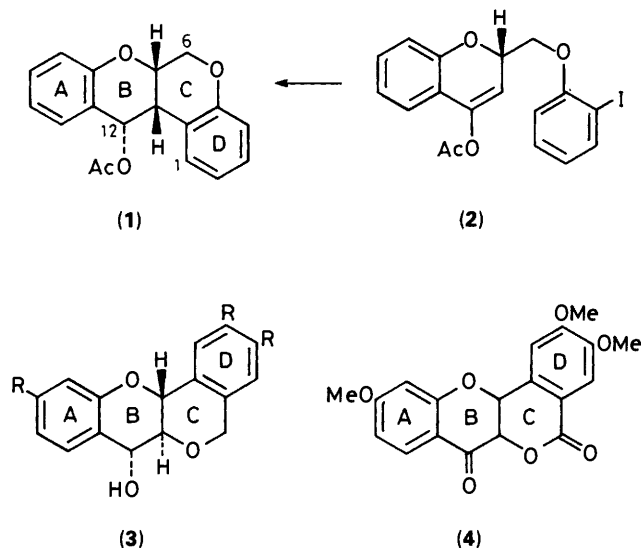


Synthesis of (\pm)-Trimethylpeltogynol via 6-endo Radical Cyclisation

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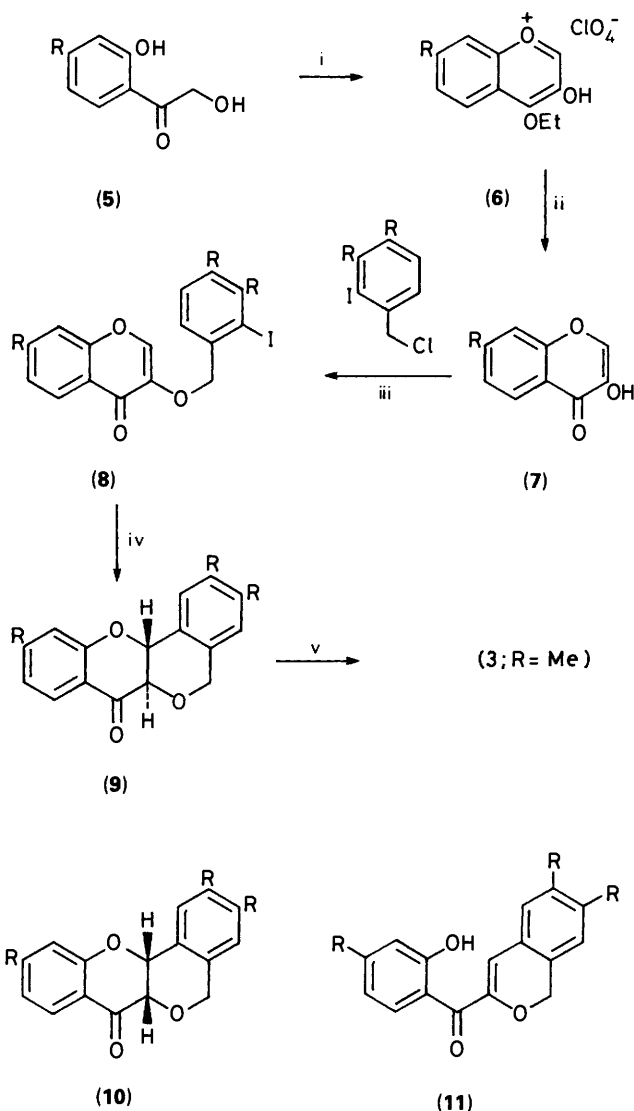
The (\pm)-trimethyl ether of the unusual heterocycle peltogynol (**3**; R = OMe), and its ring skeleton (**9**; R = H), have been synthesised via 6-endo intracyclisation of the radical derived from the iodides (**8**; R = H) and (**8**; R = OMe).

Recently¹ we demonstrated that the rotenoid ring system (**1**) could conveniently be synthesised by way of the intramolecular 6-*exo* radical cyclisation (**2**) \rightarrow (**1**). In this kinetic process three adjacent *cis* centres are set up, presumably with stereochemical control of the delivery of a hydrogen atom to C-12 by a least hindered face approach.



Our attention was subsequently taken by the closely related ring system found in (+)-peltogynol (**3**; R = OH). This natural product, isolated from the purpleheart tree *Peltogyne porphyrocardia* by Robinson and Robinson (1935)² was the first leucoanthocyanidin to be purified from a natural source, and the unusual isochromano-chromanol structure was determined by Hassall and co-workers (1958).³ (\pm)-Trimethylpeltogynol has been synthesised⁴ once, using the isocoumarin (**4**); a further seven steps were required to achieve the correct oxidation level. Attracted by the possibility that the *trans* B/C system of peltogynol could also be prepared through radical cyclisation, we embarked on an investigation of the convergent approach shown in the Scheme. We were further motivated by the desirability of developing a short route to provide compounds for comparison of biological activities with that of the rotenoids, potent blockers of oxidative phosphorylation.

The ω -hydroxyacetophenones (**5**; R = H) and (**5**; R = OMe) were converted into the corresponding 3-hydroxychromanols (**7**; R = H) and (**7**; R = OMe) by way of the pyrylium salts (**6**).⁵ 6-Iodo-3,4-dimethoxybenzaldehyde was prepared by direct



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

iodination (I_2 , AgOCOCF_3) of veratraldehyde, and converted into 6-iodo-3,4-dimethoxybenzyl chloride. Condensation of the last with chromanol (**7**; R = OMe) and ether (**8**; R = OMe) was similarly prepared from chromanol (**7**; R = H) and 2-iodobenzyl chloride. The ether (**8**; R = H) cyclised smoothly with tributyltin hydride in benzene[†] to yield the desired B/C-*trans* tetracycle (**9**; R = H) (48%). The B/C-*cis* isomer (**10**; R = H) was also isolated (12%). The ether (**8**; R = OMe) cyclised in similar fashion to afford trimethylpel-

[†] Tributyltin hydride in dry benzene (0.064 molar, 1.1 equiv.) containing azoisobutyronitrile (0.05 equiv.) was added dropwise over 60 min to a refluxing solution of the chromone in dry benzene (0.058 molar, 1 equiv.); reflux was continued for 15 h.

togynone (**9**; R = OMe) (42%), again with a minor quantity of its stereoisomer. It is not known whether the *trans*-fusion in trimethylpeltogynone represents the thermodynamically stable form, since attempted epimerisation in either acid or base leads irreversibly to the ring-opened product (**11**).⁴ Finally, reduction of the ketone (**9**; R = OMe) with borohydride provided (\pm)-trimethylpeltogynol (**3**; R = OMe) stereospecifically.

These results suggest that the enolate radical which forms the immediate product of cyclisation abstracts hydrogen to 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.

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