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Enzymatic Hydrolysis of 2,2-Bis(acetoxymethyl)cycloalkanones, and Its Application to Formal Synthesis of (−)-Malyngolide

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Asymmetric hydrolysis of 2,2-bis(acetoxymethyl)cyclopentanone (**5**) using biocatalysts and its application to a formal synthesis of (−)-malyngolide are described. For the asymmetric induction at the quaternary carbon of **5**, cholinesterase from electric eel was found to be effective to afford the (+)-monoacetate (**6**) (90% ee). Compound (+)-**6** was easily converted to the synthetic intermediate (**28**) for (−)-malyngolide.

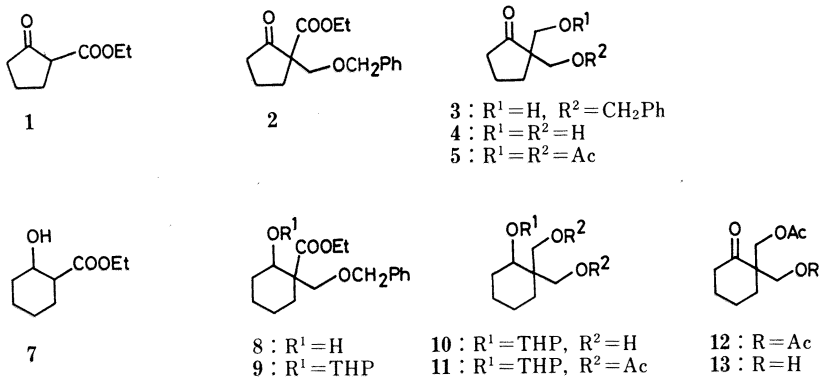
Keywords——asymmetric synthesis; enzymatic hydrolysis; *meso* compound; electric eel cholinesterase; (−)-malyngolide

In the synthesis of natural products, the ability of enzymes to discriminate between enantiotopic groups of symmetrical substrates such as *meso*-compounds seems to be highly attractive. Enzymatic hydrolyses of *meso*-compounds such as monocyclic (three-, four-, five-, and six-membered rings) 1,2-dimethyl esters have been investigated by Jones *et al.*,[1] and hydrolyses of these compounds with pig liver esterase (PLE) were found to proceed with high enantioselectivity, except for the case (17% ee) of *cis*-1,2-bis(methoxycarbonyl)cyclopentane. According to Laumen and Schneider,[2] and Jones *et al.*,[3] enzymatic hydrolysis of *cis*-1,2-bis(acetoxymethyl)cyclopentane[4] with PLE or porcine pancreatic lipase (PPL) affords the corresponding hydroxy acetate with fairly good optical purity (88—89% ee), in marked contrast to the case of the dimethyl esters. Previously,[5] we have reported that the enzymatic hydrolyses of the *trans*, *trans*-(*meso*)-2-substituted 1,3-bis(acetoxymethyl)cyclopentanes with *Rhizopus delemar* lipase (RDL) proceeds in a highly enantioselective manner.

In connection with enzymatic hydrolyses of the above five-membered *meso*-compounds with two tertiary carbons as prochiral centers, we were interested in the enzymatic hydrolyses of the *meso*-compounds with the quaternary carbon having two identical functional groups as prochiral centers, such as disubstituted malonic acid derivatives. In the enzymatic hydrolyses of acyclic *meso*-compounds such as dimethyl methylalkylmalonate, Norin *et al.*,[6,7] found that PLE and α-chymotrypsin were good enzymes for enantioselective hydrolysis (73—99% ee). However, according to Morimoto and Achiwa,[8] enzymatic hydrolysis of a cyclic *meso*-compound such as diethyl *N*-benzylpyrrolidine-3,3-dicarboxylate or diethyl tetrahydrothiophene-3,3-dicarboxylate with PLE resulted in low enantioselectivity (<20% ee). We now report that the enzymatic hydrolyses of 2,2-bis(acetoxymethyl)cycloalkanones with cholinesterase from electric eel afford the corresponding hydroxy acetates in good yields and with fairly good values of optical purity (90% ee), and this chiral synthon was applied to a formal synthesis of (−)-malyngolide.

Syntheses of substrates were carried out as follows. The benzyl ether (**2**) was obtained by alkylation of the potassium salt of the keto-ester (**1**) with benzyl chloromethyl ether, and reduction of **2** with $LiAlH_4$[9] in the presence of lithium diisopropylamide (LDA) without

protecting the carbonyl function afforded the keto-alcohol (**3**). Catalytic hydrogenolysis of **3** with 5% Pd–C/H_2 in MeOH, followed by acetylation of the diol (**4**) with Ac_2O–pyridine, afforded the substrate (**5**). The cyclohexanone diacetate (**12**) was synthesized as follows. The hydroxy ester (**7**) was converted to the benzyl ether (**8**) *via* benzyloxymethylation of the dianion generated by treatment with 2 eq of LDA. After protection of the hydroxy function as

