matography on alumina using benzene as eluant to give olefinic ketone **25**: 1.72 g, 89%; mp 125–127 °C (methanol); ^{1}H NMR (200 MHz, CD_2Cl_2) δ 1.05–2.3 (four m, 4 H, $H_{10,11}$), 2.50 (m, 2 H, benzylic H_{12}), 2.70 (m, 1 H, H_9), 3.05 (m, 1 H, H_9), 3.37 (br s, 4 H, benzylic $H_{4,5}$), 4.06 (m, 1 H, methynyl H_{10a}), 6.68 (d, 1 H, J = 2.4 Hz, olefinic H_7), 7.36 (br s, 1 H, J = 6.6 Hz, H_3), 7.50 (dd, 1 H, J = 6.6, 8.4 Hz, H_2), 7.66 (s, 1 H, H_6), 7.73 (d, 1 H, J = 8.4 Hz, H_1); mass spectrum, m/e (relative intensity) 274 (100, M^+), 246 (49, $M - C_2H_4$), 217 (29, $M - (C_2H_4 + HCO)^+$); IR (KBr) 1720 cm^{-1} (C=O); UV (methanol) [λ_{max}, nm ($\epsilon \times 10^4$)] 368 (sh, 0.29), 321 (0.90), 288 (1.42), 225 (1.54). Anal. Calcd for $C_{20}H_{18}O$: C, 87.59; H, 6.57. Found: C, 87.41; H, 6.34.

4,5,8,9,10,10a,11,12-Octahydrobenz[*j*]acephenanthrylene (26). A mixture of enone **25** (1.50 g, 5.5 mmol) in benzene (20 mL), hydrazine monohydrate (9.3 mL), diethylene glycol (60 mL), and KOH (7.0 g) was heated at 100–105 °C for 1 h under nitrogen. The volatile components were distilled at 190–200 °C, and the concentrated reaction mixture was then heated at the same temperature for 6 h. Workup as described for **4** followed by flash chromatography on alumina with benzene/hexane (1:1) as eluant afforded **26**: 1.28 g, 90%; mp 125–126 °C (hexane); ^{1}H NMR (200 MHz, CD_2Cl_2) δ 1.26–1.66 (m, 4 H, $H_{9,10}$), 1.80–2.20 (m, 2 H, H_{11}), 2.28 (m, 2 H, H_{12}), 2.96 (m, 2 H, H_8), 3.34 (br s, 5 H, $H_{4,5}$, H_{10a}), 6.44 (br s, 1 H, olefinic H_7), 7.24 (d, 1 H, J = 6.8 Hz, H_3), 7.42 (dd, 1 H, J = 6.8, 7.55 Hz, H_2), 7.55 (s, 1 H, H_6), 7.62 (d, 1 H, J = 7.55 Hz, H_1); mass spectrum, m/e (relative intensity) 260 (100, M^+), 232 (16, $M - C_2H_4$), 217 (24, $M - (C_3H_6 + H)^+$); UV (heptane) [λ_{max}, nm ($\epsilon \times 10^5$)] 343 (sh, 0.28), 327 (sh, 0.38), 295 (sh, 1.02), 256 (2.55), 230 (3.66). Anal. Calcd for $C_{20}H_{20}$: C, 92.31; H, 7.69. Found: C, 92.33; H, 8.02.

Benz[*j*]acephenanthrylene (27). A solution of **26** (1.17 g, 4.5 mmol) and DDQ (4.50 g, 19.8 mmol) in dry benzene (100 mL) was refluxed for 5 h. The cooled solution was filtered and the filtrate chromatographed on alumina. Elution with benzene/hexane (1:9) and collection of the orange-yellow, nonfluorescent band furnished pure benz[*j*]acephenanthrylene (**27**): 0.930 g, 82%; mp 170–171 °C (hexane); ^{1}H NMR (250 MHz, $CDCl_3$) see Table I; UV (heptane) [λ_{max}, nm ($\epsilon \times 10^4$)] 376 (1.26), 358 (1.19), 342 (0.85), 314 (2.02), 301 (1.24), 272 (sh, 4.14), 258 (5.52); accurate mass of molecular ion 252.0933, calcd for $C_{20}H_{12}$ 252.0937; mass spectrum, m/e (relative intensity) 252 (100, M^+), 250 (24, $M - H_2$), 226 (14, $M - C_2H_2$), 126 (23, M^{2+}), 113 (17, $(M - C_2H_2)^{2+}$); HPLC retention time 3.47 min; IR (KBr) 3040, 1610, 1460, 1430, 1390, 1340, 1250, 1180, 1160, 880, 795, 755, 710 cm^{-1}. Anal. Calcd for $C_{20}H_{12}$: C, 95.24; H, 4.76. Found: C, 94.72; H, 4.94.

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Registry No. **1**, 5349-90-6; **2**, 1148-84-1; **3**, 108665-19-6; **4**, 108665-20-9; **5**, 19770-52-6; **6**, 108665-21-0; **7**, 108665-22-1; **8**, 108665-23-2; **9**, 16683-64-0; **10**, 108665-24-3; **13**, 108665-25-4; **14**, 108665-26-5; **15**, 108665-27-6; **16**, 108665-28-7; **17**, 108674-99-3; **18**, 108665-29-8; **19**, 13055-36-2; **20** (isomer 1), 108665-30-1; **20** (isomer 2), 108665-35-6; **21**, 108665-31-2; **22**, 7467-80-3; **23**, 108675-00-9; **24**, 108665-32-3; **25**, 108665-33-4; **26**, 108665-34-5; **27**, 216-48-8; chloroacetyl chloride, 79-04-9; oxalyl chloride, 79-37-8; ethyl formate, 109-94-4; diethyl carbonate, 105-58-8; methyl vinyl ketone, 78-94-4.

A Microbially Based Approach for the Preparation of Chiral Molecules Possessing the Trifluoromethyl Group

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The synthetic approach to both enantiomers and diastereomers with the trifluoromethyl group, involving the stereoselective hydrolysis of the ester group and acyclic stereoselection, is described. The absolute configuration of these trifluoromethylated molecules is determined. Especially, (*R*)-(+)- or (*S*)-(−)-hydroxy ketones possessing the trifluoromethyl group at asymmetrical carbon have been transformed to four diastereomeric 1,3-amino alcohols and 1,3-diols of the syn and anti configuration.

One objective of research in fluorine chemistry, required to support applications in F analogues of bioactive materials synthesis,[1-6] is the development of methodology[7-11] and/or reagents[12-15] suitable for synthesis of each enantiomeric and diastereomeric relationship with unusual selectivity and control. However, in fluorine chemistry, the absolute configuration of chiral materials and/or the synthetic methods giving both enantiomers or diastereomers with enantiomeric syn and anti configuration, have not been studied in detail.

