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PAPER

Synthesis of the unique angular tricyclic chromone structure proposed for aspergillitine, and its relationship with alkaloid TMC-120B†

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The synthesis of the tricyclic angular chromone structure originally assigned to aspergillitine is reported. The synthesis was achieved in 11 steps and 15% overall yield from 2,4-dihydroxypropiophenone, through the intermediacy of 2,3-dimethyl-7-hydroxychromen-4-one. Construction of the nitrogen-bearing heterocyclic ring entailed a Stille cross-coupling reaction with *n*-$Bu_3SnCH_2CH{=}CH_2$, followed by double bond isomerization, oximation of the chromone carbonyl, and a final microwave-assisted electrocyclization of the thus formed 6π-electron aza-triene system.

Introduction

The oceans cover around 70% of the planet's surface and harbor most of the biodiversity of our world, being a unique resource that provides a diverse array of natural products, especially from bacteria, cyanobacteria, fungi and invertebrates, including bryozoans, sponges, tunicates and molluscs.

Therefore, the marine environment contains an immense treasure of useful natural products awaiting discovery. Ecological pressures, including predation and fight for survival, fouling of the surface, competition for space, and continuously evolving environmental conditions have led to the development of secondary metabolites with singular structures and diverse biological activities.

On the other hand, emerging infectious diseases, growth of antibiotic resistance and the continued fight against cancer have all contributed to the increasing interest in the isolation of marine natural products for assessing their potential usefulness against these and other relevant conditions.

In general, marine sponges are known to produce chemicals able to deter predators; many of these released by the diverse microorganisms living within the tissues of the sponge.

In addition, fungi isolated from marine sponges and other filter-feeding invertebrates have recently captured great scientific attention;[1a–c] they relate to the local environment through complex and specialized interactions and were proven to be the single most prolific source of new bioactive natural products.[1d–h]

In 2001, the group of Proksch obtained several heterocycles from a strain of *Aspergillus versicolor* isolated from the marine sponge *Xestospongia exigua*, collected along the coast line of Bali (Indonesia).

They were termed aspergillitine (**1**) and aspergiones A–F (**2a–f**), to which the original tricyclic angular 2,3-dimethylchromone structures shown in Fig. 1 were attributed,[2] on the basis of their NMR spectral analyses. Aspergillitine exhibited moderate antibacterial activity against *Bacillus subtilis*, being inactive against *Escherichia coli* and *Saccharomyces cerevisiae*.

Structures **1** and **2a–f** are unusual in several ways. First, because *Aspergillus versicolor* has been extensively studied and over the years it became the source of many interesting natural products;[3a] however, chromones were not isolated before from this fungus.[3b–h]

Secondly, because the 2,3-dimethylchromone motif is rare[4a] and 2,3-dimethylchromones are uncommon as natural products, exceptions being chromones **3a**, isolated from the mycobiont of the lichen *Graphis scripta*[4b] compound **3b**, obtained from *Thitonia diversifolia*[4c] and *Tussilago farfara*,[4d] chromone **3c**, isolated from *Ligularia microphylla*,[4e] and chaetochromin D, a bis (naphtho-γ-pyrone) derivative produced by the fungus *Chaetomium gracile*.[4f] Interestingly, 2,3-dimethylchromones have been employed as key intermediates for the synthesis of more complex natural and other products.[5]

Finally, the structure assigned to aspergillitine contains a pyridine ring instead of the pyrane-type heterocycle as found in **2a–f**, which conveys to **1** an unprecedented tricyclic core, especially in view that incorporation of nitrogen in fungal polyketides is infrequent.

Taken together, aspergillitine (**1**) and the aspergiones display a structural relationship analogous to that found between the naphthoquinones bostrycoidin and fusarubin, and between their intermediate metabolites, such as 6-deoxybostrycoidin (**4**) and 6-deoxy-3,4-anhydrofusarubin (**4a**).[6]

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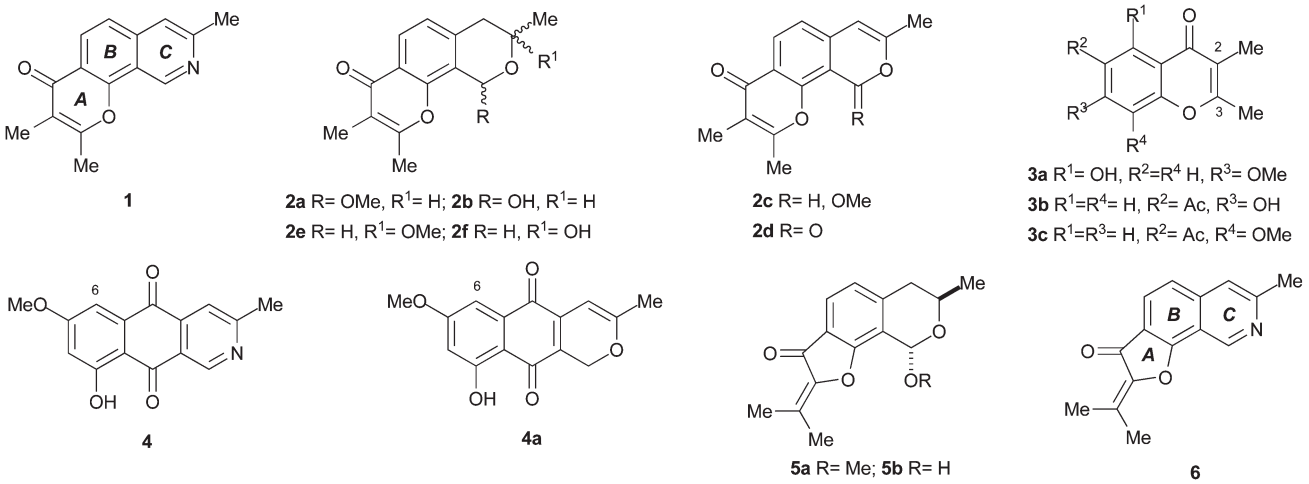


Fig. 1 Chemical structures of aspergillitine (**1**), the aspergiones A–F (**2a–2f**, respectively), and related natural products, including the naturally-occurring 2,3-dimethylchromones **3a–c**, 6-deoxybostrycoidin (**4**), 6-deoxy-3,4-anhydrofusarubin (**4a**), ustusorane C (**5a**), (+)-pseudodeflectusin (**5b**), and alkaloid TMC-120B (**6**).

Unrelated with Proksch's group report, some isochromane derivatives, including ustusorane C (**5a**)[7a] and pseudodeflectusin (**5b**),[7b] were isolated from *Aspergillus pseudodeflectus* (a parasite of the sea weed *Sargassum fusiform*) and *Aspergillus ustus* 094102, respectively. These tricycles displayed interesting cytotoxic activity against several human cancer cell lines.

Chemical syntheses of **5b** and **2b** unequivocally demonstrated that the structure originally attributed to aspergione B (**2b**) was incorrect, and suggestion was made to its reassignment as **5b**.[7c–e] Analogously, the synthesis of aspergiones A, B and ustusorane C further confirmed the identity of Proksch's aspergione A (**2a**) with **5a**.[7f]

Interestingly, the related alkaloid TMC-120B (**6**)[8a–c] was repeatedly found in *Aspergillus*, including *A. ustus* (Bain.) Thom & Church TC 1118, *A. calidoustus* and *A. insuetus*, fungi from the rhizosphere of grass and indoor isolates, and also obtained from *Penicillium* sp. PSU-F40, isolated from a gorgonian sea fan of the genus *Annella*.[8d] This compound exhibited inhibitory activity against the interleukin-5 mediated prolongation of eosinophil survival, being a potential anti-inflammatory agent and was totally synthesized,[8e–g] but connections between its structure and the spectral data reported for aspergillitine were not attempted.

Paralleling the relationship between aspergiones A and B (**2a** and **2b**) with ustusorane C and pseudodeflectusin (**5a** and **5b**), respectively, the proposed structure for aspergillitine (**1**) is identical with that of **6** concerning the isoquinoline moiety; however, they differ in that ring *A* of **1** contains a 2,3-dimethyl-pyran-4-one (2,3-dimethyl-γ-pyrone) motif, while ring *A* of **6** is the isomeric 3-isopropylidene-3*H*-furan-2-one.

We have previously studied the synthesis of natural products of marine origin,[9a,b] and have also synthesized heterocycles carrying the 3-methylisoquinoline motif.[9c] Therefore, we decided to undertake the synthesis of structure **1** with the double aim of accessing a unique and unprecedented polycyclic structure, while also contributing to reveal structural relationships between the natural product isolated by the group of Proksch and compound **6**.

Results and discussion

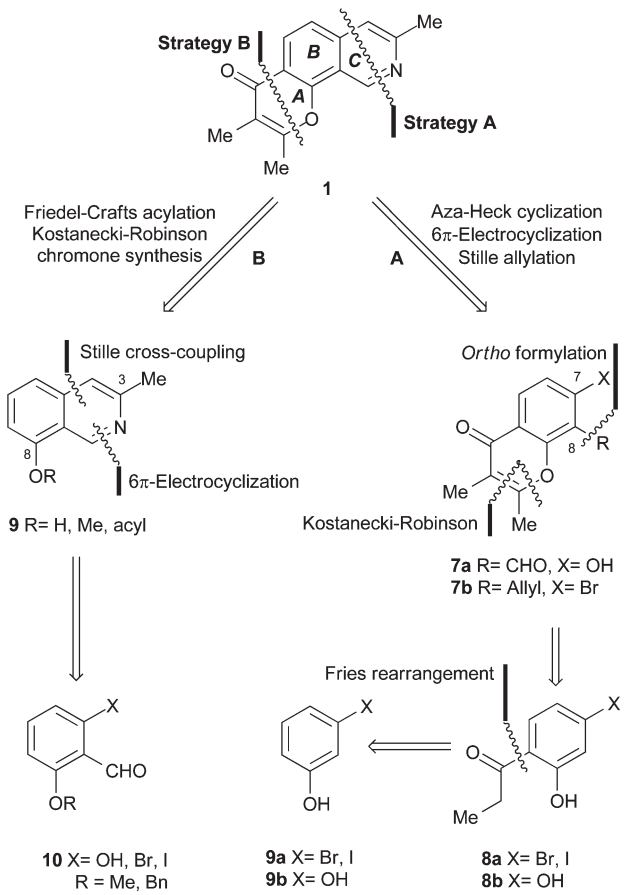
Two retrosynthetic analyses of structure **1**, which resort to the same key transformations in order to generate the *A* and *C* rings, are detailed in Scheme 1. Strategy A pivoted on a *B* → *AB* → *ABC* ring forming sequence.

