Synthesis of Linear Tripeptides for Right-Hand Segments of Complestatin

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This paper concerns a synthetic study of the right-hand segment of complestatin, an inhibitor of gp120-CD4 receptor. The effective synthesis of four important precursors for the right-hand segment of complestatin is described. Two of them are the precursor tripeptides for macrolactamization to the right-hand segment of complestatin at the last step and the other two are the precursor tripeptides for ring-closing reaction using Suzuki and Stille coupling, respectively, to the right-hand segment of complestatin at the last step. These compounds and the synthetic procedure will serve for both the synthesis of the right-hand segment and total synthesis of complestatin in the near future. In addition, consideration of the smooth acidic isomerization of complestatin to chloropeptin was carried out by density functional theory (DFT) calculation.

Key words complestatin; precursor; right-hand segment; tripeptide

Complestatin (**1**) was initially isolated from *Streptomyces* sp. WK-3419 in 1980[1,2] as an inhibitor of an alternative pathway of complement. Later, its planar structure was elucidated by Seto *et al.* by ^{1}H-NMR in 1989,[3] and the absolute structure of the amino acid constructing the A, C, E ring was also determined to be each L-form by hydrolysis of the amide bond. In 1994, **1** was isolated by Matsuzaki *et al.* from *Streptomyces* sp. WK-3490 together with chloropeptin **2** both as inhibitors of gp120-CD4 receptor (IC values of 3.3 and 2.0 μM for **1** and **2**, respectively).[4] The absolute stereostructure of chloropeptin **2** was determined in 1996[5] by combination of acid hydrolysis, molecular dynamics and NMR spectroscopy. According to the published paper concerning the planar and absolute stereostructure of complestatin **1** and chloropeptin **2**[3,5] they are bismacrocyclic hepta peptides and they differ only at the position of the phenyl-indole ring junction D, F (Fig. 1).

In compound **1**, the D ring connects at the position of C-6 in the F ring having a 17-membered ring as a right-hand segment, whereas in **2**, at the position of C-7 having a 16-membered ring. As complestatin isomerizes easily to **2** under acidic composition,[6] it is obvious that **1** has the same absolute stereostructure with **2** except the above D, F-ring junction. More recently, three new related compounds with complestatin (isocomplestatin, complestatin A and B were discovered which have potent inhibitory activity against HIV-integrase.[7] Because of their unique structure having a biaryl ether and a biphenyl moiety together and various interesting biological activities, **1**, **2** and their related compounds are an attractive target for total synthesis (Fig. 1).

Consequently, we have been interested in the total synthesis of **1** and **2** and already achieved the left-hand segment[8] of **1** and **2**. In 2003, Hoveyda *et al.* published an elegant total synthesis of **2**.[9] However, total synthesis of **1** has not yet been completed to date. Recently, we have been investigating the synthesis of the right-hand segment of **1** and we are especially interested in a cyclic reaction for the right-hand segment of **1**. In this paper, we report the synthesis of four linear compounds **4**, **5**, **6a**, **6b** as precursors for cyclic reaction to the right-hand segment (**3**) of **1** (Figs. 1, 2).

Segment **3** is a 17-membered macrocyclic lactam where

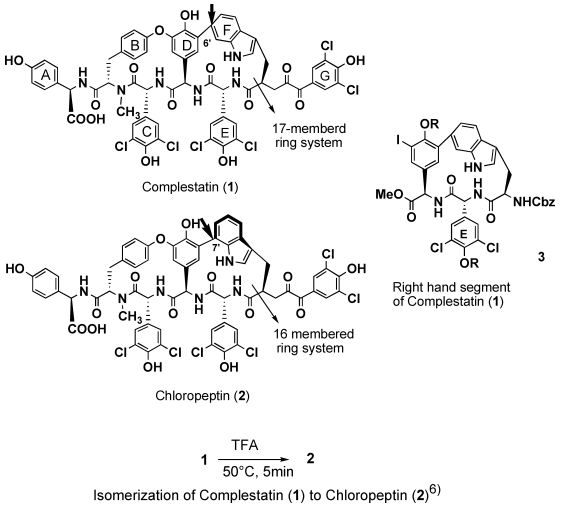

Fig. 1. Isomerization of Complestatin (**1**) to Chloropeptin (**2**)[6]

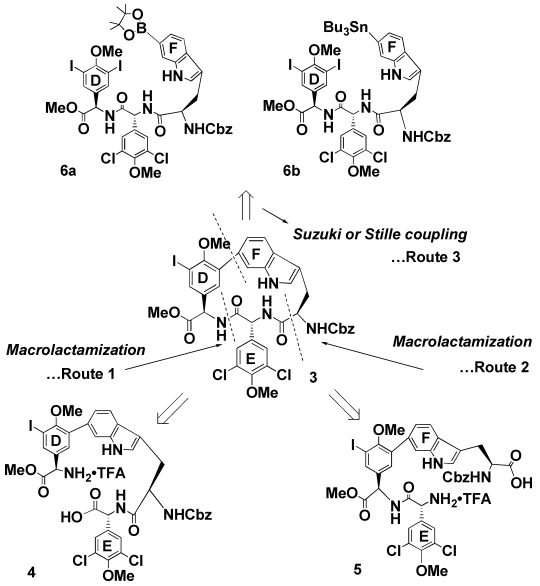

Fig. 2. Structures of Linear Tripeptides **4**, **5**, **6a**, **6b** for **3** and Cyclization Points

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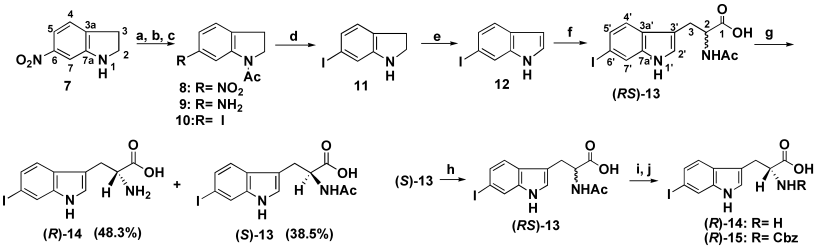


Reagents: (a) Ac_2O, pyridine, 96%; (b) H_2/Pd-C, MeOH, quant.; (c) i. $NaNO_2$, 80%AcOH, ii. KI, 62%; (d) 20%NaOH aq., MeOH, 71%; (e) salcomine, O_2, MeOH, 98%; (f) L-serine, Ac_2O-AcOH, 89%; (g) D-aminoacylase, $CoCl_2 \cdot 6H_2O$, phosphate buffer (pH. 7.4), **(*R*)-14**: 48%, **(*S*)-13**: 39%; (h) 10%NaOH, Ac_2O, 80%; (i) D-aminoacylase, $CoCl_2 \cdot 6H_2O$, phosphate buffer (pH. 7.4), 36%; (j) Cbz-Cl, 10%Na_2CO_3 aq./ether,quant..

Chart 1

the G ring is replaced by a Cbz group, having two amide and one biaryl bond and consists of three (*R*)-amino acids, (*R*)-3′5′-dichloro-4′-hydroxy-phenylglycine (E-ring), (*R*)-tryptophan (F-ring), (*R*)-4-hydroxy-phenylglycine (D-ring).

Three different routes (Routes 1, 2, 3) are considered where ring closure is carried out at the last step for constructing **3** as shown in Fig. 2. Routes 1 and 2 utilize a macrolactamization between ring D and E (Route 1) and ring E and F (Route 2), respectively, at the last step, while another more fascinating route utilizes intramolecular Pd-catalyzed ring closure by Suzuki or Stille coupling between ring D and F at the last step (Route 3). For the precursor to cyclization, compounds **4** and **5** are considered for Route 1 and 2, respectively, and **6a**, **6b** are considered for Route 3. When cyclization is carried out using Suzuki coupling,[10] **6a** is utilized. When using Stille coupling,[11] **6b** is utilized (Fig. 2).

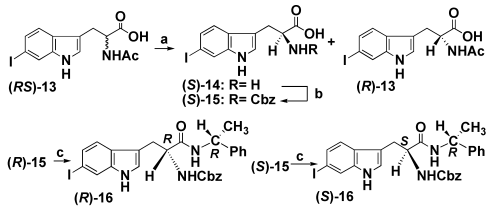
In this paper, successful synthesis of four important precursors (**4**, **5**, **6a**, **6b**) to the right-hand segment of the 17-membered ring system of complestatin (**3**) is described.

Results and Discussion

Synthesis of the Linear Precursor 4 by Route 1 1. Synthesis of (*R*)-*N*-Cbz-6-Iodo-tryptophan: First, the synthesis of **4** by the most conventional and short route (Route 1) was examined. The synthetic strategy for **4** is depicted in Fig. 3. This route is characterized by initially making a peptide bond between the E and F rings, then connecting the D-ring to the dipeptide by Stille coupling.

The success of this route depends upon effective biaryl cross-coupling between dipeptide **24** (E–F ring) and **20** (D-ring) by Stille coupling as well as stereoselective preparation of the (*R*)-tryptophan moiety. The iodide at C′-3 in **20** can be regarded as a left-hand segment and also it is a functional group needed for coupling with the left-hand segment to form **1**.

The desired (*R*)-6-iodo-tryptophan derivative (*R*)-**15** has not been synthesized yet. In this paper, a new efficient route for synthesis of (*R*)-**15** was designed by enzymatic optical resolution using D-aminoacylase which was already developed by us.[12] The iodide at C-6 in the indole ring is to connect with the D-ring. Compound (*R*)-**15** was synthesized from commercially available 6-nitroindole (**7**) (Chart 1). Protection of **7** with an acetyl group by acetic anhydride gave acetate **8** (96%), which was converted to an amino group by catalytic reduction using Pd–C (quant.), then the amino group was transformed into diazonium salts by $NaNO_2$, followed by Griess reaction using KI[13] to afford the iodide **10** in 62% yield. The alkaline hydrolysis of **10** (71%), followed by oxidation under oxygen gas using salcomine[14] gave 6-iodoindole **12** in 98% yield. As the total yield of **12** (46% from **7**) is fairly high and each step is performed with ease, our route for **12** is very convenient and available.



Reagents: (a) L-aminoacylase, $CoCl_2 \cdot 6H_2O$, Phosphate buffer (pH. 7.4), **(*S*)-14**: 38%, **(*R*)-13**: 37%; (b) Cbz-Cl, 10%Na_2CO_3 aq. / ether, 89%; (c) (*R*)-(+)-phenylethylamine, EDCI, HOBT, CH_2Cl_2 / THF=1:1, **(*R*)-16**: 65%, **(*S*)-16**: 55%.

Chart 2. Determination of Optical Purity

Addition of L-serine to **12** in AcOH–Ac_2O[12,15] gave racemic *N*-acetyl-tryptophan (*RS*)-**13** in 89% yield. Enzymatic optical resolution of (*RS*)-**13** by D-aminoacylase in phosphate buffer (pH 7.4) afforded the desired (*R*)-**14** in 48% yield and non-reacted (*S*)-**13** was recovered in 39% yield. The Na salt of (*S*)-**13** was heated with Ac_2O to reproduce racemic mixture (*RS*)-**13**, which was converted to *R*-**14** by enzymatic optical resolution in 36% yield. Thus (*R*)-**14** was totally obtained in 62% yield from (*RS*)-**13** (Chart 1). As our route for preparation of the (*R*)-6-iodo-tryptophan is very convenient and the yield of each step is fairly high, it is available for the synthesis of **1**, kistamycin[16,17] which needs (*R*)-6-halogeno-tryptophan. Conversion of (*R*)-**14** to *N*-carbamate by carbobenzyloxy (Cbz) chloride afforded (*R*)-**15** quantitatively (Chart 1).

Optical purity of (*R*)-**15** was determined as follows (Chart 2). (*R*)-**15** was condensed with (*R*)-(+)-phenylethylamine using EDCI, hydroxybenzotriazole (HOBT) to afford amide (*R*)-**16** and none of its diastereomer ((*S*)-**16**) was obtained. Compound (*S*)-**16** was obtained as follows. Enzymatic optical resolution of (*RS*)-**13** using L-aminoacylase in a similar way to D-aminoacylase provided (*S*)-**14**, which was converted to Cbz derivative (*S*)-**15**, then this was transformed into phenylethylamide (*S*)-**16** similarly. These results proved enzymatic resolution proceeded enantiomerically to give optically pure amino acid (*R*)-**14**.

2. Synthesis of the D and E-Ring Moiety (**20**, **22**): Commercially available compound **17** was treated with iodine monochloride in AcOH[18] to provide diiodide **18** in 87% yield. Protection of **18** with BOC-ON in the presence of NEt_3

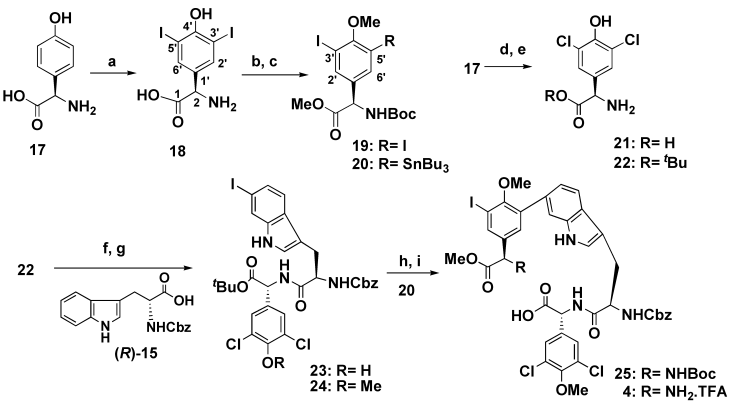
(quant.), followed by methylation with two equivalents of $TMSCHN_2$ affording the methyl ester **19** in 96% yield. Stille coupling of **19** with $(Bu_3Sn)_2$ gave **20** (28%) using $(o\text{-tolyl}_3P)_2PdCl_2$ in the presence of $^iPr_2NEt$ which was used to stabilize the resulting Bu_3Sn group and to prompt the transmetalation. Addition of $^iPr_2NEt$ shortened the reaction time from 6 h to 2 h. The low yield of this reaction is caused by instability of the Bu_3Sn group in acidic condition for purification by silica gel and the by-products produced by intermolecular carbon–carbon bond formation.

Dichlorination of **17** using surfuryl chloride in 1 M HCl in AcOH[19] gave **21** (77%), which was protected by isobutylene gas in H_2SO_4-dioxane under pressured condition to provide *tert*-butyl ester **22** in 60% yield (Chart 3).

3. Synthesis of the Precursor Tripeptide **4**: Condensation of **22** and (*R*)-**15** using FDPP in the presence of $^iPr_2NEt$ provided dipeptide **23** (64%), which was converted to methyl ether **24** by $TMSCHN_2$, quantitatively. Components **24** and **20** were connected *via* Stille coupling[20] using $Pd_2(dba)_3\cdot CHCl_3$ as a catalyst, Ph_3As as a ligand, CuI as an additive[21] and $^iPr_2NEt$ as a base in DMF to provide tripeptide **25** in 35% yield. Optimization of the reaction conditions of this reaction was carried out. Among the solvents DMF, dioxane, NMP, the yield was the best in DMF. When the reaction was performed in the absence of $^iPr_2NEt$, the reaction rate was retarded to 24 h. The role of $^iPr_2NEt$ is to raise the electron-donating property in Pd, without stopping the palladium cycle.[8] When the ligand was altered to $^tBu_3P$[22,23] in the presence of CsF, collidine, the same yield (35%) was obtained, but the reaction rate was retarded to 18 h. In the case of $^tBu_3P$, when using the dioxane, NMP as a solvent, the yield was also very low. It is reported that Ph_3As accelerates the rate of transmetalation more than PPh_3 ($Ph_3As : Ph_3P = 100 : 1$).[21]

^{t}Bu and Boc groups were deprotected at the same time by treatment with TFA to give TFA salt **4** quantitatively. The yield of each step is fairly good except in the Stille couplings (Chart 3).

Synthesis of the Linear Precursor 5 by Route 2 Route 2 is characterized with initially carrying out Stille coupling between the F and D ring moieties and then the E ring moiety is connected by peptide linkage (Fig. 3). One important key reaction in this route is to carry out Stille coupling efficiently and another is how to obtain racemization-prone electron-deficient dichlorinated amino acid. For the Stille coupling, the same optimal reaction conditions as developed in



Reagents:(a) ICl, AcOH, 87%; (b) Boc-ON, NEt_3, dioxane, H_2O ; 2 eq. $TMSCHN_2$, MeOH, benzene 96% for two steps; (c) $(o\text{-tolyl}_3P)_2PdCl_2$, $(Bu_3Sn)_2$, $^iPr_2NEt1$, CH_3CN, 28%; (d) SO_2Cl_2, 1M HCl in AcOH, 77%;. (e) isobutylene, dioxane, H_2SO_4, $NaHCO_3$, 60%; (f) **(*R*)-15**, FDPP, $^iPr_2NEt$, THF, 64%; (g) $TMSCHN_2$, benzene, MeOH, quant.; (h) **20**, $Pd_2(dba).CHCl_3$, CuI, Ph_3As, $^iPr_2NEt$, DMF, 35%; (i) TFA/$CHCl_3$ (1:1), 97%.

Chart 3

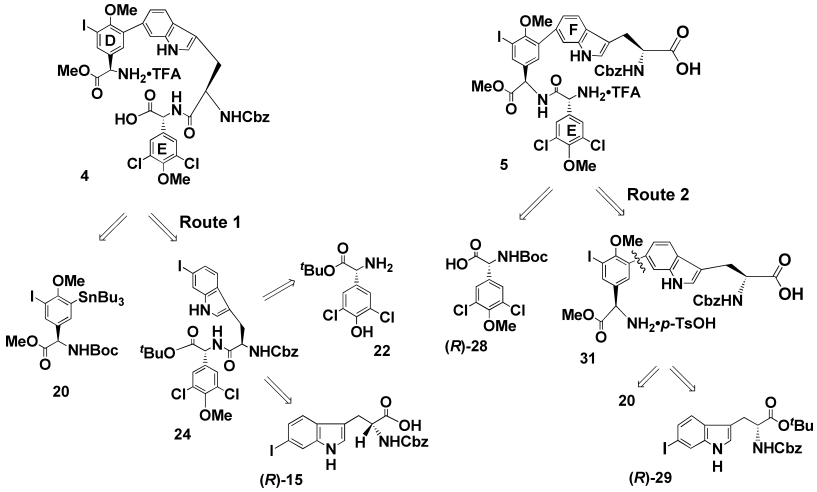
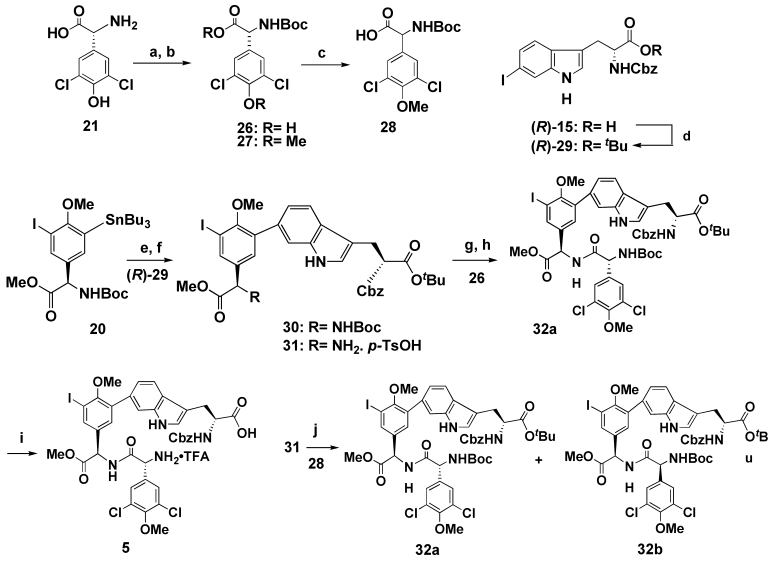


Fig. 3. Synthetic Strategy of **4**, **5** for **3** by Route 1, 2



Reagents: (a) Boc-ON, NEt_3, dioxane/H_2O, quant.; (b) 2 eq. $TMSCHN_2$, benzene/ MeOH, 86%; (c) LiOH, MeOH/THF/H_2O, 94%; (d) ^tBuBr, BTEAC, K_2CO_3, DMAC, 82%; (e) **(*R*)-29**, $Pd_2(dba)_3.CHCl_3$, CuI, Ph_3As, $^iPr_2NEt$, DMF, 41%; (f) *p*-TsOH, EtOH, 97%; (g) **26**, HATU, collidine, CH_2Cl_2/THF, 25%; (h) $TMSCHN_2$, MeOH/benzene, 34%; (i) TFA/CH_2Cl_2, 93%; (j) **28**, EDCI, HOBT, NMM, CH_2Cl_2/THF, **32a**: 34%, **32b**: 29%

Chart 4

Route 1 can be applied. The desired chlorinated amino acid ((*R*)-**28**) could not be obtained in optically pure form, regretfully, according to our process, which is a subject for future study.

