Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 12, pp. 3055-3062, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00403-3

Lipase-catalyzed Kinetic Resolution of *cis*-1-Diethylphosphonomethyl-2-hydroxymethylcyclohexane. Application to Enantioselective Synthesis of 1-Diethylphosphonomethyl-2-(5'-hydantoinyl)cyclohexane

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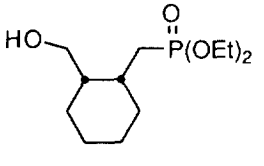
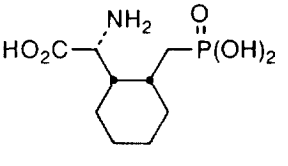
Abstract: A kinetic resolution of *cis*-1-diethylphosphonomethyl-2-hydroxymethylcyclohexane **1** by lipase has been developed. The transesterification of (±)-**1** with vinyl acetate in the presence of Lipase AK without solvent proceeded to give (+)-**1** and the corresponding acetate (+)-**5** in good yield and high enantiomeric ratio. The alcohol (+)-**1** was transformed to the optically active hydantoins **12** and **13**, possible intermediates for the synthesis of conformational constrained analogues of **AP-5**.

Enzyme-catalyzed kinetic resolution of racemic substrates to prepare enantiomerically pure compounds has now become a very powerful tool in organic synthesis.[1] Transesterifications catalyzed by lipases in organic solvent are the most widely applied for the resolution of racemic alcohols.[2] Although many kinds of racemic alcohols have been successfully resolved by lipase-catalyzed enantioselective transesterificcation reactions,[2] the resolution of primary alcohols containing phosphonate functionalities at the appropriate position are rarely explored.[3] The effects of phosphonate moiety on the transesterfication reaction are virtually unknown. We have recently required the optically active phosphono alcohols **1**, as a useful phosphonic containing chiron for the asymmetric synthesis of the conformational constrained analogue **2**[4,5] of ω-phosphono α-amino acids such as **AP-5** which is known to show potent NMDA antagonist activities.[6] In this paper, we describe our results on the lipase-catalyzed kinetic resolutions of phosphono alcohol **1**, in addition to some chemical transformations of **1** for the synthesis of ω-phosphono α-amino acid **2**.



(±)-**1**



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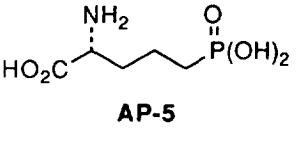


AP-5

The required racemic diethylphosphono alcohol (±)-**1** was synthesized efficiently through the ring-opening reaction of cyclic *meso*-sulfate **4**, prepared from the corresponding diol **3**. Treatment of **3** with $SOCl_2$ in CH_2Cl_2 in the presence of Et_3N, followed by oxidation with $NaIO_4$ according to the method of Sharpless[7] gave the cyclic *meso*-sulfate **4**, mp 58-59 °C, in 89% yield. The reaction of **4** with sodium diethylphosphophite in DMF for 12 h and subsequent hydrolysis with c-H_2SO_4 in THF, gave (±)-**1** in 70% yield[8] (**Scheme 1**).

