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A novel synthesis of the 2-amino-1*H*-imidazol-4-carbaldehyde derivatives and its application to the efficient synthesis of 2-aminoimidazole alkaloids, oroidin, hymenidin, dispacamide, monobromodispacamide, and ageladine A☆

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ABSTRACT

A novel synthesis of 2-amino-1*H*-imidazol-4-carbaldehyde derivatives was achieved by the reaction of *tert*-butoxycarbonylguanidine with 3-bromo-1,1-dimethoxypropan-2-one as a key step. The usefulness of the derivatives as building blocks was proved by accomplishing the efficient synthesis of the representative 2-aminoimidazole alkaloids, oroidin, hymenidin, dispacamide, monobromodispacamide, and ageladine A.

1. Introduction

Various 2-aminoimidazole alkaloids, including oroidin (**1**),[2] hymenidin (**2**),[3] dispacamide (**3**),[4] monobromodispacamide (**4**),[4] sceptrin (**5**),[5] and ageladine A (**6**),[6] have been isolated from marine sources (Fig. 1).[7] Their fascinating structures as well as various biological activities, some of which are of interest from a pharmaceutical perspective, make these alkaloids intriguing synthetic targets, and numerous total syntheses have hitherto been reported.[7,8]

Considering the synthetic steps to construct their characteristic 2-aminoimidazole moieties, the total syntheses reported thus far can be roughly divided into two categories. One is the synthetic step, in which the 2-aminoimidazole ring is produced by condensing a guanidine derivative with an α-haloketone[9] or by reacting a cyanamide with an α-aminoketone.[8h] The other step features amination of the 2-position of the preformed imidazole ring by employing explosive azide or diazonium reagents.[8b,e,10] In both syntheses, the construction of the 2-aminoimidazole moiety is usually attempted at the later synthetic stages. Accordingly, it is obvious that a number of the congeners of natural 2-aminoimidazole alkaloids, in which the substructures, except for the 2-aminoimidazole moiety, are replaced with various structural motifs different from those involved in natural products, cannot be readily prepared by applying the reported methods.

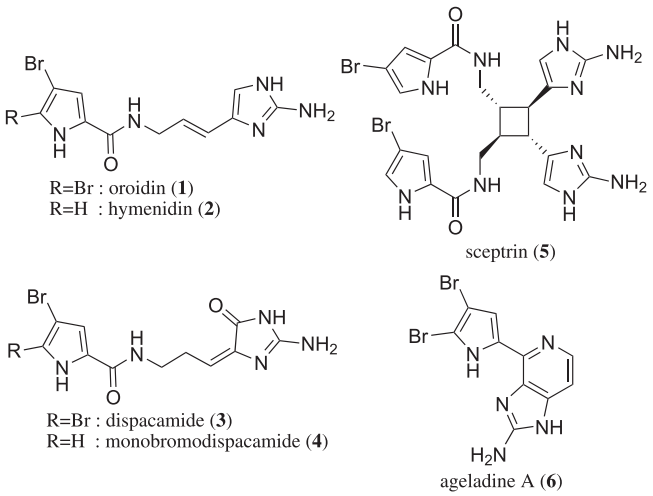

Figure 1. Structures of representative 2-amino-1*H*-imidazole alkaloids.

Taking the above issues into account, we have attempted to develop a novel synthetic strategy that can afford not only natural 2-aminoimidazole alkaloids but also their congeners more efficiently than the reported methods.[7–10] We have now found that the 2-amino-1*H*-imidazol-4-carbaldehyde derivatives **I** (Fig. 2) are the best starting materials for the novel strategy. In addition to the characteristic 2-amino-1*H*-imidazole moieties, **I** carry 4-aldehyde groups that can be added to form various structural motifs. Thus, it was expected that oroidin (**1**), dispacamide (**3**), and ageladine

☆ See Ref. 1

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A (**6**) could be synthesized from **I** by way of allylamine derivative **II** or 2′-amino-histamine derivative **III** (Fig. 2). However, a search of the literature soon disclosed that the synthesis of **I** has scarcely been explored. The only method reported by Alain in French patent[11] is considered to lack practicality due to its harsh reaction conditions, such as thermolysis. Accordingly, we embarked on exploring a novel synthetic route to **I** more efficient than that reported.[11]

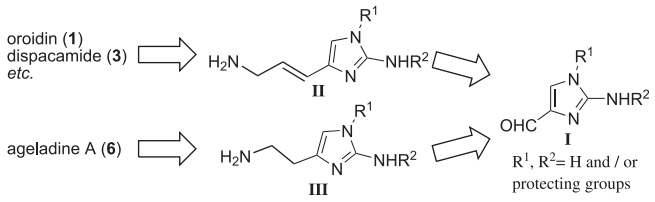


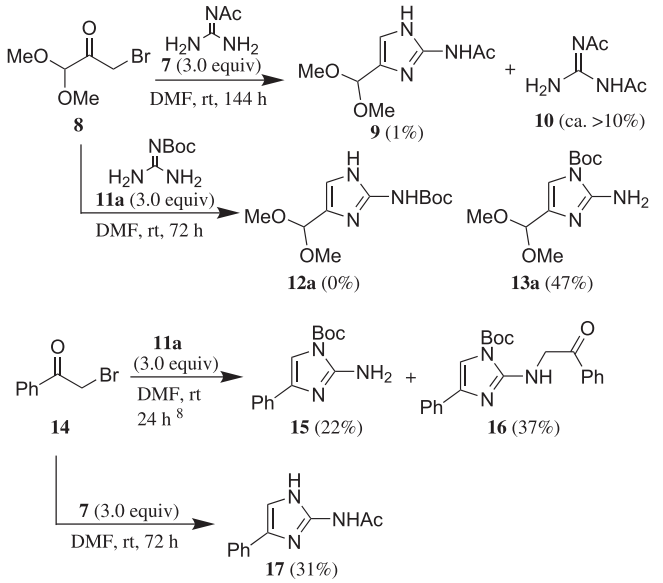
Figure 2. Retrosynthetic analysis of 2-aminoimidazole alkaloids using 2-amino-1*H*-imidazol- 4-carbaldehyde derivatives (**I**) as starting materials.

We have now found that the novel synthesis of **I** can be efficiently achieved by the reaction of *tert*-butoxycarbonylguanidine (**11a**) with 3-bromo-1,1-dimethoxypropan-2-one (**8**) as a key step. Starting with **I**, which have become readily available on a large scale, we have succeeded in accomplishing the efficient synthesis of the representative 2-aminoimidazole alkaloids, oroidin (**1**), hymenidin (**2**), dispacamide (**3**), monobromodispacamide (**4**), and ageladine A (**6**).

2. Results and discussion

2.1. Synthesis of various 2-amino-1*H*-imidazol-4-carbaldehyde derivatives

It has been reported by Webber et al.[8c] that the 4-substituted-2-acetamido-1*H*-imidazole derivatives can be prepared in good yields by the reaction of commercially available acetyl(Ac)guanidine (**7**) and α-haloketones in DMF or MeCN. For convenience, this reaction is referred to as Webber's reaction throughout this work. Expecting that application of Webber's reaction can readily produce **I**, we treated 3-bromo-1,1-dimethoxypropan-2-one (**8**) with **7** under the same conditions as employed by Webber et al.[8c] However, as shown in Scheme 1, the desired product **9** was obtained only in 1% yield along with a considerable amount of *N*,*N*-diacetylguanidine (**10**).[12] The formation of **10** was considered to occur due to the disproportionation of **7**, since **10** was produced from **7** under some conditions in the absence of **8**. Aiming to improve the disappointing results, the same reaction was next carried out using *tert*-butoxycarbonyl(Boc) guanidine (**11a**)[13] in place of **7**. While it has been reported that **11a** is usable for Webber's reaction similar to **7**,[9a] the reaction of **8** with **11a** had not been examined. To our delight, the reaction was found to take place smoothly, affording 2-amino-1-Boc-4-(dimethoxymethyl)-1*H*-imidazole (**13a**) as the sole product in 47% yield. Formation of 2-(Boc-amino)-4-(dimethoxymethyl)-1*H*-imidazole (**12a**) corresponding to the expected product of Webber's reaction was not observed at all. This result differs distinctly from that reported previously.[9a] The structure of **13a** was verified by its spectral data and single-crystal X-ray analysis (Fig. 3).[14] Thus, in the ^{1}H NMR spectra, while the signals of the C_5-proton of imidazole ring and the two protons of NH groups appeared at 6.65, 11.68, and 11.40 ppm, respectively, for **9**, **13a** showed its C_5-proton of the imidazole ring and two protons of the NH_2 group at 6.86 and 5.56 ppm. Interestingly, when phenacyl bromide (**14**), being one of the typical substrates for Webber's reaction, was used in place of **8**, a mixture of 2-amino-1-Boc-4-phenyl-1*H*-imidazole (**15**) and its 2-phenacyl derivative (**16**) was similarly obtained in 22% and 37% yields, respectively. The reaction of **15** with an excess amount of **14** present in the reaction medium might explain the formation of **16**. In this reaction too, formation of the 2-Boc-amino derivative **18** (vide infra) corresponding to the expected product of Webber's reaction could not be detected. In contrast, when **14** was treated with **7** under the same conditions as employed by Webber et al.,[6] 2-acetamido-4-phenyl-1*H*-imidazole (**17**), the normal reaction product reported by Webber et al., was obtained in 31% yield.



Scheme 1. Reactions of the acylguanidine derivatives (**7** and **11a**) with 3-bromo-1,1-dimethoxymethylpropan-2-one (**8**) and phenacyl bromide (**14**).

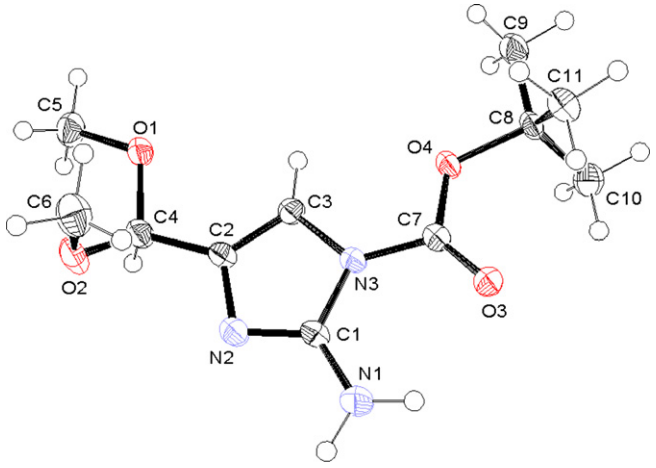


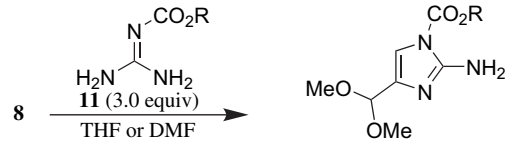
Figure 3. The X-ray crystal structure of *tert*-butyl 2-amino-4-dimethoxymethyl-1*H*-imidazol-1-carboxylate (**13a**).

Based on the results obtained above, it became obvious that the electrophilicity of the carbonyl group in **8** is more decreased sterically and electrically than that in **14**, and that the nucleophilicity of **11a** is more increased than that of **7**. It was also determined that the structure of the reaction product clearly depends on the protective group of guanidine, not on the structure of α-haloketone.

With the aim of obtaining further insight into the reaction, we next examined the reactions of **8** with various alkoxycarbonylguanidines **11b**–**e** to explore whether the reaction products are affected by the steric or the electronic effects of the protective group of guanidine. The alkoxycarbonylguanidines **11b**–**e** were obtained by the same method as that used for **11a**. As

summarized in Table 1, all the alkoxycarbonylguanidines, **11b**, **d**, and **e**, except for **11c** gave **13b**, **d**, and **e** corresponding to **13a** as the sole reaction products. Since even **11b** bearing a small methoxycarbonyl group gave only **13b** as a reaction product, it appeared evident that an electronic effect of the alkoxycarbonyl groups has a larger effect on the reaction than a steric effect. As shown in Table 2, we further studied solvent effects on the reaction. It was found that the chemical yield of **13a** showed no dependence on the reaction solvent. This feature clearly differs from that of Webber's reaction, which usually gives a good yield only in DMF and MeCN. Under optimized conditions (Table 1, run 2), **13a** could be produced in more than 60% yield. The above results clearly suggest that the reaction with **11a**, **b**, **d**, and **e** might proceed through a mechanism different from that anticipated for Webber's reaction.

Table 1
Synthesis of various alkyl 2-amino-4-dimethoxymethyl-1*H*-imidazol-1-carboxylate derivatives (**13**) in THF or DMF[a]

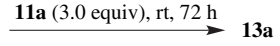


13a: R = *t*-Bu; **b**: R = Me; **c**: R = CH_2CCl_3; **d**: R = $CH_2CH{=}CH_2$; **e**: R = CH_2Ph

Run	Product	Yield in THF	(%)[b] in DMF
1	**13a**	51	47
2[c]	**13a**	62 (64[d])	
3	**13b**	<24[e]	<8[e]
4	**13c**	ND[f]	ND[f]
5	**13d**	24	26
6	**13e**	37	26

[a] All reactions were carried out in 0.25–1.0 mmol scale.
[b] Isolated yield.
[c] The reaction was performed at 50 °C for 6 h.
[d] The reaction was carried out in 10 mmol scale.
[e] This sample was contaminated by a minute amount of the unidentified by-product.
[f] The reaction gave a complex mixture as the products. Formation of **13c** could not be detected by the ^{1}H NMR.

Table 2
Synthesis of *tert*-butyl 2-amino-4-dimethoxymethyl-1*H*-imidazol-1-carboxylate (**13a**) in various solvents[a]



Run	Solv.	Yield[b] (%)
1	PhMe	42
2	EtOAc	50
3	THF	51
4	CH_2Cl_2	40
5	EtOH	44
6	MeCN	8
7	DMA[c]	47
8	DMF	47
9	NMP[d]	44
10	DMSO	51

[a] All reactions were performed in 0.25 mmol scale.
[b] Isolated yield.
[c] *N*,*N*-Dimethylacetamide
[d] *N*-Methylpyrrolidone.

