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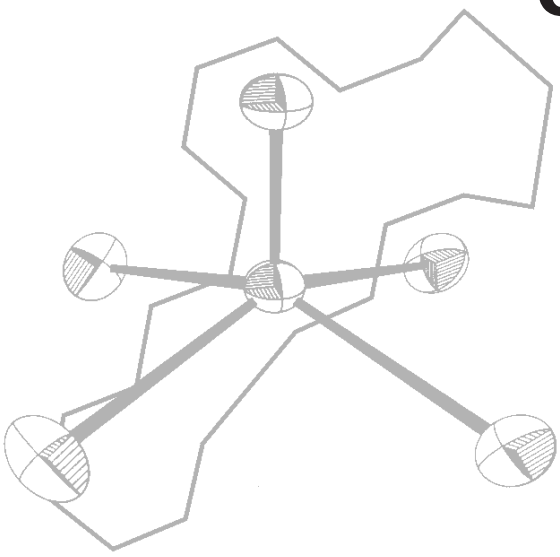

Volume 53, 2000

A journal for the publication of original research
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Aust. J. Chem., 2000, **53**, 341–347

Asymmetric Syntheses of Isochroman-4,7-diols Through Intramolecular Cyclization of Tethered Lactaldehydes*

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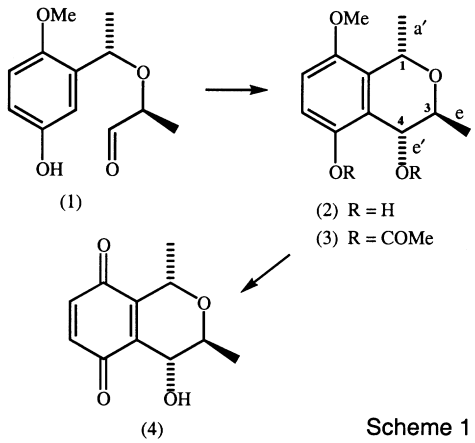
Ready cyclization through silica gel chromatography of the asymmetric phenolic lactaldehyde (14) afforded the diastereomeric pair of isochroman-4,7-diols (21) and (23) in good yield, while (17), the benzylic epimer of (14), similarly yielded the isochroman-4,7-diol (25) as a single diastereomer.

Keywords. Asymmetric synthesis; isochromandiols; lactaldehyde cyclization.

Introduction

We recently reported[1] the high yielding cyclization (Scheme 1) of the asymmetric phenolic lactaldehyde (1) with titanium tetraisopropoxide to give the isochroman-4,5-diol (2), which was characterized as its diacetate (3). The diol (2) was readily oxidized, in a second high yielding step, to afford the asymmetric quinone (4). In the cyclization of (1) to (2), it is believed that the complete diastereoselectivity that is observed arises through coordination of titanium to both the phenolic and aldehydic oxygens.[1] The isochroman-5,8-quinone (4) possessed the correct absolute stereochemistry of the substituents about the pyran ring for the enantiomer of the aphid insect pigment-derived quinone A.[2] The other product of hydrogenolysis of the broad bean aphid pigment protoaphin-*fb*,[2] glucoside B, is non-quinonoid owing to the absence in that case of oxygen at C 5 of the benzisochroman ring system. This paper describes an investigation into finding conditions for the corresponding ring-closure of the phenolic lactaldehyde (14), isomeric with (1), and its benzylic epimer (17), with a view to developing a model for the asymmetric assembly of glucoside B and other non-quinonoid benzisochromans. Compounds (14) and (17) were chosen, firstly, since the phenolic substituent in each case could only activate cyclization *para* to it, although, as a consequence, it was expected that there would not necessarily be corresponding diastereoselectivity (cf. Scheme 1) in the formation of the alcohol in these cases. Secondly, the product isochromans would possess the correct oxygenation, at C 8, for the central ring of natural products such as glucoside B and Karwinaphthol B.[3]



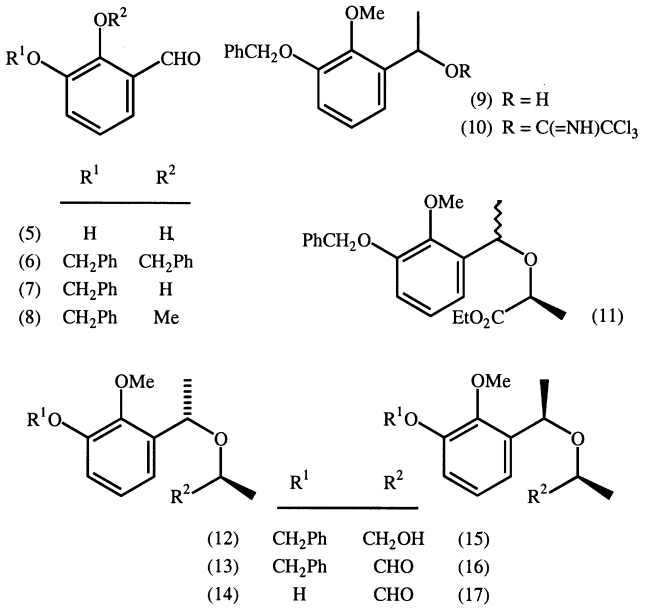
Scheme 1

Results and Discussion

3-Benzyloxy-2-hydroxybenzaldehyde (7), readily available[4] in two high yielding steps from 2,3-dihydroxybenzaldehyde (5) via the dibenzyl ether (6), was chosen as the starting material for compound (14), into which it was converted by a sequence related to that for the synthesis of its regioisomer (1).[1] Methylation of the free phenolic substituent of (7) gave the differentially protected aldehyde (8) in a yield of 94%. This aldehyde was then subjected to a Grignard reaction with methylmagnesium iodide, affording the alcohol (9) in 94%. The new alcohol function was activated to displacement by formation, using sodium hydride and trichloroacetonitrile,[5] of the corresponding trichloroacetimidate (10), in a yield of

* This paper is dedicated to Professor Don Cameron.

Manuscript received 31 January 2000 10.1071/CH00020 0004-9425/00/040341



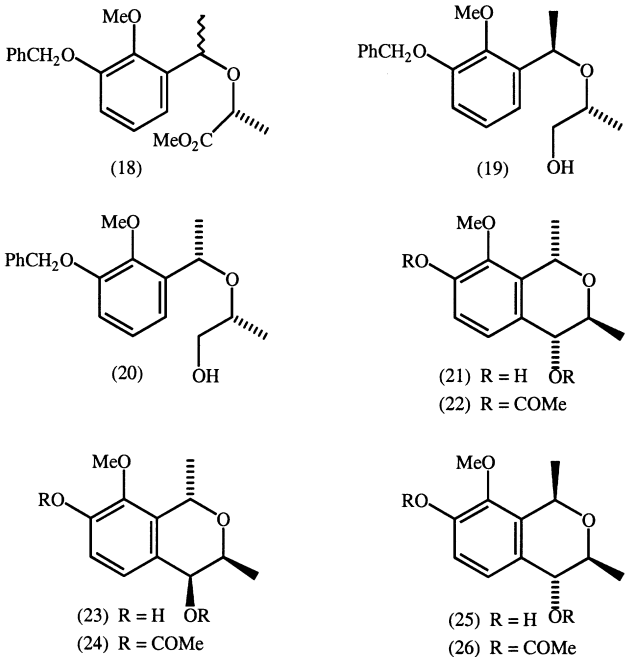
96%. Evidence for the formation of this product was observed in the ^{1}H n.m.r. spectrum, which showed the NH proton typically deshielded at δ 8.29, and the benzylic methine proton at δ 6.33, strongly downfield from that (δ 5.14) of the preceding alcohol. This reagent (10) was then used to benzylate ethyl (*S*)-lactate in the presence of a catalytic quantity of boron trifluoride diethyl etherate, in a procedure known to avoid racemization of asymmetric substrates.[5] This commercially available (*S*)-ester was chosen for these model experiments since it is considerably cheaper than esters of the enantiomeric (*R*)-series. An inseparable mixture of the diastereomeric esters (11) was formed in a combined yield of 85%, and in a ratio 3 : 1. Support for the assigned structures was provided by: the molecular ion at *m/z* 358 in the mass spectrum of the mixture, the ester carbonyl stretch at 1740 cm^{-1}, and also all signals for the individual benzylic epimers in the ^{1}H and ^{13}C n.m.r. spectra of the mixture. These esters were obtained in an overall yield of 52% over the six steps from 2,3-dihydroxybenzaldehyde (5).

