A New Approach to Piperidine Alkaloids: An Enantioselective Total Synthesis of (2*S*,6*R*)- and (2*R*,6*S*)-Dihydropinidine

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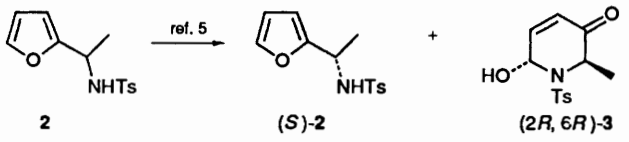
An enantioselective total synthesis of (2*S*,6*R*)- and (2*R*,6*S*)- dihydropinidine, utilizing the (2*R*,6*R*)-1,6-dihydro-6-hydroxy-2-methyl-*N*-tosyl-pyridin-3(2*H*)-one **3** and its enantiomer **3'** obtained from kinetic resolution of α-furfuryl amide **2** by modified Sharpless asymmetric epoxidation as starting material, is described.

2,6-Dialkylpiperidine alkaloids are abundant in Nature and many of them exhibit significant biological activity.[1] They have been the subject of a number of synthetic studies during recent years.[2] However, their enantioselective synthesis has received less attention.[3] As a part of a program directed at development of a new general strategy for the enantioselective synthesis of biologically active alkaloids, we have accomplished a practical, enantioselective total synthesis of (2*S*,6*R*)-dihydropinidine **1**, which was isolated from Pinus sabiniana Dougl,[4] utilizing the (2*R*,6*R*)-1,6-dihydro-6-hydroxy-2-methyl-*N*-tosyl-pyridin-3(2*H*)-one **3** obtained from kinetic resolution of α-furfuryl amide[2] by modified Sharpless asymmetric epoxidation reagent, as starting material (Scheme 1).[5]



2 (*S*)-**2** (2*R*, 6*R*)-**3**

Scheme 1

The synthesis of (2*S*,6*R*)-dihydropinidine **1** is depicted in Scheme 2. (2*R*,6*R*)-**3** on treatment with triethyl orthoformate and BF_3·Et_2O gave the single isomer (2*R*,6*R*)-**4** in 99.8% yield [m.p. 139–140 °C, $[\alpha]_D^{25}$ − 1.4 (*c* 2.5, EtOAc)]. Reduction of **4** with sodium borohydride in methanol at −60° to −20 °C furnished (2*R*,3*S*,6*R*)-**5** as an oil in 90% yield {$[\alpha]_D^{25}$ − 2.75 (*c* 3.0, EtOAc)}. The stereochemistry of the hydroxy group in compound **5** was inferred from a single band (ν_{max}/cm^{-1} 3500) in the IR spectrum in dilute carbon tetrachloride solution.[6] Additional information was gained from the ^{1}H NMR (200 MHz) spectrum: the 3-H proton of **5** shows up at 3.74 ppm as a multiplet of peaks whose high coupling constants ($J_{2,3}$ 7, $J_{3,4}$ 10.3 Hz) are characteristic of *trans* diaxial protons. Reaction of **5** with allyltrimethylsilane in the presence of titanium tetrachloride at −75 °C produced 84:16 epimeric mixture of (2*R*,3*S*,6*R*)-**6** {m.p. 127.2–127.4 °C, $[\alpha]_D^{25}$ − 0.92 (*c* 2.1, EtOAc)} and (2*R*,3*S*,6*S*)-**6b** as an oil {$[\alpha]_D^{25}$ + 6.2 (*c* 1.2, EtOAc)} in 94% yield. Reaction of **5** with allylmagnesium bromide gave lower distereoselectivity (2.9:1) and lower yield. The stereochemistry of the allyl group in diastereoisomers **6a** and **6b** was assigned by analogy to the result obtained in allylation of structurally related monocyclic analogues.[7,8]

Rigorous support for these assignments was provided by a 2D H–H NOESY spectroscopic analysis of (2*R*,3*S*,6*R*)-**7**,† which was obtained from **6b** by hydrogenation. Compound **6a** was hydrogenated by palladium on carbon in ethanol to give (2*R*,3*S*,6*S*)-**8a** in nearly quantitative yield {m.p. 98.8–100.7 °C, $[\alpha_D^{25}$ − 0.38 (*c* 5.0, EtOAc)}. Removal of the hydroxy group from (2*R*,3*S*,6*S*)-**8b** by Barton's method (Bn_3SnH–AIBN)[9] gave (2*S*,6*R*)-**9** in 73% yield {m.p. 79.4–80.5 °C, $[\alpha]_D^{25}$ − 2.0 (*c* 6.2, EtOAc)}. Cleavage of the nitrogen protecting group with sodium–naphthalene in 1,2-dimethoxyethane (DME) at −75 °C, gave the desired (2*S*,6*R*)-dihydropinidine **1** as oil, in 92% yield {$[\alpha_D^{25}$ − 1.1 (*c* 2.0, EtOH), (lit.,[4] $[\alpha]_D^{25}$ − 1.2) (*c* 1.6, EtOH)]}.

