Pergamon

Tetrahedron Letters, Vol. 36, No. 44, pp. 7967-7970, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01718-6

n-Pentenyl Furanosides: Synthesis and Glycosidation Reactions of Some *Galacto* Derivatives

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Abstract : Synthetic routes to n-pentenyl galactofuranosides and glycosidation reactions of some derived donors with alcohol and saccharide acceptors using NIS/TESOTf as the promoter are described.

The serendipitous discovery of n-pentenyl glycosides (NPGs) in our laboratories in 1988[1] has been well exploited in synthetic[2] and mechanistic[3] carbohydrate chemistry. Most investigations have thus far focused on pyranoside derivatives,[4] although some n-pentenyl furanosides have been studied as precursors for nucleoside analogs.[5] Because of our interest in glycophosphatidyl inositol (GPI) membrane anchors,[6,7] our attention was drawn to the core GPI anchor **1**, which links the cell surface glycoconjugates to the cell membrane of *Leishmania*.[8] The human diseases caused by parasites belonging to this genus are widespread throughout the tropical and subtropical regions of the world and the ability of these protozoans to survive, indeed thrive, in what ought to be the hostile environment of the host is a marvel of adaptability.[9] There is evidence that the cell surface glycoconjugates of these organisms play a key role in mediating the host-parasite interactions.[10]

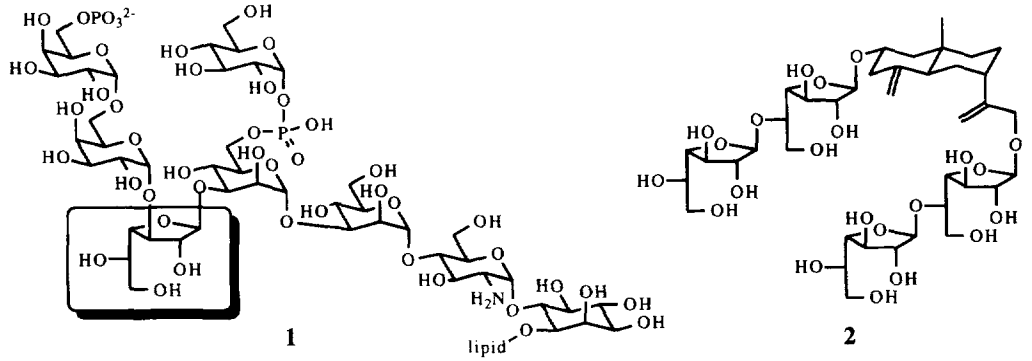
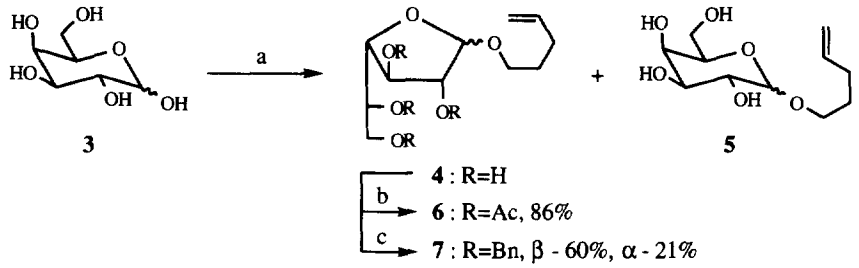


Figure 1

The presence of the galactofuranose entity in **1** is unique and striking. We were also aware of an equally unique toxin **2**, isolated from *Helminthosporium* by Arigoni and co-workers,[11] which is rich in galactofuranosyl residues. Prompted by these considerations, we report herein aspects of the synthesis and chemistry of some n-pentenyl galactofuranosides.

