JOC*Note*

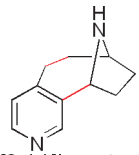
Asymmetric Synthesis of (+)-Pyrido[3,4-*b*]homotropane

Yingxia Sang,[†] Jingrui Zhao,[†,‡] Xueshun Jia,[‡] and Hongbin Zhai[†,§,*]

Laboratory of Modern Synthetic Organic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China, Department of Chemistry, Shanghai University, Shanghai 200436, China, and The State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, 38 College Road, Beijing 100083, China

zhaih@mail.sioc.ac.cn

Received January 30, 2008

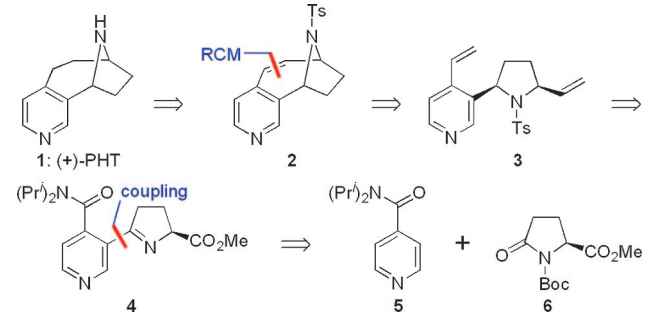


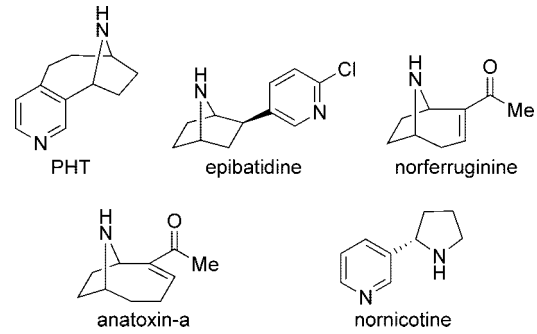
(+)-pyrido[3,4-*b*]homotropane (PHT)

(+)-Pyrido[3,4-*b*]homotropane (PHT) was efficiently constructed in 12 steps from *N*,*N*-diisopropylisonicotinamide. The synthesis features (i) RCM reaction in installing the homotropane skeleton, (ii) Snieckus ortho-lithiation of *N*,*N*-diisopropylisonicotinamide followed by acylation, (iii) Myer reduction of bulky tertiary amide to alcohol with $LiBH_3NH_2$, and (iv) utilization of L-glutamic acid to introduce and establish the requisite stereogenic centers.

As a family of ligand-gated ion channels widely present in the human brain, nicotinic acetylcholine receptors (nAChRs) participate in various biological processes related to numerous central nervous system (CNS) disorders such as Alzheimer's disease, Parkinson's disease, Tourette's syndrome, attention-deficit hyperactivity disorder (ADHD), depression, epilepsy, schizophrenia, and smoking cessation.[1] There have been a number of studies on the ligands selectively targeting and activating nAChRs because of their potential therapeutic utility in the treatment of CNS disorders.[2,3] Pyrido[3,4-*b*]homotropane (PHT) has emerged as an attractive ligand of this type due to its unique structural characteristics and impressive biological and pharmacological profiles.[1a,3]PHT is structurally related to naturally occurring epibatidine and norferruginine and to a variety of conformationally restricted nicotine analogs documented in the literature.[1a,3] Moreover, PHT can also be envisioned conceptually as a hybrid of anatoxin-a and nornicotine.[3c] So far, two groups[1a,3a,b] have communicated the synthesis of PHT. This paper reports a concise asymmetric synthesis of (+)-PHT starting from commercially available materials.

SCHEME 1. Retrosynthetic Analysis of (+)-PHT (1)





The overall retrosynthetic analysis for (+)-PHT (**1**) is outlined in Scheme 1. The target molecule should be accessible from

[†] Shanaghai Institute of Organic Chemistry.
[‡] Shanghai University.
[§] Peking University.

