Carbohydrate Research, 208 (1990) 260–263
Elsevier Science Publishers B.V., Amsterdam

Note

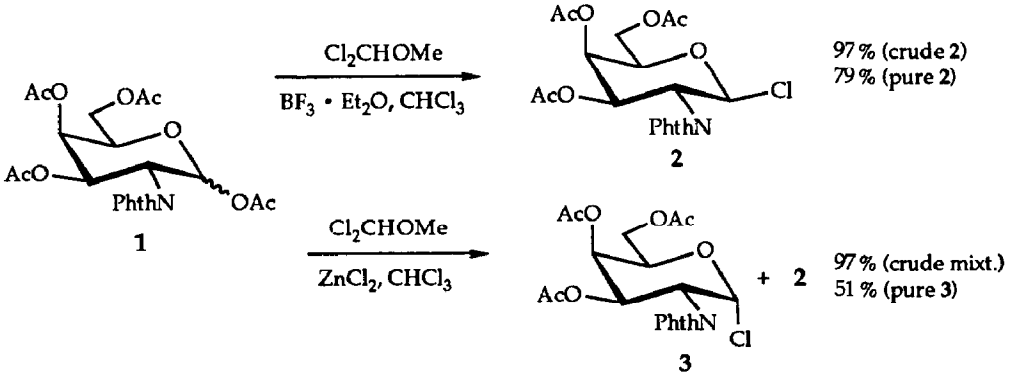
Efficient syntheses of 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β- and -α-D-galactopyranosyl chloride

Ulf Nilsson, Asim K. Ray, and Göran Magnusson*
Organic Chemistry 2, Chemical Center, Lund Institute of Technology, University of Lund, Box 124, 221 00 Lund (Sweden)

(Received March 15th, 1990; accepted for publication, April 30th, 1990)

2-Acetamido-2-deoxy-β-D-galactopyranose is a common constituent of many oligosaccharides present in glycoproteins and glycolipids. These oligosaccharides are synthesised usually by glycosylations with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-D-galactopyranosyl bromide. The α-bromide **5** was first prepared by Paulsen and Bünsch[1], but several subsequent reports on the α- and β-bromides are inconsistent. Thus, Paulsen and Paal[2] reported the α-bromide, but the n.m.r. data fitted the β-bromide. Leontein *et al.*[3] referred to the α-bromide in the Discussion but the β-bromide was used in the Experimental. Sugimoto *et al.*[4] reported the β-bromide, but no experimental details were given.

Treatment of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-α,β-D-galactopyranose (**1**) with HBr–Ac_2O–HOAc[1] gives a crude ~5:1 α,β-mixture of glycosyl bromides from which the pure α anomer **5** can be crystallised from ether. The α-bromide **5** was much less reactive than the β-bromide **4** in glycosylation reactions; with many secondary alcohols, a large excess of α,β-mixture was necessary in order to keep reaction times within reasonable limits (days) and unreacted α-bromide **5** could be isolated often. In sharp contrast, the corresponding β-chloride **2** (see below) is a good glycosyl donor and



* Author for correspondence.

0008-6215/90/$ 03.50

its routine use has given 70–80% of purified glycosylation products. These syntheses will be reported elsewhere.

The preparation of **2** follows essentially the method[5] for the synthesis of 1,2-*trans* glycopyranosyl chlorides from the corresponding 1,2-*trans* acetates. Treatment of the acetate **1** (α,β-ratio 5:2) with 1,1-dichloromethyl methyl ether (~9 equiv.) and boron trifluoride etherate (4 equiv.) in chloroform at 63° gave crude **2** in virtually quantitative yield that was sufficiently pure for use as glycosyl donor. Recrystallisation gave 79% of pure **2**. The amount of $BF_3 \cdot Et_2O$, the temperature, and the time of reaction influenced the purity of crude **2** as shown in Table I. The synthesis of **2** was performed from α,β-**1** and there was no need to start with a pure β-acetate.

