*Carbohydrate Research*, 109 (1982) 276–281
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

## Note

# Synthesis of 2-amino-2-deoxy-α-D-glucopyranosyl β-D-fructofuranoside (2-amino-2-deoxysucrose) via Koenigs–Knorr reaction*

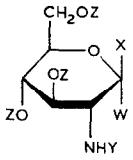
SHINKITI KOTO†, SHIGERU INADA, HIROKI OGAWA, AND SHONOSUKE ZEN
*School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108 (Japan)*
(Received January 15th, 1982; accepted for publication, February 7th, 1982)

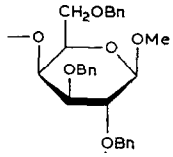
The yellow 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide[1] (**1**) was used in Umezawa's first synthesis of an antimicrobial aminoglycoside[2]. Subsequently, **1** was utilized in the synthesis of various 2-amino-2-deoxy-α-D-glucopyranosides[3]. The usefulness of **1** was recently shown in glycosylation of the anomeric hydroxyl group of protected hexoses in the synthesis of trehalosamine analogs[4]. To extend this utility, glycosylation of the anomeric hydroxyl group of 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose[5] (**2**) with **1** was attempted, as already communicated briefly[6]. Although, after Lemieux's first synthesis of sucrose[7], many alternative syntheses[8] have been carried out, and various aminodeoxysucroses[9] have been synthesized by modifying sucrose itself, no report on the synthesis of an aminodeoxysucrose via glycosylation has yet appeared.

Various conditions for stereoselective α-glycosylation by using **1** have been reported[2,3]. However, none were sufficiently effective for the glycosylation of the anomeric hydroxyl group of tetra-*O*-(*p*-chlorobenzyl)-α-D-hexopyranoses[4]. A survey of conditions showed that silver perchlorate and tribenzylamine in benzene gave the highest yield of the anomeric glycosides, together with an acceptable α-selectivity[4]. The procedure was then applied to the glycosylation of methyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside[10] (**3**), which appears very unreactive[11], to afford the anomeric products **4a** and **4b** in good yields.

Subsequently, the procedure was extended to the glycosylation of the fructofuranose derivative **2**. Chromatographic separation of the mixture furnished the major product (**5a**) in 29% yield, together with three minor ones (**5b**, **5c**, and **5d**). Sequential removal of the protecting groups from **5a** gave the free base **6a**. The $^{13}$C-n.m.r. spectrum of **6a** was firmly assigned by correlating it with that of sucrose as assigned recently[12]. The chemical shifts of the anomeric carbon atoms are very

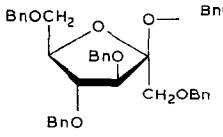
*Dedicated to Professor Sumio Umezawa on the occasion of his 73rd birthday and the 25th anniversary of the Microbial Chemistry Research Foundation.
†To whom correspondence should be addressed.



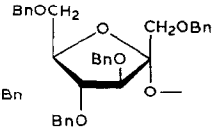




G4

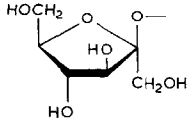
| | W | X | Y | Z |
|---|---|---|---|---|
| 1 | Br | H | Dnp | Ac |
| 4a | G4 | H | Dnp | Ac |
| 4b | H | G4 | Dnp | Ac |
| 5a | βBF | H | Dnp | Ac |
| 5b | αBF | H | Dnp | Ac |
| 5c | H | αBF | Dnp | Ac |
| 5d | H | αBF | Dnp | Ac |
| 6a | βF | H | H | H |
| 6b | αF | H | H | H |
| 6c | H | βF | H | H |
| 6d | H | αF | H | H |



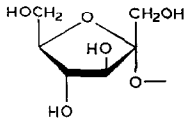

βBF



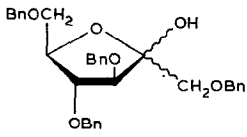

αBF



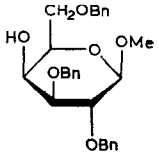

βF




αF




2




3

Ac = acetyl
Bn = benzyl
Dnp = 2,4-dinitrophenyl
Me = methyl

Scheme 1

close to those of sucrose. This may indicate* that substitution of the 2-hydroxyl group by the amino group does not alter the orientation of the interglycosidic linkages of sucrose[13].

