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A Synthesis of Pseudoconhydrine and Its Epimer via Hydroformylation and Dihydroxylation

Roderick W. Bates,*[,†] K. Sivarajan,[†] and Bernd F. Straub[‡]

[†]Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371

[‡]Organisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, D-69120, Heidelberg, Germany

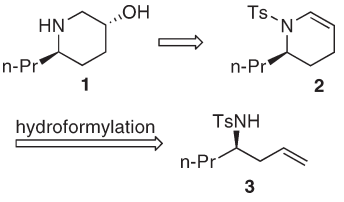
Supporting Information

ABSTRACT: A synthesis of the alkaloid pseudoconhydrine and its epimer has been achieved using tandem hydroformylation−condensation to form the six-membered ring and stereoselective dihydroxylation to introduce oxygenation. The stereoselectivity of dihydroxylation can be explained by lipophilic and electrostatic effects, supported by DFT calculations. The alkaloids can be obtained either by regioselective dehydroxylation or by rearrangement, followed by reduction.

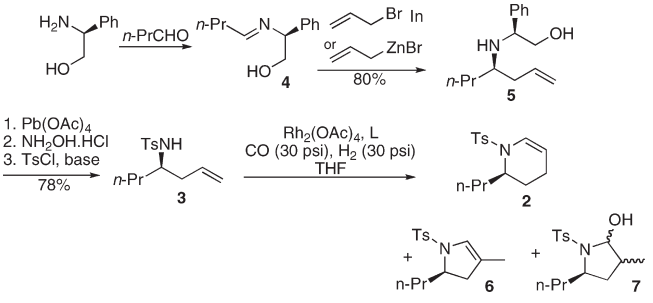
In terms of tons of product per year, hydroformylation is probably the largest transition metal-catalyzed process in current operation.[1−3] The reaction is used for the synthesis of huge amounts of bulk chemicals but has received less attention from synthetic organic chemists.[4] Notable exceptions are found in the work of Ojima[5] and, more recently, Breit,[6] as well as Taddei and Mann,[7] and Tan.[8] An advantage of hydroformylation for the synthesis of complex molecules is the good tolerance of other functional groups by the reaction. In the case of amine derivatives, this permits the design of tandem reactions, combining hydroformylation with condensation, to give enamine derivatives.[7,9−11] We became interested in employing the tandem hydroformylation−condensation chemistry, combined with oxidation of the resulting enamine derivative, to synthesize pseudoconhydrine **1**,[12−18] one of the alkaloids from hemlock (*Conium maculatum*).[19] A simple retrosynthetic analysis led to homoallylic amine derivative **3** (Scheme 1). A tosyl group was chosen for N-protection in part due to the clarity of NMR spectra compared to carbamates at the piperidine stage but also due to the robustness of this protecting group under many conditions.

The Vilaivan imine asymmetric allylation was chosen for the preparation of **3** on the grounds of requiring readily available starting materials, and simple operation.[20] The unstable imine **4** of butyraldehyde and (*S*)-phenylglycinol was prepared and treated with allyl bromide and indium (Scheme 2). Under carefully controlled conditions, the allylation product **5** was obtained in 80% yield and good diastereoselectivity. Control of temperature during addition of indium was found to be essential for obtaining this degree of stereoselectivity. Vilaivan has attributed the stereoselectivity to delivery of the allylating reagent through indium−oxygen coordination. Zinc will also coordinate effectively to oxygen. Interestingly, treatment of the imine with allylzinc bromide,[21−23] prepared by the method of Knochel,[24] yielded the same allylation product **5** in slightly higher dr. The phenylethanol moiety was cleaved according to the method of Vilaivan, and the free amine was tosylated. The ee of the sulfonamide **3** resulting from the zinc procedure, determined by chiral HPLC, was found to be 90%. The indium procedure gave, at best, an ee of 88% but was capricious.