Scheme 1

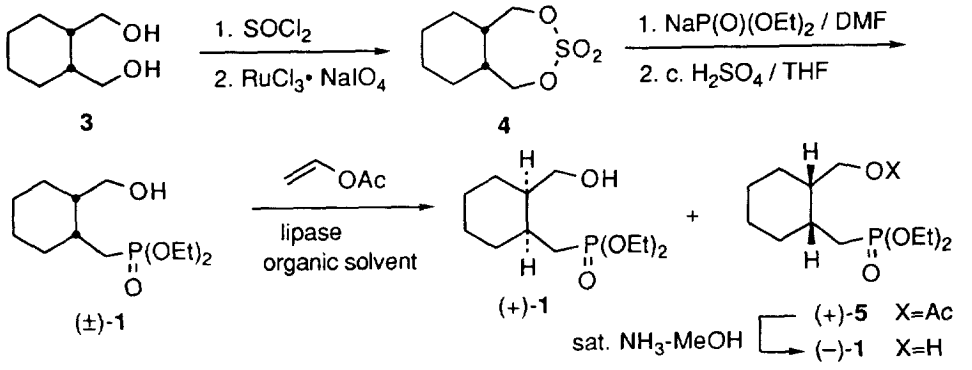


Table 1. Transesterification of phosphono alcohol **1** catalyzed by lipases

Entry[a]	Lipase[b] (mg / 100 mg of substrate)	Conditions		Conv.[c]	Alcohol (+)-**1**		Acetate (+)-**5**		E[e]
		Solvent	Time(h)	(%)	Yield(%)	Ee(%)[d]	Yield(%)	Ee(%)[d]	
1	PS (200)	THF	15	62.5	38	60	55	36	3.7
2	PS (100)	THF	15	38.9	60	62	35	97	62
3	PS (100)	t-BuOMe	12	50.0	38	14	25	14	1.27
4	PS (50)	none	52	60.0	42	98	54	64	20
5	AK (50)	none	6.5	52.0	41	>99	35	93	152

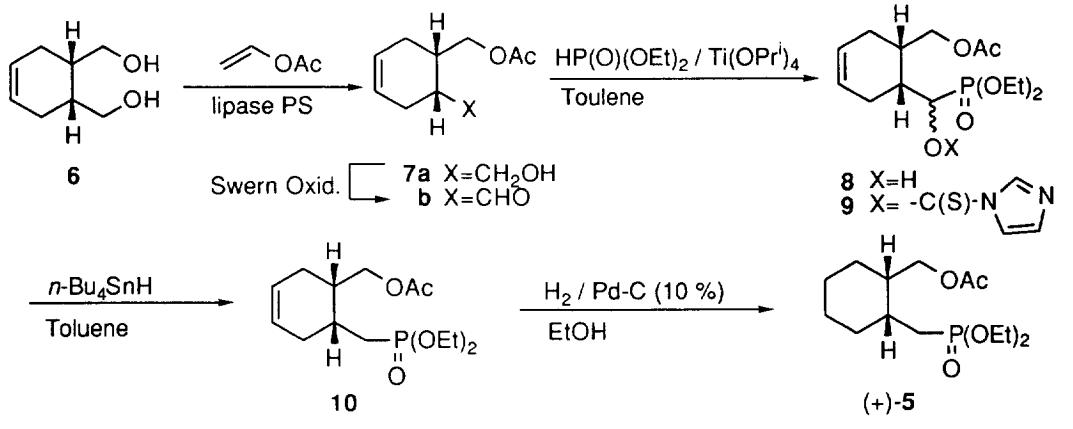
[a]All reactions were carried out at 37 °C. [b]PS (*Peudomonas cepacia.*, Amano); AK (*Psudomonas fluoresence.*, Amano) [c]The conversion degree was calculated by the expression $c=ee_s / (ee_s+ee_p)$. [d]Determined by HPLC analysis on Chiralpak AS (Daicel) using hexane:EtOH=30:1 as eluant. [e]Determined as reported by Sih (Ref.9).

For the enantioselective acylation of phosphono alcohol (±)-**1**, various commercially available lipases were examined under a variety of conditions. Although CCL[10] from *Candida cylindracea*, PPL[10] from *Poricine Pancreas* and Lipase AY from *Candida rugosa* did not effect the transesterification, lipase PS from *Peudomonas cepacia* and AK from *Peudomonas fluoresence* were found to catalyze the reaction. The enantiomeric excess (ee) of the acetate and the remaining phosphono alcohol, which were isolated form the reaction mixture by silica gel column chromatography, was determined by HPLC on a chiral phase. The results are summerized in Table 1. When the transesterification was carried out in the presence of lipase PS in THF containing a large excess of vinyl acetate (11 equiv.),[11] acylated product (+)-**5** was obtained in 35% yield with 97% *ee*, together with the corresponding alcohol (+)-**1** in 60% yield with 62% ee (entry 2). The enantioselectivity of the transesterification

highly depend on the amount of lipases and the nature of the solvent (entries 1 and 3). A significant decrease in the enantioselectivity was observed upon using t-BuOMe as a solvent (entry 3). The transesterification catalyzed by lipase PS without solvent[12] proceeded with modest enantiomeric ratio (E=20)[9] to give (+)-**1** and (+)-**5** in 98 and 64% ee, respectively, when the reaction was terminated at the conversion of 60% (entry 4). Remarkable high enantiomeric ratio (E=152)[9] was observed on the reaction catalyzed by lipase AK without solvent (entry 5).[12,13] Upon terminating the reaction at the conversion of 52%, (+)-**1**, $[\alpha]_D^{25}$ +8.9 (c 1.0, MeOH), with 99% *ee* and (+)-**5**, $[\alpha]_D^{25}$ +2.31 (c 1.0, MeOH), with 93% *ee* were obtained in 41 and 35% isolated yield, respectively. The resolved phosphono acetate (+)-**5** was converted to (–)-**1** upon treatment with sat.NH_3-MeOH at room temperature.

