HETEROCYCLES, Vol. 56, 2002, pp. 545-552, Received, 18th May, 2001

CHEMO-ENZYMATIC SYNTHESIS OF NOVEL β-AMINO ACIDS SUBSTITUTED BY (THYMIN-1-YL)METHYL FUNCTIONAL GROUP AT THE α-POSITION[¶]

Tsutomu Yokomatsu,* Ken Takada, Akihito Yasumoto, Yoko Yuasa, and Shiroshi Shibuya

School of Pharmacy, Tokyo University of Pharmacy & Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

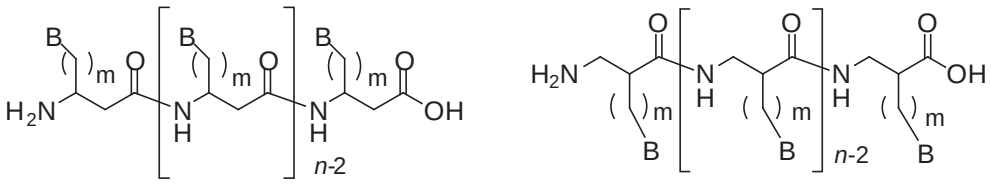
Abstract— A novel β-amino acid having (thymin-1-yl)methyl functionality at the α-position, a useful component of α-substituted β-homoalanyl peptide nucleic acids (β^2-PNAs), was synthesized as a protected form from 2-(N^3-benzoylthymin-1-yl)methyl-1,3-propanediol *via* enzymatic desymmetrization catalyzed by lipase PS.

During the past few years, interest in β-amino acids has increased considerably since the discovery of the interesting physical properties associated with β-peptides.[1,2] The β^2- and β^3-peptides respectively derived from α- and β-substituted β-amino acids with a simple alkyl side-chain can fold into well-defined helically or plated-sheet secondary structures.[2,3] Significant differences in the physical properties between β^2- and β^3-peptides are known.[2d] Moreover, β-peptides are reported to be more stable than α-peptides to enzymatic degradation.[4]

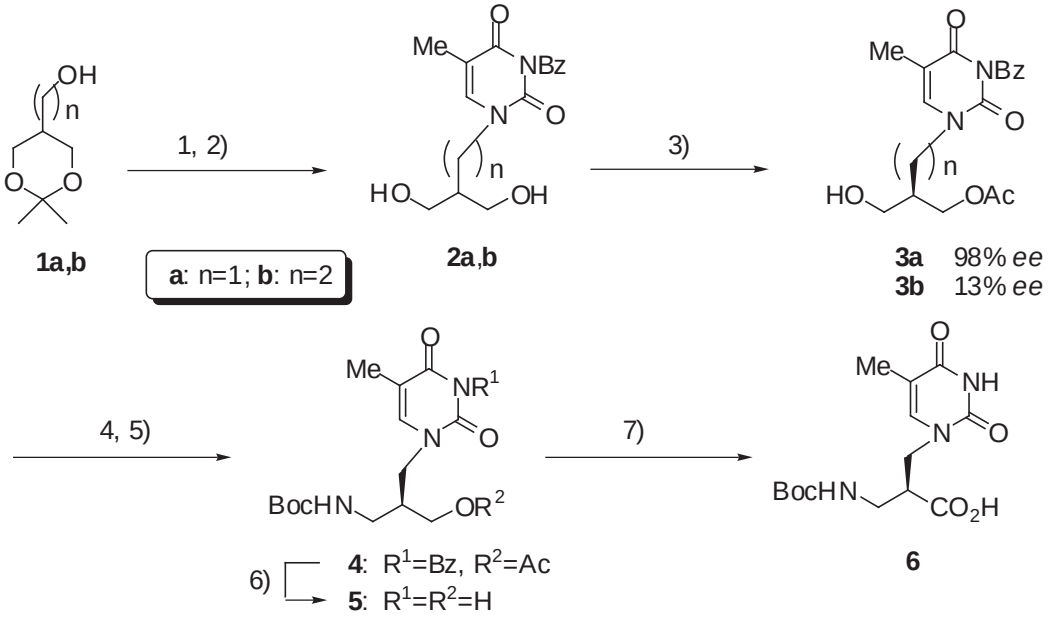
On the other hand, peptide nucleic acids (PNAs), oligomers possessing a polyamide backbone in which the nucleo bases of the DNA/RNA function as recognition units, have increased in importance because of their potential use in antigene or antisense therapy.[5] A number of modifications of the polyamide backbone in PNAs has been recently devised to increase the interaction of PNA/DNA or PNA/RNA.[5,6] In the light of the characteristic features associated with β-peptides as well as the potential usefulness of PNAs in medicinal chemistry, Diederichsen recently reported synthesis and characterization of β^3-PNAs derived from β-substituted β-amino acids with a purine nucleo base (Figure 1).[7] However, the synthesis of α-substituted β-amino acids for components of the β^2-PNAs as well as elucidation of their physical properties have not been studied.[7] We herein describe a preparation of an optically active α-substituted β-amino acid having a (thymin-1-yl)methyl side chain, a useful component of the β^2-PNAs, as a protective form amenable to the peptide synthesis.

