Enantioselective Synthesis of (−)-Curcumanolide A Using Enzymatic Transesterification of *meso*-Spirodiol

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meso-Spirodiol **12** and spirodiacetate **13** were stereoselectively prepared using π-face selective Grignard addition to norbornanone **7**. Asymmetric transesterification of *meso*-diol and hydrolysis of *meso*-diacetate were studied using lipases. *Pseudomonas fluorescens* lipase-catalyzed transesterification of *meso*-diol **12** afforded the monoacetate (−)-**21** of high enantiomeric excess (>99% ee). The formal synthesis of (−)-curcumanolide A has been achieved from the optically active (−)-**21**.

Introduction

Curcumanolide A (**1**)[1] is a natural product, isolated from the crude drug zedoary and other *Curcuma* species, and possesses the unique structure of three contiguous chiral centers and a spirolactone moiety. In 1992, Kato *et al.* reported the racemic synthesis of curcumanolide A starting from homogeranyl cyanide in 3% overall yield.[2] When we started our study of the enantioselective synthesis of curcumanolide A, no report concerning the enantioselective synthesis or the absolute configuration of curcumanolide A has been made. Therefore, we envisioned being able to synthesize both enantiomers of this target molecule starting from the *meso*-compound. While we were studying the synthesis of curcumanolide A, Honda *et al.* reported the enantiospecific first synthesis of this molecule starting from (−)-carvone and determined the absolute configuration of (−)-curcumanolide A as 5*R*,6*S*,9*S*.[3] In this paper, we describe the formal synthesis of (−)-curcumanolide A by way of π-face selective Grignard addition to norbornanone **7** and lipase-catalyzed asymmetric transesterification of *meso*-spirodiol.

Results and Discussion

Retrosynthetic Analysis. Curcumanolide A (**1**) would be prepared from Kato's intermediate diol **2**.[2] Compound **2** would be prepared from chiral monoacetates (**3a** or **3b**), and the monoacetates might be prepared from *meso*-diacetate **4** by enzymatic hydrolysis or *meso*-diol **5** by enzymatic transesterification. The ozonolysis of olefin in the norbornene skeleton was thought to be a good method for the preparation of *meso*-compounds (**4** and **5**) in a stereoselective manner. 7-Substituted norbornene derivative **6** would be prepared from norbornanone **7** by π-face selective Grignard addition through remote electronic perturbation of the ketone by the alkene.

Synthesis of Substrates for Enzymatic Reaction. *meso*-Spirodiacetate **9** was first prepared from norbornanone **7**,[4] by protection of the carbonyl function as ethylene acetal (89%),[5] followed by ozonolysis of olefin, reduction of aldehyde, and acetylation of the hydroxy functions (three-step, 59%). Compound **9** was thought to be a good substrate for the preliminary study of enzymatic hydrolysis for the synthesis of curcumanolide A.

Stereoselective preparation of 7-substituted norbornene **10** was achieved by π-face selective Grignard addition to norbornanone.[6] By the treatment with Grignard reagent prepared from 2-(2-bromoethyl)-1,3-dioxolane in THF at 0 °C, norbornanone **7** was converted into adduct **10** in 97% yield. The π-face selectivity of adduct **10** was determined to be 25 to 1, because the ^{1}H NMR spectrum showed the olefin signals at δ 5.99 (t, J = 2.1 Hz) and δ 6.13 (t, J = 2.1 Hz) in the ratio of 25 to 1. By the treatment with Jones reagent at 0 °C, a spontaneous three-step sequence [(i) deacetalization; (ii) oxidation; (iii) lactonization] occurred in one pot, and the adduct **10** was converted into lactone **11** in 88% yield. Ozonolysis of **11** at −78 °C, followed by reduction with $NaBH_4$, afforded *meso*-spirodiol **12** in 64% yield, and subsequent acetylation with Ac_2O−pyridine gave *meso*-spirodiacetate **13** in 97% yield. The stereochemistry of *meso*-diol **12** was determined to be 5*s*,6*R*,9*S* based on the NOESY ^{1}H NMR spectrum. The NOEs were observed between the methylene proton signals δ 3.73 (m, 4H) at the hydroxymethyl function and the β-methylene proton signals δ 2.21 (t, J = 8.2 Hz, 2H) at the lactone function. This meant that the carbonyl function of norbornanone **7** was reacted with Grignard reagent from the olefin site through remote electronic effect. This result was in accord with Mehta's report.[6]

meso-Diacetate **15a** was also prepared from the adduct **10**. By deprotection of the acetal function with AcOH−H_2O−THF at 50 °C, reduction of aldehyde with $NaBH_4$, and protection of alcohol with MOMCl, the adduct **10** was converted into MOM-protected norbornene **14** in 43% yield. Compound **14** was converted into *meso*-diacetate **15a** by ozonolysis of olefin, reduction with $NaBH_4$, and acetylation with Ac_2O−pyridine in 31% yield.

Enzymatic Reaction of *meso*-Compounds. Preliminary enzymatic hydrolysis of *meso*-spirodiacetate **9** was studied using three kinds of lipases, such as *Rhizo-*

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(1) (a) Shiobara,Y.; Asakawa, Y.; Kodama, K.; Yasuda, K.; Takemoto, T. *Phytochemistry* **1985**, *24*, 2629. (b) Gao, J.-F.; Ohkura, T.; Harimaya, K.; Higuchi, M.; Kawamata, T.; Ying, W.-X.; Iitaka, Y. *Chem. Pharm. Bull.* **1986**, *34*, 5122.

(2) Hirukawa, T.; Oguchi, M.; Yoshikawa, N.; Kato, T. *Chem. Lett.* **1992**, 2343.

(3) Honda, T.; Ishige, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3567.

(4) Gassman, P. G.; Marshall, J. L. *Org. Synth.* **1968**, *48*, 25 and 68.

(5) (a) Gassman, P. G.; Macmillan, J. G. *J. Am. Chem. Soc.* **1969**, *91*, 5527. (b) Gassman, P. G.; Schaffhausen, J. G. *J. Org. Chem.* **1978**, *43*, 3214.

(6) Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *J. Org. Chem.* **1993**, *58*, 1734.