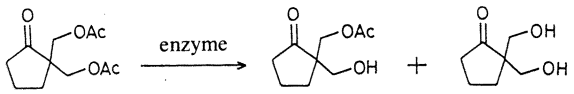


1 **2** **3** : R^1=H, R^2=CH_2Ph
4 : R^1=R^2=H
5 : R^1=R^2=Ac

7 **8** : R^1=H
9 : R^1=THP
10 : R^1=THP, R^2=H
11 : R^1=THP, R^2=Ac
12 : R=Ac
13 : R=H

Chart 1

TABLE I. Enzymatic Hydrolysis of **5**

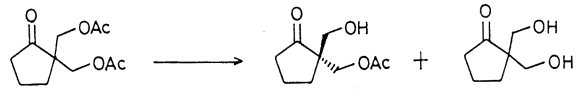


5 **6** **4**

Run	Enzyme	**6**				**4**
		Reaction time (h)	Chemical yield (%)	Optical purity (% ee)	Absolute configuration	Chemical yield (%)
1	*Pseudomonas fluorescens* lipase "Amano P"	72	18 (62)	17	*R*	5
2	*Candida cylindracea* lipase "Sigma"	24	37 (79)	17	*R*	4
3	*Candida cylindracea* lipase "Meito MY-30"	54	29 (60)	36	*R*	10
4	Porcine pancreatic lipase "Sigma, type II"	59	26 (81)	25	*S*	2
5	*Aspergillus niger* lipase "Amano A"	22	56 (75)	3	*S*	7
6	*Aspergillus niger* lipase "Amano A-6"	24	57 (74)	20	*S*	5
7	*Rhizopus niveus* lipase "Amano F"	50	20 (57)	34	*S*	8
8	*Rhizopus delemer* lipase "Seikagaku-Kogyo"	23	37 (71)	21	*R*	3
9	Pig liver esterase "Sigma, type I"	0.5	75 (88)	13	*R*	3
10	Cholinesterase from electric eel "Sigma, type V-S"	1.25	62 (83)	62	*R*	5

Substrate **5** (*ca.* 50 mg) and enzyme (*ca.* 25 mg) were used for runs 1—8. PLE (0.25 ml) was used for run 9. For run 10, see Experimental. Number in parentheses: value on the basis of recovered **5**.

TABLE II. Asymmetric Hydrolysis of **5** Catalyzed by Cholinesterase from Electric Eel



5 (+)-**6** **4**

Run	Substrate **5** (mg)	Concentration of substrate (mg/ml)	Concentration of enzyme (10^{-2} mg/ml)	(+)-**6** Reaction time (min)	(+)-**6** Chemical yield (%)	(+)-**6** Optical purity (% ee)	**4** Chemical yield (%)
1	40	6.0	2.50	75	62 (83)	62	5
2	41	6.0	1.25	90	52 (74)	77	9
3	43	2.0	1.25	95	52 (72)	77	5
4	76	6.0	1.25	35	36 (92)	90	0
5	154	6.0	0.60	60	45 (90)	72	0
6	1170	6.0	1.25	30	22 (90)	90	0

Number in parenthesis: value on the basis of recovered **5**.

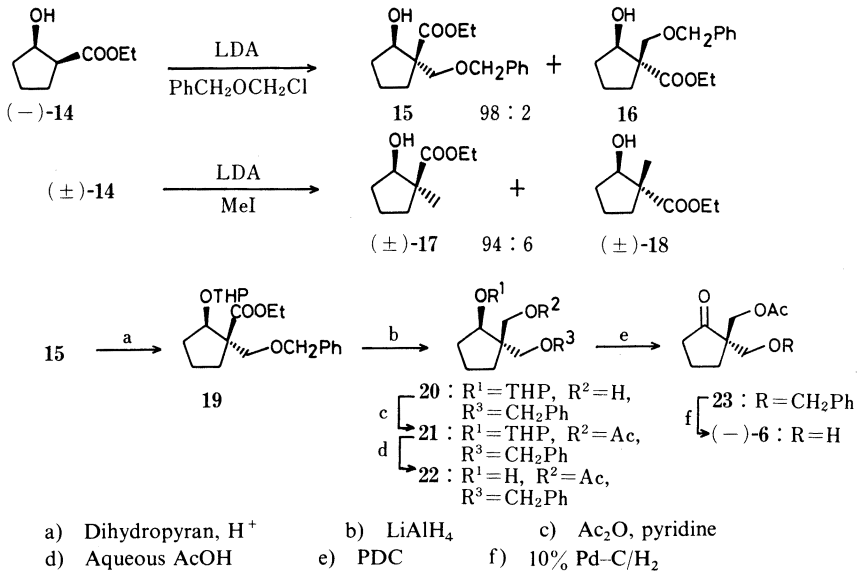


Chart 2

the tetrahydropyranyl ether, **9** was reduced with $LiAlH_4$, followed by catalytic hydrogenolysis with 10% Pd–C/H_2 in MeOH. Acetylation of **10** with Ac_2O–pyridine, followed by deprotection with aqueous AcOH and then oxidation with Jones reagent, afforded the cyclohexanone diacetate (**12**) (Chart 1).

