Preparation of 7-Halo-indoles by Thallation of *N*-Formylindoline and Their Attempted Use for Synthesis of the Right-Hand Segment of Chloropeptin

Yaeko YAMADA,* Shiho ARIMA, Chiharu OKADA, Ai AKIBA, Toshitsugu KAI, and Yoshihiro HARIGAYA

School of Pharmaceutical Sciences, Kitasato University; 5–9–1 Shirokane, Minato-ku, 108–8641 Tokyo, Japan.
Received November 14, 2005; accepted February 28, 2006; published online March 8, 2006

7-Substituted (Cl, Br, I) indoles were synthesized by using thallation of *N*-formylindoline as a key reaction. Two precursor tripeptides for the right-hand segment of chloropeptin were synthesized by using (*R*)-7′-iodo and 7′-bromotryptophans derived from each 7-substituted indole (I, Br) obtained by the above procedure.

Key words 7-substituted indole; thallation; formyl group; tripeptide

In 1994, choropeptin (**1**)[1] was isolated by Matsuzaki *et al.* from *Streptomyces* sp. WK-3490 together with complestatin (**2**) both as inhibitors of gp120-CD4 receptor (concentration causing 50% inhibition (IC_{50}) values of 2.0 and 3.3 mM for **1** and **2**, respectively). The absolute stereostructure of chloropeptin was determined in 1996[2] by combination of acid hydrolysis, molecular dynamics and NMR spectroscopy. It is a bismacrocyclic heptapeptide having a biaryl ether and biphenyl moiety. Because of its unique structure together with interesting biological activity, **1**, **2** and related compounds are an attractive target for synthesis. In 2003, Hoveyda *et al.* first reported an elegant total synthesis of **1**.[3]

We have been interested in the synthesis of **1** and **2** and already reported[4] a synthesis of the left-hand segment of **1** and **2** and also synthesis of linear tripeptides which are key intermediates for the right-hand segment of **2**.[5] Now, we are working to develop a route for the right-hand segment of **1**. We planned the synthesis of **3** as the right-hand segment of **1**. Compound **3** is a 16-membered macrocyclic lactam consisted of (*R*)-4′-hydroxy-3′,5′-dichlorophenylglycine (E-ring), (*R*)-tryptophan (F-ring), (*R*)-4′-hydroxyphenylglycine (D-ring), and the D, E-rings and E, F-rings are each connected by a peptide bond whereas, the D, F rings are connected by a biaryl bond (Fig. 1).

The success of the synthesis of **3** depends upon how to get the (*R*)-7′-substituted tryptophan and how to connect the D, F rings by biaryl coupling. In this paper, at first, an effective route for the 7-substituted indoles by using thallation of *N*-formylindoline as a key reaction and also their conversion to the (*R*)-7′-substituted tryptophan using our method already reported[6] are described. Next, an effective synthesis of two precursor tripeptides for **3** is described by using the obtained (*R*)-7′-bromo and 7′-iodotryptophan.

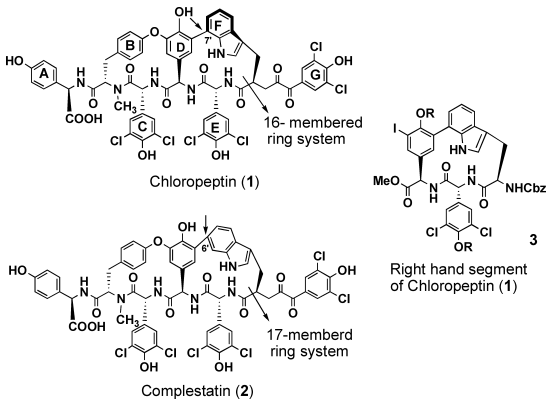

Fig. 1

Results and Discussion

At first, effective synthesis of 7-substituted indoles was performed. The direct introduction of halogen into a tryptophan at the position of 2′ and 5′-C was already reported[7]; however, selective halogenation directly at the position of 7′-C in tryptophan has not been reported. We planned the procedure for (*R*)-7′-substituted tryptophan using 7-substituted indole. Connection of a serine with it should give racemic *N*-acetyl-7′-substituted tryptophan, which should be followed by enzymatic resolution by D-aminoacylase[6] to afford (*R*)-7′-substituted tryptophan.

The synthetic procedure of the 7-substituted indoles is as follows. 7-Substituted indoles were already synthesized by Somei *et al.*[8,9] using *N*-acetyl indoline as a starting material and carrying out the thallation of it as a key reaction, followed by substitution reaction with halogen, removal of the acetyl group, dehydrogenation to afford halogeno indoles. Our procedure for 7-substituted indoles is a modification of the Somei method using *N*-formylindoline.

Considerable synthetic utility of thallium trifluoroacetate (TTFA) in organic chemistry has been reported up to date.[10] Among them, there is an attractive report, in which Taylor *et al.*[11] found that high ortho thallation occurred in substituted aromatic compounds such as benzoic acid, methyl benzoate. Also, they reported their use of the resulting arylthallium ditrifluoroacetates with aqueous KI giving selectively ortho substituted aryl iodide (Fig. 2). Somei *et al.*[8,9] also reported a regioselective synthetic method for 7-halogenoindoles by thallation at the 7-C position with TTFA chelating to an *N*-acetyl carbonyl group (Fig. 2). However, when the carbonyl

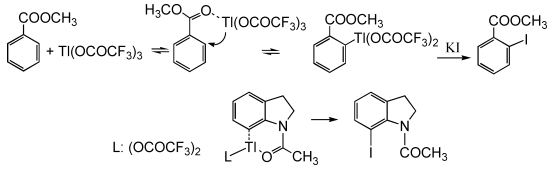

Fig. 2

* To whom correspondence should be addressed. e-mail: yamadaky@violet.plala.or.jp

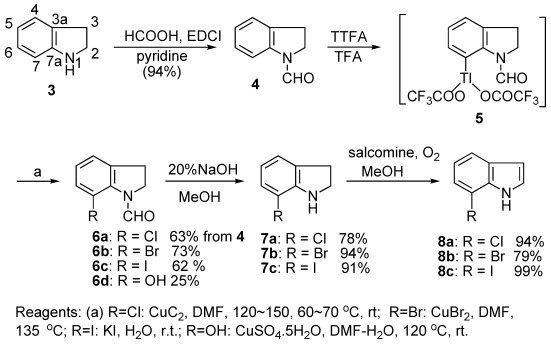

Chart 1. Synthesis of 7-Chloro, Bromo and Iodoindoles

group of *N*-acetyl is used for thallation, strong reaction condition is required for removal of the acetyl group, such as a strong base (40% NaOH).[9] The selection of the functional group is important for effective use of this thallation method as a key reaction. Various functional groups such as COOH, COOMe, CH_2OH were used for regioselective thallation of substituted benzenes in the literature.[11] However, the formyl group, which is expected more easily to be removed, has not been used as a functional group for thallation up to date, so we examined use of the *N*-formyl group to perform selective thallation at 7′-C in indoline to obtain 7-substituted indolines (Chart 1).

Three halogens (I, Br, Cl) and a hydroxyl group were examined to obtain 7-substituted indoles by thallation of *N*-formylindoline and successive synthesis of 7-iodo, bromo, chloro indoles was achieved as shown in Chart 1.

7-Bromoindole (**8b**) was obtained as follows. Indoline (**3**) was treated by HCOOH[12] and EDCI (1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide) in pyridine to give *N*-formyl derivative **4** in 94% yield. Thallation was performed by adding TTFA to the solution of **4** in TFA (trifluoroaceticic acid) to afford thallium complex **5**, which was treated with $CuBr_2$ in DMF at 135 °C to give the bromide **6b** in 73% yield from **4**. Alkaline hydrolysis of **6b** by 20% NaOH at 80 °C for 30 min afforded indoline **7b** in 94% yield. Dehydrogenation of **7b** was carried out under a stream of oxygen gas in the presence of salcomine[9] as a catalyst to give 7-bromoindole (**8b**) in 79% yield (total yield from **3**: 54%). 7-Chloroindole (**8a**) was obtained from **4** in a similar manner except for using $CuCl_2$ at the step of the substitution reaction in 46% total yield from **4**. 7-Iodoindole (**8c**) was also prepared in a similar manner as the above procedure. In this case, KI was used at the step of the substitution reaction using H_2O as a solvent and 10% NaOH was used at the step of the removal of the formyl group with ease. Thus the formyl group was removed more easily than an acetyl group (40% NaOH)[9] and it will be removed with much more mild conditions using a weak base such as $NaHCO_3$ according to the literature.[12] Using the formyl group on thallation will serve to enlarge the utility of its method in compounds having an alkaline-sensitive functional group other than indolines.

Next, synthesis of 7-hydroxyindole was examined according to the procedure in a literature.[13] Thallated complex **5** obtained from **4** in a similar way was treated by $CuSO_4 \cdot 5H_2O$ in DMF–H_2O to afford **6d** in low yield (25%), which resulted in stopping further examination. Thus, three 7-halogenoindoles were obtained using a formyl group as a functional group for thallation.