Scheme 1. Pseudoconhydrine Retrosynthesis



Scheme 2. Synthesis and Hydroformylation of the Homoallylic Amine (L = ligand: triphenyl phosphite or BIPHEPHOS)



Hydroformylation of alkene **5** (Scheme 2) was carried out using rhodium acetate (1 mol %) in THF under a mixture of CO and H_2 (30 psi of each gas). With triphenyl phosphite as the

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Scheme 3. Synthetic Routes to Pseudoconhydrine and Its Epimer

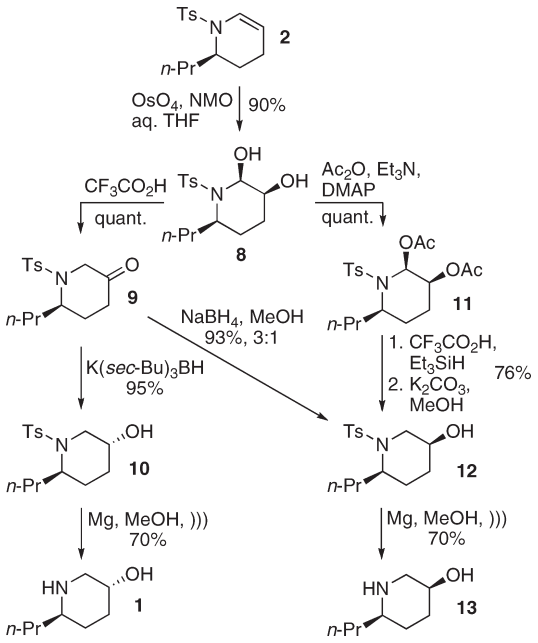

Table 1. Hydroformylation[a]

entry	ligand, loading, (mol %)	**2** yield (%)	acetals **7**, yield (%)	alkene **6**, yield (%)
1	$(PhO)_3P$, 2	56	10	15
2	$(PhO)_3P$, 6	67	20	4
3	$(PhO)_3P$, 12	78	trace	8
4	$(PhO)_3P$, 18	82	0	15
5	$(PhO)_3P$, 26	79	0	12
6	$(PhO)_3P$, 50	80	0	17
7	BIPHEPHOS, 2	quant	0	0

[a] Conditions $Rh_2(OAc)_4$ 1 mol %, THF, CO (30 psi), H_2 (30 psi) at 65 °C.

ligand, the product of linear hydroformylation, ene-sulfonamide **2**, with tandem cyclo-dehydration was obtained in 56−82% yield (Table 1). A small amount of the products of branched hydroformylation−cyclization were always obtained. While the linear product was always obtained in its dehydrated form as a cyclic ene-sulfonamide, the branched product was usually obtained as a mixture of dehydrated form **6** and the cyclic *N*,*O*-acetal **7**, itself, a complex mixture of stereoisomers. Interestingly, increasing the loading of the phosphite ligand resulted, at first, in an increased yield of the desired ene-sulfonamide **2**. This increase leveled off at about 12 mol % (P:Rh ratio = 6:1). Further increases in the phosphite loading, up to 50 mol %, did not result in any noticeable inhibition of the reaction but did cause an increase in the yield of the five-membered ring ene-carbamate **6** at the expense of the *N*,*O*-acetal mixture **7**. The optimum conditions for the formation of the desired six-membered ring ene-carbamate appear to be with 18 mol % of the phosphite. On the other hand, use of the bulky bisphosphite BIPHEPHOS[25] resulted in complete selectivity for the linear isomer **2**.

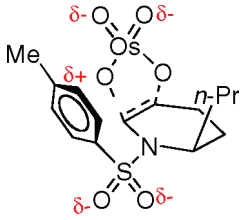

Figure 1. Transition state leading to **8**.

