other than the solvent (R-113) peak. The column temperature was 140 °C and retention time was 17.8 min. Anal. Calcd for $C_{10}F_{14}O$: C, 29.87; F, 66.15; H, 0.00. Found: C, 29.91; F, 65.80; H, 0.00. The prominent peaks in the mass spectrum were [m/z (formula, int.)] 403 ($^{13}CC_9F_{14}O$, 9.5), 402 ($C_{10}F_{14}O$, 100), 374 (C_9F_{14}, 4.1), 337 ($^{13}CC_8F_{12}$, 5.1), and 336 (C_9F_{12}, 45.0). The ^{19}F NMR spectrum consisted of an AB pattern (-120.47, -124.44 ppm) overlapped with a singlet (-121.16 ppm) in the CF_2 region and two unresolved peaks (-215.82, -224.26 ppm) in the CF region. The infrared spectrum contained a C=O absorption (1815.2 cm^{-1}).

Reaction of *F*-Adamantanone with ROH. *F*-Adamantanone (0.089 g, 0.22 mmol) was first dissolved in $CFCl_3$ contained in a 5-mm borosilicate NMR tube, and then a known amount of alcohol was added and the tube sealed. After up to 24 h for equilibration, ^{19}F NMR spectra were recorded. In temperature effect experiments, the NMR tube was sealed on the vacuum line and the spectrum was taken every 2.5 °C.

Synthesis of *F*-Noradamantane. *F*-Adamantanone (0.059 g, 0.146 mmol) was dissolved in $CFCl_3$ (R-11, 0.726 g) in a 5-mm borosilicate NMR tube. The NMR tube was sealed on the vacuum line and irradiated using a mercury lamp for 1 h. During irradiation, the atmospheric temperature increased to about 120 °C. After irradiation, the NMR tube was connected to the vacuum line. Following trap-to-trap fractionation, *F*-noradamantane (0.050 g, yield 91%) was obtained as a white solid in the -22 °C trap. Gas chromatographic separation on a Fluorosilicone QF-1 column (7 m × 3/8 in.) showed only one peak. The column temperature was 90 °C and the retention time was 12.8 min. Anal. Calcd for C_9F_{14}: C, 28.90; F, 71.10; H, 0.00. Found: C, 28.83; F, 71.42; H, 0.00. The prominent peaks in the mass spectrum were [m/z (formula, int.)] 375 ($^{13}CC_8F_{14}$, 9.0), 374 (C_9F_{14}, 100), 355 (C_9F_{13}, 7.4), and 336 (C_9F_{12}, 4.7). The ^{19}F NMR spectrum consisted of an AB pattern (-120.69, -123.88 ppm) overlapped with a singlet (-121.85 ppm) in the CF_2 region and two unresolved peaks (-211.91, -225.99 ppm) in the CF region. The infrared spectrum contained no C=O absorption.

Registry No. ADM, 700-58-3; F-ADM, 141635-73-6; F_2, 7782-41-4; CH_3OH, 67-56-1; $HOCH(CH_3)_2$, 67-63-0; $HOC(CH_3)_3$, 75-65-0; *F*-noradamantane, 141635-77-0; F-ADM (isopropyl hemiketal, 141635-75-8; F-ADM (*tert*-butyl hemiketal), 141635-76-9; F-ADM (methyl hemiketal), 141635-74-7.

Enantio- and Diastereoselective Synthesis of β-Substituted Cycloalkanecarboxylates

Cheng-Lin Fang, Hiroshi Suemune, and Kiyoshi Sakai*

Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka 812, Japan

Received September 13, 1991

Conjugate addition is a useful reaction for carbon-carbon formation. Asymmetric conjugate addition has been widely studied for the synthesis of optically active β-substituted or α,β-disubstituted carbonyl compounds.[1] In a previous paper,[2] we reported the utility of (*R*,*R*)-1,2-cyclohexanediol as a chiral auxiliary for asymmetric conjugate addition. 1,4-Addition of Ph_2CuLi to (*R*,*R*)-2-hydroxycyclohexyl (*E*)-2-pentenoate showed high diastereoselectivity. In this paper, we wish to report the enantio- and diastereoselective synthesis of β-substituted five- or six-membered cycloalkanecarboxylates using (*R*,*R*)-1,2-cyclohexanediol as a chiral auxiliary.

In pursuing the above synthesis, two types of reactions were planned. One was based on asymmetric conjugate addition and subsequent diastereoselective cyclization of the resulting enolate using substrates **1** and **2** (Table I, entries 1-5).[2a] The other was based on asymmetric conjugated addition to cycloalkenyl substrates **3** and **4** (Table I, entries 6-9) and following diastereoselective protonation.

Substrate **1** was synthesized by monoacylation of (*R*,*R*)-1,2-cyclohexanediol[3] with (*E*)-6-chloro-2-hexenoyl chloride in 60% yield. Compound **2** was synthesized from the corresponding chloride by treatment with NaI in 79% yield. Substrates **3** and **4** were also prepared by similar monoacylation with cycloalkene-1-carboxylic acid chlorides in 68% and 74% yields, respectively.

Reaction of **1** and **2** with R_2CuLi afforded the desireable trans-cyclized products **5-8A** and **5-8B** in the ratio of 7-9 to 1 (entries 1-4), which could be easily separated in an optically pure form by usual silica-gel column chromatography as reported in a previous communication.[2a]

Next, asymmetric conjugate addition to cycloalkenyl substrates (**3** and **4**) was studied. Reaction of the five-membered **3** with R_2CuLi at -30 °C (R = Ph) or at -50 °C (R = Bu) afforded, **5,6C** (49-51%) as a major product accompanied with a small amount of the other possible stereoisomers **5,6A,B,D** (entries 6 and 7). Reaction of the six-membered **4** with R_2CuLi (R = Ph, Bu) afforded two kinds of cis-oriented compounds **8,9C** (49-59%) and **8,9D** (14-29%) (entries 8 and 9). These two products could be easily isolated in an optically pure form by usual silica-gel column chromatography. The diastereomeric ratio of **C** and **D** was 2-3.5 to 1. From the above results, it is concluded that (1*R*,2*R*)-products **A** were predominantly obtained from substrates **1** and **2** and (1*S*,2*R*)-products **C** from substrates **3** and **4**.

