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Preparation of Enantiopure Substituted Piperidines Containing 2-Alkene or 2-Alkyne Chains: Application to Total Syntheses of Natural Quinolizidine-Alkaloids

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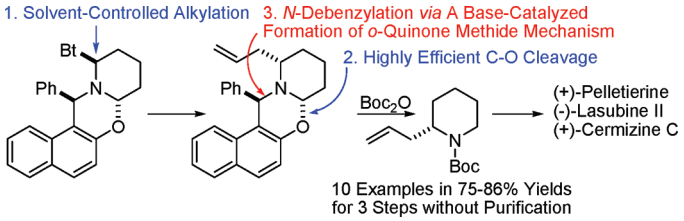

A general method for the preparation of enantiopure 2-alkene- or 2-alkyne-containing chain substituted piperidines was established by using nonracemic Betti base as a chiral auxiliary. The key step is that the auxiliary residue was removed by a novel base-catalyzed *N*-debenzylation via a formation of *o*-quinone methide mechanism in stead of the traditional hydrogenolysis, by which the alkene or alkyne groups survived. By this method, ten 2-alkene- or 2-alkyne-containing chain substituted piperidines were prepared on the gram scale within a few hours. To demonstrate the efficiency of the method and the versatility of the product, total syntheses of natural alkaloids (+)-pelletierine, (−)-lasubine II, and (+)-cermizine C were achieved by using (*S*)-2-allyl-*N*-Boc-piperidine as a versatile building block.

Introduction

A number of natural alkaloids contain the unit of chiral 2-substituted piperidine.[1] For their biological importance and novel structures, they have continuously been the challenging targets of total synthesis. Various building blocks have been applied to this purpose, prominent among them are chiral 2-alkene-containing chain substituted piperidines, because the alkene group can be easily transformed into other groups by using different reactions, such as aza-Claisen rearrangement,[2] hydroxylation,[3] catalytic hydrogenation,[4] iodine-catalyzed lactonization,[5] RCM reaction,[6] Wacker oxidation,[5] etc. (Scheme 1).

Investigation proved that the preparation of chiral 2-alkene-containing chain substituted piperidines is still a challenging subject. Although asymmetric catalytic methods are very attractive,[4a,7] the chiral pool[3,5,8] and chiral auxiliary

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SCHEME 1

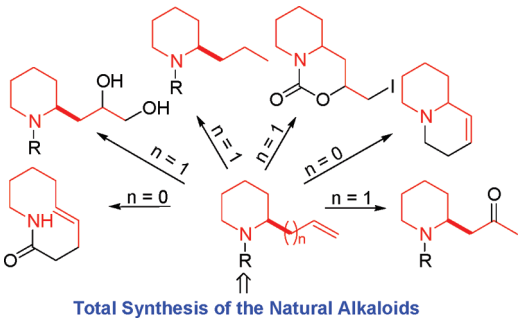
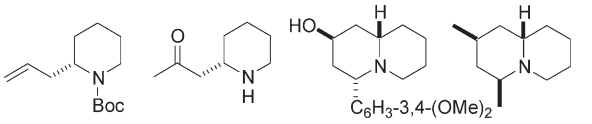


CHART 1



1h **2** (+)-Pelletierine **3** (-)-Lasubine II **4** (+)-Cermizine C

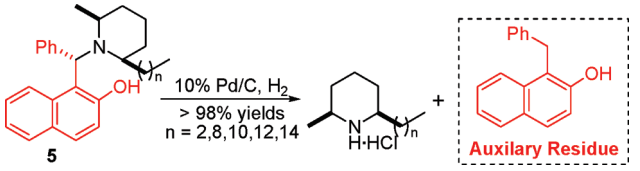
synthesis[2,4b,6a,9,10] are the major methods for this purpose because of their satisfied enantioselectivity and ease in scale up. Interestingly, nonracemic 2-phenylglycinol as an auxiliary has been well-known in the preparation of chiral piperidines,[11] but it was rarely used for the preparation of such compounds.[2a,10,12] This phenomenon may result from the fact that the removal of its *N*-benzylated auxiliary residue seriously suffered from low efficiency under non-hydrogenolysis conditions.[13] In fact, a general, efficient, and scalable method for the preparation of such compounds is still not available.

Herein, we would like to report such a method, by which the reported chiral 2-alkene- or 2-alkyne-containing chain substituted *N*-Boc-piperidines (**1**) were prepared in the gram scale within a few hours. The total syntheses of natural alkaloids (+)-pelletierine (**2**), (−)-lasubine II (**3**), and (+)-cermizine C (**4**) were achieved by using (*S*)-2-allyl-*N*-Boc-piperidine (**1h**) as a versatile building block (Chart 1).

