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# Efficient kinetic resolution of (±)-4-methyl-Hajos–Parrish ketone by baker's yeast reduction

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**Abstract**

Kinetic resolution of (±)-4-methyl-Hajos–Parrish ketone (±)-**2a** using baker's yeast reduction was investigated. The reaction rate and enantiomeric purity depended on the concentration of substrate and yeast. Under concentrated conditions, (−)-**2a** and the alcohol (+)-**3** were obtained in high enantiomeric excess. © 2000 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Optically active Hajos–Parrish ketone **2a** and its derivatives have been widely used as intermediates for natural product syntheses. (+)-**2a** is generally prepared using L-proline catalyzed aldol reaction of **1** followed by dehydration in good chemical yield and enantiomeric excess.[1] As part of a program directed towards the synthesis of trinervitane diterpenes, e.g. **4**,[2] we required its 4-methyl derivative (−)-**2b** in enantiomerically pure form. However, Paquette et al. reported that amino acid catalyzed asymmetric reaction to afford (+)-**2b** did not exceed 75% enantiomeric excess under their most favorable conditions.[3c] Recently, Hagiwara et al. prepared enantiomerically pure (+)-**2b** using stoichiometric L-phenylalanine followed by recrystallization in 45% chemical yield.[3e] To apply this method to the preparation of (−)-**2b**, expensive D-phenylalanine is required stoichiometrically. We envisioned that the requisite compound could be prepared on a large scale by kinetic resolution of (±)-**2b** using baker's yeast reduction,[4,5] which has been successfully utilized in the asymmetric reduction of α-hydroxy ketones in our laboratory.[6]

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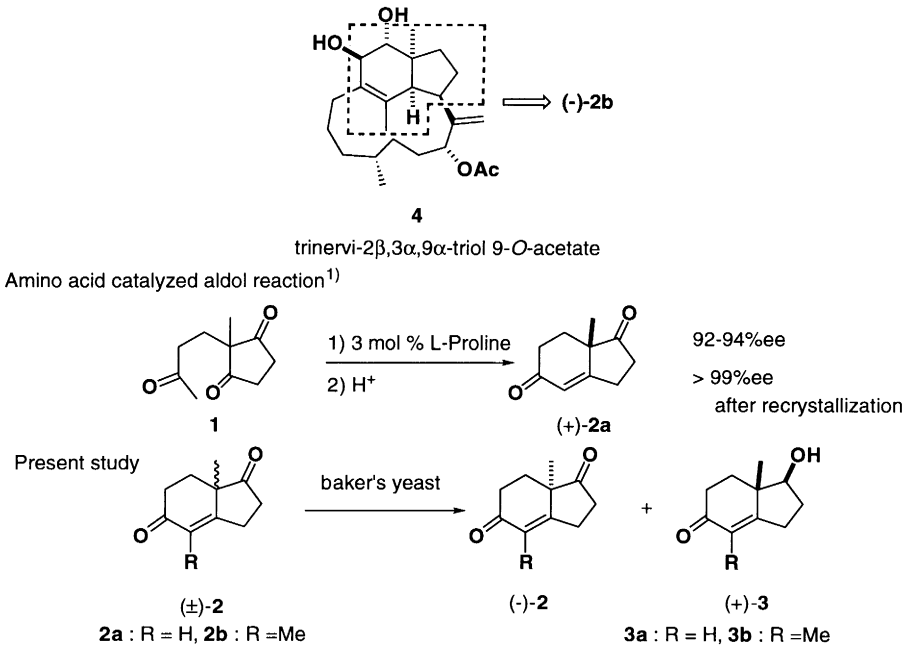
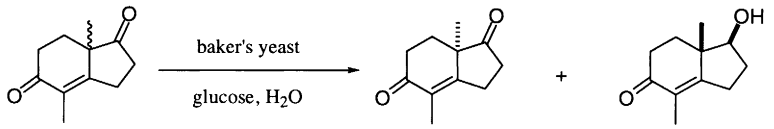



