Synthesis of enantiopure 1-substituted, 1,2-disubstituted, and 1,4,5-trisubstituted imidazoles from 1,2-amino alcohols

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Abstract—A highly versatile method for the preparation of enantiopure 1-substituted, 1,2-disubstituted, and 1,4,5-trisubstituted imidazoles was developed by using the cyclocondensation reaction of a 1,2-dicarbonyl compound, an aldehyde, a 1,2-amino alcohol, and ammonium acetate.

1. Introduction

Imidazole and its derivatives play an important role in the fields of biology and pharmacology as well as chemistry.[1–5] Imidazole ring systems are frequently found in numerous naturally occurring[1] and synthetic molecules such as fungicides, herbicides,[2] and therapeutic agents.[3] Recently, an interest to these heteroaromatic systems has been further expanded as the precursors of imidazolium-based ionic liquids[4] and *N*-heterocyclic carbenes (NHCs).[5] Among them, imidazole derivatives having a N-substituent with stereogenic center(s) have attracted special attention, because of their potential utility in a wide range of fields related to chiral recognition and asymmetric catalysis.[6,7]

Synthetic strategies for the preparation of imidazoles with a stereogenic N-substituent are classified into two categories; (i) the alkylation of an imidazole nitrogen with enantiopure electrophiles and (ii) the cyclocondensation of ring fragments, typically the combination of glyoxal, ammonia, an aldehyde, and an enantiopure primary amine. The alkylation method is quite straightforward to access target molecules, because imidazole is commercially available and because the N-alkylation of imidazole is a well-established reaction with very low possibility of complicated side reactions. In fact, several methods based on the alkylation approach have been recently reported, in which various enantiopure electrophiles were employed.[8]

However, the alkylation method still possesses serious limitations: Elecleophiles usually used for this reaction, such as alkyl halides, alcohols, and epoxides, are not so easy to obtain in an enantiopure form and in a large amount. In addition, this method is obviously disadvantageous for the preparation of N-substituted imidazoles with a stereogenic carbon at the α -position of the imidazole N(1), especially when a bulky substituent is placed on the carbon. The efficiency of N-alkylation is significantly influenced by the steric hindrance of the carbon at which a nucleophilic attack occurs. Furthermore, the stereochemistry of the stereogenic carbon in the electrophile is not necessarily preserved during the reaction.

On the other hand, the cyclocondensation of ring fragments established by Gridnev *et al.* [9a] has been applied to the preparation of various N-substituted imidazoles.[9,10] By using an enantiopure amine as a primary amine fragment in this method, imidazoles with a stereogenic N-substituent can be prepared in one step. Because stereogenic carbon does not directly participate to the cyclocondensation, there is little risk for the racemization/epimerization of the stereogenic carbon. Furthermore, enantiopure amines are easily available in a large scale. Considering the application of N-substituted imidazoles as the building blocks of biologically active compounds, asymmetric catalysts, and chiral ionic liquids, the introduction of a functional group as well as a stereogenic center adjacent to the five-membered ring core would be advantageous from the viewpoints of further derivatization and chiral recognition/induction. Therefore, the development of a novel method for the preparation of 1-substituted imidazoles with a functional group and a stereogenic center on the substituent is an important subject.

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In the course of our ongoing studies on the design and synthesis of chiral ionic liquids based on imidazoliums,[11] the synthesis of 1-substituted and 1,2-disubstituted imidazoles from 1,2-amino alcohols was highly required. Although there have been a large number of reports on the synthesis of imidazoles by the cyclocondensation of four components (glyoxal, ammonia, an aldehyde, and an amine including enantiopure one), little is concerned with the thorough examination of the optimal conditions for the cyclocondensation of glyoxal, ammonia, an aldehyde, and a 1,2-amino alcohol.[9,10] Here we report an efficient and practical method for the preparation of 1-substituted, 1,2-disubstituted, and 1,4,5-trisubstituted imidazoles with a hydroxy group and a stereogenic center on the substituent.

2. Results and discussion

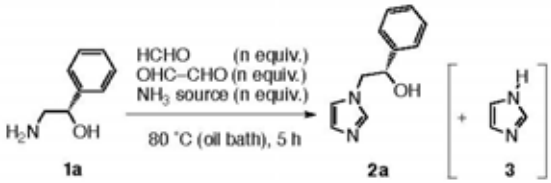
2.1. Optimization of the reaction conditions

(*S*)-2-Amino-1-phenylethanol (**1a**) was chosen as an enantiopure primary 1,2-amino alcohol for the study on the reaction conditions, because of its easy availability from (*R*)-mandelic acid and because of the detectability of the products, developed on a TLC plate, by UV absorption.[12]

For the imidazole formation by cyclocondensation, pH is known to be one of the most crucial factors to determine the yield.[9a,b] Therefore, we at first investigated the effect of an ammonia source on the efficiency of this cyclocondensation; the 1,2-amino alcohol **1a**, glyoxal (40% aqueous solution, 1.0 equiv.), formaldehyde (37% aqueous solution, 1.0 equiv.) were allowed to react in the presence of ammonia (28% aqueous solution, 1.0 equiv.), ammonium chloride, or ammonium acetate in methanol (Table 1, entries 1, 3, and 5). Comparing the yields of the product **2a**, it could be clearly deduced that acidic conditions were favorable for the cyclocondensation. This observation is in good agreement with the result in the report of Gridnev *et al*.[9a]

