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Asymmetric Synthesis of Optically Active Malic Acid †

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Abstract

Chiral reduction of 2-oxosuccinic acid esters with fermenting bakers' yeast gave (S)-(-)-malic acid esters in 34-54% isolated yield with 85-100% ee.

Key words: optically active, malic acid, bakers' yeast, asymmetric reduction, α-ketoester.

1. INTRODUCTION

Optically active malic acid has been efficiently employed as a chiral building block for asymmetric synthesis of optically active natural products.[1-4] Although optically active malic acid is commercially available, there are few reports on its asymmetric syntheses.[5,6] In this paper, we report highly asymmetric synthesis of optically active malic acid esters with fermenting bakers' yeast.

2. MATERIALS AND METHODS

Chemicals

Ethyl 2-oxosuccinate (**1a**) was obtained from sodium salt of diethyl oxalacetate purchased from Kanto Chemical Co. LTD, as shown below. Sodium salt of diethyl oxalacetate was dissolved in water, acidified with 10% HCl, and then the organic materials were extracted with ethyl acetate. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated to give **1a**. Other 2-oxosuccinates were prepared by modifying the known method.[7]

1-methyl 4-butyl 2-oxosuccinate (**1b**)

To a solution of diisopropylamine [1.88 g (2.6 ml), 25.9 mmol] in tetrahydrofuran (THF) (17 ml) was added 12.4 ml (18.6 mmol) of 15% butyllithium in hexane at -20 °C. After 20 min, butyl acetate [2.0 g (2.3 ml), 17.2 mmol] was added at -78 °C. The mixture was stirred for 10 min and subsequently a solution of dimethyl oxalate (2.07 g, 19.2 mmol) in THF (7 ml) was added dropwise. After being stirred for 30 min at -78 °C and for 1 h at room temperature, the mixture was poured into ice water and acidified with 10% HCl. The organic materials were extracted with ethyl acetate, washed with water, and dried over $MgSO_4$. Concentration

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of the solvent left 3.18 g of an oil, which was chromatographed on SiO_2 (hexane-ethyl acetate = 20:1-1:1) to give 1.82 g (52.3%) of **1b**: Colorless oil, IR: 3000, 1740, 1660, 1280, 1118, 795 cm^{-1}. ^1H NMR (60 MHz, CCl_4, coupling constants in Hz) δ=1.00 (t, *J* = 7, $CO_2(CH_2)_3CH_3$), 1.18-1.80 (m, $CO_2CH_2(CH_2)_2CH_3$), 3.85 (s, CO_2CH_3), 4.21 (t, *J* = 7, CO_2CH_2), 5.91 (s, CH_2CO). Other 2-oxosuccinates were prepared by the same method.

1-Methyl 4-*tert*-butyl 2-oxosuccinate (**1c**): Colourless oil, 53% Yield, IR: 3000, 1740, 1655, 1260, 1150, 835 cm^{-1}. ^1H NMR (60 MHz, CCl_4) δ=1.50 (s, $C(CH_3)_3$), 3.56 (s, CH_2CO), 3.78 (s, CO_2CH_3), 5.78 (s, CH=C-OH), 11.56 (broad s, OH).

1-Methyl 4-benzyl 2-oxosuccinate (**1d**): Colourless oil, 36% Yield, IR: 1740, 1660, 1100, 780 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ=3.69 (s), 3.75 (s), 5.12 (s), 5.90 (s), 7.19 (s), 11.43 (broad s).

1-Isopropyl 4-ethyl 2-oxosuccinate (**1e**): Colorless oil, 70% yield, IR: 1730, 1660, 1100, 780 cm^{-1}. ^1H NMR (60 MHz, CCl_4, coupling constants in Hz) δ=1.31 (t, *J* = 7), 1.32 (d, *J* = 7), 3.66 (s), 4.23 (q, *J* = 7), 5.06 (m, *J* = 7), 5.85 (s).

Microorganisms

Industrial bakers' yeast was purchased from Oriental Yeast Co. LTD., and it was stored in a refrigerator at 4 °C. The bakers' yeast was used within 10 days.

Fermentation procedure, and Isolation and Purification of Products

Fermentation was carried out in a thermostat bath at 32±2 °C. All glasswares were sterilized by boiling water before use.

For example, the preparation of (*S*)-(-)-diethyl malate (**2a**) is shown below. To a mixture of glucose (42 g), KH_2PO_4 (0.6 g), $NH_4H_2PO_4$ (0.6 g), $MgSO_4$ (0.16 g), $CaCO_3$ (1.6 g), and boiling water (600 ml) was added industrial bakers' yeast (12 g, Oriental Yeast Co.) and the mixture was stirred for 20 min at 33 °C. To the fermenting mixture was added **1a** (4.32 g, 23.0 mmol) and the resulting mixture was stirred at 33 °C. The amount of glucose was checked by a test paper for sugar diabetes. When the amount of glucose was less than 0.1%, glucos was added. So, glucose (42 g) was added after 7 and 19 h. After 23 h the organic materials were extracted with ethyl acetate. The crude product (3.55 g) was chromatographed on SiO_2 (hexane-ethyl acetate = 10:1) to afford 2.00 g (43%) of **2a**: Thin Layer Chromatography (hexane- ethyl acetate = 1:1), R_f 0.47.

