Stereoselective isomerisations of 4-(3′,5′-dimethoxyphenyl)-2,5-dimethyl-1,3-dioxolanes. Temperature-dependent formation of either isochromanes or dihydroisobenzofurans

Robin G. F. Giles,*[a] Rodney W. Rickards*[b] and Badra S. Senanayake[a,b]

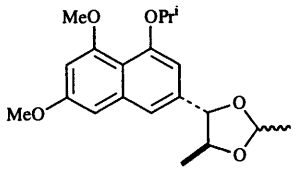
[a] *Chemistry Department, School of Mathematical and Physical Sciences, Murdoch University, Murdoch, WA 6150, Australia*

[b] *Research School of Chemistry, Australian National University, Canberra, ACT 0200, Australia*

Stereoselective isomerisation of *rel*-(2*R*,4*S*,5*R*)-4-(3′,5′-dimethoxyphenyl)-2,5-dimethyl-1,3-dioxolane 7 with titanium tetrachloride affords *rel*-(1*R*,3*R*,4*S*)-4-hydroxy-6,8-dimethoxy-1,3-dimethylisochromane 19 and its C-1 epimer 20 in high yield. The former predominates at a reaction temperature of −78 °C and the latter at −30 °C. Similar isomerisation of the 1:1 mixture of *rel*-(2*S*,4*R*,5*R*)- and *rel*-(2*R*,4*R*,5*R*)-4-(3′,5′-dimethoxyphenyl)-2,5-dimethyl-1,3-dioxolanes 8 and 9 gives *rel*-(1*R*,3*R*,4*R*)-4-hydroxy-6,8-dimethoxy-1,3-dimethylisochromane 29 and its C-1 epimer 31, with the latter predominating at both −78 and −30 °C. At 0 °C, dioxolane 7 is isomerised to *rel*-(1*S*,1′*R*,3*R*)-1-(1′-hydroxyethyl)-4,6-dimethoxy-3-methyl-1,3-dihydroisobenzofuran 25 and its C-3 epimer 26 as the sole reaction products in a 10:1 ratio. Dioxolanes 8 and 9 are similarly converted into *rel*-(1*R*,1′*R*,3*S*)-1-(1′-hydroxyethyl)-4,6-dimethoxy-3-methyl-1,3-dihydroisobenzofuran 32 and its C-3 epimer 33. These furans probably arise through further isomerisation of the intermediate isochromanes at the higher reaction temperatures.

We have recently shown[1] that 2,5-dimethyl-4-(2-naphthyl)-dioxolanes are stereoselectively isomerised by titanium tetrachloride to afford 3,4-dihydro-4-hydroxy-1,3-dimethylnaphtho[1,2-*c*]pyrans in an intramolecular version of the Mukaiyama reaction. Thus the 4,5-*trans*-substituted dioxolane **1** yielded the products **2** and **3** epimeric at C-1, while the all-*cis* bromo-analogue **4** gave rise to the debrominated product **5** as a single stereoisomer together with, in lower yield, the corresponding product **6** derived from bromine migration. The complex dioxolanes **1** and **4** used in this work were, however, derived by multistep sequences with the intention of assembling natural product derivatives, rather than of studying the isomerisation process *per se*.[1] In this paper we examine in detail the isomerisation of simple model 4-phenyldioxolanes.[2]

The model substrates chosen were the 3′,5′-dimethoxyphenyl-dioxolanes **7**, **8** and **9**, as these would address some of the questions raised in the earlier study.[1] First, successful isomerisation to isochromanes would now necessitate substitution of the aromatic ring *ortho* to a methoxy group. The initial aromatic symmetry would avoid the problem of regioisomers. In the earlier study,[1] the desired isomerisation of the dioxolanes **1** and **4** to the linear rather than the angular naphthopyrans would have required substitution *ortho* to the bulky isopropoxy substitutuents. Secondly, it was hoped that the neighbouring methoxy substituent might be of sufficient bulk to require the C-1 methyl group in the products to assume the pseudoaxial configuration in order to minimise *peri* interactions.[1] Such interactions were invoked previously to explain the complete pseudoaxial stereoselectivity at C-1 in other ring-closure reactions leading to the formation of related products.[3,4]



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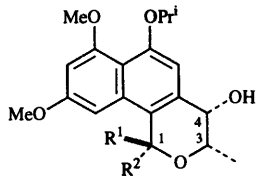
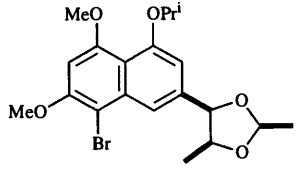


2 R^1 = H, R^2 = Me
3 R^1 = Me, R^2 = H



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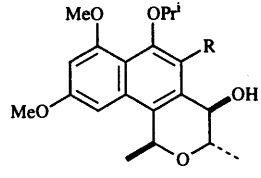

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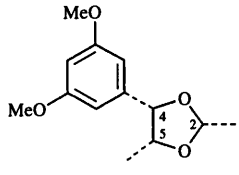
6 R = Br



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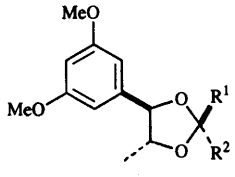
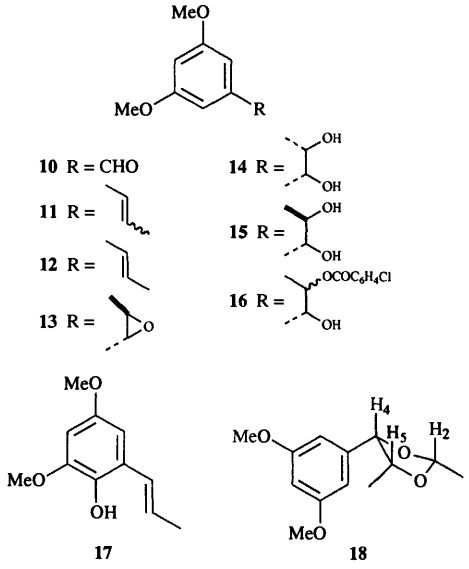


8 R^1 = Me, R^2 = H
9 R^1 = H, R^2 = Me

Results

Synthesis of the dimethoxyphenyldioxolanes

The starting material chosen for the assembly of these phenyl-dioxolanes was the readily available 3,5-dimethoxybenz-aldehyde **10**.[5] This was reacted with ethylidenetriphenylphos-phorane to afford the mixture of (*E*)- and (*Z*)-alkenes **11** in a ratio of 2:1, as judged by ^{1}H NMR spectroscopy. Treatment of this mixture with bis(acetonitrile)dichloropalladium(II) gave solely the (*E*)-isomer **12** in high yield.[6] The method of Schlosser and Christmann[7] for the direct conversion of aldehydes to (*E*)-alkenes also gave pure (*E*)-alkene **12**, but in lower overall yield. The (*E*)-alkene was treated with *m*-chloroperbenzoic acid in the presence of solid sodium hydrogen carbonate, affording the *trans*-epoxide **13** in reasonable yield (66%). A minor by-product **17** involved hydroxylation of the aromatic ring, while omission of the base gave substantial quantities of the diastereoisomeric mixture of hydroxy esters **16** arising through *m*-chlorobenzoic



acid-catalysed opening of the epoxide ring at the benzylic centre.

