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Enantio- and regiospecific reduction of ethyl 4-phenyl-2,4-dioxobutyrate with baker's yeast: preparation of (*R*)-HPB ester☆

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Abstract—Ethyl 2,4-dioxo-4-phenylbutyrate obtained by condensation of acetophenone with diethyl oxalate is reduced enantio- and regiospecifically by baker's yeast in a diisopropyl ether/water two-phase system to give (−)-ethyl (*R*)-2-hydroxy-4-oxo-4-phenylbutyrate with an ee = 98% in 80% isolated yield. The hydroxyester was hydrogenated over Pd–C to obtain (−)-ethyl (*R*)-2-hydroxy-4-phenylbutyrate (HPB ester), an important intermediate for the synthesis of ACE inhibitors. Prolonged contact of the reduction product with baker's yeast produced 3-phenyl 3-oxo propanol in 90% yield.

1. Introduction

The synthesis of enantiomerically pure (−)-ethyl (*R*)-2-hydroxy-4-phenylbutyrate (HPB ester) **6** is of great interest since it is a versatile key intermediate for the synthesis of a variety of angiotensin converting enzyme (ACE) inhibitors such as Cilazapril, Benazepril, Enalapril etc.[1] with several strategies being devised for its synthesis. These can be categorized as (a) classical resolution;[2] (b) enantioselective reduction of its prochiral precursor 2-oxo-4-phenylbutyric acid **1** or its ethyl ester by microbial[3a–f] or plant cells[3g] possessing alcohol dehydrogenase activity; (c) enzyme catalyzed enantioselective synthesis of cyanohydrin derived from hydrocinnamaldehyde **2** followed by hydrolysis;[4] (d) enantioselective hydrolysis of racemic cyanohydrin **2** catalyzed by a nitrile hydratase/amidase system,[5] and (e) kinetic resolution of racemic ester **3** using a hydrolase[6] or its biocatalytic deracemization.[7]

A cost effective technology for HPB ester has been developed by Blaser et al. starting with very cheap starting materials and having only three chemical and one enrichment step.[8] In the key step, diketo ester **4b** is enantioselectively hydrogenated to γ-keto-α-hydroxy-ester **5b** using a heterogeneous Pt catalyst modified with the chiral dihydrocinchonidine, which is then hydrogenated to **6** with overall yields of 50–60% (Scheme 1). Although the biocatalytic route via enantioselective reduction of 2-oxo acid **1** is highly efficient, the synthesis of the α-keto acid is more expensive than the synthesis of diketo ester **4b**. While **1** is usually prepared by a Grignard reaction of phenylethyl bromide with diethyl oxalate in 40–50% yield,[9] **4b** can be easily prepared by a Perkin condensation of acetophenone with diethyl oxalate in > 90% yield.[8] It is thus interesting to develop a cleaner and environmentally friendly biocatalytic route as an alternative to the catalytic route.

Stereo- and regioselective reduction of α,γ-dioxo acid **4a** to **5a** with lactate dehydrogenase from *Bacillus stearothermophilus* and *Staphylococcus epidermidis* has been described.[10] However, the system requires purified enzyme with a coupled cofactor recycle strategy using formate dehydrogenase.

The application of baker's yeast in the reduction of carbonyl compounds such as aldehydes, ketones, and ketoesters is well known.[11] Regio- and enantioselective reduction of α-ketoesters[9] and 2,4-dioxoalkanotes[12] with baker's yeast has also been described in literature. However, the variations in enantiomeric purity and isolated yields with substrate structure, reaction conditions,

