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AROMATIC AND HETEROCYCLIC 1-*C*-SUBSTITUTED DERIVATIVES OF 1,5-ANHYDRO-D-GLUCITOL

GRZEGORZ GRYNKIEWICZ AND JAMES N. BEMILLER*
Department of Chemistry and Biochemistry, Southern Illinois University, Carbondale, IL 62901 (U.S.A.)

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ABSTRACT

Reaction of anomeric 1-*O*-acyl and 1-halide derivatives of 2,3,4,6-tetra-*O*-benzyl-D-glucose with anisole, ferrocene, thiophene, furan, and 1,3,5-trimethoxybenzene in the presence of a Lewis acid gives the corresponding *C*-β-D-glucopyranosyl derivatives.

INTRODUCTION

The facility of constructing a carbon–carbon bond between the anomeric center of a monosaccharide and an aromatic or heterocyclic molecule differs considerably with furanoses and pyranoses. Numerous reactions of D-ribofuranose derivatives (either per-*O*-acylated D-ribofuranosyl halides or 1-*O*-acyl-D-ribofuranoses) have provided *C*-nucleosides and their structural analogs in good yield[1]. On the other hand, a yield of only ~1% was obtained in the key step in the synthesis of naturally occurring bergenine, namely, *C*-alkylation of 4-*O*-methylgallic acid with tetra-*O*-acetyl-α-D-glucopyranosyl bromide[2].

Although C–C bonds are formed when D-glucose itself is treated with phenols in an acidic medium[3], the only practical method available until recently for synthesis of *C*-glycopyranosyl aromatic compounds was that developed by Hurd and Bonner[4]. The reaction involves treatment of a per-*O*-acetylated glycosyl halide with a large excess of an appropriate Grignard reagent and results in the formation of a mixture of anomers. An attempt to alkylate aromatic compounds with per-*O*-acylated glycosyl halides under Friedel–Crafts conditions resulted in the formation of 1-deoxy-1,1-diphenylalditol derivatives, in addition to cyclic *C*-glycosyl compounds[5]. More-recent reports indicated that, although acetylated glycals readily alkylate electron-rich substrates under Lewis acid-catalysis[6–9], nonparticipating protecting groups must be employed when aldopyranosyl halides are used as the alkylating species[10]. Stereocontrolled glycosylation *via* glycosyl imidate derivatives[11] has been applied recently to *C*-alkylation of aromatic substrates[12].

*To whom correspondence should be addressed.

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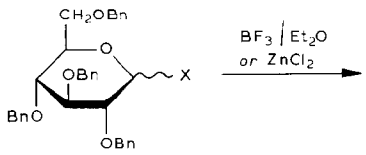
We now disclose our results on the stereoselective synthesis of some new *C*-D-glucosyl derivatives. Our general goal is to attach a versatile unit, readily convertible into other cyclic or acyclic substituents, to the anomeric center of pyranoses *via* a C–C bond. The furan nucleus, which may be envisaged as a masked, 1,4-dicarbonyl compound[13], serves this purpose; moreover, it is highly reactive in reactions of the Friedel–Crafts type. Thiophene may also be used as a C-4 vehicle[14]. Therefore, we examined reactions of the 1-*O*-acyl and 1-chloride derivatives of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose with five-membered heterocycles in the presence of various Lewis-acid catalysts.

RESULTS AND DISCUSSION

In all reactions, we found that the nature of the catalyst and of the leaving group has a greater influence on the rate of reaction than on the product ratio of the final yield. For example, an anomeric mixture of esters [1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranose (**2**), α:β ratio = 4:1 as determined by 200-MHz, ^{1}H-n.m.r. spectroscopy] reacted with an excess of furan in the presence of boron trifluoride etherate to form the same compound (**5**, m.p. 94°, $[\alpha]_D$ +71°) as that given by anomerically homogeneous 2,3,4,6-tetra-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-α-D-glucopyranose[15] (**3**), or the corresponding glycosyl chloride[16] (**4**) used in the presence of a quaternary ammonium salt to secure rapid anomeric equilibration. Catalysis with aluminum chloride, stannic chloride, zinc chloride, and boron trifluoride etherate of reactions with furan in dichloromethane solution at room temperature gave yields of product **5** in the range of 50–60%. The last-mentioned catalyst was used as a matter of convenience, and the yields were not optimized.

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl esters were next condensed with anisole, ferrocene, thiophene, and 1,3,5-trimethoxybenzene. Although the prospective synthetic utility dictated the selection of heterocycles and benzene derivatives, the choice of ferrocene stemmed from a growing interest in the synthesis of neutral-product derivatives of ferrocene for analytical and medicinal purposes[17,18]. The gross structure of the products was confirmed by elemental analysis and 200-MHz, ^{1}H-n.m.r. spectroscopy. Only for the furan derivative **5**, however, could all



1 X = OH
2 X = $OCOCH_3$ (α,β)
3 X = $OCO\text{-}C_6H_4NO_2\text{-}p$ (α)
4 X = Cl

5 R = 2-furyl
6 R = 2-thienyl
7 R = ferrocenyl
8 R = 4-methoxyphenyl
9 R = 2,4,6-trimethoxyphenyl

of the sugar-ring protons be unequivocally identified in a series of decoupling experiments [thus allowing easy deduction of the configuration (β) of the anomeric center in **5** from the relevant coupling constant, $J_{1,2}$ 6.5 Hz]. In every case examined, only one product was obtained. We assume that the same stereoselectivity is involved, resulting in exclusive formation of the β-D anomer.