Results and Discussion

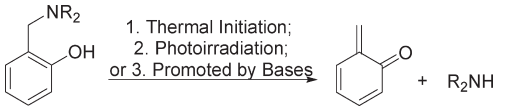
Enantiopure Syntheses of 2-Alkene- or 2-Alkyne-Containing Chain Substituted Piperidines. In our recent works, Betti base was resolved to its nonracemic isomers in kilogram scale by a kinetic resolution.[14a] (*S*)-Betti base has proved to be an excellent chiral auxiliary in total syntheses of natural alkaloids (2*S*,6*R*)-dihydropinidine and (2*S*,6*R*)-isosolenopsins.[14b] As shown in Scheme 2, one of the key steps is removal of the auxiliary residue via an *N*-debenzylation under hydrogenolysis. But, this original procedure has the same limitation as that of nonracemic 2-phenylglycinol, because no alkene group could be survived under hydrogenolysis conditions.

SCHEME 2



5

SCHEME 3



However, we realized that intermediate **5** can also be considered as a Mannich derivative of *o*-phenol, which often served as a good precursor to generate *o*-quinone methides.[15] Investigation showed that this generation could be influenced by thermal initiation,[16] photoirradiation,[17] or bases[18] (Scheme 3). Deductively, when **5** is treated by one of those conditions, the corresponding *o*-quinone methide may be formed accompanied by an *N*-debenzylation.

Thus, (*R*)-Betti base was condensed with 1,5-pentanedial in the presence of 1,2,3-benzotriazole (BtH) to give a diastereopure pyrido[2,1-*b*][1,3]oxazine (**6**) in 93% yield by a known procedure.[14b] As shown in Scheme 4, when **6** was treated with Grignard reagents (**7a**−**g**) in THF, highly diastereo- and regioselective alkylations occurred on its C11 to give the corresponding **8a**−**g** in excellent yields. However, the alkylation occurred on both C7a and C11 when Et_2O was used as solvent. All those alkylations may go through an S_N2 mechanism because the Bt-group was replaced with complete inversion of configuration. Many attempts proved that $H_2C{=}CHCH_2MgBr$ was not a suitable reagent for this alkylation. But, this problem was easily resolved by using $H_2C{=}CHCH_2TMS$ as an alternative[19] in the presence of $BF_3{\cdot}Et_2O$ and the diastereoselectivity was controlled by temperature. At room temperature, a mixture with 11*R*-isomer as the major product (11*R*:11*S* = 9:1) was obtained.

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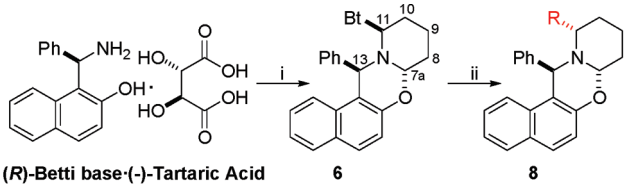
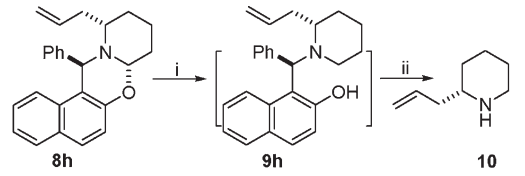
SCHEME 4



SCHEME 5

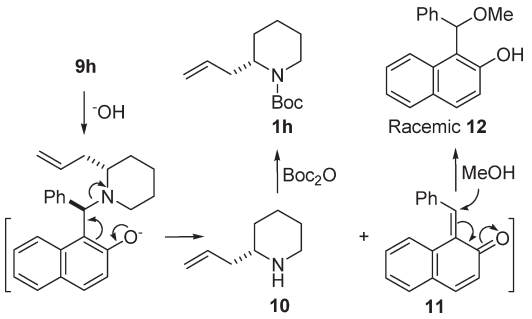


However, the ratio of 11*S*-isomer increased fast by decreasing the reaction temperature. At −20 °C, desired **8h** was obtained in 90% yield as a single product. When **8f** and **8g** were hydrogenated over Lindlar catalyst, **8f** gave an unseparated mixture, while **8g** was selectively converted into *cis*-alkene **8i** in almost quantitative yield.

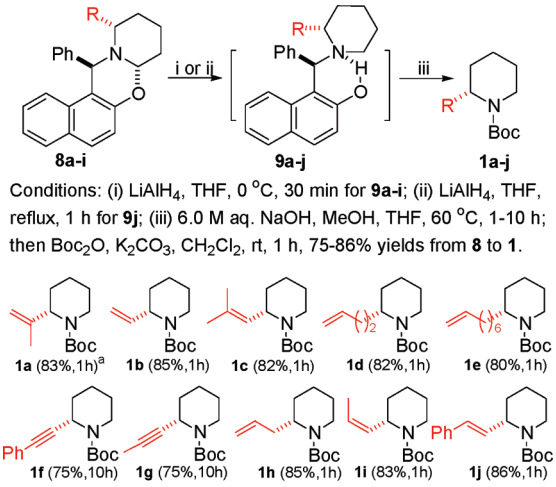
As shown in Scheme 5, when **8h** was treated with $LiAlH_4$ in THF, its C−O bond was cleaved smoothly at 0 °C within 30 min. After the reduction was quenched by aq NaOH, we interestingly found that, besides the expected **9h**, 2-allylpiperidine (**10**) was also isolated in 23% yield. However, the same reaction quenched by saturated aq NH_4Cl gave only 8% yield of **10**. Those results clearly indicated that a base-catalyzed *N*-debenzylation of **9h** occurred during the workup performance.

