Stereoselective isomerisations of 4-(2′,5′-dimethoxyphenyl)-2,5-dimethyl-1,3-dioxolanes and their 2′-chloro-5′-methoxyphenyl analogues. Temperature-dependent diastereoselective formation of isochromanes

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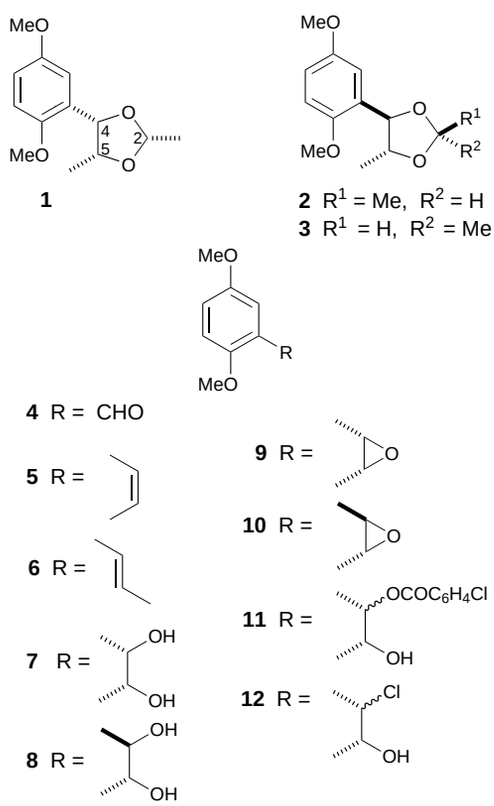
Stereoselective isomerisations of *rel*-(2*R*,4*S*,5*R*)-4-(2′,5′-dimethoxyphenyl)-2,5-dimethyl-1,3-dioxolane 1 and the 2:1 epimeric mixture of *rel*-(2*S*,4*R*,5*R*)- and *rel*-(2*R*,4*R*,5*R*)-4-(2′,5′-dimethoxyphenyl)-2,5-dimethyl-1,3-dioxolanes 2 and 3 with titanium tetrachloride at −78 °C afford *rel*-(1*R*,3*R*,4*S*)- and *rel*-(1*S*,3*R*,4*R*)-4-hydroxy-5,8-dimethoxy-1,3-dimethylisochromanes 25 and 30, respectively. The yields are only moderate owing to the competing influence of the 2′-methoxy group in the starting dioxolanes, and are improved significantly when this group is replaced by a 2′-chloro substituent. *rel*-(2*R*,4*S*,5*R*)-4-(2′-Chloro-5′-methoxyphenyl)-2,5-dimethyl-1,3-dioxolane 13 under similar conditions is isomerised smoothly to *rel*-(1*R*,3*R*,4*S*)-5-chloro-4-hydroxy-8-methoxy-1,3-dimethylisochromane 34 as the sole reaction product. In contrast the C-2 epimers *rel*-(2*R*,4*R*,5*R*)- and *rel*-(2*S*,4*R*,5*R*)-4-(2′-chloro-5′-methoxyphenyl)-2,5-dimethyl-1,3-dioxolanes 14 and 15 each favour the formation of *rel*-(1*R*,3*R*,4*R*)-5-chloro-4-hydroxy-8-methoxy-1,3-dimethylisochromane 36 at −78 °C, while at −95 °C the 1*S* product 35 predominates. Dioxolane 14 isomerises more rapidly than its C-2 epimer 15, and both these reactions are under kinetic not thermodynamic control.

We have recently established that the isomerisation of 4-(3′,5′-dimethoxyphenyl)-2,5-dimethyl-1,3-dioxolanes with titanium tetrachloride is both high yielding and highly stereoselective.[1] 4-Hydroxy-6,8-dimethoxy-1,3-dimethylisochromanes are formed at low temperatures (−78 to −30 °C), and in the case of the all-*cis*-dioxolane the diastereoselectivity at C-1 of the products is temperature-dependent. At higher temperatures (0 °C), both the parent dioxolanes and the derived isochromanes undergo further stereoselective isomerisation to afford dihydroisobenzofurans. Whereas the previous study used phenyl dioxolane substrates in which the aromatic ring was symmetrically substituted with two methoxy groups *meta* to the dioxolane substituent, in this paper we extend the study to include 2′,5′-dimethoxy- and 2′-chloro-5′-methoxy-phenyldioxolanes, as these provide better models for the potential synthesis of naturally occurring naphthopyrans and their quinones.[2,3]



Results and discussion

Synthesis of the aryl dioxolanes

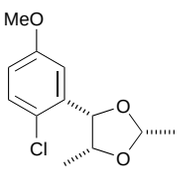
The initial synthetic targets were the stereoisomeric 2′,5′-dimethoxyphenyldioxolanes **1**, **2** and **3**. The starting aldehyde **4** was treated with ethylidenetriphenylphosphorane to give an 84% yield of a mixture of the (*Z*)- and (*E*)-alkenes **5** and **6** in a 4:1 ratio. When this mixture was reacted with bis(acetonitrile)-dichloropalladium(II),[4] this ratio was reversed, but to no better than 1:3. It has been noted previously that *ortho* substitution of styrenes can prevent the otherwise total transformation of such *E*/*Z* mixtures to the stereochemically pure *E* isomer.[4] Since the initial Wittig product was stereochemically more homogeneous than after isomerisation with the palladium complex, it was used in subsequent transformations with a view to separation of derived stereoisomers at a later stage in the reaction sequence.

The 4:1 mixture of alkenes **5** and **6** was reacted with *N*-methylmorpholine *N*-oxide and a catalytic amount of osmium tetroxide,[5] which yielded a 4:1 mixture of the *erythro*- and *threo*-diols **7** and **8**. This mixture was then enriched to 7:1 in favour of the *erythro*-isomer **7** by chromatography. The stereochemical assignments were supported by ^{1}H NMR spectroscopy, the benzylic proton of the *erythro*-diol **7** resonating further downfield (δ 4.89) and having a smaller vicinal coupling

constant (J 4.5 Hz) than that of the *threo*-diol **8** (δ 4.53, J 7.1 Hz).[6,7] Treatment of this enriched mixture of diols **7** and **8** with 1,1-dimethoxyethane in the presence of the catalyst camphorsulfonic acid, followed by chromatography of the crude product, gave the pure all-*cis*-dioxolane **1** in 72% yield.

To obtain the alternative 4,5-*trans*-dioxolanes **2** and **3**, the 4:1 mixture of (*Z*)- and (*E*)-alkenes **5** and **6** was treated with *m*-chloroperbenzoic acid in the presence of solid sodium hydrogen carbonate. The stereochemically pure *cis* product **9** was the sole epoxide isolated, in 66% yield, together with a diastereomeric mixture (1:1) of hydroxy esters **11** formed by opening of the epoxide ring at the benzylic position by *m*-chlorobenzoic acid. The *cis* stereochemistry of **9** was confirmed by the relatively large coupling constant (J 4.9 Hz) between the epoxide ring protons.[1] Ring-opening of the epoxide **9** by aqueous potassium hydroxide in dimethyl sulfoxide[1] proceeded with complete stereoselectivity through nucleophilic inversion to afford the *threo*-diol **8** in 76% yield. Acetalation of this diol **8** as above afforded the 4,5-*trans*-dioxolanes **2** and **3** in 77% yield as a 2:1 mixture of epimers at C-2. The major, but not the minor, isomer was obtained pure by chromatography. Individual assignments of stereochemistry to the dioxolanes **2** and **3** were not made.

The analogous 2′-chloro-5′-methoxyphenyldioxolane stereoisomers **13**, **14** and **15** were prepared from 2-chloro-5-methoxy-



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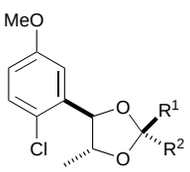
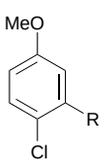


14 R^1 = H, R^2 = Me
15 R^1 = Me, R^2 = H

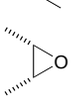


16 R = CHO

17 R =

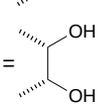
18 R =

19 R =

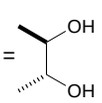


20 R =

21 R =

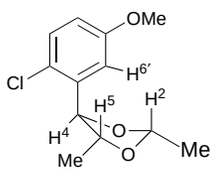


22 R =



benzaldehyde **16**.[8] Reaction with ethylidenetriphenylphosphorane gave an 80% yield of a mixture of the (*Z*)- and (*E*)-alkenes **17** and **18** in a 1:1 ratio, which was improved to 1:13 in favour of the (*E*)-isomer **18** by isomerisation with bis(acetonitrile)dichloropalladium(II).[4] This enriched mixture was converted with *m*-chloroperbenzoic acid into a 1:13 mixture of the *cis*- and *trans*-epoxides **19** and **20** in 90% yield, and thence, through epoxide ring-opening and chromatography, into the pure *erythro*-diol **21** in 86% yield. Alternatively, the 1:13 mixture of alkenes **17** and **18** was hydroxylated as before with osmium tetroxide, chromatography then affording the pure *threo*-diol **22** in 80% yield. The expected configurations for these diols were again confirmed by ^{1}H NMR spectroscopy, the benzylic proton of the *erythro*-diol **21** having a larger chemical shift and smaller vicinal coupling constant (δ 5.22, J 3.2 Hz) than the corresponding proton in the *threo*-epimer **22** (δ 4.90, J 5.5 Hz).[6,7]

Acetalation of the *erythro*-diol **21** afforded the all-*cis*-dioxolane **13** in 92% yield. Acetalation of the *threo*-diol **22**, on the other hand, gave a mixture of the required 4,5-*trans*-dioxolanes in an approximate 2:1 ratio, which could be separated by careful chromatography into the major and minor isomers **14** and **15**, pure by both GC and ^{1}H NMR spectroscopy, in yields of 55 and 21%, respectively. Stereochemical assignments at C-2 for this pair of epimers **14** and **15** were based on NOE difference spectroscopy, as were the respective preferred conformations **23** and **24**. Thus, for the major isomer



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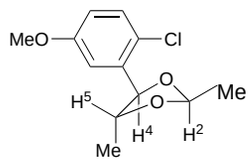

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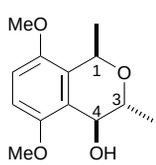
14 with the conformation **23**, irradiation of 2-H effected an 8% enhancement of 5-H, and 9% was observed for the reverse process. Irradiation of 2-H also caused a 16% enhancement of 6′-H. For the minor isomer **15** with the conformation **24**, irradiation of the C-5 methyl effected a 7% enhancement of 2-H and a 9% enhancement of 4-H. Irradiation of 2-H caused a 5% enhancement of 4-H. There was no observable enhancement of 5-H when the C-2 methyl was irradiated, or *vice versa*.