Papeo et al. have reported that the reaction of **11a** with an α-bromoketone gave the 2-amino-1-Boc-1*H*-imidazole derivative corresponding to **13a** in their total synthesis of DL-cyclooroidin.[9b] They explained this result by postulating that the Boc group migrates from the 2-amino group to the C_1-position of the 1*H*-imidazole ring during the purification step. Aiming to explore the possibility that **13a** and **15** were produced by way of **12a** and **18** (vide infra), respectively, during the reaction and/or the purification step by the same migration of Boc group as reported by Papeo et al., we independently prepared **12a** and **18** from 2-(Boc-amido)-1*H*-imidazol-4-carbaldehyde (**20a**) (vide infra) and **15** by acetalization (for **12a**) and sequential acylation and methanolysis (for **18**) (Scheme 2). When **12a** and **18** were subjected to the reaction conditions for producing **13a** and **15** from **8** and **14**, respectively, the starting materials **12a** and **18** were completely recovered without any formation of **13a** and **15**. These results clearly show that, in our reactions using **11a**, **13a**, and **15** were directly produced from **8** and **14** without proceeding through **12a** and **18**. We further examined the possibility of migration of the 1-acetyl group to the 2-amino group in the case of Webber's reaction of **7** and **14**. However, 1-acetyl-2-amino-4-phenyl-1*H*-imidazole (**19**) prepared from **15** by sequential deprotection and acetylation could not be converted to **17** under the basic conditions employed for Webber's reaction. This result also shows that **17** was directly produced from **14**, not by way of the 1-acetyl derivative **19**. Based on these results, it might be concluded that the migration of a Boc or an Ac group is not the reason why our reaction products, such as **13** and **15** were different from those of Webber's reaction.

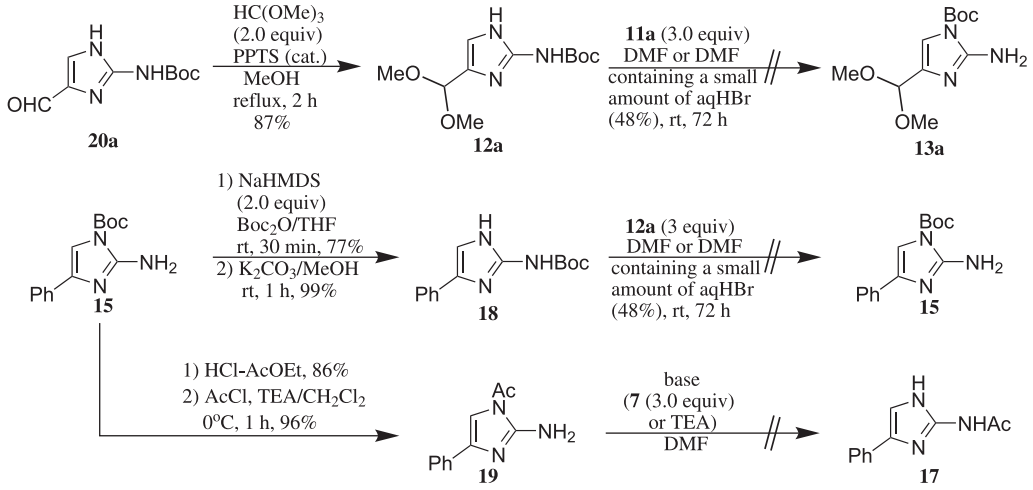
Summing up the results described above, it appeared evident that the reactions of **8** and **11** might proceed through the mechanism, which is probably different from that anticipated for Webber's reaction. Taking into account the difference between the nucleophilicity of a non-substituted amino or imino group and that of acylated ones, the formation of **17** from **14** and **7** as well as that of **9** from **8** and **7** are quite reasonable. However, the specific formation of **13a**, **b**, **d**, and **e** from **8** and **11a**, **b**, **d**, and **e** seems very curious and cannot be explained reasonably, although an electronic effect of an alkoxycarbonyl group likely plays a key role in determining the direction of the cyclization reaction.

As shown in Scheme 3, **13a**, which has become readily available in a large quantity, was converted to the 2-acylamino-1*H*-imidazol-4-carbaldehyde derivatives **20** corresponding to **I** by sequential acylation and deacetalization. Further protection of the 1-imino group in **20a**, **b** with a Boc group furnished 2-acylamino-1-Boc-1*H*-imidazol-4-carbaldehyde **21a**, **b**, which also corresponded to **I**. The attempted introduction of protective groups other than the Boc group into the 1-imino group of **20a** turned out to be fruitless. Thus, we subjected **20a** to tritylation, acetylation, triisopropylsilylation, and methoxymethylation under the standard reaction conditions. Although formations of the desired compounds corresponding to **21a** were observed for tritylation, acetylation, and triisopropylsilylation, these products were found to be too unstable to be isolated in pure states. In the case of methoxymethylation, a complex mixture was obtained as the reaction product.

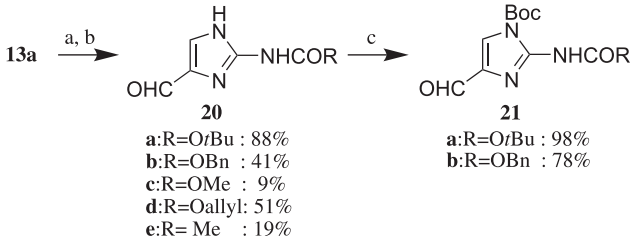
2.2. Synthesis of 2-amino-1*H*-imidazole alkaloids

With paving the way to **20** and **21** completed, the total synthesis of representative 2-aminoimidazole alkaloids, oroidin (**1**), hymenidin (**2**), dispacamide (**3**), monobromodispacamide (**4**), and ageladine A (**6**) was next examined to explore the synthetic utility of **20** and **21** corresponding to **I**.

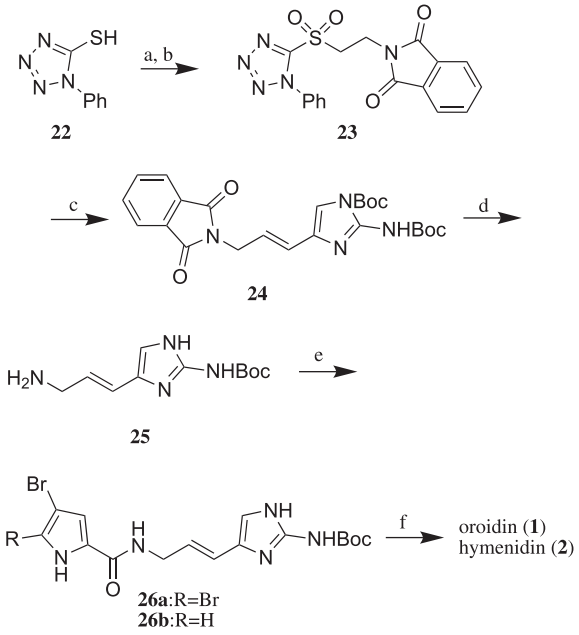
*2.2.1. Synthesis of oroidin (**1**) and hymenidin (**2**).* Oroidin (**1**) isolated from the sponge *Agelas oroides* by Forenza et al. in 1971 is one of the most representative 2-aminoimidazole alkaloids. In particular, **1** has attracted attention since it was reported by Richards et al. that **1** and its analogs showed antibiofilm activities.[15] On the other hand, hymenidin (**2**) was isolated from the Okinawan marine sponge *Hymeniacidon* sp. by Kobayashi et al. in 1986 as an inhibitor of serotonergic receptors.[3] Numerous syntheses of **1** and **2** have hitherto been reported,[8a–e] probably due to their simple and



Scheme 2. Reactions of *tert*-butyl 4-dimethoxymethyl-1*H*-imidazol-2-ylcarbamate (**12a**), *tert*-butyl 4-phenyl-1*H*-imidazol- 2-ylcarbamate (**18**) and 1-(2-amino-4-phenyl-1*H*-imidazol-1-yl)ethanone (**19**).



Scheme 3. Synthesis of various 2-amino-1*H*-imidazol-4-carbaldehyde derivatives (**20a**–**e** and **21a**, **b**) from *tert*-butyl 2-amino-4-dimethoxymethyl-1*H*-imidazol-1-carboxylate (**13a**). Reagent and conditions: (a) $(RCO)_2O$ or RCOCl, NaHMDS (2.0 equiv)/THF, 0 °C to rt, 15 min; (b) PPTS (cat.)/acetone/H_2O (3:2), rt, overnight; (c) Boc_2O, TEA/THF/MeCN (1:1), rt, 8 h.



Scheme 4. Total synthesis of oroidin (**1**) and hymenidin (**2**). Reagents and conditions: (a) *N* -(2-bromoethyl)phthalimide, K_2CO_3/acetone, reflux, 3 h; (b) *m*-CPBA, $NaHCO_3$/CH_2Cl_2, rt, overnight, 79% (two steps from **22**); (c) **21a** (1.5 equiv), NaHMDS/THF, −78 °C, 30 min, 69%; (d) H_2NNH_2/EtOH, 50 °C, 2 h, 92%; (e) 4,5-dibromo-2-trichloroacetylpyrrole or 4-bromo-2-trichloroacetylpyrrole, Na_2CO_3/DMF, rt, overnight, 79% f or **26a**, 83% for **26b**; (f) 20%HCl/EtOH, rt, 1 h, 92% for **1**, 99% for **2**.

characteristic structures as well as to the positions at which they are placed in the biosynthesis of numerous 2-aminoimidazole alkaloids.[7]

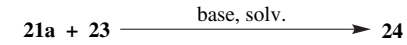
After some experimentation, the Julia/Kocienski olefination[16] of **21a** with sulfone **23** was selected to produce (*E*)-olefin **24**, as shown in Scheme 4, because the usual Wittig reaction which we first examined resulted in a lower yield and (*E*)-selectivity. A general procedure for the Julia/Kocienski olefination has been reported as follows. Thus, a base was added to a solution of a sulfone to make an anion, and an aldehyde solution was added to obtain an olefin. However, this procedure did not work well in our case, probably due to the instability of the anion of **23**. Therefore, we next examined the addition of a base to a solution of **21a** and **23**, and succeeded in obtaining the desired **24** along with the undesired (*Z*)-isomer of **24**.

Results for optimizing the reaction conditions are summarized in Table 3. Two equivalents were found to be the best amount of a base, and the best counter cation for the base was sodium (Table 3, runs 1–5). THF was more suitable than DME as a reaction solvent (Table 3, runs 2 and 6). In addition, the lower reaction temperature obviously increased the yield and (*E*)-selectivity (Table 3, runs 6 and 7). Under all the conditions delineated as above, **23** was not completely consumed until the end of the reaction. Accordingly, we attempted to increase the amount of aldehyde **21a**. Under these conditions, **23** almost completely disappeared at the end of the reaction, giving rise to **24** in 69% yield with formation of the undesired (*Z*)-isomer (10% yield), which can be readily removed by column chromatography (Table 3, run 8). Deprotection of **24** with hydrazine accompanied removal of the 1-Boc group, and the subsequent reaction with 4,5-dibromo-2-trichloroacetylpyrrole[17] afforded the protected oroidin derivative **26a** in 79% yield based on **24**. Final removal of the Boc group under acidic conditions afforded oroidin (**1**) in 92% yield.[2a,8b,c] In a similar manner, hymenidin (**2**) was prepared from **25** and 4-bromo-2-trichloroacetylpyrrole by way of **26b**.[18] Spectral and physical properties of **1** and **2** were in accord with those reported.[2a,3,8b,c]

*2.2.2. Synthesis of dispacamide (**3**) and monobromodispacamide (**4**).* Dispacamide (**3**) and monobromodispacamide (**4**) were isolated from four Caribbean *Agelas* sponges by Cafieri et al. in 1996.[4] A few syntheses of **3** and **4** showing selective antagonistic activity against histaminergic receptors have so far been achieved.[8a,f,g]

The synthesis of dispacamide (**3**) and monobromodispacamide (**4**) was examined starting with **24**, which has become readily

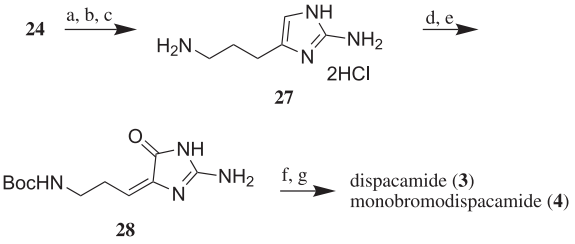
Table 3
Results f or the Julia/Kocienski olefination of 2-*tert*-butoxycarbonamido-1-*tert*-butoxycarbonyl-1*H*-imidazol-4-carbaldehyde (**21a**)



Run	Equiv of **21a**	Base (equiv)	Solv.	Temp. (°C)	Yield (%) (*E*)-**24**[a] (*Z*)-**24**[b]	
1	1.0	NaHMDS (1.0)	DME	−55	ca. (*E*)-**24**:**23**=1:1[c]	
2	1.0	NaHMDS (2.0)	DME	−55	48	12
3	1.0	NaHMDS (3.0)	DME	−78	26	5
4	1.0	LiHMDS (2.0)	DME	−55	49	16
5	1.0	KHMDS (2.0)	DME	−55	<35	8
6	1.0	NaHMDS (2.0)	THF	−55	53	8
7	1.0	NaHMDS (2.0)	THF	−55	57	6
8	1.5	NaHMDS (2.5)	THF	−78	69	10

[a] Determined by the weight of (*E*)-**24** separated by column chromatography.
[b] Determined by the ^{1}H NMR spectrum of the mixture of (*Z*)-**24** and **23**.
[c] Estimated by the TLC analysis of the crude reaction mixture.

