JOC*Note*

pubs.acs.org/joc

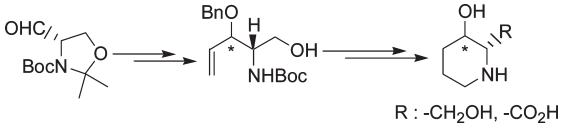
Facile Syntheses of Enantiopure 3-Hydroxypiperidine Derivatives and 3-Hydroxypipecolic Acids

Wen-Hua Chiou,* Gau-Hong Lin, and Chih-Wei Liang

Department of Chemistry, National Chung Hsing University, Taichung, Taiwan, R.O.C.

wchiou@dragon.nchu.edu.tw

Received November 4, 2009

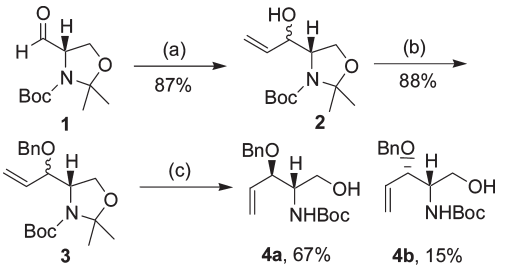


Facile syntheses of enantiopure *trans*- and *cis*-3-hydroxypiperidine derivatives and 3-hydroxypipecolic acids are reported, featuring Rh-catalyzed cyclohydrocarbonylation through common intermediates. A diaxial conformation in a 2,3-disubstituted *N*-Boc-piperidinyl structure is revealed by an X-ray crystallographic analysis.

Azasugars are carbohydrate analogues in which a nitrogen atom substitutes for the oxygen atom in the ring, and they have been found in a number of plants and microorganisms.[1,2] Since the first discovery of nojirimycin in 1966,[2] azasugars have received a great deal of attention due to their significant bioactivity. Their physiological effects result from the similarity with transition-state analogues in many carbohydrate-processing enzymes such as glycosidases and glycosyltransferases.[3,4] Since azasugars are viewed as possible therapeutic agents to treat a number of diseases such as diabetes, viral infections, and tumor metastasis, they have attracted synthetic chemists' interests to develop various approaches. As a part of the project devoted to asymmetric syntheses[5] of different azasugars and derivatives for pharmaceutical purposes, here we report the syntheses of enantiopure 3-hydroxypiperidine derivatives and 3-hydroxypipecolic acids through common intermediates via Rh-catalyzed cyclohydrocarbonylation.

Our syntheses commenced with vinyl addition on serine-derived Garner's aldehyde (**1**),[6] readily available in the (*S*)- as well as the (*R*)-form, served as a synthetically useful chiral precursor for the construction of optically active molecules. Addition of commercially available vinylmagnesium bromide at −40 °C led to a mixture of two diastereomeric products **2** in 87% combined yield. Although separation of two isomers was possible, the separation cost prompted us to find a better solution. Thus, protection of the resulting hydroxyl group was carried out by treatment with benzyl bromide in the presence of 18-crown-6 ether to give benzyl ether **3** in 88% yield. Addition of the crown ether improved the yield and reduced the reaction time. Removal of the acetonide group proceeded smoothly in an acidic condition, affording separable olefins **4** in 90% combined yield. An HPLC method has been developed to determine the diastereomeric ratio as 4.0:1 (see the Supporting Information). Both diastereomers can be easily obtained by column chromatography to give the less polar diastereomer as the major product **4a** in 67% isolated yield and the more polar product as the minor product **4b** in 15% isolated yield (Scheme 1).

SCHEME 1[a]



[a]Reagents and conditions: (a) CH_2=CHMgBr (2.0 equiv), THF, −40 °C; (b) BnBr (1.5 equiv), NaH (1.8 equiv), 18-crown-6 ether (0.5 equiv), THF, 0 °C to rt; (c) PTSA (13 mol %), MeOH, rt.

Rh-catalyzed cyclohydrocarbonylation provides a powerful tool for preparation of piperidine derivatives.[7,8] It can be viewed as a domino-type reaction, consisting of three consecutive reactions (Scheme 2). It starts with linear-selective hydroformylation of monosubstituted alkene (I) to linear aldehyde (II), followed by intramolecular addition of a carbamate to give hemiamidal (III). Hemiamidal (III) may undergo either solvent substitution to amidal (V, in a protic solvent), or dehydration to encarbamate (VI, in an aprotic solvent) via a common iminium intermediate (IV).