Isomerisation of the 2′,5′-dimethoxyphenyldioxolanes

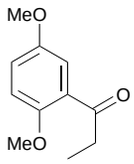
Treatment of the all-*cis*-dimethoxyphenyldioxolane **1** in methylene dichloride with one equivalent of titanium tetrachloride at −78 °C for 30 min gave, aside from starting material (20%), the isochromane **25** (18%) and a diastereomeric mixture



25

(1:1) of the chlorohydrins **12** (45%). The mass spectrum of isochromane **25** showed a molecular ion at *m*/*z* 238, major fragment ions at *m*/*z* 223 and 220, and a base peak at *m*/*z* 205. These fragment ions result from losses of a methyl radical and water, and establish the product as an isochromane rather than an isomeric dihydroisobenzofuran.[1] A further major ion at *m*/*z* 194 arose from an alternative retro Diels–Alder fragmentation of the molecular ion with loss of acetaldehyde. The stereochemistry of the isochromane **25** was defined by ^{1}H NMR spectroscopy, which showed resonances for the 1-H, 4-H and 3-H protons at δ 5.01 (q, J 6.6 Hz), δ 4.55 (d, J 7.9 Hz) and δ 3.98 (dq, J 7.9 and 6.2 Hz), respectively. The large vicinal coupling constant between 3-H and 4-H indicated axial and pseudoaxial orientations, confirming that the C-3 methyl and C-4 hydroxy groups were equatorial and pseudoequatorial.[1] The chemical shift for 3-H (δ 3.98) in particular supported the assignment of the C-1 methyl configuration as pseudoaxial,[1,9,10] as did the absence of homoallylic coupling between 1-H and the pseudoaxial 4-H. Such coupling ($J_{a',a'}$) would have been expected had the C-1 methyl been pseudoequatorial and 1-H, therefore, pseudoaxial.[1]

The ^{1}H NMR spectrum of the diastereomeric chlorohydrins **12** was unexceptional. The GC–MS analysis of this mixture, however, was noteworthy in that it showed *three pairs* of isomeric compounds. These were the chlorohydrins **12**, with a molecular ion pair at *m*/*z* 232 and 230 (ratio 1:3), the known *cis*-epoxide **9** and its *trans*-diastereomer **10** with molecular ions at *m*/*z* 194, and the structurally isomeric ketones **26** and **27** with



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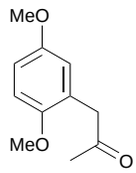

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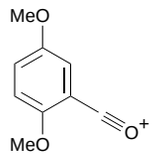

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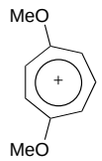

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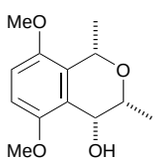
molecular ions again at *m*/*z* 194. These ketones showed the expected fragment ions **28** and **29**, respectively, as base peaks at *m*/*z* 165 and 151. It appeared that, at the GC injector temperature of 250 °C, hydrogen chloride was eliminated from the chlorohydrins **12** to afford the epoxides **9** and **10** which then rearranged thermally to the ketones **26** and **27**. In support of this hypothesis, the chlorohydrins **12**, prepared by treatment of the epoxide **9** with titanium tetrachloride, gave a similar GC–MS pattern.

Treatment of the 2 : 1 mixture of 4,5-*trans*-dioxolanes **2** and **3** with titanium tetrachloride, under the same conditions used for the all-*cis*-dioxolane **1**, gave rise to the new isochromane **30** as



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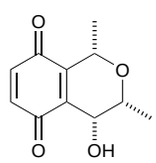

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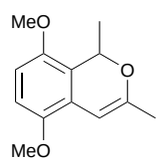

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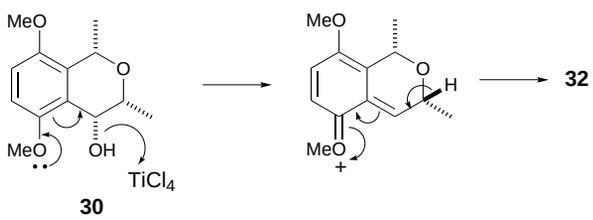
the sole product of isomerisation together with the diastereomeric mixture of chlorohydrins **12** as previously described, in yields of 45 and 31%, respectively. The isochromane **30** showed the characteristic mass spectroscopic pattern of molecular ion at *m*/*z* 238, fragment ions at *m*/*z* 223 and 220, and base peak at *m*/*z* 205,[1] together with the retro Diels–Alder fragment at *m*/*z* 194. ^{1}H NMR spectroscopy confirmed the structure **30** and revealed the stereochemistry. The three heterocyclic methine protons 1-H, 4-H and 3-H resonated at δ 4.93 (q, *J* 6.3 Hz), δ 4.58 (d, *J* 1.6 Hz) and δ 3.56 (dq, *J* 1.6 and 6.3 Hz), respectively. The assignment of the C-1 methyl configuration as pseudoequatorial followed both from NOE difference data, which showed reciprocal enhancements between pseudoaxial and axial 1-H and 3-H protons (each 8%), with no enhancement of 3-H on irradiation of the C-1 methyl group, and also from the chemical shift of the 3-H proton at δ 3.56, which is in the range typical for *cis*-1,3-dimethylisochromanes.[1,9,10] The small coupling constant between 3-H and 4-H indicated that, with 3-H axial, 4-H was pseudoequatorial and therefore the C-4 hydroxy group was pseudoaxial.[1] A two-dimensional NOESY spectrum was completely consistent with these conclusions.

Further evidence for the assigned relative stereochemistry for the isochromane **30** was adduced through its oxidation to the isochromanequinone **31**, for which the 1-H, 4-H and 3-H protons resonated at δ 4.64 (dq, *J* 1.5 and 6.0 Hz), δ 4.38 (dd, *J* 1.5 and 1.6 Hz) and δ 3.57 (dq, *J* 1.6 and 6.3 Hz), respectively. The chemical shift of the 3-H proton is consistent with those for 3-H in eleutherin[11] and its derivatives,[12] whose C-1 and C-3 methyl substituents are *cis* and equatorial; 3-H is thus axial, and its small vicinal coupling (*J* 1.6 Hz) to 4-H defines the latter as pseudoequatorial. The long-range homoallylic coupling (*J* 1.5 Hz) between 1-H and 4-H in the quinone **31** is consistent with the configuration of 1-H as pseudoaxial, since that of 4-H is pseudoequatorial. It is known[11,13] that the coupling constant between such pseudoaxial and pseudoequatorial protons ($J_{a',e'}$) is ~1.5 Hz, while two pseudoaxial protons have $J_{a',a'}$ ~3.5 Hz, and two pseudoequatorial protons give rise to $J_{e',e'}$ ~0 Hz. Thus, for quinone A and its dimethyl ether,[3,11,12] where 1-H is pseudoequatorial and 4-H is pseudoaxial (the reverse of the arrangement in quinone **31**), $J_{a',e'}$ is 1.5 Hz, while for quinone A′ and its dimethyl ether, $J_{e',e'}$ is not observed, a situation which would have arisen if the C-1 methyl in quinone **31** were also pseudoaxial.

When the isomerisaton of the dioxolane **1** or of the mixed dioxolanes **2** and **3** was undertaken for short periods at higher temperatures, either −30 or 0 °C, the chlorohydrin diastereomers **12** were again produced, together with the isochromene **32**. For the mixture of dioxolanes **2** and **3**, the respective yields of the products **12** and **32** were 38 and 36%. The dehydration product **32** arises through the influence of the methoxy substituent *peri* to the C-4 hydroxy group in each of the intermediate isochromanes **25** and **30** (shown for **30** in Scheme 1).



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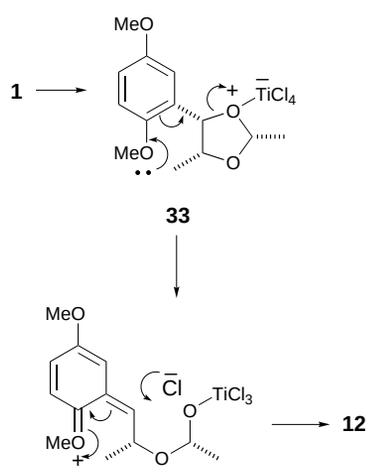
Scheme 1

The relatively low yields of the isochromanes **25** and **30** derived from these 2′,5′-dimethoxyphenyldioxolanes **1**, **2** and **3**, in comparison with those from their 3′,5′-dimethoxy isomers,[1] are ascribed to the influence of the 2′-methoxy substituent. Being *ortho* to the dioxolane ring, this group promotes the alternative C-4–O-3 bond cleavage upon reaction with the Lewis acid (shown for intermediate **33** from dioxolane **1** in Scheme 2), with formation of the chlorohydrins **12**. This effect



Scheme 2

is absent in the dioxolanes **13**, **14** and **15** in which the 2′-methoxy substituent is replaced by chlorine. Furthermore, the chlorine substituent, while maintaining the asymmetric substitution of the aromatic ring, would still allow for its ready oxidation to afford quinones, or alternatively could be removed by reductive dechlorination. The latter factors could be useful in the synthesis of naturally occurring naphthopyrans and their

Table 1 The effect of reaction conditions on isomerisation of dioxolane **13**

Entry	Conditions[a]	Conc.[a]/ mol $l^{-1} \times 10^{-3}$	Ratio of products (%) Dioxolane **13**[b]	Isochromane **34**[b]	Diol **21**[c]
1	−95 °C,[d] 15 min	6	78	20	2
2	−95 °C,[d] 60 min	6	38	52	10
3	−78 °C,[d] 30 min	6	5	93	2
4	−78 °C,[d] 30 min	6	5	91	4
5	−78 to 0 °C,[d] 30 min	3	3	93	4

[a] Dioxolane **13** in methylene dichloride treated with titanium tetrachloride (2 equiv.). [b] Estimated from GC analysis. [c] Estimated from ^{1}H NMR spectral analysis. [d] Temperature at which the reaction was quenched with methanol, or at which an aliquot was removed for quenching in entry 1.

