Rotenoid Synthesis *via* Radical Cyclisation

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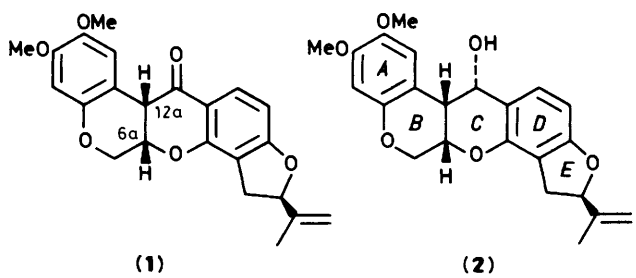
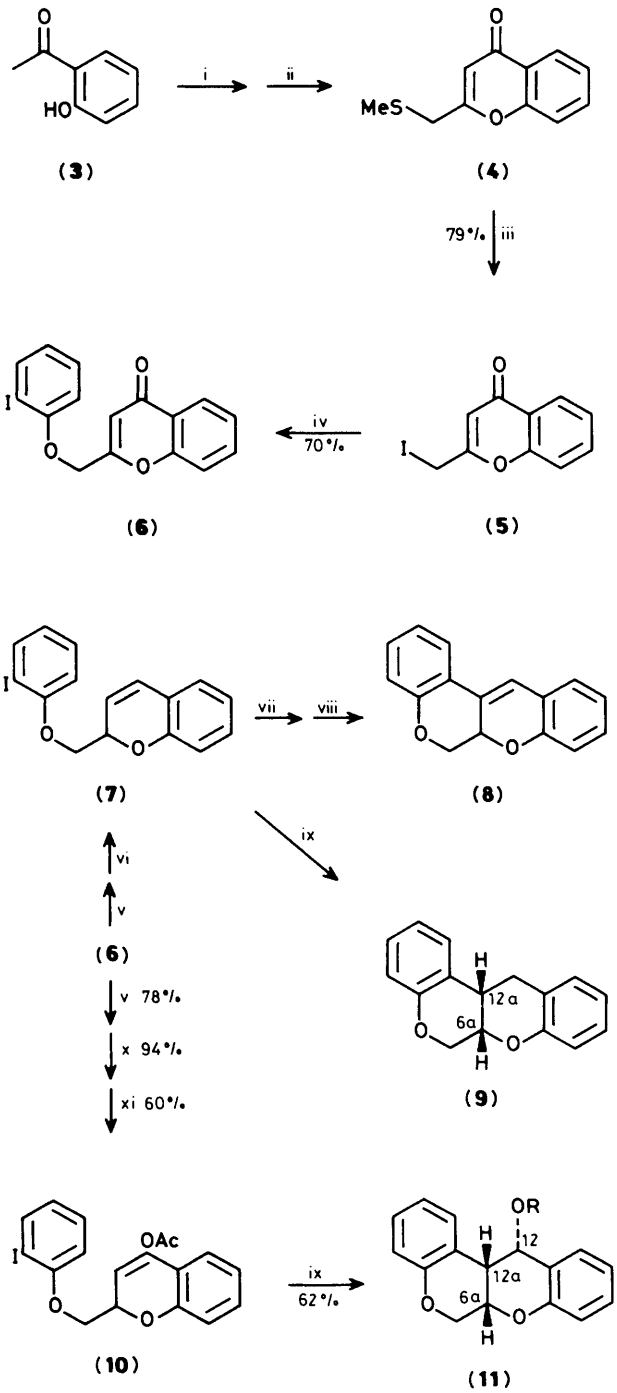
The (±)-6aα,12aα,12α-chromanochromanol acetate (**11**; R = Ac), representing the core structure of the insecticidal rotenoid alcohol (**2**), has been synthesised in six steps from the chromone (**4**); the *cis,cis*-stereochemistry is obtained in an intramolecular 6-*exo* aryl radical addition.

(6a*S*,12a*S*,5′*R*)-Rotenone (**1**) is the principal insecticide of *Derris* resin, a natural preparation at one time widely employed in agriculture.[1] Rotenone blocks mitochondrial electron transport at Complex I in insects, but is rapidly detoxified in animals, minimising environmental hazards. Structure–activity relationships have been investigated,[2] but mainly with compounds obtained by manipulation of the natural products. This limitation has contributed to the underdevelopment of the group as pesticides; since it appears that the intact *A*/*B*/*C*/*D* ring system is necessary for biological activity, further exploration of potential depends on a satisfactory short synthesis of this rotenoid feature. Since it has been shown[2] that the (12*S*)-alcohol (**2**) is markedly more active *in vitro* than the parent ketone we chose the core of (**2**), *i.e.* (**11**), as our target.

