On the optical activity of the 3-aryl-4-hydroxycoumarin isolated from *Millettia griffoniana*: molecular modelling and total synthesis

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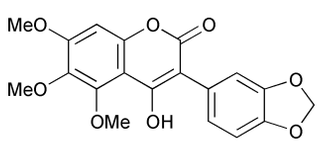
Semi-empirical calculations on 4-hydroxy-3-(3′,4′-methylenedioxyphenyl)-5,6,7-trimethoxycoumarin, a natural product recently isolated from *Millettia griffoniana*, show low rotational barriers for the C(3)–C(1′) bond (19.9 kJ mol^{-1}) and for the inversion of the out-of-plane central 6-methoxy group (9.7 kJ mol^{-1}). The structure of this compound is confirmed by its synthesis in 4 steps from 3,4,5-trimethoxyphenol in 37% overall yield, the key step being the ligand-coupling reaction of the 4-hydroxycoumarin **9** with 3,4-methylenedioxyphenyllead triacetate.

In 1998, Yankep *et al.* isolated compound **1**, 4-hydroxy-3-(3′,4′-methylenedioxyphenyl)-5,6,7-trimethoxycoumarin, from *Millettia griffoniana*.[1] Such highly oxygenated isoflavone derivatives are scarcely observed in plants. The related isoflavone, odorantin **2**, 3-(3′,4′-methylenedioxyphenyl)-5,6,7-trimethoxyisoflavone, was isolated from different sources.[2] However, in contrast to odorantin **2**, which is optically inactive, the coumarin **1** was reported to show a substantial optical rotation. This extraordinary result prompted us to undertake the total synthesis of this natural product and to carry out computational studies, seeking for some hindered rotation that might explain the reported optical rotation.



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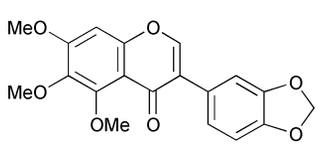

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Due to the presence of a biaryl-type link between the coumarin ring and the 3-aryl moiety, atropoisomerism could explain the optical activity, although such an observation has never been made in the case of less oxygenated congeners. In compound **1**, the presence of three contiguous methoxy groups could induce some kind of steric hindrance inhibiting the free rotation of the C(3)–C(1′) bond.

Results and discussion

Computational study

In order to explain the optical activity of compound **1**, a molecular modelling study was performed in two steps: *a*—simulated annealing calculations to determine the various possible conformers, *b*—determination of the pathway of the atropoisomeric rotation in order to calculate the activation barrier. The semi-empirical calculations were carried out by using the Ampac 6.55 package[3] with the AM1[4] hamiltonian at the restricted Hartree–Fock (RHF) level on a Silicon Graphics O_2 R 10000 station. Considering the numerous possible conformations, we first performed simulated annealing calculations.[5] The geometry optimizations were obtained by application of the Newton–Raphson method (convergence limit of gradient norm of 4.18×10^{-3}; force calculations performed to ensure that the conformations are potential-energy minima). The nine conformations which were found within 10 kJ mol^{-1} are reported in Table 1. The different conformations are due to three types of rotation: *a*) around the C(3)–aryl bond, *b*) around the C(5)–, C(6)– and C(7)–methoxy bonds, *c*) around the C(4)–hydroxy bond. The two more stable conformations (−888 kJ mol^{-1} and −887.2 kJ mol^{-1}) are conformers resulting from rotation around the C(3)–aryl bond.

In the second step to understand the reported optical activity of compound **1**, which can be explained by hindered rotation, we calculated the transition states of the rotations of both the C(3)–aryl bond and the central C(6)–methoxy moiety to obtain the barrier-height values. Newton–Raphson calculations on the gradient norm function were performed to obtain the geometry of the transition states (convergence limit of gradient norm of 4.18×10^{-1}; force calculations performed to ensure that the obtained geometries are saddle points). After determination of the transition-state geometry, we then carried out Intrinsic Reaction Coordinate (IRC) calculations[6] to verify that the obtained transition state corresponds to the correct reaction path. The rotational pathways are drawn in Figs. 1 and 2.

In the case of the rotation of the bond between C(3) and the aryl B-ring, we noted a perfect symmetry of the aryl dihedral bond angle ($\varphi = \pm 40.0°$). The energies of both geometries (left and right) are close but not identical (−886.7 and −886.9 kJ mol^{-1}) and this can be explained by the asymmetry of the methylenedioxyphenyl moiety. Furthermore, the aryl dihedral bond angle of the transition-state structure is close to zero ($\varphi = 1.2°$) and the value of the rotational barrier is 19.9 kJ mol^{-1}. We considered also a rotation of the 4-hydroxy group to facilitate the aryl-bond rotation, but the barrier height for this type of

