A New Approach to the Synthesis of Peltogynoids, Natural Isochromeno[4,3-*b*]-chromenes

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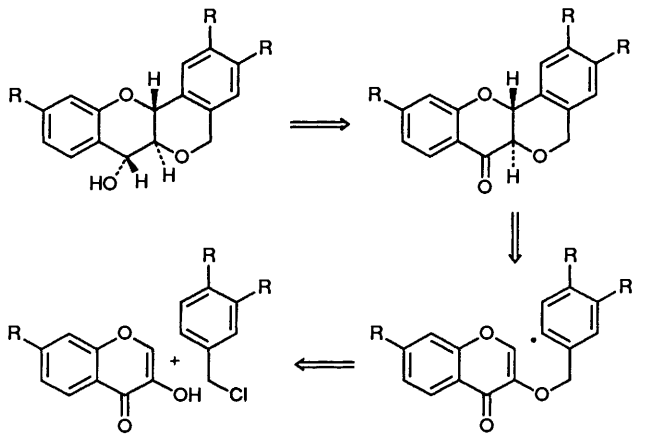
The (±)-trimethyl ether of the unusual isochromeno[4,3-*b*]chromene peltogynol **1** (R = OMe) and its ring skeleton **1** (R = H) have been synthesized *via* 6-*endo* intramolecular cyclisation of the radicals derived from the 3-(*o*-iodobenzyloxy)chromones **17** (R = OMe) and **17** (R = H) respectively. The spiroketone **13** can be prepared similarly from 2-(*o*-iodophenoxymethyl)chromone **12**.

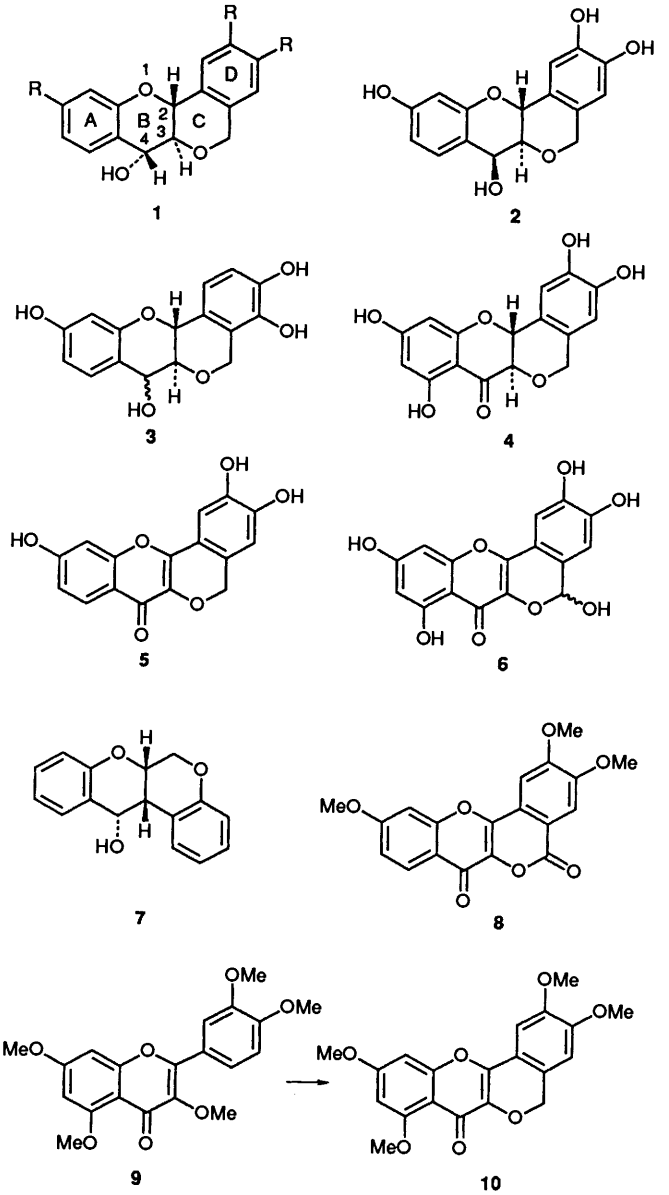
Leuco-anthocyanins, a group of colourless compounds from fruit and flowers which develop anthocyanin-like pigments on exposure to acid, were recognised early this century, *e.g.* in unripe green or red grapes.[1] The first such compound to be purified from a natural source was (+)-peltogynol **1** (R = OH), isolated from the purpleheart tree *Peltogyne porphyrocardia* by Robinson and Robinson,[2] and it is responsible for the development of the characteristic purplish-red colour of this and related heartwoods on exposure to the atmosphere. The structure **1**, with 2,3-*trans*-3,4-*trans* stereochemistry, was settled by Hassall and co-workers,[3] and the absolute configuration was determined as 2*R*, 3*S*, 4*R* by Drewes and Roux.[4] The (+)-2,3-*trans*-3,4-*cis*-(peltogynol **B**) **2**, (+)-2,3-*cis*-3,4-*trans*- and (+)-2,3-*cis*-3,4-*cis*-stereoisomers have all been isolated from plants,[3,4,5] as well as *e.g.* the closely related (+)-mopanols **3**,[4] crombeone **4**,[5b] peltogynin **5**,[5a,6] and fasciculiferin **6**.[7] The peltogynoid tetracyclic ring system is isomeric with that of the rotenoids; compare *e.g.* peltogynol **1** (an isochromeno[4,3-*b*]-chromene) with the rotenoid alcohol **7** (a chromeno[3,4-*b*]-chromene).

