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Regioselectivity in the Syntheses of Enantiopure 2-Benzopyrans through Intramolecular Cyclization of Tethered Lactaldehydes. Conformations of the Products

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Using titanium tetraisopropoxide, the enantiopure tethered lactaldehyde (α′*S*,2*S*)-2-(3′-hydroxy-α′-methylbenzyloxy)propanal (6) is cyclized with complete regio- and diastereoselectivity *ortho* to the phenolic hydroxyl group to give (1*S*,3*S*,4*R*)-3,4-dihydro-1,3-dimethyl-2-benzopyran-4,5-diol (7). Similar cyclization of the epimeric (α′*R*,2*S*)-lactaldehyde (25) yields solely the corresponding (1*R*,3*S*,4*R*)-4,5-diol (34). The 4,5-diacetate (26), but not (35), undergoes conformational inversion of the heterocyclic ring through significant 4,5-*peri* interactions between the adjacent acetoxy substituents. Spontaneous cyclizations of the corresponding phenoxide ions of the lactaldehydes (6) and (25), generated by fluoride from their silyl ethers, led to the related 4,7-diols with high regioselectivity through ring-closure *para* to the aromatic oxygen.

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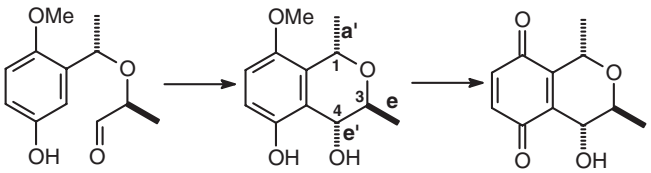
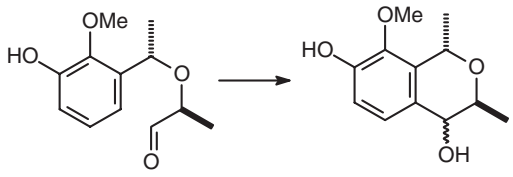
Introduction

In model studies related to the syntheses of the aphid insect pigments the protoaphins,[1] we have studied the cyclizations of two isomeric phenolic lactaldehydes to afford monochiral 2-benzopyrans. In the first of these (Scheme 1),[2] the lactaldehyde (1) afforded the 2-benzopyran-4,5-diol (2) with complete diastereoselectivity, and thence the enantiopure quinone (3) as a model for the assembly of quinone A.[1,3] In the second, the structurally isomeric phenol (4) gave the pair of C4 epimeric 2-benzopyran-4,7-diols (5) with low diastereoselectivity as a model[4] for the synthesis of glucoside B.[1] In each of these two cases only one regioisomer of the 2-benzopyran could be formed, ring closure occurring *ortho* to the activating phenolic substituent in the first case and *para* in the second, since the aromatic methoxy group blocked the alternative possibility. This paper describes conditions to promote either regioselectivity preferentially in the related phenolic lactaldehyde (6), which lacks the blocking methoxy group, when either the 4,5-diol (7) or the 4,7-diols (8) might be sought (Scheme 2).



(1) (2) (3)



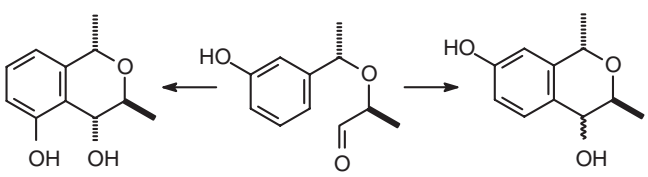
(4) (5)

Scheme 1.

Results and Discussion

Syntheses of the Phenolic Ethers (21)–(24) of the Tethered Lactaldehydes

3-Hydroxyacetophenone was chosen as the starting material for compound (6), into which it was converted by a sequence related to that for the syntheses of analogues (1)[2]



(7) (6) (8)

Scheme 2.

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and (4).[4] In a series of high-yielding reactions, the known benzyl ether (9)[5] (see Diagram 1) was reduced to the alcohol (11) and this was converted,[6] in turn, into the trichloroacetimidate (13), the ^{1}H NMR spectrum of which showed the characteristic NH proton at δ 8.30 and the benzylic α-proton at δ 5.95. The latter signal was strongly deshielded from the corresponding proton (δ 4.80) observed in the precursor alcohol (11). The imidate (13) was treated[4,6,7] with ethyl (*S*)-lactate to form an inseparable mixture of protected lactates (15) in a 55 : 45 ratio and an overall yield of 52% over the four steps from 3-hydroxyacetophenone. This mixture was subsequently reduced to the chromatographically separable mixture of alcohols (17) (52% yield) and (18) (40%). The stereochemistry of each particular diastereoisomer was assumed at this point but confirmation was obtained upon examination of the ^{1}H NMR spectra of the cyclization products obtained later in the synthesis.

The chiral lanthanide NMR shift reagent [Eu(hfc)$_3$] was used to determine[8] the enantiomeric purity of each of the alcohols (17) and (18). The respective enantiomers were assembled from methyl (*R*)-lactate in the same manner, and the specific rotation for each enantiomeric pair agreed closely (except for the sign of rotation). Upon addition of the shift reagent, a 60 : 40 mixture of each alcohol and its enantiomer showed good separation in many of the corresponding signals for the two components in the ^{1}H NMR spectrum. On the other hand, the spectrum for each of the enantiopure alcohols (17) and (18) showed the absence of the respective enantiomer. These experiments established that these diastereoisomeric alcohols were optically pure within the limits of this NMR technique.[2,4,8]

The alcohols were each separately oxidized to lactaldehyde (21) (75% yield) and (22) (80%), respectively, using the Swern procedure.[9] Subsequently, each of these aldehydes was individually reduced with lithium aluminium hydride back to its respective alcohol. Thin-layer chromatography and ^{1}H NMR spectroscopy showed no evidence of more than one diastereoisomeric alcohol, from which it was inferred that racemization had not occurred at the carbon atom positioned α to the aldehyde group during the oxidation step.

The same sequence of transformations converted the *tert*-butyldimethylsilyl ether (10), through the alcohol (12) and the imidate (14), into the inseparable mixture of diastereoisomeric silyloxy-protected lactates (16), and thence into the separated alcohols (19) and (20) (see Diagram 1). The enantiomeric purity of each of these was confirmed as described above for alcohols (17) and (18). Each of the alcohols were individually oxidized to the corresponding lactaldehydes (23) and (24).

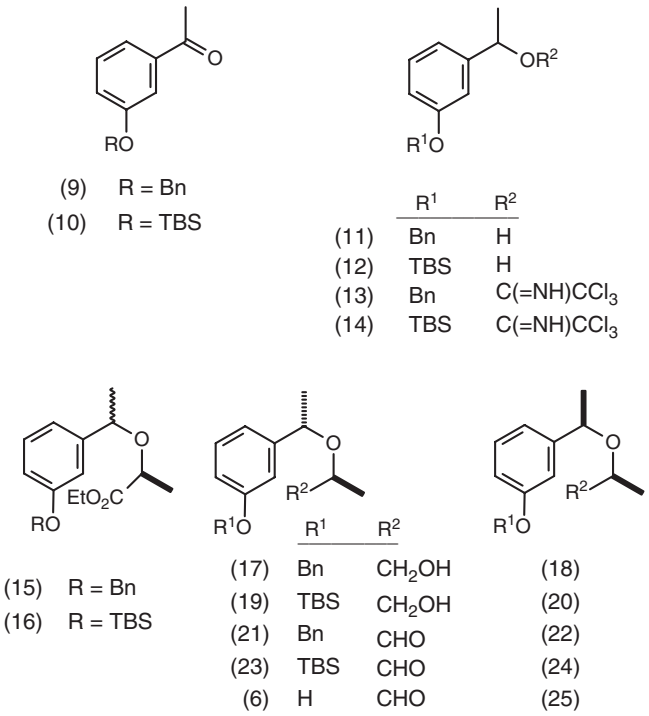


Diagram 1.

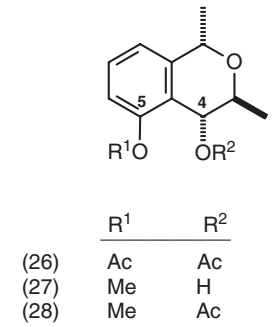
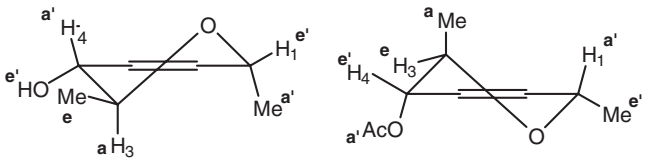


Diagram 2.

Regio- and Diastereoselective Cyclizations to Form the 2-Benzopyran-4,5-diols and Their Derivatives

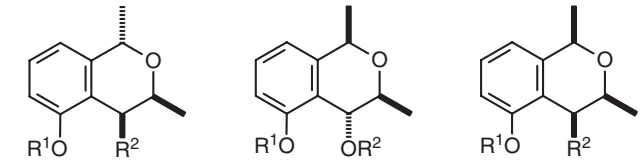
Selective phenolic *O*-debenzylation of the lactaldehyde (21) was achieved using palladium on charcoal followed by rapid chromatography to afford the crude phenol (6) (72% yield). Adventitious sulfur from the Swern oxidation was difficult to remove and poisoned the catalyst. Therefore, the first batch was sacrificed, but the desired hydrogenolysis proceeded smoothly on the second batch. This potentially unstable phenolic lactaldehyde (6) was then cyclized with complete diastereoselectivity using titanium tetraisopropoxide to form the structurally isomeric 2-benzopyran-4,5-diol (7) (73% yield). The high-resolution mass spectrum of the crude (7) confirmed its molecular formula, while its ^{1}H NMR spectrum confirmed the stereochemistry. Firstly, the chemical shift of the proton H3 (δ 3.93) for this 1,3-*trans*-dimethyl-2-benzopyran was at lower field than that for the corresponding 1,3-*cis*-dimethyl stereoisomer (34) (δ 3.54, see below).[10] Secondly, the coupling constant between H3 and H4 was 7.0 Hz, which confirmed a near *trans* arrangement of these two protons and indicated that H3 was axial and H4 was pseudoaxial. Furthermore, these data confirmed that the C3 methyl was equatorial, the C1 methyl was pseudoaxial, and the C4 hydroxyl was pseudoequatorial.

This 4,5-diol (7) was characterized as its more stable diacetate (26) (see Diagram 2), for which the gross structure was confirmed by high-resolution mass and ^{1}H NMR



(29) (30)

Diagram 3.



	R^1	R^2		R^1	R^2		R^1	R^2
(31)	Me	Cl	(34)	H	H	(37)	Me	Cl
(32)	Me	OH	(35)	Ac	Ac	(38)	Me	OH
(33)	Ac	OAc	(36)	Me	H	(39)	Ac	OAc

Diagram 4.

spectrometry. However, detailed examination of the latter revealed that the coupling constant between the protons H3 and H4 was only 2.0 Hz, which indicated a dihedral angle between these two protons that was much smaller than for the diol (7). This coupling constant was also much smaller than those for the related diacetates of the diols (2) (4.8 Hz)[2] and (5) (pseudoequatorial 4-OH, 7.4 Hz).[4] These data support the conformational inversion of the dihydropyran ring half-chair (29) of the diol (7) into the alternative half-chair (30) of the diacetate (26) (see Diagram 3). In this latter conformation the protons H3 and H4 are equatorial and pseudoequatorial, respectively, and the dihedral angle between them is therefore much smaller giving rise to the observed value of 2.0 Hz for the coupling constant. While such a conformational inversion is reasonable, it is to our knowledge the first such case reported for a 2-benzopyran or naphtho[2,3-*c*]pyran in which the C3 methyl (or alkyl) is axial. The naturally occurring quinones eleutherin and isoeleutherin are known to have alternative conformations for the dihydropyran ring, but there the C3 methyl is equatorial in each case.[11] The reason for the conformational inversion in the case of the diacetate (26) is ascribed to the fact that in (7) and (26) the 1,8-*peri*-interactions are small, unlike other related molecules for which it is general to have a substituent at C8 which is larger than hydrogen. In the case of diol (7), the 4,5-*peri*-interactions between the two hydroxy groups are sufficiently small to tolerate a pseudoequatorial orientation for the alcohol at C4. In the diacetate (26), however, the 4,5-*peri*-interactions are sufficiently large to achieve a conformational inversion at the expense of the C3 methyl and C4 acetoxy being axial and pseudoaxial, respectively, while the lack of significant 1,8-*peri*-interactions allows the C1 methyl to become pseudoequatorial.

