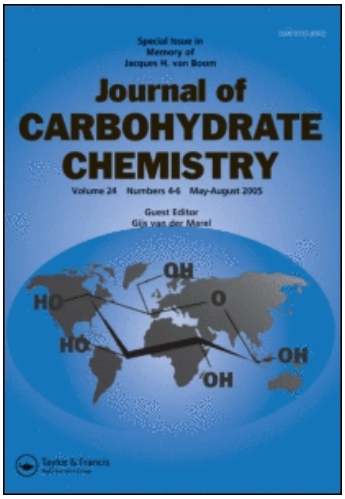

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Kristen, H. , Wrubel, Vogel F. , Mahrwald, R. and Schick, H.(1988) 'Introduction of A new Selective Oxidation Procedure Into Carbohydrate Chemistry - An Efficient Conversion of D-Galactose Into L-Fucose', Journal of Carbohydrate Chemistry, 7: 1, 277 — 281
To link to this Article: DOI: 10.1080/07328308808058921
URL: http://dx.doi.org/10.1080/07328308808058921

J. CARBOHYDRATE CHEMISTRY, 7(1), 277-281 (1988)

COMMUNICATION

INTRODUCTION OF A NEW SELECTIVE OXIDATION PROCEDURE INTO CARBOHYDRATE CHEMISTRY - AN EFFICIENT CONVERSION OF D-GALACTOSE INTO L-FUCOSE

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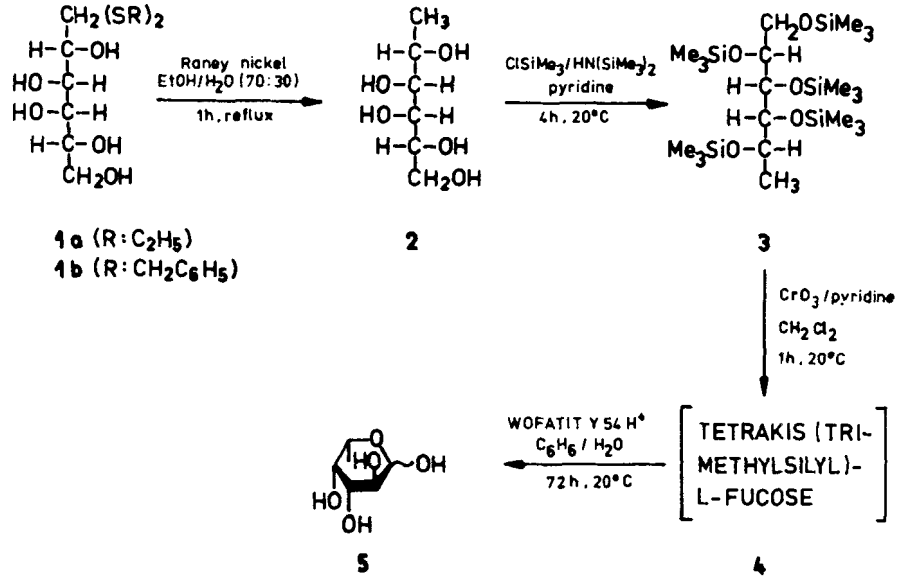
Received June 26, 1987 - Final Form December 22, 1987

L-Fucose is widely spread in natural products. Due to its occurrence in glycoconjugates of blood-group substances, in milk oligosacchraides and other biologically important carbohydrates, this 6-deoxyhexose is of particular interest for oligosaccharide syntheses.

Though seaweed is a source of L-fucose,[1] various syntheses have been developed for this sugar. However, they are generally laborious and not very efficient. The multistep synthesis of Tanimura starting from L-arabinose affords L-fucose in an overall yield of about 1%.[2] Defaye's synthesis starting from α-D-mannopyranoside seems to be important only for ^{2}H-labeled L-fucose.[3] Another procedure published recently by the same group gave more satisfying results using L-rhamnose as starting material.[4] Finally, D-galactose can be transformed into L-fucose by the route of Dejter-Juszynski and Flowers.[5]

Being interested in a more straightforward method for the conversion of D-galactose into L-fucose we intended to circumvent the synthesis of 2,3:4,5-di-*O*-isopropylidene-D-galactose diethyl dithioacetal, which requires a laborious chromatographic separation from the isomeric 2,3:5,6-di-*O*-

isopropylidene derivative formed as a by-product. Moreover, by the introduction of a recently developed novel selective oxidation procedure into carbohydrate chemistry we aimed to decrease the number of necessary reaction steps and to improve the overall yield of the conversion of D-galactose into L-fucose. The envisaged synthetic route is depicted in the reaction scheme.



