Studies of Chromenes. Part 11.[1] 3-Substitution of 7-Methoxy-2,2-dimethylchroman-4-one without Ring Opening *via* 3-Bromination

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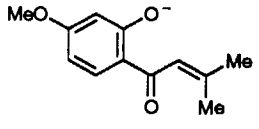
3-Bromination of 7-methoxy-2,2-dimethylchroman-4-one **3a** stabilises the anion **2a** obtained on deprotonation with LDA sufficiently for 3-alkylation to take place without the usual ring-opening. Methylation in the presence of copper(I) bromide results in 3,3-dimethylation in good yield.

The diverse biological properties of 2,2-dimethylchromenes and chromanones[2] make the synthesis of analogues of continued appeal. Our particular interest has been in 3-substituted chromanones which offer a route to the corresponding chromenes *via* reduction and dehydration. The synthesis of such derivatives from the parent chromanones is rendered difficult by the tendency to undergo ring-opening to a phenolate anion under basic conditions, particularly when a 7-methoxy group is present.[3] We have investigated several ways of overcoming this problem[4] and now report on our studies using 3-bromo-7-methoxy-2,2-dimethylchroman-4-one **3b** as an intermediate.

The tendency to ring-open reflects the greater stability of the phenolate anion **1** over the carbanion **2a** and should be curtailed by further stabilisation of the carbanion. This may be accomplished by bromination, which generally increases the acidity of the parent acids by 2–3 pK_a units.[5] Besides possibly allowing reaction of the carbanion **2b** without ring-opening, the bromine atom may itself be substituted using organocuprates and it is also readily removed.



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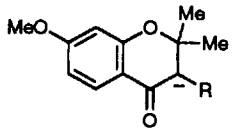
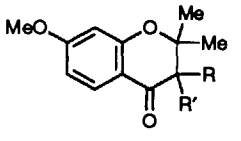


2a R = H
b R = Br

Bromination of the chromanone **3a** without any nuclear bromination was achieved using copper(II) bromide in chloroform–ethyl acetate.[6] The reaction was easily controlled so that either the monobromo- or the dibromo-products **3b** and **3c** could each be made in almost quantitative yields. Deprotonation at C-3 was accomplished using LDA in tetrahydrofuran–light petroleum under kinetic conditions. After 30 min the mixture was quenched with deuterium oxide and on work-up the 3-deuteriochromanone **3d** was recovered virtually quantitatively (> 98%, representing the limit of detection of the 3-H signal by NMR). Quenching with hydrochloric acid allowed the quantitative recovery of starting material, no ring-opening being observed. Despite its known ability to cause debromination in certain circumstances[7] the use of LDA gave better results than either sodium hydride or pre-formed dimsyl sodium (sodium dissolved in dimethyl sulfoxide).

We attribute the lack of ring opening not only to the inductively increased stability of the carbanion **2b**, but also to the bulky nature of LDA, which increases the importance of stereo-electronic control. The 3-bromochromanone exists as a dynamic equilibrium between two conformers in which the bromine is directed pseudo-axially and -equatorially (Scheme 1). Molecular mechanics calculations suggest that, although the



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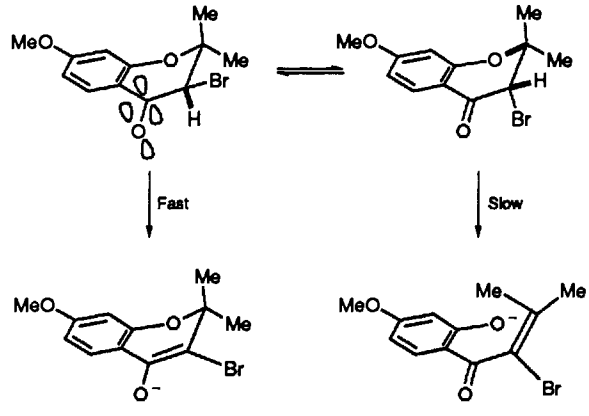
	R	R′		R	R′
a	H	H	**g**	Br	$-CH_2CH{=}CH_2$
b	H	Br	**h**	Br	$-CH_2OH$
c	Br	Br	**i**	Br	$-CH_2CH_2CO_2Me$
d	Br	D	**j**	H	$-CH_2CH_2CO_2Me$
e	Br	Me	**k**	Br	$-CH_2CH_2CN$
f	H	Me	**l**	Me	Me

former benefits from π–σ^*_{C-Br} interactions and lower torsional strain, it is only 0.8 kcal mol^{-1} (3 kJ mol^{-1}) more stable than the latter. This relatively low value is possibly due to a 1,3-interaction between the σ_{C-Br} and the axial lone pair on the ring oxygen. Stereo-electronic considerations suggest that it is deprotonation of the conformer with the axially oriented bromine that leads to ring-opening as the C–H and C(2)–O bonds are then almost antiperiplanar. Similarly deprotonation of the other conformer should lead to the stabilised carbanion since the C–H bond is then almost coplanar with the p-orbitals of the carbonyl group (Scheme 1). Because of its large steric bulk, LDA will avoid proximity to the two *gem*-dimethyl groups and will preferentially attack the pseudoaxial hydrogen to produce the carbanion. Reprotonation, which would slowly lead to ring-opening *via* equilibration, is prevented by the use of kinetic conditions.