(1) For some leading references, see: (a) Stütz, A. E. *Iminosugars as Glycosydase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, 1999. (b) Compain, P.; Martin, O. R. *Iminosugars*, 1st ed.; John Wiley & Sons Ltd.: Chichester, 2007 and references cited therein.

(2) Inouye, S.; Tsuruoka, T.; Niida, T. *J. Antibiot*. **1966**, *19*, 288–292.

(3) For recent study of azasugar inhibition, see: (a) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750–770. (b) Zechel, D. L.; Boraston, A. B.; Gloster, T.; Boraston, C. M.; Macdonald, J. M.; Tilbrook, D. M. G.; Stick, R. V.; Davies, G. J. *J. Am. Chem. Soc*. **2003**, *47*, 14313–14323.

(4) For recent reviews, see: (a) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev*. **2000**, *12*, 4683–4696. (b) Sinnott, M. L. *Chem. Rev*. **1990**, *90*, 1171–1202.

(5) For recent reviews of syntheses of piperidine azasugars, see: (a) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, *2005*, 2159–2191. (b) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1816.

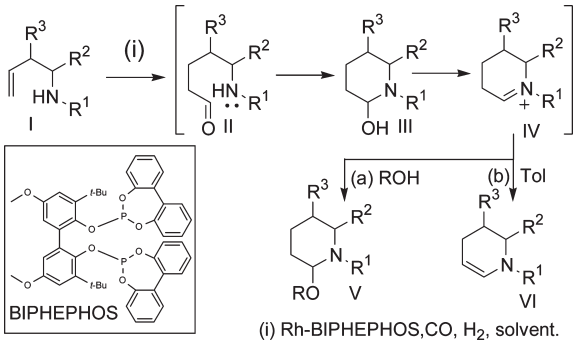
(6) (a) Garner, P.; Park, J.-M. *J. Org. Chem*. **1987**, *52*, 2361–2364. (b) Garner, P.; Park, J.-M. In *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. IX, p 300.

(7) (a) Ojima, I.; Tzamarioudaki, M.; Eguchi, M. *J. Org. Chem*. **1995**, *60*, 7078–7079. (b) Ojima, I.; Vidal, E. S. *J. Org. Chem*. **1998**, *63*, 7999–8003. (c) Chiou, W.-H.; Schoenfelder, A.; Sun, L.; Mann, A.; Ojima, I. *J. Org. Chem*. **2007**, *72*, 9418–9425.

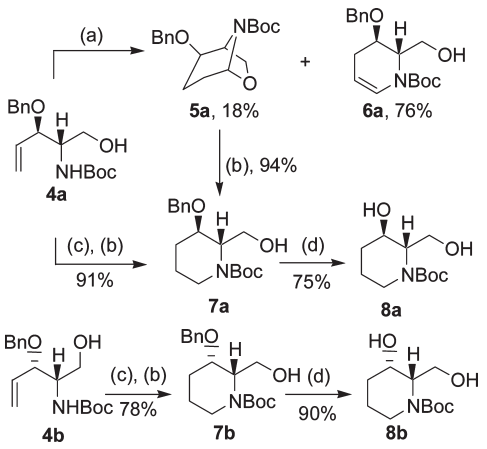
(8) For recent reviews of cyclohydrocarbonylation, see: (a) Ojima, I.; Commandeur, C.; Chiou, W.-H. In *Comprehensive Organometallic Chemistry-III*; Hiyama, T., Ojima, I., Eds.; Elsevier: Oxford, 2006; Chapter 11.15, ;pp 511−556. (b) Chiou, W.-H.; Lee, S.-Y.; Ojima, I. *Can. J. Chem*. **2005**, *83*, 681–692.

