The asymmetric synthesis of 2-benzopyrans and their quinones through intramolecular diastereoselective ring-closure of titanium phenolates of phenolic aldehydes

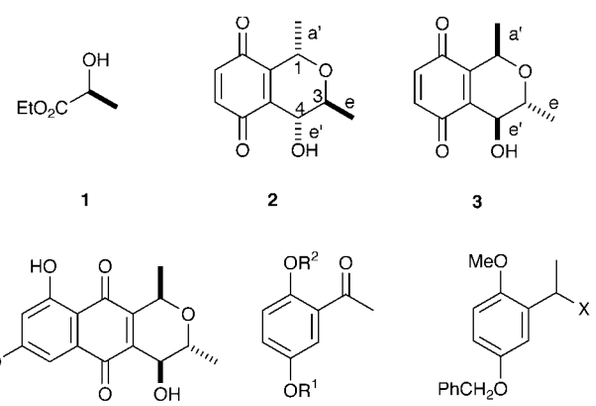
Robin G. F. Giles* and Cynthia A. Joll

Department of Chemistry, Murdoch University, Murdoch WA 6150, Australia

Received (in Cambridge, UK) 22nd February 1999, Accepted 3rd August 1999

Treatment of the phenolic aldehyde (α′*S*,2*S*)-2-(5′-hydroxy-2′-methoxy-α′-methylbenzyloxy)propanal **15** with titanium tetraisopropoxide followed by ultrasonication led to its completely diastereoselective cyclisation in high yield to afford (1*S*,3*S*,4*R*)-3,4-dihydro-1,3-dimethyl-8-methoxy-2-benzopyran-4,5-diol **18**, which was characterised as its more stable 4,5-diacetate **19**. The diastereomeric (α′*R*,2*S*)-2-(5′-hydroxy-2′-methoxy-α′-methylbenzyloxy)-propanal **17** on similar treatment gave rise to a mixture of (1*R*, 3*S*, 4*R*)- and (1*R*, 3*S*, 4*S*)-3,4-dihydro-1,3-dimethyl-8-methoxy-2-benzopyran-4,5-diols **21** and **23**, isolated as the 4,5-diacetates **22** and **24**, in a ratio of 3 : 1. Oxidative dealkylation of the diol **18** with silver(II) oxide afforded (1*S*,3*S*,4*R*)-3,4-dihydro-1,3-dimethyl-4-hydroxy-2-benzopyran-5,8-quinone **2** in high yield, while the epimeric 1*R* quinone **40** was similarly obtained from diol **21**.

In the preceding paper,[1] we described the intermolecular diastereoselective addition of a protected lactaldehyde to metal naphtholates, with a view to the conversion of the synthetic intermediates into the aphid insect pigment derivatives, quinone A and quinone A′,[2] in asymmetric form. Complementary diastereoselectivity was achieved through the use of either the titanium naphtholate, which gave rise solely to the product of *anti* addition, or the more highly coordinated magnesium naphtholate, which afforded only the product of *syn* addition.[3,4] In this paper, the corresponding intramolecular processes are investigated. The requisite chemistry was developed for model benzopyrans, in which the considerably cheaper (*S*)-ethyl lactate **1** was used once again.[1] Thus, a novel and highly effective asymmetric synthesis of the enantiomer **2** of the benzopyranquinone **3** related to quinone A **4** is described.[5]



1 **2** **3**

4

5 $R^1 = CH_2Ph$, $R^2 = Me$
6 $R^1 = R^2 = H$
7 $R^1 = R^2 = Bn$
8 $R^1 = CH_2Ph$, $R^2 = H$

9 X = OH
10 X = Br

Results and discussion

Synthesis of the phenolic aldehydes 15 and 17

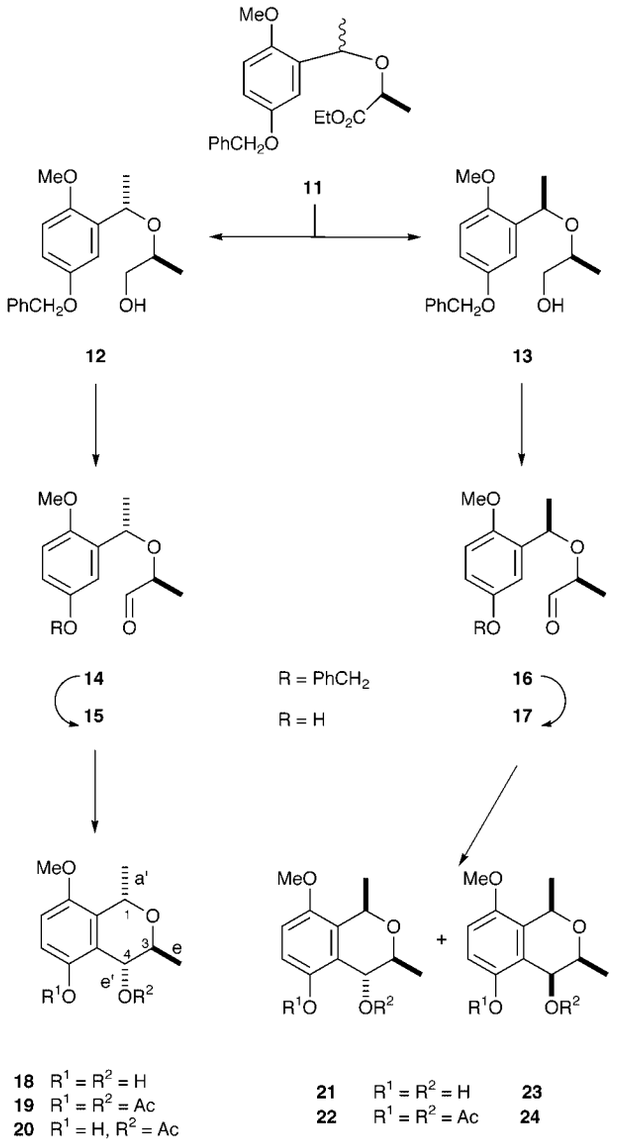
With 5-benzyloxy-2-methoxyacetophenone **5** as the preliminary synthetic target for the assembly of either of the benzopyrans **2** or **3**, reported methods[6,7] for the selective monoalkylation of 2,5-dihydroxyacetophenone **6** with either methyl iodide or benzyl bromide gave rise in our hands to the undesired monoalkylation product or to mixtures. Consequently, **6** was dibenzylated to afford the product **7**, which was selectively deprotected with magnesium bromide etherate[1,8] to yield the golden yellow *o*-hydroxyacetophenone **8**. Methylation of **8** afforded the differentially protected diether **5**, whose synthesis was achieved in three steps in an overall yield of 86% from starting material **6**.

The ketone function of **5** was reduced with lithium aluminium hydride to afford the corresponding alcohol **9**, which was in turn converted into the benzylic bromide **10** using phosphorus tribromide. The yield for each of these two steps was essentially quantitative.

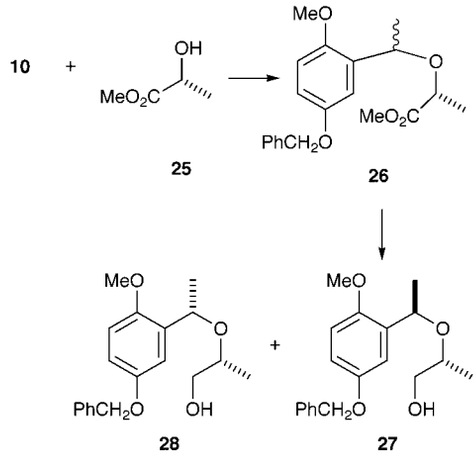
Optimum conditions were sought for the conversion of the benzyl bromide **10** into the diastereomeric mixture of esters **11** using (*S*)-ethyl lactate **1** in the presence of either silver trifluoroacetate in acetonitrile or silver(I) oxide in ether. Although the latter conditions gave slightly better yields and, in some cases, a higher proportion (70 : 30) of the (α′*S*, 2*S*) diastereomer of esters **11**, required for the assembly of the desired product **2**, comparison of the optical rotations of two product mixtures of the diastereomeric esters **11** in the same ratio showed a much lower value for the sample obtained *via* the use of silver(I) oxide, indicating that partial racemisation of the lactate moiety had occurred using this reagent. No observable racemisation occurred using silver trifluoroacetate (*vide infra*). Optimised conditions using silver trifluoroacetate and (*S*)-ethyl lactate resulted in a combined yield of 51% of the inseparable mixture of esters **11**, where the esters were present in a ratio of 55 : 45 favouring the (α′*S*,2*S*) diastereomer required for the synthesis of quinone **2**. The overall yield of this ester mixture obtained from 2,5-dihydroxyacetophenone in six steps was 46%.

Reduction of this mixture of esters with lithium aluminium hydride produced the corresponding diastereomeric alcohols **12** and **13** in a total yield of 94% (Scheme 1). Careful chromatography afforded the individual diastereomers **12** and **13** in a ratio of ~55 : 45. Identification of each particular diastereomer relied upon examination of the ^{1}H NMR spectra of the benzopyrans **18**–**24** later in the synthetic sequence.

To complete the comparison of the silver trifluoroacetate and silver(I) oxide methods of esterification, a sample of the esters **11**, prepared by the use of silver(I) oxide, was reduced with



Scheme 1



Scheme 2

lithium aluminium hydride. The optical rotation of the alcohol **13** was considerably lower {$[\alpha]_D$ +63.2 (*c* 1.0, $CHCl_3$)} than the value of $[\alpha]_D$ +82.7 recorded for the sample of **13** derived from the silver trifluoroacetate method. This confirmed the idea that some racemisation had occurred during formation of the esters **11** using silver(I) oxide.

In order to establish the optical purity of the alcohols **12** and **13** obtained by the silver trifluoroacetate method, their respective enantiomers **27** and **28** were assembled from (*R*)-methyl lactate **25** *via* the inseparable esters **26** (Scheme 2). A 60:40 mixture of the enantiomers **12** and **27** showed good separation in many of the corresponding signals for the two components in the ^{1}H NMR spectrum (500 MHz) on addition of 15 mol% of the asymmetric lanthanide shift reagent Eu(hfc)$_3$. Application of the same protocol to **12** alone showed no signals resulting from **27**. Similar experiments also confirmed the absence of the enantiomer **28** in the alcohol **13**. These experiments established that the diastereomeric alcohols **12** and **13** were optically pure within the limits of this NMR technique; *i.e.*, they had enantiomeric excesses >98%. Thus, no racemisation occurred at the carbon α to the ester group in the formation of the mixture **11**.

The individual alcohols **12** and **13** were oxidised to the corresponding aldehydes **14** and **16** in high yields using Swern methodology.[9,10] To ensure that there was no racemisation during this oxidation step, each aldehyde **14** and **16** was reduced to the respective alcohol **12** and **13** using sodium borohydride in methanol. Examination of the two products (thin layer and gas chromatography) showed no evidence of the alcohol **28** accompanying its C-2 epimer **12**, or of **27** with **13**. Furthermore, the optical rotations of these samples of alcohols **12** and **13** compared well with those of samples obtained directly from the esters **11**. It was therefore concluded that there was no racemisation at the carbon atom α to the aldehyde group during the oxidation step.

Each of the individual aldehydes **14** and **16** was subjected to selective hydrogenolysis of the aromatic benzyl ether protecting group in the presence of both an activated benzyl (lactate) ether and an aldehyde group. Each starting material was recovered unchanged unless it had been subjected either to careful and repeated chromatography or to removal of the first batch of catalyst (10% palladium on carbon) prior to addition of a second batch, whereupon the hydrogenolysis occurred smoothly to afford the phenolic aldehydes **15** and **17**, respectively, in excellent crude yields. The necessity for these precautions is ascribed to contamination of the aldehydes **14** and **16** by adventitious sulfurous material remaining from the Swern oxidations, which led to poisoning of the catalytic surface.

