Dideoxygenation on the 3′,4′-Positions of an α-Linked Disaccharide Derivative: A Key Intermediate for New Aminoglycoside Synthesis

Mitsuo HAYASHIDA,† Nobuo SAKAIRI, and Hiroyoshi KUZUHARA*
RIKEN (The Institute of Physical and Chemical Research),
Wako-shi, Saitama 351-01
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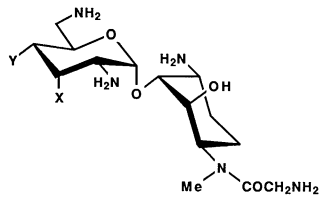
Synopsis. A 2′,6′-diamino-1,6-anhydro disaccharide derivative (**6**) was prepared from maltose. The 3′,4′-diol system of **6** was successfully converted into the 3′-ene system by application of the Corey–Winter procedure, giving the hex-3′-enopyranose derivative (**8**). Catalytic hydrogenation of **8** gave the dideoxy derivative, a key intermediate for the synthesis of a new aminoglycoside.

We have succeeded in the preparation of two new 1,4-diaminocyclitol aminoglycosides, **1**[1] and **2**,[2] employing a disaccharide maltose as the common starting material and found that **2**, the 3′-deoxy analog of **1**, had more potent antimicrobial activity than **1**.[2] These results led us an expect that the 3′,4′-dideoxy analog **3** would be more active than **2**. This paper deals with the key dideoxygenation step in the synthetic course directed towards **3**; i.e., the preparation of 1,6-anhydro-3-*O*-benzyl-4-*O*-[2,6-bis(benzyloxycarbonylamino)-2,3,4,6-tetradeoxy-α-D-*erythro*-hexopyranosyl]-2-*O*-(*p*-methoxybenzyl)-β-D-glucopyranose (**9**).

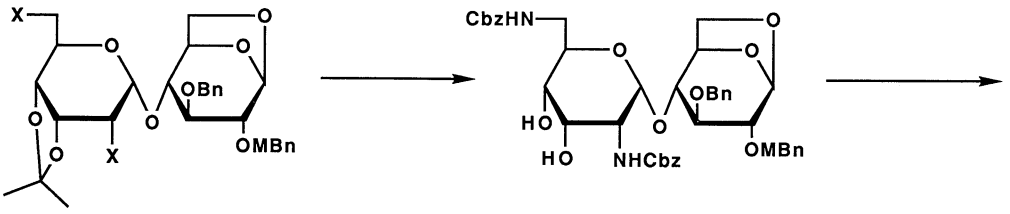


1: X = Y = OH

2: X = H, Y = OH

3: X = Y = H

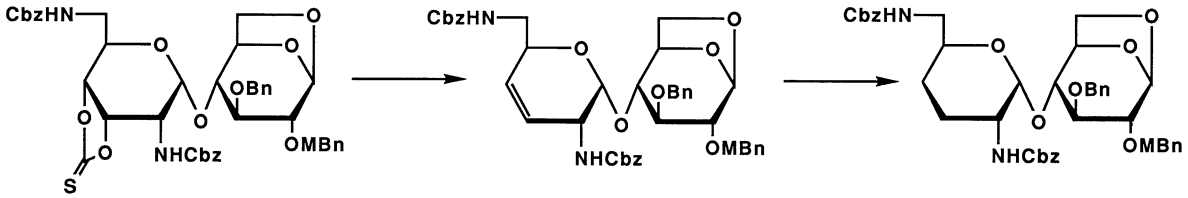
The 2′,6′-diazido derivative **4** having the differently protected 2- and 3-hydroxyl groups (with the *p*-methoxybenzyl and benzyl groups, respectively) has been one of the most important intermediates for the total synthesis of **1**. It was also employed as actual starting material for preparation of **9**. Before attempting dideoxygenation via olefin formation, **4** was reduced with lithium aluminum hydride in diethyl ether. The resulting diamino compound readily underwent *N*-benzyloxycarbonylation, giving **5** in 73% overall yield. This preliminary conversion was conducted to avoid the undesirable side reactions expected between the azido and the olefinic groups. After removal of the *O*-isopropylidene group from **5** under mildly acidic conditions, the resulting crystalline diol compound **6** was subjected to the Corey–Winter reaction[3] for olefin synthesis. In the first attempt, **6** was treated in oxolane with 1,1′-thiocarbonyldimidazole but no reaction took place;



4: X = N_3

5: X = NHCbz

6



7

8

9

MBn = *p*-methoxybenzyl

† Present address: Kaken Pharmaceutical Co., Ltd., Shinomiya, Minami-kawara-cho, Yamashina-ku, Kyoto 607.

