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PREPARATIVE ROUTES TO SPIROACETALS DERIVED FROM CHROMAN-4-ONE (2,3-DIHYDRO-4*H*-1-BENZOPYRAN-4-ONE)

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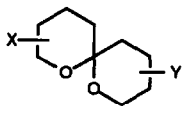
Abstract: Methyl 2-(4-hydroxybutyl)-4-oxo-4*H*-1-benzopyran-3-carboxylate **6** is transformed into the spiroacetals **13** and **14** (ratio 5 1) *via* treatment with iodomethane/potassium carbonate, the process involving sequential intramolecular conjugate addition and enolate alkylation The 2,3-epoxide **7** derived from **6** undergoes spirocyclisation to the hydroxyesters **16** and **17** upon treatment with acids The structures of **13** and **16** were confirmed by X-ray crystallography

The 1,7-dioxaspiro[5 5]undecane (spiroacetal) moiety **1** has in recent years attracted much attention due to its interesting stereoelectronic properties[1] and its presence in a variety of biologically active natural products [2] In contrast, little is known about benzannulated spiroacetals of the form **2**,[3] and our interest in these systems led us to seek methods for their preparation Having established that chromones (4-oxo-4*H*-1-benzopyrans) with electron-withdrawing substituents at C-3 can function as Michael acceptors in uncatalysed reactions with alkanols,[4] we considered that an intramolecular variant of this process might provide a particularly mild route to the desired spirocyclic system. This strategy[5] required a chromone of the form **3**, and we herein describe in detail[6] our approach to such a substrate, and two procedures by which it can be cyclised in the desired sense



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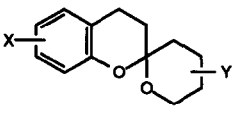

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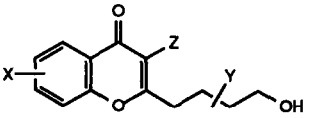

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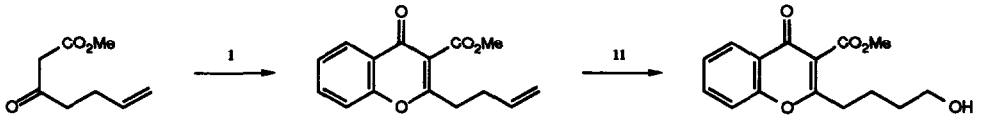
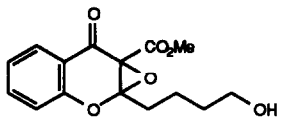
The 2-substituted chromone-3-carboxylate required for this study was prepared as shown in Scheme 1 Thus the dianion of methyl acetoacetate was allylated[7] and the product **4** transformed into the chromone ester **5** using the general method developed by Coppola and Dodsworth,[8] *i e* by treating the derived enolate anion with *o*-fluorobenzoyl chloride The conversion of **5** into the desired chromone-3-carboxylate **6** was effected in modest yield *via* hydroboration followed by oxidation with trimethylamine *N*-oxide [9]



4 **5** **6**

SCHEME 1 *Reagents* i, NaH, toluene, 20 °C, then *o*-FC_6H_4COCl, reflux, 24 h (60%), ii, BH_3-THF, 20 °C, 24 h, then Me_3NO, reflux, 2 h (43%)



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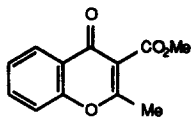

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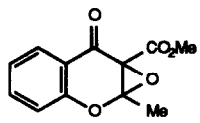