Intramolecular cyclisations of the titanium phenolates

The essence of our novel approach was to now employ an intramolecular version of the methodology of intermolecular diastereoselective *C*-arylation of asymmetric aldehydes developed by Casiraghi *et al.*[1,3,4,11] on our phenolic aldehydes **15** and **17**. A dilute solution of the freshly prepared phenolic aldehyde **15** in methylene chloride was treated with titanium tetraisopropoxide under ultrasonic irradiation, which was essential for the complete consumption of **15**. The product was the unstable benzopyrandiol **18**, for which cyclisation was confirmed by the presence of only two aromatic *ortho*-coupled protons in the ^{1}H NMR spectrum. The relative stereochemistry in the pyran ring was also apparent from this technique in that the pyran proton 3-H resonated at δ 3.89, which is consistent with values reported[12,13] for similar compounds having a *trans*-1,3-dimethyl substitution pattern and is characteristically[14] downfield from the 3-H signal at δ 3.45 in the corresponding *cis*-1,3-dimethyl isomer **21** (*vide infra*). Confirmation that the arylation process had afforded the diol **18**, equivalent to the product of *anti* addition in the intermolecular process, and not its C-4 epimer, was provided by the large coupling constant of 8.6 Hz between 3-H and 4-H, indicative of their near *trans*-diaxial arrangement. The C-4 alcohol is pseudoequatorial as a consequence of the attachment of the phenolic and aldehydic oxygens to titanium in the transition state (*vide infra*). The stereochemistry of the remaining substituents in the likely conformation of diol **18** is highly favoured since the methyl group

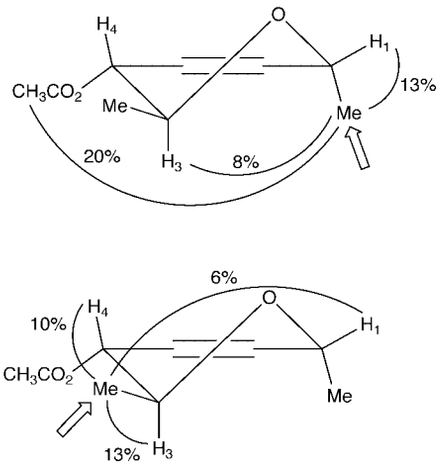
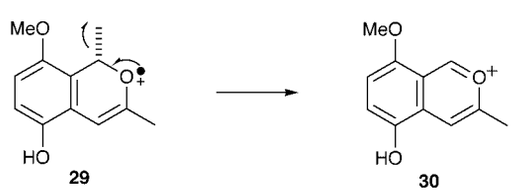


Fig. 1

at C-3 is in the preferred equatorial orientation and the C-1 methyl is pseudoaxial, thereby minimising unfavourable *peri* interactions with the neighbouring methoxy group on the aromatic ring.

The 4,5-diol **18** was immediately converted into its more stable diacetate **19** in the very good overall yield of 71% for the two steps from the phenolic aldehyde **15**. In the ^{1}H NMR spectra, the deshielding of 4-H from δ 4.55 in diol **18** to δ 5.75 in diacetate **19** and the coupling constant of 4.8 Hz between 3-H and 4-H in the latter are entirely consistent with observations made for analogous compounds.[2,12,13] The results of NOE difference spectroscopy also supported the stereochemical assignment as **19** through the data presented in Fig. 1 (the enhancements, indicated by curves, arise upon irradiation of the C-1 or the C-3 methyl group, indicated by the arrows, in two separate experiments).

In the mass spectrum of diacetate **19**, two important fragment ions, **29** and **30**, were seen at *m*/*z* 206 and 191 (the base peak) (Scheme 3).

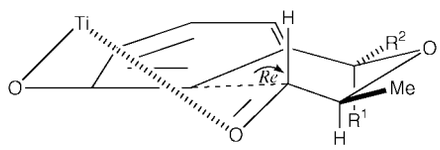


Scheme 3

An additional minor, more polar band was collected during chromatography of the crude diacetate **19**. The mass ratio of the diacetate to this minor band was 96:4. The ^{1}H NMR spectrum of this band indicated that it was composed of two benzopyrans in approximately equal ratio. Three important conclusions could be made as to the structure of each compound for the same reasons described earlier for diol **18** and diacetate **19**: first, that the methyls at C-1 and C-3 were *trans*; secondly, that both were C-4 acetates; and finally, that these acetates were both pseudoequatorial. Since the absolute configuration at C-1 in the phenolic aldehyde **15** was effectively fixed, it can be concluded that the asymmetric centres in these minor pyrans had the same absolute configurations as in the diacetate **19**. The aromatic region of the ^{1}H NMR spectrum of this band clearly showed an AB quartet and a singlet. These data allowed the assignment of phenol **20** and an analogue which is further monosubstituted on the aromatic ring.

Thus, for all the products observed, there was no racemisation at the chiral centre α to the aldehyde functionality of **15** during the titanium reaction and the intramolecular cyclisation was completely diastereoselective.

This complete diastereoselectivity for the pseudoequatorial C-4 hydroxy group can be rationalised as a consequence of effective, non-chelate reaction through a monocoordinated titanium "Felkin–Anh"-type transition state,[1,11a,15] in which intramolecular arylation occurs exclusively from the *Re* face of the aldehyde, as shown in transition state **31**. In addition, the



31 R^1 = Me, R^2 = H
32 R^1 = H, R^2 = Me

exclusive adoption of the pseudoequatorial configuration for this hydroxy group is entirely consistent with our recent observation[16] for such benzopyrans that the preferred stereochemistry for the benzylic substitutents at C-1 and C-4 is for one of them to be pseudoaxial and the other pseudoequatorial, *i.e.*, these substituents are *cis*. This is observed here even though the method of assembly of the benzopyran ring system involves ring-closure through formation of the C-4–C-4a bond, whereas previously1 [14c,16] the ring system arose through formation of the C-1–C-8a bond.

Similar cyclisation of the epimeric phenolic aldehyde **17** with titanium tetraisopropoxide under ultrasonic irradiation produced a mixture of predominantly the two diols, **21**, as the major product, and **23**, as the minor product. Since the ^{1}H NMR spectrum of the diols **21** and **23** was run on crude material, owing to their instability, only the signals for the major isomer **21** could be fully assigned. Its stereochemistry was evident from the chemical shift of the proton H-3 at δ 3.45, leading to the assignment of the *cis*-1,3-dimethyl arrangement (*cf.*, δ 3.89 for isomer **18**), and from the large coupling constant of 8.8 Hz between H-3 and H-4, which confirmed their axial/pseudoaxial relationship. Thus, the C-1 methyl substituent in this case was pseudoequatorial.

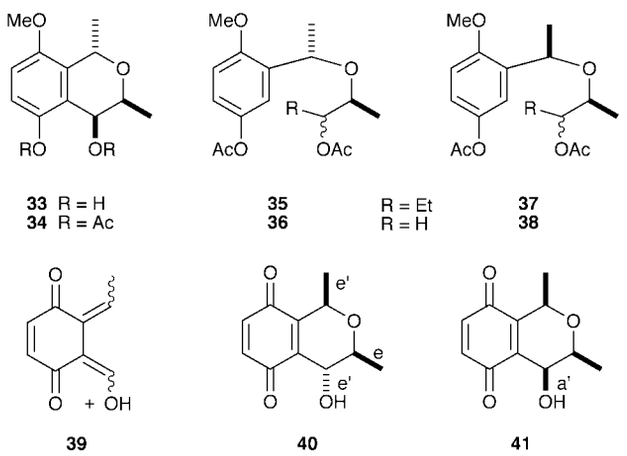
Conversion of the mixture of diols **21** and **23** into the corresponding diacetates gave an inseparable mixture of **22** and **24**, in a ratio of 3:1 and in a total yield of 64% for the two steps from the phenolic aldehyde **17**. In the ^{1}H NMR spectrum, the signals for 3-H in the *cis*-1,3-dimethyl compounds **22** and **24** appeared upfield (δ 3.62 and 3.77, respectively) of the same signal (δ 4.11) in the *trans*-isomer **19**. In the diastereomer **22**, the coupling constant between 3-H and 4-H was 7.8 Hz, which confirmed that the C-4 acetoxy substituent was pseudoequatorial. The corresponding coupling constant (*J* 1.3 Hz) for the minor component **24** indicated this C-4 acetoxy group to be pseudoaxial. The mass spectrum for the mixture of **22** and **24** was very similar to that for isomer **19**.

In this intramolecular cyclisation of the titanium phenolate **32**, a diastereoselectivity of the pseudoequatorial–pseudoaxial C-4 alcohols of 3:1 was achieved. Mechanistically, the monocoordinated titanium "Felkin–Anh" transition state **32** differs from that of the *trans*-dimethyl case **31** only in the stereochemistry of the derived C-1 methyl, which is now pseudoequatorial, leading to less favourable *peri* interactions with the aromatic methoxy group. This may cause the reduced selectivity for arylation of the *Re* face of the aldehyde, leading also to the formation of the minor product **23**. It is noteworthy that, in this minor product, the benzylic substituents at C-1 and C-4 are *cis*, which we have noted previously[16] and above is a favoured stereochemical arrangement. That **23** is formed at all in competition with *Re* arylation leading to **21** (which was exclusive in the conversion of **15** to **18**) may be the consequence of this preference.

Intramolecular cyclisations of the magnesium phenolates

In the case of the intermolecular reactions of magnesium naphtholates with an asymmetric aldehyde,[1] the magnesium naphtholates could be pre-formed using ethylmagnesium bromide, before addition of the aldehyde, and this led to complete *syn* stereoselectivity in good yields. This pre-formation of the magnesium phenolate with ethylmagnesium bromide would obviously not be possible for the phenolic aldehydes **15** and **17** and competitive reactions of the Grignard reagent with the aldehyde moiety were anticipated. Nevertheless, the reactions were investigated with a view to determining whether, for any benzopyrans formed, the stereochemistry of the cyclisation would be exclusively *syn*, as for the intermolecular reactions.

As anticipated, the reaction of phenolic aldehyde **15** with ethylmagnesium bromide was more complex than for the corresponding titanium tetraisopropoxide reaction. After acetylation of the primary products, the only benzopyran isolated was **19** in low yield (13%), identical with that obtained in high yield from the titanium phenolate. Other products isolated were **35**, from the expected Grignard reaction (19%; a 70:30



mixture of C-1 diastereomers), and **36**, derived from reduction of the aldehyde, a known[17] side-reaction in Grignard addition reactions (4%). Thus, in this intramolecular case, only the product of *anti* arylation was isolated, albeit in a low yield. This indicates that the α-chelate controlled process, evident in the intermolecular reactions with magnesium naphtholates,[1] was prohibited in the highly strained intramolecular reaction. Rather, arylation occurred through a monocoordinated magnesium phenolate transition state analogous to **31**.

The reaction of the phenolic aldehyde **17** with ethylmagnesium bromide afforded, after acetylation, the benzopyrans **22** and **24** in a combined yield of 28% and in a ratio of 30:70, respectively. Also isolated were the products **37** of Grignard addition [10% (as a 65:35 mixture of diastereomers)] and the product **38** of reduction (13%).

These results for aldehyde **17** indicate that, while some degree of chelation of the magnesium with the α-oxygen of the lactate may occur, allowing for arylation from the *Si* face of the aldehyde **17** and thus *syn* addition to furnish the major diacetate **24**, it is certainly not exclusive.

Synthesis of the asymmetric quinones 2 and 40

Having been purified as the more stable diacetate **19**, the diol **18** was readily regenerated from it using lithium aluminium hydride and immediately subjected to smooth oxidative demethylation with silver(II) oxide.[18,19] This treatment afforded the asymmetric quinone **2**, in a yield of 91% from the diol **18** and of 76% over the two steps. The mass spectrum, while not exhibiting a molecular ion, showed a base peak at *m*/*z* 164 for fragment **39**, arising from a retro Diels–Alder reaction of the molecular ion.