## 2. Results

The kinetic resolution of (±)-**2b** under various conditions is summarized in Table 1. At first the reduction was run under the standard conditions used for α-hydroxy ketones.[6] After 24 h, 20% of **2b** was reduced and (+)-**3b** was obtained preferentially, but its enantiomeric excess was only 72% ee (entry 1). The absolute stereochemistry of (−)-**2b** was determined by the comparison with the reported sign of specific rotation for (+)-**2b**.[3a,b] Complete diastereoselectivity was observed in the reduction and the relative stereochemistry was determined as *cis* because the spectroscopic data of (+)-**3b** were identical to those for the compound produced by $NaBH_4$ reduction of (−)-**2b**.[3d,e] Ethanol did not affect the efficiency of the reduction (entry 1 vs entry 2). To improve the enantioselectivity, the substrate concentration was varied. At high concentration of substrate and baker's yeast, the reaction rate and enantiomeric excess (ee) were dramatically increased (entry 3). This result indicated that several enzymes participated in the reduction.[7] Thus, a high concentration of substrate (entry 4) improved the ee of (−)-**2b** but not the reaction rate. Further high concentration of baker's yeast led to the reduction proceeding smoothly and enantiomerically pure (−)-**2b** was recovered (entry 5). Next we investigated the yield and ee under a variety of reaction times (entries 5–9). After 3 h (+)-**3b** was isolated in 93% ee and 42% yield (entry 6). Recovering enantiomerically pure (+)-**2b** require 18 h under the same reaction conditions (entries 6–9). Thus, both (−)-**2b** and (+)-**3b** were found to be obtained in good chemical yield and enantiomeric excess by changing reaction time.

Finally this reduction was applied to Hajos–Parrish ketone (±)-**2a** and Wieland–Miecher ketone (±)-**5** (Scheme 1). Kinetic behavior of (±)-**2a** was almost the same as (±)-**2b**. (+)-**3a** was obtained in 94% ee and 42% yield after 3 h, and (−)-**2a** with 99.5% ee was recovered in 42% yield after 18 h.[8] In contrast to (±)-**2**, the reduction of Wieland–Miecher ketone (±)-**5**[9] was very slow, although almost enantiomerically pure (+)-**6a** was obtained in 32% yield along with the ketone (−)-**5** with 59% ee after 24 h.[10] A small amount of (−)-**5** was also reduced from the same face as (+)-**5** to afford (−)-**6b** in 88% ee.

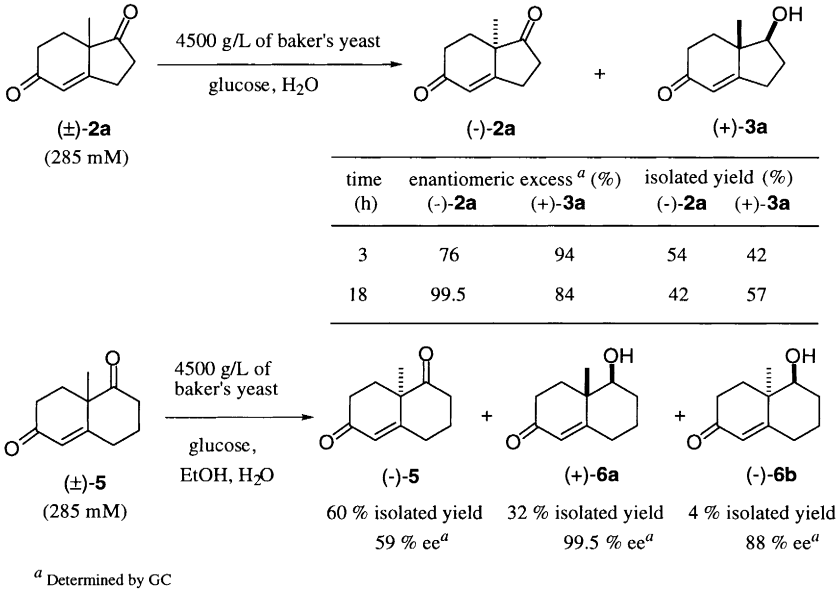
Table 1
Kinetic resolution of (±)-4-methyl-Hajos–Parrish ketone (±)-**2b** by baker's yeast reduction




(±)-**2b** (-)-**2b** (+)-**3b**

| entry | substrate concentration (mM) | baker's yeast concentration (g / l) | time (h) | enantiomeric excess (%)[b] (-)-**2b** | (+)-**3b** | relative intensity on GC analysis **2b** : **3b** | isolated yield (%) (-)-**2b** | (+)-**3b** |
|---|---|---|---|---|---|---|---|---|
| 1[a] | 19 | 100 | 24 | 20 | 72 | 1 : 0.25 | ——[c] | ——[c] |
| 2 | 19 | 100 | 24 | 25 | 75 | 1 : 0.28 | ——[c] | ——[c] |
| 3 | 95 | 500 | 24 | 90 | 88 | 1 : 0.94 | ——[c] | ——[c] |
| 4 | 285 | 500 | 24 | 35 | 95 | 1 : 0.34 | ——[c] | ——[c] |
| 5 | 285 | 4500 | 24 | 100 | 72 | 1 : 1.21 | 42 | 54 |
| 6 | 285 | 4500 | 3 | 67 | 93 | 1 : 0.59 | 57 | 42 |
| 7 | 285 | 4500 | 6 | 93 | 90 | 1 : 0.97 | ——[c] | ——[c] |
| 8 | 285 | 4500 | 8 | 97 | 88 | 1 : 1.02 | ——[c] | ——[c] |
| 9 | 285 | 4500 | 18 | 100 | 79 | 1 : 1.14 | 44 | 50 |

[a] $H_2O$ / EtOH mixure (10 / 1 ) was used as solvent. [b] Determined by GC [c] Not isolated.