For practical purposes, compounds **5–9** may be obtained by a one-flask procedure, using commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucose (**1**) as the starting material. Preparation involves carbon tetrachloride–triphenylphosphine chlorination[19] of the substrate to form **4**, followed by a zinc chloride-catalyzed alkylation reaction.

EXPERIMENTAL

General methods. — Uncorrected melting points were determined with a Thomas–Hoover Uni-melt apparatus. Optical rotations were measured with a Bendix ETL-NPL automatic polarimeter. Reactions were monitored on plates of silica gel (Merck) developed with 17:3 (v/v) hexane–acetone. Products were isolated by column chromatography on Silica gel 60 (Merck; 230–400 mesh) by gravity elution with 19:1 (v/v) light petroleum ether–ethyl acetate. ^{1}H-N.m.r. spectra for deuteriochloroform solutions, with tetramethylsilane as the internal standard, were recorded with a Nicolet NT 200 200-MHz spectrometer.

2-(2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl)furan (**5**). — *Method A.* To a solution of 2,3,4,6-tetra-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-α-D-glucopyranose[15] (**3**) (0.69 g, 1 mmol) in dichloromethane (10 mL) were added furan (2 mL) and then boron trifluoride etherate (0.1 mL), and the mixture was kept in a stoppered flask at room temperature until t.l.c. revealed disappearance of the starting ester (~2 h). The mixture was diluted with dichloromethane (20 mL), washed with aqueous sodium hydrogencarbonate, dried (magnesium sulfate), and evaporated. The oily residue was purified by chromatography to give **5**; yield 0.336 g (57%); m.p. 94° (recrystallized from hexane–ethyl acetate), $[\alpha]_D$ +71° (*c* 1, CH_2Cl_2); ^{1}H-n.m.r.: δ 3.5–3.8 (m, 4 H, H-5,6,6′) and 3.74 (t, $J_{3,4} = J_{4,5} = 9.5$ Hz, 1 H, H-4), 3.96 (pd, $J_{1,2}$ 6.5, $J_{2,3}$ 9.5 Hz, 1 H, H-2), 4.24 (t, 1 H, H-3), 4.40–5.05 (m, 8 H, 4 PhCH_2O), 5.14 (d, 1 H, H-1), 6.36 (pd, *J* 3.1 and 2.0 Hz, 1 H), 6.55 (d, 1 H) and 7.44 (m, 1 H, furan), and 7.10–7.40 (m, 20 H, 4 C_6H_5).

Anal. Calc. for $C_{38}H_{38}O_6$: C, 77.29; H, 6.62. Found: C, 77.35; H, 6.62.

Method B. To a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucose (**1**; Pfanstiehl Laboratories, Inc., Waukegan, Illinois; 0.54 g, 1 mmol) and triphenylphosphine (0.524 g, 2 mmol) in dichloromethane (10 mL) was added carbon tetrachloride (0.5 mL), and the mixture was boiled under reflux for 1 h; t.l.c. then showed that all of the **1** had been converted into **4**. After the mixture had been cooled to room temperature, furan (2 mL) was added, followed by freshly fused, anhydrous zinc chloride (1 g), and the mixture was stirred overnight, diluted with ether (50 mL), successively washed with M sodium hydroxide (3 × 20 mL) and water (2 × 20 mL),

dried (magnesium sulfate), and evaporated; chromatography afforded **5** (0.289 g, 49%).

2-(2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl)thiophene (**6**). — *A*, 62% yield; *B*, 55% yield; m.p. 108–109° (from hexane), $[\alpha]_D$ +46° (*c* 1, CH_2Cl_2); ^{1}H-n.m.r.: δ 3.45–3.85, 3.97–4.06, and 4.40–5.05 (3 groups of multiplets, 15 H, PhCH_2O and pyranose-ring protons), and 7.00–7.45 (m, 23 H, aromatic).

Anal. Calc. for $C_{38}H_{38}O_5S$: C, 56.75; H, 5.40. Found: C, 57.00; H, 5.59.

(2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl)ferrocene (**7**). — *A*, 31% yield; *B*, 19% yield; m.p. 111°, $[\alpha]_D$ −48° (*c* 1, CH_2Cl_2); ^{1}H-n.m.r.: δ 1.60 (s, 1 H), 3.25 (t, *J* 9.0 Hz, 1 H), 3.55–4.97 (m, 22 H, PhCH_2O, pyranose-ring protons and ferrocene singlet at 4.19), and 7.1–7.4 (m, 20 H, 4 C_6H_5).

Anal. Calc. for $C_{44}H_{44}FeO_5$: C, 74.59; H, 6.22. Found: C, 74.70; H, 6.36.

4-Methoxy-1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)benzene (**8**). — *A*, 23% yield; *B*, 9% yield; oil, $[\alpha]_D$ +36° (*c* 1, CH_2Cl_2); ^{1}H-n.m.r.: δ 3.8–4.1 and 4.5–5.1 (2 m, 18 H, PhCH_2O, pyranose-ring protons and OCH_3 signal at 3.95), and 7.0–7.6 (m, 24 H, aromatic).

2,4,6-Trimethoxy-1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)benzene (**9**). — *A*, 47% yield; *B*, 39% yield; physical and spectral properties in agreement with reported data[12].

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