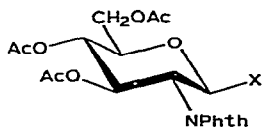
Carbohydrate Research, 97 (1981) 81–86
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

SYNTHESIS OF 3,6-DI-*O*-ACETYL-2-DEOXY-2-PHTHALIMIDO-4-*O*-(2,3,4,6-TETRA-*O*-ACETYL-β-D-GALACTOPYRANOSYL)-β-D-GLUCOPYRANOSYL CHLORIDE*

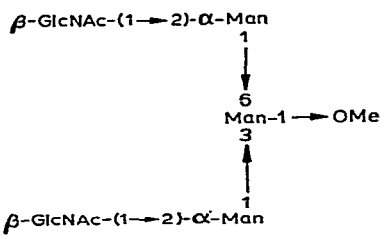
TOMOYA OGAWA** AND SATORU NAKABAYASHI***
The Institute of Physical and Chemical Research, Wako-shi, Saitama, 351 (Japan)
(Received May 19th, 1981; accepted for publication, June 10th, 1981)

ABSTRACT

A lactosaminyl donor, 3,6-di-*O*-acetyl-2-deoxy-2-phthalimido-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyl chloride, was synthesized in 10 steps, starting from 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose. Benzyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside was prepared by regioselective benzylation at the primary hydroxyl group by the stannyl method, and was used as a key intermediate.

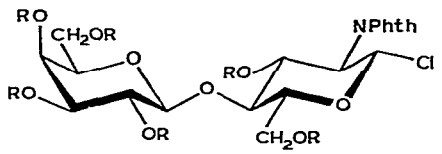


1 X = Cl
2 X = OAc
3 X = OBn
Phth = phthaloyl
Bn = $PhCH_2$



4

5



6 R = Ac

*Part XI in the series "Synthetic Studies on Cell-surface Glycans", For part X, see ref. 1.
**To whom enquiries should be addressed.
***Present address: Research Laboratories, Meiji Seika Kaisha, Ltd., Morooka-cho, Kohoku-ku, Yokohama, 222, Japan.

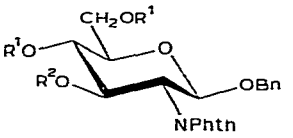
INTRODUCTION

In 1975, 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride[2] (**1**) was reported to be an efficient glycosyl donor by Lemieux *et al.*[3], and it has been used for the synthesis of several biologically important oligosaccharides[4], including glycan chains[5] of such glycoproteins as **4**.

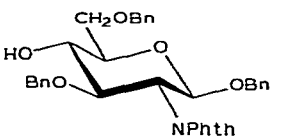
The glycan sequence **5** is involved as a common aspect in the structure of complex types of glycan chains in glycoproteins[6]. For the synthesis of such chains, the availability of an efficient, lactosaminyl donor is crucial. We report here the synthesis of 3,6-di-*O*-acetyl-2-deoxy-2-phthalimido-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyl chloride* (**6**), starting from the β-acetate **2**.

RESULT AND DISCUSSION

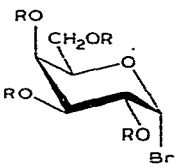
Treatment of β-acetate **2** with[7] Bu_3SnOBn in the presence of $SnCl_4$ afforded crystalline β-glycoside **3** in 72% yield. The structure of **3** was confirmed by ^1H-n.m.r. data, which showed a doublet at δ 5.38 with J 8 Hz for H-1. Deacetylation of **3** was performed under acidic conditions, according to Lemieux *et al.*[3], to give **7** in 81% yield. Benzylidenation of **7** with α,α-dimethoxytoluene and *p*-toluenesulfonic acid afforded **8**, benzylation of **8** gave **9**, and hydrolysis of benzyl ether **9** led to the isolation of 3-benzyl ether **10** in 55% overall yield from triol **7**. Monobenzylation at the primary hydroxyl group of **10** could be conveniently achieved by the stannyl



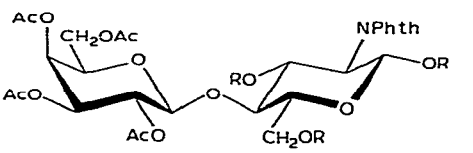
7 $R^1 = R^2 = H$
8 R^1 = benzylidene, $R^2 = H$
9 R^1 = benzylidene, $R^2 = Bn$
10 $R^1 = H, R^2 = Bn$



