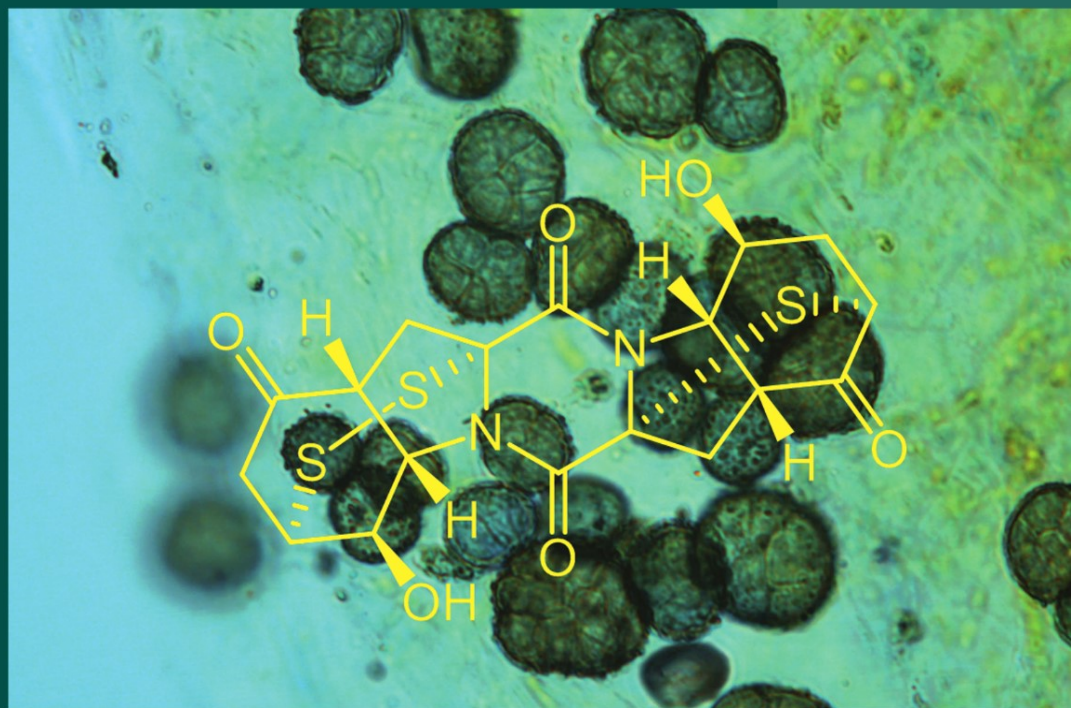


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S. Lindner, A.M. Linsenmeier, K.-S. Masters,  
A.C. Meister, B.M. Ruff, and S. Zhong

# The Chemistry of Mycotoxins



 Springer

Progress in the Chemistry  
of Organic Natural Products

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ISSN 2191-7043 ISSN 2192-4309 (electronic)  
ISBN 978-3-7091-1311-0 ISBN 978-3-7091-1312-7 (eBook)  
DOI 10.1007/978-3-7091-1312-7  
Springer Wien Heidelberg New York Dordrecht London

Library of Congress Control Number: 2012951144

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# 1 Introduction

Mycotoxins – from the Greek *μύκης* (*mykes*, *mukos*) “fungus” and the Latin *toxicum* “poison” – are a large and growing family of secondary metabolites and hence natural products produced by fungi, in particular by molds (1). It is estimated that well over 1,000 mycotoxins have been isolated and characterized so far, but this number will increase over the next few decades due the availability of more specialized analytical tools and the increasing number of fungi being isolated. However, the most important classes of fungi responsible for these compounds are *Alternaria*, *Aspergillus* (multiple forms), *Penicillium*, and *Stachybotrys*. The biological activity of mycotoxins ranges from weak and/or sometimes positive effects such as antibacterial activity (*e.g.* penicillin derivatives derived from *Penicillium* strains) to strong mutagenic (*e.g.* aflatoxins, patulin), carcinogenic (*e.g.* aflatoxins), teratogenic, neurotoxic (*e.g.* ochratoxins), nephrotoxic (*e.g.* fumonisins, citrinin), hepatotoxic, and immunotoxic (*e.g.* ochratoxins, diketopiperazines) activities (1, 2), which are discussed in detail in this volume.

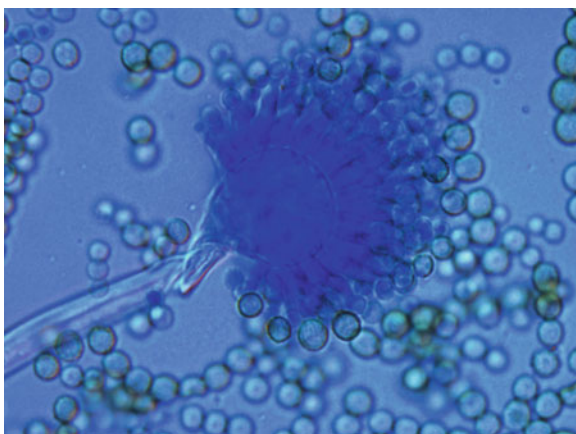
The hazardous nature of mycotoxins was first associated with a disease (mycoroxicosis) in the mid-1950s (3), however, mycotoxin-associated diseases have been known for centuries. For example, aflatoxin was isolated and identified in 1961, following a 1960 incident in which 100,000 turkey poults in the British Isles died from eating feed containing contaminated peanut meal (3).

Currently, many laboratories around the world have specialized in the detection of mycotoxins (4) in food products and contaminated housing supply materials (5). A large number of review articles, books, and book chapters have appeared on this topic in the last 50 years.

In this volume, we will focus on the most important classes of mycotoxins and discuss advances in their chemistry over the last ten years. In each section, the individual biological impact will be discussed. The chapters have been arranged according to mycotoxin class (*e.g.* aflatoxins) and/or structural classes (*e.g.* resorcylic acid lactones (6), diketopiperazines (7, 8)). The biological aspects will be treated only in brief (9). For a recent, comprehensive treatise of mycotoxin chemistry, we refer the reader to a major review (10).

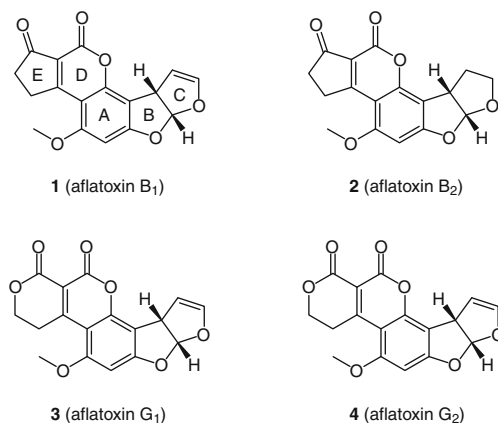
## 2 Aflatoxins

The aflatoxins were discovered in the 1960s, when they were identified as toxic compounds of the fungus *Aspergillus flavus*, which is shown in Fig. 2.1 (11, 12).



**Fig. 2.1** *Aspergillus flavus* spores as seen under the light microscope under 600-fold magnification

This fungus was found in ground nut meal, which had been fed to different farm animals. Due to this contamination, 100.000 turkeys died in 1960 in Britain of the so-called “Turkey-X disease” (13). Later, the aflatoxins were also found in other *Aspergillus* species and in some *Penicillium* fungi. The name “aflatoxin” is an abbreviation of *Aspergillus flavus* toxins (14). Up to the present, the aflatoxins are among the most acutely toxic and carcinogenic compounds known (13). Although most countries in the world now have limitations for the maximum tolerated levels of aflatoxins in food, contamination by these compounds is still a problem (15). Aflatoxins are found regularly in different foods, especially the milk of cows, which gets intoxicated by affected animal feed (13, 15, 16).

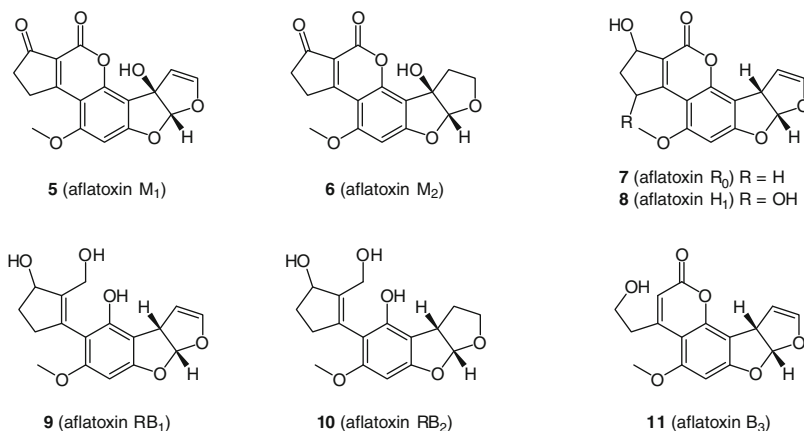


**Fig. 2.2** The aflatoxins B<sub>1</sub>, B<sub>2</sub>, G<sub>1</sub>, and G<sub>2</sub> (1–4)

The most widely examined aflatoxin is aflatoxin B<sub>1</sub> (**1**), which is also the most toxic, carcinogenic, and mutagenic aflatoxin among all that are presently known (17, 18). It was isolated together with aflatoxins B<sub>2</sub> (**2**), G<sub>1</sub> (**3**), and G<sub>2</sub> (**4**), which are shown in Fig. 2.2 (19). Their structures were revealed by the group of Büchi in 1963 (B<sub>1</sub> (**1**) and G<sub>1</sub> (**3**)) and 1965 (B<sub>2</sub> (**2**) and G<sub>2</sub> (**4**)) (20, 21). This group also elucidated the absolute stereochemistry of aflatoxins in the B and G series by chemical degradation (22). Structurally, these compounds consist of five rings, having a furofuran moiety (rings B and C), an aromatic six-membered ring (A), a six-membered lactone ring (D), and either a five-membered pentanone or a six-membered lactone ring (E).

While the aflatoxins B and G are major compounds of the fungus *Aspergillus flavus*, there are also minor aflatoxin constituents from this organism, e.g. hydroxylated derivatives of aflatoxin B<sub>1</sub> (**1**) and B<sub>2</sub> (**2**), the so-called “milk-toxins”, M<sub>1</sub> (**5**) and M<sub>2</sub> (**6**), which bear a hydroxy group at the junction of the two furan rings (19). They are called “milk toxins”, because they are metabolites of aflatoxin B<sub>1</sub> (**1**) and B<sub>2</sub> (**2**), formed when cows get fed with contaminated foodstuffs. The toxins are then contained in the cow’s milk. Other aflatoxins have a hydroxy group instead of



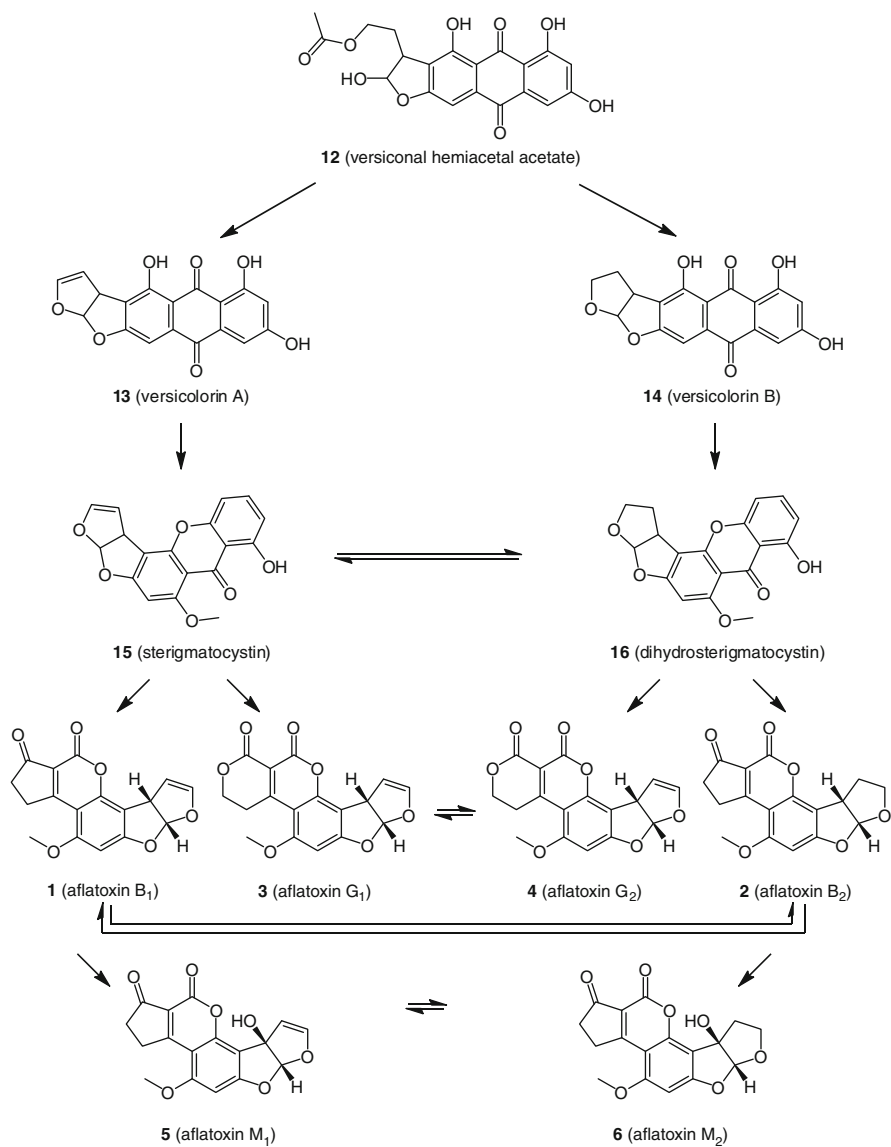


**Fig. 2.3** Selected aflatoxins

a carbonyl group at ring E (R<sub>0</sub> (**7**), RB<sub>1</sub> (**9**), RB<sub>2</sub> (**10**), and H<sub>1</sub> (**8**)). They can be formed by microbial transformation or by chemical reduction with sodium borohydride (23, 24). In some aflatoxins, the D-ring (RB<sub>1</sub> (**9**), RB<sub>2</sub> (**10**)) or the E-ring (B<sub>3</sub> (**11**)) is opened. Aflatoxin B<sub>3</sub> (**11**) is also called parasiticol, because it was first isolated from *Aspergillus parasiticus* (23). All aflatoxins shown in Fig. 2.3 are metabolic transformation products from the aflatoxins B (19).

Biosynthetically, the aflatoxins are all formed from the same precursor, versiconal hemiacetal acetate (**12**) (25). Compound **12** is formed from acetate, the units of which are converted into a polyketide. The polyketide is then metabolized to the xanthone **12** (see Scheme 2.1) (26). Intermediate **12** can then be transformed either into versicolorin A (**13**) or versicolorin B (**14**) in several steps. Versicolorin A (**13**) may be converted to sterigmatocystin (**15**), while **14** can lead to dihydrosterigmatocystin (**16**). Sterigmatocystin (**15**) can be metabolized to aflatoxins G<sub>1</sub> (**3**) or B<sub>1</sub> (**1**) and the latter may then be transformed to aflatoxin M<sub>1</sub> (**5**). Aflatoxins B<sub>2</sub> (**2**) and G<sub>2</sub> (**4**) are formed from dihydrosterigmatocystin (**16**) and aflatoxin M<sub>2</sub> (**6**) is formed by conversion from B<sub>2</sub> (**2**). Pathways also exist to convert aflatoxin B<sub>1</sub> (**1**) to B<sub>2</sub> (**2**), M<sub>1</sub> (**5**) to M<sub>2</sub> (**6**), and *vice versa*. Important biosynthesis steps are shown in Scheme 2.1.





**Scheme 2.1** Biosynthesis of aflatoxins B (1, 2), G (3, 4), and M (5, 6); an arrow can represent more than one step

## 2.1 Biological Properties

Aflatoxins are acutely toxic compounds, and produce hepatic changes, which can cause serious liver damage (27). The liver is the main organ affected, followed by the kidneys. Hemorrhage, cirrhosis, and fatty degeneration of the liver are the most common effects on ingestion, but the pancreas, gall bladder, lung, and gut may also be affected (28).

When taken orally, the aflatoxins are absorbed from the gut and are transported to the liver where they are metabolized. For example, aflatoxin B<sub>1</sub> (**1**) may be transformed to aflatoxin M<sub>1</sub> (**5**), representing a detoxification, since aflatoxin M<sub>1</sub> (**5**) is less active than aflatoxin B<sub>1</sub> (**1**) (see below) (27). However, a common metabolic process is diol formation at the double bond of the furan ring. The resultant aflatoxin B<sub>1</sub>-2,3-diol is much more toxic than aflatoxin B<sub>1</sub> (**1**) itself. Accordingly, diol formation results from metabolic activation to a very toxic species (29).

Among the naturally occurring aflatoxins, aflatoxin B<sub>1</sub> (**1**) is the most acutely toxic representative, followed by aflatoxins G<sub>1</sub> (**3**), B<sub>2</sub> (**2**), and G<sub>2</sub> (**4**). This is shown by *LD*<sub>50</sub> values of one-day-old ducklings. While the *LD*<sub>50</sub> of aflatoxin B<sub>1</sub> (**1**) is 0.36 mg/kg, the corresponding value for aflatoxin B<sub>2</sub> (**2**) is five times higher, with this compound containing a saturated furan ring. This shows that the unsaturated furan moiety has an important effect on acute toxicity. On comparing the *LD*<sub>50</sub> value of aflatoxin G<sub>1</sub> (**3**) with that of B<sub>1</sub> (**1**), where the cyclopentanone ring has been converted in the former compound into a six-membered lactone ring, **3** is considerably less potent (0.78 mg/kg). Therefore, the cyclopentanone ring is of lesser importance for the mediation of acute toxicity (27, 30).

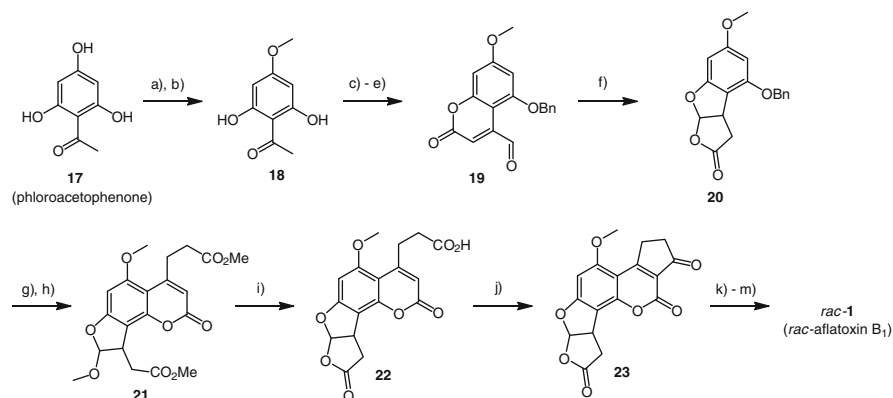
Besides their acute toxicity, aflatoxins are also highly carcinogenic. In fact, aflatoxin B<sub>1</sub> (**1**) is the most potent known liver carcinogen for mammals. It can not only induce tumors and metastases when directly injected, but also when it is given orally over a long period (13). Aflatoxins inhibit DNA-, RNA-, and protein biosynthesis by adduct formation (14, 31, 32). Their mutagenic potential is related to these biological effects. Structure-activity relationships for the carcinogenicity and mutagenicity of aflatoxins show the same general trends as for their acute toxicity. After aflatoxin B<sub>1</sub> (**1**), aflatoxin R<sub>0</sub> (**7**) is the most powerful mutagen, followed by aflatoxins M<sub>1</sub> (**5**), H<sub>1</sub> (**8**), B<sub>2</sub> (**2**), and G<sub>2</sub> (**4**) (17). When tested for their effects on chromosomes, aflatoxins cause a highly significant increase in the number of abnormal anaphases, with fragmentation of the chromosomes and inhibition of mitosis being observed (13).

The high toxicity and carcinogenicity of the aflatoxins makes it impractical to use them as pharmacological agents. Only very few studies have been carried out to investigate their potential as drugs or pesticides. In one study, it was shown that aflatoxins are able to inhibit sporulation of different fungi by inhibiting the activity of essential enzymes (33). However, the fact that they belong to the most toxic, carcinogenic, and mutagenic group of mycotoxins known, makes it improbable that these substances will ever be applied as therapeutic agents.

## 2.2 Total Syntheses of Aflatoxins

### 2.2.1 Total Syntheses of Racemic Aflatoxins

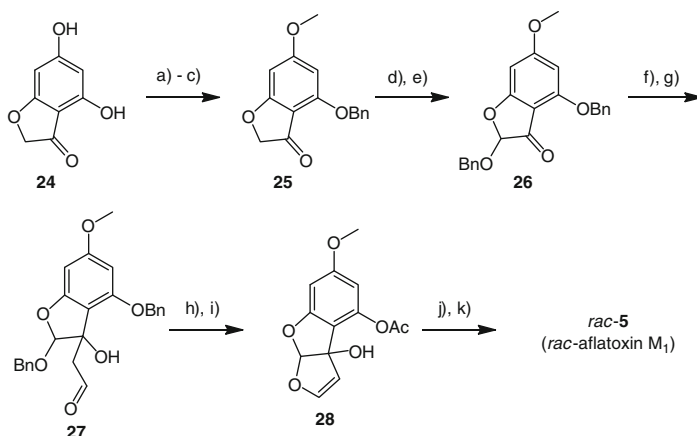
The group of *Büchi*, who also determined the structure and absolute configuration of several aflatoxins (20–22), achieved the first total synthesis of racemic aflatoxin B<sub>1</sub> (**1**) in 1966 (34, 35). They started from phloroacetophenone (**17**), which was converted in two steps into its monomethyl ether **18** (see Scheme 2.2). Selective monobenzoylation, followed by *Wittig* condensation and selenium dioxide oxidation gave the bicyclic aldehyde **19** in good yield.



**Scheme 2.2** First total synthesis of aflatoxin B<sub>1</sub> (**1**), achieved by *Büchi et al.*. Reagents and conditions: a) Ac<sub>2</sub>O, 110–165°C, 2 h, 40%; b) CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O/dioxane, rt; then HCl, MeOH, reflux, 8 h, 83%; c) BnBr, K<sub>2</sub>CO<sub>3</sub>, acetone, rt, 14 h, 82%; d) carboxymethylenetriphenylphosphorane, 170°C, 19 h, 72%; e) SeO<sub>2</sub>, xylene, reflux, 5 h, 93%; f) Zn, HOAc, 100–120°C, 1.5 h, 80%; g) H<sub>2</sub>, Pd/C, ethanol, rt, 2 h, quant; h) β-oxoadipate, HCl, MeOH, –12 to –20°C; then 3–5°C, 18 h, 57%; i) HOAc, H<sub>2</sub>O, HCl (aq.), rt, 24 h, quant; j) (COCl)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 5°C to rt, 48 h; then AlCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, –5 to 5°C, 10 h; then HCl, rt, 2 h, 37%; k) disiamylborane, diglyme/THF, 60°C, 84 h, 16%; l) *p*-TsOH (cat.), Ac<sub>2</sub>O, HOAc, rt, 12 h, 70%; m) 240°C, 15 min, 0.01 mm, 40%

Reduction of the double bond with zinc/glacial acetic acid and *in situ* rearrangement resulted in the tricyclic species **20**, which already possesses three of the five aflatoxin rings. Deprotection of the benzyl ether by hydrogenation, followed by a *Pechmann* condensation with ethyl methyl β-oxoadipate gave the lactone **21**. The two methyl esters and the methyl ether were hydrolyzed under acidic conditions and the lactone **22** formed immediately. Conversion of the acid into its chloride with oxalyl chloride formed the five-ring lactone **23**. Reduction to the corresponding lactol, acetoxylation, and pyrolysis gave racemic aflatoxin B<sub>1</sub> (**1**) in 13 steps and 0.9% overall yield from **17**.

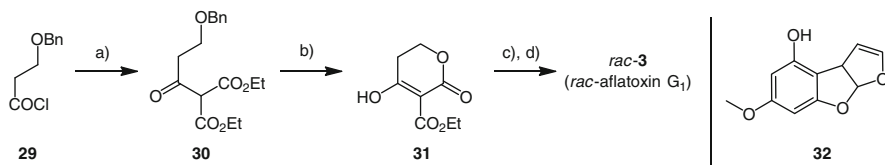
In 1969, Büchi *et al.* published the first total synthesis of racemic aflatoxin M<sub>1</sub> (**5**) (36). They started with the diol **24**, which was first dimethylated with dimethyl sulfate, then mono deprotected by aluminum chloride, and finally benzylated to afford species **25** (see Scheme 2.3).



**Scheme 2.3** Total synthesis of racemic aflatoxin M<sub>1</sub> (**5**) by Büchi *et al.* Reagents and conditions: a) Me<sub>2</sub>SO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, dimethoxyethane, reflux, 3 h, 79%; b) AlCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 1.25 h; then HCl, reflux, 64%; c) BnBr, K<sub>2</sub>CO<sub>3</sub>, dimethoxyethane/DMF, reflux, 74%; d) Me<sub>3</sub>NPhBr<sub>3</sub>, THF, 88%; e) CaCO<sub>3</sub>, BnOH, Δ, 1.5 h, 65%; f) allylmagnesium bromide, THF/Et<sub>2</sub>O, 0°C, 10 min; g) NaIO<sub>4</sub>, OsO<sub>4</sub>, NaHCO<sub>3</sub>, dioxane/water, rt, 1 h, 63% over two steps; h) H<sub>2</sub>, Pd/C, NaOAc, Ac<sub>2</sub>O/benzene, rt, 1.5 h, 27%; i) toluene, 450°C, 73%; j) NaHCO<sub>3</sub>, MeOH/H<sub>2</sub>O, rt, 0.75 h, 94%; k) 2-carboxy-3-bromocyclopent-2-enone, NaHCO<sub>3</sub>, ZnCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 20 h, 32%

Bromination at the α-position to the carbonyl group, and conversion into the benzyl ether gave acetal **26**. Grignard addition of allylmagnesium bromide to the ketone, followed by diol formation and oxidative glycol cleavage with sodium periodate and osmium tetroxide, yielded aldehyde **27**. Hydrogenolysis of the two benzyl ethers, followed by acetoxylation and pyrolysis gave the tricyclic alcohol **28**. The acetoxy group was cleaved by basic hydrolysis and the resulting alcohol was coupled with 2-carboxyethyl-3-bromocyclopent-2-enone to give racemic aflatoxin M<sub>1</sub> (**5**) in 11 linear steps from **24** and 0.7% overall yield.

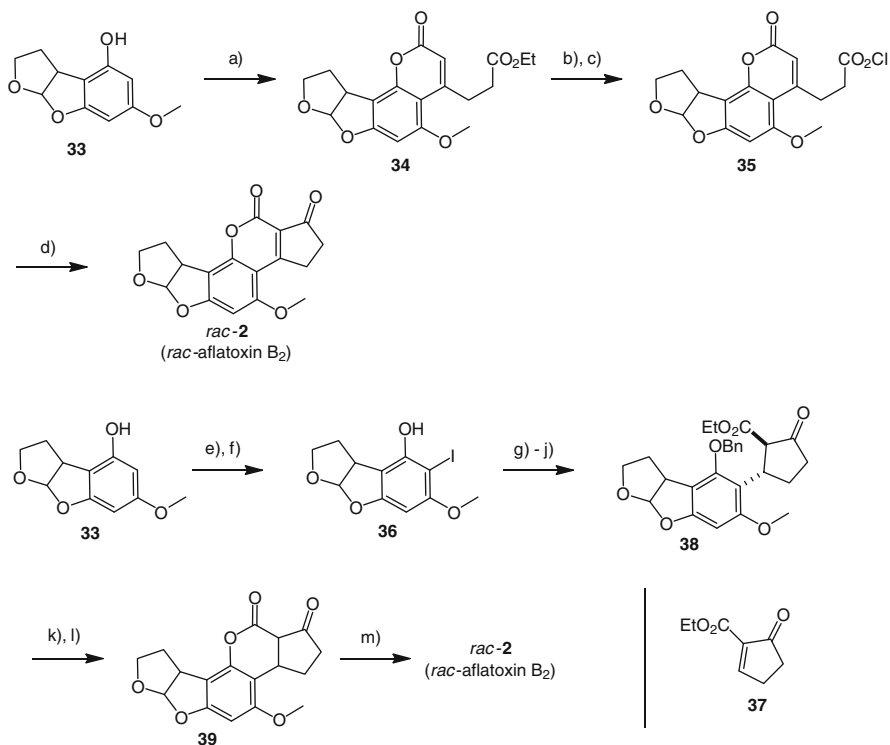
One year later, in 1970, Büchi and Weinreb presented a total synthesis of racemic aflatoxin G<sub>1</sub> (**3**) and an improved synthesis of aflatoxin B<sub>1</sub> (**1**) (37). The synthesis of **1** involved the same coupling with a cyclopentenone as described above for the total synthesis of aflatoxin M<sub>1</sub> (**5**) (see last step in Scheme 2.3). Accordingly, this group was able to increase the overall yield to 2.5% with the same number of reaction steps.



**Scheme 2.4** Total synthesis of racemic aflatoxin G<sub>1</sub> (**3**). Reagents and conditions: a) diethylmalonate, Mg, ethanol/CCl<sub>4</sub>, 0°C; then Et<sub>2</sub>O, reflux, 3 h; then **29**, Et<sub>2</sub>O, rt, 2 h, 97%; b) H<sub>2</sub>, Pd/C, EtOAc, rt, 2 h, 64%; c) (COBr)<sub>2</sub>, benzene, rt, 96%; d) **32**, ZnCO<sub>3</sub>, LiI, CH<sub>2</sub>Cl<sub>2</sub>, rt, 3 h; then reflux, 7 h; then rt, 14%

The synthesis of aflatoxin G<sub>1</sub> (**3**) is shown in Scheme 2.4. The acid chloride **29** was coupled with diethyl malonate (→ **30**), then the benzyl protecting group was removed by hydrogenolysis and lactone **31** formed. Conversion of the hydroxy group into the bromide with oxalyl bromide, followed by coupling with building block **32** gave racemic aflatoxin G<sub>1</sub> (**3**). Different syntheses of the tricycle **32** are presented in Sect. 2.3.2.

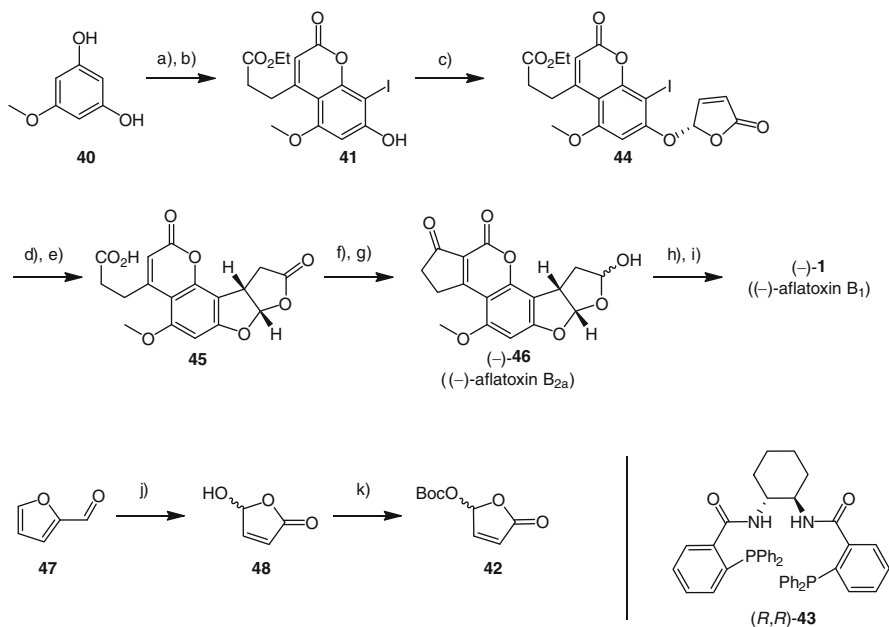
Aflatoxin B<sub>2</sub> (**2**) was first synthesized by *Roberts et al.* in 1968 (38). They started from the tricyclic compound **33**, for which the synthesis is described in Sect. 2.3.1. *Pechmann* condensation with diethyl β-oxoadipate generated the lactone **34**. Hydrolysis of the ethyl ester, followed by acid chloride formation with oxalyl chloride, gave **35**. This was used without further purification for a *Friedel-Crafts* acylation reaction to yield racemic aflatoxin B<sub>2</sub> (**2**). The synthesis is presented in Scheme 2.5, which also shows another total synthesis of aflatoxin B<sub>2</sub> (**2**). The second one was published in 1990 by *Horne et al.* (39). This group started from the same intermediate **33** and first diiodinated it. Regioselective deiodination gave **36**. The free alcohol was then protected as a benzyl ether, then a metal halogen exchange was realized with *n*-BuLi, followed by a transmetalation with lithium 2-thienylcyano cuprate. Final cuprate addition to the cyclopentanone **37** gave **38**. Cleavage of the benzyl ether by hydrogenolysis and acidic cleavage of the ester group produced the five-ring-species **39** *in situ*. Oxidation to aflatoxin B<sub>2</sub> (**2**) was achieved with DDQ.



**Scheme 2.5** Syntheses of aflatoxin B<sub>2</sub> (**2**) by Roberts *et al.* (above) and by Horne *et al.* (below). Reagents and conditions: a) diethyl β-oxoadipate, HCl, ethanol, rt, 19%; b) KOH, ethanol, reflux, 2 h, 76%; c) (COCl)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>; d) AlCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -5°C, 3 h, 38% over two steps; e) Me<sub>3</sub>BnNiCl<sub>2</sub>, MeOH/CH<sub>2</sub>Cl<sub>2</sub>; f) NaH, 0°C; then *n*-BuLi, -100°C, 15 min, 70%; g) BnBr, K<sub>2</sub>CO<sub>3</sub>; h) *n*-BuLi, -78°C; i) lithium 2-thienylcyano cuprate, -78°C to 0°C; j) **37**, -78°C to rt, 60% over three steps; k) H<sub>2</sub>, Pd/C, EtOAc, rt, 9 h, 200 psi; l) TFA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 60% over two steps; m) DDQ, dioxane, rt, quant

### 2.2.2 Enantioselective Total Syntheses of Aflatoxins

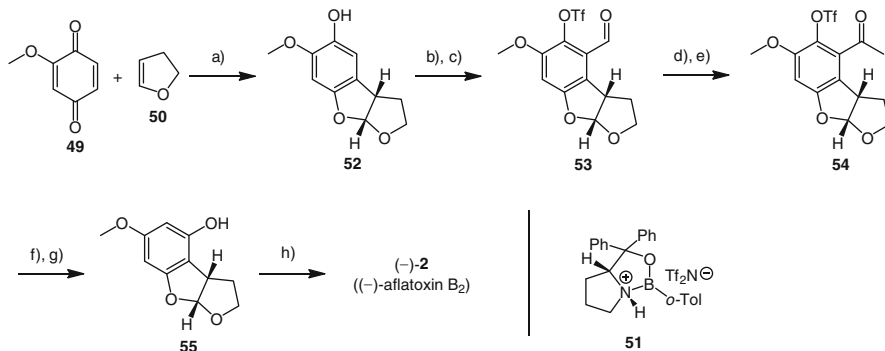
In 2003, Trost and Toste presented the first enantioselective total synthesis of aflatoxins B<sub>1</sub> (**1**) and B<sub>2a</sub> (**46**) (40, 41). In Scheme 2.6, their synthesis is shown. The starting material for this sequence is catechol **40**. A Pechmann condensation with diethyl β-oxoadipate and iodination with iodine chloride gave the lactone **41**.



**Scheme 2.6** Enantioselective total synthesis of (-)-aflatoxin B<sub>2a</sub> (**46**) and (-)-aflatoxin B<sub>1</sub> (**1**). Reagents and conditions: a) diethyl β-oxoadipate, HCl, ethanol, rt, 3 d, 47%; b) ICl, CH<sub>2</sub>Cl<sub>2</sub>, rt, 30 min, 92%; c) **42**, Pd<sub>2</sub>dba<sub>3</sub>•CHCl<sub>3</sub>, (*R,R*)-**43**, tetrabutylammonium chloride, CH<sub>2</sub>Cl<sub>2</sub>, rt, 12 h, 89%; d) (CH<sub>3</sub>CN)<sub>2</sub>PdCl<sub>2</sub>, NEt<sub>3</sub>, DMF, 60°C, 1 h, 93%; e) HCl, HOAc, H<sub>2</sub>O, rt, 2 d, quant; f) Sc(OTf)<sub>3</sub>, LiClO<sub>4</sub>, CH<sub>3</sub>NO<sub>2</sub>, 60°C, 4 h, 32%; g) DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78°C, 1 h, 57%; h) Ac<sub>2</sub>O, HOAc, rt, 20 h; i) 240°C, 15 min, 24% over two steps; j) Rose Bengal, O<sub>2</sub>, MeOH, 450 W Hg lamp, 8 h; k) Boc<sub>2</sub>O, pyridine, THF, rt, 12 h, 61% over two steps

The stereogenic centers were then introduced by palladium-catalyzed dynamic kinetic asymmetric transformation. Therefore, **41** was coupled with lactone **42** in the presence of chiral ligand (*R,R*)-**43** and gave **44** in 89% yield. The synthesis of **42** is shown below in Scheme 2.6. Compound **44** was subjected to an intramolecular Heck reaction followed by acidic cleavage of the ester function (→ **45**). The intramolecular Heck reaction only produced one diastereomer, because the *cis*-annulated rings are favored. Scandium(III)-mediated cyclization and reduction of the lactone with DIBAL-H yielded (-)-aflatoxin B<sub>2a</sub> (**46**). It was acetylated and then pyrolyzed to give (-)-aflatoxin B<sub>1</sub> (**1**) in 1.6% overall yield and nine linear steps from catechol (**40**).

In 2005, Zhou and Corey presented an enantioselective total synthesis of aflatoxin B<sub>2</sub> (**2**) (**42**). This is shown in Scheme 2.7. The stereospecificity was induced in the first step by an asymmetric [3 + 2]-cycloaddition with a chiral borazine. Methoxy *p*-benzoquinone (**49**) reacted with dihydrofuran (**50**) in the presence of **51** and gave **52** in 99% enantiomeric excess. Sequential *ortho*-formylation and triflate ester formation yielded **53**. Ketone **54** was formed by Grignard reaction and Dess-Martin-periodinane oxidation. Baeyer-Villiger oxidation and reductive removal of the triflate group, together with deacetylation produced the alcohol **55**. Conversion into (-)-aflatoxin B<sub>2</sub> ((-)-**2**) (2.5% overall yield for eight steps) was achieved by coupling with 3-bromo-2-carboxyethyl-cyclopent-2-enone.

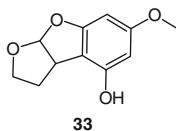


**Scheme 2.7** Enantioselective total synthesis of aflatoxin B<sub>2</sub> (2). Reagents and conditions: a) **51**, CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>CN, -78°C to rt, 7 h, 65%, 99% *ee*; b) hexamethylenetetramine, HOAc, 110°C, 48 h, 40%; c) DMAP (cat.), pyridine, Tf<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, -20°C to 0°C, 80%; d) MeMgBr, THF, -20°C, 2 h; e) *DMP*, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to rt, 85% over two steps; f) TFAA, urea·H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, rt, 63%; g) Raney-Ni, H<sub>2</sub>, MeOH, rt, 3 h, 60%; h) NaHCO<sub>3</sub>, ZnCO<sub>3</sub>, ethyl 2-bromo-5-oxocyclopent-1-enecarboxylate, CH<sub>2</sub>Cl<sub>2</sub>, rt, 20 h, 36%

## 2.3 Syntheses of Aflatoxin Building Blocks

### 2.3.1 Syntheses of Building Blocks for Aflatoxins B<sub>2</sub> and G<sub>2</sub>

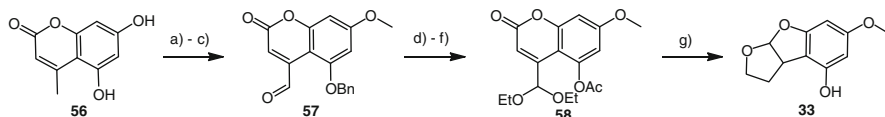
There are many different syntheses for the important building block **33** (Fig. 2.4). From this molecule, one can easily build aflatoxins B<sub>2</sub> (2) and G<sub>2</sub> (4) by the reactions presented in Sect. 2.2.



**Fig. 2.4** Building block **33** for aflatoxins B<sub>2</sub> (2) and G<sub>2</sub> (4)

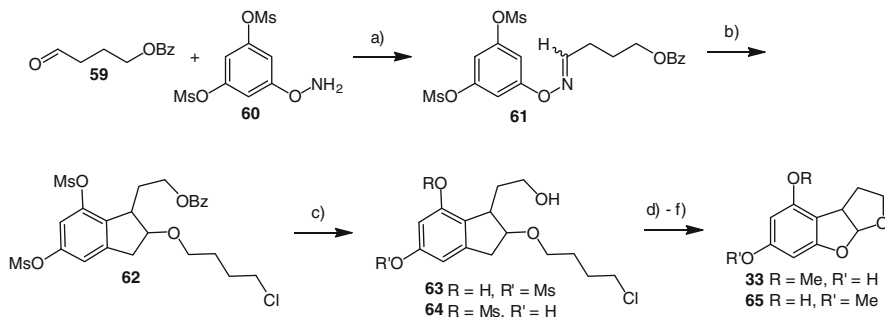
The first access to **33** was published by *Knight et al.* in 1966 and is presented in Scheme 2.8 (43). The diol **56** was monomethylated, benzylated, and then oxidized by selenium dioxide ( $\rightarrow$  **57**). The acetal was then formed with ethanol, the benzyl group was removed with hydrogen, and the resulting alcohol was converted into acetate **58**. Reduction of the lactone to the lactol afforded ring opening and following acidic hydrolysis of the acetate gave the desired building block **33** in 5.3% overall yield.





**Scheme 2.8** First synthesis of **33**. Reagents and conditions: a)  $\text{Me}_2\text{SO}_4$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$ ,  $80^\circ\text{C}$ , 0.5 h, 33%; b)  $\text{BnCl}$ ,  $\text{NaI}$ ,  $\text{Na}_2\text{CO}_3$ , acetone, reflux, 8 h, 81%; c)  $\text{SeO}_2$ , xylene, reflux, 6 h, 59%; d)  $\text{HCl}$ ,  $\text{EtOH}$ ,  $(\text{EtO})_3\text{CH}$ , rt to  $50^\circ\text{C}$ ; then rt, 89%; e)  $\text{H}_2$ , *Adams* catalyst,  $\text{EtOAc}$ , rt, 88%; f)  $\text{Ac}_2\text{O}$ , pyridine, 86%; g)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ , reflux, 4 h; then  $\text{HCl}$ , 50%

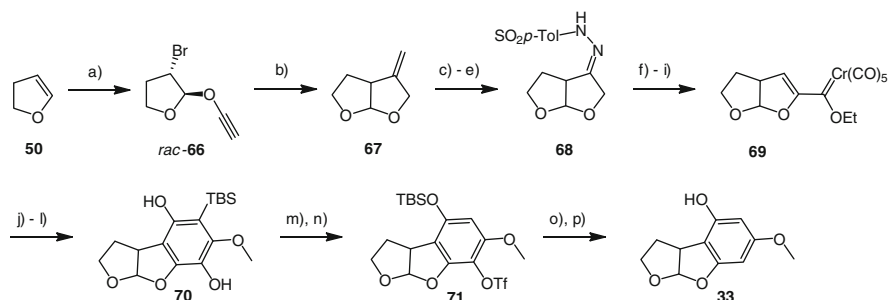
A straightforward access to **33** in six steps and 49% overall yield was published by *Castellino and Rapoport* in 1985 and is shown in Scheme 2.9 (44). The first step was an imine formation ( $\rightarrow$  **61**). By heating under acidic conditions, an oxaza-*Cope* rearrangement occurred, which, after hydrolysis, led to ring closure to the furan **62**. Under these conditions, the benzoyl group was cleaved. The free alcohol was then protected by degradation products of the solvent THF, which were formed by acid cleavage. Basic hydrogenolysis gave the regioisomers **63** and **64**, which were not separated. With catalytic amounts of *p*-*TsOH* under heating, ring closure occurred. The free alcohol was then methylated and the mesyl group was removed to form **33** together with its regioisomer **65**.



**Scheme 2.9** Short access to **33** via oxaza-*Cope* rearrangement. Reagents and conditions: a)  $\text{HCl}$ , ethanol, reflux, 83%; b)  $\text{HCl}$ ,  $\text{THF}$ ,  $65^\circ\text{C}$ , 24 h, 87%; c)  $\text{LiOH}\cdot\text{H}_2\text{O}$ ,  $\text{THF}/\text{H}_2\text{O}$ ,  $40^\circ\text{C}$ , 1 d, 95%; d) *p*-*TsOH* (cat.), 4 Å activated sieves,  $\text{CH}_3\text{CN}$ , rt, 45 min, 95%; e)  $\text{Me}_2\text{SO}_4$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{CH}_3\text{CN}$ , rt, 1.75 h, 93%; f)  $\text{Et}_4\text{NOH}$ ,  $\text{THF}/\text{H}_2\text{O}$ , reflux, 5 h, quant

Other syntheses of **33** have been presented in more recent years: *Weeratunga et al.* presented a nine-step-synthesis with 4% overall yield (45), where the key steps were a cyclization-deiodination-reaction and a lead tetraacetate-conducted ring closure. *Koreeda et al.* published their building-block-synthesis in 1993 with 11% overall yield (46), and in 1996, *Pirrung and Lee* synthesized **33** via a rhodium carbenoid dipolar cycloaddition (47).

A recent synthesis of this building block has been published by *Eastham et al.* in 2006 (48). Their key step is a *Dötz* benzannulation reaction and is shown in Scheme 2.10. The bromohydrin **66** was formed from dihydrofuran (**50**). Cobalt-mediated cyclization, followed by ozonolysis with reductive work-up yielded **68** after hydrazine formation. Reductive removal of the hydrazine function, followed by chromium-carbonyl formation gave the *Dötz* reaction precursor **69**. This reacted with an alkyne in the *Dötz* reaction, and was then oxidized and hydrogenated ( $\rightarrow$  **70**). Pyrolysis gave the protected alcohol and the remaining free alcohol was protected as a triflate ( $\rightarrow$  **71**). Reductive removal of the triflate and deprotection of the silyl ether yielded the desired **33** in 1.2% overall yield.

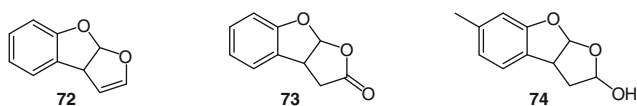


**Scheme 2.10** Synthesis of **33** via a *Dötz* reaction. Reagents and conditions: a) prop-2-yn-1-ol, NBS,  $\text{CH}_2\text{Cl}_2$ , 94%; b)  $\text{CoL}_n$ ,  $\text{NaBH}_4$ ,  $\text{NaOH}$ , ethanol, 62%; c)  $\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; d)  $\text{Me}_2\text{S}$ , 74% over two steps; e) *p*-Tol $\text{SO}_2\text{NHNH}_2$ , THF, 79%; f) Na, triglycol,  $120^\circ\text{C}$ , 73%; g) *t*-BuLi, THF,  $-78^\circ\text{C}$ ; h)  $\text{Cr}(\text{CO})_6$ ; i)  $\text{Et}_3\text{OBF}_4$ , 52% over three steps; j) *t*-butyl(methoxyethyl)dimethylsilane, THF,  $80^\circ\text{C}$ , 31%; k) CAN,  $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ ,  $0^\circ\text{C}$ , 10 min, 93%; l)  $\text{H}_2$ , Pd/C, EtOAc, quant; m) toluene,  $110^\circ\text{C}$ , quant; n)  $\text{Tf}_2\text{O}$ , pyridine, DMAP (cat.),  $\text{CH}_2\text{Cl}_2$ , 93%; o) Raney-Ni, MeOH; p) TBAF, THF, 35% over two steps

### 2.3.2 Syntheses of Building Blocks for Aflatoxins $\text{B}_1$ and $\text{G}_1$

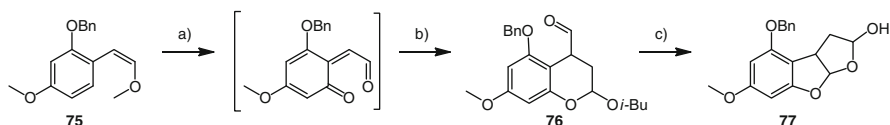
There exist many references describing the syntheses of aflatoxin  $\text{B}_1$  and  $\text{G}_1$  building blocks. Since aflatoxin  $\text{B}_1$  (**1**) can be converted *via* hydrogenolysis into aflatoxins  $\text{B}_2$  (**2**) and  $\text{G}_1$  (**3**) into  $\text{G}_2$  (**4**), the building blocks described in this chapter can also be precursors for aflatoxins  $\text{B}_2$  (**2**) and  $\text{G}_2$  (**4**).

There are different syntheses for unsubstituted model systems of aflatoxin precursors. However, these cannot be used for total synthesis (Fig. 2.5). Compound **72** has been synthesized by *Pawlowski et al.* in four steps (49). Compound **73** was obtained in four steps by *Snider et al.* *via* a ketene-[2 + 2]-cycloaddition and a *Baeyer-Villiger* oxidation (50). *Mitra et al.* synthesized **74** in the same way as *Snider et al.* (51).



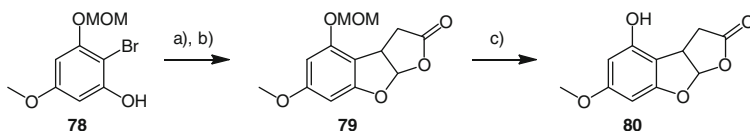
**Fig. 2.5** Model systems for aflatoxin precursors

*Matsumoto* and *Kuroda* presented a short and elegant synthesis for an aflatoxin B<sub>1</sub> precursor by a [2 + 4]-cycloaddition with singlet oxygen (see Scheme 2.11). From **75**, an intermediate was formed that reacted with *iso*-butyl vinyl ether ( $\rightarrow$  **76**). Acid hydrolysis gave the free alcohol, which induced the formation of **77** (52).



**Scheme 2.11** *Matsumoto's* synthesis of **77**. Reagents and conditions: a) <sup>1</sup>O<sub>2</sub>; b) *i*-butyl vinyl ether, 39%; c) H<sub>2</sub>SO<sub>4</sub> (cat.)

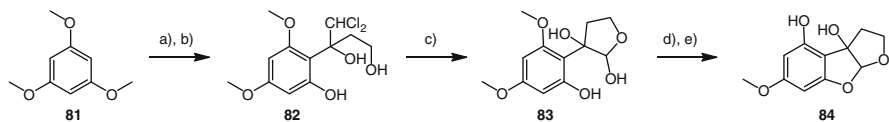
In 1988, *Sloan et al.* presented a building-block synthesis *via* radical-induced ring closure (53). The aromatic alcohol **78** was first substituted on 5-bromofuran-2(5*H*)-one, then an intramolecular, radical 1,4-addition formed **79**. Removal of the MOM-protecting group then gave **80**. The synthesis is shown in Scheme 2.12. From this intermediate, *Büchi et al.* described the synthesis of aflatoxin B<sub>1</sub> (**1**) (35). Other syntheses of building block **80** have been described by *Hoffmann et al.* and *Bujons et al.* (54, 55).



**Scheme 2.12** Building block synthesis *via* radical ring closure. Reagents and conditions: a) 5-bromofuran-2(5*H*)-one, K<sub>2</sub>CO<sub>3</sub>, acetone, reflux; b) Bu<sub>3</sub>SnH, AIBN, benzene, reflux; c) 9-BBN-Br, CH<sub>2</sub>Cl<sub>2</sub>, -78°C to 0°C, 1.5 h

### 2.3.3 Synthesis of a Building Block for Aflatoxin M<sub>2</sub>

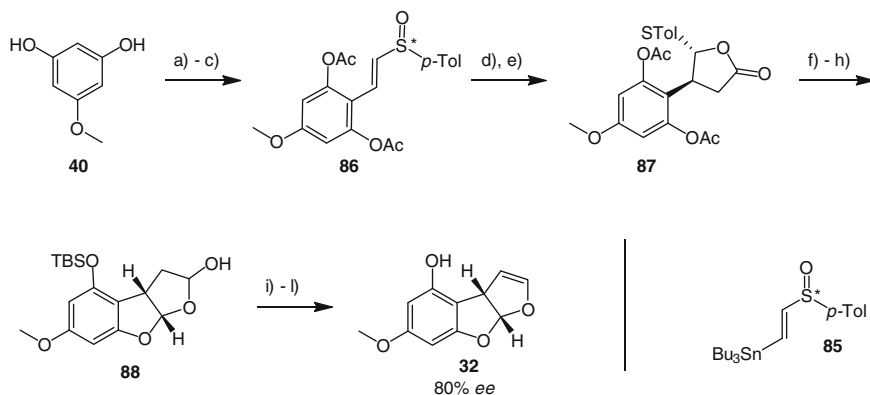
For aflatoxin M<sub>2</sub> (**6**), the required building block has been synthesized by *Kraus* and *Wang*, as shown in Scheme 2.13 (56). The starting material, 1,3,5-trimethoxybenzene (**81**), was first acylated and mono-demethylated *in situ*, then a 1,2-addition to the ketone provided **82**. Under basic conditions, ring closure and hydrolysis of the remaining chloride occurred and gave hemiacetal **83**. With *p*-toluenesulfonic acid, the last ring was closed, and with boron trifluoride, selective mono-demethylation yielded the desired building block **84**. Conversion into aflatoxin M<sub>2</sub> (**6**) can be achieved according to the protocol of *Büchi* for the synthesis of aflatoxin M<sub>1</sub> (**5**) (36, 37).



**Scheme 2.13** Synthesis of building block **84** for aflatoxin M<sub>2</sub> (**6**). Reagents and conditions: a) AlCl<sub>3</sub>, oxetan-2-one, 80–85%; b) LiCHCl<sub>2</sub>, THF, 93%; c) K<sub>2</sub>CO<sub>3</sub>, *i*-PrOH (aq.), 70%; d) *p*-TsOH, CH<sub>2</sub>Cl<sub>2</sub>, 4 h, 74%; e) BF<sub>3</sub>•OEt<sub>2</sub>, NaI, 71%

### 2.3.4 Enantioselective Syntheses of Aflatoxin Building Blocks

The first enantioselective synthesis of an aflatoxin building block was published in 1993 by *Marino* (57). He presented a synthesis of **32** in 80% enantiomeric excess and induced the stereospecificity *via* optically active vinyl sulfoxides (see Scheme 2.14). Catechol (**40**) was acylated, mono-iodinated and then coupled with chiral vinyl sulfoxide **85** under *Stille* conditions ( $\rightarrow$  **86**). Dichloro ketene lactonization under reductive conditions followed by zinc-promoted dechlorination gave the major diastereomer **87**.

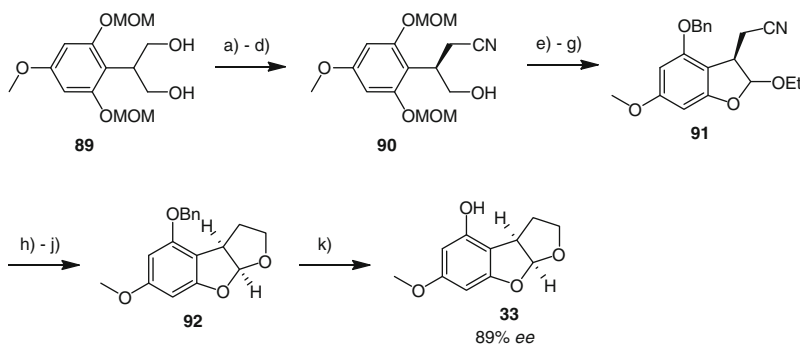


**Scheme 2.14** Enantioselective synthesis of a building block (**28**) for aflatoxin B<sub>1</sub> (**1**). Reagents and conditions: a) AcCl, pyridine, 98%; b) HgO•HBF<sub>4</sub>•SiO<sub>2</sub>, I<sub>2</sub>, 49%; c) **85**, Pd(0), PPh<sub>3</sub>, toluene, reflux, 65%; d) Zn(Cu), Cl<sub>3</sub>CCOCl, THF,  $-50^{\circ}\text{C}$ ; e) Zn, HOAc,  $\Delta$ , 70% over two steps, quant *ee*; f) HCl, acetone,  $\Delta$ , 55%; g) TBSCl, imidazole; h) DIBAL-H, 80% over two steps; i) 1-(phenylthio)pyrrolidine-2,5-dione, PBu<sub>3</sub>, benzene, 80%; j) *m*-CPBA, CH<sub>2</sub>Cl<sub>2</sub>,  $-78^{\circ}\text{C}$ ; k) pyridine, toluene,  $110^{\circ}\text{C}$ ; l) CsF, CH<sub>3</sub>CN,  $0^{\circ}\text{C}$ , 96% over three steps

With HCl, deacetylation and ring closure occurred. Then, the free aromatic alcohol was TBS-protected and the lactone was reduced with DIBAL-H to lactol **88**. The alcohol was converted into the thio ether, then oxidized with *m*-CPBA, and finally pyrolyzed. Fluoride-driven deprotection of the TBS ether then gave building block **32** in 80% *ee*.

In 1994, *Civittello* and *Rapoport* presented a further enantioselective synthesis of an aflatoxin B<sub>1</sub> building block with an oxaza-*Cope* rearrangement as a key step (58).

For aflatoxin B<sub>2</sub> (**2**), enantioselective syntheses of precursors have also been reported. *Shishido* and *Bando* presented their procedure in 1997, which gave an *ee* of 89% (**59**, **60**). The stereospecificity was induced by lipase-catalyzed monoacetoxylation of diol **89** (see Scheme 2.15). The remaining alcohol was mesyl-protected, converted into its cyanide and then deacetoxylated ( $\rightarrow$  **90**). With TPAP/NMO, the alcohol was oxidized to the aldehyde, then the MOM-groups were removed under acidic conditions, which caused lactolization. With triethoxyethane, the alcohol was protected *in situ*, and, in the next step, the remaining aromatic alcohol was benzylated ( $\rightarrow$  **91**). Under basic conditions, the nitrile was converted into the corresponding carboxylate, which was reduced to the alcohol by borane. With *p*-TsOH, ring closure afforded **92**. Hydrogenolysis of the benzyl group gave building block **33**, which can be converted into aflatoxin B<sub>2</sub> (**2**) according to *Büchi's* or *Robert's* conditions (**37**, **38**).

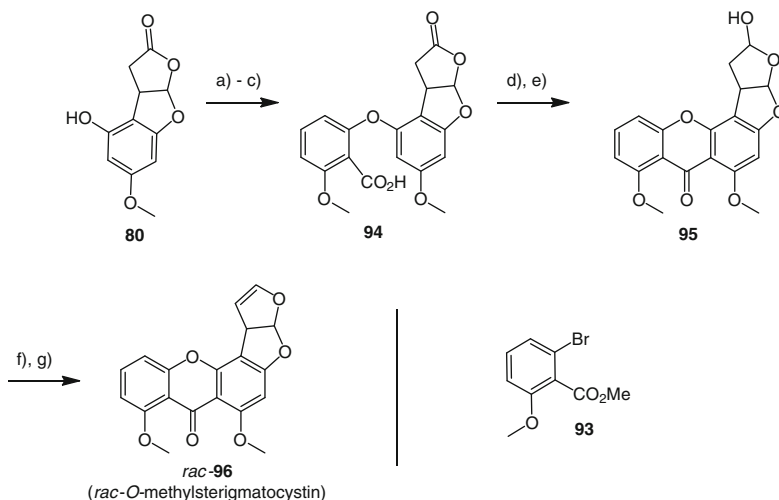


**Scheme 2.15** Enantioselective synthesis of the aflatoxin B<sub>2</sub> building block **33**. Reagents and conditions: a) Lipase AL, vinyl acetate, Et<sub>2</sub>O, rt, 72%, 89% *ee*; b) MsCl, DIPEA, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 89%; c) KCN, 18-Crown-6, DMSO, 72%; d) LiOH, THF/H<sub>2</sub>O, 83%; e) TPAP, NMO, 4 Å MS, CH<sub>2</sub>Cl<sub>2</sub>; f) HCl, HC(OEt)<sub>3</sub>, EtOH; g) BnCl, K<sub>2</sub>CO<sub>3</sub>, DMF, 50% over three steps; h) KOH, EtOH/H<sub>2</sub>O; i) BH<sub>3</sub>•SMe<sub>2</sub>, THF; j) *p*-TsOH, CH<sub>2</sub>Cl<sub>2</sub>, 43% over three steps; k) 1,4-cyclohexadiene, Pd/C, MeOH, quant

## 2.4 Syntheses of Biosynthetic Aflatoxin Precursors

Various biosynthetic precursors of aflatoxins have been synthesized. Some of these have then been converted biosynthetically into the aflatoxins. In this section, syntheses of important aflatoxin precursors will be presented.

In 1971, *rac*-*O*-methylsterigmatocystin (OMST, **96**) was synthesized by *Rance* and *Roberts* (**61**). With respect to biosynthesis, this is an important intermediate between sterigmatocystin (**15**) and the aflatoxins B<sub>1</sub> (**1**) and G<sub>1</sub> (**3**) (see Scheme 2.1). The synthesis starts with building block **80** (for its synthesis see Scheme 2.12), which was ring-opened and methyl-protected under acidic conditions (Scheme 2.16). *Ullmann* coupling with bromide **93**, followed by acidic ester and ether hydrolysis led to ring closure and gave **94**. The carboxylic acid was converted into its chloride with oxalyl chloride, which reacted *in situ* to a xanthone species. Reduction of the lactone with disiamylborane gave lactol **95**. The alcohol was acylated and *rac*-*O*-methylsterigmatocystin (**96**) was obtained by repeated sublimation.

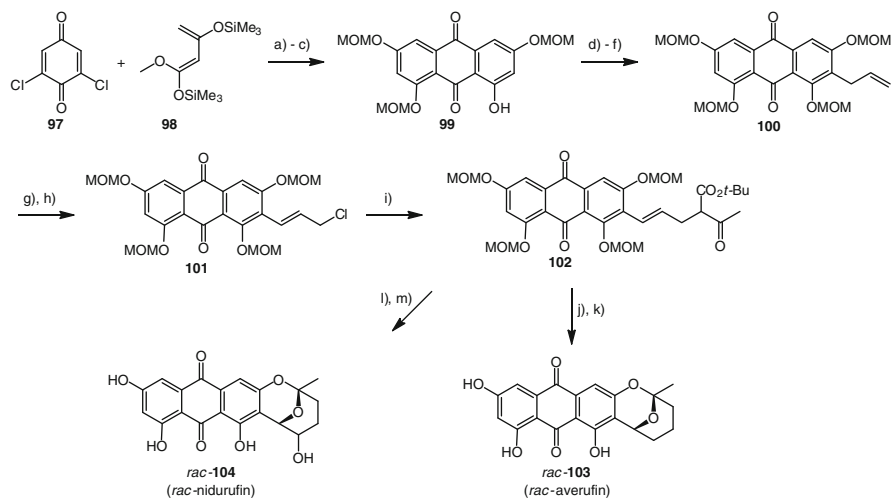


**Scheme 2.16** Synthesis of *rac*-O-methylsterigmatocystin (**96**). Reagents and conditions:

a) HCl, MeOH,  $-10^{\circ}\text{C}$ , 1 h; then rt, 18 h, 75%; b) NaOMe, MeOH; then pyridine, **93**, CuCl, reflux, 4 h, 41%; c) HOAc, HCl, rt, 88%; d)  $(\text{COCl})_2$ , benzene, reflux, 24 h, 71%; e) disiamylborane, THF, reflux, 48 h, 17%; f) HOAc,  $\text{Ac}_2\text{O}$ , *p*-TsOH (cat.), rt, 7 d, 49%; g)  $250^{\circ}\text{C}$ , 0.05 mm, 53%

Another synthesis of *rac*-O-methylsterigmatocystin (**96**) was published by Casillas and Townsend in 1999 (62). They used *N*-alkylnitrilium salts and a carbonyl-alkene interconversion as key steps for synthesizing *O*-methylsterigmatocystin (**96**) in 19 steps (see Scheme 13.6. in Sect. 13.1.3).

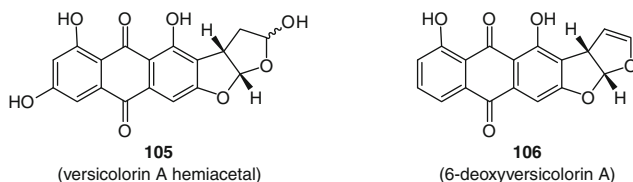
In 1985, O'Malley *et al.* published the total syntheses of *rac*-averufin (**103**) and *rac*-nidurufin (**104**) (63). These are both early precursors of the aflatoxins in their biosynthesis. Nidurufin (**104**) is the direct successor of averufin (**103**) and the direct precursor of versiconal hemiacetal acetate (**12**, see Scheme 2.1). Nidurufin (**104**) and averufin (**103**) are accessible by the same synthesis route; only the two last steps differ from each other (see Scheme 2.17). The first reaction was a double *Diels-Alder* reaction with dichloro-*p*-benzoquinone (**97**) and two equivalents of diene **98**. Then, three of the four alcohol functions were selectively MOM-protected ( $\rightarrow$  **99**). The remaining alcohol was converted into the allyl ether and then subjected to a reductive *Claisen* rearrangement, followed by MOM-protection of the redundant alcohol ( $\rightarrow$  **100**). By addition/elimination of PhSeCl, **101** was formed. Deprotonation of *t*-butyl 3-oxobutanoate, followed by reaction with **101** yielded the pivotal intermediate **102**. This could be converted into *rac*-averufin (**103**) by deprotection of the alcohols and decarboxylation at the side chain. The last step was a *p*-TsOH-catalyzed cyclization to give **103**. By treating **102** with *m*-CPBA, the double bond is epoxidized. *rac*-Nidurufin (**104**) was then formed by cyclization of this epoxide under acidic conditions.



**Scheme 2.17** Total syntheses of averufin (**103**) and nidurufin (**104**). Reagents and conditions: a) THF,  $-78^{\circ}\text{C}$  to rt, 2 h; then  $120^{\circ}\text{C}$ ; then MeOH/HCl (aq.), reflux, 0.5 h, 50%; b) MOMCl, DIPEA, THF, 0.5 h, 88%; c) MOMCl, KO $t$ -Bu, THF, 95%; d) allyl bromide, K $_2$ CO $_3$ , acetone, reflux, 12 h, 97%; e) NaHCO $_3$ , Na $_2$ S $_2$ O $_4$ , DMF/H $_2$ O,  $90^{\circ}\text{C}$ , 89%; f) MOMCl,  $t$ -BuOK, THF, 91%; g) PhSeCl, CCl $_4$ , rt; h) H $_2$ O $_2$ , pyridine,  $0^{\circ}\text{C}$  to rt, 2 h, 83% over two steps; i) NaH,  $t$ -butyl acetoacetate, DMSO, 1 h; then NaI, **101**, rt, 12 h, 70%; j) HOAc/H $_2$ O, H $_2$ SO $_4$  (cat.),  $90^{\circ}\text{C}$ , 3 h; k)  $p$ -TsOH (cat.), toluene,  $\Delta$ , 50% over two steps; l)  $m$ -CPBA, CHCl $_3$ , rt, 93%; m) HOAc/H $_2$ O, H $_2$ SO $_4$  (cat.),  $90^{\circ}\text{C}$ , 4 h; 69%

Other syntheses of *rac*-averufin (**103**) have been presented by *Townsend et al.* in 1981 and 1988, both *via* methoxymethyl-directed aryl metalation (64, 65).

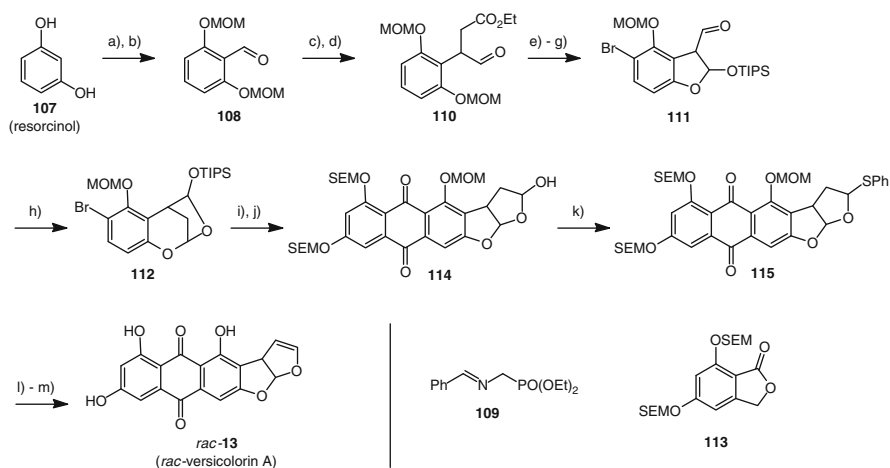
A later precursor of the aflatoxins, versicolorin A (**13**, see Scheme 2.1), has been synthesized by *Graybill et al.* in 1999. They also described the total syntheses of versicolorin B (**14**, see Scheme 2.1), versicolorin A hemiacetal (**105**), and 6-deoxyversicolorin A (**106**) (shown in Fig. 2.6) (66).



**Fig. 2.6** Versicolorin A hemiacetal (**105**) and 6-deoxyversicolorin A (**106**), synthesized by *Graybill et al.*

The synthesis of *rac*-versicolorin A (**13**) is shown in Scheme 2.18. Resorcinol (**107**) was MOM-protected and formylated to yield **108**. *Horner-Wadsworth-Emmons* reaction with **109**, followed by deprotection and reaction with ethyl bromoacetate gave, after hydrolysis, phenyl acetaldehyde **110**. With TIPSOTf and triethylamine, cyclization occurred rapidly, followed by mono deprotection.

NBS brominated the aromatic ring at the *ortho*-position to the OMOM-group and DIBAL-H reduced the ethyl ester to give aldehyde **111**. Catalytic amounts of TIPSOTf promoted lactolization ( $\rightarrow$  **112**). After lithium-bromine exchange at **112**, reaction with lactone **113** gave a xanthone species, which reacted, after deprotection of the TIPS-group, to the five-ring species **114**. Transformation of the alcohol into thioether **115**, followed by global deprotection, oxidation, and pyrolysis gave *rac*-versicolorin A (**13**).



**Scheme 2.18** Total synthesis of *rac*-versicolorin A (**13**) (66). Reagents and conditions: a) MOMCl, DIPEA, 81%; b) *n*-BuLi, DMF, 63%; c) *n*-BuLi, **109**, THF,  $-70^{\circ}\text{C}$ , 1 h; then  $-78^{\circ}\text{C}$ , **108**, 30 min; then  $15^{\circ}\text{C}$ ; d) *n*-BuLi,  $-78^{\circ}\text{C}$ ; then  $-65^{\circ}\text{C}$ , 2 h; then ethyl 2-bromoacetate,  $-78^{\circ}\text{C}$  to rt, 66% over two steps; e) TIPSOTf, TEA, THF,  $0^{\circ}\text{C}$ , 82%; f) NBS, 77%; g) DIBAL-H,  $\text{Et}_2\text{O}$ ,  $-95^{\circ}\text{C}$ , 99%; h) TIPSOTf (cat.),  $\text{CH}_2\text{Cl}_2$ ,  $-43^{\circ}\text{C}$ , 5 min, 96%; i) LiTMP, **113**,  $-78^{\circ}\text{C}$ ; then  $-43^{\circ}\text{C}$ , **112**, 2 h, 34%; j) TBAF, THF,  $-78^{\circ}\text{C}$  to  $-20^{\circ}\text{C}$ , 90%; k) 2-(phenylthio)isoindoline-1,3-dione,  $\text{PBU}_3$ , THF,  $-78^{\circ}\text{C}$  to  $0^{\circ}\text{C}$ ; then  $-78^{\circ}\text{C}$ , **114**; then  $-2^{\circ}\text{C}$ , 92%; l) HCl, HOAc, THF/ $\text{H}_2\text{O}$ ,  $65^{\circ}\text{C}$ , 5 h, 97%; m) *m*-CPBA,  $\text{CHCl}_3$ ,  $-15^{\circ}\text{C}$ , 2 h; n) toluene, reflux, 45 min, 79% over two steps

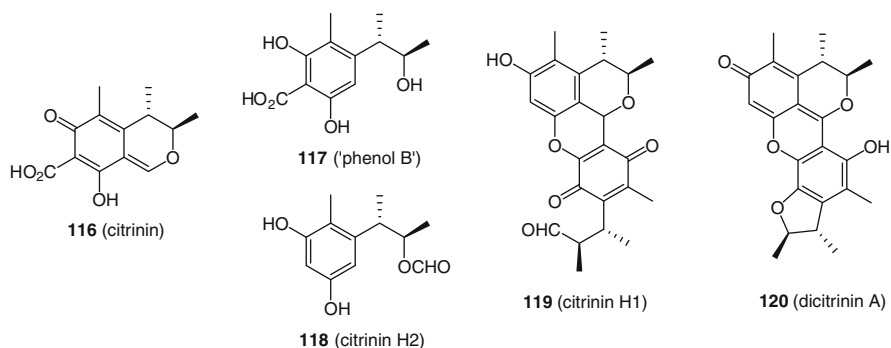


## 3 Citrinin

### 3.1 General

Citrinin (**116**) (Fig. 3.1), first reported in 1931 following its isolation from *Penicillium citrinum* (67), was found to display a significant antibiotic activity against several Gram-positive bacteria in the 1940's (68, 69). In the following decade (at the time of the widespread application of penicillin), there was a considerable interest in citrinin (**116**) and other antibacterials of fungal origin. Despite this, and its additional insecticidal properties (70), the investigation of **116** for either therapeutic or agrochemical application was abandoned due to its substantial toxicity (71), including nephrotoxicity (72).

Both *Whalley* and co-workers and *Cram* published extensively on the stereochemistry of citrinin (**116**) in the 1940's, particularly through the use of degradation studies (73, 74). Further stereochemical data were later provided from X-ray analysis (75). In particular, the (3*R*,4*S*)-configuration was determined by comparison of degradation products with compounds of known stereochemistry (76, 77). In addition to these degradation studies, a prominent product of degradation, "phenol B" (**117**) (Fig. 3.1), was utilized by several groups for enantioselective and racemic syntheses of the natural product (78, 79).



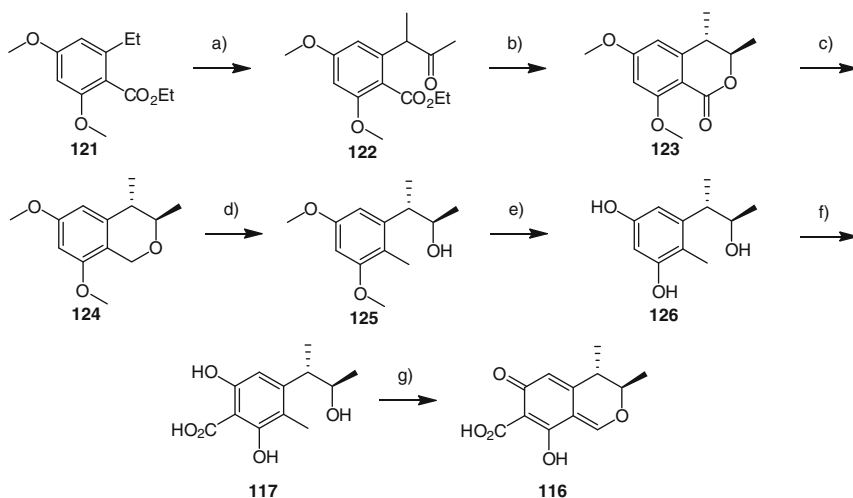
**Fig. 3.1** Citrinin (**116**) and derivatives of interest

Citrinin (**116**) has an interesting structure: as a hydroquinone activated towards nucleophilic attack, and as a potential participant in redox processes, consistent with a variety of toxic effects in biological systems. Many derivatives of **116** were also isolated by various groups, including those reported by *Curtis et al.* in 1968 (80). Under certain conditions (aqueous decomposition with heating), a decarboxylated and ring-opened derivative, citrinin H2 (**118**), was isolated and shown to have greatly diminished cytotoxicity (81). Under similar conditions, the formation of a notably toxic derivative of citrinin (**116**), citrinin H1 (**119**) (Fig. 3.1), has been observed (82). In more recent times, a new dimeric species, dicitrinin A (**120**) has been identified by *Capon et al.* at the University of Queensland (83). This compound also occurred as an artifact, generated during handling and storage of biological extracts of the organism of origin.

## 3.2 Total Syntheses of Citrinin

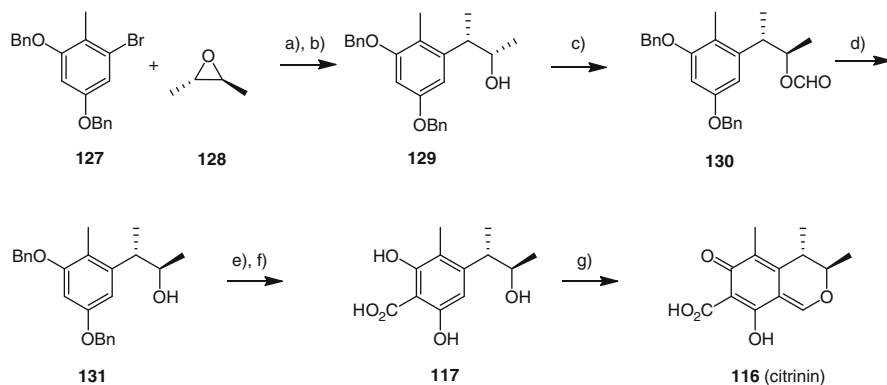
The *Barber and Staunton* synthesis of ( $\pm$ )-citrinin (*rac*-**116**) was reported in 1986 (84). This synthesis employed selective benzylic lithiation as a key transformation, and was followed shortly thereafter by an asymmetric variant to give access to (+)-citrinin (the unnatural stereoisomer of **116**).

The synthesis pathway started with the lithiation of ethylbenzene **121** at the benzylic position, followed by acylation of the toluate anion intermediate at low temperature. It is noteworthy that a potentially competing *ortho*-lithiation of the type championed by *Snieckus* (85) (*i.e.* between the two stabilizing methoxyl radicals) was not reported under these conditions. Subsequent reduction of benzylketone **122** provided smooth access to the *threo*-dimethyl-substituted bicyclic intermediate **123** *via* lactonization. DIBAL reduction ( $\rightarrow$  **124**) and reductive debenzoylation with palladium on charcoal gave the ring-opened alcohol **125**, which was further demethylated to provide a 1,3-diphenol, and then carboxylated under buffered conditions to yield acid **117**, also known as “phenol B”. This compound was formylated with trimethyl orthoformate and acid, then cyclized to give the quinone structure and natural product, **116** (Scheme 3.1).



**Scheme 3.1** Barber and Staunton's synthesis of citrinin (**116**). Reagents and conditions: a) LDA, THF,  $-78^{\circ}\text{C}$ ; then  $\text{AcCl}$   $-130^{\circ}\text{C}$ , 50%; b)  $\text{NaBH}_4$ , MeOH, 86%; c) DIBAL, toluene, 72%; d)  $\text{H}_2$ , Pd/C, AcOH, MeOH, quant; e)  $\text{BBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ , 79%; f)  $\text{KHCO}_3$ ,  $\text{CO}_2$ , glycerol,  $150^{\circ}\text{C}$ , 75%; g)  $\text{HC}(\text{OEt})_3$ , HCl, 38%

In a later study, the team made use of a chiral amide base in order to selectively deprotonate only one of the prochiral alkyl protons of **121**, with a 70% enantiomeric excess and a diastereoselectivity of 3:1 (**86**). The product was then converted *via* a *threo*-lactone to the unnatural enantiomer of citrinin (**116**), (+)-citrinin.



**Scheme 3.2** Rödel and Gerlach's synthesis of ( $\pm$ )-citrinin. Reagents and conditions: a) Mg, THF; b) oxirane **128**, catalyst ( $\text{MgBr}_2$ ,  $\text{COD}\cdot\text{CuCl}$ ), 76%; c)  $\text{Ph}_3\text{P}$ ,  $\text{HCO}_2\text{H}$ ; then DEAD, 59%; d) KOH, MeOH/ $\text{H}_2\text{O}$ /THF, reflux, 99%; e)  $\text{H}_2$ , Pd/C, AcOH/MeOH, 89%; f)  $\text{KHCO}_3$ ,  $\text{CO}_2$ , glycerol,  $150^{\circ}\text{C}$ ; g)  $\text{HC}(\text{OEt})_3$ , HCl, 41% over two steps

Rödel and Gerlach reported their synthesis of citrinin (**116**) in 1995, starting from the dibenzyl-protected aryl bromide **127** (Scheme 3.2) (87). Transformation of this material to the *Grignard* reagent provided a nucleophile for the ring-opening of enantiomerically pure (*S,S*)-2,3-dimethyl oxirane (**128**), a step mediated by magnesium dibromide and cuprous chloride•cyclooctadiene catalyst. Inversion of stereochemistry at the hydroxy group-bearing carbon of **129** was accomplished with a classic method. Thus, a *Mitsunobu* reaction with formic acid as nucleophile followed by hydrolysis allowed the *erythro*-configured intermediate to be converted to the *threo*-isomer **131** with 99% *de*. Debenzylation and then the familiar sequence of carboxylation, formylation, and cyclization followed, in order to complete the synthesis of naturally occurring (–)-citrinin with good stereoselectivity.

## 4 Ergot Alkaloids

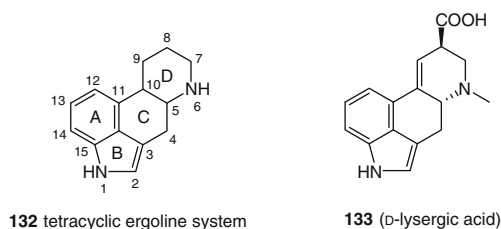
The complex family of ergot alkaloids plays an important role as pharmaceuticals, in the food industry, and in ecological systems (88). Ergot alkaloids share a common heterocyclic ergoline ring system (132), which can be chemically interpreted as a fused indole-heptahydroquinoline system. This family of indole derivatives is produced by fungi of the families Clavicipitaceae (e.g. *Claviceps* (Fig. 4.1) and *Neotyphodium*) and Trichocomaceae (including *Aspergillus* and *Penicillium*) (88–90). In addition, ergot alkaloids have also been identified in plants of the families Convolvulaceae, Poaceae, and Polygalaceae, in which there is evidence to suggest that these compounds are produced by plant-associated fungi alone or together with the host plants (88, 90).



**Fig. 4.1** *Claviceps purpurea* grown on the ears of rye

## 4.1 Structural Subclasses of Ergot Alkaloids

The characteristic structural feature of all ergot alkaloids is the presence of the tetracyclic ergoline ring (**132**) (Fig. 4.2). According to their structures, ergot alkaloids can be classified: clavine-type alkaloids, also called clavines, simply consist of the tetracyclic ergoline ring system (**132**) or its tricyclic precursors (88). Ergoamides and ergopeptines are carbon acid amide derivatives of D-lysergic acid (**133**), whereas ergopeptines can be seen as a special sub-category of the ergoamide class. Related compounds bearing more divergent functionalities are summarized in the section “Related Structures”, 4.1.5.



**Fig. 4.2** Ergoline (**132**) as the common scaffold of ergot alkaloids

### 4.1.1 Tricyclic Precursors of Ergot Alkaloids

Tricyclic ergot alkaloids can be seen biosynthetically as precursor structures in which the D-ring of the ergoline system is not closed (Fig. 4.3). The common 6,7-*seco*-D-ring motif has led to the naming “secoergolenes” or “tricyclic *seco* derivatives” (88, 91). Some important naturally occurring representatives of these tricyclic ergot alkaloids are chanoclavine-I (**134**), its two isomers chanoclavine-II (**135**) and isochanoclavine-I (**136**), chanoclavine-I aldehyde (**137**), and 6,7-*seco*-agroclavine (**138**) (88).

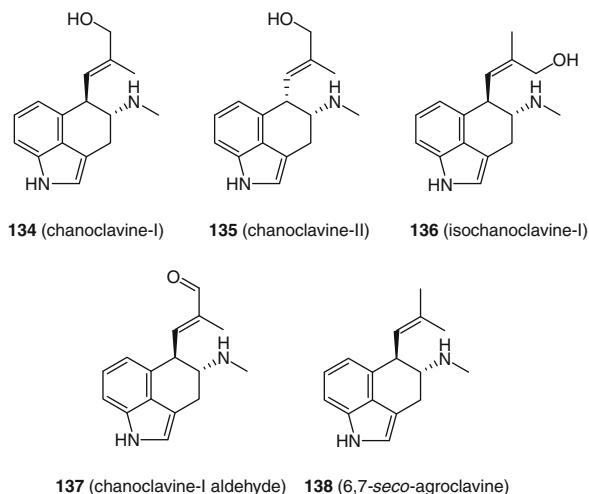


Fig. 4.3 Some ergot alkaloids consisting of only the A,B,C-ring system

### 4.1.2 Clavine-Type Alkaloids

Clavine-type alkaloids have been isolated from various fungal strains, and, in particular, they have been found in the family Trichocomaceae (Fig. 4.4) (88). Agroclavine (**139**) and elymoclavine (**140**) contain a double bond in the D-ring of the ergoline framework. Festuclavine (**141**) and pyroclavine (**142**) possess a saturated D-ring and differ in their stereochemistry at C-8. Their stereoisomers costaclavine (**143**) and epicostaclavine (**144**) have been isolated also from various fungi (88, 92).