Published on Web 02/08/2010 DOI: 10.1021/jo902324h

SCHEME 2. Rh-Catalyzed Cyclohydrocarbonylation



SCHEME 3[a]



[a]Reagents and conditions: (a) $Rh(acac)(CO)_2$ (0.5 mol %), BIPHEPHOS (1.0 mol %), CO (2 atm), H_2 (2 atm), toluene, 60 °C, overnight (~16 h); (b) Et_3SiH (3.0 equiv), $BF_3 OEt_2$·(3.0 equiv), CH_2Cl_2, −78 °C, 16 h; (c) (a) in MeOH; (d) Pd/C (5 mol %), H_2 (2 atm), MeOH, rt, 6 h.

With olefin **4a** in hand, cyclohydrocarbonylation was carried out with low loading of Rh-BIPHEPHOS (0.5 mol %) at 60 °C under 4 atm of CO and H_2 (1:1) in toluene to give a crude product. A ^{1}H NMR analysis[9] showed amidal **5a** was the major product, accompanied by a small amount of enecarbamate **6a** (**5a**/**6a** = 2.5:1). However, after flash chromatography on silica gel, encarbamate **6a** was obtained in 76% isolated yield, while bicycloamidal **5a** in 18% yield. It was obvious that isomerization proceeded between **5a** and **6a** during purification.[10] Subsequent reduction of bicycloamidal **5a** with triethylsilane−boron trifluoride etherate at −78 °C afforded functionalized piperidine derivative **7a** in 94% yield. To surmount the low yield problem, methanol was used as the solvent because it would not form **6a**. Thus, switch of toluene to methanol in the cyclohydrocarbonylation reaction, followed by direct treatment of the crude product with reducing agents, afforded piperidine **7a** in 91% yield over two steps. The identical two-step reaction sequence was applied to convert olefin **4b** to piperidine **7b** in 78% yield (Scheme 3). We tried to assign the absolute structure of **7a** by thorough NMR analyses. The ROESY pointed out clearly a strong signal between H-2 and H-3. It implied that the relative configuration of **7a** was either a *cis* arrangement or a *trans* arrangement in which both of two substituents were located at pseudodiaxial orientations.

(9) A DFT-B3LYP/6-31G* calculation by Spartan 08 indicated **5a** is more stable than **6a** by 8.9 kcal/mol in vacuo and by 8.2 kcal/mol in toluene using the SM8 model.

(10) We did an experiment to confirm the isomerization: treatment of pure amidal **5** in the mixture solution of ethyl acetate and chloroform (v/v = 1:1) containing silica gel resulted in the formation of encarbamate **6a** (**5a**/**6a** ~ 1:1) by ^{1}H NMR analysis.

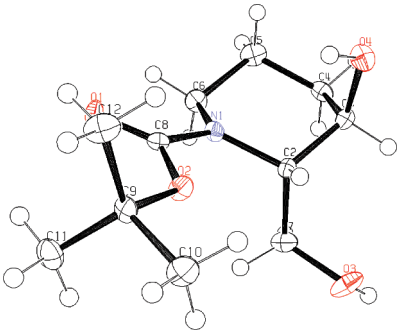


FIGURE 1. ORTEP drawing of diol **8a** showing 50% probability.

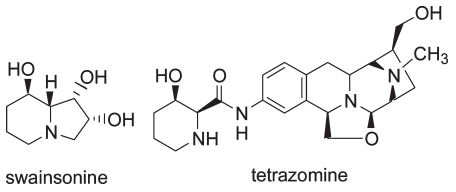


FIGURE 2. Swainsonine and tetrazomine.

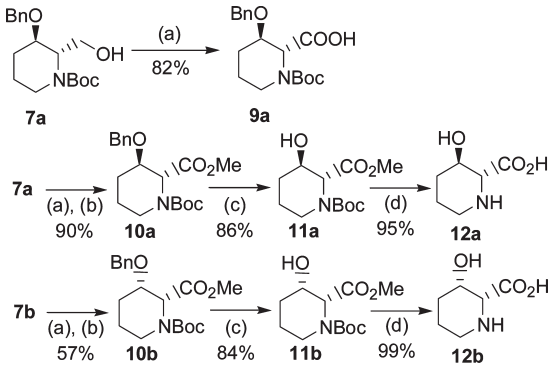
The structure of **7a** was determined by the X-ray crystallography of benzyl-free derivative **8a**, synthesized by catalytic hydrogenolysis of **7a** with palladium on carbon, affording diol **8a** in 90% yield. Solid product **8a** was recrystallized from chloroform−heptane to give a crystal suitable for the X-ray analysis (Figure 1).

