Asymmetric Reduction of a Prochiral Carbonyl Group of Aliphatic γ- and δ-Keto Acids by Use of Fermenting Bakers' Yeast

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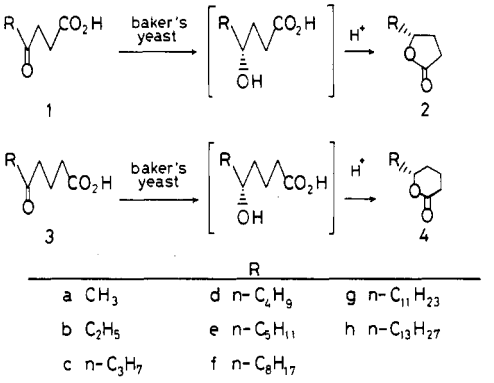
With use of fermenting bakers' yeast, γ- and δ-keto acids, $RCO(CH_2)_nCO_2H$ (n = 2 and 3; R = C_2H_5, n-C_3H_7, n-C_4H_9, n-C_5H_{11}, n-C_8H_{17}, n-$C_{11}H_{23}$, and n-$C_{13}H_{27}$), were reduced to the corresponding γ- and δ-hydroxy acids which were isolated as γ- and δ-lactones in low to good yields with >98% ee. The shortest γ- and δ-keto acid (R = CH_3) failed to give the hydroxy acids. The reduction of 5-oxohexadecanoic acid (n = 3; R = n-$C_{11}H_{23}$) was examined under various conditions to improve the chemical yield. The absolute configurations of all of the lactones were determined to be *R*, even though the Prelog rule predicts the *S* configurations for the substrates having R = C_2H_5 and n-C_3H_7. The role of the carboxy group was discussed in comparison with the results obtained for the δ-keto esters.

Recently we have reported that an asymmetric reduction of 5-oxohexadecanoic acid (**3g**) with fermenting bakers' yeast (*Saccharomyces cereviciae*) afforded, via the hydroxy acid, optically pure (*R*)-(+)-5-hexadecanolide (**4g**) known as a pheromone of the Oriental hornet (eq 2).[1] This method is considered to be most effective among 12 approaches ever reported.[2] Similarly, an asymmetric reduction of 4-oxoalkanoic acids **1** would be the most straightforward route to optically pure γ-lactones **2**, including (*R*)-(+)-4-hexanolide (**2b**)[3] (a pheromone of the *Trogoderma* species of dermestid beetles), (*R*)-(+)-4-nonanolide (**2e**)[3a,d,4] (an attractant for rice weevil), and (*R*)-(+)-4-dodecanolide (**2f**)[2b,3c,4a,5] (a defensive secretion of rove beetles) (eq 1). On the other hand, some of optically active γ- and δ-lactones have been used as key intermediates in the syntheses of natural products, such as chalcograne (a pheromone of a species of beetle) from (*S*)-(−)-**2b**,[6] retro steroids from (*S*)-(−)-**4b**,[7a] and 19-nor steroids from (*S*)-(−)-9-oxo-5-decanolide.[7b]

Although many γ- and δ-keto acids have been reported to undergo the asymmetric reduction with bakers' yeast,[2d,4a,8] most of the results reported were devoid of determining % ee by physical means and no systematic study has been undertaken. We considered that, in the asymmetric reduction of γ- and δ-keto acids using bakers' yeast, it is very important to examine how the chemical and optical yields as well as the stereochemical course are varied by changing the length of the carbon chain. The present paper deals with this question and describes the characteristics of the asymmetric reduction.



Although asymmetric reduction of aliphatic ketones by the use of optically active 2,5-dimethylborolane has recently been achieved with very high optical yields,[9] they have long been reduced only with rather low optical yields by using chiral reducing agents.[10] The asymmetric reduction of the prochiral keto group in γ- and δ-keto acids or esters appears also to be difficult and very little is reported about it.[11] Thus the use of bakers' yeast is expected to add a reliable capability to organic synthesis.[12]

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Table I. Asymmetric Reduction of 5-Oxohexadecanoic Acid (3g) and Related Acids with Fermenting Bakers' Yeast

entry	substrate	[subst], mol/L	g/mmol substrate: dry yeast	g/mmol substrate: glucose[a]	temp, °C	pH	time, h	yield of lactone,[b] %	% ee[c]	
1	**3g** as K salt	0.026	2.8	5	25–28	6–7	35	20	>98	
2		0.026	5.5	6	25–28	6–7	0.5	6 (84)		
3		0.026	5.5	6	25–28	6–7	3	20 (30)		
4		0.026	5.5	9	25–28	6–7	6	29 (2)	>98	
5		0.026	5.5	9	25–28	6–7	15	39 (0)		
6		0.026	5.5	14	25–28	6–7	30	37 (0)	>98	
7		0.026	5.5	6	25–28	6–7	44	41 (0)	>98	
8		0.026	11	25	25–28	6–7	42	28 (0)		
9		0.026	5.5	18	27	4.7[d]	42	42 (0)	>98	
10	**3g** as Na salt	0.026	5.5	12	30–35	6–7	45	39 (0)	>98	
11		0.045	4	1 (1.6)	25–28	6–7	24	40	>98	
12	**3g** as K salt	0.023	5.5	12	25–28	6–7	34	14 (0)	>98	under O_2
13		0.023	5.5	12	25–28	6–7	34	23 (0)	>98	under N_2
14		0.023	5.5	12	25–28	6–7	34	37 (0)	>98	under CO_2
15[e]	**3** (R = n-C_7H_{15})	0.0033	26	26 (13)	30	4.5–6.5	24	56	*f*	
16[e]	as Na salt	0.008	13	8 (13)	30	4.5–6.5	24	17	*f*	
17[e]	**1f** as Na salt	0.002	28	28 (43)	30	4.5–6.5	24	60	*f*	
18[e]		0.006	9	9 (13)	30	4.5–6.5	24	8	*f*	

[a] Amounts of yeast extract added are given in parentheses. [b] Recoveries of the starting acid are given in parentheses. [c] Determined by using ^1H NMR spectra (100 MHz) in the presence of Eu(hfc)$_3$. [d] Adjusted by using a citric acid–KH_2PO_4 buffer solution. [e] Reference 4a. [f] Not reported.