The structure of each product was determined by the analysis of spectroscopic data and transformation to known compounds. As a typical example, in the ^1H NMR spectra of entries 1-3, disappearance of the signals attributable to CH_2Cl and olefinic protons in substrate **1** and new appearance of the signals due to H-1 and the alkyl (phenyl, butyl, and methyl) function in cyclized products support the formation of the five-membered ring, in addition to the molecular ion peak (M^+) in mass spectra. The similar ^{13}C NMR spectra of **5A** and **5B** showed that they are diastereomers. The relative configuration of two substituents on the five-membered ring was determined from the chemical shift of H-1 in the ^1H NMR spectra, comparing 1,2-cis and 1,2-trans isomers (Table II). It is generally accepted that a proton α to a vicinal substituent is more shielded when it is cis than when it is trans.[5] These δ values of H-1 suggest that the relative configurations of **5-7A,B** are trans and those of **5-6C,D** are cis (comments and reference ^1H NMR chemical shifts for C-1 H of *cis*- and *trans*-ethyl 2-acetoxy- and 2-hydroxycyclopentanecarboxylates are provided in the supplementary material). In the case of six-membered products (**8A,B**

(1) (a) Ullenius, C.; Christeson, B. *Pure Appl. Chem.* **1988**, *60*, 57. (b) Taylor, R. J. K. *Synthesis* **1985**, 364. (c) Wilheim, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. (d) Tomioka, K.; Koga, K. In *Asymmetric Synthesis*, Vol. 2; Morroson, J. D., Ed.; Academic Press: New York, 1983; p 219. (e) Somfai, P.; Tanner, D.; Alsson, T. *Tetrahedron* **1985**, *41*, 5973. (f) Cardani, S.; Poli, G.; Scolastico, C.; Villa, R. *Tetrahedron* **1988**, *44*, 5929. (g) Bermardi, A.; Cardani, S.; Pilati, T.; Poli, G.; Scolastico, C.; Villa, R. *J. Org. Chem.* **1988**, *53*, 1600. (h) Oppolzer, W.; Kingma, A. J.; Poli, G. *Tetrahedron* **1989**, *45*, 479.

(2) (a) Fang, C.-L.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1990**, *31*, 4751. (b) Fang, C.-L.; Ogawa, T.; Suemune, H.; Sakai, K. *Tetrahedron: Asymmetry* **1991**, *2*, 389.

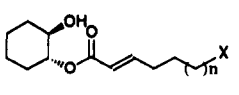
(3) (a) Xie, Z.-F.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1987**, 838. (b) Xie, Z.-F.; Nakamura, I.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1988**, 966.

(4) This complex mixture was assumed to consists of **9B**, 1,4-adduct, and a dialkylated product by 1,4-addition and subsequent substitution of iodine with a butyl group.

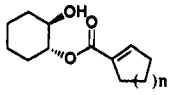
(5) Kagan, H. B. *Stereochemistry*, Vol. 1; Georg Thieme Publishers: Stuttgart, 1977; p 92.

0022-3263/92/1957-4300$03.00/0 © 1992 American Chemical Society

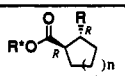
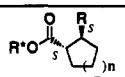
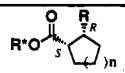
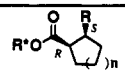
Table I. Enantio- and Diastereoselective Preparation of 2-Substituted Cycloalkanecarboxylate by Cuprate Addition of 1-4



1: n=1, X= Cl
2: n=2, X= I



3: n= 1
4: n= 2

entry	substrate			A	B	C	D
		n	R				
1	**1**	1	Ph	**5A** (44%)	**5B** (6%)		
2	**1**	1	Bu	**6A** (46%)	**6B** (5%)		
3	**1**	1	Me	**7A** (50%)	**7B** (7%)		
4	**2**	2	Ph	**8A** (54%)	**8B** (7%)		
5	**2**	2	Bu	**9A** (15%)	*a*		
6	**3**	1	Ph	**5A** (9%)	**5B** (3%)	**5C** (51%)	**5D** (6%)
7	**3**	1	Bu	**6A** (20%)	**6B** (15%)	**6C** (49%)	**6D** (11%)
8	**4**	2	Ph			**8C** (49%)	**8D** (14%)
9	**4**	2	Bu			**9C** (59%)	**9D** (29%)

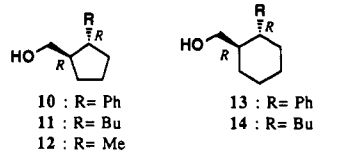
[a] See ref 4.

Table II. Chemical Shifts (δ) of H-1 of 5–9

	A	B	C	D
5	2.86	2.86	3.25	3.23
6	2.34	2.32	2.85	2.83
7	2.26	2.25		
8	2.59	2.68	2.94	2.97
9	2.06		2.60	2.60

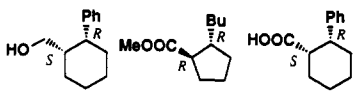
and **9A**), coupling constants ($J_{1,2}$ = 10.6–11.6 Hz) in addition to H-1 chemical shifts suggest that they have a trans orientation. The NOE observed between H-1 and H-2 in **8C** provides unambiguous proof that the relative configuration in **8C** is cis.