[¶]This paper is dedicated to Professor James P. Kutney on the occasion of his 70th birthday.

Figure 1



Our strategy for access to the required nucleo β-amino acids is based on a chemo-enzymatic route as shown in Scheme 1, in which we apply lipase-catalyzed desymmetrization of the 2-substituted 1,3-propanediols as a key reaction. While a number of applications of the lipase-catalyzed desymmetrization of prochiral diols to enantiomerically pure molecules have been reported,[10] to the best of our knowledge, effects of the nucleo bases at the terminal position in 2-substitued 1,3-propanediols on discrimination of the enantiotopic diol moiety are unknown.[10,11]

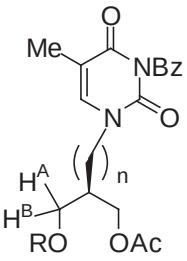


Scheme 1. 1) T(N^3-Bz), DEAD, Ph_3P, THF; 2) Amberlyst 15E, MeOH; 3) lipase PS, vinyl acetate, THF; 4) HN_3, DEAD, Ph_3P, THF; 5) H_2, Boc_2O, 10% Pd-C, EtOAc; 6) K_2CO_3, MeOH; 7) Jones reagent, acetone.

Keeping these matters in mind, we first investigated the lipase-catalyzed desymmetrization of 1,3-propanediol derivatives (**2a, b**). Treatment of alcohols (**1a, b**)[12] with N^3-benzoylthymine (T(N^3-Bz))[13] under the Mitsunobu conditions [diethyl azodicarboxylate (DEAD), Ph_3P, THF, rt], followed by

hydrolysis with Amberlyst 15E® in MeOH, gave the requisite diols (**2a**) (mp 154-156 ℃) and (**2b**) (mp 47-48 ℃) in 84 and 85% yields, respectively. The lipase-catalyzed desymmetrization of **2a** and **2b** was carried out in THF in the presence of lipase PS from *Pseudomonas cepacia* and vinyl acetate (1.5 equiv.) at 25 ℃. Under the conditions, the transesterification of diol (**2a**) proceeded rapidly (2 h) to give the optically active monoacetate (**3a**), $[\alpha]^{25}_{D}$ +3.81° (c 1.0, MeOH), in 85% yield. On the contrary, it was verified that the transesterification of the homologous diol (**2b**) requires rather longer time (12 h) to give **3b** of very small amplitude of the specific rotation, $[\alpha]^{25}_{D}$ –0.81° (c 1.0, MeOH), in 74% yield.