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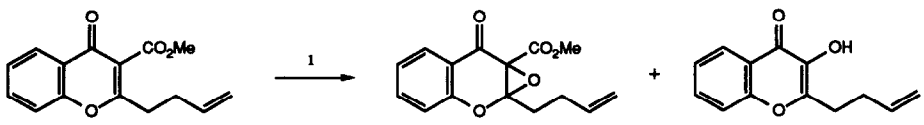
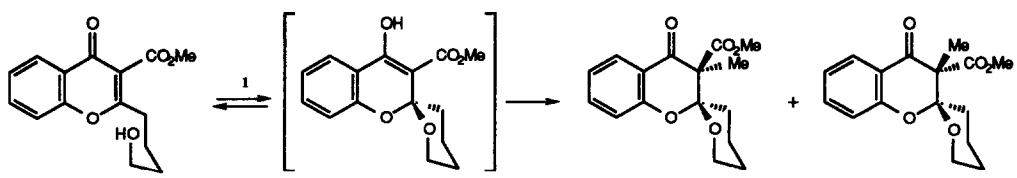
Using a potassium carbonate–hydrogen peroxide work-up in this hydration sequence gave rise to significant amounts (up to 45% yield) of the epoxide **7** Not surprisingly, such nucleophilic epoxidations of chromones, earlier described by Donnelly and coworkers,[10] are particularly facile with the highly electrophilic chromone-3-carboxylates For example, treatment of the simple ester **8** with alkaline hydrogen peroxide gave the epoxide **9** in almost quantitative yield. Under similar conditions the butenylchromone **5** was transformed into the epoxide **10**, together with variable amounts of the hydroxychromone **11** (Scheme 2). The latter product predominated when longer reaction times were used, and is presumably the outcome of ester hydrolysis followed by decarboxylation and elimination, which may occur directly or *via* the 2,3-diol arising[10] from the hydroxide-induced ring-opening of the epoxide function



5 **10** **11**

SCHEME 2 *Reagents* i, NaOH, H_2O_2, water-THF, 20 °C, 1 h

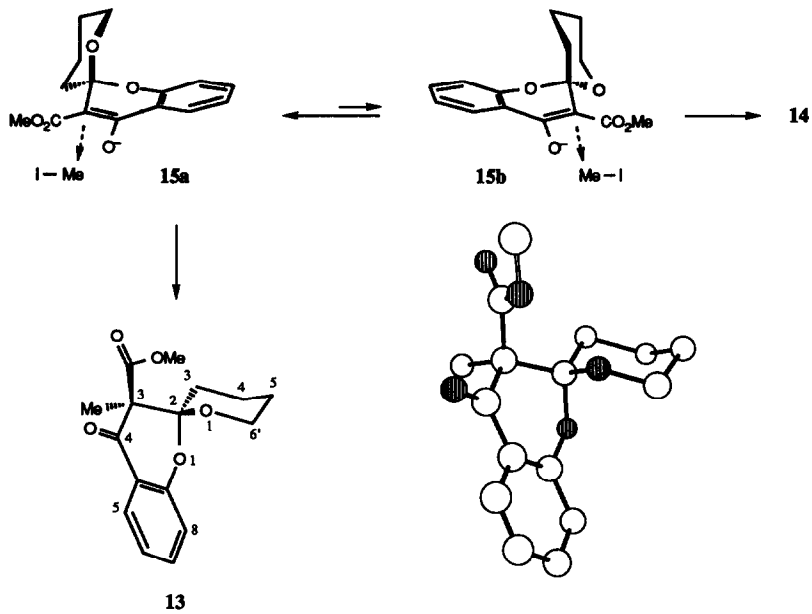
Spiroacetalisation of the ester **6** was effected under alkylating conditions, the reaction being a variant of the previously described heteroannulation process [4] Thus the pendant hydroxyalkyl group of **6** can undergo an intramolecular conjugate addition to the enone moiety, leading to the formation of an intermediate β-ketoester **12**, which is alkylated *in situ* by iodomethane The result is a mixture (ratio 5 1) of the methylated spiroacetals **13** and **14** (Scheme 3)



6 **12** **13** **14**

SCHEME 3 *Reagents* i, MeI, K_2CO_3, acetone, reflux, 6 d (61%)

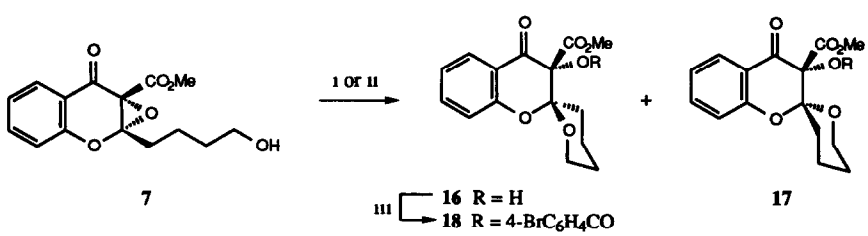
Due to the high degree of substitution at the reacting carbon atoms, the structures of the isomers **13** and **14** could not be assigned on the basis of high field ^{1}H n m r spectroscopy However, the relative stereochemistry of the major product **13** was unequivocally established by X-ray crystallography, and is consistent with the predominance of the conformer **15a** in the equilibrating mixture of enolates formed from **12** under the influence of base (Scheme 4) The mutually axial arrangement of the two ether oxygen atoms in **15a**, which is favoured due to the anomeric effect, induces a considerable steric bias in the region of the nucleophilic centre, and the methylation step occurs preferentially on the less hindered face of the enolate, *i e* that occupied by C-3'



