mmol, 2.0 equiv), and anhydrous ether (25 mL) was stirred at room temperature under nitrogen for 9.5 h. The resulting mixture was filtered, and the filtrate was evaporated under reduced pressure to yield **17** (0.65 g, 2.60 mmol, 100%) as a pale brown liquid: IR (neat) 1645, 1620, 1565, 1500, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.16 (s, 1 H), 6.29 (d, J = 13.6 Hz, 1 H), 4.14–4.05 (m, 1 H), 3.34 (t, J = 7.2 Hz, 2 H), 3.01–2.96 (m, 4 H), 2.47 (s, 3 H), 1.85–1.79 (m, 4 H), 1.75–1.67 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 162.9, 158.0, 152.9, 137.6, 94.7, 49.1, 32.1, 30.1, 25.0, 21.6.

Registry No. **1a**, 99702-45-1; **1b**, 99702-47-3; **1c**, 99702-46-2; **2a**, 100037-81-8; **2b**, 100037-82-9; **2c**, 100037-83-0; **4**, 100037-84-1; **5a**, 100037-71-6; **6a**, 100037-73-8; **6b**, 100037-74-9; **6c**, 100037-75-0; **7a**, 30433-74-0; **7b**, 100037-76-1; **7c**, 100067-45-6; **8a**, 100037-72-7; **9**, 122624-40-2; **10**, 122624-41-3; **11**, 122624-42-4; **12**, 122624-43-5; **14**, 122624-44-6; **15**, 122624-45-7; **16**, 122624-46-8; **17**, 122624-47-9; 4-iodo-1-butyne, 43001-25-8; 4-bromobutanol, 33036-62-3; 4-bromo-1-butanal, 38694-47-2; pyrrolidine, 123-75-1; 5-chloro-1-pentyne, 14267-92-6.

Asymmetric Reduction of the Prochiral Carbon–Carbon Double Bond of Methyl 2-Chloro-2-alkenoates by Use of Fermenting Bakers' Yeast

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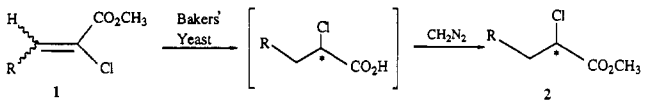
Asymmetric reduction of (*E*)- and (*Z*)-methyl 2-chloro-2-alkenoates by use of fermenting bakers' yeast gave (*R*)- and (*S*)-2-chloroalkanoic acids in 25–92% ee and ≥98% ee, respectively. The chemical yields were 10–40% for 2-chloropentenoate and 2-chloroheptenoate, but 65–70% for 2,4,4-trichloro- and 2,4,4,4-tetrachlorobutenoates. The substrates were found to be reduced after hydrolysis to the acids. The reactivity and stereoselectivity of the reduction were discussed. The reduction products, (*R*)- and (*S*)-2,4,4-trichlorobutanoic acids, were transformed to (*S*)- and (*R*)-2-amino-4,4-dichlorobutanoic acids, respectively.

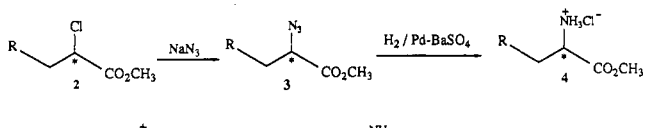
In a previous paper,[1] we have reported that (*E*)- and (*Z*)-methyl 2,4,4-trichloro-2-butenoate (**1e**) were reduced to (*R*)- and (*S*)-2,4,4-trichlorobutanoic acids (**2e**), respectively, by use of fermenting bakers' yeast (*Saccharomyces cerevisiae*) (eq 1). The *R* and *S* acids **2e** were effectively



R			
a	CH_3CH_2	d	CH_2Cl
b	$(CH_3)_2CH$	e	$CHCl_2$
c	$CH_3(CH_2)_3$	f	CCl_3

(1)

converted to optically pure L- and D-armentomycin (**5e**),[2] both enantiomers of a naturally occurring antibiotic agent (eq 2). The remarkable feature of this reduction is the



R			
b	$(CH_3)_2CH$		
e	$CHCl_2$		

(2)

highly effective stereochemical control for each geometrical isomer to produce the (*R*)- and (*S*)-α-chloro acids **2e** selectively. The *E* isomer [(*E*)-**1e**] was reduced to (*R*)-**2e** in 92% ee (60% yield), while the *Z* isomer [(*Z*)-**1e**] was reduced to (*S*)-**2e** in 98% ee (65% yield). This result attracts interest in view of the mechanism of bakers' yeast reduction and the methodology of organic synthesis.

