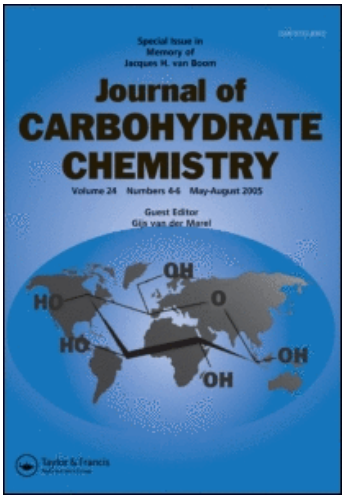

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A Chiral Synthesis of ( )-Pseudoconhydrine

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A CHIRAL SYNTHESIS OF (+)-PSEUDOCONHYDRINE

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ABSTRACT

(+)-Pseudoconhydrine, one of hemlock alkaloids, has been synthesized from methyl 2-acetamido-2,3,4-trideoxy-α-D-*erythro*-hexopyranoside by an eleven step reaction sequence. An intramolecular nucleophilic attack of the nitrogen atom on 2-acetamido-5-O-benzyl-2,3,4-trideoxy-6-O-tosyl-D-*erythro*-hexose diethyl dithioacetal to the terminal tosyloxymethylene group proceeded smoothly and gave the desired disubstituted piperidine compound. A conversion of the thioacetal group into an aldehyde, a two-carbon elongation by Wittig olefination, and a successive hydrogenation completed the chiral synthesis of the title alkaloid.

INTRODUCTION

Since its discovery from the common hemlock, pseudoconhydrine (1), *trans*-5-hydroxy-2-propylpiperidine, has been a subject of special interest for many research groups. Along with the related piperidine alkaloids (coniine, conicenine, and conhydrine), the structural elucidation of 1 was achieved rather recently.[1] The

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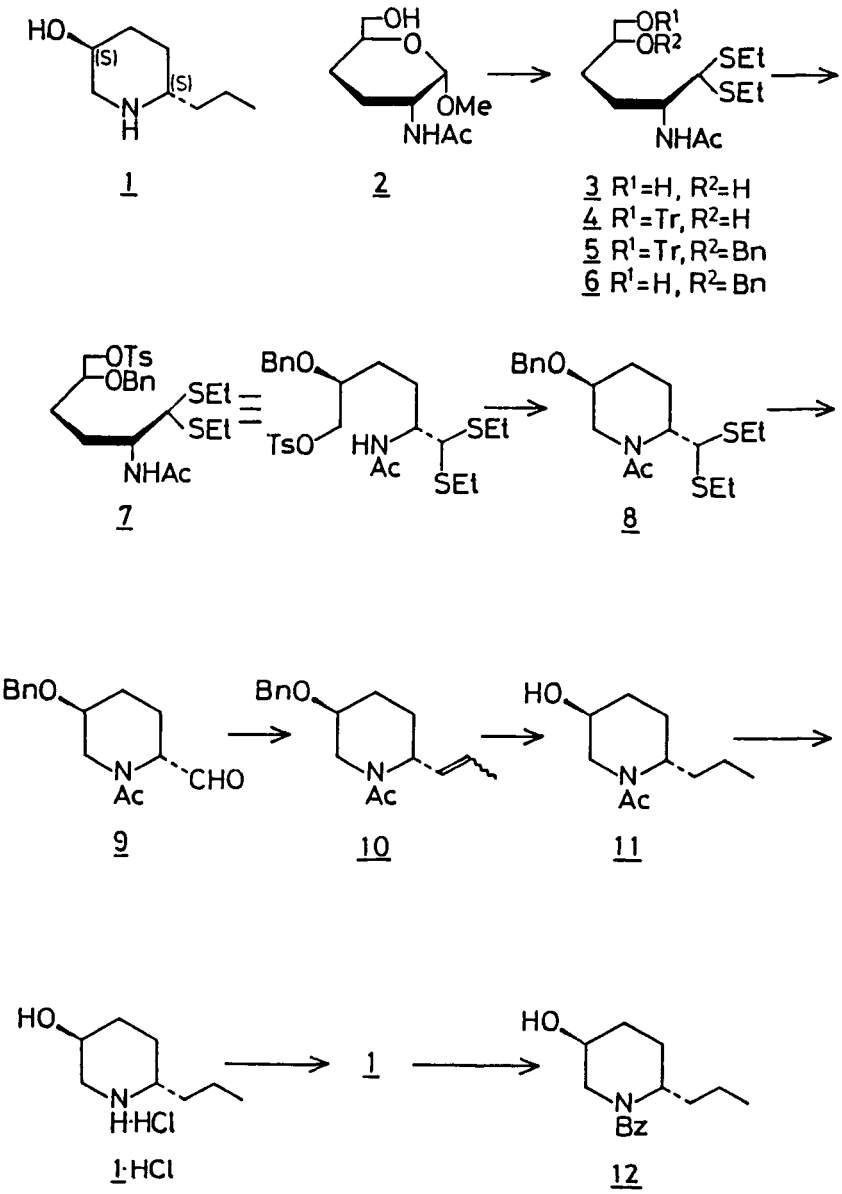
stereochemistry of 1 has been determined to be (2*S*,5*S*)-5-hydroxy-2-propylpiperidine by Hill,[2] based on the configuration of the Hofmann degradation product of 1. The synthesis of 1 has been described by several research groups.[3-7] In the course of carrying on chiral syntheses of natural products from carbohydrates,[8] we now report a synthesis of the enantiomer 1 from the 2-amino-2,3,4-trideoxy-D-*erythro*-hexose derivative (2).

