Enzyme-Catalyzed Enantioselective and Regioselective Hydrolyses of (2*RS*,7*SR*)-2,7-Diacetoxybicyclo[2.2.1]heptane and (2*RS*,7*RS*)-2,7-Diacetoxybicyclo[2.2.1]heptane

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Enzyme-catalyzed hydrolyses of (2*RS*,7*SR*)-2,7-diacetoxybicyclo[2.2.1]heptane (**2**) and its (2*RS*,7*RS*)-isomer **6** occurred with regiospecificity combined with enantiomeric specificity to give the diacetates and the monoacetates in optically active forms, and the acetoxyl group located on the methano bridge in the diacetates was preferentially hydrolyzed to give the monoacetates. Treatment with lithium aluminum hydride converted (−)-**2** and (+)-(2*S*,7*R*)-2-acetoxybicyclo[2.2.1]heptan-7-ol into (+)-(2*R*,7*S*)-bicyclo[2.2.1]heptane-2,7-diol (**1**) and (−)-(2*S*,7*R*)-bicyclo[2.2.1]heptane-2,7-diol (**1**), respectively, from which both enantiomers of **1** with ⩾98% e.e. were readily obtained by further recrystallization. Similarly, (−)-(2*R*,7*R*)-2,7-diacetoxybicyclo[2.2.1]heptane (**6**) and (+)-(2*S*,7*S*)-2-acetoxybicyclo[2.2.1]heptan-7-ol (**6**) were converted into (+)-(2*R*,7*R*)-bicyclo-[2.2.1]heptane-2,7-diol (**5**) and (−)-(2*S*,7*S*)-bicyclo[2.2.1]heptane-2,7-diol (**5**), respectively. The absolute configurations of the products were determined by a chemical correlation with *exo*-2-acetoxybicyclo[2.2.1]heptane of known absolute configuration.

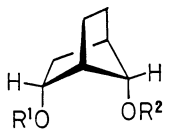
The use of enzymes as practical chiral catalysts for the preparations of optically active compounds has been well-documented.[1] Hydrolytic enzymes, which operate without requiring expensive coenzymes, are especially useful for the preparations of alcohols in optically active forms. Our continuing interests in the kinetic resolution with enzymes[2] prompted us to prepare optically active diols, which may serve as a chiral subunit for constructing chiral host molecules, by enzyme-catalyzed enantioselective hydrolysis of racemic diacetates. Recently, we reported the syntheses of bicyclo[3.3.1]nonane-2,6-diol and 3,3,7,7-tetramethylbicyclo[3.3.1]nonane-2,6-diol with high optical purity by enzyme-catalyzed enantioselective hydrolyses of the corresponding diacetates of C_2-symmetry and the preparations of chiral crown ethers using these diols as a chiral subunit.[3] An attractive additional advantage of enzymes is their ability to combine a different specificities in a single-step reaction. In this paper, we wish to report the enzyme-catalyzed enantioselective and regioselective hydrolyses of (2*RS*,7*SR*)-2,7-diacetoxybicyclo[2.2.1]heptane (**2**) and (2*RS*,7*RS*)-2,7-diacetoxybicyclo[2.2.1]heptane (**6**).

Results and Discussion

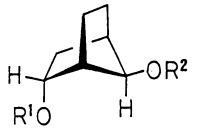
The substrates evaluated were the racemic diacetates **2** and **6**, which were derived from (2*RS*,7*SR*)-bicyclo[2.2.1]heptane-2,7-diol (**1**) and (2*RS*,7*RS*)-bicyclo[2.2.1]heptane-2,7-diol (**5**), respectively. Crandall[4] has reported that the acid-catalyzed hydration of *exo*-2,3-epoxybicyclo[2.2.1]heptane provided **1**, mp 179.5—181 °C and **5**, mp 204.5—206 °C and that performic acid hydroxylation of bicyclo[2.2.1]hept-2-ene gave also the mixture of **1**, **5**, and the other alcohols.

Treatment of bicyclo[2.2.1]hept-2-ene with 98% formic acid and 30% aqueous solution of hydrogen peroxide followed by hydrolysis with 30% aqueous solution of sodium hydroxide gave a mixture of diastereomeric diols. Chromatography of the mixture on silica gel followed by recrystallization gave **1** (25% yield), mp 178—179 °C and **5** (19% yield), mp 204—206 °C. Treatment of **1** and **5** with acetic anhydride and pyridine afforded **2** and **6**, respectively.

Enzyme-catalyzed hydrolyses of (±)-**2** and (±)-**6** were performed in 0.1 M (1 M=1 mol dm^{-3}) phosphate buffer solution at 25—30 °C, and terminated at, or closs to, the 50%-of-hydrolysis point. In every cases, the product was extracted with dichloromethane and purified by chromatography on silica gel. The results are summarized in Table 1.



