CHIROSPECIFIC SYNTHESIS OF 2*R*,5*S*-DIHYDROXYMETHYL-3*R*,4*R*-DIHDROXYPYRROLIDINE

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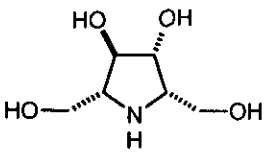
Abstract- 2*R*,5*S*-dihydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine (**1**) has been prepared from *D*-glucosamic acid which has four stereocenters in the same absolute stereochemistry as required for **1**.

Many polyhydroxylated alkaloids are important sugar analogues in which the ring oxygen atom is replaced by the nitrogen functionality. These natural and synthetic polyhydroxylated aza sugar have displayed inhibitor of glucosidase and manosidase.[1,2] There is growing interest in synthetic methodologies towards polyhydroxylated pyrrolidine since 2*R*,5*R*-dihydroxymethyl-3*R*,4*R*-dihydoxypyrrolidine (**2**), isolated from *Derris ellipica*[3] has been shown to be a potent inhibitor of viral glucoprotein processing glucosidase.[4] Among compound (**2**) derivatives or epimers, 2*R*,5*S*-dihydroxymethyl-3*R*,4*R*-dihydoxypyrrolidine (**1**) which is C-5-epimer of **2**, is a potent inhibitor of a number of glucosidase.[5a] This valuable compound (**1**) has been easily prepared from 1,4-butenediol or 5-keto-D-fructose *via* chemical and enzymatic procedures.[5] These procedures have overcome the problem of diasteroselectivity, but still may has the disadvetage of being nonenantioselective.



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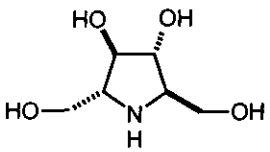

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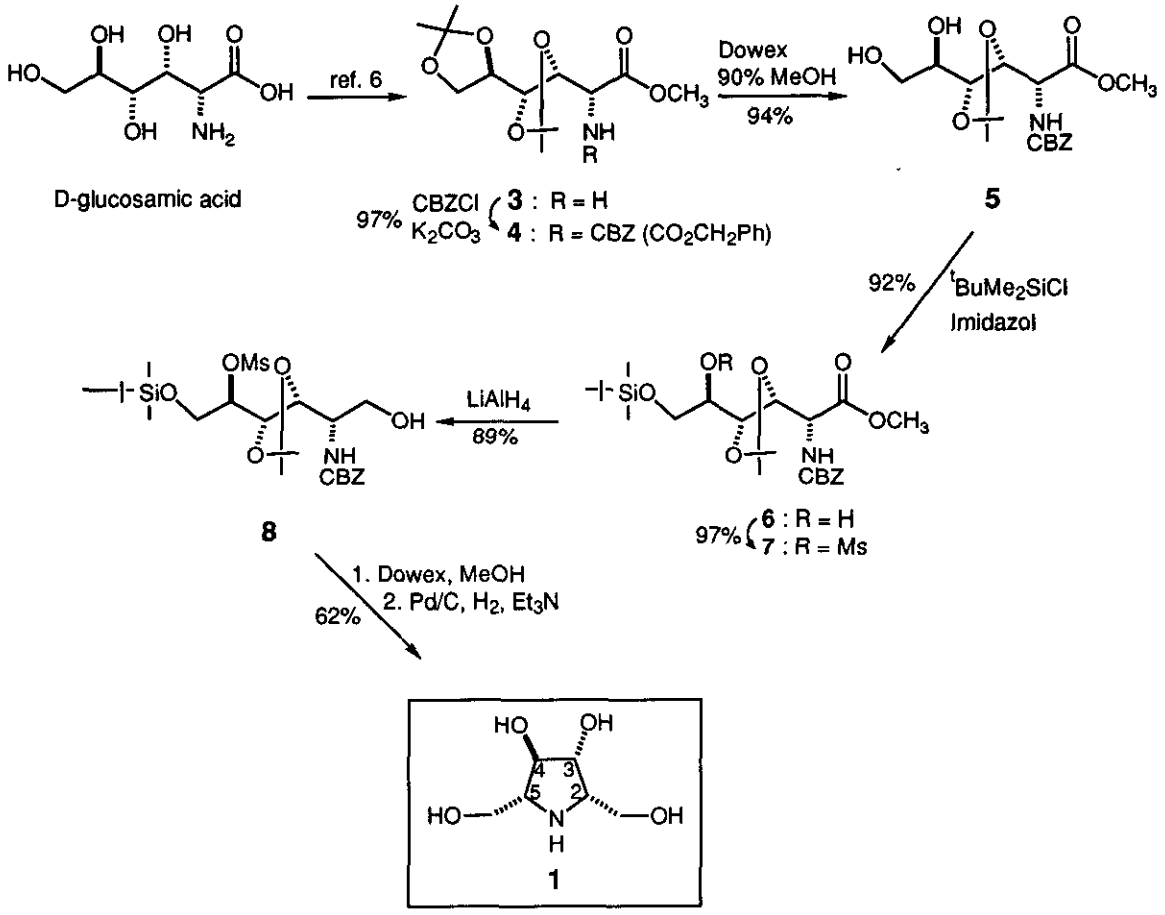
Our objective is to develop a short and efficient route to prepare enantimerically pure **1**. As our chiral educt we choose glucosamic acid which has all four stereocenters in the same absolute stereochemistry as required for C-2, C-3, C-4 and C-5 in **1**. The main feature of this method is selective hydrolysis of terminal isopropylidine group[7] and intramolecular nucleophilic amination (Scheme 1).

