Facile Synthesis of (2*S*,3*R*,4*R*)-2-Hydroxymethyl-3,4-pyrrolidinediol and 4-Acetamido-1,2,3-tri-*O*-acetyl-4-deoxy-L-xylopyranose from the Photoproduct of D-Mannose

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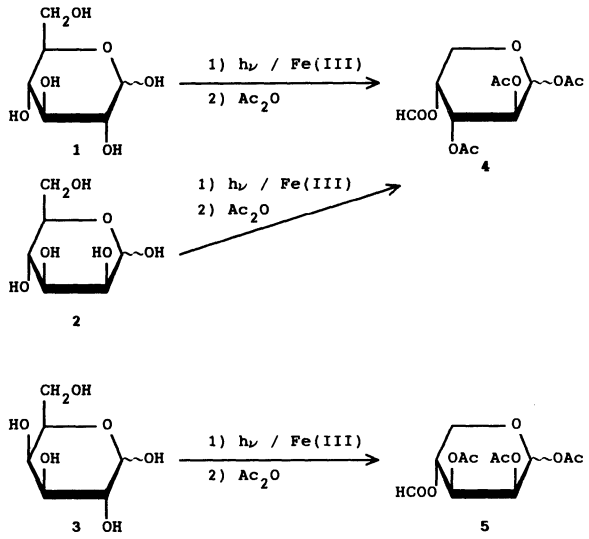
Synthesis of (2*S*,3*R*,4*R*)-2-hydroxymethyl-3,4-pyrrolidinediol and 4-acetamido-1,2,3-tri-*O*-acetyl-4-deoxy-L-xylopyranose were attained in four steps from D-mannose, using iron(III)-catalyzed photoreaction as a key reaction.

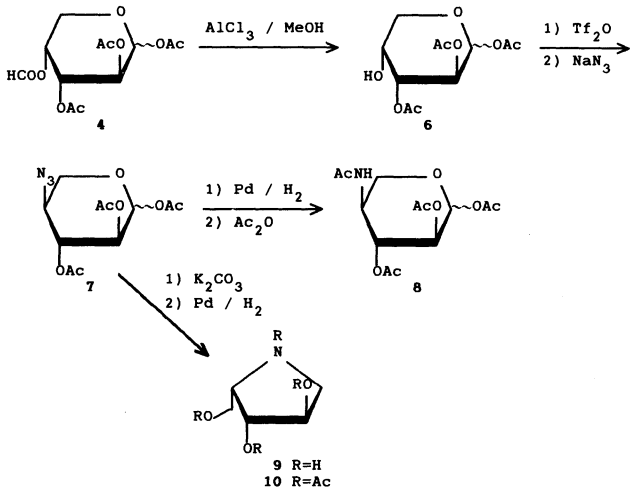
In our previous papers,[1] we reported that UV irradiation of D-glucose (**1**) or D-mannose (**2**) in the presence of iron(III) chloride followed by acetylation gave 1,2,3-tri-*O*-acetyl-4-*O*-formyl-D-arabinopyranose (**4**), while D-galactose (**3**) gave 1,2,3-tri-*O*-acetyl-4-*O*-formyl-D-lyxopyranose (**5**) under the same conditions. The most characteristic point of the reaction is that the aldohexoses produce aldopentoses in which only C4 hydroxyl group is protected by formyl group.



In order to explore the applicability of the photoproducts for synthetic purpose, we chose a pyrrolidine derivative and an amino sugar as the target compounds.

Some hydroxylated pyrrolidine derivatives have been known to possess glycosidase inhibition or immunoregulative activities.[2,3] In order to clarify the structure–bioactivity relationship, it is biologically important to prepare epimers of the bioactive molecules. Several stereoisomers of 2-hydroxymethyl-3,4-pyrrolidinediol have been synthesized.[2–6] We envisioned that (2*S*,3*R*,4*R*)-2-hydroxymethyl-3,4-pyrrolidinediol (**9**) could be synthesized quite easily by starting from our photoproduct.