It clearly revealed that the hydoxymethyl group at C-2 and the hydroxyl group at C-3 were located at the pseudoaxial positions of the piperidine, indicating both of H-2 and H-3 adopted pseudodiequatorial orientations. Such a preference for the diaxial conformation was attributed to a strong $A^{1,3}$ strain exerted by the C−N bond,[11,12] possessing partial double bond characters in the carbamate group. Since the absolute configuration of diol **8a** had been determined, parent olefin **4a** was unambiguously assigned as an *anti*-(2*S*,3*R*) configuration.

Piperidine **7a** was a versatile building block for syntheses of indolizidines or piperidines. For example, after removal of the Boc protecting group, diol **8a** could be converted to the enantiomer of 4-deoxyfagomine, an analogues of fagomine found as a potent antihyperglycemic compound.[13] Swainsonine, an inhibitor for mannosidase II, was synthesized from **7a** in five additional steps.[14] In addition, found in part of a variety of bioactive compounds, 3-hydroxypipecolate derivatives were valuable intermediates to synthesize antitumor antibiotics, such as tetrazomine (Figure 2). We described the

(11) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413.
(12) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.
(13) Asano, N.; Kato, A.; Miyauchi, M.; Kizu, H.; Tomimori, T.; Matsui, K.; Nash, R. J.; Molyneux, R. J. *Eur. J. Biochem.* **1997**, *248*, 296–303.
(14) Martín, R.; Murruzzu, C.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2005**, *70*, 2325–2328.

SCHEME 4[a]



[a]Reagents and conditions: (a) TEMPO (20 mol %), KBr (0.5 equiv), NaOCl (6.0 equiv), $NaHCO_3$, acetone, 4 °C, 3 h; (b) CH_2N_2; (c) Pd/C (5 mol %), H_2 (2 atm), MeOH, rt, 4 h; (d) (i) 6 N HCl, reflux, (ii) propylene epoxide, EtOH, reflux.

syntheses of 3-hydroxypipecolate derivatives from piperidines **7** as follows.[15]

TEMPO-catalyzed bleach reaction[16] provided a facile way to oxidize the hydroxymethyl group to corresponding carboxylic acid **9a**. We attempted catalytic hydrogenation to remove the benzyl group of **9a**, but the reaction proceeded too slow to give the desired product. Thus, the synthesis was modified by treatment of resulting crude carboxylic acid **9a** with diazomethane, affording methyl ester **10a** in 90% yield over two steps. Subsequent debenzylation with hydrogen in the presence of palladium on carbon gave free alcohol **11a** in 86% yield. Global removal of the methyl ester and the BOC protecting group in an acidic condition, followed by treatment with propylene oxide to neutralize excess hydrogen chloride gave *trans*-(2*R*,3*R*)-3-hydroxypipecolic acid (**12a**) in 95% yield, whose structure was unambiguously elucidated by NMR analyses. This protocol has proven to be applicable in the synthesis of the other diastereomer. Therefore, the synthesis of *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid (**12b**) was readily achieved using the same procedure (Scheme 4).

In conclusion, we have developed an effective methodology for the synthesis of enantiopure 3-hydroxypipecolic acid (**12a** and **12b**) via a useful building block **7**, which is also a precursor to synthesize swainsonine. Either **7a** or **7b** is easily synthesized from Garner's aldehyde in an enantiopure form through cyclohydrocarbonylation. We are currently applying this methodology toward other azasugars.

