Pergamon

Tetrahedron, Vol. 53, No. 13, pp. 4579-4592, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00170-1

A Convenient Method for Synthesis of Optically Active β-Hydroxyamines from Primary Amines through Enecarbamates as Key Intermediates[†]

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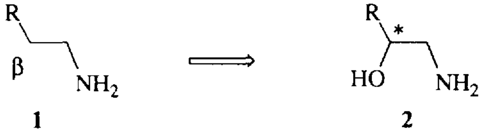
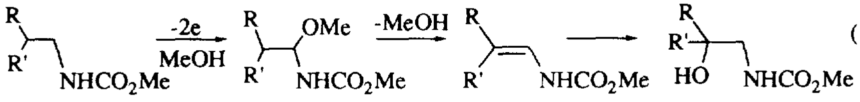
***Abstract*:** This report describes a new method to prepare optically active β-hydroxyamines starting from primary amines. The method consists of a transformation of *N*-methoxycarbonylated primary amines to the corresponding enecarbamates utilizing electrochemical oxidation and an asymmetric hydroboration of the enecarbamates to produce optically active β-hydroxyamines. © 1997 Elsevier Science Ltd.

Optically active β-hydroxyamines **2** occur widely in nature[1] and are often used in organic synthesis as exemplified by the use as chiral auxiliaries.[2] Thus, exploiting convenient methods for the synthesis of optically active **2** is worthwhile. Although a variety of synthetic methods for racemic **2** have been reported so far,[3] there have been only a few methods for the synthesis of optically active ones.[4,5] We report a new route to prepare optically active **2** from easily available achiral primary amines **1** (Scheme 1). There have not been so far any methods for the conversion of **1** to **2**.



Scheme 1

Our strategy is the transformation of *N*-protected primary amines **3** to the corresponding enecarbamates **5**[6] followed by the asymmetric introduction of a hydroxy group to the β position to produce *N*-protected optically active β-hydroxyamines **6** (eq 1). This strategy is based on our previous finding that electrochemical α-methoxylation of carbamates **3** followed by acid-catalyzed elimination of methanol from the α-methoxylated carbamates **4** afford **5**[7] as well as on the well-known asymmetric hydroboration of alkenes.[8] However, the yields of the acid-catalyzed conversion of **4** to **5** were not always satisfactory and there have not been any precedents on hydroboration of the encarbamates **5**.[5] This report describes both an improved procedure for the methanol elimination (**4** to **5**) and an asymmetric hydroboration of **5** to give **6**.



3 **4** **5** **6** (1)

Results and Discussion

The first step in our method is electrochemical oxidation of **3a-e** in methanol, which was achieved by a reported procedure[7] to give α-methoxycarbamates **4a-e** in the yields shown in Table 1. Although **4f** was hardly obtainable by the electrochemical α-methoxylation method,[9] it could be prepared by electrochemical decarboxylation of *N*-methoxycarbonylphenylalanine.[10]

Table 1. Electrochemical Oxidation of Carbamates **3a-e** in MeOH

Entry	Carbamate **3a-e**	R	R'	Supporting Electrolyte	*F*/mol	Product **4a-e**	Yield (%)
1	**3a**	Me	H	Et_4NOTs	20	**4a**	76
2	**3b**	Me	Me	Et_4NOTs	15	**4b**	63
3	**3c**	*i*-Pr	H	Et_4NOTs	23	**4c**	58
4	**3d**	$Me(CH_2)_5$	H	Et_4NBF_4	8	**4d**	86
5	**3e**	CO_2Me	H	Et_4NBF_4	6	**4e**	81
6	-[a]	Ph	H	AcONa	6	**4f**	81

[a] The starting compound was *N*-methoxycarbonylphenylalanine.

The second step is the conversion of **4** to **5**. We had already found that heating cyclic α-methoxycarbamates in the presence of a small amount of NH_4Cl gave the corresponding enecarbamates in good yields[7a] but the reaction conditions were not always satisfactory for acyclic α-methoxycarbamates **4a-f**, affording **5a-f** in low yields (Table 2). On the other hand, we found herein that the treatment of **4a-f** with NaH in THF gave **5a-f** in good yields (Entries 1~4), while the yields of **5e,f** were comparable with those obtained by acid-catalyzed procedures (Entries 5 and 6).

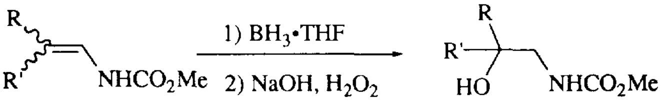
Table 2. Elimination of Methanol from α-Methoxycarbamates **4a-f**

Entry	α-Methoxycarbamate			Enecarbamate	Yield (%) (*cis*/*trans*)	
	4a-f	R	R'	**5a-f**	Δ/NH_4Cl [a]	NaH [b]
1	**4a**	Me	H	**5a**	33 (13/87)	56 (48/52)
2	**4b**	Me	Me	**5b**	29 (-)	84 (-)
3	**4c**	*i*-Pr	H	**5c**	52 (0/100)	73 (0/100)
4	**4d**	$Me(CH_2)_5$	H	**5d**	57 (40/60)	97 (45/55)
5	**4e**	CO_2Me	H	**5e**	80 (79/21)	72 (77/23)
6	**4f**	Ph	H	**5f**	60 (12/88)	60 (17/83)

[a] 5h reflux in toluene with a cat. amount of NH_4Cl.

