Efficient Routes to Chiral 2-Substituted and 2,6-Disubstituted Piperidines

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Received April 20, 1998

The syntheses of chiral 2-substituted and 2,6-disubstituted piperidines, and piperidin-2-ylphosphonates, via benzotriazole methodology are described.

The piperidine ring system is present in many naturally occurring and biologically important compounds[1−3] such as (+)-pinidione (**1**), (+)-monomorine (**2**), (+)-solenopsin (**3**), (−)-lasubinel (**4**), and (+)-myrtine (**5**), etc. Meyers et al. have continued studies on chiral bicyclic lactams **6**, which were prepared by condensation of an optically pure amino alcohol with dicarbonyl compounds, and their application to the synthesis of natural and unnatural products, including 2-substituted and 2,6-disubstituted piperidines.[4−6] Recently, Amart and co-workers reported using this type of lactam **6** to prepare enantiopure 3-alkylpiperidines.[7] Husson *et al.* have elegantly demonstrated the advantages of 3(*S*)-5-cyano-3-phenylperhydropyrido[2,1-*b*][1,3]oxazole (**7**) as a chiral 1,4-dihydropyridine equivalent for the preparation of chiral 2-substituted[8] and 2,6-disubstituted piperidines,[8−10] and chiral aminophosphonates.[11] However, this methodology requires the use of KCN as starting material, and $AgBF_4$ for removal of the cyano group. Lhommet *et al.* reported recently the preparation of (+)- and (−)-*trans*-2,6-dimethylpiperidines starting from Meyers's lactam **6** and Husson's synthon **7**.[12] Chackalamannil and Wang synthesized (*S*)-2-methyl-2,3,4,5-tetrahydropyridine *N*-oxide, as a key intermediate for the enantioselective construction of *trans*-2,6-disubstituted piperidine, from *N*-Cbz-L-alanine methyl ester in six steps.[13] Kibayashi *et al.*[14] found that 2-substituted piperidines were enantioselectively prepared by Et_2AlCl-mediated nucleophilic alkylation with Grignard reagents on chiral perhydropyrido[2,1-*b*]pyrrolo[1,2-*d*][1,3,4]oxadiazine. Comins and co-workers reported the synthesis of chiral 2-substituted and *trans*-2,6-disubstituted piperidines from pyridine derivatives.[15−17]

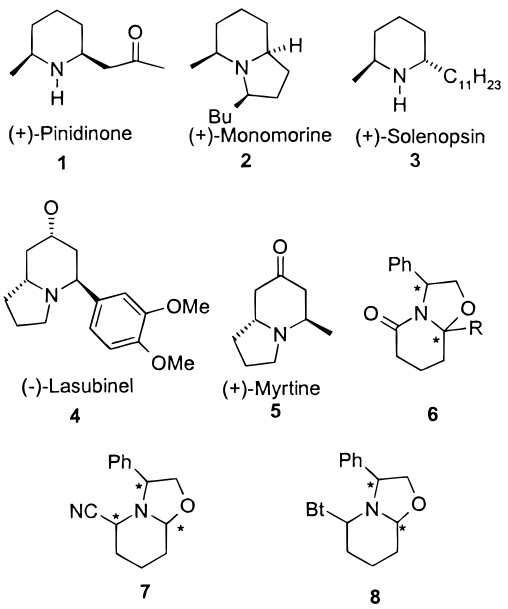

Figure 1.

Recently, benzotriazole was used as an auxiliary[18] for the synthesis of drug candidates and natural products. Bishop and McNutt reported an efficient route to the highly selective, nonpeptidal, δ opioid agonist (+)-4-[(α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]-*N*,*N*-diethylbenzamide [(+)BW373U86],[19] and Shankar *et al.* described a new method for the synthesis of polyhydroxylated piperidines as potential glycosidase inhibitors.[20] We have reported the preparation of chiral 2,5-disubstituted pyrrolidines from the reaction of (4*S*,5*R*)-5-(benzotriazol-1-yl)-4-phenyl[1,2-*a*]oxazolopyrrolidine and Grignard reagents.[21]

