Synthesis and Matrix Metalloproteinase-12 Inhibitory Activity of Ageladine A Analogs[1,2)]

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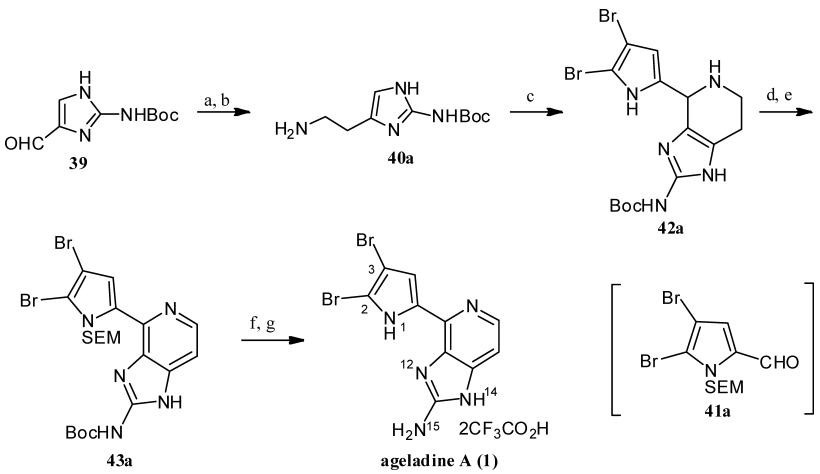
Synthesis of the 37 ageladine A analogs was accomplished by employing the total synthetic route of natural ageladine A previously explored by us. From the matrix metalloproteinase-12 (MMP-12) inhibitory activity assay carried out using the novel analogs, it appeared evident that the halogen atom at the 2-position of pyrrole ring was essential for the inhibitory activity and that the introduction of a bromine atom into the 4-position of pyrrole ring is very effective for producing potent activity. In addition, exchange of the pyrrole ring to an imidazole ring was extremely effective in increasing activity, and the analog 29 thus obtained was found to show approximately 4 times more potent activity than natural ageladine A.

Key words ageladine A; matrix metalloproteinase-12; ageladine A analog

Ageladine A (**1**), which is a pyrrol-2-aminoimidazole alkaloid isolated from the marine sponge *Agelas nakamurai* by Fusetani and colleagues[3)] inhibits various subtypes of matrix metalloproteinases (MMPs) such as MMP-1, 2, 8, 9, 12, and 13. Among these MMPs, MMP-12 is considered to be associated with inflammatory diseases caused by macrophage infiltration such as skin diseases,[4—6)] atherosclerosis,[7)] aneurysms,[8)] and cancers.[9—11)] We had been studying the possibility of using MMP-12 inhibitors against inflammatory diseases, but had not been able to find a lead compound. Accordingly, we embarked on evaluating **1** as a new lead compound for novel MMP-12 inhibitors. Three total syntheses of **1** have been reported by Meketa and Weinreb[12,13)] and Shengule and Karuso.[14)] Recently, we also completed the total synthesis of **1** based on the biosynthetic route proposed by Fusetani *et al.*, as shown in Chart 1.[1,15)] While our synthetic route is almost the same as that independently reported by Shengule and Karuso,[14)] it is anticipated to be more efficient and practical when taking into account the reagents and chemical yields for each step. We wish to report here the structure–activity relationships for MMP-12 inhibitory activity performed by using the 37 ageladine A analogs prepared by featuring our synthetic route established for **1**.[15)]

Results and Discussion

MMP-12 Inhibitory Activity of Ageladine A Analogs We first, attempted to clarify the structural features of ageladine A (**1**) itself required for its MMP-12 inhibitory activity, and synthesized the 8 analogs **2**—**9**. The MMP-12 inhibition assay was performed as per the manufacturer's (BioMol) protocol. The results of the MMP-12 inhibitory activity assay of these analogs are summarized in Table 1. The activity of two debromo-analogs **2** and **3** was found to disappear. The *N*-methylpyrrole analog **4** showed no activity at all. In addition, the 4 analogs, **5**—**8** in which the amino or imino groups of imidazo[4,5-*c*]pyridine ring system are methylated and the deamino analog **9** showed weak or no activity. From these results, it was supposed that the two bromine atoms and the three NH groups (1-NH, 14-NH, and 15-NH_2: ageladine A numbering) of **1** play an important role in its MMP-12 inhibitory activity. We paid particular attention to the influence of the bromine atoms, and anticipated that a slight



Reagents and conditions: (a) $AcONH_4/MeNO_2$, reflux, 20 min, 94%; (b) $LiAlH_4$ (3 eq)/THF, 50 °C, 1 h, 67%; (c) **41a**/EtOH, 50 °C, 6 h; (d) IBX (1.5 eq)/DMSO, rt, 2 h; (e) MnO_2/CH_2Cl_2, rt, 1 h; (f) BF_3–OEt_2 (10 eq)/CH_2Cl_2, rt, overnight; (g) TFA/MeOH, rt, 5 min, 70% (2 steps).

Chart 1. The Synthetic Route of Ageladine A (**1**) Previously Explored by Us.[1,15)]

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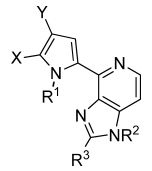
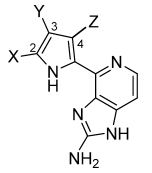
Table 1. MMP-12 Inhibitory Activity of Ageladine A (**1**) and Its Analogs **2**—**9**



Compound	X	Y	R^1	R^2	R^3	IC_{50} (μM)
1	Br	Br	H	H	NH_2	3.66
2	H	Br	H	H	NH_2	>100
3	Br	H	H	H	NH_2	>100
4	Br	Br	Me	H	NH_2	>100
5	Br	Br	H	H	NHMe	10.4
6	Br	Br	H	Me	NH_2	56.9
7	Br	Br	H	Me	NHMe	>100
8	Br	Br	H	H	NMe_2	>100
9	Br	Br	H	H	H	43.6

Table 2. MMP-12 Inhibitory Activity of Ageladine A (**1**) and Its Analogs **10**—**28**

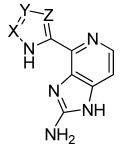


Compound	X	Y	Z	IC_{50} (μM)
1	Br	Br	H	3.66
10	Cl	Cl	H	5.02
11	Cl	Br	H	2.02
12	Me	Br	H	>100
13	Me	Br	Br	>100
14	Ph	Br	H	>100
15	Br	Me	H	>100
16	Br	Me	Br	5.02
17	Br	Ph	H	18.7
18	Br	$PhCH_2$	H	>100
19	Br	$PhCH_2$	Br	>100
20	Br	$Ph(CH_2)_2$	H	10.2
21	Br	$Ph(CH_2)_2$	Br	2.99
22	Br	*o*-CF_3-$Ph(CH_2)_2$	Br	>100
23	Br	*m*-CF_3-$Ph(CH_2)_2$	Br	>100
24	Br	*p*-CF_3-$Ph(CH_2)_2$	Br	>100
25	Br	$Ph(CH_2)_3$	H	>100
26	Br	$Ph(CH_2)_3$	Br	>100
27	Br	Br	Br	1.24
28	Br	Br	$Ph(CH_2)_2$	>100

change in the substituent on the pyrrole ring might greatly influence the inhibitory activity. We therefore carried out additional synthetic studies of ageladine A analogs to explore more detailed substituent effects of the pyrrole ring and to find analogs showing improved inhibitory activity.

The results of the examinations regarding more detailed substituent effects of the pyrrole ring are shown in Table 2. As for the 2-position of the pyrrole ring, replacement of the bromine atom with a chlorine atom obviously increased the inhibitory activity (see **11**). However, the introduction of other groups such as methyl, and phenyl groups clearly decreased the activity (see **12**—**14**). From these results, it appeared that the bromine or chlorine atom at the 2-position plays an important role in MMP-12 inhibitory activity. In

Table 3. MMP-12 Inhibitory Activity of Ageladine A (**1**) and Its Analogs **29**—**38**

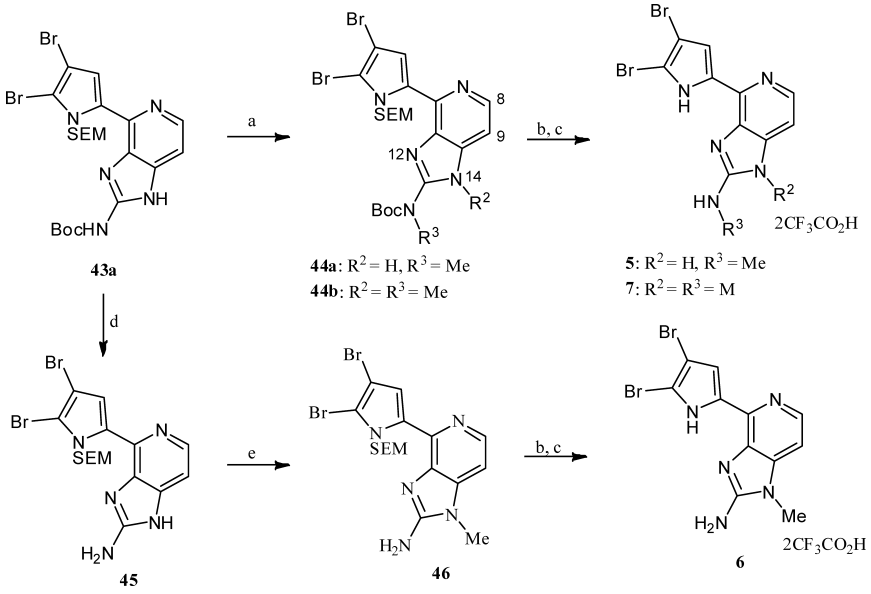


Compound	X	Y	Z	IC_{50} (μM)
1	C–Br	C–Br	C–H	3.66
29	C–Br	C–Br	N	0.86
30	C–Cl	C–Br	N	1.64
31	C–H	C–H	N	>100
32	C–Br	N	C–Br	15.7
33	C–H	N	C–H	>100
34	C–Br	N	N	88.2
35	C–H	N	N	>100
36	N	N	C–Br	>100
37	N	N	C–H	>100
38	N	N	N	>100

contrast, the 3-position of the pyrrole ring was found to show slightly different substituent effects. The bromine atom was found to be most promising (see **1**, **10**, **11**, **15**, and **17**), but the phenyl and phenethyl groups also showed weak inhibitory activity (see **17** and **20**). The benzyl, trifluoromethylphenethyl, and phenylpropyl groups, however, were not effective. As mentioned above, the 3-position can accept more different groups than the 2-position, but the number of acceptable groups seems to be fairly limited. The most interesting effects were obtained by introducing a substituent into the 4-position of the pyrrole ring. It became obvious that introducing a bromine atom into the 4-position significantly increased the inhibitory activity (see **16**, **21**, and **27**). In particular, 4-bromo-ageladine A **27** showed *ca.* 3 times more potent inhibitory activity than natural ageladine A (**1**).

Next, the exchange of the pyrrole ring to various azole rings such as an imidazole or a tetrazole ring was further examined because the initial examinations, as shown in Table 1, suggested that the acidic proton of the pyrrole ring of **1** might play an important role in MMP-12 inhibitory activity. These results are summarized in Table 3. It was found that the dibromoimidazole analog **29** shows the most potent inhibitory activity among all the synthesized analogs, with its activity being *ca.* 4 times stronger than that of **1**. In contrast, the activity of its isomer, **32**, was weak. Only analogs having a halogen atom at the 2-position exhibited inhibitory activity. It became particularly apparent that having a halogen atom at both the 2- and 3-positions is important to exhibiting activity as potent as that of ageladine A (**1**).

Summing up the results mentioned above, the following findings were obtained regarding the structure–activity relationships of **1**. First, the proton at the 1-position (NH) and the halogen atom (Br or Cl) at the 2-position are essential. Next, a bromine atom is the most effective at the 3-position, but is not essential. Unlike the specificity required for the 2-position, even the 3-phenyl or phenethyl derivatives showed activity. Introduction of a bromine atom to the 4-position strengthens the activity. However, the most potent compound is the imidazole derivative **29**, which structurally carries no bromine atom at the corresponding 4-position. It was anticipated that these findings might clarify the importance of



Reagents and conditions: (a) MeI, NaH/DMF, rt, overnight, 36% for **44a**, 27% for **44b**; (b) BF_3-Et_2O (10 eq)/CH_2Cl_2, rt, overnight; (c) TFA/MeOH, rt, 5 min, 92% (2 steps) for **5**, 83% (2 steps) for **6**, 97% (2 steps) for **7**; (d) HCl–MeOH, rt, overnight, 53%; (e) MeI, NaH/DMF, rt, 2 h, 50%.

Chart 2. Synthesis of Ageladine A Analogs (**5**—**7**)

acidity of the proton at the 1-position. Thus, the introduction of a bromine atom is considered to be effective for enhancing the acidity of the proton at the 1-position. However, tetrazole or triazole analogs (see **34**—**38**) showing increased acidity exhibited no or very weak activity. Accordingly, it appears that the presence of halogen atoms at the 2- and 3-positions is more important to MMP-12 inhibitory activity than the strength of acidity of the proton at the 1-position.

Chemistry The synthetic routes for analogs **5**—**7** are shown in Chart 2. The *N*-methyl derivatives **5**—**7** were synthesized from **43a**, which is the intermediate of our total synthesis of ageladine A (**1**).[1,15] Methylation of **43a** using NaH and iodomethane produced **44a** and **44b** in 36% and 27% yields, respectively, after separation by column chromatography. In costract, methylation after removal of the *tert*-butoxycarbonyl (Boc) group provided **46** by way of **45**. The *N*-methylated compounds **44a**, **b** and **46** were converted to the corresponding target analogs **5**—**7** by the same deprotection using borontrifluoride-etherate (BF_3-OEt_2) as that employed for our total synthesis of **1**.

The other derivatives were synthesized by applying our total synthetic route of **1**. The Pictet–Spengler reaction of histamine derivatives **40a**,[1,15] **b**, and **c**[16] with aldehydes **41** followed by our original two-step oxidation using IBX and activated MnO_2 gave imidazo[4,5-*c*]pyridine derivatives **43** (Tables 4, 5). Run 2 in Table 5 gave **43aw** as a mixture of two regioisomers that could be separated by column chromatography. However, determinations of their structures were not attempted since removal of the 2-(trimethylsilyl)ethoxymethyl (SEM) group converged **43aw** to a single product **32** (Chart 5). The alkyne derivatives **43aj**, **ak**, **al**, **am**, and **ao** obtained from **40a** and **41j**—**m**, **o** were converted to the phenethyl derivatives **47a**—**e** by catalytic reduction in good yields as shown in Table 6.

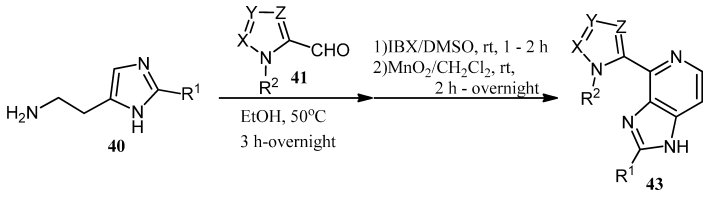
The various derivatives **43** and **47** were subjected to halogenation to afford **48** as shown in Table 7. Thus, **43ac**, **a**, **ae**, **ag**, **ah**, **ai**, **an**, and **47a** were brominated using 1 eq of tetra-*n*-butylammonium tribromide ($TBABr_3$) to give **48a**, **b**, **e**, **f**, **h**, **i**, **k**, and **p**. Further bromination of **48f**, **i**, **k**, and **p** gave rise to **48g**, **j**, **l**, and **q**. The phenethyl derivatives **47b**—**e** were converted to the dibromo-derivatives **48m**—**o** and **r** using 2 eq of $TBABr_3$. Chlorination of **43ac**, **ad**, and **ap** with 2 eq or 1 eq of *N*-chlorosuccinimide (NCS) afforded **48c**, **d**, and **s**.

The intermediates **43** and **48** synthesized above were deprotected by means of one of the 4 following methods (method C: BF_3OEt_2; method D: trifluoroacetic acid (TFA); method E: 1) aqueous sodium hydroxide solution (NaOHaq), 2) TFA; method F: 1) hydrogen chloride in methanol (HCl-MeOH), 2) di-*tert*-butyl dicarbonate (Boc_2O), triethylamine (TEA), 3) TFA), giving the 33 target ageladine A analogs **2**—**4**, **9**—**29**, **31**, and **33**—**38** (Table 8).

The analog **8** was synthesized from **43ca** by sequential substitution with dimethylamine and deprotection (Chart 3). The analog **30** was prepared from **48s** as shown in Chart 4. Thus, protection of **48s** followed by bromination afforded **51**, which was then transformed to **30** by hydrolysis followed by deprotection. As shown in Chart 5, synthesis of **32** commenced with the less polar regioisomer of **43aw**. After bromination of **43aw**, a two-step deprotection of the dibromide **53** afforded **32**. Structure determinations of the intermediates **53** and **54** were not attempted since both of the two possible regioisomers converged to **32** as a single product after deprotection.

On the other hand, the 1*H*-pyrrol-2-aldehyde derivatives **41a**, **b**, **d**—**o** used for the Pictet–Spengler reaction (vide supra) were synthesized by the methods shown in Chart 6. **41c** was prepared according to the reported method.[17] Thus, protection of **55**[18], **56**[19], **58a**—**c**,[20] and **59**[21] with a SEM group provided **41a**, **d**, **g**, **i**, **n**, and **60**, respectively. The aldehyde **41a** was further converted to **41f** by the regioselective Suzuki–Miyaura cross-coupling reaction following the procedure reported by Handy and Sabatini.[22] The 1-methyl derivative **41b** was prepared from **41a** by the usual procedure.

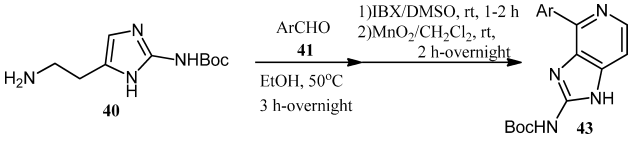
Table 4. Synthesis of the Intermediates **43** for Ageladine A Analogs-1

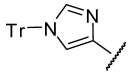
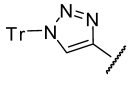
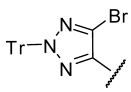


Run	40		Aldehyde 41					43
	No.	R^1	No.	X	Y	Z	R^2	No. (yield[a])
1	**a**	NHBoc	**b**	C–Br	C–Br	C–H	Me	**ab** (22%)
2	**a**	NHBoc	**c**	C–H	C–H	C–H	SEM	**ac** (51%)
3	**a**	NHBoc	**d**	C–H	C–Br	C–H	SEM	**ad** (75%)
4	**a**	NHBoc	**e**	C–Me	C–Br	C–H	SEM	**ae** (45%)
5	**a**	NHBoc	**f**	C–Ph	C–Br	C–H	SEM	**af** (52%)
6	**a**	NHBoc	**g**	C–H	C–Me	C–H	SEM	**ag** (38%)
7	**a**	NHBoc	**h**	C–H	C–Ph	C–H	SEM	**ah** (55%)
8	**a**	NHBoc	**i**	C–H	C–CH_2Ph	C–H	SEM	**ai** (69%)
9	**a**	NHBoc	**j**	C(—≡—Ph)		C–H	SEM	**aj** (58%)
10	**a**	NHBoc	**k**	C(—≡—Ph(*o*-CF_3))		C–H	SEM	**ak** (68%)
11	**a**	NHBoc	**l**	C(—≡—Ph(*m*-CF_3))		C–H	SEM	**al** (63%)
12	**a**	NHBoc	**m**	C(—≡—Ph(*p*-CF_3))		C–H	SEM	**am** (38%)
13	**a**	NHBoc	**n**	C–$(CH_2)_3$Ph		C–H	SEM	**an** (75%)
14	**a**	NHBoc	**o**	C–H	H	C(—≡—Ph)	SEM	**ao** (17%)[b]
15	**a**	NHBoc	**p**	C–H	C–H	N	SEM	**ap** (38%)
16	**a**	NHBoc	**q**	C–H	C–H	N	Tr	**aq** (15%)
17	**a**	NHBoc	**r**	C–Br	C–Br	N	SEM	**ar** (48%)
18	**a**	NHBoc	**s**	N	C–H	N	Tr	**as** (20%)
19	**a**	NHBoc	**t**	N	C–Br	N	PMB	**at** (76%)
20	**a**	NHBoc	**u**	N	N	N	PMB	**au** (75%)
21[c]	**b**	H	**a**	C–Br	C–Br	C–H	SEM	**ba** (41%)
22	**c**	Br	**a**	C–Br	C–Br	C–H	SEM	**ca** (59%)

a) Isolated yield. *b*) The reaction was performed in refluxing EtOH. Probably due to transesterification at higher temperature, the reaction product **43ao** was obtained as an ethyl carbamate instead of a *tert*-butyl carbamate. *c*) This reaction was carried out in refluxing 2-methoxyethanol (*ca.* 125 °C).

Table 5. Synthesis of the Intermediates **43** for Ageladine A Analogs-2



Run	Aldehyde 41		43
	No.	Ar	No. (yield[a])
1	**v**		**av** (29%)
2	**w**		**aw** (22%)[b]
3	**x**		**ax** (49%)
4	**y**		**ay** (36%)

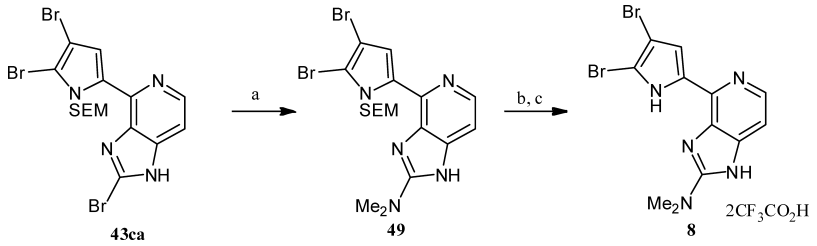
a) Isolated yield. *b*) Since **41w** was a mixture of two regioisomers, the reaction product was also obtained as a mixture of two regioisomers. The major less polar product **43aw** was separated and used for the next bromination.