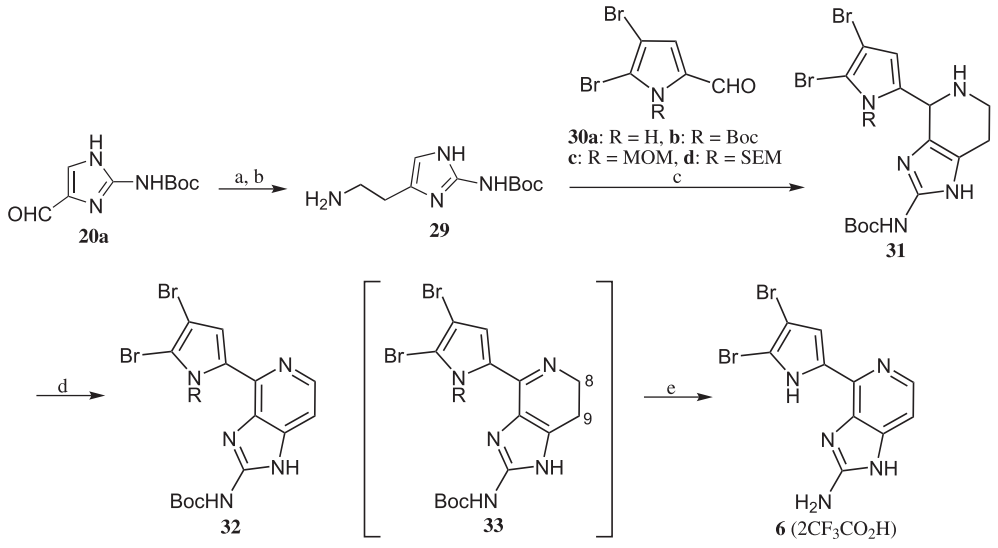
available, as described in Section 2.2.1. As shown in Scheme 5, the catalytic reduction of **24** followed by deprotection of the phthaloyl group with hydrazine and complete acidic removal of the two Boc groups in the imidazole moiety gave amine **27** as its dihydrochloride in 63% yield from **24**. The dihydrochloride **27** was converted to **3** and **4** following the procedure reported by Horne et al.[8a] with some modifications. Thus, after oxidation of **27** with tetra-*n*-butylammonium tribromide, the aliphatic primary amino group of the product was selectively protected with a Boc group to simplify the purification, affording the carbamate **28** in 40% yield based on **27**. Sequential deprotection and acylation with 4,5-dibromo- and 4-bromo-2-trichloroacetylprrole[17,18] furnished dispacamide (**3**) and monobromodispacamide (**4**), both as solids, in 85% and 69% yield, respectively, based on **28**. Spectral and physical data of **3** and **4** were almost identical to those previously reported.[4] The ^{1}H NMR spectrum of **3** and **4** clearly showed that the samples were contaminated by minute amounts of the corresponding unnatural (*Z*)-isomers (ca. <5%), which could not be removed even by repeated purification by column chromatography.



Scheme 5. Total synthesis of dispacamide (**3**) and monobromodispacamide (**4**). Reagents and conditions: (a) H_2 (4 kg/cm^2), 10% Pd/C/EtOH, 50 °C, 13 h; (b) H_2NNH_2/EtOH, 50 °C, 6 h; (c) 20% HCl/EtOH, rt, overnight, 64% (three steps from **24**); (d) tetra-*n*-butylammonium tribromide/DMSO, rt, 1.5 h; (e) Boc_2O/MeOH, rt, overnight, 40% (two steps from **27**); (f) 20% HCl/EtOH, rt, overnight; (g) 4,5-dibromo-2-trichloroacetylpyrrole or 4-bromo-2-trichloroacetylpyrrole, Na_2CO_3/DMF, rt, overnight, 85% for **3** (two steps from **28**), 69% for **4** (two steps from **28**).

*2.2.3. Synthesis of ageladine A (**6**).* Ageladine A (**6**), isolated from the marine sponge *Agelas nakamurai* by Fusetani et al. in 2003, has attracted much attention because of its inhibitory activity against various subtypes of matrix metalloproteinases (MMPs).[6] We selected **6** as a new lead compound for novel MMP-12 inhibitors and embarked on its total synthesis. Four total syntheses of **6** including ours have been reported to date.[1b,8j,k,19]

As shown in Scheme 6, we designed a synthetic scheme to **6** based on the biosynthetic route proposed by Fusetani et al.[6] in which **6** may be biosynthesized from 4,5-dibromopyrrol-2-carbaldehyde (**30a**) and histamine by sequential imino formation, the Pictet/Spengler cyclization,[20] and dehydrogenation. Just after our completion of the total synthesis delineated below, we became aware that Karuso and Shengule had succeeded in synthesizing **6**



Scheme 6. Total synthesis of ageladine A(**6**) bistrifluoroacetate. Reagents and conditions: (a) $AcONH_4$/$MeNO_2$, reflux, 20 min, 94%; (b) $LiAlH_4$ (3.0 equiv)/THF, 50 °C, 1 h, 67%; (c) See Table 4; (d) See Table 5; (e) TFA, rt, 5 h, 83% (for **32b**) or (i) BF_3/OEt_2 (10 equiv)/CH_2Cl_2, overnight, (ii) TFA/MeOH, rt, 5 min, 70% (for **32d**).

based on the proposed biosynthetic route.[8k] Taking into account the biosynthetic route, our synthetic studies of **6** commenced using non-protected **30a** prepared from commercial available pyrrol-2-carbaldehyde.[21] Thus, nitroaldol condensation of **20a** followed by reduction using lithium aluminum hydride ($LiAlH_4$) gave the histamine derivative **29** in 63% yield based on **20a**. Treatments of **29** with **30a** underwent the Pictet/Spengler reaction only under a basic condition giving rise to the tetrahydroageladine A derivative **31a** in 31% yield (Table 4, run 3). Acidic or neutral conditions were found to be completely ineffective for this cyclization reaction (Table 4, runs 1 and 2). However, the next dehydrogenation of **31a** under various conditions turned out to be fruitless, providing a complex mixture instead of the desired **32a** (Table 5, runs 1–3).

Table 4
Reactions of *tert*-butyl 4-(2-aminoethyl)-1*H*-imidazol-2-ylcarbamate (**29**) with 4,5-dibromopyrrol-2-carbaldehyde derivatives (**30**) under various conditions[a]

Run	30	Reaction conditions	Yield (%)
1	**a**	PPTS (cat.)/toluene, rt-90 °C	ND[b]
2	**a**	EtOH, 50–70 °C	ND[b]
3	**a**	pyridine, rt, 5 days	31
4	**b**	PPTS (cat.)/toluene, rt, 24 h	78
5	**b**	Toluene, 50 °C, 8 h	51
6	**b**	EtOH, rt, 5 days	46
7	**b**	Pyridine, rt, 3 days	28[c]
8	**c**	PPTS (cat.)/toluene, rt, 24 h	56
9	**c**	EtOH, 50 °C, 2 h	68
10	**d**	EtOH, 50 °C, 4 h	80

[a] All reactions were carried out in 1.0 mmol scale.
[b] Formation of desired **31a** could not be detected by the ^{1}H NMR spectral analysis of the crude reaction products.
[c] In addition to **31b**, the deprotected product **31a** was obtained in 17% yield.

Table 5
Dehydrogenation of *tert*-butyl 4-(4,5-dibromo-1*H* -pyrrol-2-yl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-c]pyridin-2-ylcarbamate derivatives (**31**) under various conditions[a]

Run	31	Reaction conditions	Yield of **32** (%)
1	**a**	MnO_2/toluene, 50–100 °C	ND[b]
2	**a**	RuHAP/toluene, 80 °C	ND[b]
3	**a**	IBX (2.5 equiv)/DMSO, 45 °C	ND[b]
4	**b**	MnO_2/toluene, 50–100 °C	ND[b]
5	**b**	IBX (2.5 equiv)/DMSO, 50 °C	13
6	**c**	MnO_2/toluene, rt, 10 h	42
7	**c**	(1) IBX (2.5 equiv)/DMSO, 50 °C, 1 h	75[c]
		(2) IBX (2.5+0.5 equiv)/DMSO, 50 °C, 1+2 h	64[d]
		(3)MnO_2/CH_2Cl_2, rt, 1 h	63[e]
8	**d**	MnO_2/CH_2Cl_2, rt, 2 h	37
9	**d**	(1) IBX (2.5 equiv)/DMSO, 45 °C, 3 h	69
		(2)MnO_2/CH_2Cl_2, rt, 1.5 h	
10	**d**	(1) IBX (1.5 equiv)/DMSO, rt, 3 h	89
		(2)MnO_2/CH_2Cl_2, rt, 2.5 h	

[a] All reactions were carried out in 1.0 mmol scale.
[b] Formation of desired **32a** could not be detected by the ^{1}H NMR spectral analysis of the crude reaction product.
[c] The ^{1}H NMR spectrum showed that this sample consisted of **32c** and its 6,7-dihydro-derivative **33c** in a ratio of 3:1.
[d] The ^{1}H NMR spectrum showed that this sample contained **32c** and **33c** in a ratio of 10:1.
[e] Further oxidation of the mixture of **32c** and **33c** (10:1) gave **32c** in 63% yield based on **31c**.

Based on these results, use of the 1-protected-pyrrole derivatives **30b–d** was next attempted. Among **30b–d**, **30b** was prepared from **30a** according to the reported procedure,[22] and the synthesis of **30c** and **30d** was also performed starting with **30a** as described in the Experimental part. The Pictet/Spengler reaction of **29** with **30b** gave **31b** under various conditions (Table 4, runs 4–7). The best result was obtained under a weakly acidic condition to afford **31b** in 78% yield based on **29** (Table 4, run 4). Dehydrogenation of **31b** using iodoxybenzoic acid (IBX) successfully gave **32b**, albeit with a rather low yield of 13% (Table 5, run 5). Treatment of **32b** with TFA smoothly underwent deprotection, furnishing **6** as its bistrifluoroacetate in 83% yield. Spectral and physical properties of **6**-2TFA were in good accord with those reported.[6] With completion of the total synthesis of **6**, we next focused on improving the explored synthetic scheme. It was anticipated that, since the dehydrogenation of **31b** gave **32b** in a very low yield, it could not be directly applied to the synthesis of various structural types of the ageladine A derivatives. Considering the unsuccessful results for the dehydrogenation of **31b** (Table 5, runs 1–3), it was conceived that the Boc group might be eliminated under the dehydrogenation conditions. We therefore examined the Pictet/Spengler reaction of **29** using 4,5-dibromo-1-methoxymethyl(MOM)pyrrol-2-carbaldehyde (**30c**), since a MOM group is well known to be more stable than a Boc group. Interestingly, in this case, the best result for the yield was obtained under a neutral condition to afford **31c** in 68% yield based on **29** (Table 4, run 9). Dehydrogenation of **31c** with activated manganese (IV) oxide (MnO_2) gave **32c** in a more improved but still lower yield of 42% (Table 5, run 6). In the case where IBX was used in place of activated MnO_2, the dehydrogenation of **31c** was carried out at 50 °C for 1 h, resulting in the formation of a 3:1 mixture of **32c** and 8,9-dihydroageladine A derivative **33c** (ageladine A numbering) (Table 5, run 7). Further addition of IBX to the reaction mixture was found to be ineffective for complete dehydrogenation, and afforded a 10:1 mixture of **32c** and **33c** in a more decreased 64% yield. However, we found that this mixture could be completely transformed to **32c** using activated MnO_2 without decreasing the chemical yield (Table 5, run 7). From these results, it appeared that the dehydrogenation of **33c** smoothly took place in the presence of activated MnO_2. Nicolaou et al. reported that the dehydrogenation of tetrahydroisoquinoline to isoquinoline is cleanly effected using 2.5 equiv IBX at 45 °C, and the use of 1.5 equiv IBX at 25 °C gave dihydroisoquinoline.[23] Therefore, we next designed a two-step dehydrogenation protocol in which the additional dehydrogenation was attempted using activated MnO_2 after preparing **33c** from **31c** by the use of 1.5 equiv IBX. However, we had no chance to apply this protocol to the dehydrogenation of **31c** since it was found that the deprotection of **32c** bearing a MOM group to produce **6** could not be accomplished.

Finally, we selected 4,5-dibromo-1-(2-trimethylsilylethoxymethyl (SEM))pyrrol-2-carbaldehyde (**30d**) as the reaction partner for **29**, since a SEM group is well known to be chemically very similar to a MOM group. The Pictet/Spengler reaction with **29** gave **31d** in 80% yield under a neutral condition similarly to that with **31c** (Table 4, run 10). Conversion of **31d** to **32d** was effected in 89% yield by the two-step dehydrogenation protocol, as expected (Table 5, run 10). Dehydrogenation of **31d** attempted using only IBX or activated MnO_2 gave the same results as those obtained for **31c** (Table 5, runs 8 and 9). From these results, it appeared evident that our two-step protocol was very promising. Simultaneous deprotection of both the SEM and the Boc groups was achieved by using excess trifluoroboran-diethylether complex, giving rise to **6**-2TFA.[6]

As mentioned above, we have succeeded in synthesizing ageladine A (**6**) by featuring its biosynthetic route and by employing **20a** and **30d** as the starting materials. Although the total synthesis of **6** independently reported by Karuso et al. is almost the same as that completed by us, their reaction conditions for the Pictet/Spengler reaction using scandium trifluoromethanesulfonate (44% yield) and for the sequential dehydrogenation and deprotection using chloranil (65%) were completely different from those explored by us. Considering the reagents and chemical yield for each step, our synthetic route (the Pictet/Spengler reaction, **29**+**30d**⇒**31d**: 80%; the dehydrogenation, **31d**⇒**32d**: 89%; deprotection, **32d**⇒**6**-2TFA: 70%) is anticipated to be more efficient and practical than that reported by Karuso et al. Application of the explored synthetic scheme to the synthesis of various structural types of the congeners of **6** may be foreseen.[1b,24]

3. Conclusions

As described above, we have succeeded in exploring a novel synthetic route to 2-amino-1*H*-imidazol-4-carbaldehyde derivatives **I**, the versatile synthetic intermediates for 2-amino-1*H*-imidazole alkaloids, by featuring the reaction of *tert*-butoxycarbonylguanidine (**11a**) with 3-bromo-1,1-dimethoxymethylpropan-2-one (**8**) as a key step. Starting with *tert*-butyl 4-formyl-1*H*-imidazol-2-ylcarbamate (**20a**) or 1-Boc-2-(Boc-amino)-1*H*-imidazol-4-carbaldehyde (**21a**) thus obtained, expeditious synthesis of the representative 2-amino-1*H*-imidazole alkaloids, oroidin (**1**), hymenidin (**2**), dispacamide (**3**), monobromodispacamide (**4**), and ageladine A (**6**), was accomplished, clearly demonstrating the synthetic utility of **I**.

4. Experimental

4.1. 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 a JEOL JNM -ECX-400 (400 MHz) spectrometer. Measurements of ^{13}C NMR spectra were carried out using a JEOL JNM-ECA-400 or a JEOL JNM -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 the spots were visualized using UV light followed by coloring with phosphomolybdic acid or anisaldehyde. Silica gel 60 N (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); chloroform ($CHCl_3$); dichloromethane (CH_2Cl_2); diethylether (Et_2O); *N*,*N*-dimethylformamide (DMF); dimethyl sulfoxide (DMSO); ethyl acetate (EtOAc); ethanol (EtOH); *n*-hexane (C_6H_{14}); methanol (MeOH); tetrahydrofuran (THF); water (H_2O), di-*tert*-butyl dicarbonate (Boc_2O); nitromethane ($MeNO_2$); triethylamine (Et_3N); hydrogen chloride (HCl); potassium carbonate (K_2CO_3); sodium hydrogen carbonate ($NaHCO_3$); sodium hydroxide (NaOH); sodium carbonate (Na_2CO_3); sodium sulfate (Na_2SO_4).