The optical purities of **3a**,**b** were determined by ^{1}H NMR (400 MHz, $CDCl_3$) analysis of the corresponding MTPA esters (**7a**,**b**) and (**8a**,**b**) respectively derived from (*S*)- and (*R*)-MTPA. The analyses revealed the acetate (**3a**) to be of high optical purity (>98% *ee*), while optical purity of homologous acetate (**3b**) was proved to be very low (13% *ee*). The enantioselectivity for the transesterification of **3b** was not improved upon using lipases from different origins in place of lipase PS.[†] These experiments clearly show that the length between the methine carbon and the thymin-1-yl moiety in **2a, b** may be a critical factor for discriminating the enantiotopic hydroxyl functionalities.



7a,b: R=(*S*)-MTPA
8a,b: R=(*R*)-MTPA

a: n=1; **b**: n=2

The absolute stereochemistry of **3a** was deduced by analyzing the ^{1}H NMR spectrum of the MTPA esters (**7a**) and (**8a**) according to the method of Yamaguchi.[14] In the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7a**, the signals due to the methylene protons (H^A and H^B) α to the (*S*)-MTPA ester functional group appear at δ 4.39 (dd, *J* =11.8, 4.6 Hz) and 4.36 (dd, *J* =11.8, 5.0 Hz), whereas the corresponding H^A- and H^B-protons of (*R*)-MTPA ester (**8a**) resonate at δ 4.50 (dd, *J* = 11.6, 4.6 Hz) and δ 4.27 (dd, *J* = 11.6, 5.2 Hz), respectively. Apparently, the difference (Δδ) of H^A- and H^B-protons of **7a** in chemical shifts is smaller than that of **8a**. On the basis of the coupling patterns and the report of Yamaguchi,[14] the absolute stereochemistry of **3a** was estimated to be *R*-configuration. The determined strereochmistry is consistent with that predicted from the empirical rule regarding enantiopreference of *Pseudomonas cepacia* lipase toward chiral primary alcohols proposed by Kazlauskas.[15]

With monoacetate (**3a**) of high optical purity in hand, transformation of **3a** to the target β-amino acid (**6**) was examined (Scheme 1). Reaction of **3a** with hydrazoic acid under the Mitsunobu conditions, followed by hydrogenation over 10% Pd-C in EtOAc in the presence of Boc_2O,[16] gave *N*-Boc-amino acetate (**4**) in 60% yield for the two-steps. Upon treatment of **4** with excess amounts of potassium carbonate in MeOH, concomitant deacetylation and debenzoylation occurred to give **5**, mp 60-62 ℃; $[\alpha]^{25}_{D}$ +4.17° (c 1.0, MeOH) in virtually quantitative yield. No racemization took place during these transformations; the enantiomeric purity (98% *ee*) of **5** was retained as analyzed by means of ^{1}H NMR (400 MHz, $CDCl_3$) after

[†] For example, the diol (**2b**) was transestrificated rapidly (2 h) in the presence of lipase AK (*Pseudomonas fluoresence*) and vinyl acetate in THF to give the monoacetate (**3b**) in 94% yield. However, the acetate obtained from this reaction was totally optically inactive. It need to do further experiments for understanding the remarkable differences between **2a** and **2b** in reactivity toward the transesterification.

transforming to the corresponding (*R*)- and (*S*)-MTPA esters. Oxidation of **5** with the Jones reagent in acetone gave *N*-Boc β-amino acid (**6**) as crystals in 79% yield.

EXPERIMENTAL

Melting points are uncorrected. All NMR data were recorded on a Bruker DPX 400 unless otherwise specified. ^{1}H and ^{13}C NMR data were collected by operating at 400 and 100 MHz, respectively. The chemical shift data for each signal are given in units of δ relative to tetramethylsilane (δ 0.00) or chloroform (δ 7.26). The chemical shifts of ^{13}C are reported relative to $CDCl_3$ (δ 77.0). IR spectra were recorded on a JASCO FTIR-620 spectrophotometer. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. MS spectra were measured on a Finnigan TSQ-700 or a VG Auto Spec E spectrometer. Lipase-PS and -AK were purchased from Amano Pharmaceutical Co., Ltd.