Stereochemistry of the resolved (+)-**1** and (+)-**5** was determined by comparison with authentic samples prepared as follows (**Scheme 2**). Lipase PS-catalyzed transesterification of *meso*-diol **6** with vinyl acetate gave the known mono-acetate **7a**,[13] $[\alpha]_D^{25}$ +14.4 (c 1.0, MeOH), in 59% yield. Swern oxidation of **7a** to the aldehyde **7b**, followed by titanium-mediated hydrophosphonylation[14] gave a diastereoisomeric mixture (1:1) of **8** in 57% yield. Deoxygenating of **8** *via* the thiocarbonylimidazolide **9** according to the method of Rasmussen[15] gave the phosphono acetate **10**,[16] $[\alpha]_D^{25}$ +9.2 (c 1.1, MeOH), in 57% yield. Ee of **10** thus obtained was estimated to be 87%.[17] Hydrogenation of **10** over Pd-C (10%) in EtOH gave (+)-**5**. Thus, sterochemistry of (+)-**1** and (+)-**5** was established at this stage.

Scheme 2



Having established an efficient method for the resolution of (±)-**1**, our attention was focused on the introduction of α-amino carboxylic acid moiety onto the ω-positions. Swern oxidation of (+)-**1**, followed by Bucherer-Bergs reaction [NaCN, $(NH_4)_2CO_3$] of the aldehyde **11** gave hydantoins **12** [mp 112-114 °C; $[\alpha]_D^{25}$ +24.6 (c 1.1, MeOH)] and **13** [mp 94-96 °C, $[\alpha]_D^{25}$ –2.94 (c 1.0, MeOH)] in 38 and 40% yield, respectively. Although diasteroselectivity was not observed for this reaction, single diastereoisomers **12** and **13** were obtained in an enantiomerically pure form by easy chromatographic separation. The stereochemistry of the individual diastereoisomers was established by X-ray crystallographic analysis on racemic adducts (±)-**12** and (±)-**13**, prepared from (±)-**1** through exactly the same procedures as above. **Fig. 1** shows the corresponding ORTEP drawings.[17] The results show that Bucherer-Bergs reaction of **11** proceeded without epimerization of stereogenetic center α to the aldehyde.

In summary, we have achieved a highly efficient method for resolution of phosphonate containing primary alcohol **1** through lipase AK-catalyzed transesterification reaction.

Scheme 3

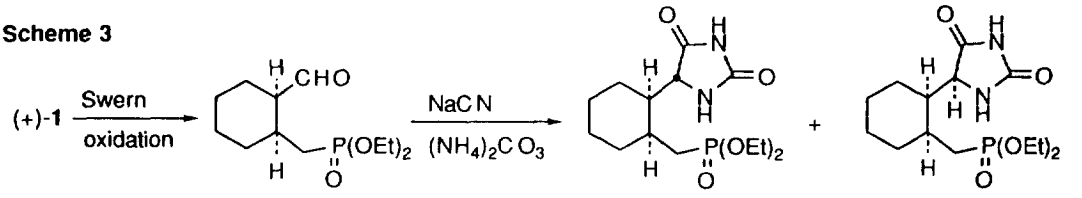
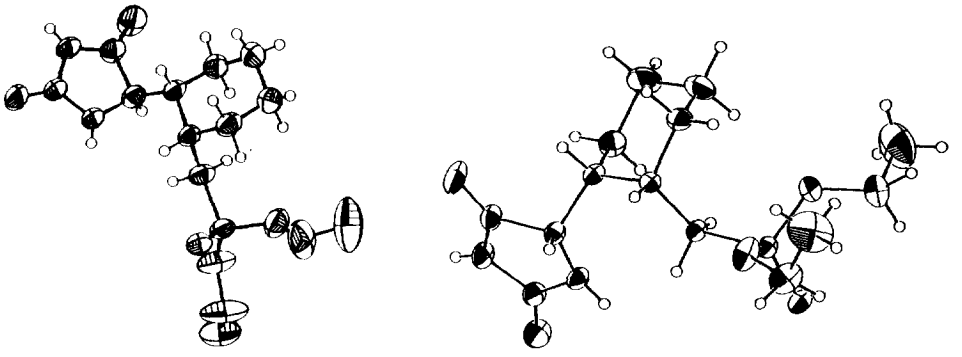


