Triacetic Acid Lactone† as a Polyketide Synthon: Synthesis of Toralactone and Polyketide-type Anthracene Derivatives

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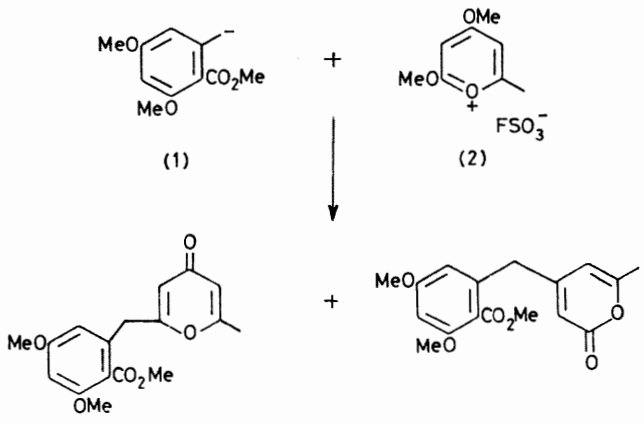
Summary Condensation of orsellinic and 6-methylsalicylic acid derivatives with triacetic acid lactone methyl ether gives naphthopyrones related to toralactone which can be converted in turn into polyketide-type anthracenes.

TRIACETIC ACID LACTONE† in the form of a derivative such as (**2**) or (**5**) has been used as a synthetic equivalent of 3,5-dioxohexanoate in several biomimetic syntheses of polyketide-type compounds.[1,2] In this and the following

† 4-Hydroxy-6-methylpyran-2-one.

communication we describe work which demonstrates further the potential in synthesis of this readily available compound.

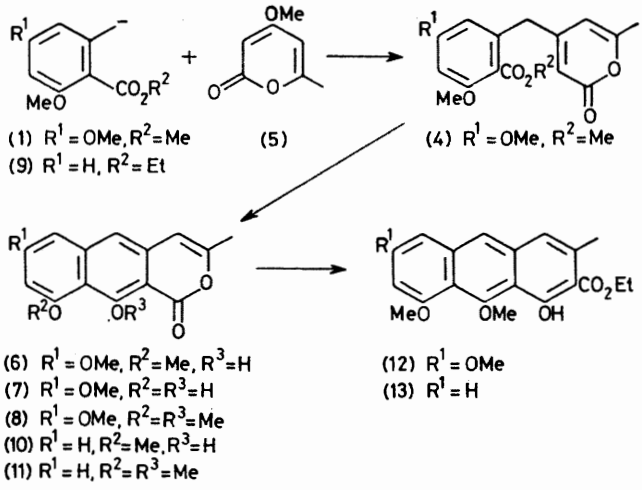
Following our recent report[2] that the reaction of the carbanion (**1**) with the pyrylium salt (**2**) gave, as the major product, the γ-pyrone (**3**) which provided the basis for the synthesis of two types of polyketide structure, we have identified one of the minor products of the reaction as the α-pyrone (**4**).‡ This compound also provides a convenient entry to polyketide-type compounds.



(1) (2) (3) (4)

Although it is only a minor product of the reaction mentioned above the α-pyrone is the major product (40%) when the carbanion (**1**) reacts with the methyl ether (**5**) of triacetic acid lactone in tetrahydrofuran (THF) at −78 °C for 1 h followed by work-up with HCl. The presence of an α-pyrone was suggested by the i.r. spectrum, ν_{max} 1735 cm^{-1} (aryl ester and α-pyrone). The ^1H n.m.r. spectrum was also consistent with the proposed structure; particularly significant were signals at δ 5·91 and 5·86 (each 1H, br. s, pyrone ring protons) and 3·67 (2H, br. s, CH_2).

The structure is confirmed by the following reactions which also establish the synthetic utility of the compound. On treatment with lithium di-isopropylamide in THF at −15 °C for 30 min, (**4**) was converted into the naphthopyrone (**6**) which is a derivative of the polyketide metabolite, toralactone (**7**). Methylation of (**6**) with diazomethane gave a product, m.p. 181 °C, whose properties were identical in every respect with those published for the dimethyl ether (**8**) of toralactone.[3]



(1) R^1 = OMe, R^2 = Me
(9) R^1 = H, R^2 = Et
(5)
(4) R^1 = OMe, R^2 = Me
(6) R^1 = OMe, R^2 = Me, R^3 = H
(7) R^1 = OMe, R^2 = R^3 = H
(8) R^1 = OMe, R^2 = R^3 = Me
(10) R^1 = H, R^2 = Me, R^3 = H
(11) R^1 = H, R^2 = R^3 = Me
(12) R^1 = OMe
(13) R^1 = H

The preparation of (**6**) from (**1**) and (**5**) can be carried out in one step if the reaction mixture is allowed to warm to room temperature in the presence of excess of base so that (**4**) cyclises *in situ*. This one-step procedure compares favourably with the multistage process described recently by Hauser[4] for achieving essentially the same transformation, the conversion of (**9**) into (**11**). Using the method described above (**9**) can be converted into (**10**) in one step followed by methylation with diazomethane to give (**11**) in 48% yield. This efficient route to the naphthopyrones (**8**) and (**11**) also makes the polyketide anthracenes (**12**) and (**13**) readily accessible. Using the modified Reformatsky reaction described by Hauser[4] we have prepared (**12**), m.p. 152—154 °C; the corresponding tetraphenolic acid is the probable precursor of a large number of polyketide anthraquinones.

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‡ All new compounds gave spectroscopic and analytical data consistent with the proposed structure.

[1] J. D. Bu'Lock and H. G. Smith, *J. Chem. Soc.*, 1960, 502; T. Money, *Chem. Rev.*, 1970, **70**, 553, and references cited therein; J. L. Bloomer, S. M. H. Zaidi, J. T. Strupezewoki, C. J. Brosz, and L. A. Gudzyk, *J. Org. Chem.*, 1974, **39**, 3615; D. A. Griffin and J. Staunton, *J.C.S. Chem. Comm.*, 1975, 675; H. Stockinger and U. Schmidt, *Annalen*, 1976, 1617.
[2] F. J. Leeper and J. Staunton, *J.C.S. Chem. Comm.*, 1978, 406.
[3] S. Takahashi and M. Takido, *J. Pharm. Soc. Japan*, 1973, **93**, 271.
[4] F. M. Hauser and R. P. Rhee, *J. Amer. Chem. Soc.*, 1977, **99**, 4533.