Enzymatic hydrolysis of the diacetate (**5**) was performed in 0.1 M phosphate buffer solution (pH 7.0) at 30 °C (Table I). Among the ten tested enzymes, cholinesterase from electric

eel afforded the monoacetate (+)-(**6**) with 62% ee (62% yield). However, the hydrolysis with PLE resulted in low enantioselectivity (13% ee), similarly to the result with diethyl *N*-benzylpyrrolidine-3,3-dicarboxylate.[8] The results of further examination of the hydrolysis with cholinesterase from electric eel are summarized in Table II. The best optical purity among the tested hydrolysis conditions was obtained in run 4 (90% ee). Shortening the hydrolysis time (30 min) and quenching the reaction before appearance of the diol (**4**) on thin layer chromatography (TLC) seem to afford (+)-**6** with higher optical purity. As shown in run 6, even a 15-fold scale-up of run 4 gave the same result (90% ee).

Similarly, hydrolysis of the cyclohexanone diacetate (**12**) with cholinesterase from electric eel afforded the monoalcohol (+)-(**13**) with 77% ee.

The absolute configuration of the hydrolyzed product (+)-**6** was determined by direct comparison with the standard compound synthesized independently (Chart 2). Benzyloxymethylation of the dianion generated from (−)-**14** (>99% ee)[10] by treatment with 2 eq of LDA[11] afforded a mixture (54% yield) of **15** and **16** with a diastereoselectivity of 98 to 2 (based on the 270 MHz proton nuclear magnetic resonance (^{1}H-NMR) spectrum). The stereochemistry of **15** was established by comparison with the methyl compounds (**17** and **18**), which were obtained in a ratio of 94 to 6 *via* the methylation of the dianion of (±)-**14**. In **17**, the nuclear Overhauser effect (NOE) between C_1-H and the C_2-Me was observed, and the C_1-H signal appeared at lower field (δ 3.98, dd, J=5.5, 3.2 Hz) than that (δ 3.75, dd, J=5.2, 5.2 Hz) of **18**. Similarly, the C_1-H signal of the main product **15** was observed at lower field (δ 4.61, m) than that (δ 4.28, m) of **16**. Thus, the stereochemistry of **15** was clarified. Next, **15** was transformed into (−)-**6** in the following manner. After protection of the alcohol with dihydropyran–*p*-toluenesulfonic acid (TsOH) and subsequent reduction with $LiAlH_4$, **15** was converted to the alcohol (**20**) in 71% yield. Acetylation of **20** with Ac_2O–pyridine followed by deprotection of the tetrahydropyranyl ether with aqueous AcOH gave the mono-alcohol (**22**), which was submitted to oxidation with pyridinium dichromate (PDC) to afford the ketone (**23**) (72% from **20**). Unexpectedly, catalytic hydrogenolysis of **23** with 10% Pd–C/H_2 in MeOH afforded (−)-**6** with only 9% ee.[12] This remarkable decrease of optical purity may be caused by the 1,5-rearrangement of the acetyl function under the catalytic hydrogenolysis conditions employed. Thus, the absolute stereochemistry of (+)-**6** was unambigously concluded to be *R*.

(−)-Malyngolide, an antibiotic active against *Mycobacterium smegmatis* and *Strep-*

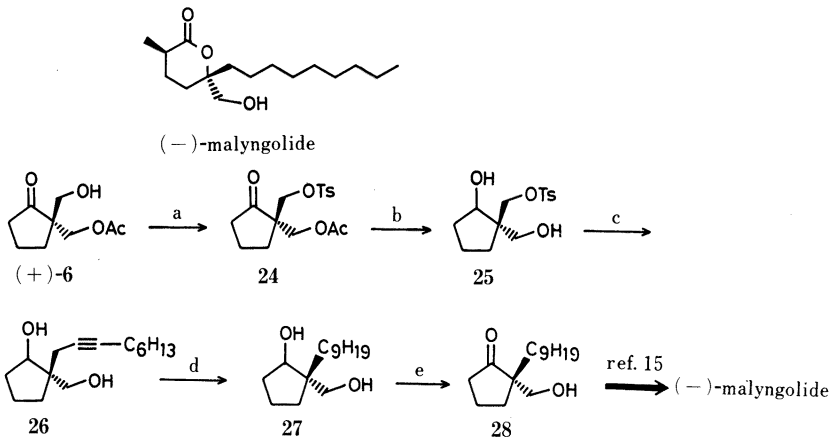


Chart 3

tococcus pyogenes, has been isolated from the blue-green marine algae *Lynbya majuscula gomont*,[13] and synthesized by many research groups.[14] Compound (+)-**6** seems to be desirable synthon for the synthesis of (−)-malyngolide, because the δ-lactone may be constructed by Baeyer–Villiger oxidation of the five-membered ring ketone, and the alkyl side chain may be introduced by elongation of the primary alcohol.