RESULTS AND DISCUSSION

The chiral starting compound 2 was prepared from 2-amino-2-deoxy-D-glucose.[9] Treatment of 2 with an excess of ethanethiol in concentrated HCl afforded the crystalline acyclic diethyl dithioacetal derivative (3) in a quantitative yield. Selective tritylation of the primary hydroxyl group of 3 with 1.4 molar equivalents of trityl chloride in pyridine afforded the 6-O-trityl derivative (4). Benzylation of 4 with benzyl bromide in the presence of sodium hydride afforded the 5-O-benzyl derivative (5), which was converted to 2-acetamido-5-O-benzyl-2,3,4-trideoxy-D-*erythro*-hexopyranose diethyl dithioacetal (6). Preferential tosylation of the primary hydroxyl group of 6 gave the 6-O-tosyl derivative (7) in 91% yield. An intramolecular cyclization of 7 with sodium hydride in DMF afforded (2*R*,5*S*)-N-acetyl-5-benzyloxy-2-[bis(ethylthio)]methylpiperidine (8) in 93% yield. Dethioacetalation of 8 with mercury (II) chloride and mercury (II) oxide in aqueous acetonitrile gave an excellent yield of (2*R*,5*S*)-N-acetyl-5-benzyloxy-2-formylpiperidine (9). Wittig olefination of 9 with ethylenetriphenylphosphorane afforded a mixture of the (*E*)- and (*Z*)-geometric isomers of (2*R*,5*S*)-N-acetyl-5-benzyloxy-2-(1-propenyl)piperidine (10) in 70% yield. Hydrogenation of the double bond and catalytic hydrogenolysis of the benzyl group in 10 were carried out in the presence of palladium black, giving N-pseudoconhydrine (11) in 87% yield. Hydrolysis of 11 in 2 M HCl under reflux afforded pseudoconhydrine (1-HCl) in 80% yield, which



gave a melting point identical with that reported.[10] Compound 1-HCl was converted to an N-benzoyl derivative (12) whose melting point and $[\alpha]_D$ coincided with those previously reported.[11] (+)-Pseudoconhydrine, 1, was prepared by treatment of the hydrochloride with IRA-400 (OH^-) resin in 90% yield. The overall yield of 1 from 2 in eleven steps was 32%.

EXPERIMENTAL

General Procedures. Melting points were determined on a Mitamura Riken micro apparatus and are uncorrected. Optical rotations were measured on a JEOL DIP-4 polarimeter in a 1-dm tube. Silica gel column chromatography was performed with Wakogel C-300, and TLC was performed on glass plates coated with Merck Kieselgel 60 F_{254}. Compounds were detected by UV light, and by spraying with H_2SO_4 followed by heating. Preparative TLC (PTLC) was performed on glass plates (20x20 cm) coated with Merck Kieselgel 60 PF_{254}. IR spectra were recorded with Hitachi Model-225 (KBr) and JEOL Model A-202 ($CHCl_3$) spectrometers. ^1H NMR spectra were recorded with a Varian EM 390 spectrometer, and chemical shifts for $CDCl_3$ solutions were reported from internal tetramethylsilane. High resolution mass spectra were taken on a Hitachi M-80 mass spectrometer. Microanalyses were performed by Mr. Saburo Nakada of the University to whom our thanks are due.

