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Synthesis of the Core Tricyclic Ring Domain of (−)-Schulzeine B

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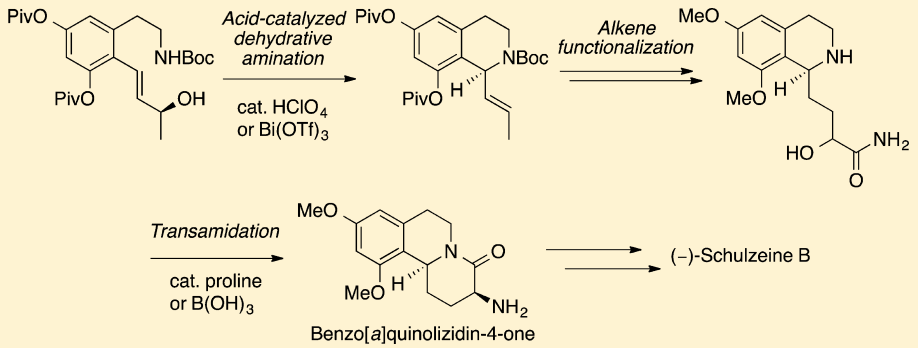
Supporting Information



ABSTRACT: A formal synthesis of (−)-schulzeine B, a marine natural alkaloid possessing potent antidiabetic activity, has been achieved. A benzo[*a*]quinolizidin-4-one is a common skeleton of schulzeines (A−C). (−)-Schulzeine B possesses an (*S*)-stereogenic center at the C-3 carbon. The chiral (3*S*,11b*S*)-3-amino-9,11-dimethoxybenzo[*a*]quinolizidin-4-one has been prepared efficiently from (2-bromo-3,5-dihydroxyphenyl)acetonitrile in 17 steps including (i) a dehydrative intramolecular amination catalyzed by $HClO_4$ and (ii) a proline or boric acid catalyzed transcycloamidation reaction for the construction of the δ-lactam ring.

Schulzeines A−C (**1**−**3**) were first isolated from an extract of a marine sponge *Penares schulzei* by Fusetani and co-workers.[1] Because they exhibit potent α-glucosidase and viral neuraminidase inhibitory activities,[1] schulzeines have received much attention as potential molecular targets for the total synthesis and design of antidiabetic and antiviral molecules. Schulzeines A−C are composed of two characteristic units; a unique fused tricyclic 3-aminobenzo[*a*]quinolizidin-4-one ring unit (**4a**, **4b**) and a sulfated 28 carbon chain fatty acid unit (**5a**, **5b**) combined with an amide bond (Figure 1). Schulzeine B has shown the most potent inhibition among A−C toward α-glucosidase, and it is characterized by an (*S*)-configuration at the C-11b carbon of the tricyclic benzo[*a*]quinolizidin-4-one. In contrast, schulzeines A and C possess the opposite (*R*)-configuration at the same carbon on the ring.

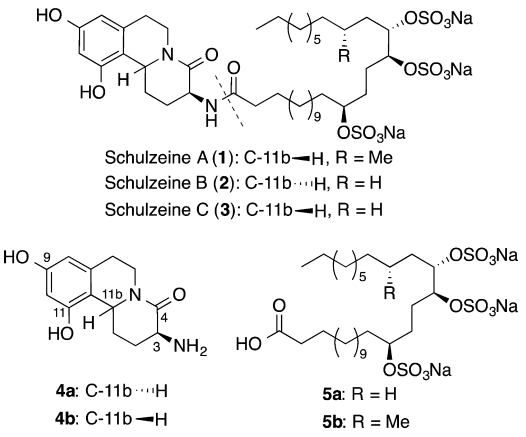


Figure 1. Schulzeines A, B, and C.

Although four total syntheses[2] and four formal syntheses[3] have been reported to date, chiral benzo[*a*]quinolizidin-4-one is still one of the most attractive ring units in alkaloids for synthetic chemists. The stereoselective synthesis of the benzo[*a*]quinolizidin-4-one ring involves two key steps that must be overcome. The first is the construction of a stereogenic center at C-11b of the benzo[*a*]quinolizidin-4-one. The second is the preparation of the δ-lactam ring. Regarding these problems selective approaches have been reported (Scheme 1). Wardrop's group has employed a Pictet−Spengler reaction for the ring construction.[2c] Ojima's group has executed the formation of both the (*R*)- and (*S*)-stereocenters at C-11b of the benzo[*a*]quinolizidin-4-one stereodifferentially. They used Pd-catalyzed intramolecular asymmetric allylic amination of an allyl carbonate with a chiral ligand, and the ring closing metathesis was performed for the synthesis of the δ-lactam ring.[3a] Itoh's group has used Cu-catalyzed asymmetric allylation and the intramolecular amidation for the δ-lactam ring synthesis.[3b] Despite these considerable efforts in the synthesis of the benzo[*a*]quinolizidin-4-one ring, a new stereodefined

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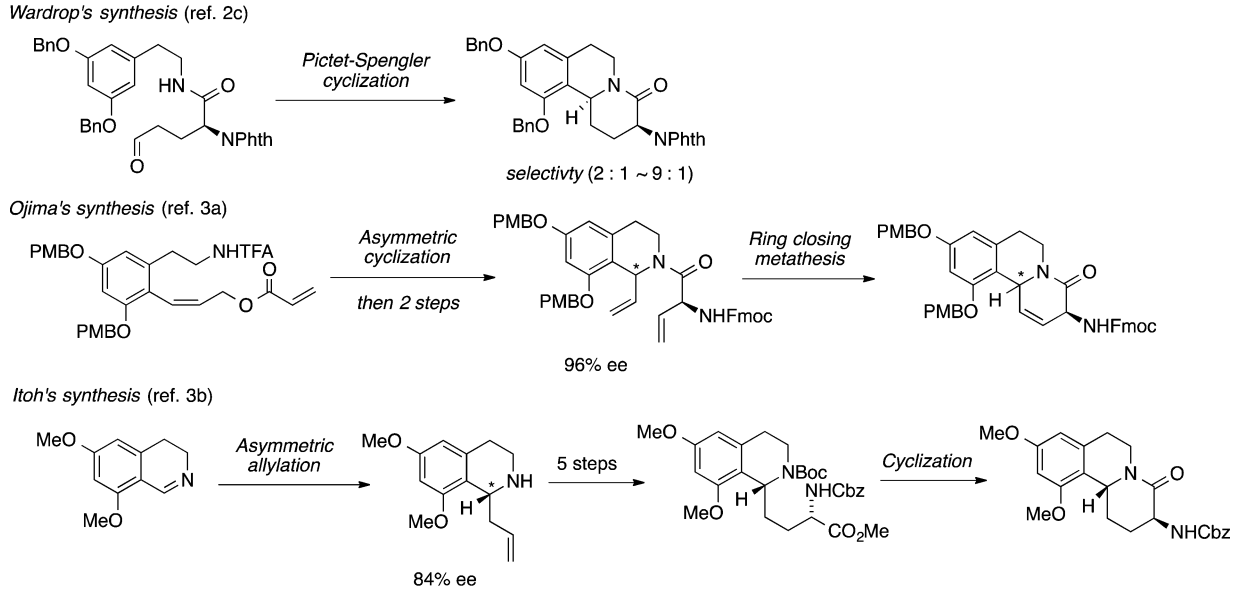
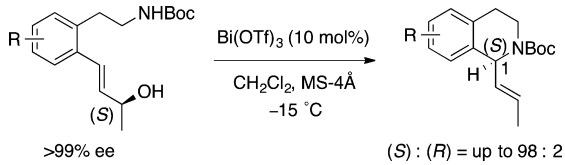
Scheme 1. Construction in Benzo[*a*]quinolizidin-4-one in Literature



synthesis to access the tricyclic ring is still desirable for diverse syntheses.