Scheme I

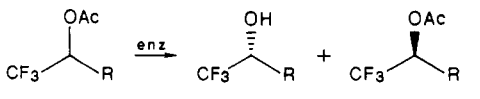

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Table I. Optical Resolution with Lipase-MY

substrate[a]	hydrolysis[b] ratio, %	time, h	$[\alpha]_D$/MeOH, deg	opt[c] purty, % ee	abs confgn
$PhCH(OH)CF_3$[d]	40	24	−11.8 (c 1.91)	57	R
$PhCH_2CH(OH)CF_3$	46	6	+44.7 (c 2.07)	94	
$PhCH_2CH_2CH(OH)CF_3$	44	6	+69.2 (c 1.55)	98	R
n-PrC≡CCH(OH)CF_3[e]	41	6	−1.85 (c 1.06)	67	
n-BuC≡CCH(OH)CF_3[e]	47	6	−1.39 (c 1.67)	55	
(E)-PhCH=CHCH(OH)CF_3[f]	37	6	+39.6 (c 1.84)	93	R
(Z)-PhCH=CHCH(OH)CF_3[f]	35	6	+38.3 (c 1.83)	90	R
$C_8H_{17}CH(OH)CF_3$	22	6	+50.0 (c 1.57)	85	R
$CF_3CH(OH)CH_2CO_2Et$[f]	41	2.5	+20.4 (neat)	96	R
$CF_3CH(OH)CH_2C(O)Ph$	23	1	+2.55 (c 1.69)	92	R
$CF_3CH(OH)CH_2C(O)CH_2CH_2Ph$	24	2	+11.7 (c 0.84)	91	R
$CF_3CH(OH)CH_2C(O)CH_2CH(Me)_2$	28	1.5	+14.0 (c 1.62)	94	R
$CF_3CH(OH)CH_2C(O)(CH_2)_5CH_3$	37	2	+12.7 (c 2.06)	90	R

[a] Each structure was determined by means of IR, NMR, and mass spectral data. For the new compounds the microanalyses were in satisfactory agreement with the calculated values (C, H, N; ±0.4). [b] The hydrolysis ratio was determined by ^{19}F NMR signal intensity. [c] The optical purity was determined by ^{19}F NMR after conversion of compound to its diastereomeric ester by optically active MTPA. [d] Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G. *J. Chem. Soc., Chem. Commun.* **1978**, 456. [e] Kitazume, T.; Sato, T. *J. Fluorine Chem.* **1985**, *30*, 189. [f] Ishikawa, N.; Koh, M.; Kitazume, T.; Choi, S. K. *J. Fluorine Chem.* **1984**, *24*, 419.

Table II. Preparation of *S* Enantiomers

substrate	yield, %	method[a]	time, h	$[\alpha]_D$/MeOH, deg	opt purty, % ee
$PhCH_2CH(OH)CF_3$	99	A	48	−39.0 (c 1.80)	82
$PhCH_2CH(OH)CF_3$	95	B	6	−47.4 (c 1.76)	98[b]
$PhCH_2CH_2CH(OH)CF_3$	99	A	24	−60.7 (c 1.55)	86
$PhCH_2CH_2CH(OH)CF_3$	94	B	6	−70.2 (c 1.67)	99[b]
(E)-PhCH=CHCH(OH)CF_3	97	A	24	−23.9 (c 1.76)	56
(Z)-PhCH=CHCH(OH)CF_3	97	A	24	−26.0 (c 1.87)	61
$CF_3CH(OH)CH_2CO_2Et$	99	A	12	−17.4 (neat)	84
$CF_3CH(OH)CH_2CO_2Et$	90	B	2	−15.6 (neat)	75
$CF_3CH(OH)CH_2C(O)CH_2CH_2Ph$	97	B	2	−9.58 (c 2.52)	75
$CF_3CH(OH)CH_2C(O)CH_2CH(Me)_2$	93	B	3	−12.7 (c 2.28)	85
$CF_3CH(OH)CH_2C(O)CH_2CH(Me)_2$	92	B	3	−14.2 (c 1.87)	94[b]
$CF_3CH(OH)CH_2C(O)(CH_2)_5CH_3$	97	B	2	−9.34 (c 2.51)	66
$CF_3CH(OH)CH_2C(O)(CH_2)_5CH_3$	90	B	2	−13.1 (c 1.45)	93[b]

[a] Method A, aqueous NaOH/acetone; method B, cellulase. [b] *S* acetate recovered from hydrolysis with lipase-MY (hydrolysis ratio 55–60%) was used.

Table III. ^{19}F and ^1H NMR Spectral Data

substrate	^{19}F NMR CF_3	^{19}F NMR J_{CF_3-CH}, Hz	^1H NMR chemical shift
$PhCH_2CH(OH)CF_3$	1.9	6.6	3.52 (2 H, d), 6.50 (1 H, q), 7.20 (Ar H), 9.60 (OH)
$PhCH_2CH_2CH(OH)CF_3$	2.4	6.4	1.60 (OH), 1.93 (1 H, td), 1.95 (1 H, t), 2.80 (2 H), 3.78 (1 H), 7.20 (Ar H)
n-PrC≡CCH(OH)CF_3	1.7	5.6	1.0, 1.53, 2.20 (7 H), 3.67 (OH), 4.40 (1 H, q)
n-BuC≡CCH(OH)CF_3	2.3	5.6	0.9, 1.50, 2.30 (9 H), 3.70 (OH), 4.73 (1 H, q)
(E)-PhCH=CHCH(OH)CF_3	0.5	6.2	3.27 (OH), 4.67 (1 H, q), 6.08 (C=CH, dd), 6.70 (C=CH, d), 7.25 (Ar H)
(Z)-PhCH=CHCH(OH)CF_3	0.8	6.5	3.27 (OH), 4.45 (1 H, qd), 5.67 (C=CH, dd), 6.80 (C=CH, d), 7.25 (Ar H)
n-$C_8H_{17}CH(OH)CF_3$	2.4	6.6	0.72 (3 H), 1.28 (12 H), 1.67 (2 H), 5.18 (1 H, q)
$CF_3CH(OH)CH_2C(O)Ph$	2.0	7.2	3.10 (1 H, dd), 3.40 (1 H, dd), 4.10 (OH), 4.63 (1 H), 7.40–7.90 (Ar H)
$CF_3CH(OH)CH_2C(O)CH_2CH_2Ph$	1.6	6.6	2.57–2.97 (6 H), 3.40 (OH), 4.40 (1 H), 7.30–7.50 (Ar H)
$CF_3CH(OH)CH_2C(O)CH_2CH(Me)_2$	2.7	7.0	0.76 (3 H, d), 1.60–1.70 (3 H), 2.07 (2 H), 3.20 (1 H), 4.30 (1 H)
$CF_3CH(OH)CH_2C(O)(CH_2)_5CH_3$	2.0	6.5	0.93 (3 H, t), 1.43 (8 H), 2.47 (2 H), 2.73 (2 H), 3.78 (OH), 4.43 (1 H)

