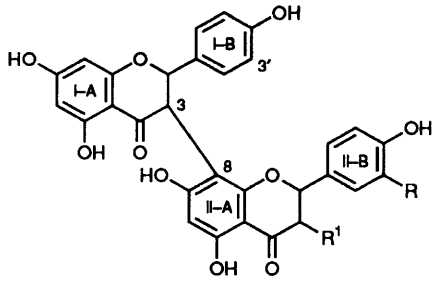
Aryllead Triacetates as Synthons for the Synthesis of Biflavonoids. Part 1. Synthesis and Reactivity of a Flavanonyllead Triacetate

Dervilla M. X. Donnelly,*[a] Brendan M. Fitzpatrick[a] and Jean-Pierre Finet*[b]
[a] *Department of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland*
[b] *Laboratoire SREP, 'Radicaux Libres et Synthèse,' URA-CNRS 1412, Université de Provence, Centre St Jérôme, 13397 Marseille Cedex 20, France*

The 8-triacetoxyplumbylflavane derivative **11** was prepared in 4 steps in 28% overall yield from 4',5,7-flavanone. It reacted with the benzofuranone allyl β-keto ester **12** to yield a 8-(benzofuran-2-yl)flavanone **13** in 66%. Removal of the allyl ester group and cleavage of the dioxolane ring afforded the 8-(3-oxobenzofuran-2-yl)flavanone. This reaction shows that complex polyfunctional aryllead triacetates can be made and selectively coupled with activated ketones.

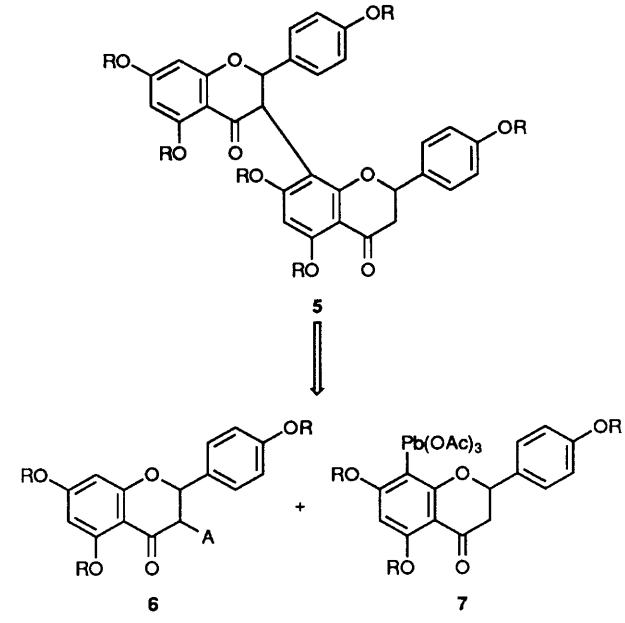
Biflavonoids are considered to be oxidative coupling products of two chalcone units leading to biflavones, flavanone-flavones or biflavanones.[1] They generally occur in the leaves of primitive gymnosperms, but the *Garcinia* biflavonoids are found only within one family of angiosperms, the Guttiferae.[2] While the amentoflavones (I-3', II-8 biflavonoids) have been isolated from the leaves of two species (*Garcinia livingstonei*,[3] *Calophyllum inophyllum*[4]), the most characteristic feature of the family is the I-3, II-8-linked *Garcinia* biflavonyl group. A range of these compounds has been isolated from bark,[5] roots[6] or heartwood[2,3,7,8] of many species of *Garcinia* and one species of *Allanblackia*.



1 R = R^1 = H (GB-1a)
2 R = OH, R^1 = H (GB-2a)
3 R = H, R^1 = OH (GB-1)
4 R = R^1 = OH (GB-2)

The biflavanones GB-1a, GB-2a, GB-1 and GB-2 **1**–**4** were isolated from the Guttiferae species, *Garcinia buchananii* Baker and *G. eugeniifolia* Wall.[2] The majority of work on the synthesis of biflavonoids has involved partial syntheses performed by modification of existing biflavonoids. Comparatively few total syntheses of biflavonoids have been attempted. The flavanone-flavone (±)-hepta-*O*-methylfukugetin and the biflavone hepta-*O*-methylsaharanflavone have been obtained by linear synthesis in poor overall yields.[9] However, *Garcinia* biflavanones have yet to be fully synthesized. Acids and bases are known to open the flavanone heterocycle to give the corresponding chalcone and so any proposed routes to *Garcinia* biflavanones must either avoid the use of acids/bases or else involve the preparation of an acid/base-resistant flavanone derivative. An attractive convergent route to the naturally occurring *Garcinia* biflavanones **5** would be selectively to link two preformed flavanone moieties (Scheme 1).

The flavanone moiety linked at position II-8 would have to be an electrophilic arylation agent, while the C-3 hydrogen of

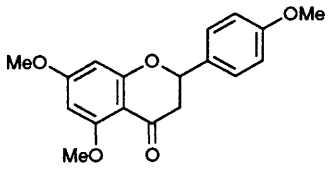


Scheme 1 Convergent retrosynthesis of *Garcinia* biflavonoids

the other flavanone moiety would have to be sufficiently acidic to ensure a high yield for the critical coupling step. For electron-rich arenes, aryllead triacetates are the most easily prepared and highest yielding arylation agents.[10] In previous communications, we have recently described the efficient convergent preparation of isoflavanones and isoflavones by aryllead-mediated C-3 arylation of chroman-4-derivatives.[11,12] For the synthesis of biflavanones, a flavanonyllead triacetate **7** would be required to couple with flavanone **6** (A = H) or some activated flavanone derivative **6** (A = electron-withdrawing group). Therefore, the required flavanonyllead triacetate was prepared and its use as an arylating agent was tested by treating it with an allyl β-keto ester.