(+)-1 R^1 = R^2 = H
(−)-2 R^1 = R^2 = Ac
(−)-3 R^1 = Ac R^2 = H
(+)-4 R^1 = H R^2 = Ac



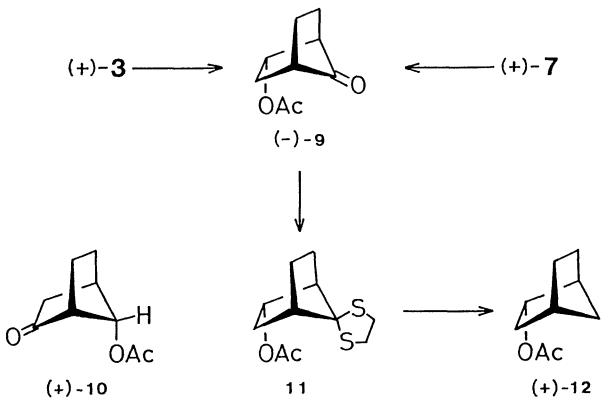
(+)-5 R^1 = R^2 = H
(−)-6 R^1 = R^2 = Ac
(−)-7 R^1 = Ac R^2 = H
(−)-8 R^1 = H R^2 = Ac

The next task was the determination of the structures of the monoacetates obtained by enzyme-catalyzed hydrolysis. Oxidation with chromium trioxide converted the (2*S*,7*R*)-isomer (+)-**3**, $[\alpha]_D$ +24.0°, which was obtained as a major monoacetate, into the ketone (−)-**9**, $[\alpha]_D$ −24.0°. The IR spectrum of **9** exhibiting the carbonyl absorption bands at 1780 and 1740 cm^{-1} indicated that a strained cyclic ketone moiety as well as an acetoxyl group was incorporated in **9**. Similarly, oxidation of the major (2*S*,7*S*)-monoacetate (+)-**7**, $[\alpha]_D$ +15.8°, gave also (−)-**9**, $[\alpha]_D$ −20.0°. The chemical conversions as well as the IR spectral data confirmed the structure of **9**, and clearly

Table 1. Enantioselective Hydrolysis of Racemic Diacetates

Substrate	Enzyme (pH)	Time[a]/h	Product (% isolated yield)	e.e.
(±)-**2**	PLE (8.0)	18	(−)-(1*S*,2*R*,4*R*,7*S*)-**2** (35%)	81%
			(+)-(1*R*,2*S*,4*S*,7*R*)-**3** (37%)	98%
			(+)-(1*S*,2*R*,4*R*,7*S*)-**4** (16%)	73%
(±)-**2**	Lipase A (7.7)	11	(+)-(1*R*,2*S*,4*S*,7*R*)-**2** (44%)	23%
			(−)-(1*S*,2*R*,4*R*,7*S*)-**3** (29%)	21%
			(−)-(1*R*,2*S*,4*S*,7*R*)-**4** (16%)	57%
(±)-**2**	CCL (7.7)	48	(−)-(1*S*,2*R*,4*R*,7*S*)-**2** (34%)	55%
			(+)-(1*R*,2*S*,4*S*,7*R*)-**3** (19%)	55%
			(+)-(1*S*,2*R*,4*R*,7*S*)-**4** (13%)	44%
(±)-**2**	Lipase N (6.9)	69	(−)-(1*R*,2*S*,4*S*,7*R*)-**1** (23%)	44%
			(−)-(1*S*,2*R*,4*R*,7*S*)-**2** (23%)	80%
			(+)-(1*R*,2*S*,4*S*,7*R*)-**3** (28%)	41%
			(+)-(1*S*,2*R*,4*R*,7*S*)-**4** (12%)	78%
(±)-**2**	Lipase F (6.9)	215	(−)-(1*R*,2*S*,4*S*,7*R*)-**1** (40%)	38%
			(−)-(1*S*,2*R*,4*R*,7*S*)-**2** (17%)	91%
			(+)-(1*R*,2*S*,4*S*,7*R*)-**3** (6%)	29%
			(+)-(1*S*,2*R*,4*R*,7*S*)-**4** (9%)	75%
(±)-**2**	Lipase R (7.7)	336	(−)-(1*S*,2*R*,4*R*,7*S*)-**2** (59%)	77%
			(+)-(1*R*,2*S*,4*S*,7*R*)-**3** (17%)	29%
			(+)-(1*S*,2*R*,4*R*,7*S*)-**4** (6%)	18%
(±)-**6**	PLE (8.0)	14	(−)-(1*S*,2*R*,4*R*,7*R*)-**6** (38%)	43%
			(+)-(1*R*,2*S*,4*S*,7*S*)-**7** (42%)	83%
(±)-**6**	Lipase A (7.7)	9	(−)-(1*S*,2*R*,4*R*,7*R*)-**6** (33%)	43%
			(+)-(1*R*,2*S*,4*S*,7*S*)-**7** (38%)	63%
			(−)-(1*S*,2*R*,4*R*,7*R*)-**2** (5%)	41%

a) The time at, or close to, the 50%-of-hydrolysis point.