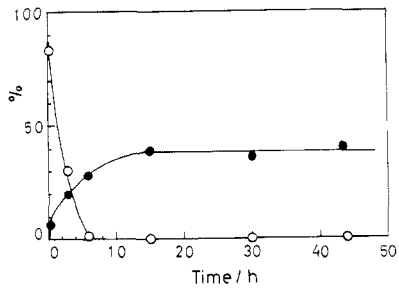

Figure 1. Time course of the reduction of 5-oxohexadecanoic acid (**3g**) with fermenting bakers' yeast at 25–28 °C and pH 6–7; (●) % yield of 5-hexadecanolide (**4g**); (○) % recovery of 5-oxohexadecanoic acid (**3g**).

Results and Discussion

Conditions for Fermentation and Reduction. Table I shows the various conditions for the reduction of 5-oxohexadecanoic acid (**3g**) with fermenting bakers' yeast (entries 1–14), together with reported conditions for related reductions (entries 15–18). As observed in entries 1–14, it is very important that the optical purity of the products is always >98% ee irrespective of the conditions used. This is in contrast to the results reported for the reduction of ethyl acetoacetate, where the optical yield is varied from 58% to 97%.[13] The yields observed in entries 1, 6, 7, and 8 indicate that 5.5 g of dry bakers' yeast per mmol of substrate is appropriate while 2.8 g is insufficient and 11 g is in excess, both giving poor yields. This result can be interpreted in terms of poisoning of the yeast[8] when used in a smaller amount and trapping of the keto acid by the yeast when used in excess. The trapping of keto acid is clearly observed in entries 2–7 (Figure 1). The yield increased rapidly in the first 3-h period to 20% and the recovery was only 30%. The material deficit amounted to 50% at this stage. After the next 3-h period, the yield was raised to 29% and the recovery decreased to 2%. The deficit amounted to 69%. Then, the yield still increased to 39% after 15 h, in spite of the fact that the starting acid had hardly been recovered before. The yield of about 40% and the deficit of about 60% remained constant thereafter. It is clear that the trapping occurred in the first 6-h period of the reaction at a rate faster than that of the reduction,[14] although the reduction was rather rapid and completed within 15 h.

Interestingly, the material deficit is dependent upon the alkyl chain length as observed, for example, for 5-oxooctanoic and 5-oxononanoic acids (**3c,d**), where the deficit is estimated to be about 30% (Table III). At present it is not easy to explain the trapping or deficit of up to 60% at the early stage of the reduction.

The pH was found to be not critical, as long as it is kept between 4.7 and 7.[15] The use of the sodium salt gave no change in the yield as compared with that for the potassium salt (entries 5, 6, 7, and 10). The use of yeast extract according to the method reported[2d] also caused no change (entries 5, 6, 7, and 11). The change in atmosphere from air to oxygen, nitrogen, or carbon dioxide could not improve the yield (entries 12–14). The last four entries selected from the paper of Tuynenburg Muys et al.[4a] also show the key role of the amount of yeast for higher yields, as we have found and noted above.

Chemical Yields. In Tables II and III are shown the results of the asymmetric reduction for series of γ- and δ-keto acids (**1a–h, 3a–h**). The reduction was carried out by using 5.5 g of dry bakers' yeast per mmol of substrate (0.024–0.027 mol/L) with 12 ± 2 g of glucose at 25–28 °C and pH 6–7 for 48 h. The products were isolated as γ- and δ-lactones. As shown in Tables II and III, both series of γ- and δ-keto acids are reduced in a similar way as their alkyl chains lengthen from CH_3 to n-$C_{13}H_{27}$. The yield is zero or very low when the alkyl group R is CH_3 or C_2H_5, then increasing to a maximum in between n-C_3H_7 and n-C_5H_{11}, and finally decreasing for n-C_8H_{17} and n-$C_{13}H_{27}$. In contrast, the recovery of the starting acid is higher when the yield is lower and is zero or nearly zero when the yield is higher. Thus the low yield accompanied by the high recovery can be attributable to sluggishness of the reduction. It is clear that the γ- and δ-keto acids having a short alkyl group (CH_3 or C_2H_5) are reduced extremely

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(14) Francke reported that the material deficit of about 10% was observed for the yeast reduction of 5-oxodecanoic acid after the first 30-min period, which remained constant thereafter. See ref 8.

(15) Francke reported that the optimum pH was at about 5 for the yeast reduction of 5-oxodecanoic acid. See ref 8.

