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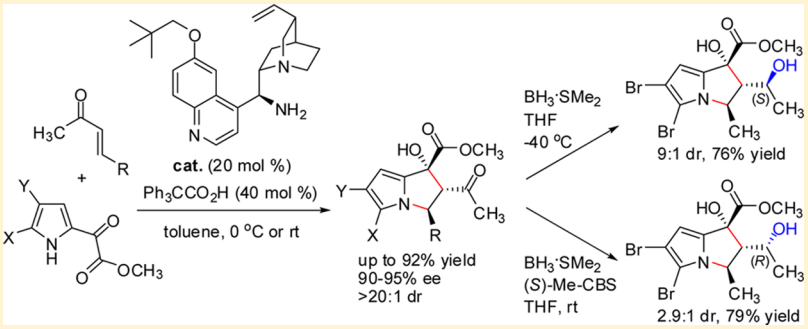
Cinchona-Based Primary Amine-Catalyzed Asymmetric Cascade Aza-Michael–Aldol Reactions of Enones with 2-(1*H*-Pyrrol-2-yl)-2-oxoacetates: Synthesis of Chiral Pyrrolizines with Multistereocenters

Hyo-Jun Lee and Chang-Woo Cho*

Department of Chemistry, Kyungpook National University, Daegu 702-701, Republic of Korea

Supporting Information



ABSTRACT: Cinchona-based primary amine-catalyzed cascade aza-Michael–aldol reactions of α,β-unsaturated ketones with 2-(1*H*-pyrrol-2-yl)-2-oxoacetates provided highly functionalized chiral pyrrolizines bearing multistereocenters including a chiral quaternary carbon center in good yields (up to 92%) with excellent levels of stereocontrol (90–95% ee, >20:1 dr in all cases). The ketone group in the cascade product was asymmetrically reduced to chiral secondary hydroxyl groups in good yields.

INTRODUCTION

Pyrrolizines are an important class of bicyclic heterocycles that exhibit a variety of appealing biological activities and thus have found application in the development of pharmaceuticals such as antitumor,[1] antileukemic,[2] analgesic, and anti-inflammatory[3] agents. However, despite their importance, little focus has been placed on the synthesis of chiral pyrrolizines. The known asymmetric synthesis of chiral pyrrolizines has utilized intramolecular cycloaddition of chiral pyrrole-based nitrone intermediates.[4] Recently, however, we reported the chiral diarylprolinol silyl ether-catalyzed asymmetric cascade aza-Michael–aldol reactions of α,β-unsaturated aldehydes with 2-trihaloacetylpyrroles as *N*-centered heteroaromatic nucleophiles as a new synthetic route to chiral pyrrolizines.[5] With the intent to prepare a wide variety of chiral pyrrolizines, we strategically utilized the organocatalytic asymmetric cascade aza-Michael–aldol reactions[6−8] of α,β-unsaturated ketones with 2-(1*H*-pyrrol-2-yl)-2-oxoacetates (Figure 1). The success of this reaction is based on the NH of the pyrroles having a low enough pK_a value to facilitate deprotonation by a base to generate the requisite pyrrole anions as the nucleophile for the initial aza-Michael reaction[9,10] in the cascade reaction. Furthermore, the α-keto ester group in the pyrroles, which acts as the electrophile for the subsequent aldol reaction, should be transformed into a versatile α-hydroxy ester group involving construction of a quaternary stereocenter.[11] Herein, we report the cinchona-based primary amine-catalyzed[12] asymmetric cascade aza-Michael–aldol reactions of α,β-unsaturated ketones with 2-(1*H*-pyrrol-2-yl)-2-oxoacetates that afford highly functionalized chiral pyrrolizines having three consecutive stereocenters (Figure 1). To the best of our knowledge, this is the only example of the use of α,β-unsaturated ketones as substrates in the organocatalytic asymmetric aza-Michael-participated cascade reactions with *N*-centered heteroaromatic nucleophiles. Concomitantly, the ketone group in the cascade product is asymmetrically reduced to versatile chiral secondary hydroxyl groups.

RESULTS AND DISCUSSION

As the initial step in the exploration of the feasibility of the organocatalytic asymmetric cascade reactions of α,β-unsaturated ketones with 2-(1*H*-pyrrol-2-yl)-2-oxoacetates, the cascade reactions of methyl 2-(4,5-dibromo-1*H*-pyrrol-2-yl)-2-oxoacetate (**1a**) to (*E*)-pent-3-en-2-one (**2a**) using $PhCO_2H$ (40 mol %) as the acid additive were performed in toluene at ambient temperature in the presence of the chiral secondary amine catalysts **I**–**III**, respectively (Table 1, entries 1–3). Neither of these catalysts afforded the corresponding cascade products, presumably due to steric constraints in generating the iminium intermediates[13] from the chiral secondary amines and the α,β-unsaturated ketone.[9d] However, in the case of the chiral primary amine catalyst **IV**, the cascade reaction furnished the desired cascade product **3a** in 32% yield and 39% ee as a single

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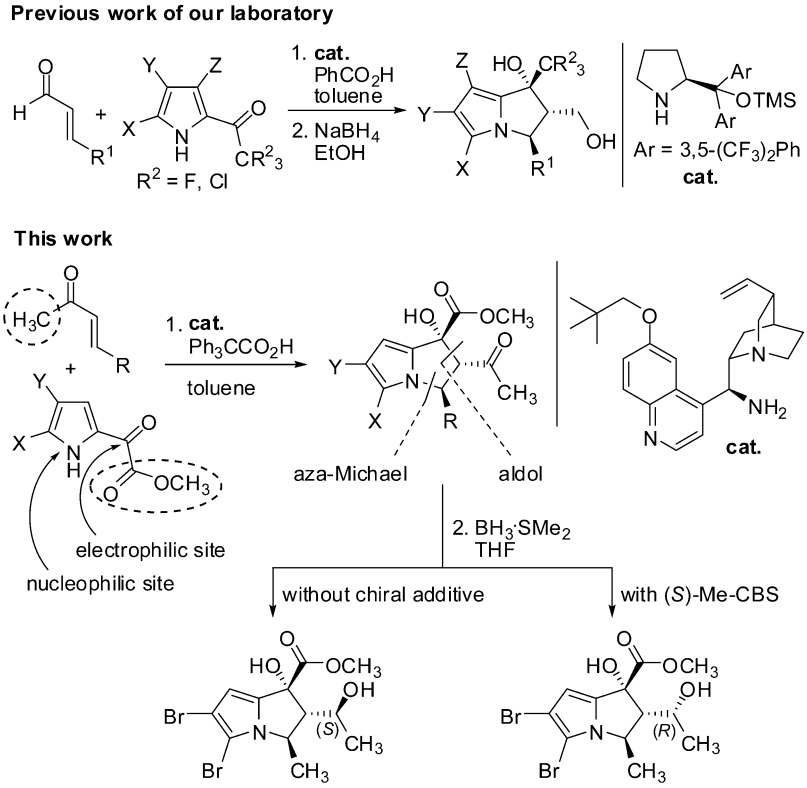