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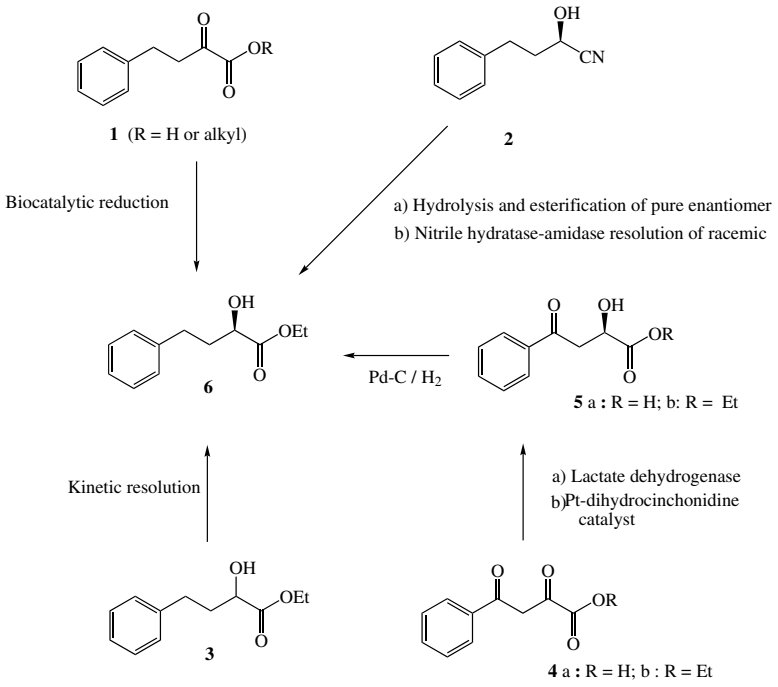
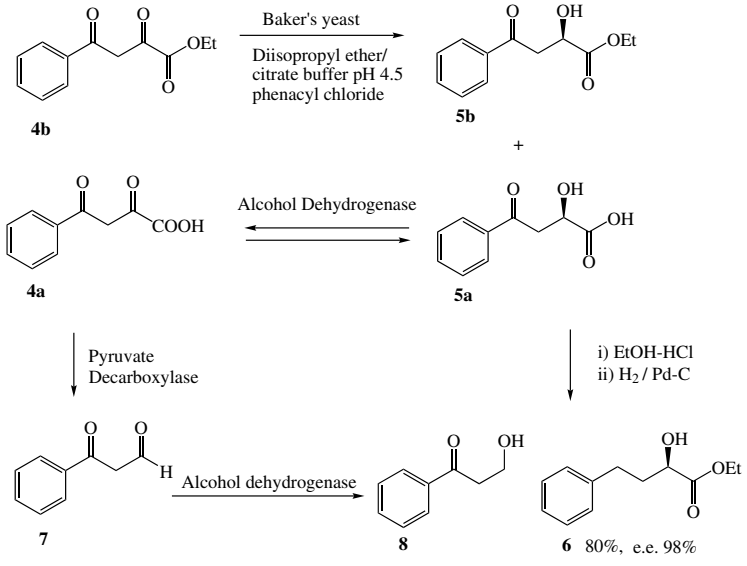


Scheme 1. Routes to (−)-ethyl (*R*)-2-hydroxy-4-phenylbutyrate (HPB ester).

presence of additives etc. are rather large. The isolated yields are modest (50–60%) while enantiomeric excesses range from 70% to 90%. However, Chang and Yang were successful in obtaining a closely related substrate, ethyl (2*R*)-2-hydroxy-4-(2-nitrophenyl)-4-oxobutyrate, in 80% ee and 85% isolated yield.[12b] Stewart and co-workers attempted the reduction of ethyl 2-oxo-4-phenylbutyrate with genetically engineered *E. coli* over-expressing alcohol dehydrogenase Y pr1p of baker's yeast. Although the enantiomeric excess of hydroxyl ester **6** was 87%, the product was obtained in only 46% yield.[12c] Herein we report the enantioselective reduction of the 2,4-dioxo ester **4b** by baker's yeast (*Saccharyomyces cerevisiae*) to give (−)-ethyl (*R*)-2-hydroxy-4-oxo-4-phenylbutyrate **5b** (ee 98%) in 80% isolated yield, which is then hydrogenated over Pd–C to obtain (−)-ethyl (*R*)-2-hydroxy-4-phenyl butyrate **6** without loss of enantiomeric purity in quantitative yield (Scheme 2).