We recently outlined[14-19] the possibility of microbial transformation of fluorinated compounds under stereocontrol. As part of our continuing effort to develop stereocontrolled syntheses of fluorinated compounds with high optical purity by use of microorganisms, we describe herein a new synthetic approach to both trifluoromethylated enantiomers, based on the enantiotopic specificity of lipases, and then the full details of the synthesis of four diastereomeric 1,3-amino alcohols and 1,3-diols possessing the trifluoromethyl group at an asymmetrical carbon.

Results and Discussion

Asymmetric Hydrolysis of 1-Substituted 2,2,2-Trifluoroethyl Acetates. Asymmetric hydrolysis of practical compounds with enzymes of microbial or animal origin has been extensively studied up to now.[20-36] However, from

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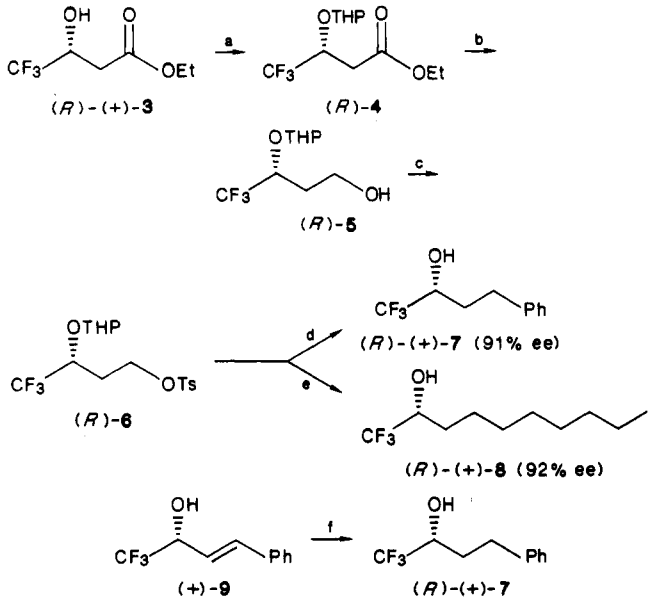
Scheme II[a]



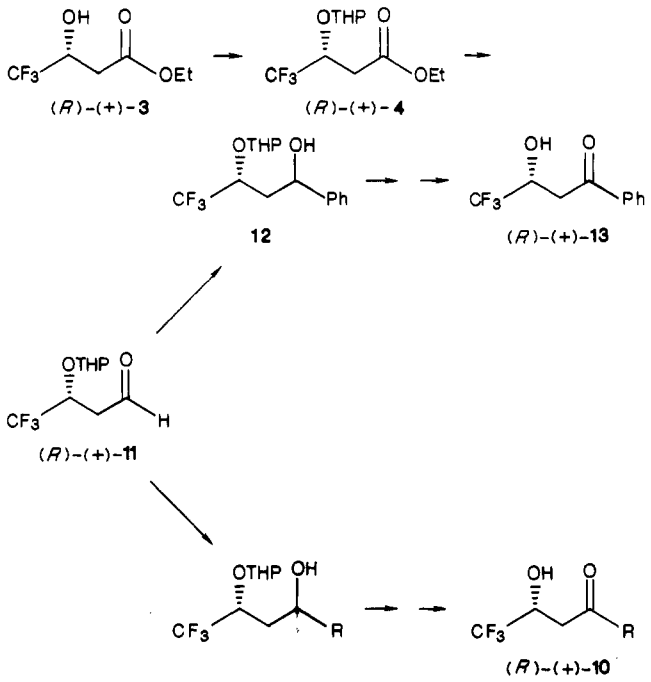
[a] (a) DHP; (b) $LiAlH_4$, Et_2O; (c) TsCl, pyridine; (d) Ph_2CuLi, Et_2O; (e) $(n\text{-}C_6H_{13})_2CuLi$, Et_2O; (f) PtO_2, H_2.

the synthetic point of view, no practical microbial hydrolysis of trifluoromethylated compounds to yield chiral molecules has been reported. To search for practical routes to prepare trifluoromethylated chiral compounds of high optical purity, we examined the asymmetric hydrolysis by a variety of lipases as shown in Scheme I, of 1-substituted 2,2,2-trifluoroethyl acetates.

When the hydrolysis was carried to less than 45% with lipase-MY (*Candida cylindracea*), the alcohol was greatly enriched the *R* enantiomer. The results shown in Table I clearly demonstrate that asymmetric hydrolysis is useful for the preparation of the desired trifluoromethylated chiral molecules, that the optical purity is sufficiently high to allow the use of these compounds as practical chiral intermediates in fluorine chemistry. The *S* enantiomers were prepared from the recovered acetates by hydrolysis using a cellulase (*Trichoderma viride*) and/or by a chemical method (2 mol/L aqueous NaOH–acetone system). Results are summarized in Table II.

Determination of Absolute Configuration. We have investigated the absolute configuration of optically active carbinols with trifluoromethyl groups in our continuing studies on the use of microorganisms for the preparation of chiral fluorinated molecules. The synthetic strategies employed are shown in Schemes II and III.

Scheme III[a]



[a] (a) DHP/CH_2Cl_2; (b) $(i\text{-}Bu)_2AlH$/hexane/−30 °C; (c) PhMgBr/THF; (d) RMgBr/THF; (e) Swern oxidation; (f) H^+.

The absolute stereochemistry of the synthetic intermediate (see Scheme II) (*R*)-(+)-ethyl 4,4,4-trifluoro-3-hydroxybutanoate (**3**) was confirmed by X-ray analysis.[37] It has been prepared by reduction (91% ee).[38] The *S* (−) enantiomer was prepared by asymmetric hydrolysis (84% ee). The protected (*R*)-(+)-**4** was selectively reduced with lithium aluminum hydride to give in good yield the optically pure compound **5**. The alcohol was then reacted with tosyl chloride to give the synthon compound **6**. Treatment of **6** with a variety of cuprates gave materials with known absolute configurations.

