Chemoenzymatic Synthesis of α-Substituted Serines *via* Enantiodivergent Transformation

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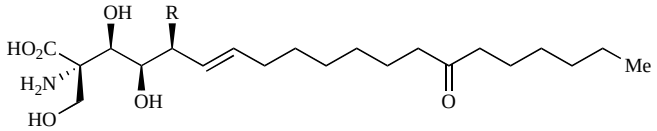
Abstract: A series of (*R*)-*N*-Cbz-2-alkyl-2-amino-3-hydroxypropyl acetates was prepared by enzymatic acetylation of *N*-Cbz-2-alkyl-2-aminopropane-1,3-diols with immobilized lipoprotein lipase from *Pseudomonas* sp. in up to 98% enantiomeric excess (ee). Enantiodivergent oxidation of (*R*)-*N*-Cbz-2-alkyl-2-amino-3-hydroxypropyl acetates readily furnished (*R*)- and (*S*)-α-substituted serines (α-benzylserines and α-methylserines). Enzymatic hydrolysis of diethyl *N*-Cbz-2-amino-2-methylmalonate catalyzed by porcine liver esterase afforded (*R*)-*N*-Cbz-2-amino-3-ethoxy-2-methyl-3-oxopropanoic acid in 97% ee. (*R*)-*N*-Cbz-2-amino-3-ethoxy-2-methyl-3-oxopropanoic acid was also transformed to both enantiomers of α-methylserine *via* enantiodivergent reduction.

Keywords: Asymmetric synthesis, Lipoprotein lipase, Acetylation, 1,3-Diols, Enantiodivergent, α-Substituted serines.

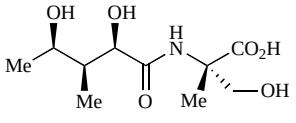
INTRODUCTION

In recent years there has been a considerable interest in the asymmetric synthesis of α,α-disubstituted α-amino acids because of their biological importance [1]. The α-substituted serine moiety has been of particular interest as a unique structure found in bioactive natural products, such as myriocin (ISP-I, thermozymocidin) [2], sphingofungin E [3], (+)-conagenin [4], and (+)-lactacystin [5] (Fig. (**1**)). Thus, the asymmetric synthesis of α-substituted serines has been an area of intensive investigation in our laboratory for the past few years.

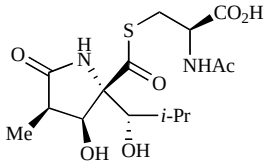


R = H; myriocin (ISP-I, thermozymocidin)

R = OH; sphingofungin E



(+)-conagenin



(+)-lactacystin

Fig. (1). Bioactive natural products including an α-substituted serine moiety.

As part of our own contribution to this area, we developed several non-enzymatic asymmetric syntheses based on novel bislactim ethers derived from diethyl aminomalonate hydrochloride [6]. Further, we applied a chemo-enzymatic synthesis of α-substituted serines utilizing enzyme-catalyzed desymmetrization of σ-symmetric compounds [7]. The synthesis of α-substituted serines was accomplished by a combination of esterase-catalyzed enantioselective hydrolysis of prochiral diethyl *N*-Cbz-2-alkyl-2-aminomalonates and enantiodivergent reduction of resultant acid esters. The enantiodivergent strategy is efficient for synthesizing the desired chiral α-substituted serine without dependence on the absolute configuration of a single starting enantiomer [8]. However, the limited specificity of substrates is a disadvantage of this chemo-enzymatic reaction. The esterase-catalyzed hydrolysis of diethyl *N*-Cbz-2-hexyl-2-aminomalonate gave only a trace amount of the corresponding acid ester. In addition, the moderate yields in the enantiodivergent transformation should be improved in this chemo-enzymatic synthesis. We therefore developed lipase-catalyzed enantioselective acetylation of prochiral *N*-Cbz-2-alkyl-2-aminopropane-1,3-diols [9]. The lipase-catalyzed acetylation of *N*-Cbz-2-amino-2-hexylpropane-1,3-diol provided satisfactory results.

In this paper, we describe in detail the lipase-catalyzed enantioselective acetylation of prochiral σ-symmetric *N*-Cbz-2-alkyl-2-aminopropane-1,3-diols and the enantiodivergent oxidation of the resultant chiral mono-acetylated product toward the construction of both enantiomers of α-substituted serines as shown in Scheme **1**. We also illustrate improved enantiodivergent reduction of (*R*)-*N*-Cbz-2-amino-2-methylmalonate to both enantiomers of α-methylserine (Scheme **1**).

RESULTS AND DISCUSSION

N-Cbz-2-alkyl-2-aminopropane-1,3-diols **4a-d**, substrates for lipase-catalyzed acetylation, were synthesized as shown in Scheme **2**. Diethyl *N*-Cbz-2-aminomalonate **2** was prepared from diethyl 2-aminomalonate hydrochloride **1** by a standard method in 97% yield [6]. Then diethyl *N*-Cbz-2-alkyl-2-aminomalonates **3a-d** were obtained by the treatment of *N*-protected diester **2** with NaH, followed by alkylation of

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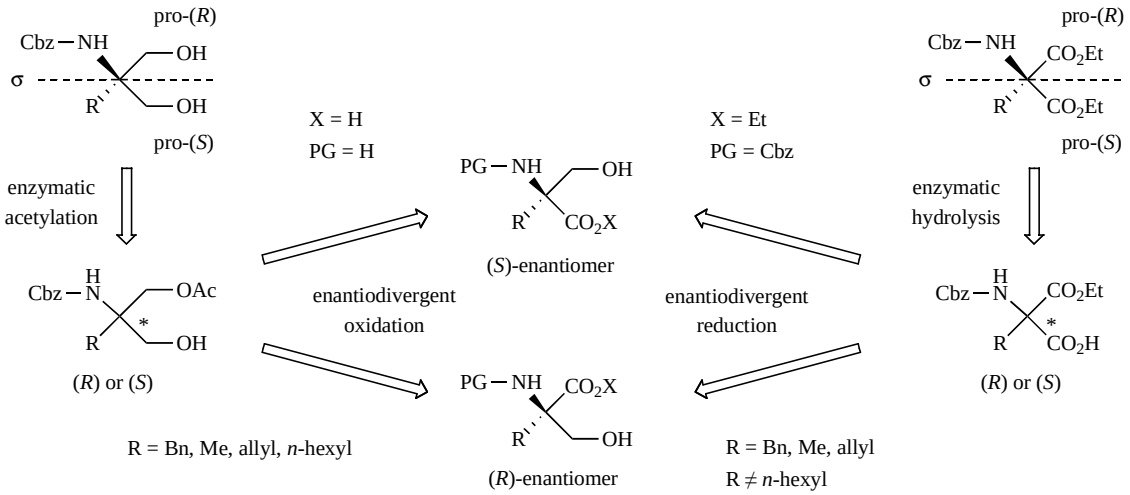
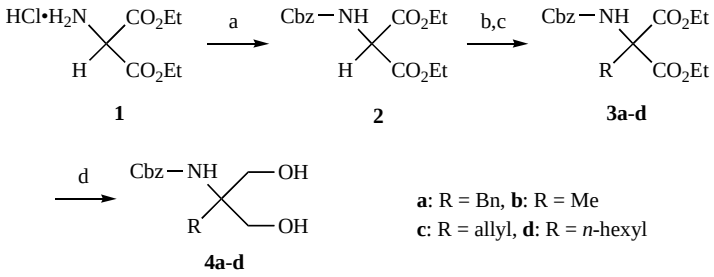


Scheme 1. Chemoenzymatic enantiodivergent synthesis of chiral α-substituted serines.



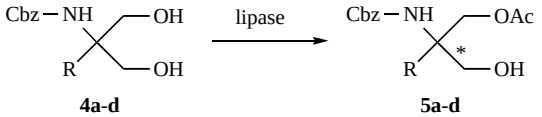
Scheme 2. *Reagents and conditions*: (a) Cbz-Cl, $NaHCO_3$, H_2O–Et_2O (1:1), rt, 6 h, 97%; (b) NaH, THF, 0 °C, 20 min; (c) **a**: BnBr, THF, 0 °C, 20 min to rt, 5 h, 82%, **b**: MeI, THF, rt, 15 min to 50 °C, 2 h, 87%, **c**: CH_2=$CHCH_2Br$, THF, 0 °C, 40 min to rt, 7 h, 88%, **d**: $Me(CH_2)_5I$, THF, 50 °C, 20 h, 77%; (d) **a**: $LiBH_4$, THF, 0 °C, 1 h to rt, 20 h, 59%, **b**: $LiBH_4$, Et_2O, rt, 24 h, 74%, **c**: $NaBH_4$, EtOH, 0 °C, 19.5 h to rt, 8 h, 58%, **d**: $LiBH_4$, THF, 0 °C, 10 h to rt, 5 h, 48%.

the resulting sodium enolate with alkyl halides in 77-88% yields. Subsequent reduction of diesters **3a-d** with $LiBH_4$ or $NaBH_4$ afforded the corresponding 1,3-diols **4a-d** in 48-74% yields, respectively.

Lipase-catalyzed acetylation of the 1,3-diols **4a-d** into the chiral monoacetates **5a-d** was investigated utilizing more than 10 kinds of commercially available lipases (Scheme **3**).

First, we attempted the acetylation of prochiral 1,3-diol **4b** with vinyl acetate in the presence of several kinds of lipases in THF at room temperature. This yielded monoacetate **5b** in 30-35% enantiomeric excess (ee) with a series of Lipase PS from *Pseudomonas* sp. (Table **1**, entries 4-6). The yield was significantly improved when an immobilized enzyme, such as Lipase PS-C or Lipase PS-D, was used. In addition, different kinds of lipases from *Pseudomonas* sp. improved both the yield and the ee (Table **1**, entries 10-12).

Lipase-catalyzed acetylation of **4b** was further investigated with LPL (lipoprotein lipase from *Pseudomonas* sp.)



a: R = Bn, **b**: R = Me, **c**: R = allyl, **d**: R = *n*-hexyl

Scheme 3. Lipase-catalyzed acetylation of *N*-Cbz-2-alkyl-2-aminopropane-1,3-diols **4a-d** (Tables **1**-**6**).

purchased from Fluka (Table **1**, entry 12). The yields of **5b** varied depending on the reaction temperature, which did not have as great an effect on the ee values (Table **2**). The yield of monoacetate **5b** was low at –30 °C, and the formation of diester by overacetylation was remarkable at 40 °C. The overacetylation did not contribute to the desymmetrization of 1,3-diol **4b** (Table **2**, entries 4 and 5).

