isolated secalonic acid D from several strains of *Penicillium oxalicum*, also a fungus causing toxicity through contamination of foodstuffs.³⁷² This compound was identified as a dimer of the hexahydroxanthone type. Tests with sodium cobalt nitrite suggested an absence of *ortho*-coupling between the two monomers. Spectral details between secalonic acid A and this novel species were almost identical, and the optical

rotation was equal but opposite. The ORD (optical rotator dispersion) and CD spectra were essentially mirror images; the authors thus concluded that secalonic acid D (447, Figure 74) is the enantiomer of secalonic acid A (446).³⁷² Spectroscopic data and comparison with other species allowed the absolute configuration to be assigned; however, the authors nonetheless reported this species as being 4,4'-linked.

Whalley and co-workers reported a partial synthesis of ergoflavin in 1971.⁴⁰⁹ This paper contained a convergent synthesis of a degradation product from secalonic acids as well as a study of ¹H NMR data, which provided proof that the secalonic acids all have in common a 2,2'-linkage, not the 4,4'-linkages that had been hitherto tentatively suggested based mainly on erroneous Gibbs test results. Whereas ergochrysin A has a 2,2'-linkage, isoergochrysin (not shown) has a 2,4'-linkage, resulting from retro-oxa-Michael addition and ring-closing isomerization at the B-ring of the molecule under basic conditions.⁴⁰⁹ The next paper from these researchers further confirmed that all the ergot pigments (secalonic acids A, B, C, and D, ergoflavin, and ergochrysins A and B) have the 2,2'-linked structures.⁴¹⁰ Ergochrysin A (451, Figure 74) can be ring-opened and isomerized to the derivative isoergochrysin; this interconversion takes place with retro-oxa-Michael ring-opening and ring-closing steps and reaches an equilibrium position in the presence of sodium–hydrogen carbonate. This isomerism must be highly selective, due to restricted rotation of the benzophenone intermediate, as no other diastereomers are found. The authors also found that the bichromone degradation products of Franck had been previously misidentified as 4,4'-linked. The identity of the biaryl linkage was proven via convergence of degradation and synthesis pathways to biaryls 464 and 467 (Scheme 35). NMR signals of the methoxy groups also reveal the nature of the biphenyl.⁴¹⁰

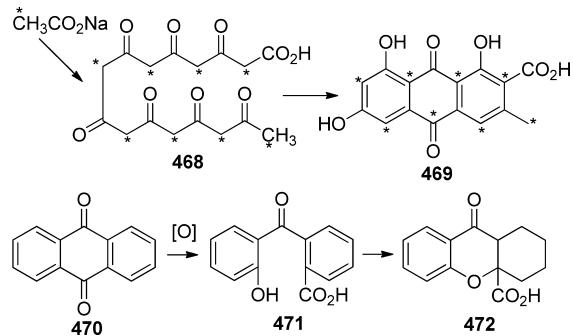
Scheme 35. Chemical Degradation and Ullmann Condensation Converges to Demonstrate 2,2'-Linkage in Ergoflavin and 2,4'-Linkage in Isoergochrysin



Howard and Johnstone reported the mass spectra of secalonic acids A–E, which contain common peak-ratio patterns related to the relative stereochemistry of the chiral centers.⁴¹¹ Particularly, a fragment peak resulting from the loss of CO₂Me at C10a is roughly three times greater in the *cis*-hydroxyl than in the *trans*-hydroxyl in the C6-position. In a similar fashion, the peak resulting from a loss of H₂O is related to the relative stereochemistry between the C5-position methyl relative to the C6 hydroxy; the authors thus suggest that the relative stereochemistry of new secalonic acids can be determined based on the mass spectrum.⁴¹¹

In 1973 Johnstone and co-workers reported the isolation of a new species from the family, which they named secalonic acid E (450, Figure 74), from the phytotoxic fungus *Phoma terrestris*.^{373,374} The new acid was isolated alongside secalonic acid A, which differs only in the orientation of the secondary hydroxyl group at C5, possibly due to nonselective cyclization from a benzophenone intermediate of the type 471 (Scheme 36). The oxidation of this species with KMnO₄ gave (R)-

Scheme 36. Biosynthetic Pathway to Secalonic Acid Components⁴⁰⁷



(+)-methylsuccinic acid, and the H5 and H6 protons were determined to be equatorial to one another by NMR ($J < 2$ Hz). Through mass-spectral,⁴¹¹ CD-spectral, and IR data, the relative configuration of the methoxycarbonyl and hydroxy groups was determined to be *trans*. Thus, the new secalonic acid E had the structure shown (450, Figure 74) and is the enantiomer of secalonic acid B (449).^{373,374}

Howard, Johnstone, and co-workers furthered their studies of this compound class with a single-crystal X-ray structure of secalonic acid A (446, Figure 74) in 1976.⁴¹² This structure confirmed the 2,2'-biphenyl linkage (initially proposed from ¹H NMR data) and the stereochemistry around the C5, C6, and C10a positions. In the crystal structure of secalonic acid A, the angle between the two biphenyl planes was determined to be 36.5°.⁴¹²

Kurobane and Vining reported the result of (1,2-¹³C)-labeled acetate feeding experiments with *Pyrochaeta terrestris* and ¹³C NMR analysis of the subsequently isolated secalonic acid A.³⁷⁵ Results indicated (a) that the sequence octaketide-anthraquinone-benzophenone-tetrahydroxanthone-ergochrome (Scheme 36) is consistent with the data obtained and (b) that xanthone ring formation cannot follow dimerization, as scrambling of labeled ¹³C at the aromatic phenoxy carbon is observed. The authors further note that rotational scrambling of the ¹³C phenol can only occur in the intermediate benzophenone 471 if it is not tightly bound to an enzyme surface, as the observed equivalent distribution of ¹³C label in secalonic acid shows that the benzophenone has reached rotational equilibrium prior to dimerization.³⁷⁵

Johnstone and Howard studied changes in ¹H NMR chemical shifts of secalonic acids A and E due to the effect of solvents and transition metals.⁴¹³ The distance of the proton(s) from the hydroxyl group determines the degree of chemical shift induced upon changing solvent from CHCl₃ to pyridine, which induces an anisotropic effect (due to hydrogen-bonding of pyridine to the hydroxyl moiety). The resulting change in shifts can be used to determine the configuration of the C-5(C-5') hydroxyl-bearing and C-6(C-6') methyl-bearing positions in the secalonic acids; for example, secalonic acid A (*trans*-

relationship) has a lesser shift for the methyl group at this position than does secalonic acid E (*cis*-relationship). The authors further developed an equation for this phenomenon that displayed general applicability with unrelated chemical species (e.g., hydroxycholestanes) and suggested that it may be useful for the structural elucidation of other fungal metabolites and natural products.⁴¹³

In 1977 Büchi and co-workers reported the isolation of the novel secalonic acid F (452, Figure 74, ergochrome BE) alongside secalonic acid D (447, ergochrome EE) from the fungus *Aspergillus aculeatus*.³⁶⁹ Comparison of the CD spectrum with that of other secalonic acids provided conclusive evidence that the configuration at C10(C10') was (R)-(-)-, and oxidation with KMnO₄ correspondingly gave (S)-(-)-methylsuccinic acid. The following year, novel secalonic acid G (458, Figure 74) was isolated alongside secalonic acids A and E from *Pyrenophaeta terrestris* and the structure elucidated by CD and NMR spectroscopy.⁴¹⁴ The 2,2'-linkage was established using deuterium isotope ¹³C chemical shift measurements of the acids and acetylated derivatives.³⁶⁹

Structure. The secalonic acids and related species are composed of several monomeric units (hemisecalonic acids A–F), which are arranged in a variety of dimers and heterodimers to give the many ergochromes known so far.⁴¹⁵ In all known secalonic acids, the methyl and methoxycarbonyl substituents are found to be *trans*. The linkage between the two aryl positions must be, based on an AB coupling of the two proton substituents of each of these rings, either 2,2', 2,4', or 4,4'. The secalonic acids are 2,2'-linked; nonetheless, the remaining possible modes of biaryl linkage have been found since in nature. The related eumitrins (493–495, Figure 75) are 2,4'-linked, whereas phomoxanthone A (572, Figure 84) is 4,4'-coupled. The secalonic acids have been revealed by shielding effects in NMR spectra⁴⁰² and X-ray diffraction to be nonplanar^{402–404} and instead have a large dihedral angle. The neutral, alkaline, and difference UV spectra of SAD have been reported.³⁸⁰

Bioactivity. Secalonic acid D (SAD) is an environmental toxin of interest, being isolated from *Penicillium oxalicum*, the dominant *Penicillium* species on freshly harvested corn (in one study contaminating 44% of the preharvest corn crop in the midwestern United States).⁴¹⁶ SAD was lethal to mice when injected intraperitoneally in the 25–50 mg/kg range, although this compound did not display toxicity to chick embryos.^{417,418} In light of this finding, together with the numerous toxic effects of this compound, researchers developed a technique to detect levels of SAD in biologically derived samples.⁴¹⁹ Teratogenic effects were observed in the development of rats that were exposed to SAD injected during fetal development. The results are alarming, given that this compound is known to contaminate foodstuffs; the rate of birth defects and spontaneous abortions caused by such teratogenicity in humans is disturbingly frequent.

Secalonic acids D and F displayed antimicrobial activity against *Bacillus megaterium*,³⁶⁹ whereas secalonic acid A displayed activity against *Bacillus subtilis* and *Piricularia oryzae*.⁹ Secalonic acid derivatives have also been suggested to be potential anticancer compounds.⁴²⁰ Screening for cytotoxic agents against myeloid leukemia revealed the extracts of marine-derived lichen *Gliocladium* sp. T31 to be highly toxic. Bioassay guided fractionation delivered secalonic acid D as the active agent across four cell lines in a range of 0.03–15 μM, indicating some selectivity in the mechanism of action.³⁸⁸ SAD

isolated from the mangrove-tree-derived endophytic fungus *Paecilomyces* sp. was additionally demonstrated to be cytotoxic to KB cells with an $IC_{50} < 1 \mu\text{g}$ per mL and inhibited human topoisomerase I with an IC_{50} of $0.16 \mu\text{mol}$ per mL.³⁷⁶ Investigations into the mechanism of action of SAD derivatives against the Meth-A fibrosarcoma revealed that the antitumor activity is mainly responsible to inhibition of Meth-A cell proliferation.⁴²¹ Secalonic acids B and D were tested against B16 murine melanoma HaCaT and found to be active in the low micromolar range, although stronger against the former than the latter.³⁸³

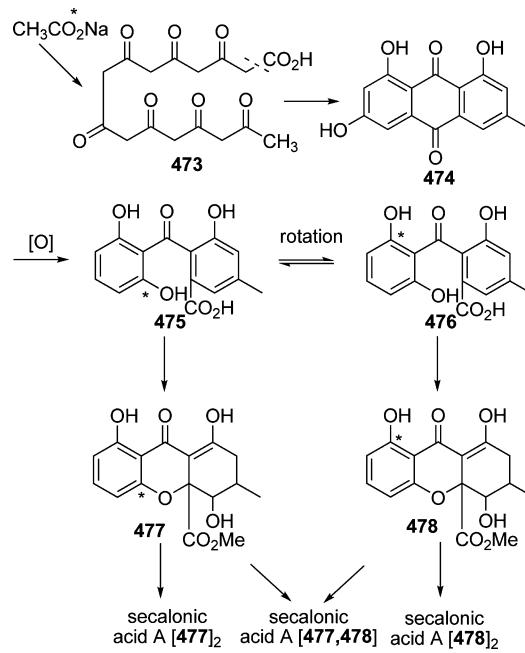
SAD was shown to be an inhibitor of protein kinase C (PKC)^{422,423} and several other Ca^{2+} -dependent enzymes, which is likely due to competitive binding of secalonic acid in the active site region of the enzyme, as demonstrated in the case of cyclic AMP-dependent protein kinase (cAK).⁴²² This binding could interfere with cell-signaling pathways and thus be involved in the teratogenic activity displayed by this toxin. This is in contrast with other known natural teratogens tested by the authors, which do not inhibit the protein kinases tested. Reddy et al. studied the exposure of mice to secalonic acid, which serves as a model for induction and study of cleft palate, and identified secalonic-acid-induced reduction of palatal levels of epidermal growth factor (EGF).⁴²⁴ Reddy et al. also described the inhibition of epidermal growth factor signaling in developing mice that had been exposed to SAD.⁴²⁴ The mechanism by which SAD is teratogenic was further elucidated by another report, which described the inhibition and alteration of transcription factors in the developing murine palate, when exposed to the toxin at normal human dietary levels.⁴²⁵ These same authors found that the induction of cleft-palate syndrome may be related to the SAD-promoted phosphorylation of palatal cAMP-protein response element binding protein (CREB)⁴²⁶ and that these results are due to reduced cellular proliferation rather than cell death.⁴²⁷ Both could lead to reduced palatal mesenchymal cell number, smaller palatal shelf, and, thus, cleft palate.

Secalonic acid B (**449**, Figure 74) was tested alongside the blennolides A, B, D, and E for biological activity, and all were found to be antifungal (*Microbotryum violaceum*) and antialgal (*Chlorella fusca*).⁴¹⁵ Additionally, secalonic acid B proved to be an effective antimicrobial agent against Gram-positive (*Bacillus megaterium*) and Gram-negative (*Escherichia coli*) bacteria.⁴¹⁵

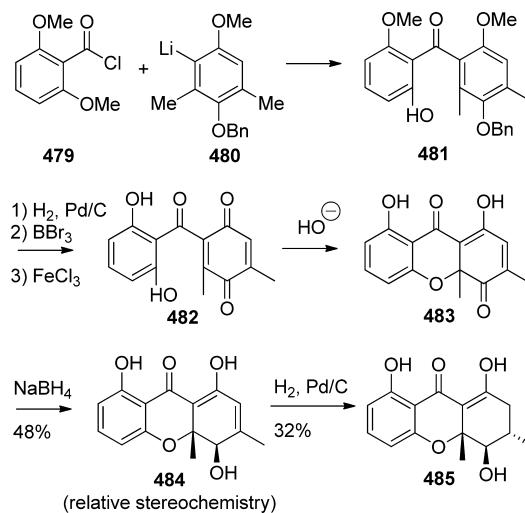
Synthesis. Franck and co-workers reported in 1973 the stereoselective synthesis of a *des*-carboxyl hemisecalonic acid, wherein the methoxycarbonyl moiety is replaced by a methyl group.⁴²⁸ The synthesis involved nucleophilic addition of aryllithium **480** (Scheme 38) to aryl chloride **479** and conversion of the resulting benzophenone **481** by oxidation, base-mediated ring-closure to a dihydroxanthone species **483**, then stereoselective reductions via **484** to **485**. The resulting tetrahydroxanthones have three stereocenters with the same relative stereochemistry as found in secalonic acid A.

Bräse and co-workers described a novel one-pot methodology for the synthesis of symmetrical biaryls as a part of their ongoing investigations in the synthesis of the secalonic acids, their monomeric units, and related tetrahydroxanthones.⁴²⁹ Building on methodology developed by Miyaura et al. for the synthesis of boronic acids by palladium coupling of arylhalides with bis(pinacolato)diborane (Scheme 32),⁴³⁰ these researchers effectively modified the original conditions through the use of a more nucleophilic base (potassium carbonate rather than acetate). The new conditions promoted the Suzuki cross-

Scheme 37. Biosynthetic Sequence Consistent with the Findings of Kurobane and Vining³⁷⁵



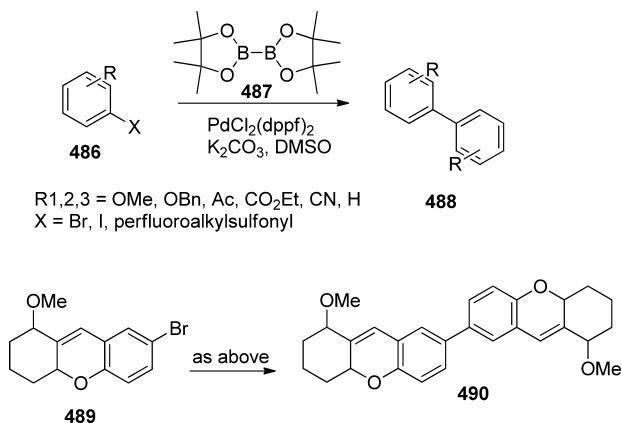
Scheme 38. Franck's Synthesis of *des*-Carboxyl Hemisecalonic Acid (Representative Stereochemistry Shown)



coupling of the in situ formed arylboronic ester (not shown) with a molecule of starting aryl halide or equivalent **486** due to the enhanced nucleophilicity⁴²⁹ of a proposed intermediate pentacoordinated palladium species.³⁹⁴

The resulting symmetrical biaryls **490** (Scheme 39) were formed under mild conditions (K_2CO_3 , DMSO, 80°C). It was furthermore found that the addition of a chelating diphenylphosphinoferrocene (dpf) ligand improved the reaction by suppressing the degradation of catalyst in the form of palladium black. The yields were substrate-dependent (steric effects appear important) but tolerated a range of functional groups and incorporated several (heterocyclic) aromatic cores with varying success (40–94% isolated yield, 21 examples). The methodology was also successfully applied to the synthesis of a

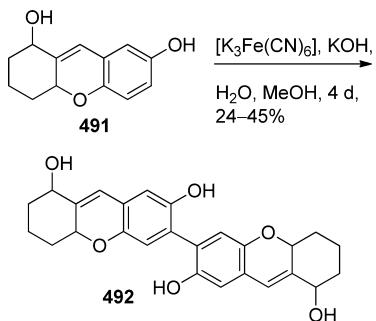
Scheme 39. Bräse's One-Pot Biaryl Synthesis



secalonic acid model, bisxanthene **490**, through the reaction of 2 equiv of bromide **489** (Scheme 32).

Sahin, Nieger, and Bräse have also published on the oxidative coupling of various hexahydroxanthenols. The application of an iron complex as oxidant converted 2-hydroxy-substituted xanthenes **491** (Scheme 40) to the 3,3-bis-coupled biaryl **492**.⁶³ It appears that these two papers represent the only chemistry published on the topic of xanthone or xanthene biaryl coupling.

Scheme 40. Bräse's Oxidative Biaryl Synthesis



Eumittrins. Eumittrins were identified as the yellow pigments in *Usnea bayleyi* by Asahina;⁴³¹ eumittrins A and B were later isolated by Nuno.⁴³² Takeda and co-workers then identified eumittrins A1, A2, and B (**493–495**, Figure 75) through spectroscopic techniques and found them to be related to the secalonic acids.⁴³³ NMR data was used to ascertain the structures, particularly with respect to the relative configuration at the tetra- and hexahydro-xanthone rings, and the acetylation of these compounds resulted in chemical shift changes consistent with a *para*-*ortho*-(2,4')-linkage.