The results shown in Scheme II suggest that (+)-1,1,1-trifluoro-4-phenyl-2-butanol, (+)-1,1,1-trifluoro-2-decanol, and (+)-1,1,1-trifluoro-4-phenyl-3-buten-2-ol produced from the asymmetric hydrolysis are the *R* enantiomers. The (*S*)-(−)-1,1,1-trifluoro-4-phenyl-2-butanol (78% ee) was obtained from (*S*)-(−)-ethyl 4,4,4-trifluoro-3-hydroxybutanoate (84% ee) in the same manner.

For the conversions given in Scheme III, the synthetic starting material was the optically pure (*R*)-(+)- or (*S*)-(−)-ethyl 4,4,4-trifluoro-3-hydroxybutanoate. Protection with dihydropyran followed by treatment of (*R*)-(+)-hydroxy ester **3** with diisobutylaluminum hydride gave the corresponding aldehyde **11**. Treatment of **11** with phenylmagnesium bromide in tetrahydrofuran at −40 °C gave the carbinol **12**, and then oxidation of carbinol gave (*R*)-(+)-3,3,3-trifluoro-2-hydroxypropyl phenyl ketone (**13**), $[\alpha]_D$ (MeOH) +2.49° (c 1.78), >95% ee. Scheme III thus illustrates the use of this starting material to prepare (*R*)-(+)-β-hydroxy ketones possessing the trifluoromethyl group.

Stereoselective Synthesis of Acyclic 1,3-Amino Alcohols. As the syntheses of 1,3-amino alcohols from β-hydroxy ketones have been reported by Narasaka and his co-workers,[39] we examined our *O*-benzyloximes pos-

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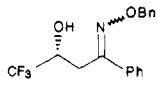
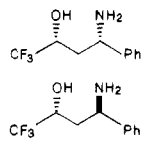
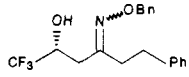
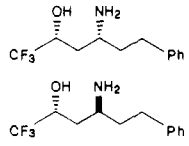
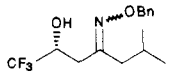
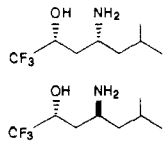
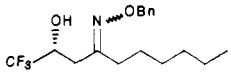
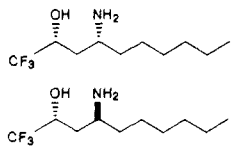
Table IV. Preparation of 1,3-Amino Alcohols

substrate	product	yield, %	syn:anti	$[\alpha]_D$/MeOH, deg
		73	87:13	+28.6 (*c* 0.96)
				−27.9 (*c* 1.07)
		68	79:21	+30.1 (*c* 0.87)
				−30.4 (*c* 0.76)
		70	82:18	+23.6 (*c* 0.53)
				−23.4 (*c* 1.98)
		67	83:17	+18.3 (*c* 1.08)
				−18.1 (*c* 0.56)

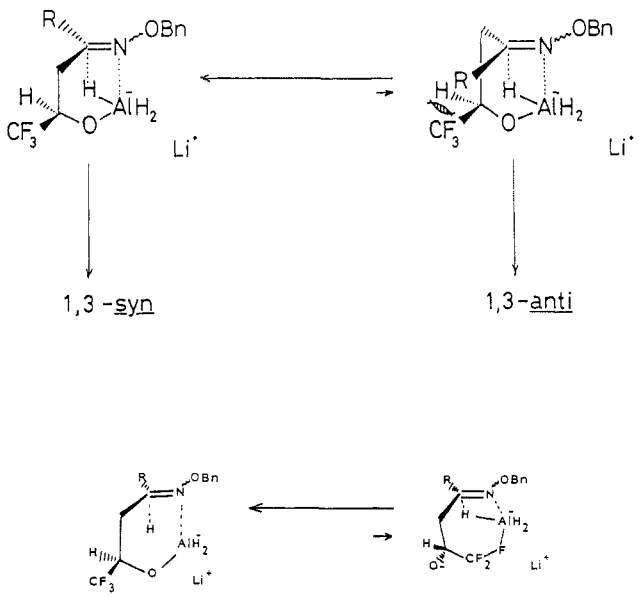


Figure 1. Transition-state model.

sessing the trifluoromethyl group based on the following hypothesis. In these reduction systems, the intramolecular reduction might be expected to proceed through cyclic transition states to result in the formation of a syn 1,3-amino alcohol as indicated by the formation of the aluminum fluoride chelate (seven-membered chelate) in Figure 1.

Using the reduction of the R enantiomer of the corresponding O-benzyloxime, we designed a diasterocontrolled approach to syn and anti 1,3-amino alcohols such as 1R,3R or 1R,3S amino alcohols possessing trifluoromethyl groups attached to the asymmetrical carbon.

Reduction with lithium aluminum hydride of a mixture of syn and anti *O*-benzyloximes yielded the amino alcohols **15** shown in Table IV. The stereochemistries of the 1,3-amino alcohols were assigned by using ^{1}H NMR (200 MHz) coupling constants after conversion of the 1,3-amino alcohols to cyclic carbamates as shown in Figure 2. Since four diasteromers take the chair conformation, the vicinal couuling constant (J_{H-H}) should be the 0–6 Hz for the eq–eq or eq–ax protons and 8–16 Hz for the ax–ax pro-

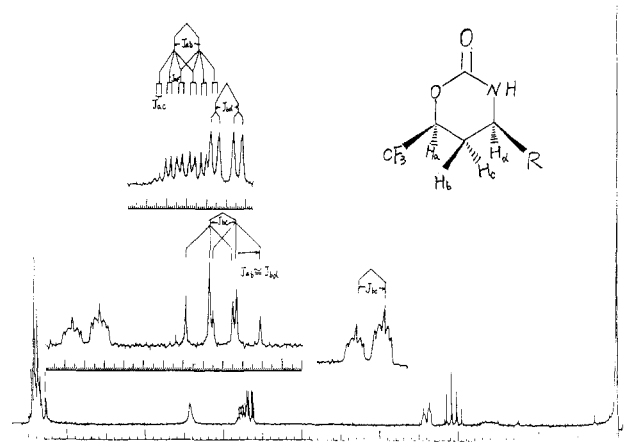


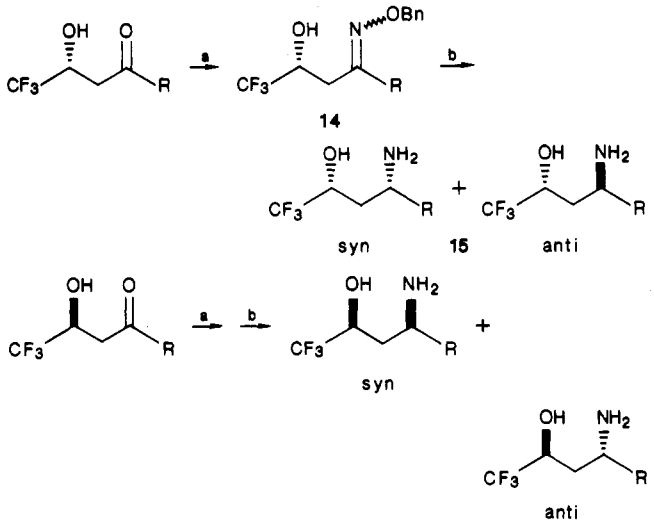
Figure 2.

tons;[40] the main product was the syn isomer.