whereas a similar treatment in toluene at 80—90 °C in an atmosphere of argon resulted in the thiocarbonic *O,O'*-diester derivative **7** in 87% yield. When **7** was heated in trimethyl phosphite under reflux in an atmosphere of argon, the crystalline 3',4'-unsaturated derivative **8** was obtained as sole product. The ^{1}H NMR spectrum of **8** revealed 3 proton signals at δ 5.69—5.75 as a multiplet. These were assignable to the olefinic protons at C-3' and C-4' and one of the amino protons. The chemical yield of this reaction, **7**→**8**, was more than 76%, which established the practical usefulness of the Corey–Winter reaction for such mutifunctionalized disaccharide systems. Taking account of the susceptibility of such protecting groups as *p*-methoxybenzyl, benzyl, and benzyloxycarbonyl to catalytic hydrogenation, **8** was first subjected to diimide reduction[4] for saturation of the 3'-double bond. However, this attempt failed, giving **8** unchanged. Unexpectedly, catalytic hydrogenation of **8** in ethyl acetate using platinum(IV) oxide as the catalyst[5] was successful, giving the dideoxy compound **9** desired in 83% yield. No deprotection was observed during this catalytic hydrogenation. Although the R_f values of **8** and **9** on TLC were very close, **9** was completely separable from traces of **8** by column chromatography using benzene–ethyl acetate as eluant.

It was confirmed that **9**, the key intermediate for synthesis of **3**, was obtainable in moderately good overall yield through five reaction steps of from **4** involving the Corey–Winter olefin synthesis.

Experimental

Melting points were determined with a Thomas–Hoover capillary melting point apparatus, and are uncorrected. Optical rotaions were determined with a Perkin–Elmer Model 241 polarimeter. IR spectra were recorded with a Shimadzu IR-430 spectrophotometer. ^{1}H NMR spectra were recorded with a JEOL JNM-GX 400 spectrometer, using tetramethylsilane as the internal standard. Column chromatography was performed on silica gel 60 (70—230 mesh; Merck).

1,6-Anhydro-3-*O*-benzyl-4-*O*-[2,6-bis(benzyloxycarbonylamino)-2,6-dideoxy-3,4-*O*-isopropylidene-α-D-allopyranosyl]-2-*O*-(*p*-methoxybenzyl)-β-D-glucopyranose (5). $LiAlH_4$ (0.5 g, 13.2 mmol) was added to a solution of 1,6-anhydro-3-*O*-benzyl-4-*O*-[2,6-diazido-2,6-dideoxy-3,4-*O*-isopropylidene-α-D-allopyranosyl]-2-*O*-(*p*-methoxybenzyl)-β-D-glucopyranose[1,2] (**4**; 1.94 g, 3.1 mmol) in dry diethyl ether (50 cm^3) below 0 °C. The mixture was stirred for 4 h at 0 °C, quenched by successive addition of ethyl acetate, methanol, and aq. potassium sodium tartrate, and extracted with diethyl ether (3×100 cm^3). The extracts were combined, washed with brine, dried (K_2CO_3), and concentrated. To a solution of the residue in dry dichloromethane–pyridine (2:1 v/v, 45 cm^3) was added benzyl chloroformate (2 cm^3) at 0 °C. The mixture was stirred for 1 h at 0 °C, diluted with water (100 cm^3) stirred for further 2 h, and extracted with dichloromethane (3×50 cm^3). The combined extracts were successively washed with aq. hydrochloric acid, aq. sodium hydrogencarbonate, and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed with benzene–ethyl acetate (85:15 v/v) as the eluant and crystallized from dichloromethane–diisopropyl ether to give **5** (1.91 g, 73%): mp 110—111.5 °C; $[\alpha]_D^{25}$ −15.2° (*c* 1.02, $CHCl_3$); IR (KBr) 3380 (NH) and 1725 cm^{-1} (NCOO); ^{1}H NMR ($CDCl_3$) δ=1.31, 1.45 (6H, 2×s, 2×CCH_3), 3.28, 3.42, 3.45 (each 1H, 3×broad s, H-2, H-3, and H-4), 3.32 (1H, m, H-6'a), 3.51—3.58 (2H, m, H-6a and H-6'b), 3.78 (3H, s, OCH_3), 3.83 (1H, m, H-4'), 3.91 (1H, d, *J*=6.7 Hz, H-6b), 4.00 (1H, m, H-5'), 4.11 (1H, m, H-2'), 4.31—4.43 (5H, m, H-3' and 2×ArCH_2O), 4.58 (1H, broad s, H-5), 4.82 (1H, broad s, H-1'), 5.04—5.14 (4H, m, 2×PhCH_2OCO), 5.27 (1H, broad s, NH), 5.37 (1H, s, H-1), and 5.63 (1H, d, *J*=9.8 Hz, NH).

