Simple Synthetic Route to Polyhydroxylated Pyrrolidines and Piperidines

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A short and simple synthetic route to polyhydroxylated piperidines and pyrrolidines were described with *D*-glucurono-δ-lactone as chiral educt. Key reaction steps included selective cleavage of terminal isopropylidene group of compound **12** with Dowex 50W-X8 resin (H^+ form), regioselective ring opening of epoxide **16** and intramolecular nucleophilic amination of compound **14** and **18**.

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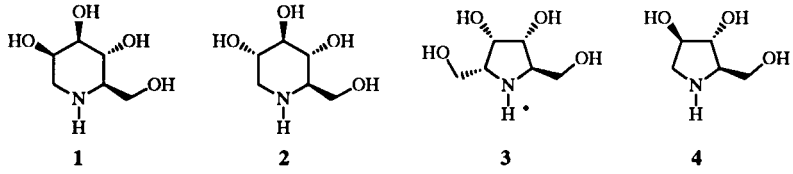
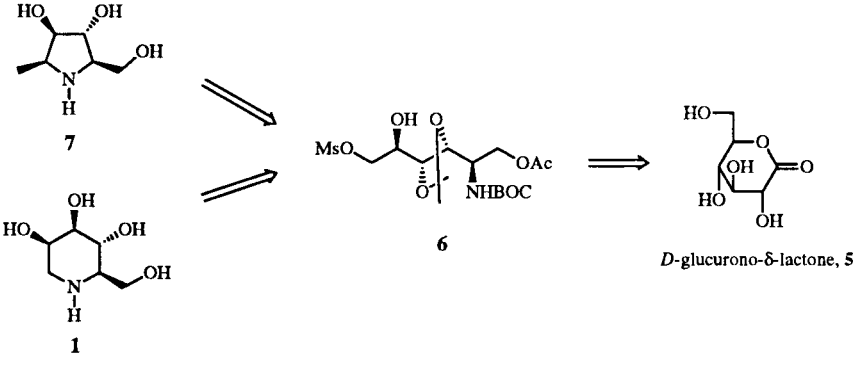
Many alkaloidal sugar mimics with it nitrogen in the ring have been isolated from plant and microorganisms and received a great deal of attention since these compounds have been shown to possess potent inhibitory activity against various glycosidases and mannosidases [1]. These compounds were known as "azasugars". Naturally occurring and designed hydroxylated piperidines and pyrrolidines (azasugars) such as 1,5-dideoxy-1,5-imino-*D*-mannitol (1-deoxymannojirimycin) **1** [2], 1,5-dideoxy-1,5-imino-*D*-glucitol (1-deoxynojirimycin) **2** [3], 2,5-dideoxy-2,5-imino-*D*-mannitol **3** [4] and 1,4-dideoxy-1,4-imino-*D*-arabinitol **4** [5] were used to treat diabetes and other metabolitic disorders and also have been implicated in the blocking of viral infections [6].



