

# Meroterpenoids produced by fungi

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This review deals with the isolation and structure elucidation of meroterpenoids (natural products of mixed biosynthetic origin which are partially derived from terpenoids) from higher and lower fungi, and discusses biosynthetic studies and biological activities as appropriate. It describes 333 fungal meroterpenoids and cites 195 references.

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## 1 Introduction

The term meroterpenoid was first applied by Cornforth, in 1968, to describe natural products of mixed biosynthetic origin which are partially derived from terpenoids.<sup>1</sup> The prefix mero- (from Greek *meros*) means 'part, partial or fragment'<sup>2</sup> and, therefore, a number of secondary metabolites can be described as meroterpenoids.<sup>3</sup> Cytokinins, *e.g.*, **1** and **2**,<sup>4</sup> phenylpropanoid compounds containing isoprenoid side chains, *e.g.*, **3–6**,<sup>5,6</sup> and alkaloids such as anticancer drugs vincristine **7** and vinblastine **8**<sup>3</sup> are also included in this class of compounds.

These natural products are most often isolated from fungi and marine organisms, but higher plants can also produce meroterpenoids, such as tetrahydrocannabinol **9**<sup>7</sup> and bakuchiol **10**.<sup>8</sup> In addition to their wide occurrence, meroterpenoids display a huge range of structural diversity, with structures varying from simple compounds like montadial A **11**, comprising a prenyl unit

linked to a phenolic derivative,<sup>9</sup> to the more complex meroterpenoids arising from highly functionalised carbon chains. Moreover, they display important biological activities, which will be discussed in this review.

Although their occurrence is general, we will limit this review to meroterpenoids that have been isolated from fungi. Due to the proliferation of trivial names that are attached to these compounds, the literature (*via* Chemical Abstracts, Web of Science, Scirus, and PubMed databases) was searched for meroterpenoids using the following search terms: meroterpene(s), meroterpenoid(s), mixed-terpenoid(s), polyketide-terpenoid(s), alpha-pyrone(s) and triprenyl-phenols.

## 2 Meroterpenoid classification

Although diverse in structure, meroterpenoids can be grouped into two major classes based on their biosynthetic origins: polyketide-terpenoids and non-polyketide-terpenoids.

Polyketides (PKs) are a large class of natural products synthesized by bacteria, fungi, and plants through the successive condensation of simple carboxylic acids.<sup>10</sup> These metabolites are related by their common biosynthetic origins derived from highly functionalised carbon chains whose assemblies are controlled by multifunctional enzyme complexes, the polyketide synthases (PKSs), which catalyse repeated sequences of decarboxylative condensation reactions between simple acyl thioesters and malonate, as shown in Fig. 1.<sup>11–15</sup>

Therefore, polyketide-terpenoid meroterpenoids are classified here by grouping the compounds first according to the number of acyl units which have contributed to the polyketide chain and then according to the type of cyclization which the (hypothetical) precursor has undergone.

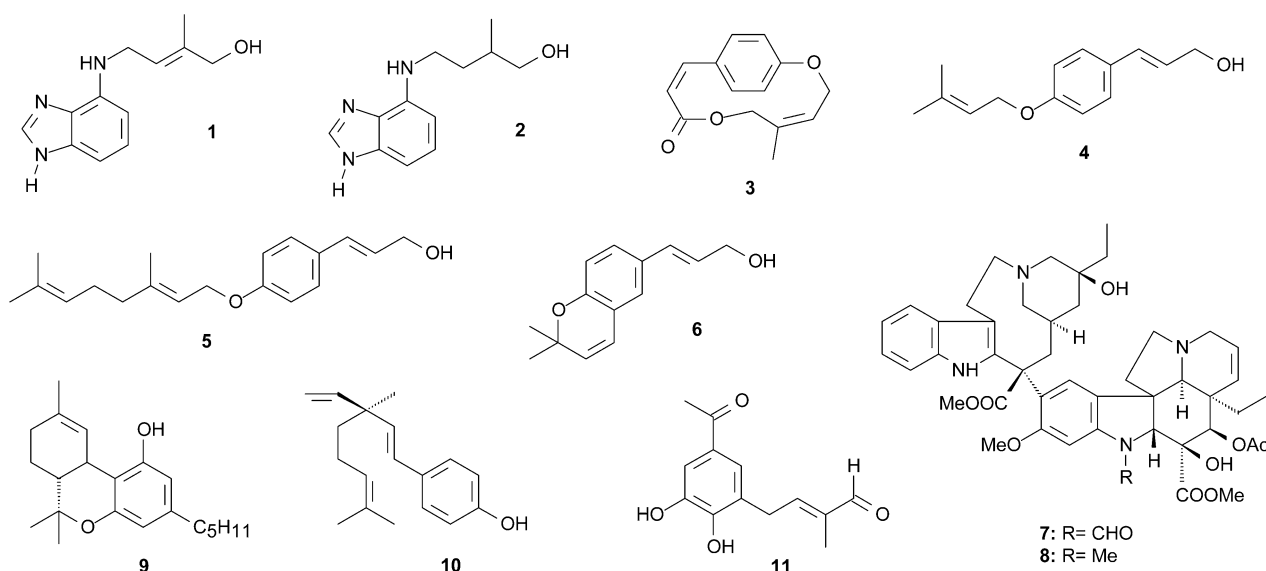
The non-polyketide group of meroterpenoids is formed from compounds which arise from the shikimate route, represented by protocatechuic acid derivatives, quinones, dehydroquinic acid or closely related subunit linked to a terpenoid moiety by at least one C–C bond.

## 3 Meroterpenoids containing triketide-terpenoid moieties

Naturally occurring bioactive spiro-diterpenoids (+)-breviones A–E **12–16** have been obtained from extracts of semi-solid

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fermented *Penicillium brevicompactum* Dierckx.<sup>16,17</sup> The structures display the breviane spiro-diterpenoid skeleton and were elucidated by chemical transformations and by homo- and heteronuclear 2D-NMR spectroscopic data. These compounds inhibit wheat coleoptile growth, therefore suggesting their use as new agrochemicals.<sup>16,17</sup>

Their biosynthesis may proceed through combined polyketide and terpenoid pathways as shown in Scheme 1.<sup>17</sup> Thus, addition of geranylgeranyl to the pyrone **17** derived from three molecules

of acetyl CoA and one methyl from methionine, followed by cyclization, would give the breviane skeleton **18**. Oxidation at C-3 and C-14 and cyclization to produce the spirocycle would lead to brevione B **13**. Dehydrogenation of **13** to give **12**, and subsequent expansion of the A ring of **12** and dehydrogenation would give brevione C **14**. A radical mechanism *via* a cyclopropane which would account for this is indicated in Scheme 1. Oxidation of C-15 in **14** may generate brevione D **15**, and further oxidation at C-1 and C-17 would result in tetrahydrofuran formation



**Regina Geris**

Regina Geris received her M.Sc. and Ph.D. degrees from the Universidade Federal de São Carlos, Brazil, where she studied the interaction between plants and endophytic fungi and their relationship to secondary metabolites, under supervision of Dr. Edson Rodrigues Filho. During her Ph.D. she carried out a traineeship in the School of Chemistry, Bristol, UK, where she developed a research project entitled "Isolation of Fungal Meroterpenoid Genes", under

the supervision of Professor Tom Simpson. In 2003 she was a post-doctoral research fellow with Dr. Edson Rodrigues Filho at the Universidade Federal de São Carlos, Brazil. She is currently working at the Instituto de Química at Universidade Federal da Bahia in Salvador, Brazil, and her research interests are focused on the chemistry of natural products from microorganisms.



**Tom Simpson**

Tom Simpson graduated from the University of Edinburgh in 1969, and gained his Ph.D. from the University of Bristol in 1973 working with Jake MacMillan. After postdoctoral work in the University of Liverpool with Stan Holker and the Australian National University with Arthur Birch, he was appointed to a Lectureship in Chemistry at the University of Edinburgh in 1978. In 1988 he moved to Professorships in Organic Chemistry in the University of

Leicester in 1988, and Bristol University in 1990, where he holds the Alfred Capper Pass Chair of Chemistry. His research, which covers all aspects of the chemistry and biosynthesis of microbial natural products, has led to ca. 180 papers. He has received a number of awards including the Royal Society of Chemistry Corday Morgan Medal (1984) the Simonsen (2002), Tilden (2001) and Hugo Muller (2004) Lectureships, and the Microbial Chemistry Medal of the Kitatsato Institution in 2005. He was elected Fellow of the Royal Society in 2001 and Fellow of the Royal Society of Edinburgh in 2006. He was a founder member and past Chairman of the NPR Editorial Board.

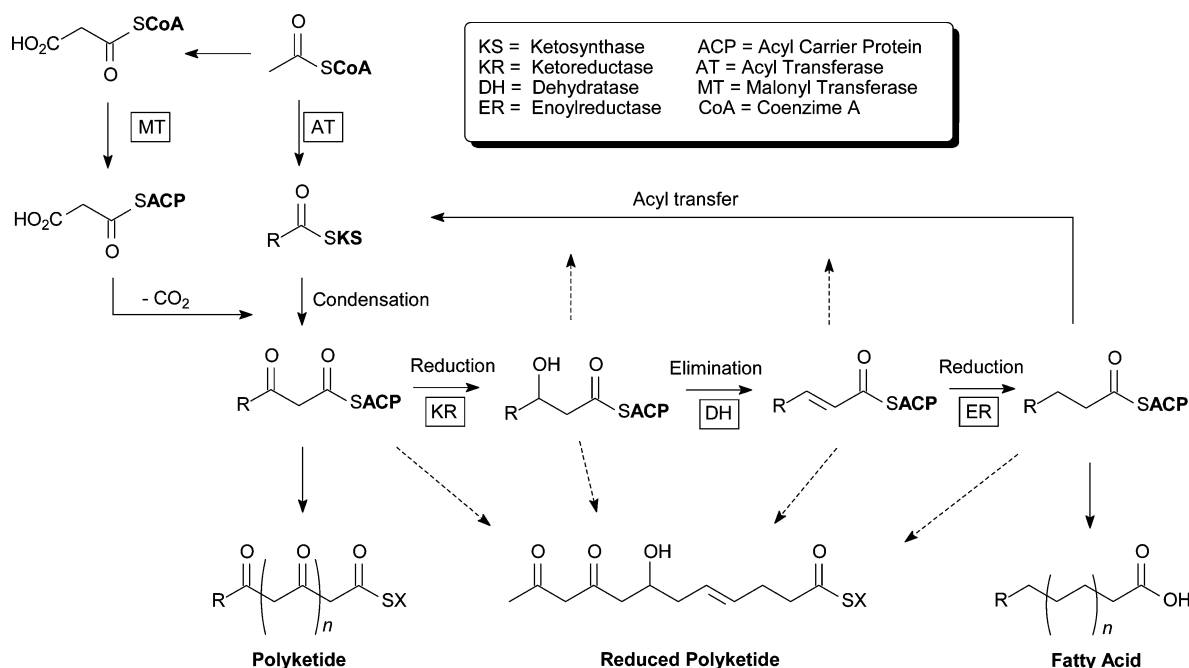


Fig. 1 The assembly of fatty acids, polyketides and reduced polyketides.

between rings A and B and conversion of C-17 to an aldehyde. Opening of the spiran and lactone rings would allow formation of the hemiketal ring, decarboxylation and formation of the seven-membered spirocycle, and finally acetylation to brevione E **16**.

Pycnophorin **19**, a metabolite with antimicrobial activity, was isolated from the full-grown mycelia-bearing pycnidia of *Macrophoma kuwatsukai* (a causal agent of ring rot of apple), and was shown to be a diterpene  $\alpha$ -pyrone (with a trisubstituted 4-hydroxy- $\alpha$ -pyrone ring) by spectroscopic studies.<sup>18</sup>

One of the differences between the biosynthesis of polyketides and fatty acids is the possibility of having a wide variety of chain-starting units (such as acetate, propionate, benzoate, cinnamate and amino-acids).<sup>11</sup> Thus, the following compounds in this review can be classified as triketides.

Ling and co-workers<sup>19,20</sup> have reported the isolation of three tremorgenic mycotoxins, territrems A **20**, B **21** and C **22**, from rice cultures of *Aspergillus terreus*. These compounds induced whole body tremor when injected into rats or mice. In addition, compound **21** might potentiate the release of acetylcholine.<sup>21</sup> To investigate the relationship between the structures and inhibition of acetylcholinesterase activity, **21** was incubated with rat liver microsomes, producing four metabolites. MB2 [4- $\alpha$ -(hydroxymethyl)-4- $\alpha$ -demethylterritrem B] **23** was the major metabolite, which arose from hydroxylation of the pro-*S*-methyl group at C-4 of **21**.<sup>21,22</sup>

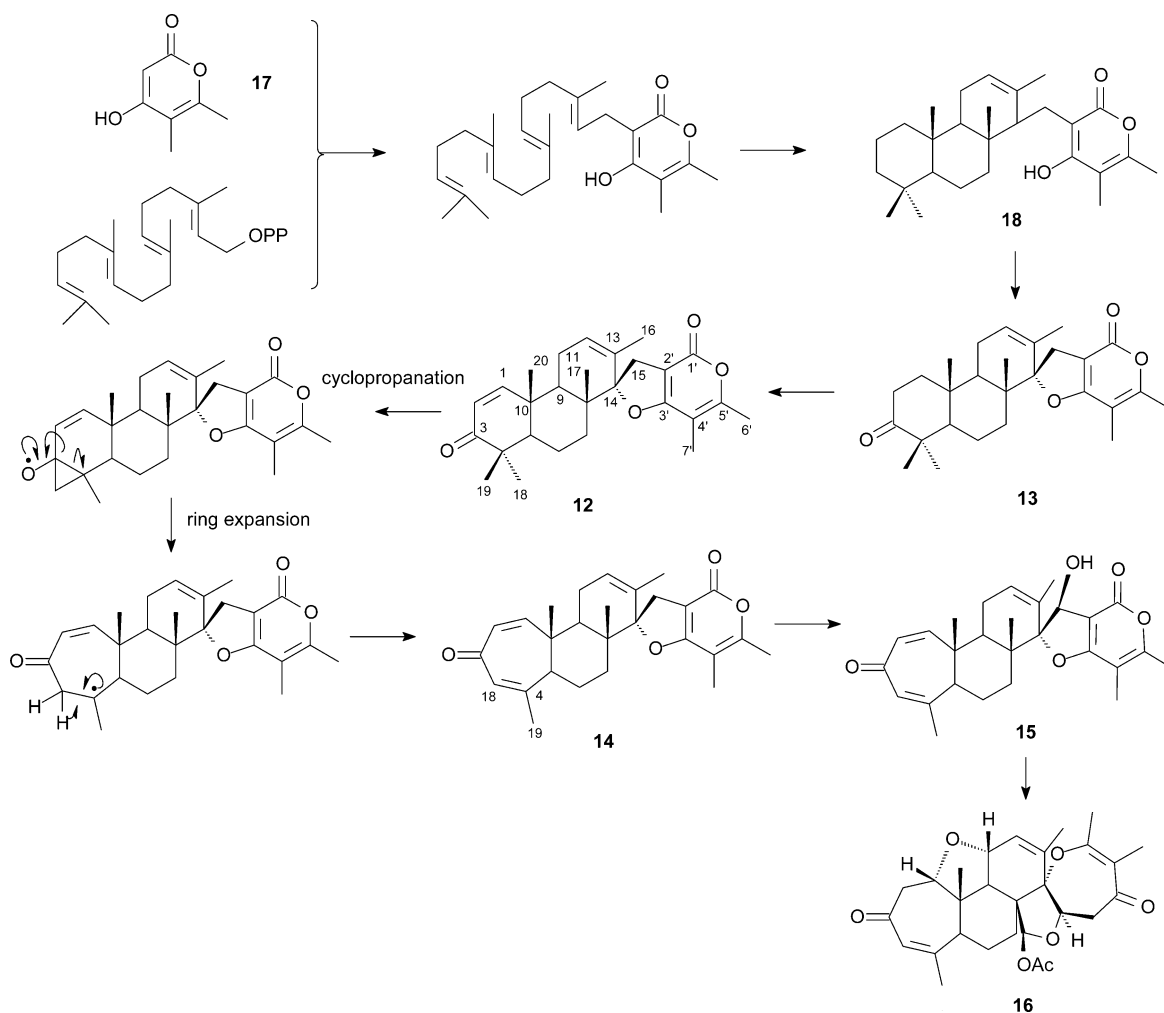
In the course of screening for selective inhibitors of acetylcholinesterase, arisugacins A **24** and B **25** were obtained from the culture broth of *Penicillium* sp. Fo-4259 together with the structurally related compounds territrems B **21** and C **22**.<sup>23,24</sup> Their structures were elucidated by extensive spectroscopic studies, including a combination of 1-D and 2-D NMR techniques.<sup>25</sup> Treatment of this microorganism with UV-light yielded a mutant strain which was a high producer of

arisugacins.<sup>26</sup> Further isolation studies led to the discovery of arisugacins C–H **26–31**.<sup>26</sup> The relative stereochemistries of **24**, **25** and **29** have been elucidated by differential NOE experiments<sup>27</sup> and modified Mosher method.<sup>28</sup> Arisugacins are proposed to be biosynthesized from a sesquiterpene, a diketide and a benzoate-derived triketide from their structural similarity to pyripyropenes.<sup>25,27</sup>

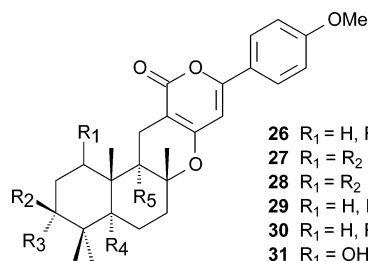
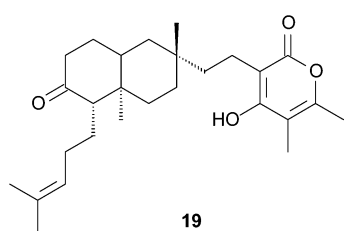
Terreulactones A–D **32–35**, isolated from a solid fermented culture of *Aspergillus terreus* Fb000501, also showed potent inhibitory activities against acetylcholinesterase,<sup>29–31</sup> and appear to be biosynthetically related to arisugacins.<sup>30,31</sup> Moreover, **32** is so far the only sesquiterpene meroterpenoid to have a fused lactone skeleton in its sesquiterpene moiety.<sup>29</sup> Further investigation on the polar metabolites of this microorganism resulted in the isolation of a seven-membered lactone containing meroterpenoid named isoterreulactone A **36**,<sup>32</sup> which appears to arise from **34** by a Baeyer–Villiger reaction.

Four pyripyropenes A–D **37–40** were isolated from the fermentation broth of *Aspergillus fumigatus* FO-1289 by a combination of solvent extraction, silica gel plus ODS column chromatography and HPLC.<sup>33</sup> These compounds showed very potent ACAT (Acyl-CoA:cholesterol acyltransferase) inhibitory activity,<sup>34</sup> and their structures were determined mainly by spectroscopic studies including various NMR measurements.<sup>35</sup> In addition, the relative and absolute stereochemistry of **37** has been elucidated by NOE experiments, X-ray crystallographic analysis and Mosher's NMR method.<sup>36</sup>

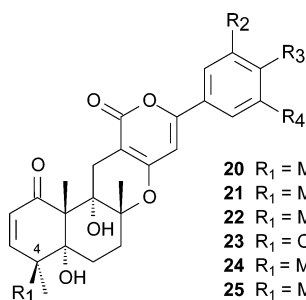
A mutant high producer of pyripyropenes, *A. fumigatus* FO-1289-2501 (treated with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine), when cultured in a production medium supplying 0.002% nicotinic acid, produced fourteen additional pyripyropenes E–R **41–54**, which were isolated from the ethyl acetate extracts of the fermentation broth.<sup>37,38</sup>



**Scheme 1** A postulated biosynthetic origin for the breviane skeleton (adapted from Macias *et al.*<sup>17</sup>).

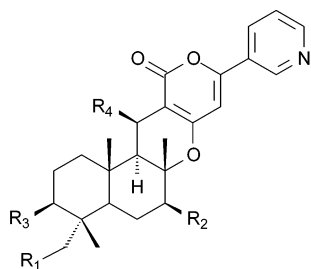
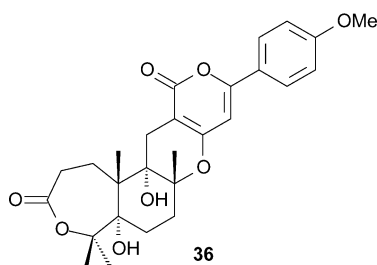
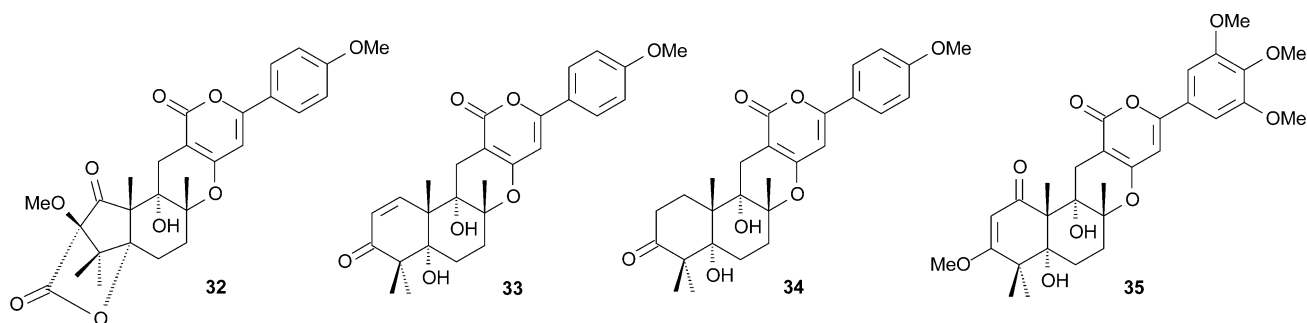


- 26 R<sub>1</sub> = H, R<sub>2</sub> = R<sub>3</sub> = O, R<sub>4</sub> = OH, R<sub>5</sub> = H  
 27 R<sub>1</sub> = R<sub>2</sub> = H, R<sub>3</sub> = OAc, R<sub>4</sub> = R<sub>5</sub> = OH  
 28 R<sub>1</sub> = R<sub>2</sub> = H, R<sub>3</sub> = R<sub>4</sub> = OH, R<sub>5</sub> = H  
 29 R<sub>1</sub> = H, R<sub>2</sub> = OH, R<sub>3</sub> = R<sub>4</sub> = R<sub>5</sub> = H  
 30 R<sub>1</sub> = H, R<sub>2</sub> = R<sub>3</sub> = O, R<sub>4</sub> = R<sub>5</sub> = H  
 31 R<sub>1</sub> = OH, R<sub>2</sub> = H, R<sub>3</sub> = OAc, R<sub>4</sub> = R<sub>5</sub> = H



- 20 R<sub>1</sub> = Me, R<sub>2</sub> + R<sub>3</sub> = OCH<sub>2</sub>O, R<sub>4</sub> = OMe  
 21 R<sub>1</sub> = Me, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = OMe  
 22 R<sub>1</sub> = Me, R<sub>2</sub> = OMe, R<sub>3</sub> = OH, R<sub>4</sub> = OMe  
 23 R<sub>1</sub> = CH<sub>2</sub>OH, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = OMe  
 24 R<sub>1</sub> = Me, R<sub>2</sub> = H, R<sub>3</sub> = R<sub>4</sub> = OMe  
 25 R<sub>1</sub> = Me, R<sub>2</sub> = H, R<sub>3</sub> = OMe, R<sub>4</sub> = H

Pyripyropenes have a common skeleton consisting of a polyoxygenated sesquiterpene,  $\alpha$ -pyrone and pyridine moieties. Three of the four hydroxyl residues on the sesquiterpene moiety are acylated by acetyl and propionyl groups to form the various pyripyropenes.<sup>39</sup> In order to establish the biosynthetic origin of 37, sodium [1-<sup>13</sup>C], [2-<sup>13</sup>C] and [1,2-<sup>13</sup>C<sub>2</sub>]acetates, DL-[2-<sup>13</sup>C] mevalonolactone and [carboxy-<sup>14</sup>C]nicotinic acid were fed to cultures of *A. fumigatus* FO-1289-2501 and their enriched products were analyzed by NMR. The likely biosynthesis is shown in Scheme 2. The acyl primer nicotinic acid 55 is



- 37  $R_1 = R_2 = R_3 = \text{OAc}, R_4 = \text{OH}$   
 38  $R_1 = \text{OCOEt}, R_2 = R_3 = \text{OAc}, R_4 = \text{OH}$   
 39  $R_1 = \text{OAc}, R_2 = \text{OCOEt}, R_3 = \text{OAc}, R_4 = \text{OH}$   
 40  $R_1 = R_2 = \text{OAc}, R_3 = \text{OCOEt}, R_4 = \text{OH}$   
 41  $R_1 = R_2 = \text{H}, R_3 = \text{OAc}, R_4 = \text{H}$   
 42  $R_1 = R_2 = \text{H}, R_3 = \text{OCOEt}, R_4 = \text{H}$   
 43  $R_1 = R_2 = \text{H}, R_3 = \text{OAc}, R_4 = \text{OH}$   
 44  $R_1 = R_2 = \text{H}, R_3 = \text{OCOEt}, R_4 = \text{OH}$   
 45  $R_1 = R_2 = R_3 = \text{OCOEt}, R_4 = \text{OH}$   
 46  $R_1 = \text{OAc}, R_2 = R_3 = \text{OCOEt}, R_4 = \text{OH}$   
 47  $R_1 = \text{OCOEt}, R_2 = \text{OAc}, R_3 = \text{OCOEt}, R_4 = \text{OH}$   
 48  $R_1 = R_2 = \text{OCOEt}, R_3 = \text{OAc}, R_4 = \text{OH}$   
 49  $R_1 = \text{OAc}, R_2 = \text{OCOEt}, R_3 = \text{OAc}, R_4 = \text{H}$   
 50  $R_1 = \text{OCOEt}, R_2 = \text{H}, R_3 = \text{OCOEt}, R_4 = \text{OH}$   
 51  $R_1 = \text{OAc}, R_2 = \text{H}, R_3 = \text{OAc}, R_4 = \text{H}$   
 52  $R_1 = \text{OCOEt}, R_2 = \text{H}, R_3 = \text{OAc}, R_4 = \text{H}$   
 53  $R_1 = \text{OCOEt}, R_2 = \text{H}, R_3 = \text{OAc}, R_4 = \text{OH}$   
 54  $R_1 = \text{OAc}, R_2 = \text{H}, R_3 = \text{OCOEt}, R_4 = \text{H}$

sequentially condensed with two acetates to form 5-(3-pyridyl)-3,5-dioxopentanoic acid **56**, which is converted to a pyridino- $\alpha$ -pyrone **57**. Then, an all-*trans* farnesyl pyrophosphate produced from three mevalonates and the putative pyridino- $\alpha$ -pyrone **57** are condensed and cyclized to form the core skeleton **58**. Finally,

three acetyl residues from acetate are introduced into the skeleton to yield **37**.<sup>39</sup>