The gluconate (**3**) was synthesized readily and in high yield from glucosamic acid as described[6] and was treated under standard condition for introducing the benzyloxycarbonyl group, and the resulting ester (**4**), a stable and crystalline compound, was obtained in 74% yield from glucosamic acid. The diisopropylidine gluconate (**4**) was exposed to 110 w/w% of Dowex 50W-X8 resin (H^+ form) in 90% methanol, and

terminal isopropylidine group was selectively hydrolyzed in excellent yield. This highly selectivity is believed to be due to bounded protons and steric effect of heterogeneous catalyst (Dowex-X8).[7a]



Scheme 1

The primary hydroxy group of **5** was selectively protected with *t*-butyldimethylsilyl chloride followed by mesylation of corresponding silylate **6** with mesyl chloride gave mesylate (**7**) in 89% yield from **5**. Simply reduction of **6** with $LiAlH_4$ in THF gave alcohol (**8**) in 89% yield. The remaining isopropylidene and *t*-butyldimethysilyl groups of **8** were easily removed by treatment of alcohol (**8**) with Dowex 50W-X8 in methanol. Subsequent hydrogenolysis of corresponding benzylcarbarmate in the presence of palladium on charcoal and triethylamine removed the benzyloxycarbonyl group and led to direct neucleophilic amination to afford **1** in 62% yield from **8**. Its physical and spectral properties correlated well with previous reported.[5]

EXPERMENTAL

General. Dowex 50W-X8 was purchased from Sigma Chemical Co. All non-aqueous reaction were carried out under an inert nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from

Na/benzophenone; acetonitrile, 2,2-dimethoxypropane, dimethylformamide (DMF), and methylene chloride were distilled from CaH_2. Column chromatography was carried out using 230-400 mesh silica gel. Mps were measured on Thomas-Hoover Capillary Apparatus and are uncorrected. Specific rotation values were measured on JASCO DIP-370 polarimeter. Proton and carbon nmr spectra were measured down field relative to tetramethyl silane in $CDCl_3$ unless otherwise noted (value in ppm); ^{1}H-nmr, ^{13}C-nmr were conducted on 200-, 300-, or 400 MHz spectrometer. The elemental analysis was carried out by the Korea Research Institute of Chemical Technology. Final solutions before evaporation were dried over anhydrous Na_2SO_4.

