Chemistry and Biology of Mycotoxins and Related Fungal Metabolites

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1. Introduction

Nature produces a variety of different species, prokaryotes and eukaryotes. Among them, fungi play a very important, but yet mostly unexplored role. Their widespread occurrence on land and in marine life makes them a challenge and a risk for humans.

During their lifespan, fungi metabolize and produce a broad range from simple to very complex organic compounds. Most of them exhibit certain biological activities. However, a specific characteristic is the production of toxins. Mycotoxins (from "myco" fungus and toxin) are nonvolatile,[1] relatively low-molecular weight,[2] fungal[3] secondary metabolic products that may affect exposed vertebrates such as animals in a variety of ways. In contrast, other metabolites such as penicillins, only (or mainly) affecting prokaryotes or other eukaryotes, are in general not classified as mycotoxins.

Mycotoxins are considered secondary metabolites because they are not necessary for fungal growth and are simply a product of primary metabolic processes. The functions of mycotoxins have not been clearly established, but they are believed to play a role in eliminating other microorganisms competing in the same environment. They are also believed to help parasitic fungi invade host tissues.[4] The amount of toxins needed to produce adverse health effects varies widely among toxins, as well as within each person's immune system.

Some mycotoxins are carcinogenic, some are vasoactive, and some cause central nervous system damage. Often, a single mycotoxin can cause more than one type of toxic effect. We will discuss this briefly in section 1.2.

Fungi that produce mycotoxins are referred to as toxigenic fungi. The most frequently studied mycotoxins (see Table 2) are produced by species of *Aspergillus*, *Claviceps*,[5] *Fusarium*, *Penicillium*,[6] *Stachybotrys*, and *Myrothecium*.[7]

However, toxins have been detected from many other fungi under certain growth conditions. An important and steadily increasing number of natural products have been isolated from marine[8] and pathogenic insecticidal fungi.[9] In most cases, the toxicology has not yet been fully elaborated, and thus, their status remains unclear. We have included the most important fungal metabolites in this review. The type and amount of toxin produced depends on the fungal strain, the growing conditions, and the presence or absence of other organisms.

Fungi may be classified by the humidity, Xerophiles (e.g., *Aspergillus restrictus*, *A. glaucus*, *A. versicolor*) and Hygrophiles (e.g., *Cladosporium*, *Fusarium*, *Mucorales*), or by temperature, Thermophiles (e.g., *Byssochlamys*, *Aspergillus fumigatus*), Thermotolerants (e.g., *Aspergillus niger*), Mesophiles (e.g., *Penicillium chrysogenum*, *P. expansum*, *P.*

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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, La Jolla (K. C. Nicolaou), he began his independent research career at the RWTH Aachen, Germany, 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, Germany. He is recipient (among other awards) of the OrChem award of the GDCh and the Lilly award. His research interests include methods in drug discovery (including drug delivery), combinatorial chemistry towards the synthesis of biologically active compounds, and total synthesis of natural products and nanotechnology.

Julia Keck, née Gall, was born 1980 in Ludwigshafen/Rhein, Germany, in 1980. She studied chemistry at the University of Karlsruhe, where she received her diploma degree in 2004. During her graduate studies in the research group of Stefan Bräse, she worked on the total synthesis of pharmacologically active natural products. After completing her Ph.D. work in 2007, she joined Evonik Degussa GmbH as R&D scientist (Innovation Management Silanes). Her research interests include asymmetric catalysis, natural product chemistry, and synthesis of organometallic compounds.

cyclopium, Aspergillus versicolor, A. flavus, *A. nidulans*, *A. fumigatus*), and Cryophiles (e.g., *Cladosporium*, *Alternaria*).

Mycotoxins accumulate on fungal spores, cell fragments, and substrates (nutrient sources). Although the toxic effects of fungal metabolites have been known for centuries (St. Anthony's fire), nowadays the threat of adverse effects from mycotoxins has gained dramatic importance due to the reduced application of antifungal treatment on food.[10]

According to the literature, far more than 400 mycotoxins are produced by some 350 species of fungi.[11] However, we found a significantly higher number of relevant bioactive/toxic fungal metabolites: around 1000 compounds are presented in this review.

Arantxa Encinas López was born in Madrid, Spain, in 1977. She studied at the Autonoma University of Madrid and received her Ph.D. in 2006 at the Medicinal Chemistry Institute of CSIC in Madrid (Ana Castro). After a postdoctoral appointment at Karlsruhe University (Stefan Bräse), she joined as a postdoctoral fellow in the Chemical Biology core department of EMBL in Heidelberg (Joe Lewis). Since January 2009, she is working as medicinal chemist in Elara pharmaceuticals GmbH on the design and synthesis of pharmacologically active compounds as novel and efficacious medicines for the treatment of cancer. Her research focuses on medicinal chemistry, including the synthesis of natural products and small molecules with biological activity and combinatorial chemistry.

Carl Nising was born in 1979 in Troisdorf, Germany. He studied chemistry at the University of Bonn, where he received his diploma degree in 2003. He then moved to the University of Karlsruhe (TH), where he obtained his Ph.D. under the supervision of Stefan Bräse in 2006. After performing postdoctoral studies at Harvard University with Andrew G. Myers, he joined Bayer CropScience AG in late 2007, where he is currently head of laboratory in fungicide research. His research interests are natural product chemistry, heterocyclic chemistry, and the development of new synthetic methods. His research was supported by fellowships of the Studienstiftung des Deutschen Volkes and the Scheringstiftung. Additionally, he was recipient of the Klaus Grohe Prize and the Wolff&Sohn Award.

In this review, the chemistry such as the total synthesis and semisynthesis of the most important mycotoxins is discussed.[12] Some aspects have been reviewed earlier.[13−17]

Many secondary metabolites have been isolated from fungi; however, since mycotoxins are always affiliated with biological activity, this is a requirement to be considered in this review. If a member of a structural class is recognized as a mycotoxin, the whole group is mentioned (e.g., anthraquinones). While mycotoxins with particular significance in terms of food safety[18] and human health are discussed in detail, less abundant and rare mycotoxins are only mentioned briefly. Since the biosynthesis of mycotoxins is an important issue, we will outline the current status (section 3). Recent studies (by Hertweck and colleagues) have demonstrated that some mycotoxins (rhizoxin and

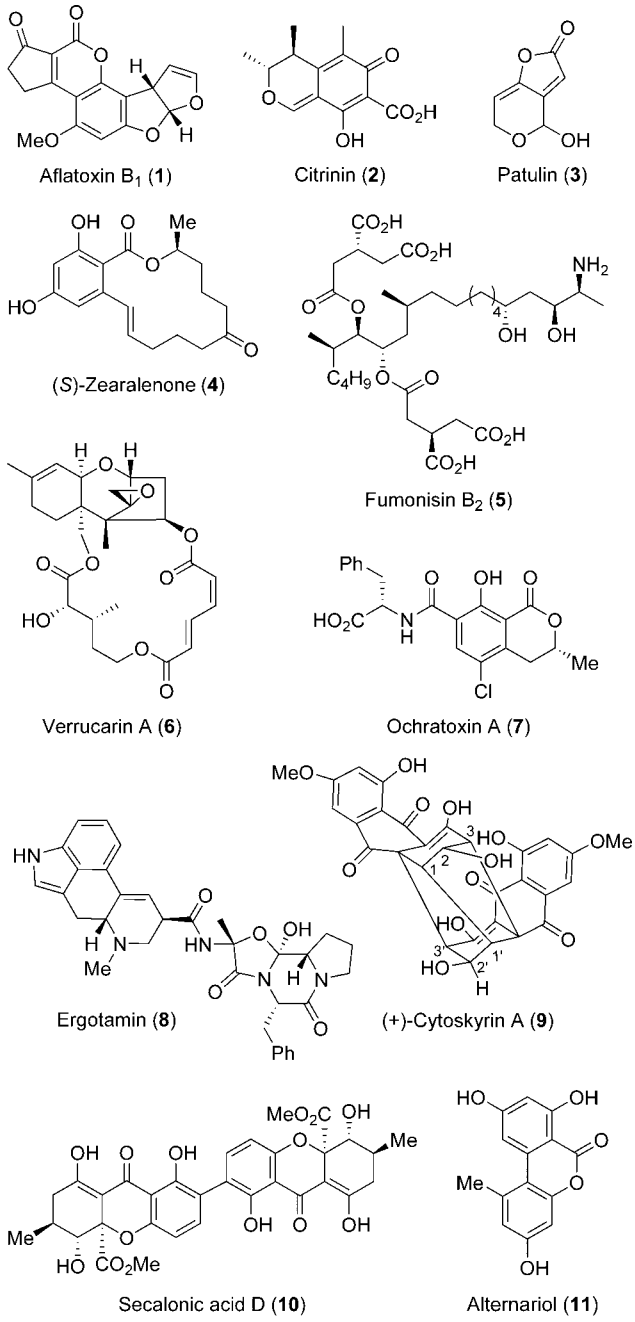


Figure 1. Important mycotoxins.

rhizonin) are not produced by fungi but by endosymbiotic bacteria that live within the fungal cytosol.[19]

1.1. Occurrence of Mycotoxins

Mycotoxins occur in many varieties of fungi. Several mycotoxins are unique to one species, but most mycotoxins are produced by more than one species. The most widespread mycotoxin is roquefortine C, which is produced by 25 species.[20] The most important mycotoxins are described in Figure 1 and Tables 1 and 2. Some of the compounds were also isolated from higher plants and bacteria; however, these sources are not included in this review. Because of the high number of mycotoxins,[21] only their names are listed in the tables. A full list of structures published by the end of 1980/mid 1990s can be found in comprehensive references,[16,22] in the *Dictionary of Natural Products*, in the useful database *Antibase*, and on several Web sites.[7,23,24]

To illustrate the variety of mycotoxins produced by fungi, Table 2 shows the mycotoxins produced by *Aspergillus* sp.

As a general overview, Table 3 includes all relevant mycotoxins and some related fungal metabolites (with alternate name, putative stereochemistry/sign of optical rotation, CA number/molecular formula if necessary, and/or common abbreviation in parentheses), together with their fungal source, their biological activity, and (if available) their total synthesis. It is organized by chemical classification of the core structure and then arranged alphabetically. Part of the Chemical Abstracts name was used for classification in the case of complex structures. Because of the large number of references, a selection was made.

1.2. Toxicology/Mycotoxicoses/Risks

The association of mycotoxins with human and animal health is not a recent phenomenon; for example, in the past, *ergotism* was suspected of being a toxicosis resulting from these toxic fungal metabolites. Nowadays, more is known regarding this family of compounds.[841,842] The mycotoxins can be acutely or chronically toxic, or both, depending on the kind of toxin, the dose, the health, the age and nutritional status of the exposed individual or animal, and the possible synergistic effects between mycotoxins.[843] Mycotoxin-producing fungi grow on a wide spectrum of feeds that include cereal grains, ground nuts, beans, and peas. They can invade the food supply at any time during production, processing, transport, or storage.

The exposure to mycotoxins is mostly by ingestion but can also occur by dermal contact or inhalation. The affection produced by these toxins is known as mycotoxicosis, which is named primary mycotoxicosis when it is provoked by consuming contaminated food and feed, or secondary mycotoxicosis when produced by eating meat or milk from animals that ingested forage containing mycotoxins.[844]

Mycotoxins affect specific tissues or organs depending on the particular toxin involved. In general, mycotoxins are specifically associated with a particular feed, are not transmissible from organism to organism (except when special circumstances are considered, like milk production for future human consumption), and are usually not responsive to any kind of direct treatment. Animals are more often affected by mycotoxins through the interference with nutrient absorption and metabolism, by affecting endocrine and neuroendocrine functions, or by suppression of the immune system. However, in humans, the presence of mycotoxins in food can be cumulative, leading to cancers (in liver, kidney, digestive tract, or reproductive system) and to immunodeficiency diseases.[845] The impact of these fungi in human carcinogenesis has been the subject of intensive study only since the early 1960s, because a mycotoxicosis can provoke tumor formation or even rapid death.

Mycotoxicoses in animals are better understood than in humans, due to the fact that the experimental studies appear more reliable.[846] Some diseases in humans involving mycotoxins are outlined in Table 4.[847]

Mycotoxins of global importance such as aflatoxins B_1 (**1**), B_2 (**15**), G_1 (**13**), and G_2 (**19**); deoxynivalenol (**231**); zearalenone (**4**); fumonisin B_1 (**92**); T-2 toxin (**224**); and ochratoxin A (**7**), produced by fungi on pre- and postharvest food and feeds, have led to the contamination of the food chain, resulting in severe economic losses and serious health problems in human beings and livestock. There are more than 350 types of mycotoxins that can occur in food.

Table 1. Chemical Classification of Mycotoxins According to Bérdy Modified after Betina[16]

code number	divisions	representative
2	macrocyclic lactones	
2.3.53	Brefeldin type	Zearalenone (**4**)
3	quinone and similar compounds	
3.1.3.2	dianthraquinone derivatives	Rugolosin
3	amino acid, peptide compounds	
4.1.3.2	diketopiperazine derivatives	
4.1.3.2.1	Gliotoxin type	Gliotoxin (**527**)
6	oxygen-containing heterocycles	
6.1	furan derivatives	
6.1.2.1	Aflatoxin type	Aflatoxin B_1 (**1**)
6.2	pyran derivatives	
6.2.3.2	Citreoviridin type	Citreoviridin
6.3	benzo[g]pyran derivatives	
6.3.4.1	dibenzo[g]pyrone derivatives	Secalonic acid D (**10**)
6.4.	small lactones	
6.4.2.1	small lactones condensed with hetero- or alicycles	Patulin (**3**)
6.4.2.5	isocoumarin derivatives	Ochratoxin A (**7**)
7	alicyclic compounds	
7.3	oligoterpenes	
7.3.3.1	Trichodermin type	T-2 toxin (**224**)
8	aromatic compounds	
8.2.1.1	Griseofulvin type	Griseofulvin

Nowadays, concern exists about interactions among mycotoxins that can produce additive and sometimes synergistic effects.[848]

Since these mycotoxins are natural contaminants, they cannot be completely eliminated without damaging food. For this reason, there are food-safety programs[849] that evaluate the levels of aflatoxins, trichothecenes, ergots, ochratoxins, and, particularly, patulin.

Most mycotoxins have specific effects on a given system in an animal, but many of them affect several systems simultaneously. To understand the different levels of toxicity provoked by mycotoxins, it is crucial to have knowledge of their biological activation. Some details of the main mycotoxins are outlined in the following sections.

1.2.1. Aflatoxins

Aflatoxins grow mainly on grains and legumes. Corn, peanuts, and cotton seed are the materials with the highest risk of contamination, but aflatoxins are also detected in almonds, figs, and a variety of other foods and feeds. Milk, milk products (nonfat powdered milk, cheese, and yogurt), eggs, and meat products are contaminated because of animal consumption of aflatoxin-contaminated feed. Moreover, aflatoxins found in tobacco have been demonstrated to be toxic to animals after inhalation and ingestion.[850]

Exposure to aflatoxins is typically through the ingestion of contaminated foodstuff, while dermal exposure results in slow and insignificant absorption.[850] Aflatoxins are most commonly known for causing acute or chronic liver disease,[851] but they are also considered immunosuppressive, hepatotoxic, mutagenic, teratogenic, and carcinogenic.[852]

Currently, the maximum concentration of aflatoxins permitted in food is set by the U.S. Food and Drug Administration (FDA). Food and milk for human consumption is allowed to contain 20 ppb and 0.5 ppb of AF, respectively. High levels up to 300 ppb are allowed in feed for cattle, hogs, and poultry. Currently, there are no standards for workplace or environmental aflatoxin exposures.

1.2.2. Ochratoxins

Ochratoxin A (**7**) is a main contaminant of cereals (corn, barley, wheat) and to some extent beans (coffee, soy, cocoa). On the basis of studies conducted on animals, it is easily absorbed through the gastrointestinal tract mainly in the duodenum and jejunum.[853] There are no studies on skin or inhalational absorption. When absorbed, it has a high binding affinity for plasma protein. In humans, ochratoxin A (**7**) interacts primarily with the kidney but, when present in high doses, it interacts with other organs such liver or spleen, or the immune system.[854]

The toxicity of ochratoxin A (**7**) involves several mechanisms:[855] (a) inhibition of protein synthesis through competition with the phenylalanine aminoacylation reaction catalyzed by Phe-tRNA synthase, resulting in the prevention of protein as well as DNA and RNA synthesis; (b) disruption of hepatic microsomal calcium homeostasis by impairing the endoplasmic reticulum membrane via lipid peroxidation. Ochratoxin A produces nephrotoxicity, mild liver damage, enterititis, immunosuppression, teratogenesis, and carcinogenesis (kidney tumors).[856]

1.2.3. Trichothecenes

Trichothecenes are present in crops, food, and animal feed contaminated with *Fusarium* species. Their mechanism of toxicity can be due to (a) inhibition of protein synthesis (specifically in eukaryotes),[857] (b) inhibition of DNA synthesis,[858] or (c) inhibition of the mitochondrial electron-transport system.[859]

The most important trichothecenes are deoxynivalenol (**230**), T-2 toxin (**224**), and zearalenone (**4**). They are responsible for the alimentary toxic aleukia (ATA) in humans and farm animals. Zearalenone (**4**) is a genitoxin that has estrogenic potency and causes reproductive problems in animals, particulary in swine.

The 12,13-epoxide of the trichothecenes is essential for their toxicity.[860] As a matter of fact, the de-epoxidation of T-2 (**224**) in mammalian systems results in a loss of toxicity.

1.2.4. Fumonisins

Fumonisins are common contaminants of corn, corn-based foods (such as sorghum and rice), and maize. There is no report on the transfer of fumonisins into milk or their absorption in tissues.

Table 2. Mycotoxins Produced by *Aspergillus* sp.

fungus	mycotoxin produced
Aspergillus aculeatus	Secalonic acid D (**10**)
Aspergillus albertensis	Ochratoxin A (**7**), Ochratoxin B (**155**)
Aspergillus alliaceus	Ochratoxin A (**7**), Ochratoxin B (**155**)
Aspergillus auricomus	Ochratoxin A (**7**), Ochratoxin B (**155**)
Aspergillus bombycis	Aflatoxin B_1 (**1**), Aflatoxin G (**13**)
Aspergillus brevipes	Viriditoxin
Aspergillus caespitosus	Fumitremorgin A
Aspergillus candidus	Citrinin (**2**), Acetylisoneosolaniol
Aspergillus carneus	Citrinin (**2**)
Aspergillus clavatus	Patulin (**3**), Tryptoquivaline A (C), Cytochalasin E (**443**)
Aspergillus flavipes	Citrinin (**2**)
Aspergillus flavus	Aflatoxin B_1 (**1**), Aflatoxin B_2 (**15**), Aflatoxin M_1 (**12**), Cyclopiazonic acid, Aflatrem (indole alkaloid), 3-Nitropropionic acid, Sterigmatocystin (**62**), Versicolorin A (**597**), Aspertoxin
Aspergillus fresenii	Xanthomegnin (**591**)
Aspergillus fumigatus	Fumitremorgin A, Verruculogen (**543**), Gliotoxin (**527**), Fumagillin, Helvolic acid, Sphingofungins, Brevianamide A (**545**), Phthioic acid, Fumigaclavin C, Aurasperone C
Aspergillus giganteus	Patulin (**3**)
Aspergillus melleus	Ochratoxin A (**7**), Viomellein, Xanthomegnin (**591**)
Aspergillus microcysticus	Aspochalasin
Aspergillus nidulans (Emericella nidulans)	Sterigmatocystin (**62**), Dechloronidulin, Emestrin
Aspergillus niger	Malformin, Ochratoxin A (**7**), Fumonisin B_2 (**5**)
Aspergillus nomius	Aflatoxin B_1 (**1**), Aflatoxin B_2 (**15**), Aflatoxin G_1 (**13**), Aflatoxin G_2 (**19**)
Aspergillus ochraceoroseus	Aflatoxin B_1 (**1**), Sterigmatocystin (**62**)
Aspergillus ochraceus	Ochratoxin A (**7**), Ochratoxin B (**155**), Ochratoxin C (**156**), Viomellein, Penicillic acid (**187**)
Aspergillus oryzae	Cyclopiazonic acid, Maltoryzine, 3-Nitropropionic acid
Aspergillus ostianus	Ochratoxin A (**7**)
Aspergillus parasiticus	Aflatoxin B_1 (**1**), Aflatoxin B_2 (**15**), Aflatoxin G_1 (**13**), Aflatoxin G_2 (**19**), Aflatoxin M_1 (**12**), Versicolorin A (**597**)
Aspergillus petrakii	Ochratoxin A (**7**)
Aspergillus pseudotamarii	Cyclopiazonic acid, Aflatoxin B_1 (**1**)
Aspergillus restrictus	Restrictocin
Aspergillus sclerotiorum	Ochratoxin B (**155**)
Aspergillus sulfureus	Ochratoxin A (**7**), Ochratoxin B (**155**)
Aspergillus terreus	Territrem A,[25] Citreoviridin, Citrinin (**2**), Gliotoxin (**527**), Patulin (**3**), Terrein, Terreic acid, Terretonin, Itaconic acid, Aspulvinone, Asterric acid, Asterriquinone, butyrolactone I, Emodin (**573**), Geodin, Itaconate, Lovastatin,[26] Questin, Sulochrin, Terrecyclic acid.
Aspergillus ustus	Austdiol, Austin, Austocystin A, Sterigmatocystin (**62**)
Aspergillus variecolor	Sterigmatocystin (**62**)
Aspergillus versicolor	Sterigmatocystin (**62**), Cyclopiazonic acid, Versicolorin A (**597**)
Aspergillus viridinutans	Viriditoxin
Aspergillus wentii	Emodin (**573**), 3-Nitropropionic acid, Ochratoxin A (**7**), Ochratoxin B (**155**),
Emericella venezuelensis	Aflatoxins (**1**, **12**−**22**)
Eurotium chevalieri	Echinulin, Neoechinulin, Gliotoxin (**527**), Xanthocillin
Neosartorya fischeri	Fumitremorgin A, Fumitremorgin C, Verruculogen (**543**), Tryptoquivaline A (C)

In animals, they provoke cerebral edema and liquefaction necrosis, and even centrilobular necrosis (hypoxic hepatitis) and hepatic fibrosis are observed in severe cases.[861] Liver disease, including tumors of the liver have also been associated with fumonisin intoxication. It has been reported that chronic exposure to fumonisins induces immunotoxicity, although this is still an area of active research.

However, the major reason for interest in fumonisins is their possible role as environmental tumor promoters in causing human cancer (concretely esophageal carcinoma).[862,863] Their mechanism of toxicity consists of the inhibition of the sphingolipid synthesis, due to their structural similarity with sphingoid bases, resulting in the disruption of sphingomyelin.[864] The disruption of sphingomyelin and metabolism in cells provokes cell damage, apoptosis, necrosis, and compensatory hyperplasia.[865] Unfortunately, awareness of its tumor-promotion mechanism has been limited by the general lack of understanding in this field. In recent years, fumonisin research has become one of the most active areas in fungal secondary metabolism.[866]

1.2.5. Patulin

Patulin is most frequently found in fruits such as apples, pears, and grapes. As a major symptom, it provokes congestion and edema of pulmonary, hepatic, and intestinal blood vessels and tissues. Moreover, sarcomas were observed when large doses of patulin were injected into animals. However, the mechanisms through which patulin causes toxicity are still not well-understood.[867]

2. Total Synthesis

Numerous mycotoxins have been targeted by total synthesis. In this section, we present the most important mycotoxins and their syntheses.

Table 3. Selected Mycotoxins and Other Secondary Metabolites: Isolation, Producing Fungus, Synthesis

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Aflatoxin	4- and 22-Hydroxyaflatoxin B1	*d*		*MTX*
Aflatoxin	5,6-Dimethoxysterigmatocystin	*Aspergillus versicolor*		MTX, cyto
Aflatoxin	5-Hydroxydihydrosterigmatocystin	*d*	27	*MTX*
Aflatoxin	5-Methoxysterigmatocystin (3a,12c-Dihydro-8-hydroxy-6,11-dimethoxy-7*H*-furol3′,2′:4,5]furo2,3-c]xanthen-7-one)	*Aspergillus versicolor*	27	MTX
Aflatoxin	Aflatoxin B_1 (**1**) (−)	*Aspergillus flavus*,[c,7] *A. nomius*[7]	*rac*: 28−31; (−): 32	MTX
Aflatoxin	Aflatoxin B_2 (**15**)	*Aspergillus flavus*, *A. nomius*[7]	*rac*: 33; (−): 34	**MTX**
Aflatoxin	Aflatoxin B_{2a} (**17**) (−)	*Aspergillus flavus*	*rac*: 28; (−): 32	**MTX**
Aflatoxin	Aflatoxin B_3 (Parasiticol)	*Aspergillus flavus*, *A. parasiticus*		**MTX**
Aflatoxin	Aflatoxin G_1 (**13**)	*Aspergillus flavus*,[c] *A. nomius*[7]	*rac*: 29	**MTX**
Aflatoxin	Aflatoxin G_2 (**19**)	*Aspergillus flavus*,[c] *A. nomius*[7]		**MTX**
Aflatoxin	Aflatoxin G_{2a} (**21**)	*Aspergillus flavus*		MTX
Aflatoxin	Aflatoxin GM_1 (**14**)	*Aspergillus flavus*		MTX
Aflatoxin	Aflatoxin GM_2 (**20**)	*Aspergillus flavus*[c]		**MTX**
Aflatoxin	Aflatoxin GM_{2a} (**22**)	*Aspergillus flavus*		MTX
Aflatoxin	Aflatoxin M_1 (**12**)	*Aspergillus flavus*[c]	*rac*: 29	**MTX**
Aflatoxin	Aflatoxin M_2 (**16**) (Dihydroaflatoxin M_1)	*Aspergillus flavus*[c]		MTX
Aflatoxin	Aflatoxin M_{2a} (**18**)	*Aspergillus flavus*		MTX
Aflatoxin	Aflatoxin P_1	Metabolic products	35	*MTX*[d]
Aflatoxin	Aflatoxin R_0 (Aflatoxicol) (2 Stereoisomers)	Microbial degradation product[d]		MTX
Aflatoxin	Aflatoxin S	*Aspergillus flavus*		MTX
Aflatoxin	Aspertoxin	*Aspergillus flavus*	Dihydro, formal synthesis:[36]	MTX
Aflatoxin	Demethylsterigmatocystin (**598**)	*Aspergillus nidulans*, *A. versicolor*[37]		MTX
Aflatoxin	Dihydroaflatoxicol	Metabolite		MTX
Aflatoxin	Dihydrodemethylsterigmatocystin (**600**) (1,2-Dihydro-6,7-hydroxydifuroxanthone)	*Aspergillus parasiticus*, *A. versicolor*[38,39]		MTX
Aflatoxin	Dihydro-*O*-methylsterigmatocystin (**602**)	*Aspergillus parasiticus*	40, 41	MTX
Aflatoxin	Dihydrosterigmatocystin (**584**) (1,2-Dihydro-6-methoxy-7-hydroxydifuroxanthone)	*Aspergillus parasiticus*, *A. versicolor*[42]		MTX
Aflatoxin	Dothistromin	*Cercospora arachidicola*[43]		MTX, cyto, mut
Aflatoxin	*O*-Methylsterigmatocystin (**63**) (5-Methoxysterigmatocystin)	*Aspergillus parasiticus*, *A. versicolor*, *Chaetomium virescens*[23]	40, 41, 44	MTX
Aflatoxin	Sterigmatocystin (**62**)	*Aspergillus versicolor*[c,7] *A. rugulosis*, *A. amstelodami*, *A. chevalieri*, *A. nidulans*, *A. ustus*, *Bipolarris sorokinina*, *Chaetomium virescens*[23]		**MTX**, carc
Alkaloid	Fustucine	*Acremonium* sp.		MTX
Alkaloid	Loline, *N*-formyllolines, *N*-acetylloline, perloline	*Acremonium coenophialum*	45	MTX
Alkaloid	Pyroclasine	*Penicillium commune*		MTX
Alkaloid	Rubrobramide	*Cladobotyrum rubrobrunnescens*	46	w cyto, phytotox
Alkinylbenzaldehyde	Frustulosin	*Stereum hirsutum*	47	MTX
Alternaria toxin	5′-Epialtenuene (5′-epi-Altenuene)	*Alternaria alternata*,[48] unidentified freshwater aquatic fungus (*Tubeufiaceae*)		**MTX**
Alternaria toxin	Altenuene (**391**) (ALT)	*Alternaria tenuis*, *A. alternata*[49−51]	52	**MTX**
Alternaria toxin	Altenuic acid I	*Alternaria tenuis*, *A. alternata*[53−55]		**MTX**
Alternaria toxin	Altenuic acid II (**552**)	*Alternaria tenuis*, *A. alternata*[53,54,56]		**MTX**
Alternaria toxin	Altenuic acid III	*Alternaria tenuis*, *A. alternata*[53,54]		**MTX**
Alternaria toxin	Altenuisol	*Alternaria tenuis*[49,57,58]		**MTX**
Alternaria toxin	Altenusin (**408**)	*Alternaria alternata*, *Penicillium* sp.[59,60]	61	**MTX**

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Alternaria toxin	Alternaric acid	*Alternaria solani*	62	Phytotox
Alternaria toxin	Alternarin	*Alternaria alternata*		**MTX**
Alternaria toxin	Alternariol (**11**) (AOH)	*Alternaria tenuis*[c], *Alternaria alternata*	63−65	**MTX**
Alternaria toxin	Alternariol 9-methyl ether (**377**) (AME)	*Alternaria tenuis*, *Alternaria alternata*[51,53]		**MTX**
Alternaria toxin	Altertenuol	*Alternaria tenuis*[49]		**MTX**
Alternaria toxin	Altertoxin I (ATX I) (a hydroxyperylenequinone)	*Alternaria alternata*		**MTX**, mut
Alternaria toxin	Altertoxin II (ATX II) (a hydroxyperylenequinone)	*Alternaria alternata*		**MTX**, mut
Alternaria toxin	Altertoxin III (ATX III) (a hydroxyperylenequinone)	*Alternaria alternata*		**MTX**, mut
Alternaria toxin	Dehydroaltenuene A	*Tubeufiacea* spp. (unidentified aquatic fungus)[66]		MTX
Alternaria toxin	Dehydroaltenuene B	*Tubeufiacea* spp. (unidentified aquatic fungus)[66]	*rac*: 67	MTX
Alternaria toxin	Dehydroaltenusin (**393**)	*Alternaria tenuis*, *Penicillium verruculosum*[59,68]	*rac*: 61, 69	MTX, kin
Alternaria toxin	Desmethyldehydroaltenusin	*Talaromyces flavus*[70]		MTX
Alternaria toxin	Dihydroaltenuene A	*Tubeufiacea* spp. (unidentified aquatic fungus)[66]		MTX
Alternaria toxin	Dihydroaltenuene B	*Tubeufiacea* spp. (unidentified aquatic fungus)[66]		MTX
Alternaria toxin	Isoaltenuene (**392**)	*Alternaria alternata*[71−73]	51, 52	**MTX**
Alternaria toxin	Neoaltenuene	*Alternaria alternata*[48]	1074a	**MTX**
Alternaria toxin	Tenuazonic acid[74]	*Alternaria tenuis*[c], *A. alternata*, *A. nomius*,[7] *Penicillium aurantiogriseum*, *P. chrysogenum*, *P. crustosum*, *P. expansum*, *P. griseofulvum*, *P. solitum*, *P. verrucosum*	Analogues: 75	**MTX**, cyto
Amino acid	Hadacidin (*N*-formyl-*N*-hydroxyglycine)	*Penicillium frequentans*	76	**MTX**, antitumor
Amino acid	Mycestericin A−G	*Mycelia sterilia*	77, 78	MTX
Amino acid	Myriocin	*Isaria sinclairii*	77, 79, 601	immuno
Amino acid	Sulfamisterin (AB 5366)	*Pycnidiella* sp.	77	MTX
Amino acid	Xylariamide A	*Xylaria* sp.	80	brine shrimp assay
Amino alkyl citrate antibiotic	Viridiofungin A, A2, A4, B, C	*Trichoderma viride*	77; A: 81	micro
Anthracenone	Physcion-9-anthrone (Physcioanthrone B)	*Aspergillus glaucus*, *A. chevalieri*		MTX
Anthracenone dimer	Physciodianthrone	*Aspergillus chevalieri*		MTX
Anthraquinoid	1,8-*O*-Dimethylaverantin	*Penicillium chrysogenum*[82]		MTX
Anthraquinoid	1-Acetyl-2,4,5,7-tetrahydroxy-9,10-anthracenedione	*Trichoderma viride*		MTX
Anthraquinoid	2-Hydroxyemodin (Alaternin)	*Ventilago leiocarpa*	microbiological synthesis: 83	MTX
Anthraquinoid	8-*O*-Methylaverufin	*Penicillium chrysogenum*[82]		MTX
Anthraquinoid	Altersolanol A (Stemphylin)	*Alternaria solani*	84	phytotox
Anthraquinoid	Altersolanol B (Dactylarin)	*Alternaria solani*	*rac*: 85	MTX, cyto
Anthraquinoid	Altersolanol J	*Cladosporium* sp.[d,86]		MTX
Anthraquinoid	Asperthecin[87] (1,2,4,5,6-Pentahydroxy-7-hydroxymethylanthraquinone)	*Aspergillus quadrilineatus*, *Emericella venezuelensis*[b]		*MTX*
Anthraquinoid	Averantin (**587**) (−)	*Aspergillus parasiticus*, *A. versicolor*[88]		MTX
Anthraquinoid	Averufanin (**589**) (Avermutin) (+)	*Aspergillus versicolor*, *A. ustus*[89]		MTX
Anthraquinoid	Averufin (**590**)[90]	*Aspergillus parasiticus*, *A. ustus*, *A. versicolor*, *Emericella navahoensis*[91]	92, 93	MTX
Anthraquinoid	Carviolin (roseo-purpurin) (1,3-Dihydroxy-6-(hydroxymethyl)-8-methoxyanthraquinone)	*Penicillium carmine-violaceum*, *Zopfiella longicaudata* (Ascomycete)[124]		w immun

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Anthraquinoid	Catenarin (1,4,5,7-Tetrahydroxy-2-methylanthraquinone)	*Penicillium islandicum*,[c] *Pyrenophora graminea*, *Dreschlera catenaria*[94]	biotransformation[95]	MTX
Anthraquinoid	Cercosporin	*Cercospora nicotianae*, *C. beticola*[96]		MTX, phyto
Anthraquinoid	Chrysazin (danthron, 1,8-dihydroxy-9,10-anthracenedione)	*Chaetomium globosum*	97	MTX
Anthraquinoid	Chrysophanol[98] (**83**)	*Penicillium islandicum*, *P. kloeckeri*, *Trichoderma harzianum*[7]	99−102, 117	MTX, not mut
Anthraquinoid	Cynodontin (1,4,5,8-Tetrahydroxy-2-methylanthraquinone)	*Helminthosporium cynodontis*,[c] *pyrenochaeta terrestis*, *cochliobolus lunatus*[103]		MTX
Anthraquinoid	Dactylariol (Altersolanol C)	*Pleospora* sp.[104]		MTX, cyto
Anthraquinoid	Demethyl solorinic acid	*Aspergillus versicolor*[105]		MTX
Anthraquinoid	Deoxyaverufinone	*Aspergillus versicolor*[106]		MTX
Anthraquinoid	Dihydrocatenarin	*Penicillium islandicum*		MTX
Anthraquinoid	Emodic acid	*Penicillium albicans*		MTX
Anthraquinoid	Emodin (**573**)	*Aspergillus wentii*,[c] *A. aculeatus*[107] *Penicillium islandicum*,[c,7] *Pyrenochaeta terrestris*,[107] *Trichoderma viride*[7]	101, 108	**MTX**, not mut
Anthraquinoid	Emodin-2-carboxylic acid	*Penicillium islandicum*		MTX
Anthraquinoid	Endocrocin (−)	*Pyrenochaeta terrestris*,[107] *Aspergillus aculeatus*,[107] *Penicillium tardum*[109]	110	MTX
Anthraquinoid	Erythroglaucin	*Aspergillus glaucus*[c], *A. chevalieri*, *A. echinulaus*, *A. niveoglaucus*, *A. ruber*, *A. umbrosus*, *Eurotium* sp., *Chaetomium globosum*[167]	111	Tox, *MTX*
Anthraquinoid	Erythroskyrine	*Penicillium islandicum*[7,112]	113	**MTX**
Anthraquinoid	F-742-C	*Trichoderma viride*[114]		MTX
Anthraquinoid	Hydroxyviocristin	*Aspergillus cristatus*	115	MTX
Anthraquinoid	Islandicin	*Penicillium islandicin*	116, 117	MTX
Anthraquinoid	Lunatin (1,3,8-trihydroxy-6-methoxyanthraquinone)	*Curvularia lunata*[b]		bact
Anthraquinoid	Macrosporin	*Alternaria porri*, *A. alternaria*, *Stemphylium eturmiunum*	by degradation from alterporriol A[118]	prob mut
Anthraquinoid	Nidurufin (an aflatoxin precursor)	*Aspergillus nidulans*, *Emericella* sp.	92	MTX, w mut
Anthraquinoid	Norsolorinic acid (**586**) (2-*n*-Hexanoyl-1,3,6,8-tetrahydroxyanthraquinone)	*Aspergillus versicolor*, *A. parasiticus*, *Emericella navahoensis*[91]		MTX, w mut
Anthraquinoid	Physcion[119] (Parietin, chrysophanic acid, emodin 3-methyl ether, 6-*O*-methylemodin, rheochrysidin, Chrysorobin, Parmel yellow, Lichen-chrysophanic acid, Przewalskinone B)	*Aspergillus glaucus*,[c] *A. echinulatus*, *A. niveoglaucus*, *A. ruber*, *A. umbrosus*, *P. herquei*, *Eurotium amsteldami*,[7] *E. chevalieri*,[7] *E. herbariorum*[7] *Chaetomium globosum*[167]	100, 102	MTX
Anthraquinoid	Questin (1-*O*-Methylemodin, Methylemodin)	*Zopfiella longicaudata* (Ascomycete)	120	MTX
Anthraquinoid	Rhein	*Rheum emodi*[121]	122	anticancer[123]
Anthraquinoid	Roseopurpurin (Roseo-purpurin, Carviolin)	*Penicillium carmine-violaceum*, *Zopfiella longicaudata* (Ascomycete)[124]		MTX, mod immun
Anthraquinoid	Rubrocristin	*Aspergillus cristatus*		MTX
Anthraquinoid	Rubroglaucin ($C_{16}H_{12}O_5$)[23]	*Aspergillus umbrosus*, *A. ruber*, *A. neveoglaucus*, *A. echinulatus*, *Gliocladium roseum*		MTX
Anthraquinoid	Triacetylemodin	*Trichoderma polysporum*	125	HIV
Anthraquinoid	Tritisporin	*Helminthosporium tritici-vulgaris*		MTX

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Anthraquinoid	Versiconal (**577**)	*Aspergillus parasiticus*		MTX
Anthraquinoid	Versiconal acetate (**574**) (*S*)	*Aspergillus flavus*, *A. parasicticus*[23]		MTX, prob mut
Anthraquinoid	Viocristin	*Aspergillus cristatus*	115	MTX
Anthraquinoid	ω-Acetylcarviolin	*Aspergillus glaucus*, *Penicillium frequetans*, *Zopfiella longicaudata* (Ascomycete)		MTX
Anthraquinoid	ω-Hydroxyemodin (citreorosein)	*Penicillium islandicum, Zopfiella longicaudata*	126	w immun
Anthraquinoid dimer	4-Oxyluteoskyrin (−)	*Penicillium islandicum*		MTX
Anthraquinoid dimer	Alterporriol A (−) (5,6,7,8-Tetrahydro-4,4′,5,6,6′,7,8-heptahydroxy-2,2′-dimethoxy-7,7′-dimethyl-1,1′-bianthracene-9,9′,10,10′-tetrone)	*Alternaria porri*	127	MTX
Anthraquinoid dimer	Alterporriol B	*Alternaria porri*	128	MTX
Anthraquinoid dimer	Alterporriol C	*Alternaria porri*	127	MTX
Anthraquinoid dimer	Alterporriol D	*Alternaria porri*		MTX
Anthraquinoid dimer	Aurantioskyrin (+)	*Penicillium islandicum*[134]		MTX
Anthraquinoid dimer	Auroskyrin (+)	*Penicillium islandicum*[134]		MTX
Anthraquinoid dimer	Cytoskyrin A (**9**)	*Cytospora* sp.[129]	(+)-2,2′-*epi*-Cytoskyrin A (**417**);[130,131] model: 132	MTX, bact
Anthraquinoid dimer	Cytoskyrin B	*Cytospora* sp.[129]		MTX
Anthraquinoid dimer	Deoxyluteoskyrin (−)	*Penicillium islandicum*		MTX
Anthraquinoid dimer	Deoxyrubroskyrin (−)	*Penicillium islandicum*	model: 132	MTX
Anthraquinoid dimer	Dianhydrorugulosin (+)	*Penicillium islandicum*		MTX
Anthraquinoid dimer	Dicatenarin (+)	*Penicillium islandicum*		MTX
Anthraquinoid dimer	Flavoskyrin (−)	*Penicillium islandicum*	model: 132	MTX
Anthraquinoid dimer	Iridoskyrin A (+)	*Penicillium islandicum*		Not mut
Anthraquinoid dimer	Lumiluteoskyrin (Photoproduct)	*Penicillium* sp.	133	Mut
Anthraquinoid dimer	Luteoskyrin (−)	*Penicillium islandicum*[c,7]		**MTX**, carc
Anthraquinoid dimer	Oxyskyrin (+)	*Penicillium islandicum*		MTX
Anthraquinoid dimer	Punicoskyrin (+)	*Penicillium islandicum*[134]		MTX
Anthraquinoid dimer	Rhodoislandin A (+)	*Penicillium islandicum*[134]		MTX
Anthraquinoid dimer	Rhodoislandin B (+)	*Penicillium islandicum*[134]		MTX
Anthraquinoid dimer	Roseoskyrin (+)	*Penicillium islandicum*[134]		MTX
Anthraquinoid dimer	Rubroskyrin (-)	*Penicillium islandicum*		Mut
Anthraquinoid dimer	Rugolusin (+)	*Penicillium rugolosum*[c]	(+): 130	**MTX**
Anthraquinoid dimer	Rugulin (**409**)	*Penicillium islandicum*, *P. rugolosum*[c]	model: 132	**MTX**
Anthraquinoid dimer	Rugulosin (**410**) (−)	*Penicillium islandicum*,[7] *P. kloeckeri*, *P. rugulosum*,[7,23] *P. variabile*[7]	(+): 130	**MTX**, mut
Anthraquinoid dimer	Skyrin (+) (*S*) (Rhodophyscin, Endothianin)	*Penicillium islandicum,*[c] *P. rugulosum*, *P. kloeckeri*[23]	135; model: 132	Bact
Anthraquinoid dimer	Skyrinol (+)	*Penicillium islandicum*		MTX
Austocystin[136] (Furoxanthenone)	4,6-Bisdemethylaustocystin A	*Aspergillus ustus*		**MTX**
Austocystin[136] (Furoxanthenone)	4-Demethylaustocystin A	*Aspergillus ustus*[137]		**MTX**
Austocystin[136] (Furoxanthenone)	6-Demethylaustocystin A	*Aspergillus ustus*[137]		**MTX**
Austocystin[136] (Furoxanthenone)	Austocystin A (−)	*Aspergillus ustus*[7]	model: 138	**MTX**, mut, cyto
Austocystin[136] (Furoxanthenone)	Austocystin B	*Aspergillus ustus*[7,89]		**MTX**, mut, cyto
Austocystin[136] (Furoxanthenone)	Austocystin C	*Aspergillus ustus*[7]		**MTX**, mut, cyto
Austocystin[136] (Furoxanthenone)	Austocystin D	*Aspergillus ustus*[7]		**MTX**, mut, cyto
Austocystin[136] (Furoxanthenone)	Austocystin E	*Aspergillus ustus*[7]		**MTX**, mut, cyto
Austocystin[136] (Furoxanthenone)	Austocystin F	*Aspergillus ustus*[7]		**MTX**, mut, cyto
Austocystin[136] (Furoxanthenone)	Austocystin G	*Aspergillus ustus*[7]		**MTX**, mut, cyto
Austocystin[136] (Furoxanthenone)	Austocystin H	*Aspergillus ustus*[7]		**MTX**, mut, cyto
Austocystin[136] (Furoxanthenone)	Austocystin I	*Aspergillus ustus*[7]		**MTX**, mut, cyto
Azaanthraquinone	Scorpinone	*Amorosia littoralis*	139	*MTX*
Azanaphthoquinone	8-*O*-Methylbostrycoidin (Bostrycoidin-9-methyl ether)	*Fusarium moniliforme*[140]	141, 142	MTX, cyto
Azaphilone	Rotiorinols A−C	*Chaetomium cupreum* CC3303[149]		fung, *MTX*
Azaphilone	Rubrorotiorin ($C_{23}H_{23}ClO_5$)[23]	*Chaetomium cupreum* CC3303,[149] *Penicillium hirayamae*	143	fung, *MTX*
Azaphilone (Benzopyran)	Mitorubrin (+)[144]	*Penicillium rubrum*[21]	*rac*: 145; (−): 146	MTX
Azaphilone (Benzopyran)	Mitorubrinic acid (−)	*Penicillium funiculosum*[21]	Semisynthesis: 145; *rac*: 147	MTX
Azaphilone (Benzopyran)	Mitorubrinic acid B	*Penicillium funiculosum*[148]		MTX

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Azaphilone (Benzopyran)	Mitorubrinol (−)[144]	*Penicillium vermiculatum*[21]	146	MTX
Azaphilone (Benzopyran)	Mitorubrinol acetate	*Hypoylon fragoforme*[21]		MTX
Azaphilone (Furobenzofuran)	Rotiorin (−)	*Chaetomium cupreum* CC3303[149]		fung, *MTX*
Benzobutyrolactone	Fumimycin	*Aspergillus fumisynnematus F746*[150]		MTX
Benzodiazepine	Cyclopenin (−)[151]	*Penicillium cyclopium*, *P. vulpinum*, *P. atramentosum*, *P. crustosum*,[7] *P. echinulatum*, *P. solitum*,[7] *P. aurantiovirens*, *P. cyclopium*, *P. freii*,[7] *P. neochinulatum*, *P. polonicum*,[7] *P. aurantiocandidum*[7] *P. discolor*[7]	152	MTX
Benzodiazepine	Cyclopenol (−)[153]	*Penicillium cyclopium*, *P. vulpinum*, *P. aurantiogriseum*, *P. aurantiovirens*, *P. verrucosum*, *P. crustosum*,[7] *P. echinulatum*, *P. solitum*,[7] *P. cyclopium*, *P. freii*,[7] *P. neochinulatum*, *P. polonicum*,[7] *P. aurantiocandidum*, *P. discolor*[7]	!	MTX
Benzodiazepine alkaloid	Asperlicin (−)	*Aspergillus alliaceus*[154]	155; C: 156; E: 156	MTX
Benzodiazepine alkaloid	Benzomalvin A−C	*Penicillium* sp.	157; A: 156	MTX
Benzodiazepine alkaloid	Circumdatin A	*Aspergillus ochraceus*[21]		MTX
Benzodiazepine alkaloid	Circumdatin B	*Aspergillus ochraceus*[21]		MTX
Benzodiazepine alkaloid	Circumdatin C	*Aspergillus ochraceus*[21]	158	MTX
Benzodiazepine alkaloid	Circumdatin D	*Aspergillus ochraceus*		MTX
Benzodiazepine alkaloid	Circumdatin E	*Aspergillus ochraceus*	156	MTX
Benzodiazepine alkaloid	Circumdatin F	*Aspergillus ochraceus*	158, 159; *rac*: 156	MTX
Benzodiazepine alkaloid	Circumdatin G	*Aspergillus ochraceus*		MTX
Benzodiazepine alkaloid	Circumdatin H	*Aspergillus ochraceus*		MTX, mitochondrial NADH oxidase inhibitor
Benzodiazepine alkaloid	Sclerotigenin	*Penicillium sclerotigenum*	156, 159	insect
Benzodipyrandione	Fuscinarin, fuscin	*Oidiodendron griseum*	160	MTX
Benzofuran	Stachybotramide	*Stachybotrys chartarum*, *S. cylindrospora*		MTX
Benzofuran	Stachybotrydial	*Stachybotrys chartarum*[161]		MTX
Benzofuran	Stachybotrylactone (Stachybotrolide)	*Stachybotrys chartarum*[161]		MTX
Benzofuranone	Leptosin C,F,I,J	*Leptoshaeria species*		MTX, cyto
Benzofurans	Stachybocin A-D	*Stachybotrys chartarum*		MTX
Benzoisochromanquinone	Thysanone (+)	*Thysanora penicilloides*	162	3C-protease inhibitor
Benzooxepine	Koninginin A−E,[163] G[164]	*Trichoderma harzianum*[7]	165	MTX
Benzopyran	Austdiol[166]	*Aspergillus ustus*[7]		**MTX**, mut, acute tox
Benzopyran	Chaetopyranin	*Chaetomium globosum*[167]		Cyto
Benzopyran	Citromycetin (Frequentic acid, 8, 9-dihydroxy-2-methyl-4-oxo-4H, 5H-Pyrano3,2-c]1]benzopyran-10-carboxylic acid)	*Penicillium glabrum*[7,168]	169	**MTX**
Benzopyran	Dihydrodeoxy-8-epi-austdiol	*Aspergillus ustus*		MTX
Benzopyran	Jesterone	*Pestalotiopsis jesteri*	170	fung, dimer: cyto
Benzopyran	Lapidosin	*Penicillium lapidosum*		no biodata
Benzopyrone	Diplodiol (Diplosporin) (**557**) (5*S*,6*R*)	*Diplodia macrospora*[c,171]		MTX
Benzopyrone	Fusarochromanone (FUCH, TDP 1)	*Fusarium equiseti*[7,172]		**MTX**, cyto
Benzoquinone dimer	Phoenicin (phenicin)	*Penicillium pheniceum*[21]	173	irreversible inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Benzoquinone	2,5-toluquinone	*Penicillium lanosum*, *P. griseofluvinum*, *P. urticale*	various syntheses (commodity)	MTX
Benzoquinone	Bovinone (a 2,5-dihydroxy-1,4-benzoquinone)	*Boletus (Suillus) bovinus* (higher fungus)[174]		MTX
Benzoquinone	Spinulosin (Hydroxyfumigatin, 3,6-dihydroxy-4-methoxy-2,5-toluquinone)	*Aspergillus fumigatus*, *Penicillium spinulosum*		MTX
Benzoxanthentrione	Bikaverin (Lycopersin; Mycogonin; Passiflorin; Fungal vacuolation factor)	*Gibberella fujikuroi*, *Fusarium oxysporon*	175	Cyto, prot
Bis-naphthopyrone	Asperpyrone A-C	*Aspergillus niger*,[176] *Aspergillus tubingensis*		Cyto
Bis-naphthopyrone	Aurasperone A	*Aspergillus niger*[176]		MTX
Bis-naphthopyrone	Aurasperone B	*Aspergillus vadensis*, *A. niger*[177]		MTX
Bis-naphthopyrone	Aurasperone C,D,E,F, iso (E: Fonsecinone D)	*Aspergillus niger*[177]		MTX
Butenolide	Spiculisporic acid[178] (γ-Butenolide)	*Penicillium minioluteum*, *P. craterforme*[7]	179	**MTX**!
Butyrolactam	Fusarin C (**87**)	*Fusarium moniliforme*, *F. crookwellense*, *F. avenaceum*,[7] *F. graminearum*,[7] *F. poae*,[7] *F. proliferatum*[7]	model: 180	MTX
Butyrolactone	Butenolide (4-Acetamido-4-hydroxy-2-butenoic acid γ-lactone; 2-Acetamido-2,5-dihydro-5-oxofuran; 4-Acetamido-4-hydroxy-2- butanol-γ-lactone; N-(2,5-Dihydro-5-oxo-2-furanyl)-acetamide)	*Fusarium equiseti*, *F. culmorum*,[7] *F. sporotrichoides*, *F. trincinctum*, *F. graminearum*,[7] *F. poae*[7]		MTX, cyto
Butyrolactone	Penicillic acid (**187**)	*Penicillium verrucosum*,[c,7] *P. atramentosum*, *P. verrucosum*, *P. cyclopium*,[7] *P. raistrickii*, *P. melanoconidium*,[7] *P. neoechinulatum*, *P. viridicatum*, *P. pulvivorum*, *P. polonicum*,[7] *P. aurantiocandidum*,[7] *P. brasilanum*,[7] *P. freii*,[7] *Aspergillus ochraceus*,[7] *A. aculeatum*, *A. aurantiogriseum*,[7]	181, 182	**MTX**
Carbazole alkaloid	Aflavazole (+)	*Aspergillus flavus*		**MTX**, insect
Carbazole alkaloid	Tubingesin A,B	*Aspergillus niger* (*A*), *A. tubingensis* (B)		**MTX**, vir (A), cyto (B)
Citreoviridin	Citreomontanin	*Penicillium pulvillorum*[183]	184	*MTX*
Citreoviridin	Citreoviral	*Penicillium citro-viride*	185, 186	MTX
Citreoviridin	Citreoviridin A	*Aspergillus terreus*,[c,7] *Penicillium citreo-viride*[c]	186−189, 620 (formal)	**MTX**
Citreoviridin	Citreoviridin C[187]	*Aspergillus terreus*[7]		**MTX**
Citreoviridin	Citreoviridin D[187]	*Aspergillus terreus*[7]		**MTX**
Citrinin type	3,7-Dimethyl-8-hydroxy-6-methylisochroman	*Penicillium steckii*		**MTX**
Citrinin type	Antibiotic Y	*Fusarium avenaceum*,[7,190] *F. acuminatum*[7]		MTX
Citrinin type	Ascochitine (*S*) (−) (Ascochytin, Acsochitine)	*Ascochyto pisi*[c,191] (*Ascochyta pisi*)	192, 193	*MTX*, phytotox
Citrinin type	Citrinin (**2**) (−)	*Penicillium citrinum*,[c7] *P. expansum*,[7] *P. hirsutum*, *P. verrucosum*,[7] *P. radicicola*, *Aspergillus carneus*, *A. terreus*[7]	194−197; *rac*: 198; (+): 199; (−): 200	**MTX**
Citrinin type[23]	Dihydrocitrinone	*Aspergillus carneus*		*MTX*
Coumarin	Dicoumarol (Dicoumarin, dicumarol, dicumarin)	*Aspergillus fumigatus*	201	**MTX**
Coumarin dimer	Aflavarin	*Aspergillus flavus*		feed