1 **2** **3** **4**

Figure 1

Scheme 1



7 **1** **6** *D*-glucurono-δ-lactone, **5**

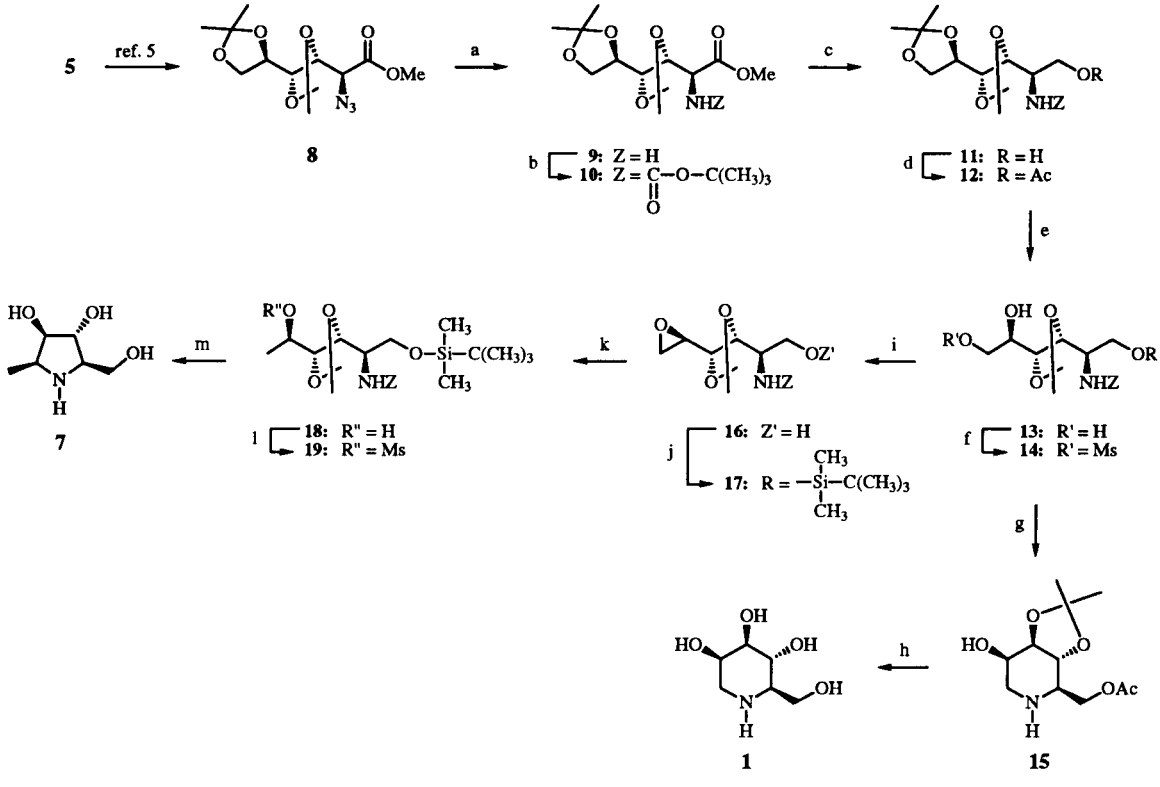
The potentially useful biological activities exhibited by azasugars have prompted extensive efforts toward their synthesis, and numerous approaches to these kinds of compounds have been reported [7]. During the course of our investigation for the synthesis of compounds having biological activity, we also reported a facile method for the synthesis of naturally occurring some piperidine and pyrrolidine compounds [8]. Although a variety of synthetic routes to azasugars have been developed, there are still some methodologies that remain unexplored.

In this paper, we would like to report the short and simple route for polyhydroxylated natural piperidine (**1**) and unnatural pyrrolidine (**7**). As shown in retrosynthesis of target molecules in Scheme 1, we used the *D*-glucurono-δ-lactone (**5**) as our starting material. The starting material transferred to compound **6** by a sequential process and cyclized to piperidine and pyrrolidine by intramolecular nucleophilic amination.

The manno azide **8** was prepared (Scheme 2) in straightforward manner from *D*-glucurono-δ-lactone (**5**) according to a known method [9]. With **8** in hand, we initially envisioned synthesizing 1-deoxymannojirimycin (**1**) according to the above-mentioned strategic planning (Scheme 2). Thus, **8** was converted to amine **10** with 10% palladium on charcoal/hydrogen under atmospheric pressure followed by protection with di-*tert*-butyl dicarbonate. Reduction of the ester was achieved by exposure of **10** to lithium aluminum hydride gave corresponding alcohol **11** and it was acetylated with acetic anhydride to form **12** in 93% yield. Alcohol **13**, obtained from regioselective deacetalizaton of diacetal **12** with Dowex 50W H^+ resin in methanol/water (9/1, v/v), was converted to mesyl **14** by selective mesylation of diol **13** in 82% yield from **13**. The deprotection of *tert*-butyl carbamate and the acetal groups of **14** with 3 *M* hydrochloric acid in ethyl acetate at 25° provided a clean amine (thin layer chromatography monitoring) and subsequent cyclization reaction by intramolecular nucleophilc amination gave polyhydroxylated piperidine **15** in 89% yield. Subsequent removal of the acetyl protecting groups in 50% methanolic ammonia at room temperature gave the free base form of deoxymannojirimycin **1** (55%) without additional ion exchange chromatography. Synthetic (-)-deoxymannojirimycin showed an optical rotation in methanol, $[a]_D^{20}$ -36.2 (c 0.34), that was in accord with published value and the ^1H nmr and ^{13}C spectral data virtually in agreement with those reported [10a] for **1**.

