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Note

Chemistry of the glycosidic linkage. *O*-Glycosylations catalyzed by stannic chloride, in the D-ribofuranose and D-glucopyranose series*†

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In connection with a synthetic program in the area of aminoglycoside antibiotics[1], it became necessary to prepare a series of cyclohexyl β-D-ribofuranosides to be used as model substrates in chemical, physicochemical, and biological studies. We were particularly interested in the preparation of glycosides derived from substituted cyclohexanols, so as to simulate some of the functional, configurational, and spatial characteristics of the natural glycosides of 2-deoxystreptamine[2].

Simple alkyl furanosides[3–5] can be prepared from the parent sugars by the classical Fischer alcoholysis[6], but, for more-complex alcohols, the Koenigs–Knorr[7] synthesis and its numerous modifications[3–5] have been used. If there is a participating group situated at C-2 of an aldose derivative, this method leads, in general, to 1,2-*trans*-glycosides, whereas, in the absence of neighboring-group participation, the method has been used as a source of 1,2-*cis*-glycosides in the aldofuranose[8] series. Such glycosylations require appropriately protected aldofuranosyl halide derivatives (which are often unstable), and the presence of a catalyst, an acid acceptor, or both. Other methods[3–5] are also available for the synthesis of furanosides, but they are somewhat indirect, and they lack the merits of stereocontrol, generality, and manipulative ease.

In recent communications from this laboratory[9–12], we described novel and practical methods for stereocontrolled *O*-glycosylations in the aldo-furanose and -pyranose series, including amino sugars[11]. We now describe an efficient method for the preparation of β-D-ribofuranosides and β-D-glucopyranosides in high yield. The method consists in treating the readily available 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[13] (**1**) and β-D-glucose pentaacetate[14] (**8**), respectively, with equimolar quantities of stannic chloride and the alcohol, in dichloromethane. Glycoside formation is invariably complete within a short period of time at room temperature

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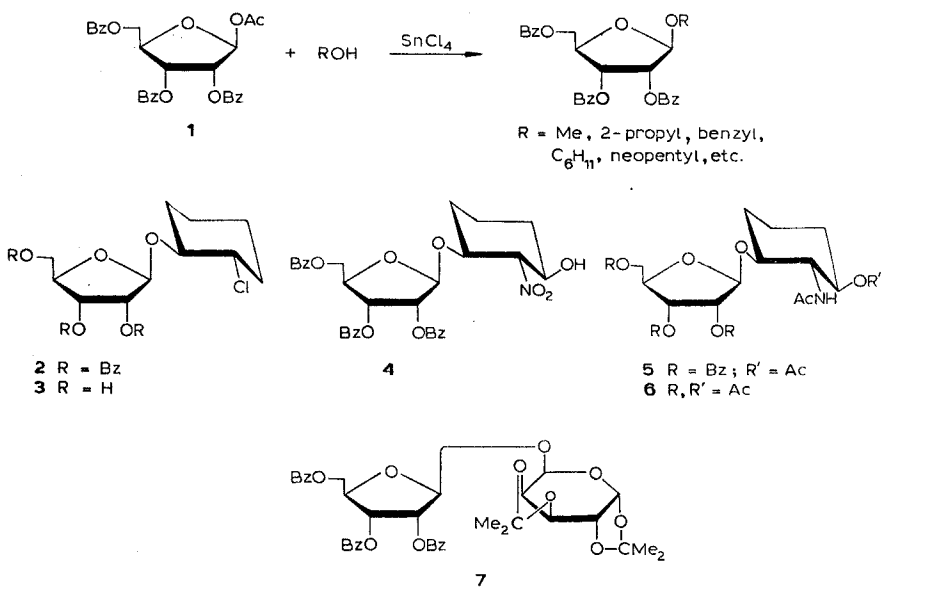
or below, and the products are of high anomeric purity, as evidenced by spectroscopic techniques. Several alkyl and cyclohexyl β-D-ribofuranoside derivatives (**2–5**) were prepared by this method, which appears to be general, and, perhaps, the most practical yet in this series (see Table I). The method was also applicable to the synthesis of disaccharides in this series, as exemplified by the preparation of 1,2:3,4-di-*O*-isopropylidene-6-*O*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-α-D-galactopyranose (**7**) in 85% yield (not optimized).