Another meroterpenoid that appears to derive from a pathway involving nicotinic acid (ring A), polyketide (ring B), and diterpenoid (rings C, D, E, and F) moieties is oxalicine A **59**, isolated from *Penicillium oxalicum*.<sup>40</sup> The stereostructure of this hexacyclic alkaloidal meroterpenoid was established from spectroscopic data and single-crystal X-ray analysis.<sup>40</sup> Later, oxalicine B **60** was obtained from the same fungus.<sup>41</sup> From rice cultures of *P. decaturense* and *P. thiersii* three insecticidal compounds were obtained (described as alkaloids in the literature): 15-deoxyoxalicine B **61**, decaturin A **62** and B **63**.<sup>41</sup> Further work on extracts of *P. thiersii* revealed three additional related compounds, 15-deoxyoxalicine A **64**, decaturin C **65** and D **66**, in addition to the known decaturins. Compounds **66** showed potent insecticidal activity against *Spodoptera frugiperda*.<sup>42</sup> The oxalicines and decaturins are biosynthetically related to pyripyropenes but with the incorporation of a diterpenoid unit rather than the sesquiterpenoid component found in the pyripyropenes.<sup>42</sup>

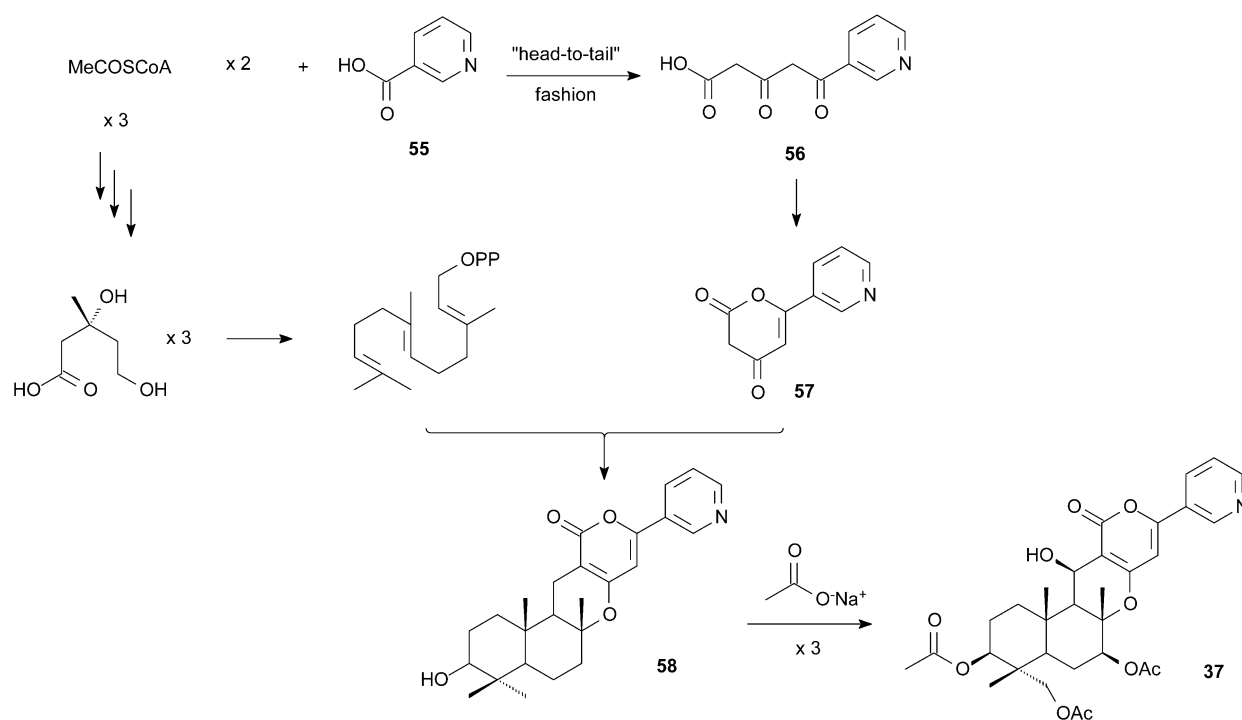
#### 4 Meroterpenoids containing tetraketide–terpenoid moieties

Tetraketide–terpenoid-derived compounds constitute the largest class of meroterpenoids. They can be conveniently subdivided according to the number of carbons introduced to the tetraketide precursor.<sup>43</sup>

Orsellinic acid **67** is the parent compound derived by cyclization of the polyketide precursor, while 6-methylsalicylic acid **68** is formed by loss of one of the oxygen atoms (by reduction) from the tetraketide precursor.<sup>43</sup> 3-Methylorsellinic acid **69**, 5-methylorsellinic acid **70**, and 3,5-dimethylorsellinic acid **71** are formed by addition of methyl groups derived from *S*-adenosylmethionine onto the basic tetraketide precursor. The timing and mechanism of these modifications are uncertain but do occur prior to release of the aromatic product from the polyketide synthase.

##### 4.1 Derived from orsellinic acid

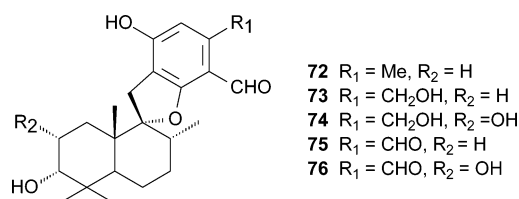
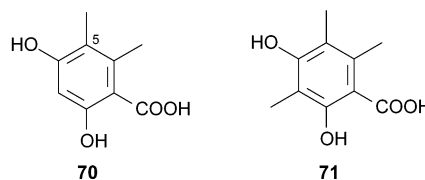
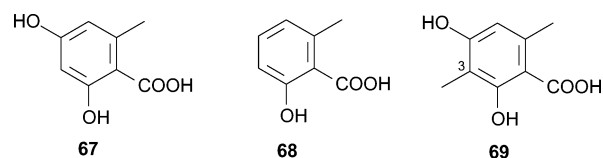
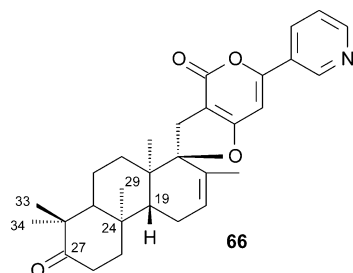
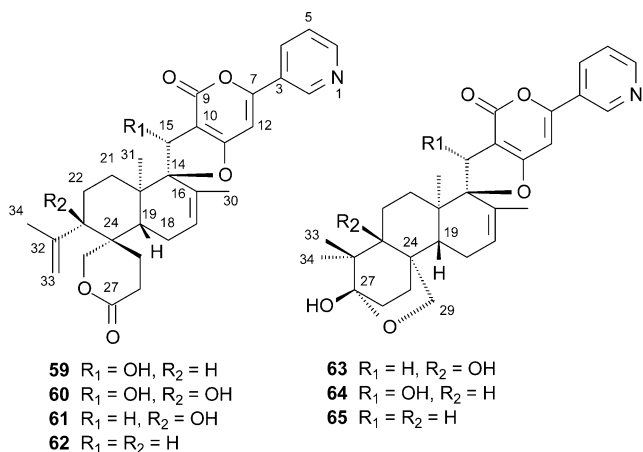
Cultures of several isolates of *Stachybotrys* spp. have produced a series of phenylspirodrimanones, many of them endowed with important biological activities such as



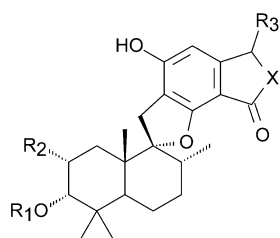
Scheme 2 Proposed biosynthetic pathway of pyripyropene A 37.

immunosuppressant<sup>44</sup> and protease inhibitor activities.<sup>45–47</sup> These include the spirobenzofuranaldehyde **72**,<sup>48</sup> the corresponding benzyl alcohols **73**<sup>44–46</sup> and **74**,<sup>45</sup> and the dialdehydes **75**<sup>44,45</sup> and **76**.<sup>44,47</sup>

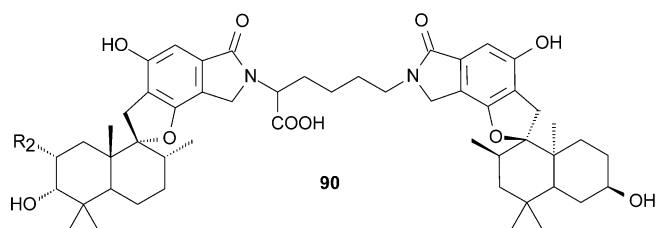
These compounds are relatively unstable and often undergo conversion to the stachybotrylactams and stachybotrylactones,<sup>49</sup> producing the following metabolites: stachybotrylactone (or stachybotrolide) **77**, stachybotrylactone acetate **78**, 2 $\alpha$ -hydroxy-stachybotrylactone **79**, 2 $\alpha$ -hydroxystachybotrylactone acetate **80**, stachybotrylactam **81**, stachybotrylactam acetate **82**, 2 $\alpha$ -acetoxystachybotrylactam acetate **83** and stachybotramide (or stachybotryn) **84**. These compounds exhibit anticomplement immunosuppressant activities.<sup>44,46</sup> The additional compounds **85**, **86** and **90**, also named as spirocyclic drimanes, are endothelin



receptor antagonists,<sup>46</sup> while **87**, **88**, and **89** act as cholesterol esterase inhibitors.<sup>50</sup>

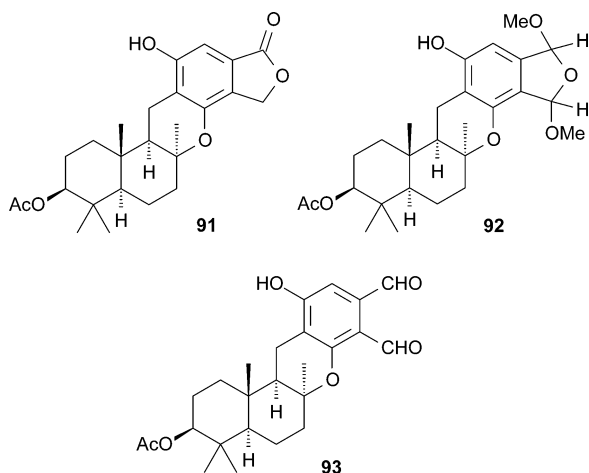


- 77** X = O, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H  
**78** X = O, R<sub>1</sub> = Ac, R<sub>2</sub> = R<sub>3</sub> = H  
**79** X = O, R<sub>1</sub> = H, R<sub>2</sub> = OH, R<sub>3</sub> = H  
**80** X = O, R<sub>1</sub> = Ac, R<sub>2</sub> = OAc, R<sub>3</sub> = H  
**81** X = NH, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H  
**82** X = NH, R<sub>1</sub> = Ac, R<sub>2</sub> = R<sub>3</sub> = H  
**83** X = NH, R<sub>1</sub> = Ac, R<sub>2</sub> = OAc, R<sub>3</sub> = H  
**84** X = NCH<sub>2</sub>CH<sub>2</sub>OH, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H  
**85** X = N(CH<sub>2</sub>)<sub>4</sub>COOH, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H  
**86** X = NCH(COOH)(CH<sub>2</sub>)<sub>2</sub>COOH, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H  
**87** X = NH, R<sub>1</sub> = H, R<sub>2</sub> = OH, R<sub>3</sub> = OMe  
**88** X = NH(CH<sub>2</sub>)<sub>3</sub>COOCH<sub>3</sub>, R<sub>1</sub> = H, R<sub>2</sub> = OH, R<sub>3</sub> = H  
**89** X = NH(CH<sub>2</sub>)<sub>4</sub>COOCH<sub>3</sub>, R<sub>1</sub> = R<sub>2</sub> = H, R<sub>3</sub> = H

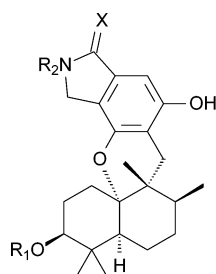


An RAS farnesyl-protein transferase (FPTase) activity bioassay guided the isolation of four tetra- and pentacyclic aromatic sesquiterpenoids, the kampanols A–C **91–93**, from *Stachybotrys kampalensis* Hansf.<sup>51</sup>

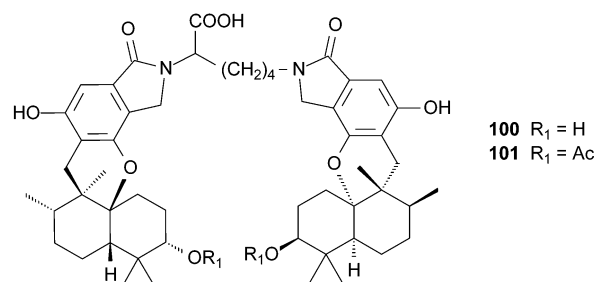
Stachyflin **94** and acetylstachyflin **95** have been isolated by solid-state fermentation of *Stachybotrys* sp. RF7260.<sup>52,53</sup> They contain a pentacyclic moiety including a *cis*-fused decalin, and showed antiviral activity against influenza A virus *in vitro* with an



IC<sub>50</sub> value of 0.003 μM for **94**. Further studies resulted in isolation of the related compounds **96–101**.<sup>54</sup>



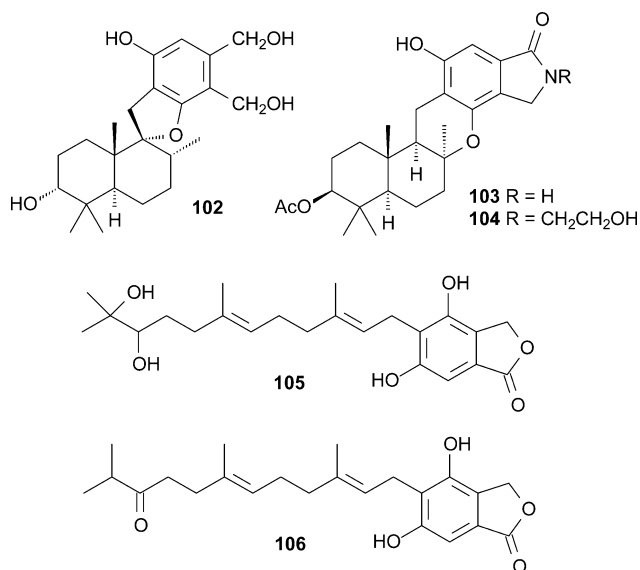
- 94** X = O, R<sub>1</sub> = R<sub>2</sub> = H  
**95** X = O, R<sub>1</sub> = Ac, R<sub>2</sub> = H  
**96** X = O, R<sub>1</sub> = Ac, R<sub>2</sub> = (CH<sub>2</sub>)<sub>4</sub>CH(NH<sub>2</sub>)COOH  
**97** X = O, R<sub>1</sub> = Ac, R<sub>2</sub> = CH(COOH)CH(CH<sub>3</sub>)<sub>2</sub>  
**98** X = NH<sub>2</sub><sup>+</sup>Cl<sup>-</sup>, R<sub>1</sub> = R<sub>2</sub> = H  
**99** X = NH<sub>2</sub><sup>+</sup>Cl<sup>-</sup>, R<sub>1</sub> = Ac, R<sub>2</sub> = H

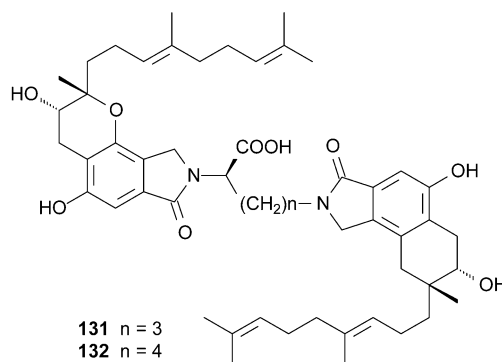
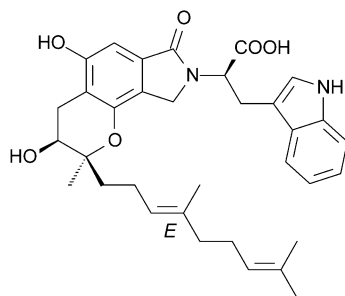
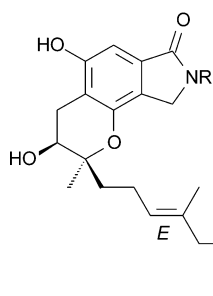
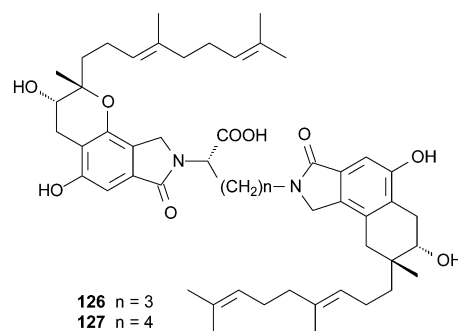
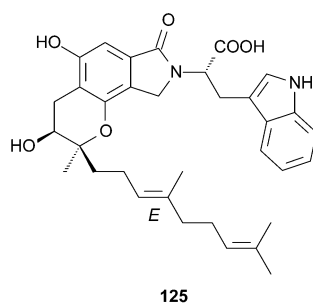
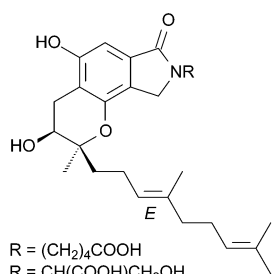
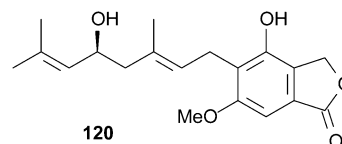
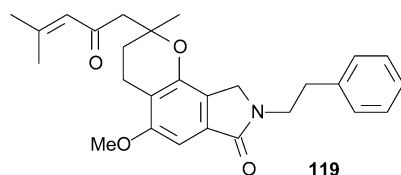
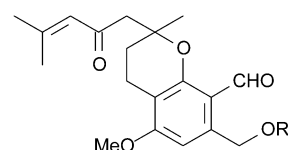
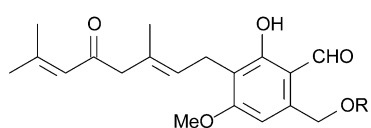
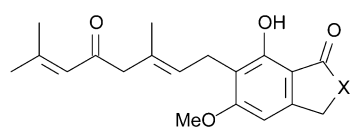
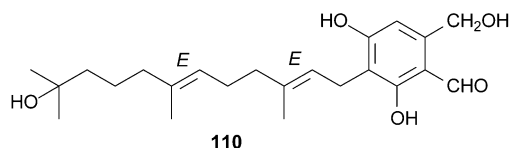
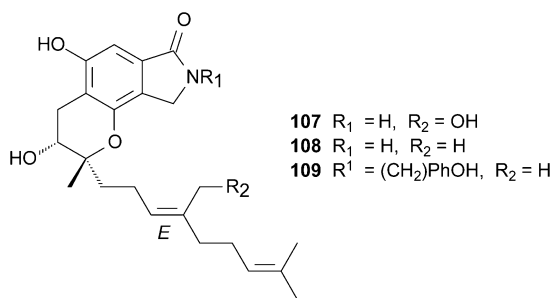


- 100** R<sub>1</sub> = H  
**101** R<sub>1</sub> = Ac

*Memnoniella echinata* is closely related to *Stachybotrys chartarum*, and produces the compounds **72** and **74** together with spirobenzofurandialcohol **102**.<sup>55</sup> These exhibited inhibitory activity against myo-inositol monophosphatase. In addition, four metabolites have been isolated from a rice culture of *M. echinata* by solvent extraction and radial silica chromatography. The structures were identified as memnobotrin A **103**, and B **104**, and the linear isoprenoid derivatives memnoconol **105** and memnoconone **106**.<sup>56</sup>

Another *Stachybotrys* sp. also produced secondary metabolites having a pyrano-isindolinone ring system, the stachybotrins A **107**, B **108** and C **109**, as well as a hydroxy-farnesyl phenol, parvisporin **110**.<sup>57,58</sup>





Other meroterpenoids, having an acyclic terpenoid backbone, are hericenone A **111** and B **112**, cytotoxic phenols isolated from the edible mushroom *Hericum erinaceum*.<sup>59</sup> Hericenones C–H **113–118** were also obtained. They showed stimulation activity for the synthesis of nerve growth factor.<sup>60,61</sup> Two additional aromatic compounds, erinacerin A **119** and B **120**, were obtained in a further investigation of *H. erinaceum*.<sup>62</sup>

Five triprenylphenol metabolites, designated staplabin **121**, SMTP-3–6 **122–125**, have been isolated from cultures of *Stachybotrys microspora*.<sup>63,64</sup> A combination of spectroscopic analyses showed that **122–125** are staplabin analogs, containing respectively a serine, a phenylalanine, a leucine or a tryptophan moiety in place of the *N*-carboxybutyl portion of staplabin. These compounds showed effects on plasminogen activation and fibrinolysis.<sup>63,64</sup> Two staplabin analogs with a pseudosymmetric structure were also obtained, SMTP-7 **126** and SMTP-8 **127**.<sup>65</sup> The former consisted of two identical staplabin core structures



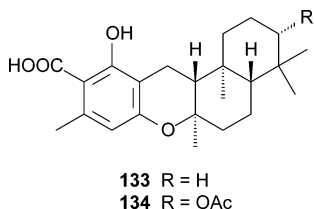
and ornithine, which bridges the two partial structures while in the latter the bridging unit was lysine. These compounds exhibited plasminogen activation and fibrinolyses levels higher than those of staplabins.<sup>65</sup>

Five other SMTPs belonging to the D-series (from precursor D-amino-acid analogs) were also isolated from the cultures of *S. microspora*. They were designated as SMTP-4D to -8D **128–132** and showed a 10-fold enhancement of urokinase-catalyzed plasminogen activity.<sup>66</sup>

The antibiotics hongoquercins A **133** and B **134** were isolated from the extracts of an unidentified fungus. They are related to a class of compounds commonly found in brown algae and dictyoceratid sponges, and exhibited moderate activity against Gram-positive bacteria.<sup>67</sup>

#### 4.2 Derived from 3-methylorsellinic acid

Xenovulene A<sup>®</sup> **135** was isolated from submerged cultures of the fungus *Acremonium strictum* during a screening programme for inhibition of benzodiazepine binding to the GABA<sub>A</sub> receptor.<sup>68</sup>

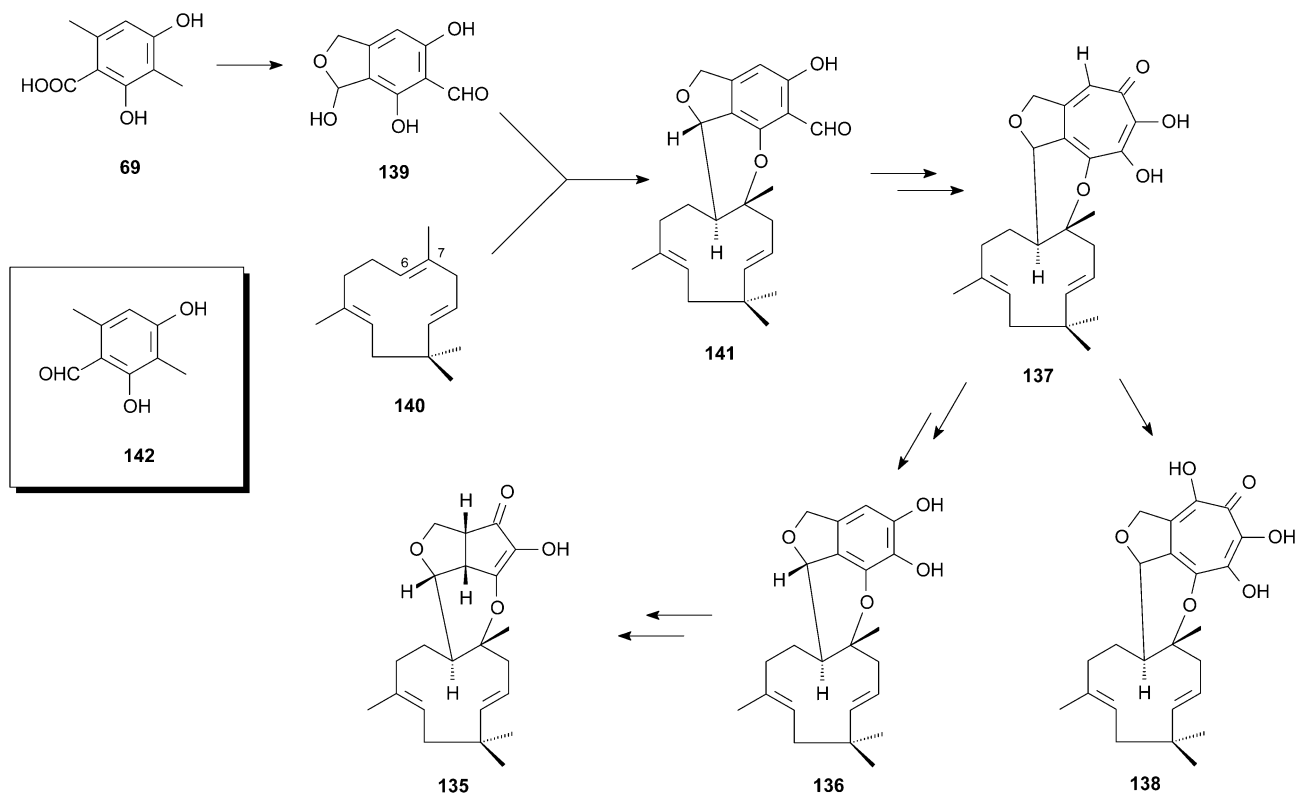


It contains an unusual polyketide-derived bicyclic cyclopentenone moiety linked by a furan ring to an 11-membered ring derived from the sesquiterpenoid humulene. A number of minor co-metabolites of **135** have been isolated in which the cyclopentenone moiety is replaced by trioxxygenated benzene **136**, or highly oxygenated tropolone rings **137** and **138**.<sup>69</sup>

Incorporation studies with <sup>13</sup>C-labelled acetates and methionine in *A. strictum* indicate that the cyclopentenone moiety in **135** is formed by a unique pathway in which a C-methylated phenolic precursor **69** would be converted by standard biosynthetic modifications to the lactol **139** (Scheme 3). This would react with the C6–C7 double bond of humulene **140** to give the key tetracyclic intermediate **141**, which undergoes ring expansion to a tropolone followed by two successive ring contractions, resulting in incorporation of the C-methyl carbon into the five-membered ring.<sup>69</sup>

However, a PKS gene has recently been isolated from xenovulene producing cultures of *A. strictum*.<sup>70</sup> Heterologous expression of the gene in *Aspergillus oryzae* resulted in the production of 3-methylorcinaldehyde **142**, suggesting that it is the actual precursor to the xenovulenes rather than the acid **69**.