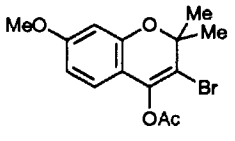
Scheme 1

Further demonstration of the resistance of this system towards ring-opening was provided by the successful acylation of the anion **2b** with acetyl chloride, which afforded the 4-acetoxy-3-bromochromene **4** in 75% yield. No ring-opened

product was observed, starting material being the only other material isolated.

Having established that deprotonation of the 3-bromochromanone was in accordance with our expectations, we attempted alkylations and other reactions of the anion. Addition of an excess of iodomethane led to the formation of the required 3-bromo-3-methyl derivative **3e** in 85% yield. In contrast, methylation following the use of thermodynamic conditions (sodium hydride or dimsyl sodium in tetrahydrofuran) led to extensive ring-opening with the formation of the dimethyl ether **5a**. Debromination of the 3-bromo-3-methyl derivative **3e** to the 3-methylchromanone **3f** was easily achieved in quantitative yield with zinc powder in wet ethyl acetate. Despite the success of the protocol in this initial example, alkylation with higher iodides gave no yield of product at all. As dehydroiodination is one explanation for the lack of reaction with higher alkyl halides, allyl bromide, which cannot undergo elimination, was used and afforded the required product **3g**, though in only 40% yield. In this one case among all the reactions described here, ring-opening was observed to give the phenol **5b** (20%) with starting material providing the balance.

Reaction of the 3-anion with formaldehyde afforded a moderate yield of the 3-bromo-3-hydroxymethylchromanone **3h** (35%). The oxirane **6** was a by-product in this reaction. Despite the modest yield, this route provides a somewhat easier access to 3-hydroxymethylchroman-4-ones than that starting from the enol acetate and using zinc(II) ion stabilisation.[4a]



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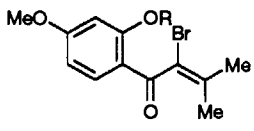
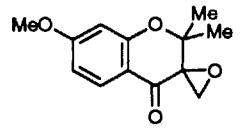


5a R = Me
b R = H

Conjugate addition was exemplified with methyl acrylate, which gave a poor to moderate yield of the adduct **3i** (36%). Subsequent debromination of the adduct gave the ester **3j**. The use of acrylonitrile gave only very poor yields of products, starting material being largely recovered. The expected 2-cyanoethyl adduct **3k** was obtained in only 14% yield together with a cyclopropane **7** (10%), derived by cyclisation with elimination of a bromide ion. The structure of the latter was established from the chemical shifts and coupling constants of the cyclopropyl protons and is that possessing the minimum steric interaction between the two 2-methyl groups and the cyano moiety.



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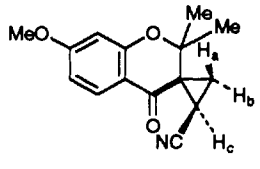

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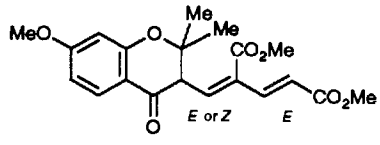
The coupling constants relating to the three cyclopropane protons H_a, H_b and H_c were J_{ab} 5.1, J_{ac} 6.5 and J_{bc} 9.1 Hz and are typical values for *gem*, *trans*, and *cis* coupling respectively. The geminal proton with the higher chemical shift (H_a δ 2.25) is assigned as being within the deshielding zone of the carbonyl group, that with the lower shift (H_b δ 1.52) therefore being remote from the carbonyl group. The remaining proton, H_c (δ 2.05), is shifted downfield by the cyano group, but not as far as H_a, suggesting that it is on the face of the cyclopropane ring remote from the carbonyl group. This was confirmed by the non-geminal coupling constants of H_a and H_b, which show H_c to be *cis* to H_b and *trans* to H_a. Interchange of the *gem* and *trans* assignments, considered in view of their numerical closeness, leads to the same geometry but would unacceptably require the proton of lowest chemical shift to be the one adjacent to the cyano group.