Further experiments showed slight improvement on the yield of **10** even by heating **9h** in aq NaOH at 60 °C. Considering the base-catalyzed *N*-debenzylation of **9h** may go through an *o*-quinone methide mechanism, MeOH was added as a nucleophilic reagent. As was expected, the yield of **10** was increased up to 59% by using MeOH as a cosolvent. Finally, when a solution of **9h** in aq NaOH (6.0 M)−MeOH−THF (1:2:2 by v/v) was heated at 60 °C for 1 h followed by treatment with Boc_2O, 2-allyl-*N*-Boc-piperidine (**1h**) was obtained in 85% yield. Control experiments proved that each component in this combined reagent was necessary. As shown in Scheme 6, we hypothesized that (a) aq NaOH was a real catalyst for the formation of **11**, (b) MeOH was used as a nucleophilic reagent to capture **11**, and (c) the

SCHEME 6



SCHEME 7



[a]The reaction time for the step of base-catalyzed *N*-debenzylation.

use of THF may increase the solubility of the reaction system. This hypothesis was strongly supported by the fact that the racemic **12** was obtained as a byproduct in 89% yield.

As shown in Scheme 7, the reductive cleavage of the C−O bond in **9a**−**i** was accomplished smoothly by a similar procedure. However, when **8f** was treated with $LiAlH_4$ in refluxed THF for 1 h, a cleavage of the C−O bond and a selective reduction of alkyne occurred simultaneously to give *trans*-alkene **9j** as a single product. Since the rotation of the 2-substituted piperidine moiety was restricted by a strong hydrogen bond, the structural assignments of **9a**−**j** suffered from ambiguous ^1H and ^{13}C NMR spectra[14b] (coalescence phenomenon). Therefore, they were directly used in the next step without further purification and characterization. Under standard conditions (aq NaOH−MeOH−THF, at 60 °C), the alkene substrates (**9a**−**e**,**h**−**j**) were *N*-debenzylated within 1 h and the alkyne substrates (**9f**−**g**) needed longer time. Since we have proved that the procedure for removal of the auxiliary does not lead to racemization of the product (see the Supporting Information), therefore, enantiopure **1a**−**j** were obtained in 75−86% overall yields from **8a**−**i**.

Total Syntheses of (+)-Pelletierine (2) and (−)-Lasubine II (3). Alkaloid **3** was isolated from the leaves of *Lagerstroemia subcostata* Koehne in 1978.[20] Due to its representative

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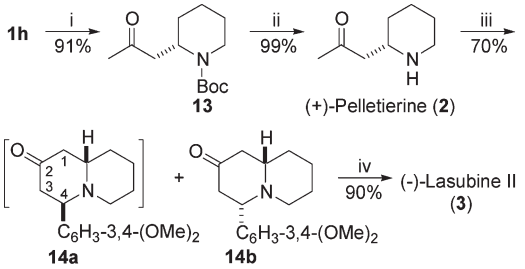
SCHEME 8



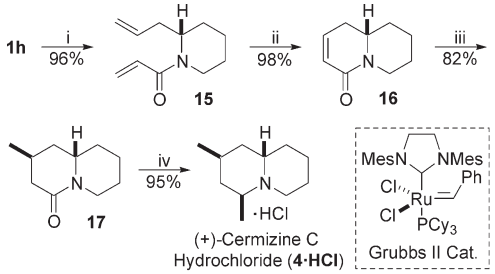
Conditions: (i) CuCl, $PdCl_2$, O_2, rt, DMF, H_2O, 10 h; (ii) TFA, DCM, rt, 2 h, 99%; (iii) 3,4-dimethoxybenzaldehyde, 2.0 M aq. NaOH, MeOH, 60 °C, 70 h; (iv) K-selectride, THF, -78 °C, 1 h.

quinolizidine-alkaloid structure, it often served as a good vehicle for the validation of new synthetic methodology. A variety of precursors have been used in asymmetrical total syntheses of **3**.[21] However, the most efficient one appeared in a racemic route, in which (±)-**3** was constructed in a single step from (±)-**2**.[22] This method has never been employed in asymmetrical synthesis of **3**, possibly because the preparation of nonracemic **2** is not a trivial task up to now.[23] On the basis of our method, **1h** was synthesized in the gram scale within a few hours in three steps. As shown in Scheme 8, **1h** carried out a Wacker oxidation to give (*S*)-*N*-Boc-pelletierine (**13**) in 91% yield. Then **13** was treated with TFA to give **2** in 99% yield.

In 1984, Kibayashi[22] reported that a base-catalyzed (1% aq NaOH) condensation between (±)-**2** and 3,4-dimethoxybenzaldehyde gave a mixture of (±)-**14a** and (±)-**14b**. Later, Pilli[24] found that (±)-**14a** could be isomerized completely into the thermodynamically more stable (±)-**14b** in the presence of 2.0 M aq NaOH. When we heated the mixture of **2** and 3,4-dimethoxybenzaldehyde in 2.0 M aq NaOH at 60 °C for 70 h, **14b** was obtained in 70% yield as a single isomer, by which the condensation and isomerization were achieved in one pot. Finally, **14b** was reduced with K-Selectride to give desired **3** in 90% yield. Thus, the total synthesis of **3** was accomplished in seven steps [starting from (*R*)-Base base] and in 40.4% overall yield.

