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An Easy Two Synthon Synthesis of a Sweet Dihydroisocoumarin, (±)-Phyllodulcin

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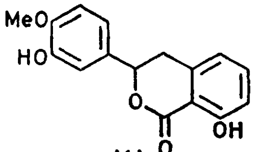
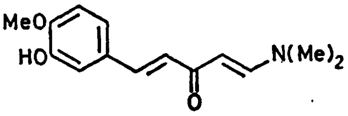
Summary A short synthesis of (±)-phyllodulcin (**1**), a sweet principle of *Hydrangea serrata* Seringe var. *thunbergii* Sugimoto, from the enaminone (**2**) by annelation with dimethyl 3-oxaglutarate is described.

A naturally occurring dihydroisocoumarin, phyllodulcin (**1**), is well known as a sweet principle of *Hydrangea serrata* Seringe var. *thunbergii* Sugimoto (Japanese name: Amacha: sweet tea).[1] Recently, we reported a biogenetic-type synthesis of (**1**) modelled on the polyketide mode of biosynthesis.[2] Although a chemical synthesis of (**1**) has also already been reported,[3] we here describe a new alternative synthesis by a simple and short route, consisting of the annelation of two easily accessible synthons, the enaminone (**2**) and dimethyl 3-oxoglutarate [$MeO_2CCH_2C(:O)CH_2CO_2Me$] to give the intermediate (**8**).

While the chemistry of enaminones has been of interest in recent years,[4] more information is needed on their role as intermediates for the present synthesis. Preliminary investigations of the annelations were carried out with the enaminones (**3**) and (**4**), prepared from benzaldehyde and cyclohexanone, respectively with bis(dimethylamino)methoxymethane, $MeOCH(NMe_2)_2$.[5] They were condensed with dimethyl 3-oxoglutarate in the presence of catalytic amounts of AcOH–AcONa and 18-crown-6 in toluene with refluxing to give the condensation products (**5**), m.p. 85—87 °C, $C_{16}H_{14}O_5$, and (**6**), m.p. 82—84 °C, $C_{14}H_{16}O_5$, in 52 and 22·7% yield, respectively. These results indicate the potential of this method in the synthesis of (**1**) from (**2**) and dimethyl 3-oxoglutarate.

The enaminone (**2**) was prepared by condensing benzylisovanillin with acetone in the presence of 10% NaOH to give, quantitatively, the benzylideneacetone (**7**), m.p.


(**1**)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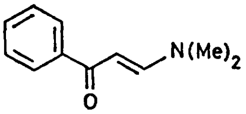
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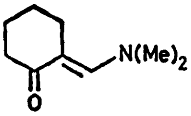
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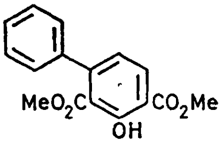
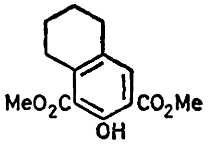

(**5**)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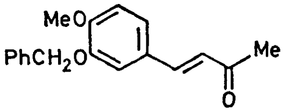
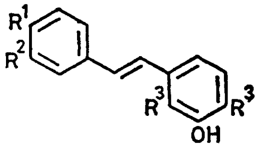
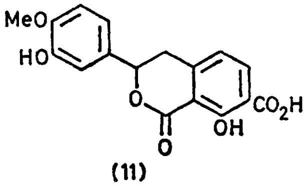

(**7**)


(**8**) R^1 = OMe, R^2 = OCH_2Ph, R^3 = CO_2Me
(**9**) R^1 = OMe, R^2 = OH, R^3 = CO_2Me
(**10**) R^1 = OMe, R^2 = OH, R^3 = CO_2H


(**11**)

87—89 °C, which was treated with bis(dimethylamino)-methoxymethane in dimethylformamide (DMF) to yield the enaminone (**2**), m.p. 126—128 °C, $C_{21}H_{23}O_3N$, in 90% yield. The reaction of (**2**) with dimethyl 3-oxoglutarate, catalysed by AcOH–AcONa, afforded the condensation product (**8**), m.p. 128—130 °C, $C_{26}H_{24}O_7$. A mixture of (**2**) (1 mol), dimethyl 3-oxoglutarate (2 mol), and catalytic amounts of AcOH–AcONa and 18-crown-6 heated at 70 °C for 12 h in benzene gave the best results (47·4% yield).

Debenzylation of (**8**) with conc. HCl in methanol afforded the diester (**9**), m.p. 163—165 °C, in 68% yield. The diester (**9**) was hydrolysed with 10% KOH in aqueous methanol to give the acid (**10**), m.p. 210—213 °C, in 98% yield. Lactonization of (**10**) by treatment with conc. H_2SO_4 at 0 °C for 10 min afforded the lactone (**11**), m.p. 201—203 °C, in 72% yield. The lactone (**11**) was decarboxylated by heating it in a sealed tube in water at 180 °C for 15 h to give (±)-phyllodulcin (**1**), m.p. 128—130 °C, in 70% yield. All the physical data for this synthetic phyllodulcin (**1**) were identical with those of the natural product except for its optical rotation.

This synthesis of (±)-phyllodulcin consists of seven steps from (**7**), including two hydrolysis steps, and gives an overall yield of *ca.* 14%.

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