Considering the availability of each ring fragment, the first priority should be given to the conversion of the 1,2-amino alcohol unit. Therefore, we then conducted the reactions by using excess amounts of the other ring fragments. As shown in Table 1, the amounts of these reagents were another crucial factor to determine the yield of **2a**, especially when ammonium acetate was used as an ammonia source. By increasing the amounts of glyoxal, formaldehyde, and ammonium acetate from 1.0 equiv. to 2.0 equiv., the yield of **2a** was significantly improved (entries 5 and 6). However, the yield did not increase any longer by using further excess amounts (4.0 equiv. each) of these reagents (entry 7). Contrary to this, when ammonium chloride was employed as an ammonia source, the yield was slightly diminished

Table 1. Synthesis of 1-substituted imidazole 2a from (S)-2-Amino-1-phenylethanol (1a)



entry	NH_3 source	n / eq.	solvent	isolated yield
1	28% NH_3 aq.	1	methanol	20
2	28% NH_3 aq.	2	methanol	44
3	NH_4Cl	1	methanol	69
4	NH_4Cl	2	methanol	63
5	NH_4OAc	1	methanol	53
6	NH_4OAc	2	methanol	71
7	NH_4OAc	4	methanol	72
8	NH_4OAc	2	water	45
9	NH_4OAc	2	ethanol	51
10	NH_4OAc	2	2-propanol	44

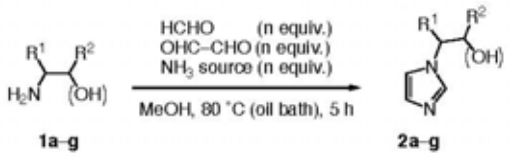
by using excess amounts of these ring fragments (entry 4). Although the use of the ring fragments in excess resulted in the formation of several undesired by-products, they could be easily removed from the desired product through the work-up process because of their high volatility and/or polarity. Thus, the conditions adopted in entries 3 and 6 (Table 1) seem to be suitable for this cyclocondensation. Worth noting is the fact that the amount of imidazole (3) generated through the reaction was surprisingly small, although the ring fragments for the construction of 3 adequately existed under the conditions of entries 2, 4, 6, and 7; when the reactions were conducted under the conditions of these entries, only less than 5% of 3 was generated with respect to 2a. It means that the 1-substituted imidazole formation is much faster than the imidazole formation.

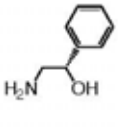
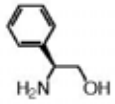
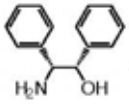
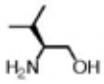
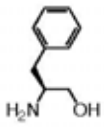
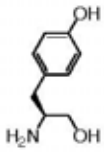
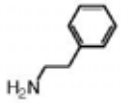
In the next stage, we examined the solvent effect for the reaction using ammonium acetate as an ammonia source. The use of water in the place of methanol caused a considerable diminish in the yield of **2a**; a notable amount of precipitates was generated just after the reaction was started, which might arise from hydrophobicity of an intermediate derived from **1a** and glyoxal (Table 1, entry 8). Contrary to this, ethanol and 2-propanol dissolved all of the four components and maintained the homogeneity of the system throughout the reaction, as did methanol. However, the yields observed by using ethanol and 2-propanol were lower than that achieved by using methanol (entries 9 and 10). These observations indicate that the dielectric constant of the reaction medium is also an important factor for the present cyclocondensation; polar solvents are fundamentally favorable as far as the substrate and intermediate are adequately soluble in the reaction media.

2.2. Synthesis of various 1-substituted imidazoles

We then carried out the reactions of various enantiopure 1,2-amino alcohols (Table 2). Under the conditions of entry 4 in Table 1 (method A), the enantiopure 1,2-amino alcohols **1a–f** could be successfully converted to the corresponding N-substituted imidazoles without the loss of enantiopurity (entries 1, 3, 5, 7, 9, and 10). The fact that the yield of **2a** (entry 1) was comparable to that of the reaction of 2-phenylethylamine (**1g**) under the same conditions (entry 10) strongly indicates that the hydroxy group in the 1,2-amino alcohols was likely to bring little influence on this reaction. Furthermore, the reaction of (*S*)-tyrosinol (**1f**) afforded the corresponding 1-substituted imidazole **2f** in the yield comparable to those of the other reactions, which clearly shows that this cyclocondensation is tolerant to a phenol moiety (entry 9). Worth noting is the fact that the reaction proceeded efficiently even when a bulky substituent

Table 2. Synthesis of 1-substituted imidazoles 2a–g from various 1,2-amino alcohols 1a–g

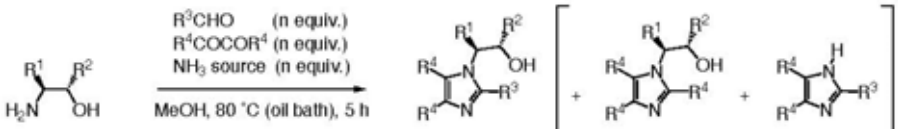


entry	primay amine 1	method[a]	isolated yield / %	ee / %[b]
1	 **1a**	A	71	>99
2		B	69	>99
3	 **1b**	A	65	>99
4		B	61	>99
5	 **1c**	A	65	>99[c]
6		B	61[d]	>99[c]
7	 **1d**	A	69	>99
8		B	54[e]	>99
9	 **1e**	A	55	>99
10	 **1f**	A	63	n. d.
11	 **1g**	A	63	