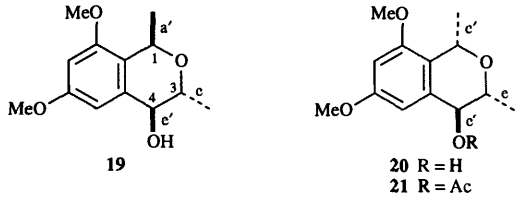
The *trans*-epoxide **13** was stereoselectively ring-opened by the method of Berti and co-workers[8] using aqueous potassium hydroxide in dimethyl sulfoxide to afford the *erythro*-diol **14**. The *threo*-diol **15** was obtained with complete stereoselectivity by treatment of the (*E*)-alkene **12** with a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide. The relative stereochemistries of the *erythro*- and *threo*-diols **14** and **15** were confirmed by their ^{1}H NMR spectra. It has been noted previously that the chemical shifts of benzylic methine protons for *erythro*-diols are typically downfield from those of the corresponding *threo*-epimers. Furthermore, the vicinal coupling constant between the benzylic proton and its neighbour are characteristically smaller (*J* 4–5 Hz) for the *erythro*-compounds than for their *threo*-epimers (*J* 7–9 Hz).[1,9] The values observed for the benzylic protons of the *erythro*- and *threo*-diols **14** and **15** are δ 4.60 (*J* 4.4 Hz) and 4.33 (*J* 7.1 Hz), respectively.

The *erythro*-diol **14** was converted into the all-*cis*-dioxolane **7** as a single diastereoisomer on treatment with 1,1-dimethoxyethane in the presence of camphorsulfonic acid. The ^{1}H NMR spectrum of the product **7** showed the three heterocyclic methine protons as a quartet at δ 5.17 (*J* 4.9 Hz), a doublet at δ 4.94 (*J* 7.0 Hz) and a doublet of quartets at δ 4.33 (*J* 7.0 and 6.4 Hz), corresponding to the protons 2-H, 4-H and 5-H respectively. An NOE difference spectrum supported the all-*cis* assignment in the conformation **18**, since irradiation of the 5-H signal showed a 9% enhancement for 2-H and a 7% enhancement for 4-H. Similar enhancements were observed on irradiation of each of the other two protons, while no change was observed for either 4-H or 5-H when the 2-CH_3 signal was irradiated.

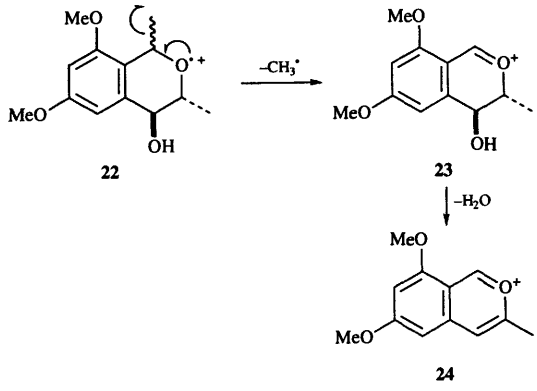
Treatment of the *threo*-diol **15** with 1,1-dimethoxyethane and a catalytic quantity of camphorsulfonic acid gave the alternative 4,5-*trans*-dioxolanes **8** and **9** as a 1:1 mixture of epimers at C-2, as shown by the relative intensities of the duplicated signals in the ^{1}H NMR spectrum. Since the subsequent isomerisation was expected to proceed through a planar oxocarbenium ion,[1] it was assumed that the stereochemistry at the C-2 centre was irrelevant.

Isomerisation of the phenyldioxolanes

The isomerisation of the dioxolanes was investigated at various temperatures. The all-*cis*-dioxolane **7** in dry methylene dichloride was first treated with two equivalents of titanium tetrachloride at −78 °C for 30 min. The reaction was then quenched at this temperature with dry methanol (Table 1, entry 1). Thin layer chromatography of the crude product showed two major components of lower R_f than the starting material, while GC–MS analysis showed two components having similar mass spectra, with molecular ions at *m/z* 238 and major fragment ions at *m/z* 223 and 205. These products were formulated as the C-1 epimeric isochromanes **19** and **20**, which

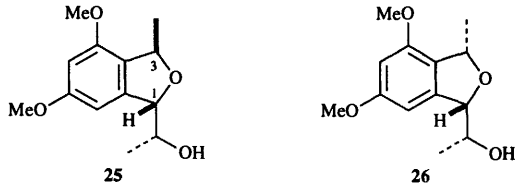


upon electron impact gave the molecular ions **22** and the fragment ions **23** and **24** resulting from the sequential loss of a methyl radical and water (Scheme 1). GC and ^{1}H NMR



Scheme 1

spectroscopy indicated that the products **19** and **20** were formed in a 4:1 ratio, and chromatographic separation afforded them in 70 and 17% yields respectively. Their isochromane structures were confirmed by acetylation of the epimer **20** to form the acetate **21**, with a concomitant large acylation shift in the ^{1}H NMR spectrum of a doublet of doublets from δ 4.31 to 5.67. This excludes the alternative dihydroisobenzofuran structures **25** and **26**, where the acylation would have caused a downfield shift in the doublet of quartets at δ 3.34.



Stereochemical assignments for the epimeric isochromanes **19** and **20** were made by comparison of their ^{1}H NMR spectra. In both cases, the coupling constant between the vicinal heterocyclic ring protons 3-H and 4-H was large (8 Hz for compound **19** and 9 Hz for the C-1 epimer **20**), confirming that 3-H and 4-H are axial and pseudoaxial respectively, so that the C-3 methyl is equatorial and the C-4 hydroxy group is pseudoequatorial[3,4] in both compounds. Three separate factors confirmed the individual assignments of the C-1 methyl configurations. First, the chemical shifts of the 3-H protons appeared at δ 3.85 for compound **19** and δ 3.34 for the C-1 epimer **20**, indicating that the methyl substituents were *trans* to each other in **19** and *cis* in **20**.[1,10,11] Secondly, homoallylic coupling (*J* 1.5 Hz) between 1-H and 4-H was observed only for compound **20**, consistent with $J_{a',a'}$ being greater than $J_{a',e'}$.[12,13] This $J_{a',a'}$ value of 1.5 Hz is smaller than that (3.5 Hz)

Table 1 Reactions of phenyldioxolane **7** and isochromanes **19** and **20** with titanium tetrachloride

Entry	Substrate(s)	Conditions[a] (T/°C, t/min)	Yield[b] (%) **19** + **20**	Ratio[c] **19**:**20**	Yield[b] (%) **25** + **26**	Yield[d] (%) **7**, **14**
1	**7**	−78,[e] 30	87	4:1	0	2, 2
2	**7**	−78,[e] 30[f]	71	3:1	0	5, 5
3	**7**	−78 to −30,[e] 30	81	1:7	0	—
4	**7**	−78 to 0,[e] 10	0	—	67 (10:1)[g]	—
5	**19** + **20**[h]	−78,[e] 60	80	4:1	0	—
6	**19** + **20**[h]	−78 to −30,[e] 20	75	1.8:1	10	—
7	**19** + **20**[h]	−78 to 0,[e] 10	53	1.2:1	16	—

[a] In CH_2Cl_2, $TiCl_4$ (2 equiv.). [b] Isolated yield of the mixture. [c] Ratio determined by GC and ^1H NMR analysis. [d] Yields of dioxolane **7** and diol **14** estimated from ^1H NMR analysis. [e] Temperature at which the reaction was quenched with methanol (entries 1–3 and 5–7) or aqueous sodium hydrogen carbonate (entry 4). [f] 10 equiv. of $TiCl_4$ were used. [g] Ratio of dihydroisobenzofurans **25**:**26** determined by GC–MS and ^1H NMR analysis. [h] A 4:1 mixture of isochromanes **19** and **20** respectively was used.

for eleutherin,[13] but is consistent with that observed for systems in which the connecting double bond is aromatic[10,11] rather than quinonoid. Finally, irradiation of the C-1 methyl of isochromane **19** in an NOE difference experiment supported its proximity to 3-H through a 14% enhancement of the latter proton. In agreement, the axial proximity of the 1-H and 3-H protons in the isochromane **20** was similarly confirmed by mutual NOE enhancements of 8%.