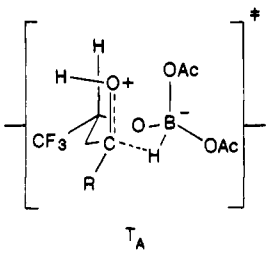
The stereoselective reduction of (*S*)-**14** yielded 1*S*,3*R* and 1*S*,3*S* amino alcohols. The final purification of 1*R*,3*R* and 1*R*,3*S* or 1*S*,3*R* and 1*S*,3*S* amino alcohols was achieved by the column chromatography on silica gel. Furthermore, the stereochemistries of these molecules were confirmed by an empirical rule,[41] which states that the chemical shift of a syn isomer of the methine carbon of ^{13}C NMR in a 1,3-amino alcohol adjacent to the hydroxy group occurs at a lower field than the in the II antiisomer.

Diastereocontrolled Synthesis of Acyclic 1,3-Diols. The stereoselective syntheses of 1,3-diols have been extensively investigated in recent years;[42–47] however, no stereocontrolled syntheses of their CF_3 analogues have been studied. Therefore, it was appropriated to investigate the stereoselective reduction of β-hydroxy ketones pos-

(40) Gaudemer, A. *Stereochemistry, Fundamentals and Methods*; Kagan, H. B.,. Ed.; Georg Thieme: Stuttgart, 1977; Vol. 1.
(41) Jager, V.; Buss, V. *Leibigs Ann. Chem.* **1980**, 101.
(42) Narasaka, K.; Pai, F. C. *Chem. Lett.* **1980**, 1415.
(43) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233.
(44) Still, W. C.; Barrish, J. C. *J. Am. chem. Soc.* **1983**, *105*, 2487.
(45) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719.
(46) Cardilla, G.; Orena, M.; Porgi, G.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1981**, 465.
(47) Hirama, M.; Uei, M. *Tetrahedron Lett.* **1982**, *23*, 5307.

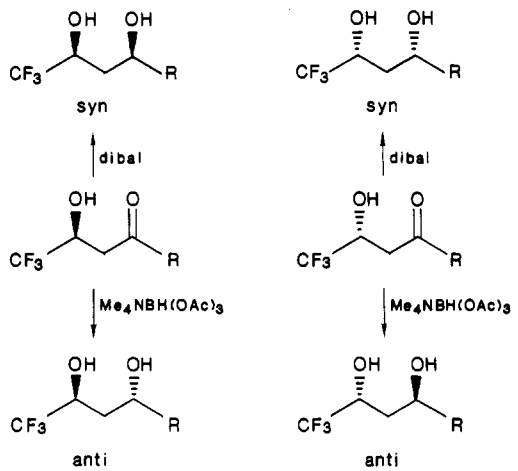


sessing trifluoromethyl groups with isobutylaluminum hydride. These reduction systems might be expected to proceed through cyclic transition states, yielding the syn diols as indicated by the formation of the metal oxygen chelate in Figure 3. The reduction of β-hydroxy ketones with a tetramethylammonium triacetoxyborohydride–an-



T_A

hydrous acetic acid system yielded the anti diols via the transition state (T_A).[48] The stereochemistries of the 1,3-diols were assigned by using ^1H NMR (200 MHz) coupling constants after conversion of the 1,3-diols to cyclic acetonide.[40]



Practically, the asymmetric hydrolyses of trifluoromethyl esters have been shown to be valuable for the preparation of biologically active compounds containing trifluoromethyl group on the asymmetrical carbon atom.

Experimental Section

General Procedure. All microbial hydrolyses were carried out in the Jarfermentor or "CULSTIR" flask. All commercially available reagents were used without further purification. Infrared

(48) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939.

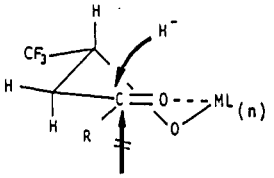


Figure 3.

spectra were obtained by using a JASCO A-102 spectrometer and KBr pellets. The ^1H (internal Me_4Si) and ^{19}F (external CF_3CO_2H) NMR spectra were recorded by using Varian EM-390 and Hitachi R-24F spectrometers. Mass spectra were obtained by using a Hitachi M-52 spectrometer at 20 eV. Specific rotations were recorded by using a JASCO DIP-140 digital polarimeter. Yields were those of the products actually isolated.

3,3,3-Trifluoro-2-hydroxypropyl Phenyl Ketone. Into the reaction vessel containing lithium diisopropyl amine (56 mmol) in tetrahydrofuran (50 mL) was added acetophenone (6.0 g, 50 mmol) in tetrahydrofuran (10 mL) with a syringe under an atmosphere of argon at −50 °C, and then the reaction mixture was stirred for 30 min at −50 °C. Into the mixture solution was bubbled trifluoroacetaldehyde (55 mmol) at that temperature, and the whole mixture was stirred for 2 h at 0 °C. After quenching with saturated NH_4Cl solution, oily materials were extracted with diethyl ether. On removal of the solvent, the resulting crude products were chromatographed on silica gel using hexane–ethyl acetate (5:1) in a yield of 50%: ^{19}F NMR ($CDCl_3$) δ +2.0 (d, J_{CF_3-CH} = 7 Hz); ^1H NMR ($CDCl_3$) δ 3.1 (CH_AH_B, dd, $J_{H_A-H_B}$ = 34 Hz, J_{H_A-CH} = 7.1 Hz), 3.4 (CH_AH_B, dd, J_{H_B-CH} = 14.1 Hz), 4.1 (OH, br), 4.63 (CH, m), 7.43–7.93 (Ar–H); IR (cm^{-1}) 3400 (OH), 1685 (C=O).