A series of nuclear Overhauser enhancement spectra (NOESY) supported the conformational assignment (30) for the diacetate (26). In addition to all the expected correlations, a NOESY spectrum showed a strong correlation between the C3 methyl group and H1, while H1 showed a strong reciprocal correlation, as would be expected from their close proximity as shown in conformation (30). Notably, H3 showed no correlation with the C1 methyl, as would be expected in the alternative conformation (29), while the reciprocal correlation between the C1 methyl and H3 was very weak. Similarly, in NOE difference spectra, irradiation of the C3 methyl group showed an 8.2% enhancement of the H1 signal, while irradiation of the C1 methyl produced a much weaker enhancement (3.2%) of the H3 signal. Inspection of the methyl intensities upon reciprocal irradiation of the individual protons also supported conformation (30).

Further examples of this conformational inversion were sought. Selective methylation of the phenolic oxygen of the crude 4,5-diol (7) afforded the 5-*O*-methyl ether (27), for which the H3–H4 coupling constant was 5.4 Hz compared with 7.9 Hz for the analogous (racemic) phenolic methyl ether of the 4,5-diol (2).[12] The coupling constants for related compounds are generally in the range 8–9 Hz.[10*c*,13] This reduction in the coupling constant presumably corresponds to a reduction in the dihedral angle between H3 and H4, which occurs as a consequence of adopting a conformation to appropriately reduce the 4,5-*peri*-interactions, but these are insufficient to achieve an inversion of the ring. Dreiding models suggest that, in the initial stages of the ring inversion, the pseudoequatorial C4 hydroxy group starts to become more pseudoaxial, and this is accompanied by a decrease in the H3–H4 dihedral angle. This is promoted, once again, by the potential for the pseudoaxial C1 methyl to become pseudoequatorial (see above). Acetylation of the alcohol in (27) yielded the acetate (28). Once again, the coupling constant between H3 and H4 was small (1.9 Hz), which suggested the same conformational inversion observed for the related diacetate (26). Since the H3–H4 coupling constant (5.4 Hz) for alcohol (27) was smaller than that found in other analogues, alcohol (32) (see Diagram 4), which is the C4 pseudoaxial epimer of (27), was assembled. This was achieved through conversion of the pseudoequatorial C4 alcohol in the 2-benzopyran (27) into the pseudoaxial chloride (31) using thionyl chloride, followed by replacement of the chlorine with water upon treatment of chloride (31) with aqueous acetonitrile containing silver nitrate.[13*b*] The H3–H4 coupling constant for compound (32) was 1.9 Hz, which (together with its other physical data) distinguished it from its C4 epimer (27).

Similar conversion of the lactaldehyde (22) into the 2-benzopyran-4,5-diol (34) was achieved through cyclization of the crude phenol (25). This cyclization was notable since it, too, was completely diastereoselective, as was the cyclization of lactaldehyde (6) reported above. In contrast, the cyclization of the benzyl epimer of (1), which is identical to compound (25) but for an additional aromatic methoxy substituent *para* to the phenolic substituent in (25), afforded the two C4 epimeric 4,5-diols.[2] We had previously ascribed[2] this lack of diastereoselectivity in that case to the additional methoxy

group, and the complete diastereoselectivity in the formation of 4,5-diol (34) bears this out.

Diol (34) exhibited a resonance in the ^{1}H NMR spectrum for the proton H3 at δ 3.54, which confirmed a *cis* arrangement of the methyl substituents (see above), and an H3–H4 coupling constant of 9.0 Hz. The coupling constant for the corresponding 4,5-diacetate (35) was 8.2 Hz. Thus the conformations of the heterocyclic rings in diol (34) and its diacetate (35) remained the same, in contrast with the earlier observation (see above) made for diol (7) and its diacetate (26), where a conformational inversion occurred on formation of the latter. In the case of diacetate (35), ring inversion to ease the *peri* interactions arising from the 4,5-diacetate does not occur because all three heterocyclic ring substituents would need to be axial.

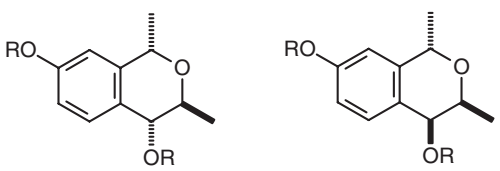
For comparison purposes, the phenolic methyl ether (36) of the diol (34) was prepared and converted through the pseudoaxial chloride (37) into the C4 epimeric pseudoaxial alcohol (38). This completed the assembly of all four possible stereoisomers (27), (32), (36), and (38) of the methyl ether based on the 3*S* stereochemistry. In the ^{1}H NMR spectrum of (36) the axial H3–pseudoaxial H4 coupling constant was 8.8 Hz, a value typical for such protons and significantly larger than for the C1 epimer (27), where the corresponding value was 5.4 Hz (see above).

Regioselective Cyclizations to Form the 2-Benzopyran-4,7-diols and Their Derivatives

The aldehyde (23) was desilylated using a mixture of saturated aqueous solutions of sodium fluoride and ammonium chloride (1 : 1). Subsequently, spontaneous cyclization occurred to yield a mixture of 2-benzopyrans, which consisted largely of the two C4 epimeric 4,7-diols (40) and (41) (see Diagram 5). Acetylation of the derived residue followed by chromatography afforded an inseparable mixture of diastereoisomeric 4,7-diacetates (42) and (43) as the major products, together with the 4,5-diacetate (33), which possesses the alternative regiochemistry, as a minor component. Presumably the fourth isomer, diacetate (26), was also formed as a minor component in this reaction but was lost after chromatographic purification owing to the small scale of the reaction. These inseparable compounds were obtained in a combined overall yield of 47% over three steps from the silyl-protected aldehyde (23), and in a ratio of about 4.6 : 4.6 : 0.8, as judged by ^{1}H NMR spectroscopy. This represented an average yield of 78% for each individual step. Identification of the components followed from the ^{1}H NMR spectrum of the mixture. Although not all the signals could be assigned to the individual epimers (42) and (43) since they were obtained in approximately equal proportions, every resonance for the mixture was readily seen (see Experimental section). These included aromatic signals for two 1,2,4-trisubstituted products, together with the expected signals for the three heterocyclic protons in each compound. In particular, each H3 signal for these 1,3-*trans*-dimethyl compounds resonated at a lower field (δ 4.18 and 4.19) than did their 1,3-*cis*-dimethyl analogues (δ 3.74 and 3.90) (see below). The minor component of the mixture was assigned the structure of a 4,5-diol since, although the aromatic protons H6 and H8 were obscured, all the other signals for (33) were clear. In particular, the aromatic proton H7 at δ 7.35 appeared as a sharp triplet (J 7.9 Hz) and confirmed the existence of the alternative 1,2,3-trisubstituted aromatic ring. The signals that readily distinguished (33) from its C4 epimer (26) were the chemical shifts of each of the heterocyclic protons (H1, H3, H4 for (26): δ 4.91, 4.25, 5.72, respectively; and for (33): δ 5.16, 4.14, 5.89, respectively) and the C1 methyl groups (for (26): δ 1.60; and for (33): δ 1.52). The coupling constant between H3 and H4 did not distinguish the two epimers since they were virtually identical ((26): J 2.0 Hz; (33): J 1.9(4) Hz), the value for (26) arising from the conformational inversion of its heterocyclic ring.

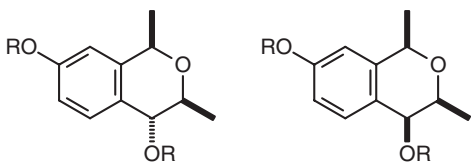
The silyl-protected aldehyde (24) was similarly desilylated and underwent spontaneous cyclization. The resultant mixture which consisted largely of (44) and (45) was then acetylated (see Diagram 6). Careful chromatography led to the isolation of the individual C4 epimeric 4,7-diacetates (46) (24%) and (47) (27%) (a combined yield of 51% represents an average yield of 80% for each of the three steps involved). The 4,5-diacetates (35) and (39), if formed, were lost upon chromatography owing to the small scale of the reaction.

It was anticipated that this spontaneous cyclization occurred through the formation of the phenoxide ion upon desilylation of the silyl ethers as drawn for the starting aldehyde (23) (Scheme 3). The oxide ion (48) promotes spontaneous electrophilic substitution predominantly at the *para* position to yield the C4 epimers (40) and (41). This regioselectivity may arise, at least in part, through greater steric compression being caused by the adjacent substituent at the alternative *ortho* site, thereby discouraging such ring closure. Related *para* cyclizations leading to carbocyclic 4,7-diols



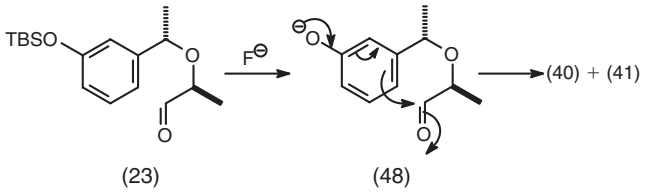
(40) R = H (41)
(42) R = Ac (43)

Diagram 5.



(44) R = H (45)
(46) R = Ac (47)

Diagram 6.



Scheme 3.

under basic conditions have been reported previously,[14] but the use of these conditions was not successful with the substrates in the current study, possibly as a consequence here of nucleophilic substitution of the benzylic oxygen by base.

Conclusions

Conditions have been identified for the regioselective cyclization of *meta*-hydroxybenzyl lactaldehydes to afford either 2-benzopyran-4,5- or -4,7-diols through ring closure either *ortho* or *para* to the phenolic hydroxy group, respectively. The 4,5-diols are obtained with complete diastereoselectivity using titanium tetraisopropoxide. *Peri* interactions between the acetoxy substituents following the conversion of the diol (7) into the 4,5-diacetate (26) lead to the adoption of the alternative half-chair conformation of the heterocyclic ring in the latter compound, in which the C3 methyl assumes the axial orientation. A related inversion is observed for the 4-acetoxy-5-*O*-methyl ether (28). On the other hand, mild generation of the corresponding phenoxide ions by treatment of the silyl ethers with fluoride leads to their spontaneous cyclization to form the 4,7-diols with high regioselectivity.

Experimental

General

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Optical rotations were measured using an Optical Activity PolAAr 2001 polarimeter for chloroform solutions of *c* 1.0 at 20°C. IR spectra were recorded as Nujol mulls for solids and as thin films between NaCl plates for oils using a Perkin Elmer 1720-X Fourier Transform Spectrometer. The sonication bath used was a Branson B3200-E4 operating at a frequency of 44 kHz. Mass spectra were obtained on a VG Autospec spectrometer operating in the electron impact mode at 70 eV (at the University of Western Australia). Elemental analyses were carried out by the Canadian Microanalytical Service Ltd. NMR spectra were recorded using a Bruker AM-300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75.5 MHz). The spectra were run at ambient temperature in deuterochloroform ($CDCl_3$) solution with tetramethylsilane (^{1}H, ^{13}C, δ 0.00) and chloroform (^{1}H, δ 7.27; ^{13}C, δ 77.0) as internal standards. In the NMR and mass 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 using a Metrohm Karl Fischer Calorimeter 684. The hydrocarbon solvent referred to as hexane routinely had a bp 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}. Merck silica gel 60 F_{254} aluminium-backed sheets were used for thin-layer chromatography (TLC). Compounds were routinely visualized under short wavelength (245 nm) ultraviolet light. The phrase 'residue obtained upon workup' refers to the residue when the organic layer was separated, dried with anhydrous magnesium sulfate ($MgSO_4$), and concentrated under reduced pressure.