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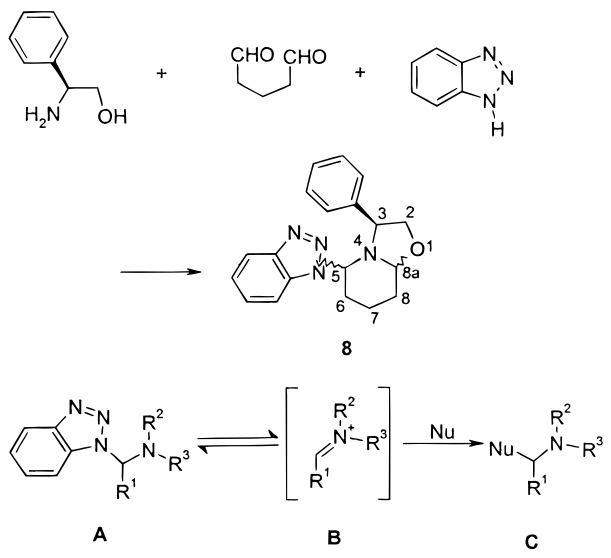
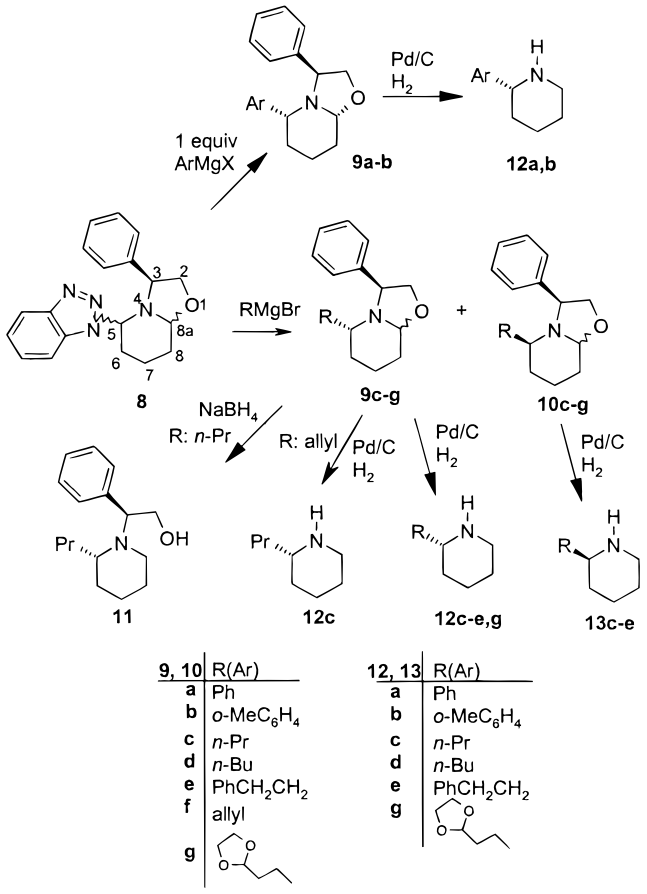
(1) Hamana, M. Total Synthesis of Heterocyclic Natural Products. *Heterocycles* **1997**, *45*, 1861.
(2) Toyooka, N.; Tanaka, K.; Momose, T. *Tetrahedron* **1997**, *53*, 9553.
(3) Bailey, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633.
(4) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503.
(5) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399.
(6) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7086.
(7) Amat, M.; Llor, N.; Hidalgo, J.; Bosch, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2237.
(8) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.
(9) Grierson, D. S.; Royer, J.; Guerrier, L.; Husson, H.-P. *J. Org. Chem.* **1986**, *51*, 4475.
(10) Royer, J.; Husson, H.-P. *J. Org. Chem.* **1985**, *50*, 670.
(11) Maury, C.; Wang, Q.; Gharbaoui, T.; Chiadmi, M.; Tomas, A.; Royer, J.; Husson, H.-P. *Tetrahedron* **1997**, *53*, 3627.
(12) Freville, S.; Bonin, M.; Celerier, J.-P.; Husson, H.-P.; Lhommet, G.; Quirion, J.-C.; Thuy, V. M. *Tetrahedron* **1997**, *53*, 8447.
(13) Chackalamannil, S.; Wang, Y. *Tetrahedron* **1997**, *53*, 11203.
(14) Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1997**, *38*, 4623.
(15) Comins, D. L.; Hong, H.; Salvador, J. M. *J. Org. Chem.* **1991**, *56*, 7197.
(16) Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *J. Org. Chem.* **1993**, *58*, 7732.
(17) Comins, D. L.; Benjelloun, N. R. *Tetrahedron Lett.* **1994**, *35*, 829.
(18) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409.
(19) Bishop, M. J.; McNutt, R. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1311.
(20) Shankar, B. B.; Kirkup, M. P.; McCombie, S. W.; Ganguly, A. K. *Tetrahedron Lett.* **1993**, *34*, 7171.