11



12 R = Ac



13 R = Bn
14 R = Ac

*Formulas **6**, **13**, and **14** are depicted in order to show the favored rotameric orientation at the interglycosidic linkage.

method[8], to give the 3,6-dibenzyl ether **11** in 66% yield. The structure assigned to **11** was confirmed by ^{13}C-n.m.r. data, which showed two deshielded signals[9], for C-3 and C-6, at δ 78.6 and 70.6.

The key glycosyl acceptor **11** was glycosylated with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**12**) in the presence[10] of powdered molecular sieve 4A and $HgBr_2$, giving a 71% yield of disaccharide **13**. The anomeric configuration at C-1′ of **13** was assigned from ^{13}C-n.m.r. data, which showed two signals, for C-1 and C-1′, at δ 97.4 ($^1J_{CH}$ 162.4 Hz) and 100.3 ($^1J_{CH}$ 162.4 Hz), respectively, in good agreement with observations of Bock and Pedersen[11]. Benzyl ether **13** was hydrogenolyzed in the presence of Pd–C, and acetylation of the product gave crystalline β-acetate **14** in 75% yield. The β-anomeric configuration at C-1 of **14** was evident from the ^{1}H-n.m.r. data, which revealed a doublet at δ 6.48 (J 8 Hz) for H-1. The synthesis of **14** by a different route was recently reported by Arnarp and Lönngren[12]. Transformation of β-acetate **14** into crystalline chloride **6** was achieved in 40% yield by treatment with hydrogen chloride in 1,2-dichloroethane. Again, the assignment of the β-anomeric configuration at C-1 was supported by the presence of a doublet at δ 6.16 (J 9 Hz) for H-1 in its ^{1}H-n.m.r. spectrum.

In conclusion, an efficient, synthetic route to the lactosaminyl donor **6**, in 5% overall yield, in 10 steps starting from the readily available tetraacetate **2**, has been developed.

EXPERIMENTAL

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. I.r. spectra were recorded with an EPI-G2 Hitachi spectrophotometer, employing KBr discs for the crystalline samples and neat films for the 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. Column chromatography was performed on columns of Silica Gel Merck (70–230 mesh; E. Merck, Darmstadt, Germany). Thin-layer chromatography was performed on precoated plates (layer thickness, 0.25 mm; E. Merck, Darmstadt, Germany) of Silica Gel 60 F_{254}.

*Benzyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**3**). — To a solution of **2** (19.0 g, 40 mmol) and Bu_3SnOCH_2Ph (17.5 g, 44 mmol) in $Cl(CH_2)_2Cl$ (150 mL) was added $SnCl_4$ (4.6 mL, 40 mmol) dropwise at 5°. The mixture was stirred for 4 h at 20–25°, poured into aqueous $NaHCO_3$, and extracted with EtOAc. The extract was washed with water, dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography on SiO_2 (500 g) with 10:1 and 2:1 toluene–EtOAc, and crystallization from i-PrOH gave **3** (15.1 g, 72%), m.p. 106–107°, $[\alpha]_D$ −11.3° (*c* 1.6); R_F 0.43

in 2:1 toluene–EtOAc; δ_H: 7.88–7.64 (m, 4 H, phthaloyl), 7.06 (s, 5 H, benzyl), 5.80 (dd, $J_{2,3}$ 10, $J_{3,4}$ 9 Hz, H-3), 5.38 (d, $J_{1,2}$ 8 Hz, H-1), 5.19 (t, $J_{3,4} = J_{4,5} =$ 9 Hz, H-4), 4.86 and 4.53 (ABq, 2 H, J 12 Hz, benzyl), 4.50–4.10 (m, 3 H, H-2,6), 4.0–3.75 (m, 1 H, H-5), and 2.12, 2.02, and 1.84 (3 Ac).

Anal. Calc. for $C_{27}H_{27}NO_{10}$: C, 61.71; H, 5.18; N, 2.67. Found: C, 61.73; H, 5.06; N, 2.59.

