Synthesis of isochroman-3-ylacetates and isochromane-γ-lactones through rearrangement of aryldioxolanylacetates

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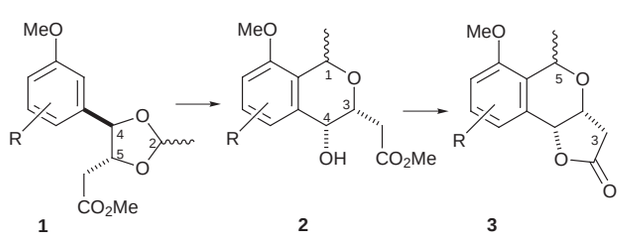
Lewis acid catalysed rearrangement of methyl 4,5-*trans*-4-aryldioxolan-5-ylacetates **1** provides a convenient route to substituted methyl isochroman-3-ylacetates **2** and isochromane-γ-lactones **3**. The choice of Lewis acid is determined by the substitution pattern of the aromatic ring. The two contiguous isochromane stereocentres are transferred unchanged from the parent dioxolanes, while the configuration of the isochromane methyl group is dependent upon the aryl substitution, the reagent and the reaction conditions. Thus treatment of the C-2 epimeric 3′,5′-dimethoxyphenyldioxolanes **4** and **5** with camphorsulfonic acid afforded a mixture of the C-5 epimeric isochromane lactones **26** and **29**, the former being favoured at lower acid concentrations, the latter at higher concentrations. Titanium tetrachloride isomerised the analogous 2′-chloro-5′-methoxyphenyldioxolanes **6** and **7** into the methyl isochroman-3-ylacetate **38**, which could be lactonised to the isochromane lactone **27**. Phosphoric acid converted the 2′,5′-dimethoxyphenyldioxolanes **8** and **9** into a mixture of the isochromane lactones **28** and **31**, while similar treatment of the hydroxylactone **22** in the presence of acetaldehyde afforded the isochromane lactone **28** directly and with complete diastereoselectivity. Oxidative demethylation and annulation of this isochromane lactone **28** afforded 5-*epi*-7-deoxykalafungin **41**.

We have recently reported the titanium tetrachloride-promoted diastereoselective isomerisation of 2,5-dimethyl-4-naphthyldioxolanes into benzoisochromanes in relation to natural product synthesis.[1] The versatility of this novel intramolecular version of the Mukaiyama reaction[2] was further explored by converting the corresponding 2,5-dimethyl-4-phenyldioxolanes in high yield into isochromanes.[3,4] These studies showed that the 4,5-stereochemistry of the parent dioxolanes is transferred intact to the 4,3-positions of the product isochromanes, so that 4,5-*trans* dioxolanes afford 3,4-*cis* isochromanes. C-1 of the isochromanes is derived from C-2 of the dioxolanes with a diastereoselectivity which depends upon the aryl substitution and 4,5-stereochemistry of the substrate, and in some cases also upon the reaction temperature. We now report the extension of this process to the conversion of methyl 4,5-*trans*-4-aryldioxolan-5-ylacetates **1** into methyl isochroman-3-ylacetates **2** and the corresponding isochromane-γ-lactones **3** (Scheme 1).



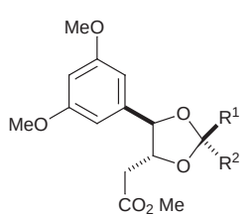
Scheme 1

These products contain the key structural elements of a number of natural naphthopyranquinones.[5]

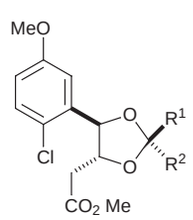
Results

Synthesis of the dioxolanes

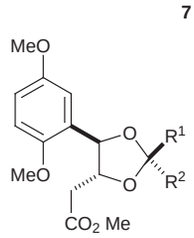
The three different substitution patterns of the 4-phenyldioxolanes previously studied,[3,4] 3,5- and 2,5-dimethoxyphenyl and 2-chloro-5-methoxyphenyl, have significant synthetic utility and were chosen again for the present investigation. The 3,5-pattern has symmetry and generates isochromane substitution typical of polyketide natural products, both 2,5-patterns provide oxidative access to the *para*-quinonoid functionality frequently found in natural benzoisochromanes, and the 2-chloro substituent can also be removed by reduction. The required substrates were therefore the pairs of diasteromeric dioxolanes **4** and **5**, **6** and **7**, and **8** and **9**.



4 R^1 = Me, R^2 = H
5 R^1 = H, R^2 = Me

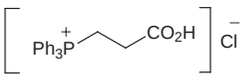


6 R^1 = Me, R^2 = H
7 R^1 = H, R^2 = Me



8 R^1 = Me, R^2 = H
9 R^1 = H, R^2 = Me

3,5-Dimethoxybenzaldehyde **11** was subjected to a Wittig reaction with the triphenylphosphonium salt **10** of 3-chloropropionic acid. The ultraviolet absorption maximum of the product **12** at 250 nm resembled that of (*E*)-1-(3′,5′-dimethoxyphenyl)prop-1-ene,[3] supporting its assignment as a styrene. In the ^{1}H NMR spectrum, the coupling constant (*J* 15.9 Hz)



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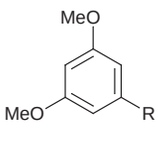

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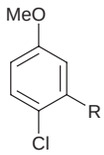

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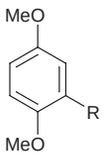

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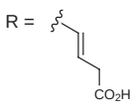
R = CHO

12

R = 

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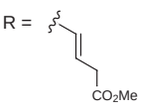
R = 

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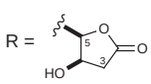
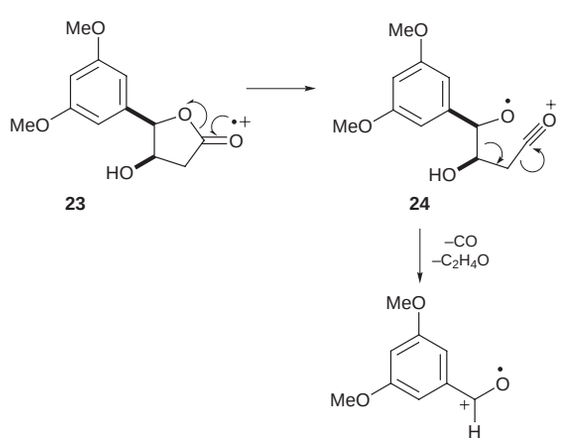
R = 

18

22

between 3-H and 4-H confirmed that the product was the (*E*)-stereoisomer. Dihydroxylation of the double bond of acid **12** with osmium tetroxide and *N*-methylmorpholine *N*-oxide[6] proved troublesome. The acid was therefore converted *via* the acid chloride into its methyl ester **13** in 83% yield. Treatment of this ester with *N*-methylmorpholine *N*-oxide and a catalytic quantity of osmium tetroxide gave in 87% yield the lactone **14** expected[7] from ring closure of the intermediate dihydroxy ester.

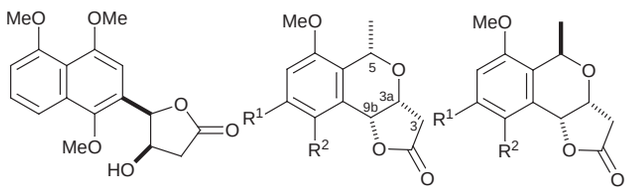
The mass spectrum of the lactone **14** showed a molecular ion at *m*/*z* 238 and a base peak at *m*/*z* 166 through loss of 72 mass units. The latter ion may arise from the expected initial cleavage of the lactone carbonyl–oxygen bond in the molecular ion **23** followed by loss of carbon monoxide and the enol of acetaldehyde from the resulting intermediate **24** (Scheme 2). Corresponding fragmentations were also observed for the related hydroxy lactones **18** and **22** discussed below. The infrared spectrum of the lactone **14** showed hydroxy and carbonyl stretching frequencies at 3467 cm^{-1} and 1776 cm^{-1}, the latter being typical of a γ-lactone. Its ^{1}H NMR spectrum showed the two C-3 methylene protons as a doublet (*J* 17.5 Hz) at δ 2.70 and a doublet of doublets (*J* 17.5 Hz and 5.4 Hz) at δ 2.85. The methine proton 4-H at δ 4.58 showed vicinal coupling (*J* 5.4 Hz)



23 **24**

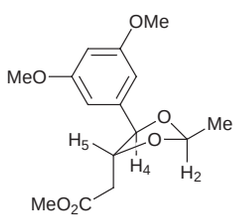
Scheme 2

to only one of the C-3 methylene protons and also to 5-H at δ 5.42 (*J* 3.8 Hz). An NOE spectrum confirmed the mutual proximity of the protons 4-H and 5-H, and thus the expected *cis* stereochemistry of lactone **14.** The ^{1}H NMR data for the heterocyclic ring protons corresponded closely with those reported for the naphthalenic analogue juglomycin A **25**.[7]



25

26 R^1 = OMe, R^2 = H **29**
27 R^1 = H, R^2 = Cl **30**
28 R^1 = H, R^2 = OMe **31**



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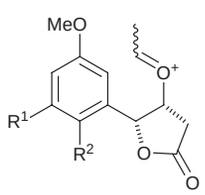


33 R^1, R^2 = H, OMe

Treatment of the lactone **14** with 1,1-dimethoxyethane and a catalytic quantity of camphorsulfonic acid in boiling methylene dichloride gave the pair of C-2 epimeric dioxolanes **4** and **5** in a combined yield of 70% and a ratio of approximately 1.3:1. Unexpectedly, a small quantity (7%) of the isochromane-γ-lactone **26** was also isolated and is discussed below. Further chromatography of the mixture of dioxolanes **4** and **5** afforded the major C-2 epimer **4** pure, and the minor epimer **5** enriched to a ratio of 3:1.