Finally, the use of methyl propiolate resulted in the addition of two ester units, the anionic product of the first addition acting as a better (less hindered) nucleophile than the initial bromo anion in a second conjugate addition. The bromine atom was also replaced by hydrogen in the course of this reaction, which gave compound **8** in poor yield. Whilst the *E*-stereochemistry of the second unit follows from the observed coupling of 16 Hz between its protons, the geometry of the first unit is uncertain but is also shown as *E* for convenience.



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There remained the possibility that conversion of the bromo anions into organocuprate reagents would create more effective nucleophiles. Addition of a catalytic quantity of copper(I) bromide, followed by an excess of iodomethane, converted the anion not to the monomethyl compound previously obtained but to the 3,3-dimethylchromanone **3l** in good yield (75%). Introduction of the second methyl group in this rather unusual reaction may be accounted for by a nucleophilic displacement of bromine from the initially produced 3-bromo-3-methylchromanone **3e** by a methyl cuprate species formed by metathesis. Alternatively the bromine of the initial product could be removed reductively with the generation of another carbanion which, as a cuprate, could react further with the iodomethane.

The ^{1}H NMR spectra of both compounds **3c** and **3l** showed broadening of the 2-*gem*-dimethyl signals at room temperature, the more so for the dibromide **3c**. Assignment of the two sets of *gem*-dimethyl signals for **3l** is based partly on this result and also on the lower chemical shift (δ 1.12) for the 3-methyl group of **3f** compared with the two 2-methyl groups of that compound (δ 1.25 and 1.34).[4a] The broadening is due to ring-flipping and the coalescence temperatures (T_c) for the NMR signals were 300–305 K for **3c** and 237–245 K for **3l** whilst the resultant signal separations ($\Delta\nu$) were 113.3 and 50.2 Hz respectively. From these figures, values for the energy barriers (ΔG) for the conformational changes may be calculated by using the Gutowsky–Holm and Eyring equations which combine to give eqn. (1). Application of this equation results in estimates for

$$\Delta G = 10.66 \times 10^{-11} \times RT_c \times \ln(\Delta\nu/T_c) \qquad (1)$$

the energy barriers of ring-flipping of 14.3 kcal mol^{-1} (60 kJ mol^{-1}) and 11.7 kcal mol^{-1} (56 kJ mol^{-1}) for **3c** and **3l** respectively.

Whilst these results show the validity of the use of bromine substitution to prevent ring-opening during 3-substitution of 7-methoxy-2,2-dimethylchroman-4-one **3a**, the yields are generally poor and the reactions limited in their applicability. The unoptimised low yields may, to some extent, reflect a degree of *O*-alkylation, the products of which could revert to starting material on work-up. Nevertheless the method has a limited use and may allow access to other 3,3-disubstituted derivatives.

Experimental

M.p.s (Kofler hot-stage) are uncorrected. IR spectra were recorded on a Nicolet 20 SXB FT instrument and UV spectra determined with a Kontron Uvikon-810 instrument. NMR spectra were obtained on a Brüker WP-200 spectrometer (working at 50 MHz for ^{13}C spectra) with tetramethylsilane as the internal standard. Mass spectra were obtained on a Kratos MS80 instrument. Elemental analyses were performed with a Carlo Erba Model 1106 CHN machine. The homogeneity of non-crystalline compounds was established by TLC in at least three solvents of differing polarities. Ether refers to diethyl ether and light petroleum to that fraction with b.p. 40–60 °C. Symbols * and # refer to alternative ^{13}C NMR assignments.

3-Bromo-7-methoxy-2,2-dimethylchroman-4-one **3b**.—To a suspension of copper(II) bromide (10.83 g, 48.6 mmol) in a mixture of dry ethyl acetate and chloroform (125 cm^3, 1:1) was added 2,2-dimethyl-7-methoxychroman-4-one **3a** (5.00 g, 24.3 mmol). The greenish mixture was stirred for a few minutes and then boiled under reflux until no starting material remained (TLC, about 1.5 h). The solvent was removed under reduced pressure and the dark-green residue chromatographed on silica gel (dichloromethane–light petroleum, 2:3) to give the title chromanone **3b** (6.93 g, 99%) obtained as colourless *prisms*, m.p. 40–41 °C (from light petroleum–dichloromethane); ν_{max}(KBr)/cm^{-1} 1681, 1610 and 1575; λ_{max}(EtOH)/nm 215sh (ε 12 500 dm^3 mol^{-1} cm^{-1}), 234 (6100), 280 (9600) and 318 (6200); $\delta_H(CDCl_3)$ 1.45 (3 H, s, 2-Me), 1.54 (3 H, s, 2-Me'), 3.76 (3 H, s, O-Me), 4.23 (1 H, s, CHBr), 6.34 (1 H, d, *J* 2.4, 8-H), 6.53 (1 H, dd, *J* 8.8 and 2.4, 6-H) and 7.76 (1 H, d, *J* 8.8, 5-H); $\delta_C(CDCl_3)$ 23.3, 26.0, 55.7 (C-2*), 56.2 (OMe*), 80.3 (C-3), 101.1 (C-8a), 110.4 (C-8#), 111.4 (C-6#), 129.5 (C-5), 160.7 (C-7), 166.8 (C-4a) and 185.1 (C=O) (Found: C, 50.2; H, 4.53; M^+, 284.0017. $C_{12}H_{13}BrO_3$ requires C, 50.6; H, 4.6%; *M*, 284.0048).

