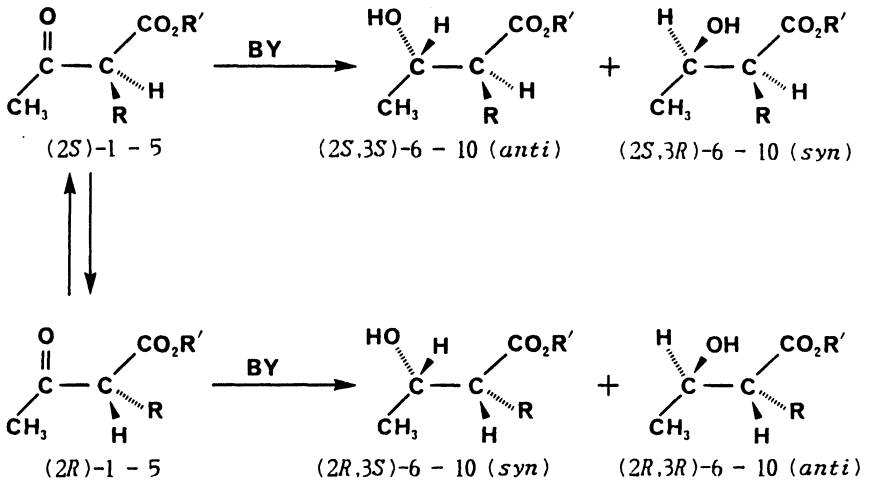
  Bull. Chem. Soc. Jpn., 62, 1179—1187 (1989)

Stereochemical Control in Microbial Reduction. 9. Diastereoselective Reduction of 2-Alkyl-3-oxobutanoate with Bakers' Yeast

Kaoru NAKAMURA,* Takehiko MIYAI,† Ashish NAGAR,†,†† Shinzaburo OKA,† and Atsuyoshi OHNO†
Department of Chemistry, Shiga University of Medical Science, Seta, Ohtsu 520—21
†Institute for Chemical Research, Kyoto University, Uji, Kyoto 611
(Received October 24, 1988)

Bakers' yeast reduces esters of 2-alkyl-3-oxobutanoic acid ($CH_3COCHRCO_2R'$; R=methyl, ethyl, propyl, propargyl, and allyl) into the corresponding (*S*)-hydroxy esters with exclusive stereoselectivity, while the configuration at the 2-position of the hydroxy esters is either *S* (anti) or *R* (syn) depending on the structure of the alkoxyl group in the carboalkoxyl moiety of the ester. Oftenly, the stereoselectivity with respect to the 2-position is not satisfactory. In general, the reduction of *t*-butyl esters exerts predominancy in the products, whereas that of 1,1-dimethylpropyl esters exerts the syn predominancy. A marked difference between these two esters in diastereoselectivity is discussed from the view point of plausible conformations of the esters.

Esters of 2-alkyl-3-hydroxybutanoic acids are important chiral building blocks for syntheses of antibiotics and other natural products. There are three major methods in the literatures to prepare the esters with high diastereo- and enantioselectivities. First of all is the aldol condensation of chiral enolates with aldehydes,[1,2] and the second method is α-alkylation of a dianion from a chiral 3-hydroxybutanoate.[3] The latter method is restricted to synthesize the hydroxy ester of anti conformation. These two methods are chemical transformations and require an optically active starting material(s) in order to obtain an optically active product. The third and biological method involves the reduction of achiral 2-alkyl-3-oxobutanoate by means of certain microbes.[4,5] The biological method has some advantages over the chemical methods in that two chiral centers are introduced into the product in one step starting from an achiral compound, and that some microbes such as bakers' yeast (BY) are quite cheap and easily obtainable. However, on the other hand, diastereoselectivity of microbial reduction is not always satisfactory and sometimes both syn and anti products are produced in nearly equal amounts, which means that dehydrogenases



1, **6**; R = CH_3-
2, **7**; R = C_2H_5-
3, **8**; R = *n*-C_3H_7-
4, **9**; R = $HC{\equiv}CCH_2$-
5, **10**; R = $H_2C{=}CHCH_2$-

a; R′ = CH_3-
b; R′ = C_2H_5-
c; R′ = *n*-C_4H_9-
d; R′ = *n*-C_6H_{13}-
e; R′ = *n*-C_8H_{17}-
f; R′ = Me_2CH-
g; R′ = Me_2CHCH_2-
h; R′ = Me_3C-
i; R′ = Me_2EtC-
j; R′ = Me_3CCH_2-

k; R′ = *cyclo*-C_5H_9-
l; R′ = *cyclo*-C_6H_{11}-
m; R′ = *cyclo*-$C_6H_{11}CH_2$-
n; R′ = $PhCH_2$-
o; R′ = $H_2C{=}CHCH_2$-
p; R′ = $MeO(CH_2)_2$-
q; R′ = $EtO(CH_2)_2$-
r; R′ = *n*-$BuO(CH_2)_2$-
s; R′ = $MeS(CH_2)_2$-
t; R′ = $Cl(CH_2)_2$-

Scheme 1.

†† Present address: Chemistry Section, D. V. Project, ONGC, Jorhat, Assam, India.

present in the microbe and responsible for the reduction cannot recognize the configuration at the α (or 2)-position of racemic α-substituted β-keto esters (alkyl 3-oxocarboxylates).

It is known that the stereochemistry of the reduction of β-keto esters by BY affords the corresponding (*S*)-hydroxy esters with moderate to high enantioselectivities,[6] and the substitution by an alkyl group at the α-position of the ester increases the selectivity.[7,8] Therefore, if an α-substituted β-keto ester has a structure which exerts a large difference in rate of reduction between its 2*S*- and 2*R*-enantiomeric isomers, one can expect to obtain the product with a high diastereomeric excess (d.e.). There remains another problem, i.e., if the rate of isomerization between the 2*S*- and 2*R*-isomers is not fast enough compared to the rate of reduction, the chemical yield of the product cannot exceed 50% even though the recognition between 2*S*- and 2*R*-isomers with an enzyme is excellent. On the other hand, if racemization at the α-position takes place much faster than the reduction, the starting material remains racemic whole through the reaction period and the product is expected to be highly diastereoselective after 100% completion of the reaction.

We would like to report in this paper that the diastereoselectivity of the reduction of an α-substituted β-keto ester with BY can be controlled by the change in the structure of alkoxyl group: the presence and absence of a methylene group next to the alkoxyl oxygen play a crucial role in determining the syn/anti selectivity, therefore the d.e., of the reduction.

Results

Various esters of 2-methyl- (**1**), 2-ethyl- (**2**), 2-propyl- (**3**), 2-propargyl- (**4**), and 2-allyl-3-oxobutanoates (**5**) were prepared from the corresponding unsubstituted esters by alkylation and subjected to the reducion with BY. The diastereoselectivities of the reduction (syn/anti ratio in the product) were monitored on GLC. The authentic samples for the anti isomers were prepared by the reaction of the dianion of 3-hydroxybutanoates with the corresponding alkyl halides.[3]

The rate of deuterium incorporation at the 2-position of ethyl 2-methyl-3-oxobutanoate (**1b**) in neutral deuterium oxide was measured on a ^{1}H NMR spectrometer. The signal from the methine proton of **1b** (δ_{TMS}: 3.8) was compared with that from the methylene protons in the ethyl group (δ_{TMS}: 4.3). The intensity of the former signal decreased gradually with a half-life of about 1.5 hours, which is at least an order of magnitude faster than the rate of reduction. On the other hand, practically no incorporation of deuterium was observed with 2-methyl-3-hydroxybutanoate (**6b**) under the same reaction conditions.

Results from the reduction of various esters are summarized in Table 1.[9] The diastereomeric composition of 2,2-dimethylpropyl 2-methyl-3-hydroxybutanoate (**6j**) obtained by the reduction with BY was measured in detail, after it was converted into **6a**, and found the ratio of 2*R*, 3*S* : 2*S*, 3*S* : 2*R*, 3*R* : 2*S*, 3*R* to be 96 : 4 : $<$1 : $<$1. Thus, it was confirmed that the contamination of the (3*R*)-isomers is negligible, if any.

Discussion

Since H–D exchange and racemization at the α-position of a β-keto ester pass through the same intermediate (enolate), there remains no doubt that fast incorporation of deuterium in **1b** under neutral conditions reveals that the starting material stays in a racemic mixture with respect to the enantiomorphism at the α-position whole through the reduction by BY, where there are many acid and base catalysts to promote the enolization. That is, all starting materials subjected to the present reduction can, at least theoretically, be converted into the product of desired configuration (kinetic resolution), provided the difference in rate of reduction for two enantiomers is large enough.

Elongation of alkyl chain in alkoxyl group of the β-keto ester did not show remarkable difference in the diastereoselectivity of the reduction for all α-substituents so far studied. This is in contrast to the reduction of β-keto esters unsubstituted at the α-position.[10] In addition, substitution of a methylene group in the alkyl chain by either a heteroatom such as oxygen or sulfur or an aromatic group did not affect the selectivity in recognizable extent as can be seen in Table 1. Thus, the change in the polarity (or hydrophobicity) of the alkoxyl group seems to exert very little effect, if any, on the selectivity. Another interesting trend seen in Table 1 is that α-allyl substituent tends to afford the anti product, whereas others prefer to yield the syn product. The latter trend is the strongest with the α-methyl substituent, the shortest alkyl group. Since the propargyl group belongs to the syn-preferential substituent, it is clear that the anti-orientation with the allyl group is not due to the presence of a π-bonding in this substituent.