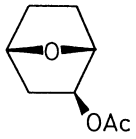
demonstrated that the acetoxyl group located on the methano bridge in **2** and **6** was preferentially hydrolyzed. Oxidation of the minor (2*R*,7*S*)-isomer (+)-**4**, $[\alpha]_D$ +34.2°, afforded (+)-**10**, $[\alpha]_D$ +1.58°, with the carbonyl absorption bands at 1750 and 1740 cm^{-1} in its IR spectrum.

The enantiomer excess (e.e.) measurements of the diols **1** and **5** were performed by HPLC on their bisphenylcarbamate derivatives which were prepared by treatment of the diols with phenyl isocyanate. On the basis of the e.e. values of **1** and **5**, conversions of the acetates into the diols with $LiAlH_4$ permitted us to calculate the e.e. values of the acetates as follows.

The e.e. value of (+)-**1**, $[\alpha]_D$ +10.5°, which was derived from (−)-**2**, $[\alpha]_D$ −64.2°, by $LiAlH_4$ reduction, was determined to be 81% and, eventually, the conversion revealed the e.e. value of (−)-**2** (81% e.e.). Similarly, the conversions of (+)-**3**, $[\alpha]_D$ +24.0°, and (+)-**4**, $[\alpha]_D$ +34.2°, into (−)-**1**, $[\alpha]_D$ −12.7°, and (+)-**1**, $[\alpha]_D$ +9.47°, respectively, determined the e.e. values of the monoacetates (+)-**3** and (+)-**4** to be 98% and 73%, respectively. In the cases of the (2*R*,7*R*)-isomer (−)-**6**, $[\alpha]_D$ −16.1°, (+)-**7**, $[\alpha]_D$ +15.8°, and (−)-**8**, $[\alpha]_D$ −4.38° were converted into (+)-**5**, $[\alpha]_D$ +0.430° (48% e.e.), (−)-**5**, $[\alpha]_D$ −0.749° (83% e.e.), and (+)-**5**, $[\alpha]_D$ +0.343° (41% e.e.), respectively, and the e.e. value of **5** was also determined by HPLC.

The optical purities of the diols **1** and **5** obtained by $LiAlH_4$ reduction as mentioned above were easily enriched to give both enantiomers of **1** and **5** with ⩾98% e.e. by further recrystallization, because both diols **1** and **5** are a crystalline solid.

Finally, the absolute configurations of the optically active products were established by a chemical correlation with the known compound **12**, whose absolute configuration has been reported by Berson.[5] Treatment of (−)-**9** with 1,2-ethanedithiol and boron trifluoride etherate in acetic acid gave **11**, the desulfurization of which with Raney nickel in refluxing ethyl acetate gave (+)-(1*S*,2*S*,4*R*)-**12**, whose structure was confirmed by comparisons of its IR spectrum and GLC behavior with those of the authentic sample.[6] The chemical conversion assigned the 1*R*,2*S*,4*S*-configuration to (−)-**9**. On the basis of this assignment, the correlation reactions mentioned above revealed unambiguously the absolute configurations of all the other products as illustrated in their structural formulas.[7]



We wish to comment briefly on the CD spectrum of (−)-**9**. The octant projection formula of (−)-(1*R*,2*S*,4*S*)-**9** exhibiting a negative Cotton effect around 300 nm is drawn as shown above and a sole substituent group of (−)-**9** lies in a lower-right octant in this formula. As Lightner[8] described that (+)-(1*R*,2*S*,4*S*)-*exo*-2-methylbicyclo[2.2.1]heptan-7-one exhibited a negative Cotton effect around 290 nm in its CD spectrum and the lone dissymmetric methyl perturber in this molecule lies not in (+)-back octant but in (−)-front octant in its octant projection diagram, the apparent "anti-octant" effect exhibited by (−)-**9** may be interpreted not as an "anti-octant" effect but as a normal octant effect with the substituent lying in a (−)-front octant.