Table II. Asymmetric Reduction of γ-Keto Acids 1 to γ-Lactones 2 with Fermenting Bakers' Yeast[a]

	RCO-$(CH_2)_2CO_2H$ (1)	(R)$\overline{OCH(CH_2)_2CO}$ (2)			
	R	% yield[b]	% ee[c]	$[\alpha]_D$, deg (c, THF)	confign
a	CH_3	0 (17)			
b	C_2H_5	13 (37)	>98	+47.4 (1.86) +52.1 (1.57, MeOH)[e]	R
c	n-C_3H_7	23[d] (51)	>98	+56.2 (1.56)	R
d	n-C_4H_9	42 (43)	>98	+53.3 (1.16)	R
e	n-C_5H_{11}	79 (3)	>98	+48.6 (1.68) +48.2 (3.69, MeOH)[f]	R
f	n-C_8H_{17}	71 (2)	>98	+42.4 (2.50) +40.3 (1.21, MeOH)[g]	R
g	n-$C_{11}H_{23}$	50 (0)	>98	+33.7 (1.39)	R
h	n-$C_{13}H_{27}$	31 (34)	>98	+28.3 (1.27)	R

[a] Incubated for 2 days at 25–28 °C and pH 6–7. [b] Recoveries of the starting acid are given in parentheses. [c] Determined by using ^{1}H NMR spectra (100 MHz) measured in the presence of Eu(hfc)$_3$. [d] The Yield was increased to 43% when the fermentation was continued for 7 days. [e] Rotation of (*R*)-**2b**: $[\alpha]^{20}_D$ +53.2° (*c* 1, MeOH), prepared from L-glutamic acid, ref 3a; $[\alpha]^{20}_D$ +50.5° (*c* 2, CH_2Cl_2), prepared from D-ribonolactone, ref 3d; $[\alpha]^{21}_D$ +53.1° (*c* 1.005, MeOH), 100% ee, prepared by bakers' yeast reduction of octyl 3-oxopentanoate, ref 3e. [f] Rotation of (*R*)-**2e**: $[\alpha]^{20}_D$ +47.2° (*c* 1, MeOH), prepared from L-glutamic acid, ref 3a; $[\alpha]^{20}_D$ +44.6° (*c* 2.4, CH_2Cl_2), prepared from D-ribonolactone, ref 3d; $[\alpha]^{20}_D$ +50.4° (*c* 8.1, MeOH), prepared by bakers' yeast reduction of **1e**, ref 4a. [g] Rotation of (*R*)-**2f**: $[\alpha]^{20}_D$ +41.1° (MeOH), prepared by bakers' yeast reduction of **1f**, ref 4a; $[\alpha]^{20}_D$ +39.0° (*c* 1.03, MeOH), 96% ee, prepared by enzymatic resolution of a derivative of 2-aminodecanoic acid, ref 5d. Rotation of (*S*)-**2f**: $[\alpha]^{20}_D$ −41.1° (*c* 5, MeOH), 99% ee, prepared by enantioselective homoaldol addition, ref 5e.

Table III. Asymmetric Reduction of δ-Keto Acids 3 to δ-Lactones 4 with Fermenting Bakers' Yeast[a]

	RCO-$(CH_2)_3CO_2H$ (3)	(R)$\overline{OCH(CH_2)_3CO}$ (4)			
	R	% yield[b]	% ee[c]	$[\alpha]_D$, deg (c, THF)	confign
a	CH_3	0 (53)			
b	C_2H_5	6 (35)	>98	+50.3 (1.63)	R
c	n-C_3H_7	64 (5)	>98	+66.5 (1.70)[d]	R
d	n-C_4H_9	68 (0)	>98	+63.2 (2.24) +53.7 (1.34, MeOH)[e]	R
e	n-C_5H_{11}	55 (5)	>98	+60.2 (1.74)[f]	R
f	n-C_8H_{17}	54 (0)	>98	+45.2 (1.58)	R
g	n-$C_{11}H_{23}$	40 (0)	>98	+39.5 (1.74)[g]	R
h	n-$C_{13}H_{17}$	17 (20)	>98	+31.7 (1.28)	R

[a] Incubated for 2 days at 25–28 °C and pH 6–7. [b] Recoveries of the starting acid are given in parentheses. [c] Determined by using ^{1}H NMR spectra (100 MHz) measured in the presence of Eu(hfc)$_3$. [d] Rotation of (*R*)-**4c**: $[\alpha]^{20}_D$ +58.4° (*c* 2.2, MeOH), prepared by bakers' yeast reduction of **3c**, ref 4a. [e] Rotation of (*R*)-**4d**: $[\alpha]^{20}_D$ +58.2° (MeOH), prepared by bakers' yeast reduction of **3d**, ref 4a. [f] Rotation of (*R*)-**4e**: $[\alpha]^{20}_D$ +55.6° (MeOH), prepared by bakers' yeast reduction of **3e**, ref 4a; $[\alpha]_D$ +53.5° (*c* 1.4, EtOH), prepared by bakers' yeast reduction of **3e**, ref 8. [g] Rotation of (*R*)-**4g**: $[\alpha]^{20}_D$ +39.97° (*c* 1, THF), prepared from a chiral C_4 synthon obtained from cinnamaldehyde and bakers' yeast, ref 2e; $[\alpha]^{20}_D$ +39.8° (*c* 4.2, THF), prepared by enantioselective hydrogenation of methyl 3-oxotetradecanoate, ref 2g; $[\alpha]_D$ +39.5° (*c* 0.85, THF), prepared from a chiral β-keto sulfoxide, ref 2i; $[\alpha]^{23}_D$ +40.8° (*c* 0.760, THF), prepared by bakers' yeast reduction of 1-hydroxy-3-(phenylthio)-2-propanone, ref 2j.

sluggishly. In fact, when the reduction of 4-oxoheptanoic acid (**1c**, R = n-C_3H_7) was continued for 7 days, the yield was increased to 43%, though it was 23% for 2 days. To explain why these short alkyl groups retard the reduction,