A confirmation of these structures, including partial absolute configuration, was performed by single-crystal X-ray analysis of a tribromo derivative of eumitrin B, although the configuration of the methoxycarbonyl junction in the 4-coupled xanthone components of **493–495** cannot be determined due to a ring-opening process during bromination.⁴³³ The eumittrins appear to have inhibitory effects upon the formation of nitric oxide in vivo.⁴³⁴

Hirtusneanoside. Hirtusneanoside (**496**, Figure 76), a L-rhamnose-O-deoxyglycoside of an unsymmetrical dimeric tetrahydroxanthone, was first isolated from the lichen *Usnea hirta* in 2007 by Rezanaka and Sigler.²⁵⁹ The structure is of

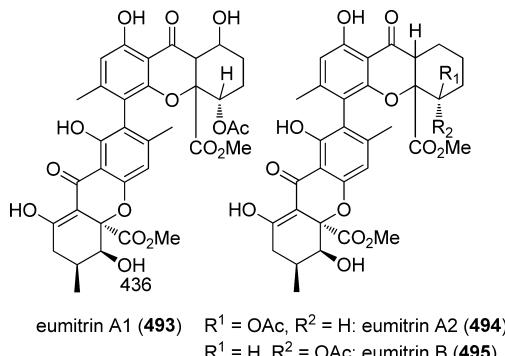


Figure 75. Eumittrins A1, A2, and B.

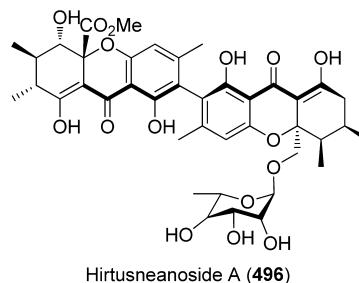


Figure 76. Hirtusneanoside (absolute configuration shown).

particular interest, as it bears an additional methyl in relation to the secalonic acids. Hirtusneanoside displayed low-micromolar LD₅₀'s against *Staphylococcus aureus* and *Bacillus subtilis* but not Gram-negative bacteria and yeast.

The absolute configuration was also determined with a combination of spectroscopic techniques and chemical degradation studies, including enzymatic hydrolysis with hesperidinase, which specifically catalyzes the hydrolysis of α-L-rhamnose, yielded this sugar with an optical rotation correlating with literature values. Oxidation of the aglycone yielded (R)-(-)-methylsuccinic acid and 2*R*,3*R*-dimethylsuccinic acid. Additionally, rotation around the biaryl 2,2'-linkage is restricted; the absolute configuration at this chiral axis was determined by its CD spectrum to be as the atropisomer shown in Figure 76.²⁵⁹

JBIR-97, -98, and -99. In 2010 Ueda, Takagi, and Shin-ya reported the isolation and structural determination of three new anthraquinones, JBIR-97, -98, and -99 (**497–499**, Figure 77), after isolating them from the culture of *Triterachium* sp. (spB081112MEf2), a fungus derived from the marine sponge *Pseudoceratina purpurea*.⁴³⁵ The compounds contain the familiar central bicyclo[2.2.1]system as found in the beticolins and xanthoquinodins (see previously and later, respectively). The authors used a barrage of MS and NMR techniques, as well

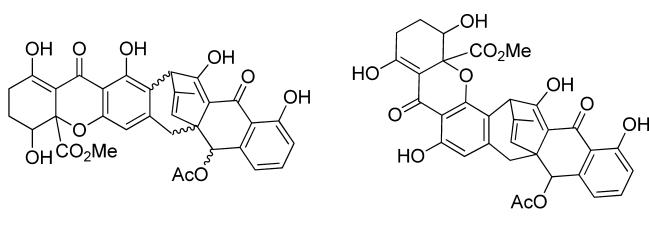


Figure 77. JBIR-97–99.

as comparison with spectral data published for the xanthoquinodins, to propose possible structures. They propose that JBIR-97 and -98 (**497** and **498**, Figure 77) are diastereomers at either the two bridgehead positions or the acetate moiety, whereas JBIR-99 is most likely the positional isomer (**499**). The compounds were also tested for activity against HeLa and ACC MESO 1 cell lines and found to be consistently cytotoxic with IC₅₀'s in the 11–59 μM range.

Kibdelones. Kibdelones A–C (**500**, **502**, and **504**, respectively, Figure 78), isokibdelone A and isokibdelone A–C (**501**–**505**), isokibdelone C rhamnoside (**506**), and 13-oxokibdelone A (**507**) are shown in Figure 78. The structures are labeled with their respective R groups: R = H for kibdelone A (**500**), R = Rh for kibdelone A rhamnoside (**501**), R = H for kibdelone B (**502**), R = Rh for kibdelone B rhamnoside (**503**), R = H for kibdelone C (**504**), R = Rh for kibdelone C rhamnoside (**505**), R = H for isokibdelone A (**507**), R = Rh for isokibdelone A rhamnoside (**508**), R = OH for 25-hydroxy-24-oxokibdelone C (**510**), and R = OMe for 25-methoxy-24-oxokibdelone C (**511**).

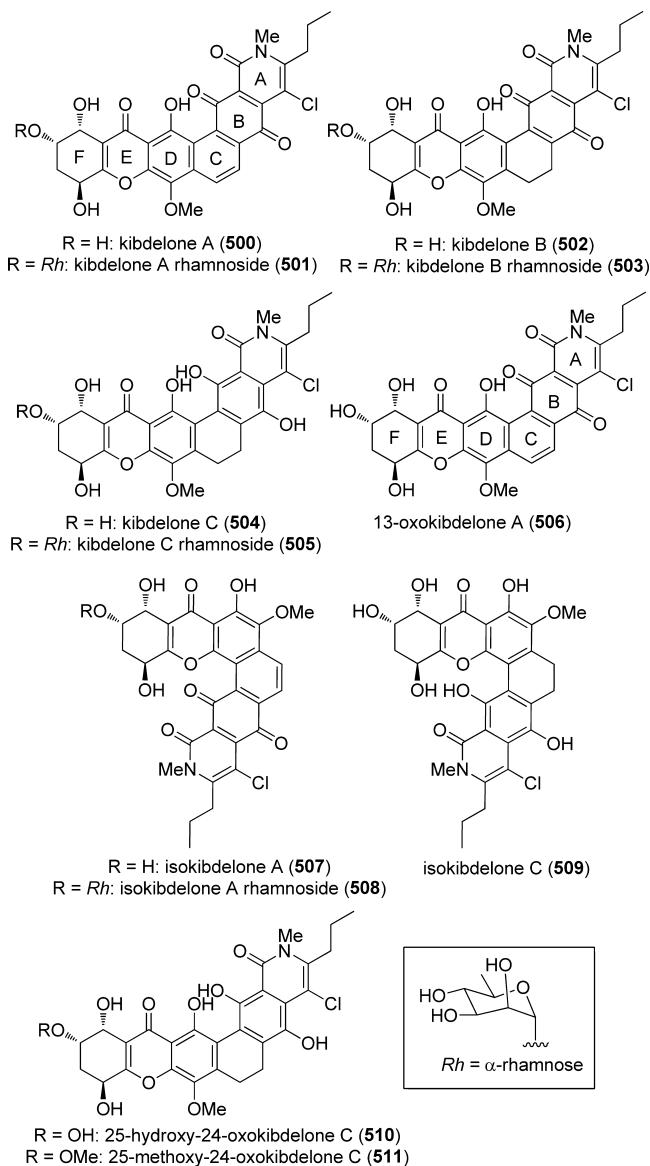


Figure 78. Kibdelone and cometabolites. All molecules shown with relative stereochemistry.

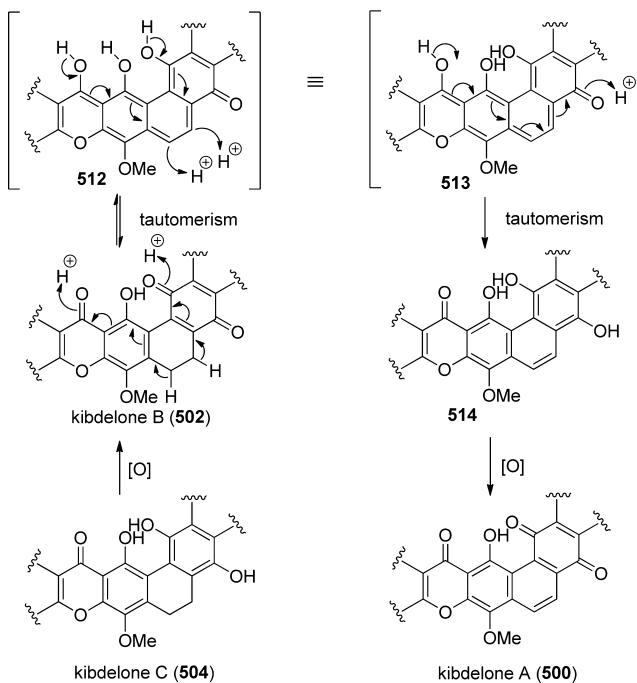
rhamnoside (**507** and **508**), and isokibdelone C (**509**) were isolated by Capon and co-workers from a rare actinomycete, *Kibdelosporangium* sp. (MST-108465),⁴³⁶ at the University of Queensland, Australia. The isolation resulted from a study of the cytotoxic, antibacterial, and nematocidal properties of this particular genus,⁴³⁷ which also yielded kibdelone A–C rhamnosides (**501**, **503**, and **505**), 13-oxokibdelone (**506**), and 25-hydroxy-24-oxo- and 25-methoxy-24-oxokibdelone C

(**510** and **511**). The authors speculate that the last two oxidized species may be artifacts resulting from solvolysis of kibdelone B.

After initial methanolic extraction, the bioassay of specific HPLC fractions gave positive results against carcinoma cells (NS-1, LD₉₉ = 1–11 μg mL⁻¹), directing the team to the isolation of a number of novel compounds. Antibacterial (*Bacillus subtilis*) and nematocidal (*Hemonchus contortus*) activities also had LD₉₉ values within this same concentration range. The authors further describe test results that show that the purified kibdelones (in contrast to the isokibdelones⁴³⁶) had potent and selective toxicity to human carcinoma cells across a range of tumors, with GI₅₀ values in the low to subnanomolar range (including leukemia, colon, CNS, melanoma, ovarian, and breast cancer cell lines).⁴³⁷

Although suitable crystals were not available for the assignment of absolute configuration of kibdelones, the relative configuration was determined utilizing NMR studies. Interestingly, the authors found that isokibdelone A adopted an alternative chair conformation of the F-ring in d₆-DMSO solution in comparison to that adopted in CDCl₃ solution. Kibdelones undergo a facile equilibration, with isolated kibdelones B and C forming a common mixture of kibdelones A–C (3:2:1 ratio at equilibrium);⁴³⁷ a similar equilibration was observed from isokibdelones B and C.⁴³⁶ Kibdelone B rhamnoside also equilibrated to the corresponding A–C sugar derivatives. The authors offered a plausible mechanism, involving air oxidation and tautomerization processes (kibdelone interconversion is shown in Scheme 41, a similar sequence

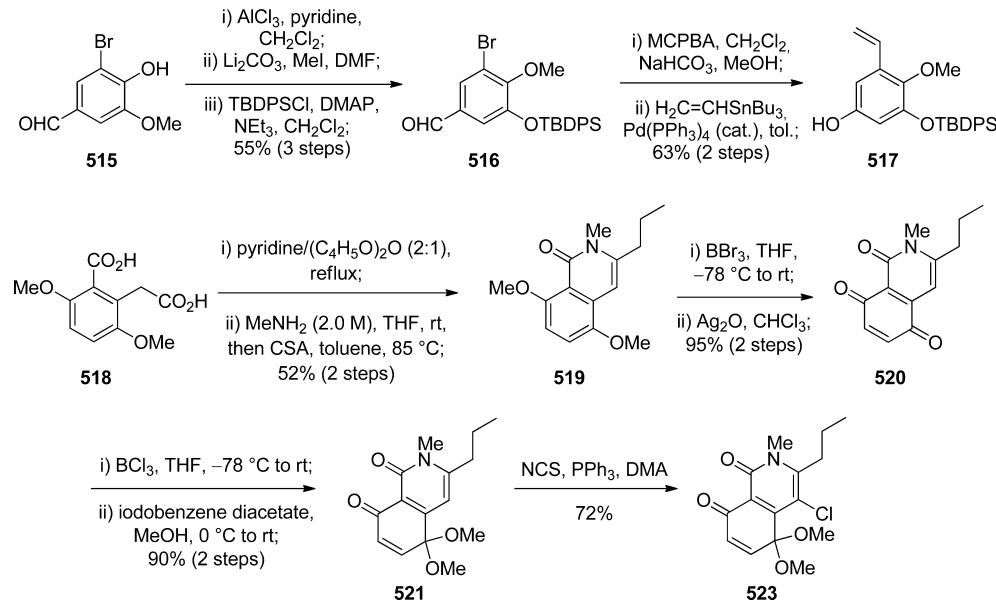
Scheme 41. Interconversion of Kibdelones



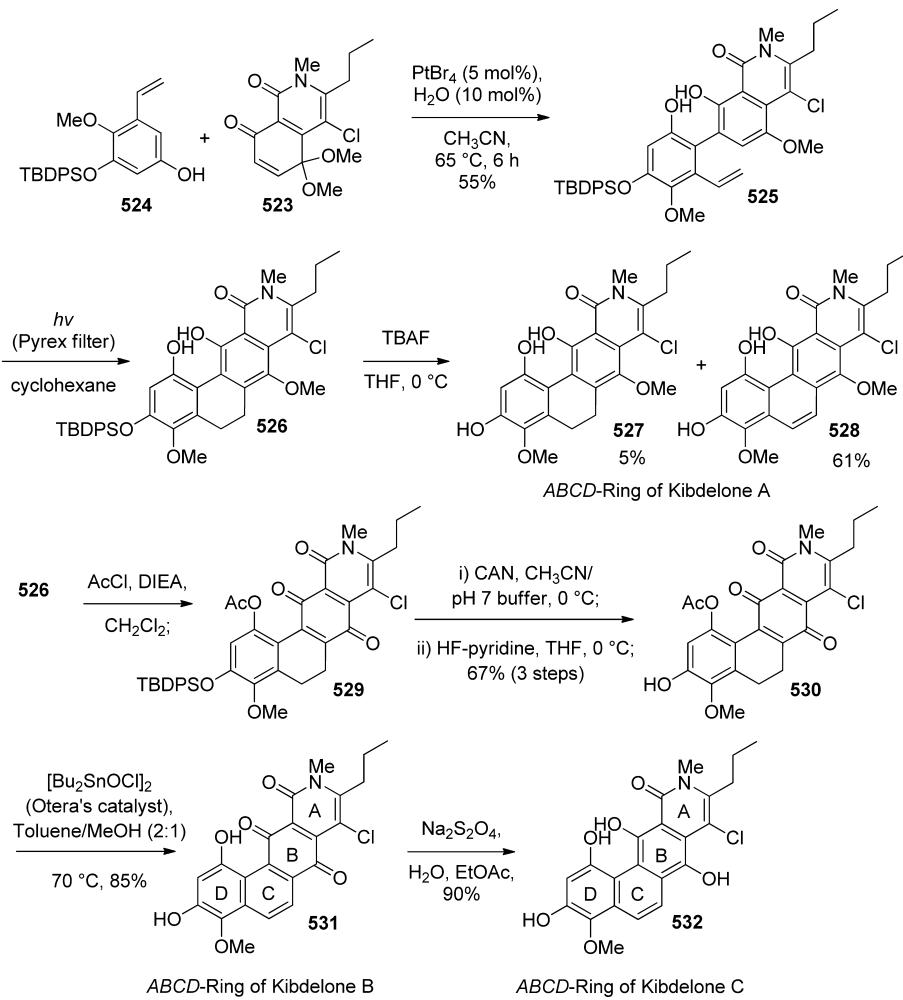
is suggested for isokibdelones⁴³⁶). Such a process for xanthone–quinone interconversion has been previously published by Carter and co-workers as part of their studies on simaomicin.⁴⁶⁷

In 2011 Porco and co-workers reported the synthesis of the ABCD-ring fragments, **531** and **532** (Scheme 43), of kibdelones A, B, and C and isokibdelone C (Figure 78).⁴³⁸ After the multistep conversion of known benzaldehyde **515** (Scheme 42)

Scheme 42. Porco Synthesis of the Kibdelone ABCD-Ring Substrates



Scheme 43. Porco Synthesis of the ABCD-Ring Components of Kibdelone



to the vinyl-substituted phenol **517**, as well as conversion of substituted phenylacetic acid derivative **518** to the isoquinoline trione **520**, these two components were to be coupled together.

Coupling of the two components through an intermolecular hydrogen-bond-promoted cycloaddition failed; however, the authors found that the ionic Diels–Alder addition of phenol

524 (Scheme 43) with the chlorinated and acetal-protected trione **523** gave biaryl **526**.

The two components were then coupled together utilizing a novel Pt^{IV}-catalyzed reaction developed within the project after screening other transition metal complexes (AuCl₃, InCl₃) and Lewis-acids (TMSOTf). PtBr₄ (5 mol %) with water (10 mol %) was found to be the best catalytic system for the coupling, giving biaryl **525** in 55% yield on multigram scale. Photocyclization (Pyrex filter, cyclohexane) afforded tetracycle **526**, which repeatedly gave the saturated system **527** in preference to the desired cyclohexadiene **528**.

Despite this setback, the direct product of radical cyclization, **527** (Scheme 43), was found to acetylate selectively to monoacetate **529**, which was oxidized and desilylated to acetate **530**. The use of Otera's distannoxane catalyst for deacetylation proved optimal and allowed the core of kibdelone B (**531**) to be formed in excellent yield. Further reduction of the quinone *B*-ring with aqueous dithionite gave the desired dihydroquinone ABCD-ring pattern representative of kibdelone C, **532**. The author's further submitted compounds with these ring systems to analysis by the NCI's 60-cell screen, which the last two compounds showed some cytotoxic activity, albeit 1000 times less than the best displayed by kibdelone C, demonstrating the importance of the *EF*-rings to the biological activity of this compound family.⁴³⁸

Kigamicins. Kigamicins A–E (**534**–**538**, Figure 79) were reported in 2003 by Kunimoto and co-workers after being

isolated from *Amicola topsis* sp. ML630-mF1 culture broth.⁴³⁹ The structure was determined for kigamicin D, the most abundant of these compounds, and the structure of the remaining four was inferred from differential spectroscopic properties. The family consists of polycyclic antibiotic xanthone framework (vide infra citreamycins, simaomicin, etc.) attached to one or more sugar residues. The absolute configuration of kigamicins A, C, and D were further reported in 2005, after the Japanese team was able to crystallize kigamicin A (**534**), which gave the relative configuration.⁴⁴⁰ Chemical degradation gave the sugar component (amicetose), the optical rotation of which was the same as that previously reported for D-amicetose; thus, the absolute configuration was determined as that shown in Figure 79. A similar process yielded the structures of kigamicins C and D. The absolute configuration of kigamicins B and E could not be determined due to a paucity of substance; nonetheless, the authors suggest that, based on biochemical pathways, the stereochemistry is likely the same as for the others.