3-Benzoyl-1-[3-hydroxy-2-(hydroxymethyl)propyl]-5-methylpyrimidine-2,4(1*H*, 3*H*)-dione (2a). To a stirred solution of alcohol (**1a**)[12] (7.3 g, 50 mmol), N^3-benzoylthymine (12.6 g, 55 mmol) and Ph_3P (14.4 g, 55 mmol) in THF (100 mL) was added DEAD (40% toluene solution 8.9 mL, 55 mmol) under ice cooling. After being stirred for 12 h at rt, the volatile component of the mixture was removed *in vacuo*. The residue was chromatographed on silica gel (*n*-hexane:EtOAc=2:1) to give an oil, which was dissolved in MeOH (200 mL) and treated with Amberlyst 15E® (3 g) for 2 h at rt. The resin was filtered and the filtrate was evaporated. The residue was chromatographed on silica gel. Elution with $CHCl_3$ gave **2a** (13.3 g, 84 %) as crystals: mp 154-156 ℃ (EtOAc/*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 7.91 (2H, d with small splits, *J* = 8.4 Hz), 7.66 (1H, t, *J* = 8.4 Hz), 7.50 (2H, t, *J* = 7.8 Hz), 7.24 (1H, t, *J* = 0.8 Hz), 3.99 (2H, d, *J* = 6.61 Hz), 3.76-3.67 (4H, m), 2.65-2.59 (2H, m), 2.13-2.02 (1H, m), 1.97 (3H, d, *J* = 0.8 Hz); ^{13}C NMR ($CDCl_3$) δ 168.6, 162.9, 151.2, 140.7, 135.1, 131.5,. 130.4, 129.2, 111.5, 61.9, 46.7, 42.5, 12.4; IR (KBr) 1747, 1691, 1650, 1441, 1252 cm^{-1}; EIMS *m/z* 318 (M^+). Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.01; H, 5.68; N, 8.96.

3-Benzoyl-1-[4-hydroxy-3-(hydroxymethyl)butyl]-5-methylpyrimidine-2,4(*1H,3H*)-dione (2b). The alcohol (**1b**)[12] was condensed with N^3-benzoylthymine, followed by hydrolysis, in an analogous manner to that for preparation of **2a** to give **2b** as hygroscopic crystals: mp 47-48 ℃ (ether/*n*-hexane); yield: 42% (for the two-step); ^{1}H NMR ($CDCl_3$) δ 7.90 (2H, d with small splits, *J* = 6.3 Hz), 7.65-7.62 (1H, m), 7.49 (2H, t, *J* = 8.0 Hz), 7.15 (1H, t, *J* = 1.1 Hz), 3.81 (2H, t, *J* = 7.2 Hz), 3.72 (2H, dd, *J* = 10.9, 4.3 Hz), 3.66 (2H, dd, *J* = 10.9, 5.6 Hz), 1.94 (3H, d, *J* = 1.1 Hz), 1.83-1.69 (3H, m); ^{13}C NMR ($CDCl_3$) δ 169.2, 163.1, 149.6, 140.8, 135.0, 131.0, 120.0, 129.0, 110.21, 63.1, 46.7, 36.6, 27.2, 11.8; EIMS *m/z* 332 (M^+). HRMS (EI) calcd for $C_{17}H_{20}N_2O_5$ (M^+): 332.1372. Found: 332.1371.