In a preliminary experiment for the introduction of the alkyl side chain, reaction of the tosylate (**24**) with Gilman reagent prepared from octyl bromide resulted in the formation of a complex mixture. However, the difficulty with this substitution reaction was overcome by treatment of the hydroxy tosylate (**25**), which was obtained from **24** by reduction with $NaBH_4$–MeOH, with lithium 1-octylide. The nonyn (**26**) obtained from **25** in 82% yield was converted to **28** *via* catalytic hydrogenation with 10% Pd–C/H_2 in MeOH and subsequent oxidation[15] with bromine and aqueous $NaHCO_3$ (Chart 3). The conversion of **28** to (−)-malyngolide was achieved by Matsuo *et al.*,[15] and thus our reactions constitute a formal synthesis of (−)-malyngolide.

Experimental

Infrared (IR) spectra were measured with a JASCO A-202 spectrometer. ^{1}H-NMR spectra were measured on JEOL JNM-FX-100 and GX-270 spectrometers. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. Optical rotations were measured on a JASCO DIP-4 polarimeter. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used. TLC was performed on Silica gel F_{254} plates (Merck). For enzymatic hydrolysis, cholinesterase from electric eel (Sigma, Type V-S) was used. All organic solvent extracts were washed with brine and dried over anhydrous sodium sulfate.

2-Benzyloxymethyl-2-ethoxycarbonylcyclopentanone (2)——Benzyl chloromethyl ether (33.7 g) in ether (100 ml) was added dropwise to a stirred suspension of potassium salt (31.0 g) of **1** in ether (1 l) at room temperature. After being stirred for 2 h, the reaction mixture was diluted with brine (300 ml) and extracted with ether. The ether extract was washed, and dried, then concentrated *in vacuo* to leave the oily residue, which was subjected to column chromatography on silica gel (150 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **2** (24.0 g, 56%) as a colorless oil. IR (neat): 1745, 1720, 1230, 1070 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.0 Hz, $OCH_2\underline{CH}_3$), 2.24—2.39 (2H, m, C_5-H), 3.75, 3.80 (1H each, d, J=12.0 Hz, C_2-CH_2), 4.12 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 4.46 (2H, s, OCH_2Ph), 7.24 (5H, s, aromatic H). FDMS m/z: 277 (M^++1), 276 (M^+), 249, 91.

2-Benzyloxymethyl-2-hydroxymethylcyclopentanone (3)——Compound **2** (5.46 g, 19.7 mmol) in tetrahydrofuran (THF) (20 ml) was added dropwise to LDA solution [prepared from diisopropylamine (2.99 g, 29.6 mmol) and BuLi (1.5 M in hexane) (19 ml, 29.6 mmol) in THF (40 ml)] at −78 °C under an N_2 atmosphere. After 30 min, this solution was added dropwise to a stirred suspension of $LiAlH_4$ (749 mg, 19.7 mmol) in THF (20 ml) at −78 °C. After being stirred for 2 h at −30 °C, and for 1.5 h at 0 °C, the reaction mixture was diluted with 2 N HCl (50 ml), and extracted with ether. The ether extract was washed, and dried, then concentrated to leave the oily residue, which was purified by silica gel column chromatography (80 g). The fraction eluted with 20—35% AcOEt in hexane (v/v) afforded **3** (2.44 g, 53%) as a colorless oil. IR (neat): 3430, 1730, 1090, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.16—2.36 (2H, m, C_5-H), 2.45 (1H, br, OH), 3.35, 3.60 (2H each, d, J=12.0 Hz, C_2-CH_2 × 2), 4.47 (2H, s, OCH_2Ph), 7.27 (5H, s, aromatic H). FDMS m/z: 234 (M^+), 203, 106.

2,2-Bis(hydroxymethyl)cyclopentanone (4)——Compound **3** (2.40 g) in MeOH (80 ml) was hydrogenated in the presence of 5% Pd–C (5.2 g) under an H_2 atmosphere. Usual work-up afforded an oily residue, which was purified by column chromatography on silica gel (50 g). The fraction eluted with 30—45% AcOEt in hexane (v/v) afforded **4** (1.28 g, 87%) as a colorless oil. IR (neat): 3450, 1720, 1450, 1390, 1040 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.70-2.18 (6H, m, C_3-, C_4-, C_5-H), 3.18, 3.38 (2H each, dd, J=12.2, 6.0 Hz, C_2-CH_2 × 2), 4.63 (2H, t, J=6.0 Hz, OH × 2). MS m/z: 144 (M^+), 113.

2,2-Bis(acetoxymethyl)cyclopentanone (5)——Acetylation of **4** (1.16 g) in a usual manner (Ac_2O–pyridine) afforded **5** (1.78 g, 97%) as a colorless oil. IR (neat): 1740 (br), 1380, 1230, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.08 (4H, m, C_3-, C_4-H), 2.05 (6H, s, OAc × 2), 2.32 (2H, m, C_5-H), 4.09, 4.12 (2H each, d, J=12.2 Hz, C_2-CH_2 × 2). MS m/z: 228 (M^+), 168, 126, 108. *Anal.* Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.93; H, 7.10.