Although many optically active α-halo acids or esters have been prepared by using naturally occurring chiral acids such as α-amino acids[3] or lactic acid[4] as starting materials, the asymmetric syntheses have been rather rare. Reported syntheses include a microbial hydrogenation of the carbon–carbon double bond of α-halo substituted enoate anions by using *Clostridium* sp. La 1[5] and an asymmetric halogenation of camphor-10-sulfonic acid derived esters with *N*-bromo- or *N*-chlorosuccinimide.[6] The present method reduces the carbon–carbon double bond of α-chloro alkenoate by use of easily available bakers' yeast. The scope and limitation of the method and its application to the preparation of α-amino acids are fully described.

Results and Discussion

Preparation of the Substrate. The substrates **1** were readily prepared by starting from aldehydes and methyl α-chloroacetoacetate according to the method reported.[7] The products obtained were a mixture of *E* and *Z* isomers except for the case of R = CCl_3, where only the *Z* isomer was produced. The separation was carried out by using a silica gel column. Determination of the *E* and *Z* geometry for **1a–c** was made by using the chemical shift of the olefinic hydrogen on the basis of the downfield shift for

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Table I. Asymmetric Reduction of Methyl 2-Chloro-2-alkenoates (1) to Methyl 2-Chloroalkanoates (2) with Fermenting Bakers' Yeast

	$RCH{=}CClCO_2CH_3$ (1)			$RCH_2CHClCO_2CH_3$ (2)			
	R	E/Z	time, h	% yield[a]	% ee	$[\alpha]_D$, deg (c, $CHCl_3$)[b]	confign
a	CH_3CH_2	E	40–44	23–28 (0)	47	+10.6 (0.62)	R
		Z	30–53	23–35 (2–3)	>98	−24.7 (1.03)	S
b	$(CH_3)_2CH$	E	41–47	6–10 (0)	68	+24.1 (1.26)	R
		Z	48–77	16–19 (5)	>98	−38.1 (0.74)	S
c	$CH_3(CH_2)_3$	E	30–60	30–40 (0)	25	+5.4 (1.63)	R
		Z	76–96	32–40 (4–8)	>98	−23.9 (1.19)	S
d	CH_2Cl	Z	30–68	0 (20–66)	–	–	–
e	$CHCl_2$	E	28–30	54–65 (0)	92	+42.4 (1.32)	R
		Z	30–32	58–71 (0)	98	−44.0 (1.69)	S
f	CCl_3	Z	11–23	41–69 (10)	>98	−10.5 (1.35)	S

[a] Recoveries of 1 are given in parentheses. [b] At temperatures of 22–26 °C.

the Z acids in comparison with the upfield shift for the corresponding E acids as reported for (E)- and (Z)-2-chloro-2-pentenoic acids.[8] For **1d–f**, in which the group R contains one to three chlorine atoms, the determination was made by conversion of **1d–f** to methyl α-chlorocrotonate[8,9] using tributyltin hydride. Details of the work will be reported in due course.

Conditions for Fermentation and Reduction. Uses of bakers' yeast in three modes (fresh, dry, and immobilized) were examined to improve the yield and the optical purity. The immobilization[10] was done by using sodium alginate or κ-carrageenan mixed with dry bakers' yeast in ratios of 0.25 and 0.5 per 1 g of the yeast. We found no appreciable improvement in the optical purity by all yeasts mentioned above, but attained higher yields with an easy extraction by use of the low-ratio (0.25:1) immobilized yeast. For example, the yield of **2e** was 45–50% and 54–65% in the cases of dry and alginate-immobilized bakers' yeast, respectively. A clear contrast was also observed in the 0% and 23–35% yields of **2a**, where the immobilization may prevent product losses due to contamination with intractable impurities. Since alginate is more easily handled than κ-carrageenan, we used the alginate-immobilized yeast generally.

The concentration of substrate was 2 mmol per 500 mL of culture broth with 2.5 g of dry bakers' yeast. We did not attempt to maximize the substrate concentration, but higher concentrations showed a tendency to suppress the fermentation.