2-Acetamido-2,3,4-trideoxy-D-*erythro*-hexose diethyl dithioacetal (3). To a solution of methyl 2-acetamido-2,3,4-trideoxy-α-D-*erythro*-hexopyranoside (2)[9] (450 mg, 2.21 mmol) in concentrated HCl (1.5 mL) was added ethanethiol (1.5 mL) at 0 °C. The solution was stirred at that temperature for 24 h, diluted with water (15 mL), and neutralized with saturated aqueous $NaHCO_3$. The solution was extracted with dichloromethane (10 mL x 10). The extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (15 g, ethanol:toluene=1:10), and fractions corresponding to R_f 0.36 on TLC (ethanol:toluene= 1:10) were concentrated to afford 3 (652 mg, quantitatively), mp 66-68 °C, $[\alpha]_D^{24}$+41.6° (*c* 1.41, $CHCl_3$); IR ν_{max}^{KBr} 3360, 3300, 2970, 2920, 2860, 1640, 1540, 1440, 1370, 1300, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25, 1.28 (3Hx2, each t, J=8 Hz, 2x$SCH_2\underline{CH_3}$), 1.38-1.65 (4H, m, H-3,3',4,4'), 2.00 (3H, s, $NCOCH_3$), 2.67, 2.69 (2Hx2, each t, J=8 Hz, 2xSCH_2CH_3), 3.10-3.85 (5H, m, H-5,6,6', 2xOH), 3.95 (1H, d, J=4 Hz, H-1), 4.05-4.47 (1H, m, H-2), 6.30 (1H, d, J=9 Hz, NH).

Anal. Calcd for $C_{12}H_{25}NO_3S_2$: C, 48.78; H, 8.53; N, 4.74; S, 21.70. Found: C, 49.00; H, 8.33; N, 4.59; S, 21.57.

2-Acetamido-2,3,4-trideoxy-6-O-trityl-D-*erythro*-hexose diethyl dithioacetal (4). To a solution of 3 (900 mg, 3.05 mmol) in pyridine (15 mL) were added trityl chloride (1.19 g, 4.26 mmol) and 4-dimethylaminopyridine (112 mg, 0.91 mmol). The mixture was stirred at 70 °C for 8 h and concentrated. The residue was partitioned between dichloromethane (80 mL) and water (80 mL), and the aqueous layer was extracted with dichloromethane (80 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (50 g, toluene containing 1 v/v% triethylamine, then ethanol:toluene=1:30 containing 1 v/v% triethylamine), and fractions corresponding to R_f 0.45 on TLC (ethanol:toluene=1:10) were concentrated to afford 4 (1.63 g, 99%) as a syrup. $[\alpha]_D^{22}$+17.0° (*c* 1.22, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3400, 3010, 1655, 1490, 1445, 1200, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20, 1.24 (3Hx2, each t, J=8 Hz, 2x$SCH_2\underline{CH_3}$), 1.35-1.60 (4H, m, H-3,3',4,4'), 1.74-2.00 (1H, m, OH), 1.94 (3H, s, $NCOCH_3$), 2.63 (4H, q, J=8 Hzm 2x$S\underline{CH_2}CH_3$), 2.88-3.28 (2H, m, H-6,6'), 3.60-3.88 (1H, m, H-5), 3.90 (1H, d, J=4 Hz, H-1), 4.10-4.41 (1H, m, H-2), 5.86 (1H, d, J=9 Hz, NH), 7.16-7.50 (15H, m, $OC(C_6H_5)_3$).

Anal. Calcd for $C_{31}H_{39}NO_3S_2$: *m/z* 537.2368. Found: M, 537.2369.

2-Acetamido-5-O-benzyl-2,3,4-trideoxy-D-*erythro*-hexose diethyl dithioacetal (6). Sodium hydride (60% emulsion in mineral oil, 188 mg, 4.69 mmol) was washed with hexane and suspended in DMF (3 mL). To the suspension was added a solution of 4 (1.80 g, 3.35 mmol) in DMF (15 mL). After 15 min stirring, benzyl bromide (0.56 mL, 4.69 mmol) was added. The mixture was stirred for 13 h, ethanol (2 mL) was added, and the mixture was concentrated. The residue was poured into water (90 mL) and the aqueous solution was extracted with dichloromethane (90 mL x 2). The extracts were dried (Na_2SO_4) and concentrated to afford crude (5) (2.62 g) as a pale yellow syrup. To a solution of the crude 5 in methanol