The very similar fungal metabolites pycnidione **143**<sup>71</sup> and eupenicfeldin **144**<sup>72</sup> were isolated from cultures of *Phoma* sp and *Eupenicillium brefeldianum*, respectively. They contain a similar fusion of a tropolone to humulene. The former is a bistropolone stromelysin inhibitor while the latter showed cytotoxic activity against the HCT-116 cell line as well as *in vivo* antitumor activity in the P388 leukemia model.



**Scheme 3** The proposed pathway to xenovulene metabolites **135–138** (adapted from Raggatt *et al.*<sup>69</sup> and Bailey *et al.*<sup>70</sup>).

Screening for inducers of erythropoietin gene expression led to the isolation of the epolones A **145** and B **146** as well as **143** from the cultures of the fungus OS-F69284.<sup>73</sup> In several independent experiments, these compounds reproducibly induced erythropoietin gene expression in epo-3-cells. The TIR<sub>5x</sub> (concentration resulting in 5-fold greater induction) of them was in the range of 1.0–1.6  $\mu$ M. In addition, noreupenifeldin **147**, a monotropolone derivative of **144**, was isolated from an unidentified ascomycete by bioassay-guided fractionation for new anthelmintics.<sup>74</sup>

### 4.3 Derived from 5-methylorsellinic acid

Several species of *Penicillium*, including *P. brevicompactum*,<sup>75,76</sup> *P. stoloniferum*, *P. scabrum*, *P. nagemi*, *P. saferi*, *P. patris-mei*, *P. griscobrunneum* and *P. viridicatum* were reported to produce mycophenolic acid (MPA) **148**, in agreement with Muth and Nash.<sup>77</sup> Due to diverse biological properties such as antiviral, antifungal, antibacterial, antitumor, immunosuppressive, and anti-psoriasis activities,<sup>77</sup> several efforts were made to elucidate its biosynthesis, and labelling studies have implicated several phenolic intermediates derived from a tetraketide in the biosynthesis of **148**, leading to isolation of demethylmycophenolic acid (DMPA) **149**, 6-farnesyl-5,7-dihydroxy-4-methylphthalide **150** and **151**.<sup>77–79</sup>

MPA has been demonstrated to consist of an acetate-derived aromatic nucleus, the 5-methylorsellinic acid **70** and a sesquiterpenoid side-chain. According to Colombo *et al.*,<sup>79</sup> 6-farnesyl-5,7-dihydroxy-4-methylphthalide **150** is converted into MPA **148** by (as shown in Scheme 4), at least two pathways: direct oxidation of the central olefinic double bond and a two-stage removal of the terminal and central units.

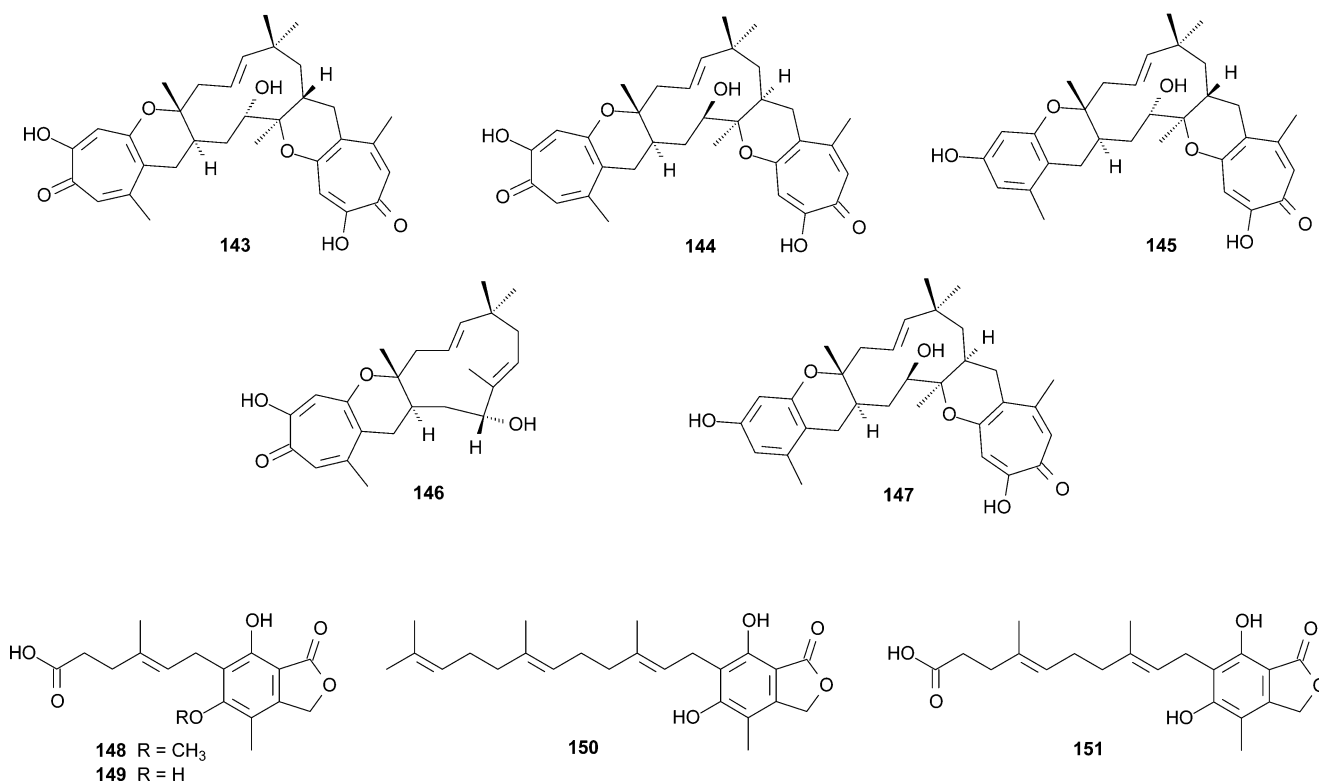
Their experiments indicated that these two pathways are equally important and the following sequence was proposed: a) epoxidation to give **152**, b) rearrangement of the epoxide to a ketone **153**, c) hydroxylation to an  $\alpha$ -hydroxy-ketone **154**, d) and finally Woodward reaction with C–C bond cleavage and formation of the acid **149**. The last step involves the transfer of a methyl-group from *S*-adenosyl-L-methionine (SAM) to DMPA **149**.<sup>77</sup>

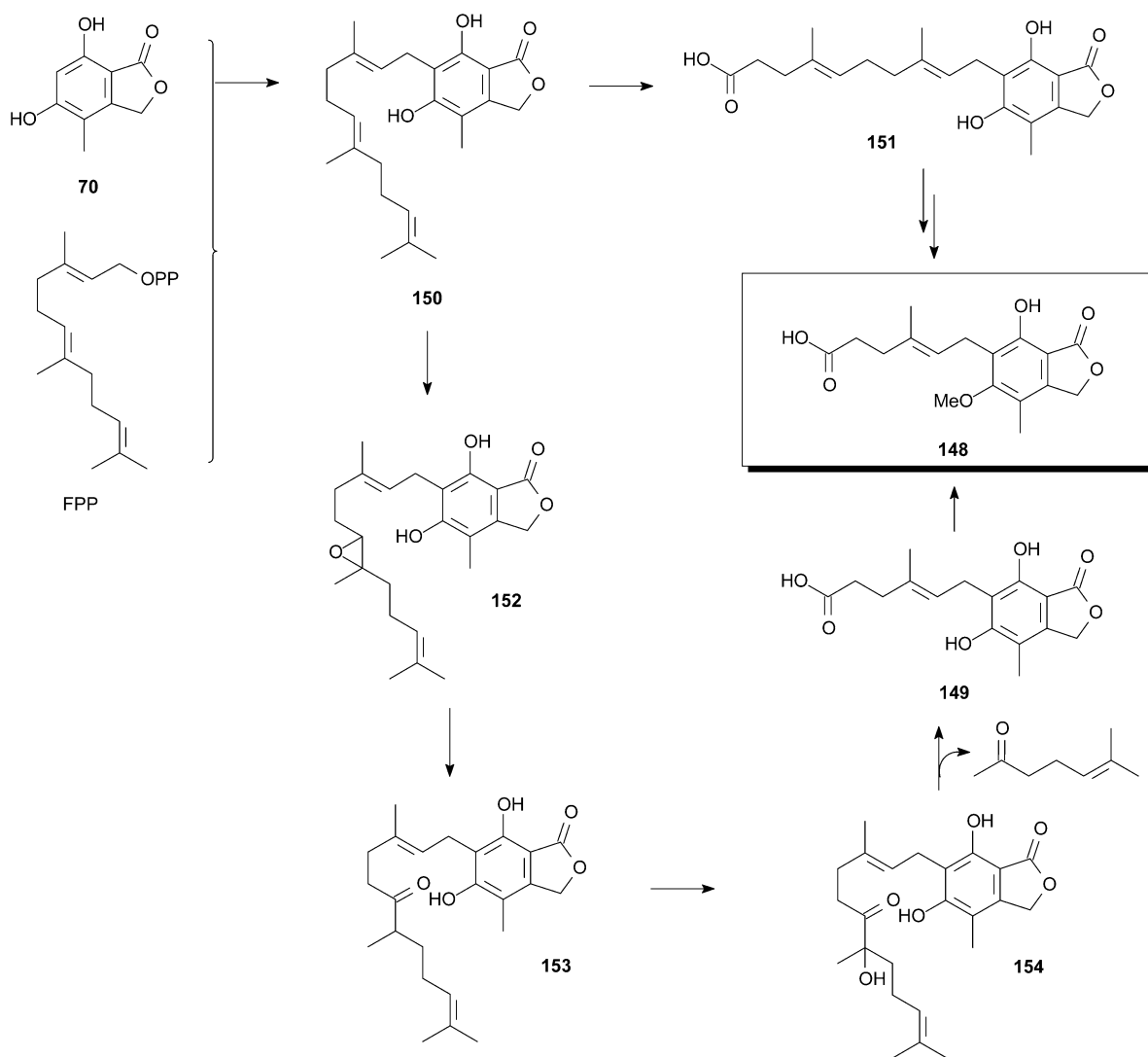
Investigations of toxigenic cultures of *Aspergillus ustus* (Bainier) Thom. & Church (strain MRC 1163) resulted in the isolation of 12 biosynthetically related metabolites, austalides A–L **155–166**.<sup>80–82</sup>

Biosynthetic studies on the austalides indicate that these meroterpenoids are also derived from phthalide **150**.<sup>83,84</sup> A plausible mechanism for the formation of austalides consistent with the known relative stereochemistry was presented by de Jesus *et al.*<sup>83</sup> and revised by Dillen *et al.*<sup>84</sup> Scheme 5 shows some steps of the proposed metabolic route. In order to generate the *cis*-fused chroman ring of the austalides, the involvement of a C-11 carbocation **167** was proposed, with subsequent stereospecific attack of the C-7 phenolic oxygen atom at C-11 (to the *Si*-face) to produce the chroman ring of the austalides **168**.<sup>83</sup> Further oxidative processes such as hydroxylations and Baeyer–Villiger oxidation lead to the other related austalides.<sup>83</sup>

### 4.4 Derived from 3,5-dimethylorsellinic acid

The first member of this group, andibenin **169**, was described in 1976 as a metabolite of *Aspergillus varicolor*.<sup>85</sup> A mixed polyketide–terpenoid biosynthesis rather than the originally



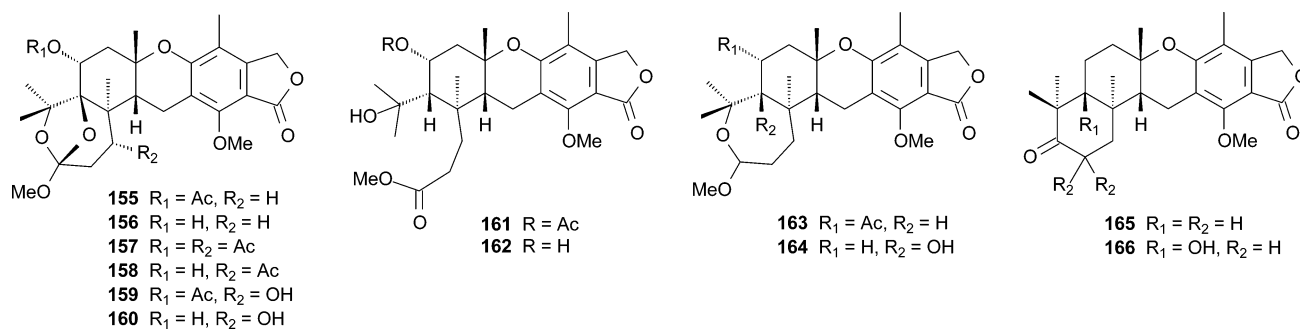


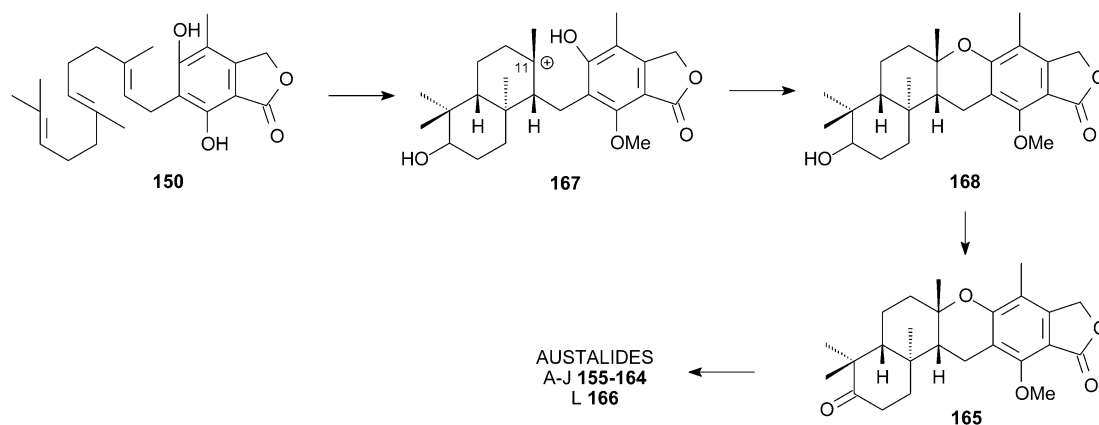
**Scheme 4** The proposed biosynthetic pathway to mycophenolic acid **148** (adapted from Muth and Nash<sup>77</sup> and Colombo *et al.*<sup>79</sup>).

suggested sesquiterpenoid origin was confirmed by stable-isotope labeling studies.<sup>86</sup> Structurally, this compound consists of an  $\alpha,\beta$ -unsaturated- $\delta$ -lactone as part of a spiro system in the A/B rings and a [4.3.1] bicyclic system (Scheme 6).

Subsequently, a large number of metabolites with a wide range of apparent structural diversity were shown to be closely related

biosynthetically to **169**: anditomin **170**, austin **171** and terretinin **172**.<sup>87</sup> They are all formed *via* a common intermediate that arises by alkylation of a polyketide intermediate 3,5-dimethylorsellinate **71** by the terpenoid precursor farnesyl diphosphate.<sup>13</sup> The mode of incorporation of the carbon skeleton in this intermediate into the metabolites described above is summarized in





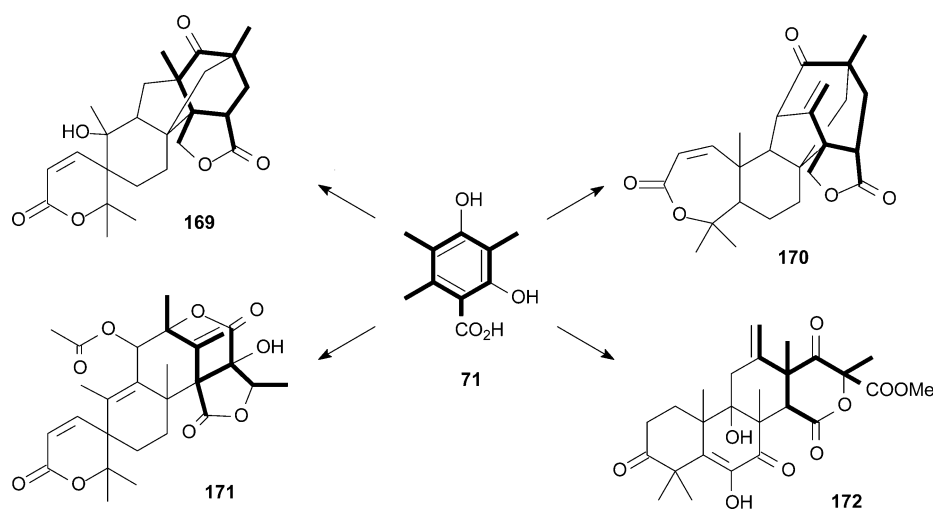
**Scheme 5** The proposed biosynthetic pathway to the australides.

Scheme 6. The carbocyclic ring can be incorporated intact (e.g. **169**), cleaved (e.g. **170**) or fragmented to an unprecedented degree (e.g. **171** and **172**).<sup>13</sup> <sup>18</sup>O<sub>2</sub>-labelling studies, incorporation of aromatic precursors and mevalonic acids variously labeled with <sup>13</sup>C, <sup>2</sup>H, and <sup>18</sup>O provided evidence for the extensive oxidative and other modifications involved in the elaboration of the highly oxygenated polycyclic structures found in these metabolites.<sup>86–88</sup>

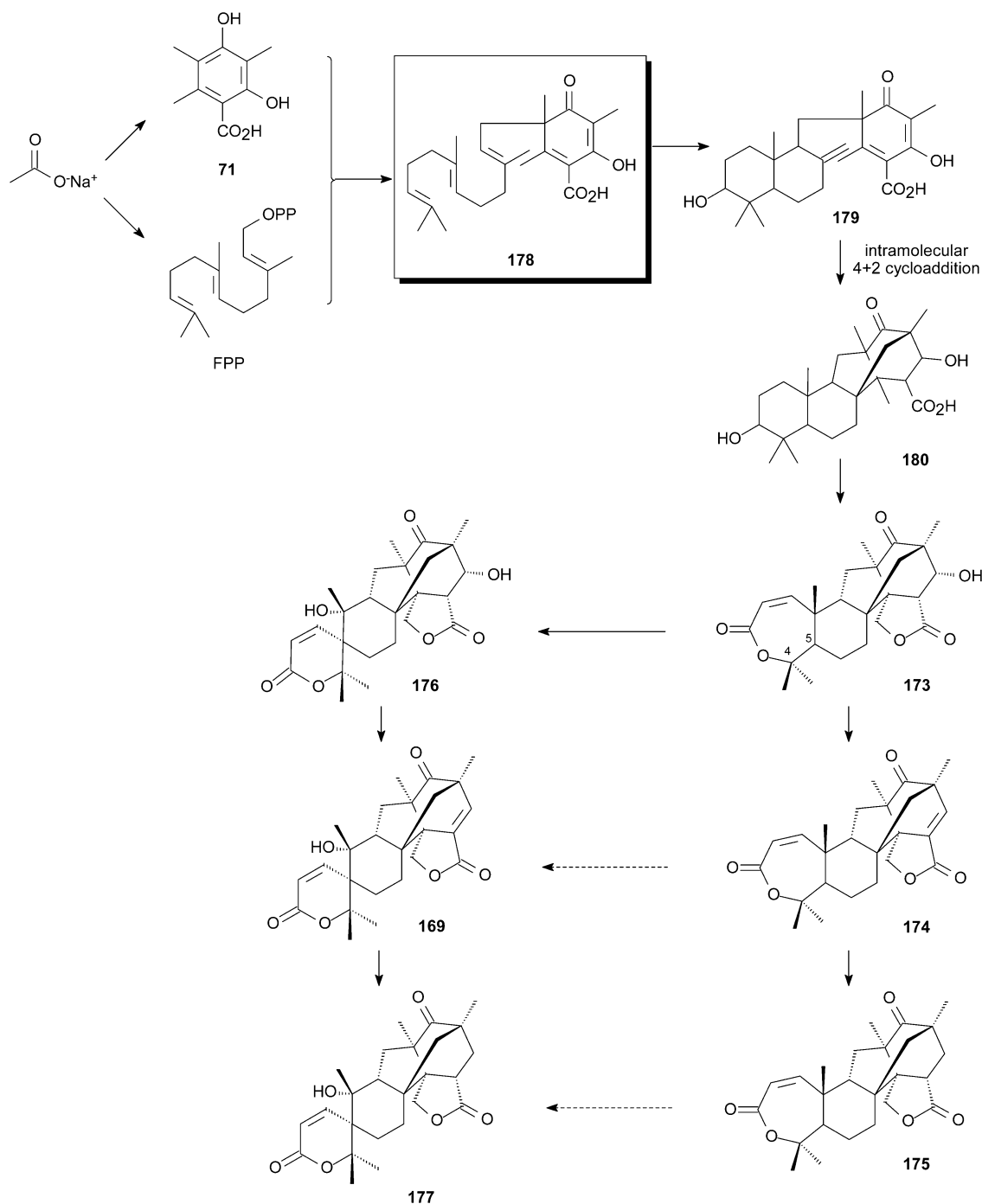
Andilesins A **173**,<sup>89</sup> B **174**,<sup>90</sup> and C **175**<sup>90</sup> were obtained from cultures of *Aspergillus varicolor* together with andibenens A **176**,<sup>90</sup> B **169**,<sup>85</sup> and C **177**.<sup>90</sup> Their biosynthetic origin was confirmed by incorporation of <sup>13</sup>C-labelled acetates and methionine.<sup>87</sup> As shown in Scheme 7, the key steps involves alkylation of a bis-*C*-methylated tetraketide-derived phenolic precursor **71** by farnesyl pyrophosphate to give intermediate **178**, followed by drimane-type cyclization of the farnesyl moiety to **179**, followed by intramolecular 4 + 2 cycloaddition to produce the bicyclooctane part of the carbon skeleton of intermediate **180**. Further oxidative modifications and rearrangements lead to **173** which is converted by dehydration into andilesin B **174** and then reduction to andilesin C **175**.<sup>91</sup>

Rearrangement of the 7-membered lactone ring in the andilesins would form the spiro-lactone found in the corresponding andibenens. This has been proposed to proceed *via* alkyl-oxygen cleavage and loss of the C-5 proton to form a tetra-substituted alkene, epoxidation of which allows the skeletal rearrangement required to form the spiro- $\delta$ -lactone.<sup>87</sup>

Four cytotoxic meroterpenoids with andilesin-like structures, tropolactones A–D **181–184**,<sup>92</sup> have been isolated from the whole-broth extract of a marine-derived *Aspergillus* species. These compounds seem to be derived from the same triene intermediate **179** in andilesin and andibenin biosynthesis. Pyran ring formation after tautomerization to enol **185** would give **186**, followed by oxidation to form the seven-membered ring lactone to give **187**, the precursor of tropolactone D. Hypothetically, the ring expansion in tropolactones A–C proceeds by a radical cyclopropanation mechanism to give stabilized radical intermediate **188**, which can then undergo ring expansion to provide tropolone **189**, from which further oxidative modifications result in **181–183** (Scheme 8).<sup>92</sup>



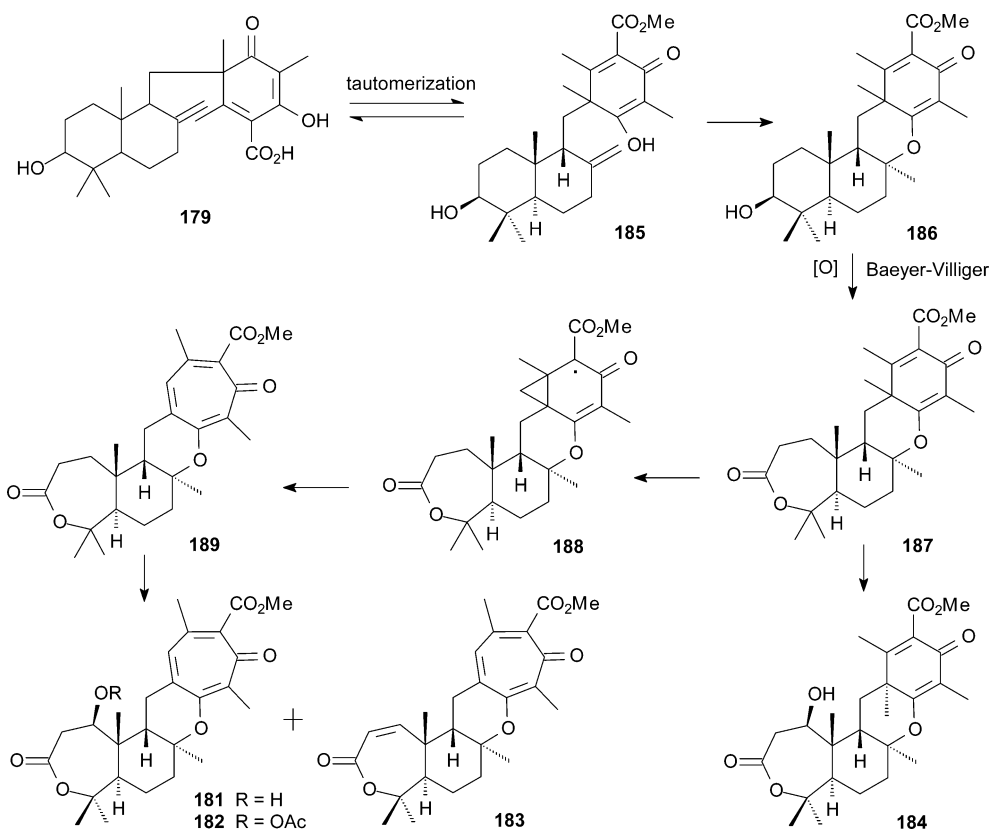
**Scheme 6** The mode of incorporation of the carbon skeleton of 3,5-dimethylorsellinic acid.



