

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

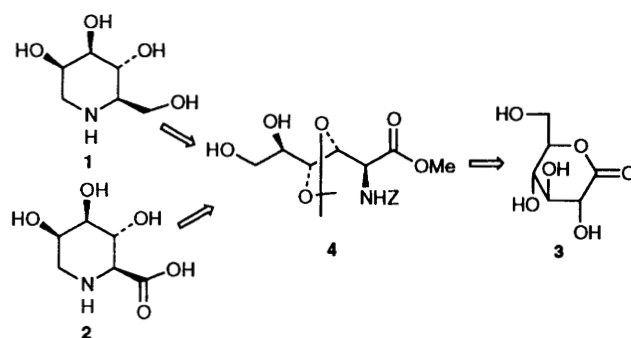
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A short and efficient synthesis of (–)-deoxymannojirimycin and (2*S*,3*R*,4*R*,5*R*)-3,4,5-trihydroxypipicollic acid is described with D-glucono-δ-lactone as chiral educt. Key transformations included selective cleavage of a terminal isopropylidene 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 mannosidase² and a bovine α-L-fucosidase.³ Since the first reported⁴ synthesis of compound **1**, several synthetic strategies⁵ 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-Trihydroxypipicollic 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 multi-hydroxy 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-trihydroxypipicollic 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 described⁸ 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.

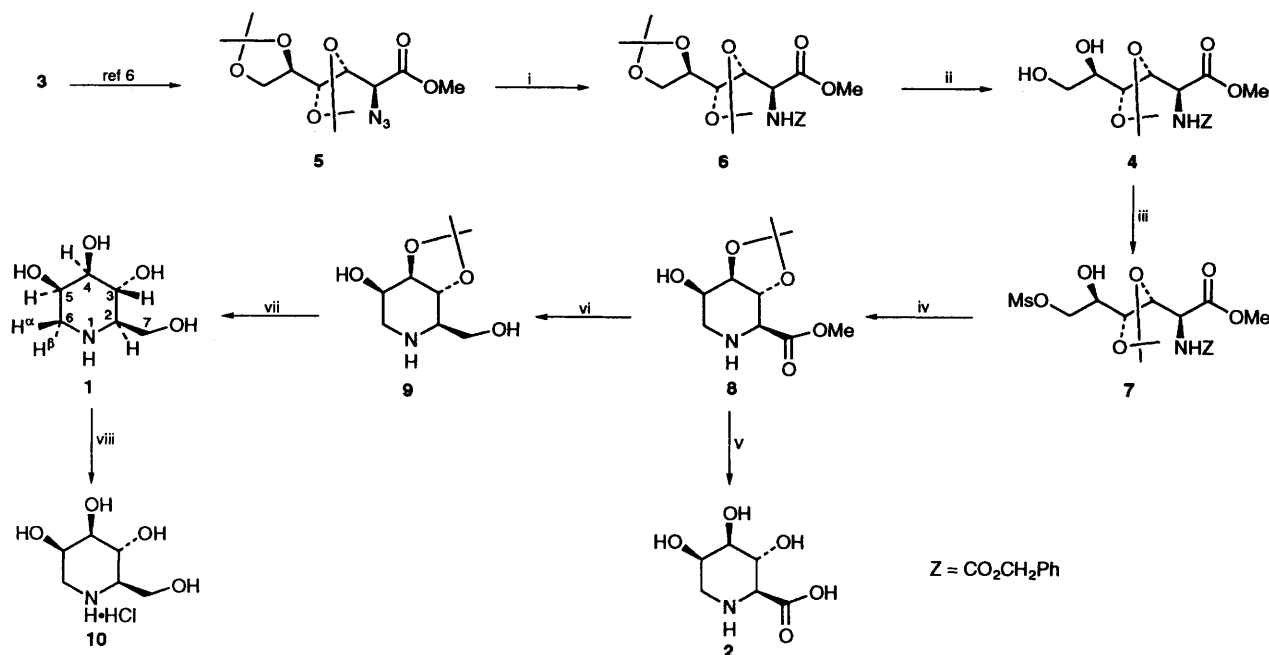
The terminal isopropylidene group was selectively cleaved by treatment of mannonate **6** with Dowex 50W-X8 resin (H⁺-form) in 90% methanol to give, easily, the crystallized diol **4** as the required key intermediate for the synthesis of the hydroxylated alkaloid (Scheme 2). Although normal acidic catalysts such as HCl, HBr, CF₃CO₂H (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 LiAlH₄ (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-trihydroxypipicollic 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-trihydroxypipicollic 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 CaH₂. 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 tetramethylsilane in CDCl₃ unless otherwise noted (values in ppm); coupling constants are reported in Hz; ¹H NMR, ¹³C NMR and 2D-COSY experiments were conducted on a Bruker ARX-300