The structure of the major dioxolane **4** was confirmed by ^{1}H NMR spectroscopy. The dioxolane ring proton 2-H appeared as a quartet at δ 5.35, with the small coupling constant (4.9 Hz) typical of 2-H protons in related 2-methyldioxolanes.[1,3,4] The proton 4-H resonated as a doublet at δ 4.59 coupled (*J* 6.9 Hz) to 5-H, a doublet of triplets (*J* 4.9 and 6.9 Hz) at δ 4.26 which was further coupled (*J* 6.9 and 4.9 Hz) to the adjacent methylene protons on the pendant acetate. The methylene protons resonated as doublets of doublets at δ 2.68 (*J* 15.0 and 6.9 Hz) and δ 2.63 (*J* 15.0 and 4.9 Hz). NOE data established the stereochemistry **4** and the preferred conformation **32** of this major diastereomer. Irradiation of the proton 4-H and the acetate methylene protons each provided a 4.2% enhancement of 2-H, while the reciprocal enhancement of 4-H on irradiation of 2-H was 2.4%. The 4,5-*trans* relationship was supported by a 12.9% enhancement of 4-H on irradiation of the acetate methylene protons.

2-Chloro-5-methoxybenzaldehyde **15** was similarly converted *via* the intermediates **16**, **17** and **18** into the mixture of C-2 epimeric dioxolanes **6** and **7**, and 2,5-dimethoxybenzaldehyde **19** *via* the intermediates **20**, **21** and **22** into the dioxolanes **8** and **9**. While a small amount of the isochromane lactone **28** (5%) analogous to **26** was produced in the conversion of lactone **22** into dioxolanes **8** and **9**, none of the related isochromane lactone **27** accompanied the synthesis of dioxolanes **6** and **7** from lactone **18**. Evidence will be presented below for the structures of these minor byproducts **26** and **28**. Their formation probably reflects the higher electrophilicity of the dimethoxyphenyl rings of the lactones **14** and **22** compared to the chloromethoxyphenyl ring of **18**. They must arise either directly from the starting lactones **14** and **22** through conversion into the intermediate oxocarbenium ions **33** with

the reagents 1,1-dimethoxyethane and camphorsulfonic acid, followed by cyclisation,[3,4] or from the product dioxolanes *via* related oxocarbenium ions of the type **35**. We now address this latter possibility.

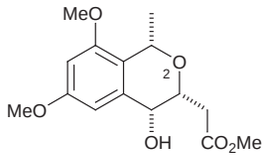
Conversion of dioxolanes into isochroman-3-ylacetates and isochromane-γ-lactones

The 1.3:1 mixture of C-2 epimeric 3′,5′-dimethoxyphenyldioxolanes **4** and **5** was treated for 18 hours in boiling methylene dichloride with camphorsulfonic acid in increasing concentrations, *ca.* 10–200 times greater than the catalytic amount (0.02 mol equiv., 4.3×10^{-4} mol l^{-1}) used for the preparation of the dioxolanes themselves from the lactone **14**. The dioxolanes **4** and **5** were converted smoothly into a mixture of the epimeric isochromane lactones **26** and **29** in a combined yield of 80–89%. At the lowest catalyst concentration (5.7×10^{-3} mol l^{-1}) the isochromane lactone **26** predominated in a ratio of 6.8:1, which was dramatically reversed at higher concentrations (5.7×10^{-2}, 8.6×10^{-2} mol l^{-1}) to 1:1.9 and 1:3.6 in favour of the epimer **29**.

The epimers **26** and **29** showed similar mass spectra, with molecular ions at *m*/*z* 264 and base peaks at *m*/*z* 249 arising from loss of a methyl radical as expected for such isochromane ring systems.[3,4] Infrared spectra showed γ-lactone absorption at 1781 and 1780 cm^{-1} respectively. In the ^{1}H NMR spectrum of **26** only two *meta*-coupled aromatic proton resonances (*J* 2.3 Hz) and two methoxy resonances were observed. The pyran ring protons 9b-H, 5-H and 3a-H resonated as a doublet (*J* 2.5 Hz) at δ 5.07, a quartet (*J* 6.5 Hz) at δ 4.79 and a doublet of doublets (*J* 2.5 and 4.6 Hz) at δ 4.35. The methylene protons of the γ-lactone ring appeared at δ 2.88 and δ 2.74 coupled geminally (*J* 17.5 Hz), and only the former resonance showed additional vicinal coupling (*J* 4.6 Hz) to 3a-H.

The only major differences between the ^{1}H NMR spectra of the isochromane lactone **26** and its C-5 epimer **29** were the chemical shifts of the protons 3a-H and 5-H, which appeared at δ 4.35 and 4.79 for the former and δ 4.77 and 5.10 for the latter. The chemical shifts of the 3a-H protons suggest the 1,3-*cis* and 1,3-*trans* stereochemistry for the epimers **26** and **29** respectively, consistent with the observation that the corresponding 3-H proton in 1,3-*cis* dimethylisochromanes appears at significantly higher field than in the 1,3-*trans* compounds.[1,3,4] A lesser difference between the spectra was the chemical shift of the C-5 methyl substituent, which appeared at δ 1.56 for the all-*cis* isochromane lactone **26** and 1.46 for the C-5 epimer **29**. For each epimer the small coupling constant (*J* 2.5 and 3.0 Hz) between 3a-H and 9b-H,[3,4] and the mutually enhanced intensities (5–12%) observed on irradiation of 3a-H and 9b-H, verified the expected 3a,9b-*cis* relationship derived from the parent lactone **14**. Assignment of the all-*cis* stereochemistry to isochromane **26** was confirmed by mutual 7–10% NOE enhancements between the ring protons 3a-H and 5-H, which are thus axial and pseudoaxial, respectively.[3,4] In contrast, irradiation of the C-5 methyl group of 3a,5-*trans* epimer **29** enhanced 3a-H (15%).

Since titanium tetrachloride had proved so effective in previous isomerisation studies,[1,3,4] the effect of this Lewis acid on the 1.3:1 mixture of epimeric 3′,5′-dimethoxyphenyldioxolanes **4** and **5** was also investigated at various temperatures. After 30 min in methylene dichloride at −78 °C the starting materials were recovered in the altered ratio of 1:1.8, suggesting that the epimer **5** was favoured under those conditions. When the reaction temperature was raised from −78 °C to −30 °C and maintained for 30 minutes, a mixture of products was obtained. GC-MS analysis of this mixture indicated the starting dioxolanes **4** and **5** in a ratio of 1:1.5 (55%), together with two other isomers. These were an isochromane ester (20%), presumed to have the structure **36** by analogy with that of ester **38** discussed below, and the dihydroisobenzofuran ester **37** (25%). If the reaction temperature was raised from −78 °C to room temperature and maintained for two hours, only the dihydroisobenzofuran ester **37** was obtained. Its mass spectrum showed a structurally distinctive base peak at *m*/*z* 193 corresponding to loss of the $CH(OH)CH_2CO_2Me$ radical from the molecular ion at *m*/*z* 296, as has been observed in analogous dihydroisobenzofurans.[3] The ^{1}H NMR spectrum of this sole product **37** established the *trans* arrangement of the heterocyclic substituents from the long range coupling constant (*J* 3.0 Hz) between the protons 1′-H and 3′-H at δ 5.26 and δ 5.40.[3,8]



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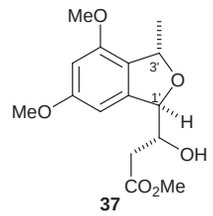

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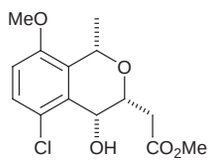

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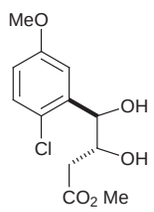