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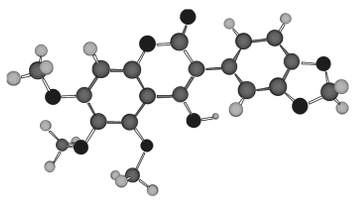
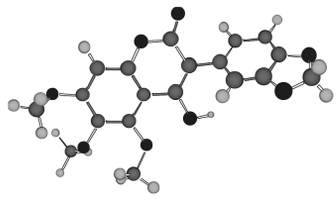
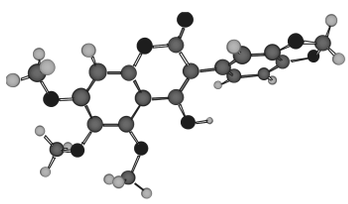
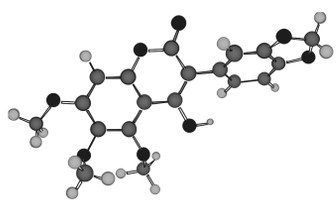
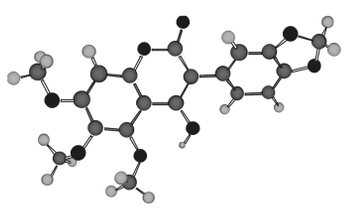
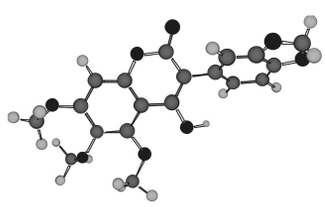
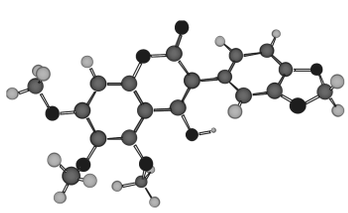
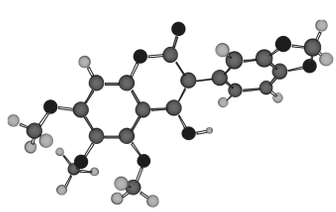
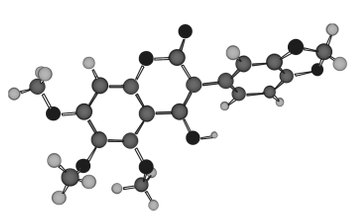
Table 1 More stable conformations of compound **1** calculated using simulated annealing method

Conformation	Energy (kJ mol^{-1})	Conformation	Energy (kJ mol^{-1})
	−888.0		−880.6
	−887.2		−880.0
	−886.3		−879.7
	−884.9		−878.8
	−884.1		

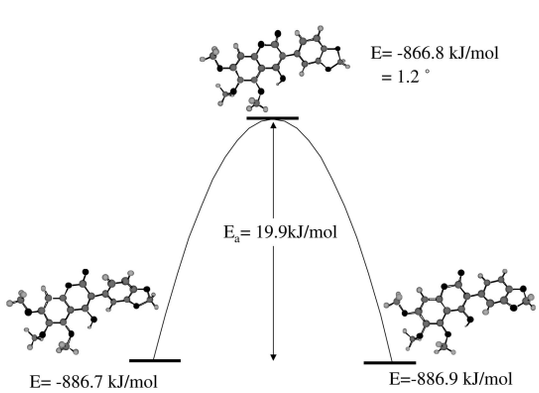


Fig. 1 Pathway of the C(3)–aryl-bond rotation.

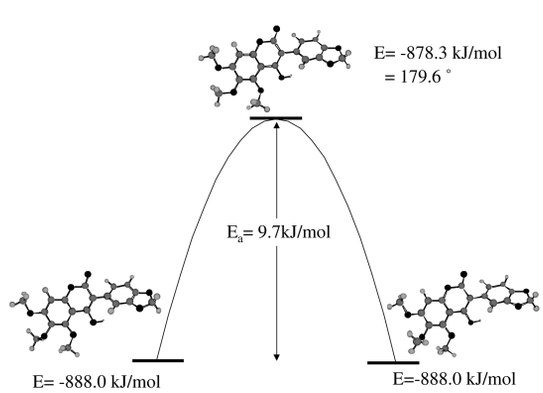


Fig. 2 Pathway of the central C(6)-methoxy-group rotation.

rotation is significantly smaller than the rotational barrier for bonds which have partly double-bond character. To estimate the barrier of the rotation of the hydroxy group, we performed the same type of calculation to obtain the transition-state structure of the hydroxy rotation. We started our transition-state search from the right side of the rotational pathway described in Fig. 1. The results for the hydroxy-group rotation are reported in Fig. 3. The barrier value is 16.2 kJ mol^{-1} and the rotation of the aryl bond is not hindered by the hydroxy moiety.

Concerning the central methoxy rotation, we also noted a perfect symmetry of the C–O dihedral angle ($\varphi = \pm 111.9°$) and the structures of both the left and right sides are similar and correspond to the most stable conformer (−888.0 kJ mol^{-1}). Just as in the first case, the dihedral angle of the transition-state structure is close to plane conformation (179.6°) and the rotational barrier value is 9.7 kJ mol^{-1}.

In conclusion, the calculated values of the barrier for both rotations do not show any important hindrance (<20 kJ mol^{-1}).

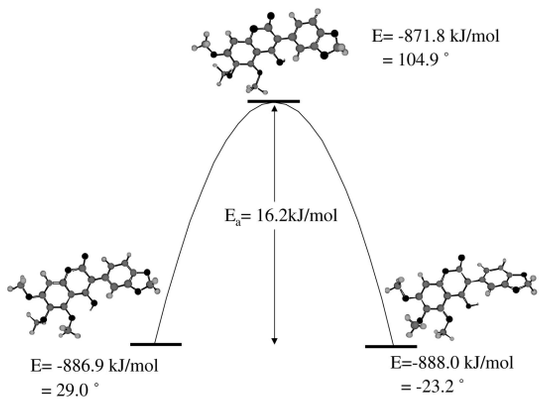
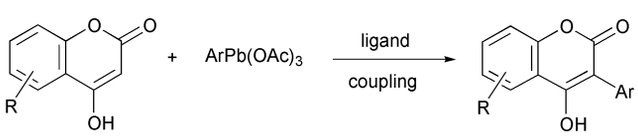


Fig. 3 Pathway of the C(4)-hydroxy-group rotation.