The aldehyde **41h** was prepared from **41d** by a Suzuki–Miyaura cross-coupling reaction. The Sonogashira cross-coupling reaction of **41d** and **60** gave **41j**—**m**, **o**, respectively. The synthesis of **41e** was performed by bromination of **57**,[20] followed by protection.

The synthetic routes to the polyazolaldehyde derivatives **41r**—**u**, **x**, and **y** are shown in Chart 7. The other polyazolaldehydes **41p**,[23] **q**,[24] **v**,[25] and **w**[23] were prepared according to the reported methods. After protection of **61**, lithiation of the 2-position of protected **61** followed by formylation gave **41r**. The aldehydes **41s**, **u**, and **y** were synthesized from **62**,[26] **66**,[27] and **67**[28] by a method similar to that used for **41r**. Preparation of **41x** was achieved starting with the acetylene **63**. 1,3-Dipolar cycloaddition of **63** with tritylazide gave **64**, which was converted into **41x** by deprotection. Reduction of **65**[29] followed by oxidation of the formed alcohol furnished **41t**.

Conclusion

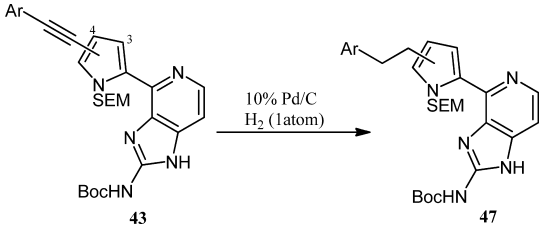
As mentioned above, we have succeeded in synthesizing the 37 ageladine A analogs **2**—**38** by employing the total synthetic route of ageladine A (**1**) previously explored by us.[1,15] From the MMP-12 inhibitory activity assay carried out using the novel analogs, it appeared evident that the proton at the 1-position and the halogen atom at the 2-position of pyrrole ring were essential for the inhibitory activity and that the introduction of a bromine atom into the 3- and/or 4-



Reagents and conditions: (a) 2 M Me_2NH in MeOH, 100 °C (sealed tube), 10 h, 53%; (b) BF_3-Et_2O (10 eq)/CH_2Cl_2, rt. overnight; (c) TFA/MeOH, rt, 5 min, 75% (2 steps).

Chart 3. Synthesis of **8**

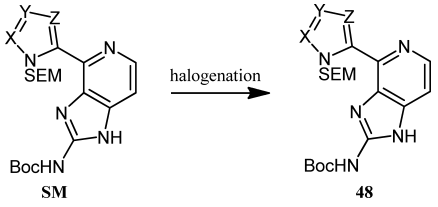
Table 6. Synthesis of the Intermediates **47** for Ageladine A Analogs



Run	43		47
	No.	Ar (position)	No. (yield[a])
1	**aj**	Ph (4-)	**a** (98%)
2	**ak**	*o*-CF_3-Ph (4-)	**b** (100%)
3	**al**	*m*-CF_3-Ph (4-)	**c** (98%)
4	**am**	*p*-CF_3-Ph (4-)	**d** (89%)
5	**ao**	Ph (3-)	**e** (84%[b])[c]

a) Isolated yield. *b*) Crude yield. *c*) The crude sample **47e** was directly subjected to the next bromination.

Table 7. Synthesis of the Intermediates **48** for Ageladine A Analogs by Halogenations



Run	SM No.	Method[a]	48			
			X	Y	Z	No. (yield[d])
1	**43ac**	A	C–Br	C–H	C–H	**a** (93%)
2	**43a**	A	C–Br	C–Br	C–Br	**b** (quant.)
3	**43ac**	B[b]	C–Cl	C–Cl	C–H	**c** (19%)
4	**43ad**	B	C–Cl	C–Br	C–H	**d** (91%)
5	**43ae**	A	C–Me	C–Br	C–Br	**e** (98%)
6	**43ag**	A	C–Br	C–Me	C–H	**f** (81%)
7	**48f**	A	C–Br	C–Me	C–Br	**g** (94%)
8	**43ah**	A	C–Br	C–Ph	C–H	**h** (96%)
9	**43ai**	A	C–Br	C–CH_2Ph	C–H	**i** (88%)
10	**48i**	A	C–Br	C–CH_2Ph	C–Br	**j** (93%)
11	**47a**	A	C–Br	C–$(CH_2)_2$Ph	C–H	**k** (91%)
12	**48k**	A	C–Br	C–$(CH_2)_2$Ph	C–Br	**l** (98%)
13	**47b**	A[c]	C–Br	C–$(CH_2)_2$Ph (*o*-CF_3)	C–Br	**m** (93%)
14	**47c**	A[c]	C–Br	C–$(CH_2)_2$Ph (*m*-CF_3)	C–Br	**n** (78%)
15	**47d**	A[c]	C–Br	C–$(CH_2)_2$Ph (*p*-CF_3)	C–Br	**o** (78%)
16	**43an**	A	C–Br	C–$(CH_2)_3$Ph	C–H	**p** (90%)
17	**48p**	A	C–Br	C–$(CH_2)_3$Ph	C–Br	**q** (92%)
18	**47e**	A[c]	C–Br	C–Br	C–$(CH_2)_2$Ph	**r** (84%[e])
19	**43ap**	B	C–Cl	C–H	N	**s** (33%)

a) Method A: $TBABr_3$ (1 eq) was used as a brominating agent. Method B: NCS (1 eq) was used as a chlorinating agent. *b*) Two equivalents of NCS were used. *c*) Two equivalents of $TBABr_3$ were used. *d*) Isolated yield. *e*) Calculated based on **43ao** (2 steps).

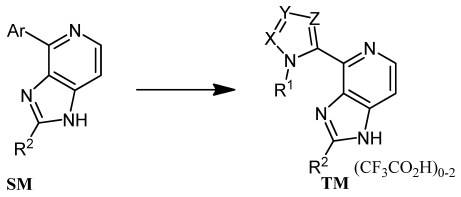
position of pyrrole ring was very effective in producing potent activity. It was also found that exchanging a pyrrole ring for an imidazole ring was quite effective, with the analog **29** thus obtained showing *ca.* 4 times more potent activity than natural ageladine A (**1**). This finding may suggest that the strength of the acidity of the proton at the 1-position of the pyrrole ring would also influence the MMP-12 inhibitory activity of **1**. These results should be useful for future studies aimed at identifying even more potent ageladine A analogs.

Experimental

General All melting points were determined with a Yanaco MP-500 melting point apparatus and are uncorrected. Infrared spectra were recorded with a JASCO FT/IR-5300 spectrometer or a Perkin-Elmer spectrum 100 spectrometer. ^{1}H-NMR spectra were measured with a JEOL JNM-ECA-400 or -ECX-400 (400 MHz) spectrometer. Measurements of ^{13}C-NMR spectra were carried out using a JEOL JNM-ECA-400 or -ECX-400 (100 MHz) spectrometer. The chemical shifts are expressed in parts per million (δ value) downfield from tetramethylsilane, using tetramethylsilane (δ=0) and/or residual solvents such as chloroform (δ=7.26) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Measurements of mass spectra were performed with a JEOL JMS-SX102X mass spectrometer. Data for elemental analyses are within ±0.3% of the theoretical values, and were determined by a Yanaco CHN-corder MT-6. Unless otherwise noted, all the experiments were carried out using anhydrous solvents under an atmosphere of argon. Throughout this study, Merck precoated TLC plates (Silica gel 60 F_{254}, 0.25 mm) were used for thin layer chromatographic (TLC) analysis, and all of the spots were visualized using UV light followed by coloring with phosphomolybdic acid or anisaldehyde. Silica gel 60N (40—50 μm, neutral; Kanto Chemical Co., Inc., Tokyo, Japan) or Chromatorex® NH DM2035 (200—350 mesh; Fuji Silysia Chemical, Ltd., Aichi, Japan) was used for the flash column chromatography. The following abbreviations were used for solvents and reagents: acetone (Me_2CO); acetonitrile (MeCN); borontrifluoride diethyletherate (BF_3-OEt_2); *N*-bromosuccinimide (NBS); *n*-butyllithium (*n*-BuLi); chloroform ($CHCl_3$); *N*-chlorosuccinimide (NCS); dichloro-bis(triphenylphosphine)palladium ($Pd(PPh_3)_2Cl_2$); dichloromethane (CH_2Cl_2); diethyl ether (Et_2O); 4-(*N*,*N*-dimethylamino)pyridine (DMAP); *N*,*N*-dimethylformamide (DMF); dimethyl sulfoxide (DMSO); ethanol (EtOH); ethyl acetate (EtOAc); ethyldiisopropylamine (iPr_2EtN); *n*-hexane (C_6H_{14}); iodoxybenzoic acid (IBX); methanol (MeOH); tetrahydrofuran (THF); water (H_2O), di-*tert*-butyl dicarbonate (Boc_2O); triethylamine (Et_3N); hydrogen chloride (HCl); iodomethane (MeI); manganese(IV) oxide (MnO_2); palladium acetate ($Pd(OAc)_2$); potassium *tert*-butoxide (*t*BuOK); potassium carbonate (K_2CO_3); pyridinium *p*-toluenesulfonate (PPTS); sodium borohydride ($NaBH_4$); sodium hydride (NaH); sodium hydrogen carbonate ($NaHCO_3$); sodium hydroxide (NaOH); sodium carbonate (Na_2CO_3); sodium sulfate (Na_2SO_4); tetra-*n*-butylanmonium tribromide ($TBABr_3$); tetrakis(triphenylphosphine)-palladium ($Pd(PPh_3)_4$); toluene (C_6H_5Me); trifluoroacetic acid (TFA); 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl).

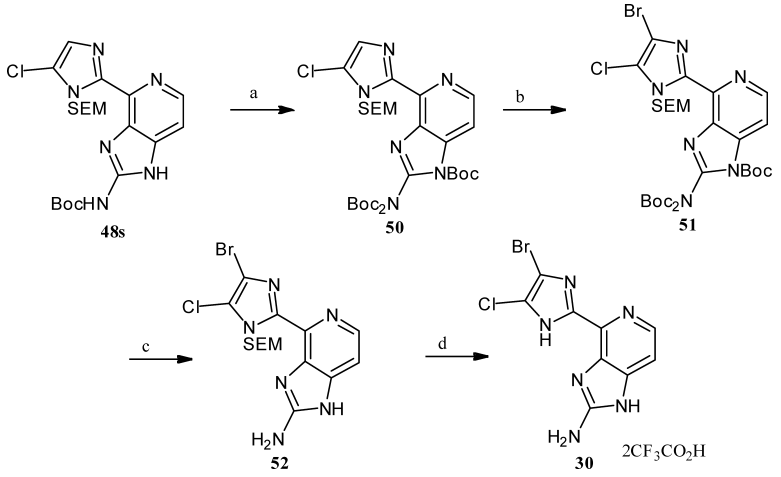
4,5-Dibromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-car-

Table 8. Synthesis of Ageladine A Analogs **2**—**4**, **9**—**29**, **31**, and **33**—**38**



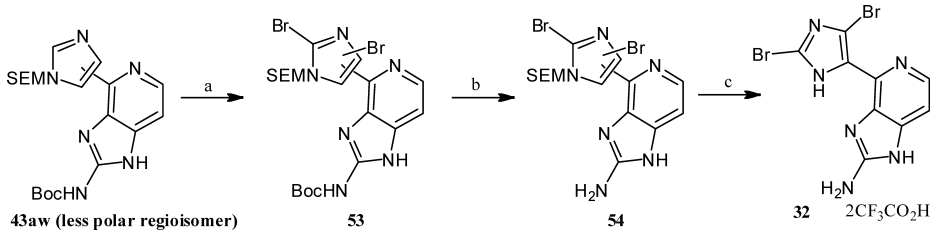
Run	SM	Method[a)]	TM					
			X	Y	Z	R^1	R^2	No. (yield[b)])
1	**43ad**	C	C–H	C–Br	C–H	H	NH_2	**2** (82%)
2	**48a**	C	C–Br	C–H	C–H	H	NH_2	**3** (86%)
3	**43ab**	D	C–Br	C–Br	C–H	Me	NH_2	**4** (82%)
4	**43ba**	C	C–Br	C–Br	C–H	H	H	**9** (67%)
5	**48c**	C	C–Cl	C–Cl	C–H	H	NH_2	**10** (91%)
6	**48d**	C	C–Cl	C–Br	C–H	H	NH_2	**11** (23%)
7	**43ae**	C	C–Me	C–Br	C–H	H	NH_2	**12** (64%)
8	**48e**	D	C–Me	C–Br	C–Br	H	NH_2	**13** (61%)
9	**43af**	C	C–Ph	C–Br	C–H	H	NH_2	**14** (65%)
10	**48f**	D	C–Br	C–Me	C–H	H	NH_2	**15** (84%)
11	**48g**	D	C–Br	C–Me	C–Br	H	NH_2	**16** (34%)
12	**48h**	C	C–Br	C–Ph	C–H	H	NH_2	**17** (75%)
13	**48i**	D	C–Br	C–CH_2Ph	C–H	H	NH_2	**18** (68%)
14	**48j**	D	C–Br	C–CH_2Ph	C–Br	H	NH_2	**19** (71%)
15	**48k**	D	C–Br	C–$(CH_2)_2$Ph	C–H	H	NH_2	**20** (71%)
16	**48l**	D	C–Br	C–$(CH_2)_2$Ph	C–Br	H	NH_2	**21** (49%)
17	**48m**	D	C–Br	C–$(CH_2)_2$Ph–*o*-CF_3	C–Br	H	NH_2	**22** (74%)
18	**48n**	D	C–Br	C–$(CH_2)_2$Ph–*m*-CF_3	C–Br	H	NH_2	**23** (61%)
19	**48o**	D	C–Br	C–$(CH_2)_2$Ph–*p*-CF_3	C–Br	H	NH_2	**24** (44%)
20	**48p**	D	C–Br	C–$(CH_2)_3$Ph	C–H	H	NH_2	**25** (69%)
21	**48q**	D	C–Br	C–$(CH_2)_3$Ph	C–Br	H	NH_2	**26** (59%)
22	**48b**	C	C–Br	C–Br	C–Br	H	NH_2	**27** (72%)
23	**48r**	E	C–Br	C–Br	C–$(CH_2)_2$Ph	H	NH_2	**28** (79%)
24	**43ar**	D	C–Br	C–Br	N	H	NH_2	**29** (64%)
25	**43aq**	D	C–H	C–H	N	H	NH_2	**31** (33%)
26	**43av**	D	C–H	N	C–H	H	NH_2	**33** (46%)
27	**43at**	D	C–Br	N	N	H	NH_2	**34** (73%)
28	**43as**	E	C–H	N	N	H	NH_2	**35** (56%)
29	**43ax**	F	N	N	C–H	H	NH_2	**36** (46%)
30	**43ay**	E	N	N	C–Br	H	NH_2	**37** (9%)
31	**43au**	E	N	N	N	H	NH_2	**38** (58%)

a) Method C: 1) BF_3OEt_2, 2) Na_2CO_3aq, 3) TFA, method D: 1) TFA, 2) Na_2CO_3aq, 3) TFA, method E: 1) NaOHaq, 2) TFA, method F: 1) HCl-MeOH, 2) Boc_2O, Et_3N, 3) TFA. *b*) Isolated yield.



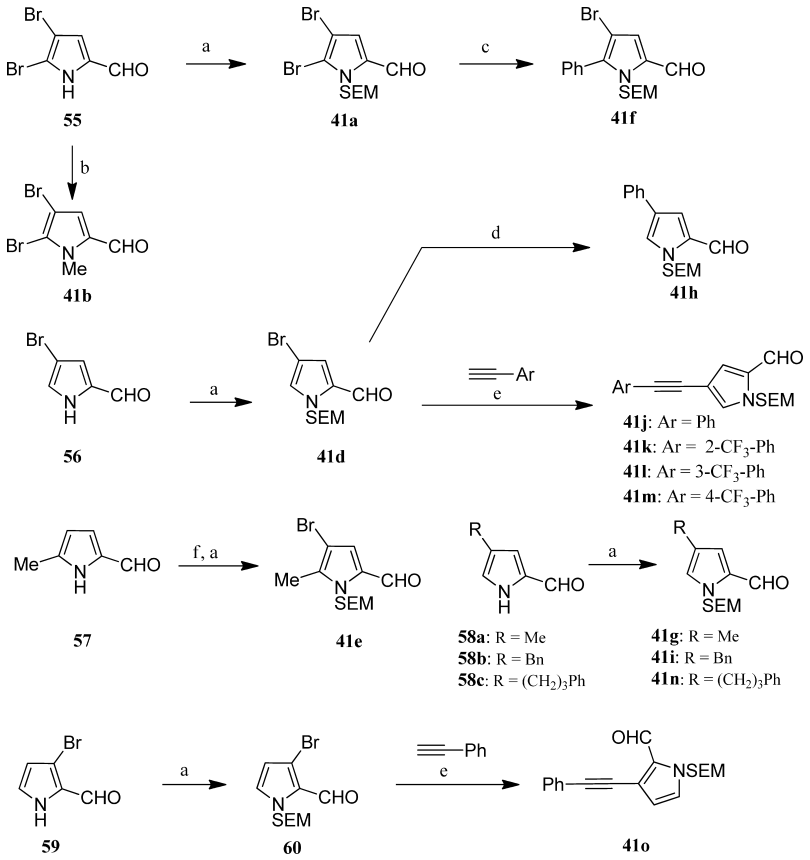
Reagents and conditions: (a) Boc_2O, DMAP (cat.)/MeCN, rt, overnight, 93%; (b) NBS/MeCN, rt, 3 d, 72%; (c) NaOHaq/EtOH, 80 °C, 8 h; (d) TFA/CH_2Cl_2, rt, overnight, 59% (2 steps).

Chart 4. Synthesis of **30**



Reagents and conditions: (a) NBS/$CHCl_3$, rt, overnight, 81%; (b) NaOHaq/EtOH, 80 °C, 8 h; c) TFA/CH_2Cl_2, rt, overnight, 78% (2 steps).

Chart 5. Synthesis of **32**



Reagents and conditions: (a) i) SEMCl, *t*BuOK/DMF, 0 °C, 1 h, 89% for **41a**, 92% for **41d**, 80% for **41e** (2 steps), 91% for **41g**, 43% for **41i**, 51% for **41n**, 89% for **60**; (b) MeI, *t*BuOK/DMF, 0 °C, 1 h, 98%; (c) $PhB(OH)_2$, $Pd(OAc)_2$, K_2CO_3/DMF, 100 °C, 7—8 h, 70%; (d) $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3/DMF, 100 °C, 8 h, 52%; (e) $PdCl_2(PPh_3)_2$, CuI, TEA/DMF, 100 °C, 5 h, 60% for **41j**, 59% for **41k**, 53% for **41l**, 54% for **41m**, 96% for **41o**; (f) NBS/THF, −78 °C.

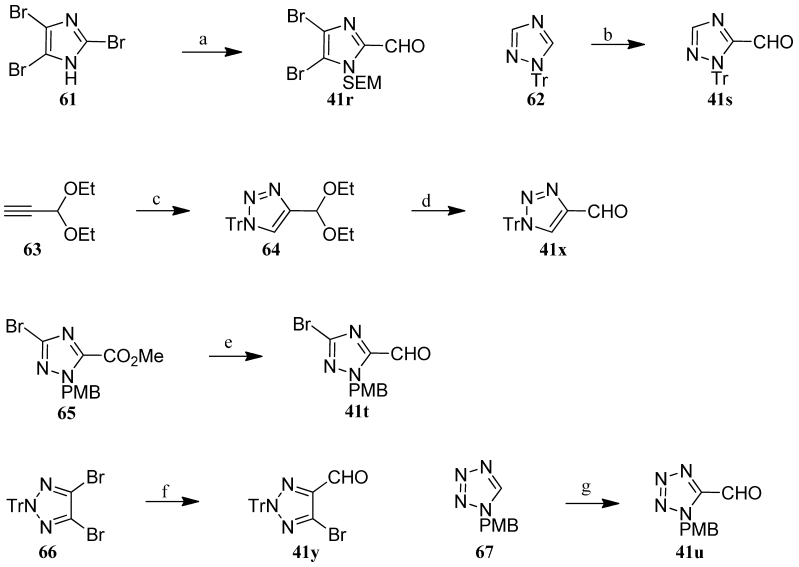
Chart 6. Synthesis of the Pyrrole-2-aldehyde Derivatives **41a**, **b**, **d**—**o**

baldehyde (41a) To a solution of **55** (1.0 g, 4.0 mmol) in DMF (20 ml) was added *t*BuOK (466 mg, 4.2 mmol) at 0 °C. After stirring at room temperature for 30 min, SEMCl (0.77 ml, 4.4 mmol) was added to the reaction mixture at 0 °C, and the whole was stirred at the same temperature for 1 h. The reaction was quenched by adding H_2O at 0 °C, and the mixture was extracted with EtOAc. The organic extracts were combined, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, C_6H_{14}/EtOAc=10/1) afforded **41a** (1.35 g, 89%) as a light brown oil. IR (ATR): 2953, 1671, 1399, 1371, 1310, 1248, 1091, 832 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.03 (9H, s), 0.88—0.92 (2H, m), 3.57—3.61 (2H, m), 5.81 (2H, s), 7.02 (1H, s), 9.40 (1H, s). Low resolution (LR)-MS (electrospray ionization (ESI^+) *m/z*: 382 [M+H$^+$]. High resolution (HR)-MS (ESI^+) *m/z*: Calcd for $C_{11}H_{18}Br_2NO_2Si$ (M+H$^+$) 381.94736, Found 381.94819.