Asymmetric Hydrolysis. A suspension of lipase-MY (*Candida cylindracea*, Meito Sangyo Co. Ltd., 5 g) in a buffer solution (60 mL, pH 7.3), prepared from a 1/15 M aqueous Na_2HPO_4 solution (46.1 mL) and 1/15 M aqueous KH_2PO_4 solution (13.9 mL), was stirred for 15 min at 40–41 °C in a "CULSTIR" flask for suspension culture with double arms and jacket (100 mL, Sibata Scientific Technology Ltd.). Into the mixture was added the acetate derivative of 1,1,1-trifluoro-4-phenyl-2-butanol (20 mmol), and then the whole mixture was stirred at 40–41 °C. After 6 h of stirring, the flocculant (200 ppm solution prepared from p-713, Dai-ichi Kogyo Seiyaku, 10 mL) was added into the stirring mixture for a few minutes. After 1 h of stirring, the mixture was acidified with 1 N HCl and then the precipitates were separated by filtration. The oily materials were extracted with diethyl ether. The ethereal extract was dried over anhydrous magnesium sulfate and then the solvent was removed. After determining the hydrolysis ratio by ^{19}F NMR signal intensities using $C_6H_5CF_3$ as an internal standard, the products were separated by column chromatography using a mixture of *n*-hexane–diethyl ether (5:1) as eluent.

Synthesis of *S* Enantiomers. (a) In the above asymmetric hydrolysis, the acetate derivative of 1,1,1-trifluoro-4-phenyl-2-butanol was hydrolyzed for 12 h with lipase-MY, and then (*R*)-(+)-1,1,1-trifluoro-4-phenyl-2-butanol (>85% ee; hydrolysis ratio 56%) and the corresponding *S* acetate derivative were separated by column chromatography.

(b) A suspension of cellulase (*Trichoderma viride*, Yakult Pharmaceutical Industry Co. Ltd., 3 g) in buffer solution (60 mL, pH 7.3) was stirred for 15 min at 40–41 °C in the "CULSTIR" flask (200 mL). Into the mixture, was added the recovered *S* acetate derivative of 1,1,1-trifluoro-4-phenyl-2-butanol (20 mmol), and then the whole mixture was stirred at 40–41 °C. After 6 h of stirring, the flocculant (200 ppm solution prepared from p-713, Dai-ichi Kogyo Seiyaku, 10 mL) was added into the stirring mixture for a few minutes. After 1 h of stirring, the mixture was acidified with 1 N HCl and then the precipitates were separated by filtration. The oily materials were extracted with diethyl ether. The ethereal extract was dried over anhydrous magnesium sulfate and then the solvent was removed. The products were separated by column chromatography using a mixture of *n*-hexane–diethyl ether (5:1) as eluent.

(c) A mixture solution of recovered the *S* acetate derivative of 1,1,1-trifluoro-4-phenyl-2-butanol (20 mmol), 2 mol/L aqueous NaOH (5 mL)–acetone (5 mL), was stirred at room temperature.

Table V. ^{19}F and ^{1}H NMR Spectral Data of 1,3-Amino Alcohols

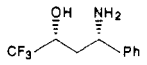
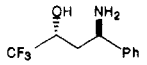
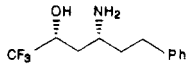
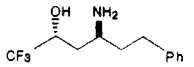
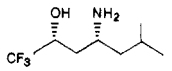
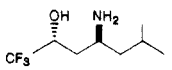
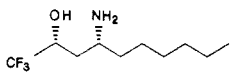
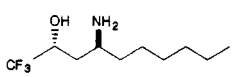
product	^{19}F NMR CF_3	^{19}F NMR J_{CF_3-CH}, Hz	^{1}H NMR chemical shift
	1.8	6.6	1.76 (2 H, m), 3.20 (3 H, br), 3.73 ($CHNH_2$, m), 4.16 (CHOH, m), 7.33 (Ar H)
	1.1	6.6	
	2.5	6.5	1.80 (4 H, m), 2.73 (2 H), 3.00 (1 H), 3.23 (3 H), 4.1 (CHOH, m), 7.33 (Ar H)
	0.7	7.0	
	2.3	6.6	1.00 (CH_3, d), 1.33 (3 H), 1.67 (H), 3.00 ($CHNH_2$, m), 3.21 (2 H), 4.07 (CHOH, m)
	1.2	7.5	
	3.2	6.6	0.93 (CH_3, t), 1.33 (8 H, m), 1.73 (2 H, ddd), 2.87 ($CHNH_2$, m), 3.30 (3 H, br), 4.03 (CHOH, m)
	1.8	7.5	

Table VI. Preparation of Syn 1,3-Diols

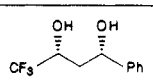
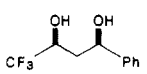
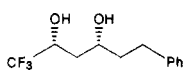
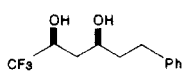
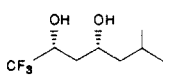
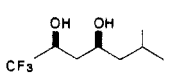
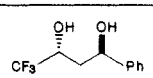
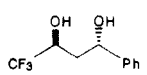
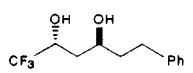
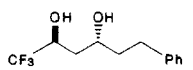
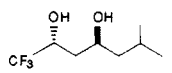
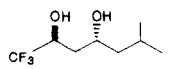
product	yield, %	diastereomeric ratio	$[\alpha]_D$/MeOH, deg
	88	97	+25.3 (*c* 0.47)
	76	96	−25.7 (*c* 1.46)
	94	95	+30.1 (*c* 0.80)
	95	97	−29.6 (*c* 0.96)
	83	97	+33.9 (*c* 0.28)
	75	95	−33.3 (*c* 1.25)

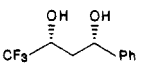
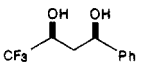
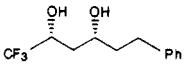
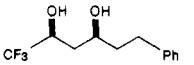
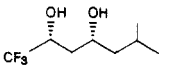
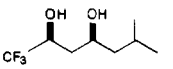
Table VII. Preparation of Anti 1,3-Diols

product	yield, %	diastereomeric ratio (% de)	$[\alpha]_D$/MeOH, deg
	75	94	+18.6 (*c* 0.86)
	81	96	−19.6 (*c* 0.59)
	90	95	+9.46 (*c* 0.70)
	83	95	−8.90 (*c* 0.89)
	86	95	+30.4 (*c* 0.69)
	74	97	−28.5 (*c* 0.92)

After 2 days of stirring, the mixture was acidified with 1 N HCl and then the precipitates were separated by filtration. The oily materials were extracted with diethyl ether. The ethereal extract was dried over anhydrous magnesium sulfate and then the solvent was removed. The products were separated by column chromatography using a mixture of *n*-hexane–diethyl ether (5:1).

Similarly, other asymmetric hydrolyses of acetate derivatives were carried out on the same scale.

