

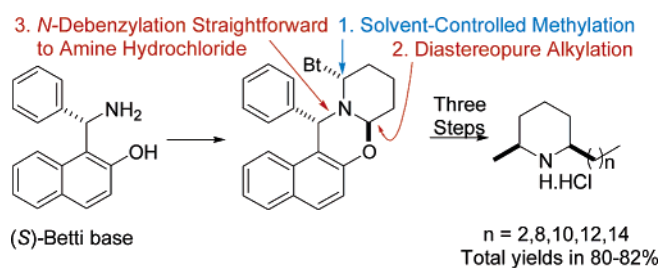
## Nonracemic Betti Base as a New Chiral Auxiliary: Application to Total Syntheses of Enantiopure (2*S*,6*R*)-Dihydropinidine and (2*S*,6*R*)-Isosolenopsins

Xinyan Wang, Yanmei Dong, Jianwei Sun, Xuenong Xu, Rui Li, and Yuefei Hu\*

Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China

yfh@mail.tsinghua.edu.cn

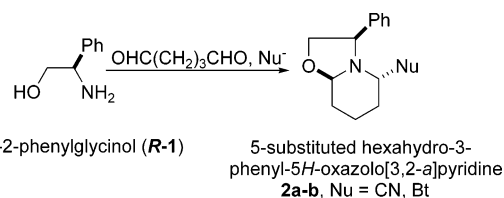
Received November 3, 2004



Total syntheses of enantiopure alkaloidal natural products (2*S*,6*R*)-dihydropinidine (as hydrochloride) and (2*S*,6*R*)-isosolenopsins (as hydrochlorides) were achieved in four steps and in 80–82% total yields by using a synthetic strategy of the formation–cleavage of 1,3-oxazinane. (*S*)-Betti base was proved to be an excellent chiral auxiliary and a novel Pd/C catalyzed *N*-debenzylation straightforward to amine hydrochloride was developed in the presence of  $\text{CH}_2\text{Cl}_2$ .

Since chiral 2,6-dialkylpiperidines exhibit notable biological activities<sup>1</sup> and have a representative structure that occurs in a number of biologically important complex alkaloidal natural products,<sup>2</sup> their synthesis has attracted considerable attention and served as a good vehicle for the testing of synthetic methodology.<sup>2–5</sup> Prominent among these synthetic methods are those that use 5-substituted hexahydro-3-phenyl-5*H*-oxazolo[3,2-*a*]pyridine (**2**) as a precursor, which was derived from chiral auxiliary 2-phenylglycinol (**1**).<sup>2b,4,5</sup> They owe their success mainly to a well-established synthetic strategy involved in the formation–cleavage of oxazolidine. As illustrated in Scheme 1, the strategy includes two key steps: construction of precursor **2** by a condensation of *R*(–)-2-

### SCHEME 1



phenylglycinol [(*R*)-**1**] and 1,5-pentandial in the presence of a nucleophilic moiety, followed by alkylations at two newly created chiral carbons (C5 and C9) separately. However, a major drawback to this otherwise efficient synthetic approach has been dissatisfactory diastereoselectivity in both key steps.<sup>2b,4,5</sup>

Since a result<sup>6</sup> obtained from four structurally similar amino-hydroxy auxiliaries revealed that their stereoselectivities can be improved significantly by increasing steric hindrance at the carbon atom connected by the hydroxyl group, it is believed that the drawbacks that occurred in the formation–cleavage of oxazolidine arose more from the structural nature of 2-phenylglycinol (**1**) than from the synthetic strategy. Therefore, there is a great need to find a better alternative chiral auxiliary to enhance the stereoselectivity of this synthetic strategy. Herein, we introduce nonracemic Betti base (**3**) as a new chiral auxiliary and a novel *N*-debenzylation straightforward to amine hydrochloride for the stereoselective syntheses of 2,6-dialkylpiperidines. As typical application examples (Chart 1), the total syntheses of enantiopure alkaloidal natural products (2*S*,6*R*)-dihydropinidine (**7a**, as hydrochloride) and (2*S*,6*R*)-isosolenopsins (**7b–e**, as hydrochlorides) were achieved under extremely mild conditions in high total yields (80–82%).