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Coumarin dimer	Desertorin A (*S*)	*Emericella* sp.	202	*MTX*
Coumarin dimer	Desertorin B (*R*)	*Emericella* sp.		*MTX*
Coumarin dimer	Desertorin C (*S*)	*Emericella* sp.		MTX
Cyclodepsipeptide	Destruxin A, B, E (E: **549**)	*Aspergillus ochraceus* *Metarhizium anisopliae*	203	MTX, E: Insec, cyto
Cyclodepsipeptide	Enniatin A[204]	*Fusarium aveanceum*,[7] *F. acuminatum*[7]	205	MTX, cyto, biot, insec, ionophoric
Cyclodepsipeptide	Enniatin A1[204]	*Fusarium aveanceum*,[7] *F. acuminatum*[7]		MTX, cyto, biot, insec, ionophoric
Cyclodepsipeptide	Enniatin A2[204]	*Fusarium langsethiae*[d]		MTX, cyto
Cyclodepsipeptide	Enniatin B1[204]	*Fusarium aveanceum*,[7] *F. acuminatum*[7]		MTX, cyto, biot, insec, ionophoric
Cyclodepsipeptide	Enniatin B[204]	*Fusarium aveanceum*,[7] *F. acuminatum*[7]		MTX, cyto, biot, insec, ionophoric
Cyclodepsipeptide	Enniatin B2[204]	*Fusarium aveanceum*, *F. acuminatum*[7]		MTX, cyto, biot, insec, ionophoric
Cyclodepsipeptide	Enniatin B3[204]	*Fusarium aveanceum*,[7] *F. acuminatum*[7]		MTX, cyto, biot, insec, ionophoric
Cyclodepsipeptide	Enniatin H, I[204]	*Fusarium langsethiae*[d]		MTX, cyto
Cyclodepsipeptide	Enniatin L, M1, M2, N[204]	Unidentified fungus		MTX
Cyclodepsipeptide	Gliotide	*Gliocladium* sp.[b]		Cyto
Cyclodepsipeptide	MK1688	*Verticillium hemipterigenum*		MTX
Cyclodepsipeptide	Roseocardin	*Trichothecium roseum*		Cardiotonic
Cyclodepsipeptide	Roseotoxin A	*Trichothecium roseum*		*MTX*, No bio data
Cyclodepsipeptide	Roseotoxin B	*Trichothecium roseum*		MTX, Tox, insec
Cyclodepsipeptide (5 AA)	Pithomycolide	*Pithomyces chartatum*	206	**MTX**
Cyclodepsipeptide (6 AA)	Beauvericin (BEAU)	*Beauversia terreus*, *Fusarium proliferatum*[7]	207	MTX, cyto, biot, insec, ionophoric
Cycloheptapeptide	Scytalidamide A,B	*Scytalidium* sp.[b]	A: 208	Cyto
Cyclohexanecarbaldehyde[23]	Frequentin	*Penicillium brefeldianum*, *P. frequentans*,[209] *P. palitans*,[210] *P. verrucosum*		biot, fung
Cyclohexanone	Palitanin	*Penicillium brefeldianum*, *P. palitans*[210]		MTX
Cyclohexenone	Terredionol (4*R*,6*R*)	*Aspergillus* sp.		MTX
Cyclohexenone (Patulin precursor)	Isoepoxydon (Epiepoxydon; U−III) (rac and (+))	*Penicillium urticae*,[211] *Apiospora montagnei*[b]	212, 213	MTX, cyto
Cyclopentabenzopyran	Presambucoin	*Fusarium culmorum*		MTX
Cyclopentabenzopyran	Sambucoin	*Fusarium sambucinum*[214]		*MTX*
Cyclopentanaphthacene	Viridicatumtoxin[215]	*Penicillium viridicatum*[c], *P. brasilanum*[7]		**MTX**, mut
Cyclopentenone[23]	Terrein[216]	*Aspergillus terreus*[7]	217	MTX
Cyclopeptide	Cylindrocyclin A	*Cylindocarpon* sp.[218]		cyto
Cyclopeptide	Echinocandin B,C (a-30912), D	*Aspergillus rugulosis*, *A. nidulans (C)*	219	MTX, fung
Cyclopeptide	Islanditoxin[220] (not identical with Cyclochlorotine)	*Penicillium islandicum*[7]		**MTX**, carc, hep
Cyclopeptide	JM47 (*cyclo*(Ala-Ala-Aoh-Pro))	*Fusarium* sp.[b]		MTX
Cyclopeptide	Okaramines A−R	*Penicillium simplicissimum* (N−R)	221; N: 222	MTX, insec
Cyclopeptide	Sporidesmolides I, III, V	*Pithomyces chartarum*	223	**MTX**
Cyclopeptide	Sporidesmolides IV	*Pithomyces chartarum*, *P. maydicus*	224	**MTX**
Cyclopeptide	Ustiloxin A−F	*Ustilaginoidea virens*	225	**MTX**
Cyclopeptide (4 AA)	Aspercolorin	*Aspergillus versicolor*[226]		MTX, tox
Cyclopeptide (4 AA)	Tentoxin (**548**)	*Alternaria alternata*	227	Herb!
Cyclopeptide (5 AA)	Argifin	*Gliocladium* sp.	228	MTX
Cyclopeptide (5 AA)	Cyclochlorotine[229]	*Penicillium islandicum*[7]	Dechloro:[230]	**MTX**, carc, hep
Cyclopeptide (5 AA)	Malformin[231] A1, A2	*Aspergillus niger*,[c,7] *A. tubingensis*, *Byssochlamys fulva*[7]	A: 232	MTX, cyto
Cyclopeptide (5 AA)	Malformin[231] B1, B2, C	*Aspergillus niger*,[c,7] *Byssochlamys fulva*[7]	C: 233	MTX, prob cyto
Cyclopeptide (modified)	Phomopsin A,[234] B[235]	*Phomopsis leptostromiformis*	model: 236	MTX
Cytochalasan	18-Deoxy-19,20-epoxycytochalasin Q	*Xylaria hypoxylon*[237]	238	MTX
Cytochalasan	18-Deoxy-19,20-epoxycytochalasin R	*Xylaria hypoxylon*[237]	238	MTX
Cytochalasan	19,20-Epoxycytochalasin C	*Xylaria hypoxylon*[237]	238	MTX
Cytochalasan	19,20-Epoxycytochalasin D	*Xylaria hypoxylon*[237]	238	MTX
Cytochalasan	19,20-Epoxycytochalasin N	*Xylaria hypoxylon*[237]	238	MTX
Cytochalasan	19,20-Epoxycytochalasin Q	*Xylaria hypoxylon*[237]	238	MTX
Cytochalasan	19,20-Epoxycytochalasin Q	*Xylaria* sp.	238	MTX, Antiplasmodial
Cytochalasan	19,20-Epoxycytochalasin R	*Xylaria hypoxylon*[237]	238	MTX
Cytochalasan	19-*O*-Acetylchaetoglobosin A-B,D	*Chaetomium globosum*		MTX

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Cytochalasan	Aspochalasan	*Aspergillus microcysticus*[c]		MTX
Cytochalasan	Aspochalasin A−L, Z	*Aspergillus microcysticus*[c,239]	240	MTX
Cytochalasan	Chaetoglobosin A−G, J (B: 7,19-Dihydroxy-10-(indol-3-yl)-5,16,18-trimethyl-[13]cytochalas-6(12),13,17,21-tetraene-20,23-dione)	*Chaetomium globosum*[c,7] *Penicillium verrucosum* (C), *P. discolor*[7] (A−C), *P. expansum*[7] (C)	C: 241	**MTX**, cyto
Cytochalasan	Chaetoglobosin K, L	*Diplodia macrospora*		MTX
Cytochalasan	Chaetoglobosin U	*Chaetomium globosum*		MTX
Cytochalasan	Cytochalasin A (**440**) (5,5-Didehydrophomin, NSC 174119)	*Phoma exigua,*[c] *Helminthosporium dematiodeum*	model: 242	MTX
Cytochalasan	Cytochalasin B (**441**) (NSC 107658, Phomin)	*Phoma exigua,*[c] *Phoma exigua var. Heteromorpha,*[243] *Curvularia lunata*, *Helminthosporium dematiodeum*	244−247; model:242	**MTX**
Cytochalasan	Cytochalasin C	*Metarhizium anisopliae*[c]	model: 248−252	MTX
Cytochalasan	Cytochalasin D (**442**) (NSC 209835, Zygosporin A)	*Metarhizium anisopliae*[c]	253; 6-epi: 254; model: 251, 255, 256; degradation studies: 257	MTX
Cytochalasan	Cytochalasin E (**443**) (NSC 175151)	*Rosellinia necatrix,*[c] *Aspergillus clavatus*[7]		**MTX**, tox
Cytochalasan	Cytochalasin F (Cytochalasin F6)	*Helminthosporium dematioideum,*[c] *Nigrosalbulum* sp.,[c] *Phoma exigua var. heteromorpha*[243]		MTX
Cytochalasan	Cytochalasin G (**444**)	*Phomopsis paspali,*[c] *pseudeurotium zonatum*	258, 259	MTX
Cytochalasan	Cytochalasin H (**445**) (Kodocytochalasin 1, Paspalin P I)	*Phomopsis paspali,*[c] *Phomopsis* sp. 68-GO-164[260]	261, 262	MTX
Cytochalasan	Cytochalasin I	*Daldania vernicosa*		MTX, cyto
Cytochalasan	Cytochalasin J (Deacetylcytochalasin H, Kodocytochalasin 2, Paspalin P II)	*Phomopsis* sp. 68-GO-164[260]		MTX
Cytochalasan	Cytochalasin K	*Chalara microspora*[c]		MTX
Cytochalasan	Cytochalasin L (**446**)	*Chalara microspora*[c]		MTX
Cytochalasan	Cytochalasin M	*Chalara microspora*[c]		MTX
Cytochalasan	Cytochalasin N	*Phomopsis* sp.,[263] *Phomopsis* sp. 68-GO-164[260]		MTX
Cytochalasan	Cytochalasin O (**447**), Cytochalasin Ohyp	*Phomopsis* sp.[263]	253	MTX
Cytochalasan	Cytochalasin P	*Phomopsis* sp.[263]		MTX
Cytochalasan	Cytochalasin Q	*Hirsutella* sp.,[264] *Halorosellinia oceanica* BCC 5149,[265] *Xylaria hypoxylon*[237]		MTX, cyto
Cytochalasan	Cytochalasin R	*Phomopsis* sp. 68-GO-164,[260] *Xylaria hypoxylon*[237]		MTX
Cytochalasan	Cytochalasin S	*Phomopsis* sp. 68-GO-164[260]		MTX
Cytochalasan	Cytochalasin T	*Phoma exigua var. heteromorpha*[243]		MTX
Cytochalasan	Cytochalasin U, V	*Phoma exigua var. heteromorpha*[266]		MTX
Cytochalasan	Cytochalasin W	*Phoma exigua var. heteromorpha*[267]		MTX
Cytochalasan	Cytochalasin X, Y, Z	*Peseudeurotium zonatum*[268]		MTX
Cytochalasan	Cytochalasin Z1, Z2, Z3	*Pyrenophora semeniperda*[269]		MTX
Cytochalasan	Cytochalasin Z4, Z5, Z6	*Phoma exigua var. heteromorpha*[270]		MTX
Cytochalasan	Deoxaphomin (Desoxyphomin; (7S,16R,20*R*)-7,20-Dihydroxy-5,16-dimethyl-10-phenyl-(13)cytochalas-6(12),13(t),21(t)-triene-1,23-dione)	*Phoma* spp.[c,271]		MTX
Cytochalasan	Dihydrocytochalasin B (21,22-Dihydrophomin)	*Pyrenophora* sp.[d]		MTX
Cytochalasan	Engleromycin	*Engleromyces goetzei*[c]		MTX
Cytochalasan	Epoxycytochalasin H	*Phomopsis* sp. 68-GO-164[260]		MTX
Cytochalasan	Epoxycytochalasin J	*Phomopsis* sp. 68-GO-164[260]		MTX
Cytochalasan	L-696,474 (**446**)	*Hypoxylon fragiforme*	247	MTX
Cytochalasan	Protophomin	*Phoma exigua*[c]		MTX
Cytochalasan	Proxiphomin	*Phoma exigua*[c]	272, 273	MTX
Cytochalasan	Zygosporin D	*Zygosporium masonii*		MTX
Cytochalasan	Zygosporin E	*Zygosporium masonii*	274, 275	MTX
Cytochalasan	Zygosporin F	*Zygosporium masonii*		MTX
Cytochalasan	Zygosporin G	*Zygosporium masonii*		MTX

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Depsicyclodipeptide (Peptolide)	Lateritin (*R*,*R*)	*Fusarium moniliforme*, *F. culmorum*, *F. avenaceum*, *F. nivale*, *Isaria japonica*, *Gibberella lateritium IFO 7188*[276]		MTX, cyto, apoptosis inducer
Depsidone	Excelsione	Endophytic fungus	277	MTX
Depsidone	Mollicellin A	*Chaetomium mollicellum*	278	MTX
Depsidone	Mollicellin B−G	*Chaetomium mollicellum*		MTX
Depsidone	Ustin[23] (Ustin-I, Nornidulin)	*Aspergillus nidulans*[279]		MTX, biot
Depsipeptide (peptolide)[280]	Sambucinin (Sambucynin) ($C_{24}H_{42}O_7N_2$)[d]	*Fusarium sambucinum*, *F. verticillioides*,[d] *F. equiseti*,[d] *F. oxsporum*,[d] *F. culmorum*,[d] *F. solani*,[d] *F. avenaceum*,[d] *F. roseum*,[d] *F. nivale*[d]		*MTX*, biot
Diarylether	Neoplaether	*Neoplaconema napellum IFB-E016* (endophyte metabolite)[281]		Cyto, fung
Dibenzofurandione	Usnic acid (+) (*R*)	*Phomopsis* sp. (mainly produced by lichen)		**MTX**, tox
Diisocyanide	Xanthoascin (Toxin-B)	*Aspergillus candidus*[282]		MTX
Diisocyanide	Xanthocillin X	*Penicillium notatum*[c], *Aspergillus chevalieri*		**MTX**
Diisocyanide	Xanthocillin X methylether	*Aspergillus* sp.	283	**MTX**
Diketopiperazine	*cyclo*(Ala-Try)	*Aspergillus chevalieri*		MTX
Diketopiperazine	*cyclo*(D-Val-Try)	*Aspergillus chevalieri*		MTX
Diketopiperazine	Cycloechinulin	*Aspergillus ochraceus*[284]		**MTX**, insect
Diketopiperazine	Dechlorogriseofulvin	*Memnoniella echinata*[285]		MTX
Diketopiperazine	Dipodazine ((*Z*)-1′,3-Didehydro-3-(3″-indolylmethylene)-piperazine-2,5-dione)	*Penicillium verrucosum*,[286] *P. dipodomyis*, *P. nalgiovense*	287	MTX, prob insect
Diketopiperazine	Echinulin	*Chaetomium globosum*, *Aspergillus chevalieri*, *Aspergillus amstelodami*		MTX
Diketopiperazine	Gypsetin	*Nannizzia gypsea*	472	MTX
Diketopiperazine	Spirotryprostatin A, B (A: **542**)	*Aspergillus fumigatus*	A: 288; B: 289	MTX
Diketopiperazine	Tryprostatin A	*Aspergillus fumigatus*[b,290]	291	MTX
Diketopiperazine	Tryprostatin B	*Aspergillus fumigatus*[21,290]	292, 293, 472	MTX
Diketopiperazine	Verrucine A-E	*Myrothecium verrucaria*,[c] *Penicillium verrucosum*[7]		MTX
Diketopiperazine (Indole alkaloid)	Austamide (**544**) (+) (NSC 159629)	*Aspergillus ustus*,[7,294] *Penicillium italicum*[464]	295	**MTX**, acute tox
Diketopiperazine (Indole alkaloid)	Brevianamide F (*cyclo*(Pro-Trp) (*cis*-Cyclo(Pro, Trp), *L*,*L*-Cyclo (tryptophanylprolyl))	*Penicillium brevicompactum*[b,473,296]		MTX
Diketopiperazine (Indole alkaloid)	Deoxyisoaustamide (+)	*Penicillium italicum*[464]	295	**MTX**
Diketopiperazine (Indole alkaloid)	Hydratoaustamide (+)	*Penicillium italicum*[464]	295	**MTX**
Diketopiperazine (Indole alkaloid)	Verruculogen[297] (**543**) (TR 1 toxin) (−)	*Aspergillus caespitosus*, *A. fumigatus*,[7] *Penicillium verrucosum*, *P. picaium*, *P. janthinellum*, *P. paxillii*, *P. brasilanum*,[7] *Neosatorya fischeri*[7]	298, 299	**MTX**
Diketopiperazine alkaloid	Fructigenine A (Rugulosuvine B, puberuline) (−)	*Fusarium moniliforme*, *F. culmorum*, *F. avenaceum*, *F. roseum*, *Penicillium fructigenum*, *P. auratiogriseum*, *P. rugulosum*[300]		MTX, cyto

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Diketopiperazine alkaloid	Fructigenine B[23] (Verrucofortine) (-)	*Penicillium auratiogriseum*, *P. verrucosum*, *P. aurantiovirens*, *P. cyclopium*, *P. polonicum*, *P. tricolor*[301]		MTX, cyto
Diketopiperazine alkaloid	Rugulosuvine A (Puberulin A)	*Penicillium rugulosum*[300]		*MTX*
Dipeptide	Aspergillazine A−E (A: **546**)	*Aspergillus unilateralis*,[302] *Spicaria elegans*[b]		MTX, cyto
Dipeptide	Trichodermamide A	*Aspergillus unilateralis*,[302] *Trichoderma virans*[b], *Spicaria elegans*[b]		Cyto
Dipeptide	Trichodermamide B	*Aspergillus unilateralis*,[302] *Trichoderma virans*[b]	303	MTX, cyto
Diterpene	Fusicoccin	*Fusicoccum amygdali* (*fungus imperfectus*)	model: 304	Cyto, phytohormonal
Diterpenoid (Atranone)	6β-Hydroxydolabella-3*E*,7*E*,12*E*-trien-14-one (1S*,6S*,11S*)	*Stachybotrys chartarum*[305]		MTX
Diterpenoid (Atranone)	Atranone A−G	*Stachybotrys chartarum*[306]		MTX, w cyto
Diterpenoid (Atranone)	Atranone H, J	*Myrothecium verrucaria*[d]		MTX
Diterpenoid (Atranone)	Epoxydolabellane	*Stachybotrys chartarum*		MTX
Epipolythiopiperazine-3,6-dione	11-Deoxyverticillin A	*Gliocladium roseum*[189]		MTX
Epipolythiopiperazine-3,6-dione	Acetylaranotin (A 21101-IV, LL-S 88 α)	*Arachniotus aureus*[307,308]		MTX
Epipolythiopiperazine-3,6-dione	Apoaranotin (A 21101-IV)	*Arachniotus aureus*[309]	degradation: 310	MTX
Epipolythiopiperazine-3,6-dione	Aranotin (**530**) (A-21101-III; Ariotin)	*Arachniotus aureus*[311,308]		MTX
Epipolythiopiperazine-3,6-dione	Aspirochlorine (A-30641)	*Aspergillus flavus*[312]	313; model: 314	MTX
Epipolythiopiperazine-3,6-dione	Aurantiometrin	*Emericella striata*[327]		MTX
Epipolythiopiperazine-3,6-dione	Bis(anhydrodethio) itomycin	*Gliocadium deliquescens*		MTX
Epipolythiopiperazine-3,6-dione	Bis(anhydrodethio) methylthiodehydrogliotoxin	*Gliocadium deliquescens*		MTX
Epipolythiopiperazine-3,6-dione	Bisdethio(methylthio) dehydrogliotoxin	*Gliocadium deliquescens*		MTX
Epipolythiopiperazine-3,6-dione	Bisdethiobis(methylthio)gliotoxin (Bisdethio(bismethylthio)gliotoxin, FR-49175, Dehydroxybisdethiobis(methylthio) gliotoxin)	*Gliocadium deliquensis*[315]		MTX
Epipolythiopiperazine-3,6-dione	Chaetomin (Chetomin)	*Chaetomium cochiliodes*[c], *C. globosum*[7,344,316,317]		**MTX**
Epipolythiopiperazine-3,6-dione	Chetracin A	*Chaetomium retardatum*[c,318]		MTX
Epipolythiopiperazine-3,6-dione	*Cis*-3,6-Dibenzyl-3,6-bis (methylthio)piperazine-2,5-dione	*Aspergillus terreus*	319	MTX
Epipolythiopiperazine-3,6-dione	Dethiosecoemestin	*Emericella striata*[327]		MTX
Epipolythiopiperazine-3,6-dione	Didehydrogliotoxin (Didehydroaspergillin)	*Penicillium terlikowskii*[c,320] *Aspergillus ustus*	*rac*: 321	MTX
Epipolythiopiperazine-3,6-dione	Dihydroxychetocin (11a,11′a-Dihydroxychaetocin, Melinacidin IV)	*Acrostalagmus chartartum*[c,322,323]		MTX
Epipolythiopiperazine-3,6-dione	Dithiosilvatin	*Aspergillus silvaticus*, *ermericella* sp.[324]	bimethyl: 325	MTX
Epipolythiopiperazine-3,6-dione	Emestrin A (Emestrin, EQ-1)	*Aspergillus* sp., *Emericella striata* 80-NE-22[327,326]		MTX
Epipolythiopiperazine-3,6-dione	Emestrin B	*Emericella striata*[327]		MTX
Epipolythiopiperazine-3,6-dione	Emethallicin B	*Emericella heterothallica*[328]		MTX
Epipolythiopiperazine-3,6-dione	Emethallicin C	*Emericella heterothallica*[328]		MTX
Epipolythiopiperazine-3,6-dione	Epicorazine A,B	*Epicoccum nigrum*[c], *podaxis pistillaris*		MTX
Epipolythiopiperazine-3,6-dione	Epicorazine C (antibiotic F 3822)	*Stereum hirsutum*,[329,c] *podaxis pistillaris*		micro
Epipolythiopiperazine-3,6-dione	Epoxyserohilone	*Nigrospora spaerica*		
Epipolythiopiperazine-3,6-dione	Exserohilone (**535**)	*Exserohilum holmii*		MTX
Epipolythiopiperazine-3,6-dione	Gliocladin A−E	*Gliocladium roseum*[189]	(+)-C: 330	*MTX*
Epipolythiopiperazine-3,6-dione	Gliotoxin (**527**) (Aspergillin)	*Aspergillus fumigatus*[c,7] *A. niger*, *Trichoderma lignorum*[c], *T. virens*,[7] *Gliocladium flavofuscum*[7]	321	**MTX**, cyto
Epipolythiopiperazine-3,6-dione	Gliotoxin acetate	*Penicillium obscurum*		MTX

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Epipolythiopiperazine-3,6-dione	Gliotoxin E (Thiogliotoxin)	*Aspergillus fumigatus*		**MTX**
Epipolythiopiperazine-3,6-dione	Gliotoxin G (Dithiogliotoxin)	*Penicillium terlikowskii*, *Aspergillus fumigatus*, *Thermoascus crustaceus*	331; partial: 332	**MTX**
Epipolythiopiperazine-3,6-dione	Gliovirin[23]	*Aspergillus niger*, *Trichoderma virens*[7,333]		MTX
Epipolythiopiperazine-3,6-dione	Hyalodendrin	*Hyalodendron* sp.	321, 334, 335	MTX
Epipolythiopiperazine-3,6-dione	Leptosin D,E,F A-K (Chaetocin derivative)	*Leptosphaeria* sp. OUPS-4		MTX, cyto
Epipolythiopiperazine-3,6-dione	Melinacidin II	*Acrostalagmus chartartum*[c,322]		MTX
Epipolythiopiperazine-3,6-dione	Melinacidin III	*Acrostalagmus chartartum*[c,322]		MTX
Epipolythiopiperazine-3,6-dione	Methylthiodioxopiperazine	*Gliocadium deliquescens*		MTX
Epipolythiopiperazine-3,6-dione	MPC 1001 (**529**)	*Cladorrhinum* sp.		MTX, tumor, biot
Epipolythiopiperazine-3,6-dione	Pretrichdermamide A	*Trichoderm* sp. BCC 5926		MTX
Epipolythiopiperazine-3,6-dione	Rostratins A-D (**531**−**534**)	*Exserohilum rostratum*[336]	model: 468	MTX, cyto
Epipolythiopiperazine-3,6-dione	Scabrosin ester A-D (**536**−**539**)	*Xanthoparmelia scabrosa* (lichen)[337]		Cyto
Epipolythiopiperazine-3,6-dione	Silvathione	*Emericella striata*[327]		MTX
Epipolythiopiperazine-3,6-dione	Sirodesmin A-C,G	*Leptosphaeria maculans*, *Sirodesmium diversum*	model: 338	MTX
Epipolythiopiperazine-3,6-dione	Sporidesmin A (**528**)	*Verticillium* sp.[c], *Pithomyces chartarum*	339; model: 340	**MTX**
Epipolythiopiperazine-3,6-dione	Sporidesmin B,G-J	*Pithomyces chartarum*		**MTX**
Epipolythiopiperazine-3,6-dione	Sporidesmin D,F, Diacetylsporidesmin C	*Pithomyces chartarum*		**MTX**, w tox
Epipolythiopiperazine-3,6-dione	Sporidesmin E	*Pithomyces chartarum*[341]		MTX
Epipolythiopiperazine-3,6-dione	Verticillin A	*Verticillium* sp., *Gliocladium roseum*[189]		MTX
Epipolythiopiperazine-3,6-dione	Verticillin B, C	*Verticillium* sp.		MTX
Epipolythiopiperazine-3,6-dione	Violaceic acid	*Emericella striata*[327]		MTX
Epipolythiopiperazine-3,6-dione dimer	Chaetocin (Chetocin)	*Chaetomium* sp.[342]		**MTX**
Epipolythiopiperazine-3,6-dione dimer	Chaetocin B,C (Chetocin)	*Chaetomium minutum*[c,342−344]		MTX
Epipolythiopiperazine-3,6-dione dimer	Dihydrochaetocin (Dihydrochetocin)	*Chaetomium retardatum*[c]		MTX
Epoxycyclohexenone/ Farnesylcyclohexenones (terpene)	Yanuthone A−E, 1-hydroxyanuthone A, 1-hydroxyyanuthone C, and 22-deacetylyanuthone A, 7-deacetoxyyanuthone A	*Penicillium notatum*[345,346]	Yanuthone: 347	MTX, cyto
(Epoxymethano)phenanthro [2,3-b:6,7-b′]bisoxirene	Hexacyclinol	*Panus rudis strain* HKI 0254[348]	349	*MTX*
Epoxyquinone	Enaminomycin A−C,	*Penicillium claviforme*, *P. griseofulvum*		**MTX**, str cyto, micro
Epoxyquinone	Epiepoformin (Desoxyepiepoxydon)	*Penicillium claviforme*, *P. griseofulvum*	350	**MTX**, str cyto, micro
Epoxyquinone	Epoformin (Desoxyepoxydon)	*Penicillium claviforme*, *P. griseofulvum*	350, 351	**MTX**, str cyto, micro
Epoxyquinone	Epoxydon	*Phoma* sp.	213, 352	Phytotox
Eremofortins	Eremofortin A−E	*Penicillium roqueforti*	B: 353	MTX
Ergot alkaloid	Agroclavine-I (Agroclavine 1)	*Claviceps purpurea*	354	MTX
Ergot alkaloid	Auranthine[355]	*Penicillium aurantiogriseum*[7]	model: 356	MTX, nephro
Ergot alkaloid	Aurantioclavine	*Penicillium vitale*[357]	358	MTX
Ergot alkaloid	Chanoclavine-I	*Claviceps purpurea*, *epichloe typhina*[359]	360	MTX
Ergot alkaloid	Chlororugulovasine A, B[375]	*Penicillium rubrum*, *P. islandicum*		MTX
Ergot alkaloid	Cladosporic acid	*Cladosporium* sp.		MTX
Ergot alkaloid	Claviciptic acid (−) (*cis*)	*Claviceps fusiformis*	361	MTX
Ergot alkaloid	Costaclavine	*Aspergillus fumigatus*, *Penicillium chermesinum*	362	MTX
Ergot alkaloid	Dihydroelymoclavine	*Claviceps* sp.		MTX
Ergot alkaloid	Egrine	*Claviceps* sp.		MTX
Ergot alkaloid	Elymoclavine	*Claviceps* sp.	363	**MTX**
Ergot alkaloid	Epoxyagroclavine-I	*Penicillium fellutanum*		MTX
Ergot alkaloid	Ergocornine (Cyclol tripeptide)	*Claviceps purpurea*		MTX
Ergot alkaloid	Ergocorninine	*Claviceps purpurea*		MTX
Ergot alkaloid	Ergocristine (Cyclol tripeptide)	*Claviceps purpurea*		MTX
Ergot alkaloid	Ergocristinine	*Claviceps purpurea*[d]		MTX
Ergot alkaloid	Ergocrystine	*Claviceps purpurea*		MTX
Ergot alkaloid	Ergometrine	*Claviceps purpurea*		MTX, drug
Ergot alkaloid	Ergometrinine	*Claviceps purpurea*		MTX
Ergot alkaloid	Ergonovine	*Claviceps* sp.	371	**MTX**, oxytocic

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Ergot alkaloid	Ergosecaline	*Claviceps purpurea*[364]		MTX
Ergot alkaloid	Ergosecalinine	*Claviceps purpurea*[364]		MTX
Ergot alkaloid	Ergotamine (**8**) (Cyclol tripeptide)	*Claviceps purpurea*	365	**MTX**
Ergot alkaloid	Ergotaminine	*Claviceps purpurea*		MTX
Ergot alkaloid	Ergotocine[366]	*Claviceps* sp.		MTX
Ergot alkaloid	Ergotoxine: mixture of equal proportions of ergocristine, ergocornine and ergocryptine	*Claviceps purpurea*		MTX
Ergot alkaloid	Festuclavine (8,9-Dihydro-agroclavine)	*Aspergillus fumigatus*, *Claviceps gigantea*		MTX
Ergot alkaloid	Fumigaclavine A−C[367] (Fumiclavine A−C)	*Aspergillus fumigatus*,[7] *Penicillium palitans*[7] (A,B), *P. roqueforti* (B,C)	368	**MTX**, C: anorexia
Ergot alkaloid	Isofumigaclavine A,B	*Penicillium roqueforti*[7]	369	**MTX**
Ergot alkaloid	Isolysergol	*Claviceps purpurea*	363	MTX
Ergot alkaloid	Isosetoclavine	*Penicillium chermesinum*	370	MTX
Ergot alkaloid	Lysergic acid (**85**)	*Claviceps paspali*	371−373	MTX
Ergot alkaloid	Pyroclavine	*Claviceps purpurea.*		MTX
Ergot alkaloid	Rugulovasine A,B[374]	*Penicillium expansum*, *P. rubrum*, *P. biforme*, *P. verruculosum*,[23] *P. craterforme*,[7] *P. atramentoseum*[7] *P. commune*,[7] *P. islandicum*	375−377	**MTX**
Ergot alkaloid	α-Ergocryptine (α-Ergokryptine, 12-Hydroxy-2-(1-methylethyl)-5-alpha-(2-methylpropyl)ergotaman-3,6,18-trione) (Cyclol tripeptide)	*Claviceps purpurea*, *C. zizaniae*	371	MTX
Ergot alkaloid	α-Ergocryptinine (α-Ergokryptinine)	*Claviceps purpurea*, *C. zizaniae*		MTX
Ergot alkaloid	β-Ergocryptine (β-Ergokryptine)	*Claviceps purpurea*		MTX
Ergot alkaloid	β-Ergocryptinine (β-Ergokryptinine)	*Claviceps purpurea*		MTX
Ergot alkaloid (diketopiperazine)	Aurantiamine[378] (alkaloid 302) (analog of viridamine)	*Penicillium aurantiogriseum*,[7] *P. freii*,[7] *P. neochinulatum*	379	MTX
Ergot alkaloid (diketopiperazine)	Viridamine (**540**)	*Penicillium viridicatum*	380	**MTX**
Fatty acid	Phthioic acid	*Aspergillus fumigatus*	381	**MTX**
Fescue alkaloid	Dihydroergosine (DHESN)	*Claviceps africana*[382]		MTX
Fescue alkaloid	Ergosine (Cyclotripeptide)	*Claviceps purpurea*, *Epichloe typhina*		**MTX**
Fescue alkaloid	Ergosinine	*Claviceps purpurea*, *Epichloe typhina*		**MTX**
Fescue alkaloid	Ergovaline	*Claviceps purpurea*		MTX
Fescue alkaloid (ergoxine group)	β-Ergonine	*Claviceps* sp.	383	MTX
Fescue alkaloid (ergoxine group)	β-Ergoptine	*Claviceps* sp.	383	MTX
Fescue Alkaloids	Lysergamide (Lysergic acid amide, ergine)	*Claviceps paspali*		MTX
Five-membered Lactone	Ascladiol (**186**) ((*E*), (*Z*)) (*E*: Patulin precursor)	*Aspergillus clavatus*[c,7,384]		**MTX**
Five-membered lactone	Avenaciolide (−)	*Aspergillus avenaceus*[385]	(−): e.g., 386, 387	MTX, fung
Five-membered Lactone	Neopatulin (**185**)	*Penicillium patulum*	388	MTX, cyto
Five-membered Lactone	Patulin (**3**) (Clavacin, Claviformin, Expansin, Penicidin, Terinin, Mycoin)	*Aspergillus clavatus*[c],[7] *A. terreus*,[7] *Claviceps paspali*[c], *P. claviforme*, *P. expansum*,[7] *P. griseofulvum*,[7] *P. roquefortii*, *P. verrucosum*, *P. carneum*,[7] *P. paneum*,[7] *P. clavigerum*, *Emericella striata*, *Byssochlamys fulva*,[7] *Paecilomyces variotii*[7]	388−394	**MTX**
Five-membered Lactone	Tetronic acid	*Aspergillus panamensis*[23]	395	MTX
Five-membered Lactone	γ-Methyltetronic acid (4-Hydroxy-5-methyl-2(5H)-furanone)	*Penicillium charlesii*[396]		*MTX*
Fumonisin	AAL toxin TA_1 (**136**)	*Alternaria alternata* f. sp. *lycopersici*[397]	398	**MTX**

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Fumonisin	AAL toxin TA_2 (**137**)	*Alternaria alternata* f. sp. *lycopersici*[397]		**MTX**
Fumonisin	AAL toxin TB_1	*Fusarium moniliforme*		**MTX**
Fumonisin	AAL toxin TB_2	*Fusarium moniliforme*		**MTX**
Fumonisin	AAL toxin TC_1	*Fusarium moniliforme*		**MTX**
Fumonisin	AAL toxin TC_2	*Fusarium moniliforme*		**MTX**
Fumonisin	AAL toxin TD_1	*Fusarium moniliforme*		**MTX**
Fumonisin	AAL toxin TD_2	*Fusarium moniliforme*		**MTX**
Fumonisin	AAL toxin TE_1	*Fusarium moniliforme*		**MTX**
Fumonisin	AAL toxin TE_2	*Fusarium moniliforme*		**MTX**
Fumonisin	Fumonisin A_1 (**88**)	*Fusarium* sp.		**MTX**
Fumonisin	Fumonisin A_2 (**89**)	*Fusarium* sp.		**MTX**
Fumonisin	Fumonisin A_3 (**90**)	*Fusarium* sp.		**MTX**
Fumonisin	Fumonisin A_4 (**91**)	*Fusarium* sp.		**MTX**
Fumonisin	Fumonisin B_1 (**92**)	*Fusarium moniliforme*,[399] *F. proliferatum*[7]	hexaacetate: 400	**MTX**
Fumonisin	Fumonisin B_2 (**5**)	*Fusarium moniliforme*,[399] *F. proliferatum*[7]	401	**MTX**
Fumonisin	Fumonisin B_3 (**93**)	*Fusarium proliferatum*[7]		**MTX**
Fumonisin	Fumonisin B_4 (**94**)	*Fusarium proliferatum*.[7]		**MTX**
Fumonisin	Fumonisin C_1 (**95**)	*Fusarium* spp.[402] *F. proliferatum*[7]		**MTX**
Fumonisin	Fumonisin C_2 (**96**)	*Fusarium* spp.		**MTX**
Fumonisin	Fumonisin C_3 (**97**)	*Fusarium* spp.[402] *F. proliferatum*[7]		**MTX**
Fumonisin	Fumonisin C_4 (**98**)	*Fusarium moniliforme*,[402] *F. proliferatum*[7]		**MTX**
Fumonisin	Fumonisin P_1 (**99**)	*Fusarium* spp.[402] *F. proliferatum*[7]		**MTX**
Fumonisin	Fumonisin P_2 (**100**)	*Fusarium* spp.[402] *F. proliferatum*[7]		**MTX**
Fumonisin	Fumonisin P_3 (**101**)	*Fusarium* spp.		**MTX**
Fumonisin	Fumonisin P_4 (**102**)	*Fusarium* spp.		**MTX**
Furan	5-Hydroxymethylfurfural	*Monocillium* sp.[70]	various dozen ("commodity")	MTX, cyto
Furan dimer	Terrestric acid[403]	*Penicillium terrestre*,[404] *Penicillium expansum*, *Penicillium hirsutum*,[7] *Penicillium verrucosum*, *Penicillium carneum*,[7] *Penicillium crustosum*,[7] *Penicillium hordei*[7]		MTX
Furan terpenoid	1,4-Ipomeadiol (1-(3-furyl)-1,4-pentanediol)	*Fusarium* sp.[405]	406	MTX
Furandione	Aspergillus acid A-D[407]	*Aspergillus flavus*[c],[7] *Aspergillus wentii*, *A. sojae*[7]	408	MTX
Furanocoumarin	4,5′,8′-Trimethylpsoralen (4,2′,8′-Trimethylpsoralen, NSC 71047, TMP)	*Sclerotinia sclerotiorum*	409	MTX
Furanocoumarin	Bergapten	*Fusarium oxysporon*	410	MTX
Furanocoumarin	Bergaptol (5-Hydroxypsoralen)	*Phytophthora megasperma* (Plant toxin)	411	MTX
Furanocoumarin	Psoralen	*Fusarium oxysporon*	412	MTX
Furanocoumarin	various Furanocoumarins	*Sclerotina*		MTX
Furanocoumarin	Xanthotoxin (8-Methoxypsoralen, Ammoidin)	*Fusarium sporotrichoides*, *Sclerotinia sclerotiorum*	413	**MTX**
Furanocyclopentane	Communiol	*Podospora communis*	A−C: 414; C: 415; E, F: 416	MTX
Furanone	1893B (+)	*Fungal strain 1893*	417	MTX
Furo[3,4-g]-1-benzopyran	Austalide A-L (B: (−))	*Aspergillus ustus*[89]	B: 418	MTX
Furobenzofuran	Monascin	*Monascus purpureus*[419,420]		MTX, cyto
Furobenzofuran	Monascorubrin	*Monascus purpureus*		MTX, cyto
Furobenzofuran	Rubropunctatin	*Monascus purpureus*		MTX, cyto
Furobenzopyran	Xyloketal A−F	*Xylaria* sp. (#2508)	421	calcium channel blocker
Furoindenobenzoxepine	Anditomin[23]	*Aspergillus variecolor*[422]		MTX
Furopyran	Isopatulin	*Penicillium urticae*	423	
Furopyrone	Benesudon (−) (4*S*,5*R*,6*S*)	*Mollisia benesuada*	424	*MTX*
Furopyranphenanthrene	Niveulone	*Dasycyphus niveus (Ascomycete)*[727]		Cyto
Furopyrone	Oxysporone[23]	*Fusarium oxuysporum*[425]		*MTX*
Furopyrone	Pintulin	*Penicillium vulpinum*[426]		tumor

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Fusariotoxin[23]	Moniliformin[427] (Semisquaric acid, potassium salt)	*Fusarium moniliforme*, *F. oxysporum*,[7] *F. avenaceum*,[7] *F. acuminatum*,[7] *F. proliferatum*[7]	428	MTX, cyto, cardiotox
Gibberelene[23]	Gibberellic acid	*Fusarium avanceum*, *F. Lateritium*, *F. monilifokuroi*, *giberella tricinta*,	429	*MTX*
Grisandiene	Bisdechlorogeodin (+)	*Penicillium glabrum*, *P. frequentans*[430]		MTX
Grisandiene	Dechlorogeodin (−)	*Chrysosporium FO-4712*[431]		MTX, herb
Grisandiene	Dihydrogeodin	*Aspergillus terreus*,[432,433] *Penicillium glabrum*		MTX
Grisandiene	Geodin (+)	*Aspergillus terreus*,[432,433] *Penicillium glabrum*	434	**MTX**, vir
Hirsutane	Phellodonic Acid	*Phellodon melaleucus*	435	*MTX*
Imidazopyridoindole[23]	Meleagrin[436]	*Penicillium vulpinum*, *P. melanoconidium*, *P. chrysogenum*[7]		MTX
Indole	20-Hydroxyaflavinine	*Aspergillus flavus*		feed
Indole	Acremoauxin A	*Acremonium roseum*[437]	438	MTX, plant growth regulator
Indole	Aflavine	*Aspergillus flavus*		*MTX*[e]
Indole	Cyclopiazonic acid[439]	*Aspergillus flavus*,[c] *A. oryzae*,[7] *A. flavus*,[7] *Penicillium verrucosum*, *P. commune*,[7] *P. griseofulvum*,[7] *P. solitum*, *P. camemberti*,[7] *P. palitans*[7]	*rac*: 440−445	**MTX**
Indole	Deoxytryptoquivaline	*Aspergillus clavatus*[446]		MTX
Indole	Desoxynortryptoquivaline	*Aspergillus clavatus*		MTX
Indole	Dihydroxyaflavinine (20,25-Dihydroxyaflavinine; Dihydroxyallavanine)	*Aspergillus flavus*[447]		Insec[e]
Indole	Epoxyfumitremorgin C	*Aspergillus fumigatus*		MTX
Indole	Mellamide	*Aspergillus melleus*		Insec
Indole	Nortryptoquivaline	*Aspergillus clavatus*		**MTX**
Indole	Nortryptoquivalone	*Aspergillus clavatus*		**MTX**
Indole (Paspalitrem type)	Aflatrem	*Aspergillus flavus*		**MTX**, neuro
Indole (Penitrems)	Pennigritrem $C_{37}H_{44}ClNO_6$	*Penicillium nigricans*, *P. janczewskii*[448]		MTX
Indole alkaloid	Communesin A[449]	*Penicillium expansum*[7]	model: 450	MTX
Indole alkaloid	Communesin B[449]	*Penicillium expansum*[7]	450, 451; model: 452	MTX, cyto
Indole alkaloid	Communesin C[449]	*Penicillium* sp.,[b,453] *P. expansum*[7,454]		MTX
Indole alkaloid	Communesin D[449]	*Penicillium* sp.		MTX
Indole alkaloid	Communesin E[449]	*Penicillium* sp.		MTX
Indole alkaloid	Communesin F	*Penicillium* sp.	455	MTX
Indole alkaloid	Communesin G[449]	*Penicillium rivulum*[456]		*MTX*
Indole alkaloid	Communesin H[449]	*Penicillium* sp.		MTX
Indole alkaloid	Cryptoechinulin A-D, E6, E10, G	*Aspergillus amstelodami*		MTX
Indole alkaloid	Marcfortine A (−)[457]	*Penicillium paneum*,[7] *P. roqueforti*		MTX
Indole alkaloid	Marcfortine B (−)[457] (30-Demethylmarcfortine A)	*Penicillium paneum*,[7] *P. roqueforti*	*rac*: 458	MTX
Indole alkaloid	Marcfortine C	*Penicillium roqueforti*	*rac*: 459	MTX
Indole alkaloid	Neoxaline	*Aspergillus japonicus*	model: 460	MTX
Indole alkaloid	Oxaline[461]	*Penicillium atramentoseum*,[7] *P. oxalicum*[7]	model: 460	MTX
Indole Alkaloid	Stephacidin A	*Aspergillus ochraceus*	462	mitochondrial NADH oxidase inhibitor
Indole alkaloid	β-Aflatrem	*Aspergillus flavus*	463	**MTX**
Indole alkaloid (diketopiperazine)	12,13-Dihydro-12-hydroxy-austamide	*Aspergillus ustus*		**MTX**
Indole alkaloid (diketopiperazine)	12,13-Dihydroaustamide (+)	*Aspergillus ustus*, *Penicillium italicum*[464]		**MTX**
Indole alkaloid (diketopiperazine)	Bipolaramide (**541**)	*Bipolaris sorokiana*[465]	466, 467; model: 468	MTX

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Indole alkaloid (diketopiperazine)	Brevianamide A[469] (**545**) (+)	*Aspergillus ustus*, *Penicillium verrucosum*,[7] *P. viridicatum*, *P. brevicompactum*[7,470]	*rac*: 471, 472	**MTX**
Indole alkaloid (diketopiperazine)	Brevianamide B	*Penicillium verrucosum*,[7] *P. viridicatum*, *P. brevicompactum*[473]	474	MTX
Indole alkaloid (diketopiperazine)	Brevianamide C, D	*Penicillium brevicompactum*[473]		MTX
Indole alkaloid (diketopiperazine)	Brevianamide E	*Penicillium brevicompactum*[475]	476, 472	**MTX**
Indole alkaloid (diketopiperazine)	Brevianamide M	*Penicillium verrucosum*		prob MTX
Indole alkaloid (diketopiperazine)	Deoxybrevianamide B	*Aspergillus ustus*		MTX
Indole alkaloid (diketopiperazine)	Isoroquefortine C	*Penicillium roqueforti*	477	MTX
Indole alkaloid (diketopiperazine)	Roquefortine A	*Penicillium roqueforti,*[c] *P. hirsutum*		**MTX**, muscle relaxant, antidepressant, local anaethetic
Indole alkaloid (diketopiperazine)	Roquefortine B	*Penicillium roqueforti*, *p. expansum*, *P. verrucosum*		**MTX**
Indole alkaloid (diketopiperazine)	Roquefortine C[478]	*Penicillium roqueforti*,[7] *P. griseofulvum*,[7] *P. chrysogenum*,[7] *P. claviforme*, *P. hirsutum*,[7] *P. expansum*,[7] *P. crustosum*,[7] *P. italicum*, *P. verrucosum*, *P. carneum*,[7] *P. hordei*,[7] *P. melanoconidium*[7] *P. paneum*,[7]	479	**MTX**
Indole alkaloid (diketopiperazine)	Roquefortine D	*Penicillium crustosum*	480	**MTX**
Indole alkaloid (diketopiperazine)	TR2-Toxin (TR-2, verruculogen TR 2)	*Penicillium verrucosum*[481]	298, 482	Not mut
Indole alkaloid (Paspalin/penitem class)	Secopenitrem B	*Aspergillus sulfureus*		**MTX**, insect
Indole alkaloid (Paspalin/penitem class)	Sulpinine A-C	*Aspergillus sulfureus*		**MTX**, insect
Indole alkaloid[23]	Asterriquinone A, B1, B, E	*Aspergillus terreus*	B: 483; E: 484; Demethy-Bl: 485	Cyto
Indole dipeptide	Aurechinulin	*Aspergillus amstelodami*	486	MTX
Indole dipeptide	Echinulin	*Eurotium (Aspergillus) repens*, *E. amstelodami*,[7] *E. Chevalieri*,[7] *E. herbariorum*[7]	487	**MTX**
Indole dipeptide	Neoechinulin A, B, C, D, E, E7, E8	*Eurotium chevalieri*, *Aspergillus amstelodami*	488	**MTX**
Indole diterpene[23]	Radarin A−D	*Aspergillus sulfureus*		MTX
Indole diterpenoid	Nominine	*Aspergillus flavus*, *Penicillium roqueforti*	489, 490	**MTX**
Indole terpenoid	Aflavinine	*Aspergillus flavus*, *Eupenicillium crustaceum*	model: 491	**MTX**, antiinsec
Indole terpenoid	Emindole DA, DB, SA	*Emericella desertorum*[327,327]	model: 492	MTX
Indole terpenoid	Thiersinine A, B	*Penicillium* sp. *(NRRL 28147)*[493]		insec
Indolizidine alkaloid	Slaframine (1*S*,6*S*,8a*S*-1-Acetoxy-6-aminoctahydroindolizidine)	*Rhizoctonia leguminicola*	494	**MTX**, neuro
Indolo diketopiperazine	Paraherquimide	*Penicillium* sp.	495	MTX
Isocoumarin	3-Methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin (*S*) (-)	*Aspergillus caespitosus, Talaromyces thailandiasis*[496]		MTX
Isocoumarin	5,6-Dihydroxymellein	*Plectophomella* sp., *Cryptosporiopsis* sp.,		*MTX*
Isocoumarin	5-Carboxymellein (R)(3,4-Dihydro-8-hydroxy-3-methyl-1-oxo-1H-2-benzopyran-5-carboxylic acid)	*Halorosellinia oceanica 1893*[b], *valsa ceratosperma)*[265]		Cyto

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Isocoumarin	5-Chloro-6-hydroxymellein	*Plectophomella* sp., *Cryptosporiopsis* sp.,		MTX
Isocoumarin	5-Chloro-6-methoxymellein	*Coniothyrium* sp., *Periconia macrospinosa*[497]		MTX
Isocoumarin	5-Methylmellein (3,4-Dihydro-8-hydroxy-3,5-dimethyl-1*H*-2-benzopyran-1-one, 5-Methylochracin)	*Phomopsis* sp.	498	*MTX*
Isocoumarin	6,7,8-Trihydroxy-3-methyl-1*H*-2-benzpyran-1-one (6,7,8-Trihydroxy-3-methylisocoumarin)	*Emericella navahoensis*[55,91,499]		*MTX*
Isocoumarin	6-Hydroxymellein[500]	*Plectophomella* sp., *Cryptosporiopsis* sp.	501	*MTX*
Isocoumarin	6-Methylcitreoisocoumarin (6-Methoxy-citreoisocoumarin, 3-(2*S*-Hydroxy-4-oxopentyl)-8-hydroxy-6-methoxy-isocoumarin, LL-Z 1640−6[650])	*Penicillium nalgiovense*[502]		MTX
Isocoumarin	8-Carboxy-3,4-dihydro-9-hydroxy-3-methylisocoumarin	*Penicillium viridicatum*	503	MTX
Isocoumarin	8-O-Methylasperentin (Asperentin-8-O methyl ether, Methylcladosporin)	*Aspergillus flavus*	504	MTX
Isocoumarin	Asperentin (Cladosporin)	*Aspergillus flavus*	504	MTX
Isocoumarin	Dichlorodiaporthin (3-(3,3-dichloro-2-hydroxy-propyl)-8-hydroxy-6-methoxy-isochromen-1-one)	*Penicillium nalgiovense*[502]		MTX
Isocoumarin	Monocerin	*Helminthosporium monoceras*, *Exserohilum monoceras*	505	MTX, phytotox
Isocoumarin	Ramulosin	*Pestalotia ramulosa*[506]	501, 507	MTX
Isocoumarin	Semi-Vioxanthin (**605**) (Semivioxanthin)	*Penicillium citreo-viride*	508	MTX
Isocoumarin	Viriditoxin (SC-28762)	*Aspergillus viridinutans*,[23] *Paecilomyces variotii*[7]		**MTX**
Isocoumarin	Xanthomegnin[509] (**607**)	*Penicillium viridicatum*[c,7] *P. aurantiogriseum*, *P. cyclopium*,[7] *P. freiii*,[7] *P. tricolor*, *P. cyclopium*, *Aspergillus sulfureus*, *A. ochraceus*[7]	510	**MTX**
Isocoumarin dimer	Viomellein[511]	*Aspergillus ochraceus*[c,7] *A. sulfureus*, *Penicillium viridicatum*[c,7] *P. cyclopium*, *P. expansum*, *P. freii*,[7] *P. tricolor*, *P. verrucosum*, *P. viridicatum*, *P. citro-viride*		**MTX**
Isocoumarin dimer	Vioxanthin (**606**)	*Penicillium freii*,[7] *P. viridicatum*,[7] *Aspergillus ochraceus*[7]	512	**MTX**
Isocoumarin-dibenzopyran	Rubrosulphin (Rubrosulfin)	*Aspergillus sulfureus*		MTX
Isocoumarin-dibenzopyran	Viopurpurin	*Aspergillus sulfureus*, *Trichophyton* spp., *Penicillium viridicatum*		MTX
Isoechinulin-type Alkaloids	Variecolorins A−L	*Aspergillus variecolor*[513]		MTX
Isoindolone	Dihydrocytochalasin B γ lactone	*Phoma* spp.		MTX
Isoprenoid	Austin	*Aspergillus ustus*[7,514]		**MTX**
Isoprenoid	Austinol	*Aspergillus ustus*[515]		**MTX**
Isoprenoid	Dehydroaustin	*Aspergillus ustus*[516]		**MTX**
Janthitrems	Janthitrem A	*Penicillium janthinellum*[c]		**MTX**
Janthitrems	Janthitrem B	*Penicillium janthinellum*[c]		**MTX**
Janthitrems	Janthitrem C	*Penicillium janthinellum*[c]		**MTX**

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Janthitrems	Janthitrem D	*Penicillium janthinellum*[c]		**MTX**
Janthitrems	Janthitrem E	*Penicillium janthinellum*[c]		**MTX**
Janthitrems	Janthitrem F (10-*O*-Acetyljanithrem E)	*Penicillium janthinellum*[c]		**MTX**
Janthitrems	Janthitrem G	*Penicillium janthinellum*[c]		**MTX**
Macrolactone	4-Keto-clonostachydiol, clonostachydiol	*Gliocladium* sp.[b], *Clonostachys cylindrospora*	517	Cyto
Macrolactone	Brefeldin A (cyanein, decumbin, ascotoxin, synergisidin)	*Penicillium simplicissium*, *P. verrucosum*, *P. brefeldianum*	518	MTX
Macrolactone	Brefeldin C (7-Deoxybrefeldin-A)	*Penicillium brefeldianum*[519]		*MTX*
Macrolactone	Microcarpalide	Unidentified endophytic fungus	520	cyto
Macrolactone	Phomol (+)	*Phomopsis* sp.[521]		Cyto, fung, bact
Macrolactone	Vermiculine (−)[23]	*Talaromyces wortmannii*	522	*MTX*
Meroterpenoid	Montadial A	Bondarzewia montana (polypore)[523]		Cyto
Naphthalene	Phomopsidin (+)	*Phomopsis* sp.	524	Antimicrotubuli
Naphthalene[23]	Solanapyrone A−E (Salnopyrone) (−)	*Ascochyta rabiei*	A: 525; D, E: 526	*MTX*
Naphthaquinone	Herbarin A, B	*Cladosporium herbarum*		MTX
Naphthopyrone	Dehydroherbarin	*Torula herbarum*	538	prob cyto
Naphthopyrone	Fonsecin B (TMD 256B2)	*Aspergillus fonsecaeus*, *A. niger*		MTX
Naphthopyrone	general structure	*Aspergillus niger*,[7] *A. carbonarius*[7]		MTX
Naphthopyrone	Rubrofusarin (**609**) (5,6-dihydroxy-8-methoxy-2-methyl-4*H*-naphtho[2,3-b]pyran-4-one)	*Aspergillus carbonarius*, *A. niger*, *A.* sp. *M39*,[142,527−529] *Fusarium culmorum*	530	MTX
Naphthopyrone	Rubrofusarin B (Hemnigerone, TMD 256A2)	*Aspergillus fonsecaeus*		MTX
Naphthopyrone dimer	Nigerone (−) (*S*)	*Aspergillus niger*[531]	(+), (−): 532	MTX
Naphthoquinone	2-Hydroxyjuglone	*Fusarium decemcellulare*[533]	various syntheses, see, e.g.: 534	MTX
Naphthoquinone	9-O-Methylfusarubin (9-O-Methyl-fusarubin, Fusarubin 9-methyl ether)	*Fusarium moniliforme*[535,536]		MTX
Naphthoquinone	Bostrycoidin (NSC-103645)	*Fusarium decemcellulare*[142,533,537]	deoxy: 538; semisynthesis: 539	MTX, prob cyto
Naphthoquinone	*cis*-Dihydrofusarubin	*Fusarium* sp.[d]		MTX
Naphthoquinone	Fusarubin	*Fusarium decemcellulare*,[533] *F. javanicum*[21]		**MTX**
Naphthoquinone	Javanicin (Yavanicin)	*Fusarium culmorum*, *F. graminearum*, *F. oxysporum*, *F. roseum*, *F. verticillioides*, *F. avenaceum*, *F. equiseti*, *F. nivale*, *F. decemcellulare*, *F. solani*	540	**MTX**
Naphthoquinone	*Trans*-Dihydrofusarubin	*Fusarium solani*[21]		MTX
Naphthoquinone	various pigments	*Fusarium oxysporon*,[7] *F. proliferatum*[7]		MTX
Naphthoxirene	Phaseolinone (+)	*Macrophomina phaseolina*, *Xylaria* sp.	formal: 541	**MTX**, mut, phyto tox, leish, RNA polymerase inhibitor, Antiplasmodial
Naphthoxocin (naphthazarin)	Isomarticin (+)	*Fusarium martiella*, *F. solani*		Phytotox
Naphtho-γ-pyrone dimer	Chaetochromin A−D	*Chaetomium* sp.[542]		**MTX**, ter, mut
Naphtho-γ-pyrone dimer	Ustilaginoidin A, D, E dihydroisoustilaginoidin A	*Dermocybe austroveneta*[543] (A)		**MTX**
Napthalene	Tanzawaic acid A−D	*Penicillium citrinum*, *P. chrysogenum*,[7] *P. steckii*	544	MTX
Napthalene[23]	Equisetin[545] (Equestin[23])	*Fusarium equiseti*,[7] *F. semitectum*[7]	546	MTX
Napthoquinone	Nectriafurone	*Fusarium culmorum*[7]	547	MTX

