Notes

Stereocontrolled Syntheses of Piperidine Derivatives Using Diastereoselective Reactions of Chiral 1,3-Oxazolidines with Grignard Reagents: Asymmetric Syntheses of the Pinidine Enantiomers

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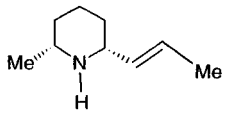
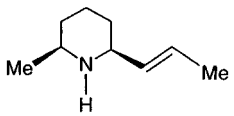
Pinidine is the main constituent of *Pinus sabiniana* and related plant species as determined, along with its chemical structure, by Tallent and co-workers over 40 years ago.[1] The complete stereochemistry of pinidine was unambiguously established by Hill to be **1a**, using chemical and spectroscopic methods.[2] Very recently, further work on the pinidine alkaloid contents of pine (*Pinus*) and spruce (*Picea*) trees and a biosynthetic hypothesis were put forward by Stermitz and co-workers.[3] They also revealed striking evidence of the toxic and teratogenic activities of pinidine that might be responsible for premature parturition or fetal abortion in pregnant range cows that consume the needles of *Pinus ponderosa* (Ponderosa pine).

The first total synthesis of pinidine was accomplished by Leete via resolution of a racemic mixture.[4a] A further synthesis of the racemate[4b] and six enantiospecific routes to **1a** and the unnatural enantiomer **1b** starting from (*S,S*)-tartaric acid,[5a] (*R,R*)-tartaric acid,[5a] (*S*)-ethyl lactate,[5b] (*R*)-alanine,[5c] methyl 6-oxoheptanoate,[5d] or 9-azabicyclo-[3.3.1]nonan-3-one derivatives[5e,f] have appeared in the literature thus far. Considering the strategies in all of the methods used to construct the 2,6-disubstituted piperidine skeleton to date, we have a high regard for the valuable synthon 1-aza-4-oxabicyclo[4.3.0]nonane derivative (**2**),[6] which was reported by Husson and co-workers, and is derived from the Robinson-type condensation of glutaraldehyde with amino alcohol. This compound, which is reactive toward nucleophilic attack at its C-5 position, is a key intermediate that provides convenient stereocontrol over both α positions of piperidine derivatives, as exemplified by the enantioselective construction of both the (+) and (−) enantiomers of coniine and dihydropinidine.[6]



1a : (-)-Pinidine



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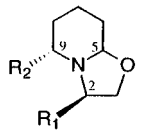

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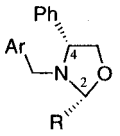

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On the other hand, our approach is based on the versatility of known chiral 1,3-oxazolidines (**3**) which can be easily synthesized by the condensation of (*R*)-*N*-alkyl-2-hydroxyethylamines with carbaldehydes.[7] These five-membered heterocyclic adducts react with various organometallic reagents in a highly diastereoselective manner to produce chiral amines in both high chemical and optical yields.[8] Finally, such reactions may be useful for the highly stereocontrolled total synthesis of naturally occurring alkaloids.[9] As part of our work on the application of the diastereoselective reaction of chiral 1,3-oxazolidine and Grignard reagent to the asymmetric synthesis of piperidine-type alkaloids, we have used simple synthons which are structurally similar to **2** as pivotal compounds to provide 2-substituted piperidines with both *R* and *S* configurations, along with cis- and trans-2,6-disubstituted piperidines.[10] We describe here the application of our procedure to the preparation of (−)-pinidine (**1a**) and (+)-pinidine (**1b**) in high enantiomeric purity.

The strategy was focused on the configurations of the two enantiomers of pinidine, (*R,R*) for (−)-pinidine and

