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Convenient synthesis of 7′ and 6′-bromo-D-tryptophan and their derivatives by enzymatic optical resolution using D-aminoacylase

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Abstract—Compounds 7′ and 6′-bromo-D-tryptophan (**1** and **2**) which are important derivatives for the synthesis of the chloropeptin and kistamycin A, respectively, were conveniently synthesized by optical resolution from *N*-acetyl-7′ and 6′-bromo-DL-tryptophan ((*RS*)-**5** and (*RS*)-**14**) using D-aminoacylase. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The enzymatic hydrolysis of *N*-acylamino acids has been known for a century and was first detected in aqueous kidney preparation.[1] Based on the finding that this enzymatic hydrolysis proceeds enantiospecifically,[2] Grennstein and co-workers developed a general and attractive procedure for the resolution of a vast number of racemic *N*-acylated amino acids to the corresponding L-amino acids catalyzed by L-aminoacylase from hog kidney in 1949.[3] As L-aminoacylase has a wide substrate specifity and high enantioselectivity, it has been applied to the optical resolution of many natural[4] as well as unnatural and rarely occurring α-amino acids.[5] But the above-mentioned enzymatic hydrolysis was used mainly to obtain L-amino acids, and D-amino acids were recovered by chemical hydrolysis of *N*-acyl-D-amino acid isolated as non-hydrolyzed isomers. Thus, partial racemization is unavoidable and high optical purity of the D-amino acid cannot been attained.

Against this background, investigations of D-specific aminoacylases have been carried out, and work on the use of D-specific aminoacylases with racemic *N*-benzoyl amino acids to obtain D-amino acids directly without chemical hydrolysis was first carried out by Kameda and co-workers in 1952.[6] However, the D-aminoacylase productivity of the strain was not satisfactory. In 1980, Sugie and co-workers reported the finding of a D-specific aminoacylase suitable for the production of natural D-amino acids together with the application of the D-aminoacylase to optical resolution of several natural DL-amino acids.[7]

Since then, several D-aminoacylases from microorganism were produced and purified, and several of them were applied to produce natural α-D-amino acid from racemic α-amino acids by enzymatic optical resolution. But this practical enzymatic optical resolution method has not yet been applied to obtain unnatural α-D-amino acids although only enzymatic deacetylation of unusual amino acid,[8] β-lactam amino acid, was reported.

Recently, several bioactive natural organic compounds which contain D-amino acids have been reported.[9–11] We are interested in the synthesis of chloropeptin[9] which has an anti-HIV activity, and we are also interested in the structure of kistamycin[10] which is known as an anti-influenza A virus agent. Both of them contain various D-amino acids as components. We have investigated the total synthesis of the chloropeptin and already reported its left-hand segment.[12] We are now progressing the synthesis of the right-hand segment of chloropeptin and also kistamycin which contains a C–C bond between 4-hydroxy-D-phenyl glycine and the D-tryptophan moiety. The 7′ and 6′-halogeno-D-tryptophan are needed to synthesize the right-hand segments of chloropeptin and kistamycin, respectively.

The aim of the present work is to construct conveniently two unusual D-amino acids, 7′-bromo-D-tryptophan (**1**) and 6′-bromo-D-tryptophan (**2**), by enzymatic optical resolution using D-aminoacylase from *Achromobacter xylosoxydans aubap. Xylosoxydans*.

2. Results and discussion

2.1. Synthesis of 7′-bromo-D-tryptophan ((*R*)-1) using L-aminoacylase

At first, we planned to synthesize 7′-bromo-D-tryptophan

Keywords: 7′ and 6′-bromo-D-tryptophan; synthesis; D-aminoacylase; optical resolution.

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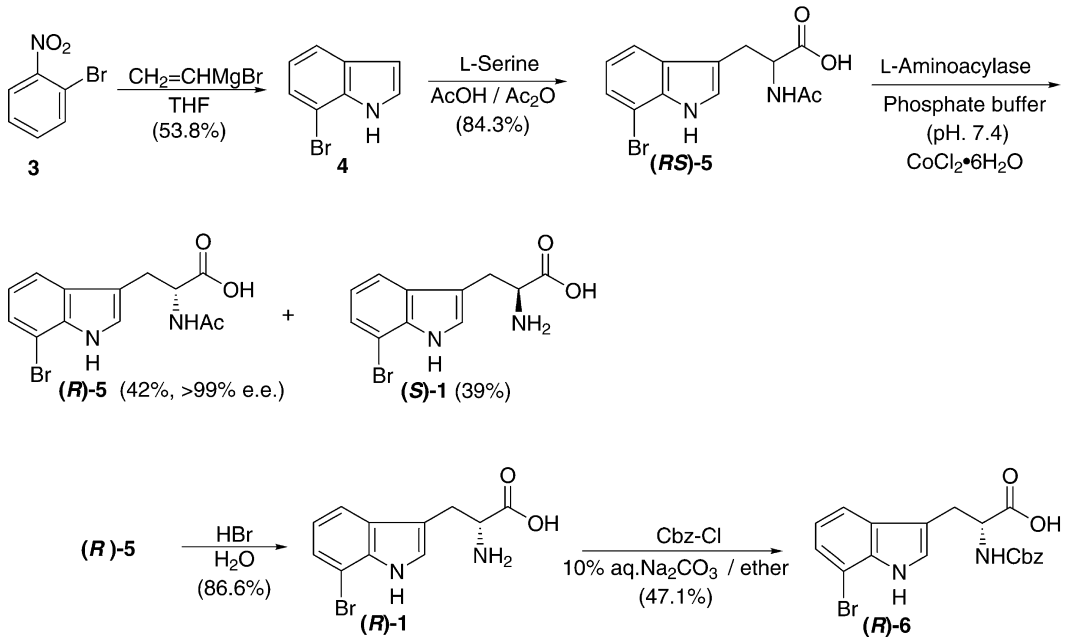
((*R*)-**1**) from racemic *N*-acetyltryptophan ((*RS*)-**5**) by optical resolution using L-aminoacylase, followed by acid hydrolysis of the obtained *N*-acetyl-D-tryptophan ((*R*)-**5**). 7-Bromoindole (**4**) which is the starting material for (*RS*)-**5** was easily obtained from 2-bromonitrobenzene by the literature method.[13] Substitution reaction of **4** with L-serine in $AcOH-Ac_2O$ at 70°C according to the literature procedure[14] gave racemic *N*-acetyltryptophan ((*RS*)-**5**) in 84% yield. Optical resolution was performed by treatment with (*RS*)-**5** and L-aminoacylase in the presence of cobalt dichloride in phosphate buffer (pH 7.4) at 37°C. Extraction with an organic solvent afforded *N*-acetyl-D-tryptophan ((*R*)-**5**) in 42% yield and the water part was chromatographed to afford 7′-bromo-D-tryptophan ((*S*)-**1**) in 39% yield. It was reported that deacetylation of an *N*-acetyltryptophan derivative using aqueous HBr proceeds without racemization.[15] Then, hydrolysis of the acetyl group of (*R*)-**5** with aqueous HBr afforded 7′-bromo-D-tryptophan ((*R*)-**1**) in 87% yield. The formation of the compound (*R*)-**1** has not yet been reported though its L-form was already reported.[16] Optical rotation of (*R*)-**1** showed +11.48° (lit.[16], *S*-form: −7.6°). The protection of the amino group with the carbobenzoxy (Cbz) group was performed by treatment with carbobenzoxy chloride (Cbz-Cl) under alkali conditions. Several attempts to extract 7′-bromo-*N*-Cbz-D-tryptophan ((*R*)-**6**) with an organic solvent after acidification of the reaction mixture failed, which is attributable to lability of the tryptophan moiety. Then, filtration of the precipitate of *N*-Cbz-tryptophan directly which results after acidification afforded (*R*)-**6** in 47.1% yield, successfully (Scheme 1).

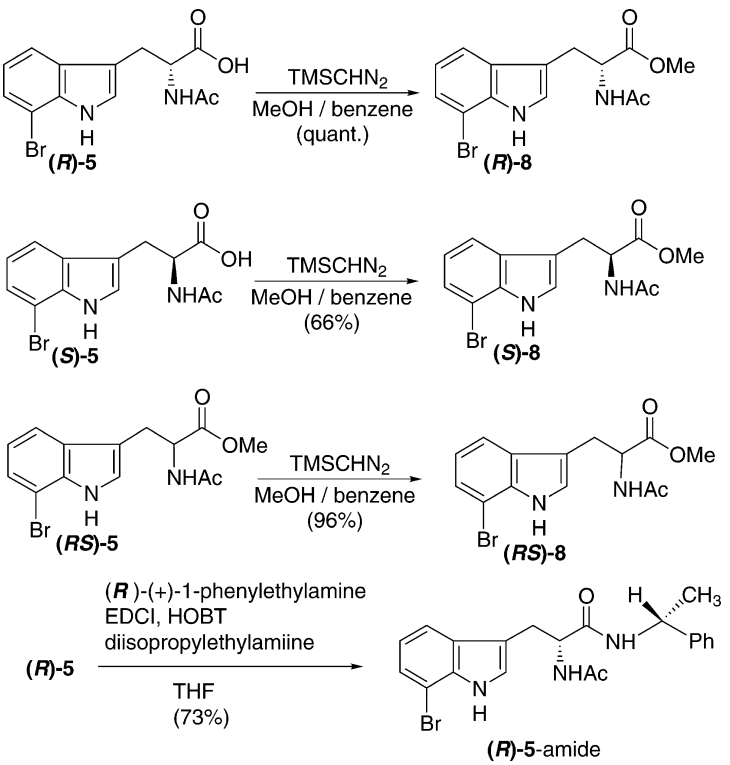
Optical purity was determined by ^1H NMR technique using a chiral shift reagent with methyl esters. Compounds (*R*)-**5**, (*S*)-**5** (which was described in Section 2.2) and (*RS*)-**5** were derivated to methyl ester by treatment with trimethylsilyldiazomethane ($TMSCHN_2$) to afford (*R*)-**8**, (*S*)-**8** and (*RS*)-**8** in 100, 66, 96%, yields, respectively. The ^1H NMR spectrum of (*RS*)-**8** in $CDCl_3$ in the presence of an appropriate amount of the chiral shift reagent showed two peaks (1:1) of methyl signal which resulted in a racemate, whereas the ^1H NMR spectrum of (*R*)-**8** and (*S*)-**8** in the presence of the chiral shift reagent under the same conditions as (*RS*)-**8** showed each one peak of the methyl signal in corresponding position to that of the racemate. Each ^1H NMR spectral data were described in Section 4. Further, (*R*)-**5** was condensed with (*R*)-(+)-phenylethylamine by treatment with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) to afford phenylethylamide (*R*)-**5**-amide in 73% yield, and none of it's diastereomer (*S*)-**5**-amide (which was described in Scheme 4) was obtained These results prove that (*R*)-**5** is optically pure, and our enzymatic optical resolution using L-aminoacylase proceeded stereospecifically (Scheme 2).

