Simple Synthesis of (−)-Deoxymannojirimycin and (2*S*,3*R*,4*R*,5*R*)-3,4,5-Trihydroxypipecolic Acid *via* Regioselective Hydrolysis

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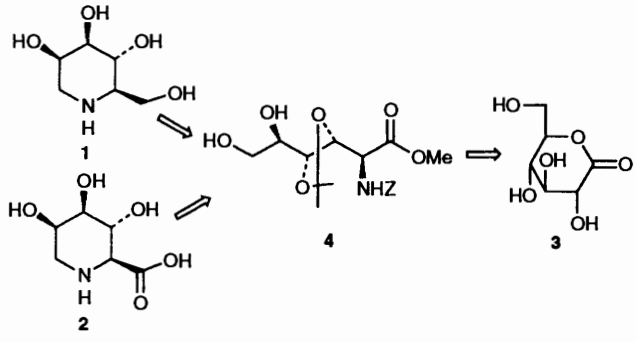
A short and efficient synthesis of (−)-deoxymannojirimycin and (2*S*,3*R*,4*R*,5*R*)-3,4,5-trihydroxypipecolic acid is described with D-glucono-δ-lactone as chiral educt. Key transformations included selective cleavage of a terminal isopropylidene group with Dowex 50W-X8 (H^+) and intramolecular nucleophilic amination.

Deoxymannojirimycin **1**, isolated from *Lonchocapus seciceus*,[1] has been shown to be potent as a specific inhibitor of both a glucoprotein-processing mannosidase[2] and a bovine α-L-fucosidase.[3] Since the first reported[4] synthesis of compound **1**, several synthetic strategies[5] have been developed to obtain this valuable compound economically. Although they have proven to be useful methods, they all suffer the disadvantage of either including non-stereoselective steps[5c,d] or else they have low overall yields (1–28%) owing to their tedious number of steps. (2*S*,3*R*,4*R*,5*S*)-3,4,5-Trihydroxypipecolic acid,[6] isolated from seeds of *Raphia racemosa*,[6] has shown to be a glucuronidase and iduronidase inhibitor,[7] and this encouraged us to synthesis of its C-5-epimer **2**.

Our objective was to develop a short and efficient route to the preparation of enantiomerically pure compounds **1** and **2**. We also report herein a selective hydrolysis of a terminal isopropylidene group. The selective derivatization in multihydroxy functionalities of similar reactivity is of great importance in carbohydrate chemistry. Our general retrosynthesis of deoxymannojirimycin **1** and of (2*S*,3*R*,4*R*,5*R*)-3,4,5-trihydroxypipecolic acid **2** is outlined in Scheme 1. It begins with the very cheap D-glucono-δ-lactone **3** and proceeds *via* intramolecular nucleophilic amination.



Scheme 1

Results and Discussion

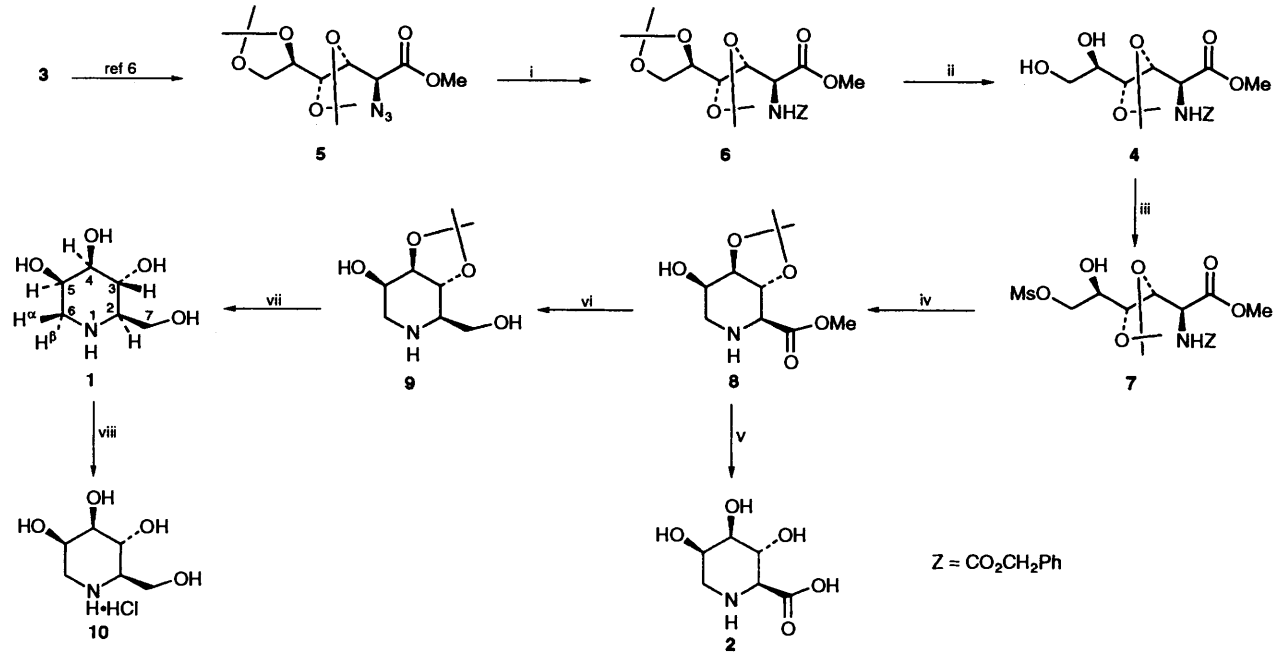
As our chiral educt we chose manno azide **5** which has four stereocentres in the same absolute stereochemistry as required for C-2, C-3, C-4 and C-5 in target molecules **1** and **2**. The manno azide **5** was synthesized in three easy steps from lactone **3** as described[8] and was then hydrogenated in the presence of palladium on charcoal. The corresponding amine was protected as its benzyloxycarbonyl (Z) derivative **6** in quantitative yield.