Epoxide formation of mesyl **14** with sodium hydroxide in methanol at room temperature afforded **16** in 87% yield. Reduction of epoxide **16** with diborane-borohydride [11] in tetrahydrofuran at reflux afforded anti-Markovnikov product **17** in 95% yield. Under these conditions neither the *tert*-butyl carbamate nor the isopropylidene group was affected. This regiospecific reduction of epoxide **16** may have resulted because of the electronegative effect of the neighbouring oxygens [11e]. The secondary alcohol **17** mesylated with methanesulfonyl chloride in the presence of triethylamine in dichloromethane at 0° gave **18** in 98% yield. Subsequent removal of the isopropylidene and *tert*-butyl carbamate protecting groups by heating **18** with Dowex 50W-X8 resin (H^+ form) in methanol/water (9/1, v/v) gave the free amino alcohol (thin layer chromatography monitoring) and followed by intramolecular nucleophilc amination in methanol with triethylamine at reflux

Scheme 2



Reagents and conditons: (a) H_2/Pd-C (10%), EtOAc, rt (b) di-*tert*-butyl carbonate, MeOH, Et_3N rt (c) $LiAlH_4$ tetrahyrofuran, 0°C (d) Ac_2O, py, rt (e) Dowex 50W-X8, 90% MeOH (f) MsCl, Et_3N, CH_2Cl_2, -10°C (g) 3*M* HCl, EtOAc, rt (h) 50% NH_3-MeOH, rt (i) NaOH, MeOH, rt (j) *tert*-butyldimethylsilyl chloride. imidazole, dimethylformamide, rt (k) $NaBH_3CN$, tetrahydrofuran, reflux (l) methanesulfonyl chloride, Et_3N, CH_2Cl_2, 0°C (m) (1) Dowex 50W-X8 H^+, 90% MeOH (2) $AlCl_3$, $LiAlH_4$, ether, 0°C, reflux.

gave 2*R*-methyl-5*S*-hydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine **7** in 74% yield. The structure of product **7** was firmly established by ^{1}H nmr, ^{13}C nmr, HMQC nmr and ^{1}H-^{1}H COSY nmr spectral data and elemental analysis data.

In conclusion, the intramolecular nucleophilic amination of amino alcohol **14** and **18** derived from *D*-glucono-6,3-lactone were successfully applied to the simple and short syntheses of new azasugar **7** which are expected to be glycosidase inhibitor and (-)-deoxymannojirimycin.

EXPERIMENTAL

General Procedures.

Dowex 50W-X8 was purchased from Sigma Chemical Co. All non-aqueous reactions were carried out under nitrogen. Tetrahydrofuran and ethyl ether were distilled from Na/benzophenone; methanol was distilled from magnesium, *N,N*-dimethylformamide, and dichloromethane were distilled from calcium hydride. Melting points were determined by using a Thomas-Hoover melting point apparatus and are uncorrected. Optical rotation values were measured with a JASCO DIP-1000 digital polarimeter in 1-dm cell. Infrared spectra were determined on a Hitachi 270-50 spectrophotometer. ^{1}H nmr, ^{13}C nmr, HMQC nmr and ^{1}H-^{1}H COSY nmr spectra were recorded on either Varian 200 MHz, 400 MHz, or Bruker ARX-300 (500 MHz) spectrometer in tetramethyl silane used as an internal standard unless otherwise noted (value in ppm); coupling constants are reported in Hz. The elemental analysis were performed with a LECO Micro Carbon Hydrogen Determinator (CHN-800) thin layer chromatography was run on Merck precoated silica gel plates. Merck silica gel 60 (230-400 mesh) was used for column chromatography.

Methyl 2-Azido-2-deoxy-3,4;5,6-di-*O*-isopropylidene-*D*-mannoate (**8**).

This compound was prepared as described [9].

Methyl 2-*tert*- Butoxycarbonylamino-2-deoxy-3,4; 5,6-di-*O*-isopropylidene-*D*-mannoate (**10**).

