# THE PRACTICAL SYNTHESIS OF *N*-PROTECTED ALLYLAMINE : THE ISOXAZOLINE ROUTE TO STATINE ANALOGUE

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**Abstract** — *The facile, practical synthesis* of optically active *N*-protected allylamine from α-amino acid is described. The evolution of this work in the synthesis of statine analogue using [3+2] cycloaddition reaction is detailed.

The synthetic approach to chiral compounds in optically pure form represents a major purpose for organic chemists. In a program directed toward the synthesis of amino alcohol derivatives, the development of synthetic methods of *N*-protected allylamine (**1**) is also a remarkable target. Optically active *N*-protected allylamines are significant building blocks to amino alkyl epoxide (**2**)[1] and iodo cyclocarbamate (**3**).[2] In addition they seem to be an useful precursor of isoxazoline derivatives (**4**). (Fig. 1)

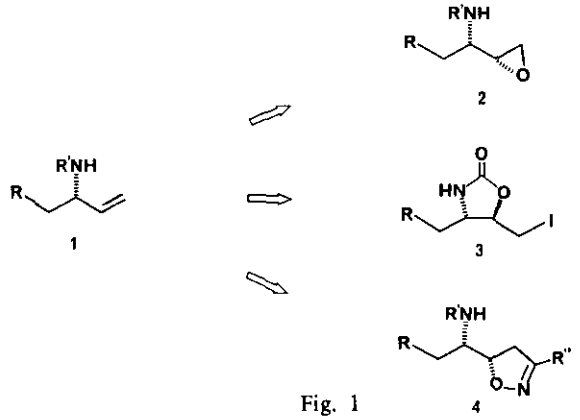
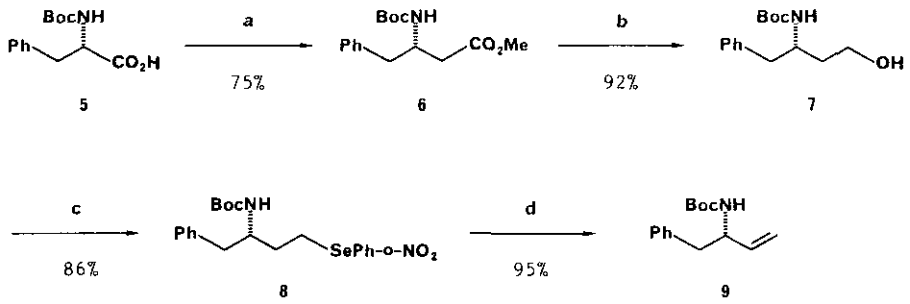



Fig. 1

In order to synthesize *N*-protected allylamine, conversion of *N*-protected α-amino acid to the corresponding amino aldehyde followed by Wittig olefination seemed to be a straightforward entry.[2] However, α-amino aldehydes are well known to be accompanying facile racemization.[3] The devised synthetic approaches involving aldehyde olefination pathway with $Ph_3PCH_3Br$-$KN(TMS)_2$ [1] or $CH_2I_2$-Zn-$Me_3Al$ [4] have been investigated to minimize the racemization. These synthetic methods resulted in a low chemical yield, and a difficult problem remained in the case of phenylalaninal because of its high propensity to racemization.

In this paper we disclose an alternative synthetic method from α-amino acid without the path through amino aldehyde as shown in Scheme 1.



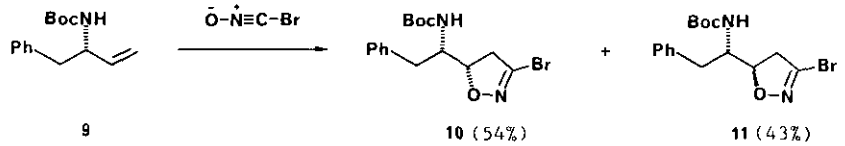

a) i) $ClCO_2{}^{i}Bu$, *N*-methylmorpholine, THF ii) $CH_2N_2$ iii) $PhCO_2Ag$, $NEt_3$, MeOH ;