For determination of absolute stereochemistry, each isolated compound was converted to carbinol derivatives (**10**–**15**) by $LiAlH_4$ reduction. When specific rotations are compared with those reported, the absolute configuration of **5**–**9A,B** could be deduced as 1*R*,2*R* for **A** and 1*S*,2*S* for **B**. The absolute stereochemistry of **6C** was determined to be 1*S*,2*R* by conversion to (1*R*,2*R*)-**16** via an epimerization process at C-1. That of **8C** was also determined to be 1*S*,2*R* by conversion to (1*S*,2*R*)-**17** via (1*S*,2*R*)-**15** (see Experimental Section, determination of absolute configuration).



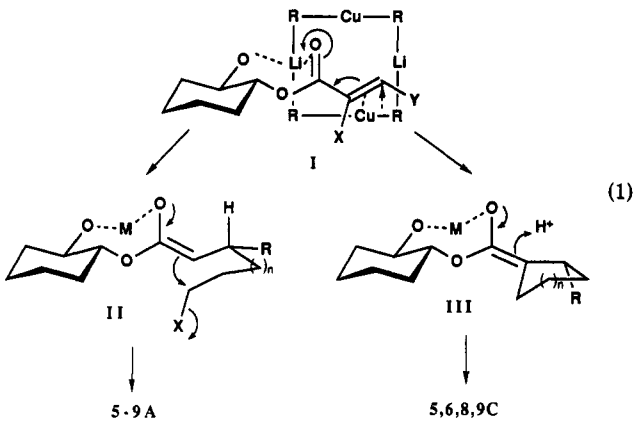
10 : R= Ph
11 : R= Bu
12 : R= Me

13 : R= Ph
14 : R= Bu



15 **16** **17**

On the basis of absolute configuration at the C-2 position of product, 1,4-addition of R_2CuLi to substrates **1**–**4** was found to proceed by attacking the *re* face at the β-position of carboxylates. The reaction processes might be considered as follows. Assumption of *s-cis* conformation for substrate and the square-planar dimeric structure[1a] for the cuprate allows us to consider the intermediate **I** (eq 1), in which a free hydroxy group and an ester carbonyl of the substrate play an important role in the formation of a chelation complex. After formation of the copper(I)–alkene π-complex, shift of the R substituent might occur from the *re* face at the β-position of carboxylates. Diastereoselective intramolecular alkylation (Table I, entries 1–5) of the resulting lithium *E*-enolate (**II**)[6] might be caused by a favorable allylic strain[7] of **II**, which adopts syncoplanar disposition between H-3 and the C–C double bond to afford 1,2-trans product **A**.[8] Diastereoselective protonation of the enolate (**III**) might be rationalized by attack of a proton from the less hindered site to give the 1,2-cis product **C**.[9]



(1)

These new methods for preparation of optically pure 1,2-cis- and trans-disubstituted cycloalkanes show the high potential of (*R,R*)-cyclohexane-1,2-diol as a chiral auxiliary. We have already developed the preparation method for (*S,S*)-cyclohexane-1,2-diol.[3] This means that preparation of the 1,2-cis- and -trans-disubstituted cycloalkanes with opposite absolute configurations is also possible.

Experimental Section

^1H and ^{13}C NMR spectra were measured with a JEOL JNM-PX-100 or a JNM-GX 270 spectrophotometer using $CDCl_3$ as a solvent. CuBr–dimethyl sulfide complex (Aldrich Chemical Company, Inc.) was purified according to ref 10. Diethyl ether and THF were dried and distilled from sodium–benzophenone

(6) Yamamoto, Y.; Yamada, J.; Uyehara, T. *J. Am. Chem. Soc.* **1987**, *109*, 5820.
(7) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162.
(8) (a) Cooke, M. P. *Tetrahedron Lett.* **1979**, *24*, 2199. (b) Yamaguchi, M.; Tsukamoto, M.; Hirao, I. *Tetrahedron Lett.* **1985**, *26*, 1723.
(9) Zimmerman, H. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1968**, *90*, 6091.
(10) House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

ketyl under an Ar atmosphere prior to use. Each reaction was carried out under an Ar atmosphere. For column chromatography, silica gel (Nakarai Tesque, silica gel 60, 230–400 mesh) was used.

Preparation of Substrates. Representative Procedure for Monoacylation of (*R*,*R*)-1,2-Cyclohexanediol. Acid chloride (2.6 mmol) was added to a solution of (*R*,*R*)-cyclohexane-1,2-diol (232 mg, 2 mmol) in CH_2Cl_2 (6 mL) and pyridine (3 mL) at rt. After being stirred for 2 h, the reaction mixture was quenched with brine. The mixture was extracted with AcOEt (25 mL × 3). The combined organic solvents were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by flash column chromatography.

(1′*R*,2′*R*)-2′-Hydroxycyclohexyl 6-chloro-2-hexenoate (1): oil (295 mg, 60%); $[\alpha]^{25}_D$ −25.6° (*c* 0.9, $CHCl_3$); IR (neat) 3450, 1710, 1655, 1185, 980 cm^{-1}; ^1H NMR δ 2.38 (2 H, m, H-4), 3.55 (1 H, m, H-2′), 3.56 (2 H, t, *J* = 6.4 Hz, H-6), 4.62 (1 H, m, H-1′), 5.90 (1 H, dt, *J* = 15.7, 1.6 Hz, H-2), 6.97 (1 H, dt, *J* = 15.7, 6.9 Hz, H-3); MS *m*/*z* 246 (M^+), 228, 210, 148, 98. Anal. Calcd for $C_{12}H_{19}ClO_3$: C, 58.51; H, 7.78; Cl, 14.21. Found: C, 58.42; H, 7.83; Cl, 14.25.

