O- and *C*-Acylation of some Carbohydrate Enolates

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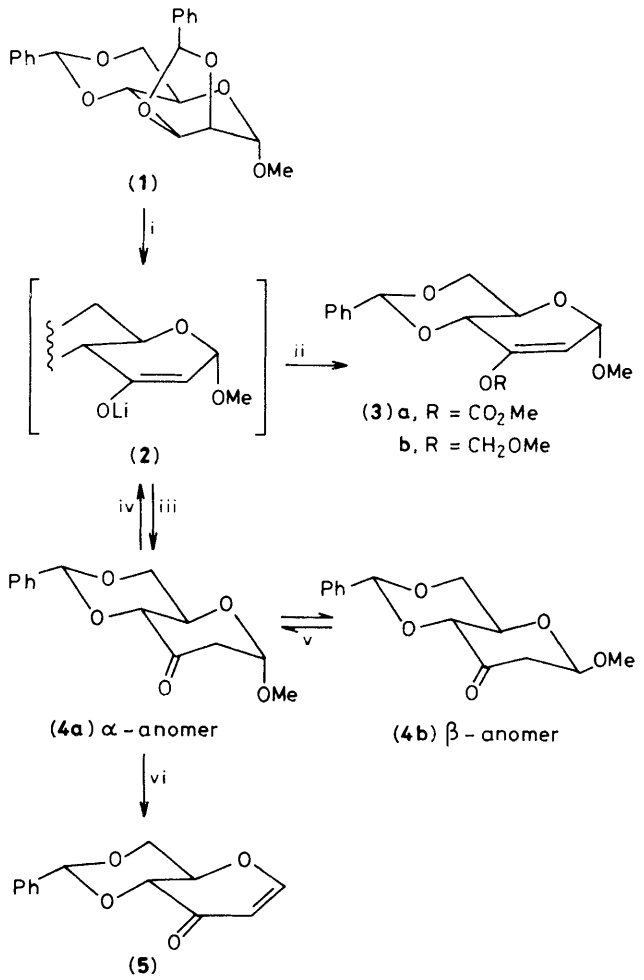
The enolate derived from methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose undergoes *O*-acylation exclusively with a variety of reagents, whereas *C*-acylation is successful only with the corresponding *C*-glycosyl derivatives.

A recent report by Chapleur[1] on the alkylation of the lithium enolate (**2**) obtained by the Rodemeyer reaction[2] of the bisbenzylidenated mannopyranoside (**1**) prompts us to disclose our own results on the *O*- and *C*-acylation reactions of similar systems. The study arose from our interest in β-keto esters, for example (**11**), for possible cyclization to an oxa *cis*-decalin.

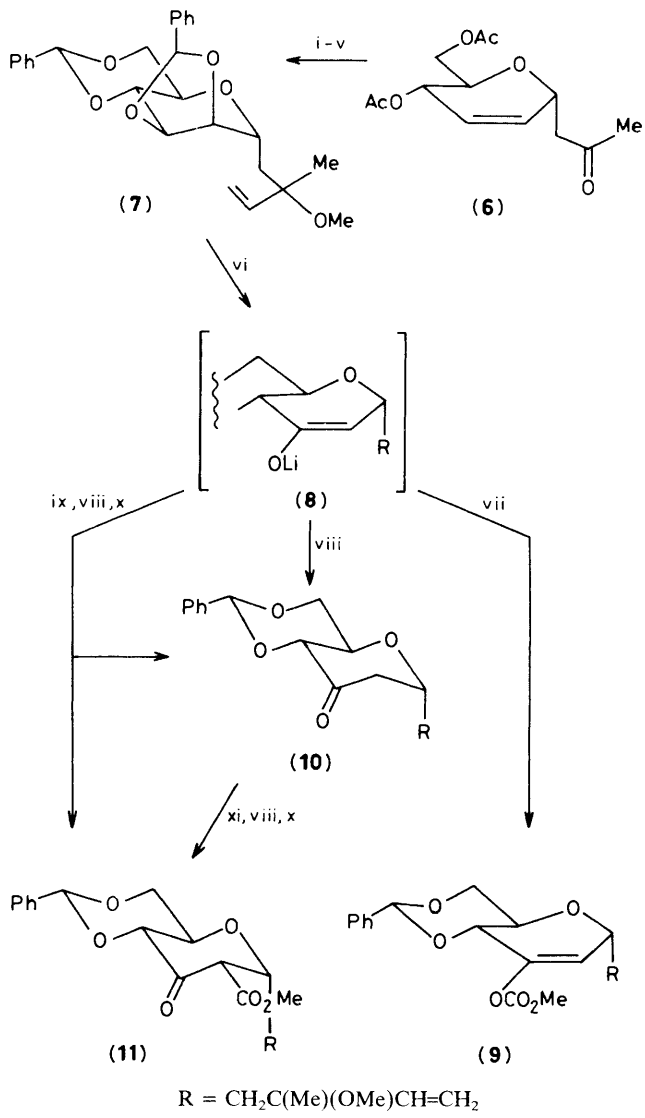
Although (**11**) is a *C*-glycopyranoside, we decided to

Table 1. Reactions of enolates derived from (**1**) and (**4a**) with electrophiles.

