Palladium−Charcoal-Catalyzed Reduction of Tri-O-acetyl-β-L-Fucopyranosyl Cyanide: A Route to Small Cluster Oligosaccharide Mimetics (SCOMs)

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ABSTRACT

Synthesis of glycosyl cyanides was optimized with a new catalyst system. Reduction of tri-O-acetyl-β-L-fucopyranosyl cyanide with Pd−hydrogen, in the presence of Ac₂O and Boc₂O, gave N-protected-mono- and -di-(2,3,4-tri-O-acetyl-β-L-fucopyranosylmethyl)-amines, which allow for the syntheses of small cluster oligosaccharide mimetics of fucopyranosylmethyl-substituted ureas. From di-(2,3,4-tri-O-acetyl-β-L-fucopyranosylmethyl) amine was also prepared a carbamoyl chloride as a potentially useful synthon for preparation of more complex C-glycosidic conjugates.

C-Glycoside carbohydrate analogues are structurally, chemically, and conformationally similar to O-glycosides but, being acid and enzyme stable, are possibly more suitable as mimetics and pseudosubstrates. Specifically, glycosyl cyanides are potential precursors of aminomethyl-C-glycosides that could be further elaborated at the amino functionality.

In 1961, Helferich and Bettin obtained per-O-acetyl-β-D-galactopyranosyl cyanide in good yield from per-O-acetyl-α-D-galactopyranosyl bromide and mercuric cyanide in nitromethane. However, the analogous reaction of per-O-acetyl-α-D-glucopyranosyl bromide gave per-O-acetyl-1,2-O-(1-cyanoethylidene)-α-D-glucopyranose in 53% yield and only 11% of the preferred per-O-acetyl-β-D-glucopyranosyl cyanide. The preparation of per-O-acetyl-glycopyranosyl cyanides by Myers and Lee brought little improvement.

Earlier, the displacement of an anomeric O-acetyl substituent with the cyanide of trimethylsilyl cyanide (TMS−CN) in the presence of BF₃−OEt₂ in nitromethane had given overall

better yields. But, BF$_3$–OEt$_2$ is hazardous, unstable, and harsh, and significant decomposition and incompatibility with glycosidic bonds were observed. However, a distinct advantage accrued from the elimination of the unstable glycosyl bromides as intermediates. We decided to investigate the use of HgBr$_2$, as a milder catalyst (Scheme 1).

**Scheme 1**

When per-O-acetyl-α- or β-d-glucopyranose 1 was treated with excess TMS–CN and 0.1 molar equiv of HgBr$_2$, in the absence of Hg(CN)$_2$, in nitromethane for 2 days, the major product was the per-O-acetyl-1,2-O-(1-cyanothioldiene)-α-d-glucopyranose 2 in 59% yield, along with only 5% of the preferred per-O-acetyl-β-d-glucopyranosyl cyanide 3 and about 28% of starting material, similar to the results of Coxon and Fletcher. When we increased the amount of HgBr$_2$ to at least 0.5 equiv, the cyanothioldiene intermediate rearranged into the desired per-O-α-β-d-glucopyranosyl cyanide 3 in 51% yield starting from per-O-acetyl-β-d-glucopyranose, or 65% yield from purified cyanothioldiene intermediate 2 within 1 day. The omission of Hg(CN)$_2$ was crucial and explained by us through an intermediacy of mercuric isocyanide species in the mechanism. With excess TMS–CN and 0.1 molar equiv of HgBr$_2$ in nitromethane, per-O-acetyl-α(or β)-L-fucopyranose 4 was converted into per-O-acetyl-β-L-fucopyranosyl cyanide 6 in 95% yield within 4 h. We observed neither the cyanosthioldienyl compound 5 as an intermediate nor decomposition but only a trace of the α-anomer of 6. Solvent and excess TMS–CN were removed in vacuo, and CH$_2$Cl$_2$ was added to extract the product and precipitate the HgBr$_2$ catalyst, which was recovered for reuse. Evaporation of CH$_2$Cl$_2$ left a crystalline residue that was recrystallized from 95% ethanol to give 6 (Scheme 1).