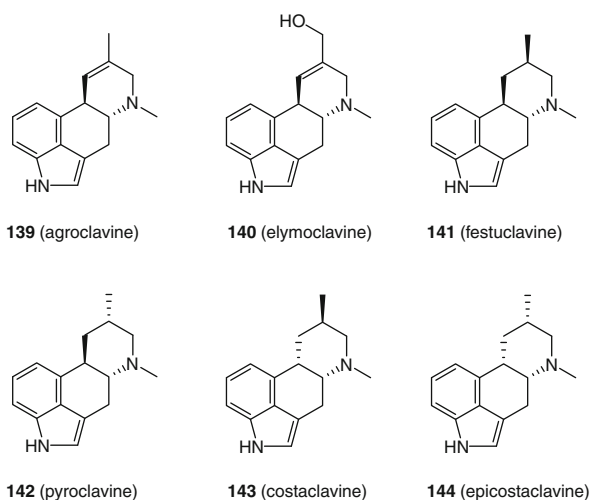
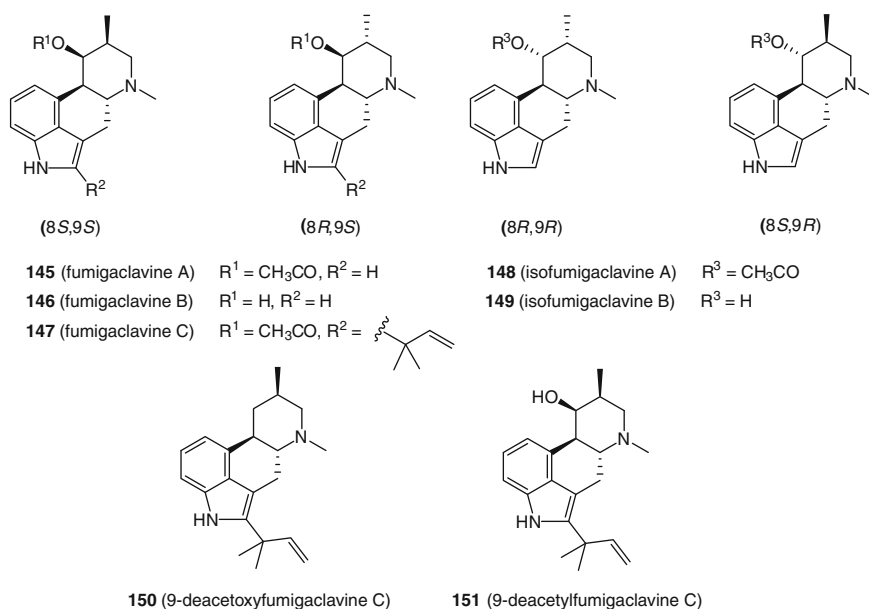


Fig. 4.4 Representative clavine-type alkaloids

As can be seen in Fig. 4.5, fumigaclavines A (**145**), B (**146**), and C (**147**) are oxidized at position C-9 and fumigaclavine C (**147**) carries a reverse prenyl moiety at C-2 (88). In his recent review, *Li* drew attention to the fact that published structures of fumigaclavines have led to some confusion about the configuration at positions C-8 and C-9 (88): structures with both (8*S*,9*S*) and (8*R*,9*S*) configurations were assigned to fumiglavines A, B, or C (88, 91, 93–98). Furthermore, *Li et al.* reported that “the (8*S*,9*R*) diastereomers of fumigaclavines A and B have been called isofumigaclavines A (**148**) and B (**149**) (99) or roquefortines A and B (100, 101), respectively” whereas “isomers with a (8*R*,9*R*) configuration have not yet been reported” (88). For a better differentiation of these compounds and to avoid confusion in the future, *Li* suggested in his recent review that “the names fumigaclavine A, B, and C should be applied to each group of all four possible diastereomers, whereby the stereochemistry at C-8 and C-9 should be defined by prefixing them with (*R*) or (*S*) descriptors” (88).

Recently *Ge* and co-workers reported the isolation of other prenylated fumigaclavines from *A. fumigatus*, namely, 9-deacetoxyfumigaclavine C (**150**) and 9-deacetylfumigaclavine C (**151**) (88, 93).



**Fig. 4.5** The structural class of fumigaclavines as classified by *Li et al.*



### 4.1.3 Ergoamides

Ergoamides are primary or secondary carbon acid amides of D-lysergic acid (**133**). One important ergoamide isolated from *Claviceps purpurea* is ergometrine (**152**), which is known also as ergonovine and ergobasine (Fig. 4.6) (88, 102, 103). An ergometrine semisynthetic derivative, methylelrgometrine (**153**), has pharmaceutical use in obstetrics. The semisynthetic ergot alkaloid, lysergic acid diethylamide (“LSD”, **154**), is undoubtedly one of the most well-known non-natural compounds and was initially developed for the treatment of various psychiatric disorders (104). Due to the fact that lysergic acid diethylamide (**154**) is a very potent hallucinogenic substance, this compound is prohibited. It is illegal to manufacture, buy, possess, process, or to distribute LSD.

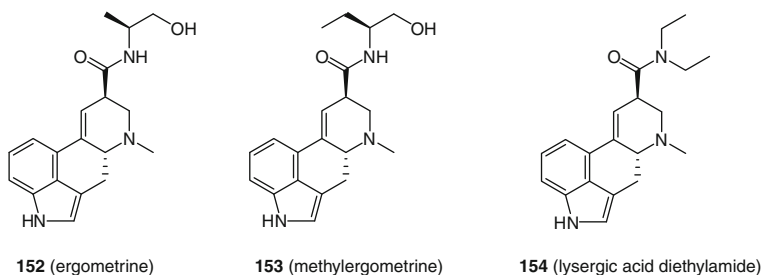


Fig. 4.6 Natural (**152**) and semi-synthetic ergoamide derivatives (**153** and **154**)

### 4.1.4 Ergopeptines

Like ergoamides, ergopeptines (**155**) are derivatives of lysergic acid (**133**) wherein the tripeptide moieties are connected *via* amide bonds (Fig. 4.7). Lactam ergot alkaloids, also called ergopeptams (**156**), are seen as precursors in the biosynthesis of ergopeptines (**155**) (105). In their biosynthesis, an oxygenase-catalyzed hydroxylation of the amino acid adjacent to the lysergic acid moiety leads to cyclization, which forms the oxazolidin-4-one moiety in ergopeptines (**155**) (105).

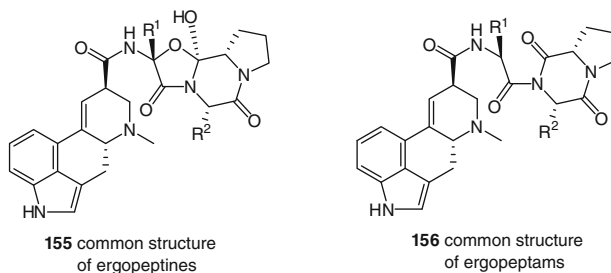
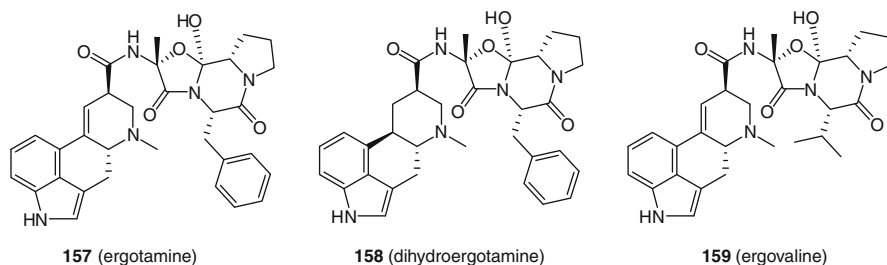


Fig. 4.7 Common structures of ergopeptines **155** and ergopeptams **156**

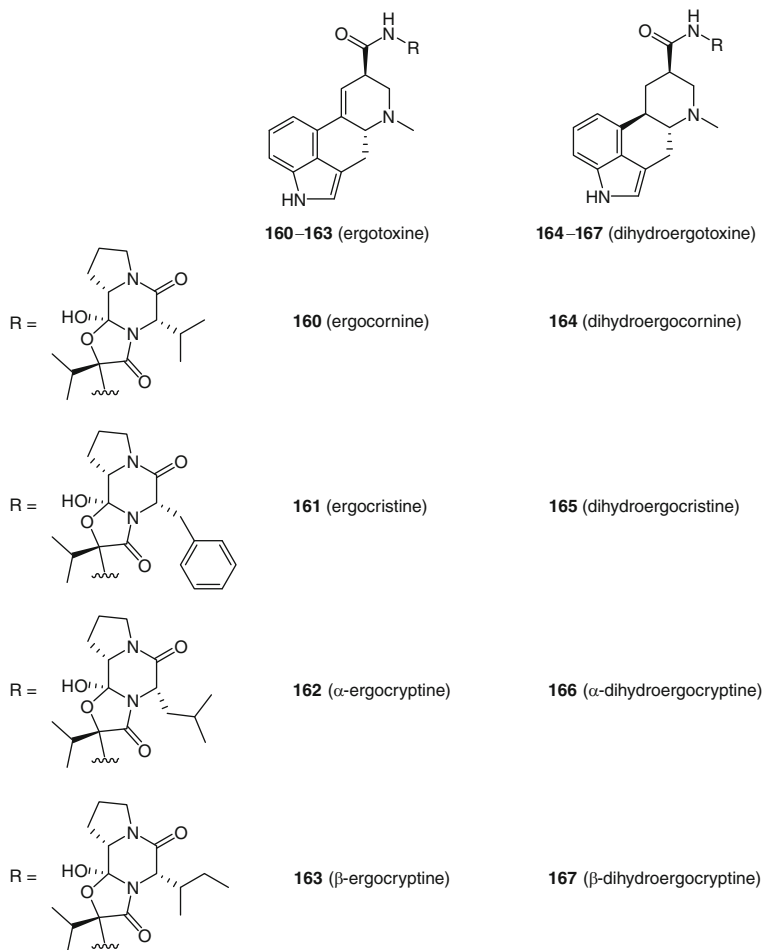
The most important representative of the ergopeptine subclass is ergotamine (**157**), which is produced by *C. purpurea* as the main ergot alkaloid (Fig. 4.8) (88, 106–108).

Whereas ergotamine (**157**) and its semi-synthetic derivative dihydroergotamine (**158**) have a clinical purpose for the treatment of several diseases (88, 109–112), ergovaline (**159**) is involved in livestock toxicoses caused by ingestion of endophyte-infected grasses (88, 113, 114).



**Fig. 4.8** Ergotamine (**157**), dihydroergotamine (**158**) and ergovaline (**159**)

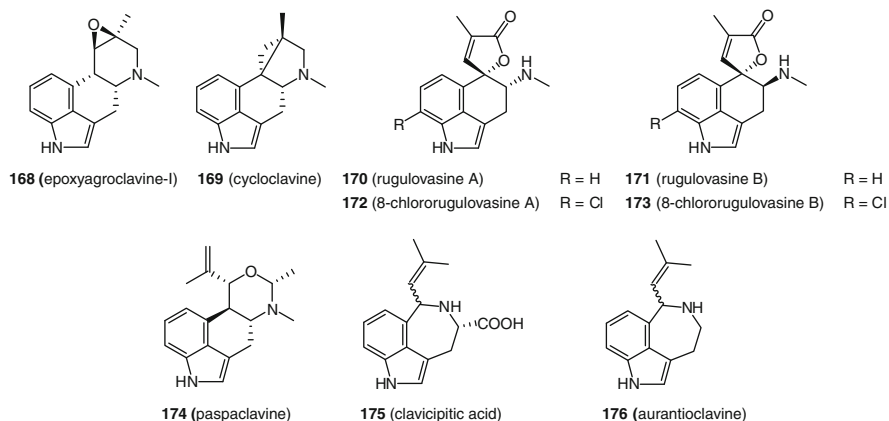
The peptide alkaloid ergotoxine was originally believed to constitute a single compound, but later was shown to be a mixture of several ergopeptines, namely, ergocornine (**160**), ergocristine (**161**),  $\alpha$ -ergocryptine (**162**), and  $\beta$ -ergocryptine (**163**) (Fig. 4.9) (115). Each component of the ergotoxine alkaloids contains a tripeptide moiety, with two of three amino acids (L-valine and L-proline) being in common in all of the compounds, while the third amino acid differs (115). The ergotoxines **160–163** isolated from natural sources can be hydrogenated to yield the 9,10-dihydroergotoxines **164–167**, composed of dihydroergocornine (**164**), dihydroergocristine (**165**),  $\alpha$ -dihydroergocryptine (**166**), and  $\beta$ -dihydroergocryptine (**167**) (115). As methanesulfonates, the 9,10-dihydroergotoxines **164–167** are approved drugs for different indications (116).



**Fig. 4.9** Ergotamines **160–163** and dihydroergotamines **164–167** are used as mixtures of different ergopeptines

### 4.1.5 Related Structures

This section of the chapter will describe alkaloids identified in fungal strains that are biosynthetically related to ergot alkaloids. These compounds carry a modified ergoline scaffold like epoxyagroclavine-I (**168**) or even an obviously different skeleton like aurantioclavine (**176**) (Fig. 4.10) (88, 91, 117).



**Fig. 4.10** Ergot alkaloids with unusual structural motifs

Epoxyagroclavine-1 (**168**), isolated from *Penicillium kapuscinski* (91), contains a clavine-type skeleton and bears an epoxide function between C-8 and C-9. In cycloclavine (**169**), isolated from *Aspergillus japonicus*, the six-membered piperidine ring is replaced by a cyclopropane-fused pyrrolidine ring (118). Rugulovasine A (**170**), its epimer rugulovasine B (**171**), as well as their 8-chlorinated derivatives **172** and **173**, contain an interesting spirocyclic 2-furanone moiety and have been identified in various fungal strains, including *Penicillium* species (88, 91, 119–121). In paspaclavine (**174**), isolated from *Claviceps paspali*, the D-ring of the ergoline skeleton is substituted with an acetalic 1,3-oxazinanone structure (122). Clavicipitic acid (**175**), isolated from *Claviceps fusiformis* (123, 124), and its decarboxylated derivative aurantioclavine (**176**), derived from *Penicillium aurantiovirens* (91, 125), have only the indole moiety in common with other ergot alkaloids, whereby the indole core is fused with a seven-membered azepane ring. This azepinoindole framework can be also found in the communesin family (126).

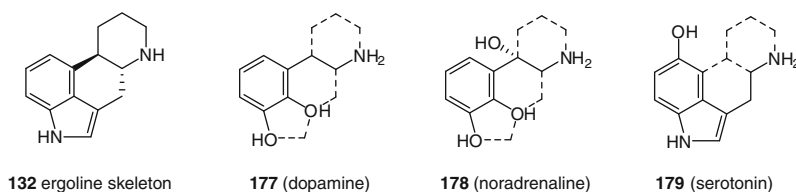
Due to the examination of biosynthetic gene clusters, the biosynthesis of ergot alkaloids is well understood and descriptions can be found in the literature (88, 89).

## 4.2 Biological Properties

It has been stated that “Ergot alkaloids, of which lysergic acid is representative, are particularly important as they possess the widest spectrum of biological activity found in any family of natural products” (127). Furthermore, for some considerable time it has been possible to distinguish between the valuable pharmacological properties of ergot alkaloids and their toxic effects (ergotism), known from livestock poisonings. The latter aspect is important from an economic point of view in terms of crop loss. In addition, the abuse of LSD (**154**),

which can be prepared from natural occurring ergot alkaloids, has to be taken into account in terms of a benefit-harm-assessment of the biological effects of ergot alkaloids.

Without going into great detail on the biological profiles of certain alkaloids, since this information can be found elsewhere (128, 129), their pharmacological effects can be reasonably explained by their general structure: many of their activities arise most probably from the structural similarity between the ergoline scaffold **132** and important neurotransmitters, such as dopamine (**177**), noradrenaline (**178**), and serotonin (**179**) (Fig. 4.11) (130). In interacting with one or all of the associated receptors, ergot alkaloids can act as either an (partial) agonist or as an antagonist or even in a dual role (130, 131).



**Fig. 4.11** Chemical similarity of the ergoline ring system **132** to the neurotransmitters dopamine (**177**), noradrenaline (**178**), and serotonin (**179**)

Some ergot alkaloids or their derivatives have found their way to clinical use, such as dihydroergotamine (**158**), which is utilized in the treatment of migraine headaches (130, 132). “Dihydroergotoxin” (**164–167**) finds application as an anti-hypertensive drug and in the treatment of cerebral dysfunction in gerontology (130, 133, 134). The ergotoxine  $\alpha$ -ergocryptine (**162**) and its semi-synthetic derivative 2-bromoergocryptine (bromocriptine, not shown) are effective in cases of hyperprolactinemia (130, 135), whereas bromocriptine is also used for the treatment of *Parkinson’s* disease (130, 136).

### 4.3 Total Syntheses

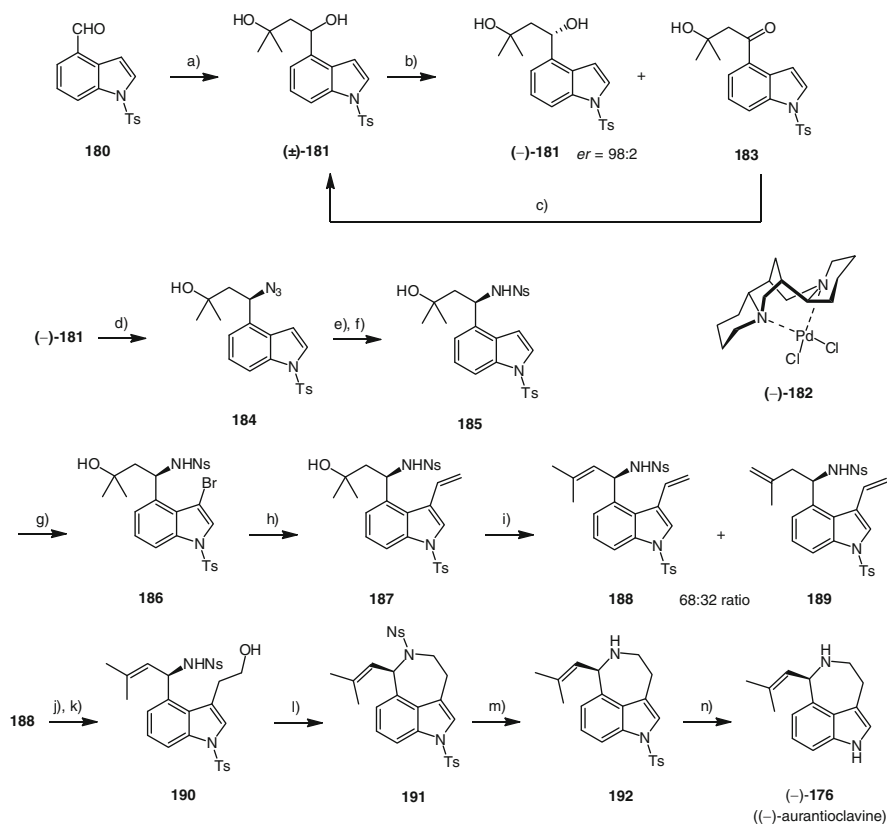
Since the first chemical experiments of *Hofmann* with ergot alkaloids in the 1930s and the first total synthesis of lysergic acid (**133**) by *Kornfeld* and *Woodward* in 1956 (137), ergot alkaloids have attracted interest from the chemical synthesis community. In this chapter, synthetic approaches within the last two decades are presented, wherein attention is focused on syntheses using the application of modern catalytic methods and metal-organic reagents. Within the body of

published total, partial, and formal synthesis procedures, enantioselective syntheses are featured more prominently in this section, in addition to reactions applied to the rapid construction of the ergoline skeleton.

### 4.3.1 *Enantioselective Synthesis via Pd-Catalyzed Oxidative Kinetic Resolution: (–)-Aurantioclavine*

In 2008, *Stoltz* and co-workers presented the enantioselective total synthesis of (–)-aurantioclavine ((–)-**176**) (Scheme 4.1), by application of a new method for kinetic resolution of secondary alcohols (*138*).

The starting material for the synthesis was tosylated indole-4-carbaldehyde (**180**) (Scheme 4.1) (*139*). Addition of the dianion, derived from isobutylene oxide (*140*), to **180**, afforded (±)-**181**. Afterwards, Pd-catalyzed oxidative kinetic resolution with (–)-sparteine ((–)-**182**) as chiral ligand was applied to the racemic diol (±)-**181**, to deliver the enantioenriched alcohol (–)-**181** with 96% *ee* and in 36% yield (91% of the theoretical maximum, selectivity factor  $S = 18.2$  (*138*, *141*)). Along with the unreacted enantioenriched alcohol, (–)-**181**, ketone **183** was isolated in 56% yield (81% of the theoretical maximum). In an additional recycling step, ketone **183** could be readily back-transformed to (±)-**181** in 95% yield by reduction with lithium aluminum hydride. The enantioenriched alcohol (–)-**181** was converted to azidoalcohol **184** with hydrazoic acid under *Mitsunobu* conditions (*142*). To avoid any racemization at the sensitive benzylic stereogenic center, this substitution reaction was conducted at low temperature. Afterwards, the azide function in **184** was hydrogenated and the resulting amine was protected as a 2-nitrobenzenesulfonamide (*143*) to furnish sulfonamide **185**. Aromatic bromination to **186** and subsequent *Stille* coupling (*144*) with tributyl(vinyl)tin afforded vinyl indole **187**. Phosphorus oxychloride in pyridine was found to be the appropriate dehydrating reagent to afford the desired trisubstituted olefin isomer **188** as the major product. Regioselective hydroboration followed by oxidative work-up delivered the amino alcohol **190**. Applying *Mitsunobu* conditions to **190** closed the seven-membered ring in excellent yield to give **191**. Deprotection of the allylic amine yielded the free amine **192**, and subsequent removal of the tosyl group by *n*-tetrabutylammonium fluoride (TBAF) finally delivered the natural product (–)-aurantioclavine ((–)-**176**) in 13 steps with <1% overall yield (*145*).



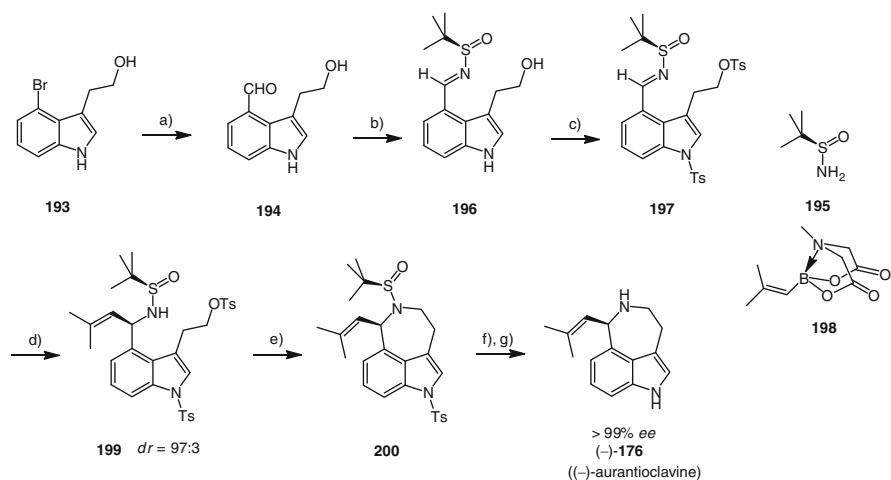
**Scheme 4.1** Reagents and conditions: a) isobutylene oxide, LiDBB, THF,  $-78^{\circ}\text{C}$ , 69%; b) 10 mol%  $(-)\text{-182}$ , MS 3 Å, *t*-BuOH, 40 to  $70^{\circ}\text{C}$ , 1 atm  $\text{O}_2$ , 98 h, (59% conversion), 51% yield, 86% of theoretical maximum for **183**, 36% yield, 91% of theoretical maximum, 96% *ee*, kinetic resolution selectivity factor  $S = 18.2$  for  $(-)\text{-181}$ ; c)  $\text{LiAlH}_4$ , THF,  $-78^{\circ}\text{C}$ , 95%; d)  $\text{HN}_3$ ,  $\text{PBu}_3$ , DIAD, toluene,  $-78^{\circ}\text{C}$  to  $-20^{\circ}\text{C}$ , 80%; e)  $\text{H}_2$ , cat. Pd/C,  $\text{HCl}/\text{MeOH}$ ,  $23^{\circ}\text{C}$ ; f) *o*-NsCl,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^{\circ}\text{C}$  to rt, 89% over two steps; g)  $\text{PyHBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^{\circ}\text{C}$  to  $23^{\circ}\text{C}$ , 72%; h) tributyl (vinyl)tin, 20 mol%  $\text{Pd}(\text{PPh}_3)_4$ , toluene  $100^{\circ}\text{C}$ , 75%; i)  $\text{POCl}_3$ , pyridine,  $0^{\circ}\text{C}$  to  $23^{\circ}\text{C}$ , 95%; j) 9-BBN, THF,  $23^{\circ}\text{C}$ , 10 h; k)  $\text{NaOH}$ ,  $\text{H}_2\text{O}_2$ ,  $\text{THF}/\text{EtOH}/\text{H}_2\text{O}$ ,  $0^{\circ}\text{C}$  to  $23^{\circ}\text{C}$ , 48% over two steps; l) DIAD,  $\text{PPh}_3$ , toluene,  $0^{\circ}\text{C}$  to rt, 95%; m)  $\text{PhSH}$ ,  $\text{K}_2\text{CO}_3$ , DMF,  $23^{\circ}\text{C}$ , 53%; n) TBAF, THF,  $70^{\circ}\text{C}$ , 68%

### 4.3.2 Asymmetric Alkenylation of Sulfinyl Imines: (-)-Aurantioclavine

Two years after Stoltz' (138) total synthesis of  $(-)\text{-aurantioclavine}$  ( $(-)\text{-176}$ ) (Scheme 4.1), Ellman and co-workers found a way to produce the enantiomerically pure natural product in six steps in 27% overall yield using a newly developed Rh(I)-catalyzed addition of *N*-methyliminodiacetic acid (MIDA) boronate **198**

(Scheme 4.2) (145). Employing a *Grignard* reagent addition sequence, the route could be shortened to five steps producing a 29% overall yield.

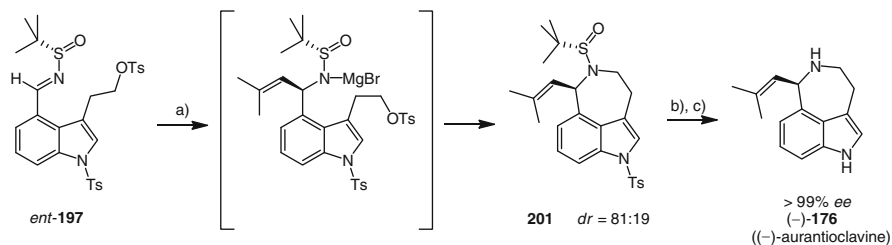
The first step was the Pd-catalyzed formylation of the commercially available bromoindole derivative **193** using a procedure reported by *Beller* and co-workers (Scheme 4.2) (146). It was found to be necessary to protect the alcohol function with  $\text{TMSCl}$  *in situ* to avoid formation of a seven-membered lactone. The crude aldehyde **194** was directly converted with **195** to the *N-t*-butanesulfinyl imine **196** in 53% yield over two steps. Double protection of the alcohol and the aromatic amine function from **196** yielded the bis-tosylated *N*-sulfinyl imine **197** in good yield. The Rh(I)-catalyzed addition of the newly developed MIDA boronate **198** (147) provided sulfonamide **199** in 78% yield and with high diastereoselectivity. Deprotonation of the sulfonamide function of **199** led to closure of the azepine ring system to furnish **200**. Subsequent removal of the protection groups in **200** afforded the natural product (–)-**176** in quantitative yield and with high optical purity.



**Scheme 4.2** Reagents and conditions: a)  $\text{TMSCl}$ , 0.5%  $\text{Pd}(\text{OAc})_2$ , 1.5%  $\text{P}(\text{Ad})_2\text{Bu}$ ,  $\text{H}_2$ : $\text{CO}$  (2:1),  $\text{TMEDA}$ ,  $100^\circ\text{C}$ , toluene; b) **195**,  $\text{Ti}(\text{OEt})_4$ , THF, 53% (over 2 steps); c)  $\text{TsCl}$ ,  $\text{NEt}_3$ ,  $\text{DMAP}$ ,  $-20^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ , 78%; d) 2 equiv. **198**, 2.5 mol%  $[\text{Rh}(\text{OH})(\text{cod})]_2$ , 5.0 mol%  $\text{dppbenz}$ , 2 equiv.  $\text{K}_3\text{PO}_4$ ,  $\text{H}_2\text{O}$ /dioxane (3:2),  $60^\circ\text{C}$ , 20 h, *dr* = 97:3, 81%; e)  $\text{NaH}$ , THF, 85%; f)  $\text{HCl}$ ,  $\text{MeOH}$ , rt, 0.5 h; g)  $\text{Mg}(0)$ ,  $\text{MeOH}$ , rt, 99% over two steps

Despite the precedence for lower selectivity, *Ellman* and co-workers realized that addition of a *Grignard* reagent proved to be more efficient (145). After *Grignard* reagent addition to *ent*-**197**, spontaneous cyclization to azepine **201** occurred upon formation of the nucleophilic sulfonamide anion (Scheme 4.3). It is interesting to mention that because *Grignard* addition provides the opposite diastereoselectivity in comparison to Rh(I)-catalyzed addition, the other enantiomer of *N-t*-butanesulfinyl imine (*ent*-**197**) had to be applied.

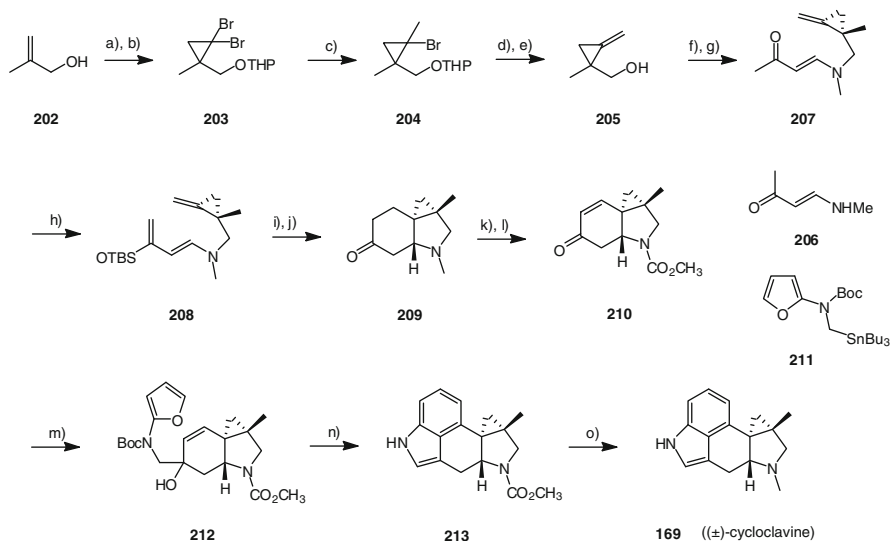




**Scheme 4.3** Reagents and conditions: a) 2,2-dimethylvinyl magnesium bromide,  $\text{CH}_2\text{Cl}_2$ ,  $-48^\circ\text{C}$  to rt,  $dr = 81:19$ , 88%; b) HCl, MeOH, rt, 0.5 h; c) Mg(0), MeOH, rt, 98% over two steps

### 4.3.3 The IMDAF-Approach to ( $\pm$ )-Cycloclavine

In 2011, *Wipf* and *Petronijevic* reported their synthesis route to ( $\pm$ )-cycloclavine (**169**) (Scheme 4.4), in which the total synthesis proceeded in 14 steps with 1.25% overall yield (*148*). One key feature of their approach included the formation of the indole moieties through an allylic alcohol-IMDAF (intramolecular *Diels-Alder* cyclization of furan) reaction (**212** to **213**) (*149*, *150*). Another pivotal step of this route is the synthesis of the cycloclavine indoline core through a stereoselective intramolecular *Diels-Alder* reaction of a methylenecyclopropane building block (**208** to **209**).



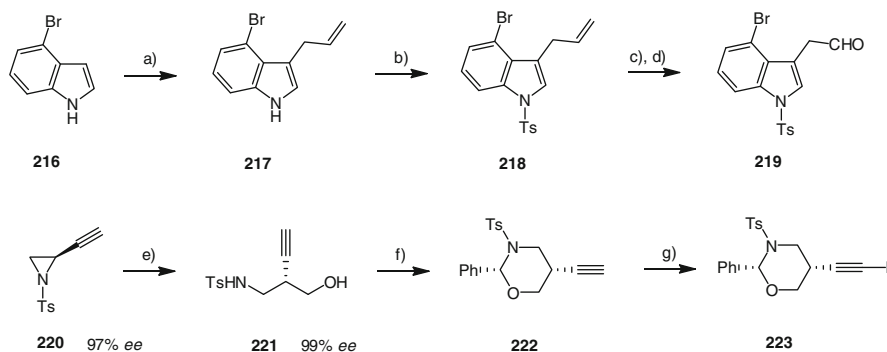
**Scheme 4.4** Reagents and conditions: a) THP, HCl (cat.), 90%; b)  $\text{CHBr}_3$ ,  $\text{Et}_3\text{N}$ , cetrinide, NaOH (aq.),  $\text{CH}_2\text{Cl}_2$ , 95%; c) *n*-BuLi, THF,  $-95^\circ\text{C}$ ; then  $\text{CH}_3\text{I}$ ,  $-95^\circ\text{C}$  to rt, 82%; d) *t*-BuOK, DMSO, rt, 69%; e) *p*-TsOH, MeOH, rt, 79%; f) MsCl,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to rt, 1 h; g) **206**, NaH, DMF, rt, 12 h, 67% (over two steps); h) NaHMDS, THF,  $-78^\circ\text{C}$ ; then TBSCl, quant. without purification; i) MW,  $\alpha,\alpha,\alpha$ -trifluorotoluene,  $195^\circ\text{C}$ , 1 h, 52% (72% brsm); j) TBAF, THF, rt, 85%; k) MeOC(O)Cl,  $70^\circ\text{C}$ , 3 h, 71%; l) LDA, THF,  $-78^\circ\text{C}$ , 1 h; then TMSCl (1.3 equiv); then Pd(OAc) $_2$  (1.3 equiv),  $\text{CH}_3\text{CN}$ , 12 h, 67%; m) *n*-BuLi, THF,  $-78^\circ\text{C}$ , **211**, 51%; n) MW,  $\alpha,\alpha,\alpha$ -trifluorotoluene,  $180^\circ\text{C}$ , 0.5 h, 44% (56% brsm); o)  $\text{LiAlH}_4$ , THF,  $66^\circ\text{C}$ , 0.5 h, quant

In the first step,  $\beta$ -methylallyl alcohol **202** was protected as a THP-ether and subsequent cyclopropanation under phase transfer conditions afforded **203** in 86% combined yield (Scheme 4.4) (151). Treatment of the dibromocyclopropane **203** with 1 equiv. *n*-BuLi at  $-95^{\circ}\text{C}$  and following exposure of the monobromo-monolithiated intermediate to methyl iodide afforded the monobromo species **204** (152). Elimination of hydrogen bromide under thermodynamic conditions and following deprotection of the THP protecting group furnished the desired cyclopropylmethylidene alcohol **205**. The free alcohol function of **205** was mesylated and the resulting mesylate was treated with the anion of the vinylogous amide **206** to give the substitution product **207** in 67% yield over the two steps. The vinylogous amide **207** was converted to the siloxy diene **208** in quantitative yield using NaHMDS with subsequent TBSCl trapping of the enolate. The raw material **208** was then heated to  $195^{\circ}\text{C}$  under microwave irradiation in  $\alpha,\alpha,\alpha$ -trifluorotoluene to furnish the *Diels-Alder*-product along with unreacted starting material **208**. Removal of the silyl protecting group from the newly formed indoline using TBAF yielded the tricyclic ketone **209** in 85% yield. For the further steps of the synthesis it was found to be necessary to protect the basic amine moiety as a carbamate function (153). In this way, dealkylative protection of **209** afforded the targeted carbamate-protected intermediate that was converted subsequently to the  $\alpha,\beta$ -unsaturated cyclic **210** ketone using *Saegusa-Ito* oxidation (154). Exposure of enone **210** with the tin-lithium exchange product of stannane **211** yielded the tertiary alcohol **212** in 51% yield. The tertiary alcohol **212** was converted in the following microwave-promoted IMDAF reaction (149, 150) at  $190^{\circ}\text{C}$  in  $\alpha,\alpha,\alpha$ -trifluorotoluene to furnish the desired indole **213** in 44% yield. In the final step, the IMDAF product **213** was deprotected with  $\text{LiAlH}_4$  to provide ( $\pm$ )-cycloclavine (**169**) in quantitative yield.

#### 4.3.4 *Enantioselective Pd-Catalyzed Domino Cyclization Strategy to (+)-Lysergic acid, (+)-Lysergol, and (+)-Isolysergol*

In 2011, the enantioselective syntheses of (+)-lysergic acid ((+)-**133**), (+)-lysergol ((+)-**214**), and (+)-isolysergol ((+)-**215**) were reported by *Ohno* and co-workers (Scheme 4.7) (155). The key feature of these total syntheses is the construction of the C/D ring system in one reaction sequence by applying a Pd-catalyzed domino cyclization of allenes bearing a nucleophilic functionality (for more information on these reaction types see (156)). Except for *Oppolzer's* intramolecular imino-*Diels-Alder* strategy, most synthesis studies have relied on a stepwise construction of the ergoline C/D ring system (155, 157). Besides the sequential regioselective bond formation for the construction of the C/D ring system, the stereospecific transfer of the axial chirality from the allene into the new stereogenic center was the second challenge. Initial experiments on a model system by *Ohno* and co-workers proved the potential of the domino reaction to face these challenges (158).

For the first step, commercially available 4-bromoindole **216** was selectively allylated at position 3 using *Tamaru's* procedure (Scheme 4.5) (159). The resulting 3-allylindole **217** was protected and subsequently converted to the aldehyde **219** by OsO<sub>4</sub>/NaIO<sub>4</sub>-mediated oxidative cleavage of the double bond in **218** (160). For the subsequent intended preparation of the enantiomerically pure allene **226** *via Myers* method (161), aldehyde **219** had to be coupled with the enantiomerically pure alkyne **223** to furnish the required propargylic alcohol **224a**.

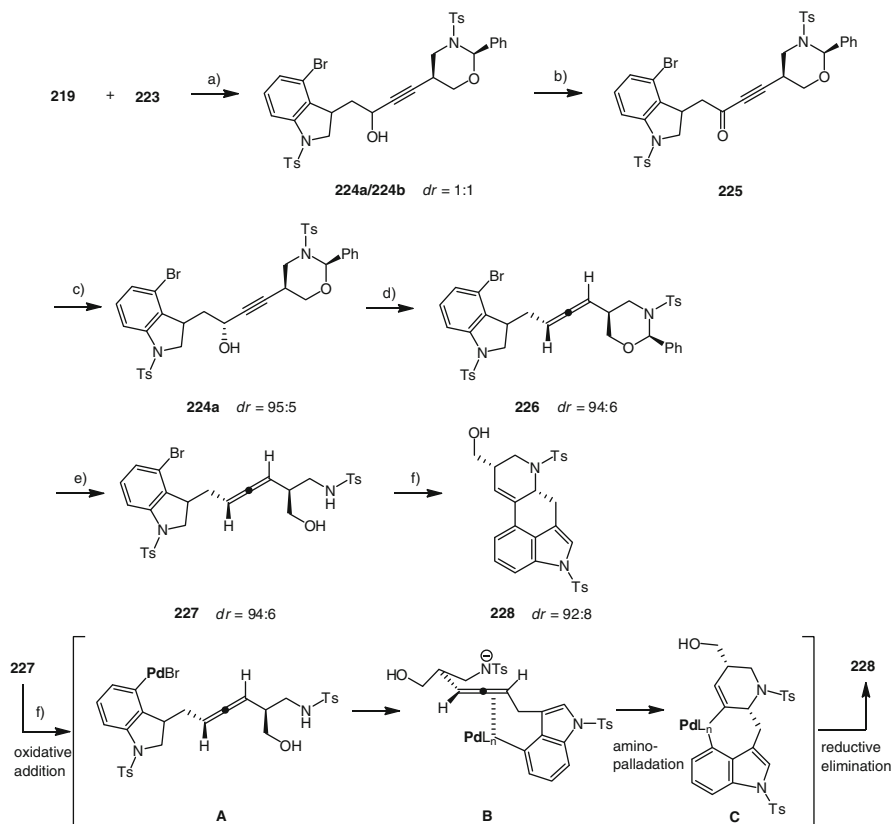


**Scheme 4.5** Reagents and conditions: a) Pd(PPh<sub>3</sub>)<sub>4</sub>, Et<sub>3</sub>B, allyl alcohol, THF, 50°C, 87%; b) TsCl, NaOH, *n*-Bu<sub>4</sub>NHSO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 96%; c) OsO<sub>4</sub>, NMO, THF/H<sub>2</sub>O; d) NaIO<sub>4</sub>, THF/H<sub>2</sub>O, 86% (over two steps); e) 3 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 1.2 equiv. InI, formalin, THF/HMPA (4:1), 70%; f) PhCH(OMe)<sub>2</sub>, CSA, ClCH<sub>2</sub>CH<sub>2</sub>Cl, 70°C, 78%; g) NIS, AgNO<sub>3</sub>, THF, 89%

In order to synthesize alkyne **223**, enantioenriched ethynylaziridine **220** was prepared by a known four-step sequence (162) from (*S*)-*Garner's* aldehyde (163, 164). A reductive coupling reaction (165, 166) of the aziridine **220** with formaldehyde in the presence of Pd(Ph<sub>3</sub>)<sub>4</sub> and InI furnished the 2-ethynyl-1,3-amino alcohol **221**. Protection of **221** as benzylidene acetal gave the alkyne **222**, which was converted in the next step to the corresponding iodoalkyne **223** (167).

With both coupling partners **219** and **223** in hand, it was revealed that conditions of the Cr(II)/Ni(0)-mediated *Nozaki-Hiyama-Kishi* (*NHK*)-reaction were optimum to furnish the desired propargylic alcohol in 90% yield in a 1:1 ratio of **224a** and **224b** (Scheme 4.6) (168–170). Even the use of chiral sulfonamide ligands did not prevent the poor diastereoselectivity of this reaction (for examples of asymmetric *NHK*-reactions see (171)). To synthesize neat **224a**, the newly generated stereogenic center in **224a/224b** had to be converted by oxidation with *DMP* to afford ketone **225**. Subsequent asymmetric reduction of **225** using (*R*)-alpine-borane (172) gave the desired neat propargylic alcohol **224a** with the correct stereocenter in high selectivity. By applying *Myers' method*, the alcohol **224a** could be stereoselectively transformed into the allene **226** using nosyl hydrazine under *Mitsunobu* conditions (161). Subsequent cleavage of the benzylidene protecting group in **226** with PTSA yielded the allenic amide **227**, which was used in the following pivotal domino cyclization reaction. The Pd-catalyzed domino cyclization of **227** provided the

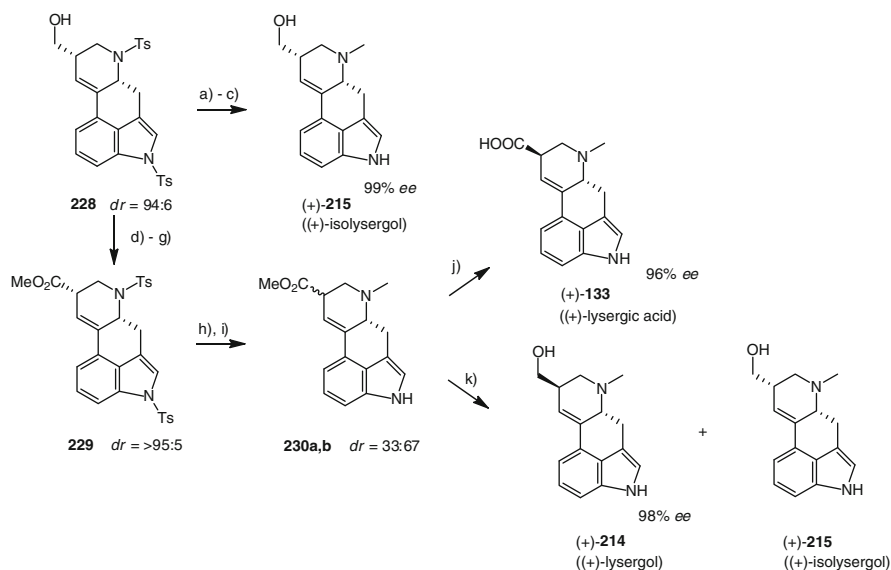
desired ergot derivative **228** as the only product in good diastereoselectivity (**158**). This outcome can be explained by the proposed mechanism in Scheme 4.6. The domino cyclization can proceed through two competing pathways: aminopalladation and carbopalladation (**155**, **158**). After oxidative addition of **227** to Pd (0), the indolylpalladium halide **A** formed underwent an amino-palladation pathway through conformer **B** to give the alkenylpalladium(II) intermediate **C** stereoselectively (**155**, **158**). Reductive elimination of intermediate **C** afforded **228** as the major isomer.



**Scheme 4.6** Reagents and conditions: a)  $\text{NiCl}_2$ ,  $\text{CrCl}_2$ , THF,  $0^\circ\text{C}$ ; b) *Dess-Martin* periodinane,  $\text{CH}_2\text{Cl}_2$ , 95%; c) (*R*)-alpine borane, THF, 86%; d)  $\text{NsNHNH}_2$ , DEAD,  $\text{Ph}_3\text{P}$ , THF,  $-15^\circ\text{C}$  to rt, 77%; e) PTSA,  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ,  $50^\circ\text{C}$ , 85%; f)  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{K}_2\text{CO}_3$ , DMF,  $100^\circ\text{C}$ , 76%

In three additional steps, (+)-isolysergol ((+)-**215**) could be prepared from **228** by cleavage of the tosyl groups with sodium naphthalenide and subsequent N-methylation (Scheme 4.7). To have synthesis access to (+)-lysergic acid ((+)-**133**) and (+)-lysergol ((+)-**214**), the primary alcohol function of **228** had to be converted into the methyl ester **229** using *Dess-Martin* reagent and  $\text{NaClO}_2$  followed by esterification with  $\text{TMSCHN}_2$ . After cleavage of the two tosyl groups and N-methylation, a diastereomeric mixture of methyl isolysergate (**230a**) and

lysergate (**230b**) was obtained.  $\text{LiAlH}_4$ -reduction of the unseparated mixture of **230a/230b** afforded (+)-lysergol ((+)-**214**) in 49% yield along with (+)-isolysergol ((+)-**215**) in 24% yield. Finally, saponification of **230a/230b**, with accompanying isomerization at C-8 to the desired isomer (173, 174), afforded (+)-lysergic acid ((+)-**133**) in 54% yield and high enantiopurity.



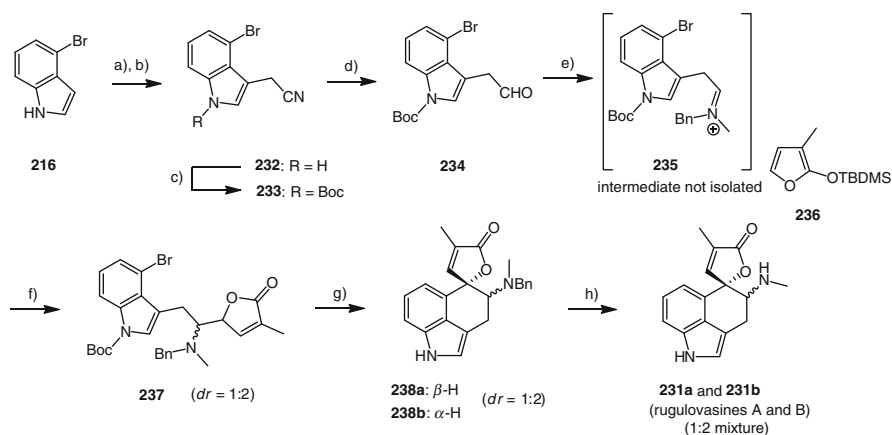
**Scheme 4.7** Reagents and conditions: a) sodium naphthalenide, THF,  $-78^\circ\text{C}$ ; b) formalin,  $\text{NaBH}_3\text{CN}$ , AcOH, MeOH; c) separation (46% over three steps); d) *Dess-Martin* periodinane,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to rt; e)  $\text{NaClO}_2$ ,  $\text{NaH}_2\text{PO}_4$ , 2-methylbut-2-ene, *t*-BuOH/THF/ $\text{H}_2\text{O}$ ; f)  $\text{TMSCHN}_2$ , MeOH/toluene,  $0^\circ\text{C}$ ; g) separation (64% over four steps); h) sodium naphthalenide, THF,  $-78^\circ\text{C}$ ; i) formalin,  $\text{NaBH}_3\text{CN}$ , AcOH, MeOH; j) 1 *N* NaOH, EtOH,  $35^\circ\text{C}$ ; then 0.1 *N* HCl to pH 6.2, 54%; k)  $\text{LiAlH}_4$ , THF,  $0^\circ\text{C}$ , 49% for (+)-**214**, 24% for (+)-**215**

### 4.3.5 Intramolecular Vinylogous Mannich Approach to Rugulovasines A and B

In their concise synthesis of rugulovasines A and B (**231a**, **231b**), *Martin* and co-workers were able to prove the usefulness of a vinylogous *Mannich* reaction (Scheme 4.8) (175–177). Whereas most natural products are isolated as single enantiomers, rugulovasines A and B (**231a**, **231b**) were both isolated in racemic form, and it was found that they both underwent interconversion *via* an achiral intermediate upon warming (120, 178, 179).

The starting material for the synthesis was 4-bromoindole (**216**), which was readily converted into the corresponding 3-indolylacetonitrile derivative **232** using a one-pot procedure (Scheme 4.8) (180). After the indole nitrogen was protected, the nitrile function of the resulting carbamate **233** was reduced with DIBAL-H to

yield the desired aldehyde **234**. The crude aldehyde **234** was then allowed to react with benzylmethylamine. The product underwent facile reaction with silyloxyfuran **236** in the presence of CSA, which presumably proceeded over the stabilized intermediate **235**. This vinylogous *Mannich* reaction provided a 1:2 mixture of diastereomeric adducts **237**. For the construction of the spirocyclic moiety, it was intended to cyclize the aminoalkyl butenolide **237** *via* an intramolecular  $S_{RN}1$  reaction. It was found that irradiation of **237** in refluxing ammonia in the presence of freshly sublimed potassium *t*-butoxide were appropriate conditions to furnish *N*-benzylated rugulovasines A and B (**238a** and **238b**) in 51% yield as an inseparable mixture (1:2). Concomitant deprotection of the Boc-protecting group during this reaction shortened the route, so just the benzyl group had to be removed in the final step. Therefore, the hydrochloride salt of **238a/238b** was allowed to react with *Pearlman's* catalyst under a hydrogen atmosphere to yield a mixture (1:2) of rugulovasines A and B (**231a** and **231b**) in 74% yield.

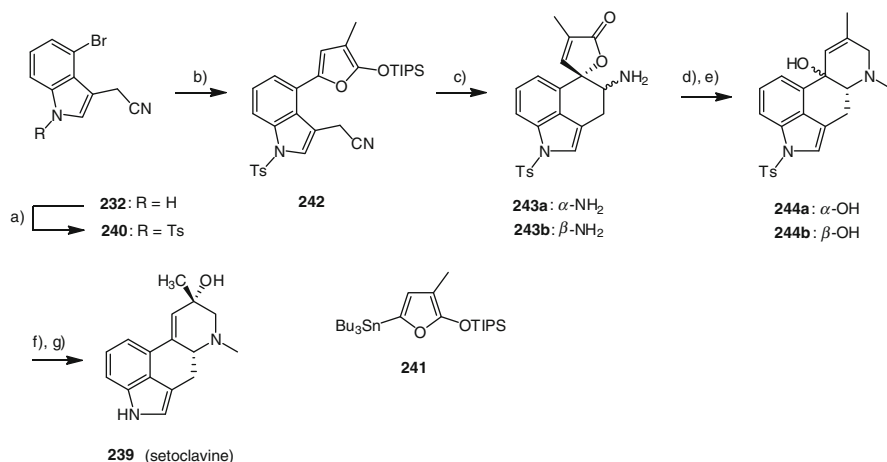


**Scheme 4.8** Reagents and conditions: a)  $\text{HNMe}_2$  (aq.),  $\text{CH}_2\text{O}$  (aq.), AcOH,  $0^\circ\text{C}$  to  $25^\circ\text{C}$ ; b) KCN, DMF/ $\text{H}_2\text{O}$  (1:1),  $140^\circ\text{C}$ , 2 h, 71% over two steps; c)  $(\text{Boc})_2\text{O}$ , DMAP,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $25^\circ\text{C}$ , 25 h, 91%; d) DIBAL,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$  to  $25^\circ\text{C}$ ; e) benzylmethylamine,  $\text{CH}_2\text{Cl}_2$ ,  $25^\circ\text{C}$ , 7 h; f) CSA; then **236**, benzene,  $80^\circ\text{C}$ , 1 h, 45% over three steps; g) *t*-BuOK,  $\text{NH}_3$ , reflux, *h\nu*, 1 h, 51%; h) HCl, EtOH,  $\text{H}_2$  (1 atm), 20% Pd(OH) $_2$ /C,  $25^\circ\text{C}$ , 9 h, 74%

### 4.3.6 Intermolecular Vinylogous Mannich Approach to Setoclavine

The group of *Martin* was able to show that the spirocyclic rugulovasine natural product class is rapidly accessible *via* intermolecular vinylogous *Mannich* reactions (see Sect. 4.3.5) (175–177). Next, they turned to the question of whether or not it would be possible to convert the butyrolactone subunit of the accessible spirocyclic

compounds into the fully fused ergoline skeleton (**175**). Such a transformation would provide access to the characteristic tetracyclic ring system found in lysergic acid (**133**) or setoclavine (**239**) (Scheme 4.9).

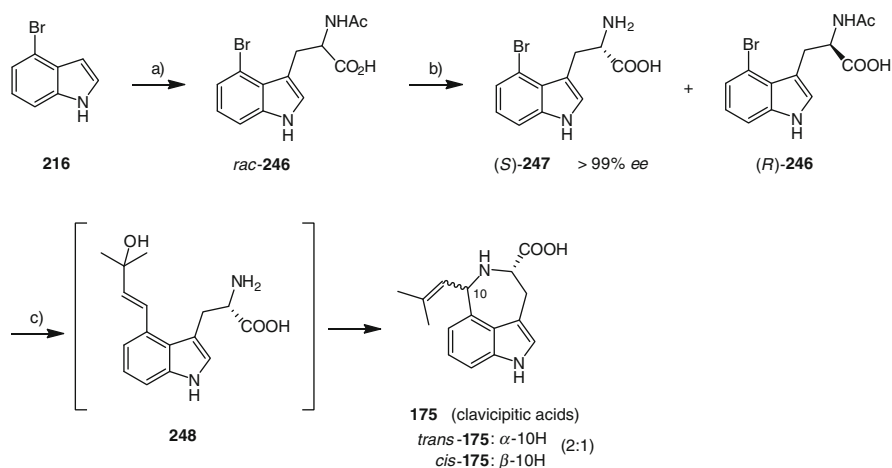


**Scheme 4.9** Reagents and conditions: a) NaH, TsCl, THF, 0°C to rt, 7 h, 73%; b) **241**, Pd(PPh<sub>3</sub>)<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, toluene, reflux, 3 h, 95%; c) DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78°C to rt, 4 h; then SiO<sub>2</sub>, 76%; d) DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>/THF, -78°C, 2 h; e) 3.5 equiv. NaBH<sub>3</sub>CN, CH<sub>3</sub>CN, AcOH; then 38% aq. CH<sub>2</sub>O, 41% (**244a**) and 29% (**244b**) over two steps; f) Mg, MeOH, rt, 1.5 h; g) 1 N HCl, rt, 64% over two steps

The synthesis of setoclavine (**239**) commenced from the previously described 3-indolylacetonitrile derivative **232** (see Sect. 4.3.5), which was *N*-protected by tosylation to give the desired *N*-tosyl derivative **240** (Scheme 4.9). *Stille* coupling of **240** with stannane **241** (**181**) to biaryl **242** and the subsequent tandem reduction/vinylogous *Mannich* reaction yielded the spirocyclic butenolides **243a** and **243b** with 76% overall yield. In the next step, the ring expansion reaction was conducted by reduction of **243a** and **243b** to the corresponding lactol that underwent facile isomerization and dehydration to generate a mixture of epimeric dihydropyridine derivatives. Afterwards, the imine function of the dihydropyridine moiety was reduced and the newly formed amine function was methylated to furnish a mixture of the diastereomeric amino alcohols **244a** and **244b** in 41 and 29% overall yield. The *N*-tosyl protecting group was readily removed by reduction with magnesium in methanol. At the same time, these conditions also facilitated the rearrangement of the diastereomeric allyl alcohols to yield the natural product setoclavine **239** as the major product along with other side products. The product spectrum of this reaction could be shifted to the natural product by treatment of the crude product mixture, obtained upon detosylation, with aqueous acid (the previously mentioned acid-catalyzed rearrangements of similar compounds were described in refs. (182–184)). Following this procedure, setoclavine (**239**) was isolated in 64% overall yield.

### 4.3.7 Biomimetic Three-Step Synthesis of Clavicipitic Acids

For the production of natural products on an industrial scale, fermentation processes are often preferable in comparison to chemical processes. In biosynthesis processes, natural products may be generated efficiently and cleanly *via* enzymatic catalysis (185). Thus, the development of synthesis approaches similar to their biosynthesis is one of the main objectives of the synthesis community. To pursue this goal, *Yokoyama* and co-workers developed a bio-similar three-step synthesis of optically active clavicipitic acid (**175**) (186), which was isolated from natural sources as an isomeric mixture (Scheme 4.10) (187).



**Scheme 4.10** Reagents and conditions: a) *rac*-serine (*rac*-**245**), Ac<sub>2</sub>O, AcOH, 50°C, 5 h; then **216**, 80°C, 4.5 h, 73%; b) “*Aspergillus acylase*”, CoCl<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>, pH 7, 37°C, 2 d, 49%; c) 0.1 equiv. Pd(OAc)<sub>2</sub>, 0.2 equiv. TPPTS, 3 equiv. K<sub>2</sub>CO<sub>3</sub>, 130°C, 8 h, sealed tube; then 60% aq. AcOH, 60°C, 2 h, 61%

In the first step, 4-bromoindole (**216**) was allowed to react with racemic serine (*rac*-**245**) heated with two equivalents of acetic anhydride prior to reaction with **216** (Scheme 4.10). There is published evidence that treatment of *rac*-**245** with acetic anhydride might lead to formation of an oxazolone (188), which can be attacked by 4-bromoindole (**216**) to furnish the racemic bromotryptophan derivative *rac*-**246**. The observation that the use of enantiomerically pure L-serine (L-**245**) also leads to the racemic bromotryptophan derivative *rac*-**246** can be reasonably explained by the formation of this oxazolone. In the next step, *N*-acetyl-4-bromotryptophan (*rac*-**246**) was treated with the enzyme “*Aspergillus acylase*” to yield the unprotected bromotryptophan (*S*)-**247** in high enantiopurity but in just moderate yield. The subsequently intended aqueous *Heck*-reaction showed an interesting pH dependence: under strongly basic conditions the desired C-4-vinylation at the indole core



occurred, whereas *N*-allylation at the amino group was observed under neutral or weakly basic conditions. Using potassium carbonate and strong heating, the *Heck* reaction proceeded smoothly in an aqueous medium to furnish the coupling product **248** as its potassium salt in 91% yield. It is noteworthy that in spite of the strongly basic conditions used (3 equiv. of base at 130°C for hours), no racemization was observed. By acidification of the reaction mixture from the *Heck* reaction, the cyclization of **248** to the natural product **175** proceeded smoothly. This one-pot procedure gave an isomeric mixture (2:1) of the natural products **175** in 61% yield (from (*S*)-**247**). After esterification of the isomeric mixture **175** with TMSCHN<sub>2</sub> and subsequent separation, it could be shown that each clavicipitic acid methyl ester showed high enantiopurity, thus avoiding the occurrence of racemization.

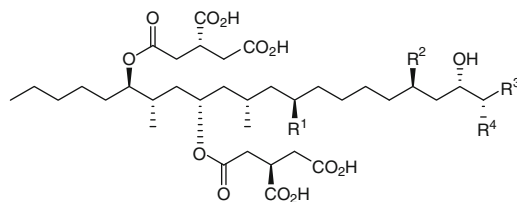
By using a related synthesis strategy, *Jia* and co-workers could accomplish the total syntheses of (–)-*trans*- and (+)-*cis*-clavicipitic acid as well as the syntheses of both aurantioclavine enantiomers (*189*). Thereby, misassignments regarding the relative configuration of *trans*- and *cis*-clavicipitic acid could be corrected.

## 5 Fumonisin

Fumonisin has been isolated from the fungus *Fusarium moniliforme* MRC 826 from corn intended for human consumption in Transkei, South Africa (190, 191) (Fig. 5.1 (192, 193), Table 5.1).



**Fig. 5.1** *Fusarium* fungus and corn fusariosis

**Table 5.1** Structures of fumonisins **249–264**

No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Trivial name
<b>253</b>	OH	OH	CH <sub>3</sub>	NHAc	Fumonisin A <sub>1</sub>
<b>254</b>	H	OH	CH <sub>3</sub>	NHAc	Fumonisin A <sub>2</sub>
<b>255</b>	OH	H	CH <sub>3</sub>	NHAc	Fumonisin A <sub>3</sub>
<b>256</b>	H	H	CH <sub>3</sub>	NHAc	Fumonisin A <sub>4</sub>
<b>249</b>	OH	OH	CH <sub>3</sub>	NH <sub>2</sub>	Fumonisin B <sub>1</sub>
<b>250</b>	H	OH	CH <sub>3</sub>	NH <sub>2</sub>	Fumonisin B <sub>2</sub>
<b>251</b>	OH	H	CH <sub>3</sub>	NH <sub>2</sub>	Fumonisin B <sub>3</sub>
<b>252</b>	H	H	CH <sub>3</sub>	NH <sub>2</sub>	Fumonisin B <sub>4</sub>
<b>257</b>	OH	OH	H	NH <sub>2</sub>	Fumonisin C <sub>1</sub>
<b>258</b>	H	OH	H	NH <sub>2</sub>	Fumonisin C <sub>2</sub>
<b>259</b>	OH	H	H	NH <sub>2</sub>	Fumonisin C <sub>3</sub>
<b>260</b>	H	H	H	NH <sub>2</sub>	Fumonisin C <sub>4</sub>
<b>261</b>	OH	OH	CH <sub>3</sub>	pyOH <sup>a</sup>	Fumonisin P <sub>1</sub>
<b>262</b>	H	OH	CH <sub>3</sub>	pyOH <sup>a</sup>	Fumonisin P <sub>2</sub>
<b>263</b>	OH	H	CH <sub>3</sub>	pyOH <sup>a</sup>	Fumonisin P <sub>3</sub>
<b>264</b>	H	H	CH <sub>3</sub>	pyOH <sup>a</sup>	Fumonisin P <sub>4</sub>

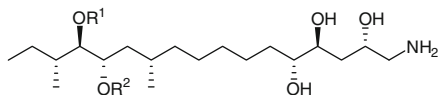
<sup>a</sup>pyOH = 3-hydroxypyridinium

The structures of the fumonisins were first characterized in 1988 by *Benzuidenhout et al.* (194). Fumonisin B<sub>1</sub> (**249**) is one of the major fumonisin representatives in culture and in naturally contaminated samples (195–197). Seven other fumonisins – B<sub>2</sub>, B<sub>3</sub>, B<sub>4</sub>, A<sub>1</sub>, A<sub>2</sub>, A<sub>3</sub>, and A<sub>4</sub> (**250–256**) have been isolated; the A-series are *N*-acetates of fumonisins B<sub>1</sub> – B<sub>4</sub> (**249–252**) and appear not to be toxic.

The analogues, fumonisins C<sub>1</sub> – C<sub>4</sub> (**257–260**), found in 1993 by *Branham and Plattner et al.* (198), exhibit the loss of the terminal methyl group, but constitute less than 5% of all fumonisins in terms of their natural abundance.

In 1996, *Musser et al.* reported the isolation and characterization of a new series of fumonisins, the P series (**261–264**), in which the amine of the B series is replaced with an *N*-linked 3-hydroxypyridinium moiety (199).

Another group of toxins called the “AAL-toxins” was found to have a structural relationship to the fumonisins, since they have only one tricarboxylic acid (TCA) moiety. AAL-toxin TA<sub>1</sub> (**265**) and TA<sub>2</sub> (**266**) (Fig. 5.2) are produced by the fungus *Alternaria alternata* f. sp. *lycopersici* and can lead to phytotoxic effects on several crops such as tomatoes and weeds (200). Due to the toxic effects of long alkyl-chain pyridinium compounds, this new class of fumonisins is of high interest (201).



AAL-toxin TA<sub>1</sub> **265** R<sup>1</sup> = H, R<sup>2</sup> = TCA

AAL-toxin TA<sub>2</sub> **266** R<sup>1</sup> = TCA, R<sup>2</sup> = H

Fig. 5.2 AAL-toxins

## 5.1 Biological Properties

Fumonisin B<sub>1</sub> (**249**) can amount up to 70% of all fumonisins in the food and is responsible for most cases of toxicosis caused by this class of mycotoxin. The toxic effects include the inhibition of sphingolipid biosynthesis, resulting in cell damage (202) and equine leukoencephalomalacia (ELEM) and hydrothorax in swine (203, 204). ELEM is a neurological disorder of horses and is accompanied by inflammation and edema formation of the CNS. Symptoms of this disease are blindness, paralysis of the facial muscles, locomotor abnormalities, hyperesthesia, and stupor, finally leading to death (205, 206). Furthermore, fumonisin B<sub>1</sub> (**249**) is a causal agent of nephrotoxicity, hepatotoxicity, and hepatocarcinogenicity, and an increased rate of apoptosis in the liver and kidney in laboratory animals is also reported (207). Hydrothorax in swine, a pulmonary edema, can occur from exposure to fumonisin B<sub>1</sub> concentrations of over 100 ppm, whereas liver lesions have been observed at a concentration of >23 ppm (208). The intake of fumonisin B<sub>1</sub> by turkeys leads to a reduction of body weight and a decrease of white blood cells (209). Broiler chickens react with a reduction in the prothrombin time, an increase in plasma fibrinogen and serum globulin levels, and a decrease in serum albumin (210).

In some regions where corn is essential for human nutrition, the occurrence of esophageal carcinoma has been reported, and this has been associated with fumonisin contamination (211). Concerning the AAL-toxins (see previous section), these were found to be associated with human esophageal cancer, equine leukoencephalomalacia, and liver diseases in humans (212). In the laboratory, these compounds have been shown to inhibit sphingolipid synthesis (213) and to cause apoptosis in tomato cells and green monkey kidney cells (214, 215).

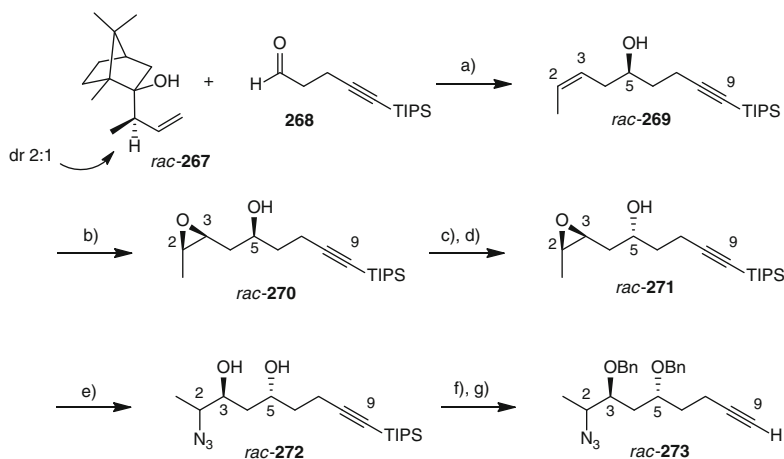
## 5.2 Total Syntheses

### 5.2.1 Total Synthesis of Fumonisin B<sub>1</sub>

Fumonisin B<sub>1</sub> (**249**), the primary mycotoxin produced by the fungus *Fusarium moniliforme*, was first synthesized by McDonald *et al.* in 2009 (216). This group

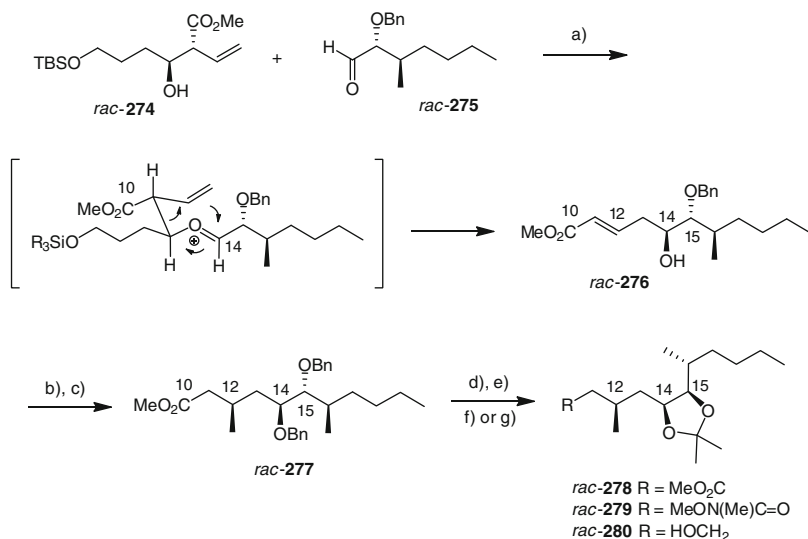
divided the synthesis into three parts, the C-1–C-9 sector, the C-10–C-20 core, and finally coupling and completion to afford fumonisin B<sub>1</sub>.

The construction of the C-1–C-9 sector (Scheme 5.1) started with a stereospecific allylic transfer using the camphor-derived reagent **267** to the alkynyl aldehyde **268** (217), furnishing the homoallylic alcohol **269** with chiral control at the C-5 alcohol group as well as (*Z*)-alkene selectivity (218). The following hydroxy group-directed epoxidation to compound **270** was catalyzed with vanadium acetylacetonate (219), and the inversion of the C-5 hydroxy group to the correct stereochemistry to give **271** was provided by a *Mitsunobu* reaction (142). With the help of the chelating reagent Ti(*O*-*i*-Pr)<sub>2</sub>(N<sub>3</sub>)<sub>2</sub>, the introduction of an azide was achieved (220), forming **272** as major regioisomer. After producing the terminal alkyne, the sector C-1–C-9 was completed by protecting the hydroxy groups as benzyl ethers, preparing the first part, **273**.



**Scheme 5.1** Synthesis of the C-1–C-9 sector. Reagents and conditions: a) cat. CSA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 5–6 h, 70%, >95:5 *er*, (*E*)-alkene only; b) cat. VO(acac)<sub>2</sub>, *t*-BuOOH, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 3 h, rt, 24 h, 73%, 10:1 *dr*; c) Ph<sub>3</sub>P, DIAD, HOAc, 0°C, 2 h, 87%; d) K<sub>2</sub>CO<sub>3</sub>, MeOH, rt, 3 h, 85%; e) Ti(*O*-*i*-Pr)<sub>2</sub>(N<sub>3</sub>)<sub>2</sub>, benzene, 80°C, 5 h, 47% of **272** + 17% of the C-3–azide regioisomer; f) Bu<sub>4</sub>NF, THF, rt, 6 h, 84%; g) NaH, BnBr, THF/DMF, 0°C to rt, 30 min, <85%

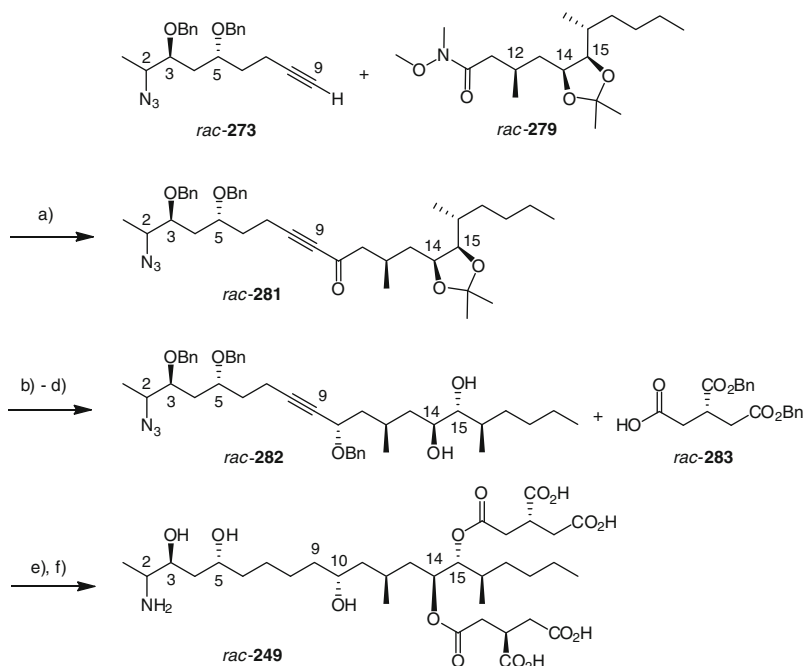
The synthesis of the second part started with a stereospecific allylic transfer reaction, which combined the deconjugative aldol product **274** with the chiral nonracemic aldehyde **275** using TMSOTf (221–223) (Scheme 5.2). In this manner, the core structure **276** could be afforded, producing the stereochemistry of the C-14 hydroxy group and (*E*)-alkene by a 2-oxonia-*Cope* rearrangement (224–227). The C-14 alcohol was then benzylated under neutral conditions (228) and ester **277** was formed by catalytic asymmetric conjugate addition of methylmagnesium bromide (229, 230). To deblock the 14,15-diol selectively at a late stage of the synthesis, the



**Scheme 5.2** Construction of the C-10-C-20 core *via* allylic transfer. Compound **275** was synthesized in five steps from 2-hepten-1-ol: (1) Ti(O-*i*-Pr)<sub>4</sub>, L-DIPT, *t*-BuOOH, 87%; (2) Me<sub>3</sub>Al, 73%; (3) PhCH(OMe)<sub>3</sub>, CSA, 74%, (4) DIBAL-H, 95%, (5) IBX, 83%. Reagents and conditions: a) TMSOTf, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 1 h, 61%, >95:5 *dr*, (*E*)-alkene only; b) 2-benzyloxy-*N*-methylpyridinium triflate, MgO, PhCF<sub>3</sub>, 85°C, 24 h, 66%; c) MeMgBr, cat. CuI, cat. (*R*)-tol-BINAP, MTBE, -20°C, 3 h, 69%; d) BCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -45°C, 2 h, 88%; e) Me<sub>2</sub>C(OMe)<sub>2</sub>, cat. TsOH, rt, 1 h, 80%; f) Me(Me-O)NH·HCl, *i*-PrMgCl, THF, -25°C, 40 min, 83%; g) LiAlH<sub>4</sub>, THF, 0°C, 15 min, 71%

benzyl ethers were replaced with acetone in compound **278** (231, 232), which was finally converted into the *Weinreb* amide **279** and the primary alcohol **280**.

For the final part (Scheme 5.3), the 20-carbon chain of fumonisins B<sub>1</sub> was coupled from the lithium acetylide derived from **273** and the *Weinreb* amide **279** (233). After enantioselective reduction of the alkynyl ketone **281** (234, 235), the C-10 stereochemistry was set, followed by benzyl ether formation and acid-catalyzed acetone removal, to provide diol **282** (236). Using tricarballic acid dibenzyl ester, the two hydroxy groups were esterified (237) and the hydrogenation of the azide, the alkyne, and the benzylic ethers led to the target product, fumonisins B<sub>1</sub> (**249**). The spectroscopic analysis matched with those of commercial fumonisins B<sub>1</sub> and further experiments on the synthetic material showed inhibitory activity on sphingolipid biosynthesis.

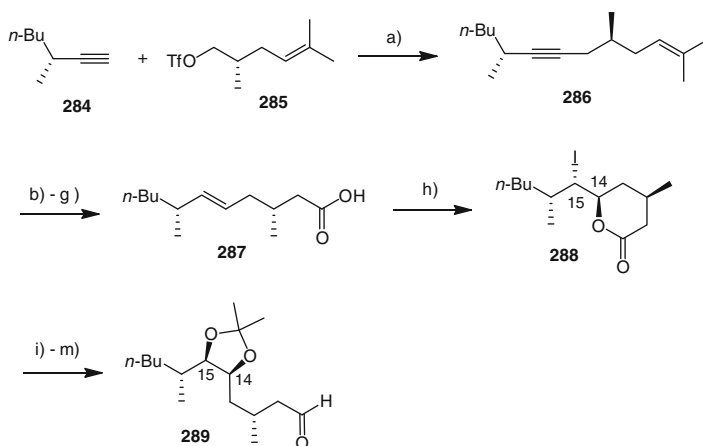


**Scheme 5.3** Synthesis of fumonisin B<sub>1</sub> (**249**). Reagents and conditions: a) **273**, *n*-BuLi, THF; then **279**,  $-78^{\circ}\text{C}$  to  $0^{\circ}\text{C}$ , 2 h, 65%; b) (*R*)-*CBS*, catecholborane,  $-78^{\circ}\text{C}$  to  $-65^{\circ}\text{C}$ , 5 h, 71–75%, 9:1 *dr*; c) NaH, BnBr, THF/DMF, rt, 40 min, 86%; d) Amberlite-120 H<sup>+</sup>, MeOH, rt, 24 h, 80%; e) **283** (was synthesized in three steps from but-3-enoyloxazolidinone: (1) LiHMDS, benzyl bromoacetate, 68%; (2) BnOLi, 80%; (3) NaIO<sub>4</sub>, cat. RuCl<sub>3</sub>–H<sub>2</sub>O, 91%) EDCl, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 20 h, 71%; f) H<sub>2</sub> Pd(OH)<sub>2</sub>/C, *t*-BuOH/THF/HCl, rt, 18 h, 45%

### 5.2.2 Enantioselective Total Synthesis of Fumonisin B<sub>2</sub>

In 1997, *Kishi et al.* reported an enantioselective total synthesis of fumonisin B<sub>2</sub> (**250**), which can also be used for the preparation of remote diastereomers of fumonisin B<sub>2</sub> and other analogues (**238**). Therefore, the molecule was divided into three fragments, wherein the first segment began with coupling of the chiral alkyne **284** (**239**, **240**) with triflate **285** (Scheme 5.4). Site-selective osmylation, Pb(OAc)<sub>4</sub> cleavage of the resultant diol, NaBH<sub>4</sub> reduction, Na/NH<sub>3</sub> reduction of the alkyne into a (*E*)-alkene, and *Swern* (**241**) and NaClO<sub>2</sub> (**242**) oxidation afforded the (*E*)-alkene acid **287**. The stereoselective introduction of the *vicinal* hydroxy groups at C-14 and C-15 was achieved by iodolactonization (**243**, **244**), followed by ring opening of the lactone with PhCH<sub>2</sub>ONa to provide the C-14–C-15 epoxide benzyl ester. Final deprotection of the resultant benzyl ester yielded the lactone alcohol with the desired stereochemistry at the C-14 and C-15 positions. The last steps for

the first fragment included a reduction of the alcohol to a triol, protection of the vicinal hydroxy groups as an acetonide, and *Swern* oxidation of the following primary alcohol provided compound **289** (245).

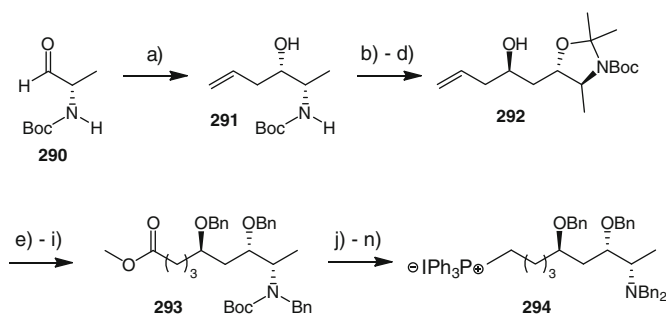


**Scheme 5.4** Synthesis of the left segment of fumonisins B<sub>2</sub> (**250**). Reagents and conditions: a) *n*-BuLi, THF,  $-78^{\circ}\text{C}$ , 30 min to rt, overnight, 70%; b)  $\text{K}_2\text{OsO}_4 \cdot \text{H}_2\text{O}$ , *t*-BuOH/ $\text{H}_2\text{O}$  (1/1), rt, 5 h, 94%; c)  $\text{Pb}(\text{OAc})_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^{\circ}\text{C}$ , 10 min; d)  $\text{NaBH}_4$ , EtOH,  $0^{\circ}\text{C}$  to rt, 1 h, 97% two steps; e)  $\text{Na}/\text{liq. NH}_3$ , *t*-BuOH, reflux, 4 h, 92%; f)  $(\text{COCl})_2$ , DMSO,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-50^{\circ}\text{C}$  to rt, 1 h; g)  $\text{NaClO}_2$ , *t*-BuOH, rt, 20 min, 92% over two steps; h)  $\text{I}_2$ ,  $\text{CH}_3\text{CN}$ ,  $-30^{\circ}\text{C}$ , overnight, 84%; i)  $\text{BnONa}$ , THF,  $-30^{\circ}\text{C}$ , 3 h; j)  $\text{H}_2$ , Pd/C, *p*-TsOH (cat.),  $\text{Et}_2\text{O}$ , rt, 2 h, 87% over two steps; k)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ,  $0^{\circ}\text{C}$ , 4 h, 90%; l) *p*-TsOH (cat.),  $(\text{CH}_3)_2\text{C}=\text{O}$ , rt, 20 min; m)  $(\text{COCl})_2$ , DMSO,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^{\circ}\text{C}$  to rt, 1 h, 79% over five steps

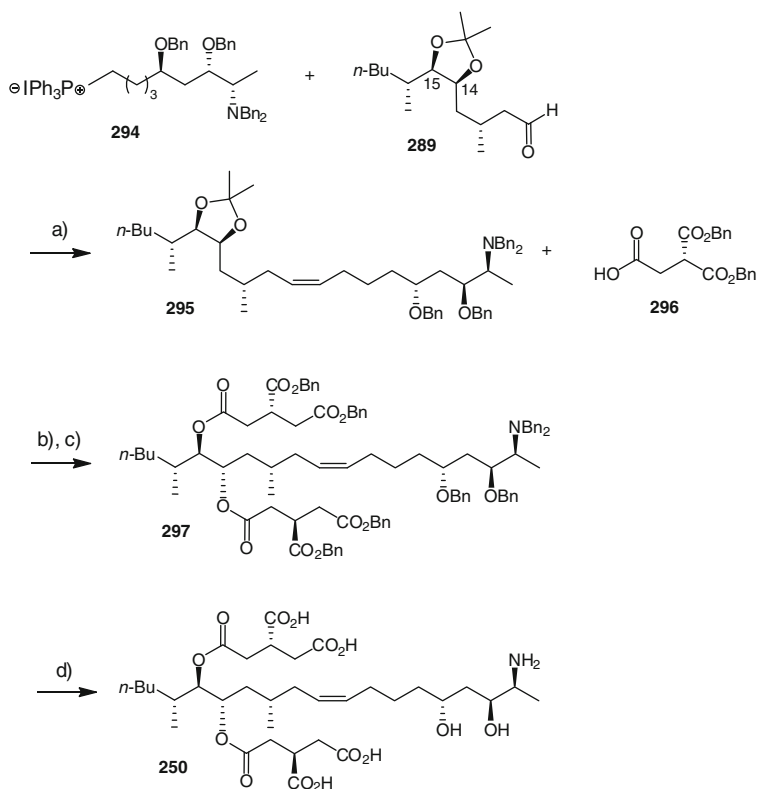
The preparation of the second part of fumonisins B<sub>2</sub> (**250**) is shown in Scheme 5.5. Allylation of  $\alpha$ -amino aldehyde **290** (246) with *Brown's* chiral (–)-*B*-allyldiisopinocampheylborane (**247**) afforded the *syn*-amino alcohol **291**. After protection of **291** as an acetonide, ozonolysis of the alkene with dimethyl sulfide work-up, and reduction of the resultant aldehyde with *B*-allyldiisopinocampheylborane provided the *anti*-alcohol **292**. Alcohol **292** was converted to ester **293** via acetonide deprotection, benzyl group protection, ozonolysis of the resultant alkene to an aldehyde, a two-carbon chain elongation under *Horner-Wadsworth-Emmons* conditions, and hydrogenation using the *Lindlar* catalyst. Removal of the Boc group, protection of the amine, and reduction of the methyl ester to an alcohol, followed by transformation into an alkyl iodide and treatment with triphenyl phosphane yielded the phosphonium salt **294**.

A *Wittig* reaction of the ylide **294** with the aldehyde **289** formed the backbone **295**, which was then treated with trifluoroacetic acid to remove the acetonide, followed by acylation of the diol with the (–)-TCA segment **296** (248). Hydrogenation of the alkene and hydrogenolysis of all benzyl protecting groups with  $\text{H}_2$  (1 atm) and *Pearlman's* catalyst afforded fumonisins B<sub>2</sub> (**250**) (Scheme 5.6).