*4.1.1. 3-Bromo-1,1-dimethoxymethylpropan-2-one (**8**)*[25]. To a solution of pyruvinaldehyde dimethylacetal (5.91 g, 50 mmol) in methyl acetate (250 mL) was added copper bromide (II) (23.5 g, 11 mmol) under an argon atmosphere and the mixture was refluxed for 2 h. After cooling to room temperature, an aqueous saturated $NaHCO_3$ solution (100 mL) was added to the mixture. The whole was stirred at room temperature for 10 min and filtered through a pad of Celite. An organic layer was separated, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Distillation of the residue afforded **8** (2.87 g, 29%) as a pale yellow oil. Bp: 60–63 °C (2.0 mm Hg). IR (ATR): 2945, 1751, 1137, 1062, 983 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.45 (6H, s), 4.20 (2H, s), 4.73 (1H, s). LRMS (CI^+) *m*/*z*: 197 ($M+H^+$). HRMS (CI^+) *m*/*z*: calcd for $C_5H_{10}BrO_3$ ($M+H^+$) 196.9813, found 196.9798.

*4.1.2. 2-Acetamido-4-dimethoxymethyl-1H-imidazole (**9**).* To a solution of **8** (394 mg, 2.0 mmol) in DMF (6 mL) was added **7** (607 mg, 6.0 mmol) under an argon atmosphere and the mixture was stirred at room temperature for 144 h. After concentration in vacuo, H_2O was added to the residue. The mixture was extracted with EtOAc, and the combined organic extract was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Purification of the residue by preparative TLC (SiO_2, $CHCl_3$/MeOH=20/1) afforded **9** (5.0 mg, 1%) as an amorphous solid and **10** (85.8 mg, ca. 10%) as a colorless solid. TLC analysis of the aqueous phase (H_2O and brine) obtained from washings of the combined organic extracts clearly showed that these phases contained a fairly large amount of **10**. Accordingly, the exact yield of **10** could not be estimated.[12] Compound **9**: IR (KBr): 3295, 1686, 1625, 1113, 1052 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.02 (3H, s), 3.18 (6H, s), 5.24 (1H, s), 6.65 (1H, s), 11.08 (1H, br s), 11.40 (1H, br s). LRMS (EI^+) *m*/*z*: 199 (M^+), 168, 126, 96. HRMS (EI^+) *m*/*z*: calcd for $C_8H_{13}N_3O_3$ (M^+) 199.0957, found 199.0947. Compound **10**: IR (ATR): 3348, 3228, 2924, 2854, 1695, 1531, 1460, 1366, 1308, 1234, 598 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (6H, s). LRMS (EI^+) *m*/*z*: 143 (M^+), 128, 86. HRMS (EI^+) *m*/*z*: calcd for $C_5H_9N_3O_2$ (M^+) 143.0695, found 143.0721.

*4.1.3. N-tert-Butoxycarbonylguanidine (**11a**).* This **11a** was prepared according to the reported procedure.[13] To a solution of NaOH (19.2 g, 480 mmol) in H_2O (48 mL) was added guanidine monohydrochloride (22.9 g, 240 mmol) and the aqueous solution was stirred at 0 °C for 10 min. To the mixture, a solution of Boc_2O (13.1 g, 60 mmol) in Me_2CO (200 mL) was added in one portion at 0 °C and the mixture was stirred at room temperature for 2.5 h. The Me_2CO was removed in vacuo and the residual suspension was extracted with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Recrystallization of the residue from C_6H_{14}/EtOAc afforded **11a** (9.57 g, 100%) as a white solid. Mp: 193–195 °C (from C_6H_{14}/EtOAc) (lit.[13] 196–197 °C). IR (ATR): 3405, 3312, 2975, 1601, 1534, 1309, 1139, 1066, 805, 470 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.33 (9H, s), 6.72 (4H, br s). LRMS (EI^+) *m*/*z*: 159 (M^+), 104, 86. Anal. Calcd for $C_6H_{13}N_3O_2 \cdot 0.05H_2O$: C, 45.02; H, 8.25; N, 26.25. Found: C, 44.82; H, 7.98; N, 26.49.

*4.1.4. N-Methoxycarbonylguanidine (**11b**).* Treatments of methyl chloroformate (4.64 mL, 60 mmol) with guanidine monohydrochloride (22.9 g, 240 mmol) in the same manner as described in Section 4.1.3 gave **11b** (2.80 g, 40%) as a white solid after recrystallization of the concentration residue from C_6H_{14}/EtOAc. Mp: 129–131 °C (from C_6H_{14}/EtOAc). IR (ATR): 3425, 3061, 1604, 1529, 1439, 1316, 474 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.43 (3H, s), 6.80 (4H, br s). LRMS (EI^+) *m*/*z*: 117 (M^+). HRMS (EI^+) *m*/*z* calcd for $C_3H_7N_3O_2$ (M^+) 117.0538, found 117.0574.

*4.1.5. N-(2,2,2-Trichloroethoxy)carbonylguanidine (**11c**).* Treatments of 2,2,2-trichloroethyl chloroformate (8.26 mL, 60 mmol) with guanidine monohydrochloride (22.9 g, 240 mmol) in a manner similar to that described in Section 4.1.3 gave **11c** (8.18 g, 58%) as a white solid after recrystallization of the concentration residue from C_6H_{14}/EtOAc. Mp: 220 °C (decomp.) (from C_6H_{14}/EtOAc). IR (ATR): 3420, 3320, 3085, 1631, 1598, 1525, 1299, 1151, 714, 544 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.70 (2H, s), 6.72 (2H, br s), 7.23 (2H, br s). LRMS (CI^+) *m*/*z*: 234 ($M+H^+$). Anal. Calcd for $C_4H_6Cl_3N_3O_2$: C, 20.49; H, 2.58; N, 17.92. Found: C, 20.39; H, 2.42; N, 2.42.

*4.1.6. N-Allyloxycarbonylguanidine (**11d**).* The same treatments of allyl chloroformate (6.37 mL, 60 mmol) with guanidine

monohydrochloride (22.9 g, 240 mmol) as those described in Section 4.1.3 gave **11d** (7.45 g, 87%) as a white solid after recrystallization of the concentration residue from C_6H_{14}/EtOAc. Mp: 132–134 °C (from C_6H_{14}/EtOAc). IR (ATR): 3442, 3397, 3331, 3024, 1583, 1523, 1305, 1158, 1088, 469 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 4.38 (2H, dt, J=4.9, 1.5 Hz), 5.10 (1H, dq, J=10.6, 1.5 Hz), 5.21 (1H, dq, J=16.9, 1.5 Hz), 5.84–5.93 (1H, m), 6.86 (4H, br s). LRMS (EI$^+$) m/z: 143 (M^+), 86. HRMS (EI$^+$) m/z calcd for $C_5H_9N_3O_2$ (M^+) 143.0695, found 143.0706.

*4.1.7. N-Benzyloxycarbonylguanidine (**11e**).* Similar treatments of benzyl chloroformate (8.57 mL, 60 mmol) with guanidine monohydrochloride (22.9 g, 240 mmol) to those described in Section 4.1.3 gave **11e** (11.0 g, 95%) as a white solid after recrystallization of the concentration residue from C_6H_{14}/EtOAc. Mp: 148–150 °C (from C_6H_{14}/EtOAc). IR (ATR): 3453, 3409, 3310, 3093, 1625, 1589, 1523, 1295, 1149, 1069, 494 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 4.94 (2H, s), 6.80 (4H, br s), 7.23–7.35 (5H, m). LRMS (EI$^+$) m/z: 193 (M^+), 108, 91, 86. HRMS (EI$^+$) m/z calcd for $C_9H_{11}N_3O_2$ (M^+) 193.0872, found 193.0872.

*4.1.8. tert-Butyl 2-amino-4-dimethoxymethyl-1H-imidazol-1-carboxylate (**13a**).* Table 1, run 2: to a solution of **11a** (478 mg, 3.0 mmol) in THF (3.0 mL) was added a solution of **8** (197 mg, 1.0 mmol) in THF (2.0 mL). After heating at 50 °C for 6 h, the solvent was removed in vacuo. Purification of the residue by column chromatography (SiO_2, EtOAc) afforded **13a** (159 mg, 62%) as a white solid. Mp: 134–136 °C (from EtOAc). IR (KBr): 3463, 1740, 1637, 1342, 1121, 1060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.59 (9H, s), 3.37 (6H, s), 5.27 (1H, d, J=1.2 Hz), 5.56 (2H, br s), 6.86 (1H, d, J=1.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0, 52.7, 85.0, 99.4, 109.3, 135.6, 149.4, 150.6. LRMS (EI$^+$) m/z: 257 [M^+], 226, 125, 96. Anal. Calcd for $C_{11}H_{19}N_3O_4$: C, 51.35; H, 7.44; N, 16.33. Found: C, 51.20; H, 7.33; N, 16.36.

*4.1.9. Methyl 2-amino-4-(dimethoxymethyl)-1H-imidazol-1-carboxylate (**13b**).* Table 1, run 3: treatments of **8** (197 mg, 1.0 mmol) with **11b** (351 mg, 3.0 mmol) in the same manner as described in Section 4.1.8 gave **13b** (52.2 mg, 24%) as a yellow amorphous after purification by column chromatography (SiO_2, EtOAc). IR (ATR): 3459, 3114, 1746, 1643, 1344, 1119, 1048, 981, 710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.36 (6H, s), 3.45 (3H, s), 5.26 (1H, d, J=0.9 Hz), 5.74 (2H, br s), 6.92 (1H, d, J=0.9 Hz). The ^1H NMR spectrum showed that this sample was contaminated by a minute amount (<ca. 5%) of the unidentified byproduct. ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.7, 54.2, 99.2, 109.1, 136.4, 150.3, 151.1. LRMS (CI$^+$) m/z: 216 [M+H$^+$] 184. HRMS (CI$^+$) m/z: calcd for $C_8H_{14}N_3O_4$ (M+H$^+$) 216.0984, found 216.0975.

*4.1.10. Allyl 2-amino-4-(dimethoxymethyl)-1H-imidazol-1-carboxylate (**13d**).* Table 1, run 5: treatments of **8** (197 mg, 1.0 mmol) with **11d** (429 mg, 3.0 mmol) in a manner similar to that described in Section 4.1.8 gave **13d** (57.7 mg, 24%) as a yellow oil after purification by column chromatography (SiO_2, EtOAc/$CHCl_3$=19/1). IR (ATR): 3457, 3109, 1749, 1638, 1331, 1178, 1111, 1051, 981, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.38 (6H, s), 4.83 (2H, td, J=5.8, 1.2 Hz), 5.28 (1H, d, J=1.2 Hz), 5.37 (1H, qd, J=10.4, 1.2 Hz), 5.44 (1H, qd, J=17.1, 1.2 Hz), 5.81 (2H, br s), 5.93–6.03 (1H, m), 6.95 (1H, d, J=1.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.7, 68.1, 99.2, 109.0, 120.1, 130.6, 136.4, 150.4, 150.5. LRMS (CI$^+$) m/z: 242 [M+H$^+$], 210. HRMS (CI$^+$) m/z: calcd for $C_{10}H_{16}N_3O_4$ (M+H$^+$) 242.1141, found 242.1159.

*4.1.11. Benzyl 2-amino-4-(dimethoxymethyl)-1H-imidazol-1-carboxylate (**13e**).* Table 1, run 6: the same treatments of **8** (197 mg, 1.0 mmol) with **11e** (580 mg, 3.0 mmol) as those described in Section 4.1.8 gave **13e** (108 mg, 37%) as a pale yellow solid after purification by column chromatography (SiO_2, EtOAc/$CHCl_3$=19/1). Mp: 132 °C (decomp.) (from C_6H_{14}/EtOAc). IR (ATR): 3467, 3034, 1742, 1402, 1339, 1249, 1117, 1060, 983, 730, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.35 (6H, s), 5.26 (1H, d, J=1.2 Hz), 5.35 (2H, s), 5.79 (2H, br s), 6.93 (1H, d, J=1.2 Hz), 7.40–7.43 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.7, 69.3, 99.2, 109.0, 128.6, 128.8, 129.0, 134.2, 136.4, 150.50, 150.53. LRMS (EI$^+$) m/z: 291 [M^+], 260, 216, 91. HRMS (EI$^+$) m/z: calcd for $C_{14}H_{17}N_3O_4$ (M^+) 291.1219, found 291.1194. Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 57.72; H, 5.88; N, 14.43. Found: C, 57.59; H, 5.76; N, 14.23.

*4.1.12. tert-Butyl 2-amino-4-phenyl-1H-imidazol-1-carboxylate (**15**).* To a solution of **11a** (239 mg, 1.5 mmol) in DMF (2.0 mL) was added a solution of **14** (99.5 mg, 0.5 mmol) in DMF (1.0 mL). After stirring at room temperature for 3 days, the solvent was removed in vacuo. Separation of the residue by column chromatography (SiO_2, EtOAc) afforded **15** (28.3 mg, 22%) as a white solid and **16** (34.5 mg, 37%) as a pale yellow amorphous solid. Compound **15**: mp: 134–136 °C (from EtOAc). IR (KBr): 3463, 1740, 1637, 1342, 1121, 1060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.59 (9H, s), 3.37 (6H, s), 5.27 (1H, d, J=1.2 Hz), 5.56 (2H, br s), 6.86 (1H, d, J=1.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0, 52.7, 85.0, 99.4, 109.3, 135.6, 149.4, 150.6. LRMS (EI$^+$) m/z: 257 [M^+], 226, 125, 96. Anal. Calcd for $C_{11}H_{19}N_3O_4$: C, 51.35; H, 7.44; N, 16.33. Found: C, 51.20; H, 7.33; N, 16.36. Compound **16**: IR (ATR): 3396, 2928, 1730, 1689, 1598, 1371, 1352, 1260, 1147, 1117, 758, 705, 688 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.67 (9H, s), 5.07 (2H, d, J=2.3 Hz), 7.16 (1H, s), 7.37 (2H, t, J=7.9 Hz), 7.57 (3H, t, J=7.3 Hz), 7.63 (1H, t, J=7.6 Hz), 7.77 (2H, d, J=7.6 Hz), 8.08 (2H, d, J=7.6 Hz). LRMS (EI$^+$) m/z: 377 [M^+], 172. HRMS (ESI$^+$) m/z: calcd for $C_{22}H_{24}N_3O_3$ (M+H$^+$) 378.18177, found 378.18258.