A remarkable change in the diastereoselectivity can be seen in anti preference with 2-allyl-3-oxobutanoates (**10**) when the alkoxyl oxygen is bound directly to a tert-carbon such as in *t*-butyl (**10h**) and 1,1-dimethylpropyl (**10i**) esters. The same structure also shifts the selectivity toward the anti direction in 2-methyl-3-hydroxybutanoates (**6**), and the syn/anti ratio becomes the worst in **6h**. Instead, the insertion of a methylene group between the alkoxyl oxygen and a bulky alkyl substituent such as in 2,2-dimethylpropyl (**j**) or cyclohexylmethyl (**m**) esters shifts the selectivity to syn direction. Consequently, the syn/anti ratio in **6** is improved by the alkoxyl group of this kind, but the value for **10** with these alkoxyl groups becomes worse.

It is interesting to note that one methylene group in the alkoxyl moiety affects the stereochemistry of the reduction. It should be emphasized that the reduction

Table 1. Syn/Anti Ratio in the β-Hydroxy Esters Obtained by the Reduction of α-Substituted β-Keto Esters by Bakers' Yeast[a)]

Compd.	R′ in ester	R in ester				
		Me **6**	Et **7**	*n*-Pr **8**	$HC{\equiv}CCH_2$- **9**	$H_2C{=}CHCH_2$- **10**
a	CH_3-	81/19 (11)	62/38 (70)	72/28 (80)	57/43 (39)	27/73 (25)
b	C_2H_5-	87/13 (59)	74/26 (80)	74/26 (70)	68/32 (80)	35/65 (59)
c	*n*-C_4H_9-	88/12 (67)	50/50 (60)	49/51 (40)	69/31 (97)	36/64 (24)
d	*n*-C_6H_{13}-	94/6 (76)	74/26 (50)	—	—	48/52 (22)
e	*n*-C_8H_{17}-	92/8 (63)	76/24 (84)	b)	—	b)
f	Me_2CH-	—	—	65/35 (70)	66/34 (86)	31/69 (27)
g	Me_2CHCH_2-	93/7 (87)	60/40 (75)	—	70/30 (82)	51/49 (43)
h	Me_3C-	72/28 (85)	21/79 (55)	25/75 (76)	17/83 (68)	6/94 (36)
i	Me_2EtC-	69/31 (19)	21/79 (4)	23/77 (5)	22/78 (48)	3/97 (9)
j	Me_3CCH_2-	96/4 (57)	69/31 (70)	80/20 (68)	77/23 (76)	56/44 (66)
k	*cyclo*-C_5H_9-	81/19 (82)	—	—	—	52/48 (63)
l	*cyclo*-C_6H_{11}-	90/10 (81)	—	—	—	25/75 (25)
m	*cyclo*-$C_6H_{11}CH_2$-	94/6 (83)	—	—	—	—
n	$PhCH_2$-	82/18 (79)	—	50/50 (70)	—	16/84 (54)
o	$H_2C{=}CHCH_2$-	—	53/47 (65)	68/32 (65)	61/39 (84)	25/75 (49)
p	$MeO(CH_2)_2$-	87/13 (75)	53/47 (80)	63/37 (80)	62/38 (—)	30/70 (37)
q	$EtO(CH_2)_2$-	87/13 (80)	58/42 (73)	57/43 (63)	—	35/65 (60)
r	*n*-$BuO(CH_2)_2$-	87/13 (90)	66/34 (82)	81/19 (80)	50/50 (—)	24/76 (56)
s	$MeS(CH_2)_2$	89/11 (84)	—	—	—	34/66 (78)
t	$Cl(CH_2)_2$	85/15 (60)	—	—	—	—

a) Numbers in parentheses are chemical yields. b) No reaction.

with BY is catalyzed by a variety of catalysts, dehydrogenases, and reductases, in this microbe, and we cannot nominate any one of enzymes as the sole candidate for the catalyst. Zhou and his co-workers reported that there are at least three dehydrogenases in BY to reduce 4-chloro-3-oxobutanoates.[11)] Furuichi and his co-workers found that benzyl 2-methyl-3-oxobutanoate is reduced by a pure enzyme into the corresponding β-hydroxy ester with the syn/anti ratio of 8/1, whereas the reduction of the same ester with a yeast affords the syn/anti ratio to be 2/1[12)] suggesting the contribution of plural enzymes in yeast. Nevertheless, the sum of individual diastereoselectivities of all enzymes involved in the reduction can be attributed to the diastereoselectivity of an "imaginary" enzyme.[13)]

Inspection of molecular structures of the esters with the aid of CPK-models seems to suggest a simple rule; *a principle of the smallest volume*. Figures 1a and 1b show molecular models for (2*R*,3*S*)-**6j** (syn) and (2*S*,3*S*)-**6j** (anti), respectively, where a bulky substituent is represented by an iodine atom. Suppose that the carboxylate oxygen assumes the syn-conformation with respect to the carbonyl oxygen to be reduced and the "hydride" from NAD(P)H attacks the carbonyl group from the front side to give the (3*S*)-hydroxy ester as seen in Fig. 1. Also suppose that the molecule is folded in the pocket of the "imaginary" enzyme so that the alkoxyl oxygen in the ester can assume the syn-conformation in the molecular plane. From Fig. 1, it is recognized that the alkoxyl oxygen in the *syn*-**6j** can assume the full syn-conformation in the molecular plane without being suffered from any strain, whereas

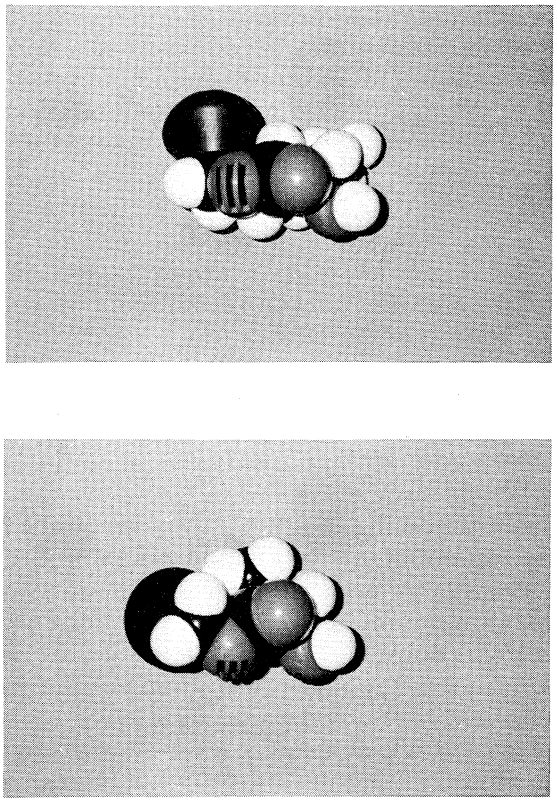


Fig. 1. CPK-models for (a) 2*R*,3*S* (*syn*)- and (b) 2*S*,3*S* (*anti*)-alkyl 2-methyl-3-hydroxybutanoates. The bulky substituent in the alkoxyl group is represented by an iodine model.

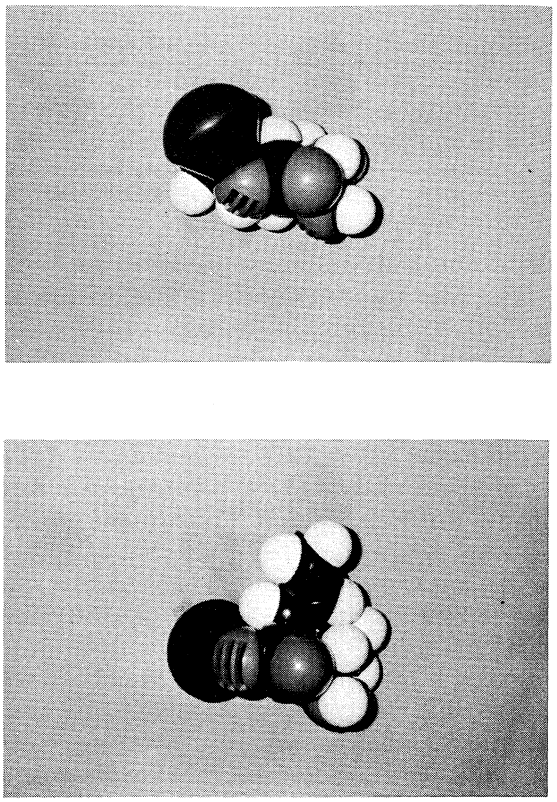


Fig. 2. CPK-models for (a) 2*R*,3*S* (*syn*)- and (b) 2*S*,3*S* (*anti*)-alkyl- 2-allyl-3-hydroxybutanoates. The bulky substituent in the alkoxyl group is represented by an iodine model.

the oxygen in the *anti*-**6j** has to be twisted from the plane to be in the syn-conformation.