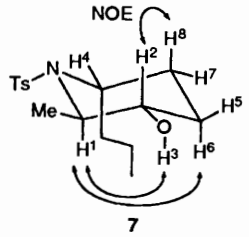
Identical allylation conditions induced the conversion of (2*S*,3*R*,6*S*)-**5'** obtained from (2*S*,6*S*)-**3'** which was derived from (*S*)-α-furfuryl amide **2** on oxidation with *m*CPBA, *via* the same sequence of reactions as (2*R*,3*S*,6*R*)-**5**, into (2*S*,3*R*,6*S*)-**6'a**, m.p. 119.4–120 °C, $[\alpha]_D^{25}$ + 0.86 (*c* 3.5, EtOAc) and (2*S*,3*R*,6*R*)-**6b'** as an oil, $[\alpha]_D^{25}$ − 0.84 (*c* 1.4, EtOAc). The overall yield from (*S*)-**2** to (2*S*,3*R*,6*S*)-**6'a** in four steps is 66.4% (Scheme 2). The synthesis of (2*R*,6*S*)- unnatural dihydropinidine **1'** hydrochloride was achieved in five steps in 63% overall yield from (2*S*,3*R*,6*S*)-**6'a** *via* the same sequence of reactions as (2*S*,6*R*)-dihydropinidine {m.p. 245–246.2 °C, $[\alpha]_D^{25}$ − 11.6 (*c* 3.0, EtOH) [lit.,[2a] $[\alpha]_D^{25}$ − 9.1 (*c* 1.03, EtOH), m.p. 215–220 °C]}.

In conclusion the enantioselective synthesis of the *cis*-2,6-dialkylpiperidine alkaloid, (2*S*,6*R*)-dihydropinidine **1** and (2*R*,6*S*)-unnatural dihydropinidine hydrochloride **1'** have been achieved efficiently in 7 steps (47.8%) and 9 steps (42%), respectively. It is evident that this strategy can also be applied to more complex molecules containing substituted piperidine skeleton.‡ The extension of this work to indolizidine and quinolizidine alkaloids is under study in our laboratory.

Experimental

Melting points were determined with a Buchi 535 melting point apparatus and were uncorrected. All reactions were carried out

† The stereochemistry of compounds **6a** and **6b** could not be analysed directly from 2D H–H NOESY, because of the overlap between the H^1, H^2, H^3 and H^4 signals. However, it could be deduced from the 2D H–H NOESY spectra of the derived compound **7** and allowed the signals at 4.15, 3.95, 3.78, 3.68 ppm to be assigned to the H^2, H^4, H^1 and H^3 protons and 2.0, 1.88, 1.72, 1.54, 1.28 ppm to be assigned to the H^8, H^6, H^5, H^7 and CH^3 protons. Thus, it was possible to assign the C^2-CH_3 and C^6-propyl in *trans*-orientation and complete the assignment of the remaining protons of the piperidine ring.



