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Yeast-mediated Synthesis of Optically Active Diols with C_2-Symmetry and (*R*)-4-Pentanolide

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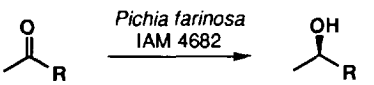
Abstract: Reduction of some diketones and a ketoacid with yeast, *Pichia farinosa* IAM 4682 was examined. The reduction of carbonyl groups proceeded highly selectively with an *anti*-Prelog fashion to give (*R*)-alcohols. (2*R*,5*R*)-2,5-Hexanediol (83% yd., >99% *e.e.*, 95% *d.e.*), (2*R*,4*R*)-2,4-pentanediol (94% yd., >99% *e.e.*, 98% *d.e.*), and (*R*)-4-pentanolide (67% yd., >99% *e.e.*) were highly efficiently obtained from the corresponding ketones. Effect of the structure of substrate on the stereochemical course as well as the selectivity were discussed.

Introduction

Recent progress of microorganism-mediated enantioselective reduction of carbonyl compounds promoted its wide range of application in asymmetric synthesis.[1] While conventional bakers' yeast has an enantiofacial preference known as "Prelog rule",[2] another type of biocatalysts with a complementary selectivity has recently become available for synthetic chemists.[3] A yeast, *Pichia farinosa*, which has been developed by ourselves[4-9] is one of the representative of those examples. Satisfactory and also unsuccessful results obtained so far as shown in Table 1 suggested us the important role of a polar neighboring functionality with the carbonyl groups in the molecules.

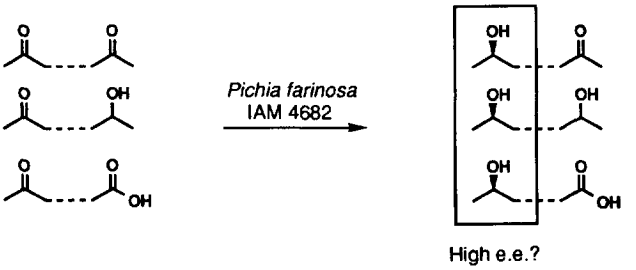
Table 1. Reduction of methyl ketones with *Pichia farinosa* IAM 4682



R	% *e.e.*
n-C_6H_{13}	0[a]
$-(CH_2)_8CO_2Me$	33[b]
$-(CH_2)_9CO_2Me$	61[b]
$-(CH_2)_{10}CO_2Me$	65[b]
$-CH_2CH{=}CH(CH_2)_6CO_2Me$	>95[b]
$-(CH_2)_2CH{=}CMe_2$	88[c]
$-(CH_2)_2SPh$	91[d]

a) unpublished result; b) ref. 7; c) ref. 4; d) ref. 9.

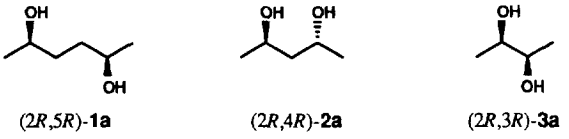
This situation invoked us a question. Does another carbonyl, hydroxyl, and/or carboxyl group work as the functional group which enhances the enantioselectivity of the reaction? Here we report on the reduction of such substrates, diketones and a ketoacid, which afforded a new routes for the preparation of highly enantiomerically enriched diols and a lactone.



Scheme 1

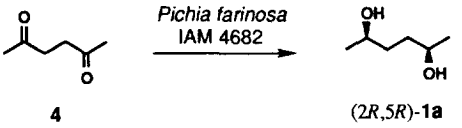
Reduction of 2,5-Hexanedione

Enantiomerically pure 2,5-hexanediol **1a** [(*R*,*R*)- and/or (*S*,*S*)-form], together with the corresponding lower homologs **2a** and **3a** (Fig. 1) have great synthetic utility as chiral auxiliary in asymmetric syntheses.[10] So far, a modern preparative methods, a couple of procedure have been reported, such as chemical[11] or biochemical[12] reduction of the corresponding diketone **4**, kinetic resolution of corresponding racemate [(2*R**,5*R**)-**1a**].[13] Among them an yeast-mediated asymmetric reduction of **4** has an advantage in terms of convenience and yield, especially compared with the optical resolution of the racemate. Only the preparation of (2*S*,5*S*)-**1a** has been report, however, by a bakers' yeast-mediated reduction of **4**.[12]

