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# Preparative synthesis of selectively substituted 1,6-anhydro-α-D-galactofuranose derivatives

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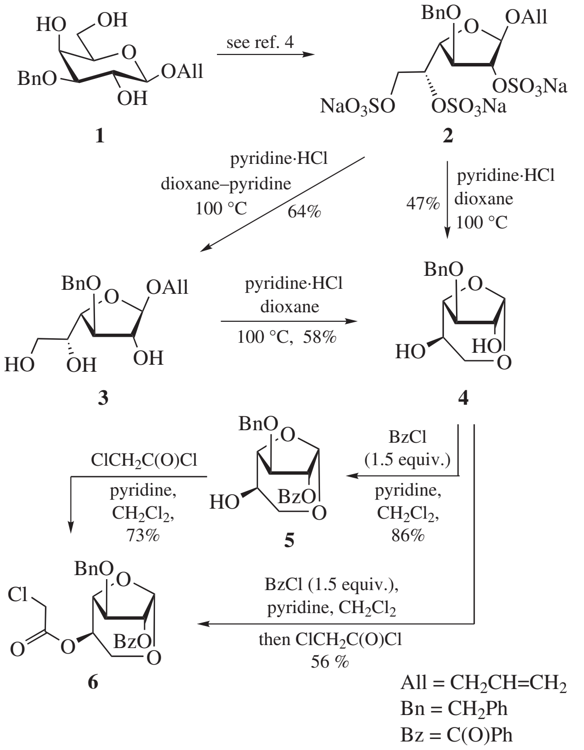
Heating of trisodium salt of allyl 3-*O*-benzyl-2,5,6-tri-*O*-sulfonato-β-D-galactofuranoside with pyridinium chloride in dioxane affords 1,6-anhydro-3-*O*-benzyl-α-D-galactofuranose which was regioselectively acylated to give useful precursors for oligosaccharide synthesis.

Growing biological interest to furanoside-containing natural carbohydrates of plant, bacterial and fungal origin challenges the development of new synthetic approaches to their chemical preparation. One of the convenient type of building blocks for assembling of a variety of galactofuranoside-containing oligosaccharides includes 1,6-anhydro-α-D-galactofuranose derivatives.[1,2] Recently, a simple three-step procedure for the synthesis of unprotected 1,6-anhydro-α-D-galactofuranose was reported.[3] However, this compound appeared to be inconvenient for the use in the assembling of oligosaccharides because of difficulties for further regioselective reactions through hydroxy groups at $C^2$, $C^3$ and $C^5$.

Here (Scheme 1) we describe a simple and convenient preparation of selectively protected 1,6-anhydro-3-*O*-benzyl-α-D-galactofuranose **4** and its derivatives **5**, **6**. Compound **4** was unexpectedly obtained during the study of solvolytic O-desulfation of trisulfate **2** – the product of the pyronaside-*into*-furanoside rearrangement[4] of allyl galactopyranoside **1**[5] under the conditions of acid promoted per-O-sulfation.[6] Particularly, O-desulfation of compound **2** upon heating in a dioxane–pyridine (10:1) mixture in the presence of Py·HCl[7,8] gave the expected triol **3**,[†] while the same treatment but in dioxane afforded only unexpected 1,6-anhydro product **4**.[‡] The same compound was formed upon heating of triol **3** in dioxane in the presence of pyridine·HCl (Scheme 1). Evidently, compound **4** is produced in the course of acid-catalyzed transacetalyzation.



**Scheme 1**

The structure of product **4** was undoubtedly proved by NMR spectroscopy and mass spectrometry. In particular, the cross-peak $H^1/C^6$ in the HMBC spectrum (Figure 1) of **4** confirmed the presence of $H^1$–$C^1$–$O^6$–$C^6$ structural fragment in **4**, while the correlation peak between $H^1$ and $C^4$ and the absence of the cross-peak $H^1/C^5$ clearly indicated the presence of the five-membered

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[†] *Allyl 3-*O*-benzyl-β-D-galactofuranoside* **3**. Dioxane (2.7 ml) was added to an intensively stirred suspension of trisodium salt of allyl 3-*O*-benzyl-2,5,6-tri-*O*-sulfonato-β-D-galactofuranoside **2**[4] (108 mg, 0.175 mmol) and Py·HCl (50 mg, 0.433 mmol) in pyridine (0.3 ml). The mixture was heated at 100 °C for 90 min and then cooled to room temperature. The mixture was dissolved in $CHCl_3$ (15 ml) and washed with saturated aqueous NaCl (15 ml). The organic layer was concentrated, and the residue was purified by column chromatography on silica gel in ethyl acetate–toluene (2:1) to give the furanoside derivative **3** (35 mg, 64%) identical to the previously described product.[4]

[‡] *1,6-Anhydro-3-*O*-benzyl-α-D-galactofuranose* **4**.