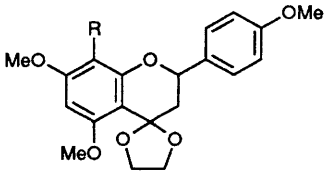
The preparation of aryllead triacetates can be performed by direct plumbylation for aromatics at least as electron-rich as the halogenobenzenes.[10] However, stirring of a mixture of 4',5,7-trimethoxyflavanone **8** with lead tetraacetate in dry chloroform gave a mixture containing only starting material and a trace of a flavanonyllead triacetate. When the reaction was performed in the presence of chloroacetic acid, a mixture containing approximately 60% of starting material **8** and 40% of a mixture of isomeric flavanonyllead triacetates was obtained. Further-

more, use of the more reactive dichloroacetic acid in place of chloroacetic acid did not give rise to complete plumbylation of the flavanone.



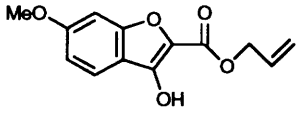
8

In view of these results, attention was turned to preparing the flavanonyllead triacetate *via* the tin–lead route.[13] The 8-bromoflavanone acetal **9** was prepared following Frick and Schmidt's procedure.[14] Although crude 4′,5,7-trimethoxy-8-(tributylstannyl)flavanone ethylene ketal was prepared in high yield *via* the 8-lithio derivative, all attempts to purify the product resulted in flavanone–tin bond scission. Fortunately, the trimethylstannyl analogue 4′,5,7-trimethoxy-8-(trimethylstannyl)flavanone ethylene ketal **10** was successfully synthesized in 60% yield. Tin-lead exchange afforded 4′,5,7-trimethoxy-8-(triacetoxyplumbyl)flavanone ethylene ketal **11** in 77% yield. Aryltrimethylstannanes are generally considered to be inferior to aryltributylstannanes as precursors to aryllead triacetates, because methyl–tin cleavage can occur at a similar rate to aryl–tin bond cleavage.[13] However, in the present case, any methyl–tin bond cleavage did not significantly retard the tin–lead exchange.



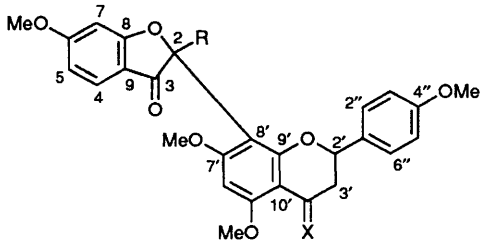
8

9 R = Br
10 R = $SnMe_3$
11 R = $Pb(OAc)_3$



12

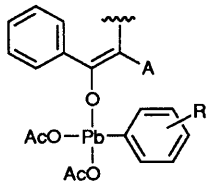
The direct α-arylation of ketones is not generally possible but requires the activation of the ketone as an enamine[15] or a β-keto ester.[16] However, the arylation of enamines is very sensitive to steric effects. β-Keto esters, on the other hand, are conveniently arylated with aryllead triacetates in high yields,[16,17] but unfortunately the sterically hindered alkyl β-keto esters can be resistant to dealkoxycarbonylation subsequent to arylation. Hindered allyl β-keto esters, however, can be smoothly deallyloxycarbonylated in high yield.[17] It was decided to study the reactivity of the plumbane **11** towards a hindered and activated enolisable substrate before using it in a *Garcinia* biflavonoid synthesis. The 3-hydroxy benzofuran-2-carboxylic acid derivative **12** seemed an attractive choice as a model substrate, as it had previously been arylated by monoaryllead triacetates in high yield.[17] Since the reaction site is reasonably hindered, a successful coupling of the plumbane **11** with ester **12** would mean that steric factors would not retard a biflavanone-forming step. The heterocyclic system **13** was prepared in 66% yield by the standard lead arylation procedure [**12** (1 mol equiv.), **11** (1.1 mol equiv.), pyridine (3.3 mol equiv.), $CHCl_3$; 60 °C; 1 h]. A 400 MHz ^{1}H NMR study of product **13** indicated that it exists as atropisomers due to the hindered rotation about the I-2, II-8 bond. At room temperature, assignment of the proton resonances was impossible, due to significant peak broadening. High-temperature studies revealed that, as the temperature was raised, the 2–8′ bond can rotate more freely, resulting in sharpening of the ^{1}H NMR signals. No rotational barrier was evident at 80 °C, and with the aid of COSY spectra two diastereoisomers were discerned in a 1.4:1 ratio. Biflavanone atropisomers, due to restricted rotation around the interflavanone linkage, have also been reported.[2,18] The ^{1}H NMR resonances of the two isomers were generally found in their characteristic chemical-shift positions. However, the difference in folding of the two isomers gave rise to some remarkable features. 2‴-H appears as a doublet for the least abundant isomer (*b*) and as a symmetrical octet for the more abundant isomer (*a*). For isomer (*b*), 4-, 2″- and 6″-H resonate at their expected frequencies, but for isomer (*a*) the signals due to these protons are found significantly further upfield. Presumably, for isomer (*a*) there is partial overlap of signals for the benzofuranone aryl ring and the anisyl group, leading to a through-space shielding of 4-, 2″- and 6″-H. In the ^{13}C NMR spectrum of compound **13** at 80 °C, the carbons of each diastereoisomer (*a*) and (*b*) show up as separate signals except for C-6 -6′, -8′, -1″, -2″, -6″, -2‴ and -4‴, where a single chemical shift is assigned to both isomers. The methoxy-group and dioxolane carbons were recorded over a chemical-shift range because of the considerable overlap of peaks. All the carbons can be considered to resonate in their characteristic chemical-shift positions. The two isomers had identical R_f-values on silica gel and alumina and thus chromatography on these supports failed to effect any separation. During lead-mediated arylations, a planar intermediate such as species **14** involving a lead-to-oxygen covalent bond has been proposed.[19] In the case of the heterocyclic system **13**, one diastereotopic pathway to compound **13** must be slightly more favoured than the other leading to the 1.4:1 ratio.