*Benzyl 2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**7**). — A solution of **3** (10 g, 19 mmol) in acetone (200 mL), H_2O (60 mL), and concentrated HCl (40 mL) was heated under reflux, with stirring, for 3.25 h at 70°. The acetone was evaporated *in vacuo*, and the aqueous phase was extracted with CH_2Cl_2. The extract was successively washed with aqueous $NaHCO_3$ and H_2O, dried ($MgSO_4$), and evaporated. The residue crystallized from i-PrOH, to give **7** (6.15 g, 81%), m.p. 169–170°, $[\alpha]_D$ −50.7° (*c* 0.38); R_F 0.44 in 10:1 $CHCl_3$–MeOH; δ_H (CD_3OD): 7.75 (s, 4 H, phthaloyl), 7.00 (s, 5 H, benzyl), 5.13 (d, $J_{1,2}$ 8 Hz, H-1), and 4.78 and 4.50 (ABq, 2 H, J 12 Hz, CH_2Ph).

Anal. Calc. for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.17; H, 5.39; N, 3.54.

*Benzyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**8**). — A solution of **7** (6 g, 15 mmol), α,α-dimethoxytoluene (3 g, 20 mmol), and *p*-TsOH (40 mg) in CH_3CN (70 mL) was stirred for 8 h at 20–25°, made neutral with Et_3N (0.1 mL), and evaporated *in vacuo*, to give crude, solid **8**, which was used directly for the next step. A small portion of this crude solid was chromatographed on SiO_2 with 3:1 toluene–EtOAc, to give an analytical sample of **8**, m.p. 187–188°, $[\alpha]_D$ −81.6° (*c* 0.25); R_F 0.57 in 2:1 toluene–EtOAc; δ_H: 7.8–7.6 (m, 4 H, phthaloyl), 7.55–7.25 (m, 5 H, benzylidene), 7.02 (s, 5 H, benzyl), 5.56 (s, C*H*-Ph), 5.26 (d, $J_{1,2}$ 8 Hz, H-1), and 4.84 and 4.50 (ABq, J 12 Hz, CH_2Ph).

Anal. Calc. for $C_{28}H_{25}NO_7$: C, 68.98; H, 5.17; N, 2.87. Found: C, 68.88; H, 5.17; N, 2.82.

*Benzyl 3-O-benzyl-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**10**). — To a solution of crude **8** in $HCONMe_2$ (100 mL) was added NaH (50%; 1 g, 21 mmol) portionwise, and the mixture was stirred for 15 min at 5°. To this mixture was added benzyl bromide (2 mL, 17 mmol) dropwise at 5°, and the mixture was stirred for 16 h at 20°. The usual processing afforded oily **9**, which was dissolved in 70% aqueous AcOH (220 mL). The solution was stirred for 1.5 h at 100°, cooled, and evaporated *in vacuo*; the usual processing, and chromatography on SiO_2 (300 g) with 1:1 toluene–EtOAc, afforded **10** as an oil (4.0 g, 55% from **7**), $[\alpha]_D$ −2.5° (*c* 0.6); R_F 0.43 in 10:1 $CHCl_3$–MeOH; δ_H: 7.60 (bs, 4 H, phthaloyl), 7.3–6.8 (m, 2 benzyl), 5.16 (d, $J_{1,2}$ 8 Hz, H-1), and 4.74, 4.71 and 4.47, 4.45 (two sets of ABq, J 12 Hz, 2 CH_2Ph).

Anal. Calc. for $C_{28}H_{27}NO_7$: C, 68.70; H, 5.56; N, 2.86. Found: C, 68.96; H, 5.55; N, 2.76.