We have reported a $Bi(OTf)_3$-catalyzed dehydrative intramolecular stereospecific amination of ζ-amino (*S*)-allyl alcohols for the construction of (*S*)-alkenyl-substituted tetrahydroisoquinoline[4,5] (Scheme 2).

Scheme 2. Dehydrative Intramolecular Stereospecific Amination Reaction[4]

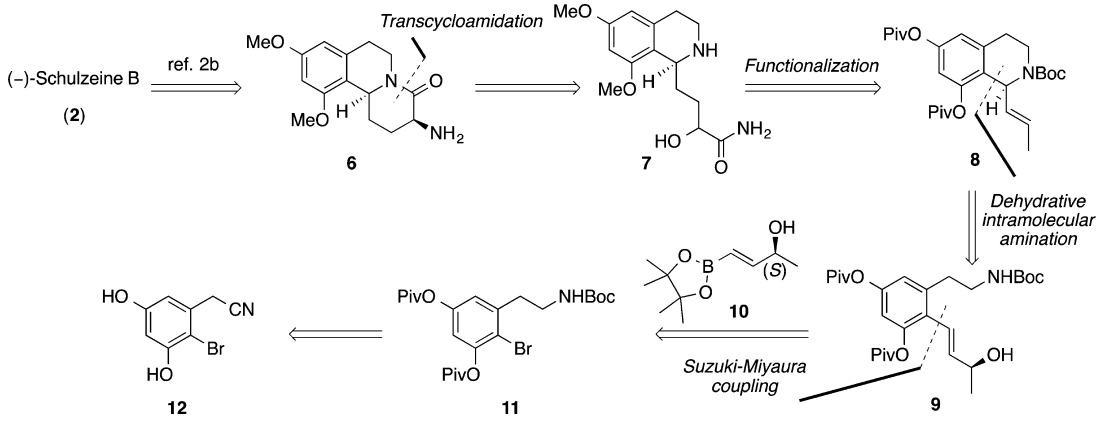


In the context of the synthesis of chiral (1*S*)-alkenyltetrahydroisoquinoline, we envisaged that the benzo[*a*]quinolizidin-4-one ring could be derived from the 1-alkenyl substituted tetrahydroisoquinoline. In this paper, we report a new synthetic approach to the benzo[*a*]quinolizidin-4-one ring and the formal synthesis of (−)-schulzeine B.

Our retrosynthetic strategy for (−)-schulzeine B is illustrated in Scheme 3. We have set (3*S*,11b*S*)-3-aminobenzo[*a*]quinolizidin-4-one **6** as the target compound, which was converted to schulzeine B by Liu and Romo.[2b] We expected that a direct transcycloamidation of α-hydroxycarboxamide **7** with the secondary amine could give **6** directly. Carboxamide **7** would be prepared from 1-alkenyl substituted tetrahydroisoquinoline **8** by conventional functionalizations. Tetrahydroisoquinoline **8** with the (*S*)-configuration on the C-1 stereogenic center could be formed by dehydrative intramolecular amination from the chiral allyl alcohol **9**. This cyclization was effectively conducted by a $Bi(OTf)_3$-catalyst from ζ-amino (*S*)-allyl alcohols by stereospecific amination.[4] Allyl alcohol **9** with an (*S*)-configuration could be prepared by Suzuki−Miyaura coupling of *N*-Boc-protected β-phenethylamine **11** with chiral boronate ester **10**[6] possessing an (*S*)-chiral allyllic alcohol unit. Compound **11** can be accessed from the corresponding aryl bromide **12**.

Based on the above synthetic plan, the synthesis started with the treatment of **12** with pivaloyl chloride and DMAP followed by the PtO_2-catalyzed hydrogenation of **13** in the presence of Boc_2O to give *N*-Boc protected amine **11** in 63% yield (quantitative yield based on the recovery of the starting

Scheme 3. Retrosynthetic Plan for (−)-Schulzeine B



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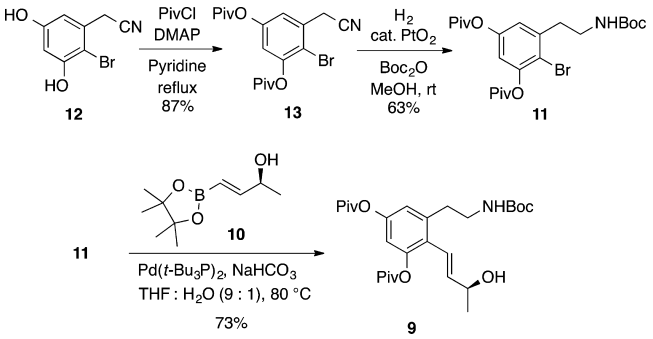
material) (Scheme 4). Suzuki−Miyaura coupling was performed with the sterically congested aryl bromide **11** and

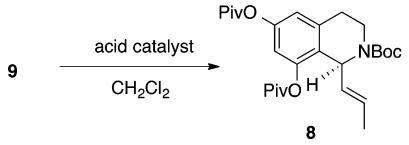
Scheme 4. Synthesis of Allyl Alcohol 9



optically pure borate **10** (ee >99%) having an (*S*)-configuration of the stereogenic center under the following reaction conditions; $Pd(t\text{-}Bu_3P)_2$ (5 mol %), $NaHCO_3$ (2 equiv), THF/H_2O (9:1), 80 °C, 6 h. The desired coupling product **9** was obtained in 73% yield from **11**.

Next, we examined the key intramolecular dehydrative amination under the original reaction conditions reported previously,[4] with $Bi(OTf)_3$ (10 mol %) catalyst in CH_2Cl_2 at −15 °C. However, no reaction occurred under the conditions in this case. The cyclization proceeded slowly at 0 °C to provide **8** in only 31% yield after 24 h with an enantiomeric ratio of 93:7 (Scheme 5, condition A).[7] While, when the

Scheme 5. Dehydrative Intramolecular Amination Reaction of Allyl Alcohol 9



Conditions and results

Condition A:
$Bi(OTf)_3$ (10 mol%), 0 °C, 1 h: 31%, (*S*) : (*R*) = 93 : 7

Condition B:
$Bi(OTf)_3$ (10 mol%), rt, 1 h: 61%, (*S*) : (*R*) = 90 : 10

Condition C:
$HClO_4$ (10 mol%), 0 °C, 3.5 h: 84%, (*S*) : (*R*) = 94 : 6

reaction was conducted at rt, its chemical yield was improved moderately to a 61% yield but with slightly lower selectivity (90:10) (condition B). After screening acid catalysts and examining several conditions, we fortunately found that $HClO_4$ was an excellent catalyst for this reaction. The reaction of **9** conducted at 0 °C for 3.5 h in the presence of $HClO_4$ (10 mol %) gave **8** with an 84% yield and excellent selectivity (S/R = 94:6) (condition C). The details of this $HClO_4$-catalyzed dehydrative amination are under investigation.[8]

