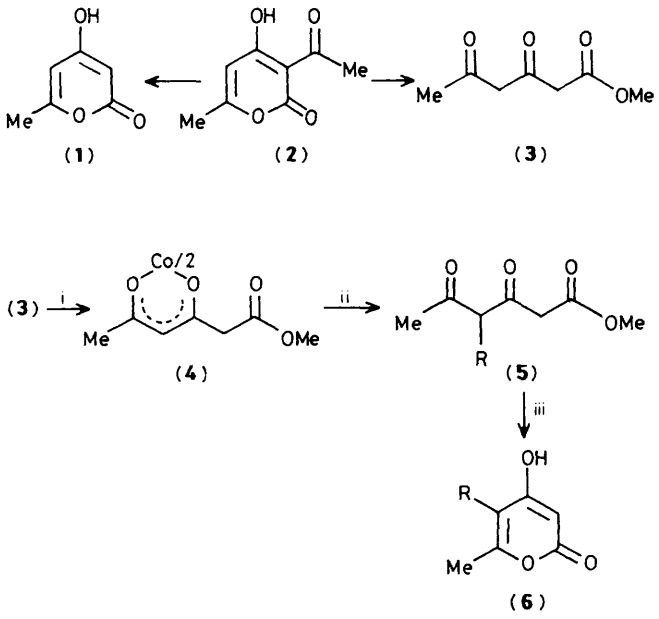
Cobalt Mediated Regioselective Alkylation of Methyl 3,5-Dioxohexanoate. Preparation of 5-Alkyl Derivatives of 4-Hydroxy-6-methyl-2-pyrone

Jordi Cervelló, Jorge Marquet, and Marcial Moreno-Mañas*

Departamento de Química, Universidad Autónoma de Barcelona, Campus de Bellaterra, 08193-Barcelona, Spain

The cobalt(II) complex of the simple polyketide model methyl 3,5-dioxohexanoate is regioselectively alkylated to afford methyl 4-alkyl-3,5-dioxohexanoates, which cyclize on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give 5-alkyl-4-hydroxy-6-methyl-2-pyrones.

An alkylation method for β-dicarbonyl compounds in the form of their cobalt(II) complexes has been reported.[1—3] The reactions of the corresponding complexes with benzylic and allylic halides and even with 1-bromoadamantane, in refluxing chloroform or chlorobenzene, give good yields of the *C*-monoalkylation products under essentially neutral conditions, no *O*-alkylation being observed. The commercially available 4-hydroxy-6-methyl-2-pyrone (**1**) (triacetic acid lactone) is a natural polyketide[4] and many related natural pyrones have been described with biogenetically relevant substituents at C-3 and C-5. Among those which have substituents at C-5, asteltoxin[5] and elasnin[6] have received particular attention.



Scheme 1. *Reagents and conditions:* i, aq. NaOH (1 equiv.) added at room temp. to a stirred mixture of (**3**), $Co(OAc)_2$, methanol, and water; ii, see text; iii, DBU, benzene, reflux.

Table 1. Reaction of (**3**) to give (**5**) and (**6**).

		% Yield		M.p., *t*/°C	
	R	(**5**)	(**6**)[a]	(**5**)	(**6**)
a	Ph_2CH	62	100	86—88	185—188
b	$Me_2C{=}CHCH_2$	42	98	Oil	140—143
c	PhCHMe	46	70	Oil	216—218
d	Fluoren-9-yl	33	96	Oil	159—161

[a] From (**5**).

Since (**1**) is easily accessible from the readily available acetylpyrone (**2**),[7] methods for the regioselective alkylation of (**1**) and its derivatives at C-3 and C-5 are desirable. Although a semigeneral method for alkylation at C-3 is available,[8] alkylations at C-5 have met with limited success,[9—11] and only by means of rearrangements from C-6.