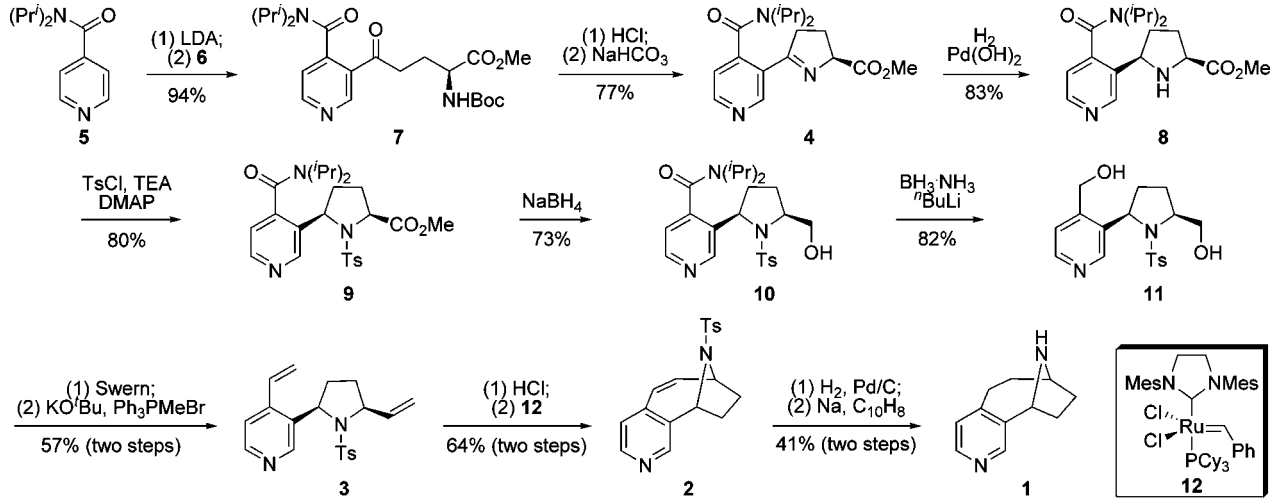
(1) (a) Carroll, F. I.; Hu, X.; Navarro, H. A.; Deschamps, J.; Abdrakhmanova, G. R.; Damaj, M. I.; Martin, B. R. *J. Med. Chem.* **2006**, *49*, 3244. (b) Decker, M. W.; Meyer, M. D.; Sullivan, J. P. *Exp. Opin. Invest. Drugs* **2001**, *10*, 1819. (c) Nordberg, A. *Biol. Psychiat.* **2001**, *49*, 200. (d) Paterson, D.; Nordberg, A. *Prog. Neurobiol.* **2000**, *61*, 75. (e) Clementi, F.; Fornasari, D.; Gotti, C. *Eur. J. Pharmacol.* **2000**, *393*, 3. (f) Decker, M. W.; Aneric, S. P. *Neuronal Nicotinic Recept.* **1999**, 395. (g) McDonald, I. A.; Cosford, N.; Vernier, J.-M. *Annu. Rep. Med. Chem.* **1995**, *30*, 41.

(2) For a recent review, see: (a) Wagner, F. F.; Comins, D. L. *Tetrahedron* **2007**, *63*, 8065. For our previous work, see: (b) Yang, X.; Luo, S.; Fang, F.; Liu, P.; Lu, Y.; He, M.; Zhai, H. *Tetrahedron* **2006**, *62*, 2240. (c) Luo, S; Fang, F.; Zhao, M.; Zhai, H. *Tetrahedron* **2004**, *60*, 5353. (d) Zhai, H.; Liu, P.; Luo, S.; Fang, F.; Zhao, M *Org. Lett.* **2002**, *4*, 4385. For a part of Rapoport's work, see: (e) Lennox, J. R.; Turner, S. C.; Rapoport, H. *J. Org. Chem.* **2001**, *66*, 7078. (f) Turner, S. C.; Zhai, H.; Rapoport, H. *J. Org. Chem.* **2000**, *65*, 861. (g) Xu, Y.-z.; Choi, J.; Calaza, M. I.; Turner, S. C.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069. For representative work from other labs, see: (h) Ondachi, P. W.; Comins, D. L. *Tetrahedron Lett.* **2008**, *49*, 569. (i) Comins, D. L.; Laura, S.; King, L. S.; Smith, E. D.; Fe'vrier, F. C. *Org. Lett.* **2005**, *7*, 5059. (j) Meijler, M. M.; Matsushita, M.; Altobell, L. J.; Wirsching, P.; Janda, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 7164. (k) Sarkar, T. K.; Basak, S.; Slanina, Z.; Chow, T. J. *J. Org. Chem.* **2003**, *68*, 4206. (l) Ullrich, T.; Binder, D.; Pyerin, M. *Tetrahedron Lett.* **2002**, *43*, 177. (m) Kanne, D. B.; Abood, L. G. *J. Med. Chem.* **1988**, *31*, 506. (n) Glassco, W.; Suchocki, J.; George, C.; Martin, B. R.; May, E. L. *J. Med. Chem.* **1993**, *36*, 3381. (o) Chavdarian, C. G.; Seeman, J. I.; Wooten, J. B. *J. Org. Chem.* **1983**, *48*, 492. (p) Wei, Z. L.; Xiao, Y. X.; Yuan, H. B.; Baydyuk, M.; Petukhov, P. A.; Musachio, J. L.; Kellar, K. J.; Kozikowski, A. P. *J. Med. Chem.* **2005**, *48*, 1721. (q) Chellappan, S. K.; Xiao, Y.; Kellar, K. J.; Kozikowski, A. P. 231st National Meeting of the American Chemical Society; Atlanta, GA, 2006; American Chemical Society: Washington, DC, 2006; Abstract MEDI-159.

