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LITHIATED DIHYDROPYRANS AS KETONE ENOLATE EQUIVALENTS: A MODEL STUDY FOR THE HERBICIDINS

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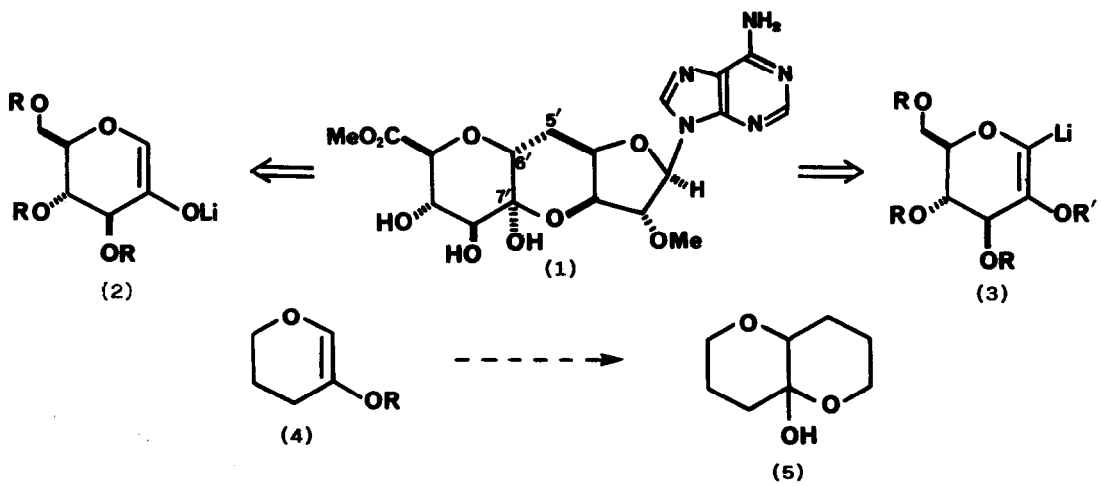
Summary: The synthesis of 6-lithio-5-methoxy-3,4-dihydro-2H-pyran (6) and its use as a regiospecific ketone enolate equivalent is described for the first time. This anion has been used to prepare the bicyclic hemiketal (5), a synthetic model for herbicidin B (1).

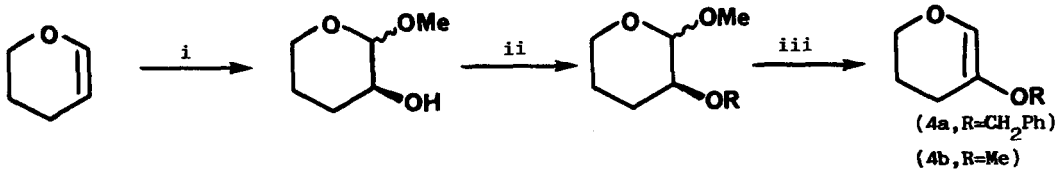
The herbicidins, illustrated below by herbicidin B (1), are a structurally unusual group of tricyclic nucleosides containing both a C-glycoside linkage (C-5 - C-6) and an adjacent hemiketal function (C-7).[1]

Any synthetic effort in this area must take account of the relationship between these two structural features, with the carbohydrate-derived enolate (2) emerging as a logical precursor. However access to this enolate, by deprotonation of the corresponding ketone, is not a trivial matter since in related systems (including carbohydrate-derived ketones) the observed mode of enolization is away, rather than towards, the conformationally constrained ring oxygen atom.[2]



ß-Lithiated enol ethers have previously been used as enolate equivalents[3] and an alkenyl anion such as (3) could therefore function as a synthetic eqivalent of the regiospecific enolate (2)[4]. With this strategy in mind we have undertaken a model study, the synthesis of the bicyclic hemiketal (5), which is based on the lithiation of a 5-alkoxy-3,4-dihydro-2H-pyran (4).[5]

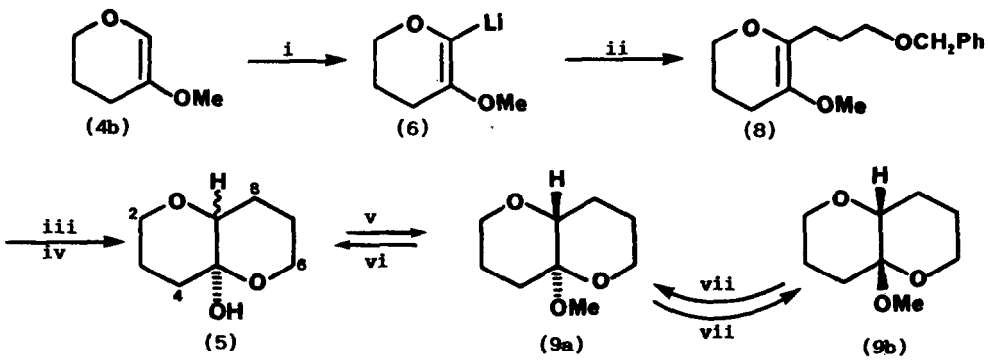
The required alkoxydihydropyrans (4a, R = CH_2Ph) and (4b, R = Me) were available in a four step sequence, starting from dihydropyran, as shown in Scheme 1.