(15) For recent syntheses of 3-hydroxypipecolic acids, see: (a) Greck, C.; Ferreira, F.; Genêt, J. P. *Tetrahedron Lett*. **1996**, *37*, 2031–2034. (b) Agami, C.; Couty, F.; Mathieu, H. *Tetrahedron Lett*. **1996**, *37*, 4001–4002. (c) Battistini, L.; Zanardi, F.; Rassu, G.; Spanu, P.; Pelosi, G.; Fava, G. G.; Ferrari, M. B.; Casiraghi, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2975–2987. (d) Jourdant, A.; Zhu, J. *Tetrahedron Lett*. **2000**, *41*, 7033–7036. (e) Bodas, M. S.; Kumar, P. *Tetrahedron Lett*. **2004**, *45*, 8461–8463. (f) Kumar, P.; Bodas, M. S. *J. Org. Chem*. **2005**, *70*, 360–363. (g) Liang, N.; Datta, A. *J. Org. Chem*. **2005**, *70*, 10182–10185. (h) Kim, I. S.; Oh, J. S.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2007**, *63*, 2622–2633. (i) Liu, L.-X.; Peng, Q.-L.; Huang, P.-Q. *Tetrahedron: Asymmetry* **2008**, *19*, 1200–1203. (j) Ohara, C.; Takahashi, R.; Miyagawa, T.; Yoshimura, Y.; Kato, A.; Adachi, I.; Takahata, H. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 1810–1813. (k) Yoshimura, Y.; Ohara, C.; Imahori, T.; Saito, Y.; Kato, A.; Miyauchi, S.; Adachi, I.; Takahata, H. *Bioorg. Med. Chem*. **2008**, *16*, 8273–8286.

(16) (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem*. **1987**, *52*, 2559–2562. (b) Sheldon, R. A.; Arends, I. W. C. E.; Brink, G.-J. t.; Dijksman, A. *Acc. Chem. Res*. **2002**, *35*, 774–781. (c) Chiou, W.-H.; Schoenfelder, A.; Sun, L.; Mann, A.; Ojima, I. *J. Org. Chem*. **2007**, *72*, 9418–9425.

Experimental Section

2-*tert*-Butyloxycarbonylamino-3-benzyloxypent-4-en-1-ol (4). To a THF solution (40 mL) of Garner's aldehyde **1** (1.053 g, 4.59 mmol, 1.00 equiv) under nitrogen at −30 °C was added dropwise a vinyl magnesium bromide THF solution (0.7 M, 13.1 mL, 9.17 mmol, 2.0 equiv) via a syringe over 30 min. The reaction mixture was allowed to warm to 0 °C and then stirred in an ice bath overnight (∼17 h). The reaction was monitored by TLC analysis. Upon completion of the reaction, the reaction mixture was poured into a chilled aqueous NH_4Cl solution (20 mL). After separation of the organic layer, the aqueous layer was extracted with ethyl acetate (50 mL × 4). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and then concentrated under reduced pressure to give a crude product. The crude product was purified by flash chromatography on silica gel using ethyl acetate/*n*-hexane (R_f = 0.37, ethyl acetate/*n*-hexane = 1/3) as the eluant to give product **2** as a colorless oil (1.026 g, 87%): GC−MS condition: Set the initial temperature 50 °C and heating rate as 25 °C per minute to 200 °C and then changed the rate to 10 °C per minute until the temperature was up to 280 °C and kept the temperature at 280 °C for 2 min, t_R: 8.82 min GC−MS *m*/*z* (relative intensity, ion): 242 (< 1, M^+ − Me), 200 (30, oxazolidinyl), 57 (100, *t*-Bu).

To a THF solution (60 mL) of alcohol **2** (2.753 g, 10.7 mmol, 1.00 equiv) in an ice bath under nitrogen was added dropwise sodium hydride (60%, 769 mg, 19.2 mmol, 1.8 equiv). After the solution was stirred in an ice bath for 30 min, benzyl bromide (1.9 mL, 15.9 mmol, 1.5 equiv) was added by a syringe, followed by addition of 18-crown-6 ether (1.410 g, 5.3 mmol, 0.5 equiv). The reaction mixture was allowed to warm to room temperature and then stirred for 5 h. The reaction was monitored by TLC analysis. Upon completion of the reaction, the reaction mixture was poured into a chilled aqueous NH_4Cl solution (100 mL). After separation of the organic layer, the aqueous layer was extracted with ethyl acetate (100 mL× 4). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and then concentrated under reduced pressure to give a crude residue. The crude product was purified by flash chromatography on silica gel using ethyl acetate/n-hexane (R_f = 0.71, ethyl acetate/*n*-hexane = 1/3) as the eluant to give product **3** as a colorless oil (3.271 g, 88%).