(3) (a) Kanne, D. B.; Aboodl, L. G. *J. Med. Chem.* **1988**, *31*, 507. (b) Kanne, D. B.; Ashworth, D. J.; Cheng, M. T.; Mutter, L. C. *J. Am. Chem. Soc.* **1986**, *108*, 7864. (c) For PHT analogs, see Gundisch, D.; Kampchen, T.; Schwarz, S.; Seitz, G.; Siegl, J.; Wegge, T. *Bioorg. Med. Chem.* **2002**, *10*, 1.

10.1021/jo8002425 CCC: $40.75 © 2008 American Chemical Society
Published on Web 03/18/2008

SCHEME 2. Synthesis of (+)-PHT (1)



hydrogenation and desulfonylation of sulfonamide **2**, obtained from RCM reaction of diene **3**. The conversion of **4** to **3** would require a series of transformations including imine hydrogenation, secondary amine protection, ester and amide reduction, oxidation, and Wittig olefination. The generation of **4** would involve ortho-deprotonation of amide **5** and the subsequent coupling with lactam **6**, followed by Boc deprotection and intramolecular imine formation.

The current synthesis of (+)-PHT (**1**) commenced from *N*,*N*-diisopropylisonicotinamide[4a,b] (**5**), which was lithiated at C-3 via a Snieckus directed ortho-metalation (DOM)[4c–e] with LDA at −78 °C and then treated with activated lactam **6** (available in three steps from L-glutamic acid[5]) at −78 °C to afford ketone **7** in 94% yield (Scheme 2). Ether proved to be a better solvent than THF for this reaction. Relatively low substrate concentration (see the Experimental Section), slow addition rate, and proper control of the temperature proved to be critical for the success of this reaction. The homo coupling of the amide (i.e., acylation of 3-lithio intermediate with another neutral amide) took place to a greater extent if *N*,*N*-diethylisonicotinamide was used instead of **5**,[6] though the diethylamido group may be better for reduction to the alcohol with $LiBH_3NH_2$.[7]

Removal of the Boc group in **7** at 0 °C with HCl (generated in situ from AcCl and MeOH) furnished an ammonium salt, exposure of which to excess cold saturated aqueous $NaHCO_3$ solution smoothly produced cyclic imine **4** as a viscous oil (77%). Due to its low stability, **4** was used in the next step as soon as possible. *cis*-Pyrrolidine **8** was produced in 83% yield after hydrogenation of **4** with Pearlman's catalyst in anhydrous degassed EtOH under 1 atm of H_2 for 36 h. $Pd(OH)_2$ was added in portions due to its susceptibility to deactivation by the nitrogen atoms present; otherwise, the reaction ceased before completion.

Amine **8** was subsequently tosylated (80%) with TsCl in the presence of Et_3N and DMAP. Ether turned out to be a suitable solvent for this transformation, while only moderate yield was obtained using dichloromethane or acetonitrile used as the solvent. Other groups such as Boc, Cbz, and Bn, once considered for protecting the secondary amine moiety in **8**, proved to be problematic in one way or another. For example, protection with Boc could be achieved in only 12% yield. Standard Cbz protection could be achieved using CbzCl but it did not survive during $LiBH_3NH_2$[7] reduction later. With benzyl-protected amine, treatment with $NaBH_4$ or $LiBH_4$ failed to reduce the ester group while DIBAL-H converted the *N*,*N*-diisopropylamido to the corresponding tertiary amine in addition to the reduction of ester functionality.