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Napthoquinone dimer	Aurofusarin (**608**) (5,5′-Dihydroxy-8,8′-dimethoxy-2,2′-dimethyl-[7,7′-bi-4*H*-naphtho[2,3-b]pyran]-4,4′,6,6′,9,9′-hexone)	*Fusarium culmorum*[528]		MTX
Nephrotoxic glycopeptides	various structures[548]	*Penicillium aurantiogriseum*,[7] *P. polonicum*[7]		**MTX**
Nucleoside	Mizoribine	*Eupenicillium brefeldianum*[21]		MTX, immun
Ochratoxin	Ochratoxin A (**7**) (−)	*Penicillium viridicatum*[c], *P. crustosum*, *P. expansum*, *P. verrucosum*,[7] *P. nordicum*,[7] *Aspergillus fumigatus*, *A. versicolor*, *A. ochraceus*,[7] *A. niger*,[7] *A. carbonarius*,[7] *Petromyces alliaceus*[7]	*rac*: 503, 549−551; formal: 552	**MTX**, nephrotox
Ochratoxin	Ochratoxin A methyl ester (**158**)	*Aspergillus ochraceus*		MTX
Ochratoxin	Ochratoxin B (**155**) (OTB, Dechloroochratoxin)	*Aspergillus ochraceus*	*rac*: 503	**MTX**
Ochratoxin	Ochratoxin B ethyl ester (**160**)	*Aspergillus ochraceus*		MTX
Ochratoxin	Ochratoxin B methyl ester (**159**)	*Aspergillus ochraceus*		MTX
Ochratoxin	Ochratoxin C (**156**) (Ochratoxin A ethyl ester)	*Aspergillus ochraceus*		**MTX**
Ochratoxin	Ochratoxin D (4-Hydroxyochratoxin A)		553	MTX
Ochratoxin	Ochratoxin α (**157**)	*Aspergillus ochraceus*	R: 552	MTX
Octahydrobenzypran	Sambutoxin	*Fusarium sambucinum*	554	Tox
Oligophenalenone dimer	Bacillisporin A−E	*Talaromyces bacillisporus*[555]		cyto
Oligophenalenone dimer	Duclauxin	*Penicillium duclauxi*, *P. stipitatum*, *P. emmonsii*, *Talaromyces bacillisporus*, *T. macrosprum*[7]		**MTX**, tumor, biot
Oxaazabicyclo[3.2.1]octane	Awajanomycin	*Acremonium* sp. AWA16−1[b]	556	Cyto
Oxaazaspiro[4.4]nonene	Synerazol	*Aspergillus fumigatus*	557; directed biosynthesis: 558	cyto[558]
Oxaazaspiro[4.4]nonene	Pseurotin A (Pseurotin)	*Aspergillus fumigatus*	559	Neuritogenic activity, biot
Oxatricyclononene	Massarinolin B	*Massarina tunica*	560	MTX
Oxirenoisobenzofuran	Integrasone	sterile mycelium from an unknown fungus	561	MTX
Paspalitrem type	Paspaline	*Claviceps paspali*, *Aspergillus* sp. *Penicillium paxilli*	562	**MTX**, tem
Paspalitrem type	Paspalinine (+)	*Claviceps paspali*	563	**MTX**
Pentaketide	Flaviolin (2,5,7-trihydroxy-1,4-naphthoquinone)	*Aspergillus fetidus*, *phialophora lagerbergii*,[23] *Sporothrix schenckii*		MTX
Pentenoid acid	Verruculone[564] (Verrucolone, Arabenoic acid)	*Penicillium italicum*,[7] *P. nordicum*,[7] *P. olsonii*, *P. verrucosum*[7,565]		MTX, herb
Peptide	Cyclosporin A	*Tolypocladium inflatum*	566	*MTX*, biot
Peptide	Sillucin	*Mucor pusillus*		micro
Peptide (4 AA)[23]	Viridic acid[567]	*Penicillium viridicatum*[7]	568	**MTX**
Peptide (Amanita toxins)	α-Amanitine	*Amanita* sp.[569]	570	*MTX*
Peptide (Peptaibol)	Alamethicin (more than one)	*Trichoderma viride*[7]	571	biot
Peptide (Peptaibol)	Suzukacillin[572]	*Trichoderma viride*[573,7]		MTX, biot
Peptide (Peptaibol)	Trichorzianine A,B (Alamethicins)	*Trichoderma harzianum*[7]		MTX
Peptide (Peptaibol)	Trichotoxin A40, A50	*Trichoderma viride*[7]	(A50)	MTX, biot
Peptide (Peptaibol)	Trichovirin (Trichotoxin B)	*Trichoderma viride*	Trichovirin I: 574	biot

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Perilene	Calphostin A-C (A: UCN-1028A; C: Cladochrome E)[26,575,576]	*Cladosporium* sp.	577	*MTX*, kin
Perilene	Calphostin D[26] (ent-Isophleichrome)	*Cladosporium* sp.[578]	576, 577, 579	*MTX*, kin
Phenalene	Funalenone	*Aspergillus niger*		HIV, cyto, collagenase inhibitor
Phenelanone	Atrovenetinone	*Penicillium* sp. *FKI-1463*		HIV
Phenol	Clavatol	*Aspergillus clavatus*, *Trichderma pseudokoningii*	580, 581	MTX
Phenol	Flavipin[23]	*Epicoccum nigrum*, *Aspergillus terreus*, *Fennelia flavipes*, *Chaetomium globosum*	582	MTX
Phenol	Fomecin B	*Tricholomopsis rutilans (Basidomycete)*[583]	584	Cyto
Phenol	Parvisporin	*Stachybotrys parvispora*[585]		Neuritogenic
Phenol	Raistrick phenols: 2,4-Dihydroxy-6-(2-oxypropyl)benzoic acid, 2,4-Dihydroxy-6-(1-hydroxy-2-oxypropyl)benzoic acid, and 2,4-Dihydroxy-6-(1,2-dioxopropyl) benzoic acid[586]	*Penicillium brevicompactum*[7]		MTX
Phenol	Sorbicillin	*Aspergillus clavatus*	581	MTX
Phomactins	Phomactin A	*Phoma* sp.[587]	588−590	*MTX*
Phomactins	Phomactin B−G	*Phoma* sp.	591	*MTX*
Phthalide	3-Butyl-7-hydroxyphthalide (−)	*Penicillium vulpinum*	592	cyto
Phthalide	3-Ethyl-5,7-dihydroxy-3,6-dimethylphthalide	*Aspergillus unguis*		MTX
Phthalide	Cyclopaldic acid[593]	*Penicillium aurantiogriseum*, *P. commune*[7]		MTX
Phthalide	Mycophenolic acid[594]	*Penicillium brevicompactum*[c,7] *P. roqueforti*,[7] *P. verrucosum*, *P. carneum*[7]	595	MTX, immun
p-Methoxyphenylquinolinone	Yaequinolone A−I	*Penicillium* sp.		Insec
Polyketide	PM-toxin B	*Phyllosticta maydis*	596	**MTX**, pathotoxin
Polyketide (Octahydronaphthalene)	Diplodiatoxin (+)	*Diplodia maydis*[597]	598	MTX
Polyol	Sphingofungin A−F	*Aspergillus* sp.[599]	77, 600, 601	**MTX**
Polyol (Bisepoxide)	Depudecin (−)	*Alternaria brassicicola*	602	antiangiogenic, Histone deacetylase inhibitor, plasm
Propionic acid[23]	3-Nitropropionic acid (Hiptalonic acid, Hiptagenic acid, Bovinocidin, Oryzacidin, Oryzasizine)	*Arthrinium* sp., *Aspergillus oryzae*,[7] *A. flavus*,[7] *Penicillium melinii*	commodity	**MTX**
Purine	Uric acid	*Penicillium cyclopium*[603]	various syntheses	MTX
Pyran	Chlamydospordiol (4-Methoxy-5-hydroxyme thyl-6-(3-butan-2-ol)-2H-pyran-2-one)	*Fusarium* spp.[604]		MTX, prob cyto
Pyrandione	Grevellin B, C, D	*Suillus grevellei*	605, 735	MTX
Pyranobenzopyrandione	Phelligridin C−G	*Phellinus igniarius*[606]		Cyto
Pyranoisoindole	SMTP-1 to -6	*Stachybotrys microspora*		MTX, plasminogen activator
Pyranoisoindole	Stachybotrin A (+) [144373-26-2][753]	*Stachybotrys.* sp.[607]		MTX, fung
Pyranoisoindole	Stachybotrin B (+)	*Stachybotr.* sp.[607]		MTX
Pyranoisoindole	Stachybotrin C	*Stachybotrys parvispora*[585]		Neuritogenic
Pyranoisoindole	Staplabin	*Stachybotrys microspora*[608]		MTX
Pyranoisoindole dimer	SMTP-7 (Orniplapin)	*Stachybotrys chartarum*,[21] *S. microspora*		MTX
Pyranoisoindole dimer	SMTP-8	*Stachybotrys microspora*		MTX, plasminogen activator
Pyrone	Asperlin (+)	*Aspergillus* sp.	609	MTX
Pyrone	Asteltoxin	*Aspergillus stellatus*	610	MTX
Pyrone	Aszonapyrone A	*Aspergillus zonatus*[611]		MTX
Pyrone	Citreoviridin X (Citreoviridinol)	*Penicillium citro-viride*	612	MTX

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Pyrone	Fusapyrone	*Fusarium semitectum*[7,613]		MTX
Pyrone	Gibepyrone A	*Fusarium oxysporum*[7]	614	MTX
Pyrone	Gibepyrone F	*Fusarium oxysporum*[7]		MTX
Pyrone	Isoasperlin	*Macrophomina phaseolina*		Phytotox
Pyrone	Kojic acid[615]	*Aspergillus fumigatus,*[c] *A. oryzae*,[7] *A. parasiticus*, *A. tamari*, *A. flavus*,[7] *A. nomius*,[7] *A. sojae*,[7] *Penicillium jensenii*, *P. lanosum*, *Petromyces alliaceus*[7]	biotransformation from glucose	MTX, mut
Pyrone	Phomalactone (Phomolactone) (+)	*Macrophomina phaseolina*, *Nigrospora sphaerica*	609, 616; Acetyl p.: 617	Phytotox
Pyrone	Verrucosidin[618] (Verrucosidin A) (+)[23]	*Penicillium melanoconidium*,[7] *P. aurantiogriseum*, *P. polonicum*,[7] *P. viridicatum*, *P. verrucosum*	(+): 619−621	**MTX**, trem
Pyranopyridine	Acuminatopyrone	*Fusarium acuminatum*, *F. chlamydosporum*[604,622,623]		MTX
Pyranopyrone	Chlamydosporol (−)	*Fusarium culmorum*, *F. chlamydosporum*, *F. acuminatum*,[7] *avenaceum*[7,623]		**MTX**, cyto
Pyrazine	Aspergillic acid (+)	*Aspergillus* sp.	*rac*: 624	MTX
Pyrazine	Flavacol	*Aspergillus ochraceus*	625	mitochondrial NADH oxidase inhibitor
Pyrazinone	Neoaspergillic acid	*Aspergillus slerotiorum*	626	Biot
Pyrazinoquinazoline	Fumiquinazoline A−G (A: **547**)	*Aspergillus fumigatus*[b]	627	MTX
Pyridine (alkaloid)	Flavipucine (3′-Isovaleryl-6-methylpyridine-3-spiro-2′-oxiran-2 (1H),-4(3H)-dione), brunnescin	*Cladobotryum rubrobrunnescens*[628]	629	Cyto, biot
Pyridine derivative	Fusaric acid	*Fusarium oxysporum*,[7] *F. proliferatum*[7]	630	MTX, cyto, hypotensive agent
Pyridone	Fischerin	*Neosatorya fischeri*		MTX, Tox
Pyridopyrazin Alkaloid	10-Epi-Verruculotoxin (3-Toluyloctahydro-2*H*-pyrido-[1,2-a]pyrazine)	*Penicillium verrucosum*[21]	631, 632	**MTX**
Pyridopyrazin Alkaloid	Verruculotoxin (*S*,*S*) (3-Toluyloctahydro-2*H*-pyrido-[1,2-a]pyrazine)	*Penicillium verrucosum*[21,633]	631, 632	**MTX**
Pyrone	Radicinin	*Alternaria radicinin*	model: 634	*MTX*
Pyrone	Radicinol, epi-Radicinol	*Alternaria Chrysanthemi*, *A. radicina*, *Cochliobolus lunata*		MTX
Pyrrolidine[23]	Versimide (MM4086) (Methyl (methylsuccinimido)acrylate) (*R*) (+)	*Aspergillus versicolor*[635]	636	MTX, insec
Pyrrolizidine alkaloid	UCS 1025A	*Acremonium sp.*	637	
Quinazoline alkaloid	Alantrypinone (PF 1198 A)	*Penicillium verrucosum*,[638] *Aspergillus* spp.		MTX
Quinazoline alkaloid	Anacine[639] (1*S*, 3*S*)	*Penicillium aurantiogriseum*,[7] *P. nordicum*,[7] *P. polonicum*, *P. verrucosum*	640	MTX
Quinazoline alkaloid	Chrysogenin[641] (Chrysogine) (*S*) (−)	*Penicillium chrysogenum*,[7] *P. griseoroseum*, *P. nalgiovense*,[7] *Fusarium culmorum*, *F. equiseti*,[7] *F. graminearum*,[7] *F. semitectum*[7]	642	MTX
Quinolinone alkaloid	3-Methoxyviridicatin (3-*O*-Methylviridicatin)	*Penicillium polonicum*	643	MTX
Quinolinone alkaloid	Penigequinolone A, B (+)	*Penicillium verrucosum*[644]		MTX
Quinolinone alkaloid	Viridicatin (2,3-Dihydroxy-4-phenylquinoline)	*Penicillium cyclopium*, *P. aurantiogriseum*, *P. solitum*, *P. aurantiovirens*, *P. freii*, *P. polonicum*[23]	645	MTX

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Quinolinone alkaloid	Viridicatol (Carbostyril)	*Penicillium cyclopium*, *P. aurantiovirens*, *P. p. freii*, *P. neoechinullatum*, *P. polonicum*[23]		MTX
Quinone	Cochlioquinone A	*Drechslera sacchari*		MTX, kin
Quinone	Epi-Cochlioquinone A	*Stachybotrys bisbyi*		MTX
Quinone	Terreic acid (5,6-Epoxy-2-hydroxytoluquinone, Y-8980, Anti-HeLa-cell substance)	*Aspergillus terreus*[c,646,647]	647, 648	**MTX**
Resorcyl lactone	11-Acetyldehydrocurvularin[661]	*Cercospora scirpola*		MTX
Resorcyl lactone	12-Oxocurvularin	*Penicillium citreo-viride*	649	MTX
Resorcyl lactone	3′-Hydroxyzearalenone (two diastereomers)	*Fusarium roseum*		MTX
Resorcyl lactone	5′-Dihydroxyzearalenone-4-methylether	Unidentified fungus[650]		MTX
Resorcyl lactone	5-Formylzearalenone	*Gibberella zeae*		MTX
Resorcyl lactone	6′,8′-Dihydroxyzearalene	*Fusarium roseum*[651]		MTX
Resorcyl lactone	7′-Dehydrozearalenone (1′,7′-Zearaldienone)	*Gibberella zeae*[652,653]		MTX
Resorcyl lactone	8′-Hydroxyzearalenone (two diastereomers)	*Fusarium roseum*		MTX
Resorcyl lactone	Aigialomycin A,B,C,D (D: **356**)[654]	*Aigialus parvus*	655−658	MTX
Resorcyl lactone	Curvularin[661]	*Curvularia* sp., *Alternaria cinerariae*	659	MTX
Resorcyl lactone	Dehydrocurvularin[660,661]	*Drechslera australiensis*		*MTX*, phytotoxin
Resorcyl lactone	Hypothemycin (**355**) (+)	*Hypomyces trichothecoides*	662	**MTX**
Resorcyl lactone	LL-Z1640-2	unidentified fungus[650]		MTX
Resorcyl lactone	LL-Z1640-3	unidentified fungus[650]		MTX
Resorcyl lactone	Monocillin I (Dechloromonorden)	*Monocillium nordinii*	663, 664	MTX
Resorcyl lactone	Monocillin II (**353**)	*Monocillium nordinii*		MTX
Resorcyl lactone	Monocillin III−V (III: **604**)	*Monocillium nordinii*		MTX
Resorcyl lactone	Monorden (**352**) (Radicicol)	*Monosporium bonorden*	665	**MTX**
Resorcyl lactone	Pochonin A (**376**)	*Pochonia chlamydosporia*	666	MTX
Resorcyl lactone	Pochonin B	*Pochonia chlamydosporia*		MTX
Resorcyl lactone	Pochonin C (**354**)	*Pochonia chlamydosporia*	667	MTX
Resorcyl lactone	Pochonin D	*Pochonia chlamydosporia*	668	
Resorcyl lactone	Pochonin E, F	*Pochonia chlamydosporia*		
Resorcyl lactone	Queenslandon (**357**)	*Chrysosporium queenslandicum*	model: 669	MTX
Resorcyl lactone	Zeaenol	*Cochliobolus lunata*, unidentified fungus[650]		MTX
Resorcyl lactone	Zearalanol (Zearanol, Zeranol) see α- or β-Zearalanol (**318**, **319**)	*Fusarium graminearum*		**MTX**
Resorcyl lactone	Zearalanone (**315**) (Zanone)	*Fusarium graminearum*, *F. crookwellense*, *F. culmorum*, *F. equiseti*, *F. moniliform* *F. verticillioides*	670	**MTX**
Resorcyl lactone	Zearalenone (**4**) (−) (*S*,*E*) (F 2 toxin, Toxin F2)	*Gibberella zeae*[c] *Fusarium crookwellense*, *F. equiseti*,[7] *F. graminearum*,[7] *F. semitectum*[7]	671−676	**MTX**
Resorcyl lactone	α-Zearalanol (**318**)	*Fusarium* sp.	1074b	**MTX**
Resorcyl lactone	α-Zearalenol (**316**) (*S*) (-)	*Fusarium roseum*		MTX
Resorcyl lactone	β-Hydroxycurvularin[661]	*Alternaria tomata*		MTX
Resorcyl lactone	β-Zearalanol (**319**)	*Fusarium* sp.		**MTX**
Resorcyl lactone	β-Zearalenol (**317**)	*Fusarium roseum*		**MTX**
Ribotoxin (149 AA)	Restrictocin	*Aspergillus fumigatus*		Ribotoxin, cyto
Sequiterpene	PR imine	*Penicillium roqueforti*		**MTX**
Sequiterpene	Spirocyclic drimane sesquiterpenes, e.g., phenylspirodrimanes (spirolactones and spirolactams)	*Aspergillus ustus*	677	MTX
Sesqui terpene lactone	Expansolide	*Penicillium expansum*		**MTX**
Sesquiterpene	HM-3, HM-4	*Helicobasidium mompa*	678	MTX
Sesquiterpene	Insulicolide A (−)	*Aspergillus versicolor*, *A. insulicola*[b]		MTX, cyto
Sesquiterpene	Insulicolide B (−)	*Aspergillus versicolor*		Cyto

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Sesquiterpene	PR toxin (PR-toxin)	*Penicillium roqueforti*[7c], *P. expansum*, *P. verrucosum*, *P. chrysogenum*		**MTX**
Sesquiterpene	Terrecyclic acid A (TCA)	*Aspergillus terreus*	679	CMTX, cytotox, anti cancer
Sesquiterpene (Cyclopropindene)	Isovelleral	*Lactarius vellereus* (Basidiomycete)	680	Cyto
Sesquiterpene (Quinone)	Lagopodin A	*Coprinus cinereus*	681	MTX
Sesquiterpene (trichthecene precursor)	Trichodiene (**611**)	*Fusarium sporotrichoides*, *Stachysbotrys* sp., *Trichothecium roseum*[682]	683	*MTX*
Six-membered lactone	Aurovertin B (NSC 329699)	*Calcarisporium arbuscula*[684]	685	*MTX*
Six-membered lactone	Aurovertin D	*Calcarisporium arbuscula*[686]		*MTX*
Sphingosine	2-Amino-14,16-dimethyloctadecan-3-ol (2-AOD-3-ol)	*Fusarium avenaceum*[687]		Cyto
Spirobenzofuran	Griseofulvin[688]	*Penicillium griseofulvum*[c7]	689	**MTX**, fung
Spirofuroisoindole	Stachybotral	*Stachybotrys elegans*[690]		MTX
Spirofuroisoindole	Stachybotrin (Stachybortrin)	*Stachybotrys elegans*, *S. alternans*, *S. atra*		MTX
Spirofuroisoindole	Stachybotrine A (+) [256620−70−4][753]	*Stachybotrys elegans*[690]		MTX
Statin	Compactin[26] (Mevastatin)	*Penicillium cyclopium*, *P. citrinum*, *P. solitum*[7]	691	MTX
Steroid	Ergosterol[23]	*Gaeumannomyces graminis*, *Penicillium aurantiogriseum*, *P. verrucosum*		*MTX*
Steroid	Fumitoxin A−D[e,692]	*Aspergillus fumigatus*[7]		MTX
Steroid	Helvolic acid (Fumigacin)	*Aspergillus fumigatus*[c]		Bact
Steroid	Poaefusarin	*Fusarium sporotrichioides*		**MTX**
Steroid	Sporofusarin	*Fusarium sporotrichioides*		**MTX**
Steroidal	Viridin	*Trichoderma viride*, *Gliocladium virens*, *Penicillium funiculosum* *Myrothecium roridum*	693	MTX, bact
Steroidal	Wortmannin (+)	*Fusarium* sp., *Talaromyces wortmannii*, *Penicillium wortmannii*, *P. funiculosum Trichoderma viride*, *Gliocladium virens*, *Myrothecium roridum*	Formal total synthesis: 694	Cyto
Steroidal (Cyclopentaphenanthrofuran)	Desmethoxyviridin	*Nodulisporium hinnuleum*, *Trichoderma viride*, *Gliocladium virens*, *Penicillium funiculosum* *Myrothecium roridum*		**MTX**
Steroidal (Cyclopentaphenanthrofuran)	Desmethoxyviridiol[695]	*Nodulisporium hinnuleum*		**MTX**
Sterol	Terretonin[696]	*Aspergillus terreus*		**MTX**
Structure unknown	Antibiotic C3368-A	unidentified fungus[697]		MTX
Structure unknown	Byssotoxin A ($C_{25}H_{26}N_2O_3$)[698]	*Byssochlamys fulva*[7]		MTX
Structure unknown	Candidulin ($C_{11}H_{15}NO_3$)[23]	*Aspergillus candidus*[699]		biot
Structure unknown	Flavutoxin (Flavotoxin)	*Aspergillus flavus*, *A. parasiticus*		**MTX**
Structure unknown	Necrocitin	*Myrothecium* sp.[700]		biot, phytotox
Structure unknown	Nidulotoxin[701]	*Aspergillus nidulans*, *A. versicolor*,[7]		MTX
Structure unknown	Pibasterol	*Penicillium islandicum*[702]		Bact, not mut
Structure unknown	Prechinulin	*Aspergillus amstelodami*, *A. repens*[703]		MTX
Structure unknown	Simatoxin	*Penicillium islandicum*		Mut
Talaromycins	Talaromycin A	*Talaromyces stipitatus*	704−714; model: 715; formal: 716	**MTX**
Talaromycins	Talaromycin B	*Talaromyces stipitatus*	704, 707, 709−711, 713, 714, 717−722; formal: 716	**MTX**
Talaromycins	Talaromycin C	*Talaromyces stipitatus*	709, 710, 723	**MTX**
Talaromycins	Talaromycin D	*Talaromyces stipitatus*		**MTX**
Talaromycins	Talaromycin E	*Talaromyces stipitatus*	709, 710, 723	**MTX**
Terpene	15-Hydroxyculmorone	*Fusarium culmorium*		MTX

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Terpene	Culmorin (−)[724]	*Fusarium culmorum*,[7] *F. crookwellense*,[7] *F. graminearum*[7]	725	MTX
Terpene	Pleurotin	*Pleurotia griseus*	726	MTX, cyto
Terpenoid	Dasyscyphin B	*Dasycyphus niveus (Ascomycete)*[727]		Cyto
Terpenoid	Dasyscyphin C	*Dasycyphus niveus*[727]		Cyto
Terphenyl	prenylated *p*-terphenyl metabolite	*Aspergillus candidus*[728]		MTX
Terphenylin	Candidusin A,B	*Aspergillus candidus*[21,729]		MTX
Terphenylin	Candidusin C (2′-Epoxy-3′,4″,6′-trimethoxy-1,1′−4′,1″-terphenyl-4,5-diol), 3,3-dihydroxyterphenyllin, 3-hydroxyterphenyllin	*Aspergillus candidus*[21]		MTX
Terphenylin-type	Terphenylin	*Aspergillus* sp.		MTX
Tetrahydofuran-benzopyran	Alboatrin	*Verticillium alboatrum*	730	MTX, phytotox
Tetrahydrofuran	Botryodiploidin (−)[731] (PSX-1, Cytostipin)	*Penicillium brasilanum*,[7] *P. brevicompactum*, *Talaromyces stipidatus*	732	**MTX**, mutic
Tetrahydrofuran	Varitriol	*Emericella venezuelensis*[b]	733	MTX
Tetrahydroquinoline alkaloid/ indole diterpenoid	Aspernomine	*Aspergillus nomius*		**MTX**, insect
TetrahydroxyAnthraquinoid	Ziganein	*Exserohilum monoceras*		MTX, phytotox
Tetrapeptide	Apicidin A, B, C	*Fusarium* sp.	A: 734	Cyto
Tetronic acid	Aspulvinone A−E (E: Aspergillide B1)	*Aspergillus terreus*	735	MTX
Tetronic acid	Byssochlamic acid[23]	*Byssochlamys fulva*, *B. nivea*[7,736]	737	MTX
Tetronic acid	Carlic acid	*Penicillium charlesii*[738]	739	MTX
Tetronic acid	Carlosic acid	*P. verrucosum*, *P. charlesii*[738]	739, 740	MTX
Tetronic acid	Carolic acid (+)	*P. verrucosum*, *P. charlesii*[738]	739	MTX
Tetronic acid	Carolinic acid	*Penicillium charlesii*[5]	741	MTX
Tetronic acid	Italicic acid	*Penicillium italicum*[7]		MTX
Tetronic acid	Multicolanic acid (**188**)	*Penicillium* spp.	742	MTX
Tetronic acid	Multicolic acid[23]	*Penicillium multicolor*[744]	methyl ester: 743	*MTX*
Tetronic acid	Multicolosic acid[23]	*Penicillium multicolor*[744]		*MTX*
Tetronic acid	Rubratoxin A	*Penicillium rubrum*,[c] *P. craterforme*[7]		**MTX**
Tetronic acid	Rubratoxin B[23]	*Penicillium rubrum*[c,745] *P. craterforme*[7]		**MTX**
Tetronic acid	Scytalidin	*Scytalidium sp*[746]		fung
Tetronic acid	Vertinolide	*Verticillium intertextum*	747	no bio data
Toluquinone[23]	Glioresein	*Gliocadium roseum*[748]		*MTX*
Tremorgen	Desoxypaxillin	*Penicillium paxilli*		MTX
Tremorgen	α-Paxitriol	*Acremonium lolii*, *Penicillium crustosum*	749	MTX
Tremorgen	*β*-Paxitriol	*Penicillium crustosum*	749	MTX
Tremorgen (Indole)	Fumitremorgin A[752] (Fumitremorgen A)[750]	*Aspergillus fumigatus*[c,7] *Penicillium brasilanum*,[7] *Neosatorya fischeri*[7]		**MTX**
Tremorgen (Indole)	Fumitremorgin B[752] (Fumitremorgen B, lonosulin)	*Aspergillus fumigatus*[c],[7] *A. caespitosus*, *Penicillium brasilanum*,[7] *Neosatorya fischeri*[7]	751	**MTX**
Tremorgen (Indole)	Fumitremorgin C[752] (Tryptoquivaline C, Tryptoquivaline A, Tryptoquivaline) [CAS: 55387-45-6][753]	*Aspergillus clavatus*,[7] *A. fumigatus*,[7,754] *Penicillium digitatum*,[7]	755, 756; model: 757	**MTX**
Tremorgen (Indole)	Fumitremorgin D−M (Tryptoquivaline D−M)	*Aspergillus fumigatus*	G: 758	MTX
Tremorgen (Indole)	Lolitrem B, C	*Acremonium* sp.		**MTX**
Tremorgen (Indole)	Lolitrem E	*Acremonium* sp.		**MTX**
Tremorgen (Indole)	Lolitriol	*Neotyphodium lolii*		neuro
Tremorgen (Indole)	Tryptoquivaline N (Deoxynortryptoquivalone, Fumitremorgin N)	*Aspergillus clavatus*[759]		MTX
Tremorgen/ Paspalitrem type	1′-*O*-Acetylpaxilline (1′-Acetoxypaxilline)	*Emericella striata*[760]		MTX

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Tremorgen/ Paspalitrem type	Paxilline (+)[761]	*Penicillium paxilli*[c]		**MTX**
Tremorgen/ Penitrems	Bromopenitrem E, F[21]	*Penicillium simplicissimum*[762]		MTX
Tremorgen/ Penitrems	Penitrem A[763,764]	*Penicillium crustosum*,[c7] *P. expansum*, *P. janczewskii*, *P. melanoconidium*,[7] *P. verrucosum*, *P. carneum*, *P. clavigenum*		**MTX**
Tremorgen/ Penitrems	Penitrem B[763,764]	*Penicillium crustosum*		**MTX**
Tremorgen/ Penitrems	Penitrem C[763,764]	*Penicillium crustosum*		**MTX**
Tremorgen/ Penitrems	Penitrem D[763,764]	*Penicillium crustosum*	765	**MTX**
Tremorgen/ Penitrems	Penitrem E[763,764]	*Penicillium crustosum*		**MTX**
Tremorgen/ Penitrems	Penitrem F[763,764]	*Penicillium crustosum*		**MTX**
Tremorgen/ Penitrems	Penitremone A	*Penicillium* sp.		MTX
Tremorgen/Territrems	Territrem A (TRA)[25,766]	*Aspergillus terreus*,[7] *Penicillium echinulatum*[7]		**MTX**, neuro, trem
Tremorgen/Territrems	Territrem B′[25]	*Aspergillus terreus*,[7] *Penicillium echinulatum*[7]		**MTX**
Tremorgen/Territrems	Territrem B[25,766]	*Aspergillus terreus*,[7] *Penicillium echinulatum*[7]	Analogues: 767	**MTX**
Tremorgen/Territrems	Territrem C[25,766]	*Aspergillus terreus*,[7] *Penicillium echinulatum*[7]		**MTX**
Trichothecene	12,13-Deoxytrichodermadiene	*Mycothecium verrucaria*[768]		MTX
Trichothecene	12,13-Epoxytrichothec-9-en-8-one-3,15-diol	*Fusarium culmorum*		MTX
Trichothecene	12,13-Epoxytrichothec-9-ene (**205**)	*Trichothecium roseum*		MTX
Trichothecene	12,13-Epoxytrichothec-9-ene-3,15-diol	*Fusarium culmorum*		MTX
Trichothecene	12,13-Epoxytrichothec-9-ene-4β,8α-diol (**218**)	*Trichothecium roseum*		MTX
Trichothecene	15-Acetoxyscirpenol (Monoacetoxyscirpenol, 4-Deacetylanguidin) (**216**)	*Fusarium roseum*		MTX
Trichothecene	15-Deacetyl-8-oxocalonectrin	*Fusarium culmorum*		MTX
Trichothecene	15-Deacetylcalonectrin (**617**)	*Calonectria nivalis*[769]	partial synthesis: 770	MTX
Trichothecene	15-Deacetylneosolaniol (**222**) (NT-2 toxin; 4β-Acetoxy-12,13-epoxy-trichothec-9-ene-3α,8α,15-triol)	*Fusarium sporotrichioides*		MTX
Trichothecene	15-*O*-Acetyl-4-deoxynivalenol (15-A-DON)	*Fusarium* sp.		MTX
Trichothecene	2′-Dehydroverrucarin A	*Mycothecium verrucaria*		MTX
Trichothecene	3′-Hydroxy HT-2 toxin (TC-1; 3-Hydroxy-4a,15-diacetoxy-8a-(isovaleryloxy)-12,13- epoxytrichothec-9- ene; 3′-OH-T-2)	*Fusarium heterosporum*, *F. oxysporum*[771]		MTX
Trichothecene	3′-Hydroxy T-2 toxin	*Fusarium sporotrichiellea*	partial synthesis: 792	**MTX**
Trichothecene	3-Acetyldeoxynivalenol (**231**) (3-Acetylvomitoxin, 3-A-DON)	*Fusarium culmorum*, *F. roseum*	partial synthesis: 772	MTX
Trichothecene	3-Acetylneosolaniol (**620**) (3-Ac-NEOS)	*Fusarium tumidum*		MTX
Trichothecene	3-Deacetylcalonectrin	*Fusarium culmorum*		MTX
Trichothecene	4-Acetoxyscirpendiol	*Fusarium roseum*, *Paecilomyces tenuipes*		MTX
Trichothecene	4-Deacetylneosolaniol (TMR-1; 15-Acetyl-T-2 tetraol; 15-Acetyltoxin T 2-tetraol; 15-Acetoxy-3α,4β,8α-trihydroxy-12,13-epoxytrichothec-9-ene)	*Fusarium sporotrichioides*[773]		Cyto
Trichothecene	4β,15-Diacetoxy-12,13-epoxytrichothec-9-ene-3α,7α,8α-triol[d]	*Fusarium* sp.		MTX
Trichothecene	4β,8α,15-Triacetoxy-12,13-epoxytrichothec-9-ene-3α,7α-diol[d]	*Fusarium* sp.[774]		MTX
Trichothecene	7,8-Dihydroxycalonectrin	*Fusarium culmorum*[775]	formal synthesis: 776	MTX
Trichothecene	7α-Hydroxydiacetoxyscirpenol (4,15-Diacetoxy-12,13-epoxy-9-trichothecene-3,7-diol)	*Fusarium lateritium*[777]		MTX

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Trichothecene	7α-Hydroxytrichodermol	*Myrothecium roridum*[778]		MTX
Trichothecene	7*β*,8*β*-Epoxyroridin E	*Cylindrocarpon* sp.[779]		MTX
Trichothecene	7*β*,8*β*-Epoxyroridin H	*Cylindrocarpon* sp.[779]		MTX
Trichothecene	7*β*,8*β*, 2′,3′-Diepoxyroridin H	*Cylindrocarpon* sp.[779]		MTX
Trichothecene	8-Acetoxy-T-2 tetraol (8-Acetyl-T-2-tetrol, TMR 2)	*Fusarium acuminatum*[780]		MTX
Trichothecene	8-Hydroxycalonectrin	*Fusarium culmorum*[781]		MTX
Trichothecene	8α-(3-Hydroxy-3-methyl-butyryloxy)-12,13-epoxytrichothec-9-ene-3α,4*β*,15-triol (3′-Hydroxy T-2 triol; 3α,4*β*,15-Trihydroxy-8α-(3-hydroxy-3-methylbutyryloxy)-12,13-epoxytrichothec-9-ene)	*Fusarium* sp.[782]		MTX
Trichothecene	Acetyl-T-2 toxin (**225**) (Ac-T-2 toxin, 3,4,15-Triacetoxy-8-(3-methyl-butyryloxy)-12,13-epoxytrichothec-9-ene)	*Fusarium poae*[783]		**MTX**
Trichothecene	Apotrichodiol (3α,13-Dihydroxyapotrichothecene)	*Fusarium* sp.[784]		MTX
Trichothecene	Baccharin B4 (**269**)	*Baccharis megapotamica*		no MTX, but related
Trichothecene	Baccharin B5 (**268**)	*Baccharis megapotamica*	785	no MTX, but related
Trichothecene	Calonectrin (**211**)	*Calonectria nivalis*,[769] *Fusarium culmorum*	786; AB-ring model: 787	MTX
Trichothecene	Crotocin (**227**)	*Cephalosporium crotocinigenum*, *Acremonium crotocinigenum*[d], *Trichothecium roseum*		MTX, nec
Trichothecene	Deepoxydiacetoxyscirpenol	*Fusarium graminearum*[788]		MTX
Trichothecene	Deoxynivalenol (**230**) (Vomitoxin)	*Fusarium culmorum*,[c] *F. gramiearum*, *F. verticillioides*[23]		MTX
Trichothecene	Diacetoxyscirpenol (**217**) (Anguidin, DAS, 4,15- Diacetoxyscirpenol)	*Fusarium equiseti*,[c] F. *scirpi*, *F. sporotrichiodes*	789	MTX, cyto
Trichothecene	Di-*O*-acetylverrucarol (**210**) (4,15-Diacetylverrucarol)	*Myrothecium* sp.[790]		MTX
Trichothecene	*epi*-Isororidin E	*Myrothecium verrucaria*		MTX, cyto
Trichothecene	*epi*-roridin E	*Stachybotrys chartarum*		MTX, cyto
Trichothecene	Fusarenone	*Fusarium crookwellense*		MTX
Trichothecene	Fusarenone X (**233**)	*Fusarium nivale*[c]		MTX
Trichothecene	Harzianum A	*Hypocrea* sp. F000527[791]		MTX, cyto
Trichothecene	HT-2 toxin (**223**)	*Fusarium culmorum*, *F. sporotrichoides*	partial synthesis: 792	**MTX**
Trichothecene	Iso T-2 toxin	*Fusarium sporotrichioides*		MTX
Trichothecene	Isoneosolaniol (**221**) (NT-1 toxin, 4*β*,8α-Diacetoxy-12,13-epoxytrichothec-9-ene-3α, 15-diol)	*Fusarium sporotrichioides*, *F. tricinctum*	partial synthesis: 793	MTX
Trichothecene	Isororidin A	*Myrothecium verrucaria*		MTX
Trichothecene	Isororidin E	*Stachybotrys chartarum*, *Cylindrocarpon* sp.		MTX, cyto
Trichothecene	Iso-Satratoxin	*Stachybotrys* sp.		MTX, prob cyto
Trichothecene	Iso-Satratoxin F	*Stachybotrys chartarum*		MTX, prob cyto
Trichothecene	Iso-Satratoxin G	*Stachybotrys chartarum*		MTX, prob cyto
Trichothecene	Iso-Satratoxin H	*Stachybotrys chartarum*		**MTX**, cyto
Trichothecene	Iso-T-2 toxin	*Fusarium sporotrichioides*[771]		MTX
Trichothecene	Isotrichodermol (**616**)	*Fusarium venenantum*		MTX
Trichothecene	Miophytocen A,B,C (A: **271**)	*Myrothecium verrucaria*		MTX
Trichothecene	Miotoxin A (**270**) (4-Hydroxyroridin E)	*Baccharis coridifolia*		MTX
Trichothecene	Myrotoxin A (**266**)	*Trichoderma roseum*,[c] *Myrothecium verrucaria*		**MTX**
Trichothecene	Myrotoxin B	*Trichoderma roseum*[c] *Myrothecium verrucaria*		**MTX**
Trichothecene	Neosolaniol (**220**)	*Fusarium culmorum*,[c] *F. sporotriochoides*	partial synthesis: 792	**MTX**

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Trichothecene	Neosolaniol monoacetate (8-Acetylneosolaniol[d])	*Fusarium tricinctum*		MTX
Trichothecene	Neosporol (**296**)[794]	*Fusarium sporotrichoides*	800, 795	MTX
Trichothecene	Nivalenol (**232**)	*Fusarium nivale,*[c] *F. crookwellense*	formal synthesis: 772, 796	**MTX**
Trichothecene	Nivalenol 4,15-diacetate (Saubinin I) (**234**)	*Fusarium nivale*		MTX
Trichothecene	Roridin A (**263**) (1′-Deoxy-1′-hydroethylverrucarin A)	*Myrothecium roridum*[c]		**MTX**
Trichothecene	Roridin D (**264**)	*Myrothecium roridum*		MTX
Trichothecene	Roridin E (**262**) (Satratoxin D)	*Stachybotrys chartarum*, *S. atra*,[797] *Myrothecium verrucaria*	785	MTX, cyto
Trichothecene	Roridin H, J, K acetate	*Myrothecium verrucaria*		MTX, cyto
Trichothecene	Roridin L-2	*Stachybotrys chartarum*		MTX, cyto
Trichothecene	Sambucinol (**297**) (11,12-Epoxy-trichothe-9-en-3,13-diol)	*Fusarium graminearum*, *F. culmorum*		MTX
Trichothecene	Satratoxin (Satratoxin A)[d]	*Stachybotrys atra*		MTX
Trichothecene	Satratoxin B	*Stachybotrys atra*[c]		MTX, prob cyto
Trichothecene	Satratoxin F	*Stachybotrys atra*[c,797]		MTX, prob cyto
Trichothecene	Satratoxin G	*Stachybotrys chartarum*, *S. atra*[797]		MTX, prob cyto
Trichothecene	Satratoxin H (**265**)[798]	*Stachybotrys atra,*[c,797] *S. chartarum*		**MTX**, cyto
Trichothecene	Scirpentriol (**215**) (SCIRP)	*Fusarium roseum*[c]		cyto
Trichothecene	Sporol (**295**)	*Fusarium sporotrichioides*	799, 800	MTX
Trichothecene	Sporotrichiol (**226**)	*Fusarium trichiodes*[c], *F. sporotrichiodes*	partial synthesis: 792	MTX
Trichothecene	Stachyobotryotoxins see trichothecenes, roridin E, verrucarol	*Stachybotrys* sp.	801	MTX
Trichothecene	T-2 tetraol (**219**)	*Fusarium* sp.	802	**MTX**
Trichothecene	T-2 tetraol tetraacetate (T-2-4ol-4Ac)	*Fusarium* sp.		**MTX**
Trichothecene	T-2 toxin (**224**) (Insariotoxin, Fusariotoxin T 2)	*Fusarium tricinctum*[c], *F. sporotrichiellea*[23]	partial synthesis: 792	**MTX**
Trichothecene	T-2 triol	*Fusarium sporotrichiellea*		**MTX**
Trichothecene	Trichodermadiene (**208**)	*Myrothecium verrucaria*[c]		MTX
Trichothecene	Trichodermadienediol A, B (**209a**, **209b**)	*Myrothecium roridum*		MTX
Trichothecene	Trichodermin (**207**) (12,13-Epoxy-Trichothec-9-en-4-ol acetate)	*Trichoderma viride*,[c,7] *T. polysporum*, *T. sporulosum*,[23] *memnoniella echinata*,[285] *Stachybotrys cylindrospora*, *S. chartarum*		MTX, biot
Trichothecene	Trichodermol (**206**) (Roridin C)	*Myrothecium roridum,*[c] *Trichoderma polysporum*, *T. sporulosum*,[23] *Memnoniella echinata*,[285] *Stachybotrys cylindrospora*, *S. chartarum*	803	MTX
Trichothecene	Trichothecin (**229**)[804]	*Trichothecium roseum*[23]	805	MTX, biot
Trichothecene	Trichothecolone (**228**) (12,13-Expoxy-4hydroxy-trichothec-9-en-8-one)	*Trichothecium roseum*[d]		Cyto
Trichothecene	Trichoverrin A (**213a**)	*Stachybotrys chartarum*, *Myrothecium verrucaria*		MTX, w cyto
Trichothecene	Trichoverrin B (**213a**)	*Stachybotrys chartarum*, *Myrothecium verrucaria*	806	MTX, w cyto
Trichothecene	Trichoverrin C	*Myrothecium verrucaria*		MTX
Trichothecene	Trichoverrol A (**212a**)	*Stachybotrys atra*, *S. chartarum*[807]		MTX
Trichothecene	Trichoverrol B (**212b**)	*Stachybotrys atra*, *S. Chartarum*[807]	807	MTX
Trichothecene	Verrucarin A (**6**)	*Mycothecium verrucaria*	808, 809	**MTX**, cyto
Trichothecene	Verrucarin B (**261**)	*Mycothecium verrucaria*		**MTX**, cyto
Trichothecene	Verrucarin J (**260**) (Satratoxin C)	*Stachybotrys atra*,[797] *S. Chartarum*	810	**MTX**; Cyto
Trichothecene	Verrucarin K	*Mycothecium verrucaria*[811]		MTX

Table 3. Continued

mycotoxin class	name (stereochemistry) (alternative name)	producing fungus (example)	ref for synthesis	comment[a]
Trichothecene	Verrucarin L	*Mycothecium verrucaria*		MTX
Trichothecene	Verrucarin M	*Myrothecium verrucaria*[812]		MTX
Trichothecene	Verrucarol (**214**)	*Stachybotrys atra*[d]	*rac*: 813−815; (−): 816	**MTX**
Trichothecene	Vertisporin (**267**)	*Verticimonosporium diffractum*[c,817]		*MTX*
Tropolone derivative	Puberulic acid[818]	*Penicillium aurantiogriseum*, *P. aurantiocandidum*[7]	819	MTX
Tropolone derivative	Puberulonic acid	*Penicillium aurantio-virens*[21]	820, 821	MTX
Versicolorin	6,8-*O*-Dimethylversicolorin A	*Aspergillus versicolor*[c,822]		**MTX**, gen
Versicolorin	6,8-*O*-Dimethylversicolorin B	*Aspergillus* sp.[d]		**MTX**, gen
Versicolorin	6-Deoxyversicolorin A	*Aspergillus versicolor*[c,823]		**MTX**
Versicolorin	8-Deoxy-*O*-methylversicolorin A	*Aspergillus ustus*		MTX
Versicolorin	Aversin (Versicolorin B dimethylether, 2,3,3a,12a-tetrahydro-4-hydroxy-6,8-dimethoxyanthra2,3-*b*]furo3,2-*d*]furan-5,10-dione)	*Aspergillus versicolor,*[c] *A. ustus*[824]		MTX
Versicolorin	Tri-*O*-methylversicolorin B (*O*-methylaversin)	*Aspergillus versicolor*	825	**MTX**
Versicolorin	Versicolorin A (**597**) (2,3-Bisfurano-1,6,8-trihydroxy-anthraquinone)[826]	*Aspergillus versicolor*[c], *A. parasiticus*, *A. flavus*		**MTX**, mut, carc
Versicolorin	Versicolorin B (**64**) (−) (2,3-Bistetrahydrofurano-1,6,8-trihydroxyanthraquinone)	*Aspergillus versicolor*[c,827]		**MTX**
Versicolorin	Versicolorin C (±) (2,3-Bistetrahydrofurano-1,6,8-trihydroxyanthraquinone[828])	*Aspergillus versicolor*[c], *A. parasiticus*, *A. flavus*	829	**MTX**
Versicolorin	Versicolorin D	*Aspergillus versicolor*[c]		**MTX**
Xanthone	7-Chloro-2-(3-furyl)-1,3,8-trimethoxyxanthone	*Aspergillus ustus*[830]		MTX
Xanthone	Ascherxanthone A	*Aschersonia* sp. BCC 8401[831]		Cyto
Xanthone	Blennolide A−E[840]	*Blennoria* sp.	832	MTX
Xanthone	Dicerandrol A, B, C	*Phomopsis longicolla*		Cyto
Xanthone	Diversonol (**426**)	*Penicillium diversum*[833]	834	MTX
Xanthone	Lichexanthone	*Penicillium patulum*, *P. diversum*	835	MTX
Xanthone	Ravenelin (**581**)	*Helminthosporium ravenelii*[836]		MTX
Xanthone	Sterigmatin	*Aspergillus versicolor*		MTX
Xanthone	Variecoxanthone A, C	*Emericella* sp.[d], *Aspergillus nidulans*[837]		MTX
Xanthone	Variecoxanthone B (Emericellin)	*Emericella* sp.[d], *Aspergillus nidulans*[837,838]		MTX
Xanthone	Vinaxanthone	*Penicillium vinceum*	839	MTX
Xanthone	α,β-Diversonolic acid[840]	*Penicillium diversum*	832b	MTX
Xanthone dimer	Phomoxanthone B (**427**) (−)	*Phomopsis* sp.		MTX
Xanthone dimer	Secalonic acid A (Ergochrome AA)	*Pyrenochaeta terrestris*,[107] *Aspergillus aculeatus*[107]		**MTX**
Xanthone dimer	Secalonic acid B (SAB, Ergochrome BB)	*Aspergillus aculeatus*		**MTX**
Xanthone dimer	Secalonic acid C (SAC, Ergochrome AB)	*Aspergillus aculeatus*		**MTX**
Xanthone dimer	Secalonic acid D (**10**) (Ergochrome EE, *ent*-Secalonic acid A, SAD)	*Penicillium oxalicum*[c,7] *Gliocladium* sp.[b]		**MTX**, cyto
Xanthone dimer	Secalonic acid E	*Pyrenochaeta terrestris*,[107] *Aspergillus aculeatus*[107]		**MTX**
Xanthone dimer	Secalonic acid F (SAF)	*Aspergillus japonicus*, *Penicillium oxalicum*[c7]		**MTX**
Xanthone dimer	Secalonic acid G	*Pyrenochaeta terrestris*,[107] *Aspergillus aculeatus*[107]		**MTX**

[a] **MTX**: important mycotoxin; MTX: less abundant/important mycotoxin; *MTX*: mycotoxin status questionable; bact: antibacterial; biot: antibiotic; carc: carcinogenic; cyto: cytotoxic; drug: used as a drug; feed: antifeedant; fung: antifungal; gen: genotoxic; hep: hepatotoxic; herb: herbicide; immun: immunosuppressive; insec: insectidal; kin: kinase inhibitor; leish: antileishmanial; micro: antimicrobial; mut: mutagenic; nec: necrotic; neph: nephrotoxic; neuron: neurotoxic; plasm: antiplasmodial; prot: antiprozoic; ter: teratogen; trem: tremorgen; tumor: antitumor; vir: antiviral; mod: moderate; str: strong; w: weak; prob: probably. [b] Marine origin. [c] See ref 8. [d] Uncertain/inconsistent data. [e] No toxic effects, but putative biogenic precursor.

Table 4. Human Diseases Provoked by Mycotoxins[847]

disease	substrate	principal fungus	toxin
Akakabi-byo	wheat, barley, oats, rice	*Fusarium* spp.	*Fusarium* metabolites
Alimentary toxic aleukia	cereal grains (toxic bread)	*Fusarium* spp.	
Balkan nephropathy	cereal grains	*Penicillium*	
Cardiac beriberi	rice	*Aspergillus* spp., *Penicillium* spp.	
Celery harvester's disease	celery (pink rot)	*Sclerotinia*	
Dendrodochiotoxicosis	fodder (skin contact, inhaled fodder particles)	*Dendrochium toxicum*	
Ergotism	rye, cereal grains	*Claviceps purpurea*	Ergot alkaloids
Esophageal tumors	corn heterocycles	*Fusarium moniliforme*	
Hepatocarcinome (acute aflatoxicosis)	cereal grains, peanuts	*Aspergillus flavus*, *A. parasiticus*	
Kashin Beck disease (Urov disease)	cereal grains	*Fusarium*	*Fusarium* metabolites
Kwashiorkor	cereal grains	*Aspergillus flavus*, *A. parasiticus*	Aflatoxins
Onyalai	millet	*Phoma sorghina, Fusarium* sp.	*Fusarium* metabolites
Reye's syndrome	cereal grains	*Aspergillus*	
Stachybotryotoxicosis	rye, cereal grains, fodder (skin contact, inhaled rye dust)	*Stachybotrys atra*	Trichothecenes
Kodua poisoning		*Aspergillus* sp.; *Penicillium* sp.	Cyclopiazonic acid

2.1. Aflatoxins

The most carcinogenic substances known to date, the aflatoxins, also gained much interest among organic chemists[868] since the elucidation of their structure by Büchi and co-workers in 1963.[869] Even though numerous syntheses of racemic aflatoxins were reported in the following years,[28−31,33] it took 40 years for the first enantioselective total synthesis of (−)-aflatoxin B_1 (**1**) and B_{2a} (**17**) to be published by Trost et al.[32] Their approach resembles in part (construction of the DE ring system) the first total synthesis of (±)-aflatoxin by Büchi et al.[28] (Scheme 1).

For the key intermediate coumarin **25**, there exist various syntheses, of which the Wittig reaction route of the original 1966's publication is presented here. After oxidation to the corresponding aldehyde **26**, the ABC ring system was formed by reduction to the lactone **27**, which was cleaved again under the conditions of the Pechmann condensation with β-oxoadipate **29** upon formation of the D ring. The resulting methoxy acetal **30** with *trans*-oriented substituents exhibited the right stereochemistry for the lactonization to carboxylic acid **31** with *cis*-fused B and C rings. Friedel-Crafts acylation and reduction of the lactone gave aflatoxin B_{2a} (**17**), which, in 1966, had not yet been identified as a naturally occurring mycotoxin. Acetylation and pyrolysis resulted in racemic (±)-aflatoxin B_1 (**1**).

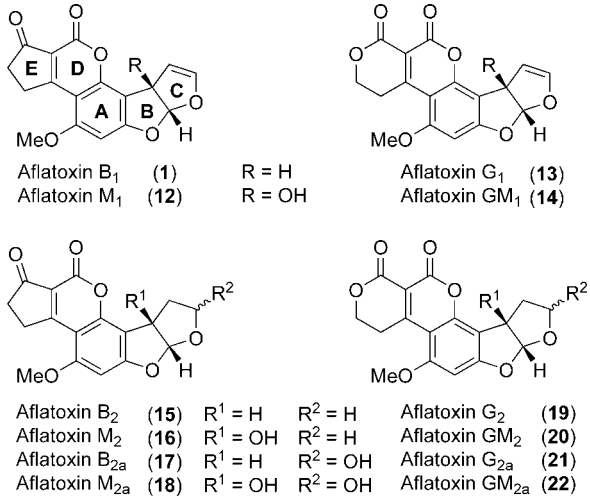
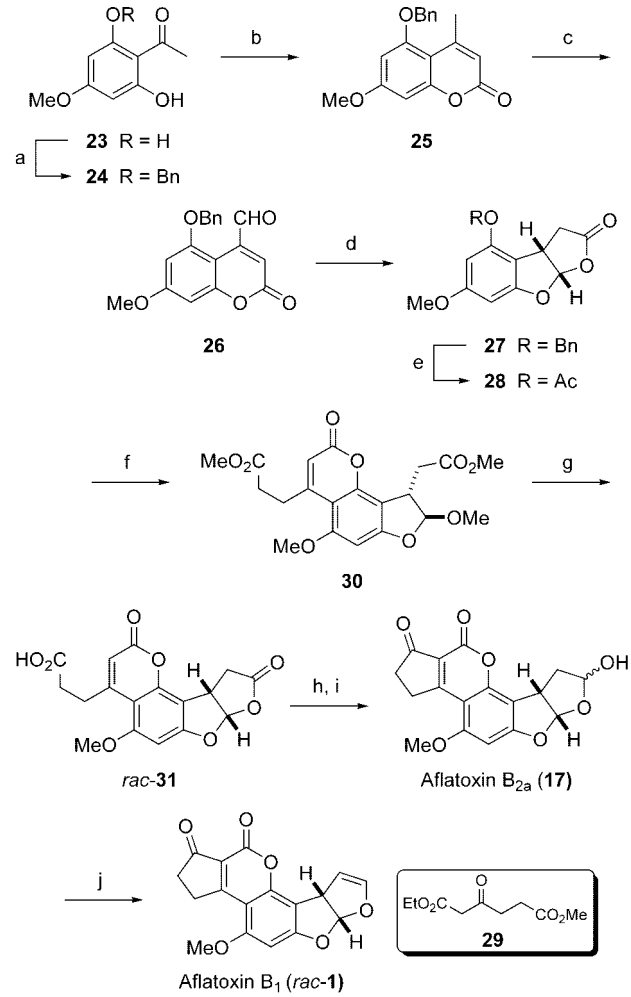


Figure 2. Aflatoxins.

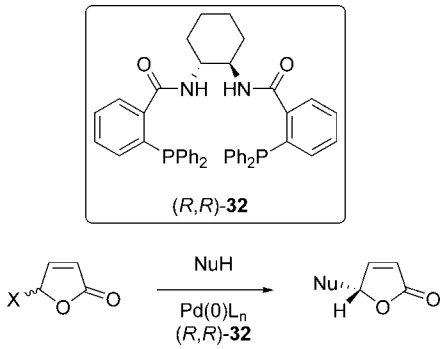
In 2003 Trost et al. presented the first enantioselective total synthesis of aflatoxin B_1 (**1**).[32,870] Their strategy was based on a palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT, see Scheme 2) of γ-acyloxybutenolide

Scheme 1. First Total Synthesis of Racemic Aflatoxin B_1 (1) by Büchi et al.[28]

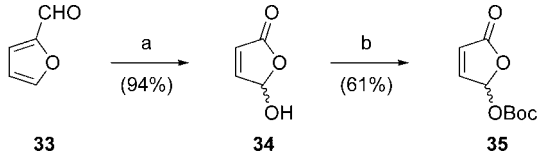


Reagents and conditions: (a) BnBr, K_2CO_3, acetone. (b) Wittig: $Ph_3P{=}CHCO_2Et$. (c) SeO_2, hot xylene. (d) Zn, HOAc. (e) H_2, Pd/C, Ac_2O. (f) **29**, HCl, MeOH. (g) HCl, HOAc, H_2O. (h) (1) $(COCl)_2$, CH_2Cl_2, 20 °C, 24 h; (2) $AlCl_3$, CH_2Cl_2, −15 °C, 4 h. (i) disiamylborane, diglyme. (j) (1) Ac_2O, AcOH, TsOH; (2) 240 °C.