Disconnection of the marked C–C and C–N bonds on ring *C* unveiled the 7,8-disubstituted chromones **7a,b** as suitable precursors, from which **1** could be accessed by installing a suitable three carbon atoms unit carrying an olefin moiety on 7-C, and a properly substituted benzylidene-amino motif on 8-C to allow an aza-triene cyclization.

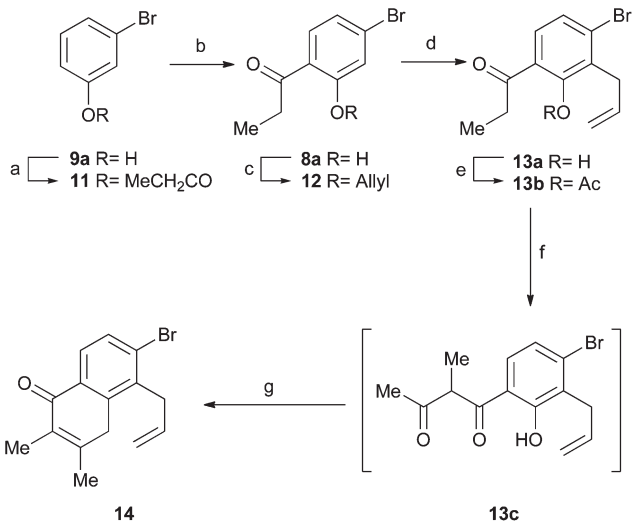
In turn, chromones **7a,b** could be made available from conveniently substituted propiophenones (**8a,b**) by means of a Kostanecki–Robinson synthesis. Properly functionalized propiophenones should result from Friedel–Crafts acylation of phenols or Fries rearrangement of their corresponding propionates.

On the other hand, strategy B was based on the installation of the chromone ring at the end of the synthesis (*B* → *BC* → *ABC*). We envisioned that 8-hydroxyisoquinoline derivatives **9**,[10] uncovered by disconnection of the marked C–C and C–O bonds, would be suitable precursors of **1**. In turn, these could be accessed from 6-substituted salicylaldehyde derivatives **10**.[11] Interestingly, this *B* → *BC* → *ABC* approach has been employed for the synthesis of the oxygen-bearing congeners, the aspergiones A and B,[7c–f] as well as for their isomers, pseudodeflectusin and ustusorane C.[8e,f]

In view of the previous analysis, strategy A was first explored due to its original conception and the comparatively easier availability of the required starting materials. Thus, esterification of 3-bromophenol (**9a**) with propionyl chloride (Scheme 2), followed by an $AlCl_3$-mediated Fries rearrangement of the resulting ester **11** furnished 61% of 4-bromopropiophenone derivative **8a**.[12] In order to install the projected 8-formyl moiety,[13] **8a** was next subjected to a Williamson allylation giving 85% yield of allyl phenyl ether **12**, which once heated in refluxing *ortho*-dichlorobenzene underwent a Claisen rearrangement to *ortho*-allyl phenol **13a** in 64% yield.



Scheme 1 Retrosynthetic analyses of aspergillitine (**1**).



Scheme 2 *Reagents and conditions*: (a) $MeCH_2COCl$, Et_3N, DMAP, Et_2O, 0 °C, 12 h (84%); (b) $AlCl_3$, Δ (61%); (c) $BrCH_2CH{=}CH_2$, K_2CO_3, EtOH, reflux (85%); (d) 1,2-Cl_2–C_6H_4; Δ (64%); (e) Ac_2O, NaOAc, reflux; (f) Et_3N, 115 °C, 14 h; (g) 1 M HCl (12% overall).

Under the conventional procedure, which employs a mineral acid hydrolysis final step, yields of **7a** were around 20%.[14a] Therefore, **7a** was subjected to a Williamson allylation and the resulting product (**16**), was submitted to Claisen rearrangement affording **17** in 66% overall yield.

Finally, a three-step Kostanecki–Robinson synthesis of chromones was carried out. Heating **13a** with fused sodium acetate in refluxing acetic anhydride afforded the corresponding acetate, but did not trigger the expected Baker–Venkataraman rearrangement; therefore, the latter transformation was carried out in Et_3N at 115 °C, and the product was cyclized under mild acid conditions,[15] furnishing **14**, albeit in only 12% overall yield and with poor mass balance.

In view of these results, the starting material was changed to the commercially available propiophenone derivative **8b** (Scheme 3). When carried out on this ketone, the Kostanecki–Robinson synthetic sequence afforded 56% yield of key chromone intermediate **15**,[16] which was immediately subjected to a Duff formylation.

Experiments towards the oxidative fission of the allyl moiety were next carried out. Initially, and in order to avoid potential overoxidation of the substrate, the phenol was protected as the corresponding mesylate **18**. However, treatment of **18** with catalytic amounts of OsO_4 and KIO_4, in a *t*-BuOH:0.1 M phosphate buffer, pH 8.0 (1 : 1) medium gave only 20% of aldehyde **7a**, presumably through the intermediacy of the readily enolizable phenylacetaldehyde **19**.[17] Therefore, and considering the instability of the mesylate group to the reaction conditions, the direct transformation of **17** was performed under the same conditions, obtaining 50% of **7a**.

Despite the slightly improved yields of **7a**, the overall sequence was deemed unsatisfactory and alternative formylation strategies were sought. Interestingly, a simple modification of the hydrolysis stage of the iminium intermediates, which included the use of milder conditions (H_2O, 100 °C) under an inert atmosphere,[14b] led to increased yields of the 8-formyl derivative (72%).

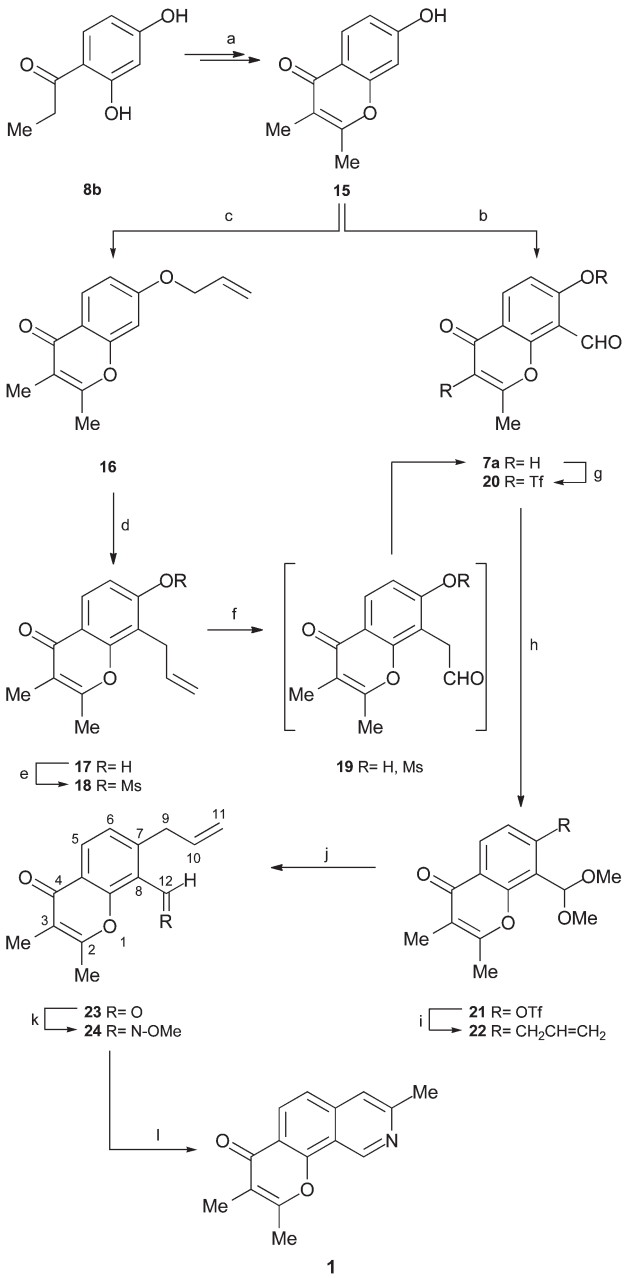
Attempts to triflate the phenolic hydroxyl of **7a** with Tf_2O under assistance of organic bases (*N*,*N*-diisopropylethylamine, 2,4,6-lutidine) met with failure, and yields of **20** lower than 20% were observed.[18,19] Contrastingly, triflate **20** was cleanly accessed in 95% yield by treatment of **7a** with NaH and *N*-phenyltriflimide in a THF–DMF solvent mixture.[19]

Although there are scattered precedents suggesting that aldehyde **20** could withstand the conditions of the Stille cross-coupling reaction,[20] the palladium-catalyzed decarbonylation of aromatic aldehydes and the Pd-catalyzed allylation of aldehydes with allyltributyltin are well-documented transformations.[21]

In fact, when the transformation was attempted with *n*-$Bu_3SnCH_2CH{=}CH_2$, products resulting from 1,2-addition to the carbonyl were obtained when $Pd(PPh_3)_2Cl_2$[20c] was employed as catalyst. On the other hand, use of $Pd(PPh_3)_4$ resulted in decarbonylation or complete degradation of the starting material.