Contrary, the alkoxyl oxygen can assume the full syn-conformation in (2*S*,3*S*)-**10h** (anti), as shown in Fig. 2 in which a bulky substituent is again represented by an iodine, but it is largely twisted from the planarity in (2*R*, 3*S*)-**10h** (syn). Thus, the reduction affords satisfactory diastereoselectivity only when the structure of an ester is such that in which the alkoxyl oxygen can assume *a planar syn-conformation* in the product β-hydroxy ester. In other words, the pocket of the "imaginary" enzyme does not have enough room and elasticity to accept a bulky molecule, and the stereoselectivity appears large either in syn or anti direction when the fundamental skeleton of β-keto ester can assume the smallest volume. The presence or absence of a methylene group adjacent to the alkoxyl oxygen is crucial to make the syn or anti conformation more stable than the other, respectively. Since the substituent at the 2-position of **7**, **8**, or **9** is larger than that in **6**, the steric bulk of the alkoxyl group becomes more important in these esters, and the syn/anti predominancy is reversed in **7h**, **8h**, and **9h**. The conformational effect is more important than the hydrophobicity of the alkoxyl group to determine the selectivity. Similar trend in the steric bulk of the alkoxyl group was also observed in the reduction of 2-methyl-3-oxopropanoates.[14] It should be emphasized again that the argument has been done for a pocket of imaginary enzyme composed of a pack of many real enzymes.

In order to confirm the proposed principle, and to prove its versatility, we have to accumulate further results from various esters. However, we believe that the principle at the present stage can suggest the structure of substituents we should try in order to obtain the β-hydroxy ester of certain configuration at least as a working hypothesis.

Experimental

Instruments. ^{1}H NMR spectra were recorded on a Varian VXR-200 spectometer in $CDCl_3$ with tetramethylsilane (TMS) as an interal reference or in D_2O with sodium 3-(trimethylsilyl)-1-propanesulfonate-1,1,2,2-d_4 (DSS) as an internal reference. Gas chromatography was recorded on a Yanaco G-1800 and a G-2800 gas chromatographs. Optical rotations were measured with a Perkin-Elmer 241 polarimeter.

Materials. Organic reagents were purchased from Nacalai Tesque Co., Tokyo Kasei Co., and Aldrich Chemical Co. unless otherwise indicated. Solvents and commercially available starting materials were generally used without additional purification unless otherwise indicated. Pyridine and benzene were refluxed on calcium hydride for 1 day and distilled before the use. Satisfactory results were obtained from elemental analyses of all of the products.

Rate of Enolization. Into 0.5 ml of D_2O containing DSS in an NMR sample tube, 20 mg of ethyl 2-methyl-3-oxobutanoate (**1b**) was added and the solution was immediately subjected to ^1H NMR spectroscopy. The intensity of signal from the methine proton (δ_{DSS}: 3.8) was compared with that from the methylene proton in the ethyl group (δ_{DSS}: 4.3). Initially, the ratio of the intensities of both signals was 1/2, but it decreased to 1/4 after 1.5 h, revealing that the rate of enolization takes place much faster than the reduction.

Preparation of Alkyl 2-Alkyl-3-oxobutanoate. In general, into 200 ml of a benzene solution containing 0.1 mol of an alkyl 3-oxobutanoate and 0.1 mol of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) was added 0.1 mol of an appropriate alkyl iodide in 100 ml of benzene. The resulted mixture was stirred for 3 h at room temperature and filtered. The filtrate was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was distilled to give an alkyl 2-alkyl-3-oxobutanoate. For 1,1-dimethylpropyl esters, the residue was subjected to a column chromatography on silica gel using hexane-ether (100 : 3) as an eluent. 2-Methyl-3-oxobutanoates, except for **1a**, **1b**, **1h**, and **1i**, were prepared by transesterification with the corresponding ethyl ester (**1b**) according to the literature procedure.[14] Chemical yields (%), boiling points (°C/mmHg[15]), and ^1H NMR spectral data (δ_{TMS} in $CDCl_3$) of the esters are summalized below in this order.