*4.1.13. 2-Acetamido-4-phenyl-1H-imidazole (**17**).* To a solution of **7** (303 mg, 3.0 mmol) in DMF (3.0 mL) was added **14** (199 mg, 1.0 mmol). After stirring at room temperature for 3 days, the solvent was removed in vacuo. Purification of the residue by column chromatography (SiO_2, EtOAc) and further recrystallization from MeOH afforded **17** (62.2 mg, 31%) as a light green solid. Mp: 229–231 °C (from MeOH) (lit.[8c] mp: 230–231 °C). ^1H NMR (400 MHz, DMSO-d_6): δ 2.06 (3H, s), 7.15 (1H, t, J=7.3 Hz), 7.24 (1H, s), 7.31 (2H, t, J=7.3 Hz), 7.69 (2H, d, J=7.3 Hz). LRMS (EI$^+$) m/z: 201 [M^+], 159.

*4.1.14. tert-Butyl 5-(dimethoxymethyl)-1H-imidazol-2-ylcarbamate (**12a**).* To a solution of **20a** (100 mg, 0.47 mmol) in MeOH (3.0 mL) were added trimethoxymethane (0.103 mL, 0.95 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg) under an argon atmosphere, and the mixture was heated at reflux for 2 h. After being cooled to room temperature, Et_3N (0.05 mL) was added to the mixture and the whole was concentrated in vacuo. Purification of the residue by column chromatography (NH–SiO_2, C_6H_{14}/EtOAc=1/1) afforded **12a** (106 mg, 87%) as a colorless amorphous solid. IR (KBr): 3272, 2979, 1717, 1621, 1287, 1254, 1165, 1070, 1046 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.54 (9H, s), 3.34 (6H, s), 5.45 (1H, d, J=0.6 Hz), 6.75 (1H, br s), 10.18 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 52.3, 81.4, 98.0, 128.8, 137.9, 143.0, 153.1. LRMS (EI$^+$) m/z: 257 [M^+], 226, 201, 170, 152, 111, 125, 96, 57. HRMS (EI$^+$) m/z: calcd for $C_{13}H_{19}N_3O_4$ (M^+) 257.1376, found 257.1355.

*4.1.15. tert-Butyl 4-phenyl-1H-imidazol-2-ylcarbamate (**18**).* To a solution of **15** (3.60 g, 14 mmol) and Boc_2O (3.03 g, 14 mmol) in THF (60 mL) was added sodium 1,1,1,3,3,3-hexamethyldisilazide (NaHMDS) (1.0 mol/L solution in THF, 29 mL, 29 mmol) at room temperature under an argon atmosphere, and the mixture was stirred for 10 min. After saturated aqueous ammonium chloride was added at 0 °C, the mixture was extracted with EtOAc. The organic extracts were combined, washed with 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=6/1) afforded *tert*-butyl 2-*tert*-butoxycarbonamido-4-phenyl-1*H*-imidazol-1-carboxylate (3.87 g, 77%) as a pale yellow amorphous solid. IR (ATR): 3394, 2983, 1755, 1718, 1590, 1546, 1365, 1246, 1146 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.49 (9H, s), 1.65 (9H, s), 7.26 (1H, s), 7.27–7.28 (1H, m), 7.35 (2H, t, J=7.9 Hz), 7.81–7.83 (2H, m), 9.15 (1H, br s). LRMS (CI^+) m/z: 360 [$M+H^+$], 304, 260, 248, 204. HRMS (CI^+) m/z: calcd for $C_{19}H_{26}N_3O_4$ ($M+H^+$) 360.1918, found 360.1923. To a solution of the carboxylate (3.79 g, 11 mmol) in MeOH (50 mL) was added K_2CO_3 (1.45 g, 11 mmol) and the mixture was stirred at room temperature for 3 h. The mixture was diluted with H_2O and extracted with EtOAc. The organic extracts were combined, washed with 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=4/1) afforded **18** (2.69 g, 99%) as a pale yellow amorphous solid. IR (ATR): 3397, 2977, 1701, 1611, 1246, 1153, 758, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (9H, s), 7.03 (1H, s), 7.22 (1H, t, J=7.4 Hz), 7.35 (2H, t, J=7.4 Hz), 7.41–7.85 (2H, m), 10.32 (1H, br s), 10.52 (1H, br s). LRMS (CI^+) m/z: 260 [$M+H^+$], 204, 186. HRMS (CI^+) m/z: calcd for $C_{14}H_{18}N_3O_2$ ($M+H^+$) 260.1399, found 260.1376.

*4.1.16. 1-Acetyl-2-amino-4-phenyl-1H-imidazole (**19**).* To a solution of **15** (300 mg, 1.2 mmol) in MeOH (3.0 mL) was added an EtOAc solution of HCl (4 mol/mL, 3.0 mL, 12 mmol). The mixture was stirred at room temperature for 3 h and then concentrated in vacuo. Trituration of the residue with EtOAc afforded 2-amino-4-phenyl-1*H*-imidazole hydrochloride (195 mg, 86%) as a colorless solid. ^1H NMR (400 MHz, DMSO-d_6): δ 7.32 (1H, t, J=7.3 Hz), 7.39 (1H, s), 7.41–7.45 (4H, m), 7.65–7.67 (2H, m), 12.23 (1H, br s), 12.91 (1H, br s). To a suspension of the hydrochloride (50 mg, 0.26 mmol) in CH_2Cl_2 (5.0 mL) were added Et_3N (0.018 mL, 0.26 mmol) and acetyl chloride (0.071 mL, 0.51 mmol) at 0 °C under an argon atmosphere. After stirring at 0 °C for 1 h, diluted with EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Trituration of the residue with C_6H_{14} afforded **19** (49.7 mg, 96%) as a white solid. Mp: 170 °C (decomp.) (from C_6H_{14}/EtOAc). IR (ATR): 3415, 3107, 1710, 1649, 1414, 1373, 1329, 1243, 1132, 1070, 965, 701, 660 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.55 (3H, s), 6.04 (2H, br s), 7.03 (1H, s), 7.27–7.30 (1H, m), 7.36–7.40 (2H, m), 7.69–7.72 (2H, m). LRMS (EI^+) m/z: 201 [M^+], 159, 104. HRMS (EI^+) m/z: calcd for $C_{11}H_{11}N_3O$ (M^+) 201.0902, found 201.0913.

*4.1.17. tert-Butyl 4-formyl-1H-imidazol-2-ylcarbamate (**20a**).* To a solution of **13a** (1.00 g, 3.9 mmol) and Boc_2O (849 mg, 3.9 mmol) in THF (10 mL), NaHMDS (1.0 mol/L solution in THF, 8.2 mL, 8.2 mmol) was added at room temperature, and the mixture was stirred for 10 min. After an aqueous saturated ammonium chloride solution was added at 0 °C, the mixture was extracted with EtOAc. The organic extracts were combined, washed with 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=1/1) afforded *tert*-butyl 2-*tert*-butoxycarbonamido-4-dimethoxymethyl-1*H*-imidazol-1-carboxylate (1.25 g, 90%) as a yellow solid. Mp: 101–103 °C (from C_6H_{14}/EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 1.52 (9H, s), 1.61 (9H, s), 3.38 (6H, s), 5.39 (1H, d, J=0.9 Hz), 7.06 (1H, d, J=0.9 Hz), 9.02 (1H, br s). LRMS (FAB^+) m/z: 358 [$M+H^+$]. HRMS (FAB^+) m/z: calcd for $C_{16}H_{28}N_3O_6$ ($M+H^+$) 358.1978, found 358.2018. To a solution of the carboxylate (2.03 g, 5.7 mmol) in Me_2O (30 mL) and H_2O (20 mL), pyridinium *p*-toluenesulfonate (143 mg, 0.57 mmol) was added, and the mixture was stirred at room temperature overnight. The mixture was diluted with brine and extracted with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Recrystallization of the residue from C_6H_{14}/EtOAc gave **20a** (1.17 g, 98%, 88% from **13a**) as a pale yellow solid. Mp: 155–157 °C (decomp.) (from C_6H_{14}/EtOAc). IR (KBr): 3409, 1711, 1648, 1604, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.58 (9H, s), 7.49 (1H, s), 9.59 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 82.6, 128.8, 137.6, 147.7, 153.1, 176.9. LRMS (EI^+) m/z: 211 [M^+], 155, 111. Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20, N, 19.89. Found: C, 51.07; H, 6.11, N, 19.93.

*4.1.18. Benzyl 4-formyl-1H-imidazol-2-ylcarbamate (**20b**).* Treatments of **13a** (1.0 g, 3.9 mmol) with benzyl chloroformate (0.61 mL, 4.3 mmol) and NaHMDS (1.0 mol/L in THF solution, 8.2 mL, 8.2 mmol) in the same manner as described in Section 4.1.17 gave *tert*-butyl 2-benzyloxycarbonamido-4-dimethoxymethyl-1*H*-imidazol-1-carboxylate (719 mg, 47%) as a pale yellow after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=1/1). ^1H NMR (400 MHz, $CDCl_3$): δ 1.59 (9H, s), 3.38 (6H, s), 5.24 (2H, s), 5.40 (1H, d, J=0.9 Hz), 7.07 (1H, d, J=0.9 Hz), 7.33–7.44 (5H, m), 9.21 (1H, br s). LRMS (CI^+) m/z: 392 [$M+H^+$]. HRMS (CI^+) m/z: calcd for $C_{19}H_{26}N_3O_6$ ($M+H^+$) 392.1822, found 392.1779. Subsequent treatments of the carboxylate (700 mg, 1.8 mmol) with pyridinium *p*-toluenesulfonate (45.0 mg, 0.18 mmol) in a manner similar to that described in Section 4.1.17 gave **20b** (381 mg, 87%, 41% from **13a**) as a pale yellow powder after recrystallization from C_6H_{14}/EtOAc. Mp: 154–156 °C (from C_6H_{14}/EtOAc). IR (KBr): 2805, 1738, 1667, 1608, 1541, 1239, 1173 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.28 (2H, s), 7.36–7.42 (6H, m), 9.51 (1H, s), 10.73 (1H, br s), 12.05 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.1, 128.3, 128.8, 128.9, 135.2, 137.6, 147.1, 153.9, 177.0. LRMS (EI^+) m/z: 245 [M^+], 91. HRMS (EI^+) m/z: calcd for $C_{12}H_{11}N_3O_3$ (M^+) 245.0800, found 245.0845.

*4.1.19. Methyl (4-formyl-1H-imidazol-2-yl)carbamate (**20c**).* The same treatments of **13a** (100 mg, 0.39 mmol) with methyl chloroformate (0.03 mL, 0.39 mmol) and NaHMDS (1.0 mol/L in THF solution, 0.82 mL, 0.82 mmol) as those described in Section 4.1.17 gave *tert*-butyl 2-methoxycarbonamido-4-dimethoxymethyl-1*H*-imidazol-1-carboxylate (53.6 mg, 44%) as a pale yellow oil after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=1/1). ^1H NMR (400 MHz, $CDCl_3$): δ 1.60 (9H, s), 3.38 (6H, s), 3.82 (3H, s), 5.39 (1H, d, J=0.9 Hz), 7.08 (1H, d, J=0.9 Hz), 9.12 (1H, br s). LRMS (CI^+) m/z: 316 [$M+H^+$]. HRMS (CI^+) m/z: calcd for $C_{13}H_{22}N_3O_6$ ($M+H^+$) 316.3342, found 316.1472. Subsequent treatments of the carboxylate (47.0 mg, 0.15 mmol) with pyridinium *p*-toluenesulfonate (3.7 mg, 0.015 mmol) in a manner similar to that described in Section 4.1.17 gave **20c** (5.3 mg, 21%, 9% from **13a**) as a white powder after purification by column chromatography (SiO_2, EtOAc/MeOH=10/1). Mp: 215 °C (decomp.) (from C_6H_{14}/EtOAc). IR (ATR): 3284, 1684, 1637, 1442, 1243, 1085, 758, 630 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.70 (3H, s), 7.71 (1H, s), 9.57 (1H, s), 10.97 (1H, br s), 12.06 (1H, br s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.5, 125.8, 138.0, 143.2, 183.0. LRMS (EI^+) m/z: 169 [M^+], 136, 124, 110, 96. HRMS (EI^+) m/z: calcd for $C_6H_7N_3O_3$ (M^+) 169.0487, found 169.0445.

*4.1.20. Allyl 4-formyl-1H-imidazol-2-ylcarbamate (**20d**).* Similar treatments of **13a** (100 mg, 0.39 mmol) with allyl chloroformate (0.04 mL, 0.39 mmol) and NaHMDS (1.0 mol/L in THF solution, 0.82 mL, 0.82 mmol) to those described in Section 4.1.17 gave *tert*-butyl 2-allyloxycarbonamido-4-dimethoxymethyl-1*H*-imidazol-1-carboxylate (90.8 mg, 68%) as a pale yellow oil after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=1/1). ^1H NMR (400 MHz, $CDCl_3$): δ 1.60 (9H, s), 3.38 (6H, s), 4.70 (2H, dt, J=5.8, 1.2 Hz), 5.26 (1H, dq, J=10.5, 1.2 Hz), 5.39 (1H, d, J=0.9 Hz), 5.40 (1H, dq, J=17.1, 1.5 Hz), 5.92–6.01 (1H, m), 7.08 (1H, d, J=0.9 Hz), 9.16 (1H, br s). LRMS (CI^+) m/z: 342 [$M+H^+$]. HRMS (CI^+) m/z: calcd for $C_{15}H_{24}N_3O_6$ ($M+H^+$) 342.1665, Found 342.1620. Subsequent treatments of the carboxylate (80.0 mg, 0.23 mmol) with pyridinium *p*-toluenesulfonate (5.9 mg,

0.023 mmol) in the same manner as described in Section 4.1.17 gave **20d** (34.1 mg, 75%, 51% from **13a**) as a white solid after purification by column chromatography (SiO_2, EtOAc). Mp: 129–131 °C (from C_6H_{14}/EtOAc). IR (ATR) 3283, 2759, 1720, 1662, 1618, 1534, 1247, 1168, 1082, 762, 642 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.77 (2H, d, J=5.8 Hz), 5.34 (1H, dd, J=10.4, 1.2 Hz), 5.42 (1H, dd, J=17.4, 1.2 Hz), 5.95–6.05 (1H, m), 7.53 (1H, s), 9.58 (1H, s), 10.74 (1H, br s), 12.01 (1H, br s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 65.6, 118.0, 128.7, 132.7, 135.8, 143.6, 153.5, 182.2. LRMS (EI^+) m/z: 195 [M^+], 150, 136, 123, 110. HRMS (EI^+) m/z: calcd for $C_8H_9N_3O_3$ (M^+) 195.0644, found 195.0645.

