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New synthetic pathways to C-glycosides

Paul H. Gross

Department of Chemistry, University of the Pacific, Stockton, CA 95211, USA

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Abstract

C-glycopyranosyl compounds exhibit antimicrobial, antifungal, and antitumor activities, most probably based on enzyme inhibition or interference with cell surface recognition phenomena. Recent developments in glycobiology have shown the importance of the glycoside component of glycoproteins for cell recognition and differentiation processes. C-glycosidic analogues of that component would be metabolically stable, and thus offer enhanced therapeutic value. Synthesis of a configurational variety of e.g. amino (glycopyranosyl) methanes is thus an important synthetic goal. The amino group would allow linking the C-glycoside to a variety of scaffolds. Our first approach has been to C-link a C–N synthon (HCN or CH_3NO_2) to the anomeric carbon of a natural carbohydrate. We have realized this with cyanide on glycal, on per-*O*-acetyl sugars and on cyclic acetal protected glycosyl fluorides, prepared by a novel method. The catalytic hydrogenation of glycosyl cyanides presented challenges and new synthetic possibilities. With CH_3NO_2, and 4,6-*O*-alkylidene protected D-glucose or D-mannose derivatives, we obtained very good yields of cyclic Henry condensation products in THF with a novel catalytic procedure. The novel reduction of the resulting nitro (4,6-*O*-benzylidene-β-D-glycopyranosyl) methane with Fe^0/Ni^0 in $THF/H_2O/CO_2$ readily supplied amino (4,6-*O*-benzylidene-β-D-glucopyranosyl) methane, derivatives of which were diastereodiversified into D-allo, D-manno, and D-altro C-glycosides. These approaches fail, however, if prerequisite natural carbohydrate precursors are not available in a given case. Thus, a total synthesis scheme was also initiated. Phthalimido acetaldehyde diethylacetal and 4-penten-2-ol, with $TiCl_4$, form 2-methyl-4-chloro-6-phthalimido-methyl tetrahydropyran, which was functionalized into phthalimido (6-deoxy-β-D,L-hexopyranosyl) methanes. Chiral extensions of this method are possible. C-'disaccharides' became available from the Ferrier 'dimerisation' of glycals, and from the hydrogenation of glycosyl cyanides.

Keywords: C-glycosides; Henry condensation; Glycosylcyanide hydrogenation

1. Introduction

C-glycosides have found increased interest in biochemical studies, and as a result, syntheses of these compounds (Levy et al., 1996) were devised in great variety. One may distinguish three general synthetic approaches to C-glycosides: by modification of natural sugars; by stereosynthetic modification of readily accessible C-glycosides; and, by total synthesis from non-carbohydrate precursors, when natural sources are not practical. We have chosen aminomethyl C-glycosides to exemplify these three synthetic categories. Aminomethyl C-glycosides, by attachment through metabolically resistant N-functionalities, readily offer the possibility for providing carbohydrate mimicry to a wide variety of scaffolds, with a range of molecular weights. These products could then be used for regulation of, or interference in cell membrane recognition events. Prime synthons for the provision of the C–N fragment in these syntheses are R–CN, CH_3NO_2 and phthalimido acetaldehyde.

2. Results and discussion

The SN'_2 reaction of trimethylsilyl cyanide with tri-*O*-acetyl-D-glucal (**1**) under BF_3-catalysis, to give 2,3-unsaturated, 4,6-*O*-acetylated α-D-glycosyl cyanide (**2a**) was described (DeLas Heras et al., 1983), but the products were not synthetically elaborated.

Indeed, we found this to be most difficult, even on the 2,3-unsaturated β-glycosyl cyanide (**2b**) which we obtained in addition to the α-form, by using a different catalyst ($Hg(CN)_2/HgBr_2$). De-*O*-acetylation with methoxide of either **2a** or **2b**, gave diastereospecifically the same methyl 6-hydroxy 2Z, 4E-hexadienoate, by elimination of the 4-acetoxy group, followed by substitution of cyanide with methoxide.

Compounds **2a** and **2b** could finally be made to react with a mixture of $PyHBr_3$/NBS in dioxane/H_2O to provide desired dibromides and bromohydrins by stereo specific attack of Br^+ from the α-face, followed by opening of the initially formed 2,3-bromonium ion with Br^-, H_2O, or with participation of the 4-acetoxy carbonyl.