On the other hand, both the yield and the ee were influenced by the solvent used in the LPL-catalyzed acetylation in Table **3**. In other words, acetylation in an acyclic ether (entries 3-7) was superior to that in a cyclic ether (entries 1 and 2). In particular, *tert*-butyl methyl ether (TBME) and cyclopentyl methyl ether (CPME) gave good results in both the yield and the ee (Table **3**, entries 6 and 7). TBME is one of the ordinary solvents employed in enzyme-catalyzed acylation [10]. These reactions in Table **3** were quenched when the appearance of the corresponding diacetate was detected by TLC (silica gel).

The prochiral 1,3-diol **4b** was also converted into the monoacetate **5b** by LPL-catalyzed acylation with various acyl donors. Equally good results were obtained by utilizing isopropenyl acetate as an acyl donor instead of vinyl acetate (Table **4**, entries 1 and 2).

Finally, optimized results of lipase-catalyzed acetylation of 1,3-diol **4a-d** with vinyl acetate (4 mol eq) in TBME were achieved by employing LPL from *Pseudomonas* sp. (Fluka, lyophilized powder, ca. 20,000 units/mmol) or immobilized

Table 1. Lipase-Catalyzed Acetylation of Propane-1,3-diol 4b [a]

Entry	4b	Lipase [b]	Time	Yield of 5b (%) [c]	Ee of 5b (%) [d]
1	200 mg	Lipase AK	24 h	27	6
2	100 mg	Lipase AYS	48 h	1	— [e]
3	100 mg	Lipase AS	48 h	2	1
4	100 mg	Lipase PS	24 h	3	35 (*R*)
5	100 mg	Lipase PS-C	24 h	55	35 (*R*)
6	100 mg	Lipase PS-D	24 h	66	30 (*R*)
7	100 mg	Lipase from *Pseudomonas cepacia*	5 d	3	34 (*R*)
8	100 mg	Lipase from *Pseudomonas fluorescens*	15 h	38	28 (*R*)
9	100 mg	Lipoprotein lipase from *Pseudomonas* sp.	14 d	10	36 (*R*)
10	80 mg	Lipoprotein lipase from *Pseudomonas* sp.	3 h	78	72 (*R*)
11	80 mg	Lipase from *Pseudomonas* sp.	2 h	78	77 (*R*)
12	100 mg	Lipoprotein lipase from *Pseudomonas* sp.	1.5 h	85	78 (*R*)

[a]Lipase (entries 1-6, 12,000 units/mmol; entries 7-12, 30 mg), vinyl acetate (5 mol eq), THF (10 ml), rt.
[b]Entries 1-6: Amano Enzyme. PS-C: immobilized on ceramic particles. PS-D: immobilized on diatomaceous earth. Entries 7, 8, 12: Fluka; entry 9: Wako Pure Chemical Industries; entry 10: Toyobo; entry 11: Sigma.
[c]Isolated yields.
[d]HPLC analysis (CHIRALPAK AD-H, *n*-hexane/2-propanol = 15/1, 1.0 ml/min, 254 nm).
[e]Not determined.

Table 2. LPL-Catalyzed Acetylation of Propane-1,3-diol 4b [a]

Entry	Temperature	Time	Yield of 5b (%) [b]	Recovery of 4b (%) [b]	Ee of 5b (%) [c]
1	rt	1.5 h	85	9	78 (*R*)
2	0 °C	7 h	58	36	76 (*R*)
3	-30 °C	2 d	22	78	76 (*R*)
4	40 °C	30 min	66	21 [d]	72 (*R*)
5	40 °C	1 h	49	0 [e]	68 (*R*)

[a]**4b** (100 mg), LPL (30 mg), vinyl acetate (5 mol eq), THF (10 ml).
[b]Isolated yields.
[c]HPLC analysis (CHIRALPAK AD-H, *n*-hexane/2-propanol = 15/1 or 30/1, 1.0 ml/min, 254 nm).
[d]Diacetate (11%) was obtained.
[e]Diacetate (50%) was obtained.

Table 3. LPL-Catalyzed Acetylation of Propane-1,3-diol 4b [a]

Entry	Solvent [b]	Time (h)	Yield of 5b (%) [c]	Recovery of 4b (%) [c]	Ee of 5b (%) [d]
1	THF	1.5	85	9	78 (*R*)
2	1,4-dioxane	2	69	19	72 (*R*)
3	Et_2O	4	56	43	85 (*R*)
4	DBE	5	17	37	88 (*R*)
5	DIPE	4	23	55	89 (*R*)
6	TBME	6	75	10	85 (*R*)
7	CPME	6	79	11	86 (*R*)
8	benzene	12	25	61	82 (*R*)
9	dichloromethane	6	12	84	78 (*R*)
10	— [e]	1.5	26	74	85 (*R*)

[a]**4b** (100 mg), LPL (30 mg), vinyl acetate (5 mol eq), solvent (10 ml), rt.
[b]DBE: di-*n*-butyl ether; DIPE: diisopropyl ether; TBME: *tert*-butyl methyl ether; CPME: cyclopentyl methyl ether.
[c]Isolated yields.
[d]HPLC analysis (CHIRALCEL OD-H, *n*-hexane/2-propanol = 10/1, 1.0 ml/min, 254 nm).
[e]Vinyl acetate (10 ml) was used as solvent.

Table 4. LPL-Catalyzed Acylation of Propane-1,3-diol 4b [a]

Entry	Acyl Donor	Time (h)	Yield (%) [b]	Recovery of 4b (%) [b]	Ee (%) [c]
1	vinyl acetate	6	75 (**5b**)	10	85 (**5b**) (*R*)
2	prop-1-en-2-yl acetate	10	74 (**5b**)	16	85 (**5b**) (*R*)
3	vinyl 2-chloroacetate	8	53 (**5ba**)	34	44 (**5ba**)
4	vinyl butyrate	3	58 (**5bb**)	0	83 (**5bb**)
5	vinyl benzoate	64	12 (**5bc**)	85	79 (**5bc**)
6	vinyl pivalate	6	12 (**5bd**)	86	59 (**5bd**)

[a] **4b** (100 mg), LPL (30 mg), acyl donor (5 mol eq), TBME (10 ml), rt.
[b] Isolated yields.
[c] HPLC analysis (CHIRALCEL OD-H, *n*-hexane/2-propanol = 10/1 or 19/1, 1.0 ml/min, 254 nm).

Table 5. LPL-Catalyzed Acetylation of Propane-1,3-diol 4[a]

Entry	4	Lipase	Time (h)	Yield of 5 (%) [b]	Yield of Diacetate (%) [b,c]	Recovery of 4 (%) [b]	Ee of 5 (%)
1	844 mg (**4a**)	LPL	18	92 (**5a**)	3	4 (**4a**)	95 (**5a**) (*R*) [d]
2	137 mg (**4b**)	LPL	3	73 (**5b**)	23	1 (**4b**)	88 (**5b**) (*R*) [e]
3	152 mg (**4c**)	LPL	5.5	83 (**5c**)	7	5 (**4c**)	96 (**5c**) [f]
4	177 mg (**4d**)	LPL	9	77 (**5d**)	10	11 (**4d**)	93 (**5d**) [g]
5	180 mg (**4a**)	Immobilized LPL	2	94 (**5a**)	3	1 (**4a**)	97 (**5a**) (*R*) [d]
6	2.65 g (**4b**)	Immobilized LPL	1.3	72 (**5b**)	26	2 (**4b**)	92 (**5b**) (*R*) [e]
7	717 mg (**4c**)	Immobilized LPL	1	90 (**5c**)	3	5 (**4c**)	98 (**5c**) [f]
8	177 mg (**4d**)	Immobilized LPL	2	82 (**5d**)	12	2 (**4d**)	96 (**5d**) [g]

[a] LPL (entry 1: 20,549 units/mmol; entries 2-4: 21,291 units/mmol; entries 5-8: 51 units/mmol), vinyl acetate (4 mol eq), TBME, rt.
[b] Isolated yields.
[c] *N*-Cbz-2-alkyl-2-aminopropane-1,3-diyl diacetate.
[d] HPLC analysis (CHIRALCEL OJ-H, *n*-hexane/2-propanol = 5/1, 1.0 ml/min, 254 nm).
[e] HPLC analysis (CHIRALCEL OD-H, *n*-hexane/2-propanol = 10/1, 1.0 ml/min, 254 nm).
[f] HPLC analysis (CHIRALPAK AD-H, *n*-hexane/2-propanol = 19/1, 1.0 ml/min, 254 nm).
[g] HPLC analysis (CHIRALCEL OD-H, *n*-hexane/2-propanol = 19/1, 1.0 ml/min, 254 nm).

Table 6. Recycling of the Immobilized LPL in the LPL-Catalyzed Acetylation of Propane-1,3-diol 4c [a]

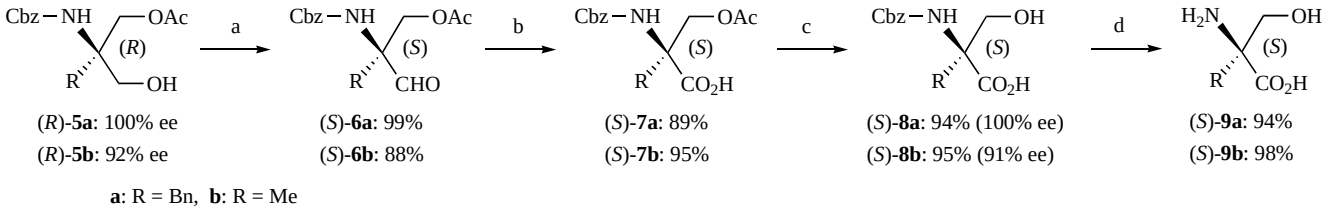
Cycle No.	4c	Time (h)	Yield of 5c (%) [b]	Yield of Diacetate (%) [b,c]	Recovery of 4c (%) [b]	Ee of 5c (%) [d]	Recovery of Immobilized LPL (%) [b]
1	717 mg	1	90	3	5	98	87
2	514 mg	5	84	6	3	97	84
3	295 mg	22	84	4	3	97	72

[a] Immobilized LPL (51 units/mmol), vinyl acetate (4 mol eq), TBME, rt.
[b] Isolated yields.
[c] *N*-Cbz-2-allyl-2-aminopropane-1,3-diyl diacetate.
[d] HPLC analysis (CHIRALPAK AD-H, *n*-hexane/2-propanol = 19/1, 1.0 ml/min, 254 nm).