Table IV. Asymmetric Reduction of δ-Keto Esters to δ-Lactones 4 with Fermenting Bakers' Yeast[a]

RCO-$(CH_2)_3CO_2R'$		(R)$\overline{OCH(CH_2)_3CO}$[b] (4)			
R	R′	% yield[c]	% ee[d]	$[\alpha]_D$, deg (c, THF)	confign
CH_3	C_2H_5	0 (60)			
C_2H_5	C_2H_5	11 (65)	>98	+55.0 (1.13)	R
n-C_3H_7	CH_3	46 (15)[e]	>98	+63.9 (1.37)	R
n-C_3H_7	C_2H_5	58 (19)	>98	+64.9 (1.77)	R
n-C_4H_9	C_2H_5	71 (10)	>98	+60.7 (2.14)	R
n-C_8H_{17}	C_2H_5	21 (33)	>98	+45.5 (1.09)	R
n-$C_{11}H_{23}$	CH_3	0 (73)[f]			

[a] Incubated for 2 days in a similar way as for δ-keto acids. [b] The reduction product was the δ-hydroxy acid, which was isolated as the δ-lactone. [c] Recoveries of the starting keto ester are given in parentheses. [d] Determined by using ^{1}H NMR spectra (100 MHz) measured in the presence of Eu(hfc)$_3$. [e] Composed of 10% of the δ-keto acid and 5% of the starting δ-keto ester. [f] Composed of 12% of the δ-keto acid and 61% of the starting δ-keto ester.

we propose that the substrate is bound to the active site of yeast reductase by using the hydrophobic interaction due to the alkyl group and that the short alkyl groups cannot provide sufficient hydrophobic interaction for binding. On the other hand, the longest alkyl group (R = n-$C_{13}H_{27}$) seems to be too long for the binding site of the enzyme.

Optical Yields. As shown in Tables I–III, the optical yield is always >98% ee, irrespective of the length of carbon chain, the position of prochiral carbonyl group, and the conditions for fermentation. We have determined the % ee by measuring ^{1}H NMR spectra in the presence of Eu(hfc)$_3$ after conversion of lactones to diols with MeLi.[16] The fact that optically pure hydroxy acids can be obtained by microbial reduction of keto acids has already been demonstrated by two papers: one is the reduction of 5,9-diketodecanoic acid with a mold, *Margarinomyces bubaki* 459,[7b] and the other the yeast reduction of β-keto acids.[17] In the latter, the important role of the carboxy group was clearly demonstrated by comparing the optical purity of >98% observed for β-hydroxy acids produced from β-keto acids with that of 67–96% observed for β-hydroxy esters produced from β-keto esters.

We have also examined the yeast reduction of δ-keto esters. The results are shown in Table IV. Contrary to our expectation, the reduction products were the corresponding δ-hydroxy acids in equilibrium with the δ-lactones, no δ-hydroxy ester being obtained. Then, there remained a question whether the δ-keto ester itself was reduced or not. To anwswer this question, we treated ethyl (±)-5-hydroxyoctanoate with bakers' yeast in a similar way, to find that 20–45% of the hydroxy ester remained unhydrolyzed, while the hydroxy acid was obtained as δ-lactone in 14–26% yields. Thus it is sugested that the δ-keto ester itself was not reduced to the δ-hydroxy ester in an appreciable amount. The δ-keto ester is likely hydrolyzed to the δ-keto acid prior to the reduction.[18] It is

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(18) Hydrolysis of the ester group in a long chain keto ester, (±)-15-deoxyprostaglandin E_1 ethyl ester, by incubation with bakers' yeast for 13 h, was reported to give the free acid (41%) and the starting ester (40%). When the ester was incubated with the yeast for 48 h, it was converted to the hydroxy acid (50%). In both cases, no description was made whether the hydroxy ester was produced or not. See: Sih, C. J.; Salomon, R. G.; Price, P.; Sood, R.; Peruzzotti, G. *J. Am. Chem. Soc.* **1975**, *97*, 857. Sih et al. also reported the yeast reduction of methyl and *tert*-butyl 5-oxo-5-(1,3-dithian-2-yl)pentanoates. See: Takaishi, Y.; Yang, Y.-L.; DiTullio, D.; Sih, C. J. *Tetrahedron Lett.* **1982**, *23*, 5489. Han, C.-Q.; Wang, Yi.-F.; Sih, C. J. *J. Org. Chem.* **1986**, *51*, 1253.

Table V. 4-Oxoalkanoic Acids 1, $RCO(CH_2)_2CO_2H$

R	yield,[a] %	mp, °C	IR,[b] cm^{-1}	^1H NMR[c]
C_2H_5[d]	15	35.0–36.1	1720, 1700	1.03 (t, 3 H), 2.1–2.9 (m, 6 H)
n-C_3H_7[e]	39	43.0–43.8	1720, 1700	0.90 (t, 3 H), 1.2–1.9 (m, 2 H), 2.2–2.8 (m, 6 H)
n-C_4H_9[f]	22	47.8–48.2	1720, 1700	0.90 (t, 3 H), 1.1–1.9 (m, 4 H), 2.2–3.0 (m, 6 H)
n-C_5H_{11}[f]	24	64.5–65.0	1720, 1700	0.89 (t, 3 H), 1.1–1.9 (m, 6 H), 2.2–2.9 (m, 6 H)
n-C_8H_{17}[e]	30	75.8–76.9	1720, 1700	0.88 (t, 3 H), 1.1–2.0 (m, 12 H), 2.2–2.8 (m, 6 H)
n-$C_{11}H_{23}$	55	88.0–90.0	1720, 1700	0.88 (t, 3 H), 1.1–2.0 (m, 18 H), 2.3–2.8 (m, 6 H)
n-$C_{13}H_{27}$	23	95.0–95.2	1720, 1695	0.88 (t, 3 H), 1.1–2.0 (m, 22 H), 2.3–2.8 (m, 6 H)