Table 2 The effect of reaction conditions on isomerisation of dioxolane **14**

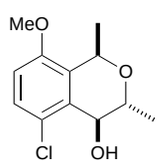
Entry	Conditions[a]	Ratio of dioxolane products **14**:**15**[b]	Ratio of isochromane products **35**:**36**[c]	Ratio of products (%)[d] Dioxolanes **14** + **15**	Isochromanes **35** + **36**	Isochromene **38**
1	−95 °C,[e] 2 min	2:1	5.8:1	63	37	0
2	−95 °C,[e] 12 min	1:1	4.6:1	21	79	0
3	−95 °C,[e] 60 min	—	28:1	0	100	0
4	−95 °C, 12 min −78 °C,[e] 30 min	—	3.8:1	3	97	0
5	−78 °C,[e] 2 min	—	1:3.2	0	100	0
6	−78°C,[e] 30 min	—	1:3.1	0	100	0
7	−78 °C, 30 min 0 °C,[e] 30 min	—	1:3.1	0	94	6
8	−78 °C,[e] 30 min 0 °C, 30 min r.t.,[e] 60 min	—	1:2.9	0	66	34
9	−78 °C,[e] 2 min		1:1	3	97	0
10	−78 °C,[e] 30 min	—	1:1	3	97	0

[a] Dioxolane **14** in methylene dichloride at a concentration of 6×10^{-3} mol l^{-1} except entries 9 and 10 which are 3×10^{-3} mol l^{-1}, treated with titanium tetrachloride (2 equiv.). [b] Determined by ^{1}H NMR spectral analysis. [c] Determined by GC analysis. [d] Estimated from GC analysis. [e] Temperature at which the reaction was quenched with methanol, or at which an aliquot was removed for quenching in entries 1 and 2.

quinones.[2,3] The isomerisation of the chlorinated dioxolanes **13**, **14** and **15** was therefore investigated.

Isomerisation of the 2′-chloro-5′-methoxyphenyldioxolanes

Isomerisation of the all-*cis*-dioxolane **13** with two equivalents of titanium tetrachloride gave rise to the isochromane **34** as a



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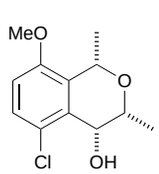
single diastereomer under all the conditions investigated, at reaction temperatures ranging from −95 to 0 °C (Table 1). Its mass spectrum showed a molecular ion pair at *m*/*z* 244/242 reflecting the presence of chlorine isotopes, and major fragment ion pairs at *m*/*z* 229/227, 211/209 and 200/198, arising from loss of a methyl radical, water and acetaldehyde and indicative of the isochromane structure. The relative stereochemistry was confirmed by criteria similar to those used previously, *viz*. the large coupling constant (*J* 6.0 Hz) between 3-H and 4-H, the chemical shift (δ 4.16) of the 3-H proton,[1,9,10] an NOE difference spectrum in which irradiation of the C-1 methyl afforded an enhancement (11%) of the 3-H proton and a two-dimensional NOESY spectrum.

In contrast to the all-*cis*-dioxolane **13**, the course of isomerisation of the mixture of C-2 epimers **14** and **15** with two equivalents of titanium tetrachloride was temperature dependent. At −95 °C, the only products formed were the isochromanes **35** and **36**, epimeric at C-1, with the former being predominant. At −78, −30 and 0 °C, however, the epimer **36** became the major product. The mass spectrum of each isomer resembled that of the isochromane **34**. Individual stereochemical assignments for these isochromanes **35** and **36** were again



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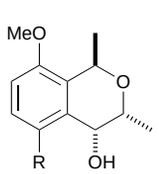


36 R = Cl
37 R = H

based on their 3-H chemical shifts of δ 3.68 and 4.11, respectively, and on supportive NOE difference spectra. In the latter experiments, reciprocal enhancements between the proximate axial protons 1-H and 3-H were both 7% for isochromane **35**. For compound **36**, irradiation of the pseudoaxial C-1 methyl gave rise to a 10% enhancement of the axial 3-H. In each case, the small coupling constant between 3-H and 4-H (1.2 Hz for **35** and 1.7 Hz for **36**) confirmed the pseudoequatorial nature of 4-H. Two-dimensional NOESY data supported these assignments.

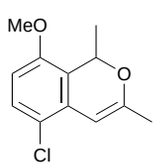
These preliminary results with mixtures of the dioxolanes **14** and **15** were confirmed when treatment of the pure epimer **14** for 60 min at −95 °C with the Lewis acid (Table 2, entry 3) resulted in an almost exclusive preference (28:1) for the isochromane **35**. Earlier sampling of an incomplete reaction at −95 °C (Table 2, entries 1 and 2) showed much lower product diastereoselectivity; this is believed to reflect an uncontrolled increase in the temperature of the sample taken and the sensi-

Table 3 The effect of reaction conditions on isomerisation of dioxolane **15**

Entry	Conditions[a]	Ratio of dioxolane products **14**:**15**[b]	Ratio of isochromane products **35**:**36**[c]	Ratio of products (%)[d]		
				Dioxolanes **14** + **15**	Isochromanes **35** + **36**	Diol **22**[b]
1	−95 °C,[e] 12 min	1:5	11.6:1	90	7	~3
2	−95 °C,[e] 60 min	1:5	9.8:1	69	30	~1
3	−95 °C,[e] 60 min	1:5	9.0:1	64	36	—
4	−78 °C, [e] 5 min		1:3.3	6	89	5
5	−78 °C,[e] 30 min	—	1:3.4	~1	95	~4
6	−78 °C,[e] 5 min	—	1:1.7	0	94	~6
7	−78 °C,[e] 30 min	—	1:1.6	0	91	~9

[a] Dioxolane **15** in methylene dichloride at a concentration of 6×10^{-3} mol l^{-1} except entries 6 and 7 which are 3×10^{-3} mol l^{-1}, treated with titanium tetrachloride (2 equiv.). [b] Determined by ^{1}H NMR spectral analysis. [c] Determined by GC analysis. [d] Estimated from GC analysis. [e] Temperature at which the reaction was quenched with methanol.

tivity of the reaction diastereoselectivity to temperature. This view was supported by an experiment commenced at −95 °C and then warmed to −78 °C (Table 2, entry 4). When the entire reaction was performed at −78 °C, the ratio of isochromanes **35** to **36** changed dramatically to ~1:3, the isochromane **36** becoming the major product (Table 2, entries 5 and 6). At this temperature, GC and ^{1}H NMR spectral analyses showed that the reaction was complete after only 2 min (entry 5) and that the ratio of products was unchanged after 30 min (entry 6). With higher temperatures and prolonged reaction times, the isochromene dehydration product **38** became increasingly sig-



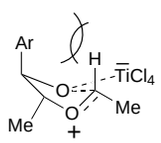
38

nificant (entries 7 and 8). Reactions carried out at higher dilution (entries 9 and 10) gave the isochromanes in ~1:1 ratio, suggesting that the diastereoselectivity is concentration dependent.

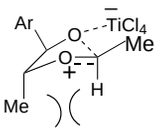
Related isomerisations were carried out on the C-2 epimeric dioxolane **15**, and similar observations were recorded. Thus, at −95 °C, isochromane **35** was the major product (Table 3, entries 1, 2 and 3). At −78 °C, there was a dramatic reversal, with the alternative isochromane **36** favoured (entries 4 and 5). The diastereoselectivity was reduced when the dioxolane **15** was isomerised under conditions of higher dilution (entries 6 and 7).

The 5-chloro-8-methoxyisochromanes **35** and **36** isolated from isomerisation of the dioxolanes **14** and **15** represent kinetic rather than thermodynamic products, since an independent experiment showed that there was no isomerisation of isochromane **35** into its C-1 epimer **36** when the former was treated with the Lewis acid at −78 °C before standing at 0 °C for 30 min. This is in contrast to the situation observed for a 6,8-dimethoxyisochromane, where the combined effect of the two methoxy groups is sufficient to cleave the C-1–O-2 bond reversibly.[1]

A comparison of Tables 2 and 3 reveals two noteworthy effects. First, under the same conditions the dioxolane **14** reacts much more rapidly than does its epimer **15**. Thus, at −95 °C after both 12 and 60 min, the reactions of compounds **14** and **15** had proceeded to very different extents (Table 2, entries 2 and 3 compared with Table 3, entries 1, 2 and 3, respectively). In fact, the reaction of **14** in 2 min proceeded to approximately the same extent as that of isomer **15** in 60 min (Table 2, entry 1 compared with Table 3, entries 2 and 3). This rate difference can be rationalised in terms of the respective titanium-coordinated intermediates **39** and **40**, for which relief of the 2,4-diaxial interaction between the hydrogen and the bulky aromatic ring



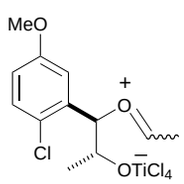
39



40

in complex **39** is more compelling than that for the corresponding 2,5-diaxial interaction between hydrogen and the smaller methyl group in complex **40**.[14]

Secondly, in the incomplete reactions at −95 °C (Table 2, entries 1 and 2 and Table 3, entries 1, 2 and 3), each of the epimerically pure dioxolanes **14** and **15** was recovered as a mixture of both these C-2 epimers. This epimerisation must arise through reversible Lewis acid-catalysed opening of the dioxolane ring to form a planar oxocarbenium ion. While the isomerisation of the dioxolanes to isochromanes involves cleavage of the C-2–O-3 bond, it is probable that this competing epimerisation of the dioxolanes involves specific cleavage of the C-2–O-1 bond to give the formal intermediate **41**. We have pre-



41

viously suggested that such ions cannot, for stereoelectronic reasons, cyclise to dihydroisobenzofurans and therefore reform the dioxolanes.[1] Furthermore, the ratios of epimeric dioxolanes recovered from incomplete reactions of **14** (Table 2) show a decreasing proportion of this isomer with time, whereas for the C-2 epimer **15** (Table 3), the ratio favours that isomer by a factor of 5:1 after both 12 and 60 min. These results suggest that there is a preference for the isomer **15** at −95 °C in the presence of titanium tetrachloride, which can be understood in terms of the lesser diaxial interactions in the correponding complex **40** than in the complex **39**, as discussed above. In contrast, the acid-catalysed formation of the pair of *free* dioxolanes **14** and **15** from the corresponding *threo*-diol **22** at the temperature of boiling methylene dichloride (~40 °C) favours the dioxolane **14**.

