

A Convenient Synthesis of Isotopically Labelled Anthraquinones, Chrysophanol, Islandicin, and Emodin. Incorporation of [*methyl*-²H₃]Chrysophanol into Tajixanthone in *Aspergillus varicolor*

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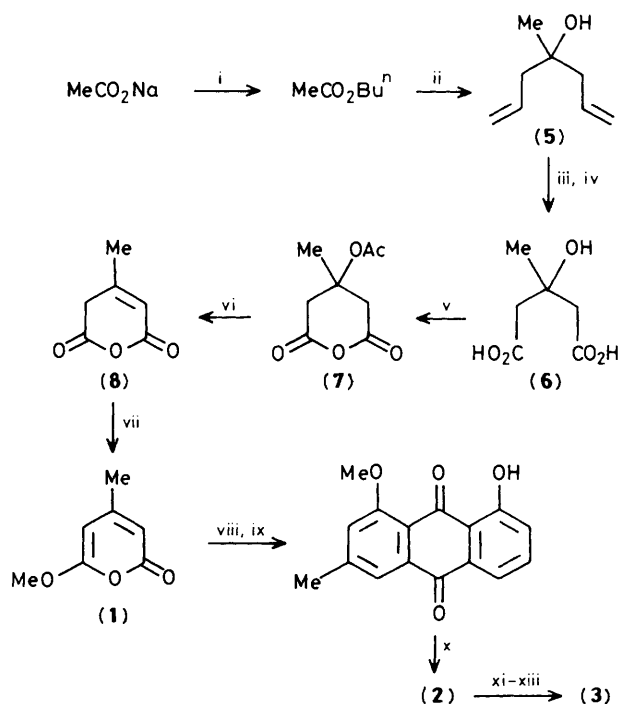
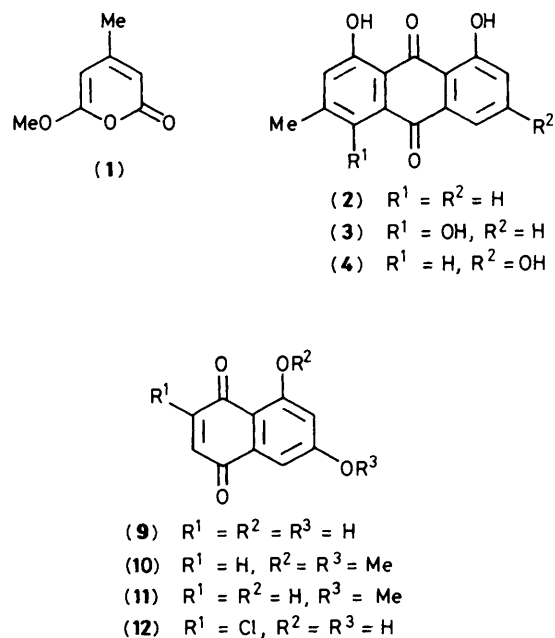
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Cycloaddition reactions of labelled 6-methoxy-3-methyl-2-pyrone (1) with naphthoquinones provide the common fungal anthraquinones, chrysophanol (2), islandicin (3), and emodin (4) suitably labelled for biosynthetic studies, as demonstrated by synthesis and incorporation of [*methyl*-²H₃]chrysophanol into the xanthone metabolite, tajixanthone (17) in *Aspergillus varicolor*.

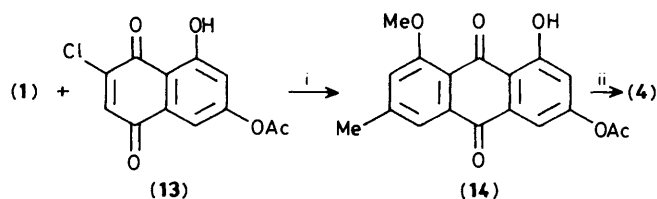
A large number of fungal metabolites including the ergochromes, various benzophenones, and xanthenes are believed to be derived *via* oxidative metabolism of anthraquinones.¹ Despite some successful studies,¹ work to establish this conclusively has been hampered by the lack of a convenient method for synthesising anthraquinones specifically labelled with either radioisotopes or stable isotopes. A convenient synthesis of chrysophanol (2) by Diels–Alder reaction of 6-methoxy-3-methyl-2-pyrone (1) was described recently.² We have also developed³ a synthesis of mevalonic acid lactone from sodium acetate, which is readily available labelled with ²H, ³H, ¹³C, or ¹⁴C. Extension of these studies to provide the common fungal anthraquinones, chrysophanol (2), islandicin

(3), and emodin (4) in labelled form suitable for biosynthetic studies is now reported.

