# Routes to Spiroacetals derived from Chroman-4-one
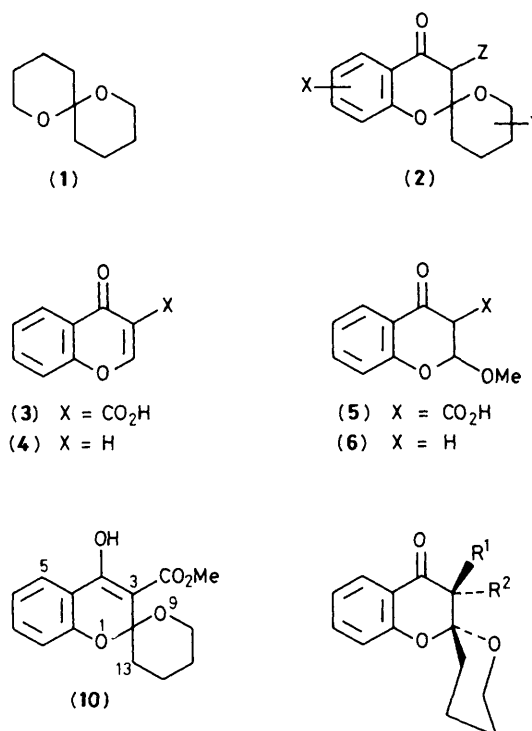
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Methyl 2-(4'-hydroxybutyl)chromone-3-carboxylate (**7**) and the derived epoxide (**13**) undergo spirocyclisation on treatment with iodomethane–potassium carbonate and Lewis acid respectively.

The 1,7-dioxaspiro[5.5]undecane (spiroacetal) moiety (**1**) has attracted considerable attention recently owing to its interesting stereoelectronic properties[1] and its presence in a range of natural products,[2] especially the avermectins[3] and milbemycins.[4] In seeking analogues of these potent antiparasitic and pesticidal agents, we required access to benzannulated systems (**2**), and herein describe two complementary routes to this hitherto unknown series of chroman-4-ones.

The first route is based on the susceptibility of chromones bearing electron-withdrawing substituents at C-3 towards conjugate addition of alkanols.[5] Model studies revealed that methanol would add to the carboxylic acid (**3**)† under mild conditions (reflux, 2—3 h), causing quantitative decarboxylation to the parent heterocycle (**4**)‡ *via* (**5**) and (**6**). Using buffered conditions (1.8 equiv. sodium acetate, methanol, room temp., 24 h) the intermediate (**6**)§ could be isolated in 34% yield, the material balance being (**4**). To exploit this reactivity in spiroacetal synthesis, a substrate (**7**) capable of intramolecular conjugate addition was prepared as shown in Scheme 1. Thus the dianion of methyl acetoacetate was allylated[8] and the product (**8**) converted into the chromone ester (**9**) using a published procedure.[9] Hydroboration of (**9**) using a triethylamine *N*-oxide work-up gave the desired ester (**7**) [oil; $\nu_{max}$ (neat) 1730, 1675—1600, and 1575 cm$^{-1}$; $\delta_H$ (60 MHz, CDCl$_3$) 1.4—2.2 (4 H, m, 2',3'-H), 2.5 (1 H, br. s, OH), 2.8 (2 H, t, $J$ 7 Hz, 1'-H), 3.7 (2 H, t, $J$ 6 Hz, 4'-H), 3.95 (3 H,



(1)

(2)

(3) X = CO$_2$H
(4) X = H

(5) X = CO$_2$H
(6) X = H

(10)

(11) R$^1$ = CO$_2$Me, R$^2$ = Me
(12) R$^1$ = Me, R$^2$ = CO$_2$Me
(14) R$^1$ = OH, R$^2$ = CO$_2$Me
(15) R$^1$ = CO$_2$Me, R$^2$ = OH