SCHEME 1. Reagents:i,mCPBA,MeOH(85%);ii,NaH,DME,$PhCH_2Br$(95%) or MeI(98%); iii,H_3O^+,then $MeSO_2Cl$,NEt_3(R=CH_2Ph,47%; R=Me,48%).

Metallation [Bu^tLi, THF, -78°C] of (4a) proceeded smoothly. However addition of allyl bromide to the resulting anion led only to the product derived from benzylic deprotonation. No evidence for the formation of an alkenyl anion was observed.

This complication does not arise with the methoxy derivative (4b) which underwent metallation [Bu^nLi, THF, 0°C to 50°C] to give alkenyl lithium (6). Alkylation of this species with the bifunctional electrophile (7, R = CH_2Ph) gave adduct (8) and enol ether cleavage followed by hydrogenolysis of the resulting ketone gave bicyclic hemiketal (5) in 42% overall yield from (4b) (Scheme 2).

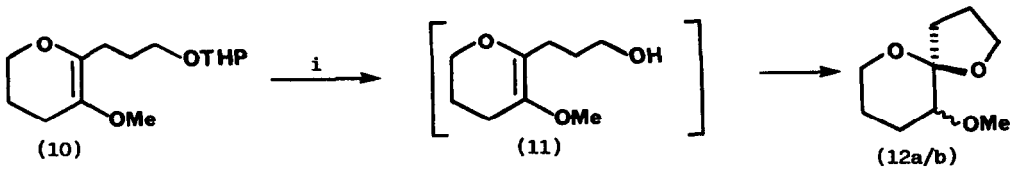


SCHEME 2. Reagents:i,Bu^nLi,THF,0°C to 50°C;ii,I⌇⌇OR(7,R=CH_2Ph)(65%); iii,Me_3SiCl,NaI,MeCN(70%);iv,H_2,10%Pd on C(93%);v,MeOH,H^+(98%);vi,H^+(98%);vii,MeOH,H^+.

Although the *cis* -configuration of hemiketal was (5) adopted in the crystalline state[6], (ORTEP diagram of *cis*-(5) is shown in Figure 1), ^1H nmr spectroscopy revealed that, on dissolution, an equilibrium was rapidly established in which *cis*- and *trans* - (5) were present in approximately equal amounts. Methanolysis of (5) gave a 1:1 mixture of the readily separable bicyclic ketals (9a) and (9b); these ketals underwent both equilibration with one another and hydrolysis back to hemiketal (5).[7]

In principle a more direct route to (5) is available if the ketone and primary hydroxyl functions can be released under the same reaction conditions, rather than in a stepwise fashion. Accordingly the THP-protected adduct (10) was prepared, in 54% yield, by reaction of (6) with (7, R = THP). However exposure of (10) to aqueous acid failed to give hemiketal (5), instead a 1:1 mixture of spiroketals (12a) and (12b) were isolated (Scheme 3).[8] Some evidence has been obtained for the intermediacy of alcohol (11) and

clearly protonation of the enol ether and the subsequent mode of cyclisation is being controlled by the ring oxygen atom. Attempts were made to interconvert the fused and spiro bicyclic ketals [(9a/b) ⇌ (12a/b)] but, even under forcing conditions, these failed.

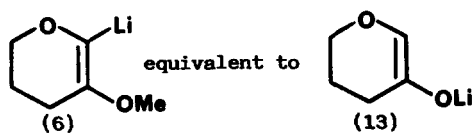


(10) (11) (12a/b)

SCHEME 3. Reagents: i, H_3O^+ [1:1 mixture of (12a/12b) (60%)]

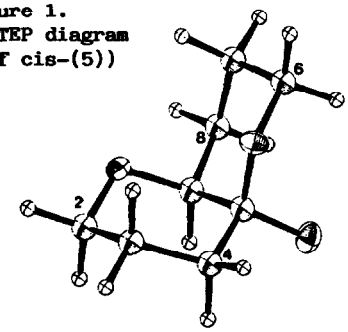
In summary, lithiation of (4b) provides alkenyl anion (6), a convenient synthetic equivalent of the regiospecific enolate (13). The bicyclic hemiketal (5) has been prepared in a straightforward manner but the choice of protecting groups is crucial to the success of this sequence.

We are currently extending the application of this methodology to encompass the more complex alkoxyglucal (3),[9] with a synthesis of herbicidin B as our objective.



(6) (13)

Figure 1. (ORTEP diagram of cis-(5))



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References and Notes

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