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# Synthesis of *N*-Protected Galactosamine Building Blocks from D-Tagatose via the Heyns Rearrangement

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N-Acetyl-D-galactosamine (11), a very important naturally occurring building block of oligosaccharides, is easily accessible via the Heyns rearrangement of D-tagatose (3) with benzylamine. The short and efficient synthesis of various differently N-protected D-galactosamine derivatives is reported.

Keywords Heyns rearrangement, D-Galactosamine, N-Protected D-galactosamine building blocks

#### INTRODUCTION

*N*-Acetyl-D-galactosamine (**11**) is a naturally occurring sugar present in glycoproteins, glycolipids, and glycosaminoglycans, which play important roles in cell recognition events.<sup>[1]</sup> Furthermore, **11** is biosynthetically incorporated into glycosphingolipids.<sup>[2]</sup>

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Consequently, different synthetic approaches for this important sugar have been investigated over the years. Paulsen and coworkers first synthesized 2-azido deoxy-D-galacto sugars starting from 1,6;2,3-dianhydro- $\beta$ -D-talopyranose by nucleophilic opening of the epoxide employing sodium azide.<sup>[3]</sup> Perry showed the transformation of D-lyxose to **11** by base-catalyzed addition of nitromethane followed by introduction of the amino function at position C-2.<sup>[4]</sup> D-Galactal was found by several groups to be a suitable starting material for the synthesis of **11**. By addition reactions, 2-azido-2-deoxy- and 2-deoxy-2nitro-D-galactose compounds were obtained that could easily be converted to derivatives of **11**.<sup>[5]</sup> Several synthetic approaches were based on the inversion of the configuration at position C-4 of D-glucose derivatives, leading to the corresponding galacto-configurated amino sugars but requiring time- and cost-intensive protecting group manipulations with only moderate yields.<sup>[6]</sup>

The Heyns rearrangement,<sup>[7]</sup> wherein ketoses react with suitable amines to form the corresponding ketosylamines, which subsequently isomerize to the 2-amino-2-deoxyaldoses (Sch. 1), was first discovered by Fischer<sup>[8]</sup> during his studies on the osazone formation of sugars and further investigated by Heyns and Koch in the 1950s when they found that D-glucosamine **2** was formed in the reaction of D-fructose **1** with ammonia.<sup>[9]</sup>

Subsequently, this reaction was extended to a wide range of different amines yielding the corresponding *N*-substituted glucosamine derivatives. Other ketosugars such as D-tagatose, L-sorbose, and D-psicose were found to react accordingly. In general, yields were found unsatisfactory and too low for preparative purpose. For example, Heyns and his group<sup>[10]</sup> showed that the reaction of Dtagatose with ammonia is straightforward and gave the best result in the ketosugar series, leading to D-galactosamine hydrochloride in an overall yield of 3.5%. Later, Weicker and coworkers<sup>[11]</sup> reinvestigated this reaction employing silica gel for the condensation of D-tagatose with ammonia and ion exchange resin for the rearrangement. This way, the crude yield of D-galactosamine hydrochloride was increased to 22 to 26%, as determined by the colorimetric Elson-Morgan method, but only 8% could be isolated after crystallization.

Recently, we showed that the Heyns rearrangement is a convenient entry to valuable 2-deoxy-2-amino sugars such as lactosamine<sup>[12]</sup> by varying the reaction conditions and choosing a suitable nitrogen protecting group.



Scheme 1: Heyns rearrangement of D-fructose.

Now we want to report the synthesis of various differently *N*-protected derivatives (7-11) of D-galactosamine starting from D-tagatose **3**. This ketose gained interest due to its approval as an alternative, nonnutritious sweetener<sup>[13]</sup> used in soft drinks and ready-to-eat cereals. Therefore, a change from a rare to a common status could be recognised for D-tagatose during the last few years, now easily prepared, for example, from galactose<sup>[14]</sup> or in a one-step de novo synthesis.<sup>[15]</sup> The *N*-protected galactosamine building blocks were synthesized in overall yields of up to 25%.