Methyl 2-Amino-2-deoxy-3,4;5,6-di-*O*-isopropylidene-*D*-gluconate (3) This was prepared as described.[6]

Methyl 2-Benzyloxycarbonylamino-2-deoxy-3,4;5,6-di-*O*-isopropylidene-*D*-gluconate(4) To a solution of gluconate (**3**) (1.6 g, 5.5 mmol) in CH_2Cl_2 (20 ml) was added aq. Na_2CO_3 (1.1 g, 10.1 mmol), and the mixture was cooled in an ice bath. To this stirred, mixed-phase solution was added dropwise a solution of benzyl chlroformate (1.22 g, 7.2 mmol) in CH_2Cl_2 (10 ml), and the mixture was then stirred at room temperature for 30 min. The organic phase was separated and aqueous phase was extracted with CH_2Cl_2 (2 x 20 ml). The combined organic phase was washed successively with water and brine, dried, and evaporated. The residue was chromatographed on silica gel [hexane-EtOAc (4:1)] to give **4** (2.26 g, 97%), as a solid; mp 74-76°C; $[\alpha]_D^{23}$ + 8.04° (c 1.12, $CHCl_3$); ^{1}H nmr (200 MHz) δ 1.35 (s, 6H), 1.38 (s, 3H), 1.43 (s, 3H), 3.75 (m, 1H), 3.79 (s, 3H), 3.98 (m, 1H), 4.10 (m, 1H), 4.44 (m, 1H), 4.71 (m, 1H), 5.13 (d, J = 2.1, 2H), 5.53 (d, J = 10, 1H), 7.36 (m, 5H); ^{13}C nmr (100 MHz) δ 25.4, 26.7, 27.1, 27.14, 52.9, 54.3, 54.8, 67.4, 67.9, 68.0, 77.3, 79.5, 79.7, 110.2, 110.4, 128.3, 128.4, 128.6, 128.8, 136.4, 156.6, 171.1; Anal. Calcd for $C_{21}H_{29}NO_8$: C, 59.56; H, 6.90; N, 3.31. Found: C, 59.38; H, 6.87; N, 3.34.

Methyl 2-Benzyloxycarbonylamino-2-deoxy-3,4-*O*-isopropylidene-*D*-gluconate (5) To a solution of diisopropylidene gluconate (**4**) (1.9 g, 4.5 mmol) in 90% MeOH was added Dowex 50W-X8 resin (2.1 g). The reaction mixture was stirred for 52 h at room temperature, then was filtered, and filtrate was evaporated. The crude residue was chromatographed on silica gel [hexane-EtOAc (1:1, then 1:5)] to give 5 (1.6 g, 93%), as a sticky oil; $[\alpha]_D^{23}$ -20.2° (c 1.14, $CHCl_3$); ^{1}H nmr (200 MHz) δ 1.35 (s, 6H), 2.48 (br s, 1H, OH), 3.31 (br s, 1H, OH), 3.72-4.17 (m, 4H), 3.78 (s, 3H), 4.47 (m, 1H), 4.73 (m, 1H), 5.13 (d, J = 3.2, 2H), 5.75 (d, J = 9.0, 1H, NH), 7.36 (m, 5H); ^{13}C nmr (100 MHz) δ 26.6, 26.8, 26.9, 52.9, 54.5, 64.1, 67.6, 73.2, 76.0, 76.8, 79.4, 109.7, 128.2, 128.4, 128.6, 135.8, 157.1, 170.4; Anal. Calcd for $C_{18}H_{25}NO_8$: C, 56.39; H, 6.57; N, 3.65. Found: C, 56.48; H, 6.32; N, 3.64.

Methyl 2-Benzyloxycarbonylamino-2deoxy-3,4-*O*-isopropylidene-6-*O*-(*tert*-butyldimethylsilyl)oxy-*D*-gluconate (6) To a solution of diol (**5**) (1.5 g, 3.9 mmol) in dry DMF (20 ml) was added imidazole (0.32 g, 4.7 mmol) and *tert*-butyldimethylchlorosilane (0.65 g, 4.3 mmol) at the room temperature. The reaction mixture was