3′-Benzyloxyacetophenone (9)

Potassium carbonate (12.68 g, 91.9 mmol) was added to a stirred solution of benzyl bromide (15.72 g, 91.9 mmol) and 3′-hydroxyacetophenone (5.0 g, 36.8 mmol) in dry dimethylformamide (50 mL). The resulting suspension was heated under reflux for 12 h. The reaction mixture was cooled, filtered through a pad of celite, and the filtrate concentrated under reduced pressure. The residue was subsequently chromatographed (10–20% ethyl acetate/hexane) to give compound (9) (6.81 g, 82%) as cream-coloured plates, mp 29.5–30°C (hexane) (lit.[5] oil) (Found: $M^{+\bullet}$, 226.0988. $C_{15}H_{14}O_2$ requires $M^{+\bullet}$, 226.0993). υ_{max}/cm^{-1} 1676 (C═O), 1578 and 1484 (C═C). δ_H 2.56 (3 H, s, $COCH_3$), 5.10 (2 H, s, OCH_2), 7.16 (1 H, ddd, *J* 2.6, 3.6 and 8.2, H4′), 7.31–7.45 (6 H, m, C_6H_5 and H5′), 7.51–7.55 (1 H, m, H6′), 7.57 (1 H, m, H2′). δ_C 26.7 ($COCH_3$), 70.2 (OCH_2), 113.6 (C4′), 120.3 (C5′), 121.3 (C6′), 127.6 (C2″,6″), 128.1 (C2′), 128.7 (C3″,5″), 129.6 (C4″), 136.5 (C1″), 138.6 (C1′), 159.0 (C3′), 197.8 (*C*OCH_3). Mass spectrum *m*/*z* 226 (14%, $M^{+\bullet}$), 92 (100), 91 (100), 65 (8).

1-(3′-Benzyloxyphenyl)ethanol (11)

To a stirred slurry of lithium aluminium hydride (336 mg, 8.85 mmol) in dry ether (30 mL) was added dropwise a solution of 3′-benzyloxyacetophenone (9) (200 mg, 0.88 mmol) in dry ether (8 mL) under argon. The mixture was stirred for 1 h under argon after which saturated ammonium chloride solution was added dropwise, followed by $MgSO_4$. Filtration through celite and subsequent chromatography (radial, 10–20% ethyl acetate/hexane) yielded the *benzyl alcohol* (11) (200 mg, 99%) as a light-yellow oil (Found: C, 78.5; H, 7.0%; $M^{+\bullet}$, 228.1144. $C_{15}H_{16}O_2$ requires C, 78.9; H, 7.1%; $M^{+\bullet}$, 228.1150). υ_{max} (film)/cm^{-1} 3392 (OH), 1585 and 1488 (C═C). δ_H 1.44 (3 H, d, *J* 6.5, 1-CH_3), 2.18 (1 H, br s, OH), 4.80 (1 H, q, *J* 6.5, H1), 5.03 (2 H, s, OCH_2), 6.85 (1 H, dd, *J* 2.0 and 7.9, H6′), 6.92 (1 H, dd, *J* 2.0 and 7.9, H4′), 7.00 (1 H, t, *J* 2.0, H2′), 7.23 (1 H, t, *J* 7.9, H5′), 7.30–7.43 (5 H, m, C_6H_5). δ_C 25.1 (C2), 69.9 (OCH_2), 70.2 (C1), 111.9 (C6′), 113.7 (C4′), 118.0 (C2′), 127.5 (C2″,6″), 127.9 (C4″), 128.5 (C3″,5″), 129.5 (C5′), 137.0 (C1′), 147.6 (C1″), 158.9 (C3′). Mass spectrum *m*/*z* 228 (6%, $M^{+\bullet}$), 92 (7), 91 (100), 86 (15), 84 (19), 65 (8), 51 (9).

3′-Benzyloxy-α′-methylbenzyl-2,2,2-trichloroethanimidate (13)

The benzyl alcohol (11) (1 g, 4.39 mmol) in dry diethyl ether (4 mL) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in oil) (70 mg, 2.92 mmol) in diethyl ether (15 mL). The mixture was stirred for 10 min under argon at −10°C. Trichloroacetonitrile (1.27 g, 8.79 mmol) was added dropwise over 10 min, and the reaction mixture was stirred for a further 30 min at that temperature, after which it was allowed to reach room temperature. The solution was concentrated and chromatographed (radial, 10% ethyl acetate/hexane) to afford the *imidate* (13) (1.41 g, 85%) as a white solid, mp 78–79°C (hexane) (Found: C, 54.9; H, 4.4; N, 3.7%; $M^{+\bullet}$, 373.0202. $C_{17}H_{16}Cl_3NO_2$ requires C, 55.0; H, 4.4; N, 3.8%; $M^{+\bullet}$ ($^{35}Cl_2^{37}Cl$), 373.0217). υ_{max}/cm^{-1} 3340 (NH), 1662 (C═N), 1597 and 1499 (C═C). δ_H 1.62 (3 H, d, *J* 6.6, α′-CH_3), 5.04 (2 H, s, OCH_2), 5.95 (1 H, q, *J* 6.6, Hα′), 6.90 (1 H, dd, *J* 2.0 and 7.9, H6′), 7.00 (1 H, dd, *J* 2.0 and 7.9, H4′), 7.05 (1 H, t, *J* 2.0, H2′), 7.25 (1 H, t, *J* 7.9, H5′), 7.28–7.43 (5 H, m, C_6H_5), 8.30 (1 H, s, NH). δ_C 22.1 (α′-CH_3), 69.9 (OCH_2), 76.9 (Cα′), 91.7 (CCl_3), 112.2 (C6′), 114.2 (C4′), 118.3 (C2′) 127.5 (C2″,6″), 127.9 (C4″), 128.5 (C3″,5″), 129.5 (C5′), 136.9 (C1′), 143.0 (C1″), 158.9 (C3′), 161.5 (C1). Mass spectrum *m*/*z* 397 (10%, [$^{35}Cl_2{}^{37}Cl$]$M^{+\bullet}$), 395 (10, [$^{35}Cl_3$]$M^{+\bullet}$), 340 (25), 338 (25), 235 (24), 234 (40), 213 (17), 179 (19), 178 (50), 177 (100), 161 (16), 151 (23), 149 (12).

*Ethyl (α′*R *or* S,*2*S*)-2-(3′-benzyloxy-α′-methylbenzyloxy)-propanoate (15)*

Boron trifluoride diethyl etherate (18 mg, 0.13 mmol) was added dropwise to a solution of imidate (13) (470 mg, 1.27 mmol) and ethyl (*S*)-lactate (300 mg, 2.54 mmol) in dry hexane and dichloromethane (15 mL, 2 : 1). The reaction mixture was stirred under nitrogen for 40 min. Solid sodium hydrogen carbonate was added to the mixture and the resulting suspension was filtered through celite. The clear

solution was then concentrated and chromatographed (radial, 10% ethyl acetate/hexane) to yield (15) as an oily, inseparable mixture of diastereoisomers (310 mg, 75%) in a ratio of 55 : 45 (Found: C, 73.5; H, 7.5%; $M^{+\bullet}$, 328.1662. $C_{20}H_{24}O_4$ requires C, 73.2; H, 7.4%; $M^{+\bullet}$, 328.1674). υ_{max} (film)/cm^{-1} 1746 (C═O), 1599 and 1487 (C═C). δ_H (major diastereoisomer) 1.28 (3 H, t, *J* 7.2, C*H*$_3$CH$_2$), 1.32 (3 H, d, *J* 6.9, 2-CH$_3$), 1.47 (3 H, d, *J* 6.5, α′-CH$_3$), 3.82 (1 H, q, *J* 6.9, H2), 4.15–4.25 (2 H, m, CH$_3$C*H*$_2$), 4.49 (1 H, q, *J* 6.5, α′-H), 5.06 (2 H, s, OCH$_2$), 6.85–7.30 (4 H, m, H2′,4′,5′,6′), 7.30–7.46 (5 H, m, C$_6$H$_5$). δ_H (minor diastereoisomer) 1.18 (3 H, t, *J* 7.1, C*H*$_3$CH$_2$), 1.40 (3 H, d, *J* 6.8, 2-CH$_3$), 1.47 (3 H, d, *J* 6.5, α′-CH$_3$), 4.00 (1 H, q, *J* 6.8, H2), 3.95–4.09 (2 H, m, CH$_3$C*H*$_2$), 4.54 (1 H, q, *J* 6.5, α′-H), 5.05 (2 H, s, OCH$_2$), 6.85–7.30 (4 H, m, H2′,4′,5′,6′), 7.30–7.46 (5 H, m, C$_6$H$_5$). δ_C (mixture of two diastereoisomers) 14.1 and 14.3 (*C*H$_3$CH$_2$), 18.3 and 19.0 (C3), 23.2 and 24.4 (α′-CH$_3$), 60.7 and 60.7 (CH$_3$*C*H$_2$), 69.9 and 70.0 (OCH$_2$), 72.0 and 72.8 (Cα′), 77.0 and 77.3 (C2), 112.6 and 112.9 (C6′), 114.0 (C4′), 119.0 and 119.2 (C2′), 127.6 and 127.5 (C2″,6″), 128.0 and 127.9 (C4″), 128.5 and 128.6 (C3″,5″), 129.4 and 129.6 (C5′), 136.9 and 137.0 (C1′), 144.7 and 144.0 (C1″), 158.9 and 159.1 (C3′), 173.1 and 173.7 (C1). Mass spectrum *m*/*z* 328 (8%, $M^{+\bullet}$), 237 (7), 227 (25), 212 (9), 211 (35), 120 (5), 92 (18), 91 (100), 65 (10).