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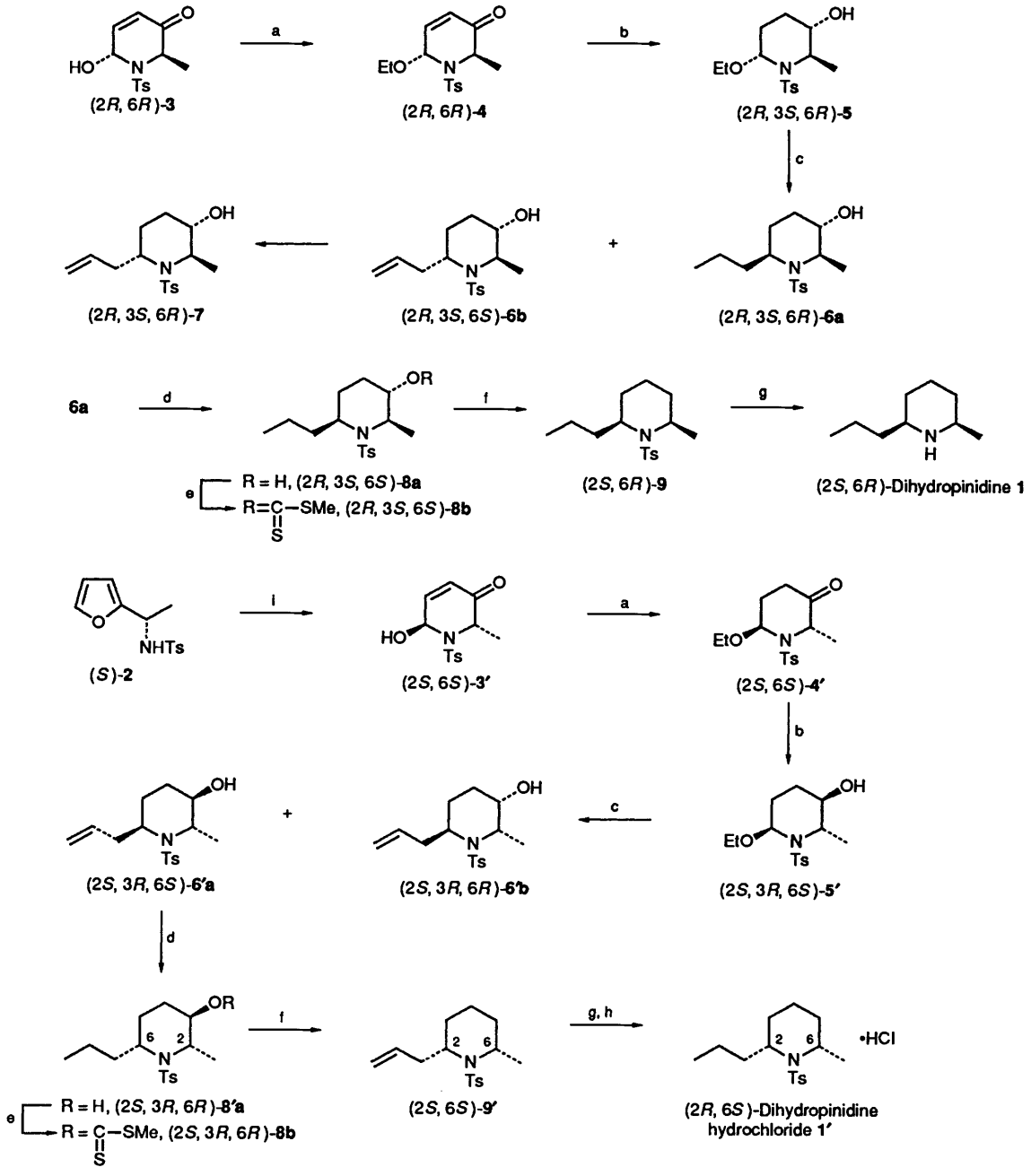
‡ The synthesis of 2,3,6-trisubstituted piperidine alkaloid azimic acid was achieved in our laboratory.



Scheme 2 *Reagents* a, $HC(OEt)_3$, BF_3·Et_2O; b, $NaBH_4$–MeOH; c, CH_2=$CHCH_2SiMe_3$–$TiCl_4$; d, H_2/10% Pd/C; e, NaH, CS_2, MeI, imidazole, THF; f, Bu_3SnH–AIBN, toulene; g, Na/nap.; h, HCl(g)–Et_2O; i, *m*-CPBA

under dried nitrogen. All additions were made using syringes. Reactions were monitored by using thin layer chromatography (TLC). IR spectra were measured on Schimadzu IR 4000 spectrometer. ^1H NMR spectra were recorded on JEOL FX-90Q (90 MHz), Varian-200 (200 MHz), AM-400 (400 MHz) and AMX-600 (600 MHz) with $CDCl_3$ as solvent and values were reported in ppm, using $(CH_3)_4Si$ or residual $CHCl_3$ as internal standard, *J* values are given in Hz. MS spectra were conducted on a Finnigan 4021 GC-MS instrument and JMS-01U spectrometer. The optical rotations were measured on Autopol spectrometer III automatic polarimeter. Elemental analyses were performed by Analytic Department of this Institute.