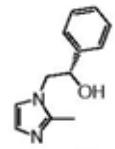
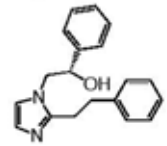
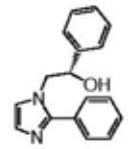
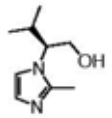
[a] Method A: n = 2; NH_3 source, NH_4OAc. Method B: n = 1; NH_3 source, NH_4Cl.
[b] Estimated by a chiral HPLC analysis.
[c] Estimated by ^1H NMR.
[d] As a mixture with the 1,2-amino alcohol **1c** (**2c**:**1c** = 61:19).
[e] As a mixture with imidazole (**3**) (**2d**:**3** = 54:5).

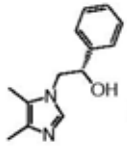
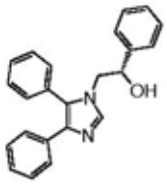
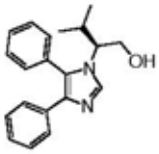
was introduced at the α position of the amino group (entries 3, 5, and 7). Thus, a highly convenient and efficient method for the synthesis of imidazoles possessing a stereogenetically pure OH-pendant N-substituent was established.

The reaction conditions of entry 3 in Table 1 (method B) were also applied to the cyclocondensation of several amino alcohols (**1a**–**d**: Table 2, entries 2, 4, 6, and 8). The method B realized yields comparable to or slightly lower than those by the method A for the reactions of **1a**–**c**. However, for the reaction of **1d**, the yield achieved by the method B was obviously lower than that accomplished by the method A. This means that the method A is suitable for the reaction of sterically hindered amino alcohols such as **1d**; ammonium acetate is better than ammonium chloride as the ammonium source. Furthermore, by using ammonium acetate, the reaction can be conducted under almost neutral conditions, which might be advantageous for the reaction of amines bearing a functional group unstable under acidic conditions. Thus, the method A is concluded to be the most



entry	1,2-amino alcohol	aldehyde	1,2-diketone	product-1	product-2	product-3
1, 2	**1a**: R^1 = H, R^2 = Ph	R^3 = CH_3	R^4 = H	**4a**	**2a**	**11**
3	**1a**: R^1 = H, R^2 = Ph	R^3 = $(CH_2)_2Ph$	R^4 = H	**5a**	**2a**	**12**
4	**1a**: R^1 = H, R^2 = Ph	R^3 = Ph	R^4 = H	**6a**	**2a**	**13**
5	**1d**: R^1 = ^{i}Pr, R^2 = Ph	R^3 = CH_3	R^4 = H	**4d**	**2d**	**11**
6	**1a**: R^1 = H, R^2 = Ph	R^3 = H	R^4 = Me	**7a**	**9a**	**14**
7	**1a**: R^1 = H, R^2 = Ph	R^3 = H	R^4 = Ph	**8a**	**10a**	**15**
8	**1d**: R^1 = ^{i}Pr, R^2 = Ph	R^3 = H	R^4 = Ph	**8d**	**10d**	**15**

entry			method[a]	ratio of the products[b] prdct-1:prdct-2:prdct-3	yield[c]
1		**4a**	A	1.00:0.31:0.17	50 (41)
2			B	1.00:0.77:0.18	29 (22)
3		**5a**	A	1.00:0.58:0.65	51 (43)
4		**6a**	A	1.00:0.50:0.58	48 (40)
5		**4d**	A	1.00:1.10:0.69 [1.00:0.16:0.60	27 (26) 34 (34)][d]

entry			method[a]	ratio of the products[b] prdct-1:prdct-2:prdct-3	yield[c]
6		**7a**	A	1.00:<0.01:<0.01	30 (30)
7[e]		**8a**	A	1.00:<0.01:<0.01	83 (83)
8[e]		**8d**	A	1.00:<0.01:0.07	85 (52)

[a] Method A: n = 2; NH_3 source, NH_4OAc. Method B: n = 1; NH_3 source, NH_4Cl.
[b] Estimated by ^1H NMR.
[c] Yield based on ^1H NMR (in a parenthesis, isolated yield).
[d] 1.0 equiv. of glyoxal was used.
[e] Reaction time, 9 h.

favorable for the cyclocondensation.

In order to demonstrate the applicability of this procedure in a large scale, we then conducted the reaction in a multi-gram scale under the same conditions and attempted to isolate the target N-substituted imidazoles by a method other than column chromatography. For example, when the reaction of 3.00 g of **1d** (29 mmol) was carried out under the same conditions of the method A, 3.69 g of the corresponding 1-substituted imidazole **2d** (24 mmol, 82% yield) was isolated with satisfactory purity by Kugelrohr distillation (3 mmHg, 170 ℃). This preparative method is undoubtedly more efficient, compared with the conventional method reported by Bao *et al.*;[10b] **2d** was prepared in three reaction steps, all of which required chromatographic purification. On the other hand, for the isolation of less volatile 1-substituted imidazoles such as **2e**, crystallization was found to be effective; when 4.54 g of **1e** (30 mmol) was treated under the same conditions, 2.97 g of **2e** (15 mmol, 50% yield) was isolated by simple crystallization from ethyl acetate/hexane.