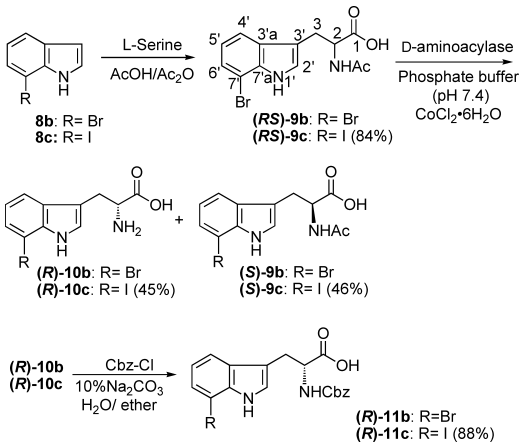

Chart 2. Synthesis of (*R*)-*N*-Cbz-7′-iodotryptophan

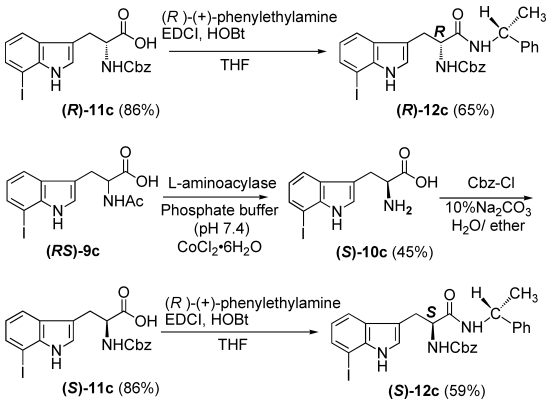

Chart 3. Determination of Optical Purity of (*R*)-7′-Iodotryptophan ((*R*)-**11c**)

Next, preparation of the (*R*)-7′-halogenotryptophan from 7-halogenoindole was carried out. The synthesis of (*R*)-7′-bromotryptophan ((*R*)-**10b**) and its Cbz derivative ((*R*)-**11b**) was already reported by us[6] by using enzymatic resolution by D-aminoacylase and its procedure is shown in Chart 2. In this paper, (*R*)-7′-iodotryptophan was prepared according to our procedure.[6] Addition of L-serine to **8c** in the presence of Ac_2O in AcOH gave racemic *N*-acetyl tryptophan ((*RS*)-**9c**) in 84% yield. This was treated with D-aminoacylase in the presence of $CoCl_2$ as a co-enzyme in phosphate buffer at pH 7.4 to provide (*R*)-7′-iodotryptophan ((*R*)-**10c**, 45%) and (*S*)-**9c** (46%).

The amino group of (*R*)-**10c** was protected by treatment with carbobenzyloxy chloride (Cbz-Cl) and 10% Na_2CO_3 in aqueous ether solution to afford (*R*)-**11c** in 88% yield (Chart 2).

Optical purity of (*R*)-**10c** was determined according to our recent report procedure same as (*R*)-7′-bromotryptophan[6] and (*R*)-6′-iodotryptophan[5] (Chart 3). Compound (*R*)-**11c** was condensed with (*R*)-(+)-phenylethylamine using DECI and hydroxy-benzotriazole (HOBT) to afford amide (*R*)-**12c** as a single product in 65% yield and none of its diastereomer (*S*)-**12c** was obtained. Compound (*S*)-**12c** was synthesized as follows. Enzymatic optical resolution of (*RS*)-**9c** using L-aminoacylase in a similar way to D-aminoacylase afforded (*S*)-**10c** in 45% yield, which was converted to Cbz derivative

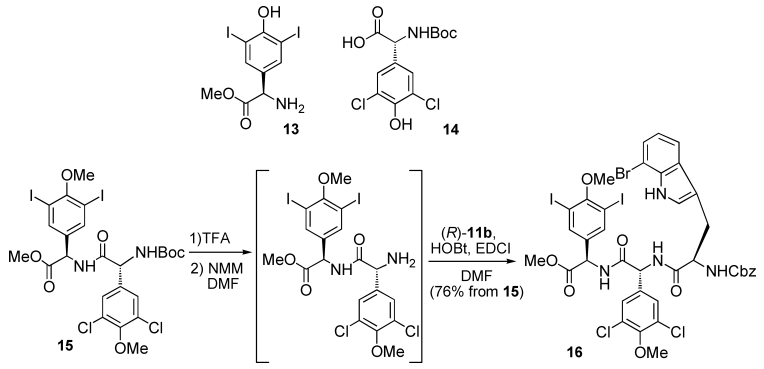

Chart 4. Synthesis of Tripeptide **16**

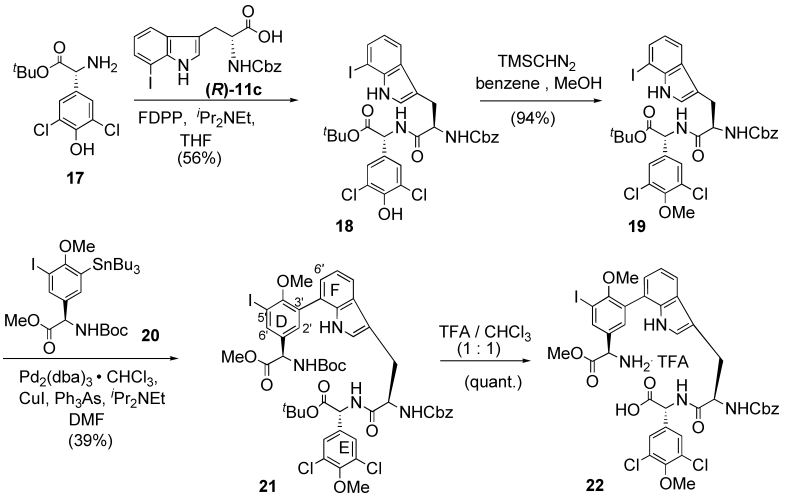

Chart 5. Synthesis of Tripeptide **22**

(*S*)-**11c** in 86% yield, then this was transformed into phenylethylamide (*S*)-**12c** in 59% yield. These results proved enzymatic resolution proceeded enantiomerically to give optically pure amino acid (*R*)-**10c**, which is the same case as that of 6′-iodotryptophan[5], 6′-bromo and 7′-bromotryptophan.[6] Thus a new amino acid (*R*)-**10c** was obtained effectively.

Next, synthesis of two precursors (**16**), (**22**) for the right-hand segment of cholopeptin by using the amino acid (*R*)-**11b** and (*R*)-**11c** was examined. The synthesis of **16** from (*R*)-**11b** was performed as shown in Chart 4. The precursor **16** should be utilized for **3** by biaryl coupling using organic metals as a catalyst. Dipeptide **15** was already obtained by us using compound **13** and **14**.[5] The synthetic method and detailed experimental procedure of compounds **13**, **14** and **15** were already described in our preliminary paper.[5] The Boc group of dipeptide **15** was removed by TFA, followed by neutralization with NMM (*N*-methylmorpholine) to afford a dipeptideamine as an intermediate, which was condensed with (*R*)-**11b** by treatment with EDCI and HOBT (hydroxy benzotriazole) to give tripeptide **16** in 76% total yield from **15**. Intramolecular carbon–carbon couplings between biaryl halide by using an organometalic catalyst of Ni such as $(Ph_3P)_2NiCl_2$ were successively achieved for the synthesis of Vancomycin[14] and a model compound in Kistamycin.[15] Intramolecular cyclization of a precursor **16** using $(Ph_3P)_2NiCl_2$ as a catalyst, Zn as an additive and Ph_3P as a ligand was performed according to the procedure[15] however, cyclic product **3** could not be obtained in spite of alternation of the amount of the catalyst (0.04—1.8 eqivalent), solvent (DMF, THF, HMPA), regretively. More reactive condition should be needed to achieve carbon–carbon coupling between biaryl halide of **16**, because fairly strong steric interaction between the tryptophan moiety and phenylglycine is considered. Next, another precursor **22** for **3** was planned as shown in Chart 5. The precursor **22** should be utilized for macrocyclic lactamization at the last step to provide **3**. The precursor **22** was prepared by using (*R*)-**11c**. The reason for using 7′-iodotryptophan is that aryl iodide is a more strong coupling reagent than aryl bromide in Stille coupling. The synthesis of 3′,5′-dichlorophenylglycine *tert*-butyl ester (**17**) was already reported by us.[5] Connection of **17** to (*R*)-**11c** by using FDPP in the presence of $^iPr_2NEt$ provided dipeptide **18** in 56% yield. The phenol was protected to afford methyl ether **19** by TMSCHN$_2$ in 94% yield. The synthesis of tributylstanann derivative **20**, which is a key compound for Stille coupling, was also already described in our paper.[5] Coupling reaction between **20** and **19** was carried out at the condition of Stille coupling using $Pd_2(dba)_3 \cdot CHCl_3$[5,16,17] as a catalyst, CuI, as an additive, Ph_3As as a ligand, $^iPr_2NEt$ as a base to give biarylic tripeptide **21** in 39% yield, successively. The Boc group of **21** was removed by TFA–$CHCl_3$ solution (1 : 1) to provide a precursor **22** for **3** quantitatively. Detailed examination of the reaction condition should be needed for macrolac-

tamization, which is a subject for future study.

