

Journal of The Chemical Society, Chemical Communications

NUMBER 13/1980

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

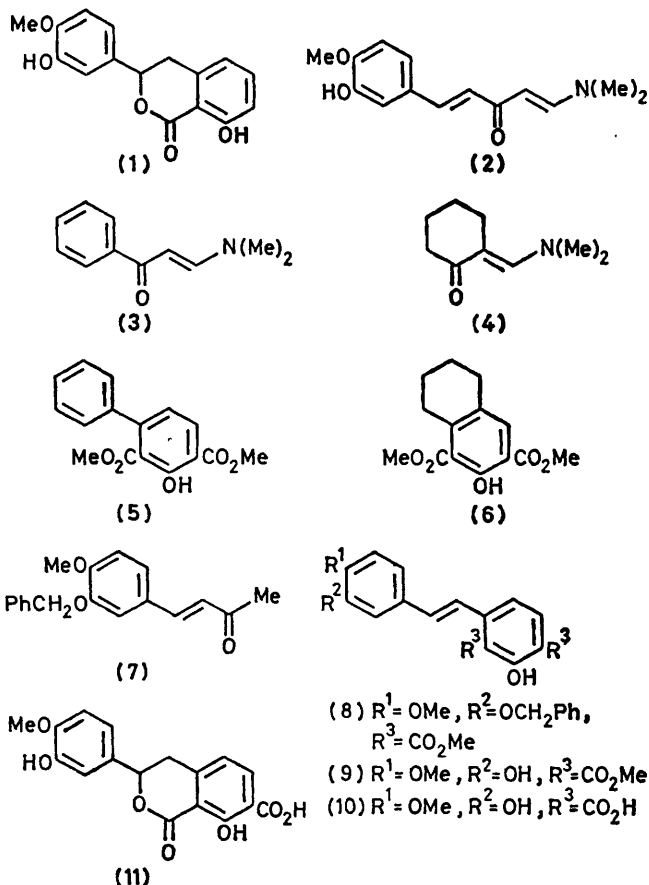
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Summary A short synthesis of (±)-phyllodulcin (1), a sweet principle of *Hydrangea serrata* Seringe var. *thunbergii* Sugimoto, from the enaminone (2) by annelation with dimethyl 3-oxoglutarate is described.

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 [MeO₂CCH₂C(=O)CH₂-CO₂Me] 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(NMe₂)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, C₁₆H₁₄O₅, and (6), m.p. 82–84 °C, C₁₄H₁₆O₅, 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.



87—89 °C, which was treated with bis(dimethylamino)-methoxymethane in dimethylformamide (DMF) to yield the enaminone (2), m.p. 126—128 °C, C₂₁H₂₃O₃N, 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, C₂₆H₂₄O₇. 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. H₂SO₄ 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%.

(Received, 20th March 1980; Com. 299.)

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