Unlike their pyranoside counterparts, hexofuranosides are not readily attainable.[12] It is well established when hexoses are treated with alcohol under Fischer glycosidation conditions, furanosides are formed initially,

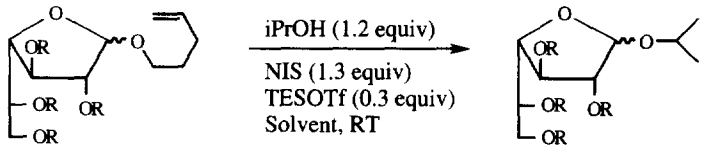
and are then converted into the pyranosides.[13] Accordingly controlled Fischer glycosidation of D-galactose **3**, under kinetic conditions using n-pentenyl alcohol and DMSO as co-solvent at 90-100°C for 6 hr afforded the n-pentenyl galactofuranoside **4** as a mixture of anomers. The corresponding anomeric mixture of pyranosides **5** was also produced in the reaction, albeit in a low yield. The furanoside **4**αβ and pyranoside **5**αβ mixtures (R_f = 0.16 and 0.28 respectively in 9 : 1 EtOAc/MeOH) could be easily separated as two groups by standard chromatographic techniques. Subsequent acylation of the former provided the tetraacyl derivative **6** as an inseparable anomeric mixture. However, α and β anomers of the tetrabenzyl furanoside **7** had sufficiently different R_f values to enable resolution by normal chromatographic methods.[14]



a. n-Pentenyl alcohol (7 equiv), DMSO (co-solvent), camphorsulfonic acid (cat), 90-100°C, 6 hr. Yield : furanoside - 43%; pyranoside - 16%, mixture of both - 10%; b. Ac_2O (8 equiv), Et_3N (12 equiv), DMAP (cat), CH_2Cl_2, 25°C, 20 hr; c. BnBr (10 equiv), NaH (6 equiv), DMF, 0°C to 25°C, 20 hr.

Scheme 1

Table 1. Glycosidation reactions using isopropanol as acceptor.



6 : R = Ac; **7** : R = Bn

8 : R = Ac; **9** : R = Bn

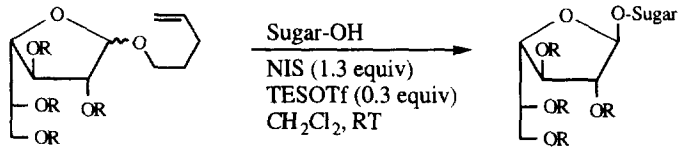
Entry	SM	Solvent	Product (β : α)[a]	Yield (%)[b]
1	**6**αβ	CH_2Cl_2	**8**β	56
2	**7**β	CH_2Cl_2	**9** (7 : 1)	82
3	-	Et_2O/CH_2Cl_2 (5 : 1)	**9** (7 : 1)	81
4	-	CH_3CN	**9** (7 : 1)	66
5	**7**α	CH_2Cl_2	**9** (6 : 1)	65
6	-	Et_2O/CH_2Cl_2 (5 : 1)	**9** (8 : 1)	70
7	-	CH_3CN	**9** (8 : 1)	74

a. From ^1H NMR analysis of crude reaction mixture after work-up; b. Isolated yield after column chromatography.

Glycosidation reactions of the n-pentenyl furanoside donors (**6αβ**, **7α**, **7β**) with a simple alcohol, isopropanol, as acceptor was first investigated. The standard NPG coupling conditions (1.3 equiv NIS and 0.3 equiv TESOTf) using different solvents were employed. The results of the glycosidation reactions are shown in **Table 1**. As expected, the reactions were instantaneous at ambient temperature in dichloromethane or acetonitrile as solvent. However, TLC analysis showed that 2 hours were required for disappearance of the furanoside donor in diethyl ether. This sluggishness may be attributed to the low solubility of NIS in ether, and so the reactions were left overnight to ensure complete conversion. A notable feature of the furanoside coupling reactions is that solvent polarity apparently plays no role in the product anomeric ratio. Thus when the solvent was changed from ether to acetonitrile, the α/β ratio of the isopropyl furanosides produced remained unchanged. Furthermore, the configuration at the anomeric center of the donor seems to have no influence on the product ratio either. In the case of **7α** and **7β**, the reactions proceeded with high degrees of β-selectivity despite the non-participatory ether group at C-2, giving rise to the β isopropyl furanoside in good yields.