Six-membered ring ene-carbamates have been shown to undergo hydroboration−oxidation[16−18] and epoxidation[26] with trans selectivity. As substituents α to the ring nitrogen of *N*-acyl and *N*-sulfonyl piperidines are known to occupy an axial position,[27] this corresponds to the reagent approaching the less-hindered face. To our surprise, dihydroxylation of ene-sulfonamide **2** under Tsuji conditions[28] gave the cis product as the major isomer (Scheme 3).[29] The diols were obtained in 90% yield as an inseparable 7:1 mixture. Surprisingly, addition of either $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ to the reaction mixture resulted in lower stereoselectivity (4.7:1 and 3.6:1, respectively).[30,31] The stereochemistry was not apparent from the ^1H NMR spectrum but was subsequently confirmed by X-ray analysis of the bis(3,5-dinitrobenzoyl) derivative,[32] and also by the eventual conversion to *epi*-pseudoconhydrine.

DFT calculations at the B3LYP/LACV3P** level of theory[33−38] indicate that the two most favored gas-phase transition states leading to the diastereoisomeric *trans*-propyl and all-*cis* products feature very similar Gibbs free energies of activation 61.4 and 57.0 kJ mol^{-1}, respectively. This translates into a predicted cis/trans ratio of 6:1 at room temperature, which is in good agreement with the experimentally obtained 7:1 ratio. The analogous free Gibbs activation energy of the reaction of ethylene with OsO_4 is predicted to amount to 69.7 kJ mol^{-1} at the same level of theory.[39] In the calculated all-cis transition state (Figure 1) which leads to the observed product **8**, the angle sum of 359.7° at the nitrogen atom reflects a planar bonding environment. The tolyl group is directed toward the osmium tetroxide moiety with a distance between the ortho-proton and the OsO_4 oxygen of 234 −236 pm in both diastereomeric transition states. The tosyl orientation thus originates from the electrostatic attraction between the partially positive tolyl group and the negatively polarized oxygen atoms on osmium, and an electrostatic repulsion of the latter with the negatively polarized sulfonyl fragment.

The cis-relationship between the 2-substituent and the 5-hydroxyl group is seen in natural products such as 5-hydroxysedamine, azimic acid, carpamic acid, cassine, and others.[40]

The diol **8** was further converted to both pseudoconhydrine and its epimer (Scheme 3). When an attempt was made to carry out an exchange of the hydroxy group α to the nitrogen under acidic conditions, it was found that facile rearrangement occurred to give the ketopiperidine **9** in good yield. There appear to be few reports of general routes to such potentially versatile building blocks.[41−44] On the basis that the *n*-propyl side chain would adopt an axial position,[27] the ketone was reduced with K-selectride.[15] A single diastereoisomer, expected to be trans isomer **10**, was obtained in 95% yield. This isomer was deprotected in 70% yield under Carpino's conditions[45] with the modification of using ultrasound, yielding, after acidification, pseudoconhydrine **1** as its hydrochloride, with spectroscopic data and optical rotation in excellent agreement with that reported.[12,13]

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On the other hand, reduction with sodium borohydride gave a 3:1 mixture of alcohols. Deprotection of the major alcohol **12** yielded *epi*-pseudoconhydrine **13**. *epi*-Pseudoconhydrine could also be prepared from the diol **8** without going through ketopiperidine **9**. To prevent rearrangement, the hydroxy groups were acetylated. Kursanov–Parnes reduction[46] of diacetate **11** with triethylsilane and trifluoroacetic acid removed the acetoxy group α to nitrogen. Methanolysis of the remaining acetate group gave hydroxypiperidine **12** as a single diastereoisomer after chromatography, identical to the major isomer from sodium borohydride reduction of ketopiperidine **9**.

While hydroformylation of homoallylic amine derivatives provides a facile route to six-membered ring ene-carbamates, dihydroxylation subsequently gives access to the *cis*-hydroxy piperidines. Facile rearrangement of the diol to the ketopiperidine, on the other hand, provides access to both stereochemical series. Pseudoconhydrine and its epimer are obtained in 37% and 30% yields, respectively, from propionaldehyde.