The ^{1}H NMR spectrum of quinone **2** exhibited four one-proton resonances in the region δ 3.5 to 5. The hydroxy proton appeared at δ 3.52 as a sharp doublet (J 2.5 Hz) coupled to 4-H. The signal for the axial 3-H, appearing at δ 3.84, was a doublet of doublet of quartets (J 0.5, 7.9 and 6.2 Hz). The long-range coupling of 0.5 Hz was to the pseudoequatorial proton 1-H, and the large coupling (J 7.9 Hz) to 4-H confirmed the almost *trans*-diaxial arrangement of 3-H and 4-H. The remaining two protons in this region were a doublet of doublet of doublets (J 1.6, 2.5 and 7.9 Hz) for 4-H at δ 4.35, and another doublet of doublet of quartets (J 0.5, 1.6 and 6.8 Hz) at δ 4.75 assigned to 1-H. The pseudoequatorial proton 1-H, in addition to its coupling with the C-1 methyl protons (J 6.8 Hz), showed both long-range coupling (J 0.5 Hz) to the axial 3-H and long-range homoallylic coupling (J 1.6 Hz) to the pseudoaxial 4-H. The latter coupling constant is consistent with that observed for the natural derivative quinone A.[2,12]

The mixture of stable diacetates **22** and **24** (3:1) was also converted into the mixture of unstable diols **21** and **23**. This mixture was subjected to oxidative demethylation with silver(II) oxide, and chromatography afforded the asymmetric quinone **40**. The small scale of this reaction did not allow for the isolation and characterisation of the expected minor quinonoid product **41**. As for its epimer **2**, the mass spectrum of quinone **40** showed the base peak at *m*/*z* 164 for the ion **39** noted above.

The ^{1}H NMR spectrum of **40** provided four one-proton resonances in the region δ 3.4 to 5. The 3-H proton for this *cis*-1,3-dimethylbenzopyranquinone resonated at δ 3.42, at higher field, as expected, than that (δ 3.84) for the 1,3-*trans* diastereomer **2**. This signal appeared as a doublet of quartets (J 8.3 and 6.1 Hz), with the former coupling constant confirming a near *trans*-diaxial arrangement for 3-H and 4-H. No long-range coupling between 3-H and 1-H was observed, in contrast to the situation for the C-1 diastereomer **2**. The C-4 hydroxy proton resonated as a doublet (J 2.0 Hz) at δ 3.69. The proton 4-H appeared as a doublet of doublet of doublets (J 2.0, 2.9 and 8.3) at δ 4.38, reflecting respective coupling to the hydroxy, to 1-H (homoallylic) and to 3-H. The proton 1-H appeared at δ 4.67 as a doublet of quartets (J 2.9 and 6.7 Hz). For this diastereomer **40**, the protons 1-H and 4-H are both pseudoaxial, giving rise to a homoallylic coupling constant (J 2.9 Hz) characteristically[13,14a] larger than that (J 1.6 Hz) observed above for compound **2**, where the corresponding protons are pseudoequatorial and pseudoaxial, respectively.

Conclusions

The use of titanium phenolates for the intramolecular diastereoselective arylation of asymmetric lactaldehydes is highly successful. The cyclisation of the phenolic aldehyde **15** led, after acetylation, to the *trans*-dimethylbenzopyran **19** in an overall yield of 71% for the two steps. The reaction proceeds with complete diastereoselectivity in favour of this product of *anti* addition. For the corresponding cyclisation of the aldehyde **17**, partial diastereoselectivity afforded the two *cis*-dimethylbenzopyrans **22** and **24** in a ratio of 3:1, favouring the product **22** of *anti* addition, and in a combined yield of 64% over the two steps.

The methodology used was sufficiently mild to prevent racemisation at the asymmetric centre α to the ester group in **11**, or to the aldehyde group in **14** to **17**. Also, no such racemisation was observed in the cyclisation reactions.

Although the intermolecular diastereoselective arylation of asymmetric aldehydes with bromomagnesium naphtholates is exceedingly effective,[1] the analogous intramolecular process is not, presumably owing to the inability, through steric constraints, to achieve additional coordination to magnesium. In this intramolecular process, alternative methods for the generation of the bromomagnesium phenolates need to be developed to avoid side reactions with the Grignard reagent used here.

Magnesium bromide–diethyl ether described earlier in this paper and elsewhere [1,8,20] is an obvious possibility.

The assembly of quinone **2** represents the first asymmetric synthesis of a compound with the correct absolute stereochemistry of the substituents about the pyran ring for the enantiomer of the aphid insect pigment-derived quinone A **4**. The use of (*R*)-lactate would provide quinone **3** with the required absolute stereochemistry.

It is anticipated that this process will be adaptable to the general synthesis of naturally occurring or derived naphthopyranquinones, including, for example, deoxyquinone A, through the reductive removal of the benzylic hydroxy group.[21] This procedure would also have much relevance in the development of asymmetric syntheses of some of the eleutherins and the ventiloquinones.[22]

Experimental

The conditions used are as described in the preceding paper.[1]

2′,5′-Dibenzyloxyacetophenone 7

A stirred suspension of 2′,5′-dihydroxyacetophenone **6** (1.00 g, 6.57 mmol), benzyl bromide (3.93 cm^3, 32.9 mmol) and anhydrous potassium carbonate (4.53 g, 32.9 mmol) in dry acetone (90 cm^3) under nitrogen was heated under reflux (18 h). The reaction mixture was then cooled in ice and filtered through a pad of Celite. Concentration of the filtrate gave a brown oil, which was subjected to column chromatography with 10 and 20% ethyl acetate–hexane as eluents to yield the dibenzyl ether **7** as a pale yellow solid (2.17 g, 99%). Recrystallisation from benzene–hexane furnished tiny needles, mp 79.5–81.5 °C (lit.,[23] 80–1 °C); ν_{max}/cm^{-1} 1678 (C=O), 1604, 1585, 1492 and 1455 (C=C); δ_H (300 MHz) 2.60 (3H, s, $COCH_3$), 5.03 and 5.10 (each 2H, s, OCH_2), 6.95 (1H, d, *J* 9.0, 3′-H), 7.07 (1H, dd, *J* 3.2 and 9.0, 4′-H) and 7.30–7.44 (11H, m, C_6H_5 and 6′-H); δ_C (75.5 MHz) 32.08 ($CO\mathit{C}H_3$), 70.59 and 71.28 (OCH_2), 114.52 (C-6′),[a] 115.13 (C-3′),[a] 121.06 (C-4′), 127.52 (C-2″, C-6″, C-2‴ and C-6‴),[b] 127.97 (C-4″),[c] 128.15 (C-4‴),[c] 128.54 (C-3″ and C-5″),[b] 128.64 (C-3‴ and C-5‴),[b] 128.92 (C-1′), 136.38 (C-1″),[d] 136.78 (C-1‴),[d] 152.68 (C-5′),[e] 152.72 (C-2′)[e] and 199.93 ($\mathit{C}OCH_3$); *m*/*z* 332 (M$^+$, 10%), 290 (9), 241 (1), 92 (24), 91 (100) and 65 (14).

5′-Benzyloxy-2′-hydroxyacetophenone 8

Following the procedure described by House,[24] a solution of magnesium bromide–diethyl ether in a 7:1 benzene–ether mixture was prepared and used immediately.

A solution of the dibenzyl ether **7** (12.2 g, 36.7 mmol) in a 7:1 benzene–ether mixture (146 cm^3) was treated with the magnesium bromide–diethyl ether solution (348 cm^3, containing 129 mmol based on the amount of bromine used). The reaction mixture was heated under reflux for 21 h and then cooled. It was poured into saturated ammonium chloride solution and extracted with ether and ethyl acetate. The organic extracts were washed with water, saturated ammonium chloride solution, water and brine, dried and concentrated to a light brown oil (14.4 g). Column chromatography with 5–20% ethyl acetate–hexane gave the monobenzyl ether **8** as an orange oil which crystallised (9.16 g). Recrystallisation from methanol afforded golden yellow prisms (8.04 g, 90%), mp 68.5–70 °C (lit.,[7] 69–70 °C); ν_{max}/cm^{-1} 2954br (OH), 1643 (C=O), 1618, 1584, 1488 and 1470 (C=C); λ_{max} (EtOH) 230 (log ε 3.0), 260 (3.1), 332 (3.1) and 362 (3.1); δ_H (300 MHz) 2.56 (3H, s, $COCH_3$), 5.03 (2H, s, OCH_2), 6.91 (1H, d, *J* 9.1, 3′-H), 7.16 (1H, dd, *J* 3.0 and 9.1, 4′-H), 7.23 (1H, d, *J* 3.0, 6′-H), 7.30–7.45 (5H, m, C_6H_5) and 11.86 (1H, s, OH); δ_C (75.5 MHz) 26.66 ($CO\mathit{C}H_3$), 71.09 (OCH_2), 115.25 (C-6′), 119.14 (C-3′), 119.18 (C-1′), 124.98 (C-4′), 127.49 (C-2″ and C-6″),[a] 128.11 (C-4″), 128.62 (C-3″ and C-5″),[a] 136.64 (C-1″), 150.70 (C-2′), 156.86 (C-5′) and 203.97 ($\mathit{C}OCH_3$); *m*/*z* 242 (M$^+$, 100%), 213 (1), 165 (5), 105 (6), 92 (22), 91 (52) and 65 (7).

5′-Benzyloxy-2′-methoxyacetophenone 5

The phenolic monobenzyl ether **8** (8.02 g, 33.1 mmol) was dissolved in dry *N*,*N*-dimethylformamide (175 cm^3) and methyl iodide (4.28 cm^3, 133 mmol), and anhydrous potassium carbonate (6.86 g, 49.7 mmol) was added with stirring. The suspension was heated (18 h, 90 °C) and then cooled and poured into water. Extraction with ether and ethyl acetate, washing of the organic layer with water, sodium hydroxide solution (1 M), water and brine, drying and concentrating gave a crude orange oil (9.50 g). Column chromatography with 5–20% ethyl acetate–hexane gave the methoxy compound **5** as a whitish solid (8.12 g, 96%). Recrystallisation of a portion of the product from benzene–hexane yielded small crystals, mp 53–56.5 °C [lit.,[7] 56 °C (hexane)]; ν_{max}/cm^{-1} 1667 (C=O), 1608, 1581, 1496 and 1468 (C=C); δ_H (300 MHz) 2.61 (3H, s, $COCH_3$), 3.85 (3H, s, OCH_3), 5.03 (2H, s, OCH_2), 6.89 (1H, d, *J* 9.0, 3′-H), 7.09 (1H, dd, *J* 3.2 and 9.0, 4′-H) and 7.28–7.44 (6H, m, C_6H_5 and 6′-H); δ_C (75.5 MHz) 31.78 ($CO\mathit{C}H_3$), 55.93 (OCH_3), 70.59 (OCH_2), 113.09 (C-6′),[a] 115.13 (C-3′),[a] 121.12 (C-4′), 127.48 (C-2″ and C-6″),[b] 127.93 (C-4″), 128.29 (C-1′), 128.51 (C-3″ and C-5″),[b] 136.83 (C-1″), 152.46 (C-5′),[c] 153.65 (C-2′)[c] and 199.22 ($\mathit{C}OCH_3$); *m*/*z* 256 (M$^+$, 100%), 179 (15), 165 (3), 91 (49) and 65 (11).