2. Results and discussion

The reduction with baker's yeast can be performed in several ways. Most commonly fermenting baker's yeast is used but product recovery is easier when yeast cells are entrapped in calcium alginate beads.[13] Reactions



Scheme 2.

can also be performed in water-organic solvent two-phase system,[14] with immobilized yeast in benzene,[15] and even with dry cells in petroleum ether.[16] Since the substrate is highly insoluble in water, and the reaction was found to be extremely sluggish in petroleum ether (<10% conversion after two weeks), the biotransformation was performed in a two-phase system of diisopropyl ether–water (10:1 v/v). With a substrate to yeast ratio of 1:20 (w/w), the reaction was complete in 48 h at room temperature. During the reduction, substantial hydrolysis of the product 2-hydroxy-4-oxo ester **5b** to **5a** was observed (45–50%). Similar observations have been made earlier during the reduction of α-ketoesters by Nakamura et al.[17] The oily product, consisting mainly of ester **5b** and acid **5a** along with 8–10% of alcohol **7**, was treated with ethanolic HCl to convert all the product into ester and then purified by column chromatography. Product **5b**, obtained in 80% isolated yield and ee 92%, had an (*R*)-configuration, as determined by its specific rotation, retention time on an HPLC column with a chiral stationary phase, and conversion to an HPB ester of known configuration. Decarboxylation of hydroxy acid **5a** to keto alcohol **8** was observed if the reaction mixture was allowed to remain in contact with yeast for longer periods. When the reaction mixture was stirred for four days, all of **4b** was converted to **8**, which could then be isolated in 90% yield. Although these results were satisfactory, we sought to attempt improvement in enantiomeric purity.

Baker's yeast is known to possess several alcohol dehydrogenases, both (*R*)- and (*S*)-specific.[17b] The use of phenacyl chloride as an (*S*)-specific dehydrogenase inhibitor has been effectively demonstrated by Ohno and co-workers.[9] We were able to improve the enantioselectivity substantially to 98% by pretreatment of the yeast cells with phenacyl chloride. However, phenacyl chloride did not prevent the formation of **8**. The observed high enantiomeric purity of the reduction product could be due to either high enantioselectivity of the alcohol dehydrogenase or it could be due to preferential hydrolysis of the (*S*)-hydroxyester, which decomposes to the keto alcohol. To ascertain this, commercially available (*R*)- and (*S*)-hydroxyesters **5b** were treated with baker's yeast and the reaction followed by HPLC. Baker's yeast showed a strong selectivity toward the (*R*)-ester and hydrolyzed it 36 times faster than the (*S*)-ester, thus ruling out the possibility of preferential decomposition of (*S*)-ester. The reduction of the carbonyl group was highly regio- and enantiospecific.

The decarboxylation of α-keto acids to the corresponding aldehydes by pyruvate decarboxylase of baker's yeast is well known.[18] The formation of **8** could occur via an initial hydrolysis of the diketo ester **4b** to diketo acid **4a** followed by decarboxylation to keto aldehyde **7**, which is then reduced to alcohol **8** by an alcohol dehydrogenase (Scheme 2). However, we did not observe the formation of the keto acid **4a** during the reaction (HPLC analysis). Results of the reaction of diketo acid **4a** (prepared by acidic hydrolysis of the ester **4b**) with baker's yeast under identical reaction conditions were inconclusive. The reaction mixture showed the formation of at least four products with only traces of the hydroxy acid **5a** and the keto alcohol **8**.

During our studies with the reduction of α-hydroxy β-keto esters with baker's yeast, we previously observed a reversible oxido reduction of the α-hydroxy group.[19] It is probable that in the present case the α-hydroxy acid **5a**, also undergoes a reversible oxido-reduction to give keto acid **4a**. However, it also appears that the decarboxylation of the keto acid leads to several side reactions if the concentration of the keto acid is large enough, but if formed in low quantity, undergoes reduction to the keto alcohol due to a favorable enzyme to substrate ratio.

