Asymmetric Induction. Nucleophilic Addition to a Chiral Glyoxylate Ester

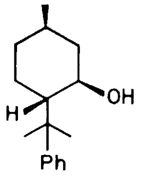
James K. Whitesell,* Apurba Bhattacharya, and Kevin Henke

Department of Chemistry, University of Texas at Austin, Austin, Texas 78712, U.S.A.

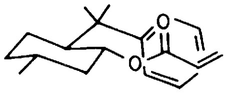
Reaction of Grignard reagents with the glyoxylate ester of 8-phenylmenthol afforded the derived α-hydroxyesters in high chemical yield with excellent levels of asymmetric induction (98.1—99.4%).

The construction of chiral, vicinal glycol systems with absolute stereochemical control by asymmetric induction represents a potentially valuable approach to the synthesis of certain classes of natural products such as the ionophore antibiotics. We present here a method for the formation of α-alkoxyesters by carbon–carbon bond formation with very high levels of asymmetric induction. These esters should be transformable into the desired glycol systems.

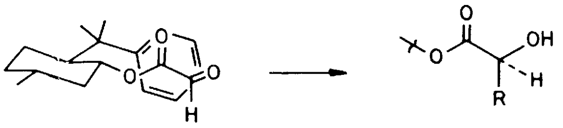
Corey and Oppolzer have shown that 8-phenylmenthol, (**1**), can be a highly effective chiral auxiliary for use in asymmetric induction. The acrylate ester, (**2**), undergoes Diels–Alder reactions,[1] cuprate additions,[2] and intramolecular ene reactions[3] with high levels of asymmetric induction. In these reactions it would appear that the conformation about the sigma bonds of the ester linkage is relatively fixed in the transition state. Thus, one face of the acrylate π-bond is exposed while the phenyl group effectively blocks the other side. We reasoned that the glyoxylate ester of (**1**) might undergo nucleophilic additions to the aldehyde carbonyl group through similarly rigid transition states.



(1)



(2)



(3) **(4)**

The α-bromoacetate ester of (**1**) was converted into the glyoxylate ester by oxidation using the procedure developed by Kornblum.[4] While the hydrate was obtained initially, the free aldehyde ester (**3**) was obtained by simple, vacuum distillation. We were quite encouraged to note that the aldehyde hydrogen absorbed at unusually high field (8.2 p.p.m.) in the ^{1}H n.m.r. spectrum, presumably because of magnetic shielding by the aromatic ring. Addition of 1 equiv. of methylmagnesium bromide to the glyoxylate in diethyl ether at 0 °C afforded the lactate ester in 62% chemical yield. Analysis by both ^{13}C n.m.r. spectroscopy and h.p.l.c. provided a diastereoisomeric ratio of 95:5. The sense of asymmetric induction was determined by reaction of the diastereoisomeric mixture with phenylmagnesium bromide. The 1,1-diphenylpropane-1,2-diol obtained had a negative rotation corresponding to an *S* configuration and to an optical purity of 94% (97:3)[5] in approximate agreement with the analyses above. This chirality would be that resulting from addition of the nucleophile to the front face of (**3**) as drawn with a *syn*-orientation of the carbonyl

Table 1.

Reagent[a]	*T*/°C	Chemical yield of (**4**)/%	Diastereomeric excess of (**4**)/%[b]
MeMgBr	0	62	90
MeMgBr	−78	86	99.4
$Me[CH_2]_5MgBr$	−78	82	99.2
$Me[CH_2]_7MgBr$	−78	80	98.1
PhMgBr	−78	90	99.1
$\overline{CH_2[CH_2]_4CH}MgBr$	−78	80	98.8
MeLi	−78	74	0
MeLi + $LiClO_4$	−78	80	60
EtO_2CCH_2ZnBr	room temp.	90	20

[a] All reactions were conducted in diethyl ether under an inert atmosphere and with 1 equiv. of nucleophile. [b] Diastereomeric ratios were determined by both ^{13}C n.m.r. and h.p.l.c. analysis for values lower than 90% while only the latter technique was used for higher ratios.

groups.† Repetition of the addition of the methyl Grignard reagent but at −78 °C raised the chemical yield to 86% while increasing the diastereomeric ratio to 99.7 : 0.3.

Other nucleophilic reagents were added to the glyoxylate, with the results summarized in Table 1. In all cases with magnesium as the counterion the level of asymmetric induction was quite high and thus this technique would appear to be quite general. These results are to be contrasted with those obtained with lithium and zinc reagents. The origin of this difference is not clear but may be the result of differences in the degree of aggregation of the various reagents as the presence of lithium perchlorate had a pronounced effect on the result from methyl-lithium addition.

Other nucleophilic species could well be added to (**3**) affording a variety of functional groups with asymmetric induction. In addition, we have found that the aldehyde of (**3**) serves as a partner in bimolecular ene reactions with high levels of induction. These latter findings are detailed in the following communication.

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† Previous attempts to induce asymmetry in additions to chiral glyoxylate esters afforded induction levels too low to make confident predictions concerning the transition states involved (ref. 6).

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