Tetrahedron Letters Vol. 21, pp 3565 - 3568 0040-4039/80/0908-3565$02.00/0

SYNTHESIS OF α- AND β-GLYCOPYRANOSIDES via 1-O-ALKYLATION

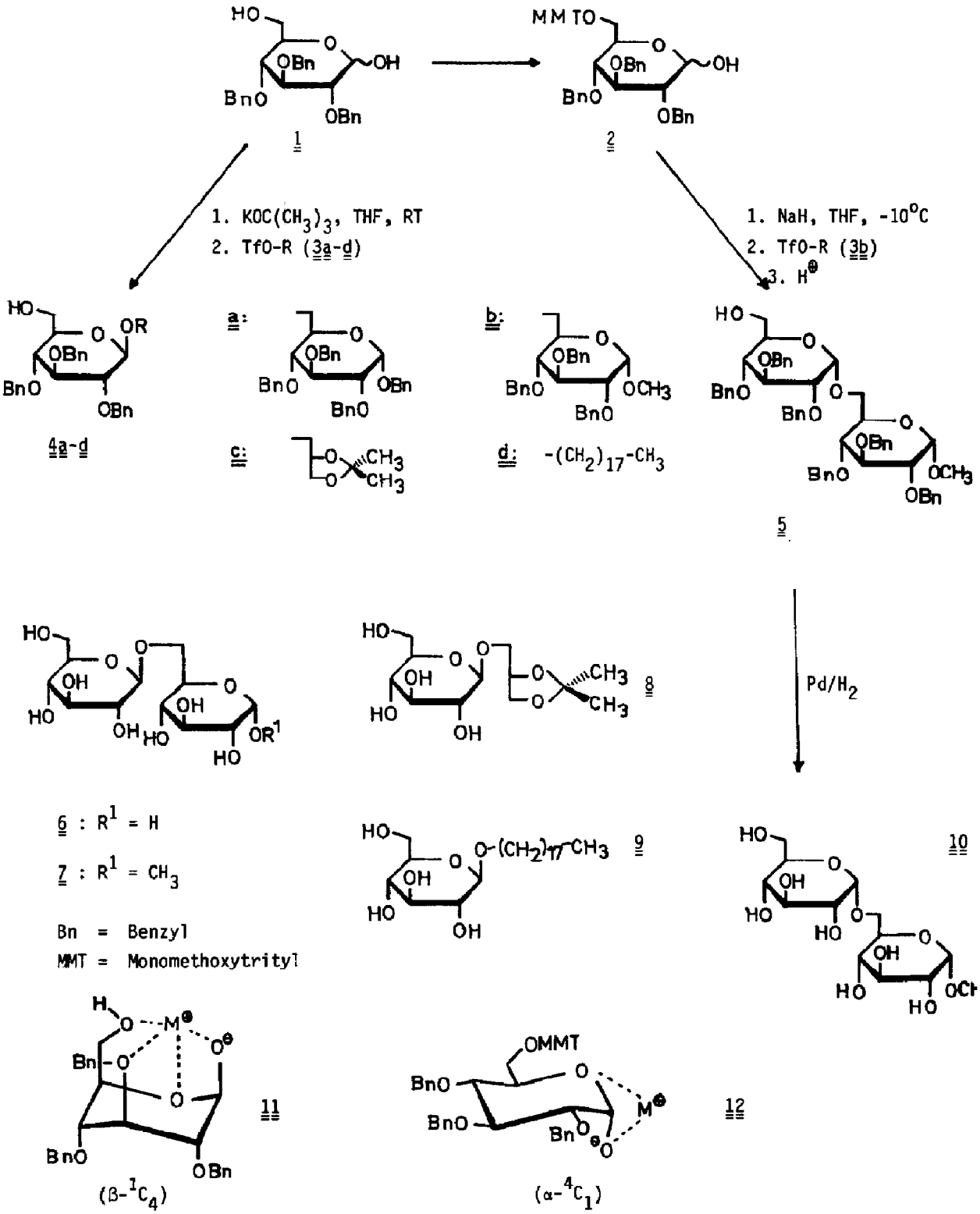
R.R. Schmidt [+], U. Moering [2], and M. Reichrath [3]
Fakultät für Chemie, Universität Konstanz, Postfach 5560
D-7750 Konstanz, Germany