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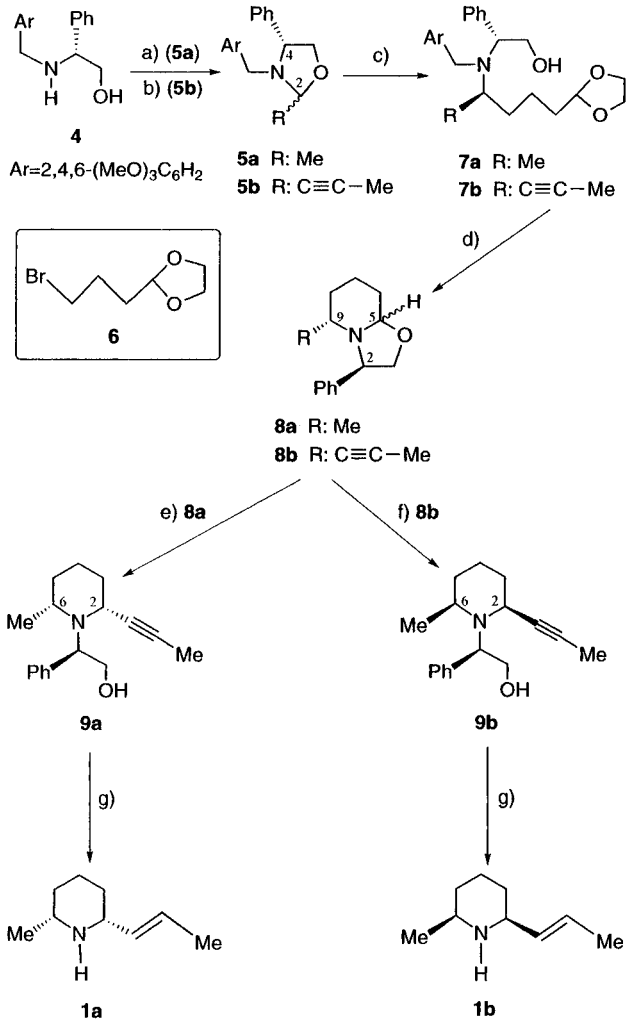
Scheme 1[a]



[a]Reagents and conditions : (a) MeCHO, MS 3A, CH_2Cl_2, rt (100%); (b) MeC≡CCHO, $MgSO_4$, CH_2Cl_2, rt (unstable); (c) **6**, Mg, THF, rt (**7a** 97%; **7b** 87%, 2 steps); (d) CF_3COOH, CH_2Cl_2, rt (**8a** 63%; **8b** 74%); (e) MeC≡CH, CH_3CH_2MgBr, THF, rt (96%); (f) MeMgBr, THF, rt (92%); (g) Na, NH_3 liquid, -78°C (**1a** 70%; **1b** 65%).

(*S,S*) for (+)-pinidine, to determine which functionality should be used in the initial oxazolidine. We postulated that control of the stereogenic center at C-6 of the piperidine ring with an *R* configuration for the methyl moiety could be achieved by introducing a methyl group at C-2 of the starting oxazolidine. On the other hand, the propenyl candidate should first be adjusted to the related oxazolidine to set up the *S* orientation of the methyl moiety at C-6 chiral center of the piperidine ring.

We paid careful attention to the bulky *N*-substituents of the starting 1,3-oxazolidines that could affect the high stereoselectivity in the reaction with Grignard reagents and act as readily removable functional groups in the next reaction. To address both purposes, we extended our previous work[7b,8e] by investigating *N*-(4-methoxybenzyl)-, *N*-(3,4-dimethoxybenzyl)-, *N*-(2,3,4-trimethoxybenzyl)-, and *N*-(2,4,6-trimethoxybenzyl)-1,3-oxazolidine derivatives, which will be reported separately. Finally, we took advantage of 1,3-oxazolidines bearing an *N*-(2,4,6-trimethoxybenzyl) substituent, which offer a superior reaction time, percentage yield, and diastereoselectivity in the reaction with Grignard reagents.

