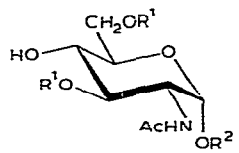
Carbohydrate Research, 95 (1981) 308–312
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

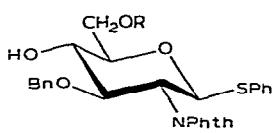
Synthesis of phenyl 6-*O*-acyl-3-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside*

TOMOYA OGAWA**, SATORU NAKABAYASHI***, AND KIKUO SASAJIMA†
The Institute of Physical and Chemical Research, Wako-shi, Saitama, 351 (Japan)
(Received March 19th, 1981; accepted for publication, April 22nd, 1981)

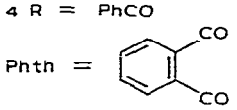
Since the first synthesis of peracetylated lactosamine by Okuyama[2], in 1958, employing partially acetylated 2-amino-2-deoxy-D-glucose (**1**), several such partially protected derivatives of 2-amino-2-deoxy-D-glucose as **2**, having a free 4-hydroxyl group, have been prepared as suitable glycosyl acceptors for the synthesis of disaccharides having a (1→4)-GlcNAc linkage, mainly by Sinaÿ[3], Jeanloz[4], Anderson[5], and their co-workers. We report here a stereo- and regio-controlled synthesis of the new glycosyl acceptors **3** and **4**.



1 $R^1 = R^2 = Ac$
2 $R^1 = Bn, R^2 = CH_2{=}CH{-}CH_2{-}$
Bn = $PhCH_2$



3 R = Ac
4 R = PhCO



In order to synthesize such 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranosides as **7**, **8**, and **9**, the stannyl approach[6] was examined, using β-chloride[7] **5** and β-acetate[7] **6**. Treatment of **5** with Bu_3SnS-*tert*-Bu in $Cl(CH_2)_2Cl$ for 5 days at 80° afforded a 21% yield of **7**, together with a 35% yield of glycal **10**.

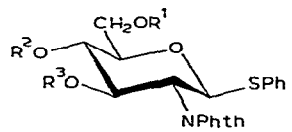
*Part IX in the series "Synthetic Studies on Cell-surface Glycans". For Part VIII, see ref. 1.
**To whom enquiries should be addressed.
***Present address: The Research Laboratory, Meiji Seika Kaisha Ltd., Morooka-cho, Kohoku-ku, Yokohama, 222, Japan.
†Present address: Sumitomo Chemical Co. Ltd., Fine Chemicals Division, Osaka Works, 3-1-98, Kasugade, Naka, Konohana-ku, Osaka, Japan.

0008-6215/81/0000–0000/$ 02.50,

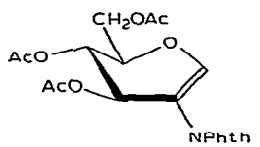
The same treatment of **5** with Bu_3SnSMe gave only glycal **10**, and recovery of some **5**. However, the reaction of β-acetate **6** with Bu_3SnSMe in the presence of $SnCl_4$ at 20° afforded crystalline **8** in 88% yield. The β configuration of C-1 of **8** was determined by ^{1}H-n.m.r. data, which showed a doublet at δ 5.39, with J 10 Hz, for H-1. Similarly, crystalline phenyl 1-thio-β-glycoside **9** could be obtained in 65% yield without use of chromatography. Due to the facile experimental operation for large-scale preparation, **9** was chosen as the key intermediate for further transformation. Deacetylation of **9** in aq. acetone in the presence[8] of conc. HCl afforded triol **11**, which was directly treated with α,α-dimethoxytoluene and p-TsOH in acetonitrile, to give the benzylidene derivative **12** in 89.8% yield from **9**. Benzylation of **12** to give **13**, and solvolysis of **13** in 70% aq AcOH for 45 min at 100°, afforded the monobenzyl ether **14** in 71% yield from **12**. Partial acylation of **14** with acetic anhydride, or benzoyl chloride, afforded the 6-*O*-acetyl (**3**) and 6-*O*-benzoyl derivative (**4**) in 56 and 58% yield, respectively.