The α-chloride **3** was prepared from **1**, using zinc chloride[6] instead of $BF_3 \cdot Et_2O$. After 3 h at 70°, the α,β-equilibrium seemed to be reached and 51% of **3** was isolated by chromatography.

Selective ^{1}H-n.m.r. data for **1–5** are shown in Table II.

TABLE I

Product composition in the reaction of **1** (0.5 mmol) with 1,1-dichloromethyl methyl ether (9 equiv.) in 0.5 mL of solvent

Catalyst (equiv.)	*Solvent*	*Temp (°)*	*Time (h)*	*Product composition (%)*[a]		
				1	**2**	**3**
$BF_3 \cdot Et_2O$ (4)	$CHCl_3$	63	1.5	0	>99	<1
$BF_3 \cdot Et_2O$ (4)	$CHCl_3$	22	68	3	96	<1
$BF_3 \cdot Et_2O$ (2)	$CHCl_3$	63	5.5	2	86	12
$BF_3 \cdot Et_2O$ (2)	Toluene	113	1	0	62	38
$ZnCl_2$ (catalytic)	$CHCl_3$	68	3	0	28	72

[a] Determined by ^{1}H-n.m.r. spectroscopy.

TABLE II

Selected ^{1}H-n.m.r. data (δ in p.p.m., *J* in Hz) for **1–5**

Compound	*H-1*	*H-3*
1β	6.45 (8.9)	5.94 (3.4, 11.4)
	[lit.[1] 6.26 (8.8); lit.[10]: 6.45 (8)]	5.94 (3.4, 11.4)
		5.94 (2.5, 10)
1α	6.34 (3.2)	6.52 (3.1, 12.3)
	[lit.[11] 6.34 (3.2)]	6.52 (3.6, 12)
2	6.17 (9.3)	5.80 (3.4, 11.2)
3	6.34 (3.7)	6.58 (3.1, 12.0)
4	6.40 (9.6)	5.77 (3.5, 11.2)
	[lit.[12] 6.36 (10)]	5.76 (3.5, 11.0)
5	6.69 (3.6)	6.53 (3.2, 12.0)
	[lit.[1] 6.69 (3.5)]	6.53 (3.1, 11.9)

3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride was reported by Akiya and Osawa[7], and the α-chloride was prepared from the β-chloride by Lemieux *et al.*[8]. It was stated that the β-chloride was as efficient a glycosyl donor as the corresponding β-bromide and that the chloride had a better stability on storage. A direct transformation of 2-(trimethylsilyl)ethyl glycosides into the corresponding chlorides (including 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride) has been reported[9].

EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. ^{1}H-N.m.r. spectra were recorded with a Varian XL-300 spectrometer. Chemical shifts are given in p.p.m. downfield from the signal for Me_4Si with reference to internal $CHCl_3$ (7.26 p.p.m.). 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-α,β-D-galactopyranose (**1**; α,β-ratio 5:2) was prepared essentially as described for the corresponding glucose derivative[8].

*3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl chloride* (**2**). — To a solution of **1** (238 mg, 0.50 mmol) in dry chloroform (0.5 mL) was added 1,1-dichloromethyl methyl ether (0.39 mL, 4.4 mmol) followed by $BF_3{\cdot}Et_2O$ (0.25 mL, 2.0 mmol). The mixture was stirred under nitrogen for 90 min at 63° [the reaction was monitored by t.l.c. $CHCl_3$–ether, 12:1; R_F 0.38, 0.30, and 0.28 for **3**, **2**, and **1**, respectively], then cooled (ice bath), diluted with chloroform (15 mL), and poured into saturated aqueous sodium hydrogencarbonate (15 mL). The organic phase was washed with water (2 x 10 mL) and dried (Na_2SO_4), and the solvent was removed to give crude **2** (219 mg, 97%) of sufficient purity for use in glycosylation reactions. Recrystallisation from ether gave **2** (179 mg, 79%), m.p. 153–154°, $[\alpha]_D^{25}$ +32° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.90–7.76 (m, 4 H, Ar), 6.17 (d, 1 H, *J* 9.3 Hz, H-1), 5.80 (dd, 1 H, *J* 3.4 and 11.2 Hz, H-3), 5.53 (bd, 1 H, *J* 3.4 Hz, H-4), 4.74 (dd, 1 H, *J* 9.3 and 11.2 Hz, H-2), 4.24–4.18 (m, 3 H, H-5,6), 2.23, 2.08, and 1.86 (s, 3 H each, 3 OAc).