1-(5′-Benzyloxy-2′-methoxyphenyl)ethanol 9

To a stirred slurry of lithium aluminium hydride (2.5 g, 66 mmol) in dry ether (35 cm^3) was added dropwise a solution of the acetophenone **5** (4.0 g, 16 mmol) in dry ether (40 cm^3) under argon. After 1 h, saturated ammonium chloride solution was added dropwise, followed by anhydrous magnesium sulfate. Filtration through Celite and concentration of the filtrate gave a yellow oil (4.5 g). Column chromatography with 20–40% ethyl acetate–hexane yielded the benzyl alcohol **9** as a pale orange oil (4.0 g, 99%). A portion of this was subjected to further column chromatography to give an oil, trituration of which (petrol, 0 °C) produced a crystalline solid. Recrystallisation from ether–hexane afforded small needles, mp 60–62 °C (Found: C, 74.5; H, 7.2. $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.0%); ν_{max}/cm^{-1} 3412 (OH), 1607, 1590, 1497 and 1454 (C=C); δ_H (300 MHz) 1.47 (3H, d, *J* 6.5, 1-CH_3), 2.74 (1H, br s, OH), 3.79 (3H, s, OCH_3), 5.00 (2H, s, OCH_2), 5.05 (1H, q, *J* 6.5, 1-H), 6.77 (1H, d, *J* 8.8, 3′-H), 6.81 (1H, dd, *J* 2.8 and 8.8, 4′-H), 7.03 (1H, d, *J* 2.8, 6′-H) and 7.27–7.44 (5H, m, C_6H_5); δ_C (75.5 MHz) 22.86 (C-2), 55.67 (OCH_3), 66.29 (C-1), 70.55 (OCH_2), 112.27 (C-3′),[a] 113.35 (C-4′),[a] 113.54 (C-6′),[a] 127.43 (C-2″ and C-6″),[b] 127.81 (C-4″), 128.46 (C-3″ and C-5″),[b] 134.66 (C-1′), 137.19 (C-1″), 150.78 (C-5′)[c] and 152.91 (C-2′);[c] *m*/*z* 258 (M$^+$, 25%), 240 (13), 167 (11), 149 (13), 135 (8), 107 (7), 91 (100), 77 (8) and 65 (26).

1-(5′-Benzyloxy-2′-methoxyphenyl)-1-bromoethane 10

A stirred solution of the benzyl alcohol **9** (6.00 g, 23.3 mmol) in dry benzene (86 cm^3) was treated with phosphorus tribromide (4.09 g, 15.1 mmol) in dry benzene (20 cm^3). After 2.5 h, normal work-up (A) with ether (minus the acid wash) gave essentially the bromo compound **10** as a yellow oil (7.46 g, quantitative). Trituration of this oil (petrol, −70 °C) produced a crystalline solid which was recrystallised from methylene chloride–hexane to afford cream plates, mp 66–69 °C (Found: C, 60.2; H, 5.2. $C_{16}H_{17}BrO_2$ requires C, 59.8; H, 5.3%); ν_{max}/cm^{-1} 1504 and 1454 (C=C); δ_H (300 MHz) 1.98 (3H, d, *J* 7.0, 1-CH_3), 3.82 (3H, s, OCH_3), 5.01 (2H, s, OCH_2), 5.66 (1H, q, *J* 7.0, 1-H), 6.77 (1H, d, *J* 8.9, 3′-H), 6.86 (1H, dd, *J* 3.0 and 8.9, 4′-H), 7.17 (1H, d, *J* 3.0, 6′-H) and 7.30–7.45 (5H, m, C_6H_5); δ_C (75.5 MHz) 25.71 (C-2), 42.88 (C-1), 56.19 (OCH_3), 70.70 (OCH_2), 112.01 (C-3′),[a] 114.58 (C-4′),[a] 115.02 (C-6′),[a] 127.58 (C-2″ and C-6″),[b] 127.97 (C-4″), 128.57 (C-3″ and C-5″),[b] 132.38 (C-1′), 137.05 (C-1″),

150.26 (C-5′)[c] and 152.87 (C-2′);[c] *m/z* 322 (M^+ {^{81}Br}, 3%), 320 (M^+ {^{79}Br}, 3), 241 (57), 150 (12), 149 (11), 122 (22), 107 (10), 91 (100) and 65 (10).

Ethyl (α′*R* and *S*,2*S*)-2-(5′-benzyloxy-2′-methoxy-α′-methylbenzyloxy)propanoate 11

Silver trifluoroacetate was prepared in approx. 93% yield over the two steps from silver nitrate following the method described by Janssen and Wilson,[25] except that traces of trifluoroacetic acid were removed azeotropically by the addition of benzene and further concentration under reduced pressure and the crude product was dried *in vacuo* and used without further purification. The solid silver trifluoroacetate (15.5 g, 70.1 mmol) was then added to a stirred solution of the bromo compound **10** (5.00 g, 15.6 mmol) and (*S*)-ethyl lactate **1** {Fluka Chemie AG; measured $[\alpha]_D$ −11.0 (neat)} (31.8 cm^3, 277 mmol) in dry acetonitrile (350 cm^3), producing an immediate yellow precipitate. After stirring for 4 h, the now grey precipitate was removed by filtration and the filtrate concentrated. The residue was dissolved in ether and the organic layer washed a number of times with water, then brine, dried and concentrated to an orange oil (7.83 g). Column chromatography (fractions monitored by gas and thin layer chromatography) with 10 and 20% ethyl acetate–hexane–0.5% triethylamine gave the diastereomeric esters **11** as a yellow oil (3.02 g, 54%). Further purification by radial chromatography and distillation produced the esters as an oil, bp 180–187 °C/0.14 mmHg (Kugelrohr) [Found: C, 70.3; H, 7.4%; M^+, 358.1771 (major diastereomer); M^+, 358.1773 (minor diastereomer). $C_{21}H_{26}O_5$ requires C, 70.4; H, 7.3%; M, 358.1780]; $[\alpha]_D^{15}$ −74.8 (mixture of diastereomers at C-α′); ν_{max} (film)/cm^{-1} 1747 (C=O), 1607, 1590, 1495 and 1455 (C=C); δ_H (major diastereomer) 1.29 (3H, t, *J* 7.1, C*H*$_3$CH$_2$), 1.32 (3H, d, *J* 6.9, 2-CH$_3$), 1.43 (3H, d, *J* 6.4, α′-CH$_3$), 3.75 (3H, s, OCH$_3$), 3.81 (1H, q, *J* 6.9, 2-H), 4.20 and 4.23 (each 1H, dq, *J* 10.8 and 7.1, CH$_3$C*H*$_2$), 4.91 (1H, q, *J* 6.4, α′-H), 5.03 and 5.05 (2H, AB, *J* 11.8, C$_6$H$_5$C*H*$_2$), 6.78 (1H, d, *J* 8.9, 3′-H), 6.85 (1H, dd, *J* 3.1 and 8.9, 4′-H), 7.07 (1H, d, *J* 3.1, 6′-H) and 7.30–7.44 (5H, m, C$_6$H$_5$); δ_H (minor diastereomer) 1.18 (3H, t, *J* 7.1, C*H*$_3$CH$_2$), 1.42 (6H, d, *J* 6.6, 2- and α′-CH$_3$), 3.78 (3H, s, OCH$_3$), 3.99 (1H, q, *J* 6.6, 2-H), 4.04 and 4.07 (each 1H, dq, *J* 10.8 and 7.1, CH$_3$C*H*$_2$), 5.00 (1H, q, *J* 6.6, α′-H), 5.02 (2H, s, C$_6$H$_5$C*H*$_2$), 6.76 (1H, d, *J* 8.9, 3′-H), 6.82 (1H, dd, *J* 3.1 and 8.9, 4′-H), 7.21 (1H, d, *J* 3.1, 6′-H) and 7.30–7.44 (5H, m, C$_6$H$_5$); δ_C (mixture of two diastereomers) 13.99 and 14.16 (*C*H$_3$CH$_2$), 18.12 and 19.02 (C-3), 22.55 and 22.76 (ArCH*C*H$_3$), 55.75 and 55.80 (OCH$_3$), 60.61 (CH$_3$*C*H$_2$), 70.41 and 70.97 (C-α′), 70.46 and 70.51 (C$_6$H$_5$*C*H$_2$), 72.31 and 72.83 (C-2), 111.23 and 111.39 (C-3′),[a] 112.75 and 113.37 (C-4′),[a] 113.97 and 114.06 (C-6′),[a] 127.36 and 127.50 (C-2″ and C-6″),[b] 127.74 and 127.80 (C-4″), 128.40 and 128.48 (C-3″ and C-5″),[b] 132.66 and 132.71 (C-1′), 137.20 and 137.28 (C-1″), 150.56 and 151.09 (C-5′),[c] 153.03 (C-2′)[c] and 173.02 and 173.86 (C-1); *m/z* (major diastereomer) 358 (M^+, 8%), 267 (3), 257 (17), 241 (32), 151 (55), 122 (10) and 91 (100); *m/z* (minor diastereomer) 358 (M^+, 10%), 267 (12), 257 (13), 241 (25), 151 (59), 122 (14) and 91 (100).

(α′*S*,2*S*)- and (α′*R*,2*S*)-2-(5′-Benzyloxy-2′-methoxy-α′-methylbenzyloxy)propan-1-ol 12 and 13

The mixture of diastereomeric esters **11** (1.82 g, 5.08 mmol) was reduced with lithium aluminium hydride as described above for the reduction of the acetophenone **5**. The pale yellow oil obtained (1.65 g) was subjected to column chromatography followed by radial chromatography (twice) with 5–50% ethyl acetate–hexane–0.5% triethylamine to achieve separation of the two alcohols:

1. Of R_f 0.26 (30% ethyl acetate–hexane), the higher R_f alcohol **13**, as an oil (0.65 g, 40%); $[\alpha]_D$ +78.8. Distillation afforded an oil, bp 165–170 °C/0.2 mmHg (Kugelrohr) (Found: C, 72.0; H, 7.9. $C_{19}H_{24}O_4$ requires C, 72.1; H, 7.65%); $[\alpha]_D$ +82.7; ν_{max} (film)/cm^{-1} 3458 (OH), 1607, 1590, 1496 and 1455 (C=C); δ_H 1.13 (3H, d, *J* 6.1, 2-CH$_3$), 1.43 (3H, d, *J* 6.5, α′-CH$_3$), 2.10 (1H, br s, OH), 3.41 (1H, dd, *J* 7.3 and 11.3, 1-Hα), 3.47 (1H, dd, *J* 3.4 and 11.3, 1-Hβ), 3.52 (1H, ddq, *J* 3.4, 7.3 and 6.1, 2-H), 3.80 (3H, s, OCH$_3$), 4.96 (1H, q, *J* 6.5, α′-H), 5.03 (2H, s, C$_6$H$_5$C*H*$_2$), 6.80 (1H, d, *J* 8.9, 3′-H), 6.84 (1H, dd, *J* 3.0 and 8.9, 4′-H), 7.05 (1H, d, *J* 3.0, 6′-H) and 7.30–7.44 (5H, m, C$_6$H$_5$); δ_C 16.16 (C-3), 22.07 (ArCH*C*H$_3$), 55.80 (OCH$_3$), 66.74 (C-1), 69.68 (C-α′), 70.52 (C$_6$H$_5$*C*H$_2$), 73.32 (C-2), 111.63 (C-3′),[a] 113.89 (C-4′),[a] 114.02 (C-6′),[a] 127.44 (C-2″ and C-6″),[b] 127.80 (C-4″), 128.47 (C-3″ and C-5″),[b] 132.65 (C-1′), 137.16 (C-1″), 150.98 (C-5′)[c] and 153.00 (C-2′);[c] *m/z* 316 (M^+, 12%), 241 (12), 240 (8), 150 (19), 122 (11), 91 (100), 77 (14) and 65 (24).