5 X = Cl
6 X = OAc

7 R = Me_3C
8 R = Me
9 R = Ph



11 $R^1 = R^2 = R^3 = H$
12 R^1, R^2 = PhCH=, R^3 = H
13 R^1, R^2 = PhCH=, R^3 = Bn
14 $R^1 = R^2$ = H, R^3 = Bn



10

EXPERIMENTAL

General. — Melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer Model 141 polarimeter for solutions in $CHCl_3$ at 25°, unless otherwise noted. Column chromatography was performed on columns of Silica Gel Merck (70–230 mesh; E. Merck, Darmstadt, Germany). Thin-layer chromatography was conducted on precoated plates (layer thickness, 0.25 mm) of Silica Gel 60 F_{254} (E. Merck, Darmstadt, Germany). I.r. spectra were recorded with an EPI-G2 Hitachi

spectrophotometer, as KBr discs for crystalline samples, and as neat films for liquid samples. ^{1}H-N.m.r. spectra were recorded with a Varian HA-100 n.m.r. spectrometer, using tetramethylsilane as the internal standard. ^{13}C-N.m.r. spectra were recorded with a JNM-FX 100FT n.m.r. spectrometer operated at 25.05 MHz. The values of δ_C and δ_H are expressed in p.p.m. downward from the internal standard for solutions in $CDCl_3$, unless otherwise noted.

tert-Butyl 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (7). — A solution of β-chloride **5** (454 mg, 1 mmol) and Bu_3SnS-*tert*-Bu (372 mg, 1 mmol) in $Cl(CH_2)_2Cl$ (5 mL) was stirred for 5 days at 80°. Evaporation to dryness, and chromatography of the residue on SiO_2 (130 g) with 15:1 $CHCl_3$–Me_2CO, afforded **7** as a syrup (107.1 mg, 21.1%); $[\alpha]_D$ +50.2° (*c* 0.235); R_F 0.72 in 15:1 CH_2Cl_2–Me_2CO; δ_H: 5.84 (t, $J_{2,3} = J_{3,4} = 10$ Hz, H-3), 5.62 (d, $J_{1,2}$ 10 Hz, H-1), 5.11 (t, $J_{3,4} = J_{4,5} = 10$ Hz, H-4), 2.07, 2.03, and 1.86 (s, 3 OAc), and 1.28 (s, *tert*-Bu).

Anal. Calc. for $C_{24}H_{29}NO_9S$: C, 56.79; H, 5.76; N, 2.76; S, 6.32. Found: C, 56.36; H, 5.67; N, 2.64; S, 6.28.

Further elution afforded oily glycal **10** (146.7 mg, 35.1%)[8]; $[\alpha]_D$ −15.0° (*c* 0.20); R_F 0.53 in 15:1 $CHCl_3$–Me_2CO; δ_H: 6.77 (s, H-1), 5.61 (d, *J* 4 Hz, H-3), and 5.32 (t, *J* 4 Hz, H-4).

Anal. Calc. for $C_{20}H_{19}NO_9$: C, 57.55; H, 4.59; N, 3.36. Found: C, 57.29; H, 4.82; N, 3.34.

Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (8). — To a solution of β-acetate **6** (477 mg, 1 mmol) and Bu_3SnSMe (340 mg, 1 mmol) in $Cl(CH_2)_2Cl$ (5 mL) was added $SnCl_4$ (0.12 mL, 1 mmol) at 0°. The mixture was stirred for 15 h at 20°, poured into aq. $NaHCO_3$, and extracted with EtOAc, the insoluble material being filtered off through Celite. The extract was washed with H_2O, dried ($MgSO_4$), and evaporated, to give an oily residue which was chromatographed on SiO_2 (150 g) with 20:1 $CHCl_3$–Me_2CO, giving **8** as a glass (409.6 mg, 88.0%) that crystallized from C_6H_6–hexane; m.p. 154–155°, $[\alpha]_D$ +50.9° (*c* 0.32); R_F 0.65 in 15:1 CH_2Cl_2–Me_2CO; δ_H: 5.86 (t, $J_{2,3} = J_{3,4} = 10$ Hz, H-3), 5.39 (d, $J_{1,2}$ 10 Hz, H-1), 5.18 (t, $J_{4,5} = J_{3,4} = 10$ Hz, H-4), 4.43 (t, H-2), 2.16 (s, S-Me), and 2.11, 2.04, and 1.86 (s, 3 OAc).

Anal. Calc. for $C_{21}H_{23}O_9NS$: C, 54.18; H, 4.97; N, 3.01; S, 6.89. Found: C, 53.97; H, 4.96; N, 2.93; S, 6.74.

Phenyl 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (9). — To a solution of β-acetate **6** (23.87 g, 50 mmol) and Bu_3SnSPh (20 g, 50.2 mmol) in $Cl(CH_2)_2Cl$ (500 mL) was added $SnCl_4$ (5.9 mL, 50 mmol) dropwise at 20–25°, and the mixture was stirred for 10 h at 25°. The usual processing afforded an oil that crystallized from Me_2CHOH, to give **9** (17.2 g, 65%), m.p. 145–146°, $[\alpha]_D$ +56.1° (*c* 0.86); R_F 0.62 in 2:1 toluene–EtOAc; δ_H: 7.94–7.64 (m, 4 H, phthalimido), 7.5–7.2 (m, 5 H, phenyl), 5.78 (t, $J_{2,3} = J_{3,4} = 10$ Hz, H-3), 5.70 (d, $J_{1,2}$ 10 Hz, H-1), 5.12 (t, $J_{3,4} = J_{4,5} = 10$ Hz, H-4), 4.34 (t, $J_{1,2} = J_{2,3} = 10$ Hz, H-2), 4.34–4.2 (m, H-6,6'), 4.0–3.8 (m, H-5), and 2.07, 2.00, and 1.82 (s, 3 OAc).