Entry	Substrate	Base	Enolate	Electrophile	Product	Yield/%
1	(**1**)	Bu^nLi	(**2**)	$ClCO_2Me$	(**3a**)	85
2	(**4a**)	$(Me_3Si)_2NLi$	(**2**)	$ClCO_2Me$	(**9**)	90
3	(**1**)	Bu^nLi	(**2**)	$ClCH_2OMe$	(**3b**)	70
4	(**4a**)	$(Me_3Si)_2NLi$	(**2**)	$ClCH_2OMe$	(**3b**)	82
5	(**1**)	"	(**2**)	$(MeO)_2CO$	(**4a**)	70—80
6	(**1**)	"	(**2**)	EtOCHO	(**4a**)	70—80
7	(**1**)	"	(**2**)	Carbonyl di-imidazole	(**4a**)	70—80
8	(**1**)	"	(**2**)	CO_2	(**4a**)	70—80
9	(**4a**)	NaH	Sodium analogue of (**2**)	$(MeO)_2CO$	Unchanged (**4a**)	



Scheme 1. i, Bu^nLi; ii, RX; iii, H^+; iv, $LiN(SiMe_3)_2$ or lithium di-isopropylamide; v, NaOMe; vi, $BF_3{\cdot}Et_2O$



Scheme 2. i, $KMnO_4$–H_2O–EtOH, −10 °C; ii, Et_3N–H_2O–MeOH; iii, $PhCH(OMe)_2$, camphor sulphonic acid, MeCN; iv, $CH_2{=}CHMgBr$; v, NaH–MeI–Bu^n_4NI–tetrahydrofuran; vi, Bu^nLi; vii, $ClCO_2Me$; viii, H^+; ix, CO_2; x, CH_2N_2; xi, methyl magnesium carbonate.

examine first the *O*-glycoside (**1**) whose reactions with n-butyl-lithium have been thoroughly studied by Rodemeyer[2] and Horton.[3] Thus the enolate formed (**2**), was quenched with methyl chloroformate or chloromethyl methyl ether; however, electrophilic attack occurred only at oxygen to give (**3a**) or (**3b**) respectively (Scheme 1).† Under similar conditions, no reaction was observed with a number of other acylating agents listed in entries 5—8 of Table 1, the product in these cases being the ketone (**4a**).[4] The enolate generated from ketone (**4a**) with lithium hexamethyldisilazane, behaved similarly, as indicated in entries 2 and 4 of Table 1. With sodium hydride and dimethylcarbonate (entry 9) neither *O*- nor *C*-acylation was observed. However, treatment of ketone (**4a**) with the Stiles' reagent[5] in order to effect *C*-acylation led, not surprisingly, to the formation of several products.

In view of the constant threat of β-elimination during these reactions, it is of interest to note that we were unable to obtain the known enone (**5**)[6] by treatment of (**4a**) with diazabicyclononane. With sodium methoxide and methanol, (**5**) was also not isolated; however, its intermediacy was apparent from the isolation of both anomers for (**4**) (**a** and **b** respectively α and β) as crystalline compounds. The transformation of (**4a**) into (**5**) was achieved with $BF_3{\cdot}Et_2O$ in 70% yield.

Our studies with *C*-glycosides utilized compound (**7**)† prepared from (**6**)[7] by the standard processes indicated in Scheme 2. The enolate (**8**), generated in the usual way, was quenched with methyl chloroformate to afford the expected *O*-acylated product (**9**).† In contrast to the result with (**1**) (Table 1, entry 8), reaction of (**8**) with gaseous carbon dioxide followed by esterification with diazomethane did lead to the desired β-keto ester, product (**11**),†‡ albeit contaminated with the ketone (**10**). It transpired that the preferred route to (**11**) involved isolation of ketone (**10**) followed by carbonation with the Stiles' reagent.‡[5]

The predominant *O*-acylation observed, is consistent with the Hard and Soft Acids and Bases theory applied to the

† All new compounds gave satisfactory spectroscopic data and high resolution mass spectrometry or elemental analyses.

‡ We have found that the success of this reaction is *highly dependent* on the source of the Stiles' reagent. The preparation described in *Org. Syn.*, Coll. Vol. V, 439, was found to be the most satisfactory.

reactions of enolates,[8] on the assumption that acylium ions are hard acids. The *C*-alkylation reactions observed by Chapleur[1] are also rationalizable, since alkyl bromides can be regarded as soft acids.

Our studies with the cyclization of (**11**) are currently underway and will be reported in due course.

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