*Benzyl 3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**11**). — Oily **10** (8.0 g, 16.3 mmol) and $(Bu_3Sn)_2O$ (9.6 g, 16.1 mmol) in toluene (200 mL)

was heated under reflux, with stirring, for 2 h at 140° with continuous removal of water, cooled, and evaporated *in vacuo*. A solution of the residue in benzyl bromide (80 mL) was stirred for 4.5 days at 80–90° under argon, cooled, and evaporated *in vacuo*, and the residue was chromatographed on SiO_2 (500 g) with 2:1 toluene–EtOAc, to give **11** (6.3 g, 66%), $[\alpha]_D$ −9.4° (*c* 0.8); R_F 0.55 in 2:1 toluene–EtOAc; δ_H: 7.63 (bs, 4 H, phthaloyl), 7.33 (s, 5 H, benzyl), 7.00–6.8 (m, 2 benzyl), 5.11 (d, $J_{1,2}$ 8 Hz, H-1), 4.79, 4.70 and 4.46, 4.44 (two sets of ABq, 2 CH_2Ph), and 4.62 (s, 2 H, CH_2Ph); δ_C: 97.3 (C-1, $^1J_{CH}$ 161.8 Hz), 78.6 (C-3), and 70.6 (C-6).

Anal. Calc. for $C_{35}H_{33}NO_7$: C, 72.52; H, 5.74; N, 2.42. Found: C, 72.60; H, 5.78; N, 2.35.

*Benzyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranosyl)-β-*D*-glucopyranoside* (**13**). — From a suspension of powdered molecular sieve 4 A (60 g, dried *in vacuo* for 14 h at 180°), $HgBr_2$ (4.0 g, 11 mmol), and **11** (6.3 g, 10.8 mmol) in $Cl(CH_2)_2Cl$ (300 mL) was distilled off $Cl(CH_2)_2Cl$ (200 mL). To the suspension was added a solution of bromide **12** (8.9 g, 21.6 mmol) in $Cl(CH_2)_2Cl$ (50 mL), and from this mixture was distilled $Cl(CH_2)_2Cl$ (50 mL). The mixture was now stirred for 8 h at 85°, cooled, and filtered through Celite. The filtrate was successively washed with aqueous $NaHCO_3$ and H_2O, dried ($MgSO_4$), and evaporated. The residue was chromatographed on SiO_2 (500 g) with 2:1 toluene–EtOAc, to give **13** (7.0 g, 71%), $[\alpha]_D$ −0.3° (*c* 0.62); R_F 0.45 in 2:1 toluene–EtOAc; δ_H: 7.61 (bs, 4 H, phthaloyl), 7.35 (s, 5 H, benzyl), 7.00–6.78 (m, 2 benzyl), 2.03 (s, 3 H, Ac), 1.99 (s, 6 H, 2 Ac), and 1.94 (s, 3 H, Ac); δ_C: 100.3 (C-1′, $^1J_{CH}$ 162.4 Hz), 97.4 (C-1, $^1J_{CH}$ 162.4 Hz), 77.9, 76.5, 74.8, 74.3, 73.7, 71.0, 70.8, 70.5, 69.5, 67.6, 67.0, 60.8 (C-6′), and 55.7 (C-2).

Anal. Calc. for $C_{49}H_{51}NO_{16}$: C, 64.68; H, 5.65; N, 1.54. Found: C, 64.80; H, 5.67; N, 1.50.

*1,3,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranosyl)-β-*D*-glucopyranose* (**14**). — A mixture of **13** (440 mg, 0.48 mmol) and 10% Pd-C (400 mg) in oxolane (8 mL) was stirred for 20 h at 40° under H_2. T.l.c. examination showed the disappearance of **13**, and the formation of a new component at R_F 0.6 in 25:2 $CHCl_3$–MeOH. Filtration (Celite), evaporation *in vacuo*, and acetylation of the residue in pyridine (8 mL)–Ac_2O (4 mL) for 4 h at 10–20° gave a crude solid. Recrystallization from i-PrOH gave β-acetate **14** (275 mg, 75%); recrystallized from EtOAc–EtOH, m.p. 285–286°, $[\alpha]_D$ +29.6° (*c* 0.24); R_F 0.17 in 2:1 toluene–EtOAc, and 0.50 in 20:1 CH_2Cl_2–acetone; δ_H: 7.92–7.64 (m, 4 H, phthaloyl), 6.48 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 2.14 (s, 2 Ac), 2.05 (s, 2 Ac), 1.98 (s, Ac), 1.96 (s, Ac), and 1.90 (s, Ac).

Anal. Calc. for $C_{34}H_{39}NO_{19}$: C, 53.33; H, 5.13; N, 1.82. Found: C, 53.21; H, 5.10; N, 1.71.