Fig. 1 Single-crystal X-ray structure of 12 and 13



Experimental Section

General: Melting points are not corrected. All reactions were carried out under nitrogen unless stated otherwise. Dry THF (tetrahydrofuran) was obtained by distillation from sodium benzophenone ketyl. CH_2Cl_2 was distilled from P_2O_5 prior to use. DMF was dried over 4A molecular sieves. ^{1}H-NMR (300 and/or 400 MHz) and ^{13}C-NMR (100 MHz) were measured in $CDCl_3$ using chloroform (δ 7.26 for ^{1}H; 77.0 for ^{13}C) as internal standard. ^{31}P-NMR (160 MHz) was taken in $CDCl_3$ using 85% H_3PO_4 as external standard with broad-band ^{1}H decoupling.

Preparation of cyclic sulfates 4. Meso diol **3** (7.54 g, 52 mmol) and Et_3N (21.01 g, 208 mmol) were treated with $SOCl_2$ (9.28 g, 78 mmol) in CH_2Cl_2 (100 mL) at 0 °C for 20 min. The mixture was diluted with ether (100 mL) and quenched with cold water. The biphasic mixture was extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated. The residue was diluted with a cold solution of CCl_4 (50 mL), CH_3CN (50 mL) and water (75 mL), and treated with $RuCl_3 \cdot H_2O$ (108 mg) and $NaIO_4$ (21.8 g, 104 mmol) at 0 °C. The mixture was stirred vigorously at same temperature for 2 h and then ether was added. The aqueous layer was extracted with ether. The combined extract was washed with brine, dried over $MgSO_4$, and evaporated to give cyclic sulfate **4** (9.5 g, 89% yield). mp 58-59 °C (hexane); ^{1}H-NMR ($CDCl_3$) δ 4.44 (2H, dd, J = 11.9, 6.5 Hz), 4.34 (2H, dd, J = 11.9, 0.5 Hz), 2.4-1.95 (2H, m), 1.95-1.35 (8H, m); ^{13}C-NMR

($CDCl_3$) δ 74.15, 38.07, 26.22, 23.60; IR (paste) 1396, 1215, 1034 cm^{-1}; CIMS (isobutene) *m/z* 207 (MH^+), 125, 109, 95, 81, 64; Anal. Calcd for $C_8H_{14}O_4S$: C, 46.59; H, 6.84; Found C, 46.14; H, 6.87.

***cis*-1-(Diethylphosphono)methyl-2-hydoxymethylcyclohexane (±)-1.** To a stirred suspension of NaH [2.16 g, 90.2 mmol; washed with hexane] in DMF (80 mL) was added diethyl phosphite (15.6 g, 112.8 mmol) dropwise at 25 °C. The mixture was stirred for 30 min at same temperature and allow to stand at 80 °C for 30 min. After being cooled to 0 °C, a solution of cyclic sulfate **4** (15.5 g, 75.2 mmol) in DMF (80 mL) was added and the solution was allowed to stand at 25 °C for 12 h with stirring, followed by heating at 80 °C for 30 min. The volatile component of the mixture was removed *in vacuo*, and the residue was dissolved in THF (50 mL), to which two drops of water had been added. The solution was acidified to pH 2-3 with a small quantity of c H_2SO_4 and stirred for 1 h. After removal of THF, the water was added. Extraction with $CHCl_3$, drying (Na_2SO_4) and solvent evaporation gave the crude products, which were purified by column chromatography (Silica gel, Et_2O-EtOAc=1:1) to give (±)-**1** (13.8 g, 70% yield) as a hygroscopic oil. ^{1}H-NMR ($CDCl_3$) δ 4.22-4.01 (4H, m), 3.43 (2H, d, *J*=7.69 Hz), 2.45-2.31 (1H, m), 1.90-1.75 (2H, m), 1.65-1.01 (8H, m),1.32 (6H, t with small split, *J* = 6.63 Hz); ^{13}C-NMR ($CDCl_3$) δ 63.84, 62.02 (d, $^2J_{PC}$=7.05 Hz), 61.77 (d, $^2J_{PC}$ = 6.19), 42.42 ($^3J_{PC}$ = 6.08 Hz), 32.25 (d,$^2J_{PC}$ = 9.1 Hz), 28.70, 24.71, 24.54 (d, $^1J_{PC}$ = 146 Hz), 24.38, 21.82, 16.42; ^{31}P-NMR ($CDCl_3$) δ 34.70; IR (neat) 3413, 2927, 1225, 1098 cm^{-1}; EIMS *m/z* 265 (M^++1), 246, 234, 191, 152. Anal. Calcd for $C_{12}H_{25}O_4P$: C, 54.51; H, 9.54. Found: C, 53.65; H, 9.54.