Figure 1. Organocatalytic asymmetric cascade aza-Michael–aldol reactions of α,β-unsaturated carbonyl compounds with pyrroles, followed by reductions.

diastereomer under otherwise identical conditions (Table 1, entry 4). Gratifyingly, the use of the quinine-derived primary amine catalyst **V** in the cascade reaction under identical conditions generated the cascade product **3a** in 70% yield and 84% ee as a single diastereomer (Table 1, entry 5). The yield and ee of the product **3a** were both decreased with the use of the catalyst **VI** having the hydroxyl group (Table 1, entry 6). Through modification of the methoxy group of the quinine-based primary amine catalyst **V** in the cascade reactions, the catalyst **VII** having the neopentyloxy group was identified as the optimal (fine-tuned) catalyst, affording a yield of 78% and 87% ee (Table 1, entry 7). Finally, when $PhCO_2H$ was replaced with Ph_3CCO_2H under otherwise identical conditions, the cascade product **3a** was obtained in 86% yield and 91% ee as a single diastereomer (Table 1, entry 8).

Subsequently, the scope of 2-(1*H*-pyrrol-2-yl)-2-oxoacetates **1** as nucleophiles in the enantio- and diastereoselective organocatalytic cascade aza-Michael–aldol reactions of (*E*)-pent-3-en-2-one (**2a**) was explored under the optimized conditions (Scheme 1). A series of methyl 2-(1*H*-pyrrol-2-yl)-2-oxoacetates bearing various dihalo substituents were selected as nucleophiles due to the potential for carbon–carbon bond formation utilizing the halo groups in the pyrrolizine products to generate a wide variety of chiral pyrrolizine derivatives.[14] In all cases, the chiral pyrrolizines **3a–f** were obtained as single diastereomers in good yields and excellent enantioselectivities. In particular, the dibromopyrrole moiety in **3a** has been found to be an important class of marine natural products that display a variety of interesting biological activities.[15]

Therefore, further exploration of the asymmetric organocatalytic cascade reactions with methyl 2-(4,5-dibromo-1*H*-pyrrol-2-yl)-2-oxoacetate (**1a**) were executed by varying the α,β-unsaturated ketones **2** at 0 °C for 24 or 48 h under otherwise identical conditions (Scheme 2). The cascade reactions of the dibromopyrrole **1a** with various α,β-unsaturated ketones bearing alkyl, aromatic-substituted alkyl, heteroaromatic-substituted alkyl, variously protected hydroxyalkyl, benzyl-protected mercaptoalkyl, and doubly *N*-protected aminoalkyl substituents afforded the desired pyrrolizines **3g–o** as single diastereomers in good yields and excellent enantioselectivities.

In an effort to explore further manipulation of the cascade products, the asymmetric reduction of the ketone **3a** was carried out with $BH_3{\cdot}SMe_2$ (120 mol %) at −40 °C in THF to afford the chiral secondary alcohol **4a** possessing four consecutive stereocenters, in 76% yield as a 9:1 mixture of diastereomers (Scheme 3).[16] The product may be formed by the hydride attack on the less hindered face of the carbonyl group through a closed transition state in which the boron atom would be intramoleculary coordinated by the two oxygens of the hydroxyl group and the ketone group. Contrastingly, in order to obtain the diastereomeric secondary alcohol **5a** as major reduction product, the asymmetric reduction of **3a** was carried out with $BH_3{\cdot}SMe_2$ (120 mol %) and (*S*)-(−)-2-methyl-CBS-oxazaborolidine (120 mol %) at room temperature in THF to afford the desired chiral secondary alcohol **5a** in 79% yield as a 2.9:1 mixture of diastereomers.[17,18] The absolute stereochemical assignment of all cascade products **3a–o** and the reduction products **4a–5a** is based upon single-crystal X-ray diffraction analysis of the isonicotinic ester derivative **6a**, which was generated from **5a**, as described in the Supporting Information. From the absolute stereochemistry of the pyrrolizines, the proposed transition states of the cascade reaction are briefly outlined in Figure 2. The aza-Michael reaction of the iminium intermediate with the pyrrole nucleophile provides the aza-Michael intermediate (Figure 2

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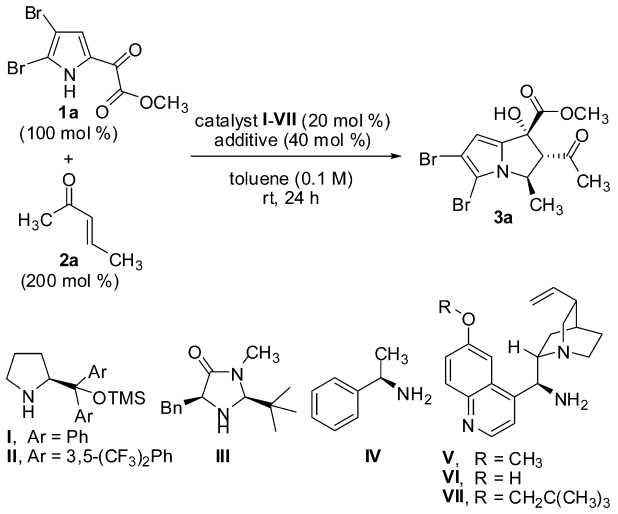
Table 1. Optimization of Organocatalytic Asymmetric Cascade Aza-Michael–Aldol Reactions of Methyl 2-(4,5-Dibromo-1*H*-pyrrol-2-yl)-2-oxoacetates (1a) to (*E*)-Pent-3-en-2-one (2a)[a]



entry	catalyst	additive	yield[b] (%)	ee[c] (%)
1	**I**	$PhCO_2H$	nr[d]	
2	**II**	$PhCO_2H$	nr[d]	
3	**III**	$PhCO_2H$	nr[d]	
4	**IV**	$PhCO_2H$	32	39
5	**V**	$PhCO_2H$	70	84
6	**VI**	$PhCO_2H$	33	74
7	**VII**	$PhCO_2H$	78	87
8	**VII**	Ph_3CCO_2H	86	91