**Scheme 5.5** Synthesis of the right-half sector of fumonisin B<sub>2</sub> (**250**). Reagents and conditions: a) (–)-Ipc<sub>2</sub>B-allyl, toluene, –78°C to rt, 1 h, 80%, 94% *de*; b) *p*-TsOH, (CH<sub>3</sub>)<sub>2</sub>C=O, rt, 2 h, 93%; c) O<sub>3</sub>, Me<sub>2</sub>S, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1/1), –78°C to rt, 2 h; d) (+)-Ipc<sub>2</sub>B-allyl, Et<sub>2</sub>O, –78°C, 6 h, 65%, *dr* 10:1; e) *p*-TsOH (*cat.*), MeOH, rt, 1.5 h, 91%; f) NaH, BnBr, TBAI, THF, rt, overnight, 88%; g) O<sub>3</sub>, Me<sub>2</sub>S, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1/1), –78°C to rt, 2 h; h) (MeO)<sub>2</sub>POCH<sub>2</sub>COOMe, NaH, THF, 0°C to rt, 30 min, 91%, 70% over five steps; i) H<sub>2</sub>/Lindlar *cat.*, rt, 2 h; j) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to rt, 30 min; k) BnBr, K<sub>2</sub>CO<sub>3</sub>, EtOH/H<sub>2</sub>O (1/1), rt, 4 h, 90%; l) DIBAL-H, Et<sub>2</sub>O, –78°C to 0°C, 1.5 h, 95%; m) I<sub>2</sub>, PPh<sub>3</sub>, imidazole, benzene, rt, 1.5 h, 88%; n) PPh<sub>3</sub>, CH<sub>3</sub>CN, reflux, 16 h, 90%, 75% over five steps

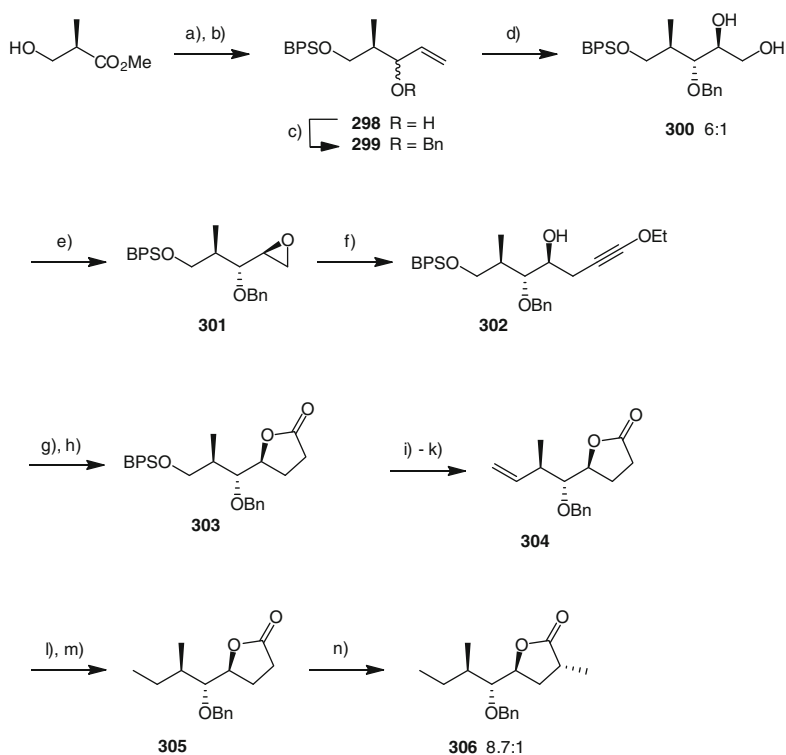


**Scheme 5.6** Completion of fumonisin B<sub>2</sub> (**250**). Reagents and conditions: a) *n*-BuLi, THF, 81%; b) TFA, H<sub>2</sub>O, THF, 95%; c) TCA (1) O<sub>3</sub>, Jones reagent, (CH<sub>3</sub>)<sub>2</sub>C=O; (2) DMAP, BnOH, EDCl, CH<sub>2</sub>Cl<sub>2</sub>, 29% over two steps; (3) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 29% over three steps, DMAP, EDCl, CH<sub>2</sub>Cl<sub>2</sub>, 90% over two steps; d) H<sub>2</sub>, Pd(OH)<sub>2</sub> on carbon, HCl, *t*-BuOH/THF (4/1), 60%

### 5.2.3 Total Synthesis of AAL-toxin TA<sub>1</sub>

Since 1988, it has been known that AAL-toxin TA<sub>1</sub> (**265**) is a tumor promoter (*190*), *Oikawa et al.* generated a synthesis route to lead to this target compound and to study the structure-activity relationships of these toxins (*249, 250*).

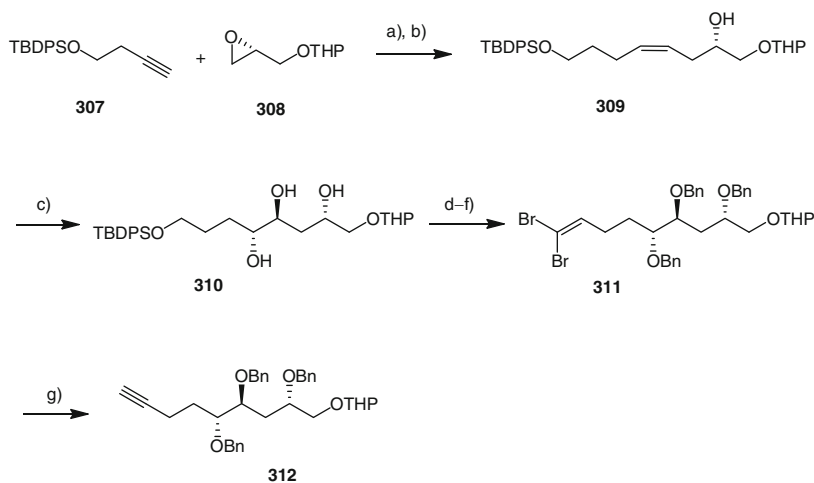
The synthesis of AAL-toxin TA<sub>1</sub> (**265**) is divided into three segments, with the first part beginning by silylation of 3-hydroxy-2-methylproprionate and treatment with DIBAL-H and vinyl magnesium bromide in a one-pot reaction, which gave the alcohol **298** (Scheme 5.7). The separation of diastereomers was carried out by benzylation to compound **299**, and oxidation with OsO<sub>4</sub> resulted in diol **300** as a 6:1 separable mixture. Further reactions comprised a *Sharpless* oxidation (*251*), an acetylide addition, and transformation into lactone **303**. Deprotection of the silyl group followed by a *Swern* oxidation and a *Wittig* reaction led to olefin **304**. The last



**Scheme 5.7** Construction of the left segment **306** of AAL-toxin TA<sub>1</sub> (**265**). Reagents and conditions: a) BPSCl, Im, DMF, quant; b) DIBAL-H, Et<sub>2</sub>O, CH<sub>2</sub>=CHMgBr, 77%; c) NaH, BnBr, *n*-Bu<sub>4</sub>Ni, THF, 91%; d) OsO<sub>4</sub>, NMO, acetone/H<sub>2</sub>O (8/1), 91%; e) MeC(OMe)<sub>3</sub>, cat. PPTS, CH<sub>2</sub>Cl<sub>2</sub>; AcBr, CH<sub>2</sub>Cl<sub>2</sub>; K<sub>2</sub>CO<sub>3</sub>, MeOH, 77%; f) ethyl ethynyl ether, *n*-BuLi, BF<sub>3</sub>·Et<sub>2</sub>O, THF; g) HgCl<sub>2</sub>, EtOH; h) K<sub>2</sub>CO<sub>3</sub>, MeOH, 3 M HCl, 59% over three steps; i) TBAF, THF, 80%; j) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; k) Ph<sub>3</sub>PCH<sub>3</sub>Br, *n*-BuLi, THF, 19% over two steps; l) H<sub>2</sub>, Pd-C, EtOAc; m) CCl<sub>3</sub>C(=NH)OBn, TfOH, CH<sub>2</sub>Cl<sub>2</sub>/cyclohexane (1/1), 57% over two steps; n) LiHMDS, CH<sub>3</sub>I, THF, 68%

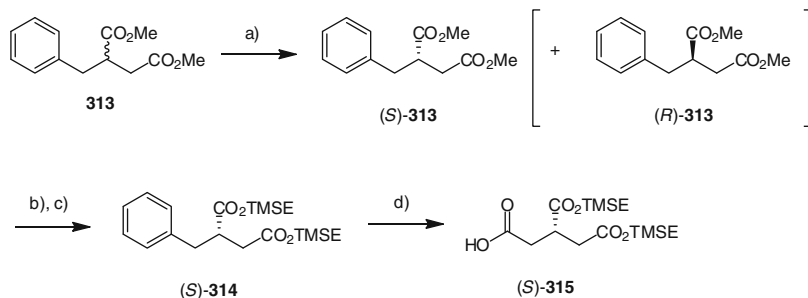
steps included hydrogenation, acidic debenzylation, and  $\alpha$ -methylation to synthesize the left segment, **306**.

The synthesis of the right segment and TCA segment was published in a preceding paper in 1996 (249). The condensation of lithium acetylide derived from 5-pentynol **307** with *n*-BuLi and epoxide **308** resulted in a homopropargylic alcohol, which was hydrogenated to the (*Z*)-olefin **309**. An asymmetric dihydroxylation afforded triol **310**, whereas the hydroxy groups were protected *via* benzylation. The right building block **312** was completed by subsequent transformation with a *Corey-Fuchs* reaction (Scheme 5.8).



**Scheme 5.8** Synthesis of right segment **312**. Reagents and conditions: a) *n*-BuLi,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , THF, 75%; b)  $\text{H}_2$ , Pd/BaSO<sub>4</sub>, quinolone, 98%; c) cat. OsO<sub>4</sub>, DHQD-IND, K<sub>3</sub>Fe(CN)<sub>6</sub>, K<sub>2</sub>CO<sub>3</sub>, *t*-BuOH/H<sub>2</sub>O, 85%, *dr* = 4:1; d) NaH, BnBr, TBAL, THF, 81%; e) TBAF, THF, 89%; f) CBr<sub>4</sub>, PPh<sub>3</sub>, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>, 75%; g) *n*-BuLi,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , THF, 75%

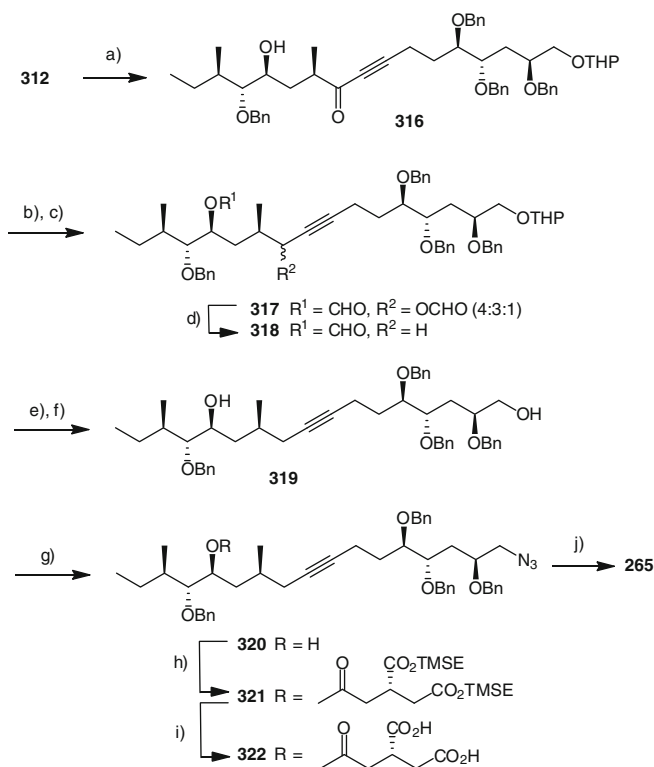
Scheme 5.9 shows the preparation of the tricarballic acid (TCA) segment **315**. Racemic methyl-2-benzylsuccinate (**313**) was separated using lipase-catalyzed



**Scheme 5.9** Formation of the TCA-segment. Reagents and conditions: a) lipase (PPL),  $\text{KH}_2\text{PO}_4$ -buffer (pH 7.2); b) 1 M NaOH, MeOH; c) TMSCH<sub>2</sub>CH<sub>2</sub>OH, EDC, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 79% over two steps; d) RuCl<sub>2</sub>, NaIO<sub>4</sub>, CCl<sub>4</sub>/CH<sub>3</sub>CN/H<sub>2</sub>O (2/2/3), 59%

hydrolysis. Hydrolysis and TMSE protection (TMSE = trimethylsilylethyl) of the (*S*)-enantiomer, followed by oxidation of the phenyl ring afforded acid **315**.

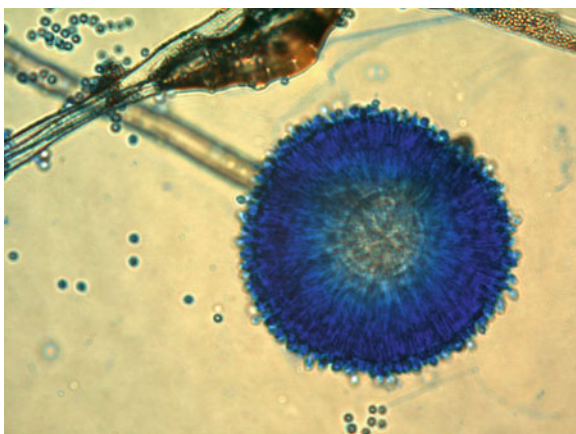
The last part of the total synthesis comprised a condensation between lactone **306** with acetylene **312**, then deoxygenation of the C-10 carbonyl by a *Luche* reduction (252) and formylation followed by palladium-catalyzed deoxygenation (253) to give product **318**. Orthogonal deprotection of the acyl and THP groups afforded diol **319** and transformation into azide **320** was conducted under *Mitsunobu* conditions (142). After acylation with the tricarballic acid moiety **315** using the *Yamaguchi* method (254), deprotection of the TMSE groups, reduction of azide and triple bond and hydrogenolysis of all benzyl groups finally gave AAL-toxin TA<sub>1</sub> (**265**) (Scheme 5.10).



**Scheme 5.10** Completion of the synthesis of AAL-toxin TA<sub>1</sub> (**265**). Reagents and conditions: a) *n*-BuLi, **306**, Et<sub>2</sub>O, 72%; b) NaBH<sub>4</sub>, CeCl<sub>3</sub>, MeOH, 85%; c) Ac<sub>2</sub>O, HCO<sub>2</sub>H, Py, 97%; d) Pd(OAc)<sub>2</sub>, *n*-Bu<sub>3</sub>P, THF, 84%; e) LiAlH<sub>4</sub>, THF; f) PPTS, EtOH, 89% over two steps; g) HN<sub>3</sub>, Ph<sub>3</sub>P, DEAD, toluene, 69%; h) 2,4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>COCl, (*S*)-**315**, Et<sub>3</sub>N, toluene; then **320**, DMAP, 71%; i) TBAF, THF; j) H<sub>2</sub>, Pd/C, *t*-BuOH/THF/1 M HCl (3/1/0.04), 76% over two steps

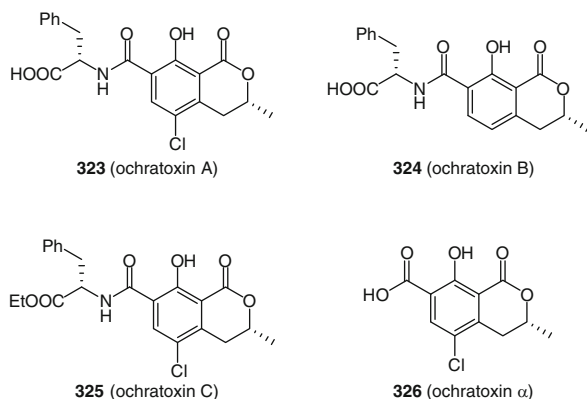
## 6 Ochratoxins

The ochratoxins were isolated and characterized from *Aspergillus ochraceus* (Fig. 6.1 (255)) in 1965 (256, 257).



**Fig. 6.1** *Aspergillus ochraceus* under a light microscope (400-fold magnification)

These compounds were found to be important mycotoxin constituents of *Aspergillus* species shortly after the discovery of the aflatoxins (see Chap. 2.). The ochratoxins are isocoumarin derivatives coupled with  $\beta$ -phenylalanine. The major representatives of this class of pentaketides are shown in Fig. 6.2. Ochratoxin B (324) is the dechloro analog of ochratoxin A (323), which is the most important member of this group with respect to its toxicity. The corresponding methyl and ethyl esters of ochratoxin A (323) and B (324) were found also in *Aspergillus* species and the ethyl ester of ochratoxin A (323) has been named ochratoxin C (325). Ochratoxin  $\alpha$  (326) is a free carboxylic acid that represents the dihydroisocoumarin nucleus of ochratoxin A (323).



**Fig. 6.2** Structures of ochratoxins A–C (**323–325**) and ochratoxin  $\alpha$  (**326**)

## 6.1 Biological Properties

Ochratoxin A (**323**) is by far the most commonly occurring member of the class of ochratoxins and therefore is the best-characterized and most thoroughly documented (258). It is produced not only by *Aspergillus ochraceus* and other *Aspergillus* species but has been found also in *Penicillium verrucosum*, and occurs with other mycotoxins associated with improperly stored food products (259) (Fig. 6.3 (260)).

Compound **323** is the most toxic of the ochratoxins and shows neurotoxic, nephrotoxic, teratogenic, hepatotoxic, and immunotoxic properties. Furthermore, in 1993 it was classified as a possible carcinogen to humans by the International Agency for Research on Cancer (261).



**Fig. 6.3** *Penicillium* ear rot caused by ochratoxin-producing fungi. (Courtesy of the University of Illinois Extension)

Ochratoxins B, C, and  $\alpha$  (**324–326**) show similar pharmacological profiles to ochratoxin A (**325**), but at about a thousand-fold higher dose level in each case. The toxicity of the ochratoxins includes effects on DNA, RNA, and protein synthesis. Also evident are inhibition of enzymes involved in various biosynthesis steps, enhancement of lipid peroxidation, which leads to hepatotoxic effects, and effects on mitochondrial ATP production (259). These molecules are easily absorbed through the gastrointestinal tract and possess high binding affinities to plasma proteins (262). These properties lead to both the good bioavailability and prolonged half-lives of the toxins.

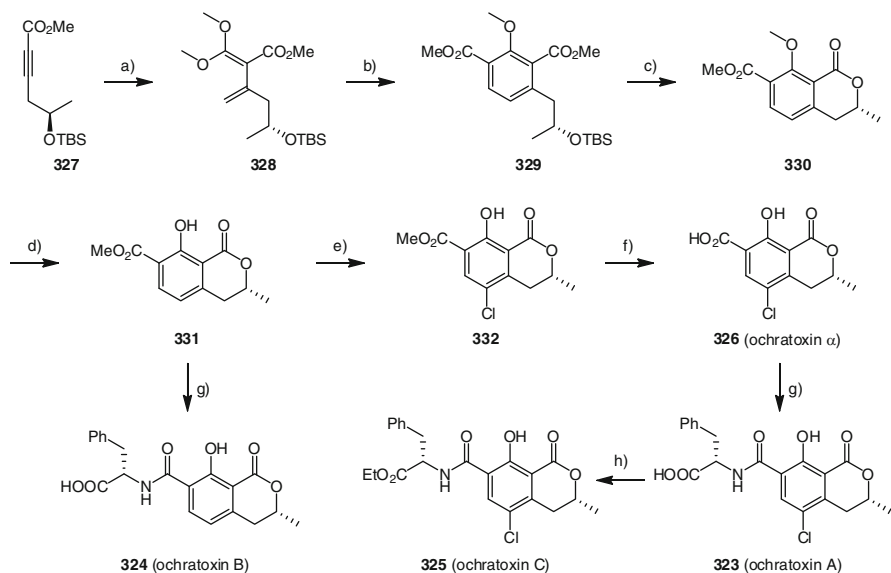
## 6.2 Total Syntheses

All ochratoxins and their derivatives have been obtained by total syntheses. The first so-produced were ochratoxins A (**323**) and B (**324**) by *Steyn et al.* in 1967 (263), two years after they were first reported as a class of mycotoxins. This group was able to synthesize racemic ochratoxin  $\alpha$  (**326**) in six steps. However, for the stereoselective synthesis of ochratoxins A (**323**) and B (**324**), (*R*)-ochratoxin  $\alpha$  (**326**) obtained through hydrolysis of the natural product was used as the starting material.

### 6.2.1 *Enantioselective Total Synthesis of (R)-Ochratoxin $\alpha$ and Ochratoxins A, B, and C*

It took another 35 years until the first (and still the only known) enantioselective total synthesis of (*R*)-ochratoxin  $\alpha$  (**326**), and therefore of ochratoxins A and B, was published by *Gill et al.* in 2002 (264, 265). Scheme 6.1 shows six steps of the nine-step synthesis, which was achieved with 10% overall yield. The first three steps of the procedure are not shown and comprise the preparation of **327** from (*R*)-2-methyloxirane according to ref. (266). Ketene dimethyl acetal and acetylenic ester **327** react in an intermolecular cycloaddition to give **328**. This diene undergoes a *Diels-Alder* reaction with methyl propiolate to yield **329**. Lactonization ( $\rightarrow$  **330**), demethylation ( $\rightarrow$  **331**), chlorination ( $\rightarrow$  **332**), and methyl ester cleavage finally furnished enantiomerically pure ochratoxin  $\alpha$  (**326**) (267).

Ochratoxin  $\alpha$  (**326**) or the dechlorinated derivative **331** can be converted easily to ochratoxin A (**323**) and C (**325**) or ochratoxin B (**324**), respectively. *Steyn et al.* formulated this approach in 1967. They converted the free acid to the acid chloride, converted this into the acid azide and coupled the product with L-phenylalanine



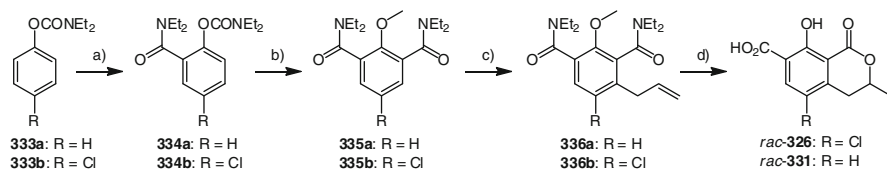
**Scheme 6.1** Total synthesis of (*R*)-ochratoxin  $\alpha$  (**326**) as well as ochratoxins A–C (**323**–**325**). Reagents and conditions: a) ketene dimethyl acetal, sealed tube, 165°C, 23 h; b) methyl propiolate, sealed tube, 145°C, 22 h, 69% over two steps; c) *p*-TsOH,  $\text{CH}_2\text{Cl}_2$ , rt, 72 h, 82%; d)  $\text{BCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ , 0°C, 10 min, 92%; e)  $\text{SO}_2\text{Cl}_2$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 48 h; f) MeOH,  $\text{LiOH}\cdot\text{H}_2\text{O}$ , reflux, 5 h, 68% over two steps; g) L-phenylalanine *t*-butyl ester, EEDQ, THF, rt, 15 h; h) EtOH

(263). A few years later, *Roberts* and *Woollven* published a more convenient method using EEDQ (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroguinoline) as coupling reagent and the *t*-butyl ester of L-phenylalanine as condensation partner for **326** (268). Later, *Kraus et al.* used this methodology for the synthesis of ochratoxin B (**324**). Since this group also developed a more efficient synthesis route toward racemic ochratoxin  $\alpha$  (**326**), they disclosed the short and industrial-scale syntheses of ochratoxins A–C in only a few steps and good yields in a patent (267).

### 6.2.2 Total Syntheses of Racemic Ochratoxins $\alpha$ and Ochratoxins A, B, and C

In 1985, *Snieckus et al.* reported another method for the preparation of racemic ochratoxin  $\alpha$  (**326**) and its dechloro analog **331** in only four steps (269). They used the readily accessible *O*-aryl carbamates **333a** and **333b** (270) as starting materials for their synthesis (Scheme 6.2). The *O*-carbamate benzamides **334a** and **334b** were obtained by metalation of the carbamates followed by quenching with diethylcarbamoyl chloride. The next step consisted of a 1,3-carbamoyl

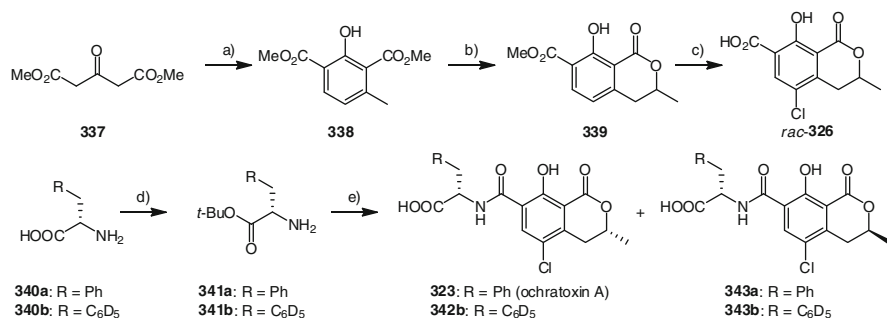




**Scheme 6.2** Total synthesis of ochratoxin  $\alpha$  (**326**, precursor to ochratoxin A) and **331**, precursor to ochratoxin B. Reagents and conditions: a) *sec*-BuLi, TMEDA, THF,  $-78^{\circ}\text{C}$ , 1 h; then diethylcarbamoyl chloride, rt, overnight, 89% (**334a**), 77% (**334b**); b) *sec*-BuLi, TMEDA, THF,  $-78^{\circ}\text{C}$  to rt, overnight, 59% (**335a**), 42% (**335b**); c) *sec*-BuLi, TMEDA,  $-78^{\circ}\text{C}$ , 30 min; then  $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ ,  $-78^{\circ}\text{C}$ , 45 min; then allyl bromide,  $-78^{\circ}\text{C}$  to rt, overnight, 55% (**336a**), 38% (**336b**); d) HCl (aq.), reflux, 6 h, 50% (*rac*-**326**), 49% (*rac*-**331**)

rearrangement to give derivatives **335a** and **335b**. Further metalation, transmetalation, and treatment with allyl bromide yielded **336a** and **336b**. A one-pot lactonization, amide hydrolysis, and demethylation finally led to the racemic isocoumarins **326** and **331** in 6% and 14% overall yields.

In 2009, *Gabriele et al.* published a new and expedient synthesis of racemic ochratoxin  $\alpha$  (**326**) (271). After coupling with protected L-phenylalanine, they were able to separate the resulting diastereoisomers by preparative TLC. Thus, they obtained enantiomerically pure (*R*)-ochratoxin A (**323**) and its (*3S*)-diastereomer **343a** in six steps and 9% and 6% overall yields, from commercially available starting materials (Scheme 6.3). Furthermore, they were able to synthesize *d*<sub>5</sub>-ochratoxin A (**342b**) and its (*3S*)-diastereomer **343b**. The former can be used as an internal standard in a stable isotope dilution assay that is an important quantification tool for micro components in food such as the ochratoxins (272).

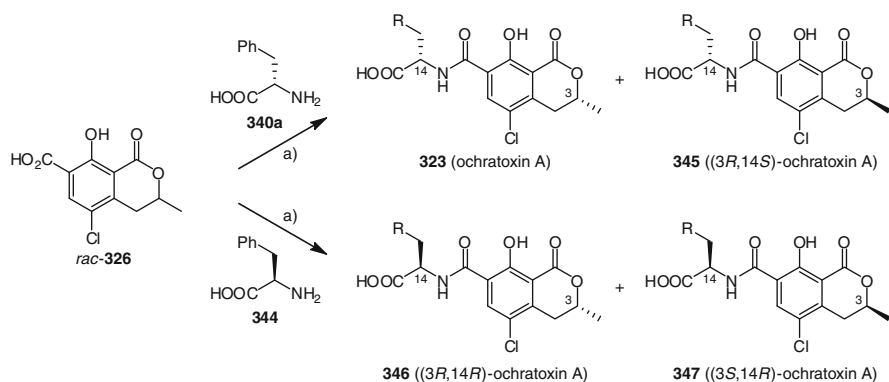


**Scheme 6.3** Total synthesis of ochratoxin A, *d*<sub>5</sub>-ochratoxin A and their (*3S*)-diastereomers. Reagents and conditions: a) NaH, but-2-ynal,  $10^{\circ}\text{C}$ , 6 h, 48%; b) LDA, MeCHO,  $-78^{\circ}\text{C}$ , 15 min; then  $0^{\circ}\text{C}$ , 15 min; 70%; c)  $\text{SO}_2\text{Cl}_2$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 24 h; then LiOH, MeOH, reflux, 5 h, 69%; d)  $\text{HClO}_4$ , *t*-BuOAc, rt, 12 h, 91% (**341a**), 90% (**341b**); e) *rac*-**326**, EDC·HCl, HOBT,  $\text{CHCl}_3$ , rt, 20 h; then TFA,  $\text{CH}_2\text{Cl}_2$ , rt, 5 h; then preparative TLC, 46% (**323**), 34% (**343a**), 47% (**342b**), 36% (**343b**)

The synthesis starts with the reaction of dimethyl-3-oxopentanedioate (**337**) and crude but-2-ynal (available by oxidation of but-2-ynol with  $\text{MnO}_2$  (**273**)) to give the substituted benzene **338** in moderate yield. Deprotonation of its methyl group, condensation with acetaldehyde and acidic work-up furnished lactone **339**. Through chlorination and ester hydrolysis, racemic ochratoxin  $\alpha$  (**326**) was obtained in 23% overall yield. L-Phenylalanine (**340a**) and L- $d_5$ -phenylalanine (**340a**) were protected and coupled with **326** in the presence of EDC (*N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide and HOBT (*N*-hydroxybenzotriazole)) to give ochratoxin A (**323**) and  $d_5$ -ochratoxin A (**342b**), as well as their (3*S*)-diastereomers. To date, this route to ochratoxin  $\alpha$  is the most efficient one with 23% overall yield in three steps, when compared to the methods of *Kraus* (17% over four steps), *Snieckus* (6% over five steps), and *Gill* (10% over nine steps).

### 6.2.3 Total Syntheses of All Stereoisomers of Ochratoxin A

The latest total synthesis of ochratoxins was published in 2010 by *Humpf et al.* and aimed at the preparation of all stereoisomers of ochratoxin A, *i.e.* the natural compound **323** (3*S*,14*S*), **345** (3*R*,14*S*), **346** (3*R*,14*R*), as well as **347** (3*S*,14*R*) (**274**, Scheme 6.4).



**Scheme 6.4** Total synthesis of all ochratoxin A stereoisomers. Reagents and conditions: a) DIPEA, HATU, DMF, rt, 2 h, 88%; then NaOH, rt, 12 h, 62%

For the synthesis of racemic ochratoxin  $\alpha$  (**326**), the authors used the method previously described by *Gabriele et al.* (**271**). Thus, L-**340a** and D-phenylalanine (**344**) were coupled with HATU (*N,N,N',N'*-tetramethyl-*O*-(7-azabenzotriazol-1-yl) uranium hexafluorophosphate)-activated **326**. Accordingly, the HPLC-separable diastereomers **323** and **345** as well as **346** and **347** could be synthesized in 53% yield from ochratoxin  $\alpha$  (**326**). Since (3*R*,14*R*)-ochratoxin A (**346**) was recently

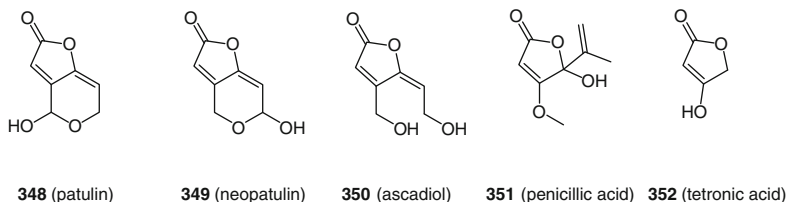
discovered to be a thermal degradation product of ochratoxin A (**323**) in food (275), the authors investigated the cytotoxic and apoptotic effects of all four compounds. They found that the stereochemistry of the ochratoxins has a large effect on their toxicity. Only **323** and **345**, with the (*S*)-configuration of the phenylalanine moiety, showed any cytotoxic potential in an assay using a cultured human liver cell line.

# 7 Patulin

## 7.1 General

Patulin (**348**) is a mycotoxin of notable importance due to its extremely widespread and frequent occurrence in foodstuffs intended for human consumption, particularly fruits and fruit products. Patulin (**348**) displays mutagenic properties (276), and, due to its ability to interfere with DNA and RNA synthesis (277–279), it has been suggested as a likely carcinogen. Despite the observation that **348** does not seem to be a particularly potent toxin, its common occurrence, and genotoxic as well as possible carcinogenic nature (280), has led the World Health Organization and European Union to set maximum recommended concentration levels in foodstuffs for human consumption, as, for example, 50  $\mu\text{g}/\text{dm}^3$  in apple juice (281). Patulin (**348**) has been found to occur in an extensive variety of foods: bananas, pineapples, grapes, peaches (282), pears (283), apples and apple juice (284), and the jams of various berries during storage (285).

The microbial culprit organisms found to produce this environmental toxin are mostly *Penicillium*, *Aspergillus*, and *Byssochlamys* species (286–288) including *P. patulum* (289), *P. urticae* (290), *P. claviforme* (291), and *P. expansum* (292). While patulin (**348**) possesses antibiotic properties (293), it has not been investigated fully in this respect due to its toxic effects against mammals and plants (294). The chemical identity of patulin (**348**) was proposed initially incorrectly in 1948 (295), with the structure corrected by Woodward and Singh the following year to the structure shown (**348**, Fig. 7.1).



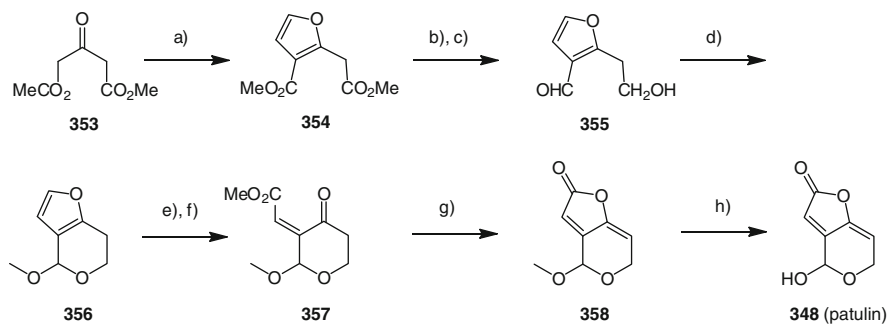
**Fig. 7.1** Patulin (**348**) and related ylidenebutenolides

Patulin (**348**) is a quite small natural product, but it nonetheless has a diverse complement of potent chemical functionality: cyclic hemiacetal (the natural product is racemic) and allylic acetal moieties are present, and the molecule potentially can react with the nucleophilic residues of biomolecules as either a 1,4- or 1,6-*Michael* acceptor (see Fig. 7.1). Neopatulin (**349**) (296), ascadiol (**350**), and penicillic acid (**351**) are structurally related ylidenebutenolides, as are also metabolites of tetronic acid (**352**).

## 7.2 Total Syntheses of Patulin

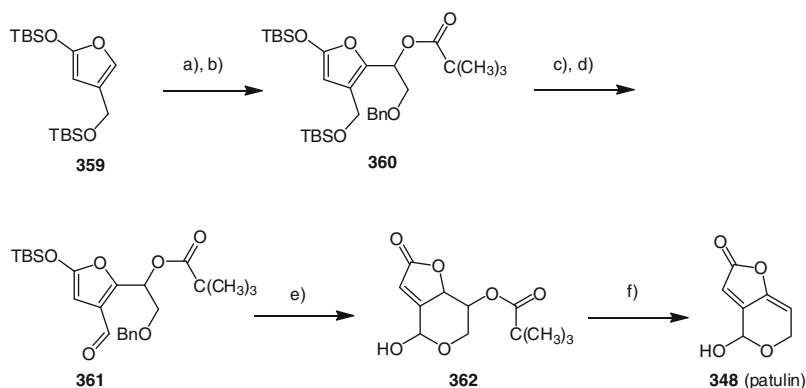
The initial synthesis of *Woodward* and *Singh* was reported for patulin (**348**) in 1950 (297). However, the yield was low and the synthesis impractical. Two almost identical syntheses were reported independently by the groups of *Stapleton* in 1988 (298, 299) and *Riguera* in 1989 (300). Both commenced from L-arabinose, a readily available starting material from the chiral pool; notwithstanding this, deprotection of a late-stage acetal intermediate to deliver the natural product was followed, perhaps unsurprisingly, by rapid racemization at the hemiacetal center. For details of these earlier syntheses, the reader is directed to our recent review (10) and the primary literature.

More recently, *Tada* and co-workers reported the total synthesis of patulin (**348**) in 1994 (Scheme 7.1) (301). Starting with the condensation of acetonedicarboxylic acid dimethyl ester (**353**) and chloroacetaldehyde to form an appropriately 2,3-disubstituted furan **354**, this was further reduced and selectively oxidized at the aromatic carbinol to deliver 3-furaldehyde **355**. *Dean-Stark* condensation of this species in the presence of methanol gave the methyloxy furanopyran **356**. Oxidative ring-opening to a carboxylate intermediate and subsequent methylation with diazomethane provided ester **357**, which was lactonized and finally demethylated to deliver the natural product **348** in 7% yield over a total of eight consecutive steps.



**Scheme 7.1** Tada *et al.* synthesis of patulin (**348**). Reagents and conditions: a)  $\text{ClCH}_2\text{CHO}$ , pyridine,  $50^\circ\text{C}$ , 24 h, 70%; b)  $\text{LiAlH}_4$ , 80%; c)  $\text{MnO}_2$ , 56%; d) PPTS, MeOH/benzene (1/2), reflux, 1.5 h, *Dean-Stark* trap, 91%; e) *m*-CPBA,  $\text{CH}_2\text{Cl}_2$ , 2 h; f)  $\text{CH}_2\text{N}_2$ , 67% (two steps); g)  $\text{Ca}(\text{OH})_2$ , benzene, reflux, 0.5 h, *Dean-Stark* trap, 41%; h) TFA/ $\text{H}_2\text{O}$  (9:1),  $50^\circ\text{C}$ , 1 h, 78%

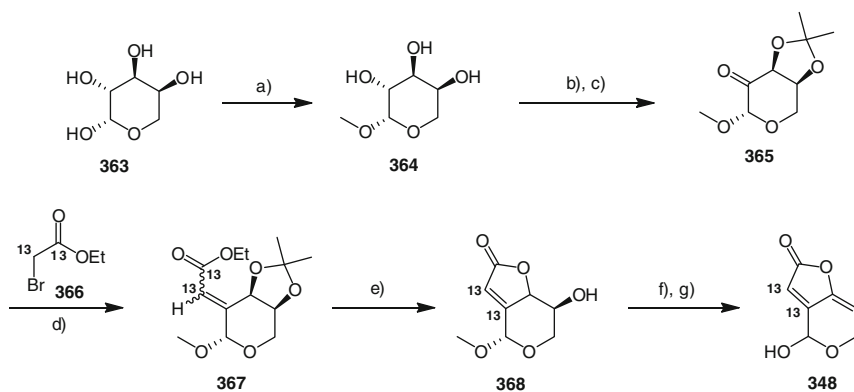
More efficient in terms of the number of steps (six) and overall yield (41%) was a later synthesis from *Boukouvalas* and co-workers (Scheme 7.2) (**302**). Bis-silyl-protected 3-hydroxymethyl 2,4-dihydrofuran-2-one (**359**) was selectively deprotected/condensed with benzyloxycetaldehyde to give the alcohol, which was protected as a pivalate ester and subjected to selective desilylation then TEMPO-mediated oxidation. The resulting aldehyde **361** was then cyclized with a *Lewis* acid. Elimination of pivalic acid from ester **362** gave mainly the desired ylidenebutenolide regioisomer and the natural product (**348**).



**Scheme 7.2** Expedient patulin (**348**) synthesis. Reagents and conditions: a)  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 10 h, 94%; b) PivCl, DMAP, pyridine,  $0^\circ\text{C}$  to rt, 24 h, 91%; c) 6 *N* HCl (aq.), MeOH, rt, 4 h, 90%; d) TEMPO, KBr, NaOCl,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 97%; e)  $\text{BCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ; then  $\text{Et}_3\text{N}$ /MeOH, 79%; f) DBU,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to rt, 0.25 h

*Rychlik* and *Schieberle* reported a synthesis of  $^{13}\text{C}$ -labeled patulin (**348**) in 1998 (**303**). The synthesis was from *L*-arabinose (**363**), as described by *Stapleton* and co-workers (**298**), with an initial methyl acetal formation, protection of a 1,2-diol, then

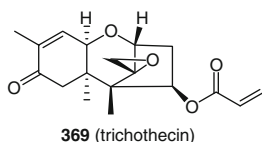
oxidation of the remaining hydroxy group to give **365**. The authors then incorporated ethyl bromo[ $^{13}\text{C}_2$ ]acetate (**366**) in a subsequent *Wadsworth-Emmons* olefination to form **367**, and completed the sequence to patulin *via* lactonization to **368**, activation to a methanesulfonate, elimination, and formation of the hemiacetal (Scheme 7.3) (298). The resulting  $^{13}\text{C}$ -labeled compound was used as an internal standard in stable isotope dilution assays, which may be of use in future studies of patulin (**348**) metabolism *in vivo*.



**Scheme 7.3** Synthesis of  $^{13}\text{C}$ -labeled patulin. Reagents and conditions: a) HCl, MeOH, 64%; b) dimethoxypropane,  $\text{H}_2\text{SO}_4$ , acetone, rt, 24 h, quant; c) PCC,  $\text{CH}_2\text{Cl}_2$ , rt, 23%; d) ethyl bromo [ $^{13}\text{C}_2$ ] acetate,  $\text{CH}_2\text{Cl}_2$ , rt, 96 h, 79%; e) HCl, MeOH, reflux, 37%; f)  $\text{MeSO}_3\text{Cl}$ , pyridine,  $0^\circ\text{C}$  to rt, 2 h; g) TFA,  $\text{H}_2\text{O}$ ,  $50\text{--}70^\circ\text{C}$ , 2 h, 50% (two steps)

## 8 Trichothecenes

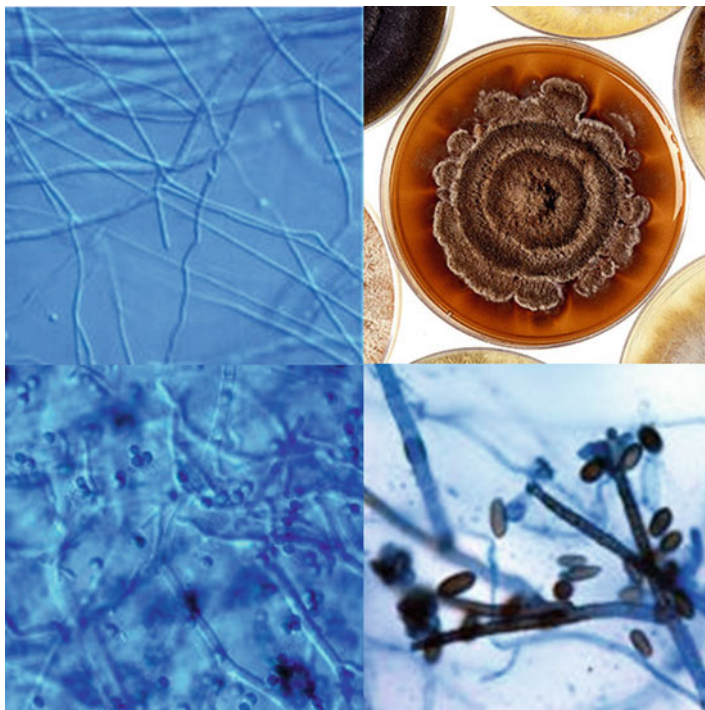
The trichothecenes belong to the sesquiterpenoid class, and are found commonly in cereal grains, with to date more than 200 different compounds of this type being known. Generally, they can be divided in two sub-groups: macrocyclic trichothecenes, constituting approximately 60%, and the remaining 40%, which are non-macrocyclic molecules (304). The first non-macrocyclic trichothecene, trichothecin (369), was isolated 1948 from *Trichothecium roesum* (305) (Fig. 8.1).



**Fig. 8.1** Trichothecin (369), first isolated from *Trichothecium roseum*

Two years earlier, “glutinosin” was isolated by the Butterwick (later Akers) Laboratories of Imperial Chemical Industries Ltd. from *Myrothecium verrucaria*. After this, “glutinosin” was identified as a mixture of verrucarins A (380) and B (381). Trichothecenes are produced by a number of different fungal genera such as *Fusarium*, *Myrothecium*, *Stachybotrys*, *Cylindrocarpon*, *Verticillium*, *Phomopsis*, *Trichoderma*, and *Cephalosporium* (306, 307). Selected fungi are shown in Fig. 8.2 (308–311).

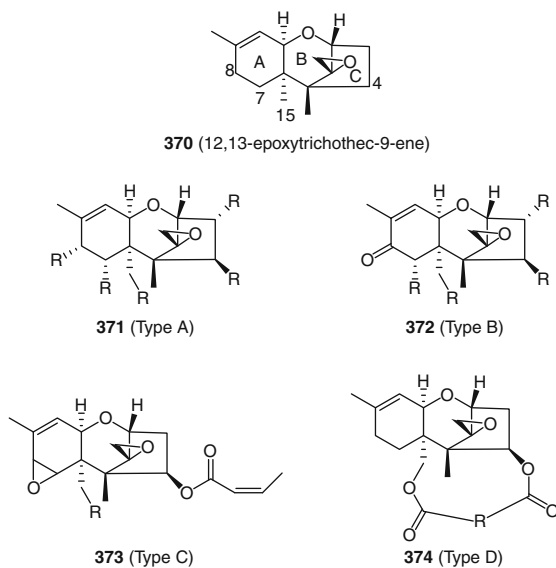




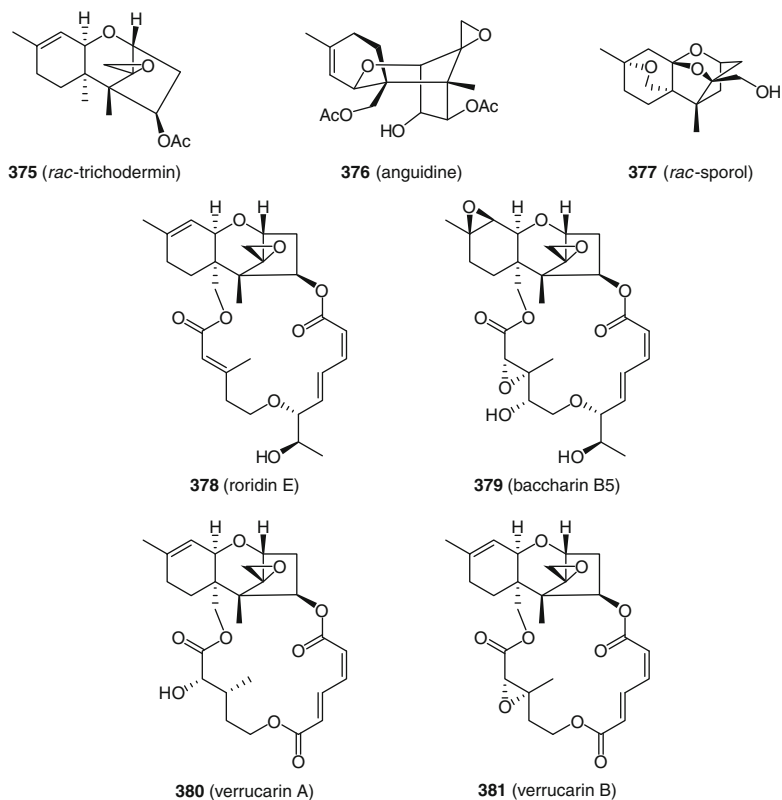
**Fig. 8.2** *Fusarium* sp. (upper left), cultures of a *Phomopsis* strain (upper right), *Trichoderma viride* (bottom left), and *Stachybotrys chartarum* (bottom right)

All trichothecenes include the tricyclic 12,13-epoxytrichothec-9-ene core, **370**. Based on this structure and its substitution pattern, the mycotoxins have been classified into four types, A (**371**), B (**372**), C (**373**), and D (**374**), by *Ueno et al.* Type A (**371**) can have a hydroxy group, an ester, or no functional group at C-8. Type B (**372**) possesses a carbonyl group at C-8, type C (**373**) has an epoxide function at C-7/C-8, and type D (**374**) mycotoxins are macrocyclic trichothecenes. Included among these four types there are some exceptions, which cannot be grouped accurately using this classification. Other classification systems for trichothecenes were proposed by *Jarvis et al.* (**312**) and *Tamm et al.* (**313**), but these will not be further discussed in this volume (Fig. 8.3).

To date, only a few total syntheses of trichothecenes have been published, such as the non-macrocyclic trichothecenes trichodermin (**375**), anguidine (**376**), and sporiol (**377**). Examples of the synthesis of macrocyclic trichothecenes are for roridin E (**378**), baccharin B5 (**379**), and verrucarin A (**380**) (Fig. 8.4).



**Fig. 8.3** Classification of trichothecenes into four types, A, B, C, and D, by Ueno *et al.*



**Fig. 8.4** Examples of trichothecenes

## 8.1 Biological Properties

The trichothecenes are found commonly in cereal and grain crops. In general, they have a very high toxicity and some represent the most toxic compounds so far known that do not contain a nitrogen atom. They are small and amphiphatic molecules and can move passively across cell membranes and are easily absorbed *via* the integumentary and gastrointestinal systems. This is the primary reason for their toxicity to animals and human beings. However, the majority of the trichothecenes show a broad range of interesting biological activities. Most of them are antibacterial, antibiotic, antifungal, and insecticidal. The biological properties originate from the macrocyclic lactone core and the epoxy group as the essential structural requirements for activity. These natural products are known to inhibit eukaryotic protein synthesis. In particular, they prevent peptide bond formation at the peptidyl transferase center of the 60S ribosomal subunit. Additionally, they are inhibitors of the mitochondrial protein synthesis and interact with protein sulfhydryl groups. Furthermore, trichothecenes show phytotoxicity and antitumor activities and are some of the most potently cytostatic materials found to date (304, 314–318).

## 8.2 Total Syntheses

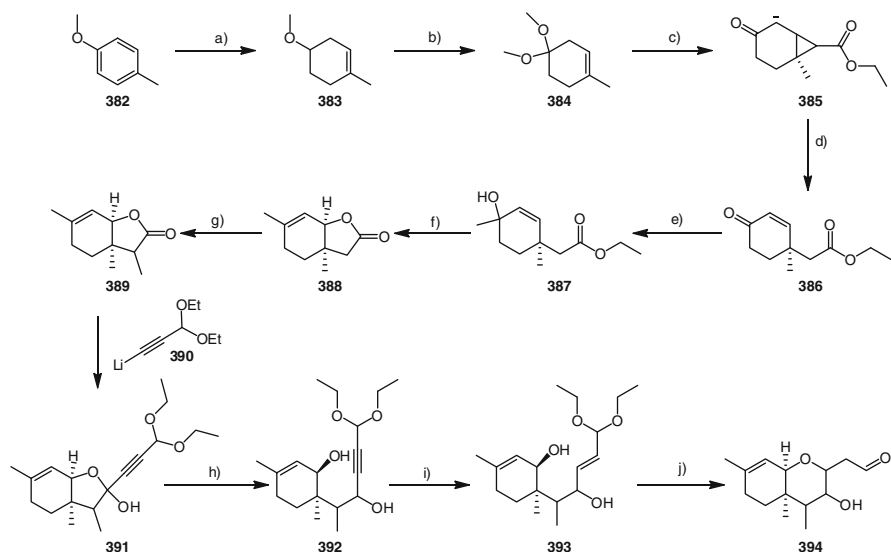
### 8.2.1 Non-Macrocyclic Trichothecenes

#### 8.2.1.1 Synthesis of Trichodermin

In 1971, *Raphael et al.* published the total synthesis of racemic trichodermin (375), which was the first synthesis of a member of the trichothecene family (319). Trichodermin (375) was isolated initially by *Vangedal et al.* from the culture fluid of a strain of *Trichoderma viride* in 1965 (320).

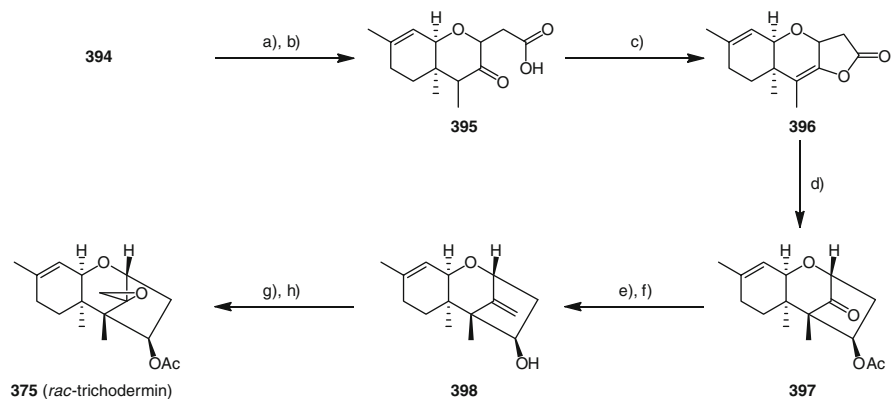
The total synthesis started with a *Birch* reduction of *p*-methoxytoluene (382) to obtain the dihydro compound 383, which was treated with *p*-toluenesulfonic acid to obtain acetal 384. Cyclopropanation with ethyl diazoacetate and transacetalization led to compound 385, which reacted to the unsaturated keto ester 386 on treatment with base. In the next step, the keto ester 386 was methylated with methylmagnesium chloride, and it reacted selectively at the 2-position to yield 387. Lactonization with further methylation with methyl iodide afforded homo-lactone 389, which reacted with lithium salt 390 to alkyne 391 and was reduced with sodium borohydride to diol 392. Partial reduction of the triple bond to the double bond was obtained with sodium in ammonia and further treatment with acid led to hydrolysis of the acetal, which subsequently cyclized to 394 (Scheme 8.1).

After having 394 in hand, *Raphael et al.* had planned to oxidize the alcohol to a ketone function; however, this molecule did not undergo an intramolecular aldol condensation. For this reason, it was necessary to oxidize the alcohol 394 in two steps to keto acid 395, which was then converted into the enol lactone 396.



**Scheme 8.1** Synthesis of the trichodermin precursor **394**. Reagents and conditions: a) Birch reduction; b) *p*-TsOH, MeOH; c)  $\text{CH}_2\text{N}_2$ ,  $\text{CO}_2\text{Et}$ , CuBr, TsOH, acetone; d) NaOAc, EtOH; e) MeMgCl; f) NaOH,  $\text{H}_2\text{SO}_4$ ; g) LDA, MeI; h)  $\text{NaBH}_4$ ; i) Na,  $\text{NH}_3$ , EtOH; j) AcOH, NaOAc,  $\text{H}_2\text{O}$

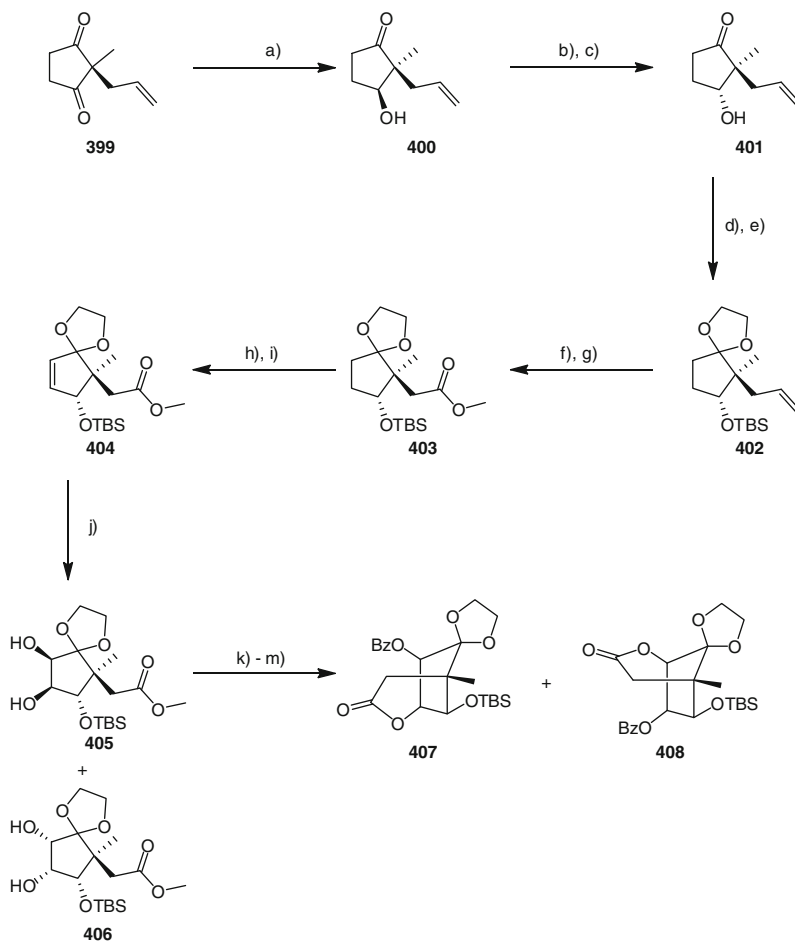
Compound **396** was obtained as an inseparable mixture of two racemates. Reduction of this mixture, followed by acetylation of the alcohol group, resulted in **397**. Subsequent Wittig reaction converted ketone **397** into methylene **398**. Deprotection of the alcohol group facilitated regio- and stereoselective epoxidation with *m*-CPBA and final acetylation of the alcohol group afforded the racemic natural product trichodermin (**375**) (Scheme 8.2).



**Scheme 8.2** Total synthesis of *rac*-trichodermin (**375**). Reagents and conditions: a)  $\text{CrO}_3$ , pyridine,  $\text{CH}_2\text{Cl}_2$ ; b)  $\text{CrO}_3$ ,  $\text{H}_2\text{SO}_4$ , acetone; c) NaOAc,  $\text{Ac}_2\text{O}$ ; d)  $\text{LiAl}(\text{O}i\text{-Bu})_3\text{H}$ ,  $\text{Ac}_2\text{O}$ , pyridine; e)  $\text{H}_2\text{C}=\text{PPh}_3$ ; f) NaOH; g) *m*-CPBA,  $\text{Na}_2\text{HPO}_4$ ,  $\text{CH}_2\text{Cl}_2$ ; h)  $\text{Ac}_2\text{O}$

### 8.2.1.2 Synthesis of Anguidine

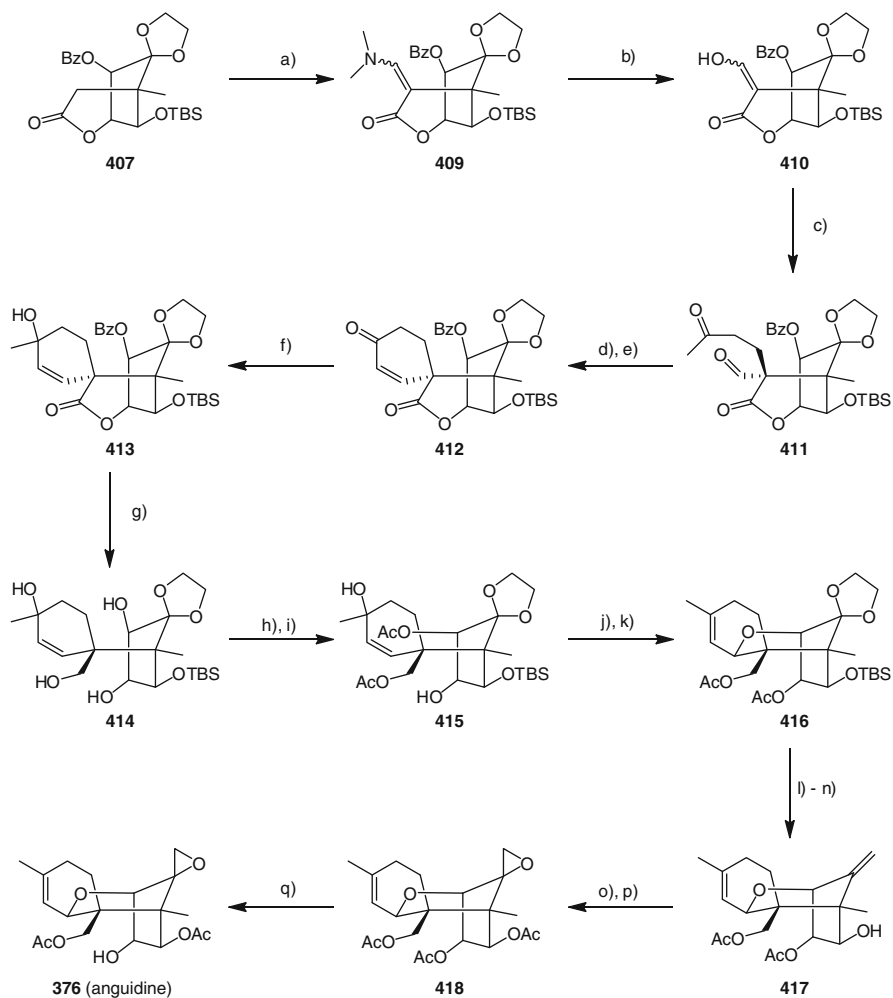
In 1960, *Brian et al.* isolated anguidine (**376**) for the first time from *Fusarium equiseti* (321). *Brooks et al.* published the synthesis of a precursor of anguidine (**376**) in 1982 (322), followed by a total synthesis in 1983 (323). When compared to the synthesis of trichodermin (**375**), where the group of *Raphael* started with the functionalization of the A-ring and condensed the C-ring during the last steps, *Brooks* first synthesized a fully functionalized C-ring system, where the A-ring was added, followed by an intramolecular ring closure to afford ring B and thereby the tricyclic system.



**Scheme 8.3** Synthesis of anguidine precursor **407**. Reagents and conditions: a) active baker's yeast, D-glucose, pH 7, rt, 70%; b) *p*-TsCl, pyridine, rt, 85%; c) KNO<sub>2</sub>, DMF, 85°C, 70%; d) imidazole, DMAP, TBSCl, DMF, 60°C, 90%; e) ethylene glycol, TsOH, HC(OEt)<sub>3</sub>, rt, 90%; f) K<sub>2</sub>CO<sub>3</sub>, NaIO<sub>4</sub>, KMnO<sub>4</sub>, *t*-BuOH, H<sub>2</sub>O, rt, 75%; g) CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O, 95%; h) PhMe<sub>3</sub>NBr<sub>3</sub>, THF, rt, 95%; i) DBU, 90°C, 85%; j) NMO, OsO<sub>4</sub>, acetone, H<sub>2</sub>O, rt, 95%; k) MeOH, KOH, rt; l) Ac<sub>2</sub>O, 0°C, 60%; m) BzCl, pyridine, Et<sub>2</sub>O, rt

To obtain the cyclopentanoid C-ring precursor **407** (Scheme 8.4), this group started with 2-allyl-2-methylcyclopentane-1,3-dione (**399**) and reduced selectively one of the two keto functions with actively fermenting baker's yeast to obtain the optically active alcohol **400**, with (*S*)-configuration at positions 2 and 3. However, for the enantioselective synthesis of anguidine (**376**), the (*R*)-configuration in position 3 was required. Therefore, the corresponding tosylate was treated with potassium nitrite to obtain the (*2S,3R*)-stereoisomer **401**. In the next steps, the alcohol and the keto groups were protected and compound **402** was obtained. Oxidation of the allyl alkene, followed by esterification, afforded **403**, which was then brominated with phenyltrimethylammonium tribromide and treated with DBU to produce olefin **404**. The double bond was oxidized with osmium tetroxide and NMO and gave a separable 5:1 mixture of the *cis vicinal* diols **405** and **406**. Then, **405** was saponified and treatment with acetic anhydride gave a 3:1 mixture of lactones. After protection with benzoyl chloride, it was possible to separate **407** and **408**. Intramolecular lactonization of the carboxylic acid of **406** was not possible due to its geometry (Scheme 8.3).

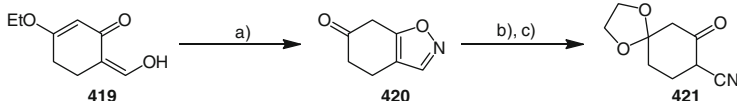
Having precursor **407** in hand, *Brooks et al.* were able to synthesize anguidine (**376**) in a further 17 steps. Thus, precursor **407** was converted into enamine **409**, which was hydrolyzed to hydroxymethylene derivative **410**. *Michael* reaction with butanone afforded the *exo* product **411**. Followed by an intramolecular *Michael* aldol condensation, enone **412** was obtained, which was methylated to the allyl alcohol **413** using methyl iodide. Subsequent reduction with lithium aluminum hydride led to tetraol **414**. This was converted to the triacetate and selectively deprotected to diol **415**. Acid-catalyzed cyclization and protection of the free OH group afforded the trichothecene skeleton **416**. Afterwards, the acetal **416** was deprotected and the ketone was reacted in a *Wittig* reaction to the olefin, which was treated with TBAF to afford compound **417**. Epoxidation with *m*-CPBA, followed by acetylation and final mono-deprotection, afforded the trichothecene, anguidine (**376**) (Scheme 8.4).



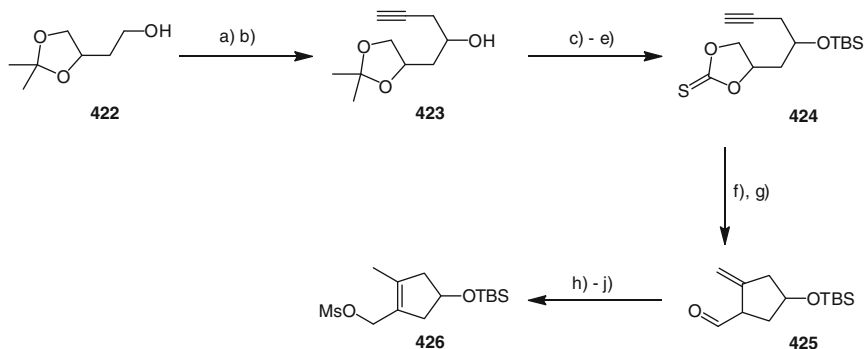
**Scheme 8.4** Total synthesis of anguidine (**376**). Reagents and conditions: a)  $\text{CH}(\text{NMe}_2)_3$ ,  $120^\circ\text{C}$ , 99%; b)  $\text{HOAc}$ ,  $\text{NaOAc}$ ,  $\text{H}_2\text{O}$ , rt, 99%; c) butanone, DIPEA, THF, rt, 95%; d) LDA, THF,  $-78^\circ\text{C}$ , 80%; e)  $\text{MsCl}$ , imidazole, DMF, rt, 80%; f)  $\text{MeLi}$ , THF,  $-78^\circ\text{C}$ , 90%; g)  $\text{LiAlH}_4$ , DME, reflux, 75%; h)  $\text{Ac}_2\text{O}$ , pyridine, rt, 95%; i)  $\text{NH}_4\text{OH}$ ,  $\text{MeOH}$ , rt, 70%; j) cat. *p*- $\text{TsOH}$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 90%; k)  $\text{Ac}_2\text{O}$ , pyridine, rt, 95%; l)  $\text{HCl}$ ,  $\text{MeOH}$ , rt, 70%; m)  $\text{CH}_2\text{PPh}_3$ , THF,  $60^\circ\text{C}$ , 75%; n) TBAF, THF, rt, 70%; o) *m*-CPBA,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 75%; p)  $\text{Ac}_2\text{O}$ , pyridine, rt, 95%; q)  $\text{NH}_4\text{OH}$ ,  $\text{MeOH}$ , rt, 65%

### 8.2.1.3 Synthesis of Sporol

Sporol (**377**) is a further non-macrocytic trichothecene, which was isolated in 1986 by *Tempesta et al.* from *Fusarium sporotrichioides* (**324**). The structure first thought to be sporol (**377**) was proven to be neosporol and a structural revision



**Scheme 8.5** Synthesis of keto-nitrile **421**. Reagents and conditions: a)  $\text{NH}_2\text{OH}\cdot\text{HCl}$ , aq. EtOH, reflux, 76%; b)  $\text{HO}(\text{CH}_2)_2\text{OH}$ , TsOH, benzene, 98%; c) *t*-BuOK, HMPA



**Scheme 8.6** Synthesis of intermediate **426**. Reagents and conditions: a) Swern oxidation; b) propargyl bromide, Zn/Hg, THF, 79% (over two steps); c) *p*-TsOH, MeOH; d)  $(\text{Im})_2\text{C}=\text{S}$ ,  $\text{CH}_2\text{Cl}_2$ ; e) TBSOTf,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 41% (over three steps); f)  $\text{Bu}_3\text{SnH}$ , AIBN, toluene, reflux, 60%; g) *DMP*; h) DMAP,  $\text{CH}_2\text{Cl}_2$ , 84%; i)  $\text{NaBH}_4$ , MeOH; j)  $\text{Ms}_2\text{O}$ ,  $\text{Et}_3\text{N}$ , DMAP

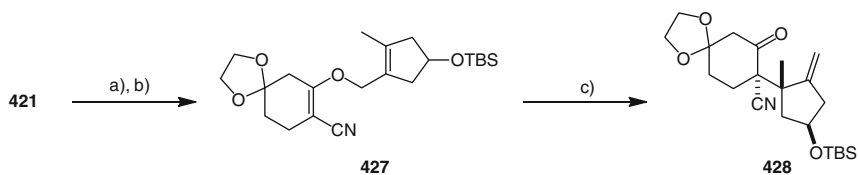
was published in 1988 (325), which was confirmed in 1992 with the total synthesis of sporol (**377**) by Ziegler *et al.* (326).

Nitrile **421** was synthesized from the hydroxy methylene ketone **419**. Initially, this was converted into isoxazole **420**, with its ketone function then protected with ethylene glycol. Treatment with potassium *t*-butoxide afforded the keto-nitrile **421** (Scheme 8.5).

The second starting material, mesylate **426**, was synthesized from alcohol **422**. Swern oxidation followed by addition of propargyl zinc bromide led to compound **423** in 79% yield, which was converted into thionocarbonate **424** (41% yield over three steps). Radical ring closure with tributyltin hydride and oxidation with *Dess-Martin* periodinane afforded ketone **425**. Treatment with DMAP led to the rearrangement of the double bond and subsequent reduction with sodium borohydride and mesylation gave compound **426** (Scheme 8.6).

The next step was O-alkylation: therefore, nitrile **421** was converted into the potassium salt and it was added to the solution of the mesylate **426**, which was not isolated but prepared *in situ*. The *Claisen* rearrangement of **427** following represents a very important key step in the total synthesis of sporol (**377**) as it set the relative stereochemistry at three different centers and product **428** could be isolated as major diastereomer in 68% yield (Scheme 8.7).

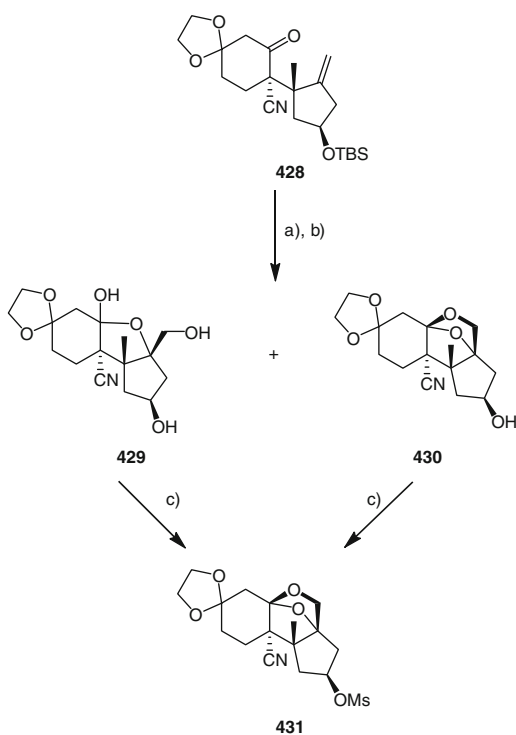




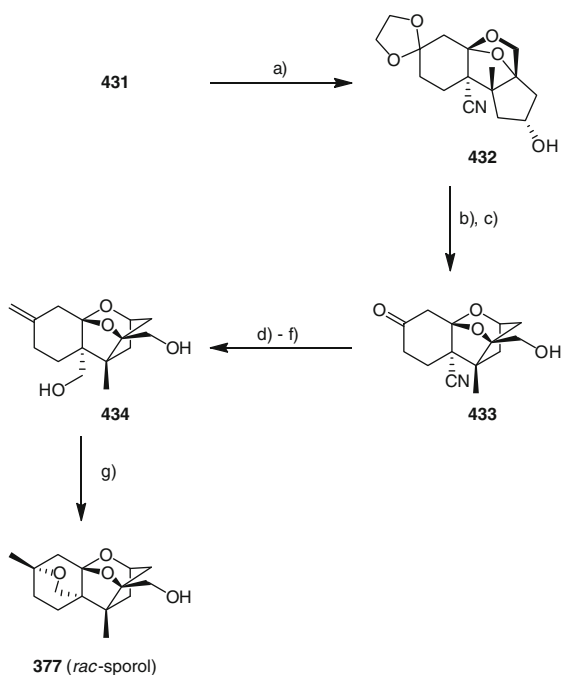
**Scheme 8.7** Preparation of **428** from keto-nitrile **421** and mesylate **426**. Reagents and conditions: a) *t*-BuOK, HMPA, 18-crown-6, 0°C; b) **426**, -20°C – 0°C, 47%; c) *n*-nonane, reflux, 68%

Having **428** on hand, Ziegler *et al.* were able to complete the total synthesis in further ten steps. First, they deprotected the alcohol group, followed by treating the compound with urea/hydrogen peroxide complex, which led to a mixture of the desired dioxolane **430** and triol **429** in a 7:2 ratio. Both compounds **429** and **430** could be transformed into mesylate **431** using  $\text{Ms}_2\text{O}$  and  $\text{Et}_3\text{N}$  (Scheme 8.8).

The next steps included inversion of the hydroxy group with potassium superoxide to **432** and subsequent conversion with camphorsulfonic acid to molecule **433**. Transformation of the keto group into an olefin was achieved *via* Wittig olefination under *Conia* conditions and reduction of the nitrile function led to compound **433**. The final ring closure with camphorsulfonic acid afforded the natural product *rac*-sporol (**377**) (Scheme 8.9).



**Scheme 8.8** Conversion of intermediates **429** and **430** into the desired compound **431**. Reagents and conditions: a) HF/ $\text{CH}_3\text{CN}$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{CH}_2\text{Cl}_2$ , 94%; b) urea· $\text{H}_2\text{O}_2$ , TFAA,  $\text{Na}_2\text{CO}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; c)  $\text{Ms}_2\text{O}$ , DMAP,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$



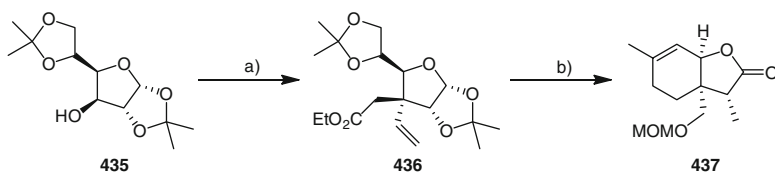
**Scheme 8.9** Total synthesis of *rac*-sporol (377). Reagents and conditions: a)  $K_2O$ , DMSO, 18-crown-6; b) CSA,  $CH_2Cl_2$ ; c) HCl, 32% (over four steps); d)  $PH_3PCH_3Br$ , *t*-BuOK, THF, 82%; e) DIBAL, aq.  $H_2SO_4$ ; f) DIBAL, 37%; g) CSA,  $CH_2Cl_2$ , 45%

## 8.2.2 Macrocyclic Trichothecenes

There exist just a few total syntheses of macrocyclic trichothecenes. However, all of these deal with the synthesis of verrucarol (454), a hydrolysis product of the naturally occurring verrucarol A (380). Verrucarol (454) represents the sesquiterpenoid moiety of most macrocyclic trichothecene derivatives. To date, there are several syntheses of this moiety. In 1998, the most recent total synthesis was published by *Tadano et al.* (327).

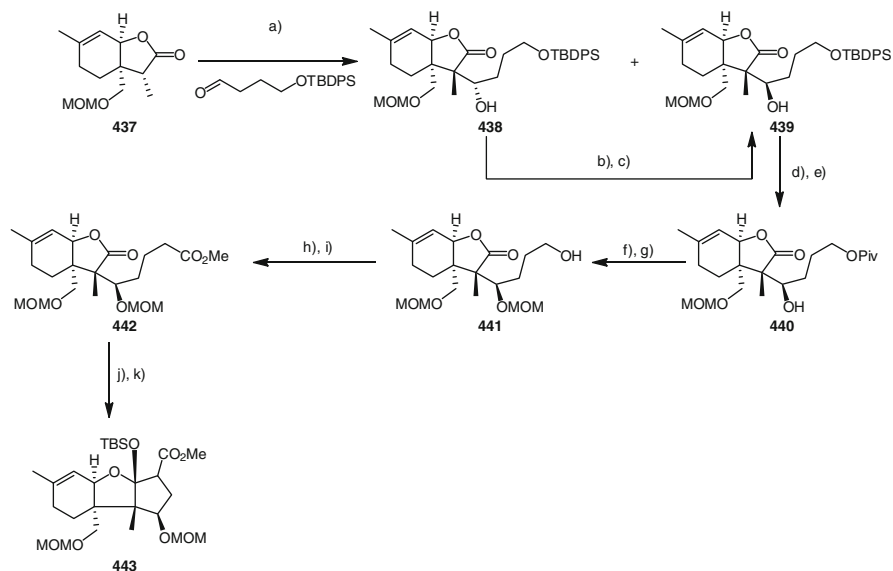
### 8.2.2.1 Synthesis of Verrucarol

The synthesis of verrucarol (454) started with the  $\alpha$ -methylated bicyclic  $\gamma$ -lactone 437, which was synthesized in 23 steps from commercially available diacetone glucose 435 (328, 329) (Scheme 8.10).



**Scheme 8.10** Synthesis of verrucarol precursor **437** in 23 steps. Reagents and conditions: a) four steps, 38%; b) 19 steps, 10–15%

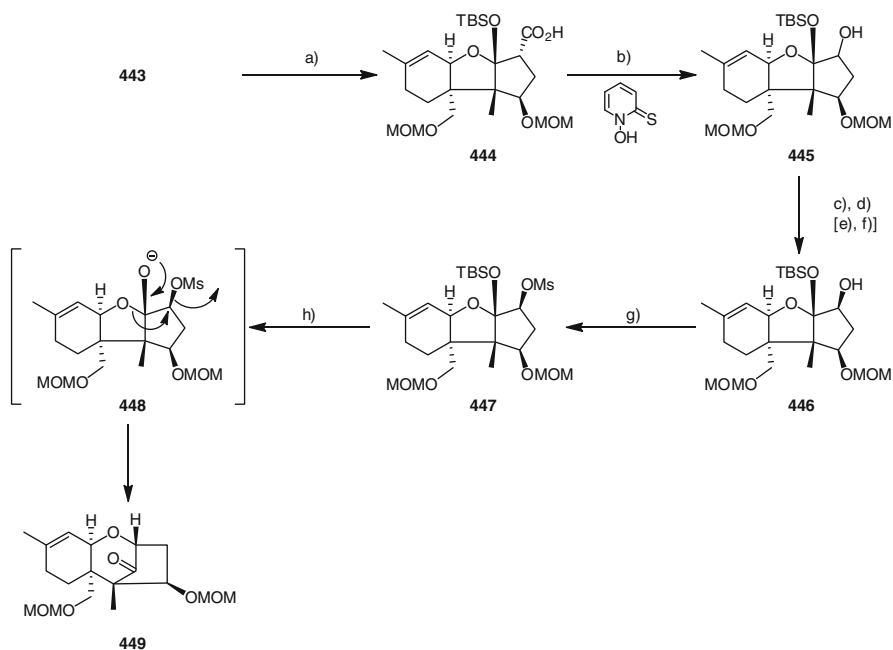
The first step was an aldol-like reaction of the enolate of **437** with 4-(*t*-butyldiphenylsilyloxy)butanal where a separable mixture of the two diastereomers **438** and **439** was obtained. Diastereomer **438** could be converted through an oxidation-reduction strategy into the other conformer **439**, which was achieved in 74% yield (**438**: 13%). In order to protect the secondary alcohol group with MOM-chloride, it was necessary to deprotect the primary alcohol group and then reprotect it with pivaloyl chloride, with **440** being obtained. The reaction of MOM-chloride with **439** was rather slow and the desired MOM-ether was only sustained in low yields. After having obtained compound **441**, Jones oxidation led to a carboxylic acid, which was directly esterified to **442**. Dieckmann cyclization followed by protection with TBSOTf afforded a separable diastereomeric mixture of the tricyclic compound, with **443** as the major product (Scheme 8.11).



**Scheme 8.11** Synthesis of verrucarol (**454**). Reagents and conditions: a) LDA/THF, PhMe,  $-78^{\circ}\text{C}$ ; b) PCC; c)  $\text{NaBH}_4$ ; d) TBAF; e) PivCl; f) MOMCl; g) NaOMe; h) Jones reagent; i)  $\text{CH}_2\text{N}_2$ ; j) KHMDS/THF,  $-78^{\circ}\text{C}$ ; k) TBSOTf

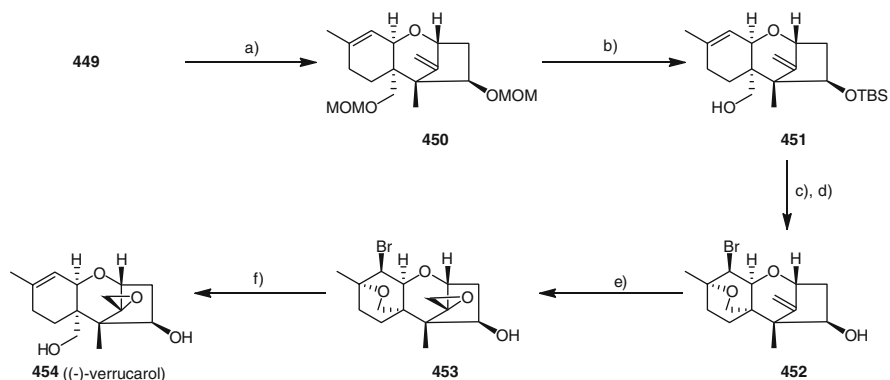
Saponification of the ester group of both diastereomers provided the same conformer **444** in 81% yield. Subsequent conversion of the carboxylic ester function into an alcohol function afforded an inseparable diastereomeric mixture of **445**. However, acetylation of the alcohol group made separation possible and deprotection with DIBAL-H afforded diastereomer **446**. The other diastereomer could be converted into the desired former *via* oxidation/reduction with PDC and DIBAL-H. Mesylation of compound **446** led to **447**, which was able to undergo ring enlargement: treating with TBAF deprotected the TBS-group and the intermediate **448** rearranged to ketone **449** (Scheme 8.12).

In the next step, alkene **450** was formed *via* a Wittig reaction, then the MOM-groups were deprotected with TMSBr and the diol was obtained, which was monoprotected with TBSOTf to give **451**. This diol is known as 12,13-deoxyverrucarol and was isolated as an alkaline hydrolysis product of verrucarol K by *Breitenstein* and *Tamm* (330).



**Scheme 8.12** Synthesis of verrucarol (**454**). Reagents and conditions: a) 4 M KOH; b) WSC, DMAP, *t*-BuSH, O<sub>2</sub>; c) Ac<sub>2</sub>O/py; d) DIBAL-H; e) PDC; f) DIBAL-H; g) MsCl; h) TBAF

To introduce an epoxy group on the terminal double bond, the other alkene function was protected by bromoetherification to produce the bromo ether, which was desilylated and compound **452** provided. In the final two steps, olefin **453** was epoxidized with *m*-CPBA and deprotected with a zinc-silver complex to obtain (–)-verrucarol (**454**) (Scheme 8.13).



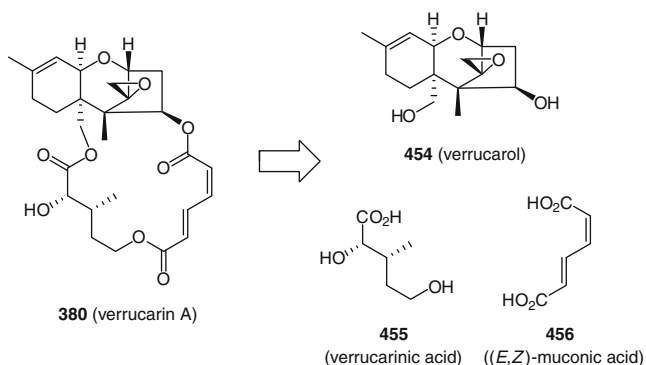
**Scheme 8.13** Synthesis of verrucarol (**454**). Reagents and conditions: a)  $\text{Ph}_3\text{P}=\text{CH}_2$ ; b)  $\text{TMSBr}$ ,  $-30^\circ\text{C}$ ,  $\text{TBSOTf}$ ; c)  $\text{NBS}$ ; d)  $\text{TBAF}$ ; e) *m*-CPBA; f)  $\text{Zn-Ag}$

The following total syntheses of verrucarin A (**380**), roridin E (**378**), and baccharin B5 (**379**) all use verrucarol (**454**) as an intermediate.

### 8.2.2.2 Synthesis of Verrucarin A

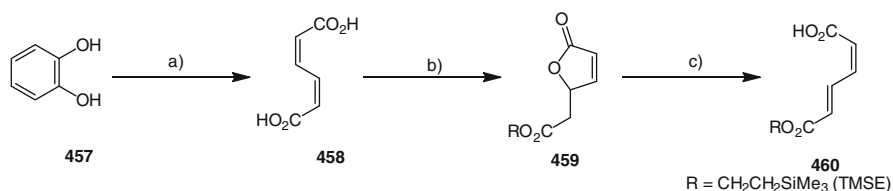
Verrucarin A (**380**) is one of the most important and best described macrocyclic trichothecenes. This compound was obtained for the first time in 1962 by isolation from *Myrothecium roridum* and *M. verrucaria* by Tamm *et al.* (331). This same group performed a considerable amount of research in this area and in 1982 they published the total synthesis of verrucarin A (**380**) (317).

In its retrosynthesis, the natural product **380** was disconnected through cleavage of the ester bonds to furnish verrucarol (**454**), verrucarinic acid (**455**), and (*E,Z*)-muconic acid (**456**) as starting compounds (Scheme 8.14).



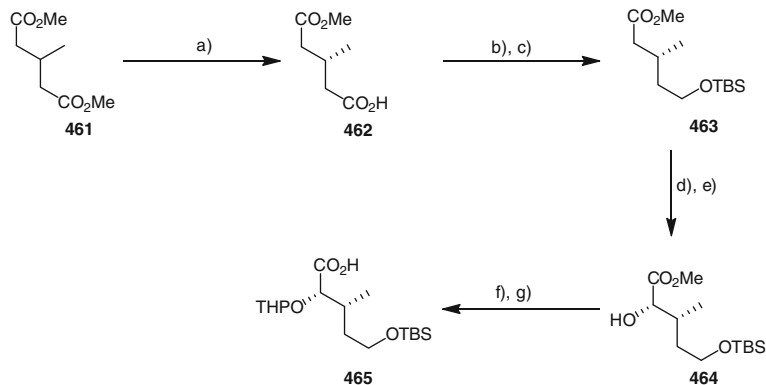
**Scheme 8.14** Retrosynthetic analysis of verrucarin A (**380**)

The half ester of (*E,Z*)-muconic acid (**456**) was synthesized in three steps as follows: Starting from catechol (**457**), oxidative cleavage with a peracid led to the (*Z,Z*)-diacid **458**, which was monoprotected *via* lactonization to provide compound **459**, and by treatment with *Eschenmoser's* base the desired monoester **460** was obtained (Scheme 8.15).