Bakers' Yeast Reduction of Methyl 2-Chloro-2-alkenoates. The reduction of ketones to optically active secondary alcohols by using bakers' yeast has been studied extensively.[11] In contrast, fewer studies have been reported for the reduction of carbon–carbon double bonds to optically active saturated carbon chains. The double bonds are limited to those conjugated with ketone or aldehyde carbonyl groups,[12] those of allylic alcohols,[13] and those of perfluoroalkylated vinyl compounds.[14] α,β-Unsaturated carboxylic acids or esters also seem to be good substrates for the bakers' yeast reduction, but they need a close examination. They have been reported to be good substrates in cases of ethyl 3-(perfluoroalkyl)-2-alkenoates[14] but not good in cases of ethyl 4-hydroxy-2-alkenoates.[12b,h]

We have found that, in the reduction of methyl 2-chloro-2-alkenoates (1), the products were obtained as free acids. However, for example, when ethyl 2,4,4-trichlorobutenoate was used as the substrate, the ethyl ester was recovered intact in 62% yield, being accompanied by a trace of the acidic reduction product. Therefore, it can be said that the ester cannot be the substrate, and that it is quite probable that methyl 2-chloro-2-alkenoates (1) were reduced after hydrolysis. The hydrolysis is likely catalyzed by hydrolytic enzymes in yeast cells,[15] and the methyl ester (1) is hydrolyzed much faster than the ethyl ester.[16] The choice of the methyl esters (1) as substrates rather than the free acids was made because of the ease of preparation and purification.

We have also found that (E)-2-heptenoic acid and its methyl ester were not reduced to heptanoic acid by bakers' yeast. The acid was recovered almost quantitatively after incubation for 4 days, and the methyl ester was hydrolyzed to the acid in 82% yield, leaving the rest in 14% recovery. The fact that methyl 2-chloro-2-heptenoate (**1c**) was reduced to optically active 2-chloroheptanoic acid (**2c**) indicates that the electronegative 2-chloro substituent[17] is essential for the reduction, the conjugate carboxyl group being insufficient to activate the carbon–carbon double bonds.

As shown in Table I, the yields of reduction products **2a–c** are rather low. This may be attributable partly to losses in the extraction process, especially for **2a**, and partly to the metabolism of yeast cells, especially for **2b**.

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The rate-enhancing effect of the chlorine-containing substituent is also observed in Table I. For substrates **1b** and **1e**, the dichloromethyl group enhances the rate, about twice as fast as the isopropyl group. Since both the groups have comparable bulkiness, the difference in the rates can be attributable to the electron-withdrawing effect of two chlorine atoms. The trichloromethyl group for **1f** further enhances the rate, twice as fast as the dichloromethyl group. The monochloromethyl group for **1d**, however, completely prevented reduction. When **1d** was subjected to the reduction conditions for 30 h, **1d** was recovered intact in 42% yield accompanied by hydrolysis to the acid in 24% yield. After 68 h, the recovery was decreased to 23% and nothing else was obtained. It is quite puzzling what has happened to **1d**.

Reactivity and Stereochemistry in the Reduction of *E* and *Z* Isomers. As shown in Table I, the reaction time for **1a–c** indicates that the *E* isomers are reduced faster than the corresponding *Z* isomers. The *Z* isomers were recovered in small amounts. Interestingly, the *E* isomers with higher reactivity afforded the reduced products with lower % ee.

The stereochemical course of the reduction is highly dependent on the geometry of the double bond to be reduced. All of the *Z* isomers led to the *S* configuration with ≥98% ee while the *E* isomers afforded the *R* configuration with 25–92% ee, depending on the R group. Why were the *E* isomers reduced with lower ee values? This may arise from the isomerization of the *E* isomers to the *Z* isomers and/or from the lower enantioselectivity of the yeast reductase toward the *E* isomers. We have observed that both the *E* and *Z* isomers are stable and can be stored without isomerization, and that the *E* isomer is not isomerized to the *Z* isomer in the culture solution. Therefore, it is concluded that the ee values reflect the enantioselectivity of the yeast reductase toward the *E* and *Z* isomers.

Interestingly the isopropyl group directs the stereochemistry more effectively than the ethyl or butyl, but less effectively than the highly polar dichloromethyl group of comparable bulkiness. Thus, the polarity of the group has again played an important role in the stereochemistry as well as in the rate enhancement discussed above.