Scheme 2. Dynamic Kinetic Asymmetric Transformation (DYKAT) of γ-Acyloxybutenolides[32]



Scheme 3. Preparation of the Key Intermediate for DYKAT by Trost et al.[32]



Reagents and conditions: (a) $^1O_2$, hν, rose bengal, MeOH. (b) Boc_2O, py, THF.

35. This intermediate was prepared from furfural (**33**) in two steps (Scheme 3).

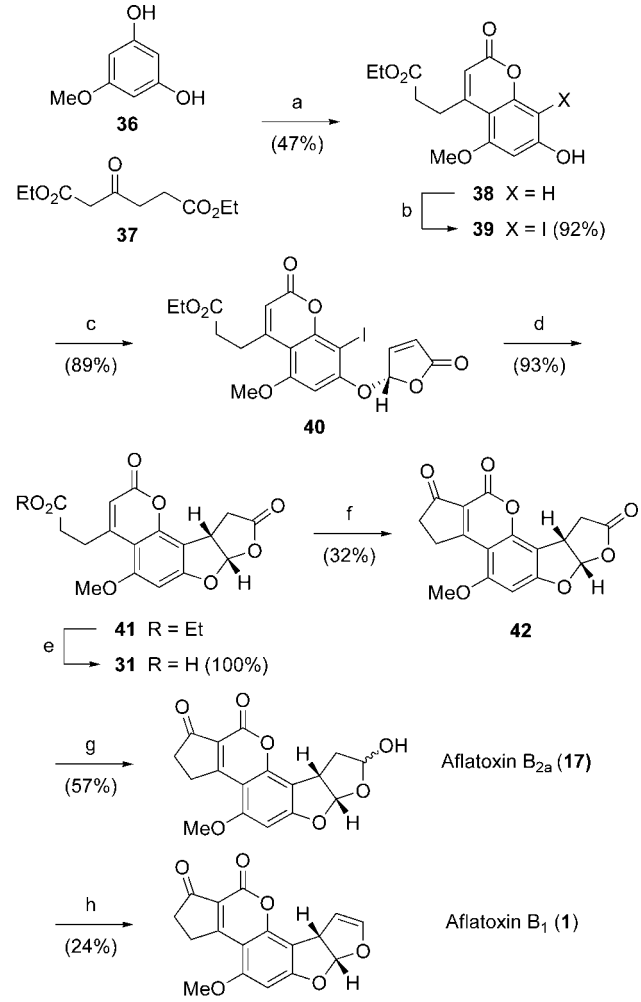
The DYKAT was performed after the assembly of the AD ring system by Pechmann condensation of the phloroglucinol monomethyl ether (**36**) with β-oxoadipate **37** (in analogy to precedent racemic syntheses)[28,33] and iodination to intermediate **39**. The intramolecular reductive Heck reaction produced tetracyclic coumarin **41** with an enantiomeric excess of >95%. Conversion to aflatoxin B_1 (**1**) followed the Büchi route[28] with modified protocols for the Friedel−Crafts acylation to **42** and the reduction producing aflatoxin B_{2a} (**17**). The complete synthesis comprised 9 consecutive steps (Scheme 4).

A very short total synthesis of aflatoxin B_2 (**15**) was published by Corey and co-workers in 2005.[34] The 8-step approach comprises an asymmetric [3 + 2]-cycloaddition using chiral oxazaborolidinium catalyst **45** for the enantioselective formation of the ABC ring system (Scheme 5). A similar quinone approach for intermediate **49** had previously been reported by Noland et al.[871]

Starting from 2-methoxy-1,4-benzoquinone (**43**) and 2,3-dihydrofuran (**44**), cycloadduct **46** was obtained with 92% ee (GC), nearly enantiomerically pure after recrystallization. The next six steps involved a relocation of the hydroxy group: orthoformylation and triflate ester formation followed by Grignard addition and Dess−Martin oxidation resulted in the corresponding methyl ketone **48**. The acetate group was replaced by the hydroxy group through Baeyer−Villiger oxidation and saponification; the triflate was removed by reduction with Raney nickel. Condensation of intermediate **49** with β-bromo-α,β-enone **50** in the presence of zinc carbonate directly gave rise to aflatoxin B_2 (**15**).

This condensation was already elaborated by Büchi and Weinreb during their total syntheses of aflatoxins M_1 (**12**), B_1 (**1**), and G_1 (**13**) in 1971[29] and is outlined in Scheme 6. The advantage was the attachment of the complete ring E, which enables straightforward variation between the five-membered cyclic ketone for aflatoxins of the B- and M-type and the six-membered lactone for aflatoxins of the G-type (see also Figure 2).

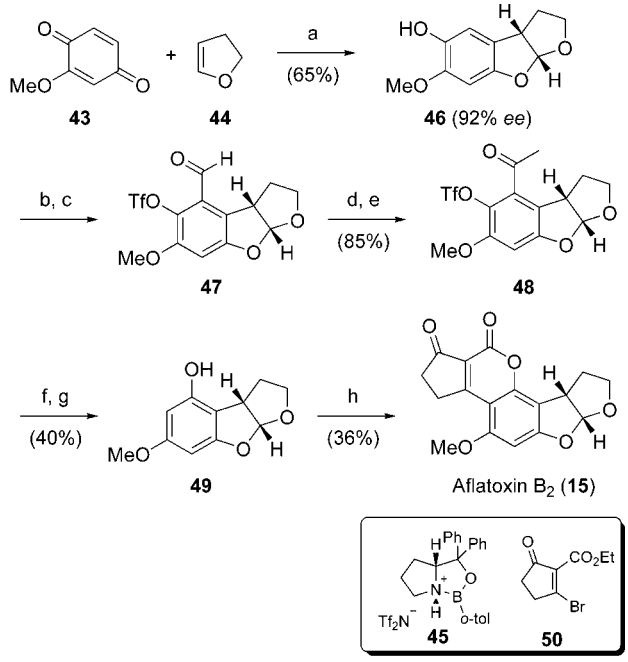
Scheme 4. Enantioselective Total Synthesis of Aflatoxins B_{2a} and B_1 by Trost et al.[32]



Reagents and conditions: (a) HCl, EtOH. (b) ICl, CH_2Cl_2, rt. (c) **35**, 2.5% Pd_2dba_3-$CHCl_3$, 7.5% (*R*,*R*)-**32**, 30% Bu_4NCl, 0.1 M CH_2Cl_2, rt. (d) 10% $(CH_3CN)_2PdCl_2$, NEt_3, HCO_2H, DMF, 50 °C. (e) HOAc, HCl, H_2O. (f) $Sc(OTf)_3$, $LiClO_4$. (g) DIBAL-H (2:1 β:α). (h) (1) Ac_2O, AcOH; (2) 240 °C.

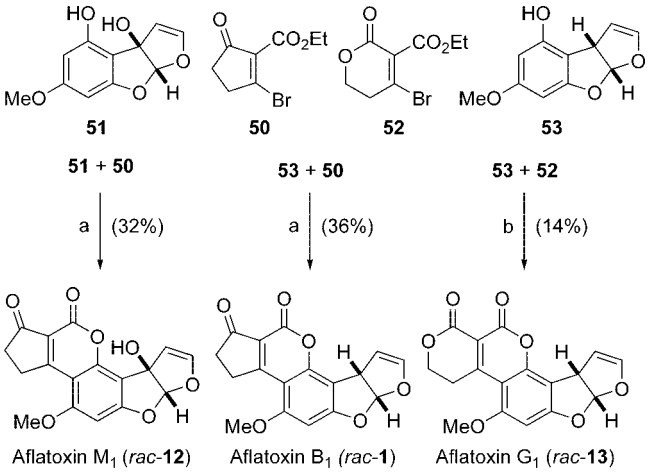
The syntheses of the building blocks **50** and **53** were described (in part) in previous publications.[28b,872] Summarized here is the total synthesis of aflatoxin M_1 (**12**, milk toxin) starting with coumaranone **54** (Scheme 7). After the successive introduction of the protective groups, bromination with phenyltrimethylammonium perbromide and conversion into the benzyl ether **57**, ring C was built up through the Grignard addition of allylmagnesium bromide with subsequent Lemieux−Johnson oxidation to form the epimeric aldehydes **58**, which after step-by-step hydrogenolysis were cyclized to diacetate **60**. Key intermediate vinyl ether **51** was formed by flash pyrolysis and saponification of the acetate. Pechmann condensation with 2-carbethoxycyclopentane-1,3-dione was not possible due to the sensitivity of **51** to acidic catalysts. Thus, the more nucleophilic bromide **50** was prepared from the corresponding enol and oxalyl bromide, and it could be condensed with phenol **51** under mild conditions with either zinc carbonate or magnesium carbonate. In the synthesis of aflatoxin G_1 (**13**), the analogous bromide **52** turned out to be much less reactive, but the addition of anhydrous lithium iodide delivered improved yields, presumably due to in situ formation of the corresponding vinyl iodide.

Scheme 5. Short, Enantioselective Total Synthesis of Aflatoxin B_2 (15) by Corey et al.[34]



Reagents and conditions: (a) **45**, CH_3CN/CH_2Cl_2 1:1, –78 °C → rt, 7 h. (b) $(CH_2)_6N_4$ (HMT), AcOH, 110 °C, 48 h, (ca. 40%). (c) Tf_2O, py, 0 °C, 2 h, (ca. 80%). (d) MeMgBr, THF, –20 °C, 2 h. (e) Dess-Martin, CH_2Cl_2, 23 °C, 3 h. (f) CF_3CO_3H, CH_2Cl_2, 48 h. (g) Raney Ni, MeOH, H_2, 4 h. (h) **50**, $ZnCO_3$, CH_2Cl_2, 23 °C, 24 h

Scheme 6. Modular Synthesis of Racemic Aflatoxins M_1, B_1, and G_1 by Büchi et al.[29]

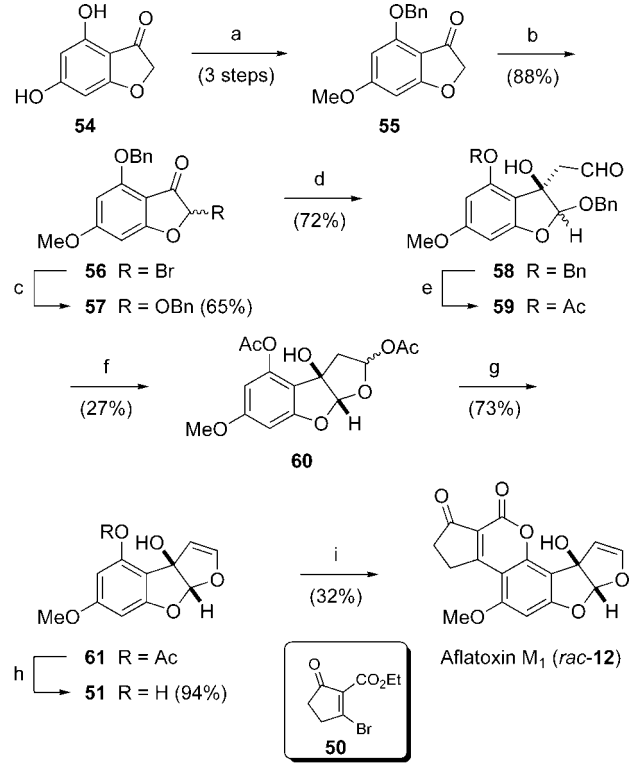


Reagents and conditions: (a) $NaHCO_3$, $ZnCO_3$, CH_2Cl_2. (b) $ZnCO_3$, LiI, CH_2Cl_2.

In summary, most syntheses have this common approach: starting from the phloroglucinol core, the tetrahydro- or dihydrofuro[2,3-*b*]benzofuran ring system (ABC tricycle) is formed and the annulation of the D and E rings is effected through a modified Pechmann condensation.

A large number of important contributions to synthetic mycological chemistry were made by Roberts and coworkers, who entered the aflatoxin field with their work on the *Aspergillus* metabolite sterigmatocystin (**62**),[873] a biosynthetic precursor to the aflatoxins. Roberts et al. published several syntheses of toxic metabolites (Figure 3), including the first total synthesis of (±)-aflatoxin B_2 (*rac*-**15**),[33] a synthesis of the coumarinolactone system of aflatoxin G_2 (**19**),[874] and the first total syntheses of (±)-*O*-methylsterigmatocystin (**63**)[40] and (±)-tri-*O*-methylversicolorin B (**65**, (±)-*O*-methylaversin).[825]

Scheme 7. Total Synthesis of Racemic Aflatoxin M_1 (12) by Büchi et al.[29]



Reagents and conditions: (a) (1) Me_2SO_4, K_2CO_3, DME, reflux (79%); (2) 2 equiv. $AlCl_3$, CH_2Cl_2, reflux (64%); (3) BnBr, K_2CO_3, DME/DMF, reflux (74%). (b) Me_3PhNBr_3, THF. (c) BnOH, $CaCO_3$. (d) AllylMgBr, THF/Et_2O, 0 °C; then OsO_4, $NaIO_4$, dioxane/H_2O 2:1, $NaHCO_3$, 7:1 epimeric mixture. (e) H_2, Pd/C, Ac_2O, NaOAc, benzene. (f) (1) H_2, Pd/C, EtOAc; (2) Ac_2O, py, –70 °C → –30 °C. (g) flash pyrolysis 450 °C. (h) $NaHCO_3$, MeOH/H_2O 1:1. (i) **50**, $NaHCO_3$, $ZnCO_3$, CH_2Cl_2.

For the synthesis of (±)-*O*-methylsterigmatocystin (**63**), the key step was presumed to be a modified Ullmann condensation of the known[28b] lactone **66** and bromo ester **67**, as in preliminary studies on (±)-dihydro-*O*-methylsterigmatocystin. However, under basic conditions, the resulting Büchi lactone (**66**) was too labile, so that an alternative route using the ring-opened compound **68** was developed (Scheme 8).[40]

The Ullmann-type diaryl ether formation of **69** proceeded well, and after several ring-closing reactions, namely lac-

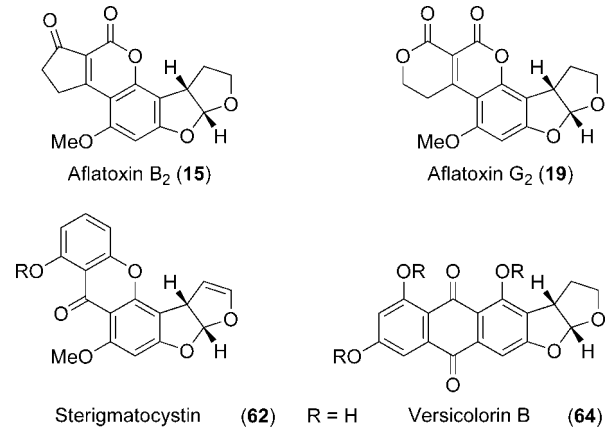
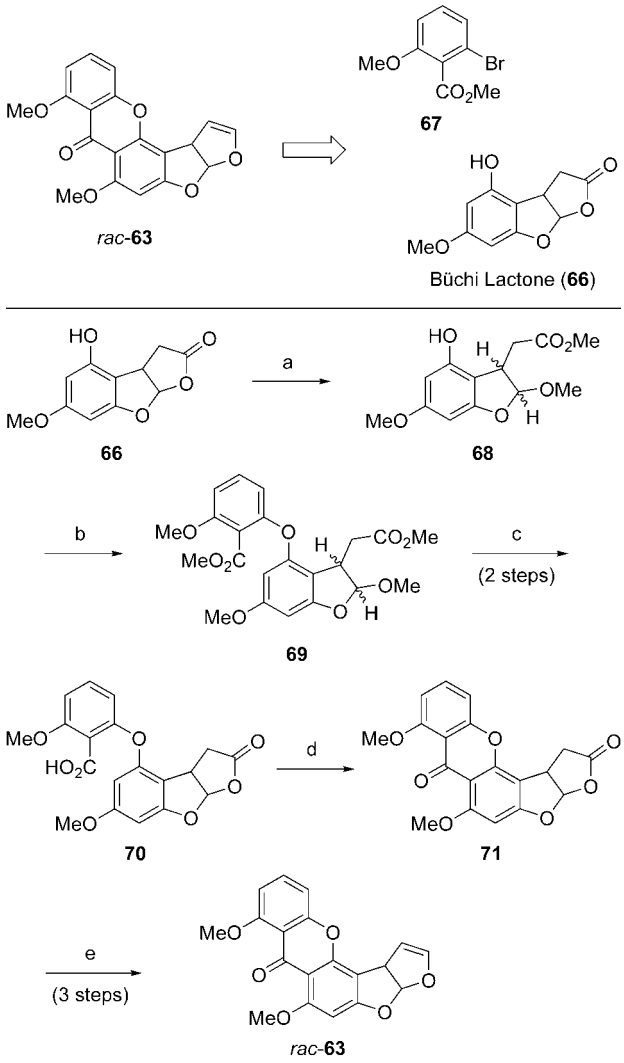


Figure 3. *Aspergillus* metabolites synthesized by Roberts et al.

Scheme 8. Total Synthesis of Racemic *O*-Methylsterigmatocystin (63) by Roberts et al.[41]



Reagents and conditions: (a) HCl, MeOH, −10 °C → rt. (b) (1) NaOMe, MeOH; (2) **67**, CuCl, py, reflux. (c) (1) 10% NaOH, EtOH/H_2O (2) AcOH, HCl. (d) $(COCl)_2$, benzene, reflux. (e) (1) disiamylborane, THF; (2) Ac_2O, AcOH, TsOH; (3) 250 °C.

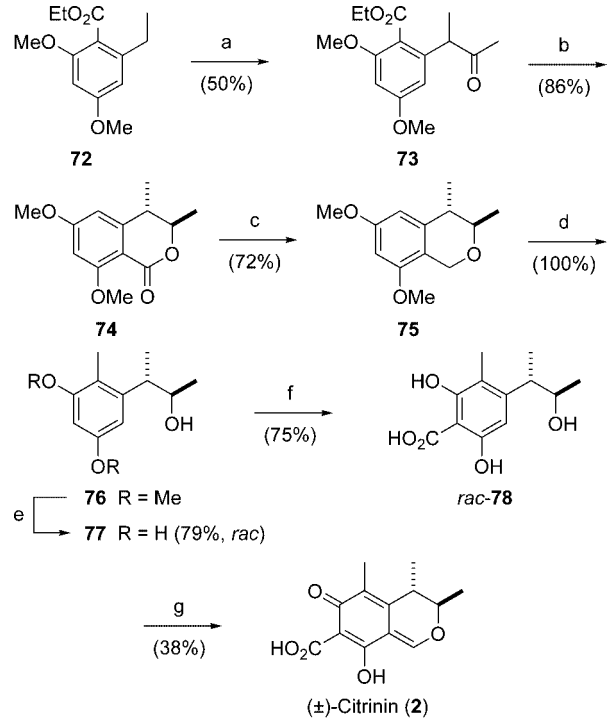
tonization and acylation, precursor **71** was obtained. The vinyl ether system of sterigmatocystin (**62**) was introduced following the protocol reported by Büchi et al.[28]

2.2. Citrinin

The fungal metabolite citrinin (**2**) was first obtained from *Penicillium citrinum*.[875,876] Citrinin (**2**) displays antibiotic activity against Gram-positive bacteria[877] and has been described as a promising insecticide.[878] However, because of its high toxicity, it has not been applied as a drug.

The structure was elucidated in the groups of Whalley and Cram at the end of the 1940s by extensive degradation studies.[879,880] The absolute configuration of the two methyl groups in natural (−)-citrinin (**2**) was shown to be (3*R*,4*S*) by chemical correlation (Figure 1).[881] Starting from the degradation product **77**, several partial syntheses of optically active and racemic citrinin (**2**) have been described,[195,197] involving a subsequent carboxylation/formylation strategy. Warren et al. extended this method to other aldehydes and ketones and received a series of analogues for the establishment of structure−activity relationships.[882]

Scheme 9. First Diastereoselective Total Synthesis of (±)-Citrinin (2) by Barber and Staunton[198]



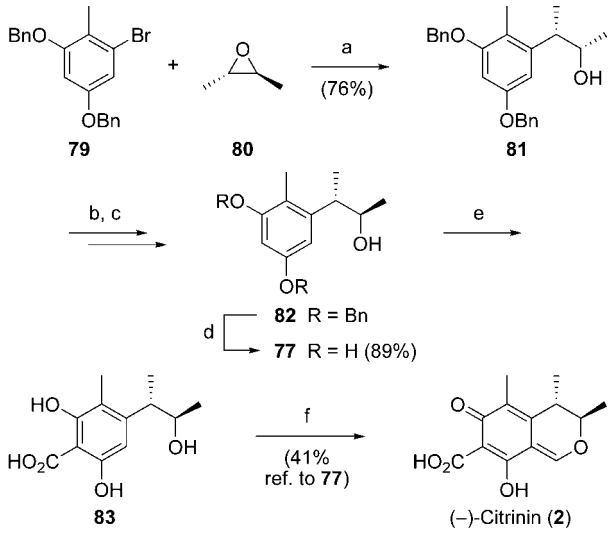
Reagents and conditions: (a) (1) LDA, THF, −78 °C; (2) AcCl, THF, −130 °C. (b) $NaBH_4$, MeOH. (c) DIBAL, toluene. (d) H_2, Pd/C, AcOH/MeOH. (e) BBr_3, CH_2Cl_2; workup with NaOH (5% in H_2O). (f) $KHCO_3$, CO_2, glycerol, 150 °C. (g) $HC(OEt)_3$, HCl.

A stereoselective synthesis of racemic (±)-citrinin (**2**) using toluate anion chemistry was published by Staunton et al. in 1986[198] and could be expanded to an asymmetric total synthesis of the unnatural enantiomer (+)-citrinin.[199] Acetylation of ethyl 2-ethyl-4,6-dimethoxybenzoate (**72**) furnished ketone **73**, which could be reduced to the *threo*-diastereoisomer of lactone **74**. Successive reduction of the carbonyl group with DIBAL and hydrogenolysis with a palladium−charcoal catalyst installed the methylene group at the aryl part. After ether cleavage using boron tribromide, the diphenol **77** was obtained, which was identical to the racemic degradation product generally referred to as phenol B. The further conversion into (±)-citrinin (**2**) required carboxylation, formylation, and cyclization and was accomplished following previous partial syntheses. Carboxylation with carbon dioxide and potassium hydrogen carbonate[194−196] yielded the acid **78**, which was then formylated using ethyl orthoformate[883] to give an aldehyde that cyclized in situ to the required quinomethide structure **2** (Scheme 9).

Subsequent studies seeking the enantioselective synthesis of citrinin (**2**) involved the generation of the *ortho*-toluate carbanion of **72** with a chiral lithium amide base.[199] It underwent addition to acetaldehyde with asymmetric induction at the nucleophilic center to produce two diastereomeric lactones (dr 3:1), however, with enantioselectivities of only ~70% ee. The mixture could be converted into the desired *threo*-lactone, but unfortunately it resulted in an unnatural enantiomer.

The first enantioselective total synthesis of (−)-citrinin (**2**) was not achieved until Rödel and Gerlach announced their Grignard approach in 1995 (Scheme 10).[200] The key step was a reaction of enantiomerically pure oxirane **80** with the corresponding magnesium organyl of **79** in the presence of

Scheme 10. First Enantioselective Total Synthesis of (−)-Citrinin (2) by Rödel and Gerlach[200]



Reagents and conditions: (a) (1) Mg, THF; (2) (*S*,*S*)-**80**, cat. ($MgBr_2$, COD CuCl). (b) Ph_3P, HCO_2H, toluene; then DEAD (59%). (c) KOH, MeOH/H_2O/THF, reflux (99%). (d) H_2, Pd/C, AcOH/MeOH. (e) $KHCO_3$, CO_2, glycerol. (f) $HC(OEt)_3$, HCl.

1,5-cyclooctadienecopper(I) chloride as the catalyst. Stereoselective ring-opening yielded (2*S*,3*S*)-**81** with the undesired *erythro* configuration. The *cis*-dimethyloxirane would lead directly to the *threo* product; however, as a *meso*-compound, it gave the racemic alcohol. The indirect route thus involved a Mitsunobu reaction that, after hydrolysis, yielded the (2*R*,3*S*)-alcohol **82** (>99% de) with the configuration of natural (−)-citrinin (**2**). The remaining steps toward the mycotoxin required debenzylation to give **77** (so-called "phenol A") and the known carboxylation−formylation−ring-closure sequence.

The contributions of Whalley et al. in the field of citrinin and other mycotoxins are reoported in several publications by the Royal Chemical Society with the series title "The Chemistry of Fungi".[195,196,880,884]

2.3. Ergot Alkaloids

The ergot alkaloids are isolated from the dried sclerotium of the fungus *Claviceps purpurea* and are classified as indole alkaloids derived from a tetracyclic ergoline ring system (**84**, Figure 4). These include lysergic acid (**85**), lysergic acid amide (precursor for the illegal narcotic, lysergic acid diethylamide (**86**), commonly known as LSD), and ergopeptines such as ergotamine (**8**). These alkaloids have attracted the attention of synthetic chemists for decades, and the total synthesis of relevant peptide derivatives has already been reviewed in several papers.[377,885] For this reason, we will not focus our attention on these derivatives but encourage an examination of the references cited below.[373]

2.4. Fumonisins

Species of the mold fungus *Fusarium* occur in almost every environment, largely due to their ability to live without oxygen; they are the most important pathogens of corn and other grains.[886] *Fusarium* spp. produce several mycotoxins, among them sesquiterpenols—the trichothecenes (see section 2.7)—or the potent mutagen Fusarin C (**87**, Figure 5), which is surprisingly not involved in the carcinogenicity of the fungus, as Vleggaar et al. reported in 1988.[887] However, they

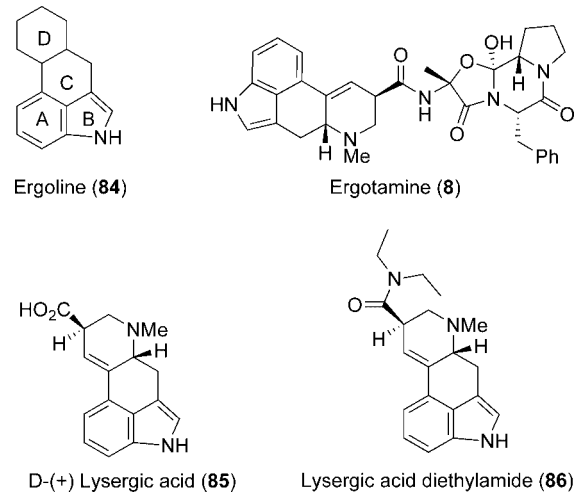


Figure 4. Representative ergot alkaloids.

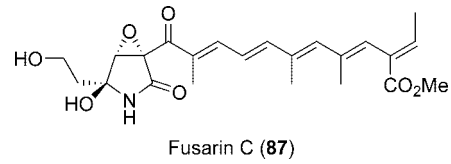


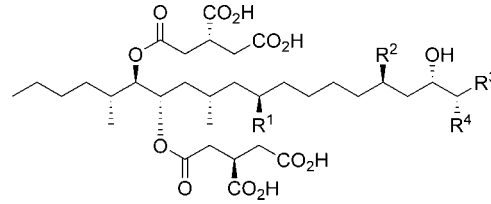
Figure 5. Fusarin C (**87**).

discovered that a novel class of mycotoxins, the fumonisins, are structurally similar to the sphingoid backbone of the sphingolipids.[888] The consumption of contaminated food has been directly correlated with human esophageal cancer.[889]

Fumonisins of the B-series (FB_{1-3}) have the most widespread occurrence (Table 5). Their *N*-acetylated congeners (A-series) and the analogues FC_{1-4}, which lack the terminal methyl group, contribute to less than 5% of the total fumonisin abundance. In 1996, Musser et al. reported about a new series, the fumonisins P_{1-3}, bearing a 3-hydroxypyridinium moiety at C-2 instead of at the amine, which occur at levels up to 30% of FB_1.[890]

Since the first characterization of the fumonisins in 1988, many groups, namely, those of Kishi, ApSimon, Hoye/Shier,

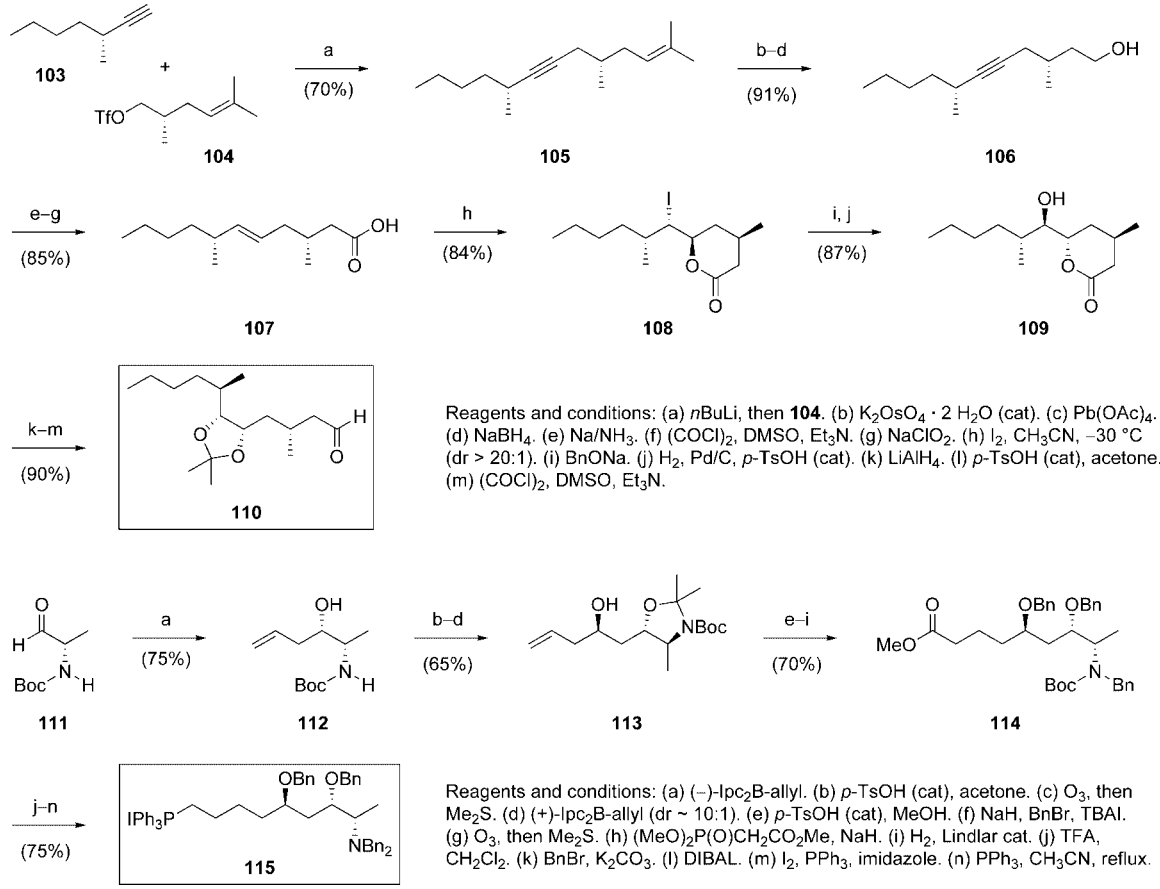
Table 5. Fumonisins



No.	R^1	R^2	R^3	R^4	trivial name
88	OH	OH	CH_3	NHAc	Fumonisin A_1
89	H	OH	CH_3	NHAc	Fumonisin A_2
90	OH	H	CH_3	NHAc	Fumonisin A_3
91	H	H	CH_3	NHAc	Fumonisin A_4
92	OH	OH	CH_3	NH_2	Fumonisin B_1
5	H	OH	CH_3	NH_2	Fumonisin B_2
93	OH	H	CH_3	NH_2	Fumonisin B_3
94	H	H	CH_3	NH_2	Fumonisin B_4
95	OH	OH	H	NH_2	Fumonisin C_1
96	H	OH	H	NH_2	Fumonisin C_2
97	OH	H	H	NH_2	Fumonisin C_3
98	H	H	H	NH_2	Fumonisin C_4
99	OH	OH	CH_3	pyOH[a]	Fumonisin P_1
100	H	OH	CH_3	pyOH[a]	Fumonisin P_2
101	OH	H	CH_3	pyOH[a]	Fumonisin P_3
102	H	H	CH_3	pyOH[a]	Fumonisin P_4

[a] pyOH = 3-hydroxypyridinium.

Scheme 11. Fumonisin B_2 (5) by Kishi et al.[401] (Synthesis of the Segments)



and Powell, have worked on the elucidation of their structure, especially of their relative and absolute configuration. Finally, in 1994, the stereochemistry of the fumonisin B_1 (**92**)[891] and the fumonisin B_2 (**5**)[892] backbones was clarified, followed by reports about the absolute configuration of the tricarballylic acid (TCA) moiety that was eventually proved through synthesis by the Kishi group.[893]

The same group published the first enantioselective total synthesis of fumonisin B_2 (**5**) two years later.[401] Their strategy was to build up the two halves containing clustered stereogenic centers separately and then to connect them by Wittig reaction. Furthermore, the TCA segments **116** (Scheme 12) were synthesized by an asymmetric Michael addition in a similar way to what had been previously reported[893] and were attached at a late stage of the synthesis. The construction of the left segment (aldehyde **110**) and the right segment (Wittig ylide precursor **115**) is outlined in Scheme 11.

The first step of the synthesis was the coupling of chiral alkyne **103**, prepared by a Swern oxidation/Corey−Fuchs protocol from (*R*)-2-methyl-1-hexanol, and the triflate **104**, synthesized using the pseudoephedrine-based asymmetric alkylation developed by Myers. The resulting alkyne **105** was then cleaved at its double bond, reduced to the alcohol **106**, and converted into acid **107** by reduction to the *trans*-alkene, followed by Swern and Kraus oxidation. The vicinal hydroxyl groups were introduced by iodolactonization, ring-opening of the lactone with benzyl alcoholate to furnish an epoxide, and deprotection of the resulting benzyl ester with concomitant epoxide ring-opening. Via this sequence, the stereogenic centers were modulated into the desired configuration, so that the preparation of the left segment **110** could be completed by protection and adjustment of the oxidation state.

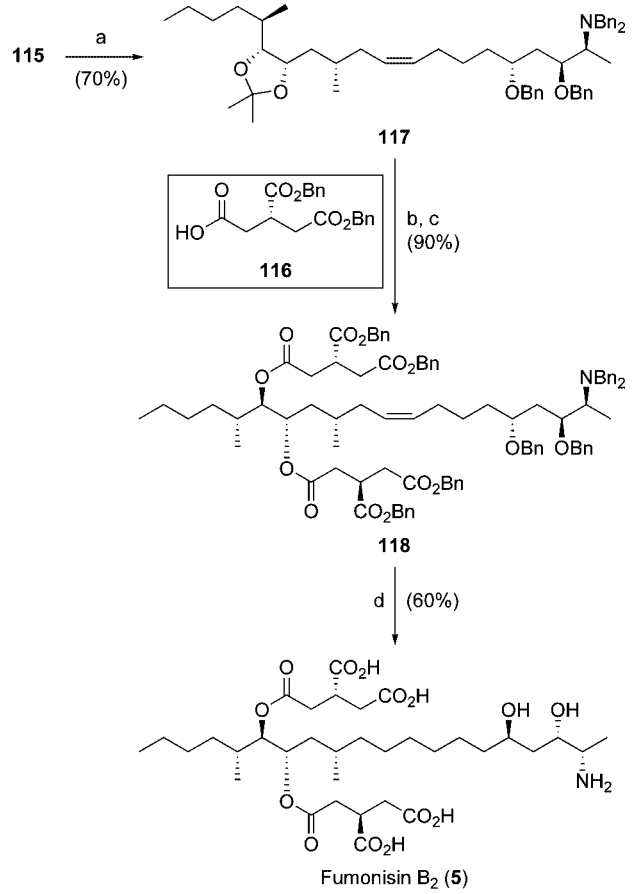
The right part **115** of fumonisin B_2 (**5**) was synthesized by two reiterative Brown allylations of Boc-protected α-amino propanal (**111**). The resulting allyl alcohol **113** was then subjected to various modifications of the protective groups and transformed into the aldehyde by ozonolysis. A chain elongation was achieved by Horner−Wadsworth−Emmons olefination to give ester **114**, which was converted into the phosphonium salt **115**. The three building blocks **110**, **115**, and **116** of the convergent total synthesis were thus at hand for interconnection.

Fumonisin B_2 (**5**) synthesis was completed by the Wittig reaction and acylation with the tricarballylic acid **116**. Hydrogenation of the double bond and hydrogenolysis of all benzyl protecting groups was accomplished in a single step using Pearlman's catalyst (Scheme 12).

One year later, in 1998, Gurjar et al. reported an approach toward the development of the backbone of fumonisin B_1 (**92**).[400] It comprised the stereoselective synthesis of the hexaacetate derivative **135** starting from natural carbohydrates as chiral substrates (Scheme 13).

The left part arising from D-glucose (**119**) was converted into the 5-ulose derivative **120**. The butyl group was introduced by Wittig olefination and palladium-catalyzed reduction. However, the reaction was not diastereoselective, so that the required isomer had to be isolated by chromatography. Inversion of the configuration at the sugar moiety was effected by an oxidation/reduction sequence to give **121**. After oxidative cleavage of the diol with sodium periodate, the lactone **123** was formed by Horner−Wadsworth−Emmons olefination and treatment with a base. The reduction to **124** was performed in two steps to achieve maximum induction during hydrogenation of the olefin. Chain elongation toward **125** included hydrolysis of the lactol and Wittig olefination,

Scheme 12. Fumonisin B_2 (5) by Kishi et al. (Combination of the Building Blocks)[401]



Reagents and conditions: (a) *n*BuLi, then **110**. (b) TFA · H_2O. (c) **116**, EDC, DMAP. (d) H_2 (1 atm), $Pd(OH)_2$/C, HCl, *t*BuOH, THF.

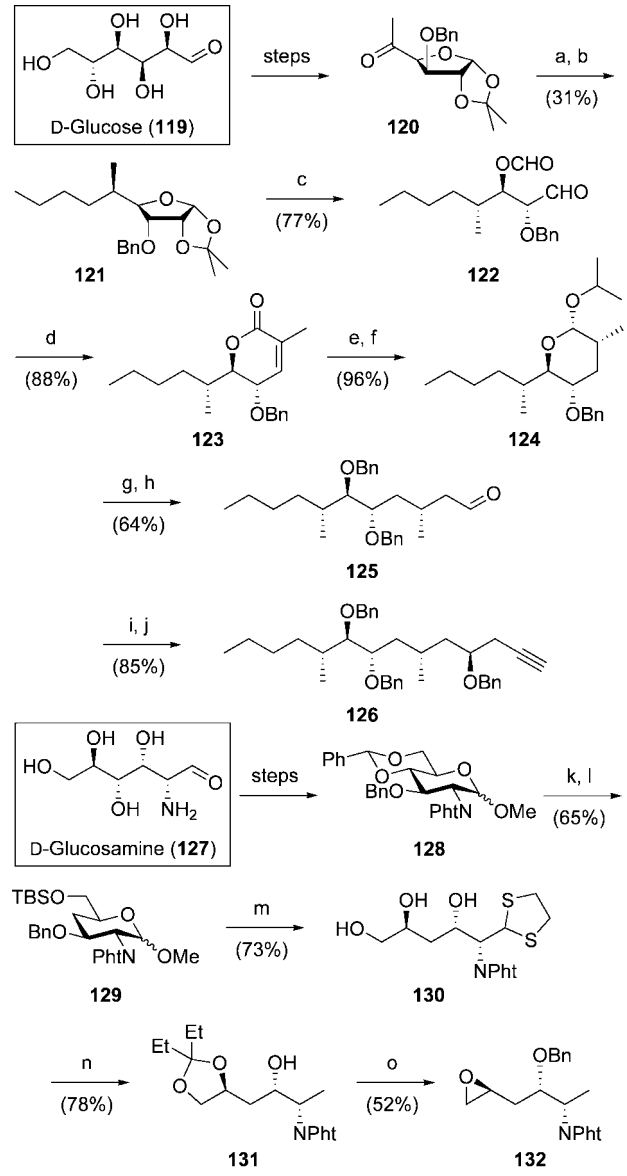
followed by hydroboration and oxidation. The subsequent addition of propargyl bromide in the presence of zinc dust resulted in a diastereomeric mixture of alcohols, which had to be separated by chromatography. Thus, the sequence comprises two nonstereoselective steps, so that the application of asymmetric reactions would improve the synthesis substantially. Building block **126** was finally obtained after benzylation.

The right segment of fumonisin B_1 (**92**) with its amino group can be traced back to D-glucosamine (**127**), which was thoroughly protected with orthogonal groups according to the literature. The resulting actual starting material **128** was then subjected to a Barton−McCombie deoxygenation at the 4-position, leading to **129**. Ring-opening occurred by conversion into the dithiolane **130** and complete reduction with Raney-nickel, with subsequent acetalization yielding precursor **131**. Transformation into the second building block **132** was realized in four steps including tosylation and epoxidation under basic conditions.

To complete the synthesis (Scheme 14), the two segments **126** and **132** were linked via an epoxide opening with the corresponding lithium acetylide. Removal of the phthalimido protective group and overall acetylation after debenzylation finally produced hexaacetyl fumonisin B_1-AP (**135**).

A structurally closely related group of mycotoxins are the AAL-toxins TA_1 (**136**) and TA_2 (**137**) isolated from *Alternaria alternata* f. sp. *lycopersici* (for toxic *Alternaria* metabolites, see also section 2.9.1).[397] They were found to be tumor promoters[894] and—because of their similar structure—an

Scheme 13. Fumonisin B_1 (92) Backbone by Gurjar et al. (Synthesis of the Building Blocks)[400]

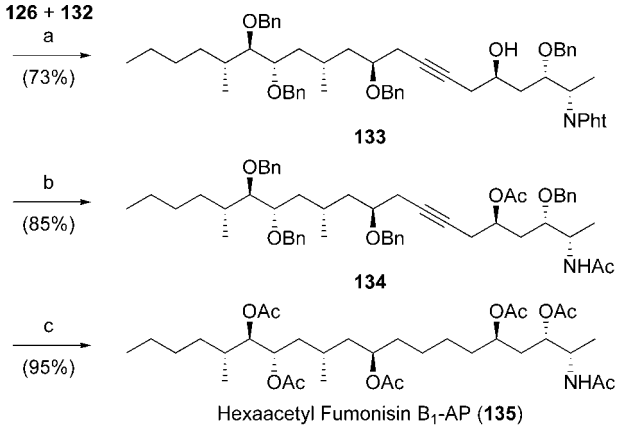


Reagents and conditions: (a) (1) $C_4H_9PPh_3Br$, *n*BuLi, THF; (2) Pd/C, H_2, EtOAc. (b) (1) Ca/liq.NH_3, Et_2O; (2) IBX, DMSO; (3) $NaBH_4$, MeOH; (4) BnBr, NaH, THF. (c) (1) 70% aq. AcOH, H_2SO_4 (cat); (2) $NaIO_4$, MeOH/H_2O 4:1. (d) (1) $(MeO)_2P(O)CH(CH_3)CO_2Et$, NaH, THF; (2) K_2CO_3, MeOH. (e) (1) DIBAL, PhMe; (2) *i*PrOH, CSA. (f) Rh-Al_2O_3, H_2 (1 atm), Et_2O. (g) (1) 70% aq. AcOH, H_2SO_4 (cat); (2) CH_3PPh_3I, *n*BuLi, THF; (3) BnBr, NaH, THF. (h) (1) 9-BBN, THF, NaOH, H_2O_2; (2) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2. (i) C_3H_3Br, Zn, aq. NH_4Cl, THF. (j) NaH, BnBr, THF. (k) (1) 60% aq. AcOH; (2) TBSCl, Im, CH_2Cl_2. (l) (1) NaH, CS_2, MeI, THF; (2) Bu_3SnH, AIBN (cat), PhMe. (m) (1) MeOH, *p*TsOH; (2) $BF_3{\cdot}Et_2O$, $HSCH_2CH_2SH$, CH_2Cl_2. (n) (1) Raney-Ni, EtOH; (2) Et_2CO, CSA, CH_2Cl_2. (o) (1) NaH, BnBr, THF; (2) MeOH, *p*TsOH; (3) TsCl, Py, CH_2Cl_2; (4) NaH, THF.

inhibitor of sphingolipid biosynthesis.[895] The AAL-toxins are the first known compounds inducing apoptosis in both mammalian and plant cells.[896] The relative and absolute stereochemistry of the sphingosine backbone was elucidated by the groups of Kishi and Oikawa.[897] The latter group also published the first total synthesis of AAL-toxin TA_1 (**136**) in 1999, with a retrosynthetic disconnection between C-9 and C-10 (Figure 6).[398]

The synthesis of lactone **138** started from methyl 3-hydroxy-2-methylpropionate (**141**), which was converted into oxirane **142** involving vinylation and dihydroxylation reac-

Scheme 14. Fumonisin B_1 (92) Backbone by Gurjar et al. (Synthesis of Hexaacetate Derivative)[400]



Reagents and conditions: (a) *n*BuLi, $BF_3{\cdot}Et_2O$, THF. (b) (1) $MeNH_2$, MeOH; (2) Ac_2O, Et_3N, CH_2Cl_2. (c) (1) $Pd(OH)_2$, H_2, MeOH; (2) Ac_2O, Et_3N, CH_2Cl_2.

tions for the implementation of the two new stereogenic centers. The epoxide was opened by acetylide addition to produce **143**, which was transformed into lactone **144** under sequential hydrolytic conditions, followed by deprotection of the silyl ether moiety, Swern oxidation, and Wittig olefination. The remaining steps comprised hydrogenation and acidic debenzylation as well as the final α-methylation toward lactone **138** (Scheme 15).

The synthesis of building blocks **139** and **140** had already been published in a preceding paper in 1996.[898] Protected 5-pentynol and (*R*)-glycidol were reacted, and the resulting homopropargylic alcohol was hydrogenated to the *cis*-olefin **147**, which in turn was subjected to an asymmetric dihydroxylation. The major product was the *anti*-triol **148** that was globally protected with benzyl groups and subsequently transformed into the second building block **139** by a Corey−Fuchs reaction (Scheme 16).

The tricarballylic acid segment **140** was obtained from racemic methyl 2-benzylsuccinate (**150**). A kinetic resolution was achieved by employing lipase-catalyzed hydrolysis of the primary ester. The (*S*)-isomer **150a** was then fully hydrolyzed, TMSE-protected (TMSE = trimethylsilylethyl), and converted into the acid **140** through degradation of the phenyl ring.

Finally, the total synthesis was completed with the combination of the three fragments (Scheme 17): acetylide addition to lactone **138** afforded ynone **152** that was deoxygenized under palladium catalysis after Luche reduction and formylation. Transformation of the THP−acetal (THP = tetrahydropyranyl) **153** into the azide **154** was effected under Mitsunobu conditions, and esterification with the tricarballylic acid moiety **140** was attained by applying the Yamaguchi method. Deprotection and exhaustive hydrogenation provided the AAL-toxin TA_1 (**136**).

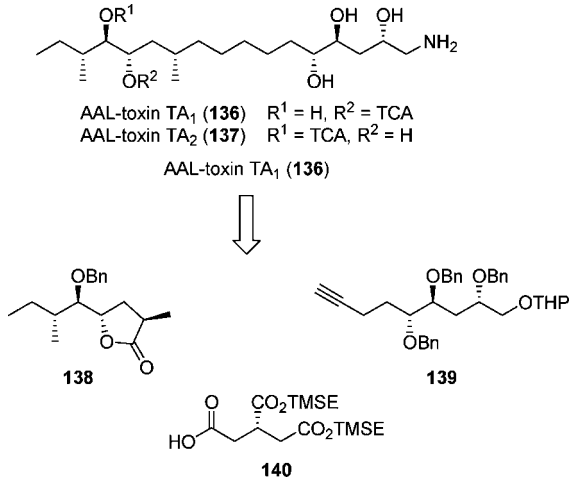
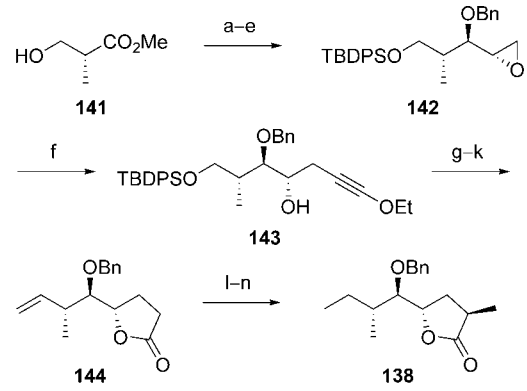


Figure 6. AAL-toxins and retrosynthetic analysis.

Scheme 15. Total Synthesis of AAL-Toxin TA_1 (136) by Oikawa (Left Segment)[398]



Reagents and conditions: (a) TBDPSCl, Im, DMF, (quant.). (b) DIBAL, Et_2O, −78 °C; then vinylMgBr (dr = 1:1, 77%). (c) NaH, BnBr, TBAI, THF (91%); chromatographic separation. (d) OsO_4, NMO, acetone/H_2O 8:1 (dr = 6:1, 91%). (e) (1) $MeC(OMe)_3$, cat. PPTS, CH_2Cl_2; (2) AcBr, CH_2Cl_2; (3) K_2CO_3, MeOH (77%). (f) ethyl ethynyl ether, *n*BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C. (g) $HgCl_2$, EtOH. (h) K_2CO_3, MeOH; then 3 M HCl (59% over 3 steps). (i) TBAF, THF (80%). (j) Swern oxidation. (k) H_3CPPh_3Br, *n*BuLi, THF (19% over 2 steps, 70% recovered aldehyde). (l) H_2, Pd/C, EtOAc. (m) $CCl_3C(NH)OBn$, TfOH, CH_2Cl_2/cyclohexane 1:1 (57% over 2 steps). (n) LiHMDS, MeI, THF, −78 °C (dr = 8.7:1, 68%).

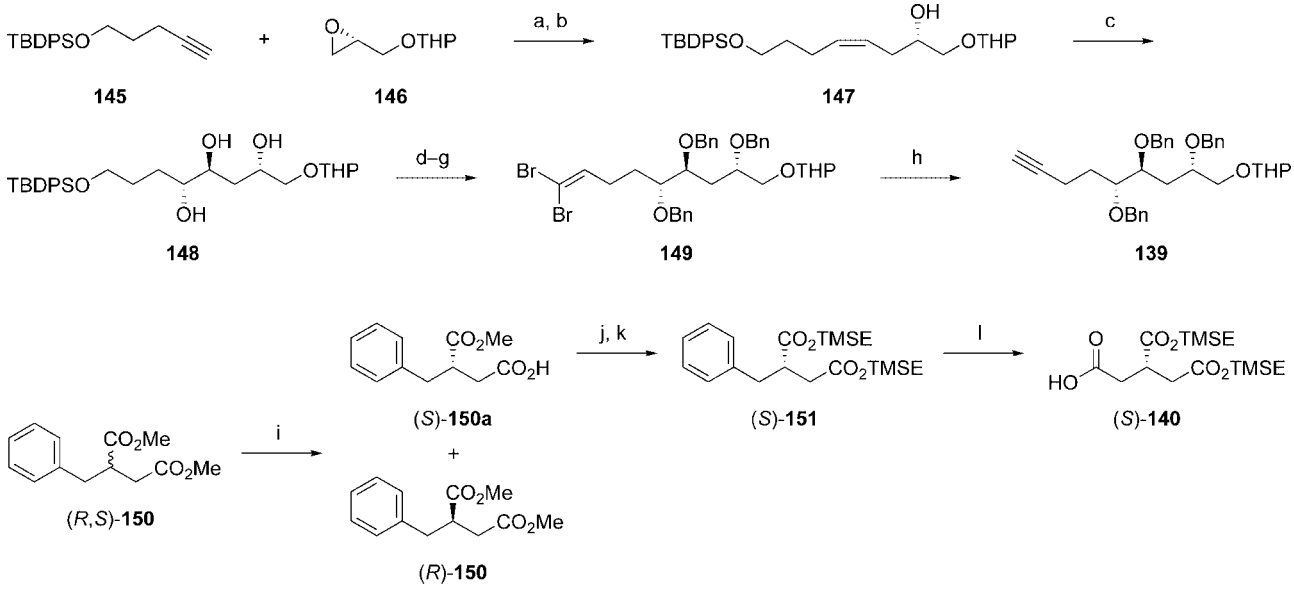
All indicated syntheses were performed in a quite convergent manner. The cumulated arrangement of the stereogenic centers in this class of natural products gave rise to strategies that throughout set the retrosynthetic dissection in the middle of the backbone. The chiral segments were either built up by asymmetric synthesis or derived from natural products such as sugars (chiral pool strategy). The modular approach offered the possibility of producing fumonisin analogues that could be applied in structure-activity relationship (SAR) investigations. Various aspects of biological activity of fumonisins and AAL-toxins that are particularly interesting for the understanding of the importance of this family of mycotoxins have been included in this review.[899]

2.5. Ochratoxin

The ochratoxins are the first major group of mycotoxins identified after the discovery of the aflatoxins; among the *Aspergillus* toxins, only ochratoxin is potentially as important as the aflatoxins. Ochratoxin A (OA, **7**) and B (OB, **155**) were characterized in 1965 by Steyn and co-workers.[900,901]

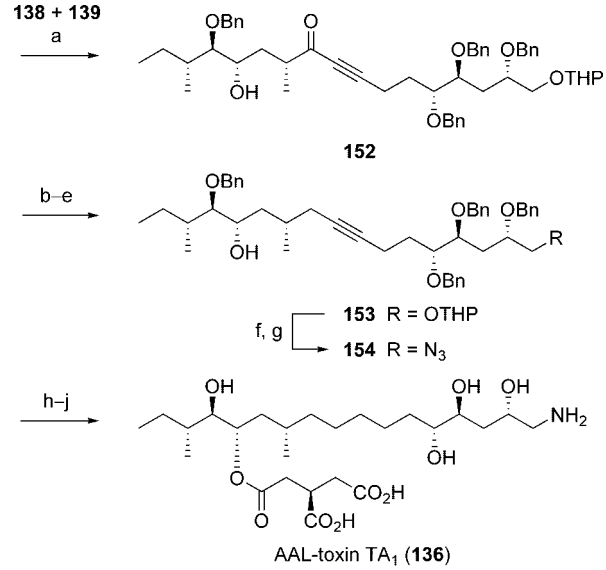
Biosynthetically, the ochratoxins are pentaketides, consisting of a dihydroisocoumarin coupled with β-phenylalanine. There are OA (**7**) and its dechloro analogue OB (**155**), their corresponding methyl esters (**158a** and **159a**, respectively) and also their ethyl esters (**156** and **159b**), ochratoxin C (OC, **156**), the 4-hydroxy derivatives from OA (**160a** and **160b**), and the dihydroisocoumarin carboxylic acid (ochratoxin α, **157**) (see Figure 7). The dihydroisocoumarins represent an extensive class of naturally occurring compounds that display a wide range of biological activities.

Scheme 16. Total Synthesis of AAL-Toxin TA_1 (136) by Oikawa (Right Segment and TCA)[398]



Reagents and conditions: (a) *n*BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C (75%). (b) H_2, $Pd/BaSO_4$, quinoline (93%). (c) cat. OsO_4, DHQD-IND, $K_3Fe(CN)_6$, K_2CO_3, *t*BuOH/H_2O (dr = 4:1, 85%). (d) NaH, BnBr, TBAI, THF, reflux (81%). (e) TBAF, THF (89%). (f) Oxidation. (g) CBr_4, PPh_3, DIPEA, CH_2Cl_2 (75%). (h) *n*BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C (75%). (i) lipase (PPL), KH_2PO_4-buffer (pH 7.2). (j) 1 M NaOH, MeOH. (k) $TMSCH_2CH_2OH$, EDC, Et_3N, DMAP, CH_2Cl_2 (79% over 2 steps). (l) $RuCl_2$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$ 2:2:3 (59%).

Scheme 17. Total Synthesis of AAL-Toxin TA_1 (136) by Oikawa et al.[398]



Reagents and conditions: (a) **139**, *n*BuLi, Et_2O, −20 °C; then **138** (72%). (b) $NaBH_4$, $CeCl_3$, MeOH (85%). (c) Ac_2O, HCO_2H, Py (97%). (d) $Pd(OAc)_2$, nBu_3P, THF (84%). (e) LAH, THF. (f) PPTS, EtOH (89% over 2 steps). (g) HN_3, PPh_3, DEAD, toluene (69%). (h) 2,4-$(NO_2)_2C_6H_4COCl$, **140**, Et_3N, toluene; then **154**, DMAP (71%). (i) TBAF, THF. (j) H_2, Pd/C, *t*BuOH/THF/1 M HCl 3:1:0.04 (76% over 2 steps).