3. IDENTIFICATION OF PRODUCTS

Analytical spectra were obtained with the following instruments: IR spectra, a JASCO Model A-102; ^1H NMR spectra (60 MHz), a JEOL JNM-PMX60SI apparatus; ^1H NMR spectra (100 MHz) and ^{13}C NMR spectra (25 MHz), a JEOL JNM-FX100 apparatus. Optical rotations were measured on a JASCO DIP-4 spectrometer. Enantiomeric excess was determined by ^1H NMR (100 MHz) spectrum in the presence of $Eu(hfc)_3$.

(*S*)-(-)-Diethyl Malate (**2a**): Colorless oil, IR and 1H NMR data were identical with those of an authentic sample. When 1H NMR (100 MHz) spectrum was measured in the presence of Eu(hfc)3 (0.5 molar ratio), only one enantiomer was observed.

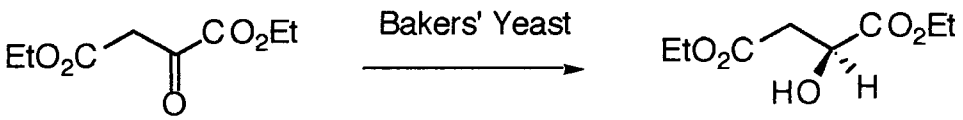
(*S*)-(-)-1-Methyl 4-*tert*-butyl 2-Hydroxysuccinate (**2c**): Colorless oil, IR: 3400, 1735, 1150, 840 cm^{-1}, ^1H NMR (60 MHz, CCl_4, coupling constants in Hz): δ=1.50 (s), 2.65 (d, *J* = 8), 3.60 (s), 3.80 (s), 4.30 (t, J = 8).

(*S*)-(-)-1-Methyl 4-Benzyl 2-Hydroxysuccinate (**2d**): Colorless oil, IR: 3500, 1740, 1170, 750 cm^{-1}, ^1H NMR (60 MHz, CCl_4, coupling constants in Hz): δ = 2.71 (d, *J* = 6), 3.61 (s), 3.83 (broad s), 4.36 (t, *J* = 6), 5.01 (s), 7.17 (s).

(*S*)-(-)-1-Isopropyl 4-Ethyl 2-Hydroxysuccinate (**2e**): Colorless oil, IR: 3400, 1740, 1180, 1040 cm^{-1}, ^1H NMR (60 MHz, CCl_4, coupling constants in Hz): δ = 1.23 (t, *J* = 7), 1.24 (d, *J* = 6), 2.63 (d, *J* = 6), 3.32 (broad s), 4.08 (q, *J* = 7), 4.27 (t, *J* = 6).

4. RESULTS

Enantioselective reductions of α-keto esters with fermenting bakers' yeast giving optically active α-hydroxy esters are well known.[7,8,9] However, the treatment of 2-oxosuccinates **1** with fermenting bakers' yeast is not reported. Recently we found that diethyl 2-oxosuccinate (**1a**) is reduced with bakers' yeast to afford almost optically pure (*S*)-(-)-diethyl malate (**2a**). Since the absolute configuration and the optical purity of the reduced



1a (*S*)-(-)-Diethyl Malate (**2a**)

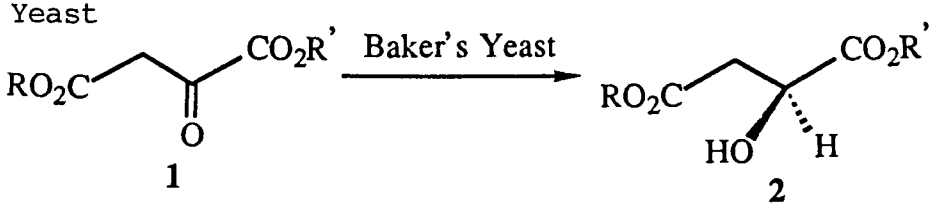
products depends strongly upon the nature of the ester moiety,[10,11] some 2-oxosuccinic acid esters **1** were prepared and reduced with fermenting bakers' yeast. These results are summarized in Table 1. Optical purity of diethyl malate (**2a**) obtained by the present reaction was shown to be 97-100% ee by comparison of the optical rotation with that of the authentic sample.[12,13] The optical purities of other esters such as **2b** (R = *n*-C_4H_9, R' = CH_3), **2c** (R = *t*-C_4H_9, R' = CH_3), and **2d** (R = $CH_2C_6H_5$, R' = CH_3) decreased than that of **2a** as shown in Table 1.

All of the reactions afforded (*S*)-malates in moderate yields regardless of the ester moiety.