2.2. Synthesis of 7′-bromo-D-tryptophan ((*R*)-1) using D-aminoacylase

However, acid hydrolysis of (*R*)-**5** is often accompanied with by-products in addition to the desired compound (*R*)-**1**, which results from lability of *N*-acylated tryptophan, and the yield and reproducitbility were often not satisfactory. So, another route was developed to increase the yield and purity of compound (*R*)-**1**. This route involves direct transformation of (*RS*)-**5** to (*R*)-**1** in one step by using D-aminoacylase supplied from Amano Enzyme Inc. Incubation of (*RS*)-**5** with D-aminoacylase in the presence of cobalt dichloride in phosphate buffer at pH 7.4 for 24 h at 37°C and extraction with an organic solvent afforded *N*-acetyl-7′-bromo-L-tryptophan ((*S*)-**5**) from the organic layer quantitatively, and the water part was chromatogaphed to afford optically pure (*R*)-**1** quantitatively from inorganic salts by using SEPABEADS SP207 resin. Protection of the amino group by treatment with Cbz-Cl in a similar way as mentioned above gave (*R*)-**6** in 99% yield. Finally, the carboxyl group was transformed to *t*-butyl ester. At first, (*R*)-**6** was treated with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of dimethylaminopyridine (DMAP) which is a general



Scheme 1.

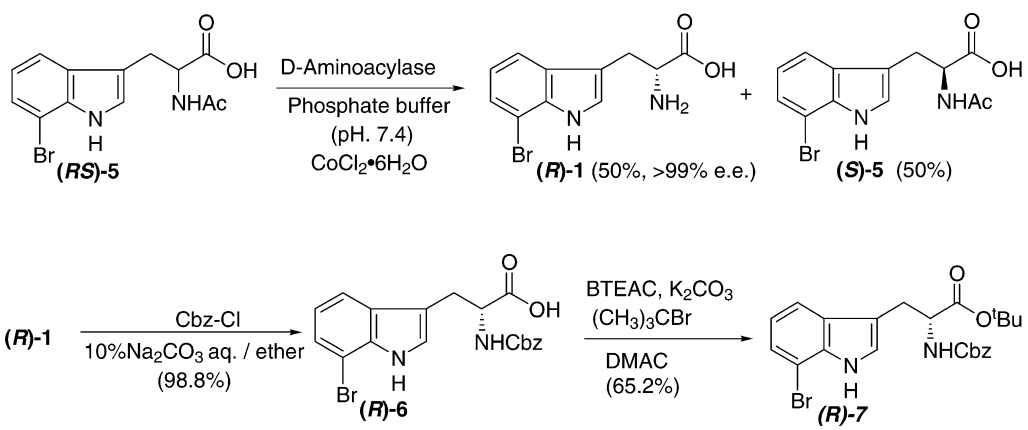


Scheme 2.

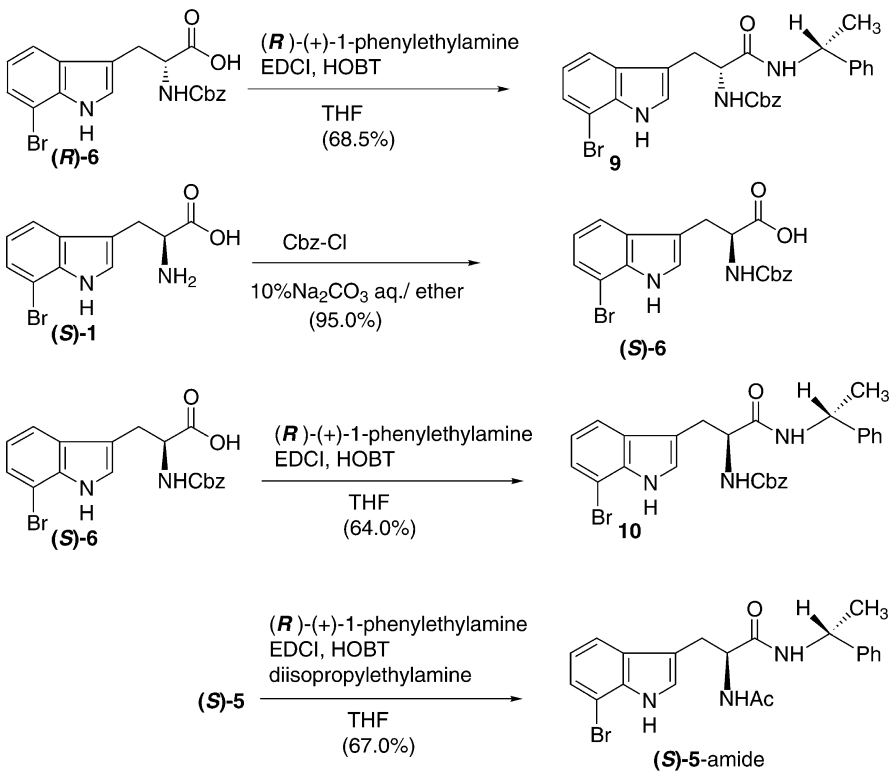
procedure for formation of *t*-butyl ester. However, complicated substances were obtained, which result from the reaction of the NH group on indole and also carbamate with Boc_2O together with esterification of the carboxyl group. So, (*R*)-**6** was treated with *tert*-butyl bromide in the presence of benzyltriethylammonium chloride (BTEAC) as a phase transfer catalyst and K_2CO_3[17] as a base to afford *t*-butyl ester ((*R*)-**7**) in 65%. In this reaction, potassium salt of the carboxylate is formed as an intermediate, then only *t*-butyl esterification occurs, selectively. This esterification method was revealed to be very appropriate for *t*-butyl esterification of reactive and labile *N*-acyltryptophan analogies which are important for peptide synthesis (Scheme 3).

Thus, synthesis of 7′-bromo-*N*-Cbz-D-tryptophan ((*R*)-**6**) and 7′-bromo-*N*-Cbz-D-tryptophan *t*-butyl ester ((*R*)-**7**) which are both useful derivatives for peptide synthesis were achieved conveniently each in two and three steps from 7-bromoindole in 42 and 27% yields, respectively, by optical resolution using a D-aminoacylase. The reaction conditions and isolation procedures are both simple and are suitable for large-scale preparation.

Optical purity was determined, and it was confirmed that this enzymatic optical resolution stereospecifically occurred as described below. Carboxylic acid (*R*)-**6** was condensed with (*R*)-(+)-1-phenylethylamine by treatment with EDCI to afford amide **9** in 69% yield and none of it's diastereomeric amide **10** was obtained. Compound **10** was obtained as follows. Conversion of 7′-bromo-L-tryptophan ((*S*)-**1**), which was obtained by enzymatic resolution using L-aminoacylase, to carbamate (*S*)-**6** by treatment with Cbz-Cl, followed by condensation with (*R*)-(+)-1-phenylethylamine in a similar way to provided diastereomeric



Scheme 3.



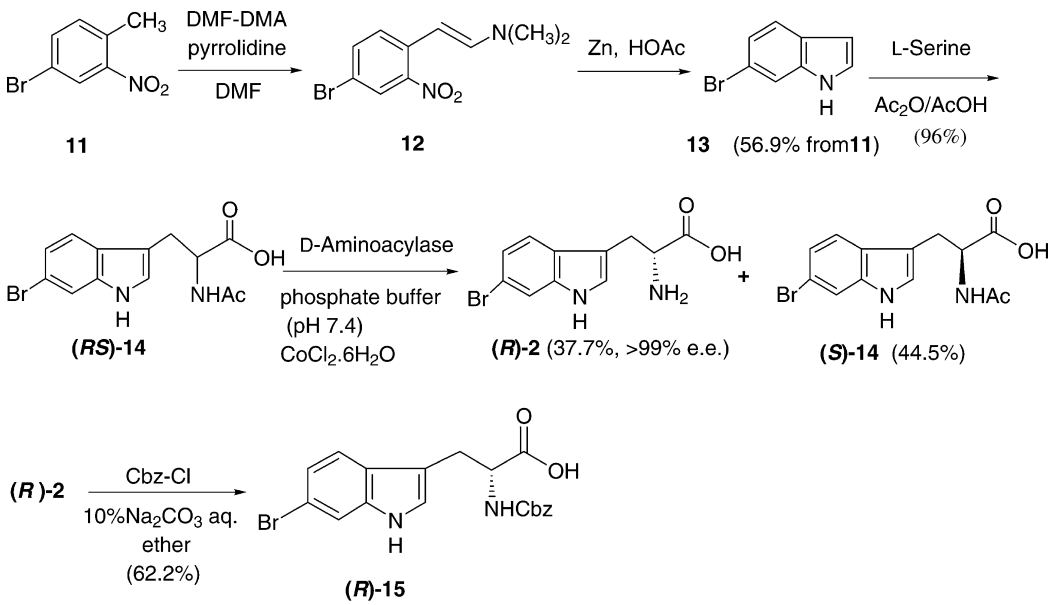
Scheme 4.

amide **10** in 64% yield and none of it's diastereomeric amide **9** was obtained. Furthermore, optically purity of remained *N*-acetyl-7′-bromo-L-tryptophan ((*S*)-**5**) obtained from organic layer by optical enzymatic resolution of (*RS*)-**5** using D-aminoacylase was determined as follows. Compound (*S*)-**5** was similary derivated to it's (*R*)-(+)-phenyl ethylamide to afford (*S*)-**5**-amide in 67% yield and none of its diastereomer ((*R*)-**5**)-amide was obtained in this reaction.