*Procedure 1*. A suspension of **2**[4] (98 mg, 0.159 mmol) and Py·HCl (50 mg, 0.433 mmol) in dioxane (3.0 ml) was stirred at 100 °C for 30 min and then cooled to room temperature. The reaction mixture was dissolved in $CHCl_3$ (15 ml) and washed with saturated aqueous NaCl (15 ml). The organic layer was concentrated and the residue was purified by column chromatography on silica gel in ethyl acetate–toluene (2:1) to give product **4** (19 mg, 47%) as white solid, $R_f = 0.69$ (EtOAc), $[\alpha]_D = 62°$ ($c = 1.0$, MeOH). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.44–7.30 (m, 5H, $H_{Ph}$), 5.24 (d, 1H, $H^1$, $J_{1,2}$ 4.6 Hz), 4.68 (d, 1H, PhC$H_a$H$_b$, $J$ 11.8 Hz), 4.64 (d, 1H, PhCH$_a$$H_b$, $J$ 11.8 Hz), 4.37–4.33 (m, 1H, $H^2$), 4.28 (d, 1H, $H^4$, $J$ 4.3 Hz), 4.13–3.99 (m, 3H, $H^5$, $H^3$, $H^{6a}$), 3.57 (t, 1H, $J_{6b,6a} = J_{6b,5} = 10.5$ Hz), 2.39 (br. s, 1H, OH), 2.20 (br. s, 1H, OH). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 137.59 (q, Ph), 128.50 (Ph), 127.91 (Ph), 98.07 ($C^1$), 82.66 ($C^3$), 82.35 ($C^4$), 79.53 ($C^2$), 71.50 (Ph$CH_2$), 65.39 ($C^6$), 62.53 ($C^5$). HRMS (ESI), *m/z*: 275.0882 [M+Na]$^+$ (calc. for $C_{13}H_{16}O_5$, *m/z*: 275.0890).

*Procedure 2*. A solution of triol **3**[4] (30 mg, 0.0967 mmol) and Py·HCl (31 mg, 0.268 mmol) in dioxane (1.5 ml) was stirred at 100 °C for 45 min and then cooled to room temperature. The mixture was dissolved in $CHCl_3$ (10 ml) and washed with saturated aqueous NaCl (10 ml). The organic layer was concentrated and the residue was purified by column chromatography on silica gel in ethyl acetate–toluene (2:1) to give product **4** (14 mg, 58%).

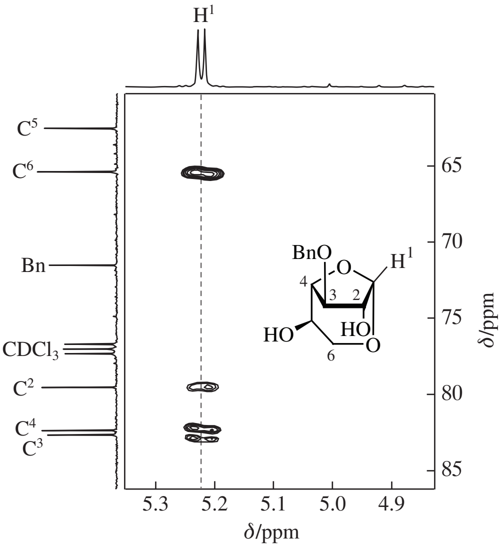

**Figure 1** Part of the HMBC spectrum of 1,6-anhydrogalactofuranose **4**.

furanoside ring. Low-field resonance of $C^6$ in the $^{13}C$ NMR spectrum of **4** also confirmed the formation of the 1,6-anhydro cycle.