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† Prepared by heating chromone-3-carbaldehyde (H. Harnisch, *Liebigs Ann. Chem.*, 1972, **765**, 8) with sulphuryl chloride (1.1 mol equiv.) and 2,2'-azobis(2-methylpropionitrile) (trace) in tetrachloromethane (reflux, 3 h), followed by evaporation, treatment with water, and crystallisation from ethyl acetate (69%).
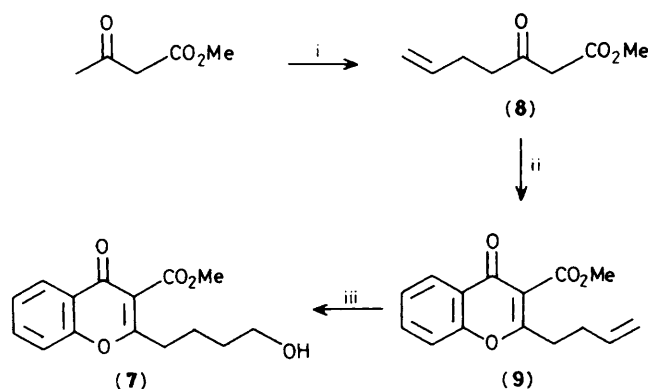
‡ A description by Ghosh and Khan[6] of the decarboxylation of (**3**) using triethylamine in refluxing ethanol is somewhat deceptive. We found that the solvent alone elicits the observed transformation.

§ All products were isolated by flash chromatography,[7] and new compounds gave satisfactory spectroscopic and microanalytical data.

s, Me), 7.1—7.5 (3 H, m, 6,7,8-H), and 8.0—8.2 (1 H, m, 5-H)].

Spirocyclisation of (**7**) was effected using alkylating conditions [MeI (6 equiv.), K$_2$CO$_3$ (2 mol equiv.), acetone, reflux, 6 days], thus trapping the equilibrating conjugate addition
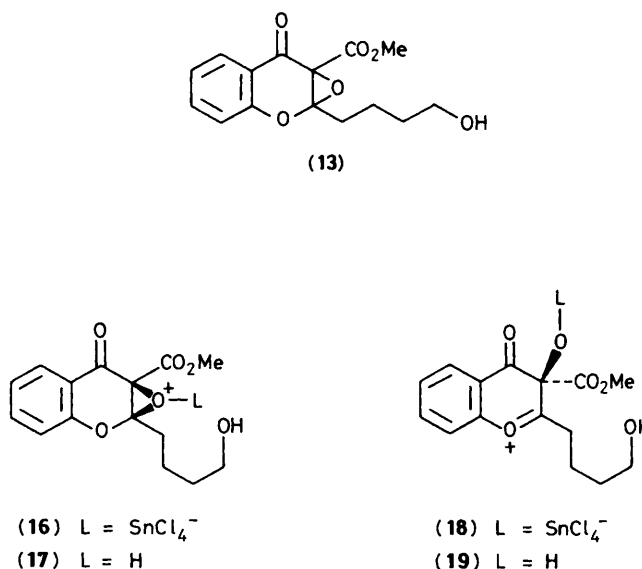
**Scheme 1.** *Reagents:* i, NaH (1.1 equiv.), tetrahydrofuran (THF), 0 °C, 0.5 h, Bu$^n$Li in hexane (1.1 equiv.), 0 °C, 0.5 h, allyl bromide (1.5 equiv.), 0 °C, 0.5 h (55%); ii, NaH, toluene, room temp., 0.5 h, *o*-FC$_6$H$_4$COCl, reflux, 24 h (60%); iii, BH$_3$–THF, 0 °C to room temp., 24 h, Me$_3$NO·2H$_2$O, reflux, 2 h (43%).