General Procedures for Resolution of (±)-1 by Lipase-catalyzed Transesterification Reaction.

In organic solvent: To a stirred solution of (±)-**1** (1.05 g, 4.0 mmol) in THF (30 mL) or t-BuOMe (30 ml) was added 4mL of vinyl acetate, followed by 1.05 g of Lipase PS. The mixture was stirred at 37 °C for several hours as indicated in Table 1. The reaction was terminated by filtering off the enzyme. After removal of the filtrate, the crude was purified by column chromatography on silica gel, eluting with hexane:EtOAc = 1:1 to furnish the acetate (+)-**5**. Successive elution with 1% MeOH-$CHCl_3$ gave the phosphono alcohol (+)-**1**.

Without solvent: To a stirred solution of (±)-**1** (1.05 g, 4.0 mmol) in 0.5 ml of vinylacetate was added lipase PS or AK (520 mg). The mixture was stirred at 37 °C for several hours as indicated in Table 1. Work up and separation of the products as above gave (+)-**1** and (+)-**5**.

(+)-**1**: an oil, $[\alpha]_D^{25}$ +8.9 (c 1.0, MeOH) for the sample (>99% ee) prepared with lipase AK. The other physical data were identical to those of (±)-**1**.

(+)-**5**: an oil, $[\alpha]_D^{25}$ +2.31 (c 1.0, MeOH) for the sample (93% ee) prepared with lipase AK; ^{1}H-NMR ($CDCl_3$) δ 4.17-3.93 (6H, m), 2.28-2.13 (1H, m), 2.05 (3H, s), 2.02-1.93 (1H, m), 1.78-1.60 (2H, m), 1.31 (3H, t, *J*=7.09 Hz); ^{13}C-NMR ($CDCl_3$) δ 171.04, 64.69, 61.35 (d, $^2J_{PC}$ = 7.0 Hz), 61.26 (d, $^2J_{PC}$ = 7.0 Hz), 38.80 (d, $^2J_{PC}$ = 13.2 Hz), 31.46, 29.43 (d, $^3J_{PC}$ = 5.0 Hz), 25.61, 25.54 (d, $^1J_{PC}$ = 138.9 Hz), 23.20, 22.67, 20.86, 16.35 (d, $^3J_{PC}$ = 5.6 Hz); ^{31}P-NMR ($CDCl_3$) 31.96; IR (neat) 3462, 2931, 1740, 1245, 1098 cm^{-1}; EIMS m/z 306(M^+), 263, 243. Anal. Calcd for $C_{14}H_{27}O_5P$: C, 54.87; H, 8.89. Found: C, 54.36; H, 8.90.

Conversion of (+)-5 to (-)-1. Acetate (+)-**5** (1.0g, 3.3 mmol) was treated with *sat.* NH_3-MeOH (10 mL) at 25 °C for 48 h. The volatile component of the mixture was removed *in vacuo* and the residue was purified by column chromatography on silica gel to give (-)-**1** (510 mg, 58% yield, 77% yield based on recovered the acetate) as an oil: $[\alpha]_D^{25}$ -6.77 (c 1.0, MeOH) for sample prepared from (+)-**5** with 83% ee. The other physical data were identical to those of (±)-**1**.