**Scheme 7** Proposed biosynthetic pathway to the andilesins and andibenens.

Anditomin **170** was isolated from *A. varicolor* and had its structure deduced from  $^1\text{H}$ ,  $^{13}\text{C}$  NMR and X-ray crystallography.<sup>93</sup> This compound represents an important modification of the meroterpenoid pathway, as it was the first metabolite in which the carbocyclic ring of the tetraketide-derived moiety had been fragmented,<sup>87</sup> representing a novel skeletal rearrangement in this class of compounds. Anditomin is closely related to andilesin C **175**, differing only in an exocyclic methylene group at C-9'. It could be obtained by the loss of hydrogen from C-11 to produce the carbocation **190**, which can rearrange to form the exocyclic methylene **191**, as shown in Scheme 9.

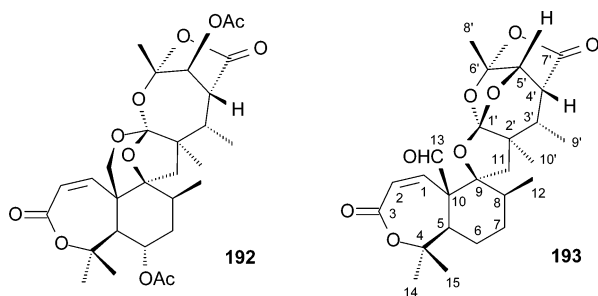
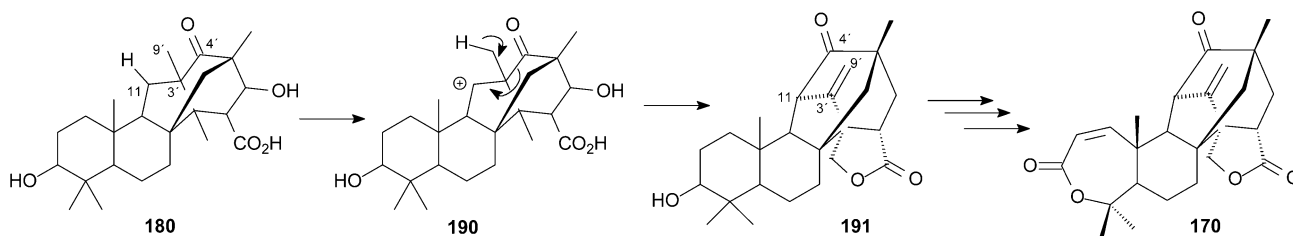
Fumigatonin **192** was isolated from cultures of *A. fumigatus* IFM 4482.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra suggested that fumigatonin contains a highly oxidized and complicated condensed ring system.<sup>94</sup> The detailed structure, as well as the relative stereochemistry of **192**, was established by X-ray analysis. It seems to be a meroterpenoid formed by a novel variation of the same key intermediate **179**, followed by fragmentation of C-4'-C-5' bond and successive oxidative processes. *Aspergillus novofumigatus*, a newly characterized *Aspergillus* species, when cultivated on YES agar, produced the fumigatonin-related compound novofumigatonin **193**. The major difference between them is the



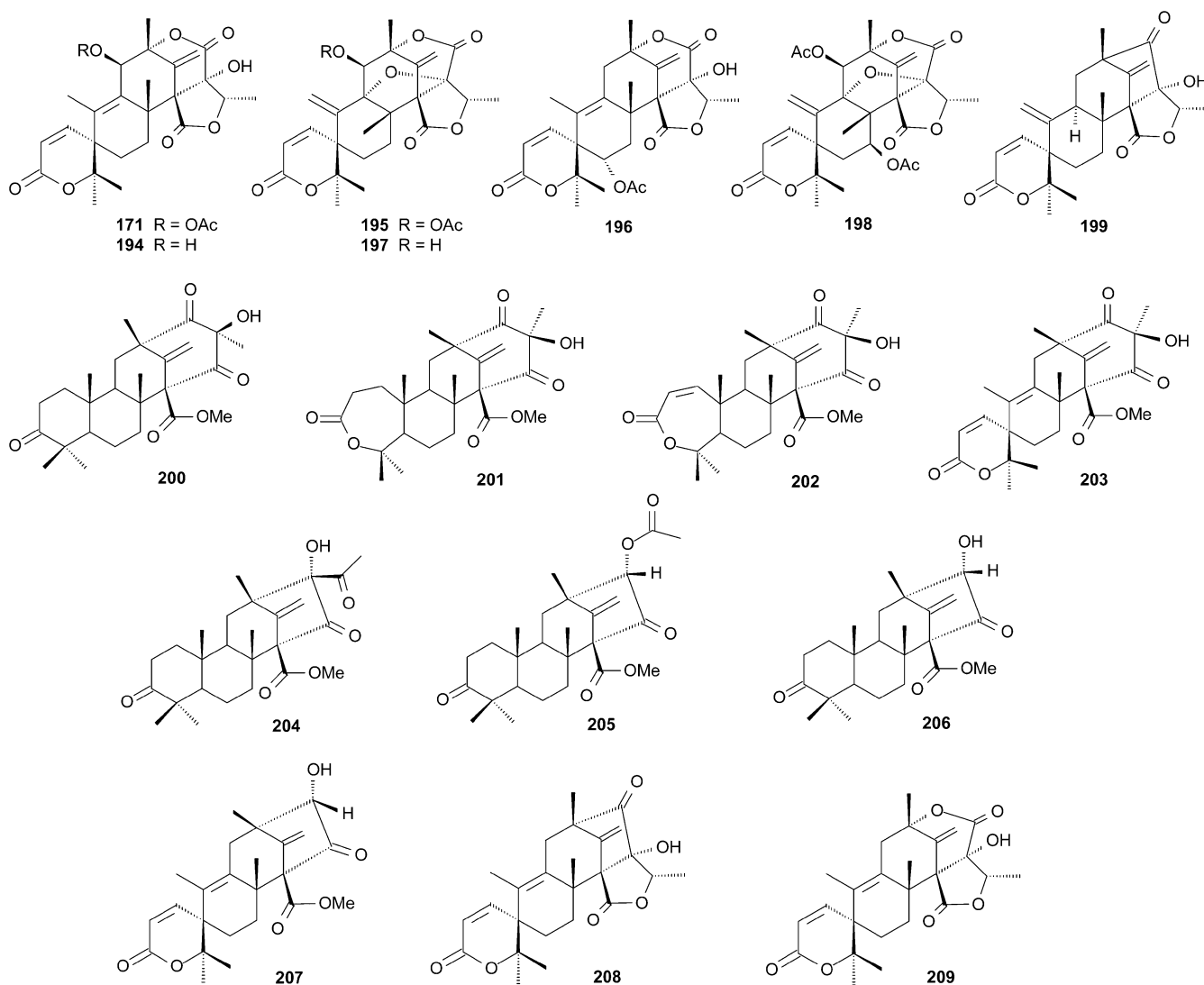
presence of an aldehyde substituent on C-10 in **193** (where **192** has an oxygen-bound methylene group) and the lack of an acetate group at C-6 in **193**.<sup>95</sup>

Investigation of a strain of *Aspergillus ustus* found on stored eyed-peas resulted in the isolation of a mycotoxin named austin **171** whose structure was determined by X-ray

crystallography.<sup>96</sup> Further closely related metabolites austinol **194** and dehydroaustin **195** were also isolated from this fungus.<sup>97</sup> The latter has also been found in cultures of a mutant strain of *A. varicolor*.<sup>98</sup> In addition, iso-austin **196** was obtained from the culture liquors of *Penicillium diversum*.<sup>97</sup>



Subsequently, a number of compounds chemically related to austin were found in a variety of fungal cultures, such as dehydroaustinol **197** from *Emericella dentata*, and acetoxydehydroaustin **198** and neo-austin **199** from *Penicillium* sp MG-11.<sup>99</sup> Chemical investigations of the fungus *Penicillium* sp LaBioMi-024 found in association with *Melia azedarach* led to the isolation of 10 novel related meroterpenoids in addition to the known **195**, **198** and **199**. These are pre-austinoids A **200**,<sup>100</sup> A1 **201**, A2 **202**,<sup>101</sup> A3 **203**,<sup>102</sup> B **204**,<sup>100</sup> B1 **205**,<sup>101</sup> and B2 **206**,<sup>102</sup> austinoneol **207**,<sup>103</sup> iso-austinone **208** and austinolide **209**.<sup>102</sup>



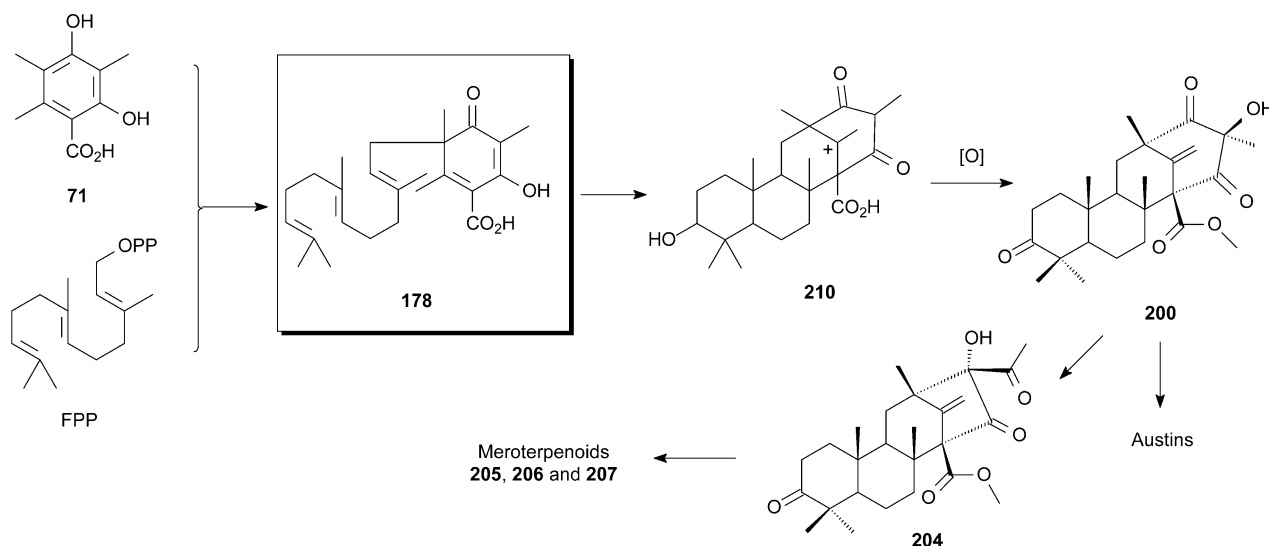
A few biological activities have been reported for this group of compounds. Meroterpenoids **171**, **195** and **198**, although not active themselves, enhanced the convulsive activity of verruculogen in a silkworm bioassay.<sup>99</sup> Moderate bacteriostatic effects were detected for **204** and **208**.<sup>100</sup> Recently, some of these compounds were evaluated for larvicidal activity against *Aedes aegypti*; **171**, **195** and **198** exhibited some activity, especially dehydroaustin **195**, which showed remarkable potential for controlling this mosquito.<sup>104</sup>

Studies on the biosynthesis of the austin group of meroterpenoids produced by *Aspergillus* and *Penicillium* have suggested that this group of metabolites is also formed by C-alkylation of **71** by farnesyl pyrophosphate. Alkylation leads to intermediate **178**, which cyclises to form a 1,3-diketone **210**, as shown in Scheme 10.<sup>87,105,106</sup> Further information about the mechanisms involved in the drastic modifications of the tetraketide- and farnesyl-derived modifications have been provided by extensive studies with <sup>13</sup>C-, <sup>2</sup>H-, and <sup>18</sup>O-labelled precursors.<sup>87,105</sup> The structures of the compounds obtained from the cultures of *Penicillium* sp. LaBioMi-024 provide support for this general route.<sup>102</sup>

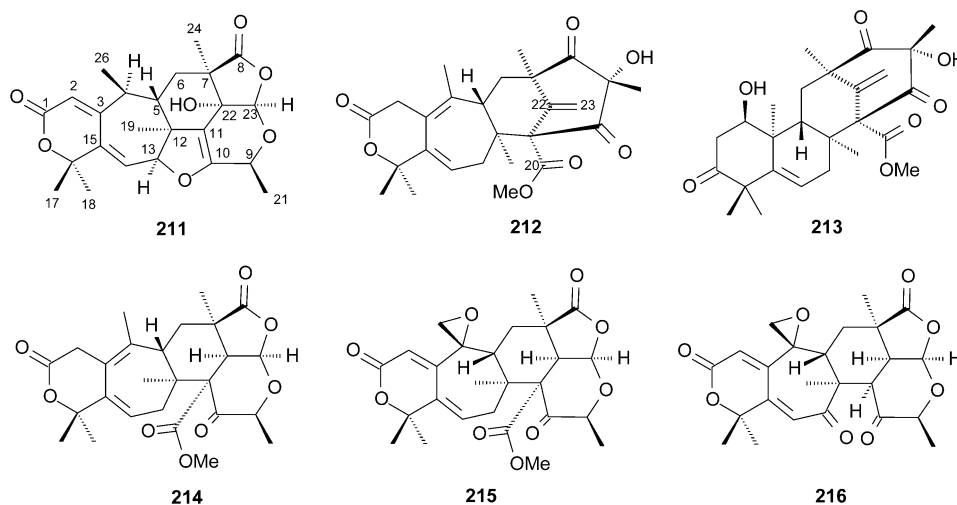
Paraherquonin **211** was isolated from *Penicillium paraherquei* IFO6234 and its structure determined by X-ray diffraction analysis.<sup>107</sup> The pathway to **211** seems to be an extension of the austin pathway to form **211** through further modification by oxidative cleavage, migration, decarboxylation and recyclization.<sup>107</sup>

Two bioactive meroterpenoids berkeleydione **212** and berkeleytrione **213** were obtained from cultures of *Penicillium rubrum* Stoll found growing in Berkeley Pit Lake.<sup>108</sup> Both compounds inhibited matrix metalloproteinase-3 and caspase-1; **212** also showed activity toward non-small-cell lung cancer in NCI's human cell line antitumor screen. Further studies using <sup>1</sup>H NMR analysis of all of the column fractions led to the isolation of the related analogues berkelyacetals A **214**, B **215**, and C **216**.<sup>109</sup> The latter was accepted in the NCI Developmental Therapeutics Program for human cell line screening and tested in the single-dose-response assay due to its inhibition of the growth of non-small-cell lung cancer NCI H460, the same cell line that was targeted by **212**.<sup>109</sup>

Cultivation of the marine fungus *Penicillium minioluteum* resulted in the production of 22-epoxyberkeleydione **217**,



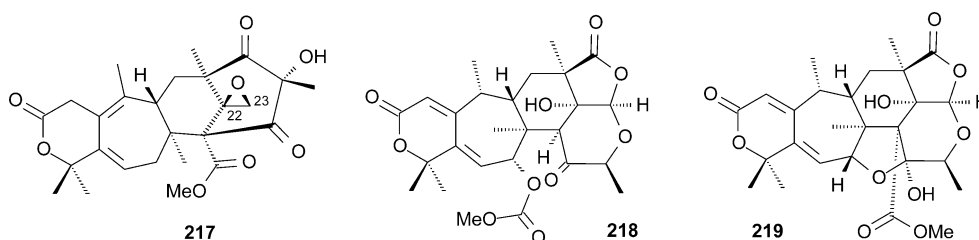
**Scheme 10** Proposed biosynthesis of meroterpenoids produced by species of the genera *Aspergillus* and *Penicillium*.



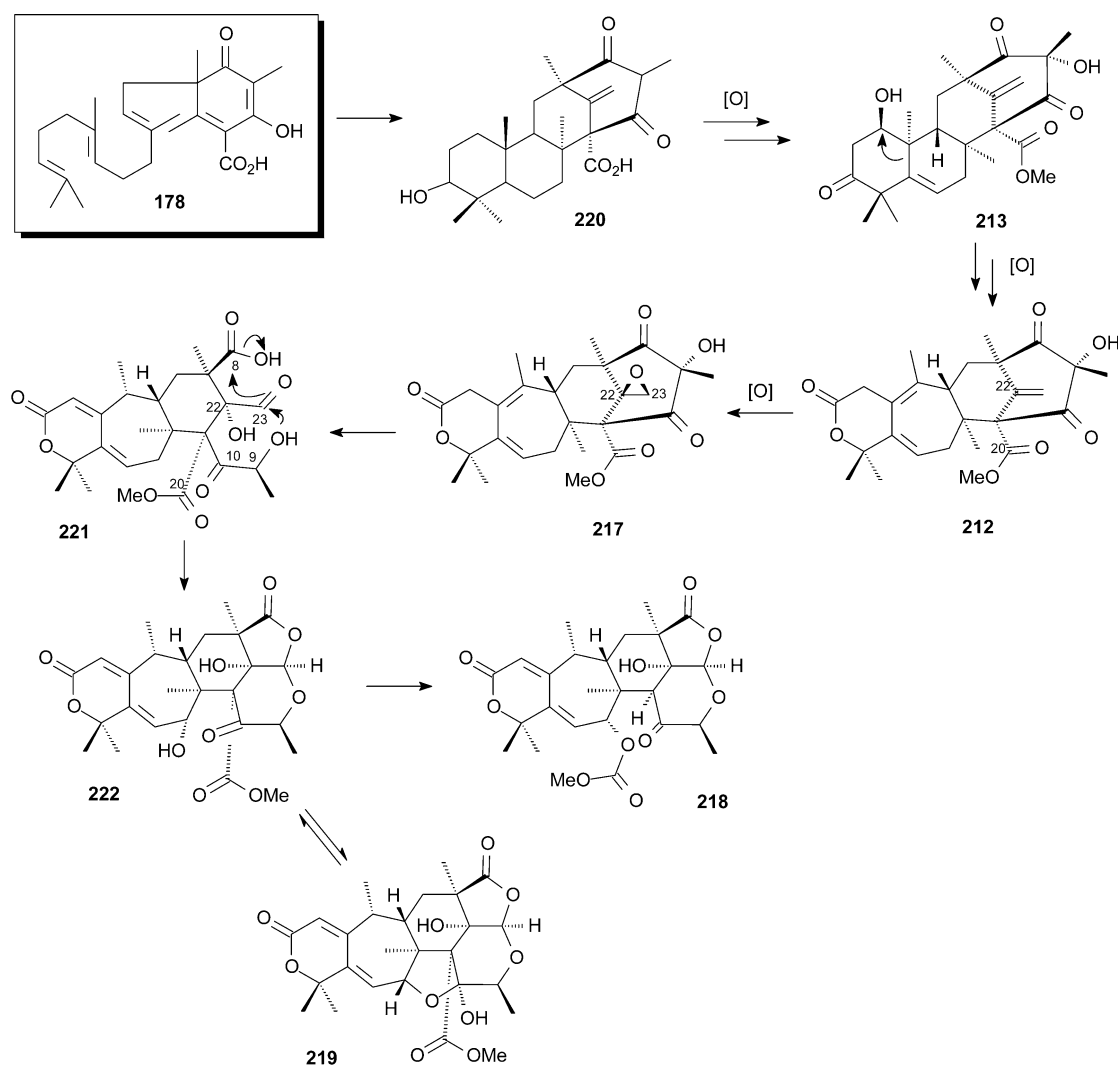
miniolulide A **218**, and miniolulide B **219**.<sup>110</sup> Their structures were determined by NMR spectroscopic analyses and X-ray crystallography.

The proposed biosynthetic pathway for this group of compounds is shown in Scheme 11. An epoxide-initiated cyclization of **178** generates a tetracyclic intermediate **220** (*cf.* **210**) from which oxidative transformations give rise to berkeleytrione **213**.<sup>110</sup> Berkeleydione **212** is supposed to be produced from **213** by a Baeyer–Villiger type oxidation of the A-ring ketone and

a subsequent 1,2-alkyl shift to form a cycloheptadiene B-ring. Epoxidation of the *exo*-methylene produces **217**, which is converted to **221** *via* retro-Claisen cleavage of C-8/C-9 and hydrolysis of the epoxide followed by oxidation of the resulting primary alcohol to an aldehyde. Acetal lactonization and introduction of a hydroxyl group at C-13 yields **222**, which forms another acetal between the 13-OH and the 10-ketone, affording miniolulide B **219**. Miniolulide A **218** results from migration of the methoxycarbonyl group (C-20) to the 9-OH on **222** by



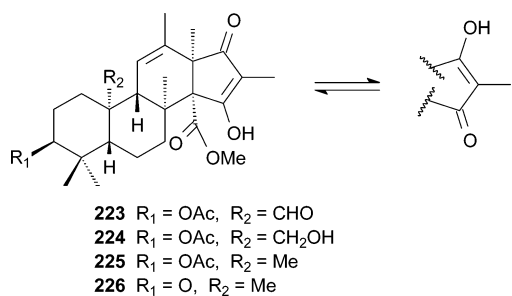




**Scheme 11** Proposed biosynthetic pathway of berkeleyones and related compounds.

intramolecular retro-Claisen condensation.<sup>110</sup> From this it can be proposed that **217** is the precursor for the berkelyacetals **214–216** and that the meroterpenoid **219** may be the precursor for paraherquinin **211**.

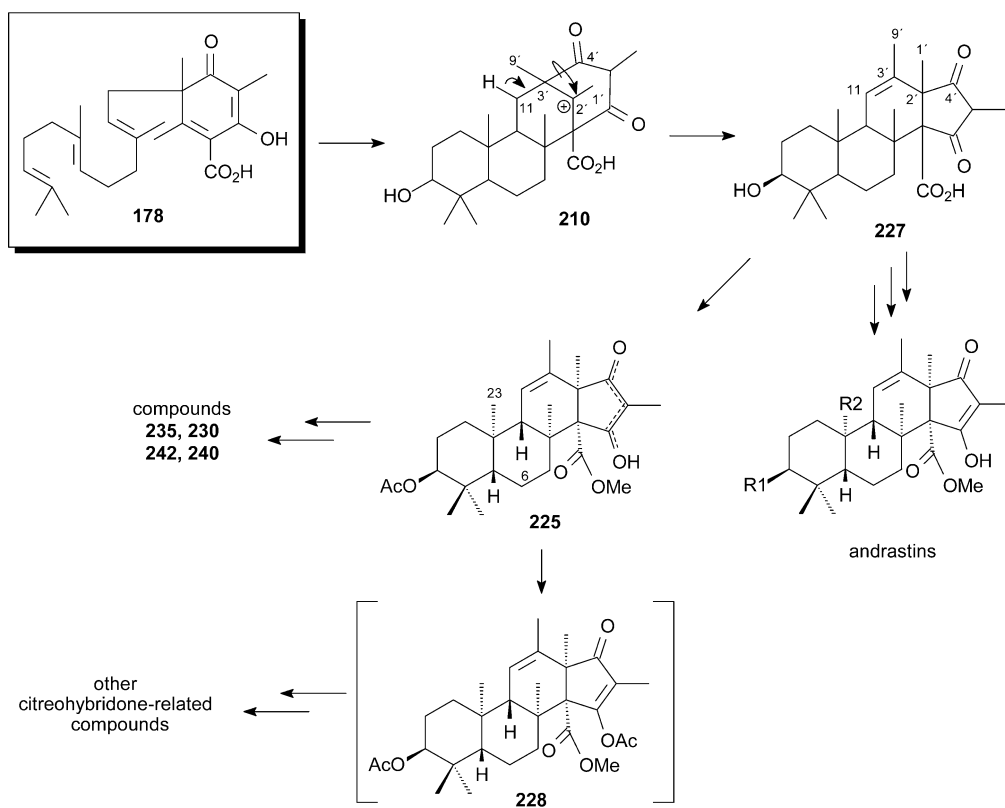
Four new protein farnesyltransferase inhibitors, andrastins A–D **223–226**, have been isolated from a cultured broth of *Penicillium* sp. Fo-3929.<sup>111,112</sup> The structure of **223** was elucidated by INADEQUATE, <sup>13</sup>C–<sup>13</sup>C coupling constants and X-ray crystallographic analysis, and its skeleton was shown to be based on