[b] 1h reflux in THF with 3.0 equiv. of NaH.

The third step is the asymmetric introduction of a hydroxy group into the β position to the nitrogen atom of **5a-f**. Before the asymmetric hydroxylation, we examined the possibility of hydroboration of **5a-f** using borane in THF (eq 2), and found that these enecarbamates **5** except **5e** could be converted to **6a-f** (Table 3).

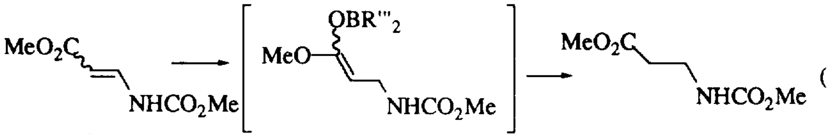


5a-f **6a-f** (2)

Table 3. Hydroboration of Enecarbamates **5a-f**

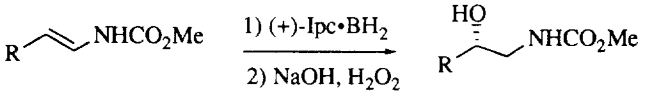
Entry	Enecarbamate **5a-f**	R	R'	β-Hydroxyamine **6a-f**	Yield (%)
1	**5a**	Me	H	**6a**	50
2	**5b**	Me	Me	**6b**	30
3	**5c**	*i*-Pr	H	**6c**	55
4	**5d**	$Me(CH_2)_5$	H	**6d**	69
5	**5e**	CO_2Me	H	**6e**	0
6	**5f**	Ph	H	**6f**	76

The reason why **5e** did not give **6e** by hydroboration is explainable in terms of the selective formation of a borane enolate **7**. In fact, the reaction of **5e** with borane gave a hydrogenation product, methyl 3-(*N*-methoxycarbonylamino)propionate **3e**, in a quantitative yield (eq 3).



5e **7** **3e** (3)

Optically active β-hydroxyamines are our final targets. Since it has been known that asymmetric hydroboration of alkenes largely depends on the stereochemistry,[8, 11] *cis* and *trans* stereoisomers of enecarbamates **5a,c,d,f** were isolated by column chromatography. At first, the *trans* stereoisomers *trans*-**5** were subjected to the hydroboration using (+)-Ipc·BH$_2$ (eq 4). The results are shown in Table 4 in which optically active **6c,d,f** were obtained with moderate enantiomeric excesses (ee's) (entries 2-4 in Table 4), while the ee of **6a** was low (entry 1 in Table 4).

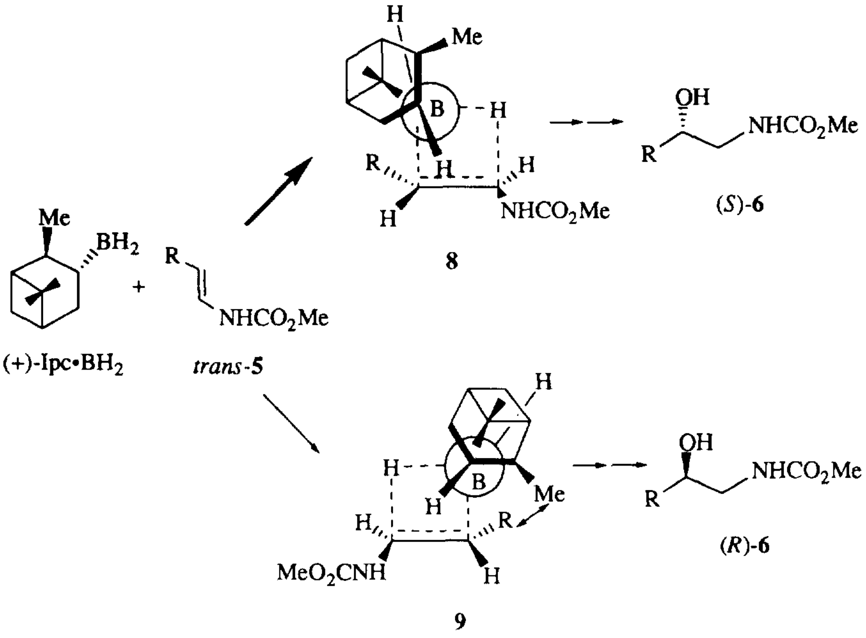


trans-**5a,c,d,f** optically active **6a,c,d,f** (4)

Table 4. Asymmetric Hydroboration of *trans*-**5a,c,d,f**

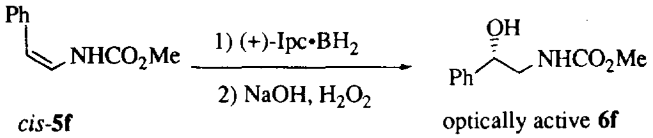
Entry	Enecarbamate *trans*-**5**	R	β-Hydroxyamine **6**	Yield (%)	$[\alpha]_D^{23}$ (c in MeOH)	%ee
1	**5a**	Me	(*S*)-(+)-**6a**	56	+1.88° (1.33)	7
2	**5c**	*i*-Pr	(*S*)-(+)-**6c**	56	+30.90° (1.10)	66
3	**5d**	Me(CH$_2$)$_5$	(*S*)-(+)-**6d**	92	+3.35° (1.40)	60
4	**5f**	Ph	(*S*)-(+)-**6f**	94	+2.80° (0.75)	70

Those results are explainable by assuming intermediates **8** and **9** similar to those proposed in the hydroboration of simple *trans*-alkenes using (+)-Ipc·BH$_2$ (Scheme 2).[8] Namely, plausible transition states leading to (*S*)- and (*R*)-**6** may be **8** and **9**, respectively, in which R group is disposed *anti* to the pinanyl group, and the difference of steric repulsion between R and the pinanyl group in **8** and **9** may reflect the ee's. In a case where R is a small group such as a methyl group, the ee was very low (entry 1 in Table 4), and relatively high ee's were observed in cases of larger R groups such as *i*-propyl, *n*-hexyl and phenyl groups (entries 2-4 in Table 4).



