Pergamon

Tetrahedron Letters 41 (2000) 629–632

TETRAHEDRON LETTERS

N-Thiodiglycoloyl derivatives of glucosamine as glycosyl donors[1]

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Received 11 October 1999; accepted 15 November 1999

Abstract

N-Thiodiglycoloyl (TDG) protection of *O*-acetylated glucosamine could be readily carried out with thiodiglycolic anhydride and then treatment with acetic anhydride in pyridine. Ensuing reaction with hydrazinium acetate and then base-catalyzed activation with trichlorocetonitrile afforded *N*-TDG protected glucosamine donor **3**. Glycosylation of acceptors **8** and **5** in dichloromethane with TMSOTf as the catalyst gave β-glycosides **6** and **9** in high yields. For TDG cleavage MeONa/MeOH treatment followed by radical desulfurization with Bu_3SnH/AIBN and reacetylation with Ac_2O/pyridine was employed, thus giving *N*-acetyl glucosamine containing compounds **7** and **10** in a convenient, high-yielding procedure.

Glucosamine frequently occurs as a constituent of glycoconjugates;[2] generally, the glucosamine moiety is *N*-acetylated and found in β-glycosidic linkage. Glycoside bond-formation with donors derived from *N*-acetylglucosamine (GlcNAc) leads to 1,3-oxazolinium intermediates,[3] which exhibit only weak glycosyl donor properties. Therefore, various alternatives have been investigated having, for instance, a phthaloyl,[2,3] tetrachlorophthaloyl,[4,5] dithiasuccinyl,[6] trichloroethoxycarbonyl[7,8] or dimethylmaleoyl group[9] in the 2-position, thus supporting, via neighbouring group participation, the formation of the β-anomer. Due to the strong electron withdrawing character of the *N*-substituents, these glucosamine derivatives exhibit increased glycosyl donor properties. However, the intermediate generation of free amino groups in all the above-mentioned methodologies is quite frequently disadvantageous.[10] Therefore, methods retaining the *N*-acetyl functionality in the activated species are of great interest.[11] Recently, we proposed the use of *N*,*N*-diacetyl derivatives of amino sugars[12] as a convenient solution to this problem. These kinds of compounds are readily available and give β-linked glycosides with reactive acceptors in very high yields. Removal of one of the *N*-acetyl groups can be performed under very mild conditions (MeONa, MeOH), thus leading directly to the desired *N*-acetyl glycosides; even the selective cleavage of one of the *N*-acetyl groups can be performed in the presence of *O*-acetyl protective groups. Therefore, this method seemed to be an ideal solution. However, for less reactive glycosyl acceptors transacetylation from donor to acceptor was observed to some extent.[12]

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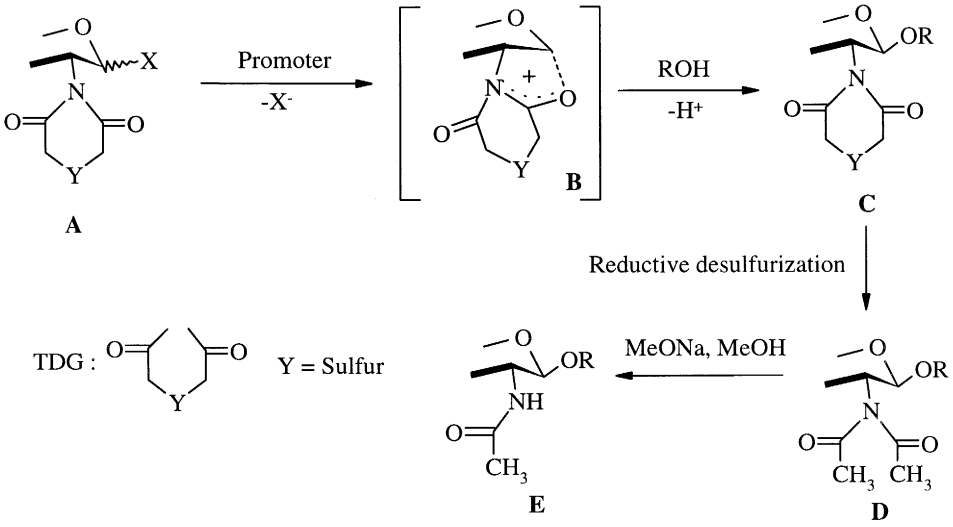
0040-4039/00/$ - see front matter
PII: S0040-4039(99)02136-X