[a] Yields based on succinic anhydride after purification by LC (silica gel, hexane–acetone 1:1 for C_2 and C_3 and 5:1 for C_4, C_5, C_8, C_{11}, and C_{13}). Satifactory analytical data (±0.3% for C and H) were obtained for all compounds listed in the table. [b] KBr. [c] In CCl_4. [d] Reinheckel, H.; Haage, K.; Gensike, R. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 785. [e] Takeda, A.; Takahashi, K.; Torii, S.; Moriwake, T. *J. Org. Chem.* **1966**, *31*, 616. [f] Stetter, H.; Rajh, B. *Chem. Ber.* **1976**, *109*, 534.

Table VI. 5-Oxoalkanoic Acids 3, $RCO(CH_2)_3CO_2H$

R	yield,[a] %	mp, °C	IR,[b] cm^{-1}	^1H NMR[c]
C_2H_5[d]	36	39.1–41.4	1720, 1700	1.10 (t, 3 H), 1.4–2.2 (m, 2 H), 2.2–2.7 (m, 6 H)
n-C_3H_7[e,f]	40	31.0–31.2	1720, 1700	0.96 (t, 3 H), 1.2–2.2 (m, 4 H), 2.2–2.7 (m, 6 H)
n-C_4H_9[f,g]	75	42.0–43.0	1720, 1700	0.90 (t, 3 H), 1.1–2.2 (m, 6 H), 2.2–2.7 (m, 6 H)
n-C_5H_{11}[f]	33	54.2–54.5	1720, 1700	0.88 (t, 3 H), 1.1–2.2 (m, 8 H), 2.2–2.7 (m, 6 H)
n-C_8H_{17}[f,g]	75	69.5–70.2	1720, 1700	0.85 (t, 3 H), 1.0–2.2 (m, 14 H), 2.2–2.7 (m, 6 H)
n-$C_{11}H_{23}$[g]	55	78.0–79.0	1715, 1700	0.88 (t, 3 H), 1.0–2.2 (m, 20 H), 2.2–2.7 (m, 6 H)
n-$C_{13}H_{27}$	70	88.2–88.6	1710, 1700	0.88 (t, 3 H), 1.0–2.2 (m, 24 H), 2.2–2.7 (m, 6 H)

[a] Yields based on glutaric anhydride after purification by LC (silica gel, hexane–acetone 1:1 for C_2 and 5:1 for C_3, C_5, and C_{13}). Satisfactory analytical data (±0.3% for C and H) were obtained for all compounds listed in the table. [b] KBr. [c] In CCl_4. [d] Levine, S. G. *J. Am. Chem. Soc.* **1960**, *82*, 2556. [e] Stetter, H.; Dierichs, W. *Chem. Ber.* **1952**, *85*, 61. [f] Lardelli, G.; Lamberti, V.; Weller, W. T.; De Jong, A. P. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 481. [g] Reference 24.

very interesting and remains to be elucidated why the keto group in δ-keto acids is reduced more rapidly than that in the corresponding δ-keto esters.[19]

As shown in Table IV, all of the δ-lactones are optically pure (>98% ee), as are the δ-lactones from the δ-keto acids. Furthermore, the yield and recovery are also very similar to those for the keto acids, except that the keto esters having a longer alkyl group (R = n-C_8H_{17} and n-$C_{11}H_{23}$) are reduced slowly or not at all. This retardation certainly comes from the low solubility of long chain δ-keto esters.

Recently Sih et al. have disclosed that bakers' yeast contains three competing oxidoreductases involved in the reduction of β-keto esters and that the % ee is determined by the binding or catalysis of the competing enzymes.[20] According to this analysis, the high value of % ee for the β-keto acids can be interpreted in terms of catalysis by a single oxidoreductase with complete enantioselectivity. The same interpretation may also be applied for the γ- and δ-keto acids, although it remains to be elucidated whether the same enzyme that reduces β-keto acids reduces γ- and δ-keto acids as well.

Absolute Configuration. The absolute configurations of all of the γ- and δ-lactones (**2** and **4**) obtained were determined to be *R*. The three γ-lactones (**2b**,[21] **2e**,[21] and **2f**[5c,h]) are naturally occurring products and their specific rotations were used for the determination. The CD spectra measured for two δ-lactones (**4b,c**) showed a negative Cotton effect at 240–243 nm followed by a positive one at 210 nm, indicating the *R* configuraiton.[22] The rest of the lactones were unambiguously assigned to the *R* configuration on the basis of the values of observed specific rotation shown in Tables II and III.

The fact that all of the γ- and δ-keto acids were reduced to the secondary alcohols of *R* configuration is not consistent with the Prelog rule,[23] which predicts the *S* configuration for secondary alcohols from 4-oxohexanoic, 5-oxoheptanoic, and 5-oxooctanoic acids (**1b**, **3b,c**) on the basis of the relative bulkiness of the two groups attached to the carbonyl group. Now it is clearly indicated that the factor that governs the configuration is not the bulkiness but the function of the group. To explain this, we propose the binding of γ- and δ-keto acids to the chiral hydrophobic pocket or crevice of yeast oxidoreductase in the following way.[24] The nonpolar chain of the substrate could be inserted into the hydrophobic domain and the polar carboxy group would be projecting toward the aqueous phase or certain polar amino acid residues near the active site. The oxygen of the keto group would be fixed by a hydrogen bonding or an electrostatic force so as to expose the *si* face to hydrogen transfer.