The compounds had been found as a result of their selective cytotoxic effects against PANC-1 cells, screening for which was performed under nutrient-starvation conditions, with which the compounds were >100 times more effective than normal.⁴⁴¹ The compounds were also active against many strains of Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*. Kigamicin D further caused inhibition of growth when applied to mouse tumor cell lines in the low μM range. In a 2004 paper the same group described the activity of kigamicin D in light of an anticancer strategy that focuses on the heightened tolerance of cancer cells to survive nutrient starvation in comparison to healthy cells.⁴⁴²

Further reports followed on the biological effects of kigamicin D, including a study that suggested that immunomodulatory effects of this compound are not due to increased cellular immunity to specific antigens that it induces.⁴⁴³ Kigamicin D was then also shown to be also selectively cytotoxic against normal human lung fibroblasts and prostate stromal cells, in addition to tumor cells, particular pancreatic cancer cells.^{444,445} In 2007 an Australian team discovered that the novel actinomycete, *Amycolatopsis regiafaucium* sp. nov., also produces kigamicins.⁴⁴⁶

In 2011 Shipman and co-workers reported the synthesis of a tetracyclic component representing part of the frameworks of the kigamicins (and other xanthones) through a Pd-catalyzed domino reaction.⁴⁴⁷ They initially developed the C–O bond formation using substrates of the type **539** and **540**, with both bromoaryl and cycloalkanone rings linked with a carbonyl unit (**541**, Scheme 44). Analogues yielding both expansion, **534**, and contraction, **535**, of the C-ring proved to be also possible under the conditions. These core analogues are interesting in a medicinal chemistry sense due to the plethora of biological activities that the xanthones display.

The ABC-ring of the xanthone is constructed from a substrate with dibromoarene substrates via Pd-catalyzed C–O coupling reaction utilizing bisphosphines or Buchwald-type biarylphosphines as ligands, finding the bulky, electron-rich ligand XPhos in combination with cesium carbonate and dioxane to be optimal. The aromatic group was coupled at the 2-position from a bromide functionality with a Suzuki reaction and could be diverse in nature (EWG/ERG); significantly, products rising from Suzuki reaction alone were not observed, suggesting the intramolecular C–O bond formation is rapid. The group tested some of their compounds against the

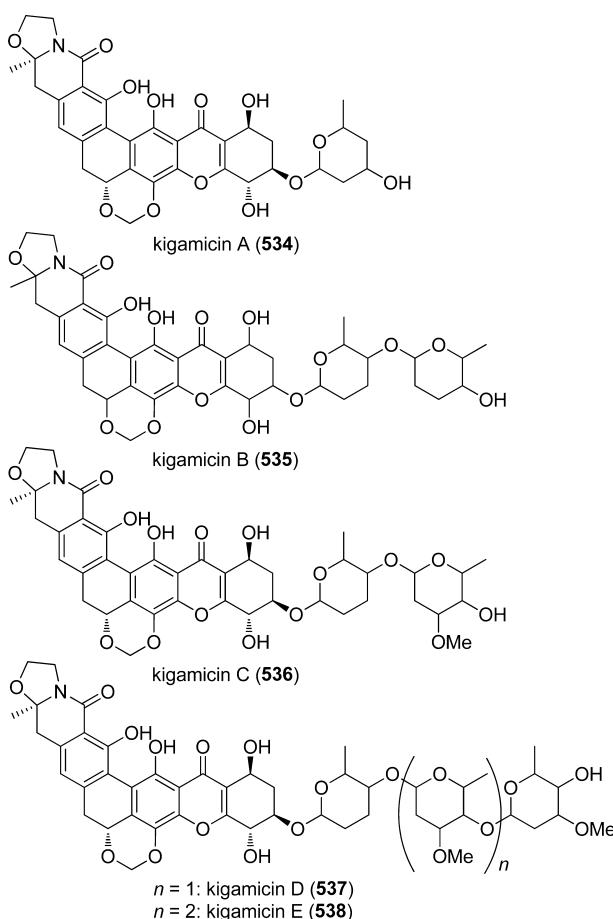
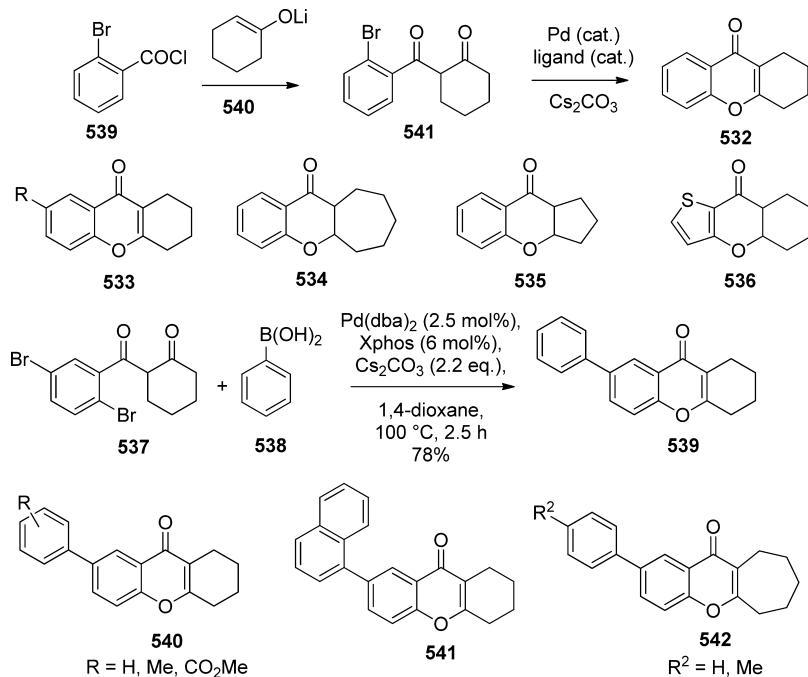


Figure 79. Kigamicins A–E.

Scheme 44. Synthesis of Tetrahydroxanthones Related to Kigamicins A–E



pancreatic cancer cell line PANC-1 and found that the existing structural motif here also exhibited the “antiausterity” effects of the kigamicins (i.e., far higher inhibitory effects under nutrient-deprived conditions).

Microsphaerins. Microsphaerins A–D (543–546, Figure 80) were found to be produced by the anamorphic soil fungus *Microsphaeropsis* sp. via a bioassay-guided isolation process.⁴⁴⁸

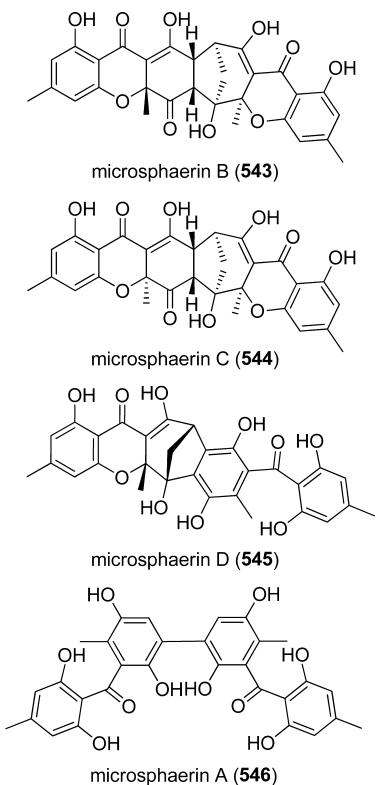


Figure 80. Microsphaerins.

These species were identified as being effective against methicillin-resistant *Staphylococcus aureus* (MRSA), which has been demonstrated to have an almost 20% lethality rate among infected patients in one study of U.S. hospitals.⁴⁴⁹ The microsphaerins were found to be active against MRSA in a whole cell assay with IC₉₀ values in the low micromolar range (1–5 μM), although cytotoxic effects precluded these compounds from further investigation for in vivo efficacy.

Microsphaeropsins A to D were isolated from two strains of *Microsphaeropsis* (B, C, and D from the first, and A and D from the second) and were characterized with the use of spectroscopic techniques (ROESY, etc.). Further confirmation was provided in the form of single-crystal X-ray analysis for microsphaerins A and D. Microsphaerins B–D possess an interesting connection in the form of a bicyclo[3.2.1]octane ring. A retro-oxa-Michael-addition process was suggested by the authors to account for the slow interconversion of microsphaerins B and C, which are diastereomeric structures at the C-5 ether-bearing position. This process is similar to that described for beticolins and parnafungins (see above and below, respectively). It appears as though microsphaerin A is the putative precursor to the other microsphaerins, which can be created by reduction of the innermost aromatic rings and subsequent cyclization upon these to form microsphaerins C and D; microsphaerin D may thus represent a halfway point in this biosynthetic process.

Neosartorin. A novel ergochrome, Neosartorin (547, Figure 81), was isolated from the mycelium of the soil mold *Neosartorya fischeri*, and the chemical structure was deduced with a variety of spectroscopic techniques.⁴⁵⁰ This compound is an isomer of eumitrins (see 436–438, Figure 75). The authors determined that the relative configuration at the C-5, -6, and -10 (and C-5', -6', and -10') positions is the same as that found in secalonic acids A and D.

Parnafungins. Parnafungins (548–552, Figure 82) were isolated as an equilibrating mixture of four interconverting species (A1–2 and B1–2) from the lichenicolous fungi

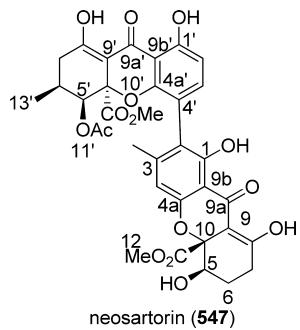


Figure 81. Neosartorin (relative configuration shown).

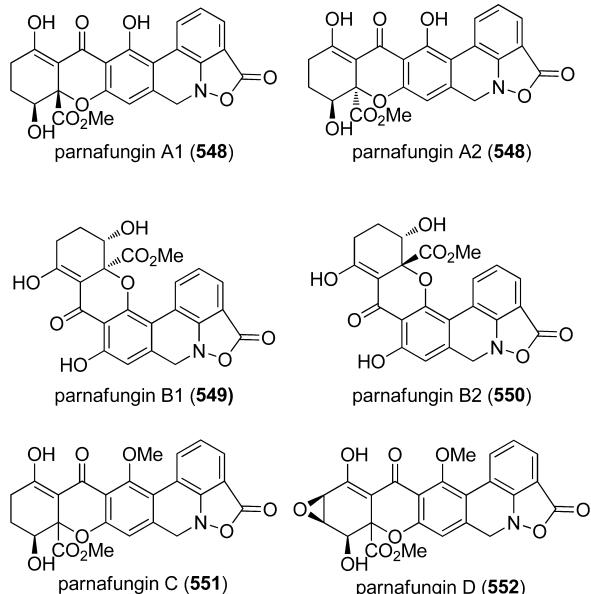


Figure 82. Parnafungins (absolute stereochemistry shown, when known).

Fusarium larvarum after hits from the crude fermentation extracts in the *Candida albicans* fitness test by a team from Merck.⁴⁵¹ *Candida albicans* (an ascomycetous yeast) is a significant human pathogen, and the fitness test uses a whole cell assay with 5000 modified *C. albicans* strains, each of which is heterozygous for a unique gene from the genome, allowing the responsible biochemical target to be identified when a new antifungal compound is applied.⁴⁵² Such chemical-genetic profiling was thus developed as a strategy to apply to the exploration of natural products for the purpose of drug discovery and, in particular, previously unexploited biochemical pathways in pathogenic fungi.^{452,453}

The interconversion between the four forms (*para*- and *ortho*-oxygen connection giving A and B) and *syn* (A1 and B1, major diastereomers) and *anti* (A2 and B2, minor diastereomers) is due to a retro-oxa-Michael addition, a process that is frequently seen among tetrahydroxanthones. This interconversion was blocked by methylation of the C-15 alcohol, allowing the structure of a derivative of A1 to be established by X-ray crystallography. The methyl carboxylate at the AB-ring junction is always in an axial orientation, whereas major diastereomers A1 and B1 have the C-15 hydroxyl in an equatorial orientation. Shortly after the initial report, parnafungins C and D were also isolated by the same team from a species that is taxonomically closely related to *F. Larvarum*⁴⁵⁴ and also produces small

amounts of parnafungin A and B mixture.^{455,454} The authors propose that parnafungins C and D are derived from methylation (and oxidation for D) of parnafungin A and not B, which supports the hypothesis that parnafungin A is the species initially biosynthesized by the fungus.⁴⁵⁵

Parnafungins are structurally unique in that they contain an unprecedented isoxazolidinone ring, which is required for their broad spectrum of antifungal activity (the compounds have no observable activity against Gram-positive or -negative bacteria). Parnafungins are suggested to inhibit mRNA processing; the target enzyme was determined to be polyadenosine polymerase (PAP) by both biochemical and genetic experimentation.⁴⁵² Several *Candida* species were sensitive to the application of purified parnafungin A/B mixture, including *Candida albicans* (MIC 0.014 µg/mL), *Candida krusei* (0.014 µg/mL), and *Saccharomyces cerevisiae* (3.3 µg/mL).

The team was able to determine that linear parnafungin A was the species from the equilibrating mixture responsible for interacting with PAP by using an ingenious affinity selection/mass spectrometry technique.⁴⁵³ The PAP enzyme is exposed to the interconverting mixture of parnafungins at physiological pH; then the sample is subjected to rapid size-exclusion chromatography (SEC), which selectively separates bound ligand from unbound ligand and protein. The ligand and protein complex is then diverted to low pH conditions, which both dissociates the ligand and freezes the interconversion, allowing the parnafungin active in binding to the target to be discerned by HPLC. Linear parnafungins C and D had similar activities to A, with D being the most efficacious.⁴⁵⁵

Ring-opened benzoquinoline isomers (553 and 554, Figure 83) were also observed to form under basic or neutral

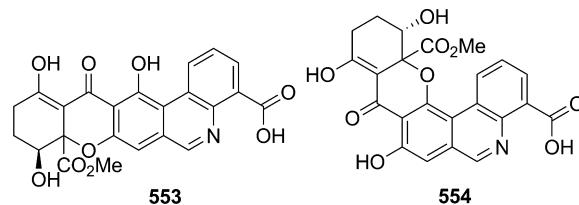


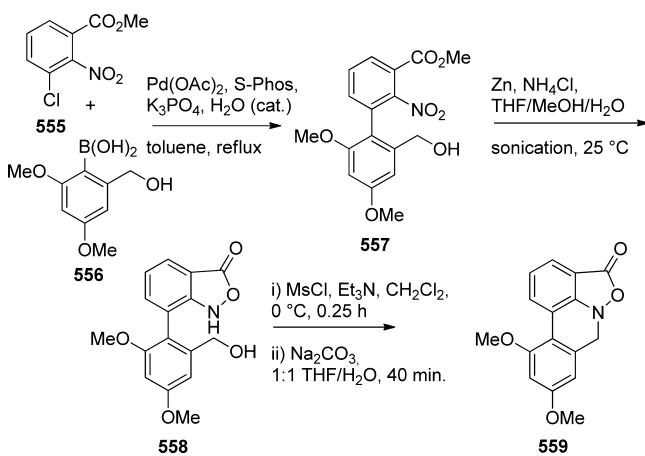
Figure 83. Isoxazolidinone ring-opened species.

conditions and somewhat more slowly under acidic conditions. It is likely that these result from the inherent instability of the isoxazolidinone core (by either E₂ elimination or a hydrolysis/elimination sequence).

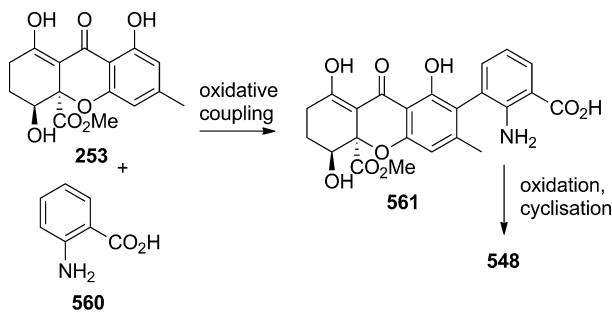
Not long after these reports, a synthesis of the tetracyclic isoxazolo[4,3,2-*d*]-phenanthridinone fragment 559 (Scheme 45) was reported by Zhou and Snider.⁴⁵⁶ After some initial investigations, they developed a sequence based on Suzuki coupling to form the biaryl segment 557: a sequential one-pot nitro-reduction-isoxazolone formation to give 558, then mesylation and ring-closing to give the target isoxazolone 559 in high yield. The authors also found that a similar ring-opening observed for parnafungins A and B took place in deuterated chloroform, and that the treatment of 559 with phenanthridine N-oxide in aqueous base gave the isoxazolidinone ring.

The authors also suggest a biosynthetic route to the parnafungins (Scheme 35a), which involves the oxidative coupling of blennolide C (253, Scheme 46) at the C-2 position to anthranilic acid (460), followed by benzylic oxidation of 561 and ring-closure.⁴⁵⁶

Scheme 45. Zhou and Snider's Synthesis of the Isoxazolone Fragment



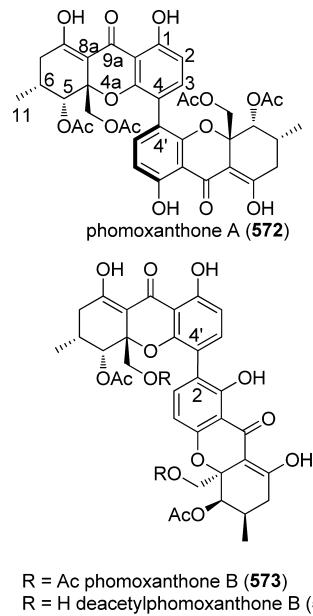
Scheme 46. Probable Biosynthesis of Parnafungins from Blennolide C and Anthranilic Acid



Another report from Zhou and Snider in late 2010 described the synthesis of hexacyclic parnafungin A and C models utilizing Suzuki coupling of 2-iodo-substituted aromatic xanthone components (**563** and **564**) with 3-carboxymethyl-2-nitrophenyl pinacol boronate (**565**) to yield intermediates of the type **566** and **567** (Scheme 47).⁴⁵⁷ These were subjected to zinc and ammonium chloride reductive formation of the benzisoxazolinone core, followed by mesylation and S_N2 cyclization under basic conditions to give **571** (parnafungin C model, R = Me) and **570** (parnafungin A model).