In conclusion, 7-substituted (Cl, Br, I) indoles were synthesized using thallation of *N*-formylindoline as a key reaction according to a modified procedure in the literature. In this paper, the formyl group was newly proved to be a useful functional group for thallation. In addition, two precursor tripeptides for the right-hand segment of chloropeptin were synthesized by using 7-iodo and 7′-bromotryptophans derived from each 7′-substituted indole (I, Br) which were obtained by the above procedure.

Experimental

General Procedures Melting points were taken on a Yanagimoto hot-stage and are uncorrected. Optical rotations were measured on a JASCO model DPI-1000 digital polarimeter. ^{1}H- and ^{13}C-NMR were recorded on Varian VXR-300, Varian MERCURY plus 300 and UNITY-400 spectrometers. All the NMR spectra were taken using $CDCl_3$ as a solvent unless otherwise described. The signals were assigned by ^{1}H–^{1}H COSY, DEPT, HMQC, HMBC experiments. Mass spectra were obtained on JEOL JMS-AX505 H, JEOL JMS-DX300 mass spectrometer (low-resolution mass spectrometry) and JEOL JMS-AX505 HA mass spectrometer (high-resolution mass spectrometry). *Rf* values and preparative TLC were done on Silica gel 60 PF254 (Merck). Flash column chromatography was done using Silica gel 60 (art.1.09385, Merck). 2 M Solution in *n*-hexane (Aldrich) was used for $TMSCHN_2$.

The abbreviations used in NMR data are as follows CHPG: 3′,5′-dichloro-4′-hydroxy-phenylglycine; IHPG: 3′,5′-dichloro-4′-hydroxyphenylglycine; Trp: tryptophan.

***N*-Formylindoline (4)** To a solution of EDCI (16.1 g, 84.0 mmol) in $CHCl_3$ (45 ml) was added formic acid (7.73 ml, 168 mmol) dropwise at 0 °C under argon. After the mixture was stirred for 5 min, a solution of **3** (5.0 g, 42.0 mmol) in pyridine (30 ml) was added dropwise during 30 min, then the temperature was raised to room temperature. After the mixture was stirred for 24 h, it was concentrated *in vacuo* to remove pyridine by azeotropic distillation with benzene (35 ml×4). The residue was dissolved in $CHCl_3$ (500 ml) and the solution was washed with saturated NaCl (100 ml×3), dried over Na_2SO_4, evaporated *in vacuo*. Resulting red-purple residue (7.15 g) was purified by flash column chromatography (hexane/AcOEt=3 : 1→2 : 1) to give **4** (5.81 g, 94%) as red-purple crystals. *Rf*: 0.33 (hexane/AcOEt=2 : 1). mp: 64—65 °C ($CHCl_3$) (lit.[18]): 62—63 °C) IR (KBr) ν_{max} cm^{-1}: 1500, 1600 (arom), 1660 (NCHO). ^{1}H-NMR (300 MHz) δ_H: 3.15, 3.18 (total 2H, t, J=8.5 Hz, 3-H$_2$), 4.05, 4.11 (total 2H, t, J=8.5 Hz, 2-H$_2$), 7.01—7.09, 7.15—7.26 (4H, m, arom-H), 8.51, 8.92 (total 1H, s, CHO). HR-EI-MS *m*/*z*: 147.0684 [M]$^+$, Calcd for C_9H_9ON: 147.0684 [M].

7-Bromo-*N*-formylindoline (6b) To a solution of **4** (1.50 g, 10.2 mmol) in TFA (10 ml) was added a solution of TTFA (13.9 g, 25.5 mmol) in TFA (25 ml) dropwise during 30 min under argon. After the mixture was stirred for 6 h at room temperature, further solution of TTFA (1.42 g, 2.60 mmol) in TFA (5 ml) was added to this mixture and this was stirred for 5 h. The reaction mixture was concentrated *in vacuo* by azeotropic distillation with a solution of benzene (30 ml×3) and 1,2-dichloroethane (30 ml×3) to provide **5** as black tarry oil. The residue was dissolved in DMF (40 ml), then $CuBr_2$ (9.11 g, 40.8 mmol) was added. After the mixture was stirred for 2 h at 135 °C, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in a mixture of $CHCl_3$/MeOH=95 : 5 (500 ml) and saturated NaCl (20 ml), then the mixture was filtered off through celite pad. After the filtrate was partitioned in an organic layer and a water layer, the organic layer was washed with saturated NaCl (50 ml×2). The water layer was extracted with $CHCl_3$ (50 ml). The combined organic layer was dried over Na_2SO_4, concentrated *in vacuo* to give a brown oil (13.7 g). The oil was purified by flash column chromatography (hexane/AcOEt=7 : 1→2 : 1) to give **6b** (1.69 g, 73%) as yellow crystals. *Rf*: 0.27 (hexane/AcOEt=2 : 1). mp: 53—54 °C ($CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 550 (Ar-Br), 1500, 1600 (arom), 1660 (NCHO). ^{1}H-NMR (300 MHz) δ_H: 3.11 (2H, t, J=8.0 Hz, 3-H$_2$), 4.15 (2H, dt, J=1.0, 8.0 Hz, 2-H$_2$), 6.90 (1H, t, J=7.9 Hz, 5-H), 7.19 (1H, dq, J=7.9, 1.2 Hz, 4-H), 7.38 (1H, dd, J=1.2, 7.9 Hz, 6-H), 9.73 (1H, s, CHO). ^{13}C-NMR (100 MHz) δ_C: 160.421 (d, N-CHO), 139.431 (s, 7a-C), 136.320 (s, 3a-C), 132.869 (d, 6-C), 125.048 (d, 5-C), 124.669 (d, 4-C), 105.704 (s, 7-C), 45.639 (t, 2-C), 27.911 (t, 3-C). HR-FAB-MS *m*/*z*: 224.9789 [M]$^+$, Calcd for $C_9H_8ONBr^{79}$: 224.9776 [M].

7-Bromoindoline (7b) To a solution of **6b** (564 mg, 2.50 mmol) in MeOH (19 ml) was added 20% aqueous solution of NaOH (19 ml) and the mixture was stirred for 30 min at 75 °C. After the reaction mixture was cooled to room temperature, it was diluted with water (50 ml), extracted with $CHCl_3$ (50 ml×2). The organic layer was washed with saturated NaCl (50 ml), dried over Na_2SO_4, concentrated *in vacuo* to afford **7b** (465 mg, 94%) as light brown oil. *Rf*: 0.72 (hexane/AcOEt=2 : 1). IR ($CHCl_3$) ν_{max} cm^{-1}: 530 (Ar-Br), 1505, 1610 (arom), 3450 (NH). ^{1}H-NMR (300 MHz) δ_H: 3.14 (2H, t, J=8.5 Hz, 3-H$_2$), 3.61 (2H, t, J=8.5 Hz, 2-H$_2$), 6.56 (1H, t, J=7.5 Hz, 5-H), 7.02 (1H, dt, J=7.5, 1.0 Hz, 4-H), 7.15 (1H, dd, J=1.0, 7.5 Hz, 6-H), 7.40 (1H, s, 1-H). ^{13}C-NMR (100 MHz) δ_C: 150.09 (s, 7a-C), 130.49 (s, 3a-C), 129.78 (d, 6-C), 123.35 (d, 4-C), 119.612 (d, 5-C), 103.21 (s, 7-C), 46,70 (t, 2-C), 30.85 (t, 3-C). HR-EI-MS *m*/*z*: 196.9840 [M]$^+$, Calcd for $C_8H_8NBr^{79}$: 196.9824 [M].

7-Bromoindole (8b) To a solution of **7b** (1.24 g, 6.30 mmol) in MeOH (250 ml) was added salcomine (205 mg, 0.630 mmol). After the solution was stirred in a stream of oxygen gas for 3 h at room temperature, the reaction mixture was concentrated *in vacuo* to provide a black oil (1.12 g), which was purified by flash column chromatography (hexane/AcOEt=20 : 1) to give **8b** (1.69 g, 73%) as light purple crystals *Rf*: 0.56 (hexane/AcOEt=3 : 1). mp: 45—48 °C ($CHCl_3$) (lit.[9]): 42—43 °C). IR (KBr) ν_{max} cm^{-1}: 510, 580 (Ar-Br), 1580, 1620 (arom), 3420 (NH). ^{1}H-NMR (400 MHz) 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, br s, 1-H). ^{13}C-NMR (100 MHz) 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). HR-EI-MS *m*/*z*: 194.9680 [M]$^+$, Calcd for $C_8H_6NBr^{79}$: 194.9684 [M].