Betti base [**3**, 1-(aminophenylmethyl)-2-naphthol] structurally is a 1,3-amino-hydroxy compound and its hydroxy group links to bulky naphthalene (Scheme 2). Its nonracemic derivatives have been employed as chiral ligands in metal ion catalyzed asymmetric reactions for a long

(3) For selected reports, see: (a) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399–5400. (b) Chenevert, R.; Dickman, M. J. *Org. Chem.* **1996**, *61*, 3332–3341. (c) Reding, M. T.; Buchwald, S. L. *J. Org. Chem.* **1998**, *63*, 6344–6347. (d) Ciblat, S.; Besse, P.; Papastergiou, V.; Veschambre, H.; Canet, J.-L.; Troin, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 2221–2229. (e) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155–158. (f) Kumareswaran, R.; Hassner, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2269–2276. (g) Itoh, T.; Yamazaki, N.; Kibayashi, C. *Org. Lett.* **2002**, *4*, 2469–2472. (h) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919–1928. (i) Shu, C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 2878–2879. (j) Singh, O. V.; Han, H. *Org. Lett.* **2004**, *6*, 3067–3070. (k) Yamauchi, S.; Mori, S.; Hirai, Y.; Kinoshita, Y. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 676–684. (l) Kranke, B.; Hebrault, D.; Schultzkukula, M.; Kunz, H. *Synlett* **2004**, 671–674.

(4) (a) Guerrier, L.; Rorer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754–7755. (b) Grierson, D. S.; Royer, J.; Guerrier, L.; Husson, H.-P. *J. Org. Chem.* **1986**, *51*, 4475–4477. (c) Royer, J.; Husson, H.-P. *J. Org. Chem.* **1985**, *50*, 670–673. (d) Poerwono, H.; Higashiyama, K.; Yamauchi, T.; Kubo, H.; Ohmiya, S.; Takahashi, H. *Tetrahedron* **1998**, *54*, 13955–13970. (e) Agami, C.; Couty, F.; Mathieu, H. *Tetrahedron Lett.* **1998**, *39*, 3505–3508.

(5) Kartritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699–6703.

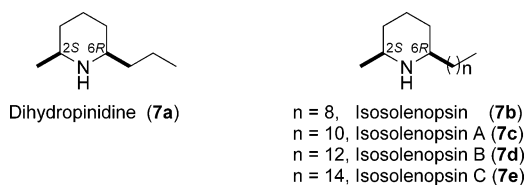
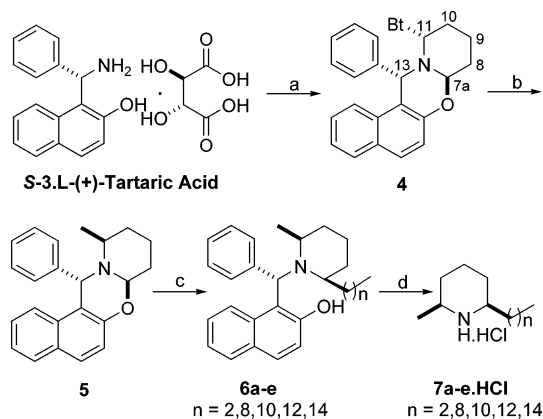
(6) Yamazaki, N.; Ito, T.; Kibayashi, C. *Tetrahedron Lett.* **1999**, *40*, 739–742.

\* Address correspondence to this author. Phone: +86-10-62795380. Fax: +86-10-62771149.

(1) For selected reports, see: (a) Blum, M. S.; Walker, J. R.; Callahan, P. S.; Novak, A. F. *Science* **1958**, *128*, 306–307. (b) Yi, G. B.; McClendon, D.; Desai, D.; Goddard, J.; Lister, A.; Moffitt, J.; Vander Meer, R. K.; deShazo, R.; Lee, K. S.; Rockhold, R. W. *Int. J. Toxicol.* **2003**, *22*, 81–86.

(2) For selected reviews, see: (a) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633–640. (b) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383–394. (c) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813. (d) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873. (e) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520–542.