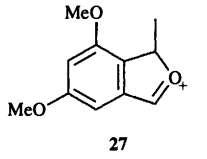
Having established the structures of the isochromanes **19** and **20**, the reaction conditions for isomerisation of the all-*cis*-dioxolane **7** were varied, and the results are summarised in Table 1. An increase in the relative stoichiometry of the titanium tetrachloride from two to ten molar equivalents (the latter was used previously for the isomerisations of dioxolanes **1** and **4**[1]) resulted in relatively minor reductions in both the yield and stereoselectivity of the reaction (entry 2). When the reaction temperature was varied, however, major changes were observed. Initially, the reagents were mixed at −78 °C and the reaction was immediately warmed to −30 °C, at which temperature it was maintained for 30 min before quenching with methanol (entry 3). This led to a complete reversal in the relative proportions of the epimeric isochromanes **19** and **20**, from 4:1 to 1:7. In a subsequent experiment (entry 4), reagent mixing at −78 °C was followed immediately by warming to 0 °C for 10 min and then quenching with aqueous sodium hydrogen carbonate. The previously observed isochromanes were now completely replaced by two epimeric dihydroisobenzofurans **25** and **26** isolated in 67% combined yield.

The structures **25** and **26** were supported by the GC–MS analysis of the crude product, which showed two similar components in a 10:1 ratio, each with a molecular ion at m/z 238 and a base peak ion **27** at m/z 193 formed by loss of a hydroxyethyl radical. The ^1H NMR spectrum of the product displayed the same component ratio. The major isomer **25** showed 3-H as a doublet of quartets at δ 5.42 coupled with J 3.1 Hz to 1-H, a doublet of doublets at δ 5.25. This homoallylic coupling constant is consistent with 1,3-*trans* stereochemistry, and compares with literature values[14] for the analogue **28** of $J_{1,3\text{-}trans}$ 2.8 Hz and $J_{1,3\text{-}cis}$ 1.6 Hz. Signal overlap prevented analysis of the corresponding spin system in the minor isomer, which was assigned the epimeric 1,3-*cis* stereochemistry **26** from the mass spectrometric evidence.

These dihydroisobenzofurans **25** and **26** appeared to result from isomerisation of the initially-formed isochromanes **19** and **20** at the higher reaction temperature. Thus, when a 4:1 mixture of the isochromanes **19** and **20** was treated with the Lewis acid at −78 °C, no change was observed (Table 1, entry 5), while increasing quantities of dihydroisobenzofurans were observed as the reaction temperature was increased (Table 1, entries 6 and 7).

Attention was then turned to the isomerisation of the 1:1 mixture of dioxolanes **8** and **9**, epimeric at C-2. Reaction with two equivalents of titanium tetrachloride at −78 °C for 30 min (Table 2, entry 1) reproducibly gave two products in a 1:7 ratio, as indicated by GC and ^1H NMR spectroscopy. Their GC–MS spectra resembled those of the isochromanes **19** and **20**, with molecular ions at m/z 238 and fragment ions at m/z 223 and 205, suggesting the diastereoisomeric isochromane structures **29** and **31** corresponding to the altered dioxolane stereochemistry. Chromatographic separation afforded the individual epimers in yields of 10 and 73% respectively. It is notable that the major isochromane epimer in this isomerisation has been shown to have the C-1 methyl substituent pseudoequatorial, in contrast to the isomerisation of the all-*cis*-dioxolane **7**.

Individual stereochemical assignments for the isochromanes **29** and **31** were based on similar criteria to those used for the isochromanes **19** and **20** described earlier. First, the 3-H protons resonated at δ 4.10 in the minor epimer **29** and at δ 3.72 in the major epimer **31**, indicating that the C-1 and C-3 methyl substituents are *trans* to each other in **29** and *cis* in **31**.[1,10,11] Secondly, the NOE difference spectrum obtained upon irradiation of the C-1 methyl of the acetate **30** derived from the epimer **29** showed a 10% enhancement of the 3-H proton, thereby supporting their mutual proximity. Similarly, irradiation of the 1-H resonance of isochromane **31** caused a 9% enhancement of the 3-H signal, and an 8% enhancement was observed for the reverse irradiation. These data establish the axial orientation of the 3-H proton in both isochromanes, and the pseudoaxial and pseudoequatorial orientations of the C-1 methyl substituents in the minor and major isochromanes **29** and **31**, respectively. For both isochromanes the coupling constant between the vicinal protons 3-H and 4-H was approximately 2 Hz, in agreement with their *cis* relationship as



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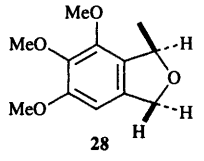

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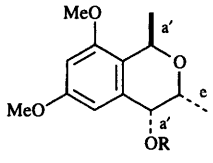
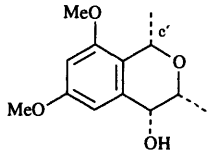


29 R = H
30 R = Ac



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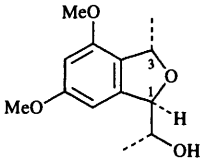

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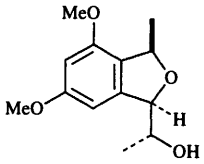

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Table 2 Reactions of phenyldioxolanes **8** + **9** and isochromane **31** with titanium tetrachloride

Entry	Substrates[a]	Conditions[b] (T/°C, t/min)	Ratio[c] **29**:**31**	Ratio[c] (**29** + **31**):(**32** + **33**)	Yield[d] (%) **29** + **31**	Yield[d] (%) **32** + **33**	Yield[e] (%) **15**, (**8** + **9**)
1	**8** + **9**	−78,[f] 30	1:7	10:0	83	0	5, (5)
2	**8** + **9**	−78 to −30,[f] 30	1:6	2:1	50	20 (4:1)[c]	0
3	**8** + **9**	−78 to 0,[f] 10	0	0:10	0	70 (6:1)[c]	5, (5)
4	**31**	−78 to 0,[f] 10	—	0:10	0	60 (6:1)[c]	—

[a] A 1:1 mixture of dioxolanes **8** and **9** was used, except entry 4 which was pure isochromane **31**. [b] In CH_2Cl_2, $TiCl_4$ (2 equiv.). [c] Ratio determined by GC and ^1H NMR analysis. [d] Isolated yield of the mixture. [e] Yields of dioxolanes **8** + **9** and diol **15** estimated from ^1H NMR analysis. [f] Temperature at which reaction was quenched with methanol (entry 1) or aqueous sodium hydrogen carbonate (entries 2–4).