In this paper we describe the facile synthesis of 4-acetamido-1,2,3-tri-*O*-acetyl-4-deoxy-L-xylopyranose (**8**) as well as **9**, using the photoproduct **4** as a key intermediate. The compounds **8** and **9** have been synthesized from 2-amino-2-deoxy-D-glucose in nine steps.[5]



Although we have utilized iron(III) chloride as the catalyst for the selective photocleavage at C1–C2 bond of the carbohydrates, the reaction was accompanied by the formation of brown material, which adhered to the inside of the vessel, causing inconvenience for the large-scale preparation. We found that iron(III) trifluoromethanesulfonate (triflate) is superior to the chloride as shown below.

A pyridine solution of D-mannose (**2**) containing iron(III) triflate or iron(III) chloride was irradiated with a high-pressure mercury lamp in a Pyrex vessel while oxygen gas was bubbled through. After the irradiation for 8 h or 24 h, the products were isolated as acetates by treating the irradiated pyridine solution with acetic anhydride. The major product was an anomeric mixture of an aldopentose derivative **4**, along with the starting material as pentaacetate. The results are shown in Table 1. Evidently iron(III) triflate catalyzed the reaction more effectively than iron(III) chloride, and no solid material separated out during the irradiation under these conditions. In view of these results, we used 1/100 equiv of iron(III) triflate

Table 1. Catalytic Activities of Iron(III) Chloride and Iron(III) Triflate

Carbohydrate	Iron salt	Mole ratio to carbohydrate	Reaction time	Relative yield/%	
			h	Product	Starting material
D-Glucose	$FeCl_3$	1	24	**4** 45	55
	$Fe(OTf)_3$	1/100	8	**4** 44	56
D-Mannose	$FeCl_3$	1	24	**4** 17	83
	$Fe(OTf)_3$	1/100	8	**4** 57	43
D-Galactose	$FeCl_3$	1	24	**5** 40	60
	$Fe(OTf)_3$	1/100	8	**5** 56	44

for the large-scale preparation.

Treatment of the crude material, obtained from **2** through the irradiation and succeeding acetylation, with aluminium chloride in aqueous methanol[1] gave 1,2,3-tri-*O*-acetyl-D-arabinopyranose (**6**) in 24% overall yield from **2** after the purification on a silica-gel chromatography. Triflation of **6** with trifluoromethanesulfonic anhydride followed by treatment with sodium azide gave 1,2,3-tri-*O*-acetyl-4-azido-4-deoxy-L-xylopyranose (**7**) in 55% yield. It has been reported that no side reactions occur under these conditions.[7]

Catalytic hydrogenation of **7** followed by acetylation gave **8** in 27% yield. Deacetylation of **7** with potassium carbonate in methanol followed by catalytic hydrogenation gave **9** in 77% yield, after purification on an ion-exchange chromatography. Acetylation of **9** gave tetraacetate **10** in 55% yield. Treatment of the acetate with hydrochloric acid afforded the corresponding hydrochloride in 83% yield. The ^{13}C NMR spectrum of the hydrochloride was identical with that reported for its enantiomer.[6]

Experimental

General. Column chromatography was performed on Wakogel C-200 (Wako), and TLC was performed on Kieselgel 60 GF_{254} (Merck). ^1H NMR spectra (60 MHz) were recorded on a Hitachi R-24 spectrometer. ^1H NMR (90 MHz) and ^{13}C NMR spectra were measured on a Hitachi R-90H spectrometer, high-resolution mass spectra on a JEOL DX-300 mass spectrometer, IR spectra on a Shimadzu IR-400 spectrometer, and optical rotations on a JASCO DIP-4 polarimeter.

The irradiations were carried out using a high-pressure mercury lamp [Sen SL-2000 (2 kW)] at the temperature of running water.