(1′*R*,2′*R*)-2′-Hydroxycyclohexyl 7-Iodo-2-heptenoate (2). A solution of (1′*R*,2′*R*)-2′-hydroxycyclohexyl 7-chloro-2-heptenoate (544 mg, 2.1 mmol) and NaI (470 mg, 3.1 mmol) in acetone (10 mL) was refluxed for 5 h. Acetone was partly removed under reduced pressure, water was added, and the mixture was extracted with AcOEt. The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography to afford **2** (580 mg, 79%) as a colorless oil: $[\alpha]^{23}_D$ −28.3° (*c* 3.0, $CHCl_3$); IR (neat) 3400, 1710, 1640, 1180 cm^{-1}; ^1H NMR δ 3.20 (2 H, t, *J* = 6.7 Hz, H-7), 3.52 (1 H, m, H-2′), 4.61 (1 H, m, H-1′), 5.86 (1 H, dt, *J* = 15.7, 1.5 Hz, H-2), 6.98 (1 H, dt, *J* = 15.7, 6.8 Hz, H-3); MS *m*/*z* 352 (M^+), 334, 254, 98. Anal. Calcd for $C_{13}H_{21}IO_3$: C, 44.31; H, 6.01; I, 36.05. Found: C, 44.25; H, 5.93; I, 36.19.

(1′*R*,2′*R*)-2′-Hydroxycyclohexyl cyclopentene-1-carboxylate (3): colorless solid [Et_2O–hexane] (286 mg, 68%); mp 55–56 °C; $[\alpha]^{22}_D$ −36.1° (*c* 2.1, $CHCl_3$); IR (Nujol) 3550, 1700, 1630, 1170 cm^{-1}; ^1H NMR δ 2.55 (2 H × 2, m, H-3,5), 3.60 (1 H, m, H-2′), 4.65 (1 H, m, H-1′), 6.81 (1 H, m, H-2); MS *m*/*z* 210 (M^+), 192, 113, 98. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.53; H, 8.63. Found: C, 68.59; H, 8.56.

(1′*R*,2′*R*)-2′-Hydroxycyclohexyl cyclohexene-1-carboxylate (4): colorless solid [Et_2O–hexane] (332 mg, 74%); mp 63–64 °C; $[\alpha]^{23}_D$ −35.1° (*c* 5.1, $CHCl_3$); IR (Nujol) 3460, 1705, 1645, 1250, 1085 cm^{-1}; ^1H NMR δ 2.21 (2 H × 2, m, H-3,6), 3.60 (1 H, m, H-2′), 4.63 (1 H, m, H-1′), 7.02 (1 H, m, H-2); MS *m*/*z* 224 (M^+), 206, 127, 110, 98. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.60; H, 8.99. Found: C, 69.68; H, 8.90.

General Procedure for Conjugated Addition with Organocuprate. Ph_2CuLi was prepared by addition of phenyllithium [1.8 M in cyclohexane–diethyl ether (70:30), 6 mmol] to a suspension of CuBr–Me_2S (3 mmol) in Et_2O (10 mL) at 0 °C with subsequent stirring for 10 min. Bu_2CuLi and Me_2CuLi were prepared in a similar manner using butyllithium (1.6 M in hexane) and methyllithium (1.11 M in ether) at −50 °C and −25 °C, respectively.

A substrate (0.6 mmol) in Et_2O (1 mL) was added to a solution of R_2CuLi (3 mmol) at 0 °C (entries 1–5), −30 °C (entries 6 and 8), or −50 °C (entries 7 and 9). After being stirred for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and diluted with Et_2O (20 mL). The mixture was stirred until the solid had been digested, the aqueous layer turned a deep blue, the ethereal layer was separated, and the aqueous layer was extracted with Et_2O (20 mL × 2). The combined solution was washed with brine and then dried (Na_2SO_4). After removal of solvent in vacuo, an oily residue was purified by flash column chromatography on silica gel (15 g).

Entry 1. (1*R*,2*R*,1′*R*,2′*R*)-2′-Hydroxycyclohexyl 2-phenylcyclopentane-1-carboxylate (5A): oil (76 mg, 44%); $[\alpha]^{26}_D$ −148.3° (*c* 0.2, $CHCl_3$); IR (neat) 3450, 1725, 1600, 1180 cm^{-1}; ^1H NMR δ 2.85 (1 H, ddd, *J* = 9.8, 8.9, 8.6 Hz, H-1), 3.28 (1 H, ddd, *J* = 9.8, 9.8, 7.6 Hz, H-2), 3.28 (1 H, m, H-2′), 4.41 (1 H, m, H-1′), 7.24–7.38 (5 H, m, Ar H); ^{13}C NMR δ 23.7 (t), 23.8 (t), 24.5 (t), 29.7 (t), 29.8 (t), 32.1 (t), 35.6 (t), 51.6 (d), 52.6 (d), 72.3 (d), 78.4 (d), 126.8 (d), 127.7 (d) × 2, 128.7 (d) × 2, 143.3 (s), 175.6 (s); MS *m*/*z* 288 (M^+), 190, 144, 118; HRMS for $C_{18}H_{24}O_3$ (M^+) calcd *m*/*z* 288.1725, found 288.1717.

(1*S*,2*S*,1′*R*,2′*R*)-2′-Hydroxycyclohexyl 2-phenylcyclopentane-1-carboxylate (5B): oil (10 mg, 6%); $[\alpha]^{24}_D$ +45.9° (*c* 1.0, $CHCl_3$); IR (neat) 3450, 1725, 1600, 1175 cm^{-1}; ^1H NMR δ 2.86 (1 H, ddd, *J* = 9.8, 8.6, 8.6 Hz, H-1), 3.28 (1 H, ddd, *J* = 9.8, 9.8, 7.6 Hz, H-2), 3.43 (1 H, m, H-2′), 4.48 (1 H, m, H-1′), 7.20–7.38 (5 H, m, Ar H); ^{13}C NMR δ 23.7 (t), 23.8 (t), 24.8 (t), 29.8 (t), 30.5 (t), 32.8 (t), 35.1 (t), 50.2 (d), 52.3 (d), 72.7 (d), 78.1 (d), 126.4 (d), 127.2 (d) × 2, 128.5 (d) × 2, 143.8 (s), 175.9 (s); MS *m*/*z* 288 (M^+), 190, 144, 118; HRMS for $C_{18}H_{24}O_3$ (M^+) calcd *m*/*z* 288.1725, found 288.1729.