Found: C, 65.81; H, 6.19; N, 3.25%. Calcd for $C_{46}H_{52}N_2O_{13}$:; C, 65.70; H, 6.23; N 3.33%.

1,6-Anhydro-3-*O*-benzyl-4-*O*-[2,6-bis(benzyloxycarbonylamino)-2,6-dideoxy-α-D-allopyranosyl]-2-*O*-(*p*-methoxybenzyl)-β-D-glucopyranose (6). A solution of **5** (1.93 g, 2.3 mmol) in 80% aq. acetic acid (22.5 cm^3) was stirred for 4 h at 60—65 °C, neutralized with aq. sodium hydrogencarbonate, and extracted with chloroform (3×50 cm^3). The extracts were combined, successively washed with aq. sodium hydrogencarbonate and brine, dried (Na_2SO_4), and concentrated. The residue was crystallized from dichloromethane–ethanol–diisopropyl ether to give **6** (1.54 g, 84%): mp 148—150 °C; $[\alpha]_D^{30}$ −24.4° (*c* 0.70, $CHCl_3$); IR (KBr) 3470 (OH), 3380 (NH), and 1690 cm^{-1} (NCOO); ^{1}H NMR ($CDCl_3$) δ=2.99, 3.19 (2H, 2×broad s, 2×OH), 3.32, 3.42 (each 1H, 2×broad s, H-2 and H-4), 3.35 (1H, m, H-6'a), 3.51—3.58 (3H, m, H-3, H-6a and H-6'b), 3.77 (3H, s, OCH_3), 3.81 (1H, m, H-2'), 3.98—4.08 (3H, m, H-6b, H-4', and H-5'), 4.24—4.42 (5H, m, H-3' and 2×ArCH_2O), 4.57 (1H, broad s, H-5), 4.78 (1H, broad s, H-1'), 5.10 (4H, m, 2×PhCH_2OCO), 5.19 (1H, broad s, NH), 5.38 (1H, s, H-1), and 5.77 (1H, d, *J*=8.9 Hz, NH).

Found: C, 64.61; H, 5.99; N, 3.36%. Calcd for $C_{43}H_{48}N_2O_{13}$: C, 64.49; H, 6.04; N, 3.50%.

1,6-Anhydro-3-*O*-benzyl-4-*O*-[2,6-bis(benzyloxycarbonylamino)-2,6-dideoxy-3,4-*O*-thiocarbonyl-α-D-allopyranosyl]-2-*O*-(*p*-methoxybenzyl)-β-D-glucopyranose (7). 1,1'-Thiocarbonyldiimidazole (0.5 g, 2.8 mmol) was added to a solution of **6** (1.12 g, 1.4 mmol) in dry toluene (20 cm^3). The mixture was stirred under an argon atmosphere for 3 h at 80—90 °C and concentrated. The residue was chromatographed with benzene–ethyl acetate (85:15 v/v) as the eluant giving **7** (1.02 g, 87%) as an amorphous solid: $[\alpha]_D^{24}$ −75.5° (*c* 1.12, $CHCl_3$); IR (KBr) 3380 (NH) and 1720 cm^{-1} (NCOO); ^{1}H NMR ($CDCl_3$) δ=3.28, 3.39, (each 1H, 2×broad s, H-2 and H-4), 3.46—3.48 (2H, m, H-3 and H-6'a), 3.57—3.60 (2H, m, H-6a and H-6'b), 3.78 (3H, s, OCH_3), 3.95 (1H, d, *J*=7.1 Hz, H-6b), 4.20—4.53 (6H, m, H-2', H-5', and 2×ArCH_2), 4.57 (1H, broad s, H-5), 4.70 (1H, broad t, H-3'), 4.87 (1H, broad s, H-1'), 5.04—5.16 (6H, m, H-4', NH, and 2×PhCH_2OCO), 5.34 (1H, s, H-1), and 5.70 (1H, broad d, *J*=8.8 Hz, NH).

Found: C, 62.85; H, 5.37; N, 3.29; S, 3.68%. Calcd for $C_{44}H_{46}N_2O_{13}S$: C, 62.70; H, 5.50; N, 3.32; S, 3.80%.