Table VIII. ^{19}F NMR and ^{1}H NMR Spectral Data of 1,3-Diols

product	^{19}F NMR CF_3	^{19}F NMR J_{CF_3-CH}, Hz	^{1}H NMR chemical shift
	2.1	6.0	1.93 (2 H, m), 2.53 (1 H, br), 3.56 (1 H, br), 4.07 (1 H, m), 4.90 (1 H, m), 7.28 (Ar H)
	1.5	6.6	
	2.1	6.0	1.83 (4 H, m), 2.67 (3 H, m), 3.93 (3 H, m), 7.17 (Ar H)
	1.5	6.8	
	2.0	6.0	0.93 (6 H, d), 1.20–2.00 (6 H, m), 4.07 (3 H, m)
	1.8	6.6	

Determination of Optical Purity. A mixture solution of (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (MTPA-Cl) (1.1 mmol) and (*R*)-(+)-1,1,1-trifluoro-4-phenyl-2-butanol (1 mmol) in pyridine (1 mL) was stirred at room temperature. After 24 h of stirring, the whole mixture was poured into water, and then oily materials were extracted with a 1 N HCl solution, 5% $NaHSO_4$, saturated $Na_2S_2O_3$ solution, and then brine. After removing the solvent, the diastereomeric ratio was determined by ^{19}F NMR signal intensities.

Determination of Absolute Configuration. (*R*)-(+)-1,1,1-Trifluoro-4-phenyl-2-butanol Derived from the *R* Tosylate (6). Into a solution of phenyl cuprate (20 mmol) in freshly dried diethyl ether (20 mL) was added *R* tosylate **6** (5 mmol) in diethyl ether (20 mL) slowly at room temperature. After 24 h of stirring at that temperature, the reaction was poured into water, and then the ethereal layer was separated. (*R*)-(+)-1,1,1-Tri-

fluoro-4-phenyl-2-butanol was purified by column chromatography on silica gel using the mixture solution of *n*-hexane–diethyl ether (5:1) as eluent: $[\alpha]_D$ (MeOH) +64.1° (*c* 1.55), 91% ee.

(*R*)-(+)-1,1,1-Trifluoro-2-decanol. Into a solution of hexyl cuprate (20 mmol) in freshly dried diethyl ether (20 mL), was added *R* tosylate **6** (5 mmol) in diethyl ether (20 mL) slowly at room temperature. After 24 h of stirring at that temperature, the reaction mixture was poured into water, and then the ethereal layer was separated. (*R*)-(+)-1,1,1-Trifluoro-4-phenyl-2-butanol was purified by column chromatography on silica gel by using the mixture solution of *n*-hexane–diethyl ether (10:1): $[\alpha]_D$ (MeOH) +54.2° (*c* 0.79), 92% ee.

(*R*)-(+)-1,1,1-Trifluoro-4-phenyl-2-butanol Derived from (+)-1,1,1-Trifluoro-4-phenyl-3-buten-2-ol. A solution of (+)-1,1,1-trifluoro-4-phenyl-3-buten-2-ol (1.0 g, 5 mmol) and platinum oxide (0.1 g) in freshly dried diethyl ether (20 mL) under atmospheric hydrogen was stirred at room temperature. After 2 days of stirring, the mixture was poured into water, and then the ethereal layer was separated. (*R*)-(+)-1,1,1-Trifluoro-4-phenyl-2-butanol was purified by column chromatography on silica gel: $[\alpha]_D$ (MeOH) +63.1° (*c* 1.37), 89% ee.

Synthesis of (*R*)-(+)-3,3,3-Trifluoro-2-hydroxypropyl Phenyl Ketone. (a) Protection of Dihydropyran. After a mixture of (*R*)-(+)-ethyl 4,4,4-trifluoro-3-hydroxybutanoate (3.7 g, 20 mmol), $[\alpha]_D$ +20.4° (*neat*) >96% ee, dihydropyran (1.4 g, 20 mmol), and *p*-toluenesulfonic acid (50 mg) in methylene chloride (40 mL) was stirred for 3.5 h at room temperature, the solvent was removed under dynamic vacuum. Distillation gave compound **4** in a yield of 95%; bp 71 °C/1 mmHg.

(b) Reduction of 4 with Diisobutylaluminum Hydride. Into the reaction vessel was placed the compound **4** (2.6 g, 10 mmol), freshly dried hexane (30 mL) was added with a syringe under atmosphere of argon, and then diisobutylaluminum hydride (11 mmol, 1 M in hexane) was added at −70 °C. After the reagent was added, the reaction mxiture was stirred for 1 h at room temperature, and then the mixture was quenched with saturated NH_4Cl solution. Oily materials were extracted with diethyl ether, and then the ethereal extract was dried over anhydrous magnesium sulfate. On removal of the solvent, distillation gave the corresponding aldehyde in a yield of 86% yield: bp 58–60 °C/1.2 mmHg; ^{19}F NMR ($CDCl_3$) δ −0.1 (CF_3, d, J_{CF_3-CH} = 8.8 Hz), −0.75 (CF_3, d, J_{CF_3-CH} = 8.8 Hz); ^1H NMR ($CDCl_3$) δ 1.33–2.00 (m, 4 × H), 2.67–2.70 (m, 2 × H), 3.33–4.00 (4 × H), 4.05 (m, 1 × H), 4.83 (m, 1 × H), 9.80 (CHO).

(c) Grignard Reaction of Compound 11. Into the reaction vessel was placed compound **11** (2.3 g, 10 mmol); freshly dried tetrahydrofuran (30 mL) was added with a syringe under an atmosphere of argon, and then phenylmagnesium bromide (12 mmol in tetrahydrofuran) was added at −40 °C. After the reagent was added, the reaction mixture was stirred for 1 h at that temperature, and then the mixture was quenched with saturated NH_4Cl solution. Oily materials were extracted with diethyl ether, and then the ethereal extract was dried over anhydrous magnesium sulfate. On removal of the solvent, product **12** was separated by column chromatography on silica gel in 96% yield.

(d) Oxidation of Compound 12. Into the three-necked flask was placed dimethyl sulfoxide (1.2 g, 20 mmol), oxalyl chloride (1.38 g, 20 mmol) was added with a syringe under an atmosphere of argon at −50 °C, and then compound **11** (2.9 g, 10 mmol) was added at that temperature. After 15 min of stirring, triethylamine (2.0 g) was added into the mixture at −50 °C, and then the mixture was warmed up to room temperature. The mixture was poured into water, and then the oily materials were extracted with diethyl ether. On removal of the solvent, the resulting products were chromatographed on silica gel.