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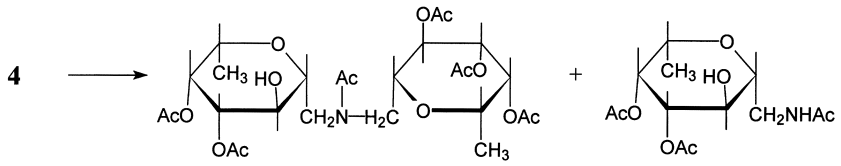

Fig. 1. Hydrogenation of (4).

With Huenig's base in CH_2Cl_2, the 2,3-bromohydrin formed an epoxide while the 2,3-dibromide and the 2,4-bromohydrin gave 1,2-unsaturated glycosyl cyanide derivatives. Another functionalization was possible by dihydroxylation with $KMnO_4$. At $-70° \rightarrow 0°C$, **2a** gave exclusively the α-D-*manno*-glycosyl cyanide (81%), but **2b** gave a low yield (32%) of a mixture of the D-*manno* and D-*allo* glycosyl cyanides. For final characterization all additional products were per-*O*-acetylated (Wei, 1991).

Tri-*O*-acetyl β-L-fucopyranosyl cyanide (**4**) was obtained from tetra-*O*-acetyl-L-fucose by a procedure analogous to those described previously (DeLas Heras et al., 1982; Utimoto and Horiie, 1982). The catalytic hydrogenation (Gallagher, 1989) of (**4**) produced, after *O*-*N*-acetyl migration, not only the expected acetamido-(3,4-di-*O*-acetyl-β-L-fucopyranosyl)-methane but also an N-linked disaccharide, formed by condensation of intermediate and final hydrogenation products (Fig. 1).

A new nucleophilic ***neutral*** fluorination reagent, *N*-methyl-2-fluoropyridinium tosylate, was used to convert the free glycosidic hydroxyl groups of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose, 2,3;4,6-di-*O*-isopropylidene-D-mannopyranose, and 2,3;5,6-di-*O*-isopropylidene-D-mannofuranose into the corresponding glycosyl fluorides, which all reacted with Et_2AlCN by unspecific SN_1-reaction, to give anomeric mixtures of glycosyl cyanides and isocyanides (Drew and Gross, 1991a).

A 1,3-proton transfer catalyst, a.k.a. bifunctional, or tautomeric catalyst, for which nucleic acids are biological examples, is 2-hydroxy pyridine (2-HP). Its homodimer (Held and Pratt, 1990) most likely has a hydrogen bond with a transfer barrier lower than the calculated zero point vibrational energy (McAlister, 1997; Jeffrey, 1997) and heterodimers may be expected to have similarly facile proton transfers. Indeed, 2-HP was used in earlier studies as a 1,3-proton transfer catalyst in reactions for which such steps are rate limiting (Swain and Brown, 1952), such as the anomerisation of 2,3,4,6-tetra-*O*-methyl-glucopyranose in aprotic solvents.

We anticipated a potential accelerating effect of 2-HP on the synthesis of nitro(4,6-*O*-benzylidene-β-D-glucopyranosyl) methane (**5**), which had been obtained previously only as a by-product (Sowden and Fischer, 1946). Indeed, the condensation of 4,6-*O*-benzylidene-α-D-glucose in THF, with 2-HP catalysis, produced the desired nitromethyl C-glycoside in 70% yield (Drew and Gross, 1991b). Presently this has been improved to 84% with improved catalysts. Obtained after *O*-acetylation, nitro (2,3-di-*O*-acetyl-β-D-glucopyranosyl) methane was reduced (with *O*-*N*-acetyl migration) by reactive Fe^0/Ni^0 (prepared by reduction of Fe^{2+}/Ni^{2+} with $NaBH_4$ (Drew and Gross, 1991b; Wang and Gross, 1995a). The resulting acetamido(3-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranosyl) methane was 2-*O*-methane sulfonylated, or was 3-*O*-deacetylated and 2,3-di-*O*-methane sulfonylated.

Anchimerically assisted sulfonate displacements led to β-C-glycosides with D-*manno*, D-*allo*, and D-*altro* configurations. The observed neighboring group reactions show some similarities to reactions previously observed for analogous *O*-glycosides, but also some significant differences due to the anchimeric assistance of the acetamido methyl group, which is present in most compounds. (Wang and Gross, 1995a). The result is a viable and extendable synthetic paradigm for the rational synthesis of a wide variety of unusual C-glycoside derivatives, potentially useful for biochemical studies.