Experimental Section

All boiling and melting points are uncorrected. IR spectra were recorded with a Jasco A-102 spectrometer. ^1H NMR spectra at 60 MHz were obtained on a JEOL PMX 60 SI spectrometer. ^1H NMR spectra at 100 MHz and ^{13}C NMR spectra at 25 MHz were obtained on a JEOL FX 100 spectrometer. Me_4Si was used as an internal standard. CD measurements were carried out on a Jasco J-500 A spectrometer equipped with a DP-501 N data processor. Bulb-to-bulb distillation was performed by using a Shibata glass tube oven GTO-250. HPLC was performed by using a Yanagimoto L 2000 chromatograph equipped with a RI detector. Elemental analyses were performed by E. Amano of this laboratory on a Yanagimoto CH analyzer MT-3.

Materials. 4-Oxopentanoic acid (**1a**) was from Tokyo Kasei. 4-Oxohexanoic, -heptanoic, -octanoic, -nonanoic, -dodecanoic, pentadecanoic, and -heptadecanoic acids (**1b–h**) were prepared by using the reaction of succinic anhydride with alkylmagnesium bromides according to the method reported.[25] Their physical and analytical data are listed in Table V. Preparations of 5-oxohexanoic, -nonanoic, -tridecanoic, and -hexadecanoic acids (**3a,d,f,g**) were described in our previous papers.[24,26] 5-Oxo-

(19) Francke suggested that 5-oxodecanoic acid is not reduced as such, but as the CoA thio ester. See ref 8.

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Table VII. Methyl or Ethyl 5-Oxoalkanoates, $RCO(CH_2)_3CO_2R'$

R	R'	yield,[a] %	bp or mp, °C (mmHg)	IR,[b] cm^{-1}	^1H NMR[c]
CH_3	C_2H_5	85	60–70 (3)	1735, 1715	1.23 (t, 3 H), 1.65–2.61 (m, 6 H), 2.08 (s, 3 H), 4.06 (q, 2 H)
C_2H_5	C_2H_5	83	60–70 (3)	1735, 1715	1.00 (t, 3 H), 1.22 (t, 3 H), 1.45–2.1 (m, 2 H), 2.1–2.6 (m, 6 H), 4.02 (q, 2 H)
n-C_3H_7	CH_3	89	70–80 (3)	1735, 1715	0.90 (t, 3 H), 1.45–2.05 (m, 4 H), 2.05–2.60 (m, 6 H), 3.56 (s, 3 H)
n-C_3H_7	C_2H_5	88	90–100 (3)	1735, 1715	0.90 (t, 3 H), 1.22 (t, 3 H), 1.45–2.1 (m, 4 H), 2.1–2.6 (m, 6 H), 4.05 (q, 2 H)
n-C_4H_9	C_2H_5	95	155–165 (8)	1735, 1715	0.90 (t, 3 H), 1.22 (t, 3 H), 1.4–2.1 (m, 6 H), 2.1–2.6 (m, 6 H), 4.04 (q, 2 H)
n-C_8H_{17}	C_2H_5	96	140–150 (0.15)	1735, 1715	0.88 (t, 3 H), 1.22 (t, 3 H), 1.0–2.1 (m, 14 H), 2.1–2.6 (m, 6 H), 4.03 (q, 2 H)
n-$C_{11}H_{23}$	CH_3	93	47.5–47.8	1735, 1715	0.87 (t, 3 H), 1.02–2.06 (m, 20 H), 2.06–2.50 (m, 6 H), 3.56 (s, 3 H)

[a] Yields based on keto acids **3**. [b] Neat for liquid and KBr for solid. [c] In CCl_4.

Table VIII. Optically Pure (*R*)-(+)-4-Alkanolides 2, (R)$\overline{OCH(CH_2)_2CO}$

R	bp or mp, °C (mmHg)	IR,[a] cm^{-1}	^1H NMR[b]
C_2H_5[c,d]	100–130 (23)	1780	0.98 (t, 3 H), 2.2–2.3 (m, 4 H), 2.3–2.6 (m, 2 H), 4.0–4.55 (m, 1 H)
n-C_3H_7[d]	130–140 (18)	1780	0.98 (t, 3 H), 1.2–2.3 (m, 6 H), 2.3–2.6 (m, 2 H), 4.10–4.60 (m, 1 H)
n-C_4H_9[d,e]	140–150 (22)	1780	0.90 (t, 3 H), 1.2–2.3 (m, 8 H), 2.3–2.6 (m, 2 H), 4.02–4.65 (m, 1 H)
n-C_5H_{11}[e,f]	80–90 (3)	1780	0.90 (t, 3 H), 1.1–2.3 (m, 10 H), 2.3–2.6 (m, 2 H), 4.05–4.60 (m, 1 H)
n-C_8H_{17}[g]	105–115 (3)	1780	0.88 (t, 3 H), 1.1–2.3 (m, 16 H), 2.3–2.6 (m, 2 H), 4.25–4.70 (m, 1 H)
n-$C_{11}H_{23}$[e]	36.5–37.2	1750	0.88 (t, 3 H), 1.1–2.3 (m, 22 H), 2.3–2.6 (m, 2 H), 4.18–4.58 (m, 1 H)
n-$C_{13}H_{27}$[e]	46.5–47.5	1750	0.88 (t, 3 H), 1.1–2.3 (m, 26 H), 2.3–2.6 (m, 2 H), 4.10–4.50 (m, 1 H)

[a] Neat for liquid and KBr for solid. [b] In CCl_4. [c] Reference 3. [d] Racemic: Nikishin, G. I.; Svitanko, I. V.; Troyansky, E. I. *J. Chem. Soc., Perkin Trans. 2* **1983**, 595. [e] Satisfactory analytical data (±0.3% for C and H) were obtained. [f] References 3a,d and 4. [g] References 2b, 3c, 4a, and 5.