(2*R*,6*R*)-6-*Ethoxy*-5,6-*dihydro*-2-*methyl*-N-*tosylpyridin*-3-(2H)-*one* **4**.—To a solution of (2*R*,6*R*)-**3**[5] (0.62 g, 2.2 mmol) in dry diethyl ether (10 cm^3) was added triethyl orthoformate (0.73 cm^3, 4.4 mmol), 3 drops of BF_3·Et_2O and 4 Å molecular sieves. The reaction mixture was stirred at room temp. for 2 h, then 5 drops of Et_3N were added to neutralize the solution. It was then washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give an oil which after being refrigerated over night, gave very pure crystalline compound **4** (0.68 g, 99.8%), $[\alpha]_D^{25}$ − 1.4 (*c* 2.5, EtOAc). An analytical sample was prepared by recrystallization from ethyl acetate–light petroleum m.p. 138.9–140 °C; ν_{max}(film)/cm^{-1} 3068 (C=C), 1700 (C=O), 1600 (C_6H_6) and 1500; δ_H($CDCl_3$) 7.57 (d, 2-H, *J* 8), 7.25 (d, 2 H, *J* 8), 6.84 (dd, 1 H, *J* 10.2, *J* 4.7, 5-H), 5.84 (d, 1 H, *J* 10.2, 4-H), 5.69 (d, 1 H, *J* 4.7, 6-H), 4.30 (q, 1 H, *J* 6.7, 2-H), 4.02, 3.7 (m, 2 × 1 H, CH_2O), 2.40 (s, 3 H, Ph-CH_3), 1.60 (d, 3 H, *J* 6.7, 2-CH_3 and 1.26 (t, 3 H, *J* 7, OCH_2CH_3); *m*/*z* 310 M^+ + 1, 4%), 309 (M^+, 2%), 308 (M^+ − 1, 3.5%), 264 (M^+ − C_2H_5O, 98%), 218 (M^+ − C_7H_7, 9.3%), 157 (M^+ − 1 − C_7H_7 − C_2H_5O − CH_3, 22%), 155 (Ts^+, 21%), 154 (M^+ − Ts, 7%), 113 (100%)

and 91 ($C_7H_7^+$, 44%) (Found: C 57.65, H 6.3, N 4.35. Calc. for $C_{15}H_{19}NO_4S\cdot\frac{1}{4}H_2O$: C, 57.44; H, 6.26; N, 4.46%).

(2R,3S,6R)-6-*Ethoxy*-2-*methyl*-N-*tosylpiperidin*-3-*ol* **5**.—To the solution of (2*R*,6*R*)-**4** (1.0 g, 3.23 mmol) in methanol (20 cm^3) at −60 to −20 °C, was added portionwise $NaBH_4$ (307 mg, 8.1 mmol). After stirring for 20 min, the reaction mixture was quenched with saturated aq. NH_4Cl solution and the white precipitate was filtered off through a pad of Celite. The organic layer was separated and the aqueous layer was extracted with ether (5 × 15 cm^3). The combined organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product which was purified through a short silica gel column [light petroleum–ethyl acetate (4:1) as eluent] to afford a colourless oil (912 mg, 90%), $[\alpha]_D^{25}$ − 2.75 (*c* 2.75, EtOAc); ν_{max}/cm^{-1} 3500 (OH), 1729, 1600 (C_6H_6) and 1500 (C_6H_6); $\delta_H(CDCl_3)$ 7.66 (d, 2 H, *J* 8.26), 7.27 (d, 2 H, *J* 8.2), 5.23 (dd, 1 H, *J* 4.6, *J* 2.8, 6-H), 3.92 (q, 2 H, *J* 7.3, OCH_2CH_3), 3.74 (dd, 1 H, *J* 7.1, *J'* 10.3, 3-H), 3.52 (m, 1 H, *J* 7, *J* 10.3, 2-H), 2.40 (s, 3 H, Ph-CH_3), 1.42–1.95 (br, 4 H, 4-H_2, 5-H_2), 1.32 (d, 3 H, *J* 6.8, 2-CH_3), 1.20 (t, 3 H, *J* 7, OCH_2CH_3); *m/z* 313 (M^+), 312 (M^+ − 1), 282 (M^+ + 1 − OH − CH_3), 268 (M^+ − C_2H_5O), 250 (M^+ − C_2H_5O − H_2O), 158 (M^+ − Ts), 155 (Ts^+), 130 (M^+ − Ts − C_2H_5), 114 (M^+ + 1 − Ts-C_2H_5O), 91 ($C_7H_7^+$, 100%) (Found: C 56.9, H 7.45, N 4.05. Calc. for $C_{15}H_{23}NO_4S\cdot\frac{1}{4}H_2O$: C, 56.67; H, 7.17; N, 4.40%).

(2R,3S,6R)- **6a** *and* (2R,3S,6S)-6-*Allyl*-2-*methyl*-N-*tosylpiperidin*-3-*ol* **6b**.—To the solution of $TiCl_4$ (0.45 cm^3, 4.09 mmol) in CH_2Cl_2 (15 cm^3) was added dropwise a solution of **5** (1.22 g, 3.9 mmol) and allyltrimethylsilane (1.17 cm^3, 7.5 mmol) in CH_2Cl_2 (15 cm^3) at −70 °C under N_2 over a 5 min period. The solution was stirred and gradually warmed to 0 °C in 2 h. The aqueous layer was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was separated by column chromatography on silica gel [hexane–ethyl acetate (90:10) as eluent] to afford crystalline (2*R*,3*S*,6*R*)-**6a** (0.95 g, 79.2%) and (2*R*,3*S*,6*S*)-**6b** (0.18 g, 15%) as an oil.

