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## Preliminary communication

# A convenient synthesis of *O*-α-L-fucopyranosyl-(1→2)-*O*-β-D-galactopyranosyl-(1→4)-D-glucopyranose (2′-*O*-α-L-fucopyranosyllactose)*

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2′-*O*-α-L-Fucopyranosyllactose (**7**) has been isolated from human milk[2] and we are utilizing this compound in a variety of biological studies in our laboratory. It is well known that the use of a hexopyranosyl glycosyl donor having a "nonparticipating" group at O-2 results in high yields of α-linked oligosaccharides[3,4]. For α-L-fucosylation of an appropriately protected acceptor, such glycosylation reagents[5–9] as methyl 1-thio-2,3,4-tri-*O*-benzyl-β-L-fucopyranoside, 2,3,4-tri-*O*-benzyl-β-L-fucopyranosyl fluoride, and 2,3,4-tri-*O*-benzyl-α,β-L-fucopyranosyl trichloroacetimidate have received much attention. However, 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide, under halide ion-catalyzed conditions, has been the most frequently utilized reagent. All of these glycosylating reagents employ *O*-benzyl protecting groups which require hydrogenolysis for removal. We describe, herein, the use of two glycosyl donors, namely, methyl 3,4-*O*-isopropylidene-2-*O*-(4-methoxybenzyl)-1-thioβ-L-fucopyranoside (**1**) and pentenyl 3,4-*O*-isopropylidene-2-*O*-(4-methoxybenzyl)-β-L-fucopyranoside (**4**) which offer a more efficient route for α-L-fucosylation and provide for a convenient and rapid synthesis of the title compound.

The synthesis of **1** has been described in a previous paper[10] illustrating the utility of **1** for α-L-fucosylation. The pentenyl glycoside **4** was prepared in four steps from 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl bromide as follows. Condensation of this bromide with 4-pentenol in the presence of active silver carbonate in dichloromethane gave a crude intermediate which, after *O*-deacetylation with sodium methoxide–methanol, provided pentenyl β-L-fucopyranoside (**2**), $[\alpha]_D^{25}$ +29° (*c* 1.8, water), in 94% yield after silica gel column chromatography; $^{13}$C-n.m.r. ($D_2O$): δ 105.52 (C-1). On treatment with 2,2-dimethoxypropane in *N*,*N*-dimethylformamide in the presence of 4-toluenesulfonic

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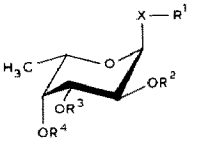
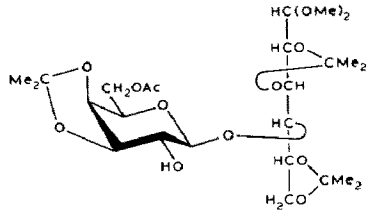
acid monohydrate, **2** gave pentenyl 3,4-*O*-isopropylidene-*β*-L-fucopyranoside (**3**) in 98% yield, $[\alpha]_D^{25}$ −23° (*c* 1.8, chloroform); $^1$H-n.m.r. ($CDCl_3$): *δ* 5.97–5.52 (m, 1 H, =CH), 1.51 and 1.35 (each s, 3 H, CMe), and 0.87 (d, *J* 7 Hz, CMe). On alkylation with NaH and 4-methoxybenzyl chloride in *N,N*-dimethylformamide, **3** afforded pentenyl 3,4-*O*-isopropylidene-2-*O*-(4-methoxybenzyl)-*β*-L-fucopyranoside (**4**) in 80% yield, $[\alpha]_D^{25}$ −45° (*c* 0.7, chloroform); $^1$H-n.m.r. ($CDCl_3$): *δ* 7.30 (d, 2 H, *J* 9 Hz, arom), 6.83 (d, 2 H, *J* 9 Hz, arom), 3.80 (s, 3 H, OMe), 1.47–1.28 (m, 6 H, CMe), and 0.90 (d, 3 H, *J* 7 Hz, CMe). Both glycosylating reagents **1** and **4** afforded a facile route for the synthesis of **7**.