Sulfonamide **9** was next converted into diol **11** after a two-stage reduction sequence comprising (i) ester reduction ($NaBH_4$, EtOH, 73%) and (ii) Myer amide reduction (BuLi, $BH_3 \cdot NH_3$, THF, 82%) involving the in situ generated $LiBH_3NH_2$, an efficient reducing species for mild and selective reduction of an amide to a primary alcohol.[7] For the second step, an excess amount of $LiBH_3NH_2$ (8 equiv) was required to ensure a clean and complete reduction. The crude diol **11** was heated with an aqueous KOH solution at 50 °C for 3 h in order to destroy the boron complex. It is noteworthy that reduction of **10** with relatively inexpensive $LiBH_3NMe_2$[8] produced a diisopropylamine rather than **11**.

Swern oxidation[9] of both primary hydroxyl groups in **11** afforded a labile dialdehyde (e.g., racemization might occur), which should be quickly olefinated[10] (Ph_3PMeBr, KO*t*Bu, THF, −78 °C, 57% over two steps). During the purification of diene **3** on a silica gel column, the ether component in the eluting system (petroleum ether/ether, 2:1) was crucial to get rid of the byproduct, $Ph_3P{=}O$ (which happened to have an R_f value very close to that of **3**) by taking advantage of solubility differences. In addition, comparable yields of **3** were obtained for the Wittig reaction when KHMDS or BuLi was used instead of KO*t*Bu.[11]

(4) (a) Swain, A.; Naegele, S. *J. Am. Chem. Soc.* **1957**, *79*, 5250. (b) Shhi, J.; Hiirsor, I. F.; Perron, Y. G. *J. Am. Chem. Soc.* **1959**, *81*, 710. (c) Snieckus, V. *Chem. Res.* **1990**, *90*, 879. (d) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (e) Snieckus, V. *Heterocycles* **1980**, *14*, 1649.

(5) (a) Barrett, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1999**, *64*, 6005. (b) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1998**, *39*, 4789.

(6) (a) Epsztajn, J.; Brzezinski, J. Z.; Czeh, K. *Monatsh. Chem.* **1993**, *124*, 549. (b) Epsztajn, J.; Brzezinski, J. Z.; Jozwiak, A. *J. Chem. Res., Miniprint.* **1986**, *1*, 6401.

(7) Myer, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623.

(8) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 637.

(9) Sudau, A.; Nubbemeyer, U. *Angew. Chem., Int. Ed.* **1998**, *37*, 1140.

(10) Kwon, T. W.; Keusenkothen, P. F.; Smith, M. B. *J. Org. Chem.* **1992**, *57*, 6169.

(11) (a) Aggarwal, V. K.; Astle, C. J.; Mark, R.-E. *Org. Lett.* **2004**, *9*, 1469. (b) Kana, S.; Sugino, E.; Shibuya, S.; Hibino, S. J. *Org. Chem.* **1981**, *46*, 2979. (c) Henegar, K. E.; Ashford, S. W.; Baughman, T. A.; Sih, J. C.; Gu, R. L. *J. Org. Chem.* **1997**, *62*, 6588.

With **3** in hand, installment of the desired bicyclo[4.2.1] system via RCM reaction[12] was vigorously explored. The free base **3** was converted[13a] into its corresponding HCl salt. RCM reaction using Grubbs second-generation catalyst[12] (**12**, 19 mol %) in refluxing toluene/dichloromethane (16:1) furnished pyrido bicycle **2** as a white solid (64% over two steps from **3**). Here, dichloromethane was included in the reaction medium to increase the solubility of the HCl salt. Exposure of the diene free base to catalyst **12** in the presence of $Ti(O^iPr)_4$ gave similar results.[13b] However, replacement of $Ti(O^iPr)_4$ with BEt_3 led to a complex reaction mixture.[14] If **3** (free base) was directly subjected to the metathesis conditions, the product was obtained in only 20–30% yield, while approximately half of the starting material remained unreacted. Presumably, basic groups such as the nitrogen atom of pyridine might coordinate to the ruthenium and thus deactivate the catalyst.[13] Moreover, the RCM reaction was rather sluggish in refluxing dichloromethane (of relatively low boiling point) as a single solvent.