13 R = $-\overset{O}{\overset{\|}{C}}-O-CH_2-CH=CH_2$, X = OCH_2CH_2O

15 R = H, X = OCH_2CH_2O

16 R = H, X = O

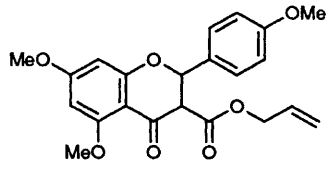


14

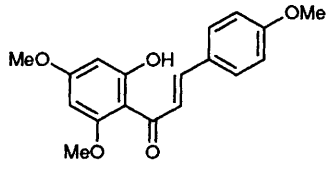
Compound **13** was converted in 92% yield into the benzofuranone-flavanone ketal **14** *via* Tsuji's palladium-catalysed deallyloxycarbonylation[20] [$Pd(OAc)_2$ 5%, PPh_3 10%, HCO_2H (4 mol equiv.), Et_3N (4.6 mol equiv.), dry THF; room temp.; 4 days]. The number of equivalents of palladium acetate, tri-

phenylphosphine, formic acid and triethylamine used by Tsuji had to be doubled in order to consume all the substrate **13**. There is no significant rotational barrier around the I-2–II-8 bond in compound **15** and so it does not exist as atropisomers. However, in addition to the two diastereoisomers, a small fraction (10%) exists as the enol tautomer. Unfortunately, the enol ^{1}H and ^{13}C NMR signals were too small to be discerned from those due to the ketone. In the ^{1}H NMR spectrum most of the aromatic signals due to each diastereoisomer could be assigned. However, in the ^{13}C NMR spectrum, except for C-4, -2″ and -6″, only a mixed signal for the two diastereoisomers could be discerned. For both the ^{1}H and ^{13}C NMR spectra the nuclei resonated at the expected chemical shifts. The ketal **15** was hydrolysed to the deprotected benzofuranone-flavanone **16** by hydrolysis of the dioxolane system in dil. acid [5% aq. HCl–tetrahydrofuran (THF); room temp.; 15 min] in 92% yield. In this case no enol tautomer was detected, compound **16** existing solely as two diastereoisomers in an *a*:*b* 1.4:1 ratio. Only some of the ^{1}H and ^{13}C NMR resonances could be separately discerned for each isomer.

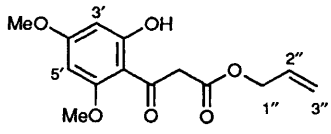
The preparation of compounds **13** illustrates the ability of the polycyclic lead triacetate **11** to arylate a hindered substrate in high yield. The existence of compound **13** as atropisomers is evidence of the hindered nature of that benzofuranone-flavanone system and thus suggests that the synthesis of a biflavanone, *via* a ligand-coupling step, should not be retarded by steric factors. It was then decided to prepare 3-allyloxycarbonyl-4′,5,7-trimethoxyflavanone **17** and to test its reactivity towards aryllead triacetates. A proposed synthesis of compound **17** involved the reaction of the lithium enolate of compound **8** with allyl cyanomethanoate at low temperature.[12,17] However when lithium diisopropylamide (LDA) was added to compound **8**, the pyranone ring underwent a reverse Michael addition to give the chalcone **18**. Addition of LDA dropwise to a mixture of compound **8** and allyl cyanomethanoate in dry THF at −78 °C also only succeeded in producing the chalcone **18**. Similarly, the alternative base, lithium bis(trimethylsilyl)amide, could not promote the displacement reaction over the isomerisation.



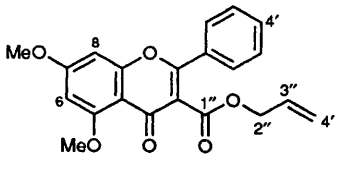
17



18



19



20

Cushmann[21] has described the conversion of alkyl 3-(2-hydroxyaryl)-3-oxopropanoates into 3-(alkoxycarbonyl)flavones through the reaction of their magnesium chelates with benzoyl chloride. A route to compound **17** was devised by modifying this method. Allyl 2-(2-hydroxy-4,6-dimethoxybenzoyl)acetate **19** was synthesized in 75% yield by treatment of the appropriate *o*-hydroxyphenylethanone with excess of lithium bis(trimethylsilyl)amide, followed by reaction with diallyl carbonate. However, the magnesium chelate of compound **19** failed to react with either *p*-anisaldehyde or the more reactive benzaldehyde. To confirm that the magnesium chelate did indeed form, the flavone **20** was prepared in 73% yield.

The failure of the methods described above to synthesize compound **17** necessitated the search for another method of activation of flavanones. The β-keto ester approach was abandoned in favour of finding another activating group that could be incorporated into the flavanone unit under mild conditions.[22]

Experimental

M.p.s were determined on a Reichert-Jung Thermovar apparatus and are uncorrected. ^{1}H NMR spectra were recorded at either 100 MHz (Bruker AC 100), 270 MHz (JEOL JNM-GX 270), 400 MHz (Bruker AM 400X), or 500 MHz (Varian Unity 500). ^{13}C NMR spectra were recorded at either 67.8 MHz (JEOL JNM-PMX270), 100.6 MHz (Bruker AM 400X), or 125.7 MHz (Varian Unity 500). All *J* values are given in Hz. IR spectra were recorded on a Perkin-Elmer 1710 Infra-red FT spectrometer. UV spectra were recorded on a Philips PU 8720 spectrophotometer. Mass spectra were recorded on a VG Analytical 770 mass spectrometer with attached INCOS 2400 data system in the EI mode. Separations by column chromatography (CC) and flash chromatography (FC) were performed using Merck Kieselgel 60 (70–230 mesh ASTM) and 60 (230–400 mesh ASTM) respectively. Lead tetraacetate was dried prior to use over potassium hydroxide pellets at 0.1 mmHg for 30 min. Ether refers to diethyl ether. Light petroleum refers to the fraction boiling in the range 40–60 °C. All solvents were purified by standard techniques.