3,3-Dibromo-7-methoxy-2,2-dimethylchroman-4-one **3c**.—By further addition of 2 equiv. of copper(II) bromide after the formation of the monobromide in the above reaction and boiling the mixture under reflux overnight, the title *dibromide* could be obtained in 99% yield as off-white *prisms*, m.p. 91–92 °C (from light petroleum–dichloromethane); ν_{max}(KBr)/cm^{-1}, 1688, 1607 and 1573; λ_{max}(EtOH)/nm 208sh (ε 20 100 dm^3 mol^{-1} cm^{-1}), 234 (6500), 283 (9800) and 317 (6800); $\delta_H(CDCl_3)$ 1.54 (6 H, br s, sharpening on heating above 32 °C and splitting on cooling below 18 °C), 3.78 (3 H, s), 6.45 (1 H, d, *J* 2.4, 8-H), 6.58 (1 H, dd, *J* 2.4 and 8.8, 6-H) and 7.86 (1 H, d, *J* 2.4, 5-H); $\delta_C(CDCl_3)$ 55.8, 75.2, 87.7, 101.1 (OMe), 109.5 (C-8*), 111.1 (C-6*), 128.0 (C-8a#), 130.7 (C-5#), 159.1 (C-7), 167.0 (C-4a) and 179.4 (C=O) (Found: C, 39.8; H, 3.3; M^+, 361.9148. $C_{12}H_{12}Br_2O_3$ requires C, 39.6; H, 3.3%; *M*, 361.9152).

General Procedure for the Generation of the Carbanion **2b** *and its Reactions.*—To a stirred solution of LDA (1.83 cm^3, 2.1 mmol; 5.00 equiv.) in dry tetrahydrofuran–light petroleum (40 cm^3, 4:1) at 0 °C in an atmosphere of nitrogen was added the 3-bromochromanone **3b** (200 mg; 0.70 mmol) in dry tetrahydrofuran (2 cm^3). After 30 min the mixture was cooled to −70 °C and a solution of an electrophile (up to 5 equiv.) in dry tetrahydrofuran added. The reaction mixture was allowed to warm to 0 °C and then stirring continued at room temperature until TLC showed no further change (usually overnight). The reaction was quenched with conc. hydrochloric acid (2 drops), unless otherwise indicated, and the solvent removed under reduced pressure before purification of the residue by chromatography on silica gel.

3-Bromo-7-methoxy-2,2-dimethyl[3-$^2H_1$]*chroman-4-one* **3d**.—A solution of the anion was prepared as above and treated with an excess of deuterium oxide (0.5 cm^3). Work-up gave a crude product which behaved as starting material on TLC. The ^1H NMR spectrum was identical to that of the starting material, except that no signal for 3-H (δ 4.23) was present (Found: M^+, 285.0109. $C_{12}H_{12}BrDO_3$ requires *M*, 285.0109).

4-Acetoxy-3-bromo-7-methoxy-2,2-dimethyl-2H-chromene **4**.—The title chromene was formed by addition of acetic anhydride (0.25 cm^3, 0.35 mmol) in tetrahydrofuran (2 cm^3) to the solution of the anion as described above. It was obtained as a colourless *oil* (solidifying around 10 °C) (172 mg, 75%); ν_{max}(film)/cm^{-1} 1780, 1646, 1575 and 1506; $\delta_H(CDCl_3)$ 1.60 (6 H, s), 2.33 (3 H, s, $MeCO_2$–), 3.77 (3 H, s, –OMe), 6.44 (1 H, d, *J* 2.0, 8-H), 6.47 (1 H, dd, *J* 9.00 and 2.00, 6-H) and 6.93 (1 H, d, *J* 9.00, 5-H) (Found: C, 51.5; H, 4.6; M^+, 326.0152. $C_{14}H_{15}BrO_4$ requires C, 51.4; H, 4.6%; *M*, 326.0153).