Absolute Configuration of the Malates **2**

The absolute configuration of the optically active malates **2** was determined as (*S*) after conversion of **2** to the 1,2-acetonide (**5**) of (*S*)-(+)-1,2,4-butanetriol by comparing the sign of optical rotation with that of an authentic sample. Reduction of (*S*)-(-)-1-methyl 4-*tert*-butyl 2-hydroxysuccinate (**2c**) with $NaBH_4$ in methanol

Table 1. Asymmetric Reduction of 2-Oxosuccinates **1** to 2-Hydroxysuccinates **2**[a] with Fermenting Baker's Yeast



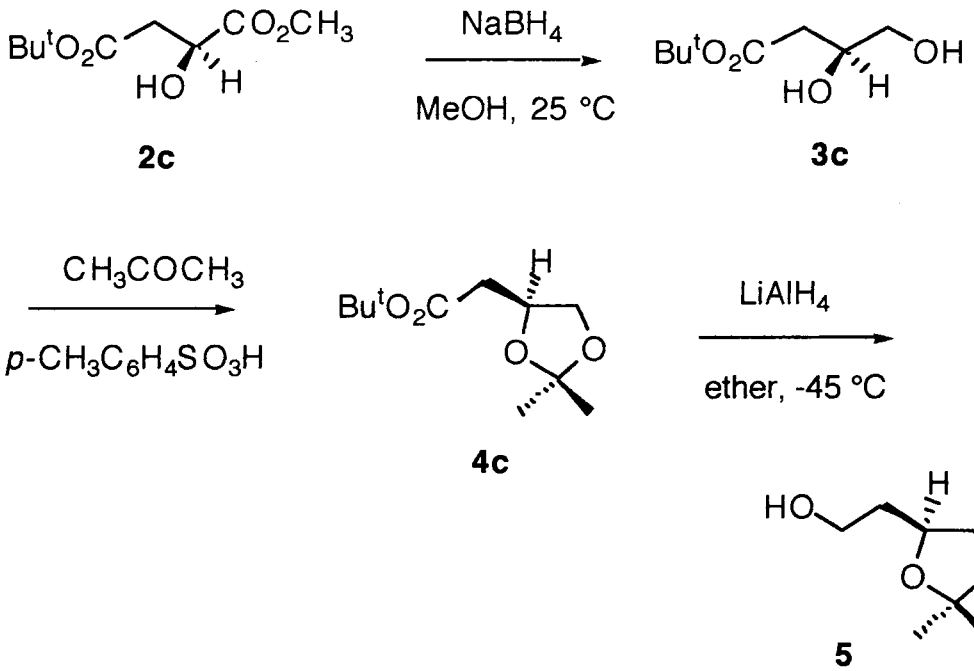
1 **2**

No.	R	R'	Chem. Yield[b] %	Optical Yield %ee	$[\alpha]_D$ (c, solvent)	Absolute Configuration
a	C_2H_5	C_2H_5	43	97-100[c]	$[\alpha]_D^{23}$ -9.94° (neat)	S
b	n-C_4H_9	CH_3	52	95[d]	$[\alpha]_D^{17}$ +1.72° (2.67, $CHCl_3$)	S
c	t-C_4H_9	CH_3	47	100[e]	$[\alpha]_D^{33}$ +4.30° (3.07, $CHCl_3$)	S
d	$CH_2C_6H_5$	CH_3	54	95[d]	$[\alpha]_D^{26}$ +0.78° (5.65, $CHCl_3$)	S
e	C_2H_5	$CH(CH_3)_2$	34	85[f]	$[\alpha]_D^{22}$ -11.25° (3.20, $CHCl_3$)	S

[a] Compounds **2** except **2a** are new. Satisfactory spectral and analytical data were obtained. [b] Isolated yield. [c] Calculated by comparison with the known data: $[\alpha]_D$ -10.3° 0.1 (neat) ; $[\alpha]_D^{25}$ -9.3° (neat) (see ref. 13). [d] Pure by ^1H NMR analysis in the presence of $Eu(hfc)_3$. [e] By comparing the optical rotation after the conversion to dimethyl malate. [f] By comparing the optical rotation after the conversion to malic acid.

at 25 °C gave *tert*-butyl (*S*)-3,4-dihydroxybutanoate (**3c**) in 78% yield. Acetonidation of diol **3c** was carried out by stirring the solution of **3c** in acetone in the presence of catalytic amount of *p*-toluenesulfonic acid for 11 h, giving *tert*- butyl (*S*)-3,4-O-isopropylidene-3,4-dihydroxybutanoate (**4c**). The subsequent reduction of the acetonide **4c** with $LiAlH_4$ in dry ether at -45 °C afforded (*S*)-(+)-1,2-isopropylidenebutane-1,2,4-triol (**5**): $[\alpha]_D^{20}$+2.68° (c 0.82, EtOH)[lit.:[3] $[\alpha]_D^{20.5}$-3.7° (c 3.6, EtOH) for (*R*)-(-)-**5**]. Its conversion was also conducted by the acetonidation of (*S*)-butane-1,2,4-triol (**6**) obtained by the direct reduction of **2** with $LiAlH_4$. Spectral data of **5** were identical with those of the literature.[3]

The present method provides optically pure (*S*)-(-)-diethyl malate in a moderate yield by experimentally simple procedures.



2c **3c** **4c** **5**

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