Entry 2. (1*R*,2*R*,1′*R*,2′*R*)-2′-Hydroxycyclohexyl 2-butylcyclopentane-1-carboxylate (6A): oil (74 mg, 46%); $[\alpha]^{24}_D$ −68.9° (*c* 1.8, $CHCl_3$); IR (neat) 3450, 1730, 1190 cm^{-1}; ^1H NMR δ 0.87 (3 H, t, *J* = 7.6 Hz, Me), 2.34 (1 H, ddd, *J* = 8.4, 8.4, 7.9 Hz, H-1), 3.56 (1 H, m, H-2′), 4.58 (1 H, m, H-1′); MS *m*/*z* 268 (M^+), 170, 98; HRMS for $C_{16}H_{28}O_3$ (M^+) calcd *m*/*z* 268.2038, found 268.2025.

(1*S*,2*S*,1′*R*,2′*R*)-2′-Hydroxycyclohexyl 2-butylcyclopentane-1-carboxylate (6B): oil (8 mg, 5%); $[\alpha]^{23}_D$ +22.0° (*c* 0.2, $CHCl_3$); IR (neat) 3450, 1730, 1190 cm^{-1}; ^1H NMR δ 0.88 (3 H, t, *J* = 6.8 Hz, Me), 2.34 (1 H, ddd, *J* = 8.3, 8.3, 8.2 Hz, H-1), 3.56 (1 H, m, H-2′), 4.59 (1 H, m, H-1′); MS *m*/*z* 268 (M^+), 170, 98; HRMS for $C_{16}H_{28}O_3$ (M^+) calcd *m*/*z* 268.2038, found 268.2033.

Entry 3. (1*R*,2*R*,1′*R*,2′*R*)-2′-Hydroxycyclohexyl 2-methylcyclopentane-1-carboxylate (7A): oil (68 mg, 50%); $[\alpha]^{24}_D$ −59.6° (*c* 1.8, $CHCl_3$); IR (neat) 3500, 1730, 1205, 1160 cm^{-1}; ^1H NMR δ 1.08 (3 H, d, *J* = 6.5 Hz, Me), 2.26 (1 H, ddd, *J* = 8.9, 8.9, 8.3 Hz, H-1), 3.55 (1 H, m, H-2′), 4.61 (1 H, m, H-1′); MS *m*/*z* 226 (M^+), 208, 128; HRMS for $C_{13}H_{22}O_3$ (M^+) calcd *m*/*z* 226.1569, found 226.1578.

(1*S*,2*S*,1′*R*,2′*R*)-2′-Hydroxycyclohexyl 2-methylcyclopentane-1-carboxylate (7B): oil (9.5 mg, 7%); IR (neat) 3450, 1730, 1200, 1160 cm^{-1}; ^1H NMR δ 1.07 (3 H, d, *J* = 6.6 Hz, Me), 2.25 (1 H, ddd, *J* = 8.6, 8.6, 8.2 Hz, H-1), 3.56 (1 H, m, H-2′), 4.60 (1 H, m, H-1′); MS *m*/*z* 226 (M^+), 208, 128. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.98; H, 9.80. Found: C, 68.87; H, 9.88.

Entry 4. (1*R*,2*R*,1′*R*,2′*R*)-2′-Hydroxycyclohexyl 2-phenylcyclohexane-1-carboxylate (8A): oil (98 mg, 54%); $[\alpha]^{23}_D$ −67.5° (*c* 3.5, $CHCl_3$); IR (neat) 3470, 1730, 1600, 1180 cm^{-1}; ^1H NMR δ 2.59 (1 H, ddd, *J* = 11.6, 11.6, 3.3 Hz, H-1), 2.73 (1 H, ddd, *J* = 11.6, 11.6, 3.4 Hz, H-2), 3.17 (1 H, m, H-2′), 4.28 (1 H, m, H-1′), 7.18–7.35 (5 H, m, Ar H); MS *m*/*z* 302 (M^+), 204, 158, 98; HRMS for $C_{19}H_{26}O_3$ (M^+) calcd *m*/*z* 302.1882, found 302.1871.

(1*S*,2*S*,1′*R*,2′*R*)-2′-Hydroxycyclohexyl 2-phenylcyclohexane-1-carboxylate (8B): oil (13 mg, 7%); $[\alpha]^{20}_D$ +0.28° (*c* 0.7, $CHCl_3$); IR (neat) 3460, 1730, 1600, 1175 cm^{-1}; ^1H NMR δ 2.68 (1 H, ddd, *J* = 11.2, 11.2, 3.4 Hz, H-1), 2.80 (1 H, ddd, *J* = 11.2, 11.2, 3.3 Hz, H-2), 3.31 (1 H, m, H-2′), 4.30 (1 H, m, H-1′), 7.18–7.35 (5 H, m, Ar H); MS *m*/*z* 302 (M^+), 204, 158, 98. Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.45; H, 8.67. Found: C, 75.41; H, 8.73.

Entry 5. (1*R*,2*R*,1′*R*,2′*R*)-2′-Hydroxycyclohexyl 2-butylcyclohexane-1-carboxylate (9A): oil (25 mg, 15%); $[\alpha]^{20}_D$ −50.8° (*c* 1.0, $CHCl_3$); IR (neat) 3450, 1730, 1175 cm^{-1}; ^1H NMR δ 0.87 (3 H, t, *J* = 6.9 Hz, Me), 2.06 (1 H, ddd, *J* = 10.9, 10.9, 3.3 Hz, H-1), 3.55 (1 H, m, H-2′), 4.60 (1 H, m, H-1′); MS *m*/*z* 282 (M^+), 184, 98. Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.28; H, 10.71. Found: C, 72.38; H, 10.63.