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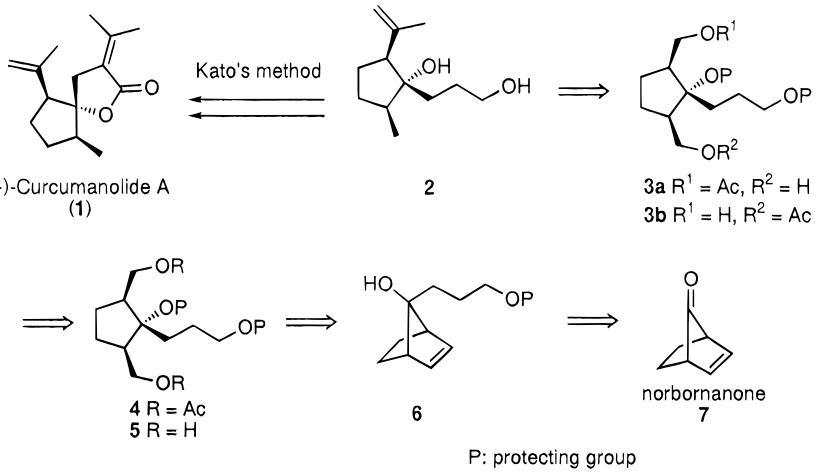
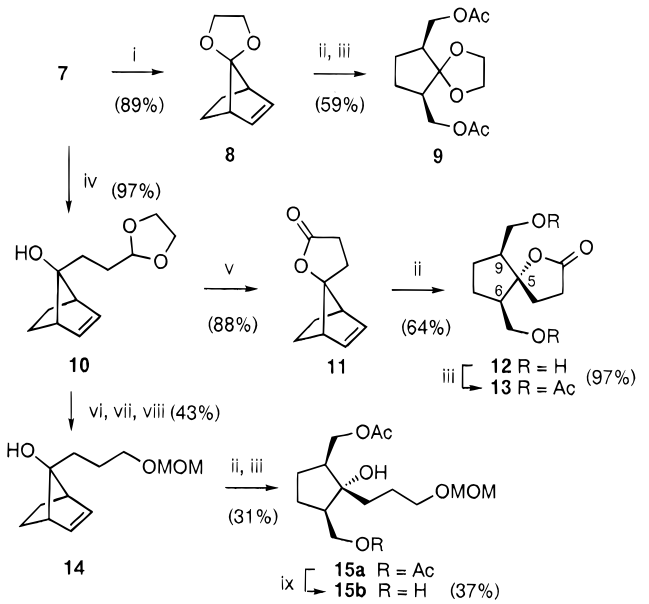
Scheme 1. Retrosynthetic Analysis of (−)-Curcumanolide A



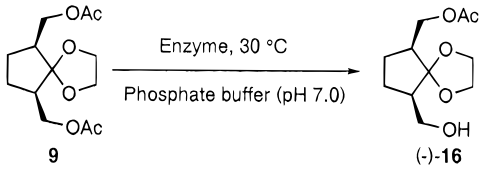
Scheme 2[a]



[a] Reagents: (i) ethylene glycol, *p*-TsOH; (ii) O_3 and then $NaBH_4$; (iii) Ac_2O, pyridine; (iv) 2-(2-bromoethyl)-1,3-dioxolane, Mg, THF; (v) Jones reagent; (vi) AcOH−THF-H_2O, 50 °C; (vii) $NaBH_4$; (viii) MOMCl; (ix) PFL.

pus delemar lipase (RDL),[7,8] *Pseudomonas fluorescens* lipase (PFL), and porcine pancreatic lipase (PPL).[9,10] The enzymatic hydrolysis was performed in 0.1 M phosphate buffer (pH 7.0) at 30 °C and was terminated when a spot of the diol appeared on the TLC plate. The results of the hydrolyses are summarized in Table 1.

Table 1. Enzymatic Hydrolysis of *meso*-Diacetate 9



entry	enzyme	reaction time (h)	monoacetate % yield	monoacetate % ee	recovery (%)
1	RDL	16	91	>99	–
2	PFL	120	51	82	40
3	PPL	48	72	33	20

The enantiomeric excess (% ee) of the hydrolyzed products was determined by ^{1}H NMR spectra after conversion into the corresponding Mosher's esters[(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA)].[11] The ^{1}H NMR spectra of (+)-MTPA ester derived from (±)-**16** showed the methoxy proton signals at δ 3.53 (m, 1.5 H) and 3.56 (m, 1.5 H), while the corresponding signal from (−)-**16** hydrolyzed by RDL was observed at δ 3.53 (m, 3 H) only. The specific rotations of all the monoalcohols obtained showed a minus sign. We previously reported the asymmetric hydrolyses of *meso*-1,3-bis(acetoxymethyl)cyclopentane derivatives using RDL.[7] In the case of *meso*-spirodiacetate **9**, hydrolysis using RDL also afforded the monoalcohol of high enantiomeric excess in good yield (91% yield, >99% ee). Hydrolysis by PFL afforded the monoalcohol of moderate enantiomeric excess (82% ee), and hydrolysis by PPL afforded the monoalcohol of low enantiomeric excess (33% ee). The absolute configuration of (−)-**16** was unambiguously determined by chemical correlation as shown in Scheme 3. (1*S*,2*R*)-2-(Ethoxycarbonyl)cyclopentanol **17** was converted to the 2-(acetoxymethyl)cyclopentanol **18** by Li-AlH_4 reduction and acetylation of primary alcohol with Ac_2O in 55% yield. Oxidation of the secondary alcohol with PCC (66%), followed by protection of the carbonyl function with ethylene glycol, afforded the ethylene acetal (**20**, 72%). The specific rotation of ethylene acetal **20** showed −13.4°. The monoalcohol (−)-**16** was also converted into the ethylene acetal **20** in 23% yield by oxidation with PCC and subsequent decarbonylation with $RhCl(PPh_3)_3$ in refluxing benzene. The specific rotation

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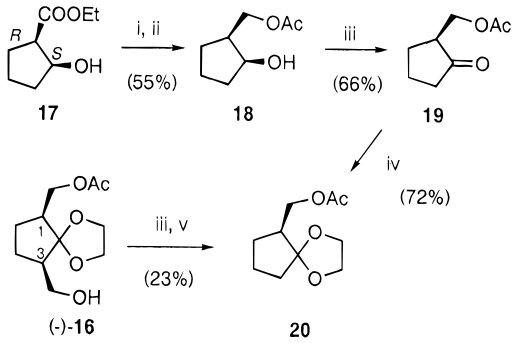
(9) (a) Xie, Z.-F. *Tetrahedron: Asymm.* **1991**, *2*, 733. (b) Suemune, H. *Yakugaku Zasshi* **1992**, *112*, 432. (c) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994. (d) Hirose, Y. *Faruaw* **1996**, *32*, 1075.

(10) (a) Tanaka, M.; Yoshioka, M.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1992**, 1454. (b) *P. fluorescens* lipase (PFL) has been reclassified as *P. cepacia* lipase (PCL). However, we use the former name for the sake of uniformity with previous results.