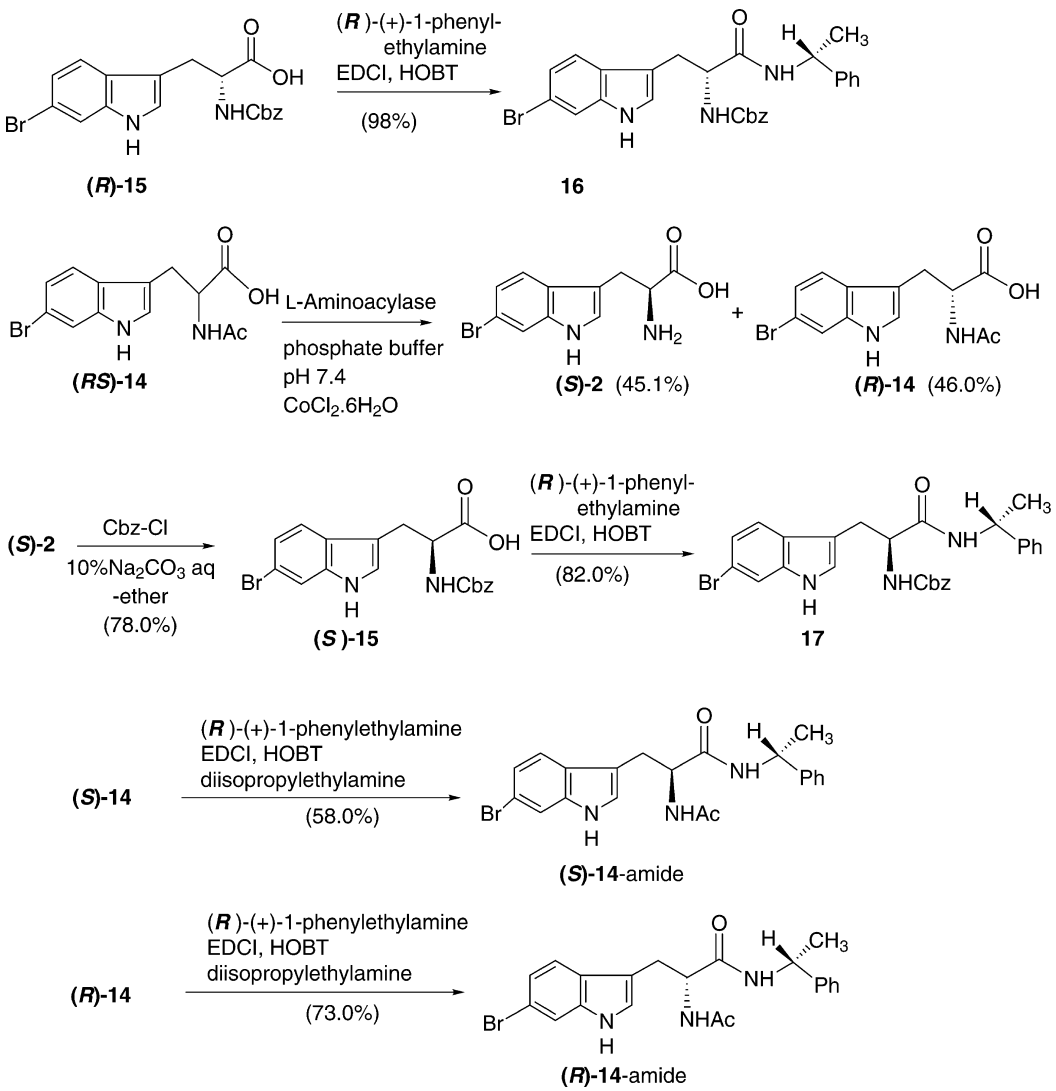
These results prove enzymatic resolution by D-aminoacylase proceed enatiomerically to give optically pure 7′-bromo-D-tryptophan ((*R*)-**1**) and *N*-acetyl-7′-bromo-L-tryptophan ((*S*)-**5**) and enzymatic resolution by L-aminoacylase proceed enatiomerically to give optically pure 7′-bromo-L-tryptophan ((*S*)-**1**) and *N*-acetyl-7′-bromo-D-trtptophan ((*R*-**5**), simultaneously (Scheme 4).

2.3. Synthesis of 6′-bromo-D-tryptophan using D-aminoacylase

Next, 6′-bromo-D-tryptophan ((*R*)-**2**) was similarly synthesized by enzymatic optical resolution using D-aminoacylase



Scheme 5.



Scheme 6.

as a key reaction. 6′-Bromoindole (**13**) was synthesized in two steps according to the literature.[18] 4-Bromo-2-nitrotoluene (**11**) was treated with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) and pyrrolidine at 110°C. The crude enamine **12** was subjected to reductive cyclization with zinc in acetic acid to afford **13** in 57% yield for two steps from **11**. Substitution reaction of **13** with L-serine in a similar way as described above gave racemic *N*-acetyl-6′-bromotryptophan ((*RS*)-**14**) in 96% yield, followed by optical resolution using D-aminoacylase afforded 6′-bromo-D-tryptophan ((*R*)-**2**) in 38% yield and (*S*)-**14** was recovered in 45% yield. Compound (*R*)-**2** was converted to 6′-bromo-*N*-Cbz-D-tryptophan ((*R*)-**15**) in 62% yield by using same condition as described (Scheme 5).

Optical purity of (*R*)-**15** was determined as follows. Optical resolution of (*RS*)-**14** by treatment with L-aminoacylase in a similar manner as described above afforded 6′-bromo-L-tryptophan ((*S*)-**2**) and (*R*)-**14** in 45 and 46% yields, respectively. Conversion of (*S*)-**2** to *N*-Cbz derivative similarly gave (*S*)-**15** in 78% yield. Condensation reaction of each carboxylic acid (*R*)-**15** and (*S*)-**15** with (*R*)-(+)-1-phenylethylamine by treatment with EDCI afforded amide **16** and **17**, respectively, in 98 and 82% yields and none of diasteromeric amide was obtained in each condensation reaction. Optically purity of remained *N*-acetyl-6′-bromo-L-tryptophan ((*S*)-**14**) obtained from organic layer by optical enzymatic resolution of (*RS*)-**14** using D-aminoacylase was determined as follows. Compound (*S*)-**14** was similary derivated to it's (*R*)-(+)-1-phenyl ethylamide to afford (*S*)-**14**-amide in 58% yield and none of its diastereomer (*R*)-**14**-amide was obtained in this reaction. Diasteremer (*R*)-**14**-amide was obtained as follows. Compound (*R*)-**14** obtained by optical enzymatic resolution using L-aminoacylase was similarly derivated to it's (*R*)-(+)-1-phenyl ethylamide (*R*)-**14**-amide in 73% yield.

These results prove enzymatic resolution by D-aminoacylase proceed enatiomerically to give optically pure 6′-bromo-D-tryptophan ((*R*)-**2**) and *N*-acetyl-7′-bromo-L-tryptophan ((*S*)-**14**) (Scheme 6).

3. Conclusion

Compounds 7′ and 6′-bromo-D-tryptophan, their *N*-Cbz

derivatives and *t*-butyl ester were conveniently synthesized enantiospecifically by optical resolution using D-amino-acylase from *N*-acetyl-7′ and 6′-bromo-DL-tryptophan in short steps. Each step proceeds to give high yields which are adequate for large-scale preparation.

4. Experimental

4.1. General

Melting points were taken on a Yanagimoto hot-stage and are uncorrected. ^{1}H and ^{13}C NMR were recorded on Varian VXR-300, XL-400 spectrometers. The signals were assigned by ^{1}H–^{1}H COSY, DEPT, HMQC, HMBC experiments. Mass spectra were obtained on a JEOL-JMX-DX 300 mass spectrometer (low-resolution mass spectrometry) and JEOL-JMS-AX505 HA mass spectrometer (high-resolution mass spectrometry). Routine monitoring of reactions was carried out using Merck 60 GF254 silica gel, glass-supported plates (TLC). Flash column chromatography was performed on silica gel 60 H (Merck). Thin-layer chromatography was done on silica gel 60 PF254 (Merck).

4.1.1. 7-Bromoindole (4). Vinyl magnesium bromide solution in THF (0.95 mol/l, 63.3 ml, 60.0 mmol) was added to a solution of 2-bromonitrobenzene (**3**) (4.04 g, 20.0 mmol) in THF (40 ml) at −40°C under argon and stirred for 20 min. The reaction mixture was poured into saturated ammonium chloride (50 ml) and THF was concentrated in vacuo. The residual aqueous solution was extracted with AcOEt (200 ml×3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give a pale yellow oil (4.52 g) and this was purified by flash column chromatography (hexane) to afford pale yellow plates **4** (2.11 g, 53.8%). R_f: 0.56 (hexane/AcOEt=3:1); mp: 35–36°C ($CHCl_3$); IR (KBr): ν_{max} cm^{-1}: 510, 580 (Ar–Br), 1580, 1620 (arom), 3420 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.66 (1H, dd, *J*=2.0, 3.0 Hz, 3-H), 7.04 (1H, t, *J*=7.5 Hz, 5-H), 7.25 (1H, t, *J*=3.0 Hz, 2-H), 7.39 (1H, d, *J*=7.5 Hz, 4-H), 7.63 (1H, d, *J*=7.5 Hz, 6-H), 8.33 (1H, brs, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 103.79 (d, 2-C), 104.61 (s, 7-C), 119.91 (d, 6-C), 120.95 (d, 5-C), 124.28 (d, 4-C), 124.65 (d, 3-C), 128.96 (s, 3a-C), 134.53 (s, 7a-C); HREI-MS: *m/z*: 194.9680 $[M]^+$, calcd for $C_8H_6NBr^{79}$: 194.9684 [M].

4.1.2. *N*-Acetyl-7′-bromo-DL-tryptophan ((*RS*)-5). L-Serine (1.06 g, 10.3 mmol) was dissolved in a solution of **4** (1.00 g, 5.13 mmol) in AcOH (12.0 ml) and Ac_2O (4.0 ml). After the solution was stirred at 75°C for 2 h under argon, the mixture was diluted with diethyl ether (100 ml) and adjusted to pH 11 with 30% NaOH (40 ml). The water layer was further washed with diethyl ether (150 ml×3), then ice-cooled. The organic layer was further extracted with 1N NaOH (30 ml×2) and a small amount of $Na_2S_2O_4$ was added to the combined alkali solution, which was then neutralized with conc. HCl, concentrated to 1/2 volume in vacuo to give precipitates, then acidified with 5% HCl to adjust to pH 3 using congo red as indicator, stored in refrigerator for 24 h. The resulted precipitates were collected by filtration and dried to give crystals. The filtrate was concentrated to 1/2 volume to give crystals, which were collected by filtration and dried. The crystals were combined to give (*RS*)-**5** as light yellow crystals (1.39 g, 84.3%). The organic layer was dried over Na_2SO_4, concentrated to give the residue (210 mg), which was purified by preparative TLC ($CHCl_3$/-MeOH=10:1) to recovered **4** (151 mg). R_f: 0.71 ($CHCl_3$/-MeOH=10:1); mp: 209–212°C (H_2O); IR (KBr): ν_{max} cm^{-1}: 1630 (NHCO), 1730 (COOH), 3400 (indole-NH); ^{1}H NMR (400 MHz, CD_3COCD_3) δ_H: 1.91 (3H, s, CH_3), 3.21 (1H, ddd, *J*=1.0, 7.5, 15.0 Hz, 3-Ha), 3.34 (1H, ddd, *J*=1.0, 5.5, 15.0 Hz, 3-Hb), 4.81 (1H, dd, *J*=5.5, 8.0, 9.0 Hz, 2-H), 6.99 (1H, t, *J*=8.0 Hz, 5′-H), 7.31 (1H, d, *J*=1.0 Hz, 2′-H), 7.32 (1H, dd, *J*=1.0, 8.0 Hz, 6′-H), 7.35 (brd, *J*=8.0 Hz, NHCO), 7.63 (1H, d, *J*=8.0 Hz, 4′-H), 10.28 (1H, brs, 1′-H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ_C: 22.69 (q, CH_3), 28.22 (t, 3-C), 53.77 (d, 2-C), 105.07 (s, 7′-C), 112.67 (s, 3′-C), 118.91 (d, 4′-C), 120.96 (d, 5′-C), 124.67 (d, 6′-C), 125.49 (d, 2′-C), 130.36 (s, 3′a-C), 135.76 (s, 7′a-C), 170.44 (s, NHCO), 173.33 (s, 1-C); HRFAB-MS *m/z*: 324.0112 $[M]^+$, calcd for $C_{13}H_{13}O_3N_2Br^{79}$: 324.0110 [M].