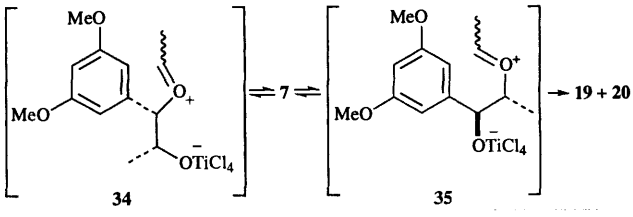
expected from the parent dioxolanes **8** and **9** and defining the pseudoaxial orientation of both C-4 hydroxy functions.[3,4] This coupling could not be observed directly in the epimer **29**, since the resonances were isochronous and gave rise to a multiplet at δ 4.10. It was clear in the acetate **30**, however, where 3-H and 4-H occurred as a doublet of quartets and a deshielded doublet at δ 4.22 and 5.74. Also as expected, neither isochromane **29** nor **31** showed observable homoallylic coupling between the 1-H and 4-H protons at normal ^1H NMR sweep width, which is consistent with the pseudoaxial configuration of the C-4 hydroxy groups.[12,13]

The reaction conditions for the isomerisation of the dioxolanes **8** and **9** were then varied, and the results are summarised in Table 2. The reagents were first mixed at −78 °C, and the reaction temperature was then raised to −30 °C for 30 min before quenching with aqueous sodium hydrogen carbonate (Table 2, entry 2). The ratio of the isochromanes **29** and **31** remained approximately the same at 1:6, but GC–MS analysis showed that one third of the material isolated was now a 4:1 mixture of the epimeric dihydroisobenzofurans **32** and **33**. If the reaction was initiated at −78 °C but then held at 0 °C for 10 min, the isochromanes **29** and **31** were not observed, the only isomerisation products identified being the dihydroisobenzofurans **32** and **33**, isolated in a combined yield of 70% and in a ratio of 6:1 (entry 3). That these resulted from isomerisation of the intermediate isochromanes **29** and **31** at the higher temperature (as for the diastereoisomeric isochromanes **19** and **20**) was supported by the fact that the pure isochromane **31** itself was completely isomerised to these dihydroisobenzofurans under the same conditions (entry 4).

GC–MS data of the dihydroisobenzofurans **32** and **33** resembled those of their diastereoisomers **25** and **26**, with molecular and base peak ions at m/z 238 and 193. The ^1H NMR spectrum of the major epimer **32** showed a doublet of quartets at δ 5.39 (J 2.9 and 6.3 Hz) and a doublet of doublets at δ 5.03 (J 2.9 and 7.3 Hz) for the 3-H and 1-H protons respectively, the 2.9 Hz homoallylic coupling constant confirming that the relative stereochemistry was *trans*.[14] The minor isomer was assigned the epimeric 1,3-*cis* stereochemistry **33** from the mass spectrometric evidence. It is assumed that, in the formation of the dihydroisobenzofurans, the *trans*-1,3-disubstituted compounds **25** and **32** predominate since these are sterically less crowded than their *cis*-epimers **26** and **33**.

Discussion

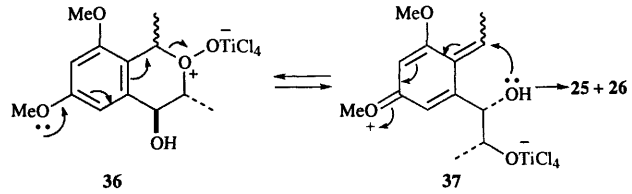
These temperature dependent stereo- and regio-selective isomerisations can be rationalised as follows. In the case of the dioxolane **7**, coordination to the Lewis acid titanium tetrachloride can in principle lead to the cleavage of either the C(2)–O(1) or the C(2)–O(3) bond, to afford the formal intermediates **34** or **35** respectively (Scheme 2). Development of



Scheme 2

the oxocarbenium intermediate **34**, however, is not assisted by the poor interaction between its electron-deficient carbon and the π orbitals of the aromatic ring, and its cyclisation to the dihydroisobenzofurans **25** and **26** would for the same reason require a disfavoured ring-closure of the 5-*enolendo-endo-trig* type.[15] In contrast, development of the alternative intermediate **35** is assisted by favourable stereoelectronic overlap, which ultimately leads to a favoured ring closure of the 6-*enolendo-endo-trig* type[15] forming the isochromanes **19** and **20**. This process is observed at lower temperatures (−78 and −30 °C, Table 1, entries 1–3), and is consistent with proposals made for related dioxolanes by Overman;[16] the precise nature of the intermediates **34** and **35** may require modification in the light of investigations into intermolecular examples of the Mukaiyama reaction recently carried out by Denmark and Almstead.[17]

The dihydroisobenzofurans **25** and **26** formed at 0 °C (Table 1, entry 4) are believed to arise from further isomerisation of the isochromanes **19** and **20** as shown in Scheme 3. Coordination of



Scheme 3

the Lewis acid to O-2 in these compounds as in the complex **36** leads to cleavage of the C(1)–O(2) bond, facilitated by the combined influence of the two aryl methoxy substituents, affording the quinomethane system **37**. Ring closure by the free benzylic hydroxy group then gives the epimeric dihydroisobenzofurans **25** and **26**. Although formally a stereoelectronically disfavoured cyclisation process, it is of the 5-*endo-trig* type,[18] not the more constrained 5-*enolendo-endo-trig* type[15] which precludes the direct conversion of the oxocarbenium intermediate **34** to the dihydroisobenzofurans **25** and **26** (*c.f.* Scheme 2). Furthermore, it leads to aromatisation of the intermediate quinomethane system **37**. This explanation is supported by the fact that treatment of 4:1 mixtures of the isochromanes **19** and **20** with the Lewis acid gave increasing quantities of the dihydroisobenzofurans **25** and **26** as the

reaction temperature was increased (Table 1, entries 5–7). Furthermore, the increase in the proportion of the isochromane **20** relative to its epimer **19** observed in the isomerisation of dioxolane **7** at −30 °C (entry 3) relative to that at −78 °C (entry 1) may arise, at least in part, through the reversible ring-opening of the isochromanes (Scheme 3) at the higher temperature, since treatment of a 4:1 mixture of isochromanes **19** and **20** (respectively) with the Lewis acid at −30 (entry 6) and at 0 °C (entry 7) gave increasing proportions of the C-1 epimer **20**.

Similar considerations apply to the isomerisations observed for the mixture of dioxolanes **8** and **9**.

Conclusions

Substituted 4-(3′,5′-dimethoxyphenyl)-1,3-dioxolanes are stereoselectively isomerised in high yield to 4-hydroxyisochromanes by titanium tetrachloride at low temperature. Cyclisation proceeds smoothly *ortho* to an aryl methoxy substituent. The vicinal stereochemistry at C-4 and C-5 of the dioxolanes is transferred unaltered to C-4 and C-3, respectively, of the isochromanes. The remaining stereogenic centre C-1 of the isochromanes is derived from C-2 of the dioxolanes. Its configuration is determined, at least in part, by kinetic and thermodynamic factors other than steric interaction with the *peri* methoxy substituent. In the case of the isomerisation of the all-*cis*-dioxolane **7**, the C-1 stereochemistry of the derived isochromane **19** or **20** can be controlled by the reaction temperature, whereas for the diastereoisomeric dioxolanes **8** and **9**, a single isochromane stereoisomer **31** is favoured over the temperature range examined.