Therefore, the carbonyl moiety of **20** was protected as the corresponding dimethyl acetal **21** in 97% yield with $HC(OMe)_3$ and catalytic amounts of camphorsulfonic acid in MeOH. This allowed access to **22** in 36% yield with the use of $Pd(PPh_3)_4$ in toluene. Nevertheless and to our great satisfaction, changing the catalytic system to $Pd(PPh_3)_2Cl_2$ in DMF settled the installation of the 7-allyl moiety in 80% yield.[22]

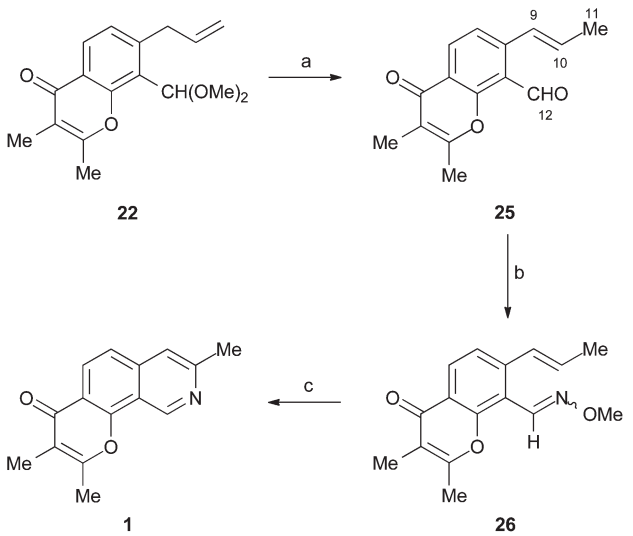
Interestingly, it was observed that the acetal was readily hydrolyzed to **23** during acidic work-up and chromatography on silica gel, and that prolonged reaction times afforded mixtures of the



Scheme 3 *Reagents and conditions*: (a) 1. Ac_2O, NaOAc, Δ; 2. Et_3N, Δ; 3. HCl (56% overall); (b) 1. Hexamine, H_2O, AcOH, 100 °C, 2.5 h (72%); c) $BrCH_2CH{=}CH_2$, K_2CO_3, EtOH, reflux, 3 h (83%); (d) 1,2-Cl_2-C_6H_4; Δ, 36 h (80%); (e) MsCl, pyridine, CH_2Cl_2, 40 °C, 48 h (93%); (f) OsO_4, KIO_4, *t*-BuOH:0.1 M phosphate buffer, pH 8.0 (1 : 1), r.t., overnight (**18** → **7a**, 20%; **17** → **7a**, 50%); (g) *N*-phenyltriflimide, NaH, THF-DMF, r.t., 4 h (95%); (h) $HC(OMe)_3$, CSA, MeOH, r.t., 24 h (97%); (i) *n*-$Bu_3SnCHCH_2{=}CH_2$, $Pd(PPh_3)_2Cl_2$, LiCl, PPh_3, BHT, DMF, Δ, 18 h (80%); (j) SiO_2 (100%); (k) $MeONH_2{\cdot}HCl$, NaOAc, EtOH, 50 °C, 12 h (76%); l) $Pd(PPh_3)_4$, *n*-Bu_4NCl, Et_3N, DMF, 80 °C (18%).

latter and ***E*-25**, resulting from conjugative terminal olefin isomerization.

Oximation of aldehyde **23** in the presence of excess methoxylamine hydrochloride and sodium acetate as base furnished 76% of oxime **24**, as a single isomer. Enhancement of the resonance



Scheme 4 *Reagents and conditions*: (a) 1. $Pd(PPh_3)_2Cl_2$, LiCl, DMF, Δ, 24 h; 2. H_2O–THF, 80 °C, 2 h (75%, overall); (b) $MeONH_2{\cdot}HCl$, NaOAc, EtOH, 50 °C, 12 h (85%); (c) 1,2-Cl_2–C_6H_4, Microwaves, 180 °C, 30 min (80%).

of the protons of the methoxy group attached to the nitrogen (δ_H = 4.04) upon irradiation of 12-H (δ_H = 8.59) in a NOE experiment suggested that **24** was the *syn* methoxime.

The direct amino-Heck cyclization of the 1,3,6-azatriene moiety under the conditions of Tsutsui and Narasaka, which does not involve initial formation of π-allyl palladium species, afforded **1** in a meager 18% yield.

Considering the literature precedents, where pyridine derivatives were prepared from *O*-pentafluorobenzoyl oximes to avoid side reactions, this outcome could be the result of the relatively poor leaving group ability of the *N*-methoxy moiety of methoxime **24** and its reduced capability to suppress these unwanted reactions.[23]

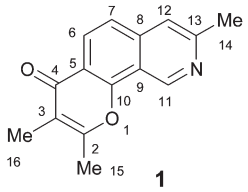
Therefore, isolated acetal **22** was subjected to isomerization with $Pd(PPh_3)Cl_2$ in DMF (Scheme 4), affording 75% of aldehyde **25** after work-up and chromatography.[24] Carrying out the olefin isomerization on the acetal was relevant to the success of the transformation, since subjecting aldehyde **23** to the same reaction conditions resulted in its complete degradation to unidentifiable products.

Finally, oximation of **25** to the *O*-methyl oxime **26** (obtained in 85% yield as a 4 : 1 *syn* : *anti* mixture of isomers) was followed by a microwave-assisted 6π-electrocyclization,[9c] which uneventfully provided 80% yield of tricyclic compound **1**.

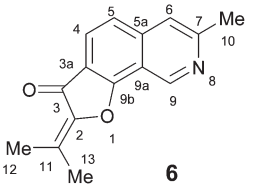
Table 1 shows the ^1H NMR chemical shifts of the synthetic structure **1**, compared to the resonances reported by Proksch *et al.* for their isolated isoquinoline derivative termed aspergillitine, as well as the chemical shifts of synthetic[8e–g] and naturally-occurring[8a] alkaloid TMC-120B.

It can be clearly observed that the chemical shifts of compound **1** do not match those corresponding to aspergillitine as the natural product isolated by Proksch *et al.* However, the resonances disclosed in ref. 2*b*, closely match those of synthetic and natural TMC-120B ($\Delta\delta_H \leq 0.08$), so it can be concluded that the ^1H NMR spectral data reported for Proksch's aspergillitine and

Table 1 Comparison among the ^{1}H NMR chemicals shifts recorded for aspergillitine as the product isolated by Proksch *et al.* and synthetic structure **1**, as well as those for natural and synthetic TMC-120B



1

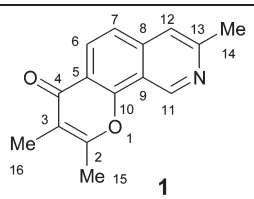


6

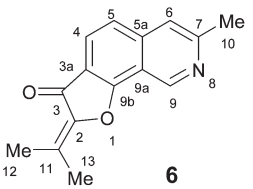
Proton number	Compound **1**[a] (Synthetic) in $CDCl_3$	Compound **1**[a] (Synthetic) in DMSO-d_6	Aspergillitine (after Proksch)[2b] in DMSO-d_6	$\Delta\delta$ (*vs.* **1**, Synthetic)[c] in DMSO-d_6	Proton number	TMC-120B[a] (**6**, Natural)[8a] in $CDCl_3$	$\Delta\delta$ (*vs.* **6**, Natural)[c] in $CDCl_3$	TMC-120B[a] (**6**, Synthetic)[8e,g] in $CDCl_3$	$\Delta\delta$ (*vs.* **6**, Synthetic)[c] in $CDCl_3$
6	8.34 (d, J = 8.6)	8.12 (d, J = 8.5)	7.82 (d, J = 8.6)	−0.30	4	7.80 (d, J = 8.5)	+0.02	7.83 (d, J = 8.6)	−0.01
7	7.61 (d, J = 8.6)	7.76 (d, J = 8.5)	7.38 (d, J = 8.6)[b]	−0.38	5	7.35 (d, J = 8.5)	+0.03	7.38 (d, J = 8.6)	0.00
11	9.77 (bs)	9.70 (bs)	9.54 (s)	−0.16	9	9.52 (s)	+0.02	9.57 (s)	−0.03
12	7.56 (bs)	7.79 (bs)	7.60 (s)[b]	−0.19	6	7.52 (s)	+0.08	7.56 (s)	+0.04
14	2.79 (s)	2.76 (s)	2.69 (s)	−0.07	10	2.74 (s)	−0.05	2.76 (s)	−0.07
15	2.59 (s)	2.56 (s)	2.38 (s)	−0.18	12	2.43 (d, J = 0.7)	−0.05	2.45 (s)	−0.07
16	2.14 (s)	2.00 (s)	2.25 (s)	+0.25	13	2.25 (d, J = 0.7)	0.00	2.26 (s)	−0.01

[a] Atom numbering for **1** and **6** according to ref. 2*b* and 8*a*, respectively. [b] Possible typographic error in the original. [c] Chemical shift differences between Proksch's data and the compound of interest in the designated solvent.

Table 2 Comparison among the ^{13}C NMR chemicals shifts recorded for aspergillitine as the product isolated by Proksch *et al.* and synthetic structure **1**, as well as those for natural TMC-120B



1



6

Carbon No.[a]	Compound **1** (Synthetic) in $CDCl_3$	Compound **1** (Synthetic) in DMSO-d_6	Proksch's data[2b] in DMSO-d_6	$\Delta\delta^b$ in DMSO-d_6	TMC-120B (**6**, Natural)[8a] in $CDCl_3$	TMC-120B (**6**, Synthetic)[8e,g] in $CDCl_3$	Proksch's data[2b] in DMSO-d_6[c]	$\Delta\delta^b$
2	161.1	162.3	144.4	+17.9	145.6	145.6	144.4	+1.2
3	118.9	118.6	133.8	−15.2	182.1	182.3	181.0	+1.3
3a					119.3	119.4	118.4	+1.0
4	177.0	176.2	181.0	−4.8	124.1	124.2	123.5	+0.7
5	124.2	123.4	118.4	+5.0	120.5	120.6	120.9	−0.3
5a					141.3	141.4	140.5	+0.9
6	126.3	125.9	123.5	+2.4	119.5	119.6	119.1	+0.5
7	122.6	119.1	120.9	+1.8	156.7	156.7	156.4	+0.3
8	139.3	139.1	140.5	−1.4				
9	117.3	117.1	113.5	+3.6	146.2	146.2	145.4	+0.8
9a					114.6	114.6	113.5	+1.1
9b					164.0	164.0	163.0	+1.0
10	118.9	118.4	163.0	−44.6	24.7	24.7	24.0	+0.7
11	146.5	146.5	145.4	+1.1	133.7	133.9	133.8	−0.1
12	119.0	119.1	119.1	0.0	17.5	17.6	16.6	+1.0
13	155.7	156.1	156.4	−0.3	20.4	20.4	19.7	+0.7
14	24.4	24.5	24.0	+0.5				
15	18.5	18.6	19.7	−1.1				
16	10.2	10.3	16.6	−6.3				

[a] Atom numbering for **1** and **6** are according to ref. 2*b* and 8*a*. [b] Differences between synthetic aspergillitine (**1**) and synthetic TMC-120B (**6**) with regards to Proksch's data. [c] Proksch's original assignments were not taken into account in order to arrange data for comparison with TMC-120B resonances.

those of alkaloid TMC-120B are in good agreement with each other.