S0022-3263(98)00719-1 CCC: $15.00
Published on Web 09/02/1998

Scheme 1



Scheme 2



9, 10	R(Ar)
a	Ph
b	*o*-MeC_6H_4
c	*n*-Pr
d	*n*-Bu
e	$PhCH_2CH_2$
f	allyl
g	

12, 13	R(Ar)
a	Ph
b	*o*-MeC_6H_4
c	*n*-Pr
d	*n*-Bu
e	$PhCH_2CH_2$
g	

We now show that (3*S*)-5-benzotriazolyl-3-phenylperhydropyrido[2,1-*b*][1,3]oxazole (**8**) is a convenient chiral 1,4-dihydropyridine equivalent for the synthesis of chiral 2-substituted and *cis*-2,6-disubstituted piperidines, and piperidin-2-ylphosphonates.

Intermediate **8** was prepared in 95% yield from (*S*)-2-phenylglycinol, glutaraldehyde (aqueous solution) and benzotriazole in methylene chloride at room temperature for 12 h (Scheme 1). The ^{1}H and ^{13}C NMR spectra show

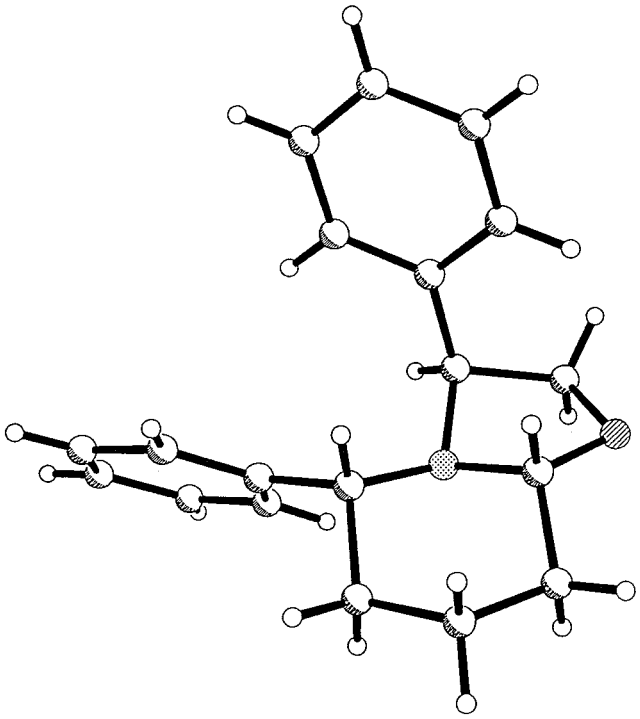


Figure 2. The X-ray structure of **9a**.

that product **8** is obtained as a diastereoisomeric mixture of Bt^1 and Bt^2 derivatives. Our previous work has demonstrated that[22,23] (i) Bt^1 and Bt^2 groups are both good leaving groups, and can be replaced by a nucleophile; (ii) the mechanism of substitution of the Bt group from adduct type **A** involves a planar iminium salt **B** as intermediate (Scheme 1). Therefore, the position at which the substituent is attached to the benzotriazole ring is not important. Thus, we used the intermediate **8** directly as a diastereomeric mixture of Bt^1 and Bt^2 isomers in subsequent reactions.

Substitution of the Benzotriazolyl Group from 8 Using Grignard Reagents. Preparation of 2-Substituted Piperidines, and (+)- and (−)-Coniine. Treatment of intermediate **8** with 1 equiv of arylmagnesium bromide at −78 °C gave crystalline (3*S*,5*R*)-5-aryl-3-phenylperhydropyrido[2,1-*b*][1,3]oxazole (**9a** and **9b**) as a single diastereoisomer in yields of 85% and 82%, respectively (Scheme 2). The configuration of **9a** was demonstrated to be that shown in Figure 2 by X-ray crystallography. The two phenyl groups in **9a** are trans, while the two substituents on the piperidine ring are cis. Hydrogenation of **9a**,**b** gave **12a**,**b** in good yields.

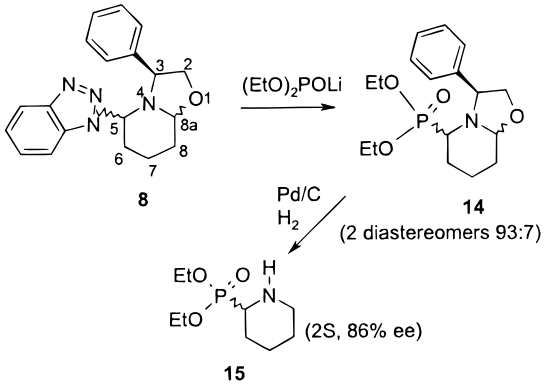
By contrast and for reasons which are not understood, the reactions of **8** with five alkylmagnesium bromides (RMgBr, R = *n*-Pr, *n*-Bu, $PhCH_2CH_2$, allyl, and $C_3H_5O_2$-CH_2CH_2) at −95 °C gave in each case a mixture of two (3*S*,5*S*)-5-alkyl-3-phenylperhydropyrido[2,1-*b*][1,3]-oxazoles **9c**−**g** (diastereoisomers at C-8a) and two (3*S*,5*R*)-5-alkyl-3-phenylperhydropyrido[2,1-*b*][1,3]oxazoles **10c**−**g** (also diastereoisomers at C-8a). The position of asymmetry in the diastereomeric pairs is demonstrated to be C-8a by the following experiments. Reduction of the **9c** diastereomeric mixture with $NaBH_4$ gave (2*S*)-2-[(2*S*)-2-propylhexahydro-1-pyridinyl]-2-phenylethan-1-ol (**11**) in 73% yield as a single diastereoisomer as determined