(2*R*,3*S*,6*R*)-**6a**: m.p. 127.2–4 °C, $[\alpha]_D^{25}$ − 0.92 (*c* 2.1, EtOAc); ν_{max}(film)/cm^{-1} 3500 (OH), 3080 (C=C), 1600 and 1500; $\delta_H(CDCl_3)$ 7.72 (d, 2 H, *J* 8), 7.28 (d, 2 H, *J* 8), 5.80 (m, 1 H, CH=), 5.04 (m, 2 H, CH_2=), 4.20 (m, 1 H, *J* 7, *J* 10.3, 3-H), 4.04 (m, 1 H, 6-H), 3.44 (m, 1 H, 2-H), 2.40 (s, 3 H, Ph-CH_3), 1.96 (m, 2 H, $-CH_2CH$=), 1.4–1.80 (br, 4 H, 4-H_2, 5-H_2) and 1.28 (d, 3 H, *J* 8, 2-CH_3); $\delta_C(CDCl_3)$ 117.5, 113.6, 111.2, 106.4, 104.0, 96.0, 56.4, 42.4, 41.7, 32.0, 21.2, 18.4, 17.6 and 12.0; *m/z* 309 (M^+), 292 (M^+ − OH), 268 (M^+ − C_3H_5, 100%), 250 (M^+ − C_3H_5 − H_2O), 155 (Ts^+) and 91 ($C_7H_7^+$) (Found: C 61.9, H 7.7, N 4.55. Calc. for $C_{16}H_{23}NO_3S$: C 62.11, H 7.49, N 4.53%).

(2*R*,3*S*,6*S*)-**6b** $[\alpha]_D^{25}$ + 6.2 (*c* 1.2, EtOAc); ν_{max}(film)/cm^{-1} 3500 (OH), 1600 (C_6H_6) and 1500 (C_6H_6); $\delta_H(CDCl_3)$ 7.70 (d, 2 H, *J* 8), 7.26 (d, 2 H, *J* 8), 5.76 (m, 1 H, CH=), 5.10 (m, 2 H, *J* 12, CH_2=), 4.30 (m, 1 H, 3-H), 3.64–3.92 (m, 2 H, 2-H, 6-H), 2.40 (s, 3 H, Ph-CH_3), 1.90 (m, 2 H, CH_2–CH=), 1.12 1.36 (br, 4 H, 4-H_2, 5-H_2), 1.08 (d, 3 H, *J* 6, 6-CH_3) (Found: 61.25, H 7.3, N 4.3. Calc. for $C_{16}H_{23}NO_3S\cdot 1/4H_2O$: C 61.22, H 7.54, N 4.46%).

(2R,3S,6S)-2-*Methyl*-6-*propyl*-N-*tosylpiperidin*-3-*ol* **8a**.—To a solution of **6a** (0.80 g, 2.59 mmol) in ethanol (10 cm^3) was added a catalytic amount of 10% palladium on carbon (20 mg). The reaction mixture was stirred under hydrogen (1 atmos) at room temp. for 1 day. Filtration and removal of the solvent gave a crystalline **8a** (0.80 g, 100%), m.p. 98.8–100.7 °C, $[\alpha]_D^{25}$ − 0.38 (*c* 5.0, EtOAc); ν_{max}(film)/cm^{-1} 3500 (OH), 1600 and 1500; $\delta_H(CDCl_3)$ 7.72 (d, 2 H, *J* 8), 7.30 (d, 2 H, *J* 8), 4.20 (m, 1 H, 3-H), 3.98 (m, 1 H, 2-H), 3.74 (m, 1 H, 6-H), 3.40 (m, 1 H, OH), 2.40 (s, 3 H, Ph-CH_3), 1.30–1.80 (br, 8 H, 4 × CH_2), 1.28 (d, 3 H, *J* 6, 2-CH_3) and 0.94 (t, 3 H, *J* 8, CH_3-CH_2); *m/z* 312 (M^+ + 1, 40%), 311 (M^+, 3%), 294 (M^+ − OH, 35%), 269 (M^+ + 1 − C_3H_7 100%), 252 (5%), 250 (4.3%), 156 (M^+ − Ts, 14%), 155 (Ts^+, 16%), 128 (12%), 113 (13%), 96 (25.5%) and 91 ($C_7H_7^+$, 44%) (Found: C 61.65, H 8.0, N 4.35. Calc. for $C_{16}H_{25}NO_3S$: C 61.70, H 8.09, N 4.49%).