Analogously, Table 2 lists the ^{13}C NMR chemical shifts of synthetic **1**, naturally occurring TMC-120B and synthetic **6**, and

the resonances reported for the tricyclic chromone alkaloid isolated from *Aspergillus versicolor*. It can be clearly observed that the latter data correctly fit structure **6**.

Taken together this means that both, the compound isolated by Proksch *et al.* and TMC-120B should be the same compound, and that structure **1** remains unobserved among natural products.

Conclusions

A concise synthesis of the proposed structure of aspergillitine was completed in 11 steps and 15% overall yield from the known 2,4-dihydroxypropiophenone (**8b**). The synthesis features minimum use of protective groups. The ^{1}H and ^{13}C NMR spectroscopic data of the synthetic aspergillitine do not match those reported by Proktsch *et al.* for the natural product.

Instead, our results confirm that the spectral data disclosed for the nitrogen heterocycle by the group of Proksch are quite similar to those recorded for the synthetic and natural alkaloid TMC-120B (**6**). Therefore, the tricyclic structure originally assigned to aspergillitine still remains unobserved in nature.

In view of its unique structural characteristics, including its planar polysubstituted azacycle character and the presence of an α,β-unsaturated carbonyl system, compound **1** may display biological activity, which will be informed in due course.

Experimental section

General information

All the reactions were carried out under dry nitrogen or argon atmospheres, employing oven-dried glassware. Anhydrous THF and Et_2O were obtained from a M. Braun solvent purification and dispenser system; anhydrous DMF was obtained by heating the PA grade product over BaO for 4 h, followed by distillation under reduced pressure; absolute MeOH and EtOH were accessed by refluxing the solvents over clean Mg/I_2 and distilling from the resulting magnesium alkoxides; anhydrous Et_3N was prepared by distillation of the commercial product from CaH_2; anhydrous CH_2Cl_2 and 1,2-dichlorobenzene were prepared by a 4 h reflux of the solvent over P_2O_5 followed by atmospheric pressure distillation; anhydrous solvents were stored in dry Young ampoules. All other reagents were used as received.

In the conventional work-up procedure, the reaction mixture was diluted with brine (5–10 mL) and the products were extracted with EtOAc (4–5 × 20 mL); the combined organic extracts were then washed once with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography with Merck's silica gel 60 H.

Elution was carried out with hexane–EtOAc mixtures, under positive pressure and employing gradient of solvent polarity techniques. All new compounds gave single spots on TLC plates (silica gel 60 GF_{254}) run in different hexane–EtOAc and EtOAc–EtOH solvent systems.

Chromatographic spots were detected by exposure to 254 nm UV light, followed by spraying with 1% methanolic $FeCl_3$, Dragendorff reagent (Munier and Macheboeuf modification),[25] or with ethanolic *p*-anisaldehyde/sulfuric acid reagent and final careful heating of the plates for improving selectivity.

Apparatus

Melting points were measured on an Ernst Leitz Wetzlar model 350 hot-stage microscope and are reported uncorrected. IR spectra were recorded with a Shimadzu Prestige 21 spectrophotometer, as thin films held between NaCl cells or as solid dispersions in KBr disks. The ^{1}H NMR spectra were acquired at 300.13 MHz on a Bruker Avance spectrometer. The peak for $CHCl_3$ in $CDCl_3$ (δ 7.26) was used as the internal standard. Chemical shifts are reported in parts per million on the δ scale and *J*-values are given in Hertz. The ^{13}C NMR spectra were recorded at 75.48 MHz on a Bruker Avance spectrometer. The peak for $CDCl_3$ (δ 77.0) was used as the internal standard. DEPT 135 and DEPT 90 experiments aided the interpretation and assignment of the fully decoupled ^{13}C NMR spectra. In special cases, 2D-NMR experiments (COSY, HMBC and HSQC) were also employed. Pairs of signals marked with asterisk (*) indicate that their assignments may be exchanged. The high resolution mass spectra were obtained with a Bruker MicroTOF-Q II instrument (Bruker Daltonics, Billerica, MA). Detection of the ions was performed in electrospray ionization, positive ion mode. Microwave-assisted reactions were performed in a CEM Discover microwave oven.

1-(4-Bromo-2-hydroxyphenyl)-propan-1-one (11). A solution of 3-bromophenol (**9a**, 200 mg, 0.865 mmol) and anhydrous Et_3N (2 mL) in dry CH_2Cl_2 (1 mL) was cooled to 0 °C and treated dropwise with propionyl chloride (0.120 mL, 1.18 mmol). The reaction was stirred overnight at room temperature, when the mixture was diluted with brine (5 mL) and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure affording propionate **11** (166 mg, 84%), as an oil. ^{1}H NMR (δ): 1.26 (t, *J* = 7.2, 3H, 3′-H), 2.58 (q, *J* = 7.2, 2H, 2′-H), 7.03 (ddd, *J* = 1.0, 2.1 and 9.0, 1H, 6-H), 7.18 (dd, *J* = 9.0, 1H, 5-H), 7.29 (t, *J* = 2.1, 1H, 2-H) and 7.36 (ddd, *J* = 1.0, 2.1 and 9.0, 1H, 4-H); ^{13}C NMR (δ): 9.0 (3′-C), 27.7 (2′-C), 120.5 (6-C), 122.3 (C-3), 125.1 (2-C), 128.9 (4-C), 130.4 (5-C), 151.3 (1-C) and 172.5 (1′-C). Without further purification, the oily product was mixed with $AlCl_3$ (365.6 mg, 2.74 mmol) and the mixture was briefly heated to 80 °C and then at 160 °C for 3 h. The reaction was cooled to room temperature, diluted with 1 M HCl (5 mL) and the products were extracted with EtOAc (4 × 20 mL). The organic extracts were dried over Na_2SO_4, concentrated under reduced pressure and chromatographed affording propiophenone **8a** (135.3 mg, 51%), as a white solid, m.p.: 48–50 °C (EtOAc, lit.: 48–49 °C).[12b] IR (KBr, *ν*): 3450, 2993, 2943, 1640, 1413, 1199, 960, 866 and 780 cm^{-1}; ^{1}H NMR (δ): 1.24 (t, *J* = 7.2, 3H, 3′-H), 3.00 (q, *J* = 7.2, 2H, 2′-H), 7.03 (dd, *J* = 1.9 and 8.5, 1H, 5-H), 7.18 (d, *J* = 1.9, 1H, 3-H) and 7.61 (d, *J* = 8.5, 1H, 6-H).

1-(2-Allyloxy-4-bromo-phenyl)-propan-1-one (12). A mixture of propiophenone **8a** (135.5 mg, 0.591 mmol) and K_2CO_3 (114.4 mg, 0.827 mmol) in absolute EtOH (3 mL) was treated dropwise with freshly distilled allyl bromide (140.1 mg, 1.16 mmol) and the reaction was heated to reflux until complete consumption of the starting phenol (3 h). The solvent was evaporated under reduced pressure, the residue was dissolved in water and the product was extracted with EtOAc (5 × 20 mL). The

combined organic phases were washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue afforded *O*-allylpropiophenone **12** (135.6 mg, 85%) as a white solid, m.p.: 59–60 °C (EtOAc). IR (KBr, *ν*): 3080, 2979, 2935, 2871, 1666, 1584, 1403, 1367, 1240, 1196, 1092, 999, 800 and 607 cm^{-1}; ^1H NMR (*δ*): 1.15 (t, *J* = 7.2, 3H, 3′-H), 2.98 (q, *J* = 7.2, 2H, 2′-H), 4.62 (dt, *J* = 1.4 and 5.4, 2H, 1″-H), 5.35 (ddd, *J* = 1.3, 2.7 and 10.5, 1H, 3″-H_{cis}), 5.43 (ddd, *J* = 1.3, 2.7 and 17.3, 1H, 3″-H_{trans}), 6.06 (ddd, *J* = 5.4, 10.5 and 17.3, 2″-H), 7.09 (d, *J* = 1.6, 1H, 3-H), 7.14 (dd, *J* = 1.6 and 8.3, 1H, 5-H) and 7.57 (d, *J* = 8.3, 1H, 6-H); ^{13}C NMR (*δ*): 8.4 (3′-C), 37.1 (2′-C), 69.8 (1″-C), 116.3 (C-3), 118.7 (3″-C), 124.1 (5-C), 127.2 (1-C), 127.5 (4-C), 131.7 (6-C), 132.0 (2″-C), 157.9 (2-C) and 202.2 (1′-C); HRMS: Found *m*/*z* = 290.9982; $C_{12}H_{13}BrNaO_2$ $[M + Na]^+$ requires *m*/*z* = 290.9991.

1-(3-Allyl-4-bromo-2-hydroxyphenyl)-propan-1-one (13a). A solution of **12** (135.6 mg, 0.504 mmol) in anhydrous *o*-dichlorobenzene (3 mL) was purged with argon and heated under reflux while stirring during 36 h. The mixture was left to attain room temperature, the solvent was removed under reduced pressure (10 mmHg) and the residue was chromatographed, affording **13a** (62 mg, 46%) as a white solid, m.p.: 222–224 °C (hexane–EtOAc). IR (KBr, *ν*): 3709, 2980, 2940, 1637, 1585, 1431, 1375, 1261, 1150, 1045, 933, 830 and 782 cm^{-1}; ^1H NMR (*δ*): 1.23 (t, *J* = 7.3, 3H, 3′-H), 3.00 (q, *J* = 7.3, 2H, 2′-H), 3.61 (d, *J* = 6.0, 2H, 1″-H), 5.04 (dd, *J* = 1.4 and 10.1, 1H, 3″-H_{cis}), 5.08 (dd, *J* = 1.4 and 17.1, 1H, 3″-H_{trans}), 5.93 (ddd, *J* = 6.0, 10.1 and 17.1, 1H, 2″-H), 7.10 (d, *J* = 8.7, 1H, 5-H), 7.49 (d, *J* = 8.7, 1H, 6-H) and 12.49 (s, 1H, O*H*); ^{13}C NMR (*δ*): 8.2 (3′-C), 31.7 (1″-C),* 33.3 (2′-C),* 115.8 (3″-C), 117.8 (1-C), 122.9 (5-C), 128.2 (6-C), 129.3 (C-3), 132.8 (4-C), 134.0 (2″-C), 161.1 (2-C) and 206.8 (1′-C); HRMS: Found *m*/*z* = 269.0167; $C_{12}H_{14}BrO_2$ $[M + H]^+$ requires *m*/*z* = 269.0172.