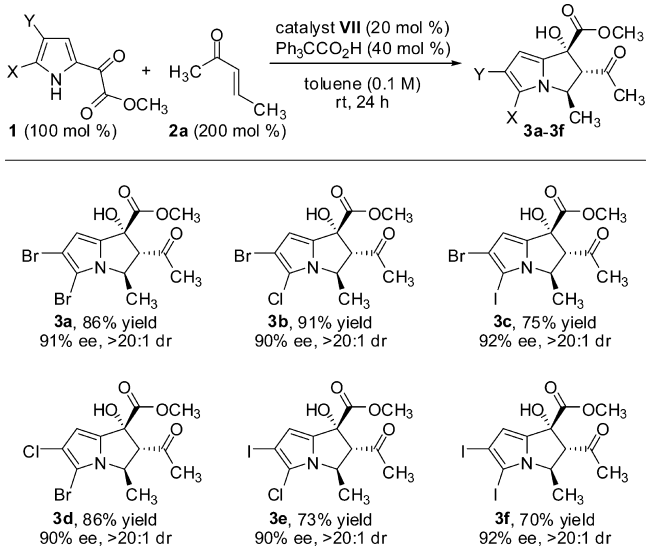
[a]Procedure: **2a** (200 mol %) was added to a mixture of **1a** (100 mol %), catalyst (20 mol %), and additive (40 mol %) in toluene (0.1 M) in one portion. The mixture was stirred at rt for 24 h. The solvent was removed, and the residue was isolated by silica gel chromatography. Diastereomeric ratio was determined by ^{1}H NMR and >20:1 dr in all cases. [b]Isolated yield. [c]Determined by chiral HPLC analysis (Chiralpak AD-H). [d]No reaction.

(a)), which subsequently undergoes aldol reaction followed by hydrolysis to afford the cascade product (Figure 2 (b)).

CONCLUSION

In conclusion, the enantio- and diastereoselective cascade aza-Michael–aldol reaction of *α,β*-unsaturated ketones with 2-(1*H*-pyrrol-2-yl)-2-oxoacetates has been achieved using the fine-tuned quinine-based primary amine **VII** as the organocatalyst and triphenylacetic acid as the acid additive. The cascade reaction affords highly functionalized chiral pyrrolizines having three consecutive stereocenters in good yields (up to 92%) with excellent levels of stereocontrol (90–95% ee, >20:1 dr in all cases). This is the only example of the use of *α,β*-unsaturated ketones as substrates in the organocatalytic asymmetric aza-Michael-participated cascade reactions with *N*-centered heteroaromatic nucleophiles. In addition, depending on the reduction conditions, the ketone group in the cascade product **3a** is asymmetrically reduced to versatile chiral secondary hydroxyl groups with either *S* or *R* configurations. This strategy provides a convenient synthetic route for generating various chiral pyrrolizines. The application of these species in the synthesis of biologically active compounds is the topic of further studies.

Scheme 1. Asymmetric Organocatalytic Cascade Aza-Michael–Aldol Reactions of (*E*)-Pent-3-en-2-one (2a) with Various Pyrroles 1[a]



[a]Procedure: **2a** (0.4 mmol) was added to a mixture of **1** (0.2 mmol), catalyst **VII** (0.04 mmol), and Ph_3CCO_2H (0.08 mmol) in toluene (2 mL) in one portion. The mixture was stirred at rt for 24 h. Enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H or Chiralcel OJ-H). Diastereomeric ratio was determined by ^{1}H NMR.

EXPERIMENTAL SECTION

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer with tetramethylsilane as the internal reference. HRMS data were measured on a magnetic sector-electric sector double focusing mass analyzer with EI or FAB ionization source. Enantiomeric excess was determined by HPLC analysis with chiral stationary phase column. Pyrroles **1**[19] and *α,β*-unsaturated ketones **2**[20] were prepared according to the reported procedures.

Preparation of Catalysts I–VII. Catalysts **I–IV** are commercially available. Catalysts **V–VI** were prepared according to the reported procedures.[21]

*(1S)-[6-(Neopentyloxy)quinolin-4-yl](8-vinylquinuclidin-2-yl)-methanamine (Catalyst **VII**).* To a cooled (0 °C) solution of (1*R*)-[6-(neopentyloxy)quinolin-4-yl](8-vinylquinuclidin-2-yl)methanol[22] (1.41 g, 3.7 mmol) and triphenylphosphine (1.16 g, 4.5 mmol) in THF (25 mL, 0.15 M) were added diphenyl phosphoryl azide (0.96 mL, 4.5 mmol) and diisopropyl azidocarboxylate (0.87 mL, 4.5 mmol), and then the mixture was stirred at room temperature for 12 h. The mixture was then heated at 50 °C for 2 h, triphenylphosphine (1.16 g, 4.5 mmol) was added, and heating was maintained for 2 h. The mixture was cooled to room temperature, and H_2O (0.5 mL) was added and then stirred for 3 h. After removal of THF, the residue was extracted with CH_2Cl_2 and 1.0 N HCl. The aqueous phase was then alkalinized with NH_4OH and washed with CH_2Cl_2. The combined organic layer was dried with $MgSO_4$. Filtration, concentration, and purification by flash chromatography (SiO_2: EtOAc/MeOH/NH_4OH = 100:100:1) provided the catalyst **VII** in 64% yield (0.90 g, 2.37 mmol) as light yellow oil: $[\alpha]^{24}_D$ +90.1 (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.74 (d, *J* = 4.4 Hz, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.59 (s, 1H), 7.44 (d, *J* = 4.4 Hz, 1H), 7.41 (dd, *J* = 9.2, 2.8 Hz, 1H), 5.86–5.77 (m, 1H), 5.04–4.96 (m, 2H), 4.59 (d, *J* = 9.6 Hz, 1H), 3.78–3.72 (m, 2H), 3.32–3.20 (m, 2H), 3.10–3.08 (m, 1H), 2.85–2.78 (m, 2H), 2.29–2.28 (m, 1H), 1.88 (s, 2H), 1.64–1.63 (m, 1H), 1.60–1.52 (m, 2H), 1.48–1.42 (m, 1H), 1.10 (s, 9H), 0.79–0.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 157.5, 147.6, 146.8, 144.6, 141.7, 131.5, 128.7, 121.6, 119.6, 114.2, 102.4, 78.0, 77.2, 61.8, 56.2, 40.9, 39.7, 31.9, 28.1, 27.5, 26.6, 26.0; FTIR (neat) 3382, 2952, 2865,