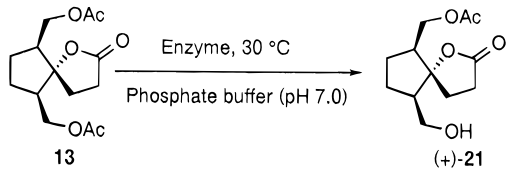
(11) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

Scheme 3[a]



[a] Reagents: (i) $LiAlH_4$; (ii) Ac_2O, pyridine; (iii) PCC; (iv) PPTS, ethylene glycol; (v) $RhCl(PPh_3)_3$, benzene.

Table 2. Enzymatic Hydrolysis of *meso*-Diacetate 13



entry	enzyme	reaction time (h)	monoacetate % yield	monoacetate % ee	recovery (%)
1	RDL	214	63	86	22
2	PFL	215	49	75	29
3	PPL	121	65	23	14

of this material showed −16.9°. Based on the comparison of specific rotation, the absolute configuration of (−)-**16** was determined to be 1*S*,3*R*. The result was in accordance with our RDL model.[7] These results encouraged us to study the synthesis of (−)-curcumanolide A using enzymatic hydrolysis.

Asymmetric hydrolysis of *meso*-diacetate **15a** was first attempted using three kinds of lipases. However, no hydrolysis proceeded for a few days. This suggests that the *cis*-oriented bulky MOM-oxypropyl substituent prevented lipases from approaching both of the acetyl functions. In the case of using RDL as a catalyst, prolongation of the reaction time (20 days) afforded a small amount of monoacetate **15b** of low enantiomeric excess (32% ee).

Therefore, hydrolysis of *meso*-spirodiacetate **13** was next tried. The results are summarized in Table 2. The specific rotations of all the hydrolyzed products indicated a plus sign. The enantiomeric excess of the hydrolyzed products was determined by ^{1}H NMR spectra of the corresponding (+)-MTPA esters. The ^{1}H NMR spectra of (+)-MTPA ester derived from racemic (±)-**21** showed the methoxy proton signals at δ 3.55 (br s) and 3.51 (br s) in the ratio of 1 to 1, while the ^{1}H NMR spectra of (+)-MTPA ester derived from the enzymatic hydrolyzed product (+)-**21** showed the corresponding signals at δ 3.55 (br s) and 3.51 (br s) in a different ratio. Unfortunately, the hydrolysis of **13** by lipases required prolonged reaction time (121−215 h), and the enantiomeric excess of the products was not satisfactory. The maximum enantiomeric excess of (+)-**21** (86% ee) was obtained in the case of using RDL. Hydrolysis by PFL afforded the monoacetate of moderate enantiomeric excess (75% ee) and hydrolysis by PPL afforded the monoacetate of low enantiomeric excess (23% ee). The absolute configuration of (+)-**21** was assumed to be 5*R*,6*S*,9*R*, based on our RDL box-type model[7] and the result of absolute configuration of (−)-**16** in the preliminary experiment.

For the improvement of enantiomeric excess, the lipase-catalyzed transesterification of *meso*-spirodiol **12** was examined using three kinds lipases aforementioned. It was anticipated that the transesterification of *meso*-diol **12** would afford monoacetate (−)-**21**, which was an enantiomer of hydrolyzed product (+)-**21**, because the transesterification of *meso*-diol and the hydrolysis of *meso*-diacetate using the same lipase are complementary. Among the lipases used, PFL-catalyzed transesterification of **12** in vinyl acetate proceeded smoothly to afford the monoacetate (−)-**21** of 94% ee in 48% yield. Furthermore, the same reaction by PFL in *n*-octane−vinyl acetate (3:1) afforded the enantiomerically pure monoacetate (−)-**21** in 56% yield (Scheme 4).

Formal Synthesis of (−)-Curcumanolide A. The product obtained by transesterification was an enantiomer of (+)-**21**; therefore, the absolute configuration of (−)-**21** was assumed to be 5*S*,6*R*,9*S*. Consequently, it was necessary for the acetoxymethyl function at C6-position in (−)-**21** to be converted into the methyl function for the synthesis of (−)-curcumanolide A. The conversion of stereochemistry in (−)-**21** with a (9*S*)-hydroxymethyl group into **23** with a (6*R*)-hydroxymethyl group was achieved in 88% yield by the protection of alcohol with TBDMSCl and subsequent solvolysis of the acetyl function with K_2CO_3 in MeOH. By substitution of alcohol with iodide, and subsequent reduction with zinc in AcOH, the alcohol **23** was converted to the lactone **25** in 63% yield. The isopropenyl function of curcumanolide A was thought to be introduced by the oxidation of alcohol to carboxylic acid, methylation, and dehydration. Protection of the lactone moiety was needed to introduce the isopropenyl function; therefore, the lactone **25** was converted into the diol **28** in 90% yield by the reduction of lactone with super hydride, the protection of primary alcohol with Ac_2O−pyridine, and deprotection of TBDMS.

Oxidation of the primary alcohol with Jones reagent, followed by esterification with CH_2N_2, afforded the methyl ester **29** in low yield. The isolated yield of **29** was improved to 56% by the adoption of PtO_2−O_2 oxidation.[12] The ester **29** was converted into the triol **30** by methylation with MeLi in 47% yield. Oxidation of **30** with PDC in DMF afforded the lactone **31** in 79% yield. The spectroscopic data of **31** were identical with the reported values. The specific rotation of **31** showed $[\alpha]^{24}_D$ −21.48, which is the same as that of Honda's reported $[\alpha]_D$ −21.39.[3] This means that (−)-**21** has the absolute configuration of 5*S*,6*R*,9*S*, and the stereochemistry of (+)-**21** is 5*R*,6*S*,9*R*, which are in accord with the RDL box-type model and our assumptions. Thus, the formal synthesis of (−)-curcumanolide A has been completed.