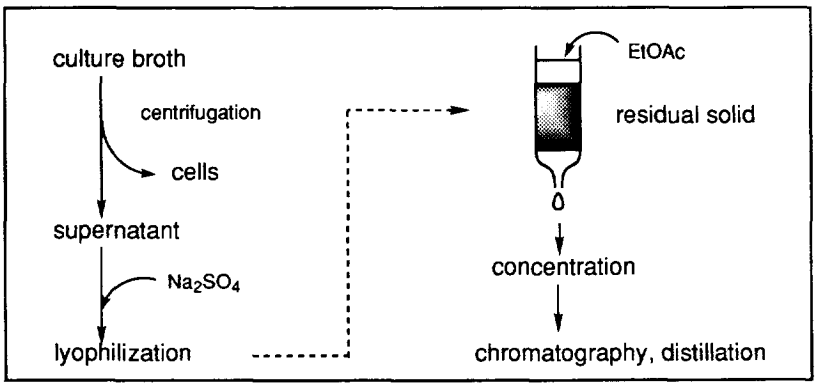


(2*R*,5*R*)-**1a** (2*R*,4*R*)-**2a** (2*R*,3*R*)-**3a**

Fig. 1



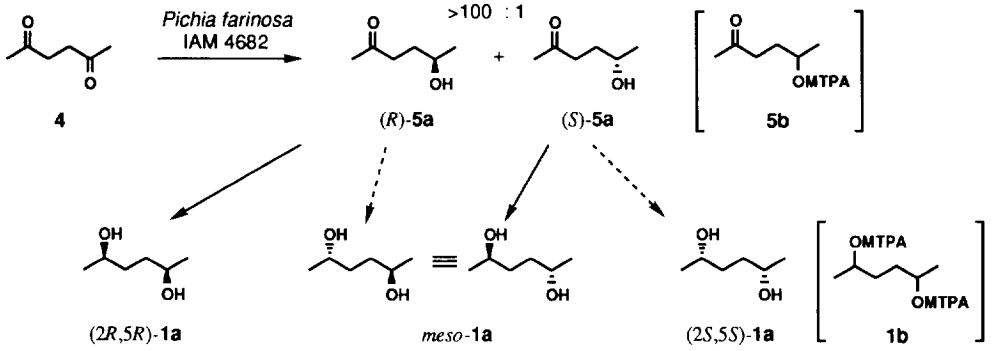
4 (2*R*,5*R*)-**1a**



Scheme 2

The reduction of **4** (500 mg, 4.38 mmol) was carried out by the harvested cells of *Pichia farinosa* IAM 4682 (wet, 40 g) in a glucose medium under anaerobic condition[4] at 30 °C for 2 days. The reaction proceeded smoothly, the substrate being completely consumed in 2 days. However, our first attempt for an extractive workup only resulted in a disappointing yield, because of the hydrophilic nature of the product, 2,5-hexanediol **1a**. At this point, it was necessary to develop an effective method for extracting highly polar organic compound. We were inspired by an extraction of a hydroxy acid from aqueous phase by absorbing water with anhydrous sodium sulfate which had been reported by Utaka and co-workers.[14] Our attempt was an exhaustive removal of water from aqueous phase by lyophilization after adding sodium sulfate as illustrated in Scheme 2. The resulting organic materials were extracted by eluting a column filled with a powdery sodium sulfate which absorbed the product, with an appropriate organic solvent system.

