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PAPER

Angular tricyclic benzofurans and related natural products of fungal origin. Isolation, biological activity and synthesis

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Naturally-occurring angular tricyclic benzofuran derivatives of fungal origin and related compounds, in which two heterocyclic rings are fused to a central benzenoid moiety, are covered. Emphasis is placed on the structure of the compounds, together with their relevant biological activities and source microorganisms, as well as country or region of origin and environmental conditions. In addition, proposed biosynthetic pathways, as well as the total syntheses of some of the compounds, including those that lead to structural revision or to correct stereochemical assignments, and related synthetic efforts, are discussed in detail.

Introduction

Microorganisms, particularly fungi, are a constant stimulus for natural products research, and as such they keep being the subject of vigorous chemical investigation. The fungi represent the second largest group of organisms, next to the insects, and are widely distributed across the planet.[1] They inhabit almost all ecological niches, occurring between the tropics, but also in temperate regions, and even in Artic and Antarctic ice. Fungi have been found in places so different as seawater[2] and dry soils, including the surface of mountain rocks. They parasitize plants, protozoa, fishes, insects, and mammals, but also display symbiotic lives with algae, sponges and other members of the plant kingdom.

Fungi are completely heterotrophic because of their inability of doing photosynthesis. Thus, they must acquire their nutrients from the environment, including living, dying, or dead organisms. Therefore, fungi have acquired the ability to survive under extreme environmental conditions, and have evolved to biosynthesize a wide variety of fascinating natural products not for fungal growth but for other purposes such as detoxification, cell differentiation, defense, signaling and communication.[3]

Many of the fungi-derived biologically active small molecules range from highly potent toxins to plant growth promoters and life-saving drugs. Thus, fungi have historically been a gold mine of lead compounds for the pharmaceutical industry.[4]

The enormous diversity of fungal-derived natural products is a consequence of the large manifold of fungal species and also a result of their ability to change the metabolic pathways when exposed to stress conditions or different environments, where even usually silent metabolic routes are awakened.[5] Recent access to the detailed structure of some fungal genomes has confirmed the large number of secondary metabolite pathways at their disposal, which can be unlocked to serve as potential sources for new and useful natural products.[6]

Most of the fungal secondary metabolites and their biosynthetic pathways still remain unveiled.[7] However, knowledge of their structure and function may facilitate a better understanding of fungal diversity and environmental adaptation processes. It should also allow the development of bioactive compounds as medicines, flavors, cosmetics, agrochemicals, crop protection agents and others.[8]

Fungal natural product research has historically been strongly related with specimens isolated from soil. However, in mankind's search of remote regions to find new ways to fight disease, fungi of marine origin are becoming an important source of novel skeletons and bioactive compounds for drug discovery. Likewise, analysis of products from fungi developing in environments subjected to decomposition, such as damp buildings, are providing new clues to the pathogenesis of specific conditions and offer an opportunity to discover new drug candidates.[9]

Reviewed here are the isolation, biological activity profiles and reported syntheses of naturally-occurring angular tricyclic benzofuran derivatives of fungal origin, and related compounds, in which two heterocyclic rings are fused to a central benzenoid moiety. They comprise furo[3,2-*h*]isochroman (**1**), furo[3,2-

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h]isoquinoline (**2**), furo[4,5-*g*]isobenzofuran (**3**), furo[2,3-*h*]isochroman (**4**) and furo[3,4-*f*]chroman (**5**) type natural products (Figure 1). On the other side, the pentacyclic aflatoxins belonging to series B, M, G and GM, which share the furo[2,3-*h*]chroman skeleton (**6**) and have been extensively studied over the last 50 years, are not covered.[10]

The majority of these compounds have been isolated during the last 15 years, mainly from saprophytic fungi commonly found in soil, decaying vegetation, seeds and grains; others have been obtained from fungi isolated from other environments, including marine and indoor spaces, or have long been known.

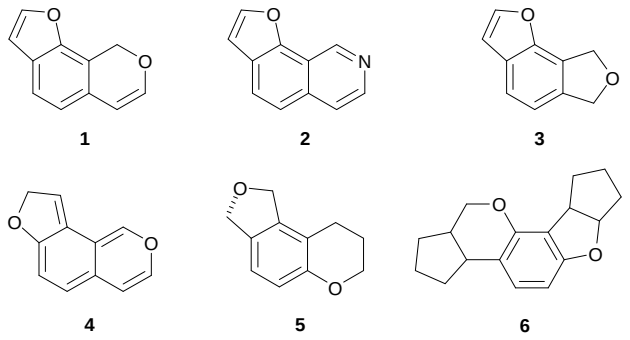


Figure 1. Naturally occurring angular tricyclic benzofuran motifs of interest.

1. Isolation and biological activity

1.1. Furo[3,2-h]isochromans. Pseudodeflectusin, pergillins and related compounds

Aspergillus ustus is one of the most prevalent fungi in soil and decaying vegetation. It is a known contaminant of stored foodstuffs such as cereals, pulses and cheese; it has also been found in indoor environments and is known to produce a number of toxic secondary metabolites of varied structure and biosynthetic origin.

The tricyclic hemiacetals pergillin (**7**) and dihydropergillin (**8**) were the first known naturally-occurring furo[3,2-*h*]isochromans (Figure **2**). They were isolated from *Aspergillus ustus* found growing on pea seed of *Pisum sativum* var. *Macrocarpon*[11] and recently reported again from *Aspergillus ustus* 094102.[L1761] Pergillin is also produced by *A. insuetus*.[S480]

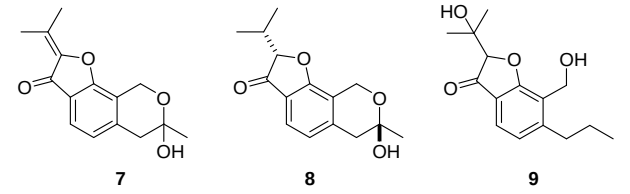
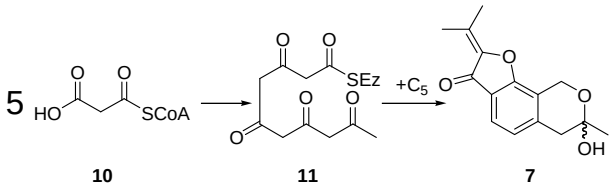


Figure 2. Chemical structures of pergillin (**7**), dihydropergillin (**8**) and brassicadiol (**9**).

Pergillin and other extrolites have been used as taxonomic markers for *Aspergilli*. In that sense and based on chemical, molecular and morphological data, *A. insuetus* has been recently separated from *A. ustus* and differentiated from *A. keveii*.[12]

It was proposed that pergillin could result from the condensation of a pentaketide and one molecule of mevalonic acid, which can yield γ,γ'-dimethylallyl pyrophosphate, and that its hemiacetal feature would result from the union of the two ends of the pentaketide chain (Scheme **1**).[13] Even though the hemiketal moiety of pergillin contains an asymmetric center, the natural product has no optical activity.



Scheme 1. Proposed biosynthetic pathway of pergillin (**7**).

Pergillin and dihydropergillin displayed moderate plant growth inhibiting properties in the wheat coleoptile assay, which were significantly inhibited by 10^{-4} M solutions, with dihydropergillin being the most potent.[14] Interestingly, however, pergillin was nontoxic to chicks at doses up to 250 mg/Kg.

It was proposed that reduction of the double bond allows the isopropyl group to form a staggered conformation with the substituted furan ring. The resulting added flexibility of this end of the molecule may account for the enhanced biological activity.

Brassicadiol (**9**) has the carbon skeleton of the furo[3,2-*h*]isochromans. The natural product was isolated by Ayer and Peña Rodríguez in 1987 during their study of the fungal metabolites that produced the damage of the black spot disease of canola,[15] one of the most widespread diseases of rapeseed. The black spot disease of canola is caused by the fungal pathogen *Alternaria brassica* (Berkeley) Saccardo, and results in low oilseed yields through reduction in photosynthesis, premature defoliation, and shattering of fruits. However, it was found that brassicadiol is not the responsible agent for the observed effects of the disease.

In 2004, the group of Mizushina isolated pseudodeflectusin (**12**), from the culture broth of *Aspergillus pseudodeflectus* Hiji005, isolated from the sea weed *Sargassum fusiform*, collected in the Miura Peninsula, Kanagawa, Japan. This new tricyclic angular isochroman derivative was found together with the structurally related alkaloid TMC-120B (**23**, *vide infra*).[16]

Pseudodeflectusin features a cyclic hemiacetal motif, which suggests that it may exist as an interconverting mixture of two isomers; however, the natural product was obtained as a single isomer. The absolute configuration of its stereogenic centers at C-7 and C-9 were not determined at that time.

The natural product exhibited cytotoxicity towards several human cancer cell lines, including those from the stomach (NUGC-3), cervix (HeLa-S3), and peripheral blood (HL-60, LD_{50}= 39 μM), but did not affect those from the lung (A549) or colon (DLD-1). Since **12** did not display any inhibition of DNA metabolic enzymes, it was considered as a promising candidate of a new type of antitumor agent, acting through an unprecedented mechanism.

The group of Zhu reported in 2009 the isolation of ustusoranes A–F (Figure 3) from *Aspergillus ustus* 094102 [isolated from the rhizosphere soil of the mangrove *Bruguiera gymnorrhiza*, (Wenchang, Hainan Province, China)],[17] together with daldinin B [**13**, a carbinolic isomer of ustusorane E (**18**) exhibiting the *R* configuration at C2][18] and the known pergillin (**7**). Their structures (**14**-**19**) were elucidated by NMR and HRMS analyses.

The molecular formula of ustusorane C (**16**) was close to that

of pseudodeflectusin,[O3539] and it was suggested to be an artifact, resulting sequential dehydration of the hemiacetal of pseudodeflectusin with silica gel (to form an oxonium ion) and quenching of the oxonium ion by MeOH, during the isolation process.

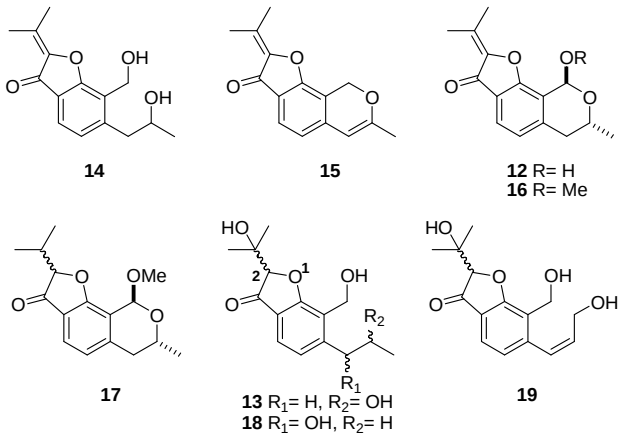


Figure 3. Chemical structures of pseudodeflectusin (**12**), Daldinin B (**13**) and ustusoranes A-F (**14**-**19**).

The 1,3-*anti*-configuration of **16**, the same of pseudodeflectusin, was inferred considering that the nucleophilic attack of MeOH on the oxonium ion should occur preferably from the less hindered side. The specific rotation of **16** ($[\alpha]^{20}_D$= +6) is of the same sign as that of natural (+)-pseudodeflectusin, whose absolute configuration had been confirmed as 7*R*,9*S* by chemical synthesis,[19] suggesting that **16** also possesses the 7*R*,9*S* configuration.

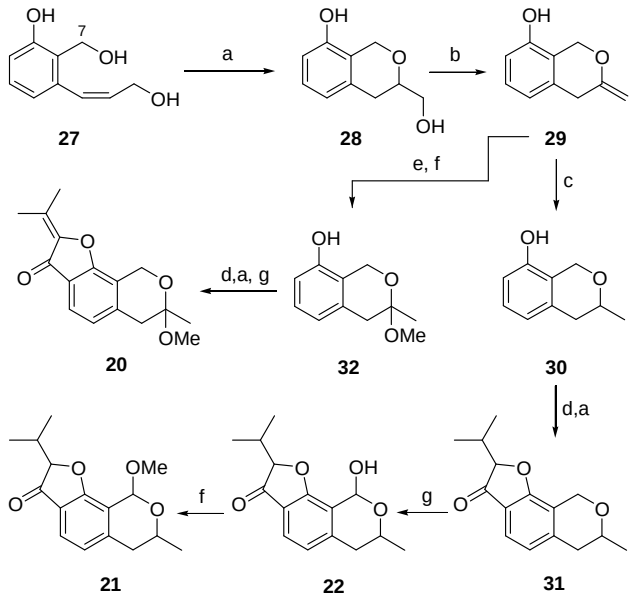
The cytotoxicity of the isolated compounds was evaluated against A549 and HL-60 cell lines using the sulforhodamine B[20] and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide[21] methods, respectively. Ustusorane E exhibited strong growth inhibition against the HL-60 cell lines with IC_{50}= 0.13 μM.

In 2010, the group of Rukachaisirikul isolated the penicisochromans A-C (**20**-**22**) as colorless gums, together with alkaloids TMC-120B (**23**) and TMC-120C (**24**) (*vide infra*) and the related (–)-penicisoquinoline (**25**), a chiral isoquinoline derivative ($[\alpha]^{20}_D$= –21), from the extract of the mycelia of the marine-derived fungus *Penicillium* PSU-F40.[22]

This fungal strain was isolated from the sea fan *Annella sp.* collected near the Similan Islands, in the Phangnga Province of Thailand. Some of the natural compounds were tested for antibacterial activity against *Staphylococcus aureus* and Methycillin-resistant *S. aureus*, but none of them was active.

The authors hypothesized that penicisochromans A-E could derive from peniciphenol (**27**), which was concomitantly isolated, through an acid-catalyzed intramolecular cyclization of the (*Z*)-3-hydroxyl-1-propenyl side chain with the benzyl alcohol, to yield isochroman A **28** (Scheme 2).

According to their proposal, dehydration and subsequent hydrogenation of **29** would generate isochroman intermediate **30**. Next, acylation of **30** with a 3-methyl-2-butenoyl unit and subsequent cyclization would yield **31**, the oxidation and *O*-methylation of which would afford penicisochromans C (**22**) and B (**21**) respectively. On the other hand, penicisochroman A (**20**) would result from Markownikov hydration and subsequent *O*-methylation of **29**, followed by acylation of intermediate **32**, cyclization and final oxidation.



Scheme 2. Biosynthesis of penicisochromans. Proposed transformations: (a) cyclization; (b) dehydration; (c) hydrogenation; (d); acylation; (e) hydration; (f) methylation; (g) oxidation.

Analogously, it was proposed that the biosynthesis of the related furo[3,2-*h*]isoquinolines (*vide infra*) would proceed along the same lines as for the furo[3,2-*h*]isochromans, from a 7-amino derivative of peniciphenol as the biosynthetic precursor.

1.2. Furo[3,2-h]isoquinolines. Panaefluorolines, TMC-120-type alkaloids, and related compounds

Compounds exhibiting prolongation of eosinophil survival are useful candidates for the development of drugs to treat bronchial asthma. In 1999, during the course of a screening for inhibitors of interleukin-5 mediated prolongation of eosinophil survival, Kohno *et al.* disclosed the isolation of several alkaloids [TMC-120A-C (**33, 23, 24**)] from *Aspergillus ustus* TC 1118 (Bain.) Thom & Church.[23] The fungus was isolated from the rhizosphere of grass collected in Kawaguchi-shi, Saitama, Japan.