*4.1.21. N-(4-Formyl-1H-imidazol-2-yl)acetamide (**20e**).* Treatments of **13a** (1.0 g, 3.9 mmol) with acetic anhydride (0.74 mL, 7.8 mmol) and NaHMDS (1.0 mol/L in THF solution, 12 mL, 12 mmol) in the same manner as described in Section 4.1.17 gave *tert*-butyl 2-acetamido-4-dimethoxymethyl-1*H*-imidazol-1-carboxylate (603 mg, 52%) as a yellow oil after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=2/3). ^1H NMR (400 MHz, $CDCl_3$): δ 1.61 (9H, s), 2.45 (3H, s), 3.38 (6H, s), 5.35 (1H, d, J=0.9 Hz), 7.10 (1H, d, J=0.9 Hz), 9.56 (1H, br s). LRMS (CI^+) m/z: 300 [$M+H^+$]. HRMS (CI^+) m/z: calcd for $C_{13}H_{22}N_3O_5$ ($M+H^+$) 300.3348, found 300.1593. Subsequent treatments of the carboxylate (570 mg, 1.9 mmol) with pyridinium *p*-toluenesulfonate (47.7 mg, 0.19 mmol) in a manner similar to that described in Section 4.1.17 gave **20e** (105 mg, 36%, 19% from **13a**) as a pale yellow powder after recrystallization from C_6H_{14}/EtOAc. Mp: 210 °C (decomp.) (from C_6H_{14}/EtOAc). IR (KBr): 3244, 1701, 1671, 1617, 1175 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.33 (3H, s), 7.56 (1H, s), 9.62 (1H, s), 11.35 (1H, br s), 11.95 (1H, br s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.9, 125.3, 137.7, 142.9, 169.3, 183.9. LRMS (EI^+) m/z: 153 [M^+], 111. HRMS (EI^+) m/z: calcd for $C_6H_7N_3O_2$ (M^+) 153.0538, found 153.0510.

*4.1.22. tert-Butyl 2-tert-butoxycarbonamido-4-formyl-1H-imidazol-1-carboxylate (**21a**).* To a solution of **20a** (500 mg, 2.4 mmol) in THF (10 mL), a solution of Boc_2O (620 mg, 2.8 mmol) in MeCN (8.0 mL) and Et_3N (0.33 mL, 2.4 mmol) were added and the mixture was stirred at room temperature for 8 h. The mixture was diluted with EtOAc, filtered, and then concentrated in vacuo. Trituration of the residue with C_6H_{14} followed by filtration and drying in vacuo gave **21a** (719 mg, 98%) as a white powder. Mp: 112–114 °C (from C_6H_{14}/EtOAc). IR (KBr) 1755, 1697, 1532, 1305, 1152 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.55 (9H, s), 1.64 (9H, s), 7.70 (1H, s), 9.10 (1H, br s), 9.92 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8, 28.1, 82.5, 88.5, 117.2, 138.1, 142.8, 148.7, 149.6, 187.2. LRMS (EI^+) m/z: 311 [M^+], 211, 155, 111. Anal. Calcd for $C_{21}H_{13}N_3O_5$: C, 54.01; H, 6.80; N, 13.50. Found: C, 53.76; H, 6.63; N, 13.70.

*4.1.23. tert-Butyl 2-(benzyloxycarbonylamino)-4-formyl-1H-imidazol-1-carboxylate (**21b**).* Treatments of **20b** (56.4 mg, 0.23 mmol) with Boc_2O (60.2 mg, 0.28 mmol) and Et_3N (0.032 mL, 0.23 mmol) in the same manner as described in Section 4.1.22 gave **21b** (62.3 mg, 78%) as a pale yellow solid after purification by column chromatography (SiO_2, C_6H_{14}/EtOAc=1/1). Mp: 100–102 °C (from C_6H_{14}/EtOAc). IR (ATR): 3336, 2815, 1719, 1663, 1617, 1537, 1243, 1214, 1174, 734, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.62 (9H, s), 5.27 (2H, s), 7.35–7.46 (5H, m), 7.71 (1H, s), 9.28 (1H, br s), 9.93 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8, 68.1, 88.8, 117.7, 128.3, 128.6, 128.8, 135.3, 138.0, 142.2, 148.6, 150.6, 187.0. LRMS (ESI^+) m/z: 346 [$M+H^+$], 290, 246. HRMS (ESI^+) m/z: calcd for $C_{17}H_{20}N_3O_5$ ($M+H^+$) 346.14030, found 346.13974.

*4.1.24. 2-[2-(1-Phenyl-1H-tetrazol-5-ylsulfonyl)ethyl]isoindolin-1,3-dione (**23**).* A mixture of **22** (1.78 g, 10 mmol), *N*-(2-bromoethyl) phthalimide (2.54 g, 10 mmol), and K_2CO_3 (2.07 g, 15 mmol) in Me_2CO (100 mL) was heated at reflux for 3 h under an argon atmosphere. The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc, and the EtOAc solution was washed with H_2O and brine, filtered, and then concentrated in vacuo. To a solution of the residue in CH_2Cl_2 (100 mL) were added $NaHCO_3$ (1.79 g, 21 mmol) and *m*-chloroperbenzoic acid (*m*-CPBA) (purity 65%) (5.65 g, 21 mmol), and the mixture was stirred overnight at room temperature. The mixture was diluted with $CHCl_3$, and the $CHCl_3$ solution was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Recrystallization of the residue from C_6H_{14}/EtOAc gave **23** (2.94 g, 79%) as a white powder. Mp: 171.0–173.0 °C (from C_6H_{14}/EtOAc). IR (ATR): 1709, 1348, 1149, 763, 719, 687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.14–4.17 (2H, m), 4.33–4.36 (2H, m), 7.55–7.63 (3H, m), 7.67–7.70 (2H, m), 7.73 (2H, dd, J=5.5, 3.1 Hz), 7.83 (2H, dd, J=5.5, 3.1 Hz). LRMS (ESI^+) m/z: 384 [$M+H^+$]. HRMS (ESI^+) m/z: calcd for $C_{17}H_{14}N_5O_4S$ ($M+H^+$) 384.07665, found 384.07681.

*4.1.25. (E)-tert-Butyl 2-(tert-butoxycarbonamido)-4-[3-(1,3-dioxoisoindolin-2-yl)prop-1-enyl]-1H-imidazol-1-carboxylate (**24**).* Table 3, run 8: to a solution of **21a** (150 mg, 0.48 mmol) and **23** (123 mg, 0.32 mmol) in THF (2.0 mL) was added NaHMDS (1.0 mol/L THF solution, 0.80 mL, 0.80 mmol) dropwise at −78 °C under an argon atmosphere. The mixture was stirred at the same temperature for 30 min, and the reaction was quenched by adding H_2O. The reaction mixture was extracted with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Separation of the residue by column chromatography (SiO_2, C_6H_{14}/EtOAc=3/1 to 5/2) afforded **24** (104 mg, 69%) as a colorless amorphous solid and the mixture of (*Z*)-isomer of **24** and **21a**.The chemical yield of the (*Z*)-isomer of **24** could be estimated as 10% by the ^1H NMR spectrum of this mixture. Compound **24**: IR (ATR): 1709, 1530, 1367, 1140, 749, 724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.50 (9H, s), 1.59 (9H, s), 4.40 (2H, d, J=5.8 Hz), 6.37 (1H, d, J=15.9 Hz), 6.45 (1H, dt, J=15.9, 5.8 Hz), 6.87 (1H, s), 7.70 (2H, dd, J=5.5, 3.1 Hz), 7.84 (2H, dd, J=5.5, 3.1 Hz), 9.12 (1H, br s). LRMS (FAB^+) m/z: 469 [$M+H^+$]. HRMS (FAB^+) m/z: calcd for $C_{24}H_{29}N_4O_6$ ($M+H^+$) 469.2087, Found 469.2071. (*Z*)-**24**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.53 (9H, s), 1.64 (9H, s), 4.83 (2H, dd, J=6.4, 1.8 Hz), 5.60 (1H, dt, J=11.6, 6.4 Hz), 6.36 (1H, dq, J=11.6, 1.8 Hz), 7.16 (1H, s), 7.71 (2H, dd, J=5.5, 2.9 Hz), 7.85 (2H, dd, J=5.5, 2.9 Hz), 9.11 (1H, br s).

*4.1.26. (E)-tert-Butyl [4-(3-aminoprop-1-enyl)-1H-imidazol-2-yl] carbamate (**25**).* To a solution of **22** (351 mg, 0.75 mmol) in EtOH (20 mL) was added hydrazine (0.12 mL, 3.8 mmol), and the mixture was heated at 50 °C for 2 h. After cooling to room temperature, the mixture was filtered and the residue was washed with $CHCl_3$. The organic layers were combined and concentrated in vacuo. Purification of the residue by column chromatography (NH–SiO_2, EtOAc, then EtOAc/MeOH=10/1) gave **25** (164 mg, 92%) as a pale yellow amorphous solid. ^1H NMR (400 MHz, $CDCl_3$): δ 1.45 (9H, s), 3.22 (2H, dd, J=5.8, 1.2 Hz), 6.07 (1H, dt, J=15.6, 5.8 Hz), 6.22 (1H, dd, J=15.6, 1.2 Hz), 6.64 (1H, s). LRMS (FAB^+) m/z: 239 [$M+H^+$]. HRMS (FAB^+) m/z: calcd for $C_{11}H_{19}N_4O_2$ 239.1508, found 239.1543.

*4.1.27. (E)-tert-Butyl [4-(3-(4,5-dibromo-1H-pyrrole-2-carboxamido) prop-1-enyl)-1H-imidazol-2-yl]carbamate (**26a**).* To a solution of **25** (142 mg, 0.60 mmol) and 4,5-dibromo-2-trichloroacetylpyrrole[17] (221 mg, 0.60 mmol) in DMF (3.0 mL) was added Na_2CO_3 (94.8 mg, 0.89 mmol) under an argon atmosphere, and the mixture was stirred overnight at room temperature. The reaction was quenched by adding ice-H_2O, 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. Trituration of the residue with C_6H_{14}/$CHCl_3$ (1/1) and subsequent filtration gave a solid. The solid was dissolved in $CHCl_3$/MeOH and the solution was filtered through a pad of NH–SiO_2.

Concentration of the filtrate afforded **26a** (230 mg, 79%) as a pale yellow powder. Mp: 215–217 °C (decomp.) (from C_6H_{14}/EtOAc). IR (ATR): 3238, 1705, 1597, 1521, 1409, 1247, 1155, 651, 618 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.44 (9H, s), 3.91 (2H, t, J=5.2 Hz), 6.02 (1H, dt, J=15.6, 5.8 Hz), 6.26 (1H, d, J=15.6 Hz), 6.71 (1H, s), 6.96 (1H, s), 8.31 (1H, t, J=5.2 Hz), 10.24 (1H, br s), 11.22 (1H, br s), 12.66 (1H, br s). LRMS (FAB$^+$) m/z: 488 [M+H$^+$]. HRMS (ESI$^+$) m/z: calcd for $C_{16}H_{20}Br_2N_5O_3$ (M+H$^+$) 487.99329, found 487.99366.

*4.1.28. (E)-tert-Butyl [4-(3-(4-bromo-1H-pyrrole-2-carboxamido) prop-1-enyl)-1H-imidazol-2-yl]carbamate (**26b**).* Treatments of **25** (137 mg, 0.58 mmol) with 4-bromo-2-trichloroacetylpyrrole[18] (176 mg, 0.60 mmol) in the same manner as described in Section 4.1.27 gave **26b** (195 mg, 83%) as a pale yellow powder after concentration of the solution obtained by filtration through a pad of NH–SiO_2. Mp: 205–207 °C (decomp.) (from C_6H_{14}/EtOAc). IR (ATR): 3189, 1642, 1612, 1511, 1292, 1242, 1155, 774, 602 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.44 (9H, s), 3.91 (2H, t, J=5.8 Hz), 6.03 (1H, dt, J=15.6, 5.8 Hz), 6.24 (1H, d, J=15.6 Hz), 6.71 (1H, s), 6.87–6.88 (1H, m), 6.95–6.96 (1H, m), 8.29 (1H, t, J=5.8 Hz), 10.22 (1H, br s), 11.23 (1H, br s), 12.80 (1H, br s). LRMS (ESI$^+$) m/z: 410 [M+H$^+$]. HRMS (ESI$^+$) m/z: calcd for $C_{16}H_{21}BrN_5O_3$ (M+H$^+$) 410.08278, found 410.07817.

*4.1.29. 2-Amino-4-[3-(4,5-dibromo-1H-pyrole-2-carboxamido)prop-1-enyl]-1H-imidazole (Oroidin) (**1**)-**26a**.* Compound **26a** (70.0 mg, 0.14 mmol) in 20% HCl/EtOH (5.0 mL) was stirred at room temperature for 1 h. After being diluted with EtOH, the ethanolic solution was filtered. The filtrate was concentrated in vacuo. Trituration of the residue with EtOAc followed by filtration and drying in vacuo gave **1** (56.0 mg, 98%) as a pale yellow powder. Mp: 218–220 °C (decomp.) (from MeOH/EtOAc) (lit.[8c] mp: 202–205 °C). IR (ATR): 3139, 1665, 1608, 1561, 1514, 1417, 1321, 1232, 957, 761 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.94 (2H, t, J=4.9 Hz), 6.13 (1H, dt, J=16.2, 4.9 Hz), 6.20 (1H, d, J=16.2 Hz), 6.89 (1H, s), 6.97 (1H, s), 7.45 (2H, s), 8.52 (1H, br s), 11.87 (1H, br s), 12.50 (1H, br s), 12.76 (1H, br s). ^1H NMR spectra was identical with that reported.[8a] ^{13}C NMR (100 MHz, DMSO-d_6): δ 39.8, 97.9, 104.6, 111.0, 113.0, 116.2, 124.7, 126.8, 128.0, 147.5, 158.7. LRMS (ESI$^+$) m/z: 388 [M+H$^+$]. HRMS (ESI$^+$) m/z: calcd for $C_{11}H_{12}Br_2N_5O$ (M+H$^+$) 387.94086, found 387.93736.