Entry 6. (1*S*,2*R*,1′*R*,2′*R*)-2′-Hydroxycyclohexyl 2-Phenylcyclopentane-1-carboxylate (5C).[11] Compound **5C** was obtained as a mixture with a small amount of **5B**: oil (93 mg, 54% yield as a mixture, **5B**:**5C** = 1:17); IR (neat) 3450, 1720, 1600, 1180 cm^{-1}; ^1H NMR δ for **5C** 3.25 (2 H, m, H-1 and H-2′), 3.44 (1 H, m, H-2), 4.18 (1 H, m, H-1′), 7.15–7.35 (5 H, m, Ar H); MS *m*/*z* 288 (M^+), 270, 190, 98.

(1*R*,2*S*,1′*R*,2′*R*)-2′-Hydroxycyclohexyl 2-Phenylcyclopentane-1-carboxylate (5D).[11] Compound **5D** was obtained as a mixture with **5A**: oil (26 mg, 15% yield as a mixture, **5A**:**5D** = 3:2); IR (neat) 3450, 1725, 1600, 1180 cm^{-1}; ^1H NMR δ for **5D** 3.23 (1 H, m, H-1), 3.26 (1 H, m, H-2′), 3.43 (1 H, ddd, *J* = 9.0, 9.0, 8.8 Hz, H-2), 4.17 (1 H, ddd, *J* = 10.8, 8.9, 4.9 Hz, H-1′), 7.20–7.35 (5 H, m, Ar H); MS *m*/*z* 288 (M^+), 270, 190, 98.

Entry 7. (1*S*,2*R*,1′*R*,2′*R*)-2′-Hydroxycyclohexyl 2-Bu-

tylcyclopentane-1-carboxylate (6C). Compound **6C** was obtained as a mixture with **6B**: oil (103 mg, 64% yield as a mixture, **6B**:**6C** = 1:3.3); IR (neat) 3470, 1730, 1180 cm^{-1}; ^1H NMR δ for **6C** 0.88 (3 H, t, J = 6.8 Hz, Me), 2.85 (1 H, m, H-1), 3.56 (1 H, m, H-2'), 4.58 (1 H, m, H-1'); MS m/z 268 (M^+), 171, 153, 98.

(1*R*,2*S*,1'*R*,2'*R*)-2'-Hydroxycyclohexyl 2-Butylcyclopentane-1-carboxylate (6D). Compound **6D** was obtained as a mixture with **6A**: oil (50 mg, 31% yield as a mixture, **6A**:**6D** = 1.7:1); IR (neat) 3470, 1730, 1180 cm^{-1}; ^1H NMR δ for **6D** 0.88 (3 H, t, J = 6.8 Hz, Me), 2.83 (1 H, m, H-1), 3.56 (1 H, m, H-2'), 4.58 (1 H, m, H-1'); MS m/z 268 (M^+), 171, 153, 98.

Entry 8. (1*S*,2*R*,1'*R*,2'*R*)-2'-Hydroxycyclohexyl 2-phenylcyclohexane-1-carboxylate (8C): oil (90 mg, 49%); $[\alpha]^{22}_D$ +33.9° (c 0.7, $CHCl_3$); IR (neat) 3560, 1720, 1600, 1170 cm^{-1}; ^1H NMR δ 2.97 (1 H, ddd, J = 11.5, 4.3, 4.0 Hz, H-1), 3.08 (1 H, ddd, J = 4.3, 4.3, 4.0 Hz, H-2), 3.16 (1 H, m, H-2'), 4.28 (1 H, ddd, J = 10.9, 8.9, 5.0 Hz, H-1'), 7.16–7.35 (5 H, m, Ar H); MS m/z 302 (M^+), 204, 98; HRMS for $C_{19}H_{26}O_3$ (M^+) calcd m/z 302.1882, found 302.1895.

(1*R*,2*S*,1'*R*,2'*R*)-2'-Hydroxycyclohexyl 2-phenylcyclohexane-1-carboxylate (8D): oil (25 mg, 14%); $[\alpha]^{23}_D$ −99.9° (c 0.9, $CHCl_3$); IR (neat) 3560, 1720, 1600, 1170 cm^{-1}; ^1H NMR δ 2.94 (2 H, m, H-1 and H-2), 3.16 (1 H, m, H-2'), 4.28 (1 H, ddd, J = 10.9, 8.9, 4.6 Hz, H-1'), 7.20–7.35 (5 H, m, Ar H); MS m/z 302 (M^+), 204, 98; HRMS for $C_{19}H_{26}O_3$ (M^+) calcd m/z 302.1882, found 302.1888.

Entry 9. (1*S*,2*R*,1'*R*,2'*R*)-2'-Hydroxycyclohexyl 2-butylcyclohexane-1-carboxylate (9C):[11] oil (100 mg, 59%); $[\alpha]^{22}_D$ −18.8° (c 1.3, $CHCl_3$); IR (neat) 3460, 1730, 1450, 1180 cm^{-1}; ^1H NMR δ 0.88 (3 H, t, J = 6.9 Hz, Me), 2.19 (1 H, br s, H-2), 2.60 (1 H, ddd, J = 7.9, 4.3, 4.0 Hz, H-1), 3.56 (1 H, m, H-2'), 4.59 (1 H, m, H-1'); MS m/z 282 (M^+), 184, 167, 98; HRMS for $C_{17}H_{30}O_3$ (M^+) calcd m/z 282.2195, found 282.2182.