SCHEME 4

FIGURE 1 X-ray structure of **13**

A second route to the desired ring system involved the acid-induced cyclisation of the chromone epoxide **7**, as shown in Scheme 5 Treating **7** with tin(IV) chloride (1 4 mol equiv) in dichloromethane at 0 °C for 1 h produced a 1 1 mixture (total 56%) of the isomeric spiroacetals **16** and **17** Alternatively, the cyclisation could be induced using a catalytic amount of *p*-toluenesulphonic acid in dichloromethane, which also gave a mixture of **16** and **17** (total 59%) but with the former predominating by at least 2 5 ·1 The separated isomers **16** and **17** did not appear to equilibrate on treatment with an excess of *p*-toluenesulphonic acid in dichloromethane Again, the structures of the two isomers could not be deduced using high field ^{1}H n m r spectroscopy, but **16** formed a crystalline *p*-bromobenzoate **18** whose structure was confirmed by X-ray crystallography (Figure 2).



SCHEME 5 *Reagents* I, CH_2Cl_2, cat. PTSA, 20 °C, 22 h (59%), II, $SnCl_4$, CH_2Cl_2, 1 h (56%), III, *p*-BrC_6H_4COCl, DMAP, CH_2Cl_2, 20 °C, 18 h (70%)

In principle the spiroacetal **16** could be formed from either **19** or **20** *via* an intramolecular displacement process with inversion at C-2, and an intermolecular equivalent of this is precedented [10] On the other hand the formation of **17** suggests the intermediacy of an oxonium species **21** or **22**, which could be stabilised *via* chelation involving A and one of the two adjacent carbonyl functions. Further coordination between A and the pendant hydroxyalkyl chain may also be a contributing factor in the nett retention which leads to **17**

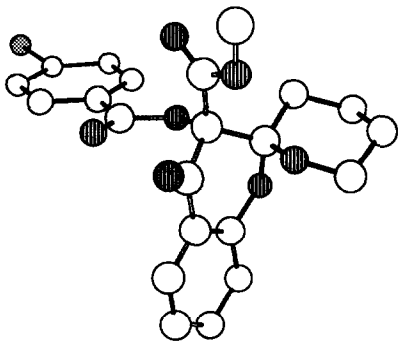
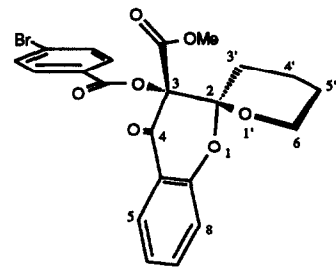


FIGURE 2 X-ray structure of **18**



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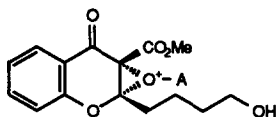
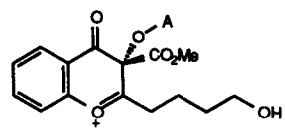


19 A = $SnCl_4^-$
20 A = H



21 A = $SnCl_4^-$
22 A = H

EXPERIMENTAL

All compounds are racemic Melting points were determined using an Electrothermal apparatus and are uncorrected Unless otherwise stated, i r spectra were of liquid paraffin ('Nujol') mulls on sodium chloride plates, recorded on Perkin Elmer 257, 177, and 580B, or Pye-Unicam SP3-100 instruments N.m r spectra were measured for solutions in deuteriochloroform unless otherwise indicated, with tetramethylsilane as the internal standard, on Varian EM360 (60 MHz), CFT-20 (80 MHz), and XL-200 (200 MHz), or Perkin-Elmer R32 (90 MHz), or Bruker AM250 (250 MHz) and AC300 (300 MHz) instruments U v spectra were recorded for ethanolic solutions using a Pye-Unicam SP800 spectrometer Mass spectra were measured on Kratos MS30 (70 eV EI) or Finnegan 4500 (low resolution ammonia CI) instruments