A number of relatively lengthy rotenoid syntheses have been described,[3] all of which depend on thermodynamic control to attain the *cis*-*B*/*C* junction, which is preferred in 12a-epimerisation of the 12-ketones. We required to obtain the 6a,12a-*cis* geometry in a kinetically preferred fashion, dispensing with the necessity for a 12-ketone. In this communication we show that 6-*exo* radical cyclisation of ring *B* fulfils this requirement, to give the basis of a convenient synthesis of alcohol (**11**).

Condensation of 2′-hydroxyacetophenone (**3**) with ethyl methylthioacetate[4] and sodium hydride, followed by treatment of the intermediate diketone with acid, gave the previously undescribed methylthiomethylchromone (**4**) (43%). Refluxing the thioether (**4**) with methyl iodide afforded the iodide (**5**), presumably by way of a sulphonium salt. Condensation of (**5**) with *o*-iodophenol provided the aryloxymethylchromone (**6**). 1,4-Reduction of the chromone (**6**) gave a saturated alcohol, which was dehydrated to the chromene (**7**). This route represents a significant improvement on our previous route[5] to the chromene (**7**), which we have shown to undergo an apparently stereochemically disallowed Heck reaction with palladium acetate to afford the stilbene (**8**). Since we considered that this conversion might involve radical intermediates we treated the chromene (**7**) with tributyltin hydride in refluxing benzene, using azoisobutyronitrile (AIBN) as initiator, and were pleased to obtain the tetracycle (**9**) (74%), as a single stereoisomer. The *cis*-stereochemistry was demonstrated by ^{1}H n.m.r. ($J_{6a,12a}$ 4.4 Hz; *cf.* $J_{6a,12a}$ 4.8 Hz in the parallel *cis*-compound derived from natural rotenone, and $J_{6a,12a}$ 9.5 Hz for its *trans*-counterpart).[6]





Scheme 1. *Reagents and conditions*: i, $MeSCH_2CO_2Et$, NaH, THF; ii, MeOH, HCl; iii, MeI, CH_2Cl_2, reflux; iv, *o*-iodophenol, K_2CO_3, dry acetone, reflux; v, $NaBH_4$, THF, reflux; vi, toluene-*p*-sulphonic acid, toluene, reflux; vii, Co^I (salen); viii, *hν*; ix, Bu_3SnH, AIBN, benzene, reflux; x, pyridinium chlorochromate; xi, isopropenyl acetate, H^+.

The oxidative closure (**7**) → (**8**) could be effected (40%) by treatment with cobalt(I) (salen),[7] followed by photolysis, as an alternative to the palladium(II) method.[5]

With the practicality of forming the desired *cis*-fused system established, we turned to the target (**11**). Conjugate reduction of the chromone (**6**) followed by oxidation with pyridinium chlorochromate generated the corresponding aryloxymethylchromanone. Methods available for forming enolic derivatives of chromanones are limited, since the enolate anions rapidly open to give the phenolate anions. However, the enol acetate (**10**) was obtained (60%) by treatment with isopropenyl acetate; purification of (**10**) was hindered by ready hydrolysis on chromatography on silica. Reaction of (**10**) in refluxing benzene with tributyltin hydride (slow addition) gratifyingly afforded the stereoisomer of the acetate (**11**; R = Ac) (62%), m.p. 128—130 °C. The stereochemistry was demonstrated by ^{1}H n.m.r. (*e.g.* $J_{6a,12a}$ 5 Hz, $J_{12,12a}$ 4.6 Hz) and has the all-*cis* arrangement of hydrogen atoms at the contiguous chiral centres. Alkaline hydrolysis cleanly gave the alcohol (**11**; R = H).

Thus the parent *A*/*B*/*C*/*D* system of the rotenoid alcohol (**2**) has been prepared in six steps from the chromone (**4**) to the acetate (**11**; R = Ac) with overall yield 14%; this synthesis should prove of value in preparing novel structural variants.

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