Gratified by this result, we continued to work on constructing the benzo[*a*]quinolizidin-4-one ring (Scheme 6). First, we needed to replace the two *O*-pivaloyl groups of **8** with an *O*-methoxy group. Reductive deprotection of the *O*-pivaloyl groups by $LiBH_4$ converted **8** to diol **14** in 98% yield. *O*-Methylation of the two phenolic hydroxyl groups under the standard conditions gave **15** in 93% yield. Next, sequential ozonolysis and a Wittig reaction provided α,β-unsaturated ester **16** in 84% combined yield. During this process, no racemization occurred on the chiral benzylic carbon center.[9] The alkene of **16** was hydrogenated in the presence of Pearlman's catalyst to give saturated ester **17** in 90% yield. $LiBH_4$ reduction of the ester afforded alcohol **18** in 79% yield. PCC oxidation of **18** and successive silylcyanation of the resulting aldehyde with TMSCN and acidic workup afforded **19** in 62% yield in two steps. At this stage, we had a cyanohydrin **19** in hand. An acid hydrolysis of the cyano group with HCl at room temperature gave α-hydroxycarboxamide **7** which was subjected to transcycloamidation.[10]

Transamidation reactions have recently been developed under the catalytic conditions[11] with organocatalysts as well as metal-catalyzed conditions.[12] Primary amides were prepared intermolecularly with good to excellent yields by organocatalysts such as L-proline[11a] and boric acid.[11b]

We examined first the L-proline-catalyzed transamidation reaction for **7**. Fortunately, the intramolecular amidation between α-hydroxycarboxamide with the secondary amine worked quite well under nonsolvent conditions at 100 °C for 12 h in the presence of L-proline (0.5 equiv) and gave the desired product **20** as a diastereomixture in 72% yield from cyanohydrin **19**. The reaction using either L-proline or DL-proline gave a similar result in chemical yield and stereoselectivity. Nguyen et al. had reported $B(OH)_3$-catalyzed amidation of carboxamide with amine intermolecularly. Fortunately, their conditions were also successful in our case and the reaction using $B(OH)_3$ (0.5 equiv) in H_2O at 100 °C for 6 h gave **20** in 78% yield.

In order to complete the formal synthesis, we needed to install the β-amino function at the C-3 position by replacing the hydroxyl group with an amino group. Mesylation of the hydroxyl group of **20** using MsCl, DMAP, and Et_3N followed by treatment with NaN_3 afforded a diastereomeric mixture of **21a** and **21b** (1.3:1) in 68% combined yield. These diastereoisomers were readily separated by flash column chromatography, and the less polar isomer **21a** was identified as having an (*S*)-configuration at the C-3 carbon. Thus, the spectroscopic data for compound **21a** matched precisely with the reported data including the specific rotation.[13] The undesired stereoisomer **21b** was epimerized in methanol in the presence of a catalytic amount of NaOMe to give a mixture of **21a** and **21b** (0.8:1). To this end, reduction of the azide group in **21a** afforded the desired amine **6** in 65% yield. The structure of **6** was supported by the ^1H, ^{13}C NMR and mass spectra and indicated completion of the formal total synthesis of (−)-schulzeine B.[14]

In conclusion, we have developed a new synthetic approach for the formal synthesis of (−)-schulzeine B by two key reactions, which are the $HClO_4$-catalyzed dehydrative intramolecular amination of ζ-amino allyl alcohol, with high stereospecificity, and the proline- or $B(OH)_3$-catalyzed intramolecular transamidation of α-hydroxycarboxamide. The current synthesis provides an efficient route to construct the benzo[*a*]quinolizidin-4-one ring with (*S*)-stereocenters on C-3 and C-11b for (−)-schulzeine B. This method would permit the synthesis for other two schulzeines A and C with use of (*R*)-allylic alcohol instead of (*S*)-allylic alcohol in the step for the synthesis of *ent*-**9**.

■ EXPERIMENTAL SECTION

General Information. ^1H NMR chemical shifts were internally referenced to the residual proton signals in $CDCl_3$ (δ 7.26) and CD_3OD (δ 3.31). ^{13}C NMR chemical shifts were internally referenced

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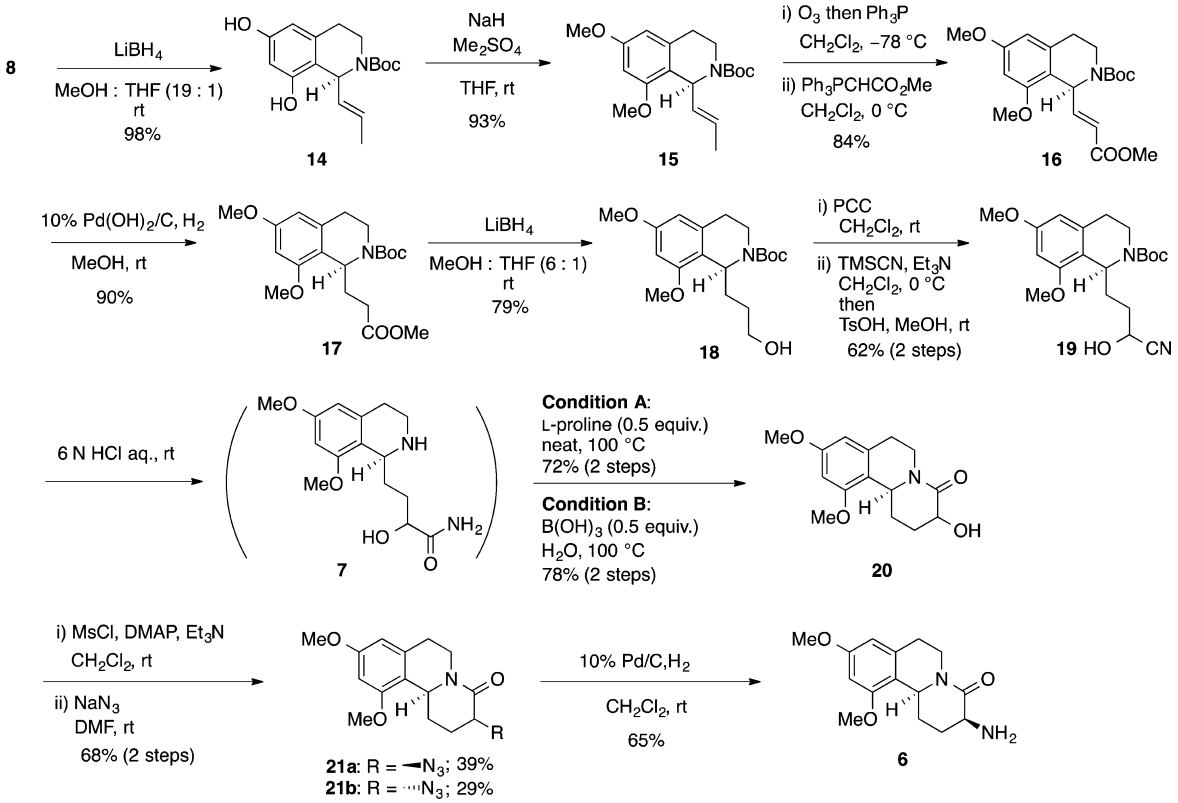
Scheme 6. Synthesis of 6



to the deuterated solvent signals in $CDCl_3$ (δ 77.00) and CD_3OD (δ 49.00). Low- and High-resolution mass spectra were acquired using the electron impact (EI) or first atom bombardment (FAB) mode with a double focusing magnetic sector. THF was dried over sodium benzophenone ketyl. CH_2Cl_2 was dried over P_4O_{10}. These solvents were distilled freshly before use.