2.3. Synthesis of 1,2-disubustituted and 1,4,5-trisubstituted imidazoles

In general, the introduction of a substituent at the C(2) position of 1-substituted imidazoles and 1,3-disubstituted imidazolium salts brings a considerable effect on the properties of the resultant imidazoles/imidazolium salts. Especially in the cases of ionic liquids consisting of 1,3-dialkylimidazolium salts, the alkylation of the C(2) position make these ionic liquids applicable under basic conditions, because the easy formation of undesired carbene species from 1,3-disubstituted imidazoliums by the action of a base can be prevented.[13] Usually, such a substituent at the C(2) position as well as at the C(4) and/or C(5) position is introduced by the lithiation of a 1-substituted imidazole, followed by treatment with an electrophile.[14] On the other hand, there has been only a few reports on the preparation of 1,2-disubstituted and 1,4,5-trisubstituted imidazoles by the cyclocondensation, although this route seems to be more convenient compared with conventional methods.9b,9e– g,15

With the optimized conditions for the cyclocondensation of a 1,2-amino alcohol, formaldehyde, glyoxal, and an ammonia source in hand, we then attempted to apply the cyclocondensation reaction to the formation of highly substituted imidazoles by replacing formaldehyde and glyoxal with other aldehydes and 1,2-diketones, respectively. At first, we attempted to synthesize 1,2-disubstituted imidazoles by using various aldehydes in the place of formaldehyde (Table 3, entries 1–6).

When **1a**, glyoxal (2.0 equiv.), acetaldehyde (2.0 equiv.), and ammonium acetate (2.0 equiv.) were allowed to react with each other in methanol (method A), the target imidazole **4a** was obtained, as was expected, accompanying the formation of two kinds of by-products, **2a** and **11**, having no substituent at the C(2) and N(1) positions, respectively (Table 3, entry 1). Although such by-products **2a** and **11** were formed, the target 1,2-disubstituted imidazole **4a** was isolated by alumina column chromatography in moderate yield (50% yield by a ^{1}H NMR analysis, 41% isolated yield). The cyclocondensation was found to be tolerant to other aldehyde components; the reaction conditions optimized for the formation of **4a** were successfully applied to the reactions involving an aliphatic or aromatic aldehyde, such as 3-phenylpropanal or benzaldehyde, as the C(2) provider, and the corresponding 1,2-disubstituted imidazoles **5a** and **6a** were obtained in yields comparable to that of **4a** (entries 3 and 4).

The formation of **11**–**13** is reasonable, because all of the ring fragments for the formation of **11**–**13** (glyoxal, acetaldehyde, and ammonium acetate) were excessively used. On the other hand, the C(2) of **2a** was most likely provided by formaldehyde or its equivalent, which would be generated *in situ* from glyoxal under the reaction conditions; the primary amine **1a** should be consumed for the formation of **2a** to diminish the yield of **4a**–**6a**.[16] The same side reaction should be considered to occur during the 1-substituted imidazole formation using formaldehyde (Tables 1 and 2) but might bring little effect on the yield of the target imidazole, because the side reaction afforded the same product. Noteworthy, the pH of the reaction mixture was again found to be an important factor to determine the yield and selectivity of the reaction; when ammonium chloride was used in the place of ammonium acetate, the ratio of the undesired **2a** considerably increased to lower the yield of **4a** (method B, entry 2).

The successful results described above prompted us to apply the cyclocondensation to the formation of 1,4,5-trisubstituted imidazoles, because several 4,5-diaryl-subsituted imidazoles have been attracted

recent attention as potent inhibitors of p38 MAP kinase.[17] We therefore conducted the cyclocondensation reaction of a 1,2-diketone, ammonium acetate, formaldehyde, and **1a** under the conditions of the method A. To our delight, the reaction proceeded smoothly to afford the target 1,4,5-trisubstituted imidazoles **7a** and **8a** in moderate to good yields (Table 3, entries 6 and 7). Contrary to the case of the reactions using glyoxal, these 1,2-diketones did not act as imidazole C(2) providers; the formation of 1,2,4,5-tetrasubstituted imidazoles **9a** and **10a** was not observed. Furthermore, another kind of possible by-products, 4,5-disucsitituted imidazoles (**14** and **15**) were not detected in both of the reactions of the 1,2-diketones.