Abstract: *1-O-Alkylation of partly protected glucopyranose 1 and galactopyranose 13 led to a convenient, short term synthesis of β-glycosides and β-disaccharides 4a-d and 14. Glucopyranose 2 with a bulky protective group at O-6 yielded exclusively the α-anome (isomaltoside derivative) 5.*

Our efforts to synthesize glycosides and disaccharides without the use of halogenoses and heav metal salt catalysis resulted in directed syntheses of α- or, alternatively, β-glycosides and -disaccharides of D-ribofuranose and D-mannofuranose via 1-O-alkylation [2-5]. Alkylating agent were primary triflates of carbohydrates and of polyhydroxy compounds. We report here on the de velopment of similar methods for the synthesis of α- or β-glycopyranosides. This directed synthesis of β-glycopyranosides was especially successful with partially protected carbohydrate derivatives. With simple alkylating agents preferential formation of α- or β-anomers was alrea observed under different conditions [6,7].

Previous studies of solvent, temperature and base variation with 2.3.4.6-tetra-O-protected glu copyranose did show [2,3] that there are good chances for highly β-selective alkylation with 6- unprotected glucopyranose at room temperature or at higher temperatures. Accordingly 2.3.4-tri O-benzyl glucose 1 was deprotonated with equimolar amounts of potassium tertiary butoxide in T at room temperature. Addition of the triflates 3a-d [2,3] resulted exclusively in the formation of β-disaccharides 4a,b and the β-glycosides 4c,d in good yields (Table 1) thus demonstrating the efficiency and conveniency of this β-glucopyranoside synthesis. Alkylation at O-6 or at O- was not observed due to the higher acidity of OH-1. Hydrogenolysis produced gentiobiose (6), methyl-α-gentiobioside (7) and the glucopyranosides 8 and 9, which were synthesized already by a different method 8,9).

Temperature dependent investigations indicated, that α-glucosidation is favored by low tempera tures and also by bulky protective groups at O-6 [2,10]. Therefore 1 was monomethoxytritylated to 2 and treated with sodium hydride in THF at -10°C. Addition of triflate 3b and subsequent r


1
2
1. KOC(CH3)3, THF, RT
2. TfO-R (3a-d)
1. NaH, THF, -10°C
2. TfO-R (3b)
3. H⊕
4a-d
a:
b:
c:
d: -(CH2)17-CH3
5
6 : R1 = H
7 : R1 = CH3
8
9
10
Pd/H2
Bn = Benzyl
MMT = Monomethoxytrityl
11
12
(β-1C4)
(α-4C1)

moval of the monomethoxytrityl group led exclusively to isomaltoside derivative 5; hydrogenolys produced methyl-isomaltoside 10 [11].

The observed higher reactivity of axial hydroxylic groups in alkylation reactions [12] demonstrates that the α-selectivity is due to α-anion 12 being in its $^4C_1$-conformation [13]. However, the corresponding $^4C_1$-conformer of the β-anion is present in an equilibrium of about 1:1 with 12 at room temperature [2,10]. Therefore the β-selectivity of the anion of 1 with no protective group at O-6, observed at room temperature or at higher temperatures, is interpreted by partial formation of the more reactive β-anion 11 in its $^1C_4$-conformation. Intramolecular complexation of the metal ion certainly contributes to the conformational stabilization. This explanation is also in accordance with observations made for the directed syntheses of α- or β-glycofuranoside via 1-O-alkylation [4,5].

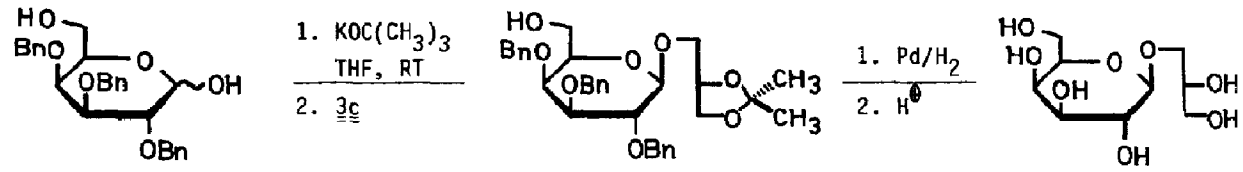
Table: Yields and optical rotations [a]