4.1.3. *N*-Acetyl-7′-bromo-D-tryptophan ((*R*)-5) and 7′-bromo-L-tryptophan ((*S*)-1). L-Aminoacylase (1500 U/g, 80 mg) in phosphate buffer solution (pH 7.41, 4 ml) and $CoCl_2{\cdot}6H_2O$ (0.2 mg) were added to a solution of (*RS*)-**5** (80 mg, 0.247 mmol) in phosphate buffer solution (8 ml). The solution was shaken for 24 h at 37°C. The reaction mixture was adjusted to pH 5 with 10% HCl, filtered through celite pad. The filtrate was washed with AcOEt (30 ml×3). The water layer was purified by column chromatography (Sepabeads SP207, 150 ml of H_2O, followed by 200 ml of MeOH). Concentration of eluate of MeOH afforded (*S*)-**1** (27 mg, 39%) as a white powder. The organic layer was dried over Na_2SO_4, concentrated in vacuo to give (*R*)-**5** (33 mg) in 42% yield as light yellow granules. (*S*)-**1**: mp: 220–222°C $[\alpha]_D^{25}=-23.99°$ (*c*=0.15, MeOH); R_f: 0.47 (1-BuOH/AcOH/H_2O=4:1:5); ^{1}H NMR (400 MHz, CD_3OD) δ_H: 3.17 (1H, dd, *J*=9.0, 15.0 Hz, 3-Ha), 3.49 (1H, dd, *J*=4.0, 15.0 Hz, 3-Hb), 3.85 (1H, dd, *J*=4.0, 9.0 Hz, 2-H), 6.98 (1H, t, *J*=8.0 Hz, 5′-H), 7.29 (1H, s, 2′-H), 7.30 (1H, d, *J*=8 Hz, 6′-H), 7.70 (1H, dd, *J*=1.0, 8.0 Hz, 4′-H); HRFAB-MS *m/z*: 283.0072 $[M]^+$, calcd for $C_{11}H_{12}O_2N_2Br^{79}$: 283.0082 [M]. (*R*)-**5**: mp 128–130°C; $[\alpha]_D^{25}=-21.98°$ (*c*=1.01, acetone); HRFAB-MS *m/z*: 325.0156 $[M+H]^+$, calcd for $C_{13}H_{14}O_3N_2Br^{79}$: 325.0159 [M+H]. The data of R_f, ^{1}H NMR were consistent with those of (*RS*)-**5**.

4.1.4. 7′-Bromo-D-tryptophan ((*R*)-1) from L-aminoacyl-ase route. 48% Aqueous hydrogen bromide (0.17 ml, 1.42 mmol) was added to a solution of (*R*)-**5** (96.0 mg, 0.296 mmol) in H_2O (0.7 ml), and stirred for 3 h at 100°C. The reaction mixture was adjusted to pH 5 with 20% aqueous NaOH, ice-cooled to give precipitates, then the precipitates were filtered. The filtrate was concentrated to 1/2 volume, ice-cooled to give precipitates which were filtered. Combined light yellow powders give (*R*)-**1** (72.4 mg, 86.6%). $[\alpha]_D^{26}=+11.48°$ (*c*=1.01, MeOH); the data of R_f and ^{1}H NMR were consistent with those of (*S*)-**1**. ^{13}C NMR (100 MHz, CD_3OD) δ_C: 28.44 (t, 3-C), 56.61 (d, 2-C), 105.68 (s, 7′-C), 111.03 (s, 3′-C), 118.91 (d, 4′-C), 121.35 (d, 5′-C), 125.30 (d, 6′-C), 126.31 (d, 2′-C), 130.13 (s, 3′a-C), 136.76 (s, 7a′-C), 174.15 (s, 1-C); HRFAB-MS

m/z: 282.0092 $[M]^+$, calcd for $C_{11}H_{11}O_2N_2Br^{79}$: 282.0004 [M].

4.1.5. 7′-Bromo-*N*-carbobenzyloxy-D-tryptophan ((*R*)-6). Cbz-Cl (18.5 μl, 0.155 mmol) in diethyl ether (0.2 ml) was dropped to a solution of (*R*)-**1** (36.4 mg, 0.129 mmol) in 10% aqueous Na_2CO_3 (1.8 ml) at 0°C, and stirred for 5 h. The reaction mixture was acidified with 10% citric acid, extracted with $CHCl_3$ (10 ml×3). The organic layer was washed with water, dried over Na_2SO_4, evaporated to give light yellow gels, which were purified by preparative TLC ($CHCl_3$/MeOH=5:1) to afford (*R*)-**6** (25.7 mg, 47.1%) as yellow amorphous solid. R_f: 0.87 (1-BuOH/AcOH/H_2-O=4:1:5); $[\alpha]_D^{23}=-27.27°$ (*c*=0.99, $CHCl_3$); ^1H NMR (400 MHz, CD_3COCD_3) δ_H: 3.23 (1H, dd, *J*=8.0, 15.0 Hz, 3-Ha), 3.38 (1H, dd, *J*=5.0, 15.0 Hz, 3-Hb), 4.58 (1H, dd, *J*=5.0, 8.0 Hz, 2-H), 5.01, 5.06 (each 1H, d, *J*=13.0 Hz, *CH*$_2$-Ph), 6.48 (1H, d, *J*=8.0 Hz, NHCO), 6.97 (1H, t, *J*=8.0 Hz, 5′-H), 7.31 (5H, m, Ph), 7.31 (1H, d, *J*=8.0 Hz, 6′-H), 7.35 (1H, d, *J*=2.5 Hz, 2′-H), 7.65 (1H, d, *J*=8.0 Hz, 4′-H), 10.25 (1H, s, 1′-H); HRFAB-MS *m/z*: 416.0358 $[M]^+$, calcd for $C_{19}H_{17}O_4N_2Br^{79}$: 416.0372 [M].

4.1.6. *N*-Acetyl-7′-bromo-D-tryptophan methyl ester ((*R*)-8). A solution of $TMSCHN_2$ (40 μl, 80.5 μmol) in benzene (0.16 ml) was dropped to a solution of (*R*)-**5** (20.1 mg, 62.0 mmol) in MeOH (0.12 ml) and benzene (0.43 ml) and stirred for 30 min at room temperature under argon. The solution was evaporated in vacuo to give a yellow solid (24.4 mg). This was purified by preparative TLC ($CHCl_3$/MeOH=7:1) to afford (*R*)-**8** (22.1 mg) quantitatively as a white powder. R_f: 0.65 ($CHCl_3$/MeOH=5:1); mp: 150–154°C; $[\alpha]_D^{26}=+62.00°$ (*c*=0.14, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 1.97 (3H, s, $COCH_3$), 3.70 (3H, s, CH_3), 3.27, 3.34 (each 1H, dd, *J*=5.5, 14.5 Hz, 3-H_2), 4.95 (1H, dd, *J*=5.5, 7.5 Hz, 2-H), 6.00 (1H, brd, *J*=7.5 Hz, NHCO), 7.00 (1H, t, *J*=7.5 Hz, 5′-H), 7.04 (1H, d, *J*=2.5 Hz, 2′-H), 7.35 (1H, d, *J*=7.5 Hz, 6′-H), 7.47 (1H, d, *J*=7.5 Hz, 4′-H), 8.33 (1H, brs, 1′-H); ^{13}C NMR (100 MHz, CD_3OD) δ_C: 23.25 (q, $COCH_3$), 27.79 (t, 3-C), 52.42 (q, OMe), 52.96 (d, 2-C), 104.90 (s, 7′-C), 111.59 (s, 3′-C), 117.85 (d, 4′-C), 120.91 (d, 5′-C), 123.20 (d, 2′-C), 124.64 (d, 6′-C), 128.92 (s, 3′a-C), 169.61 (s, NHCO), 172.24 (s, 1-C); HRFAB-MS *m/z*: 338.0273 $[M]^+$, calcd for $C_{14}H_{15}O_3N_2Br^{79}$: 338.0266 [M].

4.1.7. *N*-Acetyl-7′-bromo-L-tryptophan methyl ester ((*S*)-8). A solution of $TMSCHN_2$ (40 μl, 80.5 μmol) in benzene (0.16 ml) was dropped to a solution of (*S*)-**5** (20.3 mg, 62.7 μmol) in MeOH (0.12 ml) and benzene (0.43 ml) and stirred for 30 min at room temperature under argon. The solution was evaporated in vacuo to give a yellow solid (23.2 mg). This was purified by preparative TLC ($CHCl_3$/MeOH=7:1) to afford (*S*)-**8** (14.0 mg, 66.1%) as a white granules. Mp: 155–156°C; $[\alpha]_D^{26}=-54.00°$ (*c*=0.19, $CHCl_3$). The data of R_f, ^1H NMR were consistent with those data of (*R*)-**8**. HRFAB-MS *m/z*: 338.0273 $[M]^+$, calcd for $C_{14}H_{15}O_3N_2Br^{79}$: 338.0266 [M].

4.1.8. *N*-Acetyl-7′-bromo-D, L-tryptophan methyl ester ((*RS*)-8). A solution of $TMSCHN_2$ (40 μl, 80.5 μmol) in benzene (0.16 ml) was dropped to a solution of (*RS*)-**5** (20.0 mg, 61.7 μmol) in MeOH (0.12 ml) and benzene (0.43 ml) and stirred for 30 min at room temperature under argon. The solution was evaporated in vacuo to give a yellow solid (24.7 mg). This was purified by preparative TLC ($CHCl_3$/MeOH=7:1) to afford (*RS*)-**8** (18.7 mg, 96.4%) as white crystals. The data of R_f and ^1H NMR were consistent with those of (*R*)-**8**. HRFAB-MS *m/z*: 339.0334 $[M+H]^+$, calcd for $C_{14}H_{16}O_3N_2Br^{79}$: 339.0344 [M+H].

