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Synthesis of Danielone (α-Hydroxyacetosyringone)†

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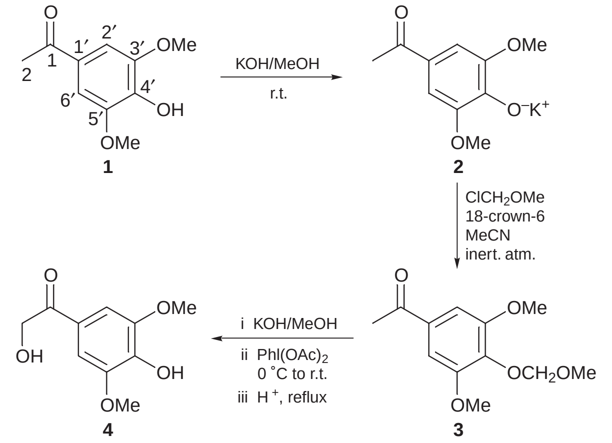
An efficient simple three step synthesis of the phytoalexin danielone (α-hydroxyacetosyringone) from acetosyringone is described.

α-Hydroxyacetosyringone (**4**), has recently been characterised as a phytoalexin, named danielone,[1] from Papaya (*Carica papaya*). On the other hand, it has also been shown[2] that α-hydroxytacetosyringone plays an important role in the specialized interaction between soil bacteria and plants, specifically activating *Agrobacterium tumefaciens* virulence (Vir) gene expression.

α-Hydroxyacetosyringone (**4**) has not been synthesized until now and we describe here an efficient, simple three step synthesis of it from commercial acetosyringone (**1**).

α-Hydroxylation of ketones is commonly accomplished by an indirect method, *viz.*, by the addition of dioxygen ($^3O_2$) to an enolate[3] with subsequent reduction of the α-hydroperoxy ketone by triethyl phosphite.[4] For example, this is a key reaction in the elaboration of the dihydroxyacetone side-chain of a cortical steroid from a C_{17}-acetyl precursor. Addition of $^3O_2$ to organometallic enolates is inherently dangerous, and a serious explosion has been encountered in these laboratories.[5] Direct hydroxylation of enolates is a less common synthetic transformation. Molybdenum peroxide pyridine-HMPA (MoOPH) oxidation of the enolate yields the corresponding acyloin but reaction with methyl ketones gives variable results.[6]

Application of the above methods on acetosyringone were unsuccessful, giving complex mixtures. However, protection of the *p*-hydroxyphenol group followed by application of Moriarty's methodology[7] for the α-hydroxylation of ketones gave excellent results.



Scheme 1

Acetosyringone (**1**) was protected using chlorodimethyl ether to give (**3**) (Scheme 1). Compound **3** reacted with iodobenzene diacetate in methanol–potassium hydroxide solution to give, after acid treatment at reflux, the deprotected product (**4**) which was identical to the natural product α-hydroxyacetosyringone.

Experimental

Preparation of Acetosyringone Potassium Salt **2**.–A solution of acetosyringone (**1**) (1.0 g, 5.1 mmol) in methanol (30 ml) was added to a solution of potassium hydroxide (4 equiv., 1.15 g, 0.2 mol) in methanol (15 ml) and the mixture was stirred at room temp. for 1 h. The mixture was cooled in an ice-bath and the solid formed was filtered off on a Büchner funnel and rinsed with light petroleum bp 30–40°C). After removal of the light petroleum a white solid remained which was dried well in a vacuum desiccator to give dry acetosyringone potassium salt (1.2 g, quantitative yield). Acetosyringone potassium salt **2**. White solid, mp > 350 °C (Found: C, 51.3; H, 4.8. $C_{10}H_{11}O_4K$ requires C, 51.26; H 4.73%); ν_{max}/cm^{-1} (film) 1622, 1509, 1458, 1374, 1297, 1213, 1184, 1117; λ_{max}/nm (EtOH) 215, 301; δ_H (200 MHz, CD_3OD) 2.47 (3H, s, CH_3CO), 3.80 (6H, s, 2 × Ar-OCH_3) 7.22 (2H, s, 2 × Ar-H); *m/z* 196 (M^+–K, 56%), 181(100), 153(7), 138(4), 108(3), 93(3) and 65(4).