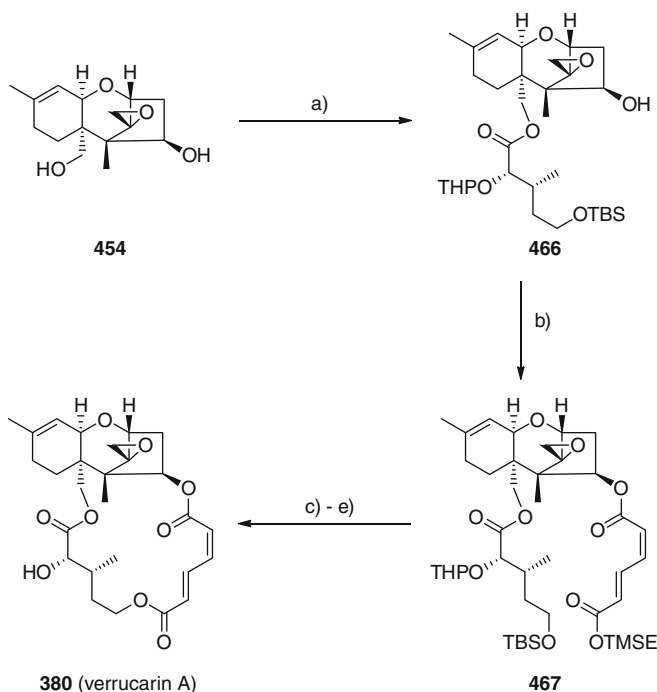
**Scheme 8.15** Preparation of half ester **460**. Reagents and conditions: a) peracid oxidation; b)  $\text{Me}_3\text{Si}(\text{CH}_2)_2\text{OH}$ , DCC, DMAP,  $\text{CH}_2\text{Cl}_2/\text{DMF}$ , 80%; c) *Eschenmoser's* base, 75%

For the second building block for verrucarol A (**380**), a derivative of verrucaric acid (**465**) was synthesized in enantiomerically pure form from diester **461**. Cleavage with pig liver esterase led to monoester **462**, which was reduced to the alcohol with borane dimethylsulfide complex and protected with TBSCl to obtain the molecule **463**.  $\alpha$ -Hydroxylation with molybdenum oxide generated alcohol **464**, and final protection and saponification afforded compound **465** (Scheme 8.16).



**Scheme 8.16** Preparation of precursor **465**. Reagents and conditions: a) pig liver esterase, 95%; b)  $\text{BH}_3 \cdot \text{SMe}_2$ , THF; c) TBSCl,  $\text{NEt}_3$ , DMAP,  $\text{CH}_2\text{Cl}_2$ ; d) LDA, THF; e)  $\text{MoO}_5 \cdot \text{Py}$ , HMPA,  $-78^\circ\text{C}$ , 2 h, 40%; f) DHP, PPTS; g) KOH, MeOH

Having verrucarol (**454**), the derivative of verrucaric acid (**465**), and the half ester of (*E,Z*)-muconic acid (**456**) all on hand, the total synthesis of verrucarol A (**380**) could be completed in a further five steps. Thus, verrucarol (**454**) was esterified first with compound **465** and second with compound **460**. Then, molecule **467** was desilylated, macrolactonized under *Yamaguchi* conditions, and finally deprotected to achieve the natural product verrucarol A (**380**) (Scheme 8.17).

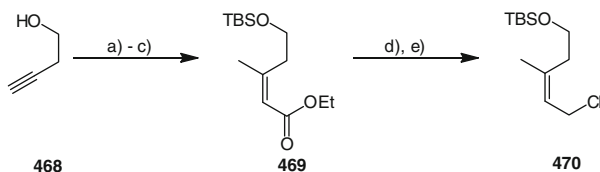


**Scheme 8.17** Total synthesis of verrucarin A (**380**): a) DCC, **465**, DMAP or 4-pyrrolidinopyridine, 55%; b) DCC, **460**, DMAP or 4-pyrrolidinopyridine, 95%; c) TBAF, THF; d) TCBACl,  $\text{NEt}_3$ , THF; e) DMAP, toluene, reflux, 50%

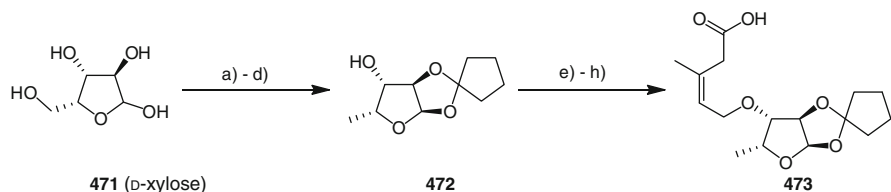
### 8.2.2.3 Synthesis of Roridin E and Baccharin B5

In 1983, *Still et al.* published methods for the total synthesis of roridin E (**378**) and baccharin B5 (**379**) (332). Roridin E (**378**) was isolated for the first time in 1965 from *Myrothecium verrucaria* and baccharin B5 (**379**) was obtained in 1976 from the plant *Baccharis megapotamica* (333, 334).

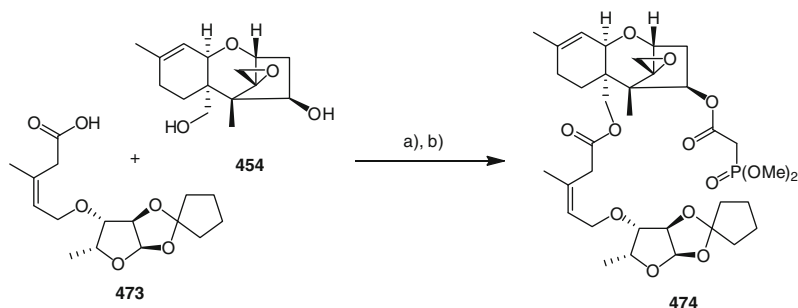
The synthesis of both compounds started from verrucarol (**454**) and D-xylose (**471**). First, intermediate **470** was synthesized. Next, butynol (**468**) was ethoxycarboxylated and then methylated to provide **469**, which was reduced and compound **470** was obtained (Scheme 8.18).



**Scheme 8.18** Preparation of chloride **470**. Reagents and conditions: a) TBSCl; b) BuLi,  $\text{ClCO}_2\text{Et}$ ; c)  $\text{Me}_2\text{CuLi}$ ; d)  $\text{LiAlH}_4$  (45% over four steps); e) NCS,  $\text{Me}_2\text{S}$



**Scheme 8.19** Synthesis of intermediate **473**. Reagents and conditions: a) cyclopentanone,  $\text{CuSO}_4$ , cat.  $\text{H}_2\text{SO}_4$ ; b) 0.2%  $\text{HCl}$ ; c) *p*-TsCl, py; d)  $\text{LiAlH}_4$ , 65% over four steps; e) **470**, NaH; f) cat. TBAI, HMPA; g) TBAF; h)  $\text{CrO}_3$ ,  $\text{H}_2\text{SO}_4$ , (75% over four steps)



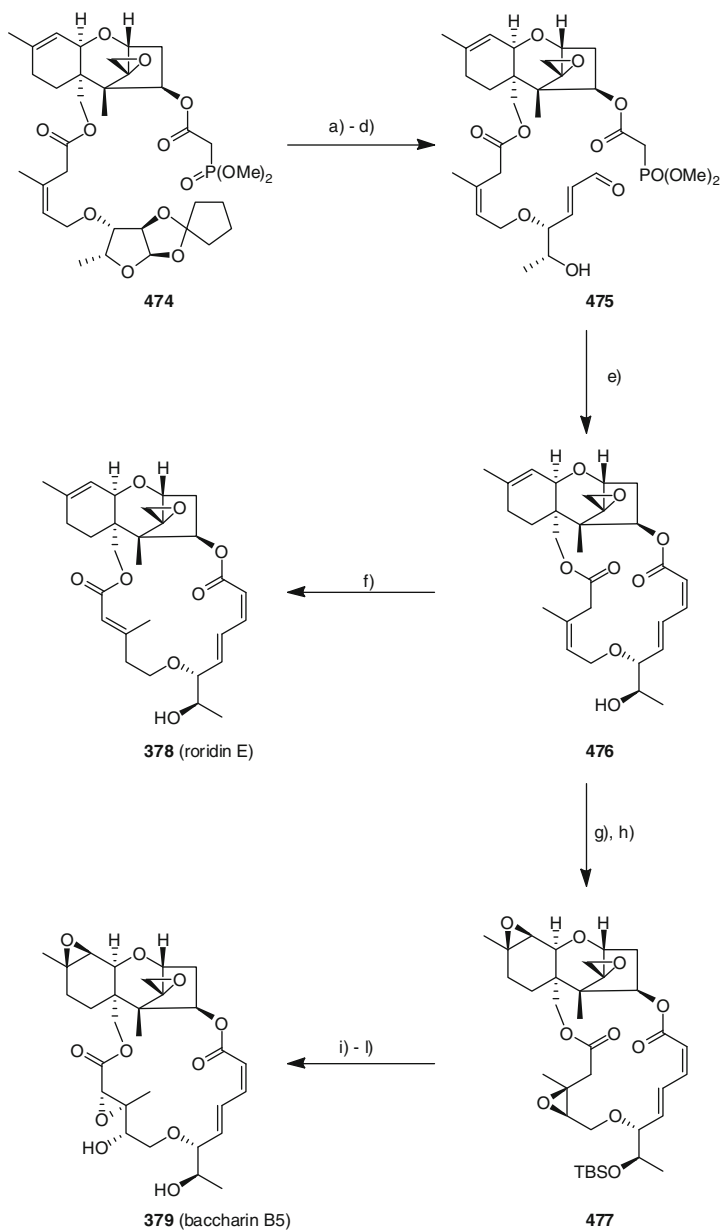
**Scheme 8.20** Synthesis of precursor **474** for roridin E (**378**) and baccharin B5 (**379**). Reagents and conditions: a) DCC, 0.1mol% 4-pyrrolidinopyridine, 95% yield at 55% conversion; b)  $\text{HO}_2\text{CCH}_2\text{PO}(\text{OMe})_2$ , DCC, 4-pyrrolidinopyridine, quant

Then, commercially available D-xylose (**471**) was treated with cyclopentanone to protect two of the four alcohol groups as acetals. Subsequent tosylation of the primary alcohol function and reduction to a methyl group led to compound **472** in 65% over four steps. In the next step, the xylose derivative was coupled with olefin chloride **470**, followed by desilylation and oxidation with *Jones* reagent to provide the xylose derivative **473**. This was coupled with verrucarol (**454**) and then converted into phosphono ester compound **474** (Scheme 8.19 and 8.20).

In the last steps of the total syntheses, ester **474** was converted into aldehyde **475** in four steps with an overall yield of 65%. Macrocyclization was possible *via* a *Horner-Wadsworth-Emmons* reaction and precursor **476** for roridin E (**378**) and baccharin B5 (**379**) was obtained. The final step in the synthesis of roridin E (**378**) was the isomerization of the double bond.

For the total synthesis of baccharin B5 (**379**) six more steps were necessary. First, the alcohol group was protected and then the unconjugated double bonds could be epoxidized selectively to provide **477** as a single product. Subsequently, the epoxide of the macrocycle **477** was eliminated to an allylic double bond, which could be epoxidized again and gave the epimer of baccharin B5. Last, the epimer was converted into baccharin B5 (**379**) *via* a *Mitsunobu* reaction (Scheme 8.21).





**Scheme 8.21** Total synthesis of roridin E (**378**) and baccharin B5 (**379**). Reagents and conditions: a) TsOH; b) NaIO<sub>4</sub>; c) Et<sub>3</sub>N, MeOH; d) Ph<sub>3</sub>PCH<sub>2</sub>CHO, 65% over four steps, (*E*):(*Z*) = 4:1; e) K<sub>2</sub>CO<sub>3</sub>, 18-crown-6, 45%; f) *t*-BuOK, 70%; g) TBSOTf, lutidine, 95%; h) *m*-CPBA, 70%; i) KO*t*-Bu, 90%; j) *t*-BuOOH, VO(acac)<sub>2</sub>, 90%; k) HCO<sub>2</sub>H, DEAD, PPh<sub>3</sub>, 40% conversion/90% yield; l) TBAF, 99%

## 9 Resorcylic Acid Lactones

The resorcylic acid lactones (RALs) are a family of benzannulated macrolides, which are produced by a variety of fungi and show versatile biological activities (6). According to their name, they consist structurally of a partially substituted  $\beta$ -resorcylic acid scaffold, which is linked to a 12- or 14-membered macrolactone moiety. Selected members of this group are shown in Fig. 9.1.

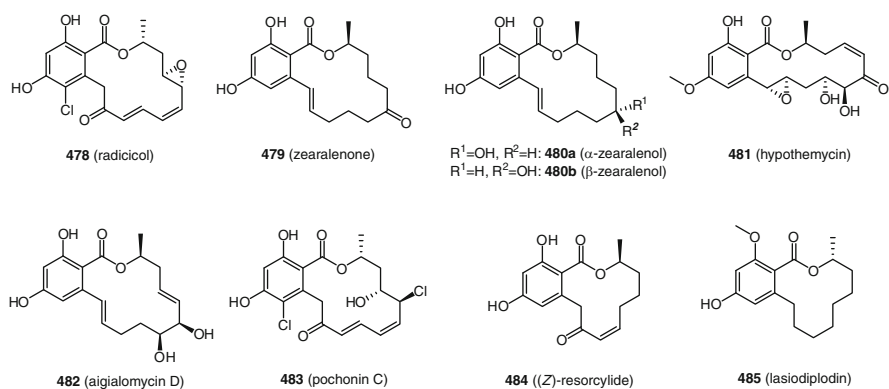


Fig. 9.1 Selected resorcylic acid lactones

Radicol (**478**) (335), formerly called monorden (336), was first isolated from *Monosporium bonorden* in 1953 (337). The most well-known member of the RAL family, zearalenone (F-2) (**479**), was found in 1962 in spoiled grain infected with *Gibberella zae*, which was fed to swine. This contamination led among other symptoms to vulvar hypertrophy, vaginal eversion, and the growth of mammary glands among the affected animals (338, 339). Figure 9.2 shows the fungus *Gibberella zae* on corn (340).



**Fig. 9.2** Corn infected with *Gibberella zeae*

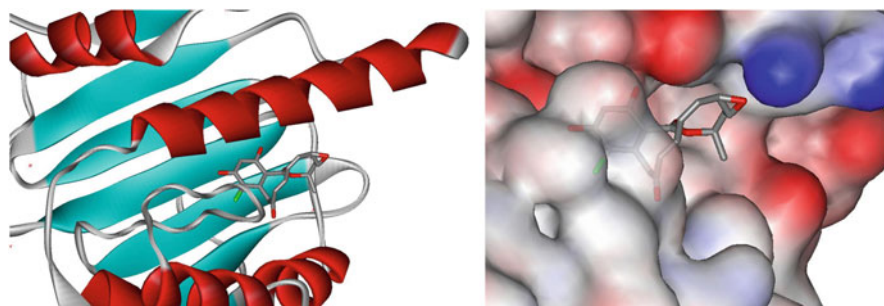
The reduced form of zearalenone (**479**),  $\alpha$ -zearalenol (**480a**) (*341*), and hypothemycin (**481**) (*342*) are further examples of the first known RALs. It should be noted that the initial structure proposed for hypothemycin (*343*) was erroneous. During the last decade, two new subgroups of 14-membered resorcylic macrolides, the aigialomycins (*344*) and the pochonins (*345*) have been isolated and characterized, leading to a renewed interest in this class of natural products. While aigialomycins A–F were isolated together with hypothemycin from the marine mangrove fungus *Aigialus parvus*, pochonins A–F were found in cultures of *Pochonia chlamydosporia* var. *catenulata*. Recently, two further subgroups, paecilomycins A–F and cochliomycins A–C, have been isolated from a *Paecilomyces* fungus and *Cochliobolus lunatus* (*346*, *347*). (*Z*)-Resorcylyde (**484**), called in the literature mostly (*cis*)-resorcylyde, and lasiodiplodin (**485**), are examples of bioactive RALs containing a 12-membered macrolactone system (*348*, *349*).

## 9.1 Biological Properties

According to their structural diversity, the RALs exhibit a variety of biological activities. Although it is classed as a mycotoxin, zearalenone (**479**) is barely toxic (*9*). Its anabolic and uterotrophic traits (*338*) are the result of its interaction with estrogenic receptors. Zearalenone (**479**) is able to bind to these receptors and thus mimic the ability of  $17\beta$ -estradiol to stimulate transcriptional activity. Therefore, it

is also called a non-steroidal estrogen (350).  $\alpha$ -Zearalenol (**480a**) possesses the same type of activity, but is about three times more potently estrogenic than zearalenone (**479**) or its non-naturally occurring  $\beta$ -isomer **480b** (341, 351). The anabolic properties of zearalenol have been used as a growth-promoting agent for cattle and sheep, but since 1989 it has been prohibited in the EU (348, 352). Zearalenol (**480**) has also been tested to treat symptoms caused by endocrinological changes at the menopause in women (353).

Radicicol (**478**) exhibits a variety of antifungal and antibiotic properties (337). Furthermore, it shows remarkably low toxicity and acts as a potent sedative (336). More recent studies have revealed the antitumor activity of radicol (**478**) (354). It inhibits selectively heat shock protein 90 (Hsp90) of tumor cells, which leads to the destruction of oncogenic cells (355) (Fig. 9.3). Hsp90 inhibitors have been shown also to reduce protein aggregates associated with *Huntington's* and *Parkinson's* diseases, as well as other tau-protein related neurodegenerative diseases (356).



**Fig. 9.3** Co-crystal structure of radicol (**478**) bound to Hsp90

Hypothemycin (**481**) and other RALs containing a (*Z*)-enone are potent inhibitors of several kinases such as mitogen-activated protein (MAP) kinase (357, 358). Along with the aigialomycins (*e.g.* aigialomycin D (**482**)), hypothemycin (**481**) exhibits antimalarial activity and both of these compounds are cytotoxic for cancer cells (344). The pochonins show antiviral activity against herpes simplex virus 1 (HSV1), with pochonin C (**483**) being the most potent among these compounds (345). The 12-membered macrolides, resorcyllide (**484**) and lasiodiplodin (**485**) inhibit the growth of plants (348, 349).

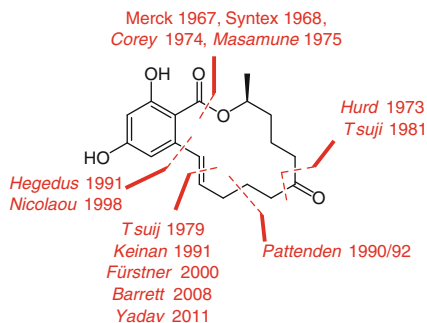
## 9.2 Total Syntheses

Since the discovery of this class of mycotoxins, the total syntheses of these molecules have been of considerable interest. To date, numerous total syntheses for RAL-mycotoxins have been published, with zearalenone (**479**) being the most

widely explored resorcylic macrolide in this regard. In general, a macrolide synthesis affords two major problems, namely, the construction of the macrolactone and the stereochemical control of the chiral centers (359). Therefore, these synthesis investigations have involved the development of new cyclization methodologies, such as macrolactonization reactions, by the groups of *Corey*, *Nicolaou*, and *Masamune* (360, 361) as well as ring-closing metathesis procedures (362). Due to the simplicity and similarity of the syntheses of the 12-membered RALs compared to the 14-membered macrolides, these will not be described in the following paragraphs. Furthermore, the first stereoselective total synthesis of paecilomycin E, which was reported by *Srihari et al.* in 2012 (363), also will not be detailed.

### 9.2.1 Total Syntheses of Zearalenone

The first total syntheses of racemic zearalenone (*rac*-**479**) were reported in the 1960s by the Merck and Syntex research groups (364, 365). In their multistep synthesis routes of the *seco* acid, the double bond was introduced by a *Wittig* reaction, but the required (*E*)-configured double bond was not formed selectively and the yields of the following lactonization were very low. The yields of macrolactonization were improved remarkably by *Corey* (360) and *Masamune* (361) using new activation methods for carboxylic acids (366). In all the syntheses of zearalenone, the macrolide was formed by lactonization, but numerous possibilities are evident for the cyclization step. Figure 9.4 illustrates some different approaches to the synthesis of zearalenone (367).



**Fig. 9.4** Several ring-closure approaches to zearalenone (**479**)

*Hurd* and *Tsuji* promoted the formation of the macrocycle at the ketone using an internal *Dieckmann* condensation or an intramolecular alkylation of a protected cyanohydrin (368, 369).

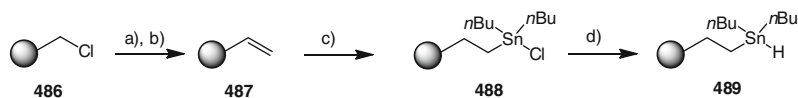
In 1990, the first enantioselective synthesis of (*S*)-(-)-zearalenone (**479**) was reported by *Pattenden et al.* (370). Using this procedure, the macrolide was formed via a 14-*endo-trig* cyclization from an allylic radical intermediate. Stereochemical information was introduced using enantiomerically pure starting material. An intramolecular alkylation method via stabilized carbanions to obtain racemic zearalenone was described by *Tsuji et al.* (366). A few years later, *Keinan et al.* explored the stereoselective modification of this reaction using the biocatalyst *Thermoanaerobicum brockii* alcohol dehydrogenase (TBADH) to generate the stereogenic center (367).

A further ring-closure approach was investigated by *Hegedus* (371) and extended by *Nicolaou et al.* (372). The two groups applied the *Stille* coupling reaction to form the macrocycle and both of them employed (*R*)-propylene oxide as a chiral building block (367). In addition, *Nicolaou* used a solid-phase strategy and the cleavage from the polymer resin came along with the intramolecular coupling reaction.

The latest total syntheses, presented by the groups of *Fürstner* (362), *Barrett* (373), and *Yadav* (374), are all based on a ring-closing metathesis (RCM) as the key step. In the following sections, several total syntheses of zearalenone (**479**) will be described.

### 9.2.1.1 Total Synthesis of (*S*)-Zearalenone by *Nicolaou*

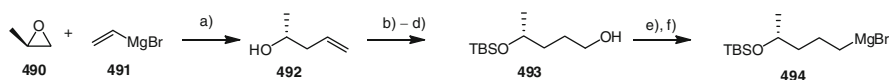
The solid-phase total synthesis of (*S*)-zearalenone by *Nicolaou et al.* (372) started with the preparation of the resins **488** and **489** from the *Merrifield* resin (**486**, Scheme 9.1). Oxidation, followed by olefination of the resulting aldehyde, gave a polystyrene vinyl resin (**487**), which was converted into dibutyltin chloride **488**. In this process, the stannylation reagent *n*-Bu<sub>2</sub>SnHCl was formed *in situ* from *n*-Bu<sub>2</sub>SnCl<sub>2</sub> and *n*-Bu<sub>2</sub>SnH<sub>2</sub>. Reduction of **488** yielded the polymer supported tin hydride **489**.



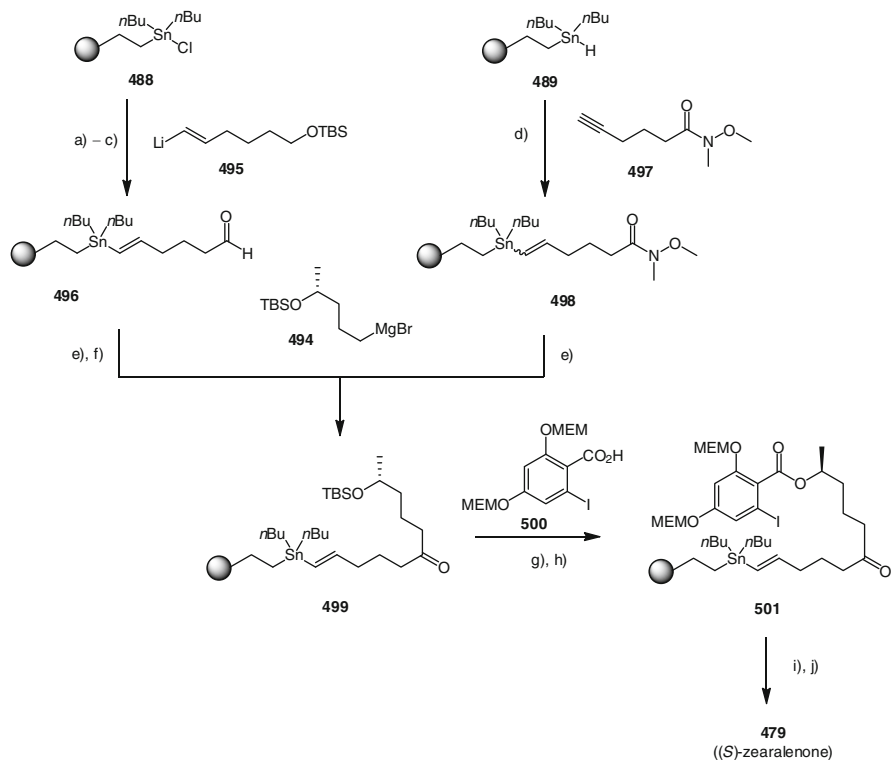
**Scheme 9.1** Preparation of the modified resins **488** and **489**. Reagents and conditions: a) K<sub>2</sub>CO<sub>3</sub>, DMSO, 145°C, 15 h; b) CH<sub>2</sub>=PPh<sub>3</sub>, THF, 23°C, 8 h; c) *n*-Bu<sub>2</sub>SnCl<sub>2</sub>, *n*-Bu<sub>2</sub>SnH<sub>2</sub>, AIBN, *hν*, toluene, 0°C, 4 h, 90% from **486**; d) LiBH<sub>4</sub>, THF, 23°C, 4 h

The stereochemical information was introduced by applying a chiral pool strategy as described by *Hegedus et al.* in 1991 (371) (Scheme 9.2). They started from the enantiomerically pure epoxide **490**, which was converted into the chiral magnesium organyl **494** in six steps.

*Hegedus* described an applied strategy for the next steps in solution (Scheme 9.3). Addition of lithium reagent **495** to chloride **488** led exclusively,



**Scheme 9.2** Preparation of the chiral precursor **494** by *Hegedus*. Reagents and conditions: a) CuI, THF, 47%; b) TBSCl; c) 9-BBN, THF, 25°C, 19 h; d) H<sub>2</sub>O<sub>2</sub>, NaOH, 0°C to 25°C, 10.5 h, 75% (over three steps); e) CBr<sub>4</sub>, PPh<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 95%; f) Mg, Et<sub>2</sub>O



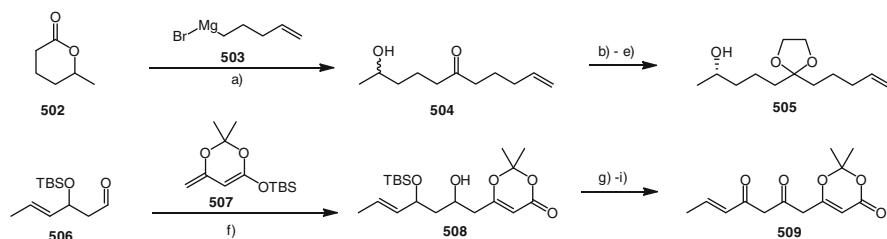
**Scheme 9.3** Total synthesis of (*S*)-zearelenone (**479**) by *Nicolaou et al.* Reagents and conditions: a) **495**, THF, -78°C to 23°C, 4 h (87%); b) TBAF, THF, 23°C, 5 h (94%); c) NCS, Me<sub>2</sub>S, 0°C, 15 min; then add resin, 0°C, 1 h; Et<sub>3</sub>N, 0°C to 23°C, 0.5 h; d) **497**, AIBN, toluene, 100°C, 4 h (90% from **488**); e) **494**, THF, 0°C to 23°C, 4 h; f) NCS, Me<sub>2</sub>S, 0°C, 15 min; then add resin, -40°C, 1.5 h, Et<sub>3</sub>N, -40°C to 23°C, 0.5 h (97%); g) TBAF, THF, 23°C, 13 h; h) **500**, PPh<sub>3</sub>, DEAD, 0°C to 23°C, 6 h (76%, two steps); i) Pd(PPh<sub>3</sub>)<sub>4</sub>, toluene, 100°C, 48 h (54%); j) 2:1 THF/HCl (aq.) (5%), 23°C, 5 d (80%)

after deprotection and oxidation, to the required (*E*)-olefin **496**, whereas the reaction of tin hydride **489** with alkyne **497** gave a nonselective (*E*)/(*Z*)-mixture of tin organyl **498**. Subsequent addition of *Grignard* reagent **494** either to

aldehyde **496** with following *Corey-Kim* oxidation or to *Weinreb* amide **498**, gave ketone **499**. Deprotection of the hydroxy group, ensued by *Mitsunobu* esterification with benzoic acid **500** (371), afforded the desired precursor **501**. Cyclization was achieved by a *Stille* coupling reaction, which resulted in cleavage from the resin, and led after acid-induced deprotection to the target molecule (*S*)-zearalenone (**479**). However, cyclization was only observed in case of the (*E*)-isomer.

### 9.2.1.2 Total Synthesis of (*S*)-Zearalenone by Barrett

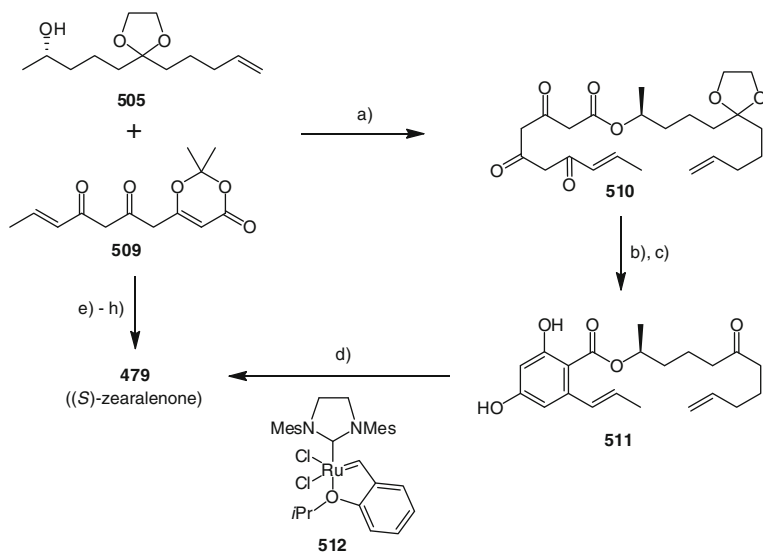
In 2008, Barrett *et al.* reported on a biomimetic synthesis of (*S*)-zearalenone involving a late-stage aromatization (373). They started with the synthesis of the two building blocks **505** and **509** (Scheme 9.4). The enantiopure alcohol **505** was prepared in five steps from ( $\pm$ )-5-hexanolide (**502**) by applying a lipase-mediated strategy. Dioxinone **509** was synthesized using a vinylogous *Mukaiyama* aldol reaction to link aldehyde **506** with olefin **507**.



**Scheme 9.4** Preparation of the building blocks **505** and **509**. Reagents and conditions: a) Et<sub>2</sub>O, THF, -78°C to rt, 77%; b) Ac<sub>2</sub>O, pyridine, 60°C, 24 h, 71%; c) ethylene glycol, *p*-TsOH·H<sub>2</sub>O, PhH, 90°C, 18 h, 73%; d) KOH, H<sub>2</sub>O, MeOH, 25°C, 3 h, 93%; e) CAL-B lipase, vinyl acetate, 35°C, 80 min (repeat once), *ee* >99%; f) BF<sub>3</sub>·Et<sub>2</sub>O, **503**, CH<sub>2</sub>Cl<sub>2</sub>, -78°C, 1.5 h, 61%; g) *DMP*, CH<sub>2</sub>Cl<sub>2</sub>, 0°C; h) HF, H<sub>2</sub>O, MeCN, 0°C; i) *DMP*, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 5 h

The two building blocks prepared were converted into triketo-ester **510** by thermolysis of the dioxinone and trapping of the intermediate triketo-ketene with alcohol **505**. Aromatization of triketo-ester **510**, followed by deprotection of the ketone gave resorcylate **511**. Finally, RCM using the second generation *Hoveyda-Grubbs* catalyst **512**, led to (*S*)-zearalenone in good yield. Further investigation revealed that the last four steps could be carried out without isolation of the intermediates in a single vessel (Scheme 9.5).



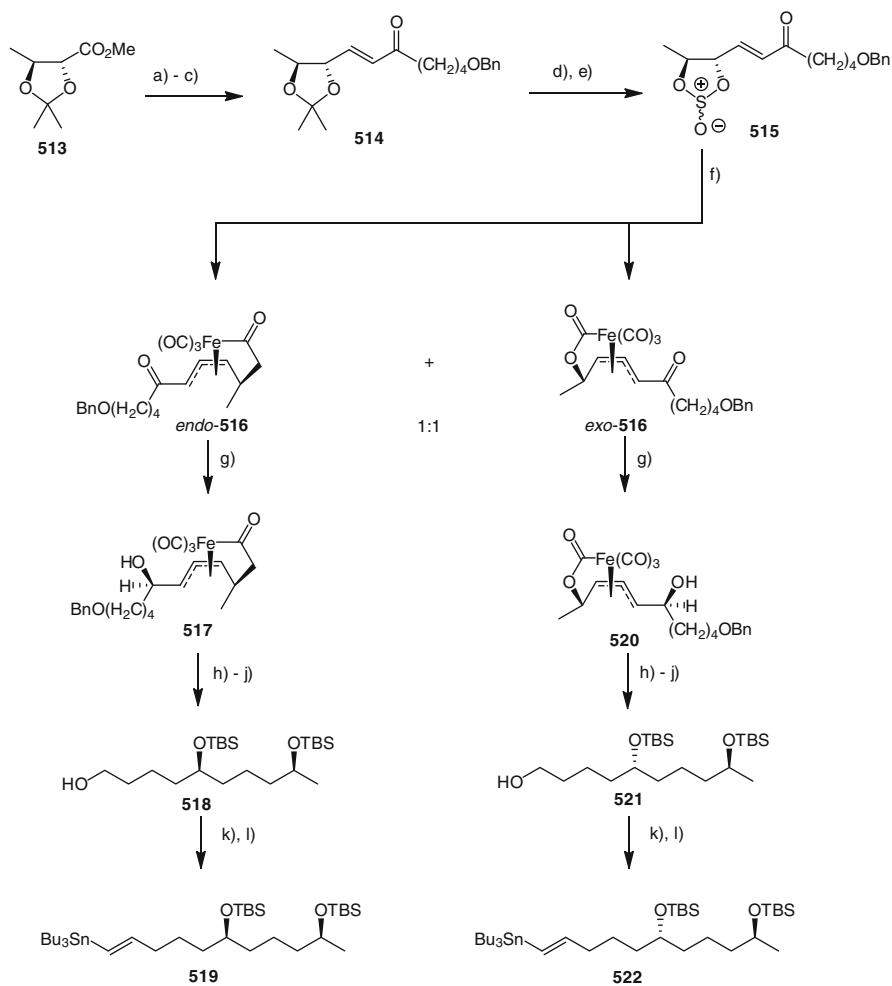


**Scheme 9.5** Total synthesis of (*S*)-zearealenone (**479**) by Barrett *et al.* Reagents and conditions: a) toluene, 110°C; b) KOMe, MeOH; c) HCl, MeOH; 82%; d) **512**, toluene, 80°C; e) toluene, 110°C, 2 h; f) Cs<sub>2</sub>CO<sub>3</sub>, MeOH, 12 h; g) Dowex 50WX8-400 resin, 24 h; h) **512**, toluene, 80°C, 24 h, 63%

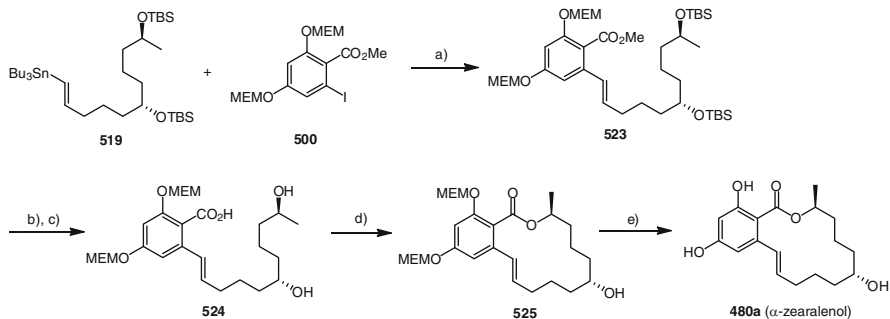
### 9.2.2 Total Synthesis of Zearealenol

One approach to the synthesis of zearealenol (**480**) is the reduction of zearealenone (**479**) (375). In 2000, an independent total synthesis of zearealenol was presented by Ley *et al.* (376). This enantioselective synthesis enables the preparation of both diastereomers, namely, naturally occurring  $\alpha$ -zearealenol (**480a**) as well as  $\beta$ -zearealenol (**480b**). Starting with reduction of ester **513**, Swern oxidation and subsequent Horner-Wadsworth-Emmons homologation led to (*E*)-olefin **514** (Scheme 9.6). The cyclic sulfite **515** was available through deprotection of the diol and ensuing treatment with thionyl chloride. Conversion with diironnonacarbonyl led to an equimolar mixture of the diastereomeric  $\pi$ -allyltricarbonyl iron complexes *endo*-**516** and *exo*-**516**, which could be smoothly separated. Following this, the stereogenic center was generated by reduction with tripropyl aluminum and ensuing decomplexation. Thus, protection and hydrogenation afforded the alcohols **518** and **521**, which were transformed into the stannanes **519** and **522**.

*Stille* coupling reaction of stannane **519** and aromatic iodide **500** led to precursor **523** (Scheme 9.7). Subsequent deprotection of both hydroxy groups and the carboxylic acid enabled macrolactonization using Mukaiyama conditions. Cleavage of the MEM-ethers finally provided  $\alpha$ -zearealenol (**480a**), while  $\beta$ -zearealenol (**480b**) could be obtained in the same way by starting from stannane **522**.



**Scheme 9.6** Synthesis of the stannanes **519** and **522** by *Ley et al.* Reagents and conditions: a)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$ , 2 h; b)  $(\text{COCl})_2$ , DMSO,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 3 h; c)  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}(\text{CH}_2)_4\text{OBn}$ , NaH, THF,  $-78^\circ\text{C}$ , 1 h, 83% (over three steps); d) AcOH/ $\text{H}_2\text{O}$  (1:1),  $40^\circ\text{C}$ , 24 h, 92%; e)  $\text{SOCl}_2/\text{Et}_3\text{N}$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$ , 30 min, 89%; f)  $\text{Fe}_2(\text{CO})_9$ , benzene, sonification,  $30^\circ\text{C}$ , 3 h, 70% (dr = 1:1); g)  $n\text{-Pr}_3\text{Al}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  94% (80%); h)  $\text{NaBH}(\text{OAc})_3$ , THF, 3 d, 75% (83%); i) TBSCl, imidazole, DMF,  $0^\circ\text{C}$ , 30 min; then rt, 24 h, 87% (85%); j) Pd/C,  $\text{H}_2$ , EtOAc, 30 min, 94% (93%); k) see (b), 86% (80%); l)  $\text{Bu}_3\text{SnCH}_2$ ,  $\text{CrCl}_2$ , DMF,  $0^\circ\text{C}$ , 67% (69%)



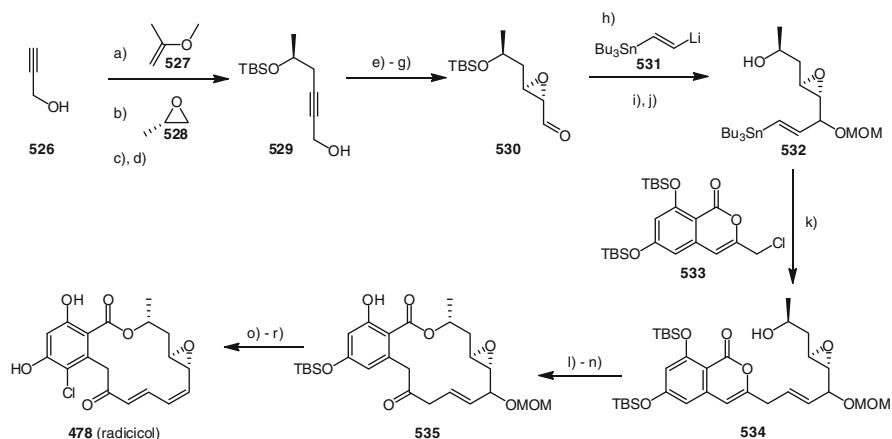
**Scheme 9.7** Synthesis of  $\alpha$ -zearalenol (**480a**) by Ley *et al.* Reagents and conditions: a) Pd<sub>2</sub>(dba)<sub>3</sub>, P(2-furyl)<sub>3</sub>, toluene, 100°C, 4 h, 82%; b) HF-pyridine, pyridine, THF, 12 h, 95%; c) 10 M aq. KOH, ethane-1,2-diol, 120°C, 4 h, 87%; d) syringe pump addition of a solution of **524**, Et<sub>3</sub>N, and MeCN over 10 h to 1-methyl-2-chloropyridinium iodide, MeCN, reflux, 64%; e) 1.5 M aq. HCl, THF, 40°C, 93%

### 9.2.3 Total Synthesis of Radicol

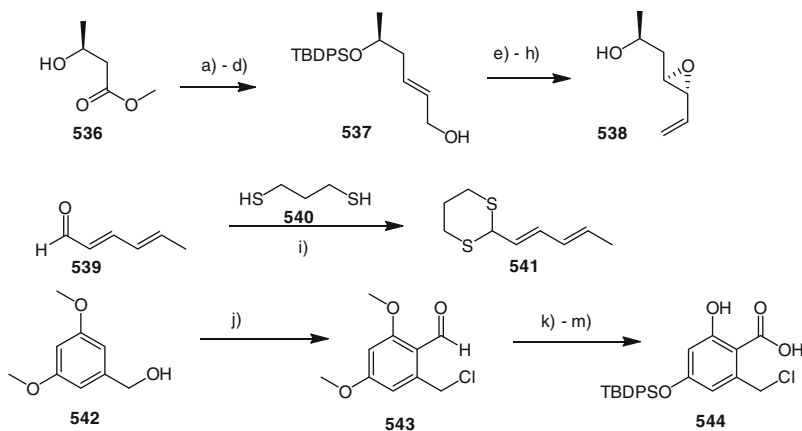
The first total synthesis of radicol (**478**) was published by Lett *et al.* in 1992 (377, 378) (Scheme 9.8). In this route, the stereogenic centers were constructed by reaction with (*S*)-propylene oxide (**528**) and by applying a Sharpless asymmetric epoxidation. Thus, aldehyde **530** could be generated, which was converted into stannane **532**. Subsequent Stille reaction with chloride **533** led to the coupling product **534**. After cleavage of this isocoumarin, affording also the deprotection of one alcohol, macrocyclization was successfully conducted using a Mitsunobu reaction, which resulted in precursor **535**. The formation of the conjugated diene was realized by the elimination of the methoxymethyl ether (OMOM), after renewed TBS protection. Chlorination and concluding deprotection furnished the natural product radicol (**478**).

Ten years later, this synthesis was improved by replacing the MOM group by a PMB protecting group, which could be smoothly removed and then exchanged for a mesylate (**379**). The following elimination of the mesylate proceeded easily and led to improved yields of the conjugated diene. Furthermore, the Stille coupling was substituted by a Miyaura-Suzuki coupling reaction in order to avoid the contamination by toxic tin organyls (**380**).

A further, modular route to radicol (**478**) was presented by Danishefsky *et al.* in 2001 (10, 381). Their synthesis started with the preparation of three key intermediates, **538**, **541**, and **544**, which then were joined together (Scheme 9.9). Horner-Wadsworth-Emmons homologation of the previously protected chiral ester **536** followed by reduction led to (*E*)-allylic alcohol **537**. Formation of the asymmetric epoxide was realized by applying Sharpless asymmetric epoxidation. Dienyl dithiane **541**, an acyl anion equivalent, was easily prepared from commercially available aldehyde **539** in one step. Beginning with the protected alcohol **542**, the third building block was obtained by formylation, ensuing conversion of the alcohol to the chloride, and closing with changing the protecting groups.

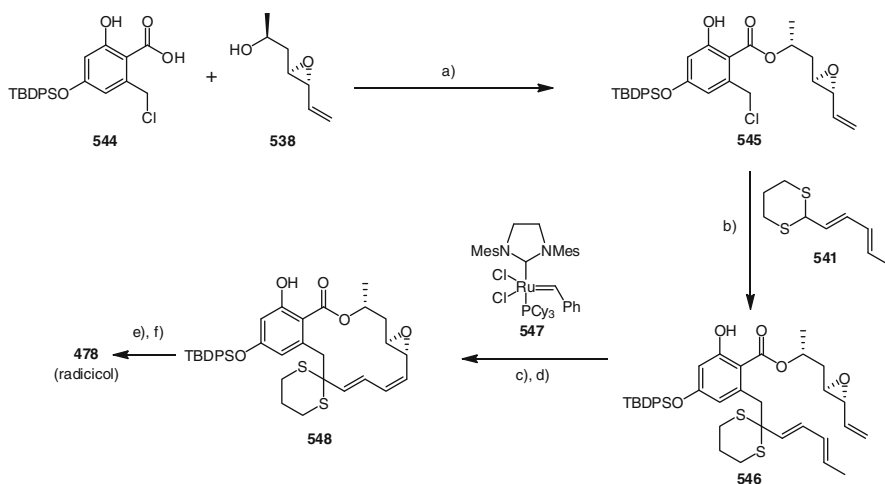


**Scheme 9.8** Synthesis of radicicol (**478**) by *Lett et al.* Reagents and conditions: a) **527**,  $\text{POCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C} - \text{rt}$ , 85%; b)  $\text{BuLi}$ , **528**,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ,  $-78^\circ\text{C}$ ; c)  $\text{TBSCl}$ , imidazole,  $\text{DMF}$ ,  $\text{rt}$ ; d) IRN 77,  $\text{MeOH}$ ,  $\text{rt}$  80% (over three steps); e)  $\text{LiAlH}_4$ ,  $\text{NaOMe}$ ,  $\text{THF}$ ,  $-10^\circ\text{C} - \text{rt}$ , 75%; f)  $\text{L-DET}$ ,  $t\text{-BuOOH}$ ,  $\text{Ti}(\text{O-}i\text{-Pr})_4$ ,  $\text{CH}_2\text{Cl}_2$ , 90%; g)  $(\text{COCl})_2$ ,  $\text{DMSO}$ ,  $\text{Et}_3\text{N}$ , 87%; h) **531**,  $-78^\circ\text{C}$ , 57%; i)  $\text{MOM-Cl}$ ,  $i\text{-Pr}_2\text{EtN}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{rt}$ , 92%; j)  $\text{TBAF}$ ,  $\text{THF}$ ,  $\text{rt}$ , 98%; k) **534**,  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ ,  $\text{PPh}_3$ ,  $\text{DME}$ , reflux, 75%; l)  $\text{DIBAL-H}$ ,  $\text{THF}$ ; m)  $\text{NaClO}_2$ ,  $\text{NaH}_2\text{PO}_4$ ,  $t\text{-BuOH}$ ,  $\text{pyridine}$ , 44%; n)  $\text{DEAD}$ ,  $\text{Ph}_3\text{P}$ ,  $\text{toluene}$ ,  $\text{rt}$ , 71%; o)  $\text{TBSCl}$ ,  $i\text{-Pr}_2\text{EtN}$ ,  $\text{DME}$ ,  $\text{rt}$ , 85%; p)  $\text{K}_2\text{CO}_3$ ,  $\text{DME}$ , reflux, 25%; q)  $\text{Ca}(\text{OCl})_2$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to  $\text{rt}$ ; r) borax,  $\text{MeOH}$ ,  $\text{THF}$ ,  $\text{rt}$



**Scheme 9.9** Syntheses of the building blocks **538**, **541**, and **544** by *Danishefsky et al.* Reagents and conditions: a)  $\text{TBDPSCl}$ , imidazole, <95%; b)  $\text{DIBALH}$ ,  $-78^\circ\text{C}$ , 92%; c)  $\text{LiCl}$ ,  $\text{DIPEA}$ ,  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$ , 95%; d)  $\text{DIBALH}$ ,  $-20^\circ\text{C}$ , 96%; e)  $(+)\text{-DET}$ ,  $\text{Ti}(\text{O-}i\text{-Pr})_4$ ,  $\text{TBHP}$ , 90%; f)  $\text{SO}_3 \cdot \text{pyridine}$ ,  $\text{Et}_3\text{N}$ ,  $\text{DMSO}$ , 90%; g)  $\text{Ph}_3\text{PCH}_2\text{Br}$ ,  $\text{NaHMDS}$ ,  $0^\circ\text{C}$ , 82%; h)  $\text{TBAF}$ , 89%; i) **540**,  $\text{MgClO}_4$ ,  $\text{H}_2\text{SO}_4$ , 64%; j)  $\text{POCl}_3$ ,  $\text{DMF}$ ,  $75^\circ\text{C}$ , 93%; k)  $\text{BBr}_3$ , 85%; l)  $\text{TBDPSCl}$ , 95%; m)  $\text{NaClO}_4$ , 95%

Next, the three building blocks were connected sequentially. Initial esterification was attempted *via* standard *Mitsunobu* conditions, which afforded poor results due to the formation of the undesired 2,4-phthalide. Nevertheless, esterification was achieved by the use of trifuryl phosphine and *diiso*-propyl azodicarboxylate, providing benzoic ester **545**. The ensuing addition of previously lithiated dithiane **541** led to the open chain precursor **546**. RCM under application of the *Grubbs* II catalyst **547** was successfully used to create the macrolide **548**. Removal of the dithiane and cleavage of the methyl ethers as well as subsequent regioselective aromatic chlorination completed this total synthesis of radicicol (**478**) (Scheme 9.10).

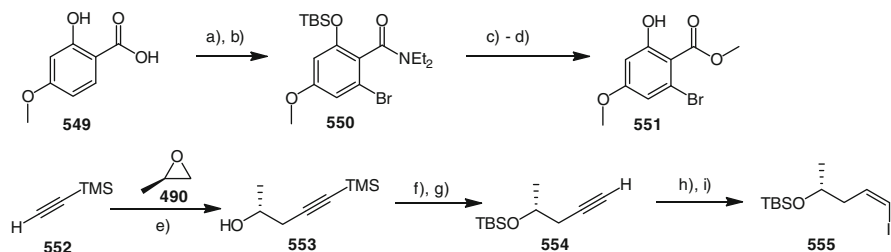


**Scheme 9.10** Syntheses of radicicol (**478**) by *Danishefsky et al.* Reagents and conditions: a)  $P(\text{fur})_3$ , DIAD, benzene, 24 h, 75%; b) **541**, *n*-BuLi,  $-78^\circ\text{C}$ , 50%; c) TBSCl, 88%; d) *Grubbs* II catalyst **547**,  $42^\circ\text{C}$ , 60%; e)  $\text{NaHCO}_3$ , MeOH, 60%; f)  $\text{SO}_2\text{Cl}_2$ , 58%

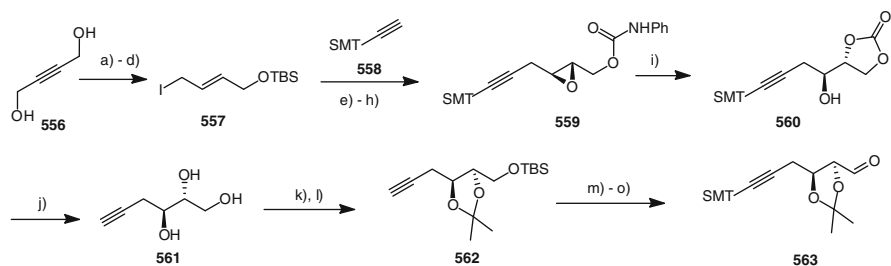
### 9.2.4 Total Synthesis of Hypothemycin

In 2002, *Lett et al.* published a convergent stereospecific synthesis of the resorcylic macrolactone LL-Z1640-2 (**567**) (Scheme 9.13) and hence hypothemycin (**481**) (382, 383). They started with the preparation of the three building blocks, **551**, **555** (Scheme 9.11), and **564** (Scheme 9.12). Methyl ester **551** was produced from 4-methoxysalicylic acid (**549**) in four steps. Reaction of alkyne **552** with enantiopure (*R*)-propylene oxide **490** afforded chiral alkyne **553**, which then was converted into (*Z*)-vinyl iodide **555**.

The two stereogenic centers of alcohol **560** were generated applying *Sharpless* asymmetric epoxidation following by carbonate-assisted epoxide opening (Scheme 9.12). Hydrolysis of the carbonate, which involved the deprotection of the terminal alkyne, led to triol **561**. After specific protection of the primary alcohol, acetone formation resulted in



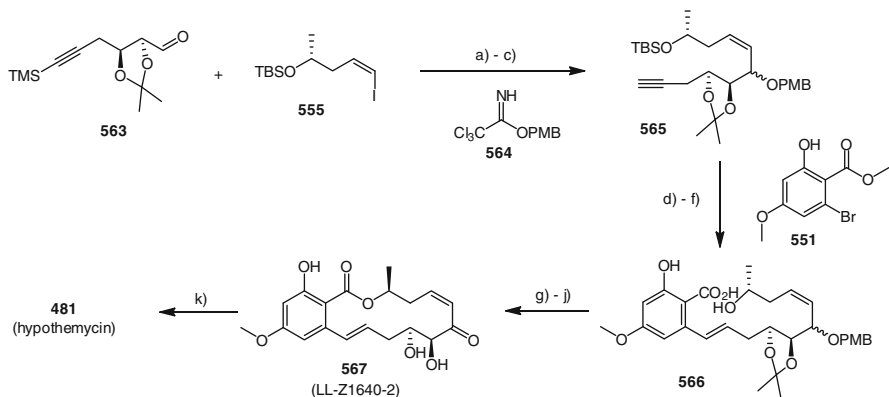
**Scheme 9.11** Syntheses of the aromatic part **551** and the iodide **555** by *Lett et al.* Reagents and conditions: a)  $\text{Et}_2\text{NAlMe}_2$  from  $\text{Me}_3\text{Al}$  and  $\text{Et}_2\text{NH}$ , toluene,  $-6^\circ\text{C}$  to rt, 45 min; then bis-OTBS, reflux, overnight, 98%; b) *t*-BuLi (pentane),  $\text{Et}_2\text{O}$ ,  $-78^\circ\text{C}$ , 10 min; then  $\text{Br}_2$ , 75%; c)  $\text{Me}_3\text{O}^+ \text{BF}_4^-$ ,  $\text{CH}_2\text{Cl}_2$ , rt, overnight; then evaporation, 76%; d) aq. satd.  $\text{Na}_2\text{CO}_3/\text{MeOH}$  (1/1), rt, 6 h; e)  $\text{Et}_2\text{O}$ ,  $-78^\circ\text{C}$ , *n*-BuLi, 30 min; then **553**, and further addition of  $\text{BF}_3\cdot\text{Et}_2\text{O}$ , 50 min,  $-78^\circ\text{C}$ , 89%; f) TBSCl, imidazole, DMF, rt; g)  $\text{K}_2\text{CO}_3$ , MeOH, rt, 5 h, 86% (over two steps); h) *n*-BuLi, THF, hexane,  $-78^\circ\text{C}$ , 15 min; then  $\text{I}_2$ , THF, 86%; i)  $\text{Si}_2\text{BH}$ , THF,  $-20^\circ\text{C}$  to  $0^\circ\text{C}$ , 3 h; then AcOH,  $65^\circ\text{C}$ , 3 h



**Scheme 9.12** Synthesis of the building block **563** by *Lett et al.* Reagents and conditions: a) Red-Al<sup>®</sup>, toluene, THF,  $0^\circ\text{C}$  to rt, overnight, 81%; b) NaH, THF, rt, 1 h; then  $-78^\circ\text{C}$ , TBSCl, 36 h, 74%; c) MsCl,  $\text{NEt}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-10^\circ\text{C}$  to rt, 30 min; d) NaI, acetone, rt, 1 h; e) **558**, THF, *n*-BuLi,  $-78^\circ\text{C}$ , 30 min; then **557** and HMPA, rt, 4 h, 90%; f) DDQ, MeCN/ $\text{H}_2\text{O}$  (9/1), rt, 2 h, 74%; g)  $\text{Ti}(\text{O}i\text{-Pr})_4$ , (+)-DET,  $\text{CH}_2\text{Cl}_2$ , *t*-BuOOH,  $-25^\circ\text{C}$ , overnight, 85%; h)  $\text{PhNCO}$ ,  $\text{CH}_2\text{Cl}_2$ , pyridine, rt, 1 h; i)  $\text{BF}_3\cdot\text{Et}_2\text{O}$ ,  $\text{Et}_2\text{O}$ ,  $-20^\circ\text{C}$ , 2 h; then 1 M  $\text{H}_2\text{SO}_4$ , rt, overnight, 91%; j) MeONa, MeOH, rt, 8 h; then Dowex 50 WX8 column eluted by MeOH, 93%; k) TBSCl, imidazole, DMF, rt, 1 h; l) 2-methoxypropene, cat. TsOH,  $\text{CH}_2\text{Cl}_2$ , rt, 1 h; m) *n*-BuLi (*n*-hexane),  $\text{Et}_2\text{O}$ ,  $-30^\circ\text{C}$ , 30 min; then TMSCl,  $-30^\circ\text{C}$  to  $-10^\circ\text{C}$ , 98%; n) DDQ, MeCN/ $\text{H}_2\text{O}$  (9/1), rt, 2 h, 73%; o) oxalyl chloride, DMSO,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 30 min; then product of (n), 30 min,  $\text{NEt}_3$ ,  $-78^\circ\text{C}$  to  $0^\circ\text{C}$

**562**. Then, aldehyde **563** was obtained by reprotection of the alkyne with subsequent selective cleavage of the TBS ether and *Swern* oxidation.

Next, the building blocks were coupled (Scheme 9.13). Transmetalation of vinyl iodide **555**, followed by reaction with aldehyde **563** gave a product mixture of two diastereomeric alcohols. Deprotection of the alkyne with ensuing protection of the alcohol afforded compound **565**. The open chain precursor **566** was obtained using a *Suzuki* coupling of bromide **551** with the vinyldisiamylborane, which was prepared *in situ*, followed by deprotection of the alcohol and the carboxylic acid. Once again, *Mitsunobu* macrocyclization was applied to obtain the macrolide. After



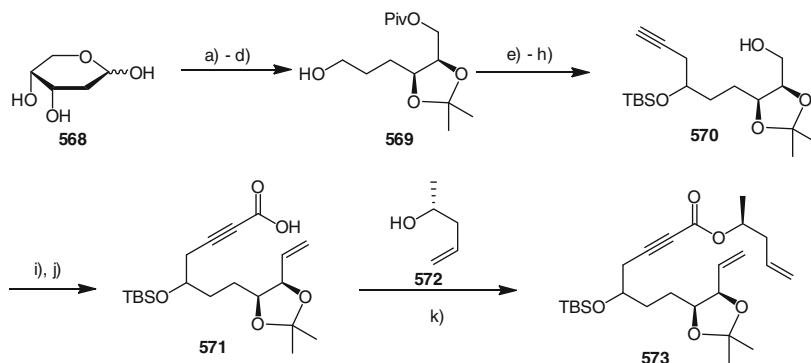
**Scheme 9.13** Syntheses of LL-Z1640-2 (**567**) and hypothemycin (**481**) by *Lett et al.* Reagents and conditions: a) **563**, Et<sub>2</sub>O, -78°C; then *t*-BuLi (*n*-pentane), 15 min; then addition of **555** in pentane, -78°C to 0°C, 77%; b) K<sub>2</sub>CO<sub>3</sub>, MeOH, rt, 5 h, 74%; c) **564**, Et<sub>2</sub>O, TfOH, rt, 4 h, 31%; d) Sia<sub>2</sub>BH, THF, -25°C to rt, 2 h; then aq. 2 M K<sub>2</sub>PO<sub>3</sub>; then addition of that mixture to a solution of **551** and Pd(OAc)<sub>2</sub>, Fu<sub>3</sub>P in DME, DME/H<sub>2</sub>O (7/1), reflux, 8 h, 71%; e) TBAF 1 M/THF, rt, 6 h, 93%; f) 2 M aq. NaOH/MeOH (1/3), reflux, overnight, 71%; g) PPh<sub>3</sub>, DEAD, cat. hydroxy acid, toluene, rt, 15 min, 67%; h) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/pH 7 buffer (9/1), rt, 30 min, 94%; i) PCC, 2,5-DMP, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 6 h, 62%; j) *p*-TsOH, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1/1), rt, 3.5 h, 76%; k) *m*-CPBA/NaHCO<sub>3</sub>, -20°C to 0°C, 4 h, 17%

removal of the PMB group, oxidation of the alcohol and deprotection of the diol, **567** (LL-Z1640-2) was obtained, which is also a known RAL. The final diastereoselective epoxidation of LL-Z1640-2 (**567**) afforded hypothemycin, albeit in poor yield.

A further synthesis of hypothemycin (**481**) was published by the group of *Winssinger* in 2009 (384). They used a partial solid-phase strategy with a benzylic sulfide linker to build up the resorcylic macrolactone. The applied macrolactonization step proceeded extremely efficiently and epoxidation of LL-Z1640-2 (**567**) with dimethyldioxirane afforded hypothemycin with excellent regio- and stereoselectivity, but in a poor yield.

## 9.2.5 Total Synthesis of Aigialomycin D

After the isolation of the aigialomycins in 2002 (344), only two years later *Danishefsky* and co-workers published the first total synthesis of aigialomycin D (**482**) (385). Their synthesis strategy is denoted by a late-state aromatization via *Diels-Alder* cyclization. Starting with readily available D-2-deoxyribose (**568**), alcohol **569** was obtained by protection of the diol, subsequent *Wittig* reaction, formation of the pivaloyl ether, and concluding hydroboration with oxidative workup (Scheme 9.14). Oxidation of the primary alcohol to aldehyde with a subsequent propargylation, led, after protection and deprotection, to alkyne **570**.



**Scheme 9.14** Synthesis of diene **573** by *Danishefsky et al.* Reagents and conditions: a) 2-methoxypropene, *p*-TsOH, DMF, 3 h, 62%; b) KHMDS,  $\text{PhP}^+\text{CH}_3\text{I}^-$ , THF,  $-78^\circ\text{C}$  to rt, 68%; c) PivCl,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ , 10 h, 90%; d) 9-BBN, THF,  $0^\circ\text{C}$  to rt, 4 h; then NaOH,  $\text{H}_2\text{O}_2$ ,  $\text{H}_2\text{O}$ , 2.5 h, 88%; e)  $\text{SO}_3\text{-Py}$ , DMSO,  $\text{CH}_2\text{Cl}_2$ ,  $\text{Et}_3\text{N}$ ,  $0^\circ\text{C}$ , 1 h; f) propargyl bromide, zinc, THF,  $0^\circ\text{C}$ , 2 h; g) TBSOTf, 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ , 10 h, 89% from **569**; h) NaOMe/MeOH, 10 h, 88%; i)  $\text{SO}_3\text{-Py}$ , DMSO,  $\text{CH}_2\text{Cl}_2$ ,  $\text{Et}_3\text{N}$ ,  $0^\circ\text{C}$ , 2 h; then KHMDS,  $\text{PhP}^+\text{CH}_3\text{I}^-$ , THF,  $-78^\circ\text{C}$  to rt, 10 h, 86% (over two steps); j) BuLi, dry ice,  $-78^\circ\text{C}$  to rt, 2 h; k) **572**, DIAD,  $\text{PPh}_3$ , toluene, 10 h, 85% (over two steps)

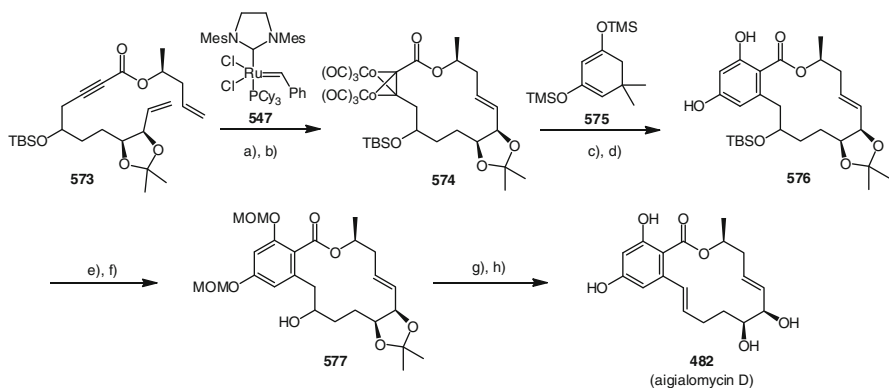
Afterwards, the implementation of a vinyl group as well as carboxylation of the ethynyl group resulted in carboxylic acid **571**, which was esterified with chiral alcohol **572** under *Mitsunobu* conditions.

After masking of the alkyne function by a dicobalthexacarbonyl complex, RCM was used to cyclize the diene **573** (Scheme 9.15). Then, decomplexation enabled a *Diels-Alder* reaction with the disiloxydiene **575**, ensued by elimination of *iso*-butylene. Two hydroxy groups of the resorcylic macrolide (**576**) obtained were protected and the TBS-ether was cleaved. Thus, dehydration with concluding deprotection of all alcohol functions furnished aigialomycin D (**482**), in an overall yield of 8%.

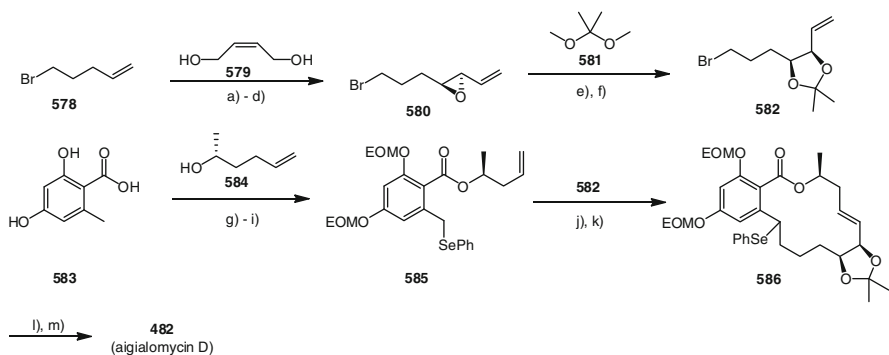
Two years later, *Winssinger* and co-workers reported on another synthesis of aigialomycin D and analogues (386). A key point of this synthesis is the application of a selenoether at the benzylic position, which was thought to facilitate subsequent alkylation at this position. As shown in Scheme 9.16, this synthesis started with the preparation of the acetonide-protected diol **582**, which was built up in six steps from bromide **578**. *Mitsunobu* esterification of orseillinic acid (**583**) with (*R*)-penten-2-ol (**584**) was followed by the protection of the hydroxy groups. Subsequent implementation of the selenoether afforded precursor **585**. After addition of the protected diol **582**, RCM led to macrolide **586**.  $\text{H}_2\text{O}_2$  was used to oxidize and eliminate the selenide. Concluding cleavage of the acetonide and of both EOM ethers thus furnished aigialomycin D (**482**). Moreover, *Winssinger et al.* developed a solid-phase synthesis by replacing the selenide with a polymer-bound thioether, which was as efficient as solution-phase synthesis.

Further syntheses of aigialomycin D (**482**) were published by the groups of *Pan* and *Harvey* (387, 388). The synthesis route of *Pan et al.* includes a *Sharpless*





**Scheme 9.15** Synthesis of aigialomycin D (**482**) by *Danishefsky et al.* Reagents and conditions: a)  $\text{Co}_2(\text{CO})_8$ , toluene, 30 min, 94%; b) *Grubbs* II catalyst **547**,  $\text{CH}_2\text{Cl}_2$ , 10 h, 80%; c) CAN, acetone,  $-10^\circ\text{C}$ , 15 min, 95%; d) **575**,  $140^\circ\text{C}$ , 36 h, 79%; e) MOMCl, DIPEA,  $\text{CH}_2\text{Cl}_2$ , 10 h, 81%; f) HF-pyridine, pyridine, THF, 10 h, 83%; g)  $[\text{PhC}(\text{CF}_3)_2\text{O}]_2\text{SPh}_2$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to rt, 2 h, 87%; h) 0.5 M HCl,  $\text{H}_2\text{O}/\text{MeOH}$ , 2 d, 69%

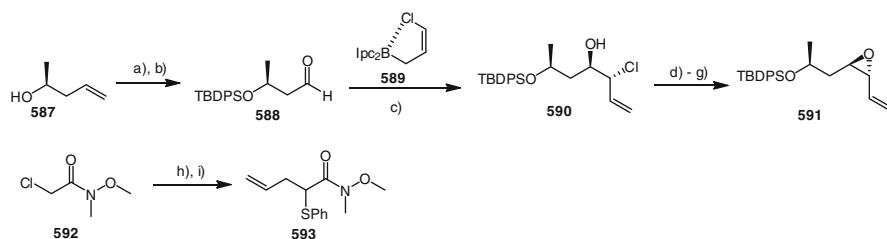


**Scheme 9.16** Synthesis of aigialomycin D (**482**) by *Winssinger et al.* Reagents and conditions: a) **579**, *Hoyveda-Grubbs* catalyst II,  $\text{CH}_2\text{Cl}_2$ ,  $23^\circ\text{C}$ , 4 h, 97%; b) L-DET,  $\text{Ti}(\text{O}i\text{-Pr})_4$ , *t*-BuOOH,  $\text{CH}_2\text{Cl}_2$ ,  $-40^\circ\text{C}$ , 30 min; then allyl alcohol,  $-24^\circ\text{C}$ , 12 h, 85%; c)  $\text{SO}_3$ -pyridine,  $\text{CH}_2\text{Cl}_2/\text{DMSO}$ ,  $0^\circ\text{C}$ , 30 min; d)  $\text{PH}_3\text{P}=\text{CH}_2$ , THF,  $-10^\circ\text{C}$ , 10 min, 70% (over two steps); e)  $\text{Sc}(\text{OTf})_3$ , THF/ $\text{H}_2\text{O}$ ,  $23^\circ\text{C}$ , 2.5 h, quant; f) dimethoxypropane,  $\text{TsOH}\cdot\text{H}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $23^\circ\text{C}$ , 12 h, 70%; g) PS-DEAD, **584**, *m*-Cl $\text{Ph}_3\text{P}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $23^\circ\text{C}$ , 0.5 h, 83%; h) DIPEA, EOMCl, TBAI, DMF,  $80^\circ\text{C}$ , 5 h, 95%; i) LDA, THF,  $-78^\circ\text{C}$ ; then  $(\text{PhSe})_2$ , 2 h, 75%; j) LDA, **582**, THF/HMPA,  $-78^\circ\text{C}$ , 20 min, 75%; k) *Grubbs* II catalyst, toluene,  $80^\circ\text{C}$ , 12 h, 92%; l)  $\text{H}_2\text{O}_2$ , THF,  $23^\circ\text{C}$ , 3 h, 85%; m) PS- $\text{SO}_3\text{H}$ , MeOH,  $50^\circ\text{C}$ , 2 h, quant

asymmetric epoxidation to generate both stereogenic centers of the diol, a *Julia-Kocienski* reaction to build up the two (*E*)-configured double bonds as well as a *Yamaguchi* macrolactonization. A key feature of the total synthesis by *Harvey* was the combination of a *Ramberg-Bäcklund* reaction and a ring-closing metathesis.

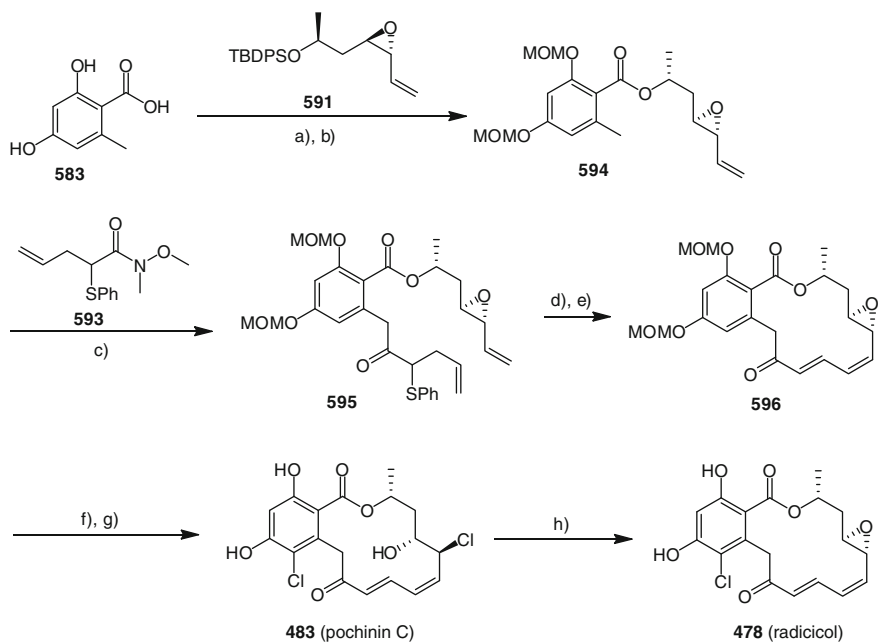
### 9.2.6 Total Synthesis of Pochonin C

In 2004, the group of *Winssinger* presented a modular synthesis of pochonin C (**483**) (389). They partitioned the target compound into three parts, which were then linked. The first key intermediate, epoxide **591**, could be synthesized in seven steps from alcohol **587** (Scheme 9.17). Silyl protection of the hydroxy group followed by ozonolysis led to aldehyde **588**, which was converted to halohydrin **590** via a modified *Brown* allylation. A  $S_N2$  reaction with thiophenol was used to invert the configuration of chloride **590**, revealing *trans*-epoxide **591** in another three steps. The second building block, *Weinreb* amide **593** was obtained smoothly from chloride **592** by reaction with thiophenol and ensuing allylation.



**Scheme 9.17** Synthesis of the building blocks **591** and **593** by *Winssinger et al.* Reagents and conditions: a) TBDPSCl, imidazole,  $\text{CH}_2\text{Cl}_2$ ,  $23^\circ\text{C}$ , 4 h, 98%; b)  $\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 5 min,  $\text{Ph}_3\text{P}$ ,  $23^\circ\text{C}$ , 2 h, 94%; c) allyl chloride,  $\text{LiNcHex}_2$ ,  $\text{IpcBOMe}$ ,  $\text{BF}_3\text{OEt}_2$ ,  $-97^\circ\text{C}$ , 4 h, 68%; d) thiophenol, *t*-BuOK,  $23^\circ\text{C}$ , 1 h; then **590**, DMF,  $0^\circ\text{C}$  to  $23^\circ\text{C}$ , 86%; e)  $\text{Me}_3\text{OBF}_4$ ,  $\text{CH}_2\text{Cl}_2$ ; f) DBU,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 4 h, 80% (two steps); g) TBAF, THF,  $23^\circ\text{C}$ , 6 h, 98%; h) PhSH,  $\text{K}_2\text{CO}_3$ , DMF,  $23^\circ\text{C}$ , 98%; i) LDA, HMPA, allyl bromide, THF,  $-78^\circ\text{C}$  to  $23^\circ\text{C}$ , 3 h, 82%

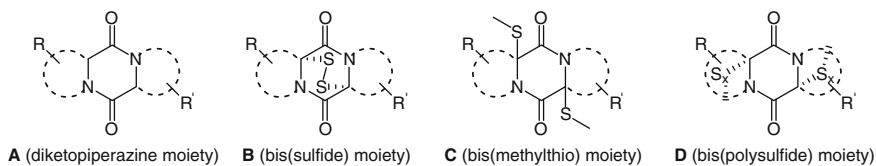
Modified *Mitsunobu* conditions were also used to connect the third part, orsellinic acid (**583**), to epoxide **591**. After MOM protection of both phenols, deprotonation with subsequent addition of *Weinreb* amide **593** afforded the precursor **595**. Oxidation and ensuing elimination of the thioether, followed by RCM led to diene **596**. The aromatic chlorination as well as the stereoselective opening of the epoxide proceeded in a single step by treatment with sulfonyl chloride. Thus, cleavage of the MOM ethers, gave the desired RAL, pochonin C (**483**). *Winssinger et al.* also presented the conversion of pochonin C (**483**) into radicicol (**478**) by treatment with potassium carbonate (Scheme 9.18).



**Scheme 9.18** Synthesis of the pochinin C (**483**) and radicicol (**478**) by *Winssinger et al.* Reagents and conditions: a) **591**, P(*m*-ClC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>, DIAD, toluene, 23°C, 3 h, 84%; b) MOMCl, DIPEA, TBAI (cat.), DMF, 80°C, 3 h, 91%; c) LDA, THF, -78°C, **593**, 81%; d) H<sub>2</sub>O<sub>2</sub>, (CF<sub>3</sub>)<sub>2</sub>CHOH, 23°C, 3 h; then toluene 80°C, 1 h, 92%; e) *Grubbs* II catalyst, toluene, 120°C, 10 min, 87%; f) SO<sub>2</sub>Cl<sub>2</sub>, Et<sub>2</sub>O, 0°C, 68%; g) HCl, 23°C, 3 h, 74%; h) K<sub>2</sub>CO<sub>3</sub>, DMF, 23°C, 1 h, 86%

## 10 (Thio)diketopiperazines

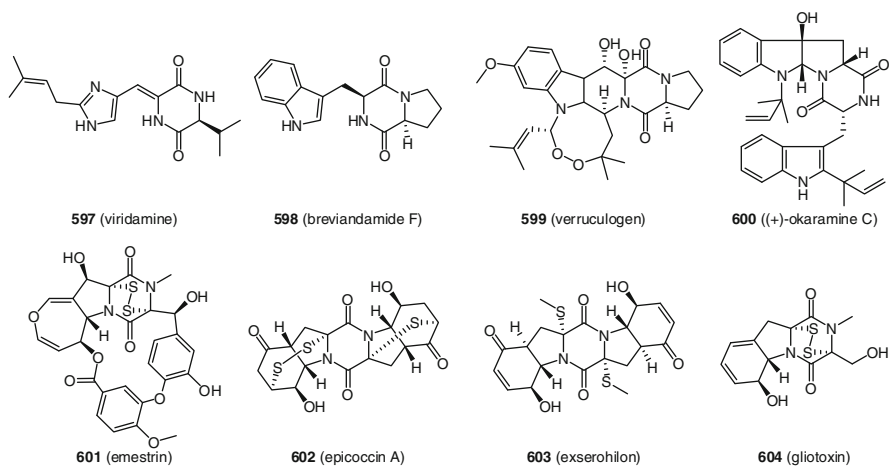
The smallest cyclic peptides built from amino acids are the so-called diketopiperazines (DKP). In recent research, the DKPs and higher functionalized analogs – the thiodiketopiperazines (TDKP) – have become attractive due to their broad biological activity (390). The DKP or TDKP moiety can be found in a great variety of mycotoxins. Both DKPs and TDKPs can, for example, be isolated from *Aspergillus*, *Candida*, *Chaetomium*, *Gliocladium*, *Penicillium*, and *Verticillium* species (7, 390). The most common structural motifs **A–D** of this class of compounds are depicted in Fig. 10.1. Many of these natural products show  $C_2$  symmetry, which means they consist of two identical amino acids ( $R = R'$  in Fig. 10.1).



**Fig. 10.1** General structural motifs of DKPs (**A**), bis(sulfide)- TDKPs (**B**), bis(methylthio) TDKPs (**C**), bis(polysulfide) TDKPs (**D**)

To date, a large number of different DKPs and TDKPs have been isolated and characterized. Selected examples are shown in Fig. 10.2 (391–399).

(+)-Okaramine **C** (**600**) can be isolated from extracts of *Penicillium simplicissimum* and *Aspergillus aculeatus* that grow on okara, which is a soybean



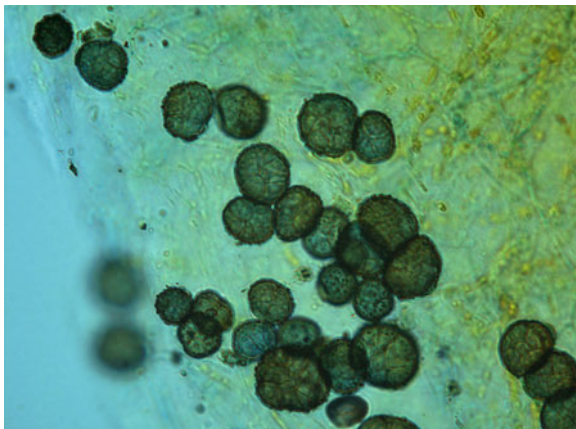
**Fig. 10.2** Selected DKPs (top) and TDKPs (bottom): viridamine (**597**), brevianamide F (**598**), verruculogen (**599**), (+)-okaramine C (**600**), emestrin (**601**), epicoccin A (**602**), exserohilon (**603**), and gliotoxin (**604**)

residue from soymilk production (Fig. 10.3 (400)). Okaramine C (**600**) and okaramines N and J possess insecticidal properties.



**Fig. 10.3** Okara or soy pulp is part of traditional Japanese, Korean, and Chinese cuisines and can be infected with the mycotoxin okaramine C (**600**)

Epicoccin A (**602**) was isolated from *Epicoccum nigrum* among several other epicoccins (B–P) (397, 401, 402) (Fig. 10.4 (403)). This class of mycotoxins is of great interest due to the bis(polysulfide) moiety and due to their antimicrobial effects.



**Fig. 10.4** *Epicoccum nigrum* under a light microscope (400-fold magnification)

Exserohilon (**603**) can be found in *Exserohilum rostratum* together with rostratins A–D (**398**) (Fig. 10.5 (404)). These mycotoxins exhibit *in vitro* cytotoxicity against the HCT-166 human colon cancer cell line (405).



**Fig. 10.5** *Exserohilum rostratum*

## 10.1 Biological Properties

Due to the great structural variety of DKP and TDKP mycotoxins, no general type of biological activity for this class of compounds can be defined. To name a few properties of this family of compounds, they have shown *e.g.* antibacterial, antifungal, antihyperglycemic, antimycotic, antitumor, antiviral, cytotoxic, and immunosuppressive effects (8). The DKPs are interesting targets for medicinal chemists since they mimic peptidic pharmacophoric groups. They can be synthesized readily with a great structural diversity from amino acid derivatives and are resistant to

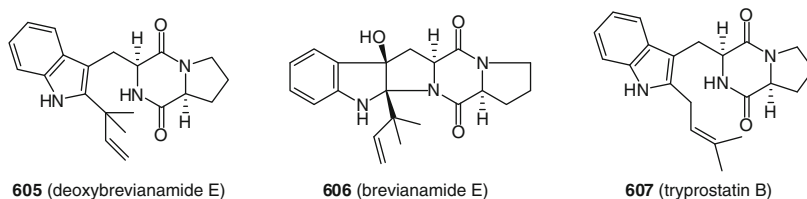
proteolysis (406). The biological properties of TDKPs can be attributed to their sulfur bridge, because the activities of these compounds decrease after its removal. One proposed mechanism is conjugation with proteins, *i.e.* with cysteine residues therein. Another theory is the production of reactive oxygen species (ROS) through a redox process between the reduced (dithiol) and oxidized (disulfide) form of TDKPs (390).

## 10.2 Total Syntheses

To date, only a few examples of the total syntheses of the large family of (T)DKPs are known. In particular, the introduction of a sulfur bridge to obtain TDKPs remains a challenge (407). After the first total synthesis in 1981 of a TDKP, gliotoxin, by *Kishi et al.* (408), it took almost 30 years until additional compounds of this type were synthesized, in and after 2009 (see Sect. 10.2.2). Selected examples of (T)DKP total syntheses will be presented in the next two sections (10.2.1 and 10.2.2).

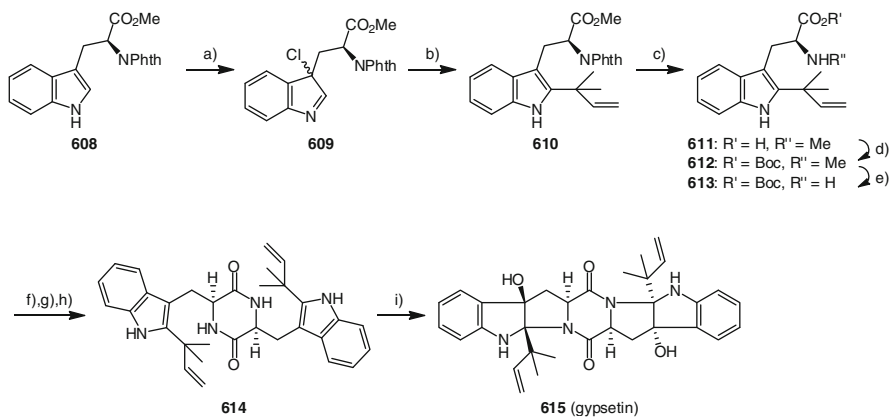
### 10.2.1 DKP Total Syntheses

In 1999, *Danishefsky et al.* published the total synthesis of the acetyl-CoA-cholesterol acyltransferase inhibitor gypsetin (**615**) (Scheme 10.1) as well as of the related mycotoxins deoxybrevianamide E (**605**), brevianamide E (**606**), and tryprostatin B (**607**) (Fig. 10.6) (409).



**Fig. 10.6** Structure of the mycotoxins deoxybrevianamide E, brevianamide E, and tryprostatin B

The starting material for this synthesis (Scheme 10.1) was *N*-phthaloyl-tryptophan methyl ester (**608**), which can be prepared from *L*-tryptophan methyl ester according to ref. (410).