Ochratoxin A (**7**) is the most important and most commonly occurring member of the family of ochratoxins, and is the subject of several publications.[902,903] It is produced by *Aspergillus ochraceus* and several related *Aspergillus* species, by a single *Penicillium* species (*P. verrucosum*), and by *A. carbonarius* with a small percentage of isolates of the closely related *A. niger*. It was first isolated by Steyn and co-workers.

Ochratoxin A (**7**) is the most toxic of the ochratoxins, exhibiting teratogenic, nephrotoxic, immunosuppresive and carcinogenic properties.[904−906] Two years after having isolated Ochratoxin A (**7**) and B (**155**) from some strains of *Aspergillus ochraceus*,[900,901] Steyn and co-workers reported the first total synthesis of racemic ochratoxin α (**157**), the carboxylic acid component of the biologically active ochratoxin A (**7**) (Scheme 18).[907]

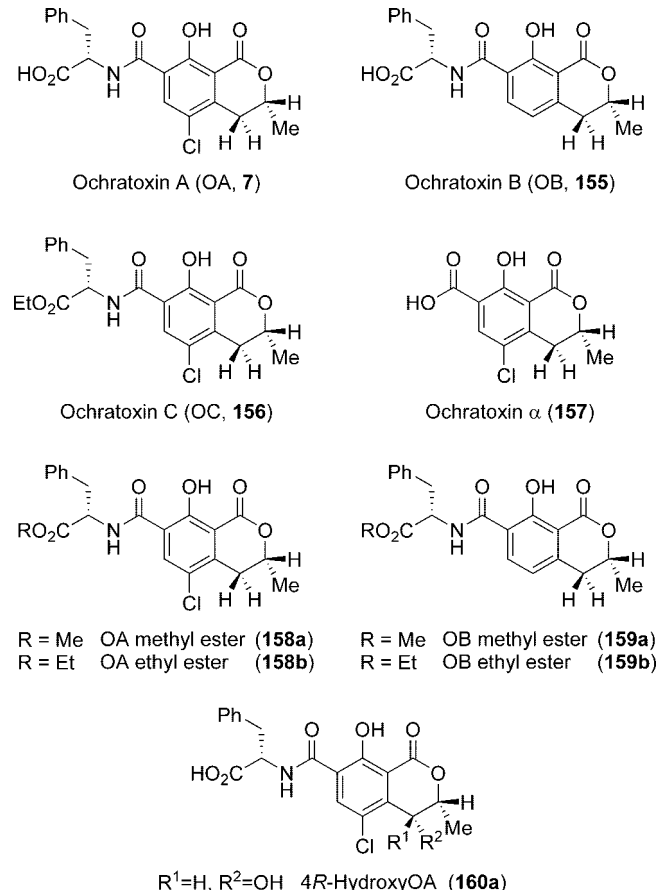
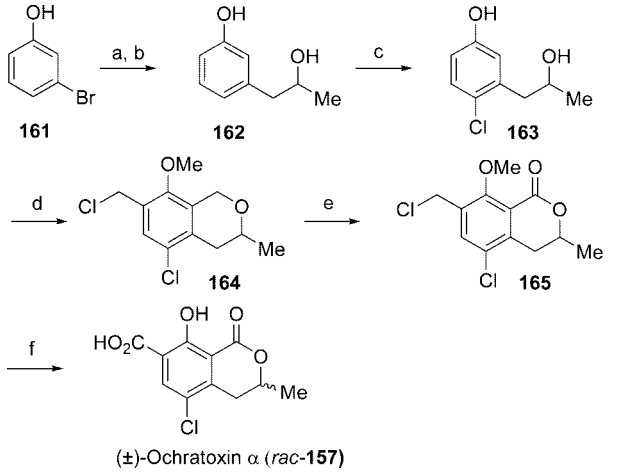


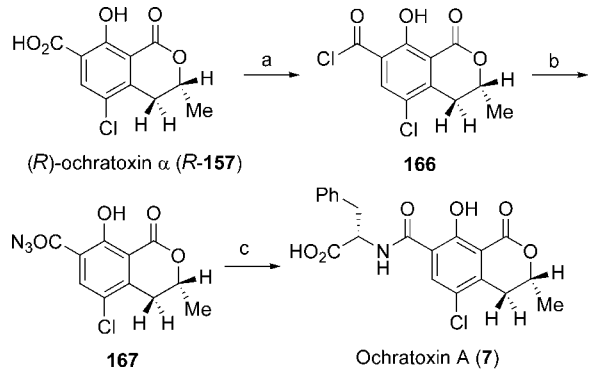
Figure 7. Structures of ochratoxins.

Scheme 18. First and Improved Synthesis of Ochratoxin α by Steyn and Holzapfel[907]



Reagents and conditions: (a) DHP, HCl, 60 °C. (b) (1) EtMgBr, THF, 1 h, 0 °C; (2) propylene oxide, 16 h; (3) MeOH-1N HCl, 12 h, rt. (c) Cl_2 (g), nitromethane, 0°C, 15 min. (d) $ZnCl_2$, chloromethylether, reflux, 45 min. (e) AcOH, CrO_3, 0 - 5 °C, 30 min. (f) (1) $(CH_2)_6N_4$; (2) aqueous AcOH; (3) Ag_2O; (4) $ZnCl_2$.

Scheme 19. First Total Synthesis of Ochratoxin A (7) by Steyn and Holzapfel[907]

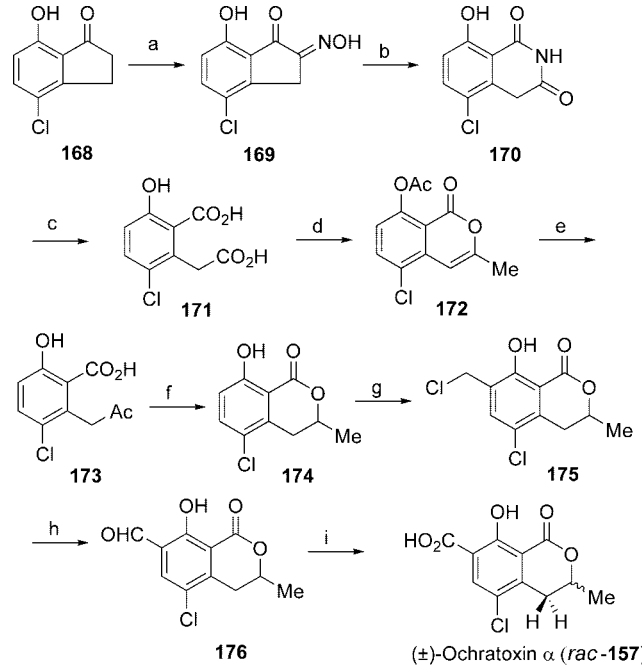


Reagents and conditions: (a) $SOCl_2$, reflux, 2 h; (b) NaN_3, 0 °C, DMF, 30 min.; (c) L-phenylalanine, H_2O, Et_3N, 5 °C, 55 h.

For the synthesis of ochratoxin A (**7**), the authors employed the enantiomerically pure (*R*)-ochratoxin α ((*R*)-**157**) obtained through hydrolysis of the natural product as starting material, instead of the derivative *rac*-**157** obtained through chemical synthesis (Scheme 19).

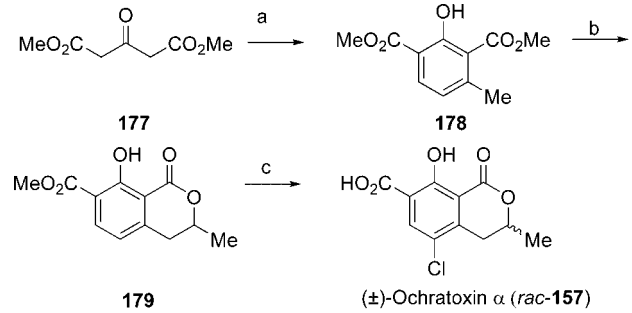
Three years later, Roberts and Woollven[551] reported an alternative synthesis of racemic ochratoxin α in eight steps with an overall yield of 62% (Scheme 20). In this case, the authors employed 4-chloro-7-hydroxyindanone (**168**) as starting material, with the advantage being that this compound possesses the phenolic hydroxyl group and the chlorine function in suitable positions. The synthetic pathway toward racemic ochratoxin α consisted of the initial formation of the isocoumarine skeleton **172** employing modifications to known procedures that employed the transformation of **168** to the corresponding oximino-compound **169**, homopthphthalimide **170** and homophthalic acid **171**.[908] The isocoumarin framework **172** was then converted in the dihydroisocoumarin **174** (via the benzoic acid **173**). Ultimately, the introduction of the required substituent at the C7-position was achieved through successive applications of the *Rieche* reaction[909] to obtain the methylene chlorinated derivative **175**, Sommelet reaction[910] to the corresponding

Scheme 20. Alternative Synthesis of Racemic Ochratoxin α by Roberts and Woollven[551]



Reagents and conditions: (a) $C_6H_{11}ONO$-HCl. (b) *p*-$MeC_6H_6SO_2Cl$. (c) (1) NaOH; (2) HCl. (d) Ac_2O-AcONa. (e) (1) NaOH; (2) HCl. (f) (1) $NaBH_4$; (2) HCl. (g) $ClCH_2PMe$-$TiCl_4$. (h) (1) $(CH_2)_6N_4$; (2) aq. AcOH. (i) Ag_2O.

Scheme 21. Short Synthesis of Ochratoxin α by Kraus[550]



Reagents and conditions: (a) $CH_3COCHCONa$ (50%). (b) LDA, CH_3CHO, THF (69%). (c) (1) SO_2Cl_2, CH_2Cl_2; (2) LiOH H_2O, MeOH (58%).

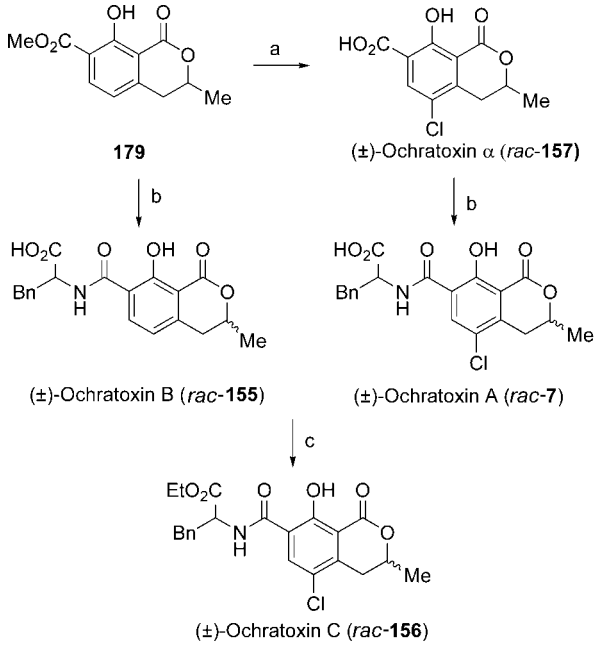
aldehyde **176**, and mild oxidation to the desired racemic ochratoxin α (rac-**157**).

Finally, by condensation of the synthesized racemic ochratoxin α (rac-**157**) with the *tert*-butyl ester of L(−)phenylalanine (employing EEDQ[911](2-ethoxy-1-ethoxycarbonyl-1,2-dihydroguinoline)) and subsequent removal of the protecting *tert*-butyl group, Roberts and Woollven obtained a diastereoisomeric mixture of ochratoxin A (**7**), which was resolved by repeated preparative thin-layer chromatography (TLC), leading to Ochratoxin A (**7**) in 90% isomeric purity.

With the aim of attaining a simple, direct, and inexpensive synthesis of ochratoxins, Kraus developed a more efficient synthetic route toward racemic ochratoxin α (*rac*-**157**) in 1981 (see Scheme 21).[550] With this methodology, he claimed (i) to improve the low overall yield, (ii) to shorten the lengthy route, and (iii) to avoid the use of several highly expensive chemicals that had been used in previous syntheses.[907,551]

One year later, Kraus extended the application of his methodology to the syntheses of ochratoxin B (**155**) and C (**156**). This work was reported in a patent that includes the

Scheme 22. Simple, Direct, and Inexpensive Synthesis of Ochratoxin A (rac-7), B (*rac*-155), and C (*rac*-156) by Kraus[912]



Reagents and conditions: (a) (1) SO_2Cl_2, CH_2Cl_2; (2) LiOH H_2O, MeOH. (b) L-(−)-phenylalanine t-butyl ester, EEDQ, THF, rt, 15 h. (c) EtOH.

synthetic route that allows, for the first time, small and industrial-scale syntheses of ochratoxins A, B, and C in pure form, with good yields and minimal synthetic steps (see Scheme 22).[912]

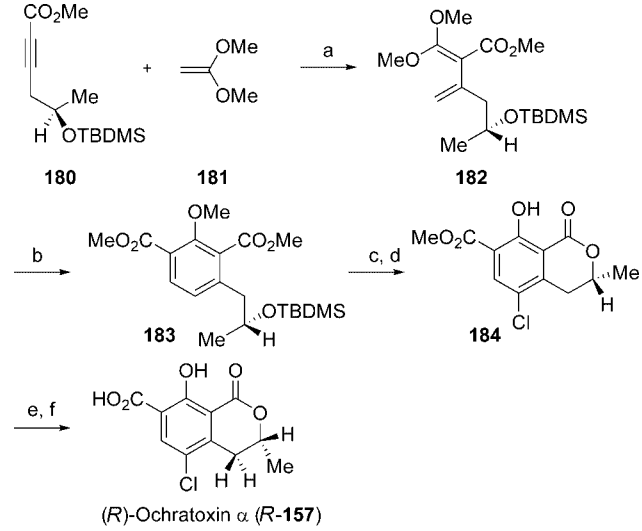
More recently, Donner and Gill reported the first total synthesis of enantiomerically pure (*R*)-ochratoxin α (*R*-**157**) in nine steps and with 10% overall yield.[552] Starting from commercially available (*R*)-propylene oxide, they applied the same strategy that they had previously developed for the stereospecific synthesis of melleins,[913] consisting of an initial cycloaddition reaction between an enantiomerically pure (*R*)-acetylenic ester **180** (derived from (*R*)-propylene oxide in three steps[913]) and ketene dimethyl acetal **181** to obtain the diene **182**, which after Diels−Alder cycloaddition with methyl propiolate, lactonization, and appropriate functionalization yielded the desired enantiomerically pure (*R*)-ochratoxin α *R*-**157** (Scheme 23).

Taking into account that the previous synthesis of the isocoumarin nucleus **157** yielded only racemic or, at best, enantiomerically enriched material, the synthetic route developed by Donner and Gill—to the enantiomerically pure intermediate (*R*)-ochratoxin α (*R*-**157**), which can be converted to (*R*)-ochratoxin A (**7**) by employing the methodology developed by Steyn and co-workers (see Scheme 19)—can be considered the first formal total synthesis of enantiomerically pure ochratoxin A (**7**) and still represents the only synthesis of (*R*)-ochratoxin ∝ published to date.[914]

2.6. Patulin

The ylidenebutenolide mycotoxin patulin (**3**) is produced by several *Penicillium* and *Aspergillus* species and is known as a common contaminant in food (e.g., apple juice). The molecule possesses antibiotic (notably antibacterial) properties[915] and is also a general plant toxin.[916] Patulin (**3**) also shows mutagenic[917] and carcinogenic activity, because of its ability to inhibit DNA, RNA, and protein synthesis.[918] Since

Scheme 23. Total Synthesis of Enantiomerically Pure Ochratoxin α by Donner and Gill[552]



Reagents and conditions: (a) sealed tube, 165 °C, 23 h. (b) methyl propiolate, sealed tube, 145 °C, 22 h, (69%, 2 steps). (c) *p*-TsOH, CH_2Cl_2, rt, 72 h (82%). (d) BCl_3, CH_2Cl_2, 0 °C, 10 min (92%). (e) SO_2Cl_2, CH_2Cl_2, rt, 48 h. (f) MeOH, LiOH·H_2O, reflux, 5 h (68%, 2 steps).

its isolation in the 1930s, patulin (**3**) (isolated from *Penicillium patulum*[919]) has been known under several names, such as clavacin,[920] clavatin,[921] claviformin (isolated from *P. claviforme*[922]), expansin,[923] mycoin, penicidin,[924] and tercinin.[925] Despite its apparently simple structure, patulin (**3**) has incited large interest within the field of natural product chemistry. Upon closer inspection, it reveals pronounced reactivity and sensitive functionality in the small bicyclic ring system, i.e., a cyclic hemiacetal, an enol ester, an allylic acetal, and a conjugate dienoate. Patulin (**3**) belongs to the family of ylidenebutenolides and is related to other fungal tetronic acid metabolites like penicillic acid (**187**) (see Figure 8).

The first study on the structure of patulin (**3**) entitled "Investigations Relating to the Synthesis of Patulin" resulted in the postulation of an incorrect structure.[926] One year later, in 1949, the correct structure[927] was published and confirmed by a partial synthesis, followed by the first total synthesis[389,928] of patulin (**3**) by Woodward and Singh, but only in very low yields.

A more practicable total synthesis was published concurrently by Gill/Pattenden[388,392] and Riguera[391] in the late 1980s. Starting from L-arabinose (**189**) as an enantiopure precursor, the acetal of patulin **194** was synthesized stereoselectively; despite this result, rapid racemization occurred after its

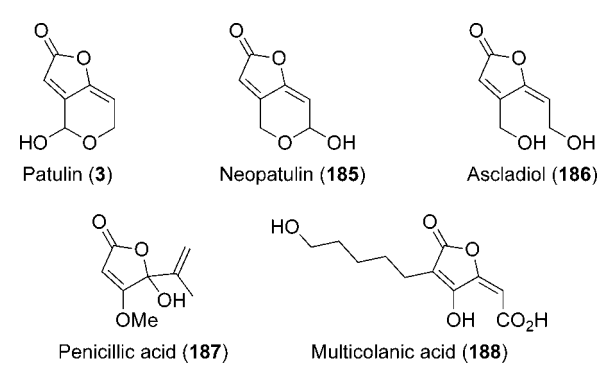
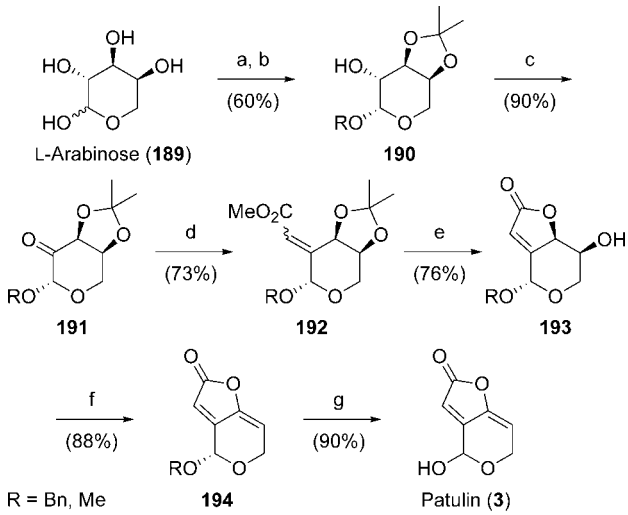


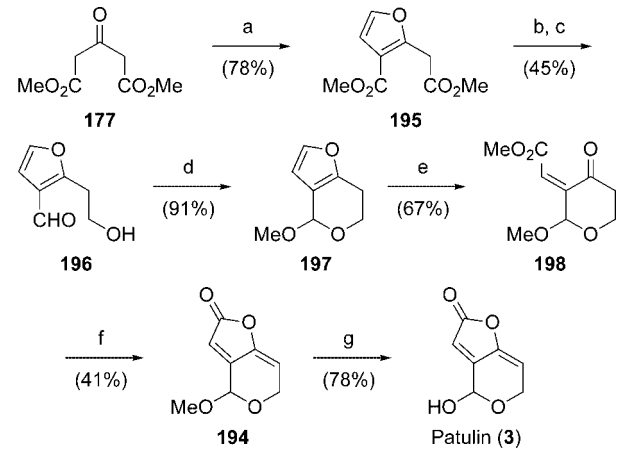
Figure 8. Patulin (**3**) and related fungal metabolites.

Scheme 24. Total Synthesis of Patulin (3) by Pattenden et al.[388,391,392]



Reagents and conditions: (a) BnOH, HCl. (b) acetone, $CuSO_4$, H_2SO_4. (c) PCC, MS 3 Å, CH_2Cl_2 *or* RuO_2, H_2O, CCl_4, $NaIO_4$. (d) Wadsworth-Emmons reaction *or* Peterson olefination (MTSA, LDA) *or* Wittig reaction: $Ph_3P{=}CHCO_2Me$, benzene, 55 °C (*E*/*Z* = 4.6:1). (e) HCl, MeOH, reflux. (f) MsCl, pyridine *or* TFAA, Et_3N. (g) aq. TFA.

Scheme 25. Total Synthesis of Patulin (3) by Tada et al.[393]

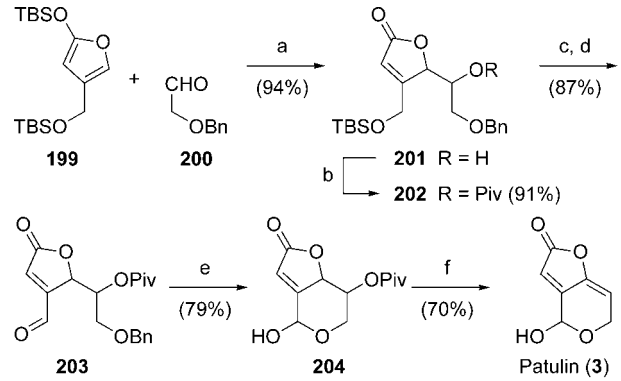


Reagents and conditions: (a) CH_2ClCHO, pyridine, 50 °C, 24 h. (b) $LiAlH_4$ (80%). (c) MnO_2 (56%). (d) PPTS, MeOH/benzene (1:2), reflux, 1.5 h, *Dean–Stark* trap. (e) (1) *m*CPBA, CH_2Cl_2, 2 h; (2) CH_2N_2. (f) $Ca(OH)_2$, benzene, reflux, 30 min, *Dean–Stark* trap. (g) TFA/H_2O (9:1), 50 °C, 1 h.

conversion into the hemiacetal, similarly to natural patulin (**3**), which also is a racemate. The first steps comprised the transformation of L-arabinose (**189**) into the isopropylidene derivative **190** with methyl or benzyl protected β-acetal. After oxidation and olefination, the α,β-unsaturated ester **192** was converted into the bicyclic lactone **193**. *Anti*-elimination and acetal cleavage completed the synthesis, and patulin (**3**) was obtained in good yield after seven steps (Scheme 24, yields from ref 388).

In 1994, Tada et al. synthesized patulin (**3**) via oxidation of furan derivatives and subsequent enol-lactonization (Scheme 25).[393] The furan ring was formed by condensation of acetonedicarboxylic acid methyl ester (**177**) with chloroacetaldehyde in pyridine. Reduction of the ester moieties and reoxidation at the benzylic position gave aldehyde **196**, which was condensed to the methyl acetal **197** upon treatment with *p*-toluenesulfonate in refluxing methanol/benzene with a *Dean−Stark* water trap. The key oxidation with *m*-CPBA (*meta*-Chloroperoxybenzoic acid), followed by methylation,

Scheme 26. Short Total Synthesis of Patulin (3) by Boukouvalas[394]



Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 10 h. (b) PivCl, DMAP, pyridine, 0 °C → rt, 24 h. (c) aq. HCl (6 N), MeOH, rt, 4 h (90%). (d) TEMPO, KBr, NaOCl, pH~9, CH_2Cl_2, 0 °C (97%). (e) BCl_3, CH_2Cl_2, −78 °C; then Et_3N/MeOH. (f) DBU, CH_2Cl_2, 0 °C → rt, 45 min.

yielded keto-ester **198**, which was again subjected to condensation conditions. With calcium hydroxide as a catalyst, efficient cyclization to the lactone **194** took place. Demethylation performed with TFA gave the natural product patulin (**3**) in 7% overall yield after eight steps.

The shortest synthesis in this context is the one published by Boukouvalas et al. in 1995 (Scheme 26).[394] After the 4-step synthesis of neopatulin (**185**)[929]—the penultimate biogenetic precursor of **3**—they reported the synthesis of patulin (**3**) starting from the same building block, silyloxyfuran **199**. An aldol reaction with benzyloxyacetaldehyde (**200**) under Lewis acid catalysis provided alcohol **201** as a mixture of diastereoisomers. The transformation into the pivaloyl ester **202** enabled the protection of the hydroxyl group as well as its activation in the later β-elimination. Desilylation and TEMPO oxidation yielded aldehyde **203**, which was immediately converted into the hemiacetal **204** through treatment with boron trichloride. Previously mentioned β-elimination was accomplished under basic conditions (DBU) and furnished patulin (**3**) with a 41% overall yield. This synthesis comprises only six steps with readily available, achiral starting materials (Scheme 26).

These approaches show how patulin (**3**) is available synthetically; however, most interest concerned its biosynthesis, as patulin (**3**) was repeatedly used as a model compound for the detailed examination of polyketide synthesis[930] in nature.[931,932]

2.7. Trichothecenes

2.7.1. Introduction

The trichothecenes are produced by various *Fungi imperfecti*, mainly of the genus *Fusarium*, but also by other genera such as *Myrothecium*, *Trichothecium*, *Trichoderma*, *Cylindrocarpon*, *Cephalosporium*, *Verticimonosporium*, or *Stachybotrys*. The family comprises a large number of substances, of which most are toxic, but only some members constitute the group of main natural contaminants of grains: deoxynivalenol (DON, **230**), nivalenol (NIV, **232**), T-2 toxin (T-2, **224**), HT-2 toxin (HT-2, **223**), and diacetoxyscirpenol (DAS, **217**). The historically reported health problems of humans intoxicated by infested food have been mainly caused by these representatives.[12]

The first known member of the trichothecene family was trichothecin (**229**),[804] characterized in 1948; however, the

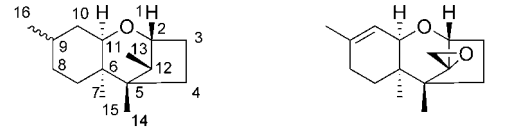


Figure 9. Structure and numbering system of "trichothecane" and 12,13-epoxytrichothec-9-enes.

individual members were not included into this class of compounds until 1967, when the sesquiterpenoid skeleton structure was given the name "trichothecane" by Tamm et al. (Figure 9).[933] Most naturally occurring trichothecenes are tetracyclic, as they contain an epoxide in the 12,13-position—which appears to be critical for bioactivity, including antiproliferative activity,[934] ability to induce apoptosis,[935] antimalarial activity,[936] and antiviral effects[937]—and they comprise a double bond at C-9,10. Thus, they can be classified as 12,13-epoxytrichothec-9-enes.

Yet, the trichothecenes can be divided into two subgroups: nonmacrocyclic (alcoholic derivatives and simple esters) and macrocyclic (more complex di- and triesters including a macrocyclic ring between C-4 and C-15). Over the decades, several classification systems have been stated by researchers engaged in this field, which exist in parallel and are listed below.

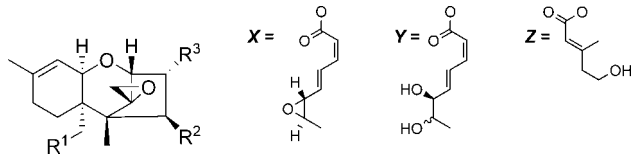
In his work,[938] Ueno defined four types according to their chemical properties and resulting fungi: type A represented by T-2 toxin (**224**) and diacetoxyscirpenol (anguidine, **217**); type B with a carbonyl function at C-8 represented by nivalenol (**232**) and deoxynivalenol (vomitoxin, **230**); type C characterized by a second epoxy function at C-7,8 (e.g., crotocin **227**) or C-9,10; and finally type D consisting of macrocyclic trichothecenes with a macrocyclic ring between C-4 and C-15 (e.g., verrucarins, roridins, satratoxins, and baccharinoids).

Another classification by Tamm and Tori[939] deals with the position of oxygen substituents at the trichothecane skeleton: (i) trichothecenes without an oxygen function at the C-8 position (Table 6); (ii) trichothecenes with an oxygen function other than a ketone at the C-8 position (Table 7); (iii) trichothecenes with a ketone at the C-8 position (Table 8); and (iv) macrocyclic trichothecenes (see Figures 11−13).

With the discovery of trichoverroids, Jarvis established a novel nomenclature[940] that differentiates between the macrocyclic representatives and those that follow biogenetic pathways. The relationship between the four types—trichothecenoid (**I**) or anguinoid (**I′**), trichoverroid (**II**), roridoid (**III**), and verrucaroid (**IV**)—is depicted in Figure 10.

The trichoverroids are biosynthetic precursors of the roridins and verrucarins. Their characterization and isolation

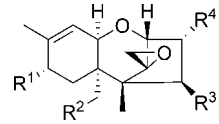
Table 6. Most Common Trichothecenes without an Oxygen Function at the C-8 Position



no.	R^1	R^2	R^3	trivial name
205	H	H	H	12,13-Epoxytrichothec-9-ene
206	H	OH	H	Trichodermol (Roridin C)
207	H	OAc	H	Trichodermin
208	H	*X*	H	Trichodermadiene
209a,**b**	H	*Y*	H	Trichodermadienediol A (*S*,*S*), B (*S*,*R*)
210	OAc	OAc	H	Di-*O*-acetylverrucarol
211	OAc	H	OAc	Calonectrin
212a,**b**	OH	*Y*	H	Trichoverrol A (*S*,*S*), B (*S*,*R*)
213a,**b**	*Z*	*Y*	H	Trichoverrin A (*S*,*S*), B (*S*,*R*)
214	OH	OH	H	*Verrucarol*[a]
215	OH	OH	OH	Scirpentriol
216	OAc	OH	OH	15-Acetoxyscirpenol
217	OAc	OAc	OH	Diacetoxyscirpenol (Anguidine)

[a] Non-naturally occurring trichothecenes in italics.

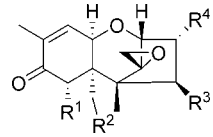
Table 7. Most Common Trichothecenes with an Oxygen Function Other than Ketone at the C-8 Position



no.	R^1	R^2	R^3	R^4	trivial name
218	OH	H	OH	H	12,13-Epoxytrichothec-9-ene-4β,8α-diol
219	OH	OH	OH	OH	T-2 tetraol
220	OH	OAc	OAc	OH	Neosolaniol
221	OAc	OH	OAc	OH	NT-1 toxin (Isoneosolaniol)
222	OH	OH	OAc	OH	NT-2 toxin (15-Deacetylneosolaniol)
223	iV[a]	OAc	OH	OH	HT-2 toxin
224	iV[a]	OAc	OAc	OH	T-2 toxin
225	iV[a]	OAc	OAc	OAc	Acetyl-T-2 toxin
226	iV[a]	OH	H	OH	Sporotrichiol
227	7β-O-8 β	H	B[b]	H	Crotocin

[a] iV = isovalerate (3-methylbutyrate). [b] B = but-2-enoate.

Table 8. Most Common Trichothecenes with a Ketone at the C-8 Position



no.	R^1	R^2	R^3	R^4	trivial name
228	H	H	OH	H	*Trichothecolone*[b]
229	H	H	B[a]	H	Trichothecin
230	OH	OH	H	OH	Deoxynivalenol (Vomitoxin)
231	OH	OH	H	OAc	3-Acetyldeoxynivalenol
232	OH	OH	OH	OH	Nivalenol
233	OH	OH	OAc	OH	Fusarenone X
234	OH	OAc	OAc	OH	Nivalenol diacetate

[a] B = but-2-enoate. [b] Non-naturally occurring trichothecenes in italics.

from *Myrothecium verrucaria* was described by Jarvis in 1982.[941] They are nonmacrocyclic but already contain the ester side chains necessary. The trichoverrins A (**213a**) and B (**213b**) undergo ring-closure to yield roridin E (**262**), which is further developed into the other roridins. They were obtained as sets of diastereomers, epimeric at C-7′ (the stereogenic center that corresponds to C-13′ in the roridins), similarly to the trichoverrols A (**212a**) and B (**212b**), as well as the trichodermadienediols A (**209a**) and B (**209b**) (see Table 6). In all three cases, the addendum "A" indicates the *threo*-configuration (*S*,*S*) and "B" stands for the *erythro*-configuration (*S*,*R*). Note that the C-6′ centers in the trichoverrins and trichoverrols are (*S*) and those in the ring-closed macrocyclic trichothecenes are (*R*).

2.7.2. Total Syntheses of the Sesquiterpenoid Core

Formal saponification of the trichoverrins yields verrucarol (**214**), the sesquiterpenoid moiety of the majority of the trichoverroids and the macrocyclic trichothecene derivatives.

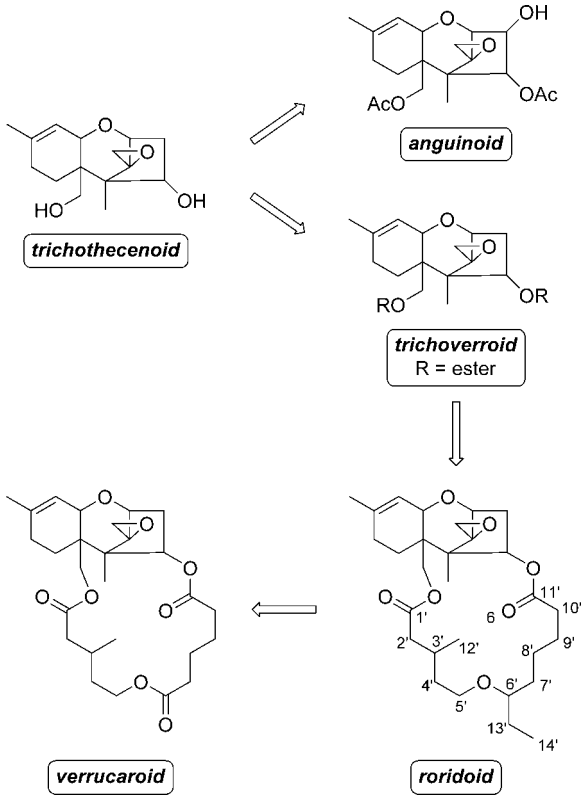


Figure 10. Jarvis's nomenclature of trichothecenes.

For this reason, verrucarol (**214**) was the focus of much synthetic interest, even though it is not a naturally occurring trichothecene itself. The first total synthesis of racemic

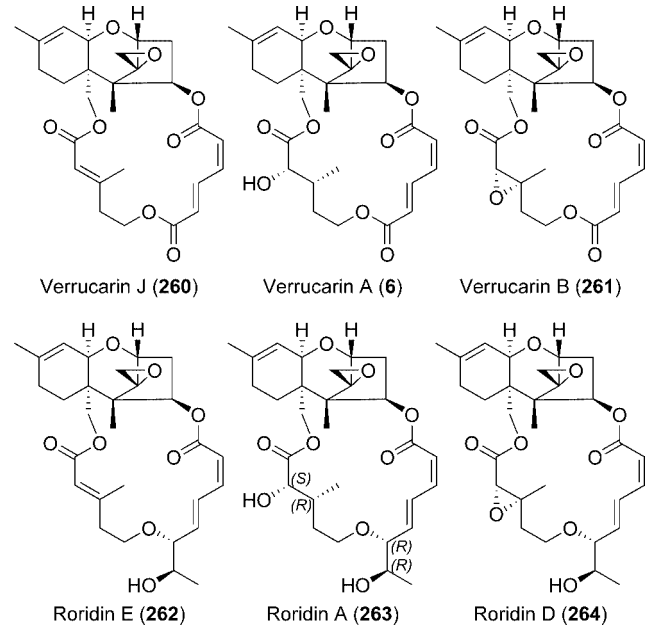


Figure 11. Examples of the verrucarins and roridins.

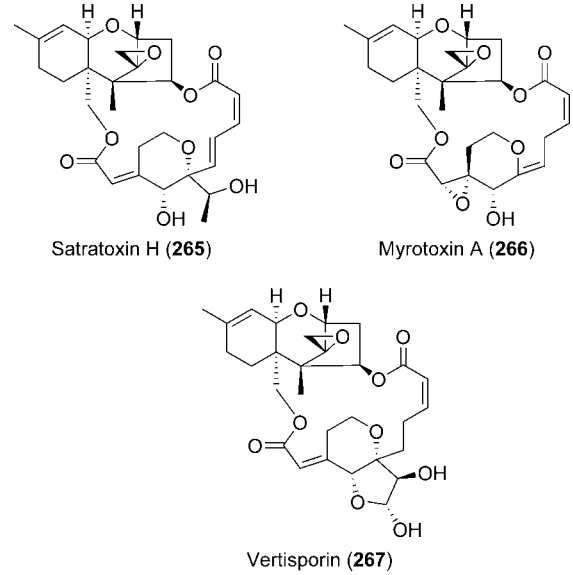


Figure 12. Macrocyclic trichothecenes with an additional tetrahydropyran moiety.

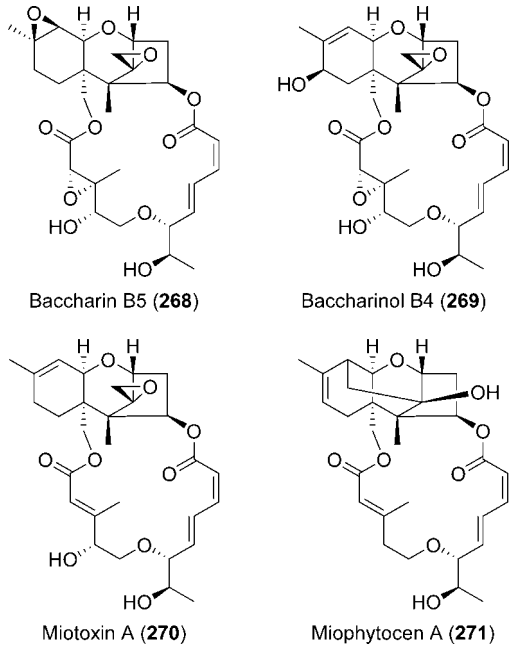


Figure 13. Macrocyclic trichothecenes isolated from *Baccharis* spp.

verrucarol (*rac*-**214**) was accomplished by Schlessinger et al. in 1982[813] and gave 3.4% yield over 17 steps (Scheme 27).

The synthesis starts with the formation of the ring system **235** according to Hajos and Parrish.[942] Through various oxidative methods, Wittig reaction, and esterification, the complex bicycle **239** was formed, which underwent a Diels−Alder cycloaddition with **240** to build up the spiro compound **241**. Saponification of the lactone and methyl addition to the keto group, followed by reduction of the carboxylic acid, resulted in precursor **242** (undetermined configuration at C^9) that was transformed into the desired trichothecene skeleton **243** by allylic addition. The *endo* double bond was protected by hydrobromination for the selective epoxidation of the *exo* double bond. Regeneration of the first was accomplished by treatment with sodium ethylamide to give racemic verrucarol (*rac*-**214**).

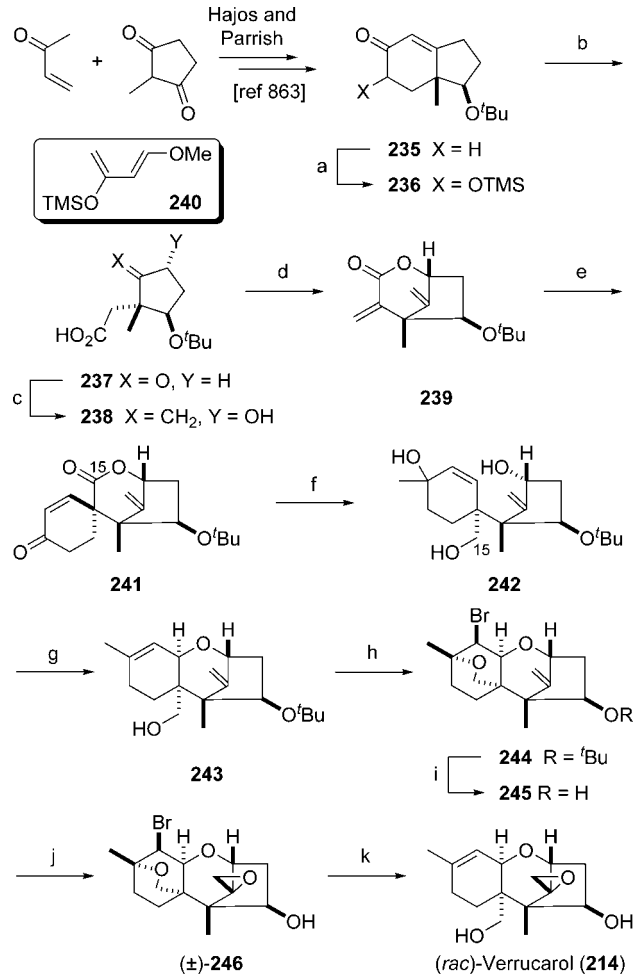
Studies toward a total synthesis were also presented by Roush in 1980,[943] and another synthesis of (±)-verrucarol (*rac*-**214**) was published by Trost in 1982.[815] The first enantioselective total synthesis of (−)-verrucarol (**214**) was finally accomplished by Tadano et al. in 1998,[816] starting from the lactone **248** derived of D-glucose (Scheme 28).

The enantiopure starting material **248** was thus derived from the chiral pool and was subjected to an aldol reaction with protected aldehyde **249**. Exchange of the protective groups and Jones oxidation yielded lactone **252**, which was converted into tricycle **253** by a Dieckmann-like condensation. The following rearrangement of the carbon skeleton into **256** with subsequent Wittig reaction gave rise to the core structure **257** of the trichothecenes. The intramolecular hydrobromination strategy for the protection of the *endo* double bond and the selective epoxidation was already described in the Schlessinger synthesis.[813] Thus, (−)-verrucarol (**214**) could be obtained in 22 steps from **248**.

2.7.3. Macrocyclic Trichothecenes

The synthesis of macrocyclic trichothecenes was reviewed in 1989 by Tamm and Jeker.[944] Examples of the most

Scheme 27. Total Synthesis of Verrucarol by Schlessinger et al.[813]



Reagents and conditions: (a) (1) LDA, THF, then TMSCl; (2) *m*CPBA. (b) (1) O_3; (2) $NaIO_4$, CrO_3 (53% from **235**). (c) (1) $Ph_3P{=}CH_2$; (2) SeO_2, *t*BuOOH (dr = 5:1). (d) (1) TsOH (55% from **237**); (2) LDA, then CH_2O (62%). (e) (1) **240**, 140 °C; (2) Amberlite IR-120 (76% from **239**). (f) (1) MeLi, THF (93%); (2) $LiAlH_4$. (g) TsOH (73%). (h) NBS, acetone. (i) $TiCl_4$ (85% from **243**). (j) *m*CPBA (70%). (k) Na, $EtNH_2$, THF (62%).

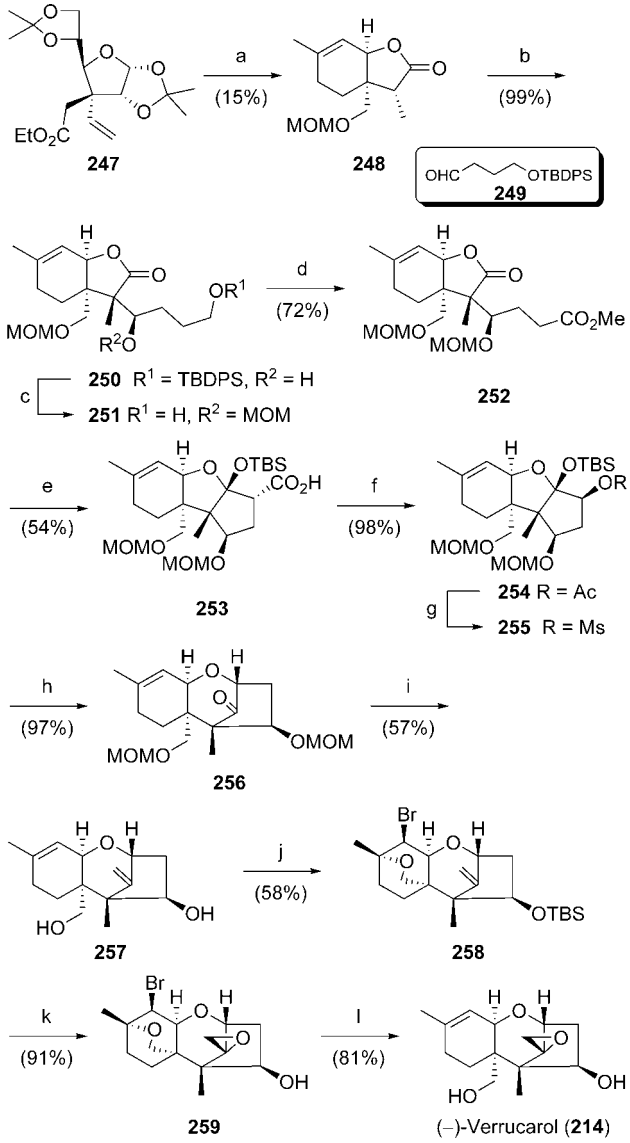
interesting macrocyclic trichothecenes are summarized in Figures 11−13. Although some trichothecenes like miophytocen A were isolated from shrubs, it is believed that they are primarily/generally produced by fungi.

One of the most important and best described macrocyclic trichothecenes is verrucarin A (**6**). Landmarks in research on macrocyclic trichothecenes are linked with Christoph Tamm, so his synthesis of this crucial representative is described (Scheme 29−31).[809]

The molecule was retrosynthetically disconnected through cleavage of the ester bonds. Thus, the starting substances for the total synthesis were verrucarol (**214**), a derivative of verrucarinic acid (**272**), and a half-ester (*E*,*Z*)-muconic acid (**273**). The synthesis of the key intermediates is shown in Scheme 30.

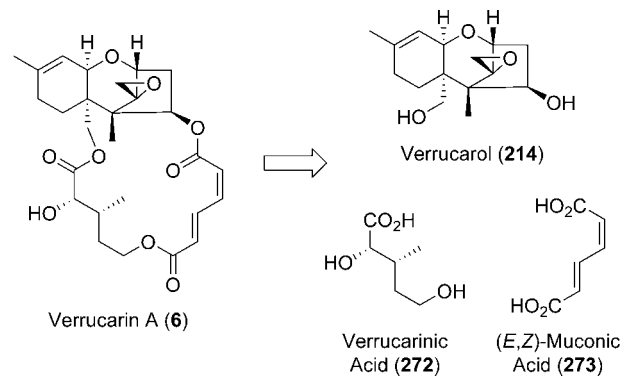
Oxidative cleavage of catechol (**274**) with a peracid resulted in the symmetric diacid (*Z*,*Z*)-**275** that was—after monoprotection through treatment with DCC (dicyclohexylcarbodiimide) and DMAP (4-(dimethylamino)pyridine)—converted into the lactone **276**. Saponification of the latter with the/a *Eschenmoser* base (3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]-1-decene) and con-

Scheme 28. Enantioselective Total Synthesis of (−)-Verrucarol by Tadano et al.[816]

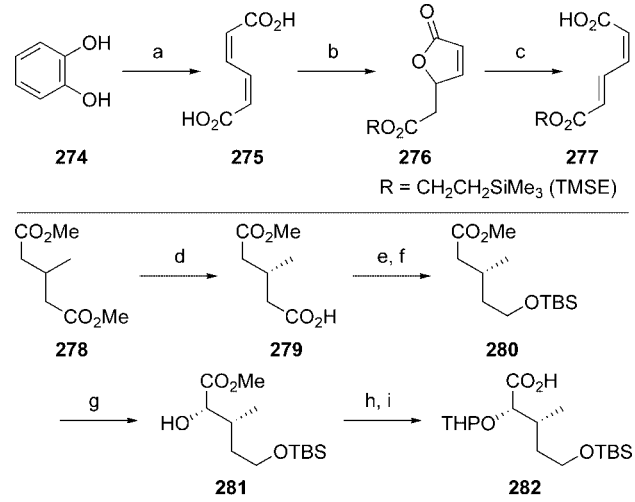


Reagents and conditions: (a) 19 steps. (b) LDA, THF/toluene, −78 °C; then **249** (dr = 1:1). (c) (1) TBAF (81%); (2) PivCl (87%); (3) MOMCl (83%); (4) NaOMe. (d) (1) Jones ox.; (2) CH_2N_2. (e) (1) KHMDS, THF, −78 °C (dr = 5:3, 82%); (2) TBSOTf (dr = 5:3, 81%); (3) KOH (single diastereomer, 81%). (f) (1) WSC, DMAP, *t*-BuSH, O_2; (2) Ac_2O, Py (dr = 2:3). (g) (1) DIBAL; (2) MsCl (99%). (h) TBAF. (i) (1) $Ph_3P{=}CH_2$ (73%); (2) TMSBr, −30 °C (78%). (j) (1) TBSOTf; (2) NBS. (k) (1) TBAF; (2) *m*CPBA. (l) Zn-Ag, EtOH.

Scheme 29. Retrosynthetic Analysis of Verrucarin A by Tamm et al.[809]



Scheme 30. Synthesis of the Key Intermediates of Verrucarin A by Tamm et al.[809]



Reagents and conditions: (a) peracid oxidation. (b) $Me_3Si(CH_2)_2OH$, DCC, DMAP, CH_2Cl_2/DMF (80%). (c) *Eschenmoser*'s base (75%). (d) pig liver esterase (95%). (e) $BH_3{\cdot}SMe_2$, THF. (f) TBSCl, NEt_3, DMAP, CH_2Cl_2. (g) (1) LDA, THF; (2) $MoO_5{\cdot}Py{\cdot}HMPA$, −78 °C, 2 h (40%). (h) DHP, PPTS. (i) KOH, MeOH.

comitant elimination gave (*E*,*Z*)-half-ester **277**. The protected verrucarinic acid **282** was received in enantiomerically pure form from the achiral compound 3-methylglutaric acid dimethylester (**278**). For this purpose, the diester **278** was selectively cleaved with pig liver esterase (PLE), reduced with borane dimethylsulfide complex, and silylated. A selective α-hydroxylation with molybdenum oxide finally resulted in the verrucarinic acid derivative **281**, which was converted into the desired product **282** by protective group manipulation.

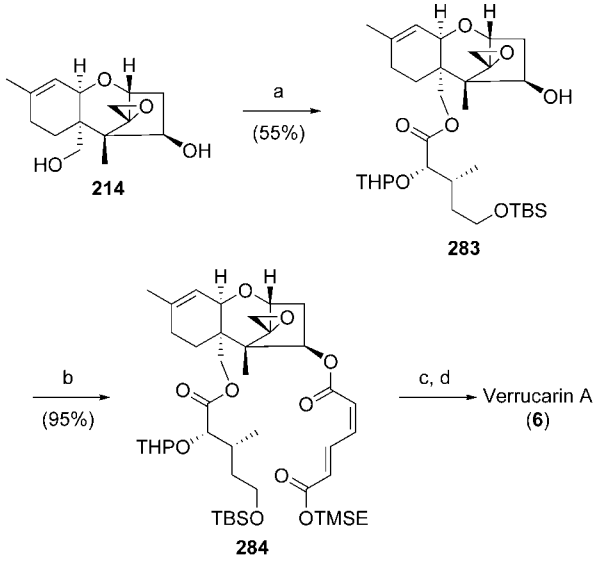
For the total synthesis, verrucarol (**214**) was successively esterified with **282** and **277** using the method developed by Steglich.[945] The primary and secondary hydroxyl functions were differentiated by their reactivity without any protecting groups. After deprotection of positions C-5′ and C-6′, a Yamaguchi macrolactonization and the cleavage of the THP−acetal with PPTS were conducted, yielding the mycotoxin verrucarin A (**6**, Scheme 31).

It should be noted that, one year earlier, Still et al. had published the very first total synthesis of verrucarin A (**6**). They started from naturally occurring anguidine (**217**) for the preparation of verrucarol (**214**), as well as propargyl alcohol and furfural as precursors of verrucarinic acid (**272**) and (*E*,*Z*)-muconic acid (**275**), respectively.[808] In 1984, the same research group also reported the first total synthesis of a roridin, namely, roridin E (**262**), as well as of baccharin B5 (**268**).[785]

In contrast to the synthesis of verrucarins (macrocyclic triesters), the macrocycle of roridines cannot be obtained by biomimetic lactonization. The macrocycle synthesis was achieved by intramolecular Horner−Wadsworth−Emmons reaction. The source of the C-6′ and C-13′ stereogenic centers was D-xylose (**285**), which was easily converted into **286** in four steps. The achiral C-1′−C-5′ segment was prepared from butynol (**287**) by ethoxycarboxylation of the lithium acetylide, conjugate methylation, and reduction. Coupling of the fragments **294** and **289** followed after conversion into the chloride; Jones oxidation finally yielded **290** (Scheme 32).

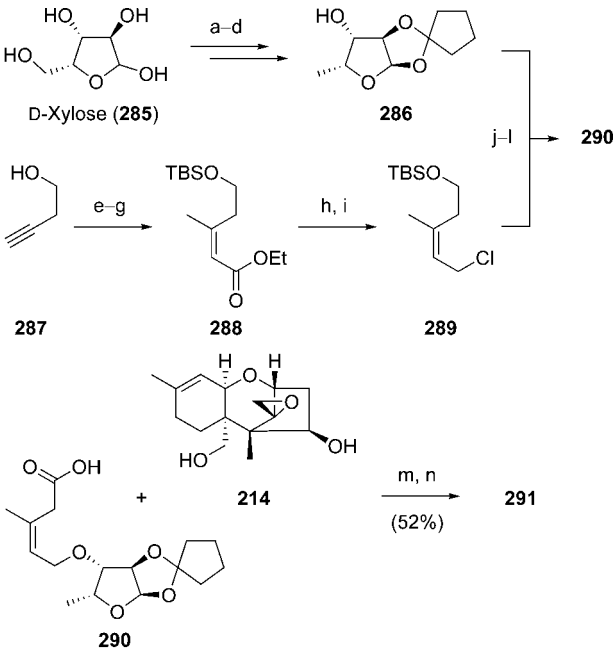
The sesquiterpenoid moiety verrucarol (**214**) was derived from anguidine (**217**)[946] or obtained by fermentation of *M.*

Scheme 31. Total Synthesis of Verrucarin A by Tamm et al.[809]



Reagents and conditions: (a) DCC, **282**, DMAP or PPy. (b) DCC, **277**, DMAP or PPy. (c) TBAF, THF. (d) (1) TCBACl, NEt_3, THF; (2) DMAP, toluene, reflux (50%).

Scheme 32. Synthesis of the Components of Roridin E (262) by Still et al.[785]

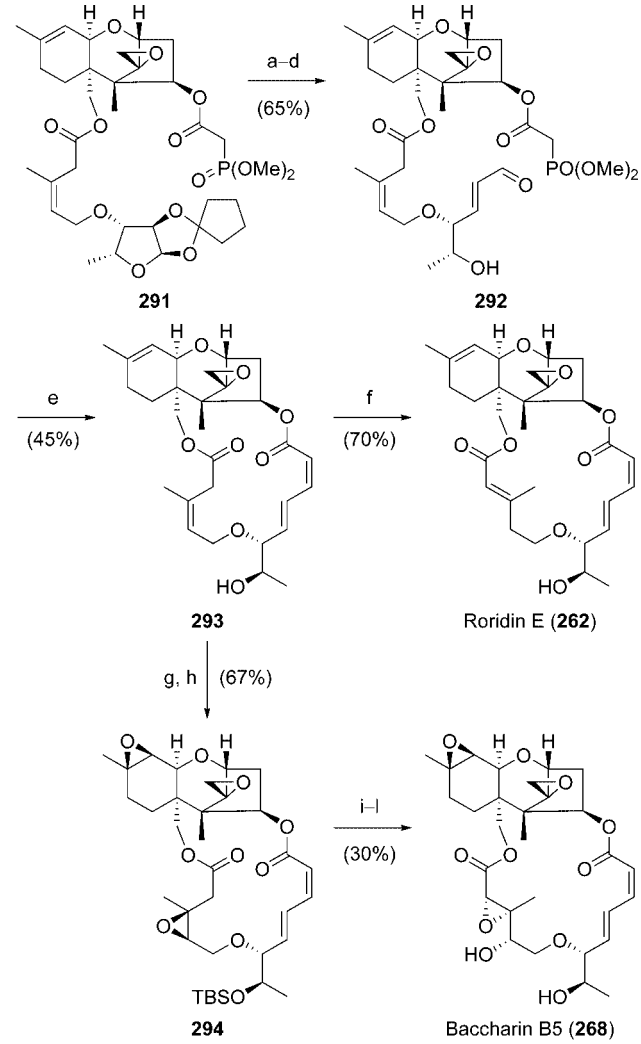


Reagents and conditions: (a) cyclopentanone, $CuSO_4$, cat. H_2SO_4. (b) 0.2% HCl. (c) TsCl, py. (d) LAH (65% over 4 steps). (e) TBSCl. (f) (1) BuLi; (2) $ClCO_2Et$. (g) Me_2CuLi. (h) LAH (45% over 4 steps). (i) NCS, Me_2S. (j) (1) **294**, NaH; (2) cat. TBAI, HMPA. (k) TBAF. (l) CrO_3, H_2SO_4 (75% over 4 steps). (m) DCC, 0.1 mol% 4-PPy (95% yield at 55% conversion). (n) $HO_2CCH_2PO(OMe)_2$, DCC, 4-PPy (quant.).

verrucaria (ATCC 24751, Strain UV-2). Esterification of its C-15 hydroxy group with **290** yielded an advanced intermediate that was subsequently converted into phosphono ester **291**, the precursor for the ring-closing olefination (see Scheme 33).