S-*Methyl* O-[(2R,3S,6S)-2-*Methyl*-6-*propyl*-N-*tosylpiperidin*-3-*yl*] *Dithiocarbonate* **8b**.—A mixture of the alcohol **8a** (0.86 g, 2.76 mmol), sodium hydride (80% purity, 0.62 g, 20.7 mmol) and imidazole (57 mg, 0.84 mmol) in anhydrous THF (45 cm^3) was refluxed for 1.5 h, then carbon disulfide (0.8 cm^3, 13.1 mmol) was added. The reaction mixture was refluxed for a further 30 min. Methyl iodide (0.88 cm^3, 14.1 mmol) was added and the mixture was further heated at reflux for 30 min. After addition of brine (10 cm^3), the mixture was extracted with ethyl acetate, dried over $MgSO_4$ and evaporated under reduced pressure to give a residue which afforded a crystalline **8b** (0.95 g, 86.0%) after purification by column chromatography on silica gel [light petroleum–ethyl acetate (95:15) as eluent]; m.p. 80.3–81.7 °C, $[\alpha]_D^{25}$ − 1.5 (*c* 12.6, EtOAc). $\delta_H(CDCl_3)$ 7.74 (d, 2 H, *J* 8), 7.28 (d, 2 H, *J* 8.0), 5.80 (m, 1 H, 3-H), 4.10 (m, 2 H, 2-H, 6-H), 2.76 (s, 3 H, CH_3S), 2.52 (s, 3 H, Ph-CH_3), 1.18–1.80 (br, 8 H), 1.30 (d, 3 H, 2-CH_3) and 0.96 (t, 3 H, CH_3CH_2); *m/z* 402 (M^+ + 1), 400 (M^+ − 1), 358 (M^+ − C_3H_7), 295 (M^+ − C_7H_7 − CH_3), 100% and 91 ($C_7H_7^+$).

(2S,6R)-6-*Methyl*-2-*propyl*-N-*tosylpiperidine* **9**.—The dithiocarbonate **8b** (1.8 g, 4.49 mmol) in dry toluene (25 cm^3) was added dropwise to a solution of tributyltin hydride (Bu_3SnH) (4.0 cm^3, 14.87 mmol) and a catalytic amount of AIBN in dry toluene (45 cm^3). The reaction mixture was refluxed under N_2 for 30 min. After addition of brine, the reaction mixture was extracted with ethyl acetate, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified *via* column chromatography on silica gel [ethyl acetate–light petroleum (10:90) as eluent] to afford crystalline **9** (1.1 g, 85%), m.p. 79.4–80.5 °C, $[\alpha]_D^{25}$ − 2.0 (*c* 6.2, EtOAc), ν_{max}(film)/cm^{-1} 1600 (C_6H_6) and 1500 (C_6H_6); $\delta_H(CDCl_3)$ 7.72 (d, 2 H, *J* 8), 7.28 (d, 2 H, *J* 8), 4.16 (m, 1 H, 6-H), 4.03 (m, 1 H, 2-H), 2.44 (s, 3 H, Ph-CH_3), 1.40–1.80 (br, 10 H, 5 × CH_2), 1.33 (d, 3 H, *J* 6.8, 2-CH_3) and 0.98 (t, 3 H, *J* 7, CH_3CH_2); *m/z* 296 (M^+ + 1, 7%), 280 (M^+ − CH_3, 3%), 252 (M^+ − C_3H_7, 100%), 155 (Ts^+, 44.5%) 140 (M^+ − Ts, 1.7%), 96 (M^+ − Ts − CH_3 − C_2H_5, 9.7%) and 91 ($C_7H_7^+$, 66.6%) (Found: M^+ 295.1615. Calc. for $C_{16}H_{25}NO_2S$, *M*, 295.1606).