TABLE I

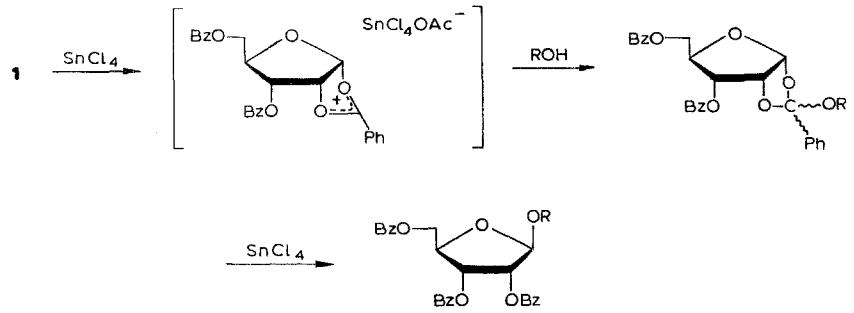
FORMATION OF ALKYL β-D-RIBOFURANOSIDE TRIBENZOATES

Alkyl group	*M.p.*	*Yield* (%)	$[\alpha]_D$ (*degrees, in* $CHCl_3$)	*References*
Methyl	syrup	93	+58	10,15
2-Propyl	syrup	87	+46	10
Ethyl	syrup	90	+50	15
Benzyl	65°	85	+20	16
Neopentyl	syrup	91	+36	10
Cyclohexyl	syrup	82	+26	10



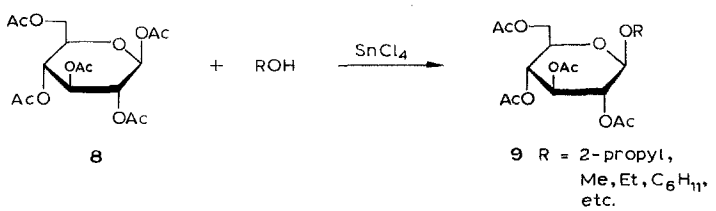
As with other methods of glycosylation in this series, the presence of a participating ester group at C-2 leads to stereoselective formation of 1,2-*trans*-glycosides[3–5,17]. These could be formed by a direct attack of the alcohol at the anomeric carbon atom of the 1,2-benzoxonium ion intermediate resulting from the sugar derivative[9,18], or of an oxonium ion that is shielded on one side by the 2-benzoyloxy

group, and stabilized by possible interaction with the unshared, *p*-orbital electrons of the carbonyl oxygen atom. On the other hand, it is also possible that the reaction proceeds by initial, kinetically controlled formation of an orthoester derivative, which, in the medium, undergoes rapid rearrangement to the 1,2-*trans*-glycoside. Previous studies[9] have, in fact, shown that, in the presence of catalytic amounts of stannic chloride, 1,2-orthoesters undergo rapid transformation into the corresponding glycosides (see Scheme 1).



Scheme 1.

Glycosylations of alcohols in the presence of Lewis acids are not without precedent[19,20]. Methyl and phenyl β-D-glucopyranoside tetraacetates have been prepared in 53 and 40% yield, respectively, from the reaction of β-D-glucose pentaacetate with the respective alcohol in the presence of an equimolar amount of stannic chloride, in refluxing benzene[19]. In our experience, β-D-glucoside formation was effected in 80% yield (not optimized) by treatment of β-D-glucose pentaacetate with



equimolar amounts of methanol and stannic chloride in dichloromethane at 0°. Such Lewis acid glycosylations were also extended successfully to the preparation of several other glycosides, including ethyl, 2-propyl, and cyclohexyl β-D-glucopyranoside tetraacetates, of high anomeric purity and in good yields. Apparently, under these mild conditions, anomerization reactions are minimized. In those cases where the glycosylation reaction was sluggish, appreciable amounts of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride were formed. After this work was completed, the preparation of several *p*-nitrophenyl and steroidal glycosides was reported that employed stannic chloride as the catalyst[21]; some anomerization was observed under

these conditions, leading to mixtures. Ogawa and Matsui have recently described related glycosylations involving alkoxystannates as potential aglycons[22].

EXPERIMENTAL

General. — Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer automatic spectropolarimeter model 141. Nuclear magnetic resonance spectra were recorded at 60 MHz for solutions in chloroform-*d*, unless otherwise stated, with tetramethylsilane as the internal standard. Infrared spectra were recorded with a Beckman IR-8 spectrometer. Mass spectra were recorded, at low resolution, with a Hitachi–Perkin–Elmer RMU-6D spectrometer, and, at high resolution, with an AEI–MS 902 spectrometer, with direct introduction of the sample into the ionizing chamber. Dichloromethane was purified by distillation from phosphorus pentaoxide.