4-Bromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-carbaldehyde (41d) Treatments of **56** (1.74 g, 10 mmol) with *t*BuOK (1.23 g, 11 mmol) and SEMCl (1.95 ml, 11 mmol) carried out in the same manner as described for **41a** gave **41d** (2.79 g, 92%) as a colorless oil after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=20/1). IR (ATR): 2953, 1668, 1375, 1248, 1083, 832, 738 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.02 (9H, s), 0.88—0.94 (2H, m), 3.52—3.57 (2H, m), 5.67 (2H, s), 6.95 (1H, d, *J*=1.8 Hz), 7.13 (1H, dd, *J*=1.8, 0.9 Hz), 9.53 (1H, d, *J*=0.9 Hz). LR-MS (CI^+) *m/z*: 304 [M+H$^+$]. HR-MS (CI^+) *m/z*: Calcd for $C_{11}H_{19}BrNO_2Si$ (M+H$^+$) 304.0368, Found 304.0322.

4-Methyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-carbaldehyde (41g) Treatments of **58a** (450 mg, 4.1 mmol) with *t*BuOK (554 mg, 4.9 mmol) and SEMCl (0.874 ml, 4.9 mmol) carried out in a similar manner to that described for **41a** gave **41g** (894 mg, 91%) as a colorless oil after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=50/1). IR (ATR): 2953, 1663, 1248, 1083, 832, 751 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.03 (9H, s), 0.88—0.92 (2H, m), 2.11 (3H, s), 3.51—3.56 (2H, m), 5.64 (2H, s), 6.77 (1H, d, *J*=1.5 Hz), 6.92 (1H, t, *J*=0.9 Hz), 9.50 (1H, d, *J*=0.9 Hz). LR-MS (EI^+) *m/z*: 239 [M$^+$]. HR-MS (EI^+) *m/z*: Calcd for $C_{12}H_{21}NO_2Si$ (M$^+$) 239.1342, Found 239.1378.

4-Benzyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-carbaldehyde (41i) The same treatments of **58b** (560 mg, 3.0 mmol) with *t*BuOK (678 mg, 6.0 mmol) and SEMCl (1.07 ml, 6.0 mmol) as those described for **41a** gave **41i** (411 mg, 43%) as a pale yellow solid after purification by column chromatography (SiO_2, C_6H_5Me/EtOAc=50/1). IR (ATR): 2952, 1663, 1084, 833, 763, 701 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.04 (9H, s), 0.86—0.90 (2H, m), 3.51—3.55 (2H, m), 3.83 (2H, s), 5.64 (2H, s), 6.78 (1H, d, *J*=1.8 Hz), 6.91 (1H, dd, *J*=1.8, 0.9 Hz), 7.20—7.23 (3H, m), 7.28—7.32 (2H, m),



Reagents and conditions: (a) i) SEMCl, *t*BuOK/DMF, 0 °C, 1 h; ii) *n*BuLi, DMF/THF, −78 °C (for crude product) (this sample contained some unidentified by-products (*ca.* 10%); (b) *n*BuLi, DMF/THF, −78 °C-rt, 45%; (c) trytylazide, CuI, diisopropylethylamine/DMF, 40 °C, 44 h, 93%; (d) PPTS (cat.)/acetone, rt, 2 d, 46%; (e) i) $NaBH_4$/MeOH, 0 °C, 30 min; ii) MnO_2/CH_2Cl_2, rt, 4 h, 80%; (f) *n*BuLi, HCO_2Et/THF, −98 °C-rt, 73%; (g) *n*BuLi, TMEDA, HCO_2Et/THF, −98 °C-rt (a mixture of **41u** and **67** (3 : 1) was obtained. This was directly used for the next reaction.).

Chart 7. Synthesis of the Azole-aldehyde Derivatives **41r**—**u**, ***x***, **y**

9.50 (1H, d, J=0.9 Hz). LR-MS (ESI^+) *m/z*: 316 [M+H$^+$]. HR-MS (ESI^+) Calcd for $C_{18}H_{26}NO_2Si$ *m/z*: 316.17328 (M+H$^+$), Found 316.17404.

4-(3-Phenylpropyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrole-2-carbaldehyde (41n) Simlar treatments of **58c** (1.32 g, 6.2 mmol) with *t*BuOK (1.04 g, 9.3 mmol) and SEMCl (1.64 ml, 9.3 mmol) to those described for **41a** gave **41n** (1.09 g, 51%) as a pale yellow oil after purification by column chromatography (SiO_2, toluene/EtOAc=50/1). IR (ATR): 2936, 1663, 1084, 833, 749, 697 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.04 (9H, s), 0.89 (2H, t, J=8.3 Hz), 1.87—1.95 (2H, m), 2.50 (2H, t, J=7.6 Hz), 2.66 (2H, t, J=7.6 Hz), 3.53 (2H, t, J=8.3 Hz), 5.65 (2H, s), 6.80 (1H, d, J=1.8 Hz), 6.94 (1H, br s), 7.17—7.21 (3H, m), 7.27—7.31 (2H, m), 9.52 (1H, d, J=0.9 Hz). LR-MS (ESI^+) *m/z*: 344 [M+H$^+$]. HR-MS (ESI^+) Calcd for $C_{20}H_{30}NO_2Si$ *m/z*: 344.20458 (M+H$^+$), Found 344.20497.

3-Bromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-carbaldehyde (60) Treatments of **59** (4.00 g, 23 mmol) with *t*BuOK (2.84 g, 25 mmol) and SEMCl (4.48 ml, 25 mmol) carried out in the same manner as described for **41a** gave **60** (6.28 g, 89%) as a pale yellow oil after purification by column chromatography (SiO_2, C_6H_5Me/EtOAc=50/1). This compound was used for the next step at once since it was unstable. ^{1}H-NMR ($CDCl_3$) δ: −0.02 (9H, s), 0.89—0.93 (2H, m), 3.53—3.57 (2H, m), 5.67 (2H, s), 6.34 (1H, d, J=2.8 Hz), 7.09 (1H, dd, J=2.8, 0.9 Hz), 9.73 (1H, d, J=0.9 Hz).

4,5-Dibromo-1-methyl-1*H*-pyrrol-2-carbaldehyde (41b) To a solution of **55** (1.00 g, 4.0 mmol) in DMF (20 ml) was added *t*BuOK (466 mg, 4.2 mmol) at 0 °C. After stirring at room temperature for 30 min, MeI (0.369 ml, 5.9 mmol) was added to the reaction mixture at 0 °C, and the whole was stirred at the same temperature for 1 h. The reaction was quenched by adding H_2O at 0 °C. The precipitates appeared were collected by filtration, washed with H_2O, and dried *in vacuo* to afford **41b** (1.03 g, 98%) as a light brown solid. This sample was directly used for the next reaction without further purification.^{1}H-NMR ($CDCl_3$) δ: 4.00 (3H, s), 6.96 (1H, s), 9.35 (1H, s).

4-Bromo-5-methyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-carbaldehyde (41e) To a solution of **57** (109 mg, 1.0 mmol) in THF (10 ml) was added NBS (178 mg, 1.0 mmol) at −78 °C under an argon atmosphere. The mixture was stirred at the same temperature for 2 h, diluted with C_6H_{14}, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, C_6H_{14}/EtOAc=5/1) afforded crude 4-bromo-5-methyl-1*H*-pyrrol-2-carbaldehyde as a red powder. To a solution of the powder in DMF (4 ml) was added *t*BuOK (114 mg, 1.0 mmol) at 0 °C. After stirring at room temperature for 30 min, SEMCl (0.181 ml, 1.0 mmol) was added to the reaction mixture at 0 °C, and the whole was stirred at the same temperature for 1 h. The reaction was quenched by adding H_2O at 0 °C, and the mixture was extracted with EtOAc. The organic extracts were combined, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, C_6H_{14}/EtOAc=50/1) afforded **41e** (245 mg, 80%) as a red oil. ^{1}H-NMR ($CDCl_3$) δ: −0.03 (9H, s), 0.86—0.90 (2H, m), 2.35 (3H, s), 3.52—3.57 (2H, m), 5.78 (2H, s), 6.91 (1H, s), 9.41 (1H, s). LR-MS (EI^+) *m/z*: 317 [M$^+$]. HR-MS (EI^+) *m/z*: Calcd for $C_{12}H_{20}BrNO_2Si$ (M$^+$) 317.0447, Found 317.0446.

4-Bromo-5-phenyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-carbaldehyde (41f) To a solution of **41a** (448 mg, 1.2 mmol) in DMF (5 ml) were added phenylboronic acid (215 mg, 1.8 mmol), $Pd(OAc)_2$ (13.1 mg, 0.059 mmol) and K_2CO_3 (405 mg, 2.9 mmol), and the reaction mixture was stirred at 100 °C for 7.5 h. The reaction mixture was diluted with EtOAc, and the whole was filtered through a pad of celite. The filtrate was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, C_6H_{14}/EtOAc=30/1) afforded **41f** (311 mg, 70%) as a light brown oil. IR (ATR): 2952, 1668, 1458, 1399, 1248, 1207, 1075, 832, 760, 697 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.05 (9H, s), 0.82—0.86 (2H, m), 3.47—3.51 (2H, m), 5.56 (2H, s), 7.08 (1H, s), 7.47—7.54 (5H, m), 9.58 (1H, s). LR-MS (EI^+) *m/z*: 379 [M$^+$]. HR-MS (EI^+) *m/z*: Calcd for $C_{17}H_{22}BrNO_2Si$ (M$^+$) 379.0603, Found 379.0626.

4-Phenyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-carbaldehyde (41h) The same treatments of **41d** (609 mg, 2.0 mmol) with phenylboronic acid (610 mg, 5.0 mmol), $Pd(PPh_3)_4$ (116 mg, 0.10 mmol) and K_2CO_3 (1.38 g, 10 mmol) as those described for **41f** gave **45h** (314 mg, 52%) as a colorless oil after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=30/1). IR (ATR): 2953, 1663, 1371, 1248, 1087, 832, 755, 692 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.02 (9H, s), 0.91—0.95 (2H, m), 3.58—3.62 (2H, m), 5.75 (2H, s), 7.24—7.28 (2H, m), 7.39 (2H, t, J=7.9 Hz), 7.44—7.45 (1H, m), 7.51—7.54 (2H, m), 9.64 (1H, d, J=0.9 Hz). LR-MS (EI^+) *m/z*: 301 [M$^+$]. HR-MS (EI^+) *m/z*: Calcd for $C_{17}H_{23}NO_2Si$ 301.1498 (M$^+$), Found 301.1525.

4-(Phenylethynyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-carbaldehyde (41j) To a solution of **41d** (2.65 g, 8.7 mmol) in DMF (50 ml) were added $Pd(PPh_3)_2Cl_2$ (306 mg, 0.44 mmol), copper(I) iodide (83.0 mg, 0.44 mmol), phenylacetylene (5.74 ml, 52 mmol) and Et_3N (25 ml), and the reaction mixture was stirred at 100 °C for 8 h. The reaction mixture was diluted with EtOAc, and the whole was filtered through a pad of celite. The filtrate was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, C_6H_{14}/EtOAc=50/1—40/1) afforded **41j** (1.70 g, 60%) as a brown oil. IR (ATR): 2952, 2217, 1667, 1367, 1248, 1085, 831, 753, 690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.01 (9H, s), 0.90—0.95 (2H, m), 3.55—3.59 (2H, m), 5.70 (2H, s), 7.11 (1H, d, J=1.8 Hz), 7.31—7.37 (4H, m), 7.48—7.51 (2H, m), 9.58 (1H, d, J=0.9 Hz). LR-MS (EI^+) *m/z*: 325 [M$^+$]. HR-MS (EI^+) *m/z*: Calcd for $C_{19}H_{23}NO_2Si$ (M$^+$) 325.1498, Found 325.1530.

4-(2-(Trifluoromethyl)phenylethynyl)-1-(2-(trimethylsilyl)ethoxymethyl)-

1*H*-pyrrol-2-carbaldehyde (41k) Treatments of **41d** (599 mg, 2.0 mmol) with $Pd(PPh_3)_2Cl_2$ (105 mg, 0.15 mmol), copper(I) iodide (28.6 mg, 0.15 mmol), (2-(trifluoromethyl)phenyl)acetylene (2.04 g, 12 mmol) and iPr_2EtN (10 ml) carried out in the same manner as described for **41j** gave **41k** (455 mg, 59%) as a brown oil after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=40/1-30/1). IR (ATR): 2954, 1670, 1315, 1166, 1129, 1089, 1056, 832, 760 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.01 (9H, s), 0.91—0.95 (2H, m), 3.56—3.60 (2H, m), 5.71 (2H, s), 7.13 (1H, d, J=1.8 Hz), 7.38—7.42 (2H, m), 7.51 (1H, td, J=7.6, 0.6 Hz), 7.62 (1H, d, J=7.6 Hz), 7.67 (1H, d, J=7.6 Hz), 9.60 (1H, d, J=1.2 Hz). LR-MS (ESI^+) *m/z*: 394 [M+H$^+$]. HR-MS (ESI^+) *m/z*: Calcd for $C_{20}H_{23}F_3NO_2Si$ (M+H$^+$) 394.14501, Found 394.14524.

4-(3-(Trifluoromethyl)phenylethynyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-carbaldehyde (41l) Treatments of **41d** (913 mg, 3.0 mmol) with $Pd(PPh_3)_2Cl_2$ (105 mg, 0.15 mmol), copper(I) iodide (28.6 mg, 0.15 mmol), (3-(trifluoromethyl)phenyl)acetylene (3.06 g, 18 mmol) and Et_3N (10 ml) carried out in a similar manner to that described for **41j** gave **41l** (620 mg, 53%) as a brown oil after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=50/1—40/1). IR (ATR): 2954, 1671, 1324, 1164, 1124, 1070, 833, 799, 694 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.01 (9H, s), 0.91—0.95 (2H, m), 3.55—3.59 (2H, m), 5.71 (2H, s), 7.12 (1H, d, J=1.8 Hz), 7.39 (1H, dd, J=1.8, 0.9 Hz), 7.47 (1H, t, J=7.9 Hz), 7.57 (1H, d, J=7.9 Hz), 7.65 (1H, d, J=7.9 Hz), 7.75 (1H, s), 9.60 (1H, d, J=0.9 Hz). LR-MS (ESI^+) *m/z*: 394 [M+H$^+$]. HR-MS (ESI^+) *m/z*: Calcd for $C_{20}H_{23}F_3NO_2Si$ 394.14501 (M+H$^+$), Found 394.14534.

4-(4-(Trifluoromethyl)phenylethynyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-carbaldehyde (41m) The same treatments of **41d** (913 mg, 3.0 mmol) with $Pd(PPh_3)_2Cl_2$ (105 mg, 0.15 mmol), copper(I) iodide (28.6 mg, 0.15 mmol), (4-(trifluoromethyl)phenyl)acetylene (3.06 g, 18 mmol) and Et_3N (10 ml) as those described for **41j** gave **41m** (635 mg, 54%) as a brown oil after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=50/1—40/1). IR (ATR): 2955, 1671, 1320, 1164, 1105, 1065, 833 cm^{-1}.^{1}H-NMR ($CDCl_3$) δ: −0.01 (9H, s), 0.91—0.95 (2H, m), 3.55—3.60 (2H, m), 5.71 (2H, s), 7.12 (1H, d, J=1.8 Hz), 7.39 (1H, dd, J=1.8, 0.9 Hz), 7.59 (4H, s), 9.60 (1H, d, J=0.9 Hz). LR-MS (EI^+) *m/z*: 393 [M$^+$]. HR-MS (EI^+) *m/z*: Calcd for $C_{20}H_{22}F_3NO_2Si$ 393.1372 (M$^+$), Found 393.1381.

3-(Phenylethynyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-carbaldehyde (41o) Similar treatments of **60** (1.00 g, 3.29 mmol) with $Pd(PPh_3)_2Cl_2$ (116 mg, 0.17 mmol), copper(I) iodide (31.4 mg, 0.17 mmol), phenylacetylene (2.16 ml, 20 mmol) and Et_3N (10 ml) to those described for **41j** gave **41o** (1.03 g, 96%) as a brown oil after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=50/1). IR (ATR): 2952, 1659, 1483, 1426, 1364, 1332, 1247, 1094, 833, 754, 689 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.02 (9H, s), 0.90—0.94 (2H, m), 3.54—3.59 (2H, m), 5.72 (2H, s), 6.45 (1H, d, J=2.8 Hz), 7.10 (1H, dd, J=2.8, 0.9 Hz), 7.34—7.37 (3H, m), 7.50—7.54 (2H, m), 9.95 (1H, d, J=0.9 Hz). LR-MS (ESI^+) *m/z*: 326 [M+H$^+$]. HR-MS (ESI^+) *m/z*: Calcd for $C_{19}H_{24}NO_2Si$ (M+H$^+$) 326.15763, Found 326.15686.

4,5-Dibromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-imidazol-2-carbaldehyde (41r) To a solution of **61** (1.00 g, 3.28 mmol) in DMF (30 ml) was added *t*BuOK (442 mg, 3.9 mmol) at 0 °C. After stirring at room temperature for 30 min, SEMCl (0.639 ml, 3.6 mmol) was added to the reaction mixture at 0 °C, and the whole was stirred at the same temperature for 1 h. The reaction was quenched by adding H_2O at 0 °C, and the mixture was extracted with EtOAc. The organic extracts were combined, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. The residue was dissolved in THF (30 ml), and *n*-BuLi (1.61 mol/l in C_6H_{14}, 2.04 ml, 3.3 mmol) was added dropwise to the solution at −78 °C, and the mixture was stirred at the same temperature for 1 h. To the mixture was added DMF (3.0 ml) at the same temperature, and the mixture was slowly warmed to room temperature. The reaction was quenched by adding a saturated ammonium chloride solution, and the whole was extracted with EtOAc. The organic extracts were combined, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, C_6H_{14}/EtOAc=20/1—10/1) afforded crude **41r** (984 mg, <78%: this sample was contaminated with some unidentified by-products (*ca.* 10%)) as a light brown oil and was directly used for the next reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: −0.02 (9H, s), 0.90—0.96 (2H, m), 3.58—3.63 (2H, m), 5.83 (2H, s), 9.61 (1H, s).

1-Trityl-1*H*-1,2,4-triazol-5-carbaldehyde (41s) To a solution of **62** (1.33 g, 4.3 mmol) in THF (20 ml) was added dropwise *n*-BuLi (1.61 mol/l in C_6H_{14}, 3.45 ml, 5.6 mmol) at −78 °C, and the mixture was stirred at the same temperature for 1 h. To the mixture was added DMF (3.0 ml) at the same temperature, and the mixture was slowly warmed to room temperature. The reaction was quenched by adding H_2O, and the whole was extracted with EtOAc. The organic extracts were combined, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, CH_2Cl_2–C_6H_{14}/EtOAc=2/1) afforded **41s** (649 mg, 45%) as a white solid. This sample was directly used for the next reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 7.08—7.15 (6H, m), 7.31—7.38 (9H, m), 8.10 (1H, s), 9.14 (1H, s).

4-Diethoxymethyl-1-trityl-1*H*-1,2,3-triazole (64) To a solution of tritylazide (2.00 g, 7.0 mmol) and **63** (3.0 ml, 21 mmol) in DMF (14 ml) were added copper(I) iodide (1.34 g, 7.0 mmol) and iPr_2EtN (9.2 ml, 53 mmol), and the mixture was stirred at 40 °C for 44 h. The reaction was quenched by adding H_2O, and the whole was extracted with EtOAc. The organic extracts were combined, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, C_6H_{14}/EtOAc=6/1—5/1) to give **64** (2.69 g, 93%) as a pale yellow solid. IR (ATR): 2974, 2899, 1493, 1444, 1113, 1047, 1019, 744, 696 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (6H, t, J=7.0 Hz), 3.56—3.72 (4H, m), 5.73 (1H, s), 7.11—7.15 (6H, m), 7.29—7.36 (9H, m), 7.50 (1H, s). LR-MS (EI^+) *m/z*: 413 [M$^+$], 243. HR-MS (EI^+) *m/z*: Calcd for $C_{26}H_{27}N_3O_2$ (M$^+$) 413.2103, Found 413.2132.

1-Trityl-1*H*-1,2,3-triazol-4-carbaldehyde (41x) To a solution of **64** (2.48 g, 6.0 mmol) in Me_2CO (400 ml) was added PPTS (151 mg, 0.60 mmol), and the reaction mixture was stirred at room temperature for 2 d. The reaction was quenched by adding aqueous $NaHCO_3$ solution, and the whole was extracted with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, C_6H_{14}/EtOAc=9/1) to give **41x** (934 mg, 46%) as a white solid. IR (ATR): 3466, 3060, 1698, 1490, 1445, 1274, 1183, 1038, 760, 746, 697 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.09—7.13 (6H, m), 7.33—7.39 (9H, m), 8.07 (1H, s), 10.18 (1H, s). LR-MS (EI^+) *m/z*: 339 [M$^+$], 282, 243, 165. HR-MS (EI^+) *m/z*: Calcd for $C_{22}H_{17}N_3O$ (M$^+$) 339.1372, Found 339.1354.