2-(2-Bromo-3,5-dihydroxyphenyl)acetonitrile (12). To a solution of 2-(2-bromo-3,5-dimethoxyphenyl)acetonitrile[15] (2.09 g, 8.16 mmol) in $CHCl_3$ (40 mL) was added BBr_3 (3.1 mL, 32.7 mmol, 4 equiv) dropwise at 0 °C, and then the mixture was refluxed for 24 h. The reaction mixture was cooled to 0 °C, and water was added to the reaction mixture. The mixture was extracted with ethyl acetate three times, and the combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated with a rotary evaporator. The residue was purified by silica gel column chromatography (50% EtOAc in hexane) to give 1.43 g of **12** (6.27 mmol, 76%) as a colorless solid. Mp 160−163 °C; R_f = 0.40 (hexane/EtOAc = 1:1); ^{1}H NMR (270 MHz, acetone-d_6) δ 7.89 (br-s, 2H), 5.69 (d, J = 2.7 Hz, 1H), 5.60 (d, J = 2.7 Hz, 1H), 2.96 (s, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 159.4, 157.0, 134.2, 118.9, 110.2, 104.6, 102.3, 25.9; MS (EI): m/z = 227 $[M + H]^+$; Anal. Calcd for $C_8H_6BrNO_2$: C, 42.14; H, 2.65; N, 6.14. Found: C, 42.41; H, 2.43; N, 5.85.

2-(2-Bromo-3,5-dipivaloyloxyphenyl)acetonitrile (13). The solution of **12** (2.54 g, 11.1 mmol), DMAP (1.34 g, 11.9 mmol, 1.1 equiv), and pivaloyl chloride (3.5 mL, 28.3 mmol, 2.5 equiv) in pyridine (35 mL) was stirred for 30 min at 100 °C. After the reaction was cooled to room temperature, water was added to the mixture and extracted with EtOAc. The organic extract was washed with 1 N HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated with a rotary evaporator. The residue was purified by silica gel column chromatography (10% EtOAc in hexane) to give 3.86 g of **13** (9.74 mmol, 87%) as a white solid. Mp 108−109 °C; R_f = 0.30 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 2.7 Hz, 1H), 6.95 (d, J = 2.7 Hz, 1H), 3.87 (s, 2H), 1.39 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 175.6, 150.6, 149.5, 132.1, 120.1, 117.5, 116.3, 114.2, 39.4, 39.3, 27.2, 27.0, 25.1. MS (EI): m/z = 395 $[M]^+$; Anal. Calcd for $C_{18}H_{22}BrNO_4$: C, 54.56; H, 5.60; N, 3.53. Found: C, 54.62; H, 5.47; N, 3.38.

***N*-Boc-2-(2-bromo-3,5-dipivaloyloxyphenyl)ethylamine (11).** A mixture of 2-(2-bromo-3,5-dipivaloyloxyphenyl)acetonitrile (**13**) (1.50 g, 3.79 mmol), PtO_2 (75.0 mg, 5% w/w), Boc_2O (1.08 g, 4.94 mmol, 1.3 equiv), and MeOH (20 mL) was charged in a pressure bottle. The bottle was pressurized with H_2 (20 atm). The mixture was stirred at room temperature for 24 h, and then hydrogen was released. The solvent was removed, and the residue was purified by silica gel column chromatography (2.5% EtOAc in benzene) to give 1.20 g of **11** (2.40 mmol, 63% yield) as a colorless solid and 0.554 g of **13** (36% recovery). Mp 125−126 °C; R_f = 0.70 (5% EtOAc in benzene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, J = 2.4 Hz, 1H), 6.81 (d, J = 2.4 Hz, 1H), 4.62 (br-s, 1H), 3.38 (q_{AB}, J = 6.8 Hz, 2H), 3.00 (t, J = 6.8 Hz, 2H), 1.44 (s, 9H), 1.39 (s, 9H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 175.8, 155.8, 150.2, 149.0, 140.9, 121.1, 115.5, 114.9, 79.2, 39.9, 39.3, 39.1, 36.4, 28.4, 27.2, 27.1; MS (EI): m/z = 499 $[M]^+$; Anal. Calcd for $C_{23}H_{34}BrNO_6$: C, 55.20; H, 6.85; N, 2.80. Found: C, 55.11; H, 6.76; N, 2.63.

***(S,E)*-*N*-Boc-2-[2-(3-hydroxybut-1-enyl)-3,5-dipivaloyloxyphenyl]ethylamine (9).** To a solution of **11** (1.00 g, 2.00 mmol) and **10**[6] (594 mg, 3.0 mmol, 1.5 equiv) in a mixture of THF (27 mL) and H_2O (3 mL) was added $NaHCO_3$ (504 mg, 6.0 mmol, 3.0 equiv). To this mixture was added Pd(t-Bu_3P)$_2$ (51 mg, 0.1 mmol, 5 mol %), and the reaction mixture was degassed with Ar. The whole mixture was stirred at 80 °C for 6 h. Then after the mixture was cooled to room temperature, water was added to the reaction mixture. The mixture was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (30% EtOAc in hexane) to give 720 mg of **9** (1.46 mmol, 73%) as a white solid. Mp 101−102 °C; R_f = 0.40 (30% EtOAc in hexane); $[\alpha]_D^{20}$ −0.52 (c 0.43, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, J = 2.2 Hz, 1H), 6.68 (d, J = 2.2 Hz, 1H), 6.45 (d, J = 16.2 Hz, 1H), 5.92 (dd, J = 16.2, 6.2 Hz, 1H), 4.80 (br-s, 1H), 4.40−4.46 (m, 1H), 3.19 (q_{AB}, J = 7.9 Hz, 2H), 2.75−2.91 (m, 2H), 1.43 (s, 9H), 1.39−1.28 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0,

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175.3, 175.1, 150.5, 149.3, 148.3, 132.2, 132.0, 120.0, 118.9, 117.3, 116.3, 116.2, 114.0, 39.3, 39.2, 39.1, 27.0, 26.9, 26.8, 24.9; MS (FAB): m/z = 514 $[M + Na]^+$; Anal. Calcd for $C_{27}H_{41}NO_7$: C, 65.96; H, 8.41; N, 2.85. Found: C, 65.69; H, 8.39; N, 2.73.

$HClO_4$-Catalyzed Intramolecular Amination. To a solution of **9** (1.60 g, 3.25 mmol) in CH_2Cl_2 (22 mL) was added $HClO_4$ (33 μL in 9.8 M solution, 0.323 mmol, 10 mol %) at 0 °C. The mixture was stirred for 3.5 h at the same temperature, and the reaction was quenched with cold sat. $NaHCO_3$. The mixture was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (10% EtOAc in hexane) to give 1.30 g of **8** (2.74 mmol, 84%) as an oil. The enantiomeric ratio of $(S)/(R)$ = 94:6 was determined by chiral HPLC analysis after replacing the *N*-Boc group with a *N*-trifluoroacetyl group (see details in Supporting Information). R_f = 0.70 (30% EtOAc in hexane); $[\alpha]_D^{20}$ +9.7 (*c* 0.45, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) The spectrum was observed as a mixture of rotamers of carbamate. δ 6.69 (s, 2H × 0.4), 6.67 (s, 2H × 0.6), 5.72 (br-s, 1H × 0.4), 5.40–5.51 (m, 1.6H), 5.11–5.17 (m, 1H), 3.95–4.14 (m, 0.6H), 3.82–3.89 (m, 0.4 Hz), 3.04–3.19 (m, 1H), 2.78–2.89 (m, 1H), 2.68–2.59 (m, 1H), 1.52–1.58 (m, 3H), 1.40 (s, 9H), 1.26 (s, 9H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture of rotamers of carbamate) δ 176.7, 175.8, 154.5, 149.7, 149.5, 148.1, 147.8, 137.5, 137.2, 129.1, 128.1, 127.8, 125.4, 125.2, 118.9, 118.7, 113.8, 79.9, 79.7, 51.3, 50.4, 39.3, 39.1, 37.7, 36.4, 28.4, 27.1, 27.0, 17.5; MS (EI): m/z = 473 $[M]^+$; Anal. Calcd for $C_{27}H_{39}NO_6$: C, 68.47; H, 8.30; N, 2.96. Found: C, 68.30; H, 8.25; N, 2.77.

