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DIRECTED METALLATIONS OF 4-ETHYLIDENETETRONIC ACID AND ITS DERIVATIVES AS A SYNTHETIC ENTRY TO NATURAL 4-OXY-2-FURANONES

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Summary: Lithium diisopropylamide (LDA) removes the α-proton from the O-methyl tetronic acid (2b) leading to the vinylic carbanion (12), whereas treatment of the trimethylsilyl derivative (14) with LDA, followed by reaction with aldehydes gives products resulting from both γ- and ε-addition; the directed metallations provide access to a range of 4-oxy-2-furanone derivatives found amongst natural products.

A wide variety of compounds containing the 4-oxy-2-furanone moiety (1) are found in Nature, and many display useful biological properties e.g. aspertetronins (3)[1], obtusilactones (4)[2] and ylidenetetronic acids (5).[3] As a synthetic entry to molecules within these classes of natural products, we have investigated the reactivity of metallated species derived from the ethylidene tetronic acid (2a). In this *Letter*, we show that with selected conditions, using appropriate derivatives of (2a), it is possible to control α-, γ- or ε-substitution within (2) to produce derivatives containing the 4-oxy-2-furanone substitution patterns found in compounds (3), (4) and (5). In the accompanying *Letter*, we describe the extension of this study to a total synthesis of the aspertetronin A structure (3).

4-Ethylidenetetronic acid (2a) is conveniently prepared on a large scale by a modification of the procedure described by Fleming and Harley-Mason.[4] It is smoothly converted into the corresponding O-methyl ether (2b) by conversion to the tetrabutylammonium salt followed by treatment with dimethyl sulphate.[5]

As anticipated, reaction between (2a) and a range of aromatic aldehydes (EtOH, reflux) led exclusively to the products (6) of α-substitution.[6] These products however, could not be isolated, but instead underwent spontaneous elimination (*in situ*) producing *Z*-*E*-mixtures of the enediones (7) which in most instances, even with a four-fold excess of the aldehyde, reacted further with the anion produced from (2a) leading to the 2:1 adducts (8).

To our initial surprise, metallation of the O-methyl ether (2b) (LDA, -78°, THF) followed by reaction with a range of electrophiles, also led to products from exclusive α-substitution in (2*b*). Thus, methylation (MeI, -78°) led to (9) (58%), and acylation with methyl acrylate produced the α-(1,2-addition) product (10) (20%), τ 2.9 (dd, *J* 17.5 and 10, $C\underline{H}{:}CH_2$), 3.7 (dd, *J* 17.5 and 2, $:C\underline{H}H$), 4.15 (dd, *J* 10 and 2, $:CH\underline{H}$), 4.25 (q, *J* 7.5, $:C\underline{H}CH_3$), 5.86 (OMe), 8.04 (d, *J* 7.5, $:CH\underline{Me}$). In addition, reaction between the anion produced from (2*b*) and 3,4-dimethoxybenzaldehyde led to the crystalline carbinol (11) (57%), m.p. 111-112°, τ 3.97 (d, *J* 8.5, $C\underline{H}OH$), 5.94 (d, *J* 8.5, $O\underline{H}$), which on treatment with dilute hydrochloric acid could be converted into the enedione [7, Ar=3,4-$(OMe)_2C_6H_3$], (*Z*:*E* 2:1), λ_{max} (EtOH) 230 (18,700), 251 inf., 426 (20,500) nm.

In separate investigations, using deuterium labelling, we were able to establish that in all these latter reactions the deprotonations were occurring exclusively at the α-centre in (2*b*) leading to the vinyl anion (12). Thus, metallation (LDA, -78°) of (2*b*), followed by quenching with D_2O led to a mono-deuterated derivative of (2*b*)[i.e. (13)] (88%, > 90% deuterium by p.m.r.) which retained the resonances [τ 4.56 (q, *J* 7.5), 8.14 (d, *J* 7.5)] associated with the *Z*-ethylidene side chain, but not the α-C-H resonance at τ 4.86. Treatment of (13) with LDA at -90° and quenching with H_2O gave the tetronic acid O-methyl ether (2*b*) (94%) containing < 5% deuterium by p.m.r. Related selective deprotonations at centres adjacent to carbonyl in a pyrone ring and other O-heterocyclic systems have recently been reported by two research groups.[7,8]