3-Bromo-1-(4-methoxybenzyl)-1*H*-1,2,4-triazol-5-carbaldehyde (41t) To a solution of **65** (2.00 g, 6.1 mmol) in MeOH (60 ml) was added $NaBH_4$ (1.16 g, 31 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 30 min. The reacton was quenched by adding saturated NH_4Claq at 0 °C, and the miture was extracted with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give (3-bromo-1-(4-methoxybenzyl)-1*H*-1,2,4-triazol-5-yl)methanol as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 2.80 (1H, br s), 3.80 (3H, s), 4.69 (2H, d, J=5.2 Hz), 5.30 (2H, s), 6.88 (2H, dt, J=8.6, 2.1 Hz), 7.24 (2H, dt, J=8.6, 2.1 Hz). To a solution of the methanol derivative in CH_2Cl_2 (100 ml) was added activated MnO_2 (11.3 g), and the mixture was stirred at room temperature for 4 h. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo* to give **41t** (1.47 g, 80%) as a white solid. This compound was directly used for the next reaction without further purification. IR (ATR): 2925, 2892, 2841, 1708, 1612, 1513, 1456, 1251, 1030, 776, 758, 700 cm^{-1}.^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s), 5.63 (2H, s), 6.86 (2H, dt, J=8.6, 2.1 Hz), 7.34 (2H, dt, J=8.6, 2.1 Hz), 9.90 (1H, s). LR-MS (EI^+) *m/z*: 295 [M$^+$], 216, 121. HR-MS (EI^+) *m/z*: Calcd for $C_{11}H_{10}BrN_3O_2$ (M$^+$) 294.9956, Found 294.9975.

5-Bromo-2-trityl-2*H*-1,2,3-triazol-4-carbaldehyde (41y) To a solution of **66** (1.41 g, 3.0 mmol) in THF (30 ml) was added dropwise *n*-BuLi (1.6 mol/l in C_6H_{14}, 2.05 ml, 3.3 mmol) at −98 °C, and the mixture was stirred at the same temperature for 10 min. Ethyl formate (3.0 ml) was added to the mixture. The mixture was stirred at the same temperature for 30 min, and then slowly warmed to room temperature. The reaction was quenched by adding saturated NH_4Claq, and exracted with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, C_6H_{14}/EtOAc=9/1—8/1) to give **41y** (917 mg, 73%) as a pale yellow powder. IR (ATR): 1704, 1444, 1273, 1136, 880, 747, 697 cm^{-1}.^{1}H-NMR ($CDCl_3$) δ: 7.09—7.13 (6H, m), 7.31—7.37 (9H, m), 10.06 (1H, s). LR-MS (EI^+) *m/z*: 417 [M$^+$], 310, 282, 243, 167. HR-MS (EI^+) *m/z*: Calcd for $C_{22}H_{16}BrN_3O$ (M$^+$) 417.0477, Found 417.0513.

1-(4-Methoxybenzyl)-1*H*-tetrazol-5-carbaldehyde (41u) To a solution **67** (951 mg, 5.0 mmol) in THF (50 ml) and *N*,*N*,*N*,*N*-tetramethylethylenediamine (5.0 ml) was added dropwise *n*-BuLi (1.6 mol/l in C_6H_{14}, 3.4 ml, 5.5 mmol) at −98 °C, and the mixture was stirred at the same temperature for 5 min. After ethyl formate (5.0 ml) was added to the reaction mixture, the whole was stirred at the same temperature for 30 min, and then warmed to room temperature slowly. The reaction was quenched by adding saturated NH_4Claq, the whole was extracted with EtOAc. The organic extracts were

combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, C_6H_{14}/EtOAc=1/1) to give a mixture of **41u** and **67** (2 : 1). Since **41u** was found to be fairly unstable, this mixture was directly used for the next reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s), 5.81 (2H, s), 6.87 (2H, dt, J=9.4, 2.5 Hz), 7.36 (2H, dt, J=9.4, 2.5 Hz), 10.26 (1H, s). LR-MS (EI$^+$) *m/z*: 218 [M$^+$], 161. HR-MS (EI$^+$) *m/z*: Calcd for $C_{10}H_{10}N_4O_2$ (M$^+$) 218.0804, Found 218.0836.

***tert*-Butyl [4-(4-Bromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43ad)** A solution of **40a**[1,15] (226 mg, 1.0 mmol) and **41d** (350 mg, 1.2 mmol) in EtOH (5 ml) was stirred at 50 °C for 4 h. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (NH-SiO_2, EtOAc) to give the 4,5,6,7-tetrahydroderivative of **43ad** as a yellow amorphous solid. ^{1}H-NMR (CD_3OD) δ: 0.01 (9H, s), 0.83—0.96 (2H, m), 1.51 (9H, s), 2.59—2.63 (2H, m), 2.93 (1H, dt, J=12.5, 5.0 Hz), 3.05—3.11 (1H, m), 3.50—3.62 (2H, m), 5.09 (1H, s), 5.24 (1H, d, J=11.0 Hz), 5.33 (1H, d, J=11.0 Hz), 5.80 (1H, J=1.8 Hz), 6.89 (1H, J=1.8 Hz). LR-MS (ESI$^+$) *m/z*: 512 [M+H$^+$]. HR-MS (ESI$^+$) *m/z*: Calcd for $C_{21}H_{35}BrN_5O_3Si$ (M+H$^+$) 512.16925, Found 512.16973. To a solution of the 4,5,6,7-tetrahydroderivative (258 mg, 0.50 mmol) in DMSO (2.5 ml) was added IBX (211 mg, 0.76 mmol), and the mixture was stirred at room temperature for 2 h. The reaction was quenched by adding H_2O and an aqueous NaOH solution (1.0 mol/l, 3.0 ml, 3.0 mmol), and the mixture was extracted with EtOAc. The organic extracts were combined, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. To a solution of the residue in CH_2Cl_2 (10 ml) was added activated MnO_2 (1.4 g), and the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (NH-SiO_2, C_6H_{14}/EtOAc=1/1) to give **43ad** (192 mg, 75%) as a pale yellow solid. IR (KBr): 3388, 2952, 1719, 1633, 1571, 1252, 1155, 1083, 836 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.23 (9H, s), 0.62 (2H, t, J=8.1 Hz), 1.57 (9H, s), 3.22 (2H, t, J=8.1 Hz), 5.68 (2H, br s), 6.86 (1H, br s), 7.07 (1H, br s), 7.38 (1H, d, J=5.5 Hz), 8.22 (1H, s). LR-MS (ESI$^+$) *m/z*: 508 [M+H$^+$]. HR-MS (ESI$^+$) *m/z*: Calcd for $C_{21}H_{31}BrN_5O_3Si$ (M+H$^+$) 508.13795, Found 508.13726.

***tert*-Butyl [4-(4,5-Dibromo-1-methyl-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43ab)** Treatments of **40a**[1,15] (324 mg, 1.4 mmol) with **41b** (459 mg, 1.7 mmol) followed by dehydrogenation using IBX (145 mg, 0.52 mmol) and activated MnO_2 (1.0 g) carried out in the same manner as described for **43ad** gave **43ab** (117 mg, 22%) as a pale yellow solid after purification by column chromatography (NH-SiO_2, C_6H_{14}/EtOAc=1/1). IR (KBr): 3358, 2986, 1716, 1632, 1571, 1465, 1272, 1254, 1156 cm^{-1}.^{1}H-NMR (CD_3OD) δ: 1.59 (9H, s), 3.79 (3H, s), 6.85 (1H, br s), 7.41 (1H, d, J=5.5 Hz), 8.23 (1H, d, J=5.5 Hz). LR-MS (ESI$^+$) *m/z*: 470 [M+H$^+$]. HR-MS (ESI$^+$) *m/z*: Calcd for $C_{16}H_{17}Br_2N_5O_2$ (M+H$^+$) 469.98273, Found 469.98284.

***tert*-Butyl [4-(1-(2-(Trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43ac)** Treatments of **40a**[1,15] (390 mg, 1.7 mmol) with **41c**[17] (435 mg, 1.9 mmol) followed by dehydrogenation using IBX (417 mg, 1.5 mmol) and activated MnO_2 (2.6 g) carried out in a similar manner to that described for **43ad** gave **43ac** (350 mg, 51%) as a pale yellow solid after purification by column chromatography (NH-SiO_2, C_6H_{14}/EtOAc=1/1). IR (ATR): 3404, 2892, 1704, 1634, 1567, 1480, 1418, 1246, 1146, 1086, 835, 715 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.25 (9H, s), 0.60 (2H, t, J=7.9 Hz), 1.57 (9H, s), 3.19 (2H, t, J=7.9 Hz), 5.69 (2H, s), 6.29 (1H, s), 6.77 (1H, br s), 7.06 (1H, s), 7.36 (1H, d, J=5.5 Hz), 8.22 (1H, s). LR-MS (ESI$^+$) *m/z*: 430 [M+H$^+$]. HR-MS (ESI$^+$) *m/z*: Calcd for $C_{21}H_{32}N_5O_3Si$ (M+H$^+$) 430.22744, Found 430.22818.

***tert*-Butyl [4-(4-Bromo-5-methyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43ae)** The same treatments of **40a**[1,15] (275 mg, 1.2 mmol) with **41e** (426 mg, 1.3 mmol) followed by dehydrogenation using IBX (512 mg, 1.83 mmol) and activated MnO_2 (3.8 g) as those described for **43ad** gave **43ae** (286 mg, 45%) as a light brown amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=10/1—4/1). IR (ATR): 3385, 2951, 1714, 1630, 1567, 1248, 1153, 1075, 858, 833, 761 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.26 (9H, s), 0.56 (2H, t, J=8.3 Hz), 1.57 (9H, s), 2.35 (3H, s), 3.06—3.11 (2H, m), 5.69 (2H, br s), 6.76 (1H, br s), 7.38 (1H, d, J=5.5 Hz), 8.22 (1H, br s). LR-MS (ESI$^+$) *m/z*: 522 [M+H$^+$]. HR-MS (ESI$^+$) *m/z*: Calcd for $C_{22}H_{33}BrN_5O_3Si$ (M+H$^+$) 522.15360, Found 522.15397.

***tert*-Butyl [4-(4-Bromo-5-phenyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43af)** Similar treatments of **40a**[1,15] (202 mg, 0.89 mmol) with **41f** (340 mg, 0.89 mmol) followed by dehydrogenation using IBX (375 mg, 1.3 mmol) and activated MnO_2 (2.3 g) to those described for **43ad** gave **43af** (271 mg, 52%) as a pale yellow solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1). mp: 110—112 °C (from C_6H_{14}–EtOAc). IR (KBr): 3390, 2953, 1716, 1633, 1571, 1474, 1252, 1155, 1081, 861, 835, 771, 700 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.28 (9H, s), 0.46 (2H, t, J=8.6 Hz), 1.58 (9H, s), 2.96 (2H, t, J=8.6 Hz), 5.61 (2H, br s), 6.91 (1H, br s), 7.42 (1H, d, J=5.5 Hz), 7.42—7.54 (5H, m), 8.25 (1H, br s). LR-MS (ESI$^+$) *m/z*: 584 [M+H$^+$]. HR-MS (ESI$^+$) *m/z*: Calcd for $C_{27}H_{35}BrN_5O_3Si$ (M+H$^+$) 584.16925, Found 584.17389.

***tert*-Butyl [4-(4-Methyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43ag)** The same treatments of **40a**[1,15] (323 mg, 1.4 mmol) with **41g** (376 mg, 1.6 mmol) followed by dehydrogenation using IBX (602 mg, 2.2 mmol) and activated MnO_2 (5.0 g) as those described for **43ad** gave **43ag** (244 mg, 38%) as a pale yellow amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1—3/1). IR (ATR): 3393, 2952, 1712, 1631, 1568, 1249, 1154, 1069, 859, 831, 766 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.25 (9H, s), 0.60 (2H, t, J=8.3 Hz), 1.57 (9H, s), 2.15 (3H, s), 3.17 (2H, br s), 5.59 (2H, br s), 6.63 (1H, br s), 6.82 (1H, br s), 7.35 (1H, d, J=5.5 Hz), 8.20 (1H, br s). LR-MS (ESI$^+$) *m/z*: 444 [M+H$^+$]. HR-MS (ESI$^+$) *m/z*: Calcd for $C_{22}H_{34}N_5O_3Si$ (M+H$^+$) 444.24309, Found 444.24362.

***tert*-Butyl [4-(4-Phenyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43ah)** Similar treatments of **40a**[1,15] (339 mg, 1.5 mmol) with **41h** (543 mg, 1.8 mmol) followed by dehydrogenation using IBX (630 mg, 2.3 mmol) and activated MnO_2 (4.0 g) to those described for **43ad** gave **43ah** (419 mg, 55%) as a brown amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1—3/1). IR (KBr): 3391, 2952, 1719, 1632, 1592, 1570, 1508, 1420, 1370, 1251, 1155, 1086, 861, 835, 754, 693 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.24 (9H, s), 0.64 (2H, t, J=7.9 Hz), 1.57 (9H, s), 3.18—3.28 (2H, m), 5.74 (2H, br s), 7.15 (1H, t, J=7.3 Hz), 7.17 (1H, br s), 7.32 (2H, t, J=7.3 Hz), 7.39 (1H, d, J=5.5 Hz), 7.42 (1H, br s), 7.60 (2H, d, J=7.3 Hz), 8.24 (1H, s). LR-MS (ESI$^+$) *m/z*: 506 [M+H$^+$]. HR-MS (ESI$^+$) *m/z*: Calcd for $C_{27}H_{36}N_5O_3Si$ (M+H$^+$) 506.25874, Found 506.25888.

***tert*-Butyl [4-(4-Benzyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43ai)** Treatments of **40a**[1,15] (339 mg, 1.5 mmol) with **41i** (395 mg, 1.3 mmol) followed by dehydrogenation using IBX (526 mg, 1.9 mmol) and activated MnO_2 (3.0 g) carried out in the same manner as described for **43ad** gave **43ai** (450 mg, 69%) as a light brown amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=3/1—2/1). IR (ATR): 3388, 2951, 1713, 1631, 1566, 1249, 1153, 1082, 833 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.24 (9H, s), 0.57—0.62 (2H, m), 1.57 (9H, s), 3.18 (2H, t, J=8.1 Hz), 3.86 (2H, s), 5.60 (2H, br s), 6.62 (1H, br s), 6.81 (1H, br s), 7.12—7.28 (5H, m), 7.34 (1H, d, J=5.8 Hz), 8.19 (1H, br s). LR-MS (ESI$^+$) *m/z*: 520 [M+H$^+$]. HR-MS (ESI$^+$) *m/z*: Calcd for $C_{28}H_{38}N_5O_3Si$ (M+H$^+$) 520.27439, Found 520.27439.

***tert*-Butyl [4-(4-(Phenylethynyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43aj)** Treatments of **40a**[1,15] (474 mg, 2.1 mmol) with **41j** (707 mg, 2.3 mmol) followed by dehydrogenation using IBX (879 mg, 3.1 mmol) and activated MnO_2 (5.0 g) carried out in a similar manner to that described for **43ad** gave **43aj** (647 mg, 58%) as a light brown amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=10/1—4/1). IR (ATR): 3391, 2951, 2216, 1714, 1630, 1567, 1248, 1153, 1082, 859, 833, 754 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.22 (9H, s), 0.62—0.66 (2H, m), 1.58 (9H, s), 3.26 (2H, br s), 5.73 (2H, br s), 6.99 (1H, br s), 7.24—7.35 (4H, m), 7.40 (1H, d, J=5.5 Hz), 7.45 (1H, d, J=6.7 Hz), 8.23 (1H, br s). LR-MS (ESI$^+$) *m/z*: 530 [M+H$^+$]. HR-MS (ESI$^+$) *m/z*: Calcd for $C_{29}H_{36}N_5O_3Si$ (M+H$^+$) 530.25874, Found 530.25854.

***tert*-Butyl [4-(4-(2-(Trifluoromethyl)phenylethynyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43ak)** The same treatments of **40a**[1,15] (226 mg, 1.0 mmol) with **41k** (450 mg, 1.1 mmol) followed by dehydrogenation using IBX (420 mg, 1.5 mmol) and activated MnO_2 (3.0 g) as those described for **43ad** gave **43ak** (405 mg, 68%) as a brown amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1—3/1). IR (ATR): 3390, 2951, 2216, 1714, 1631, 1570, 1316, 1250, 1155, 1132, 1084, 834 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.21 (9H, s), 0.64 (2H, t, J=7.9 Hz), 1.57 (9H, s), 3.27 (2H, br s), 5.76 (2H, br s), 7.02 (1H, br s), 7.36 (1H, br s), 7.40 (1H, d, J=5.5 Hz), 7.44 (1H, t, J=7.6 Hz), 7.57 (1H, t, J=7.6 Hz), 7.65 (1H, d, J=7.6 Hz), 7.69 (1H, d, J=7.6 Hz), 8.24 (1H, br s). LR-MS (ESI$^+$) *m/z*: 598 [M+H$^+$]. HR-MS (ESI$^+$) *m/z*: Calcd for $C_{30}H_{35}F_3N_5O_3Si$ (M+H$^+$) 598.24612, Found 598.24677.

***tert*-Butyl [4-(4-(3-(Trifluoromethyl)phenylethynyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl] carbamate (43al)** Similar treatments of **40a**[1,15] (226 mg, 1.0 mmol) with **41l** (600 mg, 1.5 mmol) followed by dehydrogenation using IBX (420 mg, 1.5 mmol) and activated MnO_2 (3.0 g) to those described for **43ad** gave **43al** (374 mg, 63%) as a brown amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1—3/1). IR (ATR): 3388, 2952, 2213, 1713, 1626, 1591, 1568, 1326, 1246, 1154, 1125, 1087, 834 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.22 (9H, s), 0.62—0.66 (2H, m), 1.57 (9H, s), 3.26 (2H, t, J=7.9 Hz), 5.75 (2H, br s), 7.03 (1H, br s), 7.39 (1H, br s), 7.40 (1H, d, J=5.5 Hz), 7.52—7.60 (2H, m), 7.69—7.71 (2H, m), 8.24 (1H, br s). LR-MS (ESI^+) m/z: 598 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{30}H_{35}F_3N_5O_3Si$ (M+H$^+$) 598.24612, Found 598.24620.

***tert*-Butyl [4-(4-(4-(Trifluoromethyl)phenylethynyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl] carbamate (43am)** Treatments of **40a**[1,15] (384 mg, 1.7 mmol) with **41m** (635 mg, 1.6 mmol) followed by dehydrogenation using IBX (678 mg, 2.4 mmol) and activated MnO_2 (6.0 g) carried out in the same manner as described for **43ad** gave **43am** (364 mg, 38%) as a light brown amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=10/1—4/1). IR (ATR): 3388, 2952, 2218, 1713, 1633, 1570, 1322, 1250, 1155, 1125, 1066, 836 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.22 (9H, s), 0.64 (2H, t, J=8.1 Hz), 1.58 (9H, s), 3.26 (2H, br s), 5.76 (2H, br s), 7.03 (1H, br s), 7.38 (1H, br s), 7.40 (1H, d, J=5.5 Hz), 7.63 (4H, s), 8.24 (1H, br s). LR-MS (ESI^+) m/z: 598 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{30}H_{35}F_3N_5O_3Si$ (M+H$^+$) 598.24612, Found 598.24563.

***tert*-Butyl [4-(4-(3-Phenylpropyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43an)** Treatments of **40a**[1,15] (790 mg, 3.5 mmol) with **41n** (1.00 g, 2.9 mmol) followed by dehydrogenation using IBX (1.22 g, 4.4 mmol) and activated MnO_2 (5.0 g) carried out in a similar manner to that described for **43ad** gave **43an** (1.19 g, 75%) as a light brown amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1—3/1). IR (ATR): 3393, 2930, 1711, 1630, 1566, 1249, 1152, 1081, 833, 697 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.25 (9H, s), 0.58—0.62 (2H, m), 1.55 (9H, s), 1.90—1.97 (2H, m), 2.55 (2H, t, J=7.3 Hz), 2.68 (2H, t, J=7.3 Hz), 3.20 (2H, t, J=8.3 Hz), 5.62 (2H, br s), 6.65 (1H, br s), 6.85 (1H, br s), 7.11—7.26 (5H, m), 7.34 (1H, d, J=5.5 Hz), 8.21 (1H, br s). LR-MS (ESI^+) m/z: 548 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{30}H_{42}N_5O_3Si$ (M+H$^+$) 548.30569, Found 548.30505.

Ethyl [4-(3-(Phenylethynyl)-1-(2-(trimethylsilylethoxy)methyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43ao) Treatments of **40a**[1,15] (530 mg, 2.3 mmol) with **41o** (762 mg, 2.34 mmol) in refluxing EtOH instead of EtOH at 50 °C followed by dehydrogenation using IBX (983 mg, 3.5 mmol) and activated MnO_2 (1.0 g) carried out in a similar manner to that described for **43ad** gave **43ao** (197 mg, 17%) as a brown amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=1/1—2/3). IR (ATR): 3369, 2951, 2209, 1725, 1637, 1572, 1519, 1472, 1424, 1240, 1091, 827, 752, 690 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.28 (9H, s), 0.56 (2H, t, J=8.1 Hz), 1.21 (3H, br s), 3.16 (2H, t, J=8.1 Hz), 4.15 (2H, br s), 5.60 (2H, br s), 6.48 (1H, d, J=2.4 Hz), 7.10—7.12 (3H, m), 7.20—7.23 (3H, m), 7.50 (1H, d, J=5.5 Hz), 8.37 (1H, d, J=5.5 Hz). LR-MS (ESI^+) m/z: 502 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{27}H_{32}N_5O_3Si$ (M+H$^+$) 502.22744, Found 502.22714.