Determination of Optical Purity. We have determined the % ee by measuring 100-MHz ^{1}H NMR spectra in the presence of (+)-Eu(hfc)$_3$ at 27 or 45 °C by using a 1:3 mixture of $CDCl_3$ and CCl_4 as solvent. The temperature was varied to obtain well-resolved sharp NMR signals and to shift an overlapping signal of moisture. Separation of the ester methyl signals for the *R* and *S* enantiomers **2** was ascertained by measuring the spectra of the following racemic methyl esters: (±)-**2a**,[18] 120 mol % (+)-Eu(hfc)$_3$, 45 °C, δ 5.78 and 5.84; (±)-**2b**,[18] 100 mol %, 27 °C, δ 4.34 and 4.36; (±)-**2e**,[19] 170 mol %, 27 °C, δ 4.16 and 4.22; (±)-**2f**,[19] 150 mol %, 27 °C, δ 4.81 and 4.88.

Determination of the Absolute Configuration. Commercially available (*S*)-2-aminopentanoic acid (L-norvaline), (*S*)-2-amino-4-methylpentanoic acid (L-leucine), and (*S*)-2-aminohexanoic acid (L-norleucine) were converted to the corresponding (*S*)-methyl 2-chloroalkanoates with retention of configuration according to the method reported.[20] Their specific rotations were measured and used as references. In a chiral sense, 2-chloro esters **2a–c** obtained from (*Z*)-**1a–c** showed their specific rotations in good agreement with those of 2-chloro esters prepared from L-amino acids. Therefore, **2a–c** from (*Z*)-**1a–c** were assigned the *S* configuration, and those from (*E*)-**1a–c** were assigned the *R* configuration.

The configuration of **2e** was determined by conversion to 2-amino-4,4-dichlorobutanoic acid (**5e**) according to the method reported (eq 2).[21] Thus naturally occurring (*S*)-**5e** was obtained from (*R*)-**2e**, which was prepared by the bakers' yeast reduction of (*E*)-**1e**. Similarly, (*R*)-**5e** was obtained from (*S*)-**2e** which was prepared from (*Z*)-**1e**.

The configuration of **2f** was determined by conversion to **2e** with tributyltin hydride. The specific rotation of **2e** thus obtained was found to be comparable to that of (*S*)-**2e** from (*Z*)-**1e**, indicating that **2f** has the *S* configuration.

Conversion of 2b and 2e to α-Amino Acids. The conversion of (*R*)- and (*S*)-**2e** to (*S*)- and (*R*)-2-amino-4,4-dichlorobutanoic acids [(*S*)- and (*R*)-**5e**], respectively, was carried out according to the method reported for racemic ethyl 2,4,4-trichlorobutanoate[21] with minor modifications (eq 2).

As expected, **2e** was converted to **5e** without any appreciable loss of % ee. We treated hydrochloride **5'e** with diazomethane in ether to obtain the free amino ester of **4e**. The ^{1}H NMR spectra of this free amino ester measured in the presence of (+)-Eu(hfc)$_3$ indicated that the % ee of **2e** was still retained after the sequence of substitution, hydrogenation, and hydrolysis. Thus both optically pure enantiomers of **5e** (armentomycin) were obtained by a single crystallization in the last step. This is the first preparation of both enantiomers of armentomycin.

In a similar way, (*S*)-**2b** was converted to (*R*)-**5b** (D-leucine). However, conversion of (*S*)-**2f** to (*R*)-**5f** has not been successful because of the failure to reduce (*R*)-**3f** to (*R*)-**4f** by several means used, such as 5% Pd–$BaSO_4$ in EtOH–HCl, $NaBH_4$–THF–MeOH,[22] $SnCl_2$ in MeOH,[23] and $NaBH_3CN$–THF–MeOH for **3f** and for the free acid of **3f**. The preparation of **3f** from **2f** using NaN_3 in DMF was better carried out at a lower, ice-bath temperature to secure a 64% yield compared with an 18% yield at room temperature.[21]

Experimental Section

All boiling and melting points are uncorrected. IR spectra were recorded with a JASCO A-102 spectrometer. ^{1}H NMR spectra at 60 MHz were obtained on a JEOL PMX 60SI spectrometer. ^{1}H NMR spectra at 100 MHz were obtained on a JEOL FX 100 spectrometer. TMS in organic solvents and sodium 4,4-dimethyl-4-sila-1-pentanesulfonate (DSS) in D_2O were used as internal standards. Bulb-to-bulb distillation was performed by using a Shibata GTO-250 glass tube oven. HPLC was performed by using a Hitachi chromatograph equipped with an RI detector. Elemental analyses were performed by E. Amano of this laboratory on a Yanagimoto CHN analyzer MT-3.