Conclusion

meso-Spirodiol **12** and spirodiacetate **13** were prepared stereoselectively from norbornanone. Enzymatic hydrolysis of **13** in aqueous solution and transesterification of **12** in organic solvent proceeded in enantioselective manner to afford the optically active monoacetates. The monoacetate (−)-**21** obtained by PFL-catalyzed transesterification was used for the formal synthesis of (−)-curcumanolide A. The strategy described here would be

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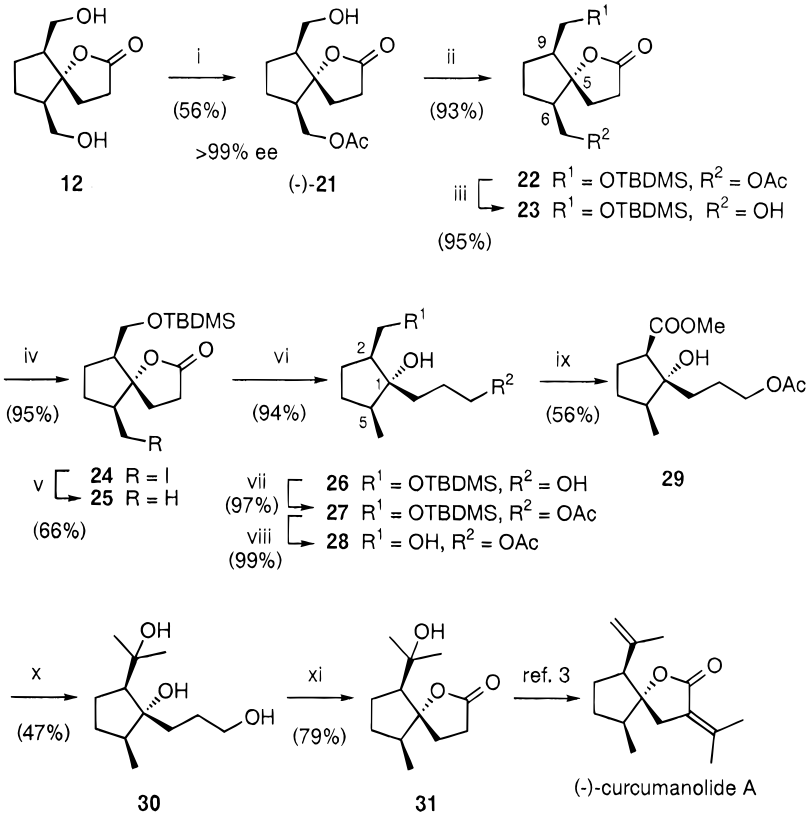
Scheme 4[a]



[a] Reagents: (i) PFL, *n*-octane−vinyl acetate (3:1); (ii) TBDMSCl, imidazole, DMF; (iii) K_2CO_3, MeOH; (iv) I_2, PPh_3; (v) Zn, AcOH; (vi) $LiEt_3BH$; (vii) Ac_2O, pyridine; (viii) TBAF, THF; (ix) PtO_2, O_2 and then CH_2N_2; (x) MeLi, THF; (xi) PDC, DMF.

useful for the enantioselective synthesis of natural products having a spiro skeleton and/or a five-membered ring.

Experimental Section

^{1}H NMR spectra were determined at 270 MHz unless otherwise noted. For O_3 oxidation, an Ishii ozone generator (7,800 V, O_2 flow rate; 0.5 mL/min) was used. Et_2O was distilled from Na/benzophenone before use. Benzene and CH_2Cl_2 were distilled from P_2O_5. Vinyl acetate (monomer) was purchased from Tokyo Kasei Corp., PPL (Type II) was purchased from Sigma Corp., RDL (EC 3.1.1.3) was purchased from Seikagaku Kogyo Corp. (Japan), and PFL (Amano PS)[10] was given courtesy of Amano Pharmaceutical Corp. (Japan), and all were used as received. Norbornanone **7** was prepared according to Marshall's methods,[4] and compound **17** was given from Takeda Pharmaceutical Corp. (Japan).

2-Norbornen-7-one Ethylene Acetal (8).[5] A mixture of norbornanone **7** (600 mg, 5.56 mmol), *p*-toluenesulfonic acid (150 mg, 0.88 mmol), and ethylene glycol (500 mg, 8.1 mmol) in benzene (40 mL) was refluxed for 4 h. After being cooled to room temperature, the mixture was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 5% EtOAc in hexane afforded **8** (755 mg, 90%) as a colorless oil: IR (neat) 3075, 2950, 1310, 1200 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 6.18 (t, J = 2.2 Hz, 2H), 3.92 (dd, J = 4.4, 10.0 Hz, 2H), 3.83 (dd, J = 4.4, 10.0 Hz, 2H), 2.53 (m, 2H), 1.90 (dm, J = 10.5 Hz, 2H), 0.97 (dd, J = 3.4, 10.5 Hz, 2H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 134.2, 125.3, 64.9, 64.5, 45.5, 22.8; EIMS *m*/*z* 152 (M^+, 100), 79 (68).

***cis*-2,2-(Ethylenedioxy)cyclopentane-1,3-dimethanol Diacetate (9).** Ozone gas was bubbled into a solution of **8** (1.34 g, 8.82 mmol) in MeOH (15 mL) and CH_2Cl_2 (12 mL) at −78 °C until the color of solution become slightly blue. $NaBH_4$ (400 mg, 10.6 mmol) was added portionwise to the reaction mixture. The reaction mixture was gradually warmed to 0 °C, and then acetone (5 mL) was added to destroy the excess reagent. The mixture was evaporated *in vacuo* to leave an oily residue, which was dissolved in pyridine (20 mL) and Ac_2O (10 mL), and the whole was stirred overnight. The reaction mixture was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, and then dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20% EtOAc in hexane afforded **9** (1.42 g, 59%) as a colorless oil: IR (neat) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.09 (dd, J = 6.9, 11.0 Hz, 2H), 4.04 (dd, J = 7.2, 11.0 Hz, 2H), 3.97 (dd, J = 5.7, 9.2 Hz, 2H), 3.94 (dd, J = 5.7, 9.2 Hz, 2H), 2.39 (m, 2H), 2.04 (s, 6H), 1.87 (m, 2H), 1.47 (m, 2H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 170.9, 116.9, 66.3, 65.1, 63.7, 46.3, 24.9, 21.0; EIMS *m*/*z* 272 (M^+, 5), 230 (4), 213 (41), 153 (100); FAB(+)HRMS calcd for $C_{13}H_{20}O_6$ (M^+) 272.1260, found 272.1266.