Reduction of the ester mixture (11) with lithium aluminium hydride gave the corresponding diastereomeric alcohols, which were separable by careful chromatography. Confirmation of the relative stereochemistry of each epimer relied upon examination of the ^{1}H n.m.r. spectra of the derived isochromans (22), (24) and (26) produced later in the sequence. These studies permitted the assignment of structure (12) to the major isomer (57%) and (15) to the minor (19%) isomer. Each epimer showed a hydroxyl stretching frequency in the infrared spectrum and the alcohol proton signal in its ^{1}H n.m.r. spectrum. In the latter, the major epimer (12) showed the diastereotopic protons of the lactol at δ 3.45 and δ 3.67, with a geminal coupling constant of 11.0 Hz and two vicinal coupling constants of 5.9 and 3.5 Hz. For the minor isomer (15), the corresponding protons were not well resolved, even at 500 MHz.

The enantiomeric excess of each of the two alcohols (12) and (15) was determined by using the chiral shift reagent Eu(hfc)$_3$.[1,6] This study was undertaken in order to determine whether any racemization at the carbon α to the ester group had occurred during the formation of the esters (11), or, less likely, during their subsequent reduction. For this purpose the enantiomer of each alcohol was prepared from the reaction of methyl (*R*)-lactate with the trichloroacetimidate (10), giving the mixture of methyl esters (18). These were reduced to the mixture of alcohols, which were separated to give the individual alcohols (19) and (20), once again in a ratio of *c*. 3 : 1. Using the method previously described[1] for the regioisomers, it was concluded that the alcohols (12) and (15) were optically pure within the limits of the n.m.r. technique, i.e. they had enantiomeric excesses of >98%. Thus essentially no racemization had occurred in the formation of the esters (11).

Each of the diastereomeric alcohols (12) and (15) was smoothly oxidized to the corresponding aldehyde by Swern methodology.[7] Thus the major aldehyde (13) was obtained in a yield of 80% from alcohol (12). The aldehydic proton resonated as a doublet at δ 9.72 (*J* 2.0 Hz) in the ^{1}H n.m.r. spectrum, while, in the ^{13}C n.m.r. spectrum, the signal for the aldehydic carbon was observed at δ 204.2. The C=O stretch of the aldehyde moiety was evident at 1733 cm^{-1} in the infrared spectrum, and the mass spectrum exhibited a molecular ion peak at *m/z* 314. Similar oxidation of the epimeric alcohol (15) afforded the alternative aldehyde (16) in a yield of 77%. In this case, the aldehydic proton resonated as a doublet at δ 9.51 with a smaller coupling constant of 1.5 Hz. The signal for the carbonyl carbon was evident at δ 203.5 in the ^{13}C n.m.r. spectrum. In the infrared spectrum, the carbonyl stretch was present at 1734 cm^{-1} and the mass spectrum gave the same molecular ion (*m/z* 314) as its epimer (13).

To determine that there was no loss of enantiomeric purity during the Swern oxidation reactions, individual samples of the aldehydes (13) and (16) were reduced to their respective alcohols (12) and (15) by sodium borohydride in methanol.



Examination of the resulting alcohols by thin-layer chromatography and ^{1}H n.m.r. spectroscopy showed that only one diastereomeric alcohol was present in each case. Therefore, it can be concluded that there was no racemization at the carbon α to the aldehyde group during the oxidation step. The optical rotations of these samples of the alcohols (12) and (15) also compared well with those of samples obtained directly from the esters.

For each of the aldehydes (13) and (16), selective hydrogenolysis of the phenolic benzyl ether was achieved, in the presence of the activated aliphatic benzyl ether and the aldehyde function, to afford the free phenol. It was necessary to chromatograph each starting material carefully in order to minimize adventitious sulfur being carried through from the previous Swern oxidation, and optimized results were then achieved if the initial batch of catalyst, palladium on carbon, was removed by filtration and a second portion added. With this procedure, the protected aldehyde (13) gave the phenolic aldehyde (14) in a yield of 93%, while 91% was achieved for the corresponding conversion of (16) into (17). The ^{1}H n.m.r. spectrum of each of the two products confirmed the absence of the benzylic group and the presence of a phenolic proton, and the O–H stretch was observed in the infrared spectrum of each compound.

The individual yields of the phenols (14) and (17) over three steps from the esters (11) (75 : 25 mixture) were 42% and 13%, respectively, with the total yield therefore being 55%. The overall yield of combined phenols in the nine steps from 2,3-dihydroxybenzaldehyde (5) was then 29%.

Chromatography of the phenolic aldehyde (14) on Merck silica gel GF_{254}, using 5–50% ethyl acetate/hexane containing a trace of triethylamine as eluent and collection of the fractions eluting with 30–50%, gave an inseparable mixture of the C 4 epimeric diols (21) and (23) in a combined yield of 69%. The assigned structures were deduced from the derived spectral data. The infrared spectrum of the mixture showed a broad OH stretch at 3352 cm^{-1} and no aldehydic carbonyl stretch. In addition to the methoxy and only two aromatic signals for each diastereomer, the ^{1}H n.m.r. spectrum of this mixture exhibited two three-proton methyl doublets, three methine protons and two hydroxy signals. Confirmation of assignment of the major diastereomer as the pseudo-equatorial alcohol (21) was provided by the large coupling constant of 7.4 Hz between the protons H 3 and H 4, indicating a near *trans*-diaxial arrangement between these two protons. The chemical shift (δ 3.84) of H 3 is consistent with values reported for similar compounds having a *trans*-dimethyl arrangement,[8–10] and is characteristically[10,11] downfield of the signal for H 3 (δ 3.38) in the corresponding *cis*-dimethyl compound described below. The proton H 4 resonated as a doublet at δ 4.24 and H 1 appeared as a quartet at δ 5.04. Support for the proposed structure of the minor diastereomer as the pseudo-axial alcohol (23) was provided by the small coupling constant of 1.6 Hz between the protons H 3 and H 4, confirming their axial–pseudo-equatorial relationship. The proton H 3 resonated at δ 4.08, typically downfield of the corresponding signal (δ 3.38) for the *cis*-dimethyl compound.[10,11] Integration of the signals of the ^{1}H n.m.r. spectrum showed that the ratio of the products (21) to (23) was approximately 1.3:1. The diastereomer (21), possessing the same absolute stereochemistry about the pyran ring as the enantiomer of glucoside B, was favoured.