(21) Katritzky, A. R.; Cui, X.-L.; Yang, B. *Tetrahedron Lett.* **1998**, *39*, 1697.

(22) Katritzky, A. R.; Fan, W.-Q. *J. Org. Chem.* **1990**, *55*, 3205.

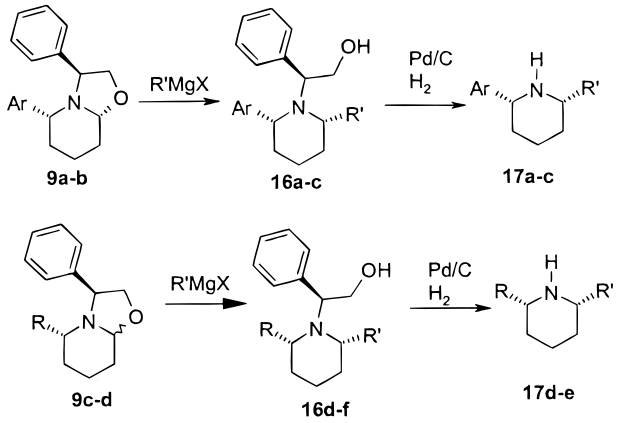
(23) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683.

Scheme 3



8 **14** **15**

Scheme 4



9	R(Ar)
a	Ph
b	*o*-MeC$_6$H$_4$
c	*n*-Pr
d	*n*-Bu

16, 17	R(Ar)	R'
a	Ph	Me
b	*o*-MeC$_6$H$_4$	Me
c	*o*-MeC$_6$H$_4$	*n*-Bu
d	*n*-Pr	Me
e	*n*-Bu	Ph
f	*n*-Bu	PhCH$_2$CH$_2$

by ^{1}H and ^{13}C NMR spectroscopy. Hydrogenation of the **9c** mixture gave (*S*)-(+)-propylpiperidine **12c** ((*S*)-(+)-coniine) in 83% yield, isolated as the hydrochloride salt. Similarly, hydrogenation of **10c** generated (*R*)-(−)-propylpiperidine **13c** ((*R*)-(−)-coniine) in 85% yield, also isolated as the hydrochloride salt. Hydrogenation of **9d**,**e**,**g** and **10d**,**e**,**g** gave **12d**,**e**,**g** and **13d**,**e**, respectively. In the hydrogenation of **9f**, the allyl group was reduced to a propyl group to give **12c** (Scheme 2).

Preparation of Piperidin-2-ylphosphonate. Intermediate **8** reacted with lithium diethyl phosphite to form diethyl [(3*S*)-3-phenylhexahydrooxazolo[3,2-*a*]pyridin-5-yl]phosphonate (**14**). Compound **14** is a 93:7 mixture of two diastereoisomers, and the NMR spectra (^{1}H and ^{13}C) of **14** are consistent with the literature[11] except for the ratio. In their analogous work, Husson and coworkers reported[10] a diastereomeric ratio of 33:67. Hydrogenation of **14** gave diethyl (hexahydro-2-pyridinyl)-phosphonate (**15**) as a colorless oil in 68% yield and 86% ee.

Synthesis of 2,6-Disubstituted Piperidines. Intermediates **9a**−**d** can further react with another Grignard reagent to give compounds **16a**−**f**, which after hydrogenation afford 2,6-disubstituted piperidines **17a**−**e**. For example, compound **9a** reacted with 1 equiv of MeMgBr to give (2*S*)-2-[(2*R*,6*R*)-2-methyl-6-phenylhexahydro-1-pyridinyl]-2-phenylethan-1-ol (**16a**) as a single isomer in 92% yield {$[\alpha]^{20}_D$ = +202.5° (*c* 1.0, CH_2Cl_2)}. The structure of **16a** was confirmed by X-ray analysis (see Figure 3): the methyl and phenyl substituents on the piperidine ring are cis. Hydrogenation of **16a** gave compound **17a** in 95% yield.