3-Bromo-7-methoxy-2,2,3-trimethylchroman-4-one **3e**.—A solution of methyl iodide (0.12 cm^3, 2.1 mmol) in dry tetrahydrofuran (2 cm^3) was added to the solution of the anion and the colourless solution stirred for a further 30 min and then allowed to warm to 0 °C. The reaction mixture was stirred for a further 2 h at this temperature and then stirred overnight at room temperature. The reaction was quenched with cold aqueous conc. ammonium chloride and extracted with ether. The extract was dried ($MgSO_4$) and the solvent removed under reduced pressure. The title compound (179 mg, 85%) was obtained, after chromatography on silica gel (dichloromethane–light petroleum, 1:5), as colourless *needles*, m.p. 96–98 °C, ν_{max}(KBr)/cm^{-1} 1673 (C=O), 1605, 1576 and 1500; λ_{max}(EtOH)/nm 216 (ε 9000 dm^3 mol^{-1} cm^{-1}), 235 (6000), 280 (9600) and 319 (6400); $\delta_H(CDCl_3)$ 1.38 (3 H, s, 2-Me), 1.68 (3 H, s, 2-Me'), 1.83 (3 H, s, 3-Me), 3.80 (3 H, s, –OMe), 6.23 (1 H, d, *J* 2.1, 8-H), 6.46 (1 H, dd, *J* 2.1 and 8.2, 6-H) and 7.60 (1 H, d, *J* 8.1, 5-H) (Found: C, 52.4; H, 5.2; M^+, 298.0198. $C_{13}H_{15}BrO_3$ requires C, 52.2; H, 5.05%; *M*, 298.0205).

2-Bromo-1-(2,4-dimethoxyphenyl)-3-methylbut-2-ene-1-one **5a**.—The methylation reaction was carried out after generation of the bromo anion by the use of a stirred suspension of sodium hydride (48 mg, 2.0 mmol) in dry tetrahydrofuran (20 cm^3). Work-up and chromatography as before gave the starting material (40 mg, 20%) and the title compound **5a** as a colourless *oil* (0.157 g, 75%); $\delta_H(CDCl_3)$ 1.80 (3 H, s), 1.95 (3 H, s), 3.73 (6 H, s), 6.30 (1 H, d, *J* 2), 6.36 (1 H, dd, *J* 8 and 2) and 7.54 (1 H, d, *J* 8) (Found: C, 52.4; H, 4.8; M^+, 298.0193. $C_{13}H_{15}BrO_3$ requires C, 52.2; H, 5.05%; *M*, 298.0204).

The addition of the bromochromanone in tetrahydrofuran (2 cm^3) to a solution of dimsyl sodium [prepared by the addition of dimethyl sulfoxide (156 mg, 2.0 mmol) to a suspension of sodium hydride (48 mg, 2.0 mmol) in dry tetrahydrofuran (40 cm^3) and stirring until evolution of hydrogen ceased] gave similar results (15% starting material, 10% debrominated starting material and 65% of the ring-opened product **5a**).

7-Methoxy-2,2,3-trimethylchroman-4-one **3f**.—The 3-bromo-3-methylchromanone **3e** (100 mg, 0.33 mmol) and zinc dust (1.0 g) were stirred overnight at room temperature in ethyl acetate (20 cm^3) to which water (3 drops) had been added. The resultant suspenion was filtered through silica gel and the product eluted with dichloromethane. Removal of the solvent left the title chromanone as a colourless solid (73 mg, 99%) identical by TLC, ^1H NMR and IR spectroscopy to an authentic sample.[4b]

3-Allyl-3-bromo-7-methoxy-2,2-dimethylchroman-4-one **3g**.—To a solution of the anion of the 3-bromochromanone **2b** (200 mg, 0.70 mmol) was added a solution of allyl bromide (0.06 cm^3,

0.70 mmol) in tetrahydrofuran (2 cm^3). The reaction mixture was then allowed to warm to 0 °C, stirred at this temperature for a further 3 h, and then overnight at room temperature. The reaction was quenched with conc. hydrochloric acid (2 drops) and the solvent reduced before purification by chromatography on silica gel. The first fraction (dichloromethane–light petroleum, 1:5) afforded the title chromanone **3g** as a colourless *oil* (91 mg, 40%); $\delta_H(CDCl_3)$ 1.56 (3 H, s), 1.67 (3 H, s), 1.50–1.80 (2 H, br m, $-CH_2C=$), 3.86 (3 H, s), 4.80–5.50 (3 H, m, $-CH=CH_2$), 6.40 (1 H, d, *J* 2, 8-H), 6.60 (1 H, dd, *J* 8 and 2, 6-H) and 7.84 (1 H, d, *J* 8, 5-H) (Found: C, 55.1; H, 5.0; M^+, 324.0357. $C_{15}H_{17}BrO_3$ requires C, 55.4; H, 5.3%; *M*, 325.0361).