b) $NaBH_4$, LiCl ; c) *o*-$NO_2PhSeCN$, *n*-$Bu_3P$, THF ; d) 30% $H_2O_2$, THF

Scheme 1

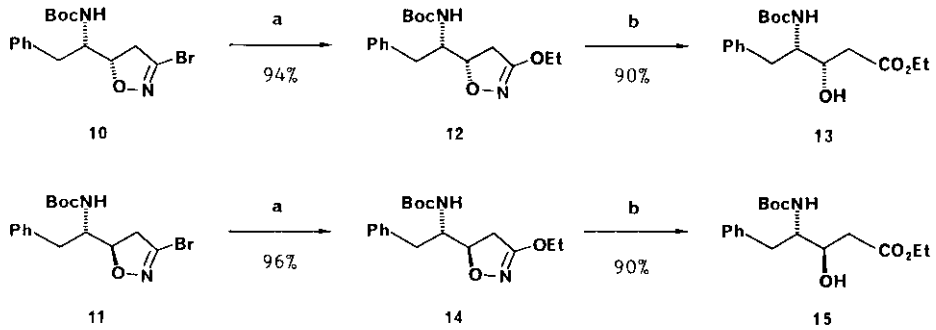
Ester (**6**) was prepared by using a modification of the procedure by Ondetti and Engel[5] starting from *N*-Boc-L-phenylalanine (**5**). Ester (**6**) was reduced and the obtained primary alcohol (**7**) was converted into aryl selenide (**8**) by treatment with *o*-nitrophenyl selenocyanate in THF at room temperature in the presence of tri-*n*-butylphosphine.[6] Selenide (**8**) was oxidized by excess hydrogen peroxide and decomposed to the desired allylamine (**9**) in a good yield. The enantiomeric purity of **9** was determined to be > 99% e.e. by hplc analysis of the diastereomeric MTPA amide.[7]

In addition, we examined the extent of diastereoselection which could be achieved in the [3+2] cycloaddition reaction of nitrile oxide to an olefin bearing an allylic asymmetric center. The resulting cycloadduct isoxazoline ring is well known to be a convenient precursor for β-hydroxy esters. We presumed that one could possibly use this method to gain access to statine analogues. Statine and its analogues are unusual β-hydroxy-γ-amino acids which are recognized as a key component of renin inhibitor. In view of the physiological significance, many synthetic methods have been intensified in many laboratories.[8] (3*S*,4*S*)-4-Amino-3-hydroxy-5-phenylpentanoic acid (AHPPA) [9] is also an important low-molecular weight renin inhibitors. We examined the [3+2] cycloaddition reaction of allylamine (**9**) using bromonitrile oxide as dipolarophile.




Scheme 2

Reaction of **9** with bromonitrile oxide prepared *in situ* from dibromoformaldoxime and sodium bicarbonate[10] afforded a ca. 1.3 : 1 mixture of *threo*- and *erythro*-isoxazolines (**10** and **11**) in 97% yield. These diastereomeric products could be conveniently separated by silica gel column chromatography and the stereochemistry of isolated compounds was determined by converting them to the known *N*-Boc-AHPPA-OEt shown below. Diastereoselectivity was observed in the case of addition of a nitrile oxide to a chiral alkene bearing an allylic oxygen substituent by means of considering "inside alkoxy" effect[11] and/or Felkin type transition state.[12] However the diastereoselection could not be detected in this case. Thus, we synthesized *N*-Boc-AHPPA-OEt (**13**, **15**) by use of nucleophilic substitution and hydrogenation procedure as depicted in Scheme 3.




a) LiOEt, EtOH ; b) $H_2$/ Raney Ni, $AlCl_3$, $H_2O$-MeOH

Scheme 3

Treatment of an ethanolic solution of the less polar isoxazoline (**10**) with LiOEt leads to the formation of 3-ethoxyisoxazoline (**12**), which could be efficiently transformed into β-hydroxy ester (**13**) according to hydrogenolysis[13] in 90% yield. The spectral (nmr, ir, ms) and hplc data of **13** were identical with those of the authentic (3*S*,4*S*) isomer.[9] Further, the obtained product (**13**) was converted to the corresponding free base and condensed with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) by the reported method.[14,15] The enantiomeric excess of the resulting thiourea was determined to be >99% e.e. by hplc analysis. More polar isoxazoline (**11**) was also converted into β-hydroxy ester in the same manner, and the structure of the product was confirmed to be (3*R*,4*S*) isomer.

In conclusion, starting from α-amino acid, we were able to establish the practical synthetic route to *N*-protected allylamine overcoming the undesired stereomutation. Subsequently, we synthesized *N*-Boc-AHPPA-OEt that is statine analogue using [3+2] cycloaddition reaction.