A mixture of azido mannoate (**8**) (3.5 g, 11.1 mmoles), 10% palladium on charcoal (350 mg) and dry ethyl acetate (130 ml) was stirred under hydrogen at atmospheric pressure at room temperature for 1 hour. The mixture was filtered, and the filterate was evaporated under reduced pressure to afford a gel-like product **9** in 94% yield. The crude compound **9** was used for next reaction without purification. Compound **9** was dried for 1 hour with vacuum pump and dissolved in methanol (30 ml). To this solution was added triethylamine and di-*tert*-butyl dicarbonate (3.12 g, 14.4 mmoles) and the reaction mixture was stirred at room temperature for 20 minutes. After addition of water (15 ml), the mixture was extracted three times with dichloromethane (50 ml), the combined organic phases were washed with brine, and dried over magnesium sulfate and the solvent was evaporated at reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane/ethyl acetate, 1:1, v/v) to afford **10** (3.98 g, 92%) as colorless oil; $[\alpha]_D^{20}$ +17.8° (c 1.03, dichloromethane); ir (potassium bromide): 3400, 2950, 1735, 1715, 1640, 1620 cm^{-1}; ^{1}H nmr (200 MHz, deuteriochloroform): δ 5.62 (d, 1H, J = 7.2 Hz), 4.42 (t, 1H, J = 6.5 Hz), 4.17 (m, 2H), 3.76 (m, 3H), 1.47 (m, 2H), 3.76 (m, 3H), 1.42 (s, OH), 1.34 (s, 9H).

Anal. Calcd. for $C_{18}H_{31}NO_8$: C, 55.51; H, 8.02; N, 3.60. Found: C, 55.37; H, 8.04; N, 3.55.

1-*O*-Acetyl-2-*tert*-butoxycarbonylamino-2-deoxy-3,4:5,6-di-*O*-isopropylidene-*D*-mannitol (**12**).

To a solution of the mannoate derivatives **10** (1.02 g, 2.6 mmoles) in dry tetrahydrofuran (20 ml) was added lithium aluminum hydride (0.2 g, 5.2 mmoles) at 0° and then the mixture was allowed to warm to room temperature and stirring was continued for 13 hours. The reaction mixture was cooled to 0° and hydrolyzed by addition of an aqueous solution of sodium hydroxide (15%, 0.5 ml) and water (1 ml) then the mixture was purified by flash chromatography (silica gel, hexane/ethyl acetate, 3:1, v/v) to afford **11** (0.89 g, 95%) as colorless oil. This was used next step directly. To a solution of compound **11** (1.54 g, 4.3 mmoles) in dry pyridine (25 ml) was added acetic anhydride (0.06 ml, 6.3 mmoles) and stirring was continued for 15 hours at room temperature. The solution was then hydrolyzed by addition of water (30 ml), extracted three times with ethyl acetate (30 ml), the combined organic phases were washed with saturated copper sulfate, brine and dried over magnesium sulfate and the solvent was evaporated at reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane/ethyl acetate 2:1, v/v) to afford **12** (1.60 g, 93%) as white solid; $[\alpha]_D^{20}$ +4.6° (c 1.2, dichloromethane); ir (potassium bromide): 3425, 2900, 1770, 1710 1510 cm^{-1}; ^{1}H nmr (400 MHz, deuteriochloroform): δ 5.07 (1 H, J = 7.47 Hz), 4.37 (dd, 1H, J = 3.13, 3.30 Hz), 4.09-4.15 (m, 2H), 4.04-4.00 (m, 3H), 3.96-3.94 (m, 1H), 3.91-3.87 (m, 2H), 2.08 (s, 3H), 1.45 (s, 3H), 1.44 (s, 9H), 1.39 (s, 3H), 1.37 (d, 6H, J = 2.5 6 Hz).

Anal. Calcd. for $C_{19}H_{33}NO_8$: C, 56.56; H, 8.24; N, 3.47. Found: C, 55.51, H, 8.28; N, 3.43.

1-*O*-Acetyl-2-*tert*-butoxycarbonylamino-2-deoxy-3,4-*O*-isopropylidene-*D*-mannitol (**13**).