The amino acids **28** and (*R*)-**29** were synthesized as follows (Chart 4). Protection of **21** using Boc-ON (**26**: quant.), followed by methylation with $TMSCHN_2$ to give **27** (86%), which was converted to acid **28**[24,25] by alkaline hydrolysis using LiOH in 94% yield. The optical purity was determined as follows. Compound **28** was condensed with (*R*)-(+)-phenylethylamine to give (*R*) and (*S*)-(*R*)-(+)-phenylethylamide of **28** ($R:S=5:4$) as a diastereomeric mixture. From the values of the optical rotation in each compound ($[\alpha]_D^{20}$ **21**: −126.73°; **26**: −121.91°; **27**: −130.06°; **28**: −15.82°), it seems racemization occurred at the step of alkaline hydrolysis resulting from the enolization labile **28**.

Tryptophan derivative (*R*)-**15** was converted to *tert*-butyl ester (*R*)-**29** by treatment with excess *tert*-butylbromide,[26] K_2CO_3 in the presence of benzyltriethylammonium chloride (BTEAC) in dimethylacetoamide (DMAC) in 82% yield.

The precursor **5** was synthesized by two processes, which are differentiated by using chiral hydroxyphenylglycine **26** and racemic hydroxyphenylglycine methyl ether **28** (Chart 4). Stille coupling between **20** and (*R*)-**29** was fairly successfully performed under the same conditions in Route 1 using $Pd_2(dba)_3\cdot CHCl_3$, CuI, Ph_3As, $^iPr_2NEt$ in DMF to provide biaryl compound **30** in 41% yield. Selective removal of the Boc group by *p*-TsOH gave the salt **31** (97%), which was condensed with chiral **26** using HATU[27] and collidine to provide a chiral phenolic tripeptide (25%), HATU was used because of its higher reactivity than that of EDCI. The reason for low producibility of this compound is considered to be the side reaction resulted in an unprotected phenol group. Conversion of the phenol to methyl ether by $TMSCHN_2$ gave **32a** in 34% yield.

Next, another procedure for **32a** was carried out. Condensation of **31** and racemic **28** using EDCI, HOBT, *N*-methylmorpholine (NMM) afforded a diastereomeric mixture of **32a** and **32b** in 34%, 29% yield, respectively, which results in using racemic mixture **28**. The Boc and *tert*-butyl groups of the desired **32a** were removed at the same time by TFA to afford the precursor **5** in 93% yield. The development of a new procedure for optically pure compound (*R*)-**28** is necessary. If such is developed, this route is superior to that using **26** because of its labile phenol group (Chart 4).

Detailed examination of reaction conditions should be needed for macrolactamization of **4** and **5** to gain right-hand segment **3**.

Synthesis of Linear Precursor 6a by Route 3-1 and Route 3-2 Initially, synthesis of **6a** was carried out according to the strategy in Route 3-1 as shown in Fig. 4. This route is characterized by using dipeptide **2** already obtained by Route 1. Conversion of **24** to boronic ester **33a**, followed by peptide formation with the D-ring moiety **35** should give **6a**. The key reaction of this route is an effective Suzuki–Miyaura coupling[29] of **24** for **33a**. A cyclic reaction of **6a** in the last step would give **3** by Suzuki coupling.[11,28]

The reason for using Suzuki coupling is the stability of the boronic ester against purification with silica gel. Recently, a successful synthesis of a model system of the 17-membered right-hand segment of **1** and **2** was reported[30] by using Suzuki coupling, which encouraged us in our work.

A precursor **6a** was synthesized as follows (Chart 5). Suzuki–Miyaura reaction of dipeptide **24** using bis(pinacolate)diboron in the presence of $PdCl_2$(dppf), KOAc in DMSO at 80 °C yielded a diasteromeric mixture of **33a** and **33b** (total yield: 64%, **33a**:**33b**=1.5:1). It seems the alkaline condition at high temperature caused racemization at the chlorinated phenylglycine moiety. Quantitative separation of each compound in this step was fairly difficult, so isolation of diastereomers was carried out at the last step. The *tert*-butyl group of the diastereomeric mixture (**33**) was removed by

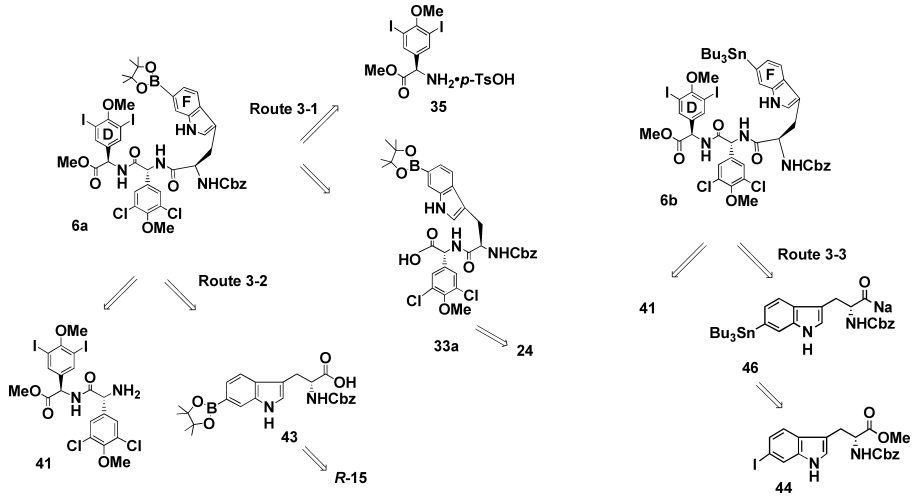
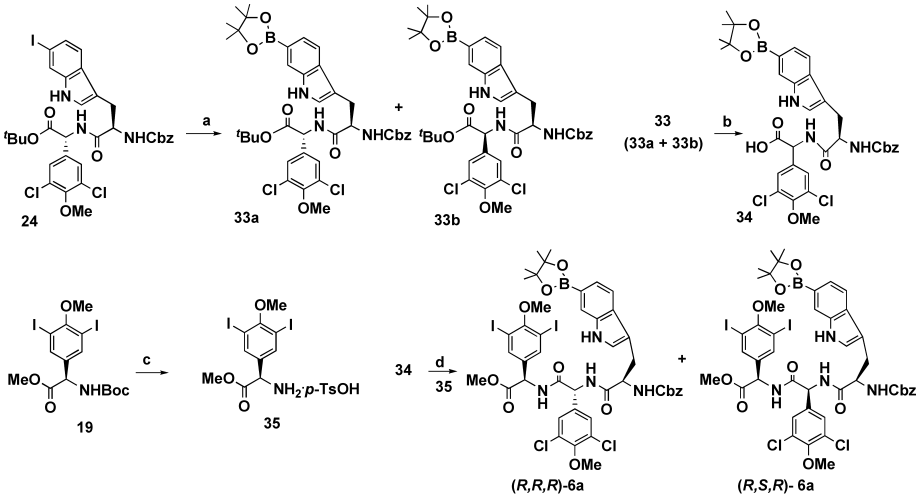


Fig. 4. Synthetic Strategy of **6a**, **6b** for **3** by Route 3



Reagent: (a) bis(pinacolate)diboron, $PdCl_2$(dppf), KOAc, DMSO, total yield: 64%,**33a**:**33b**=1.5:1; (b) TFA/CH_2Cl_2, quant.; (c) *p*-TsOH, ether, EtOH, quant.; (d) **35**, NMM, EDCI, HOBT, CH_2Cl_2/THF, (***R,R,R***)-**6a**:29%, (***R,S,R***)- **6a**: 20%

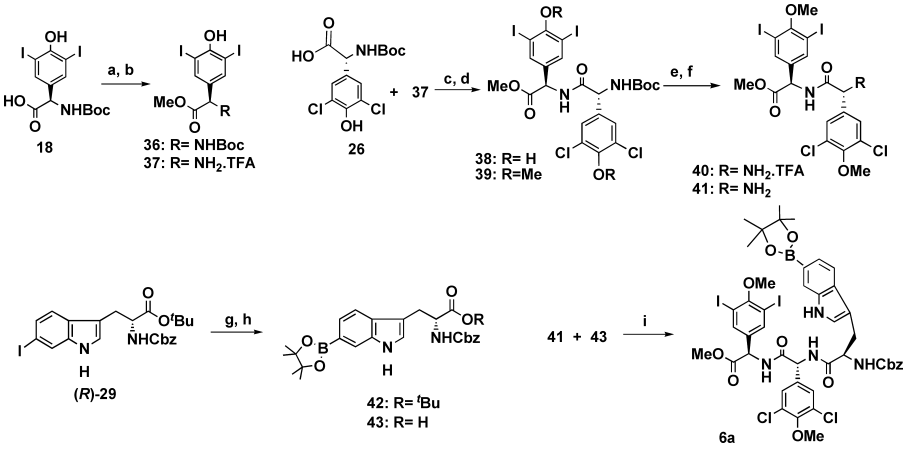
Chart 5

TFA-CH_2Cl_2 at 0 °C to room temperature to provide acid **34** quantitatively. The Boc group of **19** was removed by *p*-TsOH to give the salt **35**, quantitatively. After neutralization of the salt **35** by NMM, the resulted amine was condensed with acid **34** using EDCI to give a diasteromeric isomer (*R*,*R*,*R*)-**6a** (29%) and (*R*,*R*,*S*)-**6a** (20%). Partial elimination of the boronic ester group in the course of the removal of the *t*-butyl ester in TFA occurred and this caused the low producibility of **6a** (Chart 5).

As described above, racemization in the step of the boronic esterification of **24** is a drawback of this process. Then another route for **6a** (Route 3-2) was considered as shown in Fig. 4. This route is characterized by initially building up the dipeptide **41**, then peptide formation with the F-ring to give tripeptide **6a**. The key reaction of this route is effective boronic esterification of tryptophan (*R*)-**15** by Suzuki–Miyaura coupling. The merit of this route is that the tryptophan moiety is presumed not to be a racemization-prone compound.

The dipeptide **41** was efficiently synthesized as follows (Chart 6). Esterification of **18** by 1 equivalent $TMSCHN_2$ (**36**, 85%), then removal of the Boc group using TFA gave TFA salt **37** (quant.), which was neutralized with NMM, followed by condensation with **26** using EDCI, HOBT gave dipeptide **38** (77%), which was converted to dimethyl ether **39** (82%) by $TMSCHN_2$. Removal of the Boc group by treatment with TFA afforded the salt **40**, which was neutralized with $NaHCO_3$ to provide an amine **41** quantitatively from **39**.

Transformation of (*R*)-**29** by Suzuki–Miyaura coupling using bis(pinacolate)diboron, Pd(dppf)Cl_2 at 75 °C in dioxane for 2 h afforded **42** in 37% yield and the starting material was recovered (32%). Further extension of the reaction time and increased amount of the catalyst resulted in only an increase of the side product caused by intermolecular coupling reaction. The removal of the *t*-butyl ester group by TFA at 0 °C gave the acid **43** (quant.). Condensation of **41** with **43** by HATU in the presence of collidine afforded tripeptide **6a** as a single product in 32% yield. This result proved racemization did not occur in the course of boronic esterification of (*R*)-**29** as we expected. The lower yield is mainly attributed to partial removal of the boronic ester group by TFA in the course of the removal of the *t*-butyl group of **42**. Further op-



Reagents: (a) 1 eq. $TMSCHN_2$, MeOH, benzene, 85%; (b) TFA/THF, quant.; (c) i. NMM, THF/CH_2Cl_2, ii. EDCI, HOBt, 77%; (d) $TMSCHN_2$, MeOH/benzene, 82%; (e) TFA/CH_2Cl_2, quant.; (f) $NaHCO_3$, quant.;(g)bis(pinacolate)diboron, $Pd(dppf)Cl_2$, KOAc, dioxane, 37%; (h) TFA/CH_2Cl_2, quant.; (i) HATU, collidine, THF/CH_2Cl_2, 32%

Chart 6

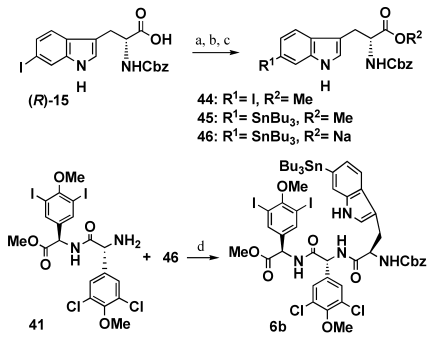
timization of this reaction conditions will be required (Chart 6).

Synthesis of the Linear Precursor 6b by Route 3-3 The strategy of Route 3-3 is shown in Fig. 4. This route is characterized by the coupling between the dipeptide **41** and F ring moiety **46** by peptide bond formation to give tripeptide **6b**. Hoveyda *et al.*[9] succeeded in the total synthesis of coupling at the ring-closing reaction in the last step though they used a trimethylstanann group. Stille coupling can be performed under neutral reaction conditions, which should prevent racemization of dichlorohydroxyphenylglycine. Furthermore, Fu *et al.* discovered[31] $Pd/P(tBu)_3$, which is a mild, highly reactive and general catalyst for Stille coupling. This catalyst would be effective for macrocyclic carbon–carbon coupling, which is assumed not to be easy in a sterically hindered compound. Tripeptide **6b** would be expected to cyclize in a similar manner.[9,31] The key reaction in this route for **6b** is effective synthesis of tributyl stannyl derivative **46**.

Synthesis of **46** is performed as follows (Chart 7). Methylation of (*R*)-**15** by $TMSCHN_2$ afforded methyl ester **44** (75%), which was converted to **45** by Suzuki–Miyaura coupling using $(Bu_3Sn)_2$ in the presence of $(o\text{-tolyl}_3P)PdCl_2$, diisopropylethylamine affording **45** (45%), followed by alkaline hydrolysis according to the procedure as described[9] in the literature to provide sodium salt **46** in 99% yield, though partial removal of the Bu_3Sn group (25%) occurred at the same time, which was confirmed by ^{1}H-NMR. The salt **46** was used as a mixture because purification was impossible. Condensation of **46** with dipeptide **41** by treatment with HATU and collidine gave tripeptide **6b** in 54% yield. Optimization of the reaction conditions in the hydrolysis procedure of **45** will increase the total yield in this route (Chart 7).

Examination to find the best condition to achieve cyclic reaction using **6a** and **6b** should be needed.

Consideration on Acidic Transformation from Complestatin (1) to Chloropeptin (2) by DFT (Density Functional Theory) Calculation Jayasuriya *et al.*[6] reported that **1** can be completely transformed into **2** by TFA at 50 °C and reported its reaction mechanism. Also, a model compound of the right-hand segment of **1** easily transforms into that of **2** by TFA according to the literature.[30]



Reagents: (a) $TMSCHN_2$,benzene, MeOH, 75%; (b) $(o\text{-tolyl}_3P)PdCl_2$, $(Bu_3Sn)_2$, ^{i}PrNEt, CH_3CN, 45%; (c) NaOH, MeOH, 99%; (d) HATU, collidine, THF/CH_2Cl_2, 54%

Chart 7

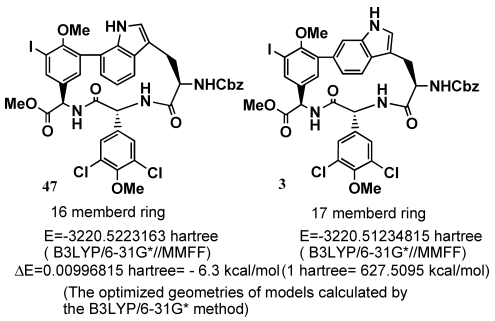


Fig. 5. Stability of the Right-Hand Segment of Complestatin **1** (**3**) and Chloropeptin **2** (**47**) Optimized by DFT Calculation

Matsuzaki *et al.* found[32] in his thesis that **1** and **2** were converted to **2** and **1**, respectively, in the solution of MeOH-TFA by monitoring HPLC and that the rate of the conversion from **1** to **2** was much faster than that of **2** to **1**, from which they assumed **2** is more stabilized than **1**. We consider from the above result that interconversion should occur between **1** and **2**, and thermodynamic equilibrium proceeds to produce **2** ultimately.

To substantiate the above result, we compared the stability of the right-hand segment of **1** and **2** by DFT calculation. Two molecules **3** and **47** were chosen as the right-hand segment of **1** and **2**. As shown in Fig. 5, the reference of the ab-

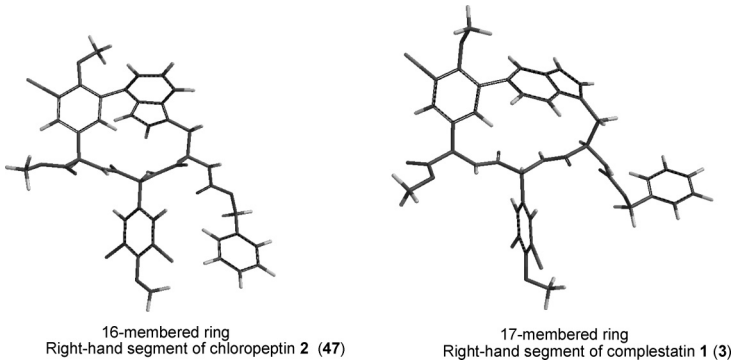


Fig. 6. Conformation of the Right-Hand Segment of **1** (**3**) and **2** (**47**)

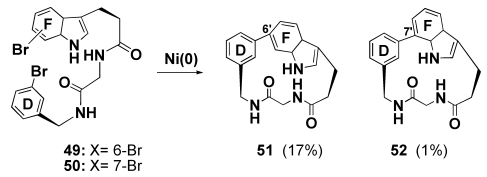


Fig. 7. Roussi's Data for 16- and 17-Membered Macrolactams[33)]

solute value (ΔE) between the 16-membered **47** and the 17-membered **3** in each most stable conformation is −6.3 kcal/mol, that is, **47** is more stable than **3**.

Each most stabilized stereostructure is shown in Fig. 6. The indole ring in 17-membered ring **3** is bent to make a strain in the whole ring whereas, in 16-membered ring **47**, the indole ring is not bent as seen in the figures. The stain of the indole ring should result in instability of **3** and also easy transformation from **1** to **2**.

We have been interested in knowing which compounds (**1**, **2**) cyclize more easily at the step of the cyclization for the right-hand segment. Roussi reported[33)] the result of the cyclic reaction of **49**, **50** under same reaction condition using $Ni(Ph_3P)_2Cl_2$ to afford simplified 17- and 16-membered ring system **51**, **52**, respectively, in each 17%, 1% yield (Fig. 7). This showed cyclization for the 16-membered ring is extremely difficult compared with that for the 17-membered ring. Both this result and our study for stability calculation indicate that the ease of cyclic reaction to macrolactam is independent of the stability of the resulting macrolactam.

A closed investigation to find reaction condition for cyclization of **4**, **5**, **6a**, and **6b** to **3** is necessary in future.

Conclusion

In conclusion, a facile route for the synthesis of the four important precursors, tripeptides **4**, **5**, **6a** and **6b**, for cyclization to the right-hand segment (**3**) of complestatin was achieved. The precursors **4** and **5** should be utilized for macrolactamization to **3** at the last step and precursors **6a** and **6b** should be utilized for ring-closing reaction to **3** each using Suzuki and Stille coupling reactions at the last step, respectively. Also, a facile route for the (*R*)-6-iodo-tryptophan which is a key compound for the synthesis of the above precursors was developed. These compounds and the synthetic procedure described in this paper will serve for the synthesis of the right-hand segment of complestatin in the near future.