#### **RESULTS AND DISCUSSION**

D-Tagatose 3 was reacted with commercial-grade benzylamine to give the corresponding N-benzyl-tagatosylamine 4, which was obtained as yellowish syrup together with unreacted starting material and side products. This mixture underwent the rearrangement in methanol in the presence of glacial acetic acid (v:v 10:1) at room temperature within 2h to give mainly N-benzyl-D-galactosamine 5. No epimerization at C-2 could be observed in the course of the rearrangement under the conditions employed, although formation of small amounts of the taloconfigurated product has been found by other workers.<sup>[10]</sup> Hydrogenolysis of the *N*-benzyl group was performed in MeOH or water/dioxane at pH 1-2 employing Pearlman's catalyst (20%) to yield a mixture of galactosamine hydrochloride 6 and unreacted 3. N-Protection was achieved in methanol employing trietylamine and 1,3-dimethyl-5-[(dimethylamino)methylene] 2,4,6 (1H, 3H, 5H)-trioxopyrimidine (DTPM-reagent).<sup>[16]</sup> Per-O-acetylation in pyridine with acetic anhydride allowed, after recrystallization from diisopropyl ether, access to the fully protected derivative 7 in an overall yield of 25% starting form D-tagatose, ready for further transformations. Likewise, the amino function of 6 can be reacted with other protecting groups. Reaction with tetrachlorophthaloyl anhydride (TCPA) in MeOH using Et<sub>3</sub>N as base gave, after per-O-acetylation, the N-TCPper-O-acetylated galactosamine 8.<sup>[17]</sup> Employing trichloroethoxycarbonylchloride (TrocCl) in aqueous dioxane in the presence of NaHCO<sub>3</sub> followed by per-O-acetylation yielded 9. Accordingly, 9-fluorenylmethoxycarbonylchloride<sup>[18]</sup> (FmocCl) furnished 10. In all cases the per-O-acetylated differently N-protected galactosamine derivatives were isolated in overall yields of 15 to 25% calculated from **3**. Additionally, regioselective N-acetylation performed in MeOH or simple per-O-acetylation led to known N-acetyl-D-galactosamine and per-O-acetylated D-galactosamine, respectively (Sch. 2).<sup>[19]</sup>

#### CONCLUSION

In summary, we have synthesized different *N*-protected galactosamine derivatives (7-11) via the Heyns rearrangement starting from commercially available *D*-tagatose **3** in overall yields of up to 25%. The reaction sequence is short and



Scheme 2: Synthesis of *N*-protected D-galactosamine derivatives 7–11 in overall yields of up to 25%.

easy to handle, requiring only cheap materials. With suitable protecting groups, a range of D-galactosamine building blocks are now readily available.

#### **EXPERIMENTAL**

<sup>1</sup>H NMR spectra were recorded on a Varian INOVA 500 operating at 499.925 MHz. <sup>13</sup>C NMR spectra were recorded at 75.47 or 50.29 MHz. Residual nondeuterated solvent was used as internal standard for determination of chemical shifts. Signals of protecting groups were found in the expected regions and are not listed explicitly. Mass spectra were measured on an HP 1100 series MSD, Hewlett Packard. Samples were dissolved in acetonitrile or acetonitrile/water mixtures. The scan mode for positive ions (mass range 100–1,000 D) was employed varying the fragmentation voltage from 50 to 250 V, with best molecular peaks observed at 150 V. Analytical TLC was performed on precoated aluminum plates silica gel 60 F254 (Merck 5554), detected with UV light (254 nm), as well as staining with 5% vanillin/sulfuric acid or cercic ammonium molybdate (100 g ammonium-molybdate/4g cerium sulfate in 1L 10 % H<sub>2</sub>SO<sub>4</sub>) and heated on a hotplate. For column chromatography silica gel 60 (230–400 mesh, Merck 9385) was used.

### 1,3,4,6,-Tetra-O-Acetyl-N-(1,3-Dimethyl-2,4,6 (1H, 3H, 5H)-Trioxopyrimidine-5-ylidene)Methyl-α-D-Galactosamine (7)

**N-Benzyl-D-Galactosamine 5**: To D-tagatose **3** (3.0 g, 16.7 mmol) benzylamine (7.5 mL, 68.7 mmol) was added at 0°C and the reaction mixture

stirred at 40°C over night until TLC (CH<sub>3</sub>Cl/MeOH/NH<sub>4</sub>OH5/1/1%) showed the condensation product as the main component in the mixture. Methanol (3 mL) was added and this solution was stirred into 400 mL petrol ether and stirred at rt for 2h. The petrol ether layer was separated and this procedure was repeated. Obtained were 4.3 g of a mixture containing *N*-benzyltagatosylamine (4), starting material **3**, and side products. The residue was dissolved in a mixture of methanol (25 mL) and glacial acetic acid (2.5 mL) and kept at rt for 1h. The solution was stirred into petrol ether (400 mL) and stirring was continued for 3h. After separation of the layers, an oily brown residue, containing *N*-benzylgalactosamine **5**, D-tagatose **3**, and side products was obtained.