5,7-Dimethoxy-2-(4″-methoxyphenyl)-8-(trimethylstannyl)-spiro{chromane-4,2′-[1,3]dioxolane} **10**.—Butyllithium (2.74 cm^3 of a 2.5 mol dm^{-3} solution in hexane) was added to a stirred solution of 8-bromo-4′,5,7-trimethoxyflavanone ethylene ketal **9**[14] (2.5 g, 5.7 mmol) in dry THF (100 cm^3) under nitrogen at −78 °C. After the mixture had been stirred for 1 h at 78 °C, a solution of trimethylstannyl chloride (1.36 g, 6.84 mmol) in dry THF (20 cm^3) was added dropwise. The reaction mixture was stirred at −78 °C for 2 h and then was allowed to reach room temperature over a period of 2 h. Saturated aq. ammonium chloride (10 cm^3) and water (50 cm^3) were added and the mixture was extracted with ether (3 × 80 cm^3). The combined extracts were washed with brine (100 cm^3) and dried (Na_2SO_4). Removal of the solvent under reduced pressure yielded a pale yellow solid, which upon crystallisation from benzene gave the *8-trimethylstannylflavanone ketal* **10** as needles (1.79 g, 60%), m.p. 193–195 °C; ν_{max}(KBr)/cm^{-1} 1592, 1570, 1213 and 1106; δ_H (270 MHz; $CDCl_3$) 7.34 (2 H, d, *J* 8.79, 2″ and 6″-H), 6.9 (2 H, d, *J* 8.79, 3″- and 5″-H), 6.11 (1 H, s, 6-H), 5.04 (1 H, dd, *J* 10.99 and 1.6, 2-H), 4.31–3.96 (4 H, m, OCH_2CH_2O), 3.87 (3 H, s, OMe), 3.82 (3 H, s, OMe), 3.74 (3 H, s, OMe), 2.38–2.04 (2 H, m, 3-H_2) and −0.13 (9 H, s, 3 × Me); δ_C (67.80 MHz; $CDCl_3$) 166.2 (C-7), 162.54 (C-5), 161.5 (C-9), 159.4 (C-4″), 132.44 (C-4), 127.98 (C-1″), 127.92 (C-2″ and -6″), 113.65 (C-3″ and -5″), 106.07 (C-10), 104.56 (C-8), 89.26 (C-6), 77.52 (C-2), 65.82

(OCH_2CH_2O), 65.03 (OCH_2CH_2O), 55.99 (OMe), 55.35 (OMe), 55.24 (OMe), 43.29 (C-3) and −7.13 (3 × Me); *m/z* 522 (M^+, 2%), 507 (35), 373 (100), 329 (50), 299 (27) and 224 (59) (Found: C, 52.95; H, 5.8; Sn, 22.0 $C_{23}H_{30}O_6Sn$ requires C, 53.01; H, 5.80; Sn, 22.77%).

5,7-*Dimethoxy*-2-(4″-*methoxyphenyl*)-8-(*triacetoxyplumbyl*)-*spiro*{*chromane*-4,2′-[1,3]*dioxolane*} **11**.—A mixture of lead tetraacetate (1.39 g, 3.14 mmol), the 8-trimethylstannylflavanone ketal **10** (1.62 g, 3.11 mmol) and mercury(II) acetate (0.049 g, 0.16 mmol) were heated at 40 °C in dry chloroform (10 cm^3) for 15 h. Chloroform was added, the mixture filtered through Celite, and the solution was concentrated to ~ 10 cm^3. This was added dropwise to light petroleum (300 cm^3) whereupon a bright yellow solid precipitated out. The solid was filtered off and dried *in vacuo* to give the 8-triacetoxyplumbylflavanone ketal **11** (1.774 g, 77%), m.p. 142–145 °C; ν_{max}(KBr)/cm^{-1} 2937, 1602, 1567, 1518, 1405 and 1215; δ_H (270 MHz; $CDCl_3$) 7.42 (2 H, d, *J* 8.79, 2″- and 6″-H), 6.92 (2 H, d, *J* 8.8, 3″- and 5″-H), 6.21 (1 H, s, 6-H), 5.23 (1 H, d, *J* 11.54, 2-H), 4.3–3.99 (4 H, m, OCH_2CH_2O), 3.9 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.81 (3 H, s, OMe), 2.42–2.12 (2 H, m, 3-H_2) and 1.9 (9 H, br s, 3 × OAc); δ_C (67.80 MHz; $CDCl_3$) 179.03 (CO), 163.15 (C-5 and -7), 160.85 (C-9), 159.62 (C-4″), 131.05 (C-4), 128.06 (C-1″, -2″ and -6″), 127.64 (C-8), 113.83 (C-3″ and -5″), 105.27 (C-10), 90.51 (C-6), 78.22 (C-2), 66.01 (OCH_2CH_2O), 65.25 (OCH_2CH_2O), 56.66 (OMe), 56.36 (OMe), 55.31 (OMe), 43.18 (C-3) and 20.61 (OCO*Me*); *m/z* 358 (12%), 312 (4), 297 (8), 267 (7), 224 (100), 208 (4), 195 (8) and 181 (13).