A solution of crude compound (2.9 g, 10 mmol) and *p*-toluenesulfonic acid (0.1 g) in methylene chloride (20 mL) was stirred for 1 h at room temperature. The mixture was poured into water and then worked up as usual. (*R*)-(+)-3,3,3-Trifluoro-2-hydroxypropyl phenyl ketone (**13**) was purified by column chromatography on silica gel, $[\alpha]_D$ (MeOH) +2.63° (*c* 1.62), >94% ee.

***O*-Benzyloxime.** A mixture of (*R*)-(+)-3,3,3-trifluoro-2-hydroxypropyl phenyl ketone (2.6 g, 10 mmol), benzoxyamine hydrochloride (12 mmol), and pyridine (2 mL) in methanol (30 mL) was refluxed for 4 h and worked up as usual. The resulting crude products were chromatographed on silica gel.

Reduction of *O*-Benzyloxime with Lithium Aluminum Hydride. Into the reaction vessel was placed lithium aluminum hydride (0.6 g) in diethyl ether (30 mL); the *O*-benzyloxime of (*R*)-(+)-3,3,3-trifluoro-2-hydroxypropyl phenyl ketone (3.65 g, 10 mmol) in diethyl ether (10 mL) was added withh a syringe under an atmosphere of argon at 0 °C, and then the whole mixture was stirred for 4 h at room temperature. After being quenched with saturated NH_4Cl solution, oily materials were extracted with ethyl acetate. On removal of the solvent, the syn and anti ratio was determined by ^{19}F NMR signal intensities. The products were separated by column chromatography.

Preparation of the Syn 1,3-Diol. Into the reaction vessel was placed diisobutyl aluminum hydride (25 mmol in hexane) in tetrahydrofuran (30 mL); (*R*)-(+)-3,3,3-trifluoro-2-hydroxypropyl phenyl ketone (3.65 g, 10 mmol) in tetrahydrofuran (10 mL) was added with a syringe under an atmosphere of argon at −70 °C, and then the whole mixture was stirred for 3 h at that temperature. After being quenched with saturated NH_4Cl solution, oily materials were extracted with ethyl acetate. On removal of the solvent, the syn and anti ratio was determined by ^{19}F NMR signal intensities. The products were separated by column chromatography on silica gel.

Preparation of the Anti 1,3-Diol. Into the reaction vessel was placed tetramethylammonium triacetoxyborohydride (1.5 g, 6.5 mmol) in acetonitrile (15 mL), and anhydrous acetic acid (5 mL) was added at −40 °C. Into the mixture was added (*R*)-(+)-3,3,3-trifluoro-2-hydroxypropyl phenyl ketone (0.25 g, 1.15 mmol) in acetonitrile (5 mL) with a syringe under an atmosphere of nitrogen at −40 °C, and then the whole mixture was stirred for 5 h at that temperature. After quenching with a saturated NH_4Cl solution, oily materials were extracted with methylene chloride. On removal of the solvent, the products were separated by column chromatography on silica gel.

Registry No. **3**, 85571-85-3; **4**, 108535-30-4; **5**, 108535-31-5; **6**, 108535-32-6; **7**, 108644-83-3; **8**, 108535-33-7; **9**, 108644-84-4; **11**, 108535-34-8; **12**, 108560-80-1; **13**, 108535-35-9; **14** (R = Ph), 108560-81-2; **14** (R = CH_2CH_2Ph), 108535-45-1; **14** (R = Bu-*i*), 108535-46-2; **14** (R = *n*-hexyl), 108535-47-3; *syn*-**15** (R = Ph), 108535-48-4; *anti*-**15** (R = Ph), 108535-49-5; *syn*-**15** (R = CH_2CH_2Ph), 108535-50-8; *anti*-**15** (R = CH_2CH_2Ph), 108535-51-9; *syn*-**15** (R = Bu-*i*), 108535-52-0; *anti*-**15** (R = Bu-*i*), 108535-53-1; *syn*-**15** (R = *n*-hexyl), 108535-54-2; *anti*-**15** (R = *n*-hexyl), 108535-55-3; (*R*)-$PhCH(OH)CF_3$, 10531-50-7; (+)-$PhCH_2CH(OH)CF_3$, 108535-39-3; (−)-*n*-BuC≡$CCH(OH)CF_3$, 108535-41-7; (−)-*n*-PrC≡$CCH(OH)CF_3$, 108535-40-6; (*R*,*E*)-PhCH=$CHCH(OH)CF_3$, 108644-85-5; (*R*,*Z*)-PhCH=$CHCH(OH)CF_3$, 108644-86-6; (*R*)-$CF_3CH(OH)CH_2COCH_2CH_2Ph$, 108535-42-8; (*R*)-$CF_3CH(OH)CH_2COCH_2CH(Me)_2$, 108535-43-9; (*R*)-$CF_3CH(OH)CH_2CO(CH_2)_5CH_3$, 108535-44-0; 3,3,3-trifluoro-2-hydroxypropyl phenyl ketone, 1524-15-8; lithium diisopropylamine, 4111-54-0; acetophenone, 98-86-2; lipase, 9014-49-7; 1,1,1-trifluoro-4-phenyl-2-butanol acetate, 108535-36-0; cellulose, 9012-54-8; dihydropyran, 25512-65-6; *p*-toluenesulfonic acid, 104-15-4; benzoxyamine hydrochloride, 2687-43-6; (2*R*,4*S*)-1,1,1-trifluoro-4-phenylbutane-2,4-diol, 108535-37-1; (2*R*,4*R*)-1,1,1-trifluoro-4-phenylbutane-2,4-diol, 108535-38-2; (2*S*,4*R*)-1,1,1-trifluoro-4-phenylbutane-2,4-diol, 108535-56-4; (2*R*,4*R*)-1,1,1-trifluoro-6-phenylhexane-2,4-diol, 108535-57-5; (2*S*,4*S*)-1,1,1-trifluoro-6-phenylhexane-2,4-diol, 108535-58-6; (2*R*,4*R*)-1,1,1-trifluoro-6-methylheptane-2,4-diol, 108535-59-7; (2*S*,4*S*)-1,1,1-trifluoro-6-methylheptane-2,4-diol, 108535-60-0; (2*S*,4*S*)-1,1,1-trifluoro-4-phenylbutane-2,4-diol, 108535-61-1; (2*R*,4*S*)-1,1,1-trifluoro-6-phenylhexane-2,4-diol, 108535-62-2; (2*S*,4*R*)-1,1,1-trifluoro-6-phenylhexane-2,4-diol, 108535-63-3; (2*R*,4*S*)-1,1,1-trifluoro-6-methylheptane-2,4-diol, 108535-64-4; (2*S*,4*R*)-1,1,1-trifluoro-6-methylheptane-2,4-diol, 108535-65-5.