At higher temperatures, both the parent dioxolanes and the derived isochromanes are further isomerised stereoselectively to dihydroisobenzofurans.

Experimental

Elemental analyses were carried out by the ANU Microanalytical Services Unit. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were measured at 300 and 75 MHz respectively on Varian Gemini-300 and VXR-300 spectrometers for solutions in [^{2}H]chloroform with tetramethylsilane as internal reference. *J* Values are given in Hz. Mass spectra were recorded at 70 eV on a VG Micromass 7070 spectrometer, while high resolution measurements were carried out on an AEI MS 902 instrument. GC–MS analyses were performed on a Hewlett Packard 5970 spectrometer and 5890 chromatograph. GC analyses employed a Varian 3400 chromatograph with flame ionisation detection, and isomers were assumed to give identical responses. Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Flash column chromatography was performed on silica gel (Merck, mesh 0.004–0.063 mm) as described by Still *et al.*[19] Light petroleum refers to the fraction bp 60–80 °C. The phrase 'residue obtained upon work-up' refers to the residue obtained when an organic phase was separated, dried ($MgSO_4$) and the solvent evaporated under reduced pressure.

(*E*)-1-(3′,5′-Dimethoxyphenyl)prop-1-ene 12

Method A. To a stirred suspension of ethyltriphenylphosphonium bromide (800 mg, 2.20 mmol) in dry tetrahydrofuran (20 ml) at −78 °C was added dropwise butyllithium (1.6 M solution in hexane, 1.8 ml, 2.20 mmol) under an atmosphere of nitrogen. The resultant orange solution was stirred at 0 °C for 5 min, and then again cooled to −78 °C. 3,5-Dimethoxybenzaldehyde **10**[5] (300 mg, 1.80 mmol) in dry tetrahydrofuran (2 ml) was added dropwise to the reaction mixture. The resultant solution was stirred at −78 °C for 15 min, allowed to warm to room temperature and then stirred for another 3 h. The reaction was quenched with water and extracted with diethyl ether. The extract was washed several times with aqueous sodium chloride, dried and evaporated to give a brown oil, which was chromatographed (eluent 5% ethyl acetate–hexane) to afford a 2:1 mixture of (*E*)- and (*Z*)-alkenes **11** (270 mg, 84%) as a colourless oil. This mixture was stirred with bis(acetonitrile)dichloropalladium(II) (5 mg) in chloroform (10 ml) at room temperature. After 2 h, the solvent was evaporated and the residue was rapidly chromatographed through a short column (eluent 5% ethyl acetate–hexane) to afford the (E)-*alkene* **12** (260 mg, 96%) as crystals, mp 55–56 °C (light petroleum) (Found: C, 73.8; H, 8.1. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%); λ_{max}/nm (MeOH) 255 (log ε 4.4) and 300 (3.5); δ_H 6.52 (2 H, d, *J* 2.3, 2′-H and 6′-H), 6.40 (1 H, dq, *J* 15.0 and 1.6, 1-H), 6.35 (1 H, t, *J* 2.3, 4′-H), 6.27 (1 H, dq, *J* 15.0 and 4.6, 2-H), 3.80 (6 H, s, 2 × OCH_3) and 1.92 (3 H, dd, *J* 4.6 and 1.6, CH_3); δ_C 160.8 (C-3′ and C-5′), 139.9 (C-1′), 130.0 (C-1), 126.2 (C-2), 103.6 (C-2′ and C-6′), 99.0 (C-4′), 55.2 (2 × OCH_3) and 18.5 (CH_3); *m*/*z* 178 (M^+, 100%), 163 (16), 147 (43), 135 (10), 121 (14) and 103 (20).

Method B. Phenyllithium (2 M solution in cyclohexane, 6.0 ml, 12 mmol) was added dropwise to a stirred suspension of ethyltriphenylphosphonium bromide (5 g, 13.0 mmol) in dry tetrahydrofuran (15 ml) at −78 °C in an atmosphere of nitrogen. After 10 min, 3,5-dimethoxybenzaldehyde **10** (2.0 g, 12 mmol) in tetrahydrofuran (10 ml) was added and the mixture stirred for another 5 min. More phenyllithium solution (6.0 ml, 12 mmol) was then added to the reaction mixture which was allowed to warm to 0 °C before the addition to the *tert*-butyl alcohol (3 ml) followed by potassium *tert*-butoxide in tetrahydrofuran (3 ml). After 3 h, the reaction mixture was centrifuged and the supernatant layer was washed with dilute hydrochloric acid (10%) and then water (3 × 50 ml), dried and evaporated to afford a yellow oil (2 g). This was chromatographed (eluent 5% ethyl acetate–hexane) to give the alkene **12** as a white solid (1.4 g, 65%), identical with material described above.

trans-1-(3′,5′-Dimethoxyphenyl)-1,2-epoxypropane 13

Method A. *m*-Chloroperbenzoic acid (400 mg, 2.32 mmol) in chloroform (30 ml) was added dropwise to the alkene **12** (300 mg, 1.68 mmol) in chloroform (5 ml) at 0 °C. The reaction mixture was stirred for 24 h, filtered, and the filtrate poured into saturated aqueous sodium hydrogen carbonate (15 ml). The organic phase was separated and the aqueous phase extracted with cold chloroform (3 × 10 ml). The residue obtained upon work-up afforded an orange oil, which was chromatographed (eluent 10% ethyl acetate–hexane) to give the *epoxide* **13** (120 mg, 37%) as crystals, mp 60–61 °C (light petroleum) (Found: C, 68.0; H, 7.6. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.3%); δ_H 6.45 (2 H, d, *J* 2.3, 2′-H and 6′-H), 6.40 (1 H, t, *J* 2.3, 4′-H), 3.79 (6 H, s, 2 × OCH_3), 3.55 (1 H, d, *J* 2.0, 1-H), 3.05 (1 H, dq, *J* 2.0 and 5.1, 2-H) and 1.45 (3 H, d, *J* 5.1, CH_3); δ_C 160.9 (C-3′ and C-5′), 140.3 (C-1′), 103.2 (C-2′ and C-6′), 100.0 (C-4′), 59.5 and 58.8 (C-1, C-2), 55.5 (2 × OCH_3) and 17.6 (CH_3); *m*/*z* 194 (M^+, 53%), 179 (100), 165 (23), 151 (13) and 135 (20). Further elution yielded the *alkene* **17** as a colourless oil (18 mg, 5.5%), δ_H 6.73 (1 H, dq, *J* 15.0 and 1.6, 1-H), 6.51 (1 H, d, *J* 2.3, 6′-H), 6.37 (1 H, d, *J* 2.3, 4′-H), 6.28 (1 H, dq, *J* 15.0 and 4.6, 2-H), 5.48 (1 H, s, 2′-OH), 3.88 and 3.79 (each 3 H, s, OCH_3) and 1.92 (3 H, dd, *J* 4.6 and 1.6, CH_3); *m*/*z* 194 (M^+, 100%), 179 (36), 151 (15) and 137 (7). This was followed by the *hydroxy ester* **16** (140 mg, 17%) as a mixture of diastereoisomers, the ^{1}H NMR spectrum of which showed significant resonances at δ_H 8.05, 6.48 (14 H, m, Ar-H of both isomers), 6.25 and 6.21 (each 1 H, d, *J* 4.0 and 6.0, 1-H of each isomer), 4.35 (2 H, m, 2-H of both isomers), 3.82 (6 H, s, 2 × OCH_3), 3.68 (6 H, s, 2 × OCH_3) and 1.25 (6 H, m, CH_3 of both isomers); *m*/*z* 350 (M^+, 3%), 308 (5), 306 (13), 167 (41), 141 (29), 139 (100) and 111 (20).