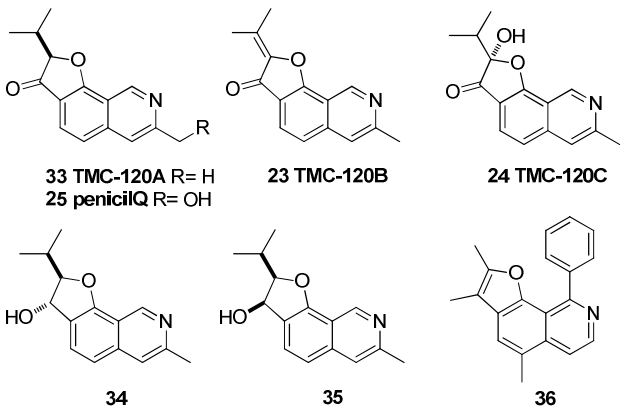


Figure 4. Chemical structures of TMC-120A-C (**33, 23, 24**), $NaBH_4$-mediated reduction products of TMC-120B (**34**, **35**) and **36**.

Their structural elucidation was carried out by a combination

of NMR spectroscopy, X-ray crystallographic analysis of TMC-120B and chemical studies on TMC-120B, including its conversion into TMC-120A by catalytic hydrogenation over 10% Pd/C (36% yield) and reduction of its α,β-unsaturated carbonyl system with $NaBH_4$, to a mixture of alcohols **34** and **35** (Figure 4). TMC-120A is optically active; however, it was suggested that TMC-120C, which has a hemiacetalic structure and displays $[\alpha]_D = 0$, may be a racemate.[K11247]

Taking into account that the synthetic 5-methyl-2,3-dimethyl-9-phenylfuro[3,2-*h*]isoquinoline **36** can be regarded as the first known furo[3,2-*h*]isoquinoline,[24] alkaloids TMC-120A-C can be considered as the first furo[3,2-*h*]isoquinoline-type alkaloids isolated from natural sources.[25]

In 2004, the group of Mizushina found TMC-120B in the culture broth of *A. pseudodeflectus* Hiji005, isolated from the sea weed *Sargassum fusiform*, collected in the Miura Peninsula, Kanagawa, Japan, together with pseudodeflectusin (**12**).[O3539]

Table 1. Inhibitory effects of compounds **23, 24, 33-35** on the survival of guinea pig peritoneal eosinophils.

Comp. Nº	**33**	**23**	**24**	**34**	**35**
IC_{50} (μM)	13.7	2.0	>39	>41	>41

When TMC-120A-C and the reduced derivatives **34** and **35** were subjected to the bioassay, TMC-120B (**23**) exhibited the best performance (Table 1), suggesting that the α,β-unsaturated ketone system of TMC-120B plays an important role for the activity, which probably involves the alkylation of biological nucleophiles through a Michael-type addition. Interestingly enough, TMC-120B was non-toxic against human leukemia HL-60 at a 42 μM level.

More recently, the group of Hibino disclosed the effects of TMC-120A (**33**), TMC-120B (**23**) and synthetic benzylidene derivative **37** in several cellular assay systems.[26] They found that the heterocycles were potent inhibitors of the production of interferon-γ (IFN-γ), induced by stimulating ovalbumin (OVA)–specific murine T cells with an OVA peptide antigen (Table 2).[27]

Table 2. Effects of TMC-120A (**33**), TMC-120B (**23**) and **37** on the production of interferon-γ (IFN-γ) and interleukin-4 (IL-4) from antigen-stimulated T-cells and on cell proliferation.

		OVA peptide (μg/mL)			
		0	0.3	3	30
IFN-γ (ng/mL)	Control	0	13.7	20.0	39.0
	33 (3 μM)	0	8.1	12.5	18.4
	23 (3 μM)	1.6	6.7	8.9	9.1
	37 (3 μM)	0.7	9.6	12.4	18.8
IL-4 (pg/mL)	Control	0	81	135	164
	33 (3 μM)	0	103.5	152.5	166
	23 (3 μM)	0	82.5	133	168
	37 (3 μM)	0	88.5	128.5	132
Thymidine uptake (fold)	Control	1	6.32	5.93	5.92
	33 (3 μM)	1.23	8.35	7.49	7.37
	23 (3 μM)	0.95	8.79	8.02	7.78
	37 (3 μM)	0.83	6.42	5.75	5.69

Stimulation by the peptide also induced production of interleukin-4 (IL-4), but the effects of the tested compounds were relatively weak at the 3 μM level. At this concentration, the heterocycles had no effect on the proliferative response, as assessed by [^{3}H] thymidine uptake. This was interpreted as evidence that suppression of the production of IFN-γ is not a result of toxic effects of the compounds.

Miller *et al.* employed TMC-120A (**33**) as a probe to study the inflammatory potential and molecular mechanisms underscoring inflammatory responses of lung cells to compounds from fungi that grow on damp building materials. The effect of pure fungal compounds on potentiating acute inflammatory response in primary mouse alveolar macrophages was evaluated testing the hypothesis that alveolar macrophages' responses to low molecular weight fungal compounds exhibit temporal and compound specificity that mimic that observed in the whole lung.

These authors found that exposure to the natural product produced a significant number of gene transcriptional changes. The results confirm that the inflammatory nature of this fungal metabolite can contribute to the development of non-allergenic respiratory health effects.[28]

It has been informed that after LC-MS analysis of building-derived isolates, Nielsen suggested in 2003 that TMC-120-related compounds were present in *A. ustus* var. *pseudodeflectus* (revised as *A. insuetus*) found in these isolates.[29] However, it was the group of Slack the one that produced the first confirmatory report of the presence of TMC-120A and TMC-120B in indoor isolates.

Aspergillus insuetus and *A. calidoustus* grown in CY medium produced several major metabolites identified almost exclusively from the filtrate extract as TMC-120A-C and novel TMC-120 derivatives **38** and **39** (Figure **5**). These isoquinoline alkaloids were detected primarily in *A. calidoustus* strains, whereas only in one strain of *A. insuetus*.[30] This novel TMC-120 derivative **39** may be a product resulting from ring opening of TMC-120C between C-2 and the oxygen at position 1.

The group of Takahashi isolated the mycobiont *Arthonia cinnabarina* (DC.) Wallr[31] from spores discharged from apothecia of the lichen *Amygdalaria panaeola* (Ach.) Hertel & Brodo, collected in Finland, which is usually found on dead and decomposing twigs. When the mycobiont was cultured on malt-yeast liquid medium, it became fluorescent and panaefluorolines A-C (**40-47**) were isolated in 2003, as yellowish green amorphous solids (Figure 5).[32] Their structures were elucidated by spectroscopic means and comparison with the published data of TMC-120A. The fluorescent pigments could not be detected in the lichen thallus by HPLC analysis.

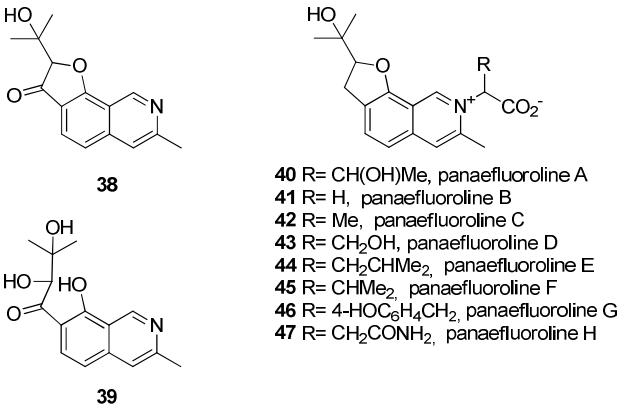


Figure 5. Chemical structures of **38**, **39** and panaefluorolines A-H (**40**-**47**).

The authors conjectured that despite isoquinoline alkaloids in higher plants are biosynthesized from tyrosine, the structures of panaefluorolines provide clues with regards to the source of their nitrogen atom, and this may be amino acids such as threonine, glycine and alanine. The more recent isolation of the panaefluorolines D-H (**43**-**47**) from the same source[33] reinforces this hypothesis.

The panaefluorolines were separated as single enantiomers, and except for panaefluoroline G, all of them were dextrorotatory; the relative configuration of the stereogenic centers of panaefluoroline D was determined by X-ray crystallography, resulting 2,2'-*anti*.

1.3. Pyrano[3,2-h]isoquinoline and pyrano[3,2-h]isochromans. Aspergillitine and aspergiones

In 2001, Lin *et al.* reported that fungal isolates of *Aspergillus versicolor* (Vuill) Tirab., which were obtained from the marine sponge *Xestospongia exigua* (Pterosiidae) collected along the coast line of Bali, Indonesia, produced a series of angular tricyclic 2,3-dimethylchromones, the aspergiones A-F (**48**-**53**). Their structures were proposed as shown in Figure 6 on the basis of extensive spectroscopic (UV, MS, ^{1}H and ^{13}C NMR, COSY, HMQC and HMBC) analyses.[34]

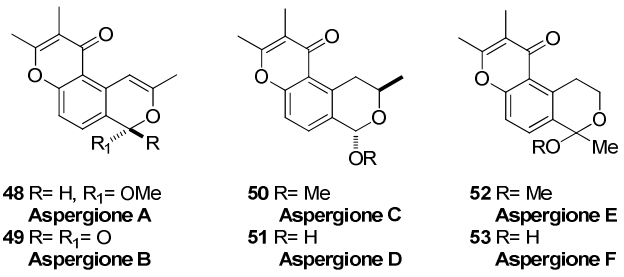


Figure 6. Chemical structures of the aspergiones A-F (**48**-**53**).

In a second communication, the structures of the aspergiones (**54**-**59**) were reformulated as depicted in Figure 7, and a new compound was reported (**60**), to which the name aspergillitine was given.[35] Except for aspergillitine and aspergione D, all the isolated compounds were optically active.

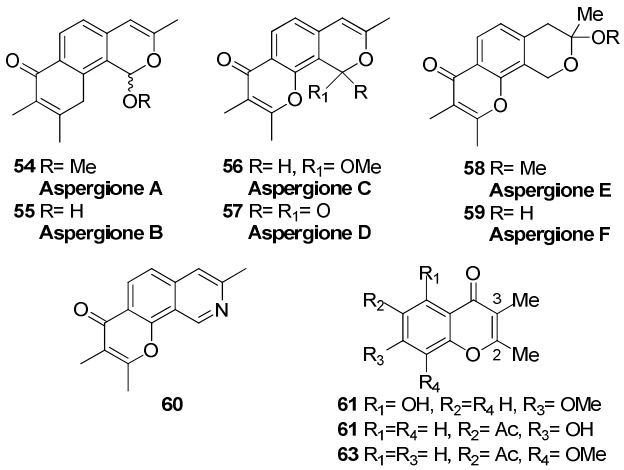


Figure 7. Chemical structures of aspergillitine (**60**), revised chemical structures proposed for the aspergiones A-F (**54**-**59**) and some natural 2,3-dimethylchromones (**61**-**63**).

The structural proposal was quite surprising, since the 2,3-dimethylchromone motif is rare[36a] and 2,3-dimethylchromones are uncommon among natural products, a few exceptions being chromones **61**, isolated from the mycobiont of the lichen *Graphis scripta*[36b] compound **62**, obtained from *Thitonia diversifolia*[36c] and *Tussilago farfara*,[36d] chromone **63**, isolated from *Ligularia microphylla*,[36e] and chaetochromin D, a bis(naphtho-γ-pyrone) derivative produced by the fungus *Chaetomium gracile*.[36f] Interestingly, 2,3-dimethylchromones have been employed as key intermediates for the synthesis of more complex natural and other products.[37]

Interestingly enough, aspergillitine displayed moderate antibacterial activity against *Bacillus subtilis*, being inactive against *Escherichia coli* and *Saccharomyces cerevisiae*. On the other hand, the aspergiones C (**56**) and E (**58**) were inactive.

1.4. Furo[4,5-g]isobenzofurans. Daldinins, concentricolide, mycophenolic acid derivatives and related compounds

Qin *et al.* studied a Chinese strain of *Daldinia concentrica* collected at Lijing, in the Southwestern Chinese province of Yunnan, reporting in 2006 the isolation of concentricolide (**64**). The structure of the natural product (Figure 8) was established by NMR spectroscopy and single crystal X-ray crystallography, and the 6*R* stereochemistry was proposed for its stereogenic center.[38]

Concentricolide inhibited HIV-1-induced cytopathic effects with an EC_{50} value of 0.31 μg/mL; it also exhibited the blockage (EC_{50}= 0.83 μg/mL) on syncytium formation between HIV-1 infected cells and normal cells, and has a therapeutic index of 247, suggesting that it is effective against HIV-1. The natural product and several related compounds, including 2,5-dinitro, 2,3-dibromo and 3-bromo derivatives were patented claiming their usefulness for the treatment and prevention of the infection caused by the human immunodeficiency virus (HIV).[39]

The OSMAC (One Strain-Many Compounds) approach towards metabolite diversity is based on the observation that individual fungal strains are able to produce more metabolites than normally detected in a routine screening program, and that very small changes in the cultivation parameters (for example, culture vessel, media composition, addition of enzyme inhibitors,

etc.), can completely shift their metabolic profile.[40]

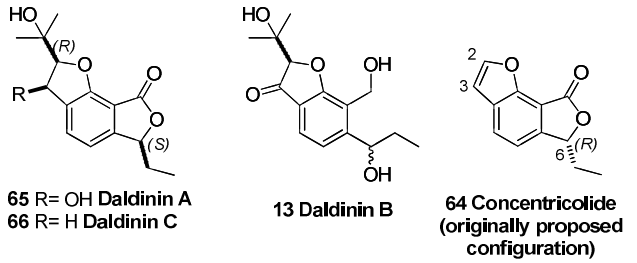


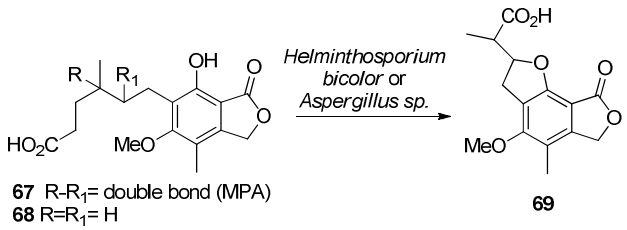
Figure 8. Chemical structures of daldinins A-C (**13, 65, 66**) and concentricolide (**64**).

Ascomycetes of the genus *Daldinia* (Xylariaceae) are rich in secondary metabolites. European and American *Daldinia sp.* have been screened for secondary metabolites since the late 1950's. Shao *et al.* studied the ascomycete *Daldinia concentrica* S0318, collected at Laojunshan (Yunnan Province, China). The researchers found that this strain produced concentricolide (**64**, 160 mg/Kg dried fruiting bodies) when cultivated in brown reagent bottles; however, when cultivated in colorless Erlenmeyer flasks, despite employing the same medium and conditions, they produced the above metabolite in addition to novel benzofuranoid derivatives, the daldinins A-C. Daldinin B has been recently found in *A. ustus* 094102,L1761 together with other related compounds.