1a: 59; 68 (16); 1.34 (3H, d, J=7.2 Hz), 2.23 (3H, s), 3.51 (1H, q, J=7.2 Hz), and 3.73 (3H, s). **1c**: 66; 110 (15); 0.92 (3H, t, J=7.2 Hz), 1.33 (3H, d, J=7.2 Hz), 1.31—1.73 (4H, m), 2.23 (3H, s), 3.49 (1H, q, J=7.2 Hz), and 4.13 (2H, t, J=6.8 Hz). **1d**: 81; 84 (1.5); 0.88 (3H, t, J=6.5 Hz), 1.18—1.72 (8H, m), 1.33 (3H, d, J=7.2 Hz), 2.23 (3H, s), 3.49 (1H, q, J=7.2 Hz), and 4.12 (2H, t, J=6.6 Hz). **1e**: 91; 78 (0.4); 0.87 (3H, t, J=6.5 Hz), 1.15—1.72 (12H, m), 1.33 (3H, d, J=7.0 Hz), 2.23 (3H, s), 3.49 (1H, q, J=7.2 Hz), and 4.12 (2H, t, 6.7 Hz). **1g**: 59; 96—98 (16); 0.92 (6H, d, J=6.8 Hz), 1.34 (3H, d, J=7.2 Hz), 1.94 (1H, m), 2.24 (3H, s), 3.52 (1H, q, J=7.2 Hz), and 3.91 (2H, dd, J=6.8 Hz, 1.3 Hz). **1h**: 60; 90 (21); 1.27 (3H, d, J=7.2 Hz), 1.44 (9H, s), 2.21 (3H, s), and 3.38 (1H, q, J=7.2 Hz). **1i**: 14; —; 0.86 (3H, t, J=7.5 Hz), 1.28 (3H, d, J=7.0 Hz), 1.42 (6H, s), 1.76 (2H, q, J=7.5 Hz), 2.22 (3H, s), and 3.40 (1H, q, J=7.0 Hz). **1j**: 45; 108 (20); 0.93 (9H, s), 1.35 (3H, d, J=7.2 Hz), 2.25 (3H, s), 3.53 (1H, q, J=7.2 Hz), and 3.82 (2H, d, J=2.2 Hz). **1k**: 76; 125 (19); 1.31 (3H, d, J=7.1 Hz], 1.49—1.97 (8H, m), 2.21 (3H, s), 3.44 (1H, q, J=7.1 Hz), and 5.17—5.25 (1H, m). **1l**: 68; 141 (21); 1.21—1.89 (10H, m), 1.32 (3H, d, J=7.2 Hz), 2.22 (3H, s), 3.46 (1H, q, J=7.2 Hz), and 4.73—4.87 (1H, m). **1m**: 72; 91 (0.5); 0.75—1.8 (11H, m), 1.33 (3H, d, J=7.2 Hz), 2.23 (3H, s), 3.50 (1H, q, J=7.2 Hz), and 3.93 (2H, d, J=6.2 Hz). **1n**: 71; 111 (1); 1.35 (3H, d, J=7.2 Hz), 2.18 (3H, s), 3.54 (1H, q, J=7.2 Hz), 5.17 (2H, s), and 7.34 (5H, s). **1p**: 55; 119 (21); 1.32 (3H, d, J=7.2 Hz), 2.22 (3H, s), 3.34 (3H, s), 3.52 (1H, q, J=7.2 Hz), 3.57 (2H, m), and 4.27 (2H, m). **1q**: 26; 130 (20); 1.19 (3H, t, J=7.0 Hz), 1.34 (3H, d, J=7.2 Hz), 2.24 (3H, s), 3.51 (2H, q, J=7.0 Hz), 3.62 (2H, t, J=4.8 Hz), 4.19 (1H, q, J=7.2 Hz), and 4.26—4.31 (2H, m). **1r**: 77; 153 (24); 0.90 (3H, t, J=7.2 Hz), 1.24—1.63 (4H, m), 1.34 (3H, d, J=7.2 Hz), 2.24 (3H, s), 3.44 (2H, t, J=6.5 Hz), 3.53 (1H, q, J=7.2 Hz), 3.61 (2H, t, J=4.8 Hz), and 4.25—4.31 (2H, m). **1s**: 55; 150 (20); 1.35 (3H, d, J=6.8 Hz), 2.13 (3H, s), 2.25 (3H, s), 2.72 (2H, t, J=6.8 Hz), 3.52 (1H, q, J=7.2 Hz), and 4.30 (2H, t, J=6.8 Hz). **1t**: 50; 128 (19); 1.37 (3H, d, J=7.1 Hz), 2.27 (3H, s), 3.56 (1H, q, J=7.1 Hz), 3.70 (2H, t, J=5.6 Hz), and 4.36—4.42 (2H, m). **2a**: 74; 78 (17); 0.90 (3H, t, J=7.5 Hz), 1.86 (2H, m), 2.20 (3H, s), 3.33 (1H, t, J=7.5 Hz), and 3.72 (3H, s). **2b**: 50; 85 (17); 0.90 (3H, t, J=7.4 Hz), 1.24 (3H, t, J=7.2 Hz), 1.85 (2H, m), 2.19 (3H, s), 3.30 (1H, t, J=7.4 Hz), and 4.16 (2H, q, J=7.2 Hz). **2c**: 67; 109 (17); 0.89 (6H, t, J=7.4 Hz), 1.22—1.43 (2H, m), 1.51—1.66 (2H, m), 1.75—1.90 (2H, m), 2.18 (3H, s), 3.29 (1H, t, J=7.4 Hz), and 4.09 (2H, t, J=6.6 Hz). **2d**: 40; 135 (17); 0.86 (3H, t, J=6.6 Hz), 0.91 (3H, t, J=7.5 Hz), 1.15—1.40 (6H, m), 1.53—1.69 (2H, m), 1.79 —1.93 (2H, m), 2.20 (3H, s), 3.31 (1H, t, J=7.4 Hz), and 4.11 (2H, t, J=6.7 Hz). **2e**: 79; 150 (17); 0.87 (3H, t, J=7.2 Hz), 0.92 (3H, t, J=7.4 Hz), 1.12—1.40 (10H, m), 1.53—1.71 (2H, m), 1.79—1.98 (2H, m), 2.21 (3H, s), 3.32 (1H, t, J=7.4 Hz), and 4.12 (2H, t, J=6.7 Hz). **2g**: 41; 104 (17); 0.90 (6H, d, J=6.8 Hz), 0.90 (3H, t, J=7.4 Hz), 1.86 (3H, m), 2.20 (3H, s), 3.33 (1H, t, J=7.4 Hz), and 3.89 (2H, d, J=6.6 Hz). **2h**: 38; 86 (17); 0.89 (3H, t, J=7.4 Hz), 1.44 (9H, s), 1.80 (2H, m), 2.22 (3H, s), and 3.20 (1H, t, J=7.2 Hz). **2i**: 13; —; 0.87 (3H, t, J=7.4 Hz), 0.91 (3H, t, J=7.5 Hz), 1.42 (6H, s), 1.76 (2H, q, J=7.5 Hz), 1.82 (2H, m), 2.20 (3H, s), and 3.23 (1H, t, J=7.4 Hz). **2j**: 93; 106 (17); 0.92 (9H, s), 0.92 (3H, t , J=7.4 Hz), 1.88 (2H, m), 2.22 (3H, s), 3.36 (1H, t, J=7.4 Hz), and 3.81 (2H, s). **2o**: 42; 100 (17); 0.91 (3H, t, J=7.4 Hz), 1.87 (2H, m), 2.20 (3H, s), 3.35 (1H, t, J=7.4 Hz), 4.58—4.63 (2H, m), 5.19—5.36 (2H, m), and 5.78—5.99 (1H, m). **2p**: 42; 124 (17); 0.89 (3H, t, J=7.5 Hz), 1.85 (2H, m), 2.19 (3H, s), 3.32 (3H, s), 3.35 (1H, t, J=7.5 Hz), 3.52—3.58 (2H, m), and 4.23—4.28 (2H, m). **2q**: 70; 88 (3); 0.92 (3H, t, J=7.5 Hz), 1.17 (3H, t, J=7.0 Hz), 1.87 (2H, m), 2.21 (3H, s), 3.36 (1H, t, J=7.5 Hz), 3.49 (2H, q, J=7.0 Hz), 3.58—3.64 (2H, m), and 4.25—4.80 (2H, m). **2r**: 74 108 (3); 0.90 (3H, t, J=7.3 Hz), 0.93 (3H, t, J=7.4 Hz), 1.24—1.62 (4H, m), 1.88 (2H, m), 2.23 (3H, s), 3.32—3.48 (3H, m), 3.59—3.64 (2H, m), and 4.26—4.31 (2H, m). **3a**: 66; 51 (1); 0.89 (3H, t, J=7.2 Hz), 1.28 (2H, m), 1.18—1.87 (2H, m), 2.19 (3H, s), 3.41 (1H, t, J=7.4 Hz), and 3.70 (3H, s). **3b**: 48; 90 (17); 0.91 (3H, t, J=7.2 Hz), 1.25 (3H, t, J=7.2 Hz), 1.21—1.39 (2H, m), 1.74—1.87 (2H, m), 2.20 (3H, s), 3.39 (1H, t, J=7.3 Hz), and 4.17 (2H, q, J=7.2 Ha). **3c**: 62; 67 (1); 0.90 (6H, t, J=7.2 Hz), 1.20—1.87 (8H, m), 2.19 (3H, s), 3.39 (1H, t, J=7.5 Hz), and 4.11 (2H, t, J=6.6 Hz). **3e**: 74; 105 (1); 0.85 (3H, t, J=6.6 Hz), 0.90 (3H, t, J=7.5 Hz), 1.13—1.40 (12H, m), 1.51—1.70 (2H, m), 1.72—1.88 (2H, m), 2.19 (3H, s), 3.49 (1H, t, J=7.4 Hz), and 4.09 (2H, t, J=6.6 Hz). **3f**: 54; 70 (1); 0.90 (3H, t, J=7.2 Hz), 1.22 (6H, d, J=6.2 Hz), 1.30 (2H, m), 1.72—1.86 (2H, m), 2.20 (3H, s), 3.35 (1H, t, J=7.5 Hz), and 5.04 (1H, m). **3h**: 60; 55 (1.5); 0.90 (3H, t, J=7.2 Hz), 1.19—1.38 (2H, m), 1.43 (9H, s), 1.69—1.82 (2H, m), 2.18 (3H, s), and 3.28 (1H, t, J=7.6 Hz). **3i**: 7; —; 0.87 (3H, t, J=7.5 Hz), 0.91 (3H, t, J=7.3 Hz), 1.18—1.48 (2H, m), 1.42 (6H, s), 1.71—1.83 (2H, m), 1.76 (2H, q, J=7.3 Hz), 2.20 (3H, s), and 3.32 (1H, t, J=7.5 Hz). **3j**: 62; 113 (17); 0.86—1.00 (3H, m), 0.92 (9H, s), 1.31 (2H, m), 1.77—1.89 (2H, m), 2.22 (3H, s), 3.44 (1H, t, J=7.4 Hz), and 3.80 (2H, s). **3n**: 59 135 (1); 0.90 (3H, t, J=7.2 Hz), 1.29 (2H, m), 1.78—1.90 (2H, m), 2.16 (3H, s), 3.46 (1H, t, J=6.4 Hz), 5.16 (2H, s), and 7.34 (5H, s). **3o**: 51; 61 (1); 0.92 (3H, t, J=7.1 Hz), 1.31 (2H, m), 1.84 (2H, m), 2.22 (3H, s), 3.44 (1H, t, J=7.2 Hz), 4.59—4.64 (2H, m), 5.21—5.37 (2H, m), and 5.80—6.01 (1H, m). **3p**: 62; 84 (1); 0.88 (3H, t, J=7.2 Hz), 1.28 (2H, m), 1.89 (2H, m), 2.19 (3H, s), 3.32 (3H, s), 3.43 (1H, t, J=7.5 Hz), 3.53—3.57 (2H, m), and 4.22—4.27 (2H, m). **3q**: 66; 90 (2); 0.91 (3H, t, J=7.4 Hz), 1.18 (3H, t, J=7.0 Hz), 1.14—1.41 (2H, m), 1.73—1.89 (2H, m), 2.22 (3H, s), 3.44 (1H, t, J=7.4 Hz), 3.49 (2H, q, J=7.0 Hz), 3.57—3.66 (2H, m), and 4.25—4.30 (2H, m). **3r**: 60; 133