A number of features in Table 1 deserve comment. With all enzymes examined here, the acetoxyl group located on the methano bridge in the diacetates **2** and **6** was preferentially hydrolyzed to yield **3** and **7** as the major monoacetate. Especially, hydrolysis of (±)-**6** with PLE occurred with complete regiospecificity for the acetoxyl group at C-7 to give (+)-**7** as a sole monoacetate. In the cases of hydrolysis of (±)-**2** catalyzed by PLE, CCL, and lipase A, elongation of the reaction time led to a formation of a small amount of **1**. In contrast with these hydrolyses, the monoacetate smoothly underwent further hydrolysis to give a significant amount of **1** by hydrolysis of (±)-**2** with lipase N and lipase F. Lipase F-catalyzed hydrolysis of (±)-**2** which was stopped after the 50%-of-hydrolysis point gave (−)-**1** with the same configuration as that of (+)-**3** in a moderate yield, and the e.e. value of (−)-**2** recovered in a low yield was enriched. A reversal of the stereochemistry was observed in lipase A-catalyzed hydrolysis of (±)-**2**, but, hydrolysis of (±)-**6** with lipase A gave the same products as those obtained by PLE-catalyzed hydrolysis.

Recently, 2,3-disubstituted bicyclo[2.2.1]heptene derivatives with high optical purity have been prepared by PLE-catalyzed hydrolysis of dimethyl (±)-(2*RS*,3*RS*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate.[9] As described above, hydrolyses of (±)-**2** and (±)-**6** catalyzed by PLE provided also a practical and facile method for the preparation of optically active bicyclo[2.2.1]heptane derivatives having functional groups at C-2 and C-7 positions, because the enzymatic hydrolyses occurred smoothly with regiospecificity as well as with high enantioselectivity.

Experimental

Melting points and boiling points are uncorrected. Infrared spectra were recorded on a Hitachi 260-10 spectrometer. Circular dichroism data were collected with a JASCO J-500 spectropolarimeter. Optical rotations were measured with a JASCO DIP-40 automatic polarimeter. ^{1}H NMR spectra were obtained from a JNM-MH-100 and chemical shift are reported in parts per million (δ) downfield from tetramethylsilane. Elemental analyses were determined on a Yanagimoto CHN-Corder, Type II.

Oxidation of Bicyclo[2.2.1]hept-2-ene. To a mixture of 98% formic acid (240 mL) and 30% aqueous solution of hydrogen peroxide (56 mL) was slowly added bicyclo[2.2.1]hept-2-ene (37.0 g, 0.394 mol) over a period of 2.5 h while the temperature of the reaction mixture was maintained at 40—45 °C. After the addition was completed, the resulting mixture was warmed at 40—45 °C for an additional 3 h. The formic acid and water were removed by distillation under reduced pressure. An ice cold solution of sodium hydroxide (32 g) in water (60 mL) was added to the residual viscous oil with care that the temperature of the mixture did not exceed 45 °C and then the mixture was stirred at room temperature for 12 h. The mixture was extracted with ethyl acetate and the extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. To the residue was added hexane and the solid precipitated was collected by filtration. The solid was chromatographed on silica gel. Early fractions eluted with dichloromethane-methanol (98/2 v/v) gave a solid, which was recrystallized from hexane-dichloromethane to provide **1** (12.6 g, 25% yield), subsequent fractions eluted with the same solvent gave a mixture (7.50 g) of **1** and **5** together with a small amount of unidentified diols, and latter fractions eluted with dichloromethane-methanol (95/5 v/v) gave a solid, recrystallization of which from dichloromethane gave **5** (9.58 g, 19% yield). (±)-**1**: mp 178—179 °C (lit,[3] mp 179.5—181 °C); IR (KBr) 3350, 1430, 1080, 1060, 1045 cm^{-1}.

Found: C, 65.40; H, 9.41% Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44%.

(±)-5: mp 204—206 °C (lit,[3] mp 204.5—205.5 °C); IR (KBr) 3300, 1350, 1090, 1070, 1000 cm^{-1}.

Found: C, 65.45; H, 9.40% Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44%.

(2*RS*,7*SR*)-2,7-Diacetoxybicyclo[2.2.1]heptane (2). A mixture of **1** (5.00 g, 0.0391 mol), acetic anhydride (12.0 g, 0.117 mol), and pyridine (30 mL) was stirred at room temperature for 12 h. After the reaction mixture was poured into ice water, it was extracted with ether. The extract was washed with dilute hydrochloric acid, aqueous solution of sodium hydrogencarbonate, and water, and dried ($MgSO_4$). After removal of the solvent, the residue was distilled to give **2** (6.96 g, 84% yield), bp 150—152 °C (13 mmHg (1 mmHg=133.322 Pa)); IR (neat film) 1740, 1365, 1250, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.1—2.5 (8H, m), 1.99 (3H, s), 2.04 (3H, s), 4.62 (1H, s), 4.6—4.8 (1H, m).

Found: C, 62.08; H, 7.57% Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60%.

