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DIRECT SYNTHESIS OF NUCLEOSIDE MONOPHOSPHATE SUGARS
SYNTHESIS OF GMP-FUCOSE[1]

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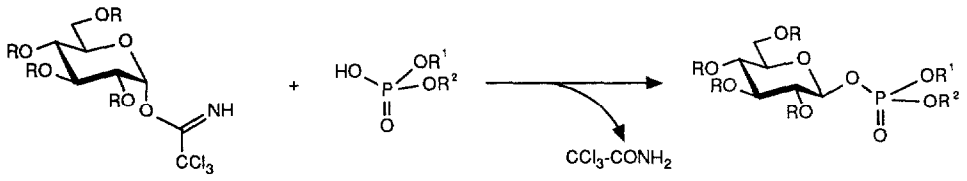
Abstract: O-(2,3,4-Tri-O-acetyl-α-L-fucopyranosyl)-trichloroacetimidate **1** furnished with acetyl protected UMP, AMP, and GMP derivatives **3a-c** directly α,β anomeric mixtures of the corresponding nucleoside monophosphate fucopyranoses. Immediate deacetylation led to the unprotected target molecules **4a**α/β-**4c**α/β. The anomeric mixtures of **4b**α/β and **4c**α/β were separable by preparative HPLC; thus, the desired GMP-β-fucose (**4c**β) was obtained in pure form.

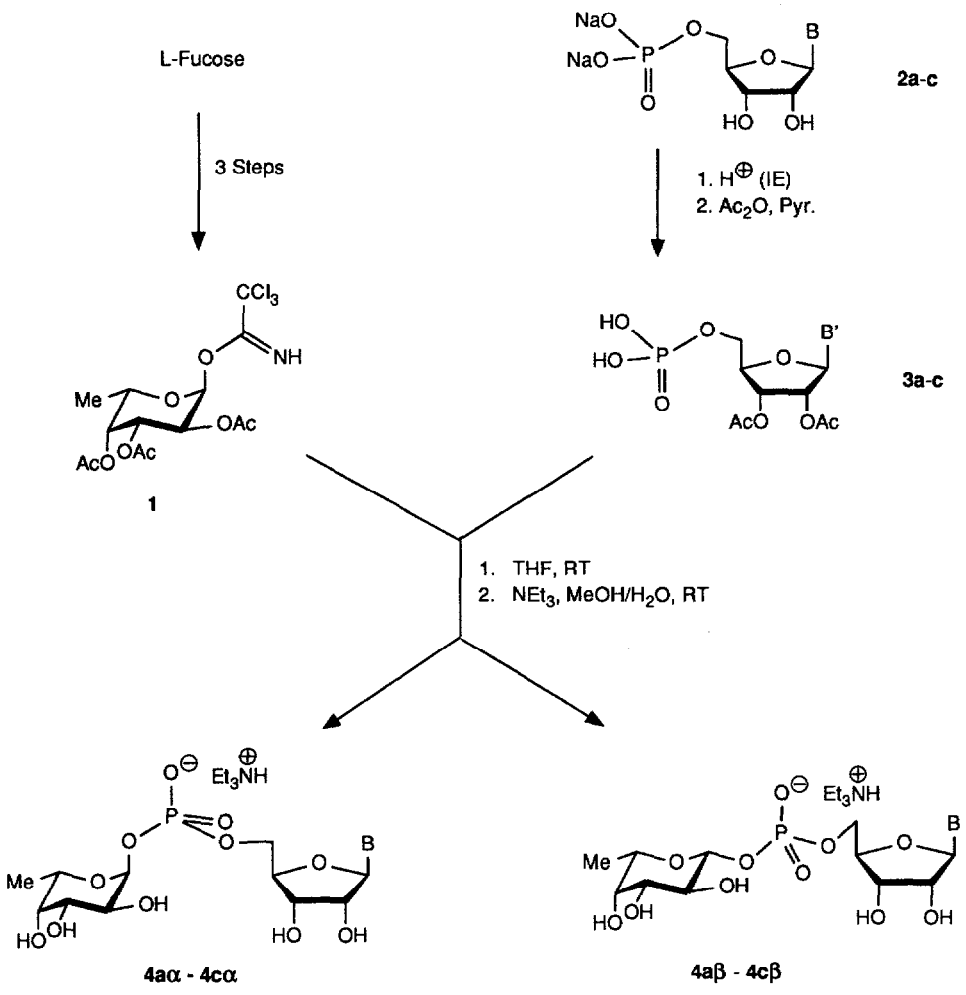
An important direct nucleophilic substitution reaction carried out in nature is O- and N-glycoside bond formation at the anomeric carbon atom of sugars[2,3]. At this activated position as leaving groups phosphates, pyrophosphates and their nucleoside and lipid monoester derivatives are utilized[2-4]. For instance, for aldoses generally nucleoside diphosphate and for 3-deoxy-2-glyculosonates (KDO, NeuAc) nucleoside monophosphate derivatives, respectively, are encountered as glycosyldonors in glycosyltransferase reactions. It remains to be shown, if the different leaving groups are means for accommodating the reactivity of the glycosyl donor to other parameters, for instance, acceptor reactivity, medium, and/or active site of the glycosyl transferase. Therefore, nucleoside monophosphate derivatives of aldoses are interesting target molecules. The recent interest in enzymatic fucosylation[5,6] where β-linked GDP-fucose is the fucosyl donor[6,7] was reason to concentrate on the synthesis of the corresponding GMP-β-fucose; however, anomerisation to the more stable α-anomer at any intermediate stage of the synthesis had to be taken into consideration in this case.