(α′S, 2S)- and (α′R,2S)-2-(3′-Benzyloxy-α′-methylbenzyloxy)-propan-1-ol (17) and (18)

The mixture of diastereoisomeric esters (15) (400 mg, 1.22 mmol) was reduced with lithium aluminium hydride as described for the reduction of 3′-benzyloxyacetophenone (9). The pale-yellow oil was subjected to chromatography (radial, 5–10% ethyl acetate/hexane) to afford the two alcohols (17) and (18) as colourless oils. The product of higher R_f was identified as *compound* (18) (140 mg, 40%), $[\alpha]_D$ +67.2° (*c* 1.0 in CHCl$_3$) (Found: $M^{+\bullet}$, 286.1555. $C_{18}H_{22}O_3$ requires $M^{+\bullet}$, 286.1568). υ_{max} (film)/cm^{-1} 3435 (OH), 1599 and 1486 (C═C). δ_H 1.10 (3 H, d, *J* 5.9, 2-CH$_3$), 1.41 (3 H, d, *J* 6.4, α′-CH$_3$), 2.24 (1 H, br s, OH), 3.35–3.46 (3 H, m, C*H*$_2$OH and H2), 4.51 (1 H, q, *J* 6.4, Hα′), 5.02 (2 H, s, OCH$_2$), 6.86–7.43 (9 H, m, H2′,4′,5′,6′ and C$_6$H$_5$). δ_C 15.6 (C3), 24.5 (α′-CH$_3$), 66.6 (C1), 69.9 (OCH$_2$), 72.7 (C2), 74.9 (Cα′), 112.8 (C6′), 113.8 (C4′), 118.8 (C2′), 127.6 (C2″,6″), 127.9 (C4″), 128.5 (C3″,5″), 129.6 (C5′), 136.9 (C1′), 145.5 (C1″), 159.0 (C3′). Mass spectrum *m*/*z* 286 (18%, $M^{+\bullet}$), 212 (22), 211 (54), 92 (14), 91 (100). The product of lower R_f was identified as *compound* (17) (180 mg, 52%), $[\alpha]_D$ −38.1° (*c* 1.0 in CHCl$_3$) (Found: C, 75.6; H, 7.7%; $M^{+\bullet}$, 286.1574. $C_{18}H_{22}O_3$ requires C, 75.5; H, 7.8%; $M^{+\bullet}$, 286.1568). υ_{max} (film)/cm^{-1} 3436 (OH), 1586 and 1486 (C═C). δ_H 1.00 (3 H, d, *J* 6.2, 2-CH$_3$), 1.43 (3 H, d, *J* 6.4 Hz, α′-CH$_3$), 1.99 (1 H, br s, OH), 3.43–3.69 (3 H, m, C*H*$_2$OH and H2), 4.56 (1 H, q, *J* 6.4, Hα′), 5.07 (2 H, s, OCH$_2$), 6.89 (1 H, dd, *J* 2.0 and 8.0, H6′), 6.92 (1 H, dd, *J* 2.0 and 8.0, H4′), 6.99 (1 H, t, *J* 2.0, H2′), 7.25 (1 H, t, *J* 8.0, H5′), 7.30–7.46 (5 H, m, C$_6$H$_5$). δ_C 17.9 (C3), 24.6 (α′-CH$_3$), 66.4 (C1), 70.6 (OCH$_2$), 74.7 (C2), 76.9 (Cα′), 113.2 (C6′), 114.3 (C4′), 119.4 (C2′), 128.1 (C2″,6′), 128.6 (C4″), 129.1 (C3″, 5″), 130.0 (C5′), 137.6 (C1′), 146.8 (C1″), 159.5 (C3′). Mass spectrum *m*/*z* 286 (10%, $M^{+\bullet}$), 212 (25), 211 (54), 92 (14), 91 (100).

(α′S,2S)-2-(3′-Benzyloxy-α′-methylbenzyloxy)propanal (21)

To a solution of oxalyl chloride (220 mg, 1.74 mmol) in dry dichloromethane (4 mL) at −70°C under an atmosphere of argon was added dropwise a solution of dimethyl sulphoxide (270 mg, 3.5 mmol) in dry dichloromethane (4 mL), keeping the temperature below −65°C. After stirring for 15 min, a solution of the (α′*S*,2*S*)-alcohol (17) (100 mg, 0.35 mmol) in dry dichloromethane (4 mL) was added dropwise. The temperature was kept below –65°C and the stirring was continued for a further 15 min at that temperature. Dry diisopropylethylamine (540 mg, 4.19 mmol) was added slowly and the reaction was stirred for a further 10 min at −70°C before being allowed to warm to room temperature over 1 h. The reaction mixture was quenched with water and exhaustively extracted with dichloromethane. The residue obtained upon workup was chromatographed (radial, 10–20% ethyl acetate/hexane) to give the *aldehyde* (21) (73 mg, 75%) as a colourless oil, $[\alpha]_D$ –107.4° (*c* 1.0 in CHCl$_3$) (Found: $M^{+\bullet}$, 284.1421. $C_{18}H_{20}O_3$ requires $M^{+\bullet}$, 284.1412). υ_{max} (film)/cm^{-1} 1733 (C═O), 1586 and 1486 (C═C). δ_H 1.17 (3 H, d, *J* 7.0, 2-CH$_3$), 1.49 (3 H, d, *J* 6.4, α′-CH$_3$), 3.69 (1 H, dq, *J* 1.8 and 7.0, H2), 4.51 (1 H, q, *J* 6.4, Hα′), 5.06 (2 H, s, OCH$_2$), 6.86–6.95 (3 H, m, H2′,4′,6′), 7.25 (1 H, t, *J* 7.8, H5′), 7.30–7.45 (5 H, m, C$_6$H$_5$), 9.66 (1 H, d, *J* 1.8, CHO). δ_C 15.2 (C3), 23.6 (α′-CH$_3$), 69.3 (OCH$_2$), 76.8 (C2), 77.0 (Cα′), 111.9 (C6′), 113.5 (C4′), 118.2 (C2′), 126.8 (C2″,6″), 127.3 (C4″), 127.9 (C3″,5″), 129.0 (C5′), 136.2 (C1′), 143.9 (C1″), 158.4 (C3′), 203.1 (C1). Mass spectrum *m*/*z* 284 (7%, $M^{+\bullet}$), 212 (12), 211 (55), 92 (11), 91 (100).

(α′R,2S)-2-(3′-Benzyloxy-α′-methylbenzyloxy)propanal (22)

According to the method described above for the preparation of aldehyde (21) from (α′*S*,2*S*)-alcohol (17), the (α′*R*,2*S*)-alcohol (18) (200 mg, 0.7 mmol) was converted into the crude aldehyde (22) as a pale-orange oil. Chromatography (radial, 10–30% ethyl acetate/hexane) afforded a *colourless oil* (160 mg, 80%), $[\alpha]_D$ +51.6° (*c* 1.0 in CHCl$_3$) (Found: C, 76.1; H, 7.0%; $M^{+\bullet}$, 284.1422. $C_{18}H_{20}O_3$ requires C, 76.0; H, 7.1%; $M^{+\bullet}$, 284.1412). υ_{max} (film)/cm^{-1} 1736 (C═O), 1586 and 1486 (C═C). δ_H 1.23 (3 H, d, *J* 6.9, 2-CH$_3$), 1.48 (3 H, d, *J* 6.5, α′-CH$_3$), 3.71 (1 H, dq, *J* 1.3 and 6.9, H2), 4.52 (1 H, q, *J* 6.5, Hα′), 5.06 (2 H, s, OCH$_2$), 6.85–7.00 (3 H, m, H2′,4′,6′), 7.23 (1 H, t, *J* 7.9, H5′), 7.32–7.44 (5 H, m, C$_6$H$_5$). 9.41 (1 H, d, *J* 1.3, CHO). δ_C 15.9 (C3), 24.7 (α′-CH$_3$), 70.9 (OCH$_2$), 76.3 (C2), 78.9 (Cα′), 113.9 (C6′), 115.2 (C4′), 120.1 (C2′), 128.4 (C2″,6″), 128.9 (C4″), 129.5 (C3′,5″), 130.6 (C5′), 137.7 (C1′), 145.7 (C1″), 160.0 (C3′), 204.1 (C1). Mass spectrum *m*/*z* 284 (5%, $M^{+\bullet}$), 212 (16), 211 (65), 92 (13), 91 (100).

3′-t-Butyldimethylsilyloxyacetophenone (10)

t-Butyldimethylsilyl chloride (16.6 g, 0.11 mol) and imidazole (7.5 g, 0.11 mol) were added to a solution of 3′-hydroxyacetophenone (10 g, 73.5 mmol) in dry dimethylformamide (150 mL). The mixture was stirred under argon for 12 h at room temperature, after which water was added and the mixture exhaustively extracted with ethyl acetate. The residue obtained upon workup was chromatographed (10% ethyl acetate/hexane) to afford (10) (17 g, 93%) as a *colourless oil* (Found: C, 67.2; H, 8.8%; $M^{+\bullet}$, 250.1379. $C_{14}H_{22}O_2Si$ requires C, 67.2; H, 8.9%; $M^{+\bullet}$, 250.1389). υ_{max} (film)/cm^{-1} 1688 (C═O), 1582 and 1484 (C═C). δ_H 0.23 (6 H, s, OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$), 1.00 (9 H, s, OSi(CH$_3$)$_2$C(C*H*$_3$)$_3$), 2.57 (3 H, s, COCH$_3$), 7.04 (1 H, ddd, *J* 1.0, 2.0 and 7.8, H4′), 7.32 (1 H, t, *J* 7.8, H5′), 7.42 (1 H, t, *J* 2.0, H2′), 7.54 (1 H, ddd, *J* 1.0, 2.0 and 7.8, H6′). δ_C –4.4 (OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$), 18.2 (OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), 25.7 (OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 26.7 (CO*C*H$_3$), 119.5 (C4′), 121.6 (C5′), 124.9 (C2′), 129.5 (C6′), 138.6 (C1′), 156.0 (C3′), 197.8 (*C*OCH$_3$). Mass spectrum *m*/*z* 250 (13%, $M^{+\bullet}$), 194 (21), 193 (100), 165 (12), 151 (19), 121 (12), 105 (11), 86 (11), 84 (17).

1-(3′-t-Butyldimethylsilyloxyphenyl)ethanol (12)

To a stirred slurry of lithium aluminium hydride (610 mg, 16.1 mmol) in dry diethyl ether (60 mL) was added dropwise a solution of compound (10) (2 g, 8 mmol) in dry diethyl ether (10 mL) under argon. The mixture was stirred for 1 h, after which saturated ammonium chloride solution was added dropwise, followed by $MgSO_4$. Filtration through filter aid and concentration of the filtrate gave a light-yellow oil. Chromatography (radial, 10–30% ethyl acetate/hexane) yielded the *alcohol* (12) (1.85 g, 93%) as a colourless oil (Found: C, 66.6; H, 9.4%; $M^{+\bullet}$, 252.1543. $C_{14}H_{24}O_2Si$ requires C, 66.7; H 9.6%; $M^{+\bullet}$, 252.1545). υ_{max} (film)/cm^{-1}3350 (OH), 1603 and 1587 (C═C). δ_H 0.21 (6 H, s, OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$), 0.99 (9 H, s, OSi(CH$_3$)$_2$C(C*H*$_3$)$_3$), 1.43 (3 H, d, *J* 6.4, 1-CH$_3$), 2.33 (1 H, br s, OH), 4.78 (1 H, q, *J* 6.4, H1), 6.73 (1 H, dd, *J* 2.0 and 7.8, H6′), 6.85 (1 H, t, *J* 2.0, H2′), 6.92 (1 H, br dd, *J* 2.0 and 7.8, H4′), 7.18 (1 H, t, *J* 7.8, H5′). δ_C –4.4 (OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$), 18.2 (OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), 25.1 (OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 25.7 (C2), 70.1 (C1), 117.1 (C6′), 118.3 (C2′), 118.9 (C4′) 129.4 (C5′), 147.6 (C1′), 155.7 (C3′). Mass spectrum *m*/*z* 252 (20%, $M^{+\bullet}$), 195 (21), 177 (100), 149 (23), 123 (12), 109 (14), 91 (10), 75 (29), 67 (14).