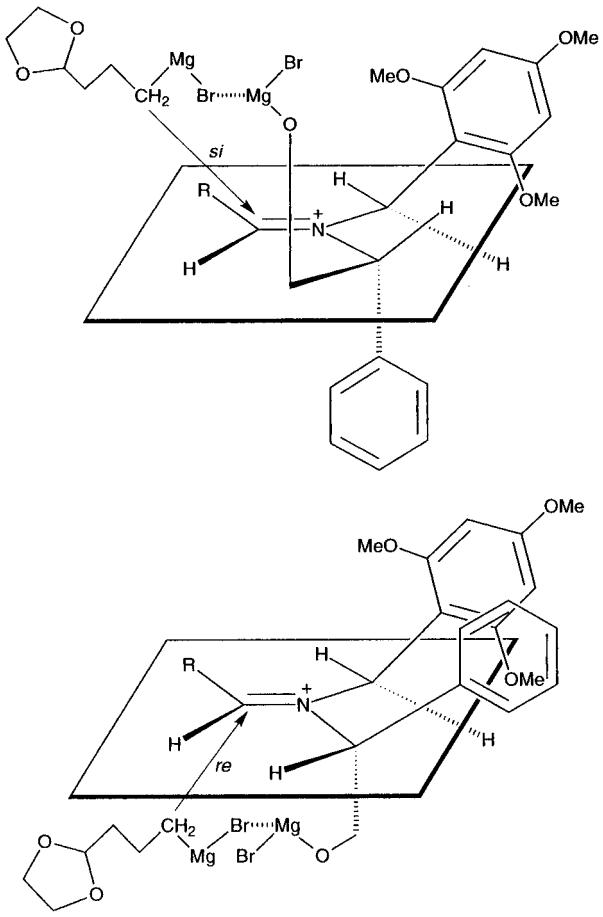


Figure 1.

As a result of our preliminary research, we ascertained that an excess of Grignard reagent (at least 3 equiv) should be added to the substrate to achieve the complete nucleophilic attack−ring opening of the oxazolidine ring within 2 days. Even though 2 equiv of Grignard reagent is sufficient for such a reaction, a longer reaction time is needed to complete the reaction.

Thus, we developed a synthesis of (−)-pinidine (**1a**) as shown in Scheme 1. In our prior work,[10] the key intermediate **8a** was prepared in three steps (61% overall yield) from the (*R*)-*N*-(2,4,6-trimethoxybenzyl)phenylglycinol (**4**) as follows. Condensation of **4** with acetaldehyde gave the initial oxazolidine **5a** as a diastereomeric mixture in a ratio of 97:3 based on measurement of the C-2 methyl peaks in the ^{1}H NMR spectrum. A carbon chain providing a six-membered heterocycle candidate was prepared through the diastereoselective reaction of **5a** with the appropriate Grignard reagent to give the diastereomerically pure amino acetal **7a**. The diastereoselectivity of this reaction can be rationalized by assuming that the Grignard reagent approaches the oxygen atom of the 1,3-oxazolidine ring to give a favorable intermediate iminium salt, and then nucleophilic attack occurs from the *si* face of the C=N bond rather than the unfavorable opposite site due to steric hindrance between the (*R*)-phenyl functionality and the bulky *N*-(2,4,6-trimethoxybenzyl) substituent as shown in Figure 1. This is supported by the experimental finding that an increase in the bulkiness of the *N*-functional group of the 1,3-oxazolidine enhanced the diastereoselectivity in the reaction with the Grignard reagent.[7b] The intramolecu-

lar ring closure of **7a** was achieved by treatment with TFA in CH_2Cl_2 to give the bicyclic compound **8a** as an inseparable diastereomeric mixture of the C-5 epimeric product in a ratio of 42:58. The methyl-substituted carbon C-9 of **8a**, which should be the C-6 moiety of the subsequent piperidine ring, shows an *R* configuration. Moreover, the reaction of **8a** with methylmagnesium bromide gave a piperidine derivative with complete cis configuration at its 2,6-dimethyl substituents.[10] On the basis of these results, we next inserted the propynyl functionality into **8a** by reacting it with propynylmagnesium bromide, which was prepared in situ from ethylmagnesium bromide and propyne, to give the 2,6-disubstituted piperidine **9a** in 96% yield. Compound **9a** had the cis configuration exclusively, which was confirmed by further conversion to the title compound **1a**.[11] The propynyl functionality was transformed into the desired (*E*)-propenyl side chain by subjecting **9a** to a specific reduction according to the Birch procedure. We took advantage of this process which provided *N*-deprotection similar to Kibayashi's method[5a] to give the volatile **1a**. Treatment with ethanolic-HCl and recrystallization from EtOH−ether gave (−)-pinidine hydrochloride (**1a**·HCl) as colorless crystals, mp 244−246 °C (lit.[5a] mp 244−246 °C); $[\alpha]^{20}_D$ −9.5 (*c* 1.01, EtOH) [lit.[5a] $[\alpha]^{24}_D$ −9.6 (*c* 0.25, EtOH)] in 70% yield.[12]

