Biogenetic-type Synthesis of (±)-Phyllodulcin, a Sweet Principle of *Hydrangea serrata* Seringe var. *thunbergii* Sugimoto

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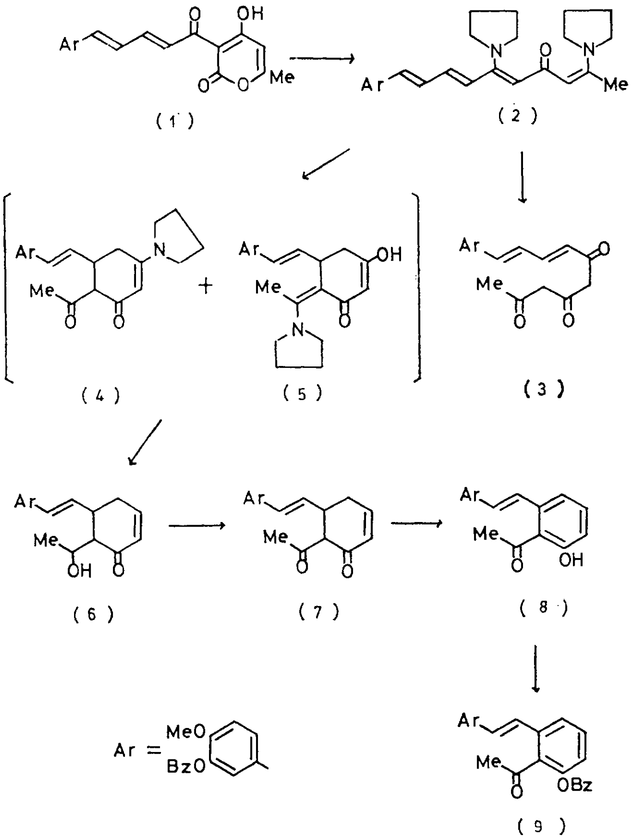
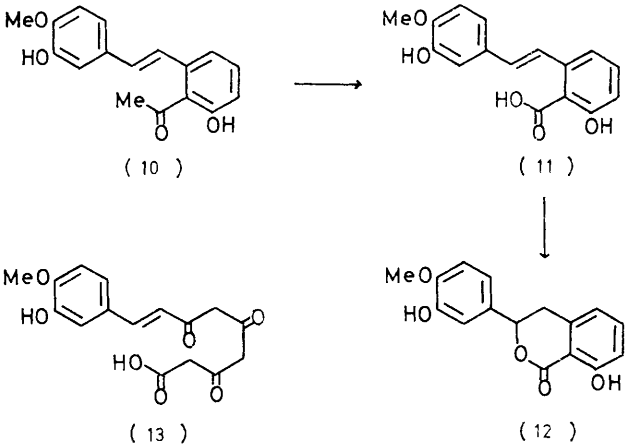
Summary The synthesis of (±)-phyllodulcin (12), a sweet principle of *Hydrangea serrata* Seringe var. *thunbergii* Sugimoto, from 3-(3-benzyloxy-4-methoxyphenyl)prop-2-enal modelled on the polyketide mode of biosynthesis is described.

Numerous synthetic attempts at the biogenetically modelled synthesis of polyketide-derived natural products have been reported.[1] The main interest has centred on the synthesis of β-polyketones and equivalent compounds and more recently on the mode of cyclization.[2] We report the synthesis of a naturally occurring isocoumarin, (±)-phyllodulcin (**12**), a sweet principle of *Hydrangea serrata* Seringe var. *thunbergii* Sugimoto (Japanese name: Amacha: sweet tea),[3] modelled on the polyketide mode of biosynthesis and synthesized from a C_6–C_3–C_6 precursor (**13**) derived from shikimic acid-acetate.[4] The triketone intermediate (**3**) was synthesized from *trans*-3-(3-benzyloxy-4-methoxyphenyl) prop-2-enal, prepared from benzylisovanillin by Isler's procedure[5] for lengthening the chain of an αβ-unsaturated aldehyde by two carbon atoms, as follows. The foregoing aldehyde and 3-acetyl-2-hydroxy-6-methylpyran-4-one were condensed in pyridine in the presence of a catalytic amount of piperidine to give a condensation product (**1**) (89·7%), m.p. 178—179·5 °C, which was transformed into the dienaminoketone (**2**) (68·8%), m.p. 152—153·5 °C, by heating at 100 °C with pyrrolidine (2 equiv.) in toluene. The enaminoketone (**2**) afforded the corresponding β-triketone (**3**) (89%), m.p. 140—142 °C, upon hydrolysis with aq. Ba(OH)$_2$.



Bz = benzyl

Although several attempts at the cyclization by an intramolecular Michael-type condensation of (**3**) were not successful, (**2**) gave the cyclized enaminoketone mixture (**4**) and (**5**), when treated with a mixture of acetic acid and pyrrolidine in EtOH–H_2O (10:1). The resultant mixture of (**4**) and (**5**) was reduced without separation with $LiAlH_4$–$AlCl_3$[6] to yield (**6**), which was oxidized under Pfitzner Moffatt oxidation conditions with dimethyl sulphoxide–dicyclohexylcarbodi-imide to afford the diketone (**7**), m.p. 118—119·5 °C in an overall yield [from (**2**)] of 8·2%.† The diketone (**7**) gave the stilbene (**8**), by halogenation with $CuCl_2$–LiCl followed by dehydrohalogenation with LiCl in dimethylformamide, yield 71·4%.



The structure of (**8**) was confirmed by direct comparison of the dibenzyl derivative (**9**), m.p. 95·5—96 °C, with an authentic sample synthesized from dibenzylphyllodulcin by conversion into the corresponding ester, m.p. 84·5—85·5 °C, treatment of the ester with NaOH in glycerine and methylation with diazomethane, followed by reaction with MeLi to afford (**9**).

The dihydroxy-stilbene (**10**), m.p. 104—105 °C, obtained by acid hydrolysis of (**8**), was oxidized to the acid (**11**) by transformation into its pyridinium salt by reaction with pyridine and iodine, followed by hydrolysis with aq. NaOH.‡ The acid (**11**) was treated with cold conc. H_2SO_4 to afford the isocoumarin (±)-phyllodulcin (**12**), m.p. 128—130 °C. The synthetic isocoumarin was identical with natural phyllodulcin in all respects except its optical rotation.

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† Oxidation of (6) by Jones' reagent yielded only a dehydration product.

‡ Oxidation of (8) and (9) by the described method did not afford the corresponding acids.

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