General procedure for lipase-catalyzed transesterification reaction of 2a,b with vinyl acetate. In a typical experiment, a mixture of **2a** (1 g, 3.1 mmol), vinyl acetate (0.43 mL, 4.7 mmol) and lipase PS (1 g) in THF (15 mL) was stirred at 25 ℃ for 2 h. The reaction was terminated by filtering off the enzyme. After concentration of the filtrate *in vacuo*, the residue was purified by column chromatography on

silica gel. Elution with $CHCl_3$ gave the monoacetate (**3a**) as an oil in 85% yield. The transesterification of **2b** with vinyl acetate was carried out in a similar manner.

(2*R*)-3-(3-Benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1-(2*H*)-yl)-2-(hydroxymethyl)propyl acetate (3a): $[\alpha]^{25}_D$ +3.81° (c 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.88 (2H, d, *J* = 7.5 Hz), 7.63 (1H, t, *J* = 7.6 Hz), 7.45 (2H, t, *J* = 7.8 Hz), 7.17 (1H, br s), 4.15 (1H, dd, *J* = 11.4, 6.3 Hz), 4.06 (1H, dd, *J* = 11.4, 6.4 Hz), 3.84 (1H, dd, *J* = 14.1, 8.1 Hz), 3.77 (1H, dd, *J* = 14.1, 5.8 Hz), 3.56 (2H, d, *J* = 3.7 Hz), 2.96 (1H, br s), 2.28-2.19 (1H, m), 2.04 (3H, s), 1.91 (3H, s); ^{13}C NMR ($CDCl_3$) δ 171.0, 168.8, 162.9, 150.5, 140.7, 135.1, 131.3, 130.3, 129.1, 111.0, 62.6, 59.3, 47.1, 40.2, 20.7, 12.3; IR (neat) 1743, 1697, 1654, 1440, 1224 cm^{-1}; EIMS *m/z* 360 (M^+). HRMS (EI) calcd for $C_{18}H_{20}N_2O_6$ (M^+): 360.1321. Found: 360.1329.

(2*R*)-4-(3-Benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-(hydroxymethyl)butyl acetate (3b): Yield: 74%; an oil; $[\alpha]^{25}_D$ –0.81° (c 1.0, MeOH) (for the sample of 13% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (2H, d, *J* = 8.5 Hz), 7.63 (1H, t, *J* = 7.6 Hz), 7.50 (2H, t, *J* = 7.6 Hz), 7.14 (1H, s with small splits), 4.14 (2H, d, *J* = 5.2 Hz), 3.92-3.78 (2H, m), 3.63 (2H, d, *J* = 4.9 Hz), 2.08 (3H, s), 1.97 (3H, d, *J* = 1.2 Hz), 1.92-1.68 (3H, m); EIMS *m/z* 374 (M^+).

Prparation of MTPA esters (7a,b) and (8a,b). To a stirred solution of (2*R*)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoic acid [(*S*)-MTPA] (91.5 mg, 0.36 mmol), *N*,*N*-dicyclohexylcarbodiimide (DCC) (74.2 mg, 0.36 mmol), and 4-dimethylaminopyridine (DMAP) (4.4 mg, 0.036 mmol) in CH_2Cl_2 (1 mL) was added a solution of **3a** or **3b** (0.18 mmol) in CH_2Cl_2 (2 mL) at 0 ℃. The mixture was stirred at the same temperature for 30 min, and then kept at rt until the starting material disappeared on TLC (3-24 h). The reaction was quenched with 10% HCl (6 mL) at 0 ℃. The mixture was extracted with $CHCl_3$. The extracts were washed successively with sat. $NaHCO_3$ and brine, and then dried ($MgSO_4$). The solution was concentrated *in vacuo*, and diluted with ether. The resulting suspension was passed through silica gel (0.5 g). The filtrate was evaporated to leave crude **7a,b**, which were analyzed by ^{1}H NMR spectroscopy without purification. The (*R*)-MTPA-esters (**8a,b**) were prepared in an analogous manner.

