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AN EFFICIENT METHOD OF SYNTHESIZING OPTICALLY PURE *N*-BOC-4-BROMO-*N*-METHYL-1-TOSYL-D-TRYPTOPHAN METHYL ESTER, A KEY INTERMEDIATE IN THE SYNTHESIS OF OPTICALLY ACTIVE ERGOT ALKALOIDS

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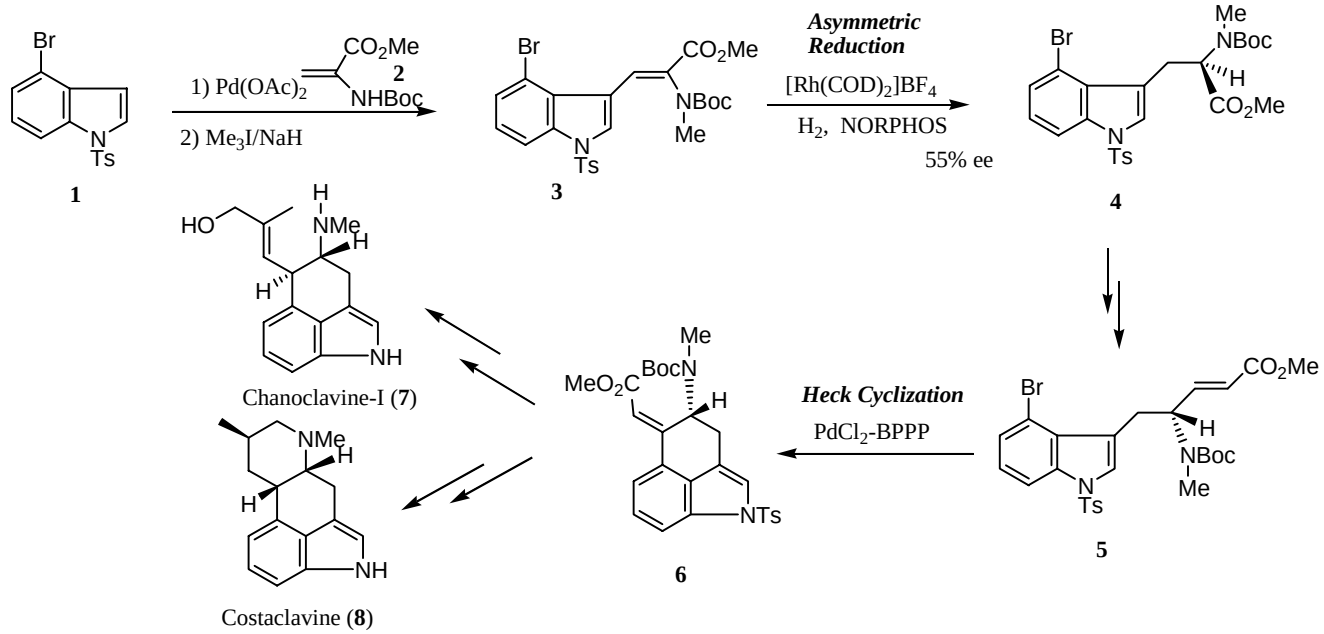
Abstract — Optically pure *N*-Boc-4-bromo-*N*-methyl-1-tosyl-**D**-tryptophan methyl ester (**D-4**), a key intermediate in the synthesis of optically active ergot alkaloids such as chanoclavine-I (**7**) and costaclavine (**8**), was prepared from *N*-acetyl-4-bromo-**D**-tryptophan (**D-11**) obtained from 4-bromoindole (**9**) and **DL**-serine (**10**) in two steps.