**Scheme 10.1** Synthesis route to gypsetin (**615**). Reagents and conditions: a) *t*-butylhypochlorite, Et<sub>3</sub>N, THF, -78°C, 30 min; b) prenyl-9-BBN, -78°C, 6 h, 95%; c) NH<sub>2</sub>NH<sub>2</sub>, EtOH, rt, 3 d, 65%; d) (Boc)<sub>2</sub>O, Et<sub>3</sub>N, THF, 1 h, quant; e) LiOH/THF/MEOH/H<sub>2</sub>O, rt, 3 h, quant; f) **613**, BOP-Cl, CH<sub>2</sub>Cl<sub>2</sub>, -78°C to 0°C, 1 h; g) TFA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; h) NH<sub>3</sub>, MeOH, reflux, 12 h, 73% from **613**; i) dimethyldioxirane, CH<sub>2</sub>Cl<sub>2</sub>/acetone, -78°C to 0°C, 40%

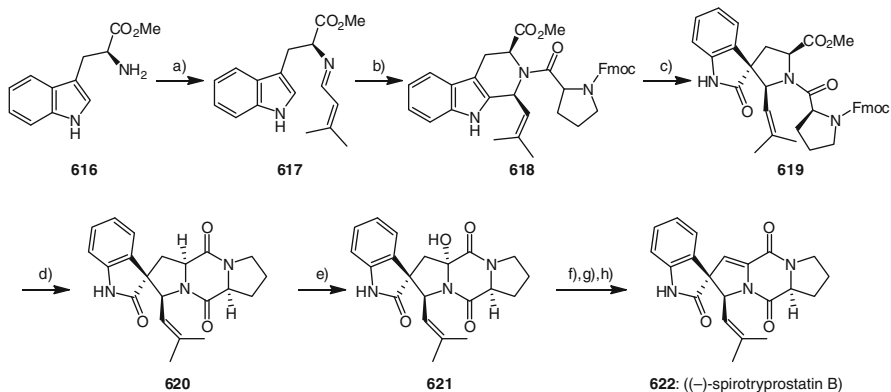
The authors assumed that the reaction of tryptophan derivative **608** with *t*-butylhypochlorite and base led to the formation of the unstable product **609**. Treatment of this intermediate with prenyl-9-BBN gave compound **610** in very good yield. Removal of the phthalimide-protecting group with hydrazine led to **611**. Introduction of the Boc-protecting group (→ **612**) followed by saponification of the methyl ester furnished derivative **613**. Coupling of this compound to **611** was accomplished with the use of BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphonic chloride) as activating agent. Removal of the Boc-protecting group, followed by ammonia-catalyzed cyclization, yielded diketopiperazine **614**. Oxidative conversion with dimethyldioxirane finally furnished the natural product gypsetin (**615**).

*Ganesan et al.* reported the total synthesis of the cell cycle inhibitor (–)-spirotryprostatin B (**622**) in 2000 (411). Their synthesis started with L-tryptophan methyl ester **616**, which was treated with senecialdehyde to give imine **617**. The indole derivative reacted in a *N*-acyl-iminium *Pictet-Spengler* condensation to yield the tetrahydro-β-carboline derivative **618** (412) (Scheme 10.2).

After NBS oxidation (→ **619**), Fmoc-deprotection led to dihydrospirotryprostatin B (**620**). A phenylselenylation reaction yielded **621** and a small amount of **622** among many side products. Compound **621** could be converted to spirotryprostatin B (**622**) by consecutive Boc-protection, elimination, and Boc-deprotection in good yields. This synthesis route is not an efficient strategy for the preparation of the natural product **622**, but gives a versatile method for the rapid synthesis of its analogs.

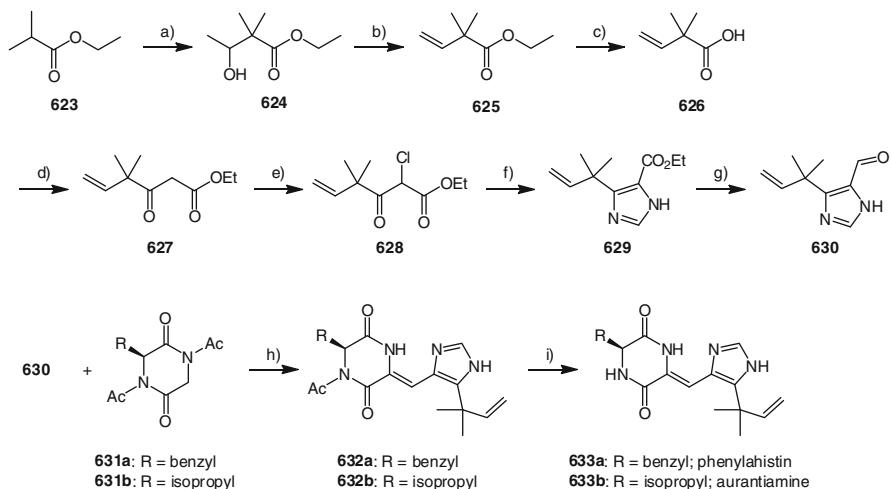
In 2000, two further diketopiperazine derivatives, the anti-microtubule compounds phenylahistin (**633a**) and aurantiamine (**633b**), were synthesized by *Hayashi et al.* (413). Their synthesis started with the aldol reaction of ethyl *iso*-





**Scheme 10.2** Total synthesis of (–)-spirotryprostatin B (**622**). Reagents and conditions: a)  $(\text{CH}_3)_2\text{C}=\text{CH}\text{-CHO}$ ,  $\text{HC}(\text{OMe})_3$ ; b) Fmoc-L-Pro-Cl, pyridine,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 1 h; then rt 6.5 h; c) NBS,  $\text{THF}/\text{AcOH}/\text{H}_2\text{O}$  (1/1/1),  $0^\circ\text{C}$ , 5 min; then rt, 12 min, 68%; d) 20% piperidine in  $\text{CH}_2\text{Cl}_2$ , rt, 12 min, quant; e) LDA,  $-75^\circ\text{C}$ , 40 min; then  $\text{PhSeBr}$ ,  $-78^\circ\text{C}$ , 1 h, 7% (+ 3% **622**); f)  $\text{Boc}_2\text{O}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ , rt, 5 h; g)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 70% over two steps; h) TFA,  $\text{Et}_3\text{SiH}$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 15 min, 74%

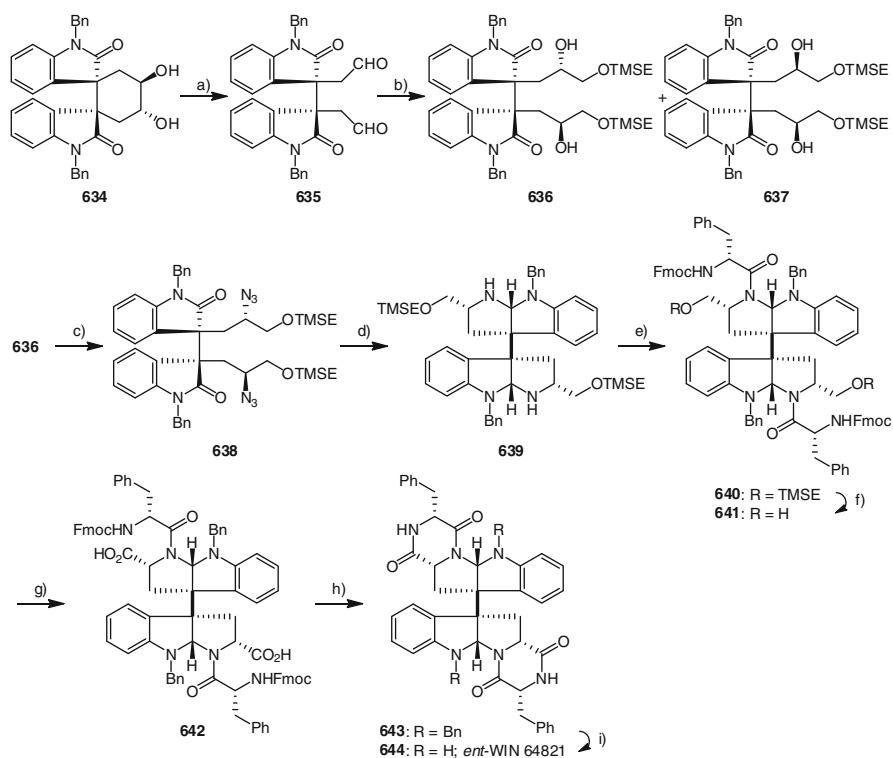
butyrate (**623**) with acetaldehyde in the presence of LDA ( $\rightarrow$  **624**), followed by elimination with *p*-tosyl chloride, to give unsaturated ester **625** (Scheme 10.3).



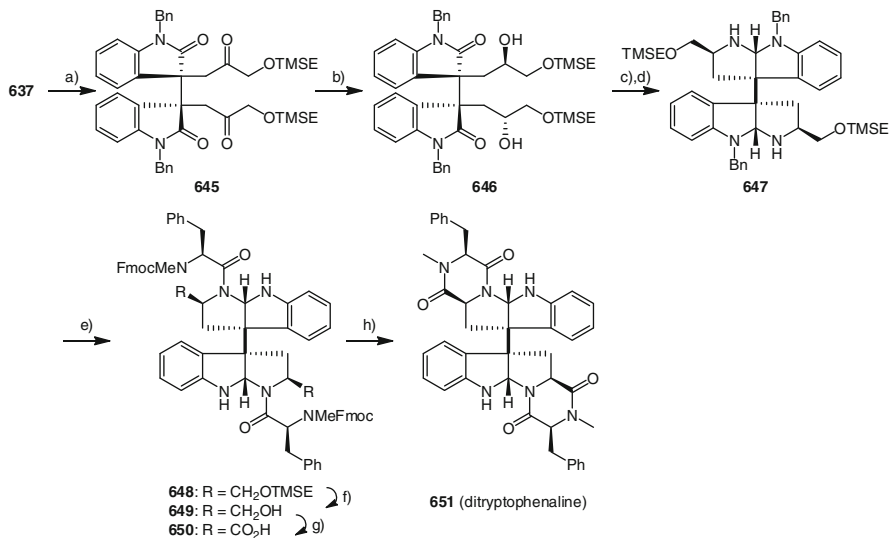
**Scheme 10.3** Total synthesis of phenylahistin (**633a**) and aurantiamine (**633b**) (413). Reagents and conditions: a) LDA,  $\text{CH}_3\text{CHO}$ , THF,  $-70^\circ\text{C}$ , 88%; b) *p*-Ts-Cl, pyridine, rt, 88%; then DBU, reflux, 96%; c)  $\text{NaOH}$  (aq.), EtOH, rt, 99%; d)  $\text{SOCl}_2$ , reflux; then  $\text{EtOCOCH}_2\text{COOH}$ , BuLi, THF,  $-70^\circ\text{C}$  to  $-10^\circ\text{C}$ , 85% over two steps; e)  $\text{SO}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ , reflux, 77%; f) formamide,  $\text{H}_2\text{O}$ , reflux, 48%; g) DIBAL-H, toluene,  $-30^\circ\text{C}$ , 50%; then  $\text{MnO}_2$ , acetone; rt, 95%; h)  $\text{Cs}_2\text{CO}_3$ , DMF, rt; i) 28%  $\text{NH}_4\text{OH}$ , rt; then enantioselective HPLC, 7% over two steps (**633a**), 20% over two steps (**633b**)

Saponification of **625** and treatment with  $\text{SOCl}_2$  gave the acid chloride of **626**, which could be condensed with monoethylmalonate to obtain the  $\beta$ -ketoester **627** in good yield. The latter was chlorinated with sulfuryl chloride to furnish derivative **628**, which led to the formation of imidazole **629** upon heating under reflux with formamide. Ester **629** was reduced to the alcohol with DIBAL-H and reoxidized with  $\text{MnO}_2$  to give aldehyde **630**. The latter was condensed with the diacetyldiketopiperazine derivatives **631a** and **631b** in the presence of cesium carbonate. Intermediate **632** was detected by HPLC analysis, but immediately deacetylated with aqueous  $\text{NH}_4\text{OH}$  to give the natural products phenylahistin (**633a**) and aurantiamine (**633b**). This efficient synthesis route can also be employed for the development of related compounds with a potential antitumor activity.

The bispyrrolidinoindoline diketopiperazine alkaloids *ent*-WIN 64821 (**644**) (Scheme 10.4) and ditryptophenaline (**651**) (Scheme 10.5) were prepared through total syntheses in 2001 by *Overman et al.* (414). The synthesis started with the



**Scheme 10.4** Total synthesis of *ent*-WIN 64281 (**644**). Reagents and conditions: a)  $\text{NaIO}_4$ , THF/ $\text{H}_2\text{O}$ , quant; b)  $n\text{-Bu}_3\text{SnCH}_2\text{OTMSE}$ ,  $n\text{-BuLi}$ , THF,  $-78^\circ\text{C}$ ; then  $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ , THF,  $-40^\circ\text{C}$  to  $0^\circ\text{C}$ , 44% (**636**), 42% (**637**); c)  $\text{Ph}_3\text{P}$ , DEAD, DPPA, toluene, rt, 84%; d) Red-Al, toluene, rt to  $100^\circ\text{C}$ , 71%; e) Fmoc-(*R*)-Phe-OH, DCC,  $\text{CH}_2\text{Cl}_2$ , rt, 94%; f)  $\text{BCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 80%; g) DMP, MeCN,  $0^\circ\text{C}$ ; then  $\text{NaClO}_2$ ,  $\text{KH}_2\text{PO}_4$ , THF/ $\text{H}_2\text{O}$ /*t*-BuOH, 2-methyl-2-butene; h) piperidine,  $\text{CH}_2\text{Cl}_2$ , rt; then DCC,  $\text{CH}_2\text{Cl}_2$ ,  $40^\circ\text{C}$ , 62% over two steps; i)  $\text{H}_2$ , 10% Pd/C, EtOH, rt, 70%



**Scheme 10.5** Total synthesis of ditryptophenaline (**651**). Reagents and conditions: a) PDC, MeCN, rt, 88%; b) NaBH<sub>4</sub>, MeOH, -78°C, 90%; c) Ph<sub>3</sub>P, DEAD, DPPA, toluene, rt, 91%; d) Red-Al, toluene, rt to 100°C, 52%; e) Na, NH<sub>3</sub>, THF, -78°C; then Fmoc-(S)-MePhe-OH, DCC, HOAt, MeCN, rt, 82% over two steps; f) BCl<sub>3</sub>, DTBMP, toluene, -78°C, 87%; g) DMP, CH<sub>2</sub>Cl<sub>2</sub>, rt; then NaClO<sub>2</sub>; h) piperidine, THF, rt; then DCC, CH<sub>2</sub>Cl<sub>2</sub>, 40°C, 54% over two steps

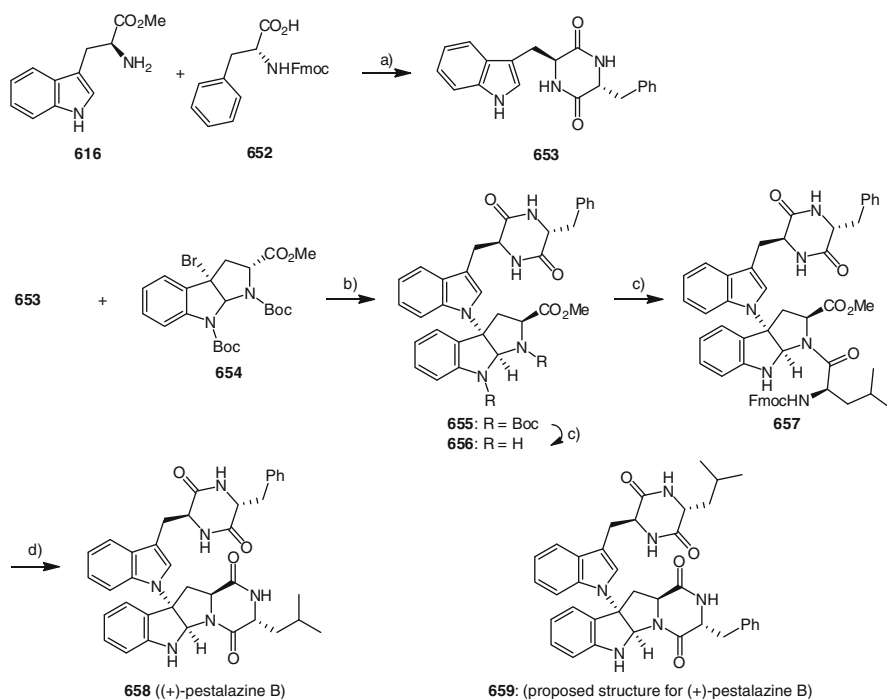
preparation of **634** in 30% overall yield and five steps from (*S*)-tartaric acid (**415**). Dialdehyde **634** could be cleaved and thus gave two separable products, **636** and **637**. The latter was used for the synthesis of ditryptophenaline (**651**, see below).

Compound **636** was converted to **638** under Mitsunobu conditions. Reduction upon heating led to the cyclization product **639**. Coupling with a (*R*)-phenylalanine derivative yielded tetrapeptide **640**, which was deprotected to give free diol **641**. Diacid **642** was obtained after two consecutive oxidation steps with Dess-Martin periodinane and NaClO<sub>2</sub>. Fmoc-deprotection, DCC-mediated cyclization (→ **643**) and benzyl deprotection furnished diketopiperazine *ent*-WIN 64821 (**644**).

The total synthesis of ditryptophenaline (**651**) used stereoisomer **637**, which was oxidized (→ **645**) and reduced to give diol **646** (Scheme 10.5). Analogous to the previously described synthesis, **646** was subjected to a Mitsunobu reaction and reduction to furnish cyclization product **647**. Benzyl deprotection and coupling with a Fmoc-protected *N*-methyl-(*S*)-phenylalanine derivative yielded tetrapeptide **648**. TMSE-deprotection, two oxidations (→ **650**), Fmoc-deprotection, and DCC-mediated cyclization finally led to the natural product ditryptophenaline (**651**).

These two syntheses were the first examples of the concise preparation of C<sub>2</sub>-symmetric bispyrrolidinoindoline diketopiperazines with a *cis*-configuration of the two hydrogen atoms between the pyrrolidine nitrogens. The versatility of the route allows an efficient structural variation that might afford synthetic alkaloids with new or better biological profiles.

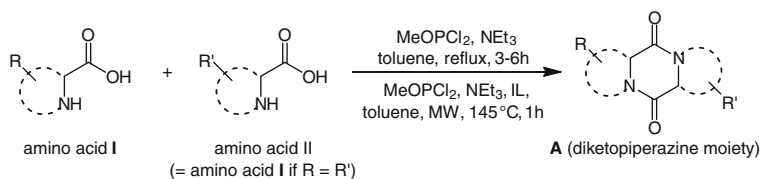
In 2010, *de Lera et al.* synthesized the heterodimeric diketopiperazine (+)-pestalazine B (**658**) (416). With this material in hand, they were able to revise the earlier proposed structure **659** for the natural product. These investigators utilized a convergent synthesis strategy, starting with the condensation of *L*-tryptophan methyl ester (**616**) and *N*-Fmoc-*D*-phenylalanine (**652**), to give diketopiperazine derivative **653** after Fmoc-deprotection (Scheme 10.6). This was reacted with 3a-bromopyrrolidinoindoline **654** (417) to furnish the dimeric product **655**. Boc-deprotection ( $\rightarrow$  **656**), coupling with *N*-Fmoc-*D*-leucine ( $\rightarrow$  **657**), and Fmoc-deprotection finally led to compound **658** for which the spectroscopic data matched those of the natural product.



**Scheme 10.6** Total synthesis of (+)-pestalazine B (**658**) and proposed structure **659** for (+)-pestalazine B. Reagents and conditions: a) EDC,  $\text{CH}_2\text{Cl}_2$ , rt, overnight; then  $\text{Et}_2\text{NH}$ , MeOH, rt, overnight, 68% over two steps; b) *t*-BuOK, MeCN,  $12^\circ\text{C}$ , 30%; c) TMSCl, MeCN,  $0^\circ\text{C}$ , 85%; d) *N*-Fmoc-*D*-leucine, HATU,  $\text{Et}_3\text{N}$ , DMF,  $0^\circ\text{C}$  to rt; then  $\text{Et}_2\text{NH}$ , MeOH, rt, 57% over two steps

A general approach for the synthesis of symmetrical and unsymmetrical diketopiperazines from unprotected amino acids has been published by *Bräse et al.* in 2007 (418) (Scheme 10.7). The phosphorus-promoted coupling method developed is a stereoselective one-pot synthesis that works either by conventional heating or in a microwave-assisted way (419). The suitability of this method for

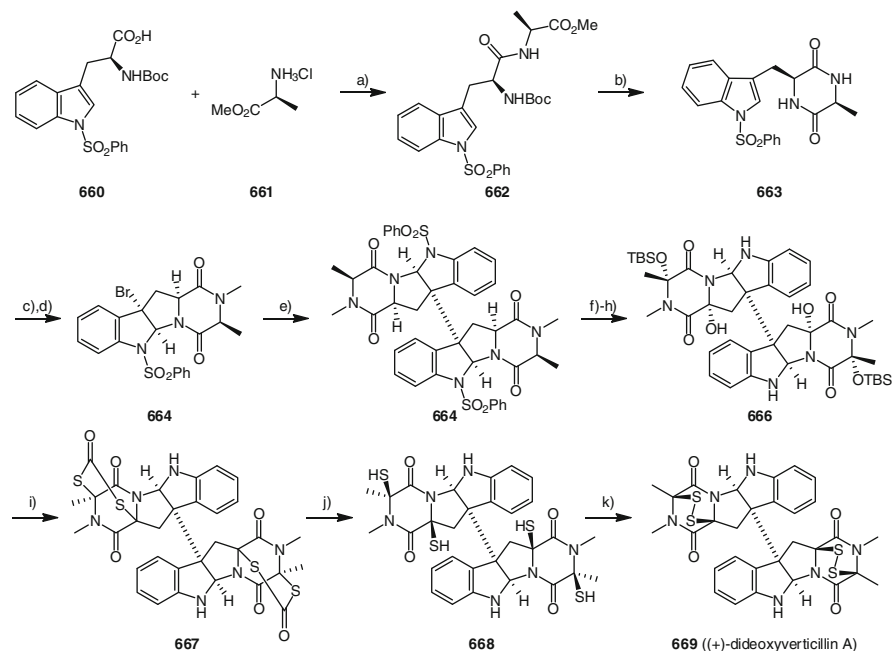
highly complex proline-type amino acids has also been shown by *Bräse et al.* in their work directed towards the synthesis of thiodiketopiperazine mycotoxins with a hydroindole core (420, 421).



**Scheme 10.7** General approach to the diketopiperazine moiety A

## 10.2.2 TDKP Total Syntheses

In 2009, *Movassaghi et al.* published the first total synthesis of a dimeric TDKP, which was at the same time only the second report on the preparation of a TDKP,



**Scheme 10.8** Total synthesis of (+)-dideoxyverticillin A (**669**). Reagents and conditions: a) HOBt, EDC•HCl, CH<sub>2</sub>Cl<sub>2</sub>, rt, 14 h, 95%; b) TFA, CH<sub>2</sub>Cl<sub>2</sub>, rt; then *t*-butanol, morpholine, rt, 84%; c) Br<sub>2</sub>, MeCN, 0 °C, 76%; d) MeI, K<sub>2</sub>CO<sub>3</sub>, acetone, rt, 77%; e) CoCl(PPh<sub>3</sub>)<sub>3</sub>, acetone, rt, 46%; f) Py<sub>2</sub>AgMNO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 63%; g) TBS-Cl, 5mol% PPY, NEt<sub>3</sub>, DMF, rt, 55%; h) 5% Na (Hg), NaH<sub>2</sub>PO<sub>4</sub>, MeOH, rt, 87%; i) K<sub>2</sub>CS<sub>3</sub>, TFA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 56%; j) ethanolamine, acetone, rt; k) KI<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 62% over two steps

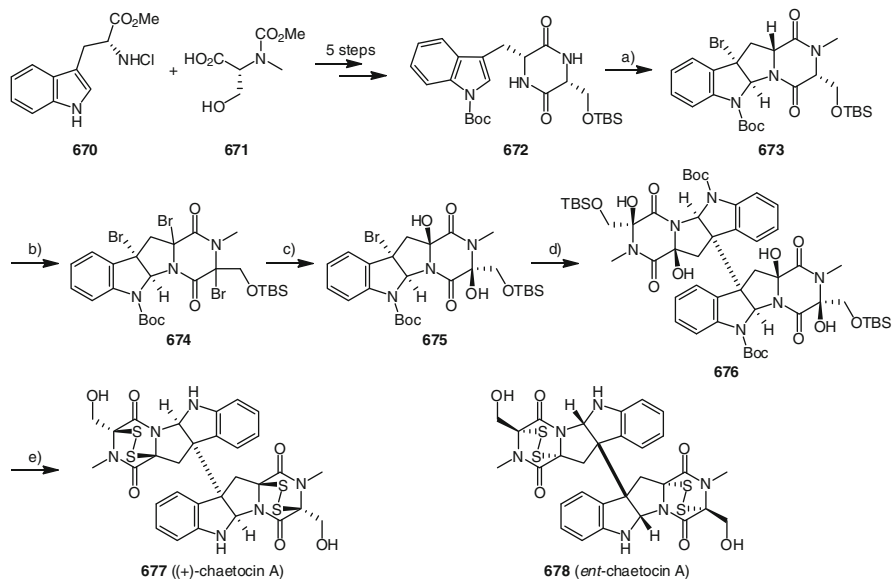
following after *Kishi et al.* in 1981 (408). The authors described the synthesis of the mycotoxin (+)-11,11'-dideoxyverticillin A (**669**), which shows inhibitory effects on tyrosine kinase EGF (epidermal growth factor) receptor and possesses antiangiogenic as well as cytotoxic activity (422) (Scheme 10.8).

The synthesis started with the coupling of the N-sulfonylated tryptophan **660** (prepared from *N*-Boc-tryptophan in one step) and L-alanine methyl ester **661** to give dipeptide **662**. The *cis*-diketopiperazine **663** was formed through cyclization with morpholine after treatment with trifluoroacetic acid. The reaction of **663** with molecular bromine followed by N-alkylation with methyl iodide furnished monomeric tetracyclic bromide **664**. The dimeric octacyclic derivative **665** was available by cobalt(I)-mediated reductive dimerization. Due to the preference of the 5,5-ring system to build *cis*-annelated products this method is an efficient strategy for the preparation of two vicinal quaternary stereogenic centers.

The following steps of the synthesis refer to the introduction of the sulfur bridge to a diketopiperazine. The method is based on the postulated biosynthesis of gliotoxin (**604**) (423), which comprises the formation of acyliminium ions through dehydration. Therefore, *Movassaghi et al.* treated diketopiperazine **665** with the mild and selective oxidizing agent bis(pyridine)-silver(I)permanganate to obtain a dimeric octacyclic tetraol as a single diastereomer (**666** without the TBS-protecting group). The mechanism involves a radical abstraction of the C<sub>α</sub>-methine protons. The observed diastereoselectivity was attributed to a very fast abstraction-addition process, which cannot be transferred to acyclic systems. Protection of two of the four hydroxy groups with TBS-Cl and deprotection of the sulfonylated indole nitrogen furnished compound **666**. This can be attacked by the sulfur nucleophile trithiocarbonate. Due to the geometry of the reagent, both sulfur atoms react from the same side of the molecule to give the bridged derivative **667**. Treatment with ethanolamine furnished the free tetrathiol **668**, which can be oxidized with potassium triiodide to obtain the *cis*-dithiodiketopiperazine, (+)-11,11'-dideoxyverticillin A (**668**). The method presented describes the total synthesis of a complex natural product in only eight steps from the readily available protected amino acids L-alanine and L-tryptophan.

One year later, in 2010, *Sodeoka et al.* reported on the total synthesis of two similar dimeric TDKPs, (+)-chaetocin A (**677**) and its antipode *ent*-chaetocin A (**678**) (424, 425) in only nine steps. The natural product was isolated from *Chaetomium minutum* (426) and shows antibacterial and cytostatic activity (427, 428) as well as an inhibitory effect on histone methyltransferases (429). The latter play an important role in gene expression and the total synthesis of inhibitors and their analogs could lead to helpful tools for epigenetic research (Scheme 10.9).

The authors started their synthesis with the preparation of diketopiperazine **672** from the commercially available D-tryptophan derivative **670** and known *N*-Cbz-protected *N*-methyl-D-serine (**671**) (430). Tetracyclic derivative **673** was available through a stereoselective bromocyclization reaction with NBS. Treatment of **673** with more NBS and the radical initiator V-70 led to a two-fold bromination at the diketopiperazine ring ( $\rightarrow$  **674**). Hydrolysis with water afforded diol **675** as a major diastereomer in a mediocre yield with three other stereoisomers as side products.



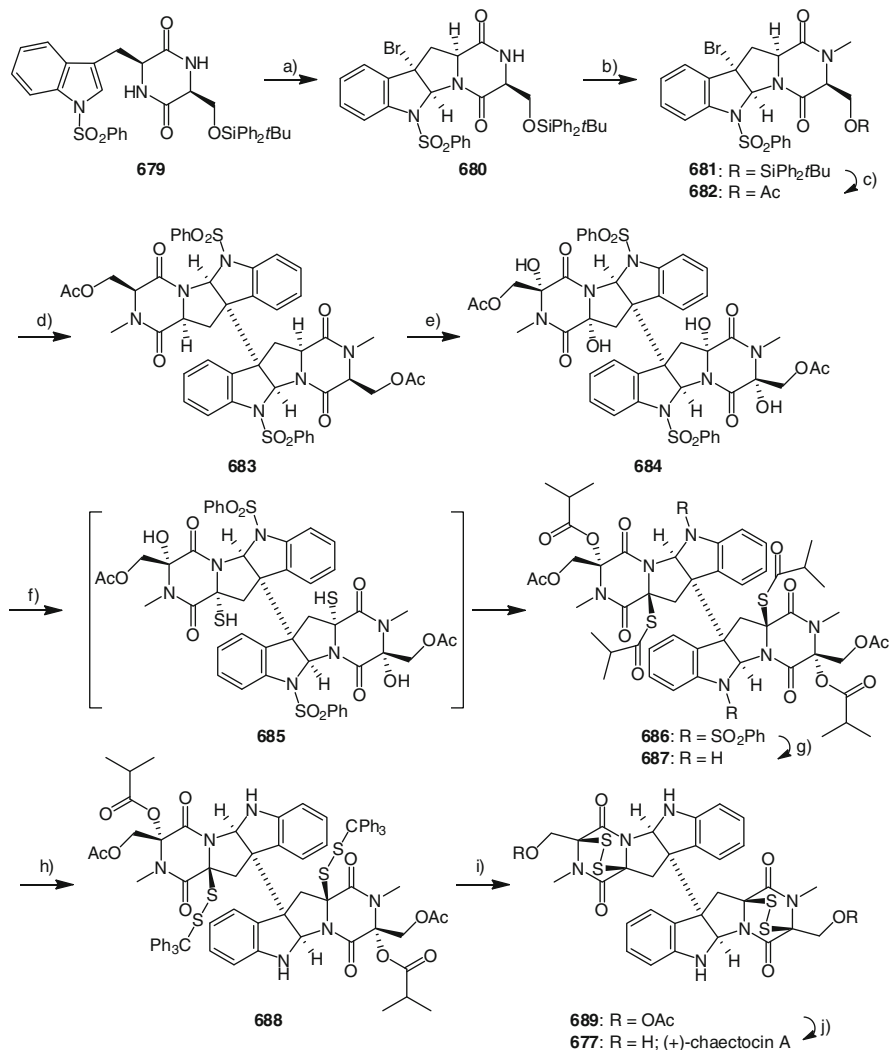
**Scheme 10.9** Total synthesis of (+)-chaetocin A (**677**) and *ent*-chaetocin A (**678**) (415, 424, 425). Reagents and conditions: a) NBS, MeCN,  $-30^{\circ}\text{C}$ , 10 h, 88%; b) NBS, V-70, CCl<sub>4</sub>, rt, 5 h; then pH 7 phosphate buffer/MeCN (1/1), rt, 3 h 47%; c) H<sub>2</sub>O; d) CoCl(PPh<sub>3</sub>)<sub>3</sub>, acetone, rt, 1.5 h, 55%; e) H<sub>2</sub>S, BF<sub>3</sub>•Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>,  $-78^{\circ}\text{C}$  to rt, sealed tube, 1.5 h; then I<sub>2</sub>

According to the procedure used by *Movassaghi et al.* for their total synthesis described earlier (431), the authors employed a cobalt(I)-mediated reductive coupling to yield dimeric product **676** as a single stereoisomer. The octacyclic compound was subjected to condensed H<sub>2</sub>S in the presence of BF<sub>3</sub>•Et<sub>2</sub>O. The crude product so obtained was treated with molecular iodine, which led to the formation of the natural product (+)-chaetocin A (**677**). In this final step, ten bond-forming and -cleaving reactions occurred, including substitution of a hydroxy group with thiol, Boc- and TBS-deprotection, and the sulfur bridge formation. By changing the starting materials for the total synthesis from *D*- to *L*-amino acids, the antipode *ent*-chaetocin A (**678**) was accessible.

Later in 2010, *Movassaghi et al.* proposed an alternative synthesis for (+)-chaetocin A (**677**) as well as syntheses for the epipolythiodiketopiperazines (+)-chaetoxin C (**693**) and (+)-12,12'-dideoxytetracin A (**694**) (432). These were the first reports on the preparation of high-order polysulfides. Studies have shown that the polysulfide bridge is important for the biological activity of these compounds and that potency increases with the number of sulfur atoms incorporated (433). Therefore, the versatile construction of this scaffold might lead to highly active substrates.

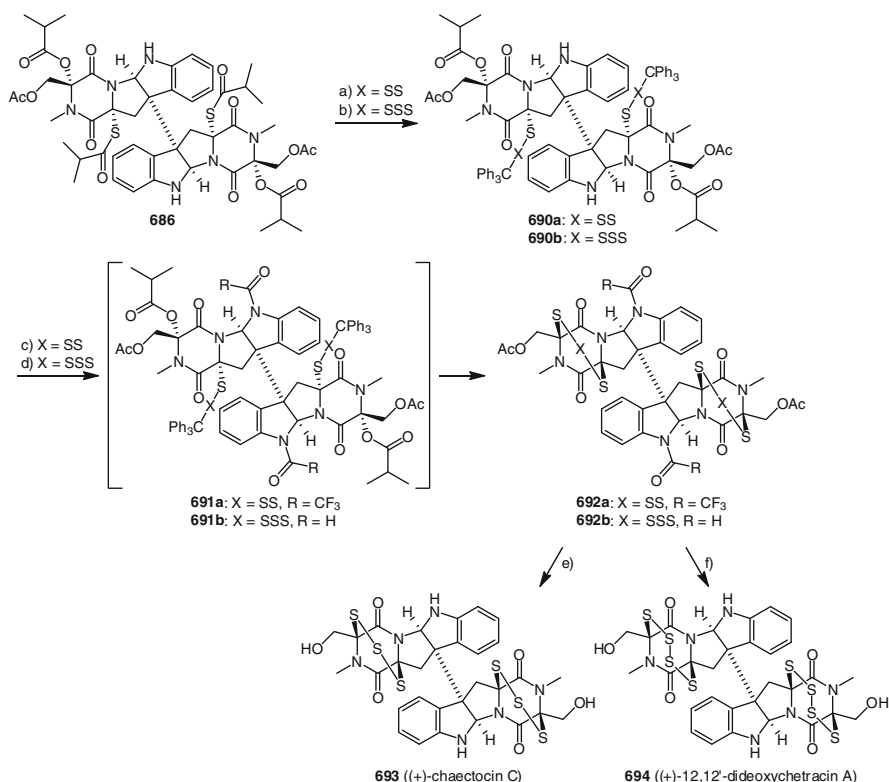
Similar to their synthesis described in Scheme 10.8, the authors started from two protected amino acids, *N*-Boc-L-tryptophan and L-serine methyl ester hydrochloride, to synthesize diketopiperazine **679** in three steps (Scheme 10.10).

Bromocyclization led to the formation of tetracyclic **680** as a single stereoisomer. Kinetic deprotonation followed by treatment with methyl iodide furnished derivative **681**. Compound **682** was obtained by exchanging the silyl ether with acetate. Again, cobalt(I)-mediated reductive coupling afforded the dimeric diketopiperazine **683**.



**Scheme 10.10** Total synthesis of (+)-chaetocin A (**677**). Reagents and conditions: a) Br<sub>2</sub>, benzene, 59%; b) LiHMDS, MeI, DMPU, THF, -78°C to -40°C, 86%; c) HF•py, THF; then AcCl, 85%; d) CoCl(PPh<sub>3</sub>)<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 59%; e) Py<sub>2</sub>AgMnO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 55%; f) H<sub>2</sub>S, TFA, MeNO<sub>2</sub>; then *i*-PrCOCl, CH<sub>2</sub>Cl<sub>2</sub>, 53% over two steps; g) *hν* (350 nm), L-ascorbic acid, 1,4-dimethoxynaphthalene, H<sub>2</sub>O, MeCN, 51%; h) N<sub>2</sub>H<sub>4</sub>, THF, 0°C; then NaH, Ph<sub>3</sub>CSCl, 90%; i) BF<sub>3</sub>•OEt<sub>2</sub>, 2,6-di-*t*-Bu-4-Me-pyridine, Et<sub>3</sub>SiH, CH<sub>2</sub>Cl<sub>2</sub>, 82%; j) Otera's cat., MeOH, toluene, 85°C, 92%





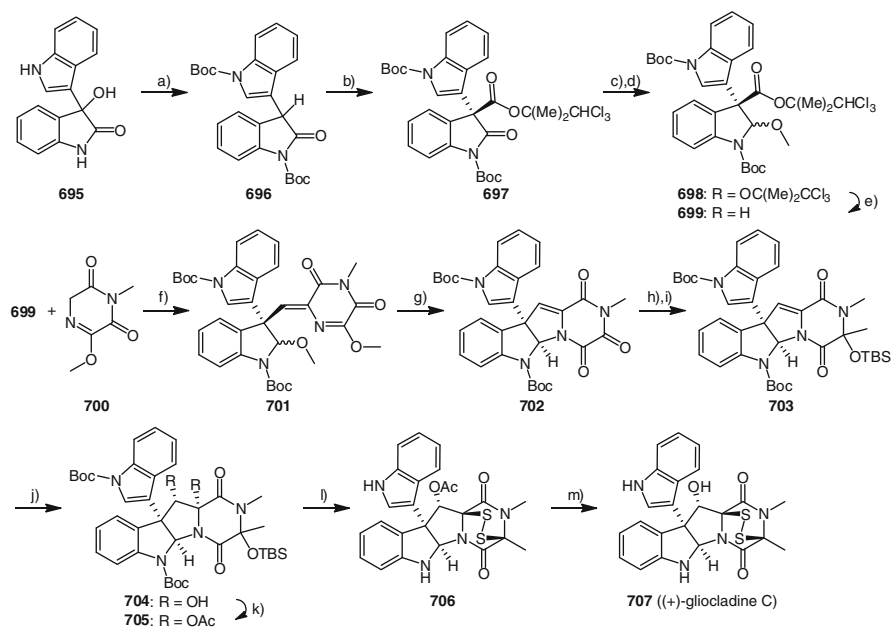
**Scheme 10.11** Total syntheses of (+)-chaetocin C (**693**) and (+)-12,12'-dideoxychetracin A (**694**). Reagents and conditions: a) N<sub>2</sub>H<sub>4</sub>, THF, 0°C; then TrSSCl, NEt<sub>3</sub>, 86%; b) N<sub>2</sub>H<sub>4</sub>, THF, 0°C, 93%; then TrSSCl, NEt<sub>3</sub>, 80%; c) TFAA, 2,6-di-*t*-Bu-4-Me-pyridine, MeCN; then BF<sub>3</sub>·OEt<sub>2</sub>, 60%; d) HCO<sub>2</sub>Ac; then MeCN, BF<sub>3</sub>·OEt<sub>2</sub>, 60%; e) *Otera's* cat.; MeOH, toluene, 90°C; then N<sub>2</sub>H<sub>4</sub>, 95%; f) HCl, MeOH, 52%

Tetrahydroxylation according to the synthesis of (+)-11,11'-dideoxyverticillin A (**669**) (422) led to tetraol **684**. Treatment with trifluoroacetic acid in hydrogen sulfide-saturated nitromethane diastereoselectively furnished bishthiohemiaminal **685**. Addition of *iso*-butyryl chloride generated the more stable compound **686**. *N*-Desulfonation under irradiation (→ **687**) followed by hydrazinolysis and sulfenylation of the free thiol furnished bis(triphenylmethandisulfide) derivative **688** in a very good yield. Ionization of the *iso*-butyryl residues and loss of a triphenylmethyl cation finally led to **689**, which was subjected to methanolysis (434) to afford the natural product (+)-chaetocin A (**677**).

Scheme 10.11 shows the total syntheses of epitriothiodiketopiperazine (+)-chaetocin C (**693**) and epitetrathiodiketopiperazine (+)-12,12'-dideoxychetracin A (**694**). *Movassagi et al.* used intermediate **686** (see Scheme 10.10) and treated it with either chloro(triphenylmethane)disulfane (X = SS) or chloro(triphenylmethane)trisulfane (X = SSS) after hydrazinolysis to obtain compounds **690a** and **690b**,

respectively. In the case of **690a**, trifluoroacetylation generated trithiodiketopiperazine **692a** in a very good yield. Methanolysis of the acetates followed by hydrazinolysis of the trifluoroacetamides finally led to the natural product (+)-chaetocin C (**693**). Compound **690b** was converted to **692b**, which could easily be converted to the dimeric tetrasulfide (+)-(+)-12,12'-dideoxychetracin A (**694**) by acid-catalyzed methanolysis. This strategy represents an efficient strategy for the divergent sulfenylation of diketopiperazines to obtain di-, tri-, and tetrameric epithiodiketopiperazine alkaloids (435).

In 2011, *Overman et al.* reported (Scheme 10.12) the total synthesis of the epithiodioxopiperazine, (+)-gliocladine C (**707**) (436). This natural compound was isolated from the fungus *Gliocladium catenulatum* (437). In the first step, 3-hydroxy-3,3'-biindolin-2-one (**695**), readily available from isatin and indole (438), was reduced and Boc-protected to give compound **696**. This oxoindole was reacted with 2,2,2-trichloro-1,1-dimethylethyl chloroformate in the presence of *Fu*'s

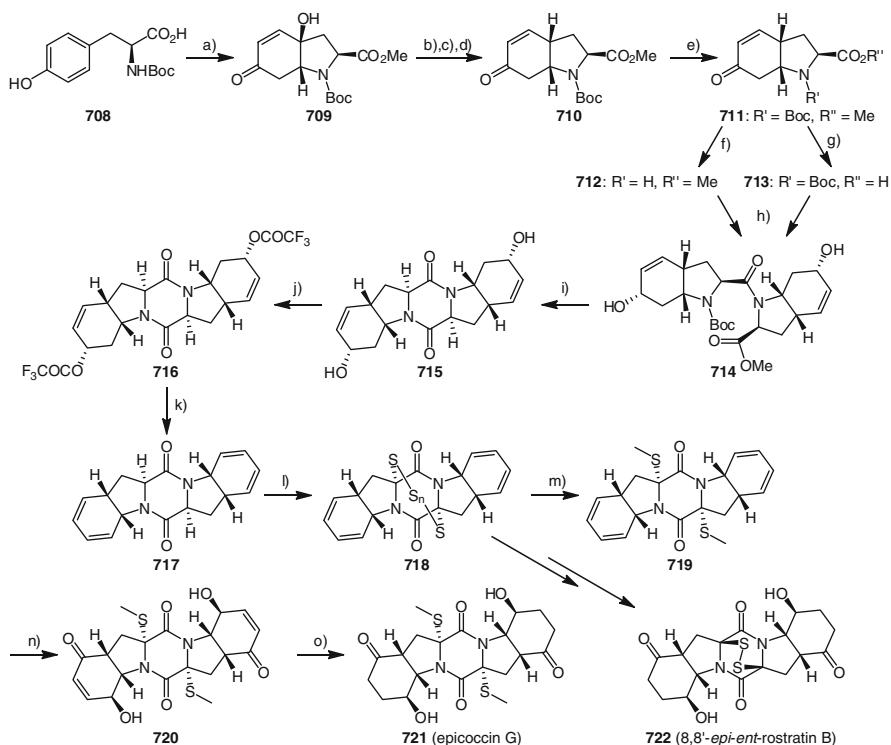


**Scheme 10.12** Total synthesis of (+)-gliocladine C (**707**). Reagents and conditions: a) TFA, Et<sub>3</sub>SiH, CH<sub>2</sub>Cl<sub>2</sub>, rt; then (Boc)<sub>2</sub>O, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt; then MeOH, 68% over two steps; b) 2,2,2-trichloro-1,1-dimethylethyl chloroformate, Et<sub>3</sub>N, (–)-(*S*)-4-pyrrolidinopyridinyl(pentamethylcyclopentadienyl)iron, THF, 40°C, 88%; c) NaBH<sub>4</sub>, MeOH, 0°C, 81%; d) HC(OMe)<sub>3</sub>, 10 mol-% PPTS, MeOH, 65°C, 83%; e) LiBH<sub>4</sub>, MeOH, Et<sub>2</sub>O, rt to 40°C, 84%; then *DMP*, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 95%; f) LDA, **699**, THF, –78°C; then **700**, –78°C; then AcOH, –78°C to –40°C, 80%; h) MeMgCl, THF, –78°C, 86%; i) TBSOTf, DMAP, Et<sub>3</sub>N, DMF, rt, 94%; j) AD-mix- $\alpha$ , H<sub>2</sub>NSO<sub>2</sub>Me, K<sub>2</sub>OsO<sub>4</sub>·2H<sub>2</sub>O, (DHQ)<sub>2</sub>PHAL, *t*-BuOH/H<sub>2</sub>O/acetone, rt, 82%; k) Ac<sub>2</sub>O, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 93%; l) H<sub>2</sub>S, BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, –78°C to rt; then O<sub>2</sub>, MeOH, EtOAc, rt, 62%; m) La(OTf)<sub>3</sub>, MeOH, 40°C, 75%

catalyst (439) to give **697** in a very good yield and a 98:2 enantiomeric ratio. Indoline *N,O*-acetal **698** was obtained by reduction of the keto group and methylation of the resulting hydroxy group with trimethyl orthoformate. *Soai* reduction and *Dess-Martin* oxidation furnished biselectrophile **699** in good yield. This was reacted with the lithium enolate of piperazinedione **700** (readily available from *N*-methylamide hydrochloride) to generate condensation product **701** exclusively as the (*Z*)-diastereomer. Cyclization and demethylation afforded the trioxopiperazine-fused cyclotryptamine **702**, which was converted to dioxopiperazine **703**. After dihydroxylation and acetylation, diacetate **705** was treated with condensed H<sub>2</sub>S and BF<sub>3</sub>•OEt<sub>2</sub> to give, after exposure to oxygen, epithiodiketopiperazine **706**. The authors explain the observed stereoselectivity with the formation of an iminium ion in the DKP ring, which is attacked from the less hindered side opposite both the angular indolyl substituent and the adjacent acetate. Removal of the acetate finally furnished the natural product, (+)-glioclidine C (**707**), in only ten steps and 11% overall yield.

*Nicolaou et al.* reported on the synthesis of epicoccin G (**721**), a symmetrical epithiodiketopiperazine, in 2011 (440). The natural product exhibits anti-HIV activity and is therefore an interesting target for a versatile synthesis strategy. The first two steps of the total synthesis consisted of a literature-known procedure for the conversion of protected tyrosine **708** to enone **709** (441) (Scheme 10.13). Consecutive acetylation, zinc reduction, and base-induced isomerization led to the deoxygenated product **710**. *Luche* reduction generated **711**, which was Boc-protected (→ **712**) and saponified (→ **713**). Dimer **714** was obtained through a BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphonic chloride)-facilitated coupling. Boc-deprotection followed by a base-induced ring closure furnished pentacyclic system **715**. Introduction of the second double bond (→ **717**) was achieved through the intermediate bistrifluoroacetate **716** on exposure to a palladium(0)-catalyst. Inspired by the work of *Schmidt et al.* in the 1970s (442), the authors used a base (NaHMDS, *Schmidt et al.* used Na in liquid NH<sub>3</sub> in their work) and molecular sulfur for the preparation of the mixture of bridged oligosulfenylated products **718**. Reduction with NaBH<sub>4</sub>, followed by the addition of MeI gave way to the bismethylthio derivative **719**. Treatment with singlet oxygen followed by a *Kornblum-DeLaMare* rearrangement (443) afforded dihydroxy enone **720**. Hydrogenation finally furnished the natural product epicoccin G (**721**).

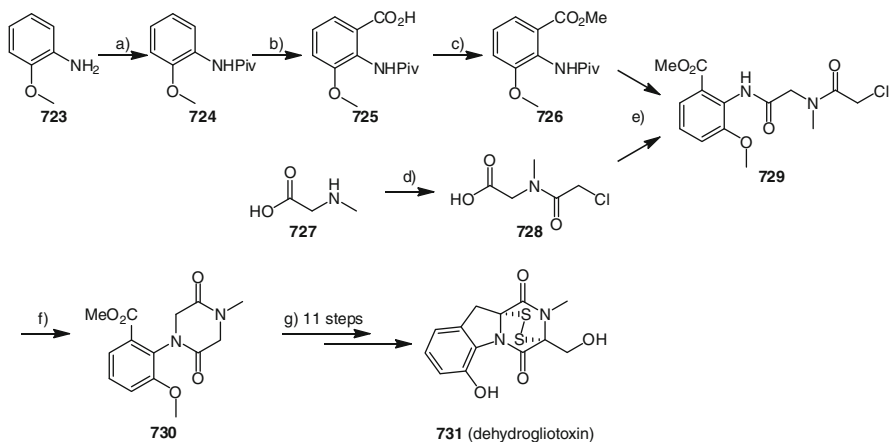
*Nicolaou et al.* were also able to apply their strategy to the synthesis of 8,8'-*epi-ent*-rostratin B (**722**), a derivative of the marine mycotoxin rostratin B with a disulfur bridge. Treatment of intermediate **718** with NaBH<sub>4</sub>, followed by reduction with potassium triiodide, addition of oxygen, *Kornblum-DeLaMare* rearrangement, and hydrogenation afforded product **722**. Thus, these authors demonstrated the versatility of their method, which represents a direct procedure for the sulfenylation of diketopiperazines to obtain both bismethylthio derivatives and epithiodiketopiperazines.



**Scheme 10.13** Total syntheses of epicoccin G (**721**) and 8,8'-*epi-ent-rostratin* B (**722**). Reagents and conditions: a) see reference; b) Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to rt, 4 h; c) Zn, AcOH, MeOH, 65°C, 0.5 h; d) DBU, toluene, 65°C, 3 h, 51% over three steps; e) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7 H<sub>2</sub>O, MeOH, -78°C to 0°C, 1 h, 92%; f) TFA/CH<sub>2</sub>Cl<sub>2</sub> (1/1), 0°C to rt, 0.5 h, 99%; g) LiOH (aq.)/THF (5/1), 0°C to rt, 3 h, 99%; h) **712**, **713**, BOP-Cl, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to rt, 15 h, 86%; i) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to rt, 1.5 h; then NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to rt, 15 h, 77% over two steps; j) (CF<sub>3</sub>CO)<sub>2</sub>O, NEt<sub>3</sub>, DMAP, MeCN, -40°C to rt, 1 h, 69%; k) Pd(PPh<sub>3</sub>)<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, dioxane, 65°C, 0.5 h, 90%; l) NaHMDS, S<sub>8</sub>, THF, rt; then **717**; then NaHMDS, rt, 0.5 h; m) NaBH<sub>4</sub>, THF/MeOH (1/1), 0°C to rt, 0.75 h; then MeI, rt, 15 h; 58% over three steps; n) O<sub>2</sub>, TPP, CH<sub>2</sub>Cl<sub>2</sub>, 400 W Philips-MH400/U sun lamp, -45°C, 40 min; then DBU, -45°C to 0°C, 1 h, 52% over two steps; o) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C (20w%), MeOH, 25°C, 1 h, 86%

After gliotoxin, its derivative dehydrogliotoxin (**731**) is one of the best characterized epithiodiketopiperazines. It was addressed again in 2011 by *Wood et al.* (444) after it had been the first TDKP (together with gliotoxin) to be synthesized in 1981 (408).

The convergent (formal) synthesis of **731** started with the preparation of aniline derivative **726** from the inexpensive *o*-anisidine (**723**) in four steps (see Scheme 10.14). Acid **728** was obtained by using a known procedure in one step (445). Its conversion to the corresponding acid chloride followed by the reaction with aniline **726** furnished bis-amide **729**. Base-mediated ring closure afforded diketopiperazine **730**, which had already been transformed into dehydrogliotoxin



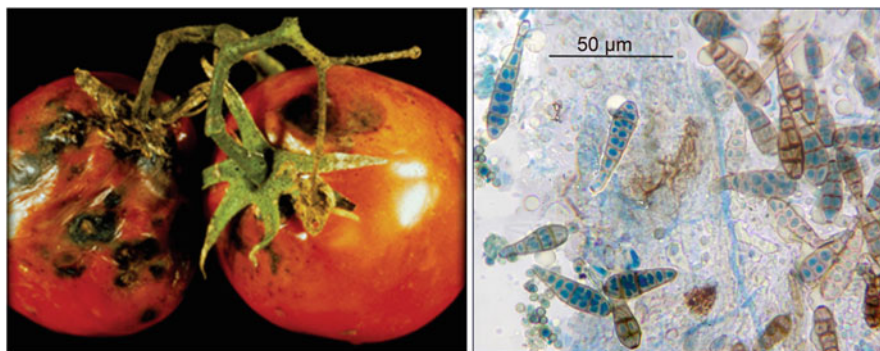
**Scheme 10.14** Formal total synthesis of dehydrogliotoxin (**731**). Reagents and conditions: a) PivCl, Na<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>O, 98%; b) *n*-BuLi, THF; then CO<sub>2</sub>, 84%; c) HCl, H<sub>2</sub>O; then CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O, 80% over two steps; d) ClCOCH<sub>2</sub>Cl, Na<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>O, 89%; e) **728**, (COCl)<sub>2</sub>, DMF, CH<sub>2</sub>Cl<sub>2</sub>; then **726**, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 54%; f) K<sub>2</sub>CO<sub>3</sub>, KI, MeOH, 83%; g) see reference

by *Kishi et al.* (408) in 11 steps. This short and efficient synthesis is applicable to similar compounds and is therefore an interesting strategy for the synthesis of new bioactive compounds.

In summary, much progress has been made in the area of (thio)diketopiperazine synthesis, especially in the last few years. Nevertheless, only a few syntheses of the numerous known (T)DKP natural products have been reported so far (see earlier in this chapter and refs. 446–448). Progress towards the preparation of synthetic fragments of challenging (T)DKP derivatives can be found also in literature (449, 450, 420, 421). Furthermore, methodological work for the thiolation of diketopiperazines has been published recently (451, 452). Thus, there will probably be additional total syntheses on this class of compounds reported in due course. Most of the mycotoxins belonging to this group are very complex molecules that have to be synthesized under both sensitive and selective conditions. This makes every transformation very demanding and it is necessary to adapt published procedures from the very first step for a (T)DKP to be synthesized.

## 11 *Alternaria* Metabolites

Metabolites of the genus *Alternaria* are apparently ubiquitous and have long been recognized as important plant pathogens, causing diverse diseases such as tobacco brown spot (453), potato and tomato blight (Fig. 11.1), and citrus seedling chlorosis (454). Although *A. alternata* has been regarded as the major mycotoxin-producing species, other species such as *A. citri*, *A. longipes*, *A. solani*, and the *A. arborescens*, *A. infectoria*, and *A. tenuissima* species groups also produce the characteristic *Alternaria* mycotoxins (455).

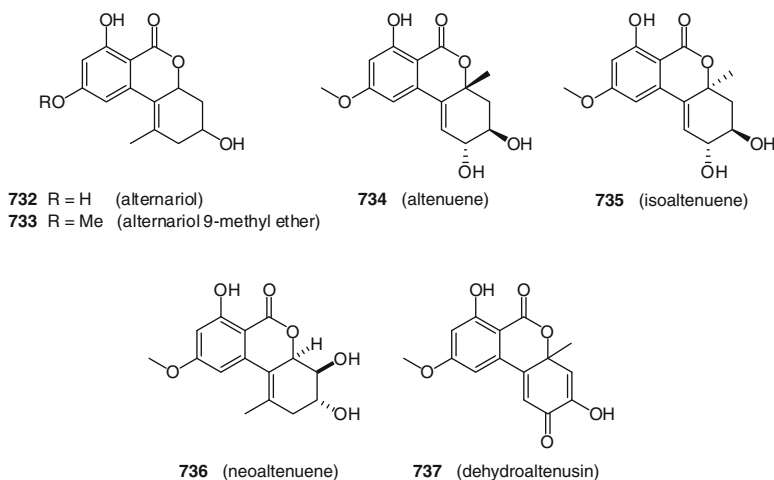


**Fig. 11.1** *Alternaria alternata* fungus on tomatoes, *Alternaria alternata* conidia. (Courtesy of Selmar Petzoldt)

The *Alternaria* toxins, alternariol (732) or alternariol 9-methyl ether (733), are produced by a variety of *Alternaria* fungi and were first isolated in 1953 (456). For example, *Alternaria tenuis* afforded an ether extract containing alternariol methyl ether and alternariol in the proportion 10:1. These compounds were the first recorded substituted dibenzo- $\alpha$ -pyrones of fungal origin (457, 458) and they also represent the main toxic metabolites (459). Figure 11.1 shows the fungus *Alternaria alternata* (460).

Less is known about minor *Alternaria* metabolites, including altenuene **734** (461–463), isoaltenuene **735** (464, 465), neoaltenuene **736** (466), and dehydroaltenuenin **737** (467–469), which have been found in infested fruits in sub-milligram amounts (Fig. 11.2).

Altenuene **734** was isolated 1970 by *Pero et al.* from the fungus *Alternaria tenuis* and is related structurally to the *A. tenuis* metabolites alternariol **732** and alternariol 9-methyl ether **733** (462). Isoaltenuene **735**, a diastereomer of altenuene, with inverted configuration at C-2', was found in rice cultures of *Alternaria alternata* in 1989 by *Visconti et al.* (464). Also from extracts of the fungus *Alternaria alternata* cultured on rice, five other dibenzo- $\alpha$ -pyrones were isolated in 1993 by the group of *Blunden and Turner* (466), among them neoaltenuene (**736**). Dehydroaltenuenin (**737**),



**Fig. 11.2** The most well-known *Alternaria* toxins (**732–737**)

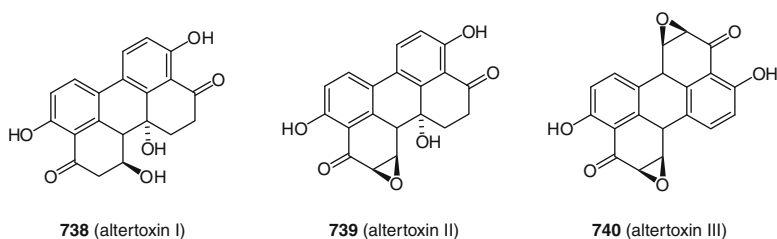
a myosin light chain kinase inhibitor, had been identified in culture broths of *Penicillium verrucosum* IAM-13756 in 1994 by *Nakanishi et al.* (467).

Another group of *Alternaria* metabolites are the hydroxyperylenequinone compounds, altertoxins I (**738**), II (**739**), and III (**740**), which were first isolated in 1973 (470) (Fig. 11.3). In 1979, *Scott and Stoltz* reported the chromatographic separation of *A. alternata* mycelium extract, which yielded several fractions mutagenic in the latter system, including an altertoxin I-containing fraction (471). In 1986, *Stack and Prival* performed an *Ames* test on an extract of the mold *Alternaria alternata* and isolated all three altertoxins, which showed mutagenicity against *Salmonella typhimurium* (472).

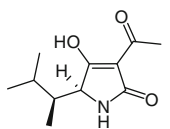
The structure of the perylene metabolite altertoxin I (**738**), first reported in 1982 by the group of *Stinson*, and the scaffolds of the other altertoxins, are unusual, since the two aromatic centers in the molecules are completely isolated from each other due to non-conjugated bonding (473).

Compounds **738–740** belong to the class of perylenequinones (474), but until now, there has been no approach to the total synthesis of altertoxins, based on the difficulty in formation of two neighboring but separate aromatic centers.

One of the most toxic components among *Alternaria* mycotoxins is tenuazonic acid (**741**) (475) (Fig. 11.4), a tetramic acid derivative, which was first isolated from the culture filtrates of *Alternaria tenuis* in 1957 by *Rosett et al.* (476) and shows potent biological activity (475). Tenuazonic acid is biosynthesized from *L-isoleucine* and its structure was revealed four years later by *Stickings* and his group (477).



**Fig. 11.3** Altertoxins I, II, and III (**738–740**)



**741** (tenuazonic acid)

**Fig. 11.4** Tenuazonic acid (**741**)

## 11.1 Biological Properties

A number of *Alternaria* species are toxic to a wide spectrum of organisms, including bacteria (456, 478), fungi (479), viruses (478), and higher plants (480, 481). Furthermore, it is known that many saprophytic species, associated with agricultural commodities, produce toxic metabolites to mammals (482).



Investigations of the cytotoxicity of the dibenzo- $\alpha$ -pyrones have indicated a high toxicity (483). Alternariol (**732**) and alternariol 9-methyl ether (**733**) exhibited  $IC_{50}$  values of 6 and 8  $\mu\text{g}/\text{cm}^3$  for HeLa and lymphoma L5178Y cells. Using *Bacillus mycoides* as a test organism, **732** was the most potent inhibitory compound from the *Alternaria* spp., but when in combination with alternariol 9-methyl ether (**733**), a striking synergistic effect was shown. Only 0.5  $\mu\text{g}$  of a 1:1 mixture of alternariol (**732**) and alternariol 9-methyl ether (**733**) was necessary to induce a zone of inhibition. Another investigation using alternariol (**732**) with female mice also showed fetotoxic effects (470).

In 1991 *Liu et al.* found that extracts of *Alternaria alternata* led to reverse mutation in *Escherichia coli*, unscheduled DNA synthesis in cultured human amnion FL cells, chromosomal aberrations, and sister chromatid exchange in human peripheral blood lymphocytes, mutation in V79 cells, and transformation of NI3T3 cells (484, 485).

The possibility that *Alternaria* toxins have causal effects in the etiology of esophageal cancer in Linxian, People's Republic of China, has been investigated since 1987 by *Dong* (486), *Zhen* (487), and *Liu et al.* (484). They observed that alternariol 9-methyl ether (**733**) and alternariol (**732**) combine with DNA isolated from the human fetal esophageal epithelium, activate the oncogenes, c-H-ras and c-mys, and promote the proliferation of human fetal esophageal cells *in vitro*. Moreover, **732** might induce squamous cell carcinoma of the fetal esophagus.

In 2004, *Mizushina et al.* reported dehydroaltenusin (**737**) as a mammalian DNA polymerase  $\alpha$  inhibitor, whereas **737** was shown to be incorporated into liposomes and prevent the proliferation of human cultured cancer cells by halting the cell cycle.

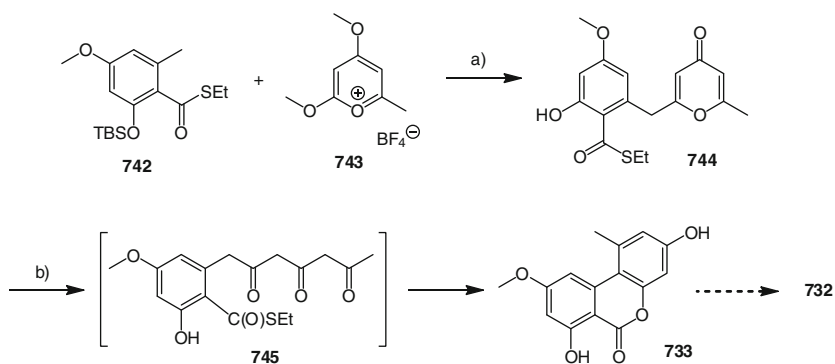
As mentioned above, altertoxins I, II, and III (**738–740**) showed mutagenic bioactivity in *Ames* tests on *Salmonella typhimurium*. It has been found that altertoxin III (**740**) is 1.5 times more potent as a mutagen when compared to altertoxin II (**739**), which, in turn, was reported to be 23 times more potent than altertoxin I (**738**) in this regard (488). This type of toxicity can be related to the number of epoxide groups in these octahydroperylene compounds (Fig. 11.3).

Tenuazonic acid (**741**) is also of great interest since it is considered to exhibit the greatest toxicity among the *Alternaria* mycotoxins. It exhibits phytotoxic, insecticidal, zootoxic, cytotoxic, antibacterial, antitumor, and antiviral activities (489, 490). Furthermore, **741** might be the causal factor of onyalai, a hematological disorder in man (491).

## 11.2 Total Syntheses

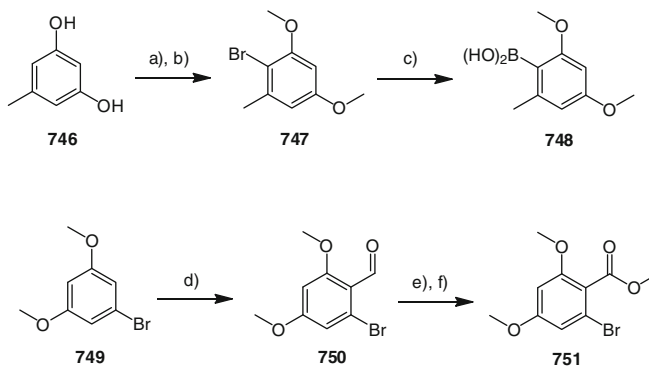
### 11.2.1 Total Synthesis of Alternariol and Alternariol 9-Methyl Ether

In 1986, *Staunton et al.* published the biomimetic syntheses of alternariol (**732**) and alternariol 9-methyl ether (**733**) (492, 493), after an earlier report by *Harris et al.* in 1967 (494). The synthesis method used is outlined in Scheme 11.1. Thus, protected orsellinate thioester **742** was treated with lithium diisopropylamide (LDA) to generate an anion, which reacted with the tetrafluoroborate pyrylium salt **743**. After cleavage of the protecting silyl group, pyrone **744** was achieved, which was then methylated to form a pyrylium salt by methyl group transfer from the previous pyrylium salt **743**. A ring opening of the pyrylium derivative with water formed the isomeric methyl enol ether. The presumed natural key intermediate **745** was obtained by acidic hydrolysis as a mixture of enol tautomers and under mild cyclization conditions alternariol 9-methyl ether **733** was produced.



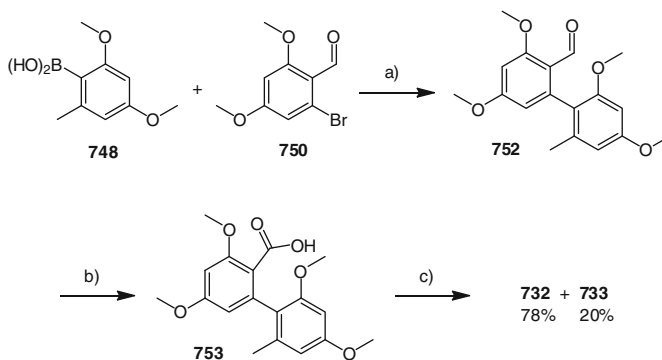
**Scheme 11.1** Biomimetic synthesis of alternariol and alternariol 9-methyl ether. Reagents and conditions: a) LDA, THF,  $-78^{\circ}\text{C}$ , acidic workup, 20%; b) NaOH, MeOH/H<sub>2</sub>O (4/1), acidic workup, >75%

*Podlech et al.* recently reported on a total synthesis of alternariol (**732**) with a palladium-catalyzed *Suzuki*-type coupling as the key reaction (495). The synthesis began by preparing the orcinol-derived boronic acid **748** by methylation and subsequent bromination with *N*-bromosuccinimide (NBS) of orcinol **746** (362), and treatment of **747** with butyllithium, followed by forming the boronic acid with triisopropyl borate (496) (Scheme 11.2). The brominated *Suzuki*-coupling partner was achieved by a *Vilsmeier* formylation of 3,5-dimethoxybromobenzene (**749**) (497), which was further oxidized under *Kraus* conditions (242) and esterified to obtain the methyl ester **751**.



**Scheme 11.2** Synthesis of the *Suzuki*-coupling partners. Reagents and conditions: a)  $\text{Me}_2\text{SO}_4$ ,  $\text{K}_2\text{CO}_3$ , acetone, reflux, 4 h, 99%; b) NBS,  $\text{CHCl}_3$ , rt, 99%; c) *n*-BuLi,  $\text{B}(\text{O}i\text{-Pr})_3$ , THF,  $-78^\circ\text{C}$ , 15 min, rt, 12 h, 99%; d)  $\text{POCl}_3$ , DMF,  $100^\circ\text{C}$ , 4 h, 78%; e)  $\text{NaH}_2\text{PO}_4$ ,  $\text{NaClO}_2$ , 2-methyl-2-butene, *t*-BuOH/ $\text{H}_2\text{O}$  (5/1), rt, 2 h, 85%; f)  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ , 70%

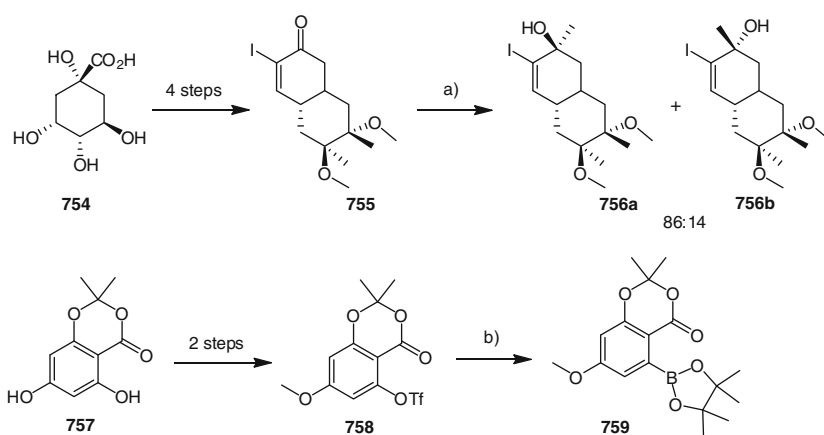
A *Suzuki* coupling of ester **751** with boronic acid **748** was not successful, but the coupling proceeded with the carbaldehyde **750**, to yield biaryl **752**, which was then transformed into the acid **753** by *Kraus* oxidation. The final step included deprotection of hydroxy group functions using boron tribromide to attain the desired molecules **732** and **733** (Scheme 11.3).



**Scheme 11.3** Synthesis of alternariol and alternariol 9-methyl ether by *Podlech et al.* Reagents and conditions: a)  $\text{K}_2\text{CO}_3$ , cat.  $\text{Pd}(\text{PPh}_3)_4$ , DMF,  $100^\circ\text{C}$ , 4 h, 78%; b)  $\text{NaH}_2\text{PO}_4$ ,  $\text{NaClO}_2$ , 2-methyl-2-butene, *t*-BuOH/ $\text{H}_2\text{O}$  (5/1), rt, 2 h, 85%; c)  $\text{BBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 24 h, 73%

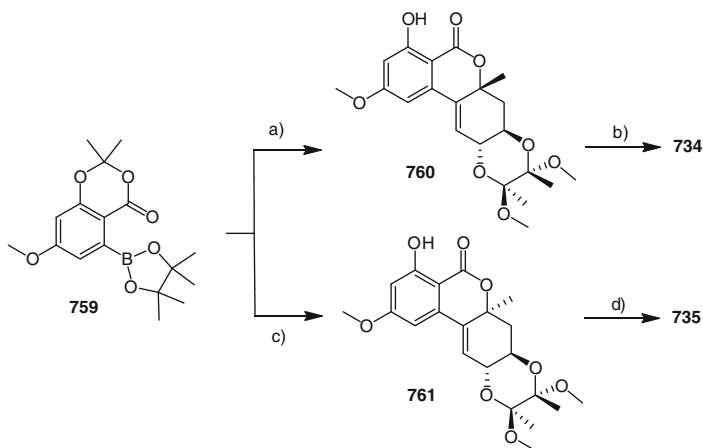
### 11.2.2 Total Synthesis of Alternuene and Isoalternuene

One year after publishing the total synthesis of alternariol and alternariol 9-methyl ether, *Podlech* and his group reported on the total synthesis of alternuene **734** and its epimer, isoalternuene (**735**) (498). At this point, there was no confident information on the absolute configuration of these natural products, so it was decided to use quinic acid (**754**) as starting material. An iodinated *Suzuki*-coupling substrate was produced in four steps by published procedures (499, 500), followed by reaction with methyl magnesium bromide, which gave a separable mixture of diastereomers **756a** and **756b**. Boronic ester **759** was synthesized in three steps beginning with commercially available acetal **757** (501) (Scheme 11.4).



**Scheme 11.4** Synthesis of building blocks for alternuene (**734**). Reagents and conditions: a) MeMgBr, THF,  $-40^{\circ}\text{C}$  to rt, 68%; b) pinacol borane,  $\text{Et}_3\text{N}$ , 5mol%  $\text{Pd}(\text{PPh}_3)_4$ , dioxane,  $80^{\circ}\text{C}$ , 2 h, 88%

Scheme 11.5 shows the completion of the alternuene and isoalternuene synthesis by the *Suzuki* coupling of iodinated compound **756** and boronic ester **759** as the key reaction, using the S-Phos ligand (502, 503). Fortunately, this *Suzuki* coupling step simultaneously promoted the formation of lactones **760** and **761**. The last step, the cleavage of the diol-protecting acetal group, was accomplished using trifluoroacetic acid (TFA). Since the absolute configuration was unknown before this synthesis was completed, commercially available alternuene was compared with the synthesized material. *Podlech* and co-workers determined that natural alternuene had an enantiomeric excess of only 2%, and thus they had synthesized the major enantiomer.

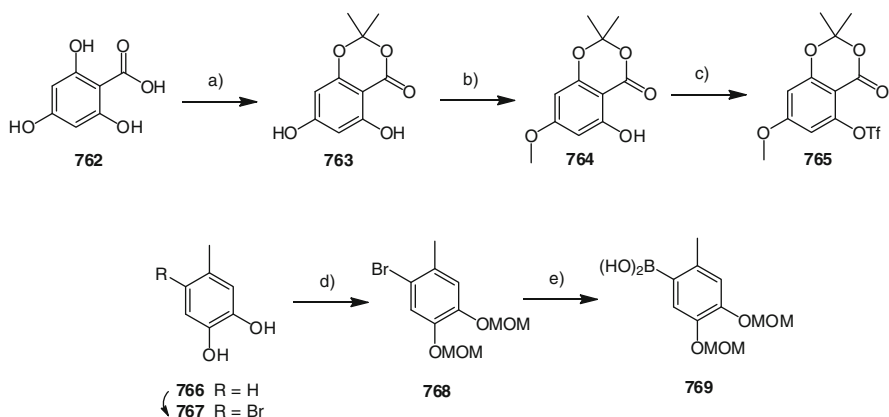


**Scheme 11.5** Suzuki coupling and completion of the total synthesis of altenuene (**734**) and isoaltenuene (**735**). Reagents and conditions: a) **756b**, 2mol% Pd(OAc)<sub>2</sub>, 4mol% S-Phos, Cs<sub>2</sub>CO<sub>3</sub>, dioxane/H<sub>2</sub>O (5/1), 80°C, 2 h, 70%; b) TFA/H<sub>2</sub>O (9/1), 10 min, rt, 55%; c) **756a**, 2mol% Pd(OAc)<sub>2</sub>, 4mol% S-Phos, Cs<sub>2</sub>CO<sub>3</sub>, dioxane/H<sub>2</sub>O (5/1), 80°C, 2 h, 72%; d) TFA/H<sub>2</sub>O (9/1), 10 min, rt, 62%

### 11.2.3 Total Synthesis of Dehydroaltenuenin

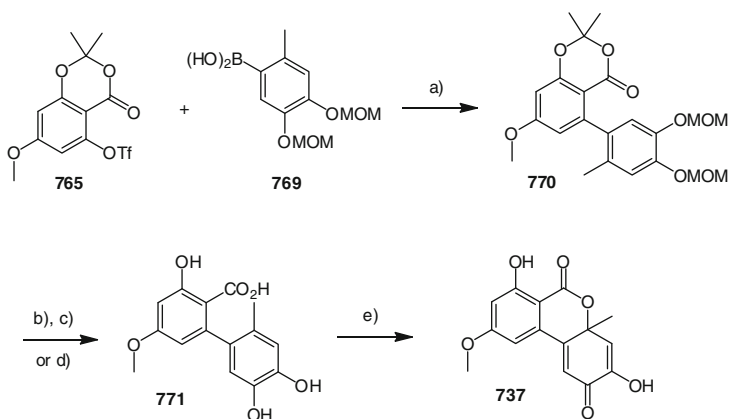
Dehydroaltenuenin (**737**), isolated from *Alternaria tenuis*, has shown promising biological activities, making it an interesting natural product for total synthesis. *Kamisuki et al.* reported the first synthesis of racemic dehydroaltenuenin in 2004 (*501*). The key step involves a Suzuki-coupling reaction of an aryltriflate with an aryl boronic acid. Synthesis of the aryltriflate began from commercially available 2,4,6-trihydroxybenzoic acid (**762**). Reaction with thionyl chloride (SOCl<sub>2</sub>) in the presence of *N,N*-dimethylaminopyridine (DMAP) led to acetonide **763**. Regioselective methylation was accomplished under *Mitsunobu* conditions with diisopropyl azodicarboxylate-triphenylphosphine in the presence of benzyl alcohol, and afforded monomethyl ether **764**. The reaction following comprised the treatment with triflic anhydride-pyridine to obtain triflate **765**. The coupling partner **769** was synthesized with 4-methylcatechol **766** as precursor, which was brominated and then protected with methoxymethyl chloride (MOMCl), gaining ether **768**. Aryl boronic acid **769** was then prepared in a one-pot reaction with *n*-butyllithium, followed by treatment with triisopropyl borate (Scheme 11.6).

The step following was a Suzuki coupling of triflate **765** and boronic acid **769** in the presence of tetrakis(triphenylphosphine)palladium, potassium phosphate, and potassium bromide to obtain the coupling product **770** (*504*). Alkaline hydrolysis of



**Scheme 11.6** Preparations of the *Suzuki* precursor material. Reagents and conditions: a) acetone,  $\text{SOCl}_2$ , DMAP, DME, rt, 56%; b) DIAD,  $\text{Ph}_3\text{P}$ , MeOH, THF, rt, 89%; c)  $\text{Tf}_2\text{O}$ , pyridine,  $0^\circ\text{C}$ , 94%; d) MOMCl, NaH, DMF,  $0^\circ\text{C}$ , 90%; e) *n*-BuLi, THF,  $-78^\circ\text{C}$  to  $-40^\circ\text{C}$ ,  $(i\text{-PrO})_3\text{B}$ ,  $\text{Et}_2\text{O}$ ,  $-78^\circ\text{C}$  to rt, 95%

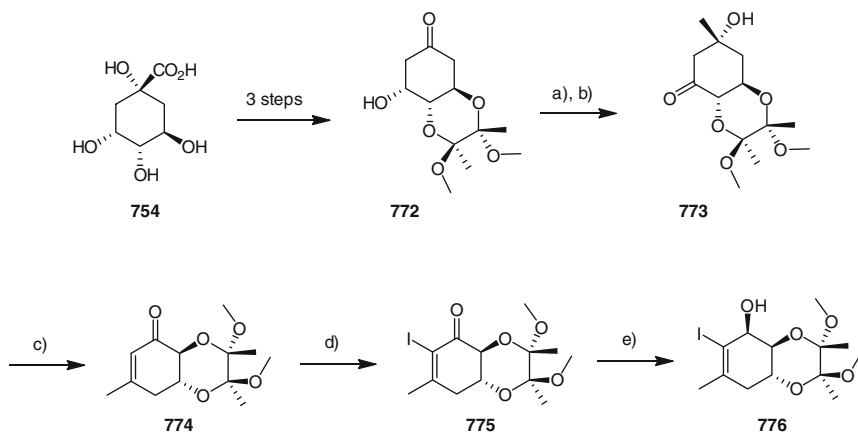
compound **770** and subsequent acid treatment yielded altenusin (**771**), which was also furnished by treatment with boron trichloride ( $\text{BCl}_3$ ) from **770** in one step. The final reaction was an oxidation initiated by  $\text{FeCl}_3$  (**476**) to afford dehydroaltenusin (**737**), for which the spectroscopic and physical properties were identical with natural dehydroaltenusin (Scheme 11.7).



**Scheme 11.7** *Suzuki*-coupling reaction for completion of dehydroaltenusin (**737**). Reagents and conditions: a)  $(\text{Ph}_3\text{P})_4\text{Pd}$ ,  $\text{K}_3\text{PO}_4$ , KBr, dioxane,  $100^\circ\text{C}$ , 93%; b) 2 M KOH, EtOH,  $60^\circ\text{C}$ ; c) 10% HCl-MeOH,  $\text{CH}_2\text{Cl}_2$ , rt, 64% over two steps; d)  $\text{BCl}_3$  (10 equiv.),  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to rt, 63%; e)  $\text{FeCl}_3$ , aq. EtOH, rt, 82%

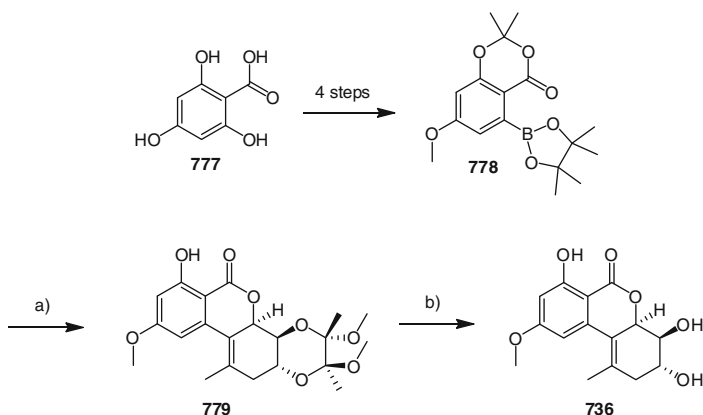
### 11.2.4 Total Synthesis of Neoaaltenuene

In 2009 *Podlech et al.* carried out the total synthesis of neoaaltenuene (**736**) for the first time in 14 steps and an overall yield of 10%, with quinic acid and phloroglucinic acid as precursor molecules. As before, the key reaction consisted of a palladium-catalyzed *Suzuki* reaction, coupling an arene boronate with an iodinated cyclohexene. Starting from quinic acid (**754**),  $\beta$ -hydroxy-ketone **772** was afforded in three steps according to a published procedure (499), by treatment with methylmagnesium bromide to gain a single isomer, most probably due to steric hindrance (505). The steps following included an oxidation step using tetrapropylammonium perruthenate (TPAP) and elimination to obtain cyclohexenone **745**. Iodination was accomplished with trimethylsilyl azide (TMSN<sub>3</sub>), iodine, and subsequent treatment with pyridine (506) to yield the iodinated enone **475**, which was then reduced using di-*iso*-butylaluminium hydride (507) to lead to alcohol **776** (Scheme 11.8).



**Scheme 11.8** Synthesis route to iodide **776**. Reagents and conditions: a) MeMgBr, THF, 50%; b) TPAP, NMO, CH<sub>2</sub>Cl<sub>2</sub>, rt, 12 h, 80%; c) *i*-Pr<sub>2</sub>NEt, Ac<sub>2</sub>O, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to rt, overnight, 90%; d) TMSN<sub>3</sub>, I<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to rt; then pyridine, overnight, 75%; e) DIBAL-H, THF, -78°C, 1.5 h, 98%

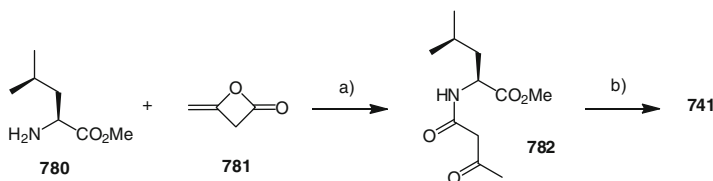
The *Suzuki*-coupling partner **778** was synthesized with phloroglucinic acid **777** as starting material in four steps, consistent with a published procedure (498, 508), followed by a *Suzuki* reaction (502, 509, 510) on the iodinated enone **776** using palladium(II) acetate, cesium carbonate, and S-Phos (2-dicyclohexylphosphanyl-2',6'-dimethoxybiphenyl) (Scheme 11.9). Fortunately, lactone **779** was directly achieved under these conditions, so there was only a deprotection step with trifluoroacetic acid remaining to prepare neoaaltenuene (**736**) in an overall yield of 10% in 14 steps.



**Scheme 11.9** Preparation of neoaltenuene (**736**). Reagents and conditions: a) **776**,  $\text{Cs}_2\text{CO}_3$ , Pd(OAc) $_2$ , S-Phos, dioxane/ $\text{H}_2\text{O}$  (6/1),  $80^\circ\text{C}$ , 2.5 h, 61%; b) TFA/ $\text{H}_2\text{O}$  (6/1), 15 min, rt, 85%

### 11.2.5 Total Synthesis of Tenuazonic Acid

Tenuazonic acid (**741**), a phytotoxin produced by *Alternaria* spp., is structurally related to the tetramic acid family of compounds, and has been found to exhibit antibiotic activity (511). Since 1964, there have been several publications on the total synthesis of **741** (512–515), including the report by Poncet and his group in 1990 (516) (Scheme 11.10). A general method to synthesize the tetramic acids is an intramolecular Dieckmann cyclization of *N*-acyl amino esters. Beginning with methyl *L*-isoleucinate **780**, the *N*-acyl compound **782** was obtained through a nucleophilic reaction (512), which then cyclized to tenuazonic acid **741** under basic conditions and neutralization by acidic work-up. The synthetic product showed a diastereomeric excess of 89%, with the major epimer presenting the same configuration as its precursor (517).