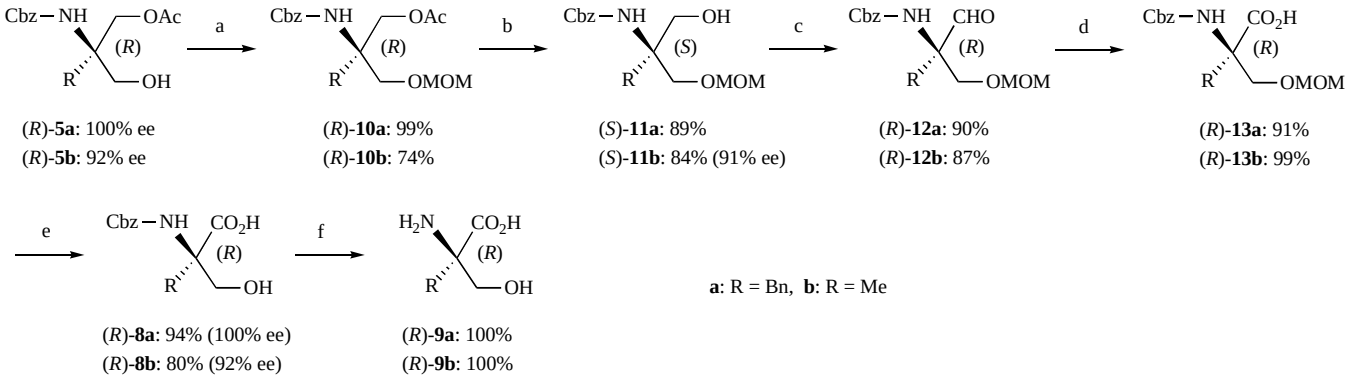
LPL from *Pseudomonas* sp. [Toyobo, LPL from *Pseudomonas* sp. immobilized on Hyflo Super-Cel (diatomaceous earth), 51 units/mmol] at room temperature (Table **5**).

The enantiomeric excess of monoacetates **5a-d** was determined by means of HPLC analysis on a chiral-stationary-phase (CSP) in comparison with racemic monoacetates **5a-d**. In addition, we attempted to recycle the immobilized LPL in the acetylation of propane-1,3-diol **4c**. The results demonstrated that the LPL retained remarkable acetylation activity for at least three cycles (Table **6**).

The absolute configuration of chiral monoacetates **5a** and **5b** was determined to be *R* by their chemical conversion into the known chiral compounds (*R*)- and (*S*)-**9a**,**b** and by comparing their specific rotations with those given in the literature (Scheme **4** and **5**) [11,12]. Thus, the pro-(*R*) hydroxymethyl group of **4a** and **4b** was selectively acetylated



Scheme 4. *Reagents and conditions*: (a) SO_3-pyridine, TEA, DMSO, rt, **a**: 30 min; **b**: 1 h; (b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O–*t*-BuOH (1:4), rt, **a**: 1 h; **b**: 1.5 h; (c) $LiEt_3BH$, THF, 0 °C, **a**: 30 min; **b**: 40 min; (d) H_2, 10% Pd-C, EtOH, rt, 3.5 h.



Scheme 5. *Reagents and conditions*: (a) MOMCl, DIPEA, **a**: CH_2Cl_2, 0 °C, 30 min to rt, 20.5 h; **b**: DMSO, rt, 7 h; (b) **a**: $LiEt_3BH$, THF, 0 °C, 50 min; **b**: K_2CO_3, MeOH, rt, 10 min; (c) SO_3-pyridine, TEA, DMSO, rt, **a**: 40 min; **b**: 50 min; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O–*t*-BuOH (1:5), rt, **a**: 1 h; **b**: 1.5 h; (e) 1 N HCl—THF (1:2), reflux, **a**: 24 h; **b**: 21 h; (f) H_2, 10% Pd-C, EtOH, rt, **a**: 4 h; **b**: 3.5 h.

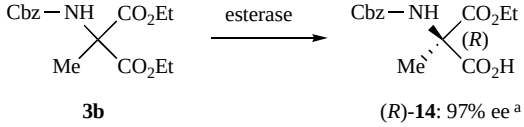
by LPL-catalyzed acetylation. The absolute configuration of the other chiral monoacetates, **5c** and **5d**, was determined by utilizing the novel diketopiperazine method (the DKP method) proposed by us [13].

Enantiodivergent transformation of (*R*)-**5a** to (*S*)-α-benzylserine [(*S*)-**9a**] was performed without isomerization, as shown in Scheme **4**. Recrystallization of (*R*)-**5a** (97% ee) from AcOEt—*n*-hexane gave (*R*)-**5a** in an enantiomerically pure form. Oxidation of (*R*)-**5a** with SO_3-pyridine in the presence of triethylamine (TEA) gave aldehyde (*S*)-**6a** in 99% yield. Further oxidation of (*S*)-**6a** with $NaClO_2$ afforded carboxylic acid (*S*)-**7a** in 89% yield [14]. Reductive deprotection of the acetyl group in (*S*)-**7a** was accomplished using $LiEt_3BH$ (Super Hydride®) [15]. Namely, the corresponding alcohol (*S*)-**8a** was prepared in 94% yield and 100% ee. The enantiomeric excess of (*S*)-**8a** was determined by means of HPLC analysis on a CSP after quantitative methylation with an excess amount of (trimethylsilyl)diazomethane ($TMSCHN_2$) [16]. Catalytic hydrogenolysis of (*S*)-**8a** with Pd-C under hydrogen at room temperature furnished the corresponding α-benzylserine (*S*)-**9a** in 94% yield as an enantiomerically pure form.

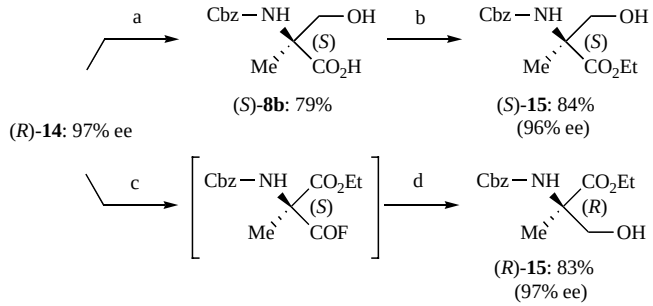
On the other hand, enantiodivergent synthesis of (*R*)-α-benzylserine [(*R*)-**9a**] from (*R*)-**5a** was achieved as shown in Scheme **5**. Treatment of (*R*)-**5a** with chloromethyl methyl ether (MOMCl) in the presence of diisopropylethylamine (DIPEA) furnished (*R*)-**10**, and then reductive deprotection of the acetyl group of the resulting (*R*)-**10** provided the desired alcohol (*S*)-**11** in 88% yield (two steps). After oxidation of (*S*)-**11** with SO_3-pyridine in the presence of TEA, the resulting aldehyde (*R*)-**12** was subjected to further oxidation to give carboxylic acid (*R*)-**13** in 82% yield (two steps). Treatment of (*R*)-**13** in 1N HCl—THF (1:2) under reflux afforded the corresponding alcohol (*R*)-**8a** in 94% yield and 100% ee. α-Benzylserine (*R*)-**9a** was quantitatively prepared from (*R*)-**8a** by catalytic hydrogenolysis.

(*S*)- and (*R*)-α-methylserine [(*S*)- and (*R*)-**9b**] was also obtained from (*R*)-**5b** in a similar enantiodivergent transformation without isomerization, as shown in Schemes **4** and **5**. In these reactions, deacetylation of (*R*)-**10b** took place under mild conditions utilizing K_2CO_3.

Although LPL-catalyzed acetylation of 1,3-diol **4b** afforded the corresponding monoacetate (*R*)-**5b** in 92% ee as already shown in Table **5**, we have previously reported that porcine liver esterase (PLE)-catalyzed hydrolysis of diester **3b** and enantiodivergent reduction of the resultant acid ester (*R*)-**14** furnished the corresponding α-methylserine derivative (*R*)- and (*S*)-**15** in 97% ee and 96% ee, respectively [7]. In this enzymatic hydrolysis of diester **3b**, (*R*)-**14** was obtained in 97% ee (Scheme **6**). Thus, we reinvestigated the enantiodivergent transformation of (*R*)-**14** to (*R*)- and (*S*)-**15**. Chemoselective reduction of (*R*)-**14** with Super Hydride® in THF instead of $LiBH_4$ in Et_2O furnished (*S*)-**8b** in 79% yield. Esterification of (*S*)-**8b** gave (*S*)-**15** in 84% yield and 96% ee as shown in Scheme **7**. On the other hand, fluorination of



Scheme 6. *Reagents and conditions*: PLE (1,293 units/mmol), 1/15 M phosphate buffer (pH 7.0)—MeCN (9:1), rt, 6 h. [a]HPLC analysis (CHIRALCEL OD-H, *n*-hexane/2-propanol = 15/1, 1.0 ml/min, 254 nm) after methylation with $TMSCHN_2$.



Scheme 7. *Reagents and conditions*: (a) $LiEt_3BH$, THF, 0 °C, 40 min; (b) EtI, K_2CO_3, acetone, reflux, 2 h; (c) DAST, THF, rt, 2 h; (d) $NaBH_4$, CH_2Cl_2—MeOH (2:5), -78 °C, 1 h.

(*R*)-**14** with diethylaminosulfur trifluoride (DAST) in THF, followed by reduction of the resultant acyl fluoride with $NaBH_4$ in CH_2Cl_2—MeOH, afforded (*R*)-**15** in 83% yield and 97% ee [17]. The enantiomeric excess of (*R*)- or (*S*)-**15** was determined by means of HPLC analysis on a CSP.