(2*RS*,7*RS*)-2,7-Diacetoxybicyclo[2.2.1]heptane (6). By using the same procedure described above, reaction of **5** (1.88 g, 0.0147 mol) with acetic anhydride (6.00 g, 0.0588 mol) and pyridine (12 mL) gave **6** (2.92 g, 94% yield), bp 144—146 °C (20 mmHg); IR (neat film) 1740, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.2—2.4 (8H, m), 2.02 (3H, s), 2.04 (3H, s), 4.5—4.6 (1H, m), 4.94 (1H, s).

Found: C, 62.10; H, 7.55% Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60%.

Enzyme-Catalyzed Hydrolyses of Racemic Diacetates. Hydrolysis with PLE: A mixture of (±)-**2** (500 mg, 2.36 mol) and PLE (600 μL) (100 Units/mg, Boehringer Mannheim Gmbh Co.) in 0.1 M phosphate buffer solution (pH 8.0, 1600 mL) was stirred at 25—30 °C. The reaction was monitored by GLC and terminated at, or closs to, the 50%-of-hydrolysis point. After stirring for 18 h, the reaction mixture was extracted with dichloromethane and the extract was washed with water, dried ($MgSO_4$), and concentrated. Silica-gel column chromatography of the residue provided (−)-**2** (eluted with benzene-ether (98/2 v/v)), (+)-**4** (eluted with benzene-ether (95/5 v/v)), and (+)-**3** (eluted with benzene-ether (9/1 v/v)). (−)-**2**: 175 mg (35% Yield); $[\alpha]_D^{24}$ −64.2° (*c* 0.750, $CHCl_3$). (+)-**3**: 148 mg (37% yield); $[\alpha]_D^{24}$ +24.0° (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.0—2.2 (8H, m), 2.05 (3H, s), 3.9—4.0 (1H, m), 4.7—4.9 (1H, m).

Found: C, 63.11; H, 8.20%. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29%.

(+)-**4**: 64 mg (16% yield); $[\alpha]_D^{23}$ +34.2° (*c* 0.680, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.0—2.2 (8H, m), 2.07 (3H, s), 3.7—3.9 (1H, m), 4.4—4.9 (1H, m).

Found: C, 63.22; H, 8.19%. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29%.

Hydrolysis with Lipase A: Hydrolysis of (±)-**2** (500 mg) with lipase A (500 mg) (from *Aspergillus niger* (Amano pharmaceutical Co. Nagoya, Japan)) was carried out in 0.1 M phosphate buffer solution (pH 7.7, 1500 mL) for 11 h. The usual workup gave (+)-**2** (220 mg, 44% yield); $[\alpha]_D^{24}$ +18.2° (*c* 0.810, $CHCl_3$), (−)-**3** (116 mg, 29% yield); $[\alpha]_D^{24}$ −5.09° (*c* 0.825, $CHCl_3$), and (−)-**4** (64 mg, 16% yield); $[\alpha]_D^{24}$ −26.7° (*c* 1.05, $CHCl_3$).

Hydrolysis with CCL: Hydrolysis of (±)-**2** (500 mg) with CCL (10.0 g) (from *Candida cylindracea* (Sigma Chemical Co.)) was carried out in 0.1 M phosphate buffer solution (pH 7.7, 1500 mL) for 48 h. The usual workup gave (−)-**2** (170 mg, 34% yield); $[\alpha]_D^{25}$ −43.6° (*c* 1.01, $CHCl_3$), (+)-**3** (76 mg, 19% yield); $[\alpha]_D^{22}$ +13.3° (*c* 0.760, $CHCl_3$), and (+)-**4** (52 mg, 13% yield); $[\alpha]_D^{23}$ +20.6°.

Hydrolysis with Lipase N: Hydrolysis of (±)-**2** (500 mg) with lipase N (500 mg) (from *Rhizopus niveus* (Amano pharmaceutical Co.)) was carried out in 0.1 M phosphate buffer solution (pH 6.9, 1500 mL) for 69 h. The usual workup gave (−)-**1** (eluted with ether) (69 mg, 23%); $[\alpha]_D^{25}$ −5.71° (*c* 1.10, MeOH), (−)-**2** (115 mg, 23% yield); $[\alpha]_D^{26}$ −63.4° (*c* 0.922, $CHCl_3$), (+)-**3** (112 mg, 28% yield); $[\alpha]_D^{23}$ +9.94° (*c* 0.650, $CHCl_3$), and (+)-**4** (48 mg, 12% yield); $[\alpha]_D^{26}$ +36.5° (*c* 0.580, $CHCl_3$).