In addition, the stability of **1** and **2** optimized was calculated by molecular dynamics calculation method.

Experimental

General Procedure Melting points were taken on a Yanagimoto hot-stage and are uncorrected. Optical rotations were measured on a JASCO model DPI-1000 digital polarimeter. NMR were recorded on a Varian MERCURY plus 300, UNITY-400 spectrometers. All the NMR spectra were taken using $CDCl_3$ as a solvent unless otherwise described. The signals were assigned by ^1H–^1H COSY, DEPT, HMQC, HMBC experiments. Mass spectra were obtained on a 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). 2M Solution in *n*-hexane (Aldrich) was used for $TMSCHN_2$.

Theoretical Calculations DFT calculation was performed using Spartan '04 (for Windows).[34)] The structures were drawn at the entry-level of input and minimized. Equilibrium geometry was obtained at B3LYP level of DFT for each molecule at the ground state form with a 6–31G* basis set.[35—37)]

***N*-Acetyl-6-nitroindoline (8)** To a solution of **7** (5.0 g, 30.5 mmol) in Ac_2O (25 ml) was added pyridine (1.25 ml). After the solution was stirred for 1.4 h at room temperature, precipitated crystals were filtered off to afford **8** (6.0 g, 96%) as yellow crystals. *Rf*: 0.11 (hexane/AcOEt=1 : 1). mp: 152—156 °C. ^1H-NMR (300 MHz) δ_H: 2.24 (3H, s, $COCH_3$), 3.27 (2H, t, J=8.5 Hz, 3-H_2), 4.16 (2H, t, J=8.5 Hz, 2-H_2), 7.23 (1H, d, J=8.0 Hz, 4-H), 7.82 (1H, dd, J=2.0, 8.0 Hz, 5-H), 8.88 (1H, d, J=2.0 Hz, 7-H). ^{13}C-NMR (75 MHz) δ_C: 24.11 (q, CO<u>C</u>H_3), 27.98 (t, 3-C), 49.17 (t, 2-C), 111.42 (d, 7-C), 118.92 (d, 5-C), 124.32 (d, 4-C), 138.43 (s, 3a-C), 143.59 (s, 7a-C), 147.62 (s, 6-C), 168.96 (s, <u>C</u>OCH_3). HR-FAB-MS *m/z*: 207.0771 $[M+H]^+$, Calcd for $C_{10}H_{11}N_2O_3$: 207.0722 [M+H].

***N*-Acetyl-6-aminoindoline (9)** To a solution of **8** (5.5 g, 26.7 mmol) in MeOH (400 ml) was added 10% Pd–C (550 mg) and the mixture was vigorously stirred for 1 h under H_2 gas. After the the solution was stirred for 1.4 h at room temperarure, Pd–C was filtered cautiously and the filtrate was concentrated *in vacuo* to give **9** (4.68 g, quant.) as light pink crystals. *Rf*: 0.23 (hexane/AcOEt=1 : 2). mp: 187—191 °C. ^1H-NMR (300 MHz) δ_H: 2.20 (3H, s, $COCH_3$), 3.07 (2H, t, J=8.0 Hz, 3-H_2), 3.65 (2H, br s, NH_2), 4.02 (2H, t, J=8.0 Hz, 2-H_2), 6.35 (1H, dd, J=2.0, 8.0 Hz, 5-H), 6.93 (1H, d, J=8.0 Hz, 4-H), 7.67 (1H, d, J=2.0 Hz, 7-H). ^{13}C-NMR (75 MHz) δ_C: 24.08 (q, CO<u>C</u>H_3), 28.09 (t, 3-C), 50.61 (d, 2-C), 106.81 (d, 7-C), 113.17 (d, 5-C), 124.12 (s, 3a-C), 125.89 (d, 4-C), 144.48 (s, 7a-C), 145.66 (s, 6-C), 171.15 (s, <u>C</u>OCH_3). HR-FAB-MS *m/z*: 176.0959 $[M]^+$, Calcd for $C_{10}H_{12}N_2O$: 176.0950 [M].

***N*-Acetyl-6-iodoindoline (10)** To a solution of **9** (2.35 g, 13.4 mmol) in aqueous solution of 80% AcOH (165 ml) were added $NaNO_2$ (1.01 g, 1.1 eq) in H_2O (4.7 ml) and KI (2.44 g, 1.1 eq) in H_2O (4.7 ml) at 0 °C under argon. After the mixture was stirred for 24 h at 0 °C, sodium hydrogen sulfate (0.1 g) was added, and AcOH was concentrated as an azeotropic mixture with toluene *in vacuo*. Resulted residue was diluted with AcOEt (150 ml), washed with H_2O (30 ml×3), dried over Na_2SO_4, concentrated *in vacuo*. Purification of the resulting black oil (4.14 g) by flash column chromatography (benzene/acetone=20 : 1) afforded **10** (2.36 g, 62%) as light yellow crystals. *Rf*: 0.27 (hexane/AcOEt=1 : 2). mp: 102—118 °C. ^1H-NMR (300 MHz) δ_H: 2.20 (3H, s, $COCH_3$), 3.12 (2H, t, J=8.5 Hz, 3-H_2), 4.01 (2H, t, J=8.5 Hz, 2-H_2), 6.87 (1H, d, J=8.0 Hz, 4-H), 7.30 (1H, dd, J=2.0, 8.0 Hz, 5-H), 8.55 (1H, d, J=2.0 Hz, 7-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C: 24.20 (q, CO<u>C</u>H_3),

27.72 (t, 3-C), 48.95 (t, 2-C), 92.06 (s, 6-C), 125.39 (d, 7-C), 125.92 (d, 5-C), 130.80 (s, 3a-C), 132.38 (d, 4-C), 143.90 (s, 7a-C), 168.68 (s, $\underline{CO}CH_3$). HR-FAB-MS *m/z*: 286.9810 $[M]^+$, Calcd for $C_{10}H_{10}NOI$: 286.9807 [M].

6-Iodoindoline (11) To a solution of **10** (2.30 g, 8.01 mmol) in MeOH (115 ml) was added an aqueous solution of 20% NaOH. After the mixture was stirred for 4.5 h at 75 °C, MeOH was concentrated and the mixture was extracted with AcOEt (350 ml×3). The organic layer was dried over Na_2SO_4, concentrated *in vacuo*. Purification of the resulting light yellow oil (1.93 g) by flash column chromatography (hexane/AcOEt=10 : 1) gave **11** (1.39 g, 71%) as light yellow crystals. *Rf*: 0.60 (hexane/AcOEt=2 : 1). mp: 83—90 °C. ^{1}H-NMR (300 MHz) δ_H: 2.98 (2H, dt, *J*=1.0, 8.5 Hz, 3-H_2), 3.26 (1H, br, 1-H), 3.56 (2H, t, *J*=8.5 Hz, 2-H_2), 6.83 (1H, d, *J*=7.5 Hz, 4-H), 6.94 (1H, d, *J*=2.0 Hz, 7-H), 7.00 (1H, dd, *J*=2.0, 7.5 Hz, 5-H). ^{13}C-NMR (75 MHz) δ_C: 29.39 (t, 3-C), 47.46 (t, 2-C), 91.84 (s, 6-C), HR-FAB-MS *m/z*: 244.9713 $[M]^+$, Calcd for C_8H_8NI: 244.9702 [M].

6-Iodoindole (12) To a solution of **11** (3.2 g, 13.1 mmol) in MeOH was added salcomine (412 mg, 0.1 eq). After the mixture was stirred for 3.5 h in a stream of oxygen at room temperature, it was concentrated *in vacuo*. Purification of the resulting black oil (3.55 g) by flash column chromatography (hexane/AcOEt=8 : 1) afforded **12** (3.12 g, 98%) as light violet crystals. *Rf*: 0.66 (benzene/acetone=50 : 1). mp: 70 —71 °C. ^{1}H-NMR (300 MHz) δ_H: 6.54 (1H, m, 3-H), 7.10 (1H, dd, *J*=2.0, 3.0 Hz, 2-H), 7.43 (total 2H, br s, 4-H, 5-H), 7.70 (1H, d, *J*=1.0 Hz, 7-H), 8.01 (1H, br s, 1-H). ^{13}C-NMR (75 MHz) δ_C: 85.66 (s, 6-C), 102.67 (d, 3-C), 119.87 (d, 7-C), 122.20 (d, 4-C), 124.51 (d, 2-C), 126.99 (s, 3a-C), 128.41 (d, 5-C), 136.87 (s, 7a-C). HR-FAB-MS *m/z*: 242.9545 $[M]^+$, Calcd for C_8H_6NI: 242.9545 [M].

(*R*,*S*)-*N*-Acetyl-6′-iodo-tryptophan (*RS*)-13 To a mixture of **12** (3.2 g, 12.3 mmol) in AcOH (30 ml) and Ac_2O (5.2 ml) was added L-serine (2.6 g, 24.6 mmol). After the solution was stirred for 2 h at 75 °C under argon, it was diluted with ether (200 ml), and adjusted with 30% aqueous NaOH to pH 10. The partitioned water layer was ice-cooled and the organic layer was diluted with additional ether (100 ml), extracted with 1 N aqueous NaOH. Then, the combined water layer was ice-cooled and $Na_2S_2O_4$ (1.5 mg) was added to this solution, which was acidified (pH=3) by 5% HCl and kept standing overnight in a refrigerator. After the precipitated crystals were filtered, the filtrate was concentrated to 1/3, the resulting crystals were filtered, repeating this procedure further twice. Collecting the crystals gave (*RS*)-**13** (4.6 g, 89%) as light yellow crystals. The organic layer described above was dried over Na_2SO_4, concentrated *in vacuo*, purified by preparative TLC ($CHCl_3$/MeOH=20 : 1) to give the starting material **12** (60.2 mg). *Rf*: 0.17 ($CHCl_3$/MeOH=20 : 1). mp: 190—195 °C. ^{1}H-NMR (300 MHz, acetone-d_6) δ_H: 1.90 (3H, s, $COCH_3$), 3.16 (1H, dd, *J*=7.5, 15.0 Hz, 3-Ha), 3.34 (1H, dd, *J*=5.0, 15.0 Hz, 3-Hb), 4.76 (1H, dt, *J*=5.0, 7.5 Hz, 2-H), 7.05 (1H, s, 2′-H), 7.29 (1H, br, NHCO), 7.33 (1H, dd, *J*=2.0, 8.0 Hz, 5′-H), 7.45 (1H, d, *J*=8.0 Hz, 4′-H), 7.79 (1H, d, *J*=2.0 Hz, 7′-H), 10.27 (1H, br s, 1′-H). ^{13}C-NMR (75 MHz, acetone-d_6) δ_C: 22.17 (q, $CO\underline{CH}_3$), 28.00 (t, 3-C), 53.84 (d, 2-C), 85.39 (s, 6′-C), 111.52 (s, 3′-C), 121.08 (d, 7′-C), 121.35 (d, 4′-C), 125.19 (d, 2′-C), 126.32 (s, 3a′-C), 128.17 (d, 5′-C), 138.36 (s, 7a′-C), 170.35 (s, $COCH_3$), 173.38 (s, 1-C). HR-FAB-MS *m/z*: 373.0033 $[M+H]^+$, Calcd for $C_{13}H_{14}N_2O_3I$: 373.0049 [M+H].

(*R*)-6′-Iodo-tryptophan [(*R*)-14] To a solution of (*RS*)-**13** (700 mg, 1.89 mmol), D-aminocylase (187 mg) in phosphate buffer (74 ml) was added $CoCl_2\cdot 6H_2O$ (15.5 mg). After the solution was shakened for 47 h at 37 °C, the reaction mixture was filtered through a celite pad. A solution of 10% HCl was dropped to this filtrate until pH=5, then extracted with AcOEt (80 ml×3). The organic layer was dried over Na_2SO_4, concentrated *in vacuo* to provide (*S*)-**13** (270 mg, 39%). The water layer was purified by column chromatography (SEPABEADS sp207, MeOH) to give the desired (*R*)-**14** (299.9 mg, 48%) as light brown crystals. (*R*)-**14**: *Rf*: 0.28 (BuOH/AcOH/H_2O=4 : 1 : 5). mp: 198—205 °C. $[\alpha]_D^{23}$ +11.97° (*c*=0.64, MeOH). ^{1}H-NMR (300 MHz, DMSO-d_6) δ_H: 3.00 (1H, dd, *J*=8.0, 14.0 Hz, 3-Ha), 3.26 (1H, br d, *J*=14.0 Hz, 3-Hb), 3.50 (1H, m, 2-H), 7.20 (1H, br d, *J*=8.5 Hz, 5′-H), 7.21 (1H, br s, 2′-H), 7.40 (1H, d, *J*=8.5 Hz, 4′-H), 7.71 (1H, br s, 7′-H), 11.28 (1H, br, 1′-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ_C: 26.84 (t, 3-C), 54.57 (d, 2-C), 84.37 (s, 6′-C), 109.67 (s, 3′-C), 119.71 (d, 7′-C), 120.56 (d, 4′-C), 124.93 (s, 3a′-C), 126.35 (d, 2′-C), 126.59 (d, 5′-C), 137.71 (s, 7a′-C). HR-FAB-MS *m/z*: 330.9968 $[M+H]^+$, Calcd for $C_{11}H_{12}N_2O_2I$: 330.9944 [M+H].

(*S*)-**13**: $[\alpha]_D^{23}$ +19.49° (*c*=0.49, MeOH). HR-FAB-MS *m/z*: 373.0055 $[M+H]^+$, Calcd for $C_{13}H_{14}O_3N_2I$: 373.0049 [M+H]. *Rf* value and ^{1}H-NMR data were quite identical with that of (*RS*)-**13** already described.

Racemization of (*S*)-*N*-Acetyl-7-iodo-tryptophan ((*S*)-13) and Optical Resolution Using D-Aminoacylase Compound (*S*)-**13** was dissolved in 10% aqueous NaOH (0.055 ml) and concentrated *in vacuo*. To the resulting residue was added Ac_2O (0.055 ml). After the mixture was stirred for 1.5 h at 90—110 °C, this was basified with 10% ammonia (0.2 ml), diluted with H_2O (1 ml), extracted with AcOEt (10 ml×3). The H_2O layer was acidified with concentrated HCl, extracted with AcOEt (10 ml×3). The AcOEt layer was dried over Na_2SO_4, concentrated *in vacuo* to afford (*RS*)-**13** (40 mg, 80%) as an oil. $[\alpha]_D^{23}$ −1.10° (*c*=4.2, MeOH). ^{1}H-NMR data was identified with that of (*S*)-**13**. To a solution of (*RS*)-**13** (40 mg, 0.108 mmol), D-aminoacylase (19.2 mg) in phosphate buffer (0.6 ml) was added $CoCl_2\cdot 6H_2O$ (1 mg). After the solution was shaken for 48 h at 37 °C, the reaction mixture was filtered through a celite pad. A solution of 10% HCl was dropped to this filtrate until pH=5, then extracted with AcOEt (20 ml×3). The water layer was purified by column chromatography (SEPABEADS sp207, MeOH) gave the desired (*R*)-**14** (13 mg, 36%) as light brown crystals. ^{1}H-NMR data was identified with that of (*R*)-**14** already obtained.

(*R*)-*N*-Carbobenzyloxy-6′-iodo-tryptophan [(*R*)-15] To a solution of (*R*)-**14** (200 mg, 0.604 mmol) in 10% aqueous Na_2CO_3 (4.0 ml) was added Cbz-Cl (103 mg, 0.604 mmol) in ether (0.8 ml). After the mixture was stirred for 3 h at 0 °C, the resulting mixture was acidified with an aqueous solution of 10% HCl (pH=3). Precipitated crystals were filtered and washed with H_2O (5 ml×3) to afford (*R*)-**15** (280 mg, quant.) as white brown crystals. *Rf*: 0.78 (BuOH/AcOH/H_2O=4 : 1 : 5). mp: 125—127 °C. $[\alpha]_D^{23}$ +15.48° (*c*=0.60, MeOH). ^{1}H-NMR (300 MHz, acetone-d_6) δ_H: 3.21 (1H, dd, *J*=7.5, 15.0 Hz, 3-Ha), 3.38 (1H, dd, *J*=3.5, 15.0 Hz, 3-Hb), 4.55 (1H, br, 2-H), 4.95, 5.07 (each 1H, d, *J*=12.5 Hz, benzyl CH_2), 7.21 (1H, s, 2′-H), 7.25 (1H, hidden, NHCO), 7.28 (1H, d, *J*=8.0 Hz, 5′-H), 7.30 (5H, m, benzyl-arom H), 7.45 (1H, d, *J*=8.0 Hz, 4′-H), 7.77 (1H, s, 7′-H). ^{13}C-NMR (75 MHz, acetone-d_6) δ_C : 28.09 (t, 3-C), 55.73 (d, 2-C), 66.53 (t, benzyl CH_2), 85.30 (s, 6′-C), 111.48 (s, 3′-C), 120.91 (d, 7′-C), 121.20 (d, 4′-C), 125.00 (d, 2′-C), 128.01 (s, 3a′-C), 128.01, 128.35, 128.95 (each d, benzyl-arom C), 128.35 (d, 5′-C), 137.93 (s, benzyl-arom C), 138.51 (s, 7a′-C), 156.54 (s, NHCO), 173.98 (s, 1-C). HR-FAB-MS *m/z*: 487.0123 $[M+Na]^+$, Calcd for $C_{19}H_{17}O_4N_2INa$: 487.0131 [M+Na].

(*S*)-6′-Iodo-tryptophan [(*S*)-14] To a solution of (*RS*)-**13** (200 mg, 0.604 mmol), L-aminocylase (54.0 mg) in phosphate buffer (25 ml) was added $CoCl_2\cdot 6H_2O$ (5.0 mg). After the solution was shakened for 18 h at 37 °C, the reaction mixture was filtered through a celite pad. A solution of 10% HCl was dropped to this filtrate until pH=5, then extracted with AcOEt (15 ml×3). The organic layer was dried over Na_2SO_4, concentrated *in vacuo* to provide (*R*)-**13** (73.2 mg, 37%). The water layer was purified by column chromatography (SEPABEADS sp207, MeOH) to give the desired (*S*)-**14** (61.1 mg, 37.8%) as light brown crystals. (*S*)-**14**: $[\alpha]_D^{24}$ −13.88° (*c*=0.48, MeOH), HR-FAB-MS *m/z*: 330.9968 $[M+H]^+$, Calcd for $C_{11}H_{12}N_2O_2I$: 330.9935 [M+H]. *Rf* value, ^{1}H-NMR data were identical with that of (*R*)-**14**.

(*S*)-*N*-Carbobenzyloxy-6′-iodo-tryptophan [(*S*)-15] To a solution of (*S*)-**14** (50.0 mg, 0.151 mmol) in 10% aqueous Na_2CO_3 (1.0 ml) was added Cbz-Cl (25.8 mg, 0.151 mmol) in ether (0.2 ml). After the mixture was stirred for 2.5 h at 0 °C, the resulting mixture was acidified with an aqueous solution of 10% HCl (pH=3). The precipitated crystals were filtered and washed with H_2O (2 ml×3) to afford (*S*)-**15** (65.6 mg, 89%) as white brown crystals. $[\alpha]_D^{24}$ −18.22° (*c*=0.70, MeOH). HR-FAB-MS *m/z*: 487.0123 $[M+Na]^+$, Calcd for $C_{19}H_{17}O_4N_2INa$: 487.0133 [M+Na]. *Rf* value and ^{1}H-NMR data were identified by comparison with that of (*R*)-**15**.