The authors note that the ready isomerization of the parnafungins A1, A2, B1, and B2 and their propensity to rapidly (<1 h) decompose to phenanthridines under neutral or basic conditions makes these natural products especially challenging synthetic targets.

Phomoxanthones. Phomoxanthones A and B (**573** and **574**, Figure 84) were isolated from the endophytic fungus *Phomopsis*

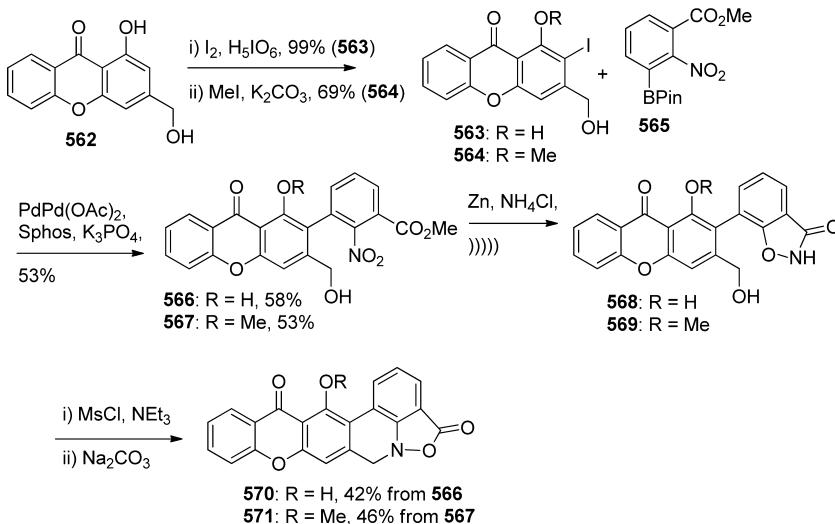


R = Ac phomoxanthone B (**573**)
R = H deacetylphomoxanthone B (**574**)

Figure 84. Phomoxanthones A and B and deacetylphomoxanthone B.

sp. after the extract from this species exhibited an antimalarial activity.⁴⁵⁸ Phomoxanthone A is a symmetrical homodimer with a 4,4'-(*para-para*)-linkage, while phomoxanthone B has a 2,4'-(*ortho-para*)-linkage, as seen with eumitrins (above). These structures are similar to ergochromes; however, the carboxymethyl substituents at C-10a (C-10a') have been replaced with acetoxyethyl substituents, and the C-6 (C-6a) hydroxyl moieties are acetylated. The relative configurations of phomoxanthones A and B were determined by NMR experiments.⁴⁵⁸ The compounds are active against *Plasmodium*

Scheme 47. Zhou and Snider's Synthesis of Parnafungin A and C Models



falciparum, *Mycobacterium tuberculosis*, and several cancer-cell lines.⁴⁵⁸

The absolute configuration and axial chirality of phomoxanthone A (572, Figure 84) was later ascertained by Krohn and co-workers with a combination of single-crystal X-ray analysis, CD, and calculated CD spectra,⁴⁵⁹ after having isolated this same compound from the extract of a different *Phomopsis* species, which had exhibited antibacterial and antifungal activity.⁴⁵⁹ Deacetylphomoxanthone B (574, Figure 84) was reported in 2007 as a metabolite from the *Phomopsis* sp. PSU-D15, where it was isolated alongside dicerandrol (440, Figure 72).⁴⁶⁰

Rugulotrosins. Rugulotrosins A and B (575 and 576, Figure 85) were reported in 2004 after being isolated from cultures of

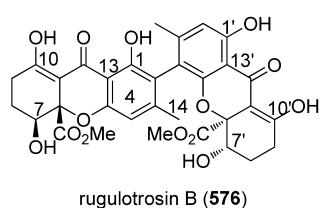
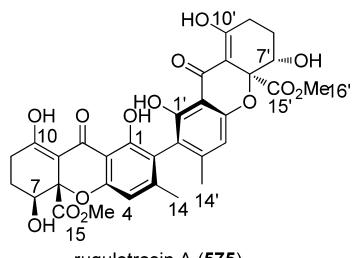


Figure 85. Rugulotrosins A and B (relative stereochemistry shown).

Penicillium sp. from soil samples. Rugulotrosin A is a symmetrical 2,2'-(*ortho*-*ortho*)-coupled dimer of tetrahydroxanthone subunits, whereas rugulotrosin B is a comparatively rarer 2,4'-(*ortho*-*para*)-coupled dimer.⁴⁶¹ The structure of these compounds was determined by spectroscopic analysis, and in the case of rugulotrosin A, it was confirmed by single-crystal X-ray analysis. The compounds were of considerable activity against *Bacillus subtilis*, and rugulotrosin A also exhibited significant activity against *Enterococcus faecalis* and *Bacillus cereus*.

Sch 42137. This compound was reported by Cooper and co-workers in 1992 as a novel antifungal antibiotic after being isolated from cultures of a soil-derived Gram-positive actinomycete bacteria, *Actinoplanes* sp. SCC 1906.⁴⁶² The structure (577, Figure 86), having both an isoquinoline and a xanthone component, is related to actinoplanones and albofungins (see

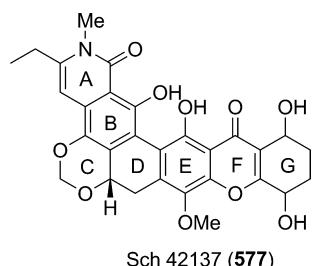


Figure 86. Sch 42137.

previous), cervinomycins (see section 3.1), lysolipin (see section 3.1), and simaomicins (see later). The authors describe the culture, isolation, and structural elucidation of the molecule and two acetate derivatives. Assistance was provided by comparison with simaomicins, for which a crystal structure was already known. The compound was tested with strong activity against six strains of *Candida albicans*, and some activity against the dermatophytes *Trichophyton mentagrophytes*, *T. Rubrum*, *T. Tonsurans*, and *Microsporon canis*.

Sch 54445. The potent mycotoxin Sch 54445 (578, Figure 87, proposed structure shown) was reported by Chu and co-

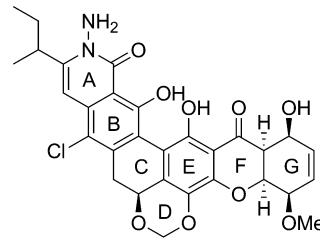


Figure 87. Sch 5445.

workers in 1997 after being isolated from the fermentation broth of *Actinoplanes* sp.⁴⁶³ It is a member of the albofungin family, possessing both a xanthone and an isoquinoline component. The structure is proposed as 578 based on information derived from a variety of spectral techniques, and although a combination of NOESY data and CD spectra with computational techniques did not elucidate the stereochemistry around the G-ring, the *anti*-configuration was proposed based on the similarity of optical rotation with albofungin, for which it is established.

This compound has high antifungal potency against yeasts, dermatophytes, and *Aspergillus* species with MIC values in the submicromolar range (~0.4 µg/mL).⁴⁶³ Like albofungin and Sch 42137 (see previously, for both), Sch 5445 was found to be highly toxic, with an LD₅₀ of 1 mg/kg (mice).

Simaomicin. Simaomicins α and β (previously designated LL-D42067 α and β , 579 and 580, respectively, Figure 88)

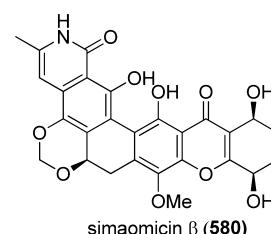
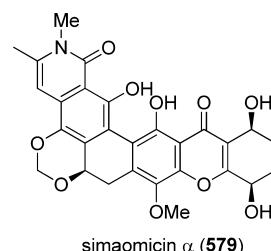


Figure 88. Simaomicins α and β .

were isolated from *Actinomadura madura* subspecies *simaensis* in 1989 by Borders and co-workers, who determined the structures (and relative configuration) using a combination of spectroscopic methods and single-crystal X-ray crystallography.⁴⁶⁴ Greenstein and co-workers also reported on simaomicin in 1990, including details of the large-scale fermentation, extraction, and biological activity.⁴⁶⁵ Simaomicin α was found to be the most potent broad-spectrum nonsynthetic anticoccidial known, when fed to chickens at a concentration at the optimal dosage of 1 ppm in their diet.⁴⁶⁴ Also, Omura and co-workers reported on the inhibition by simaomicin of G2 cell-cycle checkpoint (which prevents cells replicating damaged DNA) after it had been induced by bleomycin; interestingly, the inhibition was selective to the G2 phase and did not affect the M phase.⁴⁶⁶

In 1989 Carter and co-workers reported on the biosynthesis of simaomicin α , mainly utilizing ^{13}C -labeled acetate precursors.⁴⁶⁷ They postulated that the ring is derived by condensation of 13 acetate units in a head-to-tail fashion, followed by the enzymatic manipulation of the resulting polyketide, including condensation–cyclization, dehydration–aromatization, oxidations, oxidative cleavage, and amination. Solving the structure, which features many quaternary carbons, required the use of LR HETCOSY and other 2D NMR techniques. The authors conclude that all the carbons present in the rings of simaomicin α are derived from acetate and that the xanthone ring must be constructed with oxidative cleavage of quinine ring, then loss of C12 as CO_2 , and finally ring-closure at C13. Such a sequence was proposed by Birch and co-workers in their analysis of the biosynthesis of ravenelin;¹⁷⁰ however, identification of a symmetrical and freely rotating benzophenone was not observed for simaomicin, where there is no randomization of the labeling pattern in the resulting F-ring.⁴⁶⁷

Xanthonol. The novel unsymmetrical dimeric xanthone, xanthonol (**581**, Figure 89), was isolated from the fermentation

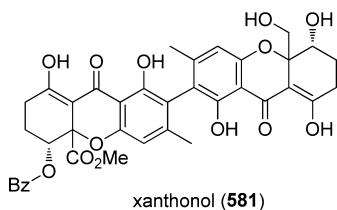


Figure 89. Xanthonol.

broth of a nonsporulating fungi found in the leaf litter of *Manikara bidentata*.⁴⁶⁸ A point of interest is that this compound features a methyl-substitution of an aryl position, in the manner of rugulotrosins, rather than the C-6(C-6') methylation observed for secalonic acids, dicerandrols, and phomoxanthones. Also interesting is the benzoylated alcohol at the CS' position. Xanthonol was found by the researchers to exhibit antihelmintic properties against the larvae of *Lucilia sericata*, *Aedes aegypti*, and *Hemonchus contortus*.

Xanthoquinodins. The xanthoquinodins A₁–A₃ and B₁–B₂ (**582**–**586**, Figure 90) were first identified as anticoccidial antibiotics isolated from *Humicola* sp. Feeding experiments with ^{13}C and extensive spectroscopic data analysis on the resulting isotopically enriched compounds allowed for the structural determination of these five compounds.^{469,470} These heterodimers, like beticolins, are also resultant from the

coupling of a xanthone with an anthraquinone, although the coupling is herein an end-to-tail fashion. The relative configurations at C-11' and C-14' are S and R, respectively, and C-2 is S and C-3 is S.

Unlike the beticolins, these different forms of xanthoquinodins can interconvert merely by heating in solution.²⁸² Heat treatment of xanthoquinodin A₁ gave a mixture of all five compounds. Heat treatment of the other compound gives mixtures with the following exception: A₃ appears to represent a final product that is effectively removed from the interconversion pool by virtue of its unique lactone ring.

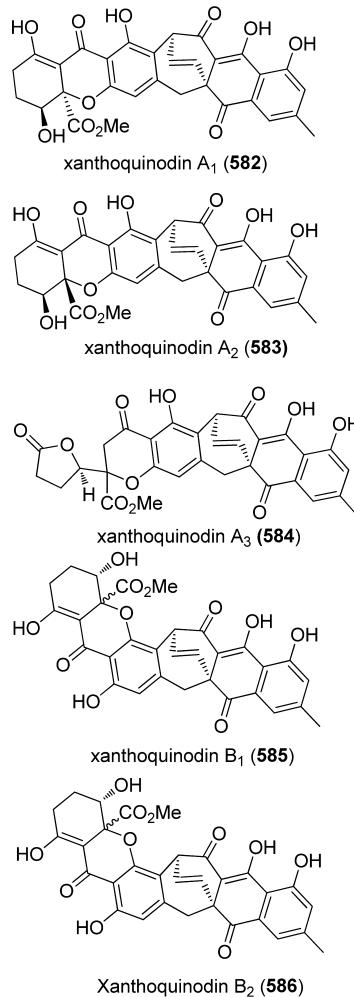
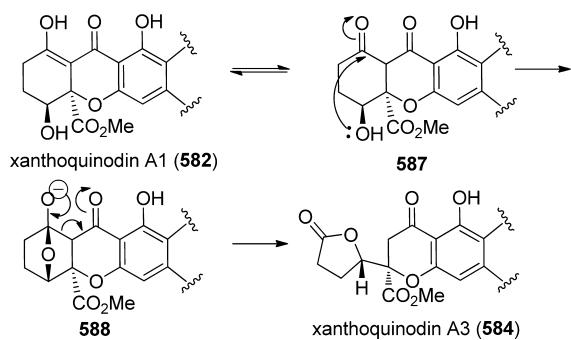


Figure 90. Xanthoquinodins.

The authors propose a biosynthetic route to these products, beginning with decarboxylation of oktaketide tail.⁴⁷⁰ One molecule is cleaved oxidatively, yielding a benzophenone intermediate that rotates freely (scrambling the ^{13}C location); this process has also been observed for beticolins, divisoronol, and purpactin A), followed by intermolecular coupling of the two units. A mechanism is suggested for the conversion of xanthoquinodin A₁ to A₃ (see Scheme 48).⁴⁶⁹ Kingsland and Barrow have recently reported the isolation of xanthoquinodin A₁ from a culture of a *Chaetomium* sp. microfungus, which was originally obtained from the scat of the emu.⁴⁷¹

Scheme 48. Proposed Mechanism of Interconversion between Xanthoquinodins A₁ and A₃



4. CONCLUSIONS

Xanthones from fungi, lichens, and bacteria comprise an ever-growing and considerably diverse group of compounds in terms of structure, occurrence, and bioactivity. General biosynthetic pathways have been defined; however, some pathways are complex, and significant pathway branching during the sequence of xanthone synthesis from polyketide through anthraquinone has been described in the primary literature, sometimes even within a single species. Additionally, the biochemical sources of structural components, for example, oxygen or methyl atoms, can differ between molecules, even those that are structurally similar. The xanthones represent attractive targets for both total synthesis and associated exploration of analogues for the purpose of exploiting the plethora of diverse and specific bioactivities that this class of compounds possesses. The syntheses of the more challenging unsaturated xanthone derivatives is an exciting contemporary area of chemical research.

AUTHOR INFORMATION

Corresponding Author

*Fax: +49 721 6084 8581. E-mail: kye.masters@kit.edu, braese@kit.edu.

Notes

The authors declare no competing financial interest.

Biographies



Kye-Simeon Masters was born in Kyogle, Australia, in 1979. A Bachelor of Science from the Australian National University in 2002 was followed by both an Honours (2004) and Doctorate (2007) in total synthesis with Prof. Bernard Flynn at Monash University, focused

on the development of complementary Stille/Heck and Heck/Stille reactions, as well as the synthesis of sesquiterpenoids frondosins B, C, and D. Following a year in scale-up and process chemistry (IDT Australia), he undertook a postdoctoral appointment with Prof. Bert Maes in Antwerp, Belgium (2008–2009), investigating the mechanism of a novel Cu-catalyzed C–H amination reaction. He continued his postdoctoral research in the laboratories of Prof. Stefan Bräse, in Karlsruhe, Germany, with an Alexander von Humboldt Fellowship (2010–2011). There he studied various topics, including the double Diels–Alder reaction, double Friedel–Crafts acylation, the use of *ortho*-halophenyl alkenes as novel substrates in Pd-catalyzed domino reactions, novel routes to *ortho*-*ortho*-biphenols, and the synthesis of the beticolins. He currently works as a medicinal chemist at Lundbeck A/S, in Copenhagen. His research interests are focused on natural product synthesis and innovations in transition metal catalysis.



Stefan Bräse was born in Kiel, Germany, in 1967. After he studied in Göttingen, Bangor (U.K.), and Marseille, he received his Ph.D. in 1995, after working with Armin de Meijere in Göttingen. After postdoctoral appointments at Uppsala University (Jan E. Bäckvall) and The Scripps Research Institute (K. C. Nicolaou), he began his independent research career at the RWTH Aachen in 1997 (associated to Dieter Enders). In 2001, he finished his Habilitation and moved to the University of Bonn as professor for organic chemistry. Since 2003, he is full professor at the University of Karlsruhe (now Karlsruhe Institute of Technology), Germany. His research interests include methods in drug discovery (including drug delivery), combinatorial chemistry towards the synthesis of biologically active compounds, total synthesis of natural products, and nanotechnology.

ACKNOWLEDGMENTS

K.-S. M. would like to acknowledge the generous funding and support provided by the Alexander von Humboldt Foundation, as well as the assistance of AK Bräse co-workers in the proofing of this review.

DEDICATION

Dedicated to Professor Jack Elix, who has researched xanthones (and taught of tropylum ions).

REFERENCES

- (1) Lesch, B.; Bräse, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 115.
- (2) Roberts, J. C. *Chem. Rev.* **1961**, *61*, 591.
- (3) Krohn reported that 1464 xanthone-based compounds were known in 2009 (see ref 24).
- (4) Oldenberg, T.; Wilkes, H.; Horsfield, B.; van Duin, A.; Stoddart, D.; Willhelms, A. *Org. Geochem.* **2002**, *33*, 595.
- (5) Robinson, R. *Structural Relations of Natural Products*; Oxford University Press: London, 1955; p 45.