The 1,2-O-(cyanothioldiene) glycopyranose side products were obtained by Myers and Lee in a larger yield from per-O-acetyl-δ-gluco- and mannopyranosyl cyanide than from per-O-acetyl δ-galactose. They tried to rearrange these syrupy byproducts into the corresponding α/β-cyanides with boron trifluoride–etherate (BF$_3$–OEt$_2$) but improved the glycosyl cyanide yield only slightly. Kini et al. found it necessary to elevate the reaction temperature to 35 °C to minimize formation of 1,2-O-(cyanothioldiene) mannopyranoses when a mixture of per-O-acetyl-α-β-mannopyranosyl cyanide was converted with TMS–CN/BF$_3$–OEt$_2$ into the α-d-mannopyranosyl cyanide.

1,2-Trans opening of the acetoxoniums preceding 2 and 5 (Scheme 1) was especially favored for the fuco-galacto configuration, for which the carbenium site of the acetoxonium may be blocked toward cyanide attack, by free orbitals of the pyranose ring oxygen. For the skew boat form (Scheme 1) of the δ-gluco configuration, the carbene site is more accessible than the anemic site, which accounted for the almost exclusive formation of the stable per-O-acetyl-1,2-O-(1-endo-cyano)thioldiene-α-δ-glucopyranose 2 before the final product. We have recently found another example of the remarkable influence of the configuration of the remote 4-O-acyl substituent (i.e., gluco vs galacto) on the reaction outcome. Vicent et al. had already found that the reactivity of cyanothioldienyl compounds, for use in oligosaccharide synthesis, depended on the exo or endo position of the cyanide group.

At 0.1 equiv of HgBr$_2$ catalyst, the rate of rearrangement (2→3) was extremely slow, but we could complete it within a day with at least 0.5 equiv. Yields of rearrangement decreased to 5% when no TMS–CN was added along with the catalyst, and complete decomposition occurred upon warming. This suggested that rearrangement required the assistance of a mercuric isocyanide complex in conjunction with the existence of equilibrium between the exo-cyanothioldienyl 2 and the acetoxonium intermediate.

One versatile approach of glycosyl cyanide modification, with which we already had considerable experience, is catalytic reduction. Hydrogenation of per-O-acetyl-β-L-fucopyranosyl cyanide 6 with catalytic palladium–charcoal in the presence of acetic anhydride (Ac$_2$O) gave the isolated O–N-acetylated products 7 and 8 in 32 and 23% yields, respectively (Scheme 2). The yield for the N-linked amino-disaccharide 8 decreased to 9% without the presence of Ac$_2$O. Since the presence of Ac$_2$O did not prevent migration, it appeared that O–N-acetylation from a 2-O-acetoxyl

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group was much faster than acetylation of the amines. The 2-hydroxyl amino-C-monosaccharide 7 and C-disaccharide 8 can be acetylated with Ac₂O in the presence of catalytic 1,4-(dimethylamino)pyridine (DMAP) to the corresponding fully protected 9 and 10 before or after isolation. In the presence of the lipophilic Boc₂O, the hydrogenation of cyanide 6 gave only 11 and an N-linked disaccharide 12 in 61 and 38% yields, respectively, without O-N-acetyl migrations (Scheme 2; Table 1). Again, the yield of disaccharide 12 was increased in the presence of the anhydride. The product mixture was easily separated by column chromatography.

Cyanides are reduced with Pd/H₂ in two stages.¹⁴ The first stage is formation of aldimines, and the second is reduction to the corresponding amine. In the production of 7 and 8, O-N-acetyl migration could occur at the aldimine or amine stage. The migration at the stage of the amine made it unavailable for further reaction. That no acetyl migratory product was observed in the presence of Boc₂O suggests fast reaction of aldimines and amines with Boc₂O at the lipophilic charcoal catalyst surface. In contrast, hydrophilic Ac₂O, present in the bulk solution, permits acetyl migrations at the surface. The more electrophilic acylated aldimines tend to favor dimerization, which indeed occurred more readily in the presence of Ac₂O and Boc₂O.¹⁵ This point was not appreciated by Lenz et al.¹⁶ in their later work with Boc₂O, probably because they did not compare hydrogenation in the presence of Ac₂O, as we did.