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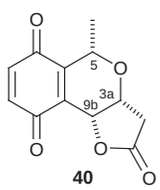

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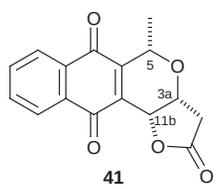

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Reaction of the 1:1 mixture of C-2 epimeric 2′-chloro-5′-methoxyphenyldioxolanes **6** and **7** with camphorsulfonic acid in boiling methylene dichloride for extended periods afforded no isochromane lactones, the dioxolanes being recovered. With titanium tetrachloride in methylene dichloride at −78 or −30 °C the dioxolanes were again recovered in high yield, but substantially enriched in one epimer (unidentified). At the higher temperatures of 0 °C and room temperature, no dioxolanes were recovered and the observed products were the rearranged isochromane ester **38** and the diol ester **39** from dioxolane cleavage, isolated in yields of 64 and 12% after 5 hours at room temperature. The mass spectrum of isochromane ester **38** provided the expected molecular ion isotope pair at *m*/*z* 302/300, with a base peak at *m*/*z* 198 arising through loss of methyl 3-oxopropanoate in a retro Diels–Alder process.[4] The ^{1}H NMR spectrum showed the isochromane to be a single diastereomer, which was assigned the all-*cis* stereochemistry from the mutual 10% NOE enhancements between the protons 1-H and 3-H, a quartet and a doublet of triplets at δ 4.94 and 4.02, respectively. The expected *cis* relationship between 3-H and 4-H followed from their small coupling constant (*J* 1.3 Hz), and the enhanced intensity (11%) of the 4-H doublet at δ 4.69 on irradiation of 3-H.

When the isochromane ester **38** was boiled in methylene dichloride with camphorsulfonic acid the isochromane lactone **27** was obtained in 83% yield. The chemical shifts and coupling constants of the heterocyclic ring protons of this lactone matched closely those of its analogue **26**. Together with NOE data which indicated the mutual proximity of 3a-H and 5-H, this confirmed the all-*cis* stereochemistry of isochromane lactone **27** and also, therefore, of the isochromane ester **38**. None of the C-5 epimer **30** of **27** was observed in this reaction.

The rearrangement conditions above were extended to the 1:1 epimeric mixture of 2′,5′-dimethoxyphenyldioxolanes **8** and **9**, where the *para* substituents provide latent quinonoid

functionality.[4] The mixture was recovered unchanged after treatment with camphorsulfonic acid in dichloromethane at reflux, while reaction with titanium tetrachloride gave rise to inseparable mixtures of products which were not further investigated. When the dioxolanes **8** and **9** were treated with phosphoric acid at room temperature, however, the epimeric isochromane lactones **28** and **31** were formed in good yield (70%) as an inseparable mixture in a 1:1 ratio. Distinctive NMR signals for 3a-H, 5-H and the C-5 methyl protons in each component, assigned from their close correspondence in shift and coupling to the signals of the analogues **26** and **29** discussed above, occurred at δ 4.28, 4.85 and 1.57 for the all-*cis* isochromane lactone **28**, and at 4.69, 5.14 and 1.46 for its epimer **31**.

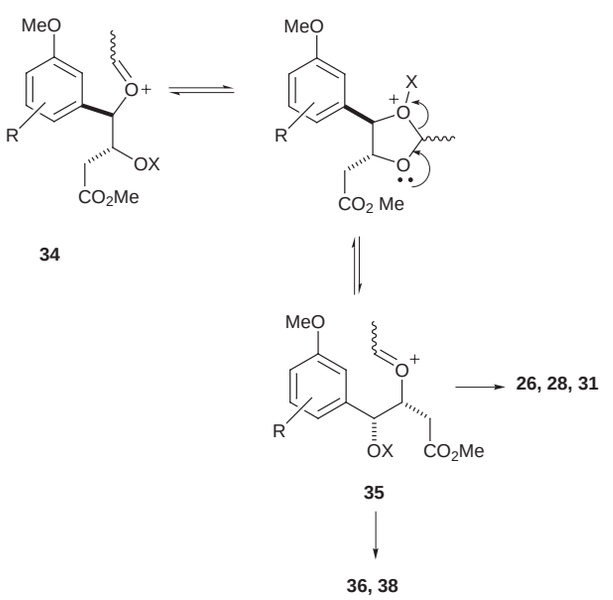
Previous syntheses of 1-methylisochromanes involved the reaction of 2-(2′-hydroxypropyl)-1,4-naphthoquinols with acetaldehyde in the presence of acid catalysts.[9,10] The hydroxylactone **22** was therefore reacted with acetaldehyde in neat phosphoric acid at room temperature, whereupon the isochromane lactone **28** was isolated as a single stereoisomer in 76% yield. Its mass spectrum showed the expected molecular ion at *m*/*z* 264 and base peak at 249 arising from loss of a methyl radical. The all-*cis* stereochemistry inferred earlier was confirmed by reciprocal NOE enhancements of 8–15% between 3a-H and 5-H, and between 3a-H and 9b-H.

Oxidative demethylation of the all-*cis* isochromane lactone **28** with cerium(IV) ammonium nitrate[11] afforded the corresponding quinone **40** in 69% yield. The homoallylic coupling constant of 1.8 Hz between 5-H and 9b-H in this product was expected from their pseudoaxial and pseudoequatorial orientations.[12,13] A Diels–Alder reaction with 1-acetoxybuta-1,3-diene, followed by enolisation and oxidation in the presence of sodium carbonate, then gave in 66% yield the known[14,15] 5-*epi*-7-deoxykalafungin **41**.

Discussion

These conversions of methyl 4,5-*trans*-4-aryl-1,3-dioxolan-5-ylacetates **1** into methyl isochroman-3-ylacetates **2** and isochromane γ-lactones **3** extend the previously reported isomerisations of 2,5-dimethyl-4-phenyl-1,3-dioxolanes, and probably proceed through similar mechanisms.[3,4]

Initial protonation (X = H) or coordination of titanium tetrachloride (X = $TiCl_4^-$) at O-3 leads to ring opening of the dioxolanylacetates **1** at the C(2)–O(3) bond to afford the corresponding intermediate oxocarbenium ions **35** (Scheme 3).

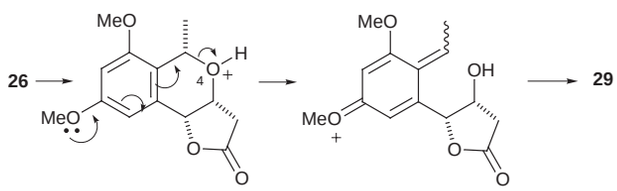


Scheme 3

These undergo an allowed 6-*enolendo-endo-trig* type electrophilic cyclisation[16] to afford isochromanes in which the two contiguous pyran stereocentres are transferred unchanged from the parent dioxolanes. Attack at O-1 of the dioxolanes and cleavage of the C(2)–O(1) bond no doubt also occurs giving rise to the alternative oxocarbenium ions **34**, but these cannot achieve the disallowed 5-*enolendo-endo-trig* type cyclisation to dihydroisobenzofurans and so reform the parent dioxolanyl acetates.

When the reagent is a Brønsted acid, lactonisation accompanies isochromane ring closure to give directly the isochromane lactones. With the Lewis acid titanium tetrachloride, lactonisation does not occur and the products remain as the γ-hydroxy esters, perhaps because the reagent is complexed to the γ-hydroxy group as in the intermediate **35**. Lactonisation can be effected subsequently by treatment with acid.

In the case of the 3′,5′-dimethoxyphenyldioxolanes **4** and **5**, the aromatic ring is sufficiently activated towards electrophilic substitution that camphorsulfonic acid in refluxing methylene dichloride is sufficient to promote isochromane lactone formation. Low acid concentrations favour the all-*cis* isomer **26** as the kinetic product. Higher acid concentrations cause epimerisation of the C-5 position through protonation of O-4 and reversible opening of the activated benzylic C(5)–O(4) bond, affording the thermodynamically favoured isochromane lactone **29** in which the C-5 methyl group is now *trans* to the fused lactone ring (Scheme 4). With titanium tetrachloride, the



Scheme 4

all-*cis* isochromane ester **36** is formed initially, but undergoes secondary rearrangement in the presence of the Lewis acid at higher temperatures to form the dihydroisobenzofuran ester **37**. Cleavage of the activated benzylic C(1)–O(2) bond is here caused by coordination of the Lewis acid to O-2, ring closure by the available free benzylic hydroxy group then ensuing to give the dihydroisobenzofuran ester.[3]

The less reactive 2′-chloro-5′-methoxyphenyldioxolanes **6** and **7** and 2′,5′-dimethoxyphenyldioxolanes **8** and **9** are unaffected by treatment with camphorsulfonic acid. The former pair with titanium tetrachloride gives the expected all-*cis* isochromane ester **38** corresponding to **36**, but which lacks the additional activating influence of a 6-methoxy group and consequently does not epimerise or rearrange to a dihydroisobenzofuran. The 2′,5′-dimethoxyphenyldioxolane pair **8** and **9** with titanium tetrachloride yields severe mixtures. This additional reactivity in the presence of the Lewis acid compared to their regioisomeric pair **4** and **5** results from alternative benzylic cleavages promoted by the 2′-methoxy substituent, as has been observed previously.[4] Treatment with phosphoric acid, however, results in efficient rearrangement to the epimeric isochromane lactones **28** and **31**. The factors controlling diastereoselectivity in this reaction have not been studied. The fact that similar acid treatment of the hydroxy lactone **22** in the presence of acetaldehyde gives the isochromane lactone **28** as the sole product implies that these alternative routes to the isochromane lactone **28** do not share common intermediates, and that the isochromane lactone **28** once formed does not epimerise.

