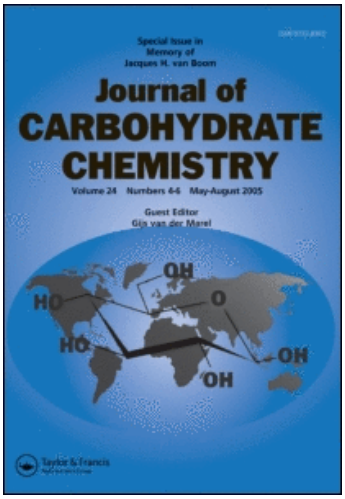

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Francesco Nicotra[a]; Luigi Panza[a]; Anna Romaó[a]; Giovanni Russo[a]
[a] Dipartimento di Chimica Organica e Industriale and Centro di Studio per le Sostanze Organiche Naturali del CNR via Venezian, Milano, Italy

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COMMUNICATION

PRACTICAL SYNTHESIS OF DISACCHARIDE H

Francesco Nicotra, Luigi Panza, Anna Romanò and Giovanni Russo*

Dipartimento di Chimica Organica e Industriale and Centro di Studio per le Sostanze Organiche Naturali del CNR
via Venezian, 21 - 20133 Milano - Italy

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Oligosaccharide components of glycoconjugates play a fundamental role in recognition phenomena and intercellular interactions. Disaccharide H, 2-*O*-(α-L-fucopyranosyl)-D-galactopyranose, is one such biologically important, L-fucose containing oligosaccharide.[1] This disaccharide is found in natural antigenic determinants such as blood group determinants and tumor associated antigens.[1,2]

In connection with a project involving extraction of Disaccharide H or its derivatives from intestinal pig mucins and their use as building blocks for the synthesis of more complex oligosaccharides, we needed considerable amounts of this compound so we looked for a simple synthetic procedure.

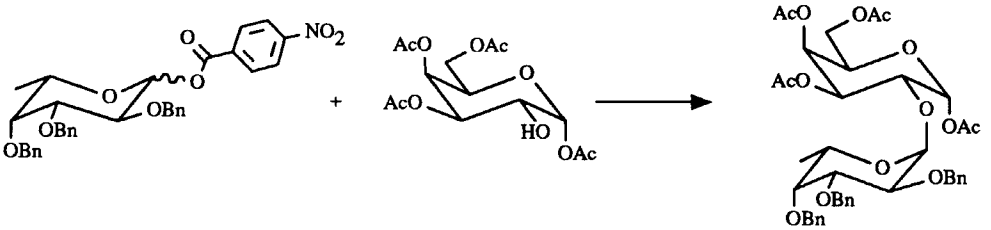
Disaccharide H has been synthesized in many different ways. Some syntheses,[3,4] based on bromide ion catalysis, gave good yields and stereoselectivity but required large excess (2-3 eq.) of glycosyl donor and long reaction times. Another approach[5] employed readily available tri-*O*-acetyl-L-fucopyranosyl bromide as donor but in this case a mixture of α and β isomers was obtained. Recently the trichloroacetimidate method was applied with good results.[6] However, the preparation of the 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl trichloroacetimidate requires very controlled experimental conditions, especially at the work-up stage, because of the instability of such an imidate towards hydrolysis.

We decided to explore a new and practical synthetic route to disaccharide H starting from easily made and stable glycosyl donor and glycosyl acceptor. To this

purpose we chose as glycosyl acceptor 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose **2**, easily prepared as described by Lemieux.[3,7] Furthermore we considered the possibility of activating the fucose as its glycosyl *p*-nitrobenzoate.[8] Although *p*-nitrobenzoate is not an excellent leaving group we considered that, in the case of the tri-*O*-benzyl-L-fucose, the formation of a positive charge on the anomeric position might be favoured by the absence of the oxygen at C-6 and by the use of benzyl protecting groups.

The tri-*O*-benzyl-L-fucopyranosyl *p*-nitrobenzoate **1** was prepared by treatment of tri-O-benzyl-L-fucopyranose[6] with *p*-nitrobenzoyl chloride in pyridine at room temperature for 1 h. A quantitative yield of a 5:1 α:β mixture of the *p*-nitrobenzoates was obtained, and this mixture was directly used for the glycosidation reactions. All the experiments were effected using a 1:1 molar ratio of **1** and **2**.

Different conditions were explored for the activation of the glycosyl donor. When trimethylsilyl triflate in methylene chloride was used as catalyst the reaction was incomplete at -78 °C but was very rapid at 0 °C. However, at the higher temperature some unidentified by-products were formed. With boron trifluoride etherate as catalyst in methylene chloride the reaction was slow at 0 °C but at room temperature gave the desired disaccharide in 15 min without formation of by-products. It is worthy of note that during the reaction the *p*-nitrobenzoic acid precipitates from the reaction mixture.



1 **2** **3**

In a typical procedure 556 mg (0.97 mmol) of **1** and 337 mg (0.97 mmol) of **2** were dissolved in 10 mL of methylene chloride. 28 μL (0.2 mmol) of boron trifluoride etherate were added by a syringe. The mixture was stirred for 15 min then 5 mL of a satd. solution of $NaHCO_3$ were added; the mixture was extracted with methylene chloride, the organic layer washed with water and the solvent removed under reduced pressure. The disaccharide was isolated by flash-chromatography (hexane-ethyl acetate 6:4) in 77% yield and in α/β ratio of 11:1. In several experiments the yield ranged between 70 and 79%. The α isomer was purified by crystallization from ether with a

total yield of about 40-50% (mp 54-56 °C, lit.[3]: 55-58 °C); when the glycosidation reaction was carried out from either the α or β tri-*O*-benzyl-L-fucopyranosyl *p*-nitrobenzoate with boron trifluoride etherate as catalyst at room temperature (ca. 20 °C), in both cases the resulting disaccharide was obtained with the same α/β ratio.

Protected disaccharide **3** was deprotected according to a known procedure to give disaccharide H, whose spectroscopic data were identical to that reported in the literature.[7]

In conclusion, a simple preparation of disaccharide H has been carried out. The glycosidation reaction is achieved in good yield and with high stereoselectivity. The synthesis is particularly suitable for the preparation of large amounts of disaccharide H, with the following advantages, which are not simultaneously available with previously published procedures:

a) short reaction times,
b) use of only 1 eq. of glycosyl donor for eq. of acceptor, thus avoiding waste of the fucosyl donor,
c) stability of the fucosyl donor before activation allows for preparation and storage of the donor without particular precautions.

Work is in progress to synthesize other fucose containing oligosaccharides.

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