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Remote Asymmetric Induction Observed in the Alkylation of Propionate Attached to a Carbohydrate Template[1]

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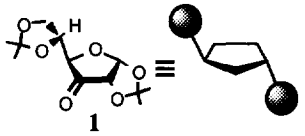
Abstract: *Alkylation of the enolates derived from the propionate esters **4a** and **4b** of 3-C-hydroxymethyl-glucose (**3**) derivatives was attempted, and remarkable remote asymmetric induction (up to 92% de) was observed.*

Asymmetric induction is a major issue of synthetic organic chemistry. Essential to this end is to provide a suitable stereogenic chemical environment. An intriguing question here is how far an accepting prochiral site can be apart from a stereogenic site for effective transfer of chirality.[2] Although several cases of remote chiral induction were reported,[3] most of the systems include an intervening prochiral π system (olefin or aromatic ring).[4] This communication is to describe our recent finding that, in certain chiral environments, effective transcription of chirality is achievable.

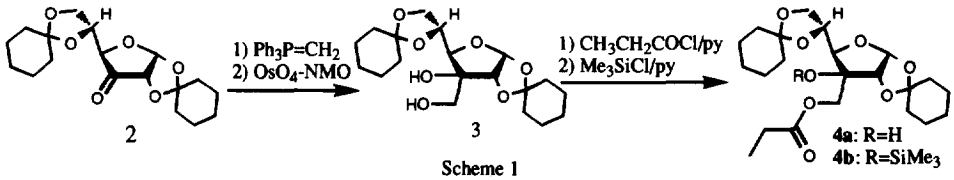
Diacetoneglucose-3-ulose **1** includes significant intrinsic merits as a stereogenic source[5]. One is easy accessibility and the other is its nature of a cyclopentanone-like structure with pseudo C_2 symmetry around C-3 of the furanose ring. This particular chiral template has been successfully utilized in both intermolecular as well as intramolecular chirality transcription.[6]



1

Figure 1

Benzylation of a propionate group attached to the carbohydrate template **1** was attempted under various conditions to explore the possibility of a remote chirality transcription on this system. Among those tested, the derivatives of 3-*C*-hydroxymethylglucose **3** were particularly interesting. The propionate ester **4a** of **3**, which had been prepared from dicyclohexylidene-glucos-3-ulose **2** *via* 1) Wittig reaction; 2) dihydroxylation; and 3) acylation, was further modified into the *O*-TMS **4b** as shown in Scheme 1.

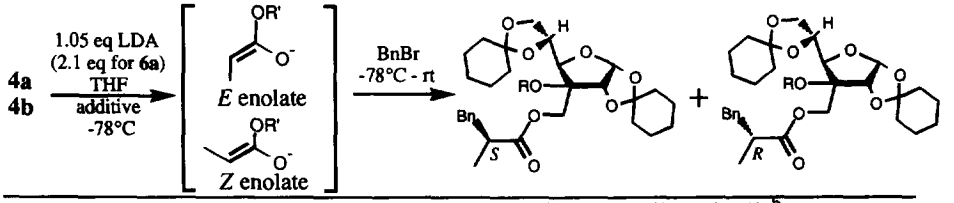


2 **3**

Scheme 1

Each enolate derived from these propionate esters **4a** and **4b** with LDA was alkylated under various conditions with benzyl bromide, and the results are summarized in Table 1. The geometry of each enolate formed was assigned by means of trapping as their TMS ketene acetals and ^{1}H NMR analysis.[7] The stereochemical outcome of each reaction was analyzed first by ^{1}H NMR analysis to estimate the diastereoselectivity and then by isolation of 2-methyl-3-phenylpropionic acid to determine the optical rotation.[8] As can be seen in Table 1, significant chirality transfer (92 and 91 % de) was observed in run 2 and 5, respectively. Simple reaction of an enolate with benzyl bromide afforded a poor yield (run 1) or a less sufficient selectivity (run 3), however, each additive (LiCl[9] or HMPA) played a key role to improve the yield and diastereoselectivity. It should be emphasized here that chirality was able to be transferred even to a remote prochiral site locating at the four-bonds away from a stereogenic center without any aid of relay-mechanism.

Table 1. Stereoselectivity in the alkylation of ester enolate derived from **4a** and **4b** with benzyl bromide.



run	ester	additive	*E*/*Z* of enolate[a]	yield (%)	de (%)[b]	conf.
1	**4a**	-	90 / 10	21	81	*R*
2	**4a**	LiCl (6 eq)	n.d.	60	92	*R*
3	**4a**	23% HMPA	>98 / <2	62	9	*R*
4	**4b**	-	6 / 94	28	43	*R*
5	**4b**	23% HMPA	>98 / <2	95	91	*S*

[a]The geometry of each enolate was assigned by derivatizing to the corresponding silyl ketene acetal, followed by ^{1}H NMR analysis. [b]de was estimated with ^{1}H NMR analysis. n.d; not determined.

It seems that, due to the participation of the free OH residing on C-3, a chelated 7-membered cyclic enolate I is formed as shown in Figure 2, thereby shielding effectively one of the diastereofaces of the enolate to control the approach of the electrophile.[10] The reason for good diastereoinduction of the silylated enolates, on the other hand, is probably due to the extended conformation of the enolate II.

In conclusion, it appears that the chiral environment around C-3 of the furanose ring of diacetone glucose is eventually significant in regulating the reactivity of prochiral π-system depending upon the reaction conditions, even in a rather remote location. These findings may encourage further exploitation of interesting and effective chiral spaces.

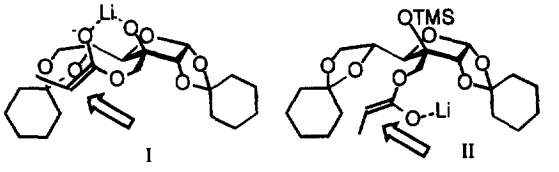


Figure 2

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