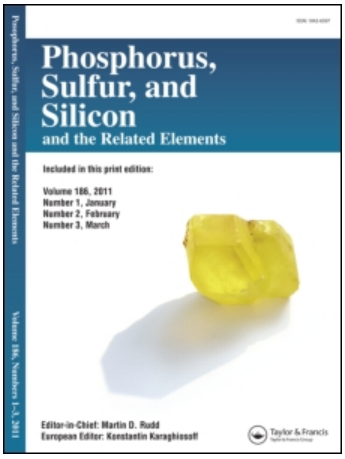


## Phosphorus, Sulfur, and Silicon and the Related Elements

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# Stereoselective Synthesis of Phosphorus Analogs of (R)-Carnitine and (R)-Gabob

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# STEREOSELECTIVE SYNTHESIS OF PHOSPHORUS ANALOGS OF (R)-CARNITINE AND (R)-GABOB

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*Bioreduction of 3-substituted-2-oxoalkanephosphonates by baker's yeast afforded corresponding 2-hydroxy-alkanephosphonates in good yields and ee value. These compounds (**2a,b**) could serve as useful chirons for the stereoselective synthesis of phosphorus analogs of (R)-Carnitine and (R)-GABOB.*

*Keywords:* Baker's yeast; bioreduction; hydroxyphosphonates



## INTRODUCTION

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, but little is known about its activity toward ketophosphonates.[4] On the other hand, chiral $\beta$-hydroxyalkanephosphonic acids have received much attention because of their unique physiological activities as well as their ability to mimic the corresponding hydroxy- or amino-alkanecarboxylic acids.[5]

As important illustrative examples, (R)-(-)-3-amino-2-hydroxybutyric acid (GABOB) and (R)-(-)-3-trimethylammonium-2-hydroxypropanoic acid [(R)-(-)-Carnitine] can be cited (Scheme 1), since the former has been used as an antiepileptic and hypotensive drug, while the latter is a vitamin-like compound, that is responsible for the metabolism of long chain fatty acids by regulating their

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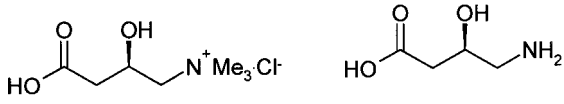



(R) - Carntine (R) - GABOB

**SCHEME 1**

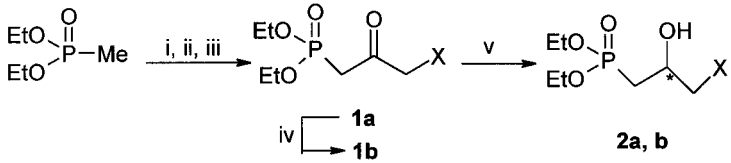
transport through mitochondrial membranes. It is most important to note that the corresponding (S)-enantiomer of Carnitine acts as a competitive inhibitor of Carnitine acyltransferase, causing depletion of the (R)-Carnitine level in heart tissue. Consequently, the synthetic study of the phosphorus analogs of GABOB and Carnitine, particularly their stereoisomers aroused our interest.

In this article, a stereoselective synthesis of 3-chloro(or azido)-2-hydroxypropane phosphonates by bioreduction with baker's yeast is discussed. In addition to phosphorus analogues, the target molecules can be regarded as useful phosphonate chirons for the preparation of optically active polyfunctional phosphonates with biological significance.



## RESULTS AND DISCUSSION

The 3-chloro-2-oxopropanephosphonate (**1a**) was prepared according to the literature,[6] while the corresponding azido derivative **1b** was obtained by reaction of **1a** with sodium azide in DMF. The substrates **1a**,**b** are stable in aqueous medium and undergo bioreduction with baker's yeast as illustrated in Scheme 2.




Reagents and conditions: i) n-$C_4H_9Li$; ii) CuCl ; iii) $ClCOCH_2Cl$; iv) $NaN_3$/DMF, $0^0C$; v) baker's yeast, 30°C

**SCHEME 2**

The biotransformation was performed by shaking an aqueous (50 ml) suspension of dried baker's yeast (5 g) and substrate (0.5 mmol) at 30°C until the disappearance of the substrate was observed, as monitored by TLC.