*4.1.30. 2-Amino-4-[3-(4-bromo-1H-pyrole-2-carboxamido)prop-1-enyl]-1H-imidazole (hymenidin) (**2**).* Treatments of **26b** (29.2 mg, 0.071 mmol) in a manner similar to that described in Section 4.1.29 gave **2** (24.4 mg, 99%) as a light brown amorphous solid after sequential trituration, filtration, and drying in vacuo. IR (ATR): 3134, 1667, 1562, 1520, 1425, 1384, 1326, 1218, 1109, 956, 920, 758 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 4.01 (2H, dd, J=5.4, 1.5 Hz), 6.07(1H, dt, J=16.0, 5.4 Hz), 6.26 (1H, d, J=16.0 Hz), 6.70 (1H, s), 6.77 (1H, d, J=1.5 Hz), 6.77 (1H, d, J=1.5 Hz). IR and ^1H NMR spectra were almost identical with that reported.[3] ^{13}C NMR (100 MHz, CD_3OD): δ 41.6, 97.5, 111.8, 113.5, 117.5, 123.0, 126.9, 127.3, 128.1, 149.1, 162.4. LRMS (ESI$^+$) m/z: 310 [M+H$^+$]. HRMS (ESI$^+$) m/z: calcd for $C_{11}H_{13}BrN_5O$ (M+H$^+$) 310.03035, found 310.002688.

*4.1.31. 4-(3-Aminopropyl)-1H-imidazol-2-amine 2HCl (**27**).* A suspension of **24** (900 mg, 1.9 mmol) and 10% Pd/C (440 mg) in EtOH (25 mL) was stirred at 50 °C for 13 h under a hydrogen atmosphere (4 kg/cm^2). 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=1/1, then EtOAc) to give a mixture of *tert*-butyl 2-*tert*-butoxycarbonamido-4-[3-(1,3-dioxoisoindolin-2-yl)propyl]-1*H*-imidazol-1-carboxylate and *tert*-butyl 4-[(3-(1,3-dioxoisoindolin-2-yl)propyl)-1*H*-imidazol-2-yl]carbamate (721 mg, 10: 7 calculated by ^1H NMR) as a pale yellow amorphous solid. Di-Boc derivative: ^1H NMR (400 MHz, $CDCl_3$): δ 1.51 (9H, s), 1.61 (9H, s), 1.99–2.06 (2H, m), 2.58 (2H, t, J=7.6 Hz), 3.76 (2H, t, J=7.0 Hz), 6.77 (1H, s), 7.69–7.73 (2H, m), 7.81–7.84 (2H, m), 9.08 (1H,s). Mono-Boc derivative: ^1H NMR (400 MHz, $CDCl_3$): δ 1.53 (9H, s), 1.98–2.06 (2H, m), 2.61 (2H, t, J=7.3 Hz), 3.76 (2H, t, J=6.7 Hz), 6.49 (1H, s), 7.69–7.72 (2H, m), 7.82–7.84 (2H, m). To a solution of the mixture in EtOH (50 mL) was added anhydrous hydrazine (0.301 mL, 9.6 mmol), and the mixture was stirred at 50 °C for 6 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (NH–SiO_2, EtOAc/MeOH=5/1) to afford *tert*-butyl [4-(3-aminopropyl)-1*H*-imidazol-2-yl]carbamate (375 mg, 81%, from **24**) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.51 (9H, s), 1.72–1.79 (2H, m), 2.59 (2H, t, J=7.6 Hz), 2.76 (2H, t, J=6.9 Hz), 6.43 (1H, d, J=0.9 Hz). LRMS (ESI$^+$) m/z: 241 [M+H$^+$]. A solution of the carbamate (223 mg, 0.93 mmol) in 20% HCl/EtOH (10 mL) was stirred at room temperature for 3 h. The precipitates appeared were collected by filtration, washed with EtOH, and dried in vacuo to afford **27** (157 mg, 79%) as a white powder. Mp: 208–210 °C (from EtOH). IR (ATR): 2959, 1665, 1465, 936, 788, 463 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.78–1.85 (2H, m), 2.51 (2H, t, J=7.8 Hz), 2.73–2.77 (2H, m), 6.62 (1H, s), 7.36 (2H, s), 8.10 (3H, s), 11.67 (1H, s), 12.20 (1H, s). LRMS (ESI$^+$) m/z: 141 [M+H$^+$]. HRMS (ESI$^+$) m/z: calcd for $C_6H_{13}N_4$ (M+H$^+$) 141.11402, found 141.11490.

*4.1.32. (E)-tert-Butyl 3-(2-amino-5-oxo-1H-imidazol-4(5H)-ylidene) propylcarbamate (**28**).* To a solution of **27** (50 mg, 0.24 mmol) in DMSO (2.0 mL) was added tetra-*n*-butylammonium tribromide (113 mg, 0.24 mmol), and the mixture was stirred at room temperature for 1.5 h. Ether (5.0 mL) was added to the reaction mixture and the whole was stirred for 5 min. The ethereal layer was removed by decantation. The same sequential operations were repeated twice. The residue was purified by column chromatography (NH–SiO_2, CH_2Cl_2/MeOH=2/1to 3/2) to give crude (*E*)-2-amino-4-(3-aminopropyliden)-1*H*-imidazol-5(4*H*)-one as a yellow amorphous solid. This product was found to be contaminated with a small amount of some unidentified products by ^1H NMR analysis. To a solution of the crude 1*H*-imidazol-5(4*H*)-one derivative in MeOH (3.0 mL) was added Boc_2O (51.3 mg, 0.24 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography (NH–SiO_2, CH_2Cl_2/MeOH=5/1) to give **28** (24.1 mg, 40%) as a white amorphous solid. IR (ATR): 3320, 3137, 1685, 1632, 1579, 1475, 1250, 1164, 623 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.42 (9H, s), 2.39 (2H, dt, J=7.9, 6.9 Hz), 3.16 (2H, t, J=6.9 Hz), 5.68 (1H, t, J=7.9 Hz). LRMS (ESI$^+$) m/z: 255 [M+H$^+$]. HRMS (ESI$^+$) m/z: calcd for $C_{11}H_{19}N_4O_3$ (M+H$^+$) 255.14571, found 255.14414.

*4.1.33. (E)-2-Amino-4-[3-(4,5-dibromo-1H-pyrrol-2-carboxamido) propyliden]-1H-imidazol-5(4H)-one (dispacamide) (**3**).* To a solution of **28** (22.5 mg, 0.089 mmol) in MeOH (1.0 mL) was added 20% HCl/EtOH (3.0 mL), and the mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in DMF (2.0 mL). To the DMF solution were added Na_2CO_3 (32.9 mg, 0.31 mmol) and 4,5-dibromo-2-trichloroacetylpyrrole[17] (34.4 mg, 0.093 mmol). The whole was stirred at room temperature for 90 h. After concentration in vacuo, the residue was purified by column chromatography (NH–SiO_2, CH_2Cl_2, then CH_2Cl_2/MeOH=2/1) to give crude **3** as a white solid. Further trituration of the crude sample with C_6H_{14} gave almost pure **3** (30.6 mg, 85%) as a colorless powder. Mp: 170 °C (decomp.) (from MeOH). IR (ATR): 3203, 1684, 1571, 1475, 1321, 658 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 2.49 (2H, dt, J=7.9, 7.0 Hz), 3.42 (2H, t, J=7.0 Hz), 5.72 (1H, t, J=7.9 Hz), 6.78 (1H, s). ^{13}C NMR (100 MHz, CD_3OD): δ 28.6, 39.5, 99.9, 106.1, 111.5, 114.3, 128.8, 137.1, 161.9,

168.0, 178.8. LRMS (ESI^+) m/z: 404 [$M+H^+$]. HRMS (ESI^+) m/z: calcd for $C_{11}H_{12}Br_2N_5O_2$ ($M+H^+$) 403.93578, found 403.93687. Spectral and physical data of **3** was almost identical with those reported.[4] Since the ^1H NMR spectrum described above showed a small signal at 5.65 ppm (0.05H, t, J=8.3 Hz), it was deduced that this sample is contaminated with a small amount of unnatural (*Z*)-isomer of **3** (ca. 5%). Attempted separation of the (*Z*)-isomer of **3** turned out to be fruitless even by repeated column chromatography.

*4.1.34. (E)-2-Amino-4-[3-(4-bromo-1H-pyrrol-2-carboxamido)propyliden]-1H-imidazol-5(4H)-one (monobromodispacamide) (**4**).* Treatments of **28** (21.5 mg, 0.085 mmol) with 4-bromo-2-trichloroacetylpyrrole[18] (24.6 mg, 0.085 mmol) in the same as described in Section 4.1.33 gave almost pure **4** (19.0 mg, 69% from **28**) as a colorless powder after trituration of the crude sample with C_6H_{14}. Mp: 170 °C (decomp.) (from MeOH). IR (ATR): 3126, 1683, 1614, 1563, 1472, 1317, 598 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 2.50 (2H, dt, J=7.8, 6.9 Hz), 3.42 (2H, t, J=6.9 Hz), 5.72 (1H, t, J=7.8 Hz), 6.74 (1H, d, J=1.5 Hz), 6.90 (1H, d, J=1.5 Hz). ^{13}H NMR (100 MHz, CD_3OD): δ 28.6, 39.5, 97.5, 111.6, 113.3, 120.8, 127.5, 136.9, 162.7, 168.3, 178.9. LRMS (ESI^+) m/z: 326 [$M+H^+$]. HRMS (ESI^+) m/z: calcd for $C_{11}H_{13}BrN_5O_2$ ($M+H^+$) 326.02526, found 326.02517. Spectral and physical data of **4** were almost identical with those reported.[4] Since the ^1H NMR spectrum described above showed a small signal at 5.66 ppm (0.05H, t, J=8.3 Hz), it was deduced that this sample is contaminated with a small amount of unnatural (*Z*)-isomer of **4** (ca. 5%). Attempted separation of the (*Z*)-isomer of **4** turned out to be fruitless even by repeated column chromatography.

*4.1.35. tert-Butyl 4-(2-aminoethyl)-1H-imidazol-2-ylcarbamate (**29**).* To a solution of **20a** (500 mg, 2.4 mmol) in $MeNO_2$ (10 mL) was added ammonium acetate (183 mg, 2.4 mmol), and the mixture was stirred at 100 °C for 25 min. The reaction mixture was diluted with EtOAc (100 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The residue was purified by column chromatography (SiO_2, C_6H_{14}/EtOAc=1/1) to yield (*E*)-*tert*-butyl [4-(2-nitrovinyl)-1*H*-imidazol-2-yl]carbamate (567 mg, 94%) as a yellow powder. ^1H NMR (400 MHz, CD_3OD): δ 1.53 (9H, s), 7.40 (1H, s), 7.69 (1H, t, J=12.8 Hz), 7.91 (1H, d, J=12.8 Hz). LRMS (EI^+) m/z: 254 [M^+]. HRMS (EI^+) m/z: calcd for $C_{10}H_{14}N_4O_4$ (M^+) 254.1015, found 254.1031. To a suspension of lithium aluminum hydride ($LiAlH_4$) (224 mg, 5.9 mmol) in THF (15 mL) was added dropwise a solution of the 2-nitrovinyl derivative (500 mg, 2.0 mmol) in THF (10 mL) at 0 °C. The mixture was stirred overnight at room temperature, and the reaction was quenched by adding an aqueous saturated Na_2SO_4 solution at 0 °C. The mixture was stirred at room temperature for 1 h, filtered through a pad of Celite, and then concentrated in vacuo. The residue was purified by column chromatography (NH–SiO_2, EtOAc/MeOH=10/1) to yield **29** (299 mg, 67%) as a brown amorphous solid. IR (ATR): 3229, 2974, 1599, 1248, 1156, 1072, 766, 616 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.53 (9H, s), 2.67 (2H, t, J=6.4 Hz), 2.95 (2H, d, J=6.4 Hz), 6.49 (1H, s). LRMS ($APCI^+$) m/z: 227 [$M+H^+$]. HRMS ($APCI^+$) m/z: calcd for $C_{10}H_{19}N_4O_2$ ($M+H^+$) 227.15080, found 227.1505.

*4.1.36. 4,5-Dibromopyrrol-2-carbaldehyde (**30a**)[21].* This compound was prepared from pyrrol-2-carbaldehyde (2.38 g, 25 mmol) according to the reported procedure. The product **30a** (4.64 g, 73%) was obtained as a pale yellow powder after recrystallization from C_6H_{14}/EtOAc. Mp: 156–158 °C (from C_6H_{14}/EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 6.95 (1H, d, J=1.8 Hz), 9.36 (1H, s), 9.65 (1H, br s). LRMS (EI^+) m/z: 251 [M^+]. HRMS (EI^+) m/z: calcd for $C_5H_3Br_2NO$ (M^+) 250.8581, found 250.8612.

*4.1.37. tert-Butyl 4,5-dibromo-2-formylpyrrol-1-carboxylate (**30b**)[22].* Treatments of **30a** (100 mg, 0.40 mmol) with Boc_2O (103 mg, 0.47 mmol) according to the reported procedure[22] afforded **30b** (96.9 mg, 69%) as a brown solid. ^1H NMR (400 MHz, $CDCl_3$): δ 1.66 (9H, s), 7.07 (1H, s), 9.72 (1H, s). This ^1H NMR spectrum was in good accord with that reported.[22]

*4.1.38. 4,5-Dibromo-1-methoxymethylpyrrol-2-carbaldehyde (**30c**).* To a solution of **30a** (100 mg, 0.40 mmol) in DMF (2.0 mL) was added potassium *tert*-butoxide (46.6 mg, 0.42 mmol) at 0 °C. After stirring at room temperature for 45 min, methoxymethyl chloride (0.036 mL, 0.47 mmol) was added to the reaction mixture at 0 °C, and the whole was stirred at the same temperature for 30 min. The reaction was quenched by adding an aqueous saturated $NaHCO_3$ solution at 0 °C. The precipitates appeared were collected by filtration, washed with H_2O, and dried in vacuo to afford **30c** (99.5 mg, 85%) as a colorless solid. Mp: 85–86 °C (from MeOH). IR (ATR): 3108, 2937, 2822, 1663, 1386, 1362, 1318, 1185, 1092, 956, 807, 772 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.35 (3H, s), 5.80 (2H, s), 7.04 (1H, s), 9.45 (1H, s). LRMS (ESI^+) m/z: 296 [$M+H^+$]. HRMS (ESI^+) m/z: calcd for $C_7H_8Br_2NO_2$ ($M+H^+$) 295.89218, found 295.89262.