(*R*)-*N*-Carbobenzyloxy-6′-iodo-tryptophan (*R*)-(+)-Phenylethylamide [(*R*)-16] To a solution of (*R*)-**15** (24.4 mg, 0.053 mmol) in CH_2Cl_2/THF=1 : 1 (1.3 ml) were added (*R*)-(+)-phenylethylamine (6.4 mg, 0.053 mmol), EDCI (10.0 mg, 0.053 mmol), HOBT (7.1 mg, 0.053 mmol) under argon. After the reaction mixture was stirred for 2 h at room temperature, the solution was concentrated *in vacuo*. After the residue was diluted with AcOEt (50 ml), washed with 10% aqueous solution of $NaHCO_3$ (5 ml×3), 10% aqueous citric acid (5 ml×3), saturated NaCl (5 ml×3), dried over Na_2SO_4, concentrated *in vacuo*, the resulting yellow brown oil (44.5 mg) was purified by preparative TLC ($CHCl_3$/MeOH=20 : 1) to afford white brown crystals (*R*)-**16** (29.8 mg, 65.3%) as white brown crystals. *Rf*: 0.34 (hexane/AcOEt=1 : 1). mp: 151—159 °C. $[\alpha]_D^{24}$ +1.43° (*c*=0.39, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 1.31 (3H, d, *J*=7.0 Hz, $CH\underline{CH}_3$), 3.04 (1H, dd, *J*=8.0, 15.0 Hz, 3-Ha), 3.24 (1H, dd, *J*=5.0, 15.0 Hz, 3-Hb), 4.40 (1H, dt, *J*=5.0, 8.0 Hz, 2-H), 4.97 (1H, q, *J*=7.0 Hz, $\underline{CH}CH_3$), 5.10 (2H, s, benzyl CH_2), 5.49 (1H, br d, *J*=7.5 Hz, 2-NHCO), 5.68 (1H, d, *J*=7.0 Hz, 1-CONH), 6.65 (1H, d, *J*=2.0 Hz, 2′-H), 6.96 (2H, m, phenylethyl-arom 2H), 7.23, 7.37 (each 1H, hidden, 4′-H, 5′-H), 7.24 (3H, m, phenylethyl-arom 3H), 7.33 (5H, m, benzyl-arom H), 7.65 (1H, s, 7′-H), 7.77 (1H, br s, 1′-H). HR-FAB-MS *m/z*: 568.1084 $[M+H]^+$, Calcd for $C_{27}H_{27}IN_3O_3$: 568.1097 [M+H].

(*S*)-*N*-Carbobenzyloxy-6′-iodo-tryptophan (*R*)-(+)-Phenylethylamide

[(*S*)-16] To a solution of (*S*)-**15** (24.4 mg, 0.053 mmol) in CH_2Cl_2/THF=1:1 (1.3 ml) was added (*R*)-(+)-phenylethylamine (6.4 mg, 0.053 mmol), EDCI (10.0 mg, 0.053 mmol), HOBT (7.1 mg, 0.053 mmol) under argon. After the mixture was stirred for 2 h at room temperature, the solution was concentrated *in vacuo*. After the residue was diluted with AcOEt (50 ml), washed by 10% aqueous solution of $NaHCO_3$ (5 ml×3), 10% aqueous citric acid (5 ml×3), saturated NaCl (5 ml×3), dried over Na_2SO_4, concentrated *in vacuo*, the resulting yellow brown oil (42.3 mg) was purified by preparative TLC ($CHCl_3$/MeOH=20:1) to afford white brown crystals (*S*)-**16** (25.3 mg, 55%) as white brown crystals. *Rf*: 0.38 (hexane/AcOEt=1:1). mp: 135—140 °C. $[\alpha]_D^{22}$ −1.72° (*c*=0.30, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 1.19 (3H, d, *J*=7.0 Hz, CH$\underline{CH_3}$), 3.10 (1H, dd, *J*=7.5, 15.0 Hz, 3-Ha), 3.24 (1H, dd, *J*=5.0, 15.0 Hz, 3-Hb), 4.46 (1H, dt, *J*=5.0, 8.0 Hz, 2-H), 4.86 (1H, q, *J*=7.5 Hz, $\underline{CH}CH_3$), 5.50 (2H, br, benzyl CH_2), 5.40 (1H, br d, *J*=8.0 Hz, 2-NHCO), 5.62 (1H, d, *J*=8.0 Hz, 1-CONH), 6.88 (1H, br, 2′-H), 7.00 (2H, m, phenylethyl-arom 2H), 7.22 (3H, m, phenylethyl-arom 3H), 7.23 (each 1H, hidden, 4′-H or 5′-H), 7.33 (5H, m, benzyl-arom-H), 7.56 (1H, d, *J*=7.5 Hz, 4′-H or 5′-H), 7.63 (1H, s, 7′-H), 8.07 (1H, br s, 1′-H). HR-FAB-MS *m/z*: 568.1099 $[M+H]^+$, Calcd for $C_{27}H_{27}IN_3O_3$: 568.1097 [M+H].

(*R*)-4′-Hydroxy-3′,5′-diiodo-phenylglycine (18) To a solution of **17** (10.5 g, 63.0 mmol) in AcOH (90 ml) was dropped ICl (22.5 g, 138.6 mmol) in AcOH (3.4 ml) during 10 min under argon. After the solution was stirred for 72 h at room temperature, the reaction mixture was poured into ice water (1000 ml). The precipitated crystals were filtered, washed with EtOH (100 ml×3) to provide **18** (22.6 g, 87%) as light brown crystals. *Rf*: 0.6 (BuOH/AcOH/H_2O=4:1:5). mp: 193—195 °C. $[\alpha]_D^{25}$ −83.96° (*c*=0.50, 1 N-HCl). ^{1}H-NMR (300 MHz, DMSO-d_6) δ_H: 4.16 (1H, s, 2-H), 7.74 (2H, s, 2′, 6′-H), 8.43 (4H, br s, COOH, NH_2, OH). HR-FAB-MS *m/z*: 419.8565 $[M+H]^+$, Calcd for $C_8H_8O_5NI_2$: 419.8594 [M+H].

(*R*)-*N*-*tert*-Butoxycarbonyl-3′,5′-diiodo-4′-methoxy-phenylglycine Methyl Ester (19) To a solution of **18** (945 mg, 2.26 mmol) in H_2O (4.0 ml) were added NEt_3 (1.9 ml, 3.39 mmol), Boc-ON (574 mg, 2.51 mmol) in 1,4-dioxane (4.0 ml). After the solution was stirred for 2 h, the resulting mixture was diluted with AcOEt (80 ml), extracted by H_2O (30 ml×3). The water layer was washed with AcOEt (30 ml×3), acidified by 10% aqueous citric acid and extracted by AcOEt (80 ml×3). The organic layer was washed with saturated NaCl (30 ml), dried over Na_2SO_4, concentrated *in vacuo* to afford Boc derivative (1.17 g, quant.) as a light brown crystals. The product was pure enough and used in the next step without purification. *Rf*: 0.85 (BuOH/AcOH/H_2O=4:1:5). mp: 72—75 °C. $[\alpha]_D^{24}$ −88.56° (*c*=0.51, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 1.28 (9H, s, Boc), 4.97 (1H, d, *J*=5.0 Hz, 2-H), 5.82 (1H, br s, OH), 7.75 (2H, s, 2′, 6′-H), 8.05 (1H, d, *J*=5.0 Hz, NHCO). ^{13}C-NMR (100 MHz) δ_C: 28.27 (q, C($\underline{CH_3}$)$_3$), 56.82 (d, 2-C), 81.93 (s, 3′, 5′-C), 82.55 (s, $\underline{C}(CH_3)_3$), 133.89 (s, 1′-C), 137.91 (d, 2′, 6′-C), 153.41 (s, 4′-C), 156.87 (s, NHCO). HR-FAB-MS *m/z*: 541.8939. $[M+Na]^+$, Calcd for $C_{13}H_{15}O_5NNaI_2$: 541.8937 [M+Na].

To a solution of above Boc derivative (1.035 g, 1.99 mmol) in a mixed solvent of MeOH (3.0 ml) and benzene (4.0 ml) was dropped $TMSCHN_2$ (3.0 ml, 4.38 mmol) in benzene (4.0 ml) during 30 min. After the mixture was stirred for 2 h and concentrated *in vacuo*, the resulting yellow oil (1.32 g) was purified by flash column chromatography (hexane/AcOEt=7:1) affording **19** (1.05 g, 96%) as white crystals. *Rf*: 0.89 ($CHCl_3$/MeOH=7:1). mp: 85—86 °C. $[\alpha]_D^{24}$ −89.60° (*c*=0.50, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 1.44 (9H, s, Boc), 3.75 (3H, s, $COOCH_3$), 3.84 (3H, s, OCH_3), 5.19 (1H, d, *J*=7.0 Hz, 2-H), 5.63 (1H, d, *J*=6.0 Hz, NHCO), 7.74 (2H, s, 2′-H, 6′-H). ^{13}C-NMR (75 MHz) δ_C: 28.27 (q×3, C($\underline{CH_3}$)$_3$), 53.11 (q, COO$\underline{CH_3}$), 55.64 (d, 2-C), 60.66 (q, OCH_3), 80.66 (s, $\underline{C}(CH_3)_3$), 90.79 (s, 3′, 5′-C), 136.68 (s, 1′-C), 138.33 (d, 2′, 6′-C), 154.57 (s, NHCO), 138.94 (s, 4′-C), 170.57 (s, 1-C). HR-FAB-MS *m/z*: 569.9250 $[M+Na]^+$, Calcd for $C_{15}H_{19}O_5NNaI_2$: 569.9250 [M+Na].

(*R*)-*N*-*tert*-Butoxycarbonyl-3′-iodo-4′-methoxy-5′-tributylstannyl-phenylglycine Methyl Ester (20) To a solution of **19** (914 mg, 1.67 mmol) in CH_3CN (7.4 ml) were added $(Bu_3Sn)_2$ (1.17 g, 2.0 mmol), (*o*-tolyl$_3$P)$_2$PdCl$_2$ (124 mg, 0.167 mmol), ^{i}Pr$_2$NEt (215 mg, 5.02 mmol) under argon. After the mixture was stirred for 2 h at 85 °C, it was concentrated *in vacuo* and the residue was dissolved in AcOEt (200 ml), which was washed with H_2O (30 ml×2), sat. NaCl aq. (30 ml×1), dried over Na_2SO_4, and concentrated *in vacuo*. After purification of the resulting yellow oil (1.32 g) by flash column chromatography (hexane/AcOEt=20), the resulting oil was further purified by preparative TLC (benzene/hexane=2:1×3) to give **20** (294 mg, 28%) as a light yellow oil. *Rf*: 0.60 (hexane/AcOEt=3:1). $[\alpha]_D^{21}$ −17.21° (*c*=0.40, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 0.90 (9H, m, $(CH_2)_3\underline{CH_3}$×3), 1.08 (6H, m, $(CH_2)_2\underline{CH_2}CH_3$×3), 1.32 (6H, m, $CH_2\underline{CH_2}$-CH_2CH_3×3), 1.44 (9H, s, Boc), 1.48—1.68 (6H, m, $\underline{CH_2}(CH_2)_2CH_3$×3), 3.73 (3H, s, $COOCH_3$), 3.76 (3H, s, OCH_3), 5.25 (1H, d, *J*=7.5 Hz, 2-H), 5.51 (1H, d, *J*=7.5 Hz, NHCO), 7.30 (1H, d, *J*=2.0 Hz, 6′-H), 7.71 (1H, d, *J*=2.0 Hz, 2′-H). ^{13}C-NMR (75 MHz) δ_C: 10.41 (t×3, C(CH_2)$_2\underline{CH_2}CH_3$×3), 13.64 (q×3, $(CH_2)_3\underline{CH_3}$×3), 27.29 (t×3, $CH_2\underline{CH_2}CH_2CH_3$×3), 28.30 (q×3, C($\underline{CH_3}$)$_3$×3), 29.00 (t×3, $\underline{CH_2}(CH_2)_2CH_3$×3), 52.75 (q, COO$\underline{CH_3}$), 56.34 (d, 2-C), 61.80 (q, OCH_3), 80.31 (s, $\underline{C}(CH_3)_3$), 90.97 (s, 3′-C), 134.31 (s, 1′-C), 136.12 (d, 6′-C), 137.22 (s, 5′-C), 138.64 (d, 2′-C), 154.79 (s, NHCO), 164.54 (s, 4′-C), 171.32 (s, 1-C). HR-FAB-MS *m/z*: 734.1354 $[M+Na]^+$, Calcd for $C_{27}H_{46}O_5NNaSn^{120}I$: 734.1340 [M+Na].

(*R*)-3′,5′-Dichloro-4′-hydroxy-phenylglycine (21) To a solution of **17** (5.0 g, 29.9 mmol) in 1.0 M HCl in AcOH (100 ml) was dropped SO_2Cl_2 (6.95 ml, 68.8 mmol) in AcOH (10 ml) during 30 min. After the mixture was stirred for 30 min at 70 °C and for 2 h at room temperature, it was diluted with ether (150 ml) and allowed to stand for 15 min. After the resulting precipitates were filtered, it was dissolved in 1 N HCl (100 ml) and filtered. The filtrate was adjusted to pH 5 by 28% aqueous ammoniac solution, then the precipitated crystals were filtered, washed with H_2O (10 ml×2), acetone (20 ml×2) to give **21** (5.401 g, 77%) as white crystals. *Rf*: 0.40 (BuOH/AcOH/H_2O=4:1:5). mp: 222—225 °C. $[\alpha]_D^{20}$ −126.73° (*c*=1.01, 1 N-HCl). ^{1}H-NMR (300 MHz, CD_3OD) δ_H: 4.47 (1H, s, 2-H), 7.43 (2H, s, 2′, 6′-H). ^{13}C-NMR (75 MHz, CD_3OD) δ_H: 58.62 (d, 2-C), 123.49 (s×2, 3′, 5′-C), 129.36 (d×2, 2′, 6′-C), 132.70 (s, 1′-C), 151.23 (s, 4′-C), 171.95 (s, 1-C). HR-FAB-MS *m/z*: 235.9928 $[M+H]^+$, Calcd for $C_8H_8O_3NCl^{35}{}_2$: 253.9981 [M+H].

(*R*)-3′,5′-Dichloro-4′-hydroxy-phenylglycine *tert*-Butyl Ester (22) A solution of **21** (1.0 g, 4.24 mmol) in 1,4-dioxane (11 ml) and conc.H_2SO_4 (1.0 ml) were added into pressure-resistant glass tube vessel (max: 1 MPa). Isobutene gas (4.90 g, 86.07 mmol) was then introduced to this solution during 1 h under cooling the vessel in dry ice–acetone (at −78 °C). After the tube was sealed tightly, the reaction temperature was raised to room temperature and allowed to stand for 72 h. Then saturated $NaHCO_3$ was added to the reaction mixture until basic and the resulting mixture was extracted with AcOEt (80 ml×3). The organic layer was dried over Na_2SO_4, concentrated *in vacuo* affording **22** (0.744 g, 60%) as white crystals. *Rf*: 0.23 (hexane/AcOEt=1:1). mp: 120—122 °C. $[\alpha]_D^{23}$ −109.260° (*c*=0.2, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 1.40 (9H, s, ^{t}Bu), 3.27 (3H, br s, NH_2, OH), 4.33 (1H, s, 2-H), 7.21 (2H, s, 2′, 6′-H). ^{13}C-NMR (75 MHz) δ_C : 27.86 (q×3, C($\underline{CH_3}$)$_3$), 57.67 (d, 2-C), 82.38 (s, $\underline{C}(CH_3)_3$), 122.25 (s, 3′, 5′-C), 126.65 (d, 2′, 6′-C), 133.20 (s, 1′-C), 147.79 (s, 4′-C), 172.16 (s, 1-C). HR-FAB-MS *m/z*: 292.0518 $[M+H]^+$, Calcd for $C_{12}H_{16}NO_3Cl^{35}{}_2$: 292.0507 [M+H].

(*R*,*R*)-6′-Iodo-*N*-carbobenzyloxy-tryptophyl-3′,5′-dichloro-4′-hydroxy-phenylglycine *tert*-Butyl Ester (23) To a solution of **22** (44.0 mg, 0.151 mmol) and (*R*)-**15** (70.0 mg, 0.151 mmol) in THF (4.4 ml) were added FDPP (87.0 mg, 0.227 mmol) and ^{i}Pr$_2$NEt (58.4 mg, 0.453 mmol). After the mixture was stirred for 24 h at room temperature under argon, the solution was concentrated *in vacuo*. Purification of the resulting yellow oil (308.8 mg) by preparative TLC ($CHCl_3$/MeOH=10:1) gave **23** (70.5 mg, 64%) as white crystals. *Rf*: 0.77 ($CHCl_3$/MeOH=5:1). mp: 100—102 °C. $[\alpha]_D^{20}$ −30.30° (*c*=0.2, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 1.34 (9H, s, ^{t}Bu), 3.11 (1H, dd, *J*=7.5, 14.3 Hz, Trp 3-Ha), 3.33 (1H, dd, *J*=4.0, 14.3 Hz, Trp 3-Hb), 4.56 (1H, dt, *J*=4.0, 7.5 Hz, Trp 2-H), 5.09 (1H, d, *J*=7.0 Hz, CHPG 2-H), 5.04, 5.10 (each 1H, d, *J*=12.0 Hz, benzyl CH_2), 5.43 (1H, d, *J*=7.5 Hz, Trp NHCO), 6.23 (1H, br, OH), 6.85 (1H, d, *J*=2.0 Hz, Trp 2′-H), 6.91 (1H, br d, *J*=7.0 Hz, CHPG NHCO), 7.08 (2H, s, CHPG 2′, 6′-H), 7.28—7.38 (5H, m, benzyl-arom H), 7.33 (2H, hidden, Trp 4′-H, 5′-H), 7.68 (1H, d, *J*=2.0 Hz, Trp 7′-H), 8.21 (1H, br, Trp 1′-H). HR-FAB-MS *m/z*: 760.0459 $[M+Na]^+$, Calcd for $C_{31}H_{30}O_6N_3Cl^{35}{}_2INa$: 760.0454 [M+Na].