The terminal isopropylidene group was selectively cleaved by treatment of mannonate **6** with Dowex 50W-X8 resin (H^+-form) in 90% methanol to give, easily, the crystallized diol **4** as the required key intermediate for the synthesis of the hydroxylated alkaloid (Scheme 2). Although normal acidic catalysts such as HCl, HBr, CF_3CO_2H (TFA) and AcOH[5b,e,9] have been found to be acceptable reagents for selective hydrolysis of terminal isopropylidene groups, depending on the particular diisopropylidene derivative to be hydrolysed there are still not enough useful hydrolytic reagents available. As shown in Table 1 Dowex 50W-X8, a heterogeneous catalyst, was a much more efficient catalyst for selective cleavage of the isopropylidene derivative containing an α-amino group. The procedure for hydrolysis is remarkably simple and mild. The primary hydroxy group was selectively mesylated by reaction of diol **4** with mesyl chloride at 0 °C to give mesyl ester **7** in 78% yield. Hydrogenolysis of compound **7** in the presence of palladium on charcoal and sodium acetate removed the Z group and led to direct intramolecular nucleophilic amination to give the piperidine ring **8** in quantitative yield. Reduction of the ester **8** with $LiAlH_4$ (LAH) gave diol **9** in 93% yield. The remaining isopropylidene group was removed by treatment of ketal **9** with Dowex 50W-X8 in methanol to give the free base form of deoxymannojirimycin **1** without the need for additional ion-exchange chromatography. The stereochemistry and clear characterization (^1H NMR spectroscopy) of product **1** was established by a 2D-COSY experiment. By treatment of compound **1** with conc. HCl, followed by removal of the solvent and recrystallization from methanol–diethyl ether, an analytically pure sample of deoxymannojirimycin hydrochloride **10** was obtained. The (2*S*,3*R*,4*R*,5*R*)-3,4,5-trihydroxypipecolic acid **2** was easily obtained by treatment of ketal ester **8** with Dowex 50W-X8 in THF–water in nearly quantitative yield without the necessity of additional ion-exchange chromatography.

In summary, we have achieved an efficient synthesis of both (−)-deoxymannojirimycin and (2*S*,3*R*,4*R*,5*R*)-3,4,5-trihydroxypipecolic acid in above 60% overall yield from manno azide **4**. We also report an improved selective hydrolysis of a terminal isopropylidene group.