4.1.9. ^1H NMR spectral data for (*R*)-8, (*S*)-8 in the presence of the chiral shift reagent. Ttris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato], europium(III) derivative made in Aldrich Chemical Company, Inc. was used as a chiral shift reagent and the shift reagent (6 mg) was added in each 0.022 M solution of (*R*)-**8** and (*S*)-**8** in $CDCl_3$. ^1H NMR (400 MHz, $CDCl_3$) (*R*)-**8**: δ_H 3.63 (1H, brd, *J*=15.0 Hz, 3-Ha), 3.80 (3H, s, CH_3), 4.12 (1H, br, 3-Hb), 6.23 (1H, br, 2-H), 6.91 (1H, m, NHCO), 7.14 (1H, t, *J*=8.0 Hz, 5′-H), 7.38 (1H, brs, 2′-H), 7.44 (1H, d, *J*=8.0 Hz, 4′-H), 7.98 (1H, brd, *J*=8.0 Hz, 6′-H), 8.47 (1H, brs, 1′-H). (*S*)-**8**: ^1H NMR (400 MHz, $CDCl_3$) δ_H: 3.57 (1H, dd, *J*=3.5, 14.0 Hz, 3-Ha), 3.79 (3H, s, CH_3), 4.55 (1H, br, 3-Hb), 6.01 (1H, br, 2-H), 6.71 (1H, br, NHCO), 7.09 (1H, t, *J*=7.5 Hz, 5′-H), 7.29 (1H, brs, 2′-H), 7.41 (1H, d, *J*=7.5 Hz, 4′-H), 7.84 (1H, brd, *J*=7.5 Hz, 6′-H), 8.45 (1H, brs, 1′-H). HRFAB-MS *m/z*: 428.090 $[M+H]^+$, calcd for $C_{21}H_{23}O_2N_3Br^{79}$: 428.0974 [M+H].

4.1.10. *N*-Acetyl-7′-bromo-D-tryptophan (*R*)-(+)-1-phenylethylamide ((*R*)-5-amide). (*R*)-(+)-1-Phenylethylamine (8.8 mg, 0.074 mmol), EDCI (28.2 mg, 0.148 mmol), diisopropylethyllamine (19 μl, 0.148 mmol), hydroxybenzotriazole (9.9 mg, 0.074 mmol) were added to a solution of (*R*)-**5** (24 mg, 0.074 mmol) in THF (2 ml) and stirred for 24 h at room temperature under argon. The reaction mixture was concentrated in vacuo, purified by preparative TLC (hexane/AcOEt=5:1) to give (*R*)-**5**-amide (23 mg, 73%) as white crystals. R_f: 0.25 (hexane/AcOEt=1:5); mp: 230–232°C. $[\alpha]_D^{25}=+5.60°$ (*c*=0.25, MeOH); ^1H NMR (300 MHz, CD_3COCD_3) δ_H: 1.35 (3H, d, *J*=7.0 Hz, CHC*H*$_3$), 1.90 (3H, s, Ac), 3.08, 3.18 (2H, dd, *J*=6.5, 14.5 Hz, 3-H_2), 4.73 (1H, dt, *J*=7.0, 6.5 Hz, 2-H), 5.02 (1H, quintet, *J*=7.0 Hz, C*H*Me), 6.95 (1H, t, *J*=7.5 Hz, 5-H′), 7.12 (1H, d, *J*=2.5 Hz, 2′-H), 7.12–7.30 (5H, m, phenyl), 7.25 (1H, d, *J*=7.0 Hz, 2-NHCO), 7.30 (1H, d, *J*=7.5 Hz, 4′-H), 7.58 (1H, brd, *J*=8.3 Hz, 1-CONH), 7.64 (1H, d, *J*=7.5 Hz, 6′-H), 10.09 (1H, brs, 1′-H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ_C: 22.41 (q, CH*C*H$_3$), 22.92 (q, $COCH_3$), 29.03 (t, 3-C), 49.15 (d, *C*HCH$_3$), 54.66 (d, 2-C), 104.99 (s, 7′-C), 112.95 (s, 3′-C), 119.18 (d, 6′-C), 120.85 (d, 5′-C), 124.59 (d, 4′-C), 125.57 (d, 2′-C), 126.80, 127.45, 129.03 (each d, phenyl), 129.10 (s, 3′a-C), 130.40 (s, 7a′-C), 145.00, (s, phenyl), 169.93, 171.16 (each s, NHCO×2). HRFAB-MS *m/z*: 428.090 $[M+H]^+$, calcd for $C_{21}H_{23}O_2N_3Br^{79}$: 428.0974 [M+H].

4.1.11. 7′-Bromo-D-tryptophan ((*R*)-1) from D-amino-acylase route. D-Aminoacylase (7.2×10^3 U/g, 257 mg) in phosphate buffer solution (pH 7.41, 10 ml) and $CoCl_2\cdot6H_2O$ (0.2 mg) were added to a solution of (*RS*)-**5** (1.0 g, 3.09 mmol) in phosphate buffer solution (115 ml). The solution was shaken for 24 h at 37°C. The reaction mixture was adjusted to pH 5 with 10% HCl, filtered through celite

pad. The filtrate was washed with AcOEt (115 ml×3). The water layer was purified by column chromatography (SEPABEADS SP207, 200 ml of H_2O, followed by 200 ml of MeOH). Concentration of eluate of MeOH afforded (*R*)-**1** (435.4 mg), quantitatively. The organic layer was dried over Na_2SO_4, concentrated in vacuo to give (*S*)-**5** (497.1 mg) quantitatively as light yellow amorphous crystals. (*R*)-**1**: mp: 244–248°C (MeOH); $[\alpha]_D^{25}=+11.42°$ (c=0.98, MeOH). HRFAB-MS *m/z*: 283.0079 $[M+H]^+$, calcd for $C_{11}H_{12}O_2N_2^{79}Br$: 283.0082 [M+H]. The data of R_f and ^1H NMR were consistent with those data of (*R*)-**1**. (*S*)-**5**: HRFAB-MS *m/z*: 325.0179 $[M+H]^+$, calcd for $C_{13}H_{14}O_3N_2Br^{79}$: 325.0188 [M+H]. The data of R_f and ^1H NMR were consistent with those of (*RS*)-**5**.

4.1.12. 7′-Bromo-*N*-carbobenzyloxy-D-tryptophan ((*R*)-6) from D-aminoacylase route. Cbz-Cl (101.6 μl, 0.852 mmol) in diethyl ether (0.3 ml) was dropped to a solution of (*R*)-**1** (200.0 mg, 0.709 mmol) in 10% aqueous Na_2CO_3 (4 ml) at 0°C, and stirred for 5 h. The reaction mixture was acidified with 10% HCl at 0°C to give precipitates which were filtered, washed with H_2O (1 ml) to afford (*R*)-**6** (231.9 mg, 98.8%) as a light yellow powder. Mp: 96–99°C (H_2O); $[\alpha]_D^{24}=-23.19°$ (c=1.00, $CHCl_3$); ^{13}C NMR (100 MHz, CD_3COCD_3) δ_C: 28.33 (t, 3-C), 55.84 (d, 2-C), 66.56 (t, *CH*$_2$-Ph), 104.99 (s, 7′-C), 112.85 (s, 3′-C), 118.95 (d, 4′-C), 120.93 (d, 5′-C), 124.58 (d, 6′-C), 125.52 (d, 2′-C), 128.51 (d, CH_2-*Ph* arom C-2, 6), 129.11 (d, CH_2-*Ph* arom C-3, 5), 130.37 (s, 3′a-C), 135.60 (s, 7′a-C), 138.11 (d, CH_2-*Ph* arom C-4), 156.78 (s, NHCO), 174.58 (s, 1-C); HRFAB-MS *m/z*: 416.0358 $[M]^+$, calcd for $C_{19}H_{17}O_4N_2Br^{79}$: 416.0372 [M]; the data of R_f and ^1H NMR were consistent with those of (*R*)-**6** obtained by using L-aminoacylase.

4.1.13. 7′-Bromo-*N*-carbobenzyloxy-D-tryptophan *tert*-butyl ester ((*R*)-7). K_2CO_3 (172.8 mg, 1.25 mmol) and *tert*-butyl chloride (257.7 μl, 2.31 mmol) were added to a solution of (*R*)-**6** (20.0 mg, 48.1 μmol), benzyltriethylammonium chloride (11.0 mg, 48.1 μmol) in dimethylacetamide (0.360 ml) and stirred for 20 h at 55°C. Ice water (30 ml) was added to the reaction mixture, extracted with AcOEt (7.5 ml×2). The organic layer was washed with H_2O (3 ml×2), dried over Na_2SO_4 to provide light yellow gels, which were purified by preparative TLC (hexane/AcOEt=5:1×2) to give (*R*)-**7** (14.8 mg, 65.2%) as white gels. R_f: 0.24 (1-BuOH/AcOH/H_2O=4:1:5); $[\alpha]_D^{25}=-22.35°$ (c=0.34, $CHCl_3$); IR ($CHCl_3$) ν_{max} cm^{-1}: 1730 (NHCOO); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 1.37 (9H, s, ^{t}Bu), 3.22, 3.29 (each 1H, dd, J=6.0, 14.0 Hz, 3-H_2), 4.62 (1H, dd, J=6.0, 8.0 Hz, 2-H), 5.07, 5.13 (each 1H, d, J=12.0 Hz, *CH*$_2$-Ph), 5.33 (1H, d, J=8.0 Hz, NHCO), 6.96 (1H, t, J=8.0 Hz, 5′-H), 7.05 (1H, d, J=3.0 Hz, 2′-H), 7.33 (5H, m, Ph), 7.34 (1H, d, J=8.0 Hz, 6′-H), 7.34 (1H, s, 2′-H), 7.53 (1H, d, J=8.0 Hz, 4′-H), 8.25 (1H, s, 1′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 27.92 (q, C(*CH*$_3$)$_3$), 28.21 (t, 3-C), 54.92 (d, 2-C), 66.80 (t, *CH*$_2$-Ph), 82.23 (s, *C*(CH$_3$)$_3$), 104.68 (s, 7′-C), 111.81 (s, 3′-C), 118.27 (d, 4′-C), 120.72 (d, 5′-C), 123.19 (d, 2′-C), 124.49 (d, 6′-C), 128.10 (d, CH_2-*Ph* arom C-2, 6), 128.48 (d, CH_2-*Ph* arom C-3, 5), 129.00 (s, 3′a-C), 134.71 (s, 7a′-C), 136.38 (d, CH_2-*Ph* arom C-4), 155.69 (s, NHCO), 170.80 (s, 1-C); HRFAB-MS *m/z*: 472.0996 $[M]^+$, calcd for $C_{23}H_{25}O_4N_2Br^{79}$: 472.0998 [M].