Methyl 3,5-dioxohexanoate (**3**), a simple polyketide model, can be efficiently prepared from (**2**)[12] and is structurally related to (**1**). Regioselective alkylation of (**3**) and subsequent cyclization would afford, in addition to the products of regioselective alkylation of (**1**) at C-3 and C-5, an easy entry to phenolic natural polyketides.[13,14] However, conventional alkylation of (**3**) gives rise to a complicated array of products,[15] no regioselectivity having being observed. In fact, regioselective alkylation of poly-β-ketoesters is only possible at the terminal methyl group through polyanion chemistry.[16]

We report here some representative examples of cobalt mediated regioselective *C*-alkylation of (**3**) at C-4 and the cyclization of the resulting diketoesters (**5**) to 5-alkyl derivatives (**6**) of (**1**). Compound (**3**) forms the cobalt(II) complex (**4**) [m.p. 75—76 °C, i.r. (KBr) 1735 cm^{-1}] as a dihydrate. When complex (**4**) was boiled in chloroform for 24 h with diphenylmethyl bromide (2 equiv.), the 4-substituted ester (**5a**)† [*m/z* 223, $(MeCOCHPh_2)^+$] was obtained. Compound (**5b**) was similarly obtained from (**4**) and $Me_2C{=}CHCH_2Br$ (Table 1). The reaction of (**4**) with 1-bromo-1-phenylethane required evaporation of the chloroform and heating at 110 °C for 15 min, and a mixture of diastereoisomers of (**5c**) was formed as an oil in 46% yield. The ^1H n.m.r. spectrum of the mixture was complicated at 80 MHz, but the mass spectrum exhibited a peak at *m/z* 161 corresponding to $(MeCOCHCMePh)^+$. The diastereoisomers (**5c**) were converted into (**6c**) without further purification. 9-Bromofluorene in refluxing chlorobenzene afforded (**5d**) in 33% yield, which without further purification was converted into (**6d**).

Refluxing in benzene of the esters (**5**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1 equiv.) afforded the 5-alkyl-pyrones (**6a—d**) (Table 1).† The protons at C-3 give singlets at δ 5.3—5.6 that disappear upon exchange with protic deuteriated solvents, providing conclusive evidence for the site of alkylation since protons at C-5 in similar compounds appear at lower fields and do not exchange with solvent protons.[8—11]

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† ^1H N.m.r. data [$CDCl_3$ for (**5a**) and (**5b**); $(CD_3)_2SO$ for (**6a**); $CDCl_3$–CD_3OD for (**6b—d**); *J* values in Hz]: (**5a**), major diketo tautomer, δ 2.00 (s, 3H), 3.09 (d, 1H, *J* 16), 3.43 (d, 1H, *J* 16), 3.60 (s, 3H), 4.70 (d, 1H, *J* 12), 4.90 (d, 1H, *J* 12), and 7.2 (deceptive s 10 H). (**5b**), major diketo tautomer, δ 1.62 (br. s, 3H), 1.70 (br. s, 3H), 2.19 (s, 3H), 2.55 (br. dd, 2H, *J* 7, 7), 3.50 (s, 2H), 3.75 (s, 3H), 3.80 (t, 1H, *J* 7), and 5.00 (br. t, 1H, *J* 7). (**6a**), 2.00 (s, 3H), 5.3 (s, 1H), 5.7 (s, 1H), and 7.0—7.4 (m, 10H). (**6b**), δ 1.75 (br. s, 6H), 2.26 (s, 3H), 3.08 (br. d, 2H, *J* 7), 5.05 (br. t, 1H, *J* 7), and 5.43 (s, 1H, exchangeable). (**6c**), δ 1.7 (d, 3H, *J* 7), 2.1 (s, 3H), 4.4 (q, 1H, *J* 7), 5.45 (s, 1H, exchangeable), and 7.2 (5H). (**6d**), δ 1.14 (s, 3H), 5.56 (s, 1H), 5.64 (s, 1H), 7.1—7.5 (m, 6H), and 7.7—7.95 (m, 2H). The existence of two diastereoisomers of (**5c**), each being present in keto and enol forms, and the presence of enol forms in (**5d**) with hindered rotation caused the ^1H n.m.r. spectra of these products to be uninformative.