(5); 0.87 (3H, t, J=7.1 Hz), 0.89 (3H, t, J=7.2 Hz), 1.20—1.62 (6H, m), 1.70—1.90 (2H, m), 2.20 (3H, s), 3.37—3.45 (3H, m), 3.56—3.61 (2H, m), and 4.25 (2H, m). **4a**: 37; 111 (19); 1.99 (1H, t, J=2.7 Hz), 2.30 (3H, s), 2.72 (2H, m), 3.71 (1H, t, J=7.5 Hz), and 3.76 (3H, s). **4b**: 19; 116 (20); 1.28 (3H, t, J=7.1 Hz), 1.99 (1H, t, J=2.6 Hz), 2.30 (3H, s), 2.71 (2H, dd, J=2.6 Hz, 7.2 Hz), 3.68 (1H, t, J=7.4 Hz), and 4.22 (2H, q, J=7.1 Hz). **4c**: 21; 136 (17); 0.92 (3H, t, J=7.2 Hz), 1.29—1.47 (2H, m), 1.56—1.70 (2H, m), 1.98 (1H, t, J=2.7 Hz), 2.30 (3H, s), 2.71 (2H, m), 3.69 (1H, t, J=7.5 Hz), and 4.16 (2H, t, J=6.6 Hz). **4f**: 25; 112 (17); 1.25 (3H, d, J=6.4 Hz), 1.26 (3H, d, J=6.4 Hz), 1.98 (1H, t, J=2.6 Hz), 2.28 (3H, s), 2.69 (2H, m), 3.64 (1H, t, J=7.5 Hz), and 5.07 (1H, m). **4g**: 33; 124 (15); 0.93 (6H, d, J=6.8 Hz), 1.95 (1H, m), 1.98 (1H, t, 2.6 Hz), 2.31 (3H, s), 2.72 (2H, m), 3.71 (1H, t, J=7.5 Hz), and 3.94 (2H, d, J=6.6 Hz). **4h**: 20; 102 (17); 1.46 (9H, s), 1.97 (1H, t, J=2.7 Hz), 2.28 (3H, s), 2.65 (2H, m), and 3.58 (1H, t, J=7.5 Hz). **4i**: 19;—; 0.87 (3H, t, J=7.4 Hz), 1.43 (6H, s), 1.77 (2H, q, J=7.4 Hz), 1.97 (1H, t, J=2.7 Hz), 2.28 (3H, s), 2.65 (2H, m), and 3.60 (1H, t, J=7.5 Hz). **4j**: 25; 131 (18); 0.93 (9H, s), 1.98 (1H, t, J=2.6 Hz), 2.31 (3H, s), 2.71 (2H, m), 3.73 (1H, t, J=7.5 Hz), and 3.84 (2H, s). **4o**: 30; 130 (18); 1.99 (1H, t, J=2.6 Hz), 2.31 (3H, s), 2.72 (2H, m), 3.73 (1H, t, J=7.5 Hz), 4.65 (2H, m), 5.22—5.38 (2H, m), and 5.80—5.99 (1H, m). **4p**: 35; 144 (21); 1.98 (1H, t, J=2.6 Hz), 2.30 (3H, s), 2.71 (2H, m), 3.35 (3H, s), 3.58 (2H, t, J=4.7 Hz), 3.73 (1H, t, J=7.4 Hz), and 4.29 (2H, t, J=4.7 Hz). **4r**: 21; 105 (0.8) 0.90 (3H, t, J=7.3 Hz), 1.35—1.62 (4H, m), 1.99 (1H, t, J=2.7 Hz), 2.26 (3H, s), 2.71 (2H, m), 3.38—3.48 (3H, m), 3.58—3.64 (2H, m), and 4.23—4.32 (2H, m). **5a**: 3; 95 (20); 2.21 (3H, s), 2.58 (2H, t, J=7.2 Hz), 3.52 (1H, t, J=7.2 Hz), 3.71 (3H, s), 4.93—5.18 (2H, m), and 5.51—5.93 (1H, m). **5b**: 41; 100 (20); 1.26 (3H, t, J=6.7 Hz), 2.21 (3H, s), 2.58 (2H, t, J=6.7 Hz), 3.51 (1H, t, J=6.7 Hz), 4.18 (2H, q, J=6.7 Hz), 4.95—5.19 (2H, m), and 5.53—5.97 (1H, m). **5c**: 30; 123 (15); 0.94 (3H, t, J=7.2 Hz), 1.28—1.49 (2H, m), 1.56—1.69 (2H, m), 2.24 (3H, s), 2.60 (2H, t, J=7.1 Hz), 3.53 (1H, t, J=7.5 Hz), 4.15 (2H, t, J=6.6 Hz), 5.02—5.16 (2H, m), and 5.65—5.86 (1H, m). **5d**: 21; 143 (15); 0.89 (3H, m), 1.29 (6H, m), 1.56—1.68 (3H, m), 2.24 (3H, s), 2.60 (2H, m), 3.53 (1H, t, J=7.5 Hz), 4.13 (2H, t, J=6.7 Hz), 5.01—5.15 (2H, m), and 5.65—5.85 (1H, m). **5e**: 45; 100 (0.7); 0.86 (3H, t, J=6.8 Hz), 1.14—1.40 (10H, m), 1.57—1.68 (2H, m), 2.21 (3H, s), 2.57 (2H, m), 3.50 (1H, t, J=7.5 Hz), 4.11 (2H, t, J=6.7 Hz), 4.91—5.13 (2H, m), and 5.62—5.83 (1H, m). **5f**: 81; 106 (20); 1.24 (6H, d, J=6.2 Hz), 2.22 (3H, s), 2.57 (2H, m), 3.47 (1H, t, J=7.4 Hz), 4.99—5.14 (3H, m), and 5.62—5.84 (1H, m). **5g**: 28; 119 (16); 0.93 (6H, d, J=6.8 Hz), 1.75—2.08 (1H, m), 2.25 (3H, s), 2.61 (2H, t, J=6.3 Hz), 3.55 (1H, t, J=7.3 Hz), 3.92 (2H, d, J=6.9 Hz, 4.99—5.18 (2H, m), and 5.56—5.97 (1H, m). **5h**: 11; 105 (16); 1.44 (9H, s), 2.21 (3H, s), 2.53 (2H, t, J=7.4 Hz), 3.40 (1H, t, J=7.4 Hz), 4.93—5.17 (2H, m), and 5.52—5.93 (1H, m). **5i**: —; —; 0.86 (3H, t, J=7.5 Hz), 1.42 (6H, s), 1.75 (2H, q, J=7.5 Hz), 2.22 (3H, s), 2.54 (2H, m), 3.42 (1H, t, J=7.5 Hz), 4.98—5.14 (2H, m), and 5.62—5.82 (1H, m). **5j**: 81; 70 (3); 0.94 (9H, s), 2.25 (3H, s), 2.61 (2H, m), 3.56 (1H, t, J=7.5 Hz), 3.82 (2H, s), 4.99—5.15 (2H, m), and 5.65—5.84 (1H, m). **5k**: 83; 145 (20); 1.51—1.95 (8H, m), 2.19 (3H, s), 2.54 (2H, m), 3.45 (1H, t, J=7.4 Hz), 4.97—5.22 (3H, m), and 5.61—5.82 (1H, m). **5l**: 62; 152 (21); 1.15—1.92 (10H, m), 2.21 (3H, s), 2.57 (2H, m), 3.47 (1H, t, J=7.4 Hz), 4.72—4.88 (1H, m), 4.98—5.13 (2H, m), and 5.62—5.82 (1H, m). **5n**: 75; 142 (2); 2.18 (3H, s), 2.60 (2H, m), 3.56 (1H, t, J=7.4 Hz), 4.98—5.12 (2H, m), 5.16 (2H, s), 5.61—5.82 (1H, m), and 7.34 (5H, s). **5o**: 89; 113 (20); 2.22 (3H, s), 2.58 (2H, m), 3.54 (1H, t, J=7.4 Hz), 4.58—4.62 (2H, m), 5.00—5.36 (4H, m), and 5.61—5.99 (2H, m). **5p**: 78; 140 (20); 2.23 (3H, s), 2.58 (2H, m), 3.35 (3H, s), 3.44—3.60 (3H, m), 4.25—4.30 (2H, m), 5.00—5.13 (2H, m), and 5.62—5.82 (1H, m). **5q**: 81; 96 (3); 1.18 (3H, t, J=7.0 Hz), 2.23 (3H, s), 2.58 (2H, m), 3.44—3.65 (5H, m), 4.24—4.31 (2H, m), 4.99—5.15 (2H, m), and 5.62—5.83 (1H, m). **5r**: 74; 132 (2) 0.89 (3H, t, J=7.1 Hz), 1.25—1.75 (4H, m), 2.23 (3H, s), 2.58 (2H, m), 3.38—3.63 (5H, m), 4.24—4.30 (2H, m), 4.99—5.13 (2H, m), and 5.65—5.84 (1H, m). **5s**: 62; 117 (1); 2.11 (3H, s), 2.27 (3H, s), 2.57 (2H, m), 2.67 (2H, m), 3.52 (1H, t, J=7.4 Hz), 4.27 (2H, m), 4.98—5.13 (2H, m), and 5.61—5.82 (1H, m).

Preparation of Racemic Esters of 3-Hydroxy-2-alkylbutanoate. Sodium borohydride (9.5 mg, 0.25 mmol) was added to a stirred and cooled solution composed of 1 mmol of alkyl 2-alkyl-3-oxobutanoate and 10 ml of tetrahydrofuran (THF) in an ice bath. The resulted solution was stirred at room temperature for 1 h and the THF was removed under reduced pressure, then the residual solution was acidified with dilute aqueous hydrochloric acid. The organic portion was extracted with ether (30 ml), and the ether layer was washed with water, aqueous sodium hydrogencarbonate, and water (10 ml each), respectively. The ethereal solution was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. Esters of 3-hydroxy-2-alkylbutanoate were obtained by distillation of the residue with a Kugelrohr apparatus. Chemical yields (%), boiling points (°C/mmHg[15]), and ^{1}H NMR spectral data (δ from TMS in $CDCl_3$) of the esters are summarized below in this order.

6a: 46; 75 (17); 1.17 (syn: s), 1.21 (anti: a) (3H, d, J=6.4 Hz), 1.22 (3H, d, J=6.4 Hz), 2.40—2.67 (2H, m), 3.70 (3H, s), and 4.01—4.28 (1H, m). **6b**: 42; 75 (17); 1.17 (s), 1.21 (a) (3H, d, J=6.3 Hz), 1.17 (3H, d, J=7.0 Hz), 1.26 (3H, t, J=7.2 Hz), 2.35—2.55 (1H, m), 2.59—2.72 (1H, b), 3.79—4.12 (1H, m), and 4.16 (2H, q, J=7.2 Hz). **6c**: 63; (17); 0.92 (3H, t, J=7.2 Hz), 1.16—1.22 (3H, m), 1.17 (3H, d, J=7.2 Hz), 1.28—1.46 (2H, m), 1.55—1.69 (2H, m), 2.36—2.53 (1H, m), 2.59—2.72 (1H, b), 3.79—4.22 (1H, m), and 4.10 (2H, t, J=6.6 Hz). **6d**: 92; 80 (2); 0.88 (3H, t, J=6.6 Hz), 1.16 (s), 1.20 (a) (3H, d, J=6.4 Hz), 1.17 (3H, d, J=6.8 Hz), 1.20—1.40 (6H, m), 1.56—1.68 (2H, m), 2.35—2.56 (1H, m), 2.63 (1H, b), 3.79—4.22 (1H, m), and 4.09 (2H, t, J=6.8 Hz). **6e**: 80; 100 (1.5); 0.87 (3H, t, J=6.5 Hz), 1.15—1.22 (6H, m), 1.15—1.40 (10H, m), 1.57—1.70 (2H, m), 2.37—2.56 (1H, m), 2.55—2.75 (1H, b), 3.81—4.22 (1H, m), and 4.09 (2H, t, J=6.6 Ha). **6g**: 66; 80 (18); 0.96 (6H, d, J=6.8 Hz), 1.17 (s), 1.21 (a) (3H, d, J=6.6 Hz), 1.19 (3H, d, J=7.2 Hz), 1.80 (1H, b), 1.84—2.04 (1H, m), 2.38—2.58 (1H, m), 3.89 (2H, d, J=6.6 Hz), and 3.77—4.21 (1H, m). **6h**: 84; 100 (16); 1.11—1.21 (6H, m), 1.45 (9H, s), 2.25—2.45 (2H, m), 3.75—4.06 (1H, m). **6i**: 68; 100 (20); 0.88 (3H, t, J=7.5 Hz), 1.12—1.21 (6H, m), 1.42 (6H, s), 1.77 (2H, q, J=7.5 Hz), 2.25—2.47 (2H, m), and 3.96—4.21 (1H, m). **6j**: 37; 130 (18); 0.94 (9H. s), 1.18 (s), 1.22 (a) (3H, d, J=6.4 Hz), 1.20 (3H, d, J=7.2 Hz), 2.40—2.60 (1H, m), 2.56—2.77 (1H, b), 3.81 (2H, s), and 3.83—4.12 (1H, m). **6k**: 75; 145 (19); 1.15 (3H, d, J=7.2 Hz), 1.16 (s), 1.20 (a) (3H, d, J=6.1 Hz), 1.50—1.98 (8H, m), 2.26—2.51 (1H, m), 2.55—2.85 (1H, b), 3.78—4.10 (1H, m), and 5.14—5.24 (1H, m). **6l**: 87; 160 (21); 1.15—1.22 (6H, m), 1.25—1.89 (11H, m), 2.34—2.53 (1H, m), 3.79—4.10 (1H, m), and 4.72—4.85 (1H, m). **6m**: 88; 175 (21); 1.17 (s), 1.21 (a) (3H, d, J=6.3 Hz), 1.18 (3H, d, J=7.2 Hz), 0.88—1.79 (11H,