## CHART 1

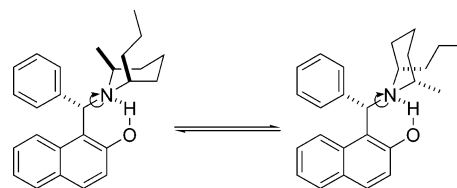
SCHEME 2<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) OHC(CH<sub>2</sub>)<sub>3</sub>CHO, BtH, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, pH 8–9, 20 min, 92%; (b) MeMgCl, THF, 0 °C, 2 h, 96%; (c) RMgBr, Et<sub>2</sub>O, –10 °C, 10 min; (d) 10% Pd/C, H<sub>2</sub>, MeOH–CH<sub>2</sub>Cl<sub>2</sub>, rt, 48 h, 90–93% for two steps.

time.<sup>7,8</sup> Surprisingly, it has never been employed as a chiral auxiliary in asymmetric synthesis. In our recent work,<sup>8d,e</sup> diastereopure (*7aR*,*11R*,*13S*)-11-(1*H*-benzotriazol-1-yl)-7*a*,8,10,11-tetrahydro-13-phenyl-9*H*,13*H*-naphtho[1,2-*e*]pyrido[2,1-*b*][1,3]oxazine (**4**) was prepared in high yield from (*S*)-Betti base [(*S*)-**3**], by which diastereopure alkylations at C7*a* and C11 in isolated cases were achieved. These results strongly suggest that a highly stereoselective synthesis of 2,6-dialkylpiperidine could be achieved by using nonracemic Betti base (**3**) as a chiral auxiliary with a similar synthetic strategy of the formation–cleavage of 1,3-oxazinane.

Our four-step route for the total syntheses of enantiopure alkaloidal natural products **7a–e** (as hydrochlorides) is shown in Scheme 2. In an improved procedure, the salt of (*S*)-Betti base [(*S*)-**3**] with L-(+)-tartaric acid [it is a precursor of (*S*)-**3** in the optical resolution] condensed with pentane-1,5-dial and benzotriazole to give a diastereopure product **4** in 92% yield under pH 8–9

## CHART 2



Restricted rotation of 2,6-dialkylpiperidine moiety in **6a**

and 0 °C within 20 min. Comparing with the formation of **2a,b** derived from nonracemic 2-phenylglycinol (**1**),<sup>2b,4,5</sup> the highly diastereoselective and convenient formation of **4** could possibly benefit from the bulky size of naphthalene and high reactivity of the hydroxy group in the naphthol moiety of Betti base (**3**). Then key precursor **5** was obtained as a single diastereomeric product in 96% yield simply by stirring the mixture of **4** and MeMgCl in THF at 0 °C for 2 h. We surprisingly observed that no alkylation occurred at C7*a* when **5** was treated with *n*-PrMgBr in THF, even at refluxing temperature overnight. However, when the same reaction proceeded in diethyl ether at –10 °C for 10 min, desired product **6a** was obtained in 96% yield. The control experiments revealed that the alkylations at C11 in **4** and C7*a* in **5** with Grignard reagents, in fact, are well solvent-controlled regioselective alkylations. Thus, no dimethylation could occur in the reaction of **4** with MeMgCl in THF at a wide range of temperatures.

Following the procedure for the preparation of **6a**, **6b–e** were produced smoothly by alkylation of **5** with the corresponding Grignard reagents (RMgBr, R = –C<sub>9</sub>H<sub>19</sub>, –C<sub>11</sub>H<sub>23</sub>, –C<sub>13</sub>H<sub>27</sub>, –C<sub>15</sub>H<sub>31</sub>), respectively. However, the structural assignments of **6a–e** suffered seriously from their ambiguous <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra. These results arose from the unusual coalescence phenomenon that occurred at room temperature led by restricted rotation of the 2,6-dialkylpiperidine moiety, because a six-membered intramolecular hydrogen bond between the nitrogen atom and the hydroxy group formed in each molecule. For example, the hydrogen bond in **6a** (Chart 2) was so strong that its –OH signal appeared at  $\delta$  12.00 ppm in <sup>1</sup>H NMR spectrum and several signals continued to be very broad weak peaks up to 60 °C in <sup>1</sup>H NMR and <sup>13</sup>C NMR measurements in CDCl<sub>3</sub>. Fortunately, the conversions of **5** into **6a–e** were almost quantitative yields and can be clearly monitored by IR and TLC. In practice, crude **6a–e** were used in the next step without further purification and characterization.