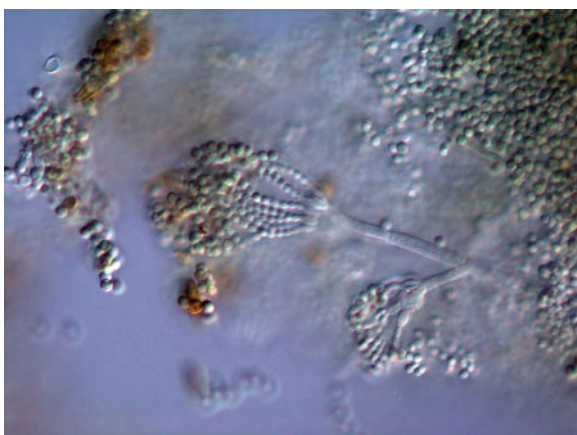


**Scheme 11.10** Preparation of tenuazonic acid by Dieckmann cyclization. Reagents and conditions: a)  $\text{NEt}_3$ ,  $\text{CHCl}_3$ , rt, 16 h (78%); b)  $\text{CH}_3\text{ONa}$ , MeOH, reflux, 2 h (97%, 89% de)



## 12 Skyrins

Skyrins are a family of natural products that have a bisanthraquinone structure with one to four bonding sites between two anthraquinone moieties. These metabolites have been isolated from a variety of fungi and lichens. The ingestion of skyrins has been related to the development of malignant and non-malignant hepatomas (liver tumors), because these compounds occur widely in contaminated rice, corn, and cereals (518). Accordingly, their biological activities have been investigated extensively. The skyrins were discovered initially in the 1950s by *Raistrick* and co-workers. The first representative isolated was skyrin (783) itself in 1954, followed by iridoskyrin (784), rubroskyrin (785), and erythroskyrin (not shown). They were all isolated from the same fungus, *Penicillium islandicum* (see Fig. 12.1 (519)), in the form of yellow or red crystals (520, 521). A detailed review on biaryls that occur in Nature – including the skyrins – has been published by *Bringmann et al.* in 2001 (474).



**Fig. 12.1** Skyrin-containing *Penicillium* species under the light microscope with 400-fold magnification

In 1955, rugulosin A (**786a**) was isolated as yellow crystals from *Penicillium rugulosum* (522). Based on chemical degradation and spectroscopic data, the first structural suggestions for the skyrins were made in the 1950s. In 1958, *Tanaka* reported the structure of skyrin (**783**) and in 1960, *Gatenbeck* determined the structures of iridoskyrin (**784**) and rubroskyrin (**785**), with the structure of **785** corrected later (523, 524). These are all bisanthraquinones: skyrin (**783**) and iridoskyrin (**784**) have only one bonding site between the two anthraquinones, while rubroskyrin (**785**) has two. All compounds possess a methyl group on the aromatic site. Skyrin (**783**) and iridoskyrin (**784**) have six aromatic hydroxy groups, with two of these differentially substituted. Rubroskyrin (**785**) bears two additional hydroxy groups at the aromatic rings and because of the second bonding site, the aromatic structure of the connected rings is reversed.

*Shibata et al.* isolated and described the skyrins rubroskyrin (**785**), rugulosin A (**786a**), and luteoskyrin (**787**). They showed that there are three bonding sites between the two anthraquinone moieties for **786a** and **787** (see Fig. 12.2). Rugulosin A (**786a**) has two hydroxy groups less than rubroskyrin (**785**), while luteoskyrin (**787**) has the same number of these functionalities. *Shibata et al.* also showed that the skyrins are optically active (**783**) (525, 526). Skyrin has the

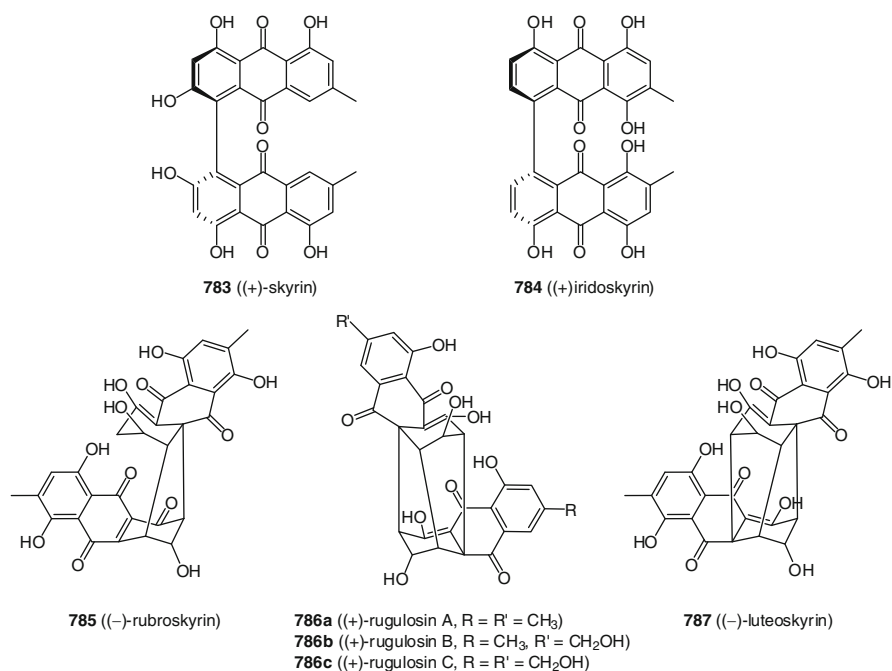


Fig. 12.2 The first isolated skyrins (**783** to **787**)

(*R*)-configuration at the C-C bond and the sign of its optical rotation is positive. The sign of optical rotation of both rubroskyrin (**785**) and luteoskyrin (**787**) is negative and is positive for rugulosin A (**786a**) (527). The structures and absolute configurations of **783**, **785**, **786a**, and **787** have been proven by determining the crystal structure of a dibromo derivative of rugulosin (527, 528).

Up to the present, several skyrin derivatives have been isolated from a large number of fungi and lichens. Beside the skyrins **783**, **784**, **785**, and **787**, oxyskyrin, skyrinol, dicatenarin, erythroskyrin, and many others have been isolated from *Penicillium islandicum* (all not shown). They are all hetero- or homo-dimeric bisanthraquinones, built either from two different or two identical anthraquinone units (525). Skyrin (**783**) itself has been isolated from many different *Penicillium* and *Endothia* species (528), and from *Preussia multispora* (529) and *Hypomyces lactifluorum* as well as from the lichens *Physcia obscura* and *Pyxine endochrysin* (530, 531). Rugulosin A (**786a**) has also been obtained from different *Penicillium* species (but not including *P. islandicum*) and *Endothia* species (528), as well as from *Myrocephium verrucaria* (532).

In 2010, Yamazaki *et al.* discovered the two new rugulosins B and C (**786b**, **786c**), which were obtained as *Penicillium radicum* constituents (533). Their structures, which were proposed using NMR spectroscopic methods, are shown in Fig. 12.2: rugulosin B (**786b**) possesses a CH<sub>2</sub>OH group instead a methyl group and is a heterodimer of two different anthraquinones, while rugulosin C (**786c**) possesses two CH<sub>2</sub>OH groups and is, like rugulosin A (**786a**), a homodimer.

An interesting crystalline 1:1 complex of (–)-luteoskyrin (**787**) and (+)-rugulosin A (**786a**) was reported by Jiang *et al.* in 2010 (518). This complex is formed by four hydrogen bonds between the two skyrins and the X-ray crystallographic structure is shown in Fig. 12.3.

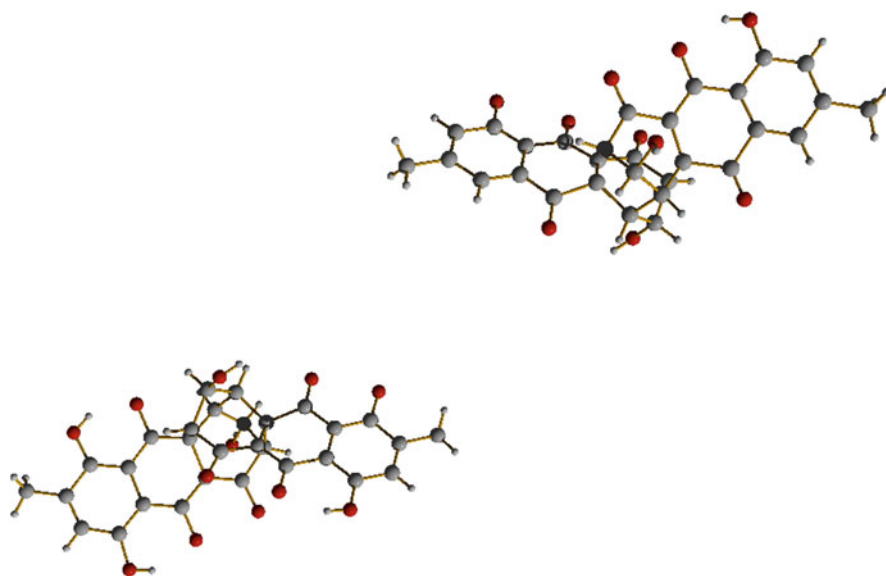
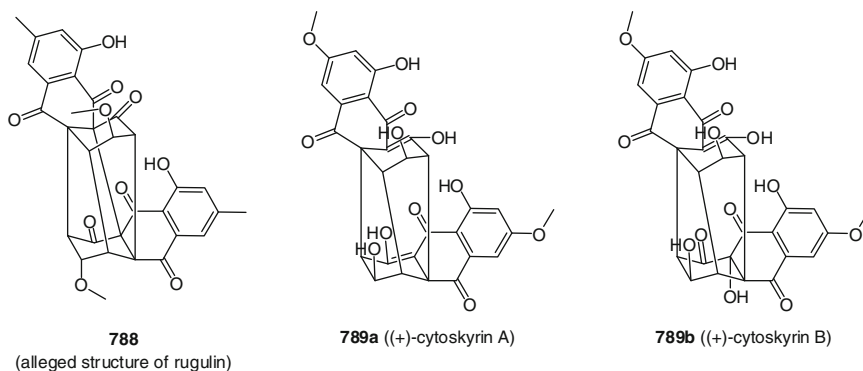


Fig. 12.3 X-ray structures of a 1:1-complex of luteoskyrin (**787**) and rugulosin A (**786a**)

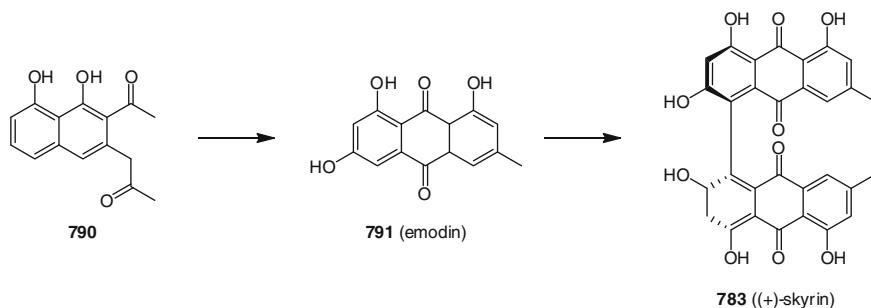
Rugulin (**788**), a skyrin with four bonds between the anthraquinone moieties, was isolated as a minor metabolite from *Penicillium rugulosum* in 1978 by *Sedmera et al.* (534). The structure as shown in Fig. 12.4 was proposed based on spectroscopic data. Instead of hydroxy groups at the connected rings, there are methoxy groups and the aromatic rings possess one hydroxy and one methyl group each. *Nicolaou et al.* synthesized this structure in 2008 and showed that the NMR spectra did not match the structure originally proposed (535). However, up to the present, the true structure of rugulin has not been clarified.

In 2000, *Brady et al.* isolated two new bisanthraquinones from the CR200 strain of a *Cytospora* species (536), which were named cytoskyrins A (**789a**) and B (**789b**) (Fig. 12.4). Both have three bonding sites between the anthraquinones and instead of a methyl group at the aromatic rings, they possess methoxy groups. Cytoskyrin B (**789b**) is a heterodimer, because it has also one hydroxy group at one of its anthraquinone moieties.



**Fig. 12.4** Purported structure of rugulin (**788**) and cytoskyrins A and B (**789a**, **789b**)

In its biosynthesis, skyrin (**783**) plays a central role (524). It is formed very early and is therefore the precursor for all skyrins: they are formed from this parent compound by gradual condensation (536). Skyrin itself is formed from emodin (**791**), an anthraquinone, by phenolic oxidation, as demonstrated by *Franck et al.* (537). They reacted emodin (**791**) with potassium hexacyanoferrate (III) and produced skyrin (**783**) in a low yield. An even earlier precursor of skyrin is the diketonaphthol **790** (538). *Franck et al.* fed *Penicillium islandicum* cultures with  $^{14}\text{C}$ -labeled diketonaphthol **790** and generated significant amounts of  $^{14}\text{C}$ -labeled skyrin (**783**). The important steps of this biosynthesis are shown in Scheme 12.1.



**Scheme 12.1** Biosynthesis sequence for skyrin (**783**). Each arrow can refer to more than one reaction

## 12.1 Biological Properties

Among the skyrins, in particular, skyrin (**783**), rugulosin A (**786a**), and luteoskyrin (**787**) have been well investigated biologically. Skyrin (**783**) is neither mutagenic nor carcinogenic, but binds to DNA and RNA (*539, 540*). It shows inhibitory effects on RNA transcription but not on the RNA polymerase of viral RNA (*541*). Skyrin (**783**) also has inhibitory effects on murine leukemia cells and on the ATPase activity of microsomes (*539*). The cytotoxic effect on human leukemia cells is weak (apoptosis at an  $IC_{30}$  value of  $40 \mu\text{g}/\text{cm}^3$ ) (*542*). Skyrin (**783**) has antioxidant activity, and acts as a scavenger for radicals ( $\bullet\text{OH}$  or carbon radicals  $\bullet\text{R}$ ) and singlet oxygen ( $^1\text{O}_2$ ), but its antioxidant potency is about five times less than that of vitamin E (*543*).

Luteoskyrin (**787**) is the most active hepatocarcinogenic, hepatotoxic and mutagenic skyrin derivative (*518, 545*), with a hepatocarcinogenic potential some 10 times greater for mice than that determined for rugulosin A (**786a**) (*546*). In a DNA-repair test in rat hepatocytes, 100% of the cells showed DNA damage with a  $10^{-5}$  molar solution of luteoskyrin (*544*). The main point of action is the liver, because luteoskyrin and rugulosin A (**786a**) get accumulated there, especially in the mitochondrial and microsomal fractions (*518, 545*). Luteoskyrin (**787**) is hepatotoxic and hepatocarcinogenic to rats as well as mice (*545*). It also shows a potent cytotoxic effect on human leukemia cells (*542*): the  $IC_{30}$  value was  $0.1 \mu\text{g}/\text{cm}^3$ , which is 400 times more potent than the  $IC_{30}$  value of skyrin (**783**). Luteoskyrin (**787**) has also inhibitory effects on the RNA-polymerase activity of viral RNA (*541*).

Rugulosin A (**786a**) is, like luteoskyrin (**787**), a hepatotoxic and carcinogenic compound to mice (*518, 546*). It is poisonous to mice and rats and causes acute liver injury with cell necrosis and fatty degeneration, but its hepatotoxic effect is about

two-fold less than that of luteoskyrin (**787**). Because of slow transportation in the bloodstream and gradual hepatic accumulation, rugulosin A (**786a**) is a slow-acting toxicant (545). For human leukemia cells ( $IC_{30}$  value,  $5 \mu\text{g}/\text{cm}^3$ ), rugulosin A (**786a**) is more cytotoxic than skyrin (**783**) but less so than luteoskyrin (**787**) (542). Rugulosin A (**786a**) has not been found to be mutagenic in the *Ames/Salmonella* assay but shows growth inhibitory effects for concentrations higher than  $0.3 \mu\text{g}/\text{plate}$  (540). Its hepatocarcinogenicity derives from forming polychelate and stable complexes with nucleic acids, but it is less potent in this regard than luteoskyrin (540, 544, 546). Rugulosin A (**786a**) causes chronic hepatocellular injury and hepatotoxicity, and, as mentioned, its hepatocarcinogenic potency is only one tenth that of luteoskyrin (**787**) (546). The  $LD_{50}$  value for female rats (Wistar strain) is 55 mg/kg; for male mice (ddys strain) it is 44 mg/kg. Rugulosin A was given intraperitoneally as a solution in olive oil (546, 547). Like luteoskyrin (**787**), rugulosin A (**786a**) shows inhibitory effects on RNA-polymerase activity (541), and is cytotoxic to tumor and mammalian cells (545, 546). Rugulosin A (**786a**) and rugulosin C (**786c**) showed antimicrobial activity against *Staphylococcus aureus* (533).

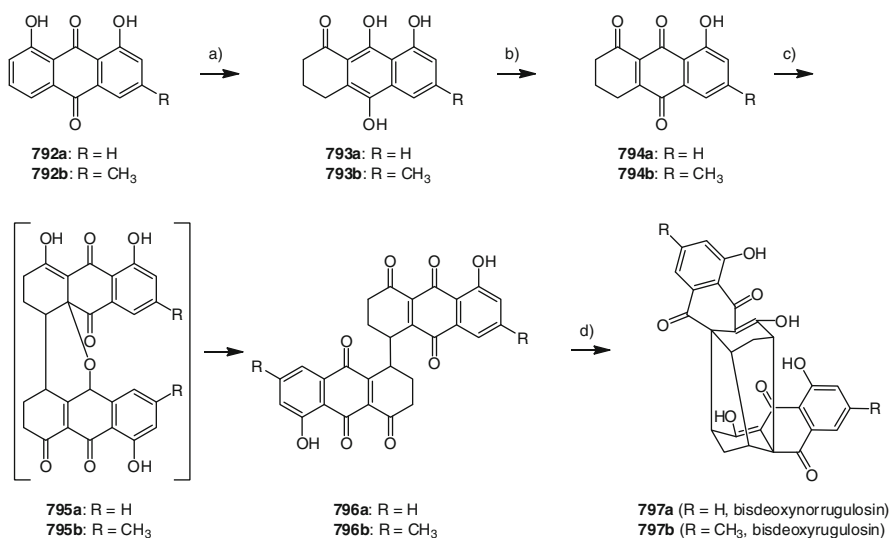
The mutagenic action of rubroskyrin (**785**) was examined by Mori and co-workers, who revealed that this activity resulted from the generation of active oxygen in the course of detoxification. Rubroskyrin (**785**) becomes reduced by NADH and is autoxidized by dissolved oxygen. Then,  $\text{H}_2\text{O}_2$  is produced, which immediately decomposes to reactive oxygen by a catalase. Thereafter, superoxide dismutase produces the very reactive superoxide anion. Once this process is completed, rubroskyrin is transformed to stable products that are not toxic (548).

Cytoskyrin A (**789a**) was found to be highly active in a biochemical induction assay, which identifies compounds that damage DNA or inhibit DNA synthesis. It inhibits the incorporation of thymidine into DNA. Rugulosin A (**786a**), luteoskyrin (**787**) and cytoskyrin B (**789b**) do not show detectable activity in this biochemical induction assay. Their activity seems to be highly dependent on the three-dimensional structure of the compound (536, 549). The antimicrobial activity of cytoskyrin A (**789a**) is in the same range as penicillin G. Compound **789a** is active against *Gram*-positive bacteria and *Escherichia coli* but not against other *Gram*-negative bacteria. It is also cytotoxic against human tumor cell lines ( $IC_{50}$  4–24  $\mu\text{g}/\text{cm}^3$ ).

To summarize, the skyrins show very different biological activities. The main organ affected is the liver (518), especially by luteoskyrin (**787**), which showed potent hepatotoxic and hepatocarcinogenic activity (544, 545). Rugulosin A (**786a**) is less active than luteoskyrin (**787**) (544–546), and skyrin (**783**) is neither a mutagenic nor a carcinogenic substance (539, 540). Cytoskyrin A (**789a**) has potential as an anticancer agent (536, 549), while skyrin (**783**) shows antioxidant effects (543).

## 12.2 Syntheses of Skyrin Model Systems

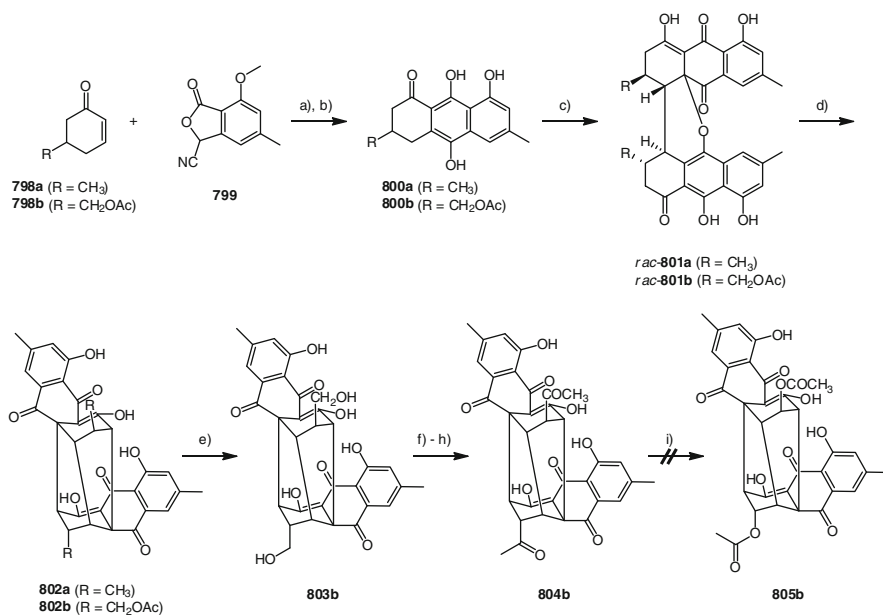
The first synthesis of a rugulosin-model system, was published by *Shibata et al.* in 1978 (550). Later syntheses have built on this first procedure, which is described in Scheme 12.2 (551). The synthesis, which is biomimetic, started with the reduction of the anthraquinone **792** with hydrogen/palladium and gave **793**. Oxidation with lead tetraacetate gave the quinone **794**, which could be further oxidized with chromium(VI) oxide to give as intermediate the flavoskyrin-type structure **795**. This is formed by a [4 + 2]-cycloaddition and was then converted *in situ* to the skyrin-like structure **796** by ether cleavage. Using pyridine, a cascade of two *Michael* reactions occurred and gave bisdeoxynorrugulosin (**797a**) and bisdeoxyrugulosin (**797b**) as products.



**Scheme 12.2** First synthesis of rugulosin model compounds (**797**) by *Shibata et al.* Reagents and conditions: a) H<sub>2</sub>, Pd/C; b) Pb(OAc)<sub>4</sub>, HOAc, rt, 84% for **794a**; c) CrO<sub>3</sub>, HOAc, rt, 3.9% for **796a**; d) pyridine, rt, 1% for **797b**

This first synthesis of *Shibata* was optimized by *Snider et al.* in 2005. With the same reactants but different reaction conditions, they could increase the overall yield to 52% (552). *Snider et al.* also attempted to synthesize rugulosin A (**786a**), but did not achieve this goal. Nevertheless, they presented a new route to a promising rugulosin precursor (see Scheme 12.3). Starting from the cyclohexenone **798** and the lactone **799**, the tricyclic species **800** was formed after deprotection. With lead tetraacetate, the flavoskyrin-type structure **801** was obtained (see also

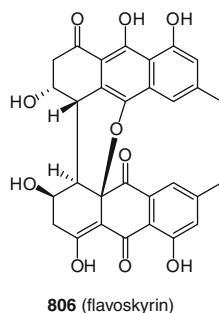
Scheme 12.2). A notable feature about this reaction is that only one diastereomer was formed. The authors explained this by the steric effect of the residue R group. With pyridine, the rugulosin-type structure **802** was formed by the same mechanism as described for *Shibata's* synthesis (see above). *Snider et al.* tried to convert **802b** into rugulosin A (**786a**). Initially, the acetate was hydrolyzed with potassium carbonate ( $\rightarrow$  **803b**), then the resulting alcohol was oxidized with *Dess-Martin*-periodinane. A *Grignard* reaction with methyl magnesium bromide, followed by repeated oxidation with *Dess-Martin*-periodinane, gave the ketone **804b**. It was planned to insert an oxygen by *Baeyer-Villiger*-oxidation, but the ester **805b** could not be formed, even under the various conditions used.



**Scheme 12.3** Racemic synthesis of rugulosin model compounds **802a** and **804b** by *Snider et al.*. Reagents and conditions: a) *t*-BuOK, DMSO, 0°C to rt, 50 min for **798a**; *t*-BuOK, THF, -78°C to 0°C, 50 min for **798b**; b) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78°C to rt, 3 h, 48% over two steps for **800a**; BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78°C to 0°C, 16 h, 40% over two steps for **800b**; c) Pb(OAc)<sub>4</sub>, HOAc, rt, 20 min; then 75°C, 40 min, 74% for **801a**, 53% for **801b**; d) pyridine, 75°C; then 85–110°C, 70% for **802a**; pyridine, 80–110°C for **802b**; e) K<sub>2</sub>CO<sub>3</sub>, MeOH, rt, 2 h, 88% over two steps for **803b**; f) DMP, 1 h; g) MeMgBr, THF, 0°C; h) DMP, CHCl<sub>3</sub>, rt, 2 h, 36% over three steps; i) *m*-CPBA

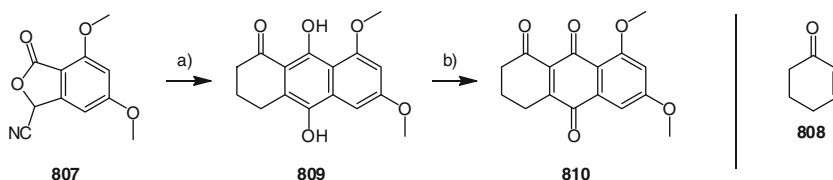
In the same year, *Nicolaou et al.* reported an interesting cascade reaction, in which it was possible to form model systems of skyrin (**783**), flavoskyrin (**806**, see Fig. 12.5), rubroskyrin (**785**), cytoskyrin A (**789a**), and the purported structure of rugulin (**788**).





**Fig. 12.5** Structure of flavoskyrin (**806**)

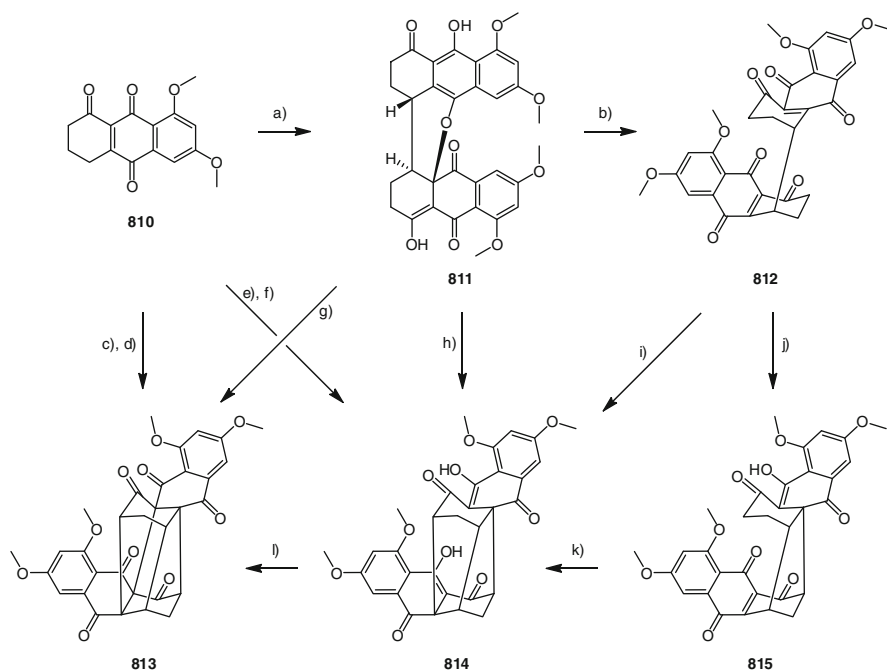
The important anthraquinone-intermediate **810** has been synthesized in two steps from the lactone **807**, which has also been used by *Snider et al.* for their synthesis. With LiHMDS and cyclohex-2-enone (**808**), the tricyclic **809** was formed (see Scheme 12.4 (553)). Oxidation with cerium ammonium nitrate gave the anthraquinone **810**.



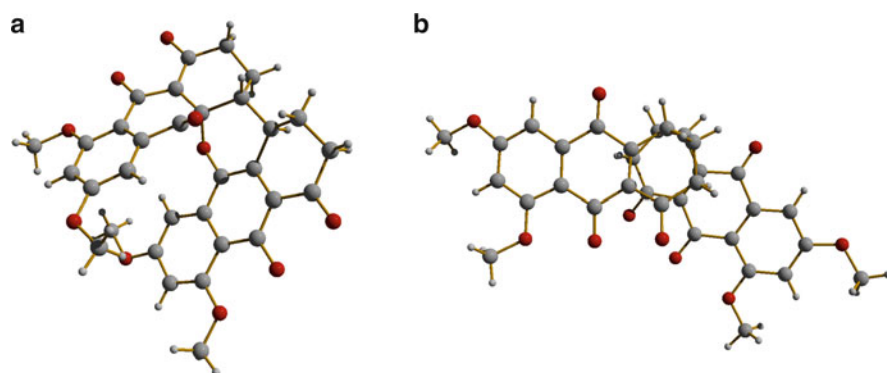
**Scheme 12.4** First steps towards *Nicolaou's* skyrin-model systems. Reagents and conditions: a) LiHMDS, THF,  $-78^{\circ}\text{C}$ ; then **808**,  $-78^{\circ}\text{C}$  to rt, 4 h; b) CAN

In the so-called “cytoskyrin cascade”, the anthraquinone **810** was converted into five different model systems (Scheme 12.5). Thus, with catalytic amounts of camphorsulphonic acid, the flavoskyrin-model system **811** was formed in excellent yield. Under the same conditions but with the addition of manganese dioxide, the rugulin-model system **813** was obtained. Reaction with camphorsulphonic acid, followed by reaction with manganese dioxide and triethylamine, gave the cytoskyrin A-model system **814**. By addition of manganese dioxide to **814**, **813** was formed. The flavoskyrin-model system **811** could be converted into the skyrin-model system **812** (with manganese dioxide) and the cytoskyrin A-model system **814** (with manganese dioxide and triethylamine). This product could also be obtained from the skyrin-model system **812** (with five equivalents of triethylamine) or the rubroskyrin-model system **815** (with triethylamine). The rubroskyrin-model system was formed from **812** with only two equivalents of triethylamine.

*Nicolaou et al.* obtained crystal structures of the model systems **811**, **812**, and **815**. The crystal structures of the skyrin- and flavoskyrin-model systems are shown in Fig. 12.6.



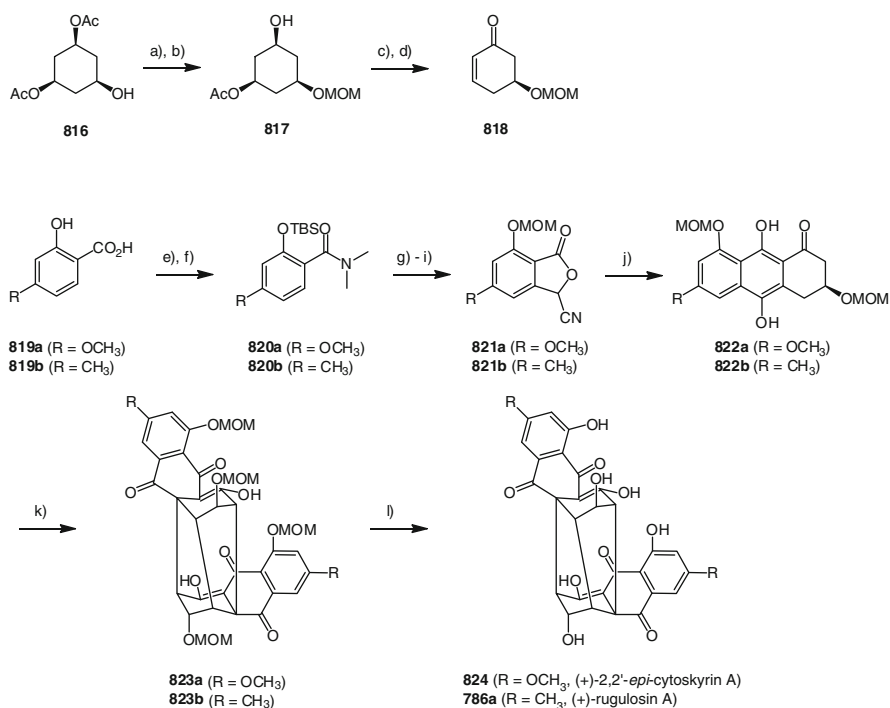
**Scheme 12.5** Nicolaou's racemic "cytosyrin-cascade" for the synthesis of five model systems by oxidation and *Michael* addition. Reagents and conditions: a) CSA (cat.),  $\text{CH}_2\text{Cl}_2$ , rt, 1 h, 94%; b)  $\text{MnO}_2$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 1 h, 83%; c) CSA (cat.),  $\text{CH}_2\text{Cl}_2$ , 1 h, rt; d)  $\text{MnO}_2$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 88 h, 75% over two steps; e) CSA (cat.)  $\text{CH}_2\text{Cl}_2$ , rt, 1 h; f)  $\text{MnO}_2$ ,  $\text{NEt}_3$ ,  $\text{CH}_2\text{Cl}_2$ , 45°C, 36 h, 66% over two steps; g)  $\text{MnO}_2$ ,  $\text{CH}_2\text{Cl}_2$ , 45°C, 48 h, quant; h)  $\text{MnO}_2$ ,  $\text{NEt}_3$ ,  $\text{CH}_2\text{Cl}_2$ , rt to 45°C, 20 h, quant; i)  $\text{NEt}_3$  (5 eq.),  $\text{CH}_2\text{Cl}_2$ , 45°C, 16 h, 95%; j)  $\text{NEt}_3$  (2 eq.),  $\text{CH}_2\text{Cl}_2$ , rt, 1 h, 65%; k)  $\text{NEt}_3$ ,  $\text{CH}_2\text{Cl}_2$ , 45°C, 16 h, 95%; l)  $\text{MnO}_2$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 20 h, 95%



**Fig. 12.6** Crystal structures of the flavoskyrin-model system **811** (left) and the skyrin-model system **812** (right), as synthesized by Nicolaou *et al.*

## 12.3 Total Syntheses of Skyrins

The first total syntheses of two skyrins were presented by *Nicolaou et al.* in 2005 (554). For both, the same route was taken, which is shown in Scheme 12.6. The starting material was the chiral diester **816**, which was MOM-protected and then regioselectively mono-hydrolyzed with porcine liver esterase. Oxidation of the remaining alcohol **817** with pyridinium chlorochromate, following elimination with diazabicyclo[5.4.0]undec-7-ene, gave the cyclohexenone **818** in good yield. The phenol **819** was first TBS-protected, and then the amide **820** was obtained from the acid chloride. With *tert*-butyllithium and DMF, the corresponding aldehyde was formed, which was converted into the deprotected nitrile by treatment with TMSCN.



**Scheme 12.6** Total syntheses of (+)-2,2'-*epi*-cytoskyrin A (**824**) and (+)-rugulosin A (**786a**) by *Nicolaou et al.* Reagents and conditions: a) MOMCl, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1.5 h; b) PLE, buffer pH 8, *t*-BuOH, rt, 4 h, 95% over two steps; c) PCC, NaOAc, CH<sub>2</sub>Cl<sub>2</sub>, rt, 12 h; (d) DBU, CH<sub>2</sub>Cl<sub>2</sub>, rt, 10 min, 68% over two steps; e) TBSCl, imidazole, DMF, rt, 16 h; f) (COCl)<sub>2</sub>, DMF (cat.), CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 2 h; then Me<sub>2</sub>NH•HCl, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 30 min, 85% over two steps for **820a**; 74% over two steps for **820b**; g) TMEDA, *t*-BuLi, DMF, THF, -78°C to rt; h) TMSCN, KCN (cat.), 18-Crown-6 (cat.), CH<sub>2</sub>Cl<sub>2</sub>, rt, 4 h; then AcOH, 12 h; i) MOMCl, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 1 h, 64% over 3 steps for **821a**; 50% over three steps for **821b**; j) LiHMDS, **818**, THF, -78°C; then **821**, -78°C to 0°C, 2 h; k) MnO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 10 min; then MnO<sub>2</sub>, NEt<sub>3</sub>, rt to 45°C, 12 h, 60% over two steps for **823a**; 50% over two steps for **823b**; l) HCl, MeOH, THF, 60°C, 12 h, 93% for **824**; 98% for **786a**

Reprotection with MOMCl gave lactone **821**. This was converted with lithium hexamethyldisilazane and the cyclohexenone **818** to the tricyclic species **822**. Oxidation with manganese dioxide, followed by dimerization, gave bisanthraquinone **823**. Global deprotection with hydrogen chloride yielded (+)-2,2'-*epi*-cytoskyrin A (**824**) and (+)-rugulosin A (**786a**). A crystal structure of the latter is shown in Fig. 12.7.

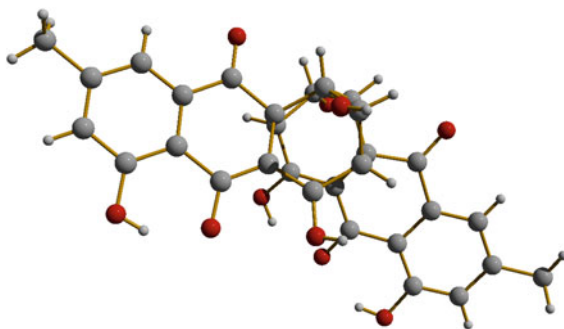
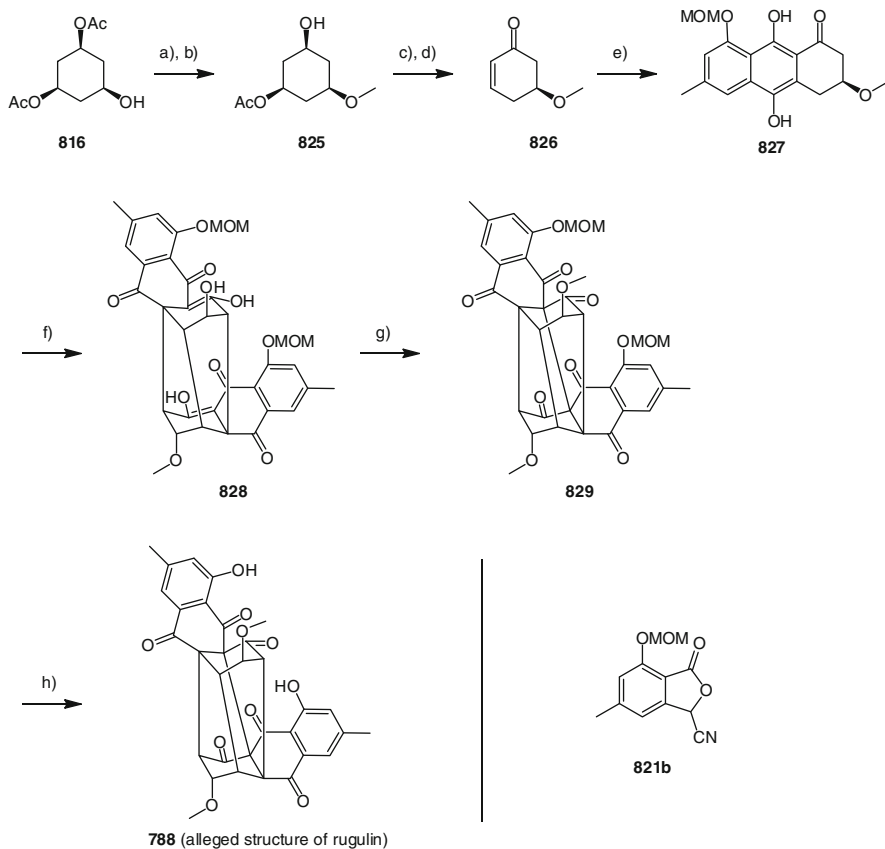


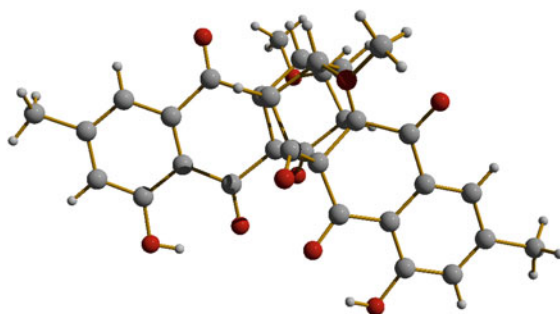
Fig. 12.7 Crystal structure of rugulosin A (**786a**), as synthesized by Nicolaou *et al.*

A compound thought to be rugulin (**788**, see Fig. 12.4) was synthesized by Nicolaou *et al.* in 2008. By comparing the NMR spectra of the synthesized substance and the isolated rugulin, it was apparent that the reported structure of rugulin was incorrect. However, the actual structure of rugulin has not been elucidated to date. The synthesis of the reported structure for rugulin (Scheme 12.7. (535, 555)) began with the same diester **816** used for the syntheses of (+)-2,2'-*epi*-cytoskyrin A (**824**) and (+)-rugulosin A (**786a**). Protection as a methyl ether and selective hydrolysis with porcine liver esterase gave the alcohol **825** in 65% *ee*. Oxidation and elimination afforded cyclohexenone **826**, which was converted with lactone **821b** into the tricyclic **827**. For the synthesis of **821b**, see Scheme 12.6. Oxidation and dimerization of **827** with manganese dioxide and triethylamine yielded the bisanthraquinone **828**. With an excess of manganese dioxide, **829** was formed, and deprotection of the MOM-ether gave a compound with the reported structure of rugulin (**788**).

The structure of the product was proved from its X-ray crystal structure, thereby providing evidence that the structure of rugulin reported is incorrect (see Fig. 12.8).



**Scheme 12.7** Total synthesis of the reported structure of rugulin (**788**) by *Nicolaou et al.*. Reagents and conditions: a) MeOTf, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 24 h; b) PLE, phosphate buffer pH 8, *t*-BuOH, rt, 35% over two steps, 65% *ee*; c) PCC, CH<sub>2</sub>Cl<sub>2</sub>, rt, 12 h; d) DBU, CH<sub>2</sub>Cl<sub>2</sub>, rt, 10 min, 90% over two steps; e) LiHMDS, **821b**, THF, -78°C, 1 h; then **826**, 52%; f) MnO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; then NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt to 45°C, 12 h, 40%; g) MnO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 18 h, 70%; h) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 10–15 min, quant



**Fig. 12.8** Crystal structure of the structure reported for rugulin (**788**), as synthesized by *Nicolaou et al.*

## 13 Xanthenes

Xanthenes are produced by a variety of multi- and unicellular fungi, with many of these having specific toxic or therapeutic effects to other species, including humans. Since 1985, the synthesis of xanthone natural products from fungi has resulted in the total synthesis of some large and structurally complex compounds. Also, new methods have been developed for the synthesis of the challenging tetrahydroxanthone core, which was hitherto almost unknown. The synthesis of xanthone natural products is also becoming of increasing interest to members of the medicinal chemistry community, as the many different biological activities possessed by the xanthone core, and the many target biomolecules with which it interacts, are beginning to become unveiled. Hence, some xanthenes have been termed “privileged structures” (556) (Fig. 13.1).

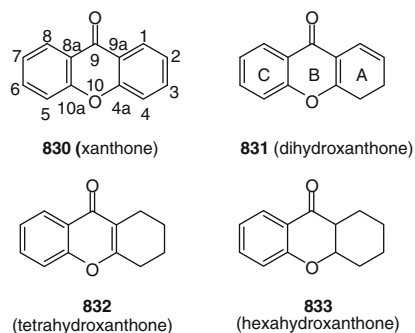
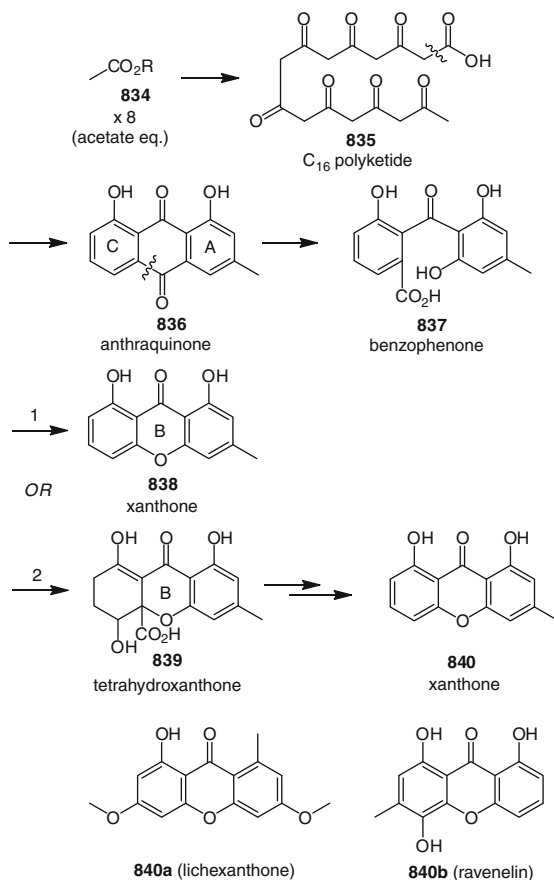


Fig. 13.1 Xanthenes

The xanthone family as found in fungi has four sub-classes, and fully aromatized, dihydroxanthenes, tetrahydroxanthenes, and hexahydroxanthenes all occur in Nature, and can be found also in combination with other xanthone components as either homodimers or heterodimers. The numbering of the xanthone nucleus is in accordance with IUPAC recommendations.

Xanthone biosynthesis occurs by distinct pathways in fungi, with the xanthone unit being completely derived from polyketide species (**835**, Scheme 13.1). Even at the time of a major review by *Roberts* it was suggested that the xanthone nucleus may be of “polyacetic acid” origin (557). Earlier, in 1953, *Birch* and *Donovan* had suggested this pathway, which utilizes the head-to-tail linkage of acetate units, to explain the generation of structures associated with many phenolic natural products (558). A polyacetate unit, **835** (Scheme 13.1) is cyclized to form an anthraquinone, **836**, followed by oxidative cleavage. The following biosynthesis pathways are dependent on the producing organism: xanthenes (e.g. **838**) may form *via* cyclization directly from a benzophenone intermediate (**837** to **838**, pathway (1)). Alternatively, it has been proposed that in some cases the fully aromatic species may result by elimination from, or allylic re-arrangement of, polyhydrogenated intermediate xanthenes (**837** to **839** to **838**, pathway (2)) (559).

While the number of methodologies for the synthesis of hydro-xanthenes is much lower, an effective and general one-step methodology for the synthesis of



**Scheme 13.1** Xanthone biosynthesis pathways in fungi

the partially reduced xanthone core has been developed in the form of a domino oxa-*Michael* aldol condensation reaction of salicylaldehyde derivatives and cyclohexenones (556, 560–566).

## 13.1 Xanthenes

### 13.1.1 *Bikaverin*

In 1957, *Nakamura* and co-workers isolated bikaverin (**841**, Fig. 13.2), a deep red colored compound, from *Gibberella fujikori* (567). Bikaverin was later re-isolated from the same source (568, 569) and the structure determined (569, 570) and confirmed by a single crystal X-ray diffraction study (571). The compound has also been isolated from *Fusarium oxysporum* (570, 572), *Fusarium f. sp. bycoppersici*, and *Mycogone jaapai* (573) and is known to have a vacuolation effect in fungi (570), a specific antiprotozoal activity against *Leishmania brasiliensis* (568), and to be cytotoxic to various tumor cell types (574, 575).

Other full (575–579) and partial (580, 581) syntheses of bikaverin (**841**) have been reported. *Vining* and co-workers have investigated the biosynthesis of this compound, finding it to be formed from a single polyketide species (582).

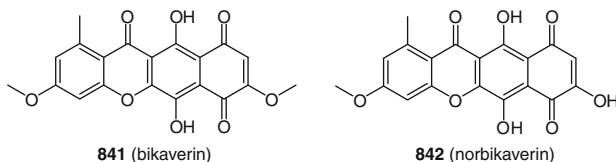
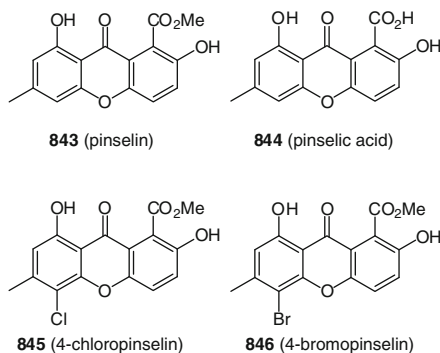


Fig. 13.2 Bikaverin (**841**) and norbikaverin (**842**)

### 13.1.2 *Pinselin and Pinselic Acid*

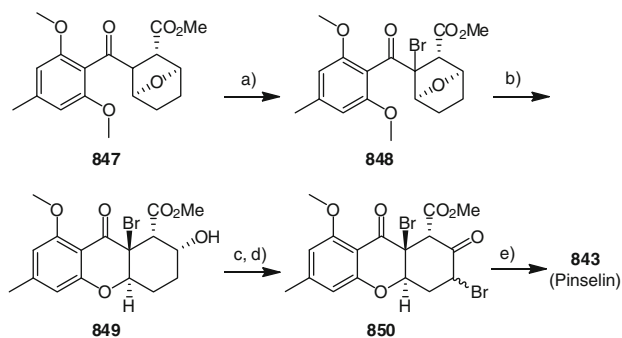
Pinselin (**843**) and pinselic acid (**844**) (Fig. 13.3) were first isolated from cultured *Penicillium amarum* and were originally identified by chemical degradation processes (583). In a rarely occurring event, pinselin (**843**) was also isolated from the plant *Cassia occidentalis* (584), although it was misidentified initially as 1,7-dihydroxy-5-methoxycarbonyl-3-methylxanthone and later corrected as being identical with pinselin (**843**) (585). 4-Bromopinselin (**845**) and 4-chloropinselin (**846**) have been isolated from *Monilinia fructicola* by *Kachi* and co-workers in 1986 (586), and the latter compound was also isolated together with some ring-expanded lactones by *Suzuki* and co-workers in 1989 (587).





**Fig. 13.3** Pinselin (**843**), pinselic acid (**844**), 4-chloropinselin (**845**), and 4-bromopinselin (**846**)

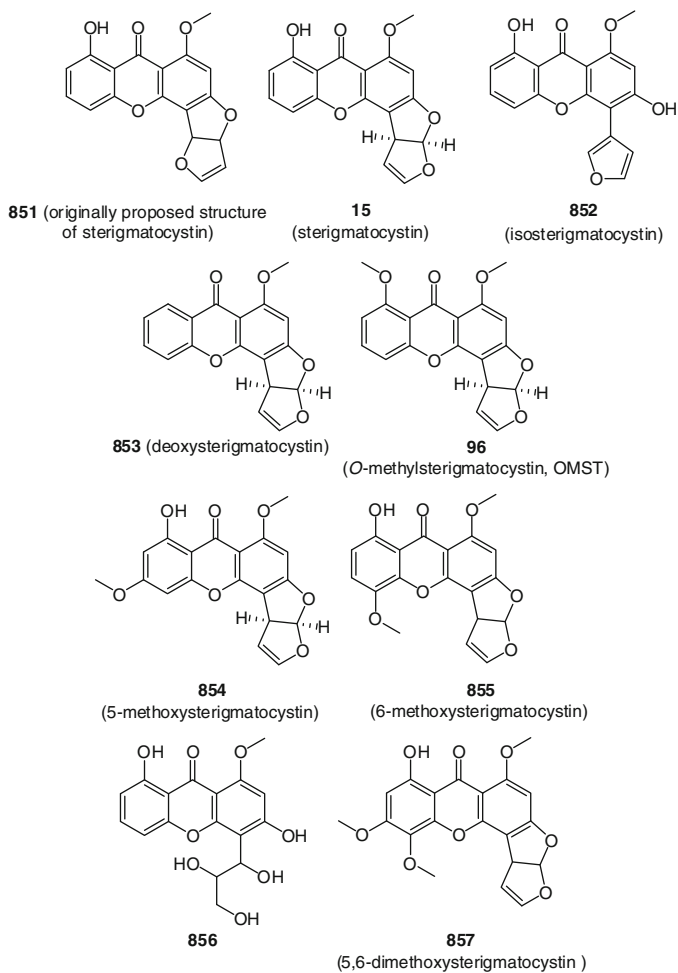
In 1985 *Whalley* and co-workers reported the synthesis of pinselin (**843**) by a *Lewis* acid-mediated furan-ring opening/pyranone-ring closing of bromide **848**, followed by oxidation of this alcohol,  $\alpha$ -bromination, and aromatization with base to give pinselin (**843**) (588, 589) (Scheme 13.2)



**Scheme 13.2** Synthesis of pinselin (**843**) by *Whalley et al.* Reagents and conditions: a)  $\text{PhNMe}_3\text{Br}_3$ ; b)  $\text{BCl}_3$ ; c)  $[\text{O}]$ ; d)  $\text{CuBr}_2$ ; e)  $\text{Et}_3\text{N}$

### 13.1.3 Sterigmatocystin and Derivatives

The optically active fungal metabolite sterigmatocystin (**15**) (Fig. 13.4, see also Sect. 13.2) was first isolated (but not structurally defined) from *Aspergillus versicolor* by *Abou-Zeid* in 1953 (590), and has been purified subsequently a number of times from this species (591–594) as well as the related *A. parasiticus* (595) and *A. multicolor* (596), and both *Emericella venezuelensis* (597) and *Emericella astellata* (598) (both of which also produced aflatoxins).



**Fig. 13.4** Sterigmatocystin (**15**) and derivatives (stereochemistry shown, where known)

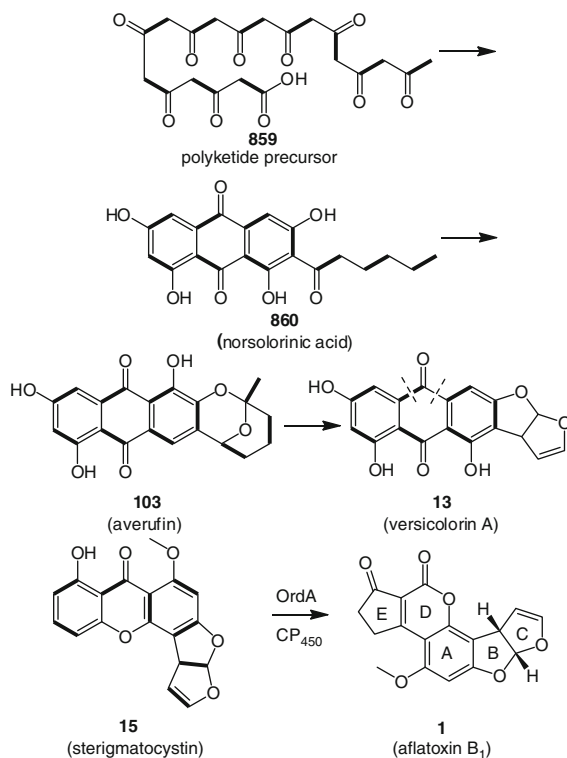
### 13.1.3.1 Isolation and Structural Determination

The structure of sterigmatocystin was originally determined (557) using a combination of spectroscopic techniques and chemical degradation (599–600). *Bullock* and co-workers reported in 1962 the characterization of isosterigmatocystin (**852**), formed by reaction of sterigmatocystin (**15**) with base, and the reassignment of the previously reported structure **851** (Fig. 13.4) to the correct structure **15** (601), which represented the first known natural dihydrofurobenzofuran ring system. Such a structural motif was later also found in the aflatoxins and other carcinogenic products from microorganisms. The same group reported in 1963 the isolation of 6-methoxysterigmatocystin (**855**) (Fig. 13.4) after isolating it and a related

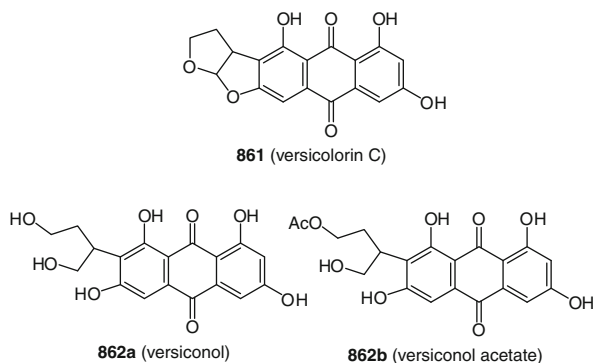


derivative of dihydrosterigmatocystin (**16**) (Fig. 13.5). Burkhardt and Forgacs described *O*-methylsterigmatocystin (**96**) (Fig. 13.5) from an isolate of a highly toxic aflatoxin-containing strain of *Aspergillus flavus* (cycad strain II) and its structure confirmation by synthesis from **15** (610). In 1984, Maes and Steyn reported 3,8-dihydroxy-4-(2,3-dihydroxy-1-hydroxymethylpropyl)-1-methoxyxanthone (**856**) (Fig. 13.4), an open-chain isomer of the difuran component of the sterigmatocystins, after isolation from *Bipolaris sorokiniana*. This species also contained sufficient amounts of anthraquinones (averufin (**103**), versicolorin C (**861**), versiconol (**862**), versiconol acetate (**863**), and sterigmatocystin (**15**) for isolation (608).

The isolation of all these compounds alongside each other provides some evidence to support the proposed acetate/polymalonate pathway to polyhydroxylated anthraquinones by cyclization/condensation to xanthenes by oxidative cleavage and to coumarins (*i.e.* aflatoxins) through rearrangement: such a sequence had already been suggested for the ergochromes (see Sect. 13.3.3) (611) and ravenelin (**840b**) (Scheme 13.1) (612, 613). In 2002, Gloer and co-workers reported the isolation of 7-deoxysterigmatocystin (**853**) (Fig. 13.4) together with two non-xanthone products from *Humicola fuscoatra*, a mycoparasitic fungus that invades other fungi (614) (Scheme 13.3 and Fig. 13.6).

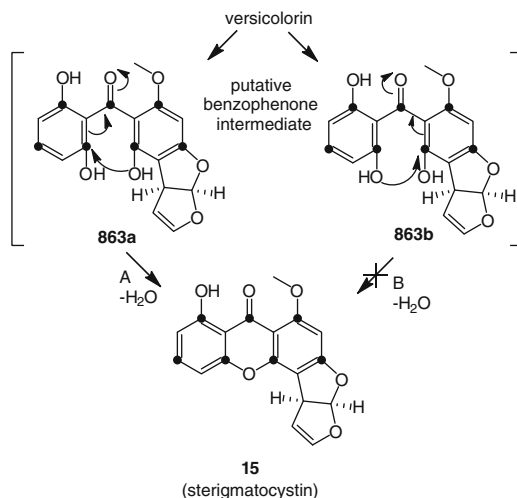


**Scheme 13.3** Suggested pathway for (sterigmatocystin) biosynthesis



**Fig. 13.6** Versicolorin C (**861**), versiconol (**862a**) and its acetate **862b**

The final steps of conversion to aflatoxin seem to be catalyzed by a single cytochrome-P<sub>450</sub> oxidative cleavage of the aromatic ring with an epoxide intermediate, O-demethylation, dehydration, decarboxylation, and rearrangement to give aflatoxin B<sub>1</sub> (**1**) (607), and the pathway also involves an intermediate reductive step. Following previous studies on the <sup>13</sup>C NMR spectrum of sterigmatocystin (**15**) (615, 617), Nakashima and Vederas reported in 1982 the use of the spin-echo resolution technique in the <sup>13</sup>C NMR analysis of **15** isolated from *Aspergillus versicolor* grown in the presence of <sup>13</sup>C-labeled sodium acetate (616). In a previous study, <sup>13</sup>C incorporation suggested that the intermediate (benzophenone) between versicolorin A (**13**) (anthraquinone) and sterigmatocystin (**15**) (xanthone) is unsymmetrical, as the resulting pattern of <sup>13</sup>C incorporation is unscrambled (617). Of two possible modes of oxa-Michael addition to form the xanthone ring of sterigmatocystin (**15**), via path A or B (Scheme 13.4), the authors determined that the cyclization occurs only from path A, *i.e.* nucleophilic attack of the hydroxy group of a benzophenone intermediate derived from oxidative ring-cleavage of versicolorin A (**13**) (618). This study by Zamir and Hufford on the intermediates in aflatoxin biosynthesis was carried out using kinetic pulse-labeling, beginning with radioactive acetate. The various intermediates could be radiotraced (with TLC analysis) so as to follow their order of appearance in the *A. versicolor* cultures. As expected, averufin (**103**) and norsolonic acid (**156**) appeared first, followed by versicolorin A (**13**), aflatoxins, and sterigmatocystin (**15**), a finding that led the authors to speculate that perhaps **15** is the result of a branched biosynthesis pathway, rather than necessarily being an aflatoxin precursor.



**Scheme 13.4** Observations of *Nakashima* and *Vederas* with respect to the mode of xanthone formation in sterigmatocystin

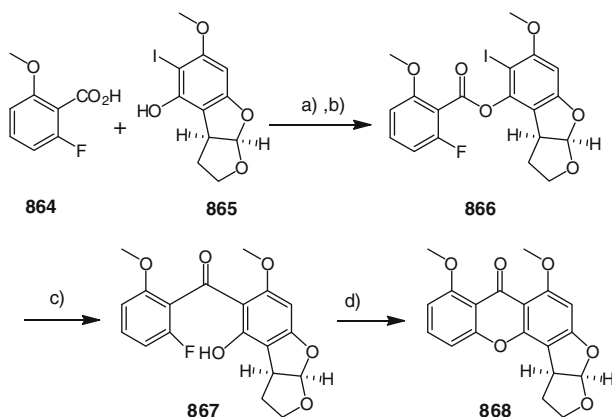
### 13.1.3.3 Bioactivity

Sterigmatocystin (**15**) has been found to be an inhibitor of the growth of transplanted P-388 and L-1210 leukemias in mice (619). Interestingly, **15** has also been isolated from an *Aspergillus fumigatus* strain, which was isolated from surgically removed human lung samples (620) and can be collected from the air in various environments when high in organic matter-derived dust, such as composting plants (621), and from *Aspergillus versicolor* samples collected from household carpet dust (622), highlighting the significant nature of this environmental toxin to humans.

### 13.1.3.4 Synthesis

*Horne* and *Rodrigo* reported in 1990 the synthesis of dihydro-*O*-methylsterigmatocystin (**868**) (623) utilizing an iodide intermediate, **865**, which they had developed for an earlier synthesis of aflatoxin B<sub>2</sub> (**2**) (39), as part of an investigation for a general method leading to the synthesis of substituted xanthenes. The key conversions are an esterification, anionic *Fries* rearrangement, and base-mediated cyclization of a phenol upon an aryl fluoride to deliver the xanthone core of **868** (623) (Scheme 13.5).

Having found that standard methods of xanthone synthesis were not applicable to the synthesis of sterigmatocystin species of their interest, *Casillas* and *Townsend* synthesized *O*-methylsterigmatocystin (**96**) in 18 steps utilizing new methodology.

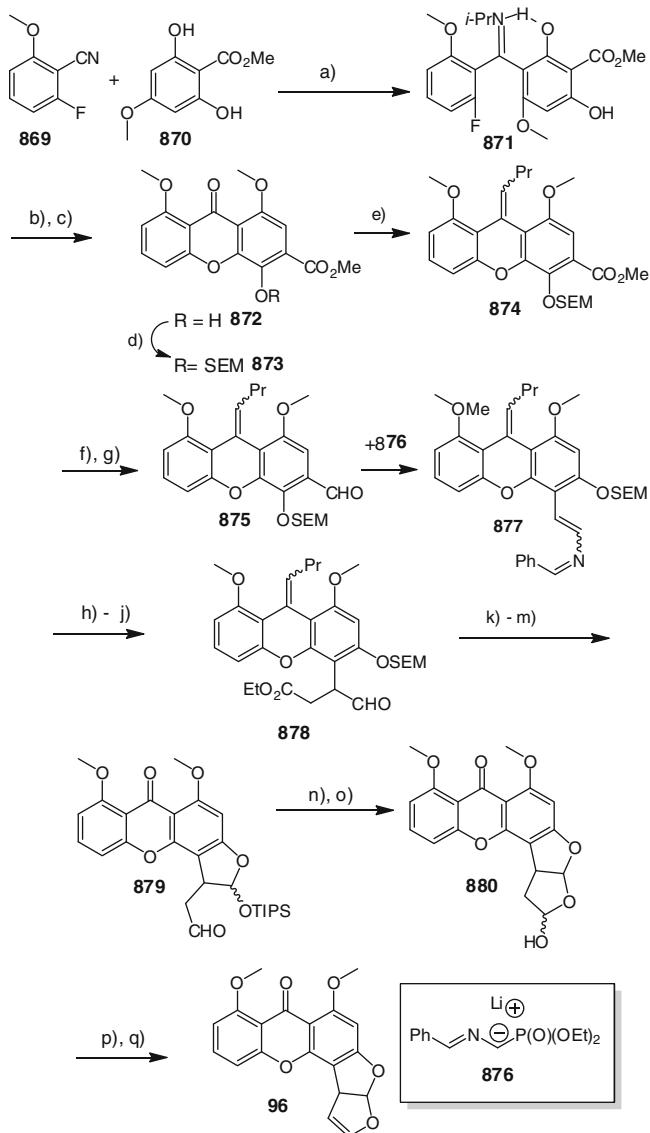


**Scheme 13.5** Horne and Rodrigo's synthesis of dihydro-*O*-methylsterigmatocystin (**868**). Reagents and conditions: a)  $(\text{COCl})_2$ , cat. DMF; b) **865**, pyridine, 95%; c) *n*-BuLi,  $-100^\circ\text{C}$ ; then  $-70^\circ\text{C}$ , 2 h, 63%; d) KOH, MeOH, quant

The synthesis involved a modified *Houben-Hoesch* reaction as the key step with *N*-alkylnitrilium salt, in conjunction with the effective, if unusual, protection of a carbonyl group as an alkene (*i.e.* via addition of *n*-butyllithium and elimination of  $\text{H}_2\text{O}$ ) (**62**) (Scheme 13.6). The facile removal of the butenyl group was then effected with *m*-chloroperbenzoic acid.

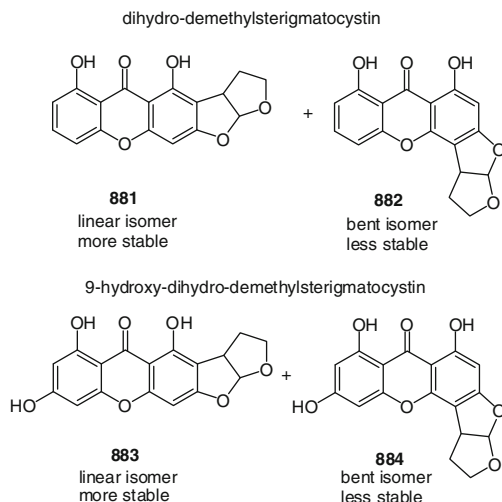
In a subsequent paper, the *Townsend* group utilized a very similar synthesis sequence with a (protected) 3-hydroxyarene variant of nitrile **869** in order to access the related 11-hydroxy-*O*-methylsterigmatocystin (a putative biosynthesis intermediate, not shown) (**607**) (Scheme 13.6). Further to the interest of these authors in the biosynthesis of these significant environmental carcinogens (**624**), this compound was used as an enzyme substrate to support a proposed biosynthesis sequence leading to aflatoxin B<sub>1</sub> (**1**). In this sequence, cytochrome P<sub>450</sub> catalyzes a series of oxidative transformations from anthraquinone to xanthone to coumarin, and the xanthone intermediates are demonstrated to involve first *O*-methylsterigmatocystin and then 11-hydroxy-*O*-methylsterigmatocystin, both of which were converted by the OrdA cytochrome P<sub>450</sub> of *Aspergillus parasiticus* (**607**).

In a later report, *Henry* and *Townsend* investigated the order of the reductive and oxidative steps of the synthesis of demethylsterigmatocystin (**881/882**), a key intermediate in the aflatoxin biosynthesis pathway. Towards this end, they synthesized sterigmatocystin analogues **881** to **884** (Fig. 13.7). It was found that the “bent” isomers (with the oxygen *ortho*- to the carbon framework of the difuranoring) isomerized spontaneously to the more stable “linear” species over a period of 2 weeks under acidic conditions (catalyzed by silica gel), thus providing another example of the facile nature of the oxa-*Michael* and retro-oxa-*Michael* reactions. It was found that an unusual sequence of oxidation-reduction-oxidation was involved in the biosynthetic conversion of versicolorin A (**13**) to demethylsterigmatocystin (**881/882**).



**Scheme 13.6** Casillas and Townsend's synthesis of *O*-methylsterigmatocystin (**96**). Reagents and conditions: a)  $\text{SbCl}_6$ , 2-chloropropane; b)  $\text{K}_2\text{CO}_3$ ; c)  $\text{MeOH}/\text{H}_2\text{O}$ ; d) SEMCl, DIPEA; e) *n*-BuLi; f)  $\text{LiAlH}_4$ ; g) TPAP, NMO; h) *n*-BuLi; i)  $\text{BrCH}_2\text{CO}_2\text{Et}$ ; j) tartaric acid (aq); k) TIPSOTf,  $\text{Et}_3\text{N}$ ; l)  $\text{LiAlH}_4$ ; m) *m*-CPBA; n) TPAP, NMO; o)  $\text{Et}_3\text{N}\cdot(\text{HF})_3$ ; p) PhSeH, Amberlyst<sup>®</sup> 15; q) *m*-CPBA





**Fig. 13.7** Sterigmatocystin derivatives used by *Townsend et al.* to investigate the biosynthesis of aflatoxins

*Essery* and co-workers developed some derivatives of 5-methoxysterigmatocystin for the purpose of testing them as antitumor agents (625). They found that the double bond of the furan system is necessary for the mediation of such activity by the parent compound.

### 13.1.4 Nidulalin A

The dihydroxanthone nidulalin A (**885**) (Fig. 13.8) was reported by *Kawai* and co-workers in 1994 from an isolate of *Emericella nidulans* (626). In 1997, *Tsuji* and co-workers reported the re-isolation of nidulalin A and the related derivatives F390B (**886**) and F390C (**887**) from a *Penicillium* sp. (627). These compounds were shown to have potent antitumor (colon 26 murine adenocarcinoma) activities as a result of their effects on DNA topoisomerase II (628). This enzyme is responsible for regulating DNA topology, with this effect regulating the key aspects of replication, translation, and transcription.

In 1998, *Fujimoto* and co-workers reported the isolation of a novel nidulalin derivative, the 1,9a-dihydro derivative of nidulalin A (**888**) (Fig. 13.8), along with the known compounds, emodin (**791**), and 1,7-dihydroxy-3-methylxanthone, from the ascomycete *Anixiella micropertusa* (629). These authors also reported the isolation of this same compound in 2006, denoting it as GS-4 (**888**) (Fig. 13.8),

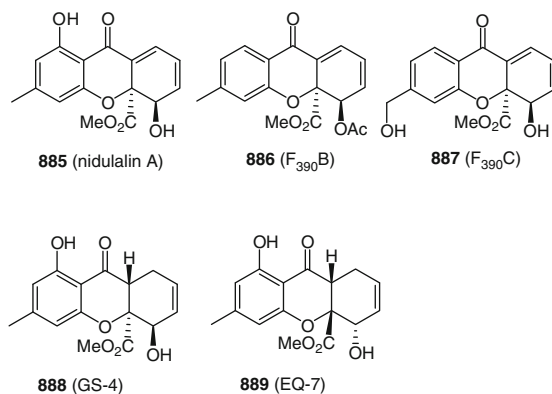
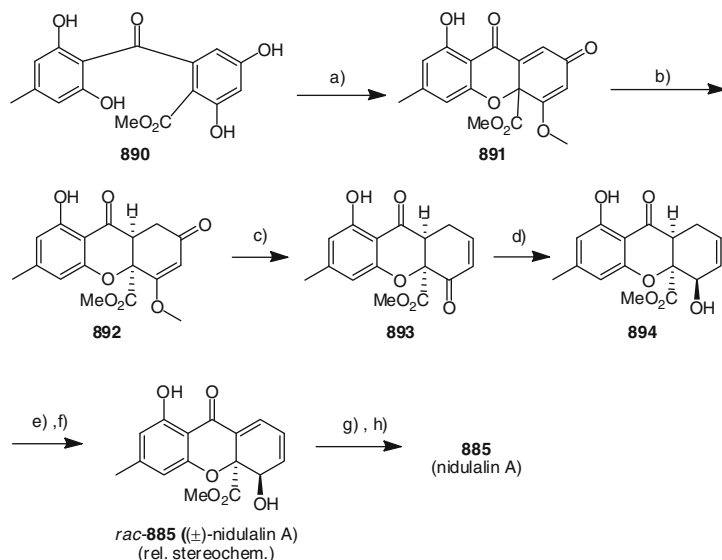


Fig. 13.8 Nidulalin A (**885**) and related xanthenes

along with nidulalin A (**885**), from the ascomycete *Gelasinospora santi-florii*, in addition to a related novel compound from *Emericella quadrilineata*, (4*S*,4*aR*,9*aR*)-4*a*-carbomethoxy-1,4,4*a*,9*a*-tetrahydro-4,8-dihydro-6-methylxanthone (**889**), which they designated as EQ-7 (630). The configuration of EQ-7 was determined at the cyclohexyl alcohol moiety, based on the modified *Mosher* method, using (*R*)- and (*S*)-(trifluoromethyl)phenylacetate ester derivatives, with the configuration inferred for GS-4.

In 1999, *Tsuji* and co-workers investigated the synthesis of esterase-stable amide analogues of the methyl ester of nidulalin A (**885**), starting from the natural product itself. These compounds were stable to hydrolysis in the presence of endogenous murine plasma esterases, and showed variable toxicity as well as increases or decreases in activity against Topo I and II as compared to **885** (628).

In 2009, *Hosokawa* and co-workers reported the synthesis of nidulalin A (**885**) (and *ent*-nidulalin A, not shown) from the benzophenone **890** (Scheme 13.7), which was cyclized under oxidative conditions to xanthone **891** (631). This was followed by a sequence of three reductions that delivered cyclohexanol **894**, which was then converted to racemic nidulalin A (**885**) in two steps. Conversion to camphanic ester diastereomers, and separation and hydrolysis, gave nidulalin A (**885**) and its unnatural enantiomer. This synthesis confirmed the absolute stereochemistry previously determined using spectroscopic methods.



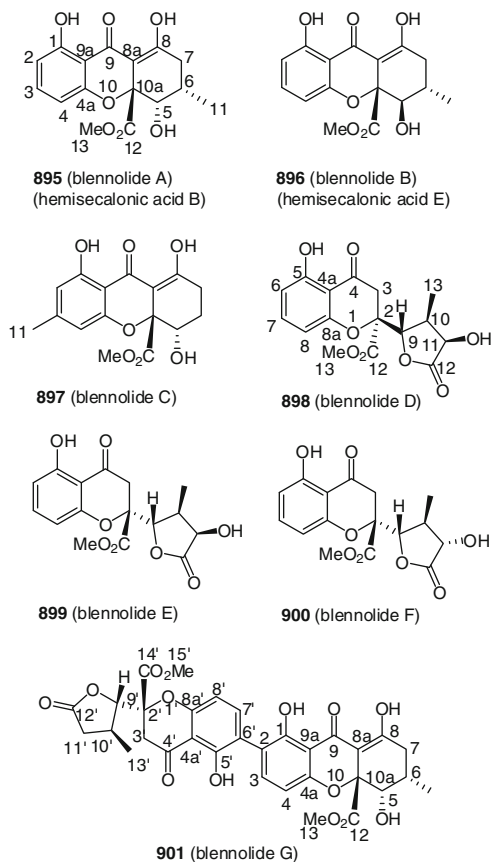
**Scheme 13.7** Synthesis of nidulalin A (**885**). Reagents and conditions: a)  $\text{Pb}(\text{OAc})_4$ ,  $\text{NaOAc}$ ,  $\text{MeNO}_2$ , 39%; b)  $\text{NaBH}(\text{OAc})_3$ ,  $\text{B}(\text{OAc})_3$ , THF, 79%; c) DIBAL, THF, quant; d)  $\text{LiAlH}_4$ , THF, 60%; e)  $\text{TMSOTf}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; f)  $\text{SeO}_2$ , 1,4-dioxane, (60%, 2 steps); g) (–)-camphanic acid,  $\text{WSCl-HCl}$ ,  $\text{DMAP}$ ,  $\text{CH}_2\text{Cl}_2$ ; h)  $\text{K}_2\text{CO}_3$ ,  $\text{MeOH}$ , 40%

## 13.2 Tetrahydroxanthenes

Tetrahydroxanthenes from fungi include the blennolides (**895–901**), dihydroglobosuxanthone (**931**) (632), diversonol (**932**) and the diversonolic esters (**972**, **973**) (Fig. 13.15). Tetrahydroxanthenes are the monomeric components of interesting mycotoxins such as the beticolins (**1063–1070**) and the secalonic acids (**1034–1046**) (see Sect. 13.5.3).

### 13.2.1 Blennolides

In 2008, the long-anticipated but never-before-detected monomeric components of the secalonic acids (blennolides and hemisecalonic acids **895** to **900**, Fig. 13.9) were isolated from an endophytic *Blennoria* sp., in addition to secalonic acid B (**1037**) (*vide infra*) (Fig. 13.9) and several other biosynthetically related isolates, named blennolides A–G (**895–901**) (633). The structure of blennolide A (**895**), the monomeric unit of secalonic acid B (**1037**), was confirmed using single-crystal X-ray analysis; blennolide B (**896**) is the monomeric unit of secalonic acid D (**1035**). The configurations of all these compounds were ascertained using CD spectra to determine the absolute stereochemistry of the 10a position as (*R*), and



**Fig. 13.9** Blennolides A–G (**895–901**)

then the other stereogenic centers on the basis of relative stereochemistry (except for blennolide D (**898**), which is (10a*S*)-configured).

Dihydrobenzopyranones **900** to **901** seem to be derived from **895** and **896** by rearrangement of the tetrahydroxanthone ring to a  $\gamma$ -lactone in a manner similar to that reported for the heterodimer xanthoquinodin A<sub>3</sub> (**1058**) (Fig. 13.28). In the case of **898**, an inversion of the C-10a stereocenter appeared to have taken place during this process. Dimer **901** is comprised of blennolide A (**895**) and 11-deoxyblennolide F (**900**) monomers, and is, like ergoxanthin (**1048**), a member of the ergochrome family rearranged to incorporate a  $\gamma$ -lactone unit. Interestingly, earlier a compound had already been assigned the structure now ascribed to blennolide C (**897**) (see entry for  $\beta$ -diversonolic ester (**973**)) (634) (Figs. 13.15 and 13.10).

In 2008, *Nicolaou* and *Li* reported the synthesis of blennolide C (**897**), in addition to the racemic synthesis of diversonol (**932**) and the diversonolic esters

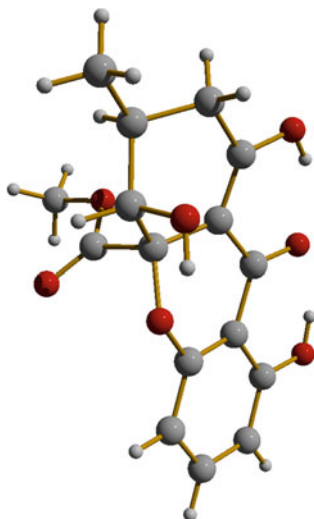
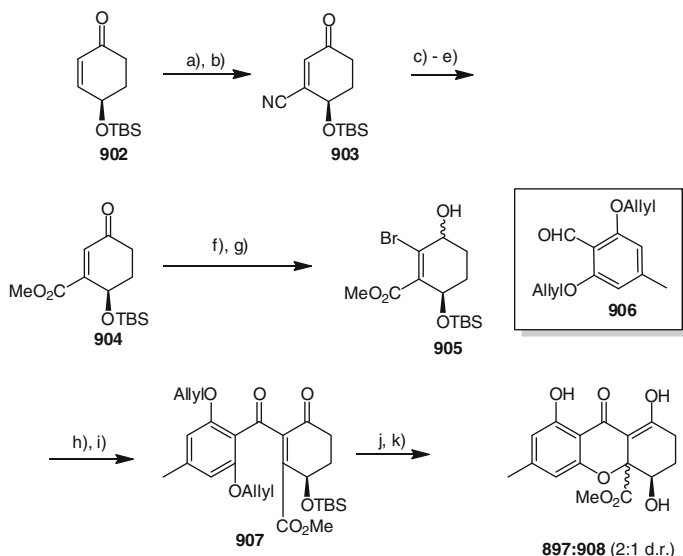


Fig. 13.10 X-ray structure of blennolide A (895)

(972, 973) (Fig. 13.15), through a commonly applicable methodology (635). The synthesis sequence (Scheme 13.8) involved manipulation of a silyl-protected 4-hydroxycyclohex-2-enone (902) through several steps to the 2-bromo-3-carboxymethyl ester 905, then reaction of this species with the aldehyde 906 to form the intermediate benzophenone 907. This product was first desilylated, then de-allylated, with a second deprotection followed by an *in situ* cyclization of the phenolic intermediate, to give blennolide C (897) and the diastereomer 908 in an approximately 2:1 diastereomeric ratio, after 11 steps from cyclohexenone 258 (635).

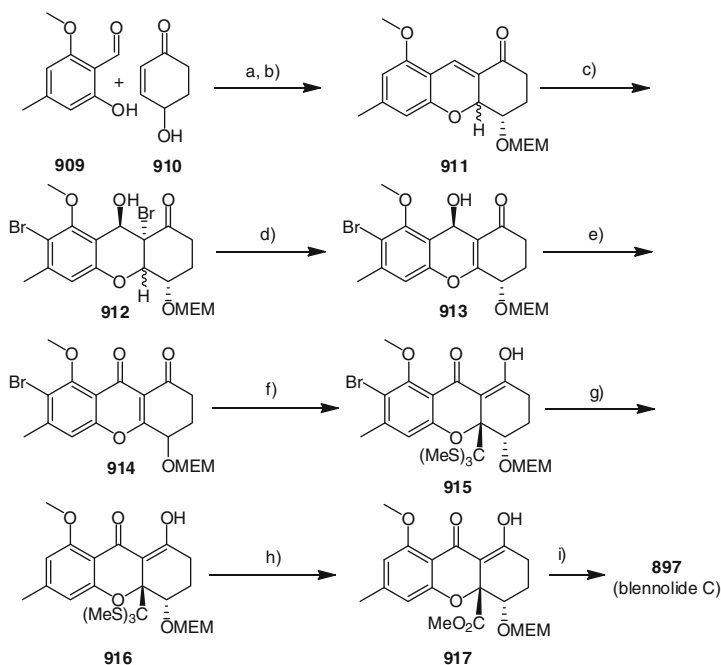
Also in 2008, Gérard and Bräse reported the synthesis of blennolide C (897) and some analogues (636), confirming the suggestion made by Krohn that this compound has the structure formerly assigned to  $\beta$ -diversonolic ester (973) (Fig. 13.15). In common with the group synthesis of diversonol (Scheme 13.13), the ABC-ring tricyclic xanthenone was constructed in a single step *via* an efficient domino oxa-Michael-aldol reaction (556–566, 637) from the substituted salicylic aldehyde 909 (Scheme 13.9) and 4-hydroxycyclohex-2-enone (910), of which the latter can be accessed enantioselectively and constructed efficiently using a synthesis developed earlier (638). Use of the weak base imidazole was made to deliver the tricycle in 61% yield as a 1.5:1 ratio of diastereomers. Hydroxy group protection and bromohydration gave the bromide 912, and elimination of HBr from this enabled the completion of the tetrahydroxanthenone core.



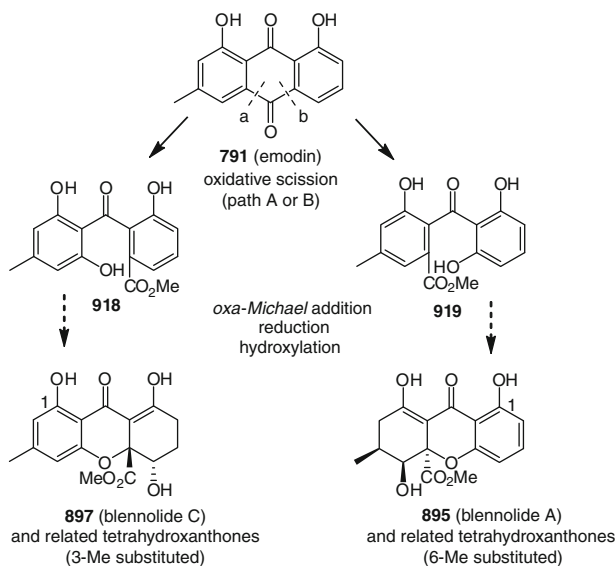
**Scheme 13.8** Nicolaou's synthesis of blennolide C (**897**). Reagents and conditions: a)  $\text{Et}_2\text{AlCN}$ , pyridine,  $\text{TMSCl}$ , toluene,  $0$ – $23^\circ\text{C}$ ; b)  $\text{IBX}$ ,  $\text{MPO}$ ,  $\text{DMSO}$ , rt, 62%, 2 steps; c)  $\text{DiBAL-H}$ ,  $\text{DMP}$ , toluene,  $-78$  to  $-40^\circ\text{C}$ , 83%; d)  $\text{NaClO}_2$ , 2-methyl-2-butene,  $\text{NaH}_2\text{PO}_4$ ,  $t\text{-BuOH}/\text{H}_2\text{O}$ ; e)  $\text{TMSCHN}_2$ ,  $\text{MeOH}$ ,  $0^\circ\text{C}$ , 90%, two steps; f)  $\text{Br}_2$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 94%; g)  $\text{CeCl}_3 \cdot 7 \text{H}_2\text{O}$ ,  $\text{NaBH}_4$ ,  $\text{MeOH}$ ,  $0^\circ\text{C}$ , 91%; h)  $\text{MeLi}$ ,  $t\text{-BuLi}$ ,  $\text{Et}_2\text{O}$ ; then aldehyde **906**; i)  $\text{IBX}$ ,  $\text{DMSO}$ , rt, 1 h, 41% (two steps); j)  $\text{HF}$ -pyridine,  $\text{THF}$ , rt, 89%; k)  $n\text{-Bu}_3\text{SnH}$ ,  $\text{Pd}(\text{PPh}_3)_4$ , benzene, rt, 60%

*Michael* addition to this enone was performed using the *Gabbat* method (639), wherein lithiated trimethylorthomethanetrithioate was added *trans* to the OMEM group. The additional steps included debromination, conversion to the methyl ester, and demethylation to provide blennolide C (**897**) in nine steps in total from 4-hydroxycyclohex-2-enone (**910**). The authors pointed out that this monomeric unit is found in the dimeric compounds neosartorin (**1078**), xanthanol (**1086**), the xanthoquinodins (**1058-1062**) (Fig. 13.28), and the beticolins (**1063 - 1070**) (636).