Deprotection of **5b**, **5c**, and **5d** gave the free bases **6b**, **6c**, and **6d**, respectively. Their anomeric configurations were straightforwardly assigned from the chemical shifts of their anomeric carbon atoms[14].

The combined yield (33%) of the β-fructofuranoside derivatives (**5a** and **5b**) compared with that (16%) of the α anomers (**5c** and **5d**) indicates that **2** is mainly the β anomer; the major signal at δ 102.5 in the $^{13}$C-n.m.r. spectrum of **2** may be assigned** to the β anomer[14].

## EXPERIMENTAL

*General methods.* — These are described in the foregoing paper[4].

*Methyl 2,3,6-tri-*O*-benzyl-4-*O*-[3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α- and -β-*D*-glucopyranosyl]-β-*D*-galactopyranosides* (**4a** *and* **4b**). — An equimolar mixture of **1** (130.7 mg, 0.24 mmol), **3** (113.8 mg), tribenzylamine (70.3 mg), and silver perchlorate (50.8 mg) in benzene (1.3 mL) was vigorously stirred for 24 h at room temperature with exclusion of moisture and light. The mixture was filtered and the filtrate chromatographed on silica gel, with gradient elution by benzene–butanone, to give **4a** (129.4 mg, 58%) and **4b** (51.5 mg, 23%).

Compound **4a** had $[\alpha]_D^{20}$ +51° (*c* 0.7, chloroform); $\delta_H$ ($CDCl_3$, $Me_4Si$): 1.77 (OAc), 2.00 (OAc), 2.05 (OAc), 3.57 (OMe), 8.21 (dd, 1 H, *J* 2 and 10 Hz, H-5 of DNP), 8.61 (1 H, *J* 9 Hz, NH), and 9.10 (d, 1 H, *J* 2, H-3 of DNP).

Compound **4b** had $[\alpha]_D^{20}$ −25° (*c* 0.5, chloroform); $\delta_H$ ($CDCl_3$, $Me_4Si$): 1.90 (OAc), 2.01 (6 H, OAc), 3.37 (OMe), 8.21 (dd, 1 H, *J* 2 and 10 Hz, H-5 of DNP), 8.57 (1 H, *J* 9 Hz, NH), and 8.97 (d, 1 H, *J* 2 Hz, H-3 of DNP).

*Anal.* Calc. for $C_{46}H_{51}N_3O_{17}$: C, 60.19; H, 5.60; N, 4.48. Found (**4a**): C, 60.07; H, 5.94; N, 4.31; (**4b**): C, 59.66; H, 5.66; N, 4.60.

*3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-*D*-glucopyranosyl 1,3,4,6-tetra-*O*-benzyl-β-*D*-fructofuranoside* (**5a**) *and isomers* (**5b**, **5c**, *and* **5d**). — An equimolar mixture of **1** (1.01 g, 1.89 mmol), syrupy **2** (1.02 g), tribenzylamine (543 mg), and silver perchlorate (393 mg) in benzene (10 mL) was stirred in the aforementioned manner. The mixture was filtered and the filtrate chromatographed on silica gel (30 g) with gradient elution by benzene–butanone (100:1→3:1, 10-mL fractions) to give five fractions: A (7–11), 365.7 mg (~37%), $R_F$ 0.75 (5:1 toluene–butanone), impure (**2**); B [12–18, 888.8 mg, **5a** ($R_F$ 0.67), **5b** ($R_F$ 0.63), and unidentified non-

*The atoms in the 2-amino-2-deoxy-D-glucopyranosyl moiety are numbered without primes, whereas those in the fructofuranosyl moiety are primed. The interglycosidic oxygen atom is unnumbered.