(*R*,*R*)-6′-Iodo-*N*-carbobenzyloxy-tryptophyl-3′,5′-dichloro-4′-methoxy-phenylglycine *tert*-Butyl Ester (24) To a solution of **23** (156 mg, 0.345 mmol) in MeOH (1.6 ml) and benzene (4.7 ml) was added $TMSCHN_2$ (0.208 ml, 0.42 mmol). After the mixture was stirred for 2 h at room temperature under argon, this was concentrated *in vacuo*. The resulted yellow oil (210.3 mg) was purified by preparative TLC (hexane/AcOEt=1:1) to give **24** (159 mg, quant.) as white crystals. *Rf*: 0.70 (hexane/AcOEt=3:1). mp: 90—93 °C. $[\alpha]_D^{20}$ −32.24° (*c*=0.2, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 1.35 (9H, s, ^{t}Bu), 3.13 (1H, dd, *J*=7.5, 14.5 Hz, Trp 3-Ha), 3.30 (1H, dd, *J*=5.0, 14.5 Hz, Trp 3-Hb), 3.87 (3H, s, OCH_3), 4.56 (1H, dt, *J*=5.0, 7.5 Hz, Trp 2-H), 5.09, 5.14 (each 1H, d, *J*=13.0 Hz, benzyl CH_2), 5.14 (1H, d, *J*=6.5 Hz, CHPG 2-H), 5.46 (1H, d, *J*=7.5 Hz, Trp NHCO), 6.86 (1H, br, Trp 2′-H), 6.92 (1H, d, *J*=6.5 Hz, CHPG NHCO), 7.14 (2H, s, CHPG 2′, 6′-H), 7.33 (1H, hidden, Trp 4′, 5′-H), 7.28—7.38 (5H, benzyl-arom H), 7.68 (1H, t, *J*=1.0 Hz, Trp 7′-H), 8.23 (1H, brs, Trp 1′-H). ^{13}C-NMR (100 MHz) δ_C: 27.79 (q×3, C($\underline{CH_3}$)$_3$), 28.04 (t, Trp 3-C), 55.58 (d, Trp 2-C), 60.73 (q,

OCH_3), 67.21 (t, benzyl CH_2), 83.66 (s, $\underline{C}(CH_3)_3$), 86.27 (s, Trp 6′-C), 110.20 (s, Trp 3′-C), 120.09 (d, Trp 5′-C), 120.23 (d, Trp 7′-C), 123.64 (d, Trp 2′-C), 126.64 (s, Trp 3a′-C), 127.25 (d, CHPG 2′, 6′-C), 127.97, 128.43 (each d, benzyl-arom 2, 6 and 3, 5-C), 127.97, 128.48 (each d, Trp 4′-C, benzyl 4′-C), 129.35 (s, CHPG 3′, 5′-C), 134.15 (s, CHPG 1′-C), 135.86 (s, benzyl-arom 1-C), 137.26 (s, Trp 7a′-C), 151.89 (s, CHPG 4′-C), 155.81 (s, Trp NHCO), 167.89 (s, CHPG 1-C), 170.39 (s, Trp 1-C). HR-FAB-MS *m/z*: 774.0579 $[M+Na]^+$, 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-methoxycarbonyl-methlyamino)-3-iodo-2-methoxy-phenyl]indol-3-yl}-2-carbobenzyloxy-aminopropionylamino)-2-(3,5-dichloro-4-methoxy-phenyl) Acetic Acid *tert*-Butyl Ester (25) To a solution of **24** (30.0 mg, 0.037 mmol) and **20** (28.4 mg, 0.037 mmol) in DMF (1.5 ml) were added $Pd_2(dba)_3\cdot CHCl_3$ (4.0 mg, 0.007 mmol), CuI (1.6 mg, 0.015 mmol), Ph_3As (5.0 mg, 0.030 mmol), $^i Pr_2NEt$ (14.3 mg, 0.111 mmol). After the mixture was stirred for 2 h at room temperature under argon, this was diluted with ether (80 ml), washed with saturated NH_4Cl (10 ml×3), 10% aqueous KF (10 ml×3), concentrated *in vacuo*. The resulting brown oil (108 mg) was purified by preparative TLC (silica gel, $CHCl_3$/MeOH=50 : 1), after that, repurified by hexane/AcOEt=1 : 1 affording **25** (14.6 mg, 35%) as yellow crystals and recovered **24** (9.6 mg) and **20** (3.7 mg). **25**: *Rf*: 0.44 ($CHCl_3$/MeOH=50 : 1). mp: 40—43 °C. $[\alpha]_D^{24}$ −22.02° (*c*=0.49, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 1.37 (9H, s, ^{t}Bu), 1.45 (9H, s, Boc), 3.21 (1H, dd, *J*=7.5, 14.5 Hz, Trp 3-Ha), 3.36, 3.88 (each 3H, s, OCH_3×2), 3.40 (1H, dd, *J*=5.0, 14.5 Hz, Trp 3-Hb), 3.75 (3H, s, $COOCH_3$), 4.64 (1H, dt, *J*=5.0, 7.5 Hz, Trp 2-H), 5.15 (2H, s, benzyl CH_2), 5.22 (1H, d, *J*=6.5 Hz, CHPG 2-H), 5.29 (1H, br d, *J*=7.5 Hz, IHPG 2-H), 5.39 (1H, br d, *J*=7.5 Hz, Trp NHCO), 5.61 (1H, br d, *J*=7.5 Hz, IHPG NHCO), 6.97 (1H, d, *J*=2.0 Hz, Trp 2′-H), 7.00 (1H, br d, *J*=6.5 Hz, CHPG NHCO), 7.18 (2H, s, CHPG 2′, 6′-H), 7.29 (1H, d, *J*=8.5 Hz, Trp 5′-H), 7.35 (5H, m, benzyl-arom H), 7.36 (1H, d, *J*=2.0 Hz, IHPG 2′-H), 7.65 (1H, br d, *J*=8.5 Hz, Trp 4′-H), 7.58 (1H, br, Trp 7′-H), 7.74 (1H, d, *J*=2.0 Hz, IHPG 6′-H), 8.16 (1H, br, Trp 1′-H). ^{13}C-NMR (100 MHz) δ_C: 27.83 (t, Trp 3-C), 27.76 (q×3, ^{t}Bu C($\underline{CH}_3)_3$), 28.30 (q×3, Boc C($\underline{CH}_3)_3$), 52.92, 60.27, 60.37 (each q, OCH_3×3), 55.50 (d, Trp 2-C), 55.91 (d, CHPG 2-C), 56.46 (d, IHPG 2-C), 67.28 (t, benzyl CH_2), 80.44 (s, Boc $\underline{C}(CH_3)_3$), 83.67 (s, ^{t}Bu $\underline{C}(CH_3)_3$), 93.67 (s, IHPG 5′-C), 110.01 (s Trp 3′-C), 111.87 (d, Trp 7′-C), 118.45 (d, Trp 5′-C), 121.22 (d, Trp 4′-C), 124.37 (d, Trp 2′-C), 127.04 (s, 3a′-C), 127.45 (d, CHPG 2′, 6′-C), 128.13, 128.29, 128.58 (each d, benzyl-arom C), 129.48 (s, CHPG 3′, 5′-C), 130.63 (d, IHPG 2′-C), 131.71 (s, IHPG 3′-C), 133.20 (CHPG 1′-C), 134.43 (s, IHPG 1′-C), 134.62 (s, IHPG 1′-C), 136.05 (s, benzyl-arom 1-C), 136.19 (s, Trp 7a′-C), 136.19 (d, IHPG 6′-C), 136.36 (s, Trp 6′-C), 152.10 (s, CHPG 4′-C), 154.74 (s, IHPG NHCO), 156.10 (s, Trp NHCO), 157.04 (IHPG 4′-C), 168.22 (s, CHPG 1-C), 170.63 (s, Trp 1-C), 171.17 (s, IHPG 1-C). HR-FAB-MS *m/z*: 1044.1951 $[M+H]^+$, Calcd for $C_{47}H_{51}O_{11}N_4Cl^{35}{}_2I$: 1044.1976 [M+H].

(*R*,*R*,*R*)-2-[3-(3-{*N*-[2-(3,5-Dichloro-4-methoxyphenyl)acetylcarboxy]-2-carbobenzyl-oxyaminopropionylamino}indol-6-yl)-5-iodo-4-methoxyphenyl]-2-methoxycarbonyl-methylammonium Trifluoroacetate (4) To a solution of **25** (10.0 mg, 0.0096 mol) in $CHCl_3$ (0.4 ml) was added TFA (0.4 ml). After the mixture was stirred for 6 h at room temperature, the reaction mixture was concentrated *in vacuo* to remove TFA by azeotropic distillation with benzene to afford **4** (9.3 mg, 97.0%). *Rf*: 0.12 ($CHCl_3$/MeOH=10 : 1). mp: 130—135 °C. $[\alpha]_D^{24}$ −19.94° (*c*=0.14, MeOH). ^{1}H-NMR (300 MHz, CD_3OD) δ_H: 3.12 (1H, dd, *J*=8.0, 16.0 Hz, Trp 3-Ha), 3.22 (3H, s, CHPG OCH_3), 3.32 (1H, dd, *J*=6.0, 16.0 Hz, Trp 3-Hb), 3.83 (3H, s, IHPG $COOCH_3$), 3.86 (3H, s, CHPG OCH_3), 4.56 (1H, dd, *J*=6.0, 8.0 Hz, Trp 2-H), 4.95 (2H, br, benzyl CH_2), 5.12, 5.25 (each 1H, br, IHPG 2-H, CHPG 2-H), 7.14 (3H, hidden, Trp 2′-H, 4′-H, 7′-H), 7.29 (5H, s, benzyl-arom H), 7.44 (2H, s, CHPG 2′, 6′-H), 7.55 (1H, d, *J*=2.5Hz, IHPG 2′-H), 7.71 (1H, dd, *J*=2.5, 5.0 Hz, Trp 5′-H), 7.99 (1H, d, *J*=2.5 Hz, IHPG 6′-H). HR-FAB-MS *m/z*: 911.0724 $[M+Na]^+$, Calcd for $C_{38}H_{55}O_9N_4Cl^{35}{}_2NaI$: 911.0706 [M+Na].

(*R*)-*N*-*tert*-Butoxycarbonyl-3′,5′-dichloro-4′-hydroxy-phenylglycine (26) To a solution of **21** (85.0 mg, 0.291 mmol) in H_2O (1.0 ml) were added NEt_3 (0.08 ml, 0.437 mmol), Boc-ON (99.0 mg, 0.323 mmol) in 1,4-dioxane (1.0 ml). After the mixture was stirred for 1 h at room temperature, the solution was concentrated *in vacuo*. The residue was dissolved in AcOEt (30 ml), extracted with H_2O (5 ml×3). The water layer was washed with AcOEt (5 ml×3), acidified by 10% aqueous citric acid, then extracted with AcOEt (5 ml×3). The organic layer was washed with saturated NaCl (3 ml×1), dried over Na_2SO_4, concentrated *in vacuo* to provide **26** (104 mg, quant.) as a yellow oil which was pure enough to use in the next procedure. *Rf*: 0.75 (BuOH/AcOH/H_2O=4 : 1 : 5). mp: 60—62 °C. $[\alpha]_D^{22}$ −121.91° (*c*=0.50, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 1.28 (9H, s, Boc), 5.01 (1H, d, *J*=6.0 Hz, 2-H), 5.70 (1H, br s, OH), 7.36 (2H, s, 2′, 6′-H), 8.07 (1H, d, *J*=6.0 Hz, NHCO). HR-FAB-MS *m/z*: 358.0238 $[M+Na]^+$, Calcd for $C_{13}H_{15}O_5NCl^{35}{}_2Na$: 358.0225 [M+Na].

(*R*)-*N*-*tert*-Butoxycarbonyl-3′,5′-dichloro-4′-methoxy-phenylglycine Methyl Ester (27) To a solution of **26** (54.5 mg, 0.163 mmol) in a mixture of MeOH (0.2 ml) and benzene (6.0 ml) was added $TMSCHN_2$ (0.21 ml, 0.424 mmol) dropwise. After the mixture was stirred for 15 min, this was concentrated *in vacuo*. The resulting yellow oil (68.8 mg) was purified by preparative TLC (hexane/AcOEt=1 : 1) to provide **27** (50.2 mg, 86%) as white crystals. *Rf*: 0.52 (hexane/AcOEt=2 : 1). mp: 106—108 °C. $[\alpha]_D^{25}$ −130.06° (*c*=0.55, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 1.41 (9H, s, Boc), 3.73 (3H, s, $COOCH_3$), 3.86 (3H, s, OCH_3), 5.22 (1H, br d, *J*=7.0 Hz, 2-H), 5.66 (1H, d, *J*=7.0 Hz, NHCO), 7.30 (2H, s, 2′, 6′-H). ^{13}C-NMR (75 MHz) δ_C: 28.32 (q, C($\underline{CH}_3)_3$), 53.15 (q, COO$\underline{CH}_3$), 56.37 (d, 2-C), 60.69 (O$\underline{CH}_3$), 80.61 (s, $\underline{C}(CH_3)_3$), 127.27 (d×2, 2′, 6′-C), 129.62 (s×2, 3′, 5′-C), 134.45 (s, 1′-C), 152.14 (s, 4′-C), 154.43 (s, NHCO), 170.30 (s, 1-C). HR-FAB-MS *m/z*: 386.0540 $[M+Na]^+$, Calcd for $C_{15}H_{19}O_5NCl^{35}{}_2Na$: 386.0538 [M+Na].

***N*-*tert*-Butoxycarbonyl-3′,5′-Dichloro-4′-methoxyphenylglycine (28)** To a solution of **27** (20.0 mg, 0.057 mmol) in MeOH (0.5 ml) and THF (0.5 ml) were added $LiOH\cdot H_2O$ (4.6 mg, 0.115 mmol) in H_2O (0.4 ml). After the mixture was stirred for 40 min at 0 °C, 10% citric acid was added to this solution until pH=4 and extracted with $CHCl_3$ (5 ml×3) dried over Na_2SO_4, concentrated *in vacuo* to afford **28** (18.0 mg, 94%). *Rf*: 0.20 ($CHCl_3$/MeOH=10 : 1). mp: 130—135 °C. $[\alpha]_D^{20}$ −15.82 (*c*=0.52, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 1.27 (9H, s, Boc), 3.90 (3H, s, OCH_3), 5.03 (1H, d, *J*=5.5 Hz, 2-H), 7.37 (2H, s, 2′, 6′-H), 8.19 (1H, d, *J*=5.5 Hz, NHCO), 12.01 (1H, br, OH). ^{13}C-NMR (75 MHz) δ_C: 28.31 (q, C($\underline{CH}_3)_3$), 57.69 (d, 2-C), 60.79 (O$\underline{CH}_3$), 82.60 (s, $\underline{C}(CH_3)_3$), 127.53 (d×2, 2′, 6′-C), 129.29 (s×2, 3′, 5′-C), 135.56 (s, 1′-C), 151.86 (s, 4′-C), 156.76 (s, NHCO), 172.18 (s, 1-C). HR-FAB-MS *m/z*: 349.0461 $[M]^+$, Calcd for $C_{14}H_{17}O_5NCl^{35}{}_2$: 349.0484 [M].

(*R*)-*N*-Carbobenzyloxy-6′-iodo-tryptophan *tert*-Butyl Ester [(*R*)-29] To a solution of (*R*)-**15** (135.0 mg, 0.269 mmol) in DMAC (3.3 ml) was added K_2CO_3 (1.27 g, 8.61 mmol), $(CH_3)_3CBr$ (2.16 ml, 17.22 mmol), benzyltriethylammonium chloride (66.0 mg, 0.269 mmol). After the mixture was stirred for 2.5 h at 55 °C under argon, it was poured into ice-water (30 ml) and extracted with AcOEt (10 ml×3). The organic layer was washed with H_2O (5 ml×3), dried over Na_2SO_4, concentrated *in vacuo*. The resulting brown oil (205 mg) was purified by flash column chromatography (hexane/AcOEt=4 : 1) giving (*R*)-**29** (125 mg, 82%) as light brown amorphous. *Rf*: 0.53 (hexane/AcOEt=3 : 2). $[\alpha]_D^{23}$ −17.97° (*c*=0.60, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 1.38 (9H, s, ^{t}Bu), 3.18, 3.27 (each 1H, dd, *J*=6.0, 14.0 Hz, 3-H_2), 4.59 (1H, dt, *J*=4.5, 6.0 Hz, 2-H), 5.05, 5.13 (each 1H, d, *J*=12.0 Hz, benzyl CH_2), 5.34 (1H, d, *J*=6.0 Hz, NHCO), 6.88 (1H, s, 2′-H), 7.32 (1H, hidden, 4′-H), 7.33 (5H, m, benzyl-arom H), 7.34 (1H, hidden, 5′-H), 7.66 (1H, s, 7′-H), 8.25 (1H, s, 1′-H). ^{13}C-NMR (75 MHz) δ_C: 27.97 (q×3, C($\underline{CH}_3)_3$), 27.97 (t, 3-C), 54.99 (d, 2-C), 66.83 (t, benzyl CH_2), 82.11 (s, $\underline{C}(CH_3)_3$), 85.90 (s, 6′-C), 110.43 (s, 3′-C), 120.00 (d, 7′-C), 120.43 (d, 4′-C), 123.05 (d, 2′-C), 127.03 (s, 3a′-C), 127.97, 128.13, 128.37 (each d, benzyl-arom C), 128.02 (d, 5′-C), 136.14 (s, benzyl-arom C), 137.16 (s, 7a′-C), 155.55 (s, NHCO), 170.68 (s, 1-C). HR-FAB-MS *m/z*: 520.0870 $[M]^+$, Calcd for $C_{23}H_{25}O_4N_2I$: 520.0859 [M].

(*R*,*R*)-3-{6-[3-(*N*-*tert*-Butoxycarbonyl-2-methoxycarbonylmethyl-amino)-5-iodo-6-methoxyphenyl]indol-3-yl}-2-carbobenzyloxy-amino-propionic Acid *tert*-Butyl Ester (30) To a solution of **20** (82.0 mg, 0.115 mmol) and (*R*)-**29** (60.0 mg, 0.115 mmol) in DMF (2.0 ml) were added $Pd_2(dba)_3\cdot CHCl_3$ (24.5 mg, 0.023 mmol), CuI (9.6 mg, 0.046 mmol), Ph_3As (35.0 mg, 0.092 mmol), $^i Pr_2NEt$ (74.4 mg, 0.345 mmol). After the mixture was stirred for 1.5 h at room temperature under argon, this was diluted with AcOEt (110 ml), washed with saturated NH_4Cl (10 ml×3), 10% aqueous KF solution (10 ml×3), dried for Na_2SO_4, concentrated *in vacuo*. Purification of the resulting brown oil (262 mg) by preparative TLC (hexane/AcOEt=3 : 2) affording **30** (38.0 mg, 41%) as light yellow crystals and (*R*)-**29** (8.0 mg) were recovered. **30**: *Rf*: 0.35 (hexane/AcOEt=3 : 2). mp: 40—44 °C. $[\alpha]_D^{21}$ −19.27° (*c*=0.33, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 1.37 (9H, s, ^{t}Bu), 1.44 (9H, s, Boc), 3.29, 3.31 (each 1H, hidden, Trp 3-H_2), 3.32 (3H, s, OCH_3), 3.73 (3H, s, $COOCH_3$), 4.64 (1H, dd, *J*=5.0, 7.5 Hz, Trp 2-H), 5.06, 5.13 (each 1H, d, *J*=12.0 Hz, benzyl CH_2), 5.29 (1H, d, *J*=7.5 Hz, IHPG 2-H), 5.38 (1H, d, *J*=7.5 Hz, Trp NHCO), 5.63 (1H, br d, *J*=7.5 Hz, IHPG NHCO), 7.05 (1H, d, *J*=2.5 Hz, Trp 2′-H), 7.27 (1H, d, *J*=7.5 Hz, Trp 5′-H), 7.34 (5H, m, benzyl-arom H), 7.35 (1H, d, *J*=2.5 Hz, IHPG 2′-H), 7.54 (1H, s, Trp 7′-H), 7.61 (1H, d, *J*=7.5 Hz, Trp 4′-H), 7.73 (1H, d, *J*=2.5 Hz, IHPG 6′-H), 8.23 (1H, s, Trp 1′-H). ^{13}C-NMR (100 MHz) δ_C: 27.91 (q×3, ^{t}Bu C($\underline{CH}_3)_3$), 27.97 (t, Trp 3-C), 28.29 (q×3, Boc C($\underline{CH}_3)_3$), 52.89 (q,

COOCH$_3$), 54.95 (d, Trp 2-C), 56.45 (d, IHPG 2-C), 60.13 (q, OCH$_3$), 66.82 (t, benzyl CH$_2$), 80.41 (s, ^{t}Bu C(CH$_3$)$_3$), 82.10 (s, Boc C(CH$_3$)$_3$), 93.62 (s, IHPG 5′-C), 110.15 (s, Trp 3′-C), 111.57 (d, Trp 7′-C), 118.87 (d, Trp 4′-C), 120.76 (d, Trp 5′-C), 123.72 (d, Trp 2′-C), 127.50 (s, Trp 3a′-C), 128.12, 128.49 (each d, benzyl-arom C), 130.63 (d, IHPG 2′-C), 131.37 (s, IHPG 3′-C), 134.56 (s, IHPG 1′-C), 136.04 (s, benzyl-arom 1-C), 136.04 (d, IHPG 6′-C), 136.09 (s, Trp 6′-C), 136.52 (s, Trp 7a′-C), 154.48 (s, IHPG NHCO), 155.75 (s, Trp NHCO), 156.99 (s, IHPG 4′-C), 170.96 (s, Trp 1-C), 171.17 (s, IHPG 1-C). HR-FAB-MS *m/z*: 813.2074 [M]$^+$, Calcd for $C_{38}H_{44}O_9N_3I$: 813.2122 [M].