- (6) Peres, V.; Nagem, T. *Quim. Nova* **1997**, *20*, 388.
- (7) Pinto, M.; Sousa, E.; Nascimento, M. *Curr. Med. Chem.* **2005**, *12*, 2517.
- (8) Carpenter, I.; Locksley, H.; Scheinmann, F. *Phytochemistry* **1969**, *8*, 2013.
- (9) Gottlieb, O. *Phytochemistry* **1968**, *7*, 411.
- (10) Dean, F. *Naturally Occurring Oxygen Ring Compounds*; Butterworths: London, 1963.
- (11) Peres, V.; Nagem, T.; Faustino de Oliveira, F. *Phytochemistry* **2000**, *55*, 683.
- (12) Sultanbawa, M. *Tetrahedron* **1980**, *36*, 1465.
- (13) Pinto, M.; Sousa, E. *Curr. Med. Chem.* **2003**, *10*, 1.
- (14) Bennett, G. J.; Lee, H.-H. *Phytochemistry* **1989**, *28*, 967.
- (15) Mandal, S.; Das, P.; Joshi, P. *J. Indian Chem. Soc.* **1992**, *69*, 611.
- (16) Brahmachari, G.; Mondal, S.; Gangopadhyay, A.; Saha, S.; Brahmachari, A. *Chem. Biodiversity* **2004**, *1*, 1627.
- (17) Peres, V.; Nagem, T. *Phytochemistry* **1997**, *44*, 191.
- (18) Birch, A. J.; Donovan, F. W. *Aust. J. Chem.* **1953**, *6*, 360.
- (19) Krohn, K.; Kouam, S.; Kuigoua, G.; Hussain, H.; Cludius-Brandt, S.; Flörke, U.; Kurtán, T.; Pescitelli, G.; Di Bari, L.; Draeger, S.; Schulz, B. *Chem.—Eur. J.* **2009**, *15*, 12121.
- (20) Wilson, D. J.; Patton, S.; Florova, G.; Hale, V.; Reynolds, K. A. *Indust. Microbiol. Biotech.* **1998**, *20*, 299.
- (21) Gupta, P.; Lewis, J. R. *J. Chem. Soc., C* **1971**, *0*, 629.
- (22) Holker, J. S. E.; Mulheim, L. J. *J. Chem. Soc., Chem. Commun.* **1968**, *24*, 1576.
- (23) Mannito, P. *Biosynthesis of Natural Products*; Wiley: New York, 1981; pp 200–202.
- (24) El-Seedi, H. H.; El-Ghorab, D. M. H.; El-Barbary, M. A.; Zayed, M. F.; Göransson, U.; Larsson, S.; Verpoole, R. *Curr. Med. Chem.* **2009**, *16*, 2581.
- (25) Beerhues, L.; Barillas, W.; Peters, S.; Schmidt, W. Biosynthesis of Plant Xanthones. In *Bioorganic Chemistry. Highlights and New Aspects*; Diederichsen, U., Lindhorst, T. K., Westermann, B., Wessjohann, L., Eds.; Wiley-VCH: Weinheim, Germany, 1999.
- (26) Barrillas, W.; Beerhues, L. *Biol. Chem.* **2000**, *381*, 155.
- (27) Bräse, S.; Encinas, A.; Gall, J.; Nising, C. *Chem. Rev.* **2009**, *109*, 3903.
- (28) Sousa, M.; Pinto, M. *Curr. Med. Chem.* **2005**, *12*, 2447.
- (29) Silva, A.; Pinto, D. *Curr. Med. Chem.* **2005**, *12*, 2481.
- (30) Gales, L.; Damas, A. *Curr. Med. Chem.* **2005**, *12*, 2499.
- (31) Vieira, L.; Kijjoa, A. *Curr. Med. Chem.* **2005**, *12*, 2413.
- (32) Cheng, G.; Sun, J.; Fridlender, Z. G.; Wang, L.-M.; Ching, L.-C. S.; Albelda, J. *Biol. Chem.* **2010**, *285*, 10553.
- (33) Gobbi, S.; Zimmer, C.; Belluti, F.; Rampa, A.; Hartmann, R. W.; Recanatini, M.; Bisi, A. *J. Med. Chem.* **2010**, *53*, 5347.
- (34) Palmeira, A.; Paiva, A.; Sousa, E.; Seca, H.; Almeida, G. M.; Lima, R. T.; Fernandez, M. X.; Pinto, M.; Vasconcelos, M. H. *Chem. Biol. Drug Des.* **2010**, *76*, 43.
- (35) Honda, N. K.; Pavan, F. R.; Coelho, R. G.; de Andrade Leite, S. R.; Micheletti, A. C.; Lopes, T. I. B.; Mitsutsu, M. Y.; Beatriz, A.; Brum, R. L.; Leite, C. Q. F. *Phytomedicine* **2010**, *17*, 328.
- (36) Riscoe, M.; Kelly, J.; Winter, R. *Curr. Med. Chem.* **2005**, *12*, 2539.
- (37) Winter, R.; Cornell, K.; Johnson, L.; Ignatushchenko, M.; Hinrichs, D.; Riscoe, M. *Antimicrob. Agents Chemother.* **1997**, *40*, 1408.
- (38) Winter, R.; Ignatushchenko, M.; Ugundahuni, O.; Cornell, K.; Oduola, A.; Hinrichs, D.; Riscoe, M. *Antimicrob. Agents Chemother.* **1997**, *41*, 1449.
- (39) Ignatushchenko, M.; Winter, R.; Bachinger, H.; Hinrichs, D.; Riscoe, M. *FEBS Lett.* **1997**, *409*, 67.
- (40) El-Seedi, H. R.; El-Barbary, M. A.; El-Ghorab, D. M. H.; Bohlin, L.; Borg-Karlsson, A.-K.; Goeransson, U.; Verpoorte, R. *Curr. Med. Chem.* **2010**, *17*, 854.
- (41) Ullmann, F.; Panchaud, L. *Chem. Ber.* **1906**, *39*, 108.
- (42) Michael, A. *Ann. Chem. J.* **1883**, *5*, 81.
- (43) Kostanecki, S. *Chem. Ber.* **1891**, *24*, 1898.
- (44) Gnerre, C.; Thull, U.; Gaillar, P.; Carrupt, P. A.; Testa, B.; Fernandes, E.; Silva, F.; Pinto, M.; Pinto, M. M.; Wolfender, J. L.; Hostettman, K.; Cruciani, G. *Helv. Chim. Acta* **2001**, *84*, 552.
- (45) Quillinan, A. J.; Scheinmann, F. *J. Chem. Soc., Perkin Trans. 1* **1973**, *2*, 1329.
- (46) Moroz, A. A.; Shwartsberg, M. S. *Russ. Chem. Rev.* **1974**, *43*, 679.
- (47) Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402.
- (48) Elix, J. A.; Gaul, K. L.; Jiang, H. *Aust. J. Chem.* **1993**, *46*, 95.
- (49) Tanase, Y. *J. Pharm. Soc. Jpn.* **1941**, *61*, 341.
- (50) Muller, P.; Venakis, T.; Eugster, C. H. *Helv. Chim. Acta* **1979**, *62*, 2350.
- (51) Nishikawa, H.; Robinson, R. *J. Chem. Soc.* **1922**, *121*, 839.
- (52) Heymann, H. *J. Am. Chem. Soc.* **1949**, *71*, 260.
- (53) Scott, A. I.; Pike, D. G.; Ryon, J. J.; Guilford, H. *Tetrahedron* **1971**, *27*, 3051.
- (54) Dubrovsky, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117.
- (55) Johnson, M. M.; Naidoo, J. M.; Fernandes, M. A.; Mmutlane, E. M.; van Otterlo, W. A. L.; de Koning, C. B. *J. Org. Chem.* **2010**, *75*, 8701.
- (56) Xie, F.; Pan, X.; Lin, S.; Hu, Y. *Org. Biomol. Chem.* **2010**, *8*, 1378.
- (57) Cho, J.; Woo, J.; Nam, W. *J. Am. Chem. Soc.* **2010**, *132*, 5958.
- (58) Ohnemüller (née Schmid), U. K.; Nising, C. F.; Nieger, M.; Bräse, S. *Eur. J. Org. Chem.* **2006**, *6*, 1535.
- (59) Ohnemüller, U. K.; Nising, C. F.; Encinas, A.; Bräse, S. *Synthesis* **2007**, *14*, 2175.
- (60) Volz, N.; Bröhmer, M. C.; Toräng, J.; Nieger, M.; Bräse, S. *Indian J. Chem.* **2009**, *48B*, 1699.
- (61) Nising, C. F.; Ohnemüller, U. K.; Friedrich, A.; Lesch, B.; Steiner, J.; Schnöckel, H.; Nieger, M.; Bräse, S. *Chem.—Eur. J.* **2006**, *12*, 3647.
- (62) Sahin, H.; Nieger, M.; Nising, C. F.; Bräse, S. *Synlett* **2009**, *19*, 3187.
- (63) Sahin, H.; Nieger, M.; Bräse, S. *Eur. J. Org. Chem.* **2009**, *32*, 5576.
- (64) Gérard, E. M. C.; Sahin, H.; Encinas, A.; Bräse, S. *Synlett* **2008**, *17*, 2702.
- (65) Santesson, J. *Act. Chem. Scand.* **1968**, *22*, 1698.
- (66) Santesson, J. *Ark. Kemi* **1969**, *30*, 363.
- (67) Elix, J. A.; Chappell, H.-M.; Jiang, H. *Bryologist* **1991**, *94*, 304.
- (68) Elix, J. A.; Crook, C. E. *Bryologist* **1992**, *95*, 52.
- (69) Hawksworth, L.; Hill, D. J. *The Lichen Forming Fungi*; Blackie: London and Glasgow, 1984.
- (70) Elix, J. A.; Jiang, H. *Aust. J. Chem.* **1990**, *43*, 1591.
- (71) Elix, J. A.; Jiang, H.; Wardlow, J. H. *Aust. J. Chem.* **1990**, *43*, 1745.
- (72) Huneck, S.; Höfle, G. *Tetrahedron* **1978**, *34*, 2491.
- (73) Santesson, J. *Acta Chem. Scand.* **1970**, *24*, 371.
- (74) Elix, J. A.; Jiang, H.; Portelli, V. A. *Aust. J. Chem.* **1990**, *43*, 1291.
- (75) Elix, J. A.; Bennett, S. A.; Jiang, H. *Aust. J. Chem.* **1991**, *44*, 1157.
- (76) Elix, J. A.; Bennett, S. A. *Aust. J. Chem.* **1990**, *43*, 1587.
- (77) Sundholm, E. *Acta Chem. Scand.* **1979**, *33*, 475.
- (78) Elix, J. A.; Gaul, K. L.; Lumbsch, H. T. *Aust. J. Chem.* **1987**, *40*, 1031.
- (79) Elix, J. A.; Gaul, H. J. *Aust. J. Chem.* **1993**, *46*, 95.
- (80) Elix, J. A.; Jones, A. J.; Lajide, L.; Coppins, B. J.; James, P. W. *Aust. J. Chem.* **1984**, *37*, 2349.
- (81) Rambold, G.; Knoph, J.-G. *Bibl. Lichenol.* **1989**, *34*, 1.
- (82) Sundholm, E. *G. Tetrahedron* **1978**, *34*, 577.
- (83) Wu, Z.-J.; Ouyang, M.-A.; Tan, Q.-W. *Pest Manage. Sci.* **2009**, *65*, 60.
- (84) Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Perkin Trans. 1* **1974**, *0*, 2250.
- (85) Nakamura, Y.; Shinomura, T.; Ona, J. *Nippon Noge Kagaku* **1957**, *31*, 669.
- (86) Bolan, J.; Fuska, J.; Kuhr, I.; Kuhrova, K. *Folia Microbiologica* **1970**, *15*, 479.

- (87) Kjaer, D.; Kjaer, A.; Pederson, C.; Bu'Lock, J.; Smith, J. *J. Chem. Soc., C* **1971**, 2792.
- (88) Cornforth, J. W.; Ryback, G.; Robinson, P. M.; Park, D. *J. Chem. Soc., C* **1971**, 2786.
- (89) de Boer, J. J.; Bright, D.; Dallinga, G.; Hewitt, T. G. *J. Chem. Soc., C* **1971**, 2788.
- (90) Robinson, P.; Park, D.; McClure, W. *Trans. Brit. Mycol. Soc.* **1969**, 52, 447.
- (91) Terashima, N.; Ishida, M.; Hamaski, T.; Hatsuda, Y. *Phytochemistry* **1972**, 11, 2880.
- (92) Balan, J.; Fuska, J.; Kuhr, I.; Kuhrova, V. *Folia Microbiologica* **1970**, 15, 479.
- (93) Fuska, J.; Ivanitskaya, L.; Makukho, L.; Volkova, L. *Antibiotiki* **1974**, 19, 890.
- (94) Katagiri, N.; Nakano, J.; Kato, T. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2710.
- (95) Barton, D.; Cottier, L.; Freund, K.; Luini, F.; Magnus, P.; Salazer, I. *J. Chem. Soc., Perkin Trans. 1* **1976**, 499.
- (96) Kjaer, D.; Kjaer, A.; Risbjerg. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2815.
- (97) de Koning, C.; Giles, R.; Engelhardt, L.; White, A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 12, 3209.
- (98) Hauser, F. M.; Hewawasam, P.; Baghadanov, V. M. *J. Org. Chem.* **1988**, 53, 223.
- (99) Deshpande, V. H.; Khan, R. A.; Ayyangar, N. R. *Synth. Commun.* **1993**, 23, 2677.
- (100) Bekaert, A.; Andrieux, J.; Plat, M. *Tetrahedron Lett.* **1992**, 33, 2805.
- (101) Kato, T.; Katagiri, N.; Nakano, J.; Kawamura, H. *J. Chem. Soc., Chem. Commun.* **1977**, 18, 645.
- (102) Iijima, I.; Taga, N.; Miyazaki, M.; Tanaka, T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3190.
- (103) Lewis, J.; Paul, J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 770.
- (104) McInnes, A. G.; Smith, D. G.; Walker, J. A.; Vining, L. C.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1975**, 66.
- (105) Pontius, A.; Krick, A.; Kehraus, S.; Brun, R.; König, G. *J. Nat. Prod.* **2008**, 71, 1584.
- (106) Knoph, J.-G. *Bibl. Lichenol.* **1990**, 36, 1.
- (107) Elix, J. A.; Robertson, F.; Wardlaw, J. H.; Willis, A. C. *Aust. J. Chem.* **1994**, 47, 2291.
- (108) Lumbsch, H. T. *J. Hattori Bot. Lab.* **1994**, 77, 1.
- (109) Lumbsch, H. T.; Feige, G. B.; Elix, J. A. *Plant Syst. Evol.* **1994**, 191, 227.
- (110) Ryan, B. D.; Poelt, J. *Bryologist* **1989**, 92, 513.
- (111) Wang, Y.; Zheng, Z.; Liu, S.; Zhang, H.; Li, E.; Guo, L.; Che, Y. *J. Nat. Prod.* **2010**, 73, 920.
- (112) Elix, J. A.; Gaul, K. L.; Lumbsch, H. T. *Aust. J. Chem.* **1987**, 40, 1031.
- (113) Li, J.; Zhang, Y.; Chen, L.; Dong, Z.; Di, X.; Qiu, F. *Chem. Nat. Compd.* **2010**, 46, 216.
- (114) Huneck, S.; Follmann, G. *J. Hattori Bot. Libr.* **1957**, 35, 319.
- (115) Chehal, K.; Holker, J.; Simpson, T.; Young, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 543.
- (116) Ishida, M.; Hamaski, T.; Hatsuda, Y. *Agric. Biol. Chem.* **1975**, 39, 2181.
- (117) Bringmann, G.; Lang, G.; Steffens, S.; Günther, E.; Schaumann, K. *Phytochemistry* **2003**, 63, 437.
- (118) Wijeratne, E.; Turbyville, T.; Fritz, A.; Whitesell, L.; Gunatilaka, A. *Bioorg. Med. Chem.* **2006**, 14, 7917.
- (119) McMasters, W. J.; Scott, A. I.; Trippett, S. *J. Chem. Soc.* **1960**, 4628.
- (120) Rhodes, A.; Boothroyd, B.; MoGonacle, M. P.; Somerfield, G. A. *Biochem. J.* **1961**, 81, 28.
- (121) Grover, P.; Shah, G.; Shah, R. *J. Sci. Ind. Res.* **1956**, 15B, 629.
- (122) Asao, T.; Büchi, G.; Abdel-Kader, M. M.; Chang, S. B.; Wick, E. L.; Wogan, G. N. *J. Am. Chem. Soc.* **1965**, 87, 882.
- (123) Broadbent, D.; Mabelis, R. P.; Spencer, H. *Phytochemistry* **1975**, 14, 2082.
- (124) Jayalakshmi, V.; Seshadri, T. R.; Neelakantan, S.; Thillaichidambaram, N. *Indian J. Chem.* **1974**, 12, 441.
- (125) Kachi, H.; Sassa, T. *Agric. Biol. Chem.* **1986**, 50, 1669.
- (126) Marcias, M.; Gamboa, A.; Ulloa, M.; Toscano, R. A.; Mata, R. *Phytochemistry* **2001**, 58, 751.
- (127) Lösgen, S.; Magull, J.; Schulz, B.; Draeger, S.; Zeeck, A. *Eur. J. Org. Chem.* **2008**, 4, 698.
- (128) Ayer, W. A.; Taylor, D. R. *Can. J. Chem.* **1976**, 54, 1703.
- (129) Asahina, Y.; Nogami, H. *Bull. Chem. Soc. Jpn.* **1942**, 17, 202.
- (130) Asahina, Y.; Shibata, S. *Chemistry of Lichen Substances*; Japan Society for the Promotion of Science: Tokyo, 1954; p165.
- (131) Aghoramurthy, K.; Sheshadri, T. *J. Sci. Ind. Res.* **1953**, 12B, 73.
- (132) Leuckert, C.; Ahmadjian, V.; Culberson, C.; Johnson, A. *Mycologica* **1990**, 82, 370.
- (133) Culberson, C. F. *Chemical and Botanical Guide to Lichen Products*; University of North Carolina Press: Chapel Hill, NC, 1969.
- (134) Okorie, D. A. *Phytochemistry* **1976**, 15, 1799.
- (135) Elix, J. A.; Musidlak, H. W.; Sala, T.; Sargent, M. V. *Aust. J. Chem.* **1978**, 31, 145.
- (136) Kathirgamanathan, S.; Ratnasooriya, W. D.; Baekstrom, P.; Anderen, R. J.; Karunaratne, V. *Pharm. Biol.* **2006**, 44, 217.
- (137) Maier, M. S.; Rosso, M. L.; Fazio, A. T.; Adler, M. T.; Bertoni, M. D. *J. Nat. Prod.* **2009**, 72, 1902.
- (138) Feige, G. B.; Lumbsch, H. T.; Huneck, S.; Elix, J. A. *J. Chromatogr.* **1993**, 646, 417.
- (139) Santesson, J. *Acta Chem. Scand.* **1968**, 22, 2393.
- (140) Santesson, J. *Ark. Kemi* **1969**, 30, 461.
- (141) Elix, J.; Crook, C. *Bryologist* **1992**, 95, 52.
- (142) Santesson, J. *Ark. Kemi* **1969**, 30, 121.
- (143) Santesson, J. *Acta Chem. Scand.* **1967**, 21, 1162.
- (144) Yoshimura, L.; Kinoshita, Y.; Yamamoto, Y.; Huneck, S.; Yamada, Y. *Phytochem. Anal.* **1994**, 5, 197.
- (145) Santesson, J. *Arkiv Chem.* **1969**, 30, 455.
- (146) Elix, J. A.; Crook, C. E.; Jiang, H.; Zhi-nin, Z. *Aust. J. Chem.* **1992**, 45, 845.
- (147) Patolia, R. J.; Trivedi, K. N. *J. Chem. Ind.* **1978**, 7, 235.
- (148) Elix, J. A.; Jones, A. J.; Lajide, L.; Coppins, B. J.; James, P. W. *Aust. J. Chem.* **1984**, 37, 2349.
- (149) Fitzpatrick, L.; Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1980**, 85.
- (150) Sundholm, E. G. *Acta Chem. Scand.* **1978**, B32, 177.
- (151) Jimenez, C.; Marcos, M.; Villaverde, M. C.; Riguera, R.; Castedo, L.; Stermitz, F. *Phytochemistry* **1989**, 28, 1992.
- (152) El-Seedi, H. R.; Hazell, A. C.; Torsell, K. B. G. *Phytochemistry* **1994**, 35, 1297.
- (153) Honda, N. K.; Pavan, F. R.; Coelho, R. G.; de Andrade Leite, S. R.; Micheletti, A. C.; Lopes, T. I. B.; Misutsu, M. Y.; Beatriz, A.; Brum, R. L.; Leite, C. Q. F. *Phytomedicine* **2010**, 17, 328.
- (154) Ingolfsdottir, K.; Chung, G. A. C.; Skulason, V. G.; Gissurarson, S. R.; Vilhelmsdottir, M. *Eur. J. Pharm. Sci.* **1998**, 6, 141.
- (155) Assante, G.; Camarda, L.; Merlini, L.; Nasini, G. *Phytochemistry* **1979**, 18, 311.
- (156) Shao, C.; Wang, C.; Wei, M.; Gu, Y.; Xia, X.; She, Z.; Lin, Y. *Magn. Reson. Chem.* **2008**, 46, 1066.
- (157) Pan, J.-H.; Deng, J.-J.; Chen, Y.-G.; Gao, J.-P.; Lin, Y.-C.; She, Z.-G.; Gu, Y.-C. *Helv. Chim. Act.* **2010**, 93, 1369.
- (158) Ahbab, M.; Borthwick, A. D.; Hooper, J. W.; Millership, J. S.; Whalley, W. B.; Ferguson, G.; Marsh, F. C. *J. Chem. Soc., Perkin Trans. 1* **1976**, 0, 1369.
- (159) Huang, Z.; Yang, R.; Yin, X.; She, Z.; Lin, Y. *Magn. Reson. Chem.* **2010**, 48, 80.
- (160) Munekata, H. *J. Biochem. Jpn.* **1953**, 40, 451.
- (161) Ginde, B. S.; Hosangadi, B. D.; Kudav, N. A.; Nayak, K. V.; Kulkarni, A. B. *J. Chem. Soc., C* **1970**, 9, 1285.
- (162) Moppett, C. E. *J. Chem. Soc., Chem. Commun.* **1971**, 9, 423.
- (163) Law, K.-K.; Chan, T.-L.; Tam, S. W. *J. Org. Chem.* **1979**, 44, 4452.
- (164) Ellis, R. C.; Whalley, W. B.; Ball, K. *J. Chem. Soc., Perkin Trans. 1* **1976**, 0, 1377.