Hydrolysis with Lipase F: Hydrolysis of (±)-**2** (500 mg) with lipase F (500 mg) (from *Rhizopus javanicus* (Amano pharmaceutical Co.)) was carried out in 0.1 M phosphate buffer solution (pH 6.9, 1500 mL) for 215 h. The usual workup gave (−)-**1** (120 mg, 40% yield); $[\alpha]_D^{25}$ −4.93° (*c* 1.20, MeOH), (−)-**2** (85 mg, 17% yield); $[\alpha]_D^{25}$ −72.2° (*c* 0.940, $CHCl_3$), (+)-**3** (24 mg, 6% yield); $[\alpha]_D^{26}$ +7.03° (*c* 0.553, $CHCl_3$), and (+)-**4** (36 mg, 9% yield); $[\alpha]_D^{27}$ +35.1° (*c* 0.540, $CHCl_3$).

Hydrolysis with Lipase R: Hydrolysis of (±)-**2** (500 mg) with lipase R (500 mg) (from *Penicillium requeforti* (Amano pharmaceutical Co.)) was carried out in 0.1 M phosphate buffer solution (pH 7.7, 1480 mL) for 336 h. The usual workup gave (−)-**2** (295 mg, 59% yield); $[\alpha]_D^{27}$ −61.1° (*c* 1.05, $CHCl_3$), (+)-**3** (68 mg, 17% yield); $[\alpha]_D^{25}$ +7.03° (*c* 0.850, $CHCl_3$), and (+)-**4** (24 mg, 6% yield); $[\alpha]_D^{27}$ +8.42° (*c* 0.538, $CHCl_3$).

Hydrolysis with PLE: Hydrolysis of (±)-**6** (500 mg, 2.36 mmol) with PLE (600 μL) was carried out in 0.1 M phosphate buffer solution (pH 8.0, 1600 mL) for 14 h. The usual workup afforded (−)-**6** (190 mg, 38% yield); $[\alpha]_D^{28}$ −14.4° (*c* 0.765, $CHCl_3$), and (+)-**7** (168 mg, 42% yield); $[\alpha]_D^{26}$ +15.8° (*c* 0.923, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.1—2.3 (8H, m), 2.00 (3H, s), 4.22 (1H, br s), 4.5—4.6 (1H, m).

Found: C, 63.25; H, 8.18%. Calcd for $C_9H_{14}O_3$: C, 63.15; H, 8.29%.

Hydrolysis with Lipase A: Hydrolysis of (±)-**6** (500 mg) with lipase A (500 mg) was carried out in 0.1 M phosphate buffer solution (pH 7.7, 1500 mL) for 9 h. The usual workup afforded (−)-**6** (165 mg, 33% yield) $[\alpha]_D^{29}$ −14.4° (*c* 1.30, $CHCl_3$), (+)-**7** (152 mg, 38% yield); $[\alpha]_D^{28}$ +12.0° (*c* 0.985, $CHCl_3$), and (−)-**8** (20 mg, 5% yield); $[\alpha]_D^{28}$ −4.73° (*c* 0.530, $CHCl_3$), ^1H NMR ($CDCl_3$) δ=1.1—2.3 (8H, m), 2.02 (3H, s), 3.6—3.8 (1H, m), 4.98 (1H, br s).

Oxidation of (+)-(2*S*,7*R*)-2-Acetoxybicyclo[2.2.1]heptan-7-ol (3). To a solution of (+)-**3**, $[\alpha]_D$ +24.0°, (147 mg, 0.865 mmol) in acetone (30 mL) was added an excess of 8 N Jones reagent[10] with ice cooling. After the mixture was stirred at room temperature for 2 h, a small amount of isopropyl alcohol was added to the reaction mixture. The solution was decanted and concentrated under reduced pressure. The residue was diluted with water and extracted with ether. The extract was washed with aqueous solution of sodium hydrogencarbonate and water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel and fractions eluted with benzene provided (−)-**9** (81 mg, 56% yield); $[\alpha]_D^{29}$ −24.0° (*c* 1.48, $CHCl_3$); IR (neat film) 1780, 1740, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.5—2.4 (8H, m), 2.01 (3H, s), 4.8—4.9 (1H, m); CD (*c* 2.33×10^{-2}, 2,2,4-trimethylpentane) [θ] (nm) -5.28×10^2 sh (292), -5.67×10^2 (296), -5.49×10^2 (301), -4.49×10^2 sh (306).

Found: C, 64.35; H, 7.18%. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19%.

Oxidation of (+)-(2*S*,7*S*)-2-Acetoxybicyclo[2.2.1]heptan-7-ol (7). By using the same procedure described above, (+)-**7**, $[\alpha]_D$ +15.8°, (400 mg, 2.35 mmol) was converted into (−)-**9** (215 mg, 56% yield); $[\alpha]_D^{26}$ −20.0° (*c* 0.913, $CHCl_3$) as an oil after silica-gel chromatography. GLC behavior and IR and CD spectra of this specimen were in agreement with those of (−)-**9** derived from (+)-**3**.