To a MeOH solution (15 mL) of oxazolidine **3** (400 mg, 1.15 mmol, 1.00 equiv) in an ice bath under nitrogen was added PTSA (27 mg, 0.14 mmol, 13 mol %). The reaction mixture was stirred at room temperature for 8 h and monitored by TLC analysis. Upon completion of the reaction, the reaction mixture was concentrated under reduced pressure to give a crude syrup. The crude product was purified by flash chromatography on silica gel using ethyl acetate/*n*-hexane (1/12) as the eluant to give major product **4a** (238 mg, 67%, R_f = 0.48, ethyl acetate/*n*-hexane = 1/3 × 3) and minor product **4b** (54 mg, 15%, R_f = 0.41, ethyl acetate/*n*-hexane = 1/3 × 3). HPLC condition: Supelcosil LC-SI, 250 mm × 4.6 mm, 5 μm; 1 vol % IPA in hexane/hexane = 1/1; flow rate 1.5 mL per min; detection UV 210 nm; t_R: 41 min for **4a**; t_R: 54 min for **4b** (**4a**:**4b** = 4.0:1).

(2*S*,3*R*)-4 (4a): white solid; mp 58−59 °C; $[\alpha]^{23}_D$ −66.6 (*c* 2.06, $CHCl_3$) [lit.[17] $[\alpha]^{25}_D$ −51.8 (*c* 0.953, $CHCl_3$)]; ^{1}H NMR (600 MHz, 25 °C, $CDCl_3$, δ) 1.40 (s, 9H, −C(CH_3)$_3$), 2.62 (brs, −OH), 3.58−3.66 (m, 2H, H-1 and H-2), 3.90−3.93 (m, 1H, H-1), 4.03−4.08 (m, 1H, H-3); 4.30 (d, *J* = 12.0 Hz, 1H, −OCH_2Ph), 4.61 (d, *J* = 12.0 Hz, 1H, −OCH_2Ph), 5.27 (d, *J* = 7.2 Hz, 1H, −N*H*Boc), 5.33−5.38 (m, 2H, H-5), 5.65 (ddd, *J* = 7.8, 10.8, 18.0 Hz, 1H, H-4), 7.25−7.33 (m, 5H, −Ph); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ) 28.3 (q, −C(CH_3)$_3$), 54.4 (d, C-2), 61.9 (t, C-1), 71.0 (t, −OCH_2Ph), 79.4 (s, −OC(CH_3)$_3$),

(17) Srivastava, A. K.; Panda, G. *Chem.—Eur. J*. **2008**, *14*, 4675–4688.

81.9 (d, C-3), 119.2 (t, C-5), 127.7 (d, *o*-Ph), 127.8 (d, *p*-Ph), 128.4 (d, *m*-Ph), 135.0 (d, C-4), 137.6 (s, *ipso*-Ph), 155.9 (s, O-*C*O-N); HRMS-FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{25}NO_4 \cdot H^+$ 308.1862, found 308.1852 (Δ = 3.3 ppm).