**The peak for the α anomer appears at δ 105.3 in $CDCl_3$ ($Me_4Si$). The ratio (2.1) is much smaller than the ratio (~5) of β anomer to the α anomer in the starting, syrupy **2**, estimated approximately from the $^{13}$C-n.m.r. spectrum. This difference implies that anomerization of the β anomer of **2** occurs before formation of the interglycosidic linkage.

nitrogeneous compound(s)]; C [22–24, 158.1 mg (8.4%), **5c** ($R_F$ 0.60) and **5d** ($R_F$ 0.59)]; D [25–27, ~100 mg, unidentified nitrogenous compounds]; and E [28–30, 444.4 mg (~50%), impure 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranose].

Fraction B was repeatedly chromatographed to furnish pure **5a** (540.3 mg, 28.7%) and **5b** (232.0 mg, 12.1%).

Compound **5a** had $[\alpha]_D^{20}$ +36° (*c* 0.7, chloroform); $\delta_H$ ($CDCl_3$, $Me_4Si$): 1.77 (OAc), 1.97 (OAc), 2.07 (OAc), 5.92 (1 H, *J* 3.6 Hz, H-1), 6.59 (d, 1 H, *J* 10 Hz, H-6 of DNP), 8.01 (dd, 1 H, *J* 3 Hz, H-5 of DNP), 8.55 (d, 1 H, *J* 10 Hz, NH), and 9.01 (d, 1 H, H-3 of DNP); $\delta_c$ ($CDCl_3$, $Me_4Si$): 20.6 (2C, OAc), 20.8 (OAc), 55.1 (C-2), 61.2 (C-6), 67.8 (C-4), 67.9 (C-3), 68.7 (C-6), 72.0 (C-6′), 72.6 (C-1′), 72.8 (2C, Bn), 73.7 (2C, Bn), 79.0 (C-3′), 79.2 (C-4′), 83.9 (C-5′), 89.2 (C-1), 104.5 (C-2′), 114.1, 124.4, 129.5, 130.8, 136.2, 147.4 (DNP), and 169.5, 169.9, 170.4 (OAc).

Compound **5b** had $[\alpha]_D^{20}$ +52° (*c* 0.3, chloroform); $\delta_H$ ($CDCl_3$, $Me_4Si$): 1.87 (OAc), 2.03 (OAc), 2.05 (OAc), 5.65 (d, 1 H, *J* 3.5 Hz, H-1), 7.04 (d, 1 H, *J* 10 Hz, H-6 of DNP), 8.21 (dd, 1 H, *J* 2.7, H-5 of DNP), 8.45 (d, 1 H, *J* 9 Hz, NH), and 9.06 (d, 1 H, H-3 of DNP); $\delta_C$ ($CDCl_3$, $Me_4Si$): 56.1 (C-2), 61.7 (C-6), 82.6 (C-5′), 83.3 (C-3′), 86.8 (C-1), 89.7 (C-4′), and 109.8 (C-2′).

*Anal.* Calc. for $C_{52}H_{55}N_3O_{17}$: C, 62.83; H, 5.58; N, 4.23. Found (**5a**): C, 63.21; H, 5.92; N, 3.93. (**5b**): C, 63.15; H, 5.75; N, 3.83.

Repeated chromatography of Fraction C with toluene–butanone gave **5c** (85.0 mg, 4.5%) and **5d** (72.2 mg, 3.8%).