***tert*-Butyl [4-(1-(2-(Trimethylsilyl)ethoxymethyl)-1*H*-imidazol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43ap)** The same treatments of **40a**[1,15] (262 mg, 1.2 mmol) with **41p**[22] (342 mg, 1.5 mmol) followed by dehydrogenation using IBX (487 mg, 1.7 mmol) and activated MnO_2 (6.0 g) as those described for **43ad** gave **43ap** (192 mg, 38%) as a white solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=1/1—1/2). IR (ATR): 3374, 2953, 1714, 1633, 1569, 1470, 1246, 1157, 1073, 828 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.17 (9H, s), 0.82 (2H, br s), 1.60 (9H, s), 3.57 (2H, br s), 6.21 (2H, br s), 7.28 (1H, br s), 7.40 (2H, d, J=1.2 Hz), 8.32 (1H, t, J=5.2 Hz). LR-MS (ESI^+) m/z: 431 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{20}H_{31}N_6O_3Si$ (M+H$^+$) 431.22269, Found 431.22246.

***tert*-Butyl [4-(1-Trityl-1*H*-imidazol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43aq)** Similar treatments of **40a**[1,15] (466 mg, 2.0 mmol) with **41q**[23] (667 mg, 2.0 mmol) followed by dehydrogenation using IBX (375 mg, 1.3 mmol) and activated MnO_2 (3.0 g) to those described for **43ad** gave **43aq** (74.0 mg, 15%) as a light brown powder after purification by column chromatography (NH-SiO_2, EtOAc). IR (ATR): 3386, 2931, 1719, 1628, 1567, 1447, 1249, 1153, 747, 700 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.59 (9H, s), 6.93—7.29 (19H, m), 7.36—7.38 (1H, m). LR-MS (ESI^+) m/z: 543 [M+H$^+$], 301. HR-MS (ESI^+) m/z: Calcd for $C_{33}H_{31}N_6O_2$ (M+H$^+$) 543.25085, Found 543.25078.

***tert*-Butyl [4-(4,5-Dibromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-imidazol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43ar)** Treatments of **40a**[1,15] (280 mg, 1.2 mmol) with **41r** (476 mg, 1.2 mmol) followed by dehydrogenation using IBX (521 mg, 1.9 mmol) and activated MnO_2 (5.0 g) carried out in the same manner as described for **43ad** gave **43ar** (352 mg, 48%) as a pale yellow solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=3/1). IR (ATR) 3376, 2957, 1713, 1629, 1569, 1517, 1483, 1462, 1367, 1246, 1148, 1090, 1057, 860, 832, 770, 681 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.17 (9H, s), 0.83 (2H, br s), 1.61 (9H, s), 3.62 (2H, br s), 6.38 (2H, br s), 7.43 (1H, br s), 8.33 (1H, d, J=5.5 Hz). LR-MS (ESI^+) m/z: 587 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{20}H_{29}Br_2N_6O_3Si$ (M+H$^+$) 587.04371, Found 587.04317.

***tert*-Butyl [4-(1-Trityl-1*H*-1,2,4-triazol-5-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43as)** Treatments of **40a**[1,15] (376 mg, 1.7 mmol) with **41s** (599 mg, 1.8 mmol) followed by dehydrogenation using IBX (697 mg, 2.5 mmol) and activated MnO_2 (5.2 g) carried out in a similar manner to that described for **43ad** gave **43as** (181 mg, 20%) as a white powder after purification by column chromatography (NH-SiO_2, C_6H_{14}/EtOAc=10/1). IR (ATR): 3369, 2981, 1724, 1633, 1568, 1475, 1245, 1149, 750, 699 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.54 (9H, s), 7.25—7.30 (6H, m), 7.35—7.42 (9H, m), 7.47 (1H, d, J=5.5 Hz), 8.30 (1H, d, J=5.5 Hz), 8.39 (1H, s). LR-MS (ESI^+) m/z: 544 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{32}H_{30}N_7O_2$ (M+H$^+$) 544.24610, Found 544.24644.

***tert*-Butyl [4-(3-Bromo-1-(4-methoxybenzyl)-1*H*-1,2,4-triazol-5-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43at)** The same treatments of **40a**[1,15] (1.35 g, 6.0 mmol) with **41t** (1.45 g, 4.9 mmol) followed by dehydrogenation using IBX (2.06 g, 7.4 mmol) and activated MnO_2 (15.0 g) as those described for **43ad** gave **43at** (1.87 g, 76%) as a white powder after trituration with C_6H_{14}-EtOAc (1/1). IR (ATR): 3380, 1979, 1725, 1571, 1512, 1246, 1151, 764 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.56 (9H, s), 3.71 (3H, s), 6.15 (2H, br s), 6.86 (2H, d, J=7.3 Hz), 7.30 (2H, br s), 7.58 (1H, d, J=5.2 Hz), 8.43 (1H, br s), 11.29 (2H, br s), 11.51 (1H, br s). LR-MS (ESI^+) m/z: 500 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{21}H_{23}BrN_7O_3$ (M+H$^+$) 500.10457, Found 500.10460.

***tert*-Butyl [4-(1-(4-Methoxybenzyl)-1*H*-tetrazol-5-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43au)** Similar treatments of **40a**[1,15] (623 mg, 2.8 mmol) with crude **41u** (<5 mmol) to those described for **43ad** gave the 4,5,6,7-tetrahydroderivative of **43au** (1.02 g, 87%). Subsequent dehydrogenation of the 4,5,6,7-tetrahydroderivative (800 mg, 1.9 mmol) using IBX (781 mg, 2.8 mmol) and activated MnO_2 (4.8 g) gave **43au** (588 mg, 75%) as a white powder after trituration with C_6H_{14}. IR (ATR): 3375, 2979, 1721, 1637, 1572, 1514, 1464, 1247, 1150, 770 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.56 (9H, s), 3.71 (3H, s), 6.30 (2H, br s), 6.86 (2H, d, J=7.6 Hz), 6.94 (2H, d, J=8.9 Hz), 7.30 (2H, br s), 7.64 (1H, d, J=5.2 Hz), 8.48 (1H, br s), 11.67 (2H, br s). LR-MS (ESI^+) m/z: 423 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{20}H_{23}N_8O_3$ (M+H$^+$) 423.18931, Found 423.18926.

***tert*-Butyl [4-(1-Trityl-1*H*-imidazol-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43av)** Treatments of **40a**[1,15] (290 mg, 1.3 mmol) with **41v**[24] (433 mg, 1.3 mmol) followed by dehydrogenation using IBX (538 mg, 1.9 mmol) and activated MnO_2 (3.0 g) carried out in the same manner as described for **43ad** gave crude **43av** (200 mg, 29%) as a pale yellow solid. This sample was used for the next deprotection without further purification since it was unsable.

***tert*-Butyl [4-(1-(2-(Trimethylsilyl)ethoxymethyl)-1*H*-imidazol-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate and *tert*-Butyl [4-(1-(2-(Trimethylsilyl)ethoxymethyl)-1*H*-imidazol-5-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43aw and 43aw′ or *vice versa*)** Treatments of **40a**[1,15] (500 mg, 2.2 mmol) with **41w**[22] (500 mg, 2.2 mmol) followed by dehydrogenation using IBX (930 mg, 3.3 mmol) and activated MnO_2 (5.0 g) carried out in a similar manner to that described for **43ad** gave less polar **43aw** (206 mg, 22%) and more polar **43aw′** (116 mg, 12%) both as a white powder after separation by column chromatography (NH-SiO_2, C_6H_{14}/EtOAc=1/1–AcOEt). **43aw**: ^{1}H-NMR (CD_3OD) δ: −0.21 (9H, s), 0.66—0.71 (2H, m), 1.57 (9H, s), 3.36 (2H, t, J=8.1 Hz), 5.97 (2H, br s), 7.40 (1H, d, J=5.2 Hz), 7.82 (1H, br s), 7.95 (1H, br s), 8.25 (1H, d, J=5.2 Hz). **43aw′**: ^{1}H-NMR (CD_3OD) δ: −0.01 (9H, s), 0.94 (2H, d, J=7.9 Hz), 1.61 (9H, s), 3.63 (2H, t, J=7.9 Hz), 5.47 (2H, s), 7.33 (1H, d, J=5.5 Hz), 7.94 (1H, br s), 7.97 (1H, s), 8.18 (1H, d, J=5.5 Hz). Less polar **43aw** obtained as a predominantproduct was directly subjected to the next bromination.

***tert*-Butyl [4-(1-Trityl-1*H*-1,2,3-triazol-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43ax)** A solution of **40a**[1,15] (660 mg, 2.9 mmol) and **41x** (934 mg, 2.8 mmol) in EtOH (40 ml) was stirred overnight at 50 °C. The reaction mixture was concentrated *in vacuo*, and the residue was triturated with C_6H_{14}–EtOAc to give the 4,5,6,7-tetrahydroderivative of **43ax** (1.16 g,

77%) as a light brown powder. ^{1}H-NMR (CD_3OD) δ: 1.50 (9H, s), 2.62 (2H, br s), 2.99—3.05 (1H, m), 3.10—3.16 (1H, m), 5.12 (1H, s), 7.06—7.13 (6H, m), 7.29—7.38 (9H, m), 7.52 (1H, s). To a solution of the 4,5,6,7-tetrahydroderivative (500 mg, 0.91 mmol) in DMSO (8.0 ml) was added IBX (384 mg, 1.4 mmol), and the mixture was stirred at room temperature for 1 h. The reaction was quenched by adding H_2O and an aqueous NaOH solution (1.0 mol/l, 5.0 ml, 5.0 mmol), and the mixture was extracted with EtOAc. The organic extracts were combined, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. To a solution of the residue in CH_2Cl_2 (20 ml) was added activated MnO_2 (3.0 g), and the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo*. The residue was triturated with C_6H_{14}–EtOAc (1 : 1) to give **43ax** (312 mg, 63%) as a pale yellow powder. IR (ATR): 3394, 2977, 1711, 1577, 1441, 1251, 1152, 697 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.52 (9H, s), 7.13—7.15 (6H, m), 7.39 (1H, d, J=5.5 Hz), 7.43—7.47 (9H, m), 8.13 (1H, s), 8.21 (1H, d, J=5.5 Hz), 11.61 (1H, br s), 11.76 (1H, br s). LR-MS (ESI$^+$) m/z: 544 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{32}H_{30}N_7O_2$ (M+H$^+$) 544.24610, Found 544.24644.

***tert*-Butyl [4-(5-Bromo-2-trityl-2*H*-1,2,3-triazol-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (43ay)** Treatments of **40a**[1,15] (226 mg, 1.0 mmol) with **41y** (502 mg, 1.2 mmol) followed by dehydrogenation using IBX (228 mg, 0.82 mmol) and activated MnO_2 (3.6 g) carried out in the same manner as described for **43ad** gave **43ay** (215 mg, 36%) as a pale yellow powder after triturate with C_6H_{14}–EtOAc (1/1). IR (ATR): 3387, 2979, 1720, 1571, 1249, 1150, 698 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.47 (9H, s), 7.09—7.49 (15H, m), 8.25 (1H, d, J=5.5 Hz), 8.35 (1H, d, J=5.5 Hz), 11.08 (1H, br s), 11.53 (1H, br s). LR-MS (ESI$^+$) m/z: 622 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{32}H_{29}BrN_7O_2$ (M+H$^+$) 622.15661, Found 622.15646.

4-(4,5-Dibromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridine (43ba) A solution of commercially available **40b** (565 mg, 5.1 mmol) and **41a** (1.95 g, 5.1 mmol) in 2-methoxyethanol (10 ml) was heated at reflux for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (NH-SiO_2, EtOAc/MeOH=50/1) to give the 4,5,6,7-tetrahydroderivative of **43ba** (1.93 g, 80%) as a yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 0.01 (9H, s), 0.90—0.95 (2H, m), 2.66 (2H, t, J=5.2 Hz), 3.01 (1H, dt, J=12.8, 5.2 Hz), 3.10—3.16 (1H, m), 3.59—3.63 (2H, m), 5.23 (1H, s), 5.38 (1H, d, J=11.0 Hz), 5.55 (1H, d, J=11.0 Hz), 5.92 (1H, s), 7.48 (1H, s). LR-MS (ESI$^+$) m/z: 475 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{16}H_{25}Br_2N_4OSi$ (M+H$^+$) 475.01644, Found 475.01606. To a solution of the 4,5,6,7-tetrahydroderivative (90.0 mg, 0.19 mmol) in DMSO (1.0 ml) was added IBX (79.5 mg, 0.28 mmol), and the mixture was stirred at room temperature for 2 h. The reaction was quenched by adding H_2O and an aqueous NaOH solution (1.0 mol/l, 3.0 ml, 3.0 mmol), and the mixture was extracted with EtOAc. The organic extracts were combined, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. To a solution of the residue in CH_2Cl_2 (10 ml) was added activated MnO_2 (0.50 g), and the mixture was stirred overnight at room temperature. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (NH-SiO_2, C_6H_{14}/EtOAc=1/1) to give **43ba** (45.7 mg, 51%) as an orange amorphous solid. IR (ATR): 2951, 1580, 1466, 1247, 1090, 1060, 833, 743 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.29 (9H, s), 0.54—0.58 (2H, m), 3.14—3.18 (2H, m), 5.90 (2H, br s), 7.05 (1H, br s), 7.57 (1H, br s), 8.34 (1H, br s), 8.39 (1H, d, J=5.5 Hz). LR-MS (ESI$^+$) m/z: 471 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{16}H_{21}Br_2N_4OSi$ (M+H$^+$) 470.98514, Found 470.98511.

2-Bromo-4-(4,5-dibromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridine (43ca) Treatments of **40c**[16] (415 mg, 1.6 mmol) with **41a** (667 mg, 1.7 mmol) followed by dehydrogenation using IBX (664 mg, 2.4 mmol) and activated MnO_2 (4.0 g) carried out in the same manner as described for **43ad** gave **43ca** (510 mg, 59%) an a orange solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=1/1). IR (ATR): 3156, 2949, 1588, 1465, 1389, 1309, 1239, 1061, 1041, 857, 835, 750 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.25 (9H, s), 0.58—0.62 (2H, m), 3.20 (2H, t, J=8.3 Hz), 5.84 (2H, s), 7.03 (1H, s), 7.53 (1H, d, J=5.5 Hz), 8.28 (1H, d, J=5.5 Hz). LR-MS (ESI$^+$) m/z: 549 (M+H$^+$). HR-MS (ESI$^+$) m/z: Calcd for $C_{16}H_{20}Br_3N_4OSi$ (M+H$^+$) 548.89565, Found 548.89476.

***tert*-Butyl [4-(4-Phenethyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (47a)** A suspension of **43aj** (322 mg, 0.61 mmol) and 10% Pd/C (16 mg) in EtOH (10 ml) was stirred at room temperature for 5 h under a hydrogen atmosphere. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1—3/1) to give **47a** (319 mg, 98%) as a light brown amorphous solid. IR (ATR): 3393, 2950, 1713, 1631, 1567, 1249, 1153, 1082, 859, 833 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.25 (9H, s), 0.57—0.61 (2H, m), 1.57 (9H, s), 2.82 (2H, t, J=7.6 Hz), 2.92 (2H, t, J=7.6 Hz), 3.13—3.17 (2H, m), 5.58 (2H, br s), 6.66 (1H, br s), 6.78 (1H, br s), 7.10—7.14 (1H, m), 7.22—7.25 (4H, m), 7.35 (1H, d, J=5.5 Hz), 8.21 (1H, d, J=5.5 Hz). LR-MS (ESI$^+$) m/z: 534 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{29}H_{40}N_5O_3Si$ 534.29004 (M+H$^+$), Found 534.29014.

***tert*-Butyl [4-(4-(2-(Trifluoromethyl)phenethyl)-1-(2-(trimethylsilyl)-ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (47b)** Treatments of **43ak** (387 mg, 0.65 mmol) with 10% Pd/C (39 mg) under a hydrogen atmosphere carried out in the same manner as described for **47a** gave **47b** (390 mg, 100%) as a pale yellow amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=3/1). IR (ATR): 3389, 2951, 1713, 1631, 1567, 1311, 1250, 1153, 1119, 1082, 833 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.24 (9H, s), 0.59—0.63 (2H, m), 1.57 (9H, s), 2.82 (2H, t, J=7.6 Hz), 3.10 (2H, t, J=7.6 Hz), 3.19 (2H, t, J=8.3 Hz), 5.62 (2H, br s), 6.70 (1H, br s), 6.86 (1H, s), 7.32—7.37 (2H, m), 7.45—7.53 (2H, m), 7.64 (1H, d, J=7.6 Hz), 8.22 (1H, d, J=4.9 Hz). LR-MS (ESI$^+$) m/z: 602 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{30}H_{39}F_3N_5O_3Si$ (M+H$^+$) 602.27742, Found 602.27753.

***tert*-Butyl [4-(4-(3-(Trifluoromethyl)phenethyl)-1-(2-(trimethylsilyl)-ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (47c)** Treatments of **43al** (359 mg, 0.60 mmol) with 10% Pd/C (36 mg) under a hydrogen atmosphere carried out in a similar manner to that described for **47a** gave **47c** (353 mg, 98%) as a yellow amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=3/1). IR (ATR): 3393, 2950, 1711, 1631, 1567, 1328, 1250, 1155, 1123, 1074, 825 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.26 (9H, s), 0.56—0.60 (2H, m), 1.57 (9H, s), 2.87 (2H, t, J=7.0 Hz), 3.03 (2H, t, J=7.0 Hz), 3.13—3.17 (2H, m), 5.60 (2H, br s), 6.81 (1H, br s), 7.35 (1H, d, J=5.5 Hz), 7.40—7.53 (4H, m), 8.21 (1H, m). LR-MS (ESI$^+$) m/z: 602 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{30}H_{39}F_3N_5O_3Si$ (M+H$^+$) 602.27742, Found 602.27813.

***tert*-Butyl [4-(4-(4-(Trifluoromethyl)phenethyl)-1-(2-(trimethylsilyl)-ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (47d)** The same treatments of **43am** (355 mg, 0.59 mmol) with 10% Pd/C (35 mg) under a hydrogen atmosphere as those described for **47a** gave **47d** (319 mg, 89%) as a pale yellow amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=6/1—3/1). IR (ATR): 3395, 2950, 1711, 1631, 1567, 1324, 1250, 1154, 1121, 1067, 824 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.27 (9H, s), 0.57 (2H, t, J=8.1 Hz), 1.57 (9H, s), 2.88 (2H, t, J=7.3 Hz), 3.03 (2H, t, J=7.3 Hz), 3.12 (2H, t, J=8.1 Hz), 5.57 (2H, br s), 6.69 (1H, br s), 6.77 (1H, s), 7.35 (1H, d, J=5.5 Hz), 7.41 (2H, d, J=7.9 Hz), 7.53 (2H, d, J=7.9 Hz), 8.21 (1H, d, J=5.5 Hz). LR-MS (ESI$^+$) m/z: 602 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{30}H_{39}F_3N_5O_3Si$ (M+H$^+$) 602.27742, Found 602.27685.

Ethyl [4-(3-Phenethyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (47e) Similar treatments of **43ao** (195 mg, 0.39 mmol) with 10% Pd/C (20 mg) under a hydrogen atmosphere to those described for **47a** gave crude **47e** (216 mg, 84%) as a brown amorphous solid after concentration of the filtrate *in vacuo*. This sample was directly used for the next bromination without further purification. ^{1}H-NMR (CD_3OD) δ: −0.21 (9H, s), 0.58 (2H, t, J=8.1 Hz), 1.34 (3H, t, J=7.3 Hz), 2.72 (4H, t, J=7.3 Hz), 3.14 (2H, br s), 4.30 (2H, q, J=7.3 Hz), 5.28 (2H, br s), 6.18 (1H, br s), 6.89—7.06 (6H, m), 7.45 (1H, d, J=5.5 Hz), 8.26 (1H, d, J=5.5 Hz).

***tert*-Butyl [4-(5-Bromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48a)** To a solution of **43ac** (175 mg, 0.41 mmol) in MeOH (10 ml) was added $TBABr_3$ (196 mg, 0.41 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. After adding Et_3N (0.50 ml) at 0 °C, the mixture was diluted with EtOAc, washed with brine, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, C_6H_{14}/EtOAc=3/1) to give **48a** (155 mg, 93%) as a white powder. IR (ATR): 3396, 2947, 2891, 1702, 1636, 1567, 1440, 1256, 1153, 1085, 834, 720 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.26 (9H, s), 0.57 (2H, t, J=8.1 Hz), 1.57 (9H, s), 3.14 (2H, t, J=8.1 Hz), 5.80 (2H, br s), 6.36 (1H, br s), 6.81 (1H, br s), 7.40 (1H, d, J=5.5 Hz), 8.22 (1H, s). LR-MS (ESI$^+$) m/z: 508 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{21}H_{31}BrN_5O_3Si$ (M+H$^+$) 508.13795, Found 508.13873.

***tert*-Butyl [4-(3,4,5-Tribromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48b)** Treatments of **43a** (150 mg, 0.26 mmol) with $TBABr_3$ (129 mg, 0.27 mmol) carried out in the same manner as described for **48a** gave **48b** (174 mg, *ca.* 100%) as a

pale yellow amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=1/1). IR (KBr): 3383, 2954, 1721, 1637, 1574, 1513, 1472, 1370, 1250, 1157, 1089, 861, 834, 770 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.22 (9H, s), 0.56 (2H, t, J=8.3 Hz), 1.57 (9H, s), 3.09 (2H, br s), 5.39 (2H, br s), 7.54 (1H, d, J=5.2 Hz), 8.31 (1H, br s). LR-MS (ESI$^+$) m/z: 664 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{21}H_{29}Br_3N_5O_3Si$ (M+H$^+$) 663.95898, Found 663.95572.