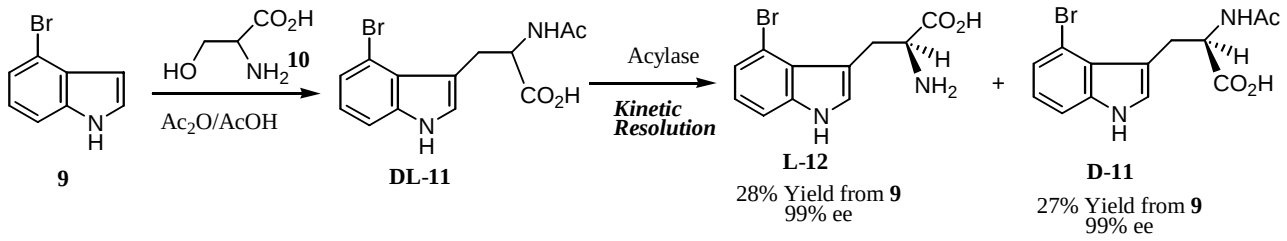
Introduction

Recently, we developed an efficient way to synthesize the optically active ergot alkaloids, chanoclavine-I (**7**)[1] and costaclavine (**8**)[2] (Scheme 1). The characteristic feature of this route was the transformation of an optically active tryptophan derivative (**4**) into a tricyclic ergoline intermediate (**6**) by Heck cyclization

Scheme 1 Synthetic Route for Chanoclavine-I (**6**) and Costaclavin (**7**)

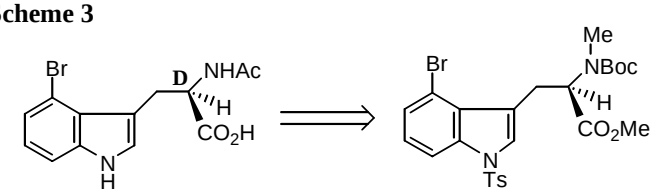


Scheme 2 Synthesis of Optically Pure 4-Bromotryptophan (**L-12**) from 4-Bromoindole (**9**) and **DL**-Serine (**10**)



of an α,β-unsaturated ester (**5**) without racemization. In this route, the absolute configuration of **4** was required to be the **D** configuration, the configuration opposite to that of natural amino acids, in order to obtain the same stereoisomer as ergot alkaloids. The compound (**4**) was obtained from1-tosyl-4-bromoindole (**1**) in three steps, including the asymmetric reduction of the dehydrotryptophan derivative (**3**).[1] However, the best optical yield of the asymmetric reduction was 67% ee (when NORPHOS was used as a chiral auxiliary), and all other attempts (using various chiral phosphine ligands) failed to yield any better results. At the same time, we[3] developed a new two-step method of synthesizing optically pure 4-bromo-**L**-tryptophan [**L-12**] from 4-bromoindole (**9**) (Scheme 2). Since optically pure **D-11** can be obtained by kinetic resolution of **DL-11** by acylase, we felt that **D-11** would be suitable for use in the synthesis of optically pure **D-4**. In the following section of this paper, we will describe a more efficient method of synthesizing **D-4** from **D-11** without racemization (Scheme 3).