(1*R*,2*S*,1'*R*,2'*R*)-2'-Hydroxycyclohexyl 2-butylcyclohexane-1-carboxylate (9D):[11] oil (49 mg, 29%); $[\alpha]^{22}_D$ −28.9° (c 1.4, $CHCl_3$); IR (neat) 3460, 1730, 1450, 1180 cm^{-1}; ^1H NMR δ 0.88 (3 H, t, J = 6.9 Hz, Me), 2.14 (1 H, br s, H-2), 2.60 (1 H, ddd, J = 7.9, 4.3, 4.0 Hz, H-1), 3.55 (1 H, m, H-2'), 4.59 (1 H, m, H-1'); MS m/z 282 (M^+), 184, 167, 98; HRMS for $C_{17}H_{30}O_3$ (M^+) calcd m/z 282.2195, found 282.2208.

Determination of Absolute Configuration. Representative Procedure for $LiAlH_4$ Reduction of 5–8. A THF solution (3 mL) of substrate (0.3 mmol) was added to a stirred suspension of $LiAlH_4$ (0.6 mmol) in THF (10 mL) at 0 °C. After the solution was stirred for 2 h at rt, several drops of 10% aqueous HCl were added at 0 °C, and the solution was dried (Na_2SO_4). Removal of the solvent in vacuo afforded an oily residue, which was purified by preparative TLC [hexane/AcOEt = 2:1 (v/v)].

(1*R*,2*R*)-2-Phenylcyclopentane-1-methanol [(1*R*,2*R*)-10]: oil (42 mg, 79% from **5A**), $[\alpha]^{23}_D$ −48.9° (c 1.2, MeOH), lit.[12] for (1*S*,2*S*)-**10** $[\alpha]^{23}_D$ +55.0° (c 1.0, MeOH); IR (neat) 3350, 1600, 765 cm^{-1}; ^1H NMR δ 2.68 (1 H, ddd, J = 9.4, 9.4, 7.9 Hz, H-2), 3.50 (1 H, dd, J = 10.6, 6.9 Hz, 1-C*H*), 3.63 (1 H, dd, J = 10.6, 5.3 Hz, 1-C*H*), 7.24 (5 H, m, Ar H); MS m/z 176 (M^+), 158, 143, 91.

(1*S*,2*S*)-2-Phenylcyclopentane-1-methanol [(1*S*,2*S*)-10]: oil [8.6 mg, 69% from **5B** (20 mg, 0.07 mmol)]; $[\alpha]^{24}_D$ +49.6° (c 0.5, MeOH).

(1*R*,2*R*)-2-Butylcyclopentane-1-methanol [(1*R*,2*R*)-11]: oil (36 mg, 78% from **6A**), $[\alpha]^{27}_D$ −56.1° (c 0.8, $CHCl_3$); IR (neat) 3350, 2940, 1460, 1020 cm^{-1}; ^1H NMR δ 0.89 (3 H, t, J = 6.6 Hz, Me), 3.44 (1 H, dd, J = 10.6, 7.6 Hz, 1-C*H*), 3.63 (1 H, dd, J = 10.6, 5.0 Hz, 1-C*H*); MS m/z 156 (M^+), 138, 125, 57; HRMS for $C_{10}H_{20}O$ (M^+) calcd m/z 156.1514, found 156.1525.

(1*R*,2*R*)-Methyl 2-Butylcyclopentane-1-carboxylate [(1*R*,2*R*)-16]. (a) Compound **6A** (200 mg) was converted to (1*R*,2*R*)-**16** by treatment with K_2CO_3–MeOH: oil (138 mg, 75%); $[\alpha]^{25}_D$ −49.5° (c 1.3, $CHCl_3$), lit.[13] $[\alpha]^{31}_D$ −50.0° (c 1.1, $CHCl_3$); ^1H NMR δ 0.87 (3 H, t, J = 6.5 Hz, Me), 1.0–2.5 (14 H, m), 3.64 (3 H, s, COOMe). (b) A mixture of **6B** and **6C** in the ratio of 1 to 3.3 (100 mg, 0.37 mmol) (Table I, entry 7) was converted to (1*R*,2*R*)-**16** (40 mg, 58% over all yield) via a sequence of base-catalyzed hydrolysis (1 N KOH), esterification with CH_2N_2, and epimerization at the C-1 position with MeONa in toluene: $[\alpha]^{31}_D$ −23.5° (c 1.2, $CHCl_3$) (47% optical purity).

(1*R*,2*R*)-2-Methylcyclopentane-1-methanol [(1*R*,2*R*)-12]: oil (24 mg, 70% from **7A**); $[\alpha]^{27}_D$ −50.4° (c 1.0, MeOH), lit.[12] for (1*S*,2*S*)-**12** $[\alpha]^{23}_D$ +52.5° (c 1.0, MeOH); IR (neat) 3350, 2950, 1450, 1020 cm^{-1}; ^1H NMR δ 1.01 (3 H, d, J = 6.3 Hz, 2-Me), 3.48 (1 H, dd, J = 10.6, 6.9 Hz, 1-C*H*), 3.65 (1 H, dd, J = 10.6, 5.0 Hz, 1-C*H*); MS m/z 96 (M^+ − 18), 83.

(1*R*,2*R*)-2-Phenylcyclohexane-1-methanol [(1*R*,2*R*)-13]: oil (41 mg, 72% from **8A**); $[\alpha]^{22}_D$ −49.8° (c 0.75, MeOH), lit.[12] for (1*S*,2*S*)-**13** $[\alpha]^{23}_D$ +51.0° (c 1.0, MeOH); IR (neat) 3300, 1600, 755 cm^{-1}; ^1H NMR δ 2.33 (1 H, ddd, J = 11.2, 11.2, 3.0 Hz, H-2), 3.22 (1 H, dd, J = 10.9, 6.3 Hz, 1-C*H*), 3.84 (1 H, dd, J = 10.9, 4.0 Hz, 1-C*H*), 7.25 (5 H, m, Ar H); MS m/z 190 (M^+), 172, 91.