1 X = S; $R^1$ = Me; $R^2$ = 4-$MeOC_6H_4CH_2$; $R^3$, $R^4$ = $CMe_2$
2 X = O; $R^1$ = $(CH_2)_3CH{=}CH_2$; $R^2$ = $R^3$ = $R^4$ = H
3 X = O; $R^1$ = $(CH_2)_3CH{=}CH_2$; $R^2$ = H; $R^3$, $R^4$ = $CMe_2$
4 X = O; $R^1$ = $(CH_2)_3CH{=}CH_2$; $R^2$ = 4-$MeOC_6H_4CH_2$; $R^3$, $R^4$ = $CMe_2$



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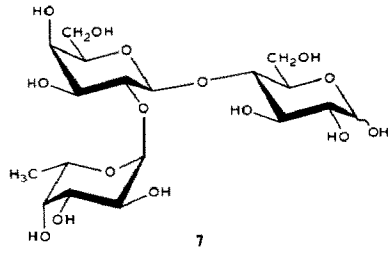

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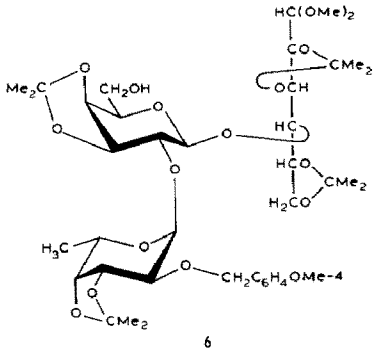

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In a typical experiment, a solution of 4-*O*-(6-*O*-acetyl-3,4-*O*-isopropylidene-*β*-D-galactopyranosyl)-2,3:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal[11] (**5**; 0.55g, 1 mmol) and **1** (0.6 g, 1.3 mmol) in 5:1 (v/v) dichloroethane–*N,N*-dimethylformamide (36 mL) was stirred in the presence of $CuBr_2$ (0.47 g, 2 mmol), tetrabutylammonium bromide (0.64 g, 2 mmol), and 4A molecular sieves (4.0 g) for 16 h at room temperature. Further amounts of **1** (0.3 g, 0.65 mmol) and $CuBr_2$–tetrabutylammonium bromide (1 mmol each) were added and the stirring continued for another 16 h. The mixture was filtered through Celite, the solids were thoroughly washed with chloroform, and the filtrate and washings were combined and washed with aq. $NaHCO_3$, and water, dried, and concentrated under reduced pressure. The crude product was *O*-deacetylated with sodium methoxide–methanol and purified by silica gel column chromatography (1:19 acetone–chloroform) to give **6** in 59% yield (on the basis of **5**), $[\alpha]_D^{25}$ −45° (*c* 0.75,

chloroform); $^1$H-n.m.r. ($CDCl_3$): $\delta$ 7.23 (d, 2 H, $J$ 9 Hz, arom), 6.75 (d, 2 H, $J$ 9 Hz, arom), 5.37 (d, 1 H, $J$ 4 Hz, H-1″α), 3.77 (s, 3 H, OMe), 3.51 (s, 6 H, 2 OMe), and 1.66–1.18 (cluster of s., 27 H, 4 $CMe_2$ and CMe).

Use of pentenyl glycoside[12] as a versatile donor for the synthesis of various oligosaccharides suggested to us the glycosylating capability of **4** for the synthesis of **7**. Thus, **4** (0.43 g, 1.1 mmol) and acceptor **5** (0.55 g, 1.0 mmol) were dissolved in 1:4 (v/v) dry dichloromethane–ether (25 mL) under Ar, and powdered 4A molecular sieves were added. Iodonium di(2,4,6-trimethylpyridine) perchlorate (1.0 g, 2.1 mmol) was added and the mixture was stirred overnight at room temperature, and then filtered through Celite, the organic layer was washed with saturated $NaHCO_3$ and 10% $Na_2S_2O_3$, dried, and concentrated *in vacuo*. The crude residue was *O*-deacetylated to afford, in 70% yield, a mixture of α- and β-linked trisaccharides (9:1 ratio, as determined by $^1$H-n.m.r. spectroscopy).

A solution of **6** (0.5 g) in trifluoroacetic acid (4.0 mL) and water (0.6 mL) was stirred for 2 h at room temperature and then evaporated to dryness. After purification by silica gel column chromatography, **7** was obtained as a white amorhous solid in a yield of 63% (0.18 g); $^{13}$C-n.m.r. ($D_2O$): $\delta$ 103.08, 102.15, 98.71, 94.63 (C-1′, C-1″, C-1β, and C-1α); it showed $[\alpha]_D^{25}$ −49.5 (initial) → −52° (after 3 days; *c* 0.5, water), which corresponds to the value reported in the literature[2,11].

In conclusion, we have developed a rapid and high-yield chemical synthesis of 2′-*O*-α-L-fucosyllactose (**7**). It is noteworthy that the removal of both protecting groups, 4-methoxybenzyl and isopropylidene, **6** was achieved in one step and did not require hydrogenolysis. Therefore, this method will be important for the large-scale preparation of **7**.

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