Therefore the optical activity of compound **1** cannot be deduced from semi-empirical calculations. Indeed, a barrier value higher than 80 kJ mol^{-1} is required to observe an optical activity resulting from atropoisomerism.[7]

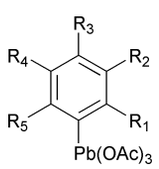
Synthesis of 3-aryl-4-hydroxycoumarins

In view of the absence of molecular-modelling support for the optical activity, we decided to synthesize the racemic form of 4-hydroxy-3-(3′,4′-methylenedioxyphenyl)-5,6,7-trimethoxycoumarin in order to compare its physical data with those reported for the natural product by Yankep *et al.* Two main synthetic routes have been devised for the synthesis of 3-aryl-4-hydroxycoumarins: *a*—ring closure of a preformed deoxybenzoin, *b*—direct arylation at C-3 of a preformed 4-hydroxycoumarin. In previous papers, we have applied the latter ligand-coupling method[8] to the synthesis of a number of derivatives bearing up to two methoxy substituents in the A-ring of the coumarin.[9,10] As an extension of this method, we decided to use this approach for the synthesis of the racemic form of compound **1** using the appropriate aryllead triacetate[11] for the introduction of the 3-aryl group (Scheme 1).



Scheme 1

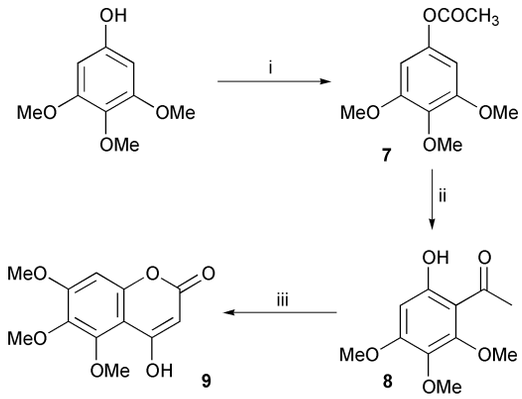
Moreover, we decided to study the influence of more-highly-oxygenated A-ring coumarin derivatives on the reactivity with other related polymethoxyphenyllead triacetates, such as compounds **3**–**6**.



3 R$_1$ = R$_4$ = R$_5$ = H, R$_2$,R$_3$ = OCH$_2$O
4 R$_1$ = R$_3$ = R$_5$ = MeO, R$_2$ = R$_4$ = H
5 R$_1$ = R$_4$ = R$_5$ = H, R$_2$ = R$_3$ = MeO
6 R$_1$ = R$_5$ = H, R$_2$ = R$_3$ = R$_4$ = MeO

4-Hydroxy-5,6,7-trimethoxycoumarin **9**, the required substrate for the ligand-coupling reaction, was obtained in 81% overall yield from 3,4,5-trimethoxyphenol, according to the sequence outlined in Scheme 2. Although different one-step routes have been reported for its synthesis, the *o*-hydroxyacetophenone **8** was preferably prepared in two steps, by *O*-acetylation of 3,4,5-trimethoxyphenol, followed by boron trifluoride-catalysed Fries rearrangement of **7**. Then, condensation of **8** with diethyl carbonate in the presence of sodium hydride afforded **9** in high yield (91%).

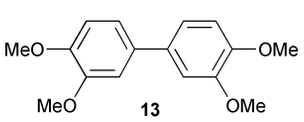
Arylation of **9** with 3,4-methylenedioxyphenyllead triacetate **3** in $CHCl_3$ in the presence of pyridine at 60 °C gave the

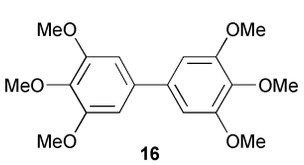


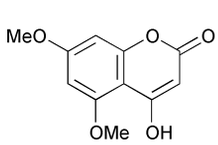
Scheme 2 *Reagents and conditions*: i) Ac_2O, AcONa (96%) ii) BF_3–Et_2O (93%) iii) NaH, $(EtO)_2CO$ (91%).

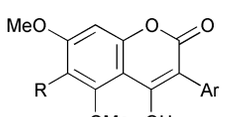
expected 4-hydroxy-3-(3′,4′-methylenedioxyphenyl)-5,6,7-trimethoxycoumarin **1** in a modest 46% yield together with unchanged **9** in 28% recovery (Table 2). Apart from the melting point which was slightly higher in our case (mp 186–187 °C for our synthetic material instead of 170–172 °C for the isolated natural product **1**), all the IR and NMR (^{1}H and ^{13}C) data were in excellent agreement with those reported by Yankep *et al.*[1] Unfortunately, due to the small quantities which were isolated from the natural source, it was not possible to obtain a sample of the authentic natural product to cross-check the optical activity.[12] However, as our synthesis confirmed the structure attributed to the natural product, it is likely that an optical activity was inadvertently but erroneously reported for this compound, although the presence of an optically active minor impurity in the isolated sample of the natural product cannot be excluded.

Due to the widespread occurrence of methoxyphenyl groups throughout many derivatives of natural flavonoids, we decided to extend our studies to the arylation of **9** with other polymethoxyphenyllead triacetates. The arylation of **9** was performed with the aryllead triacetates **4**–**6** in $CHCl_3$ in the presence of pyridine at 60 °C. The C-3 mono-arylated products were isolated in modest to good yield (19–77%).