***tert*-Butyl [4-(4,5-Dichloro-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48c)** To a solution of **43ac** (274 mg, 0.64 mmol) in THF (7.0 ml) was added NCS (170 mg, 1.3 mmol). The mixture was stirred at room temperature for 2 d, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1—3/1) to give **48c** (59.6 mg, 19%) as a pale yellow amorphous solid. IR (ATR): 3383, 2952, 1714, 1629, 1568, 1481, 1248, 1152, 1078, 859, 832, 768 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.25 (9H, s), 0.59 (2H, t, J=8.1 Hz), 1.57 (9H, s), 3.17 (2H, t, J=8.1 Hz), 5.83 (2H, br s), 6.91 (1H, br s), 7.41 (1H, d, J=5.5 Hz), 8.22 (1H, br s). LR-MS (ESI$^+$) m/z: 498 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{21}H_{30}Cl_2N_5O_3Si$ (M+H$^+$) 498.14950, Found 498.14982.

***tert*-Butyl [4-(4-Bromo-5-chloro-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48d)** Treatments of **43ad** (218 mg, 0.42 mmol) with NCS (56.2 mg, 0.42 mmol) carried out in the same manner as described for **48c** gave **48d** (209 mg, 91%) as a light brown amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=1/1). IR (ATR): 3382, 2951, 1715, 1629, 1568, 1476, 1248, 1152, 1079, 858, 832, 768 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.25 (9H, s), 0.59 (2H, t, J=8.1 Hz), 1.57 (9H, s), 3.17 (2H, t, J=8.1 Hz), 5.84 (2H, br s), 6.95 (1H, br s), 7.41 (1H, d, J=5.5 Hz), 8.23 (1H, br s). LR-MS (ESI$^+$) m/z: 542 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{21}H_{30}BrClN_5O_3Si$ (M+H$^+$) 542.09898, Found 542.09858.

***tert*-Butyl 4-(3,4-Dibromo-5-methyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48e)** Treatments of **43ae** (100 mg, 0.19 mmol) with $TBABr_3$ (101 mg, 0.21 mmol) carried out in the same manner as described for **48a** gave **48e** (113 mg, 98%) as a colorless amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=3/1—2/1). IR (ATR): 3376, 2952, 1718, 1634, 1568, 1248, 1151, 1077, 859, 830 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.24 (9H, s), 0.53 (2H, t, J=8.3 Hz), 1.57 (9H, s), 2.40 (3H, s), 2.99 (2H, br s), 5.29 (2H, br s), 7.52 (1H, d, J=5.5 Hz), 8.31 (1H, br s). LR-MS (ESI$^+$) m/z: 600 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{22}H_{32}Br_2N_5O_3Si$ (M+H$^+$) 600.06412, Found 600.06419.

***tert*-Butyl [4-(5-Bromo-4-methyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48f)** Treatments of **43ag** (221 mg, 0.50 mmol) with $TBABr_3$ (265 mg, 0.55 mmol) carried out in a similar manner to that described for **48a** gave **48f** (211 mg, 81%) as a pale yellow amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=5/1—4/1). IR (ATR): 3392, 2951, 1714, 1630, 1567, 1248, 1153, 1087, 859, 833, 766 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.26 (9H, s), 0.56 (2H, t, J=8.3 Hz), 1.57 (9H, s), 2.11 (3H, s), 3.12 (2H, t, J=8.3 Hz), 5.74 (2H, br s), 6.73 (1H, br s), 7.38 (1H, d, J=5.5 Hz), 8.22 (1H, br s). LR-MS (ESI$^+$) m/z: 522 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{22}H_{33}BrN_5O_3Si$ (M+H$^+$) 522.15360, Found 522.15388.

***tert*-Butyl 4-(3,5-Dibromo-4-methyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48g)** The same treatments of **48f** (100 mg, 0.19 mmol) with $TBABr_3$ (101 mg, 0.21 mmol) as those described for **48a** gave **48g** (108 mg, 94%) as a colorless amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=3/1). IR (ATR): 3378, 2951, 1718, 1634, 1569, 1248, 1152, 1068, 858, 830 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.24 (9H, s), 0.54 (2H, t, J=8.3 Hz), 1.57 (9H, s), 2.11 (3H, br s), 3.05 (2H, br s), 5.37 (2H, br s), 7.51 (1H, d, J=5.5 Hz), 8.31 (1H, br s). LR-MS (ESI$^+$) m/z: 600 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{22}H_{32}Br_2N_5O_3Si$ (M+H$^+$) 600.06412, Found 600.06447.

***tert*-Butyl [4-(5-Bromo-4-phenyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48h)** Similar treatments of **43ah** (151 mg, 0.30 mmol) with $TBABr_3$ (151 mg, 0.31 mmol) to those described for **48a** gave **48h** (167 mg, 96%) as a white powder after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1). mp: 157—159 °C (from C_6H_{14}–EtOAc). IR (KBr): 3404, 2964, 1705, 1637, 1561, 1474, 1269, 1253, 1155, 1087, 859, 835, 755, 697 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.24 (9H, s), 0.61 (2H, t, J=7.9 Hz), 1.57 (9H, s), 3.20 (2H, t, J=7.9 Hz), 5.89 (2H, br s), 7.07 (1H, br s), 7.27 (1H, t, J=7.3 Hz), 7.39 (2H, t, J=7.3 Hz), 7.43 (1H, d, J=5.5 Hz), 7.64—7.67 (2H, m), 8.26 (1H, br s). LR-MS (ESI$^+$) m/z: 584 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{27}H_{35}BrN_5O_3Si$ (M+H$^+$) 584.16925, Found 584.16867.

***tert*-Butyl [4-(4-Benzyl-5-bromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48i)** Treatments of **43ai** (440 mg, 0.85 mmol) with $TBABr_3$ (408 mg, 0.85 mmol) carried out in the same manner as described for **48a** gave **48i** (444 mg, 88%) as a white solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1—2/1). IR (ATR): 3384, 2951, 1710, 1631, 1566, 1250, 1153, 1072, 826, 710 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.25 (9H, s), 0.55—0.59 (2H, m), 1.56 (9H, s), 3.15 (2H, t, J=7.6 Hz), 3.85 (2H, br s), 5.78 (2H, br s), 6.71 (1H, br s), 7.12—7.25 (5H, m), 7.37 (1H, d, J=5.5 Hz), 8.20 (1H, br s). LR-MS (ESI$^+$) m/z: 598 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{28}H_{37}BrN_5O_3Si$ (M+H$^+$) 598.18490, Found 598.18466.

***tert*-Butyl [4-(4-Benzyl-3,5-dibromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48j)** Treatments of **48i** (200 mg, 0.33 mmol) with $TBABr_3$ (182 mg, 0.38 mmol) carried out in a similar manner to that described for **48a** gave **48j** (211 mg, 93%) as a white solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=2/1). IR (ATR): 3372, 2950, 1710, 1635, 1569, 1250, 1147, 1060, 834 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.22 (9H, br s), 0.55 (2H, t, J=8.3 Hz), 1.56 (9H, s), 3.08 (2H, br s), 3.92 (2H, br s), 5.40 (2H, br s), 7.15 (1H, t, J=7.3 Hz), 7.23 (2H, t, J=7.3 Hz), 7.30 (2H, d, J=7.3 Hz), 7.51 (1H, d, J=5.5 Hz), 8.30 (1H, br s). LR-MS (ESI$^+$) m/z: 676 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{28}H_{36}Br_2N_5O_3Si$ (M+H$^+$) 676.09542, Found 676.09520.

***tert*-Butyl [4-(5-Bromo-4-phenethyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48k)** The same treatments of **47a** (299 mg, 0.56 mmol) with $TBABr_3$ (284 mg, 0.59 mmol) as those described for **48a** gave **48k** (290 mg, 91%) as a pale yellow amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=5/1—4/1). IR (ATR): 3391, 2949, 1713, 1630, 1567, 1248, 1153, 1087, 859, 833, 697 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.26 (9H, s), 0.54—0.58 (2H, m), 1.57 (9H, s), 2.79 (2H, br s), 2.90 (2H, t, J=7.6 Hz), 3.09—3.13 (2H, m), 5.76 (2H, br s), 6.66 (1H, br s), 7.11—7.15 (1H, m), 7.20—7.26 (4H, m), 7.39 (1H, d, J=5.5 Hz), 8.17 (1H, d, J=5.5 Hz). LR-MS (ESI$^+$) m/z: 612 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{29}H_{39}BrN_5O_3Si$ (M+H$^+$) 612.20055, Found 612.20057.

***tert*-Butyl [4-(3,5-Dibromo-4-phenethyl-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48l)** Similar treatments of **48k** (100 mg, 0.16 mmol) with $TBABr_3$ (86.3 mg, 0.18 mmol) to those described for **48a** gave **48l** (111 mg, 98%) as a colorless amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1—3/1). IR (ATR): 3378, 2950, 1718, 1634, 1571, 1249, 1152, 1075, 831, 697 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.23 (9H, s), 0.54 (2H, t, J=8.3 Hz), 1.57 (9H, s), 2.84 (4H, br s), 3.03 (2H, br s), 5.36 (2H, br s), 7.14—7.18 (1H, m), 7.21—7.28 (4H, m), 7.52 (1H, d, J=5.5 Hz), 8.32 (1H, br s). LR-MS (ESI$^+$) m/z: 690 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{29}H_{38}Br_2N_5O_3Si$ (M+H$^+$) 690.11107, Found 690.11073.

***tert*-Butyl [4-(3,5-Dibromo-4-(2-(trifluoromethyl)phenethyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48m)** Treatments of **47b** (380 mg, 0.63 mmol) with $TBABr_3$ (641 mg, 1.3 mmol) carried out in the same manner as described for **48a** gave **48m** (447 mg, 93%) as a pale yellow amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1—3/1). IR (ATR): 3376, 2952, 1718, 1571, 1311, 1249, 1151, 1121, 831 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.23 (9H, s), 0.55 (2H, t, J=8.1 Hz), 1.57 (9H, s), 2.85 (2H, br s), 3.06 (4H, br s), 5.37 (2H, br s), 7.34—7.42 (2H, m), 7.52—7.55 (2H, m), 7.65 (2H, d, J=7.6 Hz), 8.33 (1H, br s). LR-MS (ESI$^+$) m/z: 758 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{30}H_{37}Br_2F_3N_5O_3Si$ (M+H$^+$) 758.09845, Found 758.09866.

***tert*-Butyl [4-(3,5-Dibromo-4-(3-(trifluoromethyl)phenethyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48n)** Treatments of **47c** (345 mg, 0.57 mmol) with $TBABr_3$ (579 mg, 1.2 mmol) carried out in a similar manner to that described for **48a** gave **48n** (339 mg, 78%) as a pale yellow amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1—3/1). IR (ATR): 3379, 2952, 1718, 1571, 1329, 1250, 1154, 1124, 1072, 832 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.24 (9H, s), 0.53 (2H, t, J=8.3 Hz), 1.57 (9H, s), 2.87 (2H, br s), 3.01 (4H, br s), 5.36 (2H, br s), 7.44—7.53 (5H, m), 8.32 (1H, br s). LR-MS (ESI$^+$) m/z: 758 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{30}H_{37}Br_2F_3N_5O_3Si$ (M+H$^+$) 758.09845, Found 758.09875.

***tert*-Butyl [4-(3,5-Dibromo-4-(4-(trifluoromethyl)phenethyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48o)** The same treatments of **47d** (259 mg, 0.43 mmol) with $TBABr_3$ (435 mg, 0.90 mmol) as those described for **48a** gave **48o** (256 mg, 78%) as a pale yellow amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1). IR (ATR): 3390, 2926,

1714, 1569, 1325, 1249, 1153, 1118, 1103, 1065, 829 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.24 (9H, s), 0.53 (2H, t, J=7.9 Hz), 1.57 (9H, s), 2.89 (2H, br s), 3.00 (4H, br s), 5.33 (2H, br s), 7.40 (2H, d, J=7.9 Hz), 7.53 (1H, d, J=5.5 Hz), 7.56 (2H, d, J=7.9 Hz), 8.32 (1H, br s). LR-MS (ESI$^+$) m/z: 758 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{30}H_{37}Br_2F_3N_5O_3Si$ (M+H$^+$) 758.09845, Found 758.09818.

***tert*-Butyl [4-(5-Bromo-4-(3-phenylpropyl)-1-(2-(trimethylsilyl)-ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48p)** Similar treatments of **43an** (1.15 g, 2.1 mmol) with $TBABr_3$ (1.01 g, 2.1 mmol) to those described for **48a** gave **48p** (1.18 g, 90%) as a pale yellow amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=5/1—2/1). IR (ATR): 3375, 2920, 1705, 1636, 1569, 1248, 1157, 827 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.26 (9H, s), 0.57 (2H, t, J=8.1 Hz), 1.55 (9H, s), 1.89—1.96 (2H, m), 2.54 (2H, t, J=7.0 Hz), 2.67 (2H, t, J=7.6 Hz), 3.14 (2H, t, J=8.1 Hz), 5.76 (2H, br s), 6.77 (1H, br s), 7.11—7.25 (5H, m), 7.38 (1H, d, J=5.5 Hz), 8.22 (1H, br s). LR-MS (ESI$^+$) m/z: 626 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{30}H_{41}BrN_5O_3Si$ (M+H$^+$) 626.21620, Found 626.21553.

***tert*-Butyl [4-(3,5-Dibromo-4-(3-phenylpropyl)-1-(2-(trimethylsilyl)-ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48q)** Treatments of **48p** (231 mg, 0.37 mmol) with $TBABr_3$ (196 mg, 0.41 mmol) carried out in the same manner as described for **48a** gave **48q** (239 mg, 92%) as a pale yellow amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=2/1). IR (ATR): 3378, 2947, 1717, 1634, 1570, 1250, 1153, 832 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.24 (9H, s), 0.54 (2H, t, J=8.3 Hz), 1.56 (9H, s), 1.92 (2H, br s), 2.60 (2H, br s), 2.69 (2H, t, J=7.9 Hz), 3.08 (2H, br s), 5.37 (2H, br s), 7.12—7.27 (5H, m), 7.51 (1H, d, J=5.5 Hz), 8.29 (1H, br s). LR-MS (ESI$^+$) m/z: 704 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{30}H_{40}Br_2N_5O_3Si$ (M+H$^+$) 704.12672, Found 704.12752.

***tert*-Butyl [4-(4,5-Dibromo-3-phenethyl-1-(2-(trimethylsilyl)-ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48r)** Treatments of crude **47e** with $TBABr_3$ (413 mg, 0.39 mmol) carried out in a similar manner to that described for **48a** gave **48r** (216 mg, 84% from **43ao**) as a light brown amorphous solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=5/1—3/1). IR (ATR): 3383, 2950, 1725, 1631, 1572, 1520, 1474, 1454, 1425, 1237, 1090, 1073, 831, 768, 697 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.22 (9H, s), 0.55 (2H, br s), 1.35 (3H, t, J=7.0 Hz), 2.62 (2H, t, J=7.6 Hz), 2.81 (2H, t, J=7.6 Hz), 3.06 (2H, br s), 4.31 (2H, q, J=7.0 Hz), 5.35 (2H, br s), 6.77 (2H, d, J=7.0 Hz), 6.90—6.99 (3H, m), 7.49 (1H, d, J=5.5 Hz), 8.27 (1H, d, J=5.5 Hz). LR-MS (ESI$^+$) m/z: 662 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{27}H_{34}Br_2N_5O_3Si$ (M+H$^+$) 662.07977, Found 662.08011.

***tert*-Butyl [4-(5-Chloro-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-imidazol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (48s)** The same treatments of **43ap** (431 mg, 1.0 mmol) with NCS (147 mg, 1.1 mmol) in CCl_4 (10 ml) as those described for **48c** gave **48s** (152 mg, 33%) as a white powder after trituration with CH_2Cl_2. IR (ATR): 3378, 2899, 1716, 1570, 1464, 1246, 1154, 1077, 923, 830, 677 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: −0.21 (9H, s), 0.78 (2H, t, J=7.9 Hz), 1.53 (9H, s), 3.55 (2H, t, J=7.9 Hz), 6.32 (2H, s), 7.43 (1H, s), 7.47 (1H, d, J=5.5 Hz), 8.30 (1H, d, J=5.5 Hz), 11.55 (1H, br s), 11.79 (1H, br s). LR-MS (ESI$^+$) m/z: 465 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{20}H_{30}ClN_6O_3Si$ (M+H$^+$) 465.18372, Found 465.18429.

***tert*-Butyl [4-(4,5-Dibromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-(methyl)carbamate (44a) and *tert*-Butyl [4-(4,5-Dibromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1-methyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-(methyl)carbamate (44b)** To a solution of **43a** (260 mg, 0.44 mmol) in DMF (3.0 ml) was added NaH (60% in oil, 19.5 mg, 0.49 mmol), and the reaction mixture was stirred at room temperature for 1 h. To the mixture was added MeI (0.033 ml, 0.53 mmol) at 0 °C, and the whole was stirred at the same temperature for 1 h. The reaction was quenched by adding H_2O at 0 °C, and the mixture was extracted with EtOAc. The organic extracts were combined, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. Purification of the residue by column chromatography (NH-SiO_2, C_6H_{14}/EtOAc=10/1—3/1) to give **44a** (94.7 mg, 36%) as a colorless amorphous solid and **44b** (73.1 mg, 27%) as a colorless oil. **44a**; IR (ATR): 3376, 2952, 1706, 1538, 1424, 1339, 1143, 1090, 834 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.25 (9H, s), 0.59 (2H, t, J=8.1 Hz), 1.69 (9H, s), 3.17 (2H, t, J=8.1 Hz), 3.57 (3H, s), 5.92 (2H, s), 7.07 (1H, s), 7.40 (1H, d, J=5.2 Hz), 8.23 (1H, d, J=5.2 Hz). LR-MS (ESI$^+$) m/z: 600 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{22}H_{32}Br_2N_5O_3Si$ (M+H$^+$) 600.06412, Found 600.06323. **44b**; IR (ATR): 2951, 1720, 1579, 1525, 1461, 1330, 1248, 1148, 1091, 834 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.25 (9H, s), 0.61 (2H, t, J=8.1 Hz), 1.47 (9H, s), 3.23 (2H, t, J=8.1 Hz), 3.35 (3H, s), 3.71 (3H, s), 5.96 (2H, s), 7.11 (1H, s), 7.50 (1H, d, J=5.8 Hz), 8.39 (1H, d, J=5.8 Hz). LR-MS (ESI$^+$) m/z: 614 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{23}H_{34}Br_2N_5O_3Si$ (M+H$^+$) 614.07977, Found 614.07726.

4-(4,5-Dibromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (45) To a solution of **43a** (392 mg, 0.67 mmol) in MeOH (5.0 ml) was added 20% HCl–EtOH (10 ml), and the reaction mixture was stirred overnight at room temperature. The whole was concentrated *in vacuo*, and aqueous 10% Na_2CO_3 solution (10 ml) was added to the residue. The mixture was stirred at room temperature for 1 h. Precipitates were collected by filtration, dried, and purified by column chromatography (NH-SiO_2, EtOAc/MeOH=10/1) to afford **45** (172 mg, 53%) as a pale yellow powder. IR (ATR): 2950, 1640, 1552, 1435, 1248, 1066, 832 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.25 (9H, s), 0.54—0.58 (2H, m), 3.07—3.11 (2H, m), 5.69 (2H, s), 6.70 (1H, s), 7.20 (1H, d, J=5.5 Hz), 8.14 (1H, d, J=5.5 Hz). LR-MS (ESI$^+$) m/z: 486 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{16}H_{22}Br_2N_5OSi$ (M+H$^+$) 485.99604, Found 485.99600.

4-(4,5-Dibromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-1-methyl-1*H*-imidazo[4,5-*c*]pyridin-2-amine (46) Treatments of **45** (260 mg, 0.44 mmol) with NaH (60% in oil, 14.2 mg, 0.36 mmol) and MeI (0.022 ml, 0.36 mmol) carried out in the same manner as described in **44a** gave **46** (80.7 mg, 50%) as a colorless amorphous solid after purification by column chromatography (NH-SiO_2, C_6H_{14}/EtOAc=1/1—1/3). IR (ATR): 3440, 2951, 1657, 1543, 1464, 1245, 1092, 1070, 859, 833, 798 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.23 (9H, s), 0.64—0.68 (2H, m), 3.20—3.25 (2H, m), 3.59 (3H, s), 5.98 (2H, s), 6.06 (2H, br s), 6.99 (1H, d, J=5.5 Hz), 7.03 (1H, s), 8.26 (1H, d, J=5.5 Hz). LR-MS (ESI$^+$) m/z: 500 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{17}H_{24}Br_2N_5OSi$ (M+H$^+$) 500.01169, Found 500.01106.

4-(4,5-Dibromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrrol-2-yl)-*N*,*N*-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-2-amine (49) A mixture of **43ca** (220 mg, 0.40 mmol) and dimethylamine (2 mol/l in MeOH, 10 ml, 20 mmol) was heated at 100 °C in a sealed tube for 10 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (NH-SiO_2, C_6H_{14}/EtOAc=1/1) to afford **49** (201 mg, 53%) as a pale yellow amorphous solid. IR (ATR): 3268, 2949, 1626, 1603, 1572, 1434, 1409, 1248, 1062, 915, 833, 755 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: −0.23 (9H, s), 0.55—0.59 (2H, m), 3.11—3.15 (2H, m), 3.18 (6H, s), 5.66 (2H, s), 6.75 (1H, s), 7.22 (1H, d, J=5.5 Hz), 8.11 (1H, d, J=5.5 Hz). LR-MS (ESI$^+$) m/z: 514 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{18}H_{26}Br_2N_5OSi$ (M+H$^+$) 514.02734, Found 514.02695.