***syn*-[2-(1,3-Dioxolan-2-yl)ethyl]bicyclo[2.2.1]hept-2-en-*anti*-7-ol (10).** A solution of 2-(2-bromoethyl)-1,3-dioxolane (7.04 g, 38.9 mmmol) in THF (15 mL) was added dropwise to the stirred mixture of Mg (1.03 g, 42.4 mmol) in THF (45 mL), and the mixture was sonicated for 1 h at room temperature. Then, the mixture was cooled to 0 °C, and a solution of **7** (2.12 g, 19.6 mmol) in THF (10 mL) was added dropwisely. After being stirred for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and the solution was extracted with Et_2O and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (10% EtOAc in hexane) to give **10** (4.01 g , 97%) as colorless crystals: mp 64−65 °C; IR (Nujol) 3460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.99 (t, J = 2.1 Hz, 2H), 4.86 (t, J = 4.3 Hz, 1H), 4.04−4.82 (m, 4H), 2.56 (br s, 1H), 2.42 (m, 2H), 1.99 (dm, J = 11.0 Hz, 2H), 1.70−1.90 (m, 4H), 0.96 (dd, J = 3.6, 11.0 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 135.2, 104.6, 91.9, 64.9, 48.6, 30.0, 26.2, 23.3; EIMS *m*/*z* 210 (M^+, 25), 191 (9), 149 (100); FAB-(+)HRMS calcd for $C_{12}H_{18}O_3$ (M^+) 210.1256, found 210.1249.

***anti*-2′-Oxa-3′-oxospiro[bicyclo[2.2.1]hept-2-ene-7,1′-cyclopentane] (11).** Jones reagent was added dropwise to the stirred solution of **10** (1.07 g, 5.09 mmol) in acetone (50 mL) at room temperature until the solution showed a red color. The reaction was quenched with 2-propanol, and then acetone was evaporated. The solution was diluted with water, extracted with Et_2O, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (10% EtOAc in hexane) to give **11** (737 mg , 88%) as colorless crystals: mp 55−56 °C; IR (Nujol) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.04 (t, J = 2.1 Hz, 2H), 2.63 (m, 2H), 2.50 (t, J = 8.4 Hz, 2H), 2.21 (t, J = 8.4 Hz, 2H), 2.02 (dm, J = 11.6, 2H), 1.08 (dd, J = 3.6, 11.6 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 176.8, 134.2, 100.2, 48.3, 29.3, 25.4, 23.3; EIMS m/z 165 (M^+ + H, 11), 164 (M^+, 100), 108 (23), 79 (34); FAB(+)HRMS calcd for $C_{10}H_{13}O_2$ (M^+ + H) 165.0915, found 165.0911.

(5*s*,6*R*,9*S*)-6,9-Bis(hydroxymethyl)-1-oxa-2-oxospiro-[4.4]nonane (12). Ozone gas was bubbled into a solution of **11** (632 mg, 3.85 mmol) in MeOH (15 mL) and CH_2Cl_2 (10 mL) at −78 °C until the color of solution become slightly blue. $NaBH_4$ (500 mg, 13.5 mmol) was added portionwise to the reaction mixture. The reaction mixture was gradually warmed to 0 °C, and then acetone (5 mL) was added for destroying the excess reagent. The mixture was evaporated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with EtOAc afforded **12** (492 mg, 64%) as a colorless oil: IR (neat) 3400 (br), 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (m, 4H), 2.66 (t, J = 8.2 Hz, 2H), 2.51 (m, 2H), 2.21 (t, J = 8.2 Hz, 2H), 1.95 (m, 2H), 1.50 (br, 2H), 1.40 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 177.7, 95.0, 62.3, 49.5, 29.9, 23.3, 22.0; EIMS m/z 200 (M^+, 3), 183 (14), 182 (100); FAB(+)HRMS calcd for $C_{10}H_{17}O_4$ (M^+ + H) 201.1127, found 201.1145.

(5*s*,6*R*,9*S*)-6,9-Bis(acetoxymethyl)-1-oxa-2-oxospiro[4.4]-nonane (13). A mixture of **12** (200 mg, 1.00 mmol), DMAP (10 mg), and A_2O (3 mL) in pyridine (5 mL) was stirred overnight at room temperature. The mixture was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 50% EtOAc in hexane afforded **13** (275 mg, 97%) as a colorless oil: IR (neat) 1760, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.24 (dd, J = 5.7, 11.6 Hz, 2H), 4.01 (dd, J = 8.6, 11.6 Hz, 2H), 2.65 (m, 2H), 2.60 (t, J = 8.5 Hz, 2H), 2.12 (t, J = 8.5 Hz, 2H), 2.04 (s, 6H), 1.95 (m, 2H), 1.32 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 176.1, 170.9, 93.0, 63.1, 45.8, 29.3, 22.6, 21.2, 20.8; FAB(+)HRMS calcd for $C_{14}H_{21}O_6$ (M^+ + H) 285.1338, found 285.1338.

***syn*-7-[3-(Methoxymethoxy)propyl]bicyclo[2.2.1]hept-2-en-*anti*-7-ol (14).** A solution of **10** (548 mg, 2.61 mmol) in AcOH−THF−H_2O (30 mL, 4:1:1) was stirred at 50 °C for 2 h. After being cooled to room temperature, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, and then dried over $MgSO_4$. After removal of the solvent, the residue was dissolved in MeOH (10 mL), and $NaBH_4$ (150 mg, 4.10 mmol) was added. After being stirred for 2 h, the solution was diluted with acetone, and then the solution was evaporated. The residue was diluted with brine, and the mixture was extracted with EtOAc and then dried over $MgSO_4$. Removal of the solvent afforded crude diol as colorless crystals: IR (Nujol) 3300 (br); ^1H NMR ($CDCl_3$) δ 6.00 (t, J = 2.0 Hz, 2H), 3.65 (t, J = 5.9 Hz, 2H), 2.46 (m, 2H), 2.00−2.40 (br, 2H), 1.98 (dm, J = 11.3, 2H), 1.81 (m, 2H), 1.60 (m, 2H), 0.99 (dd, J = 3.5, 11.3 Hz, 2H).

A solution of crude diol (ca. 330 mg), *N*,*N*-diisopropylamine (295 mg, 2.30 mmol), and MOMCl (0.17 mL, 2.20 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 3 h. The solution was diluted with water, extracted with EtOAc, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (10% EtOAc in hexane) to give **14** (239 mg, 43%) as a colorless oil: IR (neat) 3460 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.99 (t, J = 2.1 Hz, 2H), 4.62 (s, 2H), 3.52 (t, J = 6.1, 2H), 3.36 (s, 3H), 2.43 (m, 2H), 2.30 (br s, 1H), 1.98 (dm, J = 11.3 Hz, 2H), 1.79 (m, 2H), 1.65 (m, 2H), 0.97 (dd, J = 3.4, 11.3 Hz, 2H); EIMS m/z 212 (M^+, 0.5), 180 (28), 150 (100); FAB(+)HRMS calcd for $C_{12}H_{20}O_3$ (M^+) 212.1412, found 212.1440.