In their investigations of the blennolides, *König* and co-workers described a pathway divergence in the formation of xanthones (Scheme 13.10), which can even occur *via* both pathways at once within the same fungus, and is a result of the asymmetric nature of cleavage of the anthraquinone precursor (**559**) to yield benzophenone intermediates **918** or **919**. As a result in this case, the methyl group can end up on the reduced ring, or the non-reduced ring, allowing the fungus to create a more diverse array of biochemical agents. Interestingly, *Krohn* and co-workers have observed that both pathways can operate within a single xanthone-producing organism, for example to give rise to blennolides A and C (**897** and **895**, Scheme 13.10 (640)) (**559**). The resulting xanthone structures are isomeric, with one methylated on the aryl position and the other methylated on the tetrahydroxanthone ring. In the former case, (hetero)-dimers can be made through



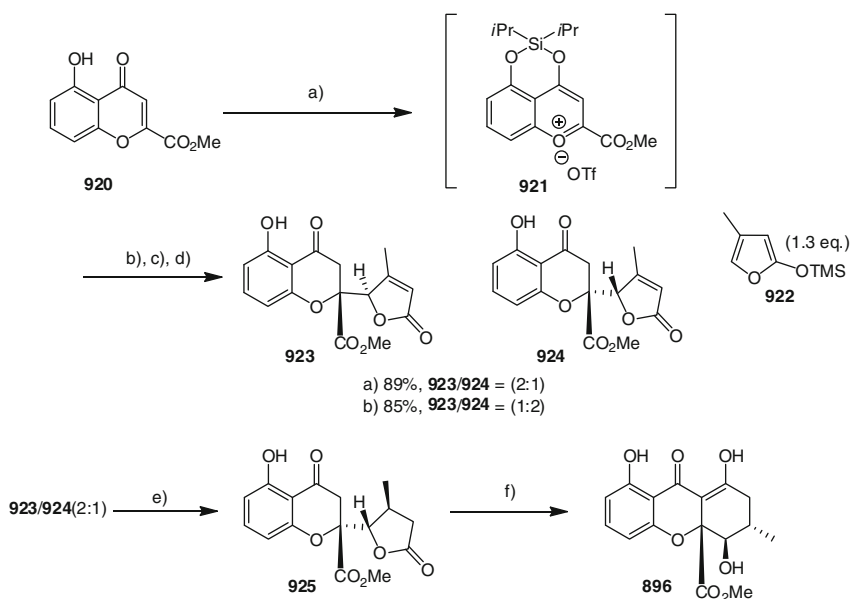
**Scheme 13.9** Gérard and Bräse's synthesis of blennolide C (**897**). Reagents and conditions: a) imidazole, dioxane/H<sub>2</sub>O, ultrasound, 7 d, 61%; b) MEMCl, *i*-Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, rt, 3 h, 75%; c) Bu<sub>4</sub>NBr<sub>3</sub>, THF/H<sub>2</sub>O, rt, 5 h, 52%; d) DABCO, dioxane, rt, 16 h, 53%; e) TPAP, NMO, CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>CN, ultrasound, 40%; f) HC(SMe)<sub>3</sub>, *n*-BuLi, THF, -78°C, 12 h, 20%; g) *t*-BuLi, H<sub>2</sub>O, 96%; h) HgO, HgCl<sub>2</sub>, MeOH/H<sub>2</sub>O, rt, 18 h, quant; i) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 5 h, 23%



**Scheme 13.10** Biosynthetic diversity in the tetrahydroxanthenes

oxidative coupling at the benzylic position (beticolins (**1063–1070**), xanthoquinodins (**1058–1062**) (Fig. 13.28), see Sect. 13.3.3).

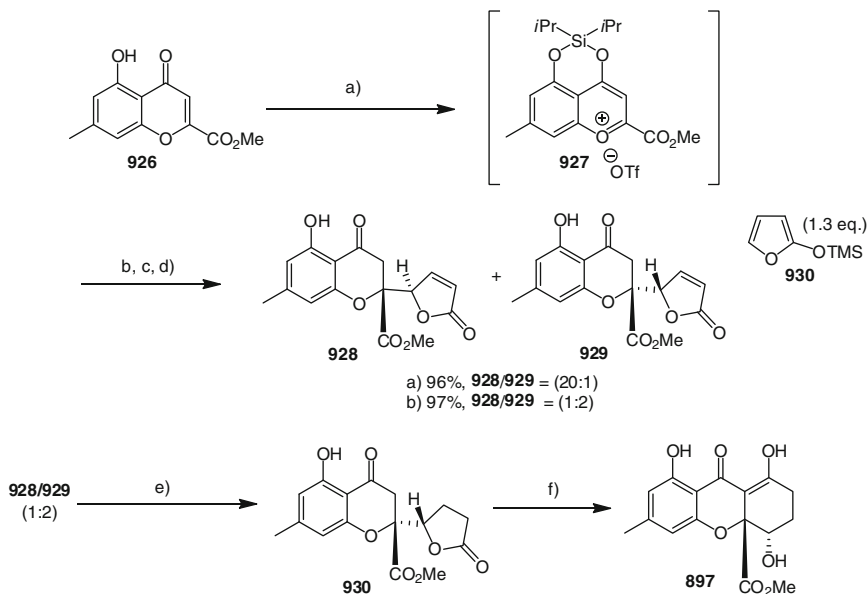
Recently, *Porco* and co-workers described a novel retro-biomimetic synthesis strategy to access the tetrahydroxanthone core, utilizing the vinylogous addition of siloxyfurans to benzopyryliums, reduction of the lactenone products, and intramolecular *Dieckmann* cyclization as the key steps (641). They utilized this strategy to synthesize diastereoselectively racemic blennolides B (**896**) and C (**897**) (Schemes 13.11 and 13.12). An expedient synthesis of blennolide B (**896**) was achieved by first conversion of chromene **920** to the benzopyrylium salt intermediate, which was then reacted with 4-methyl-2-trimethylsiloxy furan (**922**) (Scheme 13.11), prior to deprotection. Variation in temperature in the addition step gave different diastereoselectivities, likely due to epimerization of the initial product at higher temperatures. Lactenone **923** was reduced with rhodium on aluminum oxide in methanol to give lactone **925**, and *Dieckmann* condensation then provided blennolide B (**896**).



**Scheme 13.11** *Porco*'s synthesis of blennolide B (**896**). Reagents and conditions: a)  $i\text{-Pr}_2\text{Si}(\text{OTf})_2$ , 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ , rt, 0.5 h; b) **922**,  $-78^\circ\text{C}$ , 1 h; c)  $0^\circ\text{C}$ , 3 h; d)  $\text{Et}_3\text{N}\cdot(\text{HF})_3$ ; e)  $\text{Rh}/\text{Al}_2\text{O}_3$  (10mol%), MeOH, rt, 12 h, 37% from **923**; f) NaH, THF,  $60^\circ\text{C}$ , 76%

In the synthesis of blennolide C (**897**) (Scheme 13.12), the sequence commenced from methyl-substituted chromenone **926** with 2-trimethylsiloxyfuran (**930**), followed by deprotection to the chromones **928** and **929**. It was found that the contrast in selectivities at different temperatures was even greater than determined previously. The lactenone was reduced with nickel chloride hexahydrate and sodium borohydride to lactone **930**, with *Dieckmann* condensation following again, in order to deliver blennolide C (**897**).

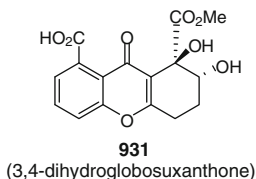




**Scheme 13.12** Porco's synthesis of blennolide C (**897**). Reagents and conditions: a)  $i\text{-Pr}_2\text{Si}(\text{OTf})_2$ , 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ , rt, 0.5 h; b) **930**,  $-7^\circ\text{C}$ , 1 h; c)  $0^\circ\text{C}$ , 3 h; d)  $\text{Et}_3\text{N}\cdot(\text{HF})_3$ ; e)  $\text{NiCl}_2\cdot 6\text{H}_2\text{O}$ ,  $\text{NaBH}_4$ , THF/MeOH,  $0^\circ\text{C}$ , 0.5 h, 61% from **928**; f)  $\text{NaH}$ , THF,  $60^\circ\text{C}$ , 16 h, 37%

### 13.2.2 Dihydroglobosuxanthone

Krohn and co-workers reported in 2009 the isolation of 3,4-dihydroglobosuxanthone A (**931**) as a result of their reinvestigation of a *Microdiplodia* sp. (559). As with the diversonic esters (A and B, **972**, **973**) (Fig. 13.15) this compound has the methyl ester located at the C-1 position, rather than the usual C-4a position, as found for remaining monomeric and dimeric members of the tetrahydroxanthone family. This compound was demonstrated to have potent antibacterial activity against *Escherichia coli*, *Bacillus megaterium*, and *Chlorella fusca* (Fig. 13.11).



**Fig. 13.11** 3,4-Dihydroglobosuxanthone A (**931**)

### 13.2.3 Diversonol

In 1978, *Turner* reported the isolation of several fungal metabolites, including a compound from the phenolic fraction of cultured *Penicillium diversum* that was named subsequently diversonol (**932**) (642). It was not made clear in the initial publication if diversonol (**932**) was obtained as a racemate or, if this was not the case, the absolute configuration. Mention was made in this initial publication to X-ray crystallographic data that were to be reported later, but it evidently such work did not come to completion (Fig. 13.12).

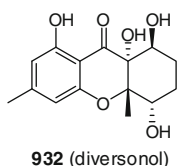
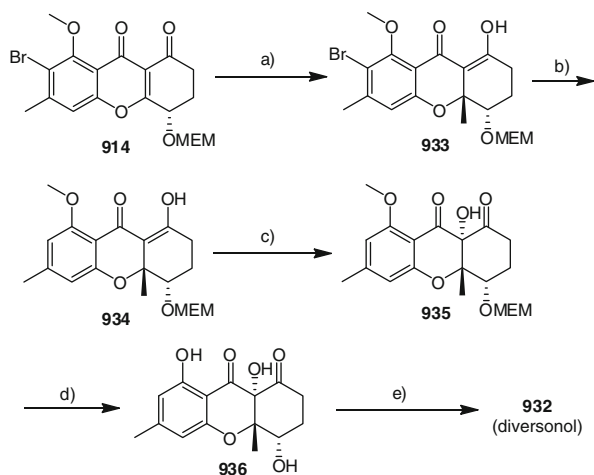


Fig. 13.12 Diversonol (**932**)

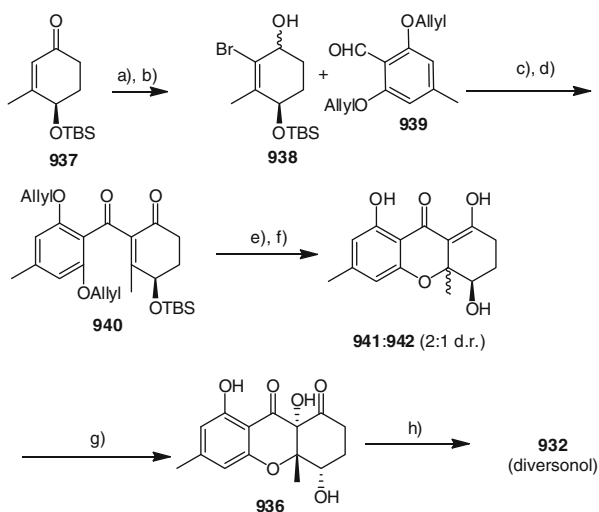
Diversonol (**932**) was selected as a target by the *Bräse* group in their ongoing studies on the synthesis of the secalonic acids (**1034–1046**) and related natural products (556, 560–566), and the successful synthesis of the racemate was reported in 2006 (643). The synthesis started with the synthetic intermediate **270** (Scheme 13.13), common with the group's synthesis of blennolide C (**897**) (see Scheme 13.9). Enone substrate **270** was doubly activated for diastereoselective



**Scheme 13.13** *Bräse*'s synthesis of diversonol (**932**). Reagents and conditions: a) MeLi, CuCN, Et<sub>2</sub>O, –78°C, 5 h, 52%; b) *t*-BuLi, THF, –78°C, NaHCO<sub>3</sub>, 4 h, 93%; c) manganese monoperoxyphthalate, EtOH, rt, 5 h, 57%; d) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 7 h, 40%; e) NaBH<sub>4</sub>, MeOH, –78°C, 0.3 h, 66%

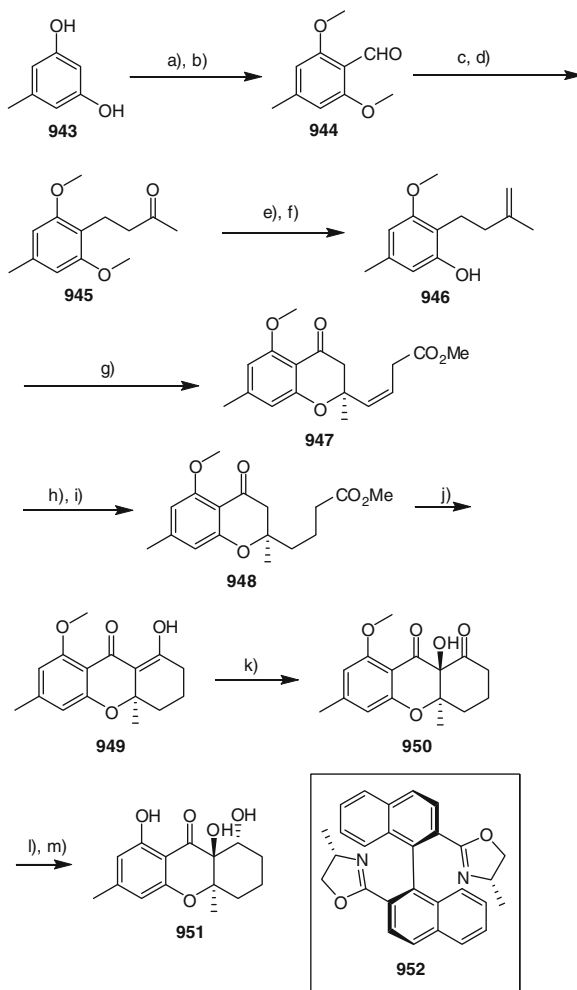
*Michael*-addition of methyl cyanocuprate to afford **290**. Debromination and diastereoselective oxidation with manganese monoperoxophthalate gave alcohol **292**, which was deprotected and finally reduced to give the polyhydroxylated core, and thus racemic diversonol (**932**), in ten steps starting from 4-hydroxycyclohexen-2-one (**266**).

In 2008, *Nicolaou* and *Li* reported a synthesis of diversonol (**932**) (Scheme 13.14) (**635**). The synthesis involved the nucleophilic addition of a lithiated cyclohexene species derived from bromide **938** with the allyl-protected aldehyde **939**, followed by oxidation, desilylation, deallylation, and spontaneous xanthone-ring closure of the intermediate phenol (not shown). As in the *Bräse* synthesis, the enol moiety is oxidized and the C-ring ketone reduced with  $\text{NaBH}_4$  to generate diversonol (**932**), which was obtained in eight steps from cyclohexenone **937**.



**Scheme 13.14** *Nicolaou*'s synthesis of diversonol (**932**). Reagents and conditions: a)  $\text{Br}_2$ ,  $\text{Et}_3\text{N}$ , 90%; b) DiBAL-H, 95%; c) MeLi, *t*-BuLi; then aldehyde; d) IBX, DMSO, rt, 1 h, 72% (two steps); e) HF-pyridine, THF, rt, 96%; f)  $n\text{-Bu}_3\text{SnH}$ ,  $\text{Pd}(\text{PPh}_3)_4$ , benzene, rt, 90%; g) magnesium monoperoxophthalate, EtOH, rt; h)  $\text{NaBH}_4$ , MeOH,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 0.3 h, 73%, two steps

In 2008, *Tietze* and co-workers reported on their stereoselective synthesis of 4-dehydroxydiversonol (**951**) utilizing pathways involving both Pd-catalyzed domino-*Wacker-Heck* and domino-*Wacker*-carbonylation reactions (**644**). The shortest and highest yielding sequence was as follows: dimethylation and *ortho*-lithiation-directed formylation of orcinol (**943**) (Scheme 13.15), followed by *Wittig* olefination, *Lombardo* methylenation, and monomethyl cleavage with sodium ethanethiolate, to give the domino-*Wacker-Heck* substrate **946**. This was reacted with methyl acrylate in the presence of Pd ditriflate and (*S,S*)-Bn-BOXAX ligand



**Scheme 13.15** Tietze's synthesis of 4-dehydroxydiversonol (**951**). Reagents and conditions: a)  $\text{Me}_2\text{SO}_4$ ,  $\text{K}_2\text{CO}_3$ , 24 h, 94%; b) *n*-BuLi, TMEDA; then DMF, 87%; c)  $\text{Ph}_3\text{PCHC}(\text{O})\text{CH}_3$ , 98%; d)  $\text{H}_2$ , Pd/C, 92%; e) Zn,  $\text{CH}_2\text{Br}_2$ ,  $\text{TiCl}_4$ , 84%; f) NaSEt, DMF, 92%; g) methyl acrylate, Pd(OTFA) $_2$ , (*S,S*)-Bn-BOXAX (**952**), *p*-benzoquinone, 55%, 88% *ee*; h)  $\text{H}_2$ , Pd/C, 98%; i) Mn(OAc) $_3$ , *t*-BuOOH, rt, 3 d, 71%; j)  $\text{TiCl}_4$ ,  $\text{Et}_3\text{N}$ , 63%; k) DMDO, 74%; l)  $\text{NaBH}_4$ , 71%; m)  $\text{BBr}_3$ , 85%

(**952**) alongside *p*-benzoquinone (as a catalyst reoxidant), giving chromane **947** in 55% yield and 88% *ee*. The same compound was synthesized by a complementary three-step sequence involving an enantioselective domino Wacker-carbonylation process, which gave chromane **947** in 96% *ee* (not shown). This species was reduced and oxidized to a chromanone before intramolecular acylation with  $\text{TiCl}_4$  and  $\text{Et}_3\text{N}$  (the use of strong bases led to poor conversions) to give the xanthone tricycle **949**. This compound was *trans*-selectively oxidized with DMDO, reduced

at the C-ring ketone, and demethylated to give (–)-(*S*)-4-dehydrodiversonol (**951**). Its relative configuration was confirmed by single-crystal X-ray crystallography (644) (Fig. 13.13).

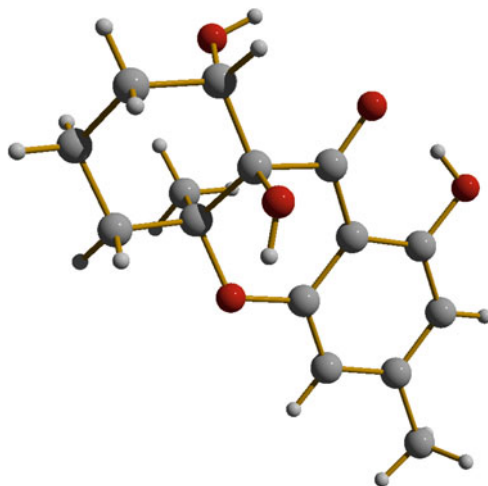
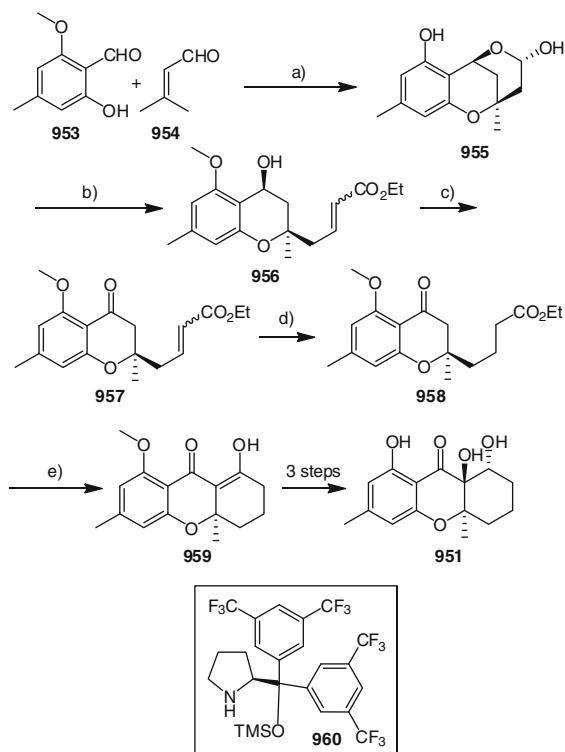


Fig. 13.13 X-Ray structure of dehydrodiversonol (**951**) (CCDC-686256)

*Volz, Bröhmer, and Bräse* also reported a synthesis of 4-dehydrodiversonol (**951**) in the following year (645). The reaction sequence involved an enantioselective domino oxa-*Michael*–aldol reaction mediated by the organocatalyst **960** (Scheme 13.16), followed by a *Wittig* ring-opening reaction to ester **956**, which was reduced to give ester **958**. This, when subjected to a similar sequence to the *Tietze* synthesis, delivered 4-dehydrodiversonol (**951**).

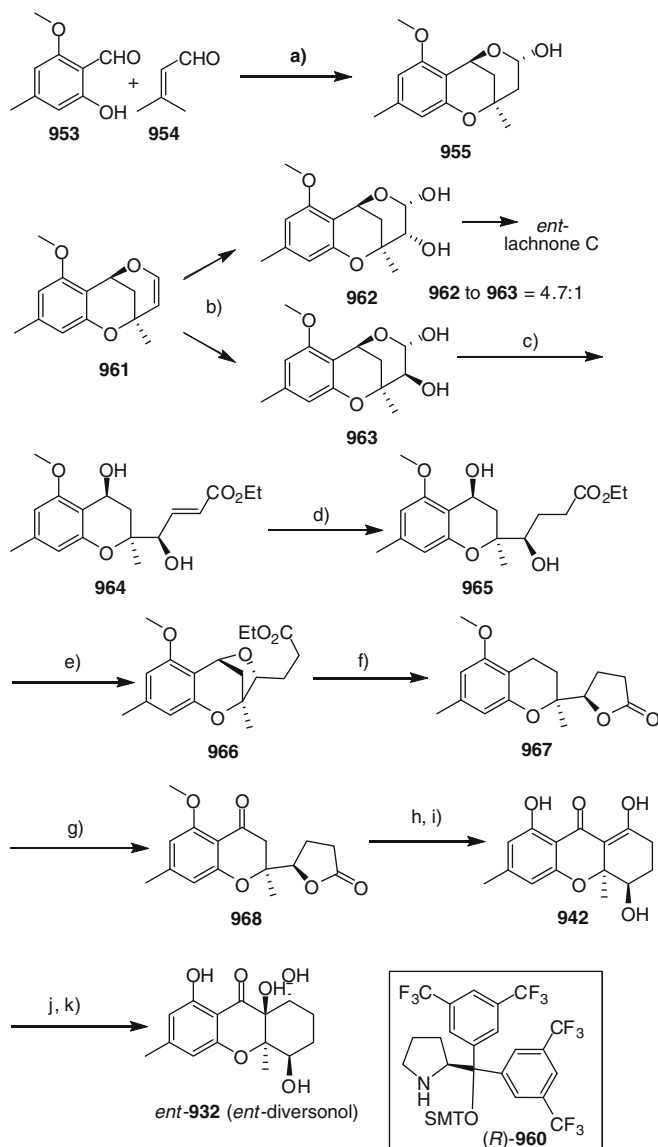
*Bröhmer, Bourcet, Nieger, and Bräse* reported an enantioselective synthesis of diversonol (**932**) in 2011 (Scheme 13.17), and allowed for the synthetic confirmation of the absolute configuration of diversonol (**932**) (646), which had previously been inferred by *Krohn* and co-workers. This synthesis strategy was executed contemporarily to that of *Porco* and co-workers (641), also using a “retrobiomimetic” approach, whereby the putative products of further secondary metabolism of xanthenes, chromone lactones (*e.g.* blennolides D to F (**898–900**)) (Fig. 13.9) were converted synthetically *via Dieckmann* cyclization to form the xanthone nucleus. A domino reaction between salicylaldehyde **913** and 3-methylcrotonaldehyde (**914**) catalyzed by *Jørgensen’s* catalyst gave enantioselective access to the tricyclic lactol **955** in 67% yield and 83% *ee*. Dehydration and 1,2-*cis*-dihydroxylation gave the two diastereomeric diols **962** and **963**, and the former (major) product of the tricyclic lactol was used in the synthesis of *ent*-lachnone C (**969**). Conversion of the minor diol



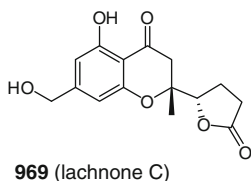
**Scheme 13.16** Volz, Bröhmer, and Bräse's synthesis of 4-dehydroxydiversonol (**951**). Reagents and conditions: a) **312**, Et<sub>3</sub>N, 79%, 87% ee; b) Ph<sub>3</sub>P = CHCO<sub>2</sub>Et, quant; c) *DMP*, 83%; d) H<sub>2</sub>, PtO<sub>2</sub>, 92%; e) TiCl<sub>4</sub>, Et<sub>3</sub>N, 64%

**963** through the aldehyde tautomer (not shown) with a *Wittig* reaction gave the  $\alpha,\beta$ -unsaturated ester **964**, which was hydrogenated and, after two consecutive acid-catalyzed steps and one reductive step, converted to chromane lactone **942**. Oxidation to chromone **942** and *Dieckmann* cyclization gave the xanthone framework.

The final steps involved demethylation with boron tribromide, then a sequence of oxidation and reduction steps taken directly from the *Nicolaou* racemic synthesis (635), delivering the unnatural isomer of diversonol (*ent*-**932**), with a superimposable CD spectrum to that supplied by *Krohn* and coworkers of the natural product (647). Hence, natural diversonol (**932**) is the enantiomer of the product *ent*-**932** shown in Scheme 13.17, namely, that of (5*S*,5*aS*,8*S*,8*aR*) configuration. Also in this study, the chromone lactones lachnone C (**969**) and *epi*-lachnone C (not shown) were synthesized enantioselectively for the first time, utilizing common synthesis intermediates (Fig. 13.14).



**Scheme 13.17** Bräse's asymmetric synthesis of *ent*-diversonol (*ent*-932). Reagents and conditions: a) (*R*)-960, Et<sub>3</sub>N, 79%, 87% *ee*; b) NMO, OsO<sub>4</sub>, 90%; c) Ph<sub>3</sub>P=CHCO<sub>2</sub>Et, 98%; d) Pd/BaSO<sub>4</sub>, H<sub>2</sub>, 74%; e) *p*-TsOH (cat), THF, rt, 94%; f) *p*-TsOH (cat), benzene, reflux, 88%; g) Mn(OAc)<sub>3</sub> (cat), *t*-BuO<sub>2</sub>H, 66%; h) NaOMe, 44%; i) BBr<sub>3</sub>, 81%; j) MMPP; k) NaBH<sub>4</sub>, 52%

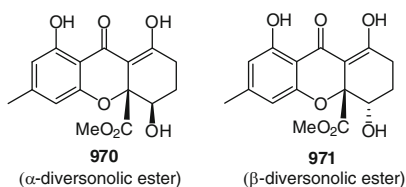


**Fig. 13.14** Lachnone C (**969**)

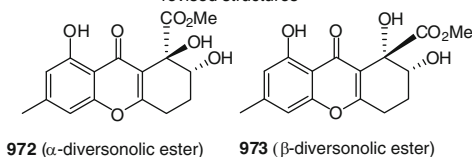
### 13.2.4 Diversonolic Esters

In 1983 *Holker, Simpson, and O'Brien* reported the isolation of the diversonolic esters (**972, 973**) (Fig. 13.15), which they obtained from *Penicillium diversum*, along with lichexanthone (**840a**) and several other known compounds (634). The authors performed a structural analysis for these new compounds based on methylation, proton-NMR analysis, chelate ferric effects, and other spectroscopic techniques, which led to the assignment of the structures of these new compounds as **970** and **971**. These substances appear reminiscent of hemisecalonic acids (ergochrome monomers), but the structures originally proposed were later found to be incorrect (see below).

originally proposed structures



revised structures

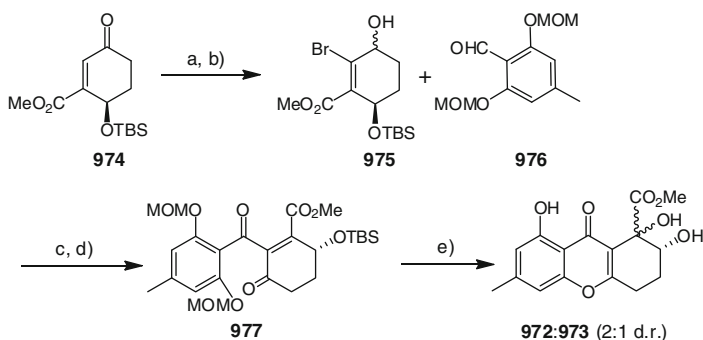


**Fig. 13.15** Diversonolic esters (**972, 973**)

Twenty-five years later, the racemic syntheses of diversonolic esters (**972, 973**) were reported by *Nicolaou and Li*, along with the synthesis of blennolide C (**897**) and diversonol (**932**) (see entries above) (85). In a twist of good fortune, the use of MOM-protecting groups as an alternative to allyl groups (see diversonol synthesis)



and oxidative conditions resulted in the synthesis of compounds **972** and **973** through nucleophilic attack of the phenolic group on either the enone in an oxa-*Michael* addition, or on the ketone, followed by loss and then readdition of water. As a result of their synthesis of these two compounds, which had identical spectroscopic characteristics to those originally reported for the diversonolic esters (**972**, **973**), the structures of **970** and **971** were revised to **972** and **973** (see Fig. 13.15) (**635**) (Scheme 13.18).



**Scheme 13.18** Nicolaou's synthesis of  $\alpha$ - and  $\beta$ -diversonol esters. Reagents and conditions: a) Br<sub>2</sub>, Et<sub>3</sub>N, 90%; b) DiBAL-H, 95%; c) MeLi, *t*-BuLi; then **976**; d) IBX, 78% (2 steps); e) HClO<sub>4</sub>(aq), 90%

## 13.3 Hexahydroxanthenes

Hexahydroxanthone derivatives have been identified in nature from various fungal sources. These include the applanatins (**978**, **979**), the isocochlioquinones (**982**, **983**), and the monodictysins (**984** - **986**).

### 13.3.1 Applanatins

Wang, Dong, and Liu reported the structure of two new hexahydroxanthenes, applanatins A (**978**) and B (**979**), and one known hexahydroxanthone, ganoderma aldehyde (**980**) (Fig. 13.16) after isolating these compounds together with ganodermic acids A, B, D, and G, from *Ganoderma applanatum*. This fungus has long been used as a traditional medicine in China, Japan, and Korea. The structures of **978** and **979** were determined spectroscopically, and the structure of ganoderma aldehyde (**980**) was revised based on its NMR data (**648**).

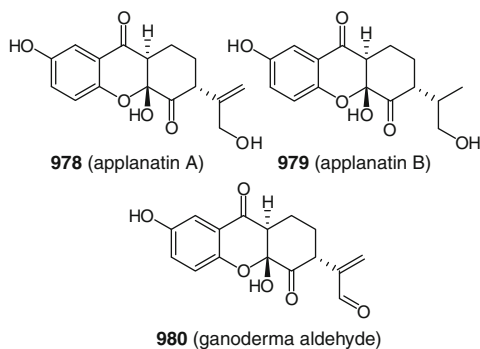


Fig. 13.16 Applanatins A (**978**) and B (**979**), and ganoderma aldehyde (**980**)

### 13.3.2 Isocochlioquinones

Isocochlioquinones, xanthone isomers of the cochlioquinone-type food crop-associated mycotoxins (649), are of mixed biosynthetic origin, with the addition of a farnesyl unit and methionine-derived methyl groups (650). Isocochlioquinones A and C (**981** and **982**) (Fig. 13.17) were isolated from *Bipolaris cynodontis* cynA (651) and the culture broth of *Bipolaris bicolor* EI-1 (652), and also from *Bipolaris oryzae* (649). These compounds were also purified from *Drechslera dematioidea*, a

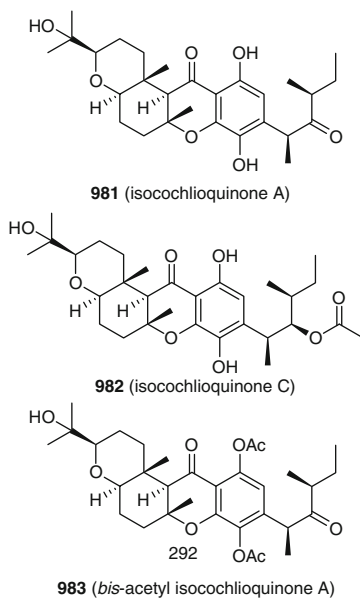
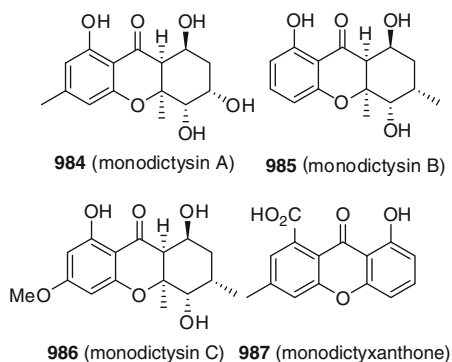


Fig. 13.17 Isocochlioquinones A and C, and bis-acetyl isocochlioquinone A

fungus that is associated with the marine red alga *Liagora viscida* (650). Isocochlioquinone A and its bis-acetyl derivative (**981** and **983**) (Fig. 13.17), were both isolated from *Drechslera dematioidea* as a result of a study on fungi associated with nest-building bees. In such an environment, the antifungal properties exhibited by these compounds lead to a protective function for the bee colony members (653). Both isocochlioquinones A and C inhibit the growth of *Plasmodium falciparum* *in vitro* ( $IC_{50}$  values  $<5 \mu\text{g}/\text{cm}^3$ ). Cochlioquinones have antiangiogenic and chemokine-receptor (CCR5) antagonist properties, and isocochlioquinone A and bis-acetyl isocochlioquinone A (**981** and **983**) were found to be cytotoxic against HeLa and KB cells in the low micromolar and mid-micromolar ranges.

### 13.3.3 Monodictysins

The hexahydroxanthone-derived monodictysins A–C (**984** to **986**) (Fig. 13.18) were isolated together with monodictyxanthone (**987**) from *Monodictys putrenidis*, a fungus occurring in the inner tissue of green algae, and reported in 2007 by König and co-workers (640). Monodictysin B (**985**) was also reported as a constituent of the fungus *Leptosphaeria* sp. in 2010 (654). Unlike the majority of dimeric xanthenes (for example the secalonic acids (**1034–1046**) and their monomeric units, the blennolides), which have carboxymethyl substituents at C-10a, the monodictysins have a methyl substituent at the C-5a position. Additionally, monodictysin A instead has a methyl group at C-3 rather than C-6, as found in monodictysin B and C, indicating an alternative oxidative cleavage in their biosynthesis. The relative configuration of monodictysin A was determined by X-ray crystal structure analysis, with those of monodictysins B and C determined using NOE experiments. A comparison of the CD spectra of these compounds was made with TDDFT calculations (Fig. 13.19).



**Fig. 13.18** Monodictysins A–C (**984**–**986**); monodictyxanthone (**987**)

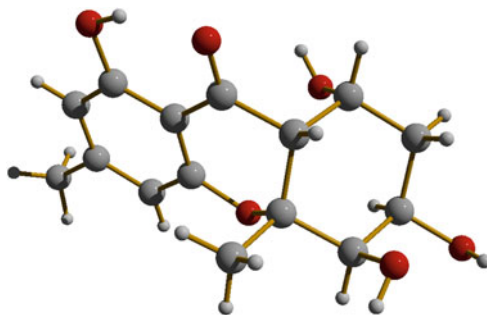


Fig. 13.19 X-ray structure of monodictysin A (**984**)

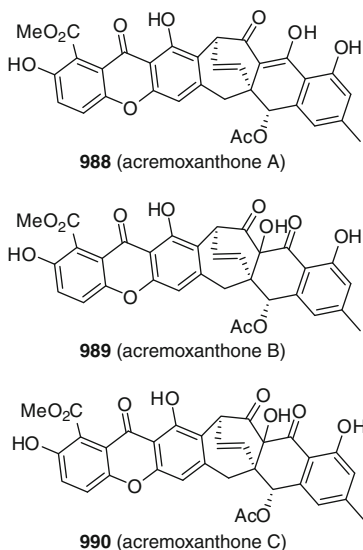
In terms of bioactivity, monodictysin B was shown to inhibit cytochrome P<sub>450</sub> 1A with an  $IC_{50}$  value of 3.0  $\mu M$ . Both monodictysins B and C were shown to effect the induction of NAD(P)H:quinone reductase (QR) in Hepa cells. The modulation of Phase II detoxifying enzymes such as QR is important for both the metabolism and excretion of carcinogens, and this target enzyme is employed frequently in the study of potential cancer chemopreventive agents (637) (**640**).

## 13.4 Xanthone Dimers and Heterodimers

Xanthone dimers and heterodimers possess increasingly complex and interesting structures, and in many cases have shown specific and selective biological properties. They include acremoxanthones A–C (**347**, **989**), vinaxanthone (**991**), and xanthofulvin (**1004**).

### 13.4.1 Acremoxanthones

Acremoxanthones A and B (**988** and **989**, Fig. 13.20 (655, 656)) were reported by the *Isaka* group in 2009 after being isolated from an air-borne fungus, together with some biosynthetically related products (655). The authors suggested that these compounds are formed by coupling of xanthone (elminthosporine) and anthraquinone (pinselin) units, resulting in a xanthoquinodin species of the type represented by the beticolins (**1063-1070**) and the xanthoquinodins (**1058-1062**). Mass spectrometric and <sup>13</sup>C NMR data of acremoxanthone A indicated a non-symmetrical structure with the molecular formula, C<sub>33</sub>H<sub>24</sub>O<sub>11</sub>. Further analysis using 2D-NMR experiments (COSY, HMBC, NOESY) data indicated that C-11' and H-10 have a *syn*-facial relationship. The relative configurations of **988** and **989** were also determined using these NOESY data; OH-9a and H-10 occupy *pseudoaxial* positions.



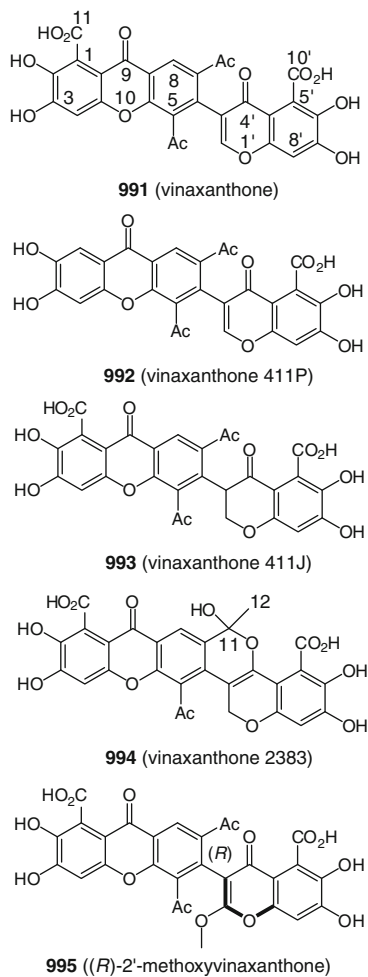
**Fig. 13.20** Acremoxanthones (**988–990**)

It has been found that both acremoxanthonones A and B show antibacterial activity (against *Staphylococcus aureus* and *Bacillus cereus*), antifungal activity (acremoxanthone A showed activity against *Candida albicans*), and antiplasmodial activity (acremoxanthone B showed activity against *Plasmodium falciparum*), as well as activity against three cancer lines (KB, BC, and NCI-H187 cells) and the Vero cell line, with  $IC_{50}$  values from 0.87 to 14  $\mu\text{g}/\text{cm}^3$ ) (655). In 2011, a third member of this series, acremoxanthone C (**990**), was isolated and characterized structurally (656). Synthesis studies have been provided by the Porco group (657).

### 13.4.2 Vinaxanthonones

Vinaxanthone (**991**) (Fig. 13.21) was isolated by Yokose and Seto in 1991 from the soil microbe, *Penicillium vinaceum*, and shown to be a novel phospholipase C (PLC) inhibitor, with an  $IC_{50}$  value in the low micromolar range (658). PLC is an enzyme that hydrolyzes phosphatidylinositol biphosphate (PIP) in the cellular membrane, and is involved in the signal transduction cascade and pathways affecting cell proliferation. Encountering difficulty in the structure elucidation process due to both the low solubility and highly substituted nature of **991**, the authors used a series of NMR techniques including 2D-INADEQUATE and selective 1D-INADEQUATE experiments to solve the structure.

Vinaxanthone (**991**) was isolated subsequently from *Penicillium glabrum* in 1994 by Wrigley and co-workers, in association with three new xanthonones



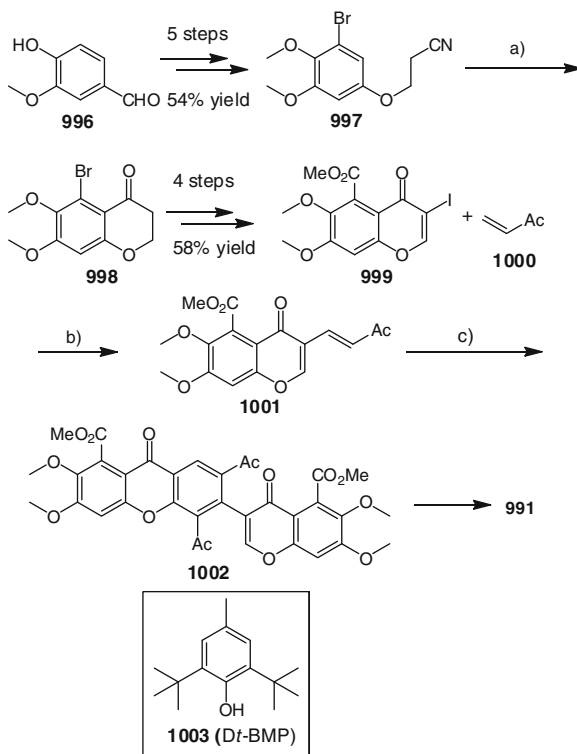
**Fig. 13.21** Vinaxanthone (**991**) and vinaxanthone species **992-994**; (*R*)-2'-methoxyvinaxanthone **995** (absolute stereochemistry shown)

(**992-994**) (Fig. 13.21), and identified as an effective CD4-binder. The protein CD4 is involved in the immune response system and is known as a cellular receptor for HIV (659). These compounds were identified based on their mass spectrometric data and the results of multiple 2D-NMR experiments (using ROESY as an alternative to NOESY). The authors propose that these polyketide-derived products result from dimerization of a  $C_{14}$ -polyketide related to polivione, also a metabolite of *P. galabrum*. In 2003, vinaxanthone was again isolated by *Kumagai* and co-workers, and shown to have semaphorin inhibitory activity (660). Semaphorins are a group of endogenous molecules that inhibit axonal growth of specific cells in the nervous system. Inhibitors of the binding of Sema3A to its receptor may be of

interest for the purpose of studying neuronal growth and regeneration, for example in the damaged nervous system (661).

In 2008, *Rezanaka* and co-workers reported the isolation and characterization (including determination of absolute configuration) of (*R*)-2'-methoxyvinaxanthone (**995**, Fig. 13.21), isolated from *Penicillium vinaceum* (662). Computational chiroptical methods were used to define this compound conformationally as the (*R*)- or (*M*)-atropisomer, due to negligible free rotation at room temperature around the biaryl bond linking the xanthone and chromone components (the calculated free energy required is 103.5 kJ/mol). This compound showed no antibacterial nor antifungal activity in standard assays, but was active in both sea urchin and crown gall tumor (potato disk) tests (662).

The total synthesis of vinaxanthone (**991**) (Scheme 13.19) was conducted in 2007 by *Tatsuta* and co-workers, starting from vanillin (**996**) (661). A sequence of 13 steps yielded the natural product, including a key intermolecular *Diels-Alder* (IMDA) reaction to link the xanthone and chromone components, constructing the xanthone C-ring in the process. Interestingly, this IMDA was assisted greatly in

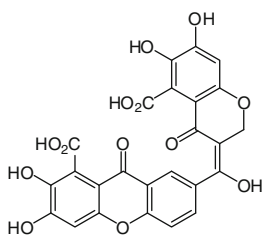


**Scheme 13.19** *Tatsuta*'s vinaxanthone (**991**) synthesis. Reagents and conditions: a)  $\text{AlCl}_3$ ,  $\text{MeONO}$  (aq), 80%; b)  $\text{Pd}(\text{OAc})_2$ ,  $\text{Et}_3\text{N}/\text{ACN}$ , 88%; c) *Dt*-BMP, air, toluene, 200°C, IMDA, 40%; d)  $\text{AlCl}_3$ , toluene

terms of selectivity by the addition of *Dt*-BMP (**1003**), since without this reagent the product distribution favored the elimination and aromatization of the products. The authors suggested that this species acts as an electron-acceptor by way of the corresponding quinone, while the addition of standard oxidants had no such effect.

### 13.4.3 Xanthofulvin

Xanthofulvin (**1004**) was first isolated by *Masubuchi* and co-workers from a *Eupenicillium* strain and found to be a chitin synthase II inhibitor ( $IC_{50} = 2.2 \mu M$ ). *Kimura* and co-workers reported the isolation of SM-216289 or xanthofulvin (**1004**, Fig. 13.22) in addition to the known tautomer, vinaxanthone (**991**, (Fig. 13.21), from cultures of *Penicillium* sp. SPF-3059 (660). The authors demonstrated that xanthofulvin (**1004**) (Fig. 13.22) is also a semaphorin inhibitor (see vinaxanthone, above); *Sema3A* was inhibited at a low concentration level ( $IC_{50} = 0.16 \mu M$ ).



**1004** (xanthofulvin, SM-216289)

**Fig. 13.22** Xanthofulvin or SM-216289 (**1004**)

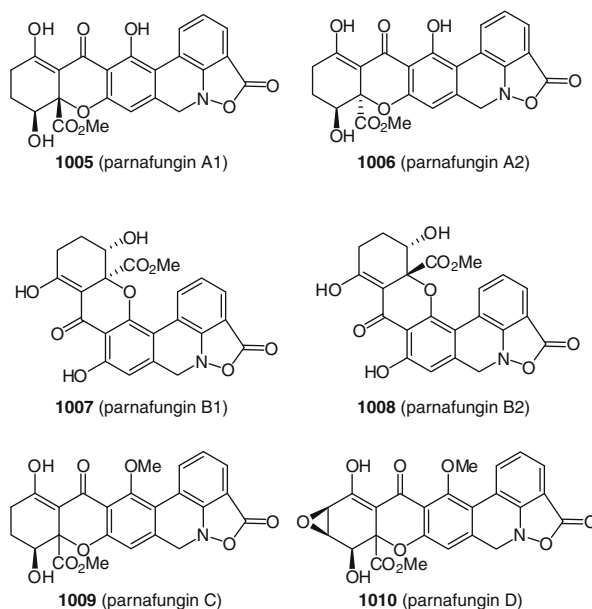
## 13.5 Tetrahydroxanthone Dimers and Heterodimers

Arguably the most structurally and biologically interesting (as well as synthetically challenging) xanthenes from fungi are in the expanding group of tetrahydroxanthone dimers and heterodimers. Those known include ascherxanthone (**1032**), the beticolins (**1063-1070**), the dicerandrols (**1071-1073**), the ergochromes (including the secalonic acids (**1034-1046**), the ergochrysin (**1039, 1042**), and the ergoxanthines (**1048**)), the microsphaerins (**1074-1077**), neosartorin (**1078**), the parnafungins (**1005-1010**) (Sect. 13.5.1), the phomoxanthenes (**1080, 1081**), the rugulotrosins (**1082, 1083**), Sch 42137 (**1084**), Sch 54445 (**1085**), xanthonol (**1086**), and the xanthoquinodins (**1058-1062**).



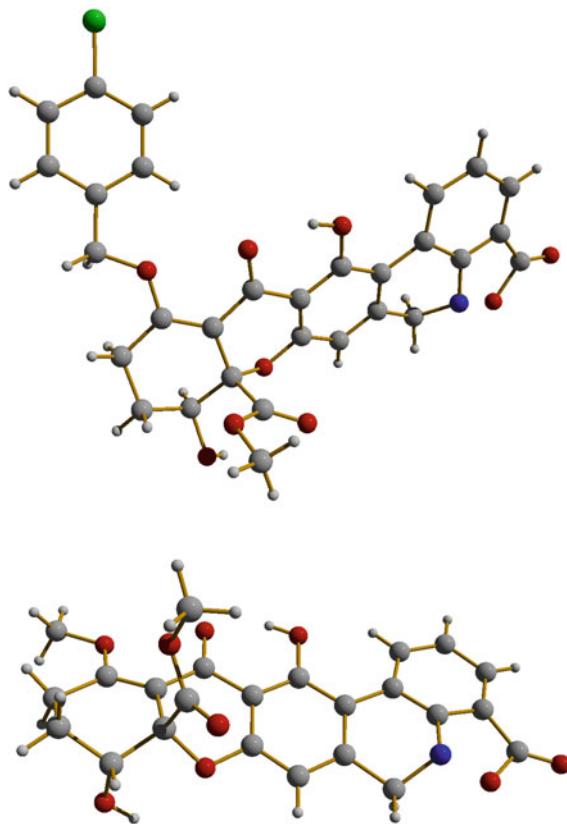
### 13.5.1 Parnafungins

The parnafungins (**1005-1010**, Fig. 13.23) were isolated by a team from Merck as an equilibrating mixture of four interconverting species (A1-2 and B1-2) from the lichenicolous fungus, *Fusarium larvarum*, after the crude fermentation extract was determined as being positive in a *Candida albicans* fitness assay (663). The latter organism (an ascomycetous yeast) is a human pathogen, and the fitness test uses a whole cell assay with 5,000 modified *C. albicans* strains, of which each is heterozygous for a specific gene from the genome, allowing the responsible biochemical target to be identified when a new antifungal compound is applied (664). Such chemical-genetic profiling was thus developed as a strategy for natural products drug discovery and, in particular, to investigate previously unexploited biochemical pathways in pathogenic fungi (664, 665).



**Fig. 13.23** Parnafungins (absolute stereochemistry shown, when known)

The interconversion between the four parnafungin forms (*para*- and *ortho*-oxygen connection giving parnafungins A and B), and *syn* (A1 (**1005**) and B1 (**1007**), major diastereomers) and *anti* (A2 (**1005'**) and B2 (**1008**), minor diastereomers), is due to a retro-oxa-*Michael*-addition, a process that is seen frequently among tetrahydroxanthenes. This interconversion was blocked by methylation of the C-15 alcohol, which allowed the structure of a derivative of parnafungin A1 (**1005**) to be established by X-ray crystallography (Fig. 13.24).



**Fig. 13.24** X-Ray structures of parnafungin A (top) and B (bottom) analogues

The methyl carboxylate at the AB ring junction is always in an *axial* orientation, while the major parnafungin diastereomers A1 (**1005**) and B1 (**1007**) have the C-15 hydroxy group in an *equatorial* orientation. Shortly after the initial report, parnafungins C (**1009**) and D (**1010**) were also isolated by the same team from a species taxonomically closely related to *F. larvarum* (666) and also produced small amounts of a parnafungin A and B mixture (667, 666). The authors propose that parnafungins C (**1009**) and D (**1010**) are derived from methylation (and oxidation for D) of parnafungin A (**1005**), rather than B (**1007**), supporting the hypothesis that parnafungin A (**1005**) is the compound biosynthesized initially by the fungal species of origin (667).

Parnafungins are structurally unique in that they contain an unprecedented isoxazolidinone ring, which is required for a broad spectrum of antifungal activity. These compounds have no observable activity against *Gram*-positive or -negative bacteria, however. Parnafungins are suggested to inhibit mRNA processing, with the target enzyme determined as polyadenosine polymerase (PAP) by both biochemical and genetic experimentation (664). Several yeast species were found to be

sensitive to the application of a purified parnafungin A/B mixture, including *Candida albicans* ( $MIC\ 0.014\ \mu\text{g}/\text{cm}^3$ ), *Candida krusei* ( $0.014\ \mu\text{g}/\text{cm}^3$ ), and *Saccharomyces cerevisiae* ( $3.3\ \mu\text{g}/\text{cm}^3$ ).

It was determined further that the linear parnafungin A (**1005**) is the species from the equilibrating mixture that is responsible for interacting with PAP, using an ingenious affinity selection/mass spectrometry technique (665). The PAP enzyme was exposed to the interconverting mixture of parnafungins at physiological pH, with the sample then subjected to rapid SEC chromatography, which separates bound ligand from unbound ligand and protein selectively. The ligand and protein complex is then diverted to low pH conditions, which both dissociate the ligand and freeze the interconversion, allowing the parnafungin active in binding to the target be discerned by HPLC. The linear parnafungins C and D had similar biological activities to A, with D being the most potent (667).

Ring-opened benzoquinoline isomers **1011** and **1012** (Fig. 13.25) were also observed to form under basic or neutral conditions, and somewhat more slowly under acidic conditions. It is likely that these result from the inherent instability of the isoxazolidinone core (by either  $E_2$  elimination or a hydrolysis/elimination sequence).

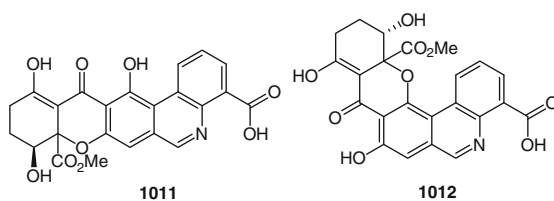
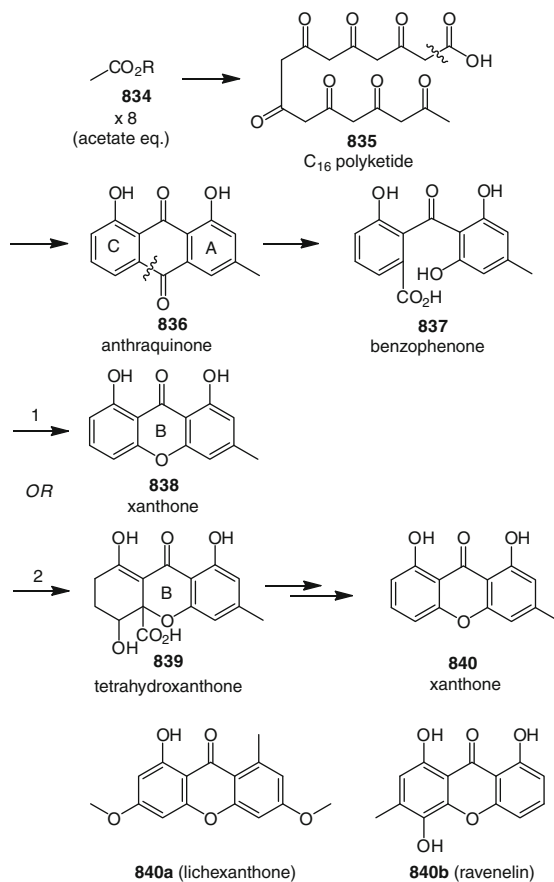


Fig. 13.25 Isoxazolidinone ring-opened species

Not long after these reports, a synthesis of the tetracyclic isoxazolo[4,3,2-*de*]phenanthridinone fragment **1017** (Scheme 13.20) was reported by Zhou and Snider (668). After some initial investigations, they developed a sequence based on Suzuki coupling to form the biaryl segment **1015**. A sequential one-pot nitro-reduction-isoxazolone formation gave **1016**, then mesylation and ring closing afforded the target isoxazolone **1016** in high yield. It was found also that a similar ring opening observed for parnafungins A (**1005**) and B (**549**) took place in deuterated chloroform, and that the treatment of **1017** with phenanthridine *N*-oxide in aqueous base gave the isoxazolidinone ring.

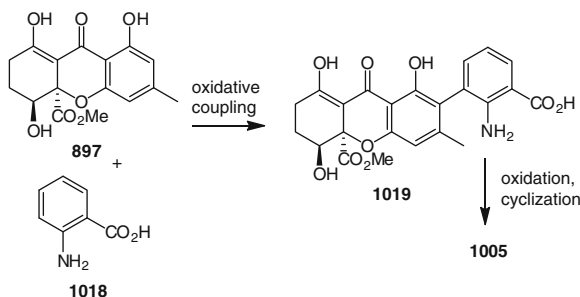
The authors also suggested a biosynthesis route to the parnafungins, involving the oxidative coupling of blennolide C (**897**) (Scheme 13.21) at the C-2 position to anthranilic acid (**1018**), followed by benzylic oxidation of **561** and ring closure (668).

Another report from Zhou and Snider in 2010 described the synthesis of hexacyclic parnafungin A and C models, utilizing Suzuki coupling of the 2-iodo-

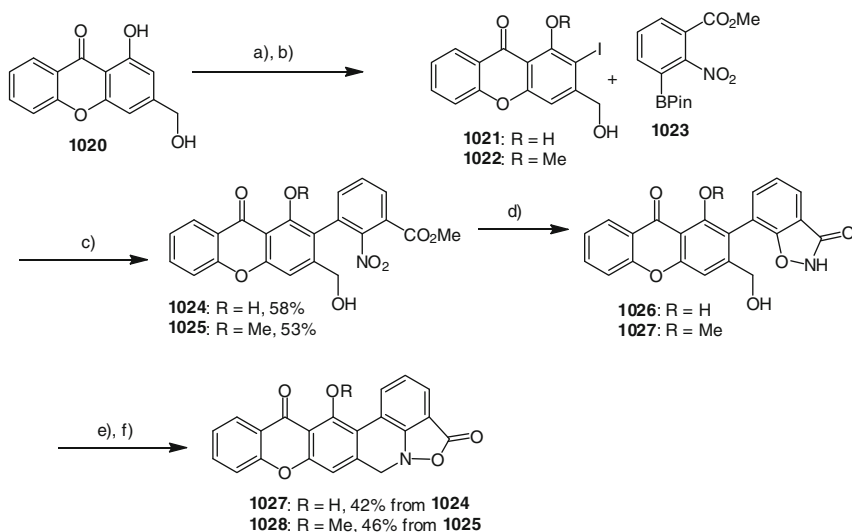


**Scheme 13.20** Snider and Zhou's synthesis of the isoxazolone fragment. Reagents and conditions: a)  $\text{Pd}(\text{OAc})_2$ , *S*-Phos,  $\text{K}_3\text{PO}_4$ ,  $\text{H}_2\text{O}$  (cat), toluene, reflux; b)  $\text{Zn}$ ,  $\text{NH}_4\text{Cl}$ ,  $\text{THF}/\text{MeOH}/\text{H}_2\text{O}$ , sonication,  $25^\circ\text{C}$ ; c)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 15 min; d)  $\text{Na}_2\text{CO}_3$ , 1:1  $\text{THF}/\text{H}_2\text{O}$ , 40 min

substituted aromatic xanthone components **1021** and **1022** with 3-carboxymethyl-2-nitrophenyl pinacol boronate (**1023**), to yield intermediates of the type **1024** and **1025** (Scheme 13.22) (669). These were subjected to zinc and ammonium chloride reductive formation of the benzisoxazolone core, followed by mesylation and  $\text{S}_{\text{N}}2$  cyclization under basic conditions to give **1029** (parnafungin C model,  $\text{R} = \text{Me}$ ) and **1028** (parnafungin A model). The authors noted that the ready isomerization of parnafungins A1, A2, B1, and B2, and their propensity to rapidly (<1 h) decompose to phenanthridines under neutral or basic conditions, makes these natural products especially challenging synthesis targets.

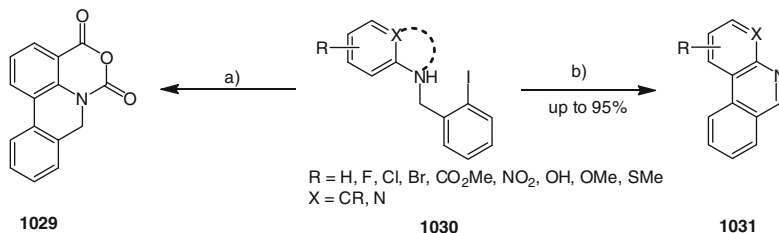


**Scheme 13.21** Possible biosynthesis of parnafungins from blennolide C (**897**) and anthranilic acid (**1018**)



**Scheme 13.22** Zhou and Snider's synthesis of parnafungin A and C models. Reagents and conditions: a)  $I_2$ ,  $H_5IO_6$ , 99% (**1021**); b)  $MeI$ ,  $K_2CO_3$ , 69% (**1022**); c)  $Pd(OAc)_2$ , *S*-Phos,  $K_3PO_4$ , 53%; d)  $Zn$ ,  $NH_4Cl$ , ultrasound; e)  $MsCl$ ,  $NEt_3$ ; f)  $Na_2CO_3$

Collaborative work by the *Williams* and *Bräse* groups led to a short synthesis of phenanthrenes to serve as model systems towards the total synthesis of parnafungin (Scheme 13.23) (670). In addition, the *Bräse* group also synthesized biaryls related to parnafungin (671), using tin chemistry (see Sect. 13.5.3).

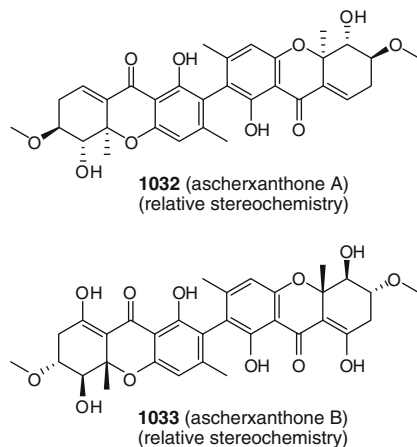


**Scheme 13.23** Photochemical synthesis of phenanthrenes. Reagents and conditions: a) acetonitrile,  $h\nu$ , quartz, 2 h; b) acetonitrile,  $h\nu$ , quartz, 2 h, up to 95%

### 13.5.2 Ascherxanthone

The symmetrical dimeric structure of ascherxanthone A (**1032**, Fig. 13.26) was reported in 2005 after being isolated from *Aschersonia* sp., an entomopathogenic fungus collected on a *Homoptera* scale insect (672). The relative configuration around C-5, C-6 and C-10a was determined using  $^1\text{H}$  NMR spectroscopy and NOESY experiments. Like diversonol (**932**) (see Sect. 13.2.3), this compound has methyl substituents at the C-4a position, but, however, the absence of a hydroxy group at C-8 and C-8' is unique among this family of natural products. The compound exhibited strong inhibitory activities for both *Plasmodium falciparum* ( $IC_{50} = 0.20 \mu\text{g}/\text{cm}^3$ ) and Vero cells ( $IC_{50} 0.80 \mu\text{g}/\text{cm}^3$ ), and cytotoxic activity against three cancer cell lines ( $IC_{50}$  values in the range from 0.16 to  $1.7 \mu\text{g}/\text{cm}^3$ ) (672).

In 2009, *Chutrakal* and co-workers reported the large-scale isolation from *Aschersonia luteola* BCC 8774 of a new compound related to ascherxanthone A, albeit with hydroxy groups in the place of the alkenyl hydrogen substituent of **1032** (673). This compound was isolated after *in vitro* screening of antifungal substances, and exhibited significant inhibitory activity ( $IC_{90} = 0.95 \mu\text{M}$ ) against a virulent



**Fig. 13.26** Ascherxanthonenes A, B (**1032**, **1033**)

strain of the rice blast fungus, *Magnaporthe grisea*. Subsequently, preliminary *in vivo* tests were also carried out. The use of NOESY and other NMR techniques confirmed that the compound possesses the same relative configuration as **1032**, and it was named ascherxanthone B (**1033**).

### 13.5.3 Secalonic Acids

The secalonic acids (**1034–1046**) (Fig. 13.27) are comprised of dimers of the blennolides (*vide supra*). This class of compounds, also named ergochromes, has been the subject to extensive investigation due to their biological activity.

Although no total synthesis has been reported so far, considerable efforts have been made in the last decade. Xanthone dimers have been synthesized using *Suzuki* chemistry (674) (Scheme 13.24) or *Stille* couplings (671) (Scheme 13.25).

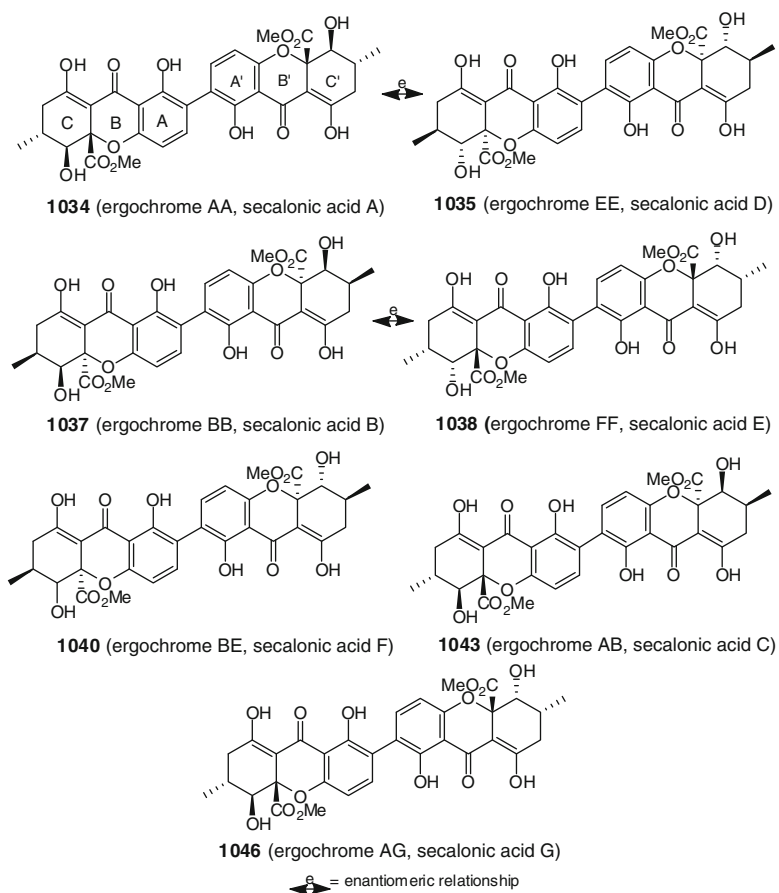
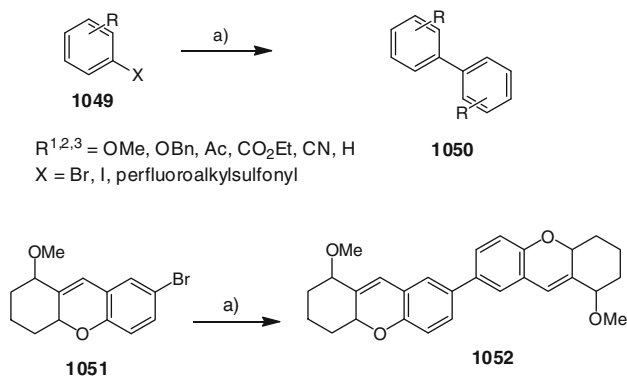


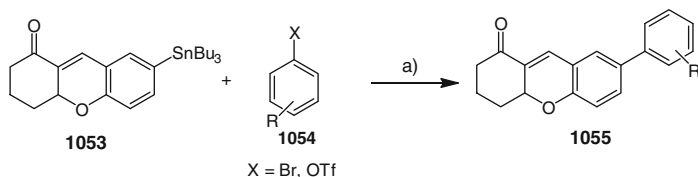
Fig. 13.27 Ergochromes: Secalonic acids, ergochrysin (**1039**, **1042**), and ergoxanthin (**1048**)

*Bräse* and co-workers described a novel one-pot methodology for the synthesis of symmetrical biaryls as a part of their ongoing investigations in the synthesis of the secalonic acids (**1034–1046**), their monomeric units, and related tetrahydroxanthones (674). Building on methodology developed by *Miyaura et al.* for the synthesis of boronic acids by palladium-coupling of arylhalides with bis(pinacolato)diborane (Scheme 13.24) (675–676), these researchers modified their original conditions effectively through the use of a more nucleophilic base (potassium carbonate rather than acetate). The new conditions promoted the *Suzuki* cross-coupling of the *in situ* formed arylboronic ester (not shown) with a molecule of starting aryl halide or equivalent **1049** due to the enhanced nucleophilicity (674) of a proposed intermediate penta-coordinated palladium species.



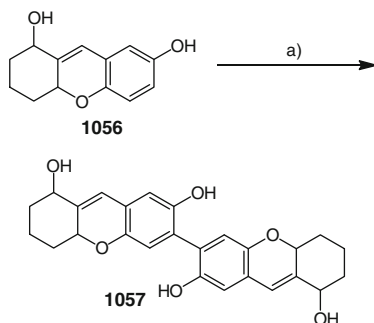
**Scheme 13.24** *Bräse's* one-pot biaryl synthesis using boron reagents. Reagents and conditions: a)  $(\text{PinB})_2$ ,  $\text{PdCl}_2(\text{dppf})_2$ ,  $\text{K}_2\text{CO}_3$ , DMSO,  $80^\circ\text{C}$ , 16 h

The resulting symmetrical biaryls **1052** (Scheme 13.24) were formed under mild conditions ( $\text{K}_2\text{CO}_3$ , DMSO,  $80^\circ\text{C}$ ). It was found also that the addition of a diphenylphosphinoferrrocene (dppf) ligand improved the reaction by suppressing the degradation of catalyst in the form of palladium black. The yields were substrate dependent (steric effects appear important), but tolerated a range of functional groups, and incorporated several (heterocyclic) aromatic cores with varying success (40–94% isolated yield, 21 examples). The methodology was applied successfully also to the synthesis of a secalonic acid model, bisxanthene **1052**, through the reaction of two equivalents of bromide **1050** (Scheme 13.24). Recently, it has been shown by the same group that the stannane **1053** can also serve as suitable partner (Scheme 13.25) (671). It is noteworthy



**Scheme 13.25** *Bräse's* biaryl synthesis using tin reagents. Reagents and conditions: a)  $\text{Pd}(\text{PPh}_3)_4$ , LiBr, CuI, toluene,  $80^\circ\text{C}$ , 40 h





**Scheme 13.26** *Bräse's* oxidative biaryl synthesis. Reagents and conditions: a)  $[\text{K}_3\text{Fe}(\text{CN})_6]$ ,  $\text{KOH}$ ,  $\text{H}_2\text{O}$ ,  $\text{MeOH}$ , 4 d, 24–45%

that these *Stille* couplings to afford the biaryls **1055** tolerate a broader range of substituents.

*Sahin*, *Nieger*, and *Bräse* have reported also the oxidative coupling of various hexahydro-xanthenols. The application of an iron complex as oxidant converted the 2-hydroxy-substituted xanthenes **1056** (Scheme 13.26) to the 3,3-*bis*-coupled biaryl **1057** (565). It appears that these two papers ((564) and (674)) represent the only chemical studies published on the topic of xanthone or xanthene biaryl-coupling.

### 13.5.4 Xanthoquinodins

The xanthoquinodins  $\text{A}_1$ – $\text{A}_3$  and  $\text{B}_1$ – $\text{B}_2$  (**1058** to **1062**, Fig. 13.28) were identified initially as anticoccidial antibiotics isolated from a *Humicola* sp. Feeding experiments with  $^{13}\text{C}$  and extensive spectroscopic data analysis on the resulting isotopically enriched compounds allowed for the structure determination of these five compounds (678, 679). These heterodimers, like the beticolins, also result from the coupling of a xanthone with an anthraquinone, although the coupling is now in an end-to-tail fashion. The relative configuration at  $\text{C-11}'$  and  $\text{C-14}'$  is *S* and *R*, respectively, and  $\text{C-2}$  is *S* and  $\text{C-3}$  is *S*.

Unlike the beticolins, these different forms of xanthoquinodins can interconvert merely by being heated in solution (655). Heat treatment of xanthoquinodin  $\text{A}_1$  gave a mixture of all five compounds. Heat treatment of the other compound  $\text{A}_2$  gives mixtures with the following exception:  $\text{A}_3$  appears to represent a final product, which is effectively removed from the interconversion pool by virtue of its unique lactone ring.

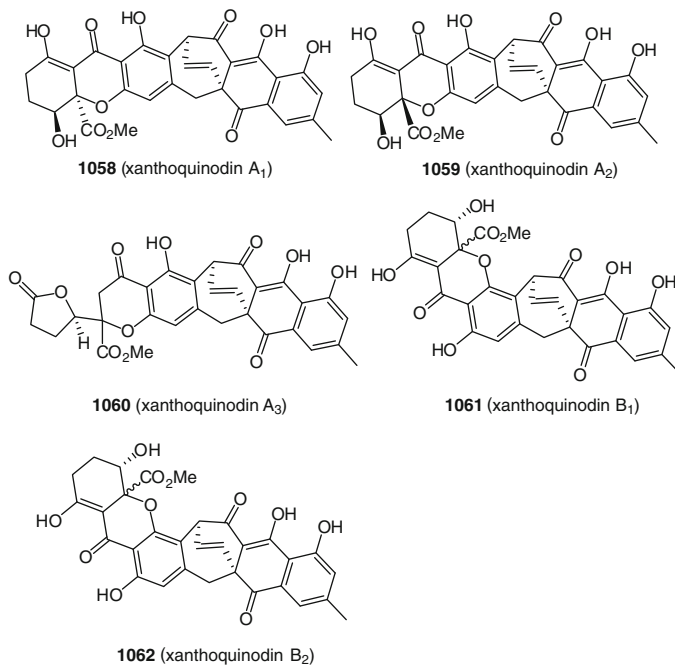
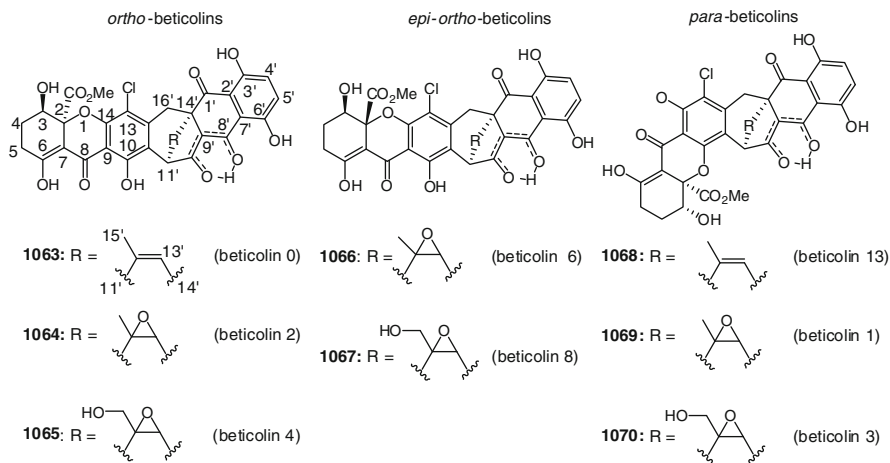


Fig. 13.28 Xanthoquinodins (1058–1062)

### 13.5.5 Beticolins

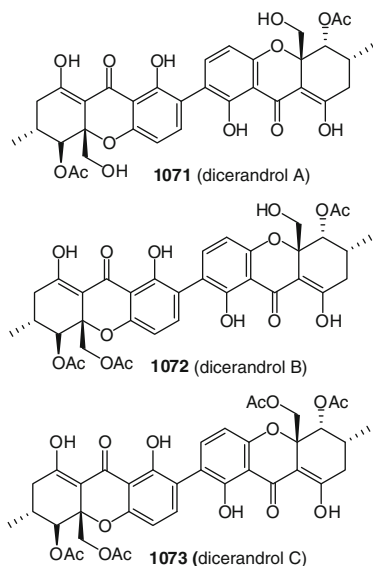
The beticolins (ascertained structures shown, **b0**, **2**, **4**, **6**, **8**, **13**, **1**, **3**, and **1063–1070**, respectively, Fig. 13.29) are a fascinating family of closely related non-host-specific mycotoxins produced by several strains of *Cercospora beticola*, a fungus responsible for cercosporiosis, a leaf spot disease of sugar beet (*Beta vulgaris*) (680–683).



**Fig. 13.29** Beticolins. Numbering shown for the *ortho*-beticolins is retained in the corresponding *para*-species according to the original position

### 13.5.6 Dicerandrols

The dicerandrols A–C (**1071** to **1073**, Fig. 13.30) were isolated from *Phomopsis longifolia*, an endophytic fungus found to be growing on the endangered Floridian mint species, *Dicerandra frutescens* (684). The structures were determined using NMR experiments in combination with a positive  $\text{FeCl}_3$  experiment, which is



**Fig. 13.30** Dicerandrols A–C (**1071**–**1073**)

indicative of a *para*-unsubstituted phenol, requiring that the dimer dicerandrol A must be linked in the more common 2,2'-manner. The relative configuration of these was determined to be the same as for secalononic acids B and E (see below). These species exhibited antimicrobial activities against *Bacillus subtilis* and *Staphylococcus aureus*, which were correlated with their extent of acylation (*i.e.* C > B > A). Dicerandrol B (**1072**) showed the most potent growth inhibitory activities for the HCT-116 colon and A549 lung tumor cell lines (684).

### 13.5.7 *Microsphaerins*

Microsphaerins A–D (**1074–1077**, Fig. 13.31) were found to be produced by the anamorphic soil fungus *Microsphaeropsis* sp. via a bioassay-guided isolation process (685). These species were identified as being inhibitory for methicillin-resistant *Staphylococcus aureus* (MRSA), which has been demonstrated to have an almost 20% lethality rate among infected patients in one study of U.S. hospitals (686).

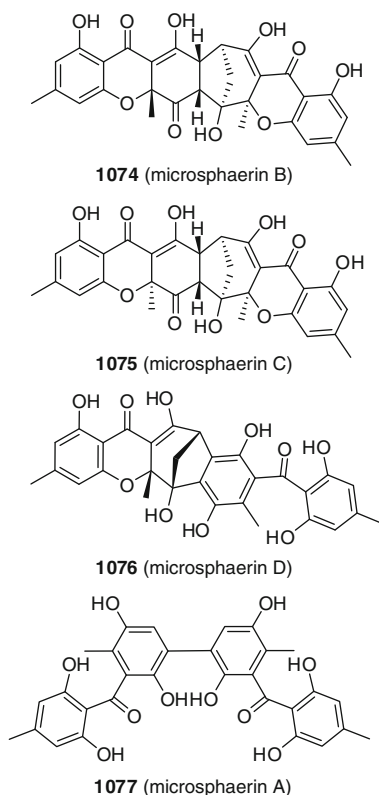


Fig. 13.31 Microsphaerins (**1074–1077**)

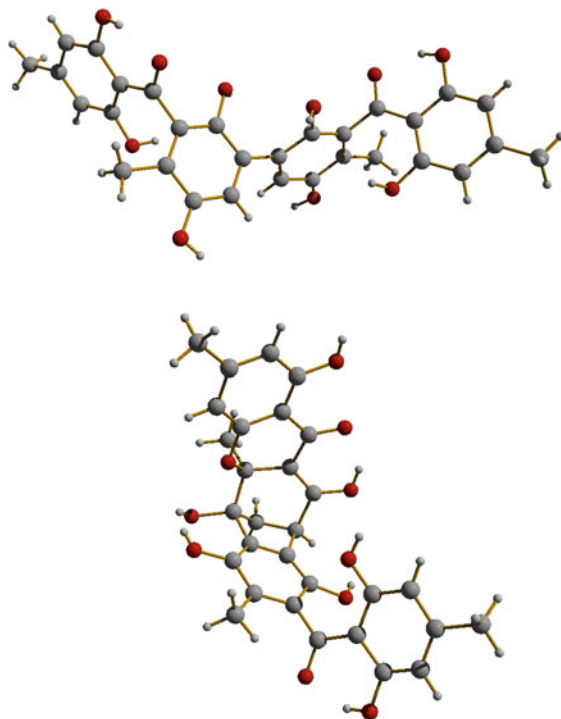


Fig. 13.32 X-ray structures of microsphaerin 1 (*top*) and 2 (*bottom*)

The microsphaerins were found to be active against MRSA in a whole cell assay with  $IC_{90}$  values in the low micromolar range (1–5  $\mu M$ ), although cytotoxic effects precluded these compounds from further investigation for their *in vivo* efficacy (Fig. 13.32).

The four compounds were isolated from two strains of *Microsphaeropsis* (B–D from the first, and A and D from the second), and were characterized structurally with the use of spectroscopic techniques inclusive of a ROESY NMR experiment. Structural confirmation was provided by the single-crystal X-ray analysis of microsphaerins A and D. Microsphaerins B–D each possess a bicyclo[3.2.1]octane ring. A retro-oxa-*Michael*-addition process was suggested to account for the slow interconversion of microsphaerins B and C, which are diastereomeric structures at the C-5 ether-bearing position. This process is similar to that described for the beticolins and parnafungins (see above, Sect. 13.5.1). It appears as though microsphaerin A is the putative precursor for the other microsphaerins, which can be formed by reduction of the innermost aromatic rings and their subsequent cyclization to form microsphaerins C and D. Accordingly, microsphaerin D may represent a half-way point in this biosynthesis process.

### 13.5.8 Neosartorin

A novel ergochrome, neosartorin (**1078**, Fig. 13.33), was isolated from the mycelium of the soil mold *Neosartorya fischeri*, and the chemical structure was deduced with a variety of spectroscopic techniques (687). This compound is an isomer of the eumitrins. It was determined that the relative configurations at the C-5, -6 and -10 (and C-5', -6' and -10') positions are the same as in secalonic acids A and D.

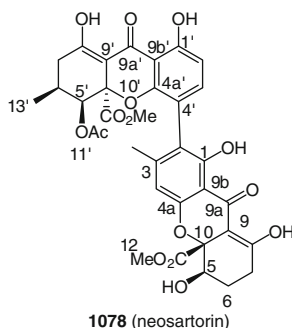
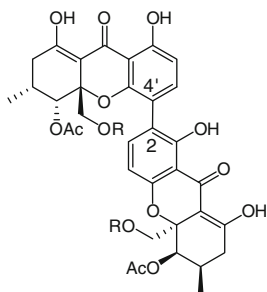
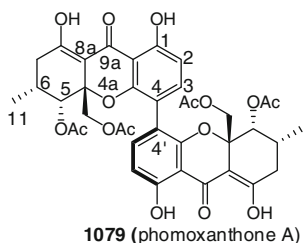


Fig. 13.33 Neosartorin (**1078**) (relative configuration shown)

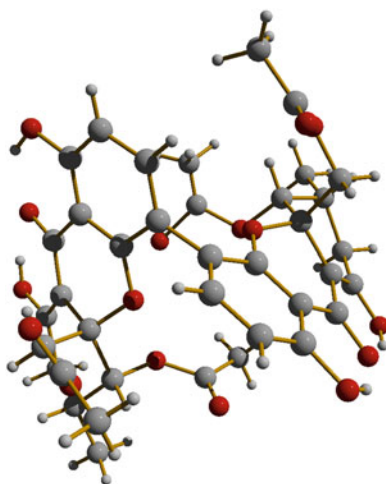
### 13.5.9 Phomoxanthonones

Phomoxanthonones A and B (**1080** and **1081**, Fig. 13.34) were isolated from the endophytic fungus, *Phomopsis* sp., when an extract from this species was found to exhibit *in vitro* antimalarial activity (688). Phomoxanthone A is a symmetrical homodimer with a 4,4'- (*para-para*)-linkage, while phomoxanthone B has a 2,4'- (*ortho-para*)-linkage, as seen with the eumitrins. These structures are similar to those of the ergochromes, however, the carboxymethyl substituents at C-10a (C-10a') have been replaced with acetoxymethyl substituents, and the C-6 (C-6a) hydroxy group moieties are acetylated. The relative configuration of both phomoxanthonones A and B was determined by NMR experiments. The compounds proved to be inhibitory *in vitro* for *Plasmodium falciparum*, *Mycobacterium tuberculosis*, and several cancer cell lines (Fig. 13.35).

The absolute configuration and axial chirality of phomoxanthone A (**1079**, Fig. 13.34) were ascertained by Krohn and co-workers using a combination of single-crystal X-ray analysis, and CD and calculated CD spectra (689). This compound was isolated from an extract of a different *Phomopsis* species, shown to exhibit antibacterial and antifungal activity. Deacetylphomoxanthone B (**1081**, Fig. 13.34) was reported in 2007 as a metabolite from *Phomopsis* sp. PSU-D15, with dicerandrol (**1071**, Fig. 13.34) also found as a constituent of this fungus (689).



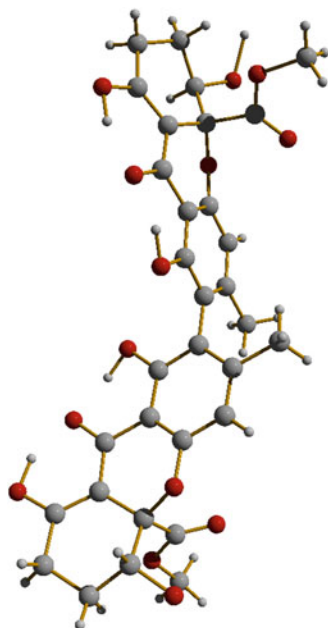
**Fig. 13.34** Phomoxanthenes A and B and deacetylphomoxanthone B (**1079-1081**)



**Fig. 13.35** X-Ray diagram for phomoxanthone A (**1079**)

### 13.5.10 *Rugulotrosins*

Rugulotrosins A and B (**1082** and **1083**, Fig. 13.36) were reported in 2004 after being isolated from cultures of a *Penicillium* sp. from soil samples. Rugulotrosin A is a symmetrical 2,2'-(*ortho-ortho*)-coupled dimer of tetrahydroxanthone subunits,



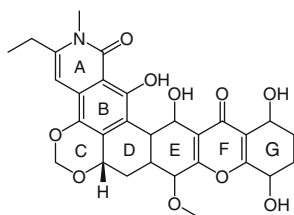
**Fig. 13.36** Rugulotrosins A and B (relative stereochemistry shown) (1082, 1083); X-ray diagram of rugulotrosin A

while rugulotrosin B is a comparatively rare 2,4'-(*ortho-para*)-coupled dimer (690). The structures of these compounds were determined by spectroscopic analysis, and that of rugulotrosin A was confirmed by single-crystal X-ray analysis. The compounds showed considerable growth inhibitory activity against *Bacillus subtilis* and rugulotrosin A also exhibited significant effects against *Enterococcus faecalis* and *Bacillus cereus*.