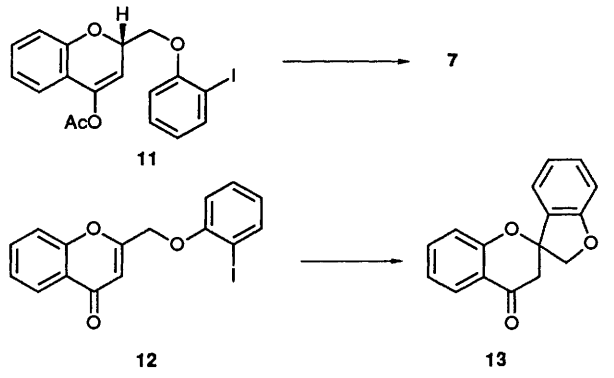
Few synthetic studies[8] have been reported on this group of natural products; (±)-trimethylpeltogynol **1** (R = OMe) has been synthesized once,[8a] using the synthetic isocoumarin[9] **8** as intermediate: a futher seven steps were required to attain the desired oxidation level of the heterocyclic rings. The ring system of peltogynin was obtained from the interesting photoconversion[10] of quercitin pentamethyl ether **9** into 'photoquercitin' **10**.

In connection with our interest in developing short synthetic routes to rotenoids, potent blockers of oxidative phosphorylation, we have shown that the alcohol **7** can be obtained from the readily available chromene **11** *via* 6-*exo* radical cyclisation.[11] Three adjacent *cis* centres are set up stereospecifically by this reaction. It appeared to us that peltogynol might be approached in a related way, but using 6-*endo* cyclisation, using the disconnections of Scheme 1. Radical addition to the enone could lead to a ring junction geometry different to the rotenoid case, since an initial enol might be involved. The chromone system was expected to be susceptible to aryl radical addition at C-2. This was verified using the chromone **12**, available from