Experimental

General.—Dowex 50W-X8 was purchased from Sigma Chemical Co. All non-aqueous reactions were carried out under nitrogen. Tetrahydrofuran (THF) was distilled from Na/benzophenone; methanol was distilled from Mg; acetonitrile, 2,2-dimethoxypropane, dimethylformamide (DMF) and methylene dichloride were distilled from CaH_2. Column chromatography was carried out using 230–400 mesh silica gel. M.p.s were measured on a Thomas-Hoover Capillary Apparatus and are uncorrected. Proton and carbon NMR spectra were measured downfield relative to tetramethylsilance in $CDCl_3$ unless otherwise noted (values in ppm); coupling constants are reported in Hz; ^1H NMR, ^{13}C NMR and 2D-COSY experiments were conducted on a Bruker ARX-300



Scheme 2 *Reagents:* i, Pd–C, H_2, Z-Cl, K_2CO_3; ii, Dowex 50W-8X, 90% MeOH; iii, MsCl, Et_3N, CH_2Cl_2; iv, Pd–C, H_2, AcONa; v, Dowex 50W-8X, aq. THF; vi, LAH, THF; vii, Dowex 50W-8X, MeOH; viii, HCl

Table 1 Selective hydrolysis of compound **6** with various acid catalysts[a]

Entry	Catalyst	Solvent	Reaction time (t/h)	Recovery of starting material[b] (%)	Yield[c] (%)
1	HCl	MeOH	4	25	58
2	HCl	Et_2O	7	15	72
3	HBr	MeOH	4	20	62
4	TFA	1,4-Dioxane	7	35	47
5	TFA	MeOH	10	27	51
6	AcOH	MeOH–water[d]	12	30	45
7	Dowex	MeOH	5 days	trace	92
8	Dowex	90% MeOH	16	trace	95

[a] All reactions were carried out at room temperature. [b] When lower- and higher-R_f spots than that of product **6** appear on TLC in significant amounts, the reactions were stopped. If the reaction time is lengthened or the temperature raised further to consume all the starting material, yields were severely diminished. [c] Isolated yields. [d] MeOH–water (1:1).

spectrometer. Elemental analyses were carried out by the Korea Research Institute of Chemical Technology. Final solutions before evaporation were dried over anhydrous Na_2SO_4.

Methyl 2-Azido-2-deoxy-3,4;5,6-di-O-isopropylidene-D-mannonate **5**.—This was prepared as described.[8]

Methyl 2-Benzyloxycarbonylamino-2-deoxy-3,4;5,6-di-O-isopropylidene-D-mannonate **6**.—A solution of manno azide **5** (3.5 g, 11.1 mmol) in EtOAc (30 cm^3) was hydrogenated over 10% palladium on charcoal (350 mg) at atmospheric pressure for 6 h. The mixture was filtered, and concentrated under reduced pressure. To a solution of the oily residue in CH_2Cl_2 (30 cm^3) was added aq. Na_2CO_3 (2.35 g, 22.2 mmol in 20 cm^3), and the mixture was cooled in an ice-bath. To this stirred, mixed-phase solution was added dropwise a solution of benzyl chloroformate (2.46 g, 14.4 mmol) in CH_2Cl_2 (20 cm^3), and the mixture was then stirred at room temperature for 30 min. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 cm^3). The combined organic phase was washed successively with water and brine, dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane–EtOAc (3:1)] to give *compound* **6** (4.51 g, 93%), as an oil, $[\alpha]_D^{20}$ +19.8 (*c* 1.8, $CHCl_3$); δ_H 1.28 (3 H, s), 1.33 (3 H, s), 1.35 (3 H, s), 1.40 (3 H, s), 3.35 (3 H, s), 3.94–4.01 (3 H, m), 4.13–4.19 (2 H, m), 5.56 (1 H, dd, *J* 6.9 and 5.7), 5.12 (2 H, d, *J* 4.2), 5.80 (1 H, br s) and 7.32 (5 H, m, ArH); δ_C 25.2, 26.6, 26.8, 27.2, 52.4, 56.5, 67.1, 67.8, 76.6, 78.8, 80.8, 110.1, 110.5, 128.1, 128.2, 128.5, 136.2, 155.8 and 170.2 (Found: C, 59.7; H, 6.9; N, 3.3. $C_{21}H_{29}NO_8$ requires C, 59.6; H, 6.9; N, 3.3%).

Methyl 2-Benzyloxycarbonylamino-2-deoxy-3,4-O-isopropylidene-D-mannonate **4**.—To a solution of mannonate **6** (3.8 g, 9 mmol) in 90% MeOH was added Dowex 50W-X8 resin (4 g). The reaction mixture was stirred for 16 h at room temperature, then was filtered, and the filtrate was evaporated. The crude residue was chromatographed on silica gel [hexane–EtOAc (1:1, then 1:5)] to give *compound* **4** (3.3 g, 95%) as a solid, m.p. 101–103 °C; $[\alpha]_D^{20}$ +46.4 (*c* 1.65, $CHCl_3$); δ_H 1.33 (3 H, s), 1.35 (3 H, s), 3.58–3.87 (3 H, m), 3.79 (3 H, s), 4.09 (1 H, dd, *J* 7.8 and 7.6), 4.23 (1 H, dd, *J* 7.8 and 3.0), 4.68 (1 H, m), 5.12 (2 H, s), 6.0 (1 H, br s) and 7.33 (5 H, m); δ_C 26.7, 27.1, 52.2, 56.3, 64.0, 67.3, 73.4, 77.5, 81.2, 110.4, 128.1, 128.3, 128.5, 136.0, 156.3 and 169.8 (Found: C, 56.6; H, 6.7; N, 3.5. $C_{18}H_{25}NO_8$ requires C, 56.4; H, 6.6; N, 3.6%).