Scheme 3

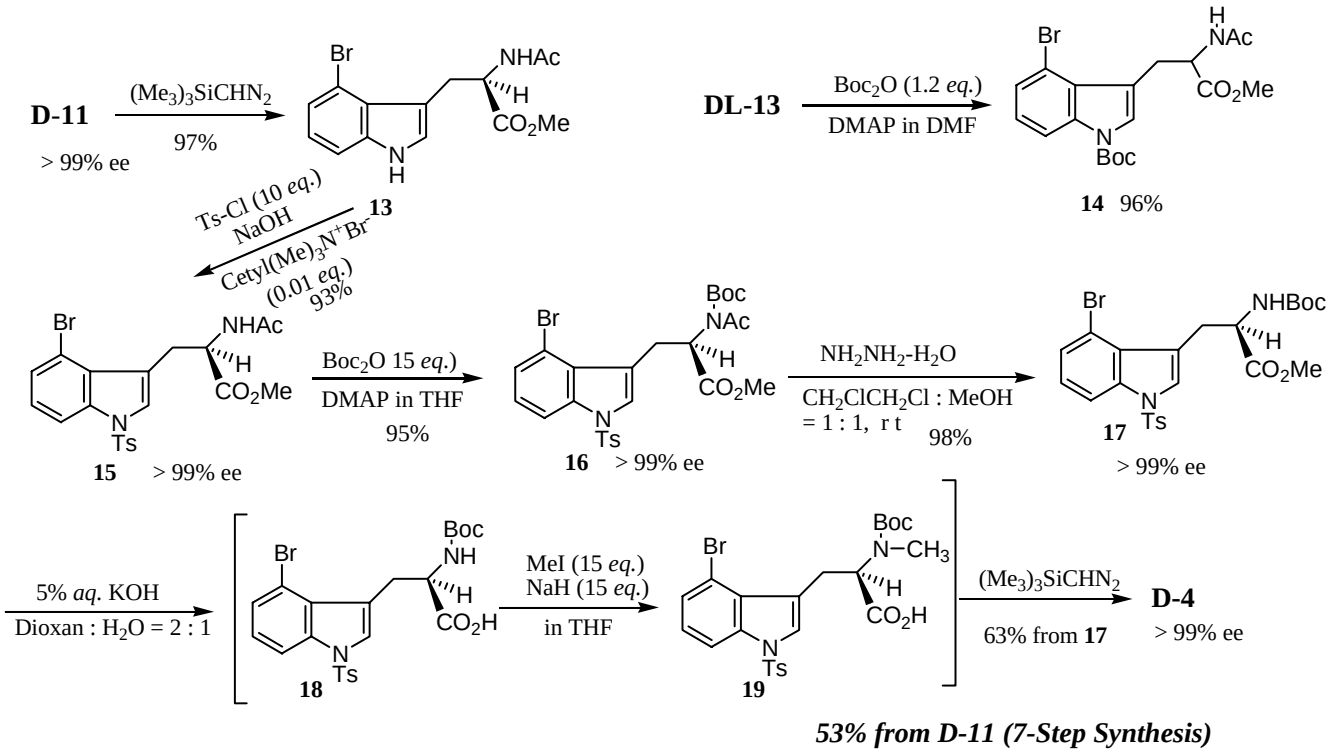


Results and Discussion

The synthetic pathway of **D-4** is shown in Scheme 4. The starting material, optically pure **D-11,** was prepared from **9** and **DL**-serine (**10**), at 27% yield by the method shown in Scheme 2.[3] The removal of the acetyl group of **D-11** is likely to be the most difficult step in the conversion, since acid hydrolysis could decompose[4] the indole ring and alkaline hydrolysis could cause racemization. In fact, serious racemization occurred during hydrolysis of **D-11** with 30% *aqueous* NaOH under reflux and with hydrazine hydrate at 70 – 80 ^{o}C, yielding the product (**D-12**) at 90% and 65% ee, respectively. Grehn *et al.*[5] have reported the conversion of the protecting group of phenethylamine from acetyl into a Boc group. Since this conversion was considered suitable for use in our synthesis, we applied it to the transformation of **D-11** to **D-4**. After esterification of the acid (**11**) with trimethylsilyldiazomethane, direct *tert*-butoxycarbonylation with 1 *eq*. of Boc_2O was carried out to selectively generate the N_{indole}-Boc product (**14**) at 96% yield. Since this result indicated that the indole nitrogen of **13** was more reactive towards Boc_2O than amide nitrogen, tosylation of **13** was carried out first to selectively generate the N_{indole}-tosylated product (**15**) at 93% yield. This compound was then allowed to react with Boc_2O in the presence of DMAP to generate product (**16**); it was obtained at 95% yield. The acetyl group was easily

removed, without racemization, by treatment with hydrazine hydrate at room temperature, yielding the

Scheme 4 : Synthetic Route for *N*-Boc-4-bromo-*N*-methyl-1-tosyl-**L**-tryptophan Methyl Ester (**D-4**)



deacetylated product (**17**), in 98% yield.