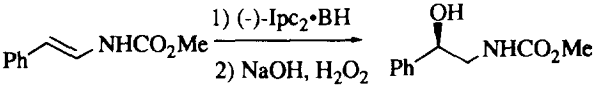
Scheme 2

In contrast, the hydroboration of *cis*-**5f** with (+)-Ipc·BH_2 resulted in a low ee even though R was a phenyl group (eq 5). Many possible transition states could be conceivable in the hydroboration of *cis*-**5** with (+)-Ipc·BH_2[8] to explain the reason why the low ee was observed in the hydroboration of *cis*-**5f** with (+)-Ipc·BH_2. The difference in relative stabilities between such many transition states would be less than that between **8** and **9**.



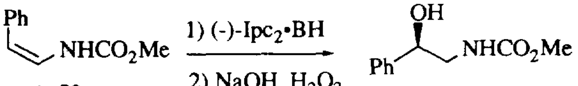
optically active **6f**
84% yield
$[\alpha]_D^{23}$ +0.31°(c 1.60 in MeOH) 8 %ee (5)

Also, the reaction of *cis*- and *trans*-**5f** with (-)-Ipc_2·BH gave low ee's (eqs 6 and 7). Since it has been known that (-)-Ipc_2·BH gives higher stereoselectivities in hydroboration of simple *cis*-alkenes than simple *trans*-alkenes,[11] the methoxycarbonylamino group of *cis*- and *trans*-**5f** may be responsible for the low ee's, though it is not clear yet what effects the methoxycarbonylamino group brought about on the stabilities of the transition states.



trans-**5f** 12% yield optically active **6f**

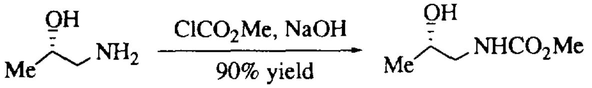
$[\alpha]_D^{23}$ -1.22°(c 1.6 in MeOH) 31% ee (6)



cis-**5f** 22% yield optically active **6f**

$[\alpha]_D^{23}$ -0.23°(c 0.86 in MeOH) 6% ee (7)

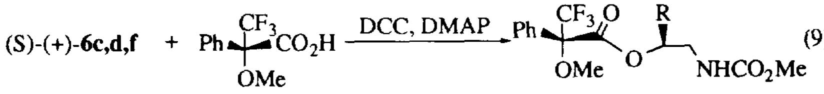
Both (*S*)-2-hydroxypropylamine and (*S*)-2-hydroxy-2-phenylethylamine have been known to possess the positive optical rotations.[12, 13] Since (*S*)-(+)-2-hydroxypropylamine **10** was easily available, the absolute configuration and ee of the obtained **6a** (entry 1 in Table 4) were determined by comparison with authentic (*S*)-(+)-**6a** prepared from **10** (eq 8), and the absolute configuration of the obtained **6f** (entry 4 in Table 4) to be *S* was determined by deprotecting **6f** to 2-hydroxy-2-phenylethylamine followed by measuring the optical rotation.[14] The fact that the absolute configuration of **6a, f** was *S* supports our working hypothesis (Scheme 2) in which the main reaction proceeded *via* an intermediate **8**.



(*S*)-(+)-**10** (*S*)-(+)-**6a** (8)

95%ee $[\alpha]_D^{23}$ +25.98°(c 3.16 in MeOH)

The ee's of **6c, d, f** were determined on the bases of ^{1}H NMR of Mosher's esters **11c, d, f** which were prepared by condensation of **6c, d, f** with Mosher's acid in the presence of DCC and DMAP (eq 9).



(9)

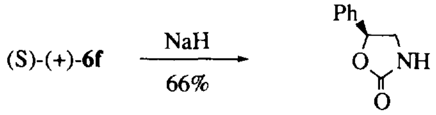
11c,d,f

	R	Yield (%)	%de
11c	*i*-Pr	87	66
11d	Me(CH$_2$)$_5$	86	60
11f	Ph	85	70

Although the absolute configurations of **6c, d** could not be determined directly, they were estimated to be *S* by assuming that the hydroboration of **5c, d** might proceed through intermediates **8** in a similar way to that of

5a,f giving (*S*)-(+)-**6a,f**.

As shown in eqs 4-7, optically active β-hydroxyamines could be obtained with moderate ee's by the reactions of *trans*-**5** with (+)-Ipc·BH_2 as a chiral hydroboration reagent. Usefulness of our method was demonstrated by the transformation of (*S*)-(+)-**6f** to resedine **12**, an alkaloid isolated from *Redeeda Lutola* (eq 10).[15]



(10)

Resedine **12**

$[\alpha]_D^{23}$ +10.0°(c 1.00 in MeOH)

Further studies on the application of our method to more complexed primary amines and on the improvement of ee are under investigation.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were measured with JASCO 810 and Shimadzu FTIR-8100A spectrometers. ^1H NMR spectra were recorded on Varian Gemini-200 (200MHz), 300 (300MHz) and UNITY plus 500 (500MHz) spectrometers with tetramethylsilane as an internal reference and $CDCl_3$ as a solvent. Optical rotations were measured by JASCO DIP-370. Elemental analyses were performed at the Microanalytical Laboratory of the Center for Instrumental Analysis in Nagasaki University.