Compound **5c** had $[\alpha]_D^{20}$ −7.5° (*c* 2.5, chloroform); $\delta_H$ ($CDCl_3$, $Me_4Si$): 1.87 (OAc), 2.05 (OAc), 2.07 (OAc), 5.04 (d, 1 H, *J* 8 Hz, H-1), 7.64 (dd, 1 H, *J* 3 and 10 Hz, H-5 of DNP), 8.31 (d, 1 H, *J* 8 Hz, NH), and 8.85 (d, 1 H, *J* 3 Hz, H-3 of DNP); $\delta_C$ ($CDCl_3$, $Me_4Si$): 58.0 (C-2), 62.3 (C-6), 79.8 (C-3′), 81.3 (C-5′), 83.5 (C-4′), 94.4 (C-1), and 105.0 (C-2′).

Compound **5d** had $[\alpha]_D^{20}$ +1.4° (*c* 2, chloroform); $\delta_H$ ($CDCl_3$, $Me_4Si$): 1.87 (OAc), 1.98 (OAc), 2.03 (OAc), 5.03 (d, 1 H, *J* 8 Hz, H-1), 8.01 (dd, 1 H, *J* 3 and 10 Hz, H-5 of DNP), 8.51 (d, 1 H, *J* 9 Hz, NH), and 8.74 (d, 1 H, *J* 3 Hz, H-3 of DNP); $\delta_C$ ($CDCl_3$, $Me_4Si$): 57.6 (C-2), 62.3 (C-6), 82.3 (C-3′), 83.5 (C-5′), 88.2 (C-4′), 96.1 (C-1), and 109.6 (C-2′).

*Anal.* Calc. for $C_{52}H_{55}N_3O_{17}$: C, 62.83; H, 5.58; N, 4.23. Found (**5c**): C, 62.46; H, 5.80; N, 4.00. (**5d**): C, 62.24; H, 5.70; N, 4.27.

*2-Amino-2-deoxy-α-D-glucopyranosyl β-D-fructofuranoside* (**6a**) *and its derivatives.* — Compound **5a** (499.0 mg, 0.50 mmol) was treated overnight with dilute sodium methoxide in methanol (0.1%, 40 mL). The solution was made neutral with acetic acid, and evaporated. Chromatography on silica gel with benzene–butanone gave the yellow deacetylated product (423.4 mg, 98%). This compound (383.4 mg, 0.44 mmol) was treated with Dowex 1-X2 (100 mesh, OH, 5 mL) in moist acetone (12 mL) overnight. Filtration, evaporation of the filtrate, and chromatography on silica gel with benzene–ethanol, afforded a colorless mass (169.5 mg, 54% from **5a**), which was hydrogenated twice over palladium (140 mg) in a mixture of methanol

(3 mL), acetic acid (1 mL), and water (3 mL). After removal of the catalyst, the solution was evaporated and passed through a column of Dowex 1–X2 irrigated with water to give the free base (66.9 mg, 43% from **5a**); $[\alpha]_D^{20}$ +72° (*c* 0.3, water); $\delta_H$ [$D_2O$, $Me_4Si$ (ext.)]: 3.20 (dd, 1 H, *J* 3.5 and 9.5 Hz, H-2), and 5.84 (d, 1 H, *J* 3.5 Hz, H-1); $\delta_C$ [$D_2O$, $Me_4Si$ (ext.)]: 56.1 (C-2), 61.4 (C-6), 63.0 (C-1′), 63.2 (C-6′), 70.7 (C-4), 73.9 (C-5), 74.6 (C-3′), 75.0 (C-3), 77.8 (C-4′), 82.3 (C-5′), 94.0 (C-1), and 104.7 (C-2′).

*Anal.* Calc. for $C_{12}H_{23}NO_{10} \cdot 0.75\ H_2O$: C, 40.62; H, 6.95; N, 3.95. Found: C, 40.70; H, 7.17; N, 3.87.