Materials. Dry bakers' yeast was purchased from Oriental Yeast, Tokyo. Sodium alginate was from Nakarai Chemicals, Kyoto, and κ-carrageenan was from Sansho, Osaka. Tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III) [Eu(hfc)$_3$] was obtained from Aldrich.

Immobilization of Bakers' Yeast.[24] Immobilization of bakers' yeast in calcium alginate gel beads was carried out by a modification of the method of Kierstan and Bucke.[25] A 6-g sample of dry bakers' yeast was suspended in 120 mL of water containing 1.5 g of sodium alginate. This suspension was transferred to a

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Table II. Methyl 2-Chloroalkanoate (2), $RCH_2CHClCO_2CH_3$[a]

R	bp, °C (Torr)	IR, cm^{-1}	^1H NMR (CCl_4): δ
CH_3CH_2	45 (15)	1740	0.97 (t, 3 H), 1.2–2.2 (m, 4 H), 3.73 (s, 3 H), 4.14 (t, J = 7 Hz, 1 H)
$(CH_3)_2CH$	40 (5)	1740	0.92 (d, 3 H), 0.96 (d, 3 H), 1.6–2.1 (m, 3 H), 3.72 (s, 3 H), 4.15 (t, 1 H)
$CH_3(CH_2)_3$	40 (2)	1750	0.90 (t, 3 H), 1.1–1.6 (m, 6 H), 1.6–2.2 (m, 2 H), 3.68 (s, 3 H), 4.10 (t, J = 7 Hz, 1 H)
$CHCl_2$	60 (3)	1750	2.6–2.95 (m, 2 H), 3.79 (s, 3 H), 4.43 (dd, J = 5.5 and 8.5 Hz, 1 H), 5.85 (dd, J = 5.8 and 7.3 Hz, 1 H)
CCl_3	70 (3)	1755	3.16 (dd, J = 3.5 and 15.0 Hz, 1 H), 3.76 (dd, J = 8.1 and 15.0 Hz, 1 H), 3.81 (s, 3 H), 4.52 (dd, J = 3.5 and 8.1 Hz, 1 H)

[a] Satisfactory analytical data (±0.3% for C and H) were obtained for all compounds listed.

dropping funnel and added dropwise to 200 mL of a 10% $CaCl_2$ solution. The gel beads of 3–4-mm diameter were collected and washed with 1 L of water three times. The yeast preparation was stored in a refrigerator (within 1–2 weeks) before use. Immobilization with κ-carrageenan was carried out according to the method of Chibata and co-workers.[26] A 1.5-g sample of κ-carrageenan was dissolved in 60 mL of water at 45 °C, and to this warm solution was added 6 g of dry bakers' yeast with stirring. When suspended completely, the mixture was cooled to 5 °C to give a gel. Then the gel was soaked in a cold 2% KCl solution for half a day and cut into cubes of about 3-mm sides. The gel cubes were finally washed with a 2% KCl solution three times and stored in a refrigerator before use.

Bakers' Yeast Reduction. The general procedure is as follows. A suspension of dry bakers' yeast (2.5 g) immobilized in calcium alginate gel beads, glucose (10 g), KH_2PO_4 (1 g), $(NH_4)H_2PO_4$ (1 g), $MgSO_4$ (0.5 g), and $CaCO_3$ (2.5 g) in boiled water (500 mL) was stirred at 30–32 °C for 1 h until most of the gel beads floated on the solution. It indicated a vigorous fermentation. Then the substrate (1) (2 mmol) was added and the culture solution was stirred for 11–96 h. Glucose (5 g) was added when the glucose was consumed after about 10 h, as checked by using glucose test paper (Diasticks II, Miles-Sankyo). The pH was about 7 at the beginning and 5 at the end of reduction. The gel beads were separated by filtration, and the filtrate was extracted with ethyl acetate three times after being adjusted to pH 2 with 10% hydrochloric acid. The organic layer was dried ($MgSO_4$) and evaporated to give the hydrolyzed acid, which was esterified with diazomethane to afford **2**. The product was purified through a silica gel column (Katayama 60, hexane–ether, 20:1) to give a colorless oil. Extraction of the gel beads with ethyl acetate afforded no reduction products or starting material (1). See Table II.