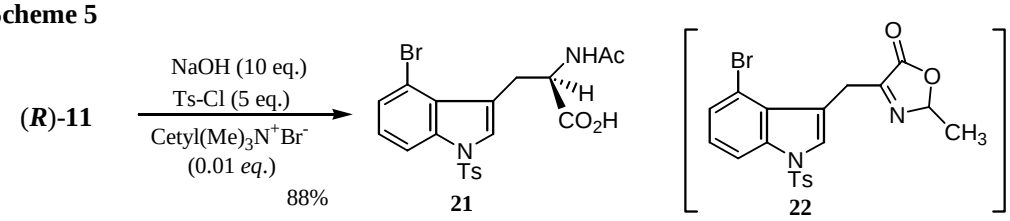
Although acetyl group is not frequently used for protection of amino acids, because of the difficulty of removal, this protecting group was indispensable for the production of a high enantiomeric excess of amino acids in a asymmetric reduction of dehydroamino acid.[6] As a result, this transformation is a useful method for obtaining optically pure Boc-protected amino acids by asymmetric synthesis.

The *N*-methylation of **17** was attempted under various conditions, but the desired product (**4**) was not obtained [CH_3I/Ag salt, $(CH_3)_2SO_4$/TBAF, and CH_3I/KOH-18-crown-6] or was obtained at only moderate yield (47%) with serious racemization (78% ee) (CH_3I/NaH in DMF). Thus, we attempted methylation after hydrolysis of 1**7**, because the resulting carboxylate anion might inhibit the attack of the base on the α-hydrogen during methylation.[7] Hydrolysis of 1**7** under anhydrous basic conditions (5% KOH-MeOH) not only hydrolyzed the ester but also removed the tosyl group, while 0.5% *aqueous* KOH-dioxane (2 : 1) hydrolyzed the ester selectively to produce the acid (**18**). Methylation of crude **18** with MeI, using NaH as a base followed by esterification of the resultant product (**19**)**,** with $(CH_3)_3SiCHN_2$, produced the target compound (**D-4**) without racemization at 63% overall yield from 1**7**.

Although the total yield of **D-4** from **D-11** was good (57% in 7 steps), this route is somewhat time-consuming, because the carboxyl group was repeatedly protected and deprotected. This lengthy process could be avoided if this transformation could be accomplished without esterification. The direct tosylation of the acid (**D-11**) generated the N-tosylated product (**21**) at 88% yield. However, serious racemization occurred due to the formation of oxazolone (**22**) through mixed anhydride of the

tosyl group (Scheme 5). Therefore, we made no further attempt at synthesis without protection of the

Scheme 5



carboxyl group.

As this synthetic pathway is the only method which yields **D-4** in optically pure form, it should constitute a significant contribution to the synthesis of optically active ergot alkaloids.

EXPERIMENTAL

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. Optical rotations were recorded on a JASCO DIP-1000 instrument. IR spectra were performed with a JASCO FT/IR-230 spectrophotometer. ^{1}H- NMR spectra were taken with a JEOL EX-400 spectrometer in chloroform-*d* ($CDCl_3$). Chemical shifts of protons are referenced to tetramethylsilane as an internal standard, or the residual chloroform (7.26 ppm) was used as the internal reference when measured in $CDCl_3$. MS were measured on a JEOL JMS-AM II 50. TLC was performed on Merck 25 DC-Platten 20×20 cm Kieselgel 60 F_{254} (Art 5715). In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise indicated.

