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INFLUENCE OF THE ESTER GROUP DURING THE ENANTIOSELECTIVE METHYLATION OF γ-ALDEHYDE ESTERS VIA THEIR CHIRAL OXAZOLIDINE DERIVATIVES

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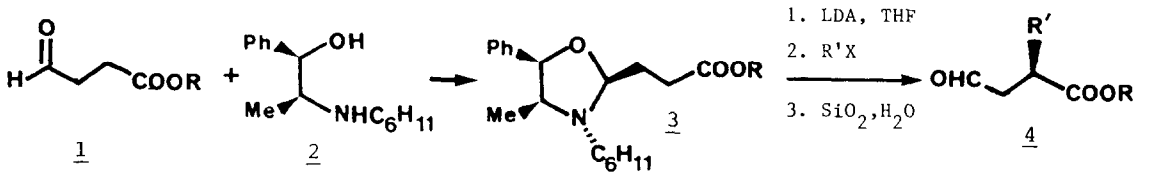
Abstract - Depending on the nature of the ester group, fair asymmetric induction (ee's up to 82%) can be attained in the title reaction.

γ-Aldehyde esters can be enantioselectively monoalkylated via their chiral oxazolidine derivatives, as shown in Scheme 1.[1] Moderate enantiomeric



Scheme 1

excesses (65% ee in the case of methylation, R'X = CH_3I) were thus attained with methyl ester (1 , R = CH_3). We wish to report that asymmetric induction is noticeably dependent upon the nature of the ester group.[2] Methylation by methyl iodide took place after LDA-mediated formation[5] of the ester enolate at -78° in THF and the aldehyde function was smoothly recovered by hydrolysis with wet silica gel. The resulting optically active products were analyzed by a previously reported method[6] and by chemical correlation with (R)(+)-2-methyl-1,4-butanediol.[1] An R absolute configuration was thus assigned to all methylated esters 4.

According to the ester group (R in Scheme 1), 4 (R'= CH_3) showed the following ee's (%) : methyl 65, t-butyl 75, benzyl 80, paramethoxybenzyl 80, orthomethoxybenzyl 71, 1-naphtylmethyl 65 , 2-naphtylmethyl 53 , (1S,2R,5S)-menthyl 64, (1R,2S,5R)-menthyl 82 .

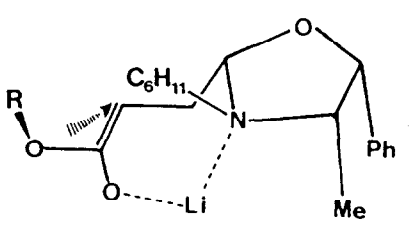


Figure 1

Provided that the orientation of the ester group is taken into account (vide infra) the chelated model which was put forward[1], in order to explain the stereochemistry of the alkylation,is consistent with the present results, as shown in Figure 1. The influence of the bulky cyclohexyl group which hinders the upper face of the enolate double bond has already been emphasized.[1] It should be noted

moreover that the use of such a nitrogen substituent induces the maximum diastereoselectivity during the oxazolidine ring formation : under thermodynamic control, which corresponds to the usual experimental conditions,[7] substrate 3 is obtained in the only stereoisomeric form shown in Scheme 1. Clearly the use of a diastereoisomerically pure starting oxazolidine is a favorable parameter.

On the other hand, crystal structure analyses[8] have shown that, contrary to what occurs in esters, the alkyl group on oxygen of ester enolates does not lie in the olefinic plane but is rotated away from the lithiated oxygen. This could explain why stereoselectivity is amenable to the nature of the ester group.

The use of menthyl esters, as second chiral auxiliaries in addition to the oxazolidine moiety,[9] shows that (1R,2S,5R)(−)-menthol led to the better stereoselectivity. This result can be rationalized by the above chelated model, the less reactive diastereoface being more hindered by the isopropyl group in the (−)-menthol-derived ester (Fig. 2A) than by the methyl group (Fig. 2B) in the (+)-menthol-derived stereoisomer (Fig. 2B).

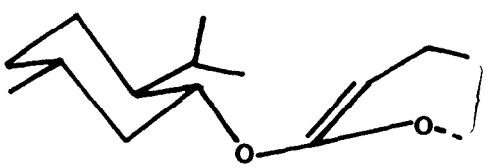


Figure 2A

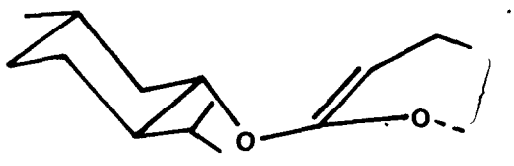


Figure 2B

We wish to thank Professor J.P. Pete for a stimulating discussion.

References and Notes

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2. The benzyl esters were produced via treatment of the cesium salt of semisuccinic aldehyde[3] with benzyl bromides, according to a procedure described for the synthesis of peptide esters.[4] Esters derived from non-primary alcohols were obtained by ozonolysis of the corresponding 4-pentenoic acid derivatives.
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5. Stereoselectivity was unaffected by the nature of the base : lithium diisopropylamide (LDA), lithium isopropylcyclohexyl amide (LICA), lithium tetramethylpiperidide (LTMP) and lithium hexamethyldisilylamide (LHMDS) gave the same results.
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9. For a recent example of synergistic effect in asymmetric synthesis, see : Yamamoto, Y.; Yamada, J. J. Chem. Soc., Chem. Commun. 1987, 1218.

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