4.1.14. 7′-Bromo-*N*-carbobenzyloxy-D-tryptophan (*R*)-(+)-1-phenylethylamide (9). (*R*)-(+)-1-Phenylethylamine (3.64 mg, 0.03 mmol), EDCI (5.8 mg, 0.03 mmol), hydroxybenzotriazole (HOBT) (4.0 mg, 0.03 mmol) were added to a solution of (*R*)-**6** (3.64 mg, 0.03 mmol) in THF (0.8 ml) and stirred for 1.5 h at room temperature under argon. The reaction mixture was concentrated in vacuo, purified by preparative TLC (hexane/AcOEt=1:2) to **9** (9 mg, 68.5%) as a white powder. R_f: 0.71 ($CHCl_3$/MeOH=5:1); mp: 198–200°C. $[\alpha]_D^{25}=+24.00°$ (c=0.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 1.32 (3H, d, J=7.5 Hz, CH*CH*$_3$), 3.06 (1H, dd, J=8.5, 14.3 Hz, 3-Ha), 3.27 (1H, dd, J=4.0, 14.3 Hz, 3-Hb), 4.44 (1H, br, 2-H), 4.97 (1H, quintet, J=7.5 Hz, C*H*Me), 5.10, 5.12 (each 1H, d, J=13.0 Hz, *CH*$_2$-Ph), 5.54 (1H, brd, J=8.5 Hz, 2-NHCO), 5.69 (1H, brd, J=6.5 Hz, 1-NH), 6.78 (1H, d, J=2.5 Hz, 2′-H), 6.93 (1H, d, J=6.5 Hz, 4′-H), 6.94 (2H, d, J=6.5 Hz, phenethylamine arom-H), 6.99 (1H, t, J=6.5 Hz, 5′-H), 7.25 (3H, m, phenethylamine arom-H), 7.34 (5H, m, benzyl-arom-H), 7.34 (1H, hidden, 6′-H), 7.63 (1H, brd, J=7.0 Hz, 4′-H), 8.21 (1H, br, 1′-H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ_C: 21.51 (q, CH*CH*$_3$), 29.06 (t, 3-C), 48.80 (d, *C*HCH$_3$), 55.47 (d, 2-C), 67.03 (t, benzyl-CH$_2$), 104.80 (s, 7′-C), 111.70 (s, 3′-C), 118.17 (d, 4′-C), 121.05 (d, 5′-C), 123.89 (d, 2′-C), 124.69, 128.57, 128.60 (each d, phenyl), 125.94 (d, 6′-C), 125.94 (d, phenyl), 127.37, 128.08, 128.04 (each d, phenyl), 134.79 (s, 3a′-C), 136.18 (s, 7a′-C), 142.52 (s, phenyl), 155.89 (s, NHCOO), 169.86 (s, CONH); HRFAB-MS *m/z*: 542.1099 $[M+Na]^+$, calcd for $C_{27}H_{26}O_3N_3Br^{79}Na$: 542.1055 [M+Na].

4.1.15. 7′-Bromo-*N*-carbobenzyloxy-L-tryptophan ((*S*)-6). Cbz-Cl (12 mg, 0.071 mmol) in diethyl ether (0.2 ml) was dropped to a solution of (*S*)-**1** (18 mg, 0.071 mmol) in 10% aqueous Na_2CO_3 (0.6 ml) at 0°C, and stirred for 30 min. The reaction mixture was acidified with 10% HCl at 0°C to give precipitates which were filtered, washed with H_2O (1 ml) to afford (*S*)-**6** (20 mg, 95%) as a light yellow powder. $[\alpha]_D^{25}=+24.00°$ (c=0.20, $CHCl_3$); HRFAB-MS *m/z*: 415.0321 $[M-H]^-$, calcd for $C_{19}H_{16}O_4N_2Br^{79}$: 415.0293 [M−H]. The data of R_f and ^1H NMR were consistent with those of (*R*)-**6**.

4.1.16. 7′-Bromo-*N*-carbobenzyloxy-L-tryptophan (*R*)-(+)-1-phenylethylamide (10). (*R*)-(+)-1-Phenylethylamine (3.64 mg, 0.03 mmol), EDCI (5.8 mg, 0.03 mmol), hydroxybenzotriazole (4.0 mg, 0.03 mmol) were added to a solution of (*S*)-**6** (10 mg, 0.03 mmol) in THF (0.8 ml) and stirred for 30 min at room temperature under argon. The reaction mixture was concentrated in vacuo, purified by preparative TLC (hexane/AcOEt=1:2) to give**10** (8.4 mg, 64.0%) as a white powder. R_f: 0.83 ($CHCl_3$/MeOH=5:1); mp: 198–200°C. $[\alpha]_D^{25}=-3.52°$ (c=0.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 1.18 (3H, d, J=6.5 Hz, CH*CH*$_3$), 3.12 (1H, dd, J=8.0, 14.3 Hz, 3-Ha), 3.35 (1H, dd, J=4.5, 14.3 Hz, 3-Hb), 4.47 (1H, br, 2-H), 4.93 (1H, quintet, J=6.5 Hz, C*H*Me), 5.10 (2H, s, *CH*$_2$-Ph), 5.42 (1H, brd, J=6.0 Hz, 2-NHCO), 5.76 (1H, d, J=7.5 Hz, 1-NH), 7.00 (1H, hidden, 5′-H), 7.02 (2H, m, phenethylamine arom-H), 7.03 (1H, brs, 2′-H), 7.24 (3H, m, phenethylamine arom-H), 7.33 (5H, m, benzyl arom-H), 7.36 (1H, d, J=6.0 Hz, 6′-H), 7.34 (5H, m, benzyl-arom-H), 7.34 (1H, hidden, 6′-H), 7.62 (1H, brd, J=7.0 Hz, 4′-H), 8.20 (1H, br, 1′-H); δ_C: 21.36 (q,

CHCH_3), 28.75 (t, 3-CH_2), 48.95 (d, CHCH$_3$), 55.60 (d, 2-C), 67.09 (t, benzyl-CH_2), 104.84 (s, 7′-C), 112.043 (s, 3′-C), 118.16 (d, 4′-C), 121.19 (d, 5′-C), 123.80 (d, 2′-C), 124.77, 128.11, 128.26, 128.59, 128.60 (each d, phenyl), 125.97 (d, 6′-C), 134.86 (s, 3a′-C), 136.10 (s, 7a′-C), 142.60 (s, phenyl), 155.89 (s, NHCOO), 169.86 (s, CONH); HRFAB-MS *m/z*: 542.1093 $[M+Na]^+$, calcd for $C_{27}H_{26}O_3N_3Br^{79}Na$: 542.1055 [M+Na].

4.1.17. *N*-Acetyl-7′-bromo-L-tryptophan (*R*)-(+)-1-phenylethylamide ((*S*)-5-amide). (*R*)-(+)-1-Phenylethylamine (8.8 mg, 0.074 mmol), EDCI (28.2 mg, 0.148 mmol), diisopropylethylamine (19 μl, 0.148 mmol), hydroxybenzotriazole (9.9 mg, 0.074 mmol) were added to a solution of (*S*)-**5** (24 mg, 0.074 mmol) in THF (2 ml) and stirred for 24 h at room temperature under argon. The reaction mixture was concentrated in vacuo, purified by preparative TLC (hexane/AcOEt=5:1) to give (*S*)-**5**-amide (21 mg, 67.0%) as white crystals. R_f: 0.38 (hexane/AcOEt=1:5); mp: 240–242°C. $[\alpha]_D^{25}$=+37.71° (*c*=0.35, MeOH); ^{1}H NMR (300 MHz, CD_3COCD_3) δ_H: 1.25 (3H, d, *J*=7.0 Hz, CHCH_3), 3.12, 3.21 (each 1H, dd, *J*=7.0, 14.5 Hz), 4.70 (1H, m, 2-H), 4.97 (1H, quintet, *J*=7.0 Hz, CHCH$_3$), 6.90 (1H, t, *J*=7.5 Hz, 5′-H), 7.15–7.30 (5H, phenyl), 7.26 (1H, brs, 2′-H), 7.33 (1H, dd, *J*=0.7, 7.5 Hz, 4′-H), 7.49 (1H, brd, *J*=8.0 Hz, 2-NHCO), 7.68 (1H, d, *J*=7.8 Hz, 6′-H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ_C: 22.43 (q, CHCH_3), 22.86 (q, Ac), 29.00 (t, 3-C), 49.31 (d, CHCH$_3$), 54.78 (d, 2-C), 105.01 (s, 7′-C), 113.19 (s, 3′-C), 119.16 (d, 6′-C), 120.87 (d, 5′-C), 124.61 (d, 4′-C), 125.55 (d, 2′-C), 126.88, 127.47, 129.04 (each d, phenyl), 126.79 (s, 3a′-C), 130.47 (s, 7a′-C), 145.22 (s, phenyl), 169.93, 171.09 (each s, NHCO×2); HRFAB-MS *m/z*: 428.0951 $[M+H]^+$, calcd for $C_{21}H_{23}O_2N_3Br^{79}$: 428.0974 [M+H].

4.1.18. 6-Bromoindole (13). Dimethylformamidedimethylacetal (8.580 g, 72 mmol) and pyrrolidine (3.0 ml) were added to a solution of 4-bromo-2-nitrotoluene (**11**) (5.185 g, 24 mmol) in DMF (48 ml) and the mixture was stirred for 1 h at 110°C, under argon. The reaction mixture was diluted with ether (300 ml), washed with H_2O (50 ml×2). The water layer was extracted with ether (120 ml) and the combined organic layer was dried over Na_2SO_4, concentrated in vacuo to give 2′-nitro-4′-bromostyryldimethylamine (**12**) as a dark violet crude substance which was used for the next reaction without purification. Zinc powder (13.6 g) was added in portions to a solution of **12** obtained above in 80% AcOH (160 ml) over 1 h at 75°C, then the reaction mixture was further stirred for 2.5 h at 85°C. After the mixture was ice-cooled and filtered, the filtrate was dissolved in AcOEt (600 ml), washed with H_2O (70 ml), saturated aqueous NaCl (70 ml), dried over Na_2SO_4, evaporated in vacuo to afford a crude substance (5.512 g), which was purified by flash column chromatography (silica gel 450 g, hexane/AcOEt=30:1–15:1) to provide white blue crystals **13** (2.675 g, 56.9% from **11**). **12**: R_f=0.40 (hexane/AcOEt=5:1); **13**: R_f=0.58 (hexane/AcOEt=5:1); mp: 95–97°C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.54 (1H, m, 3-H), 7.18 (1H, t, *J*=2.5 Hz, 2-H), 7.23 (1H, dd, *J*=2.0, 9.1 Hz, 5-H), 7.51 (1H, d, *J*=9.1 Hz, 4-H), 7.55 (1H, d, *J*=2.0 Hz, 7-H), 8.14 (1H, br, 1′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 102.74 (d, 3-C), 113.91 (d, 7-C), 121.88 (d, 4-C), 123.07 (d, 5-C), 124.79 (d, 2-C), 126.66 (s, 3a-C), 136.49 (7a-C); HREI-MS: *m/z*: 194.9697 $[M]^+$, calcd for $C_8H_6NBr^{79}$: 194.9684 [M].

