The Biosynthesis of Mangostin: The Origin of the Xanthone Skeleton

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Cinnamic, benzoic, and *m*-hydroxybenzoic acids and benzophenone (**1**) are efficient precursors to mangostin (**3**).

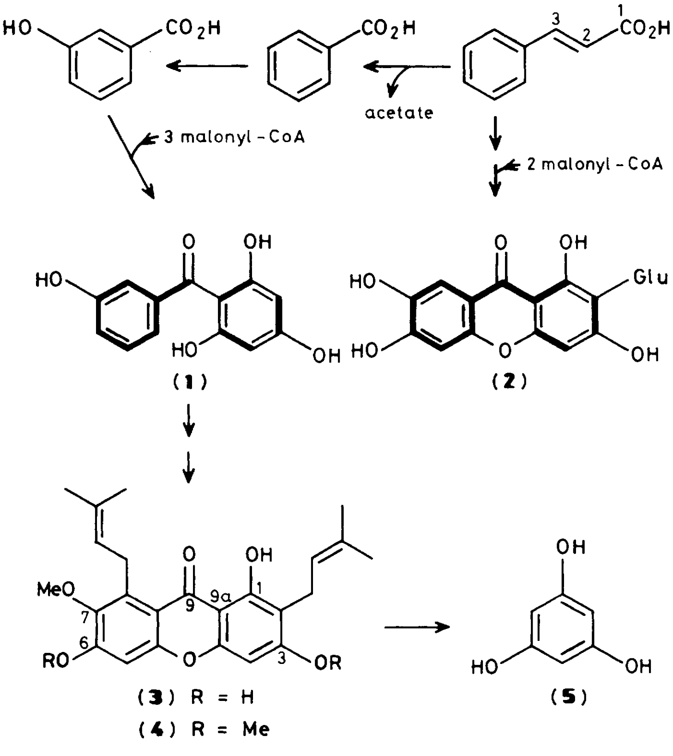
Whereas xanthones produced by fungi have been shown to be wholly acetate-derived,[1] those found in higher plants[2] appear to be formed by a mixed shikimate–acetate route. There has been much speculation regarding the nature of the shikimate moiety and the mode of xanthone formation.[3]

Tracer studies have indicated that the 1,3,7-trioxygenated xanthones of *Gentiana lutea* L. (Gentianaceae) are formed from a C_6–C_1 unit and three C_2 units *via* oxidative coupling of the intermediate benzophenone (**1**).[4]

In contrast, the *C*-glucosylxanthone, mangiferin (**2**), has been shown to derive from a C_6–C_3 unit (*p*-coumarate) and two C_2 units,[5] confirming the suspected biogenetic relationship between (**2**) and flavonoids.[3,6]

We now report the findings of preliminary studies on the biosynthesis of mangostin (**3**),[7] the major xanthone pigment of *Garcinia mangostana* L. (Guttiferae). Labelled precursors were fed to the upper aerial parts of young plants for seven days. The mangostins† were isolated and collectively converted to dimethylmangostin (**4**). Fusion of (**4**) in a mixture of sodium and potassium hydroxide (290 °C; 1 h) gave phloroglucinol (**5**).

The results (Table 1) indicate that the xanthone skeleton of mangostin is derived from *m*-hydroxybenzoate and malonate, *via* the benzophenone (**1**) (see Scheme 1). The high incorporations of benzoic and *m*-hydroxybenzoic acids strongly suggest that a direct *m*-hydroxylation of benzoate is occurring. This is



Scheme 1

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† Including β- and γ-mangostin.[8]

Table 1. Incorporation of labelled precursors and degradation results.