(*S*)-Methyl 2-Azido-4,4-dichlorobutanoate [(*S*)-3e]. According to the method reported,[21] (*R*)-**2e** (565 mg, 2.75 mmol) was converted to crude (*S*)-**3e** (585 mg). This was passed through a silica gel column (Katayama 60, hexane–ether, 50:1) to give purified (*R*)-**3e** (506 mg, 87%) as a colorless oil: bp 65 °C (3 Torr); $[\alpha]^{24}_D$ −120° (*c* 1.33, $CHCl_3$); IR (neat) 2120, 1745 cm^{-1}; ^1H NMR (CCl_4) δ 2.38–2.57 (m, 2 H), 3.80 (s, 3 H), 4.09, 4.24 (dd, J = 6 Hz, 1 H), 5.71, 5.85 (dd, J = 6 Hz, 1 H). Anal. Calcd for $C_5H_7Cl_2N_3O_2$: C, 28.32; H, 3.33; N, 19.82. Found: C, 28.05; H, 3.21; N, 19.63.

(*R*)-Methyl 2-azido-4,4-dichlorobutanoate [(*R*)-3e]: 75% yield; $[\alpha]^{26}_D$ +131° (*c* 1.28, $CHCl_3$).

(*S*)-Methyl 2-Amino-4,4-dichlorobutanoate Hydrochloride [(*S*)-4e]. In dry ethanol (12 mL) acidified with hydrogen chloride, (*S*)-**3e** (228 mg, 1.08 mmol) was stirred with 5% Pd–$BaSO_4$ (101 mg) for 24 h at room temperature under hydrogen. The mixture was filtered, and the filtrate was evaporated to give crude (*S*)-**4e** (200 mg) as slightly yellow crystals. These were washed with ether and dried in vacuo to afford (*S*)-**4e** (187 mg, 78%) as colorless crystals: mp 134–136 °C dec; IR (KBr) 1750 cm^{-1}. Anal. Calcd for $C_5H_{10}Cl_3NO_2$: C, 26.99; H, 4.53; N, 6.30. Found: C, 27.11; H, 4.47; N, 6.40.

(*R*)-Methyl 2-amino-4,4-dichlorobutanoate hydrochloride [(*R*)-4e]: colorless crystals (86% yield).

(*S*)-2-Amino-4,4-dichlorobutanoic Acid [(*S*)-5e]. According to the method reported,[21] (*S*)-**4e** (178 mg, 0.800 mmol) was hydrolyzed to the hydrochloride of (*S*)-**5e** (162 mg). This was converted by method A (using ion-exchange resin) to the free amino acid (*S*)-**5e** (120 mg, 87%) as slightly yellow crystals: $[\alpha]^{24}_D$ +17.6° (*c* 0.66, aqueous HCl, pH 1.0). These crystals (105 mg) were recrystallized from methanol–water (18:1) to afford (*S*)-**5e** (56 mg, 53%) as colorless crystals: mp 151–152 °C dec; $[\alpha]^{25}_D$ +26.8° (*c* 0.71, aqueous HCl, pH 1.0) [lit.[2a] $[\alpha]^{25}_D$ +26.2° (*c* 0.75, aqueous HCl, pH 1.0)]; IR (KBr) 3400–2100, 1610, 1585, 1500 cm^{-1}; ^1H NMR (D_2O) δ 2.50–2.95 (m, 2 H), 3.88, 4.01 (dd, J = 6 Hz, 1 H), 6.13 (t, J = 6 Hz, 1 H).

(*R*)-2-Amino-4,4-dichlorobutanoic Acid [(*R*)-5e]. In a similar way, the hydrochloride of (*R*)-**5e** was obtained from (*R*)-**4e** in 87% yield as slightly colored crystals: $[\alpha]^{23}_D$ −22.7° (*c* 0.75, aqueous HCl, pH 1.0). These crystals were recrystallized similarly to afford (*R*)-**5e** in 63% yield as colorless crystals: mp 149–151 °C dec; $[\alpha]^{24}_D$ −26.7° (*c* 0.72, aqueous HCl, pH 1.0).