*4.1.39. 4,5-Dibromo-1-[2-(trimethylsilyl)ethoxy]methylpyrrol-2-carbaldehyde (**30d**).* To a solution of **30a** (1.0 g, 4.0 mmol) in DMF (20 mL) was added potassium *tert*-butoxide (466 mg, 4.2 mmol) at 0 °C. After stirring at room temperature for 30 min, 2-(trimethylsilyl)ethoxymethyl chloride (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 **30d** (1.35 g, 89%) as a light brown oil. IR (ATR): 2953, 1671, 1399, 1371, 1310, 1248, 1091, 832 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 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). LRMS (ESI^+) m/z: 382 [$M+H^+$]. HRMS (ESI^+) m/z: calcd for $C_{11}H_{18}Br_2NO_2Si$ ($M+H^+$) 381.94736, found 381.94819.

*4.1.40. tert-Butyl [4-(4,5-dibromo-1H-pyrrol-2-yl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-2-yl]carbamate (**31a**).* Table 4, run 3: a solution of **29** (58.0 mg, 0.26 mmol) and **30a** (64.7 mg, 0.26 mmol) in pyridine (1.0 mL) was stirred at room temperature for 5 days. The reaction was quenched by adding H_2O, 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, EtOAc/MeOH=15/1) afforded **31a** (36.5 mg, 31%) as a yellow amorphous solid. IR (ATR): 3397, 2930, 1702, 1595, 1429, 1249, 1151, 767 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.50 (9H, s), 2.54–2.61 (2H, m), 3.03–3.13 (1H, m), 3.14–3.23 (1H, m), 4.97 (1H, s), 6.11 (1H, s). ^{13}C NMR (100 MHz, CD_3OD): δ 23.1, 28.5, 30.7, 40.6, 51.2, 98.5, 100.5, 112.5, 124.6, 127.7, 134.5, 142.1, 154.9. LRMS (ESI^+) m/z: 460 [$M+H^+$]. HRMS (ESI^+) m/z: calcd for $C_{15}H_{20}Br_2N_5O_2$ ($M+H^+$) 459.99838, found 459.99857.

*4.1.41. tert-Butyl [4-(4,5-dibromo-1-tert-butoxycarbonyl-1H-pyrrol-2-yl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-2-yl]carbamate (**31b**).* Table 4, run 4: to a solution of **29** (50.0 mg, 0.22 mmol) and **30b** (93.5 mg, 0.27 mmol) in toluene (5.0 mL) was added pyridinium *p*-toluenesulfonate (5.0 mg), and the mixture was stirred at room temperature for 24 h. The whole was concentrated in vacuo, and the residue was purified by column chromatography (NH–SiO_2, C_6H_{14}/EtOAc=2/3) to afford **31b** (96.7 mg, 78%) as a yellow amorphous solid. IR (ATR): 2976, 1698, 1598, 1411, 1367, 1246, 1152, 769 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.49 (9H, s), 1.51 (9H,

s), 2.51–2.72 (3H, m), 3.07–3.13 (1H, m), 4.15 (1H, br s), 5.98 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 28.2, 28.4, 38.5, 48.0, 80.9, 82.1, 97.9, 99.1, 99.6, 109.9, 110.8, 133.0, 142.4, 153.7, 155.8. LRMS (ESI^+) *m/z*: 560 [M+H$^+$]. HRMS (ESI^+) *m/z*: calcd for $C_{20}H_{28}Br_2N_5O_4$ (M+H$^+$) 560.05080, found 560.05087.

*4.1.42. tert-Butyl [4-(4,5-dibromo-1-methoxymethyl-1H-pyrrol-2-yl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-2-yl]carbamate (**31c**).* Table 4, run 9: a solution of **29** (92.7 mg, 0.41 mmol) and **30c** (146 mg, 0.49 mmol) in EtOH (5.0 mL) was stirred at 50 °C for 2 h. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography (NH–SiO_2, EtOAc/MeOH=50/1) to afford **31c** (141 mg, 68%) as a pale yellow amorphous solid. IR (ATR): 2929, 2850, 1698, 1598, 1430, 1252, 1154, 1091, 767 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ 1.52 (9H, s), 2.59 (2H, s), 2.95–3.01 (1H, m), 3.05–3.12 (1H, m), 3.36 (3H, s), 5.14 (1H, s), 5.30 (1H, br s), 5.63 (1H, br s), 5.99 (1H, br s), 9.98 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 28.3, 40.2, 48.2, 56.1, 76.0, 81.6, 98.8, 105.1, 113.1, 117.7, 132.0, 135.0, 142.4, 153.9. LRMS (ESI^+) *m/z*: 504 [M+H$^+$]. HRMS (ESI^+) *m/z*: calcd for $C_{17}H_{24}Br_2N_5O_3$ (M+H$^+$) 504.02459, found 504.02684.

*4.1.43. tert-Butyl [4-(4,5-dibromo-1-(2-(trimethylsilyl)ethoxy)methyl-1H-pyrrol-2-yl)-4,5,6,7-tetrahydro-1H-imidazo [4,5-c]pyridin-2-yl]carbamate (**31d**).* Table 4, run 10: a solution of **29** (459 mg, 2.0 mmol) and **30d** (935 mg, 2.4 mmol) in EtOH (10 mL) was stirred at 50 °C for 4 h, and then concentrated in vacuo. The residue was purified by column chromatography (NH–SiO_2, EtOAc) to give **31d** (960 mg, 80%) as a yellow amorphous solid. IR (ATR): 2951, 1702, 1598, 1430, 1367, 1274, 1249, 1155, 1079, 857, 834, 765 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ 0.02 (9H, s), 0.91–0.96 (2H, m), 1.51 (9H, s), 2.55–2.63 (2H, m), 2.94 (1H, dt, *J*=12.6, 5.0 Hz), 3.00–3.07 (1H, m), 3.61–3.67 (2H, m), 5.12 (1H, s), 5.46 (2H, s), 5.89 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.4, 17.9, 25.2, 28.3, 40.2, 48.3, 66.1, 74.3, 81.6, 98.6, 104.9, 113.1, 117.7, 131.9, 134.9, 142.3, 153.9. LRMS (ESI^+) *m/z*: 590 [M+H$^+$]. HRMS (ESI^+) *m/z*: calcd for $C_{21}H_{34}Br_2N_5O_3Si$ (M+H$^+$) 590.07977, found 590.08028.

*4.1.44. tert-Butyl 4-(4,5-dibromo-1-tert-butoxycarbonyl-1H-pyrrol-2-yl)-1H-imidazo[4,5-c]pyridin-2-ylcarbamate (**32b**).* Table 5, run 5: to a solution of **31b** (73.0 mg, 0.13 mmol) in DMSO (1.0 mL) was added iodoxybenzoic acid (IBX) (91.0 mg, 0.33 mmol), and the mixture was stirred at room temperature for 2 h. The reaction was quenched by adding H_2O and aqueous NaOH solution (1.0 mol/L, 2.0 mL, 2.0 mmol) and the whole 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 purified by column chromatography (NH–SiO_2, C_6H_{14}/EtOAc=2/1) to give **32b** (9.6 mg, 13%) as a colorless amorphous solid, which contains a small amount of some unidentified byproducts. This compound was used for the next step in Section 4.1.47 without further purification because it was unstable. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (9H, s), 1.55 (9H, s), 7.17 (1H, s), 8.25 (1H, d, *J*=5.2 Hz), 8.35 (1H, d, *J*=5.2 Hz), 10.70 (1H, br s), 10.79 (1H, br s). LRMS (ESI^+) *m/z*: 556 [M+H$^+$].

*4.1.45. tert-Butyl 4-(4,5-dibromo-1-methoxymethyl-1H-pyrrol-2-yl)-1H-imidazo[4,5-c]pyridin-2-ylcarbamate (**32c**).* Table 5, run 7: to a solution of **31c** (112 mg, 0.22 mmol) in DMSO (2.0 mL) was added IBX (156 mg, 0.56 mmol), and the mixture was stirred at 50 °C for 1 h. The reaction was quenched by adding H_2O and aqueous NaOH solution (1.0 mol/L, 2.0 mL, 2.0 mmol) and the whole 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 give a mixture of **32c** and **33c** (3:1 calculated by ^{1}H NMR) (84.1 mg, 75%) as a brown amorphous solid. The ^{1}H NMR spectrum of the mixture showed characteristic signals at 2.78 ppm (2H, t, *J*=7.0 Hz) and 3.95 ppm (2H, t, *J*=7.0 Hz) assignable to the C_9 and C_8positions of **33c** in addition to the signals of **32c** described below. To a solution of the mixture in DMSO (1.5 mL) was added IBX (30.8 mg, 0.11 mmol), and the mixture was stirred at 50 °C for 2 h. The reaction was quenched by adding H_2O and aqueous NaOH solution (1.0 mol/L, 1.0 mL, 1.0 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 give a mixture of **32c** and **33c** (10:1 calculated by ^{1}H NMR) (71.2 mg, 64%) as a brown amorphous solid. To a solution of the mixture in CH_2Cl_2 (5.0 mL) was added activated MnO_2 (30.0 mg), and the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered through a pad of Celite, and then concentrated in vacuo. The residue was purified by column chromatography (NH–SiO_2, C_6H_{14}/EtOAc=2/1) to give **32c** (70.1 mg, 63% from **31c**) as a white amorphous solid. IR (ATR): 2931, 1714, 1627, 1565, 1465, 1249, 1151, 1103, 768 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (2.7H, s), 1.63 (6.3H, s), 3.18 (0.9H, s), 3.22 (2.1H, s), 5.81 (1.4H, s), 6.11 (0.6H, s), 6.72 (0.7H, s), 7.18 (0.3H, d, *J*=5.2 Hz), 7.37 (0.3H, s), 7.52 (0.7H, d, *J*=5.5 Hz), 8.32 (0.3H, d, *J*=5.2 Hz), 8.40 (0.7H, d, *J*=5.5 Hz), 10.74 (0.3H, br s), 11.14 (0.7H, br s), 11.89 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3, 56.2, 76.7, 83.7, 100.9, 108.5, 111.6, 113.8, 127.3, 131.4, 134.1, 141.9, 146.9, 151.0, 153.5. LRMS (ESI^+) *m/z*: 500 [M+H$^+$]. HRMS (ESI^+) *m/z*: calcd for $C_{17}H_{20}Br_2N_5O_3$ (M+H$^+$) 499.99329, found 499.99344.

*4.1.46. tert-Butyl 4-(4,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrol-2-yl)-1H-imidazo[4,5-c]pyridin-2-ylcarbamate (**32d**).* Table 5, run 10: to a solution of **31d** (50.0 mg, 0.085 mmol) in DMSO (1.0 mL) was added IBX (35.6 mg, 0.13 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, 2.0 mL, 2.0 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 (5.0 mL) was added activated MnO_2 (200 mg), and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was filtered through a pad of Celite, and then concentrated in vacuo. The residue was purified by column chromatography (NH–SiO_2, C_6H_{14}/EtOAc=2/1) to give **32d** (44.3 mg, 89%) as a white amorphous solid. IR (ATR): 2951, 1716, 1629, 1567, 1466, 1417, 1248, 1152, 1087, 858, 832, 768 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ −0.25 (9H, s), 0.58 (2H, t, *J*=8.6 Hz), 1.57 (9H, s), 3.15 (2H, t, *J*=8.6 Hz), 5.83 (2H, s), 6.95 (1H, s), 7.42 (1H, d, *J*=5.5 Hz), 8.24 (1H, d, *J*=5.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.7, 17.6, 28.3, 65.9, 74.9, 83.7, 100.6, 108.5, 111.5, 113.4, 127.3, 131.1, 134.4, 141.8, 146.8, 151.2, 153.7. LRMS (ESI^+) *m/z*: 586 [M+H$^+$]. HRMS (ESI^+) *m/z*: calcd for $C_{21}H_{30}Br_2N_5O_3Si$ (M+H$^+$) 586.04847, found 586.0452.

*4.1.47. 2-Amino-4-(4,5-dibromo-1H-pyrrol-2-yl)-1H-imidazo[4,5-c]pyridine (ageladine A) (**6**).* (a) A solution of **32b** (42.0 mg, 0.075 mmol) in trifluoroacetic acid (2.0 mL) was stirred at room temperature for 5 h, and the mixture was concentrated in vacuo. Trituration of the residue with CH_2Cl_2 afforded **6**-2CF_3CO_2H (36.5 mg, 83%) as a yellow powder. The ^{1}H NMR spectrum of this sample was identical to that described in b.

(b) To a solution of **32d** (115 mg, 0.20 mmol) in CH_2Cl_2 (5.0 mL) was added borontrifluoride diethyletherate (0.25 mL, 2.0 mmol) under an argon atmosphere, and the mixture was stirred at room temperature for 7 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) and the filtrate was concentrated in vacuo. The residue was dissolved in MeOH (5.0 mL), and trifluoroacetic acid (0.05 mL) was added to the MeOH solution. The acidic methanolic solution was concentrated in vacuo. Trituration of the residue with CH_2Cl_2 gave **6**-2CF_3CO_2H (79.9 mg, 70%) as a yellow powder. Mp: 190 °C (decomp.) (from CH_2Cl_2/MeOH). IR (ATR): 3120, 2856, 1636, 1416, 1175, 1123, 793, 721 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 7.17 (1H, s), 7.42 (1H, d, J=6.4 Hz), 8.05 (1H, d, J=6.4 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 102.4, 105.5, 107.8, 115.2, 125.7, 128.6, 133.0, 136.7, 147.2, 160.9. LRMS (ESI^+) m/z: 356 [M+H^+]. HRMS (ESI^+) m/z: calcd for $C_{10}H_8Br_2N_5$ (M+H^+) 355.91465, found 355.91340. Spectral and physical properties of **6**-2CF_3CO_2H were identical to those reported.[6]

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