It was rationalized that this undesirable side reaction could be overcome by a corresponding cyclic *N*,*N*-diacyl amino protective group, thus requiring a readily removable auxiliary group Y which would enable liberation of the *N*,*N*-diacetyl group (Scheme 1). The deprotection conditions could then be maintained as mild as with the *N*,*N*-diacetyl compounds. Therefore, we turned our attention to the *N*-thiodiglycoloyl (TDG) residue as a nitrogen protecting group (Scheme 1, Y=S).

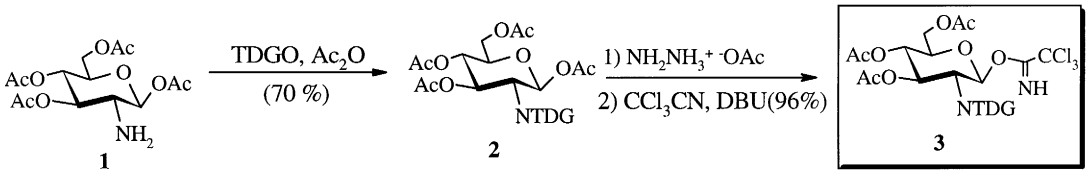


Scheme 1.

In analogy to other imido derivatives of glucosamine, the corresponding cyclic imide **A** should afford, via anchimeric assistance by one of the carbonyl groups as shown in **B**, only β-glycosides **C**. The resulting glycosides could then be transformed by radical reductive desulfurization[13] into the known *N*,*N*-diacetyl compounds **D** which, as discussed, readily affords target molecules **E**.

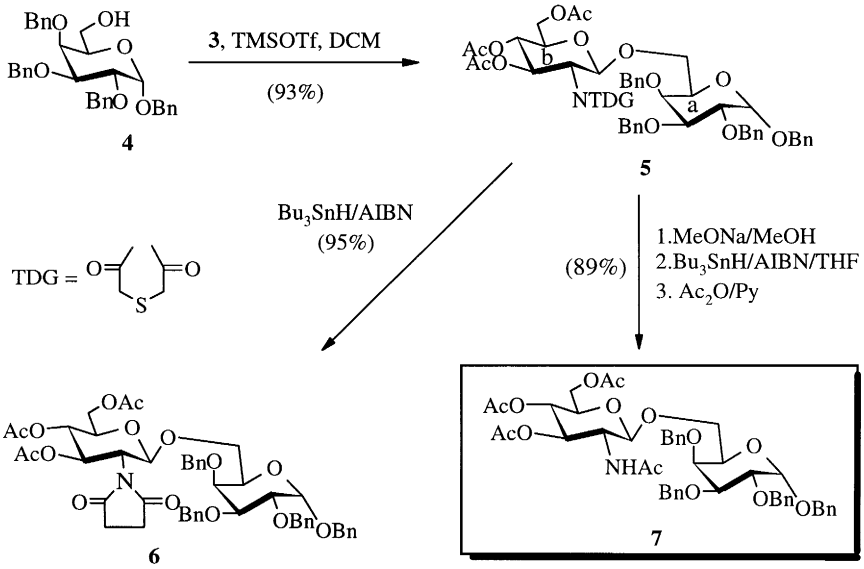
In our first attempts, we tried to protect the free glucosamine utilizing Lemieux's classic procedure.[3] At first one equivalent of NaOMe in MeOH is added to the glucosamine hydrochloride in order to liberate the free amine, and then one equivalent of commercially available thiodiglycolic anhydride is quickly added so as to avoid decomposition of the amino sugar. As expected in this case, for the six-membered ring formation the ring closure reaction did not proceed as smoothly as for the phthalimido ring closure (five-membered ring formation).[3] Hence, heating of the amide intermediate with acetic anhydride at 60°C in pyridine for 6 h was required, and the *N*-TDG-protected glucosamine was obtained as an α/β mixture in 35% overall yield.