*3′-*t*-Butyldimethylsilyloxy-α′-methylbenzyl-2,2,2-trichloroethanimidate (14)*

The alcohol (12) (1 g, 3.96 mmol) in dry diethyl ether (10 mL) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in oil) (64 mg, 2.67 mmol) in dry diethyl ether (7 mL). The mixture was stirred for 10 min under argon at −10°C. Trichloroacetonitrile (1.12 g, 7.93 mmol) was added dropwise over 10 min and the reaction mixture was stirred for a further 30 min at that temperature, after which it was allowed to warm to room temperature. The solution was concentrated and chromatographed (radial, 5% ethyl acetate/hexane) to yield the *imidate* (14) (1.41 g, 90%) as a colourless oil (Found: $M^{+\bullet}$, 395.0644. $C_{16}H_{24}Cl_3NO_2Si$ requires $M^{+\bullet}$ ($^{35}Cl_3$), 395.0641). υ_{max} (film)/cm^{-1} 3347 (NH), 1664 (C═N), 1606 and 1486 (C═C). δ_H 0.20 (6 H, s, OSi(CH_3)$_2$C(CH$_3$)$_3$), 0.99 (9 H, s, OSi(CH$_3$)$_2$C(CH_3)$_3$), 1.64 (3 H, d, *J* 6.5, α′-CH$_3$), 5.95 (1 H, q, *J* 6.5, Hα′), 6.78 (1 H, dd, *J* 2.0 and 7.8, H6′), 6.93 (1 H, t, *J* 2.0, H2′), 7.00 (1 H, br dd, *J* 2.0 and 7.8, H4′), 7.22 (1 H, t, *J* 7.8, H5′), 8.32 (1 H, s, NH). δ_C –4.0 (OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$), 18.6 (OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), 22.5 (OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 26.1 (α′-CH$_3$), 77.3 (Cα′), 92.1 (CCl$_3$), 117.8 (C6′), 119.1 (C2′), 119.9 (C4′), 129.8 (C5′), 143.3 (C1′), 156.2 (C3′), 162.0 (C1). Mass spectrum *m*/*z* 338 (25%, [M–C(CH$_3$)$_3$]$^{+\bullet}$), 235 (23), 234 (40), 178 (50), 177 (100), 151 (22), 149 (12).

*Ethyl (α′*R *or* S,*2*S*)-2-(3′-*t*-Butyldimethylsilyloxy-α′-methylbenzyloxy)propanoate (16)*

Boron trifluoride diethyl etherate (37.7 mg, 0.27 mmol) was added dropwise to a solution of imidate (14) (500 mg, 1.26 mmol) and ethyl (*S*)-lactate (300 mg, 2.54 mmol) in dry hexane and dichloromethane (20 mL, 2 : 1) at ambient temperature. The reaction was stirred under nitrogen for 40 min. Solid sodium hydrogen carbonate was added to the reaction mixture and the resulting suspension was filtered through filter aid. The clear solution was then concentrated and chromatographed (radial, 10–30% ethyl acetate/hexane) to yield the *products* (16) (390 mg, 88%) as an oily, inseparable mixture of diastereoisomers in a ratio of 65 : 35 (Found: C, 64.7; H, 8.7%; $M^{+\bullet}$, 352.2065. $C_{19}H_{32}O_4Si$ requires C, 64.8; H, 9.2%; $M^{+\bullet}$, 352.2069). υ_{max} (film)/cm^{-1} 1750 (C═O), 1603 and 1484 (C═C). δ_H (major diastereoisomer) 0.20 (6 H, s, OSi(CH_3)$_2$C(CH$_3$)$_3$), 0.99 (9 H, s, OSi(CH$_3$)$_2$C(CH_3)$_3$), 1.28 (3 H, t, *J* 7.1, CH_3CH$_2$), 1.35 (3 H, d, *J* 6.9, 2-CH$_3$), 1.46 (3 H, d, *J* 6.4, α′-CH$_3$), 3.83 (1 H, q, *J* 6.9, H2), 4.20 and 4.22 (2 × 1 H, dq, *J* 7.1 and 10.8, CH$_3$CH_2), 4.46 (1 H, q, *J* 6.4, Hα′), 6.76 (1 H, dt, *J* 2.0 and 7.8, H4′), 6.80 (1 H, t, *J* 2.0, H2′), 6.86 (1 H, br dd, *J* 2.0 and 7.8. H6′), 7.19 (1 H, t, *J* 7.8, H5′). δ_H (minor diastereoisomer) 0.20 (6 H, s, OSi(CH_3)$_2$C(CH$_3$)$_3$), 0.99 (9 H, s, OSi(CH$_3$)$_2$C(CH_3)$_3$), 1.19 (3 H, t, *J* 7.1, CH_3CH$_2$), 1.40 (3 H, d, *J* 6.7, 2-CH$_3$), 1.46 (3 H, d, *J* 6.4, α′-CH$_3$), 4.02 (1 H, q, *J* 6.7, H2), 4.05 (2 H, q, *J* 7.1, CH$_3$CH_2), 4.51 (1 H, q, *J* 6.4, Hα′), 6.73 (1 H, d, *J* 7.8, H4′), 6.80 (1 H, t, *J* 2.0, H2′), 6.94 (1 H, br dd, *J* 2.0 and 7.8, H6′), 7.17 (1 H, t, *J* 7.8, H5′). δ_C (mixture of two diastereoisomers) −4.1 (OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$), 14.5 and 14.6 (*C*H$_3$CH$_2$), 18.6 (C3), 19.4 (OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), 23.7 and 24.8 (α′-CH$_3$), 26.1 (OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 61.0 and 61.1 (CH$_3$*C*H$_2$), 72.3 and 73.0 (Cα′), 77.1 and 77.5 (C2), 118.1 and 118.5 (C4′), 119.6 and 119.8 (C2′), 119.8 and 119.9 (C6′), 129.6 and 129.8 (C5′), 145.0 and 145.2 (C1′), 156.1 and 156.3 (C3′), 173.4 and 174.1 (C1). Mass spectrum *m*/*z* 352 (20%, $M^{+\bullet}$), 295 (13), 252 (15), 251 (70), 250 (20), 249 (97), 235 (100), 177 (92), 151 (22).

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

The mixture of diastereoisomeric esters (16) (1 g, 2.84 mmol) was reduced with lithium aluminium hydride (220 mg, 5.79 mmol) as described for the reduction of 3′-*t*-butyldimethylsilyloxyacetophenone (10). The resulting pale-yellow oil was subjected to chromatography (radial, 5–15% ethyl acetate/hexane) to afford the two *alcohols* (19) and (20) as colourless oils. The compound of higher R_f was identified as (20) (355 mg, 40%), $[\alpha]_D$ +79.4° (*c* 1.0 in CHCl$_3$) (Found: C, 65.7; H, 9.6%; $M^{+\bullet}$, 310.1975. $C_{17}H_{30}O_3Si$ requires C, 65.8; H, 9.8%; $M^{+\bullet}$, 310.1964). υ_{max} (film)/cm^{-1} 3451 (OH), 1595 and 1479 (C═C). δ_H 0.20 (6 H, s, OSi(CH_3)$_2$C(CH$_3$)$_3$), 0.99 (9 H, s, OSi(CH$_3$)$_2$C(CH_3)$_3$), 1.13 (3 H, d, *J* 5.8, 2-CH$_3$), 1.43 (3 H, d, *J* 6.5, α′-CH$_3$), 1.97 (1 H, br s, OH), 3.38–3.53 (3 H, m, CH_2OH and H2), 4.51 (1 H, q, *J* 6.5, Hα′), 6.75 (1 H, dd, *J* 2.0 and 7.8, H6′), 6.80 (1 H, t, *J* 2.0, H2′), 6.91 (1 H, br dd, *J* 2.0 and 7.8, H4′), 7.20 (1 H, t, *J* 7.8, H5′). δ_C –4.4 (OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$), 15.6 (OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), 18.2 (OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 24.5 (C3), 25.7 (α′-CH$_3$), 66.8 (C1), 72.7 (C2), 74.9 (Cα′), 117.9 (C6′), 119.3 (C2′), 119.3 (C4′), 128.9 (C5′), 145.4 (C1′), 155.9 (C3′). Mass spectrum *m*/*z* 310 (9%, $M^{+\bullet}$), 236 (28), 235 (100), 177 (14), 133 (19). The compound of lower R_f was identified as (19) (411 mg, 47%), $[\alpha]_D$ −40° (*c* 1.0 in CHCl$_3$) (Found: C, 66.1; H, 9.6%; $M^{+\bullet}$, 310.1964. $C_{17}H_{30}O_3Si$ requires C, 65.8; H, 9.8%; $M^{+\bullet}$, 310.1964). υ_{max} (film)/cm^{-1} 3431 (OH), 1603 and 1483 (C═C). δ_H 0.20 (6 H, s, OSi(CH_3)$_2$C(CH$_3$)$_3$), 0.99 (9 H, s, OSi(CH$_3$)$_2$C(CH_3)$_3$), 1.01 (3 H, d, *J* 6.3, 2-CH$_3$), 1.43 (3 H, d, *J* 6.5, α′-CH$_3$), 2.06 (1 H, br s, OH), 3.45 (1 H, dd, *J* 5.7 and 10.9, H1α), 3.57 (1 H, ddq, *J* 3.4, 5.7 and 6.3, H2), 3.65 (1 H, dd, *J* 3.4 and 10.9, H1β), 4.53 (1 H, q, *J* 6.5, Hα′), 6.75 (1 H, dd, *J* 2.0 and 7.8, H6′), 6.84 (1 H, t, *J* 2.0, H2′) 6.91 (1 H, d, *J* 7.8, H4′), 7.19 (1 H, t, *J* 7.8, H5′). δ_C –4.4 (OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$), 17.4 (OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), 18.2 (OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 24.1 (C3), 25.7 (α′-CH$_3$), 65.7 (C1), 74.0 (C2), 76.3 (Cα′), 117.8 (C6′), 119.1 (C2′), 119.2 (C4′), 129.3 (C5′), 145.1 (C1′), 155.8 (C3′).Mass spectrum *m*/*z* 310 (7%, $M^{+\bullet}$), 249 (12), 237 (11), 236 (33), 235 (63), 179 (22), 178 (30), 177 (100), 151 (15), 133 (25), 121 (12).

*(α′*S,*2*S*)-2-(3′-*t*-Butyldimethylsilyloxy-α′-methylbenzyloxy)propanal (23)*

To a solution of oxalyl chloride (310 mg, 2.44 mmol) in dry dichloromethane (4 mL) at −70°C under an atmosphere of argon was added dropwise a solution of dimethyl sulphoxide (380 mg, 4.86 mmol) in dry dichloromethane (4 mL), keeping the temperature below −65°C. After stirring for 20 min, a solution of the alcohol (19) (150 mg, 0.48 mmol) in dry dichloromethane (4 mL) was added dropwise (keeping the temperature below −65°C) and the stirring was continued for a further 15 min. Dry triethylamine (590 mg, 5.83 mmol) was added slowly and the reaction was stirred for a further 10 min at −70°C before being allowed to reach room temperature over 1 h. The reaction mixture was quenched with water and exhaustively extracted with dichloromethane and the residue obtained upon workup was chromatographed (radial, 10–20% ethyl acetate/hexane) to give the *aldehyde* (23) (130 mg, 87%) as a colourless oil, $[\alpha]_D$ −108.8° (*c* 1.0 in CHCl$_3$) (Found: C, 65.9; H, 9.0%; $M^{+\bullet}$, 308.1794. $C_{17}H_{28}O_3Si$ requires C, 66.2; H, 9.2%; $M^{+\bullet}$, 308.1807). υ_{max} (film)/cm^{-1} 1737 (C═O), 1603 and 1484 (C═C). δ_H 0.20 (6 H, s, OSi(CH_3)$_2$C(CH$_3$)$_3$), 0.99 (9 H, s, OSi(CH$_3$)$_2$C(CH_3)$_3$), 1.22 (3 H, d, *J* 7.0, 2-CH$_3$), 1.49 (3 H, d, *J* 6.4 Hz, α′-CH$_3$), 3.71 (1 H, dq, *J* 1.9 and 7.0, H2), 4.49 (1 H, q, *J* 6.4, Hα′), 6.76 (1 H, dd, *J* 2.0 and 7.8, H6′), 6.80 (1 H, t, *J* 2.0, H2′), 6.86 (1 H, br dd, *J* 2.0 and 7.8, H4′), 7.20 (1 H, t, *J* 7.8, H5′), 9.68 (1 H, d, *J* 1.9, CHO). δ_C –4.3 (OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$), 16.0 (OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), 18.3 (OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 24.4 (C3), 25.8 (α′-CH$_3$), 77.6 (C2), 77.7 (Cα′) 117.9 (C6), 119.5 (C2′), 119.7 (C4), 129.7 (C5′), 144.6 (C1′), 156.1 (C3′). 204.0 (C1). Mass spectrum *m*/*z* 308 (2%, $M^{+\bullet}$), 252 (11), 236 (33), 235 (100), 207 (63), 195 (11), 177 (73), 163 (13), 151 (22), 137 (8), 121 (13), 97 (11), 85 (15).