Materials. Carbamates **3a-e**[7b, 16] and *N*-methoxycarbonylphenylalanine[17] were known compounds. These compounds were prepared by conventional method; Methyl chlorocarbonate was added to the corresponding primary amines in aqueous NaOH. After usual workup, the carbamates were isolated by column chromatography. DCC(dicyclohexylcarbodiimide), DMAP[4-(dimethylamino)pyridine] and other chemical reagents were commercially available and used without further purification.

Electrochemical Oxidation of Carbamates 3a-e and *N*-Methoxycarbonylphenylalanine. The oxidation was carried out according to the reported procedure.[7,10] A typical procedure for the electrochemical oxidation of **3a-e** was as follows. In an undivied cell equipped with platinum electrodes (2cm x 2cm), a solution of **3d** (6.0g, 32mmol) in methanol (80 mL) containing tetraethylammonium tetrafluoroborate (1.0g, 4.6mmol) was electrolyzed at 300mA for 23hrs (8.0 F/mol). During the electrolysis, the solution was kept at -10℃ by standing the cell in a cooling bath. After the electrolysis, the solution was added to water and the organic portion was extracted with ether. The ethereal solution was dried over $MgSO_4$, and then the solvent was evaporated *in vacuo* to give a residue, which was subjected on a column chromatography to isolate **4d**.

***N*-Methoxycarbonyl-1-methoxypropylamine (4a).**
76% Yield; oil; IR (neat) 3325, 2950, 2850, 1710, 1530, 1460, 1360, 1280, 1240, 1200, 1150, 1090, 1060, 1015, 960, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, *J*=7.5 Hz, 3H), 1.49-1.76 (m, 2H), 3.36 (s, 3H), 3.70 (s, 3H), 4.70-5.05 (m, 2H).; Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 49.38; H, 8.52; N, 9.54.

***N*-Methoxycarbonyl-1-methoxy-2-methylpropylamine (4b).**[7b]
63% Yield; mp 154-157℃ (ethyl acetate/hexane); IR (KBr) 2960, 1735, 1530, 1460, 1300, 1240, 1200, 1090, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, *J*=6.6 Hz, 3H), 0.95 (d, *J*=6.6 Hz, 3H), 1.76-1.90 (m, 1H), 3.34 (s, 3H), 3.70 (s, 3H), 4.54-4.66 (m, 1H), 4.92-5.00 (bs, 1H); Anal. Calcd for $C_7H_{15}NO_3$: C, 52.14; H, 9.38; N, 8.69. Found: C, 52.04; H, 8.92; N, 8.91.

***N*-Methoxycarbonyl-1-methoxy-3-methylbutylamine (4c).**[7b]
58% Yield; oil; IR (neat) 3323, 2957, 1709, 1529, 1450, 1369, 1259, 1194, 1091, 1055, 970 cm^{-1}; ^1H NMR ($CDCl_3$) d 0.92 (d, *J*=6.2 Hz, 6H), 1.33-1.80 (m, 3H), 3.35 (s, 3H), 3.70 (s, 3H), 4.85-4.95 (bs, 2H); Anal. Calcd for $C_8H_{17}NO_3$: C, 54.84; H, 9.78; N, 7.99. Found: C, 54.58; H, 9.44; N, 7.89.

***N*-Methoxycarbonyl-1-methoxyoctylamine (4d).**[16c]
86% Yield; oil; IR 3319, 2928, 2856, 1707, 1529, 1360, 1236, 1194, 1093 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H), 1.20-1.77 (m, 12H), 3.35 (s, 3H), 3.70 (s, 3H), 4.62-5.08 (bs, 2H); Anal. Calcd for $C_{11}H_{23}NO_3$: C, 60.80; H, 10.67; N, 6.45. Found: C, 60.55; H, 10.45; N, 6.29.

Methyl 3-methoxy-3-[(methoxycarbonyl)amino]propionate (4e).
81% Yield; oil; IR (neat) 3320, 2950, 1740, 1695, 1550, 1440, 1380, 1318, 1275, 1210, 1170, 1105, 1180, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.69 (m, 2H), 3.36 (s, 3H), 3.71 (s, 6H), 5.22 (dd, *J*=4.1, 9.1 Hz, 1H), 5.89 (bs, 1H); Anal. Calcd for $C_7H_{13}NO_5$: C, 43.97; H, 6.85; N, 7.33. Found: C, 43.83; H, 6.55; N, 7.32.

***N*-Methoxycarbonyl-1-methoxy-2-phenylethylamine (4f).**
81% Yield; mp 72-73℃ (ether/hexane); IR (KBr) 3323, 2949, 1700, 1527, 1454, 1361, 1255, 1093, 1053, 1034 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.93 (t, *J*=5.4 Hz, 2H), 3.34 (s, 3H), 3.66 (s, 3H), 4.92-4.97 (m, 1H), 5.09-5.19 (m, 1H), 7.36 (s, 5H); Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.53; H, 7.09; N, 6.43.