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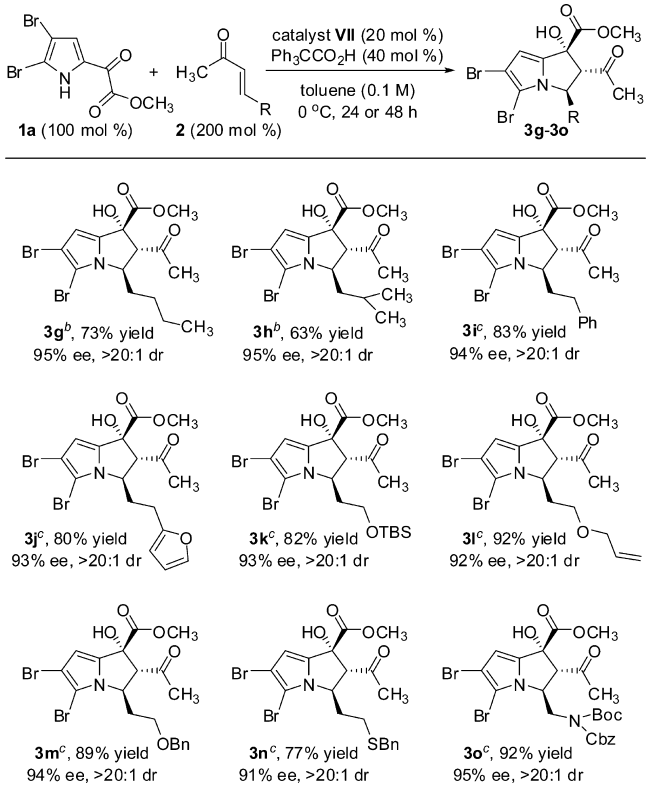
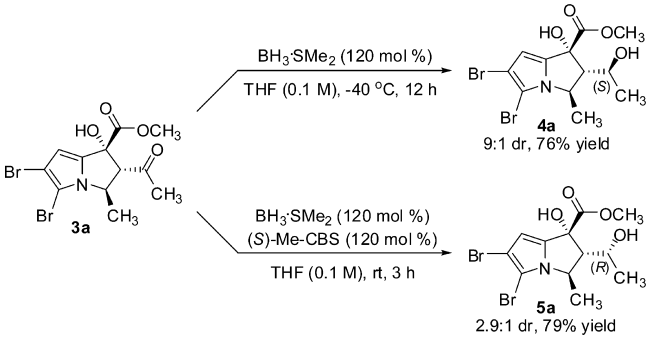
Scheme 2. Asymmetric Organocatalytic Cascade Aza-Michael–Aldol Reactions of Methyl 2-(4,5-Dibromo-1*H*-pyrrol-2-yl)-2-oxoacetates (1a) with Various *α,β*-Unsaturated Ketones 2[a]



[a]Procedure: **2** (0.4 mmol) was added to a mixture of **1a** (0.2 mmol), catalyst **VII** (0.04 mmol), and Ph_3CCO_2H (0.08 mmol) in toluene (2 mL) in one portion. The mixture was stirred at 0 °C for 24 or 48 h. Enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H). Diastereomeric ratio was determined by ^1H NMR. [b]At 0 °C for 24 h. [c]At 0 °C for 48 h.

Scheme 3. Asymmetric Reductions of the Ketone 3a



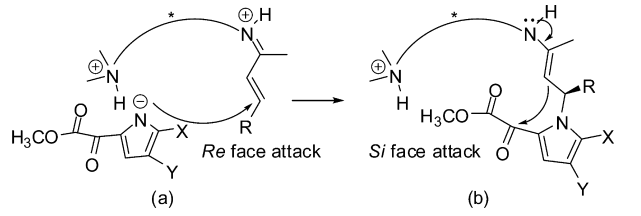


Figure 2. Proposed transition states of (a) the aza-Michael reaction and (b) the subsequent aldol reaction.

1619, 1507, 1455, 1364, 1226, 1048, 1018, 911, 851 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{24}H_{33}N_3O$ 379.2624, found 379.2622.

Typical Procedure for the Synthesis of Racemic Pyrrolizines 3. *α,β*-Unsaturated ketone **2** (0.4 mmol) was added to a mixture of pyrrole **1** (0.2 mmol), (±)-*trans*-1,2-diaminocyclohexane (0.1 mmol), and Ph_3CCO_2H (0.08 mmol) in toluene (2 mL) in one portion. The reaction mixture was stirred at rt for 12 h. The solvent was removed, and the residue was purified by silica gel column chromatography to furnish the corresponding racemic pyrrolizines **3**.

Typical Procedure for the Organocatalytic Asymmetric Cascade Aza-Michael–aldol Reactions of *α,β*-Unsaturated Ketones with 2-(1*H*-Pyrrol-2-yl)-2-oxoacetates. *α,β*-Unsaturated ketone **2** (0.4 mmol) was added to a mixture of pyrrole **1** (0.2 mmol), catalyst **VII** (0.04 mmol), and Ph_3CCO_2H (0.08 mmol) in toluene (2 mL) in one portion. The reaction mixture was stirred at 0 °C or rt for 24 or 48 h. The solvent was removed, and the residue was purified by silica gel column chromatography to furnish the corresponding products **3**.