stirred for 10 h at same temperature then 30 ml of sat. $NaHCO_3$ was added followed by extraction with EtOAc (3 x 50 ml). The combined organic layer was washed with water and brine, dried, and evaporated, and the crude residue was chromatographed on silica gel [hexane-EtOAc (5:1)] to give (**6**) (1.8 g, 94%) as sticky oil, $[\alpha]_D^{23}$ -9.3° (c 1.40, $CHCl_3$); ^1H nmr (200 MHz) δ 0.08 (s, 6H), 0.91 (s, 9H), 1.35 (s, 6H), 2.92 (d, J = 7.6, 1H, OH), 3.61-3.84 (m, 4H), 3.79 (s, 3H), 4,44 (dd, J_1= 1.9, J_2= 9.5, 1H), 4.80 (dd, J_1= 1.7, J_2= 9.5, 1H), 5.12 (d, J = 14.7, 2H), 5.65 (d, J = 9.3, 1H, NH), 7.36 (m, 5H); ^{13}C nmr (100 MHz) d 18.3, 25.7, 25.8, 26.7, 26.8, 27.0, 52.7, 54.4, 64.0, 67.3, 73.3, 75.0, 76.7, 80.1, 109.5, 128.1, 128.2, 128.5, 136.1, 156.5, 170.7; Anal. Calcd for $C_{24}H_{39}NO_8Si$: C, 57.92; H, 7.9; N, 2.81 Found: C, 58.12; H, 8.01; N, 2.78.

Methyl 2-Benzyloxycarbonylamino-2-deoxy-3,4-*O*-isopropylidene-5-*O*-methanesulfonyl oxy-6-*O*-(*tert*-butyldimethylsilyl)oxy-*D*-gluconate (7)

To a solution of silylate (**6**) (1.7 g, 3.0 mmol) in THF (20 ml) were added triethylamine (0.6 g, 6.0 mmol) and methanesulfonyl chloride (0.41 g, 3.6 mmol) at 0°C. After stirring for 1 h at 0°C, 20 ml of 5% citric acid was added and the mixture was extracted with EtOAc (3 x50 ml). The combined extracts were washed with brine, dried, and evaporated and the residue was chromatographed on silica gel [hexane-EtOAc (5:1)] to give **7** (1.67 g, 97%) as an oil; $[\alpha]_D^{23}$ +8.1° (c 1.48, $CHCl_3$); ^1H nmr (200 MHz) δ 0.11 (s, 6H), 0.91 (s, 9H), 1.39 (s, 6H), 3.12 (s, 3H), 3.79 (s, 3H), 3.89-4.08 (m, 3H), 4.66 (m, 1H), 4.75 (m, 2H), 5.13 (d, J = 6.7, 2H), 5.49 (d, J = 9.3, 1H, NH), 7.36 (m, 5H); ^{13}C nmr (100 MHz) δ 18.4, 25.8, 26.7, 26.9, 38.6, 52.8, 53.8, 62.8, 67.2, 75.0, 76.7, 77.3, 81.5, 110.1, 128.0, 128.2, 128.5, 136.0, 156.4, 170.3; Anal. Calcd for $C_{25}H_{41}NO_{10}SSi$: C, 52.15; H, 7.18; N, 2.43 Found: C, 52.21; H, 7.29; N, 2.51.

2-Benzyloxycarbonylamino-2-deoxy-3,4-*O*-isopropylidene-5-*O*-methanesulfonyloxy-6-*O*-(*tert*-butyldimethylsilyl)oxy-*D*-glucitol (8)

To an ice-cooled suspension of $LiAlH_4$ (0.18 g, 4.8 mmol) in THF was added a solution of ester (**7**) (1.4 g, 2.4 mmol). The reaction mixture was warmed to room temperature stirred for 3 h, and then quenched by the sequential addition of water (o.18 ml), 15% aq. NaOH (0.18 ml), and water (0.54 ml). The mixture was filtered and evaporated. The residue was chromatographed on silica gel [hexane-EtOAc (3:1)] to give (**8**) (1.17 g, 90%) as an oil; $[\alpha]_D^{23}$ +16.6° (c 1.32, $CHCl_3$); ^1H nmr (200 MHz) δ 0.10 (s, 6H), 0.91 (s, 9H), 1.40 (s, 3H), 2.17 (br s, 1H, OH), 3.12 (s, 3H), 3.65-4.13 (m, 6H), 4.41 (m, 1H), 4.70 (m, 1H), 5.11 (d, J = 5.6, 2H), 5.31 (d, J = 9.8, 1H, NH), 7.35 (m, 5H); ^{13}C nmr (100 MHz) δ 18.3, 25.8, 26.7, 26.9, 38.7, 51.6, 63.1, 64.3, 67.0, 74.8, 76.7, 78.6, 82.9, 110.2, 128.0, 128.15, 128.22, 128.5, 136.3, 156.5; Anal. Calcd for $C_{24}H_{39}NO_9SSi$: C, 52.82; H, 7.20; N, 2.57 Found: C, 52.68; H, 7.31; N, 2.51.