10 R = MeO, Ar = 2,4,6-(MeO)$_3$C$_6$H$_2$
11 R = MeO, Ar = 3,4-(MeO)$_2$C$_6$H$_3$
14 R = MeO, Ar = 3,4,5-(MeO)$_3$C$_6$H$_2$
18 R = H, Ar = 3,4-(OCH$_2$O)C$_6$H$_3$
20 R = H, Ar = 3,4-(MeO)$_2$C$_6$H$_3$

The highest yield was obtained with the more electron-rich 2,4,6-trisubstituted aryllead triacetate **4**, in agreement with previous observations.[9a,13] However, when the reaction was performed with 3,4-dimethoxyphenyllead triacetate **5** and

Table 2 Reaction of aryllead triacetates with 4-hydroxy-5,6,7-trimethoxychromen-2-one **9**[a]

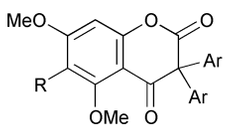
$ArPb(OAc)_3$	Products (%)		By-products[b] (%)	Unchanged **9** (%)
	Monoarylated	Diarylated		
3	**1** (46)			(28)
4	**10** (77)			
5	**11** (19)	**12** (21)	**13** (51)	(32)
6	**14** (37)	**15** (19)	**16** (27)	(44)

[a] The reactions were performed overnight at 60 °C using 1.1 equiv. of lead reagent and 3 equiv. of pyridine. [b] % yield of Ar_2 by decomposition of lead reagent.

Table 3 Reaction of aryllead triacetates with 4-hydroxy-5,7-dimethoxychromen-2-one **17**[a]

Entry	$ArPb(OAc)_3$	Reaction conditions	Products (%)		
			Monoarylated	Diarylated	Unchanged **17**
1	**3** (1.1 equiv.)	Pyridine (3.3 equiv.), 60 °C, overnight	**18** (77)		
2	**3** (1.5 equiv.)	Pyridine (3.3 equiv.), 40 °C, overnight	**18** (31)	**19** (38)	31
3	**5** (1.2 equiv.)	Pyridine (3 equiv.), reflux, 3 h	**20** (39)	**21** (40)	20

[a] Reactions were performed in $CHCl_3$.



12 R = MeO, Ar = 3,4-$(MeO)_2C_6H_3$
15 R = MeO, Ar = 3,4,5-$(MeO)_3C_6H_2$
19 R = H, Ar = 3,4-$(OCH_2O)C_6H_3$
21 R = H, Ar = 3,4-$(MeO)_2C_6H_3$

3,4,5-trimethoxyphenyllead triacetate **6**, we then isolated some unexpected coupling products in addition to the C-3 monoarylated products **11** (19%) and **14** (37%). These products were identified as the C-3 diarylated chromane-2,4-dione derivatives **12** (21%) and **15** (19%) together with the decomposition products **13** (51%) and **16** (27%) from the respective aryllead reagents **5** and **6**. These results show that 4-hydroxy-5,6,7-trimethoxycoumarin **9** behaves more like β-keto esters bearing two α-hydrogens than like phenols as reported for less highly oxygenated 4-hydroxycoumarin derivatives.[9] The decomposition products **13** and **16** could result from a disproportionation reaction followed by an intramolecular ligand coupling. This disproportionation reaction would be similar to that observed by Moloney and co-workers in the case of (2-methoxyphenyl)lead triacetate.[14] In the presence of pyridine, (2-methoxyphenyl)lead triacetate undergoes a slow transformation into the stable bis(2-methoxyphenyl)lead diacetate. Classically, in the pyridine-catalysed reactions of aryllead triacetates with β-dicarbonyl substrates, this disproportionation reaction is too slow to be detected. However, in a different reaction system [the copper-catalysed reaction of (*p*-tolyl)lead triacetate with the sodium salt of 1,2,3-benzotriazole], Avendaño and co-workers have observed the formation of tetrakis(*p*-tolyl)lead and of the oxidative decomposition product, bis(*p*-tolyl)ether.[15] Thus, as our substrate **9** reacts more slowly than the previously reported 4-hydroxycoumarin derivatives,[9] a pyridine-catalysed disproportionation of the *p*-methoxyphenyllead triacetates **5** and **6** can take place. But in contrast with the 2-methoxyphenyllead derivative which is stabilized by internal coordination between the *ortho*-oxygen and the lead atom,[14] the *p*-methoxyphenyllead derivatives **5** and **6** follow a different pathway leading to the ligand-coupling biaryl products **13** and **16**.

Following the observation of an α,α-diarylation on the C-3 centre, we decided to reinvestigate the previous literature reports[9] on the arylation of 5,7-dimethoxy-4-hydroxycoumarin **17** with the lead reagents **3** and **5** to determine any difference in substrate reactivities (Table 3).

Reaction of **17** with 1.1 equiv. of aryllead triacetate **3** afforded only the C(3)-monoarylated product **18** in good yield, as reported by Barton *et al.*[9a] (entry 1). However, when 1.5 equiv. of the lead reagent was used, the diarylated product **19** was isolated in 38% yield together with **18** (31%) and some unchanged starting material **17** (31% recovery). On the other hand, reaction of **17** with 1.2 equiv. of 3,4-dimethoxyphenyllead triacetate **5** in chloroform under reflux led to equivalent yields of the monoaryl derivative **20** (39% yield) and of the C-3 diarylated chromane-2,4-dione **21** (40% yield).

In this way, we confirmed the possible formation of diarylated products in the reaction of 4-hydroxycoumarin derivatives with aryllead triacetate reagents. Thus, the loss of conjugation of the C-ring is not a thermodynamically disfavoured process of the diarylation. The fact that an excess of lead reagent **3** is necessary to observe the formation of the diarylated product **19** (entry 2) can be explained by the weaker reactivity of the hindered enolic hydroxy group of 3-aryl-4-hydroxycoumarin **18**. In the course of this work, the absence of the diarylated compound containing two bulky 2,4,6-trimethoxyphenyl groups is a good support to this assumption. It must also be noted that the reaction of the lead reagent is faster with the 4-hydroxycoumarin **17** than with **9**. Therefore, disproportionation of the lead reagent does not take place significantly enough to result in the formation of the ligand-coupling product **13** which was observed in the reaction with **9**.