From the Boc-protected aminomethyl-C-fucopyranoside synthons, a great variety of biologically interesting glycoconjugates are accessible. Transformation of the 1° amino functionality into an isocyanate allows coupling with the former 1° amine or the 2° amine dimer. Other nucleophiles would give glycoconjugates with minimal scaffolding such as unsymmetrical areas. This could be accomplished in many ways but most commonly by phosgenation,¹⁷ which is economical and practical since the advent of crystalline “triphosgene”. We removed the Boc protective group from the aminomethyl-C-monosaccharide 11 with TosOH—H₂O in CH₂Cl₂, and the resultant salt, in solution, was directly converted with 1/6 equiv of triphosgene in a CH₂Cl₂-saturated sodium bicarbonate two-phase system (Scheme 3; Table 2), via the in situ amino- and isocyanato-monosaccharide intermediates, into the novel difucopyranosyl methyl-substituted urea 13 in 63% yield, along with 7 (12%) through O-N-acetyl migration.

When the same deprotection and two-phase phosgenation was applied to the N-linked disaccharide 12, a novel

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### Table 1. Yields for Reduction of 6

<table>
<thead>
<tr>
<th>procedure</th>
<th>ratio of starting material (6:anhydride)</th>
<th>% yield of products (7:8:11:12)</th>
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<tbody>
<tr>
<td>A</td>
<td>1:0</td>
<td>33:9:--:--</td>
</tr>
<tr>
<td>B</td>
<td>1:13</td>
<td>32:23:0:0</td>
</tr>
<tr>
<td>C</td>
<td>1:3</td>
<td>0:0:61:38</td>
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*a Isolated yields.

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tetrafucopyranosyl methyl-substituted urea 15 (28%) was obtained along with the O-N-acetyl migratory side-product 8 (48%) and the stable carbamoyl chloride 14 (15%; Scheme 3), a potentially useful reactant for preparation of more complex C-glycosidic conjugates. The yield of the tetra-substituted urea derivative was surprisingly high for a bimolecular reaction of two sterically hindered intermediates, which had to compete with the major intramolecular pathway of acetyl migration, after Boc removal. Formation of acetyl migratory side products 7 and 8 was increased if a weaker acid such as trifluoroacetic acid was employed to remove the Boc-protective group or if Hünig’s base was used in a single nonpolar organic solvent instead of a two-phase system with aqueous bicarbonate. With an excess (1/3 equiv) of triphosgene, acetyl migratory product was minimized and formation of the tetrasubstituted urea also ceased, but the yield of the interesting carbamoyl chloride 14 increased to 67%. Compound 14 was successfully isolated by column chromatography on normal SiO2, by elution with isopropyl ether.

We have summarized the synthetic possibilities for the two readily obtainable Boc-aminomethyl saccharides 11 and 12 in Scheme 3. The utility of compounds 11, 12, and 14 is readily appreciated for attaching stable, β-L-fucopyranosyl residues via amide, urethane, or urea bonds to carboxyl, hydroxyl, or amino groups of proteins or other biological scaffolds to produce, e.g., “neoglycoproteins.” This methodology should be extendable to other sugars.

We have shown that O-acetyl protective groups are removable under very mild conditions with NEt3/MeOH/H2O.18 The base and byproduct AcOH are readily removed by azeotropic water vapor distillation in vacuo or presumably also by freeze-drying, without damage to delicate biochemical substrates.

In view of these previous results,15,18 we are surprised by the results of Lentz et al.16 who claimed to have successfully hydrogenated in good yields 2-N-phthalylated and O-acetylated glycosyl cyanides in the presence of 10 equiv of NEt3, in alcoholic solvents, with avoidance of both dimerization and deprotection. In reference 19, we give our conditions for de-O-acetylation of 2,3,4-tri-O-acetyl fuco-pyranosyl cyanide, in good yield.

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**Supporting Information Available:** Experimental procedures and complete characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

<table>
<thead>
<tr>
<th>Table 2. Yields for Synthesis of SCOMs</th>
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<tr>
<td>procedure</td>
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<td>F</td>
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<sup>a</sup> Isolated yields.