Starting materials and solvents were routinely purified by conventional techniques [11] Organic solutions were dried using anhydrous magnesium sulphate and concentrated by rotary evaporation Analytical thin layer chromatography (t l c) was carried out on Camlab Polygram SIL G/UV_{254} plates Preparative (column) chromatography was carried out using 60H silica gel (Merck 7736 and hand-bellows pressure, or Merck 9385 and the flash technique[12]) Compositions of solvent mixtures are quoted as ratios of volume 'Petroleum' refers to a light petroleum fraction, b p 40–60 °C, unless otherwise stated 'Ether' refers to diethyl ether

Methyl 3-oxo-6-heptenoate **4** [7] – Methyl acetoacetate (1.74 g, 15 mmol) was added dropwise with stirring to a solution of sodium hydride (100%; 408 mg, 17 mmol) in tetrahydrofuran (50 ml) at 0 °C The resulting mixture was stirred vigorously for 0 5 h at 0 °C, and then treated dropwise with *n*-butyllithium in hexane (1 7 M, 10 0 ml, 17 mmol). After a further 0 3 h at 0 °C, allyl bromide (1 9 ml, 2.66 g, 22 mmol) was added dropwise and the mixture then stirred for a further 0 5 h A mixture of conc hydrochloric acid (3 ml), water (7 5 ml), and ether (22 ml) was then added and, after stirring for 5 min at room temperature, the product was extracted with ether (3 x 15 ml) The combined extracts were washed with brine (2 x 20 ml), dried, and evaporated Chromatography of the residue, eluting with ethyl acetate - petroleum (1:6), gave the title compound **4** (1 29 g, 55%) as an oil; ν_{max} (neat) 3080, 1750, 1720, and 1640 cm^{-1}, δ (60 MHz) 2.2–2 8 (4 H, m, 4-H_2, 5-H_2), 3 5 (2 H, s, 2-H_2), 3 75 (3 H, s, OMe), 4 8–5 2 (2 H, m, 7-H_2), and 5 4–6 1 (1 H, m, 6-H)

*Methyl 2-(3-butenyl)-4-oxo-4*H*-1-benzopyran-3-carboxylate* **5** – To a solution of the ester **4** (1 25 g, 8 mmol) in toluene (40 ml) was added sodium hydride (100%, 197 mg, 8 2 mmol) and the resulting mixture stirred vigorously for 0 3 h at room temperature *o*-Fluorobenzoyl chloride (1 28 g, 8 1 mmol) in toluene (4 ml) was then added and the mixture was heated under reflux for 24 h and then poured on to ice (40 g). After the two-phase mixture had stirred at room temperature for 10 min, the aqueous layer was extracted with ether (3 x 20 ml) and the combined extracts were dried and evaporated The residue was chromatographed, eluting with ethyl acetate - petroleum (1 5), to obtain the *title compound* **5** (1 24 g, 60%) as a pale yellow oil (Found C, 69 7, H, 5 7 $C_{15}H_{14}O_4$ requires C, 69 8, H, 5 5%), ν_{max} (neat) 2900, 1720, 1640, 1615, and 1570 cm^{-1}, δ (60 MHz) 2 3–3 1 (4 H, m, 1'-H_2, 2'-H_2), 3 9 (3 H, s, OMe), 4 8–5 3 (2 H, m, 4'-H_2), 5 5–6 2 (1 H, m, 3'-H), 7 2–7 85 (3 H, m, 6,7,8-H), and 8 05–8 3 (1 H, m, 5-H)

*Methyl 2-(4-hydroxybutyl)-4-oxo-4*H*-1-benzopyran-3-carboxylate* **6** – To a solution of the ester **5** (825 mg, 3.2 mmol) in tetrahydrofuran (50 ml) at 0 °C under argon was added dropwise a solution of borane-tetrahydrofuran complex (0 4 M, 10 ml, 4 mmol) and the resulting solution stirred for 24 h at room temperature Trimethylamine *N*-oxide dihydrate (390 mg, 3 5 mmol) was added and the resulting suspension was then heated under reflux for 2 h and allowed to cool Aqueous sulphuric acid (0 4 M, 10 ml) was added and, after stirring at room temperature for 1 h, the mixture was extracted with dichloromethane (4 x 20 ml) and the combined extracts dried and evaporated Flash chromatography of the residue, eluting with ethyl acetate - petroleum (3 1), gave the *title compound* **6** (383 mg, 43%) as an unstable oil (*M* + H^+, 277 1088 $C_{15}H_{17}O_5$ requires 277 1076), ν_{max} (neat) 3460, 3000–2800, 1730, 1675–1600, and 1575 cm^{-1}, δ (60 MHz) 1 4–2 2 (4 H, m, 2'-H_2, 3'-H_2), 2 5 (1 H, br s, OH), 2 8 (2 H, t, *J* 7 Hz, 1'-H_2), 3 7 (2 H, t, *J* 6 Hz, 4'-H_2), 3 95 (3 H, s, OMe), 7 1–7 5 (3 H, m, 6,7,8-H), and 8 0–8 2 (1 H, m, 5-H), m/z (CI, peaks >10%) 294 (M + NH_4^+, 19%) and 277 (M + H, 100)

