A Convenient Synthesis of Isotopically Labelled Anthraquinones, Chrysophanol, Islandicin, and Emodin. Incorporation of [*methyl*-$^2H_3$]Chrysophanol into Tajixanthone in *Aspergillus variecolor*

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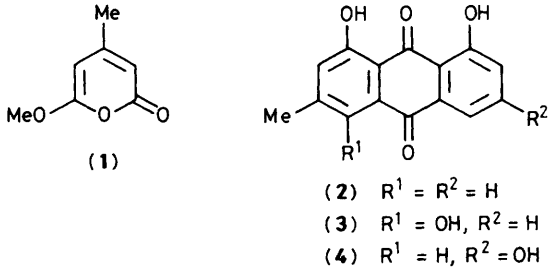
Cycloaddition reactions of labelled 6-methoxy-3-methyl-2-pyrone (**1**) with naphthoquinones provide the common fungal anthraquinones, chrysophanol (**2**), islandicin (**3**), and emodin (**4**) suitably labelled for biosynthetic studies, as demonstrated by synthesis and incorporation of [*methyl*-$^2H_3$]chrysophanol into the xanthone metabolite, tajixanthone (**17**) in *Aspergillus variecolor.*

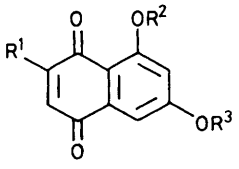
A large number of fungal metabolites including the ergochromes, various benzophenones, and xanthones are believed to be derived *via* oxidative metabolism of anthraquinones.[1] Despite some successful studies,[1] work to establish this conclusively has been hampered by the lack of a convenient method 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 developed[3] a synthesis of mevalonic acid lactone from sodium acetate, which is readily available labelled with ^2H, ^3H, ^{13}C, or ^{14}C. 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

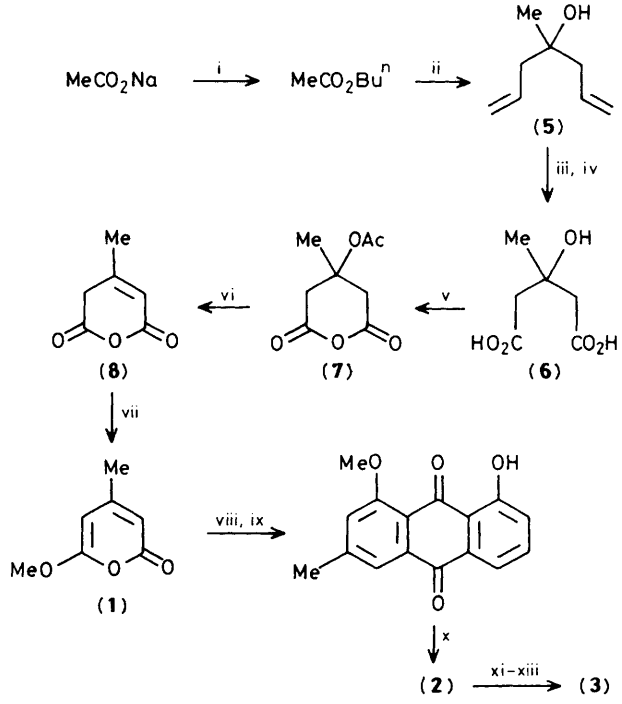


(**1**)

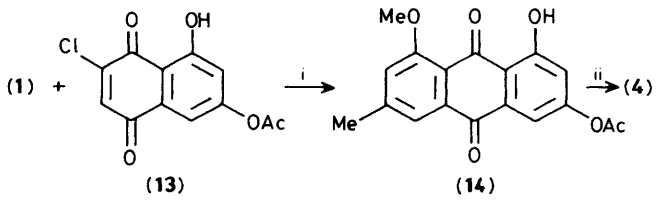
(**2**) $R^1 = R^2 = H$
(**3**) $R^1 = OH, R^2 = H$
(**4**) $R^1 = H, R^2 = OH$



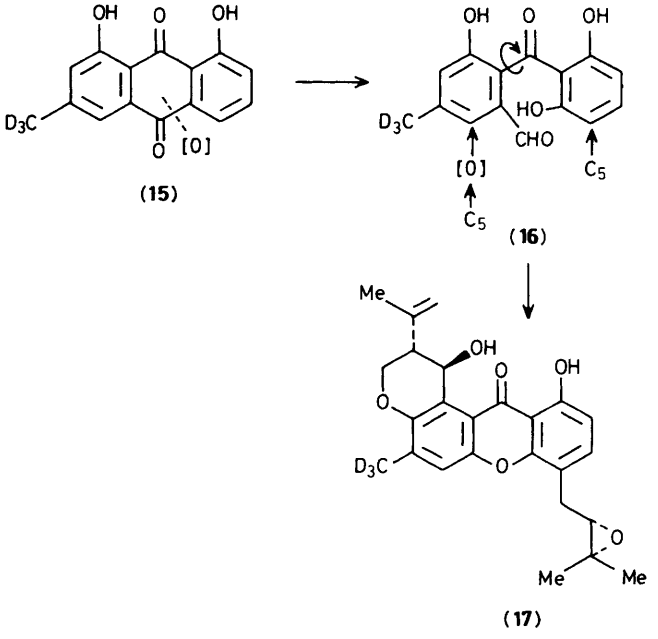
(**9**) $R^1 = R^2 = R^3 = H$
(**10**) $R^1 = H, R^2 = R^3 = Me$
(**11**) $R^1 = R^2 = H, R^3 = Me$
(**12**) $R^1 = Cl, R^2 = R^3 = H$



Scheme 1. *Reagents:* i, $(Bu^nO)_3PO$, reflux; ii, $CH_2{=}CHCH_2Br$, Mg, tetrahydrofuran, Et_2O; iii, O_3, HOAc, CH_2Cl_2; iv, H_2O_2, HOAc; v, AcCl, reflux; vi, xylene, reflux; vii, CH_2N_2; viii, 5-hydroxy-1,4-naphthoquinone, xylene, reflux; ix, Ag_2O, $MgSO_4$; x, HBr, HOAc; xi, H_3BO_4, 65% oleum; xii, Ac_2O, H_2SO_4; 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 diazomethane[2] 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 studies[7] had indicated that tajixanthone (**17**) and related metabolites in *Aspergillus variecolor* were formed *via* oxidative cleavage of chrysophanol and the resultant benzophenone (**16**) as shown in Scheme 3. Repeating the above sequence (Scheme 1) with [2-$^2H_3$]acetate gave [*methyl*-$^2H_3$]chrysophanol (**15**). This was fed in dimethyl sulphoxide solution to static cultures of *A. variecolor*. ^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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