m), 2.37—2.57 (1H, m), 2.44—2.85 (1H, b), 3.91 (s), 3.92 (a) (2H, d, J=6.1 Hz), and 3.81—4.12 (1H, m). **6n**: 73; 180 (19); 1.14—1.22 (6H, m), 2.43—2.64 (2H, m), 3.86—4.16 (1H, m), 5.14 (2H, s), and 7.35 (5H, s). **6p**: 44; 130 (22); 1.16 (s), 1.20 (a) (3H, d, J=6.4 Hz), 1.17 (3H, d, J=7.0 Hz), 2.17 (1H, b), 2.41—2.62 (1H, m), 3.37 (3H, s), 3.58 (2H, t, J=4.5Hz), 3.80—4.14 (1H, m), and 4.14—4.38 (2H, m). **6q**: 64; 120 (20); 1.15—1.23 (9H, m), 2.00 (1H, b), 2.47—2.64 (1H, m), 3.52 (2H, q, J=7.0 Hz), 3.63 (2H, t, J=4.8 Hz), 3.79—4.15 (1H, m), and 4.15—4.40 (2H, m). **6r**: 91; 170 (20); 0.90 (3H, t, J=7.1 Hz), 1.16 (s), 1.21 (a) (3H, d, J=6.4 Hz), 1.17 (3H, d, J=7.4 Hz), 1.29—1.62 (5H, m), 2.40—2.62 (1H, m), 3.45 (2H, t, J=6.5 Hz), 3.61 (2H, t, J=4.7 Hz), 3.79—4.13 (1H, m), and 4.14—4.38 (2H, m). **6s**: 79; 165 (18); 1.16—1.23 (6H, m), 2.14 (3H, s), 2.42—2.66 (2H, m), 2.74 (2H, t, J=6.6 Hz), 3.83—4.18 (1H, m), and 4.19—4.40 (2H, m). **6t**: 58; 125 (18); 1.17—1.24 (6H, m), 2.37—2.63 (2H, m), 3.70 (2H, t, J=5.5 Hz), and 4.34—4.39 (2H, m). **7a**: 35; 90 (17); 0.88 (a), 0.89 (s) (3H, t, J=7.5 Hz), 1.15 (s), 1.18 (a) (3H, d, J=6.4 Hz), 1.55—1.73 (2H, m), 2.24—2.38 (1H, m), 2.55—2.67 (1H, b), 3.67 (s), 3.68 (a) (3H, s), and 3.72—4.00 (1H, m). **7b**: 48; 70 (17); 0.90 (a), 0.91 (s) (3H, t, J=7.4 Hz), 1.17 (s), 1.20 (a) (3H, d, J=6.3 Hz), 1.26 (3H, t, J=7.2 Hz), 1.59—1.75 (2H, m), 2.22—2.63 (2H, m), 3.74—4.00 (1H, m), and 4.16 (s), 4.17 (a) (2H, q, J=7.2 Hz). **7c**: 53; 90 (17); 0.92 (6H, t, J=7.4 Hz), 1.17 (s), 1.21(a) (3H, d, J=6.4 Hz), 1.28—1.46 (2H, m), 1.54—1.76 (4H, m), 2.23—2.59 (2H, m), 3.74—4.01 (1H, m), and 4.10 (s), 4.12 (a) (2H, t, J=6.4 Hz). **7d**: 52; 110 (17); 0.87 (3H, t, J=6.6 Hz), 0.91 (a), 0.92 (s) (3H, t, J=7.4 Hz), 1.17 (s), 1.20 (a) (3H, d, J=6.2 Hz), 1.14—1.37 (6H, m), 1.56—1.73 (4H, m), 2.24—2.61 (2H, m), 3.75—4.26 (1H, m), and 4.09 (s), 4.11 (a) (2H, t, J=6.6 Hz). **7e**: 51; 150 (17); 0.86 (3H, t, J=6.8 Hz), 0.90 (a), 0.92 (s) (3H, t, J=7.4 Hz), 1.16 (s), 1.20 (a) (3H, d, J= 6.2 Hz), 1.15—1.41 (10H, m), 1.52—1.78 (4H, m), 2.20—2.63 (2H, m), 3.75—4.24 (1H, m), and 4.08 (s), 4.10 (a) (2H, t, J=6.6 Hz). **7g**: 57; 95 (17); 0.93 (6H, d, J=6.8 Hz), 0.88—0.96 (3H, t), 1.18 (s), 1.21 (a) (3H, d, J=6.1 Hz), 1.59—1.71 (2H, m), 1.82—2.03 (1H, m), 2.26—2.60 (2H, m), 3.88 (s), 3.90 (a) (2H, d, J=6.6 Hz), and 3.77—4.25 (1H, m). **7h**: 38; 70 (17); 0.92 (a), (s) (3H, t, J=7.4 Hz), 1.16 (s), 1.20 (a) (3H, d, J=6.4 Hz), 1.44 (9H, s), 1.54—1.73 (2H, m), 2.12—2.54 (2H, m), and 3.77—4.72 (1H, m). **7i**: 99; 110 (20); 0.89 (3H, t, J=7.5 Hz), 0.93 (3H, t, J=7.5 Hz), 1.18 (s), 1.21 (a) (3H, d, J=6.2 Hz), 1.53—1.72 (2H, m), 1.77 (2H, q, J=7.5 Hz), 2.13—2.26 (2H, m), and 3.79—4.00 (1H, m). **7j**: 62; 100 (17); 0.92 (s), 0.93 (a) (9H, s), 0.88—0.96 (3H, t), 1.17 (s), 1.20 (a) (3H, d, J=6.2 Hz), 1.60—1.73 (2H, m), 2.21—2.63 (2H, m), and 3.78 (s), 3.79 (a) (2H, s). **7o**: 31; 85 (17); 0.92 (a), 0.93 (s) (3H, t, J=7.5 Hz), 1.18 (s), 1.21 (a) (3H, d, J=6.4 Hz), 1.60—1.77 (2H, m), 2.28—2.72 (2H, m), 3.76—4.02 (1H, m), 4.59—4.62 (2H, m), 5.21—5.37 (2H, m), and 5.81—6.01 (1H, m). **7p**: 48; 90 (17); 0.92 (a), 0.93 (s) (3H, t, J=7.4 Hz), 1.17 (s), 1.21 (a) (3H, d, J=6.6 Hz), 1.58—1.74 (2H, m), 2.32—2.76 (2H, m), 3.36 (3H, s), 3.58 (2H, t, J=4.8 Hz), 3.71—4.03 (1H, m), and 4.18—4.40 (2H, m). **7q**: 58; 125 (21); 0.93 (a), 0.94 (s) (3H, t, J=7.4 Hz), 1.19 (3H, t, J=7.0 Hz), 1.18 (s), 1.22 (a) (3H, d, J= 6.2 Hz), 1.57—1.80 (2H, m), 2.27—2.77 (2H, m), 3.52 (2H, q, J=7.0 Hz), 3.63 (2H, t, J=5.2 Hz), 3.75—4.02 (1H, m), and 4.18—4.41 (2H, m). **7r**: 75; 120 (17); 0.89 (3H, t, J=7.1 Hz), 0.92 (a), 0.93 (s) (3H, t, J=7.4 Hz), 1.17 (s), 1.21 (a) (3H, d, J=6.4 Hz), 1.24—1.75 (6H, m), 2.27—2.77 (2H, m), 3.44 (2H, t, J=6.4 Hz), 3.61 (2H, t, J=4.8 Hz), 3.64—4.02 (1H, m), and 4.17—4.40 (2H, m). **8a**: 45; 100 (17); 0.90 (3H, t, J=7.2 Hz), 1.17 (s), 1.20 (a) (3H, d, J=6.4 Hz), 1.15—1.40 (2H, m), 1.45—1.75 (2H, m), 2.32—2.54 (2H, m), 3.69 (3H, s), and 3.78—4.06 (1H, m). **8b**: 48; 90 (18); 0.91 (3H, t, J=7.1 Hz), 1.18 (s), 1.21 (a) (3H, d, J=6.4 Hz), 1.26 (3H, t, J=7.2 Hz), 1.15—1.40 (2H, m), 1.43—1.77 (2H, m), 2.33—2.46 (2H, m), 3.78—4.06 (1H, m), and 4.16 (2H, q, J=7.2 Hz). **8c**: 60; 130 (21); 0.90 (3H, t, J=7.0 Hz), 0.92 (3H, t, J=7.2 Hz), 1.17 (s), 1.20 (a) (3H, d, J=6.2 Hz), 1.15—1.76 (8H, m), 2.31—2.62 (2H, m), 3.83—4.02 (1H, m), and 4.06—4.14 (2H, m). **8e**: 48; 110 (17); 0.86 (3H, t, J=7.0 Hz), 0.90 (3H, t, J=7.2 Hz), 1.15—1.34 (15H, m), 1.54—1.67 (4H, m), 2.25—2.60 (2H, m), and 3.80—4.13 (3H, m). **8f**: 66; 90 (17); 0.89 (3H, t, J=7.2 Hz), 1.22 (6H, d, J=6.4 Hz), 1.09—1.76 (7H, m), 2.26—2.42 (1H, m), 2.55—2.69 (1H, b), 3.78—4.00 (1H, m), and 4.93—5.14 (1H, m). **8h**: 60; 100 (17); 0.89 (3H, t, J=7.2 Hz), 1.15 (s), 1.18 (a) (3H, d, J=6.5 Hz), 1.44 (9H, s), 1.15—1.76 (4H, m), 2.19—2.36 (1H, m), 2.60—2.77 (1H, b), 3.73—3.96 (1H, m). **8i**: 80; 120 (20); 0.89 (3H, t, J=7.5 Hz), 0.92 (3H, t, J=7.4 Hz), 1.18 (s), 1.21 (a) (3H, d, J=6.6 Hz), 1.24—1.69 (4H, m), 1.43 (6 H, s), 1.77 (2H, q, J=7.4 Hz), 2.22—2.35 (1H, m), 2.45—2.74 (1H, b), and 3.76—4.00 (1H, m). **8j**: 50; 110 (21); 0.90 (3H, t, J=7.8 Hz), 0.93 (9H, s), 1.17 (s), 1.20 (a) (3H, d, J=6.0 Hz), 1.15—1.74 (4H, m), 2.35—2.49 (1H, m), 2.49—2.64 (1H, b), 3.77 (a), 3.79 (s) (2H, s), and 3.65—4.00 (1H, m). **8n**: 45; 140 (17); 0.85—0.94 (3H, m), 1.14—1.34 (5H, m), 1.45—1.90 (2H, m), 2.39—2.52 (2H, m), 3.85—4.28 (1H, m), 5.14 (a), 5.15 (s) (2H, s), and 7.35 (5H, s). **8o**: 55; 100 (17); 0.90 (3H, t, J=7.2 Hz), 1.18 (s), 1.21 (a) (3H, d, J=6.2 Hz), 1.20—1.81 (4H, m), 2.36—2.51 (2H, m), 3.82—4.02 (1H, m), 4.58—4.62 (2H, m), 5.20—5.37 (2H, m), and 5.81—6.03 (1H, m). **8p**: 40; 100 (17); 0.89 (3H, t, J=7.3 Hz), 1.16 (s), 1.20 (a) (3H, d, J=6.2 Hz), 1.12—1.79 (4H, m), 2.35—2.52 (1H, m), 2.57— 2.76 (1H, b), 3.35 (3H, s), 3.55—3.60 (2H, m), 3.80—3.98 (1H, m), and 4.15—4.39 (2H, m). **8q**: 50; 105 (17); 0.89 (3H, t, J=7.2 Hz), 1.76 (3H, t, J=7.0 Hz), 1.20 (s), 1.22 (a) (3H, d, J=6.2 Hz), 1.15—1.77 (4H, m), 2.33—2.52 (1H, m), 2.62—2.71 (1H, b), 3.46 (2H, q, J=7.0 Hz), 3.58—3.63 (2H, m), 3.81—4.00 (1H, m), and 4.16—4.40 (2 H, m). **8r**: 58; 140 (17); 0.88 (6H, t, J=7.2 Hz), 1.15 (s), 1.19 (a) (3H, d, J=6.4 Hz), 1.22—1.77 (8H, m), 2.32—2.51 (1H, m), 2.60—2.80 (1H, b), 3.43 (2H, t, J=6.5 Hz), 3.57—3.62 (2H, m), 3.77—4.00 (1H, m), and 4.14—4.38 (2H, m). **9a**: 83; 115 (18); 1.20—1.30 (3H, m), 1.97—2.02 (1H, m), 2.34—2.97 (4H, m), 3.74 (s and a) (3H, s), and 3.81—4.17 (1H, m). **9b**: 66; 120 (19); 1.21—1.32 (6H, m), 1.18—2.01 (1H, m), 2.16—2.88 (4H, m), 3.78—4.27 (1H, m), and 4.20 (s), 4.21 (a) (2H, q, J=7.4 Hz). **9c**: 87; 130 (15); 0.92 (3H, t, J=7.2 Hz), 1.22 (s), 1.25 (a) (3H, d, J=6.2 Hz), 1.25—1.70 (4H, m), 1.98—2.04 (1H, m), 2.27—2.98 (4H, m), and 3.78—4.23 (3H, m). **9f**: 73; 115 (18); 1.20—1.30 (3H, m), 1.25 (6H, d, J=6.2 Hz), 1.97—2.03 (1H, m), 2.34—2.94 (4H, m), 3.76—4.21 (1H, m), and 5.02—5.20 (1H, m). **9g**: 77; 120 (15); 0.94 (6H, d, J=6.6 Hz), 1.22 (s), 1.26 (a) (3H, d, 6.4 Hz), 1.82—2.03 (2H, m), 2.27—2.96 (4H, m) 3.81—4.11 (3H, m). **9h**: 71; 115 (28); 1.21 (s), 1.25 (a) (3H, d, J=6.6 Hz), 1.47 (9H, s), 1.98—2.02 (1H, m), 2.34—2.83 (4H, m), and 3.81—4.16 (1H, m). **9i**: 79; 120 (15); 0.90 (3H, t, J=7.4 Hz), 1.22 (s), 1.25 (a) (3H, d, J=6.1 Hz), 1.45 (6H, s), 1.60 (1H, b), 1.79 (2H, q, J=7.4 Hz), 1.98—2.01 (1H, m), 2.44—2.58 (3H, m), and 3.96—4.14 (1H, m). **9j**: 69; 135 (18); 0.95 (9H, s), 1.23 (s), 1.26 (a) (3 H, d, J=5.6 Hz), 1.98—2.01 (1H, m), 2.18—2.94 (4H, m), and 3.76—4.18 (3H, m). **9o**: 76; 120 (20); 1.23 (s), 1.26 (a) (3H, d, J=6.2 Hz), 1.65 (1H, b), 2.00 (1H, m), 2.49—2.74 (3H, m), 4.06—4.22 (1H, m), 4.62—4.66 (2H, m), 5.21—5.40 (2H, m), and 5.82—6.01 (1H, m). **9p**: 54; 130 (20); 1.22 (s), 1.26 (a) (3H, d, J=6.4 Hz), 1.73 (1H, b), 1.98—2.04