The concluding steps for the synthesis of roridin E (**262**) comprised, among others, the conversion into aldehyde **292** by deprotection, diol cleavage, deformylation, and chain elongation through a Wittig reaction. Macrocyclization to

Scheme 33. Total Synthesis of Roridin E (262) and Baccharin B5 (268) by Still et al.[785]



Reagents and conditions: (a) TsOH. (b) $NaIO_4$. (c) Et_3N, MeOH. (d) $Ph_3PCHCHO$ (65% over 4 steps, *E*/*Z* = 4:1). (e) K_2CO_3, 18-crown-6 (45%). (f) KO^{t}Bu (70%). (g) TBSOTf, lutidine (95%). (h) *m*CPBA (70%). (i) KO^{t}Bu (90%). (j) ^{t}BuOOH, $VO(acac)_2$ (90%). (k) HCO_2H, DEAD, PPh_3 (40% conversion/90% yield). (l) TBAF (99%).

the common precursor **293** of roridin E (**262**) and baccharin B5 (**268**) was achieved by Horner−Wadsworth−Emmons reaction. Isomerization of the (*Z*)-3′,4′-double bond into a (*E*)-2′,3′-double bond was effected by treatment with a base and yielded roridin E (**262**) after 16 linear steps (Scheme 33).

In the same article, the total synthesis of baccharin B5 (**268**) was reported. The use of achiral C-1′−C-5′ precursor **293** and the establishment of stereogenic centers on that segment by substrate-induced stereocontrol are the interesting features of this work. After silyl protection of **293**, the compound was treated with *m*CPBA and yielded the triepoxide **294** as a single product. Stereoselectivity was >15:1 for both the nuclear and the macrocyclic epoxide. Thus, four new stereogenic centers were established, apparently controlled by the conformation of the macrocycle. Elimination of the C-3′−C-4′ epoxide yielded the corresponding allylic alcohol with (*E*)-2′,3′-double bond. Moreover, allylic epoxidation produced the epimer of baccharin B5 (**268**), which was converted into the natural product by Mitsunobu reaction (inversion of C-4′).

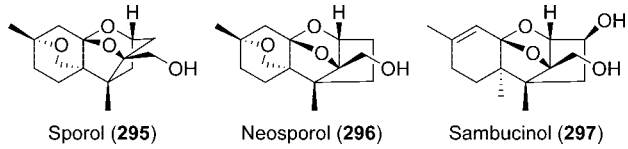
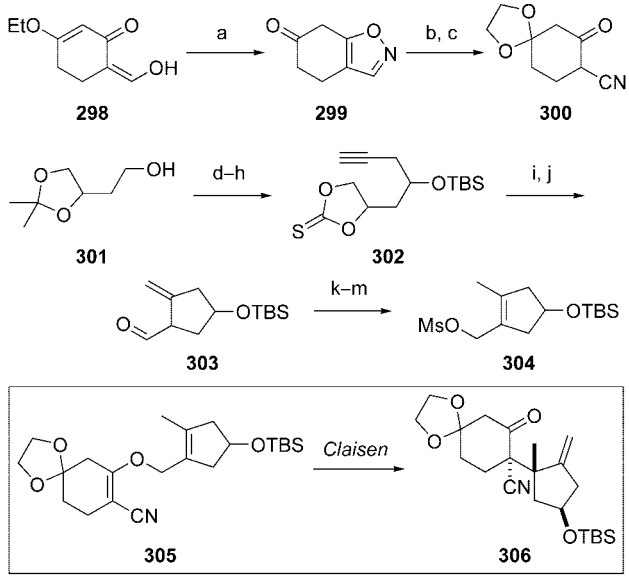


Figure 14. Structures of trichothecenes with a modified skeleton.

Scheme 34. Total Synthesis of Sporol (295) and Neosporol (296) by Ziegler et al. (Claisen Rearrangement Approach)[800]



Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, aq. EtOH, reflux (76%). (b) $HO(CH_2)_2OH$, TsOH, benzene (98%). (c) ^{t}BuOK, HMPA. (d) Swern. (e) propargyl bromide, Zn/Hg, THF (79% over 2 steps). (f) TsOH, MeOH. (g) $(Im)_2C{=}S$, CH_2Cl_2(51%). (h) TBSOTf, Et_3N, CH_2Cl_2, 0 °C (41% over 3 steps). (i) Bu_3SnH, AIBN, toluene, reflux (60%). (j) Dess-Martin. (k) DMAP, CH_2Cl_2 (84% over 2 steps). (l) $NaBH_4$, MeOH. (m) Ms_2O, Et_3N, DMAP.

2.7.4. Other Small Trichothecenes

Besides the trichothecenes already described, there exists a group of other small representatives of that mycotoxin class with a modified skeleton (non-classical trichothecane structure) as shown in Figure 14

Sporol (**295**) was isolated in 1986.[773] The initially proposed structure was synthesized in stages by Ziegler et al. in 1987[947] and proved to be neosporol (**296**). A structure revision in 1988[794] including the synthesis of neosporol (**296**)[795] and the new structure of sporol (**295**) which was confirmed through synthesis in 1992.[799] A full paper with both syntheses (shown in Schemes 34−36) was published in 1993 also by Ziegler et al.[800] The crucial step to build up the tertiary stereogenic centers is a Claisen rearrangement.[800]

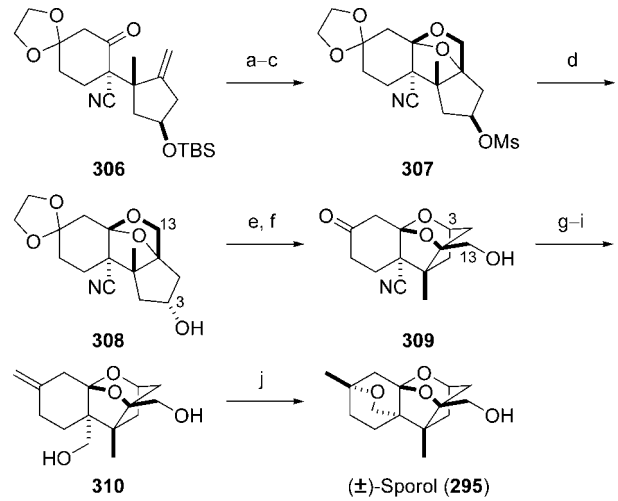
2.8. Zearalenone and Related Macrolactones

Zearalenone (**4**) and related metabolites belong to the class of benzannulated macrolactones (Figure 15).[948]

The nonaketide zearalenone (**4**) was first isolated from *Gibberella zeae* (perfect stage of *Fusarium graminearum*) in 1962.[949] It mostly occurs socialized with other *Fusarium* mycotoxins, albeit it is not categorized as toxic itself; even a sample of 20 g/(kg of weight) does not lead to death in rats.[950] Its activity in vivo resembles that of hormones; it presumably regulates the formation of the fruiting body of the fungus. This correlates with the anabolic activity of zearalenone (**4**) and its use in feed as an animal-growth promoter. Otherwise, zearalenone (**4**) possesses antibacterial and carcinogenic properties.[951] However, the best-known trait of zearalenone (**4**) and its derivatives is its estrogenic activity, which was described in 1971 by Mirocha in connection with the discovery of the mycotoxin.[952] α-Zearalenol (**316**) is 3−4 times more active as zearalenone (**4**) or the β-isomer **317**.[953] The degree of action can be explained by the topologic resemblance to estradiol and the resulting binding to the human estrogenic receptor ERβ. Thus, it can cause damage to tissues with high expression rates of this receptor. Given its properties, reports have been produced on mamma carcinomas, fetal skeleton anomalies, and uterotropic and embryopathic activity.[954]

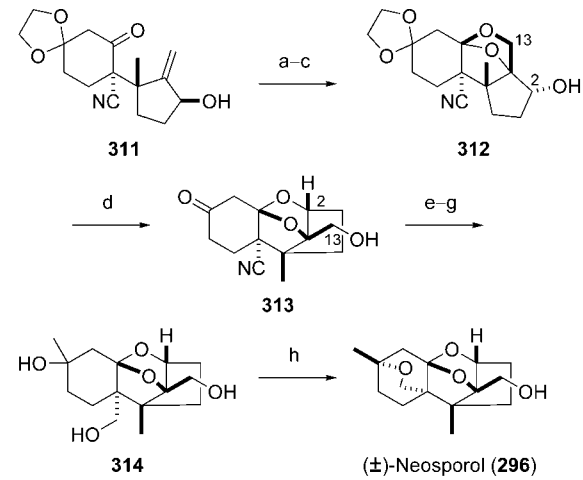
For zearalenone-like mycotoxins, there exist numerous total syntheses, with the major challenges being the establishment of the stereogenic centers and the formation of the 14-membered macrolactone. Enantioselective approaches

Scheme 35. Completion of the Total Synthesis of Sporol (295) by Ziegler et al.[800]



Reagents and conditions: (a) HF/CH_3CN, Na_2CO_3, CH_2Cl_2 (94%). (b) urea·H_2O_2, TFAA, Na_2CO_3, CH_2Cl_2 (45%). (c) Ms_2O, DMAP, Et_3N, CH_2Cl_2. (d) K_2O, DMSO, 18-crown-6. (e) CSA, CH_2Cl_2. (f) HCl (32% over 4 steps). (g) Ph_3PCH_3Br, ^{t}BuOK, THF, reflux (82%). (h) DIBAL; then aq. H_2SO_4. (i) DIBAL (37% over 2 steps). (j) CSA, CH_2Cl_2, reflux (45%).

Scheme 36. Completion of the Total Synthesis of Neosporol (296) by Ziegler et al.[800]



Reagents and conditions: (a) F_3CCO_3H, Na_2CO_3, CH_2Cl_2, 0 °C. (b) Swern (39% over 2 steps). (c) $LiAl(^tBuO)_3H$, THF (dr = 12:1). (d) 3 N HCl/dioxane, reflux (75%). (e) $MeCeCl_2$, THF (48%). (f) $LiAlH_4$, then aq. HOAc. (g) $LiAlH_4$ (80% over 2 steps). (h) $BF_3{\cdot}Et_2O$, CH_2Cl_2.

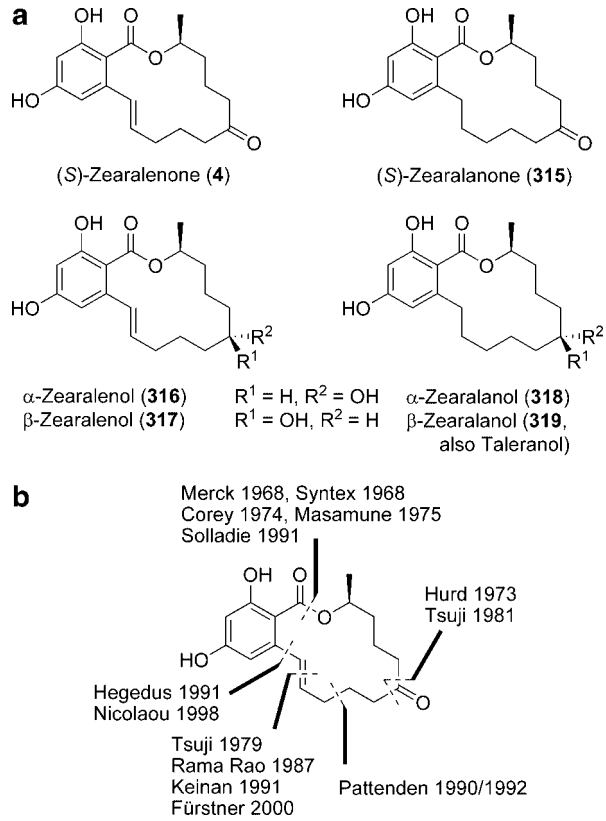


Figure 15. (a) Zearalenone family and (b) overview.

comprise classical resolution methods,[673] chiral pool strategies,[955] and asymmetric methods.[956] The different approaches for the cyclization step are shown in Figure 15b.

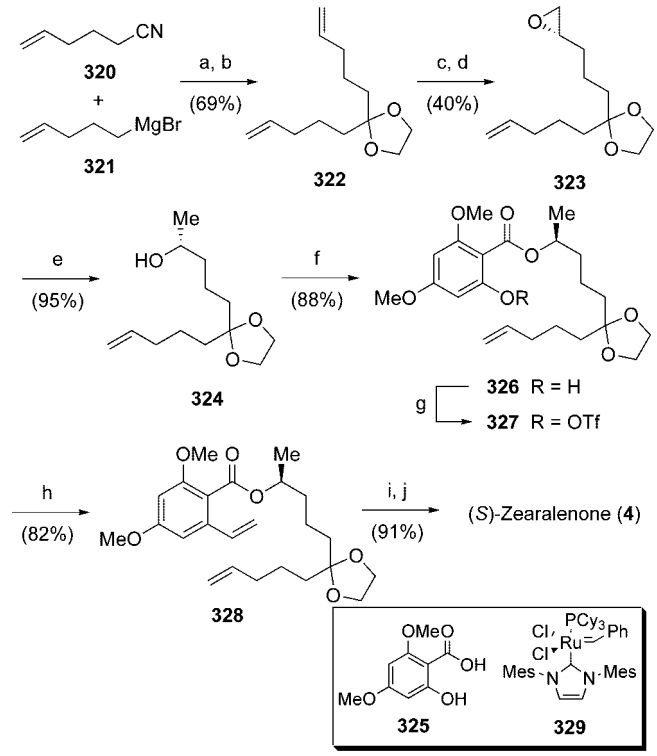
Early total syntheses from the 1960s and 1970s led to racemic material and mostly dealt with macrolactonization methods, such as the very first synthesis of zearalenone (*rac*-**4**) by the Merck group,[672] as well as the one by Syntex.[957] Important improvements were facilitated in the mid-1970s with the development of new techniques; for example, with their synthesis of zearalenone, Corey and Nicolaou presented their new mild macrolactonization method using thioesters[958] as well as the application of the Masamune reaction with thiophilic metal salts.[959] Other racemic approaches were those of Tsuji[671] or Hurd[655] with the quite atypical retrosynthetic disconnection at the ketone; the ring closure was accomplished by alkylation of a cyanohydrin or a Dieckmann condensation, respectively.

The first enantioselective synthesis of (*S*)-zearalenone (**4**) used an unusual 14-*endo*-*trig*-macrocyclization. In the last step of their synthesis, Pattenden et al. reacted a cinnamyl radical intramolecularly with an α,*β*-unsaturated electrophile to yield 55% of the desired macrocycle.[676,675]

The first enantioselective synthesis of (*S*)-zearalenone (**4**) using a macrolactonization was reported in 1991 by Solladie et al.,[960] who generated the chiral precursor via an asymmetric sulfoxide.

Olefination reactions are involved in a number of total syntheses of enantiopure (*S*)-zearalenone (**4**) as shown through the approaches of Tsuji,[961] Rama Rao,[962] Keinan,[951] and Fürstner.[673] The latter is the most recent total synthesis using a ring-closure metathesis (RCM) with a Grubbs II ruthenium catalyst **329** as the crucial step in the formation of the macrocycle. The enantiomerically pure starting material, epoxide **323**, was obtained by Jacobsen resolution[963] (Scheme 37).

Scheme 37. Total Synthesis of (*S*)-(−)-Zearalenone (4) by Fürstner et al.[673]



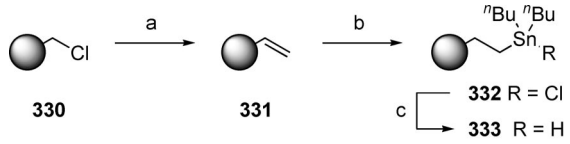
Reagents and conditions: (a) Et_2O, reflux, 3 h (70%). (b) ethylene glycol, PPTS cat., toluene, reflux, 4 h (98%). (c) *m*CPBA, CH_2Cl_2, 16 h (41%). (d) *Jacobsen* resolution (99%, 41% *ee*). (e) $LiBEt_3H$, THF, 1 h. (f) **325**, PPh_3, DEAD, Et_2O, rt, 3 h. (g) Tf_2O, py, CH_2Cl_2, 3 h (89%). (h) ethylene (40 bar), LiCl, Et_3N, $PdCl_2(PPh_3)_2$ (5 mol%), DMF, 90 °C. (i) **4** (5 mol%), toluene, 80 °C, 4 h (91%). (j) (1) aq. acetone, TsOH, 40 °C, 26 h (97%); (2) BCl_3, BBr_3, CH_2Cl_2, 0 °C, 10 min (55%).

The enantioselectivity was only moderate in that step, but the symmetric starting material **322** was readily available. The chiral epoxide **323** was opened regioselectively with lithium triethylborohydride, so that the secondary alcohol **324** was on hand for esterification with **325** under Mitsunobu conditions. A subsequent Heck reaction gave the styrene derivative **328**, which was cyclized via metathesis. Removal of the protective groups yielded (*S*)-zearalenone (**4**) in 15% yield after 10 steps (Scheme 37).

An alternative retrosynthetic disconnection at the macrocycle can be placed next to the aromatic moiety (see Figure 15) corresponding to a vinyl aryl cross-coupling. This strategy was chosen by Hegedus et al., who conducted a Stille type coupling between an aryl iodide and a vinyl tin reagent in their total synthesis in 1991.[652] An extension to this approach was presented seven years later by the Nicolaou group (Scheme 39). They used the Stille reaction under cleavage from the polymer resin and concomitant cyclization to the product (Scheme 38).[955] Starting from tin reagent **332** or **333** on solid supports (for preparation, see Scheme 38), the aliphatic part of the mycotoxin was built up and finally esterified under Mitsunobu conditions with the aromatic moiety **340**. The palladium-catalyzed cross-coupling provided the cyclized product in the liquid phase, so that only the conclusive removal of the protecting groups was not accomplished on the resin.

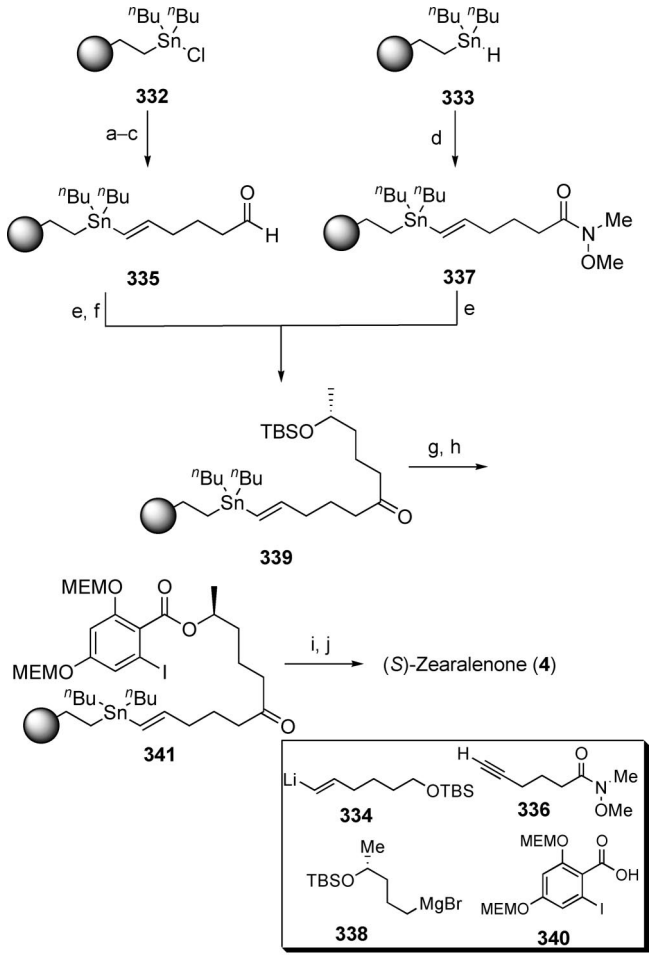
The related lactones α-Zearalenol (**316**) and *β*-Zearalenol (**317**) contain two stereogenic centers at the aliphatic macrocycle. However, they lie so far apart that direct substrate control is out of the question even in the presence

Scheme 38. Polymer-Bound Tin Reagent for Stille Coupling under Cleavage and Cyclization



Reagents and conditions: (a) (1) K_2CO_3, DMSO, 145 °C, 15 h; (2) $Ph_3P{=}CH_2$, THF, rt, 8 h. (b) $^nBu_2SnCl_2$, nBu_2SnH_2, AIBN, *hν*, toluene, 0 °C, 4 h (90% over 2 steps). (c) LiBH4, THF, rt, 4 h.

Scheme 39. Total Synthesis of (*S*)-(−)-Zearalenone (4) by Nicolaou et al.[955]

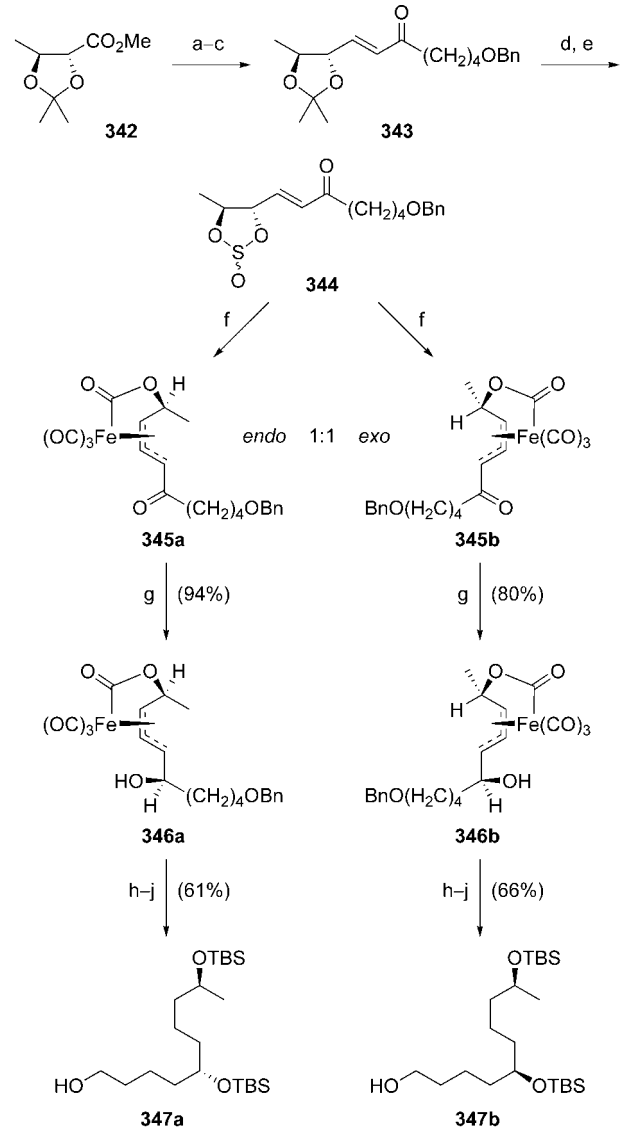


Reagents and conditions: (a) **334**, THF, –78 °C → rt, 4 h (87%). (b) TBAF, THF, rt, 5 h (94%). (c) NCS, Me_2S, 0 °C, 15 min; then addition of resin, 0 °C, 1 h; then Et_3N, 0 °C → rt, 30 min. (d) **336**, AIBN, toluene, 100 °C, 4 h (90%). (e) **338**, THF, 0 °C → rt, 4 h (92% c+e). (f) see c) (97%). (g) TBAF, THF, rt, 13 h. (h) **340**, PPh_3, DIAD, 0 °C → rt, 6 h (76% g+h). (i) $Pd(PPh_3)_4$, toluene, 100 °C, 48 h (54%). (j) 5% HCl/THF (1:2), rt, 5 d (80%).

of one stereogenic center. Regardless, the total synthesis by Ley et al. provides access to both diastereomers.[956] Formation of the chiral π-allyl tricarbonyl iron complex **345a** or **345b** fixed the conformation of the aliphatic chain, so that the stereoinformation was located closer to the position of the newly built stereogenic center. Thus, the reduction with tripropyl aluminum was conducted asymmetrically, and after decomplexation with sodium triacetoxyborohydride, the epimeric precursors of the macrocycle, **347a** or **347b**, respectively, could be prepared separately (Scheme 40).

After transformation into the corresponding tin organyl **348a**, and subsequent Stille coupling with **349**, the open-chain precursor **350a** was generated. Removal of the protecting groups yielded the dihydroxy acid, which was subjected to a Mukaiyama macrolactonization,[964] and after cleavage of the MEM-groups (β-methoxyethoxymethyl ether), α-Zearalenol (**316**) and—in the same manner—β-Zearalenol (**317**) were obtained (Scheme 41).

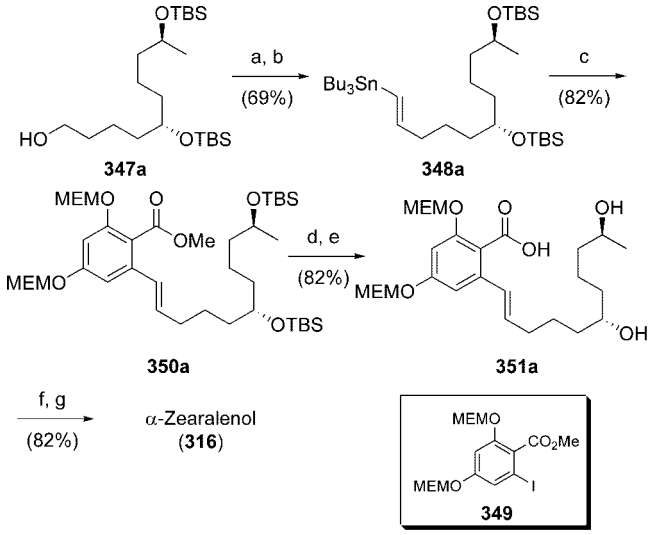
Scheme 40. Total Synthesis of Zearalenol by Ley et al. (Part 1)[956]



Reagents and conditions: (a) $LiAlH_4$, Et_2O, 0 °C, 2 h. (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 3 h. (c) $(EtO)_2P(O)CH_2CO(CH_2)_4OBn$, NaH, THF, –78 °C, 1 h (83% over 3 steps). (d) AcOH/H_2O (1:1), 40 °C, 24 h (92%). (e) $SOCl_2$, Et_3N, Et_2O, 0 °C, 30 min (89%). (f) $Fe_2(CO)_9$, benzene, sonication, 30 °C, 3 h (70%, dr = 1:1). (g) Al^nPr_3, CH_2Cl_2, 0 °C. (h) $NaBH(OAc)_3$, THF, 3 d. (i) TBSCl, imidazole, DMF, 0 °C, 30 min, then rt, 24 h. (j) Pd/C (10%), H_2, EtOAc, 30 min.

Further members of this mycotoxin subclass are shown in Figure 16. They also contain a 12- or 14-membered macrocycle but differ in the substitution patterns. Radicicol (**352**), the monocillins, and the pochonins exhibit an α,β-unsaturated ketone for example. Hypothemycin (**355**) is a more exotic relative that has recently been demonstrated as a potent and irreversible inhibitor of selected kinases bearing a cysteine residue in the ATP-binding pocket.[965] Its structure was falsely assigned at first, and the revised structure was not published until 1993.[966] A convergent stereospecific synthesis followed in 2002 by Sellès and

Scheme 41. Total Synthesis of Zearalenol by Ley et al.[956] (Part 2)



Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 3 h (86%). (b) Bu_3SnCHI_2, $CrCl_2$, DMF, 0 °C (67%). (c) **349**, $Pd_2(dba)_3$, $P(fur)_3$, toluene, 100 °C, 4 h (82%). (d) HF·py, pyridine, THF, 12 h (95%). (e) 10 M aq. KOH, $HO(CH_2)_2OH$, 120 °C, 4 h (87%). (f) syringe pump addition of **351a**, Et_3N, MeCN over 10 h to 1-methyl-2-chloropyridinium iodide, MeCN, reflux (64%). (g) 1.5 M aq. HCl, THF, 40 °C (93%).

Lett.[967] Queenslandon (**357**), an antifungal agent produced by *Chrysosporium queenslandicum* (class of *Ascomycetes*),[968] and the Aigialomycins[654] resemble more closely the zearalenone family. Several approaches exist in order to achieve total synthesis, e.g., a concise strategy to the core structure (macrolide) of Queenslandon (**357**) by Maier et al. from the year 2006.[669] The Aigialomycins, especially Aigialomycin D (**356**), were elaborated by Danishefsky,[655] Winssinger,[656] and Pan.[657] More recently, *cis*-enone resorcylic acid lactones related to hypothemycin have attracted the attention of synthetic chemists for their potent kinase inhibitory activity.[969]

The resorcylic acid lactone radicicol (**352**), first synthesized by Lett et al.,[970] came into focus after a NCI (National Cancer Institute) screening, as it proved to be a very potent inhibitor

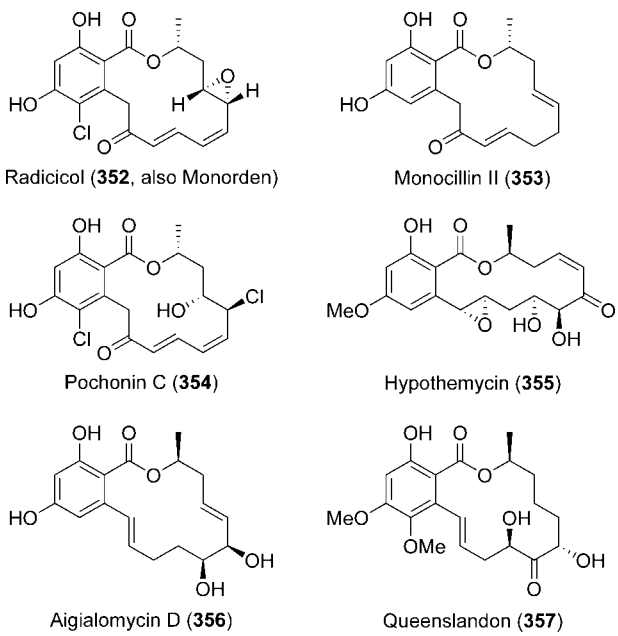
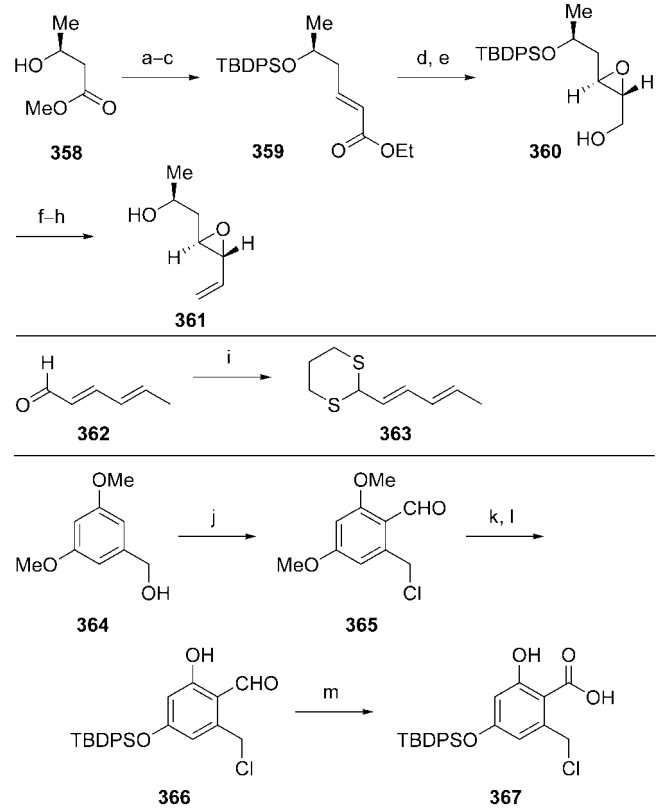


Figure 16. Related mycotoxins.

Scheme 42. Total Synthesis of Radicicol by Danishefsky et al.[663] (Part 1)



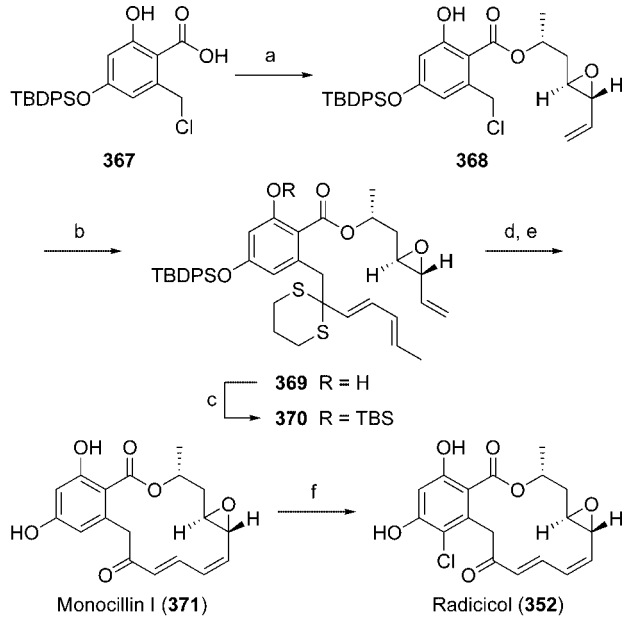
Reagents and conditions: (a) TBDPSCl, imidazole (>95%). (b) DIBAL, –78 °C (92%). (c) LiCl, DIPEA, $(EtO)_2P(O)CH_2CO_2Et$ (95%). (d) DIBAL, –20 °C (96%). (e) (+)-DET, $Ti(O^iPr)_4$, ^tBuOOH (90%, >95% *ee*). (f) SO_3·py, Et_3N, DMSO (90%). (g) Ph_3PCH_3Br, NaHMDS, 0 °C (82%). (h) TBAF (89%). (i) $HS(CH_2)_3SH$, $MgClO_4$, H_2SO_4 (64%). (j) $POCl_3$, DMF, 75 °C (93%). (k) BBr_3 (85%). (l) TBDPSCl (95%). (m) $NaClO_4$ (95%).

of the ATP-dependent chaperone Hsp90. The latter takes part in the folding of various oncogenic enzymes in cells that are exposed to external stress.[971–973] Radicicol docks in the ATP-binding pocket with an IC_{50} of 19 nM.[974] Thus, it is the most potent competitive antagonist of ATP in Hsp90. However, radicicol cannot be employed therapeutically, because it shows no activity in vivo. Efforts have been made to find synthetic alternatives that can be metabolized less rapidly. A prominent example is Cycloproparadicicol, synthesized by Danishefsky et al. with the epoxide oxygen replaced by a methylene group.[975–977]

The first synthesis of radicicol dimethylether[978] was published by Danishefsky et al. in 2000. The natural product was not obtained, as the conditions for the ether cleavage resulted in epoxide opening and decomposition. After modification of the strategy, the total syntheses of radicicol (**352**) and monocillin I (**371**) were reported in 2001.[663] The highly convergent syntheses were accomplished by the coupling of three key intermediates **361**, **363**, and **367** and final RCM. Alcohol **361** was obtained from (*S*)-3-hydroxybutyric acid (**358**). DIBAL-H-reduction to the aldehyde with subsequent Wadsworth–Horner–Emmons homologation under Roush–Masamune conditions yielded ester **359**. A second reduction to the *trans*-allylic alcohol and Sharpless-epoxidation gave epoxide **360** that was transformed into vinylepoxide **361**, containing all required stereogenic centers, through Parikh–Doering oxidation and Wittig reaction.

The second component, dienyldithiane **363**, was generated from 2,4-hexadienal (**362**) through treatment with pro-

Scheme 43. Total Synthesis of Radicicol by Danishefsky et al.[663] (Part 2)



Reagents and conditions: (a) **361**, $P(fur)_3$, DIAD, benzene, 24 h (75%). (b) **363**, *n*BuLi, −78 °C (50%). (c) TBSCl (88%). (d) *Grubbs II* catalyst **329**, 42 °C (60%). (e) (1) *m*CPBA; (2) Ac_2O, Et_3N, H_2O, 60 °C; (3) $NaHCO_3$, MeOH (60%). (f) SO_2Cl_2 (58%).

panedithiol. The resorcylic acid derivative **367** was obtained from 3,5-dimethoxybenzylic alcohol (**364**) by Vilsmeier−Haack formylation with concomitant formation of the chloride, manipulation of the protective groups, and Krauss oxidation (Scheme 42).

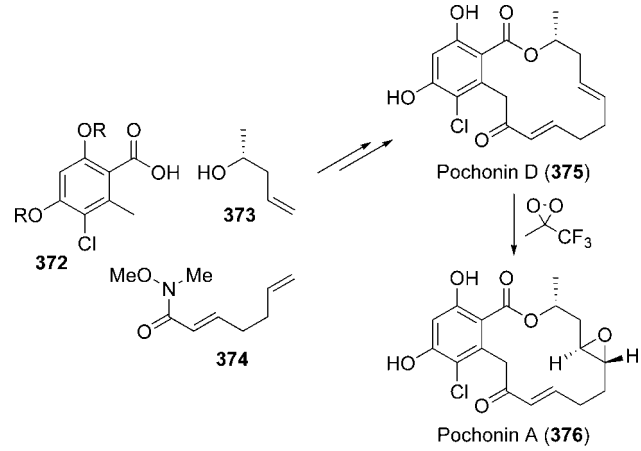
Esterification of **367** with **361** under Mitsunobu conditions and reaction with the acylanion equivalent of **363** gave the open-chain precursor **369**. The following metathesis with a second-generation Grubbs catalyst resulted in the natural product monocillin I (**371**) that was transformed into radicicol (**352**) by chlorination of the aromatic core (Scheme 43).

A closely related class of mycotoxins has gained attention since its discovery in 2003. The pochonins A−F were isolated from the fermentation broth of *Pochonia chlamydosporia* var. *catenulata* and characterized.[979] The absolute configuration of pochonin C (**354**) was elucidated by total synthesis in 2004 by Winssinger et al., confirming the assumption that pochonin C is formed by epoxide opening from radicicol (**352**).[667]

Tests concerning the biological properties of the pochonins exhibited activity against *Herpes Simplex* virus as well as antiparasitic activity (*Eimeria tenella*). In contrast to the structurally related zearalenone (**4**), none of the pochonins has an effect on the human estrogenic receptor ERβ. Potential antitumor activity was examined after the total syntheses of pochonin D (**375**) and pochonin A (**376**) by the Winssinger group. Following the total synthesis of pochonin C (**354**) and one further solid-phase-assisted synthesis,[665] the group presented a short route to the simplest representative of the class, pochonin D (**375**), in a study of potential Hsp90 inhibitors.[668] On the basis of this approach, the synthesis of pochonin A (**376**) followed with just one additional epoxidation step (Scheme 44).[666]

Essentially, the synthesis comprised an esterification of the *ortho*-methylresorcylic acid derivative **372** with the chiral secondary alcohol **373**, an addition to the Weinreb amide **374**, and a metathesis reaction for the macrocyclization. The

Scheme 44. Synthesis of Pochonin D and A According to Winssinger et al.[666,668]



epoxidation was accomplished with modest selectivity through treatment with methyl(trifluormethyl)dioxirane.

2.9. Other mycotoxins

Although many mycotoxins are presented in the literature, only a few have yet been synthesized.

2.9.1. Alternaria metabolites

Among the various secondary metabolites produced by *Alternaria* fungi, the resorcyclic lactones alternariol (**11**) and alternariol 9-methyl ether (**377**) represent the main toxic metabolites (Figure 17).[980]

Although their toxicity is low compared to other prominent mycotoxins, as, for example, the aflatoxins,[981] their relevance in the context of rotting fruits and crop has led to considerable interest within the synthetic community. Recently, Podlech and co-workers developed an interesting synthetic access to alternariol (**11**), which is based on a Suzuki coupling as the key step.[65,982] A summary of their synthesis is given in Scheme 45: Suzuki coupling of aldehyde precursor **378** and boronic acid **379** formed biaryl **380**, which, upon oxidation and demethylation, generated a separable mixture of alternariol (**11**) and alternariol 9-methyl ether (**377**). The complete synthesis comprises seven steps and produces **11** and **377** in good overall yield.

In the past decades, various groups have also developed total syntheses of alternariol and structural analogues.[64,983−985] In this context, a special emphasis has been placed on biomimetic syntheses of **11** and **377**. Harris et al. reported on the cyclization of hemiketals **383** and **384**, which are formed from the triketo ester precursors **381** and **382** upon the cleavage of the benzyl protecting group (Scheme 46).[983] The cyclization of these hemiketals under weak basic conditions led to the direct formation of alternariol 9-methyl ether (**377**) and alternariol (**11**), respectively. From a mechanistic viewpoint, this reaction was thought to proceed

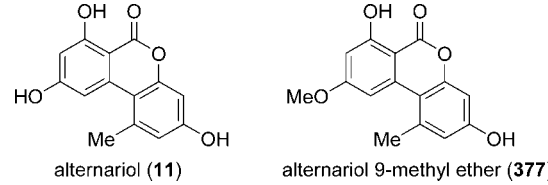
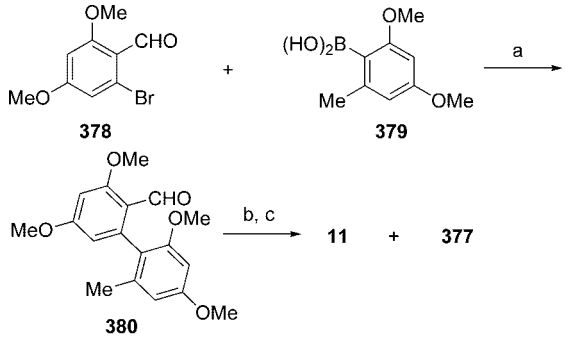


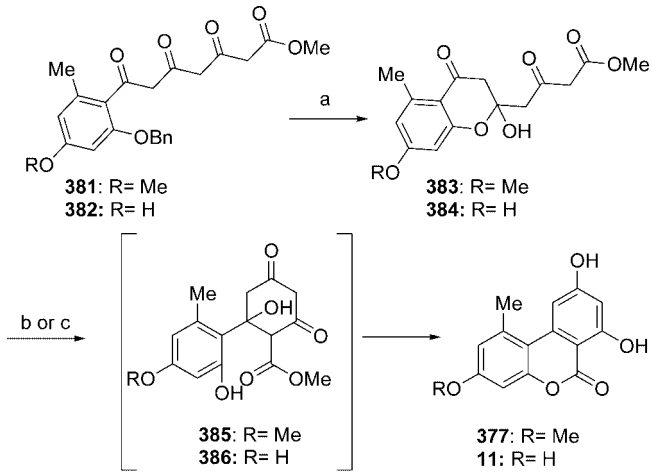
Figure 17. Molecular structures of alternariol (**11**) and alternariol 9-methyl ether (**377**).

Scheme 45. Synthesis of Alternariol (11) and Alternariol 9-Methyl Ether (377) by Podlech et al.[65]



Reagents and conditions: (a) K_2CO_3, 10 mol% $Pd(PPh_3)_4$, DMF, 100 °C, 4 h (78%). (b) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, *t*BuOH/H_2O (5:1), rt, 2 h (85%). (c) BBr_3, CH_2Cl_2, 0 °C, 24 h (73% of **11**) and (20% of **377**).

Scheme 46. Biomimetic Synthesis of Alternariol (11) and Alternariol 9-Methyl Ether (377) by Harris et al.[983]



Reagents and conditions: (a) H_2, Pd/C, EtOH, rt, (86%, R=Me), (70%, R=H). (b) NaOAc, MeOH, rt, 23 h (64%, R=Me). (c) NaOAc, HOAc, MeOH, rt, 9 d, (52%, R=H).

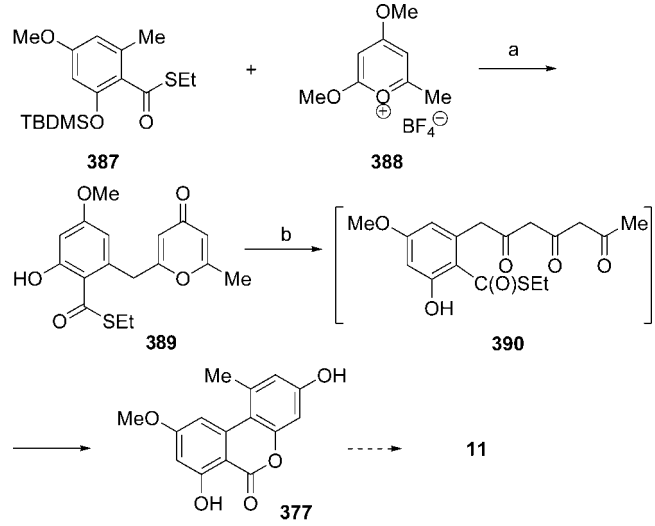
through the hemiketal opening of **383** and **384**, followed by aldol condensation to yield the common intermediates **385** and **386**, which subsequently undergo lactone formation and aromatization to give **11** and **377**. The success of this synthetic strategy gave strong support for the proposed mechanism of biosynthesis, which is also likely to proceed through aldol condensations and lactone formation of a C-14-polyketide chain.[15]

Another biomimetic approach to **11** and **377** was reported by Staunton and co-workers.[984] They employed a nucleophilic addition to the β-carbon of pyrylium salts as the key step. To this end, the addition of lithiated orsellinate thioester **387** to the tetrafluoroborate pyrylium salt **388** yielded pyrone **389**, after the cleavage of the silyl protecting group (Scheme 47). This pyrone served as a precursor for the tricarbonyl compound **390**, which is believed to be a biosynthetic intermediate in the formation of **11** and **377**. Treatment of pyrone **389** with alcoholic sodium hydroxide solution led to the exclusive formation of alternariol 9-methyl ether **377**, which was then transformed into alternariol **11**.[985]

By altering the reaction conditions for the formation of **377**, the proposed cyclization intermediate **390** could also be isolated; thus, further studies toward its potential in vivo behavior were performed.

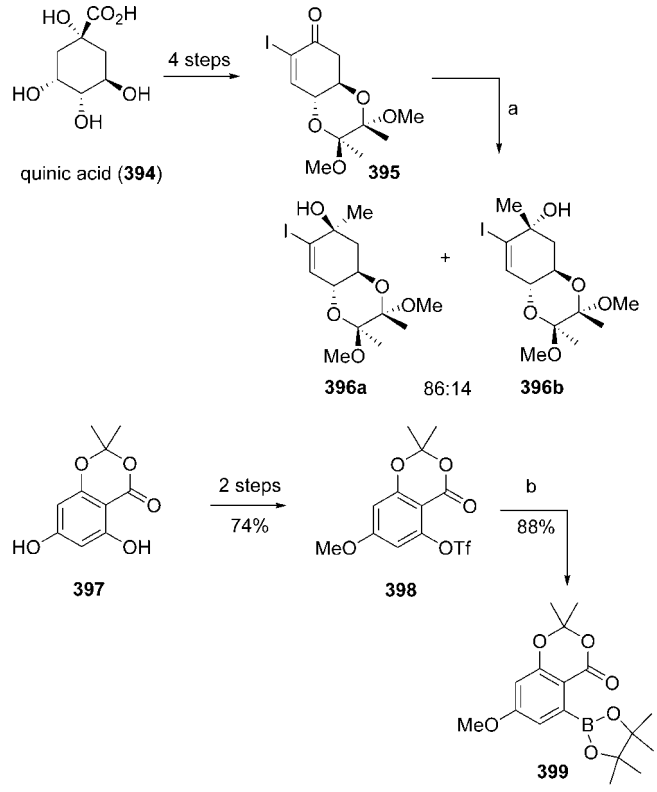
Altenuene (**391**), isoaltenuene (**392**), and dehydroaltenusin (**393**) represent minor secondary metabolites of *Alternaria*

Scheme 47. Biomimetic Synthesis of 11 by Staunton et al.[984]



Reagents and conditions: (a) LDA, THF, –78 °C, acidic workup, (20%). (b) NaOH, MeOH/H_2O (1:4), acidic workup, (80%).

Scheme 48. Preparation of Key Intermediates 396 and 399 by Podlech et al.[52]

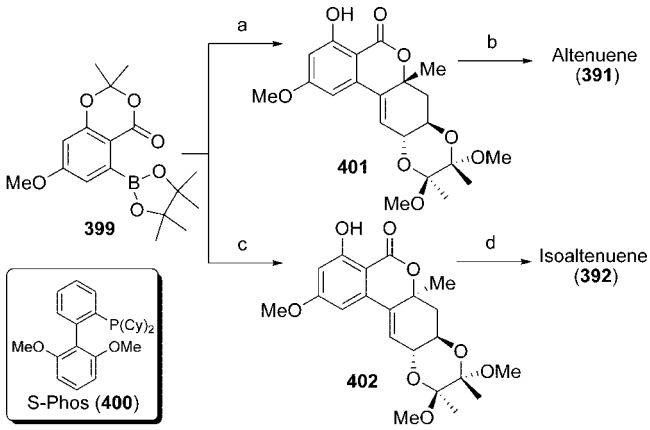


Reagents and conditions: (a) 2 equiv. MeMgBr, THF, –40°C → rt, (68%). (b) 3 equiv. pinacol borane, 3 equiv. Et_3N, 5 mol% $Pd(PPh_3)_4$, dioxane, 80 °C, 2 h, (88%).

fungi and a variety of other species (Figure 18).[70,71,986] While altenuene displayed interesting cytotoxic activity in screenings for biological activity, dehydroaltenusin was reported to be a strong mammalian DNA-polymerase α inhibitor.[987,988]

Very recently, Podlech et al. published a short total synthesis of altenuene (**391**) and isoaltenuene (**392**) starting from quinic acid (**394**) and comprising 10 synthetic steps.[52] The synthesis of the key intermediates is outlined in Scheme 48: according to the literature, 2-iodocyclohexenone **395** was prepared starting from quinic acid (**394**). Reaction of **395** with methyl magnesium bromide gave a mixture of diaster-

Scheme 49. Completion of the Total Synthesis of 391 and 392 by Podlech et al.[52]



Reagents and conditions: (a) **396b**, 2 mol% $Pd(OAc)_2$, 4 mol% **400**, 3 equiv. Cs_2CO_3, dioxane/H_2O 5:1, 80 °C, 2 h. (70%). (b) TFA/H_2O 9:1, 10 min., RT, (55%). (c) **396a**, 2 mol% $Pd(OAc)_2$, 4 mol% **400**, 3 equiv. Cs_2CO_3, dioxane/H_2O 5:1, 80 °C, 2 h. (72%). (d) TFA/H_2O 9:1,10 min., RT, (62%).

eomers **396a** and **396b** that could be separated by chromatography and employed in the synthesis of **391** and **392**, respectively. Boronic ester **399**, on the other hand, was prepared in three steps starting from commercially available acetal **397** (Scheme 48).

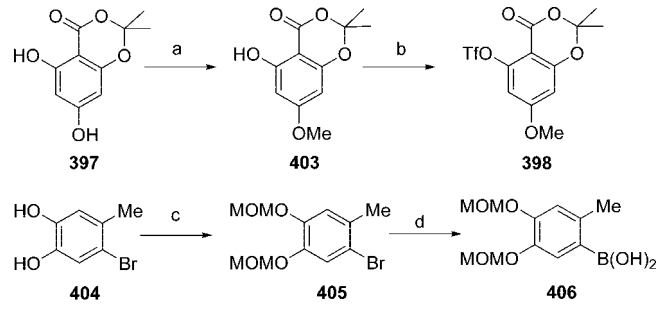
Subsequent Suzuki coupling of **396a**,**b** and boronic ester **399** was most effectively accomplished using the S-Phos ligand (**400**) developed by Buchwald and co-workers,[989] together with palladium acetate as the catalyst precursor (Scheme 49). Interestingly, application of these reaction conditions resulted not only in Suzuki coupling but also in the direct formation of lactones **401** and **402** through cleavage of the acetal group in precursor **399**. Consequently, lactones **401** and **402** could be isolated in good yields and gave altenuene (**391**) and isoaltenuene (**392**), respectively, upon acidic cleavage of the diol protecting group (Scheme 49).

When comparing the absolute configuration of synthesized altenuene (**391**) with a microbiologically prepared sample (commercially available through Sigma-Aldrich), Podlech and co-workers discovered that the enantiomeric excess of natural altenuene is only 2%. Although further experiments regarding this finding have not thus far been performed, it seems likely that the low enantiomeric excess is related to the biosynthesis of altenuene and its related metabolites.

Dehydroaltenusin (**393**) has been isolated from *Alternaria tenuis* and a variety of other fungi. Because of its promising biological activity,[988] which has been mentioned above, it is an interesting target for total synthesis. In 2003, Takahashi and co-workers reported the first total synthesis of **393** (Scheme 51).[61,69] By employing a Suzuki coupling as the key step,[982] **393** was reduced to triflate **397** (compare to Scheme 47) and aryl boronic acid **406** as the key precursors, which were readily available in only a few synthetic steps (Scheme 50).

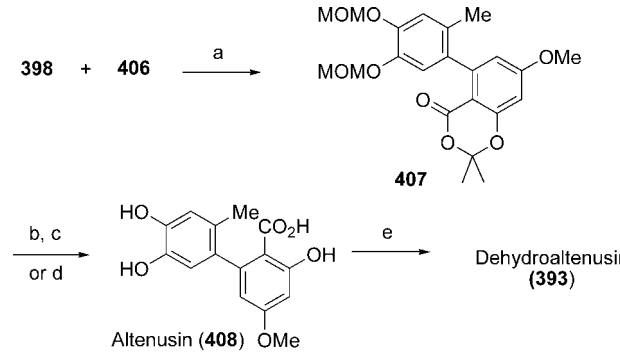
Palladium-catalyzed cross-coupling of **398** and **406** gave rise to biaryl **407** in good yield, which was subsequently transformed into altenusin (**408**) by sequential cleavage of the protecting groups (Scheme 51). Essentially the same results could be achieved by simply treating biaryl **407** with boron trichloride, thus cleaving both the methoxymethyl (MOM) and acetonide groups. The final oxidation of altenusin (**408**)—yielding dehydroaltenusin (**393**)—was performed using iron trichloride, producing an 82% yield.

Scheme 50. Synthesis of Key Intermediates 398 and 406 by Takahashi et al.[61,69]



Reagents and conditions: (a) 1.05 equiv. DIAD, 1.05 equiv. PPh_3, 1.05 equiv. MeOH, THF, rt, (89%). (b) 1.10 equiv. Tf_2O, pyridine, 0 °C, (94%). (c) 2.50 equiv. MOMCl, 2.50 equiv. NaH, DMF, 0 °C, (90%). (d) 1.10 equiv. *n*-BuLi, THF, –78 → –40 °C, then 1.10 equiv. $B(O/Pr)_3$, Et_2O, –78 °C → rt, (95%).

Scheme 51. Completion of the Total Synthesis of Dehydroaltenusin (393) by Takahashi et al.[61,69]



Reagents and conditions: (a) 5 mol% $Pd(PPh_3)_4$, 1.50 equiv. K_3PO_4, 1.00 equiv. KBr, dioxane, 100 °C, (93%). (b) 2N KOH, EtOH, 60 °C. (c) 10% HCl-MeOH, CH_2Cl_2, rt, (64% over two steps). (d) 10.0 equiv. BCl_3, CH_2Cl_2, 0 °C → rt, (60%). (e) $FeCl_3$, aq. EtOH, rt, (82%).

In summary, the total synthesis of racemic **393** comprised seven steps with an overall yield of 18%. Further studies regarding an asymmetric synthesis of **393** or structural analogues might be difficult given that it racemizes quickly via a five-membered dehydroaltenusin II (see Scheme 69).