*Methyl 2-(4-hydroxybutyl)-4-oxo-4*H*-1-benzopyran-3-carboxylate* **6** and *methyl 1a-(4-hydroxybutyl)-7-oxo-7*H*-oxireno[b][1]benzopyran-7a(1a*H*)-carboxylate* **7** – To a solution of the ester **5** (774 mg, 3.0 mmol) in tetrahydrofuran (30 ml) at 0 °C under argon was added dropwise a solution of borane-tetrahydrofuran complex (0 4 M, 9 ml, 3.6 mmol) and the resulting solution stirred for 4 h at room temperature Water (10 ml) was added, followed by hydrogen peroxide (30%, 0 4 ml, 3.9 mmol) and anhydrous potassium carbonate (552 mg, 4 mmol). The mixture was stirred for 1 h at room temperature, extracted with dichloromethane (4 x 20 ml), and the combined extracts dried and evaporated Flash chromatography of the residue, eluting with ethyl acetate - petroleum (1.1), gave the chromone **6** (232 mg, 28%) A second fraction gave the epoxide **7** (394 mg, 45%) as an oil (*M* + NH_4^+, 310 1309 $C_{15}H_{20}NO_6$ requires 310.1291), ν_{max} (neat) 3400, 2960, 2880, 1750, 1690, 1610, and 1585 cm^{-1}; δ (90 MHz) 1.5–2 2 (6 H, m, 1'-H_2, 2'-H_2, 3'-H_2), 3 7 (2 H, t, *J* 6 Hz, 4'-H_2), 3.92 (3 H, s, OMe), 7 0–7 25 (2 H, m, 6,8-H), 7 5–7.75 (1 H, m, 7-H), and 7.90–8 05 (1 H, m, 5-H), m/z (CI, peaks >10%) 310 (76%), 309 (M + NH_4^+, 100), and 293 (M + H, 16)

*Methyl 1a-methyl-7-oxo-7*H*-oxireno[b][1]benzopyran-7a(1a*H*)-carboxylate* **9** – Method A. To a solution of methyl 2-methylchromone-3-carboxylate **8**[8] (218 mg, 1 mmol) in tetrahydrofuran (5 ml) were added sodium hydroxide (3 M, 0 2 ml) and hydrogen peroxide (30%; 0.2 ml, 2 mmol), and the resulting mixture stirred at room temperature for 2 h. Water (20 ml) was then added, the mixture was extracted with dichloromethane (3 x 10 ml), and the combined extracts dried and evaporated Chromatography of the residue, eluting with ethyl acetate - petroleum (1 4), gave the *title compound* **9** (226 mg, 97%) as colourless needles, m p 84–85 °C (ethyl acetate - petroleum 1.1) (Found C, 61.5, H, 4 25 $C_{12}H_{10}O_5$ requires C, 61 5; H, 4 3%); ν_{max} 1750, 1680, 1610, and 1580 cm^{-1}, λ_{max} 254 5 nm (ε 10400) and 314 (9230), δ (60 MHz) 1.9 (3 H, s, 2-Me), 3 95 (3 H, s, OMe), 6 9–7 3 (2 H, m, 6,8-H), 7 45–7 8 (1 H, m, 7-H), and 7.9–8 1 (1 H, m, 5-H)

Method B [10] To a solution of methyl 2-methylchromone-3-carboxylate **8** (436 mg, 2 mmol) in acetone (20 ml) and water (10 ml) were added anhydrous potassium carbonate (276 mg, 2 mmol) and hydrogen peroxide (30%, 0 3 ml, 3 mmol), and the resulting mixture stirred at room temperature for 24 h Water (30 ml) was then added, the mixture was extracted with dichloromethane (3 x 20 ml), and the combined extracts dried and evaporated Chromatography of the residue as in Method A gave the epoxide **9** (318 mg, 68%), identical (t.l c., n.m.r , i r , m p) to the material obtained using method A above