- (165) Ferguson, G.; Kaitner, B.; Gilmore, J.; Omuaru, V. O. T.; Whalley, W. B. *J. Chem. Soc., Perkin Trans. I* **1985**, 1343.
- (166) Borthwick, A. D.; Curry, D. J.; Poynton, A.; Whalley, W. B.; Hooper, J. W. *J. Chem. Soc., Perkin Trans. I* **1980**, 243.
- (167) Raistrick, H.; Robinson, R.; White, D. E. *Biochem. J.* **1936**, 30, 1303.
- (168) Mull, R.; Nord, F. *Arch. Biochem.* **1944**, 4, 419.
- (169) Kahluwalla, V.; Sheshadri, T. *Proc. Indian Acad. Sci.* **1956**, 44A, 1.
- (170) (a) Birch, A. J.; Baldas, J.; Hlubucek, J. R.; Simpson, T. J.; Westerman, P. W. *J. Chem. Soc., Perkin Trans. I* **1976**, 898. (b) Birch, A. J.; Simpson, T. J.; Westerman, P. W. *Tetrahedron Lett.* **1975**, 47, 4173.
- (171) Hill, J. G.; Nakashima, T. T.; Vederas, J. C. *J. Am. Chem. Soc.* **1982**, 104, 1745.
- (172) Berkinshaw, J. H.; Hammady, I. M. M. *Biochem. J.* **1957**, 65, 162.
- (173) Davies, J. E.; Kirkaldy, D.; Roberts, J. D. *J. Chem. Soc.* **1960**, 0, 2169.
- (174) Davies, J. E.; Roberts, J. C.; Wallwork, S. *Chem. Ind.* **1956**, 0, 178.
- (175) Hatsuda, Y.; Kuyama, S. *J. Agric. Chem. Soc. Jpn.* **1954**, 28, 989.
- (176) Gorst-Allman, C. P.; Steyn, P. S. *J. Chem. Soc., Perkin Trans I* **1987**, 163.
- (177) Hamasaki, T.; Nakagomi, T.; Hatsuda, Y.; Fukuyama, K.; Katsube, Y. *Agric. Biol. Chem.* **1980**, 44, 1149.
- (178) Frisbad, J. C.; Samson, R. A. *Syst. Appl. Microbiol.* **2004**, 27, 672.
- (179) Frisbad, J. C.; Samson, R. A.; Smedsgaard, J. *Lett. Appl. Microbiol.* **2004**, 38, 440.
- (180) Hatsuda, Y.; Kuyama, S.; Tereshima, N. *J. Agric. Chem. Soc. Jpn.* **1954**, 28, 992.
- (181) Roberts, J. C. *J. Chem. Soc.* **1960**, 785.
- (182) King, F. E.; King, T. J.; Manning, L. C. *J. Chem. Soc.* **1957**, 563.
- (183) Bullock, E.; Kirkaldy, D.; Roberts, J. C.; Underwood, J. G. *J. Chem. Soc.* **1963**, 829.
- (184) Bullock, E.; Roberts, J. C.; Underwood, J. G. *J. Chem. Soc.* **1962**, 4179.
- (185) Holker, J. S. E.; Kagal, S. A. *Chem. Commun.* **1968**, 24, 1574.
- (186) Hamasaki, T.; Nakagomi, T.; Hatsuda, Y.; Fukuyama, K.; Katsube, Y. *Tetrahedron Lett.* **1977**, 32, 2765.
- (187) Shao, C.; She, Z.; Guo, Z.; Peng, H.; Cai, X.; Zhou, S.; Gu, Y.; Lin, Y. *Magn. Reson. Chem.* **2007**, 45, 434.
- (188) Zhu, F.; Lin, Y. *Chem. Nat. Prod.* **2007**, 43, 132.
- (189) Udvary, D. W.; Casillas, L. K.; Townsend, C. A. *J. Am. Chem. Soc.* **2002**, 124, 5294.
- (190) Henry, K. M.; Townsend, C. A. *J. Am. Chem. Soc.* **2005**, 127, 3724.
- (191) Maes, C. M.; Steyn, P. S. *J. Chem. Soc., Perkin Trans. I* **1984**, 1137.
- (192) Pachler, K. G.; Steyn, P. S.; Vleggaar, R.; Wessels, P. L. *J. Chem. Soc., Chem. Commun.* **1975**, 9, 355.
- (193) Burkhardt, H. J.; Forgacs, J. *Tetrahedron* **1968**, 24, 717.
- (194) Gröger, D.; Erge, D.; Franck, B.; Ohnsorge, U.; Flasch, H.; Hüper, F. *Chem. Ber.* **1968**, 101, 1970.
- (195) (a) Birch, A. J.; Baldas, J.; Hlubucek, J. R.; Simpson, T. J.; Westerman, P. W. *J. Chem. Soc., Perkin Trans. I* **1976**, 898. (b) Birch, A. J.; Simpson, T. J.; Westerman, P. W. *Tetrahedron Lett.* **1975**, 47, 4173.
- (196) Joshi, B. K.; Glover, J. B.; Wicklow, D. T. *J. Nat. Prod.* **2002**, 65, 1734.
- (197) Seto, H.; Cary, L. W.; Tanabe, M. *Tetrahedron Lett.* **1974**, 51/52, 4491.
- (198) Nakashima, T. T.; Vederas, J. C. *J. Chem. Soc., Chem. Commun.* **1982**, 4, 206.
- (199) Pachler, K. G. R.; Steyn, P. S.; Vleggaar, R.; Wessels, P. L.; Scott, D. B. *J. Chem. Soc., Perkin Trans I* **1976**, 1182.
- (200) Zamir, L. O.; Hufford, K. D. *Appl. Environ. Microbiol.* **1981**, 41, 168.
- (201) Bradner, W. T.; Bush, J. A.; Myllymaki, R. W.; Nettleton, D. E., Jr.; O'Herron, F. A. *Antimicrob. Agents Chemother.* **1975**, 8, 159.
- (202) Pepeljnjak, S.; Slobodnjak, Z.; Šegvić, M.; Peraica, M.; Pavlović, M. *Hum. Exp. Toxicol.* **2004**, 23, 15.
- (203) Bünger, J.; Westphal, G.; Mönnich, A.; Hinnendahl, B.; Hallier, E.; Müller, M. *Toxicology* **2004**, 202, 199.
- (204) Engelhart, S.; Loock, A.; Skutlarek, D.; Sagunski, H.; Lommel, A.; Färber, H.; Exner, M. *Appl. Environ. Microbiol.* **2002**, 68, 3886.
- (205) Rance, M. J.; Roberts, J. C. *Tetrahedron Lett.* **1969**, 10, 277.
- (206) Horne, S.; Rodrigo, R. *J. Org. Chem.* **1990**, 55, 4520.
- (207) Horne, S.; Weeratunga, G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1990**, 1, 39.
- (208) Casillas, L. K.; Townsend, C. A. *J. Org. Chem.* **1999**, 64, 4050.
- (209) Minto, R. E.; Townsend, C. A. *Chem. Rev.* **1997**, 97, 2537.
- (210) Essery, J. M.; O'Herron, F. A.; McGregor, D. N.; Bradner, W. T. *J. Med. Chem.* **1976**, 19, 1339.
- (211) Kamal, A.; Husain, S.; Noorani, R.; Murtaza, M.; Qureshi, J.; Qureshi, A. *Pakistan J. Sci. Ind. Res.* **1970**, 13, 251.
- (212) (a) Kamal, A.; Husain, S.; Qureshi, A. *Pakistan J. Sci. Ind. Res.* **1971**, 13, 90. (b) Kamal, A.; Husain, S.; Qureshi, A. *Pakistan J. Sci. Ind. Res.* **1971**, 14, 104.
- (213) Chexal, K. K.; Fourweather, C.; Holker, J. S. E.; Simpson, T. J.; Young, K. *J. Chem. Soc., Perkin Trans. I* **1974**, 1584.
- (214) Horeau, A. *Tetrahedron Lett.* **1961**, 2, 506.
- (215) Chexal, K. K.; Holker, J. S. E.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. I* **1975**, 549.
- (216) Ishida, M.; Hamasaki, T.; Hatsuda, Y. *Agric. Biol. Chem.* **1978**, 42, 465.
- (217) Kawahara, N.; Nozawa, K.; Nakajima, S.; Kiwai, K.-I. *J. Chem. Soc., Perkin Trans. I* **1988**, 907.
- (218) Holker, J. S. E.; Lapper, R.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. I* **1974**, 2135.
- (219) Bardshiri, E.; McIntyre, C. R.; Simpson, T. J.; Moore, R. N.; Trimble, L. A.; Vederas, J. C. *J. Chem. Soc., Chem. Commun.* **1984**, 21, 1404.
- (220) Sandifer, R. M.; Battacharya, A. K.; Harris, T. M. *J. Org. Chem.* **1981**, 46, 2260.
- (221) Schwab, J. M.; Li, W.; Thomas, L. P. *J. Am. Chem. Soc.* **1983**, 105, 4800.
- (222) Ahmed, S. A.; Bardshiri, E.; McIntyre, C.; Simpson, T. J. *Aust. J. Chem.* **1992**, 45, 249.
- (223) Ahmed, S. A.; Bardshiri, E.; Simpson, T. J. *J. Chem. Soc., Chem. Commun.* **1987**, 12, 883.
- (224) Leuckert, C.; Mayrhofer, H. *Herzogia* **1984**, 6, 373.
- (225) Elix, J. A.; Gaul, K. L.; Sterns, M.; Wahid bin Samsudin, M. *Aust. J. Chem.* **1987**, 40, 1169.
- (226) Elix, J. A.; Portelli, V. A. *Aust. J. Chem.* **1990**, 43, 1773.
- (227) Elix, J. A.; Gaul, K. L.; Jiang, H. *Aust. J. Chem.* **1993**, 46, 95.
- (228) Hesse, O. *J. Prakt. Chem.* **1898**, 58, 465.
- (229) Kennedy, G.; Breen, J.; Keane, J.; Nolan, T. J. *Sci. Proc. R. Dublin Soc.* **1937**, 21, 557.
- (230) Huneck, S. *Tetrahedron Lett.* **1966**, 30, 3547.
- (231) Santesson, J. *Ark. Kemi* **1969**, 30, 449.
- (232) Jayalakshmi, V.; Neelakantan, S.; Seshadri, T. R. *Curr. Sci.* **1968**, 3, 196.
- (233) Arshad, M.; Devlin, J. P.; Ollis, W. D. *J. Chem. Soc., C* **1971**, 7, 1324.
- (234) Neelakantan, S.; Thillaichidambaram, N. *Curr. Sci.* **1973**, 42, 21.
- (235) Takenaka, Y.; Hamada, N.; Tanahashi, T. *Phytochemistry* **2005**, 66, 665.
- (236) Hesse, O. *J. Prakt. Chem.* **1898**, 28, 465.
- (237) Santesson, J.; Wachtmeister, C. A. *Ark. Kemi* **1969**, 30, 445.
- (238) Shibamoto, T.; Bernhard, R. A. *Plant Foods Hum. Nutr.* **1974**, 24, 199.
- (239) Schmitt, I.; Lumbsch, H. T. *Mol. Phylogenet. Evol.* **2004**, 33, 43.
- (240) Huneck, S. Z. *Naturforsch., B* **1969**, 24, 756.
- (241) Huneck, S.; Santesson, J. Z. *Naturforsch., B* **1969**, 24, 756.

