Synthesis of [7′-^{14}C]- and [7′-^{13}C]-Rotenone, and [4′-^{14}C]- and [4′-^{13}C]-Rot-2′-enonic Acid: 1,4-Allylic Hydrogenolysis showing Substantial Stereoselectivity

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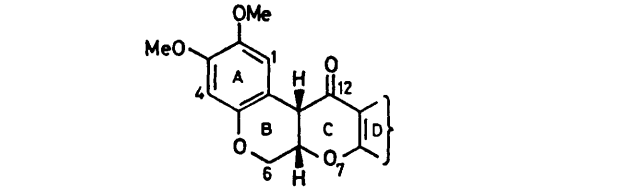
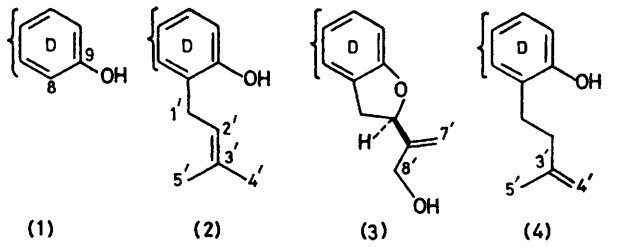
Summary C-Trimethylsilyloxy protection of the B/C-ring junction allows regenerative synthesis of (−)-rotenone isotopically labelled at the C-7′-methylene, without loss of chirality; 1,4-hydrogenolysis of (−)-rotenone labelled in this way proceeds stereoselectively with transference of 88% of the label to the 4′-*E*-methyl of (−)-rot-2′-enonic acid.

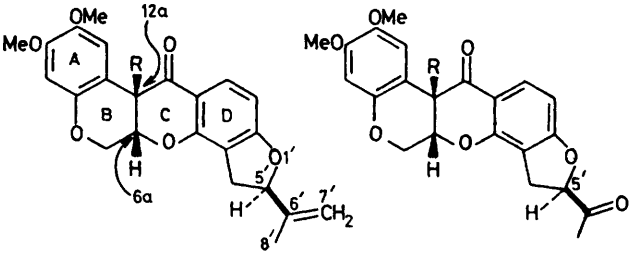
WORK on the biosynthesis of rotenoids by *Amorpha fruticosa* seedlings has shown that the basic tetracyclic system is constructed by a pathway leading through 2′,4,4′-trihydroxychalcone and 7-hydroxy-4′-methoxyisoflavone to 9-demethylmunduserone (**1**).[1] Prenylation to rot-2′-enonic acid (**2**) follows, and hemiterpenoid modification yields the major rotenoid metabolite of the seedlings, amorphigenin (**3**).[1] Although reasonable speculations have been presented,[1] the stages of prenyl elaboration between (**2**) and (**3**) have remained uninvestigated. Experimental study of these reactions is made difficult by the low incorporations of mevalonic acid by both *A. fruticosa* and *Derris elliptica* systems,[1,2] and similar difficulties have been encountered in other phenolic hemiterpenoids.[3] Incorporations of [1-^{3}H]dimethylallyl alcohol (0·0019%), [1-^{3}H]isopentenyl alcohol (0·055%), and (*R,S*)-[3-^{14}C]-3-hydroxy-3-methylglutaric acid (0·0012%) by *A. fruticosa* seedlings also contrast unfavourably with those of rot-2′-enonic acid (**2**) (*ca.* 1%). To provide tools for further biosynthetic study we have thus turned our attention to synthesis of [7′-^{14}C]-(−)-rotenone and *E*-[4′-^{14}C]-(−)-rot-2′-enonic acid, and the corresponding ^{13}C-compounds. Use of these precursors is described in the accompanying communications.

A regenerative synthetic circuit to (−)-[^{14}C]rotenone, based on nor-ketone (**8**) obtained by cleavage of natural rotenone (**5**) was sought. However, direct methyleneations of (**8**) proved unsatisfactory, and reaction with dimethylsulphoxonium methylide gave the cyclopropyl epoxide (**10**). In order to block base-catalysed racemisation and reactions of the B/C ring junction,[4] (−)-rotenone was oxidised at C-12a with chromium trioxide in a reaction involving retention of stereochemistry to give 6aβ,12aβ-rotenolone (**6**).[5] The trimethylsilyl ether (**7**) was then converted into the nor-ketone (**9**) using osmium tetroxide–periodate and (**7**) was re-formed without epimerisation at C-5′ by reaction with methylenetriphenylphosphorane. The 5′-α-series could also be entered through deprotonation of (**9**) at 5′ over alumina; Wittig reaction then gave the 5′-α-epimer of (**7**), spectroscopically distinct from the 5′-β-epimer. Protodesilylation of (**7**) using methanolic hydrochloric acid–potassium iodide gave (**6**), from which (−)-rotenone was readily and stereospecifically regenerated by zinc–acetic acid. Using [^{14}C]methyl iodide to form the methylene ylide, the natural rotenone → [7′-^{14}C]-(−)-rotenone conversion was effected in 22% chemical, 19% radiochemical, overall yield.



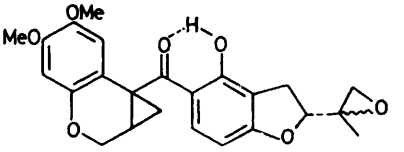


(1) (2) (3) (4)



(5); R = H
(6); R = OH
(7); R = OSiMe$_3$

(8); R = H
(9); R = OSiMe$_3$



(10)

(−)-Rot-2′-enonic acid (**2**) can be obtained from (−)-rotenone by 1,4-hydrogenolysis in pyridine.[6] Deuteriolysis in C_5D_5N over palladium on barium sulphate now shows, by examination of the ^{2}H and ^{13}C (natural abundance) n.m.r. spectra, that the reaction has substantial stereoselectivity, deuterium predominantly entering the 4′-*E*-methyl of (**2**). We have previously prepared [4′-^{2}H]-rot-2′-enonic acid by a different route, and reported the n.m.r. parameters.[7] In agreement, when [7′-^{13}C]rotenone [enriched (4%) with ^{13}C by the synthetic method above] was hydrogenolysed, a specimen of rot-2′-enonic acid was obtained in which the majority of the label was located at C-4′(*E*) but some 12% (mean of 5 estimates) was present at C-5′(*Z*). Although not providing a method for totally stereospecific labelling, this readily applied technique gives

rotenonic acid with sufficient label discrimination between the *Z*- and *E*-methyls for it to be used in biosynthetic experimentation.

[4′-^{14}C]- and [4′-^{13}C]-Rot-3′-enonic acid (**4**) was also obtained from the rotenone hydrogenolysis (separations of 2′- and 3′-isomers by p.l.c.) and the ^{13}C-labelled sample showed the expected augmentation of the 4′-vinyl carbon at 110·1 p.p.m. in accord with a 1,2-allylic cleavage between 1′-O and 5′-C.

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