(2*S*,3*R*)-1-*tert*-Butyloxycarbonyl-2-hydroxymethyl-3-benzyloxypiperidine (7a). $Rh(acac)(CO)_2$ (1.1 mg, 4.2 μmol, 0.5 mol %) and BIPHEPHOS (6.4 mg, 8.1 μmol, 1.0 mol %) were dissolved in MeOH (2 mL) under nitrogen. The resulting catalyst solution was degassed by a freeze−thaw procedure at least three times. Olefin **4a** (250 mg, 0.813 mmol, 1.00 equiv) was placed in a 50 mL flask. The catalyst solution was transferred to the reaction flask containing the substrate by a pipet, and then the total volume was adjusted to 16 mL with MeOH. The reaction flask was placed in a 300 mL stainless steel autoclave and then was pressurized with CO (2 atm) followed by H_2 (2 atm). The reaction mixture was stirred at 60 °C for 16−20 h. Upon completion of the reaction, the gas was carefully released in a good ventilated hood. The reaction mixture was concentrated under reduced pressure to give a crude product, and then diluted with CH_2Cl_2 (15 mL). To the CH_2Cl_2 solution was added dropwise triethylsilane (Et_3SiH, 390 μL, 2.44 mmol, 3.0 equiv) followed by boron trifluoride etherate ($BF_3 \cdot OEt_2$, 309 μL, 2.44 mmol, 3.0 equiv). The reaction mixture was allowed to be stirred at −78 °C overnight (~16 h). The reaction was monitored by TLC analysis. Upon completion of the reaction, a saturated $NaHCO_3$ solution (5 mL) was slowly added into the reaction mixture so that the temperature was kept below −60 °C and then warmed to room temperature. After separation of the organic layer, the aqueous layer was extracted with ethyl acetate (10 mL × 4). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and then concentrated under reduced pressure to give a crude residue. The crude product was purified by flash chromatography on silica gel using ethyl acetate/*n*-hexane (R_f = 0.49, ethyl acetate/*n*-hexane = 1/3 × 3) as the eluant to give product **7a** as a colorless oil (239 mg, 91%): $[\alpha]^{23}_D$ +39.5 (*c*: 1.73, $CHCl_3$) [lit.[12] $[\alpha]^{20}_D$ −40.1 (*c* 0.9, $CHCl_3$)]; ^{1}H NMR (600 MHz, 25 °C, $CDCl_3$, δ) 1.36−1.40 (m, 1H, H-5α), 1.44 (s, 9H, $-C(CH_3)_3$), 1.54−1.60 (m, 1H, H-4α), 1.83−1.93 (m, 2H, H-4β and H-5β), 2.33 (brs, 1H, −OH), 2.86 (t, *J* = 12.6 Hz, 1H, H-6α), 3.56 (d, *J* = 2.4 Hz, 1H, H-3), 3.61 (dd, *J* = 6.0, 10.8 Hz, 1H, H-7), 3.74 (dd, *J* = 8.4, 10.8 Hz, 1H, H-7), 3.96 (brs, 1H, H-6β), 4.48 (d, *J* = 12.0 Hz, 1H, $-OCH_2$-Ph), 4.50 (t, *J* = 6.0 Hz, 1H, H-2), 4.61 (d, *J* = 11.4 Hz, 1H, $-OCH_2$Ph), 7.23−7.33 (m, 5H, −Ph); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ) 19.5 (t, C-5), 25.1 (t, C-4), 28.3 (q, $-C(\underline{C}H_3)_3$), 39.6 (t, C-6), 55.5 (d, C-2), 60.5 (t, C-7), 70.0 (t, $-OCH_2\underline{Ph}$), 71.5 (d, C-3), 79.8 (s, $-O\underline{C}(CH_3)_3$), 127.3 (d, *p*-Ph), 127.4 (d, *o*-Ph), 128.2 (d, *m*-Ph), 138.6 (s, *ipso*-Ph), 156.3 (s, O-*C*O-N); HRMS-FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{18}H_{27}NO_4 \cdot H^+$ 322.2018, found 322.2007 (Δ = 3.4 ppm).