Allyl 2-(5,7-*Dimethoxy*-2-(4-*methoxyphenyl*)*spiro*{*chromane*-4,2′-[1,3]*dioxolan*-8-*yl*})-6-*methoxy*-3-*oxobenzofuran*-2-*carboxylate* **13**.—Dry pyridine (0.19 cm^3, 1.98 mmol) was added to a stirred mixture of prop-2-enyl-3-hydroxy-6-methoxy benzofuran-2-carboxylate **12**[17] (0.149 g, 0.60 mmol) and the 8-triacetoxyplumbylflavanone ketal **11** (0.49 g, 0.66 mmol) in dry chloroform (2 cm^3) and the resultant yellow suspension was stirred at 60 °C for 1 h. After cooling, the reaction mixture was diluted with chloroform (50 cm^3) and washed with 3 mol dm^{-3} sulfuric acid (50 cm^3). The aqueous layer was extracted with chloroform (3 × 50 cm^3). The combined organic layers were washed with 3 mol dm^{-3} sulfuric acid (50 cm^3) and again the aqueous layer was extracted with chloroform (3 × 50 cm^3). All the chloroform layers were combined, filtered through Celite, dried (Na_2SO_4), and the solvent was evaporated off under reduced pressure. The residue was purified by FC on silica gel [eluent: ethyl acetate–chloroform (3:1)] to yield the *title compound* as an *a*/*b* 1.4:1 mixture of diastereoisomers (0.24 g, 66%). This rigid cream foam proved impossible to crystallise, m.p. 104–108 °C and 126–130 °C; ν_{max}(KBr)/cm^{-1} 2363, 1749, 1711 and 1117; λ_{max}(MeOH)/nm 218.9 (49 200), 273.6 (13 690) and 315.3 (6625); δ_H (400 MHz; $C_6D_5CD_3$; *T* 80 °C)* *diastereoisomer a*: 6.93 (0.58 H, d, *J* 8.5, 4-H), 6.91 (1.16 H, d, *J* 7.28, 2″- and 6″-H), 6.55 (1.16 H, d, *J* 8.71, 3″-and 5″-H), 6.27 (0.58 H, d, *J* 1.91, 7-H), 6.12 (0.58 H, dd, *J* 8.52 and 2.02, 5-H), 5.83 (0.58 H, s, 6′-H), 5.03–4.97 (1.16 H, m, 4‴-H) and 4.43–4.3 (1.16 H, m, 2‴-H); *diastereoisomer b*: 7.21 (0.42 H, d, *J* 8.5, 4-H), 7.15 (0.84 H, d, *J* 8.52, 2″- and 6″-H), 6.66 (0.84 H, d, *J* 8.63, 3″- and 5″-H), 6.27 (0.42 H, d, *J* 1.91, 7-H), 6.21 (0.42 H, dd, *J* 8.45 and 1.88, 5-H), 5.79 (0.42 H, s, 6′-H), 4.84–4.77 (0.84 H, m, 4‴-H) and 4.22 (0.84 H, d, *J* 5.24, 2‴-H); *mixed signals*: 5.66–5.5 (1 H, m, 3‴-H^a and -H^b), 5.11 (1 H, d, *J* 12.8, 2′-H^a and -H^b), 3.99–3.91 (2 H, m, $OCH_2CH_2O^a$, $OCH_2CH_2O^b$), 3.72–3.6 (2 H, m, $OCH_2CH_2O^a$, $OCH_2CH_2O^b$), 3.36 (1.74 H, s, OMe^a), 3.35 (1.74 H, s, OMe^a), 3.34–3.33 (4.26 H, br s, OMe^a, 2 × OMe^b), 3.28 (1.26 H, s, OMe^b), 3.18 (1.74 H, s, OMe^a), 3.13 (1.26 H, s, OMe^b) and 2.34–1.93 (2 H, m, 3′-$H^{a,b}$ axial and 3′-$H^{a,b}$ equatorial); δ_C (100.61 MHz; $C_6D_5CD_3$; *T* 80 °C)* *diastereoisomer a*: 191.91 (C-3), 173.86 (C-1‴), 167.76 (C-7′), 166.31 (C-8), 162.02 (C-9′), 161.61 (C-5′), 160.39 (C-6), 158.22 (C-4″), 132.99 (C-3‴), 132.06 (C-4′), 128.61 (C-1″), ~ 128.07 (C-2″, C-6″),† 125.68 (C-4), 117.4 (C-4‴), 114.83 (C-9), 114.27 (C-3″ and -5″), 110.85 (C-5), 108.19 (C-2), 107.08 (C-8′), 106.36 (C-10′), 96.79 (C-7), 92.1 (C-6′), 78.29 (C-2′), 66.28 (C-2‴), 66.21 (OCH_2CH_2O), 66.11 (OCH_2CH_2O) and 43.5 (C-3′); *diastereoisomer b*: 191.63 (C-3), 174.14 (C-1‴), 167.86 (C-7′), 166.4 (C-8), 162.06 (C-9′), 161.41 (C-5′), 160.39 (C-6), 158.33 (C-4″), 132.93 (C-3‴), 132.56 (C-4′), 128.61 (C-1″), ~ 128.07 (C-2″ and -6″),† 125.61 (C-4), 117.4 (C-4‴), 114.74 (C-9), 114.37 (C-3″ and -5″), 111.05 (C-5), 108.12 (C-2), 107.08 (C-8′), 106.28 (C-10′), 96.88 (C-7), 92.102 (C-6′), 78.66 (C-2′), 66.28 (C-2‴), 65.51 (OCH_2CH_2O), 65.49 (OCH_2CH_2O) and 44.96 (C-3′); *mixed signals*: 56.27 (OMe), 56.07 (OMe), 55.81 (OMe), 55.23 (OMe) and 55.07 (OMe) († These signals are swamped in the signals of deuteriated toluene, and an accurate chemical-shift assignment is therefore impossible); *m/z* 604 (M^+, 17%), 519 (21), 470 (21), 455 (14), 385 (100), 369 (32), 224 (71) and 44 (35) (Found: M^+, 604.1897. $C_{33}H_{32}O_{11}$ requires *M*, 604.1935).