Treatment of **6a** with acetic anhydride in pyridine gave the peracetate; m.p. 58–60°; $[\alpha]_D^{20}$ +53° (*c* 1, chloroform); $\delta_H$ ($CDCl_3$, $Me_4Si$): 1.96 (NAc), 2.02 (6 H, OAc), 2.07 (OAc), 2.10 (9 H, OAc), 2.20 (OAc), 5.58 (d, 1 H, *J* 3.7 Hz, H-1), and 6.01 (d, 1 H, *J* 9 Hz).

*Anal.* Calc. for $C_{28}H_{39}NO_{18}$: C, 49.63; H, 5.80; N, 2.07. Found: C, 50.41; H, 6.09; N, 2.08.

Treatment of **6a** with acetic anhydride in methanol gave the *N*-acetyl derivative; m.p. 178–180°, $[\alpha]_D^{20}$ +71° (*c* 0.5, water); $\delta_H$ [$D_2O$, $Me_4Si$ (ext.)]: 2.53 (NAc) and 5.89 (d, 1 H, *J* 3.3 Hz, H-1).

*Anal.* Calc. for $C_{14}H_{25}NO_{11}$: C, 42.05; H, 6.79; N, 3.77. Found: C, 41.43; H, 6.93; N, 3.82.

*2-Amino-2-deoxy-α-*D*-glucopyranosyl α-*D*-fructofuranoside* (**6b**), *2-amino-2-deoxy-β-*D*-glucopyranosyl β-*D*-fructofuranoside* (**6c**), *and 2-amino-2-deoxy-β-*D*-glucopyranosyl α-*D*-fructofuranoside* (**6d**). — The aforementioned processes for deprotection were applied to the isomeric conjugates **5b**, **5c**, and **5d** to afford the corresponding free bases, **6b**, **6c**, and **6d**.

Compound **6b** had $[\alpha]_D^{20}$ +167° (*c* 2, water); $\delta_H$ [$D_2O$, $Me_4Si$ (ext.)]: 3.26 (dd, 1 H, *J* 3.7 and 9.3 Hz, H-1) and 5.81 (d, 1 H, *J* 3.7 Hz, H-1); $\delta_C$ [$D_2O$, $Me_4Si$ (ext.)]: 56.1 (C-2), 61.8 (2C, C-6 and C-1′), 62.5 (C-6′), 71.0 (C-4), 74.0 (C-5), 74.7 (C-3), 78.3 (C-3′), 82.4 (C-4′), 85.2 (C-5′), 92.9 (C-1), and 110.1 (C-2′).

*Anal.* Calc. for $C_{12}H_{23}NO_{10} \cdot 0.75\ H_2O$: 40.62; H, 6.95; N, 3.95. Found: C, 40.39; H, 7.14; N, 3.74.

Compound **6c** had $[\alpha]_D^{20}$ −34° (*c* 0.1, water); $\delta_C$ [$D_2O$, $Me_4Si$ (ext.)]: 57.5 (C-2), 61.7 (C-6), 62.2 (C-1′), 62.8 (C-6′), 70.6 (C-4), 74.4 (C-3′), 77.0 (2C, C-3, and C-5), 77.4 (C-4′), 82.4 (C-5′), 96.2 (C-1), and 105.4 (C-2′).

*Anal.* Calc. for $C_{12}H_{23}NO_{10} \cdot 0.5\ H_2O$: C, 41.14; H, 6.91; N, 4.00. Found: C, 41.27; H, 6.83; N, 3.90.

Compound **6d** had $[\alpha]_D^{20}$ +4.7° (*c* 0.5, water); $\delta_C$ [$D_2O$, $Me_4Si$ (ext.)]: 57.6 (C-2), 61.7 (2C, C-6 and C-1′), 62.3 (C-6′), 70.6 (C-4), 77.0 (2C, C-3 and C-5), 77.4 (C-3′), 81.9 (C-4′), 84.3 (C-5′), 97.0 (C-1), and 109.8 (C-2′).