The diastereoselectivity of the process for the configuration of the isochromane methyl group is thus dependent upon the aryl substitution, the reagent and the reaction conditions. The kinetic preference noted in related rearrangements[4] for the induction of *cis* stereochemistry of the benzylic methyl sub-

stituent relative to the benzylic hydroxy substituent in the isochromane products was observed again in this study in the formation of the isochromanes **26**, **27**, **28**, **36** and **38**.

Conclusions

Lewis acid catalysed diastereoselective rearrangement of methyl 4,5-*trans*-4-aryldioxolan-5-ylacetates **1** provides a convenient route to substituted isochromane-γ-lactones **3**. The choice of Lewis acid depends on the substitution pattern of the aromatic ring. For the 3′,5′-dimethoxyphenyldioxolanes **4** and **5**, camphorsulfonic acid was highly effective, and its concentration controlled the preferred stereochemistry of the C-5 methyl group of the resulting isochromane lactone **26** or **29**. In the case of the 2′-chloro-5′-methoxyphenyldioxolanes **6** and **7**, titanium tetrachloride stereoselectively afforded the all-*cis* hydroxyisochromane ester **38** which could be cyclised with camphorsulfonic acid to the corresponding isochromane-γ-lactone **27** without loss of stereochemistry. For the 2′,5′-dimethoxyphenyldioxolanes **8** and **9**, phosphoric acid was efficient but gave a mixture of the C-5 epimeric isochromane lactones **28** and **31**.

Reaction of the hydroxy lactone **22** with acetaldehyde in the presence of phosphoric acid yielded the all-*cis* isochromane-γ-lactone **28** with complete diastereoselectivity. Its oxidative demethylation led to quinone **40**, which on annulation was readily converted into the corresponding benzoisochromanequinone 5-*epi*-7-deoxykalafungin **41** closely related to a number of natural products.

Experimental

General

Instrumentation and general procedures were as described previously.[4]

(*E*)-4-(3′,5′-Dimethoxyphenyl)but-3-enoic acid 12

3,5-Dimethoxybenzaldehyde **11** (5.2 g, 30 mmol) in dry tetrahydrofuran (100 ml) was added in portions to a stirred solution of (2-carboxyethyl)triphenylphosphonium chloride[17] (12.5 g, 30 mmol) in dry dimethyl sulfoxide (100 ml) at room temperature. The mixture was cooled to 0 °C, sodium hydride (1.0 g, 60% dispersion in oil) was added in portions, and the mixture was then allowed to warm to room temperature and stirred for 14 h. Aqueous sodium hydroxide (10%) was added, and the resulting solution was washed with toluene (5 × 100 ml) then with diethyl ether (2 × 100 ml). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with methylene dichloride (3 × 150 ml). The combined extracts were washed with dilute hydrochloric acid, dried and evaporated to give a brown oil. Chromatography using 25% ethyl acetate–hexane as eluent gave unreacted aldehyde **11** (1.5 g, 29%) followed by the *acid* **12** as a yellow oil (3.50 g, 50%), crystallised from methylene dichloride, mp 53–54 °C (Found: C, 64.9; H, 6.5. $C_{12}H_{14}O_4$ requires C, 64.9; H, 6.4%); λ_{max}/nm (MeOH) 250 (log ε 4.3), 300 (log ε 3.4); ν_{max}/cm^{-1} (neat) 1710 (CO_2H), 1653 (C=C), 1596 (C=C aromatic); δ_H 6.53 (2H, d, *J* 2.2, 2′- and 6′-H), 6.45 (1H, dt, *J* 15.9 and 1.5, 4-H), 6.38 (1H, t, *J* 2.2, 4′-H), 6.27 (1H, dt, *J* 15.9 and 7.2, 3-H), 3.80 (6H, s, 2 × OCH_3), 3.30 (2H, dd, *J* 7.2 and 1.5, 2-CH_2); δ_C 177.6 (C-1), 160.8 (C-3′ and C-5′), 138.6 (C-1′), 133.9 (C-4), 121.4 (C-3), 104.4 (C-2′ and C-6′), 100.0 (C-4′), 55.3 (2 × CH_3O), 37.9 (C-2); *m*/*z* 222 (M^+, 82%), 182 (31), 177 (100), 168 (46), 161 (22), 147 (22), 146 (24), 139 (28), 109 (26), 103 (21), 91 (43), 79 (21), 77 (49), 69 (29).

Methyl (*E*)-4-(3′,5′-dimethoxyphenyl)but-3-enoate 13

The acid **12** (1.70 g, 7 mmol) in dry methylene dichloride (15 ml) was treated with oxalyl chloride (1.0 g, 8 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h before heating under reflux for 12 h and then removal of the solvent under reduced pressure. The residue was stirred for 2 h with methanol (20 ml) which was removed under reduced pressure to afford the crude ester (1.7 g). Chromatography in 15% ethyl acetate–hexane as eluent gave the *ester* **13** as a yellow oil (1.50 g, 83%) (Found: C, 66.2; H, 6.9. $C_{13}H_{16}O_4$ requires C, 66.1; H 6.8%); δ_H 6.53 (2H, d, *J* 2.2, 2′- and 6′-H), 6.43 (1H, dt, *J* 15.9 and 1.5, 4-H), 6.38 (1H, t, *J* 2.2, 4′-H), 6.27 (1H, dt, *J* 15.9 and 7.2, 3-H), 3.80 (6H, s, 2 × OCH_3), 3.72 (3H, s, $COOCH_3$), 3.25 (2H, dd, *J* 7.2 and 1.5, 2-CH_2); δ_C 171.8 (C-1), 160 (C-3′ and C-5′), 138.7 (C-1′), 134.4 (C-4), 122 (C-3), 104 (C-2′ and C-6′), 99.8 (C-4′), 55.2 (2 × OCH_3), 51.8 ($COOCH_3$), 38.0 (C-2); *m*/*z* 236 (M^+, 49%), 177 (100), 176 (54), 161 (21), 146 (23), 91 (36), 77 (26), 65 (24), 59 (25).

rel-(4*R*,5*R*)-2,3,4,5-Tetrahydro-4-hydroxy-5-(3′,5′-dimethoxyphenyl)furan-2-one 14

The ester **13** (1.50 g, 6.3 mmol) in acetone (20 ml) was added to a solution of osmium tetroxide (5 mg) and *N*-methylmorpholine *N*-oxide[6] (0.85 g, 7.3 mmol) in water at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 18 h. Acetone was removed under reduced pressure and the aqueous solution acidified with dilute hydrochloric acid (2 M, 20 ml). The organic materials were extracted into ethyl acetate (5 × 50 ml), and the combined extracts washed with water (3 × 100 ml), dried, filtered, and the solvent removed under reduced pressure to give a light brown oil (1.4 g). Chromatography using 40% ethyl acetate–hexane as eluent afforded the *lactone* **14** as a colourless oil (1.32 g, 87%) (Found: C, 60.5; H, 6.1. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%); ν_{max}/cm^{-1} (neat) 3467 (OH), 1776 (C=O), 1599 (C=C aromatic); δ_H 6.50 (2H, d, *J* 2.2, 2′- and 6′-H), 6.43 (1H, t, *J* 2.2, 4′-H), 5.42 (1H, d, *J* 3.8, 5-H), 4.58 (1H, dd, *J* 3.8 and 5.4, 4-H), 3.78 (6H, s, 2 × OCH_3), 2.85 (1H, dd, *J* 17.5 and 5.4, 3-H), 2.70 (1H, d, *J* 17.5, 3-H); δ_C 175.2 (C-2), 161.2 (C-3′ and C-5′), 135.1 (C-1′), 103.8 (C-2′ and C-6′), 100.8 (C-4′), 85.1 (C-5), 70.1 (C-4), 55.5 (2 × OCH_3), 38.5 (C-3); *m*/*z* 238 (M^+, 24%), 167 (43), 166 (100), 139 (36), 135 (14), 109 (33), 77 (20).