General procedure for glycosylation. — A solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**1**; 504 mg, 1 mmole) in dichloromethane (10 ml) was treated with stannic chloride (0.12 ml, 1 mmole) at 0°, and the solution was stirred for 10 min at room temperature with exclusion of moisture. The alcohol (1 mmole) was then added, and the colorless, homogeneous solution was stirred for 1–4 h at room temperature or lower (0°). The solution was then added, dropwise and rapidly, to a saturated solution of sodium hydrogencarbonate, and the mixture was processed by extraction with dichloromethane, drying of the extract (anhydrous sodium sulfate), and evaporation to dryness. Examination of the syrupy residue by t.l.c. revealed the presence of the glycoside as the major component, along with traces of 2,3,5-tri-*O*-benzoyl-D-ribose. Purification was achieved by chromatography on silica gel with 1:49 EtOAc–benzene as the developer. The simple alkyl glycosides and their physical properties are listed in Table I.

rac. trans-*2-Chlorocyclohexyl 2,3,5-tri*-O-*benzoyl-β-*D-*ribofuranoside* (**2**). — This was obtained as a colorless syrup in 78% yield; $[\alpha]_D^{25}$ +22° (*c* 0.9, $CHCl_3$); n.m.r. data: δ 7.9, 7.4 (arom. 15 H), 5.70 (m, H-2,3), 5.52, 5.40 (s, H-1, diastereoisomers), and 4.65 (m, H-5,5′).

rac. trans-*2-Chlorocyclohexyl β-*D-*ribofuranoside* (**3**). — To a solution of compound **2** (290 mg, 0.5 mmole) in methanol (10 ml) were added a few drops of a solution of sodium methoxide in methanol. After being kept overnight at 25°, the solution was made neutral with solid carbon dioxide, the solvent was removed by evaporation, the resulting syrup was dissolved in acetone, and the traces of inorganic salts were removed by filtration. This process was repeated twice, to give a clear syrup that crystallized from 1:1 acetone–chloroform, affording 133 mg (quant.) of the title compound; m.p. 147°, $[\alpha]_D^{23}$ −23.5° (*c* 0.5, MeOH).

Anal. Calc. for $C_{11}H_{19}ClO_5$: C, 49.53; H, 7.18. Found: C, 49.59; H, 6.85.

Acetylation of this product with acetic anhydride in pyridine in the usual way gave the corresponding triacetate as a chromatographically homogeneous syrup

(quant.); $[\alpha]_D^{23}$ −6.8° (*c* 1.5, $CHCl_3$); calc. for a fragment $C_{14}H_{20}ClO_6$ ($M^+ - C_3H_5O_2$): 318.979; found: 319.0937.

trans-*3-Hydroxy-2-nitrocyclohexyl 2,3,5-tri*-O-*benzoyl-β*-D-*ribofuranoside* (**4**). — This compound was obtained from *trans*-2-nitro-1,3-cyclohexanediol[23] (161 mg, 1 mmole). After 2 h at 25°, the mixture was processed as already described, to give a syrup that was chromatographed. The title compound was obtained, in 60% yield, as a colorless syrup that afforded a foam when dried under vacuum; $[\alpha]_D^{23}$ +18.5° (*c* 1.8, $CHCl_3$); ν_{max}^{film} 1550 (NO_2) and 3500 cm^{-1} (OH); n.m.r. data: δ 8.3, 7.1 (arom. 15 H), 5.7 (m, H-2,3), 5.4, 5.3 (s, H-1, diastereoisomers), 4.65 (bd, H-4′,5,5′), 4.12 (bm, –CHOH, $-CHNO_2$, –CHO of cyclohexyl moiety, 3 H), 3.28 (bs, OH, 1 H), and 1.75 (bm, CH_2, 6 H).

Anal. Calc. for $C_{32}H_{31}NO_{11}$: C, 63.47; H, 5.16; N, 2.31. Found: C, 63.32; H, 5.10; N, 2.09.

A second fraction obtained from the chromatographic separation (syrup, 30%) appeared to be a diriboside analog, as judged from its t.l.c. behavior, n.m.r. spectral characteristics, and the absence of hydroxyl absorption in its infrared spectrum. This compound was not investigated further.

rac. trans-*2-Acetamido-3-acetoxycyclohexyl 2,3,5-tri*-O-*benzoyl-β*-D-*ribofuranoside* (**5**). — This product was obtained from **1** and *rac. trans*-2-acetamido-3-acetoxycyclohexanol* (215 mg, 1 mmole). After 4 h at room temperature, the reaction mixture was processed as described before, and the product was isolated, by column chromatography, as a colorless syrup. Drying under vacuum gave a white foam (90%); $[\alpha]_D^{23}$ +19.2° (*c* 2.3, $CHCl_3$); n.m.r. data: δ 7.95, 7.32 (arom. 15 H); 6.35 (b, NH, 1 H), 5.60 (m, H-2,3), 5.30 (bd, H-1), 4.7 (m, 3 H), 4.07 (m, 3 H), 2.0 (m, NAc, OAc, 6 H), and 1.5 (m, cyclohexyl moiety, 6 H).