(2*S*)-3-(3-Benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-{[(*tert*-butoxycarbonyl)amino]methyl}propyl acetate (4). To a stirred solution of **3a** (3.6 g, 10 mmol) and Ph_3P (3.15 g, 12 mmol) in THF (100 mL) were successively added HN_3 [30 mL of benzene solution of HN_3 prepared from NaN_3 (3.00 g, 46 mmol) and 50% H_2SO_4 (20 mL) in benzene (60 mL)] and diethyl azodicarboxylate (40% toluene solution 4.72 mL, 12 mmol) at -35 ℃. The mixture was stirred at the same temperature for 30 min, and allowed to warm to room temperature. After being stirred for 2 h, the volatile component of the mixture was evaporated. The residue was dissolved in ether (30 mL), and cooled at –40 ℃ for 1 h. The precipitate was filtered and the filtrate was evaporated to give the crude azide (5.6 g), which was used in the next reaction without further purification.

A solution of the azide and Boc_2O (2.26 g, 12 mmol) in EtOAc (100 mL) was hydrogenated over 10% Pd-C (250 mg) for 2 h at rt under atmospheric pressure. The catalyst was removed through Celite, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 2:1 to 1:2) to give **4** (4.48 g, 60%) as an oil. $[\alpha]^{25}_D$ +3.61° (c 1.0, MeOH); ^{1}H NMR

($CDCl_3$) δ 7.91 (2H, d with small splits), 7.65 (1H, t with small splits, *J* = 7.5 Hz), 7.49 (2H, t, *J* = 7.8 Hz), 5.08-5.06 (1H, m), 4.13 (1H, dd, *J* = 11.7, 5.5 Hz), 4.06 (1H, dd, *J* = 11.7, 5.8 Hz), 3.80 (1H, dd, *J* = 14.2, 7.2 Hz), 3.74 (1H, dd, *J* = 14.2, 6.1 Hz), 3.24-3.10 (2H, m), 2.38-2.26 (1H, m), 2.07 (3H, s), 1.95 (3H, s), 1.41 (9H, s); ^{13}C NMR ($CDCl_3$) δ 171.9, 169.9, 164.0, 157.2, 151.4, 141.4, 136.0, 132.4, 131.3, 130.1, 111.9, 80.2, 63.2, 48.3, 39.3, 39.1, 28.5, 21.0, 12.6; IR (neat) 1746, 1698, 1655, 1509 cm^{-1}: EIMS *m/z* 459 (M^+); HRMS (EI) calcd for $C_{23}H_{29}N_3O_7$ (M^+): 459.2006. Found: 459.2009.

***tert*-Butyl (2*S*)-3-hydroxymethyl-2-[(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl]propylcarbamate (5).** A solution of **4** (4.5 g, 10 mmol) in 95% MeOH (100 mL) was treated with K_2CO_3 (2.76 g, 20 mmol) at 25 ℃ for 1 h. The solvent was evaporated and the residue was partitioned between water and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$. The extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 1:2 to 1:4) to give **5** (2.7 g, 87%) as crystals: mp 60-62 ℃ ($CHCl_3$); $[\alpha]^{25}_D$ +4.17° (c 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.07 (1H, d, *J* = 0.5 Hz), 5.29 (1H, t, *J* = 6.4 Hz), 3.79 (1H, dd, *J* = 14.0, 7.3 Hz), 3.59-3.47 (2H, m), 3.43 (1H, dd, *J* = 12.0, 5.3 Hz), 3.28 (1H, ddd, *J* = 14.5, 5.2, 5.2 Hz), 3.08 (1H, ddd, *J* = 14.5, 6.5, 6.5 Hz), 2.04-1.96 (1H, m), 1.91 (3H, d, *J* = 0.3 Hz), 1.44 (9H, s); ^{13}C NMR ($CDCl_3$) δ 164.2, 157.6, 151.8, 140.9, 111.5, 80.2, 46.8, 41.7, 38.2, 28.4 (3-carbons), 12.4; IR (KBr) 1685 cm^{-1}; EIMS *m/z* 313 (M^+). Anal. Calcd for $C_{14}H_{23}N_3O_5$: C, 53.66; H, 7.40; N, 13.41. Found: C, 54.02; H, 7.09; N, 13.07.