Compound **4** contains two OH groups of different reactivity. Thus, the treatment of diol **4** with 1.5 equiv. of BzCl in the presence of pyridine regioselectively led to 2-O-benzoylated product **5**[§] along with traces of the corresponding dibenzoate (detected by TLC). The structure of benzoate **5** was confirmed by characteristic downfield resonance of $H^2$ in the $^1H$ NMR spectrum as a result of 2-O-benzoylation (4.35 → 5.34 ppm). Further 5-O-chloroacetylation of compound **5** with 2 equiv. of $ClCH_2C(O)Cl$ gave totally protected derivative **6**.[¶] Remarkable difference in reactivity of the OH groups in diol **4** permits an easy transformation of this compound into **6** within a one-pot process by successive treatment first with BzCl and then by $ClCH_2C(O)Cl$.[††]

In conclusion, we developed the regioselective synthesis of galactofuranose derivative, which seems promising for the preparation of a variety of furanoside-containing oligosaccharides. Particularly, the galactofuranoside **6** related compounds were applied by us as key synthetic blocks for the assembling of large oligosaccharide chains related to *Aspergillus* galactomannan. These results will be published elsewhere.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.11.006.

## References

1 M. Černý, *Adv. Carbohydr. Chem. Biochem.*, 2003, **58**, 121.
2 S. S. Kulkarni, J.-C. Lee and S.-C. Hung, *Curr. Org. Chem.*, 2004, **8**, 475.
3 L. Baldoni and C. Marino, *Beilstein J. Org. Chem.*, 2014, **10**, 1651.
4 V. B. Krylov, D. A. Argunov, D. Z. Vinnitskiy, S. A. Verkhnyatskaya, A. G. Gerbst, N. E. Ustyuzhanina, A. S. Dmitrenok, J. Huebner, O. Holst, H.-C. Siebert and N. E. Nifantiev, *Chem. Eur. J.*, DOI: 10.1002/chem.201405083.
5 Y. Zhou, J. Li, Y. Zhan, Z. Pei and H. Dong, *Tetrahedron*, 2013, **69**, 2693.
6 V. B. Krylov, N. E. Ustyuzhanina, A. A. Grachev and N. E. Nifantiev, *Tetrahedron Lett.*, 2008, **49**, 5877.
7 A. I. Usov, K. S. Adamyants, L. I. Miroshnikova, A. A. Shaposhnikova and N. K. Kochetkov, *Carbohydr. Res.*, 1971, **18**, 336.
8 I. J. Miller and J. W. Blunt, *Carbohydr. Res.*, 1998, **309**, 39.

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[§] *1,6-Anhydro-2-*O*-benzoyl-3-*O*-benzyl-α-D-galactofuranose* **5**. Benzoyl chloride (26 μl, 0.22 mmol) was added dropwise to a stirred solution of galactoside **4** (37 mg, 0.147 mmol) and pyridine (60 μl, 0.735 mmol) in $CH_2Cl_2$ (2 ml) at 0 °C. After disappearance of the starting compound (TLC control), MeOH (1 ml) was added and the mixture was co-evaporated with toluene (2×10 ml) *in vacuo*. Purification of the crude product by column chromatography on silica gel (hexane–ethyl acetate, 1.5:1) gave the 2-O-benzoylated derivative **5** (45 mg, 86%) as colorless oil. $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$: 8.06 (d, 2H, $o$-$H_{Bz}$, $J$ 7.6 Hz), 7.61 (t, 1H, $p$-$H_{Bz}$, $J$ = 7.6 Hz), 7.48 (t, 2H, $m$-$H_{Bz}$, $J$ 7.6 Hz), 7.41–7.28 (m, 5H, $H_{Ph}$), 5.66 (d, 1H, $H^1$, $J_{1,2}$ 4.4 Hz), 5.34 (br. s, 1H, $H^2$), 4.70 (d, 1H, $PhCH_aH_b$, $J$ 11.8 Hz), 4.63 (d, 1H, $PhCH_aH_b$, $J$ 11.8 Hz), 4.47 (s, 1H, $H^3$), 4.36 (d, 1H, $H^4$, $J_{4,5}$ 4.2 Hz), 4.17–4.11 (m, 1H, $H^5$), 4.01 (dd, 1H, $H^{6a}$, $J_{6a,6b}$ 11.2 Hz, $J_{6a,5}$ 6.6 Hz), 3.60 (t, 1H, $H^{6b}$, $J_{6b,6a} = J_{6b,5}$ = 10.8 Hz), 2.24 (br. s, 1H, OH). $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$: 165.54 [PhC(O)], 137.21 (q, $PhCH_2$), 133.47 ($p$-$C_{Bz}$), 129.76 ($o$-$C_{Bz}$), 129.19 [q, PhC(O)], 128.51 (Ph), 128.44 (Ph), 127.89 (Ph), 96.65 ($C^1$), 81.92 ($C^4$), 80.38 ($C^2$), 79.65 ($C^3$), 71.64 ($PhCH_2$), 65.32 ($C^6$), 62.37 ($C^5$).