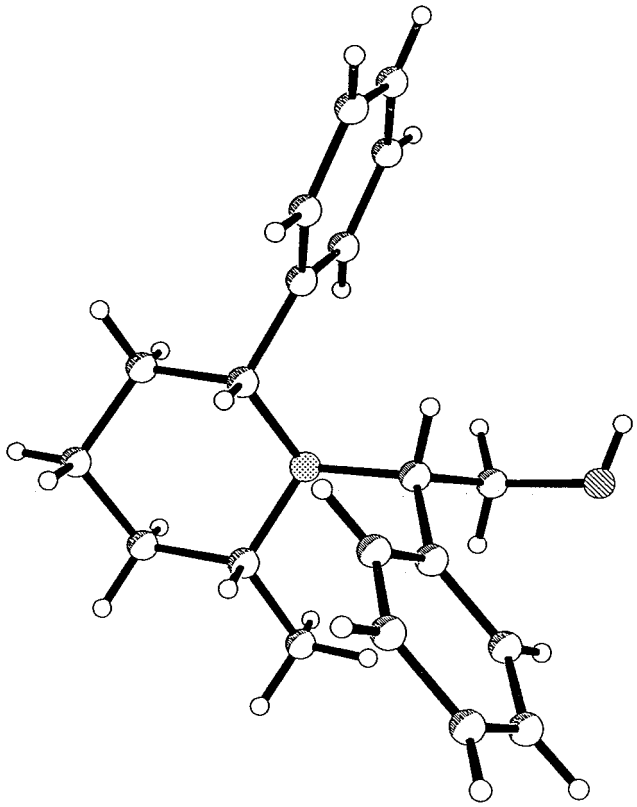


Figure 3. The X-ray structure of **16a**.

The mixture of oxazolidines **9c** (with *R* configuration at position 5 in ratio 9:4) reacted with MeMgBr to give (2*S*)-2-[(2*R*,6*S*)-2-methyl-6-propylhexahydro-1-pyridinyl]-2-phenylethan-1-ol (**16d**) in 98% yield as a single stereoisomer, as demonstrated by the ^{1}H and ^{13}C NMR analysis, oil, $[\alpha]^{20}_D$ = +18.3° (*c* 1.16, EtOH). Hydrogenation of **16d** in turn formed chiral (2*R*,6*S*)-2-methyl-6-propylpiperidine (**17d**) in 85% yield, isolated as the hydrochloride salt, mp 190−194 °C, $[\alpha]^{20}_D$ = +11.9° (*c* 0.69, EtOH) {lit.[8] $[\alpha]^{20}_D$ = +12.5° (*c* 1.0, EtOH)}.

Procedures similar to those used for **9d** afforded **16e**,**f**. Hydrogenation of **16e** gave **17e**. This provides a novel and general method to chiral *cis*-2,6-disubstituted piperidines.

In conclusion, the chemistry described above provides a convenient and efficient method to prepare chiral 2-substituted piperidines, chiral *cis*-2,6-disubstituted piperidines, and chiral piperidin-2-ylphosphonates, which are biologically active compounds of importance for the synthesis of natural products. For comparison, we note that Moody et al.[24] reported the synthesis of (*R*)-(−)-coniine from chiral 1-phenylbutanol in six steps in an overall yield of 23%. Kibayashi's method[14] provided (*S*)-(+)-coniine in 20% yield, while Husson's method gave (*S*)-(+)-coniine in 39% yield and Comins' method offered (*R*)-(−)-coniine in five steps with total yield 54%.[16] Our method gave (*S*)-(+)-coniine in three steps in an overall

(24) Moody, C. J.; Lightfoot, A. P.; Gallagher, P. T. *J. Org. Chem.* **1997**, *62*, 746.

yield of 45% from glutaraldehyde. Advantages of **8** in comparison to (3*S*)-5-cyano-3-phenylperhydropyrido[2,1-*b*][1,3]oxazole include avoiding the use of KCN as starting material, and of $AgBF_4$ for removal of the cyano group,[8] as well as higher yields and stereoselectivity.

Experimental Section

(3*S*)-5-Benzotriazolyl-3-phenylperhydropyrido[2,1-*b*]-[1,3]oxazole (8). A mixture of (*S*)-2-phenylglycinol (7.9 g, 50 mmol), glutaraldehyde (aqueous solution) (50 mmol), and benzotriazole (6.0 g, 50 mmol) in methylene chloride was stirred at room temperature for 12 h. The reaction mixture was washed with aqueous sodium hydroxide (2 N) to remove excess benzotriazole. The organic layer was dried over anhyd Na_2SO_4. After the removal of the solvent, a yellowish oil was obtained (15.2 g, 95%). ^{1}H NMR δ 7.80−8.10 (m, 1.5H), 6.80−7.50 (m, 7.5H), 5.70−5.90 (m, 1H), 5.00−5.10 (m, 0.5H), 4.75−4.80 (m, 0.5H), 3.40−4.60 (m, 3H), 1.70−2.55 (m, 6H). From NMR, this is a mixture of several compounds, comprising Bt^1 or Bt^2 isomers and diastereomers.