8-Allyl-7-bromo-2,3-dimethylchromen-4-one (14). A solution of propiophenone **13a** (67.8 mg, 0.252 mmol) in a mixture of Ac_2O (0.272 mL, 2.67 mmol) and anhydrous Et_3N (0.70 mL, 5.34 mmol) was stirred under reflux during 20 h. The solvent was removed under reduced pressure (*P* < 10 mmHg) and the residue was treated with 1 M HCl (3 mL) at 40 °C for 6 h. Then, the solution was treated with brine (5 mL) and the reaction products were extracted with EtOAc (5 × 15 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated in vacuum. The residue was chromatographed, affording chromone **14** (6 mg, 12%) as a solid, m.p.: 113–114 °C (EtOAc). IR (KBr, *ν*): 2922, 1643, 1591, 1418, 1358, 1184, 1001, 901 and 779 cm^{-1}; ^1H NMR (*δ*): 2.05 (s, 3H, 2-Me), 2.43 (s, 3H, 3-Me), 3.78 (d, *J* = 3.6, 2H, 1′-C), 5.07 (ddd, *J* = 1.6, 3.6 and 11.5, 1H, 3″-H_{cis}), 5.08 (ddd, *J* = 1.6, 3.6 and 15.2, 1H, 3-H″$_{trans}$), 5.93 (ddd, *J* = 3.8, 11.5 and 15.2, 1H, 2″-H), 7.54 (d, *J* = 8.5, 1H, 5-H) and 7.94 (d, *J* = 8.5, 1H, 6-H); ^{13}C NMR (*δ*): 10.0 (3-Me), 18.5 (2-Me), 33.7 (1′-C), 116.4 (3′-C), 117.1 (C-3), 121.8 (4a-C), 124.9 (6-C), 128.6 (5-C), 128.9 (7-C), 129.5 (8-C), 133.5 (2′-C), 154.1 (8a-C), 161.8 (2-C) and 177.7 (4-C); HRMS: Found *m*/*z* = 293.0169; $C_{14}H_{14}BrO_2$ $[M + H]^+$ requires *m*/*z* = 293.0172.

7-Hydroxy-2,3-dimethylchromen-4-one (15). A solution of 2,4-dihydroxypropiophenone **8b** (2.00 g, 12.03 mmol) in Ac_2O (50 mL, 531.2 mmol) was treated with freshly fused NaOAc (5.40 g, 60.15 mmol) and the mixture was heated under reflux for 3 h. Excess Ac_2O was distilled off under reduced pressure, the residue was suspended in EtOAc and the remaining NaOAc was filtered off *in vacuo* (*P* < 10 mmHg), furnishing a mixture of acetates. The acetates were treated with anhydrous Et_3N (2 mL) and the mixture was heated overnight at 115 °C. The reaction was cooled to room temperature, the solvent was removed under reduced pressure and the residue was treated with cold 1 M HCl (100 mL). The resulting suspension was stirred for 6 h at 40 °C and the white precipitate formed was filtered under reduced pressure and washed with cold water. Chromatography of the product afforded **15** (1.248 g, 56%) as a yellowish solid, m.p.: 315–318 °C (EtOH–H_2O, lit.: 315–317 °C).[15] IR (KBr, *ν*): 2923, 1610, 1573, 1445, 1400 and 1249 cm^{-1}; ^1H NMR ($CDCl_3$-DMSO-d_6, *δ*): 1.87 (s, 3H, 3-Me), 2.32 (s, 3H, 2-Me), 6.72 (d, *J* = 2.0, 1H, 8-H) 6.83 (dd, *J* = 2.0 and 8.8, 1H, 6-H), 7.81 (d, *J* = 8.8, 1H, 5-H) and 10.59 (s, 1H, O*H*); ^{13}C NMR ($CDCl_3$-DMSO-d_6, *δ*): 10.1 (3-Me), 18.6 (2-Me), 102.2 (8-C), 115.0 (6-C), 115.3 (C-3), 115.7 (4a-C), 127.2 (5-C), 157.5 (8a-C), 161.7 (2-C), 162.5 (7-C) and 176.3 (4-C); HRMS: Found *m*/*z* = 203.0708; $C_{12}H_{11}O_3$ $[M + H]^+$ requires *m*/*z* = 203.0708.

7-Allyloxy-2,3-dimethyl-chromen-4-one (16). Freshly distilled allyl bromide (0.644 mL, 7.45 mmol) was added dropwise to a mixture of chomone **15** (1.25 g, 6.77 mmol) and K_2CO_3 (3.274 g, 23.7 mmol) in absolute EtOH (10 mL). The reaction was stirred under reflux during 3 h, when the solvent was removed. The residue was suspended with brine (10 mL) and the reaction products were extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed with brine (5 mL), dried Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue furnished *O*-allylchromone **16** (1.253 g, 83%) as a white solid m.p.: 70–73 °C (hexane–EtOAc). IR (KBr, *ν*): 2924, 2854, 1642, 1610, 1573, 1445, 1349, 1249, 1187, 1017, 826 and 772 cm^{-1}; ^1H NMR (*δ*): 2.03 (s, 3H, 2-*Me*), 2.38 (s, 3H, 3-*Me*), 4.61 (d, *J* = 5.2, 2H, 1′-H), 5.34 (dd, *J* = 1.3, and 10.5, 1H, 3′-H_{cis}), 5.44 (dd, *J* = 1.3 and 17.2, 1H, 3′-H_{trans}), 6.06 (ddd, *J* = 5.2, 10.5 and 17,2, 1H, 2′-H), 6.77 (d, *J* = 2.2, 1H, 8-H), 6.94 (dd, *J* = 2.2 and 8.9, 1H, 6-H) and 8.09 (d, *J* = 8.9, 1H, 5-H); ^{13}C NMR (*δ*): 10.0 (3-Me), 18.4 (2-Me), 69.2 (1′-C), 100.6 (8-C), 114.3 (6-C), 116.6 (C-3), 116.7 (4a-C), 118.4 (3′-C), 127.3 (5-C), 132.3 (2′-C), 157.4 (8a-C), 161.2 (2-C), 162.4 (7-C) and 177.4 (4-C); HRMS: Found *m*/*z* = 231.1023; $C_{14}H_{15}O_3$ $[M + H]^+$ requires *m*/*z* = 231.1016.

8-Allyl-7-hydroxy-2,3-dimethyl-chromen-4-one (17). Under a nitrogen atmosphere, a solution of **16** (452 mg, 1.963 mmol) in 1,2-Cl_2-C_6H_4 (2 mL) was heated under reflux for 36 h. The solvent was removed under reduced pressure (*P* < 10 mmHg) and the residue was chromatographed, furnishing **17** (361 mg, 80%) as a white solid, m.p.: 205–207 °C (hexane–EtOAc). IR (KBr, *ν*): 3081, 2925, 2765, 1635, 1574, 1439, 1325, 1193, 1053 and 787 cm^{-1}; ^1H NMR (*δ*): 2.05 (s, 3H, 2-*Me*), 2.41 (s, 3H, 3-*Me*), 3.64 (d, *J* = 6.2, 2H, 1′-H), 5.12 (dd, *J* = 1.6 and 10.0, 1H, 3′-H_{cis}), 5.15 (dd, *J* = 1.6 and 17.2, 1H, 3′-H_{trans}), 6.00 (ddd, *J* = 6.2, 10.0 and 17.2, 1H, 2′-H), 6.26 (s, 1H, O*H*),

6.90 (d, J = 8.7, 1H, 7-H) and 8.00 (d, J = 8.7, 1H, 6-H); ^{13}C NMR (δ): 9.9, (3-Me), 18.4, (2-Me), 27.1, (1′-C), 112.8, (5-C), 113.9 (4a-C), 114.8 (6-C), 115.6 (3′-C), 124.4 (C-3), 127.1 (8-C), 135.6 (2′-C), 155.5 (8a-C), 159.4 (2-C), 161.1 (7-C) and 178.0 (4-C); HRMS: Found m/z = 231.1023; $C_{14}H_{15}O_3$ $[M + H]^+$ requires m/z = 231.1016.

7-Hydroxy-2,3-dimethyl-4-oxo-4*H*-chromene-8-carbaldehyde (7a). *Method A*: Under a nitrogen atmosphere, a mixture of **15** (28 mg, 0.147 mmol) and hexamine (103 mg, 0.735 mmol) in glacial AcOH (2.7 mL) was treated with water (0.013 mL, 0.735 mmol) and stirred 2.5 h at 100 °C. The reaction was allowed to cool to room temperature, when it was diluted with cold brine (5 mL) and the products were extracted with EtOAc (5 × 15 mL). The organic extracts were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed furnishing aldehyde **7a** (23 mg, 72%), as a white solid, m.p.: 180–182 °C (hexane–EtOAc). IR (KBr, ν): 3443, 3084, 2959, 2922, 2853, 1670, 1564, 1553, 1421, 1335, 1281, 1076 and 998 cm^{-1}; ^{1}H NMR (δ): 2.06 (d, J = 0.5, 3H, 2-Me), 2.45 (d, J = 0.5, 3H, 3-Me), 6.95 (d, J = 8.9, 1H, 6-H), 8.32 (d, J = 8.9, 1H, 5-H), 10.54 (s, 1H, 1′-H) and 12.40 (s, 1H, O*H*); ^{13}C NMR (δ): 9.9 (3-Me), 18.3 (2-Me), 108.3 (5-C), 115.2 (C-3), 115.7 (6-C), 118.1 (4a-C), 135.3 (8-C), 157.6 (8a-C), 160.6 (7-C), 167.0 (2-C), 176.2 (4-C) and 192.3 (CHO); HRMS: Found m/z = 219.0652; $C_{12}H_{11}O_4$ $[M + H]^+$ requires m/z = 219.0657.