(1H, m), 2.25—2.78 (3H, m), 3.37 (3H, s), 3.60 (2H, m), 3.77—4.22 (1H, m), and 4.22—4.42 (2H, m). **9r**: 72; 130 (17); 0.90 (3H, t, J=7.2 Hz), 1.21 (3H, d, J=6.6 Hz), 1.28—1.61 (4H, m), 1.97—2.01 (1H, m), 2.38—2.80 (3H, m), 3.05 (1H, b), 3.45 (2H, t, J=6.5 Hz), 3.59—3.65 (2H, m), and 4.03—4.42 (3H, m). **10a**: 33; 95 (21); 1.21 (s), 1.24 (a) (3H, d, J=3.4 Hz), 2.32—2.58 (4H, m), 3.71 (3H, s), 3.88—4.08 (1H, m), 5.01—5.14 (2H, m), and 5.70—5.85 (1H, m). **10b**: 53; 100 (20); 1.21—1.29 (6H, m), 2.37—2.67 (4H, m), 3.90—4.04 (1H, m), 4.18 (2H, q, J=6.7 Hz), 5.00—5.14 (2H, m), and 5.71—5.85 (1H, m). **10c**: 64; 125 (15); 0.94 (3H, t, J=7.2 Hz), 1.21 (s), 1.24 (a) (3H, d, J=6.3 Hz), 1.30—1.43 (2H, m), 1.54—1.69 (2H, m), 2.03—2.34 (1H, m), 2.36—2.68 (3H, m), 3.63—4.16 (3H, m), 4.99—5.14 (2H, m), and 5.65—5.90 (1H, m). **10d**: 44; 130 (21); 0.89 (3H, m), 1.21 (s), 1.24 (a) (3H, d, J=6.2 Hz) 1.28—1.42 (6H, m), 1.51—1.72 (2H, m), 2.37—2.67 (4H, m), 3.87—4.18 (3H, m), 4.99—5.16 (2H, m), and 5.65—5.94 (1H, m). **10e**: 86; 145 (21); 0.87 (3H, m), 1.20 (s), 1.23 (a) (3H, d, J=6.2 Hz), 1.24—1.38 (10H, m), 1.53—1.70 (2H, m), 2.28—2.62 (4H, m), 3.89—4.17 (3H, m), 4.99—5.16 (2H, m), and 5.66—5.90 (1H, m). **10f**: 50; 111 (21); 1.21 (6H, d, J=6.4 Hz), 1.21 (s), 1.23 (a) (3H, d, J=6.4 Hz), 2.34—2.59 (3H, m), 2.70 (1H, b), 3.82—4.00 (1H, m), 4.96—5.13 (3H, m), and 5.62—5.88 (1H, m). **10g**: 34; 140 (17); 0.94 (s), 0.95 (a) (6H, d, J=6.8 Hz), 1.22 (s), 1.25 (a) (3H, d, J=6.3 Hz), 1.89—2.00 (1H, m), 2.37—2.65 (4H, m), 3.85—4.06 (3H, m), 5.01—5.13 (2H, m), and 5.71—5.85 (1H, m). **10h**: 40; 100 (21); 1.21(s), 1.24 (a) (3H, d, J=6.8 Hz), 1.46 (s), 1.47 (a) (9H, s), 2.25—2.47 (4H, m), 3.85—4.01 (1H, m), 5.01—5.13 (2H, m), and 5.72—5.86 (1H, m). **10i**: 90; 120 (20); 0.88 (3H, t, J=7.4 Hz), 1.20 (s), 1.23 (a) (3H, d, J=6.0 Hz), 1.42 (6H, s), 1.75 (2H, q, J=7.4 Hz), 2.29—2.46 (3H, m), 2.42—2.83 (1H, b), 3.78—4.04 (1H, m), 4.97—5.14 (2H, m), and 5.65—5.89 (1H, m). **10j**: 30; 105 (17); 0.94 (9H, s), 1.21 (s), 1.23 (a) (3H, d, J=5.9 Hz), 1.65 (1H, b), 2.25—2.61 (3H, m), 3.78 (s), 3.79 (a) (2H, s), 3.87—4.08 (1H, m), 4.99—5.13 (2H, m), and 5.65—5.89 (1H, m). **10k**: 52; 160 (21); 1.19 (s), 1.22 (a) (3H, d, J=6.4 Hz), 1.52—1.92 (9H, m), 2.35—2.47 (3H, m), 3.86—4.03 (1H, m), 4.98—5.23 (3H, m), and 5.67—5.88 (1H, m). **10l**: 56; 180 (21); 1.19 (s), 1.22 (a), (3H, d, J=6.4 Hz), 1.20—1.86 (11H, m), 2.35—2.61 (3H, m), 3.82—4.06 (1H, m), 4.73—4.88 (1H, m), 4.98—5.12 (2H, m), and 5.64—5.89 (1H, m). **10n**: 57; 145 (2); 1.12 (s), 1.18 (a) (3H, d, J=6.2 Hz), 1.58—1.71 (1H, b), 2.32—2.63 (3H, m), 3.87—4.09 (1H, m), 4.96—5.11 (2H, m), 5.13 (s), 5.15 (a) (2H, s), 5.62—5.88 (1H, m), and 7.35 (5H, s). **10o**: 56; 125 (17); 1.21 (s), 1.22 (a) (3H, d, J=5.8 Hz), 2.25—2.62 (4H, m), 3.86—4.09 (1H, m), 4.57—4.62 (2H, m), 4.99—5.36 (4H, m), and 5.64—6.00 (2H, m). **10p**: 17; 150 (21); 1.20 (s), 1.23 (a) (3H, d, J=6.4 Hz), 2.30—2.74 (4H, m), 3.37 (3H, s), 3.55—3.61 (2H, m), 3.87—4.08 (1H, m), 4.16—4.38 (2H, m), 4.98—5.13 (2H, m), and 5.49—5.89 (1H, m). **10q**: 60; 135 (17); 1.19 (3H, t, J=7.0 Hz), 1.18(s), 1.23 (a) (3H, d, J=6.4 Hz), 2.35—2.63 (4H, m), 3.47 (2H, q, J=7.0 Hz), 3.57—3.65 (2H, m), 3.86—4.04 (1H, m), 4.13—4.38 (2H, m), 4.96—5.13 (2H, m), and 5.68—5.89 (1H, m). **10r**: 68; 140 (21); 0.89 (3H, t, J=7.2 Hz), 1.19 (s), 1.23 (a) (3H, d, J= 6.4 Hz), 1.28—1.40 (2H, m), 1.47—1.58 (2H, m), 1.61—1.79 (1H, b), 2.22—2.64 (3H, m), 3.44 (2H, t, J=6.5 Hz), 3.56—3.63 (2H, m), 3.82—4.07 (1H, m), 4.14—4.37 (2H, m), 4.97—5.13 (2H, m), and 5.63—5.89 (1H, m). **10s**: 55; 125 (17); 1.19 (s), 1.22 (a) (3H, d, J=6.4 Hz), 2.12 (3H, s), 1.61—1.86 (1H, b), 2.38—2.61 (3H, m), 2.64—2.74 (2H, m), 3.87—4.08 (1H, m), 4.21—4.35 (2H, m), 4.98—5.14 (2H, m), and 5.62—5.88 (1H, m).