(2S,6R)-*Dihydropinidine* **1**.—To a solution of naphthalene (1.0 g, 7.8 mmol) in fresh DME (10 cm^3) was added sodium (161 mg, 7 mmol) under N_2. The mixture was stirred at room temp. for 30 min. A solution of **9** (380 mg, 1.2 mmol) in DME (2 cm^3) was added to the above mixture at −78 °C. The reaction mixture was stirred for 30 min and quenched with brine (2 cm^3), then extracted with ethyl acetate, dried over anhydrous K_2CO_3 and evaporated to afford a crude product which was purified by column chromatography on silica gel [ethyl acetate–light petroleum (30:70) as eluent] to give the title compound **1** as a light yellow oil (167 mg, 92%), $[\alpha]_D^{25}$ − 1.1 (*c* 2.0, EtOH) [lit.,[4] $[\alpha]_D^{25}$ − 1.2 (*c* 1.6, EtOH)], ν_{max}(film)/cm^{-1} 2960, 2930, 2860, 2800, 1450, 1380 and 1320; *m/z* 142 (M^+ + 1, 8.1%), 141 (M^+, 4.7%), 140 (M^+ − 1, 5.8%), 126 (M^+ − CH_3, 14%), 112 (M^+ − C_2H_5, 4.0%), 98 (M^+ − C_3H_7, 100%), 83 (M^+ − C_3H_7 − CH_3, 2.4%), 70 (M^+ − 1 − C_3H_7 − CH_3 − CH_2, 25.5%), 69 (M^+ − C_3H_7 − CH_3 − CH_2, 6.7%) and 56 (M^+ + 1 − C_3H_7 − CH_3 − C_2H_4, 27.8%); $\delta_H(CDCl_3)$ 3.30 (m, 1 H, 6-H), 2.90 (m, 1 H, 2-H), 1.40–1.90 (br, 16 H), 1.32 (d, 3 H, *J* 6, 2-CH_3) and 0.98 (t, 3 H, CH_3).

(2S,6S)-1,6-*Dihydro*-6-*hydroxy*-2-*methyl*-N-*tosylpyridin*-3(2H)-*one* **3'**.—To a solution of (*S*)-**2** (1.0 g, 3.8 mmol) in dry CH_2Cl_2 (80 cm^3) was added slowly *m*CPBA [(880 mg, 80% pure, 4.0 mmol) in dry CH_2Cl_2 (40 cm^3)]. The reaction mixture was stirred at 30 °C and monitored by TLC. After 1 h, saturated aq. $NaHCO_3$ solution (50 cm^3) was added, the organic layer was separated and the aqueous layer was extracted with ether (2 × 10 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated to give a crude oil, which was purified by column chromatography on silica gel to afford (2*S*,6*S*)-**3'** (1.0 g, 94.6%); ($[\alpha]_D^{25}$ + 1.5, EtOAc). Spectroscopic data (IR, ^1H NMR, MS) are identical with those reported for (2*R*,6*R*)-**3**[5].

(2S,6S)-6-*Ethoxy*-1,6-*dihydro*-2-*methyl*-N-*tosylpyridin*-3(2H)-*one* **4'**.—The reaction was carried out by using (2*S*,6*S*)-**3'** (1.2 g, 4.26 mmol) in dry ether (20 cm^3), triethyl orthformate (1.4 cm^3, 8.5 mmol), 6 drops of $BF_3{\cdot}Et_2O$ and 4 Å molecules sieves. Work up in the way described above for (2*R*,6*R*)-**4**, gave crystalline **4'** (1.3 g, 99.8%), m.p. 138.9–139.9 °C, $[\alpha]_D^{25}$ 1.7 (*c* 2, EtOAc). Spectroscopic data (IR, ^1H NMR, MS) are identical with those reported above for (2*R*,6*R*)-**4**.

(2S,3R,6S)-6-*Ethoxy*-2-*methyl*-N-*tosylpiperidin*-3-*ol* **5'**.—The reaction was carried out using (2*S*,6*S*)-**4** (500 mg, 1.6 mmol) in methanol (10 cm^3), $NaBH_4$ (154 mg, 4.05 mmol) at −60 to −20 °C. Work up as described for (2*R*,3*S*,6*R*)-**5**, gave a colourless oil (2*S*,3*R*,6*S*)-**5'** (449 mg, 89%); $[\alpha]_D^{25}$ + 2.8 (*c* 1.8, EtOAc). Spectroscopic data (IR, ^1H NMR, MS) are identical with those reported for (2*R*,3*S*,6*R*)-**5**.

(2S,3R,6S)-**6a'** *and* (2S,3R,6R)-6-*Allyl*-2-*methyl*-N-*tosylpiperidin*-3-*ol* **6b'**.—The reaction was carried out by using (2*S*,3*R*,6*S*)-**5'** (4.0 g, 12.8 mmol), $TiCl_4$ (1.5 cm^3, 13.6 mmol), allyltrimethylsilane (3.8 cm^3, 24.3 mmol) in dry CH_2Cl_2 (100 cm^3). Work up as described above for (2*R*,3*S*,6*R*)-**6a**, gave crystalline (2*S*,3*R*,6*S*)-**6'a** (3.1 g, 79%); m.p. 119–120 °C, $[\alpha]_D^{25}$ + 0.86 (*c* 2.5, EtOAc) and (2*S*,3*R*,6*R*)-**6'b** (0.6 g, 15%) as an oil, $[\alpha]_D^{25}$ − 0.84 (*c* 1.4, EtOAc). Spectroscopic data (IR, ^1H NMR, MS) are identical with those reported for (2*R*,3*S*,6*R*)-**6a** and (2*R*,3*S*,6*S*)-**6b**.