In published literature, a number of methods have been developed for *N*-debenzylation of benzylamines. The most prominent among them was Pd/C-catalyzed hydrogenolysis featured for its convenience, high yield, and clean product.<sup>9</sup> By a routine procedure, **6a** was *N*-debenzylated smoothly over Pd/C catalyst in MeOH at room temperature and atmospheric pressure for 18 h. After purification by column chromatography, desired (2*S*,6*R*)-dihydropipinidine (**7a**) was obtained in 25% yield. However, **7a**·HCl as white crystals was obtained in 79% yield by treatment of the crude product with Et<sub>2</sub>O

(7) (a) Cardellicchio, C.; Ciccarella, G.; Naso, F.; Schingaro, E.; Scordari, F. *Tetrahedron: Asymmetry* **1998**, *9*, 3667–3675. (b) Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 14685–14692. (c) Bernardinelli, G.; Fernandez, D.; Gosmini, R.; Meier, P.; Ripa, A.; Schupfer, P.; Treptow, B.; Kundig, E. P. *Chirality* **2000**, *12*, 529–539. (d) Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 3361–3373. (e) Liu, D.-X.; Zhang, L.-C.; Wang, Q.; Da, C.-S.; Xin, Z.-Q.; Wang, R.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2001**, *3*, 2733–2735. (f) Cimarelli, C.; Mazzanti, A.; Palmieri, G.; Volpini, E. *J. Org. Chem.* **2001**, *66*, 4759–4765. (g) Wang, Y.; Li, X.; Ding, K. *Tetrahedron: Asymmetry* **2002**, *13*, 1291–1297. (h) Ji, J.; Qiu, L.; Yip, C. W.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 1589–1590.

(8) (a) Lu, J.; Xu, X.; Wang, C.; He, J.; Hu, Y.; Hu, H. *Tetrahedron Lett.* **2002**, *43*, 8367–8369. (b) Lu, J.; Xu, X.; Wang, S.; Wang, C.; Hu, Y.; Hu, H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2900–2903. (c) Dong, Y.; Sun, J.; Wang, X.; Xu, X.; Cao, L.; Hu, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 1667–1672. (d) Xu, X.; Lu, J.; Li, R.; Ge, Z.; Dong, Y.; Hu, Y. *Synlett* **2004**, 122–124. (e) Xu, X.; Lu, J.; Dong, Y.; Li, R.; Ge, Z.; Hu, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 475–479.

(9) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999. (b) Hartung, W. H.; Simonoff, R. *Org. React.* **1953**, *7*, 263–326.

TABLE 1. *N*-Debenzylation by Pd/C-Catalyzed Hydrogenolysis in CH<sub>2</sub>Cl<sub>2</sub>-MeOH

Entry	Substrate (6)	Product (7.HCl)	Time (h)	Yield (%)	Entry	Substrate (6)	Product (7.HCl)	Time (h)	Yield (%)
a			48	97	f			48	98
b			48	96	g			24	99
c			48	96	h			24	98
d			48	94	i			24	97
e			48	94	j			24	97

saturated with dry HCl after the hydrogenolysis of **6a**. These results clearly revealed that the dissatisfactory yields of **7a** resulted from the currently inefficient workup procedure because **7a** has relatively high volatility. Ideally, straightforward conversion of benzylamine into the corresponding amine hydrochloride during its hydrogenolysis could prevent the loss of volatile amine, but no such procedure has been reported in the literature up to date.

Luckily for us, when CH<sub>2</sub>Cl<sub>2</sub> was used as a cosolvent with the purpose to increase the solubility of **6a** in its *N*-debenzylation, **7a**·HCl was obtained unexpectedly in 97% yield simply by filtrating out the catalyst and evaporating off the solvent after hydrogenolysis of **6a**. The controlled experiments confirmed that the hydrochloride in **7a**·HCl comes from hydrodechlorination of CH<sub>2</sub>Cl<sub>2</sub> during the hydrogenolysis. The published literature has also reported that CH<sub>2</sub>Cl<sub>2</sub> can be hydrodechlorinated by Pd-based catalysts to release hydrochloride, chloromethane, and methane in variable ratios.<sup>10</sup>