Preparation of Enecarbamates 5. The following procedure is representative.

i) Acid Catalysis Method; A solution of a mixture of **4d** (434 mg, 2 mmol) and NH_4Cl (100 mg) in toluene (15 mL) was refluxed for 5h. To the resulting solution was added brine (15 mL) and the organic layer was separated.

The organic solution was dried over $MgSO_4$, and evaporated to give a residue. The residue was subjected to column chromatography on a silica gel using ethyl acetate/hexane (1/10) as an eluent to give *cis*-**5d** (84.4 mg, 0.46 mmol) and *trans*-**5d** (126.6 mg, 0.68 mmol) with a ratio of 40 to 60 in 57% yield. The *cis* isomers generally gave less polar than *trans* isomers.

ii) NaH Method; To a suspension of NaH (50% oily, 570 mg, 12 mmol) in THF (50 mL) was added a solution of **4d** (870 mg, 4.1 mmol) in THF (10 mL) at room temperature, and the reaction mixture was refluxed for 1h. The reaction mixture was quenched with an aqueous NH_4Cl solution (20 mL), and the organic portions were extracted with CH_2Cl_2 (50 mL x 2). The combined extracts were dried over $MgSO_4$ and evaporated to give a residue. The residue was subjected on column chromatographic purification to give *cis*-**5d** (333 mg, 1.8 mmol) and *trans*-**5d** (407 mg, 2.2 mmol) with a ratio of 45 to 55 in 97% yield. The yields of **5a-f** under the both conditions are summarized in Table 2.

N-Methoxycarbony-1-propenylamine (5a).

***cis*-5a:** oil; IR (neat) 3320, 2957, 1736, 1676, 1500, 1451, 1397, 1364, 1240, 1107, 1011, 776 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (d, *J*=7.0 Hz, 3H), 3.73 (s, 3H), 4.60-4.77 (m, 1H), 6.30-6.75 (m, 2H); Anal. Calcd for $C_5H_9NO_2$: C, 52.15; H, 7.88; N, 12.17. Found: C, 52.12; H, 7.78; N, 12.32.

***trans*-5a:** mp 64-66°C (ether); IR (KBr) 3289, 1728, 1680, 1536, 1440, 1379, 1300, 1242, 1121, 1040, 959, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (dd, *J*=1.5, 6.7 Hz, 3H), 3.71 (s, 3H), 4.90-5.08 (m, 1H), 6.05-6.40 (bs, 1H), 6.35-6.55 (m, 1H); Anal. Calcd for $C_5H_9NO_2$: C, 52.15; H, 7.88; N, 12.17. Found: C, 52.48; H, 7.71; N, 11.98.

N-Methoxycarbonyl-2-methyl-1-propenylamine (5b).

mp 52-55°C (ethyl acetate/hexane); IR (KBr) 3360, 2930, 1700, 1510, 1450, 1380, 1350, 1240, 1070, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (s, 3H), 1.68 (s, 3H), 3.71 (s, 3H), 5.80-6.25 (bs, 1H), 6.25 (d, *J*=12.0 Hz, 1H); Anal. Calcd for $C_6H_{11}NO_2$: C, 55.79; H, 8.58; N, 10.85. Found: C, 55.70; H, 8.34; N, 10.69.

N-Methoxycarbonyl-3-methyl-1-butenylamine (5c).

***trans*-5c:** oil; IR (neat) 3320, 2960, 2870, 1705, 1675, 1525, 1460, 1270, 1230, 1050, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, *J*=6.7 Hz, 6H), 2.29 (dq, *J*=6.9, 13.5 Hz, 1H), 3.71 (s, 3H), 4.99 (dd, *J*=7.1, 14.1 Hz, 1H), 6.07-6.61 (bs, 1H), 6.41 (dd, *J*=6.6, 13.9 Hz, 1H); Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.55; H, 8.98; N, 9.53.

N-Methoxycarbonyl-1-octenylamine (5d).

***cis*-5d:** oil; IR (neat) 3320, 2925, 2860, 1710, 1675, 1515, 1460, 1350, 1240, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J*=7.1 Hz, 3H), 1.25-1.39 (m, 8H), 1.92 (t, *J*=8.9 Hz, 2H), 3.73 (s, 3H), 4.62 (t, *J*=7.8 Hz, 1H), 6.16-6.37 (bs, 1H), 6.43 (d, *J*=9.8 Hz, 1H); Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.82; H, 10.34; N, 7.56. Found: C, 65.16; H, 10.24; N, 7.29.

***trans*-5d:** mp 30-31℃ (ether/hexane); IR (KBr) 3300, 2920, 2850, 1695, 1535, 1460, 1300, 1240, 1055, 955 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.88 (t, *J*=7.0 Hz, 3H), 1.24-1.35 (m, 8H), 1.98 (t, *J*=13.6 Hz, 2H), 3.70 (s, 3H), 4.99 (dt, *J*=13.9, 7.3 Hz, 1H), 6.08-6.26 (bs, 1H), 6.44 (d, *J*=12.4 Hz, 1H); Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.82; H, 10.34; N, 7.56. Found: C, 65.04; H, 10.29; N, 7.46.

Methyl 3-[(methoxycarbonyl)amino]acrylate (5e).

***cis*-5e:** oil; IR (neat) 3325, 2950, 1745, 1695, 1640, 1630, 1500, 1440, 1380, 1370, 1200, 1050, 1000, 960 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.62 (s, 3H), 3.69 (s, 3H), 4.96 (d, *J*=9.0 Hz, 1H), 7.16 (dd, *J*=9.0, 12.0 Hz, 1H), 9.64 (bs, 1H); Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.88. Found: C, 45.48; H, 5.62; N, 8.76.