Determination of the Enantiomeric Purity for the Cyclization Product 8. The enantiomeric purity of **8** was unable to determined by the ordinary method. The determination of the enantiomeric purity of **8** was performed after transformation to *N*-trifluoroacetamide **22**. The separation was made by chiral HPLC in the following conditions; HPLC column (Amycoat, YMC Co., Ltd.), Eluent (0.5% isopropanol in hexane), Flow rate (0.4 mL/min), Temperature (20 °C), Detection (254 nm), Retention time (t_S = 15.5 min, t_R = 18.0 min).

Compound **8** was treated with TMSOTf (1.5 equiv) in CH_2Cl_2 (0.06 M) at 0 °C under a nitrogen atmosphere. After 1.5 h, the reaction mixture was quenched with sat. $NaHCO_3$. The mixture was extracted with EtOAc, and the organic extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated with a rotary evaporator. The crude product was dissolved in pyridine (0.021 M) under a nitrogen atmosphere. Trifluoroacetic anhydride (1.5 equiv) was added, and the mixture was heated at 100 °C for 3 h. After cooling water was added to the reaction mixture, the mixture was extracted with EtOAc three times. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated with a rotary evaporator. The residue was purified by silica gel column chromatography (10% EtOAc in hexane) to give **22** as an oil quantitatively. R_f = 0.6 (20% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) The spectrum was observed as a mixture of rotamers of the carbamate. δ 6.74 (s, 2H × 0.35), 6.72 (s, 2H × 0.65), 6.02 (d, J = 3.7 Hz, 1H × 0.65), 5.54 (br-s, 1H × 0.35), 5.43–5.49 (m, 1H), 5.32–5.18 (m, 1H), 4.30–4.36 (m, 1H × 0.35), 3.85–3.90 (m, 0.65), 3.49–3.56 (m, 1H × 0.65), 3.28–3.21 (m, 1H × 0.35), 2.89–2.99 (m, 1H), 2.73–2.80 (m, 1H), 1.56–1.59 (m, 3H), 1.27 (s, 9H), 1.26 (s, 9H × 0.65), 1.25 (s, 9H × 0.35); ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture of rotamers of the carbamate) δ 176.6, 175.8, 150.4, 150.1, 148.3, 147.7, 136.3, 135.5, 131.2, 130.9, 127.7, 127.2, 123.4, 123.2, 119.1, 118.7, 114.6, 114.3, 52.6, 50.6, 39.2, 39.1, 38.9, 38.8, 36.8, 28.9, 27.4, 27.0, 26.9, 17.5, 17.4; ^{19}F NMR ($CDCl_3$, 150 MHz) δ 64.2, 63.4; MS (FAB): m/z = 470 $[M + H]^+$; HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{24}H_{31}F_3NO_5$: 470.2154; found: 470.2151.

(*S*,*E*)-*N*-Boc-6,8-dihydroxy-1-(prop-1-enyl)-1,2,3,4-tetrahydroisoquinoline (14). To a solution of **8** (386 mg, 0.815 mmol) in a mixture of MeOH (11.4 mL) and THF (0.6 mL) was added $LiBH_4$ (89 mg, 4.08 mmol, 5.0 equiv) at 0 °C. The reaction mixture was stirred for 2 h at room temperature and then quenched with water. The mixture was extracted with EtOAc twice. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (50% EtOAc in hexane) to give 245 mg of **14** (0.802 mmol, 98%) as a colorless oil. R_f = 0.10 (30% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) (a mixture of rotamers of carbamate) δ 7.26 (br-s, 1H), 7.12 (br-s, 1H × 0.4), 6.71 (br-s, 1H × 0.6), 6.31 (s, 1H × 0.6), 6.23 (s, 1H × 0.4), 6.17 (s, 1H × 0.6), 6.13 (s, 1H × 0.4), 5.74 (s, 1H × 0.6), 5.31–5.53 (m, 2.4H), 3.83–3.86 (m, 1H × 0.4), 3.75–3.78 (m, 1H × 0.6), 3.16–3.23 (m, 1H × 0.6), 3.02–3.08 (m, 1H × 0.4), 2.42–2.71 (m, 2H), 1.58 (br-d, J = 5.0 Hz, 3H × 0.4), 1.52 (br-d, J = 5.2 Hz, 3H × 0.6), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture of rotamers of carbamate) δ 155.6, 155.4, 155.1, 153.4, 153.1, 137.1, 136.7, 129.3, 129.2, 127.3, 114.6, 114.3, 107.6, 101.7, 101.4, 80.4, 51.7, 50.5, 38.5, 37.4, 31.5, 28.4, 17.5; MS (FAB): m/z = 306 $[M + H]^+$; HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{17}H_{24}NO_4$: 306.1705; found: 306.1711.

(*S*,*E*)-*N*-Boc-6,8-dimethoxy-1-(prop-1-enyl)-1,2,3,4-tetrahydroisoquinoline (15). To an ice cold solution of **14** (245 mg, 0.802 mmol) in dry THF (8 mL) was added NaH (192 mg 60% in wax, 4.80 mmol, 6.0 equiv) in several portions. After evolution of hydrogen ceased, Me_2SO_4 (0.2 mL, 2.10 mmol, 2.6 equiv) was added to the mixture at the same temperature. It was stirred for 4 h at room temperature, and the reaction was quenched with water. The mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (10% EtOAc in hexane) to give 251 mg of **15** (0.752 mmol, 93%) as a colorless oil. R_f = 0.75 (30% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) (a mixture of rotamers of carbamate) δ 6.30 (s, 1H × 0.6), 6.28 (s, 1H × 0.4), 6.24 (s, 1H × 0.6), 6.22 (s, 1H × 0.4), 5.79 (br-s, 1H × 0.4), 5.47–5.58 (m, 1.6H), 5.23–5.31 (m, 1H), 3.97–4.01 (m, 1H × 0.6), 3.76–3.83 (m, 1H × 0.6), 3.77 (s, 3H × 0.6), 3.75 (s, 3H), 3.74 (s, 3H × 0.4), 3.30–3.36 (m, 1H × 0.4), 3.17–3.24 (m, 1H × 0.4), 2.74–2.87 (m, 1H), 2.64–2.69 (m, 1H), 1.62 (d, J = 6.5 Hz, 3H), 1.46 (s, 9H × 0.6), 1.45 (s, 9H × 0.4); ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture of rotamers of carbamate) δ 159.1, 157.0, 156.8, 154.9, 154.6, 136.7, 136.4, 130.0, 129.8, 125.1, 124.9, 117.9, 117.4, 104.1, 104.0, 96.5, 96.3, 79.5, 79.2, 55.3, 55.2, 51.2, 50.1, 38.7, 37.1, 28.8, 28.4, 17.5; MS (FAB): m/z = 334 $[M + H]^+$; HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{19}H_{28}NO_4$: 334.2018; found: 334.2021.