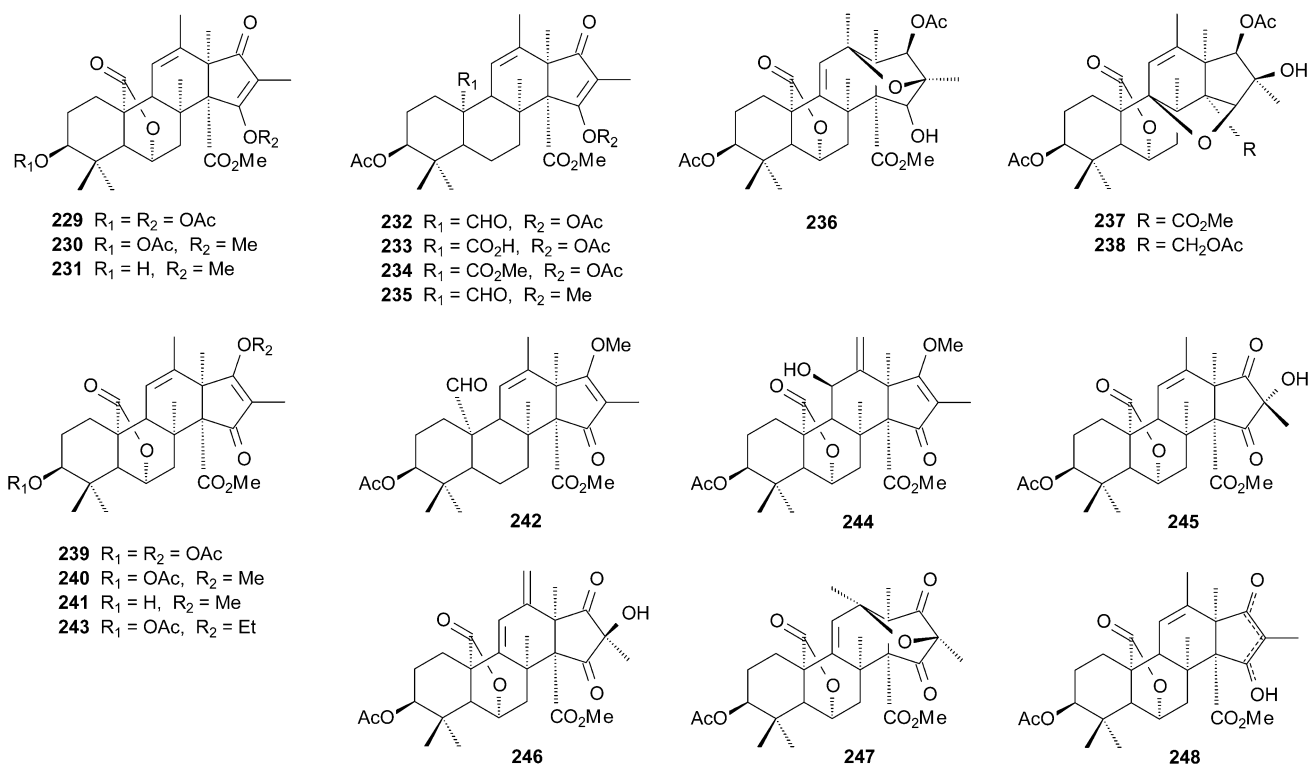
*ent*-5 $\alpha$ ,14 $\beta$ -androstane.<sup>113</sup> The structures of the other compounds were also elucidated by NMR.<sup>112,113</sup>

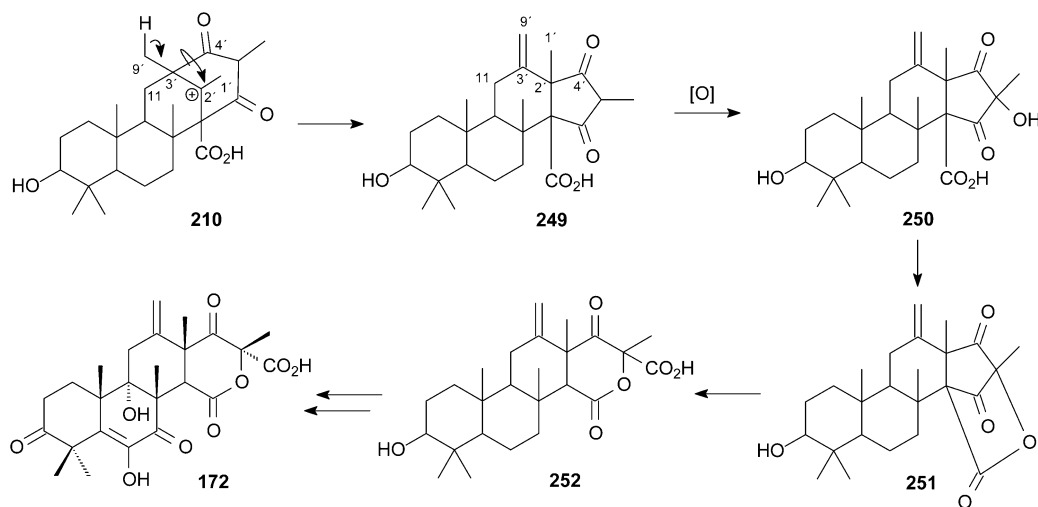
The results of incorporation studies suggested that these compounds share the same key austin intermediates **178** and **210**. As shown in Scheme 12, ring contraction of **210** with subsequent H-11 proton loss would produce the andrastin precursor **227** with an endocyclic double bond at C-11–C-3'.<sup>113</sup>

A number of metabolites, the citreohybridones, have been isolated from the mycelium of a hybrid strain KO 0031 derived from *Penicillium citreo-viride* B. IFO 6200 and 4692. After a combination of extensive spectroscopic data analysis, chemical evidence and absolute configuration determination, their structures were elucidated as citreohybridones A–G **229–235**,<sup>114,115</sup> J–L **236–238**,<sup>116</sup> isocitreohybridones A–C **239–241**,<sup>116,117</sup> G–I **242–244**,<sup>115,118</sup> citreohybridones A–C **245–247**<sup>117,119</sup> and citreohybridonol **248**.<sup>120</sup> Citreohybridonol **248** exists in an equilibrium between two different ring D tautomers. These have potent antifeedant activity against the diamond-back moth *Plutella xylostella*.<sup>118</sup>



Scheme 12 Proposed biosynthetic pathway for andrastins and citreohybridones.





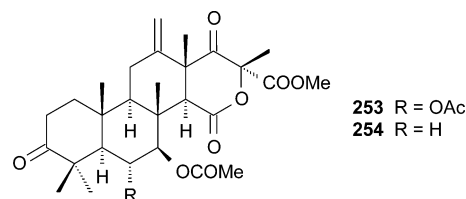
Scheme 13 Proposed biosynthetic pathway to terretonin **172**.

Incorporation of  $^{13}\text{C}$ -labelled acetate, formate and 3,5-dimethylorsellinate into citreohybridones confirmed that their biosynthesis proceeds *via* a mixed polyketide–terpenoid pathway.<sup>120,121</sup> Thus, andrastins must be precursors of citreohybridones, as shown in Scheme 12.<sup>115,118</sup>

Terretonin **172** was originally isolated in very low yields from a toxigenic strain of *Aspergillus terreus* (NRRL 6273) grown on a medium of shredded wheat in mycological broth supplemented with sucrose and yeast extract.<sup>122</sup> However, **172** could be more conveniently isolated from liquid cultures using a medium based on malt extract broth, and then complete assignments of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were made using a variety of 1D- and 2D-correlation methods.<sup>123</sup>

The biosynthetic pathway to **172** was first proposed by McIntyre *et al.*<sup>124</sup> with incorporation of labelled precursors suggesting the same key austin intermediate **210**. However, the degree of modification of the orsellinate moiety is even more drastic in **172**. Additional experiments with precursors doubly labelled with  $^{13}\text{C}$  and  $^{18}\text{O}$  allowed the biosynthetic proposal shown in Scheme 13.<sup>125</sup> The formation of the C/D rings involves an acyl shift with the loss of a proton to generate the required exocyclic double bond in **249**. Aerobic hydroxylation to **250**, intramolecular lactonization to **251** and retro-Claisen carbon–carbon bond cleavage would afford an intermediate carboxylic acid **252**. Oxidation to introduce the desired functionality in the A/B ring system and methylation of the free carboxylic acid by methionine would give **172**.<sup>125</sup>

Two additional compounds exhibiting a D-ring seco-meroterpenoid skeleton as in terretonin **172** were isolated from *Penicillium simplicissimum* and named penisimplicin A **253** and B **254**.<sup>126</sup> Their absolute structures were established by spectroscopic and chemical investigation. Their stereochemistries were confirmed by the exciton chirality method (through benzylation of a synthetic derivative of **253** with an excess of *p*-bromobenzoyl chloride to give the 6,7-di-*p*-bromobenzoate derivative), confirming, thus, the stereochemistries 6*R* and 7*R* for **253**.

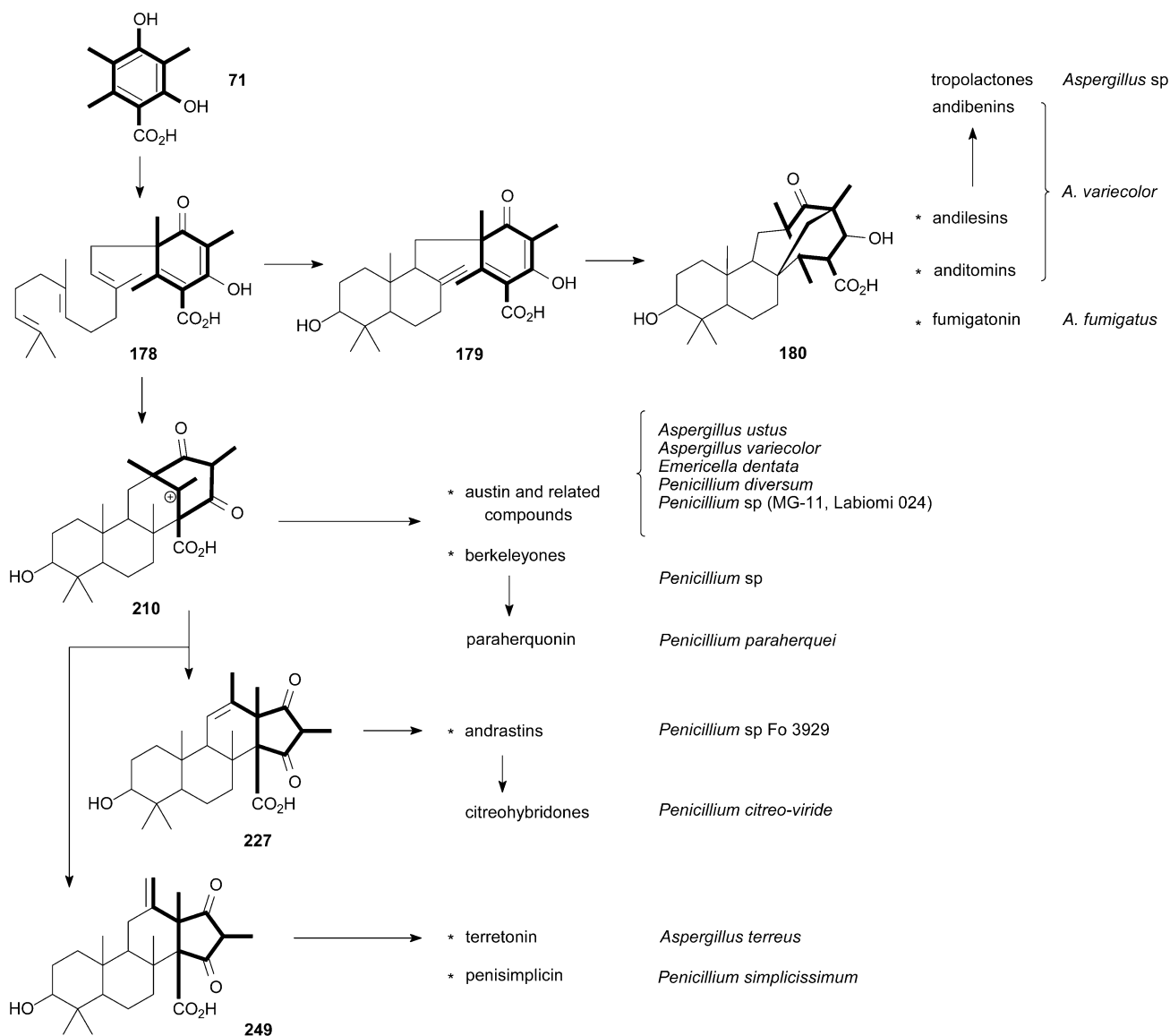


From the results discussed above it becomes clear that the 3,5-dimethylorsellinate-based meroterpenoid pathway can be seen to be relatively widespread in fungi. Moreover, meroterpenoids produced by *Aspergillus* and *Penicillium* that incorporate 3,5-dimethylorsellinate **71** seem to share the same key intermediate **178** to produce the large variety of compounds described here with obvious structural relationships. The likely biosynthetic relationships between these structurally varied metabolites were first proposed by Simpson<sup>127</sup> and updated to add the intermediate for andrastin, citreohybridone and terretonin biosynthesis.<sup>87</sup> Herein, this scheme has been extended to include the other intermediates involved in biosynthetic pathways of the additional meroterpenoids reported in the literature (Scheme 14).

#### 4.5 Derived from other tetraketides

During the course of a search for fruit rot phytotoxins produced by the fungus *Botryosphaeria berengeriana*, a causal agent of fruit rot of apple, a series of compounds designated as macrophorins A–G **255–261** were isolated.<sup>128–130</sup>

Apart from macrophorin F **260**, these meroterpenoids consist of a drimene sesquiterpene and a C-7-epoxycyclohexenone moiety, while **260** has a C-7-hydroxycyclohexenedione presumably derived as a result of rearrangement of the epoxide.<sup>130</sup> Antimicrobial and cytotoxic activity was observed for macrophorin A **255**,<sup>128–130</sup> **257** exhibited self-growth inhibiting activity,<sup>129</sup> and **259** was potently active against phytopathogenic fungi.<sup>130</sup>

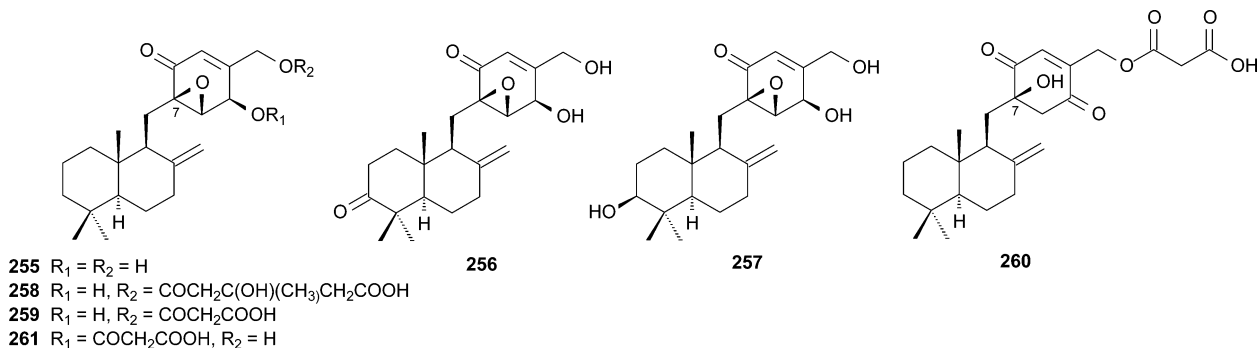


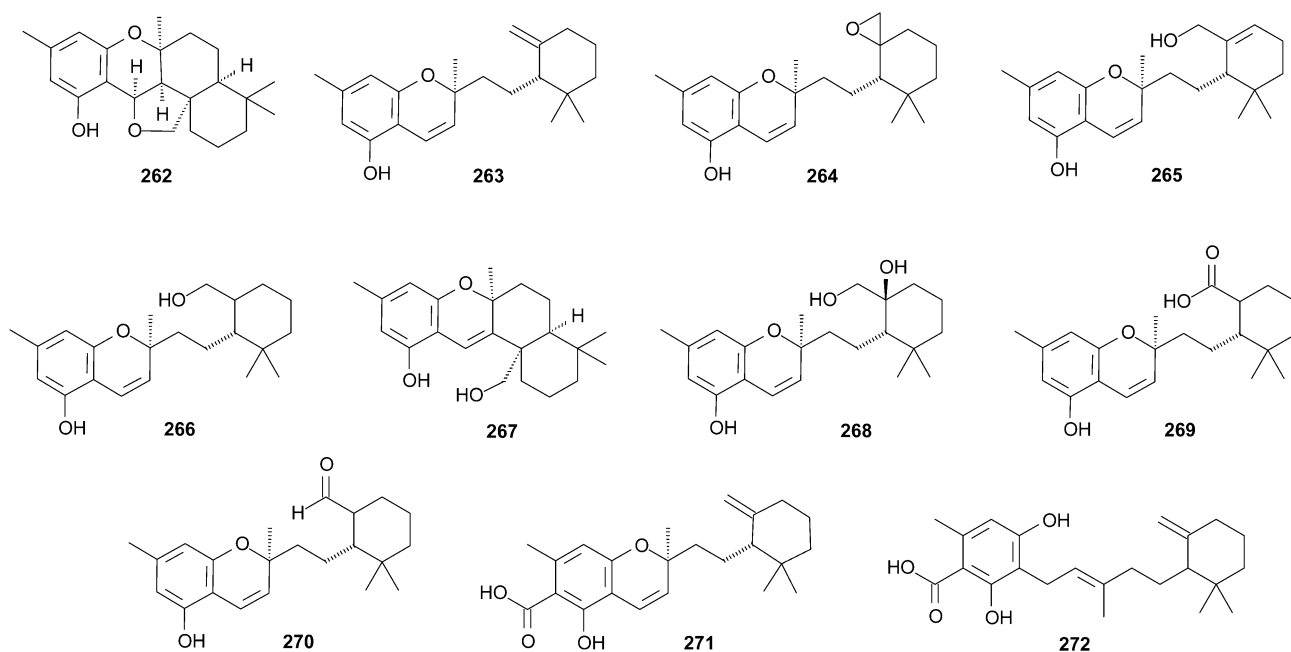
Scheme 14 The extended fungal meroterpenoid pathway.

A strain of *Helminthosporium siccans*, a parasitic organism of rye grass, gave the phenolic antibiotic siccantin **262**.<sup>131</sup> Its structure was determined by X-ray diffraction.<sup>132</sup> Subsequent work on the culture broth of this microorganism allowed the isolation of siccanchromenes A–H **263–270**,

siccanchromenic acid **271** and presiccanchromenic acid **272**, which were presumed to be possible biosynthetic intermediates of **262**.<sup>133–135</sup>

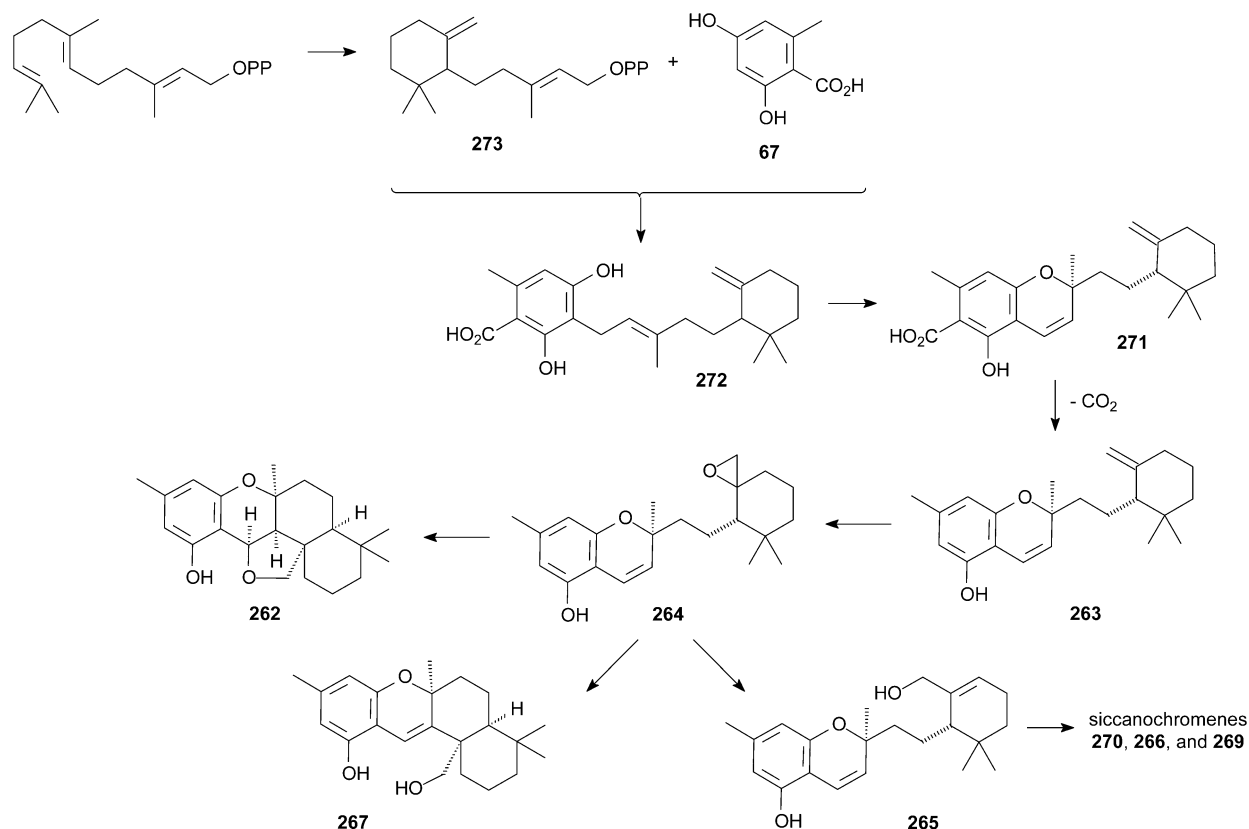
The biosynthetic pathway (Scheme 15) to **262** is based on experiments using cell-free systems and intact





cell systems of *H. siccanus*.<sup>136</sup> It involves (a) formation of *trans*- $\gamma$ -monocyclofarnesol **273** from farnesyl pyrophosphate; (b) coupling with orsellinic acid **67**; (c) oxidative conversion of the resulting presiccanchromenic acid **272** to **271**, followed by decarboxylation to siccanchromen A **263**, and (d) epoxy-olefin type cyclization of **264** to **262**. Presumably

**267** would be formed by loss of a proton from the same carbocation intermediate involved in formation of **262**, and the remaining metabolites would be formed by alternative rearrangements of the epoxide **264** to give the allylic alcohol **265** or the aldehyde **270** followed by reduction to **266** and oxidation to **269**.



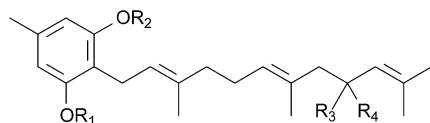
Scheme 15 Proposed biosynthetic pathway for siccandin **262**.

The lipophilic fraction of the acetone extract of fresh specimens of the mushroom *Albatrellus ovinus* collected in the neighbourhood of Zbiroh in Bohemia (Czechoslovakia) contained as the main components two closely related antibiologically active phenolic compounds, grifolin **274** and neogrifolin **275**.<sup>137</sup> The former had previously been isolated from the fungus *Grifola confluens*.<sup>138</sup> Monomethylgrifolin **276**, dimethylgrifolin **277** and dimethylneogrifolin **278** were also isolated as minor components of the acetone extract.<sup>137</sup>

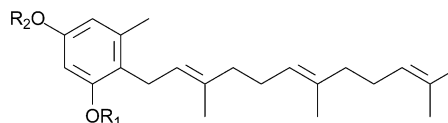
Chemical investigation of other *Albatrellus* species has resulted in a series of grifolin derivatives. Cristatic acid **279**, the first example of a grifolin containing a furan ring, was isolated from the fruiting bodies of *A. cristatus*.<sup>139</sup> Grifolic acid **280** was isolated from an American *Albatrellus* species.<sup>139</sup> In addition, gri-

folic acid methyl ester **281** and grifolinol **282** were isolated together with **277** and **283** from the methanol extract of the inedible mushroom *A. dispansus*.<sup>140</sup> The related fungus *Polyporus dispansus* produced the three farnesylphenols **283**, **284**, and **285**.<sup>141</sup>

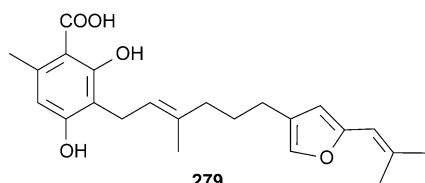
Grifolinone A **286** and the furanoid dimer grifolinone B **287** were isolated from the methanolic extract of *A. caeruleoporus* with **274** and **275**.<sup>142</sup> The pigments albatrelin **288** and 16-hydroxyalbatrelin **289**, responsible for the blue color of *A. flettii*, have been isolated and their structure elucidated by spectroscopic methods.<sup>143</sup> **288** is a dimeric meroterpenoid with a furylbenzoquinone chromophore. In addition, grifolinone C **290**, which displays an alternative mode of dimerisation through the aromatic moieties, was obtained from the fruiting bodies of



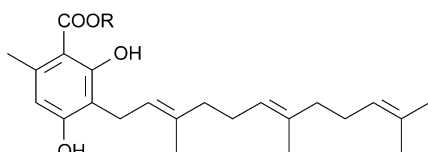
**274**  $R_1 = R_2 = R_3 = R_4 = H$   
**276**  $R_1 = H; R_2 = CH_3; R_3 = R_4 = H$   
**277**  $R_1 = R_2 = Me; R_3 = R_4 = H$



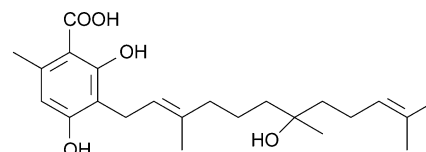
**275**  $R_1 = R_2 = H$   
**278**  $R_1 = R_2 = Me$



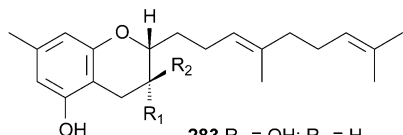
**279**



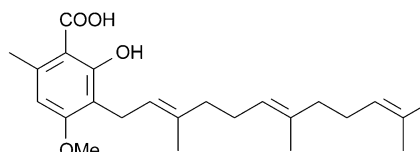
**280**  $R = H$   
**281**  $R = Me$



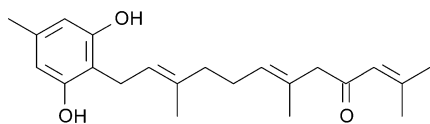
**282**



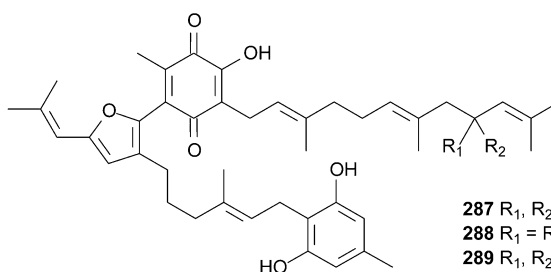
**283**  $R_1 = OH; R_2 = H$   
**284**  $R_1 = H; R_2 = OH$