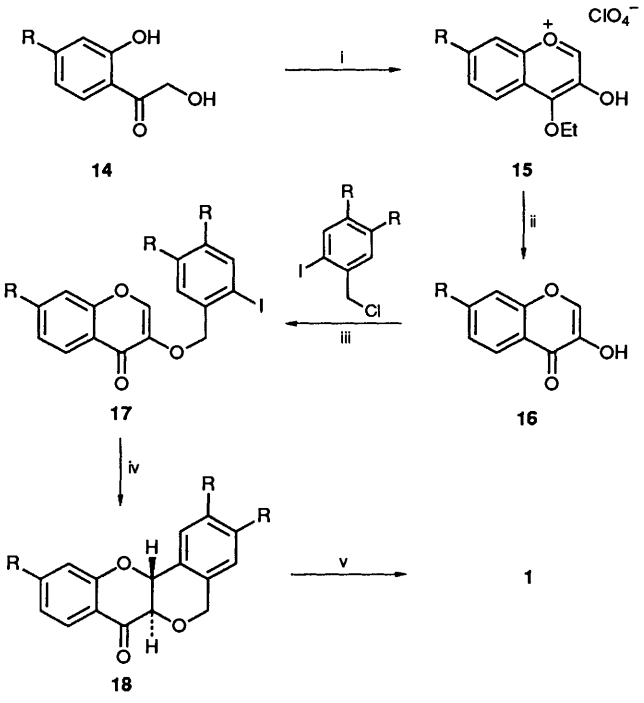
Scheme 1 General approach to Peltogynol





previous work;[12] treatment under standard conditions with tributyltin hydride and azoisobutyronitrile afforded the spiro ketone **13** in 70% yield.

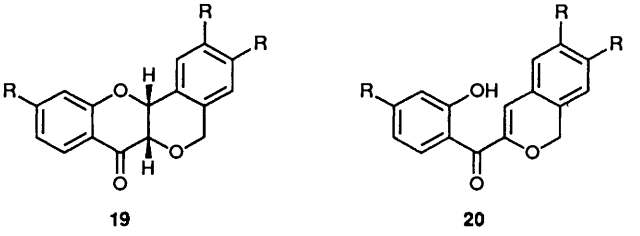
Thus the ω-hydroxyacetophenones **14** (R = H) and **14** (R = OMe) were converted into the corresponding 3-hydroxychromones **16** (R = H) and **16** (R = OMe) by way of the pyrylium salts **15**.[13] 6-Iodo-3,4-dimethoxybenzaldehyde was prepared by direct iodination of veratraldehyde with iodine and silver trifluoroacetate, and converted into 6-iodo-3,4-dimethoxybenzyl chloride. Condensation of the last with 3-hydroxychromone **16** (R = OMe) afforded the key benzyl vinyl ether **17** (R = OMe). Ether **17** (R = H) was similarly prepared from hydroxychromone **16** (R = H) and 2-iodobenzyl chloride (Scheme 2).



Scheme 2 *Reagents*: i, HCO_2Et,$HClO_4$; ii, H_3O^+; iii, Me_2CO,K_2CO_3; iv, Bu_3SnH,AIBN,Benzene; v, $NaBH_4$

The ether **17** (R = H) cyclised smoothly with tributyltin hydride in benzene to yield the desired B/C-*trans* tetracycle **18** (R = H) (48%). The B/C-*cis* isomer **19** (R = H) was also isolated (12%). The ether **17** (R = OMe) cyclised in similar fashion to provide trimethylpeltogynone **18** (R = OMe) (42%); a small quantity of the *cis* form may have formed but was not purified. It is not known whether the *trans*-fusion in trimethylpeltogynone is the thermodynamically favoured form, since attempted isomerisation in either acid or base leads to the ring-B opened product **20** (R = OMe).[8a] Finally, reduction of the ketone **18** (R = OMe) afforded (±)-trimethylpeltogynol **1** (R = OMe), stereospecifically.

These results suggest that the enolate radical which forms the immediate product of cyclisation abstracts hydrogen onto oxygen to give an enol, the ketonisation of which determines the stereochemical outcome. Hydrogen transfer to carbon would have been likely to incur steric control, leading to a greater preference for B/C-*cis* geometry.



Experimental

For experimental generalisations, see *J. Chem. Soc., Perkin Trans. 1*, 1991, 1901.