rel-(2*S*,4*R*,5*R*) and *rel*-(2*R*,4*R*,5*R*)-5-Methoxycarbonylmethyl-4-(3′,5′-dimethoxyphenyl)-2-methyl-1,3-dioxolanes 4 and 5

The lactone **14** (500 mg, 2.1 mmol), 1,1-dimethoxyethane (400 mg, 4.1 mmol) and (±)-camphorsulfonic acid[1] (10 mg, 0.043 mmol) in dry methylene dichloride (100 ml) were heated under reflux for 72 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (5 ml), poured into cold water and extracted with methylene dichloride (3 × 100 ml). The combined extracts were dried, filtered and the solvent removed under reduced pressure to give a colourless oil. Chromatography in 20% ethyl acetate–hexane as eluent afforded a 1.3 : 1 mixture of the epimeric *dioxolanes* **4** and **5** as a colourless oil (436 mg, 70%) (Found: C, 61.0; H, 6.9. $C_{15}H_{20}O_6$ requires C, 60.8; H, 6.8%); δ_H 6.53 and 6.49 (each d, *J* 2.2, 2′- and 6′-H of each isomer), 6.41 (m, 4′-H of both isomers), 5.46 and 5.35 (each q, *J* 4.9, 2-H of each isomer), 4.59 and 4.57 (each d, *J* 6.9, 4-H of each isomer), 4.26 and 4.12 (each dt, *J* 4.9 and 6.9, 5-H of each isomer), 3.79 (s, OCH_3 of both isomers), 3.67 (s, $COOCH_3$ of both isomers), 2.75–2.58 (m, CH_2 of both isomers), 1.51 and 1.46 (each d, *J* 4.9, 2-CH_3 of each isomer); *m*/*z* 296 (M^+, 8%), 193 (22), 179 (43), 165 (18), 151 (32), 87 (30), 77 (24), 59 (100). Further elution gave the isochromane lactone **26**, a white powder (34 mg, 7%), with ^{1}H NMR and mass spectral data given below. Further chromatography of the mixture of dioxolanes **4** and **5** (100 mg) using 15% ethyl acetate–hexane afforded the single *dioxolane* **4** (20 mg), δ_H 6.53 (2H, d, *J* 2.2, 2′ and 6′-H), 6.41 (1H, t, *J* 2.2, 4′-H), 5.35 (1H, q, *J* 4.9, 2-H), 4.59 (1H, d, *J* 6.9, 4-H), 4.26 (1H, dt, *J* 4.9 and 6.9, 5-H), 3.79 (6H, s, 2 × OCH_3), 3.67 (3H, s, $COOCH_3$), 2.68 (1H, dd, *J* 15.0 and

6.9, CH_2), 2.63 (1H, dd, *J* 15.0 and 4.9, CH_2), 1.51 (3H, d, *J* 4.9, 2-CH_3). The ^{1}H NMR spectrum of the fraction containing the dioxolane **5** showed about 25% contamination with the epimer **4**.

(*E*)-4-(2′-Chloro-5′-methoxyphenyl)but-3-enoic acid 16

2-Chloro-5-methoxybenzaldehyde **15** (3.0 g, 17.6 mmol) in dry tetrahydrofuran (100 ml) was added to a stirred solution of (2-carboxyethyl)triphenylphosphonium chloride (7.5 g, 18.0 mmol) in dry dimethyl sulfoxide (100 ml). The procedure described above for the synthesis of acid **12** was followed to afford the aldehyde **15** (1.0 g, 33%) and the *acid* **16** as a yellow oil (1.7 g, 50%), which was crystallised from methylene dichloride, mp 92–94 °C (Found: C, 58.2; H, 4.8; Cl, 15.7. $C_{11}H_{11}ClO_3$ requires C, 58.3; H, 4.9; Cl, 15.6%); ν_{max}/cm^{-1} (neat) 1710 (COOH), 1653 (C=C), 1596 (C=C aromatic); δ_H 7.23 (1H, d, *J* 8.8, 3′-H), 7.06 (1H, d, *J* 3.0, 6′-H), 6.88 (1H, dt, *J* 15.8 and 1.5, 4-H), 6.76 (1H, dd, *J* 8.8 and 3.0, 4′-H), 6.29 (1H, dt, *J* 15.8 and 7.2, 3-H), 3.81 (3H, s, OCH_3), 3.37 (2H, dd, *J* 7.2 and 1.5, CH_2); δ_C 177.8 (C-1), 158.3 (C-5′), 135.3 (C-2′), 130.2 (C-1′), 124.5 and 123.7 (C-3, C-4), 114.9 (C-4′ and C-6′), 111.6 (C-3′), 55.5 (OCH_3), 38.0 (C-2); *m*/*z* 228 [M$^+$ (^{37}Cl), 21%], 226 [M$^+$ (^{35}Cl), 65], 186 (29), 181 (45), 146 (100), 145 (47), 131 (30), 115 (45), 103 (49), 102 (24), 77 (51), 63 (49).

Methyl (*E*)-4-(2′-chloro-5′-methoxyphenyl)but-3-enoate 17

Phenylbutenoic acid **16** (1.7 g, 7.50 mmol) in dry methylene dichloride (15 ml) was treated with oxalyl chloride (1.0 g, 8.0 mmol) at 0 °C. The procedure described above for the synthesis of ester **13** was followed to afford the *ester* **17** as a yellow oil (1.5 g, 83%) (Found: C, 59.5; H, 5.7; Cl, 14.9. $C_{12}H_{13}ClO_3$ requires C, 59.8; H, 5.4; Cl, 14.7%); δ_H 7.25 (1H, d, *J* 8.8, 3′-H), 7.06 (1H, d, *J* 3.0, 6′-H), 6.83 (1H, dd, *J* 15.8 and 1.5, 4-H), 6.73 (1H, dd, *J* 8.8 and 3.0, 4′-H), 6.29 (1H, dt, *J* 15.8 and 7.1, 3-H), 3.80 (3H, s, OCH_3), 3.73 (3H, s, $COOCH_3$), 3.31 (2H, dd, *J* 7.1 and 1.5, CH_2); δ_C 171.1 (C-1), 158.2 (C-5′), 135.5 (C-2′), 130.2 and 129.4 (C-4, C-3), 124.5 (C-1′), 114.8 (C-4′ and C-6′), 111.5 (C-3′), 55.5 (OCH_3), 51.9 ($COOCH_3$), 38.0 (C-2); *m*/*z* 242 [M$^+$(^{37}Cl), 21%], 240 [M$^+$(^{35}Cl), 63], 183 (21), 181 (68), 146 (100), 145 (39), 131 (28), 115 (33), 103 (47), 102 (23), 77 (34), 51 (30).

rel-(4*R*,5*R*)-2,3,4,5-Tetrahydro-4-hydroxy-5-(2′-chloro-5′-methoxyphenyl)furan-2-one 18

The ester **17** (600 mg, 2.49 mmol) in acetone (10 ml) was added to a solution of osmium tetroxide (5 mg) and *N*-methylmorpholine *N*-oxide (540 mg, 4.60 mmol) in water (30 ml) at 0 °C. The procedure described for the synthesis of lactone **14** afforded the *lactone* **18** as a colourless oil (450 mg, 75%) (Found: C, 54.6; H, 4.8; Cl, 14.7. $C_{11}H_{11}ClO_3$ requires C, 54.45; H, 4.6; Cl, 14.6%); ν_{max}/cm^{-1} (KBr) 3525 (OH), 1770 (C=O), 1596 (C=C); δ_H 7.29 (1H, d, *J* 8.8, 3′-H), 7.10 (1H, d, *J* 3.1, 6′-H), 6.86 (1H, dd, *J* 8.8 and 3.1, 4′-H), 5.76 (1H, d, *J* 3.4, 5-H), 4.93 (1H, dd, *J* 3.4 and 5.4, 4-H), 3.80 (3H, s, OCH_3), 2.96 (1H, dd, *J* 17.6 and 5.4, 3-H), 2.72 (1H, d, *J* 17.6, 3-H); δ_C 174.9 (C-1), 158.7 (C-5′), 131.9 (C-2′), 130.3 (C-3′), 121.9 (C-1′), 116.4 and 113.2 (C-4′, C-6′), 82.6 (C-5), 68.3 (C-4), 55.7 (OCH_3), 38.3 (C-2); *m*/*z* 244 [M$^+$(^{37}Cl), 10%], 242 [M$^+$(^{35}Cl), 32], 173 (23), 172 (40), 171 (87), 170 (100), 169 (44), 143 (22), 77 (23), 63 (27).

rel-(2*S*,4*R*,5*R*) and *rel*-(2*R*,4*R*,5*R*)-5-Methoxycarbonylmethyl-4-(2′-chloro-5′-methoxyphenyl)-2-methyl-1,3-dioxolanes 6 and 7