General Method for the Enzymatic Hydrolysis. A Typical Example: Hydrolysis of 5 to (*R*)-2-Acetoxymethyl-2-hydroxymethylcyclopentanone ((+)-6) with Cholinesterase from Electric Eel——Compound **5** (76 mg) and cholinesterase (0.2 mg) were successively added with stirring to 0.1 M phosphate buffer (pH 7, 15 ml). The whole was stirred for 35 min at 30 °C, and hydrolysis was terminated by extracting the mixture with AcOEt. The AcOEt extract was washed, and dried, then concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel (4 g). The fraction eluted with 15% AcOEt in hexane (v/v) afforded (+)-**6** as a colorless

oil (22 mg, 36%), in addition to the recovery of **5** (49 mg, 61%). (+)-**6** (90% ee): $[\alpha]_D^{20}$ +3.24° (c=2.22, $CHCl_3$). IR (neat): 3450, 1725, 1240, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.84—2.10 (4H, m, C_3-, C_4-H), 2.05 (3H, s, OAc), 2.33 (2H, m, C_5-H), 3.60, 3.62 (1H each, d, J=12.3 Hz, CH_2OH), 4.16 (2H, s, CH_2OAc). FDMS m/z: 187 (M^++1), 155, 97. *Anal.* Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.12; H, 7.43. The optical purity of (+)-**6** was determined by 270 MHz ^{1}H-NMR ($CDCl_3$) spectroscopy after conversion to the corresponding ester of (+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA). In the spectrum of the (+)-MTPA ester, methylene protons (CH_2O-MTPA) were observed as two pairs of doublet signals due to two diastereomers at δ 4.463 (d, J=10.8 Hz) and 4.265 (d, J=10.8 Hz) as major peaks, and δ 4.401 (d, J=10.8 Hz) and 4.325 (d, J=10.8 Hz) as minor peaks. On the basis of the relative intensity of these two pairs, the optical purity was calculated.

2-Benzyloxymethyl-2-ethoxycarbonylcyclohexanol (8)——Compound **8** was synthesized from **7** in 65% yield in a manner similar to that described for the preparation of **15**. A colorless oil. IR (neat): 3500, 1740, 1230, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz, OCH_2CH_3), 3.69 (2H, s, C_2-CH_2), 4.14 (1H, m, C_1-H), 4.21 (2H, q, J=7.0 Hz, OCH_2CH_3), 4.53 (2H, s, OCH_2Ph), 7.31 (5H, s, aromatic H). FDMS m/z: 292 (M^+).

2-Benzyloxymethyl-2-ethoxycarbonyl-1-(tetrahydropyran-2-yl)oxycyclohexane (9)——The alcohol function in **8** was protected as the tetrahydropyranyl ether in a manner similar to that described for the preparation of **19**. A colorless oil. IR (neat): 1725, 1450, 1215, 1120, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.0 Hz, OCH_2CH_3), 3.52, 3.56 (1H each, d, J=12.5 Hz, C_2-CH_2), 4.12 (2H, q, J=7.0 Hz, OCH_2CH_3), 4.48 (2H, s, OCH_2Ph), 4.60—4.90 (2H, m, C_1-H, OCHO), 7.26 (5H, s, aromatic H). FDMS m/z: 377 (M^++1), 376 (M^+), 303, 85.

2,2-Bis(hydroxymethyl)-1-(tetrahydropyran-2-yl)oxycyclohexane (10)——Compound **9** (2.71 g) in ether (40 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (1.0 g) in ether (50 ml) at 0 °C. The mixture was stirred for 2 h at room temperature, and usual work-up afforded an oily residue, which was submitted to catalytic hydrogenolysis with 5% Pd–C (see compound **4**) without purification. In silica-gel column chromatography of the crude oil, the fraction eluted with 10% AcOEt in hexane (v/v) afforded **10** (1.28 g, 65%) as a colorless oil. IR (neat): 3400, 1480, 1245, 1150 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 3.50—3.80 (6H, m, CH_2O×3), 4.50—4.75 (2H, m, C_1-H, OCHO). FDMS m/z: 245 (M^++1), 244 (M^+), 161, 85.

2,2-Bis(acetoxymethyl)-1-(tetrahydropyran-2-yl)oxycyclohexane (11)——Acetylation of **10** (320 mg) in a usual manner (Ac_2O–pyridine) afforded **11** (355 mg, 96%) as a colorless oil. IR (neat): 1755, 1400, 1320, 1130 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (6H, s, OAc×2), 3.50—3.80 (2H, m, OCH_2), 4.05—4.25 (4H, m, C_2-CH_2×2), 4.53, 4.70 (1H each, m, C_1-H, OCHO). FDMS m/z: 328 (M^+), 269, 243.