*3,6-Di-*O*-acetyl-2-deoxy-2-phthalimido-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranosyl)-β-*D*-glucopyranosyl chloride* (**6**). — A solution of **14** (62 mg) in $Cl(CH_2)_2Cl$ (3 mL) was saturated with dry HCl, stirred for 16 h at 20–25°, and evaporated *in vacuo*. A solution of the residue in EtOAc (20 mL) was successively washed with

aqueous $NaHCO_3$ and H_2O, dried ($MgSO_4$), and evaporated *in vacuo*, to afford a residue that crystallized from EtOAc–i-Pr_2O to give **6** (25 mg, 40%), m.p. 189.5–190.5°, $[\alpha]_D$ +29.5° (*c* 0.33); R_F 0.27 in 2:1 toluene–EtOAc; δ_H: 7.9–7.6 (m, 4 H, phthaloyl), 6.16 (d, $J_{1,2}$ 9 Hz, H-1), 2.14 (s, Ac), 2.10 (s, Ac), 2.04 (s, Ac), 2.02 (s, Ac), 1.94 (s, Ac), and 1.90 (s, Ac).

Anal. Calc. for $C_{32}H_{36}ClNO_{17}$: C, 51.71; H, 4.89; N, 1.89. Found: C, 51.65; H, 5.11; N, 1.78.

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 Emeritus Scientist Prof. M. Matsui for his encouragement, and Miss A. Sone for technical assistance.

REFERENCES

1 T. OGAWA, S. NAKABAYASHI, AND K. SASAJIMA, *Carbohydr. Res.*, 96 (1981) 29–39.
2 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.
3 R. U. LEMIEUX, T. TAKEDA, AND B. Y. CHUNG, *ACS Symp. Ser.*, 39 (1976) 90–115.
4 D. R. BUNDLE AND S. JOSEPHSON, *J. Chem. Soc., Perkin Trans. 1*, (1979) 2736–2739; P. L. DURETTE, E. P. MEITZNER, AND T. Y. SHEN, *Tetrahedron Lett.*, (1979) 4013–4016; *Carbohydr. Res.*, 77 (1979) c1–c4.
5 T. OGAWA, K. KATANO, AND M. MATSUI, *Carbohydr. Res.*, 64 (1978) c3–c9; T. OGAWA, K. KATANO, K. SASAJIMA, AND M. MATSUI, *Tetrahedron*, in press.
6 R. KORNFELD AND S. KORNFELD, *Annu. Rev. Biochem.*, 45 (1976) 217–237; J. MONTREUIL, *Adv. Carbohydr. Chem. Biochem.*, 37 (1980) 158–223.
7 T. OGAWA AND M. MATSUI, *Carbohydr. Res.*, 51 (1976) c13–c18.
8 T. OGAWA AND M. MATSUI, *Carbohydr. Res.*, 62 (1978) c1–c4.
9 L. RADICS, M. KAJTAR-PEREDY, S. CORSANO, AND L. STANDOLI, *Tetrahedron Lett.*, (1975) 4287–4290; K. TORI, T. HIRATA, O. KOSHITANI, AND T. SUGA, *ibid.*, (1976) 1311–1314; K. YAMASAKI, H. KOHDA, T. KOBAYASHI, R. KASAI, AND O. TANAKA, *ibid.*, (1976) 1005–1008; K. TORI, S. SEO, Y. YOSHIMURA, M. NAKAMURA, Y. TOMITA' AND H. ISHII, *ibid.*, (1976) 4167–4170.
10 J.-C. JACQUINET, J.-R. POUGNY, D. DUCHET, AND P. SINAŸ, *Joint Conf. CIC–ACS, 2nd, Montreal*, (1977) CARB-44.
11 K. BOCK, I. LUNDT, AND C. PEDERSEN, *Tetrahedron Lett.*, (1973) 1037–1040; K. BOCK AND C. PEDERSEN, *J. Chem. Soc., Perkin Trans. 2*, (1974) 293–297; *Acta Chem. Scand., Ser. B*, 29 (1975) 258–264.
12 J. ARNARP AND J. LÖNNGREN, *J. Chem. Soc. Chem. Commun.*, (1980) 1000–1002.