2-(5,7-*Dimethoxy*-2-(4-*methoxyphenyl*)*spiro*{*chromane*-4,2′-[1,3]*dioxolan*-8-*yl*}-6-*methoxy*-2,3-*dihydrobenzofuran*-3-*one* **15**.—Palladium(II) acetate (1.29 mg, 0.006 mmol) and triphenylphosphine (3.06 mg, 0.012 mmol) in dry THF (0.5 cm^3) were added to a stirred solution of ester **13** (68 mg, 0.112 mmol) in dry THF (1 cm^3) under nitrogen. To this solution was added a solution of freshly distilled formic acid (20.37 mg, 0.443 mmol) and freshly distilled triethylamine (56.51 mg, 0.514 mmol) in dry THF (0.5 cm^3). The resulting solution was stirred at room temperature, under nitrogen, for 4 days. The reaction mixture was filtered through a short silica column, followed by elution with chloroform. The solvent was then removed under reduced pressure and the solid was crystallised from methanol to give *compound* **15** as plates (53.7 mg, 92%), m.p. 207–216 °C; ν_{max}(KBr)/cm^{-1} 2359, 1708, 1625, 1608, 1144 and 1117; λ_{max}(MeOH)/nm 218, 269.5 and 320.6; δ_H (270 MHz; $CDCl_3$)* 7.59 (0.42 H, d, *J* 8.31, 4-H^b), 7.4 (0.58 H, d, *J* 8.32, 4-H^a), 7.04 (0.84 H, d, *J* 8.72, 2″- and 6″-H^b), 6.82 (1.16 H, d, *J* 8.71, 2″- and 6″-H^a), 6.65 (0.84 H, d, *J* 8.72, 3″- and 5″-H^b), 6.57 (1. 16 H, d, *J* 8.72, 3″- and 5″-H^a), 6.23–6.12 (2 H, m, 5- and 7-$H^{a,b}$), 5.91 (0.42 H, s, 6′-H^b), 5.89 (0.58 H, s, 6′-H^a), 5.21 (0.42 H, d, *J* 12.39, 2′-H^b), 4.87 (0.58 H, d, *J* 12.38, 2′-H^a), 4.34–3.94 (4 H, m, $OCH_2CH_2O^{a,b}$), 3.88 (s, OMe), 3.83 (s, OMe), 3.79 (s, OMe), 3.77 (s, OMe), 3.49 (s, OMe) and 2.37–1.95 (2 H, m, 3-$H^{a,b}$ axial and 3-$H^{a,b}$ equatorial); δ_C (67.80 MHz; $CDCl_3$) 199.52 (C-3), 174.17 (C-7′), 167.2 (C-8), 161.31 (C-9′), 161.07 (C-5′), 159.05 (C-6), 157.26 (C-4″), 131.19 (C-4′), 127.78 (C-1″), 127.59 (C-2″^{b}, -6″^{b}), 127.3 (C-2″^{a}, -6″^{a}), 124.71 (C-4^b), 124.49 (C-4^a), 115.36 (C-9), 113.29 (C-3″ and -5″), 109.89 (C-5), 105.3 (C-8′), 103.27 (C-10′), 95.79 (C-7), 89.1 (C-6′), 79.55 (C-2), 77.27 (C-2′), 65.82 (OCH_2CH_2O), 65.03 (OCH_2CH_2O), 56.04 (OMe), 55.9 (OMe), 55.58 (OMe), 55.17 (OMe) and 42.8 (C-3′); *m/z* 520 (M^+, 20%), 386 (100), 371 (37), 327 (15) and 134 (21) (Found: M^+, 520.1760. $C_{29}H_{28}O_9$ requires *M*, 520.1725).

5,7-*Dimethoxy*-8-(6-*methoxy*-3-*oxo*-2,3-*dihydrobenzofuran*-2-*yl*)-2-(4-*methoxyphenyl*)*chroman*-4-*one* **16**.—5% Hydrochloric acid (0.3 cm^3) was added to a solution of the ketal **15** (44 mg, 0.084 mmol) in THF (1.5 cm^3) and the resulting solution was stirred at room temperature for 15 min. The solution was diluted with ether (10 cm^3) and washed successively with 10% aq. sodium hydroxide (10 cm^3) and water (2 × 10 cm^3). After

* NMR locants follow the priming scheme shown in the artwork, and do not coincide with the simplified scheme used in the sub-head nomenclature.

