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

**Pasit Phiasivongsa, Julie Gallagher, Chang-Nan Chen, Patrick R. Jones, Vyacheslav V. Samoshin, and Paul H. Gross***

*Department of Chemistry, University of the Pacific, 3601 Pacific Avenue, Stockton, California 95211*

*vsamoshi@uop.edu*

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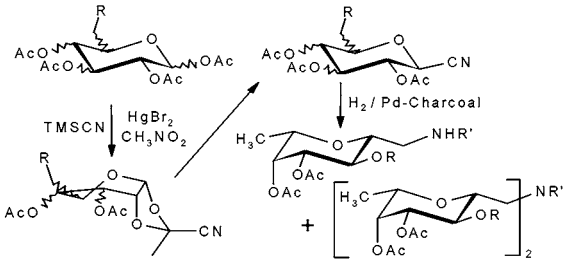
## ABSTRACT




**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 $Ac_2O$ and $Boc_2O$, 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 fucopyranosylomethyl-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[1] but, being acid and enzyme stable, are possibly more suitable as mimetics and pseudosubstrates.[2] 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.[3] However, the analogous reaction of per-*O*-acetyl-α-D-glucopyranosyl bromide[4] gave per-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)-α-D-glucopyranose **2** in 53% yield and only 11% of the preferred per-*O*-acetyl-β-D-glucopyranosyl cyanide **3**. The preparation of per-*O*-acetyl-glycopyranosyl cyanides by Myers and Lee brought little improvement.[5]

Earlier, the displacement of an anomeric *O*-acyl substituent with the cyanide of trimethylsilyl cyanide (TMS−CN) in the presence of $BF_3$−$OEt_2$ in nitromethane had given overall

* Fax: (209) 946-2607.

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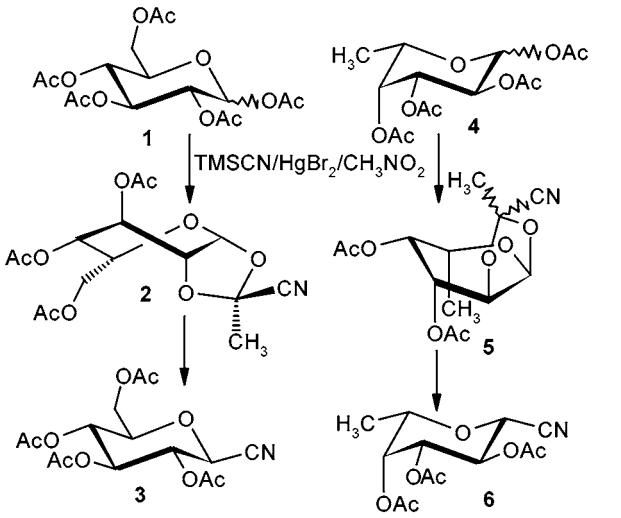
better yields.[6,7] But, $BF_3-OEt_2$ is hazardous, unstable, and harsh, and significant decomposition and incompatibility with glycosidic bonds were observed. However, a distinct advantage accrued from the elimination of the unstable glycosyl bromides as intermediates. We decided to investigate the 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-cyanoethylidene)-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.[4a] When we increased the amount of $HgBr_2$ to at least 0.5 equiv, the cyanoethylidene intermediate rearranged into the desired per-*O*-*β*-D-glucopyranosyl cyanide **3** in 51% yield starting from per-*O*-acetyl-*β*-D-glucopyranose, or 65% yield from purified cyanoethylidene 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.[8]

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 cyanoethylidene compound **5** as an intermediate[9] nor decomposition but only a trace of the α-anomer of **6**. Solvent and excess TMS−CN were removed in vacuo, and $CH_2Cl_2$ was added to extract the product and precipitate the $HgBr_2$ catalyst, which was recovered for reuse. Evaporation of $CH_2Cl_2$ left a crystalline residue that was recrystallized from 95% ethanol to give **6** (Scheme 1).

The 1,2-*O*-(cyanoethylidene) glycopyranose side products were obtained by Myers and Lee in a larger yield from per-*O*-acetyl-D-gluco- and mannopyranose than from per-*O*-acetyl D-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.[5] Kini et al. found it necessary to elevate the reaction temperature to 35 °C to minimize formation of 1,2-*O*-(cyanoethylidene) mannopyranoses when a mixture of per-*O*-acetyl-α/*β*-mannopyranoses was converted with TMS−CN/$BF_3-OEt_2$ into the α-D-mannopyranosyl cyanide.[10]

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 D-gluco configuration, the carbenium site is more accessible than the anomeric site, which accounted for the almost exclusive formation of the stable per-*O*-acetyl-1,2-*O*-(1-(*exo*-cyano)ethylidene}-α-D-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.[11] Vicent et al. had already found that the reactivity of cyanoethylidene compounds, for use in oligosaccharide synthesis, depended on the exo or endo position of the cyanide group.[12]

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*-cyanoethylidene **2** and the acetoxonium intermediate.[8]

One versatile approach of glycosyl cyanide modification, with which we already had considerable experience, is catalytic reduction.[2b] Hydrogenation of per-*O*-acetyl-*β*-L-fucopyranosyl cyanide **6** with catalytic palladium−charcoal in the presence of acetic anhydride ($Ac_2O$) gave the isolated *O*−*N*-acetyl migrated products **7** and **8** in 32 and 23% yields, respectively (Scheme 2).[13] The yield for the N-linked aminodisaccharide **8** *decreased* to 9% without the presence of $Ac_2O$. Since the presence of $Ac_2O$ did not prevent migration, it appeared that *O*−*N*-acetyl migration from a 2-*O*-acetoxyl