Method B: Under an argon atmosphere, MsCl (0.014 mL, 0.174 mmol) was dropwise added to a stirred solution of **17** (20 mg, 0.087 mmol) and anhydrous pyridine (0.041 mL, 0.521 mmol) in dry CH_2Cl_2 (2 mL), cooled in an ice bath. The reaction was stirred 48 h at 40 °C, when the solvent was evaporated under reduced pressure. Brine (10 mL) was added and the products were extracted with EtOAc (4 × 10 mL). The combined organic phases were washed with brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue afforded **18** (25 mg, 93%), as a light yellow oil. ^{1}H NMR (δ): 2.04 (s, 3H, 2-Me), 2.42 (s, 3H, 3-Me), 3.26 (s, 3H, Me–SO_3Ar), 3.69 (bd, J = 7.1, 2H, 1′-H), 5.07 (ddd, J = 1.6, 3.3 and 15.1, 1H, 3′-H$_{trans}$), 5.09 (ddd, J = 1.6, 3.3 and 11.8, 1H, 3′-H$_{cis}$), 5.94 (ddd, J = 7.1, 11.8 and 15.1, 1H, 2′-H), 7.37 (d, J = 8.9, 1H, 6-H) and 8.12 (d, J = 8.9, 1H, 5-H). Without further purification, KIO_4 (419.3 mg, 1.82 mmol) was added with stirring to a solution of **18** (25 mg, 0.081 mmol) in a 1 : 1 mixture of *t*-BuOH and 0.1 M phosphate buffer, pH = 8.0 (3 mL), followed by a 1% OsO_4 solution in *t*-BuOH (0.166 mL, 0.0065 mmol). After stirring overnight at room temperature, 10% Na_2SO_3 (0.1 mL) was added, followed by brine (5 mL), and the products were extracted with EtOAc (5 × 15 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed, furnishing **7a** (3.6 mg, 20%) which spectral data matched those of the product obtained by *Method A*. When the same transformation was performed with **17** (100 mg, 0.081 mmol), improved yields of **7a** (47 mg, 50%) were obtained. Spectral data of the product were in agreement with those recorded for the product obtained by application of *Method A*.

Trifluoromethanesulfonic acid 8-formyl-2,3-dimethyl-4-oxo-4*H*-chromen-7-yl ester (20). Under a nitrogen atmosphere, NaH (50% in mineral oil, 11.1 mg, 0.227 mmol) was added portionwise to a stirred solution of **7a** (30 mg, 0.114 mmol) in a 1 : 1 THF : DMF mixture (1 mL), cooled in an ice-water bath. The resulting suspension was stirred for 10 min, when a solution of $PhNTf_2$ (105.8 mg, 0.296 mmol) in THF (0.5 mL) was dropped into the reaction *via* cannula and the resulting mixture was stirred at room temperature during 4 h. Saturated NH_4Cl solution (5 mL) was added, the THF was removed under reduced pressure and the residue was diluted with H_2O (5 mL) and extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed once with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification of the residue provided triflate **20** (47 mg, 95%) as a yellowish solid, m.p.: 135–136 °C. IR (KBr, ν): 3072, 3047, 2930, 1705, 1640, 1597, 1431, 1319, 1216, 1140, 1058, 845, 811 and 759 cm^{-1}; ^{1}H NMR (δ): 2.09 (s, 3H, 3-Me), 2.51 (s, 3H, 2-Me), 7.33 (d, J = 8.8, 1H, 6-H), 8.51 (d, J = 8.8, 1H, 5-H) and 10.66 (s, 1H, C*H*O); ^{13}C NMR (δ): 9.9 (3-Me), 18.5 (2-Me), 117.7 (C-3) 118.6 (4a-C), 118.9 (6-C), 119.3 (q, J_{C-F} = 389, CF_3), 122.8 (8-C), 133.6 (5-C), 150.4 (8a-C), 156.5 (7-C), 162.7 (2-C), 175.7 (4-C) and 184.3 (CHO); HRMS: Found m/z = 351.0145; $C_{12}H_{11}O_4$ $[M + H]^+$ requires m/z = 351.0149.

Trifluoromethanesulfonic acid 8-dimethoxymethyl-2,3-dimethyl-4-oxo-4*H*-chromen-7-yl ester (21). Trimethyl orthoformate (0.090 mL, 0.821 mmol) and CSA (1 mg) were successively added to a solution of **20** (18 mg, 0.054 mmol) in anhydrous MeOH (1 mL). The mixture was stirred 24 h at room temperature when saturated $KHCO_3$ (2 mL) was added, and the reaction product was extracted with EtOAc (4 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure, leaving a residue which was purified chromatographically to afford **21** (15 mg, 75%), as a pale yellowish solid, m.p.: 125–127 °C (EtOAc). IR (KBr, ν): 3072, 2931, 1641, 1597, 1431, 1319, 1216, 1139, 1085, 846, 760 and 632 cm^{-1}; ^{1}H NMR (δ): 2.06 (s, 3H, 3-Me), 2.47 (s, 3H, 2-Me), 3.48 (s, 6H, 2 × OMe), 5.93 (s, 1H, O–*CH*–O), 7.26 (d, J = 8.8, 1H, 6-H) and 8.28 (d, J = 8.8, 1H, 5-H); ^{13}C NMR (δ): 9.9 (3-Me), 18.6 (2-Me), 55.1 (2C, 2 × OMe), 99.1 (O–*C*H–O), 117.7 (6-C), 118.7 (4a-C), 119.4 (q, J_{C-F} = 387, CF_3), 121.0 (C-3), 122.3 (8-C), 128.4 (5-C), 150.0 (8a-C), 153.9 (7-C), 162.5 (2-C) and 176.6 (4-C). ^{19}F NMR (δ): −73.9 (s, C*F*$_3$SO$_3$Ar); HRMS: Found m/z = 397.0561; $C_{15}H_{16}F_3O_7S$ $[M + H]^+$ requires m/z = 397.0563.

7-Allyl-8-dimethoxymethyl-2,3-dimethyl-chromen-4-one (22). Under an argon atmosphere, a stirred mixture of **21** (34 mg, 0.086 mmol) allyltributyltin (0.045 mL, 0.135 mmol) in anhydrous toluene (1.0 mL) was treated with $Pd(PPh_3)_4$ (19.8 mg, 0.011 mmol) and the reaction mixture was further stirred under reflux for 36 h. The reaction was cooled to room temperature, treated with brine NaCl (5 mL) and the reaction products were extracted with EtOAc (5 × 15 mL). The combined organic phases were washed once with brine NaCl (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue furnished **22** (9.1 mg, 36%) as a colorless

oil. IR (film, ν): 2957, 2872, 1633, 1427, 1215, 1143, 1049, 852 and 629 cm^{-1}; ^1H NMR (δ): 2.05 (s, 3H, 3-Me), 2.44 (s, 3H, 2-Me), 3.45 (s, 6H, 2 × OMe), 3.80 (dt, J = 1.4 and 6.6, 1H, 1′-H), 5.07 (ddd, J = 1.4, 3.1 and 7.8, 1H, 3′-H_{cis}), 5.08 (ddd, J = 1.4, 3.1 and 18.9, 1H, 3′-H_{trans}), 5.94 (s, 1H, O–C*H*–O), 5.97 (ddd, J = 6.6, 7.8 and 18.9, 1H, 2′-H), 7.23 (d, J = 8.3, 1H, 7-H) and 8.10 (d, J = 8.3, 1H, 6-H); ^{13}C NMR (δ): 10.0 (3-Me), 18.6 (2-Me), 37.4 (1′-C), 55.9 (2C, 2 × OMe), 101.2 (O–*C*H–O), 116.0 (3′-C), 120.5 (C-3), 124.4 (4a-C), 126.0 (5-C),* 127.5 (6-C),* 131.2 (8-C), 137.2 (2′-C), 146.0 (7-C), 153.9 (8a-C), 161.2 (2-C) and 177.8 (4-C); HRMS: Found m/z = 289.1440; $C_{17}H_{21}O_4$ $[M + H]^+$ requires m/z = 289.1440.

7-Allyl-8-formyl-2,3-dimethyl-chromen-4-one (23). Under a nitrogen atmosphere, a solution of **21** (407 mg, 1.03 mmol), anhydrous LiCl (348 mg, 8.13 mmol), PPh_3 (134.7 mg, 0.513 mmol) and $Pd(PPh_3)_2Cl_2$ (82 mg, 0.103 mmol) and BHT (1 mg) in DMF (9 mL) was treated with allyltributyltin (0.482 mL, 1.23 mmol) and the mixture was heated at 110 °C during 14 h. The volatiles were removed under reduced pressure and the residue was filtered through a short pad of Celite with the aid of EtOAc (20 mL). A saturated solution of KF was added (5 mL) and the product was extracted with EtOAc (4 × 20 mL). The combined organic phases were washed once with brine NaCl (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue gave **23** (144 mg, 60%), as an oil. IR (film, ν): 2955, 2924, 1695, 1632, 1603, 1416, 1182, 777 and 602 cm^{-1}; ^1H NMR (δ): 2.08 (s, 3H, 3-Me), 2.47 (s, 3H, 2-Me), 3.88 (dt, J = 1.4 and 6.4, 2H, 9-H), 5.05 (ddd, J = 1.4, 3.3 and 16.7, 1H, 11-H_{trans}), 5.09 (ddd, J = 1.4, 2.8 and 10.3, 1H, 11-H_{cis}), 5.99 (ddd, J = 6.5, 10.2 and 16.7, 1H, 10-H), 7.30 (d, J = 8.2, 1H, 6-H), 8.33 (d, J = 8.2, 1H, 5-H) and 10.83 (s, 1H, 12-H); ^{13}C NMR (δ): 9.9 (3-Me), 18.5 (2-Me), 37.8 (9-C), 116.9 (11-C), 117.7 (C-3), 121.3 (4a-C), 122.0 (7-C), 127.3 (6-C), 131.2 (5-C), 135.7 (10-C), 148.3 (8-C), 157.7 (8a-C), 161.5 (2-C) 176.9 (4-C) and 189.5 (12-C); HRMS: Found m/z = 243.1016; $C_{15}H_{15}O_3$ $[M + H]^+$ requires m/z = 243.1021.