Glycosidation reactions with saccharide acceptors having free hydroxyl groups at C-2, C-4, and C-6 using NIS/TESOTf conditions were next studied (**Table 2**). It is seen that in the case of the glucose acceptor **10**, the product β/α ratio was not dependent on the anomeric configuration of the donors, **7α** or **7β**; the disaccharide **18** being obtained with a high preference for β-selectivity. The coupling reactions with the tetraacetate donor **6αβ** clearly demonstrate the versatility of this process. The reactions went smoothly and in good yields, even with the sterically hindered C-4 hydroxyl group of the mannose acceptor **13**.[15] All reactions with donor **6αβ** resulted in the β-linkage product exclusively, presumably due to neighboring group participation of the C-2 ester functionality.

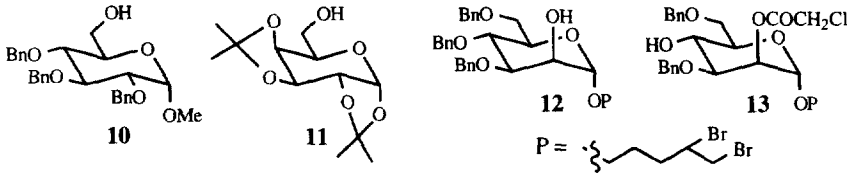
Table 2. Glycosidation reactions with saccharide acceptors.



6 : R = Ac; **7** : R = Bn **14 - 18**

SM	Sugar-OH	Product	Yield (%)[a]	SM	Sugar-OH	Product	Yield (%)[a]
6αβ	**10**	**14**	73	**6αβ**	**13**	**17**	81
6αβ	**11**	**15**	55	**7α**	**10**	**18**[b]	55
6αβ	**12**	**16**	80	**7β**	**10**	**18**[b]	80

a. Isolated yield after column chromatography; b. Product obtained as a mixture of anomers (β : α ~ 5 : 1).



In conclusion, we have shown in this preliminary report that furanosides also undergo glycosidation reactions in an efficient manner under NPG methodology. The recently reported improved method for general preparation of furanosides[16] will allow us to investigate the application of NPG chemistry to other sugars, and to examine further, the use of nitrogen bases as nucleophiles in coupling reactions.

Acknowledgments. We are grateful to the National Institutes of Health (GM 51237) for support of this work. We thank John Allen for providing the conditions for the synthesis of **4**.

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14. Pent-4-enyl 2,3,5,6-Tetra-*O*-benzylgalactofuranoside, **7β** : ^{1}H NMR ($CDCl_3$) 1.81-1.91, m, 2H; 2.26-2.33, m, 2H; 3.54-3.62, m, 1H; 3.83-4.00, m, 4H, H-5, H-6; 4.18-4.23, m, 2H, H-2, H-3; 4.33, dd, 1H, H-4; 4.46-4.93, m, 8H; 5.12-5.23, m, 2H; 5.23, s, 1H, H-1; 5.92-6.06, m, 1H; 7.39-7.55, m, 20H. ^{13}C NMR ($CDCl_3$) 28.14, 29.73, 66.22, 70.39 (C-6), 71.22, 71.40, 72.68, 72.80, 75.66 (C-5), 80.10 (C-4), 82.06 (C-3), 87.98 (C-2), 105.32 (C-1), 114.20, 126.77-127.82, 137.10, 137.30, 137.54, 137.68, 137.83.

    7α : ^{1}H NMR ($CDCl_3$) 1.76-1.87, m, 2H; 2.22-2.29, m, 2H; 3.43-3.51, m, 1H; 3.71-3.90, m, 4H, H-5, H-6; 4.14, dd, 1H, H-4; 4.21, dd, 1H, H-2; 4.46, ap. t, 1H, H-3; 4.59-4.93, m, 8H; 5.02, d, J = *4.3 Hz*, 1H, H-1, 5.09-5.20, m, 2H; 5.88-6.02, m, 1H; 7.37-7.53, m, 20H. ^{13}C NMR ($CDCl_3$) 28.55, 30.26, 67.15, 70.33 (C-6), 72.18, 72.28, 72.96, 73.26, 79.49 (C-5), 80.24 (C-4), 80.96 (C-3), 84.11 (C-2), 99.85 (C-1), 114.67, 127.31-128.42, 137.61, 138.16, 138.74.
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(*Received in USA* 10 *August* 1995; *revised* 6 *September* 1995; *accepted* 7 *September* 1995)