Finally, sulfonamide **2** was hydrogenated (H_2, Pd/C, MeOH) and desulfonylated[15] (Na, naphthalene, THF, −78 °C) to give (+)-PHT (**1**) [$[\alpha]^{28}_D$ +35 (*c* 0.10, $CHCl_3$); lit.[1a] $[\alpha]^{25}_D$ +38.3 (*c* 1.34, $CHCl_3$)] in 41% yield (over two steps from **2**). The ^1H and ^{13}C NMR spectroscopic data were in accordance with those disclosed in the literature.[1a]

In summary, (+)-pyrido[3,4-*b*]homotropane (PHT) was efficiently constructed in 12 steps from *N*,*N*-diisopropylisonicotinamide. Since PHT can be viewed as an annulated nicotine (or more precisely, nornicotine) derivative, the present work constitutes a general and rapid synthetic method to a number of nicotine analogs.

Experimental Section

The synthesis, purification, and analytical data of the intermediates **7**, **4**, **8**, and **9** are described in the Supporting Information. Note that in some cases, extra peaks appeared in the NMR spectra due to the presence of rotamers.

Compound 10. To a solution of **9** (465 mg, 0.954 mmol) in EtOH (80 mL) was added $NaBH_4$ (289 mg, 7.64 mmol) in portions at rt, and the mixture was stirred overnight. Saturated aqueous NH_4Cl solution was added, and the organic solvent was evaporated. After solid KOH (2.14 g, 38.1 mmol) was added at 0 °C, the aqueous mixture was heated at 50 °C for 3 h, cooled to rt, and extracted with CH_2Cl_2/^{i}PrOH (3:1). The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (petroleum ether/EtOAc, 3:1 to 2:3) to afford **10** (321 mg, 73%) as a light yellow foam: $[\alpha]^{28}_D$ +59 (*c* 0.79, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08–1.38 (m, 7H), 1.49–1.73 (m, 6H), 1.78–1.98 (m, 2H), 2.15–2.32 (m, 1H), 2.44 (s, 3H), 3.48–3.73 (m, 2H), 3.75–4.00 (m, 3H), 4.75 (t, J = 7.4 Hz, 0.2H), 4.91 (t, J = 7.1 Hz, 0.8H), 7.05 (d, J = 4.8 Hz, 1H), 7.33 (d, J = 7.8 Hz, 2H), 7.73 (d, J = 7.5 Hz, 1.6H), 7.84 (d, J = 8.1 Hz, 0.4H), 8.51 (d, J = 4.8 Hz, 1H), 8.89, 9.01 (s, 1H) (The OH proton is missing); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.2, 20.7, 20.8, 20.8, 21.4, 27.4, 34.8, 46.0, 51.2, 62.1, 63.0, 64.5, 118.7, 127.5, 129.7, 133.7, 136.4, 142.7, 144.1, 147.6, 149.5, 167.5. MS (ESI) 460 (M + H); HRMS (ESI) calcd for $C_{24}H_{33}N_3O_4S$ + H 460.2270, found 460.2264.

Compound 11. To a suspension of borane−ammonia complex (predried, 464 mg, 15.0 mmol) in anhydrous THF (25 mL) was added dropwise BuLi (2.3 M in hexanes, 6.4 mL, 15 mmol) at 0 °C. The resultant solution was stirred at 0 °C for 5 min and at rt for 5 min and cooled to 0 °C. A solution of **10** (752 mg, 1.64 mmol) in anhydrous THF (20 mL) was added dropwise to the above mixture at 0 °C. The mixture was slowly warmed to rt, stirred overnight, and quenched with saturated aqueous NH_4Cl solution. The organic solvents were evaporated, and solid KOH (3.46 g, 61.7 mmol) was added at 0 °C. The aqueous mixture was heated at 50 °C for 3 h, cooled to rt, and extracted with $CHCl_3$/^{i}PrOH (3:1). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed (petroleum ether/EtOAc, 1:4; EtOAc/MeOH, 200:1) to afford **11** (486 mg, 82%) as a white solid: $[\alpha]^{24}_D$ +88.2 (*c* 0.37, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45–1.63 (m, 1H), 1.67–1.94 (m, 2H), 1.99–2.15 (m, 1H), 2.39 (s, 3H), 3.71–3.92 (m, 3H), 4.69 (d, J = 14.1 Hz, 1H), 4.76–4.93 (m, 2H), 7.28 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 4.8 Hz, 1H), 7.66 (d, J = 7.5 Hz, 2H), 8.30 (d, J = 4.8 Hz, 1H), 8.71 (s, 1H) (The OH protons are missing); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 27.3, 34.0, 60.2, 61.1, 62.9, 64.7, 121.9, 127.7, 129.9, 133.3, 136.4, 144.2, 146.9, 147.6, 147.8. MS (ESI) 363 (M + H); HRMS (ESI) calcd for $C_{18}H_{22}N_2O_4S$ + H 363.1379, found 363.1373.