To determine the scope of the reaction, different benzylamines were tested. As shown in Table 1, all substrates (**6b**–**j**) were *N*-debenzylated straightforward to the corresponding amine hydrochlorides in excellent yields. **6b**–**e** gave (2*S*,6*R*)-isosolenopsin hydrochlorides (**7b**–**e**·HCl) smoothly in 94–96% yields. Another highly volatile alkaloidal natural product (*R*)-2-pipecoline<sup>11</sup> was also obtained as its hydrochloride (**7f**·HCl) in 98% yield. The method was so efficient that gaseous dimethylamine

was captured as dimethylamine hydrochloride (**7g**·HCl) in almost quantitative yield. However, the secondary benzylamines, such as *N*-ethylbenzylamine, *N*-(*tert*-butyl)benzylamine, and *N*-benzylethanolamine, failed to give the desired products. The advantage of this method is 2-fold. First, the traditional two-step operation, the *N*-debenzylation by Pd/C-catalyzed hydrogenolysis and the conversion of amine into its hydrochloride, is combined into a single easy performance. Second, volatile amine, even gaseous amine, can be obtained in high yield in its *N*-debenzylation. This method may make the widely used *N*-debenzylation by Pd/C-catalyzed hydrogenolysis more efficient in modern organic synthesis.

Since the stereochemistry of alkylations at C7a and C11 in **4** has been found in our previous works<sup>8</sup> and the absolute configurations of dihydropinidines and isosolenopsins have been well established in the literature,<sup>2b,12</sup> therefore, the stereochemistry of **7a**–**e** was easily recognized as *cis*-2*S*,6*R* from their NMR spectra and optical rotation values. We hypothesize that the regioselective alkylation on C11 in **4** may go through an S<sub>N</sub>2 mechanism. Thus the Bt-group was replaced with complete inversion of configuration. However, a planar iminium salt<sup>2b,5</sup> must serve as an intermediate in alkylation on C7a in **5**, by which a new C–C bond was formed with retention of configuration.

(11) (a) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084–7085. (b) Burke, A. J.; Davies, S. G.; Christopher Garner, A.; McCarthy, T. D.; Roberts, P. M.; Smith, A. D.; Rodriguez-Solla, H.; Vickers, R. J. *Org. Biomol. Chem.* **2004**, *2*, 1387–1394.

(12) Leclercq, S.; Thirionet, I.; Broeders, F.; Daloz, D.; Vander Meer, R.; Braekman, J. C. *Tetrahedron* **1994**, *50*, 8465–8478.

(10) (a) Malinowski, A.; Lomot, D.; Karpinski, Z. *Appl. Catal. B* **1998**, *19*, L79–L86. (b) Prati, L.; Rossi, M. *Appl. Catal. B* **1999**, *23*, 135–142.

In summary, total syntheses of enantiopure alkaloidal natural products (2*S*,6*R*)-dihydropipinidine (**7a**, as hydrochloride) and (2*S*,6*R*)-isosolenopsins (**7b–e**, as hydrochlorides) were achieved with the shortest steps and unprecedented high total yields by using a strategy of the formation–cleavage of 1,3-oxazinane. (*S*)-Betti base [(*S*)-**3**] was proved to be an excellent chiral auxiliary and its naphthol moiety played an important role in diastereoselectivity and reactivity. Thus, (*S*)-**3** condensed with pentane-1,5-dial and benzotriazole to diastereopurely yield **4** in 92% yield. By using THF as solvent, a solvent-controlled monoalkylation of **4** was achieved to give diastereopure **5** in 96% yield. Then **5** was alkylated with the corresponding Grignard reagent followed by a novel *N*-debenzylation straightforward to amine hydrochloride by Pd/C-catalyzed hydrogenolysis in the presence of CH<sub>2</sub>Cl<sub>2</sub> to yield target products **7a–e** in 90–93% yields (two steps), respectively.