The diol mixture of (21) and (23) was unstable and therefore it was converted into the respective diacetates (22) and (24), in a combined crude yield of 79%. The two diastereomers (22) and (24) were found to be separable by column, followed by preparative layer, chromatography, giving the pure diacetates (22) and (24) in 33% and 26% yields, respectively. For each of the diacetates, two carbonyl stretches were observed in the infrared spectrum, and two additional high-field singlets for the two acetate methyl groups in the ^{1}H n.m.r. spectrum. A marked deshielding of the H 4 doublet from δ 4.24 in diol (21) to δ 5.70 in diacetate (22) was consistent with results reported for analogous compounds.[10,11] The large coupling constant of 7.4 Hz between the protons H 3 and H 4 confirmed their axial–pseudo-axial relationship. The deshielding of the proton H 4 from δ 4.15 in diol (23) to δ 5.77 in diacetate (24) was also noted and the small coupling constant of 2.0 Hz between H 3 and H 4 supported their axial–pseudo-equatorial arrangement.[10,11]

Two-dimensional NOESY for each of the diacetates (22) and (24) lent further support to their assigned structures. In both cases, a close relationship between the C 1 methyl group and the proton H 3 was observed, supporting a *trans*-dimethyl substitution pattern for compounds (22) and (24).

Similar chromatography of the alternative diastereomeric phenolic aldehyde (17) afforded the isochroman-4,5-diol (25) as a single diastereomer. The relative stereochemistry was identified from its ^{1}H n.m.r. spectrum, which showed a large coupling constant (8.9 Hz) between the protons H 3 and H 4, confirming an axial–pseudo-axial relationship between them, and, therefore, an equatorial and pseudo-equatorial arrangement for the C 3 methyl and C 4 hydroxy group. This result was consistent with the coupling constant of 7.4 Hz between H 3 and H 4 observed in the C 1 epimer (21). For the new diol (25), the signal for H 3 appeared at δ 3.38, characteristically upfield of the same signal (δ 3.84) in the isochroman (21), indicating a *cis*-dimethyl substitution pattern,[10–12] and, therefore, that the methyl group at C 1 is pseudo-equatorial. H 4 resonated as a doublet at δ 4.31 and H 1 at δ 5.00.

The diastereomeric C 4 pseudo-axial alcohol was not observed in the ^{1}H n.m.r. spectrum of the crude alcohol (25) obtained from the aldehyde (17). This cyclization is therefore completely diastereoselective, whereas two diastereomers were formed in the former cyclization of aldehyde (14) to give (21) and (23). This difference must arise as a consequence of the alternative stereochemistry of the benzylic methyl substituent in the starting aldehyde (17) when compared with the epimeric aldehyde (14), although it is premature to speculate further on this at this point.

The isochroman diol (25) was converted into the diacetate (26) in a yield of 77%. This showed two carbonyl stretches in the infrared spectrum, and two singlets for the two acetate methyl groups in the ^{1}H n.m.r. spectrum. Once again, the signal for H 3 in the *cis*-dimethyl compound (26) was observed upfield (δ 3.60) of the corresponding signal in the

trans-dimethyl compounds (22) and (24) (δ 4.06 and 4.21, respectively). The large coupling constant of 9.0 Hz between H 3 and H 4 supported their axial–pseudo-axial arrangement in (26). The proton H 4 was deshielded from δ 4.31 in diol (25) to δ 5.75 in diacetate (26).[10,11] Two-dimensional NOESY of the diacetate (26) provided further support for the assigned structure in that it showed close proximity between H 1 and H 3, but no similar relationship between the 1-CH_3 group and H 3, supporting a 1,3-*cis*-dimethyl substitution pattern.

The enantiomeric excesses of the three isochroman-4,7-diols (21), (23) and (25), and therefore those of the corresponding diacetates (22), (24) and (26), are all assumed to be >98%, since the stereochemistries of the individual epimeric aldehydes (13) and (16) are fixed at the benzylic methyl group. Changes in stereochemistry during subsequent reactions of these aldehydes would give rise to diastereomers rather than enantiomers.

The cyclizations of the phenolic aldehydes (14) and (17) to give the isochromans (21) and (23) (from the former) and (25) (from the latter) were also achieved with the mild Lewis acid titanium tetraisopropoxide,[1] but without ultrasonication. The yield was not as high, at 33%, for the former, but better, at 72%, for the latter. For the phenolic aldehyde (14) the diastereoselectivity in the formation of the isochromans (21) and (23) was altered to 1 : 1.4.

In an attempt to alter the ratio of the isochromanols (21) and (23) produced in the cylization process to further favour the stereochemistry required for (the enantiomer of) glucoside B, the reaction was performed at lower temperatures in view of the recent (1996, 1997) report[10] of temperature-dependent diastereoselectivity in the formation of related isochromans by another method. When silica gel was used the observed ratio (1.3 : 1) was the same at 0°C, but was changed to 2.2 : 1 at –50°C. No cyclization occurred at –78°C. When titanium tetrachloride was used at –78°C, the ratio was unaltered at 1 : 1.4.

Conclusions

Intramolecular cyclization of the asymmetric phenolic aldehyde (14) under the mild conditions of chromatography over silica gel afforded the epimeric mixture of asymmetric *trans*-1,3-dimethyl isochroman-4-ols (21) and (23). The corresponding *cis*-1,3-dimethyl 4-ol (25) was similarly available from the aldehyde (17). In these instances, only cyclization *para* to the phenol was an option, leading to the formation of 4,7-diols.

Experimental

General

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Optical rotations were measured with an Optical Activity PolAAr 2001 polarimeter for chloroform solutions of *c* 1.0 at 20°C. Elemental analyses were carried out by the Canadian Microanalytical Service Ltd. Infrared (i.r.) spectra were recorded as KBr disks or, as indicated in the text, Nujol mulls for solids and as thin films between NaCl plates for oils; a Perkin Elmer 1720-X Fourier-transform spectrometer was used. Mass spectra were obtained on a Hewlett Packard S989 spectrometer operating in the electron impact mode at 35 eV (at the University of Western Australia). Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Bruker AM-300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75.5 MHz), or, where indicated, on a Bruker ARX-500 spectrometer. The spectra were run at ambient temperature in (D)chloroform solution, with the internal standard being tetramethylsilane ($SiMe_4$) (δ 0.00) for ^{1}H n.m.r. spectra and $SiMe_4$ (δ 0.00) and chloroform (δ 77.00) for ^{13}C n.m.r. spectra. In the ^{13}C n.m.r. spectra, assignments of signals with the same superscripts are interchangeable.

All solvents were purified by distillation and, if necessary, were dried according to standard methods. The amount of residual water present in solvents was determined by using a 684 Metrohm Karl Fischer calorimeter. The hydrocarbon solvent referred to as hexane routinely had a b.p. range of 65–70°C. Chromatography refers to dry-packed columns of Merck silica gel 60 (70–230 mesh). Preadsorption was carried out on Merck silica gel 60 (35–70 mesh). The adsorbent for radial chromatography was Merck silica gel 60 PF_{254}.

Standard workup refers to extraction with an organic solvent, then washing of the organic extracts with water and brine, drying of the organic layer with anhydrous magnesium sulfate and concentration under reduced pressure.