(*S*,*E*)-*N*-Boc-6,8-dimethoxy-1-(2-methoxycarbonylethenyl)-1,2,3,4-tetrahydroisoquinoline (16). Into a stirred solution of **15** (113 mg, 0.339 mmol) in CH_2Cl_2 (10 mL) was bubbled O_3 at −78 °C until the starting material was consumed on TLC (2–4 min). An excess of O_3 was then removed by bubbling of nitrogen. After the addition of PPh_3 (157 mg, 0.599 mmol), the reaction mixture was stirred for an additional 30 min on an ice bath. To this mixture, powder of methyl (triphenylphosphoranylidene)acetate (501 mg, 1.50 mmol, 4.4 equiv) was added at the same temperature. The reaction mixture was stirred for 3 h at 0 °C and then quenched with water. The mixture was extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residual oil was purified by silica gel column chromatography (20% EtOAc in hexane) to give 108 mg of **16** (0.286 mmol, 84%) as a colorless oil. R_f = 0.50 (30% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) (a mixture of rotamers of carbamate) δ 7.00 (dd, J = 15.5, 3.9 Hz, 1H × 0.5), 6.95 (dd, J = 15.5, 4.5 Hz, 1H × 0.5), 6.33 (s, 1H), 6.27 (s, 1H × 0.5), 6.25 (s, 1H × 0.5), 6.00 (d, J = 3.9 Hz, 1H × 0.5), 5.76 (d, J = 4.4 Hz, 1H × 0.5), 5.73 (d, J = 4.5 Hz, 1H × 0.5), 5.69 (d, J = 15.5 Hz, 1H), 3.87–3.95 (m, 1H × 0.5), 3.65–3.76 (m, 1H × 0.5), 3.71 (s, 3H × 0.5), 3.68 (s, 3H × 0.5), 3.67 (s, 3H), 3.60 (s, 3H × 0.5), 3.59 (s, 3H × 0.5), 3.19–3.26 (m, 1H × 0.5), 3.10–3.18 (m, 1H × 0.5), 2.67–2.82 (m, 1H), 2.54–2.61 (m, 1H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture of rotamers of carbamate) δ 166.8, 159.5, 156.6, 156.4, 154.3, 154.2, 147.1, 146.6, 136.7, 136.5, 119.4, 114.7, 114.1, 104.2, 104.1, 96.3, 96.1, 79.9, 79.7, 55.1, 55.0, 54.9, 51.2, 51.1, 50.7, 49.7, 39.2, 37.6, 31.3, 28.3, 28.1; MS (FAB): m/z = 378 $[M + H]^+$; HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{20}H_{28}NO_6$: 378.1917; found: 378.1913.

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(*S*,*E*)-*N*-Boc-6,8-dimethoxy-1-(2-methoxycarbonylethyl)-1,2,3,4-tetrahydroisoquinoline (17). To a solution of **16** (108 mg, 0.286 mmol) was added $Pd(OH)_2$ (11 mg, 20% on carbon), and the mixture was stirred under a hydrogen atmosphere at room temperature. The reaction was monitored by TLC. After the reaction was completed, the mixture was filtered and concentrated. The residue was purified by silica gel column chromatography (10% EtOAc in hexane) to give 98 mg of compound **17** (0.258 mmol, 90%) as a colorless oil. R_f = 0.50 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) (a mixture of rotamers of carbamate) δ 6.27 (s, 1H), 6.21 (s, 1H), 5.25 (br-d, J = 3.9 Hz, 1H × 0.45), 5.09 (br-d, J = 4.5 Hz, 1H × 0.55), 4.07−4.15 (m, 1H × 0.45), 3.82−3.90 (m, 1H × 0.55), 3.79 (s, 3H × 0.55), 3.76 (s, 3H × 0.45), 3.75 (s, 3H), 3.62 (s, 3H), 3.22−3.32 (m, 1H × 0.45), 3.07−3.19 (m, 1H × 0.55), 2.72−2.91 (m, 1H), 2.61−2.68 (m, 1H), 2.36−2.46 (m, 2H), 2.08−2.19 (m, 1H), 1.83−1.94 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture of rotamers of carbamate) δ 174.1, 173.7, 159.0, 158.9, 156.7, 156.5, 154.8, 154.5, 136.1, 135.8, 118.9, 118.6, 104.0, 103.9, 96.3, 96.1, 79.6, 79.2, 77.3, 77.0, 55.1, 55.0, 51.3, 51.2, 49.8, 48.8, 37.8, 36.0, 31.4, 31.2, 28.8, 28.7, 28.5, 28.3, 28.2; MS (FAB): m/z = 380 $[M + H]^+$; HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{20}H_{30}NO_6$: 380.2073; found: 380.2073.

(*S*,*E*)-*N*-Boc-6,8-dimethoxy-1-(3-hydroxypropyl)-1,2,3,4-tetrahydroisoquinoline (18). To a solution of **17** (98.0 mg, 0.258 mmol) in a mixture of MeOH (0.9 mL) and THF (0.15 mL) was added $LiBH_4$ (17.0 mg, 0.780 mmol, 3.0 equiv) at 0 °C. The mixture was stirred at room temperature for 1 h, and sat. NH_4Cl was added. The mixture was extracted with EtOAc, and the extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (40% EtOAc in hexane) to give 72.0 mg of **18** (0.205 mmol, 79%) as a colorless oil. R_f = 0.15 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) (a mixture of rotamers of carbamate) δ 6.21 (d, J = 8.0 Hz, 1H), 6.15 (d, J = 5.7 Hz, 1H), 5.23−5.26 (m, 1H × 0.5), 5.04−5.07 (m, 1H × 0.5), 4.06−4.11 (m, 1H × 0.5H), 3.80−3.83 (m, 1H × 0.5), 3.72 (s, 3H × 0.5), 3.68 (s, 3H × 1.5), 3.59−3.64 (m, 2H), 3.18−3.26 (m, 1H × 0.5), 3.04−3.11 (m, 1H × 0.5), 2.69−2.85 (m, 1H), 2.53−2.61 (m, 1H), 2.45 (br-s, 1H), 1.72−1.81 (m, 1H), 1.54−1.62 (m, 3H), 1.38 (s, 9H × 0.5), 1.37 (s, 9H × 0.5); ^{13}C NMR (125 MHz, $CDCl_3$) (a mixture of rotamers of carbamate) δ 158.7, 156.5, 156.3, 155.0, 154.7, 135.9, 135.6, 119.7, 119.5, 104.1, 103.9, 96.3, 96.2, 79.5, 79.3, 62.1, 55.2, 55.1, 55.0, 49.4, 48.4, 37.7, 35.8, 30.4, 30.0, 29.3, 29.0, 28.5, 28.3, 28.2; MS (FAB): m/z = 352 $[M + H]^+$; HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{19}H_{30}NO_5$: 352.2124; found: 352.2122.