*(1R,2R,3R)-Methyl 2-acetyl-5,6-dibromo-1-hydroxy-3-methyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3a**):* yellow oil (68 mg, 86%); $[\alpha]^{22}_D$ −19.8 (*c* 1, CH_3OH, 91% ee); ^1H NMR (400 MHz, $CDCl_3$) *δ* 6.07 (s, 1H), 4.99–4.92 (m, 1H), 3.94 (s, 3H), 3.92 (dd, *J* = 7.2, 0.8 Hz, 1H), 3.48 (d, *J* = 0.8 Hz, 1H), 2.19 (s, 3H), 1.67 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 201.4, 172.0, 135.9, 104.3, 101.8, 98.3, 76.5, 68.8, 56.3, 54.0, 29.8, 19.9; FTIR (neat) 3465, 2954, 1742, 1720, 1438, 1366, 1305, 1240, 1182, 1106, 1043, 788 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{12}H_{13}Br_2NO_4$ 392.9211, found 392.9210; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.95 mL/min, *λ* = 254 nm) 17.0 min (minor isomer), 18.8 min (major isomer).

*(1R,2R,3R)-Methyl 2-acetyl-6-bromo-5-chloro-1-hydroxy-3-methyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3b**):* yellow oil (64 mg, 91%); $[\alpha]^{23}_D$ −19.0 (*c* 1, CH_3OH, 90% ee); ^1H NMR (400 MHz, $CDCl_3$) *δ* 6.02 (s, 1H), 5.00–4.94 (m, 1H), 3.94 (s, 3H), 3.92 (dd, *J* = 7.2, 0.8 Hz, 1H), 3.46 (d, *J* = 0.8 Hz, 1H), 2.19 (s, 3H), 1.66 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 201.3, 172.0, 133.8, 112.4, 103.5, 97.8, 76.6, 68.9, 55.8, 54.1, 29.8, 19.5; FTIR (neat) 3467, 2926, 1743, 1720, 1447, 1366, 1307, 1240, 1182, 1108, 1041, 789 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{12}H_{13}BrClNO_4$ 348.9716, found 348.9714; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.9 mL/min, *λ* = 254 nm) 16.2 min (minor isomer), 17.5 min (major isomer).

*(1R,2R,3R)-Methyl 2-acetyl-6-bromo-5-iodo-1-hydroxy-3-methyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3c**):* yellow oil (66 mg, 75%); $[\alpha]^{22}_D$ −24.4 (*c* 1, CH_3OH, 92% ee); ^1H NMR (400 MHz, $CDCl_3$) *δ* 6.13 (s, 1H), 4.92–4.86 (m, 1H), 3.93 (d, *J* = 6.8 Hz, 1H), 3.92 (s, 3H), 3.69 (s, 1H), 2.18 (s, 3H), 1.67 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 201.6, 172.0, 139.2, 109.4, 105.0, 76.3, 68.8, 66.4, 56.9, 54.0, 29.9, 20.5; FTIR (neat) 3459, 2953, 1740, 1719, 1363, 1304, 1237, 1181, 1103, 1042, 773 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{12}H_{13}BrNO_4I$ 440.9073, found 440.9073; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.95 mL/min, *λ* = 254 nm) 21.0 min (minor isomer), 22.6 min (major isomer).

*(1R,2R,3R)-Methyl 2-acetyl-5-bromo-6-chloro-1-hydroxy-3-methyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3d**):* yellow oil (60 mg, 86%); $[\alpha]^{22}_D$ −23.9 (*c* 1, CH_3OH, 90% ee); ^1H NMR (400 MHz, $CDCl_3$) *δ* 6.02 (s, 1H), 4.98–4.92 (m, 1H), 3.94 (s, 3H), 3.91 (dd, *J* = 7.2, 0.8 Hz, 1H), 3.47 (d, *J* = 0.8 Hz, 1H), 2.19 (s, 3H), 1.67 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 201.3, 172.0, 134.9, 116.1, 101.9, 95.9, 76.6, 68.7, 56.3, 54.1, 29.8, 19.9; FTIR (neat) 3447, 2927, 1740, 1720, 1443, 1367, 1313, 1239, 1182, 1106, 1044, 787 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{12}H_{13}BrClNO_4$ 348.9716, found 348.9714; HPLC (Chiralcel OJ-H, hexane/IPA = 95/5, 0.9 mL/min, *λ* = 254 nm) 36.1 min (major isomer), 41.0 min (minor isomer).

*(1R,2R,3R)-Methyl 2-acetyl-5-chloro-6-iodo-1-hydroxy-3-methyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3e**):* yellow oil (58 mg, 73%); $[\alpha]^{23}_D$ −14.0 (*c* 1, CH_3OH, 90% ee); ^1H NMR (400 MHz, $CDCl_3$) *δ* 6.07 (s, 1H), 5.01–4.95 (m, 1H), 3.94 (d, *J* = 6.8 Hz, 1H), 3.93 (s, 3H), 3.58 (s, 1H), 2.18 (s, 3H), 1.65 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 201.3, 171.9, 135.7, 116.5, 108.0, 76.2, 69.1, 64.8, 55.6, 54.0, 29.7, 19.4; FTIR (neat) 3464, 2953, 1742, 1720, 1439, 1365, 1296, 1240, 1181, 1108, 1041, 791 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{12}H_{13}ClNO_4I$ 396.9578, found 396.9578; HPLC

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(Chiralpak AD-H, hexane/IPA = 95/5, 0.9 mL/min, λ = 254 nm) 15.8 min (minor isomer), 17.9 min (major isomer).