## EXPERIMENTAL

Melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. Infrared (ir) spectra were measured with a Nic 5SXC FT ir spectrophotometer. Proton nuclear magnetic resonance ($^1$H-nmr) spectra were recorded in deuteriochloroform, with tetramethylsilane as the internal reference with a JEOL JNM- GX 270 FT nmr. Mass spectra (ms) were obtained with a JEOL JMS-D300 mass spectrometer. Column chromatography was done on a Kieselgel 60 $F_{254}$ (Merck, 70-230 mesh). In general, reactions were carried out under a nitrogen stream.

Methyl (3*S*)-(*N*-t-butoxycarbonyl)amino-4-phenylbutyrate 6

To a solution of *N*-Boc-L-phenylalanine (5) (10.00 g, 37.7 mmol) and *N*-methylmorpholine (4.14 ml, 37.7 mmol) in ether (200 ml) at -10 °C under nitrogen was added, over a period of 5 min, isobutyl chloroformate (4.88 ml, 37.7 mmol). After the mixture was stirred for 30 min at -10 °C, the reaction mixture was filtered, and the precipitate was washed with ether. The combined filtrate was treated with a cold, ethereal solution of diazomethane (prepared from *N*-nitrosomethylurea). After stirring for 4 h at room temperature, the excess diazomethane was decomposed by HOAc. The solvent was removed *in vacuo* , and the residue was purified by silica gel column chromatography. Elution with 20% AcOEt in *n*-hexane (v/v) afforded diazoketone (9.12 g, 84 %) as a bright yellow solid. To a solution of diazoketone (9.04 g, 31.2 mmol) in anhydrous MeOH (100 ml) was added 10 ml of a solution of silver benzoate (1.0 g) in triethylamine (20 ml). After the mixture was stirred for 20 min, an additional 5 ml of the silver benzoate (0.5 g) in triethylamine solution was added. After the mixture was stirred for an additional 1 h, Celite and decolorizing carbon were added followed by saturated NaCl (30 ml). After stirring for 5 min, the mixture was filtered through Celite and the filtrate was concentrated *in vacuo* . The residue was chromatographed (20% AcOEt in *n*-hexane (v/v)) to give **6** (8.16 g, 89 %) as white crystals : mp 49-51°C, $[\alpha]_D^{20}$ -19.8° ( c 1.0, MeOH). Anal. Calcd for $C_{16}H_{23}NO_4$ : C, 65.51; H, 7.90; N, 4.77. Found : C, 65.45; H, 7.96; N, 4.70. Ir (KBr) : 1741, 1710, 1691 $cm^{-1}$. $^1$H-Nmr ($CDCl_3$) δ : 1.41 (s, 9H), 2.48 (m, 2H), 2.75-3.00 (m, 2H), 3.69 (s, 3H), 4.16 (br m, 1H), 5.03 (br s, 1H), 7.10-7.40 (m, 5H). Ms m/z : 294($M^+$+1), 146, 102, 57.

(3*S*)-(*N*-t-Butoxycarbonyl)amino-4-phenylbutan-1-ol 7

To a suspension of sodium borohydride (2.68 g, 70.8 mmol) and lithium chloride (3.00 g, 70.8 mmol) in THF (60 ml) and EtOH (90 ml) were added a solution of ester (**6**) (7.24 g, 24.7 mmol) in THF (30 ml) and EtOH (45 ml). After the reaction mixture was stirred for 18 h at room temperature under a nitrogen atmosphere, the reaction mixture was quenched with acetone, the solvent was removed *in vacuo* , and the residue was diluted with AcOEt. The resulting solution was washed with brine. After drying ($MgSO_4$), the solvent was removed *in vacuo*, and the residue was chromatographed (30% AcOEt in *n*-hexane (v/v)) to give **7** (6.00 g, 92 %) as white crystals; mp 57-59 °C, $[\alpha]_D^{20}$ +6.8° (c 1, MeOH). Anal. Calcd for $C_{15}H_{23}NO_3$ : C, 67.90; H, 8.74; N, 5.28. Found : C, 67.84; H, 8.96; N, 5.57. Ir (KBr) : 1685 $cm^{-1}$. $^1$H-Nmr ($CDCl_3$) δ

: 1.40 (m, 1H), 1.41 (s, 9H), 1.83 (m, 1H), 2.82 (m, 2H), 3.45 (m, 1H), 3.65 (m, 2H), 4.05 (m, 1H), 4.80 (br d, 1H), 7.15-7.35 (m, 5H). Ms m/z : 266($M^+$+1), 118, 74, 57.