Preliminary investigations on the isomerisation of naphthyldioxolanes have shown a preference for the formation of angular naphthopyrans.[15] The use of halogen as a blocking group and its subsequent removal could possibly be used to direct the synthesis of linear naturally occurring naphthopyrans[2] such as glucoside B.[3] The removal of chlorine from the isochromane **36** derived from isomerisation of the chlorinated dioxolanes **14** and **15** would complete a model for this process. In practice it

was found that photochemically induced reductive dechlorination of **36** could be achieved smoothly by Beckwith's method [16] to afford the new isochromane **37** in 58% yield.

Conclusions

We have shown previously that 4-(3′,5′-dimethoxyphenyl)-2,5-dimethyl-1,3-dioxolanes are stereoselectively isomerised to 4-hydroxy-6,8-dimethoxy-1,3-dimethylisochromanes in high yield by titanium tetrachloride at low temperature.[1] The present work demonstrates that whereas similar isomerisations of the corresponding 2′,5′-dimethoxyphenyldioxolanes **1**, **2** and **3** proceed in only mediocre yield, owing to the competing influence of the 2′-methoxy substituent in the starting materials, the analogous 2′-chloro-5′-methoxyphenyldioxolanes **13**, **14** and **15** are converted smoothly into isochromanes. In contrast to the 6,8-dimethoxyisochromanes derived from the previous 3′,5′-dimethoxyphenyldioxolanes, the 5,8-dimethoxy- and 5-chloro-8-methoxy-isochromanes of the present work lack the additional activation provided by the 6-methoxy substituent and do not isomerise further to dihydroisobenzofurans at higher temperatures.

In all these isomerisations, 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 third stereogenic centre C-1 of the isochromanes is derived from C-2 of the parent dioxolanes. In some cases in both the previous and present work, the same relative stereochemistry of the isochromane C-1 methyl substituent remains favoured over the temperature range examined, whereas in others the preference can be reversed by altering the reaction temperature. In the example of the C-1 epimeric 5-chloro-8-methoxyisochromanes **35** and **36** formed from the dioxolanes **14** and **15**, the dramatic diastereochemical reversal between −95 and −78 °C is kinetic not thermodynamic, and is also concentration dependent. The factors which determine this relative stereochemistry at C-1 are complex and not yet understood. It is noteworthy that in those cases where a single stereoisomer of the isochromane was formed, the substituents at C-1 and C-4 are *cis*-related, *i.e.* one is pseudoaxial while the other is pseudoequatorial. This is also true of the major stereoisomer where both epimeric isochromanes were formed in a ratio which did not vary with temperature. Finally, where both epimeric isochromanes were formed in a ratio which reversed with temperature, the same *cis*-relationship holds for the stereoisomer which is favoured at the lower temperature. This phenomenon is being investigated further.

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. Electron impact 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.*[17] 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.

(*Z*)- and (*E*)-1-(2′,5′-Dimethoxyphenyl)prop-1-enes 5 and 6

Sodium hydride (55–60% dispersion in mineral oil, 200 mg) was stirred in dimethyl sulfoxide (0.5 ml) and tetrahydrofuran (2 ml) at 60 °C for 2 h in an atmosphere of argon. The mixture was cooled to room temperature and ethyltriphenylphosphonium bromide (1.8 g, 5.20 mmol) in tetrahydrofuran (10 ml) was added and stirred for 15 min. The aldehyde **4** (500 mg, 3.01 mmol) in tetrahydrofuran (20 ml) was added and the mixture stirred at 60 °C for a further 1 h. The reaction mixture was centrifuged and the supernatant layer separated. This organic layer was washed with dilute hydrochloric acid (10%) and the residue obtained upon work-up was chromatographed (7% ethyl acetate–hexane) to give a 4:1 mixture of the (*Z*)- and (*E*)-*alkenes* **5** and **6** as a colourless oil (450 mg, 84%) (Found: C, 74.4; H, 7.9. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%); δ_H(for **5**) 6.83 (1H, d, *J* 2.8, 6′-H), 6.81 (1H, dd, *J* 7.8 and 2.8, 4′-H), 6.68 (1H, d, *J* 7.8, 3′-H), 6.47 (1H, dq, *J* 11.4 and 1.2, 1-H), 5.88 (1H, dq, *J* 11.4 and 7.1, 2-H), 3.80 (6H, s, 2 × OCH_3) and 1.85 (3H, dd, *J* 7.1 and 1.2, CH_3); δ_C(for **5**) 152.9 and 151.3 (C-2′, C-5′), 127.3, 127.1 and 125.1 (C-1, C-1′, C-2), 116.2 (C-6′), 112.1 and 111.2 (C-3′, C-4′), 56.0 and 55.7 (OCH_3) and 13.9 (CH_3); δ_H(for **6**) 6.98 (1H, d, *J* 2.8, 6′-H), 6.79 (2H, m, 3′-H and 4′-H), 6.68 (1H, dq, *J* 16.0 and 1.2, 1-H), 6.24 (1H, dq, *J* 16.0 and 6.6, 2-H), 3.80 (6H, s, 2 × OCH_3) and 1.91 (3H, dd, *J* 6.6 and 1.2, CH_3); *m*/*z* (for **5** and **6**) 178 (M^+, 100%), 163 (10), 135 (10), 121 (14) and 103 (20).

***rel*-(1*S*,2*R*)- and *rel*-(1*R*,2*R*)-1-(2′,5′-Dimethoxyphenyl)-propane-1,2-diols 7 and 8**

The 4:1 mixture of alkenes **5** and **6** (320 mg, 1.54 mmol) in a 2:1 mixture of acetone–water (9 ml) was treated with *N*-methylmorpholine *N*-oxide (246 mg, 2.10 mmol) and osmium tetroxide (5 mg) in *tert*-butyl alcohol (1 ml) at 0 °C. After stirring for 24 h, the acetone was removed under vacuum at room temperature. The remaining aqueous layer was poured into dilute hydrochloric acid (2 M, 5 ml) and the organic materials extracted into ethyl acetate (5 × 20 ml). The residue (310 mg) obtained upon work-up was chromatographed (50% ethyl acetate–hexane) to yield a 7:1 mixture of the *diols* **7** and **8** as an orange oil (270 mg, 69%) (Found: C, 62.0; H, 7.9. $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.6%); δ_H(for **7**) 7.00 (1H, d, *J* 2.2, 6′-H), 6.80 (2H, narrow m, 3′-H and 4′-H), 4.89 (1H, d, *J* 4.5, 1-H), 4.12 (1H, dq, *J* 4.5 and 6.4, 2-H), 3.78 and 3.77 (each 3H, s, OCH_3) and 1.09 (3H, d, *J* 6.4, CH_3); δ_C(for **3**) 153.1 and 150.6 (C-2′, C-5′), 129.6 (C-1′), 113.9, 112.9 and 111.3 (C-3′, C-4′, C-6′), 73.8 (C-1), 70.0 (C-2), 55.8 and 55.5 (OCH_3) and 17.2 (CH_3); δ_H(for **8**) 6.87 (1H, d, *J* 2.6, 6′-H), 6.80 (2H, narrow m, 3′-H and 4′-H), 4.53 (1H, d, *J* 7.1, 1-H), 3.95 (1H, dq, *J* 7.1 and 6.3, 2-H), 3.80 and 3.77 (each 3H, s, OCH_3) and 1.07 (3H, d, *J* 6.3, CH_3); *m*/*z* (for **7** and **8**) 212 (M^+, 12%), 168 (22), 167 (100), 139 (40), 137 (32) and 124 (23).

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

The 7:1 mixture of diols **7** and **8** (200 mg, 0.94 mmol) in dry methylene dichloride (20 ml) was treated with 1,1-dimethoxyethane (0.13 ml) and (±)-camphorsulfonic acid (10 mg, 0.042 mmol) and the solution was boiled for 1 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate. The organic layer was separated and the aqueous layer extracted with more methylene dichloride. The residue (190 mg) obtained upon work-up was chromatographed (10% ethyl acetate–hexane) to give the *dioxolane* **1** as a colourless oil (162 mg, 72%) (Found: C, 65.5; H, 7.9. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%); δ_H 7.07 (1H, d, *J* 2.1, 6′-H), 6.79 (2H, narrow m, 3′-H and 4′-H), 5.35 (1H, d, *J* 7.2, 4-H), 5.18 (1H, q, *J* 4.9, 2-H), 4.44 (1H, dq, *J* 7.2 and 6.3, 5-H), 3.78 and 3.77 (each 3H, s, OCH_3), 1.54 (3H, d, *J* 4.9, 2-CH_3) and 0.81 (3H, d, *J* 6.3, 5-CH_3); δ_C 153.5 and 149.9 (C-2′, C-5′), 126.2 (C-1′), 113.9, 112.5 and 110.5 (C-3′, C-4′, C-6′), 99.6 (C-2), 75.5 and 74.8 (C-4, C-5),

55.1 (2 × OCH_3), 19.5 (CH_3-2) and 15.5 (CH_3-5); *m*/*z* 238 (M^+, 35%), 194 (84), 179 (22), 165 (41), 163 (100), 151 (18), 135 (86) and 44 (99).

