A convenient preparative method for the glucosides of fatty alcohols and sterols

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The glucosides of simple fatty alcohols like n-octanol, n-triacontanol and benzyl alcohol as well as of cholesterol have been synthesised in very good yields (70-85 %) by reacting acetobromoglucose with zinc salts of the substrates, prepared *in situ*, and then deacetylating the glucoside peracetate. It is possible to obtain either of the anomers (α or β) selectively, by choosing appropriate reaction conditions.

Glucosides are also considered to be intermediates and precursors in the biosynthesis of secondary plant metabolites. For example, glucovanillin, present in the green fruit of vanilla, releases vanillin during curing of the beans[1]. Synthetic glucosides are reported to be useful in masking the sidestream smoke of cigarette[2]. Further, α- and β-n-octyl glucosides find use as nonionic, dialysable detergents in the isolation and purification of membrane proteins, and as drug carrier[3]. Z-Hex-3-enyl glucoside present in fresh tea leaf, releases 'leaf alcohol' during black tea manufacture which gives fresh notes in tea infusion[4].

The procedures available for O-glucoside synthesis[5] can be categorised into the following four major groups: (i) the Fischer-Helferich method, (ii) the Koenigs-Knorr method and its variants, (iii) the trichloroacetimidate method and other anomeric oxygen activations, and (iv) the anomeric O-alkylation method. Of these, the Koenigs-Knorr method is most versatile and generally applicable. In this classical method as well as its variants, activation of the anomeric position is achieved through substitution of the hydroxyl with a halogen atom. In the second step of glycosyl transfer, 1-halosugar is condensed with the substrate in the presence of salts of heavy metals like silver and mercury. However, this method has some severe, partly inherent, disadvantages such as low thermal

stability and sensitivity to hydrolysis of many glucosyl halides and the need for stoichiometric quantities of heavy metal salts which are either expensive or hazardous in nature. This becomes a serious limitation, especially in large scale preparation of glycosides. These disadvantages have been overcome to a large extent in the present method which involves the use of zinc salts. Its salient features are, (i) one-pot synthesis, (ii) easy work-up procedure, (iii) improved yields and (iv) amenability to scale-up.

The application of zinc-salt mediated substitution reaction to the synthesis of O-glucosides was studied systematically using n-octanol as the aglycone moiety and acetobromoglucose as the glucosyl donor in different solvents. The glucosides so obtained contained both α- and β-anomers in different ratios (Table I). Structure and stereochemistry of the pure anomers were determined by their physical properties and [1]H

Table I—Reaction of acetobromoglucose (50 mmoles) with ZnO and n-octanol in different solvents under reflux conditions

Entry No	Solvent	Temp. °C	Reaction period (hr)	Glucoside (yield %)	α:β
1	CH_2Cl_2	41	6	85	20:80
2	$CHCl_3$	54	5	51	25:75
3	C_6H_6	80	3	84	86:14

NMR spectral analysis.

When dichloromethane was used as solvent, the glucoside yield was excellent and β-anomer was predominantly formed. In chloroform medium, the glucoside yield was moderate, but the anomeric ratio was same. On the other hand, in benzene medium, the α- anomer was obtained as the major product.

Under solvolytic conditions (*i.e.* when the solvent is a low-molecular weight alcohol) as well as under non-solvolytic conditions and at low temperature, β-D-glucosides are formed predominantly[6]. The present study showed that the polarity of solvent had a marked effect on the anomeric composition of the products. Thus, by altering the reaction conditions, it was possible to obtain either of the anomers as the major product. The glycosidic product was easily purified by isolating the individual anomers as tetraacetate derivatives and then hydrolysing them. This constitutes a simple and convenient preparative method for 1-*O*-α/β-glucosides. The glucosides prepared are not only illustrative of the general usefulness of this method, but they also find application in food, agriculture and pharmacy.

Experimental Section

General. ^{1}H NMR spectra were recorded in CDCl$_3$ on 200/270 MHz instruments using TMS as internal standard. Optical rotations were recorded at 22 °C and 589 nm. GC was performed under the following conditions: 6'×1/8"(o.d.) SS column, OV-17 (10 %) on Chromosorb-W, N$_2$ 30 mL/min; H$_2$ FID; injection and oven temperatures 250 °C; detector temperature 300 °C. TLC (5×20 cm) plates coated with silica gel-G, type 60 (E. Merck) were used.

Acetobromoglucose (tetra-*O*-acetyl-α-D-gluco-pyranosyl bromide) was prepared[7] from D-glucose. The ZnO and ZnCO$_3$ used in the reaction were dried over P$_2$O$_5$ in a vacuum oven at 60 °C before use. CHCl$_3$, CH$_2$Cl$_2$ and C$_6$H$_6$ were dried and distilled.

***n*-Octyl glucoside.** *n*-Octanol (9.75 g, 75 mmoles) was stirred with ZnCO$_3$ (4.7 g, 37.5 mmoles) in refluxing C$_6$H$_6$ (150 mL) for 8 hr in

Soxhlet apparatus containing anhydr. Na$_2$SO$_4$ (40 g). The solvent was then removed in a flash evaporator and the residual zinc salt dried over P$_2$O$_5$ in a vacuum desiccator.