Looking for alternatives, we found that addition of one equivalent of the thiodiglycolic anhydride to the known *O*-acetylated amine **1**[14] in pyridine, followed by acetic anhydride addition and heating at 60°C for 6 h, led to the *N*-TDG-protected glucosamine **2** in 70% yield as pure β-anomer (Scheme 2). Regioselective removal of the anomeric *O*-acetyl group with hydrazinium acetate[15] in DMF and further addition of CCl_3CN in the presence of DBU afforded the desired donor **3** in high overall yield.



Scheme 2.

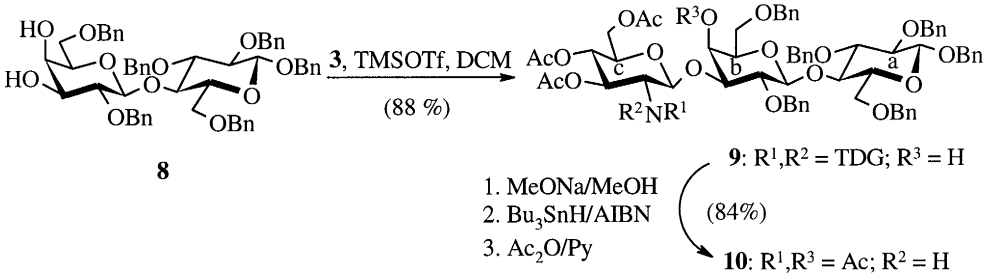
For the glycosylation with trichloroacetimidate **3** the reactive 6-*O*-unprotected galactose derivative **4**[16] was chosen as acceptor because GlcNAcβ(1–6)Gal linkages occur frequently in nature. Glycosylation of **3** with the known acceptor **4**,[16] using TMSOTf as a catalyst afforded, as expected, only the β-linked disaccharide **5** in a very high yield (93%) (Scheme 3). Encouraged by this excellent result, we concentrated our attention to the deprotection of the TDG group.



Scheme 3.

Thus, reaction of disaccharide **5** with Bu_3SnH/AIBN in toluene at 110°C resulted in complete succinoyl protected disaccharide. Obviously, a novel highly efficient intramolecular C–C bond formation between the two radicals led to the formation of the cyclic product with extrusion of (tri-*n*-butyl) tin sulfur compounds. To avoid this undesired intramolecular reaction, first cleavage of the cyclic imide structure was accomplished with MeONa/MeOH. Treatment of the residue with Bu_3SnH in THF led to direct generation of the acetamido group, and subsequent acetylation with Ac_2O/Py afforded the desired disaccharide **7**[12] in 89% yield.

Because GlcNAcβ(1–3)Galβ(1–4)Glc trisaccharides also occur frequently in nature, known 3,4 *O*-unprotected lactose **8**[10] was investigated as acceptor (Scheme 4). Reaction of trichloroacetimidate **3** with **8** under similar conditions as described for **5** afforded the expected trisaccharide **9** as a single product. The NMR data support the structural assignments.[17] The deprotection was performed under the same conditions as described for **5**, affording the known *N*-monoacetyl trisaccharide **10**[12] in 87% overall yield.



Scheme 4.

In conclusion, TDG-protected trichloroacetimidate from glucosamine was readily available and it gave, along with the investigated acceptors, excellent glycosylation yields. The deprotection sequence was mild, and afforded the naturally occurring acetamido sugars in high overall yields.