Oxidation of (+)-(2*R*,7*S*)-7-Acetoxybicyclo[2.2.1]heptan-2-ol (4). Treatment of (+)-**4**, $[\alpha]_D$ +34.2°, (50 mg, 0.29 mmol) with an excess of Jones reagent in acetone gave (+)-**10** (29 mg, 63% yield); $[\alpha]_D^{25}$ +1.85° (*c* 0.720, $CHCl_3$) as an oil after silica-gel chromatography (eluted with benzene); IR (neat film) 1750, 1740 cm^{-1}.

Found: C, 64.30; H, 7.20%. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19%.

Lithium Aluminum Hydride Reduction of (−)-(2*R*,7*S*)-2,7-Diacetoxybicyclo[2.2.1]heptane (2). To a suspension of $LiAlH_4$ (950 mg, 25.0 mmol) in dry ether (30 mL) was added a solution of (−)-**2**, $[\alpha]_D$ −64.2°, (530 mg, 2.50 mmol) in dry ether (20 mL) and then the mixture was gently refluxed for 7 h. To a chilled reaction mixture was carefully added aqueous solution of ammonium chloride with ice cooling, and an inorganic solid was removed by filtration. The filtrate was washed with water and dried ($MgSO_4$). Removal of the solvent gave (+)-**1** (220 mg, 69% yield); $[\alpha]_D^{27}$ +10.5° (*c* 1.08, MeOH), which was recrystallized from dichloromethane-

cyclohexane to give **1** (105 mg); $[\alpha]_D^{28}$ +12.8° (*c* 1.01, MeOH). IR spectrum and GLC behavior of this specimen were in agreement with those of (±)-**1**.

To a mixture of (+)-**1**, $[\alpha]_D$ +10.5°, (20 mg, 0.16 mmol) and phenyl isocyanate (74 mg, 0.63 mmol) was added one drop of pyridine, and then the mixture was stirred at room temperature for 3 h. The resulting solid was washed with benzene to give the bisphenylcarbamate as a white solid. HPLC of this derivative was carried out on Simazu LC-6A using a chiral column (250×4.6 mm) packed with cellulose tris(3,5-dimethylphenylcarbamate) on silica gel[11] (hexane/ethanol 9/1) and showed that the e.e. value of (+)-**1**, $[\alpha]_D$ +10.5°, was 81%.

Lithium Aluminum Hydride Reduction of (−)-(2*R*,7*R*)-2,7-Diacetoxybicyclo[2.2.1]heptane (6). By using the same procedure described above, treatment of (−)-**6**, $[\alpha]_D$ −14.4°, (636 mg, 3.00 mmol) with $LiAlH_4$ (1.14 g, 30.0 mmol) in dry ether gave (+)-**5** (290 mg, 76% yield); $[\alpha]_D^{25}$ +0.386° (*c* 0.955, MeOH), which was recrystallized from dichloromethane-cyclohexane to give **5** (110 mg); $[\alpha]_D^{26}$ +0.884° (*c* 0.960, MeOH). IR spectra and GLC behavior of this specimen were in agreement with those of (±)-**5**.

HPLC of the bisphenylcarbamate derived from (+)-**5**, $[\alpha]_D$ +0.884°, determined the e.e. value of this specimen to be 98%.

Lithium Aluminum Hydride Reduction of (+)-(2*S*,7*R*)-2-Acetoxybicyclo[2.2.1]heptan-7-ol (3). By using the same procedure described above, treatment of (+)-**3**, $[\alpha]_D$ +24.0°, (160 mg, 0.941 mmol) with $LiAlH_4$ (380 mg, 10.0 mmol) in ether gave (−)-**1** (117 mg, 97% yield); $[\alpha]_D^{28}$ −12.7° (*c* 1.01, MeOH) (98% e.e.).

Lithium Aluminum Hydride Reduction of (+)-(2*R*,7*S*)-7-Acetoxybicyclo[2.2.1]heptan-2-ol (4). Treatment of (+)-**4**, $[\alpha]_D$ +34.2°, (60 mg, 0.35 mmol) with $LiAlH_4$ (150 mg, 3.95 mmol) in ether gave (+)-**1** (40 mg, 89% yield); $[\alpha]_D^{25}$ +9.47° (*c* 0.850, MeOH) (73% e.e.).

Lithium Aluminum Hydride Reduction of (+)-(2*S*,7*S*)-2-Acetoxybicyclo[2.2.1]heptan-7-ol (7). Treatment of (+)-**7**, $[\alpha]_D$ +15.8°, (180 mg, 1.06 mmol) with $LiAlH_4$ (418 mg, 11.0 mmol) in ether gave (−)-**5** (105 mg, 77% yield); $[\alpha]_D^{28}$ −0.749° (*c* 0.708, MeOH) (83% e.e.).