Next, the preparation of (*S*,*S*)−(+)-pinidine (**1b**) was attempted starting from the oxazolidine **5b** bearing a propynyl moiety at C-2, as shown in Scheme 1. The initial **5b** was built up by the condensation of phenylglycinol **4** with 2-butynal in CH_2Cl_2 by the addition of dried $MgSO_4$. The ^{1}H NMR spectrum of the crude product suggested an inseparable diastereomeric mixture in a ratio of 69:31. The unstable mixture of **5b**, without purification, was treated with a Grignard reagent derived from 2-(3-bromopropyl)-1,3-dioxolane **6** to give the diastereomerically pure amino acetal **7b** in 87% overall yield from **4**. The cyclization reaction of **7b** gave the bicyclic compound **8b** in 74% yield as a single diastereomer. To introduce a methyl moiety, the requisite intermediate **8b** was treated with methylmagnesium bromide to give the 2,6-disubstituted piperidine **9b** in 92% yield with a completely cis configuration, which was confirmed by further conversion to the target compound **1b** as follows. Birch reduction was carried out to simultaneously remove the *N*-protective group and reduce the triple bond to an (*E*)-alkene to produce (+)-pinidine (**1b**). Treatment with ethanolic-HCl and recrystallization from EtOH−ether provided (+)-pinidine hydrochloride (**1b**·HCl), mp 246−247 °C (lit.[5a] mp 246−248 °C); $[\alpha]^{20}_D$ +9.5 (*c* 1.05, EtOH) [lit.[5a] $[\alpha]^{24}_D$ +9.5 (*c* 0.20, EtOH)] in 65% yield.[12]

In conclusion, we have described the enantioselective synthesis of (−)-pinidine (**1a**) in 41.1% overall yield in five steps, and of (+)-pinidine (**1b**) in 38.5% overall yield in five steps, using the diastereoselective reaction of chiral 1,3-oxazolidine and Grignard reagent as the key step, as well as the 1-aza-4-oxabicyclo[4.3.0]nonane derivative as a pivotal intermediate. This procedure should also be applicable to the synthesis of other 2,6-disubstituted piperidine compounds.

(11) The cis configuration of compouds **9a** and **9b** was determined indirectly by the comparison of optical rotation values of pinidine **1a** and **1b**, respectively, with the reference's values.

(12) The enantiomeric purities of both (−)- and (+)-pinidine (>99% ee) were determined chromatographically, as their *N*-benzoyl derivatives, by using chiral HPLC-column CHIRALCEL OD (4.6 mm i.d. × 250 mm) with hexane−isopropyl alcohol (93:7).

Experimental Section

General Procedures. Melting points were measured without correction. The ^{1}H NMR and ^{13}C NMR spectra were run in $CDCl_3$ unless otherwise noted. All chemical shifts are reported as δ values (ppm) relative to TMS and residual $CDCl_3$ as internal standards on a 270 MHz spectrometer. Column chromatography was performed on silica gel (45−75 mm, Wakogel C-300). The THF was distilled over potassium metal, and CH_2Cl_2 was distilled over phosphorus pentoxide. All other solvents and reactants were of the best commercial grade available and used without further purification unless noted.