Total Syntheses of (+)-Cermizine C (4). Alkaloid **4** was isolated in 2004 from the club moss *Lycopodium cernuum*[25] and it structurally belongs to a quinolizidine-alkaloid. The only total synthesis of **4** was reported by Snider,[26a] in which α,β-unsaturated lactam **16** was used as a key intermediate. Recently, an alternative preparation of **16** was reported, but the protocol is still tedious.[26b]

SCHEME 9



Conditions: i. (a) TFA, DCM, rt, 2 h; (b) H_2C=CHCOCl, aq. NaOH, rt, 4 h; ii. Grubbs II, DCM, reflux, 15 min; iii. Me_2CuLi, $BF_3{\cdot}OEt_2$, Et_2O, -78 °C, 1 h; iv. (a) MeMgBr, THF, 65 °C, 3 h; (b) $NaBH_3CN$, AcOH, 1 h. (c) Saturated. HCl in MeOH

We proposed that **16** may be prepared within two highly efficient steps from **1h**. As shown in Scheme 9, **1h** was treated with TFA to give a crude deprotected product. Without purification, it was directly converted into α,β-unsaturated amide **15** in 96% yield. When the mixture of **15** and Grubbs catalyst (2st generation, 3% mol) was refluxed in CH_2Cl_2 for 15 min, an extremely efficient RCM reaction was achieved to give **16** in 98% yield.

Following the procedure of Snider, **16** was stereoselectively methylated by Me_2CuLi to give **17** in 82% yield in the presence of $BF_3{\cdot}Et_2O$. We observed that this methylation was so sensitive to solvent that no reaction occurred in THF. (+)-Cermizine C (**4**) was obtained in a methylation of **17** with MeMgBr followed by a stereoselective reduction with $NaBH_3CN$. Finally, it was converted into the corresponding hydrochloride **4·HCl** in 95% yield for a convenient separation. Thus, the total synthesis of **4·HCl** was accomplished in seven steps [starting from (*R*)-Base base] and in 52.1% overall yield.

Conclusion

In conclusion, a general and efficient method for the preparation of 2-alkene- or 2-alkyne-containing chain substituted piperidines was established by using nonracemic Betti base as a chiral auxiliary. The key step is that the removal of the auxiliary residue went through a novel base-catalyzed generation of *o*-quinone methide mechanism. By using **1h** as a versatile building block, total syntheses of natural alkaloids (+)-pelletierine, (−)-lasubine II, and (+)-cermizine C were achieved in the shortest steps and highest overall yields.

Experimental Section

A Typical Procedure for Preparation of (7a*S*,11*S*,13*R*)-11-Isopropenyl-13-phenyl-7a,8,10,11-tetrahydro-9*H*,13*H*-naphtho-[1,2-*e*]pyrido[2,1-*b*][1,3]oxazine (8a). To a cold solution (ice−water bath) of **6** (4.32 g, 10 mmol) in dry THF (70 mL) was added isopropenyl magnesium bromide (0.5 M in THF, 6 mL, 30 mmol) dropwise under nitrogen. After the reaction was stirred at 0 °C for 1.0 h (monitored by TLC), a saturated aqueous solution of NH_4Cl (30 mL) was added to quench the reaction. Then the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with H_2O and brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by chromatography (silica gel, EtOAc:PE = 1:15) to give desired product **8a** (3.26 g, 92%) as a colorless crystal, mp 130−131 °C, $[\alpha]^{25}_D$ −212.3

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(c 0.3, $CHCl_3$). IR ν 3069, 2943, 1625 cm^{-1}; ^1H NMR δ 7.61−7.58 (m, 2H), 7.29−7.11 (m, 9H), 5.48 (s, 1H), 5.14 (s, 1H), 5.07−5.04 (m, 2H), 3.03−2.99 (m, 1H), 2.15−2.12 (m, 1H), 1.76 (s, 3H), 1.68−1.54 (m, 4H), 1.08−1.04 (m, 1H); ^{13}C NMR δ 150.3, 147.0, 138.0, 130.9, 130.5 (2C), 128.7 (2C), 128.4, 127.6 (2C), 127.3, 126.2, 122.7, 121.9, 118.0, 115.0, 113.6, 81.8, 62.2, 56.9, 32.2, 31.8, 20.3, 18.1; MS m/z (%) 355 (M^+, 5.09), 231 (100). Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 3.94. Found: C, 84.30; H, 7.11; N, 4.01.

By using a similar procedure, the intermediates **8b**−**g** were prepared (the experiments, characterization, and ^1H and ^{13}C NMR spectra for products **8b**−**g** are given in the Supporting Information).