being dried ($MgSO_4$), the solvent was removed under reduced pressure to yield a pale yellow solid, which was purified by CC on silica gel [eluent: ethyl acetate–hexane (4:1)] to give a solid, which upon crystallisation from methanol gave *compound* **16** as needles (37 mg, 92%), m.p. 164–168 °C; ν_{max}(KBr)/cm^{-1} 1708, 1680, 1601 and 1117; λ_{max}(MeOH)/nm 205, 233.8, 277.4 and 320.6; δ_H(500 MHz; $CDCl_3$)* 7.6 (0.42 H, d, *J* 8.3, 4-H^b), 7.38 (0.58 H, d, *J* 8.3, 4-H^a), 7.06 (0.84 H, d, *J* 8.4, 2″- and 6″-H^b), 6.95–6.87 (0.42 H, m, 5-H^b), 6.86 (1.16 H, d, *J* 8.48, 2″- and 6″-H^a), 6.69–6.62 (0.58 H, m, 5-H^a), 6.62 (2 H, d, *J* 8.55, 3″- and 5″-H), 6.25 (1 H, d, *J* 1.84, 7-H), 6.18 (0.58 H, s, 6′-H^a), 5.87 (0.42 H, s, 6′-H^b), 5.08 (1 H, dd, *J* 13.55 and 2.93, 2′-H), 3.98 (OMe), 3.97 (OMe), 3.94 (OMe), 3.85 (OMe), 3.79 (OMe) and 2.96–2.53 (2 H, m, 3′-H axial and 3′-H equatorial); δ_C(125.70 MHz; $CDCl_3$) 199.36 (C-3^{a,b}), 189.43 (C-4′^{b}), 189.37 (C-4′^{a}), 174.09 (C-7′^{a,b}), 167.53 (C-8^a), 167.47 (C-8^b), 164.92 (C-9′), 163.7 (C-5′), 163.01 (C-6), 159.44 (C-4″), 129.92 (C-1″), 127.53 (C-2″^{b} and -6″^{b}), 127.31 (C-2″^{a} and -6″^{a}), 124.89 (C-4^a), 124.65 (C-4^b), 115.01 (C-9^a), 114.14 (C-9^b), 113.64 (C-3″^{b} and -5″^{b}), 113.56 (C-3″^{a} and -5″^{a}), 110.29 (C-5), 106.23 (C-8′), 103.81 (C-10′), 95.85 (C-7), 88.79 (C-6′), 79.48 (C-2), 78.9 (C-2′), 56.32 (OMe), 56.3 (OMe), 56.08 (OMe), 55.3 (OMe), 55.25 (OMe), 45.67 (C-3′^{b}) and 45.3 (C-3′^{a}); *m/z* 476 (M$^+$, 41%), 342 (100), 327 (61), 299 (8), 283 (11) and 134 (17) (Found: M$^+$, 476.1390. $C_{27}H_{24}O_8$ requires *M*, 476.1464).

Allyl 2-(2′-Hydroxy-4′,6′-dimethoxybenzoyl)acetate **19**.—A solution of (2′-hydroxy-4′,6′-dimethoxyphenyl)ethanone (1.02 g, 5.207 mmol) in dry THF (20 cm^3) was added dropwise to a cooled (−78 °C), well stirred solution of lithium bis(trimethylsilyl)amide in THF (1 mol dm^{-3}; 15.62 cm^3, 15.62 mmol) under dry nitrogen. The resultant yellow solution was stirred at −78 °C for 1 h and at −10 °C for 2 h. It was cooled again to −78 °C, a solution of diallyl carbonate (0.8 cm^3, 16.87 mmol) in dry THF (2 cm^3) was added rapidly, and the reaction mixture was allowed to warm to room temperature over a period of 3 h. The reaction mixture was stirred at room temperature for 4 h and then poured into a mixture of conc. HCl (3 cm^3) and ice (50 g). The mixture was extracted with chloroform (3 × 50 cm^3) and the combined extracts were washed with water (2 × 50 cm^3). After being dried (Na_2SO_4), the solvent was removed under reduced pressure and the residue was purified by CC on silica gel [eluent: hexane–ethyl acetate (2:1)] to give a pale yellow solid. *Allyl 2-(2′-hydroxy-4′,6′-dimethoxybenzoyl)acetate* (1.093 g, 75%) was crystallised from methanol–hexane in needles, m.p. 49–50.5 °C; ν_{max}(KBr)/cm^{-1} 3465, 1741, 1619, 1600 and 1159; λ_{max}(MeOH)/nm 211.1 (23 460) and 291.7 (5370); δ_H(270 MHz; $CDCl_3$) 13.53 (1 H, s, OH), 6.07 (1 H, d, *J* 2.53, 3′-H), 5.9 (1 H, d, *J* 2.53, 5′-H), 5.97–5.82 (1 H, m, 2″-H), 5.35–5.18 (2 H, m, 3″-H$_2$), 4.67–4.6 (2 H, m, 1″-H$_2$), 3.94 (2 H, s, 2-H$_2$), 3.82 (3 H, s, 4′-OMe) and 3.8 (3 H, s, 6′-OMe); δ_C(67.80 MHz; $CDCl_3$) 196.33 (C-3), 167.92 (C-4′), 167.84 (C-6′), 166.8 (C-2′), 162.29 (C-1), 131.86 (C-2″), 118.54 (C-3″), 105.51 (C-1′), 93.75 (C-5′), 90.9 (C-3′), 65.58 (C-1″), 55.65 (OMe), 55.46 (OMe) and 51.11 (C-2); *m/z* 280 (M$^+$, 8%), 222 (36), 194 (9), 181 (100), 154 (9) and 137 (17) (Found C, 59.7; H, 5.8. $C_{14}H_{16}O_6$ requires C, 60.0; H, 5.75%).