## Experimental Section

(**7aR**,11*R*,13*S*)-11-(1*H*-Benzotriazol-1-yl)-**7a**,**8**,**10**,**11**-tetrahydro-13-phenyl-**9H**,13*H*-naphtho[1,2-*e*]pyridol[2,1-*b*][1,3]-oxazine (**4**). To a stirred solution of (*S*)-**3** (as a salt of L-(+)-tartaric acid, 11.97 g, 30 mmol) and benzotriazole (4.29 g, 36 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (120 mL) was added dropwise pentane-1,5-dial (25% aqueous solution, 14.40 g, 36 mmol) at 0 °C under nitrogen. Then K<sub>2</sub>CO<sub>3</sub> powder was added to adjust the pH to 8–9. Twenty minutes later (monitored by TLC), an aqueous solution of NaOH (1.0 M, 60 mL) was added and stirring was continued for another 15 min. Then resultant mixture was filtered through a pad of Celite. The filtrate was washed with H<sub>2</sub>O and brine and dried over anhydrous Mg<sub>2</sub>SO<sub>4</sub>. After the removal of the solvent, the residue was purified by recrystallization to give the desired product **4** (11.92 g, 92%) as a colorless crystal, mp 180–182 °C (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH), [α]<sub>D</sub><sup>25</sup> +164.8 (c 0.2, CHCl<sub>3</sub>) [lit.<sup>8e</sup> mp 196–197 °C (EtOH), [α]<sub>D</sub><sup>25</sup> +152.6 (c 1.6, CHCl<sub>3</sub>)].

(**7aR**,11*S*,13*S*)-**7a**,**8**,**10**,**11**-Tetrahydro-11-methyl-13-phenyl-**9H**,13*H*-naphtho[1,2-*e*]pyridol[2,1-*b*][1,3]oxazine (**5**). To a cold solution (ice–water bath) of **4** (12.96 g, 30 mmol) in dry THF (200 mL) was added MeMgCl (3.0 M in THF, 24 mL, 72 mmol) dropwise under nitrogen. After the reaction was stirred at 0 °C for 2.0 h (monitored by TLC), a saturated aqueous solution of NH<sub>4</sub>Cl (50 mL) was added to quench the reaction. Then the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with H<sub>2</sub>O and brine and dried over anhydrous Mg<sub>2</sub>SO<sub>4</sub>. After the removal of the solvent, the residue was purified by chromatography (silica gel, EtOAc: PE = 1:15) to give the desired product **5** (9.48 g, 96%) as a colorless crystal, mp 120–122 °C. [α]<sub>D</sub><sup>25</sup> +161.6 (c 0.2, CHCl<sub>3</sub>). IR: ν 2935, 1624, 1515, 1465 cm<sup>-1</sup>. <sup>1</sup>H NMR: δ 7.06–7.72 (m, 11H), 5.19 (s, 1H), 4.95–4.96 (m, 1H), 3.51–3.53 (m, 1H), 1.44–2.01 (m, 6H), 0.95–0.97 (m, 3H). <sup>13</sup>C NMR: δ 154.2, 143.8, 131.5, 129.0 (2C), 128.8, 128.6, 128.5, 128.0 (2C), 126.9, 126.2, 123.1, 122.8, 119.0, 114.2, 81.6, 60.5, 54.4, 32.1, 29.6, 18.4, 14.1. MS *m/z* (%): 329 (M<sup>+</sup>, 0.82), 313 (26), 232 (46), 231 (100), 202 (16). Anal. Calcd for C<sub>23</sub>H<sub>23</sub>NO: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.89; H, 7.11; N, 4.31.

**A Typical Procedure for the Preparation of 1-[(*S*)-[(2*S*,6*R*)-2-Methyl-6-propylpiperidyl]phenylmethyl]-2-naphthalenol (**6a**).** To a stirred solution of *n*-PrMgBr made from Mg (365 mg, 15 mmol) and 1-bromopropane (1.84 g, 15 mmol) in anhydrous Et<sub>2</sub>O (40 mL) was added dropwise a solution of **5** (494 mg, 1.5 mmol) in Et<sub>2</sub>O (15 mL) at –10 °C. Then a saturated aqueous solution of NH<sub>4</sub>Cl (10 mL) was added to quench the reaction and the separated organic layer was washed with H<sub>2</sub>O and brine and dried over anhydrous Mg<sub>2</sub>SO<sub>4</sub>. Removal of the solvent gave the crude product **6a** (538 mg, 96%) as a yellowish foamy solid, mp 102–103 °C; [α]<sub>D</sub><sup>25</sup> +134.8 (c 0.2, CHCl<sub>3</sub>). IR: ν 3447, 2961, 1525, 1447, 1231 cm<sup>-1</sup>; MS *m/z* (%): 372 (M<sup>+</sup> – H, 0.28), 233 (24), 232 (85), 231 (100). Anal. Calcd for C<sub>26</sub>H<sub>31</sub>NO:

C, 83.60; H, 8.37; N, 3.75. Found: C, 83.78; H, 8.17; N, 3.70. By the exact same procedure, compounds **6b–e** were prepared by using other Grignard reagents (RMgBr, R = –C<sub>9</sub>H<sub>19</sub>, –C<sub>11</sub>H<sub>23</sub>, –C<sub>13</sub>H<sub>27</sub>, –C<sub>15</sub>H<sub>31</sub>, respectively), which were used to the next step without further purification.

**A Typical Procedure for the Preparation of (2*S*,6*R*)-2-Methyl-6-propylpiperidine Hydrochloride [**7a**·HCl, (2*S*,6*R*)-Dihydropipinidine Hydrochloride].** A mixture of compound **6a** (560 mg, 1.5 mmol), 10% Pd–C catalyst (160 mg, 0.15 mmol) in MeOH (20 mL), and CH<sub>2</sub>Cl<sub>2</sub> (10 mL) under H<sub>2</sub> was stirred at room temperature and atmospheric pressure until the absorption of hydrogen ceased. After the catalyst was filtered out, the filtrate was evaporated and Et<sub>2</sub>O (20 mL) was added. The desired product **7a**·HCl as white crystals was collected by filtration. Mp 240–242 °C (MeOH); [α]<sub>D</sub><sup>25</sup> –13.2 (c 0.2, EtOH) [lit.<sup>3e</sup> mp 242–243 °C, [α]<sub>D</sub><sup>25</sup> –13.3 (c 1.0, EtOH)]. IR: ν 2955, 2935, 1459, 1380 cm<sup>-1</sup>. <sup>1</sup>H NMR: δ 9.41 (br s, 1H), 9.07 (br s, 1H), 3.15–2.98 (m, 1H), 2.98–2.81 (m, 1H), 2.18–1.43 (m, 10H), 1.43–1.10 (m, 3H), 0.90 (t, *J*<sub>1</sub> = 7.2 Hz, 3H). <sup>13</sup>C NMR: δ 58.4, 54.5, 35.1, 30.7, 27.4, 22.8, 19.4, 18.8, 13.7. Anal. Calcd for C<sub>9</sub>H<sub>19</sub>N·HCl: C, 60.83; H, 11.34; N, 7.88. Found: C, 60.87; H, 11.43; N, 7.76.

(**2*S*,6*R*)-2-Methyl-6-nonylpiperidine Hydrochloride [**7b**·HCl, (2*S*,6*R*)-Isosolenopsin Hydrochloride]. Mp 176–177 °C; [α]<sub>D</sub><sup>25</sup> –12.5 (c 0.2, CHCl<sub>3</sub>) [lit.<sup>3d</sup> as an enantiomeric isomer, mp 174–175 °C, [α]<sub>D</sub><sup>25</sup> +11.1 (c 0.92, CHCl<sub>3</sub>)]. IR: ν 2924, 2853, 1465, 1380 cm<sup>-1</sup>. <sup>1</sup>H NMR: δ 9.45 (br s, 1H), 9.07 (br s, 1H), 3.13–2.98 (m, 1H), 2.98–2.80 (m, 1H), 2.20–1.50 (m, 10H), 1.50–1.10 (m, 15H), 0.86 (t, *J*<sub>1</sub> = 6.6 Hz, 3H). <sup>13</sup>C NMR: δ 58.6, 54.5, 33.2, 31.8, 30.7, 29.6, 29.5, 29.3, 29.2, 27.4, 25.7, 22.9, 22.6, 19.4, 14.0. Anal. Calcd for C<sub>15</sub>H<sub>31</sub>N·HCl: C, 68.80; H, 12.32; N, 5.35. Found: C, 68.96; H, 12.46; N, 5.42.**