This method really worked well to give the desired product **1a** in 83% yield. The stereochemical composition of resulting **1a** was revealed by combining NMR analysis of **1a** itself and also its corresponding MTPA ester **1b** as follows: (2*R*,5*R*) : *meso* : (2*S*,5*S*) = 97.5 : 2.5 : 0 (Scheme 3).



Scheme 3

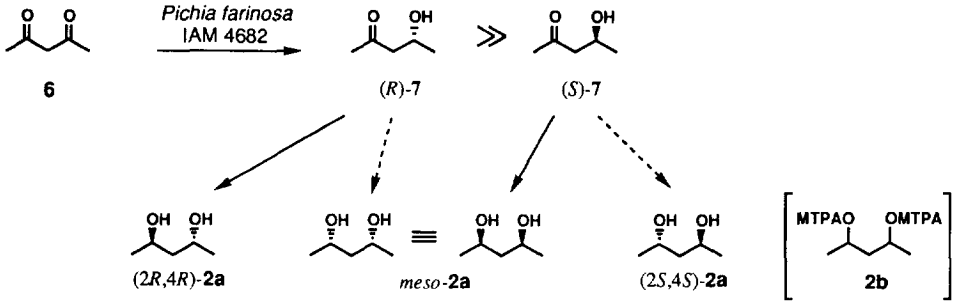
The reduction proceeded quite selectively with the *anti*-Prelog rule fashion. Recrystallization of this product afforded a enantiomerically and diastereomerically pure sample (85% recovery). We then interested in the *e.e.* of an intermediate, a hydroxy ketone **5a**. Fortunately, in a separated experiment under a lower ratio of yeast cell to substrate (10 g / 500 mg), we could isolate this intermediate and the *e.e.* was determined to be more than 99% by an NMR analysis of the corresponding (*R*)-MTPA ester **5b**. Based on the clarified data, the total scheme can be illustrated as shown in Scheme 3. The presence of carbonyl and hydroxyl groups at γ-position was really effective for an enantioselective reduction by this yeast.

Reduction of 2,4-Pentanedione

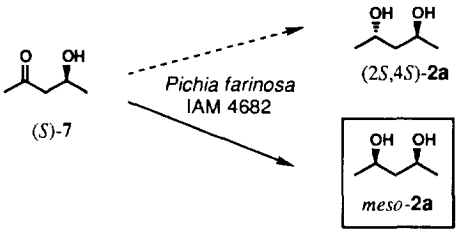
We proceeded to the reduction of 2,4-pentanedione **6**, a simplest representative of β-diketones. So far most of the examples in regard to the biochemical reduction[15,16] of β-diketones have shown that the major product is the corresponding hydroxy ketone. In our case, however, the reduction proceeded to give the corresponding diol **2a** in 94% yield. The spectral and chromatographic analyses of **2a** and the corresponding (*R*)-MTPA ester **2b** revealed that the present **2a** consisted of the stereoisomers in the following ratio; (2*R*,4*R*) : *meso* : (2*S*,4*S*) = 98.8 : 1.2 : 0 (Scheme 4). In this case also, the reduction proceeded in a quite stereoselective manner.

Recrystallization of the present (2*R*,4*R*)-**2a** afforded an enantiomerically and diastereomerically pure sample (78% recovery). In this way, we established a highly selective and effective synthesis of (2*R*,4*R*)-2,4-pentanediol **2a**, while a couple of chemical and biochemical syntheses have been reported.[17]

Next interest was the stereochemical behavior of the intermediate **7**. Does the pre-formed chiral center in **7** have an effect on the stereoselectivity in the second reduction (from **7** to **2a**)? To answer this question, we attempted the reduction of (*S*)-**7**, which had been prepared by bakers' yeast mediated reduction of **6**.[16] The reduction smoothly proceeded to give a mixture of **2a** (76%), whose ratio was (2*R*,4*R*) : *meso* : (2*S*,4*S*) = 2.9 : 97.1 : 0 (Scheme 5). As expected, *meso*-isomer was predominant. From this result, it was concluded that the reduction of each carbonyl group in β-diketone by *Pichia farinosa* IAM 4682 proceeded independently in the sense of stereochemistry.