(3*S*)-(*N*-t-Butoxycarbonyl)amino-4-phenylbutyl *o*-nitrophenyl selenide **8**

A solution of **7** (1.00 g, 3.77 mmol) in THF (20 ml) containing *o*-nitrophenyl selenocyanate (1.03 g, 4.54 mmol) under nitrogen was treated dropwise with tri-*n*-butylphosphine (1.13 ml, 4.54 mmol) at room temperature. After the reaction mixture was stirred for 1 h, the solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography. Elution with 20% AcOEt in *n*-hexane (v/v) afforded **8** (1.45 g, 86 %) as yellow crystals. Recrystallization from *n*-hexane gave an analytical sample ; mp 119-121°C, $[\alpha]_D^{20}$ +2.9° (c 1, MeOH). Anal. Calcd for $C_{21}H_{26}N_2O_4Se$ : C, 56.13; H, 5.83; N, 6.23. Found : C, 56.27; H, 5.89; N, 6.41. Ir (KBr) : 1686 $cm^{-1}$. $^1$H-Nmr ($CDCl_3$) δ : 1.42 (s, 9H), 1.78 ( m, 1H), 1.98 (m, 1H), 2.72-3.06 (m, 2H), 3.98 (m, 1H), 4.40 (br d, 1H), 7.12-7.50 (m, 8H), 8.29 (d, 1H, J=1.1 Hz). Ms m/z : 450 ($M^+$+1), 259, 131, 91, 56.

(3*S*)-(*N*-t-Butoxycarbonyl)amino-4-phenyl-1-butene **9**

To a solution of selenide (**8**) (1.00 g, 2.26 mmol) in THF (10 ml), 30% hydrogen peroxide (1.96 ml, 22.6 mmol) was added dropwise over a period of 10 min at 0 °C. This reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed with aqueous sodium carbonate and brine. After drying ($MgSO_4$), the solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography. Elution with 15% AcOEt in *n*-hexane afforded **9** (520 mg, 95 %) as crystals ; mp 66-68°C, $[\alpha]_D^{20}$ +35.9° (c 1, $CHCl_3$). Anal. Calcd for $C_{15}H_{21}NO_2$ : C, 72.84; H, 8.56; N, 5.66. Found : C, 73.11; H, 8.75; N, 5.68. Ir (KBr) : 1686 $cm^{-1}$. $^1$H-Nmr ($CDCl_3$) δ : 1.40 (s, 9H), 2.84 (d, 2H, J=6.2Hz), 4.43 (br s, 1H), 5.06-5.13 (m, 2H), 5.80 (m, 1H), 7.15-7.35 (m, 5H). Ms m/z : 248 ($M^+$+1), 156, 100, 57.

Procedure for determining enantiomeric purity of **9**

The Boc protected amine (**9**) (70 mg, 0.28 mmol) was treated with 4N HCl/dioxane (5 ml) for 30 min. Evaporation provided the amine hydrochloride, which was dissolved in $CH_2Cl_2$ (5 ml) and treated with triethylamine ( 0.09 ml, 0.65 mmol) followed by (+)-Mosher's acid chloride[7] ( 0.08 g, 0.32 mmol). The organic layer was washed with 10% citric acid, saturated sodium carbonate, and brine. After drying ($MgSO_4$), the solvent was removed *in vacuo*, and the residue was analyzed by hplc (column, Senshu Pak ODS-1251-SH; eluent, 50 : 50 $CH_3CN$-$H_2O$ mixture; flow rate, 1.0 ml/min). The enantiomeric excess of **9** was determined to be > 99%. $t_R$ of the (3*S*)-isomer, 41.7 min; $t_R$ of the (3*R*)-isomer, 38.2 min. The authentic enantiomer of **9** was synthesized in the same manner starting from *N*-Boc-D-phenylalanine.