**D-Galactosamine Hydrochloride (6)**: The residue obtained from the rearrangement (5.6 g) was dissolved in deionized water (15 mL) containing 8 mL of dioxane and dropwise acidified with concd HCl to pH 1.  $Pd(OH)_2/C$  (0.6 g) was added and this mixture was stirred under a hydrogen atmosphere at ambient pressure and ambient temperature until TLC (MeOH/CHCl<sub>3</sub>/NH<sub>4</sub>OH2/2/1) showed completed removal of the *N*-benzyl group. The catalyst was filtered off and the solution was concentrated under reduced pressure. The obtained yellowish residue (4.6 g) contained the D-galactosamine hydrochloride **6** and unreacted starting material.

**DTPM Protection:** The residue obtained from hydrogenolysis (4.6 g) was dissolved in 20 mL methanol, and triethylamine (7 mL, 50.5 mmol), and DTPM reagent (8g, 38.0 mmol in methanol) were added and the reaction was kept at rt for 2h. The solid precipitate was filtered off, and the filtrate was concentrated to 11.3 g of N-DTPM-protected D-galactosamine in a mixture with Dtagatose **3**. To a 10% solution of this crude material in pyridine, acetic anhydride (15 mL) was added dropwise at 0°C, a catalytic amount of dimethylaminopyridine was added, and the reaction was kept at rt for 16 h. The solvent was removed under reduced pressure, the residue was dissolved in CHCl<sub>3</sub>, and the solution was consecutively washed with 6% HCl and sat aqueous NaHCO<sub>3</sub>, then dried over Na<sub>2</sub>SO<sub>4</sub>. Column chromatography with ethyl acetate/petrol ether 1/2 gave exclusively the  $\alpha$ -anomer 7 in an overall yield from **3** of 25%.  $[\alpha]^{20;D} = +47.9 \ (c = 2.0, \text{ CH}_2\text{Cl}_2)$ . <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 10.09$ (m, 1H, NHDPTM), 8.10 (d, 1H, HC=CDPTM), 6.25 (d, 1H, H-1, J<sub>1,2</sub> 3.9 Hz), 5.43 (m, 1H, H-4,  $J_{4,5}$  2.9 Hz), 5.19 (dd, 1H, H-3,  $J_{2,3}$  11.0 Hz,  $J_{3,4}$  3.4 Hz), 4.25 (m, 1H, H-6, J<sub>5.6</sub>3.8 Hz), 4.05-4.03 (m, 2H, H-5, H-6'), 3.94 (ddd, 1H, H-2). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta = 170.55$ , 170.09, 170.04, 168.98 (acetyl), 165.07, 162.82, 159.53, 152.10 (DPTM), 92.78 (DPTM), 90.84 (C-1), 69.0, 68.45, 66.36 (3C, C-3, C-4, C-5) 61.17 (C-6), 57.52 (C-2), 28.14, 27.44 (DPTM), 21.03, 20.86, 20.84, 20.79 (acetyl). m/z: 514.4 [M<sup>+</sup>-H]. Anal. calcd for C<sub>21</sub>H<sub>27</sub>O<sub>12</sub>N<sub>3</sub> (513.5): C, 49.12; H, 5.31. Found: C 49.01, H 5.36.