2. Of predominantly R_f 0.17, the lower R_f alcohol **12** with a small amount (93:7) of **13** present, as a yellow oil (0.87 g, 54%; yields **13** and **12**: 44 and 50%, ratio **13**:**12**, approx. 45:55). Further chromatography gave pure **12** as a pale yellow oil (Found: M^+, 316.1673. $C_{19}H_{24}O_4$ requires M, 316.1675); $[\alpha]_D$ −56.9; ν_{max} (film)/cm^{-1} 3437 (OH), 1607, 1590, 1495 and 1455 (C=C); δ_H 1.01 (3H, d, *J* 6.3, 2-CH$_3$), 1.38 (3H, d, *J* 6.4, α′-CH$_3$), 2.05 (1H, br s, OH), 3.44 (1H, dd, *J* 5.9 and 11.3, 1-Hα), 3.57 (1H, ddq, *J* 3.6, 5.9 and 6.3, 2-H), 3.66 (1H, dd, *J* 3.6 and 11.3, 1-Hβ), 3.78 (3H, s, OCH$_3$), 4.97 (1H, q, *J* 6.4, α′-H), 5.03 and 5.05 (2H, AB, *J* 11.8, C$_6$H$_5$C*H*$_2$), 6.78 (1H, d, *J* 8.9, 3′-H), 6.84 (1H, dd, *J* 3.1 and 8.9, 4′-H), 7.12 (1H, d, *J* 3.1, 6′-H) and 7.29–7.46 (5H, m, C$_6$H$_5$); δ_C 17.20 (C-3), 22.75 (ArCH*C*H$_3$), 55.79 (OCH$_3$), 65.69 (C-1), 69.77 (C-α′), 70.55 (C$_6$H$_5$*C*H$_2$), 74.12 (C-2), 111.24 (C-3′),[a] 113.38 (C-4′),[a] 113.72 (C-6′),[a] 127.43 (C-2″ and C-6″),[b] 127.82 (C-4″), 128.50 (C-3″ and C-5″),[b] 134.01 (C-1′), 137.28 (C-1″), 150.42 (C-5′)[c] and 152.93 (C-2′);[c] *m/z* 316 (M^+, 10%), 241 (26), 240 (17), 150 (14), 149 (21) and 91 (100).

Methyl (α′*R* and *S*,2*R*)-2-(5′-benzyloxy-2′-methoxy-α′-methylbenzyloxy)propanoate 26

The procedure detailed above for the preparation of the esters **11** was followed, except that 12 equiv. of (*R*)-methyl lactate **25** were used in place of 18 equiv. of (*S*)-ethyl lactate **1**, to convert the bromo compound **10** (2.06 g, 6.42 mmol) to the diastereomeric esters **26** as a yellow oil (0.80 g, 36%) after chromatography. Further column chromatography produced the esters as an oil (Found: C, 69.6; H, 7.3. $C_{20}H_{24}O_5$ requires C, 69.75; H, 7.0%); $[\alpha]_D$ +71.9; ν_{max} (film)/cm^{-1} 1752 (C=O), 1607, 1590, 1496 and 1454 (C=C); δ_H (major diastereomer) 1.32 (3H, d, *J* 6.9, 2-CH$_3$), 1.421 (3H, d, *J* 6.4, α′-CH$_3$), 3.747 (3H, s, OCH$_3$), 3.751 (3H, s, CO$_2$CH$_3$), 3.83 (1H, q, *J* 6.9, 2-H), 4.89 (1H, q, *J* 6.4, α′-H), 5.03 and 5.05 (2H, AB, *J* 11.8, OCH$_2$), 6.77 (1H, d, *J* 8.9, 3′-H), 6.84 (1H, dd, *J* 3.1 and 8.9, 4′-H), 7.06 (1H, d, *J* 3.1, 6′-H) and 7.29–7.45 (5H, m, C$_6$H$_5$); δ_H (minor diastereomer) 1.418 (6H, d, *J* 6.6, 2- and α′-CH$_3$), 3.61 (3H, s, CO$_2$CH$_3$), 3.78 (3H, s, OCH$_3$), 4.00 (1H, q, *J* 6.6, 2-H), 5.00 (1H, q, *J* 6.6, α′-H), 5.02 (2H, s, OCH$_2$), 6.76 (1H, d, *J* 8.9, 3′-H), 6.82 (1H, dd, *J* 3.1 and 8.9, 4′-H), 7.19 (1H, d, *J* 3.1, 6′-H) and 7.29–7.45 (5H, m, C$_6$H$_5$); δ_C (mixture of two diastereomers) 18.10 and 19.10 (C-3), 22.55 and 22.77 (ArCH-*C*H$_3$), 51.75 and 51.82 (CO$_2$*C*H$_3$), 55.78 and 55.86 (OCH$_3$), 70.33 and 71.10 (C-α′), 70.51 and 70.55 (OCH$_2$), 72.28 and 72.69 (C-2), 111.35 and 111.42 (C-3′),[a] 112.78 and 113.25 (C-4′),[a] 114.04 and 114.31 (C-6′),[a] 127.40 and 127.53 (C-2″ and C-6″),[b] 127.79 and 127.84 (C-4″), 128.46 and 128.51 (C-3″ and C-5″),[b] 132.48 and 132.59 (C-1′), 137.22 and 137.29 (C-1″), 150.67 and 151.11 (C-5′),[c] 153.05 (C-2′)[c] and 173.46 and 174.36 (C-1); *m/z* 344 (M^+, 13%), 257 (9), 241 (16), 151 (41), 122 (8) and 91 (100).

(α′*R*,2*R*)- and (α′*S*,2*R*)-2-(5′-Benzyloxy-2′-methoxy-α′-methylbenzyloxy)propan-1-ol 27 and 28

The mixture of diastereomeric esters **26** (0.67 g, 1.9 mmol) was reduced with lithium aluminium hydride (0.15 g, 3.9 mmol) as described above for the reduction of the acetophenone **5**.

Repeated column chromatography of the pale yellow oil obtained (0.65 g), using 5–50% ethyl acetate–hexane–0.5% triethylamine as eluents, resulted in separation of the two alcohols (total yield: 84%; ratio **27**:**28** of approx. 55:45):

1. The higher R_f alcohol **28** as an oil (0.24 g, 39%). Distillation afforded **28** as an oil of bp 165 °C/0.2 mmHg (Kugelrohr); $[\alpha]_D$ −80.2; the ^{1}H NMR spectrum (500 MHz) was identical to that reported above for the enantiomeric alcohol **13**.

2. The lower R_f alcohol **27** as a pale yellow oil (0.28 g, 45%); $[\alpha]_D$ +55.9; the ^{1}H NMR spectrum (500 MHz) was identical to that reported above for **12**.

(α′*S*,2*S*)-2-(5′-Benzyloxy-2′-methoxy-α′-methylbenzyloxy)-propanal 14

To a solution of oxalyl chloride (0.25 cm^3, 2.9 mmol) in dry methylene chloride (8 cm^3) at −70 °C under an atmosphere of argon was added dropwise a solution of dimethyl sulfoxide (0.40 cm^3, 5.6 mmol) in dry methylene chloride (3 cm^3). After stirring for 20 min, a solution of the alcohol **12** (180 mg, 0.57 mmol) in methylene chloride (2 cm^3) was added dropwise and the stirring continued (15 min). Dry triethylamine (0.95 cm^3, 6.8 mmol) was then added dropwise and, after 5 min, the mixture was allowed to warm to room temperature. After the addition of water (9 cm^3), normal work-up (A) with methylene chloride, followed by column chromatography of the yellow oil (10 and 20% ethyl acetate–hexane–0.5% triethylamine) gave the aldehyde **14** as a pale yellow oil (155 mg, 87%). Further chromatography and distillation gave **14** as an oil, bp 150 °C/0.15 mmHg (Kugelrohr) (Found: C, 72.8; H, 7.6%; M$^+$, 314.1517. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.05%; M, 314.1518); $[\alpha]_D$ −138.0; ν_{max} (film)/cm^{-1} 1734 (C=O), 1607, 1590, 1496 and 1454 (C=C); δ_H 1.18 (3H, d, *J* 7.1, 2-CH$_3$), 1.45 (3H, d, *J* 6.4, α′-CH$_3$), 3.68 (1H, dq, *J* 2.0 and 7.1, 2-H), 3.75 (3H, s, OCH$_3$), 4.97 (1H, q, *J* 6.4, α′-H), 5.04 and 5.05 (2H, AB, *J* 11.8, OCH$_2$), 6.78 (1H, d, *J* 8.8, 3′-H), 6.86 (1H, dd, *J* 3.1 and 8.8, 4′-H), 7.07 (1H, d, *J* 3.1, 6′-H), 7.30–7.44 (5H, m, C$_6$H$_5$) and 9.72 (1H, d, *J* 2.0, 1-H); δ_C 15.95 (C-3), 22.82 (ArCH*C*H$_3$), 55.76 (OCH$_3$), 70.57 (OCH$_2$), 71.13 (C-α′), 77.88 (C-2), 111.37 (C-3′),[a] 112.97 (C-4′),[a] 114.16 (C-6′),[a] 127.41 (C-2″ and C-6″),[b] 127.87 (C-4″), 128.54 (C-3″ and C-5″),[b] 132.18 (C-1′), 137.20 (C-1″), 150.94 (C-5′),[c] 153.02 (C-2′)[c] and 204.50 (C-1); *m*/*z* 314 (M$^+$, 58%), 242 (34), 241 (100), 151 (56), 122 (48), 107 (39) and 91 (99).

(α′*S*,2*S*)-2-(5′-Hydroxy-2′-methoxy-α′-methylbenzyloxy)-propanal 15

A stirred suspension of the benzyl ether **14** (120 mg, 0.38 mmol) and 10% palladium on carbon catalyst (152 mg) in ethyl acetate (8 cm^3) was subjected to an atmosphere of hydrogen (2 h). The mixture was then filtered through Celite, a further quantity of catalyst (152 mg) added and the suspension exposed to a hydrogen atmosphere for an additional 2 h. Filtration through Celite and concentration of the filtrate afforded the potentially unstable phenol **15** as a pinkish oil (82 mg, 96%) and was used the following day for subsequent reactions; ν_{max} (film)/cm^{-1} 3390 (OH), 1732 (C=O), 1613, 1596, 1497 and 1456 (C=C); δ_H 1.23 (3H, d, *J* 7.1, 2-CH$_3$), 1.45 (3H, d, *J* 6.4, α′-CH$_3$), 3.73 (3H, s, OCH$_3$), 3.75 (1H, dq, *J* 1.8 and 7.1, 2-H), 4.97 (1H, q, *J* 6.4, α′-H), 5.79 (1H, br s, OH), 6.72 (2H, m, 3′- and 4′-H), 6.97 (1H, m, 6′-H) and 9.71 (1H, d, *J* 1.8, 1-H); δ_C 15.86 (C-3), 22.71 (ArCH*C*H$_3$), 55.83 (OCH$_3$), 71.21 (C-α′), 77.94 (C-2), 111.73 (C-3′), 113.10 (C-4′),[a] 114.66 (C-6′),[a] 132.07 (C-1′), 149.88 (C-5′),[b] 150.57 (C-2′)[b] and 204.44 (C-1); *m*/*z* 224 (M$^+$, 8%), 151 (100), 136 (40), 107 (9), 91 (11) and 77 (10).

(α′*R*, 2*S*)-2-(5′-Benzyloxy-2′-methoxy-α′-methylbenzyloxy)-propanal 16

According to the method described above for the preparation of the aldehyde **14** from the alcohol **12**, the alcohol **13** (450 mg, 1.42 mmol) was converted into the aldehyde **16** as a crude orange oil (542 mg). Column chromatography (10 and 20% ethyl acetate–hexane–0.5% triethylamine) afforded aldehyde **16** as a yellow oil (406 mg, 91%). Further chromatography and distillation produced **16** as an oil, bp 135–155 °C/0.2 mmHg (Kugelrohr) (Found: C, 72.5; H, 7.4. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.05%); $[\alpha]_D$ +59.2; ν_{max} (film)/cm^{-1} 1734 (C=O), 1608, 1590, 1497 and 1454 (C=C); δ_H 1.27 (3H, d, *J* 6.9, 2-CH$_3$), 1.44 (3H, d, *J* 6.4, α′-CH$_3$), 3.75 (1H, dq, *J* 1.6 and 6.9, 2-H), 3.77 (3H, s, OCH$_3$), 5.02 and 5.04 (2H, AB, *J* 11.7, OCH$_2$), 5.04 (1H, q, *J* 6.4, α′-H), 6.78 (1H, d, *J* 8.9, 3′-H), 6.85 (1H, dd, *J* 3.1 and 8.9, 4′-H), 7.11 (1H, d, *J* 3.1, 6′-H), 7.30–7.44 (5H, m, C$_6$H$_5$) and 9.44 (1H, d, *J* 1.6, 1-H); δ_C 15.25 (C-3), 22.46 (ArCH*C*H$_3$), 55.81 (OCH$_3$), 70.11 (C-α′), 70.56 (OCH$_2$), 78.30 (C-2), 111.50 (C-3′),[a] 113.59 (C-4′),[a] 114.44 (C-6′),[a] 127.47 (C-2″ and C-6″),[b] 127.89 (C-4″), 128.53 (C-3″ and C-5″),[b] 132.10 (C-1′), 137.15 (C-1″), 150.91 (C-5′),[c] 153.00 (C-2′)[c] and 203.76 (C-1); *m*/*z* 314 (M$^+$, 12%), 241 (49), 151 (24), 149 (15), 122 (6), 107 (5), 92 (14) and 91 (100).