Treatment of compound **5** (200 mg) with sodium methoxide in methanol for 18 h at 25°, followed by neutralization with carbon dioxide, processing, and evaporation, gave a syrup that was acetylated with acetic anhydride in pyridine. The solution was poured into water, and extracted with chloroform, and the extracts were processed in the usual way, to give a colorless, chromatographically homogeneous syrup (quant.); $[\alpha]_D^{23}$ +7.67° (*c* 1.12, $CHCl_3$); calc. for M^+, $C_{21}H_{31}NO_{11}$: 473.1897; found: 473.1892.

1,2:3,4-Di-O-*isopropylidene-6*-O-(*2,3,5-tri*-O-*benzoyl-β*-D-*ribofuranosyl*)-α-D-*galactopyranose* (**7**). — Compound **1** (504 mg, 1 mmole) was treated with stannic chloride in dichloromethane (10 ml) as previously described, and the mixture was subsequently treated with a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[24] (260 mg, 1 mmole) in the minimal volume of dichloromethane. The mixture was stirred for 4 h at 0°, and processed as usual; the product was chromatographed, to give a colorless syrup (518 mg, 85%) that crystallized from ethanol, m.p. 201–203°, $[\alpha]_D^{23}$ +4.3° (*c* 0.5, $CHCl_3$); p.m.r. data (H′ corresponds to protons on the D-galactose portion): δ 7.90, 7.30 (arom. 15 H), 5.75 (dd, H-2,3, $J_{2,3} = J_{3,2} =$

*We thank Prof. F. Lichtenthaler for providing us with a sample of this compound.

4.5 Hz), 5.55 (d, H-1′; $J_{1,2} = 4.5$ Hz), 5.2 (s, H-1), 4.5 (m, H-2,4,5,5′, 3 H), 3.56 (m, H-5′,6′,6′, 3 H), 3.56 (m, H-5′,6′,6′, 3 H), and 1.2 (m, 4 CH_3, 12 H).

Anal. Calc. for $C_{38}H_{40}O_{13}$: C, 64.75; H, 5.73. Found: C, 64.94; H, 5.43.

Debenzoylation of compound **7**, followed by acetylation in the usual way, gave the corresponding triacetyl derivative as a syrup (quant.); $[\alpha]_D^{23}$ −19° (*c* 1.35, $CHCl_3$); *m/e* 503 ($M^+ - CH_3$).

*2-Propyl 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranoside* (**9**). — A solution of β-D-glucose pentaacetate[14] (**8**; 0.78 g, 2 mmoles) in dichloromethane (20 ml) was treated with stannic chloride (0.36 ml, 3 mmoles), and the solution was stirred for 10 min at 25°. Dry 2-propanol (0.3 ml, 3 mmoles) was added, and the solution was stirred for 4 h at 25°. It was then poured into saturated, aqueous sodium hydrogencarbonate, and the organic layer was processed as usual, to give a colorless syrup that was chromatographed on silica gel with 1:10 EtOAc–benzene as the developer. The resulting, colorless syrup crystallized from ethanol, to give the title compound (556 mg, 71%); m.p. 134–135° (lit.[25] 136–137°), $[\alpha]_D^{23}$ −21° (*c* 1.0, $CHCl_3$) [lit.[25] −24.4° ($CHCl_3$)].

The following were similarly prepared: methyl β-D-glucopyranoside tetraacetate (80%), m.p. 104° (lit.[15] 104–105°), $[\alpha]_D^{23}$ −16.1° (lit.[25] −18.7°), ethyl β-D-glucopyranoside tetraacetate (74%), m.p. 104–105° (lit.[25] 106–107°), $[\alpha]_D^{23}$ −21.9° (*c* 1.2, $CHCl_3$) [lit.[25] −22.7° ($CHCl_3$)], cyclohexyl β-D-glucopyranoside tetraacetate (72%), colorless syrup, $[\alpha]_D^{23}$ −21° (*c* 1.0, $CHCl_3$); lit.[25] m.p. 120–121°; $[\alpha]_D^{23}$ −23.8° ($CHCl_3$).

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