Method B. Repetition of this procedure with anhydrous sodium hydrogen carbonate (500 mg) in the reaction mixture afforded the *epoxide* **13** (66%).

***rel*-(1*S*,2*R*)-1-(3′,5′-Dimethoxyphenyl)propane-1,2-diol 14**

The epoxide **13** (120 mg, 0.62 mmol) in dimethyl sulfoxide (7 ml) and aqueous potassium hydroxide (0.4 M, 3 ml) was stirred at 80 °C for 24 h. The solution was cooled to room temperature, poured into water and extracted with ethyl acetate (4 × 20 ml). The residue obtained upon work-up afforded an orange oil (130 mg), which was chromatographed (eluent 50% ethyl acetate–hexane) to give the *diol* **14** as a light orange oil (105 mg, 79%) (Found: C, 62.0; H, 7.9. $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.6%); δ_H 6.52 (2 H, d, *J* 2.3, 2′-H and 6′-H), 6.37 (1 H, t, *J* 2.3, 4′-H), 4.60 (1 H, d, *J* 4.4, 1-H), 3.96 (1 H, dq, *J* 4.4 and 6.4, 2-H), 3.70 (6 H, s, 2 × OCH_3) and 1.09 (3 H, d, *J* 6.4, CH_3); δ_C 160.7 (C-3′ and C-5′), 143.1 (C-1′), 104.6 (C-2′ and C-6′), 99.6 (C-4′), 77.4 (C-1), 71.2 (C-2), 55.3 (2 × OCH_3) and 17.1 (CH_3); *m*/*z* 212 (M^+, 25%), 194 (4), 169 (77), 139 (100) and 124 (22).

***rel*-(1*R*,2*R*)-1-(3′,5′-Dimethoxyphenyl)propane-1,2-diol 15**

The (*E*)-alkene **12** (350 mg, 1.95 mmol) in acetone–water (2:1, 9 ml) was treated with *N*-methylmorpholine *N*-oxide (270 mg, 2.30 mmol) and osmium tetroxide (5 mg) in *tert*-butyl alcohol (1 ml) at 0 °C.[20] After stirring for 24 h, acetone was removed under vacuum at room temperature and the remaining aqueous layer poured into dilute hydrochloric acid (2 M, 5 ml). The organic materials were extracted into ethyl acetate (5 × 20 ml) and the combined extracts washed with brine. The residue (400 mg) obtained upon work-up was chromatographed (eluent 50% ethyl acetate–hexane) to give the *diol* **15** as a light orange oil (325 mg, 77%) (Found: C, 62.0; H, 7.9. $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.6%); δ_H 6.50 (2 H, d, *J* 2.3, 2′-H and 6′-H), 6.37 (1 H, t, *J* 2.3, 4′-H), 4.33 (1 H, d, *J* 7.1, 1-H), 3.87 (1 H, dq, *J* 7.1 and 6.3, 2-H), 3.81 (6 H, s, 2 × OCH_3) and 1.11 (3 H, d, *J* 6.3, CH_3); δ_C 160.7 (C-3′ and C-5′), 143.1 (C-1′), 104.7 (C-2′ and C-6′), 99.9 (C-4′), 79.4 (C-1), 72.0 (C-2), 55.3 (2 × OCH_3) and 18.8 (CH_3); *m*/*z* 212 (M^+, 11%), 168 (69), 139 (100) and 124 (21).

***rel*-(2*R*,4*S*,5*R*)-4-(3′,5′-Dimethoxyphenyl)-2,5-dimethyl-1,3-dioxolane 7**

Diol **14** (60 mg, 0.28 mmol) in dry methylene dichloride (10 ml) was treated with 1,1-dimethoxyethane (0.04 ml) and (±)-camphorsulfonic acid (10 mg, 0.04 mmol). After heating under reflux for 1 h, the reaction was quenched with saturated aqueous sodium hydrogen carbonate and poured into water. The organic layer was separated and the aqueous layer extracted with methylene dichloride (3 × 10 ml). The residue obtained upon work-up was chromatographed (eluent 15% ethyl acetate–hexane) to give the *dioxolane* **7** as a colourless oil (50 mg, 74%) (Found: C, 65.25; H, 7.4. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%); δ_H 6.44 (2 H, d, *J* 2.2, 2′-H and 6′-H), 6.39 (1 H, t, *J* 2.2, 4′-H), 5.17 (1 H, q, *J* 4.9, 2-H), 4.94 (1 H, d, *J* 7.0, 4-H), 4.33 (1 H, dq, *J* 7.0 and 6.4, 5-H), 3.78 (6 H, s, 2 × OCH_3), 1.55 (3 H, d, *J* 4.9, 2-CH_3) and 0.99 (3 H, d, *J* 6.4, 5-CH_3); δ_C 160.4 (C-3′ and C-5′), 140.9 (C-1′), 104.9 and 100.6 (C-2′, C-4′, C-6′), 99.4 (C-2), 80.8 and 76.2 (C-4, C-5), 55.1 (2 × OCH_3), 19.5 and 16.0 (CH_3-2, CH_3-5); *m*/*z* 238 (M^+, 25%), 194 (57), 179 (100), 165 (22) and 163 (9).

***rel*-(2*S*,4*R*,5*R*)- and *rel*-(2*R*,4*R*,5*R*)-4-(3′,5′-Dimethoxyphenyl)-2,5-dimethyl-1,3-dioxolanes 8 and 9**

Diol **15** (150 mg, 0.71 mmol) in dry methylene dichloride (20 ml) was treated with 1,1-dimethoxyethane (0.1 ml) and (±)-camphorsulfonic acid (20 mg, 0.09 mmol). After heating under reflux for 1 h, the reaction was quenched with saturated aqueous sodium hydrogen carbonate and poured into water. The organic layer was separated and the aqueous layer extracted with methylene dichloride (3 × 10 ml). The residue obtained upon work-up was chromatographed (eluent 12.5% ethyl acetate–hexane) to give a 1:1 mixture of epimeric *dioxolanes* **8** and **9** as a colourless oil (110 mg, 71%) (Found: C, 65.3; H, 7.4. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%); δ_H 6.6 to 6.4 (6 H, m, 2′-H, 4′-H and 6′-H of both isomers), 5.45 and 5.39 (each 1 H, q, *J* 4.8 and 4.7 respectively, 2-H of each isomer), 4.43 and 4.40 (each 1 H, *J* 5.1 and 5.8 respectively, 4-H of each isomer), 3.88 (2 H, m, 5-H of both isomers), 3.80 (12 H, s, 2 × OCH_3 of both isomers), 1.52 and 1.48 (each 3 H, d, *J* 4.8 and 4.7 respectively, 2-CH_3 of each isomer) and 1.42 and 1.35 (each 3 H, d, *J* 6.1 and 6.3 respectively, 5-CH_3 of each isomer); *m*/*z* 238 (M^+, 12%), 194 (47), 179 (100), 178 (52), 165 (18) and 151 (10).