4.1.19. *N*-Acetyl-6′-bromo-DL-tryptophan ((*RS*)-14). L-Serine (316.8 mg, 3.078 mmol) was dissolved in a solution of **13** (300 mg, 1.539 mmol) in AcOH (3.6 ml) and Ac_2O (1.2 ml) and the mixture was stirred for 2 h at 73°C under argon. After cooled, the reaction mixture was diluted with diethyl ether (30 ml) and adjusted to pH 11 with 30% NaOH and further ether (45 ml) was added and partitioned. The ether layer was further extracted with 1N NaOH (30 ml×2) and a small amount of $Na_2S_2O_4$ was added to the combined alkali solution, which was then neutralized with conc. HCl, concentrated to 1/2 volume, acidified with 5% HCl to adjust to pH 3 using congo red as a indicator, extracted with AcOEt (100 ml×3). The AcOEt layer was washed with H_2O (30 ml×2), dried over Na_2SO_4, concentrated in vacuo adding benzene several times to remove the vapor of HCl gas to give (*RS*)-**14** (477.4 mg, 96.0%) as light brown crystals. The ether layer was dried over Na_2SO_4, concentrated to give a brown solid, which was purified by preparative TLC ($CHCl_3$/MeOH=10:1) to recovered **4** (4.5 mg). (*RS*)-**14**: R_f=0.58 (1-BuOH/AcOH/H_2O=4:1:5); mp: 84–86°C (acetone); IR (KBr): ν_{max} cm^{-1} 3200–3500 (indole-NH, amide-NH), 2400–2600 (COOH), 1700, 1710 (COOH), 1600–1640 (NHCO), 1540 (indole); ^{1}H NMR (300 MHz, CD_3COCD_3) δ_H: 1.91, 1.97 (3H, each s, $COCH_3$), 3.19 (1H, dd, *J*=7.5, 14.5 Hz, 3-Ha), 3.32 (1H, dd, *J*=5.5, 14.5 Hz, 3-Hb), 4.79 (1H, dt, *J*=5.5, 7.5 Hz, 2-H), 7.16 (1H, dd, *J*=2.5, 8.4 Hz, 5′-H), 7.24 (1H, d, *J*=3.0 Hz, 2′-H), 7.28 (1H, brd, *J*=7.5 Hz, NHCO), 7.56 (1H, d, *J*=8.4 Hz, 4′-H), 7.58 (1H, d, *J*=2.5 Hz, 7′-H), 10.25 (1H, br, 1′-H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ_C 22.62, 22.66 (each q, CH_3), 27.96, 27.99 (each t, 3-C), 53.73, 53.82 (each, d, 2-C), 111.5, 111.3 (each s, 6′-C), 114.90, 114.96 (each d, 7′-C), 114.96, (s, 3′-C), 120.92 (d, 4′-C), 122.57 (d, 5′-C), 125.40, 125.24 (each d, 2′-C), 127.73, 127.76 (each s, 3a-C), 138.10 (s, 7a-C), 165.36, 165.39 (each s, NHCO), 170.46, 170.53 (each s, COOH); HRFAB-MS *m/z*: 325.0188 $[M+H]^+$, calcd for $C_{13}H_{14}O_3N_2Br^{79}$: 325.0188 [M+H].

4.1.20. 6′-Bromo-D-tryptophan ((*R*)-2). D-Aminoacylase (0.6 U/mol, 150.4 mg) in phosphate buffer solution (pH 7.41, 8 ml) and $CoCl_2 \cdot 6H_2O$ (0.2 mg) were added to a solution of (*RS*)-**14** (600 mg, 1.846 mmol) in phosphate buffer solution (90 ml). The solution was shaken for 23 h at 37°C. The reaction mixture was adjusted to pH 5 with 5% HCl, filtered through celite pad. The filtrate was washed with AcOEt (100 ml×3). The water layer was purified by column chromatography (SEPABEADS SP207, 150 ml of H_2O, followed by 200 ml of MeOH). Concentration of eluate of MeOH afforded (*R*)-**2** (197.3 mg, 37.7%) as white yellow crystals. The organic layer was dried over Na_2SO_4, concentrated in vacuo to give (*S*)-**14** (267.3 mg, 44.5%) as a yellow oil. (*R*)-**2**: R_f=0.35 (1-BuOH/AcOH/H_2O=4:1:5); mp: 232–236°C (MeOH); $[\alpha]_D^{26}$=+22.40° (*c*=1.0, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ_H: 3.15 (1H, dd, *J*=9.0, 15.0 Hz, 3-Ha), 3.46 (1H, dd, *J*=4.0, 15.0 Hz, 3-Hb), 3.83 (1H, dd, *J*=4.0, 9.0 Hz, 2-H), 7.15 (1H, dd, *J*=2.0, 8.5 Hz, 5′-H), 7.20 (1H, brs, 2′-H), 7.53 (1H, d, *J*=2.0 Hz, 7′-H), 7.62 (1H, d, *J*=8.5 Hz, 4′-H); ^{13}C NMR (100 MHz, CD_3OD) δ_C 28.20 (t, 3-C), 56.55 (d, 2-C), 109.99 (s, 3′-C), 115.27 (s, 7′-C), 116.17 (s, 6′-C), 120.95 (d, 4′-C),

123.20 (d, 5′-C), 126.14 (d, 2′-C), 127.52 (s, 3a′-C), 139.16 (s, 7a′-C), 174.28 (s, COOH); HRFAB-MS *m/z*: 283.0092 $[M]^+$, calcd for $C_{11}H_{12}O_2N_2Br^{79}$: 283.0082 [M]. (*S*)-**14**: $[\alpha]_D^{27}=+8.22°$ (*c*=0.73, acetone); HRFAB-MS *m/z*: 325.0152 $[M+H]^+$, calcd for $C_{13}H_{14}O_3N_2Br^{79}$: 325.0188 [M+H]. R_f and ^1H NMR data coincided with that of (*RS*)-**14**.

4.1.21. 6′-Bromo-*N*-carbobenzyloxy-D-tryptophan ((*R*)-15). Cbz-Cl (40.3 μl, 0.282 mmol) in diethyl ether (0.2 ml) was dropped to a solution of (*R*)-**2** (80.0 mg, 0.282 mmol) in 10% aqueous Na_2CO_3 (1.6 ml) at 0°C, and stirred for 1.5 h. The reaction mixture was acidified with 10% HCl at 0°C to give precipitates which were filtered, washed with H_2O (0.1 ml×2) to afford (*R*)-**15** (73.3 mg, 62.2%) as yellow-gray crystals. R_f=0.34 ($CHCl_3$/MeOH/H_2O=10:2:0.1); mp: 110–114°C (acetone); $[\alpha]_D^{25}=+6.80°$ (*c*=1.0, MeOH); IR (KBr): ν_{max} cm^{-1} 3390 (indole-NH), 3280 (amide-NH), 1700 (COOH), 1640–1680 (NHCO), 1610 (benzene), 1530 (indole); ^1H NMR (300 MHz, acetone-d_6) δ_H 3.22 (1H, dd, *J*=8.0, 14.5 Hz, 3-Ha), 3.38 (1H, dd, *J*=5.0, 14.5 Hz, 3-Hb), 4.58 (1H, dt, *J*=5.5, 8.0 Hz, 2-H), 5.05 (2H, brs, benzyl-H_2), 5.05 (1H, m, 2-NHCO), 7.15 (1H, dd, *J*=2.0, 8.3 Hz, 5′-H), 7.27 (1H, brs, 2′-H), 7.57 (1H, d, *J*=8.3 Hz, 4′-H), 7.10–7.44 (5H, m, phenyl), 7.59 (1H, t, *J*=1.5 Hz, 7′-H), 10.19 (1H, br, 1′-H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ_C: 28.08 (t, 3-C), 55.46 (d, 2-C), 66.63 (t, $COOCH_2$), 111.49 (s, 3′-C), 114.96 (d, 7′-C), 115.26 (d, 6′-C), 120.90 (d, 4′-C), 122.65 (d, 5′-C), 125.38 (d, 2′-C), 128.56, 128.89, 129.15 (each d, arom-C), 127.31 (s, 3a′-C), 138.13 (s, 7a′-C), 146.0 (s, arom-C), 156.78 (s, NHCOO), 173.42 (s, 1-C); HRFAB-MS *m/z*: 416.0378 $[M+H]^+$, calcd for $C_{19}H_{17}N_2O_4Br^{79}$: 416.0372 [M+H].

4.1.22. 6′-Bromo-*N*-carbobenzyloxy-D-tryptophan (*R*)-(+)-1-phenylethylamide (16). (+)-1-Phenylethylamine (1.6 mg, 0.014 mmol), EDCI (2.6 mg, 0.014 mmol), hydroxybenzotriazole (1.8 mg, 0.014 mmol) were added to a solution of (*R*)-**15** (4.5 mg, 0.014 mmol) in THF (0.4 ml) and stirred for 3.6 h at room temperature under argon. The reaction mixture was concentrated in vacuo, purified by preparative TLC (hexane/AcOEt=1:2) to give **16** (5.5 mg, 98%) as light yellow crystals. R_f=0.58 (hexane/AcOEt=1:2); mp: 170–174°C; $[\alpha]_D^{25}=-1.25°$ (*c*=0.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 1.31 (3H, d, *J*=6.5 Hz, CH*CH*$_3$), 3.06 (1H, dd, *J*=8.5, 14.5 Hz, 3-Ha), 3.25 (1H, dd, *J*=5.0, 14.5 Hz, 3-Hb), 4.42 (1H, dt, *J*=5.0, 8.0 Hz, 2-H), 4.98 (1H, quintet *J*=7.5 Hz, *CH*CH_3), 5.11 (2H, s, benzyl-CH_2), 5.52 (1H, brd, *J*=8.0 Hz, 2-NHCO), 5.72 (1H, brd, *J*=7.5 Hz, 1-CONH), 6.70 (1H, d, *J*=2.0 Hz, 2′-H), 7.18 (1H, brd, *J*=8.5 Hz, 5′-H), 7.25 (5H, m, CHPh), 7.34 (5H, m, benzyl-arom-H), 7.45 (1H, d, *J*=2.0 Hz, 7′-H), 7.51 (1H, brd, *J*=8.5 Hz, 4′-H), 7.83 (1H, br, 1′-H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ_C 21.58 (q, CH*CH*$_3$), 28.72, 29.69 (each, t, 3-C), 48.88 (d, *C*HCH$_3$), 55.46 (each d, 2-C), 67.06, 67.07 (each t, benzyl-CH_2), 110.70, 110.74 (each, s, 6′-C), 114.12 (d, 7′-C), 115.98 (s, 3′-C), 120.19 (d, 4′-C), 123.21 (d, phenyl), 123.86 (d, 2′-C), 126.02 (d, 5′-C), 127.35, 128.12, 128.28, 128.57 (each d, phenyl), 130.88 (s, 3a′-C), 136.88 (s, 7a′-C), 142.59 (s, phenyl), 155.93 (s, NHCOO), 169.87 (s, CONH); HRFAB-MS *m/z*: 520.1230 $[M]^+$, calcd for $C_{27}H_{27}N_3O_3Br^{79}$: 520.1236 [M].