(±)-**2a** (285 mM) (-)-**2a** (+)-**3a**

| time (h) | enantiomeric excess[a] (%) (-)-**2a** | (+)-**3a** | isolated yield (%) (-)-**2a** | (+)-**3a** |
|---|---|---|---|---|
| 3 | 76 | 94 | 54 | 42 |
| 18 | 99.5 | 84 | 42 | 57 |

(±)-**5** (285 mM) (-)-**5** (+)-**6a** (-)-**6b**

60 % isolated yield, 59 % ee[a] 32 % isolated yield, 99.5 % ee[a] 4 % isolated yield, 88 % ee[a]

[a] Determined by GC

Scheme 1. Kinetic resolution of (±)-Hajos–Parrish ketone (±)-**2a** and (±)-Wieland–Miecher ketone (±)-**5**

Further work toward the synthesis of trinervitane diterpenes using (−)-**2b** obtained by this kinetic resolution is currently underway and will be reported in due course.

## 3. Experimental

### 3.1. General

Melting points (uncorrected) were determined by using a Yanagimoto micro melting point apparatus. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter using sodium light (D line, 589.3 nm) and are recorded in degrees; concentrations (*c*) are recorded in g/100 mL. Substrates (±)-**2a**,[11] (±)-**2b**[3b] and (±)-**5**[12] were prepared according to literature procedures. Baker's yeast was purchased from Kyowa Hakko Co., Ltd (Japan).

### 3.2. Determination of enantiomeric purity by gas chromatography

Enantiomeric purity analyses were carried out with both racemic and enantioenriched compounds. Enantiomeric purity was determined by gas chromatography (Shimadzu GC-14B gas chromatograph equipped with a flame ionization detector) using a chiral capillary column. Analytical conditions for each compound are as follows:

**2a**: Column: SPELCO gamma-DEX™ 225; oven temp.: 190°C; retention time: (+)-**2a**: 9.6 min. (−)-**2a**: 10.1 min.

**3a**: Column: SPELCO beta-DEX™ 120; oven temp.: 200°C; retention time: (+)-**3a**: 10.6 min. (−)-**3b**: 10.9 min.

**2b**: Column: SPELCO gamma-DEX™ 225; oven temp.: 190°C; retention time: (+)-**2b**: 10.2 min. (−)-**2b**: 10.9 min.

**3b**: Column: SPELCO beta-DEX™ 120; oven temp.: 180°C; retention time: (+)-**3b**: 20.8 min. (−)-**3b**: 21.5 min.

**5**: Column: SPELCO gamma-DEX™ 225; oven temp.: 210°C; retention time: (+)-**5**: 8.4 min. (−)-**5**: 8.8 min.

**6**: Column: SPELCO beta-DEXrm 225; oven temp.: 180°C; retention time: (+)-**6a**: 31.7 min. (−)-**6a**: 32.8 min. (+)-**6b**: 36.2 min. (−)-**6b**: 35.4 min.

### 3.3. Representative procedure for baker's yeast reduction

#### 3.3.1. Kinetic resolution of 4,7a-dimethyl-2,3,7,7a-tetrahydro-6H-indene-1,5-dione **2b** (Table 1 entry 9)

A mixture of 9.0 g of baker's yeast, 3.5 g of glucose and 2 mL of $H_2O$ was incubated for 0.5 h. The mixture was added to (±)-**2b** (104.3 mg, 0.585 mmol). After stirring for 18 h at room temperature, 10 g of Celite and 30 mL of AcOEt were added and stirred for 1 h. The mixture was filtered through Celite, which was washed with AcOEt. The combined filtrates were concentrated under reduced pressure. The crude product (211.4 mg) was analyzed by gas chromatography to determine the enantiomeric purity of **2b** and **3b**. Flash chromatography of crude product on silica gel (4:1 hexane:EtOAc to 1:1 hexane:EtOAc) gave 46.4 mg (0.257 mmol, 44%) of (−)-**2b** and 53.0 mg (0.294 mmol, 50%) of (+)-**3b**.

In the case of the reduction of solid substrate ((±)-**2a** and (±)-**5**), the substrate was dissolved in a small amount of ethanol (100 mg of **2a** or **5** in 0.2 mL of ethanol).

### 3.4. (−)-(7aR)-7a-Methyl-2,3,7,7a-tetrahydro-6H-indene-1,5-dione (−)-**2a**

Colorless needles: mp 65–66°C (lit.[1] 64–66°C); $[\alpha]_D^{25}$ −355 (*c* 1.0, toluene) (lit.[1] for (−)-**2a** $[\alpha]_D^{25}$ +347.5–349 (*c* 1.0, toluene)).