***tert*-Butyl 2-(di(*tert*-butoxycarbonyl)amino)-4-(5-chloro-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-imidazol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-1-carboxylate (50)** To a solution of **48s** (135 mg, 0.29 mmol) in MeCN (3.0 ml) were added Boc_2O (316 mg, 1.5 mmol) and DMAP (10 mg). The mixture was stirred overnight at room temperature and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, C_6H_{14}/EtOAc=3/1—3/2) to afford **50** (180 mg, 93%) as a light brown amorphous solid. IR (ATR): 2980, 1756, 1369, 1338, 1247, 1144, 1118, 1099, 836 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.14 (9H, s), 0.72 (2H, t, J=8.1 Hz), 1.41 (18H, s), 1.69 (9H, s), 3.39 (2H, t, J=8.1 Hz), 5.95 (2H, s), 7.28 (1H, s), 7.94 (1H, d, J=5.5 Hz), 8.61 (1H, d, J=5.5 Hz). LR-MS (ESI$^+$) m/z: 665 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{30}H_{46}ClN_6O_7Si$ (M+H$^+$) 665.28858, Found 665.28773.

***tert*-Butyl 4-(4-Bromo-5-chloro-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-imidazol-2-yl)-2-(di(*tert*-butoxycarbonyl)amino)-1*H*-imidazo[4,5-*c*]pyridin-1-carboxylate (51)** To a solution of **50** (190 mg, 0.29 mmol) in MeCN (3.0 ml) was added NBS (76.4 mg, 0.43 mmol). The mixture was stirred at room temperature for 3 d and then concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, C_6H_{14}/EtOAc=4/1—3/1) to afford **51** (153 mg, 72%) as a colorless oil. IR (ATR): 2980, 1760, 1369, 1336, 1240, 1142, 1117, 1098, 834 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.15 (9H, s), 0.64—0.68 (2H, m), 1.42 (18H, s), 1.69 (9H, s), 3.24—3.29 (2H, m), 5.75 (2H, s), 7.97 (1H, d, J=5.5 Hz), 8.68 (1H, d, J=5.5 Hz). LR-MS (ESI$^+$) m/z: 743 [M+H$^+$]. HR-MS (ESI$^+$) m/z: Calcd for $C_{30}H_{45}BrClN_6O_7Si$ (M+H$^+$) 743.19909, Found 743.19920.

***tert*-Butyl [4-(2,5-Dibromo-1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-imidazol-4- or 5-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]carbamate (53)** To a solution of **43aw** (90 mg, 0.21 mmol) in $CHCl_3$ (3.0 ml) was added NBS (112 mg, 0.63 mmol), and the mixture was stirred overnight at room temperature. The whole was directly purified by column chromatography (SiO_2, C_6H_{14}/EtOAc=1/1) to afford **53** (100 mg, 81%) as a white powder. This sample was directly subjected to the next deprotection. ^{1}H-NMR (CD_3OD) δ: −0.22 (9H, s), 0.58 (2H, d, J=8.3 Hz), 1.57 (9H, s), 3.11—3.16 (2H, m), 5.44 (2H, s), 7.57 (1H, d, J=5.5Hz), 8.34 (1H, d, J=5.5 Hz).

4-(5-Bromo-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (3) ⟨Method C⟩ To a solution of **48a** (100 mg, 0.20 mmol) in CH_2Cl_2 (5.0 ml) was added BF_3-OEt_2 (0.25 ml, 2.0 mmol) under an argon atmosphere, and the mixture was stirred at room temperature for 18 h. The reaction was quenched by adding aqueous 10% Na_2CO_3 solution, and the reaction mixture was extracted with EtOAc. The combined extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. The residue was dissolved in MeOH, and the methanolic solution was filtered through a pad of NH-SiO_2 (washed with MeOH); the filtrate was then concentrated *in vacuo*. The residue was dissolved in MeOH (2.0 ml), and TFA (0.10 ml) was added to the MeOH solution. The acidic methanolic solution was concentrated *in vacuo*. Trituration of the residue with CH_2Cl_2 gave **3**-2TFA (85.4 mg, 86%) as a yellow powder. mp: 115 °C (decomp., from MeOH–CH_2Cl_2). ^{1}H-NMR (CD_3OD) δ: 6.42 (1H, d, J=4.0 Hz), 7.11 (1H, d, J=4.0 Hz), 7.38 (1H, d, J=6.4 Hz), 8.00 (1H, d, J=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 104.9, 106.4, 114.2, 114.4, 125.2, 129.7, 132.3, 136.6, 146.8, 160.7. LR-MS (ESI^+) m/z: 278 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{10}H_9BrN_5$ (M+H$^+$) 278.00413, Found 278.00488.

4-(4-Bromo-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (2) Treatments of **43ad** (145 mg, 0.29 mmol) with BF_3-OEt_2 (0.358 ml, 2.9 mmol) and TFA (0.10 ml) carried out in the same manner as described for **3** gave **2**-2TFA (118 mg, 82%) as a pale yellow amorphous solid. IR (KBr): 3343, 3190, 1671, 1639, 1438, 1205, 1146, 725 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.15 (1H, d, J=1.5 Hz), 7.24 (1H, d, J=1.5 Hz), 7.39 (1H, d, J=6.4 Hz), 8.00 (1H, d, J=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 99.6, 104.9, 113.8, 124.5, 125.1, 129.8, 132.3, 137.0, 146.6, 160.6. LR-MS (ESI^+) m/z: 278 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{10}H_9BrN_5$ 278.00413 (M+H$^+$), Found 278.00450.

4-(4,5-Dibromo-1*H*-pyrrol-2-yl)-*N*-methyl-1*H*-imidazo[4,5-*c*]pyridin-2-amine (5) Treatments of **44a** (70.0 mg, 0.12 mmol) with BF_3–OEt_2 (0.146 ml, 1.2 mmol) and TFA (0.10 ml) carried out in a similar manner to that described for **3** gave **5**-2TFA (63.7 mg, 92%) as a yellow amorphous solid. IR (KBr): 3406, 1654, 1431, 1203, 1140 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 3.13 (3H, s), 7.17 (1H, s), 7.40 (1H, d, J=6.4 Hz), 8.04 (1H, d, J=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 29.6, 102.3, 104.7, 107.4, 114.7, 117.4, 125.4, 127.5, 132.3, 146.6, 160.7. LR-MS (ESI^+) m/z: 370 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{11}H_{10}Br_2N_5$ (M+H$^+$) 369.93030, Found 369.99450.

4-(4,5-Dibromo-1*H*-pyrrol-2-yl)-1-methyl-1*H*-imidazo[4,5-*c*]pyridin-2-amine (6) The same treatments of **46** (72.0 mg, 0.14 mmol) with BF_3–OEt_2 (0.181 ml, 1.4 mmol) and TFA (0.10 ml) as those described for **3** gave **6**-2TFA (71.2 mg, 83%) as a yellow powder after trituration with CH_2Cl_2. mp: 160 °C (decomp. from CH_2Cl_2). IR (ATR): 3131, 2892, 1655, 1426, 1177, 1124, 831, 791, 721 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 3.73 (3H, s), 7.19 (1H, s), 7.51 (1H, d, J=6.4 Hz), 8.08 (1H, d, J=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 30.1, 102.4, 103.8, 107.8, 115.1, 125.7, 128.6, 132.3, 136.5, 146.7, 160.8. LR-MS (ESI^+) m/z: 370 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{11}H_{10}Br_2N_5$ (M+H$^+$) 369.93030, Found 369.93090.

4-(4,5-Dibromo-1*H*-pyrrol-2-yl)-*N*,1-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-2-amine (7) Similar treatments of **44b** (60.0 mg, 0.0975 mmol) with BF_3-OEt_2 (0.122 ml, 0.98 mmol) and TFA (0.10 ml) to those described for **3** gave **7**-2TFA (57.8 mg, 97%) as a yellow amorphous solid. IR (KBr): 3448, 3284, 1697, 1686, 1649, 1625, 1426, 1204, 1138 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 3.20 (3H, s), 3.69 (1H, s), 7.21 (1H, s), 7.50 (1H, d, J=6.4 Hz), 8.08 (1H, d, J=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 29.9, 30.0, 102.2, 103.2, 107.4, 115.0, 125.4, 127.5, 132.0, 136.2, 146.7, 160.2. LR-MS (ESI^+) m/z: 384 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{12}H_{12}Br_2N_5$ (M+H$^+$) 383.94595, Found 383.94957.

4-(4,5-Dibromo-1*H*-pyrrol-2-yl)-N,N-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-2-amine (8) Treatments of **49** (192 mg, 0.37 mmol) with BF_3–OEt_2 (0.468 ml, 3.7 mmol) and TFA (0.10 ml) carried out in the same manner as described for **3** gave **8**-2TFA (172 mg, 75%) as a yellow powder after trituration with CH_2Cl_2. mp: 140 °C (decomp., from CH_2Cl_2). IR (ATR): 3117, 1784, 1633, 1198, 1134, 791, 691 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 3.30 (6H, s), 7.18 (1H, s), 7.40 (1H, d, J=6.4 Hz), 8.04 (1H, d, J=6.4 Hz). ^{13}H-NMR (CD_3OD) δ: 38.6, 102.4, 104.8, 107.6, 115.2, 125.5, 127.9, 132.2, 137.5, 147.3, 160.9. LR-MS (ESI^+) m/z: 384 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{12}H_{12}Br_2N_5$ (M+H$^+$) 383.94595, Found 383.94591. *Anal.* Calcd for $C_{12}H_{11}Br_2N_5$–$2C_2HF_3O_2$: C, 31.34; H, 2.14; N, 11.42. Found: C, 31.11; H, 2.05; N, 11.58.

4-(4,5-Dibromo-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridine (9) Treatments of **43ba** (84.4 mg, 0.179 mmol) with BF_3-OEt_2 (0.225 ml, 1.8 mmol) and TFA (0.10 ml) carried out in a similar manner to that described for **3** gave **9**-2TFA (67.9 mg, 67%) as a pale yellow powder after trituration with CH_2Cl_2. mp: 200 °C (decomp. from CH_2Cl_2). IR (ATR): 2785, 1671, 1612, 1411, 1177, 1116, 824, 806, 723 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.45 (1H, s), 7.80 (1H, d, J=6.4 Hz), 8.29 (1H, d, J=6.4 Hz), 8.68 (1H, s). ^{13}C-NMR (CD_3OD) δ: 103.1, 108.3, 110.5, 118.0, 125.7, 135.0, 136.0, 136.8, 144.1, 148.5. LR-MS (ESI^+) m/z: 341 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{10}H_7Br_2N_4$ (M+H$^+$) 340.90375, Found 340.90286.

4-(4,5-Dichloro-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (10) The same treatments of **48c** (83.0 mg, 0.17 mmol) with BF_3–OEt_2 (0.210 ml, 1.7 mmol) and TFA (0.10 ml) as those described for **3** gave **10**-2TFA (75.3 mg, 91%) as a pale yellow powder after trituration with CH_2Cl_2–MeOH. mp 150 °C (decomp., from MeOH–CH_2Cl_2). IR (KBr): 3455, 1686, 1648, 1212, 1126, 1035, 724 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.14 (1H, s), 7.43 (1H, d, J=6.4 Hz), 8.06 (1H, d, J=6.4 Hz). ^{13}C-NMR (DMSO-d_6) δ: 104.7, 110.0, 113.3, 115.1, 116.0, 118.0, 120.9, 121.7, 126.8, 158.7. LR-MS (ESI^+) 268 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{10}H_8Cl_2N_5$ (M+H$^+$) 268.01568, Found 268.01564.

4-(4-Bromo-5-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (11) Similar treatments of **48d** (170 mg, 0.31 mmol) with BF_3–OEt_2 (0.393 ml, 3.1 mmol) and TFA (0.10 ml) to those described for **3** gave **11**-2TFA (39.2 mg, 23%) as a pale yellow powder after trituration with CH_2Cl_2–MeOH. mp: 130 °C (decomp., from MeOH–CH_2Cl_2). IR (KBr): 3147, 2923, 1719, 1664, 1474, 1438, 1202, 1135, 794, 724 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.16 (1H, s), 7.42 (1H, d, J=6.4 Hz), 8.06 (1H, d, J=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 98.3, 105.3, 114.8, 121.0, 123.5, 128.6, 133.0, 136.6, 146.9, 160.7. LR-MS (ESI^+) m/z: 312 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{10}H_8BrClN_5$ (M+H$^+$) 311.96516, Found 311.96500.

4-(4-Bromo-5-methyl-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (12) Treatments of **43ae** (140 mg, 0.27 mmol) with BF_3–OEt_2 (0.34 ml, 2.7 mmol) and TFA (0.10 ml) carried out in the same manner as described for **3** gave **12**-2TFA (88.9 mg, 64%) as a pale yellow amorphous solid after trituration with CH_2Cl_2–MeOH. IR (ATR): 3149, 1707, 1655, 1431, 1185, 1135, 796, 721 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.36 (3H, s), 7.09 (1H, s), 7.34 (1H, d, J=6.7 Hz), 7.96 (1H, d, J=6.7 Hz). ^{13}C-NMR (CD_3OD) δ: 11.9, 99.3, 104.6, 114.6, 122.2, 130.0, 132.2, 134.1, 135.9, 146.3, 160.2. LR-MS (ESI^+) m/z: 292 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{11}H_{11}BrN_5$ (M+H$^+$) 292.01978, Found 292.02030.

4-(4-Bromo-5-phenyl-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (14) Treatments of **43af** (226 mg, 0.39 mmol) with BF_3–OEt_2 (0.49 ml, 3.9 mmol) and TFA (0.10 ml) carried out in a similar manner to that described for **3** gave **14**-2TFA (146 mg, 65%) as a yellow powder after trituration with CH_2Cl_2–MeOH. mp: 130 °C (decomp., from MeOH–CH_2Cl_2). IR (KBr): 3104, 1711, 1654, 1474, 1194, 1137, 722 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.28 (1H, s), 7.39 (1H, d, J=6.4 Hz), 7.42 (1H, tt, J=7.3, 1.2 Hz), 7.50 (2H, t, J=7.3 Hz), 7.81—7.84 (2H, m), 8.03 (1H, d, J=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 98.2, 104.8, 116.5, 124.2, 127.8, 129.0, 129.4, 129.9, 131.5, 132.3, 134.7, 137.1, 146.4, 160.6. LR-MS (ESI^+) m/z: 354 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{16}H_{13}BrN_5$ (M+H$^+$) 354.03543, Found 354.03625. *Anal.* Calcd for $C_{16}H_{12}BrN_5$–$2C_2HF_3O_2$, C, 41.26%, H, 2.42%, N, 12.03%, Found: C, 41.16%, H, 2.42%, N, 12.30%.

4-(5-Bromo-4-phenyl-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (17) Treatments of **48h** (167 mg, 0.29 mmol) with BF_3–OEt_2 (0.36 ml, 2.9 mmol) and TFA (0.10 ml) carried out in the same manner as described for **3** gave **17**-2TFA (134 mg, 75%) as a yellow powder after trituration with CH_2Cl_2–MeOH. mp: 220 °C (decomp. from MeOH–CH_2Cl_2). IR (KBr): 3067, 1713, 1668, 1457, 1202, 1142, 996 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.32 (1H, tt, J=7.3, 1.2 Hz), 7.35 (1H, s), 7.41 (1H, d, J=6.4 Hz), 7.43 (2H, t, J=7.3 Hz), 7.63—7.66 (2H, m), 8.04 (1H, d, J=6.4 Hz). ^{13}C-NMR (DMSO-d_6) δ: 102.6, 104.7, 113.1, 114.6, 117.5, 124.3, 124.7, 126.8, 127.1, 127.4, 128.6, 133.1, 133.4, 158.9. LR-MS (ESI^+) m/z: 354 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{16}H_{13}BrN_5$ (M+H$^+$) 354.03543, Found 354.03540. *Anal.* Calcd for $C_{16}H_{13}BrN_5$–$2C_2HF_3O_2$–H_2O, C, 40.02%, H, 2.69%, N, 11.67%, Found: C, 40.13%, H, 2.59%, N, 11.74%.

4-(3,4,5-Tribromo-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (27) Treatments of **48b** (144 mg, 0.22 mmol) with BF_3–OEt_2 (0.271 ml, 2.2 mmol) and TFA (0.10 ml) carried out in a similar manner to that described for **3** gave **27**-TFA (86.1 mg, 72%) as a pale yellow powder after trituration with CH_2Cl_2. mp: 185 °C (decomp. from CH_2Cl_2). IR (KBr): 3333, 3179, 1681, 1661, 1636, 1433, 1205, 1184, 1115, 720 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.53 (1H, d, J=6.4 Hz), 8.24 (1H, d, J=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 103.0, 104.3, 106.7, 108.5, 116.8, 119.7, 122.4, 126.4, 135.4, 162.3. LR-MS (ESI^+) m/z: 434 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{10}H_7Br_3N_5$ (M+H$^+$) 433.82516, Found 433.82799.

4-(3,4-Dibromo-5-methyl-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (13) ⟨Method D⟩ To a solution of **48e** (94.1 mg, 0.16 mmol) in CH_2Cl_2 (3.0 ml) was added TFA (3.0 ml), and the mixture was stirred

overnight at room temperature. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in MeOH (5.0 ml). To the mixture was added aqueous 10% Na_2CO_3 solution (3.0 ml), and the whole was extracted with EtOAc. The combined extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. The residue was dissolved in MeOH (3.0 ml), and TFA (0.15 ml) was added to the MeOH solution. The acidic methanolic solution was concentrated *in vacuo*. Trituration of the residue with MeOH–CH_2Cl_2 gave **13**-2TFA (56.8 mg, 61%) as a pale yellow amorphous solid. IR (ATR): 3168, 1657, 1631, 1178, 1120, 719 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.39 (3H, s), 7.49 (1H, d, J=6.4 Hz), 8.18 (1H, d, J=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 12.5, 101.4, 102.6, 107.4, 118.6, 127.6, 133.5, 134.0, 135.5, 150.8, 161.9. LR-MS (ESI^+) *m/z*: 370 [M+H^+]. HR-MS (ESI^+) *m/z*: Calcd for $C_{11}H_{10}Br_2N_5$ (M+H^+) 369.93030, Found 369.93036.

4-(4,5-Dibromo-1-methyl-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (4) Treatments of **43ab** (90.0 mg) with TFA (3.0 ml) carried out in the same manner as described for **13** gave **4**-2TFA (94.3 mg, 82%) as a pale yellow amorphous solid after trituration with CH_2Cl_2–MeOH. IR (KBr): 3351, 3166, 1672, 1431, 1202, 1139, 722 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 3.69 (3H, s), 6.80 (1H, s), 7.54 (1H, d, J=6.4 Hz), 8.22 (1H, d, J=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 36.4, 100.4, 108.1, 111.6, 116.7, 125.7, 128.1, 135.5, 136.7, 150.5, 161.8. LR-MS (ESI^+) *m/z*: 370 [M+H^+]. HR-MS (ESI^+) *m/z*: Calcd for $C_{11}H_{10}Br_2N_5$ (M+H^+) 369.93030, Found 369.93000.

4-(5-Bromo-4-methyl-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (15) Treatments of **48f** (85.0 mg, 0.16 mmol) with TFA (3.0 ml) carried out in a similar manner to that described for **13** gave **15**-2TFA (71.4 mg, 84%) as a pale yellow amorphous solid after trituration with CH_2Cl_2–MeOH. IR (ATR): 3140, 2928, 1716, 1648, 1463, 1439, 1177, 1128, 792, 721 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.11 (3H, s), 7.00 (1H, s), 7.35 (1H, d, J=6.7 Hz), 7.96 (1H, d, J=6.7 Hz). ^{13}C-NMR (CD_3OD) δ: 11.6, 104.7, 106.5, 114.1, 122.5, 124.0, 129.7, 132.1, 136.2, 146.4, 160.5. LR-MS (ESI^+) *m/z*: 292 [M+H^+]. HR-MS (ESI^+) *m/z*: Calcd for $C_{11}H_{11}BrN_5$ (M+H^+) 292.01978, Found 292.02019.

4-(3,5-Dibromo-4-methyl-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (16) The same treatments of **48g** (86.6 mg, 0.14 mmol) with TFA (3.0 ml) as those described for **13** gave **16**-2TFA (29.3 mg, 34%) as a pale yellow amorphous solid after trituration with CH_2Cl_2–MeOH. IR (ATR): 3147, 1655, 1632, 1421, 1172, 1122, 718 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.10 (3H, s), 7.49 (1H, d, J=6.4 Hz), 8.18 (1H, d, J=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 11.1, 102.5, 104.9, 107.9, 120.8, 121.6, 127.3, 134.3, 135.5, 151.5, 162.2. LR-MS (ESI^+) *m/z*: 370 [M+H^+]. HR-MS (ESI^+) *m/z*: Calcd for $C_{11}H_{10}Br_2N_5$ (M+H^+) 369.93030, Found 369.93003.

4-(4-Benzyl-5-bromo-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (18) Similar treatments of **48i** (240 mg, 0.40 mmol) with TFA (3.0 ml) to those described for **13** gave **18**-2TFA (170 mg, 68%) as a pale yellow amorphous solid after trituration with CH_2Cl_2. IR (ATR): 3124, 2927, 1706, 1651, 1460, 1191, 1137, 721 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 3.84 (2H, s), 6.95 (1H, s), 7.16—7.30 (5H, m), 7.34 (1H, d, J=6.7 Hz), 7.92 (1H, d, J=6.7 Hz). LR-MS (ESI^+) *m/z*: 368 [M+H^+]. HR-MS (ESI^+) *m/z*: Calcd for $C_{17}H_{15}BrN_5$ (M+H^+) 368.05108, Found 368.05123. *Anal.* Calcd for $C_{17}H_{14}BrN_5$–$2C_2HF_3O_2$–$1.5H_2O$: C, 40.47%, H, 3.07%, N, 11.24%, Found: C, 40.44%, H, 2.84%, N, 11.42%.