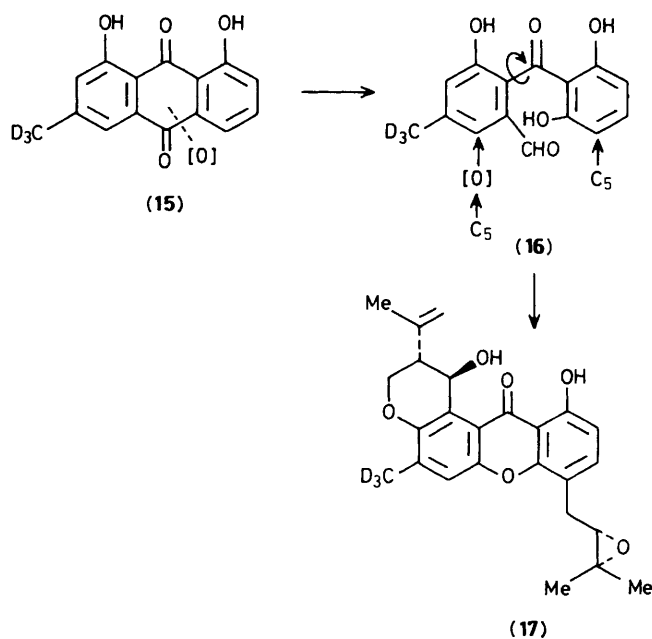
The pyrone (1) was synthesised as shown in Scheme 1. Sodium acetate was converted in high yield into the *n*-butyl ester, which was treated with allylmagnesium bromide to give the alcohol (5). Ozonolysis, and cyclisation of the resultant



Scheme 1. Reagents: i, (BuⁿO)₃PO, reflux; ii, CH₂=CHCH₂Br, Mg, tetrahydrofuran, Et₂O; iii, O₃, HOAc, CH₂Cl₂; iv, H₂O₂, HOAc; v, AcCl, reflux; vi, xylene, reflux; vii, CH₂N₂; viii, 5-hydroxy-1,4-naphthoquinone, xylene, reflux; ix, Ag₂O, MgSO₄; x, HBr, HOAc; xi, H₃BO₄, 65% oleum; xii, Ac₂O, H₂SO₄; xiii, MeOH, HCl.



Scheme 2. Reagents: i, xylene, reflux; ii, HBr, HOAc.



Scheme 3

β -hydroxy- β -methyl-glutaric acid (6) by treatment with acetyl chloride, gave the acetoxy-anhydride (7) which on heating gave β -methylglutaconic anhydride (8). Treatment of (8) with diazomethane² gave the pyrone (1). Reaction of (1) with 5-hydroxy-1,4-naphthoquinone in refluxing xylene gave, after oxidation and deprotection, chrysophanol (2) in 62% yield.⁴

Direct hydroxylation of chrysophanol, using the method of Cameron,⁵ gave islandicin (3), after purification *via* the triacetate, in 65% yield.

Emodin (4) proved more difficult to obtain. Attempted cycloaddition reactions with the naphthoquinones (9)—(12) all failed to give isolable products. However, when the pyrone (1) was heated in xylene with an excess of 6-acetoxy-2-chloro-8-hydroxy-1,4-naphthoquinone (13)⁶ the anthraquinone (14) was produced in 70% yield after chromatographic isolation. Deprotection furnished emodin (4) in essentially quantitative yield (Scheme 2).

Previous studies⁷ had indicated that tajixanthone (17) and related metabolites in *Aspergillus varicolor* were formed *via* oxidative cleavage of chrysophanol and the resultant benzo-phenone (16) as shown in Scheme 3. Repeating the above sequence (Scheme 1) with [2-²H₃]acetate gave [methyl-²H₃]chrysophanol (15). This was fed in dimethyl sulphoxide solution to static cultures of *A. varicolor*. ²H N.m.r. analysis of the isolated tajixanthone showed only one signal at 2.3 p.p.m. corresponding to the aromatic methyl position, to demonstrate the intact and specific incorporation of chrysophanol.

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