(1*S*,2*S*)-2-Phenylcyclohexane-1-methanol [(1*S*,2*S*)-13]: oil [8.6 mg, 65% from **8B** (20 mg, 0.07 mmol)]; $[\alpha]^{20}_D$ +50.1° (c 0.4, MeOH).

(1*R*,2*R*)-2-Butylcyclohexane-1-methanol [(1*R*,2*R*)-14]:[11] oil [6.7 mg, 56% from **9A** (20 mg, 0.07 mmol)]; $[\alpha]^{18}_D$ −45.4° (c 0.5, $CHCl_3$); IR (neat) 3350, 2930, 1020 cm^{-1}; ^1H NMR δ 0.89 (3 H, t, J = 6.6 Hz, Me), 3.55 (1 H, dd, J = 10.6, 5.4 Hz, 1-C*H*), 3.70 (1 H, dd, J = 10.6, 2.5 Hz, 1-C*H*); MS m/z 170 (M^+), 152, 57. Anal. Calcd for $C_{11}H_{22}O$: C, 77.57; H, 13.03. Found: C, 77.69; H, 12.96.

(1*S*,2*R*)-2-Phenylcyclohexane-1-methanol [(1*S*,2*R*)-15]: 40 mg, 70% from **8C**; $[\alpha]^{22}_D$ +58.2° (c 1.5, $CHCl_3$); IR (Nujol) 3450, 1600, 700 cm^{-1}; ^1H NMR δ 2.95 (1 H, m, H-2), 3.42 (1 H, dd, J = 10.9, 5.8 Hz, 1-C*H*), 3.56 (1 H, dd, J = 10.9, 8.6 Hz, 1-C*H*), 7.25 (5 H, m, Ar H); MS m/z 190 (M^+), 172, 104, 91; HRMS for $C_{13}H_{18}O$ (M^+) calcd m/z 190.1358, found 190.1351.

(1*R*,2*S*)-2-Phenylcyclohexane-1-methanol [(1*R*,2*S*)-15]: 12 mg, 75% from **8D** (25 mg, 0.08 mmol); $[\alpha]^{23}_D$ −59.0° (c 0.8, $CHCl_3$); HRMS for $C_{13}H_{18}O$ (M^+) calcd m/z 190.1358, found 190.1365.

(1*S*,2*R*)-2-Phenylcyclohexane-1-carboxylic Acid [(1*S*,2*R*)-17]. Jones oxidation of (1*S*,2*R*)-**15** (35 mg, 0.18 mmol) afforded (1*S*,2*R*)-**17** (32 mg, 85%) as a colorless oil: $[\alpha]^{23}_D$ +73.3° (c 0.8, MeOH), lit.[14] $[\alpha]^{23}_D$ +71.1° (c 0.1, MeOH); ^1H NMR δ 2.34 (1 H, m), 2.86 (2 H, m, H-1 and H-2), 7.15–7.34 (5 H, m, Ar H); MS m/z 204 (M^+), 130, 117.

Acknowledgment. We gratefully acknowledge financial support from TERUMO LIFE SCIENCE FOUNDATION.

Registry No. **1**, 141845-93-4; **2**, 141845-94-5; **3**, 141753-26-6; **4**, 141753-27-7; **5A**, 131139-97-4; **5B**, 131233-20-0; **5C**, 141846-01-7; **5D**, 141846-02-8; **6A**, 131139-99-6; **6B**, 131233-22-2; **6C**, 141846-03-9; **6D**, 141846-04-0; **7A**, 131140-01-7; **7B**, 131233-23-3; **8A**, 131139-98-5; **8B**, 131233-21-1; **8C**, 141846-05-1; **8D**, 141845-96-7; **9A**, 131140-00-6; **9C**, 141845-97-8; **9D**, 141846-06-2; (1*R*,2*R*)-**10**, 123166-19-8; (1*S*,2*S*)-**10**, 97235-28-4; (1*R*,2*R*)-**11**, 141845-98-9; (1*R*,2*R*)-**12**, 64681-41-0; (1*R*,2*R*)-**13**, 123166-18-7; (1*S*,2*S*)-**13**, 37982-26-6; (1*R*,2*R*)-**14**, 141753-28-8; (1*R*,2*S*)-**15**, 141845-95-6; (1*S*,2*R*)-**15**, 141845-99-0; (1*R*,2*R*)-**16**, 141846-00-6; (1*S*,2*R*)-**17**, 113215-85-3; (1'*R*,2'*R*)-2'-hydroxycyclohexyl 7-chloro-2-heptenoate, 141753-29-9; $Cl(CH_2)_3CM{=}CHCOCl$, 72448-96-5; 1-cyclopentenyl formoyl chloride, 59253-90-6; 1-cyclohexenyl formoyl chloride, 36278-22-5; (*R*,*R*)-1,2-cyclohexanediol, 1072-86-2.

Supplementary Material Available: ^1H NMR spectra of **6–8A**, **6–7B**, **8–9C**, **8–9D**, (1*R*,2*R*)-**11**, (1*S*,2*R*)-**15**, and (1*R*,2*S*)-**15**, ^{13}C NMR spectra of **5A** and **5B**, and comments and reference ^1H NMR chemical shifts used in the NMR assignments of C-1 H in **5C**, **5D**, **6C**, and **6D** (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) Absolute stereochemistry of **5C,D** and **9A,C,D** was assumed by analogy of other products.

(12) Youssef, A. A.; Sharaf, S. M. *Egypt. J. Chem.* **1975**, *18*, 231.

(13) Okano, K. The Dissertation of the doctor degree, Kyushu Univ. Japan, 1989, p 24.

(14) Schulz, A. G.; Macielag, M.; Podhorez, D. E.; Suhadolnic, J. C. *J. Org. Chem.* **1988**, *53*, 2456.