(1*s*,2*R*,5*S*)-2,5-Bis(acetoxymethyl)-[1-[3-(methoxymethoxy)propyl]]cyclopentanol (15a). Compound **15a** was prepared from compound **14** in a similar manner to that described for the preparation of **9**. colorless oil: IR (neat) 3450 (br), 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.96 (s, 2H), 4.13 (dd, J = 6.3, 11.2 Hz, 2H), 4.02 (dd, J = 7.9, 11.2 Hz, 2H), 3.55 (t, J = 5.9 Hz, 2H), 3.67 (s, 3H), 2.49 (br s, 1H), 2.27 (m, 2H), 2.06 (s, 3H), 2.02 (m, 2H), 1.78 (m, 2H), 1.64 (m, 2H), 1.48 (m, 2H); FAB(+)HRMS calcd for $C_{16}H_{29}O_7$ (M^+ + H) 333.1913, found 333.1905.

Enzymatic Hydrolysis of *Meso* Compounds. General Methods. A suspension of substrate (100 mg) and enzyme (10 mg) in acetone (0.1 mL) and 0.1 M phosphate buffer (10 mL, pH 7.0) was stirred at 30 °C, and the reaction was monitored by TLC. When a spot of the diol appeared on TLC, hydrolysis was terminated by extracting the mixture with EtOAc. The EtOAc extract was dried over $MgSO_4$ and then concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel.

2-(Acetoxymethyl)-5-(hydroxymethyl)-[1-[3-(methoxymethoxy)propyl]]cyclopentanol (15b): colorless oil; $[\alpha]^{25}_D$ −3.08 (*c* 0.51, $CHCl_3$); IR (neat) 3440, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.63 (s, 2H), 4.17 (dd, J = 6.6, 10.9 Hz, 1H), 4.07 (dd, J = 7.9, 10.9 Hz, 1H), 3.76 (dd, J = 8.6, 10.8 Hz, 1H), 3.66 (dd, J = 6.1, 10.8 Hz, 1H), 3.56 (t, J = 5.9 Hz, 2H), 3.37 (s, 3H), 2.80 (br s, 1H), 2.26 (m, 2H), 2.06 (s, 3H), 1.55-2.05 (m, 7H), 1.35 (m, 2H); FAB(+)HRMS calcd for $C_{14}H_{27}O_6$ (M^+ + H) 291.1807, found 291.1815.

MTPA Ester of 15b. The 270 MHz ^1H NMR spectrum of (+)-MTPA ester derived from the monoacetate (±)-**15b** showed the methoxy proton signals at δ 3.53 (m) and 3.55 (m) in the ratio of 1 to 1, while the corresponding signal from (−)-**15b** hydrolyzed by RDL was observed at δ 3.53 (m) and 3.55 (m) in the ratio of 66 to 34.

(1*S*,3*R*)-1-(Acetoxymethyl)-2,2-(ethylenedioxy)-3-(hydroxymethyl)cyclopentane (16): colorless oil; $[\alpha]^{25}_D$ −4.57 (*c* 1.18, $CHCl_3$); IR (neat) 3450, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93−4.13 (m, 6H), 3.60−3.73 (m, 2H), 2.22−2.41 (m, 3H), 2.05 (s, 3H), 1.45−1.95 (m, 4H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 171.0, 118.4, 66.2, 64.9, 63.7, 61.9, 48.9, 46.6, 25.6, 23.6, 21.0; EIMS m/z 230 (M^+, 8), 212 (8), 171 (100); FAB(+)HRMS calcd for $C_{11}H_{18}O_5$ (M^+) 230.1154, found 230.1169.

MTPA Ester of 16. The 270 MHz ^1H NMR spectrum of (+)-MTPA ester derived from the monoacetate (±)-**16** showed the methoxy proton signals at δ 3.53 (m, 1.5 H) and 3.56 (m, 1.5 H), while the corresponding signal from (−)-**16** hydrolyzed by RDL was observed at δ 3.53 (m, 3 H) only.

(5*R*,6*S*,9*R*)-6-(Acetoxymethyl)-9-(hydroxymethyl)-1-oxa-2-oxospiro[4.4]nonane (21): colorless oil, 63% yield by PFL, 86% ee; $[\alpha]^{21}_D$ +4.98 (*c* 1.05, $CHCl_3$); IR (neat) 3450, 1770, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.22 (dd, J = 5.6, 11.5 Hz, 1H), 4.01 (dd, J = 8.6, 11.5 Hz, 1H), 3.70 (m, 2H), 2.50−2.80 (m, 3H), 2.45 (m, 1H), 2.25 (ddd, J = 6.3, 10.2, 13.2, 1H) 2.09 (ddd, J = 7.3, 10.2, 13.2, 1H), 2.04 (s, 3H), 1.94 (m, 2H), 1.72 (br, 1H), 1.32 (m, 2H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 176.8, 171.0, 93.9, 63.3, 62.2, 49.1, 46.1, 29.5, 23.2, 22.7, 21.6, 20.8; EIMS m/z 242 (M^+, 2), 224 (6), 182 (45), 164 (100); FAB(+)HRMS calcd for $C_{12}H_{19}O_5$ (M^+ + H) 243.1232, found 243.1237.

PFL-Catalyzed Transesterification of Diol 12. A suspension of diol **12** (116 mg, 0.58 mmol) and PFL (20 mg) in *n*-octane−vinyl acetate (3:1, 10 mL) was stirred at room temperature for 8 h. PFL was filtered off, and the filtrate was concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 60% EtOAc in hexane afforded (−)-**21** (79 mg, 56%) as a colorless oil: >99% ee; $[\alpha]^{20}_D$ −6.41 (*c* 1.01, $CHCl_3$).

MTPA Ester of 21. The 270 MHz ^1H NMR spectrum of (+)-MTPA ester derived from the monoacetate (±)-**21** showed the methoxy proton signals at δ 3.55 (br s) and 3.51 (br s) in the ratio of 1 to 1, while the corresponding signal from (+)-**21** hydrolyzed by RDL was observed at δ 3.51 (br s) and 3.55 (br

s) in the ratio of 93 to 7, and the corresponding signal from (−)-**21** transesterified by PFL was observed at δ 3.55 (br s, 3 H), only.