(*R*,*R*)-2-{3-[3-(*tert*-Butoxycarbonyl-2-carbobenzyloxyaminoethyl)indol-6-yl]-4-iodo-5-methoxyphenyl}-2-methoxycarbonylmethyl-ammonium *p*-Toluenesulfonate (31) To a solution of **30** (32.7 mg, 0.040 mmol) in EtOH (1.0 ml) was added *p*-TsOH (9.2 mg, 0.052 mmol). After the solution was stirred for 30 min at room temperature, EtOH was concentrated *in vacuo*. EtOH (1.0 ml) was again added and the solution was stirred for 30 min. This procedure was repeated further three times to provide **31** (35.4 mg, 97%) as yellow brown crystals. *Rf*: 0.51 (CHCl$_3$/MeOH=10 : 1). mp: 135—142 °C. $[\alpha]_D^{21}$ −4.40° (*c*=0.18, MeOH). ^{1}H-NMR (300 MHz, CD$_3$OD) δ_H: 1.34 (9H, s, ^{t}Bu), 2.20 (3H, s, *p*-TsOH CH$_3$), 3.14, 3.24 (each 1H, dd, *J*=8.0, 17.0 Hz, Trp 3-H$_2$), 3.32, 3.83 (each 3H, s, OCH$_3$×2), 4.44 (1H, dd, *J*=5.0, 8.0 Hz, Trp 2-H), 5.07 (2H, m, benzyl CH$_2$), 5.33 (1H, br, IHPG 2-H), 7.17 (1H, br s, Trp 2′-H), 7.21, 7.69 (2H, d, *J*=8.0 Hz, *p*-TsOH 3, 5-H), 7.30 (5H, m, benzyl-arom H), 7.37 (1H, br d, *J*=8.5 Hz, Trp 5′-H), 7.51 (1H, d, *J*=2.5 Hz, IHPG 2′-H), 7.57 (1H, d, *J*=1.5 Hz, Trp 7′-H), 7.65 (1H, d, *J*=8.5 Hz, Trp 4′-H), 7.69 (2H, d, *J*=8.0 Hz, *p*-TsOH 2, 6-H), 7.86 (1H, d, *J*=2.5 Hz, IHPG 6′-H). HR-FAB-MS *m/z*: 736.1523 [M+Na]$^+$, Calcd for $C_{33}H_{36}N_3O_7INa$: 736.1496 [M+Na].

(*R*,*R*,*R*)-3-[6-(5-{1-[2-(3,5-Dichloro-4-methoxyphenyl)-2-*tert*-butoxycarbonylamino-acethylamino]-1-methoxycarbonylmethyl}-3-iodo-2-methoxyphenyl)indol-3-yl]-2-carbobenzyloxyaminopropionic Acid *tert*-Butyl Ester (32a) To a solution of **31** (10.0 mg, 0.011 mmol) and **26** (4.9 mg, 0.012 mmol) in a mixed solvent of CH$_2$Cl$_2$ and THF (1 : 1, 2.0 ml) were added HATU (7.0 mg, 0.018 mmol) and collidine (0.49 ml, 0.037 mmol). After the mixture was stirred for 1.5 h at 0 °C under argon, this was concentrated *in vacuo*. The residue was dissolved in AcOEt (50 ml), then the organic solution was washed with saturated NaHCO$_3$ (10 ml×3), 10% aqueous citric acid (10 ml×3), saturated NaCl (10 ml×3). The organic layer was dried over Na$_2$SO$_4$, concentrated *in vacuo*. The resulting brown oil (22.2 mg) was purified by preparative TLC (hexane/AcOEt=1 : 1) to give a phenol (3.2 mg, 25%) as white brown crystals. *Rf*: 0.46 (hexane/AcOEt=1 : 1). $[\alpha]_D^{21}$ −18.62° (*c*=0.40, CHCl$_3$). ^{1}H-NMR (300 MHz) δ_H: 1.40 (9H, s, ^{t}Bu), 1.68 (9H, s, Boc), 3.26 (2H, m, Trp 3-H$_2$), 3.34 (3H, s, IHPG OCH$_3$), 3.73 (3H, s, IHPG COOCH$_3$), 4.66 (1H, dt, *J*=5.0, 8.0 Hz, Trp 2-H), 5.09, 5.14 (each 1H, d, *J*=12.0 Hz, benzyl CH$_2$), 5.10 (1H, hidden, IHPG 2-H), 5.38 (1H, d, *J*=8.0 Hz, Trp NHCO), 5.45 (1H, d, *J*=8.0 Hz, CHPG 2-H), 5.50 (1H, d, *J*=8.0 Hz, IHPG NHCO), 5.75 (1H, br, OH), 6.90 (1H, br d, *J*=8.0 Hz, CHPG NHCO), 7.06 (1H, d, *J*=2.0 Hz, Trp 2′-H), 7.26 (1H, dd, *J*=2.0, 8.0 Hz, Trp 5′-H), 7.28 (1H, d, *J*=2.0 Hz, IHPG 2′-H), 7.32 (2H, s, CHPG 2′, 6′-H), 7.34 (5H, m, benzyl-arom H), 7.51 (1H, d, *J*=2.0 Hz, Trp 7′-H), 7.62 (1H, d, *J*=8.0 Hz, Trp 4′-H), 7.69 (1H, d, *J*=2.0 Hz, IHPG 6′-H), 8.16 (1H, br s, Trp 1′-H). HR-FAB-MS *m/z*: 1053.1738 [M+Na]$^+$, Calcd for $C_{46}H_{49}Cl^{35}{}_2IN_4O_{11}$: 1053.1717 [M+Na].

To a solution of above phenol (2.5 mg, 2.7 μmol) in MeOH (0.1 ml) and benzene (1.0 ml) was added TMSCHN$_2$ (1.9 μl, 3.24 μmol). After the mixture was stirred for 1.5 h at room temperature under argon, this was concentrated *in vacuo*. Purification of the resulting yellow brown oil (10.3 mg) by preparative TLC (hexane/AcOEt=1 : 1) afforded **32a** (0.8 mg, 34%) as white brown crystals. *Rf*: 0.35 (hexane/AcOEt=1 : 1).

(*R*,*R*,*R*) and (*S*,*R*,*R*)-3-[6-(5-{1-[2-(3,5-Dichloro-4-methoxyphenyl)-2-*tert*-butoxycarbonylamino-acetylamino]-1-methoxycarbonylmethyl}-3-iodo-2-methoxyphenyl)indol-3-yl]-2-carbobenzyloxyaminopropionic Acid *tert*-Butyl Ester (32a, 32b) To a solution of **31** (35.5 mg, 0.039 mmol) and **28** (16.0 mg, 0.039 mmol) in a mixed solution of CH$_2$Cl$_2$ and THF (1 : 1, 3.0 ml) were added EDCI (16.0 mg, 0.078 mmol), HOBT (11.3 mg, 0.078 mmol), NMM (17.1 mg, 0.117 mmol). After the mixture was stirred for 2.5 h at 0 °C under argon, the resulting solution was concentrated *in vacuo*. The residue was dissolved in AcOEt (30 ml) and the solution was washed with saturated NaHCO$_3$ (5 ml×3), 10% aqueous citric acid (5 ml×3), saturated NaCl (5 ml×3), dried over Na$_2$SO$_4$, concentrated *in vacuo*. Purification of the yellow-brown oil (95.1 mg) by preparative TLC (hexane/AcOEt=1 : 1) provided **32a** (13.9 mg, 34%) and **32b** (11.7 mg, 29%) both as white brown crystals.

32a *Rf*: 0.34 (hexane/AcOEt=1 : 1). $[\alpha]_D^{24}$ −13.48° (*c*=1.18, CHCl$_3$). mp: 103—110 °C. ^{1}H-NMR (400 MHz) δ_H: 1.38 (9H, m, ^{t}Bu), 1.40 (9H, s, Boc), 3.29 (3H, s, IHPG OCH$_3$), 3.30 (2H, hidden, Trp 3-H$_2$), 3.72 (3H, s, COOCH$_3$), 3.92 (3H, s, CHPG OCH$_3$), 4.64 (1H, dt, *J*=5.0, 7.5 Hz, Trp 2-H), 5.09, 5.13 (each 1H, d, *J*=12.0 Hz, benzyl CH$_2$), 5.20 (1H, br d, *J*=7.0 Hz, IHPG 2-H), 5.35 (1H, br d, *J*=7.5 Hz, Trp NHCO), 5.47 (1H, br d, *J*=7.0 Hz, CHPG 2-H), 5.80 (1H, br, IHPG NHCO), 6.99 (1H, d, *J*=7.0 Hz, CHPG NHCO), 7.02 (1H, d, *J*=2.0 Hz, IHPG 2′-H), 7.07 (1H, d, *J*=2.0 Hz, Trp 2′-H), 7.08 (1H, hidden, Trp 7′-H), 7.25 (1H, dd, *J*=2.0, 7.5 Hz, Trp 4′-H), 7.33 (2H, s, CHPG 2′, 6′-H), 7.34 (5H, m, benzyl-arom H), 7.57 (1H, hidden, Trp 5′-H), 7.58 (1H, d, *J*=2.0 Hz, IHPG 6′-H), 8.49 (1H, br s, Trp 1′-H). ^{13}C-NMR (100 MHz) δ_C: 27.93 (q×3, ^{t}Bu C(CH$_3$)$_3$), 27.93 (t, Trp 3-C), 28.26 (q×3, Boc C(CH$_3$)$_3$), 53.32 (q, COOCH$_3$), 54.94 (d, Trp 2-C), 55.38 (d, CHPG 2-C), 57.22 (IHPG 2-C), 60.10 (q, IHPG OCH$_3$), 60.94 (q, CHPG OCH$_3$), 66.84 (t, benzyl CH$_2$), 80.74 (s, Boc C(CH$_3$)$_3$), 82.10 (s, ^{t}Bu C(CH$_3$)$_3$), 93.67 (s, IHPG 5′-C), 110.24 (s, Trp 3′-C), 111.21 (d, Trp 7′-C), 118.77 (d, Trp 5′-C), 120.68 (d, Trp 4′-C), 123.80 (d, Trp 2′-C), 127.41 (s, Trp 3a′-C), 127.77, 128.13, 128.50 (each d, benzyl-arom C), 129.61 (d×2, CHPG 2′, 6′-C), 129.73 (d, IHPG 2′-C), 130.09 (s×2, CHPG 3′, 5′-C), 131.18 (s, IHPG 3′-C), 133.02 (s, CHPG 1′-C), 135.78 (s, Trp 7a′-C), 136.06 (s, Trp 6′-C), 136.30 (s, IHPG 1′-C), 136.37 (s, benzyl-arom 1-C), 136.69 (d, IHPG 6′-C), 152.07 (s, CHPG 4′-C), 155.78 (s, Trp NHCO), 157.24 (s, IHPG 4′-C), 168.15 (s, CHPG NHCO), 168.15 (s, CHPG 1-C), 170.28 (s, IHPG 1-C), 170.78 (s, Trp 1-C). HR-FAB-MS *m/z*: 1044.2003 [M]$^+$, Calcd for $C_{47}H_{51}O_{11}N_4ICl^{35}{}_2$: 1044.1976 [M].

32b *Rf*: 0.43 (hexane/AcOEt=1 : 1). $[\alpha]_D^{21}$ −31.04° (*c*=0.92, CHCl$_3$). mp: 44—49 °C. ^{1}H-NMR (300 MHz) δ_H: 1.37 (9H, m, ^{t}Bu), 1.41 (9H, s, Boc), 3.30 (2H, m, Trp 3-H$_2$), 3.34 (3H, s, IHPG OCH$_3$), 3.73 (3H, s, IHPG COOCH$_3$), 3.90 (3H, s, CHPG OCH$_3$), 4.64 (1H, dt, *J*=5.0, 7.5 Hz, Trp 2-H), 5.10, 5.13 (each 1H, d, *J*=12.0 Hz, benzyl CH$_2$), 5.12 (1H, hidden, IHPG 2-H), 5.35 (1H, br d, *J*=7.5 Hz, Trp NHCO), 5.44 (1H, br d, *J*=6.5 Hz, CHPG 2-H), 5.66 (1H, br, IHPG NHCO), 6.91 (1H, d, *J*=6.5 Hz, CHPG NHCO), 7.07 (1H, d, *J*=2.0 Hz, Trp 2′-H), 7.30 (1H, dd, *J*=2.0, 7.5 Hz, Trp 5′-H), 7.32 (1H, d, *J*=2.0 Hz, IHPG 2′-H), 7.32 (2H, s, CHPG 2′, 6′-H), 7.34 (5H, m, benzyl-arom H), 7.50 (1H, s, Trp 7′-H), 7.62 (1H, d, *J*=7.5 Hz, Trp 4′-H), 7.69 (1H, d, *J*=2.0 Hz, IHPG 6′-H), 8.16 (1H, br s, Trp 1′-H). ^{13}C-NMR (75 MHz) δ_C: 27.93 (q×3, ^{t}Bu C(CH$_3$)$_3$), 27.93 (t, Trp 3-C), 28.22 (q×3, Boc C(CH$_3$)$_3$), 53.21 (q, COOCH$_3$), 54.94 (d, Trp 2-C), 55.67 (d, CHPG 2-C), 57.32 (IHPG 2-C), 60.13 (q, IHPG OCH$_3$), 60.73 (q, CHPG OCH$_3$), 66.83 (t, benzyl CH$_2$), 80.79 (s, Boc C(CH$_3$)$_3$), 82.12 (s, ^{t}Bu C(CH$_3$)$_3$), 93.82 (s, IHPG 5′-C), 110.44 (s, Trp 3′-C), 111.54 (d, Trp 7′-C), 118.90 (d, Trp 4′-C), 120.72 (d, Trp 5′-C), 123.79 (d, Trp 2′-C), 127.50 (s, Trp 3a′-C), 127.79, 128.14, 128.50 (each d, benzyl-arom C), 129.94 (s, benzyl-arom 1-C), 130.66 (d×2, CHPG 2′, 6′-C), 130.66 (d, IHPG 2′-C), 131.17 (s, Trp 6′-C), 133.47 (s, CHPG 1′-C), 135.16 (s, IHPG 1′-C), 136.08 (s, Trp 7a′-C), 136.21 (s×2, CHPG 3′, 5′-C), 136.21 (d, IHPG 6′-C), 136.70 (s, IHPG 3′-C), 152.42 (s, CHPG 4′-C), 155.76 (s, Trp NHCO), 157.28 (s, IHPG 4′-C), 168.51 (s, CHPG 1-C), 170.22 (s, IHPG 1-C), 170.24 (s, CHPG NHCO), 170.99 (s, Trp 1-C). HR-FAB-MS *m/z*: 1044.2003 [M]$^+$, Calcd for $C_{47}H_{51}O_{11}N_4ICl_2$: 1044.1976 [M].

(*R*,*R*,*R*)-2-(2-{3-[3-(2-Carbobenzyloxy-aminopropionylcarboxy)indol-6-yl]-5-iodo-4-methoxyphenyl}-2-methoxycarbonylmethylamino)-2-(3,5-dichloro-4-methoxyphenyl)methylammonium Trifluoroacetate (5) To a solution of **32a** (13.0 mg, 0.014 mmol) in CH$_2$Cl$_2$ (0.5 ml) was added TFA (0.5 ml) and the mixture was stirred for 1.5 h at room temperature. Then TFA was removed *in vacuo* by azeotropic distillation with benzene to afford **5** (10.5 mg, 93%) as white yellow crystals. *Rf*: 0.20 (CHCl$_3$/MeOH=10 : 1). mp: 92—97 °C. $[\alpha]_D^{24}$ −9.20° (*c*=0.40, MeOH). ^{1}H-NMR (300 MHz, CD$_3$OD) δ_H: 3.21 (1H, dd, *J*=8.0, 17.0 Hz, Trp 3-Ha), 3.28 (3H, s, IHPG OCH$_3$), 3.37 (1H, dd, *J*=5.0, 17.0 Hz, Trp 3-Hb), 3.76 (6H, s, CHPG OCH$_3$, COOCH$_3$), 4.53 (1H, dd, *J*=4.5, 8.0 Hz, Trp 2-H), 5.02, 5.07 (each 1H, d, *J*=12.0 Hz, benzyl CH$_2$), 5.07 (1H, br s, CHPG 2-H), 5.59 (1H, s, IHPG 2-H), 7.01 (1H, dd, *J*=2.0, 8.5 Hz, Trp 5′-H), 7.15 (1H, br, Trp 2′-H), 7.21 (1H, d, *J*=2.5 Hz, IHPG 2′-H), 7.29 (5H, m, benzyl-arom H), 7.43 (2H, s, CHPG 2′, 6′-H), 7.49 (1H, br s, Trp 7′-H), 7.55 (H, d, *J*=2.5 Hz, IHPG 6′-H), 7.59 (1H, d, *J*=8.5 Hz, Trp 4′-H). ^{13}C-NMR (75 MHz, CD$_3$OD) δ_H: 53.46, 61.39 (each q, CHPG OCH$_3$, COOCH$_3$), 56.08 (d, Trp 2-C), 56.31 (IHPG 2-C), 56.96 (d, CHPG 2-C), 60.46 (q, IHPG OCH$_3$), 67.49 (t, benzyl CH$_2$), 93.85 (s, IHPG 5′-C), 111.21 (s, Trp 3′-C), 112.66 (d, Trp 7′-C), 111.26 (d, Trp 4′-C), 120.78 (d, Trp 5′-C), 125.69 (d, Trp 2′-C), 128.57 (s, Trp 3a′-C), 128.78, 129.16, 129.28 (each d, benzyl-arom C), 130.03 (d×2, CHPG 2′, 6′-C), 131.16 (s×2, CHPG 3′, 5′-C), 131.47 (s, CHPG 1′-C), 131.86 (s, IHPG 3′-C), 132.33 (d, IHPG 2′-C), 134.59 (s, IHPG 1′-C), 137.31 (d, IHPG 6′-C), 137.79 (s, benzyl-arom 1-C), 138.05 (s, Trp 7a′-C), 138.17 (s, Trp 6′-C), 154.81 (s, CHPG 4′-C), 158.20 (s, Trp

NHCO), 158.39 (s, IHPG 4′-C), 167.28 (s, CHPG 1-C), 171.26 (s, IHPG 1-C), 175.32 (s, Trp 1-C). HR-FAB-MS *m/z*: 911.1684 $[M+Na]^+$, Calcd for $C_{38}H_{35}O_9N_4Cl^{35}{}_2NaI$: 911.1724 [M+Na].

(*R*,*R*) and (*R*,*S*)-6-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-*N*-carbobenzyloxy-tryptophyl-3′,5′-dichloro-4′-methoxyphenylglycine *tert*-Butyl Ester (33a, 33b) To a solution of **24** (20 mg, 0.027 mmol) in DMSO (0.8 ml) were added $PdCl_2$(dppf) (2.0 mg, 0.0027 mmol), bis(pinacolate)diboron (8.23 mg, 0.032 mmol), KOAc (7.94 mg, 0.081 mmol). After the mixture was stirred for 2.5 h at 80 °C under argon, the solution was diluted with benzene (50 ml), washed with saturated NaCl (2 ml×3). The organic layer was dried over Na_2SO_4, concentrated *in vacuo*. Purification of the brown oil by preparative TLC ($CHCl_3$/MeOH=30 : 1) afforded a mixture of **33a** and **33b** (13 mg, 64%) both as light brown crystals. Purification of the diastereomeric mixture by preparative TLC gave **33a** and **33b** as a single product.

