

M. Moreno-Mañas\* and R. Pleixats

Department of Chemistry, Universitat Autònoma de Barcelona,  
Bellaterra, 08193-Barcelona, Spain

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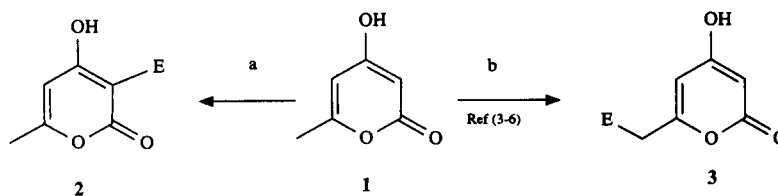
Triacetic acid lactone methyl ether, **4**, can be lithiated at C-3 under kinetically controlled conditions. Further reaction with (*E*)-2-methyl-3-(4-nitrophenyl)propenal results in an unusual condensation at C-3.

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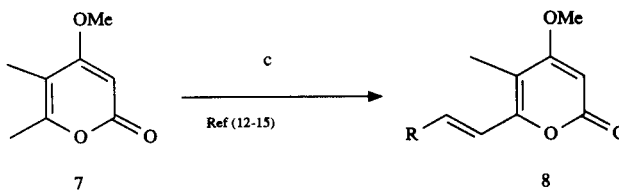
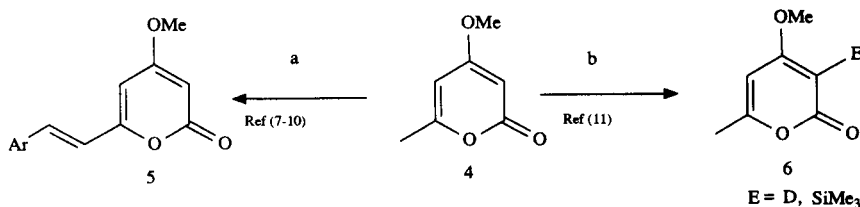
4-Hydroxy-6-methyl-2-pyrone (triacetic acid lactone), **1**, is a natural product [1] which can be prepared by deacetylation of the industrially available 3-acetyl-4-hydroxy-6-methyl-2-pyrone (dehydroacetic acid) [2]. Pyrone **1** reacts with a broad range of electrophiles at the activated C-3 position to afford products of the general structure **2** (Scheme I). However, the use of two equivalents of a strong base followed by quenching with electrophiles results in reaction at the methyl group at C-6 to produce compounds **3** (Scheme I). This dianion chemistry developed by Harris [3] has been successfully used by others [4-6].

The strong activation of position C-3 is no longer present in the methyl ether of **1**, the pyrone **4**. Treatment of **4** with aromatic aldehydes in the presence of magnesium methoxide in refluxing methanol has been reported by several groups to yield pyrones **5** arising from activation of the methyl group at C-6 [7-10] (Scheme II).

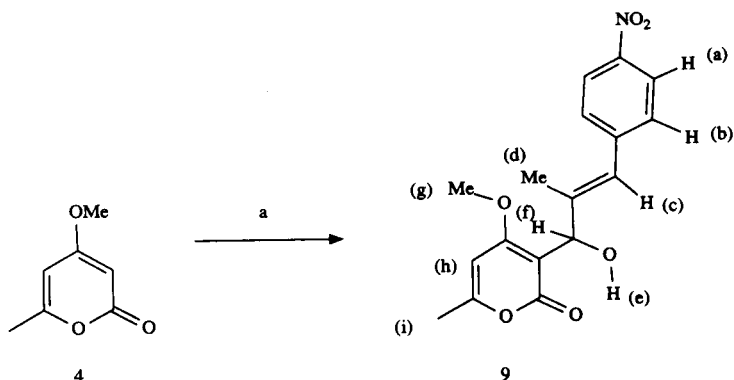
However, in 1980 Staunton and co-workers reported [11] that treatment of **4** with one equivalent of either lithium diisopropylamide or *n*-butyllithium in THF at  $-78^\circ$  followed by quenching with deuterium oxide or with trimethylsilyl chloride produced compounds **6** from attack at C-3 (Scheme II). Staunton and co-workers suggested that kinetically controlled lithiation takes place at C-3 whereas thermodynamically controlled metallations occur at the methyl group at C-6. Since then, several condensations of 4-methoxy-5,6-dimethyl-2-pyrone, **7**, under conditions close to those used by Staunton have been reported to occur at the carbon atom at C-6 rather than at C-3 (Scheme II). These reactions are steps in syntheses of naturally occurring 4-methoxy-2-pyrones such as asteltoxin [12-13] and citreoviridin [14-15]. Also, 5-ethoxycarbonyl-4-methoxy-6-methyl-2-pyrone has been lithiated at the methyl group [16]. These reports seem to be in contradiction with Staun-



Scheme I. a.- Electrophile. b.-i: Strong base (2 equivalents); ii: Electrophile.



Scheme II. a.- Magnesium methoxide, refluxing methanol, Ar-CHO. b.- i: LDA or *n*-BuLi, THF,  $-78^\circ$ ; ii: Deuterium oxide or Me<sub>3</sub>Si-Cl. c.- i: LDA, THF  $-78^\circ$ ; ii: R-CHO.