Reduction of Alkyl-3-oxobutanoates with Bakers' Yeast. One mmol of an alkyl 2-alkyl-3-oxobutanoate was added to a suspension of 20 g of bakers' yeast in 25 ml of water and the mixture was stirred at room temperature for 2 days. Then Hyflo-Super-Cell (10 G) was added to the mixture and the resulted suspension was filtered. The organic portion was concentrated under reduced pressure and the residue was subjected to column chromatography on silica gel with an eluent of hexane-ethyl acetate (9 : 1) mixture to give the corresponding hydroxy ester. The diastereomeric ratios and chemical yields are listed in Table 1.

Determination of Syn/Anti Ratio. The syn/anti ratio in the product was determined on GLC (PEG. 1.5 m) with column temperatures: **6a**, 80 °C; **6b**, 90 °C; **6c**, 110 °C; **6d**, 120 °C; **6e**, 150 °C; **6g**, 110 °C; **6h**, 80 °C; **6i**, 120 °C; **6j**, 100 °C; **6k**, 120 °C; **6l**, 130 °C; **6m**, 150 °C; **6n**, 160 °C; **6p**; 130 °C; **6q**, 130 °C; **6r**, 130 °C; **6s**, 130 °C; **6t**, 130 °C.

Determination of Diastereomeric Composition. The reduced product **6j** was converted into the corresponding methyl ester and the ^{1}H NMR spectrum of its MTPA ester[16] was compared with those of the authentic samples prepared by methylation of racemic and (*S*)-methyl 3-hydroxybutanoates.[3]

The authors wish to thank for financial support by a Grant-in-Aid from the Ministry of Education, Science and Culture under the Grant No. 62216011.

References

1) S. Masamune, W. Choy, F. A. J. Kerdesky, and B. Imperiali, *J. Am. Chem. Soc.*, **103**, 1566 (1981).

2) P. A. Barlett, *Tetrahedron*, **36**, 3 (1980).

3) G. Fráter, U. Muller, and W. Günther, *Tetrahedron*, **40**, 1269 (1984).

4) H. Akita, A. Furuichi, H. Koshiji, K. Horikoshi, and T. Oishi, *Chem. Pharm. Bull.*, **31**, 4376 (1983).

5) K. Nakamura, T. Miyai, K. Nozaki, K. Ushio, S. Oka, and A. Ohno, *Tetrahedron Lett.*, **27**, 3155 (1986).

6) B. S. Deol, D. D. Ridley, and G. W. Simpson, *Aust. J. Chem.*, **29**, 2459 (1976).

7) T. Fujisawa, T. Itoh, and T. Sato, *Tetrahedron Lett.*, **25**, 5083 (1984).

8) H. Akita, H. Matsukura, and T. Oishi, *Tetrahedron Lett.*, **27**, 5397 (1986).

9) The diastereomeric composition of the product seems to depend on the activity of bakers' yeast employed for the reduction. For example, the ratio preliminary reported for **6e** was 95/5,[5] which turned out to be 92/8 in the present report. In the preliminary experiment which was run 2 years ago, the yeast employed was less active than that employed presently and unable to reduce the substrate completely unless glucose was added at each 6 h. The yeast in the present work reduced **6e** within 1 day without adding extra glucose.

10) M. Hirama, M. Shimizu, and M. Iwashita, *J. Chem. Soc., Chem. Commun.*, **1983**, 559.

11) B. N. Zhou, A. S. Gopalan, F. van Middlesworth, W. R. Shieh, and C. J. Sih, *J. Am. Chem. Soc.*, **105**, 3958 (1983).

12) A. Furuichi, H. Akita, H. Matsukura, T. Oishi, and K. Horikoshi, *Agric. Biol. Chem.*, **51**, 293 (1987).

13) Kinetic parameters for a reaction composed of multi-

steps are treated as those for an "imaginary" single-step process. Contrary, a real system which is in resonance is expressed by a sum of "imaginary" canonical forms. Thus, to have an image for a nonexistent subject is a common procedure in chemistry.

14) K. Nakamura, T. Miyai, K. Ushio, S. Oka, and A. Ohno, *Bull. Chem. Soc. Jpn.*, **61**, 2089 (1988).

15) All Boiling points are uncorrected. $t/°C=T/K-273.15$. $p/mmHg=P/13.5951\times980.665\times10^{-2}Pa=P/133.322Pa$.

16) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).