(α′*R*, 2*S*)-2-(5′-Hydroxy-2′-methoxy-α′-methylbenzyloxy)-propanal 17

In a similar manner to the hydrogenolysis of benzyl ether **14** described immediately above, the benzyl ether **16** (494 mg, 1.57 mmol) was deprotected to give the phenol **17** as a pinkish oil (352 mg, 100%) and was used the following day for subsequent reactions. Column chromatography of a sample of crude phenol **17** with 20 and 50% ethyl acetate–hexane–0.5% triethylamine produced purified phenol **17** as a viscous pale yellow oil (92%) (Found: M$^+$, 224.1048. $C_{12}H_{16}O_4$ requires M, 224.1049); $[\alpha]_D$ +70.5; ν_{max} (film)/cm^{-1} 3378 (OH), 1732 (C=O), 1611, 1597, 1497 and 1455 (C=C); δ_H 1.29 (3H, d, *J* 6.9, 2-CH$_3$), 1.43 (3H, d, *J* 6.4, α′-CH$_3$), 3.75 (3H, s, OCH$_3$), 3.83 (1H, dq, *J* 1.3 and 6.9, 2-H), 5.04 (1H, q, *J* 6.4, α′-H), 6.37 (1H, br s, OH), 6.71 (2H, m, 3′-and 4′-H), 7.01 (1H, m, 6′-H) and 9.48 (1H, d, *J* 1.3, 1-H); δ_C 15.02 (C-3), 22.35 (ArCH*C*H$_3$), 55.84 (OCH$_3$), 70.14 (C-α′), 78.22 (C-2), 111.85 (C-3′), 113.61 (C-4′),[a] 114.96 (C-6′),[a] 131.82 (C-1′), 150.04 (C-5′),[b] 150.43 (C-2′)[b] and 203.77 (C-1); *m*/*z* 224 (M$^+$, 7%), 151 (100), 136 (31), 107 (6), 91 (4) and 77 (6).

(1*S*,3*S*, 4*R*)-4,5-Diacetoxy-3,4-dihydro-1,3-dimethyl-8-methoxy-2-benzopyran 19

Fresh, neat titanium tetraisopropoxide (0.157 cm^3, 0.53 mmol) was added to an ice-cooled solution of freshly prepared phenol **15** (103 mg, 0.46 mmol) in dry methylene chloride (25 cm^3) under argon. After standing for 15 min in the ice-bath, the orange solution was transferred to the ultrasonication bath for a further 5 h (bath temperature range: 10–30 °C). The reaction mixture was then poured into methylene chloride and saturated sodium fluoride solution and stirred vigorously. After 2–3 days, when the colour had discharged, the organic layer was separated and the aqueous layer re-extracted with methylene chloride. The combined organic layers were washed with water and brine, dried and concentrated to an orange oil (approx. 103 mg), which was the cyclised product, (1*S*,3*S*,4*R*)-3,4-dihydro-4,5-dihydroxy-1,3-dimethyl-8-methoxy-2-benzopyran **18**; δ_H 1.38 (3H, d, *J* 6.1, 3-CH$_3$), 1.51 (3H, d, *J* 6.6, 1-CH$_3$), 3.14 (1H, br s, 4-OH), 3.74 (3H, s, OCH$_3$), 3.89 (1H, dq, *J* 8.6 and 6.1, 3-H), 4.55 (1H, d, *J* 8.6, 4-H), 5.00 (1H, q, *J* 6.6, 1-H), 6.66 and 6.69 (2H, AB, *J* 8.8, 7- and 6-H) and 7.62 (1H, br s, 5-OH); δ_C 18.42 (*C*H$_3$C-3), 18.73 (*C*H$_3$C-1), 55.55 (OCH$_3$), 67.35 (C-3),[a] 68.32 (C-4),[a] 70.80 (C-1),[a] 110.68 (C-7), 114.19 (C-6), 121.44 (C-8a),[b] 129.10 (C-4a),[b] 148.29 (C-5)[c] and 149.50 (C-8).[c]

The crude, fairly clean cyclised product **18** was then immediately dissolved in dry pyridine (2 cm^3) and acetic anhydride (2 cm^3) and stirred (20 h). Water and ether were added and stirring continued (3 h). Normal work-up (A) (ether) produced a yellow oil (124 mg). Radial chromatography with 20% ethyl acetate–hexane yielded the title diacetate **19**, of R_f 0.32 (30% ethyl

acetate–hexane), as a pale yellow oil (101 mg, 71% over two steps) (Found: C, 62.6; H, 6.8. $C_{16}H_{20}O_6$ requires C, 62.3; H, 6.5%); $[\alpha]_D$ −104.1; ν_{max} (film)/cm^{-1} 1732 (C=O), 1597 and 1484 (C=C); δ_H 1.20 (3H, d, *J* 6.6, 3-CH_3), 1.58 (3H, d, *J* 6.5, 1-CH_3), 2.09 (3H, s, 4-O_2CCH_3), 2.23 (3H, s, 5-O_2CCH_3), 3.81 (3H, s, OCH_3), 4.11 (1H, dq, *J* 4.8 and 6.6, 3-H), 4.99 (1H, q, *J* 6.5, 1-H), 5.75 (1H, d, *J* 4.8, 4-H) and 6.83 and 6.94 (2H, AB, *J* 8.9, 7- and 6-H); δ_C 17.30 (*C*H_3C-3), 19.46 (*C*H_3C-1), 20.84 (*C*H_3CO_2C-4),[a] 21.13 (*C*H_3CO_2C-5),[a] 55.46 (OCH_3), 66.04 (C-4),[b] 66.86 (C-3),[b] 68.20 (C-1),[b] 110.50 (C-7), 121.17 (C-6), 124.17 (C-8a),[c] 130.33 (C-4a),[c] 142.82 (C-5), 152.85 (C-8), 169.82 (*C*O_2C-4)[d] and 170.58 (*C*O_2C-5);[d] *m/z* 308 (M^+, 4%), 266 (4), 206 (54), 192 (24), 191 (100), 163 (32), 149 (15), 135 (9), 121 (10), 107 (8), 91 (10), 77 (8) and 43 (63). A minor band, of R_f 0.19, was also collected: a yellow oil (4 mg, approx. 3%) composed of two benzopyrans in approximately equal ratio as analysed by ^{1}H NMR spectroscopy, one of which was possibly (1*S*,3*S*,4*R*)-4-acetoxy-3,4-dihydro-1,3-dimethyl-5-hydroxy-8-methoxy-2-benzopyran **20** and the other perhaps a derivative of this, further monosubstituted on the aromatic ring: δ_H 1.22 and 1.25 (each 3H, d, *J* 6.5, 3-CH_3), 1.57 and 1.60 (each 3H, d, *J* 6.3, *J* 6.5, 1-CH_3), 2.10 and 2.13 (each 3H, s, 4-O_2CCH_3), 3.66 and 3.80 (each 3H, s, OCH_3), 4.11 and 4.18 (each 1H, dq, *J* 5.5 and 6.5, *J* 5.4 and 6.5, 3-H), 4.95 and 5.03 (each 1H, q, *J* 6.3, *J* 6.5, 1-H), 5.76 and 5.84 (each 1H, d, *J* 5.0, *J* 5.3, 4-H), 6.32 (1H, s, 6- or 7-H) and 6.74 and 6.77 (2H, AB, *J* 9.0, 7- and 6-H).

(1*R*,3*S*,4*R*)- and (1*R*,3*S*,4*S*)-4,5-Diacetoxy-3,4-dihydro-1,3-dimethyl-8-methoxy-2-benzopyran 22 and 24

Freshly prepared phenol **17** (123 mg, 0.55 mmol) was treated with titanium tetraisopropoxide as described above for the phenol **15** to give a mixture of two diastereomeric cyclised products, (1*R*,3*S*,4*R*)- and (1*R*,3*S*,4*S*)-3,4-dihydro-4,5-dihydroxy-1,3-dimethyl-8-methoxy-2-benzopyran **21** and **23**, major and minor, respectively, as an orange oil (approx. 123 mg); ν_{max} (film)/cm^{-1} 3380br (OH), 1610 and 1485 (C=C); δ_H (major diastereomer only) 1.42 (3H, d, *J* 6.1, 3-CH_3), 1.50 (3H, d, *J* 6.3, 1-CH_3), 2.68 (1H, br s, 4-OH), 3.45 (1H, dq, *J* 8.8 and 6.1, 3-H), 3.75 (3H, s, OCH_3), 4.62 (1H, d, *J* 8.8, 4-H), 4.92 (1H, q, *J* 6.3, 1-H), 6.729 and 6.733 (2H, AB, *J* 5.5, 7- and 6-H) and 7.60 (1H, br s, 5-OH); δ_C (major diastereomer only) 17.96 (*C*H_3C-3), 21.59 (*C*H_3C-1), 55.48 (OCH_3), 71.24 (C-3),[a] 71.34 (C-4),[a] 73.38 (C-1),[a] 111.29 (C-7), 114.60 (C-6), 123.10 (C-8a),[b] 128.96 (C-4a),[b] 149.06 (C-5)[c] and 149.10 (C-8);[c] *m/z* (mixture) 224 (M^+, 22%), 206 (10), 191 (71), 180 (21), 163 (15), 151 (100), 136 (30), 107 (10), 91 (11), 77 (10) and 43 (13).

The crude product mixture of **21** and **23** was then converted, as described above for the cyclised product **18**, to the crude diacetate products as a yellow oil (153 mg). Column chromatography with 10 and 20% ethyl acetate–hexane as eluents yielded an approx. 75:25 mixture of the inseparable title diacetates **22** and **24** as a pale yellow oil (108 mg, 64% over two steps), R_f 0.30 (30% ethyl acetate–hexane) [Found: C, 61.8; H, 6.7%; M^+, 308.1260 (mixture). $C_{16}H_{20}O_6$ requires C, 62.3; H, 6.5%; M, 308.1260]; $[\alpha]_D$ +77.8 (mixture of diastereomers at C-4); ν_{max} (film)/cm^{-1} 1765 and 1740 (C=O), 1594, 1481 and 1445 (C=C); δ_H (major diastereomer **22**) 1.30 (3H, d, *J* 6.3, 3-CH_3), 1.55 (3H, d, *J* 6.4, 1-CH_3), 2.10 (3H, s, 4-O_2CCH_3), 2.22 (3H, s, 5-O_2CCH_3), 3.62 (1H, dq, *J* 7.8 and 6.3, 3-H), 3.81 (3H, s, OCH_3), 4.93 (1H, q, *J* 6.4, 1-H), 5.85 (1H, d, *J* 7.8, 4-H) and 6.82 and 6.92 (2H, AB, *J* 8.8, 7- and 6-H); δ_H (minor diastereomer **24**) 1.24 (3H, d, *J* 6.4, 3-CH_3), 1.63 (3H, d, *J* 6.3, 1-CH_3), 2.12 (3H, s, 4-O_2CCH_3), 2.27 (3H, s, 5-O_2CCH_3), 3.77 (1H, dq, *J* 1.3 and 6.4, 3-H), 3.82 (3H, s, OCH_3), 4.94 (1H, q, *J* 6.3, 1-H), 5.84 (1H, underlying d, *J* 1.3, 4-H) and 6.87 and 6.95 (2H, AB, *J* 8.9, 7- and 6-H); δ_C (major diastereomer **22**) 18.50 (*C*H_3C-3), 21.01 (*C*H_3C-1), 21.07 (*C*H_3CO_2C-4),[a] 21.53 (*C*H_3CO_2C-5),[a] 55.40 (OCH_3), 67.96 (C-4), 70.92 (C-3),[b] 71.91 (C-1),[b] 110.38 (C-7), 121.26 (C-6), 126.93 (C-8a),[c] 130.77 (C-4a),[c] 142.20 (C-5), 153.29 (C-8), 169.61 (*C*O_2C-4)[d] and 170.48 (*C*O_2C-5);[d] δ_C (minor diastereomer **24**) 16.73 (*C*H_3C-3), 20.92 (*C*H_3C-1), 20.95 (*C*H_3CO_2C-4),[a] 21.29 (*C*H_3CO_2C-5),[a] 55.40 (OCH_3), 64.25 (C-4), 70.55 (C-3),[b] 70.73 (C-1),[b] 111.10 (C-7), 120.78 (C-6), 125.99 (C-8a),[c] 130.10 (C-4a),[c] 142.40 (C-5), 153.74 (C-8), 170.30 (*C*O_2C-4)[d] and 170.83 (*C*O_2C-5);[d] *m/z* (mixture) 308 (M^+, 1%), 266 (2), 248 (8), 233 (3), 206 (19), 192 (12), 191 (100), 163 (16), 149 (7), 91 (4) and 43 (26).