Precursor[a]	Incorporation[b]	% Activity in phloroglucinol (5)[c]
[2-^{14}C]Malonic acid	1.16	71
Cinnamic acids		
[3-^{14}C] (15 μCi)	1.24	1.1
[2-^{14}C] (15 μCi)	0.82	93
p-Hydroxy-[2-^{14}C] (15 μCi)	0.06	—
m-Hydroxy-[2-^{14}C] (10.5 μCi)	0.14	—
[2,3-$^{13}C_2$]-[3-^{14}C] (7 μCi)	0.87	—
[Carboxy-^{14}C]benzoic acids		
Benzoic acid	5.72	<1
p-Hydroxybenzoic acid	0.19	5.1
m-Hydroxybenzoic acid	13.3	3.4
[1,3,5-$^{14}C_3$]2,3′,4,6-Tetrahydroxybenzophenone[d] (**1**) (2.5 μCi)	2.86	—

[a] 50 μCi unless otherwise stated. [b] 100 × total activity in (**4**)/total activity fed. [c] 100 × specific activity of (**5**)/specific activity of (**4**). [d] Synthesised[11] from [2,4,6-$^{14}C_3$]phloroglucinol[12] and *m*-hydroxybenzonitrile.

a hitherto unknown process, although the *m*-hydroxylation of cinnamate has recently been implicated in the biosynthesis of dihydrophenanthrenes.[9] An alternative route to *m*-hydroxybenzoate involving the reduction of a more highly oxygenated species such as 3,4-dihydroxybenzoate appears unlikely.

The breakdown of cinnamate to benzoate is known to give acetate as a by-product.[10] The incorporation of [2-^{14}C]-cinnamic acid, while appearing to support a mangiferin-type route, could alternatively be due to cinnamate-derived [^{14}C]acetate, being utilised in polyketide formation.

To clarify the role of cinnamate, [2,3-$^{13}C_2$]cinnamic acid (98% $^{13}C_2$; 22 mg) in the presence of [3-^{14}C]cinnamic acid was similarly fed to a plant. The ^{13}C n.m.r.‡ spectrum of the resultant dimethylmangostin (**4**) showed no coupling between C-9 and C-9a even though the specific incorporation (0.29% by ^{14}C) was sufficient for such coupling to be clearly visible had the precursor been incorporated intact.

The isolation also of radioactive dimethylgartanin (**6**) and dimethyl-8-deoxygartanin (**7**)[13] from the feeding of the benzophenone (**1**) suggests that (**1**) is a precursor to all the prenylated xanthones found in *G. mangostana* (Scheme 2). It remains to be seen whether prenylation and further oxidation occur at the benzophenone or xanthone stage. Furthermore the participation of the benzophenone (**1**) in xanthone biosynthesis in the two major xanthone-producing taxa: Guttiferae and Gentianaceae, gives support to the idea[3c] that the majority of xanthones in higher plants are derived from a common precursor.

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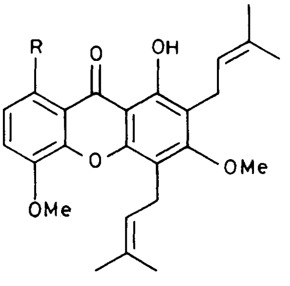
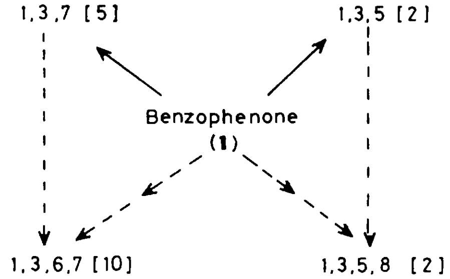


(**6**) R = OH
(**7**) R = H



Scheme 2. Alternative routes to the various oxygenation patterns of prenylated xanthones in *G. mangostana*. Nos. in brackets indicate number of xanthones with each pattern.

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‡ 100 mg of (**4**) in 0.4 ml of $CDCl_3$ recorded at 22.5 MHz on Jeol FX90 Q; proton noise decoupled, pulse delay 2.2 s, 18 000 transients; proton gated decoupled, pulse delay 8.5 s, 18 000 transients.