*Methyl 1a-(3-butenyl)-7-oxo-7*H*-oxireno[b][1]benzopyran-7a(1a*H*)-carboxylate* **10** and *2-(3-butenyl)-3-hydroxy-4*H*-1-benzopyran-4-one* **11** – Method A To a solution of the ester **5** (258 mg, 1 mmol) in tetrahydrofuran (10 ml) and water (5 ml) were added sodium hydroxide (3 M, 0 33 ml, 1 mmol) and hydrogen peroxide (30%, 0 125 ml, 1 2 mmol), and the resulting mixture stirred at room temperature for 1 h. Water (15 ml) was then added, the mixture was extracted with dichloromethane (4 x 15 ml), and the combined organic extract dried and evaporated Flash chromatography of the residue, eluting with ethyl acetate - petroleum (1 4), gave the *title compound* **10** (167 mg, 61%) as a colourless oil (Found C, 66 1, H, 5 5 $C_{15}H_{14}O_5$ requires C, 65 7, H, 5 15%), ν_{max} (neat) 1740, 1680, and 1600 cm^{-1}, δ (60 MHz) 1 6–2 7 (4 H, m, 1'-H_2, 2'-H_2), 3 9 (3 H, s, OMe), 4 85–5 25 (2 H, m, 4'-H_2), 5 5–6 1 (1 H, m, 3'-H), 6 9–7 25 (2 H, m, 6,8-H), 7 4–7 7 (1 H, m, 7-H), and 7 8–8 0 (1 H, m, 5-H)

The aqueous phase from the above extraction was acidified with concentrated hydrochloric acid (0 5 ml), re-extracted with dichloromethane (4 x 15 ml), and the combined organic extract dried and evaporated Crystallisation of the residue from dichloromethane - ether (1 1) gave the *title compound* **11** (60 mg, 28%) as colourless plates, m p 128–130 °C (Found C, 72 0, H, 5 5 $C_{13}H_{12}O_3$ requires C, 72 2, H, 5 6%), ν_{max} 3285, 1610, and 1570 cm^{-1}, λ_{max} 233 5 nm (ε 21400), 281 5 (6090), and 319 5 (9760); δ (200 MHz) 2 45–2.60 (2 H, m, 2'-H_2), 2 90–3 00 (2 H, m, 1'-H_2),4 95–5 15 (2 H, m, 4'-H_2), 5 8–6 0 (1 H, m, 3'-H), 6 45 (1 H, s, OH), 7 3–7 5 (2 H, m, 6,8-H), 7 6–7 7 (1 H, m, 7-H), and 8 22 (1 H, dd, *J* 2, 8 Hz, 5-H)
The yield of **10** was variable using the above procedure, higher yields generally being obtained with shorter reaction times With a substrate hydroxide peroxide mol ratio of 1 6 20 and a reaction time of 10 minutes, a yield of **10** of 80% was observed When the reaction time was extended to 24 h, the sole product was the hydroxychromone **11** (75%)
Method B To a solution of the ester **5** (774 mg, 3 mmol) in acetone (20 ml) and water (10 ml) were added anhydrous potassium carbonate (552 mg, 4 mmol) and hydrogen peroxide (30%, 0 4 ml, 4 mmol), and the resulting mixture stirred at room temperature for 24 h Water (30 ml) was then added, the mixture was extracted with dichloromethane (4 x 20 ml), and the combined extracts dried and evaporated Chromatography of the residue as in Method A gave the epoxide **10** (525 mg, 64%), identical (t.l c , n m r , i r , m p) to the material obtained previously The aqueous phase from the above extraction was acidified with concentrated hydrochloric acid (1 ml), re-extracted with dichloromethane (3 x 25 ml), and the combined organic extract dried and evaporated This gave the hydroxybenzopyranone **11** (161 mg, 25%) as a crystalline solid, identical (t.l c , n m r) to the material obtained previously