2-Bromo-1-(2-hydroxy-4-methoxyphenyl)-3-methylbut-2-en-1-one **5b**.—The second fraction from the preceding experiment, eluted with dichloromethane–light petroleum (3:10), was the ring-opened phenol obtained as a colourless *oil* (40 mg, 20%); ν_{max}(KBr)/cm^{-1} 3200–2600 (OH), 1635, 1602 and 1510; $\delta_H(CDCl_3)$ 1.80 (3 H, s), 2.05 (3 H, s), 3.86 (3 H, s), 6.45 (1 H, dd, *J* 8 and 2, 6-H), 6.53 (1 H, d, *J* 2, 8-H), 7.54 (1 H, d, *J* 8, 5-H) and 12.3 (1 H, s, OH) (addition of deuterium oxide caused the singlet at δ 12.3 to disappear) (Found: C, 50.3; H, 4.8; M^+, 284.0038. $C_{12}H_{13}BrO_3$ requires C, 50.55; H, 4.6%; *M*, 284.0048).

Also eluted was the starting material (80 mg, 40%).

7-Methoxy-2,2-dimethylspiro[chroman-3,2′-oxiran]-4-one **6**.—To a stirred solution of the anion was added paraformaldehyde (211 mg, 0.70 mmol). The reaction mixture was allowed to warm to 0 °C, stirred at this temperature for 3 h, and then stirred at room temperature overnight. The reaction mixture was poured into an ice-cold solution of saturated aqueous ammonium chloride and the organic layer separated. The aqueous layer was extracted with ether (3 × 25 cm^3) and the combined organic layers dried ($MgSO_4$). The solvent was removed under reduced pressure and the yellowish residue chromatographed on silica gel. The first fraction, eluted with dichloromethane–light petroleum (1:10), gave the title oxirane as a colourless *oil* (19 mg, 11%); ν_{max}(film)/cm^{-1} 2979, 2938, 2872, 2845, 1684, 1609, 1576 and 1498; λ_{max}(EtOH)/nm 212 (ε 6500 dm^3 mol^{-1} cm^{-1}), 233sh (3200), 278 (4200) and 318 (2500); $\delta_H(CDCl_3)$ 1.40 (3 H, s), 1.45 (3 H, s), 3.07 (1 H, d, *J* 6.0, –O–CH), 3.22 (1 H, d, *J* 6.0, O–CH′), 3.81 (3 H, s), 6.42 (1 H, d, *J* 2, 8-H), 6.60 (1 H, dd, *J* 8 and 2, 6-H) and 7.84 (1 H, d, *J* 8, 5-H) (Found: C, 66.4; H, 6.0; M^+, 234.0878. $C_{13}H_{14}O_4$ requires C, 66.7; H, 6.0%; *M*, 234.0892).

3-Bromo-3-hydroxymethyl-7-methoxy-2,2-dimethylchroman-4-one **3h**.—The second fraction from the preceding experiment, eluted with dichloromethane–light petroleum (3:10), was the title compound (77 mg, 35%) obtained as a colourless *oil*; ν_{max}(film)/cm^{-1} 3432 (broad, –OH), 2986, 2934, 2842, 1656, 1605 and 1502; λ_{max}(EtOH)/nm 212 (ε 12 400 dm^3 mol^{-1} cm^{-1}), 232sh (6750), 280 (8800) and 319 (5700); $\delta_H(CDCl_3)$ 1.51 (3 H, s), 1.67 (3 H, s), 3.05 (1 H, br t, *J* 6, –OH), 3.79 (3 H, s), 4.11 (2 H, dd, J_{gem} 3.0, J_{OH} 6, CH_2–OH), 6.35 (1 H, d, *J* 2, 8-H), 6.54 (1 H, dd, *J* 8 and 2, 6-H) and 7.76 (1 H, d, *J* 8, 5-H) (the signal at δ 3.05 disappeared on treatment with deuterium oxide) (Found: C, 49.7; H, 5.0; M^+, 314.0134. $C_{13}H_{15}BrO_4$ requires C, 49.4; H, 4.8%; *M*, 314.0153).