Preparation of Mono Acetate 7a. To a stirred solution of **6** (4.5 g) in viny acetate (3 mL) was added lipase PS (2.5 g). The mixture was stirred at 37 °C for 12 h. The reaction was terminated by filtering off the enzyme. After removal of the solvent, the crude was purified by silica gel column chromatography (hexane: EtOAc=7:1) to give the mono-acetate **7a** (3.4 g, 59% yield) as an oil. $[\alpha]_D^{25}$+14.4 (c 1.13, MeOH), lit.[13] $[\alpha]_D^{25}$-19.4 for ***ent*-7**; ^{1}H-NMR ($CDCl_3$) δ 5.63 (2H, broad s), 4.18 (1H, dd, *J*=10.9, 6.0 Hz), 3.94 (1H, dd, *J*=10.9, 8.6 Hz), 2.28-1.82 (7H, m), 2.04 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 171.4, 125.6, 125.1, 65.0, 63.6, 37.2, 33.2, 27.0, 26.0, 21.0; IR (neat) 3432, 3025, 1739 cm^{-1}; EIMS m/z 185 (M^++1). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.87; H, 8.83.

Preparation of 8. The alcohol **7** (1.67 g, 9 mmol) was oxidized with DMSO (22 mmol), $(COCl)_2$ (11 mmol) and Et_3N (45 mmol) at -78 °C in CH_2Cl_2 according to the method of Swern [18] to give the crude aldehyde **7b** as an oil, which was submitted the hydrophosphonylation without purification. A mixture of **7b** and $HP(O)(OEt)_2$ (1.5 g, 10.8 mmol) in toluene (6 mL) was cooled to 0 °C. Then a solution of $Ti(OPr^i)_4$ (0.54 mL, 1.8 mmol) in toluene (8 mL) was added dropwise. The mixture was stirred at the same temperature for 24 h. Water was added to quench the reaction. The separated aqueous layer was extracted with EtOAc. The combined extract was washed with brine and dried over Ma_2SO_4. The solvent was removed and the residue was chromatographed on silica gel (hexane: EtOAc=1:1) to give **8** (1.6 g, 57% yield) as an oil. $[\alpha]_D^{25}$+10.2 (c 1.1, MeOH); ^{1}H-NMR ($CDCl_3$) δ 5.93 (1H, s), 5.75-5.56 (2H, m), 4.27-4.09 (4H, m), 4.09-3.94 (2H, m), 2.35-2.07 (6H, m), 2.04 (1.5 H, s), 2.03 (1.5 H, s), 1.38-1.30 (6H, m); IR (neat) 3307, 1738, 1244, 1036 cm^{-1}, EIMS *m/z* 321 (M^++1). Anal. Calcd for $C_{14}H_{25}O_6P$: C, 52.47; H, 7.87. Found: C, 52.38; H, 7.99.

(Thiocarbonyl)imizazolide 9. Thiocarbonylimidazole (1.7 g, 9.6 mmol) was added to a solution of **8** (1.6 g, 4.8 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was heated under reflux for 10 h. After cooling, the solution was concentrated *in vacuo*. (Thiocarbonyl)imizazolide **9** was isolated by column chromatography on silica gel (hexane:EtOAc=1:1) in 70% yield: an oil, $[\alpha]_D^{25}$ –3.16 (c 1.1, MeOH), ^{1}H-NMR ($CDCl_3$) δ 8.37 (0.5H, d, *J*=0.93 Hz), 8.31 (0.5H, s), 7.67 (0.5H, s with small splits), 7.62 (0.5H, s with small splits), 7.07 (0,5H, s with small splits), 7.04 (5H, s with small splits), 6.34 (0.5H, dd, *J*=8.5, 8.5 Hz), 6.09 (0.5H, dd, J=9.9, 8.5 Hz), 5.7-5.55 (2H, m), 4.25-4.1 (5.75H, m), 3.95 (0.25H, dd, *J*=9.7, 9.7 Hz), 2.09 (1.5H, s), 1.99 (1.5H, s), 1.42-1.21 (6H, m); IR (neat) 3220, 2985, 1740, 1242, 1097 cm^{-1}; EIMS m/z 431 (M^++1).