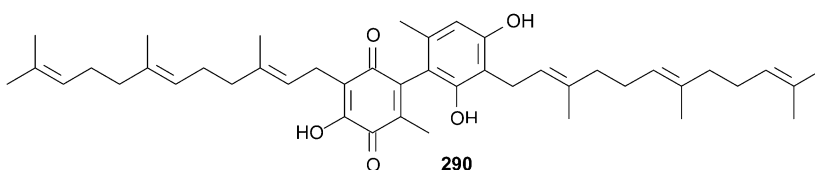
**285**



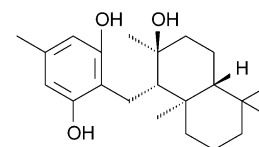
**286**



**287**  $R_1, R_2 = O$   
**288**  $R_1 = R_2 = H$   
**289**  $R_1, R_2 = OH$



**290**



**291**

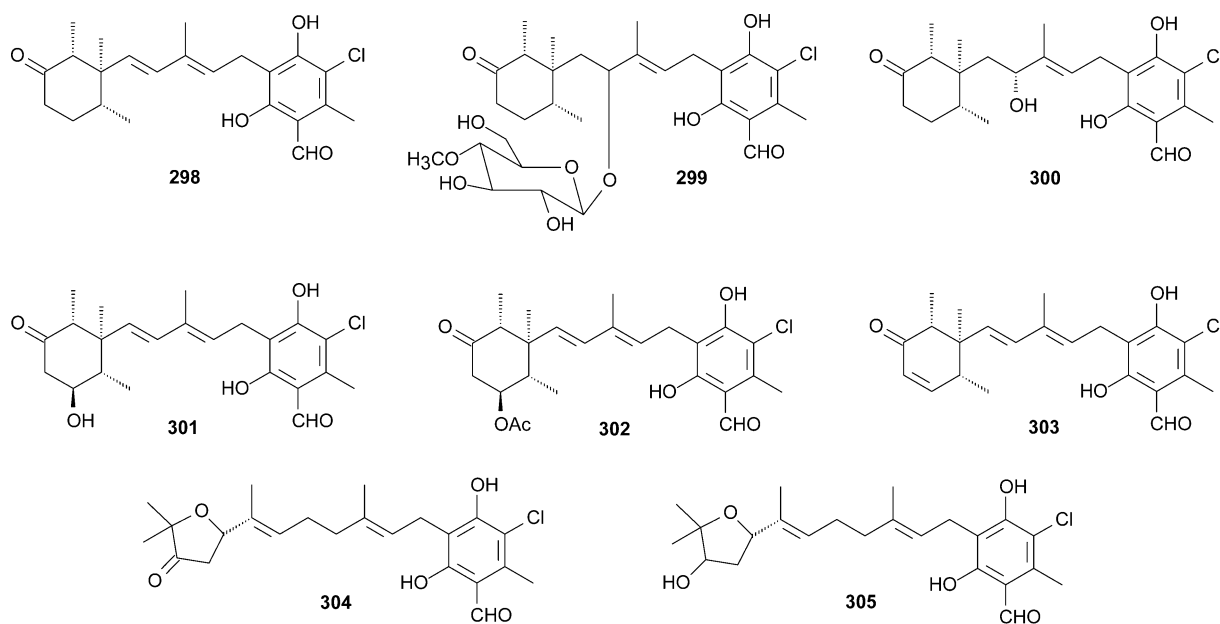
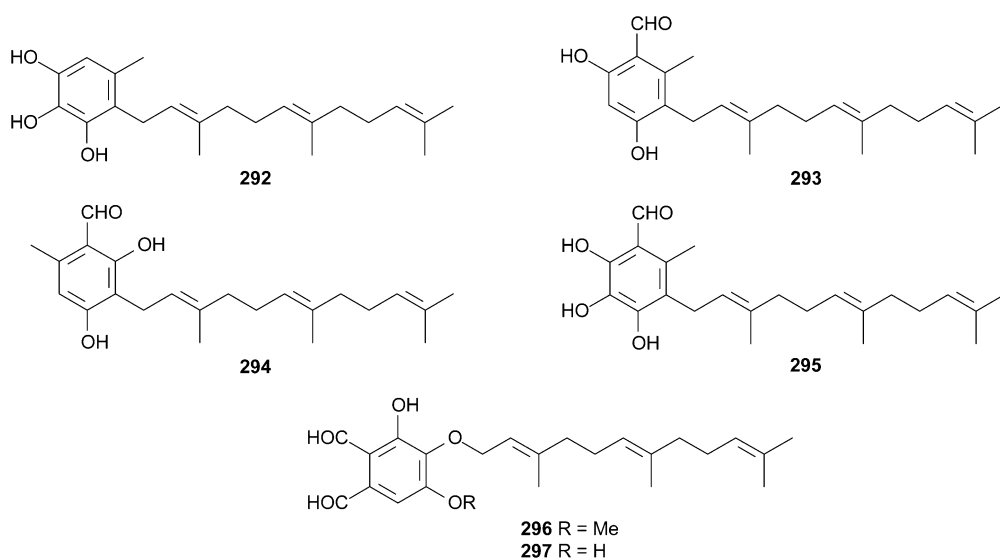
*A. confluens*, accompanied by **274**, **275**, **287**, and **288**.<sup>144</sup> In a further study of *A. confluens*, albaconol **291** was isolated along with grifolin **274**.<sup>145</sup>

The compounds **274** and **275** and their derivatives possess interesting biological activities: anti-oxidative activity,<sup>146</sup> anti-microbial activity,<sup>138–140</sup> plant growth inhibitory activity,<sup>147</sup> tyrosinase inhibitory activity,<sup>148</sup> control of anticholesteremic activity,<sup>149</sup> activity on human and rat vanilloid receptors,<sup>150</sup> and cytotoxic activity against Hep G2 human lung carcinoma cells.<sup>144</sup>

During a screening of the fungus *Albatrellus ovinus* for compounds interacting with mammalian CNS receptors, it was found that ethyl acetate extract displaces the binding of the dopamine D<sub>1</sub> receptor subfamily. The active compounds isolated by bioassay-guided fractionation of the crude extract and

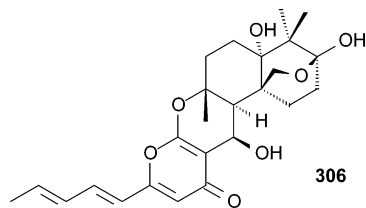
identified by spectroscopic techniques were ovinol **292**, ovinol **293**, ilicicolin B **294**, scutigeral **295**, in addition to **274** and **275**.<sup>151</sup> Asperugin A **296** and B **297** are farnesyloxy-phthalaldehyde metabolites of *Aspergillus rugulosus*.<sup>152,153</sup>

The antibiotic ascochlorin **298** was obtained as a terpenoid metabolite from *Acremonium luzulae*.<sup>154</sup> Recently, ascochlorin analogs were isolated from the insect-pathogenic fungus *Verticillium hemipterigenum* and were named vertihemipterin A **299**, 4',5'-dihydro-4'-hydroxyascochlorin **300**, 8'-hydroxyascochlorin **301**, LL-Z1272 **302**, 8',9'-dehydroascochlorin **303**, ascofuranone **304** and ascofuranol **305**.<sup>155</sup> With the exception of **300** and **305**, all the ascochlorin analogues exhibited significant antitumor and cytotoxic activities.<sup>155</sup> Compounds **298** and **303** also showed antiviral potency.



## 5 Meroterpenoids containing other polyketide-terpenoid moieties

UV-guided fractionation of an extract of *Penicillium hesseltinei*, isolated from the cheek pouch of a kangaroo rat (*Dipodomys spectabilis*), yielded hesseltin A **306**, a compound of mixed polyketide-terpenoid origin (pentaketide-farnesyl moiety).<sup>156</sup> This compound exhibited antiviral activity toward HSV-1.



The two yellow pigments cochlioquinones A **307** (also named as luteoleersin) and B **308**, produced in submerged culture by *Cochliobolus miyabeanus* (*Helminthosporium oryzae*), are derived from a hexaketide-farnesyl intermediate. Their structures were determined on the basis of IR, UV, NMR spectra and by chemical correlations.<sup>157,158</sup> The search for inhibitors of CCR5 led to the recent isolation of three active cochlioquinones from *Bipolaris brizae* (Nisikado) Shoem, namely 17-methoxycochlioquinone A **309**, isocochlioquinone A **310** and the known **307**.<sup>159</sup> In addition, two active *epi*-cochlioquinone compounds, 11-*O*-methyl-*epi*-cochlioquinone A **311** and *epi*-cochlioquinone A **312**, were isolated from *Stachybotrys chartarum*. These compounds were found to compete effectively with MIP-1 $\alpha$  for binding to human CCR5.<sup>159</sup> Moreover, **312** has also been isolated from the fermentation broth of *Stachybotrys bisbyi* SANK17777 and exhibited an acyl-CoA:cholesterol acyltransferase (ACAT) inhibitor activity.<sup>160</sup>

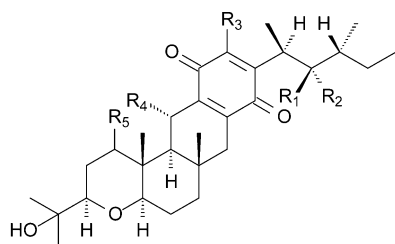
Another structurally related compound alboleersin (14,17-didehydro-14,17-dideoxo-14,17-dihydroxycochlioquinone A) **313**

was isolated in addition to **307**, from the plant pathogen fungus *Helminthosporium leersii*.<sup>161</sup>

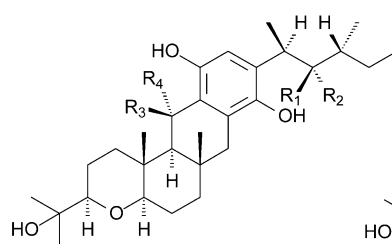
Ten phytotoxic compounds were obtained from a culture of *Bipolaris cynodonthis*, a leaf-blight-causing fungal pathogen of gramineous plants. The purified compounds were identified and named as cochlioquinones C **314**, D **315** and E **316**, isochlioquinone C **317**, cochlioquinols I **318**, II **319** and III **320**, in addition to the known cochlioquinones **307**, **308** and **310**.<sup>162</sup>

Stemphone **321**, a cytotoxic and antibacterial yellow pigment, is produced by *Stemphylium sarcinaeforme*.<sup>163</sup> Its structure was determined from chemical and spectral data and by X-ray crystallographic analysis.<sup>164</sup> Stemphones B **322** and C **323** were isolated along with **315** from the fermentation broth of *Aspergillus* sp. FKI-2136. Stemphone C showed potent imipenem activity against methicilin-resistant *Staphylococcus aureus* (MRSA).<sup>165</sup>

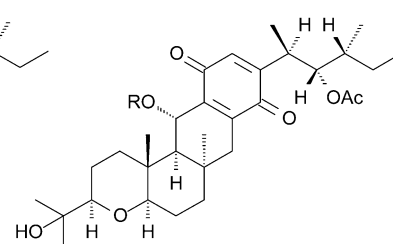
Previous studies have established the mixed biosynthesis of cochlioquinones **307** and **308**, through the introduction of a farnesyl unit onto an aromatic precursor whose secondary methyl groups are derived from methionine.<sup>166</sup> Experiments using <sup>18</sup>O<sub>2</sub> as isotopic tracer and mass spectrometry showed that the two oxygen atoms of the 2-(2-hydroxypropyl)tetrahydropyran system are derived from two different oxygen molecules at separate steps on the biosynthetic pathway, suggesting the intermediary of two epoxides (Scheme 16).<sup>167</sup> Further studies with <sup>13</sup>C- and <sup>14</sup>C-labelled compounds, <sup>18</sup>O<sub>2</sub>, <sup>13</sup>C NMR spectroscopy and mass spectrometry indicated a possible biosynthetic sequence, namely prenylation of an acetogenin-derived aromatic nucleus **324** leading to intermediate **325**, decarboxylation-hydroxylation to **326** and then cyclization of the farnesyl chain to cochlioquinone B **308** (Scheme 16).<sup>168</sup> Thus the three rings of the terpenoid moiety seem to be biosynthesized *via* a bis-epoxide **327**. It was proposed that opening of these epoxides is promoted by the cyclization process which starts from attack of the phenolic hydroxyl-group to lead to **327**.<sup>168</sup>



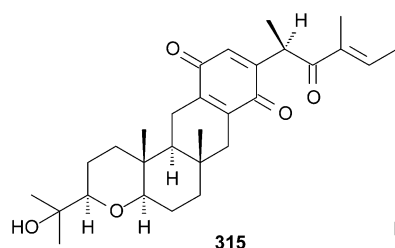
- 307** R<sub>1</sub> = H; R<sub>2</sub> = OAc; R<sub>3</sub> = H; R<sub>4</sub> = OH; R<sub>5</sub> = H  
**308** R<sub>1</sub> = R<sub>2</sub> = O; R<sub>3</sub> = R<sub>4</sub> = R<sub>5</sub> = H  
**309** R<sub>1</sub> = H; R<sub>2</sub> = OAc; R<sub>3</sub> = Me; R<sub>4</sub> = OH; R<sub>5</sub> = H  
**314** R<sub>1</sub> = R<sub>2</sub> = O; R<sub>3</sub> = H; R<sub>4</sub> = OH; R<sub>5</sub> = H  
**316** R<sub>1</sub> = R<sub>2</sub> = O; R<sub>3</sub> = R<sub>4</sub> = H; R<sub>5</sub> = OH



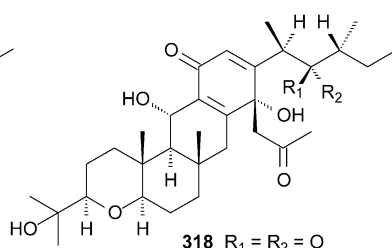
- 310** R<sub>1</sub> = H; R<sub>2</sub> = OAc; R<sub>3</sub> = R<sub>4</sub> = O  
**313** R<sub>1</sub> = H; R<sub>2</sub> = OAc; R<sub>3</sub> = H; R<sub>4</sub> = OH  
**317** R<sub>1</sub> = R<sub>2</sub> = O; R<sub>3</sub> = R<sub>4</sub> = O



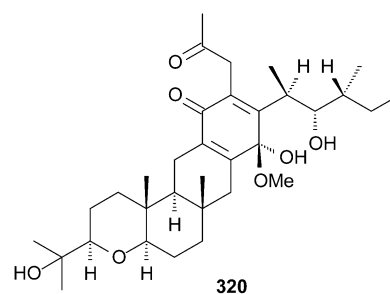
- 311** R = Me  
**312** R = H



315

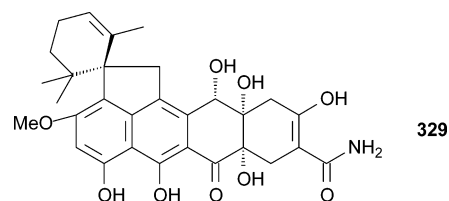
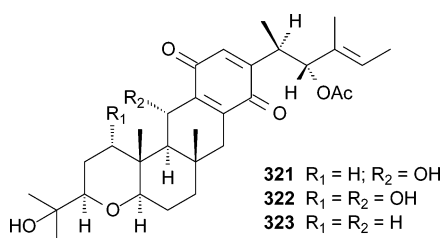


- 318** R<sub>1</sub> = R<sub>2</sub> = O  
**319** R<sub>1</sub> = H; R<sub>2</sub> = OH



320



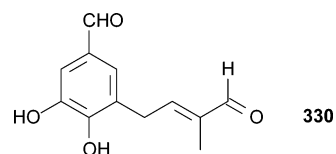


However, an alternative to the literature proposal (which is in line with cyclizations of triterpenes, which are carbocation-mediated and proceed in a step-wise sequence) would be as follows (Scheme 17). The process is initiated by protonation of the distal epoxide group in **327**, allow opening of this ring to generate a secondary carbocation (anti-Markovnikov), which is assisted by the other epoxide producing the preferred tertiary carbocation, suitably placed to allow electrophilic addition to a double bond, formation of a six-membered ring and production of a new tertiary carbocation (Markovnikov addition), which is finally quenched by the phenolic hydroxyl group.

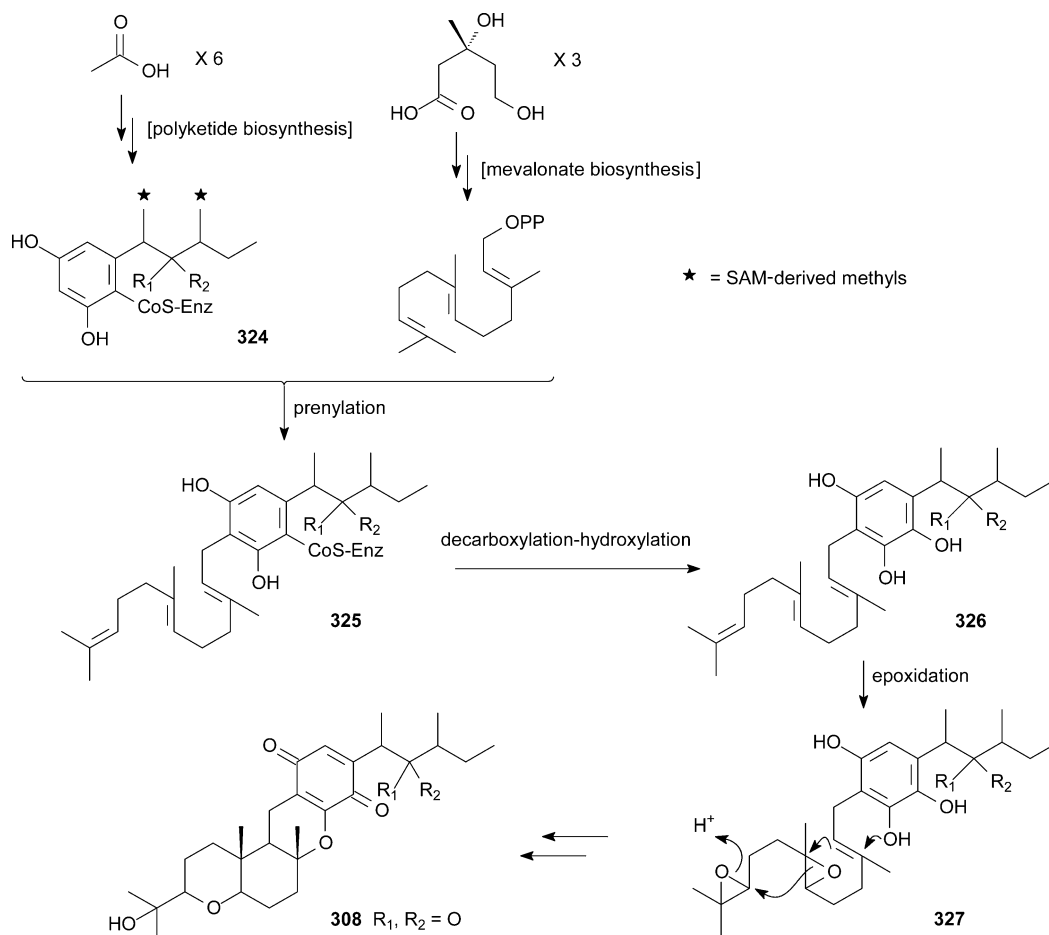
Viridicatumtoxin **329**, a mycotoxin from *Penicillium viridicatum*,<sup>169</sup> was shown to be formed by a mixed polyketide-terpenoid (nonaketide backbone) biosynthetic pathway through incorporation of labelled precursors.<sup>170</sup> The spirocyclic ring system in **329** is presumably derived from geranyl pyrophosphate.<sup>171</sup>

## 6 Meroterpenoids containing non-polyketide-terpenoid moieties

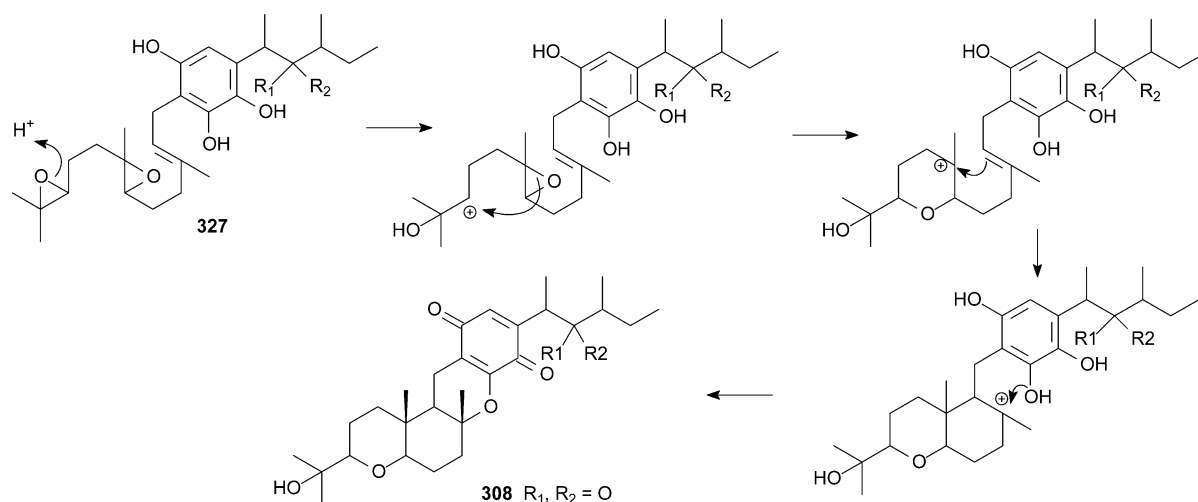
The meroterpenoid montadial A **330** has been isolated from the polypore *Bondarzewia montana*, a rare white-rot fungus that grows at the base of *Abies* trees and other conifers.<sup>172</sup> It exhibits cytotoxic effects against L1210 tumor cells (lymphocytic leukaemia of rice) and a weak phytotoxic effect against *Setaria italica*.



A group of structurally related 2,5-dihydroxy-1,4-benzoquinones with oligoprenyl side chains has been isolated from several



**Scheme 16** Possible biosynthetic sequence for cochlioquinones and derivatives (adapted from Canonica *et al.*<sup>166-168</sup>).



**Scheme 17** Alternative proposal to the literature biosynthetic sequence to the cochliquinones and derivatives.

basidiomycetes belonging to the order Boletales.<sup>173</sup> The pigment from *Chroogomphus helveticus* and *C. rutilus* was identified as helveticone (2,4-dihydroxy-3-farnesyl-1,4-benzoquinone) **331**,<sup>174</sup> also named boviquinone-3.<sup>174</sup> A related compound boviquinone-4 **332** was produced by *Boletus (Suillus) bovinus*.<sup>175</sup> A key step in the biosynthesis of the fungal meroterpenoids **331** and **332** is the prenylation of 3,4-dihydroxybenzoic acid **333**. Biosynthetic investigations allowed the proposal that in fruiting-bodies of *S. bovinus* **332** is formed by geranylgeranylation of **333** at C-2, whereas in *C. rutilus* the farnesyl side chain of **331** is introduced at C-5 (Scheme 18).<sup>173</sup>

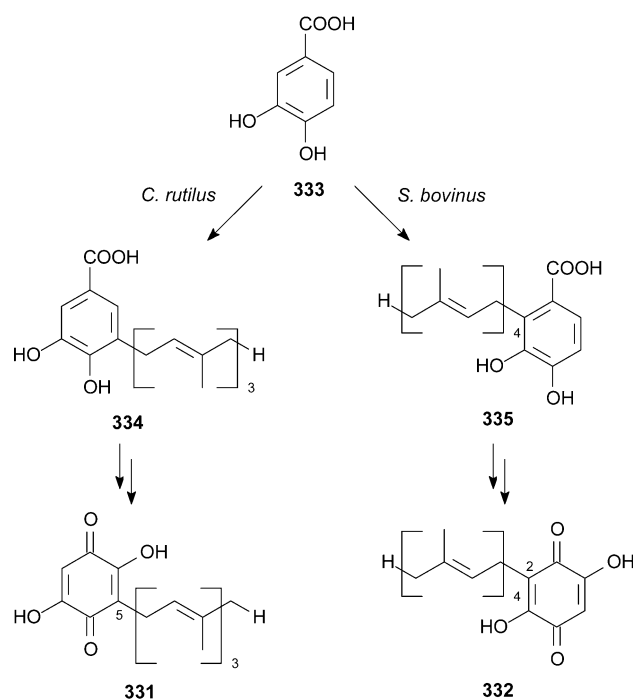
Tridentoquinone **336**, a red ansaquinone pigment, was isolated from the fruiting body of the fungus *Suillus tridentinus*.<sup>176</sup> Its structure, a [13](3,6)-benzofuranophane, was assigned from chemical evidence and X-ray crystal structure analysis. Bolegrevilol **337** was obtained from the edible mushroom *S. grevillei*.<sup>177</sup> This compound is a lipid peroxidation inhibitor. Studies on the structure and biosynthesis of **336** led to the isolation of tridentorubin **338** and deoxytridentoquinone **339**.<sup>178</sup>

Feeding experiments with [<sup>13</sup>C]-labeled 4-hydroxybenzoic acid **340** and 3,4-dihydroxybenzoic acid **333** proved the incorporation of these precursors into metabolites **336–338** during their biosynthesis in the fruiting bodies of *S. tridentinus* (Scheme 19). This excludes the possibility that boviquinone-4 **332** is a precursor of **336**.<sup>178</sup> The labelled carbonyl group in **336** corresponds to C-1 of 3,4-dihydroxybenzoic acid **333**, suggesting 6-(geranylgeranyl)benzene-1,2,4-triol **341** as possible intermediate. This triol could then either be acetylated to yield bole-grevilol **337** or oxidized to hydroxybenzoquinone **342**, the immediate precursor of deoxytridentoquinone **339**. The latter could be formed by oxidative cycloaddition of the hydroxyquinone moiety of **341** to the terminal double bond of the side chain, probably by a radical mechanism. Hydroxylation of ansaquinone **339** would then yield tridentoquinone **336**. The labelling pattern observed for tridentorubin **338** can be explained by addition of **342** to **336**.