7-Chloro-*N*-formylindoline (6a) To a solution of **4** (502 mg, 3.40 mmol) in TFA (16.5 ml) was added a solution of TTFA (3.7 g, 6.80 mmol) in TFA (8.5 ml) dropwise during 20 min under argon. After the mixture was stirred for 24 h at room temperature, the reaction mixture was concentrated *in vacuo* by azeotropic distillation with a solution of benzene (20 ml×3) and 1,2-dichloroethane (20 ml×3) to provide **5** as a black tarry oil. After the residue was dissolved in DMF (15 ml), $CuCl_2$ (1.83 g, 13.6 mmol) was added to the mixture. After the mixture was stirred for 24 h at room temperature, further it was stirred for 30 min at 120—150 °C, 6 h at 60—70 °C, then stirred for 22 h at room temperature under argon. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in a mixture of $CHCl_3$/MeOH=95 : 5 (100 ml) and saturated NaCl (10 ml), filtered off through celite pad. After the filtrate was partitioned in organic and water layers, the organic layer was washed with saturated NaCl (20 ml×3), dried over Na_2SO_4, concentrated *in vacuo.* The resulting residue was purified by flash column chromatography (hexane/AcOEt=5 : 1) to give **6a** (392 mg, 63%) as light yellow crystals. *Rf*: 0.30 (hexane/AcOEt=2 : 1). mp: 116—118 °C ($CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 3.14 (2H, t, J=8.5 Hz, 3-H$_2$), 4.15 (2H, dt, J=1.0, 8.5 Hz, 2-H$_2$), 6.95 (1H, t, J=8.0 Hz, 5-H), 7.12 (1H, dq, J=8.0, 1.0 Hz, 4-H), 7.18 (1H, dd, J=1.0, 8.0 Hz, 6-H), 9.63 (1H, s, CHO). ^{13}C-NMR (100 MHz) δ_C: 27.62 (t, 3-C), 45.54 (t, 2-C), 118.35 (s, 7-C), 124.15 (d, 4-C), 124.55 (d, 5-C), 129.65 (d, 6-C), 135.80 (s, 3a-C), 137.75 (s, 7a-C), 160.53 (s, CHO). HR-FAB-MS *m*/*z*: 182.0364 [M]$^+$, Calcd for $C_9H_9ONCl^{35}$: 182.0373 [M].

7-Chloroindoline (7a) To a solution of **6a** (765 mg, 0.17 mmol) in MeOH (30 ml) was added 20% aqueous solution of NaOH (30 ml) and the solution was stirred for 30 min at 80 °C. After the reaction mixture was cooled to room temperature, it was diluted with water (200 ml), extracted with $CHCl_3$ (200 ml×3). The organic layer was washed with saturated NaCl (100 ml×2), dried over Na_2SO_4, concentrated *in vacuo*. Resulting residue was purified by flash column chromatography (hexane/AcOEt=20 : 1) to afford **7a** (465 mg, 94%) as light peach crystals. *Rf*: 0.59 (hexane/AcOEt=2 : 1). mp 41—42 °C ($CHCl_3$: MeOH=10 : 1). ^{1}H-NMR (300 MHz) δ_H: 3.11 (2H, t, J=8.5 Hz, 3-H$_2$), 3.62 (2H, t, J=8.5 Hz, 2-H$_2$), 6.52 (1H, t, J=7.5 Hz, 5-H), 6.99 (1H, dd, J=7.5, 1.0 Hz, 4-H), 7.01 (1H, dd, J=1.0, 7.5 Hz, 6-H), 7.40 (1H, s, 1-H). HR-EI-MS *m*/*z*: 153.0341 [M]$^+$, Calcd for $C_8H_8NCl^{35}$: 153.0341 [M].

7-Chloroindole (8a) To a solution of **7a** (509 mg, 3.32 mmol) in MeOH (32 ml) was added salcomine (107 mg, 0.33 mmol). After the mixture was stirred in a stream of oxygen gas for 24 h at room temperature, the reaction mixture was concentrated *in vacuo*. Resulting residue was purified by flash column chromatography (hexane/AcOEt=20 : 1) to give **8a** (470 mg, 94%) as light purple crystals *Rf*: 0.63 (hexane/AcOEt=3 : 1). mp: 57—58 °C ($CHCl_3$) (lit.[9]): 59.0—59.5 °C (hexane)). IR (KBr) ν_{max} cm^{-1}: 740, 780 (Ar-Cl), 1480, 1560 (arom), 3400 (NH). ^{1}H-NMR (400 MHz) δ_H: 6.59 (1H, dd, J=2.5, 3.5 Hz, 3-H), 7.04 (1H, t, J=8.0 Hz, 5-H), 7.18, 7.54 (each 1H, dd, J=1.0, 8.0 Hz, 4-H, 6-H), 7.26 (1H, d, J=3.5 Hz, 2-H), 8.54 (1H, br, 1-H).

HR-EI-MS *m/z*: 151.0196 $[M]^+$, Calcd for $C_8H_6NCl^{35}$: 51.0189 [M].

***N*-Formyl-7-iodoindoline (6c)** A mixture of **4** (1.00 g, 6.80 mmol) and TTFA (7.3 g, 13.6 mmol) in TFA (28 ml) was stirred for 24 h under argon at room temperature. The reaction mixture was concentrated *in vacuo* by azeotropic distillation with benzene (10 ml×5) to provide **5** as tarry oil. The residue was dissolved in a solution of KI (9.06 g, 54.4 mmol) in H_2O (32.6 ml) and the mixture was stirred for 1 h at room temperature. The reaction mixture was dissolved in a solution of CH_2Cl_2/MeOH=95 : 5 (600 ml) and filtered off through celite pad. The filtrate was partitioned in organic and water layers. After the water layer was extracted with CH_2Cl_2 (100 ml×4), combined organic layer was washed with 10% $Na_2S_2O_3$ (100 ml×2), saturated NaCl (100 ml), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/AcOEt=5 : 1→3 : 1) to give **6c** (1.56 g, 62%) as light brown crystals. *Rf*: 0.36 (hexane/AcOEt=2 : 1). mp: 99 °C. ^{1}H-NMR (400 MHz) δ_H: 3.08 (2H, t, J=8.0 Hz, 3-H_2), 4.16 (2H, t, J=8.0 Hz, 2-H_2), 6.77 (1H, t, J=7.5 Hz, 5-H), 7.22 (1H, dq, J=7.5, 1.0 Hz, 4-H), 7.64 (1H, dd, J=1.0, 7.5 Hz, 6-H), 9.74 (1H, s, CHO). ^{13}C-NMR (100 MHz) δ_C: 28.39 (t, 3-C), 45.75 (t, 2-C), 76.00 (s, 7-C), 125.46 (d, 4-C), 125.86 (d, 5-C), 136.33 (s, 3a-C), 139.45 (d, 6-C), 142.98 (s, 7a-C), 160.42 (d, CHO). HR-FAB-MS *m/z*: 273.9752 $[M+H]^+$, Calcd for C_9H_9ONI: 273.9729 [M+H].

7-Iodoinoline (7c) To a solution of **6c** (463 mg, 1.7 mmol) in MeOH (14 ml) was added 10% aqueous NaOH (14 ml) and the mixture was stirred for 30 min at room temperature. The reaction mixture was cooled to room temperature, then diluted with H_2O (30 ml). The solution was extracted with $CHCl_3$ (36 ml×2) and the organic layer was washed with NaCl (36.0 ml), dried over Na_2SO_4, concentrated *in vacuo* to afford **7c** (376 mg, 91%) as light yellow oil. *Rf*: 0.60 (hexane/AcOEt=2 : 1). ^{1}H-NMR (300 MHz) δ_H: 3.14 (2H, t, J=8.5 Hz, 3-H_2), 4.16 (2H, t, J=8.0 Hz, 2-H_2), 6.56 (1H, t, J=7.5 Hz, 5-H), 7.02 (1H, dt, J=1.0, 7.5 Hz, 4-H), 7.15 (1H, dd, J=1.0, 7.5 Hz, 6-H), 7.40 (1H, s, 1-H). HR-FAB-MS *m/z*: 244.9702 $[M]^+$, Calcd for C_8H_8NI: 244.9709 [M].

7-Iodoindole (8c) To a solution of **7c** (695 mg, 2.83 mmol) in MeOH (90.4 ml) was added salcomine (93 mg, 0.28 mmol). After the mixture was stirred for 4 h under bubbling oxygen gas, this was concentrated *in vacuo* to provide black oil (1.25 g). Purification of the oil by flash column chromatography (hexane/AcOEt=100 : 1) gave **8c** (682 mg, 99%) as light purple crystals. *Rf*: 0.72 (benzene/acetone=20 : 1). mp: 55—57 °C (hexane) (lit.[9]): 55.0—56.0 °C (hexane)) ^{1}H-NMR (400 MHz) δ_H: 6.70 (1H, dd, J=2.0, 3.0 Hz, 3-H), 6.89 (1H, t, J=7.5 Hz, 5-H), 7.27 (1H, t, J=3.0 Hz, 2-H), 7.55 (1H, d, J=7.5 Hz, 4-H), 7.61 (1H, d, J=7.5 Hz, 6-H), 8.24 (1H, s, 1-H). ^{13}C-NMR (100 MHz) δ_C: 76.35 (s, 7-C), 104.18 (d, 3-C), 120.85 (d, 6-C), 121.52 (d, 5-C), 123.54 (s, 3a-C), 124.33 (d, 2-C), 127.83 (s, 7a-C), 130.62 (d, 4-C). HR-FAB-MS *m/z*: 242.9545 $[M]^+$, Calcd for C_8H_6NI: 242.9545 [M].