3-Allyloxycarbonyl-5,7-dimethoxyflavone **20**.—A mixture of allyl 2-(2′-hydroxy-4′,6′-dimethoxybenzoyl)acetate **19** (0.35 g, 1.249 mmol), magnesium (0.045 g, 1.875 mmol), dry ethanol (7.5 cm^3) and dry carbon tetrachloride (2 drops) was heated at 55 °C until all of the magnesium had dissolved (6 h). The solvent was removed under reduced pressure, and benzene (15.6 cm^3) and benzoyl chloride (0.145 cm^3, 1.249 mmol) were added to the residue. This mixture was refluxed for 14 h and cooled to room temperature. Aq. acetic acid (10%; 20 cm^3) was added and the mixture was extracted with chloroform (3 × 30 cm^3). The combined extracts were washed with brine (2 × 30 cm^3) and dried (Na_2SO_4). The solvent was evaporated off under reduced pressure and the residue was purified by CC on silica gel [eluent: hexane–ethyl acetate (1:1)] to give the *title compound* as an oil (0.332 g, 73%); ν_{max}($CHCl_3$)/cm^{-1} 1730, 1633, 1628 and 1460; δ_H(270 MHz; $CDCl_3$) 7.72 (2 H, dd, *J* 8.06 and 1.65, 3′- and 5′-H), 7.55–7.42 (3 H, m, 2′-, 4′- and 6′-H), 6.49 (1 H, d, *J* 2.38, 8-H), 6.37 (1 H, d, *J* 2.38, 6-H), 5.93–5.77 (1 H, m, 3″-H), 5.33–5.13 (2 H, m, 4″-H$_2$), 4.75–4.67 (2 H, m, 2″-H$_2$), 3.93 (3 H, s, OMe) and 3.88 (3 H, s, OMe); δ_C(67.80 MHz; $CDCl_3$) 173.73 (C-4), 164.93 (C-7), 164.44 (C-5), 161.09 (C-9), 159.87 (C-1″), 159.33 (C-2), 131.43 (C-3″), 131.38 (C-1′), 131.24 (C-4′), 128.61 (C-2′-and -6′), 127.82 (C-3′ and -5′), 119.3 (C-3), 118.85 (C-4″), 108.19 (C-10), 96.39 (C-6), 92.6 (C-8), 66.23 (C-2″), 56.28 (OMe) and 55.74 (OMe); *m/z* 366 (M$^+$, 10%), 325 (34), 307 (42), 280 (67) and 129 (100) (Found: M$^+$, 366.1031. $C_{21}H_{18}O_6$ requires *M*, 366.1098).

Acknowledgements

B. M. F. and J.-P. F. thank CNRS/EOLAS/RIA and the 'Ministère Français des Affaires Etrangères' for Exchange Fellowships.

References

1 H. Geiger and C. Quinn, in *The Flavonoids*, ed. J. B. Harborne, T. J. Mabry and H. Mabry, Chapman and Hall, London, 1975, p. 692; in *The Flavonoids: Advances in Research*, ed. J. B. Harborne and T. J. Mabry, Chapman and Hall, London, 1982, p. 505; in *The Flavonoids; Advances in Research Since 1980*, ed. J. B. Harborne, Chapman and Hall, London, 1988, p. 110.
2 B. Jackson, H. D. Locksley, F. Scheinmann and W. A. Wolstenholme, *J. Chem. Soc. C*, 1971, 3791.
3 A. Pelter, R. Warren, K. K. Chexal, B. K. Handa and W. Rahman, *Tetrahedron*, 1971, **27**, 1625.
4 P. D. Desai, M. D. Dutia, A. K. Ganguly, T. R. Govindachari, B. S. Joshi, V. N. Kamat, D. Prakash, D. F. Rane, S. S. Sathe and N. Viswanathan, *Indian J. Chem.*, 1967, **5** 523.
5 M. Konoshima and Y. Ikeshiro, *Tetrahedron Lett.*, 1970, 1717.
6 B. S. Joshi, V. N. Kamat and N. Viswanathan, *Phytochemistry*, 1970, **9**, 881.
7 C. G. Karanjgaokar, P. V. Radhakrishnan and K. Venkataraman, *Tetrahedron Lett.*, 1967, 3195.
8 H. D. Locksley and I. G. Murray, *J. Chem. Soc. C*, 1971, 1332.
9 Y. Ikeshiro and M. Konoshima, *Tetrahedron Lett.*, 1972, 4383.
10 J. T. Pinhey, *Aust. J. Chem.*, 1991, **44**, 1353.
11 D. M. X. Donnelly, B. M. Fitzpatrick, B. A. O'Reilly and J.-P. Finet, *Tetrahedron*, 1993, **49**, 7967.
12 D. M. X. Donnelly, J.-P. Finet and B. A. Rattigan, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1729.
13 R. P. Kozyrod, J. Morgan and J. T. Pinhey, *Aust. J. Chem.*, 1985, **38**, 1147.
14 W. Frick and R. R. Schmidt, *Liebigs Ann. Chem.*, 1989, 565.
15 G. L. May and J. T. Pinhey, *Aust. J. Chem.*, 1982, **35**, 1859.
16 J. T. Pinhey and B. A. Rowe, *Aust. J. Chem.*, 1980, **33**, 113.
17 D. H. R. Barton, D. M. X. Donnelly, J.-P. Finet, P. J. Guiry and J. M. Kielty, *Tetrahedron Lett.*, 1990, **31**, 6637.
18 J. Sonnenbichler, I. Madubunyi and H. Scheer, *Z. Naturforsch., C. Biosci.*, 1987, **42**, 855.
19 D. H. R. Barton, D. M. X. Donnelly, J.-P. Finet and P. J. Guiry, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1365.
20 J. Tsuji, M. Nisar and I. Shimizu, *J. Org. Chem.*, 1985, **50**, 3416.
21 M. Cushmann, D. Nagarathnam, D. L. Burg and R. L. Geahlen, *J. Med. Chem.*, 1991, **34**, 798.
22 D. M. X. Donnelly, B. M. Fitzpatrick, S. M. Ryan and J.-P. Finet, following paper.

Paper 4/00432I
Received 24*th January* 1994
Accepted 7*th March* 1994

* See footnote on preceding page.