The Stereospecific Asymmetric Reduction of Functionalised Ketones

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Summary The reduction of functionalised ketones with actively fermenting yeast gives secondary alcohols of high optical purity in moderate yields; the method is of value for the synthesis of optically active α- and β-hydroxyesters.

ALTHOUGH the stereospecific asymmetric reduction of ketone functional groups with actively fermenting yeast (*Saccharomyces cerevisiae*) is well known,[1] there are few reports on the similar reductions of ketones with adjacent functional groups. Such reductions have been limited to the reduction of simple aliphatic α-hydroxyketones,[2] to keto acids which are known natural substrates (*e.g.* oxaloacetic acid), and to aliphatic chloroketones (*e.g.* 3-chlorobutanone).[1] We have now investigated the reductions of other functionalised ketones, particularly ketoesters, to give optically active functionalised secondary alcohols, some of which we required in connection with other work and which were otherwise difficult to obtain.

The carbonyl compound was added to a fermenting yeast–sucrose suspension and the mixture kept at room temperature for 1—2 days. The product was isolated by extraction of the reaction mixture with either ether or ethyl acetate. In this way several grams of the carbonyl compound may be reduced in one batch; *e.g.* a mixture containing phenacyl alcohol (10 g), yeast (100 g) and sugar (150 g) in water (800 ml) readily gave *R*-(−)-phenyl ethanediol (4·8 g), $[\alpha]_D^{25} = -45{\cdot}8°$. Typical results from the reductions of various functionalised ketones are given in the Table. Surprisingly α-chloroketones are readily reduced under the slightly acidic reaction conditions, although the yields are low. The *R*-(−)-2-chloro-1-phenylethanol, from the reduction of phenacyl chloride, was separated from unreacted starting material by chromatography on silica gel and was optically pure. This product was not racemised under the conditions of the reaction even when left in the yeast medium for six days, but racemised extensively on distillation under reduced pressure.

α- and β-keto esters also are reduced rapidly and with high stereospecificity; for example ethyl phenylglyoxalate gave *R*-(−)-ethyl mandelate and ethyl acetoacetate gave *S*-(+)-ethyl 3-hydroxybutanoate in good yield. However, ethyl laevulate was not reduced under the reaction conditions, and phenylglyoxylic acid underwent decarboxylation prior to reduction and hence gave benzyl alcohol.

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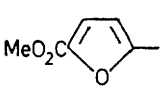
TABLE

Functional group	Reactant	Product	Yield, $[\alpha]_D^{25}$	lit. $[\alpha]_D^{25}$
Aromatic α-hydroxyketone	$PhCOCH_2OH$	*R*-(−)-$PhCH(OH)CH_2OH$	45% −45·8° (Me_2CO, *c* 2)	−39·9° (Me_2CO, *c* 6·6)
α-Formyloxyketone ..	$ArCOCH_2OCHO$	$ArCH(OH)CH_2OH$	62% −25·9° ($CHCl_3$, *c* 1)	Not reported
α-Chloroketone	$PhCOCH_2Cl$	*R*-(−)-$PhCH(OH)CH_2Cl$	32% −45·4° (C_6H_{12}, *c* 3)	−47·8° (C_6H_{12}, *c* 2·8)[4]
α-Ketoester	$PhCOCO_2Et$	*R*-(−)-$PhCH(OH)CO)_2Et$	68% −130° ($CHCl_3$, *c* 1)	−128·4° ($CHCl_3$, *c* 1)[5]
α-Ketoacid	$PhCOCO_2H$	$PhCH_2OH$	65% —	—
β-Ketoester	$MeCOCH_2CO_2Et$	*S*-(+)-$MeCH(OH)CH_2CO_2Et$	80% +38·5° ($CHCl_3$, *c* 1)	Not reported
δ-Ketoester	$MeCOCH_2CH_2CO_2Et$	No reaction		

Ar = 

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