In conclusion, semi-empirical calculations performed on compound **1** do not show any significant hindrance which is required to observe an optical activity. However, the structure of the natural product isolated from *Millettia griffoniana* was correctly attributed by Yankep *et al.*, as confirmed by our total synthesis. Therefore, it can be concluded that there are still no known natural 3-aryl-4-hydroxycoumarin structures which would be optically active by virtue of an atropoisomerism phenomenon. The synthetic work led us to observe the formation of α,α-diarylation products in the reactions of 4-hydroxycoumarins, even when a small excess of the aryllead triacetate reagent is used. Such an observation was not made in our previous reports in which only stoichiometric amounts of the lead reagents were used.

Experimental

Melting points were taken on a Büchi capillary apparatus and are uncorrected. NMR spectra were obtained on a Bruker AC100, 200 or 300 spectrometer as indicated. Chemical shifts (δ) are reported in ppm for a solution of the compound in $CDCl_3$ with internal reference Me_4Si and *J*-values in hertz. IR spectra were recorded on a Mattson 1000 Infrared Fourier

Transform spectrophotometer. Combustion analyses were performed in the Laboratory for Microanalysis of the Centre National de la Recherche Scientifique, Vernaison. Separation by column chromatography was performed using Merck Kieselgel 60 (70–230 mesh). Ether refers to diethyl ether. Petroleum spirit refers to the fraction with distillation range 40–65 °C. All solvents were purified by standard techniques. Aryllead triacetates **3**–**5** were prepared in good yields either by plumbylation[16] or by tin–lead exchange.[17]

3,4,5-Trimethoxyphenyllead triacetate 6

A mixture of lead tetraacetate (8.96 g, 20 mmol), tributyl(3,4,5-trimethoxyphenyl)stannane[18] (8.2 g, 20 mmol) and mercuric acetate (0.319 g, 1 mmol) in dry chloroform (40 cm^3) was stirred at 40 °C for 4 hours. The reaction mixture was then filtered through Celite and the solvent distilled off under reduced pressure. The red residue was dissolved in a small amount of ether (20 cm^3) and petroleum spirit (100 cm^3) was slowly added to induce crystallization. 3,4,5-Trimethoxyphenyllead triacetate **6** (9 g, 89%) was obtained as fine light yellow crystals, mp 123–127 °C; δ_H (100 MHz) 2.12 (9H, s, MeCO), 3.85 (3H, s, 4-OMe), 3.89 (6H, s, 3-OMe and 5-OMe) and 6.87 (2H, s, H-2 and H-6).

Preparation of 4-hydroxy-5,6,7-trimethoxychromen-2-one 9

3,4,5-Trimethoxyphenyl acetate 7. A mixture of 3,4,5-trimethoxyphenol (5 g, 27 mmol) and sodium acetate (5 g, 61 mmol) in acetic anhydride (25 cm^3, 0.265 mol) was heated at 110 °C for 2 hours. The mixture was concentrated under vacuum, diluted with water, and extracted with dichloromethane. The organic phase was washed with water, and dried over anhydrous Na_2SO_4. The solvent was distilled off and the residue was dried, using an oil-pump for a few minutes, to afford compound **7** as a light brown oil (5.91 g, 96%) which crystallized from ethanol, mp 74 °C (lit.,[19] 73–74 °C).

1-(6-Hydroxy-2,3,4-trimethoxyphenyl)ethanone 8. Boron trifluoride–diethyl ether (6 cm^3, 47 mmol) was added dropwise to a solution of compound **7** (3 g, 13.3 mmol) in glacial acetic acid (3 cm^3). The mixture was stirred at 70 °C during 2 hours, then poured into 10% aq. NaOH (125 cm^3). After washing with ether, the aqueous layer was cooled, acidified with conc. HCl, then extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, and the solvent distilled off under reduced pressure to afford 1-(6-hydroxy-2,3,4-trimethoxyphenyl)ethanone **8** as a brown oil (2.8 g, 93%) (lit.,[20] 30.5–31.2 °C from aq. EtOH); δ_H (200 MHz) 2.63 (3H, s, Me), 3.75 (3H, s, OMe), 3.86 (3H, s, OMe), 3.96 (3H, s, OMe), 6.21 (1H, s, H-5) and 11.16 (1H, s, OH).

4-Hydroxy-5,6,7-trimethoxychromen-2-one 9. Sodium hydride (7.08 g, 0.17 mol of a 60% dispersion in oil) was slowly added to a solution of compound **8** (4 g, 17.7 mmol) in diethyl carbonate (50 cm^3). The mixture was refluxed for 5 hours, then stirred at room temperature overnight. Methanol (100 cm^3) was cautiously added and the resulting mixture was poured into ether (200 cm^3) and extracted with water (5 × 50 cm^3). The combined aqueous layers were washed with ether (20 cm^3), cooled, then quickly acidified with 10% aq. HCl and extracted with dichloromethane. The organic layers were dried over Na_2SO_4 and the solvents distilled off under reduced pressure. The residue was washed with ether to afford 4-hydroxy-5,6,7-trimethoxychromen-2-one **9** as fine pink needles (4.06 g, 91%), mp 169 °C (from CH_2Cl_2–Et_2O, 2 : 1); δ_H (200 MHz) 3.86 (3H, s, 6-OMe), 3.92 (3H, s, 7-OMe), 4.16 (3H, s, 5-OMe), 5.59 (1H, s, H-3), 6.66 (1H, s, H-8) and 9.77 (1H, s, OH); δ_C (75.5 MHz) 56.4 (6-OMe), 61.3 (7-OMe), 62.7 (5-OMe), 90.9 (C-3), 96.7 (C-8), 100.9 (C-10), 137.3 (C-6), 149.0 (C-9), 151.1 (C-7), 157.2 (C-5), 163.0 (C-2) and 166.1 (C-4) (Found: C, 57.00; H, 4.67. $C_{12}H_{12}O_6$ requires C, 57.14; H, 4.67%).