***trans*-5e:** mp 173-174℃ (ether); IR (KBr) 3275, 1745, 1690, 1620, 1530, 1440, 1320, 1265, 1230, 1200, 1155, 1080, 1120, 1000, 950 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.59 (s, 3H), 3.69 (s, 3H), 5.39 (d, *J*=14.5 Hz, 1H), 7.69 (dd, *J*=14.5, 11.0 Hz, 1H), 9.72 (d, *J*=11.0 Hz, 1H); Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.88. Found: C, 45.18; H, 5.52; N, 8.77.

N-Methoxycarbonyl-2-phenylethenylamine (5f).

***cis*-5f:** oil; IR (neat) 3302, 1734, 1701, 1670, 1599, 1545, 1446, 1336, 1325, 1309, 1288, 1259, 1055, 954 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.74 (s, 3H), 5.64 (d, *J*=9.3 Hz, 1H), 6.71 (t, *J*=10.3 Hz, 1H), 6.95-7.00 (bs, 1H), 7.34-7.45 (m, 5H); Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 68.28; H, 6.34; N, 7.71.

***trans*-5f:** mp 122-124℃ (ether/hexane); IR (KBr) 3298, 1736, 1701, 1677, 1545, 1336, 1325, 1288, 1259, 1055, 956 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.76 (s, 3H), 5.96 (d, *J*=14.6 Hz, 1H), 6.64-6.70 (bs, 1H), 7.16 (dd, *J*=3.4, 14.6 Hz, 1H), 7.27-7.40 (m, 5H); Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.56; H, 6.22; N, 7.85.

Hydroboration of Enecarbamats 5 with $BH_3 \cdot$ THF Complex. The following procedure is representative. To a solution of **5d** (370 mg, 2 mmol) in THF (2 mL) was injected $BH_3 \cdot$THF complex (4 mL, 4 mmol) at 0℃. After the solution was stirred at room temperature for 1h and refluxed for 1h, the reaction mixture was oxidized with 10% NaOH (1 mL) and 30% H_2O_2 (2 mL) at room temperature, and then the reaction mixture was stirred for 12h at room temperature. THF was removed under a reduced pressure and the residue was extracted with CH_2Cl_2 (50 mL x 3). The combined extracts were dried over $MgSO_4$ and evaporated. The residual oil was purified by column chromatography on a silica gel using ethyl acetate/hexane (1/1) as an eluent to afford *N*-methoxycarbonyl-2-hydroxyoctylamine (**6d**) (280 mg, 1.4 mmol) in 69% yield.The yields of **6a-f** are summarized in Table 3.

N-Methoxycarbonyl-2-hydroxypropylamine (6a).

oil; IR (neat) 3400, 2936, 2880, 2361, 2342, 2150, 1723, 1538, 1450, 1380, 1264, 1196, 1115, 1017, 930 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.18 (d, *J*=6.3 Hz, 3H), 2.25-2.55 (bs, 1H), 2.97-3.14 (m, 1H), 3.25-3.40 (m, 1H), 3.68 (s, 3H), 3.85-4.00 (m, 1H), 5.10-5.30 (bs, 1H); Anal. Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52. Found: C, 44.83; H, 7.99; N, 10.01.

***N*-Methoxycarbonyl-2-hydroxy-2-methylpropylamine (6b).**
oil; IR (neat) 3350, 2970, 1700, 1530, 1460, 1370, 1255, 1150, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 6H), 1.91-2.12 (bs, 1H), 3.18 (d, *J*=6.3 Hz, 2H), 3.69 (s, 3H), 4.93-5.24 (bs, 1H); Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 49.32; H, 8.89; N, 9.36.

***N*-Methoxycarbonyl-2-hydroxy-3-methylbutylamine (6c).**
oil; IR (neat) 3400, 2964, 1734, 1556, 1280, 1150, 1082, 958 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, *J*=6.6 Hz, 6H), 1.68 (q, *J*=6.7 Hz, 1H), 2.08-2.32 (bs, 1H), 3.08 (t, *J*=9.6 Hz, 1H), 3.41 (d, *J*=7.1 Hz, 1H), 3.69 (s, 3H), 4.96-5.27 (bs, 1H); Anal. Calcd for $C_7H_{15}NO_3$: C, 52.16; H, 9.38; N, 8.69. Found: C, 52.43; H, 9.15; N, 8.48.

***N*-Methoxycarbonyl-2-hydroxyoctylamine (6d).**
oil; IR (neat) 3350, 2930, 2810, 1710, 1540, 1460, 1375, 1270, 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J*=6.5 Hz, 3H), 1.18-1.54 (m, 10H), 1.67 (d, *J*=2.5 Hz, 1H), 2.12-2.26 (bd, 1H), 3.37 (d, *J*=3.4 Hz, 1H), 3.04 (d, *J*=5.7 Hz, 1H), 3.68 (s, 3H), 3.62-3.80 (m, 1H); Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.09; H, 10.41; N, 6.89. Found: C, 59.10; H, 10.21; N, 6.86.