Preparation of (7a*S*,11*S*,13*R*)-11-(2-Propenyl)-13-phenyl-7a,8,10,11-tetrahydro-9*H*,13*H*-naphtho[1,2-*e*]pyrido[2,1-*b*][1,3]-oxazine (8h). Allyltrimethylsilane (11.4 g, 100 mmol) and $BF_3\cdot OEt_2$ (14.2 g, 100 mmol) were added to a solution of **6** (4.32 g, 10 mmol) in dry CH_2Cl_2 (200 mL) at −20 °C. After stirring for 12 h at −20 °C, the reaction mixture was then poured into saturated aqueous K_2CO_3 (100 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with H_2O and brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by chromatography (silica gel, EtOAc:PE = 1:15) to give desired product **8h** (3.20 g, 90%) as a white crystal, mp 123−124 °C, $[\alpha]^{25}_D$ −162.8 (c 0.18, $CHCl_3$). IR ν 3059, 2937, 1621 cm^{-1}; ^1H NMR δ 7.70−7.60 (m, 2H), 7.29−7.01 (m, 9H), 5.52−5.39 (m, 1H), 5.12 (s, 1H), 4.894.86 (m, 1H), 4.79−4.70 (m, 2H), 3.32−3.29 (m, 1H), 2.28−2.17 (m, 1H), 2.15−1.17 (m, 7H); ^{13}C NMR δ 154.5, 143.9, 136.9, 131.7, 128.9 (2C), 128.8, 128.7, 128.5, 128.0 (2C), 126.9, 126.3, 123.2, 122.9, 119.1, 116.3, 114.3, 81.4, 60.7, 59.1, 35.2, 29.4, 27.2, 13.6; MS m/z (%) 355 (M^+, 2.37), 231 (100). Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 3.94. Found: C, 84.79; H, 7.20; N, 3.90.

(7a*S*,11*S*,13*R*)-11-[(1*Z*)-1-Propenyl]-13-phenyl-7a,8,10,11-tetrahydro-9*H*,13*H*-naphtho[1,2-*e*] pyrido[2,1-*b*][1,3]oxazine (8i). A mixture of compound **8g** (3.53 g, 10 mmol) and Lindlar catalyst (5% $Pd/CaCO_3$ poisoned with lead, 353 mg) in THF (80 mL) under H_2 was stirred at room temperature and atmospheric pressure until the absorption of hydrogen ceased. After the catalyst was filtered out and the filtrate was evaporated, the residue was purified by chromatography (silica gel, EtOAc:PE = 1:15) to give desired product **8i** (3.52 g, 99%) as a white crystal, mp 113−114 °C, $[\alpha]^{25}_D$ −174.5 (c 0.16, $CHCl_3$). IR ν 3054, 2934, 1621 cm^{-1}; ^1H NMR δ 7.68−7.60 (m, 2H), 7.23−7.18 (m, 9H), 5.65−5.62 (m, 1H), 5.29 (s, 1H), 5.22−5.12 (m, 1H), 4.98−4.95 (m, 1H), 3.92−3.89 (m, 1H), 1.98−1.79 (m, 4H), 1.65−1.53 (m, 4H), 1.51−1.30 (m, 1H); ^{13}C NMR δ 152.4, 141.9, 132.8, 131.8, 129.5 (2C), 128.7, 128.6, 128.4, 127.9 (2C), 127.1, 126.1, 124.6, 122.7 (2C), 118.5, 114.6, 81.5, 59.7, 54.9, 31.4, 30.4, 16.5, 13.0; MS m/z (%) 355 (M^+, 10.83), 231 (100). Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 3.94. Found: C, 84.52; H, 7.12; N, 4.18.

A Typical Procedure for the Preparation of (*S*)-2-Isopropenyl-piperidine-1-carboxylic Acid *tert*-Butyl Ester (1a). To a cold solution (ice-water bath) of **8a** (1.07 g, 3 mmol) in dry THF (20 mL) was added $LiAlH_4$ (170 mg, 4.5 mmol) under nitrogen. After the mixture was stirred at 0 °C for 30 min (monitored by TLC), a saturated aqueous solution of NH_4Cl (30 mL) was added to quench the reaction. Then the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O and brine and dried over anhydrous Na_2SO_4.

After removal of the solvent, the residue was diluted by a solution of THF (4 mL), CH_3OH (4 mL), and aq NaOH (6.0 M, 2 mL). After the reaction mixture was stirred at 60 °C for 1 h, it was cooled to 0 °C, then diluted with CH_2Cl_2 (30 mL) and stirred with aq HCl (1.0 M, 10 mL) for 0.5 h. The mixture was extracted with aq HCl (1.0 M, 3 × 10 mL), and the combined aqueous layers were neutralized by aq NaOH (6.0 M) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and filtered.