Methyl 2-Benzyloxycarbonylamino-2-deoxy-3,4-O-isopropylidene-6-O-methanesulfonyloxy-D-mannonate **7**.—To a solution of diol **4** (1.5 g, 3.9 mol) in CH_2Cl_2 (30 cm^3) at 0 °C was added triethylamine (435 mg, 4.3 mmol), and then dropwise, over a period of 10 min *via* a syringe pump, a solution of methanesulfonyl chloride (492 mg, 4.3 mmol) in CH_2Cl_2 (10 cm^3). The reaction mixture was stirred for an additional 10 min at 0 °C, then was quenched with saturated aq. Na_2CO_3 (20 cm^3). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 cm^3). The combined organic phase was washed successively with water and brine, dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel [CH_2Cl_2–EtOAc (6:1)] to give *compound* **7** (1.40 g, 78%) as an oil, $[\alpha]_D^{20}$ +51.2 (*c* 1.3, $CHCl_3$); δ_H 1.32 (3 H, s), 1.34 (3 H, s), 3.09 (3 H, s), 3.80 (3 H, s), 3.91 (1 H, m), 4.06 (1 H, m), 4.20 (1 H, dd, *J* 7.8 and 2.4), 4.33 (1 H, dd, *J* 11 and 2.7), 4.51 (1 H, dd, *J* 11.1 and 2.1), 4.68 (1 H, m), 5.14 (2 H, d, *J* 1.5), 5.98 (1 H, br s) and 7.35 (5 H, m); δ_C 26.8, 27.1, 37.5, 52.6, 56.0, 67.4, 71.5, 72.0, 76.5, 77.5, 82.1, 110.9, 128.2, 128.4, 128.6, 135.9, 156.3 and 169.2 (Found: C, 49.6; H, 5.9; N, 2.9. $C_{19}H_{27}NO_{10}S$ requires C, 49.4; H, 5.9; N, 3.0%).

(2S,3R,4R,5R)-*Methyl 2,6-Dideoxy-2,6-imino-3,4-O-isopropylidene-D-mannonate* **8**.—A mixture of mesyl ester **7** (780 mg, 1.69 mmol), sodium acetate (680 mg, 8.4 mmol) and 10% palladium on charcoal (100 mg) in MeOH (15 cm^3) was hydrogenated at atmospheric pressure for 10 h. The catalyst was filtered off, the filtrate was refluxed for 1 h, the MeOH was evaporated off, and water (10 cm^3) was added. By the addition of 1 mol dm^{-3} NaOH, the pH was adjusted to 12–13 and the aqueous solution was extracted with CH_2Cl_2–Pr^iOH (5 × 20 cm^3). The combined organic phases were dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel [$CHCl_3$–Pr^iOH (8:1)] to give *compound* **8** (371 mg, 95%) as a solid, m.p. 156–158 °C; $[\alpha]_D^{20}$ −13.7 (*c* 0.9, $CHCl_3$); δ_H 1.43 (3 H, s), 1.46 (3 H, s), 2.73 (1 H, dd, *J* 14.7 and 2.4, 6-H^β), 3.20 (1 H, dd, *J* 14.7 and 2.4, 6-H^α), 3.43–3.49 (2 H, m), 3.792 (1 H, m), 3.798 (3 H, s) and 4.25 (1 H, m); δ_C 26.6, 26.8, 49.1, 52.5, 61.2, 67.5, 72.6, 80.7, 109.4 and 171.2 (Found: C, 51.8; H, 7.5; N, 6.1. $C_{10}H_{17}NO_5$ requires C, 51.9; H, 7.4; N, 6.1%).