EXPERIMENTAL SECTION

(*S*)-2-((*R*)-Hept-1-en-4-ylamino)-2-phenylethanol (5). (a) Indium powder (240 mg, 2.09 mmol) was added portionwise to a solution of imine **4** (200 mg, 1.05 mmol) and allyl bromide (0.27 mL, 3.14 mmol) in methanol (10 mL) at −10 °C. The resulting mixture was stirred at −10 °C for 6 h. The reaction mixture was diluted with 10% aqueous $NaHCO_3$, extracted with ethyl acetate, dried over magnesium sulfate, filtered, and evaporated. The residue was purified by silica gel flash column chromatography to give 195 mg (80% yield) of the allylation product **4** as a colorless oil.

(b) 1,2-Dibromoethane (0.01 mL, 0.12 mmol) was added to a suspension of zinc dust (226 mg, 3.45 mmol) in THF (20 mL). The mixture was heated gently until ebullition of the solvent and stirred for 5 min. After the heating and stirring process was repeated three times, chlorotrimethylsilane (0.02 mL, 0.136 mmol) was added and the mixture was stirred for another 15 min. Allyl bromide (0.1 mL, 1.15 mmol) was added dropwise and stirring was continued for 1 h. The mixture was added via cannula to a solution of imine **4** (200 mg, 1.05 mmol) in THF (10 mL) at −20 °C and stirred for 6 h. The reaction mixture was then poured into a water and ethyl acetate mixture and stirred vigorously. The mixture was then filtered, and the water layer was extracted with ethyl acetate, dried over magnesium sulfate, and evaporated. The product was then purified by silica gel flash column chromatography to give 195 mg (80% yield) of the allylation product **4** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (t, 3H, J = 6.8 Hz), 1.41−1.14 (m, 4H), 2.10−2.28 (m, 2H), 2.48−2.60 (m, 1H), 3.47 (dd, 1H, J = 10.5, 8.7 Hz), 3.66 (dd, 1H, J = 10.5, 4.6 Hz), 3.88 (dd, 1H, J = 8.7, 4.6 Hz), 5.04−5.14 (m, 2H), 5.74−5.86 (m, 1H), 7.24−7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.2, 37.2, 38.1, 53.7, 61.7, 67.0, 117.4, 127.4, 127.7, 128.8, 135.5, 141.5; MS (ESI+) m/z 243.1 (100).

(*R*)-*N*-Tosylhept-1-en-4-amine (3). Lead tetraacetate (456 mg, 1.03 mmol) was added to a solution of amino alcohol **5** (200 mg, 0.857 mmol) in dry CH_2Cl_2/MeOH (1:1) at 0 °C and stirred (30 min) until confirmed complete by TLC. Hydroxylamine hydrochloride (596 mg, 8.57 mmol) was added to the resulting mixture and stirred for another 30 min. The residue remaining after removal of the solvents was washed with hexane and suspended in CH_2Cl_2 followed by filtration of the lead precipitates. The organic solvent was evaporated and the residue was dried in vacuo. The residue was taken up in dry CH_2Cl_2 (10 mL), and Et_3N (0.25 mL, 1.77 mmol) and TsCl (168 mg, 0.883 mmol) were added and stirred overnight. The reaction mixture was then diluted with sat. aq ammonium chloride, extracted with ethyl acetate, dried over magnesium sulfate, filtered, and evaporated. The crude product was purified by silica gel flash column chromatography to give 179 mg (78% yield) of the sulfonamide product **3** as a colorless solid: FTIR (neat, cm^{-1}): ν_{max} 1359, 1165; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, 3H, J = 7.3 Hz), 1.09−1.44 (m, 4H), 2.09 (approx t, 2H, J = 6.9 Hz), 2.42 (s, 3H), 3.20−3.34 (m, 1H), 4.32−4.44 (m, 1H), 4.88−5.06 (m, 2H), 5.48−5.62 (m, 1H), 7.29 (d, 2H, J = 8.2 Hz), 7.74 (d, 2H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 18.8, 21.7, 36.9, 39.2, 53.2, 119.1, 127.3, 129.8, 133.5, 138.4, 143.4; MS (ESI+) m/z 268 (M^+ + 1, 100); HRMS Calcd for $C_{14}H_{21}NO_2S$ (M^++H) 268.1371, found 268.1366; $[\alpha]^{22.3}_D$ = 19.1 (c = 2, $CHCl_3$).