For the synthetic method to prepare 1,2-disubsituted and 1,4,5-trisubstituted imidazoles thus established, the scope of the primary amine component was investigated. As a primary amine unit, (*S*)-valinol (**1d**) was used in the place of (*S*)-2-amino-1-phenylethanol (**1a**), because **1d** with a sterically congested amino group seemed to be suitable to evaluate the effect of the substituent neighboring an amino group on the efficiency of the reaction. In the cyclocondensation of **1d**, glyoxal (2.0 equiv.), acetaldehyde (2.0 equiv.), and ammonium acetate (2.0 equiv.), the target 1,2-disubstituted imidazole **4d** was obtained, but considerable amounts of the by-products **2d** and **11** were generated to diminish the yield of **4d** (entry 5). The ratio of the by-product lacking a C(2) substituent significantly increased compared with the case of **1d** (entry 1 vs. entry 5), most likely because the isopropyl group on **1d** brought an unfavorable effect on the formation of the sterically crowded product possessing a C(2) substituent. However, by reducing the amount of glyoxal from 2.0 equiv to 1.0 equiv., the formation of the undesired by-product **2d** could be efficiently suppressed to improve the yield of **4d**. Contrary to the case of the synthesis of **4d**, the formation of a 1,4,5-trisubstituted imidazole was hardly influenced by a substituent on a primary amine unit; the cyclocondensation of **1d**, benzil (2.0 equiv.), formaldehyde (2.0 equiv.), and ammonium acetate (2.0 equiv.) proceeded smoothly, and only a small amount of **15** was afforded as a by-product. As a result, the yield of the target 1,4,5-trisubstituted imidazole **8d** was comparable to that of **8a** from **1a** (entry 8).

3. Conclusion

We developed a highly versatile method for the preparation of 1-substituted imidazoles by the cyclocondensation of glyoxal, ammonium acetate, formaldehyde, and a 1,2-amino alcohol. The choice of an ammonium source, which gives significant influence on the pH of the reaction mixture, was found to be an important factor to determine the efficiency and selectivity of the reaction. The protocol optimized here was applicable to the transformation of various enantiopure 1,2-amino alcohols, including sterically hindered 1,2-amino alcohols, to the corresponding enantiopure 1-substituted imidazoles with maintaining the enantiopurity. By this method, target imidazoles could be prepared in multi-gram scales and easily isolated in satisfactorily pure forms without resorting column chromatography. Furthermore, the procedure was successfully applied to the synthesis of 1,2-disubstituted and 1,4,5-trisubstituted imidazoles by the proper choice of an aldehyde and a 1,2-dicarbonyl compound. The synthetic procedure established here is expected to contribute to the development of enantiopure imidazole/imidazolium-based molecules, such as bio-active reagents, ionic liquids, NHC-ligands, and NHC catalysts.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 operating at 300 and 75 MHz, respectively. IR spectra were recorded on a JASCO model FT/IR-480plus. High resolution FAB-MS spectra were recorded on a JEOL JMS-HX110 spectrometer using 3-nitrobenzyl alcohol matrix. Melting points were determined on a Yamato MP-21.

4.2. Synthesis and characterization of imidazoles

General procedure: A methanol solution (6 mL) of aqueous glyoxal (40% w/v, 0.87 g, 6.0 mmol) or a 1,2-dicarbonyl compound (6.0 mmol), ammonium acetate (0.46 g, 6.0 mmol), aqueous formaldehyde (36% w/v, 0.50 g, 6.0 mmol) or an aldehyde (6.0 mmol), and a 1,2-amino alcohol (3.0 mmol) was refluxed for 5 h. Unless otherwise noted, the reaction mixture was treated as follows: The reaction mixture was concentrated under reduced pressure. The resultant residue was treated with 2 M

aqueous KOH solution (100 mL) and extracted with CH_2Cl_2 (4 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

2a: Purified by silica gel (deactivated with 10 wt% water) column chromatography eluted with CH_2Cl_2/MeOH (100:0 to 95:5, v/v). Mp 147.5–150.5 °C. $[\alpha]^{25}_D$ = +45.3 (*c* 1.2, MeOH). IR (KBr): 3120, 2891, 2850, 2788, 1636, 1601, 1513, 1449 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.04–4.17 (m, 2H), 4.93 (dd, J_1 = 7.2 Hz, J_2 = 4.5 Hz, 1H), 6.89 (s, 1H), 6.94 (s, 1H), 7.26–7.41 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 54.27, 72.62, 119.60, 125.64, 127.51, 128.05, 128.11, 137.38, 141.55. HR MASS calcd for $[M + H]^+$ $C_{11}H_{13}N_2O$ 189.1028, found 189.1021. Anal. calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.24; H, 6.60; N, 14.88.

Analytical chiral HPLC: column, CHIRALCEL OD-H (0.46 x 25 cm); eluent, hexane/2-propanol = 85:15, v/v; flow, 1.0 mL/min; (*R*) 21.1 min, (*S*) 23.7 min.

2b: Purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH (99:1 to 95:5, v/v). Mp 117.5–120.0 °C. $[\alpha]^{25}_D$ = +25.9 (*c* 1.3, MeOH). IR (KBr): 3148, 3108, 3033, 2958, 2925, 2859, 2652, 1984, 1961, 1882, 1812, 1685, 1601, 1583, 1495, 1460, 1451, 1410, 1371 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.13–4.25 (m, 2H), 5.27 (dd, J_1 = 7.8 Hz, J_2 = 4.8 Hz, 1H), 6.94–6.96 (m, 2H), 7.15–7.18 (m, 2H), 7.31–7.35 (m, 3H), 7.51 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 63.81, 64.42, 118.77, 127.04, 128.48, 128.53, 129.04, 136.84, 137.53. HR MASS calcd for $[M + H]^+$ $C_{11}H_{13}N_2O$ 189.1028, found 189.1024. Anal. calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.00; H, 6.58; N, 14.73.