(*S*,*E*)-*N*-Boc-6,8-dimethoxy-1-(3-cyano-3-hydroxypropyl)-1,2,3,4-tetrahydroisoquinoline (19). To a solution of **18** (72.0 mg, 0.205 mmol) in CH_2Cl_2 (5 mL) were added NaOAc (5.0 mg, 0.061 mmol, 0.30 equiv) and PCC (132 mg, 0.612 mmol, 3.0 equiv), and the mixture was stirred for 3 h at room temperature. The whole mixture was directly passed through Florisil column eluted with 30% EtOAc in hexane and the fractions were concentrated in vacuo. The crude aldehyde was dissolved in dry CH_2Cl_2, and Et_3N (3 μL, 0.04 mmol, 0.2 equiv) was added. To this solution TMSCN (24 μL, 0.192 mmol, 0.94 equiv) was added at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1 h at 0 °C and then concentrated. A solution of *p*-TsOH (30.0 mg, 0.174 mmol, 0.85 equiv) in MeOH (2 mL) was added to the crude residual oil, and the mixture was stirred for 30 min at room temperature. Sat. $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (30% EtOAc in hexane) to give 48.0 mg of **19** (0.128 mmol, 62% in two steps) as a colorless oil. R_f = 0.25 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) (a mixture due to rotamers and diastereomers) δ 6.30−6.32 (m, 1H), 6.23−6.24 (m, 1H), 5.29 (br-s, 1H), 4.70 (br-s, 1H), 3.85 (s, 3H × 0.5), 3.82 (s, 3H × 0.5), 3.76 (s, 3H), 3.11 (m, 1H), 2.75−2.90 (m, 1H), 2.56−2.70 (m, 1H), 1.72−2.00 (m, 4H), 1.47 (s, 9H × 0.5), 1.46 (s, 9H × 0.5); ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture due to rotamers and diastereomers) δ 159.5, 159.4, 156.7, 155.4, 135.9, 120.3, 120.0, 118.9, 118.8, 104.6, 96.8, 96.7, 80.4, 80.3, 61.3, 61.2, 55.3, 48.9, 37.8, 32.2, 29.1, 28.8, 28.4; MS (FAB): m/z = 377 $[M + H]^+$; HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{20}H_{29}N_2O_5$: 377.2076; found: 377.2080.

Synthesis of Compound 20. Hydrolysis of 19 and L-Proline-Catalyzed Intramolecular Cycloamidation. Compound **19** (75.4 mg, 0.200 mmol) was stirred in 6 N HCl (0.5 mL) for 3 h at room temperature. The mixture was diluted with H_2O, and the whole mixture was passed through basic resin (Amberlite; IRA-400) eluted with water. The fractions were collected and concentrated in vacuo. L-Proline (12.0 mg, 0.104 mmol, 0.52 equiv) was added to the crude amide, and the mixture was heated at 100 °C for 24 h without solvent. The mixture was purified directly by silica gel column chromatography (50% EtOAc in hexane) to give 40.0 mg of 3-hydroxy-9,11-dimethoxybenzo[*a*]quinolizidin-4-one (**20**) (0.144 mmol, 72% in two steps) as an oil. R_f = 0.25 (50% EtOAc in hexane); ^{1}H NMR (400 Hz, $CDCl_3$) (a mixture of diastereomers) δ 6.30 (d, J = 2.1 Hz, 1H × 0.4), 6.29 (d, J = 2.1 Hz, 1H × 0.6), 6.23 (d, J = 2.1 Hz, 1H × 0.4), 6.19 (d, J = 2.1 Hz, 1H × 0.6), 4.78−4.85 (m, 1H × 0.6), 4.65−4.71 (m, 1H × 1.4), 4.25 (br-s, 1H × 0.4), 4.00 (br-s, 1H × 0.6), 3.75 (s, 3H × 0.4), 3.74 (s, 3H × 0.6), 3.73 (s, 3H × 0.6), 3.72 (s, 3H × 0.4), 2.95−2.99 (m, 1H), 2.21−2.82 (m, 5H), 1.77−1.85 (m, 1H), 1.28−1.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture of diastereomers) δ 173.2, 171.6, 159.3, 159.0, 157.6, 156.9, 137.5, 137.0, 117.4, 116.6, 104.5, 104.3, 97.1, 96.9, 56.2, 55.3, 55.2, 55.1, 48.7, 39.1, 39.0, 30.4, 29.5, 27.8, 27.6, 26.7, 26.5; MS (FAB): m/z = 278 $[M + H]^+$; HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{15}H_{20}NO_4$: 278.1392; found: 278.1389.

Boric Acid Catalyzed Intramolecular Cycloamidation. Boric acid (6 mg, 0.1 mmol, 0.5 equiv) and H_2O (2 μL, 1 equiv) were added to the amide obtained from the hydrolysis of **19** (75 mg, 0.20 mmol) by the same procedure described for the above-mentioned L-proline catalyzed reaction. The mixture was heated at 100 °C for 11 h, and the crude product was purified directly by silica gel column chromatography (50% EtOAc in hexane) to give 43.3 mg of **19** (0.156 mmol, 78% in 2 steps) as an oil.

Preparation of Azides 21a and 21b. To a solution of compound **20** (35.0 mg, 0.126 mmol) in CH_2Cl_2 (1 mL) were added DMAP (7.7 mg, 0.063 mmol, 0.5 equiv), Et_3N (53 μL, 0.380 mmol, 3 equiv), and MsCl (20 μL, 0.258 mmol, 2.0 equiv) successively at room temperature. The mixture was stirred for 1 h at room temperature, and water was added. The mixture was extracted with CH_2Cl_2 and washed with water, brine, and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the crude product was dissolved in DMF (1 mL). NaN_3 (16.0 mg, 0.246 mmol, 2.0 equiv) was added, and the mixture was stirred for 5 h at room temperature. Water was added, and the mixture was extracted with Et_2O. The organic extract was washed with water and brine and dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (30% EtOAc in hexane) to give 15.0 mg of less polar diastereomer **21a** (0.050 mmol, 39%) as a foamy solid and 11.0 mg of polar diastereomer **21b** (0.036 mmol, 29%) as a white solid. **21a**: R_f = 0.45 (30% EtOAc in hexane); $[\alpha]_D^{20}$ −383.9 (*c* 0.60, $CHCl_3$) [lit. $[\alpha]_D^{20}$ −375.8 (*c* 1.0, $CHCl_3$)];[2b] ^{1}H NMR (400 Hz, $CDCl_3$) δ 6.38 (d, J = 2.2 Hz, 1H), 6.31 (d, J = 2.2 Hz, 1H), 4.85−4.91 (m, 1H), 4.72 (dd, J = 11.1, 3.5 Hz, 1H), 4.18 (t, J = 6.6 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.82−2.95 (m, 1H), 2.65−2.78 (m, 2H), 2.55−2.65 (m, 1H), 2.10−2.22 (m, 1H), 1.78−1.88 (m, 1H), 1.38−1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 159.2, 157.2, 137.5, 116.7, 104.4, 97.0, 58.3, 55.3, 55.2, 52.6, 38.9, 30.0, 26.1, 25.4; MS (FAB): m/z = 303 $[M + H]^+$; HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{15}H_{19}N_4O_3$: 303.1457; found: 303.1464. **21b**: Mp 105−106 °C; R_f = 0.41 (30% EtOAc in hexane); $[\alpha]_D^{20}$ −117.7 (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (d, J = 2.2 Hz, 1H), 6.29 (d, J = 2.2 Hz, 1H), 4.95 (ddd, J = 12.2, 5.6, 1.7 Hz, 1H), 4.75 (dd, J = 10.6, 3.0 Hz, 1H), 4.11 (dd, J = 11.3, 6.8 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 2.96−2.81 (m, 2H), 2.61−2.71 (m, 2H), 2.16−2.26 (m, 1H), 1.72−1.85 (m, 1H), 1.30−1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 159.1, 157.5, 137.6, 117.1, 104.5, 97.1, 59.6, 55.3, 55.2, 39.2, 39.1, 30.2, 27.7, 26.9; MS (FAB): m/z = 303 $[M + H]^+$; HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{15}H_{19}N_4O_3$: 303.1457; found: 303.1452.