3-Benzyloxy-2-methoxybenzaldehyde (8)

The phenol (7)[4] (2.70 g, 11.8 mmol) in dry dimethylformamide (50 cm^3) was treated with iodomethane (4.00 cm^3, 60.0 mmol) in the presence of anhydrous potassium carbonate (4.15 g, 30.0 mmol) and the mixture heated at 60°C overnight in an atmosphere of nitrogen. Standard workup with diethyl ether followed by column chromatography (10% ethyl acetate–hexane) yielded the product as a cream solid (2.68 g, 94%). Recrystallization from ethyl acetate/hexane gave the methyl ether (8) as fine white *needles*, m.p. 77–78°C (Found: C, 74.4; H, 5.9. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%). ν_{max} 1676, 1597, 1578, 1481, 1459 cm^{-1}. δ_H 4.02, s, OCH_3; 5.15, s, OCH_2; 7.09, t, *J* 8.0 Hz, H 5; 7.20, dd, *J* 1.6 and 8.0 Hz, H 4; 7.32–7.47, m, C_6H_5 and H 6; 10.44, s, CHO. δ_C 62.4, OCH_3; 71.2 CH_2; 119.8, C 6;[a] 120.2, C 5;[a] 124.1, C 4;[a] 127.4, C 2′, C 6′;[b] 128.2, C 4′; 128.7, C 3′, C 5′;[b] 130.0, C 1; 136.4, C 1′; 152.1, C 3;[c] 153.2, C 2;[c] 190.1, CHO. *m/z* 242 (M, 100%), 151 (12), 150 (9), 149 (9), 136 (8), 121 (8), 108 (12).

1-(3′-Benzyloxy-2′-methoxyphenyl)ethanol (9)

Methyl iodide (6.50 cm^3, 103 mmol) was added dropwise to dry magnesium turnings (1.26 g, 51.6 mmol), in dry ether (50 cm^3) at room temperature in a nitrogen atmosphere. The mixture was allowed to stir for 30 min, after which a solution of the aldehyde (8) (2.50 g, 10.3 mmol) in dry ether (50 cm^3) was added dropwise. After addition was complete, the mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous ammonium chloride solution. The organic layer was separated and washed with water, dried and evaporated. The residue (3.11 g) was purified by column chromatography (twice) with 20–50% ethyl acetate–hexane as eluent to provide the alcohol (9) (2.51 g, 94%) as a pale yellow *oil* (Found: C, 74.2; H, 7.1. $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.0%). ν_{max} 3405, 1588, 1470 cm^{-1}. δ_H 1.50, d, *J* 6.4 Hz, 1-CH_3; 2.53, br s, OH; 3.92, s, OCH_3; 5.10, s, OCH_2; 5.14, q, partially obscured by OCH_2 signal, *J* 6.4 Hz, H 1; 6.90, dd, *J* 3.1 and 6.6 Hz, H 4′; 6.98–7.05, m, H 5′, 6′; 7.30–7.46, m, C_6H_5. δ_C 23.9, C 2; 61.0, OCH_3; 66.1, C 1; 70.8, CH_2; 113.4, C 6′;[a] 118.5, C 5′;[a] 124.1, C 4′;[a] 127.3, C 2″, C 6″;[b] 128.0, C 4″; 128.6, C 3″, C 5″;[b] 137.0, C 1′; 139.2, C 1″; 146.6, C 3′;[c] 151.6 C 2′.[c] *m/z* 258 (M, 23%), 151 (12), 150 (100), 149 (17), 135 (24).

3′-Benzyloxy-2′-methoxy-α′-methylbenzyl 2,2,2-Trichloroacetimidate (10)

The alcohol (9) (1.00 g, 3.88 mmol) in dry ether (10 cm^3) was added very slowly (over approx. 10 min) to a stirred suspension of sodium hydride (23 mg, 0.97 mmol; NaH as a 60% oil suspension, washed with dry hexane before use) in dry ether (10 cm^3) at room temperature in an atmosphere of nitrogen. After evolution of hydrogen ceased (10–15 min) the mixture was cooled to –10°C (ice/salt bath). The mixture was allowed to stir for 10 min at this temperature before the slow addition (over approx. 10 min) of trichloroacetonitrile (0.39 cm^3, 3.88 mmol). During this addition the bath temperature was maintained between –10 and 0°C. After the addition was complete, the

mixture was stirred for a further 30 min at this temperature and then for another 30 min at room temperature. The mixture was then concentrated and the residue dissolved in hexane (10 cm^3) and methanol (0.200 cm^3) and shaken vigorously for 1 min. Any insoluble material was removed by filtration, the residue washed with a little more hexane and the filtrate and washings were concentrated to give an orange oil (1.82 g). The crude product was purified by column chromatography with 10% ethyl acetate–hexane/0.5% Et_3N to give the imidate (10) (1.50 g, 96%) as a pale yellow *oil* (Found: M^+ {2×^{35}Cl, ^{37}Cl} 403.0311, and M^+ {2×^{37}Cl, ^{35}Cl} 405.0291. $C_{18}H_{18}Cl_3NO_3$ requires M^+ {2×^{35}Cl, ^{37}Cl} 403.0323, and M^+{2x^{37}Cl, ^{35}Cl} 405.0293). ν_{max} 3338, 1664, 1591, 1472 cm^{-1}. δ_H 1.61, d, *J* 6.5 Hz, α′-CH_3; 3.97, s, OCH_3; 5.11, s, OCH_2; 6.33, q, *J* 6.5 Hz, H α′; 6.91, dd, *J* 1.6 and 8.0 Hz, H 4′; 7.03, t, *J* 8.0 Hz, H 5′; 7.10, dd, *J* 1.6 and 8.0 Hz, H 6′; 7.29–7.47, m, C_6H_5; 8.29, br s, NH. δ_C 21.8, ArCH**C**H_3, 60.7, s, OCH_3; 70.7, C α′; 72.5, CH_2; 91.8, C 2; 113.4, C 6′;[a] 117.9, C 4′;[a] 124.2, C 5′;[a] 127.3, C 2′′, C 6′′;[b] 127.9, C 4′′; 128.6, C 3′′, C 5′′;[b] 135.8, C 1′; 137.0, C 1′′; 146.1, C 3′;[c] 151.5, C 2′;[c] 161.5, C 1. *m/z* 405 (M^+ {2×^{37}Cl, ^{35}Cl}, 6%), 403 (M^+ {2×^{35}Cl,^{37}Cl}, 21), 401 (M^+ {3×^{35}Cl}, 21), 374 (27), 372 (83), 370 (91), 314 (19), 312 (100), 310 (99), 240 (20), 149 (16), 91 (100), 77 (11).

*Ethyl (α′*R *or* S,*2S)-2-(3′-Benzyloxy-2′-methoxy-α′-methylbenzyloxy)propanoate (11)*