(*syn*)-7-Allyl-2,3-dimethyl-4*H*-chromen-4-one-8-carbaldehyde *O*-methyl-oxime (24). *O*-Methylhydroxylamine hydrochloride (752 mg, 9.01 mmol) and NaOAc (739.5 mg, 9.01 mmol) were successively added to a solution of **23** (93 mg, 0.384 mmol), in absolute EtOH (3 mL) and the reaction was stirred 14 h at 50 °C. The solvent was removed under reduced pressure, EtOAc (5 mL) and brine (5 mL) were added and the reaction products were extracted with EtOAc (4 × 20 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed yielding **24** (80 mg, 77%), as an oil. IR (film, ν): 3377, 2954, 2926, 1639, 1633, 1415, 1182, 1047 and 743 cm^{-1}; ^1H NMR (δ): 2.05 (s, 3H, 3-Me), 2.42 (s, 3H, 2-Me), 3.78 (dt, J = 1.3 and 6.5, 2H, 9-H), 4.04 (s, 3H N-OMe), 5.06 (dd, J = 1.4 and 13.2, 1H, 11-H_{trans}), 5.09 (dd, 1H, J = 1.3 and 10.3, 11-H_{cis}), 5.99 (ddd, J = 6.5, 10.3 and 13.2, 1H, 10-H), 7.28 (d, J = 8.4, 1H, 6-H), 8.12 (d, J = 8.4, 1H, 5-H), 8.59 (s, 1H, 12-H); ^{13}C NMR (δ): 10.0 (3-Me), 18.6 (2-Me), 37.5 (9-C), 62.3 (N-OMe), 117.2 (11-C), 120.9 (C-3), 123.0 (7-C), 123.3 (4a-C), 126.3 (5-C), 129.1 (6-C), 131.7 (10-C), 142.1 (8-C), 143.7 (12-C), 154.5 (8a-C), 161.1 (2-C), and 177.7 (4-C); HRMS: Found m/z = 272.1101; $C_{16}H_{17}NNaO_3$ $[M + H]^+$ requires m/z = 294.1090.

(*E*)-2,3-Dimethyl-4-oxo-7-(1′propenyl)-4*H*-chromene-8-carbaldehyde (25). Under a nitrogen atmosphere, a solution of **22** (123 mg, 0.427 mmol) and LiCl (145 mg, 3.42 mmol) in DMF (3 mL) was treated with $Pd(PPh_3)Cl_2$ (30 mg, 0.043 mmol) and the mixture was heated at 130 °C during 48 h. The reaction was diluted with EtOAc (40 mL), filtered through a short pad of Celite and the filtrate was washed with saturated $NaHCO_3$ (5 mL), brine (5 mL) and water (5 mL). The organic phase was dried over Na_2SO_4, and concentrated under reduced pressure, and the residue was chromatographed, furnishing **25** (70 mg, 70%), as an off-white solid, m.p. 106–107 °C (hexane–EtOAc). IR (KBr, ν): 3419, 2956, 2848, 1653, 1398, 1096, 802, 692 and 669 cm^{-1}; ^1H NMR (δ): 2.00 (dd, J = 1.7 and 15.6, 3H, 12-H), 2.08 (d, J = 0.6, 3H, 3-Me), 2.46 (d, J = 0.6, 3H, 2-Me), 6.45 (ddd, J = 6.8, 13.4 and 15.7, 1H, 11-H), 7.39 (dd, J = 1.7 and 15.6, 1H, 10-H), 7.54 (d, J = 8.5, 1H, 6-H), 8.38 (d, J = 8.5, 1H, 5-H) and 10.80 (s, 1H, 9-H); ^{13}C NMR (δ): 9.9 (3-Me), 18.5 (2-Me), 19.2 (12-C), 117.7 (3-C), 118.0 (11-C), 121.0 (4a-C), 123.2 (6-C), 128.0 (10-C), 130.7 (5-C), 140.9 (7-C), 144.8 (8-C), 157.5 (8a-C), 161.5 (2-C), 178.9 (4-C) and 189.8 (9-C); HRMS: Found m/z = 243.1010; $C_{15}H_{15}O_3$ $[M + H]^+$ requires m/z = 240.1016.

(*E*)-2,3-Dimethyl-4-oxo-7-(1′-propenyl)-4*H*-chromene-8-carbaldehyde *O*-methyl-oxime (26). *O*-Methylhydroxylamine hydrochloride (259 mg, 3.1 mmol) and NaOAc (255 mg, 3.1 mmoL) were successively added to a solution of **25** (32 mg, 0.132 mmol) in absolute EtOH (3 mL) and the reaction was stirred 14 h at 50 °C. The solvent was removed under reduced pressure and the residue was chromatographed, affording **26** (30.6 mg, 85%) as a white solid, m.p.: 65–66 °C (hexane–EtOAc). IR (KBr, ν): 2926, 2853, 1643, 1607, 1416, 1186, 1066, 966, 775 and 603 cm^{-1}; Major isomer (*syn*)-^1H NMR (δ): 1.94 (dd, 3H, J = 1.8 and 6.7, 11-H), 2.05 (s, 3H, 3-Me), 2.42 (s, 3H, 2-Me), 4.06 (s, 3H, N-OMe), 6.38 (dd, 1H, J = 6.7 and 15.7, 10-H), 7.06 (dd, 1H, J = 1.8 and 15.7, 9-H), 7.51 (d, 1H, J = 8.5, 6-H), 8.07 (d, 1H, J = 8.5, 5-H) and 8.56 (s, 1H, 12-H); ^{13}C NMR (δ): 10.0 (3-Me), 18.5 (2-Me),* 19.0 (11-C),* 62.3 (N-OMe), 117.2 (3-C), 122.7 (10-C), 123.1 (4a-C), 126.3 (6-C), 126.8 (8-C), 129.1 (5-C), 131.7 (9-C), 142.1 (7-C), 143.6 (12-C), 154.5 (8a-C), 161.6 (2-C) and 177.4 (4-C). HRMS: Found m/z = 272.1281; $C_{16}H_{18}NO_3$ $[M + H]^+$ requires m/z = 272.1287.

2,3,8-Trimethyl-4*H*-pyrano[3,2-*h*]isoquinolin-4-one (1). *Method A*: Under a nitrogen atmosphere, a solution of **22** (20 mg, 0.074 mmoL) and Bu_4NCl (103 mg, 0.396 mmol) in DMF (1.5 mL) was successively treated with $Pd(PPh_3)_4$ (8.6 mg, 0.0074 mmol) and Et_3N (0.060 mL, 0.396 mmol) and the reaction mixture was heated by 4 h at 80 °C. Then, the volatiles were removed under reduced pressure (P < 10 mmHg), the residue was dissolved in EtOAc (20 mL) and filtered through a short pad of Celite. Brine (5 mL) was added to the filtrate and the product was extracted with EtOAc (4 × 20 mL). The combined organic phases were washed once with brine NaCl (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure.

Chromatography of the residue gave **1** (3 mg, 18%), as a solid. The spectral data of **1** matched those obtained for the compound accessed through *Method B*.

Method B: A solution of **26** (27 mg, 0,1 mmoL) in 1,2-dichlorobenzene (2 mL) was placed in a microwave oven and irradiated for 30 min at 180 °C. The solvent was removed under reduced pressure and the residue was chromatographed, affording **1** (18 mg, 81%) as a pale pink solid, m.p.: 168–170 °C (EtOAc). IR (KBr, *ν*): 3406, 2954, 2920, 2850, 1616, 1419, 1180, 1097, 1022, 923, 877, 798 and 746 cm^{-1}; ^1H NMR (δ): 2.14 (s, 3H, 3-Me), 2.59 (s, 3H, 2-Me), 2.79 (s, 3H, 13-Me), 7.56 (bs, 1H, 12-H), 7.61 (d, $J = 8.6$, 1H, 7-H), 8.34 (d, $J = 8.6$, 1H, 6-H) and 9.77 (bs, 1H, 11-H); ^{13}C NMR (δ): 10.2 (3-Me), 18.5 (2-Me), 24.4 (13-Me), 117.3 (9-C), 118.9 (10-C), 118.9 (3-C), 119.0 (12-C), 122.6 (7-C), 124.2 (5-C), 126.3 (6-C), 139.3 (8-C), 146.5 (11-C), 155.7 (13-C), 161.1 (2-C) and 177.0 (4-C); for spectral data in DMSO-d_6, please see Tables 1 and 2; HRMS: Found $m/z = 243.1019$; $C_{15}H_{14}NO_2$ $[M + H]^+$ requires $m/z = 240.1021$.

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Notes and references

1 (*a*) D. Faulkner, *Nat. Prod. Rep.*, 2001, **18**, 1–49; (*b*) U. Hentschel, M. Schmid, M. Wagner, L. Fieseler, C. Gernert and J. Hacker, *FEMS Microbiol. Ecol.*, 2001, **35**, 305–312; (*c*) T. S. Bugni and C. M. Ireland, *Nat. Prod. Rep.*, 2004, **21**, 143–163; (*d*) U. Höller, A. D. Wright, G. F. Matthée, G. M. König, S. Draeger, H. J. Aust and B. Schulz, *Mycol. Res.*, 2000, **104**, 1354–1365; (*e*) K. Liberra and U. Lindequist, *Pharmazie*, 1995, **50**, 583–588; (*f*) M. A. F. Biabani and H. Laatsch, *J. Prakt. Chem.*, 1998, **340**, 589–607; (*g*) J. Wang, *J. Ind. Microbiol. Biotechnol.*, 2006, **33**, 545–551; (*h*) X. Liu, F. Xu, C. Shao, Z. She, Y. Lin and W. Chan, Bioactive metabolites from marine microorganisms, in *Studies in Natural Products Chemistry Bioactive Natural Products (Part O)*, Elsevier, Amsterdam, vol. 35, 2008, pp. 197–310.

2 (*a*) W. H. Lin, H. Z. Fu, J. Li and P. Proksch, *Chin. Chem. Lett.*, 2001, **12**, 235–238; (*b*) W. H. Lin, G. Brauers, R. Ebel, V. Wray, A. Berg, Sudarsono and P. Proksch, *J. Nat. Prod.*, 2003, **66**, 57–61. It should be noticed that structures for **2a–f** are different from those proposed in the first report of their isolation (ref. 2*a*).