The single pot synthesis of β-keto alcohol **8** in 90% yield is an interesting route since **8** is an intermediate in the synthesis of 1-phenyl-1,3-propanediol, an important intermediate to drugs such as Fluoxetine.[20]

3. Conclusion

In conclusion, we have shown that a simple biocatalyst like baker's yeast can be used in the preparation of HPB ester in acceptable chemical yield and enantiomeric excess. Alternatively, the reaction can be prolonged to obtain 3-phenyl 3-oxo propanol.

4. Experimental

Dried baker's yeast (Blue Bird) was obtained from the local supermarket. Authentic samples of (*R*)- and (*S*)-ethyl 2-hydroxy-4-oxo-4-phenylbutyrate were obtained from Fluka. All other reagents were obtained from SD Fine Chem, India. HPLC analyses were carried out on a Hewlett Packard HP1090 unit with diode array detector and HP Chem Station software.

4.1. Ethyl 2,4-dioxo-4-phenylbutyrate 4b

Diethyl oxalate (14.6 mL, 0.1 mol) was added dropwise to a suspension of sodium ethoxide (6.8 g, 0.1 mol) in benzene (50 mL) at 8–10 °C followed by the dropwise addition of acetophenone (12.4 mL, 0.1 mol) in 30 min. The reaction mixture was stirred at 8–10 °C overnight. The resulting yellow solid was filtered, washed with benzene (2 × 20 mL), dissolved in water (20 mL) followed by addition of hydrochloric acid (25 mL, 6 M). The organic layer was extracted with diisopropyl ether, washed with brine, dried over sodium sulfate, and evaporated to give a yellow oil, which was recrystallized from hexane to obtain a pale yellow solid with low melting point (21.45 g, 92%, mp 35–37 °C). The material was sufficiently pure for direct use. IR (neat) ν (cm^{-1}): 460, 520, 600, 705, 755, 880, 1000, 1060, 1190, 1280, 1380, 1480, 1500, 1565, 1590, 1700. ^{13}C NMR ($CDCl_3$, 200 MHz): δ_{ppm} 192, 170, 162, 135, 134, 98, 63, 14. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.45 (t, 3H, $J_{1,2} = 7.00$ Hz, $J_{1,3} = 9.0$ Hz), 4.40 (q, 2H, $J_{1,2} = 7.5$ Hz, $J_{1,3} = 9.5$ Hz), 7.05 (S, 1H), 7.45–7.62 (m, 3H), 8.01 (d, 2H, $J = 8$ Hz).

4.2. 2,4-Dioxo-4-phenylbutyric acid 4a

Ethyl 2,4-dioxo-4-phenylbutyrate **4b** (2.2 g, 10 mmol) was dissolved in a mixture of acetonitrile (70 mL) and 6 M HCl (30 mL) and stirred at room temperature for 12 h. Analysis by HPLC showed that all of the ester was hydrolyzed. Acetonitrile was then removed by rotary evaporation while keeping the temperature of the water bath below 35 °C. The white solid separating out of the solution was filtered and redissolved in NaOH solution (0.2 M, 50 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL) to remove any traces of the unreacted ester. The aqueous layer was then cooled in ice and acidified. The precipitated acid was filtered, dried, and recrystallized from diisopropyl ether. The dioxo acid **4a** was obtained as white crystals (1.8 g, 94%, mp 149–150 °C; lit.[20] mp 148–150 °C). ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz): δ_{ppm} 3.98–4.56 (br s, 2H), 7.18–8.01 (m, 5H).

4.3. (*R*)- and (*S*)-2-Hydroxy-4-oxo-4-phenylbutyric acid 5a

The authentic samples of (*R*)-**5a** and (*S*)-**5a** for HPLC analysis were prepared from commercial samples of (*R*)-**5b** (Fluka cat. no. 75777) and (*S*)-**5b** (Fluka cat. no. 70224) by a method similar to the preparation of **4a** from **4b** as described in Section 4.2. Mp 143–144 °C. IR (Nujol mull) ν (cm^{-1}): 1451, 1596, 1678, 1734, 3062, 3476. ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz): δ_{ppm} 3.60 (1H, d, J = 6.6 Hz), 3.63 (1H, d, J = 4.5 Hz), 4.75 (1H, dd, J = 4.5 and 6.3 Hz), 7.53–7.65 (m, 3H), 8.0 (2H, d, J = 8 Hz). ^{13}C NMR ($CDCl_3$, 200 MHz) δ_{ppm} 197.4, 175.7, 136.7, 133, 128.3, 127.8, 66.5, 42.3.