Reduction of 9 with Tri-*n*-buthylstannane. A solution of **9** (1.4 g, 3.25 mmol) in toluene (10 mL) was added dropwise over 30 min to a stirred solution of refluxing toluene (40 mL) and tri-*n*-butylstannane (1.3 mL; 4.7 mmol). The mixture was heated for an additional 15 h. The solution was extracted with acetonitrile and the combined extract was washed with hexane. After concentration of the acetonitrile layer *in vacuo*, the crude was purified by column chromatography on silica gel (hexane:EtOAc= 1:1) to give **10** (989 mg, 80% yield) as an oil. $[\alpha]_D^{25}$ +9.2 (c 1.1, MeOH); ^{1}H-NMR ($CDCl_3$) δ 5.61 (2H, broad s), 4.13-4.02 (4H, m), 4.01-3.92 (2H, m), 2.37-2.05 (6H, m), 2.03 (3H, s), 1.75-1.68 (2H, m), 1.30 (6H, t with a small split, *J*=7.1 Hz). ^{13}C-NMR ($CDCl_3$) δ 171.07, 125.85, 64.71, 61.48 (d, $^2J_{PC}$=7.8 Hz), 36.16 (d, $^2J_{PC}$=13. 8 Hz), 29.92 (d, $^3J_{PC}$=4.6 Hz), 28.63 (d, $^3J_{PC}$=3.7 Hz), 26.04, 25.86 (d, $^3J_{PC}$=140.8 Hz), 20.91, 16.41 (d, $^3J_{PC}$=5.7 Hz); ^{31}P-NMR ($CDCl_3$) δ 31.82; IR(neat) 3454,1740, 1242, 1098 cm^{-1}; EIMS *m/z* 305 (M^++1). Anal. Calcd for $C_{14}H_{25}O_5P$: C, 55.24; H, 8.28. Found: C, 55.63; H, 8.36.

Hydrogenation of 10. A mixture of **10** (100 mg) and 10% palladium on carbon (50 mg) in EtOH (1 ml) was hydrogenated at 4 kg/cm^2 pressure of hydrogen for 10 h. The mixture was filtrated through Celite, concentrated and purified through a silica gel column (hexane:EtOAc=1:1). The product was obtained as a

colorless oil (90% yield; 87% ee) whose ^{1}H-NMR and a sigh of specific rotation were identical to (+)-**5** obtained by the resolution of (±)-**1**.

(1R,2S)-2-Diethylphosphonomethylcyclohexane-1-carboxyaldehyde 11. A solution of oxalyl chloride (2.0 g,7.6 mmol) in CH_2Cl_2 (20 mL) was cooled to -78 °C and treated with 1.3 mL (18.3 mmol) of DMSO. After the solution was stirred for 10 min, alcohol (+)-**1** (1.7 g, 6.3 mmol) in CH_2Cl_2 (20 mL) was added. After the mixture was stirred for an additional 30 min, triethylamine (5.3 mL) was added, and the mixture was stirred for 30 min at -78 °C and 1 h at room temperature. Water was added, the layers was separated, the organic phase was washed with brined and dried over $MgSO_4$. Evaporation of the solvent gave the crude **11** (1.7 g) as an oil which was used for the next reaction without purification: **11** $[\alpha]_D^{25}$ +4.4 (c 1.0, MeOH); ^{1}H-NMR ($CDCl_3$) δ 9.72 (1H, s), 1.34 (6H, t, *J*=7.0 Hz); ^{31}P-NMR ($CDCl_3$) δ 30.96.

Bucherer-Bergs Reaction of aldehyde 11. To a solution of crude aldehyde **11** (1.83 g, 7 mmol) in 20 mL of 50% aq. MeOH was successively added NaCN (380 mg, 7.7 mmol) and $(NH_4)_2CO_3$ (2.4 g, 25.2 mmol). The mixture was heated at 60 °C for 4 h. MeOH was evaporated and aqueous solution was extracted with $CHCl_3$. The combined extract was washed with brine, dried (Na_2SO_4), and concentrated. The crude products were purified on silica gel column chromatography. Elution with hexane : EtOAc (1:1) gave hydantoin **12** (890 mg, 38% yield) as colorless crystal. Successive elution with Et_2O:EtOAc (1:1) gave the isomer **13** (950 mg, 40% yield) as colorless crystal.