***N*-Formyl-7-hydoxyindoline (6d)** To a solution of **4** (502 mg, 3.40 mmol) in TFA (15 ml) was added a solution of TTFA (3.7 g, 6.80 mmol) in TFA (8.0 ml) dropwise during 20 min under argon. After the mixture was stirred for 24 h at room temperature, the reaction mixture was concentrated *in vacuo* by azeotropic distillation with a solution of benzene (20 ml×3) to provide **5** as a black tarry oil. The residue was dissolved in a mixture of DMF–H_2O (1 : 1, 15 ml) and $CuSO_4 \cdot 5H_2O$ (3.40 g, 13.6 mmol) was added to the mixture. After the mixture was stirred for 5 h at 120 °C, then stirred for 5 d at room temperature under argon. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in a mixture of $CHCl_3$/MeOH=95 : 5 (150 ml) and saturated NaCl (20 ml). The mixture was filtered off through celite pad. After the filtrate was partitioned in organic and water layers, the organic layer was washed with saturated NaCl (20 ml×3), dried over Na_2SO_4, concentrated *in vacuo*. Resulting residue was purified by flash column chromatography (silica gel, benzene/acetone=50 : 1→30 : 1) to give **6d** (139 mg, 25%) as light yellow crystals. mp: 133—134 °C. ^{1}H-NMR (300 MHz) δ_H: 2.86, 2.93 (each 2H, t, J=9.0 Hz, 3-H_2), 3.89, 4.06 (each 2H, t, J=9.0 Hz, 2-H_2), 6.70, 6.78 (each 1H, dq, J=7.0, 1.0 Hz, 4-H), 6.94, 7.08 (each 1H, t, J=7.0 Hz, 5-H), 7.02, 7.03 (each 1H, d, J=7.0 Hz, 6-H), 10.05, 11.65 (each 1H, s, CHO), 12.47 (total 2H, s, OH). Each paired signal is attributable to stereoisomers resulted in two kinds of aldehyde groups; one of which makes chelation with the OH group and the other is not chelated and oppositely directed to the OH group. HR-FAB-MS *m/z*: 163.0633 $[M]^+$, Calcd for $C_9H_9O_2N$: 163.0633 [M].

(*R*,*S*)-*N*-Acetyl-7′-iodotryptophan ((*RS*)-9c) To a solution of **8c** (1.15 g, 5.87 mmol) in AcOH (13.8 ml) and Ac_2O (4.6 ml) was added D-serine (1.23 g, 11.7 mmol). After the solution was stirred for 2.5 h at 75 °C under argon, the reaction mixture was diluted with ether (115 ml). The solution was made basic by adding 30% aqueous solution of NaOH dropwise, then ether (173 ml) was added to this solution. The mixture was partitioned into organic and water layers. The water layer was ice-cooled and the organic layer was extracted with 1 N aqueous NaOH (35 ml×2). After the combined alkaline water layer was ice-cooled, $Na_2S_2O_4$ (50 mg) was added to this solution, which was neutralized with 5% HCl, and was concentrated *in vacuo* until precipitates were separated out, then the mixture was allowed to stand for overnight in refrigerator. The precipitates were filtered off to afford (*R*,*S*)-**9c** (1.60 g, 84%) as white crystals. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by preparative TLC ($CHCl_3$/MeOH=30 : 1) gave starting material **8c** (86 mg).

(*R*,*S*)-**9c** *Rf*: 0.7 (butanol/AcOH/H_2O=4 : 1 : 5). mp: 215—220 °C. ^{1}H-NMR (300 MHz, acetone-d_6) δ_H: 1.91 (3H, s, $COCH_3$), 3.18 (1H, dd, J=7.5, 15.0 Hz, 3-Ha), 3.32 (1H, dd, J=5.0, 15.0 Hz, 3-Hb), 4.80 (1H, dt, J=5.0, 7.5 Hz, 2-H), 6.88 (1H, t, J=7.5 Hz, 5′-H), 7.27 (1H, br, NHCO), 7.30 (1H, d, J=2.5 Hz, 2′-H), 7.53 (1H, d, J=7.5 Hz, 6′-H), 7.66 (1H, d, J=7.5 Hz, 4′-H), 10.02 (1H, br s, 1′-H). ^{13}C-NMR (75 MHz, acetone-d_6) δ_C: 22.66 (q, CO<u>C</u>H_3), 28.28 (t, 3-C), 53.62 (d, 2-C), 76.56 (7′-C), 112.83 (s, 3′-C), 119.68 (d, 4′-C), 121.47 (d, 5′-C), 121.55 (d, 2′-C), 125.06 (d, 6′-C), 129.23 (s, 3a′-C), 131.18 (d, 7a′-C), 170.09 (s, <u>C</u>OCH_3), 173.35 (s, 1-C). HR-FAB-MS *m/z*: 373.0055 $[M+H]^+$, Calcd for $C_{13}H_{14}O_3N_2I$: 373.0049 [M+H].

(*R*)-7′-Iodotryptophan ((*R*)-10c) To a solution of (*RS*)-**9c** (1.8 g, 4.84 mmol) and D-aminoacylase (578 g) in phosphate buffer (227 ml, pH 7.4) was added $CoCl_2 \cdot 6H_2O$ (3 mg). After the solution was shaken for 24 h at 37 °C, the reaction mixture was adjusted at pH 5 with 1 N HCl, then filtered off through celite pad. The filtrate was extracted with AcOEt (400 ml×3) and the organic layer was dried over Na_2SO_4, concentrated *in vacuo* to afford (*S*)-**9c** (482 mg, 46%). The water layer was purified by column chromatography (SEPABEADS SP207, H_2O: 1 l→MeOH: 2 l) to provide (*R*)-**10c** (717 mg, 45%) as white powder.

(*R*)-**10c** *Rf*: 0.41 (butanol/AcOH/H_2O=4 : 1 : 5). mp: 175—179 °C. $[\alpha]_D^{20}$ +9.25° (*c*=0.50, MeOH). ^{1}H-NMR (300 MHz, CD_3OD) δ_H: 3.16 (1H, dd, J=8.5, 15.5 Hz, 3-Ha), 3.48 (1H, dd, J=4.5, 15.5 Hz, 3-Hb), 3.85 (1H, dt, J=4.5, 9.0 Hz, 2-H), 6.85 (1H, t, J=7.5 Hz, 5′-H), 7.29 (1H, s, 2′-H), 7.51 (1H, d, J=7.5 Hz, 6′-H), 7.73 (1H, d, J=7.5 Hz, 4′-H). ^{13}C-NMR (75 MHz, CD_3OD) δ_C: 28.55 (t, 3-C), 56.58 (d, 2-C), 76.83 (s, 7′-C), 111.19 (s, 3′-C), 119.72 (d, 4′-C), 121.84 (d, 5′-C), 126.12 (d, 6′-C), 128.99 (s, 3a′-C), 131.90 (d, 6′-C), 131.90 (s, 7a′-C), 174.28 (s, 1-C). HR-FAB-MS *m/z*: 352.9774 $[M+Na]^+$, Calcd for $C_{11}H_{11}O_2N_2INa$: 353.0049 [M+Na].

(*R*)-*N*-Carbobenzyloxy-7′-iodotryptophan ((*R*)-11c) To a solution of (*R*)-**10c** (225 mg, 0.64 mmol) in 10% aqueous Na_2CO_3 (4.0 ml) was added Cbz-Cl (145 mg, 0.85 mmol) in ether (0.2 ml). After the mixture was stirred for 1.25 h at 0 °C, it was acidified with 10% HCl (pH 3). Resulting precipitates were filtered off, washed with water (2 ml×2) and dried to provide (*R*)-**11c** (258.6 mg, 88%) as white crystals. *Rf*: 0.75 (butanol/AcOH/H_2O=4 : 1 : 5). mp: 122—124 °C. $[\alpha]_D^{27}$ −22.13° (*c*=0.47, acetone). ^{1}H-NMR (300 MHz, acetone-d_6) δ_H: 3.22 (1H, d, J=8.5, 15.0 Hz, 3-Ha), 3.38 (1H, dd, J=5.0, 15.0 Hz, 3-Hb), 4.63 (1H, s, 2-H), 5.04 (2H, s, benzyl-CH_2), 6.83 (1H, t, J=7.5 Hz, 5′-H), 7.20—7.46 (8H, m, benzyl-arom-5H, NHCO, 1′-H, 2′-H), 7.53 (1H, d, J=7.5 Hz, 6′-H), 7.68 (1H, d, J=7.5 Hz, 4′-H). HR-FAB-MS *m/z*: 464.0211 $[M]^+$, Calcd for $C_{19}H_{17}O_4N_2I$: 464.0233 [M].