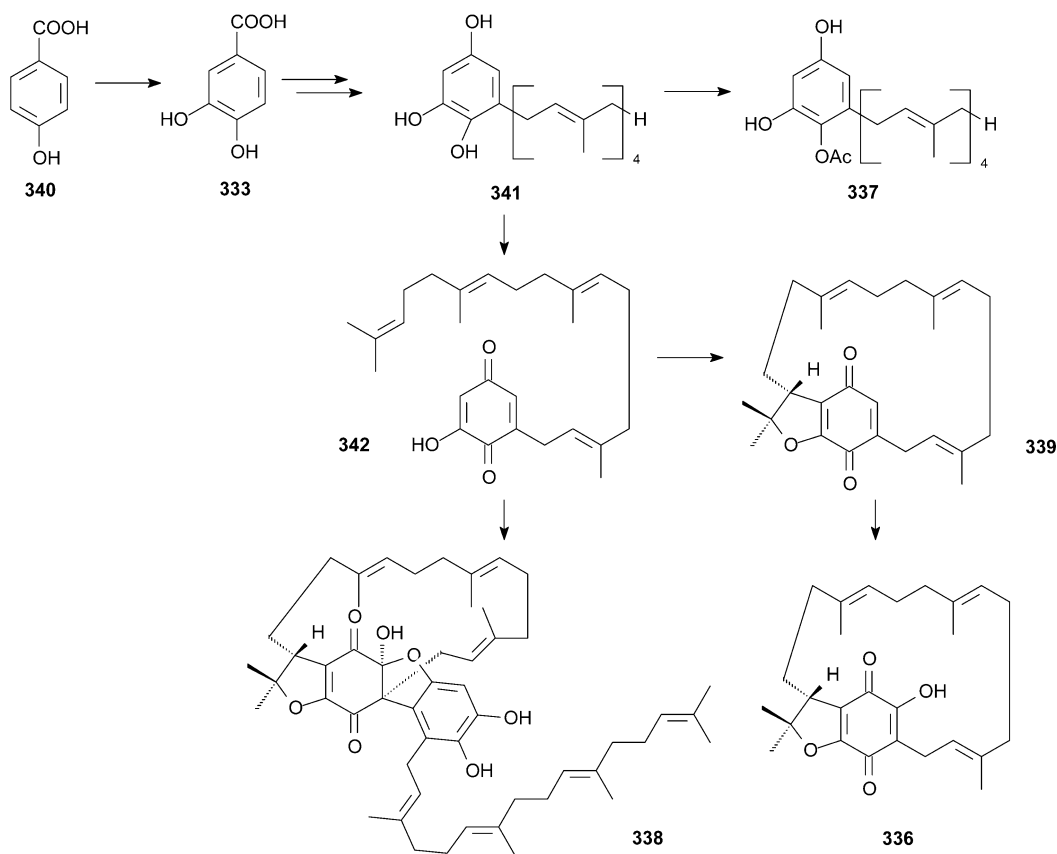
A number of terpenoid compounds named tricycloalternarenes (TCAs) were isolated from the culture of the phytopathogenic fungus *Alternaria alternata*, which originated from *Brassica sinensis*.<sup>179,180</sup> Their structures were elucidated by spectroscopic

methods, and were identified as TCAs 1a–8a **343–350**, 11a **351**, 1b–7b **352–358**, and 9b–11b **359–361**. These metabolites are closely related to the minor ACTG-toxins (*Alternaria citri* tangerine-toxins) which damage leaves of sensitive varieties of *Citrus reticulata*.<sup>180</sup> Moreover, these compounds are non-specific toxins.<sup>180</sup> Precursors of TCAs were also found in a methanol extract obtained from the lyophilized culture filtrate of *A. alternata*. They were named bicycloalternarenes (BCAs) 1–11 **362–372**.<sup>181</sup>

Incorporation of [2-<sup>13</sup>C]-mevalonate, [1-<sup>13</sup>C]-acetate and [1-<sup>13</sup>C]-glucose showed that BCAs are biosynthesized by the classic mevalonate pathway.<sup>182</sup> The polyketide pathway does not participate in the biosynthesis of BCAs because there is no



**Scheme 18** Proposed pathways for the biosynthesis of boviquinone-3 **334** and -4 **335**.



**Scheme 19** Proposed pathways for the biosynthesis of tridentoquinone **336** and related compounds.

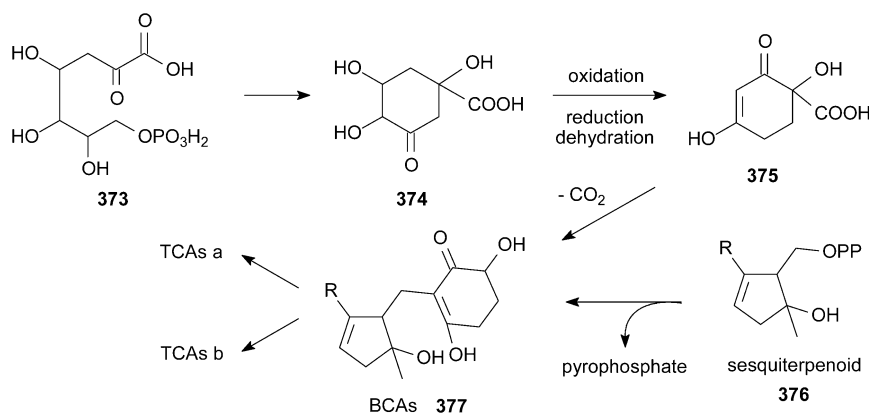
incorporation of [ $^{13}\text{C}$ ]-acetate into the C-ring of these compounds. The labelling pattern in this nonterpenoid part of BCAs after feeding with [ $1\text{-}^{13}\text{C}$ ]-glucose and [ $\text{U-}^{13}\text{C}_6$ ]-glucose, respectively, allows the assumption that metabolites of the shikimate pathways are involved.

A hypothetical pathway to the BCAs is summarized in Scheme 20.<sup>182</sup> Tetrose and phosphoenolpyruvate react in the first step of the shikimate pathway to 3-deoxy-D-arabino-heptulosonic acid 7-phosphate (DAHP) **373**, subsequently giving 3-dehydroquinic acid **374**, which after oxidation, reduction and dehydration processes gives the intermediate **375**. The next step involves the alkylation of precursor **375** by sesquiterpenoid **376**

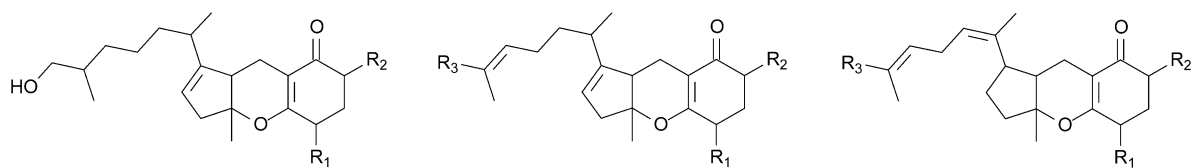
to give the intermediate **377**. Further modification leads to BCA and TCA compounds. The keto–enol tautomerism of the 1,3-diketone structure in the six-membered ring of BCAs allied to the free rotation of this ring leads to the different structures and labelling patterns observed in the hydroxycyclohexenone ring of the TCAs.<sup>182</sup>

## 7 Miscellaneous meroterpenoids

Screening of fungi as sources of bioactive metabolites has led to the discovery of natural products with insecticidal activities. Most of these are indole diterpenoids (despite them being



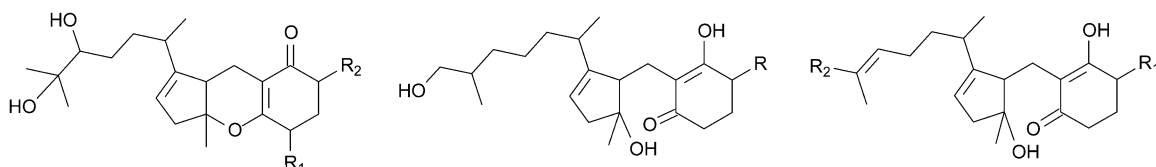
**Scheme 20** Hypothetical pathways to bicycloalternarenes (BCAs) and tricycloalternarenes (TCAs).



**343** R<sub>1</sub> = OH, R<sub>2</sub> = H  
**351** R<sub>1</sub> = OMe, R<sub>2</sub> = H  
**352** R<sub>1</sub> = H, R<sub>2</sub> = OH  
**361** R<sub>1</sub> = H, R<sub>2</sub> = OMe

**344** R<sub>1</sub> = OH, R<sub>2</sub> = H, R<sub>3</sub> = CH<sub>2</sub>OH  
**345** R<sub>1</sub> = OH, R<sub>2</sub> = H, R<sub>3</sub> = Me  
**346** R<sub>1</sub> = OMe, R<sub>2</sub> = H, R<sub>3</sub> = Me  
**353** R<sub>1</sub> = H, R<sub>2</sub> = OH, R<sub>3</sub> = CH<sub>2</sub>OH  
**354** R<sub>1</sub> = H, R<sub>2</sub> = OH, R<sub>3</sub> = Me  
**355** R<sub>1</sub> = H, R<sub>2</sub> = OMe, R<sub>3</sub> = Me  
**360** R<sub>1</sub> = H, R<sub>2</sub> = OMe, R<sub>3</sub> = CH<sub>2</sub>OH

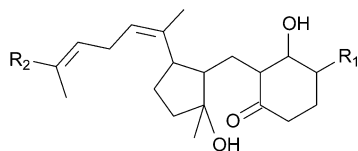
**347** R<sub>1</sub> = OMe, R<sub>2</sub> = H, R<sub>3</sub> = Me  
**350** R<sub>1</sub> = OH, R<sub>2</sub> = H, R<sub>3</sub> = CH<sub>2</sub>OH  
**356** R<sub>1</sub> = H, R<sub>2</sub> = OMe, R<sub>3</sub> = Me  
**359** R<sub>1</sub> = H, R<sub>2</sub> = OH, R<sub>3</sub> = Me



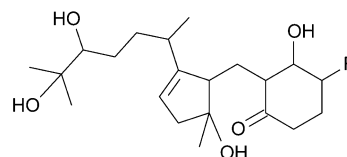
**348** R<sub>1</sub> = OH, R<sub>2</sub> = H  
**349** R<sub>1</sub> = OMe, R<sub>2</sub> = H  
**357** R<sub>1</sub> = H, R<sub>2</sub> = OH  
**358** R<sub>1</sub> = H, R<sub>2</sub> = OMe

**362** R = OH  
**372** R = OMe

**363** R<sub>1</sub> = OH, R<sub>2</sub> = CH<sub>2</sub>OH  
**364** R<sub>1</sub> = OH, R<sub>2</sub> = Me  
**365** R<sub>1</sub> = OMe, R<sub>2</sub> = Me  
**371** R<sub>1</sub> = OMe, R<sub>2</sub> = CH<sub>2</sub>OH



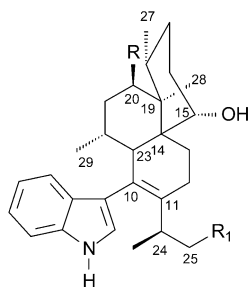
**366** R<sub>1</sub> = OMe, R<sub>2</sub> = Me  
**369** R<sub>1</sub> = OH, R<sub>2</sub> = CH<sub>2</sub>OH  
**370** R<sub>1</sub> = OH, R<sub>2</sub> = Me



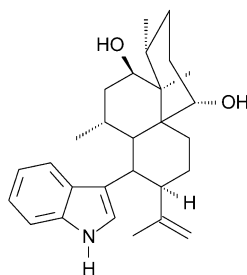
**367** R = OH  
**368** R = OMe

classified as such previously, they can also be regarded as having a terpenoid–nonpolyketide origin). Several isolates of *Aspergillus* spp. are known for their production of these compounds as major components of their sclerotia (key survival structures).

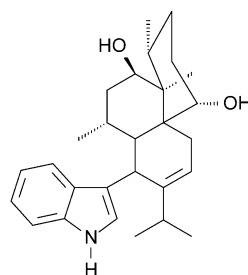
From the cultures of sclerotia of *A. flavus* were found aflavinine **378**,<sup>183</sup> 20,25-dihydroxyaflavinine **379**,<sup>184,185</sup> 2-hydroxyaflavinine **380**, 14-hydroxy-10,23-dihydro-24,25-dehydroaflavinine **381**, 10,11-dihydro-11,12-dehydro-20-hydroxyaflavinine **382**<sup>185</sup> and



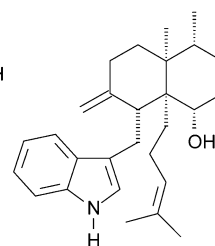
**378** R = R<sub>1</sub> = H  
**379** R = R<sub>1</sub> = OH  
**380** R = OH, R<sub>1</sub> = H



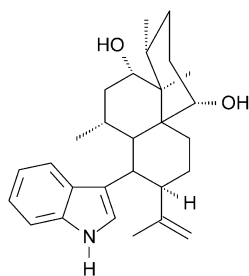
**381**



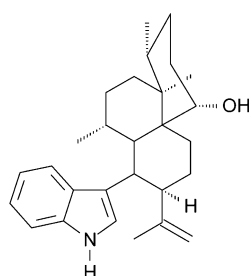
**382**



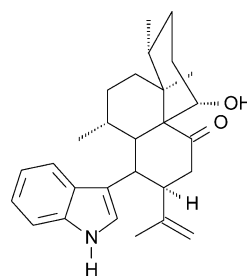
**383**



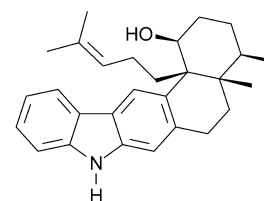
**384**



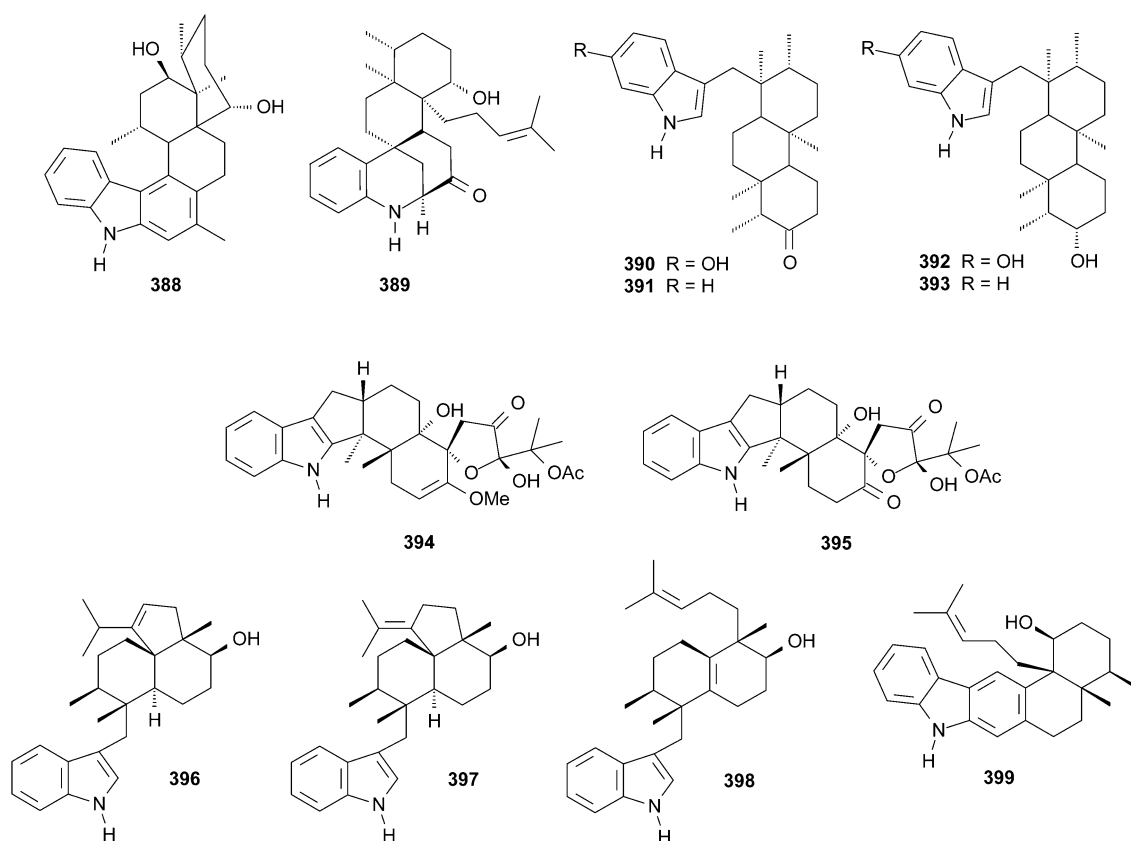
**385**



**386**



**387**



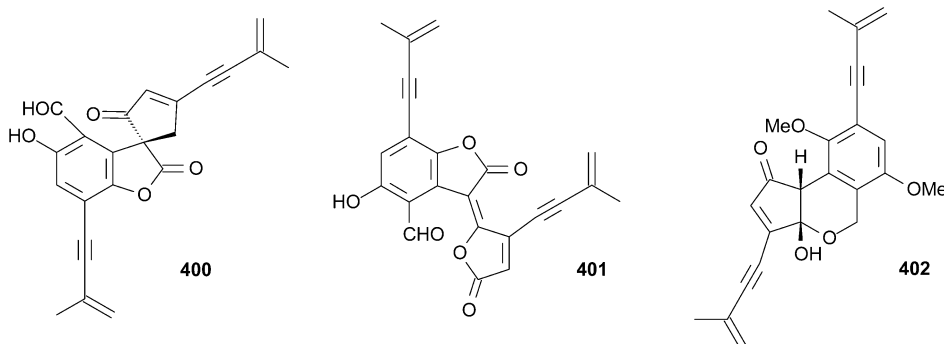
aflavazole **388**.<sup>186</sup> Nominine **383**<sup>187</sup> and aspernominine **389**<sup>188</sup> were found in cultures of *Aspergillus nomius*. The related aflavinins 14-*epi*-14-hydroxy-10,23-dihydro-24,25-dehydroaflavinine **384**, 10,23-dihydro-24,25-dehydroaflavinine **385**, 10,23-dihydro-24,25-dehydro-21-oxo-aflavinine **386**,<sup>189</sup> and **387**<sup>190</sup> were isolated from *Aspergillus tubingens*, while radarins A–D **390–393** were found in sclerotia of *Aspergillus sulfureus*.<sup>191</sup> In addition to their insecticide activities, compounds **389–393** also show cytotoxicity toward human solid tumor cell lines.<sup>188,191</sup>

A further five anti-insect indole diterpenoids, thiersinines A–B **394–395**<sup>192</sup> and thiersindoles A–C **396–398**,<sup>193</sup> were isolated from organic extracts of *Penicillium thiersii*. They are biosynthetically related to aflavinins. In addition, tubingensin A **399**, an antiviral and antiinsectan carbazole alkaloid biosynthetically related to the aflavinins was isolated from sclerotia of *Aspergillus tubingensis*.<sup>194</sup>

Finally, three chromogenic meroterpenoids, ochroleucin A1 **400**, A2 **401** and B **402**, were obtained from the mushrooms *Russula ochroleuca* and *R. viscida*.<sup>195</sup>

## 8 Conclusions

In this review, the structures of 333 fungal meroterpenoids have been reported, as well as the biosynthetic pathways which led to the production of the majority of these compounds. As discussed in each section, meroterpenoids show an enormous structural diversity, arising from successive modifications such as alkylation, condensation, oxidation and reduction. Despite of this, they can be classified according to their fundamental backbone as polyketide–terpenoid and non-polyketide–terpenoid. What is most notable is that most of the fungal meroterpenoids described here (81%) are polyketide-derived, as shown in Fig. 2. Moreover,



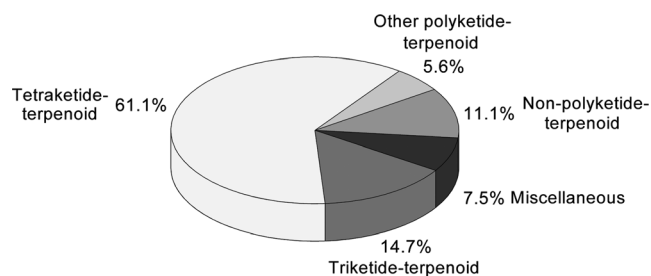


Fig. 2 Distribution of fungal meroterpenoids into categories according to their fundamental backbone.

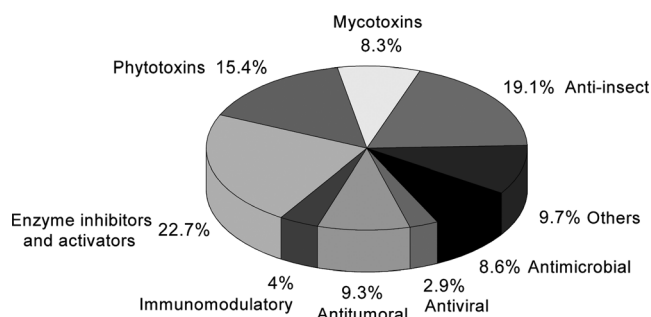


Fig. 3 Distribution of biological activities of fungal meroterpenoids.

within this group the tetraketide-terpenoid class is predominant, and comprises about 61% of all meroterpenoids.

A second point discussed in this review is the wide range of biological activities described for these compounds. Fig. 3 shows the distribution of biological activities of these compounds, grouped into nine main areas: antimicrobial (including antibacterial and antifungal), antiviral, antitumoral, immunomodulatory (and immunosuppressant), enzyme inhibitors and activators, phytotoxins (and agrochemicals), mycotoxins, anti-insect (including antifeeding and larvicidal) and others (receptors, nerve growth factor, and plasminogen activation).

The data reported here support the current views on searching for new therapeutics through biological screening programmes. The ability of microorganisms to produce natural products with diverse structures and biological properties should prompt us to further explore their extracts.

## 9 Acknowledgements

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## 10 References

- 1 J. W. Cornforth, *Chem. Br.*, 1968, **4**, 102.
- 2 *IUPAC Compendium of Chemical Terminology*, 2nd edn, 1997.
- 3 R. Croteau, T. N. Kutchan and N. G. Lewis, in *Biochemistry & Molecular Biology of Plants*, ed. B. Buchanan, W. Gruissem and R. Jones, American Society of Plant Physiologists, 2000, p. 1250.
- 4 L. Ge, J. W. H. Yong, S. N. Tan, X. H. Yang and E.S.O., *J. Chromatogr., A*, 2004, **1048**, 119.
- 5 G. Sabitha, R. Swapna, R. Satheesh Babu and J. S. Yadav, *Tetrahedron Lett.*, 2005, **46**, 6145.

- 6 G. Brader, M. Bacher, O. Hofer and H. Greger, *Phytochemistry*, 1997, **45**, 1207.
- 7 C. H. Ashton, *Br. J. Psychiatry*, 2001, **178**, 101.
- 8 C. N. Backhouse, C. L. Delporte, R. E. Negrete, S. Erazo, A. Zuniga, A. Pinto and B. K. Cassels, *J. Ethnopharmacol.*, 2001, **78**, 27.
- 9 B. Sontag, N. Arnold, W. Steglich and T. Anke, *J. Nat. Prod.*, 1999, **62**, 1425.
- 10 A. J. Birch, *Science*, 1967, **156**, 202.
- 11 T. J. Simpson, *Chem. Ind.*, 1995, 407.
- 12 D. O'Hagan, *Nat. Prod. Rep.*, 1995, **12**, 1.
- 13 T. J. Simpson, *Top. Curr. Chem.*, 1998, **195**, 1.
- 14 J. Staunton and K. J. Weissman, *Nat. Prod. Rep.*, 2001, **18**, 380.
- 15 R. J. Cox, *Org. Biomol. Chem.*, 2007, **5**, 2010.
- 16 F. A. Macias, R. M. Varela, A. M. Simonet, H. G. Cutler, S. J. Cutler, S. A. Ross, D. C. Dunbar, F. M. Dugan and R. A. Hill, *Tetrahedron Lett.*, 2000, **41**, 2683.
- 17 F. A. Macias, R. M. Varela, A. M. Simonet, H. G. Cutler, S. J. Cutler, F. M. Dugan and R. A. Hill, *J. Org. Chem.*, 2000, **65**, 9039.
- 18 T. Sassa, H. Sato and H. Kajijura, *Tetrahedron Lett.*, 1986, **27**, 2121.
- 19 K. H. Ling, C.-K. Yang and F.-T. Peng, *Appl. Environ. Microbiol.*, 1979, **37**, 355.
- 20 K. H. Ling, H. H. Liou, C.-H. Yang and C.-K. Yang, *Appl. Environ. Microbiol.*, 1984, **47**, 98.
- 21 F.-C. Peng, *J. Nat. Prod.*, 1997, **60**, 842.
- 22 S.-S. Lee, *J. Nat. Prod.*, 1992, **55**, 251.
- 23 S. Omura, F. Kuno, K. Otoguro, T. Sunazuka, K. Shiomi, R. Masuma and Y. Iwai, *J. Antibiot.*, 1995, **48**, 745.
- 24 F. Kuno, K. Otoguro, K. Shiomi, Y. Iwai and S. Omura, *J. Antibiot.*, 1996, **49**, 742.
- 25 F. Kuno, K. Shiomi, K. Otoguro, T. Sunazuka and S. Omura, *J. Antibiot.*, 1996, **49**, 748.
- 26 K. Otoguro, K. Shiomi, Y. Yamaguchi, N. Arai, T. Sunazuka, R. Masuma, Y. Iwai and S. Omura, *J. Antibiot.*, 2000, **53**, 50.
- 27 M. Handa, T. Sunazuka, K. Nagai, R. Kimura, K. Otoguro, Y. Harigaya and S. Omura, *J. Antibiot.*, 2001, **54**, 386.
- 28 T. Sunazuka, M. Handa, K. Nagai, T. Shirahata, Y. Harigaya, K. Otoguro, I. Kuwajima and S. Omura, *Tetrahedron*, 2004, **60**, 7845.
- 29 W.-G. Kim, K.-M. Cho, C.-K. Lee and I.-D. Yoo, *Tetrahedron Lett.*, 2002, **43**, 3197.
- 30 W.-G. Kim, K.-M. Cho, C.-K. Lee and I.-D. Yoo, *J. Antibiot.*, 2003, **56**, 351.
- 31 K.-M. Cho, W.-G. Kim, C.-K. Lee and I.-D. Yoo, *J. Antibiot.*, 2003, **56**, 344.
- 32 I.-D. Yoo, K.-M. Cho, C.-K. Lee and W.-G. Kim, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 353.
- 33 S. Omura, H. Tomoda, Y. K. Kim and H. Nishida, *J. Antibiot.*, 1993, **46**, 1168.
- 34 H. Tomoda, Y. K. Kim, H. Nishida, R. Masuma and S. Omura, *J. Antibiot.*, 1994, **47**, 148.
- 35 Y. K. Kim, H. Tomoda, H. Nishida, T. Sunazuka, R. Obata and S. Omura, *J. Antibiot.*, 1994, **47**, 154.
- 36 H. Tomoda, H. Nishida, Y. K. Kim, R. Obata, T. Sunazuka, S. Omura, J. Bordner, M. Guadliana, G. Dormer and A. B. Smith, *J. Am. Chem. Soc.*, 1994, **116**, 12097.
- 37 H. Tomoda, N. Tabata, D.-J. Yang, H. Takayanagi, H. Nishida and S. Omura, *J. Antibiot.*, 1995, **48**, 495.
- 38 H. Tomoda, N. Tabata, D.-J. Yang, I. Namatame, H. Tanaka and S. Omura, *J. Antibiot.*, 1996, **49**, 292.
- 39 H. Tomoda, N. Tabata, Y. Nakata, H. Nishida, T. Kaneko, R. Obata, T. Sunazuka and S. Omura, *J. Org. Chem.*, 1996, **61**, 882.
- 40 R. Ubillas, C. L. Barnes, H. Gracz, G. E. Rottinghaus and M. S. Tempesta, *J. Chem. Soc., Chem. Commun.*, 1989, 1618.
- 41 Y. Zhang, C. Li, D. C. Swenson, J. B. Gloer, D. T. Wicklow and P. F. Dowd, *Org. Lett.*, 2003, **5**, 773.
- 42 C. Li, J. B. Gloer, D. T. Wicklow and P. F. Dowd, *J. Nat. Prod.*, 2005, **68**, 319.
- 43 W. B. Turner, *Fungal Metabolites*, Academic Press, London, 1971, vol. 1, pp. 74 and 213.
- 44 B. B. Jarvis, J. Salemme and A. Moraes, *Nat. Toxins*, 1995, **3**, 10.
- 45 R. Kaneto, K. Dobashi, I. Kojima, K. Sakai, N. Shibamoto, T. Yoshioka, H. Nishida, R. Okamoto, H. Akagawa and S. Mizuno, *J. Antibiot.*, 1994, **47**, 727.