Scheme 4



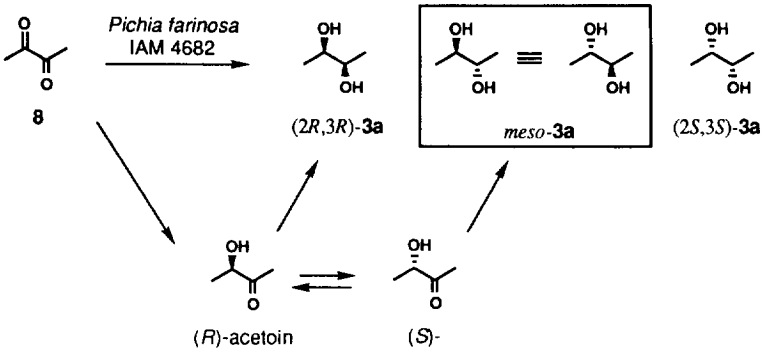
Scheme 5

Reduction of 2,3-Butanedione (Diacetyl)

So far tremendous efforts have been devoted to the preparation of 2,3-butanediol in an optically active form.[18] Our further attempt was the preparation (2*R*,3*R*)-2,3-butanediol by the reduction of 2,3-butanedione by this yeast. In the case of the reduction of α-diketones,[19] the situation is different in two points compared with the reduction of β- and γ-diketones: 1) a large steric hindrance (α-hydroxyl group) of the intermediate may change the stereochemical course of the reduction in the second step; 2) moreover, a racemization of the intermediate is possible *via* a keto-enol isomerization of α-hydroxy ketone.

In this context, 2,3-butanedione **8** was treated with the cells of *Pichia farinosa*. We were very surprised that the product **3a** could only be obtained in as low as 40%, and as a complex stereoisomeric mixture: (2*R*,3*R*) : *meso* : (2*S*,3*S*) = 35.1 : 64.4 : 0.5 (Scheme 6).

A possible explanation of the preferential formation of *meso*-isomer is as follows. It has been reported that the supposed intermediate, (*R*)-acetoin is prone to racemize in the cell of microorganisms.[20] If the reduction of (*S*)-acetoin thus formed is faster than that of (*R*)-isomer, and the reduction proceeds with the *anti*-Prelog fashion, *meso*-isomer becomes predominant, while (2*R*,3*R*)-**3a** is the second major component (Scheme 6). Similar examples of *meso*-predominant formation of **3a** in the reduction of **8** have been observed.[17e,19i]

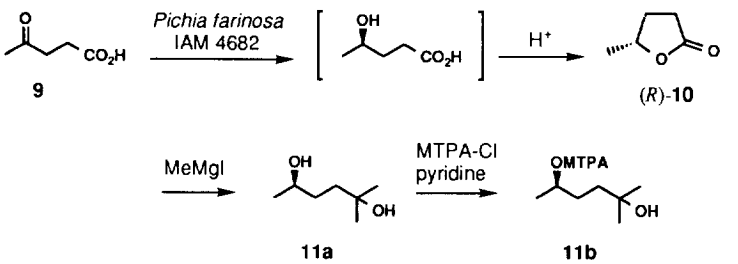


Scheme 6

Reduction of Levulinic Acid

It has become clear that a carbonyl and a hydroxyl group have an important effect to increase the stereoselectivity of reduction of the other carbonyl group. Then, we were interested in the effect of substitution of $COCH_3$ group in γ-diketone **4** with CO_2H group on the stereoselectivity of the reduction. If the reaction proceeds in the same manner, the expecting product is optically active 4-pentanolide (γ-valerolactone) **10**, which has been widely used as the starting material of natural product synthesis.[21] So far, chemical[22] and biochemical[23,24] procedure for preparing **10** in optically active forms have been reported. Among them, bakers' yeast mediated reduction of levulinic acid **9** or its ester have only provided (*S*)-enantiomer of **10**.