(*S*)-7′-Iodotryptophan ((*S*)-10c) To a solution of (*RS*)-**9c** (300 mg, 0.806 mmol) in phosphate buffer (38 ml, pH 7.4) were added L-aminoacylase (96.3 mg), $CoCl_2 \cdot 6H_2O$ (9.2 mg). After the solution was shaken for 24 h at 37 °C, the reaction mixture was adjusted at pH 5 with 1 N HCl, then filtered off through celite pad. The filtrate was extracted with AcOEt (70 ml×3). The water layer was purified by column chromatography (SEPABEADS SP207, H_2O: 300 ml→MeOH: 600 ml) to provide (*S*)-**10c** (120 mg, 45%) as white powder. *Rf*: 0.41 (butanol/AcOH/H_2O=4 : 1 : 5). mp: 240—242 °C. $[\alpha]_D^{20}$ −7.50° (*c*=0.13, MeOH). HR-FAB-MS *m/z*: 330.9946 $[M+H]^+$, Calcd for $C_{11}H_{12}O_2N_2I$: 353.9944 [M+H]. ^{1}H-NMR data were identical with that of (*R*)-**10c**.

(*S*)-*N*-Carbobenzyloxy-7′-iodotryptophan ((*S*)-11c) To a solution of (*S*)-**10c** (263 mg, 0.795 mmol) in 10% aqueous Na_2CO_3 (5.0 ml) was added Cbz-Cl (35.5 mg, 0.795 mmol) in ether (0.3 ml). After the mixture was stirred for 2 h at 0 °C, it was acidified with 10% HCl. Resulting preciptates were filtered off, washed with water (2 ml×2) and dried to provide (*S*)-**11c** (318.7 mg, 86%) as white crystals. *Rf*: 0.75 (butanol/AcOH/H_2O=4 : 1 : 5). mp: 108—110 °C. $[\alpha]_D^{20}$ +20.63° (*c*=0.40, acetone). HR-FAB-MS *m/z*: 487.0132 $[M+Na]^+$, Calcd for $C_{19}H_{17}O_4N_2INa$: 487.0131 [M+Na]. Data of MS, ^{1}H-NMR data were identical with that of (*R*)-**11c**.

(*R*)-*N*-Carbobenzyloxy-7′-iodotryptpphan (*R*)-(+)-Phenylethylamide ((*R*)-12c) To a solution of (*R*)-**11c** (20 mg, 0.043 mmol) in THF (1 ml) were added (*R*)-(+)-phenylethylamine (5.2 mg, 0.043 mmol), EDCI (8.3 mg, 0.043 mmol), HOBT (5.8 mg, 0.043 mmol). After the mixture was stirred for 2 h at room temperature under argon, the solution was concentrated *in*

vacuo. Resuted residue was purified by preparative TLC ($CHCl_3$: MeOH=5 : 1) to give (*R*)-**12c** (15.7 mg, 65%) as white brown powder. *Rf*: 0.84 ($CHCl_3$: MeOH=5 : 1). mp: 193—195 °C. $[\alpha]_D^{20}$ +10.12° (*c*=0.17, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 1.31 (3H, d, *J*=7.5 Hz, CH(C<u>H</u>$_3$), 3.04 (1H, dd, *J*=8.3, 14.3 Hz, 3-Ha), 3.24 (1H, dd, *J*=5.5, 14.3 Hz, 3-Hb), 4.44 (1H, m, 2-H), 4.97 (quint., *J*=7.5 Hz, C<u>H</u>(CH_3)), 5.09 (2H, s, benzyl-CH_2), 5.54 (1H, br, 2-NHCO), 5.74 (1H, d, *J*=7.5 Hz, 1-NHCO), 6.76 (1H, d, *J*=2.0 Hz, 2′-H), 6.85 (1H, t, *J*=7.5 Hz, 5′-H), 6.93 (2H, m, phenylethyl-arom H), 7.25 (3H, m, phenylethyl-arom H), 7.33 (5H, m, benzyl-arom H), 7.53 (1H, d, *J*=7.5 Hz, 6′-H), 7.62 (1H, br d, *J*=7.5 Hz, 4′-H), 7.85 (1H, br, 1′-H). HR-FAB-MS *m/z*: 568.1093 $[M+H]^+$, Calcd for $C_{27}H_{27}O_3N_3I$: 568.1097 [M+H].

(*S*)-*N*-Carbobenzyloxy-7′-iodotryptpphan (*R*)-(+)-Phenylethylamide ((*S*)-12c) To a solution of (*S*)-**11c** (20 mg, 0.043 mmol) in THF (1 ml) were added (*R*)-(+)-phenylethylamine (5.2 mg, 0.043 mmol), EDCI (8.3 mg, 0.043 mmol), HOBT (5.8 mg, 0.043 mmol). After the mixture was stirred for 2 h at room temperature under argon, the solution was concentrated *in vacuo*. Resuted residue was purified by preparative TLC ($CHCl_3$: MeOH=5 : 1) to give (*S*)-**12c** (14.3 mg, 59%) as white brown powder. *Rf*: 0.82 ($CHCl_3$: MeOH=5 : 1). mp: 185—187 °C. $[\alpha]_D^{20}$ −4.51° (*c*=0.25, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 1.17 (3H, d, *J*=7.5 Hz, CH(C<u>H</u>$_3$), 3.09 (1H, dd, *J*=8.0, 14.0 Hz, 3-Ha), 3.30 (1H, dd, *J*=5.5, 14.0 Hz, 3-Hb), 4.46 (1H, m, 2-H), 4.91 (quint., *J*=7.0 Hz, CH(CH_3)), 5.09 (2H, s, benzyl-CH_2), 5.51 (1H, br, 2-NHCO), 5.75 (1H, d, *J*=7.5 Hz, 1-NHCO), 6.87 (1H, t, *J*=7.5 Hz, 5′-H), 6.98 (1H, d, *J*=2.0 Hz, 2′-H), 7.01 (2H, m, phenylethyl-arom H), 7.22 (3H, m, phenylethyl-arom H), 7.33 (5H, m, benzyl-arom H), 7.56 (1H, d, *J*=7.5 Hz, 6′-H), 7.63 (1H, br d, *J*=7.5 Hz, 4′-H), 8.09 (1H, br, 1′-H). HR-FAB-MS *m/z*: 568.1095 $[M+H]^+$, Calcd for $C_{27}H_{27}O_3N_3I$: 568.1097 [M+H].

(*R*,*R*,*R*)-7′-Bromo-*N*-carbobenzyloxytryptophyl-3′,5′-dichloro-4′-methoxyphenylglycyl-3′,5′-diiodo-4′-methoxyphenylglycine Methyl Ester (16) Dipeptide **15** (101 mg 0.13 mmol) was dissolved in TFA (0.5 ml) at 0 °C and the mixture was allowed to stand 30 min. The reaction mixture was concentrated *in vacuo* to provide TFA salts (108 mg) as light yellow crystals. To a solution of this salt in DMF (0.2 ml) were added NMM (21.3 μl, 0.194 mmol), (*R*)-**11b** (64.5 mg, 0.16 mol) in DMF (0.5 ml), EDCI (37.2 mg, 0.19 mmol) in DMF (0.8 ml), HOBt (21.0 mg, 0.16 mmol), and the mixture was stirred for 7 h at −5 °C under argon. After the reaction mixture was concentrated *in vacuo*, resulting residue was dissolved in AcOEt (30 ml). The solution was washed with 10% citric acid (5 ml×2), saturated $NaHCO_3$ (5 ml×2), saturated NaCl (5 ml×2), dried over Na_2SO_4, concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, $CHCl_3$: MeOH=500 : 1) to afford **16** (105 mg, 76%) as white yellow crystals. *Rf*: 0.52 (benzene/acetone=5 : 1). mp: 178—180 °C ($CHCl_3$). $[\alpha]_D^{25}$ −45.59° (*c*=0.25, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 3.11 (1H, dd, *J*=7.5, 15.0 Hz, Trp 3-Ha), 3.36 (1H, dd, *J*=5.0, 15.0 Hz, Trp 3-Hb), 3.70 (3H, s, COOMe), 3.83 (3H, s, IHPG OMe), 3.88 (3H, s, CHPG OMe), 4.58 (1H, m, Trp 2-H), 5.08, 5.13 (each 1H, d, *J*=12.0 Hz, C<u>H</u>$_2$-Ph), 5.31 (1H, br d, *J*=7.0 Hz IHPG 2-H), 5.38 (1H, d, *J*=6.0 Hz, CHPG 2-H), 5.47 (1H, br d, *J*=7.0 Hz, Trp NHCO), 6.83 (1H, br, IHPG NHCO), 6.93 (1H, br s, Trp 2′-H), 6.94 (1H, br t, *J*=7.0 Hz, Trp 5′-H), 7.13 (1H, br, CHPG NHCO), 7.14 (2H, s, CHPG 2′, 6′-H), 7.30 (1H, d, *J*=7.0 Hz, Trp 6′-H), 7.32 (5H, m, CH_2-<u>Ph</u>), 7.54 (1H, br d, *J*=7.0 Hz, Trp 4′-H), 7.76 (2H, s, IHPG 2′, 6′-H), 8.15 (1H, br s, Trp 1′-H). ^{13}C-NMR (100 MHz) δ_C: 28.47 (t, Trp 3-C), 53.39 (q, COO<u>C</u>H$_3$), 54.83 (d, CHPG 2-C), 55.41 (d, Trp 2-C), 55.94 (d, IHPG 2-C), 60.71 (q, OCH_3×2), 67.33 (t, C<u>H</u>$_2$-Ph), 91.04 (s, IHPG 3′, 5′-C), 105.03 (s, Trp 7′-C), 111.28 (s, Trp 3′-C), 117.92 (d, Trp 4′-C), 121.10 (d, Trp 5′-C), 123.87 (d, Trp 2′-C), 124.86 (d, Trp 6′-C), 127.79 (d, CHPG 2′, 6′-C), 128.17, 128.316 (each d, benzyl-arom-C), 128.57 (s, Trp 3a′-C, benzyl-arom-C), 129.93 (s, CHPG 3′, 5′-C), 133.84 (s, CHPG 1′-C), 134.96 (s, Trp 7a′-C), 135.44 (s, IHPG 1′-C), 135.44 (d, CH_2-<u>Ph</u>), 138.55 (s, IHPG 2′, 6′-C), 152.61 (s, CHPG 4′-C), 156.04 (s, Trp NHCO), 159.41 (s, IHPG 4′-C), 167.68 (s, CHPG 1-C), 169.60 (s, IHPG 1-C), 170.85 (s, Trp 1-C). HR-FAB-MS *m/z*: 1098.8838 $[M+Na]^+$, Calcd for $C_{38}H_{33}O_8N_4Cl^{35}{}_2Br^{79}I_2Na$: 1098.8846 [M+Na].