Lithium Aluminum Hydride Reduction of (−)-(2*R*,7*R*)-7-Acetoxybicyclo-[2.2.1]heptan-2-ol (8). Treatment of (−)-**8**, $[\alpha]_D$ −4.38°, (25 mg, 0.15 mmol) with $LiAlH_4$ (58 mg, 1.5 mmol) in ether gave (+)-**5** (16 mg, 85%), $[\alpha]_D^{27}$ +0.343° (*c* 0.600, MeOH) (41% e.e.).

(+)-exo-2-Acetoxybicyclo[2.2.1]heptane (12). A mixture of (−)-**9** (110 mg, 0.655 mmol), 1,2-ethanedithiol (0.5 mL), boron trifluoride etherate (0.5 mL), and acetic acid (2 mL) was stirred at room temperature for 24 h. The reaction mixture was poured into ice water and extracted with ether. The extract was washed with aqueous solution of potassium carbonate and water, dried ($MgSO_4$), and concentrated under reduced pressure. The residual oil was dissolved in ethyl acetate (15 mL) and an excess of Raney nickel was added to the solution. After the mixture was refluxed for 12 h, the solid was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel and fractions eluted with pentane gave (+)-**12** (55 mg, 55% yield); $[\alpha]_D^{25}$ +11.5° (*c* 1.15, $CHCl_3$). Its IR spectrum and GLC behavior were in agreement with those of the authentic sample prepared according to Berson's procedure.[6]

References

1) M. A. Findeis and G. M. Whitesides, *Annu. Rep. Med. Chem.*, **19**, 263 (1984); G. M. Whitesides and C.-H. Wong, *Angew. Chem., Int. Ed. Engl.*, **24**, 617 (1985); R. Porter and S. Clark, "Enzymes in Organic Synthesis," Pitman, London (1985); J. Tramper, H. C. van der Plas, and P. Linko, "Biocatalysts in Organic Syntheses," Elsevier, Amsterdam, Oxford, New York, Tokyo (1985); M. P. Schneider, "Enzymes as Catalysts in Organic Synthesis," Reidel, Dordrecht (1986); J. B. Jones, *Tetrahedron*, **42**, 3351 (1986) and references cited therein.

2) M. Nakazaki, H. Chikamatsu, K. Naemura, M. Nishino, H. Murakami, and M. Asao, *J. Chem. Soc., Chem. Commun.*, **1978**, 667; M. Nakazaki, H. Chikamatsu, K. Naemura, Y. Hirose, T. Shimizu, M. Asao, *ibid.*, **1978**, 668; M. Nakazaki, H. Chikamatsu, K. Naemura, M. Nishino, H. Murakami, and M. Asao, *J. Org. Chem.*, **44**, 4588 (1979); M. Nakazaki, H. Chikamatsu, K. Naemura, Y. Sasaki, and T. Fujii, *J. Chem. Soc., Chem. Commun.*, **1980**, 626; M. Nakazaki, K. Naemura, H. Chikamatsu, M. Iwasaki, and M. Hashimoto, *Chem. Lett.*, **1980**, 1571; K. Naemura, T. Katoh, H. Chikamatsu, and M. Nakazaki, *ibid.*, **1984**, 1371.

3) K. Naemura, T. Matsumura, M. Komatsu, Y. Hirose, and H. Chikamatsu, *J. Chem. Soc., Chem. Commun.*, **1988**, 240.

4) J. K. Crandall, *J. Org. Chem.*, **29**, 2830 (1964).

5) J. A. Berson, J. S. Walia, A. Remanik, S. Suzuki, P. R. Warnhoff, and D. Willner, *J. Am. Chem. Soc.*, **83**, 3986 (1961).

6) J. A. Berson and S. Suzuki, *J. Am. Chem. Soc.*, **81**, 4088 (1959); J. A. Berson and D. A. Ben-Efraim, *ibid.*, **81**, 4094 (1959).

7) The structural formulas in this paper with (+) and (−) rotational specifications are illustrated in their absolute configuration.

8) D. A. Lightner and D. E. Jackman, *J. Am. Chem. Soc.*, **96**, 1938 (1974).

9) J. van der Eycken, M. Vandewalle, G. Heinemann, K. Laumen, M. P. Schneider, J. Kredel, and J. Sauer, *J. Chem. Soc., Chem. Commun.*, **1989**, 306.

10) J. Meinwald, J. Crandall, and W. E. Hymans, "Organic Syntheses," Wiley, New York (1973); Coll. Vol. V, p. 868.

11) Y. Okamoto, M. Kawashima, and K. Hatada, *J. Chromatogr.*, **363**, 173 (1986).