General Procedure for the Synthesis of Chiral 5-Substituted-3-phenylperhydropyrido[2,1-*b*][1,3]oxazole (9). To a solution of (3*S*)-5-benzotriazolyl-3-phenylperhydropyrido-[2,1-*b*][1,3]oxazole (**8**) (0.96 g, 3 mmol) in dry THF (20 mL) was added Grignard reagent (3 mmol) at low temperature (for aryl Grignard reagents, −78 °C; for alkyl Grignard reagents, −95 °C) under nitrogen. The mixture was kept at this temperature for 12 h and then quenched by adding water. The mixture was washed with aqueous NaOH solution (2 N, 2 × 10 mL) and water (2 × 10 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhyd Na_2SO_4. After removal of solvent, the residue was applied to a column of silica gel to give products **9** and **10**.

(3*S*,5*R*,8a*R*)-3,5-Diphenylperhydropyrido[2,1-*b*][1,3]-oxazole (9a): 0.71 g, 85% yield, mp 88−90 °C; $[\alpha]^{20}_D = +183.8°$ (*c* 0.89, EtOH); ^{1}H NMR δ 7.16−7.38 (m, 8H), 6.79 (d, 2H, J = 6.6 Hz), 4.28−4.38 (m, 3H), 4.06−4.14 (m, 1H), 2.98−3.05 (m, 1H), 2.08−2.17 (m, 1H), 1.76−1.86 (m, 1H), 1.60−1.68 (m, 1H), 1.24−1.60 (m, 3H); ^{13}C NMR δ 143.2, 138.2, 129.3, 128.2, 127.6, 127.5, 127.2, 127.0, 89.7, 71.5, 61.1, 61.0, 36.5, 30.8, 22.3. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.67; H, 7.58; N, 5.02. Found: C, 81.64; H, 7.54; N, 4.94.

(3*S*,5*S*)-5-Propyl-3-phenylperhydropyrido[2,1-*b*][1,3]-oxazole (9c): 0.42 g, 57% yield, oil; as a mixture of two diastereoisomers in ratio of 9:4, the data for the minor isomer is given in brackets. ^{1}H NMR δ 7.22−7.42 (m, 5H), 4.23 (dd, 1H, J = 9.3, 3.0 Hz) [4.55 (dd, 1H, J = 6.6, 1.9 Hz)], 4.10 (t, 1H, J = 7.2 Hz) [4.38 (t, 1H, J = 8.2 Hz)], 4.02 (t, 1H, J = 7.8 Hz) [4.34 (dd, 1H, J = 2.7, 9.0 Hz)], 3.57 (t, 1H, J = 7.2 Hz) [3.97−4.02 (m, 1H, overlapped)], 2.83−2.92 (m, 1H) [2.14−2.23 (m, 1H)], 1.97−2.06 (m, 1H), 1.14−1.82 (m, 9H), 0.92−1.06 (m, 1H), 0.74−0.85 (m, 3H); ^{13}C NMR δ 139.5, 128.4 [128.8], 127.8 [128.1], 127.5 [127.2], 87.6 [90.4], 73.3 [72.5], 61.2 [61.0], 52.2 [54.8], 31.6 [36.0], 27.4 [30.7], 24.7 [30.3], 20.5 [21.6], 17.9 [18.5], 14.2 [14.1].

(3*S*,5*R*)-5-Propyl-3-phenylperhydropyrido[2,1-*b*][1,3]-oxazole (10c):[8] 0.06 g, 8% yield, oil; as a mixture of two diastereoisomers in ratio of 14:9, the data for the minor isomer is given in brackets. ^{1}H NMR δ 7.22−7.42 (m, 5H), 4.34 (t, 1H, J = 7.7 Hz) [4.49 (t, 1H, J = 3.0 Hz)], 4.15 (t, 1H, J = 7.5 Hz) [4.35−4.42 (m, 1H)], 3.60−3.78 (m, 2H), 2.26−2.38 (m, 1H) [2.45−2.55 (m, 1H)], 1.95−2.08 (m, 1H), 1.70−1.91 (m, 1H), 1.50−1.70 (m, 3H), 0.98−1.49 (m, 5H), 0.51 (t, 3H, J = 6.9 Hz) [0.86 (t, 3H, J = 6.9 Hz)]; ^{13}C NMR δ 144.8 [143.1], 128.2 [128.4], 127.2 [126.9], 126.8 [126.7], 96.2 [89.3], 74.7 [69.6], 65.6 [65.8], 62.2 [57.3], 36.9 [38.3], 30.3 [31.0], 27.1 [29.7], 22.5 [18.8], 18.6 [18.2], [14.4] 13.9.