(20 mL) was added *p*-toluenesulfonic acid (monohydrate, 1.27 g, 6.69 mmol). The mixture was stirred for 2 h, neutralized with saturated aqueous $NaHCO_3$, and concentrated. The residue was partitioned between dichloromethane (90 mL) and water (90 mL), and the aqueous layer was extracted with dichloromethane (90 mL). The extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (50 g, ethanol:toluene=1:20), and fractions corresponding to R_f 0.26 on TLC (ethanol:toluene= 1:10) were concentrated to afford 6 (1.01 g, 78%). An analytical sample was obtained by recrystallization from ether-petroleum ether, mp 77-79 °C, $[\alpha]_D^{23}$+38.4° (*c* 1.00, $CHCl_3$); IR ν_{max}^{KBr} 3300, 2960, 2910, 2860, 1650, 1535, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22, 1.26 (3Hx2, each t, J=8 Hz, 2x$SCH_2\underline{CH_3}$), 1.41-1.78 (4H, m, H-3,3', 4,4'), 1.96 (3H, s, $NCOCH_3$), 2.20-2.45 (1H, m, OH), 2.66, 2.67 (2Hx2, each q, J=8 Hz, 2x$S\underline{CH_2}CH_3$), 3.35-3.80 (3H, m, H-5,6,6'), 3.91 (1H, d, J=4 Hz, H-1), 4.02-4.42 (1H, m, H-2), 4.58 (2H, s, $O\underline{CH_2}C_6H_5$), 5.90 (1H, d, J=9 Hz, NH), 7.37 (5H, s, $OCH_2C_6\underline{H_5}$).

Anal. Calcd for $C_{19}H_{31}NO_3S_2$: C, 59.18; H, 8.10; N, 3.63; S, 16.63. Found: C, 59.42; H, 8.06; N, 3.48; S, 16.79.

2-Acetamido-5-O-benzyl-2,3,4-trideoxy-6-O-tosyl-D-*erythro*-hexose diethyl dithioacetal (7). To a solution of 6 (630 mg, 1.63 mmol) in pyridine (10 mL) was added *p*-toluenesulfonyl chloride (799 mg, 4.09 mmol). The mixture was stirred for 6 h and concentrated. The residue was partitioned between dichloromethane (80 mL) and water (80 mL), and the aqueous layer was extracted with dichloromethane (80 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (40 g, ethanol:toluene=1:30), and fractions corresponding to R_f 0.47 on TLC (ethanol:toluene= 1:15) were concentrated to afford 7 (800 mg, 91%) as a pale yellow syrup, $[\alpha]_D^{24}$+6.1° (*c* 1.25, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3010, 1660, 1490, 1415, 1360, 1200, 1185, 1170, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23, 1.24 (3Hx2, each t, J=8 Hz, 2x$SCH_2\underline{CH_3}$), 1.41-1.75 (4H, m, H-3,3',4,4'), 1.93 (3H, s, $NCOCH_3$), 2.41 (3H, s, $OSO_2C_6H_4\underline{CH_3}$), 2.64 (4H, q, J=8 Hz, 2x$S\underline{CH_2}CH_3$), 3.44-3.70 (1H, m, H-5), 3.87

(1H, d, J=4 Hz, H-1), 3.96-4.31 (3H, m, H-2,6,6'), 4.50 (2H, ABq, J=9 and 14 Hz, $OC\underline{H}_2C_6H_5$), 5.74 (1H, d, J=9 Hz, NH), 7.32 (5H, s, $OCH_2C_6\underline{H}_5$), 7.55 (4H, ABq, $OSO_2C_6\underline{H}_4CH_3$).

Anal. Calcd for $C_{26}H_{38}NO_5S_3$: *m/z* 540.1909. Found: M+H, 540.1906.

(2*R*,5*S*)-N-Acetyl-5-benzyloxy-2-[bis(ethylthio)]methylpiperidine (8). Sodium hydride (60% emulsion in mineral oil, 21.4 mg, 0.89 mmol) was washed with hexane (1 mL x 3), and suspended in DMF (0.5 mL). To the suspension was added a solution of 7 (240 mg, 0.45 mmol) in DMF (2 mL). The mixture was heated at 100 °C with stirring for 1 h, then ethanol (1 mL) was added, and concentrated. The residue was partitioned between dichloromethane (30 mL) and water (30 mL), and the aqueous layer was extracted with dichloromethane (30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by PTLC (ethyl acetate:hexane=1:2) to afford 8 (153 mg, 93%, R_f 0.48 on TLC: ethyl acetate:hexane=1:2) as a syrup, $[\alpha]_D^{22}$ -28.6° (*c* 1.05, $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ 3010, 1630, 1425, 1205 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24, 1.25 (3Hx2, each t, J=8 Hz, $2xSCH_2\underline{CH}_3$), 1.59-2.06 (4H, m, H-3,3',4,4'), 2.10 (3H, s, $NCOCH_3$), 2.40-2.88 (1H, m, H-6), 2.67, 2.69 (2Hx2, each q, J=8 Hz, $2xSC\underline{H}_2CH_3$), 3.12-4.95 (4H, m, H-2,5,6',$C\underline{H}(SCH_2CH_3)_2$), 4.51 (2H, ABq, $OC\underline{H}_2C_6H_5$), 7.34 (5H, s, $OCH_2C_6\underline{H}_5$).

