A Novel Biogenetic-type Synthesis of an Orsellinic Acid Derivative

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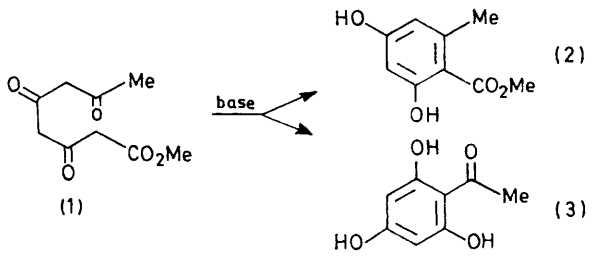
Summary A synthesis of an orsellinic acid derivative (**8**) modelled on the polyketide mode of biosynthesis is described.

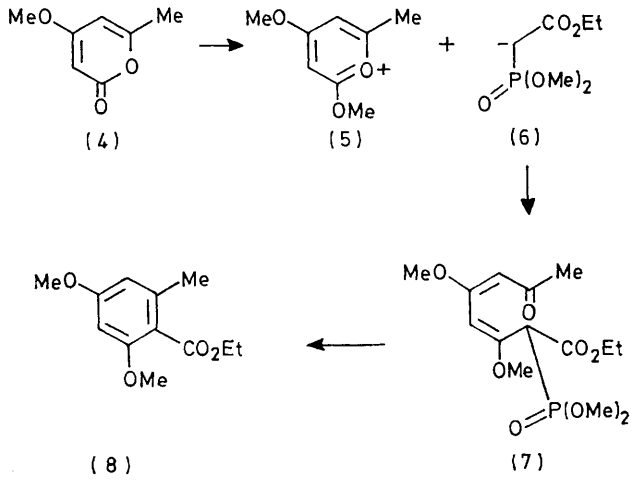
THE enormous synthetic potential of the polyketide mode of biosynthesis is reflected in the wide range of skeletal types which are represented among the phenolic compounds derived in this way.[1] In the search for equivalent biogenetic-type syntheses[2] reliable methods have been developed for the synthesis of β-polyketones and equivalent compounds. Unfortunately the inherent flexibility of the approach has proved so far to be a serious limitation on the efficiency with which the intermediates can be cyclised to form aromatic compounds since usually more than one mode of cyclisation is followed leading to low yields and complex mixtures of products. The β-polyketone (**1**) for example, is reported[3] to undergo competing cyclisations to form both orsellinic acid (**2**) and acetylphoroglucinol (**3**).

We presume that this competition is avoided in nature by the controlling effect of an enzyme which will determine both the manner of chain-folding and the site of carbanion formation. We now describe a biogenetic-type synthesis in which the control over the mode of cyclisation is exercised by internal constraints resulting from suitable derivatisation of the β-polyketone chain.



(1) (2) (3)

The readily available[4] monomethylether (**4**) of triacetic lactone is converted by treatment with methyl fluorosulphonate in refluxing chloroform into the novel pyrylium



salt (**5**) (95%) [m.p. 87—89 °C (decomp.), λ_{max} (EtOH) 258·5 nm, ν_{max} (MeCN) 1670 (s), 1660 (s), 1278 (s), 1249 (s) cm^{-1}, τ (CD_3CN) 3·06 (1H, d, J 2 Hz), 3·40 (1H, d, J 2 Hz), 5·71 (3H, s), 5·85 (3H, s), 7·42 (3H, s)], This was treated in tetrahydrofuran with the Wittig reagent (**6**) which according to precedent[5] should lead to the modified β-polyketone (**7**) and subsequently to an aromatic product. The intermediate (**7**) has the ideal geometry for cyclisation in the orsellinic acid mode and, in addition, the positioning of the phosphoryl residue should ensure that carbon–carbon bond formation takes place at the appropriate position. In practice this intermediate could not be isolated because it underwent rapid cyclisation *in situ* to form the orsellinic acid derivative (**8**) under all conditions tried so far. Under optimum conditions, with an extra equivalent of base (NaH), a 65% conversion of (**5**) to (**8**) was obtained. As expected, no product corresponding to the acylphloroglucinol mode of cyclisation could be detected.

This efficient transformation of (**4**) to (**8**) should form the basis of a general approach to the synthesis of polyketide metabolites in which the aromatic system is biosynthesised by the orsellinic acid mode of cyclisation. The α-pyrone can be suitably modified by existing methods[6] and a suitable range of Wittig reagents is available.

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