Radical Cyclisation of 2-(o-*Iodophenoxymethyl*)*chromen*-4-*one* **12**.—Tributyltin hydride (0.31 g) and azoisobutyronitrile (AIBN) (0.05 equiv.) in dry benzene (4.2 cm^3) were added over 30 min to 2-(*o*-iodophenoxymethyl)chromen-4-one (0.2g) in benzene (9.1 cm^3) at reflux under nitrogen. The mixture was refluxed for 4 h, when it was cooled and evaporated. The residue was chromatographed on silica (ethyl acetate–hexane, 2:3), to yield the *spiroketone* 4-oxochroman-2-spiro-3′-(1-benzopyran) **13** (0.1 g, 77%), m.p. 133–135 °C (Found: C, 76.05; H, 4.8%; M^+, 252.078. $C_{16}H_{12}O_3$ requires C, 76.18; H, 4.79%; *M*, 252.079); ν_{max}/cm^{-1} 1680, 1605 and 1575; δ_H(90 MHz) 3.12 (1 H, d, *J* 18.0, 3-Ha), 3.31 (1 H, d, *J* 18.0, 3-Hb), 4.31 (1 H, d, *J* 12.0, 9-Ha), 4.77 (1 H, d, *J* 12.0, 9-Hb), 6.80–6.99 (3 H, m, ArH), 7.08 (1 H, d, *J* 8.0, ArH), 7.20–7.50 (3 H, m, ArH) and 7.95 (1 H, d, *J* 8.0, ArH).

3-(o-*Iodobenzyloxy*)*chromen*-4-*one* **17** (*R* = *H*).—3-Hydroxychromen-4-one[13] (230 mg) was stirred with potassium carbonate (0.4 g) in dry acetone (10 cm^3), and *o*-iodobenzyl chloride (0.4 g) was added. The mixture was refluxed under nitrogen for 15 h, cooled, and diluted with water (10 cm^3). The organic products, obtained by standard chloroform extraction (3 × 5 cm^3), were purified by chromatography on silica (chloroform). The major product crystallized from methanol to yield the *title compound* **17** (R = H), (0.31 g) as yellow needles, m.p. 108–110 °C (Found: C, 50.75; H, 2.9%; M^+, 377.974. $C_{16}H_{11}IO_3$ requires C, 50.80; H, 2.98%; *M*, 377.980); δ_{max}/cm^{-1} 1640 and 1610; δ_H(90 MHz) 5.20 (2 H, s, CH_2), 6.9–7.9 (7 H, m, ArH), 7.82 (1 H, s, 2-H) and 8.32 (1 H, *J* 8, 5-H).

Radical Cyclisation of 3-(o-*Iodobenzyloxy*)*chromen*-4-*one*.—Tributyltin hydride (0.31 g) and azoisobutyronitrile (AIBN) (0.05 equiv.) in dry benzene (4.2 cm^3) were added over 45 min to 3-(*o*-iodobenzyloxy)chromen-4-one (0.2 g) in benzene (9.1 cm^3) at reflux under nitrogen. The mixture was refluxed for 4 h, when it was cooled and evaporated. The residue was chromatographed on silica (ethyl acetate–hexane, 1:9), to yield (i) 6a,13-trans-6a,13-*dihydro*-5H-*isochromeno*[4,3-b]*chromene* **18** (*R* = *H*), (60 mg, 69%), m.p. 158–160 °C from methanol; (Found: C, 76,0; H, 4.8%; M^+, 252.079. $C_{16}H_{12}O_3$ requires C, 76.18; H, 4.79%; *M*, 252.079); ν_{max}/cm^{-1} 1700, 1600 and 1570; δ_H(250 MHz) 4.49 (1 H, d, *J* 12.2, 3-H), 5.05 (2 H, s, CH_2), 5.42 (1 H, d, *J* 12.2, 2-H), 7.09–7.19 (3 H, m), 7.31–7.46 (2 H, m), 7.55–7.61 (1 H, m), 7.72–7.80 (1 H, m) and 8.0 (1 H, d, *J* 8) (all ArH), and (ii) 6a,13-cis-6a,13-*dihydro*-5H-*isochromeno*[4,3-b]*chromene* **19** (R = H), (20

mg, 23%), m.p. 121–124 °C from methanol (Found; C, 75.95; H, 4.8%; M^+, 252.078); ν_{max}/cm^{-1} 1689, 1605 and 1571; δ_H(250 MHz) 4.05 (1 H, d, *J* 3.3, 3-H), 5.01 (1 H, d, *J* 15.1, CH_2-a), 5.18 (1 H, d, *J* 15.1, CH_2-b), 5.95 (1 H, d, *J* 3.3, 2-H), 7.00–7.10 (3 H, m), 7.25–7.35 (3 H, m), 7.48–7.57 (1 H, m) and 7.92 (1 H, dd, *J* 8.0, 2.5) (all ArH).