***N*-Methoxycarbonyl-2-hydroxy-2-phenylethylamine (6f).**
mp 94-95℃ (ether); IR (KBr) 3350, 3070, 3040, 2950, 1700, 1550, 1453, 1250, 1196, 1154, 1094, 1067, 1001, 831 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.68-2.78 (bs, 1H), 3.24-3.40 (m, 1H), 3.48-3.65 (m, 1H), 3.68 (s, 3H), 4.80-4.89 (m, 1H), 5.00-5.18 (bs, 1H), 7.30-7.39 (m, 5H); Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.51; H, 6.65; N, 7.18.

Hydroboration of Enecarbamates 5 with (+)-Monoisopinocamphenylborane [(+)-Ipc·BH_2]. Asymmetric Synthesis of (*S*)-(+)-*N*-Methoxycarbonyl-2-hydroxy-2-phenylethylamine [(*S*)-(+)-6f]. The following procedure is representative. A solution of (+)-Ipc·BH_2 in THF (10 mL) was prepared from $(Ipc \cdot BH_2)_2$·TMEDA complex (530 mg, 1.28 mmol) and $BF_3 \cdot OEt_2$ (0.32 mL, 2.56 mmol) according to a general procedure.[11] To the solution, a solution of *trans*-**5f** (114 mg, 0.64 mmol) in THF (5 mL) was injected at 0℃ under a nitrogen atmosphere. After the resulting solution was stirred at room temperature for 1h and then refluxed for 1h, 10% NaOH (1 mL) and 30% H_2O_2 (2 mL) were successively added at room temperature. After usual workup, the chromatographic purification of the residue on a silica gel (ethyl acetate/hexane=1/5 as an eluent) gave (*S*)-(+)-*N*-methoxycarbonyl-2-hydroxy-2-phenylethylamine **6f** (124 mg, 0.63 mmol) in 94% yield. The optical rotation was $[\alpha]^{23}_D$ +2.80° (c 0.75 in MeOH). The ee of this **6f** (70% ee) was determined on the basis of the ^{1}H NMR spectrum of Mosher's ester **11f**, which showed the benzylic proton signals at δ 5.95-6.02 (m) and 6.04-6.08 (m) in an integral ratio of 85 to 15.

(*S*)-(+)-*N*-Methoxycarbonyl-2-hydroxypropylamine [(*S*)-(+)-6a]. This optically active compound

6a was obtained in 56% yield by the hydroboration of *trans*-**5a** with (+)-Ipc·BH_2 carried out under conditions similar to those described for **6f**. The optical rotation of this **6a** showed $[\alpha]^{23}_D$ +1.88° (c 1.33 in MeOH). The ee of this **6a** (7% ee) was determined by comparison with authentic sample prepared from commercially available (*S*)-(+)-2-hydroxypropylamine **10** (95% ee) as described below.

(*S*)-(+)-*N*-Methoxycarbonyl-2-hydroxy-3-methylbutylamine [(*S*)-(+)-6c]. This optically active compound was obtained in 56% yield by the hydroboration of *trans*-**5c** with (+)-Ipc·BH_2 carried out under conditions similar to those described for **6f**. The optical rotation of this **6c** showed $[\alpha]^{23}_D$ +30.90° (c 1.10 in MeOH). The ee of this **6c** (66% ee) was determined on the basis of the ^1H NMR spectrum of Mosher's ester **11c** in which the methoxy proton signals appeared at δ 3.53 (s) and 3.56 (s) in an integral ratio of 83 to 17.

(*S*)-(+)-*N*-Methoxycarbonyl-2-hydroxyoctylamine [(*S*)-(+)-6d]. This optically active compound was obtained in 92% yield by the hydroboration of *trans*-**5d**. The optical rotation of this **6d** showed $[\alpha]^{23}_D$ +3.35° (c 1.40 in MeOH). The ee of this **6d** (60% ee) was determined on the basis of the ^1H NMR spectrum of Mosher's ester **11d** in which the methoxy proton signals appeared at δ 3.50 (s) and 3.67 (s) in an integral ratio of 80 to 20.

Hydroboration of Enecarbamates 5f with (-)-Diisopinocamphenylborane [(-)-Ipc$_2$·BH]. A solution of (-)-Ipc$_2$·BH in THF (10 mL) was prepared from (+)-α-pinene (1.02 g, 6.6 mmol) and BH_3·Me_2S (0.34 mL, 3.3 mmol) according to a general method.[11] To the solution, a solution of *trans*-**5f** (0.33g, 1.85 mmol) in THF (5 mL) was injected at 0℃ under nitrogen atmosphere. After 1h at 0℃, the solution was allowed to warm up and then the solution was refluxed for 1h. Oxidation with 10% NaOH (1 mL) and 30% H_2O_2 (1 mL) gave (*R*)-(-)-**6f** (44 mg, 0.22 mmol) in 12% yield after usual workup. The optical rotation of this **6f** was $[\alpha]^{23}_D$ -1.22° (c 1.6 in MeOH). So, the ee of this **6f** was determined to be 31% by comparison of the optical rotation of (*S*)-(+)-**6f** prepared with (+)-Ipc·BH_2. Hydroboration of *cis*-**5f** was also carried out according to the method described above. The optical rotation of thus obtained **6f** was $[\alpha]^{23}_D$ -0.23° (c 0.86 in MeOH), and the ee was 6%.