***N*-Acetyl-4-bromo-DL-tryptophan (DL-11)**

A mixture of **DL**-serine (1.20 g, 11.4 mmol) and acetic anhydride (2.4 mL, 23 mmol) in AcOH (7.0 mL) was heated for 1 h at 80 °C, and then 4-bromoindole (**9**) (1.12 g, 5.70 mmol) was added to the solution. After being heated at 80 °C for 1.5 h, the reaction mixture was basified with 30% *aqueous* NaOH and washed three times with benzene-AcOEt (1 : 1). The *aqueous* layer was acidified with concentrated HCl and extracted three times with benzene-AcOEt (1 : 1). The organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, resulting crude amorphous solid (1.13 g) was subjected to chromatography over neutralized silica gel (benzene : AcOEt = 1 : 5 ~ 1 : 8) to give the acid (**DL-11**) (1.06 g, 57%) as a pale brown amorphous solid. IR (KBr) cm^{-1}: 3320, 1733, 1718. ^{1}H-NMR (DMSO-d_6) δ: 1.78 (3H, s), 3.07 (1H, dd, *J* = 15.0, 10.0 Hz), 3.54 (1H, dd, *J* = 15.0, 5.0 Hz), 4.55 (1H, ddd, *J* = 10.0, 8.0, 5.0 Hz), 6.96 (1H, t, *J* = 8.0 Hz), 7.17 (1H, d, *J* = 8.0 Hz), 7.23 (1H, d, *J* = 4.0 Hz), 7.36 (1H, d, *J* = 8.0 Hz), 8.16 (1H, d, *J* = 10.0 Hz). EI-MS *m/z*: 324 (M^+, 1.4), 326 (M^++2, 1.3), 208 (100). *Anal.* Calcd for $C_{13}H_{13}N_2O_3Br$: C, 48.02; H, 4.03; N, 8.62. Found: C, 48.06; H, 4.05; N, 8.52.

***N*-Acetyl-4-bromo-D-tryptophan Methyl Ester (D-13)**

To a solution of **DL-*N*-**Acetyl-4-bromotryptophan (**DL-11**) (151 mg, 0.465 mmol) in buffer solution of 20 mM NaH_2PO_4 (pH 7.51, 30.0 mL) was added $CoCl_2$·$6H_2O$ (6.50 mg, 0.27 mmol) and acylase from *Aspergillus genus* (61.1 mg, 1833 units), and the resulting mixture was shaked in constant-temperature

water bath at 37°C for 2 days. Then, the mixture was acidified by 5% *aqueous* HCl, and extracted with AcOEt-benzene (1 : 1). The combined organic layer was dried over $MgSO_4$, and evaporated *in vacuo* to give a pale red viscous oil. To a solution of crude *N*-acetyl-4-bromo-**D**-tryptophan **(D-11)** (78.3 mg, 0.241 mmol) in AcOEt (6.00 mL) and MeOH (1.20 mL) was added trimethylsilyldiazomethane 2.0 M solution in hexane (0.61 mL, 1.21 mmol). The reaction mixture was stirred at rt for 30 min, quenched by the addition of AcOH at 0 °C, and then extracted with AcOEt. The combined organic extracts were washed successively with saturated $NaHCO_3$, brine, and dried over $MgSO_4$. After evaporation of solvent , the resultant residue was purified by silica gel column chromatography (benzene : acetone = 2 : 1) to give *N*-acetyl-4-bromo-**D**-tryptophan methyl ester **(D-13)** (74.4 mg, 47%) as a white powder. The optical purity was 99% ee based on HPLC using a chiral column (SUMIPAX OA-4600 *n*-hexane : *i*-PrOH : AcOH = 100 : 20 : 1). This solid was recrystallized from AcOEt – hexane to give colorless prisms. mp 198 - 202°C. $[\alpha]^{27}_D$ –16.2° (*c*= 0.263, $CHCl_3$). IR (KBr) cm^{-1}: 3379, 1735, 1648. ^{1}H-NMR ($CDCl_3$) δ: 1.86 (3H, s), 3.44 (1H, dd, *J* = 15.0, 8.0 Hz), 3.62 (1H, dd, *J* = 15.0, 6.0 Hz), 3.68 (3H, s), 4.92 (1H, ddd, *J* = 8.0, 8.0, 6.0 Hz), 6.06 (1H, d, *J* = 8.0 Hz), 6.95 (1H, dd, *J* = 8.0, 8.0 Hz), 7.04 (1H, d, *J* = 4 Hz), 7.24 (1H, d, *J* = 8.0 Hz), 7.26 (1H, d, *J* = 8.0 Hz), 8.24 (1H, br s). EI-MS *m/z*: 340 (M^++2, 3.5), 338 (M^+, 3.5), 210 (100). *Anal.* Calcd for $C_{14}H_{15}N_2O_3Br$: C, 49.58; H, 4.46; N, 8.26. Found: C, 49.64; H, 4.45; N, 8.24.