	Yield [%]	$[\alpha]_{578}^{20}$
4a	54	26.5° (c=1.0, $CHCl_3$)
4b	51	9.4° (c=1.0, $CHCl_3$)
4c	79	15.1° (c=1.03, $CHCl_3$)
4d	43	2.4° (c=1.0, $CHCl_3$)
5	80	59.0° (c=1.0, $CHCl_3$); Lit. [b]: 62.9° (c=1.0, $CHCl_3$)
6	87	14.0° (c=1.0, H_2O after 4 h); Lit. [c]: 10.0° (c=3.0, H_2O).
7	97	63.5° (c=1.0, H_2O)
8	63	-10.0° [d] (c=0.85; $CHCl_3$); Lit. [d,e] -10.5° (c=0.51, $CHCl_3$).
9	64	-19.7° (c=0.81, CH_3OH); Lit. [f]: -21.8°.
10	84	50° (c=1.0, H_2O); Lit. [g]: 50°C (c=5.8, H_2O)
14	80	-14.8° (c=0.9, $CHCl_3$)
15	84	- 3.5° (c=1.45, H_2O); Lit. [h]: -7° (c=2.0, H_2O).

a) All new compounds gave correct elemental analyses. b) R. Eby and C. Schuerch, Carbohydr.Res. 50, 203 (1976). c) V. Stefanovic, Chem.Ber. 94, 2359 (1961). d) Comparison with 2.3-O-Isopropylidene-D-glyceryl 2.3.4.6-tetra-O-acetyl-β-D-glucopyranoside. e) see ref. 8; f) see ref. 9; g) M.L. Wolfram, L.W. Georges, and I.L. Miller, J.Am.Chem.Soc. 71, 125 (1949) h) see ref. 15.

Analogous β-selectivity was observed with 2.3.4-tri-O-benzyl galactose 13 [14]. From -30°C to

room temperature ß-galacto-pyranoside 14 was obtained exclusively with 3c as alkylating agent. The easier formation of the ß-$^1C_4$ conformer with galactopyranose may be responsible for this extended ß-selectivity. For structural analysis purposes 14 was completely deprotected to yield 1 which was synthesized already independently [15].



13 14 15

References and Footnotes

1) O-Alkylation at the anomeric center, part 3. - Part 2 see preceding communication. — This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

2) U. Moering, Diplomarbeit, Universität Konstanz, 1980.

3) M. Reichrath, Thesis, Universität Konstanz, 1979.

4) R.R. Schmidt and M. Reichrath, Angew.Chem. 91, 497 (1979); Angew.Chem.Int.Ed.Engl. 18, 466 (1979); and references cited therein.

5) R.R. Schmidt, M. Reichrath, and U. Moering, accompanying paper.

6) W. Roth and W. Pigman, J.Am.Chem.Soc. 82, 4608 (1960); D.M. Hall and O.A. Stamm, Carbohydr. Res. 12, 421 (1970); A. Zamojski and H. Bazymska, Rocz.Chem. 49, 2113 (1975)

7) A.H. Haines, Adv.Carbohydr.Chem.Biochem. 33,55-56 (1976).

8) T. Ogawa, K. Katano, and M. Matsui, Carbohydr.Res. 70, 37 (1979).

9) R. Hori and Y. Kegami, Yakugaku Zasski, 79, 80 (1959).

10) P.E. Pfeffer, G.G. Moore, P.D. Hoagland, and E.S. Rothman in Synthetic Methods for Carbohydrates, ed. H.S. Elkhadem, ACS Symposium Series 39, American Chemical Society, Washington D.C., 1976, p. 155-178.

11) Similar investigations with 3c indicated that the stereochemical result is dependent on the alkylating agent used [2].

12) See ref. 7, p. 57-58.

13) The metal ion may be intramolecularly complexed to O-1, O-5, and O-6 according to model considerations.

14) 13 was obtained according to a procedure by R. Gigg and C.D. Warren, J.Chem.Soc. 1965, 2205

15) B. Wickberg, Acta Chem.Scand. 12, 1187 (1958).

(Received in Germany 11 June 1980)