Table IX. Optically Pure (*R*)-(+)-5-Alkanolides 4, (R)$\overline{OCH(CH_2)_3CO}$[a]

R	bp or mp, °C (mmHg)	IR,[b] cm^{-1}	^1H NMR[c]
C_2H_5[d]	100–120 (23)	1740	1.00 (t, 3 H), 1.2–2.2 (m, 6 H), 2.2–2.7 (m, 2 H), 3.90–4.40 (m, 1 H)
n-C_3H_7[e]	70–80 (2)	1740	0.98 (t, 3 H), 1.2–2.2 (m, 8 H), 2.2–2.7 (m, 2 H), 3.95–4.50 (m, 1 H)
n-C_4H_9[f]	70–80 (2)	1740	0.92 (t, 3 H), 1.1–2.1 (m, 10 H), 2.1–2.5 (m, 2 H), 3.90–4.40 (m, 1 H)
n-C_5H_{11}[g]	160–170 (5)	1740	0.90 (t, 3 H), 1.1–2.2 (m, 12 H), 2.2–2.6 (m, 2 H), 3.95–4.45 (m, 1 H)
n-C_8H_{17}[h]	120–130 (0.4)	1735	0.88 (t, 3 H), 1.1–2.3 (m, 18 H), 2.3–2.8 (m, 2 H), 4.00–4.60 (m, 1 H)
n-$C_{11}H_{23}$[i]	37.5–38.0	1730	0.88 (t, 3 H), 1.0–2.3 (m, 24 H), 2.3–2.7 (m, 2 H), 4.00–4.50 (m, 1 H)
n-$C_{13}H_{27}$	47.0–48.5	1730	0.88 (t, 3 H), 1.0–2.1 (m, 28 H), 2.1–2.6 (m, 2 H), 3.97–4.30 (m, 1 H)

[a] Satisfactory analytical data (±0.3% for C and H) were obtained for all compounds listed in the table. [b] Neat for liquid and KBr for solid. [c] In CCl_4. [d] Reference 7a. [e] Reference 4a. [f] References 4a and 24. [g] References 4a and 8. [h] Reference 24. [i] References 1, 2, and 24.

Table X. Chemical Shifts (δ) of the Geminal Methyl Groups in (±)-$RCH(OH)(CH_2)_nC(OH)(CH_3)_2$ in the Presence of $Eu(hfc)_3$

n = 2			n = 3		
R	$Eu(hfc)_3$, mol %	δ	R	$Eu(hfc)_3$, mol %	δ
n-C_3H_7	0	1.23	C_2H_5	0	1.22
	20	*R* 1.51; 1.59		20	*R* 1.86; 1.90
		S 1.54; 1.62			*S* 1.69; 1.93
	30	*R* 2.07; 2.33	n-C_4H_9	30	*R* 3.86; 4.12
		S 2.16, 2.41			*S* 3.24; 4.32
n-C_8H_{17}[a]	80	*R* 4.04; 4.84	n-C_8H_{17}	20	*R* 1.73; 1.77
		S 4.16; 4.96			*S* 1.62; 1.79
			n-$C_{11}H_{23}$	40	*R* 2.36; 2.46
					S 2.12; 2.52

[a] Reported data. See: Sugai, T.; Mori, K. *Agric. Biol. Chem.* **1984**, *48*, 2497.

heptanoic, -octanoic, -decanoic, and -octadecanoic acids (**3b,c,e,h**) were prepared by using the reaction of glutaric anhydride with alkylmagnesium bromides according to the method reported.[25] Their physical and analytical data are listed in Table VI. δ-Keto esters tabulated in Table VII were prepared by esterification of δ-keto acids (**3a–d,f,g**). Dry bakers' yeast was purchased from Oriental Yeast. A chiral shift reagent, tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III) [Eu(hfc)$_3$] was purchased from Aldrich.

Asymmetric Reduction of γ- and δ-Keto Acids (1 and 3) with Fermenting Bakers' Yeast. General Procedure. A suspension of 2.8 g of dry bakers' yeast, 3.1 g of glucose, 7 mg of KH_2PO_4, and 4 mg of $MgSO_4$ in 9 mL of boiled water was stirred magnetically at 25–28 °C for 30 min. To this vigorously fermenting medium was added 0.5 mmol of 4- or 5-oxoalkanoic acid (**1** or **3**) in 1 mL of 1 M KOH with 9 mL of water, and the suspension was adjusted to pH 7 with 1 M KOH. It was stirred for 48 h with the pH kept in between 6 and 7 by addition of 1 M KOH. The consumption of glucose was checked by using glucose test paper (Diasticks II, Miles-Sankyo) and glucose was added in 1.5-g portions. Then the suspension was stirred with 4 g of Celite for 3–6 h (at 0 °C if necessary). The mixture was filtered and the filtrate was adjusted to pH 2 and extracted with ether. The Celite was also washed with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), and evaporated in reduced pressure to give a crude material. This was refluxed in benzene with a catalytic amount of *p*-TsOH for 1 h, the benzene–water azeotrope being passed through a molecular sieves column. The benzene solution was washed with brine, aqueous $NaHCO_3$, and brine and evaporated. The residue was chromatographed over a silica gel column (Wako gel C 200, 20 g, hexane–acetone 30:1 → 20:1) to give the lactone (**2** or **4**), which usually contained a small amount of impurities. Then it was purified by HPLC (Yanapac SA-I, 250 × 7.5 mm, hexane–AcOEt 5:1, flow rate 2 mL/min, detector RI) to give the analytically pure lactone. The yields listed in Tables I–IV are based on these HPLC-purified lactones. In order to recover the starting keto acid, the combined washings were acidified to pH 2 and extracted with ether. The ethereal extract was combined with the material eluted lastly from the silica gel column with methanol. The combined extracts were