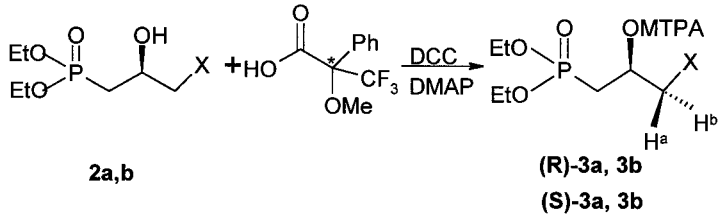
**TABLE I** Reduction of **1a-b** with Baker's Yeast

| Substrate | R | X | Yield (%) | ee (%)[a] | Config[b] |
|---|---|---|---|---|---|
| **1a** | Et | Cl | 82 | 72 | R |
| **1b** | Et | $N_3$ | 77 | 92 | S |

[a]ee (%) was determined by the use of quinine as a chiral solvating agent.[7–8]

[b]the absolute configuration was determined according to Mosher's methods.[9]

As shown in Table I, 2-keto propanephosphonates (**1a,b**) can be transformed conveniently into the corresponding 2-hydroxypropanephosphonates (**2a,b**) in good yields and ee value. The enantioselectivity of the reaction was determined by means of $^{31}P$ NMR spectroscopy using quinine as a chiral discriminating agent.[7–8] In the meantime, the absolute configurations of the 2-hydroxypropanephosphonates were preliminarily assigned on the basis of $\Delta\delta$ values in the $^{1}H$ NMR spectra of their $\alpha$-methoxy-$\alpha$-trifluoromethylphenyl-acetic acid (MTPA) esters using the modified Mosher's method (Scheme 3).[9]

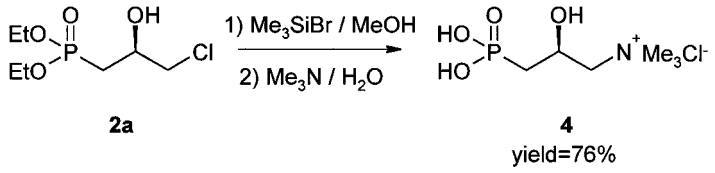



**SCHEME 3**

According to Mosher's method, bioreduction of 3-substituted-2-oxoalkanephosphonates (**1a,b**) by baker's yeast obeys Prelog's rule.[10]

3-Chloro-2-hydroxypropanephosphonates (**2a**) could be converted to the free phosphonic acid in the presence of a stoichiometric amount of trimethylbromosilane by classic procedures based on transsilylation, which then can be readily transformed into (S)-2-hydroxy-3-trimethylamino propanephosphonic acid (**4**) with a stoichiometric amount of trimethylamine-water solution in 76% yield, which is the phosphorus analog of (R)-Carnitine (Scheme 4).

Diethyl 3-azido-2-hydroxypropanephosphonate (**2b**), on hydrogenation using palladium on carbon as catalyst, provided diethyl 3-amino-2-hydroxypropane-phosphonate (**5**) in 95% yield, which could serve as a useful three-carbon phosphonate chiron.[11–13] Esters of

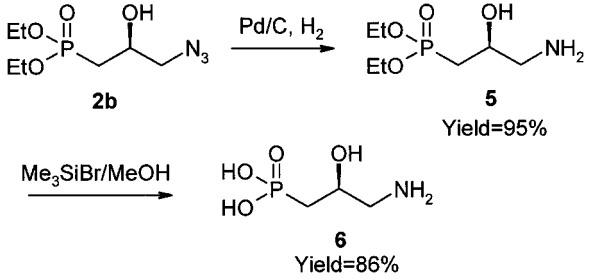



**2a** **4**

yield=76%

**SCHEME 4**

phosphonic acid (**5**) can be readily transformed into (S)-3-amino-2-hydroxypropanephosphonic acid (**6**) by classic procedures based on transsilylation in 86% yield, which is the phosphorus analog of (R)-GABOB (Scheme 5).




**2b** **5**

Yield=95%

**6**

Yield=86%

**SCHEME 5**

Therefore, reduction of 3-substituted-2-oxoalkanephonates by baker's yeast afforded the corresponding hydroxyalkanephosphonates in good yields and ee values. The 3-substituted-alkanephosphonate chirons are used for the stereospecific synthesis of the phosphorus analogs of GABOB and Carnitine, which display promising or potential biological activities.

## EXPERIMENTAL

IR spectra were recorded on a Shimadzu IR-440 spectrometer. EI mass spectra (MS) were run on an Hp-5989A mass spectrometer. $^{1}H$ and $^{13}P$ NMR spectra were recorded on a Bruker AMX-330(300 MHz)spectrometer in $CDCl_3$ solutions and chemical shifts ($\delta$) were reported in ppm downfield relative to TMS (internal standard) and 80% phosphoric acid (external standard) in the phosphorus spectra.