33a *Rf*: 0.58 ($CHCl_3$: MeOH=50 : 1). mp: 82—88 °C. $[\alpha]_D^{27}$ +11.52° (*c*=0.17, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 1.34 (9H, s, ^{t}Bu), 1.38 (12H, s, boronic ester CH_3×4), 3.18 (1H, dd, *J*=7.5, 15.0 Hz, Trp 3-Ha), 3.39 (1H, dd, *J*=5.0, 15.0 Hz, Trp 3-Hb), 3.89 (3H, s, OCH_3), 4.58 (1H, dt, *J*=8.0, 5.0 Hz, Trp 2-H), 5.10, 5.13 (each 1H, d, *J*=12.0 Hz, benzyl CH_2), 5.12 (1H, hidden, CHPG 2-H), 5.36 (1H, br d, *J*=8.0 Hz, Trp NHCO), 6.84 (1H, br d, *J*=7.0 Hz, CHPG NHCO), 7.00 (1H, d, *J*=2.5 Hz, Trp 2′-H), 7.13 (2H, s, CHPG 2′, 6′-H), 7.34 (5H, m, benzyl-arom H), 7.55 (1H, d, *J*=7.5 Hz, Trp 5′-H), 7.60 (1H, d, *J*=7.5 Hz, Trp 4′-H), 7.86 (1H, s, Trp 7′-H), 8.13 (1H, s, Trp 1′-H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C: 24.75 (q×4, boronic ester C($\underline{CH_3}$)$_2$×2), 27.48 (q×3, ^{t}Bu C($\underline{CH_3}$)$_3$), 27.48 (t, Trp 3-C), 55.09 (d, Trp 2-C), 55.49 (d, CHPG 2-C), 60.60 (q, OCH_3), 65.15 (t, benzyl CH_2), 81.75 (s, ^{t}Bu $\underline{C}(CH_3)_3$), 83.04 (s×2, boronic ester $\underline{C}(CH_3)_2$×2), 110.03 (s, Trp 3′-C), 117.78 (d, Trp 5′-C), 118.18 (d, Trp 7′-C), 119.96 (s, Trp 6′-C), 123.63 (d, Trp 2′-C), 125.71 (s, CHPG 3′, 5′-C), 127.21, 127.46, 128.02, 128.30 (each d, benzyl-arom C), 128.30 (d, CHPG 2′, 6′-C), 129.45 (s, Trp 3a′-C), 134.73 (s, CHPG 1′-C), 135.58 (s, Trp 7a′-C), 136.74 (s, benzyl-arom 1-C), 150.90 (s, CHPG 4′-C), 151.57 (s, Trp NHCO), 168.32 (s, Trp 1′-C), 171.60 (s, CHPG 1-C). HR-FAB-MS *m/z*: 774.2499 $[M+Na]^+$, Calcd for $C_{38}H_{44}O_8N_3Cl^{35}{}_2B^{11}Na$: 774.2496 [M+Na].

33b *Rf*: 0.56 ($CHCl_3$/MeOH=50 : 1). mp: 78—84 °C. $[\alpha]_D^{21}$ +23.14° (*c*=0.21, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 1.34 (9H, s, ^{t}Bu), 1.38 (12H, s, boronic ester C(CH_3)$_2$×2), 3.16 (1H, dd, *J*=7.0, 15.0 Hz, Trp 3-Ha), 3.37 (1H, m, Trp 3-Hb), 3.90 (3H, s, OCH_3), 4.59 (1H, br, Trp 2-H), 5.10, 5.12 (each 1H, d, *J*=12.0 Hz, benzyl CH_2), 5.19 (1H, d, *J*=7.0 Hz, CHPG 2-H), 5.37 (1H, br d, *J*=7.0 Hz, Trp NHCO), 6.66 (1H, br d, *J*=7.0 Hz, CHPG NHCO), 6.93 (1H, d, *J*=2.5 Hz, Trp 2′-H), 7.05 (2H, s, CHPG 2′, 6′-H), 7.34 (5H, m, benzyl-arom H), 7.55 (1H, dd, *J*=2.5, 7.5 Hz, Trp 5′-H), 7.65 (1H, br d, *J*=7.5 Hz, Trp 4′-H), 7.86 (1H, s, Trp 7′-H), 8.09 (1H, s, Trp 1′-H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C: 24.75 (q×4, boronic ester C($\underline{CH_3}$)$_2$×2), 27.48 (q×3, ^{t}Bu C($\underline{CH_3}$)$_3$), 27.48 (t, Trp 3-C), 55.25 (d, Trp 2-C), 55.60 (d, CHPG 2-C), 60.57 (q, OCH_3), 65.15 (t, benzyl CH_2), 81.69 (s, ^{t}Bu $\underline{C}(CH_3)_3$), 83.04 (s×2, boronic ester $\underline{C}(CH_3)_2$×2), 109.91 (s, Trp 3′-C), 117.75 (d, Trp 5′-C), 118.18 (d, Trp 7′-C), 119.96 (s, Trp 6′-C), 123.63 (d, Trp 2′-C), 125.71 (s, CHPG 3′, 5′-C), 127.27, 127.93, 128.15, 128.89 (each d, benzyl-arom C), 128.30 (d, CHPG 2′, 6′-C), 129.45 (s, Trp 3a′-C), 134.68 (s, CHPG 1′-C), 135.53 (s, Trp 7a′-C), 136.81 (s, benzyl-arom 1-C), 150.90 (s, CHPG 4′-C), 155.51 (s, Trp NHCO), 168.27 (s, Trp 1′-C), 171.64 (s, CHPG 1-C). HR-FAB-MS *m/z*: 774.2468 $[M+Na]^+$, Calcd for $C_{38}H_{44}O_8N_3Cl_2B^{11}Na$: 774.2496 [M+Na].

(*R*,*RS*)-6-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-*N*-carbobenzyloxy-tryptophyl-3′,5′-dichloro-4′-methoxyphenylglycine (34) To a solution of **33** (11.5 mg, 0.015 mmol) in CH_2Cl_2 (0.2 ml) was added TFA (0.2 ml) at 0 °C and the solution was stirred for 1 h, then 2 h at room temperature. TFA was removed *in vacuo* by azeotropic distillation with benzene to provide **34** (10.4 mg, quant.) as white-brown crystals. *Rf*: 0.40 (benzene/acetone=5 : 1). mp: 100—110 °C. ^{1}H-NMR (300 MHz) δ_H: 1.37 (12H, s, boronic ester CH_3×4), 3.15 (1H, m, 3-Ha), 3.32 (1H, dd, *J*=5.0, 14.0 Hz, 3-Hb), 3.83 (3H, s, OCH_3), 4.60 (1H, br, Trp 2-H), 5.08 (2H, br, benzyl CH_2), 5.19 (1H, d, *J*=6.5 Hz, CHPG 2-H), 5.64 (1H, br, Trp NHCO), 6.89, 6.95 (total 1H, br, CHPG NHCO), 7.00, 7.03 (total 1H, brs, Trp 2-H), 7.11 (2H, s, CHPG 2′, 6′-H), 7.31 (5H, m, benzyl-arom H), 7.52 (1H, d, *J*=7.5 Hz, Trp 5′-H), 7.58 (1H, d, *J*=7.5 Hz, Trp 4′-H), 7.81, 7.86 (total 1H, s, Trp 7′-H), 8.23, 8.42 (total 1H, br s, Trp 1′-H). HR-FAB-MS *m/z*: 695.1932 $[M]^+$, Calcd for $C_{34}H_{36}O_8N_3Cl_2B^{11}$: 695.1973 [M].

(*R*)-2-(3,5-Diiodo-4-methoxyphenyl)-2-methoxy-carbonylmethylammonium *p*-Toluene-sulfonate (35) To a solution of **19** (72.5 mg, 0.125 mmol) in ether (1.0 ml) was added *p*-TsOH (24.0 mg, 0.138 mmol) in EtOH (1.5 ml) with stirring. After the mixture was stirred for 30 min at room temperature, EtOH was removed *in vacuo*. The residue was again dissolved in EtOH (1.0 ml) and the solution was stirred for 30 min. Concentration of the solvent gave **35** (83.8 mg, quant.) as a light yellow oil. *Rf*: 0.16 (hexane/AcOEt=2 : 1). mp: 212—214 °C. $[\alpha]_D^{24}$ −60.90° (*c*=0.24, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H : 2.47 (3H, s, *p*-TsOH CH_3), 3.58, 3.79 (each 3H, s, OCH_3×2), 5.18 (1H, s, 2-H), 7.16, 7.60 (2H, d, *J*=7.5 Hz, *p*-TsOH 3, 5-H), 7.60 (2H, d, *J*=7.5 Hz, *p*-TsOH 2, 6-H), 7.82 (2H, s, 2′, 6′-H), 8.66 (3H, br s, NH_3^+). HR-FAB-MS *m/z*: 447.8914 $[M]^+$, Calcd for $C_{10}H_{12}O_3NI_2$: 447.8907 [M].

(*R*,*R*,*R*) and (*R*,*S*,*R*)-6-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-*N*-carbobenzyloxy-tryptophyl-3′,5′-dichloro-4′-methoxy-phenylglycyl-3′,5′-diiodo-4′-methoxyphenylglycine Methyl Ester ((*R*,*R*,*R*)-6a, (*R*,*S*,*R*)-6a) To a solution of **35** (9.29 mg, 0.015 mmol) in THF (0.3 ml) was added NMM (1.82 mg, 0.018 mmol) and the solution was stirred for 5 min at room temperature. Then **34** (10.4 mg, 0.015 mmol) in CH_2Cl_2 (0.3 ml), EDCI (5.8 mg, 0.03 mmol) in CH_2Cl_2 (0.3 ml), HOBT (2.3 mg, 0.015 mmol) were added to this solution, which was stirred for 2 h under argon at 0 °C. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in AcOEt (100 ml), which was washed with saturated $NaHCO_3$ (5 ml×2), 10% aqueous citric acid (5 ml×2), saturated NaCl (5 ml×2), dried over Na_2SO_4, concentrated *in vacuo*. Purification of the resulting yellow brown oil (40.0 mg) by preparative TLC (hexane/AcOEt=1 : 1) afforded (*R*,*R*,*R*)-**6a** (3.4 mg, 29%) and (*R*,*S*,*R*)-**6a** (4.7 mg, 20%) as yellow brown crystals.

(*R*,*R*,*R*)-**6a** *Rf*: 0.17 (hexane/AcOEt=2 : 1). mp: 109—115 °C. $[\alpha]_D^{22}$ −49.57° (*c*=0.13, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 1.37 (12H, s, boronic ester C($\underline{CH_3}$)$_2$×2), 3.17 (1H, dd, *J*=7.0, 15.0 Hz, Trp 3-Ha), 3.41 (1H, dd, *J*=5.5, 15.0 Hz, Trp 3-Hb), 3.69 (3H, s, $COOCH_3$), 3.81 (3H, s, IHPG OCH_3), 3.87 (3H, s, CHPG OCH_3), 4.63 (1H, br, Trp 2-H), 5.09 (2H, m, benzyl CH_2), 5.33 (1H, d, *J*=7.0 Hz, IHPG 2-H), 5.44 (1H, br d, *J*=7.0 Hz, Trp NHCO), 5.47 (1H, d, *J*=6.5 Hz, CHPG 2-H), 6.87 (1H, br, CHPG NHCO), 6.89 (1H, d, *J*=2.0 Hz, Trp 2′-H), 7.10 (2H, s, CHPG 2′,6′-H), 7.30 (5H, m, benzyl-arom H), 7.44 (1H, br, IHPG NHCO), 7.55 (1H, d, *J*=8.0Hz, Trp 5′-H), 7.63 (1H, d, *J*=8.0 Hz, Trp 4′-H), 7.76 (2H, s, IHPG 2′, 6′-H), 7.87 (1H, s, Trp 7′-H), 8.09 (1H, s, Trp 1-H). ^{13}C-NMR (100 MHz) δ_C: 24.91 (q×4, boronic ester C(CH_3)$_2$×2), 27.97 (t, Trp 3-C), 53.34 (q, $COOCH_3$), 54.83 (d, IHPG 2-C), 55.61 (d, Trp 2-C), 56.00 (CHPG 2-C), 60.67 (q, IHPG OCH_3), 60.72 (q, CHPG OCH_3), 67.35 (t, benzyl CH_2), 83.61 (s×2, boronic ester $\underline{C}(CH_3)_2$×2), 91.00 (s×2, IHPG 3′, 5′-C), 109.90 (s, Trp 3′-C), 117.86 (d, Trp 4′-C), 118.54 (d, Trp 7′-C), 119.99 (s, benzyl 1′-C), 122.55 (s, Trp 6′-C), 124.84 (d, Trp 2′-C), 125.91 (d, Trp 5′-C), 127.75, 128.17, 128.25 (each d, benzyl-arom C), 128.55 (d×2, CHPG 2′, 6′-C), 129.53 (s, Trp 3a′-C), 129.80 (s×2, CHPG 3′, 5′-C), 133.88 (s, CHPG 1′-C), 135.54 (s, benzyl-arom 1′-C), 135.96 (s, Trp 7a′-C), 138.60 (s, IHPG 1′-C), 138.60 (d×2, IHPG 2′, 6′-C), 152.49 (s, CHPG 4′-C), 156.14 (s, Trp NHCO), 159.33 (s, IHPG 4′-C), 167.85 (s, CHPG 1-C), 169.65 (s, IHPG 1-C), 171.26 (s, Trp 1-C). HR-FAB-MS *m/z*: 1147.0604 $[M+Na]^+$, Calcd for $C_{44}H_{45}O_{10}N_4Cl^{35}{}_2B^{11}NaI_2$: 1147.0601 [M+Na].

(*R*,*S*,*R*)-**6a** *Rf*: 0.12 (hexane/AcOEt=2 : 1). mp: 111—118 °C. $[\alpha]_D^{23}$ −34.72° (*c*=0.15, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 1.37 (12H, s, boronic ester C($\underline{CH_3}$)$_2$×2), 3.20, 3.29 (each 1H, dd, *J*=5.0, 14.0 Hz, Trp 3-H_2), 3.61 (3H, s, IHPG $COOCH_3$), 3.77 (3H, s, IHPG OCH_3), 3.88 (3H, s, CHPG OCH_3), 4.62 (1H, dt, *J*=5.0, 8.0 Hz, Trp 2-H), 5.05 (2H, m, benzyl CH_2), 5.37 (1H, d, *J*=6.5 Hz, IHPG 2-H), 5.95 (1H, br d, *J*=8.0 Hz, Trp NHCO), 5.72 (1H, d, *J*=7.0 Hz, CHPG 2-H), 6.86 (1H, br d, *J*=7.0 Hz, CHPG NHCO), 6.95 (2H, s, CHPG 2′, 6′-H), 6.96 (1H, m, Trp 2′-H), 7.32 (5H, m, benzyl-arom H), 7.50 (2H, brs, IHPG 2′, 6′-H), 7.56 (1H, d, *J*=8.0 Hz, Trp 5′-H), 7.66 (1H, d, *J*=8.0 Hz, Trp 4′-H), 7.85 (1H, s, Trp 7′-H), 7.89 (1H, br d, *J*=6.5 Hz, IHPG NHCO), 8.13 (1H, s, Trp 1-H). ^{13}C-NMR (100 MHz) δ_C: 24.90 (q×4, boronic ester C($\underline{CH_3}$)$_2$×2), 28.82 (t, Trp 3-C), 53.41 (q, $COO\underline{CH_3}$), 54.25 (d, IHPG 2-C), 55.28 (CHPG 2-C), 55.96 (d, Trp 2-C), 60.58 (q, IHPG OCH_3), 60.80 (q, CHPG OCH_3), 67.22 (t, benzyl CH_2), 83.56 (s×2, boronic ester $\underline{C}(CH_3)_2$×2), 90.79 (s×2, IHPG 3′, 5′-C), 110.02 (s, Trp 3′-C), 117.81 (d, Trp 4′-C), 118.59 (d, Trp 7′-C), 120.00 (s, benzyl 1′-C), 122.20 (s, Trp 6′-C), 124.58 (d, Trp 2′-C), 125.82 (d, Trp 5′-C), 128.22, 128.25, 128.49 (each d, benzyl-arom C), 129.38 (s, Trp 3a′-C), 129.64 (s×2, CHPG 3′, 5′-C), 134.11 (s, CHPG 1′-C), 135.10 (s, benzyl-arom 1′-C), 135.85 (s, Trp 7a′-C), 137.99 (s, IHPG 1′-C), 137.99 (d×2, IHPG 2′, 6′-C), 152.33 (s, CHPG 4′-C), 156.13 (s, Trp NHCO), 159.07 (s, IHPG 4′-C), 167.94 (s, CHPG 1-C), 170.03 (s, IHPG 1-C), 171.67 (s, Trp 1-C). HR-FAB-MS *m/z*: 1147.0597 $[M+Na]^+$, Calcd for $C_{44}H_{45}O_{10}N_4Cl^{35}{}_2B^{11}NaI_2$: 1147.0601 [M+Na].

(*R*)-*N*-*tert*-Butoxycarbonyl-4′-hydroxy-3′,5′-diiodo-phenylglycine Methyl Ester (36) To a solution of **18** (2.50 g, 4.82 mmol) in MeOH (7.5 ml) and benzene (32.5 ml), was added $TMSCHN_2$ (2.9 ml, 5.78 mmol)

in benzene (5.0 ml) in portions under argon. After the mixture was stirred for 1 h at room temperature, the solution was concentrated *in vacuo*. The residue (2.52 mg) was purified by flash column chromatography (hexane/AcOEt=5 : 1) to provide **36** (2.17 g, 85%) as a light yellow crystals. *Rf*: 0.76 ($CHCl_3$/MeOH=7 : 1). mp: 62—65 °C ($CHCl_3$). $[\alpha]_D^{25}$ −98.21° (*c*=1.01, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 1660 (NHCOO), 1730 (COOMe), 3260 (NHCOO), 3440 (OH). ^{1}H-NMR (400 MHz) δ_H: 1.43 (9H, s, Boc), 3.73 (3H, s, CH_3), 5.16 (1H, d, *J*=6.0 Hz, 2-H), 5.61 (1H, d, *J*=6.0 Hz, NHCO), 5.84 (1H, s, OH), 7.66 (2H, s, 2′, 6′-H). ^{13}C-NMR (100 MHz) δ_C: 28.25 (q, C($\underline{CH_3}$)$_3$), 53.02 (d, 2-C), 80.57 (s, 3′, 5′-C), 82.44 (s, $\underline{C}(CH_3)_3$), 133.02 (s, 1′-C), 137.83 (d, 2′, 6′-C), 153.73 (s, 4′-C), 154.55 (s, NHCO), 170.79 (s, 1-C). HR-FAB-MS *m/z*: 555.9114 $[M+Na]^+$, Calcd for $C_{14}H_{17}O_5NI_2Na$: 555.9094 [M+Na].

(*R*,*R*)-*N*-*tert*-Butoxycarbonyl-3′,5′-dichloro-4′-hydroxy-phenylglycyl-4′-hydroxy-3′,5′-diiodo-phenylglycine Methyl Ester (38) A solution of **36** (301 mg, 0.564 mmol) in TFA (0.6 ml) was stirred for 30 min at 0 °C and concentrated *in vacuo* to give **37** as light orange crystals, which were dissolved in THF (0.7 ml), then neutralized by NMM (66.0 μl, 0.655 mmol) at −5 °C. To the resulting solution were added **26** (358 mg, 0.564 mmol) in CH_2Cl_2 (0.7 ml), HOBt (88.5 mg, 0.655 mmol). After the mixture was stirred for 5 h at −5 °C, it was concentrated *in vacuo*. The residue was dissolved in AcOEt (50 ml), washed with 10% citric acid (10 ml×2), saturated $NaHCO_3$ (10 ml×2), saturated NaCl (10 ml×2), dried over Na_2SO_4, concentrated *in vacuo*. The resulting purple crystals (405.0 mg) were purified by flash column chromatography (hexane/AcOEt=2 : 1) to give **38** (343.8 mg, 77%) as a light yellow amorphous. *Rf*: 0.56 ($CHCl_3$/MeOH=5 : 1). mp: 135—137 °C (AcOEt). $[\alpha]_D^{24}$ −84.79° (*c*=0.50, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 1650 (NHCO), 1700 (COOMe), 3300 (OH). ^{1}H-NMR (400 MHz) δ_H: 1.41 (9H, s, Boc), 3.72 (3H, s, CH_3), 5.12 (1H, br, CHPG 2-H), 5.34 (1H, d, *J*=6.5 Hz, IHPG 2-H), 5.68 (1H, d, *J*=6.5 Hz, CHPG NHCO), 7.12 (1H, br d, *J*=6.5 Hz, IHPG NHCO), 7.27 (2H, s, CHPG 2′, 6′-H), 7.62 (2H, s, IHPG 2′, 6′-H). HR-FAB-MS *m/z*: 772.8794 $[M+Na]^+$, Calcd for $C_{22}H_{22}O_7N_2Cl^{35}{}_2Br^{79}I_2Na$: 772.8791 [M+Na].