(2S,3R,6R)-2-*Methyl*-6-*propyl*-N-*tosylpiperidin*-3-*ol* **8'a**.—The reaction was carried out using (2*S*,3*R*,6*S*)-**6a'** (250 mg, 0.81 mmol) and a catalytic amount of 10% palladium on carbon (10 mg) in ethanol (5 cm^3). Work up as described above for (2*R*,3*S*,6*S*)-**8a**, gave crystalline **8'a** (251 mg, 99.8%), m.p. 99.0–100 °C, $[\alpha]_D^{25}$ + 0.35 (*c* 2.5, EtOAc). Spectroscopic data (IR, ^1H NMR, MS) are identical with those reported for (2*R*,3*S*,6*S*)-**8a**.

S-*Methyl*O-[(2S,3R,6R)-2-*Methyl*-6-*propyl*-N-*tosylpiperidin*-3-*yl*] *Dithiocarbonate* **8'b**.—The reaction was carried out using (2*S*,3*R*,6*R*)-**8'a** (150 mg, 0.48 mmol), NaH (109 mg, 80% pure, 0.965 mmol), imidazole (10 mg, 0.14 mmol), carbon disulfide (0.14 cm^3, 2.3 mmol), and methyl iodide (0.154 cm^3, 2.4 mmol) in anhydrous THF (8 cm^3). Work up as described above for (2*R*,3*S*,6*S*)-**8b**, gave crystalline **8'b** (169.4 mg, 87.5%), m.p. 80–82 °C. Spectroscopic data (IR, ^1H NMR, MS) are identical with those reported for (2*R*,3*S*,6*S*)-**8b**.

(2R,6S)-6-*Methyl*-2-*propyl*-N-*tosylpiperidine* **9'**.—The reaction was carried out using (2*S*,3*R*,6*R*)-**8'b** (900 mg, 2.24 mmol), Bu_3SnH (2.0 cm^3, 7.43 mmol), in dry toluene (30 cm^3). Work up as described above for (2*S*,6*R*)-**9**, afforded crystalline (2*R*,6*S*)-**9'** (0.54 g, 83%); $[\alpha]_D^{25}$ + 2.3 (*c* 2.1, EtOAc), m.p. 79–81.0 °C. Spectroscopic data (IR, ^1H NMR, MS) are identical with those reported for (2*S*,6*R*)-**9**.

(2R,6S)-*Dihydropinidine Hydrochloride* **1'**.—The reaction was performed as described above for (2*S*,6*R*)-**1** using (2*R*,6*S*)-**9'** (570 mg, 1.75 mmol), naphthalene (1.5 g, 11.7 mmol) and Na (242 mg, 10.5 mmol) to afford a light yellow oil (2*R*,6*S*)-**1'** (246 mg, 90.3%). The oily product was used directly for the preparation of (2*R*,6*S*)-**1'** hydrochloride. To the solution of (2*R*,6*S*)-**1'** (50 mg) in dry Et_2O (5 cm^3), was bubbled HCl at room temp. for 5 min, the precipitate was filtered off, and recrystallized [ethyl acetate–ethanol (2:1)] to give **1'** hydrochloride as a powder (61 mg, 96.8%), m.p. 245–246.2 °C, $[\alpha]_D^{25}$ − 11.6 (*c* 3.0, EtOH), [lit.,[2a] $[\alpha]_D^{25}$ − 9.1 (*c* 1.03, EtOH), m.p. 215–220 °C]; ν_{max}(film)/cm^{-1} 3300 (NH); *m*/*z* 141 (M^+), 140 (M^+ − 1), 98 ($M^+ - C_3H_7$), 84 ($M^+ + 1 - CH_3C_3H_7$), 83 ($M^+ - C_3H_7 - CH_3$), 69 ($M^+ - C_3H_7 - CH_3 - CH_2$), 55 ($M^+ - C_3H_7 - CH_3 - C_2H_4$); $\delta_H(CD_3OD)$ 3.25 (m, 1 H, 6-H), 2.90 (m, 1 H, 2-H), 1.40–1.90 (br, 10 H, 5 × CH_2), 1.39 (t, 3 H, *J* 6, CH_3CH_2), 1.16 (d, 3 H, *J* 7, 6-CH_3) [Found: M^+ 140.1368. Calc. for $C_9H_{19}N$, (M-1) 140.1440].

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