[¶] *1,6-Anhydro-2-*O*-benzoyl-3-*O*-benzyl-5-*O*-chloroacetyl-α-D-galactofuranose* **6**. Chloroacetyl chloride (28 μl, 0.25 mmol) was added to a stirred solution of galactoside **5** (45 mg, 0.126 mmol) and pyridine (40 μl, 0.5 mmol) in $CH_2Cl_2$ (2 ml). After 20 min, the mixture was diluted with $CHCl_3$ (15 ml) and washed with saturated $NaHCO_3$ (15 ml). The organic layer was concentrated, pyridine was co-evaporated with toluene (15 ml), and the residue was purified by column chromatography [silica gel, hexane–ethyl acetate (5:1)] to give product **6** (40 mg, 73%) as colorless syrup. $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$: 8.05 (d, 2H, $o$-$H_{Bz}$, $J$ 7.6 Hz), 7.63 (t, 1H, $p$-$H_{Bz}$, $J$ 7.6 Hz), 7.50 (t, 2H, $m$-$H_{Bz}$, $J$ 7.6 Hz), 7.38–7.28 (m, 5H, Ph), 5.69 (d, 1H, $H^1$, $J_{1,2}$ 4.5 Hz), 5.38 (dd, 1H, $H^2$, $J_{2,1}$ 4.5 Hz, $J_{2,3}$ 2.3 Hz), 5.17 (ddd, 1H, $H^5$, $J$ 10.9, 6.6 and 4.4 Hz), 4.72 (d, 1H, $PhCH_aH_b$, $J$ 12.2 Hz), 4.62 (d, 1H, $PhCH_aH_b$, $J$ 12.2 Hz), 4.52 (d, 1H, $H^4$, $J_{4,5}$ 4.4 Hz), 4.35 (d, 1H, $H^3$, $J_{3,2}$ 2.3 Hz), 4.17–4.12 (m, 1H, $H^{6a}$), 4.02 [d, 1H, $C(O)CH_aH_bCl$, $J$ 14.9 Hz], 3.99 [d, 1H, $C(O)CH_aH_bCl$, $J$ 14.8 Hz], 3.68 (t, 1H, $H^{6b}$, $J_{6b,6a} = J_{6b,5}$ = 10.9 Hz). $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$: 165.88 [$C(O)CH_2Cl$], 165.35 [PhC(O)], 136.94 (q, $PhCH_2$), 133.59 ($p$-$C_{Bz}$), 129.77 ($o$-$C_{Bz}$), 129.07 [q, PhC(O)], 128.57 (Ph), 128.52 (Ph), 128.06 (Ph), 127.85 (Ph), 97.15 ($C^1$), 80.20 ($C^2$), 79.60 ($C^3$), 78.88 ($C^4$), 71.57 ($PhCH_2$), 65.41 ($C^5$), 62.21 ($C^6$), 40.33 [$C(O)CH_2Cl$]. HRMS (ESI), $m/z$: 455.0859 $[M+Na]^+$ (calc. for $C_{13}H_{16}O_5$, $m/z$: 455.0868).

[††] *1,6-Anhydro-2-*O*-benzoyl-3-*O*-benzyl-5-*O*-chloroacetyl-α-D-galactofuranose* **6** *(one-pot method)*. Benzoyl chloride (12 μl, 0.100 mmol) was added to a stirred solution of galactoside **4** (17 mg, 0.067 mmol) and pyridine (22 μl, 0.27 mmol) in $CH_2Cl_2$ (2 ml) at 0 °C. Immediately after the disappearance of the starting compound (TLC control), chloroacetyl chloride (11 μl, 0.134 mmol) was added. After 20 min, the reaction was quenched with MeOH (0.5 ml) and co-evaporated with toluene. Purification of the crude product by column chromatography on silica gel (hexane–ethyl acetate, 7:1) gave desired product **6** (16 mg, 56%).