Communications to the Editor

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SYNTHESES OF PSEUDO-α-D-GLUCOPYRANOSE AND PSEUDO-β-L-IDOPYRANOSE, TWO OPTICALLY ACTIVE PSEUDO-HEXOPYRANOSES, FROM D-GLUCOSE BY USING STEREOSELECTIVE REDUCTIVE DEACETOXYLATION WITH SODIUM BOROHYDRIDE AND CYCLITOL FORMATION FROM NITROFURANOSE AS KEY REACTIONS

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Two optically active pseudo-hexopyranoses, pseudo-α-D-glucopyranose and pseudo-β-L-idopyranose, have been synthesized from D-glucose by using stereoselective deacetoxylations with $NaBH_4$ and cyclitol formations from nitrofuranose derivatives as key reactions.

KEYWORDS —— pseudo-α-D-glucopyranose; pseudo-β-L-idopyranose; pseudo-sugar; pseudo-hexopyranose optically active; stereoselective deacetoxylation; D-glucose; nitrofuranose cyclitol cyclization

During the course of our chemical transformation studies starting from carbohydrates leading to cyclitols,[1] we found a versatile method for synthesizing aminoglycoside antibiotics using monosaccharides as starting materials.[2] With this method, we successfully synthesized several clinically important aminoglycoside antibiotics such as ribostamycin and dibekacin.[3]

As an extension of these studies, we have found a new method for synthesizing pseudo-sugar[4] from monosaccharide. This synthesis pathway comprises stereoselective deacetoxylations with $NaBH_4$ and cyclitol formations from nitrofuranoses as key reactions. Here we report syntheses of two optically active pseudo-hexopyranoses, pseudo-α-D-glucopyranose (1)[5] and pseudo-β-L-idopyranose (15)[6] from D-glucose.[7]

Mild benzoylation of 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose (1) with benzoyl chloride in CH_2Cl_2 containing pyridine (0°C, 20 min) furnished 6-O-benzoyl-3-O-benzyl-1,2-isopropylidene-α-D-glucofuranose (2a)[8] (88%). On the other hand, treatment of 1 with t-butyldimethylsilyl chloride in DMF in the presence of imidazole (21°C, 0.5 h) yielded 2b (94%), colorless oil, $[\alpha]_D^{22}$ -19° ($CHCl_3$), $C_{22}H_{36}O_6Si$.[9] Swern oxidation[10] of 2a or 2b yielded an unstable ketone 3a or 3b, which subsequently was treated with CH_3NO_2 in DMF in the presence of NaH and 15-crown-5 (23°C, 12 h) to furnish 4a (45%), a white powder, $[\alpha]_D^{22}$ -34° ($CHCl_3$), $C_{24}H_{27}NO_9$ and 5a (24%),[11] colorless oil, $[\alpha]_D^{22}$ -51° ($CHCl_3$), $C_{24}H_{27}NO_9$ from 3a, or 4b (45%), a white powder, $[\alpha]_D^{22}$ -34° ($CHCl_3$), $C_{23}H_{37}NO_8Si$, and 5b (44%), a white powder, $[\alpha]_D^{22}$ -61° ($CHCl_3$), $C_{23}H_{37}NO_8Si$ from 3b.

Removal of the isopropylidene group of 4a with 70% aq. AcOH (80°C, 12 h)