(13)



(16)　L = SnCl$_4^-$　　　　(18)　L = SnCl$_4^-$
(17)　L = H　　　　　　　(19)　L = H

product **(10)** as the isomeric β-ketoesters **(11)** [m.p. 123—124 °C; δ$_H$ (80 MHz, CDCl$_3$) 1.47 (3 H, s, 3-Me), 1.5—2.2 (6 H, m, 11,12,13-H), 3.5—3.7 (2 H, m, 10-H), 3.75 (3 H, s, OMe), 7.00 (2 H, t, *J* 8 Hz, 6,8-H), 7.44 (1 H, ddd, *J* 2, 8, 8 Hz, 7-H), and 7.84 (1 H, dd, *J* 2, 8 Hz, 5-H); ν$_{max.}$ (Nujol mull) 1725 and 1690 cm$^{-1}$] and **(12)** [oil; δ$_H$ (80 MHz, CDCl$_3$) 1.56 (3 H, s, 3-Me), 1.5—2.2 (6 H, m, 11,12,13-H), 3.4—3.8 (2 H, m, 10-H), 3.53 (3 H, s, OMe), 6.97 (2 H, t, *J* 8 Hz, 6,8-H), 7.42 (1 H, ddd, *J* 2, 8, 8 Hz, 7-H), and 7.81 (1 H, dd, *J* 2, 8 Hz, 5-H); ν$_{max.}$ (neat) 1735 and 1700 cm$^{-1}$], ratio *ca.* 5 : 1 (total 61%). The assignment of **(11)** as the major product of the reaction, although not proven, is consistent with a mechanistic model in which the methylating species approaches C-3 of **(10)** from the less hindered side, *i.e.* that occupied by O-9, which can also assist by co-ordination of the incoming electrophile.

A second route to the desired ring system utilised the chromone epoxide **(13)**, which was conveniently prepared from **(9)** *via* a one-pot hydroboration–oxidation sequence (borane–THF, 0 °C to room temp., 4 h, then H$_2$O–H$_2$O$_2$–K$_2$CO$_3$, room temp., 1 h) in 45% yield. Treatment of **(13)** with tin(IV) chloride (1.4 mol equiv., dichloromethane, 0 °C, 1 h) gave a 1 : 1 mixture (total 56%) of the isomeric spiroacetals **(14)**¶ [oil; δ$_H$ (250 MHz, CDCl$_3$) 1.5—2.0 (6 H, m, 11,12, 13-H), 3.75—3.90 (1 H, m, 10-H$_{eq}$), 3.82 (3 H, s, OMe), 4.02 (1 H, dt, *J* 4, 11 Hz, 10-H$_{ax}$), 4.18 (1 H, s, OH), 7.00—7.10 (2 H, m, 6,8-H), 7.55 (1 H, m, 7-H), and 7.87 (1 H, dd, *J* 2, 8 Hz, 5-H); ν$_{max.}$ (neat) 1730 and 1700 cm$^{-1}$; *p*-bromobenzoate, m.p. 165—166 °C (toluene–light petroleum)] and **(15)**¶ [oil; δ$_H$ (250 MHz, CDCl$_3$) 1.5—2.2 (6 H, m, 11,12,13-H), 3.55—3.75 (2 H, m, 10-H$_2$), 3.67 (3 H, s, OMe), 4.10 (1 H, s, OH), 7.07 (2 H, ABq, *J* 8 Hz, 6,8-H), 7.54 (1 H, m, 7-H), and 7.86 (1 H, dd, *J* 2, 8 Hz, 5-H); ν$_{max.}$ (neat) 1730 and 1700 cm$^{-1}$]. In contrast, treatment of the epoxide **(13)** with toluene-*p*-sulphonic acid (*ca.* 5 mol %, dichloromethane, room temp., 22 h) gave a mixture of **(14)** and **(15)** (total 59%) with the former predominating by at least 2.5 : 1. The separated isomers **(14)** and **(15)** did not appear to equilibrate on treatment with an excess of toluene-*p*-sulphonic acid in dichloromethane.

The spiroacetals **(14)** and **(15)** could arise from **(16)** or **(17)** *via* displacement with inversion at C-2 and from the oxonium species **(18)** or **(19)** *via* addition, which may be subject to steric and/or co-ordination effects. The assignment of **(14)** as the major product in the proton-catalysed process is based on the speculation that the displacement mechanism, for which there is an intermolecular equivalent,[10] makes a significant contribution to the observed result.

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¶ The structures **(14)** and **(15)** are not readily distinguishable spectroscopically; the assignments are tentative and may be reversed.

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