(5*R*,6*R*,9*S*)-6-(Acetoxymethyl)-9-[(*tert*-butyldimethylsiloxy)methyl]-1-oxa-2-oxospiro[4.4]nonane (22). A mixture of (−)-**21** (635 mg, 2.62 mmol), imidazole (535 mg, 7.86 mmol), and TBDMSCl (1.18 g, 7.83 mmol) in DMF (20 mL) was stirred at room temperature for 6 h. The solution was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The EtOAc extract was washed with brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel (20% EtOAc in hexane) to give **22** (867 mg, 93%) as a colorless oil: $[\alpha]^{25}_D$ −10.7 (*c* 0.97, $CHCl_3$); IR (neat) 1775, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.19 (dd, *J* = 5.9, 11.5 Hz, 1H), 4.01 (dd, *J* = 8.2, 11.5 Hz, 1H), 3.69 (dd, *J* = 4.8, 10.9 Hz, 1H), 3.62 (dd, *J* = 6.6, 10.9 Hz, 1H), 2.45−2.73 (m, 3H), 2.27−2.45 (m, 2H), 2.07 (m, 1H), 2.04 (s, 3H), 1.89 (m, 2H), 1.22−1.55 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 170.9, 94.1, 63.3, 61.9, 49.1, 46.3, 29.6, 25.8, 23.6, 22.7, 22.2, 20.8, 18.2, −5.5, −5.6; FAB(+)HRMS calcd for $C_{18}H_{33}O_5Si_1$ (M^+ + H) 357.2097, found 357.2097.

(5*R*,6*R*,9*S*)-9-[(*tert*-Butyldimethylsiloxy)methyl]-6-(hydroxymethyl)-1-oxa-2-oxospiro[4.4]nonane (23). A mixture of **22** (850 mg, 2.38 mmol) and K_2CO_3 (165 mg, 1.19 mmol) in MeOH (20 mL) was stirred at room temperature for 2 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc, and then the EtOAc extract was dried over $MgSO_4$. After removal of the solvent, the oily residue was purified by column chromatography on silica gel (25% EtOAc in hexane) to give **23** (713 mg, 95%) as a colorless oil: $[\alpha]^{25}_D$ −7.60 (*c* 0.99, $CHCl_3$); IR (neat) 3450, 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.68 (m, 4H), 2.63 (m, 2H), 2.13−2.48 (m, 4H), 1.89 (m, 2H), 1.30−1.60 (m, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 94.9, 62.3, 62.1, 49.7, 49.5, 29.8, 25.8, 23.6, 23.2, 22.5, 18.2, −5.5, −5.6; FAB(+)HRMS calcd for $C_{16}H_{31}O_4Si_1$ (M^+ + H) 315.1991, found 315.1990.

(5*S*,6*S*,9*S*)-9-[(*tert*-Butyldimethylsiloxy)methyl]-6-(iodomethyl)-1-oxa-2-oxospiro[4.4]nonane (24). A mixture of I_2 (1.53 g, 6.03 mmol) and PPh_3 (1.58 g, 6.02 mmol) in CH_2Cl_2 (30 mL) was stirred at 0 °C for 2 h. Then, a solution of **23** (948 mg, 3.01 mmol) and pyridine (500 mg, 6.33 mmol) in CH_2Cl_2 (30 mL) was added dropwise to the stirred solution, and the whole was stirred for 3 h. The solution was diluted with saturated aqueous $Na_2S_2O_3$, and extracted with Et_2O. The etheral extract was washed with water, and dried over $MgSO_4$. After removal of the solvent, the oily residue was purified by column chromatography on silica gel (5% EtOAc in hexane) to give **24** (1.21 g, 95%) as a yellowish oil: $[\alpha]^{25}_D$ −5.72 (*c* 1.02, $CHCl_3$); IR (neat) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (dd, *J* = 4.3, 11.2 Hz, 1H), 3.59 (dd, *J* = 7.3, 11.2 Hz, 1H), 3.25 (dd, *J* = 4.3, 9.4 Hz, 1H), 2.99 (dd, *J* = 9.4, 10.7 Hz, 1H), 2.69 (ddd, *J* = 8.9, 8.9, 17.8 Hz, 1H), 2.64 (m, 1H), 2.52 (ddd, *J* = 4.6, 9.9, 17.8 Hz, 1H), 1.75−2.45 (m, 5H), 1.25−1.55 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 93.7, 62.2, 50.7, 49.4, 29.5, 27.8, 25.8, 21.6, 21.5, 18.2, 3.2, −5.5, −5.6; FAB(+)HRMS calcd for $C_{16}H_{30}O_3Si_1I_1$ (M^+ + H) 425.1011, found 425.1009.

(5*R*,6*S*,9*S*)-9-[(*tert*-Butyldimethylsiloxy)methyl]-6-methyl-1-oxa-2-oxospiro[4.4]nonane (25). A suspension of **24** (1.25 g, 2.95 mmol) and zinc dust (960 mg, 14.7 mmol) in AcOH (20 mL) was stirred at room temperature for 20 min and then at 80 °C for 30 min. Zinc dust was filtered off, and the filtrate was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The EtOAc extract was washed with brine and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 5% EtOAc in hexane afforded **25** (581 mg, 66%) as a colorless oil: $[\alpha]^{26}_D$ −2.76 (*c* 1.02, $CHCl_3$); IR (neat) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (dd, *J* = 5.0, 11.2 Hz, 1H), 3.60 (dd, *J* = 7.4, 11.2 Hz, 1H), 2.67 (ddd, *J* = 8.6, 10.0, 18.0 Hz, 1H), 2.49 (ddd, *J* = 5.0, 10.0, 18.0 Hz, 1H), 2.16−2.38 (m, 3H), 1.76−2.05 (m, 3H), 1.10−1.46 (m, 2H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 95.4, 62.7, 48.8, 42.6, 29.8, 28.1, 25.8, 22.9, 21.7, 18.2, 13.5, −5.5, −5.6; FAB(+)HRMS calcd for $C_{16}H_{31}O_3Si_1$ (M^+ + H) 299.2042, found 299.2039.

(1*R*,2*S*,5*S*)-2-[(*tert*-Butyldimethylsiloxy)methyl]-5-methyl-1-(3-hydroxypropyl)cyclopentanol (26). Super hydride (1.0 M, 15 mL, 15 mmol) was added dropwise to the stirred solution of **25** (492 mg, 1.65 mmol) in THF (30 mL) at room temperature, and the solution was stirred for 2 h. The solution was diluted with brine, neutralized with 10% aqueous HCl, extracted with EtOAc, and then dried over $MgSO_4$. After removal of the solvent, the oily residue was purified by column chromatography on silica gel (30% EtOAc in hexane) to give **26** (487 mg, 98%) as a colorless oil: $[\alpha]^{26}_D$ +10.24 (*c* 1.31, $CHCl_3$); IR (neat) 3300 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.64−3.70 (m, 4H), 2.60 (br, 1H), 1.50−2.23 (m, 7H), 1.18−1.32 (m, 4H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.9, 64.2, 64.1, 52.3, 45.5, 29.3, 27.6, 27.3, 25.9, 23.3, 18.1, 14.8, −5.5; FAB(+)HRMS calcd for $C_{16}H_{35}O_3Si_1$ (M^+ + H) 303.2355, found 303.2351.