Ethylmagnesium bromide treatment of the phenol 15

A solution of the Grignard reagent ethyl magnesium bromide in dry ether was prepared and an aliquot (0.32 cm^3, containing 0.44 mmol) was transferred to a round-bottomed flask which was then flushed with argon. A solution of the freshly prepared phenol **15** (82 mg, 0.37 mmol) in dry ether (7.5 cm^3) was added, leading to a heavy suspension. The ether was removed under vacuum and dry methylene chloride (19 cm^3) added to the cream solid. The resulting suspension was transferred to the ultrasonication bath for 6 h (bath temperature range: 10–30 °C). The reaction mixture was then poured into methylene chloride and saturated ammonium chloride solution and stirred vigorously. After 3 days, the organic layer was separated and the aqueous layer re-extracted with methylene chloride. The combined organic layers were washed with water and brine, dried and concentrated to a crude product mixture as a pale yellow oil (79 mg). Subsequent treatment of this mixture with acetic anhydride and pyridine as described above for the crude cyclised product **18** gave an orange oil (83 mg); thin layer chromatography (TLC) (30% ethyl acetate–hexane) showed at least eight components, two of which were major. Isolation of these two bands by column chromatography (5–20% ethyl acetate–hexane as eluents) gave:

1. Of R_f 0.37 (30% ethyl acetate–hexane), (α′*S*,2*S*,1*R* or *S*)-2-(5′-acetoxy-2′-methoxy-α′-methylbenzyloxy)-1-ethylpropyl acetate **35**, a 70:30 mixture of diastereomers at C-1, as an oil (23 mg, 19% over two steps), further purified by preparative thin layer chromatography (PLC) (20% ethyl acetate–hexane as eluent) (Found: M^+, 338.1728 (mixture). $C_{18}H_{26}O_6$ requires M, 338.1729); $[\alpha]_D$ −78.0 (*c* 0.6, $CHCl_3$) (mixture of diastereomers at C-1); ν_{max} (film)/cm^{-1} 1763 and 1738 (C=O), 1610, 1495 and 1464 (C=C); δ_H (major diastereomer) 0.93 (3H, t, *J* 7.4, 1″-CH_3), 1.02 (3H, d, *J* 6.5, 2-CH_3), 1.32 (3H, d, *J* 6.4, α′-CH_3), 1.48–1.62 (2H, m, 1-CH_2), 2.08 (3H, s, 1-O_2CCH_3), 2.276 (3H, s, 5′-O_2CCH_3), 3.48 (1H, dq, *J* 5.0 and 6.5, 2-H), 3.81 (3H, s, OCH_3), 4.89 (1H, m, 1-H), 4.95 (1H, q, *J* 6.4, α′-H), 6.81 (1H, d, *J* 8.8, 3′-H), 6.92 (1H, dd, *J* 2.9 and 8.8, 4′-H) and 7.17 (1H, d, *J* 2.9, 6′-H); δ_H (minor diastereomer) 0.89 (3H, t, *J* 7.5, 1″-CH_3), 1.08 (3H, d, *J* 6.5, 2-CH_3), 1.30 (3H, d, *J* 6.4, α′-CH_3), 1.69–1.77 (2H, m, 1-CH_2), 2.10 (3H, s, 1-O_2CCH_3), 2.278 (3H, s, 5′-O_2CCH_3), 3.40 (1H, dq, *J* 3.0 and 6.5, 2-H), 3.80 (3H, s, OCH_3), 5.02 (1H, m, 1-H), 5.03 (1H, q, *J* 6.4, α′-H), 6.81 (1H, d, *J* 8.8, 3′-H), 6.93 (1H, dd, *J* 2.9 and 8.8, 4′-H) and 7.14 (1H, d, *J* 2.9, 6′-H); δ_C (major diastereomer) 10.01 (C-2″), 16.38 (C-3), 21.06 (*C*H_3CO_2C-1),[a] 21.12 (*C*H_3CO_2C-5′),[a] 22.39 (C-1″), 22.67 (ArCH*C*H_3), 55.64 (OCH_3), 70.79 (C-α′), 74.32 (C-2), 77.03 (C-1), 110.62 (C-3′), 119.75 (C-6′),[b] 120.33 (C-4′),[b] 134.43 (C-1′), 144.21 (C-5′), 153.68 (C-2′), 169.91 (*C*O_2C-1)[c] and 170.82 (*C*O_2C-5′);[c] δ_C (minor diastereomer) 10.21 (C-2″), 15.89 (C-3), 21.06 (*C*H_3CO_2C-1),[a] 21.12 (*C*H_3CO_2C-5′),[a] 22.64 (ArCH*C*H_3), 23.01 (C-1″), 55.52 (OCH_3), 69.30 (C-α′), 73.80 (C-2), 76.03 (C-1), 110.56 (C-3′), 119.51 (C-6′),[b] 120.38 (C-4′),[b] 134.04 (C-1′), 144.30 (C-5′), 153.96 (C-2′), 169.86 (*C*O_2C-1)[c] and 170.94 (*C*O_2C-5′);[c] *m/z* (mixture) 338 (M^+, 1%), 296 (11), 194 (22), 193 (79), 151 (100), 136 (24) and 43 (30).

2. Of R_f 0.30, an oil (20 mg), an approx. 75:25 mixture of: the diacetate **19** (13% over two steps) [the ^{1}H and ^{13}C NMR spectra (500 and 126 MHz) of which were identical to that reported above for the same compound obtained through the titanium phenolate of **15**; the mass spectrum of which showed a similar

fragmentation pattern to that reported above, except that no molecular ion was present] and, probably, (α′*S*,2*S*)-2-(5′-acetoxy-2′-methoxy-α′-methylbenzyloxy)propyl acetate **36** (4% over two steps); δ_H 1.12 (3H, d, *J* 6.4, 2-CH_3), 1.34 (3H, d, *J* 6.4, α′-CH_3), 2.09 (3H, s, 1-O_2CCH_3), 2.28 (3H, s, 5′-O_2CCH_3), 3.59 (1H, ddq, *J* 4.2, 5.4 and 6.4, 2-H), 3.81 (3H, s, OCH_3), 4.04 (1H, dd, *J* 5.4 and 11.4, 1-Hα), 4.13 (1H, dd, *J* 4.2 and 11.4, 1-Hβ), 5.01 (1H, q, *J* 6.4, α′-H), 6.82 (1H, d, *J* 8.8, 3′-H), 6.94 (1H, dd, *J* 2.9 and 8.8, 4′-H) and 7.16 (1H, d, *J* 2.9, 6′-H); δ_C 18.04 (C-3), 20.90 (CH_3CO_2C-1),[a] 21.06 (CH_3CO_2C-5′),[a] 22.79 (ArCH-CH_3), 55.58 (OCH_3), 66.91 (C-1), 69.86 (C-α′), 71.17 (C-2), 110.62 (C-3′), 119.50 (C-6′),[b] 120.46 (C-4′),[b] 133.93 (C-1′), 144.30 (C-5′), 153.85 (C-2′), 169.84 (CO_2C-1)[c] and 171.02 (CO_2C-5′);[c] *m*/*z* 268 [(M − CH_2=CO), 44%], 193 (41), 167 (48), 151 (100), 136 (32), 107 (22), 101 (68) and 91 (13).

Ethylmagnesium bromide treatment of the phenol 17

Following the procedure for the ethylmagnesium bromide treatment of the phenol **15** directly above, the freshly prepared phenol **17** (85 mg, 0.38 mmol) was converted to an orange oil (81 mg), which was then treated with acetic anhydride as described directly above to give an orange oil (103 mg). TLC (30% ethyl acetate–hexane) of this oil showed at least eight spots, two of them major. Isolation of these two bands by column chromatography (5–20% ethyl acetate–hexane) and further purification by PLC (20% ethyl acetate–hexane) gave:

1. Of R_f 0.37 (30% ethyl acetate–hexane), (α′*R*,2*S*,1*R* or *S*)-2-(5′-acetoxy-2′-methoxy-α′-methylbenzyloxy)-1-ethylpropyl acetate **37**, a 65:35 mixture of diastereomers at C-1, as an oil (13 mg, 10% over two steps); δ_H (major diastereomer) 0.78 (3H, t, *J* 7.4, 1″-CH_3), 1.13 (3H, d, *J* 6.3, 2-CH_3), 1.35 (3H, d, *J* 6.4, α′-CH_3), 1.49–1.65 (2H, m, 1-CH_2), 2.03 (3H, s, 1-O_2CCH_3), 2.27 (3H, s, 5′-O_2CCH_3), 3.45 (1H, dq, *J* 5.0 and 6.3, 2-H), 3.81 (3H, s, OCH_3), 4.76 (1H, m, 1-H), 4.97 (1H, q, *J* 6.4, α′-H), 6.82 (1H, d, *J* 8.8, 3′-H), 6.94 (1H, dd, *J* 2.9 and 8.8, 4′-H) and 7.13 (1H, d, *J* 2.9, 6′-H); δ_H (minor diastereomer) 0.83 (3H, t, *J* 7.4, 1″-CH_3), 1.14 (3H, d, *J* 6.3, 2-CH_3), 1.32 (3H, d, *J* 6.4, α′-CH_3), 1.49–1.65 (2H, m, 1-CH_2), 2.01 (3H, s, 1-O_2CCH_3), 2.27 (3H, s, 5′-O_2CCH_3), 3.41 (1H, dq, *J* 4.0 and 6.3, 2-H), 3.80 (3H, s, OCH_3), 4.72 (1H, m, 1-H), 4.93 (1H, q, *J* 6.4, α′-H), 6.80 (1H, d, *J* 8.8, 3′-H), 6.93 (1H, dd, *J* 2.9 and 8.8, 4′-H) and 7.19 (1H, d, *J* 2.9, 6′-H); δ_C (major diastereomer) 9.71 (C-2″), 15.56 (C-3), 20.99 (CH_3CO_2C-1),[a] 21.03 (CH_3CO_2C-5′),[a] 22.88 (C-1″), 23.09 (ArCHCH_3), 55.62 (OCH_3), 68.22 (C-α′), 72.88 (C-2), 77.50 (C-1), 110.58 (C-3′), 119.89 (C-6′),[b] 120.56 (C-4′),[b] 133.63 (C-1′), 144.29 (C-5′), 153.88 (C-2′), 169.80 (CO_2C-1)[c] and 170.87 (CO_2C-5′);[c] δ_C (minor diastereomer) 9.99 (C-2″), 15.35 (C-3), 20.99 (CH_3CO_2C-1),[a] 21.03 (CH_3CO_2C-5′),[a] 22.04 (C-1″), 23.13 (ArCHCH_3), 55.59 (OCH_3), 68.01 (C-α′), 73.02 (C-2), 77.98 (C-1), 110.55 (C-3′), 119.84 (C-6′),[b] 120.48 (C-4′),[b] 133.73 (C-1′), 144.29 (C-5′), 154.00 (C-2′), 169.80 (CO_2C-1)[c] and 170.87 (CO_2C-5′);[c] *m*/*z* (major diastereomer) 338 (M^+, 3%), 296 (30), 194 (22), 193 (76), 151 (100), 136 (18) and 107 (6); *m*/*z* (minor diastereomer) 338 (M^+, 2%), 296 (22), 209 (9), 194 (19), 193 (72), 167 (13), 166 (13), 151 (100), 136 (20) and 107 (6).