(*R*)-1,2,3,4-Tetrahydro-2-propyl-1-tosylpyridine (2). Amine **3** (100 mg, 0.375 mmol), $Rh_2(OAc)_4$ (1.8 mg, 3.75 × 10^{-3} mmol), and $P(OPh)_3$[47] (20 μL, 0.075 mmol) were dissolved in THF (3 mL) in a Fisher-Porter tube. The Fisher-Porter tube was purged (three times) with H_2/CO (1:1) and finally charged with H_2 (30 psi)/CO (30 psi). The reaction mixture was stirred vigorously at 65 °C for 18 h. The solvent was removed under reduced pressure and the residue was purified by silica gel flash column chromatography to give 83 mg (80% yield) of the ene-sulfonamide **2** as a colorless oil: FTIR (neat, cm^{-1}): ν_{max} 1359, 1165, 1645; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81−0.99 (m, 1H), 0.93 (t, 3H, J = 7.32), 1.22−1.99 (m, 8H), 2.41 (s, 3H), 3.91 (br s, 1H), 5.02 (t, 6.4 Hz), 6.58 (d, 1H, J = 8.2 Hz), 7.28 (d, 2H, J = 8.2 Hz), 7.66 (d, 2H, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 17.5, 19.3, 21.8, 23.0, 33.9, 53.0, 109.6, 123.8, 127.2, 129.8, 136.4, 143.4; MS (ESI+) m/z 280 (M^+ + 1, 100); HRMS Calcd for $C_{15}H_{21}NO_2S$ (M^+ + H) 280.1371, found 280.1376; $[\alpha]^{22.5}_D$ = −311.6 (c = 1, $CHCl_3$).

(2*S*,3*S*,6*R*)-6-Propyl-1-tosylpiperidine-2,3-diol (8). $MeSO_2NH_2$ (120 mg, 1.25 mmol) was added to a solution of ene-sulfonamide **2** (350 mg, 1.25 mmol) in THF (4 mL), and the mixture was stirred until it was completely dissolved. To the resulting solution were added NMO (0.77 mL, 3.76 mmol), H_2O (0.44 mL), and K_2OsO_4 (46 mg, 0.125 mmol), and the mixture was stirred overnight. The reaction mixture was quenched with sat. aq $Na_2S_2O_3$, washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to give 353 mg (90% yield) of the diol **8** as a yellowish oil and as an inseparable mixture of diastereoisomers: FTIR (neat, cm^{-1}): ν_{max} 1329, 1161, 3503; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, 3H, J = 7.3 Hz), 1.20−2.00 (m, 6H), 2.21 (t, 1H, J = 7.8 Hz), 2.42 (s, 3H), 3.00−3.12 (m, 1H), 3.22−3.36 (m, 1H), 3.82−3.92 (m, 1H), 5.37 (t, 1H, J = 3.2 Hz), 7.29 (d, 2H, J = 8.2 Hz), 7.69 (d, 2H, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.8, 21.7, 22.6, 26.5, 36.7, 52.5, 69.4, 78.4, 127.0, 130.0, 138.3, 143.7; MS (ESI+) m/z 314 (M^+ + 1, 9), 296 (M^+ − OH, 100); HRMS Calcd for $C_{15}H_{23}NO_4S$ (M^+ + H) 314.1426, found 314.1436.