The structures of the natural products were elucidated by NMR spectroscopy and X-ray crystallography of daldinin A, which allowed establishment of the relative configuration of C2 and C6. Taking into account the simultaneous production of daldinins A, B and concentricolide, and that the latter has been unambiguously determined as the *S*-(-) enantiomer, it is not unlikely that the daldinins A and B share the 2*S*,6*S* absolute configuration. It has been suggested that the secondary metabolites constituents of *Daldinia* are of great chemotaxonomic significance for this and other genera of the Xylariaceae.[41]

Interestingly enough, in 1994, the group of Asakawa reported three azaphilone natural products from *D. concentrica* collected in Tokushima, Japan, to which the names daldinin A-C were given.[42] An unsuccessful attempt to synthesize the azaphilone-type daldinin A was informed in 2001.[43]

On the other side, mycophenolic acid (**67**) is an antifungal, antitumor, antiviral, antimitotic, immunosuppressive and antipsoriatic[44] agent isolated from several species of Penicillium, especially *Penicillium brevicompactum*. Fermentation of dihydromycophenolic acid **68** by *Helminthosporium bicolor* and *Aspergillus sp.* yielded tricycle **69**, possessing a furo[4,5-*g*]isobenzofuran core; the compound was also found when mycophenolic acid itself was submitted to fermentation other microorganisms, especially *Penicillium daleae*, *P. raistrickii* and *Aspergillus carbonarius*.[45]



Scheme 3. Biotransformation of **67** to furo[4,5-*g*]isobenzofuran **69**.

1.5. Microsphaerophthalide G, a novel furo[3,4-f]benzo[5,6-e][1,3]dioxine

Microsphaerophthalide G (**70**) is one of the phthalides recently isolated from the endophytic fungus *Microsphaeropsis arundinis* PSU-G18, in turn isolated from the leaves of *Garcinia hombroniana*.[46] The natural product (Figure 9) was isolated in minor amounts, together with several other phthalide derivatives, among them the related phenols **71** and **72**. The (*S*)- configuration was assigned based on its specific optical rotation ($[\alpha]^{28}_{D}$= ─40.9), compared with other 3-substituted naturally-occurring phthalides. Interestingly, despite more than 180 phthalides have been reported to date,[47] the 3-oxygenated phthalides[48] are rare natural products.[49]

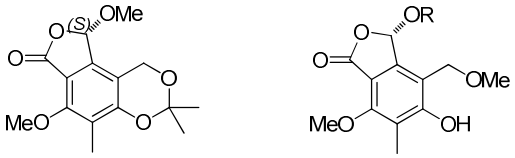


Figure 9. Chemical structures of Microsphaerophthalide G (**70**) and related phtalides (**71** and **72**).

1.6. Furo[2,3-h]isochromans. Lactonic azaphilones

The azaphilones are a structurally diverse family of fungal secondary metabolites, which have been isolated mainly from perfect and imperfect stages of ascomycetes such as *Aspergillus*, *Penicillium*, *Hypoxylon*, *Chaetomium*, *Hypoxylon*, *Monascus* and others.[50,O315] These secondary metabolites are a relatively small subset of the polyketide class of natural products and feature a pyrone-quinone structure containing a highly oxygenated bicyclic core and a quaternary centre.

The name azaphilone reflects their affinity for nitrogen-containing compounds like ammonia; they react with amines (proteins, amino acids and nucleic acids) to yield red or purple vinylogous γ-pyridones where the pyranic oxygen is replaced with a nitrogen atom.[51]

Currently, there are around 40 known naturally-occuring azaphilones that contain the furo[2,3-*h*]isochroman motif, and some representative examples are depicted in Figure 10. Despite different approaches towards the synthesis of azaphilones have been reported in recent times,[52] none of them has been applied yet to the elaboration of these tricyclic heterocycles.

The isolation and biological activities of the azaphilones have been recently reviewed.[O315,53] (+)-5-Bromoochrephilone (**75**), ochrephilone (**73**), (+)-isorotiorin (**76**), 5-chloroisorotiorin (**77**), isochromophilone I (**74**) and tetrahydroisochromophilone (**78**), (Figure 10) were isolated from *Penicillium multicolor* FO-2338 and *P. sclerotiorum* X11853, and demonstrated to be gp120-CD4 binding inhibitors.[54] (+)-Isorotiorin and ochrephilone displayed also endothelin receptor binding properties,[55] while ochrephilone and isochromophilone I proved to possess antitrypanosomal activity. Ochrephilone was fivefold less active against trypanosomes than isochromophilone I, a result attributed to the presence of a chlorine atom in the latter.[56]

The related rubrorotiorin (**79**) was isolated from *Penicillium multicolor* FO-2338, *Chaetomium cupreum* CC3003 (isolated from Thai soil) and *P. hirayamae* Udawaga, and demonstrated to be a cholesteryl ester transfer protein (CETP), gp120-CD4 binding inhibitor, and also to display antifungic activity against *Candida albicans* (IC_{50}= 0.6 μg/mL).[57]

The related deflectins have been isolated by the group of Anke in 1981 from *Aspergillus deflectus*, a member of the *A. ustus* group,[58] and reisolated in 2010 from cultures of a strain of *Aspergillus deflectus* CBS 109.55 grown on RA medium.[59] Deflectins 1b (**80**) and 2a exhibited antibacterial and weak antifungic properties, with cytotoxic activity against Ehrlich carcinoma cells of mice, being lytic towards bacteria and red blood cells. In this assay, deflectins 1a (**81**), 1c (**82**) and 2b were inactive. This prompted the authors to suggest that in sensitive cells, one of the primary targets of the deflectins might be the cytoplasmic membranes.

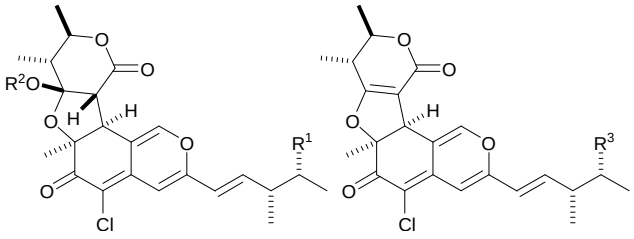
Azaphilone derivatives RP 1551-1 (**83**), 3, 4, 5, 6, 8 and M1, isolated by the group of Toki in 1999 from *Penicillium sp.* SPC-21609, demonstrated to possess antibiotic activity against *Bacillus subtilis*, *Enterococcus faecium* and *Staphylococcus aureus*.[60] They also proved to inhibit the binding of platelet-derived growth factor (PDGF) AA to the extracellular domain of PDGF α-receptor (IC_{50}= 0.1 to 2 μM) without affecting PDGF BB binding to the extracellular domain of PDGF α-receptor.

On the other hand, chermesinones B (**86**) and C (**93**), were isolated in 2011 from the culture of the mangrove (*Kandelia candel*, collected from the South China Sea in Guangdong Province, China) endophytic fungus *Penicillium chermesinum* (ZH4-E2).[61]

Chermesinone B is the C-12 epimer of monochaetin (**87**), a natural product isolated in 1970 from *Monochaetia compta*, that was reformulated as a tricyclic lactonic azaphilone by Steyn and Vleggaar in 1986.[62]

Chaetomium sp. is the third most common indoor fungal contaminant of mouldy damp buildings and the largest saprophytic Ascomycetes genera. It is also a common colonizer of soil and cellulose-containing substrates. The chaetomugilins A-F (**96**, **98-102**), seco-chaetomugilins[63] as well as the dechlorinated derivatives dechloro-chaetomugilins[64] have been isolated since 2005 by several research groups, from various strains of *Chaetomium globosum* obtained from different sources.[65] Particularly relevant was the exhaustive study carried out by the group of Yamada, of products from *Chaetomium globosum* isolated from the marine fish *Mugil cephalus*, which unveiled most of this family members.[Y249,66]

Table 3. Cytotoxicity of the chaetomugillins A-F against P388 and HL-60 cell lines.



Chaetomugillin	R_1	R_2	R_3	P388 IC_{50} (μM)	HL-60 IC_{50} (μM)
A	OH	H		8.7	7.3
B	OH	Me		18.7	16.5
C			OH	3.6	2.7
D	H	H		7.5	6.8
E	H	Me		15.7	13.2
F			H	3.3	1.3
5-Fluorouracil				1.7	2.7

The seco-chaetomugilin A as well as the chaetomugilins A-F (Table 3) and K-O displayed selective cytotoxicity or growth inhibition activity against several tumor cell lines. In addition, chaetomugilins A (**96**) and B (**98**, also isolated from a *C. globosum* found as an endophyte of *Gingko biloba*),[67] exhibited antifungal activity.[M7580]

The chaetoviridins A-D were first isolated in 1990 from the soil strain *Chaetomium globosum flavo-viridae* by the group of Takahashi. Since then, chaetoviridins A (**88**) and B were also found in *Penicillium multicolor* FO-2338 and demonstrated to be antifungal agents against *M. grisea* and *Puccnicia recondite* (wheat leaf rust). These were also found to be inhibitors of the CETP and of the growth (*in vitro*) of *Magnaporthe grisea* (rice blast) and *Pythium ultimum* mycelia, with MIC values of 1.23 and 33.3 μg/mL, respectively. Chaetoviridin A also displayed anti-inflammatory activity.[68,P309]

Other members of this group have been isolated more recently. Collado, Pupo and coworkers greatly expanded in 2011 the amount of known chaetoviridins with their isolation of chaetoviridins G-I and several epimeric compounds from *Chaetomium globosum* isolated from the leaves of *Viguiera robusta* (Asteraceae) and cultivated in PDB medium for 21 days.[69]

Watanabe, Tang and co-workers recently disclosed the identification and characterization of the *caz* biosynthetic cluster from *Chaetomium globosum* and the characterization of a highly reducing polyketide synthase (PKS) that acts in both a sequential and convergent manner with a nonreducing PKS to biosynthesize chaetomugilin and chaetoviridin. Their studies, involving genetic inactivation, assessed the involvement of individual *caz* genes in the biosynthesis of the azaphilones. In addition, through *in vitro* reconstitution, it was demonstrated the *in vitro* synthesis of chaetoviridin A from cazisochromene, a pyranoquinone intermediate, using the highly reducing PKS and an acyltransferase.[70]

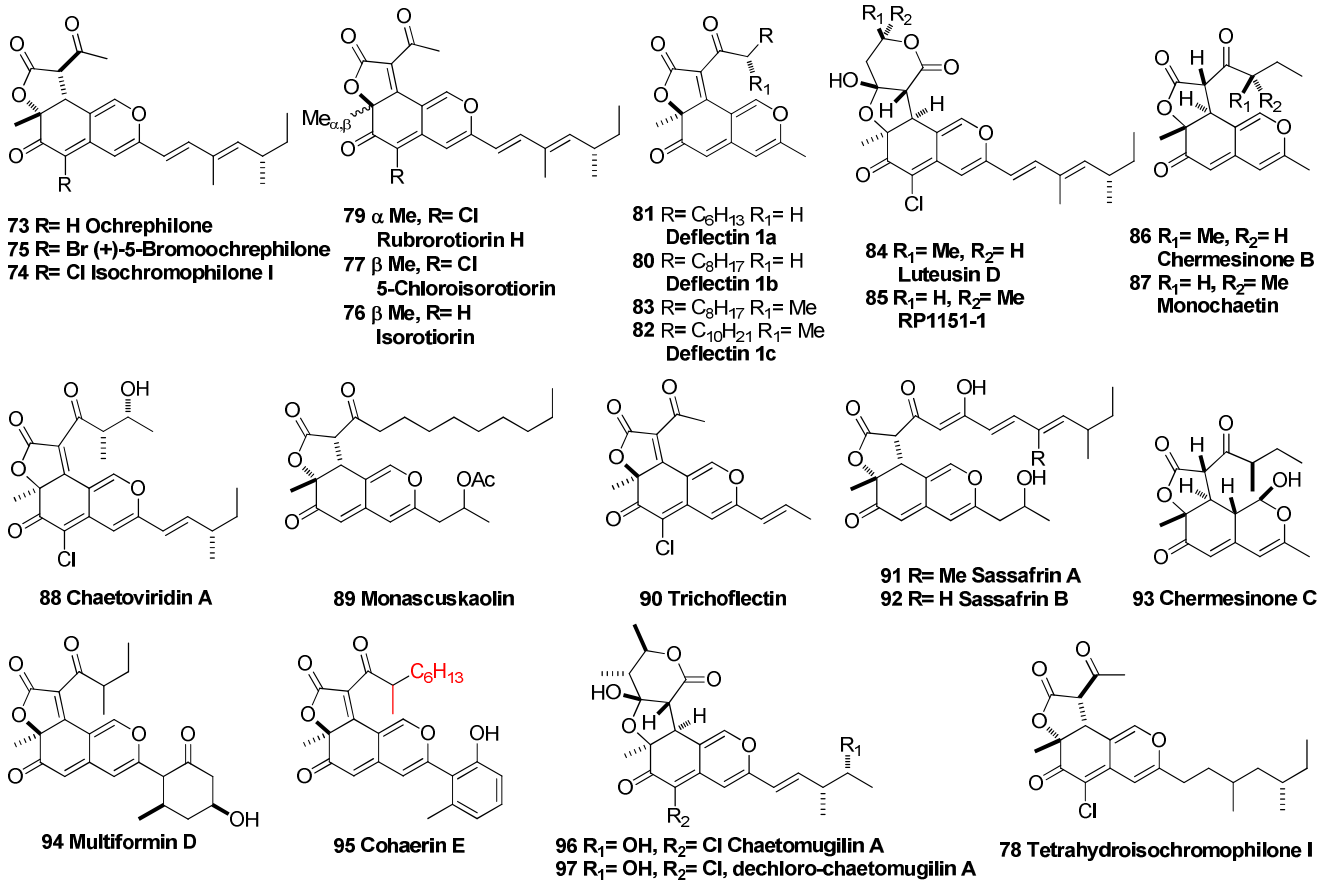


Figure 10. Structural diversity of the lactonic angular azaphilones. Chemical structures of selected members of this family.

The structure of chaetoviridin A (**88**) was confirmed by a single-crystal X-ray diffraction analysis[B1182] and the absolute configurations of chaetoviridin D, 5'-epichaetoviridin A and 4'-epichaetoviridin A were determined employing Mosher's method. The antibiotic activity of the compounds was evaluated using an *in vivo Caenorhabditis elegans* infection model. Chaetoviridin A showed weak inhibitory activity of monoamine oxidase (IC_{50}= 0.012 μg/mL); it also proved to be inductor of chlamidospore-like cells (40-50% at 100 μg/disc) as well as inhibitor if the growth of *Pyricuralia oryzae* (2.5 μg/mL).[T625]

Monascuskaolin (**89**) was recently isolated from the ethanolic extract of the red yeast rice fermented with the yellow mutant of the fungus *Monascus kaoliang* BCRC 31506. The natural product also exhibited inhibition on NO production in LPS-stimulated RAW 264.7 macrophages *in vitro* (MIC= 7.62 μg/mL).[71]

The luteusins C, D (**84**) and E were isolated in 1996 by the group of Yoshida from *Talaromyces luteus* IFM42239, and their structures were established by spectroscopic means.[72] The compounds were tested as MAO inhibitors, but demonstrated to be inactive. On the other hand, trichoflectin (**90**) was obtained from *Trichopezizella nidulus*.[73] This azaphilone was found to be an antimicrobial agent and an inhibitor of the biosynthesis of dihydroxynaphthalene melanin in fungi.