5,6a,7,13-*Tetrahydroisochromeno*[4,3-b]*chromen*-7-*ol* **1** (R = H).—The *trans*-ketone **18** (R = H) (26 mg) in ethanol (7.5 cm^3) was treated with sodium borohydride (33.4 mg) in water (2 cm^3), and the solution was stirred at room temperature for 2 h. More water was added and the stirring was continued for 10 min, when the mixture was extracted with ether. Drying and evaporation of the extracts gave a solid which crystallized from methanol to yield the *title product* (16.1 mg, 62%), m.p. 148 °C (Found: C, 75.5; H, 5.55%; M^+, 254.094. $C_{16}H_{14}O_3$ requires C, 75.56; H, 5.53%; *M*, 254.094); ν_{max}/cm^{-1} 3580 and 3400; δ_H(250 MHz) 2.82 (1 H, d, *J* 5.3, OH), 3.75 (1 H, dd, *J* 8.5, 9.1, 3-H), 4.95 (2 H, s, CH_2), 5.0 (1 H, d, *J* 9.1, 2-H), 5.10 (1 H, dd, *J* 5.3, 8.5, 4-H), 6.95–7.08 (3 H, m), 7.2–7.4 (3 H, m), 7.59 (1 H, dd, *J* 2.0, 7.7) and 7.75 (1 H, dd, *J* 2.0, 7.7) (all ArH).

2-*Bromo*-2′-*hydroxy*-4′-*methoxyacetophenone*.—2′-Hydroxy-4′-methoxyacetophenone (2.5 g) in chloroform (12.5 cm^3) was added to a vigorously stirred suspension of copper(II) bromide (5.6 g) in refluxing ethyl acetate (12.5 cm^3). The mixture was then refluxed until the colour changed from green to amber, when it was cooled, filtered, and evaporated. The yellow residue was purified by column chromatography (silica; hexane–ethyl acetate, 2:1) to provide the *title compound* (2.3 g, 62%), m.p. 70–72 °C from methanol (Found: C, 43.95; H, 3.6%; M^+, 245.970. $C_9H_9BrO_3$ requires C, 44.11; H, 3.70%; *M*, 245.971); ν_{max}/cm^{-1} 3565, 1625 and 1570; δ_H(250 MHz) 2.55 (1 H, s, OH), 3.85 (3 H, s, OMe), 4.35 (2 H, s, CH_2), 6.42 (1 H, d, *J* 3.0, 3′-H), 6.52 (1 H, dd, *J* 3.0, 8.0, 5′-H) and 7.65 (1 H, d, *J* 8.0, 6′-H).

2,2′-*Dihydroxy*-4′-*methoxyacetophenone*.—2-Bromo-2′-hydroxy-4′-methoxyacetophenone (1.1 g) was refluxed in water (50 cm^3) for 20 h. The hot solution was decanted from deposited tar and filtered. The cooled filtrate was extracted with ether. The extracts, on drying and evaporation, gave a solid which crystallized from methanol to afford the *title compound* (0.62 g, 76%), m.p. 126–128 °C (Found: C, 59.35; H, 5.5%; M^+, 182.059. $C_9H_{10}O_4$ requires C, 59.32; H, 5.54%; *M*, 182.058); ν_{max}/cm^{-1} 3500–2900vb, 1630, 1600 and 1580; δ_H(90 MHz) 2.44 (1 H, s, OH), 3.84 (3 H, s, OMe), 4.81 (2 H, s, CH_2), 6.47 (1 H, d, *J* 3.0, 3′-H), 6.50 (1 H, dd, *J* 3.0, 8.0, 5′-H) and 7.45 (1 H, d, *J* 8.0, 6′-H).