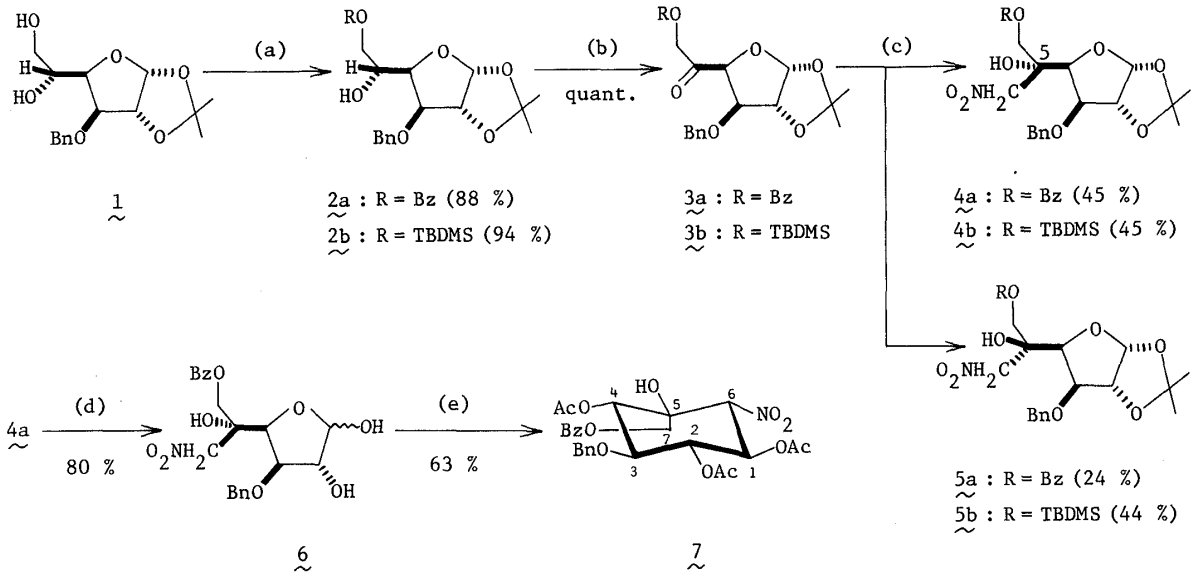
furnished 6 (80 %), colorless oil, IR ($CHCl_3$): 3398, 1718, 1550, 1375 cm^{-1}, MS (m/z): 433 (M^+). Treatment of 6 with KF in DMF in the presence of 18-crown-6 (23°C, 3 h) and subsequent acetylation of the product with Ac_2O and p-TsOH·H_2O, provided 7, colorless oil, $[\alpha]_D^{22}$ +10° ($CHCl_3$), $C_{27}H_{29}NO_{12}$, IR ($CHCl_3$): 3394, 1736, 1564, 1361 cm^{-1}. The detailed ^1H NMR decoupling experiments (500 MHz, $CDCl_3$) with 7 resulted in the following assignment (J in Hz): δ 4.15, 4.32 (both d, J=12, 7-H_2), 4.21 (dd, J=10, 10, 3α-H), 4.96 (d, J=11, 6β-H), 5.26 (dd, J=10, 10, 2β-H), 5.27 (d, J=10, 4β-H), 5.99 (dd, J=10, 11, 1α-H). The NOE's were observed between the following pairs of protons[12]: 7-H (δ 4.15) & 1α-H (14 %); 7-H (δ 4.32) & 1α-H (5 %); 1α-H & 7-H (δ 4.15) (1 %); 1α-H & 7-H (δ 4.32) (2 %); 3α-H & 7-H (δ 4.32) (6 %). Based on these spectral data, the stereostructure 7 was verified and consequently the 5(R) configuration in 4a was determined.

Acetylation of 4a or 4b with Ac_2O in the presence of p-TsOH·H_2O (23°C, 3 h) and subsequent $NaBH_4$ treatment of the product in EtOH (23°C, 2 h) to eliminate the acetoxyl group, furnished 8a (69 %), mp 111.5-113.5°C, $[\alpha]_D^{20}$ -34° ($CHCl_3$), $C_{24}H_{27}NO_8$ or 8b (70 %), colorless oil, $[\alpha]_D^{22}$ -37° ($CHCl_3$), $C_{23}H_{37}NO_7Si$. The 5(R) configuration in 8a and 8b was substantiated by the following conversions (vide infra) to pseudo-α-D-glucopyranose (11). Acetylation of 4a followed by $NaBD_4$ treatment in EtOH gave 8c, mp 111.5-113.0°C, $[\alpha]_D^{22}$ -37° ($CHCl_3$), $C_{24}H_{26}DNO_8$, MS (m/z): 458 (M^+). Thus, we found that the reductive deacetoxylation reaction with $NaBH_4$ (from 4a to 8a, or from 4b to 8b) proceeded stereoselectively to provide an S_N2-type reaction product.

Removal of the isopropylidene group of 8a with 80 % aq. AcOH (80°C, 12 h) gave 9a (83 %), colorless oil, IR ($CHCl_3$): 3366, 1724, 1555, 1376 cm^{-1}, MS (m/z): 417 (M^+). Similar treatment of 8b with 80 % aq. AcOH provided 9b (43 %), colorless oil, IR (neat): 3378, 1734, 1553, 1370 cm^{-1}, MS (m/z): 355 (M^+) and 9c (28 %), colorless oil, IR (neat): 3350, 1545, 1381 cm^{-1}, MS (m/z): 313 (M^+).