(*R*,*R*)-7′-Iodo-*N*-carbobenzyloxytryptophyl-3′,5′-dichloro-4′-hydroxyphenylglycine *tert*-Butyl Ester (18) To a mixture of **17** (200 mg, 0.68 mmol) and (*R*)-**11c** (315 mg, 0.68 mmol) in THF (10 ml) were added FDPP (260 mg, 0.41 mmol), DIEA (183 mg, 0.41 mmol). After the solution was stirred for 22 h at room temperature under argon, the reaction mixture was concentrated *in vacuo*. Resulting residue was purified by preparative TLC ($CHCl_3$/MeOH=10 : 1) to afford **18** (286 mg, 56%) as white crystals. *Rf*: 0.77 ($CHCl_3$/MeOH=10 : 1). ^{1}H-NMR (400 MHz) δ_H: 1.34 (9H, s, ^{t}Bu), 3.13 (1H, dd, *J*=7.0, 15.0 Hz, Trp 3-Ha), 3.35 (1H, dd, *J*=5.0, 15.0 Hz, Trp 3-Hb), 4.58 (1H, br, Trp 2-H), 5.11, 5.15 (total 2H, each d, *J*=14.0 Hz, benzyl-CH_2), 5.13 (1H, hidden, CHPG 2-H), 5.38 (1H, d, *J*=7.5 Hz, Trp NHCO), 6.07 (1H, br s, OH), 6.83 (1H, t, *J*=7.5 Hz, Trp 5′-H), 6.90 (1H, br, CHPG NHCO), 7.00 (1H, d, *J*=2.0 Hz, Trp 2′-H), 7.10 (2H, s, CHPG 2′, 6′-H), 7.34 (5H, m, benzyl-arom 5H), 7.54 (1H, d, *J*=7.5 Hz, Trp 4′-H), 7.55 (1H, d, *J*=7.5 Hz, Trp 6′-H), 8.18 (1H, s, Trp 1′-H). HR-FAB-MS *m/z*: 760.0459 $[M+Na]^+$, Calcd for $C_{31}H_{30}O_6N_3Cl^{35}{}_2NaI$: 760.0454 [M+Na].

(*R*,*R*)-7′-Iodo-*N*-carbobenzyloxytryptophyl-3′,5′-dichloro-4′-methoxyphenylglycine *tert*-Butyl Ester (19) To a solution of **18** (45.0 mg, 0.06 mmol) in a mixture of MeOH (0.45 ml) and benzene (0.75 ml) was added a solution of $TMSCHN_2$ (40.5 μl, 0.08 mmol) in benzene (0.75 ml). After the mixture was stirred for 24 h at room temperature under argon, the reaction mixture was concentrated *in vacuo*. Resulting residue was purified by preparative TLC (hexane/AcOEt=2 : 1) to give **19** (52.0 mg, 94%) as light yellow crystals. *Rf*: 0.38 (hexane/AcOEt=2 : 1). $[\alpha]_D^{24}$ −24.0° (*c*=0.5, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 1.35 (9H, s, ^{t}Bu), 3.13 (1H, dd, *J*=7.5, 15.0 Hz, Trp 3-Ha), 3.35 (1H, dd, *J*=5.0, 15.0 Hz, Trp 3-Hb), 3.88 (3H, s, OMe), 4.59 (1H, br q, *J*=6.5 Hz, Trp 2-H), 5.11, 5.15 (each 1H, d, *J*=12.5 Hz, benzyl-CH_2), 5.16 (1H, d, *J*=6.5 Hz, CHPG 2-H), 5.39 (1H, br d, *J*=7.0 Hz, Trp NHCO), 6.85 (1H, t, *J*=7.5 Hz, Trp 5′-H), 6.89 (1H, br d, *J*=6.5 Hz, CHPG NHCO), 7.01 (1H, d, *J*=2.0 Hz, Trp 2′-H), 7.15 (2H, s, CHPG 2′, 6′-H), 7.34 (5H, m, benzyl-arom-5H), 7.54 (1H, d, *J*=7.5 Hz, Trp 4′-H), 7.56 (1H, d, *J*=10.0 Hz, Trp 6′-H), 8.18 (1H, s, Trp 1′-H). ^{13}C-NMR (100 MHz) δ_C: 27.75 (q, C(C<u>H</u>$_3$)$_3$), 28.28 (t, Trp 3-C), 55.47 (d, Trp 2-C), 55.85 (d, CHPG 2-C), 60.71 (q, CHPG OCH_3), 67.22 (t, benzyl-CH_2), 83.67 (s, <u>C</u>(CH_3)), 111.62 (s, Trp 3′-C), 118.72 (d, Trp 4′-C), 121.57 (d, Trp 5′-C), 123.62 (d, Trp 2′-C), 127.39 (d, CHPG 2′, 6′-C), 127.39 (s, Trp 3a′-C), 128.10, 128.24, 128.55 (d, benzyl-arom), 129.47 (s, CHPG 3′, 5′-C), 131.04 (d, Trp 6′-C), 134.31 (s, CHPG 1′-C), 136.02 (s, benzyl-arom 1-C), 136.99 (s, Trp 7a′-C), 152.07 (s, CHPG 4′-C), 155.98 (s, Trp NHCO), 168.05 (s, CHPG 1-C), 170.47 (s, Trp 1-C). HR-FAB-MS *m/z*: 774.0624 $[M+Na]^+$, Calcd for $C_{32}H_{32}O_6N_3Cl^{35}{}_2NaI$: 774.0611 [M+Na].