4-Hydroxy-3-(3′,4′-methylenedioxyphenyl)-5,6,7-trimethoxychromen-2-one 1

To 4-hydroxy-5,6,7-trimethoxychromen-2-one **9** (0.252 g, 1 mmol) and 3,4-methylenedioxyphenyllead triacetate **3** (0.556 g, 1.1 mmol) in dry chloroform (1 cm^3) was added dry pyridine (0.267 cm^3, 3.3 mmol). The mixture was stirred for 4 hours at room temperature, then heated at 60 °C overnight. The reaction solution was diluted with chloroform (60 cm^3) and washed with 3 M aq. H_2SO_4 (2 × 50 cm^3). The aqueous layer was extracted with chloroform (4 × 50 cm^3) and the combined extracts were dried over $MgSO_4$. The solvent was distilled off under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2–EtOH, 19 : 1) to afford unchanged **9** (0.070 g, 28% recovery) and 4-hydroxy-3-(3′,4′-methylenedioxyphenyl)-5,6,7-trimethoxychromen-2-one **1** which recrystallized as white plates from ethanol (0.170 g, 46%), mp 186–187 °C (lit.,[1] 170–172 °C); R_f (CH_2Cl_2–EtOH, 19 : 1), 0.69; δ_H (300 MHz) 3.88 (3H, s, 6-OMe), 3.94 (3H, s, 7-OMe), 4.18 (3H, s, 5-OMe), 5.98 (2H, s, OCH_2O), 6.70 (1H, s, H-8), 6.88 (1H, d, *J* 8.4, H-5′), 7.01 (1H, dd, *J* 8.4 and 1.7, H-6′), 7.02 (1H, d, *J* 1.7, H-2′) and 10.15 (1H, s, 4-OH); δ_C (75.5 MHz) 56.4 (7-OMe), 61.3 (6-OMe), 62.8 (5-OMe), 96.6 (C-8), 100.9 (OCH_2O), 101.1 (C-3), 103.9 (C-10), 108.0 (C-5′), 111.1 (C-2′), 124.2 (C-6′), 124.5 (C-1′), 137.5 (C-6), 146.9 (C-5), 147.2 (C-7), 149.0 (C-4′), 149.8 (C-3′), 156.8 (C-9), 160.8 (C-2) and 162.5 (C-4); IR (CCl_4) ν_{max} cm^{-1} 3417, 3146, 2952, 2916, 1708, 1638, 1614, 1573, 1502, 1455, 1397 and 1284 (Found: C, 61.05; H, 4.28. $C_{19}H_{16}O_8$ requires C, 61.29; H, 4.33%).

4-Hydroxy-5,6,7-trimethoxy-3-(2′,4′,6′-trimethoxyphenyl)-chromen-2-one 10

A mixture of 4-hydroxy-5,6,7-trimethoxychromen-2-one **9** (0.252 g, 1 mmol), 2,4,6-trimethoxyphenyllead triacetate **4** (0.608 g, 1.1 mmol) and dry pyridine (0.243 cm^3, 3 mmol) in dry chloroform (5 cm^3) was stirred at 60 °C overnight. The solvent was distilled off under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2) to afford compound **10** (0.320 g, 77%) as fine light yellow plates, mp 200–205 °C; R_f (CH_2Cl_2) 0.36; δ_H (200 MHz) 3.75 (6H, s, 2′-OMe and 6′-OMe), 3.82 (3H, s, 4′-OMe), 3.84 (3H, s, 6-OMe), 3.91 (3H, s, 7-OMe), 4.13 (3H, s, 5-OMe), 6.21 (2H, s, H-3′ and H-5′), 6.68 (1H, s, H-8) and 9.81 (1H, s, OH); δ_C (75.5 MHz) 55.4 (4′-OMe), 56.1 (2′-OMe and 6′-OMe), 56.4 (6-OMe), 61.4 (7-OMe), 62.7 (5-OMe), 91.3 (C-3′ and C-5′), 96.7 (C-8), 97.9 (C-1′), 101.6 (C-3), 101.7 (C-10), 137.4 (C-6), 149.0 (C-9), 150.5 (C-7), 156.5 (C-5), 159.3 (C-2′ and C-6′), 161.7 (C-2 and C-4′) and 162.2 (C-4).

3-(3′,4′-Dimethoxyphenyl)-4-hydroxy-5,6,7-trimethoxychromen-2-one 11

Under argon, dry pyridine (0.243 cm^3, 3 mmol) was added to a mixture of 4-hydroxy-5,6,7-trimethoxychromen-2-one **9** (0.252 g, 1 mmol) and 3,4-dimethoxyphenyllead triacetate **5** (0.574 g, 1.1 mmol) in dry chloroform (2 cm^3). The reaction mixture was heated at 60 °C overnight, cooled, and filtered through Celite. The residue was purified by column chromatography (Et_2O–$CHCl_3$, 1 : 1) to afford 3,3′,4,4′-tetramethoxybiphenyl **13** (0.070 g, 51% by decomposition from **5**), 3,3-bis-(3′,4′-dimethoxyphenyl)-5,6,7-trimethoxychromane-2,4-dione **12** (0.110 g, 21%) and a mixture of 3-(3′,4′-dimethoxyphenyl)-4-hydroxy-5,6,7-trimethoxychromen-2-one **11** and unchanged **9**. This mixture was purified by column chromatography (EtOH–CH_2Cl_2, 1 : 9) to give **11** (0.073 g, 19%) and unchanged starting material **9** (0.081 g, 32% recovery); R_f (Et_2O–$CHCl_3$, 1 : 1) 0.18.