Treatment of 9a or 9b with KF in DMF in the presence of 18-crown-6 followed by deacylation with 1 % NaOMe-MeOH and introduction of the isopropylidene groups with 2,2-dimethoxypropane, p-TsOH·H_2O, and $CuSO_4$ in acetone, yielded 10 (72 %), a white powder, $[\alpha]_D^{22}$ -14° ($CHCl_3$), $C_{20}H_{27}NO_7$, IR (KBr): 1536, 1380 cm^{-1}, MS (m/z): 393 (M^+), 378 (M^+-CH_3), 347 (M^+-NO_2). The ^1H NMR spectrum (500 MHz, $CDCl_3$) of 10 substantiated the structure with signals due to two isopropylidene groups, one benzyl group, and all protons on the nitrocyclitol moiety [δ 2.71 (dddd, J=6, 10, 10, 12, 5α-H), 3.66 (dd, J=10, 11), 4.10 (dd, J=6, 11) (7-H_2), 3.56 (dd, J=7, 10, 3α-H), 3.61 (dd, J=10, 10, 4β-H), 4.18 (dd, J=5, 7, 2β-H), 4.40 (dd, J=5, 12, 6β-H), 4.68 (dd, J=5, 5, 1β-H)]. 9c was also converted to 10 (72 %) by KF treatment and introduction of isopropylidene groups. Treatment of 10 with n-Bu_3SnH in benzene in the presence of α,α'-azobis-iso-butyronitrile (AIBN) (80°C, 5 h) to eliminate the nitro group and subsequent removal of the di-O-isopropylidene group (70 % aq.AcOH, 25°C, 20 h) and benzyl group (Na, liq.NH_3, -78°C, 10 min), finally furnished pseudo-α-D-glucopyranose (11, 30 %).[13]

On the other hand, acetylation followed by stereoselective deacetoxylation of 5a or 5b, as described above for 4a or 4b, yielded 12a (69 %), $[\alpha]_D^{25}$ -34° ($CHCl_3$), $C_{24}H_{27}NO_8$ or 12b (70 %), colorless oil, $[\alpha]_D^{22}$ -42° ($CHCl_3$), $C_{23}H_{37}NO_7Si$. Treatment of 12a or 12b with 80 % aq. AcOH gave 13a (83 %), colorless oil, IR ($CHCl_3$): 3480, 1721, 1557, 1379 cm^{-1} or 13b (42 %), colorless oil, IR (neat): 3397, 1731,



1

2a : R = Bz (88 %)
2b : R = TBDMS (94 %)

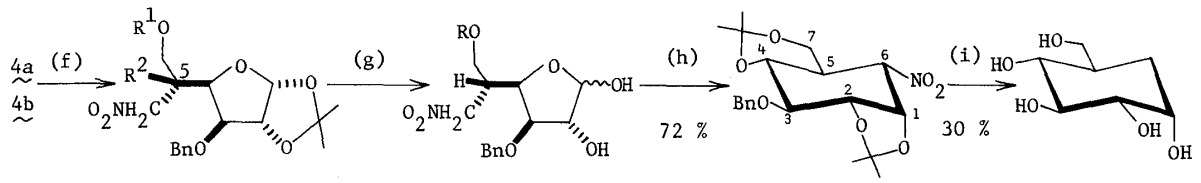
3a : R = Bz
3b : R = TBDMS

4a : R = Bz (45 %)
4b : R = TBDMS (45 %)

5a : R = Bz (24 %)
5b : R = TBDMS (44 %)

6

7

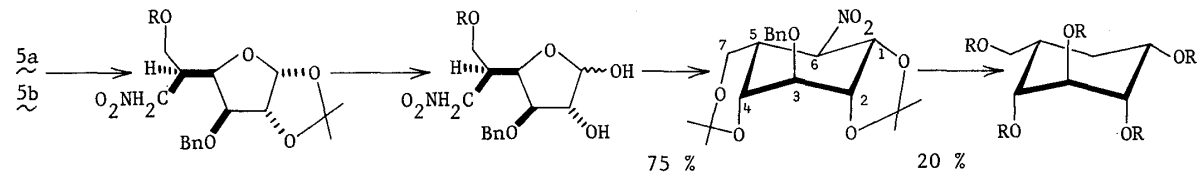


8a : R^1 = Bz , R^2 = H (69 %)
8b : R^1 = TBDMS , R^2 = H (70 %)
8c : R^1 = Bz , R^2 = D (70 %)

9a : R = Bz (83 %)
9b : R = Ac (43 %)
9c : R = H (28 %)