Analytical chiral HPLC: column, CHIRALCEL OD-H (0.46 x 25 cm); eluent, hexane/2-propanol = 80:20, v/v; flow, 1.0 mL/min; (*R*) 9.5 min, (*S*) 12.7 min.

2c: Purified by silica gel (deactivated with 10 wt% water) column chromatography eluted with CH_2Cl_2/MeOH (100:0 to 95:5, v/v) followed by crystallization from EtOAc. Mp 161.5–163.0 °C. $[\alpha]^{25}_D$ = –37.6 (*c* 2.1, MeOH). IR (KBr): 3098, 2933, 2841, 1971, 1904, 1832, 1709, 1685, 1636, 1602, 1586, 1508, 1493, 1451, 1397 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.23 (d, *J* = 6.9 Hz, 1H), 5.41 (d, *J* = 6.9 Hz, 1H), 6.89–6.90 (m, 2H), 7.14–7.18 (m, 2H), 7.26–7.31 (m, 5H), 7.34–7.38 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 67.81, 75.14, 118.67, 126.50, 128.28, 128.49, 128.53, 128.62, 128.71, 136.15, 136.75, 141.10. HR MASS calcd for $[M + H]^+$ $_{17}H_{17}N_2O$ 265.1341, found 265.1359. Anal. calcd for $_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.12; H, 6.12; N, 10.45.

2d: Purified by silica gel (deactivated with 10 wt% water) column chromatography eluted with CH_2Cl_2/MeOH (99:1 to 97:3, v/v). Mp 106.5–111.5 °C. $[\alpha]^{25}_D$ = –27.1 (*c* 1.6, MeOH). IR (KBr): 3112, 3090, 2957, 2926, 2856, 2726, 1691, 1599, 1504, 1494 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.74 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 2.07–2.14 (m, 1H), 3.64–3.71 (m, 1H), 3.85–3.91 (m, 2H), 6.92 (m, 2H), 7.32 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 19.31, 20.01, 30.01, 62.69, 67.09, 118.15, 128.26, 136.81. HR MASS calcd for $[M + H]^+$ $C_8H_{15}N_2O$ 154.1184, found 155.1186. Anal. calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.19; H, 9.32; N, 18.14.

Analytical chiral HPLC: column, CHIRALCEL OD-H (0.46 x 25 cm); eluent, hexane/2-propanol = 90:10, v/v; flow, 1.0 mL/min; (*R*) 18.0 min, (*S*) 32.4 min.

2e: Purified by silica gel (deactivated with 10 wt% water) column chromatography eluted with CH_2Cl_2/MeOH (99:1 to 95:5, v/v). Mp 86.0–87.5 °C. $[\alpha]^{25}_D$ = –114.7 (*c* 1.1, MeOH). IR (KBr): 3157, 3113, 2962, 2933, 2833, 1963, 1886, 1653, 1604, 1590, 1505 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.99 (dd, J_1 = 13.8 Hz, J_2 = 8.4 Hz, 1H), 3.15 (dd, J_1= 13.8 Hz, J_2 = 6.5 Hz, 1H), 3.83–3.85 (m, 2H), 4.21–4.26 (m, 1H), 6.89–6.91 (m, 2H), 7.00–7.03 (m 2H), 7.19–7.27 (m, 4H). 13C NMR ($CDCl_3$): δ 38.41, 62.26, 64.21, 117.61, 126.99, 128.59, 128.76, 128.90, 136.47, 137.10. HR MASS calcd for [M + H]+ $C_{12}H_{15}N_2O$ 203.1184, found 203.1182. Anal. calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.27; H, 7.20; N, 13.81.

Analytical chiral HPLC: column, CHIRALCEL OD-H (0.46 x 25 cm); eluent, hexane/2-propanol = 90:10, v/v; flow, 1.0 mL/min; (*R*) 24.5 min, (*S*) 37.2 min.

2f: The reaction mixture was concentrated under reduced pressure. The resultant residue was dissolved in water (6 mL), and the aqueous solution was neutralized by the addition of solid NaHCO3 until the pH reached at 7.0–8.0.

The resultant mixture was extracted with 1-butanol (6 x 2 mL), and the organic layers combined were

washed with brine (6 mL). The organic solution was concentrated under reduced pressure, and the resultant residue was subjected to silica gel (deactivated with 10 wt% water) column chromatography eluted with $CH_{2Cl2/MeOH}$ (90:10, v/v). The separated product was crystallized from $CHCl_3$/MeOH to give **2f**. Mp 175.5–180.5 ℃. $[\alpha]^{25}_D$ = –133.2 (*c* 1.1, MeOH). IR (KBr): 3142, 3124, 3023, 2931, 2806, 2677, 1614, 1593, 1515, 1504, 1454, 1386, 1373, 1234 cm^{-1}. ^1H NMR (CD_3OD): δ 2.89 (dd, J_1 = 14.2 Hz, J_2 = 9.3 Hz, 1H), $_D$ 3.06 (dd, J_1 = 14.2 Hz, J_2 = 5.7 Hz, 1H), 3.77–3.85 (m, 2H), 4.25–4.34 (m, 1H), 6.59–6.64 (m, 2H), 6.82–6.87 (m, 2H), 6.92 (m, 1H), 7.16 (m, 1H), 7.47 (s, 1H). 13C NMR (CD_3OD): δ 39.27, 64.36, 65.79, 117.08, 119.85, 129.57, 130.27, 131.76, 139.00, 158.09. HR MASS calcd for [M + H]+ $C_{12}H_{15}N_2O_2$ 219.1134, found 219.1139. Anal. calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.87; H, 6.45; N, 12.58.