A solution of the imidate (10) (3.66 g, 9.10 mmol) and ethyl (*S*)-lactate (2.10 cm^3, 18.2 mmol) in a mixture of hexane (30 cm^3) and dichloromethane (15 cm^3) was treated with boron trifluoride diethyl etherate (0.19 cm^3) under an atmosphere of nitrogen and the mixture stirred at room temperature overnight. The resulting solid was removed by filtration and the filtrate poured into saturated sodium hydrogencarbonate solution. The organic layer was separated and the aqueous phase extracted with dichloromethane. The combined organic extracts were washed with water, dried and evaporated. The crude residue (4.04 g) was subjected to column chromatography with 10% ethyl acetate–hexane/0.5% Et_3N to afford the esters (2.78 g, 85%), a pale yellow oil, as a mixture of two inseparable diastereomers in a ratio of approximately 75 : 25. Further purification by Kugelrohr distillation gave the esters (11) as a colourless *oil*, b.p. 203–213°C/0.3 mmHg (Found: C, 69.8; H, 7.2%; M^+, 358.1776. $C_{21}H_{26}O_5$ requires C, 70.4; H, 7.3%; M^+, 358.1780). $[\alpha]_D$ –57.5° (*c*, 1.1 in $CHCl_3$). ν_{max} (thin film). 1740, 1587, 1471 cm^{-1}. δ_H (500 MHz; major diastereomer) 1.29, t, *J* 7.1 Hz, C**H**$_3$CH$_2$; 1.35, d, *J* 6.9 Hz, 2-CH_3; 1.47, d, *J* 6.4 Hz, α′-CH_3; 3.83, s, OCH_3; 3.84, q, *J* 6.9 Hz, H 2; 4.20, 4.24, dq, *J* 10.8 and 7.1 Hz, each 1H, CH_3C**H**$_2$; 4.96, q, *J* 6.4 Hz, H α′; 5.11, s, OCH_2; 6.86–7.13, m, H 4′, 5′ and 6′; 7.30–7.47, m, C_6H_5. δ_H (minor diastereomer) 1.18, t, *J* 7.1 Hz, C**H**$_3$CH$_2$; 1.42, d, *J* 6.7 Hz, 2-CH_3; 1.46, d, *J* 6.4 Hz, α′-CH_3; 3.88, s, OCH_3; 3.98, q, *J* 6.7 Hz, H 2; 4.03, 4.05, dq, *J* 10.8 and 7.1 Hz, each 1H, CH_3C**H**$_2$; 5.03, q, *J* 6.4 Hz, H α′; 5.10, s, OCH_2; 6.86–7.13, m, H 4′, 5′ and 6′; 7.30–7.47, m, C_6H_5. δ_C (75.5 MHz; mixture of two diastereomers) 14.1, 14.2 **C**H_3CH$_2$; 18.2, 19.0, C 3; 23.2, 23.6, ArCH**C**H_3; 60.6, 60.7, CH_3**C**H_2; 60.8, 60.9, OCH_3; 70.7, 70.8, OCH_2; 71.1, C α′; 72.2, 72.8, C 2; 113.0, C 6′;[a] 118.5, 119.3, C 4′;[a] 124.1, 124.3, C 5′;[a] 127.3, C 2′′, C 6′′;[b] 127.9, C 4′′; 128.6, C 3′′, C 5′′;[b] 137.0, C 1′; 137.1, C 1′′; 146.5, 147.1, C 3′;[c] 151.4, 151.5, C 2′;[c] 173.0, 173.9, C 1. *m/z* 358 (M^+, 99%), 343 (11), 279 (15), 267 (16), 241 (100), 167 (18), 151 (94), 135 (23), 107 (33).

*(α′*S,*2S)- and (α′*R,*2S)-2-(3′-Benzyloxy-2′-methoxy-α′-methylbenzyloxy)propan-1-ol (12) and (15)*

A solution of the esters (11) (2.09 g, 5.85 mmol) in dry ether (20 cm^3) was added dropwise to a suspension of lithium aluminium hydride (935 mg, 23.4 mmol) in dry ether (20 cm^3) at room temperature under nitrogen. The mixture was allowed to stir at room temperature for 2 h. Saturated aqueous ammonium chloride solution was added to quench the reaction, followed by anhydrous magnesium sulfate. The solid was removed by filtration and the filtrate concentrated to give the alcohols as a yellow oil (1.79 g). Repeated chromatography (5–50% ethyl acetate–hexane/0.5% Et_3N) was required to separate the two alcohols:

(i) R_F 0.26 (30% ethyl acetate–hexane). The higher R_F alcohol (15) was obtained as a pale yellow oil (344 mg, 19%). Kugelrohr distillation afforded a colourless *oil*, b.p. 179–185°C/0.3 mmHg (Found: C, 72.5; H, 7.5. $C_{19}H_{24}O_4$ requires C, 72.1; H, 7.6%). $[\alpha]_D$ +56.3°. ν_{max} (thin film) 3450, 1586, 1498, 1478, 1457 cm^{-1}. δ_H 1.14, d, *J* 6.0 Hz, 2-CH_3; 1.45, d, *J* 6.5 Hz, α′-CH_3; 2.26, br s, OH; 3.41–3.48, m, H 1α, H 2, H 1β; 3.89, s, OCH_3; 5.05, q, *J* 6.5 Hz, H α′; 5.10, s, OCH_2; 6.89, dd, *J* 2.8 and 6.7, H 4′; 7.01–7.08, m, H 5′, 6′; 7.30–7.47, m, C_6H_5. δ_C 16.1, C 3; 23.3, ArCH**C**H_3; 61.0, OCH_3; 66.8, C 1; 68.9, C α′; 70.7, CH_2; 73.3, C 2; 113.1, C 6′;[a] 118.8, C 4;[a] 124.4, C 5′;[a] 127.3, C 2′′ and C 6′′;[b] 127.9, C 4′′; 128.6, C 3′′, C 5′′;[b] 136.9, C 1′; 137.3, C 1′′; 146.9, C 3′;[c] 151.6, C 2′.[c] *m/z* 316 (M, 21%), 240 (32), 150 (27), 91 (100), 77 (15).

(ii) The lower R_F (0.23) alcohol (12) was isolated as a pale yellow *oil* (1.05 g, 57%; combined yield of the alcohols 76%; ratio (12) to (15) was approximately 75 : 25) (Found: M^+, 316.1668. $C_{19}H_{24}O_4$ requires M^+, 316.1675). $[\alpha]_D$ –25.3°. ν_{max} (thin film) 3442, 1588, 1469 cm^{-1}. δ_H 1.03, d, *J* 6.2 Hz, 2-CH_3; 1.43, d, *J* 6.4 Hz, α′-CH_3; 2.07, br s, OH; 3.45, dd, *J* 5.9 and 11.0 Hz, H 1α; 3.57, ddq, *J* 3.5, 5.9 and 6.2 Hz, H 2; 3.67, dd, *J* 3.5 and 11.0 Hz, H 1β; 3.88, s, OCH_3; 5.05, q, *J* 6.4 Hz, H α′; 5.10, s, OCH_2; 6.88, dd, *J* 2.0 and 7.8 Hz, H 4′; 7.04, t, *J* 7.8 Hz, H 5′; 7.09, dd, *J* 2.0 and 7.8 Hz, H 6′; 7.30–7.47, m, C_6H_5. δ_C 16.1, C 3; 22.3, ArCH**C**H_3; 59.7, OCH_3; 64.6, C 1; 68.6, C α′; 69.5, CH_2; 72.9, C 2; 111.6, C 6′;[a] 117.8, C 4′;[a] 123.0, C 5′;[a] 126.1, C 2′′, C 6′′;[b] 126.8, C 4′′; 127.4, C 3′, C 5′′;[b] 135.8, C 1′; 137.2, C 1′′; 145.2, C 3′;[c] 150.3, C 2′.[c] *m/z* 316 (M^+, 46%), 240 (8), 150 (10), 91 (100), 77 (7).