(2*R*,6*R*,1′*R*)-*N*-(2′-Hydroxy-1′-phenylethyl)-2-(1-propynyl)-6-methylpiperidine (9a). A stirred solution of ethylmagnesium bromide (2.93 mL, 8.8 mmol) in THF (20 mL), which was cooled with ice water−NaCl, was bubbled with propyne gas for 3−5 min. To the resulting solution of propynylmagnesium bromide was added dropwise a solution of the bicyclic compound **8a** (prepared in three steps in 61% overall yield from **4**)[10] (0.48 g, 2.2 mmol) in THF (10 mL). After stirring at room temperature under N_2 for 18 h, the reaction mixture was quenched with water, and the organic solution was decanted from the insoluble solid. The residue was extracted with ether (2 × 20 mL), the organic extracts were combined, dried over Na_2SO_4, and evaporated under reduced pressure to give an oil. Column chromatography on silica gel with CH_2Cl_2−MeOH (19:1) afforded the 2,6-disubstituted piperidine **9a** as a pale yellow oil (0.55 g, 96%). $[\alpha]^{20}_D$ +2.9 (*c* 1.12, $CHCl_3$). ^{1}H NMR δ 1.13 (d, 3 H, J = 6.7 Hz), 1.33−1.67 (m, 3 H), 1.73−1.87 (3 H, m), 1.85 (d, 3 H, J = 2.4 Hz), 2.52 (br s, 1 H), 2.83 (m, 1 H), 3.76 (m, 1 H), 3.89 (dd, 1 H, J = 5.5, 11.0 Hz), 3.93 (dd, 1 H, J = 4.9, 11.0 Hz), 4.09 (dd, 1 H, J = 4.9, 5.5 Hz), 7.24−7.36 (m, 3 H), 7.42 (dd, 2 H, J = 1.8, 7.6 Hz). ^{13}C NMR δ 3.6, 15.0, 17.0, 32.7, 32.9, 45.4, 50.2, 63.8, 64.7, 80.0, 80.9, 127.4, 128.3, 128.6, 140.0. EIMS *m*/*z* (relative intensity): 257 $[M]^+$ (3), 226 $[M - CH_2OH]^+$ (100). IR ($CHCl_3$): 3400 (OH) cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.08; H, 9.19; N, 5.36.

Synthesis of (−)-Pinidine Hydrochloride (1a·HCl). To stirred liquid ammonia (50 mL) in a flask equipped with a dry ice condenser was added a solution of *N*-substituted piperidine **9a** (0.54 g, 2.1 mmol) in THF (5 mL). Sodium (1.0 g, 43.5 mmol) was added portionwise to the reaction mixture solution. After being stirred for 9 h, THF (10 mL) was added, the reaction vessel was opened to the atmosphere, and its contents were allowed to warm to room temperature over 16−18 h. The residue was quenched by the addition of MeOH and water and extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over Na_2SO_4 and carefully evaporated below 30 °C under reduced pressure. The remaining oil was subjected to column chromatography on silica gel with CH_2Cl_2−MeOH (5:1) to give (−)-pinidine as a colorless oil (0.204 g, 70%). Treatment with ethanolic-HCl gave (−)-pinidine hydrochloride (**1a**·HCl), which was recrystallized from EtOH−ether to afford colorless needles, mp 244−246 °C. $[\alpha]^{20}_D$ −9.5 (*c* 1.01, EtOH). ^{1}H NMR δ 1.43−1.96 (m, 6 H), 1.59 (d, 3 H, J = 6.7 Hz), 1.68 (dd, 3 H, J = 1.8, 6.7 Hz), 3.09 (m, 1 H), 3.45 (m, 1 H), 5.75 (dd, 1 H, J = 7.3, 15.9 Hz), 5.91 (dq, 1 H, J = 6.7, 15.9 Hz), 9.20 (br s, 1 H), 9.50 (br s, 1 H). ^{13}C NMR δ 17.8, 19.5, 22.8, 28.8, 30.2, 54.3, 59.9, 126.9, 132.4. EIMS *m*/*z* (relative intensity): 139 $[M]^+$ (34), 124 $[M - CH_3]^+$ (84).

(2*R*,4*R*)-*N*-(2,4,6-Trimethoxybenzyl)-2-(1-propynyl)-4-phenyl-1,3-oxazolidine (5b). To a solution of the phenylglycinol **4** (7.0 g, 22.06 mmol) in CH_2Cl_2 (100 mL) was added 2-butynal (4.5 g, 66.18 mmol) and an equal amount of dried $MgSO_4$. The reaction mixture was stirred at room temperature under N_2 for 1 h and filtered over a pad of Celite. The reaction flask was rinsed twice with CH_2Cl_2, and then the combined CH_2Cl_2 solution was evaporated under reduced pressure and dried under vacuum to afford a diastereomeric mixture (69:31) of **5b** as a pale yellow oil, which was unstable and used without further purification. ^{1}H NMR δ major component: 1.89 (d, 3 H, J = 1.8 Hz), 3.65 (s, 3 H), 3.68 (s, 6 H), 3.61−3.96 (m, 4 H), 4.05 (t, 1 H, J = 6.7 Hz), 4.95 (q, 1 H, J = 1.8 Hz), 6.04 (s, 2 H), 7.19−7.36 (m, 3 H), 7.45 (dd, 2 H, J = 1.8, 7.9); minor component: 1.97 (d,