4-(4-Benzyl-3,5-dibromo-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (19) Treatments of **48i** (230 mg, 0.34 mmol) with TFA (3.0 ml) carried out in the same manner as described for **13** gave **19**-TFA (135 mg, 71%) as a yellow amorphous solid after trituration with CH_2Cl_2. IR (ATR): 3339, 3158, 1662, 1201, 1177, 1132, 719 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 3.90 (2H, s), 7.14—7.30 (5H, m), 7.51 (1H, d, J=6.4 Hz), 8.18 (1H, d, J=6.4 Hz). LR-MS (ESI^+) *m/z*: 446 [M+H^+]. HR-MS (ESI^+) *m/z*: Calcd for $C_{17}H_{14}Br_2N_5$ (M+H^+) 445.96160, Found 445.96117. *Anal.* Calcd for $C_{17}H_{13}Br_2N_5$–$C_2HF_3O_2$: C, 40.67%, H, 2.51%, N, 12.48%, Found: C, 40.74%, H, 2.47%, N, 12.31%.

4-(5-Bromo-4-phenethyl-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (20) Treatments of **48k** (90.0 mg, 0.15 mmol) with TFA (3.0 ml) carried out in a similar manner to that described for **13** gave **20**-2TFA (63.4 mg, 71%) as a pale yellow amorphous solid after trituration with CH_2Cl_2–MeOH. IR (ATR): 3017, 1650, 1626, 1433, 1185, 1132, 721 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.27—2.81 (2H, m), 2.91 (2H, t, J=7.8 Hz), 6.98 (1H, s), 7.13—7.26 (5H, m), 7.35 (1H, d, J=6.4 Hz), 7.95 (1H, d, J=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 29.5, 37.4, 104.7, 106.3, 124.2, 126.7, 127.0, 129.3, 129.5, 129.8, 132.1, 136.3, 142.6, 146.5, 160.4. LR-MS (ESI^+) *m/z*: 382 [M+H^+]. HR-MS (ESI^+) *m/z*: Calcd for $C_{18}H_{17}BrN_5$ (M+H^+) 382.06673, Found 382.06675.

4-(3,5-Dibromo-4-phenethyl-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (21) The same treatments of **48l** (90.07 mg, 0.13 mmol) with TFA (3.0 ml) as those described for **13** gave **21**-2TFA (44.3 mg, 49%) as a pale yellow amorphous solid after trituration with CH_2Cl_2–MeOH. IR (ATR): 3172, 1656, 1631, 1422, 1202, 1181, 1114, 718 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.26—2.72 (2H, m), 2.76—2.81 (2H, m), 7.18—7.32 (5H, m), 7.50 (1H, d, J=6.1 Hz), 7.75 (2H, br s), 8.26 (1H, d, J=6.1 Hz), 12.73 (1H, br s). ^{13}C-NMR (DMSO-d_6) δ: 27.7, 35.3, 100.0, 102.4, 112.6, 115.6, 118.6, 121.5, 121.9, 122.2, 126.1, 128.28, 128.34, 128.36, 128.41, 140.6. LR-MS (ESI^+) *m/z*: 460 [M+H^+]. HR-MS (ESI^+) *m/z*: Calcd for $C_{18}H_{16}Br_2N_5$ (M+H^+) 459.97725, Found 459.97738.

4-(3,5-Dibromo-4-(2-(trifluoromethyl)phenethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (22) Similar treatments of **48m** (231 mg, 0.30 mmol) with TFA (3.0 ml) to those described for **13** gave **22**-2TFA (171 mg, 74%) as a yellow amorphous solid after trituration with CH_2Cl_2–MeOH. IR (ATR): 3331, 3161, 1651, 1630, 1312, 1171, 1102, 720 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.82—2.88 (2H, m), 3.04 (2H, t, J=7.9 Hz), 7.38 (2H, t, J=7.9 Hz), 7.51 (1H, d, J=6.7 Hz), 7.53 (1H, t, J=7.9 Hz), 7.66 (1H, d, J=7.9 Hz), 8.20 (1H, d, J=6.7 Hz). LR-MS (ESI^+) *m/z*: 528 [M+H^+]. HR-MS (ESI^+) *m/z*: Calcd for $C_{19}H_{15}Br_2F_3N_5$ (M+H^+) 527.96463, Found 527.96461.

4-(3,5-Dibromo-4-(3-(trifluoromethyl)phenethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (23) Treatments of **48n** (223 mg, 0.29 mmol) with TFA (3.0 ml) carried out in the same manner as described for **13** gave **23**-2TFA (136 mg, 61%) as a yellow amorphous solid after trituration with CH_2Cl_2–MeOH. IR (ATR): 3335, 3162, 1650, 1631, 1329, 1201, 1119, 720 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.84—2.88 (2H, m), 2.98 (2H, t, J=7.3 Hz), 7.43—7.49 (4H, m), 7.50 (1H, d, J=6.4 Hz), 8.19 (1H, d, J=6.4 Hz). LR-MS (ESI^+) *m/z*: 528 [M+H^+]. HR-MS (ESI^+) *m/z*: Calcd for $C_{19}H_{15}Br_2F_3N_5$ (M+H^+) 527.96463, Found 527.96521.

4-(3,5-Dibromo-4-(4-(trifluoromethyl)phenethyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (24) Treatments of **48o** (247 mg, 0.33 mmol) with TFA (3.0 ml) carried out in a similar manner to that described for **13** gave **24**-2TFA (108 mg, 44%) as a yellow amorphous solid after trituration with CH_2Cl_2–MeOH. IR (ATR): 3355, 3167, 1659, 1633, 1324, 1178, 1115, 1066, 710 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.84—2.88 (2H, m), 2.98 (2H, t, J=7.5 Hz), 7.38 (2H, d, J=8.3 Hz), 7.49 (1H, d, J=6.4 Hz), 7.56 (2H, d, J=8.3 Hz), 8.18 (1H, d, J=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 28.5, 36.2, 101.9, 105.5, 107.8, 121.2, 124.2, 124.6, 126.2, 126.3, 127.2, 129.3, 129.6, 130.4, 134.3, 146.9, 162.2. LR-MS (ESI^+) *m/z*: 528 [M+H^+]. HR-MS (ESI^+) *m/z*: Calcd for $C_{19}H_{15}Br_2F_3N_5$ (M+H^+) 527.96463, Found 527.96446.

4-(5-Bromo-4-(3-phenylpropyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (25) The same treatments of **48p** (315 mg, 0.50 mmol) with TFA (5.0 ml) as those described for **13** gave **25**-2TFA (218 mg, 69%) as a yellow amorphous solid after trituration with CH_2Cl_2. IR (ATR): 3062, 2930, 1711, 1650, 1462, 1188, 1133, 722 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.91—1.98 (2H, m), 2.53 (2H, t, J=7.6 Hz), 2.68 (2H, t, J=7.6 Hz), 7.06 (1H, s), 7.13—7.27 (5H, m), 7.36 (1H, d, J=6.4 Hz), 7.97 (1H, d, J=6.4 Hz). LR-MS (ESI^+) *m/z*: 396 [M+H^+]. HR-MS (ESI^+) *m/z*: Calcd for $C_{19}H_{19}BrN_5$ (M+H^+) 396.08238, Found 396.08261.

4-(3,5-Dibromo-4-(3-phenylpropyl)-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (26) Similar treatments of **48q** (370 mg, 0.52 mmol) with TFA (5.0 ml) to those described for **13** gave **26**-TFA (182 mg, 59%) as a pale yellow amorphous solid after trituration with CH_2Cl_2. IR (ATR) 3337, 3167, 2937, 1661, 1633, 1201, 1170, 1114, 702 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.86—1.94 (2H, m), 2.58 (2H, t, J=7.6 Hz), 2.69 (2H, t, J=7.6 Hz), 7.13—7.27 (5H, m), 7.49 (1H, d, J=6.4 Hz), 8.17 (1H, d, J=6.4 Hz). LR-MS (ESI^+) *m/z*: 474 [M+H^+]. HR-MS (ESI^+) *m/z*: Calcd for $C_{19}H_{18}Br_2N_5$ (M+H^+) 473.99290, Found 473.99244. *Anal.* Calcd for $C_{19}H_{17}Br_2N_5$-$C_2HF_3O_2$: C, 42.81%, H, 3.08%, N, 11.89%, Found: C, 42.88%, H, 3.09%, N, 11.87%.

4-(4,5-Dibromo-1*H*-imidazol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (29) Treatments of **43ar** (100 mg, 0.17 mmol) with TFA (3.0 ml) carried out in the same manner as described for **13** gave **29**-2TFA (64.2 mg, 64%) as a pale yellow powder after trituration with CH_2Cl_2–MeOH. IR (ATR): 3329, 2973, 1708, 1671, 1476, 1444, 1316, 1184, 1135, 1005, 834, 791, 761, 720, 707 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.41 (1H, d, J=5.8 Hz), 8.38 (1H, d, J=5.8 Hz). ^{13}C-NMR (CD_3OD) δ: 107.5, 112.1, 126.9, 130.7, 140.7, 142.8, 145.0, 155.3. LR-MS (ESI^+) *m/z*: 357 [M+H^+]. HR-MS (ESI^+) *m/z*: Calcd for $C_9H_7Br_2N_6$ (M+H^+) 356.90989, Found 356.90979. *Anal.* Calcd for $C_9H_6Br_2N_6$–$2C_2HF_3O_2$: C, 26.64%, H, 1.38%, N, 14.34%, Found: C, 26.26%, H, 1.27%, N, 14.05%.

4-(1*H*-Imidazol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (31) Treatments of **43aq** (74.0 mg, 0.14 mmol) with TFA (3.0 ml) carried out in a similar manner to that described for **13** gave **31**-2TFA (19.2 mg, 33%) as a light

brown amorphous solid after trituration with CH_2Cl_2. IR (ATR): 3105, 3012, 1712, 1616, 1435, 1174, 1137, 829, 753, 719, 635 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.39 (1H, d, J=5.5 Hz), 7.53 (2H, s), 8.26 (1H, d, J=5.5 Hz). LR-MS (ESI^+) m/z: 201 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_9H_9N_6$ (M+H$^+$) 201.08887, Found 201.08811. *Anal.* Calcd for $C_9H_9N_6$–$2C_2HF_3O_2$–$0.2H_2O$: C, 36.16%, H, 2.43%, N, 19.46%, Found: C, 35.99%, H, 2.35%, N, 19.32%.

4-(1*H*-Imidazol-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (33) The same treatments of **43av** (38.8 mg, 0.072 mmol) with trifluoroacetic acid (2.0 ml) as those described for **13** gave **33**-2TFA (14.2 mg, 46%) as a light brown amorphous solid after trituration with CH_2Cl_2. IR (ATR): 3089, 2875, 1667, 1634, 1426, 1194, 1118, 795, 721, 628 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.45 (1H, d, J=6.4 Hz), 8.13 (1H, s), 8.15 (1H, d, J=6.4 Hz), 8.27 (1H, d, J=0.9 Hz). LR-MS (EI^+) m/z: 200 [M$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_9H_8N_6$ (M$^+$) 200.0810, Found 200.0779.

4-(5-Bromo-4*H*-1,2,4-triazol-3-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (34) To a solution of **43at** (610 mg, 1.2 mmol) in CH_2Cl_2 (15 ml) was added TFA (10 ml) at 0 °C. The mixture was stirred at room temperature for 2 h, and then concentrated *in vacuo*. To the residue was added TFA (10 ml), and the solution was stirred at room temperature for 48 h, and concentrated *in vacuo*. The residue was triturated with CH_2Cl_2 to give **34**-TFA (351 mg, 73%) as a white amorphous solid. IR (ATR): 3318, 3066, 2684, 1698, 1661, 1614, 1331, 1182, 1127, 721 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.52 (1H, d, J=6.1 Hz), 8.31 (1H, d, J=6.1 Hz). LR-MS (ESI^+) m/z: 280 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_8H_7BrN_7$ (M+H$^+$) 279.99463, Found 279.99415. *Anal.* Calcd for $C_8H_6BrN_7$–$C_2HF_3O_2$–H_2O: C, 29.14%, H, 2.20%, N, 23.79%, Found: C, 29.20%, H, 2.09%, N, 24.05%.

4-(1*H*-1,2,3-Triazol-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (36) ⟨Method F⟩ A solution of **43ax** (260 mg, 0.48 mmol) in 10% HCl–MeOH (20 ml) was stirred at room temperature for 8 h, and concentrated *in vacuo*. The residue was triturated with CH_2Cl_2 to give a white power, and the powder was dissolved in 6 mol/l HCl (10 ml). The solution was stirred at 60 °C for 15 h, and concentrated *in vacuo*. To a solution of the residue in MeOH (10 ml) were added TEA (0.5 ml) and Boc_2O (200 mg). The mixture was stirred overnight at room temperature, and concentrated *in vacuo*. The residue was triturated with H_2O and CH_2Cl_2 to give *tert*-butyl 2-amino-4-(1*H*-1,2,3-triazol-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-1-carboxylate as a light brown powder. To a solution of the carboxylate derivative in MeOH (8.0 ml) was added TFA (4.0 ml). The mixture was stirred overnight at room temperature, and then concentrated *in vacuo*. The residue was triturated with MeOH–CH_2Cl_2 to give **36**-TFA (70.1 mg, 46%) as a white amorphous solid. IR (ATR): 3154, 2914, 1660, 1196, 1127, 801, 720 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.51 (1H, d, J=6.4 Hz), 8.21 (1H, d, J=6.4 Hz), 8.74 (1H, s). LR-MS (ESI^+) m/z: 202 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_9H_8N_7$ (M+H$^+$) 202.08412, Found 202.08402. *Anal.* Calcd for $C_9H_7N_7$–$C_2HF_3O_2$–$0.2H_2O$: C, 37.67%, H, 2.66%, N, 30.75%, Found: C, 37.39%, H, 2.66%, N, 30.53%.

4-(4,5-Dibromo-3-phenethyl-1*H*-pyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (28) ⟨Method E⟩ To a solution of **48r** (120 mg, 0.18 mmol) in EtOH (5.0 ml) was added an aqueous NaOH solution (3.0 ml, 3.0 mmol, 1.0 mol/l). The reaction mixture was stirred at 80 °C for 8 h, and then concentrated *in vacuo*. To the residue was added H_2O, and the whole was extracted with EtOAc. The organic extracts was conbined, washed H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (NH-SiO_2, EtOAc/MeOH=10/1) to give the deethoxycarbonyl derivative (89.0 mg, 83%) as a colorless amorphous solid. ^{1}H-NMR (CD_3OD) δ: −0.19 (9H, s), 0.57 (2H, dd, J=8.9, 7.6 Hz), 2.58 (2H, br s), 2.78 (2H, br s), 3.09 (2H, t, J=8.3 Hz), 5.34 (2H, br s), 6.79 (2H, d, J=6.4 Hz), 6.95—7.03 (3H, m), 7.24 (1H, d, J=5.5 Hz), 8.14 (1H, d, J=5.5 Hz). To a solution of the deethoxycarbonyl derivative in CH_2Cl_2 (3.0 ml) was added TFA (3.0 ml). The reaction mixture was stirred overnight at room temperature, and then concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with queous 10% Na_2CO_3 solution, H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. The residue was dissolved in MeOH, and the methanolic solution was filtered through a pad of NH-SiO_2 (washed with MeOH), and the filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH (5.0 ml), and TFA (0.12 ml) was added to the MeOH solution. The acidic methanolic solution was concentrated *in vacuo*. Trituration of the residue with CH_2Cl_2 gave **28**-2TFA (81.0 mg, 95%) as a pale yellow amorphous solid. IR (ATR): 3084, 1654, 1576, 1544, 1429, 1189, 1134, 799, 723 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.70 (2H, t, J=6.1 Hz), 3.06 (2H, t, J=6.1 Hz), 6.65—6.67 (2H, m), 6.73 (1H, tt, J=7.3, 1.2 Hz), 6.80 (2H, tt, J=7.3, 1.2 Hz), 7.35 (1H, d, J=6.4 Hz), 7.97 (1H, d, J=6.4 Hz). LR-MS (ESI^+) m/z: 460 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_{18}H_{16}Br_2N_5$ (M+H$^+$) 459.97725, Found 459.97668.

4-(4-Bromo-5-chloro-1*H*-imidazol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (30) Treatments of **52** (160 mg, 0.22 mmol) with an aqueous NaOH solution (3.0 ml, 3.0 mmol, 1.0 mol/l) followed by deprotection of the SEM group using TFA (3.0 ml) carried out in the same manner as described for **28** gave **30**-2TFA (64.0 mg, 59%) as a pale yellow amorphous solid after trituration with CH_2Cl_2–MeOH. IR (ATR): 3358, 3113, 1711, 1677, 1478, 1192, 1146, 993, 720 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.41 (1H, d, J=5.5 Hz), 8.38(1H, d, J=5.5 Hz). LR-MS (ESI^+) m/z: 313 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_9H_7BrClN_6$ (M+H$^+$) 312.96041, Found 312.95984.

4-(2,5-Dibromo-1*H*-imidazol-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (32) Treatments of **54** (100 mg, 0.17 mmol) with an aqueous NaOH solution (1.0 mol/l, 3.0 ml, 3.0 mmol) followed by deprotection of the SEM group using TFA (3.0 ml) carried out in a similar manner to that described for **28** gave **32**-2TFA (70.2 mg, 78%) as a pale yellow amorphous solid after trituration with CH_2Cl_2. IR (ATR): 2797, 1703, 1655, 1430, 1175, 1129, 720 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.94 (1H, d, J=6.4 Hz), 8.26 (1H, d, J=6.4 Hz). ^{13}C-NMR (CD_3OD) δ: 108.7, 120.9, 128.0, 132.0, 137.1, 150.7, 160.8, 161.5, 161.9. LR-MS (ESI^+) m/z: 357 [M+H$^+$]. HR-MS (ESI^+) Calcd for $C_9H_7Br_2N_6$ m/z: 356.90989 (M+H$^+$), Found 356.90985.

4-(4*H*-1,2,4-Triazol-3-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (35) The same treatments of **43as** (173 mg, 0.32 mmol) with an aqueous NaOH solution (1.0 mol/ml, 10 ml, 10 mmol) followed by deprotection of the trityl group using TFA (3.0 ml) in as those described for **28** gave **35**-TFA (56.2 mg, 56%) as a light brown powder after trituration with CH_2Cl_2. mp: 233 °C (decomp., from CH_2Cl_2), IR (ATR): 3114, 2930, 1709, 1671, 1490, 1174, 1127, 796, 722 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.53 (1H, d, J=6.4 Hz), 8.23 (1H, d, J=6.4 Hz), 8.77 (1H, s). LR-MS (ESI^+) m/z: 202 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_8H_8N_7$ (M+H$^+$) 202.08412, Found 202.08347.

4-(5-Bromo-1*H*-1,2,3-triazol-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (37) Similar treatments of **43ay** (200 mg, 0.32 mmol) with an aqueous NaOH solution (1.0 mol/ml, 5.0 ml, 5.0 mmol) followed by deprotection of the trityl group using TFA (3.0 ml) to those described for **28** gave **37**-TFA (11.2 mg, 9%) as a pale yellow amorphous solid after trituration with CH_2Cl_2. IR (ATR): 3364, 3082, 2927, 2702, 1680, 1619, 1197, 1180, 1146, 722 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 7.53 (1H, d, J=6.1 Hz), 8.39 (1H, d, J=6.1 Hz). LR-MS (ESI^+) m/z: 280 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_8H_7BrN_7$ (M+H$^+$) 279.99463, Found 279.99384.

4-(1*H*-Tetrazol-5-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine (38) Treatments of **43au** (575 mg, 1.4 mmol) with an aqueous NaOH solution (1.0 mol/ml, 10 ml, 10 mmol) carried out in the same manner as described for **28** gave the de-*tert*-butoxycarbonyl derivative (385 mg, 88%) as a white powder. Subsequent deprotection of the de-*tert*-butoxycarbonyl derivative (85.0 mg, 0.26 mmol) using TFA (3.0 ml) gave **38** (35.2 mg, 66%) as a light brown solid after trituration with CH_2Cl_2. mp: 250 °C (decomp., from MeOH), IR (ATR): 3408, 3061, 2665, 1662, 1572, 1418, 1322, 812 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.39 (1H, d, J=6.4 Hz), 7.54 (2H, br s), 8.12 (1H, d, J=6.4 Hz). LR-MS (ESI^+) m/z: 203 [M+H$^+$]. HR-MS (ESI^+) m/z: Calcd for $C_7H_7N_8$ (M+H$^+$) 203.07937, Found 203.07985. *Anal.* Calcd for $C_7H_6N_8$–$0.6H_2O$: C, 39.47%, H, 3.41%, N, 52.61%, Found: C, 39.69%, H, 3.14%, N, 52.48%.

MMP-12 Inhibition Assay The MMP-12 inhibition assay was performed as per the manufacturer's (BioMol) protocol. Human MMP-12 catalytic domain (residues 84—255) obtained from Biomol (Plymouth Meeting, PA, U.S.A.) was diluted in assay buffer (50 mM Tris pH 7.5, 0.05% Brij-35, 10 mM $CaCl_2$, 1 mM DTNB) to a concentration of 0.007 U/μl. The MMP-12 solution (44 μl) was premixed with 1 μl of inhibitors dissolved in DMSO in a 384-well plate, and the mixture was incubated for 20 min at room temperature. Then, 5 μl of 1 mM MMP chromogenic substrate (thiopeptolide) obtained from Biomol was added to the mixture and the reaction mixture was incubated for 30—80 min at 37 °C. The reaction was terminated by adding 7 μl of 0.2 M EDTA (pH 8.0). The intensity of the color developed by the digested substrate was measured at 405 nm.

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