- 46 B. E. Roggo, P. Hug, S. Moss, A. Stampfli, H. P. Kriemler and H. H. Peter, *J. Antibiot.*, 1996, **49**, 374.
- 47 H. Kaise, M. Shinohara, W. Miyazaki, T. Izawas, Y. Nakano, M. Sugawara and K. Sugiura, *J. Chem. Soc., Chem. Commun.*, 1979, 726.
- 48 B. B. Jarvis, *Phytochemistry*, 2003, **64**, 53.
- 49 W. A. Ayer and S. Miao, *Can. J. Chem.*, 1993, **71**, 487.
- 50 K. Sakai, K. Watanabe, K. Masuda, M. Tsuji, K. Hasumi and A. Endo, *J. Antibiot.*, 1995, **48**, 447.
- 51 S. B. Singh, D. L. Zink, M. Williams, J. D. Polishook, M. Sanchez, K. C. Silverman and R. B. Lingham, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2071.
- 52 K. Minagawa, S. Kouzuki, J. Yoshimoto, Y. Kawamura, H. Tani, T. Iwata, Y. Terui, H. Nakai, S. Yagi, N. Hattori, T. Fujiwara and T. Kamigauchi, *J. Antibiot.*, 2002, **55**, 155.
- 53 K. Minagawa and S. Kouzuki, *J. Antibiot.*, 2002, **55**, 239.
- 54 K. Minagawa, S. Kouzuki, H. Tani, K. Ishii, T. Tanimoto, Y. Terui and T. Kamigauchi, *J. Antibiot.*, 2002, **55**, 239.
- 55 S. Stefaneli, F. Sponga, P. Ferrari, C. Sottani, E. Corti, C. Brunati and K. Islam, *J. Antibiot.*, 1996, **49**, 611.
- 56 S. F. Hinkley, J. C. Fettinger, K. Dudley and B. B. Jarvis, *J. Antibiot.*, 1999, **52**, 988.
- 57 X. Xu, F. S. de Guzman, J. B. Gloer and C. A. Shearer, *J. Org. Chem.*, 1992, **57**, 6700.
- 58 Y. Nozawa, M. Ito, K. Sugawara, K. Hanada and K. Mizoue, *J. Antibiot.*, 1997, **50**, 641.
- 59 H. Kawagish, M. Ando and T. Mizuno, *Tetrahedron*, 1990, **31**, 373.
- 60 H. Kawagish, M. Ando, H. Sakamoto, S. Yoshida, F. Ojima, Y. Ishiguro, N. Ukai and S. Furukawa, *Tetrahedron Lett.*, 1991, **32**, 4561.
- 61 H. Kawagish, M. Ando, K. Shinba, H. Sakamoto, S. Yoshida, F. Ojima, Y. Ishiguro, N. Ukai and S. Furukawa, *Phytochemistry*, 1992, **32**, 175.
- 62 Y. Yaoita, K. Danbara and M. Kikuchi, *Chem. Pharm. Bull.*, 2005, **53**, 1202.
- 63 C. Shinohara, K. Hasumi, W. Hatsumi and A. Endo, *J. Antibiot.*, 1996, **49**, 961.
- 64 K. Hasumi, S. Ohyama, T. Kohyama, Y. Ohsaki, R. Takayasu and A. Endo, *J. Antibiot.*, 1998, **51**, 1059.
- 65 W. Hu, S. Ohyama and K. Hasumi, *J. Antibiot.*, 2000, **53**, 241.
- 66 W. Hu, Y. Kitano and K. Hasumi, *J. Antibiot.*, 2003, **56**, 832.
- 67 D. M. Roll, J. K. Manning and G. T. Carter, *J. Antibiot.*, 1998, **51**, 635.
- 68 A. M. Ainsworth, M. I. Chicarelli-robinson, B. R. Copp, U. Fauth, P. J. Hylands, J. A. Holloway, M. Latif, G. B. Obeirne, N. Porter, D. V. Renno, M. Richards and N. Robinson, *J. Antibiot.*, 1995, **48**, 568.
- 69 M. E. Raggatt, T. J. Simpson and M. I. Chicarelli-Robinson, *Chem. Commun.*, 1997, 2245.
- 70 A. M. Bailey, R. J. Cox, K. Harley, C. M. Lazarus, T. J. Simpson and E. Skellam, *Chem. Commun.*, 2007, 4053.
- 71 G. H. Harris, K. Hoogsteen, K. C. Silverman, S. L. Raghoobar, G. F. Bills, R. B. Lingham, J. L. Smith, H. W. Dougherty, C. Cascales and F. Pelaez, *Tetrahedron*, 1993, **49**, 2139.
- 72 F. Mayerl, Q. Gao, S. Huang, S. E. Klohr, J. A. Matson, D. R. Gustavson, R. L. Berry, C. Fairchild and W. C. Rose, *J. Antibiot.*, 1993, **46**, 1082.
- 73 P. Cai, D. Smith, B. Cunningham, S. Brown-Shimer, B. Katz, C. Pearce, D. Venables and D. Houck, *J. Nat. Prod.*, 1998, **61**, 791.
- 74 S. Ayers, D. L. Zink, J. S. Powell, C. M. Brown, A. Grund, G. F. Bills, G. Platas, D. Thompson and S. B. Singh, *J. Nat. Prod.*, 2008, **71**, 457.
- 75 P. W. Clutterbuck, W. Percival, A. E. Oxford, H. Raistrick and G. Smith, *Biochem. J.*, 1932, **26**, 1441.
- 76 L. Canonica, W. Kroszczyński, B. M. Ranzi, B. Rindone, E. Santaniello and C. Scolastico, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2639.
- 77 W. L. Muth and C. H. Nash III, *Antimicrob. Agents Chemother.*, 1975, **8**, 321.
- 78 L. Colombo, C. Gennari, D. Potenza, C. Scolastico and F. Aragozzini, *J. Chem. Soc., Chem. Commun.*, 1979, 1021.
- 79 L. Colombo, C. Gennari, D. Potenza, C. Scolastico, F. Aragozzini and R. Gualandris, *J. Chem. Soc., Perkin Trans. 1*, 1982, 365.
- 80 R. M. Horak, P. S. Steyn, R. Vleggaar and C. J. Rabie, *J. Chem. Soc., Chem. Commun.*, 1981, 1265.
- 81 R. M. Horak, P. S. Steyn, R. Vleggaar and C. J. Rabie, *J. Chem. Soc., Perkin Trans. 1*, 1985, 345.
- 82 R. M. Horak, P. S. Steyn, R. Vleggaar and C. J. Rabie, *J. Chem. Soc., Perkin Trans. 1*, 1985, 363.
- 83 A. E. de Jesus, R. M. Horak, P. S. Steyn and R. Vleggaar, *J. Chem. Soc., Chem. Commun.*, 1983, 716.
- 84 J. L. M. Dillen, R. M. Horak, V. J. Maharaj, S. F. Marais and R. Vleggaar, *J. Chem. Soc., Chem. Commun.*, 1989, 393.
- 85 A. W. Dunn, R. A. W. Johnstone and B. Sklarz, *J. Chem. Soc., Chem. Commun.*, 1976, 270a.
- 86 J. S. E. Holker and T. J. Simpson, *J. Chem. Soc., Chem. Commun.*, 1978, 626.
- 87 T. J. Simpson, S. A. Ahmed, C. R. McIntyre, F. E. Scott and I. H. Sadler, *Tetrahedron*, 1997, **53**, 4013.
- 88 T. J. Simpson, *Tetrahedron Lett.*, 1981, **22**, 3785.
- 89 A. W. Dunn, R. A. W. Johnstone, B. Sklarz, L. Lessinger and T. J. King, *J. Chem. Soc., Chem. Commun.*, 1978, 533.
- 90 T. J. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2118.
- 91 C. R. McIntyre, F. E. Scott, T. J. Simpson, L. A. Trimble and J. C. Vederas, *J. Chem. Soc., Chem. Commun.*, 1986, 501.
- 92 M. Cueto, J. B. MacMillan, P. R. Jensen and W. Fenical, *Phytochemistry*, 2006, **67**, 1826.
- 93 T. J. Simpson and M. D. Walkinshaw, *J. Chem. Soc., Chem. Commun.*, 1981, 914.
- 94 E. Okuyama and M. Yamazaki, *Tetrahedron Lett.*, 1984, **25**, 3233.
- 95 C. Rank, R. K. Phipps, P. Harris, P. Fristrup, T. O. Larsen and C. H. Gottfredsen, *Org. Lett.*, 2008, **10**, 401.
- 96 K. K. Chexal, J. P. Springer, J. Clardy, R. J. Cole, J. W. Kirksey, J. W. Dornier, H. G. Cutler and B. J. Strawter, *J. Am. Chem. Soc.*, 1976, **98**, 6748.
- 97 T. J. Simpson, D. J. Stenzel, A. J. Bartlett, E. O'Brien and J. S. E. Holker, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2687.
- 98 T. J. Simpson, D. J. Stenzel, A. J. Bartlett, E. O'Brien and J. S. E. Holker, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2687.
- 99 H. Hayashi, M. Mukaiyama, S. Murao, M. Arai, A. Y. Lee and J. Clardy, *Biosci., Biotechnol., Biochem.*, 1994, **58**, 334.
- 100 R. M. G. Santos and E. Rodrigues-Fo, *Phytochemistry*, 2002, **61**, 907.
- 101 R. M. G. Santos and E. Rodrigues-Fo, *Z. Naturforsch., C*, 2003, **58**, 663.
- 102 (a) R. M. G. Santos, *Ph.D. Thesis*, Universidade Federal de São Carlos, Brasil, 2003; (b) T. P. Fill, G. K. Pereira, R. M. G. Santos and E. Rodrigues-Fo, *Z. Naturforsch., B*, 2007, **62**, 1035.
- 103 R. M. G. Santos and E. Rodrigues-Fo, *J. Braz. Chem. Soc.*, 2003, **14**, 722.
- 104 R. Geris, E. Rodrigues-Fo, H. H. G. Silva and I. G. Silva, *Chem. Biodiversity*, 2008, **5**, 341.
- 105 F. E. Scott, T. J. Simpson, L. A. Trimble and J. C. Vederas, *J. Chem. Soc., Chem. Commun.*, 1986, 214.
- 106 S. A. Ahmed, F. E. Scott, D. J. Stenzel, T. J. Simpson, R. N. Moore, L. A. Trimble, K. Arai and J. C. Vederas, *J. Chem. Soc., Perkin Trans. 1*, 1989, 807.
- 107 E. Okuyama and M. Yamazaki, *Tetrahedron Lett.*, 1983, **24**, 3113.
- 108 D. B. Stierle, A. A. Stierle, J. D. Hobbs, J. Stokken and J. Clardy, *Org. Lett.*, 2004, **6**, 1049.
- 109 D. B. Stierle, A. A. Stierle and B. Patacini, *J. Nat. Prod.*, 2007, **70**, 1820.
- 110 M. Lida, T. Ooi, K. Kito, S. Yoshida, K. Kanoh, Y. Shizuri and T. Kusumi, *Org. Lett.*, 2008, **10**, 845.
- 111 K. Shiomi, R. Uchida, J. Inokoshi, H. Tanaka, Y. Iwai and S. Omura, *Tetrahedron Lett.*, 1996, **37**, 1265.
- 112 R. Uchida, K. Shiomi, J. Inokoshi, H. Tanaka, Y. Iwai and S. Omura, *J. Antibiot.*, 1996, **49**, 1278.
- 113 R. Uchida, K. Shiomi, J. Inokoshi, T. Sunazuka, H. Tanaka, Y. Iwai, H. Takayanagi and S. Omura, *J. Antibiot.*, 1996, **49**, 418.
- 114 S. Kosemura, K. Matsunaga, S. Yamamura, M. Kubota and S. Ohba, *Tetrahedron Lett.*, 1991, **32**, 3543.
- 115 S. Kosemura and S. Yamamura, *Tetrahedron Lett.*, 1997, **38**, 6221.
- 116 S. Kosemura, *Tetrahedron Lett.*, 2002, **43**, 1253.
- 117 S. Kosemura, K. Matsunaga and S. Yamamura, *Chem. Lett.*, 1991, 1811.
- 118 S. Kosemura, *Tetrahedron*, 2003, **59**, 5055.
- 119 S. Kosemura, S. Matsuo and S. Yamamura, *Phytochemistry*, 1996, **43**, 1231.
- 120 S. Kosemura, H. Miyata, K. Matsunaga and S. Yamamura, *Tetrahedron Lett.*, 1992, **33**, 3883.

- 121 S. Kosemura, H. Miyata, S. Yamamura, K. Albone and T. J. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1994, 135.
- 122 J. P. Springer, J. W. Dorner, R. J. Cole and R. H. Cox, *J. Org. Chem.*, 1979, **44**, 4852.
- 123 C. R. McIntyre, D. Reed, I. H. Sadler and T. J. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1987.
- 124 C. R. McIntyre and T. J. Simpson, *J. Chem. Soc., Chem. Commun.*, 1981, 1043.
- 125 C. R. McIntyre, F. E. Scott, T. J. Simpson, L. A. Trimble and J. C. Vederas, *Tetrahedron*, 1989, **45**, 2307.
- 126 S. Komai, T. Hosoe, T. Itabashi, K. Nozawa, K. Okada, G. M. C. Takaki, T. Yaguchi, K. Takizawa, K. Fukushima and K. Kawai, *Chem. Pharm. Bull.*, 2005, **53**, 1114.
- 127 T. J. Simpson, *Chem. Soc. Rev.*, 1987, **16**, 123.
- 128 T. Sassa and H. Yoshikoshi, *Agric. Biol. Chem.*, 1983, **47**, 187.
- 129 T. Sassa and M. Nukina, *Agric. Biol. Chem.*, 1984, **48**, 1923.
- 130 T. Sassa, A. Ishizaki, M. Nukina, M. Ikeda and T. Sugiyama, *Biosci., Biotechnol., Biochem.*, 1998, **62**, 2260.
- 131 K. Ishibashi, *J. Antibiot.*, 1962, **15**, 161.
- 132 K. Hirai, S. Nozoe, K. Tsuda, Y. Litaka, K. Ishibashi and M. Shirasaka, *Tetrahedron Lett.*, 1967, **8**, 2177.
- 133 S. Nozoe, K. T. Suzuki and S. Okuda, *Tetrahedron Lett.*, 1968, **9**, 3643.
- 134 S. Nozoe and K. Suzuki, *Tetrahedron Lett.*, 1969, **10**, 2457.
- 135 S. Nozoe and K. Suzuki, *Tetrahedron*, 1971, **27**, 6063.
- 136 K. T. Suzuki and S. Nozoe, *Bioorg. Chem.*, 1974, **3**, 72.
- 137 J. Vrkoc, m. Budesinsky and L. Doleis, *Phytochemistry*, 1977, **16**, 1409.
- 138 Y. Hirata, *Biochem. Org. Chem.*, 1950, **7**, 119.
- 139 L. Zechlin, M. Wolf, W. Steglich and T. Anke, *Liebigs Ann. Chem.*, 1981, 2099.
- 140 T. Hashimoto, D. N. Quang, M. Nukada and Y. Asakawa, *Heterocycles*, 2005, **65**, 2431.
- 141 N. Ishii, A. Takahashi, G. Kusano and S. Nozoe, *Chem. Pharm. Bull.*, 1988, **36**, 2918.
- 142 D. N. Quang, T. Hashimoto, Y. Arakawa, C. Kohchi, T. Nishizawa, G. H. Soma and Y. Asakawa, *Bioorg. Med. Chem.*, 2006, **14**, 164.
- 143 B. Koch and W. Steglich, *Eur. J. Org. Chem.*, 2007, 1631.
- 144 X.-L. Yang, C. Qin, F. Wang, Z.-J. Song and J.-K. Liu, *Chem. Biodiversity*, 2008, **5**, 484.
- 145 D. Zhi-Hui, D. Ze-Jun and L. Ji-Kai, *Helv. Chim. Acta*, 2001, **84**, 259.
- 146 M. Nukata, T. Hashimoto, I. Yamamoto, N. Iwasaki, M. Tanaka and Y. Asakawa, *Phytochemistry*, 2002, **59**, 731.
- 147 M. Ikeda, H. Kanou and M. Nukina, *Nogaku*, 1989, **10**, 849.
- 148 H. Misasa, Y. Matsui, H. Uehara, H. Tanaka, M. Ishihara and H. Shibata, *Biosci. Biotechnol. Biochem.*, 1992, **56**, 1660.
- 149 K. Sugiyama, T. Yoshida and H. Sakamoto, *Jpn. Pat. JP 07101854*, 1995.
- 150 V. Hellwig, R. Nopper, F. Mauler, J. Freitag, J.-K. Liu, Z. H. Ding and M. Stadler, *Arch. Pharm. (Weinheim)*, 2003, **336**, 119.
- 151 K. Dekermendjian, R. Shan, M. Nielsen, M. Stadler, O. Sterner and M. R. Witt, *Eur. J. Med. Chem.*, 1997, **32**, 351.
- 152 J. A. Ballantine, C. H. Hassall and G. Jones, *J. Chem. Soc.*, 1965, 4672.
- 153 J. A. Ballantine, C. H. Hassall, B. D. Jones and G. Jones, *Phytochemistry*, 1967, **6**, 1157.
- 154 N. Cagnoli-Bellavita, P. Ceccherelli and T. F. M. Ribaldi, *Phytochemistry*, 1975, **14**, 807.
- 155 S. Prapairat, I. Masahiko, K. Prasat, B. Uraivan and T. Yodhathai, *J. Antibiot.*, 2004, **57**, 10.
- 156 R. K. Phipps, B. O. Petersen, K. B. Christensen, J. Φ. Duus, J. C. Frisvad and T. O. Larsen, *Org. Lett.*, 2004, **6**, 3441.
- 157 J. Beljak, O. Gribanovski-Sassu, B. M. Ranzi and A. Scala, *Ann. Inst. Superiore Sanita*, 1971, **7**, 14.
- 158 L. Canonica, C. G. Casinovi, A. Fiecchi, C. Galeffi, G. B. Marini-Bettolo, A. Scala and A. M. Vaccaro Torracca, *Gazz. Chim. Ital.*, 1976, **106**, 147.
- 159 K. Yoganathan, L. K. Yang, C. Rossant, Y. Huang, S. NG, M. S. Butler and A. D. Buss, *J. Antibiot.*, 2004, **57**, 59.
- 160 T. Fujioka, K. Yao, K. Hamano, T. Hosoya, T. Kagasaki, Y. Furukawa, H. Haruyama, S. Sato and T. Koga, *J. Antibiot.*, 1996, **49**, 409.
- 161 K. D. Barrow and W. S. Murphy, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2837.
- 162 C. H. Lim, H. Miyagawa, M. Akamatsu, Y. Nakagawa and T. Ueno, *Nippon Noyaku Gakkaishi*, 1998, **23**, 281.
- 163 P. M. Scott and J. W. Lawrence, *Can. J. Microbiol.*, 1968, **14**, 1015.
- 164 C. Huber, W. A. Court, J. P. Devlin, O. E. Edwards and P. M. Scott, *Tetrahedron Lett.*, 1974, **15**, 2545.
- 165 N. Koyama, T. Nagahiro, Y. Yamaguchi, R. Masuma, H. Tomoda and S. Omura, *J. Antibiot.*, 2005, **58**, 695.
- 166 L. Canonica, B. M. Ranzi, B. Rindoni, A. Scala and C. Scolastico, *J. Chem. Soc., Chem. Commun.*, 1973, 213.
- 167 L. Canonica, L. Colombo, C. Gennari, B. M. Ranzi and C. Scolastico, *J. Chem. Soc., Chem. Commun.*, 1978, 679.
- 168 L. Canonica, M. G. Beretta, L. Colombo, C. Gennari, B. M. Ranzi and C. Scolastico, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2686.
- 169 R. D. Hutchison, P. S. Steyn and S. J. van Rensburg, *Toxicol. Appl. Pharmacol.*, 1973, **24**, 507.
- 170 A. E. de Jesus, W. E. Hull, P. S. Steyn, F. R. van Heerden and R. Vlegaar, *J. Chem. Soc., Chem. Commun.*, 1982, 902.
- 171 R. M. Horak, V. J. Maharaj, S. F. Marais, F. R. van Heerden and R. Vlegaar, *J. Chem. Soc., Chem. Comm.*, 1988, **23**, 1562.
- 172 B. Sontag, N. Arnold, W. Steglich and T. Anke, *J. Nat. Prod.*, 1999, **62**, 1425.
- 173 A. Mühlbauer, J. Beyer and W. Steglich, *Tetrahedron Lett.*, 1998, **39**, 5167.
- 174 W. Steglich, F. Esser and I. Pils, *Z. Naturforsch., B*, 1971, **26**, 336.
- 175 R. L. Edwards and P. C. Beaumont, *J. Chem. Soc.*, 1971, **14**, 2582.
- 176 H. Besl, H. J. Hecht, P. Luger, V. Pasupathy and W. Steglich, *Chem. Ber.*, 1975, **108**, 3675.
- 177 T. Hayashi, A. Kanetoshi, M. Ikura and H. Shirahama, *Chem. Pharm. Bull.*, 1989, **37**, 1424.
- 178 M. Lang, A. Mühlbauer, C. Gräf, J. Beyer, S. Lang-Fugmann, K. Polborn and W. Steglich, *Eur. J. Org. Chem.*, 2008, 816.
- 179 B. Liebermann, R. Ellinger, W. Gunther, W. Ihn and H. Gallander, *Phytochemistry*, 1997, **46**, 297.
- 180 R. P. Nussbaum, W. Gunther, S. Heinze and B. Liebermann, *Phytochemistry*, 1999, **52**, 593.
- 181 B. Liebermann, R.-P. Nussbaum and W. Gunther, *Phytochemistry*, 2000, **55**, 987.
- 182 B. Liebermann, R.-P. Nussbaum, W. Gunther and J. M. Teuscher, *Phytochemistry*, 2001, **56**, 551.
- 183 R. T. Gallager, T. McCabe, K. Hirotsu and J. Clardy, *Tetrahedron Lett.*, 1980, **21**, 243.
- 184 D. T. Wicklow, P. F. Dowd, M. R. TePaske and J. B. Gloer, *Trans. Brit. Mycol. Soc.*, 1988, **91**, 433.
- 185 J. B. Gloer, M. R. TePaske and J. Sima, *J. Org. Chem.*, 1988, **53**, 5457.
- 186 M. R. TePaske and J. B. Gloer, *J. Org. Chem.*, 1990, **55**, 5299.
- 187 J. B. Gloer, B. L. Rinderknecht, D. T. Wicklow and P. F. Dowd, *J. Org. Chem.*, 1989, **54**, 2530.
- 188 G. M. Staub, J. B. Gloer, D. T. Wicklow and P. F. Dowd, *J. Am. Chem. Soc.*, 1992, **114**, 1015.
- 189 M. R. TePaske and J. B. Gloer, *Tetrahedron*, 1989, **45**, 4961.
- 190 M. R. TePaske, J. B. Gloer and D. T. Wicklow, *J. Org. Chem.*, 1989, **54**, 4743.
- 191 J. A. Laakso and J. B. Gloer, *J. Org. Chem.*, 1992, **57**, 138.
- 192 C. Li, J. B. Gloer, D. T. Wicklow and P. F. Dowd, *Org. Lett.*, 2002, **4**, 3095.
- 193 C. Li, J. B. Gloer and D. T. Wicklow, *J. Nat. Prod.*, 2003, **66**, 1232.
- 194 M. R. TePaske, J. B. Gloer, D. T. Wicklow and P. F. Dowd, *J. Org. Chem.*, 1989, **54**, 4743.
- 195 B. Sontag, M. Ruth, P. Spittler, N. Arnold, W. Steglich, M. Reichert and G. Bringmann, *Eur. J. Org. Chem.*, 2006, 1023.