***cis*-1-(2′,5′-Dimethoxyphenyl)-1,2-epoxypropane 9**

m-Chloroperbenzoic acid (500 mg, 2.91 mmol) in chloroform (30 ml) was added dropwise to the 4:1 mixture of alkenes **5** and **6** (450 mg, 2.52 mmol) in chloroform (10 ml) at 0 °C and the reaction mixture stirred with sodium hydrogen carbonate (100 mg) for 24 h. This mixture was filtered and the filtrate poured into saturated aqueous sodium hydrogen carbonate (15 ml). The organic phase was separated and the aqueous phase extracted with chloroform (3 × 10 ml). The residue (800 mg) obtained upon work-up was chromatographed (10% ethyl acetate–hexane) to afford first the *epoxide* **9** as a white solid (300 mg, 66%), mp 65–66 °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 6.83 (1H, d, *J* 2.2, 6′-H), 6.78 (2H, narrow m, 3′-H and 4′-H), 4.16 (1H, d, *J* 4.9, 1-H), 3.80 and 3.76 (each 3H, s, OCH_3), 3.38 (1H, dq, *J* 4.9 and 5.2, 2-H) and 1.06 (3H, d, *J* 5.2, CH_3); δ_C 153.0 and 152.0 (C-2′, C-5′), 125.0 (C-1′), 113.4, 113.0 and 110.9 (C-3′, C-4′, C-6′), 55.8 and 55.7 (OCH_3), 55.1 and 54.7 (C-1, C-2) and 12.6 (CH_3); *m*/*z* 194 (M^+, 46%), 179 (11), 165 (20), 163 (43), 151 (32) and 135 (100). This was followed by the mixture of hydroxy esters **11** (13 mg, 7%) which showed significant resonances at δ_H 8.07, 7.97, 7.41, 7.38, 6.92, 6.84, 6.78 (14H, Ar-H of both isomers), 6.38 and 6.26 (each 1H, d, *J* 3.9 and 5.9 respectively, 1-H of each isomer), 4.23 (2H, m, 2-H of both isomers), 3.84 and 3.72 (each 6H, s, OCH_3) and 1.20 (6H, d, *J* 6.5, CH_3 of both isomers); *m*/*z* 350 (M^+, 2%), 306 (9), 167 (23), 151 (6), 140 (28), 139 (100) and 111 (24).

***rel*-(1*R*,2*R*)-(2′,5′-Dimethoxyphenyl)propane-1,2-diol 8**

The epoxide **9** (300 mg, 1.55 mmol) in dimethyl sulfoxide (15 ml) and potassium hydroxide (0.4 M, 6 ml) was stirred at 80 °C. After 24 h, the resulting solution was cooled to room temperature, poured into water and extracted with ethyl acetate (4 × 20 ml). The residue obtained upon work-up was chromatographed (50% ethyl acetate–hexane) to give the *diol* **8** as a light orange oil (250 mg, 76%) (Found: C, 62.6; H, 7.9. $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.6%); δ_H 6.87 (1H, d, *J* 2.6, 6′-H), 6.80 (2H, narrow m, 3′-H and 4′-H), 4.53 (1H, d, *J* 7.1, 1-H), 3.95 (1H, dq, *J* 7.1 and 6.3, 2-H), 3.80 and 3.77 (each 3H, s, OCH_3) and 1.07 (3H, d, *J* 6.3, CH_3); *m*/*z* 212 (M^+, 11%), 168 (22), 167 (100), 139 (52), 137 (34) and 124 (23).

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

The diol **8** (230 mg, 1.08 mmol) in dry methylene dichloride (25 ml) was treated with 1,1-dimethoxyethane (0.16 ml) and (±)-camphorsulfonic acid (10 mg) in a manner similar to that for the diol mixture **7** and **8**. The product (230 mg) was chromatographed (10% ethyl acetate–hexane) to give a *ca.* 2:1 mixture of *dioxolanes* **2** and **3** as a colourless oil (200 mg, 77%); δ_H 7.12 (2H, d, *J* 2.5, 6′-H of both isomers), 6.80 (4H, narrow m, 3′-H and 4′-H of both isomers), 5.38 (2H, m, 2-H of both isomers), 4.96 and 4.87 (each 1H, d, *J* 6.0, 4-H of each isomer), 3.93 (2H, dq, *J* 7.0 and 6.4, 5-H of both isomers), 3.79 and 3.75 (each 6H, s, OCH_3 of both isomers), 1.50 and 1.42 (each 3H, d, *J* 5.0, 2-CH_3 of each isomer) and 1.36 and 1.34 (each 3H, d, *J* 6.4, 5-CH_3 of each isomer). Chromatographic separation of the mixture afforded a single diastereoisomer (40 mg, 40%) (Found: C, 65.5; H, 7.6. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%); δ_H 7.12 (1H, d, *J* 2.5, 6′-H), 6.80 (2H, narrow m, 3′-H and 4′-H), 5.38 (1H, q, *J* 5.0, 2-H), 4.96 (1H, d, *J* 6.0, 4-H), 3.97 (1H, dq, *J* 6.0 and 6.4, 5-H), 3.79 and 3.75 (each 3H, s, OCH_3), 1.50 (3H, d, *J* 5.0, 2-CH_3) and 1.36 (3H, d, *J* 6.4, 5-CH_3); *m*/*z* 238 (M^+, 14%), 194 (36), 179 (10), 165 (18), 163 (39), 151 (8), 135 (46) and 44 (100).

(*Z*)- and (*E*)-1-(2′-Chloro-5′-methoxyphenyl)prop-1-enes 17 and 18

Sodium hydride (55–60% dispersion in mineral oil, 400 mg) was stirred with dimethyl sulfoxide (1 ml) and tetrahydrofuran (4 ml) at 60 °C for 2 h in an atmosphere of argon. The mixture was cooled to room temperature and ethyltriphenylphosphonium bromide (3.2 g, 8.80 mmol) in tetrahydrofuran (10 ml) was added and stirred for 15 min. The aldehyde **16** (1 g, 6.02 mmol) in tetrahydrofuran (40 ml) was added and the mixture stirred at 60 °C for another 1 h. The reaction mixture was centrifuged and the supernatant layer separated. The residue obtained upon work-up was chromatographed (7% ethyl acetate–hexane) to give a 1:1 mixture (confirmed by GC analysis) of the (*Z*)- and (*E*)-olefins **17** and **18** as a colourless oil (850 mg, 80%). This mixture in ethanol (10 ml) with bis(acetonitrile)dichloropalladium(II) (10 mg) was heated under reflux for 2 h. The catalyst was removed by filtration and the filtrate evaporated to afford a residue which was chromatographed (7% ethyl acetate–hexane) to give the (*E*)-*alkene* **18** (93% by GC) contaminated with the (*Z*)-olefin **17** (7% by GC) (Found: C, 65.8; H, 6.1; Cl, 19.4. $C_{10}H_{11}ClO$ requires C, 65.8; H, 6.2; Cl, 19.3%); δ_H(for **18**) 7.25 (1H, d, *J* 8.8, 3′-H), 7.03 (1H, d, *J* 2.9, 6′-H), 6.78 (1H, dq, *J* 16.0 and 1.8, 1-H), 6.72 (1H, dd, *J* 8.8 and 2.9, 4′-H), 6.24 (1H, dq, *J* 16.0 and 6.6, 2-H), 3.81 (3H, s, OCH_3) and 1.95 (3H, dd, *J* 6.6 and 1.8, CH_3); δ_C(for **18**) 158.2 (C-5′), 136.6 and 133.8 (C-1′, C-2′), 130.1, 128.5 and 127.3 (C-1, C-2, C-6′), 113.8 and 111.4 (C-3′, C-4′), 55.4 (OCH_3) and 18.7 (CH_3); *m*/*z* 184 [M^+(^{37}Cl), 31%], 182 [M^+(^{35}Cl), 100], 147 (90) and 132 (13). Inspection of the 1:1 mixture indicated the following data for the (*Z*)-olefin **17**; δ_H 7.32 (1H, d, *J* 8.8, 3′-H), 6.91 (1H, d, *J* 2.9, 6′-H), 6.72 (1H, dd, *J* 8.8 and 2.9, 4′-H), 6.55 (1H, dq, *J* 11.5 and 1.8, 1-H), 5.96 (1H, dq, *J* 11.5 and 7.1, 2-H), 3.84 (3H, s, OCH_3) and 1.85 (3H, dd, *J* 7.1 and 1.8, CH_3).

***trans*-1-(2′-Chloro-5′-methoxyphenyl)-1,2-epoxypropane 20**

m-Chloroperbenzoic acid (600 mg, 3.49 mmol) in chloroform (20 ml) at 0 °C was added dropwise to the 1:13 mixture of olefins **17** and **18** (450 mg, 2.71 mmol) in chloroform (10 ml) and the solution stirred with sodium hydrogen carbonate (100 mg) for 24 h. The reaction mixture was 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 (500 mg) obtained upon work-up was carefully chromatographed (10% ethyl acetate–hexane) to afford the 1:13 mixture of epoxides **19** and **20** as an orange oil (440 mg, 90%). A small portion of this was rechromatographed to yield the pure *epoxide* **20** (Found: C, 60.7; H, 5.3; Cl, 17.6. $C_{10}H_{11}ClO_2$ requires C, 60.5; H, 5.6; Cl, 17.85%); δ_H 7.23 (1H, d, *J* 8.5, 3′-H), 6.76 (1H, d, *J* 2.3, 6′-H), 6.74 (1H, dd, *J* 8.5 and 2.3, 4′-H), 3.88 (1H, d, *J* 2.0, 1-H), 3.76 (3H, s, OCH_3), 2.87 (1H, dq, *J* 2.0 and 5.1, 2-H) and 1.50 (3H, d, *J* 5.1, CH_3); δ_C 159.3 (C-5′), 137.2, 130.3 and 130.2 (C-1′, C-2′, C-3′), 115.5 and 111.1 (C-4′, C-6′), 59.3 and 57.6 (C-1, C-2), 56.1 (OCH_3) and 18.4 (CH_3); *m*/*z* 200 [M^+(^{37}Cl), 13%], 198 [M^+(^{35}Cl), 35], 183 (11.5), 169 (32), 167 (55), 154 (14) and 119 (100).