(**2*S*,6*R*)-2-Methyl-6-decanylpiperidine Hydrochloride [**7c**·HCl, (2*S*,6*R*)-Isosolenopsin A Hydrochloride]. Mp 147–148 °C; [α]<sub>D</sub><sup>25</sup> –9.9 (c 0.2, CHCl<sub>3</sub>) [lit.<sup>12</sup> [α]<sub>D</sub><sup>20</sup> –10.3 (c 1.3, CHCl<sub>3</sub>)]. IR: ν 2921, 2852, 1383 cm<sup>-1</sup>. <sup>1</sup>H NMR: δ 9.43 (br s, 1H), 9.06 (br s, 1H), 3.13–2.96 (m, 1H), 2.96–2.80 (m, 1H), 2.20–1.48 (m, 10H), 1.48–1.10 (m, 19H), 0.86 (t, *J*<sub>1</sub> = 6.5 Hz, 3H). <sup>13</sup>C NMR: δ 58.6, 54.5, 33.2, 31.8, 30.7, 29.6 (3C), 29.5, 29.3, 29.2, 27.4, 25.6, 22.8, 22.6, 19.4, 14.1. Anal. Calcd for C<sub>17</sub>H<sub>35</sub>N·HCl: C, 70.43; H, 12.52; N, 4.83. Found: C, 70.44; H, 12.46; N, 4.80.**

(**2*S*,6*R*)-2-Methyl-6-tridecanylpiperidine Hydrochloride [**7d**·HCl, (2*S*,6*R*)-Isosolenopsin B Hydrochloride]. Mp 140–142 °C; [α]<sub>D</sub><sup>25</sup> –9.4 (c 0.2, CHCl<sub>3</sub>) [lit.<sup>3d</sup> as an enantiomeric isomer, mp 145–146 °C, [α]<sub>D</sub><sup>25</sup> +8.5 (c 1.0, CHCl<sub>3</sub>)]. IR: ν 2919, 2851, 1591, 1465, 1385 cm<sup>-1</sup>. <sup>1</sup>H NMR: δ 9.43 (br s, 1H), 9.07 (br s, 1H), 3.13–2.97 (m, 1H), 2.97–2.80 (m, 1H), 2.20–1.49 (m, 10H), 1.49–1.10 (m, 23H), 0.86 (t, *J*<sub>1</sub> = 6.6 Hz, 3H). <sup>13</sup>C NMR: δ 58.6, 54.5, 33.2, 31.9, 30.7, 29.6, 29.5, 29.3, 29.2, 27.4, 25.7, 22.9, 22.6, 19.4, 14.0. Calcd for C<sub>19</sub>H<sub>39</sub>N·HCl: C, 71.77; H, 12.68; N, 4.40. Found: C, 71.60; H, 12.48; N, 4.41.**

(**2*S*,6*R*)-2-Methyl-6-pentadecanylpiperidine Hydrochloride [**7e**·HCl, (2*S*,6*R*)-Isosolenopsin C Hydrochloride]. Mp 137–139 °C; [α]<sub>D</sub><sup>25</sup> –8.0 (c 0.2, CHCl<sub>3</sub>) [lit.<sup>3d</sup> as an enantiomeric isomer, mp 140–141 °C, [α]<sub>D</sub><sup>25</sup> +8.2 (c 1.0, CHCl<sub>3</sub>)]. IR: ν 2919, 2850, 1591, 1465, 1441, 1385 cm<sup>-1</sup>. <sup>1</sup>H NMR: δ 9.41 (br s, 1H), 9.05 (br s, 1H), 3.12–2.98 (m, 1H), 2.98–2.80 (m, 1H), 2.20–1.45 (m, 10H), 1.45–1.10 (m, 27H), 0.86 (t, *J*<sub>1</sub> = 6.3 Hz, 3H). <sup>13</sup>C NMR: δ 58.5, 54.4, 33.2, 31.8, 30.6, 29.6 (7C), 29.5, 29.3, 29.2, 27.4, 25.6, 22.8, 22.6, 19.4, 14.0. Calcd for C<sub>21</sub>H<sub>43</sub>N·HCl: C, 72.89; H, 12.82; N, 4.05. Found: C, 72.83; H, 12.66; N, 4.08.**

Products **7f–j**·HCl were prepared by the exact same procedure and have identical physical data as reported in published literature.

**Acknowledgment.** We are grateful to the National Natural Science Foundation of China for financial support.

**Supporting Information Available:** <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of compounds **4**, **5**, and **7a–j**·HCl. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO0480444