To the filtrate of the free amine were immediately added Boc_2O (650 mg, 3 mmol) and K_2CO_3 (830 mg, 6 mmol). After the mixture was stirred for 1 h at room temperature, it was concentrated under vacuum. Then the residue was diluted with THF (10 mL) and aq NaOH (6.0 M, 5 mL). After the unreacted Boc_2O was destroyed (ca. 1 h), the reaction mixture was neutralized by aq HCl (1.0 M) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by chromatography (silica gel, EtOAc:PE = 1:15) to give desired product **1a** (560 mg, 83%) as a colorless oil, $[\alpha]^{25}_D$ −56.3 (c 0.22, $CHCl_3$). IR ν 2939, 1693, 1411 cm^{-1}; ^1H NMR δ 4.97 (d, J = 1.4 Hz, 1H), 4.74 (s, 1H), 4.65 (br, s, 1H), 3.96 (d, J = 13.7 Hz, 1H), 2.74−2.69 (m, 1H), 2.01−1.97 (m, 1H), 1.68 (s, 3H), 1.64−1.51 (m, 5H), 1.45 (s, 9H); ^{13}C NMR δ 155.3, 142.8, 111.5, 79.1, 54.7, 39.9, 28.3 (3C), 26.2, 25.4, 20.7, 19.4; MS m/z (%) 154 (22), 128 (62), 84 (50), 57 (100). Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.19; H, 10.10; N, 6.45.

By using a similar procedure, the compounds **1b**−**j** were prepared. (The experiments, characterization, and ^1H and ^{13}C NMR spectra for products **1b**−**j** are given in the Supporting Information.)

(*S*)-2-(2-Oxo-propyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (13). A suspension of $PdCl_2$ (39 mg, 0.22 mmol) and CuCl (220 mg, 2.2 mmol) in a solution of DMF and H_2O (10:1) (3 mL) was stirred under oxygen atmosphere at room temperature for 1 h. A solution of **1h** (500 mg, 2.2 mmol) in DMF and H_2O (10:1) (2 mL) was added to the reaction mixture. After 10 h at room temperature, the mixture was quenched with 20% $KHSO_4$ and extracted with Et_2O (3 × 10 mL). The extracts were washed with saturated $NaHCO_3$ and brine and dried with anhydrous Na_2SO_4 After removal of the solvent, the residue was purified with chromatography (silica gel, EtOAc:PE = 1:5) to yield **13** (487 mg, 91%), $[\alpha]^{25}_D$ −12.7 (c 0.22, $CHCl_3$). IR ν 2934, 1686, 1412 cm^{-1}; ^1H NMR δ 4.73 (br, d, J = 3.4 Hz, 1H), 3.97 (br, d, J = 12.0 Hz, 1H), 2.78 (t, J = 12.7 Hz, 1H), 2.66 (d, J = 7.2 Hz, 2H), 2.19 (s, 3H), 1.71−1.50 (m, 6H), 1.45 (s, 9H); ^{13}C NMR δ 206.8, 154.5, 79.4, 47.0, 44.1, 39.2, 29.9, 28.2, 28.1 (3C), 25.1, 18.7; MS m/z (%) 241 (M^+, 0.12), 84 (100). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.82; H, 9.75; N, 5.67.

Preparation of (*S*)-(+)-Pelletierine (2). To a stirred solution of **13** (434 mg, 1.8 mmol) in CH_2Cl_2 (5 mL) was added TFA (4 mL) dropwise at 0 °C under N_2. The resulting solution was stirred at 0 °C for 2 h. Then, aq NaOH (6.0 M) was added until pH 10. The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were washed with brine and dried with $MgSO_4$. Removal of the solvent under vacuum gave teh product (*S*)-(+)-pelletierine (**2**) as a yellowish oil (253 mg, 99%), which was pure enough to use in the next step without purification. The analytical data were obtained from a purified sample by chromatography (silica gel, EtOAc:PE = 3:7). $[\alpha]_D^{25}$ +19.4 (c 0.47, EtOH) [lit.[27] for (*R*)-(−)-pelletierine, $[\alpha]^{25}_D$ −22.1 (c 4.1, EtOH)]. IR ν 3326, 2930, 1709, 1356 cm^{-1}; ^1H NMR δ 3.04−2.89 (m, 2H), 2.71−2.61 (m, 1H), 2.56−2.49 (m, 2H), 2.36 (s, 1H), 2.14 (s, 3H), 1.77−1.70 (m, 1H), 1.62−1.54 (m, 2H), 1.52−1.30 (m, 2H), 1.22−1.08 (m, 1H); ^{13}C NMR δ 208.0, 52.1, 50.4, 46.5, 32.2, 30.3, 25.7, 24.3; MS m/z (%) 141 (M^+, 3.6), 84 (100). Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.36; H, 10.75; N, 9.87.