CONCLUSIONS

In conclusion, LPL-catalyzed acetylation of 1,3-diols **4a-d** gave the corresponding monoacetates **5a-d** in 92-98% ee. Both enantiomers of α-benzylserine [(*R*)- and (*S*)-**9a**] and α-methylserine [(*R*)- and (*S*)-**9b**] were obtained by enantiodivergent oxidation of (*R*)-**5a** and (*R*)-**5b** without any isomerization. In addition, reinvestigation of the enantiodivergent transformation of (*R*)-**14** to (*R*)- and (*S*)-**15** resulted in optimization of our previously reported method. The development of applications exploiting the synthesis of novel functional molecules containing α-substituted serines is currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-420 IR Fourier transform spectrometer. ^{1}H NMR (400 or 300 MHz) and ^{13}C NMR (100 or 75 MHz) spectra were recorded on JEOL JNM-AL400 and JEOL JNM-AL300 spectrometers, respectively. Chemical shifts are given in δ values (ppm) using tetramethylsilane (TMS) as an internal standard. Fast atom bombardment mass spectra (FABMS) and electron impact mass spectra (EIMS) were recorded on a JEOL JMS SX-102A spectrometer. Electron spray ionization mass spectra (ESIMS) were recorded on a Waters LCT Premier spectrometer. Elemental combustion analyses were performed using a Yanagimoto CHN CORDER MT-5. HPLC analyses were performed using a JASCO PU-980 apparatus equipped with a JASCO UV/VIS detector, using CHIRALPAK AD-H, CHIRALCEL OD-H or CHIRALCEL OJ-H (Daicel Chemical Industries). All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F_{254}). Preparative TLC (PTLC) was performed on 0.5-mm silica gel plates (Merck 5744; 60 F_{254}). Column chromatography was carried out on silica gel [Silica Gel 60N (Kanto Chemical; spherical, neutral, 63–210 μm), COSMOSIL 75 SL-II-PREP (Nacalai Tesque; spherical, 42–105 μm) or Silica Gel 60 (Merck; 40-63 μm)]. Anhydrous THF, CH_2Cl_2, MeOH, and DMF were used as purchased from Kanto Chemical. Anhydrous DMSO was commercially obtained from Wako Pure Chemical Industry. All other reagents were used as purchased.

Diethyl 2-(Benzyloxycarbonylamino)malonate (2)

To a stirring solution of diethyl 2-aminomalonate hydrochloride (500 mg, 2.36 mmol) and $NaHCO_3$ (515 mg, 6.14 mmol) in H_2O (15 mL) was added Cbz-Cl (219 μL, 1.53 mmol) and Et_2O (15 mL). After being stirred at room temperature for 2 h, $NaHCO_3$ (515 mg, 6.14 mmol) and Cbz-Cl (219 μL, 1.53 mmol) were added, and the resulting mixture was stirred at room temperature for 4 h. The solvent was removed *in vacuo*, AcOEt (30 mL) was added to the oily residue and the resultant solution was washed with 5% HCl (10 mL), H_2O (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [Silica Gel 60, *n*-hexane—AcOEt (2:1)] to afford **2** (711 mg, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08-1.05 (m, 6H), 4.03-4.53 (m, 4H), 5.00 (d, *J*=7.5 Hz, 1H), 5.13 (s, 2H), 5.80 (d, *J* =6.8 Hz, 1H), 7.06-7.83 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 57.7, 62.5, 67.3, 128.0, 128.1, 128.4, 135.8, 155.2, 166.1; IR (neat) 3376, 2985, 2361, 1505, 1217, 1026, 742 cm^{-1}; EIMS calcd for $C_{15}H_{19}NO_6$ MW 309.1212, found *m/z* 309.1209 (M^+); Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 58.21; H, 6.17; N, 4.40%.

Alkylation of Diethyl 2-(Benzyloxycarbonylamino) malonate (2) with Benzyl Bromide

A solution of **2** (3.0 g, 9.7 mmol) in anhydrous THF (10 mL) was added to a stirred suspension of NaH (abs. 60%, 407 mg, 10.1 mmol) in anhydrous THF (10 mL) at 0 °C under argon. The mixture was stirred at 0 °C for 20 min, and then benzyl bromide (1.27 mL, 10.6 mmol) was added to the solution. After being stirred at 0 °C for 20 min, the reaction mixture was allowed to warm to room temperature and then stirred for 5 h. The reaction mixture was concentrated *in vacuo* and was treated with 1 N HCl (10 mL) and then extracted with $CHCl_3$ (50 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [Silica Gel 60N, *n*-hexane—AcOEt (7:1)] to afford **3a** (3.19 g, 82%) as colorless oil.

Diethyl 2-Benzyl-2-(benzyloxycarbonylamino)malonate (3a)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.32 (m, 6H), 3.61 (s, 2H), 4.04-4.32 (m, 4H), 5.15 (s, 2H), 5.96 (s, 1H), 6.85-6.99 (m, 2H), 7.08-7.46 (m, 8H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 13.9, 38.1, 62.5, 66.8, 67.3, 127.0, 128.0, 128.1, 128.3, 128.4, 129.8, 134.7, 136.2, 154.1, 167.1; IR (neat) 3426, 2983, 1742, 1495, 1370, 1212, 1074, 749 cm^{-1}; EIMS calcd for $C_{22}H_{25}NO_6$ MW 399.1682, found *m/z* 399.1662 (M^+); Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 65.91; H, 6.27; N, 3.48%.

Diethyl 2-(Benzyloxycarbonylamino)-2-methylmalonate (3b)

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09-1.43 (m, 6H), 1.77 (s, 3H), 4.02-4.40 (m, 4H), 5.10 (s, 2H), 6.20 (s, 1H), 7.21-7.62 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.2, 62.5, 63.1, 66.8, 127.9, 128.0, 128.3, 136.1, 154.2, 168.4; IR (neat) 3423, 2985, 1732, 1499, 1376, 1206, 754 cm^{-1}; EIMS calcd for $C_{16}H_{21}NO_6$ MW 323.1369, found *m/z* 323.1372 (M^+); Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.03; H, 6.52; N, 4.51%.

Diethyl 2-Allyl-2-(benzyloxycarbonylamino)malonate (3c)

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11-1.29 (m, 6H), 3.06 (d, *J*=6.8 Hz, 2H), 3.99-4.35 (m, 4H), 4.97-5.25 (m, 4H), 5.51-5.68 (m, 1H), 6.14 (s, 1H), 7.20-7.44 (m. 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 37.3, 62.5, 66.3, 66.7, 119.7, 127.9, 128.0, 128.3, 131.0, 136.1, 154.1, 167.3; IR (neat) 3067, 1741, 1643, 1495, 1227, 1138, 1029, 927, 741 cm^{-1}; EIMS calcd for $C_{18}H_{23}NO_6$ MW 349.1525, found *m/z* 349.1531 (M^+); Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.55; H, 6.52; N, 3.95%.

Diethyl 2-(Benzyloxycarbonylamino)-2-hexylmalonate (3d)

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77-0.92 (m, 3H), 1.02-1.39 (m, 14H), 2.16-2.41 (m, 2H), 3.96-4.36 (m, 4H), 5.09 (s, 2H), 6.17 (s, 1H), 7.17-7.61 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.0, 22.5, 23.3, 28.9, 31.5, 32.4, 62.4, 66.7, 127.9, 128.0, 128.3, 136.2, 154.1, 167.9; IR (neat) 3425, 2930, 2860, 1732, 1495, 1370, 1251, 1201, 739 cm^{-1}; EIMS calcd for $C_{21}H_{31}NO_6$ MW 393.2151, found *m/z* 393.2149 (M^+); Anal. Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 64.03; H, 7.89; N, 3.78%.

Reduction of Diethyl 2-Benzyl-2-(benzyloxycarbonylamino)malonate (3a) with $LiBH_4$

To a solution of **3a** (510 mg, 1.28 mmol) in anhydrous THF (10 mL) was added $LiBH_4$ (112 mg, 5.12 mmol) at 0 °C under argon. After being stirred at 0 °C for 1 h, the reaction mixture was allowed to warm to room temperature and then stirred for 20 h. The reaction mixture was concentrated *in vacuo* and was treated with 1 N HCl (10 mL) and then extracted with $CHCl_3$ (30 mL x 6). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [Silica Gel 60N, *n*-hexane—AcOEt (1:1)] to afford **4a** (236 mg, 59%).

Benzyl 2-Benzyl-1,3-dihydroxypropan-2-ylcarbamate (4a)

Colorless needles ($CHCl_3$—*n*-hexane), mp 81-82 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.92 (s, 2H), 3.10-3.21 (m, 2H), 3.61 (dd, *J*=7.1, 11.7 Hz, 2H), 3.80 (dd, *J*=5.9, 11.7 Hz, 2H), 5.10 (s, 2H), 5.16 (s, 1H), 7.15-7.21 (m, 2H), 7.21-7.31 (m, 3H), 7.31-7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.9, 59.7, 65.3, 66.9, 126.9, 128.1, 128.3, 128.5, 128.6, 130.3, 135.6, 136.1, 156.5; IR (KBr) 3382, 3299, 1695, 1542, 1523, 1454, 1282, 1241, 1027 cm^{-1}; EIMS calcd for $C_{18}H_{22}NO_4$ MW 316.1549, found *m/z* 316.1531 (M^+ + H); Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.36; H, 6.75; N, 4.44%.

Benzyl 1,3-Dihydroxy-2-methylpropan-2-ylcarbamate (4b)

White powder ($CHCl_3$—*n*-hexane), mp 79-80 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 3H), 3.09-3.24 (m, 2H), 3.66 (dd, *J*=6.6, 11.5 Hz, 2H), 3.80 (dd, *J*=5.9, 11.5 Hz, 2H), 5.08 (s, 2H), 5.26 (s, 1H), 7.29-7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 57.2, 66.8, 67.7, 128.1, 128.2, 128.6, 136.1, 156.4; IR (KBr) 3274, 3087, 1691, 1673, 1558, 1455, 1288, 1267, 1253 cm^{-1}; EIMS calcd for $C_{12}H_{18}NO_4$ MW 240.1236, found *m/z* 240.1253 (M^+ + H); Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.07; H, 7.14; N, 5.83%.