1,2,3-Tri-*O*-acetyl-D-arabinopyranose (6). A pyridine solution (900 cm^3) of D-mannose (9 g, 50.0 mmol) and iron(III) triflate (252 mg, 5.01×10^{-1} mmol) was irradiated in a Pyrex vessel for 8 h while oxygen gas was bubbled through. Acetic anhydride (70 cm^3, 0.742 mmol) was added to the solution, and the solution was stirred for 14 h at room temp. The solution was concentrated under reduced pressure (35 °C) and the residue was partitioned between diethyl ether (100 cm^3) and brine (100 cm^3). After extraction of the aqueous layer with diethyl ether (100 $cm^3\times2$), the combined ether solution was dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was dissolved in methanol (500 cm^3) containing aluminium chloride (410 mg, 3.07 mmol) and water (25 cm^3). After stirred for 36 h at room temp, the solution was concentrated in vacuo, and water (50 cm^3) was added. The mixture was shaken with dichloromethane, the extract was dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was chromatographed (silica gel/Et_2O) to afford **6** (3.26 g, 24%) as a syrup (R_f=0.30, Et_2O).[1]

1,2,3-Tri-*O*-acetyl-4-azido-4-deoxy-L-xylopyranose (7). To a stirred solution of **6** (1.85 g, 6.70 mmol) in a mixture of dry dichloromethane (160 cm^3) and dry pyridine (0.81 cm^3) was added trifluoromethanesulfonic anhydride (1.24 cm^3, 7.37 mmol) dropwise at 0 °C under an atmosphere of nitrogen. After stirring for 1 h at 0 °C, the solution was poured into 100 cm^3 of ice-water. The organic layer was separated, and the aqueous layer was extracted with two 50 cm^3 portions of dichloromethane. The combined extract was dried over $MgSO_4$ and the solvent was removed to give a brown syrup. The crude triflate was dissolved in *N,N'*-dimethylformamide (80 cm^3), and sodium azide (435 mg, 6.70 mmol) and 15-crown-5 (1.33 cm^3, 6.70 mmol) were added to the solution. After stirred for 24 h at room temp, the solution was concentrated and the residue was partitioned between diethyl ether (30 cm^3) and water (30 cm^3). After extraction of the aqueous layer with diethyl ether (30 $cm^3\times2$), the combined extract was dried over $MgSO_4$. The solvent was evaporated and the residue was chromatographed (silica gel/Et_2O) to afford **7** (1.11 g, 55%, α/β=1/2) as a colorless syrup (R_f=0.74, Et_2O). IR (neat) ν_{max} 2110, 1750 cm^{-1}. ^1H NMR ($CDCl_3$) δ=2.00, 2.03, 2.08, 2.09, 2.11, 2.16 (9H, singlets, Ac), 3.39—4.14 (3H, m, H_4, H_5, $H_{5'}$), 4.88—5.45 (2H, m, H_2, H_3), 5.61 (1/3H, d, J=7.4 Hz, α-H_1), 6.19 (2/3H, d, J=3.5 Hz, β-H_1). ^{13}C NMR ($CDCl_3$), for α anomer, δ=58.48 (C_4), 63.94 (C_5), 70.10 (C_3), 72.93 (C_2), 92.14 (C_1); for β anomer, δ=59.09 (C_4), 61.56 (C_5), 69.49 (C_3), 70.43 (C_2), 89.34 (C_1).

4-Acetamido-1,2,3-tri-*O*-acetyl-4-deoxy-L-xylopyranose (8). A solution of **7** (660 mg, 2.19 mmol) in acetic acid (25 cm^3) was hydrogenated in the presence of 10% Pd-C (900 mg) under hydrogen (1 atm) for 2 h. The catalyst was filtered and the solvent was evaporated. To the residue dissolved in pyridine (30 cm^3) was added acetic anhydride (1.5 cm^3, 15.9 mol) and the mixture was stirred for 18 h at room temp. The solution was concentrated and the residue was partitioned between dichloromethane (15 cm^3) and brine (15 cm^3). After extraction of the aqueous layer with dichloromethane (15 $cm^3\times2$), the combined extract was dried over $MgSO_4$. The solvent was removed and the residue was chromatographed on silica gel (MeOH). A fraction corresponding to R_f 0.65 (MeOH) was β-8 (187 mg, 27%), a syrup, $[\alpha]_D^{23}$ −69° (*c* 3.56, MeOH). IR (neat) ν_{max}=3280, 2964, 1750, 1640, 1520 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.93 (3H, s, NAc), 2.01, 2.07, 2.13 (9H,