2g: Purified by silica gel (deactivated with 10 wt% water) column chromatography eluted with CH_2Cl_2/MeOH (99:1 to 95:5, v/v) followed by Kugelrohr distillation (3 mmHg, 160 ℃). Colorless oil. IR (NaCl): 3111, 3028, 2928, 1672, 1604, 1508, 1455 cm^{-1}. ^1H NMR (CD_3OD): δ 3.04 (t, *J* = 7.2 Hz, 2H), 4.16 (t, *J* = 7.2 Hz, 2H), 6.83 (m, 1H), 7.02–7.07 (m, 3H), 7.24–7.32 (m, 4H). 13C NMR (CD_3OD): δ 38.14, 48.80, 119.06, 127.28, 128.89, 129.06, 129.69, 137.38, 137.74. HR MASS calcd for [M + H]+ $C_{11}H_{13}N_2$ 173.1078, found 173.1072.

4a: Purified by alumina column chromatography eluted with hexane/CH_2Cl_2 (33:67 to 0:100, v/v). Mp 145.5– 150.0 ℃. $[\alpha]^{25}_D$ = +23.6 (*c* 1.2, MeOH). IR (KBr): 3111, 2846, 1654, 1532, 1505, 1436 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H), 3.98–4.01 (m, 2H), 4.90 (t, *J* = 5.9 Hz, 1H), $_D$6.72 (d, *J* = 1.4 Hz, 1H), 6.81 (d, *J* = 1.4 Hz, 1H), 7.26– 7.37 (m, 5H). 13C NMR ($CDCl_3$): δ 12.79, 53.80, 73.33, 120.00, 125.99, 126.49, 128.21, 128.72, 141.59, 145.20. HR MASS calcd for [M + H]+ $C_{12}H_{15}N_2O$ 203.1184, found 203.1180. Anal. calcd for $C_{12}H_{14}N_2O$ • 1/6H_2O: C, 70.21; H, 6.99; N, 13.65. Found: C, 70.08; H, 6.97; N, 13.15.

4d: Purified by alumina column chromatography eluted with hexane/CH_2Cl_2/MeOH (25:75:0 to 0:99:1, v/v/v). Viscous oil. $[\alpha]^{25}_D$ = –20.4 (*c* 3.3, MeOH). IR (NaCl): 3156, 2963, 1529, 1498, 1421, 1278, 1147, 1083, 1028, 990, 747, 680 cm^{-1}. ^1H NMR (CDCl3): δ 0.73 (d, *J* = 6.6 Hz, 3H),$_D$ 1.06 (d, *J* = 6.6 Hz, 3H), 1.96–2.08 (m, 1H), 2.35 (s, 3H), 3.68–3.75 (m, 1H), 3.79–3.85 (m, 1H), 3.93–3.97 (m, 1H), 6.83 (d, *J* = 1.5 Hz, 1H), 6.85(d, *J* = 1.5 Hz, 1H). $_{13}$C NMR ($CDCl_3$): δ 13.7, 19.9, 20.3, 30.7, 63.4, 65.2, 116.0, 127.3, 145.7. HR MASS calcd for $[M + H]^+$ $C_9H_{17}N_2O$ 169.1341, found 169.1341.

5a: Purified by alumina column chromatography eluted with hexane/CH_2Cl_2/MeOH (33:67:0 to 0:98:2, v/v/v). Viscous oil. $[\alpha]^{25}_D$ = +11.7 (*c* 1.0, MeOH). IR (KBr): 3061, 3027, 2931, 1952, 1881, 1811, 1671, 1603, 1528, 1493, 1453 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.71–2.77 (m, 2H), 2.98 (t, *J* = 7.8 Hz, 2H), 3.87–3.90 (m, 2H), 4.76 (t, *J* = 5.9 Hz, 2H), $_D$6.84 (d, *J* = 1.4 Hz, 1H), 6.91 (d, *J* = 1.4 Hz, 1H), 7.09– 7.12 (m, 2H), 7.16–7.37 (m, 9H). 13C NMR ($CDCl_3$): δ 28.38, 34.18, 53.14, 72.91, 119.97, 125.90, 126.12, 126.27, 127.95, 128.36, 128.39, 128.51, 141.15, 141.87, 147.75. HR MASS calcd for [M + H]+ $C_{19}H_{21}N_2O$ 293.1654, found 293.1659.