Compound **11** as fine yellow needles, mp 140 °C (from chloroform–ether–pentane, 2 : 2 : 1); R_f (Et_2O–$CHCl_3$, 1 : 1) 0.29; δ_H (200 MHz) 3.87 (3H, s, OMe), 3.88 (3H, s, 6-OMe),

3.89 (3H, s, OMe), 3.93 (3H, s, 7-OMe), 4.16 (3H, s, 5-OMe), 6.69 (1H, s, H-8), 6.92 (1H, d, *J* 8.2, H-5′), 7.07 (1H, d, *J* 1.9, H-2′) and 7.10 (1H, dd, *J* 8.2 and 1.9, H-6′); δ_C (75.5 MHz) 55.8 (3′- and 4′-OMe), 56.3 (6-OMe), 61.2 (7-OMe), 62.8 (5-OMe), 96.5 (C-8), 101.2 (C-3), 101.5 (C-10), 110.7 (C-5′), 113.8 (C-2′), 123.2 (C-6′), 123.6 (C-1′), 137.5 (C-6), 147.9 (C-3′), 148.4 (C-4′), 148.9 (C-9), 149.9 (C-7), 156.7 (C-5), 160.7 (C-2) and 162.6 (C-4) (Found: C, 61.74; H, 5.27. $C_{20}H_{20}O_8$ requires C, 61.85; H, 5.19%).

Compound **12** R_f (Et_2O–$CHCl_3$, 1 : 1) 0.45; δ_H (200 MHz) 3.73 (6H, s, OMe), 3.78 (3H, s, 6-OMe), 3.83 (6H, s, OMe), 3.86 (3H, s, 7-OMe), 3.91 (3H, s, 5-OMe), 6.40 (1H, s, H-8), 6.57 (2H, d, *J* 8.3, H-6′), 6.59 (2H, s, H-2′) and 6.80 (2H, d, *J* 8.3, H-5′).

Compound **13** as colourless needles, mp 133 °C (lit.,[21] 133–134 °C); R_f (Et_2O–$CHCl_3$, 1 : 1) 0.58; δ_H (200 MHz) 3.92 (6H, s, OMe), 3.95 (6H, s, OMe), 6.93 (2H, d, *J* 7.8, H-5), 7.06 (2H, d, *J* 2.0, H-2) and 7.11 (2H, dd, *J* 7.8 and 2.0, H-6).

4-Hydroxy-5,6,7-trimethoxy-3-(3′,4′,5′-trimethoxyphenyl)-chromen-2-one 14

A mixture of 4-hydroxy-5,6,7-trimethoxychromen-2-one **9** (0.252 g, 1 mmol), 3,4,5-trimethoxyphenyllead triacetate **6** (0.554 g, 1.1 mmol) and dry pyridine (0.243 cm^3, 3 mmol) in dry chloroform (2 cm^3) was stirred at 60 °C overnight. The solvent was distilled off and the residue was purified by column chromatography (Et_2O) to afford 3,3′,4,4′,5,5′-hexamethoxybiphenyl **16** (0.050 g, 27% decomposition from **6**), 3,3-bis(3′,4′,5′-trimethoxyphenyl)-5,6,7-trimethoxychromane-2,4-dione **15** (0.110 g, 19%) and a mixture of 4-hydroxy-5,6,7-trimethoxy-3-(3′,4′,5′-trimethoxyphenyl)chromen-2-one **14** and unchanged **9**. This mixture was purified by recrystallization from chloroform–ether (1 : 5) to afford compound **14** (0.155 g, 37%) and starting material **9** (0.110 g, 44% recovery).

Compound **14** as yellow plates from ether, mp 192 °C; R_f (Et_2O) 0.16; δ_H (300 MHz) 3.87 (12H, s, 3′-OMe, 4′-OMe, 5′-OMe and 6-OMe), 3.95 (3H, s, 7-OMe), 4.17 (3H, s, 5-OMe), 6.71 (1H, s, H-8), 6.74 (2H, s, H-2′ and H-6′) and 10.18 (1H, s, OH); δ_C (75.5 MHz) 56.1 (3′-OMe and 5′-OMe), 56.5 (7-OMe), 60.8 (4′-OMe), 61.4 (6-OMe), 63.0 (5-OMe), 96.7 (C-8), 101.2 (C-3), 104.3 (C-10), 107.9 (C-2′ and C-6′), 126.6 (C-1′), 137.5 (C-6), 137.6 (C-4′), 149.1 (C-5), 150.0 (C-7), 152.9 (C-3′ and C-5′), 157.1 (C-2 and C-9) and 161.1 (C-4) (Found: C, 60.30; H, 5.27. $C_{21}H_{22}O_9$ requires C, 60.28; H, 5.30%).

Compound **15** as yellow oil; R_f (Et_2O), 0.38; δ_H (100 MHz) 3.69 (3H, s, 6-OMe), 3.78 (3H, s, 7-OMe), 3.80 (12H, s, 3′-OMe and 5′-OMe), 3.83 (6H, s, 4′-OMe), 3.88 (3H, s, 5-OMe), 6.26 (1H, s, H-8) and 6.48 (4H, s, H-2′ and H-6′).

Compound **16** as cream plates, mp 124 °C (lit.,[22] 123–124 °C); R_f (Et_2O) 0.49; δ_H (100 MHz) 3.88 (12H, s, 3-OMe, 5-OMe, 3′-OMe and 5′-OMe), 3.94 (6H, s, 4-OMe and 4′-OMe) and 7.07 (4H, s, H-2, H-2′, H-6 and H-6′).