2,2-Bis(acetoxymethyl)cyclohexanone (12)——Compound **11** (170 mg) in a mixture (20 ml) of THF (4 ml), AcOH (12 ml) and H_2O (4 ml) was stirred for 3 h at 40 °C, diluted with brine, then extracted with AcOEt. The AcOEt extract was washed, and dried, then concentrated *in vacuo* to afford an oily residue, which was roughly chromatographed on silica gel. The alcohol obtained in this manner was submitted to Jones oxidation, and usual work-up and column chromatography on silica gel afforded **12** (95 mg, 78%) as a colorless oil. IR (neat): 1745, 1715, 1240, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (6H, s, OAc×2), 2.48 (2H, m, C_6-H), 4.14, 4.43 (2H each, d, J=12.0 Hz, C_2-CH_2×2). FDMS m/z: 242 (M^+), 227, 106.

(+)-2-Acetoxymethyl-2-hydroxymethylcyclohexanone ((+)-(13))——Compound **12** was submitted to hydrolysis with cholinesterase from electric eel, in a manner similar to that described for the enzymatic hydrolysis of **5**. A colorless oil. $[\alpha]_D^{25}$ +1.59° (c=0.81, $CHCl_3$, 77% ee). IR (neat): 3450, 1740, 1715, 1240, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s, OAc), 2.44 (2H, m, C_6-H), 3.60, 3.72 (1H each, d, J=12.2 Hz, CH_2OH), 4.16, 4.45 (1H each, d, J=12.0 Hz, CH_2OAc). FDMS m/z: 201 (M^++1), 200 (M^+), 169. (+)-MTPA ester of (+)-**13**: ^{1}H-NMR ($CDCl_3$) δ: 4.085, 4.007 (ratio of intensity=0.885/0.115, d, J=11.5 Hz, one of CH_2OAc).

(1*R*,2*R*)-2-Benzyloxymethyl-2-ethoxycarbonylcyclopentanol (15) and (1*R*,2*S*)-2-Benzyloxymethyl-2-ethoxycarbonylcyclopentanol (16)——Compound (−)-**14** (1.74 g) in THF (7 ml) was added dropwise to a stirred solution of LDA [prepared from diisopropylamine (3.37 g, 33 mmol) in THF (10 ml) and hexamethylphosphoramide (HMPA) (3 ml), and BuLi (1.5 M in hexane) (20.4 ml, 30.8 mmol)] at −78 °C under an N_2 atmosphere. After 30 min, benzyl chloromethyl ether (2.28 g) in THF (10 ml) was added dropwise to the above stirred solution. After being stirred for 3 h at −78 °C, the reaction mixture was diluted with 20% aqueous NH_4Cl (10 ml), and extracted with ether. The ether extract was washed, and dried, then concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel (80 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded **15** (1.63 g, 54%) as a colorless oil. Compound **16** was isolated by preparative TLC. **15**: $[\alpha]_D^{29}$ +0.95° (c=1.47, $CHCl_3$). IR (neat): 3450, 1710, 1260, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.0 Hz, OCH_2CH_3), 2.68 (1H, d, J=4.1 Hz, OH), 3.73, 3.82 (1H each, d, J=9.6 Hz, C_2-CH_2), 4.17 (2H, q, J=7.0 Hz, OCH_2CH_3), 4.52 (2H, s, OCH_2Ph), 4.61 (1H, m, C_1-H), 7.26 (5H, s, aromatic H). MS m/z: 278 (M^+), 260, 205, 187. *Anal.* Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found; C, 68.98; H, 7.91. **16**: A colorless oil. IR (neat): 3450, 1715, 1270, 1165 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.0 Hz, OCH_2CH_3), 3.13 (1H, br, OH), 3.49, 3.52 (1H each d, J=9.4 Hz, C_2-CH_2), 4.17 (2H, q, J=7.0 Hz, OCH_2CH_3), 4.28 (1H, m, C_1-H), 4.52 (2H, s, OCH_2Ph), 7.26 (5H, s, aromatic H).

(1*RS*,2*RS*)-2-Ethoxycarbonyl-2-methylcyclopentanol (17) and (1*RS*,2*SR*)-2-Ethoxycarbonyl-2-methylcyclopentanol (18)——Compounds **17** and **18** were obtained from (±)-**14** (297 mg) in ratio of 94 to 6 (240 mg, 75%) in a manner similar to that described for **15**. **17**: IR (neat): 3450, 1700, 1260, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, s,

C_2-CH_3), 1.28 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 3.18 (1H, br, OH), 3.98 (1H, dd, J=5.5, 3.2 Hz, C_1-H), 4.18 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$). MS m/z: 172 (M^+), 154, 127, 99. Compound **18** was obtained as a mixture with **17**. ^{1}H-NMR ($CDCl_3$) δ: 3.74 (t, J=5.5 Hz, C_1-H in **18**).

(1*R*,2*R*)-2-Benzyloxymethyl-2-ethoxycarbonyl-1-(tetrahydropyran-2-yl)oxycyclopentane (19)——Dihydropyran (460 mg) in CH_2Cl_2 (10 ml) and *p*-TsOH (10 mg) were successively added to a stirred solution of **15** (1.00 g) in CH_2Cl_2 (10 ml) at 0 °C. After 3 h, the reaction mixture was diluted with 5% aqueous $NaHCO_3$ (10 ml), and extracted with AcOEt. The AcOEt extract was washed, and dried, then concentrated *in vacuo* to afford an oily residue, which was submitted to silica-gel column chromatography. The fraction eluted with 10% AcOEt in hexane (v/v) gave **19** (1.10 g, 84%) as a colorless oil. IR (neat): 1740, 1438, 1074, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 3.57, 3.76 (1H, each, d, J=9.5 Hz, C_2-$C\underline{H}_2$), 4.15 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 4.49 (2H, s, OCH_2Ph), 4.67, 4.91 (1H each, m, C_1-H, OCHO), 7.30 (5H, s, aromatic H). MS m/z: 362 (M^+), 289, 277, 271.