*Methyl (α′*R *or* S,*2*R*)-2-(3′-Benzyloxy-2′-methoxy-α′-methylbenzyloxy)propanoate (18)*

The method described above for the preparation of the esters (11) was followed, except that 2 mol. equiv. of methyl (*R*)-lactate were used instead of 2 mol equiv. of ethyl (*S*)-lactate, to convert the imidate (10) (1.89 g, 4.70 mmol) into the diastereomeric esters (18), isolated as a pale yellow oil (1.29 g, 80%, after chromatography). Further purification by column chromatography (10% ethyl acetate–hexane/0.5% Et_3N) gave the esters as a colourless *oil* (Found: C, 70.1; H, 6.7%; M^+, 344.1621. $C_{20}H_{24}O_5$ requires C, 69.8; H, 7.0%; M^+, 344.1624). $[\alpha]_D$ +54.8°. ν_{max} (thin film) 1747, 1589, 1469 cm^{-1}. δ_H (500 MHz, major diastereomer) 1.36, d, *J* 6.9 Hz, 2-CH_3; 1.47, d, *J* 6.4 Hz, α′-CH_3; 3.75, s, CO_2CH_3; 3.83, s, OCH_3; 3.86, q, *J* 6.9 Hz, H 2; 4.96, q, *J* 6.4 Hz, H α′; 5.11, m, OCH_2; 6.83–7.13, m, H 4′, 5′, 6′; 7.31–7.47, m, C_6H_5. δ_H (minor diastereomer) 1.43, d, *J* 6.7 Hz, 2-CH_3; 1.46, d, *J* 6.4 Hz, α′-CH_3; 3.59, s, CO_2CH_3; 3.89, s, OCH_3; 4.01, q, *J* 6.7 Hz, H 2; 5.04, q, *J* 6.4 Hz, H α′; 5.11, m, OCH_2; 6.83–7.13, m, H 4′, 5′, 6′; 7.31–7.47, m, C_6H_5. δ_C (75.5 MHz; mixture of two diastereomers) 18.2, 19.1, C 3; 23.2, 23.6, ArCH**C**H_3; 51.7, 51.8, CO_2**C**H_3; 60.8, 60.9, OCH_3; 70.5, 71.1, C α′; 70.7, CH_2; 72.2, 72.7, C 2; 113.0, 113.1, C 6′;[a] 118.4, 119.2, C 4′;[a] 124.2, 124.3, C 5′;[a] 127.3, C 2′′, C 6′′;[b] 127.92, 127.95, C 4′′; 128.56, 128.58, C 3′′, C 5′′;[b] 136.9, 137.0, C 1′; 137.04, C 1′′; 151.4, C 3′;[c] 151.5, C 2′;[c] 173.4, 174.3, **C**O_2CH_3. *m/z* 344 (M^+, 100%), 257 (20), 241 (55), 151 (49), 150 (57), 149 (33), 135 (24), 119 (14).

*(α′*R,*2*R)- and (α′*S,*2*R)-2-(3′-Benzyloxy-2′-methoxy-α′-methylbenzyloxy)propan-1-ol (19) and (20)*

The mixture of the diastereomeric esters (18) (1.07 g, 3.11 mmol) was reduced with lithium aluminium hydride (4 mol. equiv.), as described above for the reduction of the esters (11), to afford the corresponding alcohols (19) and (20) as a yellow oil (855 mg). Repeated column chromatography with 5–50% ethyl acetate–hexane/0.5% Et_3N as eluent resulted in the separation of the two alcohols (total yield 66%; ratio (19) to (20) of approximately 75 : 25):

(i) The higher R_F alcohol (20) was obtained as a pale yellow oil (167 mg, 17%). Distillation produced (20) as a colourless oil, b.p. 185–195°C/0.3 mmHg (Kugelrohr); $[\alpha]_D$ –58.8°. The ^{1}H n.m.r. spectrum (300 MHz) was identical to that reported for the enantiomeric alcohol (15).

(ii) The lower R_F alcohol (19) was isolated as a pale yellow oil (481 mg, 49%); $[\alpha]_D$ +25.4°. The ^{1}H n.m.r. spectrum (300 MHz) was identical to that reported above for (12).

*(α′*S,*2S)-2-(3′-Benzyloxy-2′-methoxy-α′-methylbenzyloxy)propanal (13)*

A solution of dimethyl sulfoxide (1.40 cm^3, 20.0 mmol) in dry dichloromethane (5 cm^3) was added dropwise to a solution of oxalyl

chloride (0.88 cm^3, 10.0 mmol) in anhydrous dichloromethane (10 cm^3) at –70°C under a nitrogen atmosphere. After stirring for 20 min at this temperature, a solution of the alcohol (12) (633 mg, 2.00 mmol) in dry dichloromethane (8 cm^3) was added dropwise and the stirring continued for 15 min. Dry triethylamine (3.30 cm^3, 23.8 mmol) was then added dropwise and, after a further 5 min at –70°C, the mixture was allowed to warm to room temperature. Water was then added and the organic layer separated. The aqueous phase was extracted with dichloromethane . The combined organic extracts were washed successively with dilute hydrochloric acid solution, water, saturated sodium hydrogencarbonate solution, water and brine, and then dried and evaporated to give an orange oil (702 mg). The crude product was purified by column chromatography (hexane–10% ethyl acetate–hexane/0.5% Et_3N) to afford the aldehyde (13) as a pale yellow oil (502 mg, 80%). Further chromatography and distillation furnished a colourless *oil*, b.p. 175–185°C/0.3 mmHg (Kugelrohr) (Found: C, 72.3; H, 6.9. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.0%). $[\alpha]_D$ –75.9° (*c*, 0.5 in $CHCl_3$). ν_{max} (thin film) 1733, 1586, 1498, 1479, 1455 cm^{-1}. δ_H 1.22 d, *J* 7.0 Hz, 2-CH_3; 1.50, d, *J* 6.4 Hz, α′-CH_3; 3.71 dq, *J* 2.0 and 7.0 Hz, H 2; 3.83, s, OCH_3; 5.01, q, *J* 6.4 Hz, H α′; 5.11, s, OCH_2; 6.90, t, *J* 7.8 Hz, H 5′; 7.04–7.06, m, H 4′, 6′; 7.30–7.47, m, C_6H_5; 9.72, d, *J* 2.0 Hz, H 1. δ_C 15.9, C 3; 23.5, ArCH**C**H_3; 60.9, OCH_3; 70.7, CH_2; 71.3, C α′; 77.8, C 2; 113.2, C 6′;[a] 118.5, C 5′;[a] 124.3, C 4′;[a] 127.3, C 2′′, C 6′′;[b] 128.0, C 4′′; 128.6, C 3′′, C 5′′;[b] 136.6, C 1′; 136.9, C 1′′; 146.9, C 3′;[c] 151.5, C 2′;[c] 204.2, C 1. *m/z* 314 (M, 29%), 241 (100), 137 (14), 107 (7).

(α′R,2S)-2-(3′-Benzyloxy-2′-methoxy-α′-methylbenzyloxy)propanal (16)

Utilizing the procedure described above for the preparation of the aldehyde (13) from alcohol (12), the alcohol (15) (295 mg, 0.93 mmol) was transformed into the aldehyde (16), which was isolated as an orange oil (298 mg). Purification of this crude oil by column chromatography (hexane–10% ethyl acetate–hexane/0.5% Et_3N) provided the aldehyde (16) as a pale yellow oil (226 mg, 77%). Further chromatography and distillation yielded the pure product as a colourless *oil*, b.p. 155–167°C/0.3 mmHg (Kugelrohr) (Found: C, 72.2; H, 7.0. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.0%). $[\alpha]_D$ +17.5°. ν_{max} (thin film) 1734, 1583, 1479, 1456 cm^{-1}. δ_H 1.29, d, *J* 6.8 Hz, 2-CH_3; 1.49, d, *J* 6.4 Hz, α′-CH_3; 3.76, dq, *J* 1.5 and 6.8 Hz, H 2; 3.87, s, OCH_3; 5.09, q, *J* 6.4 Hz, H α′; 5.10, s, OCH_2; 6.89, dd, *J* 2.0 and 7.8 Hz, H 4′; 7.04, t, *J* 7.8 Hz, H 5′; 7.09, dd, *J* 2.0 and 7.8 Hz, H 6′; 7.30–7.47, m, C_6H_5; 9.51, d, *J* 1.5 Hz, H 1. δ_C 15.1, C 3; 23.3, ArCH**C**H_3; 61.0, OCH_3; 70.2, C α′; 70.7, CH_2; 78.2, C 2; 113.3, C 6′;[a] 118.9, C 4′;[a] 124.4, C 5′;[a] 127.3, C 2′′, C 6′′;[b] 128.0, C 4′; 128.6, C 3′′, C 5′′;[b] 136.6, C 1′; 136.9, C 1′′; 146.9, C 3′;[c] 151.5, C 2′;[c] 203.5, C 1. *m/z* 314 (M, 65%), 241 (100), 151 (45), 137 (21), 135 (21), 107 (12), 91 (100), 63 (27).