*(α′*R,*2*S*)-2-(3′-*t*-Butyldimethylsilyloxy-α′-methylbenzyloxy)propanal (24)*

According to the method described above for the preparation of aldehyde (23) from alcohol (19), the alcohol (20) (150 mg, 0.48 mmol) was converted into the aldehyde (24) as a crude, pale-yellow oil which was chromatographed (radial, 10–20% ethyl acetate/hexane) to give a *colourless oil* (130 mg, 87%), $[\alpha]_D$ + 123.2° (*c* 1.0 in CHCl$_3$) (Found: $M^{+\bullet}$, 308.1792. $C_{17}H_{28}O_3Si$ requires $M^{+\bullet}$, 308.1807). υ_{max} (film)/cm^{-1} 1735 (C═O), 1601 and 1486 (C═C). δ_H 0.2 (6 H, s, OSi(CH_3)$_2$C(CH$_3$)$_3$), 0.99 (9 H, s, OSi(CH$_3$)$_2$C(CH_3)$_3$), 1.27 (3 H, d, *J* 6.8, 2-CH$_3$), 1.49 (3 H, d, *J* 6.4, α′-CH$_3$), 3.75 (1 H, dq, *J* 1.5 and 6.8, H2), 4.53 (1 H, q, *J* 6.4, Hα′), 6.77 (1 H, dd, *J* 2.0 and 7.8, H6′), 6.84 (1 H, t, *J* 2.0, H2′), 6.92 (1 H, d, *J* 7.8, H4′), 7.20 (1 H, t, *J* 7.8, H5′), 9.49 (1 H, d, *J* 1.5, CHO). δ_C −4.4 (OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$), 15.1

($OSi(CH_3)_2C(CH_3)_3$), 18.2 ($OSi(CH_3)_2C(CH_3)_3$), 23.8 (C3), 25.7 (α′-CH_3), 77.0 (C2), 78.0 (Cα′) 118.2 (C6′), 119.7 (C2′), 119.8 (C4′), 129.6 (C5′), 144.3 (C1′), 156.0 (C3′), 203.2 (C1). Mass spectrum *m/z* 308 (2%, $M^{+\bullet}$), 251 (8), 236 (36), 235 (100), 233 (14), 208 (17), 207 (97), 179 (21), 178 (20), 177 (12), 163 (12), 151 (17), 149 (11), 86 (10), 84 (18).

(α′S,2S)-2-(3′-Hydroxy-α′-methylbenzyloxy)propanal (6)

A suspension of the pure benzyl ether (21) (200 mg, 0.7 mmol) and 10% palladium on carbon catalyst (200 mg, 100%) in dry ethyl acetate (10 mL) was stirred under a hydrogen atmosphere for 1.5 h. The mixture was filtered through filter aid, subjected to another portion of 10% palladium on carbon catalyst (200 mg, 100%), and exposed to a hydrogen atmosphere for a further 1.5 h. The reaction mixture was again filtered through filter aid, concentrated and purified through rapid chromatography (radial, 35% ethyl acetate/hexane) to afford the potentially unstable *phenol* (6) (98 mg, 72%) as a light-pink oil. (Found: $M^{+\bullet}$, 194.0950. $C_{11}H_{14}O_3$ requires $M^{+\bullet}$, 194.0942). υ_{max} (film)/cm^{-1} 3389 (OH), 1730 (C=O), 1592 and 1484 (C=C). δ_H 1.23 (3 H, d, *J* 7.0, 2-CH_3), 1.50 (3 H, d, *J* 6.4, α′-CH_3), 3.76 (1 H, dq, *J* 1.8 and 7.0, H2), 4.51 (1 H, q, *J* 6.4, Hα′), 6.29 (1 H, br s, OH), 6.73–6.95 (3 H, m, H2′,4′,6′), 7.20 (1 H, t, *J* 7.9, H5′), 9.68 (1 H, d, *J* 1.8, CHO). δ_C 15.8 (C3), 24.2 (α′-CH_3), 77.6 (C2), 77.7 (Cα′), 113.0 (C6′), 115.0 (C4′), 118.5 (C2′), 129.9 (C5′), 144.6 (C1′), 156.2 (C3′), 204.3 (C1). Mass spectrum *m/z* 194 (7%, $M^{+\bullet}$), 177 (19), 149 (15), 122 (15), 121 (100).

(α′R,2S)-2-(3′-Hydroxy-α′-methylbenzyloxy)propanal (25)

In a similar manner to the hydrogenolysis of benzyl ether (21) described above, the benzyl ether (22) (100 mg, 0.35 mmol) was deprotected to give the potentially unstable phenol (25), which was rapidly chromatographed (radial, 30% ethyl acetate/hexane) to afford a *light-pink oil* (48 mg, 71%) (Found: $[M-H]^{+\bullet}$, 193.0853. $C_{11}H_{13}O_3$ requires $[M-H]^{+\bullet}$, 193.0864). υ_{max} (film)/cm^{-1} 3378 (OH), 1729 (C=O), 1608 and 1589 (C=C). δ_H 1.27 (3 H, d, *J* 6.8, 2-CH_3), 1.48 (3 H, d, *J* 6.4, α′-CH_3), 2.06 (1 H, br s, OH), 3.79 (1 H, dq, *J* 1.5 and 6.8, H2), 4.52 (1 H, q, *J* 6.4, Hα′), 6.73–6.95 (3 H, m, H2′,4′,6′), 7.17 (1 H, t, *J* 7.8, H5′), 9.45 (1 H, d, *J* 1.5, CHO). δ_C 15.0 (C3), 23.7 (α′-CH_3), 77.1 (C2), 78.1 (Cα′), 113.4 (C6′), 115.3 (C4′), 118.7 (C2′), 129.9 (C5′), 144.3 (C1′), 156.4 (C3′), 203.8 (C1). Mass spectrum *m/z* 193 (9%, $[M-H]^{+\bullet}$), 177 (27), 150 (11), 149 (21), 122 (12), 121 (100).

(1S,3S,4R)-4,5-Diacetoxy-3,4-dihydro-1,3-dimethyl-2-benzopyran (26)

Fresh, neat titanium tetraisopropoxide (120 mg, 0.42 mmol) was added to a solution of the (α′*S*,2*S*) phenolic aldehyde (6) (55 mg, 0.28 mmol) in dry dichloromethane (15 mL) at 0°C under argon. After standing for 10 min at 0°C, the reaction mixture was sonically irradiated at 8–35°C for 5 h, and dichloromethane (30 mL) and a mixture of saturated aqueous solutions of sodium fluoride and ammonium chloride (60 mL, 1 : 1) were added. The mixture was stirred until the yellow colour disappeared. The aqueous layer was extracted with dichloromethane and the residue obtained upon workup was chromatographed (radial, 50% ethyl acetate/hexane) to give the potentially unstable *(1S,3S,4R)-3,4-dihydro-1,3-dimethyl-2-benzopyran-4,5-diol* (7) (40 mg, 73%) as a light-yellow oil (Found: $[M-H]^{+\bullet}$, 193.0852. $C_{11}H_{13}O_3$ requires $[M-H]^{+\bullet}$, 193.0864). υ_{max} (film)/cm^{-1} 3319 (OH), 1591 and 1464 (C=C). δ_H 1.34 (3 H, d, *J* 6.3, 3-CH_3), 1.49 (3 H, d, *J* 6.7, 1-CH_3), 3.52 (1 H, br s, 4-OH),[a] 3.93 (1 H, dq, *J* 6.3 and 7.0, H3), 4.56 (1 H, d, *J* 7.0, H4), 4.90 (1 H, q, *J* 6.7, H1), 6.55 (1 H, d, *J* 7.9, H6), 6.69 (1 H, d, *J* 7.9, H8), 7.12 (1 H, t, *J* 7.9, H7), 7.98 (1 H, br s, 5-OH).[a] δ_C 17.7 (3-CH_3), 21.5 (1-CH_3), 69.0 (C3),[a] 69.8 (C4),[a] 70.1 (C1),[a] 114.2 (C8), 116.8 (C6), 120.3 (C7), 128.9 (C8a), 140.6 (C4a), 155.8 (C5). Mass spectrum *m/z* 194 (20%, $M^{+\bullet}$), 193 (17), 178 (14), 177 (100), 176 (10), 159 (24), 150 (34), 149 (11). The crude diol (7) (40 mg, 0.21 mmol) was immediately dissolved in dry pyridine (2 mL) and acetic anhydride (2 mL) and stirred for 24 h at room temperature. The reaction mixture was quenched and exhaustively extracted with ethyl acetate. The combined organic extracts were washed with dilute hydrochloric acid (5 M), water, and saturated sodium chloride solution. The residue obtained upon workup was chromatographed (radial, 10–20% ethyl acetate/hexane) to afford the *diacetate* (26) (42 mg, 74%) as a colourless oil, $[\alpha]_D$ −88.8° (*c* 1.0 in $CHCl_3$) (Found: C, 65.1; H, 6.5%; $[M-CH_3CO_2H]^{+\bullet}$, 218.0951. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5%; $[M-CH_3CO_2H]^{+\bullet}$, 218.0942). υ_{max} (film)/cm^{-1} 1770 and 1733 (C=O), 1612 and 1587 (C=C). δ_H 1.25 (3 H, d, *J* 6.9, 3-CH_3), 1.60 (3 H, d, *J* 6.5, 1-CH_3), 2.09 (3 H, s, 4-$OCOCH_3$), 2.27 (3 H, s, 5-$OCOCH_3$), 4.25 (1 H, dq, *J* 2.0 and 6.9, H3), 4.91 (1 H, q, *J* 6.5, H1), 5.72 (1 H, d, *J* 2.0, H4), 7.02 (1 H, d, *J* 8.0, H8), 7.06 (1 H, d, *J* 8.0, H6), 7.37 (1 H, t, *J* 8.0, H7). δ_C 17.6 (3-CH_3), 22.9 (4-$OCOCH_3$), 23.2 (5-$OCOCH_3$), 23.9 (1-CH_3), 67.7 (C3),[a] 67.8 (C4),[a] 72.9 (C1),[a] 122.9 (C8), 124.1 (C6), 124.3 (C7), 131.6 (C8a),143.8 (C4a),152.1 (C5), 171.5 (4-$OCOCH_3$), 172.7 (5-$OCOCH_3$). Mass spectrum *m/z* 278 (11%, $M^{+\bullet}$), 236 (13), 234 (96), 218 (100), 203 (65), 192 (72).