3 (*a*) S. Bräse, A. Encinas, J. Keck and C. F. Nising, *Chem. Rev.*, 2009, **109**, 3903–3990; (*b*) Y. Zhuang, X. Teng, Y. Wang, P. Liu, G. Li and W. Zhu, *Org. Lett.*, 2011, **13**, 1130–1133; (*c*) T. J. Greshock, A. W. Grubbs, P. Jiao, D. T. Wicklow, J. B. Gloer and R. M. Williams, *Angew. Chem., Int. Ed.*, 2008, **47**, 3573–3577; (*d*) P. Jiao, S. V. Mudur, J. B. Gloer and D. T. Wicklow, *J. Nat. Prod.*, 2007, **70**, 1308–1311; (*e*) L. J. Fremlin, A. M. Piggott, E. Lacey and R. J. Capon, *J. Nat. Prod.*, 2009, **72**, 666–670; (*f*) S. Tsukamoto, T. Kawabata, H. Kato, T. J. Greshock, H. Hirota, T. Ohta and R. M. Williams, *Org. Lett.*, 2009, **11**, 1297–1300; (*g*) M. Berger–Deguee and Y. Berger, *Phytochemistry*, 1982, **21**, 1449–1451; (*h*) G. N. Belofsky, P. R. Jensen, M. K. Renner and W. Fenical, *Tetrahedron*, 1998, **54**, 1715–1724.

4 (*a*) S. B. Singh, D. L. Zink, G. F. Bills, A. Teran, K. C. Silverman, R. B. Lingham, P. Felock and D. J. Hazuda, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 713–717; (*b*) Y. Takenaka, T. Tanahashi, N. Nagakura and N. Hamada, *Heterocycles*, 2000, **53**, 1589–1593; (*c*) Y. H. Kuo and B. Y. Lin, *Chem. Pharm. Bull.*, 1999, **47**, 428–429; (*d*) D. Wu, M. Zhang, C. Zhang and Z. Wang, *Biochem. Syst. Ecol.*, 2008, **36**, 219–222; (*e*) Q. Wang and D. Chen, *Helv. Chim. Acta*, 2007, **90**, 2432–2437; (*f*) K. Koyama and S. Natori, *Chem. Pharm. Bull.*, 1987, **35**, 578–584.

5 (*a*) K. S. Rehder and J. A. Kepler, *Synth. Commun.*, 1996, **26**, 4005–4021; (*b*) F. Zamattio, J. D. Brion, L. Belachmi and G. Le Baut, *J. Heterocycl. Chem.*, 1991, **28**, 2013–2019; (*c*) D. Yu, C.-H. Chen, A. Brossi and K.-H. Lee, *J. Med. Chem.*, 2004, **47**, 4072–4082; (*d*) N. R. Ayyangar, R. A. Khan and V. H. Deahpande, *Tetrahedron Lett.*, 1988, 2347–2348; (*e*) L. W. McGarry and M. R. Detty, *J. Org. Chem.*, 1990, **55**, 4349–4356.

6 (*a*) J. H. Tatum and R. A. Baker, *Phytochemistry*, 1983, **22**, 543–547; (*b*) R. M. Van Wagoner, P. G. Mantle and J. L. C. Wright, *J. Nat. Prod.*, 2008, **71**, 426–430; (*c*) B. Kesteleyn and N. De Kimpe, *J. Org. Chem.*, 2000, **65**, 640–644.

7 (*a*) Z. Lu, Y. Wang, C. Miao, P. Liu, K. Hong and W. Zhu, *J. Nat. Prod.*, 2009, **72**, 1761–1767; (*b*) A. Ogawa, C. Murakami, S. Kamisuki, I. Kuriyama, H. Yoshida, F. Sugawara and Y. Mizushina, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3539–3543; (*c*) M. Tobe, T. Tashiro, M. Sasaki and H. Takikawa, *Tetrahedron*, 2007, **63**, 9333–9337; (*d*) F. Saito, K. Kuramochi, A. Nakazaki, Y. Mizushina, F. Sugawara and S. Kobayashi, *Eur. J. Org. Chem.*, 2006, 4796–4799; (*e*) Y. Sato, K. Kuramochi, T. Suzuki, A. Nakazaki and S. Kobayashi, *Tetrahedron Lett.*, 2011, **52**, 626–629; (*f*) K. Kuramochi, F. Saito, A. Nakazaki, T. Takeuchi, K. Tsubaki, F. Sugawara and S. Kobayashi, *Biosci., Biotechnol., Biochem.*, 2010, **74**, 1635–1640.

8 (*a*) J. Kohno, H. Hiramatsu, M. Nishio, M. Sakurai, T. Okuda and S. Komatsubara, *Tetrahedron*, 1999, **55**, 11247–11252; (*b*) J. Kohno, M. Sakurai, N. Kameda, M. Nishio, K. Kawano, N. Kishi, T. Okuda and S. Komatsubara, *J. Antibiot.*, 1999, **52**, 913–916; (*c*) G. J. Slack, E. Puniani, J. C. Frisvad, R. A. Samson and J. D. Miller, *Mycol. Res.*, 2009, **113**, 480–490; (*d*) K. Trisuwana, V. Rukachaisirikul, Y. Sukpondmaa, S. Phongpaichit, S. Preedanon and J. Sakayaroj, *Tetrahedron*, 2010, **66**, 4484–4489; (*e*) T. Kumemura, T. Choshi, A. Hirata, M. Sera, Y. Takahashi, J. Nobuhiro and S. Hibino, *Chem. Pharm. Bull.*, 2005, **53**, 393–397; (*f*) T. Kumemura, T. Choshi, A. Hirata, M. Sera, Y. Takahashi, J. Nobuhiro and S. Hibino, *Heterocycles*, 2003, **61**, 13–17; (*g*) T. Choshi, T. Kumemura, H. Fujioka, Y. Hieda and S. Hibino, *Heterocycles*, 2011, **84**, 587–595.

9 (*a*) E. L. Larghi, B. V. Obrist and T. S. Kaufman, *Tetrahedron*, 2008, **64**, 5236–5245; (*b*) E. L. Larghi, M. L. Bohn and T. S. Kaufman, *Tetrahedron*, 2009, **65**, 4257–4282; (*c*) C. C. Silveira, E. L. Larghi, S. R. Mendes, A. B. J. Bracca, F. Rinaldi and T. S. Kaufman, *Eur. J. Org. Chem.*, 2009, 4637–4645.

10 T. Choshi, T. Kumemura, J. Nobuhiro and S. Hibino, *Tetrahedron Lett.*, 2008, **49**, 3725–3728.

11 (*a*) N. M. F. S. A. Cerqueira, A. M. F. Oliveira-Campos, P. J. Coelho, L. H. Melo de Carvalho, A. Samat and R. Guglielmetti, *Helv. Chim. Acta*, 2002, **85**, 442–450; (*b*) V. Bertini, S. Alfei, M. Pocci, F. Lucchesini, N. Picci and F. Iemma, *Tetrahedron*, 2004, **60**, 11407–11414; (*c*) M. Rawat, V. Prutyanov and W. D. Wulff, *J. Am. Chem. Soc.*, 2006, **128**, 11044–11053.

12 (*a*) M. Schellenbaum, *US Patent 4004033*, 1977; (*b*) S. Caron and E. Vázquez, *Synthesis*, 1999, 588–592.

13 T. X. T. Luu, T. T. Lam, T. N. Le and F. Duus, *Molecules*, 2009, **14**, 3411–3424.

14 (*a*) P. Da Re, L. Verlicchi and I. Setnikar, *J. Org. Chem.*, 1960, **25**, 1097–1100; (*b*) K. B. Bahnck and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 2008, **130**, 13177–13181.

15 (*a*) P. Nussbaumer, P. Lehr and A. Billich, *J. Med. Chem.*, 2002, **45**, 4310–4320; (*b*) V. Rossollin, V. Lokshin, A. Samat and R. Guglielmetti, *Tetrahedron*, 2003, **59**, 7725–7731.

16 S. Kirkiacharian, A. T. Lormier, H. Chidiack and F. Bouchoux, *Farmaco*, 2004, **59**, 981–986.

17 (*a*) J. R. Keeffe, A. J. Kresge and N. P. Schepp, *J. Am. Chem. Soc.*, 1990, **112**, 4862–4868; (*b*) Y. Chiang, A. J. Kresge, P. A. Walsh and Y. Yin, *J. Chem. Soc., Chem. Commun.*, 1989, 869–871.

18 (*a*) C. W. Y. Chung and P. H. Toy, *Tetrahedron*, 2005, **61**, 709–715; (*b*) B. F. Zhong and F. E. McDonald, *Org. Lett.*, 2005, **7**, 3617–3620.

19 Y.-S. Yao and Z.-J. Yao, *J. Org. Chem.*, 2008, **73**, 5221–5225.

20 (*a*) T. Choshi, T. Kumemura, J. Nobuhiro and S. Hibino, *Tetrahedron Lett.*, 2008, **49**, 3725–3728; (*b*) S. B. J. Kan and E. A. Anderson, *Org. Lett.*, 2008, **10**, 2323–2326; (*c*) J. M. Saá, G. Martorell and A. García–Raso, *J. Org. Chem.*, 1992, **57**, 678–685.

21 (*a*) R. Bautista, P. Bernal, L. E. Montiel, F. Delgado and J. Tamariz, *Synthesis*, 2011, 929–933; (*b*) T. Shirasaka, Y. Takuma and N. Imaki, *Synth. Commun.*, 1990, **20**, 1213–1221; (*c*) Q. Yao and M. Sheets, *J. Org. Chem.*, 2006, **71**, 5384–5387.
22 (*a*) G. Martorell, A. García–Raso and J. M. Saá, *Tetrahedron Lett.*, 1990, **31**, 2357–2358.
23 (*a*) H. Tsutsui and K. Narasaka, *Chem. Lett.*, 2001, 526–527; (*b*) M. Kitamura and K. Narasaka, *Chem. Rec.*, 2002, **2**, 268–277.
24 D. Gauthier, A. T. Lindhart, E. P. K. Olsen, J. Overgaard and T. Skrydstrup, *J. Am. Chem. Soc.*, 2010, **132**, 7998–8009.
25 H. Wagner, S. Bladt and V. Rickl, *Drug Analysis: A Thin Layer Chromatography Atlas*, Springer, Heidelberg, 2nd edn, 2009, p. 360.