dried ($MgSO_4$) and evaporated to give a residue, which was treated with CH_2N_2. The crude methyl ester thus obtained was chromatographed over a silica gel column (Wako gel C 200 , 5 g, hexane–acetone 20:1) and then analyzed by GLC (SE-30, 1 m × 3 mm, 120 → 200 °C).

Asymmetric Reduction of δ-Keto Esters with Fermenting Bakers' Yeast. The fermentation was carried out in the same way as described for keto acids, except for no use of 1 M KOH. The substrate was added to the medium with a few milliliters of the medium and the workup was somewhat different. After being stirred with Celite, the yeast suspension (pH 6–7) was filtered and the filtrate was extracted with AcOEt. The combined extracts and washings were evaporated after washing and drying ($MgSO_4$) to give a residue, which was chromatographed over a silica gel column in a similar way. The fractions separated were analyzed by GLC to detect the δ-hydroxy ester, the lactone, and the starting keto ester. No δ-hydroxy ester was detected. Then the aqueous solution was acidified to pH 2 with 10% HCl and extracted with AcOEt. The organic materials extracted were treated with CH_2N_2. The resulting products were purified by chromatography and identified by GLC as the lactone and the δ-hydroxy acid methyl ester.

Determination of the Optical Purity (% ee) by Using ^1H NMR Spectroscopy.[16] The lactone **2** (or **4**) in anhydrous ether was treated with a large excess of 1.6 M MeLi in hexane to give the corresponding 2-methylalkane-2,5(or 2,6)-diol. After being purified by bulb-to-bulb distillation, 2–4 mg of the diol was dissolved in a mixture of CCl_4–$CDCl_3$ (3:1, dried over molecular sieves 3 Å) and the ^1H NMR spectrum was measured by using a JEOL FX-100 spectrometer. The diol showed a sharp singlet at δ 1.22 or 1.23 for the two tertiary carbinol methyl groups and a multiplet at δ 3.4–3.7 for the secondary carbinol hydrogen. In the presence of 20–40 mol % $Eu(hfc)_3$, the singlet shifted downfield and separated into two pairs of sharp singlets for the racemic diol. The optically active diols from the yeast reduction always showed only one pair of sharp singlets, indicating the existence of the only one enantiomer with a purity of >99%. It was often observed that the pair of singlets was broadened and/or overlapped with the signal of the hydroxy group. These difficulties were overcome by measuring the spectra at elevated temperatures of 45–50 °C. Table X shows the separation of the methyl signal for various racemic diols.

CD Spectra. (*R*)-(+)-5-Heptanolide (**4b**): CD (*c* 0.280, cyclohexane) $[\theta]_{280}$ 0, $[\theta]_{243}$ −571, $[\theta]_{223}$ 0, and $[\theta]_{215}$ +229. (*R*)-(+)-5-Octanolide (**4c**): CD (*c* 0.323, cyclohexane) $[\theta]_{278}$ 0, $[\theta]_{240}$ −791, $[\theta]_{223}$ 0, and $[\theta]_{210}$ +264; (*c* 0.520, EtOH) $[\theta]_{267}$ 0, $[\theta]_{238}$ −301, $[\theta]_{227}$ 0, $[\theta]_{210}$ +792, and $[\theta]_{205}$ +615.

Registry No. **1b**, 1117-74-4; **1c**, 924-97-0; **1d**, 4316-44-3; **1e**, 6064-52-4; **1f**, 4144-55-2; **1g**, 109788-69-4; **1h**, 109393-06-8; **2b**, 63357-95-9; **2c**, 88270-38-6; **2d**, 107797-24-0; **2e**, 63357-96-0; **2f**, 69830-91-7; **2g**, 109788-70-7; **2h**, 107736-79-8; **3b**, 3637-13-6; **3c**, 3637-14-7; **3d**, 3637-15-8; **3e**, 624-01-1; **3f**, 869-99-8; **3g**, 70444-63-2; **3h**, 16694-31-8; **4b**, 108943-43-7; **4c**, 108943-45-9; **4d**, 99461-67-3; **4e**, 2825-91-4; **4f**, 99461-66-2; **4g**, 59812-96-3; **4h**, 109788-71-8; $MeCO(CH_2)_3CO_2Et$, 13984-57-1; $EtCO(CH_2)_3CO_2Et$, 70432-50-7; $PrCO(CH_2)_3CO_2Me$, 16856-44-3; $PrCO(CH_2)_3CO_2Et$, 5205-40-3; $BuCO(CH_2)_3CO_2Et$, 24071-99-6; n-$C_8H_{17}CO(CH_2)_3CO_2Et$, 109788-72-9; n-$C_{11}H_{23}CO(CH_2)_3CO_2Me$, 54527-00-3.