### 13.5.11 Sch 42137

The natural product Sch 42137 was reported by *Cooper* and co-workers in 1992 as a novel antifungal antibiotic, after its isolation from cultures of a soil-derived *Gram*-positive actinomycete bacterium, *Actinoplanes* sp. SCC 1906 (691). The structure (1084, Fig. 13.37), having both an isoquinoline and xanthone component, is related to the actinoplanones and the albofungins (see above), the cervinomycins (see Sect. 13.3.1), lysolipin (see Sect. 13.3.1), and the simaomicins (see below). The authors described the culturing, isolation, and structure elucidation of the parent molecule and two acetate derivatives. These compounds were compared spectroscopically to the simaomicins, since for a member of which a crystal structure was already known. Sch 42137 demonstrated potent inhibitory activity for six strains of





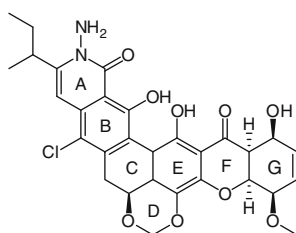
**1084** (Sch 42137)

**Fig. 13.37** Sch 42137 (**1084**)

*Candida albicans*, and also inhibited the growth of the dermatophytes *Trichophyton mentagrophytes*, *T. rubrum*, *T. tonsurans*, and *Microsporon canis*.

### 13.5.12 Sch 54445

The potent Sch 54445 (**1085**, Fig. 13.38, proposed structure shown) was reported by *Chu* and co-workers in 1997 after being isolated from the fermentation broth of *Actinoplanes* sp. (692). This is a member of the albofungin family, possessing both a xanthone and an isoquinoline component. The structure was proposed as **1085** based on information derived from a variety of spectroscopic techniques, although a combination of NOESY data and CD spectra with computational techniques proved not sufficient to elucidate the stereochemistry around the G-ring. However, an *anti*-configuration was proposed based on the similarity of the optical rotation to albofungin, a compound for which the stereostructure has been established.



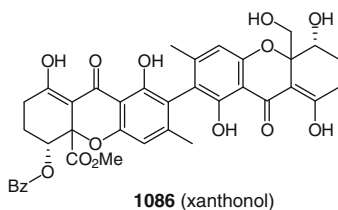
**1085** (Sch 54445)

**Fig. 13.38** Sch 5445 (**1085**)

Sch 54445 was found to have antifungal potency against several yeast, dermatophyte, and *Aspergillus* species, with *MIC* values in the sub-micromolar range ( $\sim 0.4 \mu\text{g}/\text{cm}^3$ ). Like albofungin and Sch 42137 (**1084**) (see above, for both), Sch 5445 was found to be highly toxic when administered to mice, with an  $LD_{50}$  of 1 mg/kg.

### 13.5.13 Xanthonol

The novel unsymmetrical dimeric xanthone, xanthonol (**1086**) (Fig. 13.39), was isolated from the fermentation broth of a non-sporulating fungus found in the leaf litter of *Manikara bidentata* (693). A point of interest is that this compound exhibits a methyl group substitution in an aryl position, in the same manner as the rugulotrosins, rather than the C-6(C-6') methylation observed for the secalonic acids, dicerandrols and phomoxanthenes. Also interesting is the benzoyleated alcohol at the C-5' position. Xanthonol (**1086**) has been found to exhibit antihelmintic properties against the larvae of *Lucilia sericata*, *Aedes aegypti*, and *Haemonchus contortus*. Synthesis efforts have been made by the Bräse group using the procedure described in Sect. 13.2.1. (694) (Scheme 13.9).



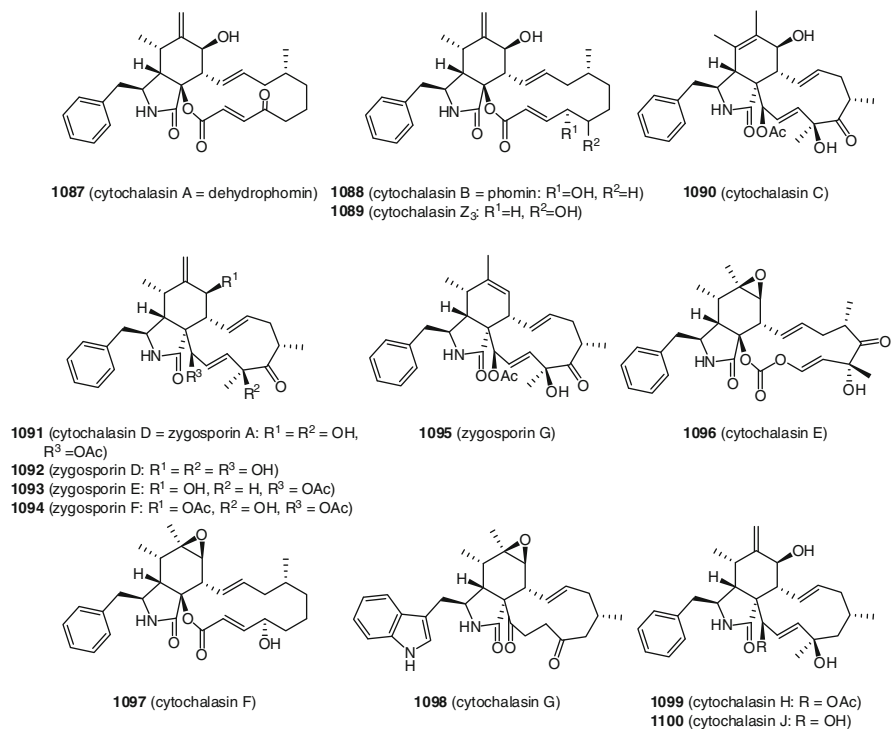
**Fig. 13.39** Xanthonol (**1086**)

## 14 Cytochalasans

The cytochalasans are a group of structurally diverse fungal metabolites exhibiting a wide range of biological activities. Their name is derived from the Greek (*κύτος*, *kytos*, cell; *χάλασις*, *chhalasis*, relaxation) due to their most well-known effect, namely, the influence on actin filament networks in eukaryotic cells, which results in a deterioration of the dynamic processes involving the cytoskeleton formation. Together with some other biological properties, the cytochalasans represent a group of potential drug candidates, especially as anticancer agents.

The first two cytochalasans (cytochalasin A (**1087**) and B (**1088**), Fig. 14.1) were isolated in 1966 and structurally determined in the same year. They were discovered independently by *Tamm* and *Rothweiler* at the University of Basel (695) and *Aldridge et al.* at Imperial Chemical Industries Ltd. (696). At the time of their isolation, these two compounds were named dehydrophomin and phomin, after the species of their isolation (*Phoma* S298). To date, more than 100 cytochalasans have been discovered, and are produced only by fungal organisms such as *Ascochyta*, *Aspergillus*, *Chaetomium*, *Chalara*, *Daldinia*, *Hypoxyton*, *Metarhizium*, *Penicillium*, *Phoma*, *Phomopsis*, *Pseudeurotium*, *Rosellinia*, *Xylaria*, and *Zygosporium* (10).

Structural characteristics of the cytochalasans include a highly substituted, fully hydrogenated and conserved isoindolone core, which is fused to a 11- to 16-membered macrocyclic ring – typically a carbocycle, a lactone, or a cyclic carbonate. The nitrogen atom of the perhydroisoindolone moiety results from

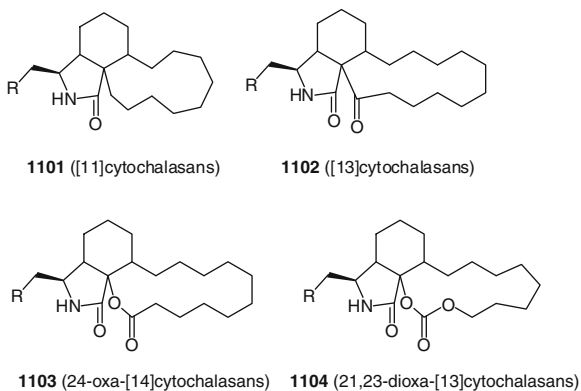


**Fig. 14.1** Structures of selected cytochalasins

an amino acid precursor, *e.g.* phenylalanine, tyrosine, tryptophan, leucine, or alanine, hence these compounds are polyketide-amino acid hybrids. This is also affirmed by biosynthetic radioactive labeling studies, supporting the incorporation of malonate/acetate units, phenylalanine, and methyl groups from methionine (697). Moreover, the cytochalasins are divided into various groups according to the amino acid substituent present at the perhydroindolone core: cytochalasins (benzyl group), pyrichalasin (*p*-methoxybenzyl group), chaetoglobosins ((indol-3-yl)methyl group), aspochalasin (2-methylpropyl group), andalachalasin (methyl group), while other names for several subgroups and derivatives also exist due to the large number of known compounds of this type. The high diversity of cytochalasins is evident as the result of a wide variety of substitution patterns. Since a detailed depiction of all compounds in this series would go beyond the scope of this chapter, the reader is referred for more detailed information to a

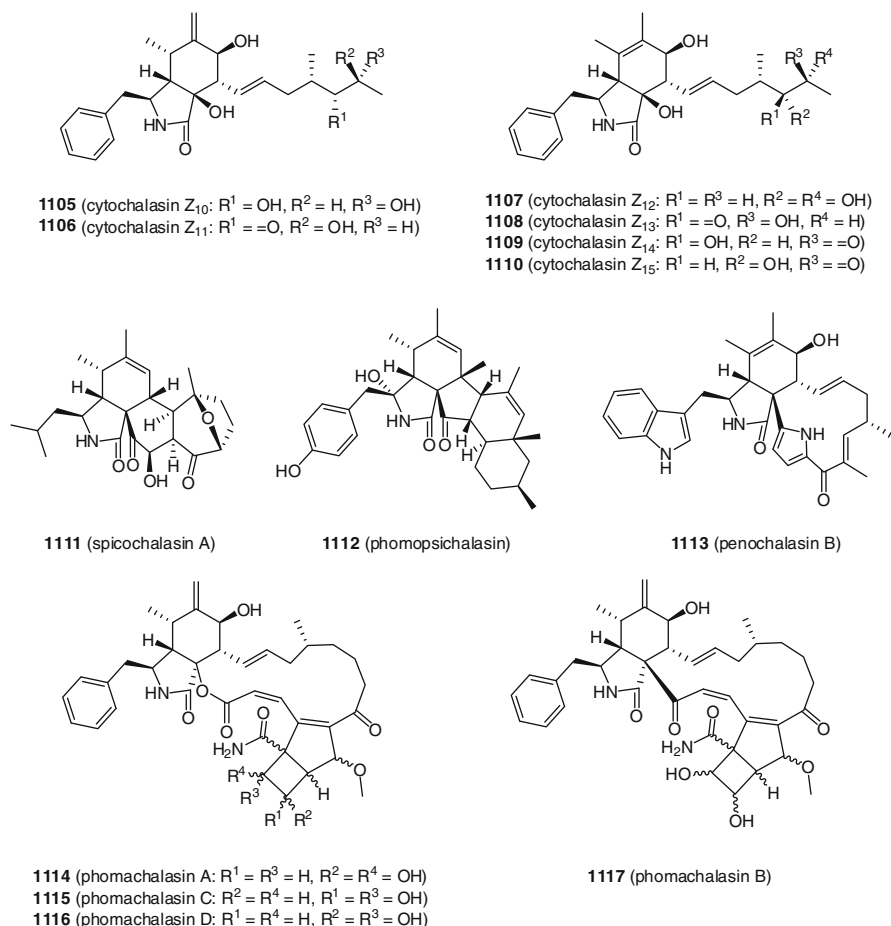
comprehensive review with many examples given, including some biosynthesis schemes, as published by *Hertweck et al.* (698).

*Binder* and *Tamm* introduced a systematic nomenclatural scheme based on the size of the macrocycle for this compound class (699) (Fig. 14.2). However, on account of their structural complexity, the trivial names of these mycotoxins are employed typically, with these based on either their organism of origin (*e.g.* zygosporens from *Zygosporium* spp.) or as a result of their biological activity (*e.g.* the cytochalasins).



**Fig. 14.2** Systematic nomenclature of the cytochalasan scaffold, where R derives from the incorporated amino acid and the number in brackets designates the size of the macrocycle

Furthermore, uncommon structures are also known among the cytochalasans (Fig. 14.3). For instance, cytochalasins  $Z_{10}$ – $Z_{15}$  (**1105**–**1110**) bear an open carbon chain instead of a macrocycle (700). Spicochalasin A (**1111**) (701) and phomopsichalasin (**1112**) (702) show novel pentacyclic structures, while the macrocycles of the penochalasins (*e.g.* **1113**) (703) include a pyrrole ring. In 2011, four novel cytochalasans, named phomachalasins A–D (**1114**–**1117**), were isolated from *Phoma exigua* var. *exigua*. These contain a 15- or 16-membered macrocyclic ring, the largest such ring systems so far known among this mycotoxin class. In addition, this is fused to an unusual hexasubstituted bicyclo[3.2.0]heptene unit (704).



**Fig. 14.3** Selected cytochalasins with unusual structures

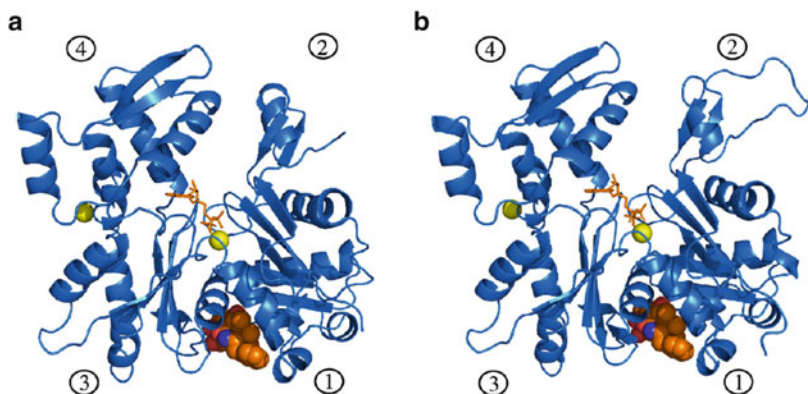
## 14.1 Biological Properties

Many biological effects have been observed by the cytochalasins. The most well-documented ones result from an influence on cellular processes, such as intracellular motility, exo- and endocytosis, and cytokinesis, and is based on the interference with actin filament network formation. This is due to interaction with actin (705), one of the key components of the cytoskeleton, leading to inhibition of cytokinesis (cell division) without any influence on karyokinesis (nuclear division). Thus, multinucleated cells were observed after treatment of proliferating cells with

a subtoxic amount of cytochalasans (706). When the cytochalasin concentration exceeded a cytotoxic concentration, even total denucleation appeared. They are therefore useful compounds for the investigation and understanding of actin-involved cellular processes like cell division and migration (707).

In a pioneering paper on the cytochalasin molecular mode of action, *Spudich* and *Lin* discovered a decrease in viscosity of actomyosin from rabbit muscle – the active protein complex of actin and myosin – when treated with cytochalasin B (1088) in micromolar concentrations. Actin was identified as direct binding partner of cytochalasin B (1088), thus the first proof on the target of this compound was provided (705). Further studies by several groups revealed that cytochalasins B (1088) and D (1091) inhibit, but not completely arrest, actin filament elongation (708, 709). A plausible mechanism was proposed by *Goddette* and *Frieden* (710).

Recently, in 2008, the exact binding situation between cytochalasin and actin was clarified, as *Trybus et al.* achieved the crystallization of cytochalasin D (1091) in complex with actin (Fig. 14.4) (711).



**Fig. 14.4** Crystal structures of actin in complex with cytochalasin D (1091). The actin subdomains (blue) are labeled 1–4. Cytochalasin D (1091) is displayed as space-filling representation (orange), ATP in stick representation (orange) and two  $\text{Ca}^{2+}$  ions as yellow spheres. Cytochalasin D (1091) is located in the hydrophobic cleft between subdomains 1 and 3 and connected to the protein *via* six hydrogen bonds (not shown). a) Crystal obtained by soaking protein crystals in ligand solution; b) crystal obtained by co-crystallization

Apart from the effect on cellular processes, most cytochalasins also exhibit a range of highly cytotoxic properties, including inhibitory activity against a variety of cancer cell lines, such as HeLa (712), P388 leukemia (713), and HT29 colonic adenocarcinoma cells (714). Cytochalasin E (1096) is known to possess cytotoxic, antiangiogenic, and tumor growth inhibitory effects (715, 716). A promising

strategy for therapeutic applications in cancer treatment is the targeting of actin, which plays an important role in cellular morphology changes particularly present in transformed cells. However, because cytotoxic effects towards tumor cells are not of high enough selectivity, no actin-targeting compounds have yet entered clinical trials (717).

Furthermore, cytochalasans exhibit antimicrobial effects, whereas cytochalasin A (1087), for example, inhibits the growth of *Bacillus subtilis* and *Escherichia coli* and cytochalasin D (1091) acts as an antifungal agent against *Botrytis cinerea* (718, 719). Antiparasitic activities have been demonstrated for cytochalasins B (1088), D (1091), E (1096), and for dihydrocytochalasin B, which inhibit growth and differentiation and influence excystation/encystation of the amoeba *Entamoeba invadens* (720). Cytochalasin B (1088) is able also to influence monosaccharide transport systems (721–725) and hormone release (726, 727). Moreover, in 1992, the antiviral cytochalasan L-696,474 (1139, Scheme 14.3) was discovered, exhibiting an inhibitory effect on HIV-1-protease (728–730).

*Penicillium expansum* is a common fungus present on rotten fruit (Fig. 14.5, (731)). This organism is relevant in respect to the production of highly toxic mycotoxins, which can cause disease after consumption of contaminated food. A screening procedure has revealed that chaetoglobosins – or tryptophan-derived [13]cytochalasans – are produced consistently in all *P. expansum* strains evaluated to date in both cultures and natural samples (732). Since they might represent a potential health hazard, the investigation of toxic effects is a subject of interest. It is known that the chaetoglobosins are toxic towards chick embryos (733), 1-day-old cockerels (734), rats (735), and mice (736, 737), and they also show cytotoxicity towards HeLa cells and teratogenicity in mice (736).



**Fig. 14.5** An apple contaminated with *Penicillium expansum*



## 14.2 Total Syntheses

Chemical syntheses of cytochalasans are challenging with regard to the numerous stereogenic centers and functional groups at the perhydroisoindolone core and the construction of the macrocyclic ring, respectively. Many cytochalasans are commercially available because they are useful tools for biological studies, which is another reason why there are only few total syntheses to date. One extensively investigated approach to the formation of isoindolones has been facilitated by the use of *Diels-Alder* reactions (738). Indeed, all total cytochalasan syntheses require a *Diels-Alder* reaction at some point in the procedure. One possibility is the simultaneous creation of the isoindolone and the macrocycle by [4 + 2]cycloaddition, while another approach implies the subsequent fusion of the macrocycle to a previously built up isoindolone (739).

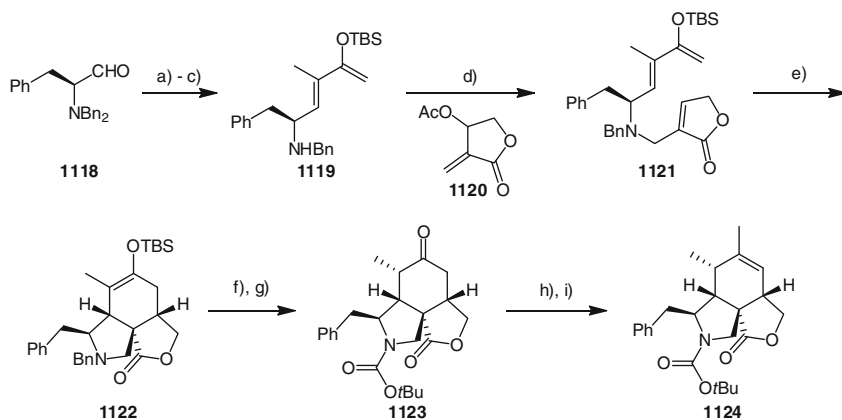
In the late 1980s, the number of total syntheses for these compounds showed an upswing, and several were reported by *Thomas et al.*, who accomplished the preparation of cytochalasins H (**1099**), D (**1091**), G (**1098**), and O (**1160**), following their *Diels-Alder* strategy for the stereoselective synthesis of many of the cytochalasan cores.

### 14.2.1 Total Synthesis of Cytochalasin B and L-696,474

Cytochalasin B (**1088**) belongs to the [14]cytochalasan group and was isolated from *Helminthosporium dematioideum* (696) and *Phoma* S298 (695). Its first total synthesis was accomplished by *Stork et al.* in 1978 (740). Later, this group published a more simplified synthesis, utilizing an intramolecular *Diels-Alder* reaction as the key step, forming both perhydroisoindolone and the macrocyclic moiety in a single reaction (741).

In 2004, *Myers* and *Haidle* reported a convergent and modular total synthesis of cytochalasin B (**1088**) and the [11]cytochalasan L-696,474 (**1139**) (742), using a late-stage macrocyclization step involving an intramolecular *Horner-Wadsworth-Emmons* olefination. Their strategy is applicable for the synthesis of cytochalasans of different ring sizes, as exemplified by these two total syntheses. Both macrolactone and macrocarbocyclic cytochalasans can lead back retrosynthetically to the same precursors. The synthesis of the tricyclic isoindolone precursor to cytochalasin B (**1088**) and L-696,474 (**1139**) is shown in Scheme 14.1.

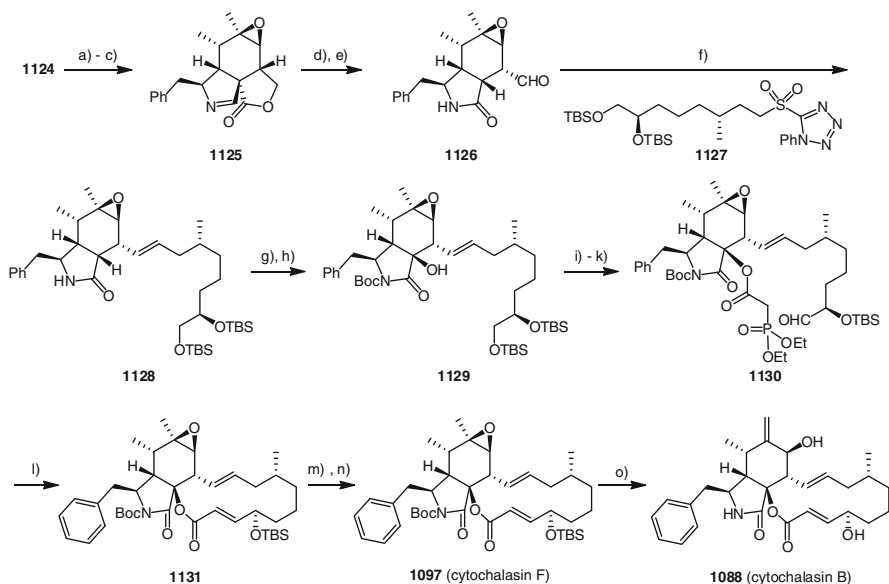
The starting material for this synthesis was *N,N*-dibenzyl phenylalanal (**1118**), which is readily accessible from the corresponding amino acid (743). This was submitted to a *Horner-Wadsworth-Emmons* reaction with diethyl 3-oxo-2-butylphosphonate. The olefin obtained was then mono-*N*-debenzylated, and then treated with *t*-butyldimethylsilyl triflate and 2,6-lutidine to give the silyl enol ether **1119**. Addition-elimination by treatment with methylene lactone **1120**, synthesized earlier (744), provided *Diels-Alder* substrate **1121**, which at high temperature



**Scheme 14.1** Synthesis of the tricyclic precursor **1124** to cytochalasin B (**1088**) and L-696,474 (**1139**). Reagents and conditions: a) diethyl 3-oxo-2-butylphosphonate, Ba(OH)<sub>2</sub>, THF/H<sub>2</sub>O, rt, 87%; b) 2,3-dichloro-5,6-dicyanobenzoquinone, CH<sub>2</sub>Cl<sub>2</sub>/pH 7 buffer, rt, 86%; c) *t*-butyldimethylsilyl triflate, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, -78°C to rt, 99%; d) MeOH, rt, 98%; e) *m*-xylene, 150°C, 77%; f) H<sub>2</sub>, 10% Pd/C, Boc<sub>2</sub>O, Et<sub>3</sub>N, EtOH, rt, 96%; g) TBAF, AcOH, THF, 0°C; h) KHMDS, THF, -78°C; then 2-[*N,N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, 93% over two steps; i) Me<sub>2</sub>CuLi, THF, -78 to 0°C, 95%

underwent a diastereoselective [4 + 2] cycloaddition to tricycle **1122**. The desired *endo* diastereomer was obtained in 77% yield (compared to 14% of the *exo* diastereomer). After this, the benzyl group was exchanged by a Boc protecting group and the silyl enol ether was cleaved in a highly diastereoselective manner, which afforded  $\alpha$ -methyl ketone **1123** as the only product. After regioselective formation of the corresponding enol triflate, addition of lithium dimethyl cuprate afforded substituted alkene **1124** as a building block, from which point on the total syntheses of cytochalasin B (**1088**) ( $\rightarrow$  macrolactone route, Scheme 14.2) and L-696,474 (**1139**) ( $\rightarrow$  macrocarbocyclic route, Scheme 14.3) diverge. The completion of cytochalasin B (**1088**) from precursor **1124** is shown in Scheme 14.2.

The tricyclic system **1124** underwent a smooth epoxidation by treatment with DMDO (quantitative yield). Afterwards, cleavage of the *N*-Boc group and oxidation of the resulting free amine furnished epoxy imine **1125**. In the single-step procedure following, both opening of the  $\gamma$ -lactam ring and deformylation occurred, thus delivering a hydroxylactam, which was then transformed to aldehyde **1126** by oxidation with *Dess-Martin* periodinane. Attachment of the necessary aliphatic chain for later macrocyclization by *Julia-Kocienski* coupling with *N*-phenyltetrazole sulfone **1127** (for preparation of **1127**, see Ref. (742)) afforded olefin **1128**. Boc-protection of the lactam group and subsequent  $\alpha$ -oxygenation with *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine furnished the tertiary alcohol **1129**, which was transformed into a phosphonate. Then, the primary and less hindered TBS group was selectively deprotected and oxidized to aldehyde **1130**. The following key step in the total synthesis – an intramolecular *Horner-Wadsworth-Emmons* reaction – allowed the formation of macrolactone **1131** in 60% yield. Cleavage of

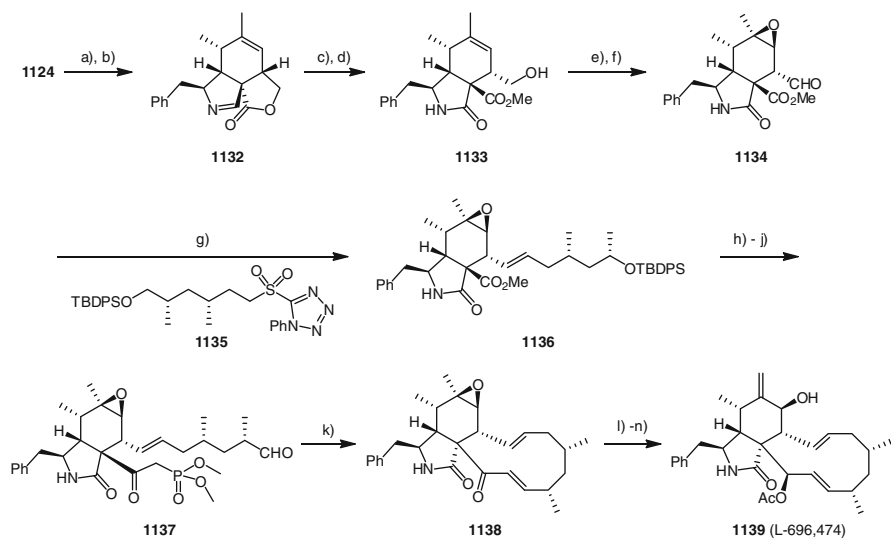


**Scheme 14.2** Total synthesis of cytochalasin B (**1088**), starting from precursor **1124**. Reagents and conditions: a) dimethyldioxirane, acetone, rt, quant.; b) trifluoroacetic acid,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ; c) [bis(trifluoroacetoxy)iodo]benzene, 4 Å MS,  $\text{CH}_2\text{Cl}_2$ , rt, 92% over two steps; d) ethylenediamine, *t*-amyl alcohol, rt, 96%; e) *Dess–Martin* periodinane,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ , rt; f) **1127**, KHMDS, THF,  $-78^\circ\text{C}$ ; then **1126**,  $-100$  to  $-40^\circ\text{C}$ , 60% over two steps; g) LiHMDS, THF,  $-78^\circ\text{C}$ ; then  $\text{Boc}_2\text{O}$ ,  $-78$  to  $-40^\circ\text{C}$ , 80%; h) KHMDS, THF,  $-78^\circ\text{C}$ ; then *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine,  $-100$  to  $-78^\circ\text{C}$ , 85%; i) diethylphosphonoacetic acid, DCC,  $\text{CH}_2\text{Cl}_2$ , rt, 81%; j)  $\text{HF}\cdot\text{pyridine}$ , THF,  $-20^\circ\text{C}$ , 69%; k) *Dess–Martin* periodinane,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ , rt; l)  $\text{NaOCH}_2\text{CF}_3$ ,  $\text{CF}_3\text{CH}_2\text{OH}$ , DME, rt, 65% over two steps; m)  $\text{Mg}(\text{OCH}_3)_2$ , MeOH, rt, 95%; n) TBAF, THF, rt, 96%; o)  $\text{MgSO}_4$ , benzene,  $70^\circ\text{C}$ , 66%

the *N*-Boc group and the silyl ether provided compound **1097**, which is a natural product (cytochalasin F) and could be transformed finally to cytochalasin B (**1088**) by allyl alcohol rearrangement under elevated temperatures in the presence of magnesium sulfate.

The macrocyclic cytochalasin L-696,474 (**1139**) was also synthesized from tricyclic precursor **1124** following a similar strategy that involved also a *Julia–Kocienski* olefination for attachment of an aliphatic chain (Scheme 14.3).

First, removal of the *N*-Boc group and oxidation of the resulting amine generated imine **1132**. In order to invert the quaternary stereogenic center present at the pyrrolidine ring, **1132** was subjected to a non-hydrolytic ring opening with 1,3-diaminopropane in the presence of trifluoroethanol in buffer solution, followed by re-closing to the amine **1133**. After epoxidation at the cyclohexene moiety, which proceeded diastereoselectively, the hydroxy group was transformed into an aldehyde ( $\rightarrow$  **1134**) suitable for *Julia–Kocienski* olefination with the separately synthesized *N*-phenyl tetrazole **1135** (for preparation of **1135**, see Ref. (742)). Thus, the aliphatic chain for later macrocyclization could be attached to the



**Scheme 14.3** Total synthesis of L-696,474 (**1139**), starting from precursor **1124**. Reagents and conditions: a) trifluoroacetic acid,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ; b) [bis(trifluoroacetoxy)iodo]benzene, 2,6-lutidine,  $4 \text{ \AA}$  MS,  $\text{CH}_2\text{Cl}_2$ , rt, 90% over two steps; c) 1,3-diaminopropane,  $\text{CF}_3\text{CH}_2\text{OH}$ ,  $\text{Et}_2\text{O}$ , rt;  $\text{Et}_2\text{O}$ -pH 7 buffer; d) KOH,  $\text{I}_2$ , MeOH, rt, 96% over two steps; e) dimethyldioxirane, acetone, rt, 95%; f) *Dess-Martin* periodinane,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ , rt; g) **1135**, KHMDS, THF,  $-78^\circ\text{C}$ ; then **1134**,  $-100$  to  $-40^\circ\text{C}$ , 86% over two steps; h)  $(\text{MeO})_2\text{POCH}_2\text{Li}$ , THF,  $-78^\circ\text{C}$  to rt; i) TBAF, AcOH, THF, rt, 81% over two steps; j) *Dess-Martin* periodinane,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ , rt; k)  $\text{NaOCH}_2\text{CF}_3$ ,  $\text{CF}_3\text{CH}_2\text{OH}$ , DME,  $80^\circ\text{C}$ , 52% over two steps, 5:1 mixture of diastereomers; l)  $\text{CeCl}_3 \cdot 7 \text{ H}_2\text{O}$ ,  $\text{NaBH}_4$ , THF/MeOH,  $-40^\circ\text{C}$ ; m)  $\text{Ac}_2\text{O}$ , pyridine, rt, 86% over two steps; n)  $\text{MgSO}_4$ , benzene,  $60^\circ\text{C}$ , 77%

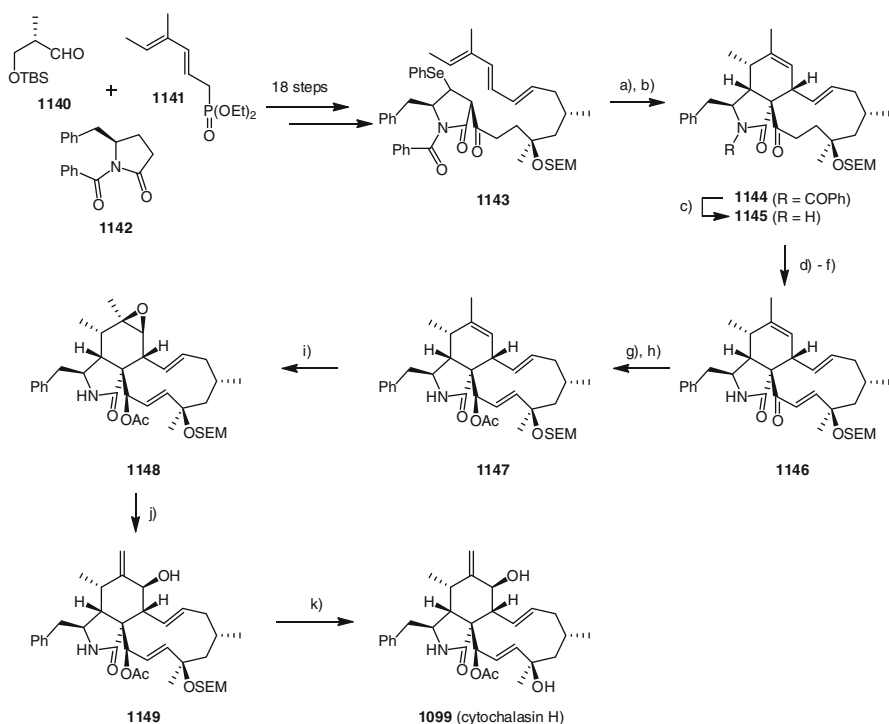
perhydroisoindolinone core in good yield ( $\rightarrow$  **1136**). Transformation into a phosphonate and subsequent deprotection/oxidation of the primary TBDPS group then afforded *Horner-Wadsworth-Emmons* (HWE) substrate **1137**. The HWE reaction following accomplished the key macrocyclization with the best diastereoselectivity (5:1) when treated with sodium 2,2,2-trifluoroethoxide in hot DME, which yielded the desired [11]cytochalasan **1138**. The final steps towards the natural product **1139** comprised diastereoselective reduction of the macrocyclic ketone, followed by acetylation and treatment with magnesium sulfate in heated benzene.

### 14.2.2 Total Synthesis of Proxiphomin

Proxiphomin was the first [13]cytochalasan to be synthesized (745, 746). This synthesis was carried out by *Thomas* and *Whitehead* in 1985, after which several other cytochalasan syntheses followed using the same approach (intramolecular *Diels-Alder* reaction). In the next sections, the syntheses of cytochalasin H (**1099**) and G (**1098**) are outlined in detail.

### 14.2.3 Total Synthesis of Cytochalasin H

Cytochalasin H (**1099**), an isomer of cytochalasin D (**1091**), was synthesized in 1986 by *Thomas and Whitehead* utilizing an intramolecular *Diels-Alder* reaction to build up both the isoindolone and macrocycle moieties in a single step (747–749). The formation of the *Diels-Alder* precursor **1143** together with the steps following for the completion of the synthesis of cytochalasin H (**1099**) are outlined in Scheme 14.4.



**Scheme 14.4** Total synthesis of cytochalasin H (**1099**). Reagents and conditions: a) *m*-CPBA, H<sub>2</sub>O<sub>2</sub>, −40 to 0°C; b) toluene, 80–100°C, 37% over two steps; c) KOH, MeOH, 0°C, 98%; d) LDA, THF/*n*-hexane, −78°C; then TMS-Cl, 98%; e) PhSeCl, TBAF, THF, 0°C, 78%; f) pyridine, H<sub>2</sub>O<sub>2</sub>, H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, rt, 68%; g) NaBH<sub>4</sub>, EtOH, 0°C, 72%; h) pyridine, DMAP, Ac<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, rt, 94%; i) *m*-CPBA, CH<sub>2</sub>Cl<sub>2</sub>, −20 to 0°C, 19% (37% regioisomer); j) Al(*Oi*-Pr)<sub>3</sub>, *o*-xylene, 125°C, 67%; k) 5% HF (aq.), acetonitrile, rt, 40%

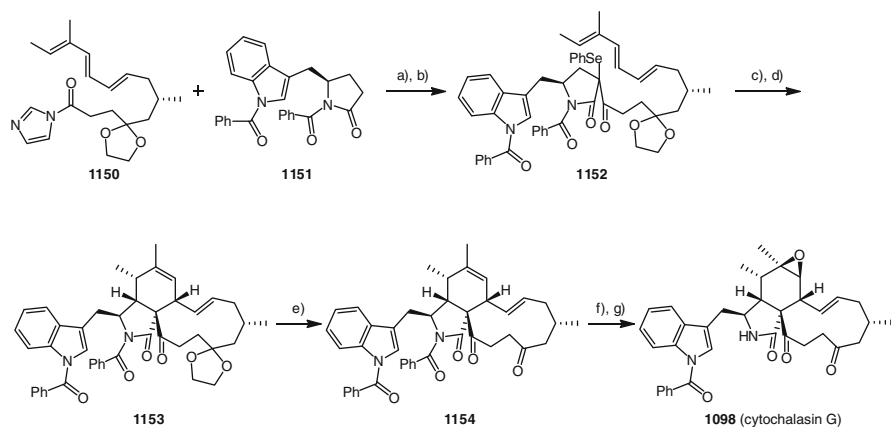
*Diels-Alder* precursor **1143** was accessible from aldehyde **1140**, dienylnphosphonate **1141**, and benzoyl pyrrolidinone **1142** in 18 steps. Elimination of the phenylselenenyl group generated a double bond, which was subjected to an intramolecular, diastereoselective *Diels-Alder* reaction at elevated temperatures to yield

tricycle **1144**. After deprotection of the amine moiety ( $\rightarrow$  **1145**), the macrocyclic double bond was introduced by  $\alpha$ -deprotonation of the ketone, and subsequent phenylselenenylation followed by elimination ( $\rightarrow$  **1146**). Reduction with sodium borohydrate and O-acetylation gave compound **1147**. The final functionalization at the cyclohexene ring to create an *exo*-double bond was realized by epoxidation to **1148** (unfortunately, epoxidation occurred mainly at the unwanted double bond present in the macrocycle; however, separation of the regioisomers was possible), followed by elimination and ring opening to **1149**, which, after SEM-deprotection, finally yielded cytochalasin H (**1099**).

In addition, the same research group conducted an alternative approach to cytochalasin H (**1099**) by formal synthesis. For this purpose, they prepared a phenylalanine analogue of cytochalasin G (**1098**) and treated it with a methyl-*Grignard* reagent to yield a key intermediate for the cytochalasin H (**1099**) synthesis (750).

#### 14.2.4 Total Synthesis of Cytochalasin G

The first total synthesis of a tryptophan-derived cytochalasin – cytochalasin G (**1098**) – was accomplished in 1986 by *Thomas* and co-workers (751, 752). The same strategy as for cytochalasin H (**1099**), an intramolecular *Diels-Alder* reaction, was used as the key step (Scheme 14.5).

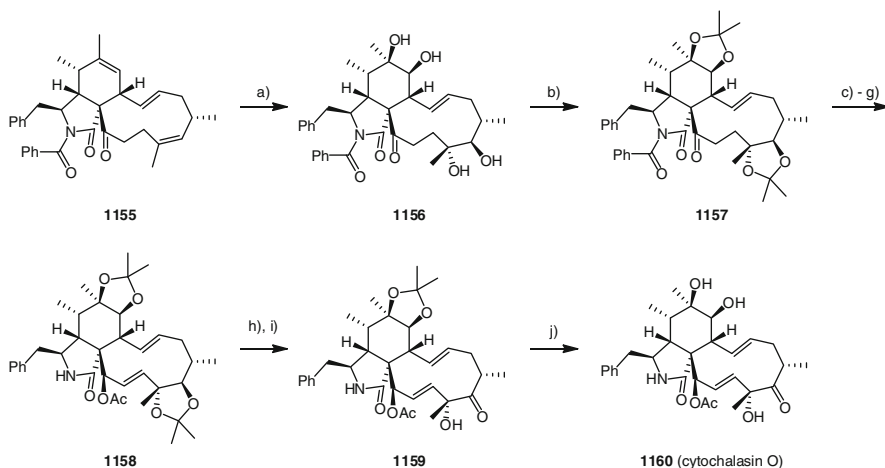


**Scheme 14.5** Total synthesis of cytochalasin G (**1098**). Reagents and conditions: a) **1151**, LiHMDS,  $-70^{\circ}\text{C}$ , THF/*n*-hexane; then addition to **1150**, THF,  $-70$  to  $0^{\circ}\text{C}$ ; b) LiHMDS,  $-70^{\circ}\text{C}$ ; then PhSeCl in THF,  $-70^{\circ}\text{C}$ , 57% over two steps; c)  $\text{H}_2\text{O}_2/\text{H}_2\text{O}$ , *m*-CPBA,  $\text{CHCl}_3$ ,  $-50^{\circ}\text{C}$ ; d) toluene,  $86^{\circ}\text{C}$ , 31% over two steps; e) HCl (aq.), THF, rt, 71%; f) *m*-CPBA,  $\text{CH}_2\text{Cl}_2$ , rt, 39%; g) NaOH (aq.), MeOH, rt, 62%

The *Diels-Alder* substrate was prepared by connecting the building blocks **1150** and **1151** with a following phenylselenenyl-mediated elimination of **1152** to the corresponding diene-dienophile system. After cycloaddition, tricycle **1153** was obtained, which, on further deprotection and epoxidation, could be transformed into cytochalasin G (**1198**).

### 14.2.5 Total Synthesis of Cytochalasins D and O

In 1990, *Merifield* and *Thomas* reported a total synthesis of cytochalasin D (**1091**) (753, 754). Some years later, they also achieved the total synthesis of cytochalasin O (**1160**) by functionalization of a late-stage intermediate of cytochalasin D (**1091**) (754). These syntheses proceeded similarly to the above-described syntheses of cytochalasins H (**1099**) (Scheme 14.4) and G (**1098**) (Scheme 14.5), in utilizing a *Diels-Alder* reaction to form the tricyclic core. Therefore, only the total synthesis of cytochalasin O (**1160**), structurally characterized by the presence of a *syn*-diol moiety, is described in the following scheme starting from *Diels-Alder* product **1155** (Scheme 14.6).



**Scheme 14.6** Total synthesis of cytochalasin O (**1160**), starting from *Diels-Alder* product **1155**. Reagents and conditions: a) OsO<sub>4</sub>, pyridine, -20°C, 69%; b) 2,2-dimethoxypropane, *p*-toluenesulfonic acid, CHCl<sub>3</sub>, rt; c) LDA, PhSeCl, THF, -35°C, 52% over two steps; d) NaOH, MeOH (aq.), rt; e) H<sub>2</sub>O<sub>2</sub> (aq.), pyridine, CH<sub>2</sub>Cl<sub>2</sub>, rt, 88% over two steps; f) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7 H<sub>2</sub>O, MeOH, 10°C, 98%; g) Ac<sub>2</sub>O, NEt<sub>3</sub>, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 81%; h) *p*-toluenesulfonic acid, MeOH, rt, 74%; i) oxalyl chloride, DMSO, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -60°C to rt, 66%; j) HCl (aq.), MeOH, reflux, 78%

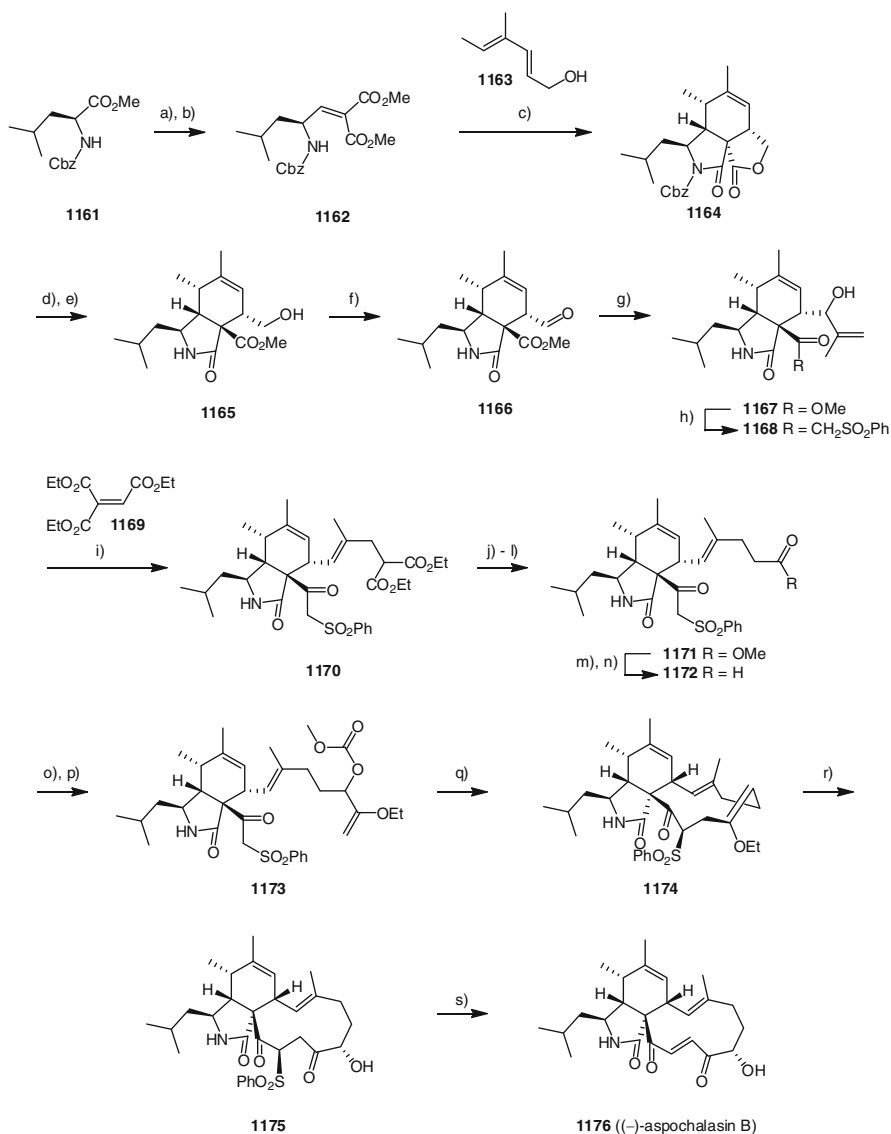
After oxidation with an excess of osmium tetroxide to tetraol **1156**, this was protected to give bis-acetonide **1157**. As a result of the previously developed protocol, a phenylselenenyl mediated elimination, as well as N-deprotection was carried out. The resulting  $\alpha,\beta$ -unsaturated ketone was reduced to the corresponding alcohol with sodium borohydride in excellent yield and afterwards acetylated to compound **1158**. One acetonide functionality was removed selectively, and the resulting diol was converted into the  $\alpha$ -hydroxyketone **1159**. Finally, cytochalasin O (**1160**) was obtained through deprotection of the remaining diol in good yield. By comparison of several properties of this product with an authentic sample, the absolute stereochemistry at the cyclohexane ring of cytochalasin O (**1160**) was finally confirmed as a result of the total synthesis that was carried out.

### 14.2.6 Total Synthesis of (–)-Aspochalasin B

A different approach to cytochalasan natural products was investigated by *Trost et al.* and resulted in the total synthesis of the leucine-derived [11]cytochalasin, (–)-aspochalasin B (**1176**), in 1989 (755). The strategy consisted in synthesizing an isoindolone part and the utilization of a palladium-catalyzed formation of the 11-membered carbocycle (Scheme 14.7).

As starting material for this synthesis, the Cbz-protected leucine ester **1161** was used. Reduction of the ester group and condensation with malonic acid dimethyl ester gave olefin **1162**, which was reacted with diene **1163** in a *Diels-Alder* reaction to yield tricycle **1164**. The lactone ring was hydrolyzed and the resulting carboxylic acid converted to the methyl ester using diazomethane ( $\rightarrow$  **1165**). The following *Swern* oxidation proceeded in excellent yield and delivered aldehyde **1166**. Addition of dipropenylcuprate ( $\rightarrow$  **1167**), introduction of a sulfone unit ( $\rightarrow$  **1168**), and treatment with ethyl  $\beta,\beta$ -diethoxyacrylate (**1169**) to undergo condensation/rearrangement allowed for the preparation of **1170**, which upon decarboxylation, methyl esterification, chemoselective reduction and oxidation yielded the corresponding aldehyde **1172**. For the introduction of another  $C_2$  unit, again a cuprate was the reagent of choice, leading to an enol ether alcohol, which was trapped with methyl chloroformate ( $\rightarrow$  **1173**). Next, the key step of this total synthesis was a Pd-catalyzed macrocyclization, which proceeded *via* a *syn*- $\pi$ -allyl palladium complex with a remarkable diastereoselectivity and delivered a single isomer **1174** with a (*Z*)-configured enol ether double bond. Treatment with peracetic acid gave an enol ether epoxide, which was immediately hydrolyzed to hydroxy ketone **1175**. The second macrocyclic double bond was finally introduced by sulfone elimination, hence yielding (–)-aspochalasin B (**1176**) in 19 overall steps from simple starting materials.



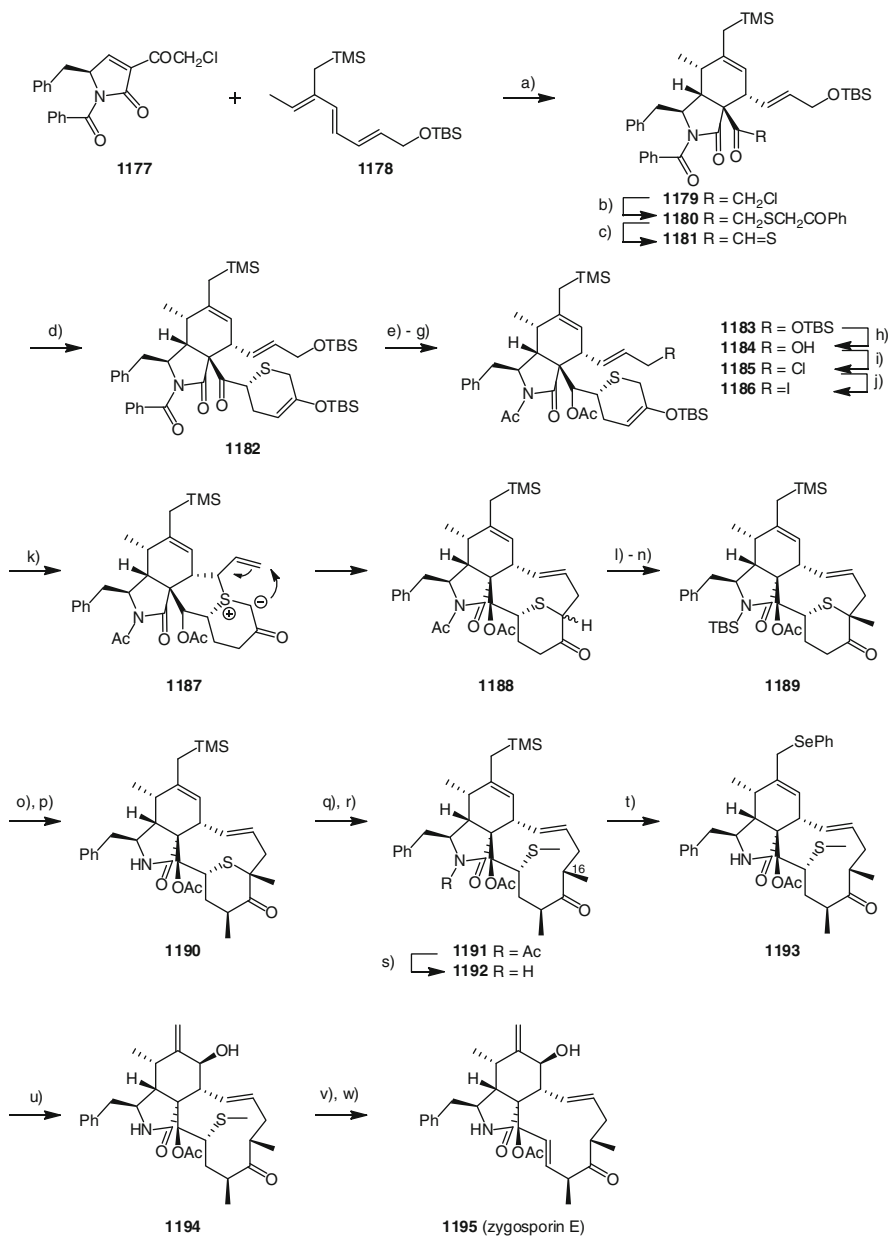


**Scheme 14.7** Total synthesis of (–)-aspochalasin B (**1176**). Reagents and conditions: a) DIBAL-H, toluene,  $-78^{\circ}\text{C}$ ; b)  $\text{CH}_2(\text{CO}_2\text{CH}_3)_2$ ,  $\text{TiCl}_4$ ,  $\text{CCl}_4$ , THF,  $0^{\circ}\text{C}$ ; then pyridine, rt, 51% over two steps; c) **1163**, xylene, BHT,  $130^{\circ}\text{C}$ , 33–40%; d) KOH, H<sub>2</sub>O, MeOH, benzene, rt; then NaHSO<sub>4</sub>; e)  $\text{CH}_2\text{N}_2$ , ether, MeOH, 94%; f) oxalyl chloride, DMSO,  $\text{CH}_2\text{Cl}_2$ , NEt<sub>3</sub>,  $-78^{\circ}\text{C}$ , 90% – quant; g)  $[\text{CH}_2=\text{C}(\text{CH}_3)_2\text{CuLi}]$ , THF,  $-78^{\circ}\text{C}$ , 58%; h) *n*-BuLi,  $\text{CH}_3\text{SO}_2\text{Ph}$ , THF, HMPA,  $0^{\circ}\text{C}$ , 80%; i) **1169**, PPTS, rt, 68%; j) 1 M KOH (aq.), THF, rt; then HCl; k) toluene, reflux; l)  $\text{CH}_2\text{N}_2$ , ether, rt, 71% over three steps; m) *n*-BuLi, DIBAL-H, THF,  $0^{\circ}\text{C}$ ; n) PCC,  $\text{CH}_2\text{Cl}_2$ , rt, 47% over two steps; o)  $[\text{CH}_2=\text{C}(\text{OEt})_2\text{CuLi}]$ , THF, ether,  $-78^{\circ}\text{C}$ ; p)  $\text{ClCO}_2\text{CH}_3$ , pyridine,  $0^{\circ}\text{C}$ , 42% over two steps; q) 10% Pd(PPh<sub>3</sub>)<sub>4</sub>, 10% dppp, THF, rt; then reflux, 49%; r) peracetic acid, AcOH,  $\text{K}_2\text{CO}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; then PPTS, H<sub>2</sub>O, THF, rt, 62%; s) benzyltrimethylammonium fluoride, THF,  $\text{CH}_2\text{Cl}_2$ , rt, 53%

### 14.2.7 Total Synthesis of Zygospurin E

In the first total synthesis of zygospurin E (**1195**), *Vedejs et al.* also utilized a *Diels-Alder* reaction to form the isoindolone core (**739**), but used an alternative strategy for stereochemical control at the macrocycle. During the macrocycle construction, a sulfur functionality served as a tool for stereospecific introduction of ring substituents (**756**, **757**). The zygospurin E (**1195**) route is outlined in Scheme 14.8.

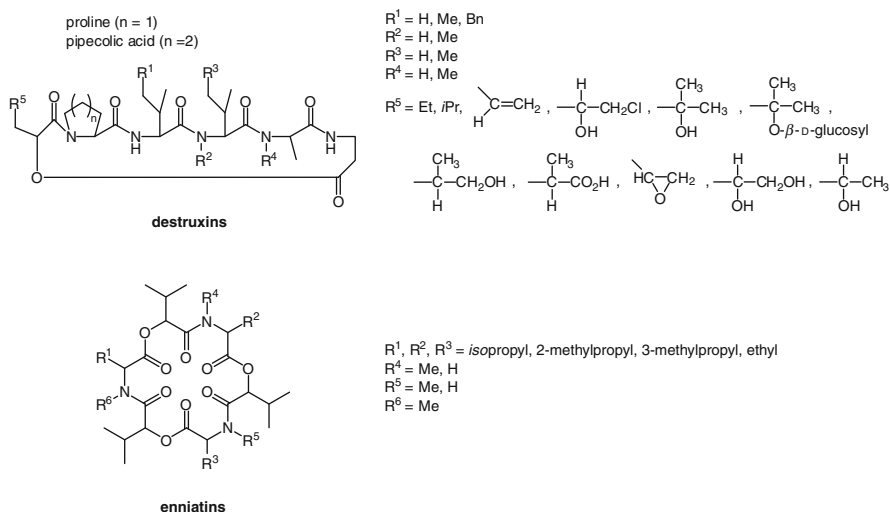
In this sequence, reaction of triene **1178** with the doubly activated dienophile **1177** proceeded at room temperature *via* the least hindered *endo* transition state, delivering the desired adduct **1179** as major isomer (>15:1). To this compound, four additional carbon atoms were required for the 11-membered macrocycle. A strategy using a sulfur-containing group facilitated this procedure. A phenacylthio group was introduced ( $\rightarrow$  **1180**), which upon sun-lamp irradiation was converted to the corresponding thioaldehyde **1181**. This reactive species underwent a *Diels-Alder* cycloaddition with (*t*-butyldimethylsilyloxy)butadiene yielding **1182** (10:1 ratio with a minor isomer). After removal of the *N*-benzoyl group, the carbonyl group adjacent to the quaternary stereogenic center was reduced and subsequently treated with acetic anhydride, which led to both O- and N-acetylation ( $\rightarrow$  **1183**). Then, the allylic silyl ether group had to be converted to a functionality suitable for a sulfur-mediated ring formation. This was realized by converting silyl ether **1183**, after deprotection ( $\rightarrow$  **1184**), to an allyl iodide **1186**, which upon heating underwent a ring expansion *via* sulfur ylide **1187**. The resulting thioether **1188** was isolated in 78% yield. Deprotonation generated the bridgehead enolate, hence methylation occurred only at this position. The introduction of another methyl group worked best after exchanging the *N*-acyl group by a silyl group and treating the resulting compound **1189** with LiHMDS and iodomethane. Afterwards, the nitrogen was desilylated ( $\rightarrow$  **1190**) and re-acetylated. The sulfur functionality was methylated to a sulfonium salt, which was cleaved by treatment with *Rieke* zinc ( $\rightarrow$  **1191**). Unfortunately, the product with the desired stereochemistry could only be isolated in a 1:2.6 ratio with its C-18 epimer (87% overall and 24% for **1191**). Nevertheless, the total synthesis was continued and after subsequent deacetylation to **1192**, an electrophilic selenylation to compound **1193** was carried out by treatment with a reagent freshly prepared from diphenyl diselenide and *Meerwein's* reagent ( $\text{Me}_3\text{OBF}_4$ ). After oxidation of the selenide, the system underwent a highly selective 2,3-sigmatropic shift to allylic alcohol **1194**. The final transformation consisted in elimination of the methylthio group *via* oxidation and sulfoxide pyrolysis at 135°C, which finally generated zygospurin E (**1195**).



**Scheme 14.8** Total synthesis of zygospurin E (**1195**). Reagents and conditions: a) rt, 93%; b) phenylacetyl thiol, K<sub>2</sub>CO<sub>3</sub>, THF, 88%; c) sunlamp irradiation; d) (*t*-butyldimethylsilyloxy) butadiene, DBU, THF, 0°C, 60% over two steps; e) LiEt<sub>3</sub>BH, THF, -78°C; f) DIBAL-H, toluene, 0°C; g) Ac<sub>2</sub>O, DMAP, NEt<sub>3</sub>, THF, 20°C, 52% over three steps; h) Et<sub>3</sub>NHF, MeOH; i) Bu<sub>3</sub>P, CCl<sub>4</sub>, 78% over two steps; j) NaI, K<sub>2</sub>CO<sub>3</sub>, MeCN; k) Δ, 71% over two steps; l) LDA, THF, MeI, 99%; m) K<sub>2</sub>CO<sub>3</sub>, THF, MeOH, rt, 98%; n) TBS-Cl, DMAP, DBU, MeCN, rt, 76%; o) LiHMDS, -78 to -40 to -78°C; then MeI; p) Et<sub>3</sub>NHF, THF, MeOH, rt, 79% over two steps; q) Ac<sub>2</sub>O, DMAP, NEt<sub>3</sub>, THF, rt, 88%; r) allyltrimethylsilane, Me<sub>3</sub>OBF<sub>4</sub>, DME, 35°C to rt; then AcOH, Riecke zinc, THF, 24%; s) K<sub>2</sub>CO<sub>3</sub>, THF, MeOH, -15°C, 70%; t) PhSeSe<sup>+</sup>(Me)Ph•BF<sub>4</sub><sup>-</sup>, CH<sub>2</sub>Cl<sub>2</sub>, -78°C, 97%; u) NaIO<sub>4</sub>, pH 7 buffer, dioxane, 0°C to rt, 88%; v) *m*-CPBA, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78°C, 77%; w) CaCO<sub>3</sub>, xylenes, 135°C, 52%

## 15 Peptidic Mycotoxins

Peptides are omnipresent in all living organisms. In particular, fungi produce a large number of mycotoxins containing peptide moieties. (Thio-)diketopiperazines (cyclodipeptides) represent a large family of peptidic mycotoxins, which were comprehensively illustrated in the corresponding chapter. Apart from diketopiperazines, there also exist other structural motifs containing one or more amino acid residues. These motifs can be both linear and cyclic. Depsipeptides, *e.g.* destruxins (Fig. 15.1) (758) and enniatins (759), are mostly cyclic peptide structures which, apart from amide bonds, also contain ester bonds by incorporation of  $\alpha$ -hydroxy acids.



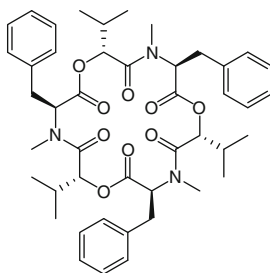
**Fig. 15.1** General structures of destruxins and enniatins

Peptidic mycotoxins are, among others, produced by *Aspergillus*, *Fusarium*, *Penicillium*, *Pithomyces*, and *Trichoderma* (10).

## 15.1 Biological Properties

The destruxins, cyclic peptides containing five amide bonds and one ester bond, were first isolated by *Kodaira* in 1961 from *Oospora destructor* (760), hence the naming of these compounds. Well-documented biological effects are insecticidal and phytotoxic activities (758). Furthermore, also antitumor, inotropic, or enzyme inhibitory effects are reported. Destruxin E, for example, was synthesized in 2010 (761).

Enniatins isolated from *Fusarium avenaceum* show cytotoxic activities towards various cell lines of human origin (759). In addition, they show antibiotic (762), phytotoxic (763), and insecticidal (764–766) effects, and inhibit the enzyme acyl-CoA:cholesterol acyl transferase (767). Due to their structural properties, the enniatins are able to form complexes with alkali metal ions, thus influencing and increasing the ionic permeability of membranes (768, 769). Beauvericin (**1196**) (Fig. 15.2) is a highly symmetric member of the enniatins (hexacyclopeptide with alternating *N*-methylphenylalanine and hydroxy-*iso*-valeryl residues) and was first isolated from *Beauveria bassina*, but is also produced by *Fusarium* species. It possesses a pronounced ability to induce programmed cell death in mammalian cell lines (770).



1196 (beauvericin)

Fig. 15.2 Structure of beauvericin

Enchinocandins B, C, and D were isolated from *Aspergillus rugulosus* and *Aspergillus nidulans* (771, 772). Some semisynthetic derivatives are utilized clinically as antimycotics (773, 774).

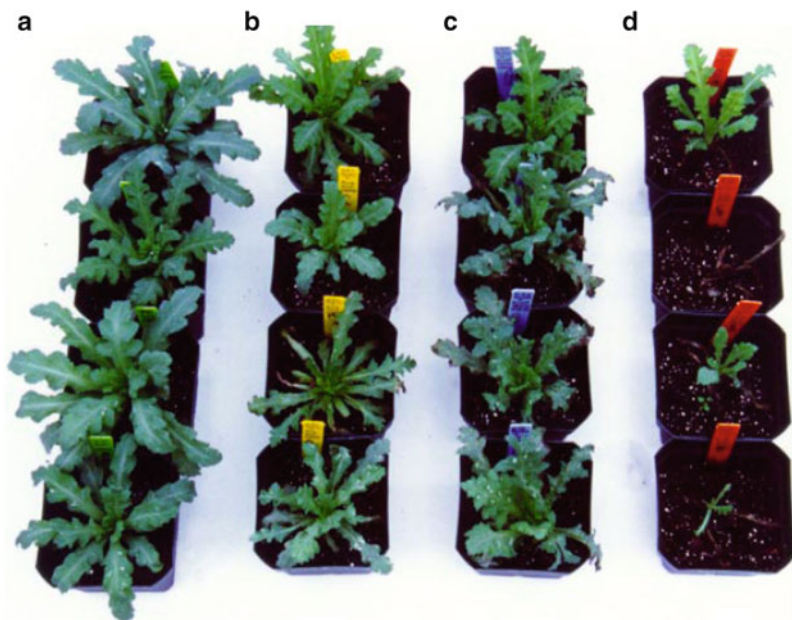
The so-called Nep1-like proteins (NLPs), a family of highly conserved and mostly 24 kDa proteins, are produced by a variety of taxonomically unrelated

microorganisms, including oomycetes, bacteria, and some fungi. They play a crucial role as elicitors in plant necrosis (775).

The first member of the NLP group, Nep1 itself, was discovered in culture filtrates of *Fusarium oxysporum* (Fig. 15.3) and was found to induce ethylene production and necrosis in leaves of the coca plant, *Erythroxylum coca* (776). Furthermore, Nep1 enhances the damaging effect to poppy plants in combination with treatment of *Pleospora papaveracea* significantly (777) (Fig. 15.4).



**Fig. 15.3** *Fusarium oxysporum* under the light microscope (Courtesy of Selmar Petzoldt)



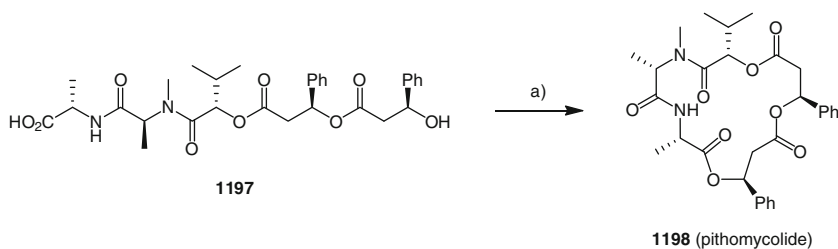
**Fig. 15.4** Necrosis on poppy plants 7 days after treatment. a) Negative control; b) after treatment with Nep1 protein ( $5 \mu\text{g}/\text{cm}^3$ ); c) after treatment with *Pleospora papaveracea* ( $5 \times 10^5$  conidia per  $\text{cm}^3$ ); d) after treatment with both Nep1 protein and *P. papaveracea*

## 15.2 Total Syntheses

We will make no attempt here to describe existing syntheses of classical peptides, but will only focus on compounds with more specialized structural features and/or on challenging synthesis pathways.

### 15.2.1 Total Synthesis of *Pithomycolide*

Pythomycolide (**1198**), a cyclodepsipeptide of the pasture fungus *Pithomyces chartarum*, has an unusual structure in bearing two  $\beta$ -substituted residues, thus forming a 17-membered ring. It is known to bind strongly to  $\text{Na}^+$  and  $\text{Ca}^{2+}$  ions in organic solvents. The total synthesis was conducted in 1994 by *Le Quesne et al.* on the macrolactonization of compound **1197** to the natural product pithomycolide (**1198**) (Scheme 15.1) (778, 779).

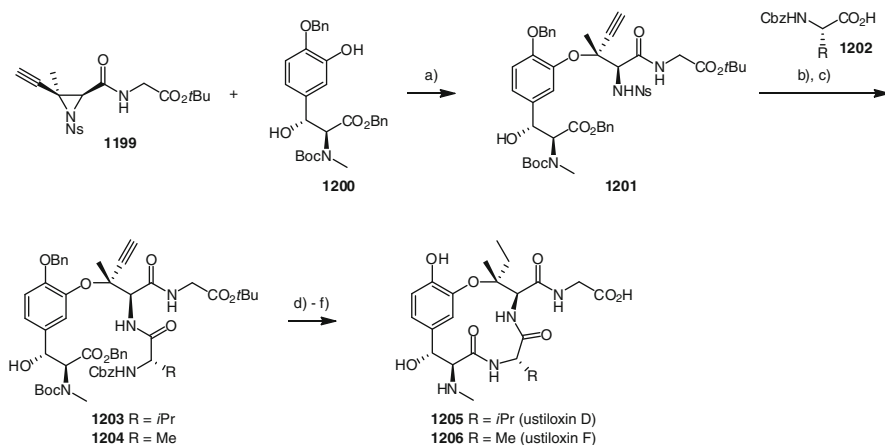


**Scheme 15.1** Synthesis of pithomycolide (**1198**). Reagents and conditions: a) BOP-Cl, DIPEA,  $\text{CH}_2\text{Cl}_2$ , 11%

### 15.2.2 Total Synthesis of *Ustiloxins D and F*

The ustiloxins, isolated from the fungus *Ustilaginoidea virens* associated with rice plants, show antimetabolic properties by inhibiting microtubule formation (780, 781). Structurally, they are characterized by the presence of two peptide bonds and one unusual tertiary alkyl-aryl ether connection. The first total synthesis of ustiloxin D (**1205**) was achieved in 2002 (782) by *Joullié et al.*, followed by a shorter synthesis by *Wandless et al.* (783, 784). Later on, its synthesis was conducted again (785) along with ustiloxin F (**1206**) (786) in a more convergent manner than previously by *Joullié et al.* (Scheme 15.2).

Ethynyl aziridine **1199** and tyrosine derivative **1200** were connected to **1201** by ring opening of the aziridine in 90% yield. After removal of the nosyl protecting group, the resulting free amine was subsequently coupled with *N*-Cbz valine (for



**Scheme 15.2** Convergent total synthesis of ustiloxin D (**1205**) and F (**1206**). Reagents and conditions: a) CuOAc (1 mol%), DBU, toluene, 0°C, 90%; b) PhSH, Cs<sub>2</sub>CO<sub>3</sub>, DMF, rt, 78%; c) **1202**, EDC•HCl, HOBT, NaHCO<sub>3</sub>, DMF, 0°C to rt; d) H<sub>2</sub>, Pd black, EtOH, rt; e) EDC•HCl, HOBT, NaHCO<sub>3</sub>, DMF, rt; f) TFA, Et<sub>3</sub>SiH, CH<sub>2</sub>Cl<sub>2</sub>, rt, 8.7% over four steps for **1205**; 8.8% over four steps for **1206**

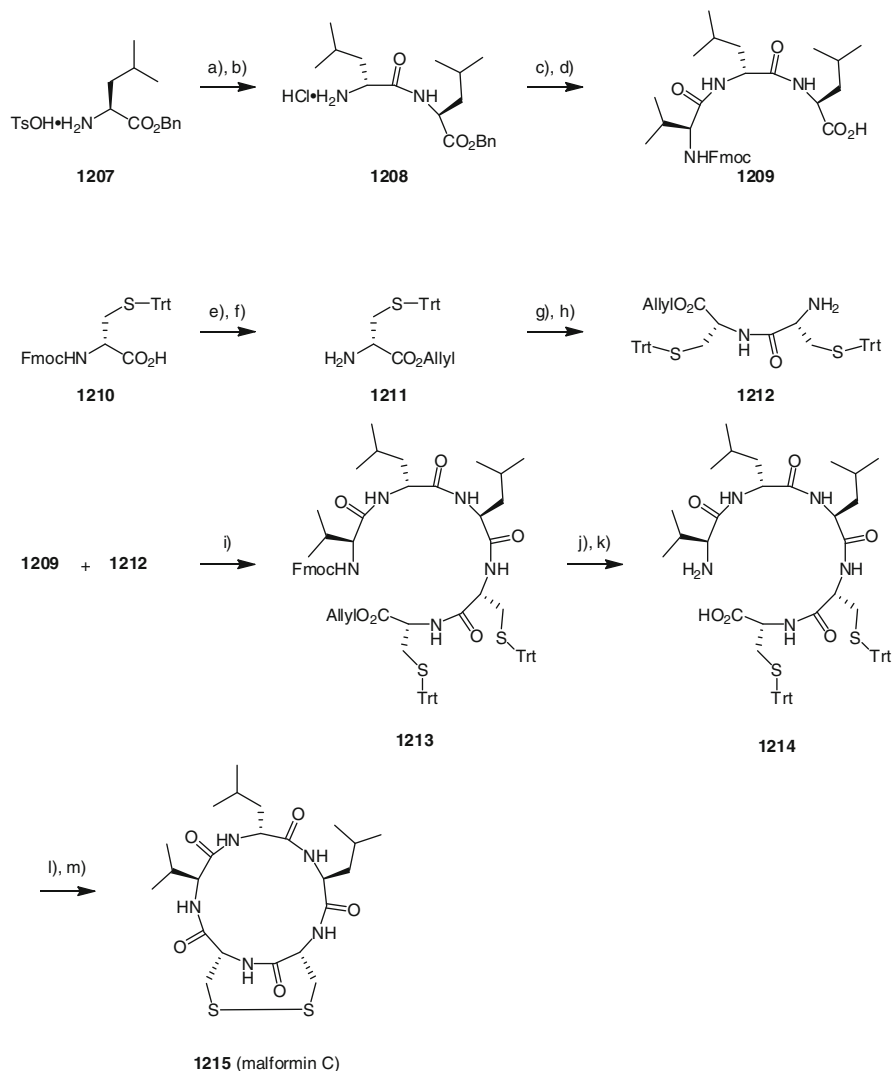
the synthesis of ustiloxin D) or *N*-Cbz alanine (for the synthesis of ustiloxin F). Treatment with hydrogen and palladium resulted in deprotection of all of the benzyl ester, benzyl ether, and Cbz groups, as well as hydrogenation of the alkyne bond, in a single step. On achieving this, the macrocycle was formed through peptide coupling utilizing EDC•HCl and HOBT. Finally, subsequent deprotections yielded ustiloxin D (**1205**) and ustiloxin F (**1206**) in one further step.

### 15.2.3 Total Synthesis of Malformin C

Malformin C (**1215**), isolated from *Aspergillus niger* FKI-2342, is a G2 checkpoint inhibitor and thus regarded as a promising anticancer agent (787). In 2008 a convergent total synthesis of this tricyclic peptide containing a disulfide bond was accomplished by *Omura et al.* (788) (Scheme 15.3).

L-Leucine benzyl ester (**1207**) was coupled with Boc-D-leucine, which after Boc-deprotection gave dipeptide **1208**. This was converted into tripeptide **1209** by condensation with Fmoc-L-valine and hydrogenolytic removal of the benzyl ester. Furthermore, another dipeptide **1212** was prepared starting from commercially available Fmoc-D-S-tritylcysteine (**1210**), which was first converted into its allyl ester, subsequently freed of the Fmoc group ( $\rightarrow$  **1211**), and then coupled with another equivalent of Fmoc-D-S-tritylcysteine (**1210**), followed by Fmoc deprotection ( $\rightarrow$  **1212**). Tripeptide **1209** and dipeptide **1212** were afterwards coupled to





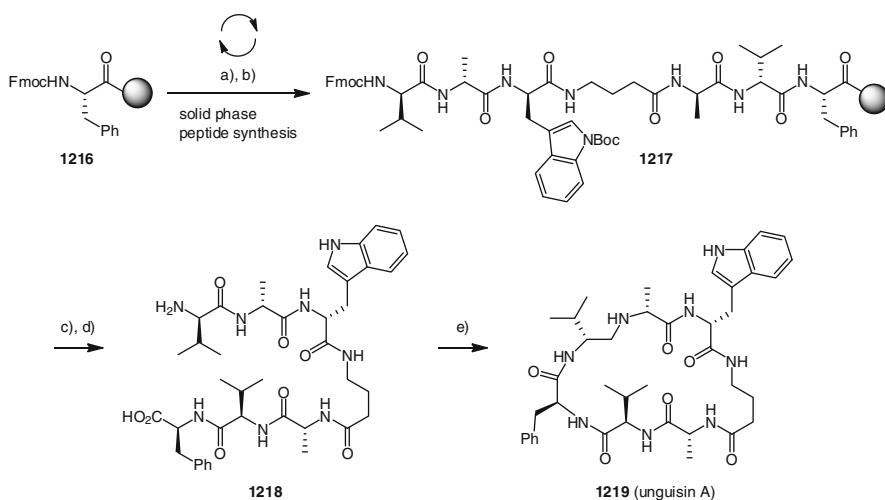
**Scheme 15.3** Total synthesis of malformin C (**1215**). Reagents and conditions: a) Boc-D-Leu-OH, EDC•HCl, HOBT, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 98%; b) 4 M HCl/dioxane, 0°C; c) Fmoc-L-Val-OH, EDC•HCl, HOBT, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>/DMF (4:1), rt; d) H<sub>2</sub>, Pd(OH)<sub>2</sub>, EtOAc, 40°C, 86% over three steps; e) Cs<sub>2</sub>CO<sub>3</sub>, allyl bromide, DMF, rt; f) piperidine, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 93% over two steps; g) Fmoc-D-Cys(Trt)-OH (**1210**), EDC•HCl, HOBT, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>, rt; h) piperidine, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 72% over two steps; i) HBTU, HOBT, NMM, CH<sub>2</sub>Cl<sub>2</sub>/DMF (4:1), rt, 93%; j) piperidine, CH<sub>2</sub>Cl<sub>2</sub>, 0°C; k) 1 M NaOH, THF, rt, 81% over two steps; l) HATU, HOAT, NMM, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 69%; m) I<sub>2</sub>, DMF, rt, 85%

pentapeptide **1213** in very good yields (93%). The remaining protecting groups were removed, which yielded cyclization precursor **1214**. Macrocyclization proceeded best when **1214** was treated with HATU/HOAt and NMM in a highly diluted solution. Eventually, the resulting cyclic pentapeptide was subjected to oxidative conditions using iodine in DMF, which provided the natural product **1215**.

### 15.2.4 Total Synthesis of Unguisin A

Recently, a total synthesis of the moderately antibacterial unguisin A (**1219**) was reported (789). This naturally occurring cyclopeptide from *Emericella unguis* possesses an unusual  $\gamma$ -butyric acid residue contained within the macrocycle. Its total synthesis, a combination of solid phase and solution chemistry, is outlined in Scheme 15.4.

Starting from Fmoc-L-phenylalanine bound to Wang resin (**1216**), standard solid-phase peptide synthesis using the Fmoc-strategy was carried out, until the desired heptapeptide **1217** was obtained. Deprotection and cleavage from the solid phase yielded fully unprotected heptapeptide **1218**, and consequent cyclization delivered unguisin A (**1219**) in 81% yield.



**Scheme 15.4** Total synthesis of unguisin A (**1219**). Reagents and conditions: a) 10% piperidine, DMF; b) Fmoc-amino acid (3 equiv.), HBTU (2.9 equiv.), DIPEA (6 equiv.), DMF; c) 10% piperidine, DMF; d) TFA/*tri*iso-propylsilane/ $\text{H}_2\text{O}$  (95/2.5/2.5), 96% from **1216**; e) 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate, DIPEA, DMF, 81%

# Abbreviations

9-BBN	9-Borabicyclo[3.3.1]nonane
Ac	Acetyl
Ad	Adamantyl
AD	Asymmetric dihydroxylation
AIBN	Azo-bis- <i>iso</i> -butyronitrile
ATPase	Adenosine triphosphatase
BHT	Butylhydroxytoluene
BIA	Bioinductive assay
Bn	Benzyl
Boc	<i>t</i> -Butyloxycarbonyl
BOP-Cl	Bis(2-oxo-3-oxazolidinyl)phosphonic chloride
brsm	Based on recovered starting material
Bu	Butyl
BuLi	<i>n</i> -Butyllithium
Bz	Benzoyl
CAN	Cerium ammonium nitrate
CBS	<i>Corey-Bakshi-Shibata</i> catalyst
Cbz	Benzyloxycarbonyl
CNS	Central nervous system
CoA	Coenzyme A
cod	1,5-Cyclooctadiene
CSA	Camphorsulfonic acid
Cys	Cysteine
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexyl carbodiimide
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DEAD	Diethyl azodicarboxylate
DET	Diethyl tartrate
DHP	Dihydropyran

DHQ	Dihydroquinidine
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutyl aluminum
DIPEA	Diisopropyl ethyl amine
DIPT	<i>N,N</i> -Diisopropyltryptamine
DKP	Diketopiperazine
DMAP	Dimethylaminopyridine
DMDO	Dimethyldioxirane
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	<i>Dess-Martin</i> periodinane
DMSO	Dimethylsulfoxide
DNA	Desoxyribonucleic acid
DPPA	Diphenylphosphoryl azide
dppbenz	1,2-Bis(diphenylphosphino)benzene
dppp	1,3-Bis(diphenylphosphino)propane
<i>dr</i>	Diastereomeric ratio
DTBMP	di- <i>t</i> -Butylmethylpyridine
EDC	( <i>N</i> -Ethyl- <i>N'</i> -(3-dimethylaminopropyl)carbodiimide
<i>ee</i>	Enantiomeric excess
EEDQ	2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
EGF	Epidermal growth factor
ELEM	Equine leukoencephalomalacia
equiv.	Equivalents
<i>er</i>	Enantiomeric ratio
Et	Ethyl
EU	European Union
Fmoc	Fluorenylmethyloxycarbonyl
h	Hour
HATU	<i>N,N,N',N'</i> -tetramethyl- <i>O</i> -(7-azabenzotriazol-1-yl)uronium hexafluorophosphate
HBTU	<i>O</i> -Benzotriazole- <i>N,N,N',N'</i> -tetramethyl-uronium hexafluorophosphate
HIV	Human immunodeficiency virus
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HOAt	Hydroxy-7-azabenzotriazole
HOBt	<i>N</i> -Hydroxybenzotriazole
HPLC	High-performance liquid chromatography
Hsp	Heat shock protein
IBX	2-Iodoxybenzoic acid
<i>IC</i>	Inhibitory concentration
IPC	<i>Isopinocampheyl</i>
kDa	kilodalton

KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LD	Lethal dose
LDA	Lithium diisopropylamide
Leu	Leucine
LiDBB	Lithium 4,4'-di- <i>tert</i> -butyl biphenyl
LiHMDS	Lithium bis(trimethylsilyl)amide
<i>m</i> -CPBA	<i>meta</i> -Chloroperbenzoic acid
Me	Methyl
MIDA	<i>N</i> -Methyliminodiacetic acid
MOM	Methoxymethyl
Ms	Mesyl
MS	Molecular sieves
MTBE	Methyl <i>tert</i> -butyl ether
MW	Microwave
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	<i>N</i> -Bromosuccinimide
NCS	<i>N</i> -Chlorosuccinimide
Nep1	Necrosis and ethylene-inducing peptide1
NHK	<i>Nozaki-Hiyama-Kishi</i>
NIS	<i>N</i> -Iodosuccinimide
NLP	Nep1-like protein
NMM	<i>N</i> -Methylmorpholine
NMO	<i>N</i> -Methylmorpholine oxide
NMR	Nuclear magnetic resonance
Ns	2-Nitrophenylsulfonyl
OMST	<i>O</i> -Methylsterigmatocystin
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
PHAL	Phthalazine
Phe	Phenylalanine
Phth	Phthaloyl
Piv	Pivalyl (= 2,2-dimethylpropanoyl)
PLE	Porcine liver esterase
PMB	Paramethoxybenzyl ether
PPTS	Pyridinium <i>para</i> -toluenesulfonate
PPY	4-(1-Pyrrolidinyl)pyridine
Pr	Propyl
Pro	Proline
PS	Polystyrene
PTSA	<i>para</i> -Toluenesulfonic acid
Py	Pyridine
R	Residue

RAL	Resorcylic acid lactones
Red-Al	Sodium bis(2-methoxyethoxy)aluminum hydride
RNA	Ribonucleic acid
ROS	Reactive oxygen species
rt	Room temperature
SEM	[2-(Trimethylsilyl)ethoxy]methyl
Sia	Siamyl (1,2-dimethylpropyl)
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
<i>t</i>	<i>tert</i> -
TBAF	<i>tetra</i> -butyl ammonium fluoride
TBAI	<i>tetra</i> -butyl ammonium iodide
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBHP	<i>tert</i> -butyl hydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
TBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
TCA	Tricarboxylic acid
TDKP	Thiodiketopiperazine
TEA	Triethylamine
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	Triflyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic acid anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TIPS	<i>Triiso</i> -propyl silyl
TLC	Thin-layer chromatography
TMEDA	<i>N,N,N',N'</i> -Tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
TMSE	Trimethylselenonium
Tol	Toluyl
TPAP	<i>tetra</i> -propylammonium perruthenate
TPPTS	3,3',3''-Phosphinidynetris(benzenesulfonic acid) trisodium salt
Tr	Trityl (=triphenylmethyl)
Ts	<i>para</i> -Toluenesulfonyl
Val	Valine
WSC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride

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