(2*S*)-3-[(*tert*-Butoxycarbonyl)amino]-2-[(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl]propionic acid (6). To a solution of **5** (2.5 g, 7.9 mmol) in acetone (126 mL) was added Jones reagent (13 mL) under ice cooling. After being stirred for 12 h at rt, the reaction was quenched with 2-propanol. The mixture was diluted in water, and extracted with $CHCl_3$. The extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel ($CHCl_3$:MeOH=500:1 to 200:1) to give **6** (2.46 g, 79%) as crystals: mp 211-214 ℃ ($CHCl_3$); $[\alpha]^{25}_D$ +2.89° (c 1.0, MeOH); ^{1}H NMR (DMSO-d_6) δ 12.6 (1H, br s), 11.3 (1H, s), 7.43 (1H, s), 6.89 (1H, t, *J* = 5.6 Hz), 3.79 (1H, dd, *J* = 13.9, 6.2 Hz), 3.69 (1H, dd, *J* = 13.9, 8.4 Hz), 3.19-3.03 (2H, m), 2.93-2.81 (1H, m), 1.72 (3H, s), 1.36 (9H, s); ^{13}C NMR (DMSO-d_6) δ 173.5, 164.4, 155.7, 151.1, 142.1, 108.3, 78.1, 47.6, 44.6, 28.4 (3 carbons), 12.1; IR (KBr) 3369, 1687, 1521 cm^{-1}; EIMS *m/z* 327 (M^+); CIMS (isobutane) *m/z* 328 (MH^+), 384 ($MC_3H_9^+$). Anal. Calcd for $C_{14}H_{21}N_3O_6$: C, 51.37; H, 6.47; N, 12.84. Found: C, 51.93; H, 6.59; N, 11.97. HRMS (EI) calcd for $C_{14}H_{21}N_3O_6$ (M^+): 327.1430. Found: 327.1425.

ACKNOWLEDEMENT

This work was supported in part by Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

REFERENCES AND NOTES

1 a) G. P. Dado and S. H. Gellman, *J. Am. Chem. Soc.*, 1994, **116**, 1054. b) D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell, and S. H. Gellman, *J. Am. Chem. Soc.*, 1996, **118**, 13071. c) D. H. Appella, L. A. Christianson, D. A. Klein, D. R. Powell, X. Huang, J. J. Barchi, Jr., and S. H. Gellman, *Nature*, 1997, **387**, 381 and references cited therein.

2 a) D. Seebach, M. Overhand, F. N. M. Kühnle, B. Martinoni, L. Oberer, U. Hommel, and H. Widmer, *Helv. Chim. Acta*, 1996, **79**, 913. b) D. Seebach, P. E. Ciceri, M. Overhand, B. Jaun, D. Rigo, L. Oberer, U. Hommel, R. Amstutz, and H. Widmer, *Helv. Chim. Acta*, 1996, **79**, 2043. c) D. Seebach and J. L Matthews, *Chem. Commun.*, 1997, 2015. d) T. Hintermann and D. Seebach, *Synlett*, 1997, 437.

3 The designation of β^2- and β^3-peptides is proposed by Seebach to distinguish the positional isomers of β-peptides.[2d]

4 T. Hinterman and D. Seebach, *Chimia*, 1997, **50**, 244.

5 For a review of PNA: B. Hyrup and P. E. Nielsen, *Bioorg. Med. Chem.*, 1996, **4**, 5.

6 a) D. D. Weller, D. T. Daly, W. K. Olson, and J. E. Summerton, *J. Org. Chem.*, 1991, **56**, 6000. b) S.-B. Huang, J. S. Nelsen, and D. D. Weller, *J. Org. Chem.*, 1991, **56**, 6007. c) N. M. Howarth and L. P. G. Wakelin, *J. Org. Chem.*, 1997, **62**, 5441.

