Carbohydrates as Chiral Templates: Reactivity and Stereoselectivity of Carbohydrate Ester Enolates

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As a result of intramolecular co-ordination of the lithium ion, carbohydrate ester enolates show peculiar properties: decomposition above −70 °C to form alcoholate and ketene, stereoselective alkylation at very low temperature, and, for those containing strongly complexing ligands, inertness towards carbon electrophiles.

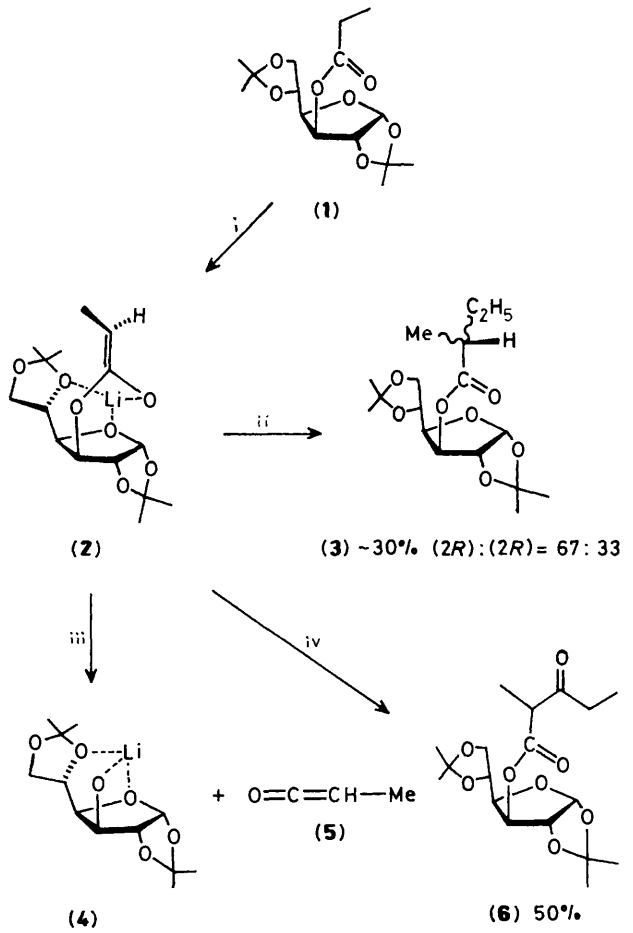
Ester enolates of camphor-derived alcohols have been successfully used in the stereoselective synthesis of α-branched carboxylic esters.[1,2] The direction of asymmetric induction can be rationalised as a front-site attack of the electrophile, but only for sterically shielding frameworks. If the shielding group contains complexing heteroatoms, an unexpected reversal of the induction has been found.[1] Similar unexplained effects of complexing groups have been reported for reactions of amide enolates.[3,4]

Continuing our studies on the use of carbohydrates as chiral templates in asymmetric synthesis,[5] we have investigated carbohydrate ester enolates.[6] Carbohydrates have a pronounced complexing ability towards cations. Here, we describe three formerly unobserved effects arising from the intramolecular complexation of the lithium cation in carbohydrate ester enolates: i, carbohydrate ester enolates decompose above −70 °C to give ketenes; ii, depending on the carbohydrate structure, they can be alkylated diastereoselectively in

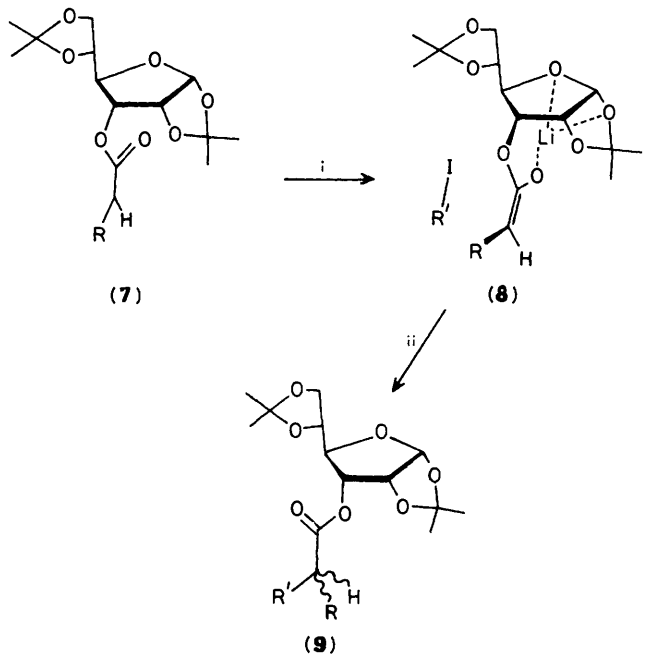
the absence of polar compounds at very low temperature, but, iii, if the carbohydrate framework contains strongly complexing ligands, the ester enolate is completely unreactive towards carbon electrophiles.