Anal. Calc. for $C_{26}H_{25}O_9NS$: C, 59.20; H, 4.78; N, 2.66; S, 6.08. Found: C, 59.14; H, 4.77; N, 2.55; S, 6.32.

Phenyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**12**). — A solution of **9** (3.0 g, 5.7 mmol) in acetone (50 mL), H_2O (25 mL), and conc. HCl (10 mL) was stirred for 3 h at 50–60°, for a further 2 h after adding conc. HCl (0.5 mL), and then for 1 h after adding conc. HCl (0.2 mL), at 50–60°. The acetone was evaporated *in vacuo*, and the residual solution was extracted with EtOAc. The extracts were combined, washed, successively with H_2O, aq. $NaHCO_3$, and H_2O, dried ($MgSO_4$), and evaporated, to give oily **11**. A small amount of **11** was submitted to chromatography on SiO_2 with 10:1 $CHCl_3$–MeOH, to give an analytical sample of *phenyl 2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside* (**11**); $[\alpha]_D$ +49.5° (*c* 0.18); R_F 0.5 in 10:1 $CHCl_3$–MeOH; δ_H (CD_3OD): 7.9–7.65 (m, 4 H, phthalimido), 7.45–7.0 (m, 5 H, phenyl), 5.57 (d, $J_{1,2}$ 10 Hz, H-1).

Anal. Calc. for $C_{20}H_{19}NO_6S \cdot 0.5\ H_2O$: C, 58.53; H, 4.91; N, 3.41; S, 7.81. Found: C, 58.57; H, 4.82; N, 3.17; S, 7.32.

A solution of crude **11**, α,α-dimethoxytoluene (3.5 mL), and $TsOH \cdot H_2O$ (50 mg) in MeCN (50 mL) was stirred for 15 h at 20°, and the acid was neutralized with Et_3N (0.04 mL). The solution was evaporated, and chromatography of the residue on SiO_2 (250 g) with 3:1 toluene–EtOAc gave **12** (2.5 g, 89.8% from **9**), $[\alpha]_D$ +36.3° (*c* 0.65); R_F 0.54 in 3:1 toluene–EtOAc; δ_H: 7.9–7.55 (m, 4 H, phthalimido), 7.5–7.1 (m, 10 H, 2 phenyl), 5.63 (d, $J_{1,2}$ 10 Hz, H-1), and 5.50 (s, benzylidene).

Anal. Calc. for $C_{27}H_{23}NO_6S$: C, 66.25; H, 4.74; N, 2.86; S, 6.54. Found: C, 66.76; H, 4.81; N, 2.72; S, 6.23.

Phenyl 3-O-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**14**). — To a solution of **12** (13.5 g, 27.6 mmol) in $HCONMe_2$ (150 mL) was added NaH (50%, 1.6 g, 33.3 mmol), and the mixture was stirred for 10 min at 20°. To this mixture was added benzyl bromide (3.4 mL, 28.6 mmol), and the mixture was stirred for 15 h at 20°. MeOH (20 mL) was now carefully added, to decompose the excess of NaH, and the mixture was diluted with H_2O (450 mL), and extracted with EtOAc. The usual processing afforded oily **13**; R_F 0.89 in 3:1 toluene–EtOAc.

A solution of this oil in AcOH (350 mL) and H_2O (150 mL) was stirred for 45 min at 100°, and evaporated *in vacuo*. A solution of the residue in EtOAc was successively washed with aq. $NaHCO_3$ and H_2O, dried ($MgSO_4$), and evaporated, to give an oily residue. Chromatography on SiO_2 (700 g) with 2:1 toluene–EtOAc afforded oily **14** (9.6 g, 70.8% from **12**), $[\alpha]_D$ +91.6° (*c* 1.3); R_F 0.21 in 2:1 toluene–EtOAc; δ_H: 7.9–7.6 (m, 4 H, phthalimido), 7.4–7.1 (m, 5 H, phenyl), 7.1–6.9 (m, 5 H, $PhCH_2$), 5.57 (d, $J_{1,2}$ 10 Hz, H-1), and 4.70 and 4.50 (2 d, J_{AB} 12 Hz, CH_2Ph).