10

11



12a : R = Bz (69 %)
12b : R = TBDMS (70 %)

13a : R = Bz (83 %)
13b : R = Ac (42 %)
13c : R = H (30 %)

14

15 : R = H
15a : R = Ac

Bz : C_6H_5CO ,
Bn : $C_6H_5CH_2$,

TBDMS : t-butyldimethylsilyl
AIBN : α,α'-azobis-iso-butyronitrile

(a) BzCl / pyridine / CH_2Cl_2; or TBDMSCl / imidazole / DMF (b) Swern oxid. (c) CH_3NO_2 / NaH / 15-crown-5 / DMF (d) 70 % aq. AcOH (80°C) (e) KF / 18-crown-6 / DMF; Ac_2O / p-TsOH·H_2O (f) Ac_2O / p-TsOH·H_2O; $NaBH_4$ / EtOH (g) 80 % aq. AcOH (80°C) (h) KF / 18-crown-6 / DMF; 1 % NaOMe-MeOH; 2,2-dimethoxypropane / p-TsOH·H_2O / $CuSO_4$ / acetone (i) n-Bu_3SnH / AIBN / benzene (80°C); 70 % aq. AcOH; Na / liq.NH_3

1547, 1360 cm^{-1} and 13c (30 %), colorless oil, IR (neat): 3411, 1551, 1370 cm^{-1}.

KF treatment of 13a or 13b followed by deacylation and introduction of isopropylidene groups yielded 14 (75 %), colorless oil, $[\alpha]_D^{22}$ -38° ($CHCl_3$), $C_{20}H_{27}NO_7$, IR (neat): 1543, 1369 cm^{-1}. The ^1H NMR spectrum (500 MHz, $CDCl_3$, J in Hz) of 14 corroborated the structure with signals due to protons on the nitrocyclitol moiety: δ 2.20 (dddd, J=2, 3, 3, 9, 5-H), 3.56 (dd, J=13, 2), 3.96 (dd, J=13, 3) (7-H_2), 3.81 (dd, J=3, 3, 3-H), 4.24 (dd, J=3, 3, 4-H), 4.32 (dd, J=3, 6, 2-H), 4.69 (dd, J=6, 12, 1-H), 5.18 (dd, J=9, 12, 6-H).

Elimination of the nitro group of 14 and subsequent deprotection as described for 10 yielded pseudo-β-L-idopyranose (15, 20 %),[14] which, by acetylation, was converted to the pentaacetate (15a).[6] The detailed comparisons of the ^1H NMR data for 14, 15 and 15a with those for 10 and 11 have led us to formulate the stereostructure of pseudo-β-L-idopyranose as 15.

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9) The molecular composition of the compound given with the chemical formula was determined either by elemental analysis or by high resolution mass spectrometry.
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11) 5a was fairly unstable and readily decomposed to 3a during silica gel column chromatography.
12) The magnitude of NOE (%) given in the parenthesis was obtained when the underlined proton was irradiated.
13) 11, mp 150-152°C, $[\alpha]_D^{22}$ +60° (MeOH), ^1H NMR (500 MHz, d_5-Py., J in Hz): δ 1.89 (ddd, J=3, 13, 14, 6β-H), 2.35 (ddd, J=4, 4, 14, 6α-H), 2.74 (m, 5-H), 3.90 (dd, J=3, 10, 2-H), 3.95 (dd, J=9, 10, 4-H), 4.15 (dd, J=5, 11), 4.19 (dd, J=5, 11) (7-H_2), 4.46 (ddd, J=3, 3, 4, 1-H), 4.50 (dd, J=9, 10, 3-H). ^{13}C NMR (22.5 MHz, d_5-Py.,): δc 31.9, 39.4, 64.5, 69.5, 75.6, 75.6, 76.1.
14) 15, a hygroscopic white powder, $[\alpha]_D^{22}$ +7° (H_2O), ^1H NMR (500 MHz, d_5-Py., J in Hz): δ 2.09 (ddd, J=4, 5, 12, 6β-H), 2.34 (ddd, J=12, 12, 12, 6α-H), 2.75 (m, 5-H), 4.58 (br. s, 2-H, 4-H), 4.65 (ddd, J=4, 4, 12, 1-H), 4.76 (dd, J=3, 4, 3-H). ^{13}C NMR (22.5 MHz, d_5-Py.): δc 28.3, 39.9, 64.3, 68.9, 72.3, 72.6, 75.7.

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