(α′S,2S)-2-(3′-Hydroxy-2′-methoxy-α′-methylbenzyloxy)propanal (14)

A stirred suspension of the benzyl ether (13) (435 mg, 1.39 mmol) and 10% palladium on carbon catalyst (560 mg) in ethyl acetate (10 cm^3) was subjected to an atmosphere of hydrogen for 2 h. The catalyst was then removed by filtration through a pad of Celite, a further amount of catalyst (560 mg) added and the suspension subjected to a hydrogen atmosphere for a further 2 h. Filtration through Celite and concentration of the filtrate furnished the unstable phenol (14) as a yellow oil (290 mg, 93%) which was used immediately for subsequent reactions. ν_{max} (thin film) 3413, 1732, 1591, 1475, 1440 cm^{-1}. δ_H 1.21, d, *J* 7.0 Hz, 2-CH_3; 1.53, d, *J* 6.4 Hz, α′-CH_3; 3.70, dq, *J* 2.0 and 7.0 Hz, H 2; 3.75, s, OCH_3; 4.92, q, *J* 6.4 Hz, H α′; 5.81, br s, OH; 6.89, dd, *J* 1.8 and 7.8 Hz, H 4′; 6.97, dd, *J* 1.8 and 7.8 Hz, H 6′; 7.05, t, *J* 7.8 Hz, H 5′; 9.70, d, *J* 2.0 Hz, H 1. δ_C 15.8, C 3; 23.5, ArCH**C**H_3; 61.8, OCH_3; 71.0, C α′; 77.7, C 2; 115.3, C 6′;[a] 118.2, C 4′;[a] 125.4, C 5′;[a] 136.0, C 1′; 144.9, C 3′;[b] 148.8, C 2′;[b] 204.0, C 1. *m/z* 224 (M, 10%), 151 (100), 136 (35), 107 (6), 91 (14), 77 (6).

(α′R,2S)-2-(3′-Hydroxy-2′-methoxy-α′-methylbenzyloxy)propanal (17)

The benzyl ether (16) (173 mg, 0.55 mmol) was subjected to hydrogenolysis, according to the method described above for the benzyl ether (13), to afford the phenol (17) as a yellow oil (112 mg, 91%) which was used immediately for subsequent reactions. ν_{max} (thin film) 3406, 1732, 1593, 1472 cm^{-1}. δ_H 1.29, d, *J* 6.8 Hz, 2-CH_3; 1.53, d, *J* 6.4 Hz, α′-CH_3; 3.75, dq, *J* 1.7 and 6.8 Hz, H 2; 3.79, s, OCH_3; 4.98, q, *J* 6.4 Hz, H α′; 5.60, br s, OH; 6.88, dd, *J* 2.0 and 7.8 Hz, H 4′; 7.02–7.05, m, H 5′, 6′; 9.45, d, *J* 1.7 Hz, H 1. δ_C 15.2, C 3; 23.2, ArCH**C**H_3; 62.0, OCH_3; 70.2, C α′; 78.2, C 2; 115.4, C 6′;[a] 118.6, C 4′;[a] 125.6, C 5′;[a] 135.9, C 1′; 144.9, C 3′;[b] 148.7, C 2′;[b] 203.3, C 1. *m/z* 224 (M, 61%), 151 (100), 136 (20), 107(8), 91 (8), 77 (4).

(1S,3S,4R)- and (1S,3S,4S)-8-Methoxy-1,3-dimethylisochroman-4,7-diols (21) and (23)

The crude phenol (14) (110 mg, 0.49 mmol) was subjected to column chromatography on silica gel with 5–50% ethyl acetate–hexane/trace Et_3N as eluent to provide the cyclized product (76 mg, 69%) as a mixture of inseparable diastereomers (21) and (23) in a ratio of approximately 1.3 : 1. ν_{max} (thin film) 3352, 1607, 1590, 1493 cm^{-1}. δ_H (major diastereomer (21)) 1.32, d, *J* 6.3 Hz, 3-CH_3; 1.55, d, *J* 6.6 Hz, 1-CH_3; 2.90, br s, 4-OH; 3.77, s, OCH_3; 3.84, dq, *J* 7.4, 6.3 Hz, H 3; 4.24, d, *J* 7.4 Hz, H 4; 5.04, q, *J* 6.6 Hz, H 1; 5.86, br s, 7-OH; 6.80–6.85, m, H 5, 6. δ_H (minor diastereomer (23)) 1.35, d, *J* 6.4 Hz, 3-CH_3; 1.50, d, *J* 6.7 Hz, 1-CH_3; 2.70, br s, 4-OH; 3.76, s, OCH_3; 4.08, dq, *J* 1.6 and 6.4 Hz, H 3; 4.15, d, *J* 1.6 Hz, H 4; 5.10, q, *J* 6.7 Hz, H 1; 5.75, br s, 7-OH; 7.03, 7.13, d, *J* 8.3 Hz, H 6, 5. δ_C (mixture of two diastereomers) 17.0, 18.0, 3-CH_3; 19.0, 20.2, 1-CH_3; 60.3, OCH_3; 66.5, 69.4, C 3;[a] 67.8, C 1;[a] 68.80, 70.7, C 4;[a] 123.6, 128.2, C 6;[b] 126.5, 128.6, C 5;[b] 132.3, C 8a;[c] 133, C 4a;[c] 142.3, C 7;[d] 142.5, C 8.[d]

(1S,3S,4R)- and (1S,3S,4S)-4,7-Diacetoxy-8-methoxy-1,3-dimethylisochromans (22) and (24)

The crude mixture of the diols (76 mg, 0.34 mmol) was immediately dissolved in dry pyridine (2 cm^3) and acetic anhydride (2 cm^3) and stirred at room temperature for 20 h. Water and ether were added and stirring was continued (3 h). The organic layer was separated and then washed with water, dilute hydrochloric acid, water and then brine, dried and concentrated to give the diacetates as a yellow oil (83 mg, 79% combined crude yield). Examination of the crude product by t.l.c. and ^1H n.m.r. spectroscopy showed two major products (similar R_F by t.l.c.) and no other material. Separation of the two diacetates was achieved by column chromatography (10% ethyl acetate–hexane/0.5% Et_3N) followed by p.l.c. (20% ethyl acetate–hexane) to yield:

(i) The higher R_F (0.32, 30% ethyl acetate–hexane) product (22) (35 mg, 33%) as a pale yellow *oil* (Found: C, 62.6; H, 6.8%; M^+, 308.1248. $C_{16}H_{20}O_6$ requires C, 62.3; H, 6.5%; M^+, 308.1260). $[\alpha]_D$ –66.3° (*c*, 0.7 in $CHCl_3$). ν_{max} (thin film) 1772, 1742, 1490 cm^{-1}. δ_H 1.25, d, *J* 6.3 Hz, 3-CH_3; 1.59, *J* 6.6 Hz, 1-CH_3; 2.16, s, 4-$OCOCH_3$; 2.34, s, 7-$OCOCH_3$; 3.81, s, OCH_3; 4.06, dq, *J* 7.4 and 6.3 Hz, H 3; 5.07, q, *J* 6.6 Hz, H 1; 5.70, d, *J* 7.4 Hz, H 4; 6.93–6.98, m, H 5, 6. δ_C 18.1, 3-CH_3; 20.0, 1-CH_3; 20.9, 4-OCO**C**H_3;[a] 21.2, 7-OCO**C**H_3;[a] 60.7, OCH_3; 66.5, C 4;[b] 67.8, C 3;[b] 71.2, C 1;[b] 122.3, C 5; 123.3, C 6; 131.1, C 8a;[c] 134.7, C 4a;[c] 142.6, C 8; 147.1, C 7; 168.8, 4-O**C**OCH_3;[d] 171.1, 7-O**C**OCH_3. *m/z* 308 (M, 16%), 293 (11), 266 (11), 264 (9), 248 (20), 233 (42), 222 (16), 206 (60), 191 (85), 180 (100), 163 (12), 149 (24).