# 1,3,4,6-Tetra-O-Acetyl-2-Deoxy-2-(Tetrachlorophthalimido)- $\alpha/\beta$ -D-Galactosamine (8)

To a 10% solution of crude galactosamine hydrochloride 6 (6.1 g, 28.3 mmol) in methanol, tetrachlorophthaloyl anhydride (TCPA, 10.0 g, 45.5 mmol) and triethylamine (8.0 mL, 57.7 mmol) were added at  $0^{\circ}$ C; 1 mL THF and 1mL dioxane were added for better solubility; and the reaction was stirred at ambient temperature for 20 h until TLC ( $CHCl_3/MeOH/$  $NH_4OH4/4/1$ ) showed completed conversion of the starting material. The reaction mixture was concentrated to a residue that was per-O-acetylated in 150 mL pyridine, 50 mL acetic anhydride, and a catalytic amount of dimethylamino pyridine. The solvent was removed under reduced pressure, the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, and the solution was consecutively washed with 6% HCl and sat aqueous NaHCO<sub>3</sub>, then dried over Na<sub>2</sub>SO<sub>4</sub>. Column chromatography with ethyl acetate/petrol ether 1/4 gave an  $\alpha/\beta$  mixture with a ratio of 3:1 of 8 in an overall yield from D-tagatose of 15%. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 6.41$  (d, 1H, H-3 $\alpha$ ,  $J_{2,3}$  12.2 Hz,  $J_{3,4}$  2.9 Hz), 6.38 (d, 1H, H-1 $\beta$ ,  $J_{1,2}$  8.8 Hz), 6.28 (d, 1H, H-1 $\alpha$ ,  $J_{1,2}$  3.4 Hz), 5.83 (dd, 1H, H-3 $\beta$ ,  $J_{3,4}$ 3.4 Hz,  $J_{2,3}$  11.2 Hz), 5.65 (bd, 1H, H-4 $\alpha$ ,  $J_{4,5}$  2 Hz), 5.50 (bd, 1H, H-4 $\beta$ ,  $J_{4,5}$ 3 Hz), 4.87 (dd, 1H, H-2 $\alpha$ ), 4.63 (dd, 1H, H-2 $\beta$ ), 4.49 (m, 1H, H-5 $\alpha$ ,  $J_{5.6}$ 6.8 Hz,  $J_{5.6'}$  4.4 Hz), 4.21–4.10 (m, 5H, H-6 $\alpha$ , H-6 $\alpha$ , H-5 $\beta$ , H-6 $\beta$ , H-6 $\beta$ ). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta = 91.3$  (C-1 $\alpha$ ), 90.2 (C-1 $\beta$ ), 72.0 (C-5 $\beta$ ), 69.6 (C-5 $\alpha$ ), 67.8 (C-4 $\beta$ ), 67.0 (C-4 $\alpha$ ), 66.5 (C-3 $\beta$ ), 64.7 (C-3 $\alpha$ ), 61.5 (C-6 $\alpha$ ), 61.3 (C-6 $\beta$ ), 51.2 (C-2 $\alpha$ ), 50.3 (C-2 $\beta$ ). m/z: 616.3 [M<sup>+</sup>-H]; Anal. calcd for C<sub>22</sub>H<sub>19</sub>O<sub>11</sub>NCl<sub>4</sub> (615.24): C, 42.95; H 3.12. Found: C, 42.85; H, 3.15.

# 1,3,4,6-Tetra-O-Acetyl-2-Deoxy-2-(Trichloroethoxycarbonyl)- $\alpha/\beta$ -D-Galactosamine (9)

To a 10% solution of crude galactosamine hydrochloride **6** (1.3 g, 6.12 mmol) in deionized water, NaHCO<sub>3</sub> (1.8 g, 21.4 mmol) and trichloroethoxycarbonyl chloride (TrocCl, 1.3 mL, 9.4 mmol) were added and the reaction stirred at ambient temperature for 20 h until TLC (CHCl<sub>3</sub>/MeOH/NH<sub>4</sub>OH4/4/1) showed complete conversion of the starting material. The reaction mixture was concentrated to a residue, which was treated with 10 mL pyridine, 5 mL acetic anhydride, and a catalytic amount of dimethyla-minopyridine. The solvent was removed under reduced pressure, the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, and the solution was consecutively washed with 6% HCl and sat aqueous NaHCO<sub>3</sub>, then dried over Na<sub>2</sub>SO<sub>4</sub>. Column chromatography with ethyl acetate/petrol ether 1/5 gave an  $\alpha/\beta$  mixture with a ratio of 2:1 of **9** in an overall yield from D-tagatose of 20%. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 6.25$  (d, 1H, H-1 $\alpha$ , J<sub>1,2</sub> 3.4 Hz), 5.74 (d, 1H, H-1 $\beta$ , J<sub>1,2</sub> 8.8 Hz), 5.42 (bd, 1H, H-4 $\alpha$ , J<sub>4,5</sub> 2.0 Hz), 5.37 (bd, 1H, H-4 $\beta$ , J<sub>4,5</sub> 2.0 Hz), 5.20 (dd, 1H, H-3 $\alpha$ , J<sub>2,3</sub> 11.5 Hz, J<sub>3,4</sub> 3.4 Hz,), 5.12 (dd, 1H, H-3 $\beta$ , J<sub>2,3</sub> 11.2 Hz, J<sub>3,4</sub>