We were very pleased that the reduction of **9** smoothly proceeded, and the desired lactone (*R*)-**10** could be obtained in 67% yield only by eluting the hydroxy acid from adsorbent with a solvent system of ethyl acetate-formic acid, and the subsequent distillation of the crude product. The *e.e.* of the product **10** was determined to be >99%, by the NMR measurement and HPLC analysis after converting to an MTPA ester[25] **11b**.



Scheme 7

Conclusion

New highly efficient preparative methods for (2*R*,5*R*)-2,5-hexanediol (**1a**, 83%), (2*R*,4*R*)-2,4-pentanediol (**2a**, 94%), and (*R*)-4-pentanolide (**10**, 67%) were established based on the reduction the corresponding ketones by *Pichia farinosa* IAM 4682. Another carbonyl, hydroxy, and/or carboxyl neighboring group really worked as the functional group which enhance the enantioselectivity of the *anti*-Prelog reduction.

EXPERIMENTAL

All b.ps were uncorrected. IR spectra were measured as films on a Jasco IRA-202 spectrometer. ^{1}H NMR spectra were measured in $CDCl_3$ with TMS as the internal standard at 270 MHz on a JEOL JNM EX-270 spectrometer or at 400 MHz on a JEOL JNM α-400 spectrometer. ^{13}C NMR spectra were measured in $CDCl_3$ at 100 MHz on a JEOL JNM α-400 spectrometer. Mass spectra were recorded on Hitachi M-80B spectrometer at 70 eV. Hitachi GC-353 gas chromatograph was used for GLC analyses. Jasco 880-PU pump and 875-UV detector were used for HPLC analyses. Optical rotations were recorded on a Jasco DIP 360 polarimeter. Wako Gel B-5F and silica gel 60 K070-WH (70-230 mesh) of Katayama Chemical Co. were used for preparative TLC and column chromatography, respectively.

(2R,5R)-2,5-Hexanediol **1a**. *Pichia farinosa* IAM 4682 was incubated in a glucose medium [containing glucose (2 g), peptone (0.7 g), yeast extract (0.5 g), K_2HPO_4 (0.2 g), KH_2PO_4 (0.3 g), pH 6.5, total volume 100 mL] for 2 days at 30 °C. The wet cells were harvested by centrifugation and washed with 33.5 mM phosphate buffer (pH 6.5). The wet cells (40 g) were re-suspended in an incubation broth [containing glucose (5 g), peptone (0.7 g), yeast extract (0.5 g), K_2HPO_4 (0.2 g), KH_2PO_4 (0.3 g), pH 6.5, total volume 100 mL] in a 500 mL shaking culture (Sakaguchi) flask together with diketone **4** (500 mg, 4.38 mmol). After the air inside the flask was purged and replaced with argon, the flask was equipped with a balloon charged with argon, and shaken on a gyrorotary shaker for 2 days at 30 °C. The mixture was centrifuged (3000 rpm) for 20 min. After the decantation of the supernatant, the residue was re-suspended in water and centrifuged again. To the combined supernatant and washings was added sodium sulfate (10 g), and the mixture was lyophilized overnight at −10 °C. The residue was packed in a glass column and eluted with ethyl acetate. The extract was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (5 g). Elution with hexane-ethyl acetate (1 : 1 to 0 : 1) followed by distillation afforded **1a** (429 mg, 83%), b.p. 140 °C/20 Torr (bulb-to-bulb distillation); IR νmax 3300, 2900, 1650, 1370, 1200, 1120, 1030, 920, 820 cm^{-1}. Its ^{13}C NMR spectrum indicated that the sample consisted of mostly (2*R**,5*R**)-**1a** and a small amount of *meso*-**1a** as contaminant: δ 23.59, 35.95, 68.26 for (2*R**,5*R**)-**1a** and 23.17, 34.75, 67.66 for *meso*-**1a**. Those chemical shifts were confirmed by measuring spectra of authentic samples, respectively. In contrast, there was no remarkable difference between ^{1}H NMR of (2*R**,5*R**)-**1a** and that of *meso*-isomer: 1.21 (6H, d, J = 6.2 Hz), 1.58 (4H, m), 2.60 (2H, s), 3.86 (2H, m).