Wolfrom and Karabinos[6] already described the reduction of D-galactose diethyl dithioacetal (**1a**) with Raney nickel to 1-deoxy-D-galactitol, i.e., L-fucitol (**2**). The yield reported was only 24%. We could increase this yield up to 62% using more active Raney nickel. For this purpose the catalyst was prepared from the aluminum nickel alloy (50 g) following the common procedure.[7] However, when the violent reaction had ceased the reaction mixture was quenched by addition of cold water (500 mL). Then the liquid phase was decanted and the black residue was washed with water (15 x 50 mL) and ethanol (1 x 100 mL) by successive stirring and decantation. The so obtained neutral catalyst was used immediately after preparation. Accordingly, D-galactose diethyl dithioacetal (**1a**)[8] (10 mmol; 2.86 g) or

D-galactose dibenzyl dithioacetal (**1b**)[9] (10 mmol; 4.10 g), dissolved by heating in a mixture of ethanol (210 mL) and water (90 mL) were added to the catalyst and the mixture was refluxed. TLC monitoring[10] (solvent system A) indicated complete reduction within 1 h. Filtration through silica gel, concentration, codistillation with toluene/ethanol and recrystallization from dry ethanol afforded L-fucitol (**2**) (1.03 g; 62%). Mp 154 °C; lit.[6] mp 153-154 °C; $[\alpha]_D^{22}$ +0/8° (*c* 1.0, water); lit.[11] $[\alpha]_D$ +4.7° (10% borax); ^{1}H NMR[12] (DMSO-d_6) δ 1.00 (d, 3H, CH_3); ^{13}C NMR[12] (DMSO-d_6) δ 72.8, 70.2, 69.7, 65.5, 63.0 (C-1,2,3,4,5), 19.9 (C-6).

The oxidation of L-fucitol (**2**) to L-fucose (**5**) by the Pfitzner-Moffat reagent[13] would require a selective protection of all the secondary hydroxyl groups. However, the recently observed different behaviour of trimethylsilyl ethers of primary and secondary alcohols towards Collins reagent disclosed a novel method for the selective oxidation of primary hydroxyl groups in the presence of secondary ones, especially promising for carbohydrate syntheses.[14] To prove the potential of this method L-fucitol (**2**) (10 mmol; 1.66 g) was converted into 1,2,3,4,5-pentakis-*O*-(trimethylsilyl)-L-fucitol (**3**) by treatment with a mixture of chlorotrimethylsilane (50 mmol; 5.43 g), hexamethyldisilazane (100 mmol); 16.14 g), and pyridine (4 mL) in an atmosphere of dry argon.[15] The reaction mixture was stirred at ambient temperature for 4 h. Diethyl ether (50 mL) was added to remove ammonium chloride. The mixture was filtered and the filtrate was concentrated. The residue was treated once more with diethyl ether (50 mL). Filtration and concentration then afforded **3** (5.20 g; 98.7%) as a colourless oil, nearly pure according to GLC and TLC (solvent system B). Without further purification or characterization this product was dissolved in dichloromethane (30 mL) and oxidized immediately by addition to a solution of Collins reagent[16] prepared according to the literature[14] from chromium (VI) oxide (60 mmol; 6.00 g) and pyridine (120 mmol; 9.60 g) in dichloromethane (200 mL). The reaction mixture was vigorously stirred at 20 °C until TLC monitoring (solvent system B) indicated complete conversion of **3**. This required about 1 h. Concentration of the reaction mixture to about one quarter of the original volume, codistillation with toluene (2 x 50 mL) to a volume of about 50 mL, dilution with ethyl acetate (200 mL), filtration through silica gel, and evaporation of the solvent *in vacuo* afforded a yellow-brownish syrup (4.24 g) of tetrakis-*O*-(trimethylsilyl)-L-fucose (**4**).[17]

To convert this product into L-fucose (**5**) it was dissolved in benzene (100 mL) and shaken at ambient temperature for 72 h with the acidic ion exchange resin Wofatit Y 54 H^+ (50 mL) and water (100 mL). Filtration,

phase separation, evaporation of the aqueous phase, codistillation with toluene/ethanol, column chromatography on silica gel 60 (E. Merck) with ethyl acetate/methanol (3:1), and recrystallization from dry ethanol furnished L-fucose (**5**; 1.44 g; 87% related to **2**). Mp 137 °C; lit.[4] mp 137-139 °C; $[\alpha]_D^{22}$ -74.3° (*c* 1.0, water, equilibrium); lit.[4] $[\alpha]_D^{23}$ -75° (*c* 0.8, water, equilibrium); ^{1}H NMR (DMSO-d_6) 6.31 (d, 1H, $J_{1,2}$ = 6.0 Hz, H-1), 5.94 (d, 1H, $J_{1,2}$ = 4.5 Hz, H-1); ^{13}C NMR (DMSO-d_6) δ 97.1 (C-1β), 92.4 (C-1α), 73.5, 71.7, 69.5, 68.4, 65.0 (C-2,3,4,5), 16.5 (C-6). Efforts to achieve the deprotection of **4** with an acidic ion exchange resin in methanol did not deliver pure L-fucose (**5**), but a mixture of **5** and methyl L-fucoside. Therefore, we preferred the two-phase system benzene/water.

The successful conversion of L-fucitol (**2**) into L-fucose (**5**) in an overall yield of 87% gives evidence that the employed method deserves further consideration in carbohydrate chemistry.

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17. The exact structure of this product is still uncertain. It failed to undergo typical aldehyde reactions. The fragmentation pattern in the mass spectrum and the presence of a single spot on TLC raised the question as to whether a pyranose had been formed by migration of a trimethylsilyl group. Results concerning this problem will be published later.