(1S,3S,4R)-3,4-Dihydro-4-hydroxy-1,3-dimethyl-5-methoxy-2-benzopyran (27)

A suspension of the diol (7) (900 mg, 4.64 mmol), potassium carbonate (320 mg, 2.32 mmol), and methyl iodide (330 mg, 2.32 mmol) in dry dimethylformamide (8 mL) was stirred at room temperature for 12 h under nitrogen. The reaction was quenched with water and exhaustively extracted with ethyl acetate. The combined organic extracts were washed with water, saturated sodium hydrogen carbonate solution, and saturated sodium chloride solution. The residue obtained upon workup was then chromatographed (radial, 15% ethyl acetate/petroleum ether) to give the *methyl ether* (27) (850 mg, 88%) as white prisms, mp 78–80°C (hexane), $[\alpha]_D$ +9.6° (*c* 1.0 in $CHCl_3$) (Found: C, 69.4; H, 7.6%; $[M-H]^{+\bullet}$, 207.1019. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.8%; $[M-H]^{+\bullet}$, 207.1021). υ_{max}/cm^{-1} 3409 (OH), 1588 and 1473 (C=C). δ_H 1.32 (3 H, d, *J* 6.5, 3-CH_3), 1.56 (3 H, d, *J* 6.7, 1-CH_3), 3.38 (1 H, br s, OH), 3.88 (3 H, s, OCH_3), 4.09 (1 H, dq, *J* 5.4 and 6.5, H3), 4.59 (1 H, d, *J* 5.4, H4), 4.90 (1 H, q, *J* 6.7, H1), 6.68 (1 H, d, *J* 8.0, H6), 6.77 (1 H, d, *J* 8.0, H8), 7.22 (1 H, t, *J* 8.0, H7). δ_C 17.5 (3-CH_3), 21.6 (1-CH_3), 55.5 (OCH_3), 66.9 (C3),[a] 68.7 (C4),[a] 69.9 (C1),[a] 108.3 (C8), 117.4 (C6), 123.4 (C8a), 128.4 (C7), 140.8 (C4a), 157.9 (C5). Mass spectrum *m/z* 207 (13%, $[M-H]^{+\bullet}$), 192 (15), 191 (100), 173 (25), 164 (53).

(1S,3S,4R)-4-Acetoxy-3,4-dihydro-1,3-dimethyl-5-methoxy-2-benzopyran (28)

Compound (27) (60 mg, 0.29 mmol) was dissolved in dry pyridine (2 mL) and acetic anhydride (2 mL) and stirred for 24 h at room temperature. The reaction mixture was quenched with water and exhaustively extracted with ethyl acetate. The combined organic extracts were washed with dilute hydrochloric acid (5 M), water, and saturated sodium hydrogen carbonate solution to afford a crude yellow oil. The residue was chromatographed (radial, 15% ethyl acetate/hexane) to give the *monoacetate* (28) (55 mg, 76%) as pure white needles, mp 96–97°C (hexane), $[\alpha]_D$ −77.5° (*c* 1.0 in $CHCl_3$) (Found: C, 67.4; H, 7.3%; $[M-H]^{+\bullet}$, 249.1149. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.3%; $[M-H]^{+\bullet}$, 249.1126). υ_{max} (cm^{-1}) 1719 (C=O), 1589 and 1474 (C=C). δ_H 1.25 (3 H, d, *J* 6.9, 3-CH_3), 1.57 (3 H, d, *J* 6.5, 1-CH_3), 2.09 (3 H, s, $OCOCH_3$), 3.81 (3 H, s, OCH_3), 4.31 (1 H, dq, *J* 1.9 and 6.9, H3), 4.88 (1 H, q, *J* 6.5, H1), 5.79 (1 H, d, *J* 1.9, H4), 6.75 and 6.77 (2 × 1 H, d, *J* 8.0, H6,8), 7.31 (1 H, t, *J* 8.0, H7). δ_C 15.6 (3-CH_3), 21.3 (1-CH_3), 21.9 (4-$OCOCH_3$), 55.6 (OCH_3), 65.7 (C3),[a] 66.4 (C4),[a] 70.9 (C1),[a] 108.3 (C8), 116.5 (C6), 117.7 (C8a), 129.6 (C7), 141.4 (C4a), 158.3 (C5), 170.9 (4-$OCOCH_3$). Mass spectrum *m/z* 191 (100%, $[M-CH_3CO_2]^{+\bullet}$), 190 (20), 175 (11), 173 (28).

(1S,3S,4S)-3,4-Dihydro-4-hydroxy-1,3-dimethyl-5-methoxy-2-benzopyran (32)

Compound (27) (120 mg, 0.58 mmol) was dissolved in dry diethyl ether (7 mL) and phosphorus pentachloride (240 mg, 1.15 mmol) was added. The mixture was stirred for 10 min at room temperature then quenched with water (25 mL). More diethyl ether (25 mL) was added and the organic phase was washed exhaustively with deionized water. The residue obtained upon workup was immediately redissolved in

acetonitrile (9 mL), and then deionized water (2 mL) containing silver nitrate (540 mg, 3.18 mmol) was added. The mixture was stirred for 4 h at room temperature, during which time a white precipitate formed. Water was added and the mixture was exhaustively extracted with diethyl ether to afford the crude pseudoaxial C4 epimeric alcohol (32). This was chromatographed (radial, 15% ethyl acetate/hexane) to afford first, regenerated alcohol (27) (46 mg, 38%), followed by its C4 epimeric *alcohol* (32) [38 mg, 32%, or 51% based on recovered alcohol (27)] as white needles, mp 93–94°C (hexane), $[\alpha]_D + 18.3°$ (*c* 1.0 in $CHCl_3$) (Found: C, 69.4; H, 7.7%; $[M-H]^{+\bullet}$, 207.1003. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.8%; $[M-H]^{+\bullet}$, 207.1021). υ_{max}/cm^{-1} 3522 (OH), 1587 and 1468 (C═C). δ_H 1.39 (3 H, d, *J* 6.5, 3-CH_3), 1.48 (3 H, d, *J* 6.8, 1-CH_3), 2.20 (1 H, br s, OH), 3.89 (3 H, s, OCH_3), 4.03 (1 H, dq, *J* 1.9 and 6.5, H3), 4.57 (1 H, d, *J* 1.9, H4), 4.99 (1 H, q, *J* 6.8, H1), 6.63 (1 H, d, *J* 8.0, H8), 6.76 (1 H, d, *J* 8.0, H6), 7.24 (1 H, t, *J* 8.0, H7). δ_C 16.8 (3-CH_3), 20.8 (1-CH_3), 55.6 (OCH_3), 62.8 (C3),[a] 66.8 (C4),[a] 71.1 (C1),[a] 108.2 (C8), 117.6 (C6), 124.3 (C8a), 128.8 (C7), 140.1 (C4a), 157.5 (C5). Mass spectrum *m*/*z* 207 (18%, $[M-H]^{+\bullet}$), 192 (16), 191 (100), 173 (25), 164 (41), 163 (13), 149 (20), 117 (11), 111 (11), 109 (19), 105 (11), 97 (22), 95 (26), 93 (11), 85 (15), 83 (32), 81 (31), 79 (13), 69 (66).

*(1*R*,3*S*,4*R*)-4,5-Diacetoxy-3,4-dihydro-1,3-dimethyl-2-benzopyran (35)*

The phenolic aldehyde (25) (350 mg, 1.79 mmol) was treated with titanium tetraisopropoxide, as described above for the phenolic aldehyde (6), to afford the potentially unstable *2-benzopyran-4,5-diol* (34) (270 mg, 77%) as a pale-orange oil (Found: $[M-H]^{+\bullet}$, 193.0865. $C_{11}H_{13}O_3$ requires $[M-H]^{+\bullet}$, 193.0864). υ_{max} (film)/cm^{-1} 3338 (OH), 1614 and 1588 (C═C). δ_H 1.40 (3 H, d, *J* 6.1, 3-CH_3), 1.47 (3 H, d, *J* 6.5, 1-CH_3), 3.46 (1 H, d, *J* 6.7, 4-OH), 3.54 (1 H, dq, *J* 6.1 and 9.0, H3), 4.62 (1 H, dd, *J* 6.7 and 9.0, H4), 4.72 (1 H, q, *J* 6.5, H1), 6.61 (1 H, d, *J* 7.9, H8), 6.71 (1 H, d, *J* 7.9, H6), 7.12 (1 H, t, *J* 7.9, H7), 8.12 (1 H, br s, 5-OH). δ_C 19.9 (3-CH_3), 23.0 (1-CH_3), 72.7 (C3),[a] 74.7 (C4),[a] 76.5 (C1),[a] 116.2 (C8), 117.5 (C6), 122.8 (C7), 130.6 (C8a), 142.8 (C4a), 157.0 (C5). Mass spectrum *m*/*z* 194 (34%, $M^{+\bullet}$), 193 (24), 178 (16), 177 (100), 159 (25), 150 (59), 149 (17), 91 (27). Using the method described above for the conversion of diol (7) into its diacetate (26), the product (34) was acetylated to afford the *diacetate* (35) as a colourless oil, $[\alpha]_D + 89.5°$ (*c* 1.0 in $CHCl_3$) (Found: $[M-H]^{+\bullet}$, 277.1075. $C_{15}H_{17}O_5$ requires $[M-H]^{+\bullet}$, 277.1076). υ_{max} (film)/cm^{-1} 1768 and 1737 (C═O), 1609 and 1584 (C═C). δ_H 1.33 (3 H, d, *J* 6.3, 3-CH_3), 1.54 (3 H, d, *J* 6.5, 1-CH_3), 2.11 (3 H, s, 4-OCOCH_3), 2.25 (3 H, s, 5-OCOCH_3), 3.74 (1 H, dq, *J* 6.3 and 8.2, H3), 4.83 (1 H, q, *J* 6.5, H1), 5.97 (1 H, d, *J* 8.2, H4), 7.02 (1 H, d, *J* 8.0, H8), 7.06 (1 H, d, *J* 8.0, H6), 7.37 (1 H, t, *J* 8.0, H7). δ_C 19.0 (3-CH_3), 21.0 (4-OCO*C*H_3),[a] 21.1 (5-OCO*C*H_3),[a] 21.2 (1-CH_3),[a] 68.7 (C3),[b] 71.6 (C4),[b] 72.7 (C1),[b] 121.4 (C8), 121.7 (C6), 128.9 (C7), 125.4 (C8a), 143.4 (C4a), 149.2 (C5), 169.2 (4-O*C*OCH$_3$), 170.5 (5-O*C*OCH$_3$). Mass spectrum *m*/*z* 234 (18%, $M^{+\bullet}$), 219 (16), 218 (64), 203 (25) 192 (30), 176 (54), 161 (100), 150 (69), 149 (30), 134 (60), 133 (45).

*(1*R*,3*S*,4*R*)-3,4-Dihydro-1,3-dimethyl-5-methoxy-2-benzopyran-4-ol (36)*

A portion of the crude diol (34) (200 mg, 1.03 mmol) was immediately dissolved in dry dimethylformamide (8 mL). Potassium carbonate (710 mg, 5.15 mmol) and methyl iodide (710 mg, 5.15 mmol) were added and the resulting suspension was stirred at room temperature for 12 h under nitrogen. The reaction mixture was quenched with water and exhaustively extracted with ethyl actetate. The residue obtained upon workup was chromatographed (radial, 15% ethyl acetate/hexane) to afford the *methyl ether* (36) (147 mg, 68%) as a clear oil, $[\alpha]_D + 132.6°$ (*c* 1.0 in $CHCl_3$) (Found: C, 68.7; H, 7.7%; $[M-H]^{+\bullet}$, 207.1010. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.8%; $[M-H]^{+\bullet}$, 207.1021). υ_{max} (film)/cm^{-1} 3557 (OH), 1584 and 1476 (C═C). δ_H 1.48 (3 H, d, *J* 6.1, 3-CH_3), 1.50 (3 H, d, *J* 6.5, 1-CH_3), 3.65 (1 H, dq, *J* 6.1 and 8.8, H3), 3.87 (3 H, s, OCH_3), 3.98 (1 H, d, *J* 1.5, OH), 4.66 (1 H, dd, *J* 1.5 and 8.8, H4), 4.80 (1 H, q, *J* 6.5, H1), 6.75 (1 H, d, *J* 8.1, H8), 6.78 (1 H, d, *J* 8.1, H6), 7.22 (1 H, t, *J* 8.1, H7). δ_C 19.8 (3-CH_3), 21.4 (1-CH_3), 55.5 (OCH_3), 69.3 (C3),[a] 72.9 (C4),[a] 75.0 (C1),[a] 108.7 (C8), 116.9 (C6), 125.3 (C8a), 128.3 (C7), 141.8 (C4a), 157.5 (C5). Mass spectrum *m*/*z* 207 (28%, $[M-H]^{+\bullet}$), 192 (14), 191 (100), 173 (30), 164 (68), 163 (15), 161 (12), 97 (11), 95 (15), 83 (16), 81 (18), 69 (22).