The lactone **18** (600 mg, 2.48 mmol) in dry methylene dichloride (100 ml) was treated with 1,1-dimethoxyethane (400 mg, 4.1 mmol) and (±)-camphorsulfonic acid (10 mg, 0.043 mmol) as for the synthesis of dioxolanes **4** and **5** above, to afford the hydroxy lactone **18** (40 mg, 10%) followed by a 1 : 1 mixture of the epimeric *dioxolanes* **6** and **7** as a colourless oil (550 mg, 81%) (Found: M$^+$ − C_2H_4O, 256.0502. $C_{12}H_{13}{}^{35}ClO_4$ requires M$^+$ − C_2H_4O, 256.0502); δ_H 7.23 (2H, d, *J* 9.1, 3′-H of both isomers), 7.14 and 7.05 (each 1H, d, *J* 3.1, 6′-H of each isomer), 6.78 (2H, dd, *J* 9.1 and 3.1, 4′-H of both isomers), 5.53 and 5.38 (each 1H, q, *J* 4.9, 2-H of each isomer), 5.13 and 5.11 (each 1H, d, *J* 6.9, 4-H of both isomers), 4.31 (2H, m, 5-H of both isomers), 3.80 (6H, s, OCH_3 of both isomers), 3.60 (6H, s, $COOCH_3$ of both isomers), 2.95–2.75 (4H, m, CH_2 of both isomers), 1.56 and 1.48 (each 3H, d, *J* 4.9, 2-CH_3 of each isomer); *m*/*z* 302 [M$^+$(^{37}Cl), 2%], 300 [M$^+$(^{35}Cl), 6], 265 (8), 258 (15), 256 (47), 226 (25), 197 (18), 183 (22), 169 (45), 167 (57), 155 (36), 119 (28), 91 (25), 77 (23), 59 (100).

(*E*)-4-(2′,5′-Dimethoxyphenyl)but-3-enoic acid 20

2,5-Dimethoxybenzaldehyde **19** (2.0 g, 12.05 mmol) in tetrahydrofuran (200 ml) was added in portions to (2-carboxyethyl)-triphenylphosphonium chloride (5.0 g, 12.05 mmol) in dry dimethyl sulfoxide (100 ml) at room temperature. The procedure described for the synthesis of acid **12** afforded unreacted aldehyde **19** (0.3 g, 15%) followed by the *acid* **20** as a yellow oil (1.8 g, 67%) (Found: C, 65.0; H, 6.4. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%); ν_{max}/cm^{-1} (neat) 1710 (COOH), 1653 (C=C), 1596 (C=C aromatic); δ_H 7.02 (1H, d, *J* 2.3, 6′-H), 6.83 (1H, dt, *J* 15.9 and 1.5, 4-H), 6.80 (2H, m, 3′ and 4′-H), 6.31 (1H, dt, *J* 15.9 and 7.2, 3-H), 3.82 and 3.80 (each 3H, s, OCH_3), 3.34 (2H, dd, *J* 7.2 and 1.5, 2-CH_2); δ_C 177.6 (C-1), 153.8 and 151.1 (C-2′ and C-5′), 128 (C-4), 126.5 (C-1′), 121.7 (C-3), 113.8, 112.2 and 112.1 (C-3′, C-4′, C-6′), 56.2 (OCH_3), 55.7 (OCH_3), 38.3 (C-2); *m*/*z* 222 (M$^+$, 100%), 177 (45), 161 (77), 147 (15), 146 (15), 91 (27), 77 (21), 65 (25), 55 (19).

Methyl (*E*)-4-(2′,5′-dimethoxyphenyl)but-3-enoate 21

Phenylbutenoic acid **20** (1.7 g, 7.0 mmol) in methylene dichloride (15 ml) was treated with oxalyl chloride (1.0 g, 8 mmol) as for the preparation of ester **13** to afford the *ester* **21** as a yellow oil (1.5 g, 83%) (Found: C, 66.25; H, 7.15. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%); ν_{max}/cm^{-1} (neat) 1750 ($COOCH_3$), 1653 (C=C); δ_H 7.01 (1H, d, *J* 2.3, 6′-H), 6.82 (1H, dt, *J* 15.9 and 1.4, 4-H), 6.78 (2H, m, 3′ and 4′-H), 6.30 (1H, dt, *J* 15.9 and 5.6, 3-H), 3.80, 3.78 and 3.72 (each 3H, s, 2 × OCH_3 and $COOCH_3$), 3.28 (2H, dd, *J* 5.6 and 1.4, CH_2); δ_C 172.1 (C-1), 153.6 and 150.9 (C-2′, C-5′), 128.0 and 126.6 (C-1′, C-4), 122.4 (C-3), 113.6, 112.1 and 111.9 (C-3′, C-4′, C-6′), 56.1 (OCH_3), 55.6 (OCH_3), 51.8 ($COOCH_3$), 31.5 (C-2); *m*/*z* 236 (M$^+$, 95%), 181 (11), 177 (100), 162 (23), 161 (84), 147 (20), 146 (24), 121 (17), 103 (12), 91 (32), 77 (19), 65 (29).

rel-(4*R*,5*R*)-2,3,4,5-Tetrahydro-4-hydroxy-5-(2′,5′-dimethoxyphenyl)furan-2-one 22

The ester **21** (400 mg, 1.69 mmol) in acetone (10 ml) was added to osmium tetroxide (5 mg) and *N*-methylmorpholine *N*-oxide (226 mg, 1.94 mmol) in water (30 ml) at 0 °C. The procedure described for the synthesis of hydroxy lactone **14** afforded the *lactone* **22** as a colourless oil (370 mg, 92%) (Found: C, 60.25; H, 6.1; $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%); ν_{max}/cm^{-1} (neat) 3420 (OH), 1772 (C=O), 1612 cm^{-1} (C=C); δ_H 7.06 (1H, d, *J* 2.2, 6′-H), 6.84 (2H, m, 3′-H and 4′-H), 5.72 (1H, d, *J* 3.5, 5-H), 4.78 (1H, dd, *J* 3.5 and 5.3, 4-H), 3.80 and 3.76 (each 3H, s, OCH_3), 2.87 (1H, dd, *J* 17.5 and 5.3, 3-H), 2.66 (1H, d, *J* 17.5, 3-H); δ_C 175.4 (C-2), 153.8 and 149.6 (C-2′, C-5′), 122.1 (C-1′), 114.8 (C-6′), 112.9 and 111.3 (C-3′, C-4′), 81.8 (C-5), 68.7 (C-4), 55.8 (2 × OCH_3), 38.2 (C-3); *m*/*z* 238 (M$^+$, 100%), 167 (97), 166 (96), 151 (35), 139 (38), 137 (35), 120 (22).

rel-(2*S*,4*R*,5*R*) and *rel*-(2*R*,4*R*,5*R*)-5-Methoxycarbonylmethyl-4-(2′,5′-dimethoxyphenyl)-2-methyl-1,3-dioxolanes 8 and 9

The lactone **22** (320 mg, 1.34 mmol) in dichloromethane (100

ml) was treated with 1,1-dimethoxyethane (400 mg, 4.1 mmol) and (±)-camphorsulfonic acid (10 mg, 0.043 mmol) as for the synthesis of dioxolanes **4** and **5** to afford, first, recovered lactone **22** (100 mg, 31%), followed by the isochromane lactone **28** (17 mg, 5%) and finally the *dioxolanes* **8** and **9** in a 1:1 ratio as a colourless oil (190 mg, 60%) (Found: C, 60.8; H, 6.9. $C_{15}H_{20}O_6$ requires C, 60.8; H, 6.8%); ν_{max}/cm^{-1} (KBr disc) 1685 (C=O), 1654 (C=C); δ_H 7.12 and 7.02 (each 1H, d, *J* 2.2, 6′-H of each isomer), 6.78 (4H, m, 3′-H and 4′-H of both isomers), 5.41 and 5.34 (each 1H, q, *J* 4.8, 2-H of each isomer), 5.04 and 4.98 (each 1H, d, *J* 6.0, 4-H of each isomer), 4.28 (2H, m, 5-H of both isomers), 3.78, 3.76 and 3.68 (each 6H, s, 2 × OCH_3 and $COOCH_3$ of both isomers), 2.85 (4H, m, CH_2 of both isomers), 1.51 and 1.47 (each 3H, d, *J* 4.8, 1-CH_3 of each isomer); *m*/*z* 296 (M^+, 42%), 252 (37), 194 (30), 193 (59), 179 (29), 165 (52), 161 (26), 153 (48), 151 (54), 87 (35), 59 (100).

rel-(3a*R*,5*S*,9b*R*)- and *rel*-(3a*R*,5*R*,9b*R*)-3,3a,5,9b-Tetrahydro-6,8-dimethoxy-5-methyl-2*H*-furo[3,2-*c*][2]benzopyran-2-ones 26 and 29

(a) The phenyldioxolane mixture **4** and **5** (1.3:1, 100 mg, 0.34 mmol) and (±)-camphorsulfonic acid (20 mg, 0.086 mmol) in dry methylene dichloride (15 ml) were heated under reflux for 18 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (1 ml) and extracted with methylene dichloride. The organic extracts were dried, filtered and concentrated to give a residue (90 mg), which was chromatographed in 40% ethyl acetate–hexane to afford a mixture of the isochromane lactones **26** and **29**, in 6.8:1 ratio from GC-MS and ^{1}H NMR analysis, as a colourless oil (80 mg, 86%).