(2*S*,3*S*,6*R*)-6-Propyl-1-tosylpiperidine-2,3-acetate (11). Acetic anhydride (0.07 mL, 0.702 mmol), triethylamine (0.11 mL, 0.798 mmol), and DMAP (4 mg, 0.032 mmol) were added to a solution of diol **8** (100 mg, 0.320 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 h. The reaction mixture was diluted with sat. aq NH_4Cl, extracted with CH_2Cl_2, washed with water, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by silica gel flash column chromatography to give a quantitative yield of the diacetate **11** as a colorless oil and as an inseparable mixture of diastereoisomers:[48] FTIR (neat, cm^{-1}): ν_{max} 1738, 1732, 1339, 1163; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 3H, J = 7.32 Hz), 1.18−1.40 (m, 2H), 1.47−1.81 (m, 6H), 1.97 (s, 3H), 2.03 (s, 3H), 2.42 (s, 3H), 3.95 (approx q, 1H, J = 6.4 Hz), 4.61 (approx dt, 1H, J = 11.9, 4.1 Hz), 6.79 (d, 1H, J = 3.7 Hz), 7.30 (d, 2H, J = 8.2 Hz), 7.72 (d, 2H, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 19.4, 20.5, 21.0, 21.2, 21.8, 26.4, 35.5, 52.6, 69.9, 76.1, 127.3, 130.0, 137.9, 144.0, 169.3, 170.1; MS (ESI+) m/z 314 (M^+ − OAc, 100), 296 (M^+ − C_3H_6, 14); HRMS Calcd for $C_{19}H_{27}NO_6SNa$ (M^+ + Na) 420.1457, found 420.1461.

(*R*)-6-Propyl-1-tosylpiperidin-3-one (9). Trifluoroacetic acid (10 μL, 0.128 mmol) was added to a solution of diol **8** (100 mg, 0.320 mmol) in CH_2Cl_2 (3 mL), and the mixture was stirred for 2 h.

The reaction mixture was evaporated, taken up in CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by silica gel flash column chromatography to give quantitative yield of the ketone **9** as a colorless oil: FTIR (neat, cm^{-1}): ν_{max} 1730, 1342, 1160; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, J = 7.1 Hz), 1.30−1.76 (m, 6H), 1.94−2.06 (m, 1H), 2.14−2.26 (m, 1H), 2.41 (s, 3H), 3.64 (d, 1H, J = 18.8 Hz), 4.01 (approx quin, 1H, J = 14.2, 7.3 Hz), 4.16 (d, 1H, J = 18.3 Hz), 7.76 (d, 2H, J = 7.8 Hz), 7.65 (d, 2H, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.2, 21.7, 26.1, 35.6, 36.1, 51.1, 52.9, 127.2, 130.2, 136.7, 144.0, 206.7; MS (ESI+) m/z 296 (M^+ + 1, 100); HRMS Calcd for $C_{15}H_{21}NO_3S$ (M^+ + H) 296.1320, found 296.1320; $[\alpha]^{22.3}_D$ = 71.3 (c = 0.5, $CHCl_3$).

(3*S*,6*R*)-6-Propyl-1-tosylpiperidin-3-ol (12). $NaBH_4$ (0.02 mg, 0.51 mmol) was added to a solution of ketone **9** (100 mg, 0.339 mmol) in MeOH and the mixture was stirred at room temperature for 2 h. The reaction mixture was evaporated, taken up in CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to give 93 mg (93% yield) of the hydroxypiperidine **12** as a yellowish oil and as a 3:1 mixture of diastereoisomers.