***rel*-(1*S*,2*R*)-1-(2′-Chloro-5′-methoxyphenyl)propane-1,2-diol 21**

The 1:13 mixture of epoxides **19** and **20** (350 mg, 1.77 mmol) in dimethyl sulfoxide (15 ml) and potassium hydroxide (0.4 M, 6 ml) was stirred at 80 °C. After 24 h, the resulting solution was cooled to room temperature, poured into water and extracted with ethyl acetate (4 × 20 ml). The residue obtained upon work-up was chromatographed (50% ethyl acetate–hexane) to afford the *diol* **21** as a light orange oil (330 mg, 86%) (Found: C, 55.7; H, 6.2; Cl, 16.2. $C_{10}H_{13}ClO_3$ requires C, 55.4; H, 6.05; Cl, 16.4%); δ_H 7.27 (1H, d, *J* 8.7, 3′-H), 7.23 (1H, d, *J* 2.9, 6′-H), 6.81 (1H, dd, *J* 8.7 and 2.9, 4′-H), 5.22 (1H, d, *J* 3.2, 1-H), 4.26 (1H, dq, *J* 3.2 and 6.5, 2-H), 3.85 (3H, s, OCH_3) and 1.10 (3H,

d, *J* 6.5, CH_3); δ_C 158.3 (C-5′), 139.0 (C-2′), 129.7 (C-3′) 123.2 (C-1′), 114.3 and 113.3 (C-4′, C-6′), 73.4 (C-1), 69.1 (C-2), 55.4 (OCH_3) and 15.9 (CH_3); *m*/*z* 218 [M^+(^{37}Cl), 2%] 216 [M^+(^{35}Cl), 5], 174 (21), 173 (15), 172 (69), 171 (29), 143 (37), 137 (34), 109 (38), 77 (51) and 44 (100).

rel-(2*R*,4*S*,5*R*)-4-(2′-Chloro-5′-methoxyphenyl)-2,5-dimethyl-1,3-dioxolane 13

The diol **21** (250 mg, 1.16 mmol) in dry methylene dichloride (25 ml) was treated with 1,1-dimethoxyethane (0.16 ml) and (±)-camphorsulfonic acid (10 mg, 0.04 mmol) as for the preparation of dioxolane **1**. The crude product was purified by chromatography (10% ethyl acetate–hexane) to give the *dioxolane* **13** as a colourless oil (260 mg, 92%) (Found: M^+, 242.0711. $C_{12}H_{15}ClO_3$ requires *M*, 242.0710); δ_H 7.30 (1H, d, *J* 8.7, 3′-H), 7.17 (1H, d, *J* 3.1, 6′-H), 6.85 (1H, dd, *J* 8.7 and 3.1, 4′-H), 5.48 (1H, d, *J* 7.2, 4-H), 5.26 (1H, q, *J* 4.7, 2-H), 4.60 (1H, dq, *J* 7.2 and 6.4, 5-H), 3.89 (3H, s, OCH_3), 1.64 (3H, d, *J* 4.7, 2-CH_3) and 0.95 (3H, d, *J* 6.4, 5-CH_3); δ_C 158.3 (C-5′), 137.2 (C-2′), 129.6 (C-3′), 123.0 (C-1′), 114.3 and 113.6 (C-4′, C-6′), 100.0 (C-2), 76.5 and 75.2 (C-4, C-5), 55.4 (OCH_3), 19.7 (CH_3-2) and 16.3 (CH_3-5); *m*/*z* 244 [M^+(^{37}Cl), 3%], 242 [M^+(^{35}Cl), 9], 200 (18), 198 (55), 169 (40), 167 (77), 154 (14), 119 (38), 77 (16), 72 (100) and 44 (78).

rel-(1*R*,2*R*)-1-(2′-Chloro-5′-methoxyphenyl)propane-1,2-diol 22

The 1:13 mixture of olefines **17** and **18** (200 mg, 1.08 mmol) in a 2:1 mixture of acetone–water (6 ml) was treated with *N*-methylmorpholine *N*-oxide (155 mg, 1.32 mmol) and osmium tetroxide (5 mg) in *tert*-butyl alcohol (0.5 ml) at 0 °C. After stirring for 24 h, acetone was removed under vacuum at room temperature. The remaining aqueous layer was poured into dilute hydrochloric acid (2 M, 5 ml) and extracted into ethyl acetate (5 × 20 ml). The residue obtained upon work-up was chromatographed (50% ethyl acetate–hexane) to give the *diol* **22** as a light orange oil (200 mg, 80%) (Found: M^+, 216.0553. $C_{10}H_{13}ClO_3$ requires *M*, 216.0552); δ_H 7.25 (1H, d, *J* 8.9, 3′-H), 7.03 (1H, d, *J* 3.0, 6′-H), 6.77 (1H, dd, *J* 8.9 and 3.0, 4′-H), 4.90 (1H, d, *J* 5.5, 1-H), 3.92 (1H, dq, *J* 5.5 and 6.6, 2-H), 3.78 (3H, s, OCH_3) and 1.19 (3H, d, *J* 6.6, CH_3); δ_C 158.5 (C-5′), 139.8 (C-2′), 130.1 (C-3′), 123.8 (C-1′), 114.7 and 113.2 (C-4′, C-6′), 74.4 (C-1), 71.5 (C-2), 55.5 (OCH_3) and 18.7 (CH_3); *m*/*z* 218 [M^+(^{37}Cl), 1%], 216 [M^+(^{35}Cl), 3], 174 (27), 172 (87), 145 (16), 143 (55), 137 (47), 109 (50), 108 (69), 77 (58) and 44 (100).

rel-(2*R*,4*R*,5*R*)- and rel-(2*S*,4*R*,5*R*)-4-(2′-Chloro-5′-methoxyphenyl)-2,5-dimethyl-1,3-dioxolanes 14 and 15

Diol **22** (200 mg, 0.93 mmol) in dry methylene dichloride (20 ml) was treated with 1,1-dimethoxyethane (0.10 ml) and (±)-camphorsulfonic acid (10 mg, 0.043 mmol) as for the preparation of the dioxolane **1**. The crude product (200 mg) was chromatographed (10% ethyl acetate–hexane) to give a 2:1 diastereomeric mixture of dioxolanes **14** and **15** as a colourless oil (190 mg, 85%). Further chromatography of this mixture (10% ethyl acetate–hexane) afforded first the single *dioxolane* **14** as a colourless oil (105 mg, 55%) (Found: C, 59.2; H, 6.2; Cl, 14.6. $C_{12}H_{15}ClO_3$ requires C, 59.4; H, 6.2; Cl, 14.6%); δ_H 7.24 (1H, d, *J* 8.8, 3′-H), 7.03 (1H, d, *J* 3.1, 6′-H), 6.77 (1H, dd, *J* 8.8 and 3.1, 4′-H), 5.49 (1H, q, *J* 4.7, 2-H), 4.97 (1H, d, *J* 7.4, 4-H), 3.91 (1H, dq, *J* 7.4 and 6.1, 5-H), 3.80 (3H, s, OCH_3), 1.49 (3H, d, *J* 6.1, 5-CH_3) and 1.46 (3H, d, *J* 4.7, 2-CH_3); δ_C 158.6 (C-5′), 138.0 (C-2′), 130.3 (C-3′), 123.7 (C-1′), 114.5 and 112.9 (C-4′, C-6′), 102.2 (C-2), 81.5 and 80.4 (C-4 and C-5), 55.5 (OCH_3), 20.8 (CH_3-2) and 17.5 (CH_3-5); *m*/*z* 244 [M^+(^{37}Cl), 2%], 242 [M^+(^{35}Cl), 6], 200 (9), 198 (28), 169 (19), 167 (33), 154 (14), 119 (15), 77 (16), 72 (80) and 42 (100). This was followed by the *dioxolane* **15** as a colourless oil (40 mg, 21%); δ_H 7.24 (1H, d, *J* 8.8, 3′-H), 7.14 (1H, d, *J* 3.1, 6′-H), 6.78 (1H, dd, *J* 8.8 and 3.1, 4′-H), 5.42 (1H, q, *J* 4.8, 2-H), 5.02 (1H, d, *J* 5.4, 4-H), 4.03 (1H, dq, *J* 5.4 and 6.5, 5-H), 3.80 (3H, s, OCH_3), 1.54 (3H, d, *J* 4.8, 2-CH_3) and 1.43 (3H, d, *J* 6.5, 5-CH_3); mass spectral fragmentation pattern identical to isomer **14**.