Benzyl 1-Hydroxy-2-(hydroxymethyl)pent-4-en-2-ylcarbamate (4c)

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (d, *J*=7.6 Hz, 2H), 3.36-3.54 (m, 2H), 3.61 (dd, *J*=7.1, 11.7 Hz, 2H), 3.83 (dd, *J*=5.1, 11.7 Hz, 2H), 5.07 (s, 2H), 5.11-5.24 (m, 2H), 5.29 (s, 1H), 5.72-5.88 (m, 1H), 7.29-7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.4, 59.0, 65.9, 67.0, 120.0, 128.1, 128.3, 128.6, 132.2, 136.0, 156.6; IR (neat) 3396, 2948, 2888, 1697, 1513, 1455, 1240, 1039 cm^{-1}; FABMS calcd for $C_{14}H_{20}NO_4$ MW 266.1392, found *m/z* 266.1418 (M^+ + H).

Benzyl 1-Hydroxy-2-(hydroxymethyl)octan-2-ylcarbamate (4d)

Colorless plates ($CHCl_3$—*n*-hexane), mp 69-70 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.8 Hz, 3H), 1.17-1.36 (m, 8H), 1.48-1.61 (m, 2H), 3.27-3.42 (m, 2H), 3.62 (dd, *J*=6.8, 11.5 Hz, 2H), 3.86 (dd, *J*=5.9, 11.5 Hz, 2H), 5.07 (s, 2H), 5.19 (s, 1H), 7.28-7.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.5, 22.9, 29.7, 31.6, 33.2, 59.5, 66.3, 66.8, 128.1, 128.2, 128.5, 136.1, 156.6; IR (KBr) 3280, 2954, 2937, 2911, 2883, 2856, 1673, 1467, 1428, 1336 cm^{-1}; EIMS calcd for $C_{17}H_{28}NO_4$ MW 310.2018, found *m/z* 310.2004 (M^+ + H); Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 65.79; H, 8.78; N, 4.50%.

Enzyme-Catalyzed Acetylation of Benzyl 2-Benzyl-1,3-dihydroxypropan-2-ylcarbamate (4a) with Immobilized Lipoprotein Lipase

Immobilized LPL from *Pseudomonas* sp. (Toyobo; LIP-301, 50 mg, 29.5 units) and vinyl acetate (196 μL, 2.292 mmol) were added to a stirred solution of **4a** (180 mg, 0.573 mmol) in TBME (10 mL) at room temperature. After being stirred at room temperature for 2 h, the reaction mixture was filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [Silica Gel 60N, *n*-hexane—AcOEt (2:1)] to afford (*R*)-**5a** (193 mg, 94%. 97% ee) as a white solid. The ee of **5a** was determined by HPLC analysis (CHIRALCEL OJ-H, *n*-hexane/2-propanol = 5/1, 1.0 ml/min, 254 nm).

(R)-2-Benzyl-2-(benzyloxycarbonylamino)-3-hydroxypropyl Acetate [(R)-5a]

100% ee; Colorless needles (AcOEt—*n*-hexane), mp 66.5-67 °C; $[\alpha]_D^{24}$ +4.8 (*c* 1.02 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.95 (d, *J*=13.6 Hz, 1H), 3.15

(d, *J*=13.4 Hz, 1H), 3.44-3.57 (m, 1H), 3.61 (dd, *J*=7.1, 11.9 Hz, 1H), 3.69 (dd, *J*=6.6, 11.5 Hz, 1H), 4.11 (d, *J*=11.5 Hz, 1H), 4.24 (d, *J*=11.5 Hz, 1H), 4.93 (s, 1H), 5.11 (s, 2H), 7.03-7.15 (m, 2H), 7.16-7.30 (m, 3H), 7.30-7.48 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 37.1, 59.1, 63.7, 64.3, 66.7, 126.8, 128.21, 128.24, 128.4, 128.5, 130.4, 135.4, 136.2, 155.7, 171.1; IR (KBr) 3448, 2362, 1708, 1558, 1454, 1376, 1234, 1081, 1039 cm^{-1}; ESIMS calcd for $C_{20}H_{23}NO_5Na$ MW 380.1474, found *m*/*z* 380.1475 (M^+ + Na); Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.11; H, 6.52; N, 3.95%.

(R)-2-(Benzyloxycarbonylamino)-3-hydroxy-2-methylpropyl Acetate [(R)-5b]

92% ee; Colorless oil; $[\alpha]_D^{30}$ –7.2 (*c* 1.63 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 3H), 2.09 (s, 3H), 3.41-3.51 (brs, 1H), 3.58-3.68 (m, 2H), 4.21 (d, *J*=11.2 Hz, 1H), 4.25 (d, *J*=11.2 Hz, 1H), 5.07 (s, 2H), 5.15 (s, 1H), 7.31-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 20.8, 56.4, 66.1, 66.4, 66.7, 128.0, 128.1, 128.4, 136.0, 155.6, 171.0; IR (neat) 3359, 2946, 1714, 1536, 1455, 1375, 1241, 1045 cm^{-1}; ESIMS calcd for $C_{14}H_{19}NO_5Na$ MW 304.1161, found *m*/*z* 304.1167 (M^+ + Na).

2-(Benzyloxycarbonylamino)-2-(hydroxymethyl)pent-4-enyl Acetate (5c)

98% ee; Colorless oil; $[\alpha]_D^{27}$ –15.0 (*c* 1.19 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.34 (dd, *J*=8.0, 14.1 Hz, 1H), 2.57 (dd, *J*=6.8, 13.9 Hz, 1H), 3.52-3.80 (m, 3H), 4.16 (d, *J*=11.4 Hz, 1H), 4.30 (d, *J*=11.4 Hz, 1H), 5.07 (s, 2H), 5.11 (s, 1H), 5.13-5.21 (m, 2H), 5.68-5.87 (m, 1H), 7.29-7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 36.8, 58.2, 64.5, 64.6, 66.6, 119.6, 127.9, 128.0, 128.3, 131.7, 135.9, 155.6, 170.8; IR (neat) 3407, 3068, 3033, 3008, 2956, 2894, 1729, 1714, 1641, 1538, 1515, 1506, 1455, 1380, 1236, 1041 cm^{-1}; ESIMS calcd for $C_{16}H_{21}NO_5Na$ MW 330.1317, found *m*/*z* 330.1302 (M^+ + Na).

2-(Benzyloxycarbonylamino)-2-(hydroxymethyl)octyl Acetate (5d)

96% ee; Colorless oil; $[\alpha]_D^{26}$ –7.6 (*c* 0.97 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.1 Hz, 3H), 1.16-1.35 (m, 8H), 1.53-1.64 (m, 1H), 1.67-1.80 (m, 1H), 2.08 (s, 3H), 3.54-3.77 (m, 3H), 4.15 (d, *J*=11.4 Hz, 1H), 4.29 (d, *J*=11.4 Hz, 1H), 5.04 (s, 1H), 5.07 (s, 2H), 7.29-7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.7, 22.5, 22.8, 29.6, 31.5, 32.5, 58.7, 64.5, 65.1, 66.6, 127.9, 128.0, 128.3, 136.0, 155.7, 170.9; IR (neat) 3353, 2954, 2929, 2859, 1729, 1536, 1455, 1378, 1238, 1041 cm^{-1}; ESIMS calcd for $C_{19}H_{29}NO_5Na$ MW 374.1943, found *m*/*z* 374.1949 (M^+ + Na).

2-(Benzyloxycarbonylamino)-3-hydroxy-2-methylpropyl 2-Chloroacetate (5ba)

44% ee; Colorless oil; $[\alpha]_D^{27}$ –2.4 (*c* 0.85 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 3H), 3.25-3.47 (m, 1H), 3.61-3.75 (m, 2H), 4.07 (s, 2H), 4.35 (d, *J*=11.0 Hz, 1H), 4.40 (d, *J*=11.0 Hz, 1H), 5.07 (s, 2H), 5.12 (s, 1H), 7.29-7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 40.6, 56.2, 66.3, 66.8, 67.3, 127.9, 128.1, 128.4, 135.8, 155.7, 167.1; IR (neat) 3403, 3066, 3033, 2954, 2890, 2360, 1729, 1712, 1529, 1454, 1411, 1371, 1249, 1191, 1074 cm^{-1}; ESIMS calcd for $C_{14}H_{18}ClNO_5Na$ MW 338.0771, found *m*/*z* 338.0770 (M^+ + Na).

2-(Benzyloxycarbonylamino)-3-hydroxy-2-methylpropyl Butyrate (5bb)

83% ee; Colorless oil; $[\alpha]_D^{27}$ –6.4 (*c* 0.73 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J*=7.3 Hz, 3H), 1.30 (s, 3H), 1.54-1.72 (m, 2H), 2.32 (t, *J*=7.3 Hz, 2H), 3.49 (brs, 1H), 3.59 (dd, *J*=6.1, 12.0 Hz, 1H), 3.65 (dd, *J*=6.1, 11.7 Hz, 1H), 4.21 (d, *J*=11.2 Hz, 1H), 4.27 (d, *J*=11.5 Hz, 1H), 5.07 (s, 2H), 5.15 (s, 1H), 7.27-7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 18.3, 19.6, 36.0, 56.3, 65.7, 66.3, 66.6, 127.9, 128.0, 128.3, 136.0, 155.6, 173.6; IR (neat) 3361, 2965, 2877, 1727, 1714, 1546, 1531, 1515, 1504, 1454, 1380, 1249, 1182, 1074 cm^{-1}; ESIMS calcd for $C_{16}H_{23}NO_5Na$ MW 332.1474, found *m*/*z* 332.1451 (M^+ + Na).

2-(Benzyloxycarbonylamino)-3-hydroxy-2-methylpropyl Benzoate (5bc)

79% ee; Colorless oil; $[\alpha]_D^{24}$ –10.7 (*c* 0.58 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 3.45-3.86 (m, 3H), 4.45-4.75 (m, 2H), 5.02-5.16 (m, 2H), 5.27 (s, 1H), 7.27-7.53 (m, 7H), 7.54-7.65 (m, 1H), 7.99-8.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 56.7, 66.3, 66.5, 66.8, 128.1, 128.2, 128.52, 128.57, 129.4, 129,7, 133.4, 136.1, 155.8, 166.8; IR (neat) 3357, 3066, 3033, 2944, 2890, 1714, 1536, 1452, 1371, 1315, 1276, 1116, 1070 cm^{-1}; ESIMS calcd for $C_{19}H_{21}NO_5Na$ MW 366.1317, found *m*/*z* 366.1284 (M^+ + Na); Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.22; H, 6.42; N, 4.04%.