Anal. Calc. for $C_{27}H_{25}NO_6S$: C, 65.98; H, 5.13; N, 2.85; S, 6.51. Found: C, 65.59; H, 5.33; N, 2.75; S, 6.37.

Phenyl 6-O-acetyl-3-O-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**3**). — To a solution of **14** (1 g) in $Cl(CH_2)_2Cl$ (10 mL) and pyridine (1 mL) was added Ac_2O (0.5 mL) at 5°, and the mixture was stirred for 1.5 h at 5°; then, MeOH (1 mL) was added, and the mixture was stirred for 30 min at 20°. Evaporation of the

solution, addition and evaporation of toluene, and chromatography of the residue on SiO_2 (50 g) with 9:1 toluene–EtOAc afforded crystalline **3** (610 mg, 56%), m.p. 126.5–128°, $[\alpha]_D$ +56.5° (*c* 0.43); R_F 0.20 in 9:1 toluene–EtOAc; δ_H: 7.85–7.6 (m, 4 H, phthalimido), 7.45–7.1 (m, 5 H, phenyl), 7.1–6.85 (m, 5 H, $PhCH_2$), 5.53 (d, $J_{1,2}$ 10 Hz, H-1), 4.73 and 4.50 (2 d, 2 H, $PhCH_2$), and 2.15 (s, OAc).

Anal. Calc. for $C_{29}H_{27}NO_7S$: C, 65.28; H, 5.10; N, 2.62; S, 6.00. Found: C, 65.30; H, 5.11; N, 2.57; S, 6.05.

*Phenyl 6-O-benzoyl-3-O-benzyl-2-deoxy-2-phthalimido-1-thio-β-*D*-glucopyranoside* (**4**). — To a solution of **14** (1.0 g, 2 mmol) in $Cl(CH_2)_2Cl$ (10 mL) and pyridine (1 mL) was added BzCl (0.5 mL, 4.3 mmol) at 5°, and the mixture was stirred for 1 h at 20°. Further pyridine (1 mL) and BzCl (0.5 mL) were added at 20°, and after 15 min, an excess of MeOH was added. The usual processing, and chromatography on SiO_2 (100 g) with 3:1 toluene–EtOAc afforded oily **4** (685 mg, 57.5%), $[\alpha]_D$ +39.7° (*c* 0.32); R_F 0.66 in 2:1 toluene–EtOAc; δ_H: 8.2–6.8 (m, 19 H, aromatic), 5.55 (d, $J_{1,2}$ 10 Hz, H-1).

Anal. Calc. for $C_{34}H_{29}NO_7S$: C, 68.56; H, 4.91; N, 2.35; S, 5.37. Found: C, 68.41; H, 5.06; N, 2.33; S, 5.29.

ACKNOWLEDGMENTS

We thank Dr. J. Uzawa and Mrs. T. Chijimatsu for recording and measuring the n.m.r. spectra, and Dr. H. Homma and his staff for the elemental analyses. We also thank Miss A. Sone for her technical assistance.

REFERENCES

1 T. Ogawa and S. Nakabayashi, *Carbohydr. Res.*, 93 (1981) c1–c5.
2 T. Okuyama, *Tohoku J. Exp. Med.*, 48 (1958) 313–317.
3 J.-C. Jacquinet, J.-M. Petit, and P. Sinaÿ, *Carbohydr. Res.*, 38 (1974) 305–311; J.-C. Jacquinet and P. Sinaÿ, *ibid.*, 46 (1976) 138–142; *J. Org. Chem.*, 42 (1977) 720–724; P. Rollin and P. Sinaÿ, *J. Chem. Soc. Perkin Trans. 1*, (1977) 2513–2517; J.-C. Jacquinet and P. Sinaÿ, *ibid.*, (1979) 314–322; J.-M. Petit, J.-C. Jacquinet, and P. Sinaÿ, *Carbohydr. Res.*, 82 (1980) 130–134.
4 C. D. Warren and R. W. Jeanloz, *Carbohydr. Res.*, 53 (1977) 67–84.
5 M. A. Nashed, C. W. Slife, M. Kiso, and L. Anderson, *Carbohydr. Res.*, 58 (1977) c13–c16; 82 (1980) 237–252.
6 T. Ogawa and M. Matsui, *Carbohydr. Res.*, 54 (1977) c17–c21.
7 B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, 19 (1954) 1786–1792; S. Akiya and T. Osawa, *Yakugaku Zasshi*, 77 (1957) 726–730.
8 R. U. Lemieux, T. Takeda, and B. Y. Chung, *ACS Symp. Ser.*, 39 (1976) 90–115.