Synthesis of (*S*)-(+)-*N*-Methoxycarbonyl-2-hydroxypropylamine [(*S*)-(+)-6a]. To a solution of commercially available (*S*)-(+)-2-hydroxypropylamine (*S*)-(+)-**10** (95% ee, 0.15g, 2.0 mmol) in 20% aqueous NaOH (2 mL), methyl chlorocarbonate (0.23 mL, 3.0 mmol) was added with stirring over 10min, and then the solution was stirred overnight at room temperature. The resulting solution was extracted with ether (20 mL x 2), and the combined extracts were dried over $MgSO_4$ and evaporated to give (*S*)-(+)-**6a** (oil, 0.23g, 1.73 mmol) in 90% yield. Optical rotation of this compound was $[\alpha]^{23}_D$ +25.98° (c 3.16 in MeOH).

Deprotection of (*S*)-(+)-6f. The deprotection of (*S*)-(+)-**6f** was carried out according to a reported method.[18]

Preparation of Mosher's Esters 11c,d,f. To a solution of (*S*)-(+)-**6c,d,f** (0.41 mmol) in CH_2Cl_2 (1 mL), a solution of DCC (0.25g, 1.23 mmol), (*S*)-(-)-MTPA acid (0.19g, 0.82 mmol), and DMAP (0.1g, 0.82 mmol) in CH_2Cl_2 (1 mL) was added at room temperature. The mixture was stirred for 30min, and then allowed to stand for 8h at room temperature. Chromatographic purification on a silica gel using ethyl acetate/hexane (1/3) as an eluent gave Mosher's esters **11c,d,f** in 87%, 86%, 85% yields, respectively.

11c: oil; IR (neat) 1747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 and 0.91 (d and d, *J*=6.9 Hz, 4.98H) 0.96(t, *J*=6.6 Hz, 1.02H) 1.58-1.59 (m, 0.17H) 1.59-1.62 (m, 0.83H) 1.92-2.00 (m, 1H) 3.21-3.28 (m, 0.17H) 3.33-3.39 (m, 0.83H) 3.53 (s, 2.49H) 3.56 (s, 0.51H) 3.65-3.68 (bs, 2.49H) 3.63-3.65 (bs, 0.51H) 4.68-4.74 (bs, 0.83H) 4.52-4.57 (bs, 0.17H) 4.98-5.04 (m, 1H) 7.38-7.43 (m, 3H) 7.52-7.58 (m, 2H); Anal. Calcd for $C_{17}H_{22}NO_5F_3$: C, 54.11; H, 5.88; N, 3.71. Found: C, 54.40; H, 5.67; N, 3.50.

11d: oil; IR (neat) 1749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (t, *J*=6.9 Hz, 3H) 1.16-1.21 (m, 8H) 1.50-1.70 (m, 2H) 3.18-3.24 (m, 0.2H) 3.30-3.38 (m, 0.8H) 3.44-3.50 (m, 1H) 3.50 (s, 2.4H) 3.67 (s, 0.6H) 3.64-3.70 (m, 3H) 4.52-4.60 (bs, 0.2H) 4.72-4.80 (bs, 0.8H) 5.10-5.20 (m, 1H) 7.38-7.45 (m, 3H) 7.53-7.58 (m, 2H); Anal. Calcd for $C_{20}H_{28}NO_5F_3$: C, 57.27; H, 6.73; N, 3.34. Found: C, 57.42; H, 6.87; N, 3.28.

11f: oil; IR (neat) 1749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.46 (m, 1H) 3.46 (s, 0.45H) 3.52 (s, 2.55H) 3.62-3.68 (m, 1H) 3.65 (s, 0.45H) 3.67 (s, 2.55H) 4.62-4.72 (bs, 0.15H) 4.81-4.90 (bs, 0.85H) 5.95-6.02 (m, 0.15H) 6.04-6.08 (m, 0.85H) 7.30-7.44 (m, 10H); Anal. Calcd for $C_{20}H_{20}NO_5F_3$: C, 58.39; H, 4.90; N, 3.40. Found: C, 58.14; H, 5.02; N, 3.36.

Synthesis of 5-Phenyl-2-oxazolidinone (12). To suspension of NaH (50% oily, 89 mg, 1.9 mmol) in THF (40 mL) was added a solution of (*S*)-(+)-**6f** (0.12 g, 0.62 mmol) in THF (10 mL) at room temperature and the reaction mixture was refluxed for 3h. The resulting solution was quenched with an aqueous NH_4Cl (10 mL) , and the organic layer was extracted with ether (20 mL x 2). The combined extracts were dried over $MgSO_4$ and evaporated to give a residue. The residue was adsorbed on column of a silica gel, and the column was eluted with ethyl acetate/hexane (1/2) to afford **12** (67 mg, 0.41 mmol) in 66% yield. The optical rotation was $[\alpha]^{23}_D$ +10.0° (c 1.0 in MeOH): mp 71-73℃ (ether/hexane); IR (KBr) 3276, 2890, 1950, 1880, 1719, 1489, 1458, 1426, 1370, 1238, 1076, 1026, 1001, 928 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.54 (t, *J*=7.8 Hz, 1H), 3.98 (t, *J*=8.4 Hz, 1H), 5.35-5.50 (bs, 1H), 5.63 (t, *J*=8.0 Hz, 1H), 7.35-7.47 (m, 5H); Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.08; H, 5.56; N, 8.46.

Acknowledgment : This work was supported in part by a Grant-in-Aid for Scientific Research (B) (No. 07455364) from the Ministry of Education, Science and Culture, Japan.

References and Notes

† This paper is dedicated to Professor Dr. Hans J. Schäfer on the occasion of his 60th birthday.

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(*Received in Japan* 16 *January* 1997; *accepted* 12 *February* 1997)