### 3.5. (+)-(1S,7aS)-1-Hydroxy-7a-methyl-1,2,3,6,7,7a-hexahydro-inden-**5**-one (+)-**3a**

Colorless needles: mp 47–48°C; $[\alpha]_D^{20}$ +82.5 (*c* 1.1, $CHCl_3$); IR (KBr) 3383, 1640 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.79 (1H, brs), 3.86 (1H, ddd, *J*=5.8, 7.4, 10.4 Hz), 2.71 (1H, tdd, *J*=2.2, 11.8, 19.8 Hz), 2.33–2.61 (3H, m), 2.06–2.20 (2H, m), 1.71–1.98 (3H, m), 1.15 (3H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 15.1, 26.4, 29.2, 33.3, 34.1, 45.2, 80.7, 123.5, 174.8, 199.1; MS (EI) 109 (base), 166 ($M^+$); HRMS (EI) calcd for $C_{10}H_{14}O_2$ ($M^+$) 166.0993, found 166.0996. The spectroscopic data were identical to those for the compound produced by $NaBH_4$ reduction of (−)-**2a**.[8]

### 3.6. (−)-(7aR)-4,7a-Dimethyl-2,3,7,7a-tetrahydro-6H-indene-1,5-dione (−)-**2b**

Colorless needles: mp 43–44°C; $[\alpha]_D^{21}$ −328 (*c* 1.1, $CHCl_3$) (lit.[3b] $[\alpha]_D^{25}$ −337 (*c* no description, $CHCl_3$)).

### 3.7. (+)-(1S,7aS)-1-Hydroxy-4,7a-dimethyl-1,2,3,6,7,7a-hexahydro-inden-5-one (+)-**3b**

94% ee: Colorless oil. $[\alpha]_D^{25}$ +68.7 (*c* 1.1, $CHCl_3$); IR (film) 3416, 1642 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.84 (1H, dd, *J*=7.4, 10.4 Hz), 2.50–2.62 (2H, m), 2.34–2.46 (2H, m), 2.28 (1H, brs), 1.72–1.92 (2H, m), 1.66 (3H, s), 1. 12 (3H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 10.7, 15.2, 25.6, 29.5, 33.3, 34.0, 45.0, 80.9, 128.9, 167.9, 198.8; MS (EI) 123, 180 ($M^+$, base); HRMS (EI) calcd for $C_{11}H_{16}O_2$ ($M^+$) 180.1149, found 180.1139. The spectroscopic data were identical to those for the compound produced by $NaBH_4$ reduction of (−)-**2b**.[3d,e]

### 3.8. (−)-(8aR)-8a-Methyl-3,4,8,8a-tetrahydro-2H,7H-naphthalene-1,6-dione (−)-**5**

76% ee: Colorless solid: mp 45–49°C (lit.[10a] 49–50°C); $[\alpha]_D^{21}$ −72.4 (*c* 1.1, toluene) (lit.[10a] for (+)-**5** $[\alpha]_D^{25}$ +97.3 (*c* 1.0, toluene)).

### 3.9. (+)-(4aS,5S)-5-Hydroxy-4a-methyl-4,4a,5,6,7,8-hexahydro-3H-naphthalen-2-one (+)-**6a**

Colorless needles: mp 42–43°C (lit.[10b] 45–48°C); $[\alpha]_D^{20}$ +202 (*c* 0.72, benzene) (lit.[10b] $[\alpha]_D^{26}$ +198.5 (*c* 0.93, benzene)). The spectroscopic data were identical to those for the compound produced by $NaBH_4$ reduction of (−)-**5**.[10b]

### 3.10. (−)-(4aR,5S)-5-Hydroxy-4a-methyl-4,4a,5,6,7,8-hexahydro-3H-naphthalen-2-one (−)-**6b**

88% ee: Colorless solid: mp 93–94°C (lit.[9] 94–95°C); $[\alpha]_D^{20}$ −90.0 (*c* 1.0, benzene) (lit.[9] $[\alpha]_D^{25}$ −111 (*c* 1.3, benzene)). IR (KBr) 3434, 1644 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.86 (1H, brs), 3.66 (1H, brs), 2.58 (1H, m), 2.36–2.50 (3H, m), 2.04 (1H, m), 1.64–1.86 (4H, m), 1.51 (1H, td, *J*=4.4, 12.1 Hz), 1.25 (3H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 19.8, 21.8, 28.7, 30.7, 31.7, 34.0, 40.9, 75.3, 126.9, 167.8, 199.4; MS (EI) 162 (base), 180 ($M^+$); HRMS (EI) calcd for $C_{l1}H_{16}O_2$ ($M^+$) 180.1149, found 180.1126.

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