Anal. Calcd for $C_{19}H_{29}NO_2S_2$: *m/z* 367.1638. Found: M, 367.1646.

Mixture of (*E*)- and (*Z*)-(2*R*,5*S*)-N-Acetyl-5-benzyloxy-2-(1-propeny)piperidine (10). To a solution of 8 (163 mg, 0.44 mmol) in acetonitrile:water (4:1, 5 mL) were added mercury (II) chloride (602 mg, 2.22 mmol) and mercury (II) oxide (576 mg, 2.66 mmol). The mixture was stirred in the dark for 30 min, and the inorganic materials were removed by filtration through a Celite-pad. The filtrate was diluted with dichloromethane (30 mL), washed with 1 M KI solution (20 mL x 3), dried (Na_2SO_4), and concentrated to afford crude (9) (145 mg, R_f 0.24 on TLC: ethyl acetate:hexane= 3:2). To a suspension of ethyltriphenylphosphonium bromide

(412 mg, 1.11 mmol) in THF (4 mL) was added butyllithium (1.28 M in hexane, 0.52 mL, 0.67 mmol) under an argon atmosphere. The mixture was stirred at room temperature for 30 min, butyllithium (0.35 mL, 0.44 mmol) was added and the mixture stirred for 30 min. To the resultant red solution was added a solution of the crude 9 in THF (1.5 mL). The mixture was stirred for 30 min at room temperature, diluted with ethyl acetate (40 mL). The solution was washed with water (30 mL), saturated aqueous NaCl (30 mL), and water (30 mL) successively. The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (15 g, ethyl acetate:hexane=1:5), and fractions corresponding to R_f 0.53 on TLC (ethyl acetate:hexane=3:2) were concentrated to afford 10 (84.5 mg, 70%) as a colorless syrup, IR $\nu_{max}^{CHCl_3}$ 3010, 1620, 1435, 1425, 1205 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15-2.25 (4H, m, H-3,3',4,4'), 1.67 (3H, d, J=5 Hz, $CH=CHCH_3$), 2.06 (3H, s, $NCOCH_3$), 2.67-5.60 (4H, m, H-2,5,6,6'), 4.50 (2H, s, $OCH_2C_6H_5$), 5.55-5.72 (2H, m, $CH=CHCH_3$), 7.31 (5H, s, $OCH_2C_6H_5$).

Anal. Calcd for $C_{17}H_{23}NO_2$: *m/z* 273.1727. Found: M, 273.1710.

(2*S*,5*S*)-N-Acetyl-5-hydroxy-2-propylpiperidine, N-acetyl-(+)-pseudoconhydrine (11). To a solution of 10 (63 mg, 0.24 mmol) in ethanol (3 mL) was added palladium black (0.2 mL), and the mixture was acidified with acetic acid (pH 4). The mixture was hydrogenated under 3.3 atm initial hydrogen pressure (Parr apparatus) for 16 h. The catalyst was removed by filtration through a Celite-pad, and the filtrate concentrated to afford 11 (41.5 mg, 97%) as a colorless syrup. An analytical sample was obtained by silica gel column chromatography (ethanol:toluene=1:15, R_f 0.42 on TLC; ethanol:toluene=1:5), $[\alpha]_D^{24}$+28.7° (*c* 0.76, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3370, 3010, 2960, 2930, 1640, 1430, 1205 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80-1.05 (3H, m, CH_2CH_3), 1.50-2.10 (8H, m, H-3, 3',4,4', $CH_2CH_2CH_3$), 2.11 (3H, s, $NCOCH_3$), 2.55-4.93 (4H, m, H-2, 5,6,6'), 2.92-3.25 (1H, m, OH).

Anal. Calcd for $C_{10}H_{19}NO_2$: *m/z* 185.1414. Found: M, 185.1411.

