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STEREOCHEMICAL CONTROL OF YEAST REDUCTIONS: SYNTHESIS OF R-(+)-α-LIPOIC ACID

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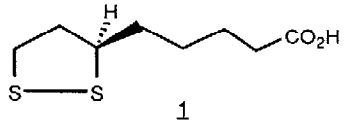
Abstract: The stereoselectivity of the reduction of alkyl 7-cyano-3-oxo-heptanoates with bakers' yeast was found to be influenced by the nature of the ester group. The octyl ester 2c was reduced in 82%ee and 77% chemical yield to the corresponding S alcohol, which was converted to R-(+)-α-lipoic acid (1).

Bakers' yeast is a cheap and readily available reagent that has recently found much use for the preparation of chiral alcohols[1]. A variety of compounds including ketones, α-ketoesters[2], and β-ketoesters[3], have been successfully reduced with bakers' yeast to provide alcohols of high optical purity. It has been shown that the reduction of carbonyl groups by bakers' yeast can be a complex process since a number of alcohol dehydrogenases in yeast are capable of this function[4]. Often, low optical purity of products can be the result of competing dehydrogenases of opposite enantiospecificity acting on the carbonyl substrate. Recently, a number of methods have been developed for achieving stereochemical control of bakers' yeast reductions[3,5]. It has been shown that changing the size of the ester group in a β-ketoester can have a substantial effect in the optical purity and configuration of the chiral alcohol that is obtained[3]. We would like to report our studies of the bakers' yeast reduction of some alkyl 7-cyano-3-oxo-heptanoates, to obtain synthetically valuable chiral intermediates, and their use in the synthesis of R-(+)-α-lipoic acid, (1), a molecule of considerable biological significance.

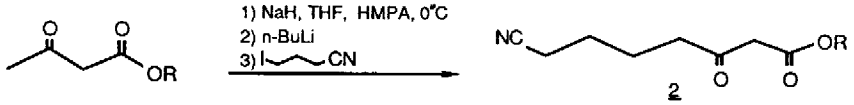


1

R-(+)-α-lipoic acid (1) is a cofactor in the biochemical decarboxylation of α-ketoacids. It has also been reported to be a growth factor for a variety of microorganisms[6]. The R configuration of (+)-α-lipoic acid was first confirmed by Golding via synthesis of its enantiomer

from S-malic acid about 6 years ago[7]. Subsequently, a number of reports have appeared describing the enantiospecific synthesis of R-(+)-α-lipoic acid[8]. Some of the syntheses utilize naturally available chiral starting materials like S-malic acid, D-glucose, or D-mannose. An elegant asymmetric synthesis of 1, via chiral acetal template methodology and another based on a Sharpless epoxidation have also been published. We would like to describe the first synthesis of this molecule that uses bakers' yeast to produce the key chiral intermediate.

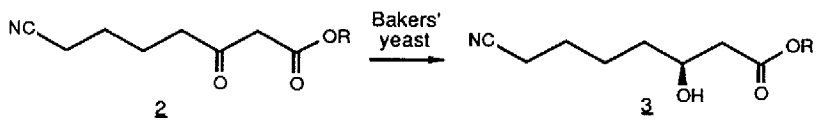
The substrates necessary for the bakers' yeast reduction were prepared by the alkylation of the dianion from alkyl acetoacetates[9] with 4-iodobutyronitrile.



2

The results of the bakers' yeast reduction of 2 are given in Table I[10]. The enantiomeric excess of 3 was determined by derivatization with Mosher's reagent (+)-methoxytrifluoromethylphenylacetyl chloride[11], followed by ^{1}H NMR studies using shift reagents. The absolute configuration was determined by subsequent conversion to ethyl R-(+)-α-lipoate 7. While all the ketoesters 2 were reduced by bakers' yeast to the corresponding S alcohols 3, the reduction of the octyl ester 2c gave the highest enantioselectivity and chemical yields.

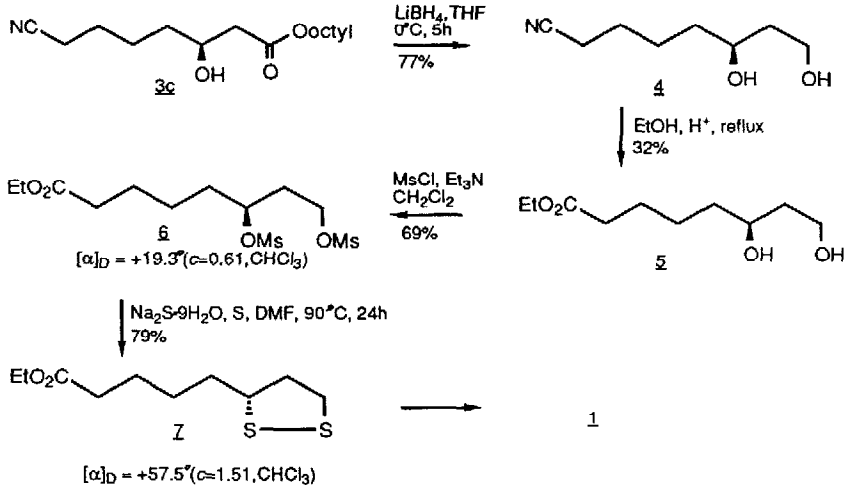
Table I: Bakers' Yeast Reduction of alkyl 7-cyano-3-oxoheptanoates



2 3

R	Yield	ee	Absolute Configuration	$[\alpha]_D$ (c,$CHCl_3$)
a. ethyl	36%(2g/L)	36%	S	+7.93°(1.98)
	46%(3g/L)	56%	S	+9.80°(1.22)
b.t-butyl	60%(3g/L)	46%	S	+8.64°(1.55)
c. octyl	62%(2g/L)	77%	S	+10.3°(2.70)
	77%(3g/L)	82%	S	+10.4°(2.39)

Octyl 7-cyano-3-oxo-heptanoate 2c was reduced by bakers' yeast in 77% yield and 82%ee to the S alcohol 3c. The alcohol 3c was then converted to R-(+)-α-lipoic acid as shown in Scheme 1. Reduction of 3c with $LiBH_4$ in THF at room temperature proceeded smoothly to give the diol 4. The diol was converted to the ethyl ester 5 (EtOH, H^+) and then to the dimesylate 6, a well established key intermediate in the synthesis of R-(+)-α-lipoic acid[8a,b]. Treatment of 6 with $Na_2S \cdot 9H_2O$ and S in DMF gave ethyl R-(+)-α-lipoate 7. This reaction is known to proceed with inversion of configuration[8a]. Thus the configuration of the chiral alcohol, 3c, obtained from bakers' yeast reduction was confirmed to be S[12]. It has already been reported that the ethyl ester 7 is hydrolyzed to R-(+)-α-lipoic acid(1) with 0.1M KOH in EtOH at room temperature[8b].



Scheme 1

In conclusion, the stereoselectivity of bakers' yeast reduction of β-ketoesters is clearly influenced by variation of the ester groups. This provides a valuable method for controlling the stereochemical outcome of such reductions. We have utilized bakers' yeast reduction to obtain a valuable new synthetic intermediate, which can then be converted by a short sequence of steps to R-(+)-α-lipoic acid, a biologically important enzyme cofactor.

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