3-*Hydroxy*-7-*methoxychromen*-4-*one*.—2,2′-Dihydroxy-4′-methoxyacetophenone (1.95 g) was dissolved in excess of triethyl orthoformate and cooled to 0 °C. The solution was treated with perchloric acid (1.1 g), shaken vigorously, and set aside to warm to room temperature. Dry ether (200 cm^3) was added when a blue-black oil separated. The solvent was decanted off, and residual ether removed in a stream of nitrogen. The oil was then refluxed in water for 10 min. Precipitated tar was filtered off, and the cooled filtrate was extracted with ether (3 × 15 cm^3). The dried extracts were evaporated to give a solid which crystallized from methanol to provide the *title compound* (0.82 g, 40%), m.p. 175–176 °C (Found: C, 62.6; H, 4.15%; M^+, 192.047. $C_{10}H_8O_4$ requires C, 62.49; H, 4.20% *M*, 192.042); ν_{max}/cm^{-1} 3410, 1615 and 1580; δ_H(90 MHz) 3.95 (3 H, s, OMe), 6.40 (1 H, bs, OH), 6.90 (1 H, d, *J* 3.0, 8-H), 7.07 (1 H, dd, *J* 3.0, 8.0, 6-H), 8.0 (1 H, s, 2-H) and 8.24 (1 H, d, *J* 8.0, 5-H).

6-*Iodo*-3,4-*dimethoxybenzaldehyde*.—3,4-Dimethoxybenzaldehyde (0.3 g) and silver trifluoroacetate (1.1 g) were stirred vigorously in dichloromethane (20 cm^3), and iodine (0.64 g) in dichloromethane (20 cm^3) was added *via* syringe over 30 min. The resulting mixture was allowed to stir at room temperature for 15 h, when it was filtered and evaporated. The residue was chromatographed (silica, chloroform) to afford the *title compound* (0.33 g, 79%), m.p. 85–95 °C (decomp.) (Found: C, 37.0; H, 3.1%; M^+, 291.964. $C_9H_9IO_3$ requires C, 36.99; H, 3.11%: *M*, 291.960); ν_{max}/cm^{-1} 1670 and 1582.

6-*Iodo*-3,4-*dimethoxybenzyl Alcohol*.—The above aldehyde (0.44 g) was dissolved in THF (15 cm^3) with sodium borohydride in aq. methanol (20%, 16.3 cm^3). The mixture was refluxed for 90 min, cooled, and diluted with water. Standard extraction with ether gave the *title compound* (0.39 g, 87%), m.p. 77–78 °C (Found: C, 36.75; H, 3.7%; M^+, 293.975. $C_9H_{11}IO_3$ requires C, 36.74; H, 3.77%; *M*, 293.975); ν_{max}/cm^{-1} 3500, 1590 and 1570; δ_H(90 MHz) 2.02 (1 H, bs, OH), 3.82 (6 H, s, 2 × OMe), 4.68 (2 H, s, CH_2), 7.12 (1 H, s, 2-H) and 7.32 (1 H, s, 5-H).

6-*Iodo*-3,4-*dimethoxybenzyl Chloride*.—The above alcohol (0.40 g) in benzene (3 cm^3) at 0 °C was treated with thionyl chloride (0.22 cm^3). The solution was allowed to warm to room temperature and then set aside for 15 h, before partioning between ether and water. The organic solution was dried and evaporated, and the residue was crystallized from methanol to yield the *title compound* (0.38 g, 90%), m.p. 84–85 °C (Found: C, 34.3; H, 3.7%; M^+, 311.942. $C_9H_{10}ClIO_2$ requires C, 34.62; H, 3.23%; *M*, 311.941); δ_H(90 MHz) 3.87 (6 H, s, 2 × OMe), 4.64 (2 H, s, CH_2), 7.00 (1 H, s, 2-H) and 7.28 (1 H, s, 5-H).