General Procedure for Synthesis of 2-(2,6-Disubstitutedpiperidinyl)-(2*S*)-Phenylethanol (16): To a solution of compound **9** (3 mmol) in dry THF (20 mL) was added Grignard reagent (9 mmol) at −20 °C under nitrogen. The mixture was kept at this temperature for 20 h and then quenched by adding water. The mixture was washed with aqueous NaOH solution (2 N, 2 × 10 mL) and water (2 × 10 mL) and extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over anhyd Na_2SO_4. After the removal of solvent, the residue was purified by column chromatography (silica gel) to give product **16**.

(2*S*)-2-[(2*R*,6*R*)-2-Methyl-6-phenylpiperidinyl]-2-phenyl-1-ethanol (16a): 0.81 g, 92% yield, mp 76−78 °C; $[\alpha]^{20}_D = +202.5°$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.42−7.75 (m, 10H), 4.19−4.31 (m, 2H), 4.13 (t, 1H, J = 7.2 Hz), 3.75−3.84 (m, 1H), 3.70 (s, 1H), 3.06−3.16 (m, 1H), 1.84−2.05 (m, 3H), 1.70−1.58 (m, 3H), 1.54 (d, 3H, J = 6.4 Hz); ^{13}C NMR δ 145.2, 137.1, 128.8, 128.7, 128.2, 127.8, 127.4, 127.2, 64.8, 62.2, 61.8, 50.5, 35.2, 32.4, 23.9, 21.2. Anal. Calcd for $C_{20}H_{25}NO$: C, 81.30; H, 8.54; N, 4.74. Found: C, 81.22; H, 8.77; N, 4.38.

Synthesis of Diethyl [(3*S*)-3-Phenylhexahydrooxazolo-[3,2-*a*]pyridin-5-yl]phosphonate (14). To a solution of diethyl phosphite (0.41 g, 3 mmol) in dry THF (20 mL) was added a solution of *n*-butyllithium in hexane (1.9 mL, 3 mmol) at −78 °C. The mixture was stirred 15 min before the addition of a solution of 2-benzotriazolyl-9-phenyloxazolopiperidine (0.96 g, 3 mmol) in dry THF (10 mL) at the same temperature. The mixture was kept at this temperature for 2 h and then allowed to warm to room temperature and stirred for 20 h. The reaction mixture was quenched with water, and washed with aqueous NaOH solution (2 N, 2 × 15 mL) and water (2 × 20 mL). The mixture was extracted with ethyl acetate (3 × 30 mL), and the combined organic layers were dried over anhyd Na_2SO_4. After removal of solvent, the residue was applied to a column (silica gel) to give product as a colorless oil[11] **14** (a mixture of diastereomers, ratio is 93:7), 0.75 g, 81% yield; ^{1}H NMR δ 7.20−7.46 (m, 5H), 4.75 (dt, 1H, J = 3.3, 9.5 Hz), 4.52 (q, 1H, J = 7.4 Hz), 4.16 (t, 1H, J = 7.8 Hz), 3.94−4.12 (m, 4H), 3.59 (t, 1H, J = 7.2 Hz), 3.29 (t, 1H, J = 6.1 Hz), 1.20−2.20 (m, 12H); ^{13}C NMR δ 139.6, 128.5, 128.3, 127.7, 127.2, 87.7, 73.4, 62.0, 61.5 (d, J = 7.1 Hz), 60.9 (d, J = 7.7 Hz), 50.8 (d, J = 125.5 Hz), 31.3, 25.6 (d, J = 3.8 Hz), 19.7, 16.5 (d, J = 5.7 Hz).

(2*S*)-2-[(2*S*)-2-Propylhexahydro-1-pyridinyl]-2-phenyl-1-ethanol (11). A mixture of **9c** (0.26 g, 1 mmol) and $NaBH_4$ (0.27 g, 0.75 mmol) in ethanol (20 mL) was stirred at room temperature for 20 h. Then water was added to quench the reaction. After removal of ethanol, the mixture was extracted with $CHCl_3$ (2 × 20 mL), and the organic layer was dried over anhyd Na_2SO_4. The solvent was removed, and crude product was applied to a column (silica gel) to give pure product **11** as colorless oil,[8] 0.18 g, 73%; ^{1}H NMR δ 7.17−7.39 (m, 5H), 4.31 (dd, 1H, J = 5.2, 10.2 Hz), 3.97 (t, 1H, J = 10.4 Hz), 5.58 (dd, 1H, J = 5.2, 10.2 Hz), 2.83−2.92 (m, 1H), 2.14−2.43 (m, 1H), 1.21−1.75 (m, 10H), 1.02−1.20 (m, 1H), 0.95 (t, 3H, J = 7.4 Hz); ^{13}C NMR δ 136.2, 128.8, 128.0, 127.5, 60.4, 59.5, 57.2, 45.5, 34.8, 31.5, 26.3, 24.1, 17.8, 14.7.