*(1R,2R,3R)-Methyl 2-acetyl-5,6-diiodo-1-hydroxy-3-methyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3f**):* yellow oil (68 mg, 70%); $[\alpha]^{22}_{D}$ −23.2 (*c* 1, CH_3OH, 92% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 6.19 (s, 1H), 4.94−4.88 (m, 1H), 3.96 (d, *J* = 6.4 Hz, 1H), 3.92 (s, 3H), 3.55 (d, *J* = 0.8 Hz, 1H), 2.19 (s, 3H), 1.67 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 172.1, 140.7, 110.1, 79.4, 75.8, 72.9, 69.1, 57.0, 54.1, 29.9, 20.6; FTIR (neat) 3446, 2924, 1734, 1717, 1436, 1360, 1294, 1234, 1180, 1102, 1040, 772 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{12}H_{13}NO_4I_2$ 488.8934, found 488.8935; HPLC (Chiralpak AD-H, hexane/IPA = 93/7, 0.95 mL/min, λ = 254 nm) 17.3 min (minor isomer), 19.3 min (major isomer).

*(1R,2R,3R)-Methyl 2-acetyl-5,6-dibromo-3-butyl-1-hydroxy-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3g**):* yellow oil (64 mg, 73%); $[\alpha]^{22}_{D}$ −22.0 (*c* 1, CH_3OH, 95% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 1H), 4.97 (ddd, *J* = 8.8, 6.4, 2.8 Hz, 1H), 4.10 (d, *J* = 6.4 Hz, 1H), 3.93 (s, 3H), 3.47 (d, *J* = 0.8 Hz, 1H), 2.20 (s, 3H), 2.18−2.09 (m, 1H), 2.04−1.94 (m, 1H), 1.42−1.32 (m, 2H), 1.29−1.19 (m, 1H), 1.14−1.03 (m, 1H), 0.91 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 172.0, 136.0, 104.3, 101.9, 98.1, 76.9, 65.5, 60.0, 54.0, 32.1, 30.1, 25.9, 22.4, 13.8; FTIR (neat) 3467, 2956, 1741, 1723, 1438, 1366, 1306, 1232, 1176, 1088, 1047, 777 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{15}H_{19}Br_2NO_4$ 434.9681, found 434.9679; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.95 mL/min, λ = 254 nm) 10.7 min (minor isomer), 12.3 min (major isomer).

*(1R,2R,3R)-Methyl 2-acetyl-5,6-dibromo-1-hydroxy-3-isobutyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3h**):* yellow oil (55 mg, 63%); $[\alpha]^{22}_{D}$ −79.6 (*c* 1, CH_3OH, 95% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 1H), 4.94 (ddd, *J* = 10.8, 4.8, 3.2 Hz, 1H), 4.05 (d, *J* = 4.8 Hz, 1H), 3.91 (s, 3H), 3.67 (s, 1H), 2.24 (ddd, *J* = 13.6, 10.4, 3.2 Hz, 1H), 2.20 (s, 3H), 1.59 (ddd, *J* = 14.0, 10.8, 3.6 Hz, 1H), 1.54−1.44 (m, 1H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.95 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 172.1, 135.5, 104.4, 102.1, 97.9, 77.3, 66.7, 59.0, 54.1, 43.3, 30.3, 25.4, 23.8, 21.4; FTIR (neat) 3465, 2957, 1741, 1724, 1438, 1365, 1307, 1236, 1173, 1088, 796 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{15}H_{19}Br_2NO_4$ 434.9681, found 434.9680; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.95 mL/min, λ = 254 nm) 10.7 min (minor isomer), 12.1 min (major isomer).

*(1R,2R,3R)-Methyl 2-acetyl-5,6-dibromo-1-hydroxy-3-phenethyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3i**):* yellow oil (81 mg, 83%); $[\alpha]^{20}_{D}$ −50.9 (*c* 1, CH_3OH, 94% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.28 (m, 2H), 7.23−7.17 (m, 3H), 6.10 (s, 1H), 5.04 (ddd, *J* = 8.8, 6.0, 2.8 Hz, 1H), 4.14 (d, *J* = 6.0 Hz, 1H), 3.94 (s, 3H), 3.47 (d, *J* = 0.4 Hz, 1H), 2.66−2.58 (m, 1H), 2.53−2.38 (m, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 172.0, 140.2, 136.0, 128.5, 128.2, 126.3, 104.5, 102.2, 98.2, 76.9, 65.3, 59.8, 54.1, 33.6, 30.1, 30.1; FTIR (neat) 3470, 2924, 1738, 1718, 1437, 1362, 1304, 1230, 1180, 1091, 731 cm^{-1}; HRMS (FAB) calcd for $[M + 1]^+$ $C_{19}H_{19}Br_2NO_4$ 482.9681, found 482.9683; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.95 mL/min, λ = 254 nm) 20.2 min (minor isomer), 21.3 min (major isomer).

*(1R,2R,3R)-Methyl 2-acetyl-5,6-dibromo-3-[2-(furan-2-yl)ethyl]-1-hydroxy-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3j**):* yellow oil (76 mg, 80%); $[\alpha]^{22}_{D}$ −28.0 (*c* 1, CH_3OH, 93% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 1.6, 0.8 Hz, 1H), 6.29 (dd, *J* = 3.2, 2.0 Hz, 1H), 6.09 (s, 1H), 6.01 (dd, *J* = 3.2, 0.8 Hz, 1H), 5.02 (ddd, *J* = 8.8, 6.0, 2.8 Hz, 1H), 4.05 (d, *J* = 6.0 Hz, 1H), 3.92 (s, 3H), 3.61 (s, 1H), 2.70−2.61 (m, 1H), 2.58−2.44 (m, 2H), 2.42−2.34 (m, 1H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 172.0, 153.7, 141.2, 136.0, 110.3, 105.6, 104.5, 102.3, 98.2, 76.8, 65.3, 59.5, 54.1, 30.4, 30.1, 22.8; FTIR (neat) 3467, 2925, 1740, 1720, 1437, 1363, 1305, 1234, 1154, 1092, 1008, 734 cm^{-1}; HRMS (FAB) calcd for $[M + 1]^+$ $C_{17}H_{18}O_5NBr_2$ 473.9552, found 473.9554; HPLC (Chiralpak AD-H, hexane/IPA = 90/10, 0.9 mL/min, λ = 254 nm) 12.5 min (minor isomer), 15.3 min (major isomer).