The group of Asakawa disclosed the isolation of sassafrins A (**91**), B (**92**) and C. These are the red pigment of *Creospharea sassafras* (Schwein.: Fr.) Y.-M. Ju, F. San Martin & J. D. Rogers (previously classified as *Hypoxylon sassafras*) collected in Rimont (Ariége, France). *H. sassafras* is a xylariaceous fungus widespread around the world and found in Brazil, Canada, Chile, France, Italy, Taiwan, and North America;[74] the sassafrins were suggested as taxonomic markers of this fungus, placing it as a member of a distinct genus within the Xylaraciae.[T1743]

The natural products displayed moderate to strong antibacterial and antifungal activity against a panel of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Salmonella enteritidis*, *Escherichia coli*, *Aspergillus niger* and *Candida albicans*. However, collectively observed, these effects appeared to be non-selective, because all of the azaphilones affected both, fungi and bacteria.[Q1743]

These results confirmed previously reported bioactivities for other azaphilones, pointing towards the role of azaphilones as defense metabolites that may protect the stromata of Xylariaceae against colonizing microbes and feeding enemies.

On the other hand, this may also explain the lack of total syntheses of these compounds and why they have not been pursued intensively for drug development. Sassafrins A-C were tested together with other 12 xylareaceous azaphilones as agents that suppresses nitric oxide (NO) production stimulated by lipopolysaccharide (LPS) in RAW 264.7 cells and as antioxidants.[75] Nitric oxide (NO) is a mediator in the inflammatory response involved in host defense. Despite these compounds were not the most potent, these azaphilones helped establishing structure-activity relationships.

The group of Asakawa also reported the isolation of multiformins A-D as novel azaphilones from the xylariaceous inedible mushroom *Hypoxylon (=Annulohypoxylon)*

multiforme.[76] These compounds displayed non-selective antimicrobial activity. In addition, multiformin D (**94**) proved to suppress nitric oxide (NO) production stimulated by lipopolysaccharide (LPS) in RAW 264.7 cells and behaves as an antioxidant.Q34 Some sassafrins and multiformins also displayed nematicidal activity (Table 4).[77]

These pigments are located in extremely high concentrations in granules directly beneath the stromatal surface, particularly in young stromata. This suggests that they may act as an outward directed chemical defense to protect the maturing teleomorphs. Being essential for survival of their producers, they co-evolved with morphological and biological features, and therefore may have taxonomic significance.[78]

The tricyclic cohaerins C-E, isolated in 2006 from *Hypoxylon (=Annulohydroxylon) cohaerens* (collected from decaying tree trunks of *Fagus sylvatica* near Niš city, Serbia and Montenegro), also proved to inhibit the production of nitric oxide (NO) stimulated by lipopolysaccharide (LPS) in RAW 264.7 cells and to be strong non-selective antimicrobials.Q34,[79]

Table 4. Activity of multiformins A-D and sassafrins A-C as inhibitors of NO production, antioxidants and nematicides.

Compound	Inhibition of NO production (IC_{50}, μM)	Antioxidant activity (IC_{50}, μM)	Nematicidal activity (LD_{50}, μM)
Multiformin A			
Multiformin B			10
Multiformin C			10
Multiformin D	13.8	418	100
Sassafrin A	14.7	105	50
Sassafrin B	15.7	54.4	50
Sassafrin C	10.0	62.4	25

1.7. The furo[3,4-f]chroman derivative fuscinarin

Fuscinarin (**103**) is a novel pentaketide metabolite, recently isolated from the mitosporic fungus *Oidiodendron griseum*, a widespread fungus that has been isolated from wood pulp and soil,[80] together with the known fuscin (**104**), repeatedly isolated from *Oidiodendron* species[81] and 10-methoxydihydrofuscin (**105**).

These natural products (Figure 11) effectively competed with the macrophage inflammatory protein 1R (MIP-1R) for binding to human chemokine receptor CCR5 in a scintillation proximity binding assay, exhibiting IC_{50} values of 80, 21 and 154 μmol/L, respectively. Fuscin, an inhibitor of mitochondrial SH-dependent transport-linked functions, has been repeatedly targeted for synthesis.[82]

Fuscinarin shares its tricyclic motif with the tetraterpenoid lactonic antibiotic KS-505a (**107**), isolated from *Streptomyces argenteolus* A-2. The compound is an inhibitor of bovine brain Ca^{2+} and calmodulin-dependent cyclic-nucleotide phosphodiesterase and inhibitor of neurite formation in NG108-15 neuroblastoma × glioma hybrid cells. When administered intraperitoneally, the natural product exhibited *in vivo* anti-amnesia activity in an electroconvulsive shock-induced amnesia model in the rat.[83]

The natural product also exhibits antitrypanosomal activity *in vitro* and *in vivo* against *Trypanosoma brucei brucei* strain GUTat 3.1 and *T. brucei rhodesiense* strain STIB900 (IC_{50}= 1.03 and 1.66 μg/mL, respectively), with selectivity indexes of 26.5 and 16.5, respectively in the acute mouse model. Data suggest that KS-505a is possibly a new candidate compound for discovering more potent new antitrypanosomal drugs.[84]

On the other side, the four optically inactive diastereomeric chromanols **108**-**111** were found in *Aspergillus duracaulis*, as probable metabolic derivatives of 5-*O*-isopentenyl cyclopaldic acid.[85a,b] Compound **109** was also isolated from submerged cultures of the Ascomycete *Lachnum papyraceum* (Karst.) Karst (Hyaloscyphaceae) and shown to possess antibiotic activity.[80c]

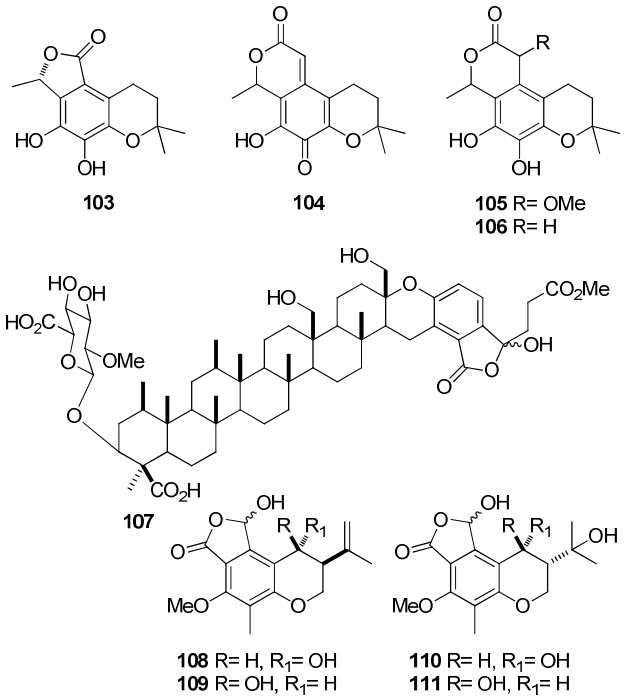


Figure 11. Chemical structures of fuscinarin (**103**), fuscin (**104**), dihydrofuscin (**106**) and 10-methoxydihydrofuscin (**105**), tricycles from *A. duracaulis* **108**-**111** and KS-505a (**107**).

2. Reported syntheses of the natural products

2.1. Total syntheses of pseudodeflectusin

The group of KobayashiS4796,[86] disclosed in 2006 the first total synthesis of (+)-pseudodeflectusin, which served to assign the absolute configuration of the natural product. The authors observed that ochratoxin A (**112**, Figure 12), isolated from some strains of *Aspergillus ochraceus*,[87] has a benzoisochroman skeleton similar to that of pseudodeflectusin; therefore, they considered very likely that the latter has the same absolute configuration. Since the absolute configuration of ochratoxin A was determined by comparison of the optical rotation of the degraded natural product with *R*-(–)-mellein (**113**),[88] a total synthesis of **112** employing *R*-(–)-mellein (**113**) as key intermediate was proposed.

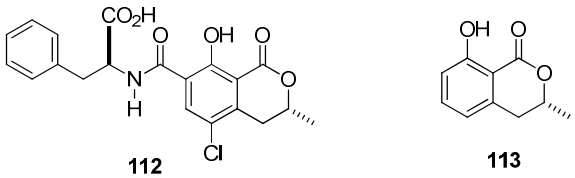


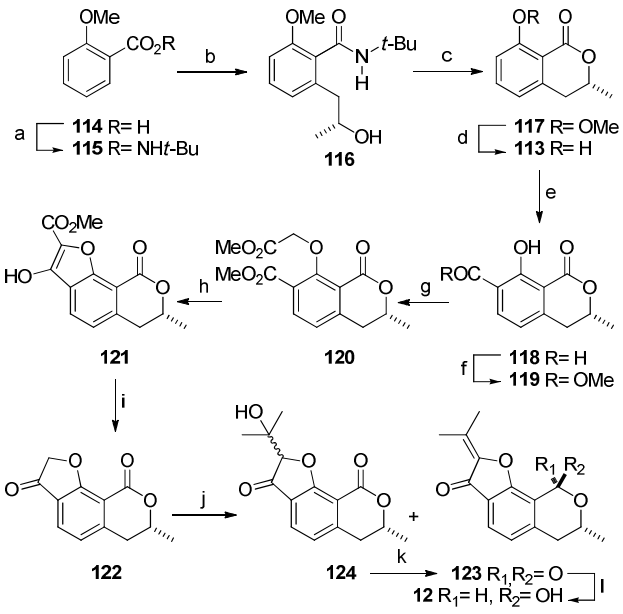
Figure 12. Chemical structures of ochratoxin A (**112**) and *R*-(-)-mellein (**113**).

As shown in Scheme 4, condensation of *o*-anisic acid (**114**) with *tert*-butylamine under DCC promotion afforded 75% of benzamide **115**, which once submitted to *ortho*-metalation with *n*-BuLi-TMEDA, followed by quenching of the orange-colored dianion with *R*-(+)-propylene oxide,[89] gave 61% of alcohol (–)-**116**. Next, intramolecular cyclization assisted by *p*-tosic acid furnished δ-lactone (–)-**117** in 72% yield, while final demethylation with BCl_3 in CH_2Cl_2 afforded (–)-mellein [(–)-**113**] as key intermediate in 95% yield.

Formylation of (–)-**113** with Cl_2CHOCH_3 under $TiCl_4$ promotion afforded 88% of aldehyde (–)-**118**, accompanied by 8% of the *para* isomer;[90] the former was transformed into the related methyl ester (–)-**119** in 91% yield with the NaCN/MnO_2 reagent in MeOH.[91] Interestingly, ester **119** was previously prepared both in racemic and optically active forms.[92]

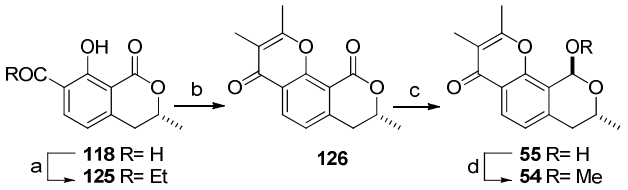
Alkylation of the phenol moiety of **119** with methyl bromoacetate and potassium carbonate proceeded in 98% yield, while NaOMe-assisted cyclization of the resulting (–)-**120** furnished intermediate β-ketoester (–)-**121**, which upon hydrolysis and decarboxylation with LiOH in aqueous DMSO gave 80% of furanone (–)-**122**.[93]

The methylethylidene moiety was installed by reaction of (–)-**122** with acetone under *p*-TsOH·H_2O promotion, which yielded a 2:1 mixture of the expected product **123** and tertiary alcohol **124** in combined 73% yield. Mesylation of alcohol **124** in pyridine was followed by elimination of MsOH from the tertiary mesylate and furnished 72% of (–)-**123**. To complete the synthesis, lactone (–)-**123** was partially and selectively reduced with DIBAL at –78°C, affording 28% of the expected lactol **12** [(+)-pseudodeflectusin].[94]



Scheme 4. *Reagents and conditions*: (a) *t*-$BuNH_2$, DCC, DMAP/CH_2Cl_2 (75%); (b) *n*-BuLi, TMEDA, *R*-(+)-propylene oxide/THF, –78°C (61%, 32% recovery of **115**); (c) *p*-TsOH·H_2O/toluene, reflux (72%); (d) BCl_3/CH_2Cl_2, –78°C to 0°C (95%); (e) Cl_2CHOCH_3, $TiCl_4/CH_2Cl_2$, –10°C (88%); (f) NaCN, MnO_2/MeOH (91%); (g) K_2CO_3, $BrCH_2CO_2Me$, DMF, 50°C (98%); (h) NaOMe/MeOH, reflux (93%); (i) LiOH.H_2O, DMSO, H_2O, 75°C (80%); (j) *p*-TsOH.H_2O/acetone, reflux (**123**, 49%; **124**, 24%, **122**, 9%); (k) MsCl, DMAP, pyridine (72%); (l) DIBAL (2.5 equiv.), THF, –78°C (**12**, 28%; **123**, 49%).

However, it was found that the specific optical rotation of synthetic **12** {$[\alpha]_D^{23}$ = +63.7 (*c* = 0.08, MeOH)} was higher than that of natural **12** {$[\alpha]_D^{23}$= +11};[O3539] this was ascribed to contaminants in the sample of the latter.[S4796] On the other hand, chiral HPLC comparison between the synthetic compound, its racemate and the natural product confirmed the stereochemistry of the latter as **12**. Furthermore, the authors unambiguously established the 1,3-*anti* configuration of both stereogenic centers and thus the configuration of the C-9 stereocenter by X-ray crystallography.



Scheme 5. *Reagents and conditions*: (a) 1. EtMgBr, THF, –5°C; 2. MnO_2, CH_2Cl_2 (52% overall); (b) Ac_2O, DBU, pyridine, 60°C (53%); (c) DIBAL, CH_2Cl_2, –78°C (99%); (d) *p*-TsOH, MeOH (91%).

Because the published NMR data of aspergione B (*vide infra*) were close to those of pseudodeflectusin, the authors also synthesized the structure originally assigned to (±)-aspergione B, employing aldehyde (±)-**118** as key intermediate (Scheme 5). The addition of EtMgBr to aldehyde (±)-**118** gave a 1:1 diastereomeric mixture of the alcohols, which upon MnO_2 oxidation afforded ketone (±)-**125**. Kostanecki-Robinson synthesis of the chromone framework proceeded in 53% yield of **126** by treatment of (±)-**125** with Ac_2O and DBU in pyridine at 60 °C,[95] while final selective reduction of the lactone moiety in (±)-**126** with DIBAL in CH_2Cl_2 afforded (±)-**55**. NMR data comparison confirmed that the compound to which the structure of aspergione B was assigned, is actually pseudodeflectusin.