(2*S*,5*S*)-5-Hydroxy-2-propylpiperidine hydrochloride, (-)-pseudoconhydrine hydrochloride (1-HCl). A solution of 11 (38 mg, 0.205 mmol) in 2 M HCl (2 mL) was heated under reflux for 20 h. The solution was concentrated with ethanol to give 1-HCl as crystals, which were recrystallized from ethanol and ethyl acetate to afford 1-HCl (29.6 mg, 80%) as needles, mp 208-209 °C (lit.[4] mp 214-215 °C, lit.[10] mp 212-213 °C), $[\alpha]_D^{24}$-5.6° (*c* 1.00, MeOH); IR ν_{max}^{KBr} 3370, 2940, 2860, 2790, 2560, 2510, 2410, 1610, 1595, 1460, 1430, 1405, 1370, 1310, 1270, 1215, 1120, 1105, 1075, 1015 cm^{-1}; ^1H NMR (D_2O, acetonitrile as internal standard) δ 0.79 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$), 1.04-2.16 (8H, m, H-3,3',4,4',$\underline{CH_2}\underline{CH_2}CH_3$), 2.62 (1H, dd, J=10 and 12 Hz, H-6), 2.81-3,42 (2H, m, H-2,6'), 3.61-3.95 (1H, m, H-5).

Anal. Calcd for $C_8H_{18}NOCl$: C, 53.47; H, 10.10; N, 7.82; Cl, 19.73. Found: C, 53.39; H, 9.90; N, 7.82; Cl, 19.95.

(2*S*,5*S*)-N-Benzoyl-5-hydroxy-2-propylpiperidine, N-benzoyl-(+)-pseudoconhydrine (12). To a solution of 1-HCl (19 mg, 0.11 mmol) in ethanol:water (1:1 v/v%, 1 mL) were added sodium carbonate (11 mg, 0.11 mmol) and benzoyl chloride (0.015 mL, 0.13 mmol). The mixture was stirred for 3 h and concentrated. The residue was partitioned between dichloromethane (8 mL) and water (8 mL), and the aqueous layer was extracted with dichloromethane (8 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (5 g, ethyl acetate:hexane=1:2), and fractions corresponding to R_f 0.22 were concentrated to afford 12 (16 mg, 60%). An analytical sample was obtained by recrystallization from ether, mp 130-131 °C (lit.[11] mp 132-133 °C); $[\alpha]_D^{26}$+21.3° (*c* 0.75, $CHCl_3$) (lit.[11] $[\alpha]_D^{17}$+23.4°); IR ν_{max}^{KBr} 3400, 2960, 2940, 2860, 1605, 1595, 1460, 1450, 1260, 1080, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71-0.97 (3H, m, $CH_2\underline{CH_3}$), 1.00-1.89 (8H, m, H-3,3',4,4',$\underline{CH_2}\underline{CH_2}CH_3$), 1.90-4.70 (4H, m, H-2,5,6,6'), 2.50-2.81 (1H, m, OH), 7.40 (5H, s, $COC_6\underline{H_5}$).

Anal. Calcd for $C_{15}H_{21}NO_5$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.99; H, 8.57; N, 5.82.

(2*S*,5*S*)-5-Hydroxy-2-propylpiperidine, (+)-pseudoconhydrine (1). Compound 1-HCl (12 mg, 0.07 mmol) was passed through an IRA-400 (OH^-) (5 mL) column from which 1 was eluted with water (9 mg, 90%). An analytical sample was obtained by sublimation, mp 93-94 °C (lit.[4] mp 91.5-92 °C), $[\alpha]_D^{26}$+10.2° (*c* 0.43, EtOH) [lit.[4] $[\alpha]_D^{23}$+11.1° (*c* 1.715, EtOH)]; IR $\nu_{max}^{CHCl_3}$ 3600, 3400, 3010, 2930, 2930, 1220, 1205, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3H, bt, J=6 Hz, $CH_2\underline{CH_3}$), 1.06-2.18 (10H, m, H-3,3',4,4',$\underline{CH_2}\underline{CH_2}CH_3$, NH, OH), 2.21-2.56 (1H, m, H-2), 2.41 (1H, dd, J=10.5 and 11 Hz, H-6), 3.19 (1H, ddd, J=2, 5 and 11 Hz, H-6'), 3.56 (1H, dt, J=4.5 and 10.5 Hz, H-5).

Anal. Calcd for $C_8H_{17}NO_6$: *m/z* 143.1308. Found: M, 143.1304.

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