Methyl 3-(3-Bromo-7-methoxy-2,2-dimethyl-4-oxochroman-3-yl)propanoate **3i**.—To a solution of the anion at −70 °C was added a solution of methyl acrylate (0.066 cm^3, 0.77 mmol, 1.1 equiv.) in dry tetrahydrofuran. The reaction mixture was stirred and allowed to warm to 0 °C and was then stirred at room temperature overnight. The reaction was quenched with conc. hydrochloric acid (2 drops) and the solvent removed under reduced pressure to give a colourless oil which was chromatographed on silica gel. The title compound was obtained using dichloromethane–light petroleum (3:10) as the eluent as colourless *needles* (92 mg, 36%); m.p. 66–67 °C (from light petroleum); ν_{max}(KBr)/cm^{-1} 1738, 1677 and 1611; λ_{max}(EtOH)/nm 208 (ε 10 900 dm^3 mol^{-1} cm^{-1}), 217sh (8300), 234 (4750), 278 (6300) and 318 (3700); $\delta_H(CDCl_3)$ 1.58 (3 H, s), 1.66 (3 H, s), 2.2–2.8 (4 H, m, $-CH_2CH_2-$), 3.68 (3 H, s), 3.85 (3 H, s), 6.40 (1 H, d, *J* 2, 8-H), 6.60 (1 H, dd, *J* 8 and 2, 6-H) and 7.82 (1 H, d, *J* 8, 5-H) (Found: C, 51.8; H, 4.9; M^+, 370.0396. $C_{16}H_{19}BrO_5$ requires C, 51.8; H, 5.2%; *M*, 370.0415).

Methyl 3-(7-Methoxy-2,2-dimethyl-4-oxochroman-3-yl)propanoate **3j**.—Debromination of compound **3i** (50 mg, 0.185 mmol) with zinc dust as described previously, followed by chromatography on silica gel (dichloromethane–light petroleum, 11:9) gave the title compound (39 mg, 99%) as a colourless *oil*; ν_{max}(film)/cm^{-1} 3057, 2930, 2851, 1736, 1678 and 1579; $\delta_H(CDCl_3)$ 1.24 (3 H, s), 1.34 (3 H, s), 1.80 (2 H, m, $-CH_2$–CH_2CO_2Me), 2.40 (3 H, m, 3-H and $-CH_2-CH_2-CO_2Me$), 3.51 (3 H, s), 3.67 (3 H, s), 6.21 (1 H, d, *J* 2.3, 8-H), 6.37 (1 H, dd, *J* 8.8 and 2.3, 6-H) and 7.59 (1 H, d, *J* 8.8, 5-H); $\delta_C(CDCl_3)$ 21.2 ($-CH_2CH_2CO_2Me$), 22.7 ($-CH_2CH_2CO_2Me$), 26.5 (2-Me), 32.1 (2-Me′), 51.4 (C-2), 53.8 (C-3), 55.4 ($-CO_2Me$), 82.0 (7-OMe), 100.8 (C-8), 109.2 (C-6), 113.4 (C-4a), 128.3 (C-5), 161.0 (C-8a), 166.1 (C-7), 173.4 ($-CO_2Me$) and 193.5 (C-4) (Found: C, 65.9; H, 6.6; M^+, 292.1293. $C_{16}H_{20}O_5$ requires C, 65.7; H, 6.9%; *M*, 292.1311).

2′-Cyano-7-methoxy-2,2-dimethylspiro[chroman-3,1′-cyclopropan]-4-one **7**.—To a solution of the anion at −78 °C was added a solution of acrylonitrile (0.05 cm^3, 0.70 mmol, 1 equiv.) in tetrahydrofuran (2 cm^3). The reaction mixture was stirred and allowed to reach 0 °C and then stirred at this temperature for 3 h. It was then stirred overnight at room temperature. The reaction was quenched with conc. hydrochloric acid (2 drops) and the solvent removed under reduced pressure. Chromatography of the brownish residue on silica gel gave starting material as the first fraction (148 mg, 72%). The second fraction (dichloromethane–light petroleum, 1:10) was the title cyclopropane (18 mg, 10%) obtained as colourless *needles*; m.p. 135–138 °C (from dichloromethane–light petroleum); ν_{max}(KBr)/cm^{-1} 2936, 2845, 2343 (C≡N), 1672 (C=O), 1609, 1578 and 1499; $\delta_H(CDCl_3)$ 1.27 (1 H, dd, *J* 5.1 and 9.1, –CH–CH–CN), 1.30 (3 H, s, 2-Me), 1.44 (3 H, s, 2-Me′), 2.05 (1 H, dd, *J* 6.6 and 9.1, $-CH_2-CH-CN$), 2.25 (1 H, dd, *J* 5.1 and 6.6, –CH′–CH–CN), 3.86 (3 H, s), 6.05 (1 H, d, *J* 2.1, 8-H), 6.41 (1 H, dd, *J* 2.1 and 8.3, 6-H) and 7.90 (1 H, d, *J* 8.3, 5-H) (Found: M^+, 257.1052. $C_{15}H_{15}NO_3$ requires *M*, 257.1048).