2.9.2. Skyrins

The skyrins represent an interesting class of bisanthraquinone natural products that have recently attracted considerable interest. Some of the most prominent members (see Figure 19) of this class of mycotoxins are cytoskyrin A (**9**),[129] rugulin (**409**),[990] and rugulosin (**410**, Figure 19).[134,991]

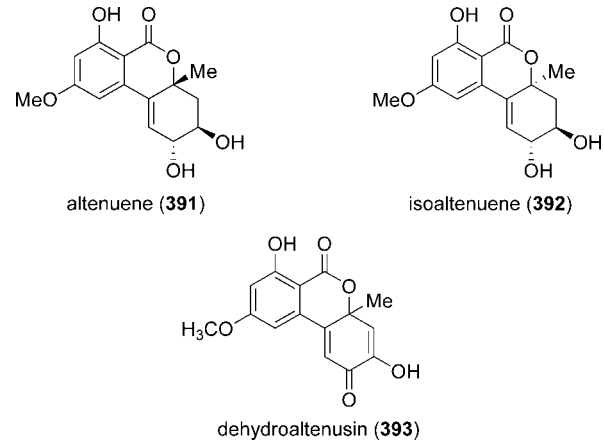


Figure 18. Molecular structures of altenuene (**391**), isoaltenuene (**392**), and dehydroaltenusin (**393**).

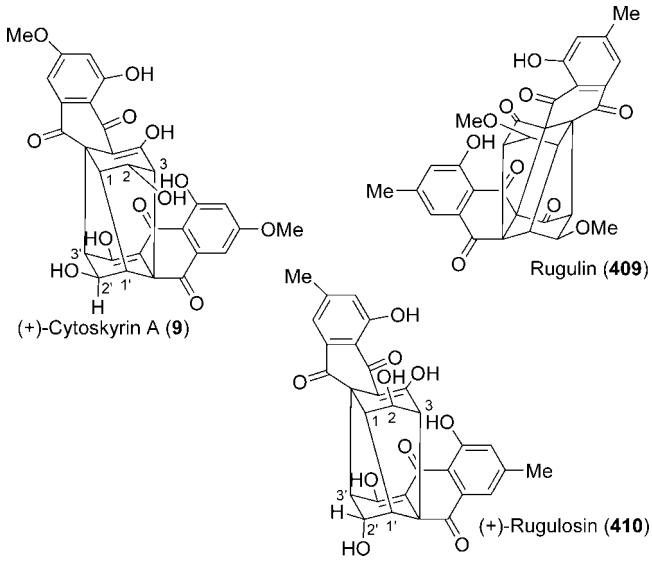


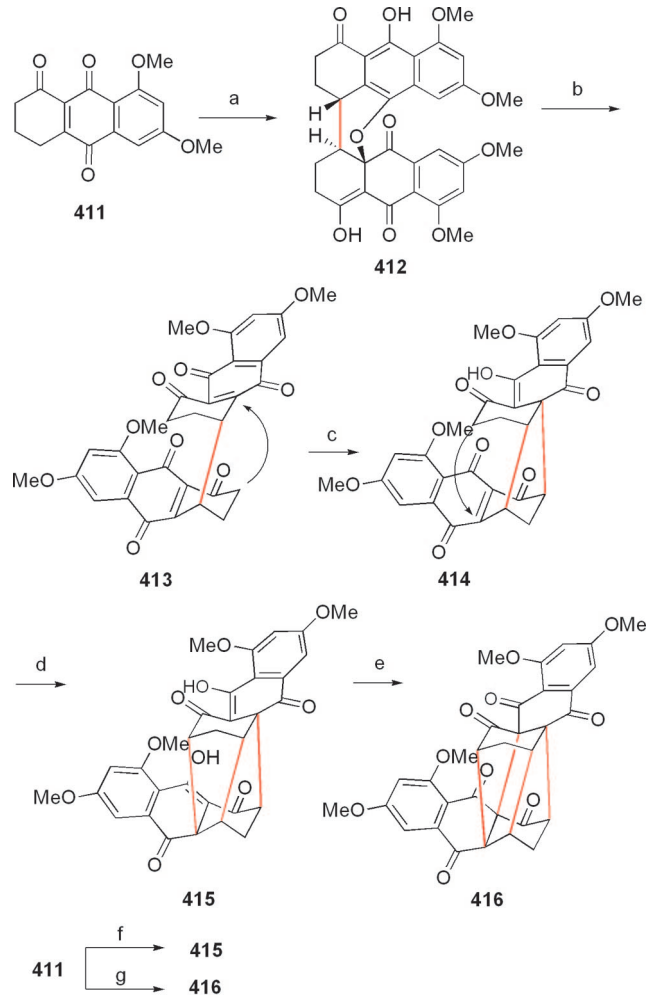
Figure 19. Prominent bisanthraquinone natural products.

Isolated from an endophytic fungus (*Cytospora* sp.), cytoskyrin A (**9**)[129] displays particularly promising biological activity such as strong cytotoxicity (12.5 ng mL^{-1}) in the biochemical induction assay (BIA). Because of these facts and their challenging cagelike structures, the skyrins represent interesting targets for total synthesis.

Recently, Nicolaou and co-workers developed an elegant synthetic access to cytoskyrin A (**9**)[129] and rugulosin (**410**),[991] which was based on a cascade reaction ("cytoskyrin cascade").[132] In preliminary model studies, it was established that readily available quinone **411** could be converted into **412** in a single step involving enolization and dimerization (Scheme 52). The dimer **412** could in turn be oxidized to yield bisanthraquinone **413** in good yield. With this intermediate in hand, further studies toward cagelike model systems were performed. In this context, exposure of **413** to mild basic conditions resulted in C−C-bond formation through enolization, furnishing the dimeric intermediate **414**. However, an even more complex structure **415** could be obtained through prolonged exposure of **413** to basic conditions.

Although the step-by-step formation of the cytoskyrin-type structure **415** and its transformation into the rugulin-type structure **416** (through oxidation) were themselves impressive, the Nicolaou group found an even more pleasing solution to this synthetic challenge. Since all synthetic steps mentioned previously only required weak bases (NEt_3) or oxidants (MnO_2), it was reasoned that **415** and **416** should also be accessible in a one-pot cascade sequence. Consequently, **411** could be converted with excellent yields into the nonacyclic cytoskyrin system **415** in one synthetic operation involving five steps (enolization−dimerization−oxidation−double intramolecular Michael reaction). Under very similar conditions, **411** was transformed into the rugulin-type model system **416** in a one pot-procedure. These elegant transformations, which were elucidated by careful reactivity analysis of the given systems, highlight the power of cascade reactions in targeting complex molecular structures.[992] With these transformations in hand, the stage was now set for the total synthesis of skyrin natural products (**9**, **409**, **410**). Indeed, Nicolaou and co-workers reported the total synthesis of rugulosin (**410**, Figure 20) and 2,2′-*epi*-cytoskyrin A (**417**) shortly after the discovery of the cytoskyrin cascade.[130]

Scheme 52. Synthesis of Model Compounds by Nicolaou et al.[132]



Reagents and conditions: (a) CSA, CH_2Cl_2, 25 °C, 1 h (94%). (b) MnO_2, CH_2Cl_2, 25 °C, 1 h (83%). (c) Et_3N, CH_2Cl_2, 25 °C, 1 h (65%). (d) Et_3N, CH_2Cl_2, 45 °C, 16 h (95%). (e) MnO_2, CH_2Cl_2, 25 °C, 20 h (95%). (f) CSA, CH_2Cl_2, 25 °C, 1 h; then MnO_2, 25 °C, 88 h (75%). (g) CSA, CH_2Cl_2, 25 °C, 1 h; then MnO_2, Et_3N , 45 °C, 36 h (66%).

When comparing the model systems (**412**−**416**, Scheme 52) with the targeted natural products **410** and **417**, it becomes apparent that two hydroxyl functions (at C2 and C2′) had to be attached to the molecular structure of the model systems. However, the introduction of hydroxyl-substituted precursors into the cytoskyrin cascade was considered a challenge due to possible elimination reactions prior to the first dimerization step in the cascade.[993] Moreover, issues regarding the stereochemical outcome of the early dimerization reaction of the cytoskyrin cascade had to

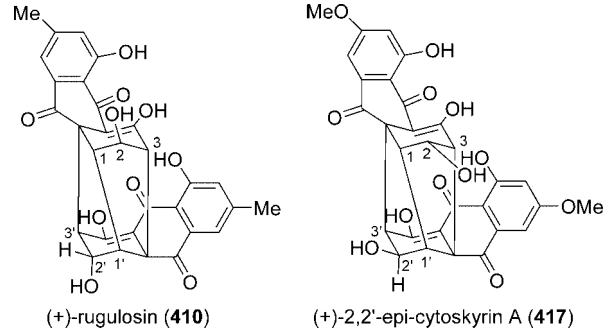


Figure 20. Rugulosin (**410**) and 2,2′-epi-cytoskyrin A (**417**).

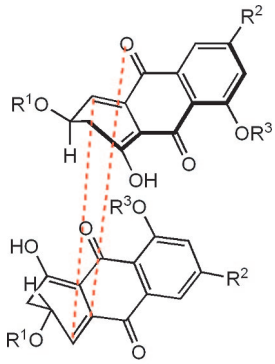


Figure 21. Suggested spatial arrangement for the dimerization of **418**.

be addressed, since a chiral starting material was employed, leading to the formation of three new stereogenic centers. In this context, several spatial arrangements for the dimerization were considered and it was argued that an arrangement as in Figure 21 (*exoanti*) should be favored due to steric preferences.

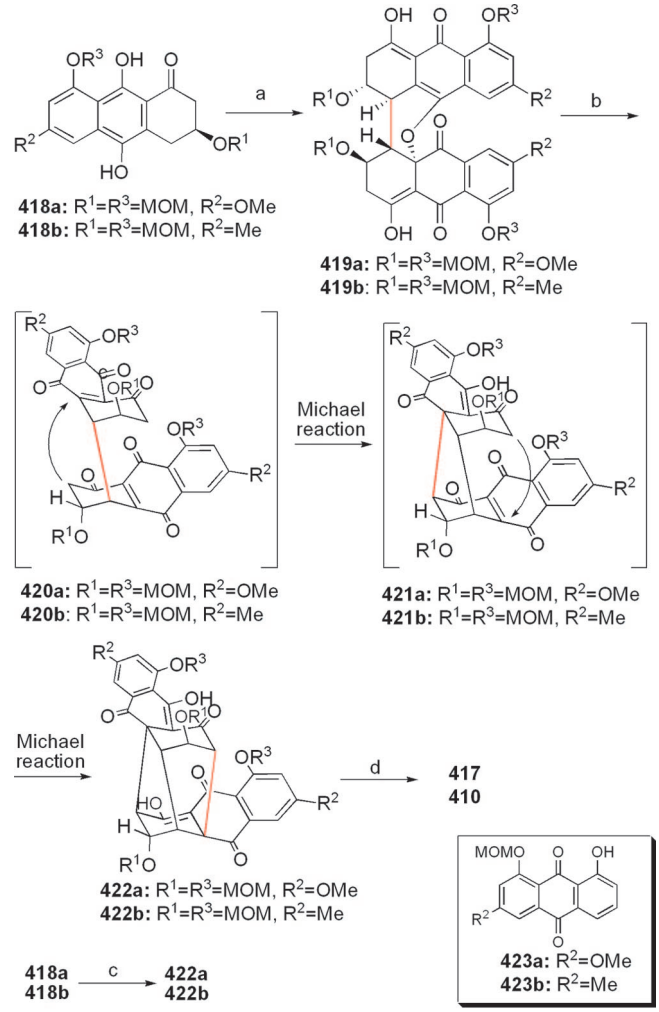
Indeed, exposure of readily available anthradihydroquinones **418a** and **418b** to the previously developed oxidative conditions[132] led to the formation of the dimeric compounds **419a** and **419b** as single diastereomers and in good yield (Scheme 53).

This reaction presumably proceeds via oxidation of the anthradihydroquinone moiety followed by enolization and dimerization. After careful optimization of the workup procedures and the reaction conditions, compounds **419a** and **419b** could then be transformed into the highly complex precursors **422a** and **422b** through another cascade process involving an oxidation and two Michael reactions. Most importantly, further optimization of the reaction conditions allowed for the direct transformation of tricyclic compounds **418a** and **418b** into precursors **422a** and **422b** through a fascinating seven-step cascade. An interesting feature of these cascade processes is their high selectivity. The only side-products that could be isolated were monomers **423a** and **423b** resulting from the aforementioned elimination/aromatization process. Starting from precursors **422a** and **422b**, the last step that remained was the removal of the acetal protective groups, which could easily be achieved by exposure to acidic conditions, yielding (+)-2,2′-epi-cytoskyrin **417** and (+)-rugulosin **410** in excellent yield. In summary, these impressive total syntheses of bioactive mycotoxins should serve as inspiring examples for the power of cascade sequences to attain highly complex molecular targets.

2.9.3. Xanthones

The xanthone structure is a very interesting framework that exhibits a large variety of pharmacological activities.[994] The biological activity of these compounds is due to their tricyclic scaffold but varies depending on the nature and position of the substituents. While DMXAA (**424**, Figure 22) is undergoing clinical trials as an antitumor agent, mangiferin (**425**) possesses antioxidant, anti-inflammatory, immunomodulatory, and antiviral effects. Because the range of natural xanthones is relatively limited due to their biosynthetic pathways, there has been a growing interest in the development of synthetic xanthones with different substitution pattern.[995,996]

Scheme 53. Synthesis of (+)-2,2′-*epi*-Cytoskyrin A (417) and (+)-Rugulosin (410)[130,131]



Reagents and conditions: (a) MnO_2, CH_2Cl_2, 25 °C, 1 h (64% **419a**), (32% **419b**). (b) MnO_2, Et_3N, CH_2Cl_2, 45 °C, 12 h (71% **422a**), (81% **422b**). (c) MnO_2, CH_2Cl_2, 25 °C, 10 min; then MnO_2, Et_3N, 45 °C, 12 h (60% **422a**), (50% **422b**). (d) conc. HCl, MeOH, THF, 60 °C, 12 h (93% **417**), (98% **410**).

Because of their importance for medicinal chemistry, recent developments in isolation and characterization of naturally occurring xanthones, the classic and new synthetic routes to obtain them, together with new insights into their biological activities, have recently been reviewed.[997] For this reason, we will focus our interest herein on the synthesis of tetrahydroxanthenones, which represent the core of many natural products (see examples **10**, **426**−**428** in Figure 22) but have so far received limited attention, with only a few stereoselective syntheses of these natural products having been reported.[998,999]

Because the structure of diversonol (**426**) is very similar to that of the secalonic acid monomers (compare structures of **10** and **426**, Figure 22),[840] the total synthesis of diversonol (**426**) was expected to be a step toward the total synthesis of the secalonic acids. In 2006, Bräse et al. published the first total synthesis of diversonol (**426**) in racemic form (Scheme 54).[834] The synthetic sequence was based on access to the tetrahydroxanthenone framework that had previously been developed by the same group in 2004[1000] and consisted of the domino oxa-Michael-aldol condensation between a substituted salicylic aldehyde (**429**) and 4-hydroxycyclohexenone (**430**). The tetrahydroxanthenone derivative **431**

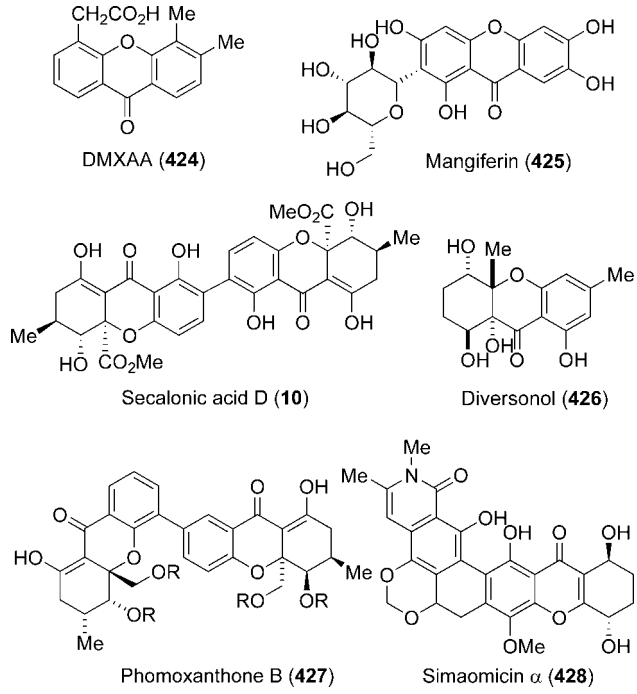
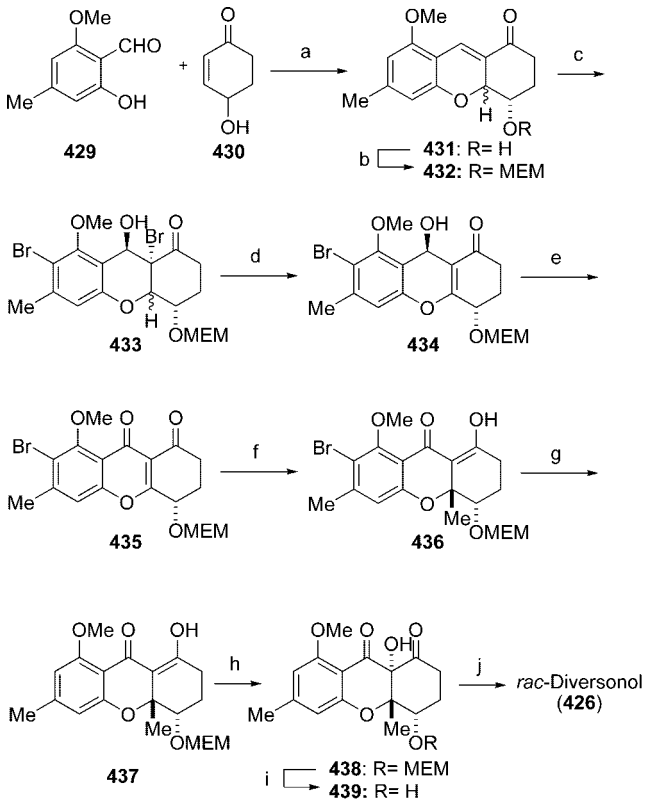


Figure 22. Bioactive natural and synthetic xanthones.

Scheme 54. First Total Synthesis of Racemic Diversonol (426) by Bräse et al.[834]



Reagents and conditions: (a) imidazole, dioxane/H_2O, sonication, 9 d (61%). (b) MEMCl, *i*PrNEt, CH_2Cl_2, rt, 3 h (75%). (c) tetrabutylammonium tribromide, THF/H_2O, rt, 5 h (52%). (d) DABCO, dioxane, rt, 16 h (53%). (e) TPAP, NMO, CH_2Cl_2/CH_3CN, sonication (40%). (f) MeLi, CuCN, Et_2O, −78 °C, 5 h (52%). (g) *t*BuLi, THF, −78 °C, $NaHCO_3$, 4 h (93%). (h) magnesium monoperoxophthalate, EtOH, rt, 5 h (57%). (i) BBr_3, CH_2Cl_2, rt, 7 h (40%). (j) $NaBH_4$, MeOH, −78 °C, 20 min (66%).

obtained after this reaction was further functionalized. Starting with the protection of the free hydroxyl functionality as a MEM ether, the resulting derivative **432** was then

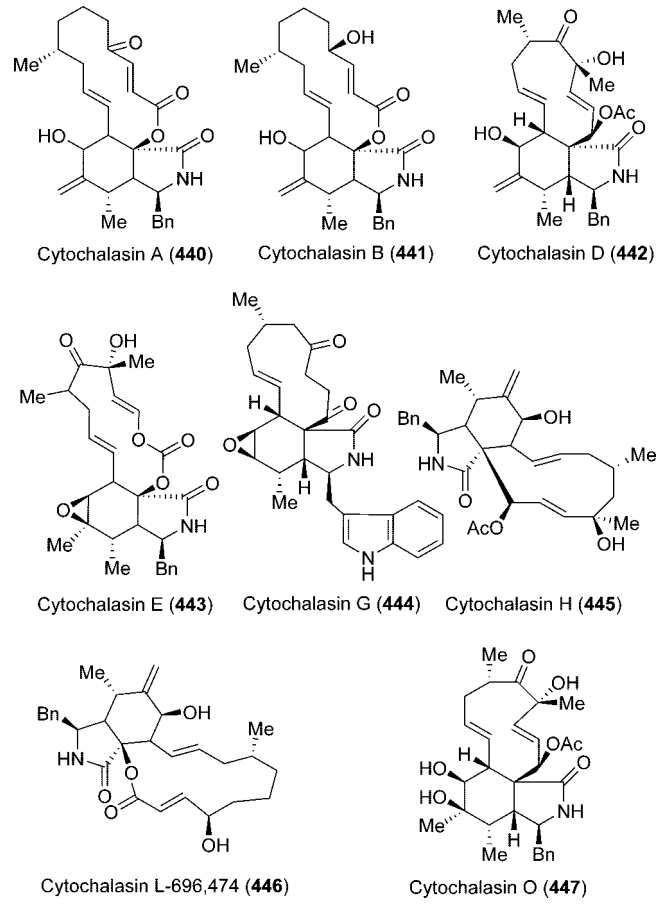


Figure 23. Structure of some Cytochalasans with different macrocyclic fused rings.

stereoselectively converted in the bromohydrin **433**, which after elimination of hydrogen bromide yielded the conjugated system **434**. Oxidation under Ley conditions to the corresponding diketone **435** and subsequent cuprate addition allowed the incorporation of the methyl substituent in position 4a. The concluding stages comprised dehalogenation, diastereoselective hydroxylation on C9a, and final MEM deprotection.

2.9.4. Cytochalasans

The cytochalasans are metabolic products of microorganisms, and in some cases of molds, of considerable importance because of their potent biological activity. As a matter of fact, their name is derived from Greek (*cytos*, cell; *chalasis*, relaxation) owing to this unique biological property.

The isolation of the first two substances of this class and the determination of their structures were achieved at about the same time—independently of each other—by Tamm[1001] and by Aldridge et al.[1002] in the research laboratories of ICI Ltd. in England. To date, more the 80 cytochalasans have been isolated from a range of fungi such as *Phomosis*,[260,263] *Chalara*,[1003] *Hyposylon*,[1004] *Xylaria*,[237,1005] *Daldinia*,[1006−1008] *Pseudeurotium*,[268] and *Phoma exigua*.[270]

Cytochalasans are structurally characterized by the presence of a hydrogenated and highly substituted bicyclic isoindolone unit fused to a macrocyclic ring. The macrocyclic appendage varies widely within the cytochalasans. It can either be a lactone, a carbonate, or more frequently a carbocycle as exemplified by cytochalasin B, E, and D, respectively (see Figure 23), and seems to play an important role in the determination of biological activity.

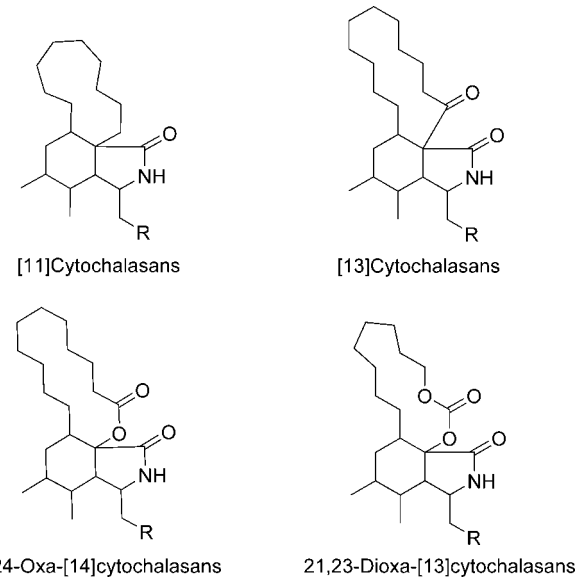


Figure 24. Nomenclature of the Cytochalasan scaffold.

The systematic nomenclature applied to cytochalasans consists of taking the hydrogenated isoindole as core structure (including the macrocycle and carbon substituents on the isoindole except for the benzyl ring) and naming it "cytochalasan". The size of the macrocycle is indicated by the corresponding number in brackets (see Figure 24).

The total synthesis of cytochalasans has been of considerable interest for several years; both inter- and intramolecular Diels−Alder reactions have been used to assemble the isoindolone components stereoselectively. The stereogenic centers around the macrocyclic ring can be introduced either before or after the Diels−Alder reaction. In this sense, the general synthetic routes toward the formation of cytochalasans can be divided into two strategies:

(1) Simultaneous formation of the six-membered isoindolone ring and the large macrocycle in a late-stage Diels−Alder cyclization.[253,258,273,1009−1011]

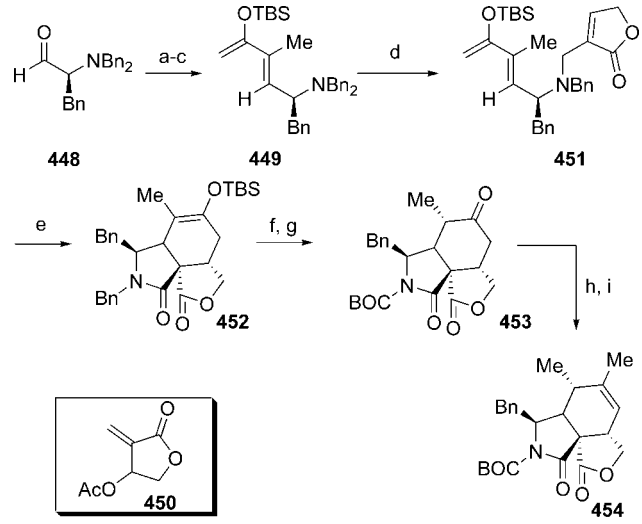
(2) Initial formation of the isoindolone core (through the use of an intramolecular Diels−Alder reaction) and subsequent appendix of the macrocycle.[274,240]

Although the Diels−Alder strategy was most often used to generate the eleven-membered ring of the [11]cytochalasans, other reaction types have been performed with this purpose, such as ring-expansion,[275,1012,1013] ring-fragmentation,[249] Pd-assisted macrocyclizations,[1014] or Reformatsky reactions.[1015] Moreover, most of the cytochalasans are commercially available[1016] for biological studies, which explains why there are only a few total syntheses known in the field.

Cytochalasin B was the first cytochalasin isolated (together with cytochalasin A (**440**), *dehydrophomin*) and was originally named *phomin*.[1001] Cytochalasin A and B are both [14] cytochalasans and are produced by *Helminthosporium dematioideum*.

The first total synthesis of cytochalasin B was reported by Stork and co-workers[245] in 1978 and consisted of the simultaneous formation of the isoindolone core and the macrocyclic fused ring in a late-stage intramolecular Diels−Alder condensation. Most recently, Myers and Haidle[247] have developed an enantioselective and convergent synthetic route in which the isoindolone core is synthesized first by a Diels−Alder reaction, with the macrocyclic appendage (previously functionalized with the right stereochemistry) introduced at a late(r) stage in the synthetic sequence. It is also possible to synthesize cytochalasin L-696,474 (**446**) employing this strategy by using common precursors **454** (Scheme 55) and a late-stage macrocyclization reaction (namely, through an intramolecular Horner−Wadsworth−Emmons olefination ring closure (Schemes 56 and 57))[1017−1019]

Scheme 55. Synthesis of a Key Tricyclic Precursor (454) to Cytochalasans B and L-696,474 by Haidle and Myers[247]



Reagents and conditions: (a) Diethyl 3-oxo-2-butylphosphonate, $Ba(OH)_2$, THF-H_2O, 23 °C. (b) 2,3-Dichloro-5,6-dicyanobenzoquinone, CH_2Cl_2-pH 7 buffer, 23 °C. (c) *tert*-Butyldimethylsilyl trifluoromethanesulfonate, 2,6-lutidine, CH_2Cl_2, −78 - 23 °C. (d) **450**, MeOH, 23 °C. (e) m-Xylene, 150 °C. (f) H_2, 10% Pd/C, BOC_2O, Et_3N, 23 °C. (g) TBAF, AcOH, THF, 0 °C. (h) (1) KHDMS, THF, −78 °C; (2) 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine. (i) $(CH_3)_2CuLi$, THF, −78 °C → 0°C.

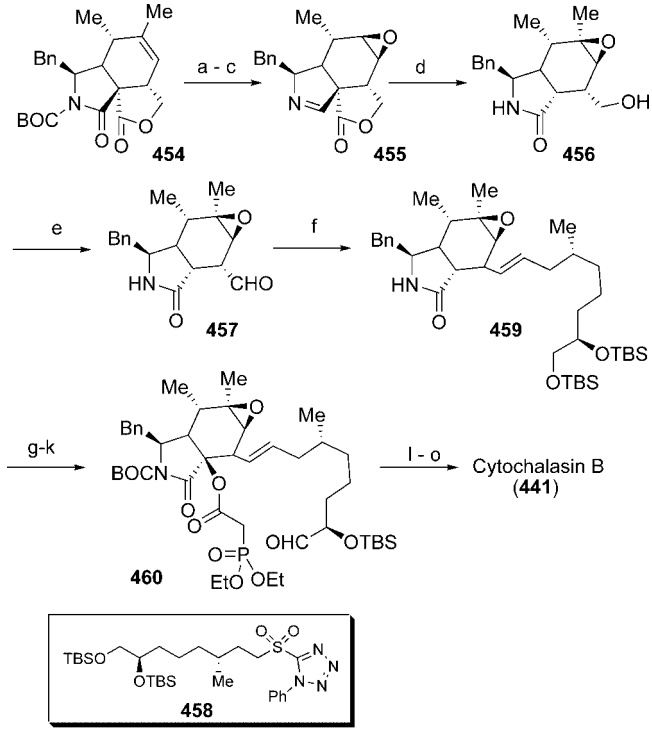
Cytochalasin H (445). This cytochalasin is an isomer of Cytochalasin D (**442**), differing from the latter given the lack of carbonyl function at C(17) and the opposite configuration at C-18. The synthesis of the eleven-membered ring precursor **473** of cytochalasin H (**445**) (Scheme 57) was reported by Thomas and Whitehead[1010] in 1986. Afterward, the same group reported the first total synthesis of cytochalasin H (**445**) by using an intramolecular Diels−Alder reaction in a highly stereoselective way.[262] The stereogenic centers at C-16 and C-18 were introduced prior to cyclization using conventional acyclic stereochemical control (Scheme 58).

Three years later, the same authors reported an alternative approach in which the conformational preferences of the rings control the stereochemistry. They employed a shorter route for the synthesis of the intermediate **477** (Scheme 59).[1020]

Cytochalasin D (**442**), a carbocyclic cytochalasin, is an isomer of cytochalasin H (**445**), differing from the latter given a carbonyl function at C-17 and the opposite configuration at C-18. It was isolated from the microorganism *Metarrhizum anisopliae*, and its first total synthesis was published by Vedejs and Reid in 1984.[1021] These authors had previously reported the advantages of using *N*-acylpyrrolinones for Diels−Alder reactions in the cytochalasin area.[1022]

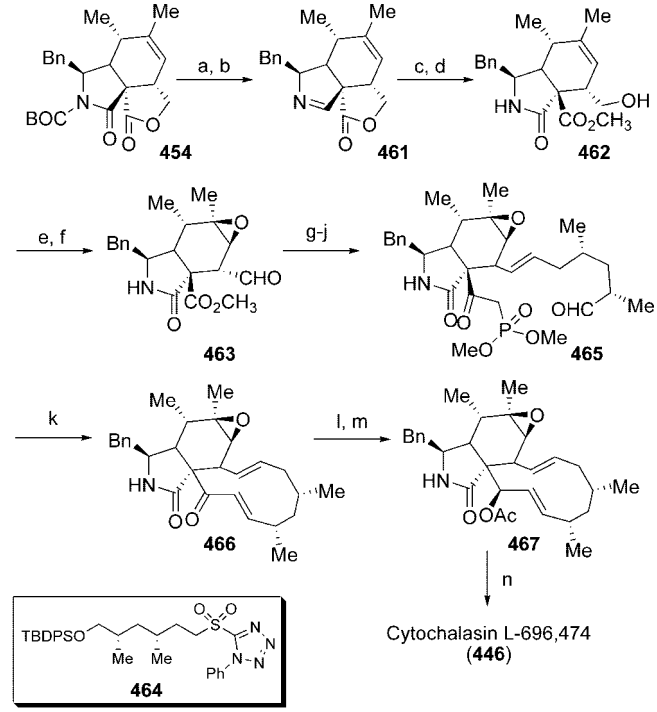
Some years later, Merifield and Thomas, who had previously achieved the total synthesis of cytochalasin H (**445**), developed another synthetic route for the total synthesis of cytochalasin D (**442**). The strategy consisted of employing the same approach used for cytochalasin H (**445**)—an intramolecular Diels−Alder reaction to form the reduced

Scheme 56. Enantioselective and Modular Total Synthesis of Cytochalasin B by Haidle and Myers[247]



Reagents and conditions: (a) Dimethyldioxirane, acetone, 23 °C. (b) TFA, CH_2Cl_2, 0 °C. (c) [Bis(trifluoroacetoxy)iodo]benzene, 4 Å MS, CH_2Cl_2, 23 °C. (d) Ethylenediamine, tert-amylalcohol, 23 °C. (e) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 23 °C. (f) (1) **458**, KHMDS, THF, −78 °C, (2) **457**, −100 °C - 40 °C. (g) Lithium bis(trimethylsilyl)amide, THF, −78 °C; BOC_2O, −78 → −40 °C. (h) KHMDS, THF, −78 °C; trans-2-(phenylsulfonyl)-3-phenyloxazirine, −100 → −78°C. (i) Diethylphosphonoacetic acid, 1,3-dicyclohexylcarbodiimide, CH_2Cl_2, 23 °C. (j) HF-Pyridine, THF, 20 °C. (k) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 23 °C. (l) $NaOCH_2CF_3$, CF_3CH_2OH, DME, 23 °C. (m) $Mg(OCH_3)_2$, MeOH, 23 °C. (n) TBAF, THF, 23 °C. (o) $MgSO_4$, benzene, 70 °C.

Scheme 57. Enantioselective and Modular Total Synthesis of Cytochalasin L-696,474 (446) by Haidle and Myers[247]



Reagents and conditions: (a) TFA, CH_2Cl_2, 0 °C. (b) [Bis(trifluoroacetoxy)iodo]benzene, 2,6-lutidine, 4 Å MS, CH_2Cl_2, 23 °C. (c)1,3-diaminopropane, CF_3CH_2OH, Et_2O, 23 °C; Et_2O-pH 7 buffer. (d) KOH, I_2, MeOH, 23 °C. (e) Dimethyldioxirane, acetone, 23 °C. (f) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 23 °C. (g) (1) **453**, KHMDS, THF, −78 °C; (2) **464**, −100 °C → 40 °C. (h) $(CH_3O)_2POCH_2Li$, THF, −78 °C → 23 °C. (i) TBAF, AcOH, THF, 23 °C. (j) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 23 °C. (k) $NaOCH_2CF_3$, CF_3CH_2OH, DME, 80 °C. (l) $CeCl_3\ 7H_2O$, $NaBH_4$, THF-MeOH, −40 °C. (m) Ac_2O, Py, 23 °C. (n) $MgSO_4$, benzene, 70 °C.

isoindolone ring and the macrocycle simultaneously (Scheme 60).[1011] Through this method, only the stereogenic centers at C-16 and C-3 were present before the cyclization. The remaining parts of the molecule were introduced either during the Diels−Alder reaction itself or later in the synthesis using the conformational preference of the macrocyclic ring to control the stereochemistry.

Cytochalasin G (444). Unlike the aforementioned cytochalasans A, B, H, and L, which are derived biosynthetically from phenylalanine (as indicated by the presence of the phenyl substituent at C-10), cytochalasin G incorporates tryptophan during its biosynthesis; this is the reason why it possesses an indolylmethyl substituent at C-3.

The first total synthesis of this molecule was described by Thomas and co-workers in 1986.[258,259] Their approach consisted of performing the acylation of a (5*R*)-*N*-benzoyl-5-indolylmethylpyrrolidinone (**507**, previously synthesized following Scheme 62) by using a long-chain imidazolide **487** followed by oxidation and Diels−Alder cyclization (Scheme 61).

The synthesis of the two key intermediates **487** and **486** was performed in an asymmetrical way by the authors and is described in detail in the corresponding papers.

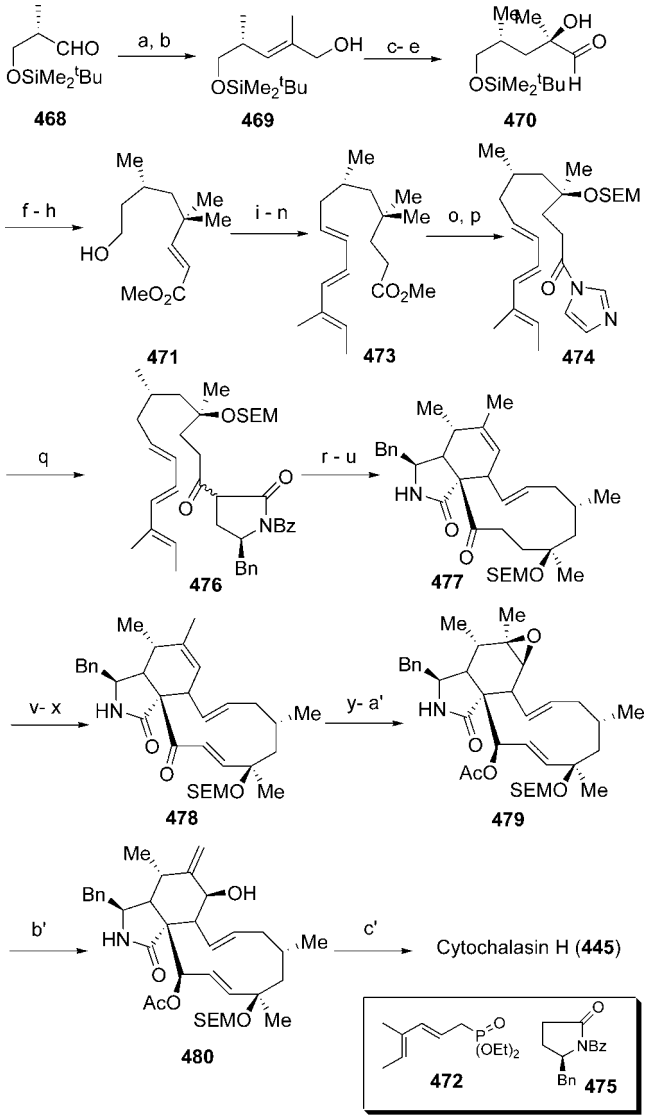
Cytochalasin O. The total synthesis of this[11] cytochalasin was performed by Merifield and Thomas during the course of their work in the total synthesis of cytochalasin D (**442**).[253] They realized that, when carrying out the oxidation of the Diels−Alder adduct **448** (Scheme 60) in the presence of excess osmium tetraoxide, they obtained the tetraol **515** (Scheme 63) as a major product, together with **499** (the intermediate for the synthesis of cytochalasin D (**442**)) and **516**.

Synthesis of Intermediates. Because of the complexity of this family of molecules, some research groups have decided to prepare structurally simplified analogues of the cytochalasans. In 1975, Weinreb and Auerbach described the first stereospecific synthesis of the isoindolone nucleus by internal Diels−Alder addition of a diene ester and butenolide.[1023] Through this method, the regiochemistry of the cycloaddition was controlled, but the stereochemistry of the C-3 benzyl center was not. Another example is the asymmetric synthesis of perhydroisoindolone intermediates designed by Krafft et al.[1024] The key reaction of this synthetic pathway consisted of a Diels−Alder reaction/addition between trienes and optically active pyrrolidenones that had been previously synthesized (Scheme 64).

2.9.5. Peptidic Mycotoxins

Many mycotoxins contain a cyclopeptide core structure; in particular, a dipeptide moiety (hence, diketopiperazines) can be found in important mycotoxins. Besides the incorporation of tryptophanes yielding indole alkaloids, fungi produce a large number of epipolythiodiketopiperazines such as gliotoxin (**527**), which are depicted in Figure 25. In

Scheme 58. Total Synthesis of Cytochalasin H (445) by Thomas and Whitehead[262]



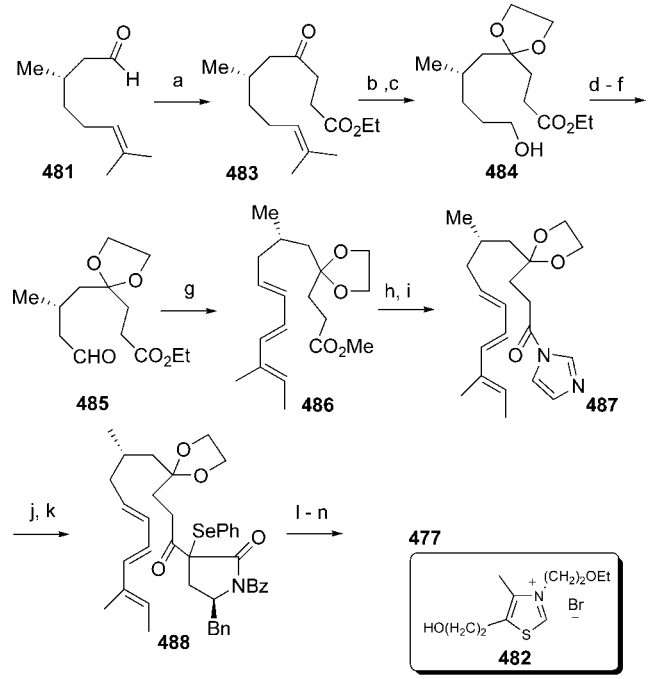
Reagents and conditions: (a) $Ph_3PC(Me)CO_2Me$, benzene, reflux. (b) $LiAlH_4$. (c) MCPBA. (d) $LiAlH_4$. (e) N-chlorosuccinimide, Me_2S, Et_3N, CH_2Cl_2, –20 °C. (f) Ph_3PCHCO_2Me. (g) $ClCH_2OCH_2CH_2SiMe_3$, Et_2NPr^i. (h) Dowex 50W-X8. (i) H_2, Pd-C, MeOH. (j) Me_2SO, oxalyl chloride. (k) $Ph_3P{=}CH_2$. (l) 9-BBN, H_2O_2, OH^-. (m) Me_2SO, oxalyl chloride. (n) phosphonate (**472**)-Li. (o) NaOH, H_2O-MeOH then tartaric acid. (p) carbonyl-1,1-di-imidazole. (q) **474**, $LiN(SiMe_3)_2$ (r) $LiN(SiMe_3)_2$, PhSeCl. (s) MCPBA, H_2O_2, –40 °C (15 min), 0 °C. (t) toluene, 80-100 °C. (u) KOH, MeOH. (v) LDA, Me_3SiCl. (w) $Bu^n{}_4NF$, PhSeCl. (x) H_2O_2, Py. (y) $NaBH_4$. (z) excess of Ac_2O, Py, DMAP. (a') MCPBA. (b') Ac_2O, Py, DMAP. (c') aqueous HF in MeCN.

addition, many cyclic and noncyclic peptides can be found as toxic metabolites of fungi, exemplified in Figure 26.

3. Biosynthesis

Fungal products such as mycotoxins, antibiotics, alkaloids, and so forth are often referred to as secondary metabolites—a term introduced into microbial biochemistry by Bu'Lock. In this paragraph, the biosyntheses of mycotoxins are discussed since this has an impact on the formation of the different classes of mycotoxins. However, it is not intended to provide a full review of this field. For comprehensive overviews, we refer to recent topical reviews[875,1025,1026] and book chapters.[1027]

Scheme 59. Alternative Synthesis of the Intermediate 477 of Cytochalasin H (445) by Thomas and Whitehead[262]



Reagents and conditions: (a) ethyl acrylate, **482**, Et_3N, Dioxane, 80 °C. (b) ethylene glycol, toluene p-sulfonic acid, benzene, reflux. (c) (1) O_3, CH_2Cl_2/MeOH, –70 °C; (2) $NaBH_4$. (d) PBu_3, o-nitrophenylselenocyanate, THF. (e) H_2O_2/NaOH, THF, 0 °C. (f) (1) O_3, MeOH; (2) O_2, Me_2S. (g) (1) **472**, n-BuLi, THF, –60 °C, –30 °C; (2) –72 °C. (h) (1) NaOH, EtOH, rt; (2) tartaric acid. (i) CDI, THF, rt. (j) **475**, $LiN(SiMe_3)_2$, THF, –72 °C. (k) $LiN(SiMe_3)_2$, PhSeCl. (l) MCPBA, H_2O_2, $CHCl_3$, –50 °C (m) toluene, 80 °C (n) NaOH, MeOH, rt.

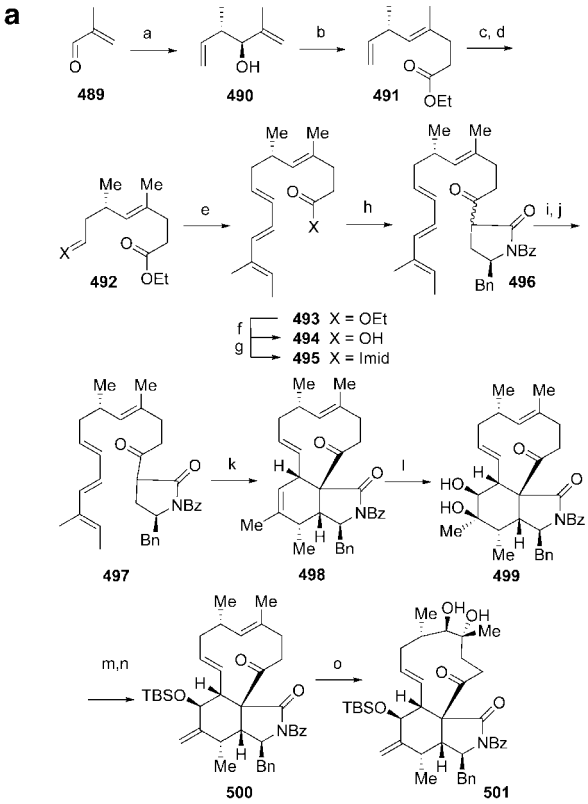
Several physiological factors play regulatory roles in both the primary and secondary metabolism of microorganisms. During the last few years, many efforts have been undertaken not only to elucidate the biochemical origin of mycotoxins but also to use this knowledge either to influence the biosynthesis (to produce more, less,[1028,1029] and/or different mycotoxins by incorporation of new building blocks[558]) or to monitor mycotoxins on a molecular level.

The publication of the genomes of *A. fumigatus*, a human pathogen, *A. oryzae*, used in food production, and *A. nidulans*, a genetic model organism, represents an important milestone in the *Aspergillus* research community, expanding knowledge of their physiology and mechanisms of gene regulation. Three additional genome projects are being funded by the NIAID with the goals of better elucidating the *A. fumigatus* genome and improving the genome annotation: *N. fischeri* (*A. fischerianus*), *A. clavatus*, and *A. terreus*. Since a growing number of filamentous fungi have been sequenced, one can assume that this genetic information will have a great impact on the analysis of mycotoxin formation in the coming decade (see Table 9).

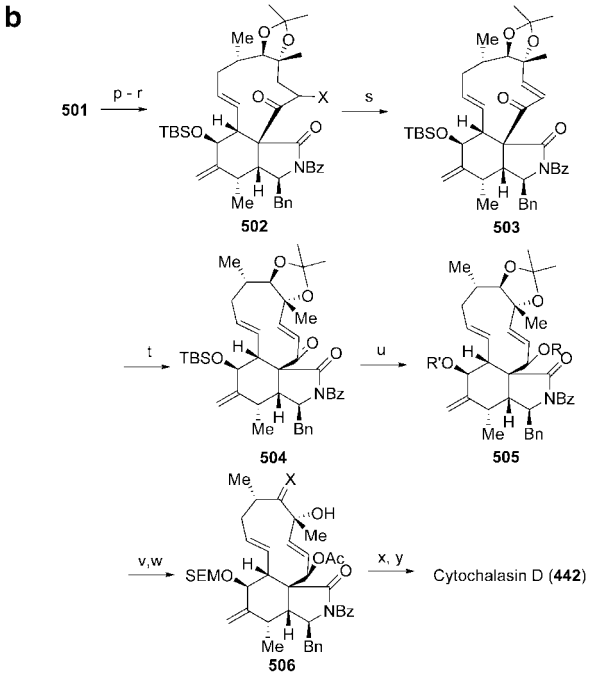
3.1. Polyketide-Derived Mycotoxins

Most of the fungal metabolites (such as Patulin (**3**) and related compounds, the anthraquinoids, etc.) are polyketides.[930] The mechanisms of biosynthesis are known in great detail for many mycotoxins[1031,1032] (see, e.g., the cytochalasins (**440**−**447**)[1033]) and have been reviewed several times. Fungal polyketide biosynthesis typically involves multiple enzymatic steps, and the encoding genes are often found in gene clusters. It has been demonstrated that this

Scheme 60. (a) Total Synthesis of Cytochalasin D (442) by Merifield and Thomas;[1011] (b) Total Synthesis of Cytochalasin D (442) by Merifield and Thomas (Part 2)[1011]



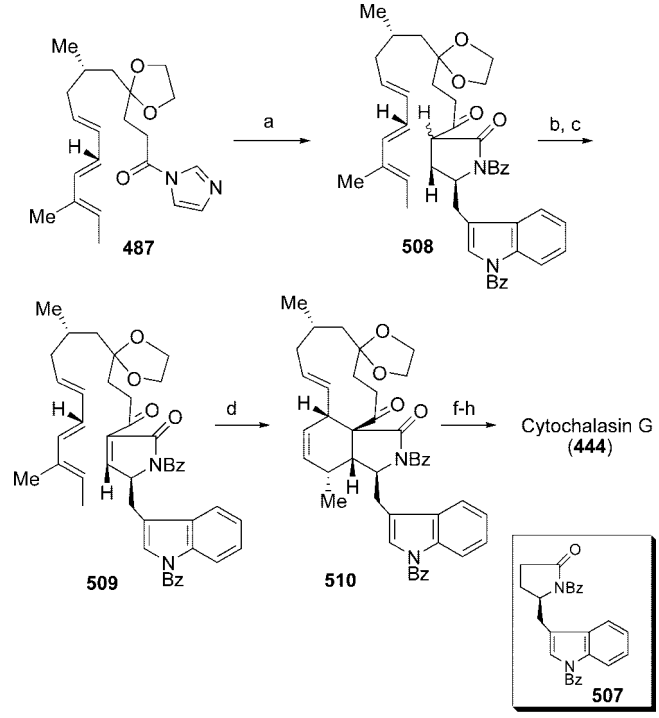
Reagents and conditions: (a) (*E*)-But-2-enyldi-isopinocampheylborane, −78 °C, 3 h, then H_2O_2. (b) $MeC(OEt)_3$, propanoic acid, 140 - 170 °C. (c) 9-bora-bicyclo[3.3.1]nonane then H_2O_2. (d) $(COCl)_2$, DMSO. (e) dienylphosphonate$^-$ Li, THF, hexamethylphosphoramide. (f) NaOH, EtOH, H_2O. (g) $CO(imidazole)_2$, THF. (h) $(5R)^{-5}$-phenylmethylpyrrolidinone lithium enolate. (i) $LiN(SiMe_3)_2$, PhSeCl. (j) m-chloroperoxybenzoic acid, H_2O_2, −50 °C. (k) toluene, 80 °C. (l) OsO_4, (m) $^tBuMe_2SiOTf$, 2,6-lutidine. (n) $SOCl_2$, Et_3N. (o) OsO_4.



Reagents and conditions: (p) 2,2- dimethoxypropane, $CHCl_3$, toluene-p-sulphonic acid. (q) LDA, PhSeCl.(r) KOH, MeOH. (s) H_2O_2, H_2O, Py. (t) $NaBH_4$, $CeCl_3$, (u) Ac_2O, Et_3N, 4-dimethylaminopyridine. (v) Bu_4NF. (w) SEMCl, iPr_2CN. (x) H_3O^+. (y) $(COCl)_2$, DMSO. (z) HF, MeCN, H_2O.

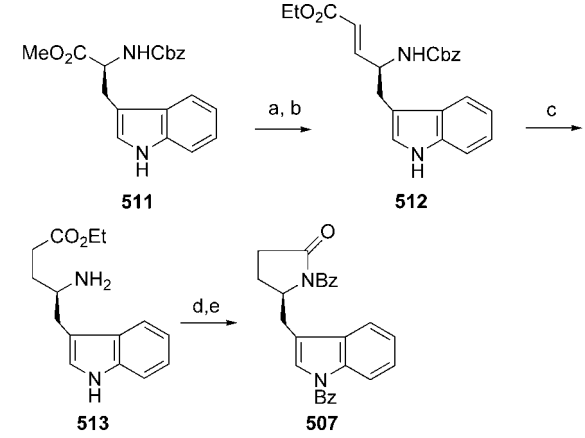
biosynthesis is strongly dependent on the growth environment.[1034] The enzymatic machinery for the formation of the

Scheme 61. Total Synthesis of Cytochalasin G (444) by Thomas et al.[258]



Reagents and conditions: (a) **507**-Li (b) $LiN(SiMe_3)_2$, PhSeCl. (c) m-chloroperoxybenzoic acid, H_2O_2, –40 °C then 0 °C. (d) toluene, 80 °C. (e) aq. HCl, THF. (f) m-chloroperoxybenzoic acid. (g) NaOH, MeOH, H_2O.

Scheme 62. Asymmetric Synthesis of the Pyrrolidinone Intermediate 507

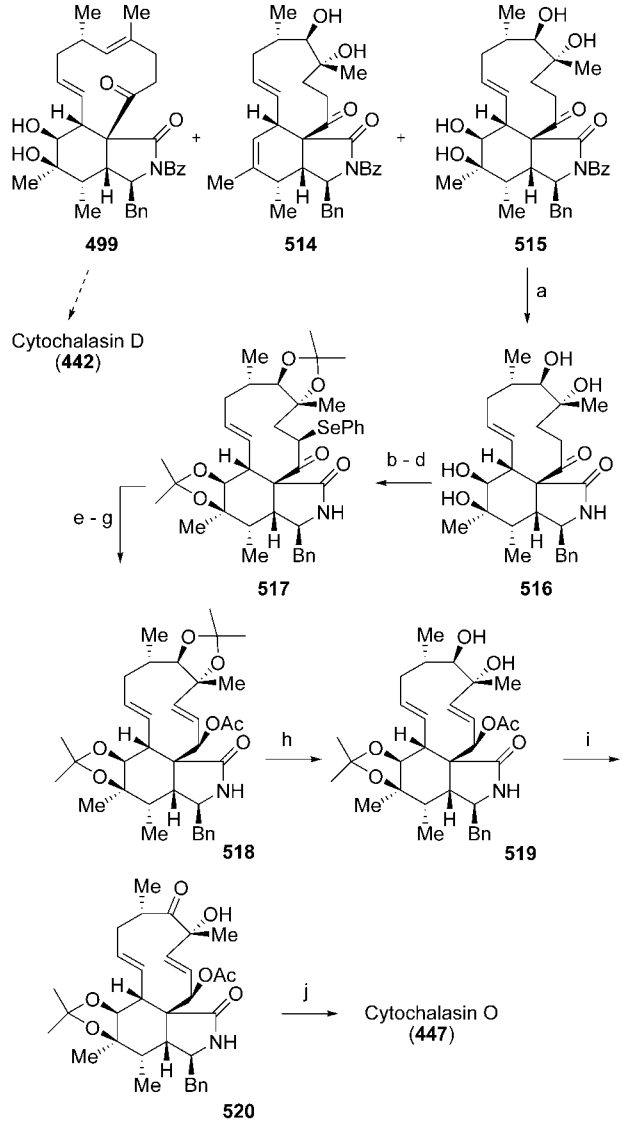


Reagents and conditions: (a) Bu^i_2AlH. (b) **472**, LDA (c) H_2, Pd-C, AcOH, EtOH. (d) NaOEt, EtOH. (e) PhCOCl, Et_3N, DMAP.

polyketides consists of different modules characteristic of each fungus (e.g., keto synthases, acyl transferases,[1035] carboxylases, cyclases, dehydrases, aromatases, reductases, thioesterases, (Claisen) cyclases, laccasses, etc.) It is interesting to note that, while bacteria do have similar enzymes, the folding of the growing polyketide chain delivers different structures.[19]

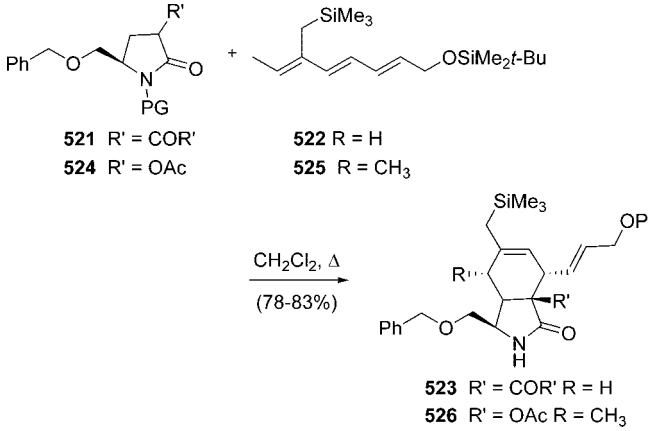
Depending on the chain length, different classes of mycotoxins are formed: tetraketides (e.g., patulin (**3**)), pentaketides (e.g., citrinin (**2**), ochratoxin A (**7**)) (Scheme 66−68), hexaketides (e.g., Diaporthin), heptaketides (e.g., *Alternaria* toxins[1036,1037]), octaketides (e.g., aflatoxins (**1**)), xanthones like secalonic acids (such as **10**); nonaketides (e.g., resorcyl lactones such as zearalenone (**4**)[1038]), and decaketides (e.g., vioxanthin (**606**)).