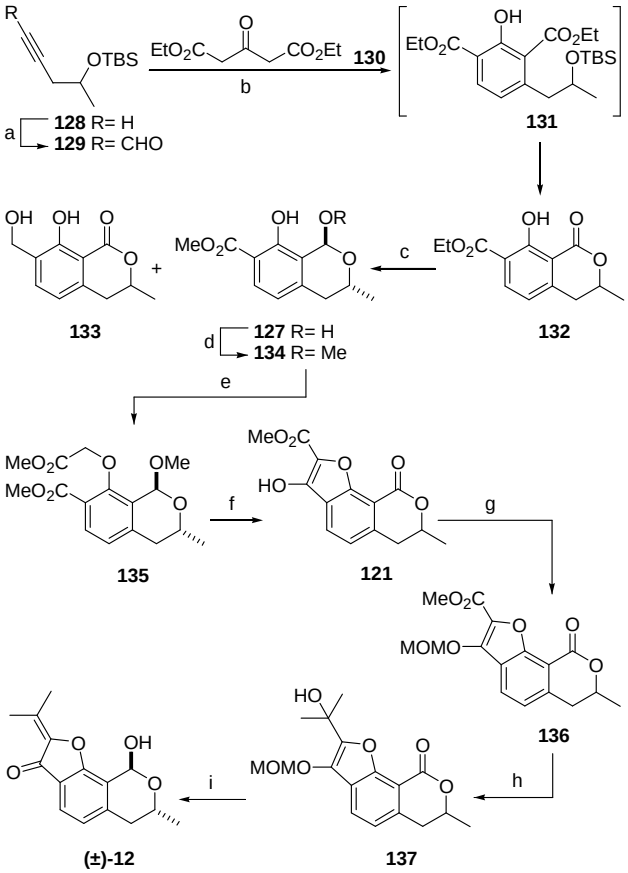
In order to avoid the inconveniencies associated to the chemoselective reduction of the lactone, and taking into account the relatively moderate performance of the final transformations of Kobayashi's synthesis, Tobe *et al.* developed in 2007 an alternative synthesis of (±)-pseudodeflectusin which features the preparation of an acetalic intermediate (**127**) early in the sequence (Scheme 6).[96] Thus, formylation of alkyne **128**[97] by lithiation followed by reaction with DMF afforded 91% of aldehyde **129**, which was cyclocondensed with 3-oxopentane dicarboxylate (**130**) to afford 43% of lactone **132**[98] after deprotection of intermediate TBS ester **131** and subsequent cyclization in the presence of HCl.

Submission of the lactone moiety to the critical reduction with DIBAL gave lactol **127** in mixture with benzylic alcohol **133** (19%), while acetalization of the lactol furnished acetal **134** in 58% overall yield, when the transformation was carried out as a one-pot process. Remarkably, both the lactol and the acetal were

isolated as single 1,3-*trans* diastereomers.

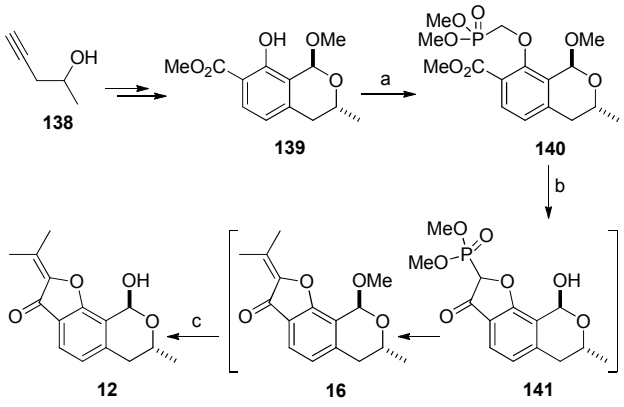
Next, alkylation of the free phenol with ethyl bromoacetate (**137**) paved the road for a Dieckmann condensation,[99] which afforded enolester **121** in 84% overall yield. In turn, the enol was captured as the corresponding MOM ether, which enabled to add MeLi to the ester moiety to access **136**, without risking addition to the carbonylic carbon.

Final treatment with tosic acid in aqueous THF effected the removal of the MOM ether protective group and dehydration of the tertiary alcohol, affording the desired product (**12**) in 43% overall yield for the last three steps. Despite most of the synthetic work was devoted to construction of the properly functionalized furanone motif, this 8-step route proceeded in 8.2% overall yield.



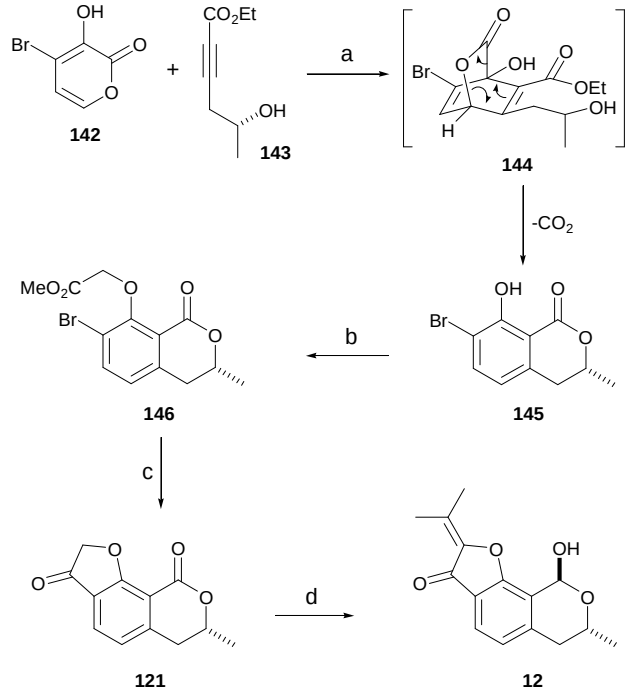
Scheme 6. *Reagents and conditions:* (a) ^{n}BuLi, THF, DMF (91%); (b) 1. Cs_2CO_3, THF; 2. HCl_{dil} (43%); (c) DIBAL, toluene, -78 ºC; (d) MeOH, AcOH (58%); (e) $BrCH_2CO_2Et$, K_2CO_3, acetone, reflux (90%); (f) ^{t}BuOK, THF (93%); (g) MOMCl, DBU, CH_2Cl_2; (h) MeLi, THF; (i) *p*-TsOH, THF-H_2O (43% overall).

The group of Fujiota disclosed in 2012 a short alternative synthesis of (±)-pseudodeflectusin which hinges on an efficient elaboration of the furanone moiety (Scheme 7).[100] The sequence entailed a four step transformation of alkyne **138** into acetal **139**, reminiscent to Tobe's lactonic intermediate **132**, which was then almost quantitatively converted to the *O,P*-acetal **141** by reaction with $TfOCH_2P(O)(OMe)_2$.



Scheme 7. *Reagents and conditions:* (a) $TfOCH_2P(O)(OMe)_2$, Cs_2CO_3, MeCN, rt, 4h (99%); (b) 1. LDA, THF, 0 ºC, 0.5h; 2. Me_2CO, NH_4Cl, rt, 24h; (c) 1M HCl, rt, 32h (82%, overall).

This was followed by a one-pot cyclization under LDA promotion followed by a Horner-Wadsworth-Emmons reaction with acetone to afford (±)-pseudodeflectusin in 82% yield. The overall synthetic sequence involved 6-steps from **138** and proceeded in 16% overall yield.



Scheme 8. *Reagents and conditions:* (a) NaH (1.1 equiv.), dioxane, 200 ºC, 5h (78%); (b) $BrCH_2CO_2Me$, K_2CO_3, DMF, rt (93%); (c) $TMSSnBu_3$, CsF, 4Å MS, THF-DMF, -78 ºC→-50 ºC (58%); (d) ref. S2546.

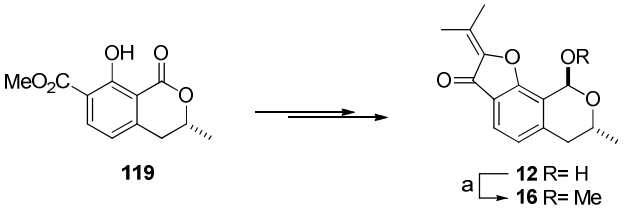
In 2012, the group of Kobayashi reported a more efficient second generation synthesis of (+)-pseudodeflectusin (Scheme 8). To that end, pyrone **142** was subjected to a Diels-Alder reaction with chiral alkyne **143** in the presence of a base. Under these conditions, deprotonation of the hydroxy group of the pyrone favors the reaction.[101]

The reaction was performed at 200 ºC, where the pyrone salt is stable, employing dioxane, which cleanly afforded the product **145** in 78% yield, in a cascade process involving a regioselective Diels–Alder reaction, followed by lactonization to form the heterocyclic ring and decarboxylation to yield the aromatic

moiety. Alkylation of the free phenol with methyl bromoacetate, followed by treatment with $TMSSnBu_3$[102] cleanly afforded moderate yields of the intermediate furanone **121**, which was easily converted into the natural product **12** following known steps.S4796

2.2. Total synthesis of ustusorane C

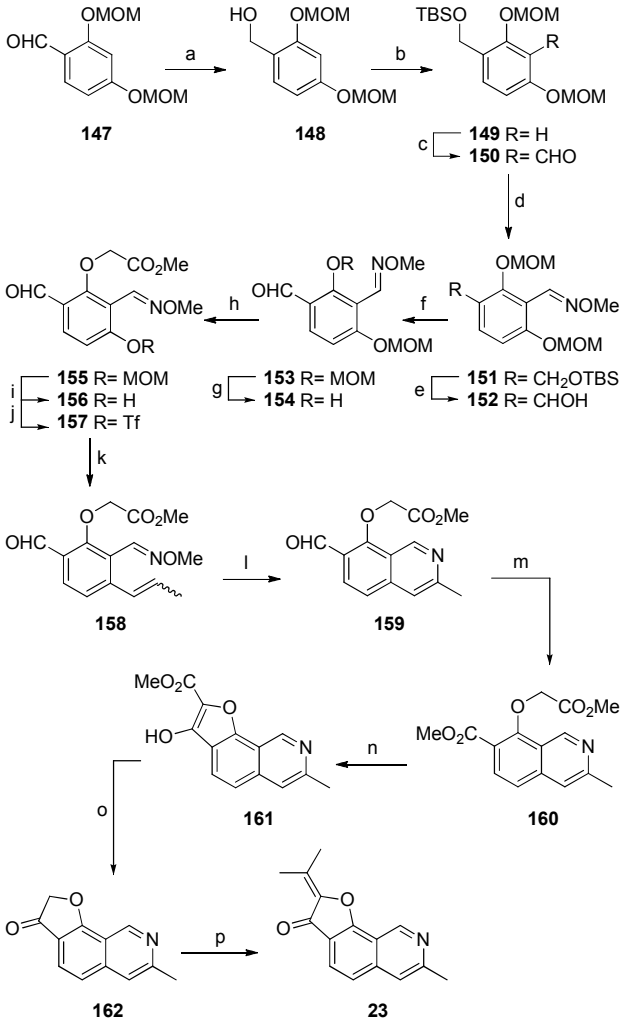
Ustusorane C (**16**) is the methyl acetal derivative of pseudodeflectusin. Kuramochi and coworkers reported in 2010 the total synthesis of ustusorane C employing an extension of the sequence used for the preparation of pseudodeflectusin (Scheme 9). Based on an exhaustive analysis of NMR data of synthetic and natural products, these authors suggested that aspergiones A and B should be structurally revised to ustusorane C (**16**) and pseudodeflectusin (**12**), respectively.[103]



Scheme 9. *Reagents and conditions:* (a) $TsOH.H_2O$, MeOH (100%).

2.3. Total syntheses of alkaloid TMC-120B

The group of Hibino reported the first total synthesis of TMC-120B in 2003[104] from the known aldehyde **147** (Scheme 10).[105] Reduction of the formyl moiety of **147** followed by silylation of the resulting alcohol **148** afforded 77% of intermediate **149**. This was followed by *ortho*-lithiation of **149** and DMF quench of the lithiated species to give 75% of aldehyde **150**.[106] In turn, this was treated with hydroxylamine methyl ether in EtOH to yield 89% of the oxime methyl ether **151**.



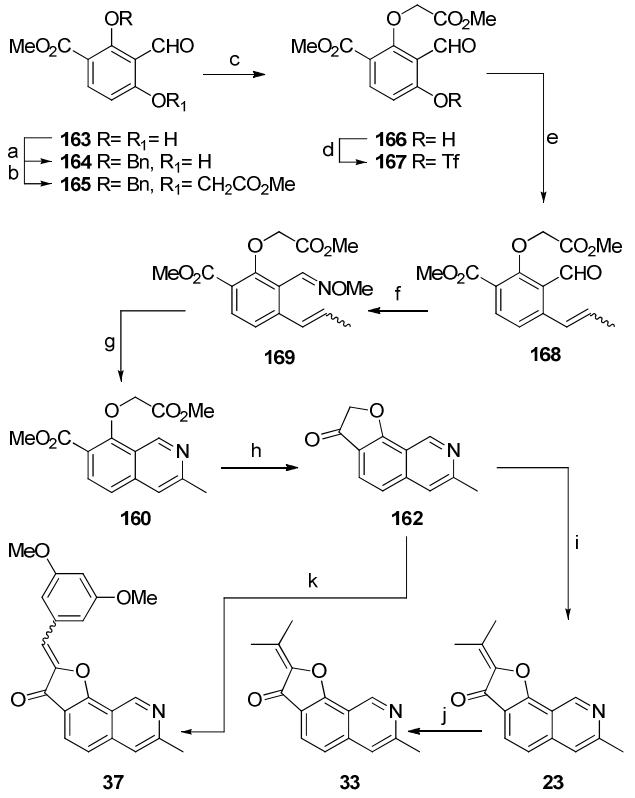
Scheme 10. *Reagents and conditions:* (a) $NaBH_4$, EtOH, rt, 2h (90%); (b) TBDMSCl, imidazole, DMF, rt, 12h (85%); (c) 1. ^{n}BuLi, THF, 40 min; 2. DMF, 0 ºC, 20 min (75%); (d) $MeONH_2.HCl$, NaOAc, EtOH, 80 ºC, 12h (89%); (e) TBAF, THF, rt, 1.5h (92%); (f) MnO_2, CH_2Cl_2, rt, 24h (89%); (g) $HCl_{conc.}$, MeOH, 0 ºC, 3h (92%); (h) NaH, DMF, $BrCH_2COOMe$, rt, 12h (93%); (i) AcOH, 90 ºC, 12h (80%); (j) Tf_2O, pyridine, CH_2Cl_2, 0 ºC, 4h (85%); (k) $Bu_3SnCH{=}CHMe$, Et_4NCl, $PdCl_2(PPh_3)_2$, DMF, 80 ºC, 4h (83%); (l) 1,2-$Cl_2C_6H_4$, 180 ºC, 30 min (44%); (m) NaCN, AcOH, MnO_2, MeOH, rt, 4h (83%); (n) NaOEt, MeOH, 80 ºC, 12h (66%); (o) $LiOH.H_2O$, DMSO-H_2O, 70 ºC, 2h (75%); (p) 1. LDA, Me_2CO, THF, -78 ºC, 4h; 2. $MeSO_2Cl$, DMAP, pyridine, 0 ºC, 2h (33%).