3-Bromo-(5*R*,*S*)-[(1*S*)-(*N*-t-butoxycarbonyl)amino-2-phenylethyl-4,5-dihydroisoxazoles **10**,**11**

To a suspension of dibromoformaldoxime (984 mg, 4.85 mmol) and sodium bicarbonate (1.36 g, 16.2 mmol) in AcOEt (10 ml) and $H_2O$ (1 ml), olefin (**9**) (400 mg, 1.62 mmol) was added at 0 °C. After the reaction mixture was stirred for 3 h at 0 °C, saturated NaCl was added to the reaction mixture and extracted with AcOEt. After

drying ($MgSO_4$), the solvent was removed *in vacuo* and the residue was chromatographed (10% AcOEt in *n*-hexane (v/v)) to give the separated diastereomers, less polar isomer (**10**) (323 mg, 54 %) and more polar isomer (**11**) (255 mg, 43 %) as white crystals. Recrystallization from *n*-hexane gave analytical samples; less polar isomer (**10**) ; mp 114-116°C, $[\alpha]_D^{20}$ + 68.3° (c 1, $CHCl_3$). Anal. Calcd for $C_{16}H_{21}N_2O_3Br$ : C, 52.04; H, 5.73; N, 7.59. Found : C, 52.04; H, 5.73; N, 7.54. Ir (KBr) : 1690 $cm^{-1}$. $^1$H-Nmr ($CDCl_3$) δ : 1.40 (s, 9H), 2.80-3.20 (m, 4H), 4.00 (m, 1H), 4.60-4.75 (m, 2H), 7.15-7.40 (m, 5H). Ms m/z : 369 ($M^+$), 164, 120, 57. more polar isomer (**11**) ; mp 125-127°C, $[\alpha]_D^{20}$ -94.6° (c 1, $CHCl_3$). Anal. Calcd for $C_{16}H_{21}N_2O_3Br$ : C, 52.04; H, 5.73; N, 7.59. Found : C, 52.11; H, 5.75; N, 7.57. Ir (KBr) : 1680 $cm^{-1}$. $^1$H-Nmr ($CDCl_3$) δ : 1.37 (s, 9H), 2.80-3.30 (m, 4H), 3.97 (m, 1H), 4.44 (m, 1H), 4.60 (m, 1H), 7.15-7.40 (m, 5H). Ms m/z : 369($M^+$), 164, 120, 57.

(5*S*)-[(1*S*)-(*N*-t-Butoxycarbonyl)amino-2-phenylethyl-3-ethoxy-4,5-dihydroisoxazole **12**

A solution of lithium ethoxide was prepared from lithium (100 mg, 14.4 mmol) and EtOH (10 ml). **10** (300 mg, 0.81 mmol) was added and the resulting solution was refluxed for 30 min. After stirring for 30 min, the reaction mixture was poured into ice-cold water (50 ml), and extracted with ether. The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography. Elution with 20% AcOEt in *n*-hexane (v/v) afforded **12** (256 mg, 94 %) as white crystals. Recrystallization from *n*-hexane gave an analytical sample; mp 87-89°C, $[\alpha]_D^{20}$ +20.2° (c 1, $CHCl_3$). Anal. Calcd for $C_{18}H_{26}N_2O_4$ : C, 64.65; H, 7.84; N, 8.38. Found : C, 64.70; H, 7.76; N, 8.31. Ir (KBr) : 1686, 1621 $cm^{-1}$. $^1$H-Nmr ($CDCl_3$) δ : 1.34 (t, 3H, J= 7Hz), 1.40 (s, 9H), 2.75-3.00 (m, 4H), 3.95 (m, 1H), 4.17 (q, 2H, J=7Hz), 4.56 (m,1H), 4.84 (br d, 1H, J=10Hz), 7.15-7.40 (m, 5H). Ms m/z : 334 ($M^+$), 120, 114, 57.

(5*R*)-[(1*S*)-(*N*-t-Butoxycarbonyl)amino-2-phenylethyl-3-ethoxy-4,5-dihydroisoxazole **14**

This compound was obtained in 96% yield (194 mg) from **11** (223 mg, 0.60 mmol) by the same procedure as used for the synthesis of **12**. Recrystallization from *n*-hexane gave an analytical sample; mp 127-129°C, $[\alpha]_D^{20}$ -64.1° (c 1, $CHCl_3$). Anal. Calcd for $C_{18}H_{26}N_2O_4$ : C, 64.65; H, 7.84; N, 8.38. Found : C, 64.61; H, 7.68; N, 8.37. Ir (KBr) : 1680, 1626 $cm^{-1}$. $^1$H-Nmr ($CDCl_3$) δ : 1.35 (t, 3H, J=7Hz), 1.36 (s, 9H), 2.80-3.05 (m, 4H), 4.00 (m, 1H), 4.19 (q, 2H, J=7Hz), 4.35-4.55 (m, 2H), 7.15-7.40 (m, 5H). Ms m/z : 334($M^+$), 120, 114, 57.