(b) The reaction was repeated using (±)-camphorsulfonic acid (300 mg, 1.29 mmol), affording a 1:3.6 mixture of isochromane lactones **26** and **29** as a colourless oil (82 mg, 89%). This mixture was separated by HPLC using 20% tetrahydrofuran–hexane as eluent to afford, first, the *isochromane lactone* **26** (15 mg, 18%), which was crystallised from methylene dichloride–hexane, mp 138–140 °C (Found: C, 63.3; H, 6.1. $C_{14}H_{16}O_5$ requires C, 63.6; H, 6.1%); ν_{max}/cm^{-1} (KBr) 1781 (C=O), 1600 (C=C); δ_H 6.58 (1H, d, *J* 2.3, 9-H), 6.48 (1H, d, *J* 2.3, 7-H), 5.07 (1H, d, *J* 2.5, 9b-H), 4.79 (1H, q, *J* 6.5, 5-H), 4.35 (1H, dd, *J* 2.5 and 4.6, 3a-H), 3.82 and 3.80 (each 3-H, s, OCH_3), 2.88 (1H, dd, *J* 17.5 and 4.6, 3-H), 2.74 (1H, d, *J* 17.5, 3-H), 1.56 (3H, d, *J* 6.5, 5-CH_3); δ_C 175.3 (C-2), 159.4 and 157.1 (C-6, C-8), 129.1 and 121.8 (C-5a, C-9a), 105.6 (C-9), 100.4 (C-7), 76.9, 70.9 and 69.8 (C-3a, C-5, C-9b), 55.5 (OCH_3), 55.3 (OCH_3), 38.3 (C-3), 21.3 (CH_3). This was followed by the *isochromane lactone* **29** (47 mg, 57%), which was crystallised from methylene dichloride–hexane, mp 127–128 °C (Found: C, 63.7; H, 6.3. $C_{14}H_{16}O_5$ requires C, 63.6; H, 6.1%); ν_{max}/cm^{-1} (KBr) 1780 (C=O), 1612 (C=C); δ_H 6.58 (1H, d, *J* 2.1, 9-H), 6.46 (1H, d, 2.1, 7-H), 5.10 (1H, q, *J* 6.6, 5-H), 5.01 (1H, d, *J* 3.0, 9b-H), 4.77 (1H, dd, *J* 5.4 and 3.0, 3a-H), 3.82 and 3.81 (each 3H, s, OCH_3), 2.99 (1H, dd, *J* 17.8 and 5.4, 3-H), 2.69 (1H, d, *J* 17.8, 3-H), 1.46 (3H, d, *J* 6.6, 5-CH_3); δ_C 174.8 (C-2), 159.6 and 155.9 (C-6, C-8), 128.2 and 121.6 (C-5a, C-9a), 104.9 (C-9), 99.7 (C-7), 75.5, 67.3 and 65.8 (C-3a, C-5, C-9b), 55.4 (2 × OCH_3), 37.7 (C-3), 18.5 (CH_3); *m*/*z* 264 (M^+, 10%), 249 (100), 221 (2), 193 (3), 177 (7), 162 (10).

Methyl *rel*-(1*S*,3*R*,4*R*)-4-hydroxy-6,8-dimethoxy-1-methylisochroman-3-ylacetate 36 and methyl *rel*-(1′*R*,3*R*,3′*S*)-3-hydroxy-3-(1′,3′-dihydro-4′,6′-dimethoxy-3′-methylisobenzofuran-1′-yl)-propanoate 37

To a stirred solution of a 1.3:1 mixture of dioxolanes **4** and **5** (50 mg, 0.17 mmol) in dry methylene dichloride (25 ml) at −78 °C was added titanium tetrachloride (0.05 ml, 0.34 mmol). The reaction mixture was warmed to −30 °C, stirred for 30 minutes, then quenched with methanol (0.1 ml) and saturated aqueous sodium hydrogen carbonate (2 ml) before pouring into water. The organic layer was separated, the aqueous layer extracted with methylene dichloride (3 × 10 ml), and the organic extracts dried and evaporated to give a colourless oil. Analysis by GC, GC-MS and ^{1}H NMR spectroscopy indicated a mixture of three compounds: dioxolanes **4** and **5** (55%); isochromane ester **36** (20%), GC-MS *m*/*z* 296 (M^+, 13%), 281 (100), 221 (6), 207 (7), 203 (14), 193 (8), 179 (11), 175 (6); and dihydroisobenzofuran **37** (25%). Repetition of the reaction at room temperature for 2 h gave a crude product (40 mg), GC, GC-MS and ^{1}H NMR spectroscopy of which indicated the *dihydroisobenzofuran ester* **37**, δ_H 6.43 (1H, d, *J* 2.5, 7′-H), 6.36 (1H, d, *J* 2.5, 5′-H), 5.40 (1H, dq, *J* 3.0 and 6.2, 3′-H), 5.26 (1H, t, *J* 3.0, 1′-H), 4.31 (1H, ddd, *J* 8.8, 3.0 and 4.0, 3-H), 3.82 and 3.81 (each 3H, s, OCH_3), 3.72 (3H, s, $COOCH_3$), 2.62 (1H, dd, *J* 16.0 and 4.0, 2-H), 2.53 (1H, dd, *J* 16.0 and 8.8, 2-H), 1.47 (3H, d, *J* 6.2, 3′-CH_3); *m*/*z* 296 (M^+, 4%), 278 (21), 193 (100), 151 (7). Attempted chromatography of the dihydroisobenzofuran **37** on silica gel or neutral alumina resulted in decomposition.

Methyl [*rel*-(1*S*,3*R*,4*R*)-5-chloro-4-hydroxy-8-methoxy-1-methylisochroman-3-yl]acetate 38

To the dioxolanes **6** and **7** (1:1, 250 mg, 1.03 mmol) in methylene dichloride (40 ml) stirred at 0 °C in an atmosphere of argon was added titanium tetrachloride (0.23 ml, 2.06 mmol). After stirring at room temperature for 5 h, the reaction was quenched with saturated aqueous sodium hydrogen carbonate (2 ml) and poured into water. The organic layer was separated, the aqueous layer extracted with methylene dichloride (3 × 10 ml), and the organic extracts dried and evaporated to give a colourless oil. Analysis by GC and GC-MS indicated a mixture of two compounds. Chromatography using 40% ethyl acetate–hexane as eluent first afforded the *isochromane ester* **38** as a colourless oil (160 mg, 64%) (Found: C, 55.9; H, 5.9; Cl, 11.9. $C_{14}H_{17}ClO_5$ requires C, 55.9; H, 5.7; Cl, 11.8); δ_H 7.26 (1H, d, *J* 8.8, 6-H), 6.78 (1H, d, *J* 8.8, 7-H), 4.94 (1H, q, *J* 6.2, 1-H), 4.69 (1H, d, *J* 1.3, 4-H), 4.02 (1H, dt, *J* 1.3 and 7.1, 3-H), 3.80 (3H, s, OCH_3), 3.72 (3H, s, $COOCH_3$), 2.84 (2H, m, CH_2), 1.54 (3H, d, *J* 6.2, 1-CH_3); *m*/*z* 302 [M^+(^{37}Cl), 2%], 300 [M^+(^{35}Cl) 6], 287 (5), 285 (15), 253 (10), 225 (12), 209 (18), 200 (32), 198 (100), 183 (27), 169 (36). This was followed by the diol ester **39** as a colourless oil (30 mg, 12%), δ_H 7.24 (1H, d, *J* 8.8, 3′-H), 7.10 (1H, d, *J* 3.0, 6′-H), 6.79 (1H, dd, *J* 8.8 and 3.0, 4′-H), 5.02 (1H, d, *J* 5.7, 4-H), 4.15 (1H, m, 3-H), 3.80 (3H, s, OCH_3), 3.70 (3H, s, $COOCH_3$), 2.68 (1H, dd, *J* 17.0 and 7.5, 2-H), 2.48 (1H, dd, *J* 17.0 and 3. 2, 2-H); *m*/*z* 274 [M^+(^{35}Cl), 1%], 256 (12), 183 (12), 174 (30), 172 (100).