Baker's yeast was purchased from Sigma Co. Int. Spots in TLC monitoring were visualized by dipping the plate into a solution of 24 g of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ and 1 g of $Ce(SO_4)_2{\cdot}4H_2O$ in 500 ml of 10%

$H_2SO_4$ in water, followed by heating with a hot gun. 3-Substituted-2-oxopropanephosphonates (**1a,1b**) were prepared according to the literature.[6]

## General Procedure for the Reaction of Baker's Yeast

Baker's yeast 5 g was suspended in water (50 ml), then each phosphonate **1a,b** (0.5 mmol) was added and the mixture was shaken at 30°C, while being monitored by TLC. The biomass was removed and extracted with ethyl ether, and with chloroform (20 ml × 3). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvents removed under reduced pressure. The product was separated by column chromatography (hexane/acetone = 3/2).

## Conversion of 2-Hydroxypropanephosphonates (2) to the Corresponding $\alpha$-Methoxy-$\alpha$-trifluoromethylphenyl-acetic Acid (MTPA) Esters



### *General Procedure*

To a stirred solution of 0.1 mmol (R)[or (S)]-$\alpha$-methoxy-$\alpha$-trifluoromethylphenyl-acetic acid(MTPA) in 1 ml anhydrous $CH_2Cl_2$ was added 0.1 mmol of hydroxypropanephosphonates (**2**) and 2–3 mg of DMAP. The dicyclo-hexylcarbodiimide (DCC) (0.1 mmol) was added to the reaction mixture at 0°C, which was then stirred for 8 h at 0°C. Precipitated urea was then filtered off. $CH_2Cl_2$ (20 ml) was added, and the solution was washed twice with saturated $NaHCO_3$ solution, and then dried with $MgSO_4$. The solvent was removed by evaporation and the ester was purified by column chromatography (hexane/acetone = 3/2).

### *(R)-diethyl 3-Chloro-2-hydroxypropanephosphonate (2a)*

Colorless oil; 94 mg (yield 82%), ee 70%; IR ($\upsilon$): 3337, 2962, 1222 (P=O) $cm^{-1}$, $^1H$ NMR ($\delta$) : 4.35 (1H, −OH); 4.10 (m, 4H, $OCH_2CH_3$); 3.65 (d, 2H, $CH_2Cl$); 3.30 (m, 1H, CHOH); 2.10 (m, 2H, $CH_2P$); 1.65 (m, 2H, $CH_2$); 1.40 (m, 2H, $CH_2$); 0.95 (m, 6H, $CH_3CH_2O$—P); $^{31}P$ NMR ($\delta$): 28.9 ppm; MS (m/e, %) : 231(M+1), 181, 153, 125 (base), 107,81; Anal. Calcd for $C_7H_{16}ClO_4P$ (230.60): C, 36.52; H, 6.96; P, 13.43; Found: C, 36.56; H, 7.16; P, 12.95.

**(R)-(3a)** $^1H$ NMR ($\delta$): 7.55 (2H, Ph), 7.42 (3H, Ph), 5.52 (1H, HCO), 4.13 (m, 4H, $POCH_2$), 3.87 (m, 2H, $CH_2Cl$), 3.56 (s, 3H, $OCH_3$), 2.21 (m, 2H, $PCH_2$), 1.31 (m, 6H, $POCH_2CH_3$);

**(S)-(3a)** $^1H$ NMR ($\delta$): 7.55 (2H, Ph), 7.42 (3H, Ph), 5.52 (1H, HCO), 4.13 (m, 4H, $POCH_2$), 3.82 (m, 2H, $CH_2Cl$), 3.56 (s, 3H, $OCH_3$), 2.28 (m, 2H, $PCH_2$), 1.31 (m, 6H, $POCH_2CH_3$);

### *(S)-diethyl 3-Azido-2-hydroxypropanephosphonate (2b)*

Colorless oil; 90 mg (yield 77%), ee 92%; IR ($\upsilon$): 3343(—OH), 2986, 2105 (vs), 1225 (P═O), 1050 (P—$OC_2H_3$) $cm^{-1}$. $^1H$ NMR ($\delta$): 4.20 (1H, OH), 4.13 (m, 6H, $OCH_2CH_3$), 3.37 (d, 2H, $CH_2N_3$), 2.01 (m, 2H, $CH_2P$), 1.35 (m, 6H, $OCH_2CH_3$). $^{31}P$ NMR ($\delta$): 29.1. MS (m/e, %): 238 (M, base), 181, 153, 125, 107, 72; Anal. Calcd. for $C_7H_{16}N_3O_4P$ (238.17): C, 35.30; H, 6.35; N, 17.64; Found: C, 35.22; H, 6.75; N, 17.29.