Compound 3. To a solution of $(COCl)_2$ (0.70 mL, 8.0 mmol) in CH_2Cl_2 (20 mL) was added DMSO (1.2 mL, 17 mmol) dropwise at −78 °C. The mixture was stirred at −78 °C for 15 min, and a solution of **11** (185 mg, 0.510 mmol) in CH_2Cl_2 (8 mL) was added dropwise. Stirring continued for 45 min, and then Et_3N (4.6 mL, 33 mmol) was added. The mixture was stirred at −78 °C for 1 h and then quenched with saturated aqueous $NaHCO_3$ solution, evaporated to remove CH_2Cl_2, and extracted with EtOAc. The combined extracts were dried ($NaSO_4$), filtered, and concentrated to afford a crude dialdehyde, which was used into the next step without purification.

A mixture of KO^{t}Bu (290 mg, 2.58 mmol) and Ph_3PCH_3Br (940 mg, 2.63 mmol) in THF (8 mL) was stirred at −78 °C for 1 h. A solution of the above crude dialdehyde in THF (8 mL) was added dropwise via syringe at −78 °C. The mixture was allowed to warm slowly to rt, stirred overnight, quenched with saturated aqueous $NaHCO_3$ solution, evaporated to remove THF, and extracted with EtOAc. The combined organic extracts were dried ($NaSO_4$), filtered, and concentrated to give a residue, which was chromatographed (petroleum ether/ether, 2:1) to afford diene **3** (103 mg, 57% for two steps) as a white solid: $[\alpha]^{25}_D$ +23.7 (*c* 0.40, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.66–1.92 (m, 3H), 2.02–2.17 (m, 1H), 2.40 (s, 3H), 4.38 (q, J = 6.3 Hz, 1H), 5.13 (dd, J = 7.5, 5.7 Hz, 1H), 5.22 (d, J = 15.6 Hz, 1H), 5.33 (d, J = 17.1 Hz, 1H), 5.54 (d, J = 11.1 Hz, 1H), 5.80 (d, J = 17.1 Hz, 1H), 5.96–6.12 (m, 1H), 6.94 (dd, J = 17.1, 11.1 Hz, 1H), 7.22–7.30 (m, 3H), 7.63 (d, J = 8.1 Hz, 2H), 8.44 (d, J = 5.4 Hz, 1H), 8.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 30.6, 33.7, 59.9, 63.6, 116.5, 119.7, 120.3, 127.6, 129.5, 131.9, 134.3, 135.0, 138.2, 142.5, 143.6, 148.3, 148.7. MS (ESI) 355 (M + H); HRMS (ESI) calcd for $C_{20}H_{22}N_2O_2S$ + H 355.1480, found 355.1475.

Compound 2. To a stirred solution of diene **3** (46 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added dropwise a saturated solution of HCl (g) in Et_2O, and the solvents were evaporated to give the HCl salt of **3**. To a solution of the above HCl salt in anhydrous degassed CH_2Cl_2 (5 mL) and toluene (80 mL) was added **12** (11 mg, 0.013 mmol) at rt. The resultant mixture was heated at reflux under argon. After 10 h, an additional portion of **12** (11 mg, 0.013 mmol) was added, and the mixture was refluxed under argon for another 10 h (at that point the reaction reached completion as examined by TLC analysis), cooled to rt, and quenched with saturated aqueous $NaHCO_3$ solution. The two layers were separated, and the aqueous layer was extracted with EtOAc. The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (petroleum ether/ether, 2:1) to afford **2** (27 mg, 64% over two steps) as a white solid: $[\alpha]^{28}_D$ +32 (*c* 0.16,

(12) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(13) (a) Felpin, F.-X.; Girard, S.; Giang, V.-T.; Robins, R. J.; Villie'ras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305. (b) Yang, Q.; Xiao, W. J.; Yu, Z. *Org. Lett.* **2005**, *7*, 871.

(14) Lutz, C.; Graf, C.-D.; Knochel, P. *Tetrahedron* **1998**, *54*, 10317.