To estimate the *e.e.* and *d.e.* of the present sample, it was converted into the corresponding bis (*R*)-MTPA ester **1b** in a conventional manner. ^{1}H NMR δ 1.16 and 1.32 (each d, J = 6.2 and 6.3 Hz, total 2.5%) for *meso*-**1b**, 1.25 (d, J = 6.2 Hz, 97.5%) for (2*R**,5*R**)-**1b**, 3.49 and 3.55 (broad s, -OMe, total 2.5%) for *meso*-**1b**, 3.51 (broad s, -OMe, 97.5%) for (2*R*,5*R*)-**1b**. No signal at δ 3.53 (broad s, -OMe) for (2*S*,5*S*)-**1b** was observed in this sample. Those chemical shifts were confirmed by measuring spectra of MTPA esters prepared from authentic samples. Therefore, the *e.e.* and the *d.e.* were determined to be more than 99% and 95%, respectively.

The distilled sample was solidified in a refrigerator. Recrystallization from ether[10b] afforded an analytical sample (85% recovery). M.p. 52.4-52.8 °C (lit.[11c] m.p. 53.0-53.3 °C, lit.[11e] m.p. 53-54 °C, lit.[13b] m.p. 52-53 °C, lit.[13e] m.p. 52.5-53 °C); $[\alpha]_D^{22}$ −35.6 (*c*=0.99, $CHCl_3$) [lit.[11c] $[\alpha]_D^{20}$ +35.1 (*c*=9.49, $CHCl_3$) for (2*S*,5*S*)-isomer, lit.[11e] $[\alpha]_D^{25}$ −39.6±0.5 (*c*=1, $CHCl_3$), lit.[13b] $[\alpha]_D^{25}$ −35.7 (*c*=, $CHCl_3$), lit.[13e] $[\alpha]_D^{20}$ −36.6 (*c*=1.0, $CHCl_3$)]. HRMS Found: 118.1019. Calc. for $C_6H_{14}O_2$: 118.0993.

Another incubation using less amount (5 g) of wet cells of *Pichia farinosa*, a hydroxy ketone **5a** (5.6 mg) was obtained together with the desired diol. This was converted into the corresponding MTPA ester and found to be over 99% *e.e.* by ^{1}H NMR measurement; δ 3.52 (broad s, -OMe). No signal at δ 3.56 (broad s, -OMe) for (*S*)-**5b** was observed in this sample. The authentic sample was prepared from racemic **5a**, which had been prepared by the reduction of **4** with a small amount of sodium borohydride in a conventional manner.

(2R,4R)-2,4-Pentanediol **2a**. In the same manner as described for the reduction of **4**, diketone **6** (500 mg, 5.0 mmol) was incubated with *Pichia farinosa*. The crude product was purified by silica gel column chromatography (12 g). Elution with hexane-ethyl acetate (1 : 1 to 1 : 5) afforded **2a** (490 mg, 94%). Its ^{13}C NMR spectrum indicated that the sample consisted of mostly (2*R**,4*R**)-**2a** and a small amount of *meso*-**2a** as contaminant: δ 23.38, 45.56, 65.36 for (2*R**,4*R**)-**2a** and 24.19, 46.39, 69.04 for *meso*-**2a**. Those chemical shifts were confirmed by measuring spectra of authentic samples, respectively.