(*R*,*R*,*R*)-2-(3-{6-[5-(*N*-*tert*-Butoxycarbonyl-2-methoxycarbonylmethlyamino)-3-iodo-2-methoxyphenyl]indol-3-yl}-2-carbobenzyloxyaminopropionylamino)-2-(3,5-dichloro-4-methoxyphenyl) Acetic Acid *tert*-Butyl Ester (21) To a solution of **20** (65 mg, 0.092 mmol), **19** (138 mg, 0.183 mmol) in DMF (6.5 ml) were added $Pd_2(dba)_3CHCl_3$ (19 mg, 0.018 mmol), CuI (7 mg, 0.037 mmol), Ph_3As (22 mg, 0.073 mmol). After the mixture was stirred for 2 h at room temperature under argon, the reaction mixture was diluted with ether (100 ml), then the solution was washed with saturated NH_4Cl (20 ml×2), 10% KF (20 ml×3), dried over Na_2SO_4, concentrated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$) to give **21** (36.7 mg, 39%) as light brown powder. *Rf*: 0.24 ($CHCl_3$). $[\alpha]_D^{24}$ −26.40° (*c*=0.5, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 1.33 (9H, s, ^{t}Bu), 1.44 (9H, s, Boc), 3.22 (1H, dd, *J*=7.5, 15.0 Hz, Trp 3-Ha), 3.27, 3.29 (total 3H, each s, CHPG OCH_3), 3.37 (1H, dd, *J*=5.5, 15.0 Hz, Trp 3-Hb), 3.74 (3H, s, IHPG COOCH_3), 3.86 (3H, s, IHPG OCH_3), 4.61 (1H, br, Trp 2-H), 5.13, 5.15 (total 2H, each d, *J*=12.0 Hz, benzyl-CH_2), 5.24 (1H, dd, *J*=2.5, 7.5 Hz, CHPG 2-H), 5.31 (1H, d, *J*=7.5 Hz, IHPG 2-H), 5.44 (1H, br d, *J*=6.5 Hz, Trp NHCO), 5.67 (1H, br d, *J*=7.5 Hz, IHPG NHCO), 6.92 (1H, d, *J*=2.0 Hz, Trp 2′-H), 7.13, 7.16 (each 1H, s, CHPG 2′, 6′-H), 6.97 (1H, br, CHPG NHCO), 7.23 (1H, t, *J*=7.5 Hz, Trp 5′-H), 7.34 (5H, m, benzyl-arom-H), 7.45 (1H, d, *J*=2.0 Hz, IHPG 6′-H), 7.49 (1H, d, *J*=7.5 Hz, Trp 4′-H), 7.66 (1H, d, *J*=7.5 Hz, Trp 6′-H), 7.83 (1H, d, *J*=2.0 Hz, IHPG 2′-H), 8.53 (1H, s, Trp 1′-H). ^{13}C-NMR (400 MHz) δ_C: 27.71 (q, CHPG C(C<u>H</u>$_3$)$_3$), 27.82 (t, Trp 3-C), 28.28 (q, IHPG C(C<u>H</u>$_3$)$_3$), 52.97 (q, IHPG COO<u>C</u>H$_3$), 55.20, 55.47 (each br s, Trp 2′-C), 55.73, 55.83 (each d, CHPG 2-C), 56.38 (d, IHPG 2-C), 60.45, 60.52 (each q, CHPG OCH_3), 60.68, 60.71 (each q, IHPG OCH_3), 67.18 (t, benzyl CH_2), 80.48 (s, Boc <u>C</u>(CH_3)$_3$), 83.56 (s, ^{t}Bu C(CH_3)$_3$), 93.47 (s, IHPG 5′-C), 109.91 (s, Trp 3a′-C), 111.33 (s, Trp 3′-C), 118.99, 119.16 (d, Trp 4′-C), 120.06, 120.13 (d, Trp 5′-C), 121.57 (s, Trp 7′-C), 123.31, 123.41 (d, Trp 6′-C), 124.02, 123.80 (each d, Trp 2′-C), 127.43, 123.46 (each d, CHPG 2′, 6′-C), 128.10, 128.23, 128.54 (d, benzyl arom-C), 129.46 (s, benzyl 4′-C), 131.51, 131.64 (d, IHPG 6′-H), 132.71 (s, IHPG 3′-C), 133.78, 133.84 (s, CHPG 1′-C), 134.27, 134.37 (s, IHPG 1′-C), 135.12 (s, benzyl arom 1-C), 136.09 (s, Trp 7a′-C), 136.89 (d, IHPG 2′-C), 152.06 (s, CHPG 4′-C), 154.72 (s, IHPG NHCO), 156.03 (s, Trp NHCO), 156.29 (s, IHPG 4′-C), 168.18 (s, CHPG 1-C), 170.68 (s, Trp NHCO), 170.94 (s, IHPG 1-C). HR-FAB-MS *m/z*: 1067.1903 $[M+Na]^+$, Calcd for $C_{47}H_{51}O_{11}N_4Cl^{35}{}_2NaI$: 1067.1874 [M+Na].

(*R*,*R*,*R*)-2-[3-(3-{*N*-[2-(3,5-Dichloro-4-methoxyphenyl)acetylcarboxy]-2-carbobenzyl-oxyaminopropionylamino}indol-7-yl)-5-iodo-4-methoxyphenyl]-2-methoxycarbonylmethylammonium Trifluoroacetate (22) A solution of **21** (5 mg, 0.0048 mmol) in TFA (0.6 ml) was stirred for

3.4 h at 0 °C under argon. The reaction mixture was concentrated *in vacuo* to remove TFA by azeotropic distillation with benzene to afford **22** contitatively. *Rf*: 0.30 ($CHCl_3$: MeOH = 5 : 1). ^{1}H-NMR (400 MHz, CD_3OD) δ_H: 3.13 (1H, dd, *J* = 8.0, 14.5 Hz, Trp 3-Ha). 3.31 (1H, dd, *J* = 6.0, 14.5 Hz, Trp 3-Ha), 3.23 (3H, s, IHPG OMe), 3.83 (3H, COOMe), 3.86 (3H, s, OMe), 4.56 (1H, dd, *J* = 6.5, 7.7 Hz, Trp 2-H), 5.04 (2H, s, benzyl CH_2), 5.23 (1H, s, IHPG 2-H), 5.34 (1H, br s, CHPG 2-H), 7.14 (1H, d, *J* = 3.0 Hz, Trp 2′-H), 7.14 (1H, hidden Trp 5′-H), 7.29 (5H, benzyl arom-H), 7.44 (2H, br s, CHPG 2′, 6′-H), 7.55 (1H, d, *J* = 2.5 Hz, IHPG 6′-H), 7.70 (2H, m, Trp 6′, 4′-H), 7.99 (1H, d, *J* = 2.0 Hz, IHPG 2′-H). ^{13}C-NMR (100 MHz, CD_3OD) δ_C: 54.20 (q, COOMe), 56.25 (d, IHPG 2-C), 57.00 (d, CHPG 2-C), 57.18 (d, Trp 2-C), 60.89 (t, Trp 3-C), 60, 89 (q, IHPG OMe), 61.22 (q, CHPG OMe), 67.71 (t, benzyl CH_2), 94.50 (s, IHPG 5′-C), 111.32 (s, Trp 3′-C, Trp 3a′-C), 120.25 (d, Trp 5′-C), 120.25 (d, Trp 6′, 4′-C), 122.25 (s, Trp 7′-C). 123.62 (d, Trp 5′-C), 125.61 (d, Trp 2′-C), 128.77, 128.85, 129.27, 129.32, 129.39 (each d, benzy-arom-C), 129.46, 129.54 (each d, CHPG 2′, 6′-C), 130.01, 130.41 (each s, CHPG 3′, 5′-C), 130.72 (s, IHPG 3′-C), 133.44 (d, IHPG 6′-C), 135.13 (s, Trp 7a′-C), 135.20 (s, IHPG 1′-C), 136.60 (s, CHPG 1′-C), 138.09 (s, benzyl 1′-C), 139.27 (d, IHPG 2′-C), 153.33 (CHPG 4′-C), 158.33 (s, NHCOO), 160.16 (s, IHPG 4′-C), 169.80 (s, COOMe), 172.31 (s, COOH), 173.95 (s, Trp 1-C). HR-FAB-MS *m*/*z*: 889.0934 $[M+H]^+$, Calcd for $C_{38}H_{56}O_9N_4Cl^{35}{}_2I$: 889.0904 [M+H].

References

1) Matsuzaki K., Ikeda H., Ogino T., Matsumoto A., Woodruff H. B., Tanaka H., Omura S., *J. Antibiot.*, **47**, 1173—1174 (1994).
2) Gouda H., Matsuzaki K., Tanaka H., Hirono S., Omura S., MaCauley J. A., Sprengeler P. A., Furst G. T., Smith A. B., *J. Am. Chem. Soc.*, **118**, 13087—13088 (1996).
3) Deng H., Jung J.-K., Liu T., Kunz K. W., Snapper M. L., Hoveyda H., *J. Am. Chem. Soc.*, **125**, 9032—9034 (2003).
4) Kai T., Kajimoto N., Konda (Yamada) Y., Harigaya Y., Takayanagi H., *Tetrahedron Lett.*, **40**, 6289—6292 (1999).
5) Yamada Y., Akiba A., Arima S., Okada C., Yoshida K., Itou F., Kai T., Satou T., Takeda K., Harigaya Y., *Chem. Pharm. Bull.*, **53**, 1277—1290 (2005).
6) Konda-Yamada Y., Okada C., Yoshida K., Umeda Y., Arima S., Sato N., Kai T., Takayanagi H., Harigaya Y., *Tetrahedron*, **58**, 7851—7861 (2002).
7) Hasegawa M., Yamada K., Nagahama Y., Somei M., *Heterocycles*, **51**, 2815—2821 (1999).
8) Somei M., Saida Y., *Heterocycles*, **23**, 3113—3114 (1983).
9) Somei M., Saida Y., Funamoto T., Ohta T., *Chem. Pharm. Bull.*, **35**, 3146—3154 (1987).
10) Mckillop A., Bromley D., *J. Org. Chem.*, **37**, 88—92 (1972).
11) Taylor E. C., Kienzle F. K., Robey R. L., McKillop A., Hunt J. D., *J. Am. Chem. Soc.*, **93**, 4845—4850 (1971).
12) Waki M., Meienhofer J., *J. Org. Chem.*, **42**, 2019—2020 (1977).
13) Somei M., Iwasa E., Yamada F., *Heterocycles*, **24**, 3065—3069 (1986).
14) Nicolaou K. C., Chu X.-J., Ramanjulu J. M., Nararajam S., Brase S., Rubsam F., Boddy C. N. C., *Angew. Chem. Int. Ed. Engl.*, **36**, 1539—1540 (1997).
15) Beugelmans R., Roussi G., Zamora E. G., Carbonnelle A. C., *Tetrahedron*, **55**, 5089—5112 (1999).
16) Wipf P., Yokokawa F., *Tetrahedron Lett.*, **39**, 2223—2226 (1998).
17) Farina V., Kapadia S., Krishnan B., Wang C., Liebeskind L. S., *J. Org. Chem.*, **59**, 5905—5911 (1994).
18) Shaw J. T., Tyson F. T., *J. Am. Chem. Chem.*, **78**, 2538—2540 (1956).