Scheme 2 Reagents: i, Pd-C, H₂, Z-Cl, K₂CO₃; ii, Dowex 50W-8X, 90% MeOH; iii, MsCl, Et₃N, CH₂Cl₂; iv, Pd-C, H₂, 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 ₂ O	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 Na₂SO₄.

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

Methyl 2-Benzoyloxycarbonylamino-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 cm³) 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 CH₂Cl₂ (30 cm³) was added aq. Na₂CO₃ (2.35 g, 22.2 mmol in 20 cm³), 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 CH₂Cl₂ (20 cm³), and the mixture was then stirred at room temperature for 30 min. The organic phase was separated and the aqueous phase was extracted with CH₂Cl₂ (2 × 20 cm³). 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, [α]_D²⁰ +19.8 (*c* 1.8, CHCl₃); 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. C₂₁H₂₉NO₈ requires C, 59.6; H, 6.9; N, 3.3%).

Methyl 2-Benzoyloxycarbonylamino-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; [α]_D²⁰ +46.4 (*c* 1.65, CHCl₃); 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. C₁₈H₂₅NO₈ requires C, 56.4; H, 6.6; N, 3.6%).

Methyl 2-Benzoyloxycarbonylamino-2-deoxy-3,4-O-isopropylidene-6-O-methanesulfonyloxy-D-mannonate 7.—To a solution of diol **4** (1.5 g, 3.9 mmol) 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 ($2 \times 20 \text{ cm}^3$). 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, $[\alpha]_{\text{D}}^{20} +51.2$ (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. $\text{C}_{19}\text{H}_{27}\text{NO}_{10}\text{S}$ 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 –PrⁱOH ($5 \times 20 \text{ cm}^3$). The combined organic phases were dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel [CHCl_3 –PrⁱOH (8:1)] to give **compound 8** (371 mg, 95%) as a solid, m.p. 156–158 °C; $[\alpha]_{\text{D}}^{20} -13.7$ (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^B), 3.20 (1 H, dd, J 14.7 and 2.4, 6-H^A), 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. $\text{C}_{10}\text{H}_{17}\text{NO}_5$ 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 –PrⁱOH (3:1)] to give **compound 9** (188 mg, 93%) as a solid, m.p. 137–139 °C; $[\alpha]_{\text{D}}^{20} -18.2$ (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^B), 2.82 (1 H, m), 3.18 (1 H, dd, J 14.4 and 1.8, 7-H^A), 3.45 (1 H, dd, J 9 and 2.4, 6-H^B), 3.67–3.73 (2 H, m), 3.83 (1 H, dd, J 9 and 3.3, 6-H^A) 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. $\text{C}_9\text{H}_{17}\text{NO}_4$ 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; $[\alpha]_{\text{D}}^{20} -36.2$ (c 0.342, MeOH) [lit.,^{5b} m.p. 185–187 °C; $[\alpha]_{\text{D}}^{20} -26.7$ (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^B), 3.04 (1 H, dd, J 14.3 and 2.7, 6-H^A), 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-H₂) 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; $[\alpha]_{\text{D}}^{20} -9.2$ (c 0.34, water) [lit.,^{5e} m.p. 175–180 °C; $[\alpha]_{\text{D}}^{20} -10.9$ (c 0.3, water)] (Found: C, 35.9; H, 7.2; N, 6.9. Calc. for $\text{C}_6\text{H}_{14}\text{ClNO}_4$: C, 36.1; H, 7.1; N, 7.0%).

(2S,3R,4R,5R)-3,4,5-Trihydroxypipicollic 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.); $[\alpha]_{\text{D}}^{20} +21$ (c 0.72, water); δ_{C} (D_2O ; 200 MHz) 3.08 (1 H, dd, J 13.6 and 1.96, 6-H^B), 3.30 (1 H, dd, J 13.6 and 4.0, 6-H^A), 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. $\text{C}_6\text{H}_{11}\text{NO}_5$ requires M, 177.0637).

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