(*R*,*R*)-*N*-*tert*-Butoxycarbonyl-3′,5′-dichloro-4′-methoxy-phenylglycyl-3′,5′-diiodo-4′-methoxy-phenylglycine Methyl Ester (39) To a solution of **38** (115.8 mg, 0.154 mmol) in benzene/MeOH=5 : 1 (0.6 ml) was added $TMSCHN_2$ (193 μl, 0.386 mmol) in portions under argon. After the mixture was stirred for 3 min at room temperature, the solution was concentrated *in vacuo*. The residue (116 mg) was purified by preparative TLC (hexane/AcOEt=3 : 1) to provide **39** (99.0 mg, 82%) as light yellow crystals. *Rf*: 0.83 ($CHCl_3$/MeOH=50 : 1). mp: 129—131 °C ($CHCl_3$). $[\alpha]_D^{24}$ −73.18° (*c*=0.55, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 1.42 (9H, s, Boc), 3.73 (3H, s, COOMe), 3.83 (3H, s, IHPG OMe), 3.88 (3H, s, CHPG OMe), 5.14 (1H, br, CHPG 2-H), 5.36 (1H, d, *J*=6.5 Hz, IHPG 2-H), 5.67 (1H, d, *J*=6.5 Hz, CHPG NHCO), 7.12 (1H, br d, *J*=6.5 Hz, IHPG NHCO), 7.32 (2H, s, CHPG 2′, 6′-H), 7.72 (2H, s, IHPG 2′, 6′-H). ^{13}C-NMR (100 MHz) δ_C: 28.29 (q, C($\underline{CH_3}$)$_3$), 53.42 (q, COO$\underline{CH_3}$), 54.77 (d, IHPG 2-C), 57.34 (d, CHPG 2-C), 60.66 (q, IHPG OCH_3), 60.73 (q, CHPG OCH_3), 80.92 (s, $\underline{C}(CH_3)_3$), 90.96 (s, IHPG 3′, 5′-C), 127.76 (d, CHPG 2′, 6′-C), 129.97 (s, CHPG 3′, 5′-C), 134.83 (s, CHPG 1′-C), 135.51 (s, IHPG 1′-C), 138.45 (d, IHPG 2′, 6′-C), 152.53 (s, CHPG 4′-C), 154.91 (s, CHPG NHCO), 159.27 (s, IHPG 4′-C), 168.60 (s, CHPG 1-C), 169.79 (s, IHPG 1-C). HR-FAB-MS *m/z*: 800.9098 $[M+Na]^+$, Calcd for $C_{24}H_{26}O_7N_2Cl^{35}{}_2Br^{79}I_2Na$: 800.9104 [M+Na].

(*R*,*R*)-3′,5′-Dichloro-4′-methoxy-phenylglycyl-3′,5′-diiodo-4′-methoxy-phenylglycine Methyl Ester TFA Salt (40) To a solution of **39** (147 mg, 0.189 mmol) in CH_2Cl_2 (0.5 ml), was added TFA (0.5 ml) at 0 °C. After the mixture was stirred for 2.75 h, the solution was concentrated with benzene azeotrope to give **40** (152 mg, quant.) as light brown crystals. *Rf*: 0.67 (hexane/AcOEt=1 : 1). mp: 163—166 °C. $[\alpha]_D^{23}$ −72.16° (*c*=0.2, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 2.80 (2H, br, NH_2), 3.72 (3H, s, OMe), 3.79 (3H, s, OMe), 3.93 (3H, s, OMe), 5.27 (1H, br, CHPG 2-H), 5.33 (1H, d, *J*=6.0 Hz, IHPG 2-H), 7.53 (2H, br s, CHPG 2′, 6′-H), 7.65 (1H, br d, *J*=6.0 Hz, IHPG NHCO), 7.72 (2H, br s, IHPG 2′, 6′-H). HR-FAB-MS *m/z*: 700.8571 $[M+Na]^+$, Calcd for $C_{19}H_{18}O_5N_2Cl^{35}{}_2I_2Na$: 700.8580 [M+Na].

(*R*,*R*)-3′,5′-Dichloro-4′-methoxy-phenylglycyl-3′,5′-diiodo-4′-methoxy-phenylglycine Methyl Ester (41) After the salt **40** was neutralized by sat.$NaHCO_3$ (3 ml), the mixture was extracted with AcOEt (30 ml×3). The organic layer was washed with saturated NaCl (2 ml×2), dried over Na_2SO_4, concentrated *in vacuo* to provide **41** (124 mg, quant.) as white crystals. *Rf*: 0.60 ($CHCl_3$/MeOH=10 : 1). mp: 187—189 °C. $[\alpha]_D^{23}$ −71.7° (*c*=0.2, $CHCl_3$). ^{1}H-NMR (400 MHz). δ_H: 1.86 (2H, br, NH_2), 3.74 (3H, s, OMe), 3.80 (3H, s, OMe), 3.89 (3H, s, OMe), 4.95 (1H, br, CHPG 2-H), 5.37 (1H, d, *J*=6.0 Hz, IHPG 2-H), 7.48 (2H, br s, CHPG 2′, 6′-H), 7.72 (2H, br s, IHPG 2′, 6′-H), 8.14 (1H, br d, *J*=7.0 Hz, IHPG NHCO). HR-FAB-MS *m/z*: 678.8788 $[M+H]^+$, Calcd for $C_{19}H_{18}O_5N_2Cl^{35}{}_2I_2$: 678.8761 [M+H].

(*R*)-6-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-*N*-carbobenzyloxy-tryptophan *tert*-Butyl Ester (42) To a solution of (*R*)-**29** (18.3 mg, 0.035 mmol) in DMSO (0.8 ml), were added Pd(dppf)Cl_2 (2 mg, 0.0028 mmol), diboron (10.7 mg, 0.042 mmol), KOAc (10.3 mg, 0.105 mmol) under argon. After the mixture was stirred for 3.0 h at 77 °C, the reaction mixture was extracted with AcOEt (50 ml). The organic layer was washed with saturated NaCl (2 ml×5), dried over Na_2SO_4, concentrated *in vacuo*. The resulting residue (83.5 mg) was purified by preparative TLC (benzene/acetone=10 : 1) to give **42** (6.7 mg, 36.6%) as a yellow oil and starting material (*R*)-**29** (5.9 mg, 32%) was recovered. $[\alpha]_D^{23}$ −18.8° (*c*=0.12, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 1.35 (9H, s, ^{t}Bu), 1.37 (12H, s, $(CH_3)_2$×2), 3.24, 3.30 (each 1H, dd, *J*=5.5, 16.5 Hz, 3-H_2), 4.61 (1H, dt, *J*=5.5, 8.0 Hz, 2-H), 5.04 (2H, s, benzyl CH_2), 5.28 (1H, br d, *J*=8.0 Hz, NHCO), 7.06 (1H, d, *J*=2.3 Hz, 2′-H), 7.33 (5H, m, benzyl-arom H), 7.34 (1H, hidden, 5′-H), 7.53 (1H, dd, *J*=1.0, 8.0 Hz, 4′-H), 7.58 (1H, d, *J*=8.0 Hz, 5′-H), 7.84 (1H, s, 7′-H), 8.10 (1H, br s, 1′-H). HR-FAB-MS *m/z*: 543.26590 $[M+Na]^+$, Calcd for $C_{29}H_{37}O_6N_2BNa$: 543.2642 [M+Na].

(*R*)-6-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-*N*-carbobenzyloxy-tryptophan (43) To a solution of **42** (12.4 mg, 0.238 mmol) in CH_2Cl_2 (0.3 ml), was added TFA (0.3 ml) at 0 °C. After the solution was stirred for 3.5 h at 0 °C, it was concentrated with benzene azeotrope to give **43** (11.4 mg, quant.) as a yellow oil. *Rf*: 0.38 (benzene/acetone=10 : 1). $[\alpha]_D^{23}$ −18.8° (*c*=0.12, $CHCl_3$). ^{1}H-NMR (300 MHz). δ_H: 1.35 (9H, s, ^{t}Bu), 1.37 (12H, s, $(CH_3)_2$×2), 3.24, 3.30 (each 1H, dd, *J*=5.5, 16.5 Hz, 3-H_2), 4.61 (1H, dt, *J*=5.5, 8.0 Hz, 2-H), 5.04 (2H, s, benzyl CH_2), 5.28 (1H, br d, *J*=8.0 Hz, NHCO), 7.06 (1H, d, *J*=2.3 Hz, 2′-H), 7.33 (5H, m, benzyl-arom H), 7.34 (1H, hidden, 5′-H), 7.53 (1H, dd, *J*=1.0, 8.0 Hz, 4′-H), 7.58 (1H, d, *J*=8.0 Hz, 5′-H), 7.84 (1H, s, 7′-H), 8.10 (1H, br s, 1′-H). HR-FAB-MS *m/z*: 543.26590 $[M+Na]^+$, Calcd for $C_{29}H_{37}O_6N_2BNa$: 543.2642 [M+Na].

***R*,*R*,*R*-6-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-*N*-carbobenzyloxy-tryptophyl-3′,5′-dichloro-4′-methoxy-phenylglycyl-3′,5′-diiodo-4′-methoxy-phenylglycine Methyl Ester (6a)** To a solution of **43** (11.4 mg, 0.025 mmol) in THF/CH_2Cl_2=3 : 1 (1 ml), were added **41** (16.7 mg, 0.025 mmol), HATU (9.3 mg, 0.025 mmol), γ-collidine (14.9 mg, 0.125 mmol in THF/CH_2Cl_2=3 : 1; 0.2 ml) under argon at 0 °C. After the solution was stirred for 1 h at 0 °C, and for 1.5 h at room temperature, the reaction mixture was extracted by AcOEt (50 ml). The organic layer was washed with sat.$NaHCO_3$ (5 ml×2), dried over Na_2SO_4, concentrated *in vacuo*. The residue (45.7 mg) was purified by preparative TLC (hexane/AcOEt=1 : 1) to give **6a** (8.9 mg. 32%). *Rf*: 0.71 ($CHCl_3$/MeOH=10 : 1). mp: 109—115 °C. $[\alpha]_D^{22}$ −49.57° (*c*=0.13, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 1.37 (12H, s, boronic ester C($\underline{CH_3}$)$_2$×2), 3.17 (1H, dd, *J*=7.0, 15.0 Hz, Trp 3-Ha), 3.41 (1H, dd, *J*=5.5, 15.0 Hz, Trp 3-Hb), 3.69 (3H, s, $COOCH_3$), 3.81 (3H, s, IHPG OCH_3), 3.87 (3H, s, CHPG OCH_3), 4.63 (1H, br, Trp 2-H), 5.09 (2H, m, benzyl CH_2), 5.33 (1H, d, *J*=7.0 Hz, IHPG 2-H), 5.44 (1H, br d, *J*=7.0 Hz, Trp NHCO), 5.47 (1H, d, *J*=6.5 Hz, CHPG 2-H), 6.87 (1H, br, CHPG NHCO), 6.89 (1H, d, *J*=2.0 Hz, Trp 2′-H), 7.10 (2H, s, CHPG 2′, 6′-H), 7.30 (5H, m, benzyl-arom H), 7.44 (1H, br, IHPG NHCO), 7.55 (1H, d, *J*=8.0 Hz, Trp 5′-H), 7.63 (1H, d, *J*=8.0 Hz, Trp 4′-H), 7.76 (2H, s, IHPG 2′, 6′-H), 7.87 (1H, s, Trp 7′-H), 8.09 (1H, s, Trp 1-H). HR-FAB-MS *m/z*: 1147.0604 $[M+Na]^+$, Calcd for $C_{44}H_{45}O_{10}N_4Cl^{35}{}_2B^{11}NaI_2$: 1147.0601 [M+Na].

(*R*)-*N*-Cbz-6-Iodo-tryptophan Methyl Ester (44) To a solution of (*R*)-**15** (10 mg, 0.022 mmol) in MeOH (0.22 ml) and benzene (0.72 ml), added $TMSCHN_2$ (0.018 ml, 0.036 mmol) in portions under argon. After the mixture was stirred for 15 min at room temperature, the solution was concentrated *in vacuo*. Resulted residue was purified by preparative TLC (hexane/AcOEt=1 : 1) to provide **44** (7.7 mg, 75%) as light yellow crystals. *Rf*: 0.68 ($CHCl_3$/MeOH=5 : 1). $[\alpha]_D^{23}$ −36.5° (*c*=0.54, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 3.26, 3.28 (each 1H, dd, *J*=5.0, 17 Hz, 3-H_2), 3.60 (3H, s, OMe), 4.70 (1H, dt, *J*=8.0, 5.0 Hz, 2-H), 5.07, 5.12 (each 1H, d, *J*=12.0 Hz, benzyl CH_2), 5.29 (1H, d, *J*=8.0 Hz, NHCOO), 6.80 (1H, d, *J*=2.0 , 2′-H), 7.25 (1H, d, *J*=8.5 Hz, 4′-H), 7.34 (1H, dd, *J*=1.5, 8.5 Hz, 5′-H), 7.70 (1H, d, *J*=1.5 Hz, 7′-H), 8.05 (1H, br s, 1′-NH), 7.34 (5H, m, arom-H). HR-FAB-MS *m/z*: 478.0395 $[M]^+$, Calcd for $C_{20}H_{19}O_4N_2I$: 478.0390 [M].

(*R*)-*N*-Cbz-6-Tributylstannyl-tryptophan Methyl Ester (45) To a solution of **44** (16 mg, 0.033 mmol) in CH_3CN (0.5 ml) were added $(Bu_3Sn)_2$ (38.7 mg, 0.066 mmol) in CH_3CN (0.5 ml), (*o*-$tolyl_3P)_2PdCl_2$ (2.6 mg, 0.0033 mmol), ^{i}Pr_2NEt (17.4 μl, 0.10 mmol) under argon. After the solution was stirred for 0.5 h at 75 °C, the mixture was diluted with AcOEt (50 ml), the organic layer was washed with H_2O (3 ml×2), saturated NaCl (3 ml×2), dried over Na_2SO_4, concentrated *in vacuo*. The residue (45 mg) was purified

by flash column chromatography (hexane/AcOEt=4 : 1→3 : 1 (contained 1% NEt_3)) to provide **45** (9.6 mg, 45%) as a yellow oil. *Rf*: 0.87 (hexane/AcOEt=1 : 1). $[\alpha]_D^{23}$ −26.3° (*c*=0.60, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 0.88 (9H, t, $CH_3\times3$), 1.07, 1.34 (6H, m, $CH_2\times3$), 1.55 (6H, m, $CH_2\times3$), 3.29, 3.31 (each 1H, dd, *J*=5.5, 15 Hz, 3-H_2), 3.69 (3H, s, OMe), 4.71 (1H, dt, *J*=8.5, 5.5 Hz, 2-H), 5.08, 5.12 (each 1H, d, *J*=12.5 Hz, benzyl CH_2), 5.31 (1H, br d, *J*=8.5 Hz NHCOO), 6.93 (1H, d, *J*=2.0 Hz, 2′-H), 7.15 (1H, d, *J*=7.5 Hz, 4′-H), 7.33 (5H, m, arom-H), 7.44 (1H, d, *J*=1.5 Hz, 7′-H), 7.49 (1H, dd, *J*=1.5, 8.5 Hz, 5′-H), 7.97 (1H, br, 1′-NH). HR-FAB-MS *m/z*: 665.2405 $[M+Na]^+$, Calcd for $C_{32}H_{46}O_4N_2NaSn$: 665.2377 [M+Na].

(*R*)-*N*-Cbz-6-Tributylstannyl-tryptophan Carboxylic Acid Sodium Salt (46) To a solution of **45** (7.5 mg, 0.012 mmol) in MeOH (0.95 ml) was added 1 N NaOH (0.19 ml). After the solution was stirred for 3 h at 0 °C, MeOH was evaporated. The mixture was extracted with AcOEt (5 ml×3) and the organic layer was washed with H_2O (1 ml×3), saturated NaCl (1 ml), dried over Na_2SO_4, concentrated *in vacuo* to give **46** (7.5 mg, 99%) as a light yellow oil. *Rf*: 0.12 ($CHCl_3$/MeOH=10 : 1). $[\alpha]_D^{23}$ −7.20° (*c*=0.1, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ_H: 0.90 (9H, t, $CH_3\times3$), 1.10, 1.34 (each 6H, m, $CH_2\times3$), 1.57 (6H, m, $CH_2\times3$), 3.14 (1H, dt, *J*=7.0, 14.5 Hz, 3-Ha), 3.53 (1H, dt, *J*=4.0, 14.5 Hz, 3-Hb), 4.40 (1H, dd, *J*=4.0, 7.0 Hz, 2-H), 5.07, 5.12 (each 1H, d, *J*=12 Hz, benzyl CH_2), 7.02 (1H, s, 2′-H), 7.24—7.32 (1H, hidden, 4′-H), 7.42 (1H, s, 6′-H), 7.57 (1H, d, *J*=8.0 Hz, 5′-H), 7.97 (1H, br, 1′-H). HR-FAB-MS *m/z*: 673.1967 $[M+Na]^+$, Calcd for $C_{31}H_{43}O_4N_2Na_2Sn$: 673.2040 [M+Na].

(*R*,*R*,*R*)-*N*-Carbobenzyloxy-6-tributylstannyl-tryptophyl-3′,5′-dichloro-4′-methoxy-phenylglycyl-3′,5′-diiodo-4′-methoxy-phenylglycine Methyl Ester (6b) To a solution of **46** (7.5 mg, 0.012 mmol) in THF/CH_2Cl_2 (3 : 1) (1 ml), were added **41** (7.86 mg, 0.012 mmol), HATU (4.4 mg, 0.012 mol), collidine (7.0 mg, 0.058 mmol) in THF/CH_2Cl_2 (3 : 1) (0.2 ml) at 0 °C under argon and stirred for 2 h. The reaction mixture was diluted with AcOEt (50 ml), washed with saturated $NaHCO_3$ (3 ml×2), dried over Na_2SO_4, concentrated *in vacuo*. Purification of the residue (18.5 mg) by flash column chromatography (silica gel, $CHCl_3$/MeOH=100 : 1 (contained 1% NEt_3)) afforded **6b** (8.1 mg, 54%) as yellow brown crystals. *Rf*: 0.76 ($CHCl_3$/MeOH=10 : 1). $[\alpha]_D^{23}$ +5.54° (*c*=0.36, $CHCl_3$). ^{1}H-NMR (400 MHz, CD_3OD) δ_H: 0.87 (9H, t, $CH_3\times3$), 1.06 (6H, m, $CH_2\times3$), 1.34 (6H, m, $CH_2\times3$), 1.56 (6H, m, $CH_2\times3$), 3.20 (1H, dd, *J*=7.0, 12.0 Hz, Tryp 3-Ha), 3.29 (1H, dd, *J*=5.0, 12.0 Hz, Trp 3-Hb), 3.73 (3H, s, OMe), 3.77 (3H, s, OMe), 3.88 (3H, s, OMe), 4.71 (1H, m, Trp 2-H), 5.12, 5.21 (each 1H, d, *J*=12.0 Hz, benzyl CH_2), 5.37 (1H, d, *J*=8.5 Hz, 2-H), 5.58 (1H, d, *J*=7.0 Hz, CHPG 2-H), 5.68 (1H, br, IHPG NHCO), 6.74 (1H, br s, CHPG NHCO), 6.84 (1H, d, *J*=2.0 Hz, 2′-H), 7.12 (2H, s, CHP 2′, 6′-H), 7.14 (1H, d, *J*=9.0 Hz, 4′-H), 7.25, 7.29 (total 5H, m, benzyl arom-H), 7.54 (1H, br d, *J*=9.0 Hz, 5′-H), 7.67, 7.71, 7.76 (total 2H, each s, IHPG 2′, 6′-H), 8.20 (1H, br s, 1′-H). HR-FAB-MS *m/z*: 1311.0793 $[M+Na]^+$, Calcd for $C_{50}H_{60}O_8N_4NaSnI_2$: 1311.0797 [M+Na].

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