(2R,3R,4R,5R)-1,4-*Dideoxy-1,6-imino-3,4-O-isopropylidene-D-mannitol* **9**.—To an ice-cooled solution of the ester **8** (230 mg, 0.99 mmol) in THF (10 cm^3) was added $LiAlH_4$ (75 mg, 1.98 mmol). The reaction mixture was warmed to room temperature, stirred for 3 h, and then quenched by the sequential addition of water (75 mm^3), 15% aq. NaOH (75 mm^3), and water (225 mm^3). The mixture was filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel [$CHCl_3$–Pr^iOH (3:1)] to give *compound* **9** (188 mg, 93%) as a solid, m.p. 137–139 °C; $[\alpha]_D^{20}$ −18.2 (*c* 0.2, $CHCl_3$); δ_H 1.43 (3 H, s), 1.45 (3 H, s), 2.75 (1 H, dd, *J* 14.4 and 1.3, 7-H^β), 2.82 (1 H, m), 3.18 (1 H, dd, *J* 14.4 and 1.8, 7-H^α), 3.45 (1 H, dd, *J* 9 and 2.4, 6-H^β), 3.67–3.73 (2 H, m), 3.83 (1 H, dd, *J* 9 and 3.3, 6-H^α) and 4.28 (1 H, m); δ_C 26.7, 26.9, 49.6, 60.5, 62.5, 67.3, 71.7, 77.5, 80.9 and 109.3 (Found: M^+, 203.1163. $C_9H_{17}NO_4$ requires M, 203.1158).

(−)-*Deoxymannojirimycin* **1**.—A solution of compound **9** (110 mg, 0.54 mmol) and Dowex 50W-X8 (110 mg) in MeOH was refluxed for 3 h. The mixture was filtered, and then was washed with MeOH. The remaining residue was eluted with 2 mol dm^{-3} NH_4OH. The ammoniacal solution was evaporated, then co-evaporated with toluene to give compound **1** (85 mg, 97%), m.p. 183–185 °C; $[\alpha]_D^{20}$ −36.2 (*c* 0.342, MeOH) {lit.,[5b] m.p. 185–187 °C; $[\alpha]_D^{20}$ −26.7 (*c* 0.3, MeOH)}; δ_H(D_2O; assignments made by ^1H–^1H COSY) 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 (1 H, dd, *J* 14.3 and 2.7, 6-H^α), 3.58 (1 H, dd, *J* 9.1 and 2.6, 4-H), 3.64 (1 H, dd, *J* 9.2 and 9.1, 3-H), 3.80 (2 H, d, *J* 3.9, 7-H_2) and 4.03 (1 H, m, 5-H); δ_C 50.9, 63.13, 63.33, 70.9, 71.7 and 77.2.

(−)-*Deoxymannojirimycin Hydrochloride* **10**.—To the free base **1** was added conc. HCl. The mixture was evaporated, then co-evaporated with toluene. The crystalline residue was recrystallized from methanol–diethyl ether. ^1H and ^{13}C NMR data were consistent with those reported,[1,5] m.p. 178–181 °C; $[\alpha]_D^{20}$ −9.2 (*c* 0.34, water) {lit.,[5e] m.p. 175–180 °C; $[\alpha]_D^{20}$ −10.9 (*c* 0.3, water)} (Found: C, 35.9; H, 7.2; N, 6.9. Calc. for $C_6H_{14}ClNO_4$: C, 36.1; H, 7.1; N, 7.0%).

(2S,3R,4R,5R)-3,4,5-*Trihydroxypipecolic Acid* **2**.—A solution of compound **8** (90 mg, 0.39 mmol) and Dowex 50W-X8 (120 mg) in THF–water (3:1) was refluxed overnight. The mixture was filtered, and then was washed with MeOH. The remaining residue was eluted with 2 mol dm^{-3} NH_4OH. The ammoniacal solution was evaporated, then co-evaporated with toluene to give the *acid* **2** (61 mg, 89%), m.p. 207–210 °C (decomp.); $[\alpha]_D^{20}$ +21 (*c* 0.72, water); δ_C(D_2O; 200 MHz) 3.08 (1 H, dd, *J* 13.6 and 1.96, 6-H^β), 3.30 (1 H, dd, *J* 13.6 and 4.0, 6-H^α), 3.36 (1 H, d, *J* 9.2, 2-H), 3.68 (1 H, dd, *J* 8.8 and 3.1, 4-H), 3.98 (1 H, dd, *J* 9.0 and 9.0 C-H) and 4.14 (1 H, m, 5-H); δ_C(D_2O; 50 MHz) 61.0, 76.6, 80.9, 83.3, 87.1 and 187.9 (Found: M^+, 177. 0639. $C_6H_{11}NO_5$ requires M, 177.0637).

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