To a solution of compound **12** (3.87 g, 9.6 mmoles) in 90% methanol (30 ml) was added Dowex 50W-X8 resin (H^+ form, 0.5 g) and stirring was continued for 18 hours at room temperature. The reaction mixture was filtered through a pad of Celite to remove the Dowex 50W-X8 resin and the solvent was removed at reduced pressure. The crude product was purified by the flash chromatography (silica gel, hexane/ethyl acetate, 1:1, v/v) to afford **13** (3.60 g, 98%) as white solid; $[\alpha]_D^{20}$ +7.2° (c 1.0, dichloromethane), mp 94°; ir (potassium bromide): 3500, 3400, 3000, 1750, 1720 cm^{-1}; ^{1}H nmr (400 nmr, deuteriochloroform): δ 5.41 (d, 1H, J = 7.66 Hz), 4.33 (d, 1H, J = 9.79 Hz), 4.20 (t, 1H, J = 10.5 Hz), 4.12 (t, 2H, J = 6.12 Hz), 3.97-3.94 (m, 2H), 3.82 (d, 2H, J = 9.04 Hz), 3.68 (s, 2H), 3.55 (s, 1H), 2.08 (s, 3H), 1.45 (s, 9H), 1.39 (d, 6H, J = 8.47 Hz).

Anal. Calcd. for $C_{16}H_{29}NO_8$: C, 52.86; H, 8.05; N, 3.86. Found: C, 52.84; H, 8.01; N, 3.83.

1-*O*-Acetyl-2-*tert*-butoxycarbonylamino-2-deoxy-3,4-*O*-isopropylidene-6-*O*- methanesulfonyloxy-*D*-mannitol (**14**).

To a solution of the diol **13** (3.87 g, 9.6 mmoles) in dry dichloromethane (30 ml) was added triethylamine (0.44 ml, 3.2 mmoles) and methanesulfonyl chloride (0.41 ml, 5.28 mmoles) at 0° and stirring was continued for 5 minutes. The solution was then hydrolized by addition of water (20 ml) and extracted three

times with dichloromethane (90 ml), and the extract was dried over magnesium sulfate and the solvent was removed at reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane/ethyl acetate, 3:2, v/v) to afford **14** (1.03 g, 83%) as colorless oil; $[\alpha]_D^{20}$ + 13.21, (c 1.0, dichloromethane); ir (potassium bromide): 3500, 3400, 1750, 1720 cm^{-1}; ^1H nmr (200 MHz, deuteriochloroform): δ 5.13 (d, 1H, J = 14.55 Hz), 4.47 (d, 1H, J = 22 Hz), 4.30-4.24 (m, 3H), 4.14-4.06 (m, 2H), 3.92-3.82 (m, 3H), 3.08 (s, 3H), 2.08 (s, 3H), 1.42 (s, 9H), 1.36 (d, 6H, J = 4.4 Hz).

Anal. Calcd. for $C_{17}H_{31}NO_{10}S$: C, 46.24; H, 7.08; N, 3.17. Found: C, 46.19; H, 7.11; N, 3.19.

(-)-Deoxymannojirimycin (**1**).

To a solution of **14** (300 mg, 0.72 mmole) in ethyl acetate (20 ml) was added 3*M* hydrochloric acid (0.07 ml, 1.44 mmoles) and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture hydrolized by addition of water (10 ml) and extracted three times with ethyl acetate (60 ml), and dried over magnesium sulfate and the solvent was removed at reduced pressure to give crude product **15** in 89% yield. The crude product **15** was used for the next step without purification. A solution of the crude product in 50% methanolic ammonia (5 ml) was stirred at room temperature for 3 hours. The reaction mixture was applied to silica a gel column (1.5 x 5 cm) directly. The column eluted with 2*N* ammonium hydroxide (40 ml) and combined the fractions containing product. The ammoniacal solution was co-evaporated with toluene (60 ml) azotropically under reduced pressure to afford compound **1** (64.5 mg, 55%) as white solid mp 183-185°, $[\alpha]_D^{20}$ -36.2 (c 0.34, methanol) [lit 10a] mp 185-187°; $[\alpha]_D^{20}$ -26.7 (c 0.30, methanol)}; ^1H-^1H COSY nmr (400 MHz, deuterium oxide): δ 2.52 (1 H, dt, J = 9.2 and 3.9, 2-H), 2.80 (1 H, dd, J = 14.3 and 1.3 6-H^{β}), 3.04 (1H, dd, J = 14.3 and 2.3, 6-H^{α}), 3.58 (1H, dd, J = 9. 1 and 2.6, 4-H), 3.64 (1H, dd, J = 9.2 and 9.2, 3-H), 3.80 (2H, d, J = 3.9, 7-H_2), 4.0.3 (1H, m, 5-H); ^{13}C nmr (deuterium oxide): δ 50.9, 63.13, 63.33, 70.9, 77.2.