3 H, $J = 1.8$ Hz), 3.75 (s, 3 H), 3.79 (s, 6 H), 3.61−3.96 (m, 3 H), 4.10 (t, 1 H, $J = 6.7$ Hz), 4.32 (t, 1 H, $J = 7.9$ Hz), 5.31 (q, 1 H, $J = 1.8$ Hz), 5.97 (s, 2 H), 7.19−7.36 (m, 5 H).

(4*S*,1′*R*)-2-[4-[*N*-(2,4,6-Trimethoxybenzyl)-*N*-(2′-hydroxy-1′-phenylethyl)amino]heptyn-5-yl]-1,3-dioxolane (7b). To a stirred solution of Grignard reagent, prepared from 2-(3-bromopropyl)-1,3-dioxolane **6** (13.0 g, 66.65 mmol) and Mg turnings (1.70 g, 69.93 mmol) in THF (25 mL) was added portionwise a solution of the oxazolidine **5b** in THF (25 mL). After being stirred at 0 °C under N_2 for 2 d, the reaction mixture was worked up in the same manner as described for the preparation of **9a** to give a viscous oil. Column chromatography on silica gel with hexanes−EtOAc (1:1) afforded the amino acetal **7b** as a pale yellow oil (9.2 g, 87% overall yield from **4**). $[\alpha]^{20}_D$ −184.9 (*c* 1.51, $CHCl_3$). ^{1}H NMR δ 1.43 (d, 3 H, $J = 1.8$ Hz), 1.48−1.74 (m, 6 H), 3.39 (m, 2 H), 3.64 (br s, 1 H), 3.75 (t, 1 H, $J = 12.8$ Hz), 3.82 (s, 3 H), 3.84 (s, 6 H), 3.83−4.02 (m, 7 H), 4.81 (t, 1 H, $J = 4.9$ Hz), 6.15 (s, 2 H), 7.24−7.34 (m, 3 H), 7.45 (dd, 2 H, $J = 1.8, 7.9$ Hz). ^{13}C NMR δ 3.3, 21.1, 33.5, 34.8, 39.5, 49.2, 55.0, 55.2, 60.7, 61.9, 64.6, 78.8, 79.2, 90.5, 104.4, 107.3, 126.9, 127.5, 129.4, 138.0, 159.8, 160.6. EIMS *m*/*z* (relative intensity): 452 $[M - CH_2OH]^+$ (25), 181 $[(OCH_3)_3C_6H_2CH_2]^+$ (65). IR ($CHCl_3$): 3400 (OH) cm^{-1}, 1140 (C−O−C) cm^{-1}. Anal. Calcd for $C_{28}H_{37}NO_6$: C, 69.54; H, 7.71; N, 2.90. Found: C, 69.40; H, 7.74; N, 2.84.

(2*R*,9*S*)-9-(1-Propynyl)-2-phenyl-1-aza-4-oxabicyclo[4.3.0]-nonane (8b). TFA (8.68 g, 76.1 mmol) was added to a solution of the acetal **7b** (4.6 g, 9.51 mmol) in CH_2Cl_2 (300 mL). After being stirred at room temperature for 3 d, the reaction mixture was quenched with the addition of water and then potassium carbonate. The organic solution was separated, washed with water, dried over Na_2SO_4, and evaporated under reduced pressure to give a yellow oil. The crude oil was subjected to column chromatography on silica gel with CH_2Cl_2 to afford the bicyclic product **8b** as a pale yellow oil (1.68 g, 74%). $[\alpha]^{20}_D$ −372.6 (*c* 1.14, $CHCl_3$). ^{1}H NMR δ 1.45−1.75 (m, 5 H), 1.86 (d, 3 H, $J =$ 1.8 Hz), 1.97 (m, 1 H), 3.66 (t, 1 H, $J = 7.9$ Hz), 3.67 (dd, 1 H, $J = 3.1, 7.9$ Hz), 3.92 (t, 1 H, $J = 7.9$ Hz), 4.16 (dd, 1 H, $J = 3.1$, 6.7 Hz), 4.16 (t, 1 H, $J = 7.9$ Hz), 7.23−7.41 (m, 5 H). ^{13}C NMR δ 3.8, 19.1, 30.5, 30.8, 46.4, 63.0, 72.8, 74.9, 81.6, 89.1, 127.6, 127.9, 128.4, 138.8. EIMS *m*/*z* (relative intensity): 241 $[M]^+$ (5), 226 $[M - CH_3]^+$ (3). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.48; H, 7.98; N, 5.69.