rel-(1*R*,3*R*,4*S*)-4-Hydroxy-5,8-dimethoxy-1,3-dimethylisochromane 25

To the dioxolane **1** (55 mg, 0.22 mmol) in dry methylene dichloride (35 ml) at −78 °C was added titanium tetrachloride (25.3 μl, 0.22 mmol). After stirring at −78 °C for 30 min, the mixture was quenched with methanol (0.1 ml) and saturated aqueous sodium hydrogen carbonate (0.5 ml) was added. The resultant mixture was poured into water, the organic layer separated and the aqueous layer extracted with methylene dichloride (3 × 10 ml). The residue obtained upon work-up was chromatographed (25% ethyl acetate–hexane) to give unreacted dioxolane **1** (11 mg, 20%) (^{1}H NMR and mass spectra in agreement with those quoted above) followed by the *isochromane* **25** as a colourless oil (10 mg, 18%) (Found: M^+, 238.1205. $C_{13}H_{18}O_4$ requires *M*, 238.1205); δ_H 6.82 and 6.72 (each 1H, d, *J* 9.0, 6-H and 7-H), 5.01 (1H, q, *J* 6.6, 1-H), 4.55 (1H, d, *J* 7.9, 4-H), 3.98 (1H, dq, *J* 7.9 and 6.2, 3-H), 3.85 and 3.76 (each 3H, s, OCH_3), 1.55 (3H, d, *J* 6.6, 1-CH_3) and 1.49 (3H, d, *J* 6.2, 3-CH_3); *m*/*z* 238 (M^+, 15%), 223 (53), 220 (15), 205 (100), 195 (16), 194 (46) and 179 (67). Subsequent fractions afforded the (1:1) mixture of the chlorohydrins **12** as a colourless oil (25 mg, 45%); δ_H 7.15 and 7.05 (each 1H, d, *J* 2.1, 6′-H of each isomer), 6.82 (4H, m, 3′-H and 4′-H of both isomers), 5.43 and 5.42 (each 1H, d, *J* 6.0 and 6.4, 1-H of each isomer), 4.15 (2H, dq overlapped, 2-H of both isomers), 3.80 and 3.76 (each 6H, 2 × OCH_3 of each isomer) and 1.25 and 1.14 (each 3H, d, *J* 6.0 and 6.4, CH_3 of each isomer). GC–MS analysis of the chlorohydrin mixture **12** showed six components: two isomeric chlorohydrins **12** with retention times 13.4 and 13.5 min and identical spectra, *m*/*z* 232 [M^+(^{37}Cl), 10%], 230 [M^+(^{35}Cl), 31], 194 (27), 188 (28), 186 (84), 171 (36) and 151 (100); the epoxides **9** and **10** with retention times 11.4 and 11.6 min and identical spectra, *m*/*z* 194 (M^+, 98%), 179 (13), 165 (47) and 151 (100); the ketone **26** with retention time 11.5 min and *m*/*z* 194 (M^+, 56%), 165 (100) and 150 (60); and the ketone **27** with retention time 11.8 min and *m*/*z* 194 (M^+, 80%), 151 (100) and 121 (53).

rel-(1*S*,3*R*,4*R*)-4-Hydroxy-5,8-dimethoxy-1,3-dimethylisochromane 30

To the 2:1 mixture of dioxolanes **2** and **3** (40 mg, 0.22 mmol) in dry methylene dichloride (15 ml) at −78 °C was added titanium tetrachloride (18.4 μl, 0.22 mmol). After stirring at −78 °C for 30 min, the reaction mixture was quenched with methanol (0.1 ml) and saturated aqueous sodium hydrogen carbonate (2 ml) was added. The resultant mixture was poured into water, the organic layer separated and the aqueous layer extracted with methylene dichloride (3 × 10 ml). The combined organic extracts were dried and evaporated to give a colourless oil (38 mg), shown by GC and GC–MS analysis to contain a number of products. This mixture was chromatographed (25% ethyl acetate–hexane) to give several compounds: unreacted dioxolanes **2** and **3** (8 mg, 20%) (^{1}H NMR and mass spectra in agreement with those quoted above); the chlorohydrin mixture **12** as a colourless oil (12 mg, 31%) (^{1}H NMR and GC–MS data are given above); and the *isochromane* **30** as a colourless oil (18 mg, 45%) (Found: C, 65.6; H, 7.9. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%); δ_H 6.77 and 6.73 (each 1H, d, *J* 8.5, 6-H and 7-H), 4.93 (1H, q, *J* 6.3, 1-H), 4.58 (1H, d, *J* 1.6, 4-H), 3.84 and 3.78 (each 3H, s, OCH_3), 3.56 (1H, dq, *J* 1.6 and 6.3, 3-H), 1.58 (3H, d, *J* 6.3, 1-CH_3) and 1.39 (3H, d, *J* 6.3, 3-CH_3); δ_C 151.5 and 150.2 (C-5, C-8), 129.3 and 126.9 (C-4a, C-8a), 112.3 and 108.9 (C-6, C-7), 72.2, 71.1 and 63.8 (C-1, C-3, C-4), 55.8 and 55.6 (OCH_3), 21.6 (1-CH_3) and 16.7 (3-CH_3); *m*/*z* 238 (M^+, 13%), 223 (7), 220 (26), 206 (13), 205 (100), 194 (56), 190 (20), 179 (16) and 175 (30).

rel-(1*S*,3*R*,4*R*)-4-Hydroxy-1,3-dimethylisochromane-5,8-quinone 31

To the isochromane **30** (20 mg, 0.08 mmol) and silver(II) oxide (50 mg) in dioxolane (2 ml) was added nitric acid (6 M, 0.2 ml). The reaction mixture was stirred for 5 min and a mixture of chloroform (6 ml) and water (2 ml) was then added. The residue obtained upon work-up was chromatographed (20% ethyl acetate–hexane) to give the *quinone* **31** as a yellow oil (13 mg, 75%); δ_H 6.80 and 6.74 (each 1H, d, *J* 10.0, 6-H and 7-H), 4.64 (1H, dq, *J* 1.5 and 6.0, 1-H), 4.38 (1H, dd, *J* 1.6 and 1.5, 4-H), 3.57 (1H, dq, *J* 1.6 and 6.3, 3-H), 1.53 (3H, d, *J* 6.0, 1-CH_3) and 1.37 (3H, d, *J* 6.3, 3-CH_3); δ_C 187.3 and 186.3 (C-5 and C-8), 145.3 and 139.8 (C-4a, C-8a), 137.3 and 136.1 (C-6, C-7), 72.2, 69.8 and 61.5 (C-1, C-3, C-4), 20.3 (1-CH_3) and 15.9 (3-CH_3); *m*/*z* 210 (M^+ + 2H, 10%), 208 (5), 193 (27), 164 (100) and 136 (64).

5,8-Dimethoxy-1,3-dimethyl-1*H*-isochromene 32

The 2:1 mixture of dioxolanes **2** and **3** (40 mg, 0.22 mmol) was treated with titanium tetrachloride as above and the reaction mixture stirred at 0 °C for 10 min before quenching with methanol (0.1 ml). ^{1}H NMR analysis of the crude residue showed a 3:1 mixture of the chlorohydrins **12** (20 mg, 38%) and the *isochromene* **32** (20 mg, 36%) (Found: M^+, 220.1099. $C_{13}H_{16}O_3$ requires *M*, 220.1099); δ_H 6.65 and 6.58 (each 1H, d, *J* 9.0, 6-H and 7-H), 5.81 (1H, s, 4-H), 5.61 (1H, q, *J* 6.0, 1-H), 3.79 and 3.76 (each 3H, s, OCH_3), 1.91 (3H, s, 3-CH_3) and 1.35 (3H, d, *J* 6.0, 1-CH_3); *m*/*z* 220 (M^+, 9%), 205 (21), 149 (27) and 57 (100).

rel-(1*R*,3*R*,4*S*)-5-Chloro-4-hydroxy-8-methoxy-1,3-dimethylisochromane 34

Titanium tetrachloride (47.0 μl, 0.4 mmol) was added to a stirred solution of dioxolane **13** (50 mg, 0.20 mmol) in dry methylene dichloride (33 ml) at −95 °C in an atmosphere of argon. After 15 min an aliquot (10 ml) of the reaction mixture was removed by syringe and immediately quenched with methanol (0.1 ml). The rest of the reaction mixture was kept at −95 °C for 60 min before quenching with methanol (0.1 ml). Duplicate portions of dioxolane **13** (15 mg, 0.06 mmol) in methylene dichloride (10 ml) were stirred with titanium tetrachloride (14.1 μl, 0.12 mmol) at −78 °C for 30 min in an atmosphere of argon before quenching with methanol (0.1 ml) at −78 °C. To a fourth portion (15 mg, 0.06 mmol) at lower concentration in methylene dichloride (20 ml) at −78 °C was added titanium tetrachloride (14.1 μl, 0.12 mmol), and the temperature raised to 0 °C for 30 min before quenching. The quenched reactions were neutralised with saturated aqueous sodium hydrogen carbonate, and the organic phases washed with water, dried and evaporated. Analysis of the crude residues by GC and ^{1}H NMR spectroscopy indicated mixtures of the dioxolane **13**, diol **21** and isochromane **34** (see Table 1).

The residues obtained from the duplicate experiments at −78 °C were combined and purified by chromatography on silica gel (25% ethyl acetate–hexane) to afford isochromane **34** as white crystals (23 mg, 77%), mp 108–110 °C (methylene dichloride–hexane) (Found: C, 59.2; H, 6.0; Cl, 14.9. $C_{12}H_{15}ClO_3$ requires C, 59.4; H, 6.2; Cl, 14.6%); δ_H 7.25 (1H, d, *J* 8.8, 6-H), 6.75 (1H, d, *J* 8.8, 7-H), 4.96 (1H, q, *J* 6.3, 1-H), 4.57 (1H, d, *J* 6.0, 4-H), 4.16 (1H, dq, *J* 6.0 and 6.5, 3-H), 3.81 (3H, s, OCH_3), 1.56 (3H, d, *J* 6.3, 1-CH_3) and 1.27 (3H, d, *J* 6.5, 3-CH_3); δ_C 153.9 (C-8), 133.0 (C-5), 130.5, 128.2 and 125.7 (C-4a, C-6, C-8a), 110.5 (C-7), 69.9, 68.3 and 66.2 (C-1, C-3, C-4), 55.4 (OCH_3), 19.6 (3-CH_3) and 17.6 (1-CH_3); *m*/*z* 244 [M^+(^{37}Cl), 8%], 242 [M^+(^{35}Cl), 24], 229 (35), 227 (100), 211 (13), 209 (34), 200 (19), 198 (58), 183 (56) and 169 (29).