3.4 Hz), 4.82 (d, 1H, CH<sub>2</sub> Troc,  $\alpha$ , J 12.2 Hz), 4.73 (d, 1H, CH<sub>2</sub> Troc,  $\beta$ , J 12.2 Hz), 4.69 (d, 1H, CH<sub>2</sub> Troc,  $\beta$ , J 12.2 Hz), 4.60 (d, 1H, CH<sub>2</sub> Troc,  $\alpha$ , J 12.2 Hz), 4.42 (m, 1H, H-2 $\alpha$ ), 4.24 (bdd, 1H, H-6' $\alpha$ ), 4.16–4.03 (m, 6H, H-2 $\beta$ , H-5 $\alpha$ , H-5 $\beta$ , H-6 $\alpha$ , H-6 $\beta$ , H-6' $\beta$ ). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 171.0, 170.7, 170.6, 170.4, 169.5, 169.1 (acetyl), 154.6 (C=O Troc,  $\beta$ ), 154.4 (C=O Troc,  $\alpha$ ), 95.5 (C-1 $\alpha$ ), 92.8 (C-1 $\beta$ ), 91.3 (CCl<sub>3</sub>), 74.6 (CH<sub>2</sub> Troc,  $\alpha$ ), 74.6 (CH<sub>2</sub> Troc,  $\beta$ ), 71.9 (C-5 $\beta$ ), 70.3 (C-3 $\beta$ ), 68.8 (C-5 $\alpha$ ), 68.1 (C-3 $\alpha$ ), 66.9 (C-4 $\alpha$ ), 66.6 (C-4 $\beta$ ), 61.4 (2C, C-6 $\alpha$ , C6 $\beta$ ), 51.8 (C-2 $\beta$ ), 49.3 (C-2 $\alpha$ ). m/z: 616.3 [M<sup>+</sup>-H]; Anal. calcd for C<sub>17</sub>H<sub>22</sub>O<sub>11</sub>NCl<sub>3</sub> (522.75): C, 39.06; H, 4.25. Found: C, 39.01; H, 4.29.

#### 1,3,4,6-Tetra-O-Acetyl-2-deoxy-2-(9-Fluorenylmethoxycarbonylamino)-α-D-Galactose (10)

To a 10% solution of crude galactosamine hydrochloride 6 (1.8 g, 8.4 mmol) in dioxane, NaHCO3 (2.5 g, 30 mmol) and 9-fluorenylmethoxycarbonylchloride (3.5 g, 13.5 mmol) were added and the reaction stirred at ambient temperature until TLC  $(CHCl_3/MeOH/NH_4OH4/4/1)$  showed complete conversion of the starting material. The reaction mixture was concentrated to a residue, which was treated with 20 mL pyridine, 10 mL acetic anhydride, and a catalytic amount of dimethylaminopyridine. The solvent was removed under reduced pressure, the residue was dissolved in  $CH_2Cl_2$ , and the solution was consecutively washed with 6% HCl and sat aqueous NaHCO<sub>3</sub>, then dried over Na<sub>2</sub>SO<sub>4</sub>. Column chromatography with ethyl acetate/petrol ether 1/5 gave exclusively the  $\alpha$ -anomer of 10 in an overall yield from D-tagatose of 26%.  $[\alpha]^{20,D} = +24.5$  (c = 1.7, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 10.09$  (m, 1H, NHDPTM), 7.70 (d, 2H, Fmoc), 7.53 (d, 1H, Fmoc), 7.50 (d, 1H, Fmoc), 7.38 (t, 2H, Fmoc), 7.28 (t, 2H, Fmoc), 6.25 (d, 1H, H-1, J<sub>1,2</sub> 3.9 Hz), 5.44 (m, 1H, H-4, J<sub>4.5</sub> 1.9 Hz), 5.21 (dd, 1H, H-3,  $J_{2,3}$  11.4 Hz,  $J_{3,4}$  3.0 Hz), 4.45 (dd, 1H, H-6',  $J_{5,6'}$  7.2 Hz,  $J_{5,6}$  6.8 Hz,  $J_{6.6}$  11.2 Hz), 4.36 (dd, 1H, H-6), 4.26 (t, 1H, CH<sub>2</sub>Fmoc), 4.19 (t, 1H,  $CH_2Fmoc$ ), 4.15–4.05 (m, 3H, H-2, H-5, CHFmoc). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta = 171.2, 170.7, 170.5, 169.2, 156.1$  (acetyl), 143.9, 141.4, 128.0, 127.3, 125.1, 120.3 (Fmoc), 91.7 (C-1), 68.8 (CH<sub>2</sub>Fmoc), 68.2, 67.2, 67.0 (C-3, C-4, C-5), 61.6 (C-6), 49.0 (C-2), 47.3 (CHFmoc), 21.1, 20.9 (Acetyl). m/z: 570.8 [M<sup>+</sup>-H]; Anal. calcd for C<sub>29</sub>H<sub>31</sub>O<sub>11</sub>N (569.62): C, 61.15; H, 5.50. Found: C, 60.95; H, 5.57.

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