Scheme III. a.-i: *n*-BuLi, THF,  $-78^{\circ}$ ; ii: (*E*)-4-O<sub>2</sub>N-Ph-CH=C(CH<sub>3</sub>)-CHO.

ton's results. However, it is difficult to ascertain what the role of the additional substituent at C-5 is.

Therefore, from the above data it could be concluded that condensations of pyrone **4** at its C-3 position are exceptional.

However, we now want to report a condensation which is totally in agreement with Staunton's results. Thus, reaction of **4** with *n*-butyllithium in THF at  $-78^{\circ}$  followed by reaction with (*E*)-2-methyl-3-(4-nitrophenyl)propenal afforded 3-(1-hydroxy-2-methyl-3-(4-nitrophenyl)-(*E*)-2-propen-1-yl)-4-methoxy-6-methyl-2-pyrone, **9**, (Scheme III) in 65% yield as the only isolated product.

Structure **9** is evident from the pmr (deuteriochloroform) spectrum (see Table) which shows two absorptions due to both methyl groups. The hydrogen bridged hydroxylic proton (e) gives a doublet at  $\delta$  4.83 ( $J_{ef} = 11.1$ ) whereas the methine proton (f) presents a doublet at 5.39 with the same coupling constant. Upon deuterium oxide addition the signals of (e) disappeared and those of (f) became a singlet. NOEDIFF experiments permitted both the assign-

ment of the *E* configuration to the double bond and the determination of the preferred conformation of the molecule which is as indicated. Thus, upon irradiation at 1.87 (protons (d) of the methyl group at the side chain) signals for (f) gave  $\eta = 15.8\%$  but no NOE effect was detected for the ethylenic proton (c) at 6.67 thus indicating their mutual *trans* relationship. Moreover, a value  $\eta = 4.7\%$  was observed for the signals of the (b) protons at 7.39. These experiments are consistent with the *E* configuration of the double bond.

Irradiation at 3.97 (protons (g) of the methoxy group) gave a NOE effect  $\eta = 25.2\%$  upon the signal at 6.18 (proton (h)). No other NOE effects were apparent. This rules out a possible hydrogen bridge between the hydroxylic proton and the lone pairs of the ether oxygen atom. Further evidence for the hydrogen bridge existing through the carbonyl group is the low frequency stretching absorption of the last in the ir spectrum (potassium bromide) which appears at  $1680\text{ cm}^{-1}$ . Careful analysis of the pmr spectra including decoupling of the signal at 1.87 (protons (d)) permitted evaluation of all chemical shifts and coupling constants as indicated in the Table.

Table

Pmr Spectrum (deuteriochloroform) of Pyrone **9**

Proton	$\delta$	J	Irradiation at 1.87 (d)	Irradiation at 3.97 (g)
(a)	8.14	$J_{ab} = 8.80$	---	---
(b)	7.39	$J_{bc} = 0.73$	$\eta = 4.7$	---
(c)	6.67	$J_{cd} = 1.40$ $J_{cf} = 1.50$	$\eta = 0.0$	---
(d)	1.87	$J_{df} = 0.70$	---	---
(e)	4.83 [a]	$J_{ef} = 11.1$	---	$\eta = 0.0$
(f)	5.39 [b]		$\eta = 15.8$	---
(g)	3.97		---	---
(h)	6.18	$J_{hi} = 0.85$	---	$\eta = 25.2$
(i)	2.32		---	---

[a] Disappears upon deuterium oxide addition. [b] Becomes a singlet upon deuterium oxide addition.

## EXPERIMENTAL

3-(1-Hydroxy-2-methyl-3-(4-nitrophenyl)-(*E*)-2-propen-1-yl)-4-methoxy-6-methyl-2-pyrone (**9**).

A 1.6M solution of *n*-butyllithium in hexane (2.3 ml, 3.68 mmoles) was dropwise added (syringe) under argon into a stirred solution of **4** [7] (420 mg, 3.0 mmoles) in anhydrous THF (16 ml) cooled to  $-78^{\circ}$ , the mixture becoming red. After 20 minutes a solution of (*E*)-2-methyl-3-(4-nitrophenyl)propenal [17] (573 mg, 3.0 mmoles) in anhydrous THF (4 ml) was slowly added from a syringe. The temperature was allowed to rise to ambient temperature and after 4 hours the mixture was treated with diluted hydrochloric acid and partitioned with dichloromethane. The organic layer was washed with water, dried and evaporated to afford a residue which was chromatographed through a column of silica

gel. Pyrone **9** (65% yield) had mp 138-142° dec (from 2-propanol); ir (potassium bromide): 3455, 1680, 1542, 1380, 1340  $\text{cm}^{-1}$ ; pmr (deuteriochloroform): see above; cmr (deuteriochloroform):  $\delta$  14.6, 20.2, 56.6, 70.0, 95.2, 103.8, 122.5, 123.1, 129.5, 142.7, 145.0, 145.9, 163.6, 164.3, 166.7; ms: m/e 91 (25), 77 (36), 69 (48), 60 (22), 57 (40), 55 (30), 51 (34), 45 (66), 43 (100), 42 (47).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{17}\text{NO}_6$ : C, 61.63; H, 5.17; N, 4.23. Found: C, 61.67; H, 5.39; N, 4.15.

#### Acknowledgements.

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