- (242) Belofsky, G. N.; Gloer, K. B.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Nat. Prod.* **1998**, *61*, 1115.
- (243) Řezanaka, T.; Jáchymová, J.; Dembitsky, V. M. *Phytochemistry* **2003**, *62*, 607.
- (244) Rezanaka, T.; Dembitsky, V. M. *J. Chromatogr., A* **2003**, *995*, 109.
- (245) Poelt, J.; Huneck, S. *Österr. Bot. Z.* **1968**, *115*, 411.
- (246) Sundholm, E. *Tetrahedron* **1978**, *34*, 577.
- (247) Malmström, J.; Christopherson, C.; Barrero, A. F.; Oltra, J. E.; Justicia, J.; Rosales, A. *J. Nat. Prod.* **2002**, *65*, 364.
- (248) Ayer, W. A.; Browne, L. M.; Lin, G. *J. Nat. Prod.* **1989**, *52*, 119.
- (249) Abdel-Lateff, A.; Klemke, C.; König, G. M.; Wright, A. D. *J. Nat. Prod.* **2003**, *66*, 706.
- (250) Davis, R. A.; Pierens, G. K. *Magn. Reson. Chem.* **2006**, *44*, 966.
- (251) Wijeratne, E. M. K.; Turbyville, T. J.; Fritz, A.; Whitesell, L.; Gunatilaka, A. A. L. *Bioorg. Med. Chem.* **2006**, *14*, 7917.
- (252) Hussain, H.; Krohn, K.; Flörke, U.; Schulz, B.; Draeger, S.; Pescitelli, G.; Antus, S.; Kurtán, T. *Eur. J. Org. Chem.* **2007**, *2*, 292.
- (253) Kawahara, N.; Sekita, S.; Satake, M.; Udagawa, S.; Kawai, K. *Chem. Pharm. Bull.* **1994**, *42*, 1720.
- (254) Sato, S.; Nakagawa, R.; Fudo, R.; Fukuda, Y.; Yoshimura, T.; Kaida, K.; Ando, T.; Kameyama, T.; Tsuji, T. *J. Antibiot.* **1997**, *50*, 614.
- (255) Sato, S.; Suga, Y.; Yoshimura, T.; Nakagawa, R.; Tsuji, T.; Umemura, K.; Andoh, T. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2653.
- (256) Fujimoto, H.; Satoh, Y.; Yamaguchi, K.; Yamazaki, M. *Chem. Pharm. Bull.* **1998**, *46*, 1506.
- (257) Fujimoto, H.; Asai, T.; Kim, Y.-P.; Ishibashi, M. *Chem. Pharm. Bull.* **2006**, *54*, 550.
- (258) Tatsuta, K.; Yoshihara, S.; Hattori, N.; Yoshida, S.; Hosokawa, S. *J. Antibiot.* **2009**, *62*, 469.
- (259) Řezanaka, T.; Sigler, K. *J. Nat. Prod.* **2007**, *70*, 1487.
- (260) Zhang, W.; Krohn, K.; Ullah, Z.; Flörke, U.; Pescitelli, G.; Di Bari, L.; Antus, S.; Kurtán, T.; Rheinmeiner, J.; Draeger, S.; Schulz, B. *Chem.—Eur. J.* **2008**, *14*, 4913.
- (261) Holker, J. S. E.; O'Brien, E.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. I* **1983**, 1365.
- (262) Nicolaou, K. C.; Li, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6579.
- (263) Gérard, E. M. C.; Bräse, S. *Chem.—Eur. J.* **2008**, *14*, 8086.
- (264) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37*, 1218.
- (265) Nising, C. F.; Ohnemüller, U. K.; Bräse, S. *Synthesis* **2006**, *16*, 2643.
- (266) Gabbutt, C. D.; Hepworth, J. D.; Urquhart, M. W. J.; Vasquez de Miguel, L. M. *J. Chem. Soc., Perkin Trans. I* **1997**, 1819.
- (267) Krick, A.; Kehraus, S.; Gerhäuser, C.; Klimo, K.; Nieger, M.; Maier, A.; Fiebig, H.-H.; Atobdierei, I.; Raabe, G.; Fleischhauer, J.; König, G. M. *J. Nat. Prod.* **2007**, *70*, 353.
- (268) Qin, T.; Johnson, R. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2011**, *133*, 1714.
- (269) Turner, W. B. *J. Chem. Soc., Perkin Trans. I* **1978**, 1621.
- (270) Nising, C. F.; Ohnemüller (née Schmid), U. K.; Bräse, S. *Angew. Chem.* **2006**, *45*, 307.
- (271) Tietze, L. F.; Spiegl, D. A.; Stecker, F.; Major, J.; Raith, C.; Große, C. *Chem.—Eur. J.* **2008**, *14*, 8956.
- (272) Volz, N.; Bröhmer, M. C.; Nieger, M.; Bräse, S. *Synlett* **2009**, *4*, 550.
- (273) Bröhmer, M. C.; Bourcet, E.; Nieger, M.; Bräse, S. *Chem.—Eur. J.* **2011**, *17*, 13706.
- (274) Siddiqui, I. N.; Zahoor, A.; Hussain, A.; Ahmed, I.; Ahmad, V. U.; Padula, D.; Draeger, S.; Schulz, B.; Meier, K.; Steinert, M.; Kurt, T.; Flörke, Pescitelli, G.; Krohn, K. *J. Nat. Prod.* **2011**, *74*, 365.
- (275) Wang, F.; Dong, Z.-J.; Liu, J.-K. *Z. Naturforsch.* **2007**, *62b*, 1329.
- (276) Phuwapraisirisan, P.; Sawang, K.; Siripong, P.; Tip-pyang, S. *Tetrahedron Lett.* **2007**, *48*, 5193.
- (277) Osterhage, C.; König, G. M.; Höller, U.; Wright, A. D. *J. Nat. Prod.* **2002**, *65*, 306.
- (278) Miyagawa, H.; Nagal, S.; Tsurushima, T.; Sato, M.; Ueno, T.; Fukami, H. *Biosci., Biotechnol., Biochem.* **1994**, *58*, 1143.
- (279) Lim, C.-H.; Miyagawa, H.; Akamatsu, T.; Nakawa, Y.; Ueno, T. *J. Pestic. Sci.* **1998**, *23*, 281.
- (280) Bicalho, B.; Gonçalves, R. A. C.; Zibordi, A. P. M.; Manfio, G. P.; Marsaioli, A. J. *Z. Naturforsch., C* **2003**, *58*, 746.
- (281) Lin, J.; Liu, S.; Sun, B.; Niu, S.; Li, E.; Liu, X.; Che, Y. *J. Nat. Prod.* **2010**, *73*, 905.
- (282) Isaka, M.; Palasarn, S.; Aunchareon, P.; Komwijit, S.; Jones, E. B. *G. Tetrahedron Lett.* **2009**, *50*, 284.
- (283) Ōmura, S.; Iwai, Y.; Hinotozawa, K. *J. Antibiot.* **1982**, *35*, 645.
- (284) Nakagawa, A.; Ōmura, S.; Kushida, K.; Shimizu, H.; Lukacs, G. *J. Antibiot.* **1987**, *40*, 301.
- (285) Ōmura, S.; Nakagawa, A.; Kushida, K.; Lukacs, G. *J. Am. Chem. Soc.* **1986**, *108*, 6088.
- (286) Kelly, T. R.; Jagoe, C. T.; Li, Q. *J. Am. Chem. Soc.* **1989**, *111*, 4522.
- (287) Mehta, G.; Venkateswarlu, Y. *J. Chem. Soc., Chem. Commun.* **1988**, *17*, 1200.
- (288) Mehta, G.; Shah, S. R.; Venkateswarlu, Y. *Tetrahedron* **1994**, *50*, 11729.
- (289) Mehta, G.; Shah, S. R. *Tetrahedron Lett.* **1991**, *32*, 5195.
- (290) Yadav, J. S. *Pure Appl. Chem.* **1993**, *65*, 1349.
- (291) Qiao, Y.; Okazaki, T.; Ando, T.; Mizoue, K.; Kondo, K.; Eguchi, T.; Kakinuma, K. *J. Antibiot.* **1998**, *51*, 282.
- (292) Kondo, K.; Eguchi, T.; Kakinuma, K.; Qiao, Y. *J. Antibiot.* **1998**, *51*, 288.
- (293) Eguchi, T.; Kondo, K.; Kakinuma, K.; Uekusa, H.; Ohashi, Y.; Mizoue, K.; Qiao, Y.-F. *J. Org. Chem.* **1999**, *64*, 5371.
- (294) Masuo, R.; Ohmori, K.; Hintermann, L.; Yoshida, S.; Suzuki, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3462.
- (295) Hintermann, L.; Masuo, R.; Suzuki, K. *Org. Lett.* **2008**, *10*, 4859.
- (296) Malet-Cascon, L.; Romero, F.; Espliego-Vasquez, F.; Gravalos, D.; Fernandez-Puentes, J. L. *J. Antibiot.* **2003**, *56*, 219.
- (297) Perez-Baz, J.; Canedo, L. M.; Garcia Gravalos, D.; Romero, F.; Francisco, F.; Espliego, F. New polycyclic xanthones and their use; PCT Int. Appl. WO 2002000663 A2 20020103, 2002.
- (298) Drautz, H.; Keller-Schierlein, W.; Zähner, H. *Arch. Micrbiol.* **1975**, *106*, 175.
- (299) Donadio, S.; Staver, M. J.; McAlpine, J. B.; Swanson, S. J.; Katz, L. *Science* **1991**, *252*, 675.
- (300) Dobler, M.; Keller-Schierlein, W. *Helv. Chim. Acta* **1977**, *60*, 178.
- (301) Bockholt, H.; Udvarnoki, G.; Rohr, J.; Mocek, U.; Baele, J. M.; Floss, H. *G. J. Org. Chem.* **1994**, *59*, 2064.
- (302) Carter, G. T.; Borders, D. T.; Goodman, J. J.; Ashcroft, J.; Greenstein, M. J.; Maiese, W.; Pearce, C. J. *J. Chem. Soc., Perkin Trans. I* **1991**, 2215.
- (303) Duthaler, R.; Mathies, P.; Petter, W.; Heuberger, C.; Scherrer, V. *Helv. Chim. Acta* **1984**, *67*, 1217.
- (304) Duthaler, R.; Wegmann, H.-U. *Helv. Chim. Acta* **1984**, *67*, 1755.
- (305) Duthaler, R.; Scherrer, V. *Helv. Chim. Acta* **1984**, *67*, 1767.
- (306) Aoki, M.; Itezono, Y.; Shirai, H.; Nakayama, N.; Sakai, A.; Tanaka, Y.; Yamaguchi, A.; Shimma, N.; Yokose, K. *Tetrahedron Lett.* **1991**, *32*, 4737.
- (307) Wrigley, S. K.; Latif, M. A.; Gibson, T. M.; Chicarelli-Robinson, M. I.; Williams, D. H. *Pure Appl. Chem.* **1994**, *66*, 2383.
- (308) Kumagai, K.; Hosotani, N.; Kikuchi, K.; Kimura, T.; Saji, I. *J. Antibiot.* **2003**, *56*, 610.
- (309) Tatsuta, K.; Kasai, S.; Amano, Y.; Yamaguchi, T.; Seki, M.; Hosokawa, S. *Chem. Lett.* **2007**, *36*, 10.
- (310) Řezanaka, T.; Řezanaka, P.; Sigler, K. *J. Nat. Prod.* **2008**, *71*, 820.
- (311) Kumagai, K.; Hosotani, N.; Kikuchi, K.; Kimura, T.; Saji, I. *J. Antibiot.* **2003**, *56*, 610.
- (312) Terui, Y.; Yiwen, C.; Jun-ying, L.; Ando, T.; Yamamoto, H.; Kawamura, Y.; Tomishima, Y.; Uchida, S.; Okazaki, T.; Munetomo, E.; Seki, T.; Yamamoto, K.; Murakami, S.; Kawashima, A. *Tetrahedron Lett.* **2003**, *44*, 5427.

- (313) Maiese, W. M.; Lechevalier, M. P.; Lechevalier, H. A.; Korshalla, J.; Goodman, J.; Wildey, M. J.; Kuck, N.; Greenstein, M. J. *Antibiot.* **1989**, *42*, 846.
- (314) Carter, G. T.; Nietsche, J. A.; Williams, D. R.; Borders, D. B. *J. Antibiot.* **1990**, *43*, 504.
- (315) Qadri, S. M. H.; Saldin, H.; Ueno, Y.; Al-Ballaa, S. R. *Cancer Chemotherapy* **1992**, *38*, 395.
- (316) Hopp, D. C.; Milanowski, D. J.; Rhea, J.; Jacobsen, D.; Rabenstein, J.; Smith, C.; Romari, K.; Clarke, M.; Francis, L.; Irigoyen, M.; Luche, M.; Carr, G. J.; Mocek, U. *J. Nat. Prod.* **2008**, *71*, 2032.
- (317) Kobayashi, K.; Nishino, C.; Ohya, J.; Sato, S.; Mikawa, T.; Shiobara, Y.; Kodama, M. *J. Antibiot.* **1988**, *41*, 502.
- (318) Kobayashi, K.; Nishino, C.; Ohya, J.; Sato, S.; Mikawa, T.; Shiobara, Y.; Kodama, M. *J. Antibiot.* **1988**, *41*, 741.
- (319) Gurevich, A. I.; Karapetyan, M. G.; Kolosov, M. N.; Omelchenko, V. V.; Onoprienko, V. V.; Petranko, G. I.; Popravko, S. A. *Tetrahedron Lett.* **1972**, *18*, 1751.
- (320) Gurevich, A. I.; Deschko, T. I.; Kogan, G. A.; Kolosov, M. N.; Kudryashkova, V. V.; Onoprienko, V. V. *Tetrahedron Lett.* **1974**, *33*, 2801.
- (321) Isaka, M.; Palasarn, S.; Kocharin, K.; Saenboonreung, J. *J. Nat. Prod.* **2005**, *68*, 945.
- (322) Chutrakul, C.; Boonruangprapal, T.; Suvannakad, R.; Isaka, M.; Sirithunya, P.; Toojinda, T.; Kirtikara, K. *J. Appl. Microbiol.* **2009**, *107*, 1624.
- (323) Fransden, N. *Arch. Mikrobiol.* **1955**, *22*, 145.
- (324) Schrösser, E. *Phytopathol. Z.* **1962**, *44*, 295.
- (325) Schrösser, E. *Phytopathol. Z.* **1964**, *50*, 386.
- (326) Assante, G.; Locci, R.; Camarada, L.; Merlini, L.; Nasini, G. *Phytochemistry* **1977**, *16*, 243.
- (327) (a) Kuyama, S.; Tamura, T. *J. Am. Chem. Soc.* **1957**, *79*, 5725.
(b) Lousberg, R.; Weiss, U.; Salemink, C.; Arnone, A.; Merlini, L.; Nasini, G. *J. Chem. Soc., D* **1971**, *1463*. (c) Weiss, U.; Merlini, L.; Nasini, G. *Fortschr. Chem. Org. Naturst.* **1987**, *52*, 1. (d) Mací, F.; Vianello, A. *Plant Cell Environ.* **1979**, *2*, 267.
- (328) Schrösser, E. *Phytopathol. Mediterr.* **1971**, *10*, 154.
- (329) Balis, C.; Payne, M. G. *Phytopathology* **1971**, *61*, 1477.
- (330) Ducrot, P.-H. *C. R. Acad. Sci. Paris, Chim.* **2001**, *4*, 273.
- (331) Arnone, A.; Nasini, G.; Merlini, L.; Ragg, E.; Assante, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, *0*, 145.
- (332) Milat, M.-L.; Prangé, T.; Ducrot, P.-H.; Tabet, J.-C.; Einhorn, J.; Blein, J.-P. *J. Am. Chem. Soc.* **1992**, *114*, 1478.
- (333) Ducrot, P.-H.; Milat, M.-L.; Blein, J.-P.; Lallemand, J.-Y. *J. Chem. Soc., Chem. Commun.* **1994**, *19*, 2215.
- (334) CBT 1 was isolated directly from SiO₂ chromatography as a dimeric dimagnesium salt.
- (335) Jalal, M. A. F.; Hossain, M. B.; Robeson, D. J.; van der Helm, D. *J. Am. Chem. Soc.* **1992**, *114*, 5967.
- (336) Robeson, D. J.; Jalal, M. A. F. *Phytochemistry* **1993**, *33*, 1546.
- (337) Milat, M.-L.; Blein, J.-P.; Einhorn, J.; Tabet, J.-C.; Ducrot, P.-H.; Lallemand, J.-Y. *Tetrahedron Lett.* **1993**, *34*, 1483.
- (338) Ducrot, P.-H.; Lallemand, J.-Y.; Milat, M.-L.; Blein, J.-P. *Tetrahedron Lett.* **1994**, *35*, 8797.
- (339) Prangé, T.; Neuman, A.; Milat, M.-L.; Blein, J.-P. *Acta Crystallogr., B* **1995**, *B51*, 308.
- (340) Milat, M.-L.; Blein, J.-P. *J. Chromatogr., A* **1995**, *699*, 277.
- (341) Goudet, C.; Benitah, J.-P.; Milat, M.-L.; Sentenac, H.; Thibaud, J.-B. *Biophys. J.* **1999**, *77*, 3052.
- (342) Ducrot, P.-H.; Einhorn, J.; Kerhoas, L.; Lallemand, J.-Y.; Milat, M.-L.; Blein, J.-P.; Neuman, A.; Prangé, T. *Tetrahedron Lett.* **1996**, *37*, 3121.
- (343) Prangé, T.; Neuman, A.; Milat, M.-L.; Blein, J.-P. *J. Chem. Soc., Perkin Trans. 2* **1997**, *9*, 1819.
- (344) Macrí, F.; Vianello, A. *Physiol. Plant Pathol.* **1979**, *15*, 161.
- (345) Macrí, F.; Vianello, A.; Cerana, R.; Rasi-Caldogno, F. *Plant Sci. Lett.* **1980**, *18*, 207.
- (346) Macrí, F.; Dell'Antone, P.; Vianello, A. *Plant, Cell Environ.* **1983**, *6*, 555.
- (347) Blein, J.-P.; Bourdil, I.; Rossignol, M.; Scalla, R. *Plant Physiol.* **1988**, *88*, 429.
- (348) Rustérucci, C.; Milat, M.-L.; Blein, J.-P. *Phytochemistry* **1996**, *42*, 979.
- (349) Ding, G.; Maume, G.; Milat, M.-L.; Humbert, C.; Blein, J.-P.; Maume, B. *Cell Biol. Int.* **1996**, *20*, 523.
- (350) Simon-Plas, F.; Gomès, E.; Milat, M.-L.; Pugin, A.; Blein, J.-P. *Plant Physiol.* **1996**, *111*, 773.
- (351) Gapillout, I.; Mikes, V.; Milat, M.-L.; Simon-Plas, F.; Pugin, A.; Blein, J.-P. *Phytochemistry* **1996**, *43*, 387.
- (352) Gomès, E.; Gordon-Weeks, R.; Simon-Plas, F.; Pugin, A.; Milat, M.-L.; Leigh, R.; Blein, J.-P. *Biochim. Biophys. Acta* **1996**, *1285*, 38.
- (353) Mikes, V.; Milat, M.-L.; Collange, E.; Pâris, M.; Blein, J.-P. *Biophys. Chem.* **1994**, *52*, 259.
- (354) Mikes, V.; Milat, M.-L.; Pugin, A.; Blein, J.-P. *Biochim. Biophys. Acta* **1994**, *1195*, 124.
- (355) Gomès, E.; Venema, K.; Simon-Plas, F.; Milat, M.-L.; Palmgren, M.; Blein, J.-P. *FEBS Lett.* **1996**, *398*, 48.
- (356) Gomès, E.; Simon-Plas, F.; Milat, M.-L.; Gapillout, I.; Mikès, V.; Pugin, A.; Blein, J.-P. *Physiol. Plant.* **1996**, *98*, 133.
- (357) Goudet, C.; Véry, A.-A.; Milat, M.-L.; Idefonse, M.; Thibaud, J.-B.; Sentenac, H.; Blein, J.-P. *Plant J.* **1998**, *14*, 359.
- (358) Goudet, C.; Milat, M.-L.; Benitah, J.-P.; Sentenac, H.; Thibaud, J.-B. *Biophys. J.* **1999**, *77*, 3052.
- (359) Goudet, C.; Milat, M.-L.; Sentenac, H.; Thibaud, J.-B. *Mol. Plant-Microbe Interact.* **2000**, *13*, 203.
- (360) Balasubramanian, S. V.; Sidkar, S. K.; Easwaran, K. R. K. *Biochem. Biophys. Res. Commun.* **1992**, *189*, 1038.
- (361) Fyles, T. M.; Loock, D.; van Straaten-Nijenhuis, W. F.; Zhou, X. *J. Org. Chem.* **1996**, *61*, 8866.
- (362) Duffault, J.-M.; Tellier, F. *Synth. Commun.* **1998**, *28*, 2467.
- (363) Schüffler, A.; Liermann, J. C.; Kolshorn, H.; Opatz, T.; Anke, H. *Tetrahedron Lett.* **2009**, *50*, 4813.
- (364) Wagenaar, M. M.; Clardy, J. *J. Nat. Prod.* **2001**, *64*, 1006.
- (365) Kraft, F. *Arch. Pharm.* **1906**, *244*, 79.
- (366) Bergmann, W. *Ber. Dtsch. Chem. Ges.* **1932**, *65*, 1486.
- (367) Bergmann, W. *Ber. Dtsch. Chem. Ges.* **1932**, *65*, 1489.
- (368) Yamazuki, M.; Maebashi, Y.; Miyaki, K. *Chem. Pharm. Bull.* **1971**, *19*, 199.
- (369) Anderson, R.; Büchi, G.; Kobbe, B.; Demain, A. L. *J. Org. Chem.* **1977**, *42*, 352.
- (370) Kurobane, I.; Vining, L. C.; McInnes, A. G. *J. Antibiot.* **1979**, *32*, 1256.
- (371) Zeng, R.; Luo, S.; Shi, Y. *Ying Yong Sheng Tai Xue Bao* **2004**, *15*, 145.
- (372) Steyn, P. S. *Tetrahedron* **1970**, *26*, 51.
- (373) Howard, C. C.; Johnstone, R. A. W.; Entwistle, I. D. *J. Chem. Soc., Chem. Commun.* **1973**, *19*, 464.
- (374) Howard, C. C.; Johnstone, R. A. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, *2440*.
- (375) Kurobane, I.; Vining, L. C. *Tetrahedron Lett.* **1978**, *16*, 1379.
- (376) Guo, Z.; She, Z.; Shao, C.; Wen, L.; Liu, F.; Zheng, Z.; Lin, Y. *Magn. Reson. Chem.* **2007**, *45*, 777.
- (377) Franck, B.; Thiele, O. W.; Reschke, T. *Angew. Chem.* **1961**, *14*, 494.
- (378) Franck, B.; Thiele, O. W.; Reschke, T. *Chem. Ber.* **1962**, *95*, 1328.
- (379) Franck, B.; Baumann, G. *Chem. Ber.* **1963**, *96*, 3209.
- (380) Franck, B.; Gottschalk, E. M. *Angew. Chem.* **1964**, *76*, 438.
- (381) Franck, B.; Gottschalk, E. M.; Ohnsorge, U.; Baumann, G. *Angew. Chem.* **1964**, *76*, 438.
- (382) Aberhart, D. J.; Chen, Y. S.; DeMayo, P.; Stothers, J. B. *Tetrahedron* **1965**, *21*, 1417.
- (383) Millot, M.; Tomasi, S.; Studzinska, E.; Rouaud, I.; Boustie, J. J. *Nat. Prod.* **2009**, *72*, 2177.
- (384) Molina, M. C.; Crespo, A.; Vicente, C.; Elix, J. *Plant Phys. Biochem.* **2003**, *41*, 175.