***rel*-(1*R*,3*R*,4*S*)-4-Hydroxy-6,8-dimethoxy-1,3-dimethylisochromane 19 and *rel*-(1*S*,3*R*,4*S*)-4-hydroxy-6,8-dimethoxy-1,3-dimethylisochromane 20**

Method A. Dioxolane **7** (30 mg, 0.13 mmol) in dry methylene dichloride (20 ml) was treated with titanium tetrachloride (16.4 μl, 0.26 mmol) at −78 °C in an atmosphere of nitrogen. The reaction mixture was stirred at −78 °C for 30 min and quenched with methanol (0.1 ml). Saturated aqueous sodium hydrogen carbonate (2 ml) was added and the mixture poured into water. The organic layer was separated and the aqueous layer extracted with methylene dichloride (3 × 10 ml). The residue obtained upon work-up, after GC and ^{1}H NMR analysis (Table 1, entry 1), was chromatographed (eluent 20% ethyl acetate–hexane) to give the *isochromane* **19** as a white solid (21 mg, 70%), crystals, mp 134–135 °C (methylene dichloride–hexane) (Found: C, 65.6; H, 7.8. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%); δ_H 6.69 (1 H, d, *J* 2.3, 5-H), 6.35 (1 H, d, *J* 2.3, 7-H), 4.96 (1 H, q, *J* 6.5, 1-H), 4.23 (1 H, d, *J* 8.0, 4-H), 3.85 (1 H, dq, *J* 8.0 and 6.3, 3-H), 3.80 and 3.75 (each 3 H, s, OCH_3), 1.56 (3 H, d, *J* 6.5, 1-CH_3) and 1.34 (3 H, d, *J* 6.3, 3-CH_3); δ_C 159.9 and 156.3 (C-6, C-8), 138.0 and 120.9 (C-4a, C-8a), 101.7 (C-5), 97.9 (C-7), 71.3, 68.8 and 67.7 (C-1, C-3, C-4), 55.2 and 55.1 (2 × OCH_3), 19.0 and 18.0 (1-CH_3, 3-CH_3); *m*/*z* 238 (M^+, 7%), 223 (44), 220 (17), 205 (100), 195 (7) and 179 (20). Further elution afforded the *isochromane* **20** as a colourless oil (5 mg, 17%) (Found: M^+, 238.1205. $C_{13}H_{18}O_4$ requires *M*, 238.1205); δ_H 6.76 (1 H, d, *J* 2.4, 5-H), 6.38 (1 H, d, *J* 2.4, 7-H), 4.92 (1 H, dq, *J* 1.5 and 6.3, 1-H), 4.31 (1 H, dd, *J* 1.5 and 9.0, 4-H), 3.85 and 3.78 (each 3 H, s, OCH_3), 3.34 (1 H, dq, *J* 9.0 and 6.2, 3-H), 1.48 (3 H, d, *J* 6.3, 1-CH_3), 1.42 (3 H, d, *J* 6.2, 3-CH_3); δ_C 159.6 and 156.4 (C-6 and C-8), 140.0 and 120.3 (C-4a, C-8a), 100.4 and 97.7 (C-5, C-7), 74.1, 71.2 and 70.8 (C-1, C-3, C-4), 55.2 and 55.1 (2 × OCH_3), 21.2 and 18.2 (1-CH_3, 3-CH_3); *m*/*z* 238 (M^+, 8%), 223 (23), 220 (18), 205 (100), 195 (7) and 179 (26). The use of additional titanium tetrachloride (10 equiv.) gave similar results (Table 1, entry 2).

Method B. The reagents were mixed at −78 °C as above, and the reaction mixture was then warmed immediately to −30 °C and stirred for 30 min. Work-up as above gave the *isochromanes* **19** (3 mg, 10%) and **20** (22 mg, 73%) (Table 1, entry 3).

Method C. 4:1 Mixtures of isochromanes **19** and **20** (15 mg, 0.06 mmol) in methylene dichloride (10 ml) were stirred under argon with titanium tetrachloride (14.1 μl, 0.12 mmol) under the reaction regimes described in Table 1, entries 5–7, before quenching with methanol (0.1 ml) and work-up as in method A above. The resulting mixtures of the isochromanes **19** and **20**, and of the dihydroisobenzofurans **25** and **26**, were analysed by GC and ^{1}H NMR spectroscopy with the results shown in Table 1.

***rel*-(1*S*,3*R*,4*S*)-4-Acetoxy-6,8-dimethoxy-1,3-dimethylisochromane 21**

The pyran **20** (25 mg, 0.11 mmol) in acetic anhydride (2 ml) and pyridine (0.5 ml) was stirred at 55 °C for 1 h. The mixture was poured into an ice-cold dilute hydrochloric acid solution (10 ml). Extraction with methylene dichloride gave a residue which was chromatographed (eluent 12.5% ethyl acetate–hexane) to yield the *acetate* **21** (23 mg, 78%) as crystals, mp 74–75 °C (diethyl ether) (Found: M^+, 280.1311. $C_{15}H_{20}O_5$ requires *M*, 280.1312); δ_H 6.31 (1 H, d, *J* 2.1, 5-H), 6.17 (1 H, d, *J* 2.1, 7-H),

5.67 (1 H, dd, *J* 1.5 and 9.0, 4-H), 4.86 (1 H, dq, *J* 6.0 and 1.5, 1-H), 3.72 and 3.70 (each 3 H, s, OCH_3), 3.50 (1 H, dq, *J* 9.0 and 6.3, 3-H), 2.12 (3 H, s, $COCH_3$), 1.41 (3 H, d, *J* 6.0, 1-CH_3) and 1.21 (3 H, d, *J* 6.3, 3-CH_3); *m/z* 280 (M^+, 1.5%), 220 (19), 206 (13), 205 (100), 194 (11) and 193 (13).

rel-(1*R*,3*R*,4*R*)-4-Hydroxy-6,8-dimethoxy-1,3-dimethylisochromane 29 and rel-(1*S*,3*R*,4*R*)-4-hydroxy-6,8-dimethoxy-1,3-dimethylisochromane 31

A 1:1 mixture of dioxolanes **8** and **9** (30 mg, 0.13 mmol) in dry methylene dichloride (20 ml) was treated with titanium tetrachloride (27.6 μl, 0.26 mmol) at −78 °C in an atmosphere of nitrogen. After stirring at −78 °C for 30 min the reaction was quenched with methanol (0.1 ml). Saturated aqueous sodium hydrogen carbonate (2 ml) was added and the resulting mixture poured into water. The organic layer was separated and the aqueous layer extracted with methylene dichloride (3 × 10 ml). The residue obtained upon work-up, after GC and ^1H NMR analysis (Table 2, entry 1), was chromatographed (eluent 20% ethyl acetate–hexane) to afford the *isochromane* **29** as white crystals (3 mg, 10%), mp 101–102 °C (methylene dichloride) (Found: C, 65.6; H, 7.8. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%); δ_H 6.50 (1 H, d, *J* 2.3, 5-H), 6.39 (1 H, d, *J* 2.3, 7-H), 5.03 (1 H, q, *J* 6.5, 1-H), 4.10 (2 H, m, 3-H and 4-H), 3.80 and 3.77 (each 3 H, s, OCH_3), 1.45 (3 H, d, *J* 6.5, 1-CH_3) and 1.36 (3 H, d, *J* 6.3, 3-CH_3); *m/z* 238 (M^+, 9%), 223 (57), 205 (100), 194 (12) and 179 (30). Further elution gave the *isochromane* **31** (22 mg, 73%) as crystals, mp 70–71 °C (methylene dichloride–hexane) (Found: C, 65.25; H, 7.9. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%); δ_H 6.48 (1 H, d, *J* 2.4, 5-H), 6.41 (1 H, d, *J* 2.4, 7-H), 4.87 (1 H, q, *J* 6.3, 1-H), 4.12 (1 H, d, *J* 1.6, 4-H), 3.81 and 3.78 (each 3 H, s, OCH_3), 3.72 (1 H, dq, *J* 1.6 and 6.6, 3-H), 1.54 (3 H, d, *J* 6.3, 1-CH_3) and 1.35 (3 H, d, *J* 6.6, 3-CH_3); δ_C 159.3 and 156.4 (C-6, C-8), 138.6 and 120.0 (C-4a, C-8a), 104.6 (C-5), 99.0 (C-7), 71.9, 71.2 and 69.6 (C-1, C-3, C-4), 55.3 and 55.1 (2 × OCH_3), 21.3 and 16.9 (1-CH_3, 3-CH_3); *m/z* 238 (M^+, 11%), 223 (100), 205 (34), 194 (21), 179 (45) and 165 (11).