***N*-Acetyl-1-Boc-DL-tryptophan Methyl Ester (14)**

To a mixture of *N*-acetyl-4-bromo-**DL**-tryptophan methyl ester **(DL-13)** (106.9 mg, 0.32 mmol), dimethylaminopyridine (4.1 mg, 0.03mmol) in CH_3CN (4.0 mL) was added a solution of di-*tert*-butyl dicarbonate (74.9 mg, 0.35 mmol) in CH_3CN (1 mL) at rt and the mixture was kept for 1 h. After the addition of AcOEt to the reaction mixture, the organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the resulting residue (138.8 mg) was purified by silica gel column chromatography (benzene : AcOEt = 2 : 1) to give **14** (136.1 mg, 98%) as a colorless solid, which was recrystallized from AcOEt-hexane to give colorless prisms. mp 165 ~ 168 °C.. IR (KBr) cm^{-1}: 3326, 1776, 1740, 1651. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (9H, s), 1.95 (3H, s), 3.38 (1H, dd, *J* = 15.0, 8.0 Hz), 3.63 (1H, dd, *J* = 15.0, 6.0 Hz), 3.73 (3H, s), 4.99 (1H, ddd, *J* = 8.0, 8.0, 6.0 Hz), 6.11 (1H, br d, *J* = 8.0 Hz), 7.13 (1H, t, *J* = 8.0 Hz), 7.39 (2H, d, *J* = 8.0 Hz), 7.47 (1H, s), 8.18 (1H, d, *J* = 8.0 Hz). EI-MS *m/z*: 440 (M^++2), 438 (M^+), 210 (bp). *Anal.* Calcd for $C_{19}H_{23}N_2O_5Br$: C, 51.95; H, 5.28; N, 6.38. Found: C, 51.79; H, 5.25; N, 6.32.

***N*-Acetyl-4-bromo-1-tosyl-D-tryptophan Methyl Ester (15)**

Cetyltrimethylammonium bromide (1.10 mg, 0.003 mmol) and powdered sodium hydroxide (117 mg, 2.93 mmol) were added to a solution of **D-13** (100 mg, 0.295 mmol) in 1,2-dichloromethane (8.00 mL) at -20°C. And a suspension of *p*-toluenesulfonyl chloride (TsCl, 555 mg, 2.91 mmol) in 1,2-dichloroethane (8.00 mL) was added to the reaction mixture. The resulting mixture was stirred at -20°C for 1 h, and then acidified with 5% *aqueous* HCl. After extracting with AcOEt, the combined organic extract was washed successively with *aqueous* $NaHCO_3$, brine, and dried over $MgSO_4$. After evaporation of the solvent, the resultant residue was purified by silica gel column chromatography (benzene : AcOEt = 1 : 1)

to give **15** (135 mg, 93%) as a colorless viscous oil. The optical purity was 99% ee based on HPLC using a chiral column (SUMIPAX OA-4600 *n*-hexane : *i*-PrOH : AcOH = 100 : 20 : 1). $[\alpha]^{21}_{D}$ -6.0° (*c*= 2.75, $CHCl_3$). IR (KBr) cm^{-1}: 3281, 1744, 1655. ^{1}H-NMR ($CDCl_3$) δ: 1.93 (3H, s), 2.35 (3H, s), 3.32 (1H, dd, *J* = 15.0, 8.0 Hz), 3.61 (1H, dd, *J* = 15.0, 6.0 Hz), 3.70 (3H, s), 5.01 (1H, ddd, *J* = 8.0, 8.0, 6.0 Hz), 6.04 (1H, d, *J* = 8.0 Hz), 7.13 (1H, dd, *J* = 8.0, 8.0 Hz), 7.24 (2H, d, *J* = 8.0 Hz), 7.39 (1H, d, *J* = 8.0 Hz), 7.47 (1H, s), 7.72 (2H, d, *J* = 8.0 Hz), 7.95 (1H, d, *J* = 8.0 Hz). EI-MS *m/z*: 494 (M^++2, 4.0), 492 (M^+, 3.8), 91 (100). *Anal.* Calcd for $C_{21}H_{21}N_2O_5BrS$: C, 51.12; H, 4.29; N, 5.68. Found: C, 51.08; H, 4.40; N, 5.51.