Acetobromoglucose (20.55 g, 50 mmoles) was added in parts to a suspension of the zinc salt of *n*-octanol suspended in CH$_2$Cl$_2$ (150 mL) under stirring and the mixture set to total reflux. Refluxing was continued till the spot due to acetobromoglucose disappeared on TLC plate (spray with 1 % acetone solution of *o*-tolidine reagent and exposure to sunlight gave a bluish green spot). The reaction mixture was filtered at the pump and residue washed with the solvent. Combined filtrate and the washings were washed repeatedly with distilled water, dried over anhydr. Na$_2$SO$_4$ and the solvent distilled off. To the residue, Ac$_2$O (10.5 mL) and pyridine (4 mL) were added and the mixture was kept aside at room temperature for 24 hr and then poured onto crushed ice. The separated solid filtered at the pump, washed with cold water and dried in a desiccator[7]. The crude product (19.7 g, 85 %) was chromatographed over SiO$_2$ (100 to 200 mesh, 150 g) using hexane-EtOAc mixtures as eluents. Coloumn fractions were checked by TLC (solvent: hexane-EtOAc (60:40), sprayed with 10 % H$_2$SO$_4$ in MeOH and heated at 110 °C/15 min. *n*-Octyl *O*-α- and β-glucoside tetraacetates were progressively eluted with 20 to 30 % EtOAc in hexane mixtures. While the α-anomer was a viscous liquid (3.9g, [α]$_D$+102.4°), the β-anomer crystal-lised from MeOH (15.7 g, m.p. 54°, [α]$_D$ -23.8°; lit.[8] , m. p. 54°, [α]$_D$ -22°).

n-Octyl *O*-(α or β)-glucoside tetraacetate (3.7 g) was stirred with 20 mL of MeOH containing 1% NaOMe at room temperature for 2 hr and then neutralised with Amberlyst 15' (H$^+$ form) resin. The resin was filtered off and MeOH removed in a flash evaporator. The residue crystallised from anhydr. EtOAc in pellets (2.35 g, 99 %). α: m.p.123°, [α]$_D$+117.5°; β: m.p. 68-69°, [α]$_D$ -27.5° (lit.[8] α: m.p.124°, [α]$_D$ +117.9°; β: m.p. 69°, [α]$_D$ - 28°).

Benzyl glucoside. The zinc salt of benzyl alcohol (3.24 g, 30 mmoles) was prepared using zinc oxide (1.2 g, 15 mmoles) as in the previous

case. Acetobromoglucose (8.22 g, 20 mmoles) was added to a suspension of zinc salt of benzyl alcohol in CH_2Cl_2 (50 mL) and the mixture set to total reflux. On completion of the reaction (8 hr), the reaction mixture was worked-up and the crude product acetylated as before to get benzyl O-(α and β)-glucoside tetraacetate (7.18 g, 82 %). Its α- and β- anomers were separated by SiO_2 column chromatography and crystallised from MeOH (yield: α-anomer 0.77 g and β-anomer 6.23 g); α: m.p. 110-12°, $[\alpha]_D$ +143.8°; β: m.p. 97- 98° $[\alpha]_D$ -43.4° (lit.[9] α: m.p. 111°, $[\alpha]_D$ +143°; β: m.p. 98°, $[\alpha]_D$ -44°).

Benzyl O- (α / β)-glucoside tetraacetate (4.38 g) was stirred with 20 mL of MeOH containing 1 % NaOMe at room temperature for 2hr and then neutralised with cation (H^+ form) resin. The resin was filtered off and MeOH removed in a flash evaporator. The residue was crystallised from anhydr. diethyl ether in needles (2.69 g, 99 %). α: m.p.121°, $[\alpha]_D$ +132°; β: m.p. 123° (lit.[10] α: m.p. 121-22° $[\alpha]_D$ +133°; β: m.p.123-35°).

Cholesterol glucoside. The zinc salt of cholosterol was prepared by reacting ZnO (1.2 g, 15 mmoles) and cholosterol (11.5 g, 30 mmoles) in CH_2Cl_2. Acetobromoglucose (8.22 g) was added and the mixture set to total reflux. On completion of the reaction (16 hr), the reaction mixture was worked-up and acetylated. The yield of cholesterol-O-(α/β)-D-glucoside tetraacetate was 10.5 g (73 %). The α- and β-anomers were separated by SiO_2 gel column chromatography and crystallised from MeOH (yield: α-anomer 1.26 g and β-anomer 9.24 g). α: m.p.191-92°, $[\alpha]_D$ +90.2°; β: m.p. 155-56° $[\alpha]_D$ -27.4° (lit.[11] α: m.p. 193°, $[\alpha]_D$ +92°; β: m.p. 157°, $[\alpha]_D$ -26°).

Cholesterol-O-(α/β)-glucoside tetraacetate (7.16 g) was stirred with 20 mL of MeOH containing 1% NaOMe at room temperature for 2 hr and then neutralised with cation (H^+ form) resin. The resin was filtered off and MeOH removed in a flash evaporator. The residue was crystallised from anhydr. EtOAc in pellets (5.46 g, 99 %). α: m.p. 208° $[\alpha]_D$ +24°; β:m.p. 262°, $[\alpha]_D$ -49° (lit.[12] α: m.p. 205-11°, $[\alpha]_D$ +23°; β: m.p. 262-64°, $[\alpha]_D$ +50°).

n-Triacontanol-α and β-glucoside. To the zinc salt prepared from 6.15 g of *n*-triacontanol and 1.0 g of $ZnCO_3$ and suspended in CH_2Cl_2 (100 mL), acetobromoglucose (4.11 g) was added and the mixture set to total reflux. On disappearance of acetobromoglucose (12 hr), the reaction mixture was worked-up and acetylated as before to get *n*-triacontanol -α and β-D-glucoside tetraacetates (5.18 g, 70 %). The product mixture was stirred with 20 mL of MeOH containing 1 % NaOMe at room temperature for 2 hr, and then neutralised with cation (H^+ form) resin. The resin was filtered off and the methanolic solution concentrated in a flash evaporator. The residue was crystallised from methanol, yield 3.99 g (99%).

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