2*R*,5*S*-Dihydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine (1)

A solution of compound (**8**) (0.8 g, 1.5 mmol) and Dowex 50W-X8 (0.9 g) in MeOH was refluxed for 3 h. Dowex was filtered off , and then the filtrate was evaporated off. A solution of crude residue in MeOH (20 ml) was hydrogenated over 10% palladium on charcoal (80 mg) at atmospheric pressure for 3 h. The

catalyst was filtered off, and to filtrate was added triethylamine (0.37 g, 4.5 mmol). The mixture was refluxed for 2 h, and concentrated under reduced pressure. The remaining residue was chromatographed on Dowex 50W-8X (2N NH_4OH). The ammoniacal solution was evaporated, then co-evaporated with toluene to give compound (**1**) (0.15 g, 62%) as a solid; mp 140-143°C {lit.,[5b] 139-142.5°C}; $[\alpha]_D^{23}$ +16.2° (c 2.75, H_2O) {lit.,[5a] $[\alpha]_D^{20}$ +20.75°(c 4.00, H_2O)}; ^1H nmr (300 MHz, D_2O) δ 3.00 (dd, J_1 = 5.4, J_2 = 5.7, 1H), 3.31 (dd, J_1 = 5.9, J_2 = 5.7, 1H), 3.66-3.77 (m, 4H), 3.85 (m, 1H), 4.10 (m, 1H); ^{13}C nmr (75 MHz) δ 62.8, 63.2, 64.9, 67.3, 80.0, 81.8; Anal. Calcd for $C_6H_{15}NO_4$: C, 44.17; H, 8.08; N, 8.58. Found: C, 44.04; H, 7.97; N, 8.63.

REFERENCES

1. N. Asano, K. Oseki, H. Kizu, and K. Matsui, *J. Med. Chem.*, **1994**, 37, 3701.
2. (a) R. A. Gruters, J. J. Neefies, M. Tersmette, R. E. Y. de Goede, A. Tulp, H. G. Huisman, F. Miedema, and H. L. Ploegh, *Nature*, **1987**, 320, 77. (b) G. W. J. Fleet, A. Karpas, R. A. Dwek, L. E. Fellow, A. S. Tyms, S. Petersson, S. K. Namgoong, N. G. Ramsden, P.W. Smith, J. C. Son, F. Wilson, D. R.Witty, G. S.Jasco, and T. W. Rademacher, *FEBS Lett.* **1988**, 237, 128.
3. A. Walter, G. Dardenne, M. Marlier, and J. Casimir, *Phytohemistry*, **1976**, *25*, 747.
4. (a) A. D. Elbein, M. Mitchell, B. A. Sanford, L. E. Fellow, and S. V. Evans, *J. Biol. Chem.*, **1984**, *259*, 12409. (b) L. E. Fellows, *Pestic. Sci.*, **1986**, 17, 602.
5. (a) K.-C. Kevin, K. Tesuya, C. Lihren, Z. Ziyang, I. Yoshitaka, and W. Chi-Huey, *J. Org. Chem.*,**1991**, 56, 6280. (b) A. B. Reitz and E. W. Baxter, *Tetrahedron Lett.*, **1990**, 31, 6777.
6. M. A. Brook and T. H. Chan, *Synthesis*, **1983**, 201.
7. (a) K. H. Park, Y. J. Yoon, and S. G. Lee, *Tetrahedron Lett.*, **1994**, 35, 9737. (b) H. Setoi, H. Takeno, and M. Hashimoto, *J. Org. Chem.*, **1985**, 50, 3948.

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