Methyl cis-*3,3',4,4',5',6'-hexahydro-3-methyl-4-oxospiro[*2H-*1-benzopyran-2,2'-[*2H*]pyran]-3-carboxylate* **13** and *methyl* trans-*3,3',4,4',5',6'-hexahydro-3-methyl-4-oxospiro[*2H-*1-benzopyran-2,2'-[*2H*]pyran]-3-carboxylate* **14** – A mixture of the chromone ester **6** (69 mg, 0 25 mmol), iodomethane (251 mg, 1 5 mmol), anhydrous potassium carbonate (70 mg, 0 5 mmol), and acetone (15 ml) was heated under reflux for 6 days The cooled reaction mixture was then poured into water (30 ml) and extracted with dichloromethane (3 x 15 ml) The combined extracts were dried and evaporated, and the residue purified by flash chromatography, eluting with ethyl acetate - petroleum (1 4), to obtain as the major product the *title compound* **13** (37 mg, 51%) which formed colourless crystals, m p 123–124 °C (Found C, 66 0, H, 6 3 $C_{16}H_{18}O_5$ requires C, 66 2, H, 6 25%), ν_{max} 1725, 1690, 1610, and 1585 cm^{-1}, δ (250 MHz) 1 50 (3 H, s, Me), 1 5–2 2 (6 H, m, 3'-H_2, 4'-H_2, 5'-H_2), 3 55–3 75 (2 H, m, 6'-H_2), 3 81 (3 H, s, OMe), 6 8–7 1 (2 H, m, 6,8-H), 7 3–7 6 (1 H, m, 7-H), and 7 75–7 9 (1 H, m, 5-H) A second fraction from the column gave the title compound **14** (7 mg, 10%) as an oil, ν_{max} (neat) 1735, 1700, 1610, and 1585 cm^{-1}, δ (80 MHz) 1 56 (3 H, s, Me), 1 5–2 3 (6 H, m, 3'-H_2, 4'-H_2, 5'-H_2), 3 4–3 8 (2 H, m, 6'-H_2), 3 53 (3 H, s, OMe), 6 9–7 2 (2 H, m, 6,8-H), 7 3–7 6 (1 H, m, 7-H), and 7 8–8 0 (1 H, m, 5-H)

Methyl trans-*3,3',4,4',5',6'-hexahydro-3-hydroxy-4-oxospiro[2H-1-benzopyran-2,2'-[2H]pyran]-3-carboxylate* **16** and *methyl* cis-*3,3',4,4',5',6'-hexahydro-3-hydroxy-4-oxospiro[2H-1-benzopyran-2,2'-[2H]pyran]-3-carboxylate* **17** – Method A A stirred solution of the epoxyalcohol **7** (400 mg, 1 37 mmol) in dichloromethane (30 ml) at room temperature was treated with *p*-toluenesulphonic acid (10 mg, 0 06 mmol). After 22 h, t.l.c analysis of the solution [elution with ethyl acetate - petroleum 1 3] indicated that two products had been formed The mixture was evaporated and the residue purified by flash chromatography, eluting with ethyl acetate - petroleum (1·4), gave two fractions The most mobile fraction was the pure *title compound* **16** (155 mg, 39%), ν_{max} (neat) 3470, 3000–2850, 1730, 1700, 1610, and 1580 cm^{-1}, δ (300 MHz) 1.5–2 0 (6 H, m, 3'-H_2, 4'-H_2, 5'-H_2), 3 70–3 90 (1 H, m, 6'-H_{eq}), 3 81 (3 H, s, OMe), 4 01 (1 H, dt, $J_{5'\text{-eq},6'\text{-ax}}$ 3, $J_{5'\text{-ax},6'\text{-ax}}$ 11.5, and $J_{6'\text{-ax},6'\text{-eq}}$ 11 5 Hz, 6'-H_{ax}), 4 19 (1 H, s, OH), 7 00–7 10 (2 H, m, 6,8-H), 7 55 (1 H, ddd, *J* 1 8, 7 2, 8 4 Hz, 7-H), and 7 86 (1 H, dd, *J* 1 8, 8 0 Hz, 5-H) The hydroxyester **16** was further characterised as the *p*-bromobenzoate derivative **18** (*vide infra*)

A second fraction from the column was found to contain both **16** and **17** (total 80 mg, 20%) The analytical data for **17** are included under Method B below