rel-(3a*R*,5*S*,9b*R*)-9-Chloro-3,3a,5,9b-tetrahydro-6-methoxy-5-methyl-2*H*-furo[3,2-*c*][2]benzopyran-2-one 27

The isochromane **38** (150 mg, 0.62 mmol) and (±)-camphorsulfonic acid (100 mg, 0.43 mmol) in methylene dichloride (10 ml) were heated under reflux for 3 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (2 ml), and the organic layer was separated, washed with water, dried and evaporated. Chromatography using 25% ethyl acetate–hexane as eluent afforded the isochromane lactone **27** as a colourless oil (112 mg, 83%) (Found: C, 57.8; H, 4.9; Cl, 13.5. $C_{13}H_{13}ClO_4$ requires C, 58.1; H, 4.9; Cl, 13.2%); ν_{max}/cm^{-1} (neat) 1780 (C=O), 1590 (C=C); δ_H 7.34 (1H, d, *J* 8.8, 8-H), 6.88 (1H, d, *J* 8.8, 7-H), 5.30 (1H, d, *J* 2.2, 9b-H), 4.86 (1H, q, *J* 6.3, 5-H), 4.34 (1H, dd, *J* 2.2 and 4.4, 3a-H), 3.83 (3H, s, OCH_3), 2.90 (1H, dd, *J* 17.2 and 4.4, 3-H), 2.73 (1H, d, *J* 17.2, 3-H), 1.57 (3H, d, *J* 6.3, 5-CH_3); δ_C 175.4 (C-2), 154.6 (C-6), 131.5, 128.3 and 126.7 (C-5a, C-9, C-9a), 112.6 and 112.0 (C-7, C-8), 74.1, 71.1 and 69.7 (C-3a, C-5, C-9b), 55.5 (OCH_3), 38.1 (C-3), 21.1 (CH_3); *m*/*z* 270 [M^+(^{37}Cl), 5%], 268 [M^+(^{35}Cl), 15%], 255 (35), 253 (100), 225 (14), 197 (11), 169 (12).

rel-(3a*R*,5*S*,9b*R*)-3,3a,5,9b-Tetrahydro-6,9-dimethoxy-5-methyl-2*H*-furo[3,2-*c*][2]benzopyran-2-one 28

To a stirred solution of lactone **22** (600 mg, 2.52 mmol) in freshly distilled acetaldehyde (110 mg, 2.50 mmol) was added orthophosphoric acid (6 ml). After 22 h at room temperature, water (100 ml) was added and the aqueous solution was extracted with methylene dichloride (3 × 50 ml). The organic extracts were washed with water, dried, and evaporated to give a brown residue, which was dissolved in toluene (7 ml) to which hexane (30 ml) was added. The resultant precipitate was filtered and the filtrate concentrated to afford an orange residue, which was chromatographed using 33% ethyl acetate–hexane as eluent to give the *isochromane lactone* **28** as a yellow oil (532 mg, 76%) (Found: M^+, 264.0998. $C_{14}H_{16}O_5$ requires 264.0998); ν_{max}/cm^{-1} (KBr disc) 1786 (C=O), 1602 (C=C); δ_H 6.89 and 6.78 (each 1H, d, *J* 8.9, 7-H and 8-H), 5.32 (1H, d, *J* 2.3, 9b-H), 4.84 (1H, q, *J* 6.5, 5-H), 4.28 (1H, dd, *J* 2.3 and 4.3, 3a-H), 3.84 and 3.78 (each 3H, s, OCH_3), 2.84 (1H, dd, *J* 17.2 and 4.3, 3-H), 2.69 (1H, d, *J* 17.2, 3-H), 1.57 (3H, d, *J* 6.5, 5-CH_3); δ_C ($CDCl_3$) 175.7 (C-2), 152.7 and 149.7 (C-6, C-9), 130.3 (C-5a), 117.7 (C-9a), 112.3 and 108.9 (C-7, C-8), 72.5, 70.9 and 69.6 (C-3a, C-5, C-9b), 56.1 (OCH_3), 55.6 (OCH_3), 38.2 (C-3), 21.1 (5-CH_3); *m*/*z* 264 (M^+, 50%), 249 (100), 221 (12), 165 (15), 91 (19), 77 (22).

rel-(3a*R*,5*S*,9b*R*)- and *rel*-(3a*R*,5*R*,9b*R*)-3,3a,5,9b-Tetrahydro-6,9-dimethoxy-5-methyl-2*H*-furo[3,2-*c*][2]benzopyran-2-ones 28 and 31

The mixed dioxolanes **8** and **9** (1 : 1, 150 mg, 0.05 mmol) were treated with orthophosphoric acid (2 ml) at room temperature for 18 h. Water (50 ml) was added, the aqueous solution was extracted with methylene dichloride (3 × 20 ml), and the organic extracts were washed with water, dried, and evaporated to give a brown residue. This residue was dissolved in toluene (7 ml), hexane (20 ml) was added, the resultant precipitate was filtered and the filtrate concentrated to afford an orange residue. Chromatography using 33% ethyl acetate–hexane as eluent gave the isochromane lactones **28** and **31** in 1 : 1 ratio by ^{1}H NMR analysis, as a yellow oil (119 mg, 70%), δ_H 6.90–6.76 (4H, m, 7-H and 8-H of both isomers), 5.33 (2H, br d, *J* ~2.9, 9b-H of both isomers), 5.14 (1H, q, *J* 6.5, 5-H of **31**), 4.85 (1H, q, *J* 6.5, 5-H of **28**), 4.69 (1H, dd, *J* 2.9 and 5.0, 3a-H of **31**), 4.28 (1H, dd, *J* 2.3 and 4.3, 3a-H of **28**), 3.84 (6H, s, OCH_3 of both isomers), 3.79 and 3.78 (each 3H, s, OCH_3 of each isomer), 2.92 (1H, dd, *J* 17.2 and 5.0, 3-H of **31**), 2.84 (1H, dd, *J* 17.2 and 4.3, 3-H of **28**), 2.69 (1H, d, *J* 17.2, 3-H of **28**) and 2.66 (1H, d, *J* 17.2, 3-H of **31**), 1.57 (3H, d, *J* 6.5, 5-CH_3 of **28**), 1.46 (3H, d, *J* 6.5, 5-CH_3 of **31**).

rel-(3a*R*,5*S*,9b*R*)-3,3a,5,6,9,9b-Hexahydro-5-methyl-2*H*-furo-[3,2-*c*][2]benzopyran-2,6,9-trione 40

To a stirred solution of isochromane lactone **28** (200 mg, 0.75 mmol) in acetonitrile (15 ml) and water (20 ml) was added cerium(IV) ammonium nitrate (870 mg, 1.59 mmol) in water (1.5 ml) during five minutes at room temperature. The mixture was stirred for a further 30 minutes then extracted with methylene dichloride (3 × 10 ml). The extracts were washed with water, dried and evaporated to afford an orange residue which was chromatographed using 25% ethyl acetate–hexane as eluent to give the *quinone* **40** as an orange oil (120 mg, 69%) (Found: M^+, 234.0529. $C_{12}H_{10}O_5$ requires 234.0528); δ_H 6.87 and 6.83 (each 1H, d, *J* 8.3, 7-H and 8-H), 5.10 (1H, dd, *J* 2.5 and 1.8, 9b-H), 4.64 (1H, dq, *J* 1.8 and 6.5, 5-H), 4.32 (1H, dd, *J* 2.5 and 4.7, 3a-H), 2.87 (1H, dd, *J* 17.5 and 4.7, 3-H), 2.69 (1H, d, *J* 17.5, 3-H), 1.57 (3H, d, *J* 6.5, 5-CH_3); *m*/*z* 234 (M^+, 28%), 219 (22), 191 (24), 179 (39), 91 (24), 77 (33), 55 (100).

rel-(3a*R*,5*S*,11b*R*)-3,3a,5,6,11,11b-Hexahydro-5-methyl-2*H*-furo[3,2-*b*]naphtho[2,3-*d*]pyran-2,6,11-trione 41

The quinone **40** (30 mg, 0.13 mmol) and 1-acetoxybuta-1,3-diene (60 mg, 0.54 mmol) in benzene (5 ml) was heated at 60 °C for 5 h. The solvent was evaporated, the residual oil dissolved in ethanol (3 ml) to which was added 1% sodium carbonate solution (0.3 ml), and the mixture stirred at room temperature for a further 5 h. Dilution with ethyl acetate (10 ml), washing with water, drying and evaporation gave a crude oil, which was chromatographed in 25% ethyl acetate–hexane as eluent to afford *5-epi-7-deoxykalafungin* **41** as an orange oil (24 mg, 66%), crystallised from hexane–diethyl ether, mp 191–193 °C, lit.,[16] 190–193 °C (decomp.), with ^{1}H NMR and MS data in agreement with literature.[16]

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Paper 8/07005I