4.1.23. 6′-Bromo-L-tryptophan ((*S*)-2). L-Aminoacylase (2170 U/mg, 100 mg) in phosphate buffer solution (pH 7.41, 8 ml) and $CoCl_2{\cdot}6H_2O$ (0.2 mg) was added to a solution of (*RS*)-**14** (100 mg, 0.309 mmol) in phosphate buffer solution (15 ml). The solution was shaken for 24 h at 37°C. The reaction mixture was adjusted to pH 5 with 10% HCl, filtered through celite pad. The filtrate was washed with AcOEt (30 ml×2). Thewater layer was purified by column chromatography (SEPABEADS SP207, 150 ml of H_2O, followed by 200 ml of MeOH). Concentration of eluate of MeOH afforded (*S*)-**2** (39 mg, 45%) as white plates. The organic layer was washed with saturated aqueous NaCl (10 ml), dried over Na_2SO_4, concentrated in vacuo to give (*R*)-**14** (31 mg, 46%) as a white powder. (*S*)-**2**: mp: 125–127°C; $[\alpha]_D^{27}=-18.57°$ (*c*=0.14, MeOH); HRFAB-MS *m/z*: 283.0082 $[M]^+$, calcd for $C_{11}H_{12}O_2N_2Br^{79}$: 283.0076 [M]. R_f, ^1H NMR data coincided with that of (*R*)-**2**. (*R*)-**14**: mp: 88–92°C; $[\alpha]_D^{27}=-12.5°$ (*c*=0.16, acetone); HRFAB-MS *m/z*: 324.0107 $[M]^+$, calcd for $C_{13}H_{13}O_3N_2Br^{79}$: 324.0110 [M]. R_f and ^1H NMR data were coincided to that of (*RS*)-**14**.

4.1.24. 6′-Bromo-*N*-carbobenzyloxy-L-tryptophan ((*S*)-15). Cbz-Cl (21.1 mg, 0.124 mmol) in diethyl ether (0.2 ml) was dropped to a solution of (*S*)-**2** (35 mg, 0.124 mmol) in 10% aqueous Na_2CO_3 (1.0 ml) at 0°C, and stirred for 1.5 h. The reaction mixture was acidified with 10% HCl at 0°C to give precipitates which were filtered, washed with H_2O (1 ml×5) to afford (*S*)-**15** (32 mg, 78.0%) as gray granules. Mp: 115–120°C (acetone); R_f=0.34 ($CHCl_3$/MeOH/H_2O=10:2:0.1); $[\alpha]_D^{27}=-8.99°$ (*c*=0.20, acetone); HRFAB-MS *m/z*: 415.0321 $[M-H]^+$, calcd for $C_{19}H_{16}O_4N_{279}Br$ 415.0293 [M−H]. R_f and ^1H NMR data coincided with that of (*R*)-**15**.

4.1.25. 6′-Bromo-*N*-carbobenzyloxy-L-tryptophan (*R*)-(+)-1-phenylethylamide (17). (*R*)-(+)-1-Phenylethylamine (1.8 mg, 0.015 mmol), EDCI (2.9 mg, 0.015 mmol), hydroxybenzotriazole (2.0 mg, 0.015 mmol) were added to a solution of (*S*)-**15** (5 mg, 0.015 mmol) in THF (0.4 ml) and stirred for 3.6 h at room temperature under argon. The reaction mixture was concentrated in vacuo, purified by preparative TLC (hexane/AcOEt=1:2) to give **17** (5.1 mg, 82%) as a light yellow powder. R_f=0.38 (hexane/AcOEt=1:1); mp: 170–174°C; $[\alpha]_D^{26}=+4.00°$ (*c*=0.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 1.17 (3H, d, *J*=7.0 Hz, CH*CH*$_3$), 3.11 (1H, dd, *J*=8.0, 14.5 Hz, 3-Ha), 3.33 (1H, dd, *J*=5.0, 14.5 Hz, 3-Hb), 4.45 (1H, dt, *J*=5.0, 8.0 Hz, 2-H), 4.93 (1H, quintet *J*=7.5 Hz, *CH*CH_3), 5.10 (2H, br, benzyl-CH_2), 5.41 (1H, brd, *J*=8.0 Hz, 2-NHCO), 5.77 (1H, brd, *J*=7.0 Hz, 1-CO*NH*), 6.94 (1H, br, 2′-H), 7.04 (1H, d, *J*=8.5 Hz, 5′-H), 7.25 (5H, m, CHPh), 7.34 (5H, m, benzyl-arom.-H), 7.45 (1H, d, *J*=2.0 Hz, 7′-H), 7.51 (1H, brd, *J*=8.5 Hz, 4′-H), 7.83 (1H, br, 1′-H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ_C 21.41 (each q, CH*CH*$_3$), 28.50 (t, 3-C), 48.95 (d, *C*HCH$_3$), 55.55 (d, 2-C), 67.11 (t, benzyl-CH_2), 110.98 (s, 6′-C), 114.16 (d, 7′-C), 116.06 (s, 3′-C), 120.19 (d, 4′-C), 123.34 (d, phenyl), 123.77 (d, 2′-C), 125.98 (d, 5′-C), 127.37, 128.15, 128.30, 128.59 (each d, phenyl), 136.09, 136.93 (each s, 3′a, 7a′-C), 142.58 (s, phenyl), 155.93 (s, NHCOO), 169.90 (s, CONH); HRFAB-MS *m/z*: 520.1224 $[M]^+$, calcd for $C_{27}H_{27}O_3N_3Br^{79}$: 520.1236 [M].

4.1.26. *N*-Acetyl-6′-bromo-L-tryptophan (*R*)-(+)-1-phenylethylamide ((*S*)-14-amide). (*R*)-(+)-1-Phenylethylamine (16.6 mg, 0.138 mmol), EDCI (35.2 mg,

0.184 mmol), hydroxybenzotriazole (12.42 mg, 0.092 mmol), diisopropylethylamine (16 μl, 0.138 mmol) were added to a solution of (*S*)-**14** (30 mg, 0.092 mmol) in THF (2.5 ml) and stirred for 7 h at room temperature under argon. The reaction mixture was concentrated in vacuo, purified by preparative TLC (hexane/AcOEt=1:5) to give (*S*)-**14**-amide (23 mg, 58%) as a white powder. R_f=0.31 (hexane/AcOEt=1:5); mp: 200–205°C; $[\alpha]_D^{24}$=+32.67° (*c*=0.3, MeOH); ^{1}H NMR (300 MHz, CD_3COCD_3) δ_H: 1.24 (3H, d, *J*=7.0 Hz, CH*CH*$_3$), 1.85 (3H, s, CO*CH*$_3$), 3.12, 3.20 (each 1H, ddd, *J*=14.0, 7.0, 0.8 Hz, 3-H$_2$), 4.71 (1H, dt, *J*=8.0, 7.0 Hz, 2-H), 4.97 (1H, quintet *J*=7.0 Hz, *CH*CH$_3$), 7.15 (1H, dd, *J*=8.5, 2.0 Hz, 5′-H), 7.21 (1H, t, *J*=1.2 Hz, 2′-H), 7.23–7.30 (6H, m, phenyl, 1-CONH), 7.52 (1H, brd, *J*=8.0 Hz, 2-NHCO), 7.58 (1H, d, *J*=2.0 Hz, 7′-H), 7.60 (1H, d, *J*=8.5 Hz, 4′-H), 10.25 (1H, br, 1′-H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ_C 22.39, 22.45 (each q, CH*CH*$_3$), 22.78, 22.82 (each q, CO*CH*$_3$), 28.94 (t, 3-C), 49.12, 49.28 (each d, *C*HCH$_3$), 54.67, 54.78 (each d, 2-C), 111.95 (s, 6′-C), 114.82 (d, 7′-C), 115.16 (s, 6′-C), 121.18 (d, 4′-C), 122.42, 122.47 (d, 5′-C), 125.32, 125.23 (d, 2′-C), 126.87, 127.46, 129.03 (each d, phenyl), 138.14 (s, 7a′-C), 145.21 (s, phenyl), 169.89, 171.08 (each s, NHCO×2); HRFAB-MS *m/z*: 428.0947 [M+1], calcd for $C_{21}H_{23}O_2N_3Br^{79}$: 428.0974 [M+H].

4.1.27. *N*-Acetyl-6′-bromo-D-tryptophan (*R*)-(+)-1-phenylethylamide ((*R*)-14-amide). (*R*)-(+)-1-Phenylethylamine (8.8 mg, 0.074 mmol), EDCI (28 mg, 0.148 mmol), hydroxybenzotriazole (9.9 mg, 0.074 mmol), diisopropylethylamine (19 μl, 0.148 mmol) were added to a solution of (*R*)-**14** (24 mg, 0.074 mmol) in THF (2.5 ml) and stirred for 24 h at room temperature under argon. The reaction mixture was concentrated in vacuo, purified by preparative TLC (hexane/AcOEt=1:5) to give (*R*)-**14**-amide (20 mg, 63.4%) as a white powder. R_f=0.22 (hexane/AcOEt=1:5); mp: 247–250°C; $[\alpha]_D^{25}$=+7.14° (*c*=0.28, MeOH); ^{1}H NMR (300 MHz, CD_3COCD_3) δ_H: 1.35 (3H, d, *J*=7.0 Hz, CH*CH*$_3$), 1.90 (3H, s, CO*CH*$_3$), 3.05, 3.16 (each 1H, ddd, *J*=14.0, 6.5, 0.8 Hz, 3-H$_2$), 4.72 (1H, dt, *J*=7.5, 6.5 Hz, 2-H), 5.02 (1H, quintet *J*=7.0 Hz, *CH*CH$_3$), 7.01 (1H, d, *J*=2.5 Hz, 2′-H), 7.11 (1H, dd, *J*=8.5, 1.7 Hz, 5′-H), 7.21 (1H, brd, *J*=7.5 Hz, 2-NHCO), 7.23 (5H, phenyl), 7.55 (1H, d, *J*=8.5 Hz, 4′-H), 7.57 (1H, d, *J*=1.7 Hz, 7′-H), 7.58 (1H, brd, *J*=7.0 Hz, 1-CONH), 10.18 (1H, br, 1′-NH). ^{13}C NMR (100 MHz, CD_3COCD_3) δ_C 22.42 (q, CH*CH*$_3$), 22.93 (q, CO*CH*$_3$), 28.94 (t, 3-C), 49.18 (d, *C*HCH$_3$), 54.71 (d, 2-C), 111.81 (s, 3′-C), 114.85 (d, 7′-C), 115.56 (s, 6′-C), 121.20 (d, 4′-C), 122.45 (d, 5′-C), 125.41 (d, 2′-C), 126.85, 127.46, 129.02 (each s, phenyl-H), 127.77 (s, 3a′-C), 138.29 (s, 7a′-C), 145.05 (s, phenyl), 169.88, 171.17 (NHCO×2); HRFAB-MS *m/z*: 428.0990 $[M+1]^+$, calcd for $C_{21}H_{23}O_2N_3Br^{79}$: 428.0974 [M+H].

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