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(3*S*,11b*S*)-3-Amino-9,11-dimethoxy-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizidin-4-one (6). To a solution of compound **21a** (17.0 mg, 0.056 mmol) in MeOH (2 mL) was added Pd−C (2 mg, 10% on carbon), and the mixture was stirred under a hydrogen atmosphere at room temperature. After the completion of the reaction monitored by tlc, the reaction mixture was filtered. The filtrate was concentrated in vacuo to give 10 mg of **6** (0.036 mmol, 65%) as an oil.[3b] R_f = 0.20 (30% EtOAc in hexane); $[\alpha]_D^{20}$ −368.8 (*c* 0.30, $CHCl_3$); ^1H NMR (500 MHz, CD_3OD) δ 6.33 (d, *J* = 2.1 Hz, 1H), 6.26 (d, *J* = 2.1 Hz, 1H), 4.72 (dd, *J* = 10.7, 2.7 Hz, 1H), 4.52−4.60 (m, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.50−3.60 (m, 1H), 2.60−2.67 (m, 2H), 2.24−2.42 (m, 2H), 2.11−2.27 (m, 1H), 1.36−1.47 (m, 1H), 1.22−1.33 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.0, 161.0, 158.4, 138.5, 117.7, 105.7, 97.9, 55.8, 55.7, 51.3, 51.2, 40.1, 40.0, 30.5, 29.1; MS (FAB): *m*/*z* = 277 $[M + H]^+$; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{21}N_2O_3$: 277.1552; found: 277.1556.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra of all new compounds and chiral HPLC chart for **22**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01173.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Takada, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Am. Chem. Soc.* **2004**, *126*, 187−193.

(2) (a) Gurjar, M. K.; Pramanik, C.; Bhattasali, D.; Ramana, C. V.; Mohapatra, D. K. *J. Org. Chem.* **2007**, *72*, 6591−6594. (b) Liu, G.; Romo, D. *Org. Lett.* **2009**, *11*, 1143−1146. (c) Bowen, E. G.; Wardrop, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 6062−6063. (d) Yang, C.; Bao, Y.-H.; Liang, P.; Ye, J.-L.; Wang, A.-E.; Huang, P.-Q. *Tetrahedron* **2011**, *67*, 6281−6288.

(3) (a) Lin, C.-F.; Ojima, I. *J. Org. Chem.* **2011**, *76*, 6240−6249. (b) Miyazaki, M.; Ando, N.; Sugai, K.; Seito, Y.; Fukuoka, H.; Kanemitsu, T.; Nagata, K.; Odanaka, Y.; Nakamura, K. T.; Ito, T. *J. Org. Chem.* **2011**, *76*, 534−542. (c) Kuntiyong, P.; Akkarasamiyo, S.; Piboonsrinakara, N.; Hemmara, C.; Songthammawat, P. *Tetrahedron* **2011**, *67*, 8034−8040. (d) Jang, J.; Jung, J.-W.; Ahn, J.; Sim, J.; Chang, D.-J.; Kim, D.-D.; Suh, Y.-G. *Org. Biomol. Chem.* **2012**, *10*, 5202−5204.

(4) (a) Kawai, N.; Abe, R.; Uenishi, J. *Tetrahedron Lett.* **2009**, *50*, 6580−6583. (b) Kawai, N.; Abe, R.; Matsuda, M.; Uenishi, J. *J. Org. Chem.* **2011**, *76*, 2102−2114. (c) Kawai, N.; Matsuda, M.; Uenishi, J. *Tetrahedron* **2011**, *67*, 8648−8653.

(5) When chiral ζ-amino (*R*)-allylic alcohols were used, chiral (*R*)-1-alkenyltetrahydroisoquinoline was obtained; Kurata, K.; Inoue, K.; Nishimura, K.; Hoshiya, N.; Kawai, N.; Uenishi, J. *Synthesis* **2015**, *47*, 1238−1244.

(6) Andrade, L. H.; Barcellos, T. *Org. Lett.* **2009**, *11*, 3052−3055.

(7) The enantiomeric ratio of **8** was determined by HPLC analysis after conversion of **8** to (*S*,*E*)-*N*-trifluoroacety-6,8-dipivaloyloxy-1-(prop-1-enyl)-1,2,3,4-tetrahydroisoquinoline (**22**) in two steps. See details of the chemical transformation and HPLC analysis in the Experimental Section and SI.

(8) The details will be published in due course.

(9) Jannapu Reddy, R.; Kawai, N.; Uenishi, J. *J. Org. Chem.* **2012**, *77*, 11101−11108.

(10) Although we examined the cyclization of carboxylic acid and its ester with the secondary amine under several conditions, the desired product **19** was obtained in poor yield.

(11) (a) Rao, S. N.; Mohan, D. C.; Adimurthy, S. *Org. Lett.* **2013**, *15*, 1496−1499. (b) Nguyen, T. B.; Sorres, J.; Tran, M. Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 3202−3205. (c) Allen, C. L.; Atkinson, B. N.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 1383−1386. (d) Starkov, P.; Sheppard, T. D. *Org. Biomol. Chem.* **2011**, *9*, 1320−1323. (e) Vanjari, R.; Allam, B. K.; Singh, K. N. *RSC Adv.* **2013**, *3*, 1691−1694.

(12) (a) Atkinson, B. N.; Chhatwal, A. R.; Lomax, H. V.; Walton, J. W.; Williams, J. M. *Chem. Commun.* **2012**, *48*, 11626−11628. (b) Zhang, M.; Imm, S.; Bähn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3905−3909. (c) Tamura, M.; Tonomura, T.; Shimizu, K.; Satsuma, A. *Green Chem.* **2012**, *14*, 717−724. (d) Stephenson, N. A.; Zhu, J.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 10003−10008. (e) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Cui, Q.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 647−654. (f) Kissounko, D. A.; Hoerter, J. M.; Guzei, I. A.; Cui, Q.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 1776−1783. (g) Dineen, T. A.; Zajac, M. A.; Myers, A. G. *J. Am. Chem. Soc.* **2006**, *128*, 16406−16409. (h) Kissounko, D. A.; Guzei, I. A.; Gellman, S. H.; Stahl, S. S. *Organometallics* **2005**, *24*, 5208−5210. (i) Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 3422−3423.

(13) **21a**; $[\alpha]_D^{20}$ −384 (*c* 0.6, $CHCl_3$) lit. $[\alpha]_D^{20}$ −376 (*c* 1.0, $CHCl_3$) in ref 2b.

(14) Synthetic **6** indicated its specific rotation, $[\alpha]_D^{20}$ −369 (*c* 0.30, $CHCl_3$).

(15) Choi, Y.-L.; Kim, B.-T.; Heo, J.-N. *J. Org. Chem.* **2012**, *77*, 8762−8767.

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