(2*S*,6*S*,1′*R*)-*N*-(2′-Hydroxy-1′-phenylethyl)-2-(1-propynyl)-6-methylpiperidine (9b). To a stirred solution of bicyclic compound **8b** (0.84 g, 3.48 mmol) in THF (20 mL) was added dropwise a 3 mol/L solution of methylmagnesium bromide in ether (3.5 mL, 10.5 mmol). After being stirred at 0 °C under N_2 for 2 d, the reaction mixture was worked up in the same manner as described for the preparation of **9a** to give a pale yellow oil. Column chromatography on silica gel with hexanes−EtOAc (4:1) afforded the 2,6-disubstituted piperidine **9b** as a colorless oil (0.82 g, 92%). $[\alpha]^{20}_D$ −191.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 1.29 (d, 3 H, $J = 6.7$ Hz), 1.36−1.89 (m, 6 H), 1.78 (d, 3 H, $J = 1.8$ Hz), 2.01 (br s, 1 H), 3.23 (m, 1 H), 3.35 (m, 1 H), 3.84 (dd, 1 H, $J = 5.5, 11.0$ Hz), 3.88 (dd, 1 H, $J = 6.1, 11.0$ Hz), 4.17 (dd, 1 H, $J = 5.5, 6.1$ Hz), 7.23−7.38 (m, 3 H), 7.41 (dd, 2 H, $J = 1.8, 7.9$ Hz). ^{13}C NMR δ 3.5, 15.0, 16.7, 32.3, 32.6, 47.2, 49.5, 63.4, 65.0, 80.1, 80.5, 127.5, 128.4, 128.6, 140.4. EIMS *m*/*z* (relative intensity): 257 $[M]^+$ (4), 226 $[M - CH_2OH]^+$ (100). IR ($CHCl_3$): 3400 (OH) cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.12; H, 8.97; N, 5.30.

Synthesis of (+)-Pinidine Hydrochloride (1b·HCl). In the same manner as described for the preparation of **1a**, a solution of *N*-substituted piperidine **9b** (0.41 g, 1.59 mmol) in THF (5 mL) was subjected to reduction using the Birch procedure to give an oil which was purified by column chromatography on silica gel with CH_2Cl_2−MeOH (5:1) to give (+)-pinidine as a colorless oil (0.144 g, 65%). Treatment with ethanolic-HCl gave (+)-pinidine hydrochloride (**1b**), which was recrystallized from EtOH−ether to afford the pure **1b**·HCl as colorless needles, mp 246−247 °C. $[\alpha]^{20}_D$ +9.5 (*c* 1.05, EtOH). ^{1}H NMR δ 1.43−1.96 (m, 6 H), 1.59 (d, 3 H, $J = 6.7$ Hz), 1.68 (dd, 3 H, $J = 1.8$, 6.7 Hz), 3.09 (m, 1 H), 3.47 (m, 1 H), 5.75 (dd, 1 H, $J = 7.3, 15.9$ Hz), 5.90 (dq, 1 H, $J = 6.7, 15.9$ Hz), 9.20 (br s, 1 H), 9.54 (br s, 1 H). ^{13}C NMR δ 17.7, 19.4, 22.8, 28.7, 30.2, 54.2, 59.8, 126.9, 132.4. EIMS *m*/*z* (relative intensity): 139 $[M]^+$ (44), 124 $[M - CH_3]^+$ (100).

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