(ii) The lower R_F (0.29, 30% ethyl acetate–hexane) diacetate (22) (27 mg, 26%) as a pale yellow *oil* (Found: C, 62.3; H, 6.9%; M^+, 308.1265. $C_{16}H_{20}O_6$ requires C, 62.3; H, 6.5%; M, 308.1260). $[\alpha]_D$ +122.5° (*c*, 0.6 in $CHCl_3$). ν_{max} (thin film) 1773, 1742, 1593, 1462 cm^{-1}. δ_H 1.27, d, *J* 6.4 Hz, 3-CH_3; 1.53, d, *J* 6.7 Hz, 1-CH_3; 2.11, s, 4-$OCOCH_3$; 2.34, s, 7-$OCOCH_3$; 3.83, s, OCH_3; 4.21, dq, *J* 2.0 and 6.4 Hz, H 3; 5.20, q, *J* 6.7 Hz, H 1; 5.77, d, *J* 2.0 Hz, H 4; 6.98, d, *J* 8.4 Hz, H 6; 7.14, d, *J* 8.4 Hz, H 5. δ_C 16.8, 3-CH_3; 18.9, 1-CH_3; 20.9, 4-OCO**C**H_3;[a] 21.1, 7-OCO**C**H_3;[a] 60.7, OCH_3; 64.8, C 4;[b] 67.6, C 3;[b] 68.6, C 1;[b] 122.5, C 5; 126.0, C 6; 130.5, C 8a;[c] 134.4, C 4a;[c] 143.2, C 7; 147.2, C 8; 168.8, 4-O**C**OCH_3;[d] 171.0, 7-O**C**OCH_3.[d] *m/z* 264 [(M–CH_3CHO), 21%], 248 (13), 233 (24), 206 (13), 191 (41), 180 (100), 163 (18), 149 (19), 113 (11).

*(1*R,*3*S,*4*R*)-8-Methoxy-1,3-dimethylisochroman-4,7-diol (25)*

The crude phenol (17) (63 mg, 0.28 mmol) was subjected to column chromatography (5–50% ethyl acetate–hexane/trace Et_3N) to produce the cyclized product as a single diastereomer as a pale yellow oil (36 mg, 57%). ν_{max} (thin film) 3348, 1610, 1585, 1490 cm^{-1}. δ_H 1.41, d, *J* 6.1 Hz, 3-CH_3; 1.57, d, *J* 6.3 Hz, 1-CH_3; 1.88, br s, 4-OH; 3.38, dq, *J* 8.9, 6.1 Hz, H 3; 3.73, s, OCH_3; 4.31, d, *J* 8.9 Hz, H 4; 5.01, q, *J* 6.3 Hz, H 1; 5.79, br s, 7-OH; 6.89, d, *J* 8.4 Hz, H 6; 7.24, dd, *J* 0.65, 8.4 Hz, H 5. δ_C 18.3, 3-CH_3; 21.4, 1-CH_3; 60.0, OCH_3; 71.0, C 3;[a] 71.2, C 4;[a] 75.1, C 1;[a] 114.7, C 5;[b] 122.2, C 6;[b] 131.1, C 8a;[c] 132.6, C 4a;[c] 142.6, C 7;[d] 148.2, C 8.[d]

*(1*R,*3*S,*4*R*)-4,7-Diacetoxy-8-methoxy-1,3-dimethylisochroman (26)*

The crude cyclized product (25) (36 mg, 0.16 mmol) was immediately converted into the diacetate, according to the method described above for the mixture of diols (21) and (23), to provide the product (26) as a pale yellow oil. Purification by column chromatography (10–20% ethyl acetate–hexane/0.5% Et_3N) afforded the pure diacetate (26) as a pale yellow *oil* (38 mg, 77%) (Found: C, 62.4; H, 6.6%; M^+, 308.1265. $C_{16}H_{20}O_6$ requires C, 62.3; H, 6.5%; M^+, 308.1260). $[\alpha]_D$ +16.0° (*c*, 0.9 in $CHCl_3$). ν_{max} (thin film) 1769, 1743, 1590, 1485, 1453 cm^{-1}. δ_H 1.30, d, *J* 6.2 Hz, 3-CH_3; 1.56, d, *J* 6.3 Hz, 1-CH_3; 2.18, s, 4-$OCOCH_3$; 2.34, s, 7-$OCOCH_3$; 3.60, dq, *J* 9.0, 6.2 Hz, H 3; 3.78, s, OCH_3; 5.02, q, *J* 6.3 Hz, H 1; 5.75, d, *J* 9.0 Hz, H 4; 6.89, dd, *J* 0.6 and 8.4 Hz, H 5; 6.97, d, *J* 8.4 Hz, H 6. δ_C 18.2, 3-CH_3; 20.9, 1-CH_3; 21.1, 4-$OCO\mathbf{C}H_3$;[a] 21.9, 7-$OCO\mathbf{C}H_3$;[a] 60.5, OCH_3; 71.2, C 4;[b] 71.3, C 3;[b] 72.0, C 1;[b] 121.2, C 5; 122.0, C 6; 133.6, C 8a;[c] 134.2, C 4a;[c] 142.6, C 7; 147.7, C 8; 169.0, 4-$O\mathbf{C}OCH_3$;[d] 170.9, 7-$O\mathbf{C}OCH_3$.[d] *m/z* 264 [(M–CH_3CHO), 37%], 222 (26), 206 (15), 190 (23), 180 (100), 179 (23), 149 (10).

Variable-Temperature Cyclizations

(a) Using silica gel. A solution of the phenol (0.27 mmol) in dry dichloromethane (2 cm^3) was added to a slurry of silica gel (1.0 g) in dry dichloromethane (3 cm^3) and a drop of triethylamine in an atmosphere of nitrogen at the desired bath temperature. The mixture was stirred at this temperature for 3 h. Filtration through Celite and concentration of the filtrate gave the crude diol(s). This crude reaction mixture was immediately converted into the corresponding diacetate(s), and the ratio/purity was determined by ^1H n.m.r. spectroscopy.

(b) Using titanium isopropoxide. A solution of the phenol (0.45 mmol) in dry dichloromethane (8 cm^3) was treated with neat titanium tetraisopropoxide (0.51 mmol) in a nitrogen atmosphere at the desired bath temperature. The mixture was stirred at this temperature for 5 h. It was then poured into more dichloromethane, saturated sodium fluoride solution was added and the whole stirred vigorously until the colour had discharged (24 h). Standard workup (dichloromethane) produced the cyclized product(s). The crude material was immediately acetylated to give the diacetate(s), and the ^1H n.m.r. spectrum determined as in *(a)* above.

Acknowledgments

We thank the Senate of Murdoch University for financial support and for Murdoch University Research Scholarships (to Y.G. and F.J.O.), and for an Overseas Postgraduate Research Scholarship (to F.J.O.).

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