**(R)-(3b):** $^1H$ NMR ($\delta$): 7.54 (2H, Ph), 7.41 (3H, Ph), 5.39 (m, 1H, HCO), 4.10 (m, 4H, $POCH_2$), 3.72 (m, 2H, $CH_2N_3$), 3.57 (s, 3H, $OCH_3$), 2.16 (m, 2H, $CH_2P$), 1.32 (m, 6H, $POCH_2CH_3$);

**(S)-(3b):** $^1H$ NMR ($\delta$): 7.54 (2H, Ph), 7.41 (3H, Ph), 5.39 (m, 1H, HCO), 4.13 (m, 4H, $POCH_2$), 3.62 (m, 2H, $CH_2N_3$), 3.57 (s, 3H, $OCH_3$), 2.23 (m, 2H, $CH_2P$), 1.34 (m, 6H, $POCH_2CH_3$).

### *Conversion of (R)-diethyl 3-Chloro-2-hydroxypropanephosphonate (2a) to (S)-2-hydroxy-3-trimethylamino-propanephosphonic Acid (4)*

To a solution of **2a** (230 mg, 1 mmol) in dichloromethane (10 ml) trimethylbromosilane (312 g, 2 mmol) was added in one portion at room temperature. The reaction mixture was stirred at room temperature for 12 h. Then the solvent was evaporated under reduced pressure and anhydrous methanol (5 ml) was added to the residue. The solution was stirred at room temperature for 1 h. The product was purified to afford 220 mg of (S)-2-hydroxy-3-trimethylaminopropanephosphonic acid (4), yield 76%. $^1H$ NMR (300 MHz, $D_2O$) : $\delta$ 4.18–4.13 (m, 1H, CHOH), 3.69–3.47 (m, 2H, m, $CH_2N$), 2.80 (s, 9H, $NCH_3$), 1.95–1.82 (m, 2H, $PCH_2$). MS m/z (rel. intensity): 199 ($M^+$—Cl)(3.02), 125 (9.99), 115 (7.08), 91 (5.69), 58 (100.00), 44 (5.90), 43 (11.90), 42 (39.51). $^{31}P$ NMR (120 MHz, $D_2O$): $\delta$ 21.658.

### *Conversion of (S)-diethyl 3-Azido-2-hydroxypropanephosphonate (2b) to (S)-diethyl 3-Amino-2-hydroxypropanephosphonate (5)*

The mixture of (S)-diethyl 3-azido-2-hydroxypropanephosphonate (**2b**) (200 mg) and palladium (10%) on carbon (10 mg in 20 ml MeOH) was stirred for 4 h under hydrogen gas at 25°C. The mixture was filtered, and the solvents removed under reduced pressure. The product was purified to afford 167 mg of (S)-diethyl 3-amino-2-hydroxypropanephosphonate (**5**), yield 95% . IR (film) ($cm^{-1}$): $\upsilon_{max}$ 3391, 2984, 1446, 1393, 1370, 1228, 1029, 966, 829. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 4.12–4.08 (m, 4H, $POCH_2CH_3$), 4.05–4.02 (m, 1H, CHOH), 2.82 (3H, $NH_2$+OH), 2.81–2.78 (m, 2H, $CH_2NH_2$), 2.01–1.80 (m, 2H, $PCH_2$), 1.32–1.25 (m, 6H, $POCH_2CH_3$). $^{31}P$ NMR (160 MHz, $CDCl_3$):

$\delta$ 30.370. MS m/z (rel. intensity): 194 ($M^+$—OH)(6.69), 181 (45.22), 138 (73.05), 125 (100), 111 (46.85), 82 (20.43), 56 (57.46). HRMS calcd. For ($C_7H_{18}NO_4P$—OH) 194.0947, found: 194.0936.

### *(S)-3-amino-2-hydroxypropanephosphonic Acid (6)*

To a solution of 3-amino-2-hydroxypropanephosphonate (**5**) (211 mg, 1 mmol) in dichloromethane (10 ml) trimethylbromosilane (2 mmol) was added in one portion at room temperature. The reaction mixture was stirred at room temperature for 12 h. Then the solvent was evaportated under reduced pressure. The product was purified to afford 130 mg of (S)-3-amino-2-hydroxypropanephosphonic acid (**6**), yield 86%. $^1$H NMR (300 MHz, $D_2O$): $\delta$ 4.05–4.02 (m, 1H, CHOH), 2.82 (3H, $NH_2 + OH$), 2.81–2.78 (m, 2H, $CH_2NH_2$), 2.01–1.80 (m, 2H, $PCH_2$). MS m/z (rel. intensity): 138 (1.97), 125 (9.01), 108 (40.99), 80 (100). IR (film) ($cm^{-1}$): $\upsilon_{max}$ 3400, 2716, 1484, 1131, 1046, 986.



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