*(1*R*,3*S*,4*S*)-3,4-Dihydro-4-hydroxy-1,3-dimethyl-5-methoxy-2-benzopyran-4-ol (38)*

Compound (36) (100 mg, 0.48 mmol) was treated with phosphorus pentachloride (20 mg, 0.96 mmol) followed by silver nitrate (450 mg, 2.65 mmol), as described for the conversion of compound (27) into epimer (32). This afforded the crude pseudoaxial C4 epimeric alcohol (38), which was chromatographed (radial, 15% ethyl acetate/hexane) to afford a *light-yellow oil* (55 mg, 55%), $[\alpha]_D + 76.6°$ (*c* 1.0 in $CHCl_3$) (Found: $[M-H]^{+\bullet}$, 207.1016. $C_{12}H_{15}O_3$ requires $[M-H]^{+\bullet}$, 207.1021). υ_{max} (film)/cm^{-1} 3502 (OH), 1586 and 1462 (C═C). δ_H 1.42 (3 H, d, *J* 6.5, 3-CH_3), 1.56 (3 H, d, *J* 6.5, 1-CH_3), 2.04 (1 H, br s, OH), 3.74 (1 H, dq, *J* 1.7 and 6.5, H3), 3.86 (3 H, s, OCH_3), 4.59 (1 H, d, *J* 1.7, H4), 4.78 (1 H, q, *J* 6.5, H1), 6.75 (1 H, d, *J* 8.0, H8), 6.79 (1 H, d, *J* 8.0, H6), 7.26 (1 H, t, *J* 8.0, H7). δ_C 16.9 (3-CH_3), 21.8 (1-CH_3), 55.6 (OCH_3), 63.2 (C3),[a] 73.3 (C4),[a] 73.7 (C1),[a] 108.4 (C8), 116.6 (C6), 125.0 (C8a), 129.0 (C7), 140.7 (C4a), 157.5 (C5). Mass spectrum *m*/*z* 208 (13%, $M^{+\bullet}$), 207 (42), 192 (16), 191 (100), 173 (23), 164 (50), 163 (13).

*(1*S*,3*S*,4*R*)- and (1*S*,3*S*,4*S*)-4,7-Diacetoxy-3,4-dihydro-1,3-dimethyl-2-benzopyrans (42) and (43), and (1*S*,3*S*,4*S*)-4,5-Diacetoxy-3,4-dihydro-1,3-dimethyl-2-benzopyran (33)*

The aldehyde (23) (300 mg, 0.97 mmol) was dissolved in tetrahydrofuran (25 mL) and a mixture of saturated aqueous solutions of ammonium chloride and sodium fluoride (40 mL, 1 : 1) was added. The solution was then stirred for 16 h at room temperature whereupon it was exhaustively extracted with diethyl ether, dried ($MgSO_4$), and concentrated to afford a mixture consisting largely of two crude C4 epimeric benzo[*c*]pyran-4,7-diols (40) and (41) (91 mg, 50%). This mixture was immediately dissolved in dry pyridine (2 mL) and acetic anhydride (2 mL) and stirred for 24 h at room temperature. The reaction mixture was quenched with water and exhaustively extracted with ethyl acetate. The combined organic extracts were washed with dilute hydrochloric acid (5 M), water, and saturated sodium hydrogen carbonate solution, and the residue obtained upon workup was chromatographed (radial, 10–30% ethyl acetate/hexane) to give the diastereoisomeric diacetates (42), (43), and (33) as an inseparable oily mixture (128 mg, 47% overall yield from aldehyde (23)) (Found: C, 65.1; H, 6.5%; $[M-H]^{+\bullet}$, 277.1094. $C_{15}H_{18}O_5$ requires C, 64.8; H, 6.5%; $[M-H]^{+\bullet}$, 277.1075). υ_{max} (film)/cm^{-1} 1733 (C═O), 1615 and 1500 (C═C). δ_H (mixture of diastereoisomers (42) and (43)) 1.25 (3 H, d, *J* 6.7, 3-CH_3), 1.27 (3 H, d, *J* 6.4, 3-CH_3), 1.50 (3 H, d, *J* 6.8, 1-CH_3), 1.56 (3 H, d, *J* 6.6, 1-CH_3), 2.10 (3 H, s, 4-OCOCH_3), 2.12 (3 H, s, 4-OCOCH_3), 2.28 (3 H, s, 7-OCOCH_3), 2.29 (3 H, s, 7-OCOCH_3), 4.18 (1 H, dq, *J* 4.0 and 6.4, H3), 4.19 (1 H, dq, *J* 2.0 and 6.7, H3), 4.93 (1 H, q, *J* 6.6, H1), 5.11 (1 H, q, *J* 6.8, H1), 5.63 (1 H, d, *J* 4.0, H4), 5.78 (1 H, d, *J* 2.0, H4), 6.81 (1 H, d, *J* 2.3, H8), 6.84 (1 H, d, *J* 2.2, H8), 6.96 (1 H, dd, *J* 2.3 and 8.5, H6), 6.98 (1 H, dd, *J* 2.2 and 8.4, H6), 7.30 (1 H, d, *J* 8.5, H5), 7.40 (1 H, d, *J* 8.4, H5). δ_H (minor diastereoisomer (33)) 1.24 (3 H, d, *J* 6.4, 3-CH_3), 1.52 (3 H, d, *J* 6.9, 1-CH_3), 2.10 (3 H, s, 4-OCOCH_3), 2.27 (3 H, s, 5-OCOCH_3), 4.14 (1 H, dq, *J* 1.9 and 6.4, H3), 5.16 (1 H, q, *J* 6.9, H1), 5.89 (1 H, d, *J* 1.9, H4), 7.35 (1 H, t, *J* 7.9, H7) (H6,8 were obscured by signals of the major isomers). δ_C (mixture of diastereoisomers (42) and (43)) 16.65 and 16.73 (3-CH_3), 20.1 and 21.2 (4-OCO*C*H_3), 21.3 (1-CH_3 for each isomer), 21.5 and 21.8 (7-OCO*C*H_3), 65.6 and 67.8 (C3),[a] 68.2 and 69.3 (C4),[a] 70.8 and 70.9 (C1),[a] 117.8 and 118.3 (C8), 120.6 (C6), 128.4 and 129.2 (C5), 130.7 and 131.5 (C8a), 141.4 and 141.4 (C4a), 150.7 and 150.8 (C7), 169.4 and 169.5 (4-O*C*OCH$_3$), 171.1 and 171.2 (7-O*C*OCH$_3$). Mass spectrum *m*/*z* 234 (24%, $[M–CH_3CHO]^{+\bullet}$), 218 (37), 203 (11), 192 (57), 177 (12), 176 (43), 162 (13), 161 (100), 105 (14), 91 (19).

*(1*R*,3*S*,4*R*)- and (1R,3*S*,4*S*)-4,7-Diacetoxy-3,4-dihydro-1,3-dimethylisochromane (46) and (47)*

According to the method described above, the aldehyde (24) (290 mg, 0.94 mmol) was deprotected and cyclized to afford a mixture consisting largely of the two crude C4 epimeric benzopyran-4,7-diols (1*R*,3*S*,4*R*)- and (1*R*,3*S*,4*S*)-3,4-dihydro-4,7-dihydroxy-1,3-dimethylpyran-4,7-diols (44) and (45) (91 mg, 50%). These were immediately acetylated as above to afford a pale-yellow oil, which was carefully chromatographed (radial, 10–30% ethyl acetate/hexane) to give two products. The product of higher R_f was *compound* (46) (63 mg, 24%), mp 50–51°C (hexane), $[\alpha]_D$ −8.3° (*c* 1.0 in $CHCl_3$) (Found: C, 65.2; H, 6.6%; $M^{+\bullet}$, 278.1155. $C_{15}H_{18}O_5$ requires C, 64.8; H, 6.5%; $M^{+\bullet}$, 278.1154). υ_{max} (film)/cm^{-1} 1741 (C═O), 1614 and 1498 (C═C). δ_H 1.32 (3 H, d, *J* 6.2, 3-CH_3), 1.52 (3 H, d, *J* 6.5, 1-CH_3), 2.18 (3 H, s, 4-$OCOCH_3$), 2.30 (3 H, s, 7-$OCOCH_3$), 3.74 (1 H, dq, *J* 6.2 and 9.0, H3), 4.88 (1 H, q, *J* 6.5, H1), 5.85 (1 H, d, *J* 9.0, H4), 6.83 (1 H, d, *J* 2.2, H8), 6.96 (1 H, dd, *J* 2.2 and 8.5, H6), 7.16 (1 H, d, *J* 8.5, H5). δ_C 17.8 (3-CH_3), 20.4 (4-OCO*C*H_3), 20.4 (7-OCO*C*H_3), 20.8 (1-CH_3), 70.8 (C3),[a] 72.2 (C1),[a] 72.4 (C4),[a] 116.4 (C8), 119.5 (C6), 126.9 (C5), 130.5 (C8a), 140.9 (C4a), 149.2 (C7), 168.7 (4-O*C*OCH_3), 170.3 (7-O*C*OCH_3). Mass spectrum *m*/*z* 234 (62%, $[M - CH_3CHO]^{+\bullet}$), 218 (34), 193 (15), 192 (100), 176 (43), 161 (74), 151 (11), 150 (92), 149 (35), 133 (16). The compound of lower R_f was identified as *compound* (47) (70 mg, 27%), and was obtained as white needles, mp 70–72°C (hexane), $[\alpha]_D$ +226.9° (*c* 1.0 in $CHCl_3$) (Found: C, 64.9; H, 6.4%; $[M–H]^{+\bullet}$, 277.1097. $C_{15}H_{18}O_5$ requires C, 64.8; H, 6.5%; $[M-H]^{+\bullet}$, 277.1075). υ_{max} (cm^{-1}) 1734 (C═O), 1612 and 1498 (C═C). δ_H 1.32 (3 H, d, *J* 6.5, 3-CH_3), 1.58 (3 H, d, *J* 6.5, 1-CH_3), 2.11 (3 H, s, 4-$OCOCH_3$), 2.30 (3 H, s, 7-$OCOCH_3$), 3.90 (1 H, dq, *J* 1.9 and 6.5, H3), 4.81 (1 H, q, *J* 6.5, H1), 5.80 (1 H, d, *J* 1.9, H4), 6.90 (1 H, d, *J* 2.2, H8), 7.00 (1 H, dd, *J* 2.2 and 8.2, H6), 7.42 (1 H, d, *J* 8.2, H5). δ_C 16.2 (3-CH_3), 20.4 (4-OCO*C*H_3), 20.5 (7-OCO*C*H_3), 20.6 (1-CH_3), 67.6 (C3), 71.5 (C1), 72.4 (C4), 116.7 (C8), 119.8 (C6), 129.1 (C8a), 131.0 (C5), 140.1 (C4a), 150.2 (C7), 168.7 (4-O*C*OCH_3), 170.5 (7-O*C*OCH_3). Mass spectrum *m*/*z* 277 (11%, $[M-H]^{+\bullet}$), 234 (17), 219 (100), 192 (11), 159 (11).

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