*Anal.* Calc. for $C_{12}H_{23}NO_{10} \cdot 0.75\ H_2O$: C, 40.62; H, 6.95; N, 3.95. Found: C, 40.24; H, 6.97; N, 4.12.

REFERENCES


1 P. F. LLOYD AND M. STACEY, *Tetrahedron*, 9 (1960) 116–124.
2 S. UMEZAWA AND S. KOTO, *Bull. Chem. Soc. Jpn.*, 39 (1966) 2014–2017.
3 K. HEYNS, K. PROPP, R. HARRISON, AND H. PAULSEN, *Chem. Ber.*, 100 (1967) 2655–2663; W. MEYER ZU RECKENDORF AND N. WASSILIADOW-MICHELI, *ibid.*, 103 (1970) 1792–1796; A. HASEGAWA, D. NISHIMURA, T. KUROKAWA, AND M. NAKAJIMA, *Agric. Biol. Chem.*, 36 (1972) 1773–1776; S. OGAWA, Y. FUNAKI, K. IWATA, AND T. SUAMI, *Bull. Chem. Soc. Jpn.*, 49 (1976) 1975–1979.
4 S. KOTO, S. INADA, AND S. ZEN, *Bull. Chem. Soc. Jpn.*, 54 (1981) 2728–2734.
5 R. K. NESS, H. W. DIEHL, AND H. G. FLETCHER, JR., *Carbohydr. Res.*, 13 (1970) 23–32.
6 S. KOTO, S. INADA, AND S. ZEN, *Chem. Lett.*, (1980) 183–184.
7 R. U. LEMIEUX AND G. HUBER, *J. Am. Chem. Soc.*, 78 (1956) 4117–4119.
8 H. TSUCHIDA AND M. KOMOTO, *Agric. Biol. Chem.*, 29 (1965) 239–242; A. KLEMER AND B. DIETZEL, *Tetrahedron Lett.*, (1970) 275–278; R. K. NESS AND H. G. FLETCHER, JR., *Carbohydr. Res.*, 17 (1971) 465–470; D. E. ILEY AND B. FRASER-REID, *J. Am. Chem. Soc.*, 97 (1975) 2563–2565.
9 S. UMEZAWA, T. TSUCHIYA, S. NAKADA, AND K. TATSUTA, *Bull. Chem. Soc. Jpn.*, 40 (1967) 395–401; I. JEŽO, *Chem. Zvesti*, 25 (1971) 364–368; R. KHAN, K. S. MUFTI, AND M. R. JENNER, *Carbohydr. Res.*, 30 (1973) 183–186; T. SUAMI, T. IKEDA, S. NISHIYAMA, AND R. ADACHI, *Bull. Chem. Soc. Jpn.*, 48 (1975) 1953–1954; N. K. SHARMA, J. L. NORULA, AND S. K. MATTEY, *J. Indian Chem. Soc.*, 58 (1981) 795–798.
10 H. B. BORÉN, P. J. GAREGG, L. KENNE, Å. PILOTTI, S. SIGFRID, AND C.-G. SWAHN, *Acta Chem. Scand.*, 27 (1973) 2740–2748; H. M. FLOWERS, *Carbohydr. Res.*, 39 (1975) 245–251.
11 M. DEJTER-JUSZYNSKI AND H. M. FLOWERS, *Carbohydr. Res.*, 41 (1975) 308–312; P. A. GENT, R. GIGG, AND A. A. E. PENGLIS, *J. Chem. Soc. Perkin Trans. 1*, (1976) 1395–1404.
12 A. J. JONES, P. HANISCH, AND A. K. MCPHAIL, *Aust. J. Chem.*, 32 (1979) 2763–2766.
13 G. M. BROWN AND H. A. LEVY, *Acta Crystallogr. Sect. B*, 29 (1973) 790–797.
14 A. S. PERLIN, N. CYR, H. J. KOCH, AND B. KORSCH, *Ann. N. Y. Acad. Sci.*, 222 (1973) 935–942.