To determine the *e.e.* and *d.e.* of the present sample, it was converted into the corresponding bis (*R*)-MTPA ester **2b** in a conventional manner. ^1H NMR δ 1.22 and 1.36 (each d, J = 6.3 Hz, total 1.2%) for *meso*-**2b**, 1.26 (d, J = 6.1 Hz, 98.8%) for (2*R*,4*R*)-**2b**. No signal at δ 1.28 (d, J = 6.1 Hz) for (2*S*,4*S*)-**2b** was observed in this sample. Those chemical shifts were confirmed by measuring spectra of MTPA esters prepared from authentic samples. Present sample as well as authentic samples were further analyzed by HPLC. HPLC: column, Senshu Science Co. Ltd. PEGASIL silica, 4.6 mm x 250 mm; solvent, hexane-ethyl acetate-methanol (3000 : 100 : 1); flow rate, 0.3 mL/min, detected at 254 nm; t_R (min): 70.2 [98.8%, (2*R*,4*R*)-**2b**], 92.7 [1.2%, *meso*-**2b**]. No peak at t_R 95.1 min for (2*S*,4*S*)-**2b** was observed. Therefore, the *e.e.* and the *d.e.* were determined to be more than 99% and 97.6%, respectively.

This sample was solidified in a refrigerator. Recrystallization from ether afforded an analytical sample (78.4% recovery). M.p. 48.0-48.8 °C (lit.[17d] m.p. 50.5 °C), $[\alpha]_D^{22}$ –43.6 (*c*=2.00, $CHCl_3$) [lit.[17b] $[\alpha]_D^{25}$ –41.3 ($CHCl_3$), lit.[17d] $[\alpha]_D^{25}$ –41.2 (*c*=10, $CHCl_3$), lit.[17a] $[\alpha]_D^{20}$ –21.4 (*c*=10.5, ethanol), lit.[17d] $[\alpha]_D^{20}$ –53.7 (*c*=10, ethanol)]. ^1H NMR δ 1.23 (6H, d, J = 6.1 Hz), 1.59 (2H, dd, J = 5.2, 6.1 Hz), 2.94 (2H, s), 4.15 (2H, ddq, J = 5.2, 6.1, 6.1 Hz). Its NMR spectrum indicated that the recrystallized sample contained no *meso*-**2a**. An authentic ^1H NMR spectrum of *meso*-**2a**: δ 1.20 (6H, d, J = 6.4 Hz), 1.49 (1H, dd, J = 9.6, 14.4 Hz), 1.56 (1H, ddd, J = 3.2, 3.2, 14.4 Hz), 3.08 (2H, s), 4.10 (2H, m).

meso-2,4-Pentanediol **2a**. According to the reported procedure,[16] (*S*)-4-hydroxy-2-pentanone **7** was obtained by the bakers' yeast mediated reduction of 2,4-pentanedione. In this procedure, a small amount (0.9%) of (2*S*,4*S*)-2,4-pentanediol **2a** was also obtained. GLC analysis of this sample as well as authentic samples revealed that **2a** obtained was a pure 2*S*,4*S*-isomer. GLC: column, GL-Science Co., WCOT Fused silica CP-Chirasil-DEX CB, 0.32 mm x 25 m; 80 °C + 2 °C / min, flow rate, 1.5 mL/min, press. 100 kPa; t_R (min): 11.2 [one peak, (2*S*,4*S*)-**2a**]. No peak at t_R 10.1 min for *meso*-**2a** or 11.0 min for (2*R*,4*R*)-**2a** was observed. Those retention times were confirmed by the measurement of authentic samples.

The hydroxy ketone (*S*)-**7** mentioned above (120 mg, 1.18 mmol) was incubated with *Pichia farinosa* as described for **5**. The crude product was purified by silica gel column chromatography (4 g). Elution with hexane-ethyl acetate (1 : 5) followed by distillation afforded *meso*-**2a** (93.2 mg, 76%), b.p. 130 °C/21 Torr (bulb-to-bulb distillation); IR νmax 3350, 3000, 1380, 1330, 1130, 1050, 930, 830 cm^{-1}. GLC analysis as in the same manner as described above indicated that this sample contained *meso*-**2a** (97.1%) and (2*R*,4*R*)-**2a** (2.9%).

