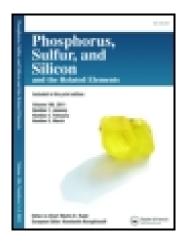
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ENANTIOSELECTIVE REDUCTION OF 2-KETOALKANEPHOSPHONATE BY BAKER'S YEAST

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Bioreduction of 2-oxo-3-halo (or azido) alkanephosphonates and 4-ethoxy-4,2-dioxobutanephosphonates by baker's yeast afforded 3-substituted 2-hydroxyalkanephosphonates in moderate to good yields and ee value. Moreover, a regio- and stereoselective bioreduction of 2,3-dioxoalkanephosphonates and 2,4-dioxoalkanephosphonates by baker's yeast was studied also. The resulting chiral hydroxy compounds can be used as chirons for the stereoselective synthesis of biologically active molecules.

Keywords: Baker's yeast; dicarbonyl phosphonates; monocarbonyl phosphonates

Baker's yeast (Saccharomyces cerevisiae) is now well recognized as a valuable stereoselective reagent in biotransformations of organic molecules.^{1–3} The asymmetric reduction of carbonyl groups with this microbiological substance has been studied extensively; nevertheless, there are only a few reports dealing with the enzymatic reduction of their phosphorus analogs, namely, β -ketoalkanephosphonates.⁴ On the other hand, chiral hydroxyalkanephosphonic acids have received much attention due to their unique physiological activities. As a part of our systematic study on the biotransformation of organicphosphorus compounds, we report in this paper the bioreductive behaviors of monocarbonyl phosphonates and dicarbonyl phosphonates.

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FIGURE 1

RESULTS AND DISCUSSION

Reduction of Monocarbonyl Phosphonates

Bioreduction of 3-substituted 2-oxoalkanephosphonates by baker's yeast (Figure 1 and Table I) afforded 3-substituted 2-hydroxyalkanephosphonates in moderate to good yields and *ee* value. These compounds could serve as useful chirons for the stereoselective synthesis of phosphorus analogs of biologically active molecules, including (R)-carnitine and (R)-GABOB.

Reduction of Dicarbonyl Phosphonates

The reduction of 4-alkoxy-4,2-dioxobutanephosphonate is shown in Figure 2.

2-Ketoalkanephosphonates are commonly employed as synthetic reagents, particularly in the Horner–Wadsworth–Emmons reaction. The nonracemic 3(4)-hydroxy-2-oxo-alkanephosphonates should be important as synthetic building blocks, since they are phosphorusfunctionalized aldols. The Horner–Emmons olefination leading to nonracemic 1-hydroxy-4-alken-3-ones is therefore attractive. An

Substrate	R	Х	Time (h)	Yield (%)	ee (%) ^a	$Configuration^b$
1a	Me	CH_2Cl	24	74	70	R
1b	\mathbf{Et}	CH_2Cl	12	82	72	R
1c	iPr	CH_2Cl	24	57	13	_
1d	nBu	CH_2Cl	24	88	70	R
1e	\mathbf{Et}	CH_2Br	24	35^c	83	R
1f	iPr	CH_2Br	24	41^c	52	_
1g	nBu	CH_2Br	24	55^c	87	R
1h	\mathbf{Et}	CH_2N_3	12	77	92	${f S}$
1i	\mathbf{Et}	CF_3	48	86	52	_
1j	\mathbf{Et}	C_3F_7	24	55	20	—

TABLE I Reduction of 1 with Baker's Yeast

^{*a*}The *ee* (%) was determined by the use of quinine as a chiral solvating agent.

^bThe absolute configuration was determined according to Mosher's methods. ^cThe 2-oxo-propane-phosphonate was isolated as a by-product.

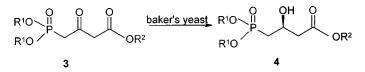


FIGURE 2 $R^1 = Me$, Et, *i*-Pr, *n*-Bu; $R^2 = Me$; yield 46–77%, *ee* 55–85%.

interesting route to a nonracemic 3(or 4)-hydroxy-2-ketophosphonate has been developed by bioreduction of dialkyl 2,3(or 4)dioxoalkanephosphonates.

Regio- and Stereoselective Reduction of Dialkyl 2,3-Dioxoalkanephosphonates

 α -Hydroxyketones are versatile chiral synthons for the construction of optical active organic compounds due to reactive functional groups: carbonyl and hydroxyl groups, which can easily be transformed to vicinal diols, amino ketones, and other functional groups. To obtain chiral α -hydroxyketones, reduction mediated by yeast is a powerful tool. In yeast reduction, two regioisomeric α -hydroxyketones are produced, and these hydroxyketones can be successively reduced to the diol. Therefore, chemical yields of the α -hydroxyketones are low. For asymmetric synthesis in such a reduction process, chemoselectivity, regioselectivity, and enantioselectivity should be taken in consideration (Figure 3).

Regio- and Stereoselective Reduction of Dialkyl 2,4-Dioxoalkanephosphonates

A series of phosphorus-based carbonyl compounds, namely, dialkyl 2,4dioxoalkanephosphonates (8), was prepared by reaction of carbanion

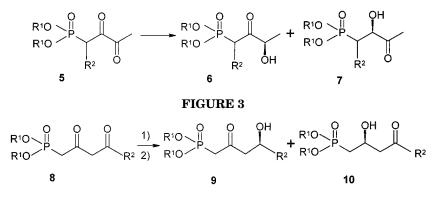


FIGURE 4 $R^1 = Et$, *n*-Bu; $R^2 = Me$, CF_3 , C_3H_7 ; (1) baker's yeast; (2) yield **9/10** = 45/24 or 67\%, *ee* **9** 90–94%.

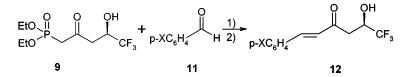


FIGURE 5 X = H, *p*-MeO, *p*-Me, *p*-Cl, *p*-Br, *p*-F, *m*-NO₂; (1) DBU, LiCl, 12–24 h, rt; (2) yield 53–72%.

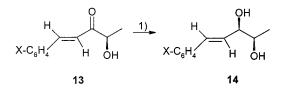


FIGURE 6 X = H, Me, MeO; (1) baker's yeast.

resulted from 2-methyl-2-oxoethanephosphonate with substituted acetates. Bioreduction of **8** by baker's yeast at 30°C for 24–48 h offered an isomeric mixture consisting of **9/10**, when R¹ is methyl, in 45/24% yield as well as 92/80% *ee* value, respectively. It is interesting to note that when R² is CF₃ or C₃F₇, a regio- and stereoselective reduction was observed. Only **9** was obtained, in 54–67% yield and 90–94% *ee* value.

The chiral 4-hydroxy-2-oxoalkylphosphonates **9** thus obtained underwent Horner-Emmons olefination as expected. Thus a series of *trans*-6,6,6-trifluoro-5-hydroxy-1-(substituted)phenyl-1-hexen-3-ones **12** was prepared by reaction of 5,5,5-trifluoro-4-hydroxy-2oxopentanephosphonates with substituted benzaldehyde under very mild condition in 33-67% yields (Figure 5).

It is interest to note that under the Horner-Wadsworth-Emmons reaction, compound 6 gave 13 conveniently and that provided 14, a chiral vicinal diol, upon another baker's yeast reduction (Figure 6).

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