Scheme 63. Total Synthesis of Cytochalasin O by Merifield and Thomas[253]



Reagents and conditions: (a) NaOH aq., MeOH. (b) 2,2-dimethoxypropane, b) p-toluene sulfonic acid. (c) LDA, benzeneselenylchloride. (d) NaOH aq., MeOH. (e) aq. H_2O_2, Py. (f) $NaBH_4$, $CeCl_3$. (g) acetic anhydride, Et_3N, DMAP. (h) toluene-p-sulfonic acid, MeOH. (i) oxalyl chloride, Me_2SO, Et_3N. (j) aq. HCl, MeOH, reflux.

Scheme 64. Asymmetric Synthesis of Perhydroisoindolones by Krafft et al.[1024]



Patulin (**3**) is formed via the oxidative cleavage of the tetraketide 6-methylsalicylic acid (**550**, Scheme 65). This transformation comprises monooxygenase-mediated epoxidation of gentisaldehyde (**554**) to the epoxyquinone phyllostine and rearrangement of the latter to neopatulin (**185**), the ylidenebutenolide isomer of patulin (**3**). Enzymatic reduction of neopatulin (**185**) to (*E*)-ascladiol (**186**) and oxidative ring-closure then yields patulin (**3**).

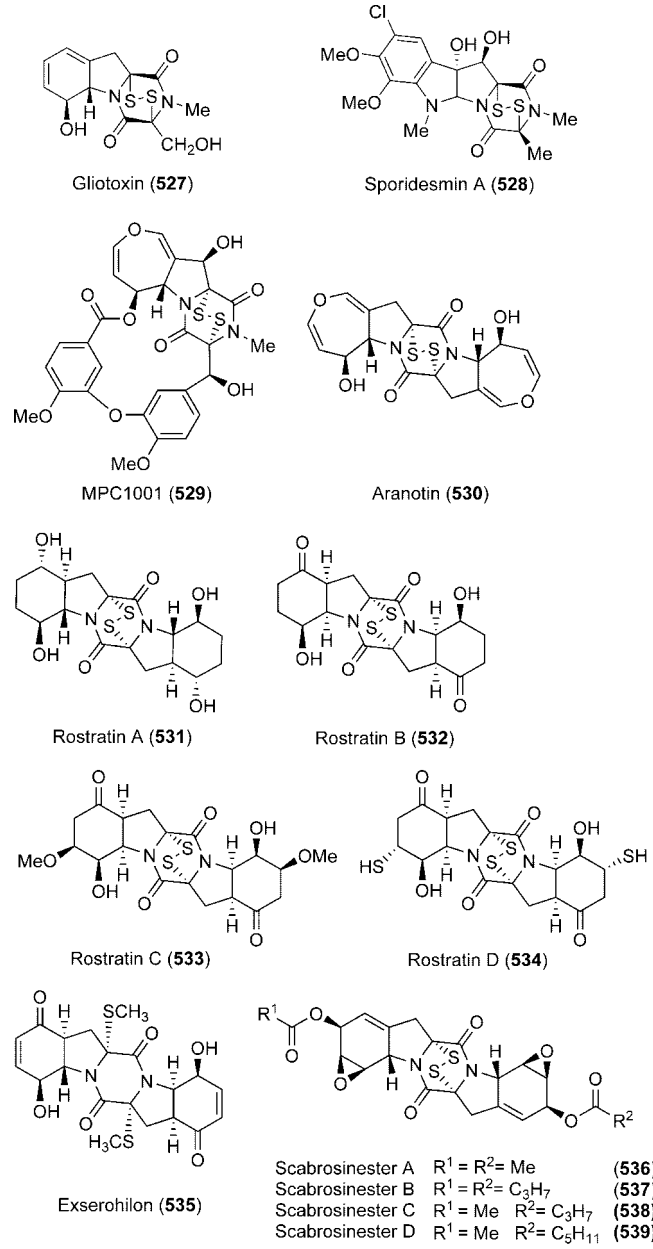


Figure 25. Some peptidic polyepithiodiketopiperazines.

The ochratoxins A and B (**7**, **155**) are derived from the pentaketide intermediate ochratoxin β (**563**).[1040,1041] The already-chlorinated ochratoxin α (**157**) was biotransformed into ochratoxin A (**7**), indicating that chlorination is primarily a penultimate biosynthetic step in the biosynthesis of ochratoxin A (**7**). Experiments illustrated that some ochratoxin B (**155**) may arise through dechlorination of ochratoxin A (**7**).

The mycotoxin alternariol and its congeners were formed starting from a heptaketide pathway (Scheme 69).[1042,1043]

The biosyntheses of octaketide-derived mycotoxins are still the subject of a number of investigations since the crucial classes of aflatoxins, xanthones, and many anthraquinones are octaketides (Scheme 71). Pioneering works by Franck

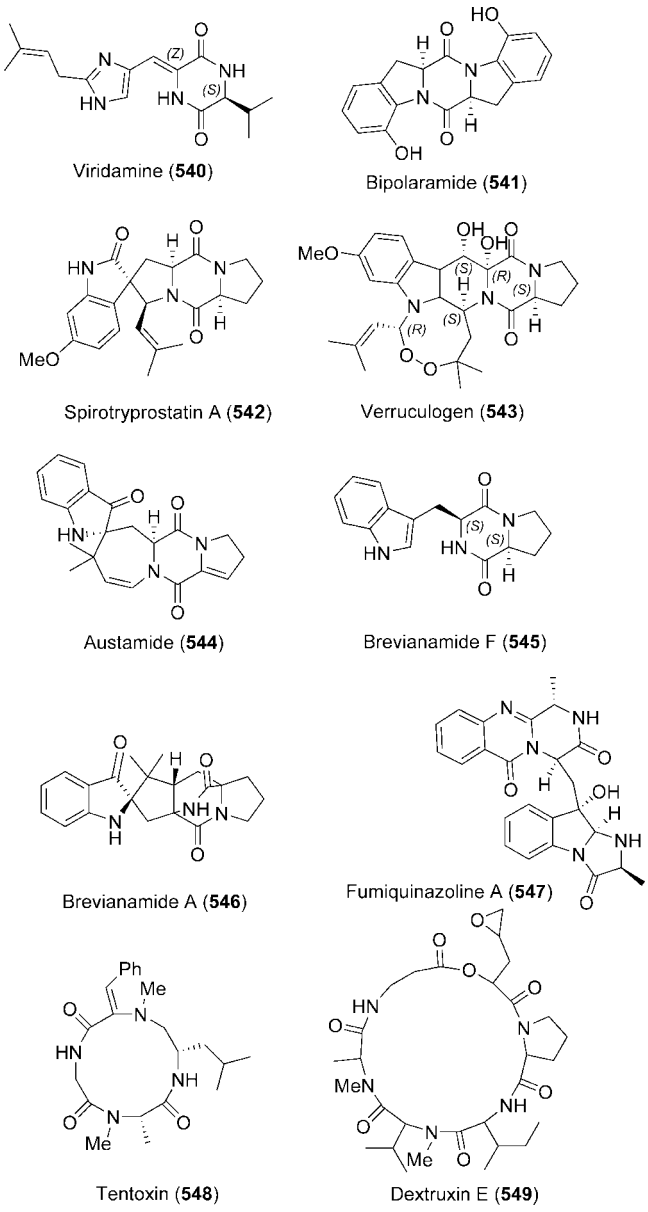
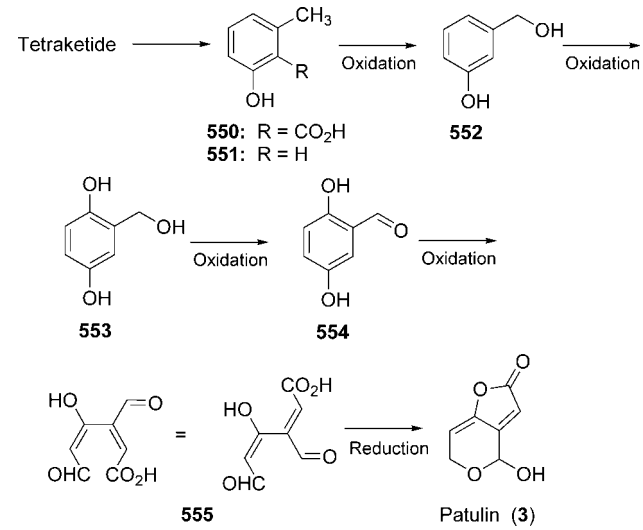


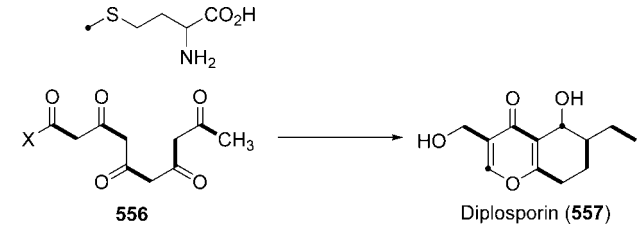
Figure 26. Peptidic mycotoxins.

et al. for the synthesis of xanthones and recently detailed investigations of Townsend in the field of aflatoxin biosynthesis[1044] have unified mycotoxins' biosynthetic origin into a greater picture (see above). The concurrent incorporation of labeled anthraquinones into secalonic acid D (**10**) by *Penicillium oxalicum* was studied by Franck et al.[1045] Emodin (**573**) and islandicin (**577**) were partially incorporated into

Scheme 65. Example of a Tetraketide Biosynthesis: Patulin[1031,1039]



Scheme 66. Example of a Pentaketide Biosynthesis: Diplosporin (557)[1031]



secalonic acid D (**10**) by way of chrysophanol (**83**); however, islandicin (**577**) is presumed to be a shunt pathway. Ergochromes are thus secoanthraquinones.[840]

The key transformation is a Bayer−Villiger-type ring-opening to a carboxylic acid **578**, which in turn reacts either in a 1,2-addition to form tajixanthone-type xanthones or by a conjugate 1,4-addition to generate the ergochromes.[1046]

Depending on the folding pattern, nonaketides produce resorcyl lactones like zearalenones or the recently isolated pochonins.[1031]

The biosynthesis of aflatoxin proceeds via numerous transformations, which are mostly well-studied.[1031,1048]

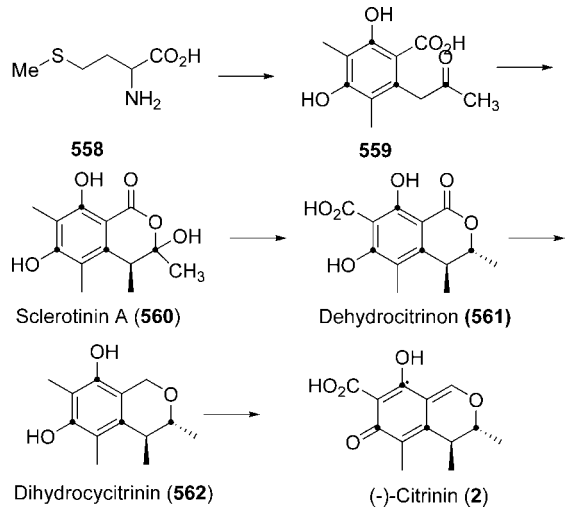
Many mycotoxins consist of homodimers of phenolic compounds. Examples include vioxanthin and the secalonic acids. Recent studies have shed light on the biosynthesis of oxidative biaryl coupling promoted by various enzymes.[1049]

The biosynthetic pathway for aurofusarin (**608**) in *Fusarium graminearum* reveals a close link between the naphthoquinones and naphthopyrones.[1032]

Table 9. Overview over Mycotoxin Biosynthesis with Examples

Polyketide *Acetate−Malonate*	Terpene *Mevalonate*	Citrate-Based *Pyruvate−Acetate*	*Amino Acid*
Aflatoxins	Fumagallin	Byssochlamic acid	Aspergillic acid
Alternariol (**11**)	Roridin	Erythroskyrin	Cyclopenein
Citrinin (**2**)	Trichothecene	Glauconic acid	Cyclopenol[153]
Citreoviridin	Diacetoxyscripenol (**217**)	Rubratoxin	Cyclopiazonic acid
Emodin[1030] (**573**)	Fusicoccin		Ergot alkaloids
Luteoskyrin			Clavin alkaloids
Maltoryzin			Fumitremogen
Ochratoxins			Gliotoxin (**527**)
Patulin (**3**)			Islandoxin
Penicillinic acid			Paspalin
Sterigmatocystin (**62**)			Tryptoquivaline
Zearalenone (**4**)			Penitrem Sporidesmin (e.g., **528**)

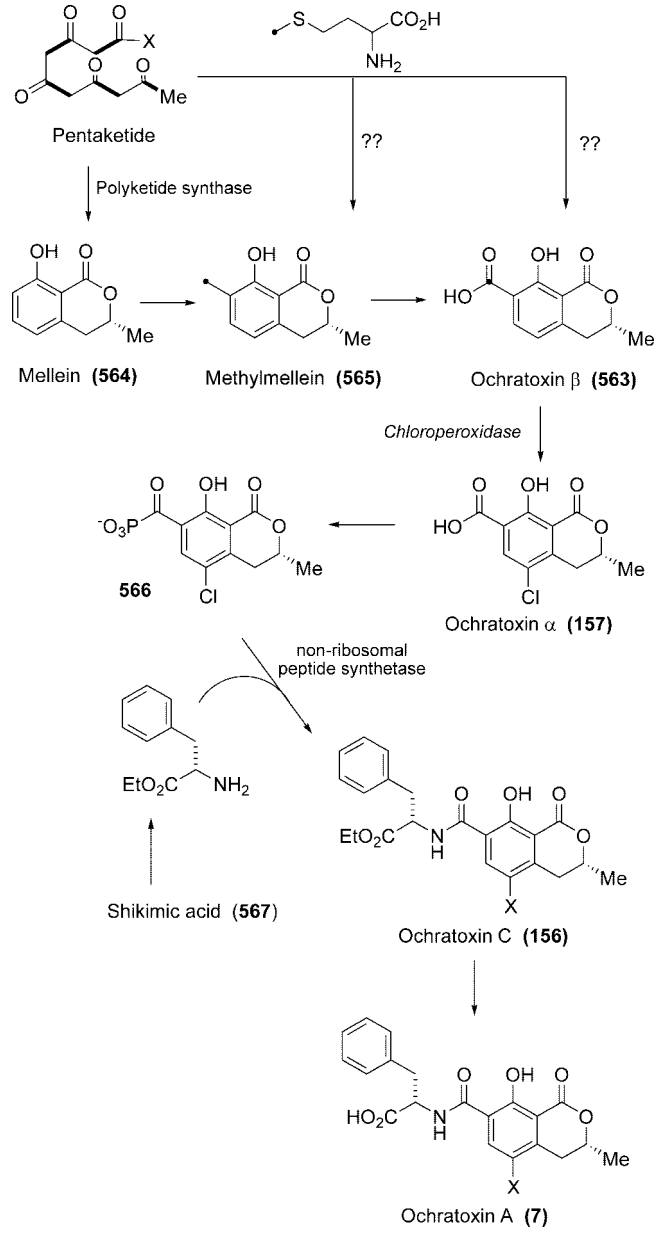
Scheme 67. Example of a Pentaketide Biosynthesis: Citrinin (2)[1031]



Fungal polyketide biosynthesis typically involves multiple enzymatic steps, and the encoding genes are often found in gene clusters. A gene cluster containing PKS12—the polyketide synthase gene[930] responsible for the synthesis of the pigment aurofusarin (**608**)—was analyzed through gene replacement using an *Agrobacterium tumefaciens*-mediated transformation to detect the biosynthetic pathway of aurofusarin (**608**). Replacement of aurR1 with hygB shows that it encodes a positive-acting transcription factor that is required for the full expression of PKS12, aurJ, aurF, gip1, and FG02329.1, which belong to the gene cluster. AurR1 and PKS12 deletion mutants are unable to produce aurofusarin (**608**) and rubrofusarin (**609**, Figure 27). Bio- and chemoinformatics combined with chemical analysis of replacement mutants (DaurJ, DaurF, Dgip1, DaurO, and DPKS12) indicate a five-step enzyme-catalyzed pathway for the biosynthesis of aurofusarin (**608**), with rubrofusarin (**609**) as an intermediate. This links the biosynthesis of naphthopyrones and naphthoquinones together. Replacement of the putative transcription factor aurR2 results in an increased level of rubrofusarin relative to aurofusarin (**608**). Gip1, a putative laccase, is proposed to be responsible for the dimerization of two oxidized rubrofusarin molecules, resulting in the formation of aurofusarin (Figure 27).

Fumonisins (**5**, **88**−**102**) are polyketide-derived mycotoxins produced by the maize pathogen *Fusarium verticillioides*. Previous analyses identified naturally occurring variants of the fungus that are deficient in fumonisin C-10 hydroxylation or that do not produce any fumonisins. It has been demonstrated that gene deletion and genetic complementation localized the C-10 hydroxylation deficiency to a cytochrome P450 monooxygenase gene in the fumonisin biosynthetic gene (FUM) cluster.[1050] Sequence analysis indicated that the hydroxylation deficiency resulted from a single nucleotide insertion that caused a frame shift in the coding region of the gene. Genetic complementation localized the fumonisin-nonproduction phenotype to the polyketide synthase gene in the FUM cluster, and sequence analysis indicated that the nonproduction phenotype resulted from a nucleotide substitution, which introduced a premature stop codon in the coding region. These results provide the first direct evidence that altered fumonisin production phenotypes of naturally occurring *F. verticillioides* variants can result from single-point mutations in the FUM cluster.

Scheme 68. Example of a Pentaketide Biosynthesis: Ochratoxins[1031]



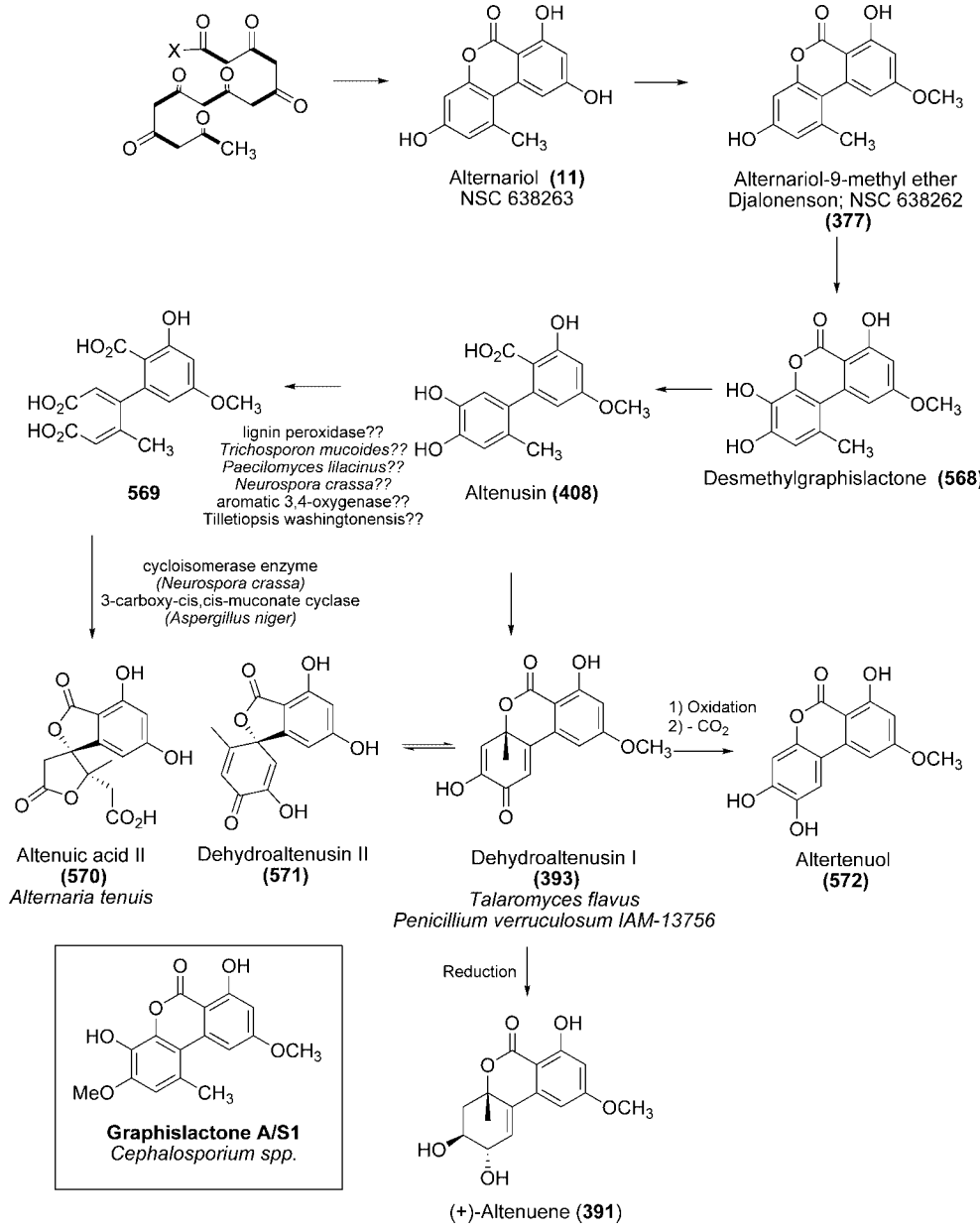
3.2. Terpenoid Mycotoxins

The trichothecenes (**205**−**234**)[1035] are prototypical terpenoid mycotoxins. Their biosynthesis has been elucidated in great detail[1051,1052] and been recently reviewed.[1053] The biosyntheses of the verrucarins (**6**, **260**−**261**) and roridins (**262**−**264**)[1054] have also been investigated.

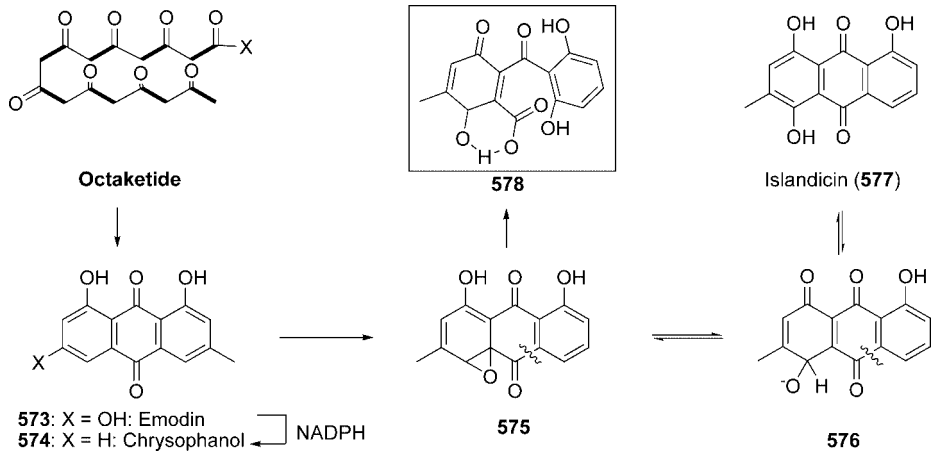
3.3. Mycotoxins Incorporating Amino Acids

Fungi use amino acids in relatively high amounts/concentrations. Quite often, mycotoxins incorporating amino acids are partially derived from polyketides or terpenoids. A number of cyclopeptides (e.g., enniatin[1055]) derived from fungi are cytotoxic and, therefore, are per se mycotoxins. Cyclic dipeptides such as epipolythiodioxopiperazines are common structures, whose biosyntheses have been recently reviewed.[1056,1057]

Scheme 69. Example of a Heptaketide Biosynthesis: Alternariol (11), Altenusin (408), Altenuene (391)[1042,1043]



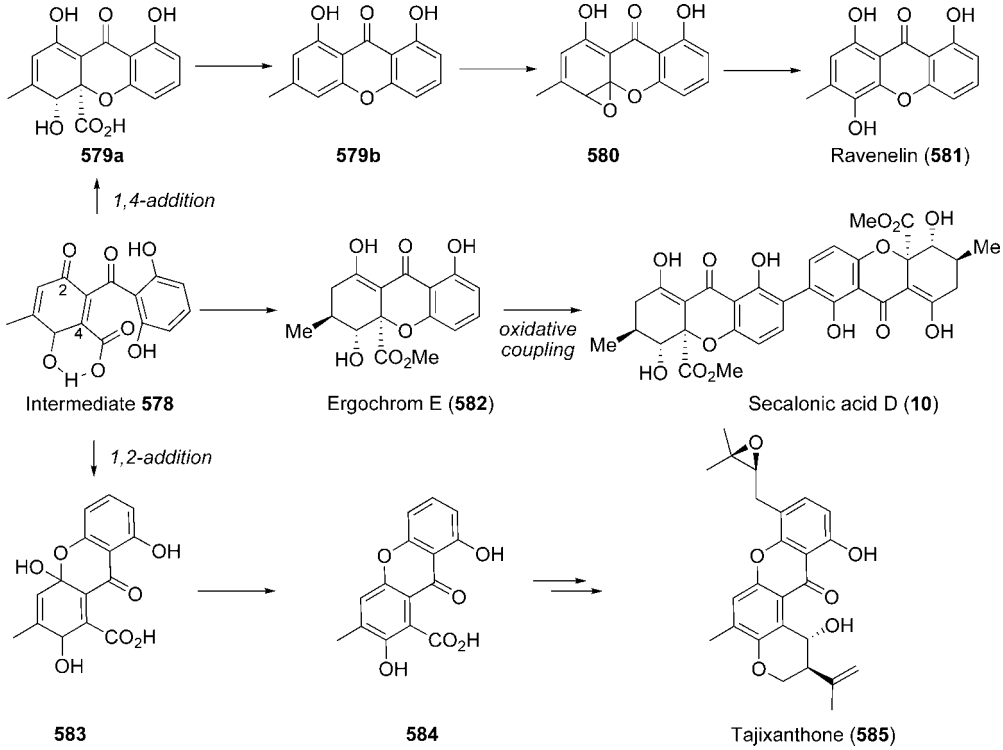
Scheme 70. Example of an Octaketide Biosynthesis (Part I): Emodin (573) and Islandicin (577)[1046]



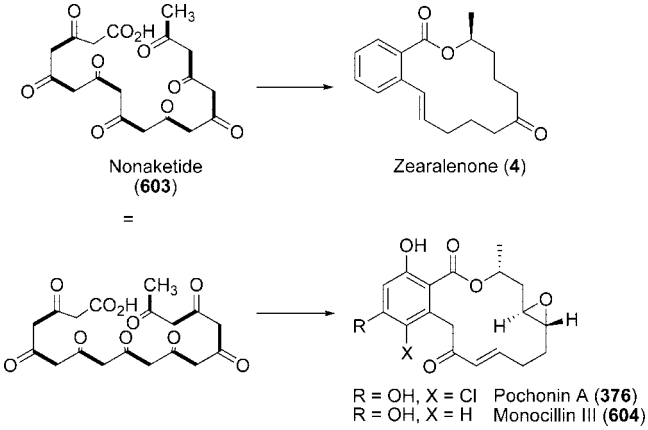
3.3.1. Mixed Biosynthesis

In some cases, a mixed origin has been established for mycotoxins. For example, the mycotoxins austin and terretonin in *Aspergillus ustus* and *A. terreus*, respectively, are mixed polyketides−terpenoids shown by incorporation of 3,5-dimethylorsellinate.[1058]

Scheme 71. Example of an Octaketide Biosynthesis (Part II): Ravenelin, Ergochroms, and Secalonic Acids[1046,1047]



Scheme 72. Example of a Nonaketide Biosynthesis: Zearalenone (4), Pochonins 376, and Monocillins 604[1031]



3.3.2. Directed Biosynthesis

The biosynthesis of novel mycotoxins can be influenced either by genetic modification or by feeding of biosynthetic precursors. For example, *Aspergillus fumigatus* TP-F0196 produces pseurotin A, synerazol, and gliotoxin (**527**). Phenylalanine is a common biosynthetic precursor of these antibiotics. Feeding fluorophenylalanine to the culture induced the production of novel fluorinated analogues.[558] These fluorinated antibiotics were obtained from the culture broth through solvent extraction and purified via chromatography, and their antimicrobial and antitumor activities were investigated. Among the novel fluorinated analogues, 19- and 20-fluorosynerazols exhibited potent antiangiogenic activity in the chorioallantoic membrane assay. In addition, 19-fluorosynerazol displayed more potent cytocidal activity against several cancer cell lines than synerazol.

4. Structure−Activity Relationships

The structure−activity relationship among the best-known mycotoxins was reviewed by Betina almost 20 years ago.[1059] In that work, the following features were described as common structural characteristics important for bioactivity present in most mycotoxins (Figure 28):

(1) The oxirane ring. Appears in cytochalasans and trichothecenes. Some trichothecenes even have two epoxy rings in their structure.

(2) Quinoid moieties (benzoquinone, naphthoquinone, and anthraquinone). An example is the benzoquinone moiety of terreic acid—a diabetogenic mycotoxin.

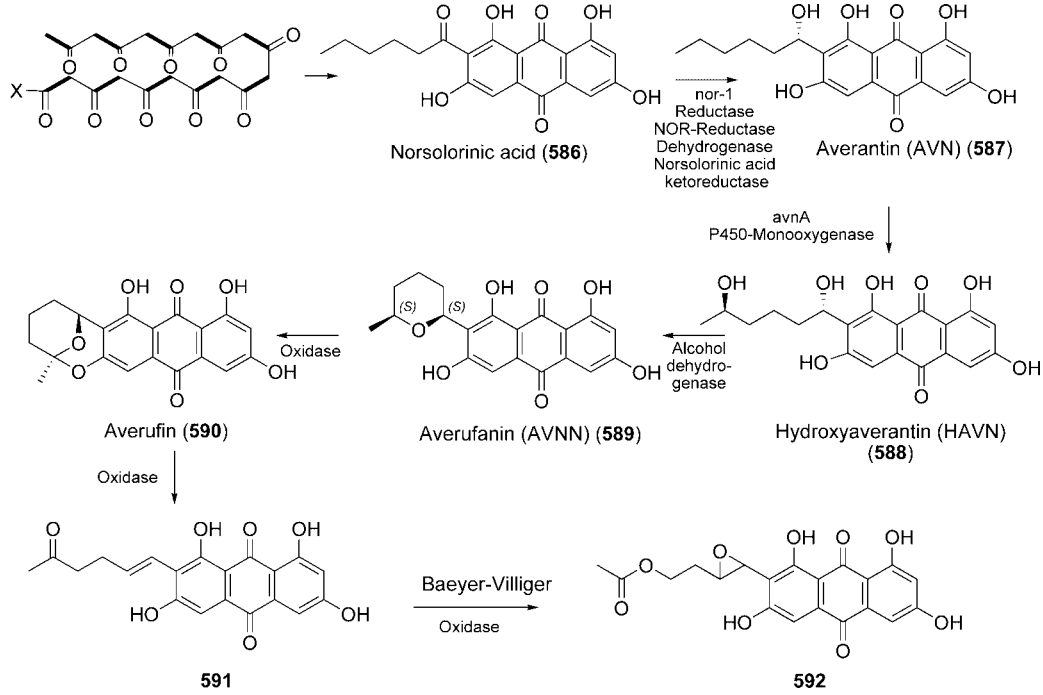
(3) Five-membered or six-membered lactones, either saturated or unsaturated. Small lactones are known to be highly toxic, acting as potential alkylating agents. As an example, Patulin (**3**) can react as an alkylating agent with DNA molecules. That is the reason why this family of molecules has mutagenic, carcinogenic, or teratogenic activity.

(4) Macrocyclic structures. Macrocyclic lactones (present in zearalenones like **4**, cytochalasans, and some trichothecenes) act as mycoestrogenes, whereas other macrocyclic compounds (such as cytochalasins or zygosporins like **440**) are cytotoxic compounds with particular effect on mammalian, protozoal, fungal, plant, and bacterial cells.

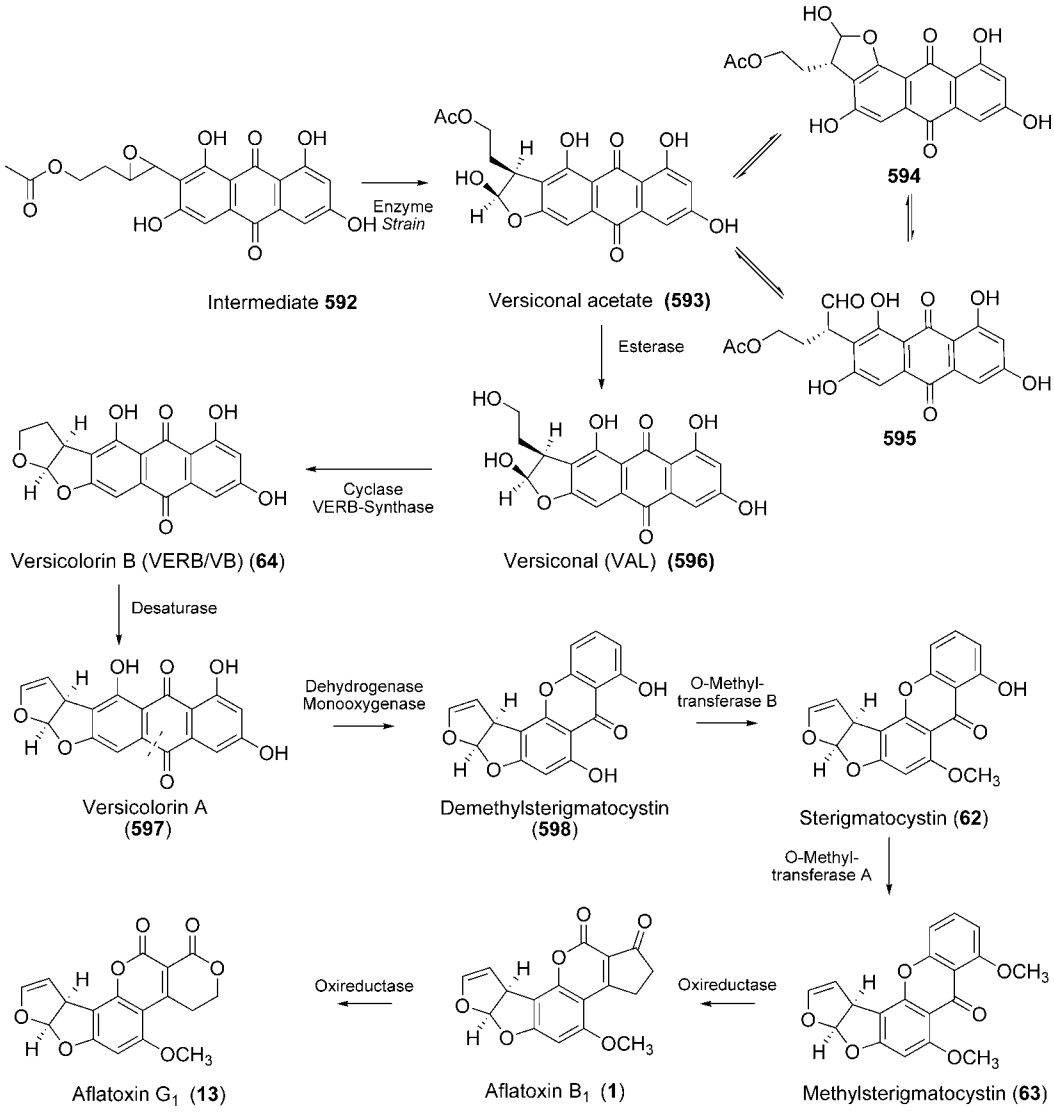
(5) Isocoumarins (with ochratoxins as the best example). The dihydroisocoumarin moiety in combination with L-β-phenylalanin (in ochratoxin A (**7**)) leads to inhibition of protein synthesis at the stage of amino acid activation, whereas in combination with benzoquinone (as in viomellein mycotoxins) it produces the uncoupling of oxidative phosphorylation.

After a detailed description of the common structural features present in mycotoxins crucial for the biological activities, some structure−activity relationship conclusions were drawn regarding the main mycotoxin families:

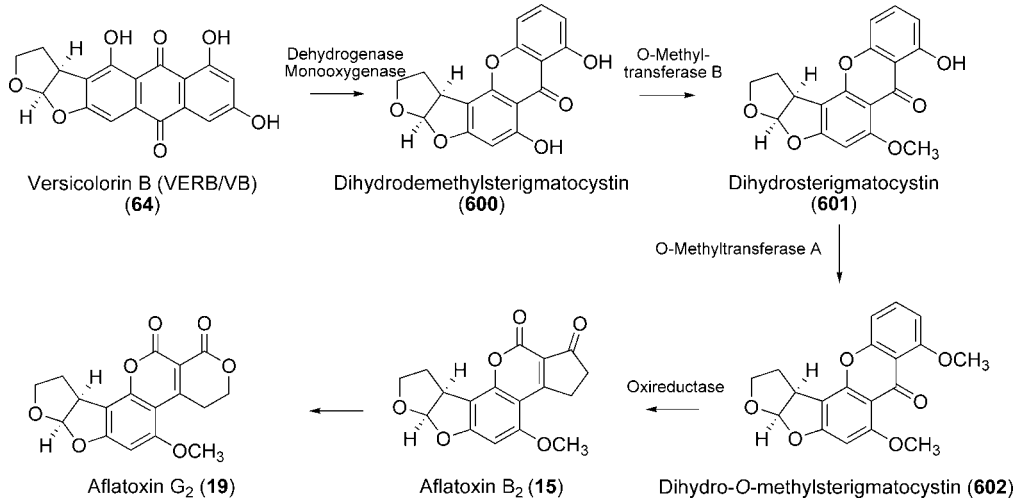
Scheme 73. Example of a Decaketide Biosynthesis: Aflatoxins and Related Compounds (Part I)[1031]



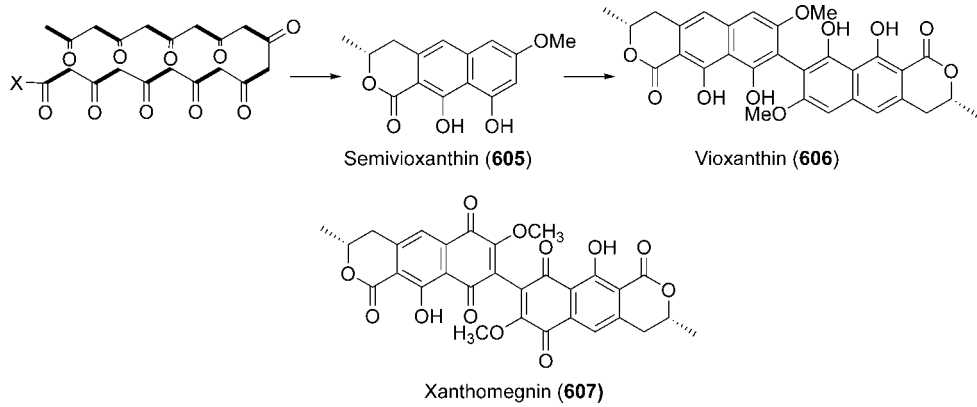
Scheme 74. Example of a Decaketide Biosynthesis: Aflatoxins and Related Compounds (Part II)[1031]



Scheme 75. Example of a Decaketide Biosynthesis: Aflatoxins and Related Compounds (Part IV)[1031]



Scheme 76. Example of a Decaketide Biosynthesis: Vioxanthin (606) and Related Compounds[1031]



Aflatoxins. The structural characteristics of primary importance in the biological activity of aflatoxins are as follows (Figure 29):

(a) The dihydrofuran moiety;

(b) The double bond in C2−C3; and

(c) The substituents linked to the coumarin skeleton.

Aflatoxin B_1, containing a cyclopentanone ring system, is much more potent than aflatoxin G_1 (**13**) with its unsaturated δ-lactone. When the coumarine ring is replaced by xanthone in sterigmatocystin (**62**), the main features of bioactivity of the aflatoxins are retained. In versicolorin A (**597**), the coumarin is replaced by an anthraquinoid moiety, changing the mode of action to an uncoupling of oxidative phosphorylation. The order of toxicity of the four major aflatoxins is $B_1 > G_1 > B_2 > G_2$.

Ochratoxins. By comparing the toxicity of ochratoxin A (**7**), B, C, and α and their structural differences, it could be said that the presence of the chlorine atom and the L-β-phenylalanine moiety are responsible for its toxicity and the inhibition of protein synthesis. Ochratoxin A (**7**) is the most toxic of the ochratoxins, and its structure comprises ochratoxin α linked to L-β-phenylalanine.

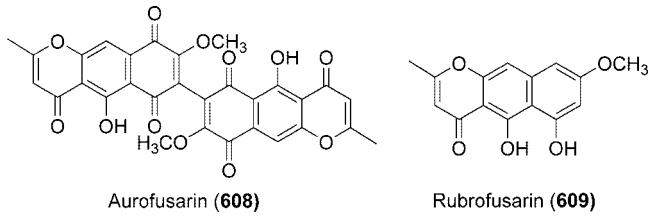


Figure 27. Aurofusarin (**608**) and rubrofusarin (**609**).

Trichothecenes. The most important features for this class are as follows:

(a) The double bond at C9−C10.

(b) The presence of the 12,13-epoxide. Verrucarin K, the first natural trichothecene lacking the 12,13-epoxy group, has not shown general toxicity; however, it presents high cytotoxic activity, suggesting that the macrocyclic part itself possesses cytotoxic activity.

(c) The presence of hydroxyl or other substituents at appropriate positions of the trichothecene nucleus. Baccharins that have a different O-substituent in the A ring have higher antileukemic activity than roridins and verrucarins.

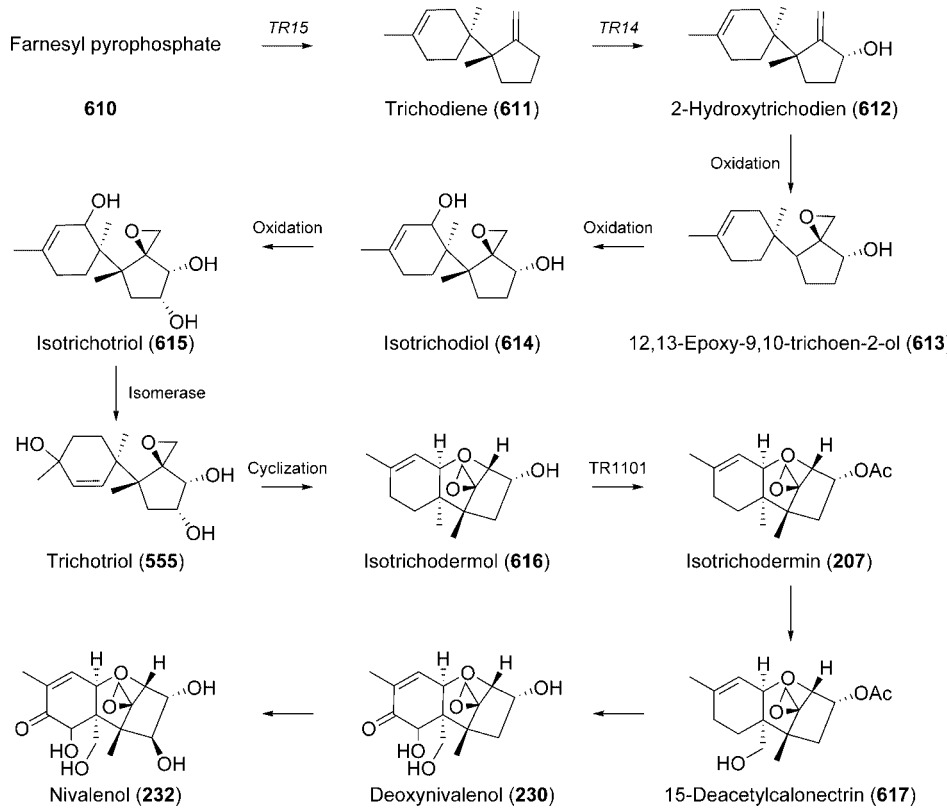
(d) The structure and position of the side chain.

(e) The presence of a second oxirane ring at C9−C10 on the trichothecene nucleus.

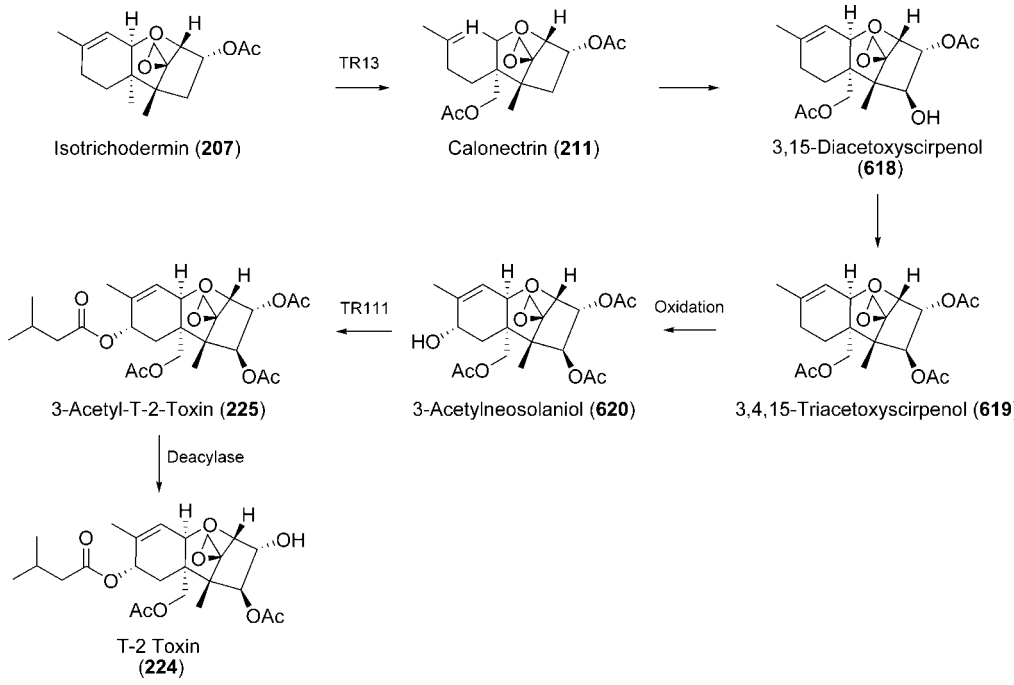
(f) The presence of a macrocycle, because it is important for their antileukemic activity.

Depending on the structure of the trichothecene, its biological activity can range from antibiotic, phytotoxic, cytotoxic, cancerostatic, antileukemic, immunosuppresive, antiviral, to insecticidal. As an example, the simple opening of the 12,13-epoxide ring results in nontoxic compounds (Verrucarin A is highly toxic but Verrucarin K is not). The presence of a C4 hydroxyl group in nivalenol (**232**) in comparison to the absence in Deoxynivalenol (**230**) makes it 10 times more toxic. Since that publication, a systematic

Scheme 77. Putative Biosynthesis of the Trichothecenes: Nivalenol (232)[1053]



Scheme 78. Putative Biosynthesis of the Trichothecenes: T-2 Toxin (224)[1053]



evaluation of structure−activity relationships (SARs) has not been conducted in the mycotoxin area.

Only a few studies have evaluated fumonisin analogues for their cytotoxicity, plant toxicity, and sphingolipid alterations. The results regarding the effects of fumonisin on the elevation of free sphingoid bases[1060] suggest that hydrolysis to remove the tricarballylic side chains reduces the biological activity and acetylation of the amino group eliminates the activity. The most potent inhibitors of ceramide synthase were the *Alternaria alternata* toxin, toxins $TA_{1,2}$ (**136/137**), which have a number of structural differences from that of FB1 (**92**), most notably a shorter hydrocarbon chain backbone than fumonisin, positioning of the amino group C1 instead of C2, and the absence of one of the TCA groups.

The reduced ability of hydrolyzed fumonisins to block ceramide synthase, and the different potencies of the other analogues relative to each other, could be related to varying degrees of membrane permeability and thereby differences in accessibility of the toxins to ceramide synthase sites within the liver cells.

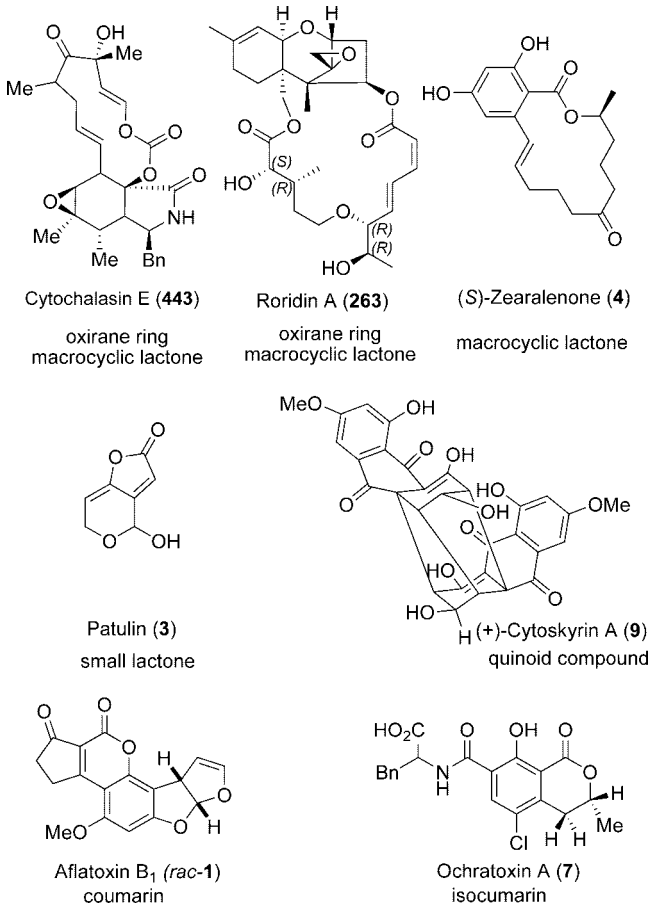


Figure 28. Common features in mycotoxins.

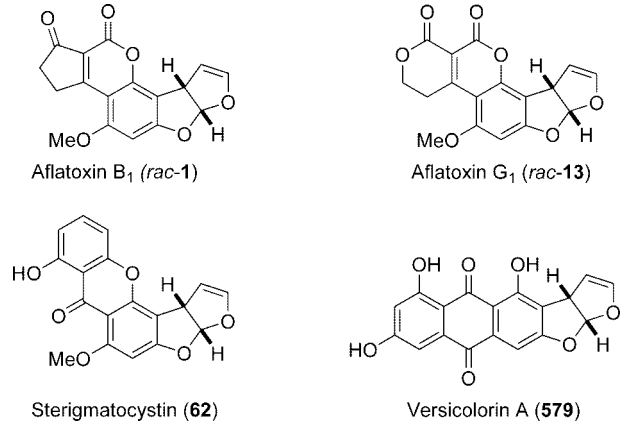


Figure 29. Structure of different aflatoxins.

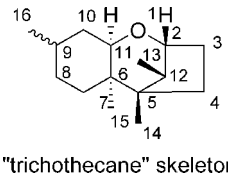


Figure 30. Main structure of the trichothecene skeleton.

In 2001, a SAR study on zearalenones was undertaken to better understand their estrogenicity on a human estrogen receptor.[1061] The estrogenicity of zearalenone and 16 structural analogues was compared. Overall, about one-half of the analogues examined in that study exhibited higher estrogenicity than zearalenone (the most abundant toxin of the class produced by *Fusarium* species). The analogues examined provided information about the roles played by several parts of the zearalenone molecule in estrogenic activity with the human estrogen receptor of MCF7. The 6′ functional group has the largest effect on estrogenicity. The strongest estrogenicity was observed with α-zearalenol (**320**) (α-OH at the 60 position). The order of estrogenicity for 60 substituents is α-OH ≫ NH_2 ≥ O < β-OH ≈ β-OAc. Current activity with trichothecenes has focused on immune responses and cell-signaling pathways.

5. Mycotoxins and Related Compounds As Potential Therapeutics

There is increasing interest in plant extracts as potential therapeutic agents.[1062] In general, as we have explained in section 1.2, mycotoxins are toxic metabolites. In contrast, some of the compounds provide interesting pharmaceutical use.

The ergot alkaloids exhibit complex and variable pharmacological impacts because of their action as agonist or antagonist at the adrenergic, dopaminergic, and serotonergic receptors. The earliest authenticated reports of the effects of ergot were located in Chinese writings in ~1100 BC, when the substance was used in obstetrics. Nowadays, there are several commercialized derivatives, most of which are not naturally occurring, that are indicated by the Food and Drug Administration (FDA) for the treatment of different diseases. These applications were thoroughly reviewed by Schiff in 2006. As an example, the ergonovine, a lysergic acid amide alkaloid, behaves as an agonist of tryptaminergic receptors in smooth muscles. For this reason, it is employed for uterine stimulation in the routine management of postpartum uterine atony and hemorrhage. It is also utilized as a diagnosis test for Prinymetal's angina. Ergotamine derivatives, such as ergotamine (**8**) or dihydroergotamine, are peptide alkaloids used in abortions or prevention of vascular headaches, such as migraines, migraine variants, cluster headaches, and histaminic cephalea. Bromocriptine, also a peptide alkaloid, is a semisynthetic derivative commercialized for the treatment of Parkinsonism juxtaposed with L-dopa therapy in patients who are experiencing a deteriorating response or fluctuating reactions to the drug. Another indication of bromocriptine is the therapy of hyperprolactinemia (state of persistent elevation of serum prolactin levels that may result in infertility and amenorrhea in females and galactorrhea in both males and females). Although the hallucinogen ergot alkaloid Lysergic acid diethyl amide (LSD) is no longer clinically employed, it was used unsuccessfully in psychiatry (just after the discovery of its pharmacological effects) for the treatment of acute obsessive illnesses such as alcoholic schizophrenia.

The trichothecenes have been associated with various biological properties, such as the following:

(a) Antiviral, especially as inhibitors of the replication of Herpes Simplex Virus type 2[1063] and type 1.[1064] Some derivatives have also shown inhibition capacity against arenavirus Junin (JUNV), the ethiological agent of the Argentine hemorrhagic fever.[937]

(b) Antibiotic.

(c) Antimalarial.[936,1065]

(d) Antileukemic.[1066]

(e) Immunotoxic.[1067]

In 2004, the Oshima group described the development of synthetic spirocyclic tricothecanes with activity in neurotrophic factor biosynthesis.[1068] Recently, Zaichenko reviewed the experimental data in the biological activity of macrocyclic trichothecenes from the last 30 years. The

authors have shown the multifaceted biological effects of, in particular, their antibiotic, phytotoxic, insecticidal, cytotoxicity, and antitumor activities.[1069]

Zearalenone is classified as a nonsteroidal estrogen or mycoestrogen. It has been used to treat postmenopausal symptoms in women, and its reduced form, zearalenol, has shown increased estrogenic activity and has been commercialized as an anabolic agent to promote growth in sheep and cattle. Moreover, zearalenone and zearalenol (**320**) are patented as oral contraceptives.

Citrinin displays antibiotic activity against Gram-positive bacteria[877] and was even described as the "antibiotic of the future" in 1952.[1070] More recently citrinin has been tested against *Leshmania*, showing very promising activity in the inhibition of growth.[1071]

Patulin is known as bacterial mycotoxin. It inhibits potassium uptake and activates the p38 kinase. In the 1990s, *Fusarium* sp. was shown to inhibit HIV-1 integrase.[1072] Some mycotoxins derivatives are described as antimitotic agents.[1073]

6. Conclusions/Summary

Mycotoxins are a major threat to human life.[846] While a number of diseases associated with the toxicological impact of mycotoxins have been eradicated, globally increasing population density, together with a stricter usage of fungicides, has caused increasing awareness of the different classes of mycotoxins. Refinements of chromatographical techniques and methods of chemical and biological characterization have led to the discovery of new toxins excreted from lower and higher fungi.

The structure−activity relationship has been established for some classes of mycotoxins; however, most mycotoxins remain unexplored. The comprehensive understanding of biochemical pathways−both production and metabolism of fungal metabolites−should be a goal in mycology.

It is expected that microarray techniques will be extremely helpful in this regard; the first "mycochips" are already on the market. However, simple and reliable methods for the detection of mycotoxins are still needed.

7. Abbreviations

AA	amino acid
Aoh	(s)-2-amino-7-oxoheptanoic acid
TCA	tricarballylic acid

8. Acknowledgments

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