2-(Benzyloxycarbonylamino)-3-hydroxy-2-methylpropyl Pivalate (5bd)

59% ee; Colorless oil; $[\alpha]_D^{27}$ –4.4 (*c* 0.54 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.30 (s, 3H), 3.36-3.67 (m, 3H), 4.19 (d, *J*=11.2 Hz, 1H), 4.26 (d, *J*=11.2 Hz, 1H), 5.06 (s, 2H), 5.16 (s, 1H), 7.27-7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 27.1, 38.9, 56.6, 65.6, 66.5, 66.7, 128.1, 128.2, 128.5, 136.1, 155.7, 178.8; IR (neat) 3357, 2973, 1731, 1716, 1558, 1540, 1521, 1508, 1455 cm^{-1}; ESIMS calcd for $C_{17}H_{26}NO_5$ MW 324.1811, found *m*/*z* 324.1811 (M^+ + H).

(*S*)-2-Benzyl-2-(benzyloxycarbonylamino)-3-oxopropyl Acetate [(*S*)-6a]

To a solution of (*S*)-**5a** (351 mg, 0.98 mmol, 100% ee) and TEA (1.37 mL, 9.82 mmol) in anhydrous DMSO (10 mL) was added SO_3-pyridine (1.25 g, 7.86 mmol) at room temperature under argon. After being stirred at room temperature for 30 min, the reaction mixture was treated with 1 N HCl (5 mL) and then extracted with $CHCl_3$ (20 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [Silica Gel 60N, *n*-hexane—AcOEt (3:1)] to afford (*S*)-**6a** (345 mg, 99%) as colorless oil. $[\alpha]_D^{28}$ +1.5 (*c* 1.59 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3H), 3.16 (d, *J*=13.9 Hz, 1H), 3.38 (d, *J*=13.9 Hz, 1H), 4.47 (d, *J*=11.7 Hz, 1H), 4.66 (d, *J*=11.7 Hz, 1H), 5.10 (d, *J*=12.2 Hz, 1H), 5.19 (d, *J*=12.2 Hz, 1H), 5.47 (s, 1H), 6.89-7.02 (m, 2H), 7.11-7.52 (m, 8H), 9.53 (s, 1H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 20.5, 35.7, 62.9, 66.1, 66.7, 127.1, 128.0, 128.1, 128.3, 129.8, 133.4, 136.0, 154.7, 170.2, 197.1; IR (neat) 3403, 3340, 3031, 2360, 1957, 1745, 1716, 1500, 1455, 1376, 1317, 1226, 1076, 1043 cm^{-1}; ESIMS calcd for $C_{20}H_{21}NO_5Na$ MW 378.1317, found *m/z* 378.1313 (M^+ + Na).

(S)-2-(Benzyloxycarbonylamino)-2-methyl-3-oxopropyl Acetate [(S)-6b]

Colorless oil. $[\alpha]_D^{26}$ –12.7 (*c* 1.05 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 3H), 2.04 (s, 3H), 4.38 (d, *J*=11.7 Hz, 1H), 4.51 (d, *J*=11.7 Hz, 1H), 5.11 (s, 2H), 5.61 (s, 1H), 7.32-7.37 (m, 5H), 9.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 20.6, 62.2, 64.1, 66.9, 128.0, 128.1, 128.4, 135.8, 154.8, 170.4, 197.7; IR (neat) 3342, 3033, 1743, 1521, 1455, 1375, 1238, 1076, 1049, 916, 742, 698 cm^{-1}; ESIMS calcd for $C_{14}H_{17}NO_5Na$ MW 302.1104, found *m/z* 302.0989 (M^+ + Na).

(*S*)-3-Acetoxy-2-benzyl-2-(benzyloxycarbonylamino)propanoic Acid [(*S*)-7a]

To a solution of (*S*)-**6a** (308 mg, 0.867 mmol), 2-methyl-2-butene (367 μL, 3.47 mmol) and NaH_2PO_4 (135 mg, 0.867 mmol) in H_2O—*tert*-BuOH (1:4, 10 mL) was added $NaClO_2$ (235 mg, 2.60 mmol) at room temperature. After being stirred at room temperature for 1 h, the reaction mixture was treated with 1 N HCl (5 mL) and then extracted with $CHCl_3$ (20 mL x 6). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [COSMOSIL 75 SL-II-PREP, $CHCl_3$—MeOH (80:1)] to afford (*S*)-**7a** (285 mg, 89%) as a pale yellow amorphous. $[\alpha]_D^{26}$ –44.8 (*c* 0.69 in MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.06 (s, 3H), 3.05 (d, *J*=13.4 Hz, 1H), 3.15 (d, *J*=13.4 Hz, 1H), 4.06 (d, *J*=11.2 Hz, 1H), 4.28 (d, *J*=11.2 Hz, 1H), 5.01-5.11 (m, 2H), 6.94-7.08 (m, 2H), 7.15-7.46 (m, 9H), 13.1 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 30.5, 36.9, 63.9, 64.9, 66.6, 127.0, 128.0, 128.2, 128.3, 129.6, 134.1, 136.0, 154.4, 170.7, 173.7; IR (neat) 3409, 3033, 2360, 1743, 1724, 1511, 1500, 1251, 1054 cm^{-1}; ESIMS calcd for $C_{20}H_{21}NO_6Na$ MW 394.1267, found *m/z* 394.1269 (M^+ + Na).

(S)-3-Acetoxy-2-(benzyloxycarbonylamino)-2-methylpropanoic Acid [(S)-7b]

White solid, mp 85-89 °C; $[\alpha]_D^{27}$ –12.7 (*c* 1.00 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 3H), 2.03 (s, 3H), 4.38 (d, *J*=11.2 Hz, 1H), 4.54 (d, *J*=11.2 Hz, 1H), 5.06 (s, 2H), 7.26-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 20.6, 58.9, 65.7, 66.7, 127.9, 128.0, 128.3, 135.8, 154.8, 170.9, 175.1; IR (KBr) 3336, 3160, 2985, 1747, 1716, 1687, 1540, 1288, 1135, 1087, 1045, 755, 700 cm^{-1}; ESIMS calcd for $C_{14}H_{17}NO_6Na$ MW 318.0954, found *m/z* 318.0953 (M^+ + Na).

(*S*)-2-Benzyl-2-(benzyloxycarbonylamino)-3-hydroxypropanoic Acid [(*S*)-8a]

To a solution of (*S*)-**7a** (174 mg, 0.468 mmol) in anhydrous THF (7 mL) was slowly added 1 M solution of $LiEt_3BH$ (2.1 mL, 2.1 mmol) at 0 °C under argon. After being stirred at 0 °C for 30 min, the reaction mixture was treated with 1 N HCl (5 mL) and then extracted with $CHCl_3$ (20 mL x 6). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [COSMOSIL 75 SL-II-PREP, $CHCl_3$—MeOH (90:1)] to afford (*S*)-**8a** (144 mg, 94%, 100% ee) as colorless needles ($CHCl_3$—*n*-hexane). After quantitative methylation of (*S*)-**8a**, the ee of the corresponding methyl ester was determined by HPLC analysis (CHIRALCEL OJ-H, *n*-hexane/2-propanol = 5/1, 1.0 ml/min, 254 nm). mp 129-130 °C; $[\alpha]_D^{24}$ –66.2 (*c* 1.00 in EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.06-3.18 (m, 2H), 3.37 (brs, 1H), 3.53 (d, *J*=10.7 Hz, 1H), 3.62 (d, *J*=10.7 Hz, 1H), 5.01-5.15 (m, 2H), 6.72 (brs, 1H), 6.99-7.08 (m, 2H), 7.13-7.26 (m, 3H), 7.26-7.46 (m, 5H), 11.0-13.8 (brs, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 37.4, 64.2, 67.1, 67.3, 127.8, 129.06, 129.10, 129.14, 129.5, 131.1, 137.1, 138.4, 156.6, 174.7; IR (KBr) 3446, 3353, 3064, 3033, 2362, 2343, 1739, 1718, 1685, 1502, 1469, 1455, 1394, 1243, 1218, 1068, 1049 cm^{-1}; EIMS calcd for $C_{18}H_{19}NO_5$ MW 329.1263, found *m/z* 329.1241 (M^+); Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.34; H, 5.59; N, 4.20%.

(S)-2-(Benzyloxycarbonylamino)-3-hydroxy-2-methylpropanoic Acid [(S)-8b]

White solid, mp 123-126 °C; $[\alpha]_D^{29}$ –3.8 (*c* 0.87 in MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.46 (s, 3H), 3.79-3.84 (m, 2H), 5.06 (s, 2H), 7.26-7.37 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 20.5, 61.6, 66.0, 67.2, 128.5, 128.7, 129.1, 137.7, 157.0, 176.0; IR (KBr) 3440, 3291, 1733, 1691, 1556, 1459, 1267, 1174, 1089, 1047, 842, 757 cm^{-1}; ESIMS calcd for $C_{12}H_{15}NO_5Na$ MW 276.0848, found *m/z* 276.0830 (M^+ + Na).

(*S*)-2-Amino-2-benzyl-3-hydroxypropanoic Acid [(*S*)-α-Benzylserine, (*S*)-9a] [11]

The mixture of (*S*)-**8a** (41 mg, 0.124 mmol) and 10% Pd-C (6.6 mg) in EtOH (5 mL) was stirred at room temperature for 3.5 h under hydrogen. The reaction mixture was filtered, and concentrated *in vacuo* to furnish (*S*)-**9a** (22.7 mg, 94%) as colorless needles (H_2O—EtOH). mp 221-222 °C (dec); $[\alpha]_D^{20}$ +16.5 (*c* 0.66 in H_2O), {lit. [11c]: $[\alpha]_D$ +16.4 (*c* 0.81 in H_2O), lit. [11d]: $[\alpha]_D^{20}$ +16.6 (*c* 0.9 in H_2O), lit. [11e]: $[\alpha]_D^{20}$ +16.0 (*c* 0.71 in H_2O)}; ^{1}H NMR (400 MHz, D_2O) δ 2.95 (d, *J*=14.1 Hz, 1H), 3.26 (d, *J*=14.1 Hz, 1H), 3.78 (d, *J*=11.9 Hz, 1H), 4.05 (d, *J*=11.9 Hz, 1H), 7.19-7.51 (m, 5H); ^{13}C NMR (75 MHz, D_2O) δ 40.8, 67.0, 69.8, 130.7, 131.9, 132.8, 136.4, 176.6; IR (KBr) 3066, 2497, 2003, 1633, 1590, 1496, 1455, 1434, 1407, 1326, 1297, 1184, 1114, 1062 cm^{-1}; ESIMS calcd for $C_{10}H_{14}NO_3$ MW 196.0974, found *m/z* 196.0965 (M^+ + H).