4.4. (−)-Ethyl (*R*)-2-hydroxy-4-oxo-4-phenylbutyrate 5b and 3-phenyl 3-oxo propanol 8

Yeast cells (20 g) were suspended in sodium citrate buffer (0.1 M, pH 4.5, 50 mL) containing glucose (5 g). The cells were allowed to activate for 3 h, diisopropyl ether added (200 mL), followed by the addition of phenacyl chloride (150 mg) dissolved in diisopropyl ether (10 mL). The contents were vigorously stirred on a magnetic stirrer at room temperature for 3 h. Substrate **4b** (1.1 g, 50 mmol) dissolved in diisopropyl ether (50 mL) was added and the contents stirred. Since keto alcohol **8** was found to form as a side reaction, it was necessary to monitor the reaction by reverse phase HPLC, which was generally complete in 48 h. The reaction mixture was cooled in ice and acidified with 6 M HCl (10 mL). The organic phase was decanted and aqueous phase along with yeast cells extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporation to give a yellow viscous oil (1 g) consisting of hydroxyester **5b**, hydroxy acid **5a**, and keto alcohol **8** in proportions 50:43:7 (HPLC analysis). This oil was dissolved in ethanolic HCl (50 mL) and stirred at room temperature till all the hydroxy acid was converted to ester (HPLC analysis). Ethanol was then evaporated and the residual oil purified by column chromatography using hexane–ethyl acetate (25%) as the eluent. The fraction with R_f = 0.36 gave **5b** as a solid with low melting point (0.88 g, 80%). $[\alpha]_D^{25} = -7.25$ (c 1.0, chloroform), lit.[8b] $[\alpha]_D^{20} = -5.4$ (c 1.0, chloroform) ee 98% (HPLC analysis on chiral stationary phase). IR (neat) ν (cm^{-1}) 445, 660, 690, 1010, 1095, 1200, 1245, 1380, 1430, 1585, 1680, 1760, 2855, 2940, 3465. ^{13}C NMR ($CDCl_3$, 200 MHz): δ_{ppm} 197, 174, 134, 129, 128, 67, 62, 43, 14. ^{1}H NMR ($CDCl_3$, 200 MHz): δ_{ppm} 1.30 (t, 3H, $J_{1,2}$ = 7.5 Hz, $J_{1,3}$ = 9 Hz), 3.5 (d, 2H, J = 6 Hz), 4.30 (q, 2H, $J_{1,2}$ = 7 Hz, $J_{1,3}$ = 9.5 Hz), 4.64–4.62 (m, 1H), 7.40–7.60 (m, 3H), 7.95 (d, 2H, J = 8 Hz). Alcohol **8** was obtained as a fraction eluting with R_f = 0.31 (75 mg. 10%); IR (neat) ν (cm^{-1}) 460, 580, 665, 720, 780, 810, 880, 940, 1000, 1040, 1155, 1200, 1240, 1340, 1410, 1595, 1705, 3045, 3495. ^{13}C NMR ($CDCl_3$, 200 MHz): δ_{ppm} 200, 136, 132, 128, 57, 40. ^{1}H NMR ($CDCl_3$, 200 MHz): δ_{ppm} 3.2 (t, 2H, $J_{1,2}$ = 7.00 Hz, $J_{1,3}$ = 9.0 Hz), 4.00 (t, 2H, $J_{1,2}$ = 7.5 Hz, $J_{1,3}$ = 9.5 Hz), 7.45–7.62 (m, 3H), 8.01 (d, 2H, J = 8 Hz).