2. Of R_f 0.30 (30% ethyl acetate–hexane), an oil (51 mg), radial chromatography (methylene chloride as eluent) of which gave separation into two components: of R_f 0.13 (methylene chloride), an oil (33 mg, 28% over two steps), the major components of which were identified (by ^{1}H and ^{13}C NMR spectroscopy) to be a 30:70 mixture of the diacetates **22** and **24**; and of R_f 0.09 (methylene chloride), a yellow oil (15 mg, 13% over two steps), probably (α′*R*,2*S*)-2-(5′-acetoxy-2′-methoxy-α′-methylbenzyloxy)propyl acetate **38**; δ_H 1.17 (3H, d, *J* 6.3, 2-CH_3), 1.36 (3H, d, *J* 6.4, α′-CH_3), 2.04 (3H, s, 1-O_2CCH_3), 2.26 (3H, s, 5′-O_2CCH_3), 3.59 (1H, ddq, *J* 3.9, 7.1 and 6.3, 2-H), 3.81 (3H, s, OCH_3), 3.95 (1H, dd, *J* 7.1 and 11.5, 1-Hα), 4.00 (1H, dd, *J* 3.9 and 11.5, 1-Hβ), 4.96 (1H, q, *J* 6.4, α′-H), 6.81 (1H, d, *J* 8.8, 3′-H), 6.95 (1H, dd, *J* 2.9 and 8.8, 4′-H) and 7.24 (1H, d, *J* 2.9, 6′-H); δ_C 16.31 (C-3), 20.74 (CH_3CO_2C-1),[a] 21.04 (CH_3CO_2C-5′),[a] 23.21 (ArCHCH_3), 55.60 (OCH_3), 67.90 (C-1), 68.50 (C-α′), 70.73 (C-2), 110.56 (C-3′), 119.65 (C-6′),[b] 120.55 (C-4′),[b] 133.75 (C-1′), 144.32 (C-5′), 153.98 (C-2′), 169.76 (CO_2C-1)[c] and 170.93 (CO_2C-5′).[c]

(1*S*,3*S*,4*R*)-3,4-Dihydro-1,3-dimethyl-4-hydroxy-2-benzopyran-5,8-quinone 2

The diacetate **19** (85 mg, 0.28 mmol) was reduced with lithium aluminium hydride as described above for the reduction of the acetophenone **5**. This produced the crude diol **18** as a yellow oil (52 mg, 84%). The diol **18** (52 mg, 0.23 mmol), silver(II) oxide[14,18,19] (115 mg, 0.93 mmol) and dioxane (8 cm^3) were stirred together at room temperature and the reaction was initiated by the addition of nitric acid (0.3 cm^3, 6 M). After 3 min, the reaction was quenched by the addition of methylene chloride–water (8:2; 25 cm^3) and the organic layer was then washed with saturated sodium hydrogen carbonate solution, water and brine, dried and concentrated to give virtually pure (by TLC and ^{1}H NMR spectroscopy) quinone **2** as a deep orange crystalline solid (44 mg, 91%). Recrystallisation from methylene chloride–hexane afforded large orange plates, mp 96.5–99.5 °C (Found: C, 63.1; H, 6.0. $C_{11}H_{12}O_4$ requires C, 63.45; H, 5.8%); $[\alpha]_D$ +313.1; ν_{max}/cm^{-1} 3493 (OH), 1653 (C=O) and 1603 (C=C); λ_{max} (EtOH) 228 (log ε 3.7), 247 (3.7), 263 (3.7) and 328 (2.9); δ_H 1.37 (3H, d, *J* 6.2, 3-CH_3), 1.52 (3H, d, *J* 6.8, 1-CH_3), 3.52 (1H, d, *J* 2.5, OH), 3.84 (1H, ddq, *J* 0.5, 7.9 and 6.2, 3-H), 4.35 (1H, ddd, *J* 1.6, 2.5 and 7.9, 4-H), 4.75 (1H, ddq, *J* 0.5, 1.6 and 6.8, 1-H) and 6.73 (2H, s, 6- and 7-H); δ_C 18.43 (CH_3C-3), 18.85 (CH_3C-1), 66.83 (C-3), 67.18 (C-1),[a] 67.29 (C-4),[a] 136.36 (C-6),[b] 136.87 (C-7),[b] 138.62 (C-8a),[c] 145.17 (C-4a),[c] 185.92 (C-8)[d] and 188.43 (C-5);[d] *m*/*z* 191 (M − OH, 3%), 177 (7), 164 (100), 136 (34), 121 (8), 107 (18), 100 (16), 79 (16), 71 (30) and 57 (26).

(1*R*,3*S*,4*R*)-3,4-Dihydro-1,3-dimethyl-4-hydroxy-2-benzopyran-5,8-quinone 40

The mixture of diacetates **22** and **24** from the titanium tetraisopropoxide cyclisation (207 mg, 0.67 mmol) was reduced with lithium aluminium hydride as described above for the reduction of the acetophenone **5**. This produced a crude mixture of diols **21** and **23** as a yellow oil (150 mg, quantitative). The mixture of diols **21** and **23** was oxidatively demethylated by the method for the oxidative demethylation of the diol **18** described above to give a red oil (119 mg). Column chromatography (10 and 20% ethyl acetate–hexane) yielded only the quinone **40** as an orange oil (35 mg, 25%), R_f 0.30 (30% ethyl acetate–hexane). Trituration of this oil (petrol, −70 °C) produced a crystalline solid which was recrystallised from methylene chloride–hexane to afford orange needles (17 mg), mp 67.5–69 °C [Found: C, 63.4; H, 5.8%; $(M - CH_3CHO)^+$, 164.0467. $C_{11}H_{12}O_4$ requires C, 63.45; H, 5.8%; (M − CH_3CHO), 164.0473]; $[\alpha]_D$ +241.9 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} 3435 (OH), 1649 (C=O) and 1601 (C=C); λ_{max} (EtOH) 236 (log ε 3.7), 258 (3.7) and 324 (2.9); δ_H 1.41 (3H, d, *J* 6.1, 3-CH_3), 1.45 (3H, d, *J* 6.7, 1-CH_3), 3.42 (1H, dq, *J* 8.3 and 6.1, 3-H), 3.69 (1H, d, *J* 2.0, OH), 4.38 (1H, ddd, *J* 2.0, 2.9 and 8.3, 4-H), 4.67 (1H, dq, *J* 2.9 and 6.7, 1-H) and 6.71 (2H, s, 6- and 7-H); δ_C 18.28 (CH_3C-3), 20.54 (CH_3C-1), 67.66 (C-3), 69.97 (C-1),[a] 72.98 (C-4),[a] 136.14 (C-6),[b] 137.24 (C-7),[b] 140.08 (C-8a),[c] 145.27 (C-4a),[c] 186.58 (C-8)[d] and 188.64 (C-5);[d] *m*/*z* 190 (M − H_2O, 11%), 177 (17), 175 (26), 164 (100), 149 (36), 136 (58), 135 (26), 108 (18), 107 (36), 79 (24), 71 (22) and 57 (31).

Acknowledgements

We gratefully acknowledge receipt of an Australian Postgraduate Research Award (C. A. J.) and financial support from the Senate of Murdoch University.

References

1 R. G. F. Giles, C. A. Joll, M. V. Sargent and D. M. G. Tilbrook, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 3029.
2 D. W. Cameron, R. I. T. Cromartie, D. G. I. Kingston and Lord Todd, *J. Chem. Soc.*, 1964, 51.
3 G. Casiraghi, M. Cornia, G. Casnati, G. G. Fava, M. F. Belicchi and L. Zetta, *J. Chem. Soc.*, *Chem. Commun.*, 1987, 794.
4 G. Casiraghi, M. Cornia and G. Rassu, *J. Org. Chem.*, 1988, **53**, 4919.
5 A preliminary account of some of this work has been reported previously. R. G. F. Giles and C. A. Joll, *Tetrahedron Lett.*, 1995, **36**, 1125.
6 W. E. Wymann, R. Davis, J. W. Patterson, Jr. and J. R. Pfister, *Synth. Commun.*, 1988, **18**, 1379.
7 W. Baker and G. F. Flemons, *J. Chem. Soc.*, 1948, 2138.
8 J. E. Baldwin and G. G. Haraldsson, *Acta Chem. Scand.*, *Ser. B*, 1986, **40**, 400.
9 K. Omura and D. Swern, *Tetrahedron*, 1978, **34**, 1651.
10 A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165.
11 (*a*) G. Casiraghi, M. Cornia, G. G. Fava, M. F. Belicchi and L. Zetta, *Carbohydr. Res.*, 1989, **186**, 207; (*b*) F. Bigi, G. Casnati, G. Sartori, C. Dalprato and R. Bortolini, *Tetrahedron: Asymmetry*, 1990, **1**, 861; (*c*) F. Bigi, G. Casnati, G. Sartori, G. Araldi and G. Bocelli, *Tetrahedron Lett.*, 1989, **30**, 1121.
12 D. W. Cameron, D. G. I. Kingston, N. Sheppard and Lord Todd, *J. Chem. Soc.*, 1964, 98.
13 T. A. Chorn, R. G. F. Giles, I. R. Green and P. R. K. Mitchell, *J. Chem. Soc.*, *Perkin Trans. 1*, 1983, 1249.
14 (*a*) R. G. F. Giles, I. R. Green, V. I. Hugo, P. R. K. Mitchell and S. C. Yorke, *J. Chem. Soc.*, *Perkin Trans. 1*, 1983, 2309; (*b*) T. Kometani, Y. Takeuchi and E. Yoshii, *J. Chem. Soc.*, *Perkin Trans. 1*, 1981, 1197; (*c*) R. G. F. Giles, R. W. Rickards and B. S. Senanayake, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 2241.
15 M. T. Reetz, *Angew. Chem.*, *Int. Ed. Engl.*, 1984, **23**, 556.
16 R. G. F. Giles, R. W. Rickards and B. S. Senanayake, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 3361.
17 *e.g.*, E. C. Ashby and A. B. Goel, *J. Am. Chem. Soc.*, 1981, **103**, 4983.
18 R. N. Hammer and J. Kleinberg, *Inorg. Synth.*, 1953, **4**, 12.
19 C. D. Snyder and H. Rapoport, *J. Am. Chem. Soc.*, 1972, **94**, 227.
20 H. Maeda and G. A. Kraus, *J. Org. Chem.*, 1996, **61**, 2986.
21 J. H. Bowie and D. W. Cameron, *J. Chem. Soc.* (*C*), 1967, 712.
22 (*a*) R. H. Thomson, *Naturally Occurring Quinones*, 2nd edn., Academic Press, London, 1971; (*b*) R. H. Thomson, *Naturally Occurring Quinones III, Recent Advances*, 3rd edn., Chapman and Hall, London, 1987; (*c*) R. H. Thomson, *Naturally Occurring Quinones IV, Recent Advances*, 4th edn., Blackie Academic and Professional, Chapman and Hall, London, 1997.
23 S. G. Morris, *J. Am. Chem. Soc.*, 1949, **71**, 2056.
24 H. O. House, *J. Am. Chem. Soc.*, 1955, **77**, 3070.
25 D. E. Janssen and C. V. Wilson, *Org. Synth.*, 1963, **Coll. Vol. IV**, 547.

Paper 9/01457H