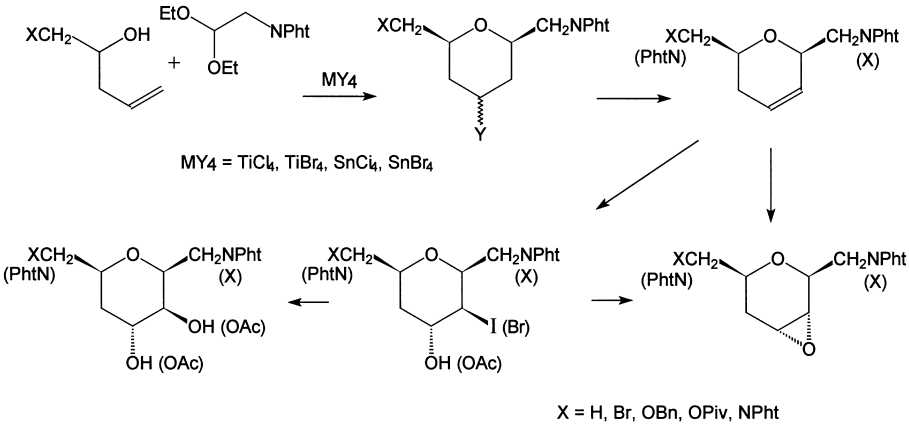

Fig. 2. Total C-glycoside synthesis.

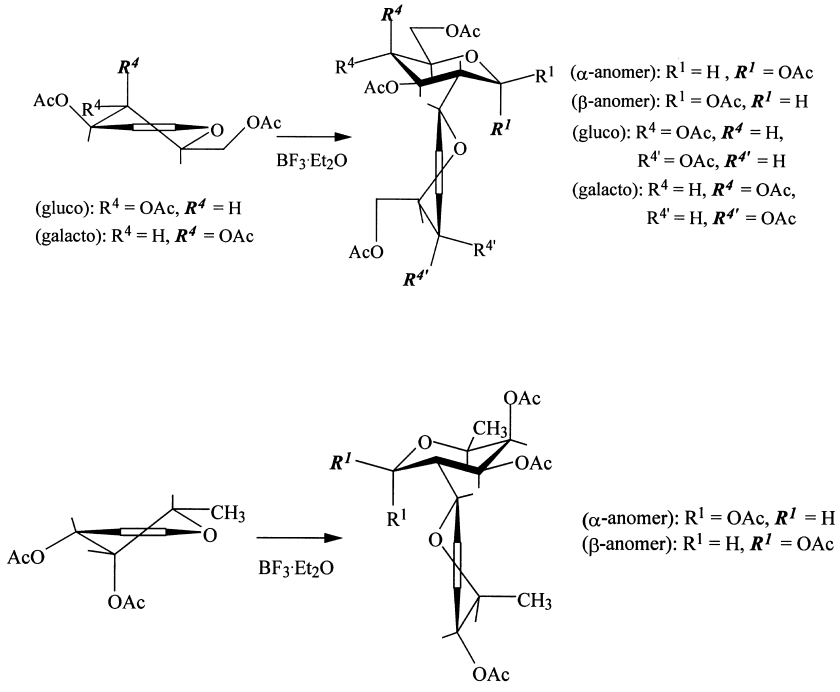

Fig. 3. C-glycosides by Ferrier dimerisation.

The 2-HP catalyzed condensation of 4,6-*O*-benzylidene-D-glucopyranose with nitromethane could be extended to nitroethane and nitropropane. Those Henry condensation products were formed in lower yields and with low diastereo selectivity (Wang and Gross, 1995b).

A systematic, general approach for the total syntheses from nonnatural achiral starting materials, of fully or partially functionalized amino methyl tetrahydropyrans, in a potentially comprehensive array of configurations, provided the basis for a variety of consecutive transformations towards the target aminomethyl C-glycopyranosides (Fig. 2) (Gross et al., 1998).

C-disaccharides are also available from the 'Ferrier' dimerisation of glycals. These C–C linked Ferrier dimers have been fully functionalized by us (Franz and Gross, 1997) into C-disaccharides, synthesized from per-*O*-acetylated D-glucal, D-galactal and L-fucal, with a novel catalyst, in very good yields, after significant improvements in the syntheses of the glycals themselves (Fig. 3).

In OsO_4 catalyzed dihydroxylations of the double bonds, we obtained the *allo*-configuration in the case of the *gluco* dimer, and a mixture of *talo* and *gulo* configurations for the D-*galacto* and L-*fuco* dimers.

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