(S)-2-Amino-3-hydroxy-2-methylpropanoic Acid [(S)-α-Methylserine, (S)-9b] [12]

Colorless needles (H_2O—EtOH). mp 222-225 °C (dec); $[\alpha]_D^{28}$ +6.3 (*c* 0.21 in H_2O), {lit. [12a]: $[\alpha]_D^{22}$ +6.5 (*c* 1.01 in H_2O), lit. [12b]: $[\alpha]_D^{25}$ +5.3 (*c* 1.02 in H_2O)}; ^{1}H NMR (400 MHz, D_2O) δ 1.43 (s, 3H), 3.67 (d, *J*=12.2 Hz, 1H), 3.92 (d, *J*=12.2 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 21.3, 65.3, 67.6, 178.3; IR (KBr) 3417, 1633, 1461, 1407, 1353, 1278, 1060 cm^{-1}; ESIMS calcd for $C_4H_{10}NO_3$ MW 120.0661, found *m/z* 120.0657 (M^+ + H).

(*R*)-2-Benzyl-2-(benzyloxycarbonylamino)-3-(methoxymethoxy)propyl Acetate [(*R*)-10a]

To a solution of (*R*)-**5a** (800 mg, 2.238 mmol, 100% ee) and DIEA (1.9 mL, 11.19 mmol) in anhydrous CH_2Cl_2 (20 mL) was slowly added MOMCl (850 μL, 11.19 mmol) at 0

°C under argon. After being stirred at 0 °C for 30 min, the reaction mixture was allowed to warm to room temperature and then stirred for 20.5 h. The reaction mixture was treated with an aqueous solution saturated with NH_4Cl (10 mL) and then extracted with $CHCl_3$ (30 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [Silica Gel 60N, *n*-hexane—AcOEt (2:1)] to afford (*R*)-**10a** (889 mg, 99%) as white powder ($CHCl_3$—*n*-hexane). mp 79-79.5 °C; $[\alpha]_D^{24}$ –16.5 (*c* 1.04 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (s, 3H), 3.11 (d, *J*=13.4 Hz, 1 H), 3.22 (d, *J*=13.4 Hz, 1H), 3.35 (s, 3H), 3.56 (d, *J*=9.5 Hz, 1 H), 3.64 (d, *J*=9.5 Hz, 1H), 4.27 (d, *J*=11.0 Hz, 1H), 4.31 (d, *J*=11.0 Hz, 1H), 4.59 (s, 2H), 4.95 (s, 1H), 5.06-5.15 (m, 2H), 7.06-7.13 (m, 2H), 7.16-7.28 (m, 3H), 7.28-7.46 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 36.9, 55.5, 57.8, 64.3, 66.4, 67.9, 96.8, 126.7, 128.1, 128.2, 128.3, 128.5, 130.5, 135.7, 136.5, 154.9, 170.5; IR (KBr) 3332, 3066, 3027, 2948, 2898, 1731, 1554, 1494, 1469, 1454, 1375, 1251, 1110 cm^{-1}; ESIMS calcd for $C_{22}H_{27}NO_6Na$ MW 424.1736, found *m*/*z* 424.1736 (M^+ + Na); Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.64; H, 6.71; N, 3.50%.

(R)-2-(Benzyloxycarbonylamino)-3-(methoxymethoxy)-2-methylpropyl Acetate [(R)-10b]

Colorless oil; $[\alpha]_D^{29}$ –1.8 (*c* 1.14 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3H), 2.07 (s, 3H), 3.33 (s, 3H), 3.54 (d, *J*=9.8 Hz, 1H), 3.65 (d, *J*=9.8 Hz, 1H), 4.20 (d, *J*=11.2 Hz, 1H), 4.31 (d, *J*=11.0 Hz, 1H), 4.60 (s, 2H), 5.06 (s, 2H), 5.18 (s, 1H), 7.30-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 20.8, 54.9, 55.3, 65.9, 66.3, 70.3, 96.6, 127.9, 128.3, 136.3, 154.7, 170.5; IR (neat) 3351, 2946, 1733, 1523, 1455, 1376, 1238, 1147, 1047, 917, 742, 698 cm^{-1}; ESIMS calcd for $C_{16}H_{23}NO_6Na$ MW 348.1423, found *m*/*z* 348.1427 (M^+ + Na).

Benzyl (*S*)-2-Benzyl-1-hydroxy-3-(methoxymethoxy)propan-2-ylcarbamate [(*S*)-11a]

To a solution of (*R*)-**10a** (159 mg, 0.396 mmol) in anhydrous THF (10 mL) was slowly added 1 M solution of $LiEt_3BH$ (1.18 mL, 1.18 mmol) at 0 °C under argon. After being stirred at 0 °C for 50 min, the reaction mixture was treated with 1 N HCl (5 mL) and then extracted with $CHCl_3$ (20 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [Silica Gel 60N, *n*-hexane—AcOEt (1:1)] to afford (*S*)-**11a** (127 mg, 89%) as a colorless oil. $[\alpha]_D^{28}$ +8.1 (*c* 0.94 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (d, *J*=13.4 Hz, 1H), 3.17 (d, *J*=13.4 Hz, 1H), 3.36 (s, 3H), 3.45 (d, *J*=9.7 Hz, 1H), 3.63 (d, *J*=9.7 Hz, 1H), 3.66-3.80 (m, 3H), 4.62 (s, 2H), 5.11 (s, 2H), 5.22 (s, 1H), 7.11-7.29 (m, 5H), 7.29-7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.3, 55.5, 59.3, 65.1, 66.5, 69.4, 96.8, 126.4, 127.9, 128.0, 128.1, 128.3, 130.3, 135.8, 136.2, 155.8; IR (neat) 3413, 3336, 3062, 3029, 2946, 2886, 1716, 1513, 1454, 1251, 1220 cm^{-1}; ESIMS calcd for $C_{20}H_{25}NO_5Na$ MW 382.1630, found *m*/*z* 382.1630 (M^+ + Na).

Benzyl (S)-1-Hydroxy-3-(methoxymethoxy)-2-methylpropan-2-ylcarbamate [(S)-11b]

Colorless oil; $[\alpha]_D^{28}$ –1.7 (*c* 0.96 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 3H), 3.34 (s, 3H), 3.51-3.77 (m, 5H), 4.61 (s, 2H), 5.08 (s, 2H), 5.40 (s, 1H), 7.31-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 55.3, 56.4, 66.5, 67.5, 71.6, 96.6, 127.9, 128.0, 128.3, 136.2, 155.8; IR (neat) 3415, 2940, 1706, 1511, 1454, 1245, 1147, 1045, 742, 698 cm^{-1}; ESIMS calcd for $C_{14}H_{21}NO_5Na$ MW 306.1317, found *m*/*z* 306.1317 (M^+ + Na).

Benzyl (*R*)-2-Benzyl-1-(methoxymethoxy)-3-oxopropan-2-ylcarbamate [(*R*)-12a]

To a solution of (*S*)-**11a** (470 mg, 1.307 mmol) and TEA (1.82 mL, 13.07 mmol) in anhydrous DMSO (10 mL) was added SO_3-pyridine (1.66 g, 10.46 mmol) at room temperature under argon. After being stirred at room temperature for 40 min, the reaction mixture was treated with 1 N HCl (5 mL) and then extracted with $CHCl_3$ (20 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [Silica Gel 60N, *n*-hexane—AcOEt (2:1)] to afford (*R*)-**12a** (418 mg, 90%) as colorless needles ($CHCl_3$—*n*-hexane). mp 72-72.5 °C; $[\alpha]_D^{24}$ –2.1 (*c* 1.00 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15-3.36 (m, 5H), 3.86-4.02 (m, 2H), 4.55 (s, 2H), 5.09 (d, *J*=12.2 Hz, 1H), 5.17 (d, *J*=12.2 Hz, 1H), 5.50 (s, 1H), 6.93-7.00 (m, 2H), 7.14-7.28 (m, 3H), 7.28-7.42 (m, 5H), 9.59 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.6, 55.5, 66.6, 66.7, 67.8, 96.7, 127.0, 128.20, 128.23, 128.4, 128.5, 130.0, 134.3, 136.3, 155.0, 199.1; IR (KBr) 3357, 3066, 2942, 1716, 1508, 1255, 1037 cm^{-1}; ESIMS calcd for $C_{20}H_{23}NO_5Na$ MW 380.1474, found *m*/*z* 380.1507 (M^+ + Na); Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.06; H, 6.56; N, 3.90%.

Benzyl (R)-1-(Methoxymethoxy)-2-methyl-3-oxopropan-2-ylcarbamate [(R)-12b]

Colorless oil; $[\alpha]_D^{27}$ +18.3 (*c* 0.77 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 3H), 3.29 (s, 3H), 3.75-3.85 (m, 2H), 4.57 (s, 2H), 5.11 (s, 2H), 5.70 (s, 1H), 7.30-7.37 (m, 5H), 9.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 55.3, 62.7, 66.7, 68.9, 96.5, 127.9, 128.0, 128.3, 136.0, 155.1, 199.4; IR (neat) 3342, 2946, 1714, 1517, 1455, 1402, 1259, 1149, 1045, 777, 742, 698 cm^{-1}; ESIMS calcd for $C_{14}H_{19}NO_5Na$ MW 304.1161, found *m*/*z* 304.1164 (M^+ + Na).

(*R*)-2-Benzyl-2-(benzyloxycarbonylamino)-3-(methoxymethoxy)propanoic Acid [(*R*)-13a].

