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PREPARATION AND APPLICATION OF A CHIRAL C_3-BUILDING BLOCK FOR AMINO ALCOHOL SYNTHESIS BY BAKERS' YEAST REDUCTION OF 1-ACYLOXY-3-AZIDO-2-PROPANONE

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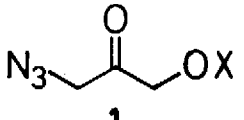
Summary: *Bakers' yeast-mediated reduction of 1-acyloxy-3-azido-2-propanone gives (S)-1-acyloxy-3-azido-2-propanol with high enantiomeric excess, which is a useful chiral C_3-building block for amino alcohols such as β-blockers.*

Recently trifunctional chiral building blocks with different hetero atom functionalities at both terminal carbons have been prepared from sulfur-functionalized ketones by bakers' yeast-mediated asymmetric reduction.[1] The terminal hetero atom functional groups are very effective both for stereocontrol in the enantioselective reduction and for further manipulation of reduction products to natural product synthesis. In this paper, we wish to present a new trifunctional chiral building block for amino alcohol, (S)-1-acyloxy-3-azido-2-propanol (2), prepared by the bakers' yeast-mediated reduction of 1-acyloxy-3-azido-2-propanone.

The substrates 1 were easily prepared by the reaction of 1-acyloxy-3-chloro-2-propanone with sodium azide[2] starting from 1,3-dichloro-2-propanone[3] or 3-chloro-1,2-propanediol.[4] A mixture of 40 g of pressed bakers' yeast (Oriental Yeast Co.) and 48 g of saccharose in 400 ml of water was stirred at room temperature for 30 min, then 10 ml of an ethanol solution of ketone 1 (8.0 mmol) was added to the fermenting yeast. Reaction progress was monitored by TLC until 1 was totally consumed. After usual work-up, the reduction product 2 was isolated by silica-gel column chromatography (hexane-ethyl acetate). Optical purity of 2 was determined by ^{1}H-NMR measurement or HPLC analysis of the corresponding (+)-MTPA ester. The configuration of **2a** was defined to be S by comparison of the rotation of 3-azido-1,2-propanediol(**2d**) derived by hydrolysis of **2a**, $[\alpha]_D^{23}$ -12.6° (c 0.95, CH_3OH), with that of authentic sample, $[\alpha]_D^{23}$ -7.4° (c 1.01, CH_3OH), prepared from (R)-3-tosyloxy-1,2-*O*-isopropylidene-1,2-propanediol, $[\alpha]_D^{23}$ -3.8°(c 1.01, C_5H_5N), lit.[5] $[\alpha]_D$ -7.3° (c



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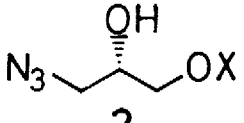

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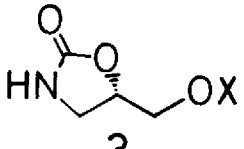

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a X=$COCH_3$, b X=COPh, c X=$COC(CH_3)_3$, d X=H

Table 1. The bakers' yeast reduction of ketone **1** to alcohol **2**

Ketone	Time/h	Yield/%	%ee[a]	$[\alpha]_D^{23}$/° (CH_3OH)
1a	0.5	70	>96	-12.6 (c 0.95)
	20	74[b]	75[b,c]	-10.8 (c 0.98)[b]
1b	6	95	78	-9.8 (c 0.98)
1c	14	74	90	-15.2 (c 1.25)

[a] Determined by ^1H NMR of the corresponding (+)-MTPA ester. [b] Values for (S)-3-azido-1,2-propanediol(2d). [c] Determined by HPLC of the corresponding di-MTPA ester.

5.5, C_5H_5N). The (S)-configuration of **2b** and **2c** were supported by its negative sign of the rotation in agreement with that of authentic samples prepared by acylation of **2d**. The results of the bakers' yeast reduction are listed in Table 1.

As shown in Table 1, the acetyl group is the best choice of protection of the hydroxyl group in ketone **1**. The reduction of **1a** proceeds much faster than that of **1b** and **1c**, and the highest enantioselectivity can be achieved by the reduction of **1a**. However, a longer reduction time in the case of **1a** resulted in formation of **2d**. The low enantiomeric excess of **2d** may be due to kinetic resolution in hydrolysis of **2a** in favor of formation of (R)-**2d** and/or to reduction of **1d**, produced first by hydrolysis of **1a**, to give (R)-**2d**.[6]

The utility of **2a** as a chiral synthon involving nitrogen atom was demonstrated in the synthesis of **3d**, a precursor of β-blockers[7] as follows: phenoxycarbonylation of **2a** ($ClCO_2Ph$-DMAP, 83%) and reduction of azide (H_2/10% Pd-C) gave oxazolidinone **3a** in 87% yield, $[\alpha]_D^{23}$ +47.6° (c 0.93, C_2H_5OH). Deacetylation of **3a** with K_2CO_3 in C_2H_5OH gave (S)-5-hydroxymethyl-2-oxazolidinone **3d** in 97% yield, $[\alpha]_D^{23}$ +29.1° (c 2.7, C_2H_5OH), lit.[7] $[\alpha]_D$ +29.7° (c 2.7, C_2H_5OH).

Thus, the bakers' yeast reduction of 1-acetoxy-3-azido-2-propanone provides a useful chiral building block for the synthesis of amino alcohols.

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