Method B. A stirred solution of the epoxyalcohol **7** (180 mg, 0 62 mmol) in dichloromethane (20 ml) at 0 °C under argon was treated with anhydrous tin(IV) chloride (0 1 ml, 222 mg, 0 85 mmol) After 1 h, t l c analysis of the brown solution [elution with ethyl acetate - petroleum 1 3] indicated that two products had been formed The mixture was poured into water (30 ml), extracted with dichloromethane (4 x 25 ml), and the extract dried and evaporated Flash chromatography of the residue, eluting with ethyl acetate - petroleum (1 4), gave three fractions The first (most mobile) fraction contained a small amount of the pure *trans*-isomer **16**, an intermediate fraction contained both **16** and **17** (total 101 mg, 56%), and the third (least mobile) yielded a small amount of the pure *title compound* **17** as an oil (Found C, 61 4, H, 5 5 $C_{15}H_{16}O_6$ requires C, 61 6, H, 5 5%), ν_{max} (neat) 3470, 3000–2850, 1730, 1700, 1610, and 1580 cm^{-1}, δ (300 MHz) 1 50–2 20 (6 H, m, 3'-H_2, 4'-H_2, 5'-H_2), 3 55–3 70 (2 H, m, 6'-H_2), 3 67 (3 H, s, OMe), 4 10 (1 H, s, OH), 7 00–7 10 (2 H, m, 6,8-H), 7 5–7 6 (1 H, m, 7-H), and 7 86 (1 H, dd, *J* 1 3, 8 Hz, 5-H)

Methyl trans-*3-(4-bromobenzoyloxy)-3,3',4,4',5',6'-hexahydro-4-oxospiro[2H-1-benzopyran-2,2'-[2H]pyran]-3-carboxylate* **18** – A solution of the hydroxyester **16** (27 mg, 0 09 mmol) and 4-(dimethylamino)pyridine (25 mg, 0 2 mmol) in dichloromethane (20 ml) was stirred with *p*-bromobenzoyl chloride (41 mg, 0 19 mmol) at room temperature for 18 h The solution was then evaporated and the residue extracted with a small amount of ethyl acetate - petroleum (1 4) The extract was chromatographed, eluting with ethyl acetate - petroleum (1 4) to obtain the *title compound* **18** (31 mg, 70%), which formed colourless crystals, m p. 165–166 °C (toluene - petroleum) (Found C, 55.6, H, 4 0, Br, 17 2 $C_{22}H_{19}BrO_7$ requires C, 55 6, H, 4.0, Br, 16 8%), ν_{max} (neat) 3070, 3000–2850, 1740, 1710, 1610, and 1590 cm^{-1}, δ (300 MHz) 1 50–2 30 (6 H, m, 3'-H_2, 4'-H_2, 5'-H_2), 3 80–4 00 (2 H, m, 6'-H_2), 3 83 (3 H, s, OMe), 7 00–7 10 (2 H, m, 6,8-H), 7 45–7 60 (3 H, m, 7-H, 3"-H, and 5"-H), and 7 80–7 90 (3 H, m, 5-H, 2"-H, and 6"-H)

Crystallographic Data[13]	**13**	**18**
Empirical Formula	$C_{16}H_{18}O_5$	$C_{22}H_{19}BrO_7$
Colour; Habit	Colourless, irregular	Colourless needles
Crystal Size (mm)	0 4 x 0 3 x 0 3	0 7 x 0.3 x 0 15
Crystal System	Orthorhombic	Triclinic
Space Group	$Pca2_1$	$P1$
Unit Cell Dimensions	a = 12 788(3) Å	a = 7 631(2) Å
	b = 7 333(2) Å	b = 11.160(2) Å
	c = 16 077(3) Å	c = 12 792(2) Å
		α = 100.13(2)°
		β = 102.09(2)°
		γ = 92 40(2)°
Volume	1507 6(6) Å^3	1045 1(4) Å^3
Z	4	2
Formula weight	290 3	475.3
Density (calc)	1 279 g/cm^3	1 510 Mg/m^3
Data Collection Diffractometer, Siemens R3m/V, radiation, Mo K_α (λ = 0 71073 Å), temp 293 °K		
Reflections Collected	1909	4010
Independent Reflections	1677 (R_{int} = 0 00%)	3711 (R_{int} = 3 43%)
Observed Reflections	1066 (F > 6.0σ(F))	1850 (F > 4 0σ(F))
Solution and Refinement System, Siemens SHELXTL PLUS (VMS)		
Number of Parameters refined	188	271
Final R indices (obs data)	R = 5 01 %, wR = 6 16 %	R = 5 11 %, wR = 4 38 %
R Indices (all data)	R = 7 88 %, wR = 8 18 %	R = 12 02 %, wR = 5 29 %

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