Next, desilylation of **151** was carried out with TBAF in 92% yield and oxidation of the resulting benzylic alcohol afforded benzaldehyde **153** in 89% yield. Selective cleavage of the *ortho*-disubstituted MOM-ether group furnished 92% of **154**, which was alkylated with methyl bromoacetate (93%). The removal of the remaining MOM-ether in hot AcOH gave 80% of 4-hydroxy benzaldehyde **156**, which was transformed into 85% of a mixture of propenyl derivatives **158** by Stille cross-coupling of the intermediate triflate **157** with tributyl-1-propenyltin under $PdCl_2(PPh_3)_2$ catalysis. The 6π-electrocyclization of the propenyl methoxime was performed in refluxing *ortho*-dichlorobenzene,[107] furnishing 44% of the isoquinoline **159**.

Continuing with the reaction sequence, the formyl group was oxidized to the related methyl ester **160** in 83% yield employing Corey's protocolC5616 and the resulting product was subjected to

an intramolecular Dieckmann condensation with NaMeO to afford β-keto ester **161** in 66% yield. Hydrolysis and decarboxylation of **161** with LiOH in aqueous DMSO[T2011] gave 75% of the expected furanone **162**, which upon treatment with LDA followed by acetone quench of the intermediate anion afforded an aldol intermediate. This intermediate was transformed to the final product by reaction with mesyl chloride in pyridine, under DMAP promotion in 33% yield.[108] The synthesis proceeded in 16 steps with 2.5% overall yield; 13 of these steps were devoted to build the trisubstituted isoquinoline moiety (7% yield).

More recently, these authors presented an improved access to key intermediate **160** and reported a most efficient synthesis of TMC-120B, together with a total synthesis of TMC-120A (Scheme 11).[C587] The starting material was methyl 3-formyl-2,4-dihydroxy benzoate (**163**),[109] which was subjected to reaction with benzyl bromide and NaH in DMF. This performed the selective benzylation of the less hindered 6-hydroxy group to give 62% of **164**, and was followed by alkylation of the product with $BrCH_2CO_2Me_3$ to afford 78% of the diester **165**. Catalytic hydrogenolysis of the benzyl ether gave the 4-hydroxybenzoate **166** in near quantitative yield, which was transformed into triflate **167** with triflic anhydride and pyridine at 0 ºC (80%).



Scheme 11. *Reagents and conditions:* (a) NaH, BnBr, DMF, rt, 12h (62%); (b) $BrCH_2CO_2Me$, K_2CO_3, DMF, 50 ºC, 12h (78%); (c) 10% Pd/C, H_2 (1 atm), EtOAc, rt, 2h (98%); (d) Tf_2O, pyridine, CH_2Cl_2, 0 ºC, 2.5h (80%); (e) $Bu_3SnCH{=}CHMe$, Et_4NCl, $Pd(PPh_3)_2Cl_2$, DMF, 80 ºC, 50 min (94%); (f) $NH_2OMe.HCl$, NaOAc, EtOH, reflux, 1h; (g) 1,2-Cl_2-C_6H_4, MW (180 ºC), 15 min (47% overall); (h) 1. NaOEt, MeOH, 80 ºC, 12h (66%); 2. $LiOH.H_2O$, DMSO-H_2O, 70 ºC, 2h (75%); (i) 1. LDA, Me_2CO, THF, -78 ºC, 4h; 2. $MeSO_2Cl$, DMAP, pyridine, 0 ºC, 2h (33%); (j) 10% Pd/C, H_2 (1 atm), EtOAc, rt, 1h (99%); (k) 1. LDA, 3,5-$(MeO)_2$-C_6H_3CHO, -78 ºC→rt, 4h; 2. MsCl, DMAP, pyridine, rt, 1h (61%).

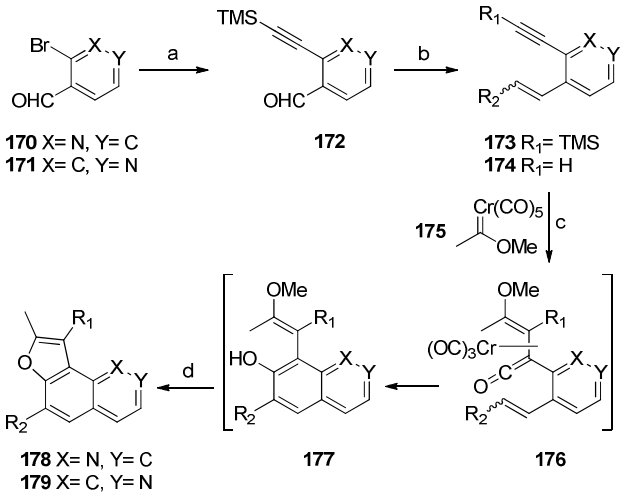
This paved the road to a Stille cross-coupling reaction with tributyl propenylstannane under $PdCl_2(PPh_3)_2$ catalysis, in the presence of Et_4NCl, which afforded 94% of the 2-propenylbenzaldehyde derivative **168**. Oximation of the latter with hydroxylamine methyl ether in refluxing EtOH gave the corresponding methoxime **169**, which was subjected to a microwave-assisted 6π-electron cyclization reaction in *ortho*-dichlorobenzene. Under these conditions, the expected 3,7,8-trisubstituted isoquinoline **160** was obtained in 47% yield from **168**. In this way, the intermediate isoquinoline **160** was accessed from **163** in seven steps and 16% overall yield.

While catalytic hydrogenation of TMC-120B under the same conditions reported by Kohno (10% Pd/C, H_2, 1 atm, EtOAc)[K11247] afforded 99% TMC-120A, attempts to asymmetric reduction with several chiral reagents met with failure.

On the other hand, LDA-mediated metallation of the furanone intermediate **162** followed by addition of 3,5-dimethoxy benzaldehyde and treatment with the methanesulfonyl chloride/pyridine reagent afforded 61% of the benzylidene derivative **37**, the activity of which was also tested (*vide supra*).

Interestingly, 4-phenyl tetrahydroisoquinoline derivatives including the furo[3,2-*h*]isoquinoline tricyclic skeleton of panaefluorolines and the TMC-120 alkaloids have been patented as useful for the treatment of various neurological and psychological disorders.[110]

In addition, analogous furo[2,3-*h*]quinoline and furo[2,3-*h*]isoquinoline derivatives have been recently synthesized by coupling appropriate enyne derivatives with Fischer carbene complexes in a reaction involving the simultaneous one-pot formation of three carbon–carbon bonds and one carbon–oxygen bond, leading to the construction of both the furan and benzene rings.[111]



Scheme 12. *Reagents and conditions:* (a) (Trimethylsilyl)acetylene, $(Ph_3P)_2PdCl_2$, CuI, THF, Et_3N, rt; (b) $Ph_3P{=}CHR_2$, THF, rt; (c) PPh_3, THF, reflux; (d) $H_2SO_{4(cat)}$ (R_1= H, R_2= CO_2Me, X= N, Y= C, 73%; R_1= H, R_2= CO_2Me, X= C, Y= N, 71%).

In these syntheses (Scheme 12), the starting bromoaldehydes **170,171**[112] were subjected to a Sonogashira reaction with (trimethylsilyl)acetylene and the resulting alkynyl aldehydes **172**, were treated with appropriate Wittig reagents to afford the enyne derivatives **173** in good yield. Remarkably, however, when

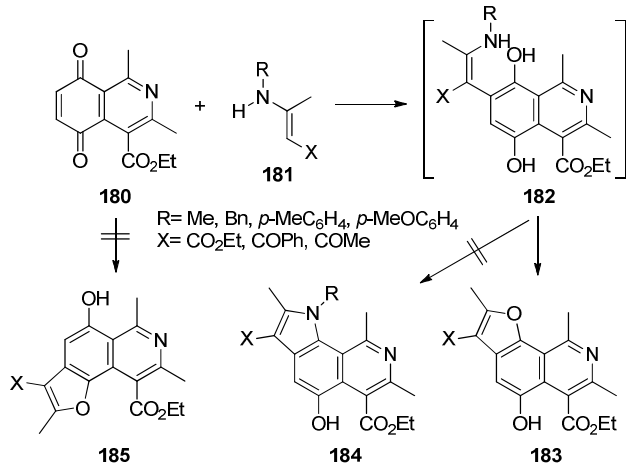
reactive or semi-stabilized ylides were employed, desilylated terminal alkynes **174** were obtained exclusively.

Coupling of the enyne derivative **174** (R_2 = CO_2Me) with the carbene complex **175** in refluxing THF for 20 h in the presence of PPh_3, followed by treatment with catalytic H_2SO_4 gave furoquinoline **178** in 73% yield, through the intermediacy of chromium complex **176** and enolether **177**. Analogously, isoquinoline derivative **179** was isolated in 71% yield.

The mechanism of this transformation resembles that of Dötz benzannulation, because the chromium carbene-generated ketene complex **176** formed by CO insertion cyclizes to afford a phenol derivative (**177**), which provides the furoquinoline or furoisoquinoline products (**178**/**179**), upon acid treatment.[113] The presence of PPh_3 as a ligand additive greatly enhanced the yields of the cyclized products.[114]

Interestingly, furo[2,3-*h*]isoquinoline derivatives and the related thieno heterocycles have been prepared as potential photochemo therapeutic agents with increased antiproliferative activity and decreased toxic side effects.[115]

On the other side, polysubstituted furo[2,3-*h*]quinolones have been prepared by use of the Ninitzescu reaction, entailing the condensation of quinones with enamines (Scheme 13).[116] In view of the results, it seems that reaction of quinone **180** with enamines **181** lead to the hydroquinone-adducts **182**. Nucleophilic attack of the phenol hydroxy group on the α-position of the enamines yield the observed benzofuran derivatives; this prevails on formation of the five membered nitrogen derivatives **184** or the furans resulting from formation and subsequent reactions of the alternate quinone-adducts.



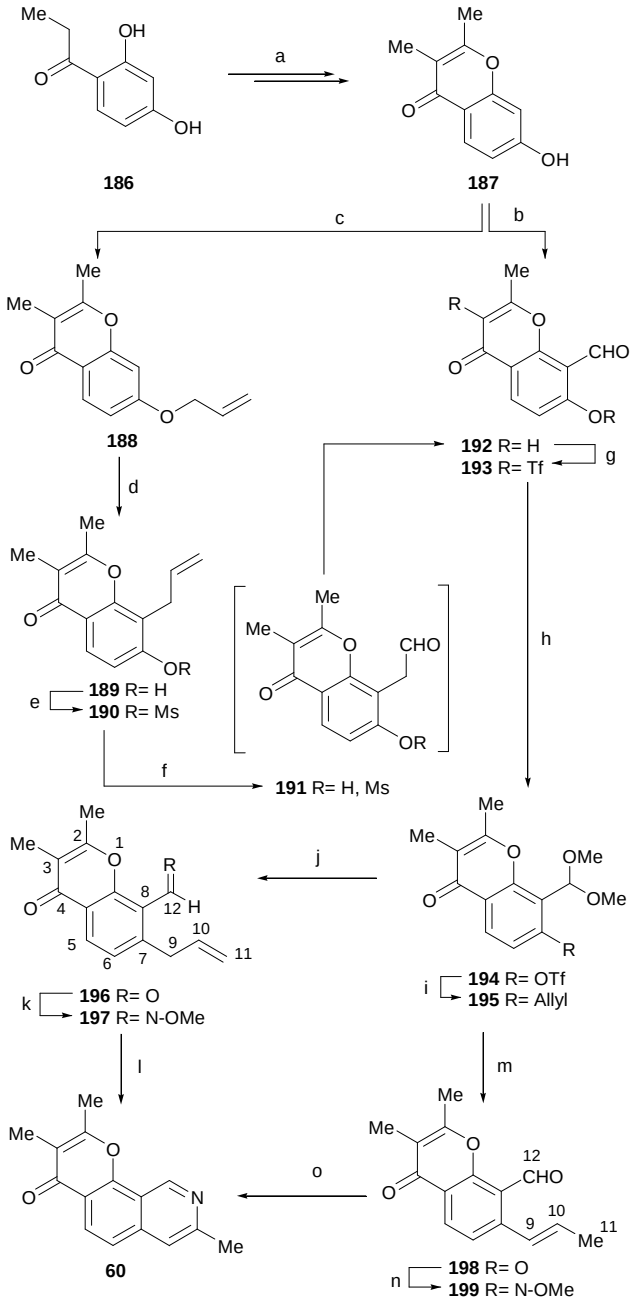
Scheme 13. Furo[2,3-*h*]isoquinoline derivatives by the Ninitzescu reaction.

2.4. Synthesis of the structure originally assigned to aspergillitine. Relationship with alkaloid TMC-120B

Paralleling the relationship between aspergiones A and B (**48** and **49**) with ustusorane C and pseudodeflectusin (**16** and **12**), respectively, the structure proposed by Proksch *et al.* for aspergillitine (**60**) is identical with that of TMC-120B with regards to the isoquinoline moiety; however, they differ in that ring *A* of **60** contains a 2,3-dimethyl-pyran-4-one (2,3-dimethyl-γ-pyrone) motif, while ring *A* of **23** is the isomeric 3-isopropylidene-3*H*-furan-2-one.

The synthesis of the structure originally assigned to aspergillitine was undertaken with the double aim of accessing a unique and unprecedented polycyclic structure and in order to contribute to reveal structural relationships between the natural product isolated by the group of Proksch and TMC-120B.

To that end, the commercially available propiophenone derivative **186** was subjected to a Kostanecki-Robinson synthesis, affording 56% of chromone intermediate **187** (Scheme 14).[117] *O*-allylation, followed by Claisen rearrangement and mesylation of the free phenol afforded **190**, which was treated with catalytic OsO_4 and KIO_4, affording 20% of aldehyde **192**, presumably through the intermediacy of the readily enolizable phenylacetaldehyde **191**.[118] However, carrying out the reaction on the free phenol gave 50% of **192**.



Scheme 14. *Reagents and conditions:* (a) 1. Ac_2O, NaOAc, Δ; 2. Et_3N, Δ; 3. HCl (56% overall); (b) 1. Hexamine, H_2O, AcOH, 100 ºC, 2.5h (72%);

(c) $BrCH_2CH=CH_2$, K_2CO_3, EtOH, reflux, 3h (83%); (d) 1,2-Cl_2-C_6H_4; Δ, 36h (80%); (e) MsCl, pyridine, CH_2Cl_2, 40 ºC, 48h (93%); (f) OsO_4, KIO_4, ^{t}BuOH:0.1M phosphate buffer, pH 8.0 (1:1), rt, overnight (**190→192**, 20%; **189→192**, 50%); (g) *N*-phenyltriflimide, NaH, THF-DMF, rt, 4h (95%); (h) $HC(OMe)_3$, CSA, MeOH, rt, 24h (97%); (i) $^n Bu_3SnCHCH_2=CH_2$, $Pd(PPh_3)_2Cl_2$, LiCl, PPh_3, BHT, DMF, Δ, 18h (80%); (j) SiO_2 (100%); (k) $MeONH_2$.HCl, NaOAc, EtOH, 50 ºC, 12h (76%); (l) $Pd(PPh_3)_4$, $^n Bu_4NCl$, Et_3N, DMF, 80 ºC (18%); (m) 1. $Pd(PPh_3)_2Cl_2$, LiCl, DMF, Δ, 24h; 2. H_2O-THF, 80 ºC, 2h (75%, overall); (n) $MeONH_2$.HCl, NaOAc, EtOH, 50 ºC, 12h (85%); (o) 1,2-Cl_2-C_6H_4, MW, 180 ºC, 30 min (80%).