(*R*)-Methyl 2-Azido-4-methylpentanoate [(*R*)-3b]. From (*S*)-**2b** (61 mg, 0.37 mmol) was obtained (*R*)-**3b** (52 mg, 0.30 mmol, 82%) after purification by LC (Merck silica gel 60, hexane–ether, 100:1) and HPLC (Unisil Q, hexane–ether, 50:1) as a colorless oil: IR (neat) 2130, 1750 cm^{-1}; ^1H NMR (CCl_4) δ 0.96 (dd, 6 H), 1.52–1.70 (m, 3 H), 3.42 (t, 1 H), 3.75 (s, 3 H). Anal. Calcd for $C_7H_{13}N_3O_2$: C, 49.11; H, 7.65; N, 24.54. Found: C, 49.25; H, 7.36; N, 24.42.

(*R*)-Methyl 2-Amino-4-methylpentanoate Hydrochloride [(*R*)-4b]. From (*R*)-**3b** (103 mg, 0.60 mmol) was obtained (*R*)-**4b** (68 mg, 0.38 mmol, 62%) as crude crystals: IR (KBr) 1740 cm^{-1}.

(*R*)-2-Amino-4-methylpentanoic Acid (D-Leucine) [(*R*)-5b]. From (*R*)-**4b** (68 mg, 0.38 mmol) was obtained (*R*)-**5b** (38 mg, 0.29 mmol, 77%) after crystallization: mp 290–292 °C dec (lit.[27] mp 293–295 °C); $[\alpha]^{26}_D$ −15.9° (*c* 0.97, 6 N HCl) [lit.[27] [α] +15.1° (6 N HCl) for L-leucine]. The IR spectrum was identical with that for the authentic sample.

(*S*)-Methyl 2-Chloropentanoate [(*S*)-2a] from L-Norvaline. According to the method reported,[20] L-norvaline (176 mg, 1.50 mmol) was converted to the α-chloro acid. This acid was treated with CH_2N_2 in ether to give a crude oil (150 mg). This was purified by LC (Merck 60, hexane–ether, 100:1) and distilled to afford pure (*S*)-**2a** (44 mg, 19%): bp 45 °C (15 Torr); $[\alpha]^{25}_D$ −24.3° (*c* 1.40, $CHCl_3$). The IR and ^1H NMR spectra were identical with those of the yeast reduction product **2a**.

(*S*)-Methyl 2-chloro-4-methylpentanoate [(*S*)-2b] from L-leucine: 32% yield; bp 45 °C (15 Torr); $[\alpha]^{22}_D$ −34.3° (*c* 1.68, $CHCl_3$). The IR and ^1H NMR spectra were identical with those of the yeast reduction product **2b**.

(*S*)-Methyl 2-chlorohexanoate from L-norleucine: 19% yield; bp 55 °C (15 Torr); $[\alpha]^{22}_D$ −21.7° (*c* 1.28, $CHCl_3$); IR (neat) 1755 cm^{-1}; ^1H NMR (CCl_4) δ 0.93 (t, 3 H), 1.2–1.6 (m, 4 H), 1.7–2.2 (m, 2 H), 3.72 (s, 3 H), 4.12 (t, J = 7 Hz, 1 H).

Methyl 2-Amino-4,4-dichlorobutanoate. The hydrochloride **5e′** was stirred in ether with a large excess of CH_2N_2 until the crystals disappeared. Evaporation of the ether afforded an oil: ^1H NMR ($CDCl_3$–CCl_4, 1:3) δ 2.23 (ddd, J = 4.0, 10.0, and 14.0 Hz, 1 H), 2.56 (ddd, J = 4.0, 9.1, and 14.0 Hz, 1 H), 3.58 (dd, J = 4.0 and 10.0 Hz, 1 H), 3.62 (s, 3 H), 5.97 (dd, J = 4.0 and 10.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 47.6 (t), 52.0 (d), 52.6 (q), 70.7 (d), 174.7 (s). For the racemate: ^1H NMR with 100 mol % Eu(hfc)$_3$, δ 6.88 and 6.77 for OCH_3.

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