rel-(1*R*,3*R*,4*R*)-4-Acetoxy-6,8-dimethoxy-1,3-dimethylisochromane 30

The pyran **29** (6 mg, 0.11 mmol) in acetic anhydride (2 ml) and pyridine (0.5 ml) was stirred at 55 °C for 1 h. The mixture was then poured into ice cold dilute hydrochloric acid (10 ml). Extraction with methylene dichloride gave a residue which was chromatographed (eluent 12.5% ethyl acetate–hexane) to yield the *acetate* **30** as an oil (6 mg, 85%) (Found: C, 64.4; H, 6.9. $C_{15}H_{20}O_5$ requires C, 64.3; H, 7.1%); δ_H 6.46 (1 H, d, *J* 2.1, 5-H), 6.43 (1 H, d, *J* 2.1, 7-H), 5.74 (1 H, d, *J* 2.1, 4-H), 5.12 (1 H, q, *J* 6.5, 1-H), 4.22 (1 H, dq, *J* 2.1 and 6.3, 3-H), 3.80 and 3.78 (each 3 H, s, OCH_3), 2.12 (3 H, s, $COCH_3$), 1.46 (3 H, d, *J* 6.5, 1-CH_3) and 1.25 (3 H, d, *J* 6.3, 3-CH_3); *m/z* 280 (M^+, 1%), 265 (8), 220 (15), 206 (12), 205 (85), 193 (10) and 43 (100).

rel-(1*S*,1′*R*,3*R*)-1-(1′-Hydroxyethyl)-4,6-dimethoxy-3-methyl-1,3-dihydroisobenzofuran 25 and rel-(1*S*,1′*R*,3*S*)-1-(1′-hydroxyethyl)-4,6-dimethoxy-3-methyl-1,3-dihydroisobenzofuran 26

Dioxolane **7** (30 mg, 0.13 mmol) in dry methylene dichloride (20 ml) was treated with titanium tetrachloride (27.6 μl, 0.26 mmol) at −78 °C in an atmosphere of nitrogen. After 1 min, the solution was warmed to 0 °C and stirred for 10 min. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (1 ml) and poured into water. The organic layer was separated and the aqueous layer extracted with methylene dichloride (3 × 10 ml). The residue obtained upon work-up was chromatographed (eluent 20% ethyl acetate–hexane) to give the *dihydroisobenzofurans* **25** and **26** as a colourless oily mixture (20 mg, 67%) in 10:1 ratio as indicated by GC–MS and ^1H NMR analysis (Table 1, entry 4) (Found: M^+, 238.1205. $C_{13}H_{18}O_4$ requires *M*, 238.1205); δ_H(major isomer) 6.38 (2 H, m, 5-H and 7-H), 5.42 (1 H, dq, *J* 3.1 and 6.2, 3-H), 5.25 (1 H, dd, *J* 3.3 and 3.1, 1-H), 3.95 (1 H, m, 1′-H), 3.81 and 3.80 (each 3 H, s, OCH_3), 1.49 (3 H, d, *J* 6.2, 3-CH_3) and 1.13 (3 H, d, *J* 6.5, 2′-CH_3); *m/z* 238 (M^+, 81%), 193 (100), 175 (7) and 165 (7).

rel-(1*R*,1′*R*,3*S*)-1-(1′-Hydroxyethyl)-4,6-dimethoxy-3-methyl-1,3-dihydroisobenzofuran 32 and rel-(1*R*,1′*R*,3*R*)-1-(1′-hydroxyethyl)-4,6-dimethoxy-3-methyl-1,3-dihydroisobenzofuran 33

Method A. A 1:1 mixture of dioxolanes **8** and **9** (30 mg, 0.13 mmol) in methylene dichloride (15 ml) was treated with titanium tetrachloride as described for the dioxolane **7** above. The residue obtained upon work-up was chromatographed (eluent 20% ethyl acetate–hexane) to give the *dihydroisobenzofurans* **32** and **33** as a colourless oily mixture (21 mg, 70%) in a 6:1 ratio as indicated by GC–MS and ^1H NMR analysis (Table 2, entry 3) (Found: M^+, 238.1205. $C_{13}H_{18}O_4$ requires *M*, 238.1205); δ_H(major isomer) 6.37 (2 H, m, 5-H and 7-H), 5.39 (1 H, dq, *J* 2.9 and 6.3, 3-H), 5.03 (1 H, dd, *J* 2.9 and 7.3, 1-H), 3.88 (1 H, m, 1′-H), 3.81 and 3.80 (each 3 H, s, OCH_3), 1.48 (3 H, d, *J* 6.3, 3-CH_3) and 1.33 (3 H, d, *J* 6.5, 2′-CH_3); *m/z* (mixture) 238 (M^+, 7%), 205 (22), 193 (100), 175 (7) and 165 (11).

Method B. A 1:1 mixture of dioxolanes **8** and **9** (10 mg, 0.05 mmol) in dry methylene dichloride (7 ml) was treated with titanium tetrachloride (9.2 μl, 0.1 mmol) at −78 °C in an atmosphere of nitrogen. After 1 min, the resulting solution was warmed to −30 °C and stirred for 30 min. The crude residue obtained as in method A above was analysed by GC–MS and ^1H NMR spectroscopy which indicated a mixture of compounds **29** (10%), **31** (56%), **32** (27%) and **33** (7%) (Table 2, entry 2). Column chromatography afforded mixtures of the isochromanes **29** and **31** (5 mg, 50%) and of the dihydroisobenzofurans **32** and **33** (2 mg, 20%).

Method C. The isochromane **31** (10 mg, 0.05 mmol) in dry methylene dichloride (7 ml) was treated with titanium tetrachloride (9.2 μl, 0.1 mmol) at −78 °C in an atmosphere of nitrogen. After 1 min, the resulting solution was warmed to 0 °C and stirred for 10 min. GC–MS and ^1H NMR analysis of the crude residue (10 mg) obtained as in method A above indicated a 6:1 mixture of dihydroisobenzofurans **32** and **33** respectively (Table 2, entry 4). Chromatography (eluent 20% ethyl acetate–hexane) afforded a mixture of compounds **32** and **33** (6 mg, 60%).

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