4.5. Reaction of 2,4-dioxo-4-phenylbutyric acid 4a with baker's yeast

Yeast cells (2 g) were suspended in sodium citrate buffer (0.1 M, pH 4.5, 5 mL) containing glucose (0.5 g). The cells were allowed to activate for 3 h after which 2,4-dioxo-4-phenylbutyric acid **4a** (96 mg, 0.5 mmol) dissolved in diisopropyl ether (25 mL) was added. The contents were vigorously stirred on a magnetic stirrer at room temperature and the reaction monitored by reverse phase HPLC. The product profile showed the formation of at least four products with only traces of hydroxy acid **5a** and keto alcohol **8**.

4.6. Hydrolysis of (*R*)- and (*S*)-ethyl 2-hydroxy-4-oxo-4-phenylbutyrate 5b with baker's yeast

The hydroxyester (*R*)-**5b** or (*S*)-**5b** (55 mg, 0.25 mmol) dissolved in ethanol (1 mL) was added to the yeast cells (1 g) activated for 3 h in citrate buffer (0.1 M, pH 4.5, 10 mL) containing glucose (1 g). The reaction mixture was then stirred at room temperature on a magnetic stirrer. Aliquots of the reaction mixture (100 μL) were withdrawn every 30 min, mixed with an equal volume of the mobile phase of HPLC analysis (40% acetonitrile in water containing 0.2% formic acid), centrifuged, and the supernatant analyzed by HPLC. It was observed that 50% of the (*R*)-ester was hydrolyzed in 1 h and all of the ester hydrolyzed within 2.5 h, while the (*S*)-ester required 36 h for 50% hydrolysis.

4.7. (−)-Ethyl (*R*)-2-hydroxy-4-phenyl butyrate (HPB ester) 8

Ester **5b** (0.44 g, 2 mmol) was dissolved in ethanolic HCl (1 M, 20 mL). The 5% Pd–C (40 mg) catalyst was added and the ester hydrogenated with a hydrogen filled balloon for 6 h. After completion of hydrogenation, the catalyst was filtered off and the solvent evaporated in vacuo to obtain an almost quantitative yield of **8** (0.42 g, 98%). IR (neat) ν (cm^{-1}) 720, 800, 1000, 1075, 1205, 1340,

1505, 1745, 2760, 3080, 3480. ^{1}H NMR ($CDCl_3$, 200 MHz): δ_{ppm} 1.28 (t, 3H, $J = 7.1$ Hz), 1.90–2.10 (m, 4H), 2.76 (m, 2H), 2.80 (s, br, 1H), 4.2 (m, 3H), 7.15–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ_{ppm} 175, 142, 127, 128, 130, 98, 72, 63, 32, 43, 16. $[\alpha]_D^{25} = -18.1$ (*c* 1.0, chloroform), lit.[8b] −20.8 (*c* 1.0, chloroform).

4.8. Reverse phase HPLC analysis

The disappearance of dioxo ester **4b** was followed by reverse phase HPLC. Column C-18 (250 × 5 mm), Chrompack, The Netherlands. Mobile phase 70% acetonitrile–water containing 0.2% formic acid. Flow rate 0.7 mL/min. Detection wavelength 316 nm. Retention times **4b**: 9.3 min, **4a**: 8.2 min. The product profile was analyzed on the same column at 246 nm with a mobile phase of 40% acetonitrile–water containing 0.2% formic acid. Retention times: **5b**: 10.4 min, **5a**: 5.4 min, **8**: 7.0 min.

4.9. HPLC with chiral stationary phase

Enantiomeric excesses were determined by HPLC analysis on Chiralcel OD column (250 × 5 mm), Daicel Chemical Industries, Japan. Mobile phase 10% isopropyl alcohol in hexane containing 0.1% trifluoroacetic acid; flow rate 0.7 mL/min. Compound **5b**: detection wavelength 246 nm; retention times: (*R*)-hydroxyester 20.5 min; (*S*)-hydroxyester 19.1 min; **6**: detection wavelength 254 nm; retention times: (*R*)-hydroxyester 11.1 min; (*S*)-hydroxyester 8.5 min.

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