rel-(1*S*,3*R*,4*R*)- and rel-(1*R*,3*R*,4*R*)-5-Chloro-4-hydroxy-8-methoxy-1,3-dimethylisochromanes 35 and 36

Titanium tetrachloride (47.0 μl, 0.4 mmol) was added to a stirred soluton of a 2:1 mixture of dioxolanes **14** and **15** (50 mg, 0.2 mmol) in dry methylene dichloride (60 ml) at −78 °C in an atmosphere of argon. After 30 min the reaction was quenched with methanol (0.1 ml). The resultant solution was neutralised with saturated aqueous sodium hydrogen carbonate, washed with water, dried and evaporated. Analysis of the resulting crude residue by GC and ^{1}H NMR spectroscopy indicated a 1:2 mixture of isochromanes **35** and **36**. Chromatography (20% ethyl acetate–hexane) afforded first the *isochromane* **35** as a colourless oil (13 mg, 26%) (Found: C, 59.35; H, 6.4; Cl, 14.95. $C_{12}H_{15}ClO_3$ requires C, 59.4; H, 6.2; Cl, 14.6%); δ_H 7.28 (1H, d, *J* 8.8, 6-H), 6.78 (1H, d, *J* 8.8, 7-H), 4.93 (1H, q, *J* 6.2, 1-H), 4.56 (1H, d, *J* 1.2, 4-H), 3.81 (3H, s, OCH_3), 3.68 (1H, dq, *J* 1.2 and 6.3, 3-H), 1.56 (3H, d, *J* 6.2, 1-CH_3) and 1.40 (3H, d, *J* 6.3, 3-CH_3); δ_C 154.7 (C-8), 135.1 (C-5), 130.0, 127.9 and 125.7 (C-4a, C-6, C-8a), 111.0 (C-7), 72.0, 71.0 and 66.1 (C-1, C-3, C-4), 55.3 (OCH_3), 21.6 (1-CH_3) and 16.8 (3-CH_3); *m*/*z* 244 [M^+(^{37}Cl), 2.5%], 242 [M^+(^{35}Cl), 8], 229 (8), 227 (25), 211 (11), 209 (30), 200 (31), 198 (100), 169 (52). This was followed by the *isochromane* **36** as white crystals (25 mg, 50%), mp 107–108 °C (methylene dichloride–hexane) (Found: C, 59.7; H, 6.4; Cl, 14.4. $C_{12}H_{15}ClO_3$ requires C, 59.4; H, 6.2; Cl, 14.6%); δ_H 7.28 (1H, d, *J* 8.8, 6-H), 6.75 (1H, d, *J* 8.8, 7-H), 5.09 (1H, q, *J* 6.6, 1-H), 4.50 (1H, d, *J* 1.7, 4-H), 4.11 (1H, dq, *J* 1.7 and 6.5, 3-H), 3.81 (3H, s, OCH_3), 1.48 (3H, d, *J* 6.6, 1-CH_3) and 1.40 (3H, d, *J* 6.5, 3-CH_3); δ_C 153.9 (C-8), 133.9 (C-5), 129.7, 128.1 and 126.0 (C-4a, C-6, C-8a), 110.6 (C-7), 68.5, 66.2 and 65.0 (C-1, C-3, C-4), 55.4 (OCH_3), 17.8 (1-CH_3) and 16.9 (3-CH_3); *m*/*z* 244 [M^+(^{37}Cl), 4%], 242 [M^+(^{35}Cl), 11], 229 (12), 227 (35), 211 (13), 209 (38), 200 (22), 198 (68) and 42 (100).

Isomerisation of dioxolane 14

To the dioxolane **14** (100 mg, 0.41 mmol) in stirred dry methylene dichloride (66 ml) was added titanium tetrachloride (75.2 μl, 0.80 mmol) at −95 °C in an atmosphere of argon. Portions (5 ml) of the reaction mixture were removed by syringe and immediately quenched with methanol (0.1 ml) after 2 min and 12 min. The rest of the reaction mixture was warmed to −78 °C, kept for 30 min and then quenched with methanol (0.1 ml).

Further aliquots of the dioxolane **14** (15 mg, 0.06 mmol) in methylene dichloride (10 or 20 ml) were stirred with titanium tetrachloride (14.1 μl, 0.12 mmol) and quenched under the conditions of temperature and time detailed in Table 2. The quenched reaction solutions were neutralised with saturated aqueous sodium hydrogen carbonate, washed with water, dried and evaporated. The residues were analysed by GC, GC–MS and ^{1}H NMR spectroscopy with the results given in Table 2. The *isochromene* **38** formed in entries 7 and 8 was identified by GC–MS (Found: M^+, 226/224. $C_{12}H_{13}ClO_2$ requires *M*, 226/224); *m*/*z* 226 [M^+(^{37}Cl), 8%], 224 [M^+(^{35}Cl), 25], 211 (34), 209 (100), 196 (7) and 194 (22).

Isomerisation of dioxolane 15

Aliquots of the dioxolane **15** (15 mg, 0.06 mmol) in methylene dichloride (10 or 20 ml) were stirred with titanium tetrachloride (14.1 μl, 0.12 mmol) and quenched under the conditions of temperature and time detailed in Table 3. The quenched reaction solutions were neutralised with saturated aqueous sodium hydrogen carbonate, washed with water, dried and evaporated. The residues were analysed by GC, GC–MS and ^{1}H NMR spectroscopy with the results given in Table 3.

Attempted isomerisation of isochromane 35

Isochromane **35** (15 mg, 0.06 mmol) in methylene dichloride (10 ml) was treated with titanium tetrachloride (14.1 μl, 0.12 mmol) at −78 °C. After 2 min the reaction mixture was warmed to 0 °C and stirred for 30 min in an atmosphere of argon before quenching with methanol (0.1 ml) at 0 °C. The residue obtained

upon work-up was shown by GC, GC–MS and ^{1}H NMR spectroscopy to contain unchanged isochromane **35**.

***rel*-(1*R*,3*R*,4*R*)-1,3-Dimethyl-4-hydroxy-8-methoxyisochromane 37**

Following the procedure of Beckwith and Goh,[16] a mixture of the isochromane **36** (10 mg, 0.04 mmol), di-*tert*-butyl peroxide (4 μl, 0.02 mmol) and lithium aluminium hydride (50 mg) in dry tetrahydrofuran (10 ml) was irradiated with a 250 W high-pressure Hg lamp for 5 h, cooled, diluted with aqueous hydrochloric acid and extracted with diethyl ether. The residue obtained upon work-up gave a colourless oil (5 mg, 58%) identified by GC–MS and ^{1}H NMR spectroscopy as the *isochromane* **37** (Found: M^+, 208. $C_{12}H_{16}O_3$ requires *M*, 208); δ_H 7.25 (1H, t, *J* 8.8, 6-H), 7.00 and 6.80 (each 1H, d, *J* 8.8, 5-H and 7-H), 5.09 (1H, q, *J* 6.6, 1-H), 4.18 (1H, d, *J* 1.7, 4-H), 4.11 (1H, dq, *J* 1.7 and 6.5, 3-H), 3.81 (3H, s, OCH_3), 1.50 (3H, d, *J* 6.6, 1-CH_3) and 1.45 (3H, d, *J* 6.5, 3-CH_3); *m*/*z* 208 (M^+, 15%), 193 (27), 175 (45) and 164 (100).

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References

1 R. G. F. Giles, R. W. Rickards and B. Senanayake, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 2241.
2 (*a*) R. H. Thomson, *Naturally Occurring Quinones*, Academic Press, London, 1971; (*b*) R. H. Thomson, *Naturally Occurring Quinones III*, *Recent Advances*, Chapman and Hall, London, 1987; (*c*) R. H. Thomson, *Naturally Occurring Quinones IV*, *Recent Advances*, 4th edn., Blackie Academic and Professional, Chapman and Hall, London, 1997.
3 D. W. Cameron, R. I. T. Cromartie, D. G. I. Kingston and Lord Todd, *J. Chem. Soc.*, 1964, 51.
4 R. G. F. Giles, V. R. Lee Son and M. V. Sargent, *Aust. J. Chem.*, 1990, **43**, 777.
5 (*a*) V. VanRheenen, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett.*, 1976, 1973; (*b*) R. Ray and D. S. Matteson, *Tetrahedron Lett.*, 1980, **21**, 449.
6 G. Casiraghi, M. Cornia and G. Rassu, *J. Org. Chem.*, 1988, **53**, 4919.
7 M. K. Meilahn, C. N. Statham, J. L. McManaman and M. E. Munk, *J. Org. Chem.*, 1975, **40**, 3551.
8 A. Bhati, *J. Chem. Soc.*, 1963, 730.
9 T. Kometani, Y. Takeuchi and E. Yoshii, *J. Chem. Soc.*, *Perkin Trans. 1*, 1981, 1197.
10 R. G. F. Giles, I. R. Green, V. I. Hugo, P. R. K. Mitchell and S. C. Yorke, *J. Chem. Soc.*, *Perkin Trans. 1*, 1983, 2309.
11 D. W. Cameron, D. G. I. Kingston, N. Sheppard and Lord Todd, *J. Chem. Soc.*, 1964, 98.
12 R. G. F. Giles, I. R. Green, V. I. Hugo, P. R. K. Mitchell and S. C. Yorke, *J. Chem. Soc.*, *Perkin Trans. 1*, 1984, 2383.
13 M. Karplus, *J. Chem. Phys.*, 1960, **33**, 1842.
14 P. A. Bartlett, W. S. Johnson and J. D. Elliott, *J. Am. Chem. Soc.*, 1983, **105**, 2088. For a discussion of related effects, see S. E. Denmark and N. G. Almstead, *J. Am. Chem. Soc.*, 1991, **113**, 8089.
15 R. G. F. Giles, I. R. Green, L. S. Knight, V. R. Lee Son and S. C. Yorke, *J. Chem. Soc.*, *Perkin Trans. 1*, 1994, 865.
16 A. L. J. Beckwith and S. H. Goh, *J. Chem. Soc.*, *Chem. Commun.*, 1983, 907.
17 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

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