(1*R*,2*R*)-2-Benzyloxymethyl-2-hydroxymethyl-1-(tetrahydropyran-2-yl)oxycyclopentane (20)——Reduction of **19** (670 mg) with $LiAlH_4$ in a usual manner and subsequent purification by silica gel column chromatography afforded **20** (498 mg, 84%) as a colorless oil. IR (neat): 3450, 1450, 1350, 1070, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.10 (1H, t, J=6.0 Hz, OH), 3.30—3.65 (4H, m, $OC\underline{H}_2CH_2$, $C\underline{H}_2OH$), 3.78, 3.89 (1H each, d, J=10.1 Hz, $C\underline{H}_2OCH_2Ph$), 4.10 (1H, m, OCHO), 4.50 (2H, s, OCH_2Ph), 4.57 (1H, m, OCHO), 7.29 (5H, s, aromatic H). FDMS m/z: 321 (M^++1), 320 (M^+), 235, 91.

(1*R*,2*S*)-2-Acetoxymethyl-2-benzyloxymethyl-1-(tetrahydropyran-2-yl)oxycyclopentane (21)——Acetylation of **20** (343 mg) with Ac_2O–pyridine and subsequent purification by column chromatography on silica gel afforded **21** (384 mg, 99%) as a colorless oil. IR (neat): 1730, 1430, 1360, 1230, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, OAc), 3.40, 3.52 (1H each, d, J=10.2 Hz, $C\underline{H}_2OCH_2Ph$), 3.90 (1H, m, C_1-H), 3.98, 4.08 (1H each, d, J=10.1 Hz, $C\underline{H}_2OAc$), 4.47, 4.50 (1H each, d, J=10.0 Hz, OCH_2Ph), 4.62 (1H, m, OCHO), 7.31 (5H, s, aromatic H). FDMS m/z: 363 (M^++1), 321, 277, 262.

(1*R*,2*S*)-2-Acetoxymethyl-2-benzyloxymethycyclopentanol (22)——Compound **21** (420 mg) in a mixture of THF (4 ml), AcOH (12 ml) and H_2O (4 ml) was stirred at 50 °C. After 4 h, the reaction mixture was diluted with brine (20 ml), and extracted with AcOEt. The AcOEt extract was washed, and dried, then concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 10% AcOEt in hexane (v/v) afforded **22** (258 mg, 87%) as a colorless oil. $[\alpha]_D^{20}$ +1.23° (c=1.62, $CHCl_3$). IR (neat): 3430, 1720, 1450, 1230, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.01 (3H, s, OAc), 2.90 (1H, br, OH), 3.56 (2H, s, $C\underline{H}_2OCH_2Ph$), 4.00 (1H, m, C_1-H), 3.97, 4.07 (1H each, d, J=12.0 Hz, $C\underline{H}_2OAc$), 7.32 (5H, s, aromatic H). FDMS m/z: 278 (M^+), 91.

(*S*)-2-Acetoxymethyl-2-benzyloxymethylcyclopentanone (23)——A mixture of **22** (180 mg) and PDC (1.2 g) in CH_2Cl_2 (10 ml) was stirred for 12 h at room temperature. The reaction mixture was diluted with ether (20 ml), and the resultant precipitate was filtered off. The filtrate was concentrated *in vacuo* to afford an oily residue, which was submitted to column chromatography on silica gel (10 g). The fraction eluted with 3% AcOEt in hexane (v/v) afforded **23** (150 mg, 84%) as a colorless oil. $[\alpha]_D^{20}$ +0.54° (c=1.47, $CHCl_3$). IR (neat): 1730, 1220, 1090, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.02 (3H, s, OAc), 2.29 (2H, m, C_5-H), 3.40, 3.51 (1H each, d, J=10.3 Hz, $C\underline{H}_2OCH_2Ph$), 4.05, 4.11 (1H each, d, J=11.6 Hz, $C\underline{H}_2OAc$), 4.47 (2H, s, OCH_2Ph), 7.26 (5H, s, aromatic H). FDMS m/z: 277 (M^++1), 276 (M^+), 249, 91.

Catalytic Hydrogenolysis of 23——Compound **23** (40 mg) in MeOH (20 ml) was submitted to catalytic hydrogenolysis with 10% Pd–C (200 mg). Usual work-up and subsequent purification by silica gel column chromatography afforded (−)-**6** (19 mg, 9% ee) as a colorless oil. $[\alpha]_D^{20}$ −0.3° (c=1.74, $CHCl_3$).