6a: Purified by alumina column chromatography eluted with hexane/CH_2Cl_2/MeOH (33:67:0 to 0:99:1, v/v/v). Mp 152.5–153.5 ℃. $[\alpha]^{25}_D$ = –3.6 (*c* 1.0, MeOH). IR (KBr): 3121, 3061, 3031, 2933, 2885, 2835, 2760, 1957, 1896, 1820, 1604, 1577, 1537, 1508, 1492, 1474, 1447, 1425 cm^{-} $_{D1}$. 1H NMR ($CDCl_3$): δ 4.15 (d, *J* = 6.0 Hz, 2H), 4.86 (t, *J* = 6.0 Hz, 1H), 7.01 (d, *J* = 1.4 Hz, 1H), 7.08 (d, *J* = 1.4 Hz, 1H), 7.14–7.17 (m, 2H), 7.26–7.29 (m, 3H), 7.35–7.43 (m, 5H). 13C NMR ($CDCl_3$): δ 53.89, 73.33, 121.55, 125.88, 127.87, 128.13, 128.48, 128.64, 128.80, 129.28, 130.46, 144.40, 148.04. HR MASS calcd for [M + H]+ $C_{17}H_{17}N_2O$ 265.1341, found 265.1341. Anal. calcd for $_{17}H_{16}N_2O$• H_2O: C, 72.26; H, 6.38; N, 9.92. Found: C, 72.91; H, 5.95; N, 9.91.

7a: Purified by silica gel (deactivated with 10 wt% water) column chromatography eluted with CH_2Cl_2/MeOH (100:0 to 90:10, v/v) followed by aluminum column chromatography eluted with hexane/$CH_{2Cl2/MeOH}$ (33:67:0 to 0:98:2, v/v/v). Mp 152.0–156.5 ℃. $[\alpha]^{25}_D$ = $_D$+22.9 (*c* 1.1, MeOH). IR (KBr): 3119, 3084, 3061, 2977, 2920, 2863, 2789, 2710, 1948, 1877, 1800, 1699, 1653, 1598, 1558, 1541, 1506, 1496, 1451, 1386, 1344. ^1H NMR ($CDCl_3$): δ 2.00 (s, 3H), 2.09 (s, 3H), 3.83–3.99 (m, 2H), 4.87 (dd, J_1 = 8.4 Hz, J_2 = 3.5 Hz, 1H), 7.28–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 8.82, 12.82, 53.67, 72.78, 121.89, 126.19, 128.25, 128.93, 133.14, 136.13, 141.75. HR MASS calcd for $[M + H]^+$ $C_{13}H_{17}N_2O$ 217.1341, found 217.1364. Anal.

calcd for $C_{13}H_{16}N_2O$• 1/4H_2O: C, 70.66; H, 7.47; N, 12.68. Found: C, 70.84; H, 7.48; N, 12.54.

8a: Purified by silica gel (deactivated with 10 wt% water) column chromatography eluted with CH_2Cl_2/MeOH (100:0 to 95:5, v/v). Mp 223.0–223.5 ℃. $[\alpha]^{25}_D$ = +63.2 (*c* 1.2, $CHCl_3$). IR (KBr): 3117, 3060, 2892, 2847, 2722, 1952, 1896, 1643, 1603, 1508, 1496, 1480, 1444. ^{1}H NMR ($CDCl_3$): δ 3.58 (dd, J_1 = 14.1 Hz, J_2 = 2.2 Hz, 1H), 3.74 (dd, J_1 = 14.1 Hz, J_2 = 9.6 Hz, 1H), 4.63 (dd, J_1 = 9.6 Hz, J_2 = 2.2 Hz, 1H), 6.67 (d, *J* = 6.9 Hz, 2H), 7.10–7.14 (m, 2H), 7.18–7.42 (m, 11H), 7.81 (s, 1H). ^{13}C NMR (CDCl3): δ 54.04, 72.48, 125.99, 126.76, 127.01, 128.02, 128.27, 128.77, 128.86, 129.08, 130.48, 131.70, 134.87, 137.35, 138.32, 141.63, 144.75. HR MASS calcd for $[M + H]^+$ $_{23}H_{31}N_2O$ 341.1654, found 341.1658. Anal. calcd for $_{23}H_{30}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.00; H, 6.06; N, 8.08. $_D$

8d: Purified by silica gel (deactivated with 10 wt% water) column chromatography eluted with CH_2Cl_2/MeOH (100:0 to 99:1, v/v). Mp 161.0–163.0 ℃. $[\alpha]^{25}_D$ = –55.9 (*c* 1.8, MeOH). IR (KBr): 3127, 2964, 1894, 1820, 1773, 1602, 1506 cm^{-1}. ^{1}H NMR (CD_3OD): δ 0.75 (d, *J* = 6.6 Hz, 3H), $_D$0.95 (d, *J* = 6.6 Hz, 3H), 2.17–2.29 (m, 1H), 3.56–3.63 (m, 1H), 3.85 (dd, J_1 = 11.7 Hz, J_2 = 3.3 Hz, 1H), 3.97 (dd, J_1= 11.7 Hz, J_2 = 6.6 Hz, 1H), 7.12–7.22 (m, 3H), 7.30–7.39 (m, 4H), 7.45–7.54 (m, 3H). 13C NMR ($CDCl_3$): δ 20.95, 32.56, 64.22, 65.76, 128.34, 128.89, 129.93, 130.84, 130.95, 132.23, 132.83, 133.77, 136.49, 137.64, 138.88. HR MASS calcd for [M + H]+ $C_{20}H_{23}N_2O$ 307.1810, found 307.1806. Anal. calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.27; H, 7.34; N, 8.97.

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