7 a) U. Diederichsen and H. W. Schmidt, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 302. b) U. Diederichsen and H. W. Schmidt, *Eur. J. Org. Chem.*, 1998, 827.

8 For enantioselective synthesis of β-substituted β-amino acids: a) E. Juaristi, D. Quintana, and J. Escalante, *Aldrichim. Acta*, 1994, **27**, 3. b) D. C. Cole, *Tetrahedron*, 1994, **50**, 9517. c) J. L. Matthrews, C. Braun, C. Guibuourdenche, M. Overhand, and D. Seebach, in *"Enantioelective Synthesis of β-Amino Acids"*, ed. by E. Juaristi, Wiley-VCH, New York, 1997. d) D. A. Evans, L. D. Wu, J. J. M. Wiener, J. S. Johonson, D. H. B. Ripin, and J. S. Tedrow, *J. Org. Chem.*, 1999, **64**, 6411.

9 For enantioselective synthesis of α-substituted β-amino acids: a) D. A. Evans, F. Urpi, T. C. Somer, J. C. Clark, and M. T. Bilodeau, *J. Am. Chem. Soc.*, 1990, **112**, 8251. b) E. Juaristi, D. Quintana, M. Balderas, and E. García-Pérez, *Tetrahedron: Asymmetry*, 1996, **7**, 2233 and references cited therein.

10 For reviews for lipase-catalyzed synthesis of biologically active compound. a) C.-S. Chen and C. J. Sih, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 695. b) K. Faber and S. Riva, *Synthesis*, 1992, 895. c) F. Theil, *Chem. Rev.*, 1995, **95**, 2203.

11 Recent examples for lipase-catalyzed desymmetrization of prochiral 2-substituted 1,3-propanediols: a) K. Tsuji, Y. Terao, and K. Achiwa, *Tetrahedron Lett.*, 1989, **30**, 6189. b) G. Guanti, E. Narisano, T. Podgorski, S. Thea, and A. Williams, *Tetrahedron*, 1990, **46**, 7081. c) T. Itoh, J. Chika, Y. Takagi, and S. Nishiyama, *J. Org. Chem.* 1993, **58**, 5717. d) T. Yokomatsu, M. Sato, and S. Shibuya, *Tetrahedron: Asymmetry*, 1996, **7**, 2743. e) B. Morgan, D. R. Dodds, A. Zaks, D.

R. Andrews, and R. Klesse, *J. Org. Chem*. 1997, **62**, 7736. f) T. Yokomatsu, T. Minowa, T. Murano, and S. Shibuya, *Tetrahedron*, 1998, **54**, 9341.

12 The alcohol (**1a**) was prepared according to the method of Dubois: J. Dubois, C. Fourès, S. Bory, S. Falcou, M. Gaudry, and A. Marquet, *Tetrahedron*, 1991, **47**, 1001. The homologous alcohol (**1b**) was obtained from triethylethane-1,1,2-tricarboxylate according to the method of Harnden: M. R. Harnden, R. L. Jarvest, T. H. Bacon, and M. R. Boyd, *J. Med. Chem.*, 1987, **30**, 1636.

13 K. A. Cruickshank, J. Jiricny, and C. B. Reese, *Tetrahderon Lett.*, 1984, **25**, 681.

14 F. Yasuhara, S. Yamaguchi, R. Kasai, and O. Tanaka, *Tetrahedron Lett.*, 1986, **27**, 4033.

15 A. N. E. Weissfloch and R. J. Kazlauskas, *J. Org. Chem.*, 1995, **60**, 6959.

16 S. Saito, H. Nakajima, M. Inaba, and T. Moriwake, *Tetrahedron Lett.*, 1989, **30**, 837.