12: mp 112-114 °C (ether) for (+)-**12**, mp 184-186 (EtOAc:hexane) for (±)-**12**; $[\alpha]_D^{25}$ +24.6 (c 1.1, MeOH); ^{1}H-NMR ($CDCl_3$) δ 8.51 (1H, broad s), 7.60 (1H, broad s), 4.22-4.05 (4H, m), 3.67 (2H, d, *J* = 10.99 Hz), 2.5-2.27 (2H, m), 1.83-0.99 (10H, m), 1.33 (6H, t, *J* = 7.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 174.78, 156.01, 62.06 (d, $^2J_{PC}$ = 6.7 Hz), 61.82 (d, $^2J_{PC}$ = 6.6 Hz), 59.56, 44.05 (d, $^2J_{PC}$ = 8.4 Hz), 31.51 (d, $^3J_{PC}$ = 3.7 Hz), 28.64, 24.86, 22.43 (d, $^1J_{PC}$ = 140.2 Hz), 22.44, 19.63, 16.10; ^{31}P-NMR ($CDCl_3$) δ 33.78; IR (paste) 1770, 1713, 1255, 1102 cm^{-1}; EIMS *m/z* 332 (M^+), 316, 287, 265, 234, 153 (100%), 125, 108. Anal. calcd for $C_{14}H_{25}N_2O_5P$: C, 50.58; H, 7.59; N, 8.43. Found: C, 50.49; H, 7.67; N, 8.32.

13: mp 94-96 (ether) for (-)-**13**, mp 169-171 °C (*i*-PrOH) for (±)-**13**; $[\alpha]_D^{25}$ –2.94 (c 1.0, MeOH); ^{1}H-NMR ($CDCl_3$) δ 9.51 (1H, broad s), 7.31 (1H, broad s), 4.19-3.95 (5H, m), 2.40-1.40 (12H, m), 1.33 (3H, t, *J*=7.0 Hz), 1.31 (3H, t, *J*=7.1 Hz); ^{13}C-NMR ($CDCl_3$) δ 175.34, 158.37, 63.10, 62.04 (d, $^2J_{PC}$ = 6.6 Hz), 43.07 (d, $^2J_{PC}$ = 9.1 Hz), 33.36 (broad s), 32.70, 25.55, 24.50 (d, $^1J_{PC}$ = 138.8 Hz), 21.00, 20.00, 16.41 (d, $^3J_{PC}$ = 5.63 Hz); ^{31}P-NMR ($CDCl_3$) δ 32.69; IR (paste) 1769, 1723, 1257, 1097 cm^{-1}; EIMS m/z 332 (M^+), 288, 260, 233, 194, 177, 153 (100%), 125, 83. Anal. calcd for $C_{14}H_{25}N_2O_5P$: C, 50.58; H, 7.59; N, 8.43. Found: C, 50.71; H, 7.56; N, 8.35.

Acknowledgments This work was supported in part by Grant-in-Aid for Scientific Research (07672293) from the Ministry of Education, Science and Culture of Japan. Thanks are also due to Amano Pharmaceutical Co., Ltd. for their kindly providing lipases and to MAC Science Co., Ltd. for X-ray crystallographic analysis of (±)-**13**.

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17. Determined by HPLC analysis on Chiralpak AS (Daicel).
18 Data collections were performed by Mac-Science MXC 18 (for (±)-**12**) or DIP 2000 (for (±)-**13**) diffarectmeters. The structures were solved by direct methods using SHELXS86 (Sheldrik, 1986) and refined with a full matrix least-squares method. Crystal Data of (±)-**12**: $C_{14}H_{25}N_2O_5P$, Mr=332.00, monoclinic, space group P21/n, a=13.712(2)Å, b=9.532(2)Å, c=13.671(2)Å, β=107.42(1)°, V=1704.8(6)Å^3, T=293K, Z=4, Dx=1.29 gcm^{-1}, (Cu-Kα)=1.54178Å, μ=15.39 cm^{-1}, R=0.068 over 2731 independent reflections. Crystal Data of (±)-**13**: $C_{14}H_{25}N_2O_5P$, Mr=332.00, monoclinic, space group P21/c, a=12.960Å, b=10.692Å, c=13.410Å, β=111.846°, V=1073.74Å^3, T=293K, Z=4, Dx=1.28 gcm^{-1}, (Mo-Kα)=0.71073Å, μ=1.760 cm^{-1}, R=0.0548 over 2627 independent reflections.
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(*Received in Japan* 27 *September* 1995)