To a solution of (*R*)-**12a** (353 mg, 0.987 mmol), 2-methyl-2-butene (418 μL, 3.95 mmol) and NaH_2PO_4 (154 mg, 0.987 mmol) in H_2O—*tert*-BuOH (1:5, 12 mL) was added $NaClO_2$ (268 mg, 2.96 mmol) at room temperature. After being stirred at room temperature for 1 h, the reaction mixture was treated with 1 N HCl (5 mL) and then extracted with $CHCl_3$ (20 mL x 6). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. An aqueous solution saturated with $NaHCO_3$ (5 mL) was added to the concentrated solution and then the aqueous layer was

washed with $CHCl_3$ (5 mL). The aqueous layer was acidified with 1 N HCl (10 mL) and then extracted with $CHCl_3$ (20 mL x 6). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to gave (*R*)-**13a** (336 mg, 91%) as a white powder. mp 59-60 °C; $[\alpha]_D^{17}$ +55.4 (*c* 0.66 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (d, *J*=13.4 Hz, 1H), 3.28 (s, 3H), 3.50 (d, *J*=13.4 Hz, 1H), 3.95 (d, *J*=9.3 Hz, 1H), 4.26 (d, *J*=9.3 Hz, 1H), 4.59 (s, 2H), 5.07 (d, *J*=12.2 Hz, 1H), 5.20 (d, *J*=12.2 Hz, 1H), 5.66 (s, 1H), 6.96-7.07 (m, 2H), 7.12-7.28 (m, 3H), 7.28-7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.9, 55.3, 65.0, 66.5, 68.9, 96.5, 127.1, 128.1, 128.3, 128.4, 129.8, 134.7, 136.4, 154.7, 176.2; IR (KBr) 3374, 3033, 2950, 1739, 1716, 1509, 1455, 1405, 1257, 1214, 1151, 1112, 1056 cm^{-1}; ESIMS calcd for $C_{20}H_{23}NO_6Na$ MW 396.1423, found *m*/*z* 396.1429 (M^+ + Na); Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.03; H, 6.19; N, 3.68%.

(R)-2-(Benzyloxycarbonylamino)-3-(methoxymethoxy)-2-propanoic Acid [(R)-13b]

Colorless oil; $[\alpha]_D^{27}$ +1.3 (*c* 0.98 in MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.53 (s, 3H), 3.26 (s, 3H), 3.82 (d, *J*=9.8 Hz, 1H), 3.88 (d, *J*=9.8 Hz, 1H), 4.56 (s, 2 H), 5.06 (s, 2H), 7.25-7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 55.4, 60.0, 66.7, 70.6, 96.6, 128.1, 128.2, 128.5, 136.2, 155.2, 177.1; IR (neat) 2948, 1714, 1506, 1454, 1257, 1043, 977, 917, 754, 698 cm^{-1}; ESIMS calcd for $C_{14}H_{19}NO_6Na$ MW 320.1110, found *m*/*z* 320.1108 (M^+ + Na).

(*R*)-2-Benzyl-2-(benzyloxycarbonylamino)-3-hydroxypropanoic Acid [(*R*)-8a]

To a solution of (*R*)-**13a** (280 mg, 0.75 mmol) in anhydrous THF (10 mL) was added 1 N HCl (5 mL) at room temperature. After being refluxed for 24 h, the reaction mixture was extracted with $CHCl_3$ (20 mL x 8). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [COSMOSIL 75 SL-II-PREP, $CHCl_3$—MeOH (90:1)] to afford (*R*)-**8a** (231 mg, 94%, 100% ee) as colorless needles ($CHCl_3$—*n*-hexane). mp 129-130 °C; $[\alpha]_D^{24}$ +65.8 (*c* 1.00 in EtOH); Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.35; H, 5.89; N, 4.25%.

(R)-2-(Benzyloxycarbonylamino)-3-hydroxy-2-methylpropanoic Acid [(R)-8b]

White solid, mp 124-127 °C; $[\alpha]_D^{27}$ +3.7 (*c* 1.04 in MeOH); ESIMS calcd for $C_{12}H_{15}NO_5Na$ MW 276.0848, found *m*/*z* 276.0843 (M^+ + Na).

(*R*)-2-Amino-2-benzyl-3-hydroxypropanoic Acid [(*R*)-α-Benzylserine, (*R*)-9a] [11]

The mixture of (*R*)-**8a** (256 mg, 0.777 mmol) and 10% Pd-C (41 mg) in EtOH (15 mL) was stirred at room temperature for 4 h under hydrogen. The reaction mixture was submitted to filtration with celite, and concentrated *in vacuo* to furnish (*R*)-**9a** (152 mg, 100%) as colorless needles (H_2O—EtOH). mp 221-222 °C (dec); $[\alpha]_D^{24}$ -16.1 (*c* 0.69 in H_2O); ESIMS calcd for $C_{10}H_{14}NO_3$ MW 196.0974, found *m*/*z* 196.0963 (M^+ + H).

(R)-2-Amino-3-hydroxy-2-methylpropanoic Acid [(R)-α-Methylserine, (R)-9b] [12]

Colorless needles (H_2O—EtOH). mp 260-265 °C (dec); $[\alpha]_D^{29}$ –5.7 (*c* 0.22 in H_2O); ESIMS calcd for $C_4H_{10}NO_3$ MW 120.0661, found *m*/*z* 120.0655 (M^+ + H).

Enzyme-catalyzed Hydrolysis of Diethyl 2-(Benzyloxycarbonylamino)-2-methylmalonate (3b) with Porcine Liver Esterase

PLE (Sigma; E-2884, 1.6 mL, 6,000 units) was added to a stirred solution of **3b** (1.5 g, 4.64 mmol) in 1/15 M phosphate buffer (pH 7.0, 405 mL) and MeCN (46 mL) at room temperature. After being stirred at room temperature for 6 h, the reaction mixture was treated with 1 N HCl (30 mL) and then extracted with AcOEt (200 mL x 5). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [COSMOSIL 75 SL-II-PREP, $CHCl_3$—MeOH (9:1)] to afford (*R*)-**14** (1.34 g, 98%, 97% ee) as a colorless amorphous. $[\alpha]_D^{28}$ +25.8 (*c* 0.45 in MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02-1.22 (m, 3H), 1.57 (s, 3H), 3.98-4.20 (m, 2H), 5.03 (d, *J*=12.9 Hz, 1H), 5.05 (d, *J*=12.7 Hz, 1H), 7.23-7.57 (m, 6H), 13.4 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8, 21.5, 61.4, 62.9, 65.6, 127.5, 127.8, 128.2, 136.7, 154.5, 168.5, 169.8; IR (neat) 2985, 2360, 1732, 1506, 1456, 1275, 1119, 1066, 1020 cm^{-1}; ESIMS calcd for $C_{14}H_{17}NO_6Na$ MW 318.0954, found *m*/*z* 318.0932 (M^+ + Na).

(*S*)-2-(Benzyloxycarbonylamino)-3-hydroxy-2-methylpropanoic Acid [(*S*)-8b]

To a solution of (*R*)-**14** (130 mg, 0.440 mmol) in THF (7 mL) was slowly added 1 M solution of $LiEt_3BH$ (2.2 mL, 2.2 mmol) at 0 °C under argon. After being stirred at 0 °C for 40 min, the reaction mixture was treated with 1N HCl (10 mL) and then extracted with $CHCl_3$ (20 mL x 6). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [COSMOSIL 75 SL-II-PREP, $CHCl_3$—MeOH (80:1)] to afford (*S*)-**8b** (88 mg, 79%) as a pale yellow amorphous. $[\alpha]_D^{22}$ –3.6 (*c* 0.65 in MeOH).

Ethyl (*S*)-2-(Benzyloxycarbonylamino)-3-hydroxy-2-methylpropanoate [(*S*)-15]

To a solution of (*S*)-**8b** (77 mg, 0.304 mmol) in acetone (7 mL) was added EtI (244 μL, 3.04 mmol) and K_2CO_3 (46 mg, 0.344 mmol) at room temperature. After being refluxed for 2 h, the reaction mixture was treated with 1 N HCl (5 mL) and then extracted with $CHCl_3$ (15 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [Silica Gel 60N, *n*-hexane—AcOEt (2:1)] to afford (*S*)-**15** (71 mg, 84%, 96% ee) as a colorless oil. The ee of (*S*)-**15** was determined by HPLC analysis (CHIRALPAK AD-H, *n*-hexane/2-propanol = 10/1, 1.0 ml/min, 254 nm). $[\alpha]_D^{28}$ +3.2 (*c* 3.04 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,26 (t, *J*=6.8 Hz, 3H); 1.51 (s, 3H), 2.81-2.94 (m, 1H), 3.81 (dd, *J*=7.8, 11.0 Hz, 1H) 4.05 (dd, *J*=5.6, 11.0 Hz, 1H), 4.15-4.30 (m, 2H), 5.09 (s, 2H), 5.67 (s, 1H), 7.28-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.3, 61.2, 61.8, 66.3, 66.7, 127.9, 128.0, 128.3, 135.9, 155.3, 172.8; IR

(neat) 3361, 2983, 1716, 1508, 1455, 1373, 1249 cm^{-1}; ESIMS calcd for $C_{14}H_{19}NO_5Na$ MW 304.1161, found *m*/*z* 304.1147 (M^+ + Na).

Ethyl (*R*)-2-(Benzyloxycarbonylamino)-3-hydroxy-2-methylpropanoate [(*R*)-15]

To a solution of (*R*)-**14** (100 mg, 0.34 mmol) in anhydrous THF (5 mL) was added DAST (56.8 μL, 0.41 mmol) at 0 °C under argon. After being stirred for 2 h at room temperature, the reaction mixture was concentrated *in vacuo*, treated with ice water (3 mL) and then extracted with CH_2Cl_2 (10 mL x 3). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. To the concentrated solution (ca. 2 mL) was added $NaBH_4$ (19.2 mg, 0.51 mmol) at -78 °C under argon, and then MeOH (5 mL) was slowly added to the solution at -78 °C over 3 min. After being stirred at -78 °C for 1 h, the reaction mixture was treated with 1 N HCl (5 mL) and then extracted with $CHCl_3$ (15 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [Silica Gel 60N, *n*-hexane—AcOEt (1:1)] to afford (*R*)-**15** (79 mg, 83%, 97% ee) as a colorless oil. The ee of (*R*)-**15** was determined by HPLC analysis (CHIRALPAK AD-H, *n*-hexane/2-propanol = 10/1, 1.0 ml/min, 254 nm). $[\alpha]_D^{28}$ –3.0 (*c* 3.14 in $CHCl_3$); ESIMS calcd for $C_{14}H_{19}NO_5Na$ MW 304.1161, found *m*/*z* 304.1185 (M^+ + Na).

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