3-Bromo-3-(2-cyanoethyl)-7-methoxy-2,2-dimethylchroman-4-one **3k**.—The third fraction from the preceding experiment [dichloromethane–light petroleum (1:5) as eluent], was the title compound (24 mg, 14%); obtained as a colourless *oil*; ν_{max}(film)/cm^{-1} 3083, 2986, 2363 (C≡N), 1684 (C=O), 1611, 1587 and 740 (C–Br); $\delta_H(CDCl_3)$ 1.51 (3 H, s, 2-Me), 1.63 (3 H, s, 2-Me′), 1.76–2.97 (4 H, m, $-CH_2CH_2CN$), 6.41 (1 H, d, *J* 2.1, 8-H), 6.58 (1 H, dd, *J* 2.1 and 8.2, 6-H) and 7.75 (1 H, d, *J* 8.2, 5-H) (Found: M^+, 337.0303. $C_{15}H_{16}BrNO_3$ requires *M*, 337.0313).

Dimethyl (1E/Z,3E)-2-(Methoxycarbonyl)-5-(7-methoxy-2,2-dimethyl-4-oxochroman-3-yl)pent-1,3-enoate **8**.—To a solution of the anion was added a solution of methyl prop-2-ynoate (59 mg, 0.70 mmol, 1.0 equiv.) in the same solvent (2 cm^3). The reaction mixture was allowed to warm to 0 °C, stirred at this temperature for 3 h, and then stirred at room temperature overnight. The reaction was quenched by the addition of conc.

hydrochloric acid (2 drops) and the solvent removed under reduced pressure. The yellowish residue was chromatographed on silica gel (dichloromethane–light petroleum, 3:10) to give the title compound as a colourless *oil* (82 mg, 31%); ν_{max}(film)/cm^{-1} 1729, 1609, 1578; δ_H 1.53 (3 H, s, 2-Me), 1.62 (3 H, s, 2-Me'), 3.26 (1 H, d, *J* 3.01, 3-H), 3.56 (3 H, s, –CO_2Me), 3.61 (3 H, s, –CO_2Me'), 3.78 (3 H, s, –OMe), 5.87 (1 H, d, *J* 16.1, =C*H*CO_2Me), 6.14 (1 H, d, *J* 3.2, >CHC*H*=), 6.33 (1 H, d, *J* 2, 8-H), 6.48 (1 H, dd, *J* 8 an 2.0, 6-H), 7.36 (1 H, d, *J* 16.1, =CC*H*=CHCO_2Me) and 7.70 (1 H, d, *J* 8, 5-H) (Found: M$^+$, 374.1375. $C_{20}H_{22}O_7$ requires *M*, 374.1365).

7-*Methoxy*-2,2,3,3-*tetramethylchroman*-4-*one* **3l**.—To a stirred solution of the anion at 0 °C was added copper(I) bromide (20 mg; 10%) and stirring was continued for 15 min. The resulting dark-green solution was cooled to −78 °C and a solution of iodomethane (0.16 cm^3, 2.8 mmol, 4 equiv.) in tetrahydrofuran (2 cm^3) added. The reaction mixture was stirred at this temperature for about 2 h and then allowed to warm to room temperature overnight. The reaction mixture was poured into cold saturated aqueous ammonium chloride (50 cm^3), then ether (50 cm^3) was added and the organic layer separated. The aqueous layer was extracted with ether (3 × 25 cm^3) and the combined organic layers washed with aqueous ammonium chloride that had been raised to pH 8 by the addition of conc. ammonia solution, and then with water. The ether solution was dried ($MgSO_4$) and the solvent removed under reduced pressure. Column chromatography of the residue gave the title compound **3l** as a colourless *oil* (124 mg, 75%); solidifying ~4 °C; ν_{max}(film)/cm^{-1} 2985, 2930, 2858, 1680, 1610, 1583 and 1497; λ_{max}(EtOH)/nm 215 (ε 13 800 dm^3 mol^{-1} cm^{-1}), 233 (9000), 271 (10 000) and 313 (14 800); δ_H($CDCl_3$) 1.17 (6 H, s, 3-Me_2), 1.39 (6 H, s, 2-Me_2), 3.81 (3 H, s, OMe), 6.40 (1 H, d, *J* 2, 8-H), 6.55 (1 H, dd, *J* 8 and 2, 6-H) and 7.73 (1 H, d, *J* 8, 5-H) (the signal at δ 1.39 broadened and eventually split into two on cooling below −36 °C) (Found: M$^+$, 234.1266. $C_{14}H_{18}O_3$ requires *M*, 234.1256).

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