Asymmetric Induction. Reduction, Nucleophilic Addition to, and Ene Reactions of Chiral α-Ketoesters

James K. Whitesell,* Don Deyo, and Apurba Bhattacharya

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

Ketoesters of 8-phenylmenthol undergo reduction with potassium tri-isopropoxyborohydride, addition of Grignard reagents, and ene reactions with asymmetric induction levels of 90% and above.

We recently reported two methods for carbon–carbon bond formation that afforded (*S*)-α-hydroxyesters with high levels of asymmetric induction using (−)-8-phenylmenthol as the chiral auxiliary in ene and Grignard reactions of its glyoxylate ester.[1,2] An inherent limitation of these techniques is that access to the opposite, (*R*), chirality is restricted by the relative difficulty associated with obtaining (+)-8-phenylmenthol. We have found that reversal of the order of addition of the substituents through reduction of ketoesters (**1**) of (−)-8-phenylmenthol affords the (*R*) chirality with practical levels of asymmetric induction.

The level of induction to be expected in addition reactions to ketoesters such as (**1**) will be a combination of two factors: the inherent diastereoface selectivity imparted by the chiral auxiliary, and the degree of bias in the transition state for either the *cisoid* or the *transoid* orientation of the carbonyl groups. Our previous results have shown that 8-phenylmenthol can impart an exceptionally high level of diastereoface selection. However, initial attempts at reduction of (**1a**) with sodium borohydride afforded disappointing levels of induction, presumably because of poor control of the second factor, the orientation of the carbonyl groups. Therefore a range of reducing agents was examined, with emphasis placed on counterion differences (Table 1). This survey led to the discovery that potassium tri-isopropoxyborohydride reduction of (**1a**) afforded the lactate ester (**2**) with a 90% diastereoisomeric excess (d.e.) and with the opposite chirality (*R*) as previously obtained by addition of methyl Grignard reagent to the glyoxylate ester. Analogous reduction of (**1b**) afforded the (*R*)-mandelic acid ester with an induction level of 50%.

We have also examined the addition of Grignard reagents to (**1a**) and (**1b**). Reaction of (**1a**) with phenyl Grignard reagent and of (**1b**) with methyl Grignard reagent afforded the tertiary alcohols *S*-(**3**) and *R*-(**3**), respectively. In both cases, ^{13}C n.m.r. analysis showed no cross-contamination (minimum detection level 5%) indicating asymmetric induction of at least 90%. Conformation of these levels of induction and assignment of the absolute configurations to *S*-(**3**) and *R*-(**3**) was obtained by reduction with di-isobutylaluminium hydride to afford the diols *S*-(**4**) and *R*-(**4**) with optical purities of 88 and 92%, respectively.[3] The sense of asymmetric induction obtained with ketones (**1**) is consistent with addition from the front face as drawn, and is thus the same as that obtained in the ene and nucleophilic addition reactions of the parent aldehyde.[1,2] It should be noted that both enantiomers of the diol (**4**) were prepared in high optical purity using a single enantiomer of the chiral auxiliary.

The $SnCl_4$ catalysed ene reaction of (**1a**) with hex-1-ene at −78 °C afforded the adduct (**5**) which appeared as a single diastereoisomer by ^{13}C n.m.r. analysis (d.e. >90%). This adduct is a tertiary, homoallylic alcohol and thus the synthetic equivalent of the product from a crossed-aldol reaction, involving a ketone as the electrophile.

These observations add to a growing list of uses of 8-phenylmenthol[1,2,4] from which we conclude that this chiral auxiliary will find a wide range of practical applications in synthetic chemistry.

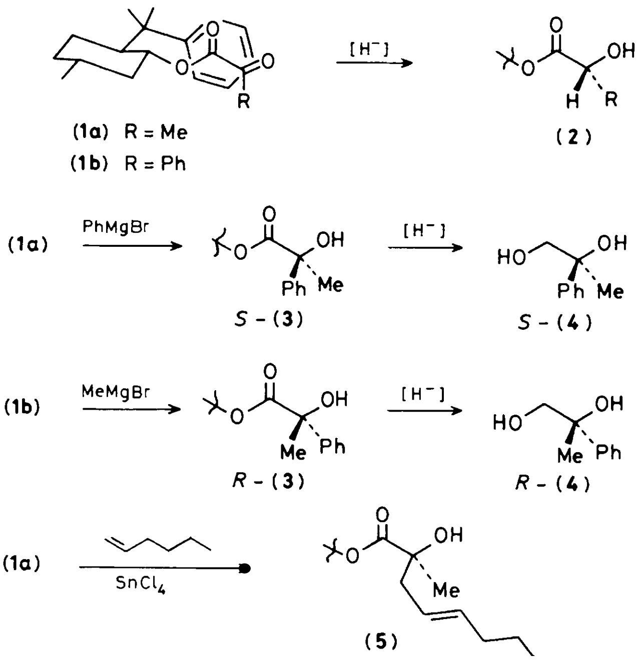

Table 1

Reagent[a]	Chemical yield of (2), %	Diastereoisomeric excess of (2), %[b]
$K(Pr^iO)_3BH$/THF (ref. 5)	90	90
BH_3/THF	96	0
2 equiv. Bu^i_2AlH/THF	68	33
$NaBH_4$/MeOH	90	33
$Li(Bu^tO)_3AlH$/THF	90	60
$Li(Bu^tO)_3AlH$–LiBr/THF–Et_2O	90	33

[a] All reactions were carried out at −78 °C and with one equiv. of reductant unless stated otherwise. [b] Diastereoisomeric ratios were determined by both ^{13}C n.m.r. and h.p.l.c. analysis.

This research was supported by grants from the Public Health Service and from the Robert A. Welch Foundation.

Received, 29th September 1982; Com. 1148

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