- (385) Yoshioka, I.; Nakanishi, T.; Izumi, S.; Kitagawa, I. *Chem. Pharm. Bull.* **1968**, *16*, 2090.
- (386) Santos, L. C.; Honda, N. K.; Carlos, I. Z.; Villegas, W. *Fitoterapia* **2004**, *75*, 473.
- (387) Yoshioka, I.; Yamauchi, H.; Murata, K.; Kitagawa, I. *Chem. Pharm. Bull.* **1972**, *20*, 1082.
- (388) Ren, H.; Tian, L.; Gu, Q.; Zhu, W. *Arch. Pharm. Res.* **2006**, *29*, 59.
- (389) Fujimoto, Y.; Yokoyama, E.; Morooka, N.; Tsunoda, H.; Tatsumi, T. *Proc. Jpn. Assoc. Mycotoxicol.* **1983**, *17*, 52.
- (390) Frisvad, J. C.; Smedsgaard, J.; Larsen, T.; Samsen, R. A. *Stud. Mycol.* **2004**, *49*, 201.
- (391) Freeborn, A. *Pharm. J.* **1912**, *88*, 568.
- (392) Barger, G. *Ergot and Ergotism*; Gurney and Jackson: London, 1931.
- (393) Bergmann, W. *Ber. Dtsch. Chem. Ges.* **1932**, *65*, 1486.
- (394) Eglington, G.; King, F. E.; Lloyd, G.; Loder, J.; Marshall, J. R.; Robertson, A.; Whalley, W. B. *J. Chem. Soc.* **1958**, 1833.
- (395) Stoll, A.; Renz, A.; Brack, A. *Helv. Chim. Acta* **1952**, *35*, 2022.
- (396) ApSimon, J. W.; Corran, J. A.; Creasey, N. G.; Marlow, W.; Whalley, W. B.; Sim, K. Y. *Proc. Chem. Soc.* **1963**, 313.
- (397) Aberhart, D.; deMayo, P. *Tetrahedron* **1966**, *22*, 2359.
- (398) Franck, B.; Baumann, G. *Chem. Ber.* **1966**, *99*, 3875.
- (399) Franck, B.; Gottschalk, E.-M.; Ohnsorge, U.; Hüper, F. *Chem. Ber.* **1966**, *99*, 3842.
- (400) Eglington, G.; King, F. E.; Lloyd, G.; Loder, J.; Marshall, J. R.; Robertson, A. *J. Chem. Soc.* **1958**, *80*, 1833.
- (401) ApSimon, J. W.; Corran, J. A.; Creasey, N. G.; Sim, K. Y.; Whalley, W. B. *Proc. Chem. Soc.* **1963**, 209.
- (402) ApSimon, J. W.; Corran, J. A.; Creasey, N. G.; Sim, K. Y.; Whalley, W. B. *J. Chem. Soc.* **1965**, 4130.
- (403) Asher, J. D. M.; McPhail, A. T.; Robertson, J. M.; Silverston, J. D.; Sim, G. A. *Proc. Chem. Soc.* **1963**, 210.
- (404) ApSimon, J. W.; Corran, J. A.; Creasey, N. G.; Marlow, W.; Whalley, W. B.; Sim, K. Y. *J. Chem. Soc.* **1965**, 4144.
- (405) Franck, B.; Baumann, G.; Ohnsorge, U. *Tetrahedron Lett.* **1965**, *25*, 2031.
- (406) (a) Franck, B.; Baumann, G. *Chem. Ber.* **1966**, *99*, 3863. (b) Franck, B.; Baumann, G. *Chem. Ber.* **1966**, *99*, 3875.
- (407) Franck, B.; Hüper, F.; Gröger, D.; Erge, D. *Chem. Ber.* **1968**, *101*, 1955.
- (408) Leistner, E.; Zenk, M. H. *Tetrahedron Lett.* **1967**, *5*, 475.
- (409) Hooper, J. W.; Marlow, W.; Whalley, W. B.; Borthwick, A. D.; Bowden, R. *Chem. Commun.* **1971**, 111.
- (410) Hooper, J. W.; Marlow, W.; Whalley, W. B.; Borthwick, A. D.; Bowden, R. *J. Chem. Soc., C* **1971**, *21*, 3580.
- (411) Howard, C. C.; Johnstone, R. A. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2033.
- (412) Howard, C. C.; Johnstone, R. A. W.; King, J.; Lessinger, L. J. *Chem. Soc., Perkin Trans. 1* **1976**, 1820.
- (413) Johnstone, R. A. W.; Howard, C. C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1583.
- (414) Kurobane, I.; Vining, L. C.; McInnes, A. G. *Tetrahedron Lett.* **1978**, *47*, 4633.
- (415) Zhang, W.; Krohn, K.; Ullah, Z.; Flörke, U.; Pescitelli, G.; Di Bari, L.; Antus, S.; Kurtán, T.; Rheinmeiner, J.; Draeger, S.; Schulz, B. *Chem.—Eur. J.* **2008**, *14*, 4913.
- (416) Carlton, W. W.; Tiute, J.; Misilev, P. *Toxicol. Appl. Pharmacol.* **1968**, *13*, 372.
- (417) Misilvec, P.; Tuite, J. *Mycologia* **1970**, *62*, 67.
- (418) Ciegler, A.; Hayes, A. W.; Vesonder, R. F. *Appl. Environ. Microbiol.* **1980**, *39*, 285.
- (419) Reddy, C. S.; Reddy, R. V.; Hayes, A. W. *J. Chromatogr.* **1981**, *208*, 17.
- (420) Ishida, T.; Ohoishi, J.; Yoshida, K.; Akashi, K.; Takada, I. *Chem. Abs.* **1975**, *82*, 72787c.
- (421) Shimizu, M.; Nakamura, M.; Kataoka, T.; Iwaguchi, T. *Cancer Chemother. Pharmacol.* **1983**, *11*, 144.
- (422) Wang, B. H.; Polya, G. H. *Planta Med.* **1996**, *62*, 111.
- (423) Reddy, C. S. *Hum. Exp. Toxicol.* **2005**, *24*, 203.
- (424) Reddy, R. V.; Bouchard, G.; Johnson, G.; Reddy, C. S. *Toxic Subst. Mech.* **1998**, *17*, 19.
- (425) Balasubramanian, G.; Hanumegowda, U.; Reddy, C. S. *Toxicol. Appl. Pharmacol.* **2000**, *169*, 142.
- (426) Hanumegowda, U. M.; Dhulipala, V. S.; Reddy, C. S. *Toxicol. Sci.* **2002**, *66*, 55.
- (427) Hanumegowda, U. M.; Judy, B.; Welshons, W. V.; Reddy, C. S. *Toxicol. Sci.* **2002**, *66*, 159.
- (428) Franck, B.; Stöckigt, J.; Zeidler, U.; Franckowiack, G. *Chem. Ber.* **1973**, *106*, 1198.
- (429) Nising, C. F.; Schmidt, U. K.; Nieger, M.; Bräse, S. *J. Org. Chem.* **2004**, *69*, 6830.
- (430) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447. (c) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001.
- (431) Asahina, Y. *J. Jpn. Bot.* **1967**, *42*, 1.
- (432) Nuno, M. *J. Jpn. Bot.* **1971**, *46*, 294.
- (433) Yang, D.-M.; Takeda, N.; Itaka, Y.; Sankawa, U.; Shibata, S. *Tetrahedron* **1973**, *29*, 519.
- (434) Oshima, K.; Fujimiya, Y.; Soda, M.; Takano, F.; Fushitani, S. *Japan Kokai Tokyo Koho* **2002**, JP 2002047181; *Chem. Abstr.* **2002**, *136*, 161395.
- (435) Ueda, J.-Y.; Takagi, M.; Shin-ya, K. *J. Antibiot.* **2010**, *63*, 615.
- (436) Ratnayake, R.; Lacey, E.; Tennant, S.; Gill, J. H.; Capon, R. J. *Org. Lett.* **2006**, *8*, 5267.
- (437) Ratnayake, R.; Lacey, E.; Tennant, S.; Gill, J. H.; Capon, R. J. *Chem.—Eur. J.* **2007**, *13*, 1610.
- (438) Sloman, D. L.; Mitasev, B.; Scully, S. S.; Beutler, J. A.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 2511.
- (439) Kunimoto, S.; Someno, T.; Yamazaki, Y.; Lu, J.; Esumi, H.; Nagawana, H. *J. Antibiot.* **2003**, *56*, 1012.
- (440) Someno, T.; Kunimoto, S.; Nakamura, H.; Naganawa, H.; Ikeda, D. *J. Antibiot.* **2005**, *58*, 56.
- (441) Kunimoto, S.; Lu, J.; Yamazaki, Y.; Kinoshita, N.; Honma, Y.; Hamada, M.; Ohsono, M.; Takeuchi, T. *J. Antibiot.* **2003**, *56*, 1004.
- (442) Lu, J.; Kunimoto, S.; Yamazaki, Y.; Kaminishi, M.; Esumi, H. *Cancer Sci.* **2004**, *95*, 547.
- (443) Masuda, T.; Ohba, S.; Kawada, M.; Iijima, M.; Inoue, H.; Osono, M.; Ikeda, D.; Kunimoto, S. *J. Antibiot.* **2006**, *59*, 215.
- (444) Masuda, T.; Ohba, S.; Kawada, M.; Osono, M.; Ikeda, D.; Esumi, H.; Kunimoto, S. *J. Antibiot.* **2006**, *59*, 209.
- (445) Hirokawa, Y.; Levitzki, A.; Lesse, G.; Baell, J.; Xiao, Y.; Zhu, H.; Maruta, H. *Cancer Lett.* **2007**, *245*, 242.
- (446) Tan, G. Y. A.; Robinson, S.; Lacey, E.; Brown, R.; Kim, W.; Goodfellow, M. *Int. J. Syst. Evol. Biol.* **2007**, *57*, 2562.
- (447) Turner, P. A.; Griffin, E. M.; Whatmore, J. L.; Shipman, M. *Org. Lett.* **2011**, *13*, 1056.
- (448) Yoganathan, K.; Cao, S.; Crasta, S. C.; Aitipamula, S.; Whitton, S. R.; Ng, S.; Buss, A. D.; Butler, M. S. *Tetrahedron* **2008**, *64*, 10181.
- (449) Klevens, R. M.; Morrison, M. A.; Nadie, J.; Petit, S.; Geshman, K.; Ray, S.; Harrison, L. H.; Lynefield, R.; Dumyati, G.; Townes, J. M.; Craig, A. S.; Zell, E. R.; Fosheim, G. E.; McDougal, L. K.; Carey, R. B.; Fridkin, S. K. *J. Am. Med. Assoc.* **2007**, *298*, 1763.
- (450) Proksa, B.; Uhrín, D.; Liptaj, T.; Šturdíková, M. *Phytochemistry* **1998**, *48*, 1161.
- (451) Parish, C. A.; Smith, S. K.; Calati, K.; Zink, D.; Wilson, K.; Roemer, T.; Jiang, B.; Xu, D.; Bills, G.; Platas, G.; Peláez, F.; Dáez, M. T.; Tsou, N.; McKeown, A. E.; Ball, R. G.; Powles, M. A.; Lai, Y.; Liberator, P.; Harris, G. *J. Am. Chem. Soc.* **2008**, *130*, 7060.
- (452) Jiang, B.; Xu, D.; Allococo, J.; Parish, C.; Davison, J.; Veillette, K.; Sillaots, S.; Hu, W.; Rodriguez-Saurez, R.; Trosok, S.; Zhang, L.; Li, Y.; Rahkhoodaei, F.; Ransom, T.; Martel, N.; Wang, H.; Gauvin, D.; Wiltsie, J.; Wisniewski, D.; Salowe, S.; Khan, J. N.; Hsu, M.-J.; Giacobbe, R.; Abruzzo, G.; Flattery, A.; Gill, C.; Youngman, P.; Wilson, K.; Bills, G.; Platas, G.; Pelsez, F.; Diez, M. T.; Kauffman, S.; Becker, J.; Harris, G.; Liberator, P.; Roemer, T. *Chem. Biol.* **2008**, *15*, 363.

- (453) Adam, G. C.; Parish, C. A.; Wisniewski, D.; Meng, J.; Liu, M.; Calati, K.; Stein, B. D.; Athanasopoulos, J.; Liberator, P.; Roemer, T.; Harris, G.; Chapman, K. T. *J. Am. Chem. Soc.* **2008**, *130*, 16704.
- (454) Bills, G. F.; Platas, G.; Overy, D.; Collado, J.; Fillola, A.; Jiménez, M. R.; Martin, J.; González del Val, A.; Vicente, F.; Tormo, J. R.; Peláez, F.; Calati, K.; Harris, G.; Parish, C.; Xu, D.; Roemer, T. *Mycologia* **2009**, *101*, 449.
- (455) Overy, D.; Calati, K.; Kahn, J. N.; Hsu, M.-J.; Martin, J.; Collado, J.; Roemer, T.; Harris, G.; Parish, C. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1224.
- (456) Zhou, Q.; Snider, B. B. *Org. Lett.* **2009**, *11*, 13.
- (457) Zhou, Q.; Snider, B. B. *J. Org. Chem.* **2010**, *75*, 8224.
- (458) Isaka, M.; Jaturapat, A.; Rukseree, K.; Danwisetkanjana, K.; Tanticharoen, M.; Thebtaranonth, Y. *J. Nat. Prod.* **2001**, *64*, 1015.
- (459) Elsässer, B.; Krohn, K.; Flörke, U.; Root, N.; Aust, H.-J.; Draeger, S.; Schulz, B.; Antus, S.; Kurtán, T. *Eur. J. Org. Chem.* **2005**, *21*, 4563.
- (460) Rukachaisirikul, V.; Sommart, U.; Phongpaichit, S.; Sakayaroj, J.; Kitikara, K. *Phytochemistry* **2008**, *69*, 783.
- (461) Stewart, M.; Capon, R.; White, J.; Lacey, E.; Tennant, S.; Gill, J.; Shaddock, M. *J. Nat. Prod.* **2004**, *67*, 728.
- (462) Cooper, R.; Truumees, I.; Gunnarsson, I.; Loebenberg, D.; Horan, A.; Marquez, J.; Patel, M.; Puar, M.; Das, P.; Mittelman, S. *J. Antibiot.* **1992**, *45*, 444.
- (463) Chu, M.; Truumees, I.; Mierzwa, R.; Terracciano, J.; Patel, M.; Leonberg, D.; Kaminski, J. J.; Das, P.; Puar, M. S. *J. Nat. Prod.* **1997**, *60*, 525.
- (464) Lee, T. M.; Carter, G. T.; Borders, D. B. *J. Chem. Soc., Chem. Commun.* **1989**, *22*, 1771.
- (465) Maiese, W. M.; Korshalla, J.; Goodman, J.; Torrey, M. J.; Kantor, S.; Labeda, D. P.; Greenstein, M. *J. Antibiot.* **1990**, *43*, 1059.
- (466) Arai, M.; Sato, H.; Kobayashi, H.; Masashi, S.; Kawabe, T.; Tomoda, H.; Ōmura, S. *Biophys. Biochem. Res. Commun.* **2004**, *317*, 817.
- (467) Carter, G. T.; Goodman, J. J.; Torrey, M. J.; Borders, D. B.; Gould, S. J. *J. Org. Chem.* **1989**, *54*, 4321.
- (468) Ondeyka, J. D.; Dombrowski, A. W.; Polishook, J. P.; Felcetto, T.; Shoop, W. L.; Guan, Z.; Singh, S. B. *J. Antibiot.* **2006**, *59*, 288.
- (469) Tabata, N.; Tomoda, H.; Matsuzaki, K.; Ōmura, S. *J. Am. Chem. Soc.* **1993**, *115*, 8558.
- (470) Matsuzaki, K.; Tabata, N.; Tomoda, H.; Iwai, Y.; Tanaka, H.; Ōmura, S. *Tetrahedron Lett.* **1993**, *34*, 8251.
- (471) Kingsland, S. R.; Barrow, R. A. *Aust. J. Chem.* **2009**, *62*, 269.
- (472) Horiguchi, K.; Suzuki, Y.; Sassa, T. *Agricul. Biol. Chem.* **1989**, *53*, 2141.
- (473) Pornpakakul, S.; Liangsakul, J.; Ngamrojanavanich, N.; Roengsumran, S.; Sihanonth, P.; Piapukiew, J.; Sangvichien, E.; Puthong, S.; Petsom, A. *Arch. Pharm. Res.* **2006**, *29*, 140.
- (474) Masubuchi, M.; Okuda, T.; Shimada, H. *Eur. Pat. Appl.* **1993**, EP 537622 A1 19930421.