The metallations could be 'directed' to the γ- and ε-sites in (2*b*) by prior conversion to the α-trimethylsilyl derivative (14) (LDA, -78°; Me_3SiCl) (77%). When this derivative was treated with LDA followed by benzaldehyde, the γ-substituted furanone (15) ($\sim$ 70%) τ 2.8 (5H), 3.91 (dd, *J* 16.5 and 10.5, $C\underline{H}{:}CH_2$), 4.5 (dd, *J* 16.5 and 2, $:C\underline{H}H$), 4.71 (dd, *J* 10.5 and 2, $:CH\underline{H}$), 5.12 ($C\underline{H}.OH$), 6.19 (OMe), 9.73 ($SiMe_3$) was obtained; the carbinol was unstable, and during short periods of storage underwent (retro ene-type?) decomposition producing the methyl ether (14). Attempts to alkylate at the γ-centre in (14) were less successful, and treatment of (14) with LDA followed by acetyl chloride led to the enol acetate (16) (76%) ν_{max} 1790 cm^{-1}, τ 6.2 (OMe), 7.75 (OCOMe). Interestingly, the only product isolated from reaction between propionaldehyde and the metallated trimethylsilyl derivative (14) was the relatively stable secondary carbinol (18) (17%). This carbinol, which is probably the thermodynamic product produced from (17) (kinetic product) by retroaldol-realdolisation, furnishes the polyene (19), λ_{max} (EtOH) 292 nm, on treatment with sulphuric acid in T.H.F.

Work is now in progress to further investigate the synthetic potential of metallated species derived from (2) and related O-heterocycles.

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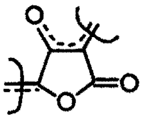

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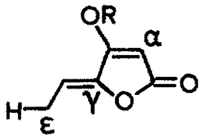
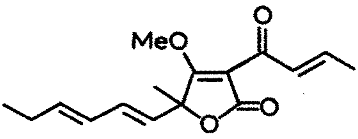


(2)

a, R=H; b, R=Me



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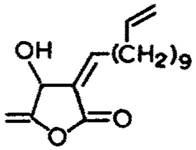

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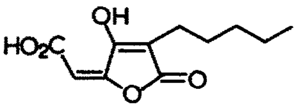

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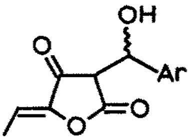

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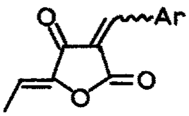

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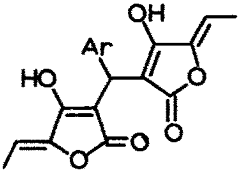

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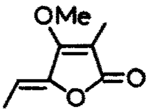

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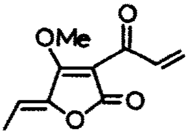

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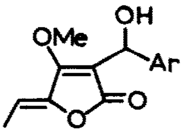

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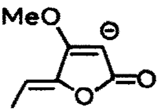

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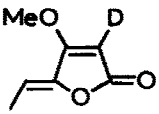

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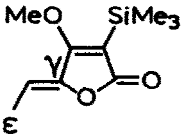

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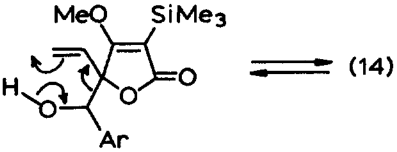

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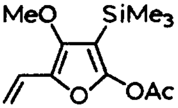

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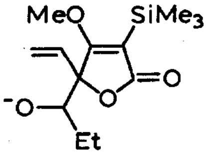

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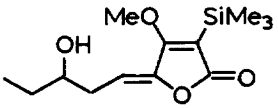

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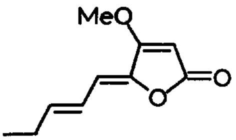

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