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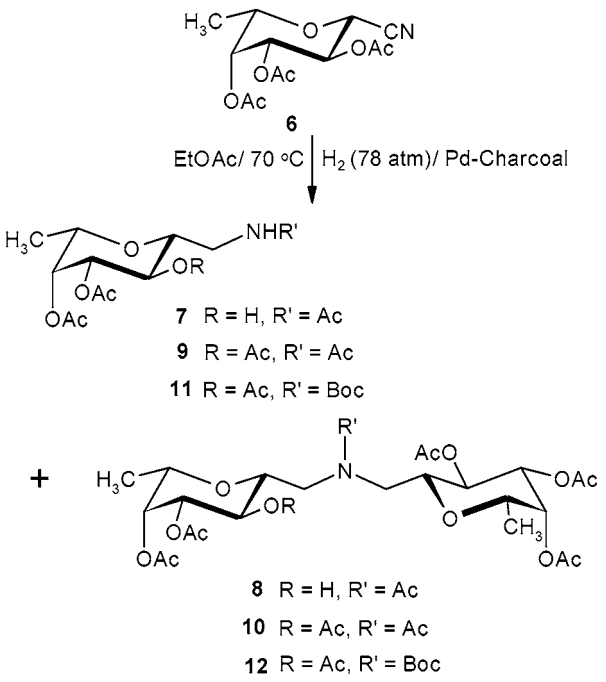
**Scheme 2**




group was much faster than acetylation of the amines. The 2-hydroxyl amino-C-monosaccharide **7** and C-disaccharide **8** can be acetylated with $Ac_2O$ 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 $Boc_2O$, 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 di-

**Table 1.** Yields for Reduction of **6**

| procedure | ratio of starting material (**6**:anhydride) | % yield[a] of products (**7**:**8**:**11**:**12**) |
|---|---|---|
| A | 1:0 | 33:9:−:− |
| B | 1:13 | 32:23:0:0 |
| C | 1:3 | 0:0:61:38 |

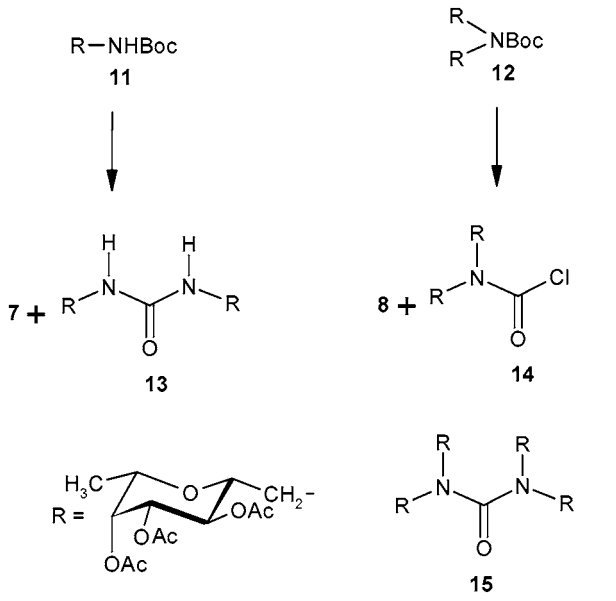
[a] Isolated yields.

saccharide **12** was increased in the presence of the anhydride. The product mixture was easily separated by column chromatography.

Cyanides are reduced with $Pd/H_2$ 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 $Boc_2O$ suggests fast reaction of aldimines and amines with $Boc_2O$ at the lipophilic charcoal catalyst surface. In contrast, hydrophilic $Ac_2O$, 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 $Ac_2O$ and $Boc_2O$.[15] This point was not appreciated by Lenz et al.[16] in their later work with $Boc_2O$, probably because they did not compare hydrogenation in the presence of $Ac_2O$, 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 ureas. 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 $TosOH-H_2O$ in $CH_2Cl_2$, and the resultant salt, in solution, was directly converted with 1/6 equiv of triphosgene in a $CH_2Cl_2$-saturated sodium bicarbonate two-phase system (Scheme 3; Table 2),

**Scheme 3**




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 2.** Yields for Synthesis of SCOMs

| procedure | ratio of starting material (**11** or **12**:triphosgene) | % yield[a] of products (**7**:**13**:**8**:**14**:**15**) |
|---|---|---|
| D | 1:1/6 | 12:63:−:−:− |
| E | 1:1/6 | −:−:48:15:28 |
| F | 1:1/2 | −:−:21:67:0 |

[a] Isolated yields.

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 tetrasubstituted 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 $SiO_2$, 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, $\beta$-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 $NEt_3$/MeOH/$H_2O$.[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 $NEt_3$, in alcoholic solvents, with avoidance of both dimerization and deprotection. In reference 19, we give our conditions for de-*O*-acetylating 2,3,4-tri-*O*-acetyl fucopyranosyl 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.

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(19) **Deprotection Procedure.** A cold (0 °C) mixture of $NEt_3$ (2.8 mL, 20 mmol), $H_2O$ (4 mL), methanol (10 mL), and 2,3,4-tri-*O*-acetyl-$\beta$-L-fucopyranosyl cyanide **6** (1 g, 3.3 mmol) was stirred overnight, to reach rt after 3 h. TLC ($SiO_2$, EtOAc) showed complete consumption of the starting material ($R_f$ = 0.7) and formation of the de-*O*-acetylated product ($R_f$ = 0.4), with two slower spots. Solvents were evaporated in vacuo with several additions of $H_2O$, and the residual was chromatographed ($SiO_2$, EtOAc) to give $\beta$-L-fucopyranosyl cyanide (330 mg, 1.9 mmol, 58%): mp 145−147 °C. Anal. Calcd for $C_7H_{11}NO_4$ (173.17): C, 48.55; H, 6.40; N, 8.09. Found: C, 48.48; H, 6.70; N, 8.01.