***N*-Acetyl-4-bromo-*N*-Boc-1-tosyl-D-tryptophan Methyl Ester (16)**

To a stirred solution of *N*-acetyl-4-bromo-1-tosyl-**D**-tryptophan methyl ester (**15**) (59.0 mg, 0.120 mmol) in THF (2.00 mL) were added 4-dimethylaminopyridine (8.20 mg, 0.07 mmol) and di-*tert*-butyl dicarbonate (0.40 mL, 1.74 mmol). The reaction mixture was stirred for 3 h at rt, diluted with water, and then extracted with AcOEt. The combined organic extracts were washed with brine, dried over $MgSO_4$. After evaporation of the solvent, the resultant yellow viscous oil was purified by silica gel column chromatography (benzene : AcOEt = 30 : 1) to give **16** (67.6 mg, 95%) as a colorless viscous oil. $[\alpha]^{20}_{D}$ +94.3° (*c*= 0.40, $CHCl_3$). IR (neat) cm^{-1}: 2980, 1731, 1695. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (9H, s), 2.34 (3H, s), 2.36 (3H, s), 3.29 (1H, dd, *J* = 15.1, 10.7 Hz), 3.76 (3H, s), 4.00 (1H, dd, *J* = 15.1, 3.9 Hz), 5.59 (1H, dd, *J* = 10.7, 3.9 Hz), 7.12 (1H, dd, *J* = 8.3, 8.3 Hz), 7.23－7.30 (3H, m), 7.39 (1H, d, *J* = 8.3 Hz), 7.71 (2H, d, *J* = 8.3 Hz), 7.93 (1H, d, *J* = 8.3 Hz). MS *m/z*: (FAB) 595 (M^++2, 1.7), 593 (M^+, 2.0), 57 (100). *Anal.* Calcd for $C_{26}H_{29}N_2O_7BrS$: C, 52.62; H, 4.93; N, 4.72. Found: C, 52.74; H, 5.09; N, 4.48.

***N*-Boc-4-bromo-1-tosyl-D-tryptophan Methyl Ester (17)**

To a stirred solution of *N*-acetyl-4-bromo-*N*-Boc-1-tosyl-**D**-tryptophan methyl ester (**16**) (137 mg, 0.231 mmol) in 1,2-dichloroethane (3.60 mL) and methanol (0.90 mL) was added NH_2NH_2•H_2O (0.035 mL, 0.72 mmol). The reaction mixture was stirred for 48 h at rt and then diluted with water, and extracted with AcOEt. The combined organic extract was washed with brine, dried over ($MgSO_4$), and evaporated *in vacuo* to give a colorless viscous oil. The resultant residue was purified by silica gel column chromatography (benzene : AcOEt = 10 : 1) to give **17** (125 mg, 98%) as a white powder. The optical purity was 99% ee based on HPLC using a chiral column (Daicel Chiralcel OD *n*-hexane : *i*-PrOH = 9 : 1). The powder was recrystallized from benzene-hexane to yield sharp white needles. mp 145 ~ 146 °C. $[\alpha]^{25}_{D}$ +13° (*c*= 2.47, $CHCl_3$). IR (KBr) cm^{-1}: 3381, 1744, 1689. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (9H, s), 2.35 (3H, s), 3.20 ~ 3.31 (1H, m), 3.58 (1H, dd, *J* = 14.6, 5.4 Hz), 3.70 (3H, s), 4.69 (1H, ddd, *J* = 8.8, 8.8, 5.4 Hz), 5.00 ~ 5.10 (1H, m), 7.12 (1H, dd, *J* = 7.8, 7.8 Hz), 7.24 (2H, d, *J* = 8.3 Hz), 7.38 (1H, d, *J* = 7.8 Hz), 7.48 (1H, s), 7.73 (2H, d, *J* = 8.3 Hz), 7.93 (1H, d, *J* = 7.8 Hz). EI-MS *m/z*: 553 (M^++2, 0.67), 551 (M^+, 0.74), 91 (100). *Anal.* Calcd for $C_{24}H_{27}N_2O_6BrS$: C, 52.27; H, 4.93; N, 5.08. Found: C, 52.27; H, 4.93; N, 5.10.