Because the overall sequence for installation of the 8-formyl unit was deemed unsatisfactory, alternative formylation strategies were sought, among them a Duff formylation. In an optimized process, modification of the hydrolysis stage of the iminium intermediates, which included the use of milder conditions (H_2O, 100 ºC),[16b] afforded 72% of the 8-formyl derivative **192**.

Attempts of triflating the phenol **192** with Tf_2O and a base (*N*,*N*-diisopropylethylamine, 2,4,6-lutidine) were unsuccessful;[119] therefore, the transformation was carried out treatment of **192** with NaH and *N*-phenyltriflimide in a THF-DMF solvent mixture, furnishing 95% of **194**.[120]

Stille's cross-coupling of aldehyde **196** with $^n Bu_3SnCH_2CH=CH_2$ met with failure,[121] yielding products resulting from 1,2-addition to the carbonyl or decarbonylation of the formyl moiety.[122] Therefore, the reaction was performed on the dimethyl acetal [prepared in 97% yield by reaction with $HC(OMe)_3$ in MeOH under CSA catalysis]. This gave access to **195** in 80% yield when $Pd(PPh_3)_2Cl_2$ in DMF were employed.[123] The acetal readily hydrolyzed to **196** during acidic work-up and chromatography on silica gel; oximation of the resulting aldehyde **196** with methoxylamine afforded 76% of the *syn*-methoxime **197**.

The direct amino-Heck cyclization of the 1,3,6-azatriene moiety under the conditions of Tsutsui and Narasaka gave 18% of the tricyclic product.[124] Therefore, acetal **195** was subjected to isomerization with $Pd(PPh_3)Cl_2$ in DMF, affording 75% of aldehyde **198** after work-up and chromatography.[125]

Finally, oximation of **198** to the *O*-methyl oxime **199** (obtained in 85% yield as a 4:1 *syn:anti* mixture of isomers), followed by a microwave-assisted 6π-electrocyclization,[126] provided 80% yield of tricyclic compound **60**. The synthesis was completed in 11 steps and 15% overall yield from 2,4-dihydroxypropiophenone (**186**).

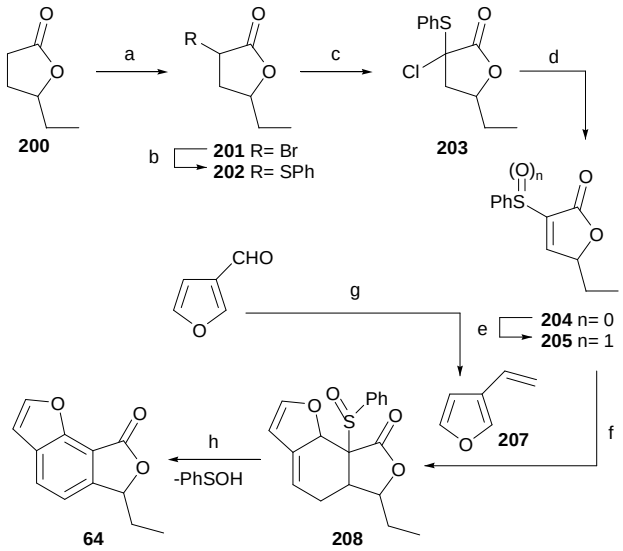
The ^1H and ^{13}C NMR spectroscopic data of synthetic and natural TMC-120B, as well as those of "natural" and synthetic aspergillitine were compared. Resonances of the synthetic aspergillitine did not match those reported by Proktsch *et al.* for the natural product; being very close to those recorded for the synthetic and natural alkaloid TMC-120B (**23**).

Taken together, this means that both, the compound isolated by Proksch *et al*. and TMC-120B should be the same compound, and that the tricyclic structure originally assigned to aspergillitine still remains unobserved among natural products.

2.5. Total syntheses of concentricolide. Determination of its absolute configuration

The total synthesis of concentricolide (**64**) and further investigations on the requirements of its partial analogs for pharmacological activity are undoubtedly important to find new medicines for treating AIDS. Fang and Liu reported in 2009 the first total synthesis of racemic concentricolide from 5-ethyldihydrofuran-2(3*H*)-one (**200**).[127] To that end, the starting furanone was brominated to give 3-bromo-5-ethyl-dihydrofuran-2(3*H*)-one (**201**),[128] which was subjected to nucleophilic attack with thiophenol to afford the 3-phenylthio derivative **202** in **56**% yield (Scheme 15). Exposure of **202** to NCS effected an α-chlorination yielding 82% of **203**. Elimination of HCl by treatment with Li_2CO_3 in refluxing THF gave 35% of the key intermediate furan-2(5*H*)-one **204**.

Oxidation of the sulfide with *m*-CPBA afforded sulfoxide **205** in 82% yield. Next, a Diels-Alder reaction was performed between sulfoxide **205** and vinylfuran **207** [prepared by reaction of 3-formylfuran (**206**) with $TMSCH_2Cl$] for 3 days in the presence of hydroquinone to prevent unwanted reactions.[129] This afforded **208**, which without purification was stirred with $CaCO_3$ in anhydrous toluene to give **64** after loss of PhSOH and further oxidation with concomitant aromatization during column chromatography. The yield of product was less than 4%.

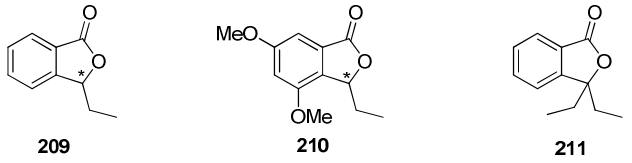


Scheme 15. *Reagents and conditions:* (a) PBr_3/Br_2, 70-90 ºC (57%); (b) PhSH, Et_3N, Et_2O (98%); (c) NCS, CCl_4, reflux (82%); (d) Li_2CO_3, LiBr, THF, reflux (35%); (e) *m*-CPBA, CH_2Cl_2, 0°C (82%); (f) hydroquinone (0.1 equiv.), rt, PhMe, 72h; (g) 1. $TMSCH_2Cl$, Mg, Et_2O, reflux, 9h; 2. 3-formylfuran, 0 ºC, 4h (50%); (h) 1. $CaCO_3$, PhMe, reflux, 19h; 2. [O]-Column chromatography (3.8%).

When concentricolide was isolated, its absolute configuration was proposed as (6*R*) based on an X-ray crystallographic study.[Q127] However, the Mo radiation cannot be used to determine absolute configurations in X-ray experiments. This prompted Ren *et al.* to perform a density functional theory (DFT) study of the absolute configuration of concentricolide, which allowed to propose its configurational reassignment, employing the B3LYP/aug-cc-pVDZ//B3LYP/6-31G(d) and B3LYP/aug-cc-pVDZ//MP2/6-31+G(d) methods, respectively. Similar studies have been successfully performed for other natural products, helping to establish their absolute configurations.[130]

Analogs **209** (*ee*= 99%) and **210** (*ee*= 63%, *S*-enantiomer purified by chiral HPLC to *ee*= 99%) were obtained as racemates and in optically active forms by catalytic enantioselective

addition of Et_2Zn to the corresponding aldehydes (Figure 13),[131] employing (*S*)-2-[(3,3-dimethylbutyl)(methyl)amino]-3-ethyl-1-(1*H*-indol-3-yl)pentan-3-ol or 3-[(1*S*,3*S*)-2-methyl-1-neopentyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]-indol-3-yl]pentan-3-ol, as chiral auxiliaries.[132]



209 **210** **211**

Figure 12. Test compounds employed for the theoretical study on the absolute stereochemistry of concentricolide.

Compounds (*R*)-**209**, (*S*)-**209**, (*R*)-**210**, (*S*)-**210**, (±)-**209**, (±)-**210** and **211** were submitted to theoretical (DFT) and anti-HIV (experimental) studies.[133] The (*R*) configurations of **209** and **210** exhibited better anti-HIV-1 activity than the corresponding (*S*)-enantiomers, being (*R*)-**210** the most potent (EC_{50}= 28 μM; control of zidovudine EC_{50}= 12 μM) in MT4+HIV-LLAI tests. The 3,3-diethylisobenzofuran-1(3*H*)-one displayed very low activity.

The calculated values (Table 5) were close to the experimental or reported ones;[134] therefore, the absolute configuration of *concentricolide* {$[\alpha]^{22}_D$= −59.2} was re-assigned as (6*S*).

Chang and Chien recently reported the first enantioselective total synthesis of *R*-(+)-concentricolide[135] from 2-iodophenol (**212**) in 7 steps, which served to unambiguously establish the absolute configuration of the natural product (Scheme 16).

Table 5. The computed and experimental specific optical rotation values for compounds **64**, **209** and **210** in the gas phase.

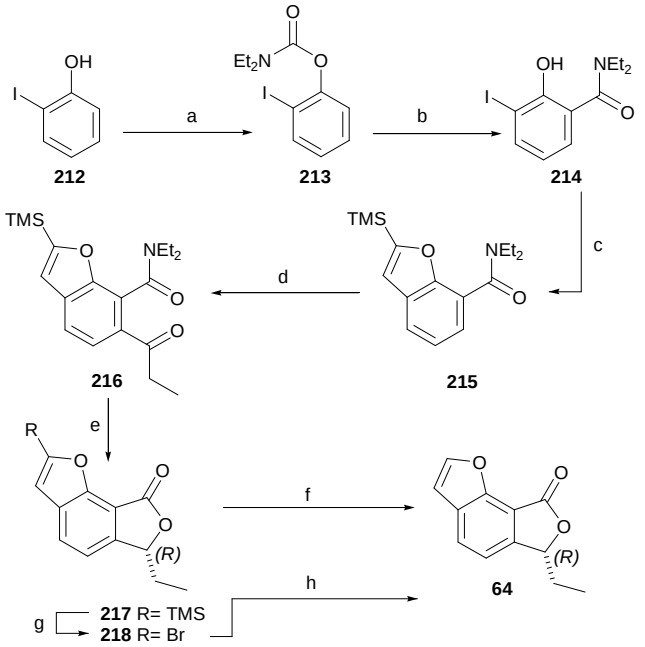
Compd.	Purity (%)	$[\alpha]_D$ Calcd.	Method[a]	Config. proposed	$[\alpha]_D$ Exptl.
64	97	-43.8	A	*S*	-59.2
		-66.1	B		
209	99	-97.3	A	*S*	-81.9
		-102.0	B		-76.0
210	99	-102.8	A	*S*	-98.8
		-83.2	B		
64	Assigned configuration →			*S*	-59.2

[a]Method A: B3LYP/aug-cc-pVDZ//B3LYP/6-31G(d); Method B: B3LYP/aug-cc-pVDZ//MP2/6-31+G(d).

The phenol was converted into the carbamate (**213**),[136] which in turn was subjected to an anionic *ortho*-Fries rearrangement to afford **214**.[137] A Sonogashira coupling of **214** with TMS-acetylene under cuprous and palladium catalysis provided 88% of intermediate benzofuran **215** after cyclization of the acetylenic intermediate.[138]

Ortho-metallation of benzofuran **215** with ^{t}BuLi-TMEDA followed by addition of *N*-methoxy-*N*-methylpropionamide afforded 76% of the propanoyl derivative **216**.[139]

Enantioselective reduction of the ketone moiety under CBS conditions with the *S*-^{n}Bu-CBS catalyst[140] afforded 86% of **217** as a mixture of rotamers, which upon treatment with KOAc furnished 82% of phthalide **64** (*ee*= 80%).



Scheme 16. *Reagents and conditions:* (a) *N*,*N*-diethyl chloroformamide, K_2CO_3, CH_3CN, reflux, 2h (95%); (b) LDA, THF, -60 ºC (72%); (c) trimethylsilylacetylene, Et_3N, $Pd(PPh_3)_2Cl_2$ (1 mol%), CuI (2 mol%), CH_3CN, 65 ºC, 96h (88%); (d) TMEDA, ^{t}BuLi, THF, -80 ºC, 1.5h; *N*-methoxy-*N*-methylpropionamide (76%); (e) (*S*)-B-^{n}Bu-CBS catalyst (0.5 equiv), BH_3.THF, 0 ºC (86%); (f) KOAc, 1,2-$Me_2C_6H_4$, 130 ºC, 1h; (g) TBAF, AcOH, rt, 10 min (82%); (h) Br_2, CH_2Cl_2, rt, 10 min; (i) Zn, AcOH, H_2O, 100 ºC, 1h (95%).

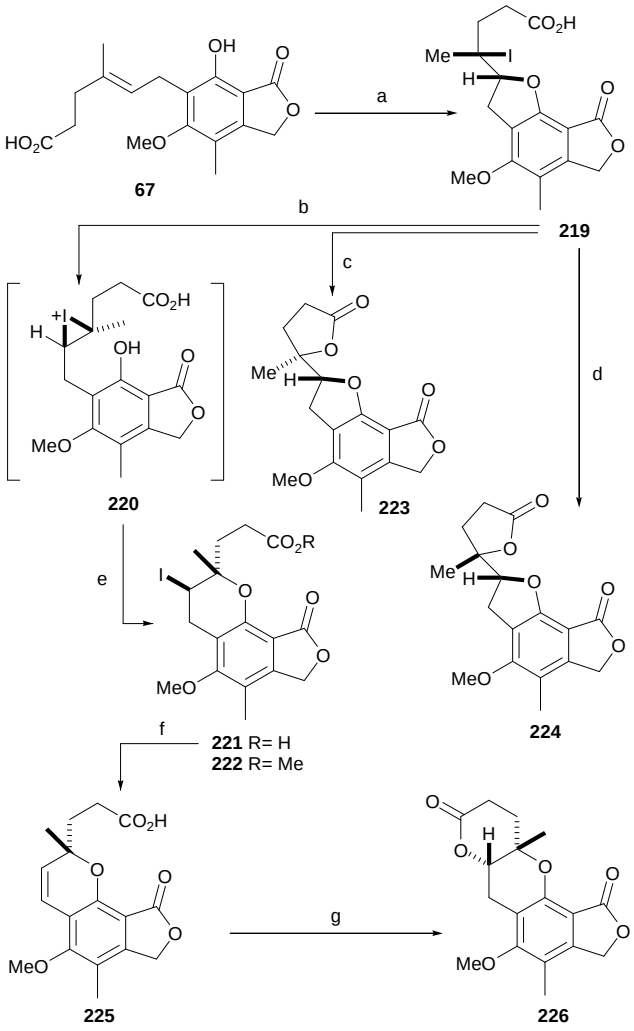
The unexpectedly low enantioselectivity of the product was assigned to the participation of the anilide group in the pre-transition state of the borane-CBS catalyst-ketone assembly. Slow interconversion of the conformers, may negatively affect the facial selectivity of the hydride attack. Desilylation of **217** with TBAF proceeded in a medium buffered with acetic acid to prevent loss of chirality,[141] affording 86% of *R*-(+)-concentricolide {$[\alpha]^{25}_D$= +26.1}.