Trifluoroacetic acid (19 μL, 0.252 mmol) was added to a solution of the diacetate **11** (100 mg, 0.252 mmol) and Et_3SiH (0.40 mL, 2.52 mmol) in CH_2Cl_2,. The resulting mixture was stirred (3 h) at room temperature until confirmed complete by TLC. The reaction mixture was diluted with water, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and evaporated. The residue was taken up in MeOH (3 mL). K_2CO_3 (52 mg, 0.378 mmol) was added, and the mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated, taken up in CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered, evaporated, and purified by silica gel flash column chromatography to give 57 mg (76% yield) of the piperidinol **12** as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.3 Hz), 1.15−1.83 (m, 8H), 2.42 (s, 3H), 2.71 (dd, 1H, J = 13.3, 11.0 Hz), 3.37−3.50 (m, 1H), 3.85 (ddd, 1H, J = 13.3, 5.0, 1 Hz), 3.92−4.01 (m, 1H), 7.28 (d, 2H, J = 7.8 Hz), 7.70 (d, 2H, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.9, 21.7, 26.7, 28.4, 31.4, 46.4, 51.9, 66.3, 127.1, 129.9, 138.5, 143.3; MS (GC) m/z 254 ($M^+ - C_3H_7$, 100), 155 ($M^+ - C_8H_{16}NO$, 24); HRMS Calcd. for $C_{15}H_{23}NO_3S$ (M^+ + H) 298.1477, found 298.1483; $[\alpha]^{21.9}_D$ = −2.2 (c = 1, $CHCl_3$).

(3*R*,6*R*)-6-Propyl-1-tosylpiperidin-3-ol (10). K-Selectride (0.37 mL of a 1 M solution in THF, 0.37 mmol) was added to a solution of ketopiperidine **9** (100 mg, 0.339 mmol) in THF (3 mL) at 0 °C, and the mixture was stirred and allowed to warm slowly to room temperature. The reaction mixture was diluted with water, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, evaporated, and purified by silica gel flash column chromatography to give 95 mg (95% yield) of the trans isomer **10** as a colorless oil. ^1H and ^{13}C NMR spectroscopic data were in agreement with literature values.[12]

General Procedure for Detosylation. Mg turnings (163 mg, 6.72 mmol) were added to a solution of tosylpiperidinol (100 mg, 0.336 mmol) in MeOH (3 mL) portionwise over 3 h as the reaction mixture was being sonicated (ultrasonic cleaning bath) or until confirmed to be complete by TLC. The reaction mixture was acidified with 2 M HCl, washed with CH_2Cl_2, neutralized with 2 M NaOH, and extracted with CH_2Cl_2. The organic layer was reacidified with 2 M HCl, and the aqueous layer was evaporated to give 42 mg (70% yield) of the piperidinol salt as a brownish solid.

(3*R*,6*R*)-6-Propylpiperidin-3-ol Hydrochloride (1). ^1H and ^{13}C NMR spectroscopic data were in agreement with literature values:[12] $[\alpha]^{22.7}_D$ = −10.4 (c = 0.11, EtOH); mp 185−185.5 °C [lit.[14] mp 214−215 °C].

(3*S*,6*R*)-6-Propylpiperidin-3-ol Hydrochloride (13). ^1H NMR (400 MHz, D_2O) δ 0.78 (t, 3H, J = 7.32 Hz), 1.20−1.90 (m, 8H), 2.90−3.20 (m, 3H), 4.08 (s, 1H); ^{13}C NMR (100 MHz, D_2O) δ 12.9, 17.8, 22.7, 27.6, 35.1, 49.1, 56.6, 61.5; MS (ESI+) m/z 144 (M^+ + 1, 100); HRMS Calcd for $C_8H_{17}NO$ (M^+ + H) 144.1388, found 144.1385; $[\alpha]^{22.7}_D$ = −8.1 (c = 0.2, EtOH) {lit.[12] $[\alpha]^{20}_D$ = −10.2 (c = 1.0, EtOH)}; mp 120−121 °C [lit.[12] mp 148 °C].

■ ASSOCIATED CONTENT

Supporting Information. ^1H NMR and ^{13}C NMR spectra for compounds **1**, **2**, **3**, **5**, **6**, **8**, **9**, **10**, **11**, **12**, and **13**. ORTEP and CIF files for compound **8**-bis(dinitrobenzoate ester) and details of DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: roderick@ntu.edu.sg.

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