(15) (a) Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548. (b) Trost, B. M.; Marrs, C. M. J. *Am. Chem. Soc.* **1993**, *115*, 6636.

$CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.80–1.93 (m, 1H), 2.06–2.15 (m, 2H), 2.30 (s, 3H), 2.45–2.60 (m, 1H), 4.69–4.78 (m, 1H), 5.10 (dd, J = 9.5, 4.1 Hz, 1H), 6.00 (d, J = 11.8 Hz, 1 H), 6.08 (dd, J = 12.0, 5.1 Hz, 1 H), 6.67 (d, J = 5.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 8.30 (d, J = 4.8 Hz, 1H), 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 8.2 (unidentified impurity), 21.4, 29.6 (grease), 34.6, 39.7, 58.6, 60.2, 60.5, 125.7, 127.2, 128.3, 128.8, 136.5, 136.7, 140.3, 142.7, 147.4, 149.0. MS (ESI) 675 (2 M + Na), 327 (M + H); HRMS (ESI) calcd for $C_{18}H_{18}N_2O_2S$ + H 327.1167, found 327.1162.

Compound (+)-1. A mixture of **2** (23 mg, 0.070 mmol) and 5% Pd/C (3.0 mg) in degassed MeOH (8 mL) was stirred under H_2 (1 atm) at rt for 5 h. The solid mass was filtered off, and the filtrate was concentrated to give a crude hydrogenation product as a pale yellow oil, which was directly used into the next step without further purification: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.72–1.95 (m, 4H), 2.25–2.49 (m, 2H), 2.39 (s, 3H), 2.69 (dt, J = 15.9, 3.6 Hz, 1H), 2.93 (td, J = 16.1, 3.6 Hz, 1 H), 4.47–4.58 (m, 1H), 5.04–5.14 (m, 1H), 6.99 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 7.8 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H), 8.35 (d, J = 4.8 Hz, 1H). 8.38 (s, 1H).

A solution of sodium naphthalenide in anhydrous THF was prepared for subsequent use by adding THF (10 mL) to a mixture of sodium (77 mg, 3.3 mmol) and naphthalene (438 mg, 3.42 mmol) followed by stirring the resultant mixture at rt for 2 h. To a well-stirred solution of the above crude hydrogenation product in THF (10 mL) was added dropwise sodium naphthalenide solution (0.30 mL, 0.10 mmol) at −78 °C. After the mixture was stirred for 1 h, an additional portion of sodium naphthalenide solution (0.30 mL, 0.10 mmol) was added dropwise and stirring continued for 1 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution, stirred for 24 h, and filtered. The solid mass was washed with ether. The combined filtrates were concentrated under reduced pressure to give a residue, which was chromatographed (petroleum ether/EtOAc, 1:1 to 1:2; then EtOAc/MeOH/29% $NH_3 \cdot H_2O$, 10:1:0.1) to give (+)-**1** (5.0 mg, 41% over two steps) as a white solid: $[\alpha]^{28}_D$ +35 (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.59–1.72 (m, 1H), 1.78–1.95 (m, 3H), 2.06–2.32 (m, 2H), 2.24 (br s, 1H, NH), 2.34–2.50 (m, 1H), 2.70 (dt, J = 14.5, 3.8 Hz, 1H), 3.09 (td, J = 14.5, 3.5 Hz, 1H), 3.77–3.86 (m, 1H), 4.36 (dd, J = 10.4, 2.1 Hz, 1H), 7.06 (d, J = 5.1 Hz, 1H), 8.29 (s, 1 H), 8.30 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.8, 31.4, 31.7, 33.6, 58.2, 60.5, 125.5, 142.6 (relatively weak), 148.1, 148.5, 149.2; HRMS (ESI) calcd for $C_{11}H_{15}N_2$ + H 175.1235, found 175.1230.

Acknowledgment. Financial support was provided by the grants from NSFC (90713007; 20772141; 20625204; 20632030), STCSM ("Post-Venus" Program, 05QMH1416), and MOST_863 (2006AA09Z405; 2006AA09Z446). We are grateful to Professor Minzhi Deng (SIOC, CAS) for providing the $LiBH_3NMe_2$ reagent as a gift and to Professor Fayang Qiu (GIBH, CAS) for enlightening discussions.

Supporting Information Available: Experimental procedures and analytical data for compounds **7**, **4**, **8**, and **9** and copies of ^1H and ^{13}C NMR spectra for compounds **1**−**4**, and **7**–**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8002425