1,6-Anhydro-3-*O*-benzyl-4-*O*-[2,6-bis(benzyloxycarbonylamino)-2,3,4,6-tetradeoxy-α-D-*erythro*-hex-3-enopyranosyl]-2-*O*-(*p*-methoxybenzyl)-β-D-glucopyranose (8). A mixture of **7** (1.18 g, 1.4 mmol) and trimethyl phosphite (15 cm^3) was stirred under an argon atmosphere for 48 h at 110 °C and concentrated. The residue was chromatographed witht benzene–ethyl acetate (85:15 v/v) as the eluant and crystallized from dichloromethane–ethanol to give **8** (0.82 g, 76%): mp 131.5—132.5 °C; $[\alpha]_D^{23}$ −89.6° (*c* 0.82, $CHCl_3$); IR (KBr) 3320 (NH) and 1690 cm^{-1} (NCOO); ^{1}H NMR ($CDCl_3$) δ=3.28—3.34 (3H, m, H-2, H-4, and H-6'a), 3.42 (1H, m, H-6'b), 3.57 (1H, broad s, H-3), 3.66 (1H, dd, *J*=7.1 and 6.6 Hz, H-6a), 3.79 (3H, s, OCH_3), 4.07 (1H, d, *J*=7.1 Hz, H-6b), 4.23—4.40 (6H, m, H-2', H-5', and 2×ArCH_2O), 4.48 (1H, broad d, H-5), 4.80 (1H, broad d, *J*=3.0 Hz, H-1'), 4.99—5.14 (5H, m, NH and 2×PhCH_2OCO), 5.33 (1H, s, H-1), and 5.69—5.75 (3H, m, H-3', H-4', and NH).

Found: C, 67.42; H, 5.98; N, 3.54%. Calcd for $C_{43}H_{46}N_2O_{11}$: C, 67.35; H, 6.05; N, 3.65%.

1,6-Anhydro-3-*O*-benzyl-4-*O*-[2,6-bis(benzyloxycarbonylamino)-2,3,4,6-tetradeoxy-α-D-*erythro*-hexapyranosyl]-2-*O*-(*p*-methoxybenzyl)-β-D-glucopyranose (9). A suspension of **8** (307 mg, 0.4 mmol) and platinum(IV) oxide (60 mg) in ethyl acetate (20 cm^3) was shaken under a hydrogen atmosphere at room temperature for 48 h. The catalyst was filtered off and washed with ethyl acetate. The filtrate and washings were combined and concentrated. The residue was chromatographed with benzene–ethyl acetate (4:1 v/v) as the eluant and crystallized from dichloromethane–ethanol to give **9** (256 mg, 83%): mp 126.0—127.5 °C; $[\alpha]_D^{27}$ −19.1° (*c* 1.08, $CHCl_3$); IR (KBr) 3320 (NH) and 1695 cm^{-1} (NCOO); ^1H NMR ($CDCl_3$) δ=1.14 (1H, broad q, *J*=13 Hz, H-4′ax), 1.67 (1H, broad d, *J*=13.7 Hz, H-4′eq), 1.78 (1H, broad q, *J*=13 Hz, H-3′ax), 1.90 (1H, broad d, *J*=13 Hz, H-3′eq), 3.15 (1H, m, H-6′), 3.30—3.53 (4H, m, H-2, H-3, H-4, and H-6′b), 3.62 (1H, t, *J*=6.8 Hz, H-6a), 3.75 (1H, m, H-2′), 3.79 (3H, s, OCH_3), 3.91 (1H, m, H-5′), 4.02 (1H, d, *J*=6.8 Hz, H-6b), 4.29—4.43 (4H, m, 2×ArCH_2O), 4.51 (1H, broad d, H-5), 4.65 (1H, broad s, H-1′), 4.99—5.09 (5H, m, NH and 2× PhCH_2OCO), 5.35 (1H, s, H-1), and 5.50 (1H, d, *J*=9.3 Hz, NH).

Found: C, 67.10; H, 6.26; N, 3.57%. Calcd for $C_{43}H_{48}N_2O_{11}$: C, 67.17; H, 6.29; N, 3.64%.

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References

1) N. Sakairi, M. Hayashida, and H. Kuzuhara, *Tetrahedron Lett.*, **28**, 2871 (1987).

2) N. Sakairi, M. Hayashida, A. Amano, and H. Kuzuhara, *J. Chem. Soc., Perkin Trans. 1*, in press.

3) E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, **85**, 2677 (1963).

4) J. W. Hamersma and E. I. Snyder, *J. Org. Chem.*, **30**, 3985 (1965).

5) N. L. Drake and A. B. Ross, *J. Org. Chem.*, **23**, 719 (1958).