5,7-Dimethoxy-4-hydroxy-3-(3′,4′-methylenedioxyphenyl)-chromen-2-one 18

A mixture of 5,7-dimethoxy-4-hydroxychromen-2-one[9a] **17** (0.222 g, 1 mmol), 3,4-methylenedioxyphenyllead triacetate **3** (0.556 g, 1.1 mmol) and dry pyridine (0.267 cm^3, 3.3 mmol) in dry chloroform (1 cm^3) was stirred at 60 °C overnight. The red-orange reaction mixture was diluted with chloroform (60 cm^3) and washed with 3 M aq. H_2SO_4 (2 × 50 cm^3). The aqueous layer was extracted with chloroform (4 × 50 cm^3) and the organic phase was dried over Na_2SO_4. The solvent was distilled off and the residue was purified by column chromatography ($CHCl_3$–EtOH, 95 : 5) to afford 5,7-dimethoxy-4-hydroxy-3-(3′,4′-methylenedioxyphenyl)chromen-2-one **18** (0.263 g, 77%), which crystallized as light orange needles from ethanol, mp 234 °C (lit.,[9a] 234–235 °C); R_f ($CHCl_3$–EtOH, 95 : 5) 0.65; δ_H (200 MHz) 3.86 (3H, s, 7-OMe), 4.01 (3H, s, 5-OMe), 5.95 (2H, s, OCH_2O), 6.37 (1H, d, *J* 2.2, H-6), 6.52 (1H, d, *J* 2.2, H-8), 6.85 (1H, d, *J* 8.4, H-5′), 6.96–7.01 (2H, m, H-2′ and H-6′) and 9.61 (1H, s, OH).

3,3-Bis(3′,4′-methylenedioxyphenyl)-5,7-dimethoxychromane-2,4-dione 19

To a solution of 5,7-dimethoxy-4-hydroxychromen-2-one **17** (0.222 g, 1 mmol) in dry chloroform (2 cm^3) was added dry pyridine (0.267 cm^3, 3.3 mmol). The mixture was stirred for 10 min at room temperature, then a solution of 3,4-methylenedioxyphenyllead triacetate **3** (0.758 g, 1.5 mmol) in dry chloroform (2 cm^3) was added dropwise, then the mixture was heated at 40 °C overnight. After work-up, purification by column chromatography (Et_2O–$CHCl_3$, 1 : 1) afforded 3,3-bis(3′,4′-methylenedioxyphenyl)-5,7-dimethoxychromane-2,4-dione **19** (0.176 g, 38%); R_f (Et_2O–$CHCl_3$, 1 : 1) 0.53; δ_H (200 MHz) 3.82 (3H, s, OMe), 3.87 (3H, s, OMe), 5.97 (4H, s, OCH_2O), 6.21 (2H, s, H-2′), 6.52–6.58 (4H, m, H-6, H-6′ and H-8) and 6.73 (2H, d, *J* 8.1, H-5′), **18** (0.105 g, 31%) R_f (Et_2O–$CHCl_3$, 1 : 1) 0.41 and unchanged **17** (0.070 g, 31% recovery) R_f (Et_2O–$CHCl_3$, 1 : 1) 0.25.

5,7-Dimethoxy-3-(3′,4′-dimethoxyphenyl)-4-hydroxychromen-2-one 20

Under argon, dry pyridine (0.243 cm^3, 3 mmol) was added to a mixture of 5,7-dimethoxy-4-hydroxychromen-2-one **17** (0.222 g, 1 mmol) and 3,4-dimethoxyphenyllead triacetate **5** (0.625 g, 1.2 mmol) in dry chloroform (2 cm^3). The resulting mixture was refluxed for 3 hours, cooled and filtered through Celite. The solvent was distilled under reduced pressure and the residue was purified by column chromatography (Et_2O) and then preparative TLC ($CHCl_3$–Et_2O, 1 : 1) to afford 3,3-bis(3′,4′-dimethoxyphenyl)-5,7-dimethoxychromane-2,4-dione **21** (0.197 g, 40%), 5,7-dimethoxy-3-(3′,4′-dimethoxyphenyl)-4-hydroxychromen-2-one **20** (0.140 g, 39%) and unchanged starting material **17** (0.044 g, 20%).

Compound **20** as light yellow needles, mp 200 °C (from EtOH) (lit.,[23] 200–202 °C); R_f (Et_2O–$CHCl_3$, 1 : 1) 0.2; δ_H (200 MHz) 3.86 (3H, s, 7-OMe), 4.01 (3H, s, 5-OMe), 6.29 (1H, d, *J* 2.1, H-6), 6.42 (1H, d, *J* 2.1, H-8), 6.87 (1H, d, *J* 8.2, H-5′) and 7.05–7.08 (2H, m, H-2′ and H-6′).

Compound **21** as yellow plates, mp 178 °C; R_f (Et_2O–$CHCl_3$, 1 : 1) 0.34; δ_H (200 MHz) 3.73 (6H, s, 2 × OMe), 3.80 (3H, s, 7-OMe), 3.83 (6H, s, OMe), 3.86 (3H, s, 5-OMe), 6.20 (2H, s, H-2′), 6.53–6.61 (4H, m, H-6, H-6′ and H-8) and 6.77 (2H, d, *J* 8.3, H-5′); δ_C (75.5 MHz) 55.8 (3′-OMe), 55.9 (4′-OMe and 7-OMe), 56.4 (5-OMe), 72.5 (C-3), 93.8 (C-6), 95.5 (C-8), 104.8 (C-10), 110.7 (C-5′), 112.4 (C-2′), 121.8 (C-6′), 129.0 (C-1′), 148.9 (C-3′), 149.0 (C-4′), 156.4 (C-9), 161.7 (C-5), 166.1 (C-7), 169.0 (C-2) and 187.4 (C-4) (Found: C, 65.47; H, 5.25. $C_{27}H_{26}O_9$ requires C, 65.58; H, 5.30%).

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