The enolate (**2**) of the 3-O-propionyl-α-D-glucofuranose derivative (**1**) reacts with ethyl iodide at −70 °C to give the 2-methylbutyrate (**3**) in low yield and diastereoselectivity. In addition to the product of O-alkylation, compound (**6**) is formed in 50% yield, apparently a result of an ester condensation. This unexpected result can be understood on observing that the enolate (**2**) slowly decomposes even at −70 °C to give the alcoholate (**4**) and the ketene (**5**). This decomposition can be proven by trapping the alcoholate (**4**) at −60 °C as the silyl ether using trimethylsilyl chloride. Also, the ketene can be trapped with *N*-phenylbenzaldimine to give the corresponding β-lactam. Ketene formation from ester enolates normally requires markedly higher temperatures.[7] In the case of (**2**) it is strongly favoured since the intramolecular complexation renders the carbohydrate (**4**) a good leaving group. The ketene (**5**) with intact (**2**) forms the unexpected product (**6**). (**5**) also reacts with (**4**) to reform (**2**) as a *Z*/*E*-mixture which was supported by n.O.e. experiments on the corresponding silyl ketene acetals. The *Z*,*E*-mixture (**2**) is responsible for the low diastereoselectivity of the alkylation (Scheme 1).

The esters of D-allofuranose (**7**) form only the *Z*-enolates (**8**) after deprotonation at −90 °C (n.O.e. on silyl ketene acetals). They are essentially more reactive than (**2**). Without addition of activating compounds, *e.g.* hexamethylphosphoric triamide (HMPTA), they are alkylated at −95 °C. The yields and diastereoselectivities in the formation of the branched carboxylic esters (**9**) (see Table 1) are distinctly higher than those achieved in the ethylation of (**2**).



Scheme 1. *Reagents and conditions:* i, lithium di-isopropylamide (LDA), tetrahydrofuran (THF), −78 °C; ii, EtI, −70 °C; iii, −70 °C; iv, O=C=CH–Me (**5**).

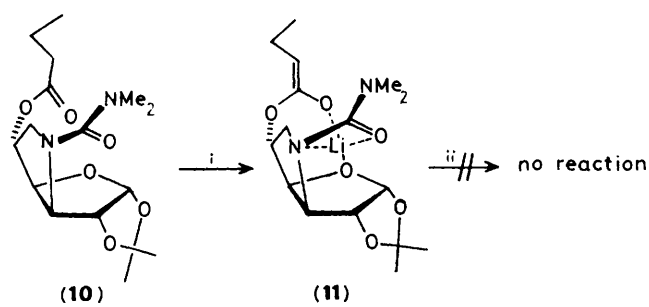


Scheme 2. *Reagents and conditions:* i, LDA, THF, −90 °C; ii, R'I, −95 °C.

Table 1. Asymmetric alkylation of ester enolates (**8**) according to Scheme 2

Enolate	R	R'	Yield (%)	Diastereoselectivity[a] (**9**)	(*R*):(*S*)
(**8a**)	Me	Et	27	(**9a**)	1:5
(**8b**)	Et	Me	65	(**9a**)	4.5:1
(**8c**)	Pr^n	Me	58	(**9c**)	4:1
(**8d**)	Pr^i	Me	75	(**9d**)	6:1
(**8e**)	Bu^t	Me	~100	(**9c**)	10:1
(**8f**)	Ph-$(CH_2)_2$	Me	55	(**9f**)	4:1
(**8g**)[b]	*o*-CH_3O-C_6H_4	Me	84	(**9g**)	1:5

[a] α-Me signal; 400 MHz ^{1}H n.m.r., configuration assignment in relation to the known 2-methyl butyrate. [b] *E*-Enolate.



Scheme 3. *Reagents and conditions:* i, LDA, THF, −78 °C; ii, MeI or PhCHO.

The unique pathway of the alkylations (Scheme 2) becomes evident in the alternative preference for the (2*S*)/(2*R*)-diastereoisomers (**9a**) starting either from (**8a**) or (**8b**). If the substituent R is large (**8d/8e**), a high yield and diastereoselectivity is achieved. In the case of (**8g**), the *E*-enolate is formed due to the complexing assistance of the *o*-methoxy group. Consequently, the (*S*)-diastereoisomer of (**9g**) is preferably obtained.

To estimate the influence of the complexing strength, we have deprotonated the butyrate (**10**) of the 3-imino-3,6-anhydro-glucofuranose. Surprisingly, the ester enolate (**11**) does not react with methyl iodide or with benzaldehyde at −70 °C (see Scheme 3). At higher temperature ketene formation (but not formation of an ester condensation product) occurs. Deuteriation using DCl/D_2O at −70 °C gives the deuteriobutyrate (70%).[8] The intertness of (**11**) towards carbon electrophiles suggests that the nucleophilicity of such enolates is only latent. For the reaction with electrophiles to proceed, the nucleophile must be liberated by an interaction between the lithium ion and the leaving group of the electrophile. In (**11**) the framework opposes this interaction and, consequently, the reaction fails.

It follows that in reactions of the enolates the electrophile is introduced from the lithium site. This may explain the observed stereoselectivity in the alkylations of (**2**) and (**8**) (see Scheme 2) and the reversals of asymmetric induction described earlier.[1,3,4] It is also in agreement with the interpretation of inductions observed on oxazoline enolates.[9]

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