Hydrogenation for Preparation of Compounds 12, 13, 15, 17. Typical Procedure. A solution of **9a** (1 mmol) in methanol (50 mL) with Pd/C catalyst (10%, 60 mg) was hydrogenated at room temperature under 20 psi of hydrogen for 24 h. The catalyst was filtered off, and hydrochloric acid (12 N, 1 mL) was added into the filtrate. The pure hydrochloride salt precipitated to give product **12a** as a white solid, 0.18 g, 92% yield.

(2*R*)-2-Phenylpiperidine Hydrochloride Salt (12a): mp 196−198 °C; $[\alpha]^{20}_D = -3.1°$ (*c* 1.0, MeOH); ^{1}H NMR δ 9.55 (br s, 2H), 7.55−7.65 (m, 2H), 7.20−7.40 (m, 3H), 3.80−3.94 (m, 1H), 2.92−3.06 (m, 1H), 2.62−2.79 (m, 1H), 1.84−2.22 (m, 4H), 1.45−1.75 (m, 2H); ^{13}C NMR δ 136.4, 129.0, 128.9, 127.9, 61.2, 45.5, 30.2, 23.1, 21.6. HRMS Calcd for $C_{11}H_{16}NCl$: 161.1204 (M^+ − HCl). Found 161.1202.

(2*R*)-2-Propylpiperidine Hydrochloride Salt (13c): mp 218−221 °C; $[\alpha]^{20}_D = -7.3°$ (*c* 1.0, EtOH) [lit.[8] mp 217−218 °C, $[\alpha]^{20}_D = -5.8°$ (*c* 1.0, EtOH)]; 0.14 g, 83% yield; ^{1}H NMR δ 9.53 (br s, 1H), 9.23 (br s, 1H), 3.40−3.52 (m, 1H), 2.70−3.02 (m, 2H), 1.60−2.10 (m, 7H), 1.35−1.58 (m, 3H), 0.95 (t, 3H, J = 6.9 Hz); ^{13}C NMR δ 57.2, 44.8, 35.4, 28.2, 22.5, 22.3, 18.6, 13.7.

Diethyl (2*R*)-(Piperidin-2-yl)phosphonate (15): colorless oil;[11] 0.30 g, 68% yield; ^{1}H NMR δ 4.16 (qd, 4H, J = 7.4 Hz),

3.07−3.16 (m, 1H), 2.94 (td, 1H, J = 11.8, 1.9 Hz), 2.59 (td, 1H, J = 11.5, 2.1 Hz), 1.82−2.02 (m, 4H), 1.25−1.65 (m, 3H), 1.34 (t, 6H, J = 6.9 Hz); ^{13}C NMR δ 62.1 (d, J = 6.7 Hz), 54.2 (d, J = 159.1 Hz), 47.3 (d, J = 16.4 Hz), 26.2 (d, J = 3.8 Hz), 25.9, 24.5 (d, J = 15.4 Hz), 16.4.

(2*R*,6*R*)-2-Methyl-6-phenylpiperidine (17a): oil; $[\alpha]^{20}_{D}$ = +22.17° (*c* 0.69, EtOH); 0.17 g, 95% yield; ^{1}H NMR δ 7.20−7.42 (m, 5H), 3.68 (dd, 1H, J = 2.4, 10.5 Hz), 2.77−2.89 (m, 1H), 1.87−1.96 (m, 1H), 1.72−1.82 (m, 1H), 1.44−1.72 (m, 4H), 1.15−1.22 (m, 1H), 1.14 (d, 3H, J = 6.2 Hz); ^{13}C NMR δ 145.5, 128.2, 126.9, 126.6, 62.4, 53.1, 34.2, 33.8, 25.3, 23.0. Anal. Calcd for $C_{12}H_{17}N$: C, 82.22; H, 9.78; N, 8.00. Found: C, 81.86; H, 10.07; N, 7.80.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra, and CHN analyses or HRMS (if new compounds), for compounds **9b**,**d**−**g**, **10d**−**g**, **12b**−**e**,**g**, **13d**,**e**, **16b**−**f**, **17b**−**e** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO980719D