(2*R*,3*R*)-1-*tert*-Butyloxycarbonyl-2-methoxycarbonyl-3-benzyloxypiperidine (10a). To a solution of alcohol **7a** (337 mg, 1.05 mmol, 1.00 equiv) in acetone (8 mL) in an ice bathwere added an aqueous $NaHCO_3$ solution (5%, 8 mL), KBr (60 mg, 0.5 mmol, 0.5 equiv), and tetramethylpiperidine nitroxyl free radical (TEMPO, 30 mg, 0.20 mmol, 0.20 equiv). Then, a commercial bleach solution (4.5 mL, 1.0 M by titration, 4.5 mmol, 3.2 equiv) was added dropwise via a syringe over 5 min. The solution became white cloudy. After the solution was stirred for 1 h in an ice bath, additional $NaHCO_3$ (5%, 8 mL) and additional bleach (4.5 mL, 1.0 M, 4.5 mmol, 3.2 equiv) were added. The reaction mixture was stirred in an ice bath for another 1 h. Concentration of the reaction mixture under reduced pressure to remove volatile substances gave a clean aqueous solution. The aqueous solution was washed with ether (10 mL) and covered with ethyl acetate (20 mL). The solution with two phases was acidified with an aqueous $KHSO_4$ solution (2 M) in an ice bath until pH became 2−3. A white precipitate was observed during acidification. After separation of the organic layer, the resulting aqueous layer was extracted with ethyl acetate (30 mL × 4). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and then concentrated to give crude acid **9a**. To the solution of crude acid **9a** in MeOH (~0.1 M) was added an ether solution of diazomethane slowly until a yellow color persisted. Concentration under reduced pressure gave a yellow crude syrup. The crude product was purified by flash chromatography on silica gel using ethyl acetate/*n*-hexane (R_f = 0.38, ethyl acetate/*n*-hexane = 1/3) as the eluant to give product **10a** as a colorless oil (330 mg, 90% yield over two steps): $[\alpha]^{25}_D$ +2.1 (*c* 0.92, $CHCl_3$); ^{1}H NMR (600 MHz, 50 °C, $CDCl_3$, δ) 1.34−1.52 (m, 2H, H-4 and H-5), 1.45 (s, 9H, $-C(CH_3)_3$), 1.87−1.96 (m, 2H, H-4 and H-5), 3.00 (brs, 1H, H-6), 3.73 (s, 3H, $-CO_2CH_3$), 4.02 (brs, 1H, H-6), 4.05 (brs, 1H, H-3), 4.51 (d, *J* = 12.0 Hz, 1H, $-OCH_2$Ph), 4.64 (d, *J* = 12.0 Hz, 1H, $-OCH_2$Ph), 5.15 (brs, 1H, H-2), 7.24−7.36 (m, 5H, −Ph); ^{13}C NMR (150 MHz, 50 °C, $CDCl_3$, δ) 18.7 (t, C-5), 26.1 (t, C-4), 28.3 (q, $-C(CH_3)_3$), 41.5 (t, C-6), 52.0 (q, $-CO_2CH_3$), 57.0 (d, C-2), 70.6 (t, $-OCH_2$Ph), 72.4 (d, C-3), 80.1 (s, $-OC(CH_3)_3$), 127.4 (d, *o*-Ph and *p*-Ph), 128.3 (d, *m*-Ph), 138.3 (s, *ipso*-Ph), 155.9 (s, O-*C*O-N), 170.8 (s, C-7); EI-HRMS (*m*/*z*) $[M]^+$ calcd for $C_{19}H_{27}NO_5^+$ 349.1889, found 349.1892 (Δ = 0.9 ppm).

(2*R*,3*R*)-3-Hydroxypipecolinic acid (12a). A solution of methyl ester **11a** (48 mg, 0.19 mmol, 1.00 equiv) in a hydrochloric acid solution (6 N, 4 mL) was stirred under reflux for 1 h and then concentrated under reduced pressure to give a residue. Reflux of the crude product in EtOH (3 mL) and propylene oxide (0.35 mL) gave a brown precipitate. Filtration followed by washing with cold ether afforded the titled product as a light brown solid (27 mg, 0.18 mmol, 95%): mp 241 °C dec [lit.[15c] mp 234−239 °C dec; $[\alpha]^{25}_D$ −15.9 (*c* 2.70, H_2O); lit.[15k] $[\alpha]^{28}_D$ −12.9 (*c* 1.0, H_2O)]; ^{1}H NMR (600 MHz, 25 °C, D_2O, δ) 1.64−1.76 (m, 2H, H-4 and H-5), 1.90−1.96 (m, 1H, H-4), 1.97−2.04 (m, 1H, H-5), 3.09 (ddd, *J* = 3.6, 8.4, 12.0 Hz, 1H, H-6), 3.35 (ddd, *J* = 4.2, 7.2, 12.0 Hz, 1H, H-6), 3.61 (d, *J* = 7.2 Hz, 1H, H-2), 4.14 (ddd, *J* = 3.0, 7.2, 7.2 Hz, 1H, H-3); ^{13}C NMR (150 MHz, 25 °C, D_2O, δ) 18.4 (t, C-5), 28.3 (t, C-4), 42.5 (t, C-6), 62.0 (d, C-2), 66.0 (d, C-3), 172.1 (s, C-7). HRMS-FAB (*m*/*z*) $[M + H]^+$ calcd for $C_6H_{11}NO_3 \cdot H^+$ 146.0817, found 146.0810 (Δ: 4.8 ppm).

Acknowledgment. We thank the National Science Council, Taiwan (NSC96-2113-M-005-003-MY2 and NSC97-2113-M-005-004), and the Instrument Center of National Chung Hsing University for support of this research.

Supporting Information Available: Experimental procedure, characterization data, as well as ^{1}H and ^{13}C NMR spectra for all compounds and the crystallographic data of **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.