1-*O*-(*tert*-Butyldimethylsilyl)oxy-2-*tert*-butoxycarbonylamino-2-deoxy-3,4-*O*-isopropylidene-5,6-epoxy-*D*-mannitol (**17**).

To a solution of mesylate **14** (920 mg, 2 mmoles) in dry methanol (20 ml) was added sodium hydroxide (100 mg, 3.0 mmoles) and stirring was continued for 5 minutes at room temperature. The reaction mixture was then hydrolized by addition of water (10 ml) and extracted three times with ethyl acetate (90 ml), and the extract was dried over magnesium sulfate and the solvent was removed at reduced pressure to give a corresponding epoxide **16**. The crude product was used for the next step without purification. A solution of epoxide (0.46 g, 1.7 mmoles) in dry *N,N*-dimethylformamide (15 ml) was treated with imidazole (0.23 g, 3.39 mmoles) and *tert*-butyldimethylchlorosilane (0.38 g, 2.54 mmoles) and stirring was continued for 15 hours at room temperature. The solution was then hydrolized by addition of water (30 ml) and extracted three times with ethyl acetate (90 ml), and dried over magnesium sulfate and the solvent was removed at reduced pressure. The crude product purified by flash chromatography (silica gel, hexane/ethyl acetate, 5:1, v/v) to afford 17 (0.60 a, 92%) as a colorless oil; $[\alpha]_D^{20}$ -5.0° (c 4.6, dichloromethane); ir (potassium bromide): 3450, 2960, 1730, 1520 cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 5.02 (d, 1H, J = 8.90 Hz), 4.05-4.00 (m, 2H), 3.92 (d, 1H, J = 9.84 Hz), 3.72 (dd, 2H, J = 12.0, 3.1 Hz), 3.05 (s, 1H), 2.84 (t, 1H, J = 4.86 Hz), 2.80-2.75 (m, 1H), 1.47 (s, 9H), 1.43 (s, 6H), 0.93 (s, 9H), 0.10 (s, 6H).

Anal. Calcd. for $C_{20}H_{39}NO_6Si$: C, 57.52; H, 9.42; N; 3.36. Found: C, 57.49, H, 9.41-, N, 3.32.

2*R*-*tert*-Butoxycarbonylamino-3*R*,4*R*-*O*-isopropylidene-5*S*-hydroxy-1-*O*-(*tert*-butyldimethylsilyloxy)hexane (**18**).

To a solution of epoxide **17** (330 mg, 0.85 mmole) in dry tetrahydrofuran (5 ml) was added sodium cyanoborohydride (1 *M* in tetrahydrofuran) (8.48 ml) and stirring was continued at reflux for 15 hours. The reaction mixture was cooled to room temperature and hydrolized by addition of water (10 ml) and extracted three times with ethyl acetate (30 ml), and the extract was dried over magnesium sulfate and the solvent was evaporated to dryness. The residual crude product was purified by column chromatography (silica gel, hexane/ethyl acetate (5:1, v/v) to afford **18** (0.60 g, 95%) as colorless oil; $[\alpha]_D^{20}$ -9.60 (c 1.7, dichloromethane): ir (potassium bromide): 3460, 3400, 2850-2990, 1715, 1710 cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 4.95 (d, 1H, J = 6.8 Hz), 4.04 (dd, 2H, J = 6.2, 11.3 Hz), 3.83-3.88 (m, 3H), 3.75 (dd, 2H, J = 3.8, 9.8 Hz), 2.70 (s, OH), 1.45 (s, 9H), 1.40 (d, 6H, J = 3.0 Hz), 1.25 (d, 3H, J = 6.4 Hz), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C nmr (deuteriochloroform): δ -4.8, 19.0, 19.4, 26.5, 26.6, 27.7, 27.8, 27.9, 29.0, 29.1, 54.9, 63.0, 69.0, 69.1, 77.4, 77.7, 78.0, 80.4, 83.0, 109.7.