Ethyl (4*S*)-(*N*-t-butoxycarbonyl)amino-(3*S*)-hydroxy-5-phenylpentanoate **13**

To a solution of **12** (155 mg, 0.46 mmol) in *EtOH* (5 ml) and $H_2O$ (1 ml), aluminium chloride (247 mg, 1.85 mmol) and catalytic amount of Raney Ni were slowly added at 0 °C. The reaction mixture was stirred for 1 h at room temperature under hydrogen. The reaction mixture was filtered, and ether was added to the filtrate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography. Elution with 20% AcOEt in *n*-hexane (v/v) afforded **13** (140 mg,

*90 %) as white crystals, and a >99:1 threo-erythro mixture (hplc analysis: column,* Senshu Pak ODS-1251-SH; eluent, 55 : 45 water-acetonitrile mixture; $t_R$ of *threo*-**13**, 17.3 min. $t_R$ of *erythro*-**15**, 14.8 min; flow rate, 1.0 ml/min). The product was converted to the corresponding free base and condensed with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) by the reported method.[14,15] The enantiomeric excess of **13** was determined to be >99% by hplc analysis (column, Senshu Pak silica-1251-N; eluent, 93:7 *n*-hexane–2-propanol mixture; flow rate, 1.5 ml/min; $t_R$ of (3*S*,4*S*)-isomer, 11.7 min; $t_R$ of (3*R*,4*R*)-isomer, 10.1 min). Recrystallization from *n*-hexane gave an analytical sample; mp 88-89°C, $[\alpha]_D^{20}$ -36.0° (c 1, MeOH) (lit.[9] mp 88-89°C, $[\alpha]_D^{24}$ -35.9° (c 1.0, MeOH)). Anal. Calcd for $C_{18}H_{27}NO_5$ : C, 64.07; H, 8.07; N, 4.15. Found : C, 64.06; H, 8.15; N, 4.11. Ir (KBr) : 1730, 1682 $cm^{-1}$. $^1$H-Nmr ($CDCl_3$) δ : 1.24 (t, 3H, J=7Hz), 1.41 (s, 9H), 2.37 (dd, 1H, J=16.8 and 2.6 Hz), 2.59 (dd, 1H, J=16.8 and 9.9 Hz), 2.91 (d, 2H, J=7.7 Hz), 3.46 (br d, 1H, J=2.6Hz, exchangeable), 3.73 (m, 1H), 3.98 (m, 1H), 4.13 (q, 2H, J=7Hz), 4.93 (br d, 1H), 7.15-7.35 (m, 5H). Ms m/z : 338 ($M^+$+1), 146, 100, 57.

Ethyl (4*S*)-(*N*-t-butoxycarbonyl)amino-(3*R*)-hydroxy-5-phenylpentanoate **15**

This compound was obtained in 90% yield (93 mg) from **14** (102 mg, 0.31 mmol) by the same procedure as used for the synthesis of **13**. The enantiomeric excess of **15** was determined to be >99% by hplc analysis of the corresponding GITC derivative (column, Senshu Pak silica-1251-N; eluent, 93:7 *n*-hexane–2-propanol mixture; flow rate, 1.5 ml/min; $t_R$ of (3*R*,4*S*)-isomer, 12.7 min; $t_R$ of (3*S*,4*R*)-isomer, 10.6 min). mp 139-141°C, $[\alpha]_D^{20}$ -14.8° (c 1, MeOH) (lit.[9] mp 140-140.4°C, $[\alpha]_D^{24}$ -14.2° (c 1.0, MeOH)). Anal. Calcd for $C_{18}H_{27}NO_5$ : C, 64.07; H, 8.07; N, 4.15. Found : c, 64.07; H, 8.10; N, 4.08. Ir (KBr) : 1734, 1683 $cm^{-1}$. $^1$H-Nmr ($CDCl_3$) δ : 1.27 (t, 3H, J=7Hz), 1.34 (s, 9H), 2.44-3.02 (m, 4H), 3.58 (br s, 1H, exchangeable), 3.85 (m, 1H), 3.99 (m, 1H), 4.17 (q, 2H, J=7Hz), 4.54 (br d, 1H), 7.15-7.35 (m, 5H). Ms m/z : 338 ($M^+$+1), 146, 100, 57.

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