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Preparation of (4*S*,9a*S*)-4-(3,4-dimethoxyphenyl)octahydro-2*H*-quinolizin-2-one (14b). To a stirring solution of (*S*)-(+)-pelletierine (**2**) (141 mg, 1.0 mmol) and 3,4-dimethoxylbenzaldehyde (166 mg, 1.0 mmol) in CH_3OH (10 mL) was added aq NaOH (2.0 M, 5 mL) under N_2. After the resulting mixture was stirred at 60 °C for 70 h, it was neutralized by addition of aq HCl (10%) and extracted with CH_2Cl_2 (3 × 10 mL), then the combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography (silica gel, EtOAc:PE = 1:1) to give the desired product **14b** (202 mg, 70%) as a yellow oil, $[\alpha]^{25}_D$ −70.6 (*c* 0.22, $CHCl_3$) [lit.[21f] $[\alpha]^{25}_D$ −86 (*c* 0.3, $CHCl_3$), lit.[28] for (4*R*,10*R*)-**14b**, $[\alpha]^{25}_D$ +71 (*c* 0.25, $CHCl_3$)]. IR ν 2944, 1715, 1510, 1261 cm^{-1}; ^1H NMR δ 6.91 (s, 1H), 6.82 (m, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.20 (dd, *J* = 12.0, 3.1 Hz, 1H), 2.80−2.60 (m, 2H), 2.55−2.20 (m, 4H), 1.78−1.20 (m, 7 H); ^{13}C NMR δ 207.6, 149.2, 148.2, 135.0, 119.3, 110.9, 109.6, 69.8, 62.2, 55.8, 55.7, 52.6, 50.7, 48.6, 34.2, 25.7, 24.0; MS *m*/*z* (%) 289 (M^+, 25.07), 191 (100). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.62; H, 8.07; N, 4.68.

Preparation of (−)-Lasubine II (3). To a solution of **14b** (145 mg, 0.5 mmol) in dry THF (10 mL) was added a solution of K-Selectride in THF (1.0 M, 0.6 mL, 0.6 mmol) at −78 °C under N_2. After the resulting mixture was stirred at −78 °C for 1 h, it was quenched by aq NaOH (1.0 M, 5 mL). After the mixture was stirred for 1 h at room temperature, it was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography (silica gel, EtOAc:PE = 1:1) to give the desired product (−)-lasubine II (**3**) (131 mg, 90%) as a yellow oil, $[\alpha]^{25}_D$ −51.0 (*c* 0.12, MeOH) [lit.[21f] $[\alpha]^{25}_D$ −53 (*c* 0.13, MeOH), lit.[28] for (2*R*,4*R*,10*R*)-(+)-lasubine II, $[\alpha]^{25}_D$ +50 (*c* 0.3, MeOH)]. IR ν 3563, 2932, 1515 cm^{-1}; ^1H NMR δ 6.90−6.77 (m, 3H), 4.15 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.21 (dd, *J* = 11.3, 3.5 Hz, 1H), 2.69 (d, *J* = 11.7 Hz, 1H), 2.40−2.38 (m, 1H), 1.95−1.20 (m, 12H); ^{13}C NMR δ 148.8, 147.6, 137.1, 119.6, 110.7, 110.3, 64.6, 63.3, 56.3, 55.8, 55.6, 53.0, 42.6, 40.2, 33.4, 26.0, 24.7; MS *m*/*z* (%) 291 (M^+, 100), 164 (95). Anal. Calcd for $C_{17}H_{25}NO_3$: 70.07; H, 8.65; N, 4.81. Found: 70.11; H, 8.69; N, 4.70.

Preparation of (2*S*)-*N*-Acryloyl-2-allylpiperidine (15). To a stirred solution of **1h** (450 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) was added TFA (4 mL) dropwise at 0 °C under N_2. After the resulting mixture was stirred at 0 °C for 2 h, aq NaOH (6.0 M) was added until pH 10. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with brine.

To a stirred solution of the crude amine and aq NaOH (10%, 2 mL) was added a solution of acryloyl chloride (272 mg, 3 mmol) in CH_2Cl_2 (5 mL) dropwise at room temperature under N_2. After the resulting mixture was stirred for 4 h, H_2O (5 mL) were added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent under vacuum gave a crude product, which was purified by chromatography (silica, EtOAc:PE = 1:1) to give product **15** (344 mg, 96%) as a colorless oil, $[\alpha]^{25}_D$ −70.6 (*c* 0.42, $CHCl_3$). IR ν 2937, 1643, 1609, 1432 cm^{-1}; ^1H NMR δ 6.60−6.52 (m, 1H), 6.21 (d, *J* = 16.8 Hz, 1H), 5.65−5.60 (m, 2H), 5.04−5.10 (br, 2H), 4.11 and 4.91 (br, 1H), 3.75 and 4.55 (br, 1H), 2.70 and 3.11 (br, 1H), 2.46−2.27 (m, 2H), 1.71−1.58 (m, 5H), 1.52−1.30 (br, 1H); ^{13}C NMR δ 165.5, 134.8, 133.9, 128.3, 126.4, 117.5, 116.4, 52.6, 47.3, 41.1, 36.5, 34.5, 33.9, 28.3, 26.9, 25.8, 24.9, 18.5; MS *m*/*z* (%) 179 (M^+, 0.37), 84 (100). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.78; H, 9.62; N, 7.60.