The configuration of the final product was deduced by application of the CBS rule and also by X-ray analysis of bromide **218**, prepared in 82% yield by treatment of intermediate **217** with bromine in CH_2Cl_2. Zinc/AcOH-mediated debromination of **218** also provided *R*-(+)-concentricolide {$[\alpha]^{25}_D$= +34.8}. Employing the enantiomer of the CBS catalyst for the key reduction step, afforded *S*-(-)-concentricolide {$[\alpha]^{25}_D$= -35.1}.

2.6. Syntheses and uses of some tricyclic mycophenolic acid derivatives

The tricyclic derivative **219** of mycophenolic acid was prepared in roughly 50% yield by shaking mycophenolic acid in bicarbonate solution with iodine in ethyl acetate (Scheme 17). Its stereochemistry was initially proposed on mechanistic grounds, but it was recently confirmed by single crystal X-ray diffraction studies of its methyl ester.[B354] Precipitation of the sodium salt and warming yielded dilactone **223**, while treatment with MeOH and concentrated H_2SO_4 afforded the rearranged chromane ester **222** in nearly quantitative yield, presumably though the intermediacy of iodonium species **220**. The most stable conformer of **222** displays the methyl group quasi axial to the pyran ring, while the

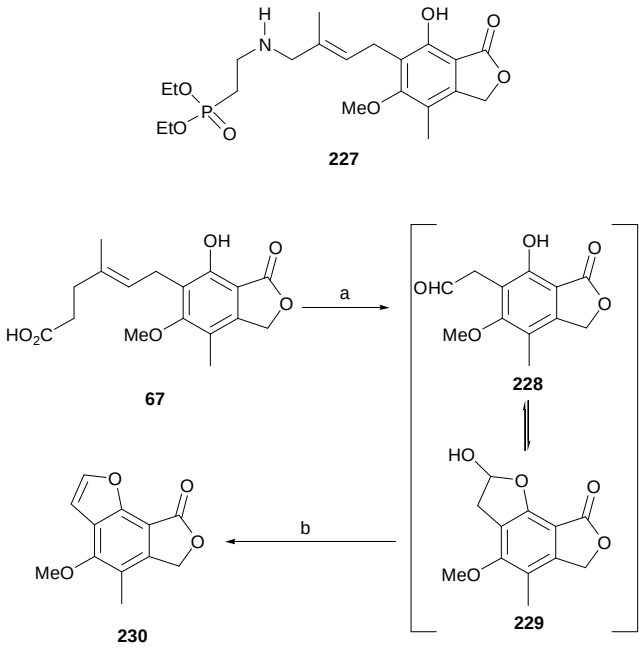
iodine is equatorial.



Scheme 17. *Reagents and conditions:* (a) $NaHCO_3$, I_2, H_2O-EtOAc (50%); (b) H_2SO_4, MeOH; (c) 1. $NaHCO_3$; 2. 50ºC, 5 min; (d) NaOH; (e) H_2SO_4, MeOH; (f) $NaHCO_3$; (g) $NaHCO_3$.

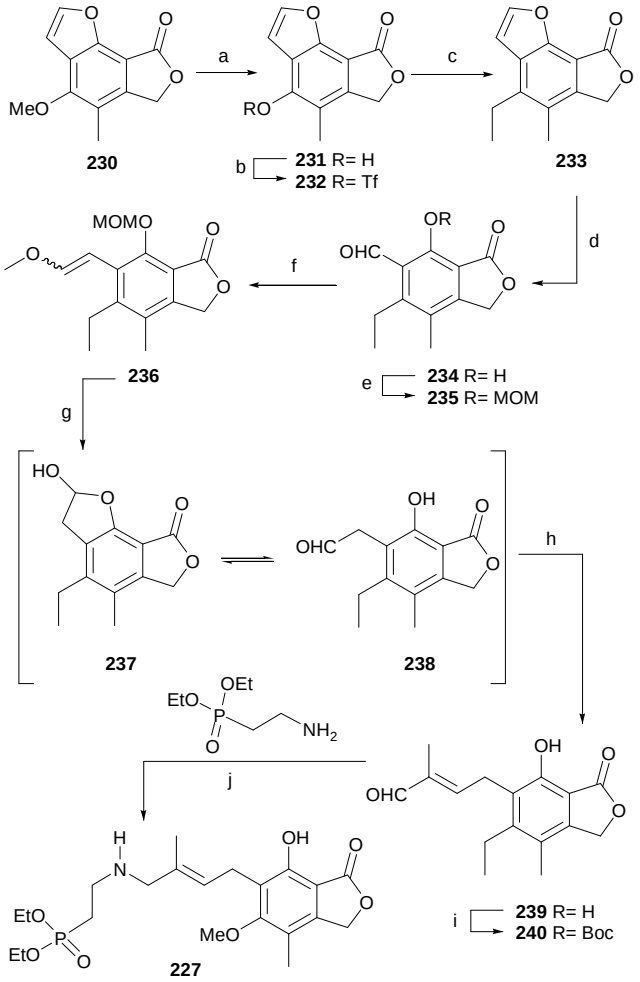
The stereochemistry of the related iodoacid **221** was deduced from formation of mycochromenic acid (**225**) together with tetracyclic dilactone (**226**) upon treatment with bicarbonate. This dilactone showed an equatorial proton geminal to the lactone ether oxygen, which requires the *cis* fused ring system (J_{vic} 2 and 4 Hz). Interestingly, however, exposure of iodide **219** to NaOH afforded lactone **224**, diasteromeric with **223**.C353,J1725

It has been recently discovered that the phosphonate-containing analogue of mycophenolic acid **227** might act as inositol monophosphate dehydrogenase isoforms I and II (IMPDH) inhibitor (IC_{50}= 37 and 13 nM, respectively), while exhibiting more prolonged cellular retention.[142] An improved synthesis of **227** was conceived employing tricyclic derivative **230** as starting material (Scheme 18). This compound features a furan moiety as a joint protecting group for a salicylaldehyde moiety.[143] Tricycle **230** was easily made available by oxidation of the double bond of the side chain with peracetic acid and cleavage of the so produced diol[144] with periodate (79% overall yield). This was followed by acetalization (**228**) and quantitative dehydration of the resulting phenylacetic acid derivative **229** under *p*-tosic acid promotion.



Scheme 18. *Reagents and conditions:* (a) 1. CH_3CO_3H, THF, rt, overnigth; 2. NaOH, rt, 30 min; 3. $NaIO_4$, H_2O, 5 ºC, 45 min (79%); (b) TsOH, PhMe, reflux, 4h (100%).

The synthesis (Scheme 19) started with the installation of the ethyl side chain.[145] To this end, boron-tribromide-assisted demethylation of **230** was carried out to yield phenol **231** (97%), which was converted into the related triflate (**232**) and subsequently submitted to Suzuki coupling with ethylboronic acid under palladium catalysis to afford 96% of intermediate **233**. Ozonation of **233** proceeded in 61% yield, simultaneously uncovering the neighbor formyl and phenol moieties (**234**). Temporary protection of the phenol as the MOM ether (**235**) was followed by homologation of the benzaldehyde to the corresponding phenylacetaldehyde by way of a Wittig reaction with methoxymethyl triphenylphosphonium chloride and acid hydrolysis of the methyl vinyl ether intermediate,[146] which concomitantly removed the MOM ether protecting group. Subjection of aldehyde **238** to a second Wittig reaction towards the unsaturated aldehyde **239** was carried out without need of protecting the phenol, which was quantitatively transformed into Boc derivative **240** before performing the reductive amination required to complete the side chain. Final acidic hydrolysis of the phosphate and Boc moieties furnished the final product.

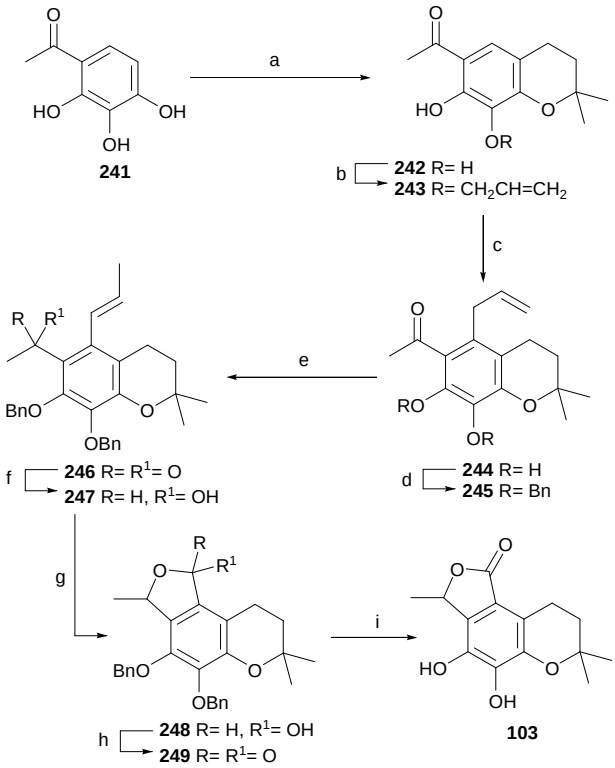


Scheme 19. *Reagents and conditions:* (a) BBr_3, CH_2Cl_2, 4h (97%); (b) Tf_2O, pyridine, CH_2Cl_2, rt, 1.5 h (88%); (c) $EtB(OH)_2$, Cs_2CO_3, $PdDppdCl_2$-CH_2Cl_2, THF, 70 ºC, overnight (96%); (d) 1. O_3, CH_2Cl_2, -78 ºC; 2. SMe_2 (61%); (e) MOMCl, DIPEA, CH_2Cl_2 (89%); (f) $Ph_3PCH_2OCH_3Cl$, KHDMS, THF, -78 ºC→ rt, 1h (71%); (g) H_2SO_4 (77%); (h) Ph_3P=(Me)CHO, PhMe, 80 ºC (75%); (i) $(Boc)_2O$, pyridine, CH_2Cl_2, 30 min (100%); (j) 1. $H_2NCH_2P(O)(OEt)_2$. oxalate, $NaBH(OAc)_3$, AcOH, DMF; 2. 20% TFA, CH_2Cl_2, 0 ºC.

2.7. Total syntheses of fuscinarin

The group of Zi-Xiang recently reported the first total synthesis of fuscinarin (**103**) from gallacetophenone (**241**).[147] The starting ketone (Scheme 20) was reacted with 2-methyl-3-buten-2-ol in refluxing 80% HCOOH to afford 86% of chroman **242** (Scheme 16).[148] This was selectively transformed into the monoallyl ether **243** in 88% yield and further converted into **244** by means of a conventional *para*-Claisen rearrangement (140 ºC, 6 days, 97% yield). Conducting the reaction under microwave irradiation for 5 min also furnished the product in 96% yield.[149]

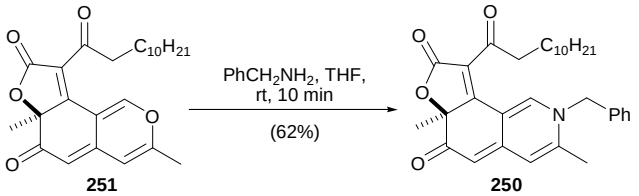
The catechol **244** was protected as the bis-benzyl ether **245** in 93% yield, which was isomerized to the *trans* β-methylstyrene **246** in 96% yield, after treatment with NaOH under phase transfer catalysis.[150] Reduction of the carbonyl moiety with $NaBH_4$ afforded alcohol **247** in 91% yield, the ozonolysis of which gave moderate yield of lactol **248** after quenching with SMe_2.[151] PCC/Al_2O_3 oxidation of the lactol resulted in 90% of lactone **249**, which once subjected to hydrogenolytic debenzylation afforded fuscinarin almost quantitatively.



Scheme 20. *Reagents and conditions:* (a) 2-methyl-3-buten-2-ol; 80% HCO_2H, reflux, 8h (86%); (b) $BrCH_2CH{=}CH_2$, K_2CO_3, acetone, rt, overnight (88%); (c) MW, 5 min, 100 ºC (96%); (d) BnBr, acetone, K_2CO_3, reflux, 6h (93%); (e) TBAB, $NaOH_{aq.}$, PhMe, 75 ºC (96%); (f) $NaBH_4$, EtOH, 8h (91%); (g) O_3, CH_2Cl_2, -78 ºC, Me_2S (65%); (h) PCC/Al_2O_3, CH_2Cl_2, rt (90%); (i) 5% Pd/C, H_2, EtOH, rt (98%).

2.8. Synthetic efforts in the area of lactonic azaphilones and synthesis of similar tricycles

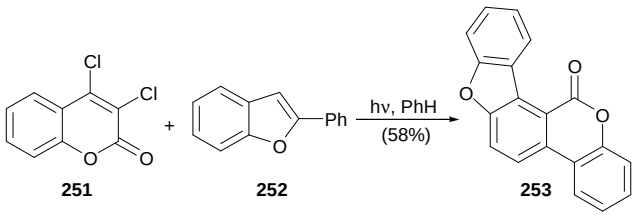
In an attempt to identify the structural requirements involved in the Hsp90 inhibitory activity and exploiting the well-known reactivity of azaphilones with amines, the group of Dalavalle[P6031] converted deflectin **82** into benzylamine derivative **250** (Scheme 21). The derivative exhibited no appreciable Hsp90 binding, like the parent azaphilones, thus confirming the detrimental effect on bioactivity of an angular structure.



Scheme 21. Reactivity of azaphilones with amines.

Interestingly, the photoassisted naphthoannulation of 3,4-dichlorocoumarin (**251**) with 2-phenylbenzofurans, which involves radical cyclization and tandem electrocyclic reactions (Scheme 22), afforded 58% of polycyclic lactone **253**,[152] which shares the tricyclic furo[2,3-*h*]isochroman skeleton with the azaphilones. This compound may be of interest from the point of view of its optoelectric properties; it is bright yellow (UV absorption λ_{max}= 403 nm, e= 2.31 × 10^4 L mol^{-1} cm^{-1} in benzene)

and strongly fluorescent (λ_{em}= 441 nm, ϕ_f= 0.21) in the blue region.



251 **252** **253**

Scheme 22. The photoassisted naphthoannulation of 3,4-dichloro-coumarin (**251**) with 2-phenylbenzofuran (**252**).

In conclusion, fungi are a rich source of chemical diversity, being the source of many drugs and other useful compounds. As only a small part of the mycota is known and most fungi produce several unknown metabolites, fungi are still one of the most promising sources for new lead compounds.

Fungi-derived naturally-occurring angular tricyclic benzofurans in which two heterocyclic rings are fused to a central six-membered motif are a continuously growing set of families of compounds. These were isolated, mostly during the last 15 years, from a handful of fungal species growing in different environments around the world, and exhibit a wide range of interesting biological activities, many of them potentially useful.

Some of these tricycles have been subjects of total syntheses for structural or stereochemical confirmation and biological activity examination, while others still await synthetic and bioactivity studies. It is expected that in the near future, more compounds sharing the angular tricyclic benzofuran motif will be isolated and evaluated as candidates for new developments in the areas of Chemistry and Biology.

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