(*S*)-2-Acetoxymethyl-2-*p*-tosyloxymethylcyclopentanone (24)——A mixture of (+)-**6** (218 mg), *p*-TsCl (670 mg) and pyridine (2 ml) in CH_2Cl_2 (6 ml) was stirred at room temperature for 30 h. Usual work-up afforded an oily residue, which was purified by column chromatography on silica gel (8 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **24** (372 mg, 93%) as a colorless oil. $[\alpha]_D^{25}$ −1.15° (c=1.04, $CHCl_3$). IR (neat): 1740, 1598, 1360, 1240, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, OAc), 2.29 (2H, m, C_5-H), 2.45 (3H, s, CH_3), 3.82—4.18 (4H, m, C_2-CH_2 × 2), 7.33, 7.72 (2H each, d, J=8.2 Hz, aromatic H). FDMS m/z: 340 (M^+).

(1*RS*, 2*S*)-2-Hydroxymethyl-2-*p*-tosyloxymethylcyclopentanol (25)——A mixture of **24** (360 mg) and $NaBH_4$ (100 mg) in MeOH (5 ml) was stirred at 0 °C for 5 h. Usual work-up afforded an oily residue, which was chromatographed on silica gel (8 g). The fraction eluted with 30% AcOEt in hexane (v/v) afforded a diastereomeric mixture **25** (238 mg, 56% de, 75%), as a colorless oil. IR (neat): 3400, 1600, 1360, 1180, 960 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s, CH_3), 3.43, 3.65 (0.22H each, d, J=11.0 Hz, $C\underline{H}_2OH$), 3.60, 3.75 (0.78H each, d, J=11.6 Hz, $C\underline{H}_2OH$), 3.92, 4.08 (0.78H each, d, J=9.8 Hz, $C\underline{H}_2OTs$), 4.03, 4.33 (0.22H each d, J=9.7 Hz, $C\underline{H}_2OTs$), 4.06 (1H, m, C_1-H), 7.35, 7.80 (2H each, d, J=8.3 Hz, aromatic H). FDMS m/z: 301 (M^++1), 228, 176.

(1*RS*, 2*R*)-2-(2-Nonynyl)-2-hydroxymethylcyclopentanol (26)——BuLi (1.5 M hexane, 1.5 ml) was added to a stirred solution of 1-octyn (330 mg) in THF (6 ml) at −78 °C under an Ar atmosphere. The mixture was stirred for 0.5 h at room temperature, then **25** (180 mg) in THF (1.0 ml) was added at −20 °C, and the whole was stirred for 4 h at 0 °C. The reaction mixture was diluted with 10% aqueous NH_4Cl, and extracted with AcOEt. The AcOEt extract was washed and dried. The solvent was removed *in vacuo* to afford an oily residue, which was subjected to column chromatography on silica gel (5 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded **26** (120 mg, 84%) as

a colorless oil. IR (neat): 3350, 2230, 1460, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.0 Hz, CH_3), 2.10—2.25 (4H, m, $CH_2C{\equiv}CCH_2$), 4.08 (2H, s, $C\underline{H}_2OH$), 4.38 (1H, m, C_1-H). MS m/z: 238 (M^+), 220, 207, 189.

(1*RS*,2*R*)-2-Hydroxymethyl-2-nonylcyclopentanol (27)——Compound **26** (100 mg) in MeOH (5 ml) was submitted to catalytic hydrogenation with 10% Pd–C (100 mg). Usual work-up afforded an oily residue, which was purified by column chromatography on silica gel (5 g). The fraction eluted with 12% AcOEt in hexane (v/v) afforded **27** (76 mg, 75%) as a colorless oil. IR (neat): 3350, 1100, 1050 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.0 Hz, CH_3), 3.35 (2H, s, $C\underline{H}_2OH$), 3.60 (1H, m, C_1-H). FDMS m/z: 243 ($M^+ + 1$), 225, 211.

(*R*)-2-Hydroxymethyl-2-nonylcyclopentanone (28)——Bromine (106 mg) in CH_2Cl_2 (2 ml) was added to a mixture of **27** (70 mg), HMPA (20 mg), CH_2Cl_2 (2 ml) and 8% aqueous $NaHCO_3$ (2.5 ml) at 5 °C. The whole was vigorously stirred for 1.5 h at 0—5 °C, then the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with 5% aqueous $Na_2S_2O_3$ and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was chromatographed on silica gel (4 g). The fraction eluted with 10% AcOEt in hexane afforded **28** (50 mg, 71%) as a colorless oil. $[\alpha]_D^{25}$ +8.12° (c=0.50, $CHCl_3$). IR ($CHCl_3$): 3500, 1720, 1460 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.9 Hz, CH_3), 1.91 (2H, t, J=4.4 Hz, C_2-CH_2R), 2.22 (2H, m, C_5-H), 3.30 3.65 (1H each, d, J=10.7 Hz, $C\underline{H}_2OH$). FDMS m/z: 241 ($M^+ + 1$), 240 (M^+), 210. *Anal.* Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.03; H, 11.68.

References and Notes

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