Preparation of 3′,5′-Dimethoxy-4′-methoxymethoxyacetophenone **3**.–A mixture of 18-crown-6 (0.1 equiv., 136 mg, 0.5 mmol) and acetosyringone potassium salt (350 mg, 1.5 mmol) in dry acetonitrile (15 ml) was stirred at room temp. for 1 h under nitrogen. Chlorodimethyl ether (1.4 equiv., 0.16 ml, 2.1 mmol) was added and the mixture was stirred at room temp. for 2 h under nitrogen. The mixture was cooled in an ice-bath, water added, and the product extracted with ethyl acetate, washed with water and brine and dried with anhydrous sodium sulfate. The crude reaction product was purified by column chromatography using light petroleum–ethyl acetate (1:1) as eluent to give 3′,5′-dimethoxy-4′-methoxymethoxyacetophenone (**3**) (298.6 mg, 83%) as a white solid, mp 68–70 °C (Found: C, 60.0; H, 6.6. $C_{12}H_{16}O_5$ requires C, 59.99; H, 6.71%); M^+ at *m/z* 240.100685 (calc. for $C_{12}H_{16}O_5$, 240.099774); ν_{max}/cm^{-1} (film) 2966, 2938, 1678, 1585, 1456, 1414, 1254, 1205, 1164, 1128, 1078, 950, 856; λ_{max}/nm (EtOH) 218, 280; δ_H (200 MHz, $CDCl_3$) 2.58 (3H, s, CH_3CO), 3.58 (3H, s, OCH_3), 3.90 (6H, s, 2 × Ar-OCH_3), 5.19 (2H, s, OCH_2O), 7.21 (2H, s, 2 × Ar-H); δ_C (50 MHz, $CDCl_3$) 26.28 (q, OCH_3), 56.13 (q, 2 × Ar-OCH_3), 57.10 (q, C-2), 98.04 (t, OCH_2O), 105.66 (d, C-2′ and C-6′), 132.80 (s, C-1′), 139.05 (s, C-4′), 153.10 (s, C-3′ and C-5′), 196.71 (s, C-1); *m/z* 240 (M^+, 100%), 210(85), 195(50), 179(7), 181(7), 139(9), 137(8), 109(7), 66(6).

Preparation of α-Hydroxyacetosyringone **4**.–A solution of potassium hydroxide (8 equivalents, 370 mg, 6.6 mmol) in methanol (10 ml) was stirred at room temp. When the potassium hydroxide was dissolved the mixture was cooled in an ice-bath and a solution of 3′,5′-dimethoxy-4′-methoxymethoxyacetophenone (198 mg, 0.8 mmol) in methanol (10 ml) was added slowly. Then iodobenzene diacetate (1.5 equiv., 398.6 mg, 1.24 mol) was added in small portions and the reaction mixture stirred at room temperature overnight, then cooled in an ice-bath and a solution of hydrochloric acid 6% added until the reaction mixture was acidic by pH indicator. After refluxing at 60 °C for 1 h the reaction mixture was cooled at room temp. and water added. The product was extracted with ethyl acetate, the organic layers washed with water and brine and dried over anhydrous sodium sulfate. The crude product was chromatographed on silica gel in a small plug with light petroleum–ethyl acetate (1:1) as eluent to give (**4**) as a yellow solid (130 mg, 60%); M^+ at *m/z* 212.067631 (calc. for $C_{10}H_{12}O_5$, 212.068474); ν_{max}/cm^{-1} (film) 3495, 3239, 1675, 1614, 1587, 1519, 1455, 1325, 1216, 1096, 847. The remainder of the spectroscopic data were identical to those given in the literature for the natural product.

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† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

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5 **WARNING**: Stirring of a solution of butyrolactone and LDA under an $^3O_2$ flow resulted in a sudden powerful explosion.

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