(1*R*,2*S*,5*S*)-1-(3-Acetoxypropyl)-2-[(*tert*-butyldimethylsiloxy)methyl]-5-methylcyclopentanol (27). Compound **27** was prepared from compound **26** in a similar manner to that described for the preparation of **13:** 97% yield; colorless oil; $[\alpha]^{24}_D$ +9.18 (*c* 1.01, $CHCl_3$); IR (neat) 3450 (br), 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.08 (t, *J* = 6.8 Hz, 2H), 3.70 (dd, *J* = 6.3, 10.2 Hz, 1H), 3.65 (dd, *J* = 9.4, 10.2 Hz, 1H), 2.80 (br, 1H), 2.05 (s, 3H), 1.45−2.25 (m, 6H), 1.20 (m, 2H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); FAB(+)HRMS calcd for $C_{18}H_{37}O_4Si_1$ (M^+ + H) 345.2461, found 345.2439.

(1*R*,2*S*,5*S*)-1-(3-Acetoxypropyl)-2-(hydroxymethyl)-5-methylcyclopentanol (28). Tetrabutylammonium fluoride (1 M, 0.2 mL, 0.2 mmol) was added dropwise to the stirred solution of **27** (34.6 mg, 0.10 mmol) in THF (2 mL) at room temperature, and the solution was stirred for 1 h. The solution was diluted with saturated aqueous NH_4Cl, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 50% EtOAc in hexane afforded **28** (23 mg, 99%) as a colorless oil: $[\alpha]^{22}_D$ +7.13 (*c* 1.06, $CHCl_3$); IR (neat) 3400 (br), 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10 (t, *J* = 6.6 Hz, 2H), 3.70 (m, 2H), 2.07 (s, 3H), 1.50−2.25 (m, 10H), 1.26 (m, 2H), 0.94 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 82.3, 65.3, 63.9, 52.4, 45.6, 29.2, 26.8, 23.7, 23.4, 21.0, 14.6; FAB(+)HRMS calcd for $C_{12}H_{23}O_4$ (M^+ + H) 231.1596, found 231.1615.

(1*R*,2*R*,5*S*)-1-(3-Acetoxypropyl)-2-(methoxycarbonyl)-5-methylcyclopentanol (29). H_2 gas was bubbled to the stirred suspension of PtO_2 (200 mg, 0.88 mmol) in H_2O (30 mL) for 1 h. Then, compound **28** (280 mg, 1.22 mmol) was added and O_2 gas was bubbled at 60 °C for 10 h. PtO_2 was filtered off, and the filtrate was extracted with EtOAc. The EtOAc extract was dried over $MgSO_4$ and concentrated *in vacuo* to leave an oily residue. The residue was dissolved in Et_2O (20 mL). The solution was treated with ethereal CH_2N_2 solution at 0 °C until the color of solution maintained yellow, and the whole was left at room temperature for 2 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (15% EtOAc in hexane) to give **29** (175 mg, 56%) as a colorless oil: $[\alpha]^{23}_D$ −29.67 (*c* 0.81, $CHCl_3$); IR (neat) 3450, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.04 (t, *J* = 6.6 Hz, 2H), 3.71 (s, 3H), 2.82 (t, *J* = 9.2 Hz, 1H), 2.17 (br s, 1H), 2.05 (s, 3H), 2.00 (m, 3H), 1.72 (m, 2H), 1.35−1.59 (m, 4H), 0.97 (d, *J* = 6.6 Hz, 3H); FAB(+)HRMS calcd for $C_{13}H_{23}O_5$ (M^+ + H) 259.1545, found 259.1542.

(1*R*,2*S*,5*S*)-2-(2-Hydroxyisopropyl)-1-(3-hydroxypropyl)-5-methylcyclopentanol (30). An ethereal solution of MeLi (1.5 M, 3.6 mL) was added to the stirred solution of **29** (174 mg, 0.67 mmol) in THF (15 mL) at 0 °C, and the solution was stirred for 2 h. The solution was diluted with saturated aqueous NH_4Cl, extracted with EtOAc, and dried over $MgSO_4$. After removal of the solvent, the oily residue was purified by column chromatography on silica gel (45% EtOAc in hexane) to leave **30** (69 mg, 47%) as a colorless oil: $[\alpha]^{23}_D$ +3.51 (*c* 1.20, $CHCl_3$); IR (neat) 3350 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.65 (t, *J* = 5.6 Hz, 2H), 2.30−3.20 (br, 2H), 1.33 (s, 3H), 1.27 (s, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 1.00−2.15 (m, 11H); FAB(+)HRMS calcd for $C_{12}H_{25}O_3$ (M^+ + H) 217.1804, found 217.1808.

(5*R*,6*S*,9*S*)-9-(2-Hydroxyisopropyl)-6-methyl-1-oxa-2-oxospiro[4.4]nonane (31). A mixture of **30** (68 mg, 0.31 mmol), PDC (500 mg, 1.33 mmol), and molecular sieves 3A (20 mg) in DMF (2 mL) was stirred overnight at room temperature. The mixture was diluted with brine, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 15% EtOAc in hexane gave **31** (52 mg, 79%) as a colorless oil: $[\alpha]^{24}_D$ −21.48 (*c* 0.82, $CHCl_3$), [lit. $[\alpha]_D$ −21.39 (*c* 0.6, $CHCl_3$)]; IR (neat) 3460, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.97 (ddd, J = 9.6, 10.6, 13.5 Hz, 1H), 2.47−2.70 (m, 2H), 2.15−2.30 (m, 2H), 1.63−1.93 (m, 4H), 1.31 (s, 3H), 1.22 (s, 3H), 1.15−1.30 (m, 2H), 0.91 (d, J = 6.6 Hz, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 177.3, 95.0, 71.6, 53.9, 43.9, 31.5, 29.7, 29.6, 26.5, 20.6, 20.0, 12.7; FAB(+)HRMS calcd for $C_{12}H_{21}O_3$ (M^+ + H) 213.1491, found 213.1499.

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Supporting Information Available: Copies of the ^1H NMR spectra of all new compounds, partial ^1H NMR spectra of MTPA esters for the determination of ee, ^{13}C NMR spectra of compounds **8**−**13**, **16**, **21**−**26**, **28**, and **31**, GC data of **11** and **31**, experimental section for the determination of absolute configuration of (−)-**16** (43 pages). This material is contained in 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.

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