singlets, 3×OAc), 3.53—4.03 (3H, m, H_4, H_5, $H_{5'}$), 4.94—5.20 (2H, m, H_2, H_3), 5.96 (1H, bs, NHAc), 6.23 (1H, d, J=3.0 Hz, H_1). ^{13}C NMR ($CDCl_3$) δ=20.43, 20.73 (OAc-Me), 23.05 (NAc-Me), 49.88 (C_4), 62.11 (C_5), 69.27, 69.67 (C_2, C_3), 89.55 (C_1), 168.70, 169.31, 170.04 (OAc-CO), 171.69 (NAc-CO). HRMS, Found: m/z 318.1193. Calcd for $C_{13}H_{20}NO_8$: M+H, 318.1189.

(2*S*,3*R*,4*R*)-2-Hydroxymethyl-3,4-pyrrolidinediol (9). To a stirred solution of **7** (1.00 g, 3.32 mmol) in 10% aqueous methanol (10 cm^3) was added aqueous saturated potassium carbonate solution (0.5 cm^3) at 0 °C. After the solution was stirred for 15 min at 0 °C, acetic acid (25 cm^3) was added. The mixture was stirred under hydrogen (1 atm) with 10% Pd-C (1 g) for 3 days. After removal of the catalyst, the filtrate was concentrated to a volume of 1 cm^3. This solution was loaded onto an acid ion exchange column (Dowex 50X8-100, H^+ form). Acetic acid and inorganic substances were washed away with water and then the basic material was eluted from the column with 2.8% aqueous ammonium hydroxide. The solvent was removed from the eluate to give **9** (342 mg, 77%) as a syrup, ^{13}C NMR (D_2O with dioxane reference) δ=53.57 (C_5), 62.26 (CH_2OH), 64.06 (C_2), 69.30 (dioxane), 79.06, 79.33 (C_3, C_4). HRMS, Found: m/z 102.0568. Calcd for $C_4H_8NO_2$: M−CH_2OH, 102.0555.

Acetylation of **9** with pyridine-acetic anhydride gave acetate **10** in 55% yield as a syrup (R_f=0.50, MeOH: $CHCl_3$=1:15) after purification by column chromatography (silica gel/MeOH:$CHCl_3$=1:15). $[\alpha]_D^{24}$ −19° (c 4.37, MeOH). ^{1}H NMR ($CDCl_3$) δ=2.02—2.06 (12H, singlets), 3.24—3.45 (1H, m), 3.86—4.26 (4H, m), 5.18—5.30 (2H, m). ^{13}C NMR ($CDCl_3$) δ=20.52, 20.64, 20.82 (OAc-Me), 22.17 (NAc-Me), 50.25 (C_5), 55.28 (CH_2OH), 60.10 (C_2), 73.57, 74.12 (C_3, C_4), 169.46, 169.61, 169.77, 169.95 (CO). HRMS, Found: m/z 302.1231. Calcd for $C_{13}H_{20}NO_7$: M+H, 302.1240.

The hydrochloride of **9** was prepared by refluxing a solution of **10** (98 mg, 0.326 mmol) in methanol (2 cm^3) and aqueous HCl (4 mol dm^{-3}, 2 cm^3) for 16 h followed by concentration and purification through a column (Florigil/MeOH). The hydrochloride was obtained as powder (46 mg, 83%). ^{13}C NMR (D_2O with dioxane reference)[6] δ=53.32 (C_5), 60.09 (CH_2OH), 65.67 (C_2), 69.30 (dioxane), 77.14 (C_3, C_4).

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