2,3-Butanediol **3a**. In the same manner as described for the reduction of **4**, diketone **8** (500 mg, 5.8 mmol) was incubated with *Pichia farinosa*. The crude product was purified by silica gel column chromatography (10 g). Elution with chloroform-ethyl acetate (4 : 1 to 1 : 4) afforded **3a** (209.5 mg, 40%). GLC analysis was carried out as in the same manner as described for **2a**: t_R (min): 5.5 [0.5%, (2*S*,4*S*)-**3a**], 5.7 [35.1%, (2*R*,4*R*)-**3a**], 6.2 [64.5%, *meso*-**3a**]. Therefore, the *e.e.* and the *d.e.* were determined to be 97.2% [for (2*R*,4*R*)-**3a**] and 29% (for *meso*-**3a**), respectively.

(R)-4-Pentanolide **10**. In the same manner as described for the reduction of **4**, levulinic acid **9** (500 mg, 4.31 mmol) was incubated with *Pichia farinosa* (20 g of wet cell mass). After removing cells by centrifugation, the supernatant was acidified by adding sulfuric acid to pH 2. Sodium sulfate (10 g) was dissolved into the mixture and lyophilized. The resulting solid was washed with ethyl acetate containing formic acid (1%-5%). The solution was concentrated under atmospheric pressure and the residue was distilled *in vacuo* to give (*R*)-**10** (287.7 mg, 67%) b.p. 90 °C/28 Torr, $[\alpha]_D^{20}$ +31.0 (*c*=1.00, CH_2Cl_2) [lit.[22a] $[\alpha]_D^{23}$ +30.1 (*c*=0.85, CH_2Cl_2), lit.[22b] $[\alpha]_D^{21}$ +29.4 (*c*=9.2, CH_2Cl_2), lit.[23] $[\alpha]_D$ +31.6(*c*=23.1, CH_2Cl_2), lit.[24a] $[\alpha]_D$ −32 (*c*=0.85, CH_2Cl_2) for (*S*)-isomer]; IR νmax 3000, 1780, 1460, 1430, 1390, 1350, 1310, 1280, 1180, 1130, 1060, 1005, 950, 900, 810 cm^{-1}; ^1H NMR δ 1.38 (3H, d, *J* = 6.1 Hz), 1.80 (1H, dddd, *J* = 7.8, 9.4, 9.4, 12.5 Hz), 2.33 (1H, dddd, *J* = 6.1, 6.5, 7.8, 12.5 Hz), 2.50 (1H, ddd, *J* = 7.8, 9.4, 17.5 Hz), 2.55 (1H, ddd, *J* = 6.1, 9.4, 17.5 Hz), 4.62 (1H, ddq, *J* = 6.1, 6.5, 7.8 Hz); ^{13}C NMR δ 21.02, 29.07, 29.66, 77.32, 177.39.

To determine the *e.e.* and *d.e.* of the present sample, it was converted into the corresponding (*R*)-MTPA ester **11b** *via* **11a** according to the reported procedure.[25] ^1H NMR δ 1.20, 1.28 and 3.54 (each s). No signal at δ 1.12, 1.36 or 3.57 (each s) for (*S*)-**11b** was observed in this sample. Those chemical shifts were confirmed by measuring spectra of MTPA esters prepared from authentic samples, respectively. Present sample as well as authentic samples were further analyzed by HPLC. HPLC: column, Senshu Science Co. Ltd. PEGASIL silica, 4.6 mm x 250 mm; solvent, hexane-ethyl acetate (5 : 1); flow rate, 1.0 mL/min, detected at 254 nm; t_R (min): 35.6 [98.8%, (*R*)-**11b**], 38.1 [0.2%, for (*S*)-**11b**]. Therefore, the *e.e.* was determined to be more than 99.5%

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