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17. Values of $[\alpha]_D$ were measured at 20°C and ^{1}H NMR spectra were recorded in $CDCl_3$ at 250 MHz. Compound **2**: $[\alpha]_D$ +11 (*c* 0.7, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$); δ=1.91–2.39 (4 s, 12H, 4Ac), 3.50 (m, 4H, 2CH_2S), 3.85 (m, 1H, 5-H), 4.11 (m, 1H, 6-H), 4.32 (m, 1H, 6′-H), 5.03 (dd, 1H, $J_{1,2}$=$J_{2,3}$=9.5 Hz, 2-H), 5.18 (dd, 1H, $J_{3,4}$=$J_{4,5}$=9.5 Hz, 4-H), 5.81 (dd, 1H, $J_{2,3}$=$J_{3,4}$=9.5 Hz, 3-H), 6.51 (d, 1H, $J_{1,2}$=9.5 Hz, 1-H). Compound **3**: $[\alpha]_D$ +14.5 (*c* 1, $CDCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.91–2.39 (4 s, 12H, 4Ac), 3.54 (m, 4H, 2CH_2S), 3.88 (m, 1H, 5-H), 4.28 (m, 2H, 6-H, 6′-H), 5.15 (dd, 1H, $J_{1,2}$=$J_{2,3}$=9.5 Hz, 2-H), 5.22 (dd, 1H, $J_{3,4}$=$J_{4,5}$=9.5 Hz, 4-H), 5.83 (dd, 1H, $J_{2,3}$=$J_{3,4}$=9.5 Hz, 3-H), 6.82 (d, 1H, $J_{1,2}$=9.5 Hz, 1-H), 8.21 (s, 1H, NH). Compound **5**: $[\alpha]_D$ +6 (*c* 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.01–2.39 (3s, 9H, 3OAc), 3.60 (m, 4H, 2CH_2S), 3.90 (m, 4H, H-5a, H-2a, H-5b, H-6b), 4.02 (m, 3H, H-6′b, H-3a, H-6a), 4.12 (dd, $J_{3,4}$=$J_{4,5}$<1 Hz, H-4a), 4.30 (m, 1H, H-6′a), 4.50–4.85 (m, H, 3CH_2Ph, H-1a), 5.05 (dd, 1H, $J_{1,2}$=1.5, $J_{2,3}$=9.8 Hz, H-2b), 5.20 (dd, 1H, $J_{3,4}$=$J_{4,5}$=9.8 Hz, H-4b), 5.55 (dd, 1H, $J_{2,3}$=$J_{3,4}$=9.8 Hz, H-3b), 5.90 (d, 1H, $J_{1,2}$=9.5 Hz, H-1b), 7.35–7.75 (m, 20H, Ar). Compound **6**: $[\alpha]_D$ +15 (*c* 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.01–2.39 (3s, 9H, 3OAc), 3.05 (m, 4H, 2CH_2), 3.90–4.00 (m, 4H, H-5a, H-2a, H-5b, H-6b), 4.10 (m, 3H, H-6′b, H-3a, H-6a), 4.15 (dd, $J_{3,4}$=$J_{4,5}$<1 Hz, H-4a), 4.28 (m, 1H, H-6′ a), 4.50–4.85 (m, 7H, 3CH_2Ph, H-1a), 5.10 (dd, 1H, $J_{1,2}$=1.5, $J_{2,3}$=9.8 Hz, H-2b), 5.22 (dd, 1H, $J_{3,4}$=$J_{4,5}$=9.8 Hz, H-4b), 5.56 (dd, 1H, $J_{2,3}$=$J_{3,4}$=9.8 Hz, H-3b), 5.84 (d, 1H, $J_{1,2}$=9.5 Hz, H-1b), 7.35–7.75 (m, 20H, Ar). Compound **9**: $[\alpha]_D$ −38 (*c* 1, $CDCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.90–2.28 (3s, 9H, 3OAc), 3.60 (m, 4H, 2CH_2S), 3.71–4.32 (m, 12H, H-2a, H-3a, H-4a, H-5a, H-6a, H-6b, H-6′a, H-6′b, H-2b, H-5b, CH_2Ph), 4.51–4.82 (m, 7H, 3CH_2Ph, H-1a), 5.12 (dd, 1H, $J_{3,4}$=$J_{4,5}$=9.8 Hz, H-4), 5.22 (d, 1H, $J_{1,2}$=10.2 Hz, H-1b), 5.65 (d, 1H, $J_{2,3}$=10.3, $J_{3,4}$=9.8 Hz, H-3), 7.15–7.45 (m, 20H, 5Ar).