*(1R,2R,3R)-Methyl 2-acetyl-5,6-dibromo-3-[2-(tert-butyldimethylsilyloxy)ethyl]-1-hydroxy-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3k**):* yellow oil (88 mg, 82%); $[\alpha]^{22}_{D}$ −31.1 (*c* 1, CH_3OH, 93% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 1H), 5.02 (ddd, *J* = 8.8, 5.6, 2.8 Hz, 1H), 4.50 (d, *J* = 6.0 Hz, 1H), 3.90 (s, 3H), 3.73 (t, *J* = 6.0 Hz, 2H), 3.63 (s, 1H), 2.56−2.49 (m, 1H), 2.18 (s, 3H), 2.15−2.07 (m, 1H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 172.3, 136.1, 104.3, 102.1, 98.0, 76.9, 65.5, 59.3, 59.3, 54.0, 35.3, 30.1, 25.7, 18.2, −5.4, −5.4; FTIR (neat) 3474, 2954, 2927, 1740, 1722, 1437, 1360, 1306, 1252, 1093, 834, 777 cm^{-1}; HRMS (FAB) calcd for $[M + 1]^+$ $C_{19}H_{29}Br_2NO_5Si$ 537.0182, found 537.0185; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.95 mL/min, λ = 254 nm) 7.80 min (minor isomer), 8.85 min (major isomer).

*(1R,2R,3R)-Methyl 2-acetyl-3-[2-(allyloxy)ethyl]-5,6-dibromo-1-hydroxy-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3l**):* yellow oil (86 mg, 92%); $[\alpha]^{19}_{D}$ −45.0 (*c* 1, CH_3OH, 92% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1H), 5.88−5.78 (m, 1H), 5.26−5.20 (m, 1H), 5.19−5.16 (m, 1H), 5.02 (ddd, *J* = 9.6, 6.4, 2.8 Hz, 1H), 4.44 (d, *J* = 6.4 Hz, 1H), 3.92 (s, 3H), 3.86−3.84 (m, 2H), 3.59−3.54 (m, 1H), 3.52 (s, 1H), 3.51−3.46 (m, 1H), 2.76−2.69 (m, 1H), 2.15 (s, 3H), 2.13−2.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 172.4, 136.2, 134.2, 117.3, 104.2, 102.2, 97.9, 76.7, 72.0, 66.6, 66.6, 59.6, 54.1, 33.2, 30.3; FTIR (neat) 3330, 2958, 1739, 1704, 1369, 1309, 1229, 1105, 1050, 955, 797 cm^{-1}; HRMS (FAB) calcd for $[M + 1]^+$ $C_{16}H_{19}Br_2NO_5$ 462.9630, found 462.9633; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.95 mL/min, λ = 254 nm) 23.5 min (minor isomer), 26.0 min (major isomer).

*(1R,2R,3R)-Methyl 2-acetyl-3-[2-(benzyloxy)ethyl]-5,6-dibromo-1-hydroxy-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3m**):* yellow oil (92 mg, 89%); $[\alpha]^{22}_{D}$ −45.1 (*c* 1, CH_3OH, 94% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 6.06 (s, 1H), 5.04 (ddd, *J* = 9.6, 6.0, 2.8 Hz, 1H), 4.43 (d, *J* = 6.0 Hz, 1H), 4.38 (s, 2H), 3.86 (s, 3H), 3.64−3.52 (m, 2H), 3.48 (d, *J* = 0.8 Hz, 1H), 2.73−2.66 (m, 1H), 2.19−2.10 (m, 1H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 172.3, 137.6, 136.2, 128.3, 127.7, 127.7, 104.3, 102.2, 97.9, 76.8, 73.1, 66.8, 66.5, 59.6, 54.0, 33.1, 30.1; FTIR (neat) 3446, 2926, 2861, 1740, 1721, 1437, 1362, 1306, 1234, 1096, 739, 698 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{20}H_{21}Br_2NO_5$ 512.9786, found 512.9788; HPLC (Chiralpak AD-H, hexane/IPA = 90/10, 0.9 mL/min, λ = 254 nm) 16.4 min (minor isomer), 29.8 min (major isomer).

*(1R,2R,3R)-Methyl 2-acetyl-3-[2-(benzylthio)ethyl]-5,6-dibromo-1-hydroxy-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3n**):* yellow oil (82 mg, 77%); $[\alpha]^{22}_{D}$ −51.0 (*c* 1, CH_3OH, 91% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.23 (m, 5H), 6.06 (s, 1H), 4.98 (ddd, *J* = 8.4, 6.0, 2.4 Hz, 1H), 4.05 (d, *J* = 6.0 Hz, 1H), 3.90 (s, 3H), 3.73 (s, 2H), 3.49 (d, *J* = 1.2 Hz, 1H), 2.47−2.32 (m, 2H), 2.26−2.15 (m, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 171.9, 137.6, 136.0, 128.8, 128.5, 127.1, 104.5, 102.3, 98.0, 76.8, 65.5, 59.3, 54.1, 36.0, 32.1, 30.1, 25.6; FTIR (neat) 3466, 2953, 1740, 1721, 1437, 1359, 1306, 1237, 1180, 1091, 770, 702 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{20}H_{21}Br_2NO_4S$ 528.9558, found 528.9553; HPLC (Chiralpak AD-H, hexane/IPA = 90/10, 0.95 mL/min, λ = 254 nm) 13.8 min (minor isomer), 18.8 min (major isomer).

*(1R,2R,3S)-Methyl 2-acetyl-3-[[(benzyloxycarbonyl)(tert-butoxycarbonyl)amino]methyl]-5,6-dibromo-1-hydroxy-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**3o**):* yellow oil (119 mg, 92%); $[\alpha]^{22}_{D}$ +26.0 (*c* 1, CH_3OH, 95% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.33 (m, 5H), 6.07 (s, 1H), 5.23 (d, *J* = 2.8 Hz, 2H), 5.20−5.15 (m, 1H), 4.65 (dd, *J* = 14.0, 4.4 Hz, 1H), 4.38 (d, *J* = 5.6 Hz, 1H), 3.98 (dd, *J* = 14.0, 9.2 Hz, 1H), 3.88 (s, 3H), 3.56 (d, *J* = 0.4 Hz, 1H), 2.02 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 172.1, 153.9, 151.8, 136.5, 135.1, 128.5, 128.5, 104.8, 102.7, 98.5, 83.8, 76.7, 68.9, 64.7, 58.5, 54.1, 47.9, 29.7, 27.8; FTIR (neat) 3446, 2980, 1734, 1370, 1303, 1258, 1150, 1116, 777 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{25}H_{28}Br_2N_2O_8$ 642.0212, found 642.0214; HPLC (Chiralpak AD-H, hexane/IPA = 80/20, 0.85 mL/min, λ = 254 nm) 11.0 min (major isomer), 13.6 min (minor isomer).