Anal. Calc. for $C_{20}H_{20}ClNO_9$: C, 52.9; H, 4.4; N, 3.1. Found: C, 53.1; H, 4.4; N, 3.0.

*3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-α-D-galactopyranosyl chloride* (**3**). — To a solution of **1** (238 mg, 0.5 mmol) in dry chloroform (0.5 mL) was added 1,1-dichloromethyl methyl ether (0.39 mL, 4.4 mmol) followed by a catalytic amount (< 5 mg) of freshly fused zinc chloride. The mixture was stirred under nitrogen for 3 h at 65–70°, then cooled, diluted with chloroform (15 mL), washed with cold saturated aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and concentrated to give a mixture (220 mg, 97%) of **3** and **2**. Column chromatography ($CHCl_3$–ether, 25:1) furnished **3** (113 mg, 51%) and recrystallisation from ether–heptane (10:1) gave a product with m.p. 157–159°, $[\alpha]_D^{25}$ +97° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.87–7.74 (m, 4 H, Ar), 6.57 (dd, 1 H, *J* 3.0 and 12.0 Hz, H-3), 6.34 (d, 1 H, *J* 3.7 Hz, H-1), 5.71 (dd, 1 H, *J* 1.1 and 3.0 Hz, H-4), 4.93 (dd, 1 H, *J* 3.7 and 12.0 Hz, H-2), 4.63 (bt, 1 H, H-5), 4.21–4.15 (m, 2 H, H-6), 2.17, 2.07, and 1.90 (s, 3 H each, 3 OAc).

ACKNOWLEDGMENTS

This work was supported by the Swedish Natural Science Research Council and The National Swedish Board for Technical Development.

REFERENCES

1 H. Paulsen and A. Bünsch, *Carbohydr. Res.*, 100 (1982) 143–167.
2 H. Paulsen and M. Paal, *Carbohydr. Res.*, 137 (1985) 39–62.
3 K. Leontein, M. Nilsson, and T. Norberg, *Carbohydr. Res.*, 144 (1985) 231–240.
4 M. Sugimoto, M. Numata, K. Koike, Y. Nakahara, and T. Ogawa, *Carbohydr. Res.*, 156 (1986) c1–c5.
5 I. Farkas, I. Szabó, and R. Bognár, *Carbohydr. Res.*, 48 (1976) 136–138.
6 P. Kovac and R. Palovcik, *Carbohydr. Res.*, 56 (1977) 399–403.
7 S. Akiya and T. Osawa, *Chem. Pharm. Bull. (Tokyo)*, 8 (1960) 583–587.
8 R. U. Lemieux, T. Takeda, and B. Y. Chung, *ACS Symp. Ser.*, 39 (1976) 90–115.
9 K. Jansson, G. Noori, and G. Magnusson, *J. Org. Chem.*, 55 (1990) 3181–3185.
10 T. Ogawa and K. Beppu, *Carbohydr. Res.*, 101 (1982) 271–277.
11 T. C. Wong, R. R. Jowns, and Y. C. Lee, *Carbohydr. Res.*, 170 (1987) 27–46.
12 S. Sabesan and R. U. Lemieux, *Can. J. Chem.*, 62 (1984) 644–654.