Anal. Calcd. for $C_{20}H_{41}NO_8Si$: C, 57.24, H, 9.85; N; 3.34. Found: C, 57.28, H, 9.8 1, N, 3.32.

2*R*-*tert*-Butoxycarbonylamino-3*R*,4*R*-*O*-isopropylidene-5*S*-*O*-mesyl-1-*O*-(*tert*-butyldimethylsilyloxy)hexane (**19**).

To a solution of **17** (0.1 g, 0.26 mmole) in dry dichloromethane (15 ml) was added triethylamine (0.04 ml, 0.31 mmole) and stirring was continued at room temperature for 5 minutes. To the reaction mixture added dropwise methanesulfonyl chloride (0.02 ml, 0.31 mmole) in dichloromethane (2 ml) and stirred for 10 minutes and then water added (10 ml) and extracted three times with dichloromethane (60 ml) and the combined organic layers were washed with 60 ml of brine and dried over magnesium sulfate. The solvent was evaporated at reduced pressure and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 5:1, v/v) to afford **19** (0.11, 98%) as colorless oil; $[\alpha]_D^{20}$ + 12.5° (c 3. 1, dichloromethane); ir (potassium bromide): 3400, 1950, 1720, 1370 cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 4.99 (d, 1H, J = 9.3 Hz), 4.84-4.78 (m, 1H), 4.30 (t, 1H, J = 6.0 Hz), 3.97 (dd, 1H, J = 8.6, 6.7 Hz), 3.90 (dd, 1H, J = 10.0, 2.5 Hz), 3.81-3.76 (m, 1H), 3.72 (dd, 1H, J = 3.5, 9.9 Hz), 3.06 (s, 1H), 1.47 (s, 12H), 1.42 (d, 6H, J = 6.9 Hz), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C nmr (deuteriochloroform): δ -4.8, 17.7, 19.0, 26.5, 26.6, 27.8, 28.0, 29.1, 39.4, 55.1, 63.0, 77.4, 77.7, 78.0, 79.4, 80.6, 81.2, 110.7, 156.5.

Anal. Calcd. for $C_{21}H_{43}NO_8Si$: C, 54.16; H, 9.31, N; 3.01. Found: C, 54.18; H, 9.34, N, 3.04.

2*R*-Methyl-5*S*-hydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine (**7**).

To a solution of **19** (132 mg, 0.31 mmole) in methanol/water (9/1, 15 ml) was added Dowex 50W-X8 resin (100 mg) and stirring was continued at reflux for 24 hours and allowed to cool to room temperature. The reaction mixture was then filtered through a pad of Celite and the residue washed with ammonia solution (2*N*, 20 ml) and combined. The ammonical solution was co-evaporated with toluene azotropically to afford the crude product. The crude compound was purified by Dowex-X2 resin (OH^- form) chromatography with water to afford **7** (38 mg, 74%) as a white

solid, mp 124°; $[\alpha]_D^{20}$ -43.30 (c 0.8, water); ir (potassium bromide): 3500-3250, 2950, 1640 cm^{-1}; ^1H-^1H HMQC nmr (500 MHz, deuterium oxide): δ 3.93 (s, 1H), 3.87 (q, 1H, J = 6.5 Hz), 3.68 (dd, 1H, J = 6.2, 11.2 Hz), 3.62 (d, 1H, J = 3.6 Hz), 3.44 (t, 1H, J = 11.2 Hz), 3.15-3.12 (m, 1H), 1.18 (d, 3H, J = 6.6 Hz); ^{13}C nmr (deuterium oxide): δ 18.2, 47.9, 69.1, 72.4, 73.0, 74.1.

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