Asymmetric Reduction of the Ketone 3a Using BH_3·SMe_2. To a cooled (−40 °C) solution of the ketone **3a** (79 mg, 0.2 mmol) in THF (2 mL, 0.1 M) was added BH_3·SMe_2 (2.0 M solution in THF, 0.12 mL, 0.24 mmol), and then the mixture was stirred at −40 °C for 12 h. The mixture was quenched with MeOH and then stirred at room temperature for 30 min. After the addition of H_2O, the mixture was

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extracted with ethyl acetate. The organic layer was washed with 1.0 N HCl and brine and then dried over $MgSO_4$. Filtration, concentration, and purification by flash chromatography (SiO_2: 30% EtOAc in hexanes) provided **4a** as the major diastereomer in 68% yield (54 mg) and **5a** as the minor diastereomer in 8% yield (6 mg), respectively (total yield: 76%).

Asymmetric Reduction of the Ketone 3a Using BH_3·SMe_2 and (*S*)-Me-CBS. To (*S*)-(−)-2-methyl-CBS-oxazaborolidine (1.0 M solution in toluene, 0.24 mL, 0.24 mmol) was added BH_3·SMe_2 (2.0 M solution in THF, 0.12 mL, 0.24 mmol) at room temperature. After 15 min, a solution of the ketone **3a** (79 mg, 0.2 mmol) in THF (2 mL, 0.1 M) was added dropwise, and the mixture was stirred at room temperature for 3 h. The mixture was quenched with MeOH and then stirred for 30 min. After the addition of H_2O, the mixture was extracted with ethyl acetate. The organic layer was washed with 1.0 N HCl and brine and then dried over $MgSO_4$. Filtration, concentration, and purification by flash chromatography (SiO_2: 30% EtOAc in hexanes) provided **5a** as the major diastereomer in 59% yield (47 mg) and **4a** as the minor diastereomer in 20% yield (16 mg), respectively (total yield: 79%).

*(1R,2S,3R)-Methyl 5,6-dibromo-1-hydroxy-2-[(S)-1-hydroxyethyl]-3-methyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**4a**):* ivory oil; $[\alpha]^{23}_{D}$ −52.1 (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (s, 1H), 4.51−4.45 (m, 1H), 4.13−4.05 (m, 1H), 4.02 (s, 1H), 3.85 (s, 3H), 3.09 (d, *J* = 7.6 Hz, 1H), 2.90 (dd, *J* = 6.8, 6.8 Hz, 1H), 1.70 (d, *J* = 6.0 Hz, 3H), 1.34 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 137.1, 103.7, 101.7, 97.5, 77.8, 66.0, 62.8, 57.5, 53.7, 21.5, 20.0; FTIR (neat) 3446, 2975, 1733, 1437, 1381, 1256, 1163, 1128, 1031, 969, 783 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{12}H_{15}Br_2NO_4$ 394.9368, found 394.9364.

*(1R,2S,3R)-Methyl 5,6-dibromo-1-hydroxy-2-[(R)-1-hydroxyethyl]-3-methyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**5a**):* ivory oil; $[\alpha]^{25}_{D}$ −62.0 (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (s, 1H), 4.79−4.73 (m, 1H), 4.33−4.28 (m, 1H), 4.17 (s, 1H), 3.84 (s, 3H), 2.83 (d, *J* = 2.8 Hz, 1H), 2.79 (dd, *J* = 4.8, 2.4 Hz, 1H), 1.68 (d, *J* = 6.4 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 136.5, 103.7, 101.7, 97.3, 77.9, 65.1, 62.4, 55.4, 53.9, 22.1, 20.6; FTIR (neat) 3467, 2976, 1739, 1437, 1380, 1337, 1256, 1163, 1127, 1030, 774 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{12}H_{15}Br_2NO_4$ 394.9368, found 394.9370.

*(1R,2S,3R)-Methyl 5,6-dibromo-1-hydroxy-2-[(R)-1-(isonicotinoyloxy)ethyl]-3-methyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate (**6a**).* To a cooled (0 °C) solution of **5a** (116 mg, 0.3 mmol) in CH_2Cl_2 (1 mL, 0.3 M) were added triethylamine (0.19 mL, 1.05 mmol) and isonicotinoyl chloride hydrochloride (330 mg, 0.75 mmol), and then the mixture was stirred at 0 °C for 1 h. The mixture was then stirred at room temperature for 12 h. The mixture was quenched by saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with saturated NH_4Cl and brine and then dried over $MgSO_4$. Filtration, concentration, and purification by flash chromatography (SiO_2: 60% Et_2O in hexanes) provided the ester **6a** in 55% yield (83 mg, 0.165 mmol) as yellow solid: mp 142−143 °C; $[\alpha]^{23}_{D}$ −46.3 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 6.0 Hz, 2H), 7.45−7.43 (m, 2H), 6.03 (s, 1H), 5.69−5.63 (m, 1H), 4.71−4.65 (m, 1H), 4.17 (s, 1H), 3.85 (s, 3H), 3.06 (dd, *J* = 4.8, 4.4 Hz, 1H), 1.74 (d, *J* = 6.4 Hz, 3H), 1.46 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 163.9, 150.4, 137.3, 136.9, 122.7, 104.1, 101.6, 97.0, 77.2, 70.4, 60.7, 57.7, 53.9, 21.3, 18.6; FTIR (neat) 3446, 2925, 1733, 1437, 1410, 1380, 1285, 1243, 1162, 1121, 756 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{18}H_{18}Br_2N_2O_5$ 499.9582, found 499.9585.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds. Chiral HPLC analysis data of **3a−o**. X-ray crystallographic data for **6a** (CIF) (CCDC 909688). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cwcho@knu.ac.kr.

Notes

The authors declare no competing financial interest.

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