***N*-Boc-4-bromo-*N*-methyl-1-tosyl-D-tryptophan Methyl Ester (D-4]**

To a solution of *N*-Boc-4-bromo-1-tosyl-**D**-tryptophan methyl ester (**17**) (56.1 mg, 0.102 mmol) in 1,4-dioxane (5.00 mL) and H_2O (2.50 mL) was added a solution of 5% aqueous KOH (0.30 mL, 0.267 mmol) at 0°C. The resulting mixture was stirred at rt for 30 min, allowed to acidify with 5% *aqueous* AcOH at

0°C, and then extracted with AcOEt. The combined organic extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to afford the crude acid (47.5 mg, **18**) as a white powder. To a solution of crude **18** (47.5 mg, 0.88 mmol) in THF (2.35 mL) was added 60% sodium hydride (53.5 mg, 1.33 mmol). The reaction mixture was stirred at rt for 5 min, then CH_3I (0.094 mL, 1.51 mmol) was added. The mixture was stirred for 1.5 h at rt, quenched by the addition of H_2O, acidified by 5% *aqueous* AcOH at 0°C, and extracted with AcOEt. The combined organic extract was washed with brine, dried over $MgSO_4$, concentrated, and evaporated *in vacuo* to give a pale yellow viscous oil (64.4 mg). 2.0 M Solution of trimethylsilyldiazomethane in hexane (0.28 mL, 0.56 mmol) was added to a solution of crude *N*-Boc-4-bromo-*N*-methyl-1-tosyl-**D**-tryptophan (**19**, 64.4 mg, 1.16 mmol) in AcOEt (5.6 mL) and MeOH (1.5 mL). The reaction mixture was stirred for 30 min at rt, quenched by the addition of AcOH at 0°C, and extracted with AcOEt. The combined organic extracts were washed with saturated *aqueous* $NaHCO_3$ and brine, then dried over $MgSO_4$. After evaporation of the solvent, the resultant residue was purified by silica gel column chromatography (benzene : AcOEt = 20 : 1) to give **D-4** (33.2 mg, 63% from **17**) as a colorless viscous oil. The optical purity was 99% ee based on HPLC using a chiral column (Daicel Chiralcel OD *n*-hexane : *i*-PrOH = 50 : 1). $[\alpha]^{23}_{D}$ +35° (*c*= 2.14, $CHCl_3$). IR (neat) cm^{-1}: 3430, 1741, 1692. ^{1}H-NMR ($CDCl_3$) δ: 1.15, 1.21, 1.47 (total 9H, each s), 2.34 (3H, s), 2.64 (3H, s), 3.15 (3/5 ×1H, dd, *J* = 15.0, 11.5 Hz), 3.37 (2/5×1H, dd, *J* = 15.0, 11.5 Hz), 3.74 (1H, dd, *J* = 15.0, 4.4 Hz), 3.77 (3H, s), 4.89 (2/5×1H, dd, *J* = 11.5, 4.4 Hz), 4.96 (3/5×1H, dd, *J* = 11.5, 4.4 Hz), 7.11 (1H, dd, *J* = 7.8, 7.8 Hz), 7.2 – 7.28 (2H, m), 7.38 (1H, d, *J* = 7.8 Hz), 7.43 (1H, s), 7.68 - 7.74 (2H, m), 7.93 (1H, d, *J* = 8.0 Hz). MS *m/z*: (FAB) 496 (M^+- ^{tert}Bu + 2, 47), 496 (M^+- ^{tert}Bu, 45), 57 (100),. *Anal*. Calcd for $C_{25}H_{29}N_2O_6SBr$: C, 53.10; H, 5.17; N, 4.95. Found: C, 53.26; H, 5.21; N, 4.95.

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