3-(2′-*Iodo*-4′,5′-*dimethoxybenzyloxy*)-7-*methoxychromen*-4-*one*.—3-Hydroxy-7-methoxychromen-4-one (0.25 g) and 2-iodo-3,4-dimethoxybenzyl chloride (0.38 g) were refluxed in dry acetone (5 cm^3) over anhydrous potassium carbonate (0.34 g) for 15 h under nitrogen. The mixture was cooled, diluted with water, and extracted with chloroform. The extracts were dried, and evaporated to a residue which was chromatographed on silica (ethyl acetate–hexane, 1:9), to afford the *title compound* (0.25 g, 46%) as yellow needles from methanol, m.p. 138–141 °C (Found: C, 48.7; H, 3.65%; M^+, 468.005. $C_{19}H_{17}IO_6$ requires C, 48.72; H, 3.66%; *M*, 468.007); ν_{max}/cm^{-1} 1620, 1591 and 1582; δ_H(90 MHz) 3.90 (6 H, s) and 3.93 (3 H, s) (3 × OMe), 5.21 (2 H, s, CH_2), 6.92 (1 H, s, 5′-H), 7.08 (1 H, dd, *J* 3.0, 8.0, 6-H), 7.37 (1 H, s, 2′-H), 7.39 (1 H, d, *J* 3.0, 8-H), 7.85 (1 H, s, 2-H) and 8.32 (1 H, d, *J* 8.0, 5-H).

(±)-*Trimethylpeltogynone*.—Tributyltin hydride (76 mg) and azoisobutyronitrile (AIBN) (0.05 equiv.) in dry benzene (1.03 cm^3) were added over 45 min to 3-(2′-iodo-4′,5′-dimethoxybenzyloxy)-7-methoxychromen-4-one (80 mg) in benzene (5.7 cm^3) at reflux under nitrogen. The mixture was refluxed for 4 h, when it was cooled and evaporated. The residue was chromatographed on silica (chloroform). The major product was the *title compound* (24.4 mg, 42%), m.p. 203 °C from methanol, (lit.[8a,8b] m.p. 203–205°, 205–211°) (Found: C, 66.7; H, 5.35%; M^+, 342.112. $C_{19}H_{18}O_6$ requires C, 66.65; H, 5.30%; *M*, 342.110); ν_{max}/cm^{-1} 1690, 1610 and 1575; δ_H(250 MHz) 3.89 6 H, s) and 3.99 (3 H, s) (3 × OMe), 4.40 (1 H, d, *J* 12.0, 3-H), 4.99 (2 H, s, CH_2), 5.31 (1 H, d, *J* 12.0, 2-H), 6.56 (1 H, s, 5′-H), 6.61 (1 H, d, *J* 2.3, 8-H), 6.68 (1 H, dd, *J* 2.3, 8.8, 6-H), 7.18 (1 H, s, 2′-H) and 7.95 (1 H, d, *J* 8.8, 5-H).

(±)-*Trimethylpeltogynol*.—Trimethylpeltogynone (25.8 mg) was dissolved in ethanol (7 cm^3), and sodium borohydride (32.4 mg) and water (2.0 cm^3) was added. The mixture was set aside for 2 h, when it was diluted with water, stirred for 10 min, and then extracted with ether. The extracts were evaporated, and the residue was crystallized from methanol to afford the *title compound* (22.1 mg, 88%), m.p. 180–185 °C (lit.[8a] m.p. 185–188 °C) (Found: C, 66.5; H, 5.55%; M^+, 344.127. $C_{19}H_{20}O_6$

requires C, 66.25; H, 5.86%; *M*, 344.126); ν_{max}/cm^{-1} 3420, 1615 and 1580; δ_H(400 MHz) 2.45 (1 H, d, *J* 5.2, OH), 3.69 (1 H, dd, *J* 8.8, 10.2, 3-H), 3.80 (3 H, s), 3.89 (3 H, s) and 3.98 (3 H, s) (3 × OMe), 4.88 (1 H, d, *J* 14.0, CH_2-a), 4.91 (1 H, d, *J* 14.0, CH_2-b), 4.94 (1 H, d, *J* 10.2, 2-H), 4.98 (1 H, dd, *J* 5.2, 8.8, 4-H), 6.52 (1 H, s, 5′-H), 6.53 (1 H, d, *J* 2.3, 8-H), 6.64 (1 H, dd, *J* 2.3, 8.6, 6-H), 7.17 (1 H, s, 2′-H) and 7.46 (1 H, d, *J* 8.6, 5-H).

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