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Preparation of (9a*S*)-1,6,7,8,9,9a-Hexahydro-4*H*-quinolizin-4-one (16). To a stirred solution of **15** (270 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was added Grubbs 2st generation catalyst (38 mg, 0.045 mmol) in one portion at room temperature under N_2. After the resulting solution was refluxed for 15 min, the solution was allowed to cool to room temperature. Removal of the solvent under vacuum gave a crude product, which was purified by chromatography (silica, EtOAc:PE = 1:1) to give product **16** (227 mg, 98%) as a colorless oil, $[\alpha]^{25}_D$ +45.7 (*c* 0.42, $CHCl_3$); [lit.[26a] $[\alpha]^{22}_D$ +47 (*c* 1.0, $CHCl_3$); lit.[26b] $[\alpha]^{22}_D$ +45.1 (*c* 1.0, $CHCl_3$)]. IR ν 2933, 1668, 1613 cm^{-1}; ^1H NMR δ 6.51−6.45 (m, 1H), 5.89−5.84 (m, 1H), 4.49 (d, *J* = 13.4 Hz, 1H), 3.57−3.40 (m, 1H), 2.60−2.45 (m, 2H), 2.25−2.13 (m, 1H), 1.86−1.68 (m, 3H), 1.56−1.38 (m, 3H); ^{13}C NMR δ 165.2, 137.9, 124.3, 54.5, 42.7, 33.1, 30.8, 24.6, 23.7; MS *m*/*z* (%) 151 (M^+, 7.05), 18 (100). Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.55; H, 8.77; N, 9.08.

Preparation of (2*S*,9a*S*)-2-Methyloctahydro-4*H*-quinolizin-4-one (17). To a suspension of CuI (383 mg, 2.0 mmol) in dry Et_2O (20 mL) was added dropwise a solution of MeLi in Et_2O (1.6 M, 2.5 mL, 4 mmol) at 0 °C. After the resulting solution was stirred at 0 °C for 30 min, it was cooled to −78 °C and $BF_3 \cdot OEt_2$ (0.26 mL, 2.0 mmol) was added dropwise. Five minutes later, a solution of **16** (151 mg, 1.0 mmol) in dry Et_2O (10 mL) was added dropwise and the resulting solution was stirred for 1 h. Then a saturated NH_4Cl solution (30 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. After the solvent was evaporated under vacuum, the residue was purified by chromatography (silica gel, EtOAc:PE = 1:1) to give product **17** (137 mg, 82%) as a colorless oil, $[\alpha]^{25}_D$ −20.2 (*c* 0.4, $CHCl_3$) [lit.[26a] $[\alpha]^{25}_D$ −21 (*c* 1.0, $CHCl_3$)]. IR ν 2931, 1637, 1442 cm^{-1}; ^1H NMR δ 4.78−4.74 (m, 1H), 3.35−3.32 (m, 1H), 2.46−2.38 (m, 2H), 2.08−1.86 (m, 3H), 1.71−1.20 (m, 7H), 0.98 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR δ 168.2, 55.3, 42.8, 40.4, 36.6, 33.4, 25.2, 24.8, 24.3, 20.2; MS *m*/*z* (%) 167 (M^+, 25.69), 18 (100). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.93; H, 10.29; N, 8.20.

Preparation of (+)-Cermizine C Hydrochloride (4·HCl). To a stirring solution of lactam **17** (250 mg, 1.5 mmoL) in dry THF (15 mL) was added dropwise a solution of MeMgBr in THF (1.0 M, 6 mL, 6 mmoL). After the mixture was allowed to heat at 60 °C for 3 h, it was then cooled to 0 °C. Then $NaBH_3CN$ (570 mg, 9 mmoL) was added followed by addition of glacial acetic acid (0.75 mL). The resulting mixture was stirred for 1 h, a saturated solution HCl in MeOH (15 mL) was added, then the mixture was stirred for another 10 min. After the solvent was evaporated under vacuum, the residue was purified by chromatography (silica gel, $CHCl_3$:MeOH = 10:1) to give product **4·HCl** (288 mg, 95%) as a yellow wax, $[\alpha]^{25}_D$ +8.4 (*c* 0.3, MeOH) [lit.[26a] $[\alpha]^{23}_D$ −2.0 (*c* 0.4, MeOH); lit.[25] $[\alpha]^{25}_D$ +4.0 (*c* 0.8, MeOH)]. IR ν 2931, 1637, 1442 cm^{-1}; ^1H NMR (CD_3OD) δ 3.90−3.80 (m, 1H), 3.66−3.56 (m, 2H), 3.08 (ddd, *J* = 13.1, 13.1, 3.3 Hz, 1H), 2.26−2.10 (m, 1H), 2.08−1.56 (m, 9H), 1.41−1.20 (m, 4H), 0.95 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (CD_3OD) δ 61.3, 51.2, 49.9, 41.7, 38.3, 25.5, 24.7, 23.8, 21.6, 18.5, 17.7; MS *m*/*z* (%) 167 (M^+, 5.04), 152 (100). Anal. Calcd for $C_{11}H_{22}ClN$: C, 64.84; H, 10.88; N, 6.87. Found: C, 64.94; H, 10.91; N, 6.62.

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Supporting Information Available: Experiments, characterization, and ^1H and ^{13}C NMR spectra for **1a**−**j**, **2**, **3**, **4·HCl**, **8a**−**i**, **12**, **13**, **14b**, and **15**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.