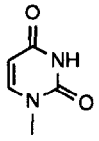
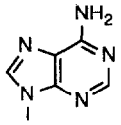
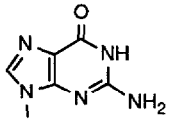
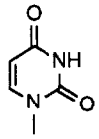
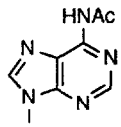
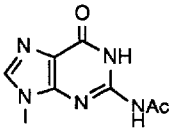
Scheme 1



R = Bn, Ac; R^1, R^2 = Alkyl, Aryl, H

Scheme 2



	a	b	c
B			
B'			

The ease and stereoselectivity in direct glycosyl phosphate formation from O-glycosyl-trichloroacetimidates and phosphorous acid derivatives (as shown for the α-trichloroacetimidate of glucose in Scheme 1) adds to their usefulness as widely applicable glycosyl donors[3,7-9]. Therefore, this method was chosen for obtaining the target molecules. Depending on the anomeric configuration of the trichloroacetimidate moiety both anomers can be often obtained by inversion of configuration (Scheme 1, R = Bn); also neighboring group participation of protective groups in 2-position leads to anomeric stereocontrol[8,9] (Scheme 1, R = Ac). Therefore, O-acetyl protected O-α-fucosyl-trichloroacetimidate **1** was required as starting material which was readily obtained from L-fucose in a three step procedure[7] (Scheme 2).

Nucleoside monophosphates are commercially available as disodium salts (**2**). However, according to Scheme 1 the acid of **2** soluble in dry aprotic solvents is required for this reaction[9,10]. To this end, a sodium/proton exchange was carried out in compounds **2a-c** and acetylation with acetic anhydride in pyridine led to the required protected derivatives **3a-c**[11]. These compounds could be isolated practically pure and in high yields (**3a**: 91%; **3b**: 91%; **3c**: 84%)[12]. Reaction of trichloroacetimidate **1** with UMP derivative **3a** in dry THF at room temperature furnished directly the desired O-acetyl protected UMP-fucose; however, due to the long reaction times needed for completion of the reaction (~ 24h) partial anomerisation of the firstly formed β-product to the α-anomer occurred. Thus, after subsequent base catalyzed removal of the acetyl protective groups with triethylamine in methanol/water a 1:1-mixture of UMP-fucose **4a**α and **4a**β (60% yield) was obtained as triethylammonium salts by preparative HPLC (Merck, LiChrospher 100, RP 18; eluent: 0.05 M TEAB in H_2O/CH_3CN = 99:1). Reaction of O,N-acetyl protected AMP derivative **3b** with trichloroacetimidate **1** under the same conditions led even to faster anomerisation thus providing AMP-α- and -β-fucose (**4b**α/β) in a 2:1 ratio (yield: 45%); the anomers could be separated by preparative HPLC with the system described above. Because the β-anomer of GMP-fucose **4c**β was the desired product for biological testing the reaction time for the reaction of O,N-acetyl protected GMP derivative **3c** with **1** was reduced to 2 h; this resulted in a lower yield of **4c**α/β (34%), however, in a more favorable α:β-ratio (2:5). Compounds **4c**α and **4c**β were again readily separable by preparative HPLC as described above, thus furnishing the desired GMP-β-fucose **4c**β in pure form. The structures of the final products were assigned by NMR and mass spectral data[12].

REFERENCES AND FOOTNOTES

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12. Values of δ_H (250 MHz), and δ_{31P} (161,7 MHz, 85% H_3PO_4 external standard) were measured for solution in D_2O.

3a: δ_H = 7.71 (d, $J_{5,6}$ = 7.5 Hz, H-6), 5.97 (d, $J_{1',2'}$ = 4.1 Hz, H-1'), 5.75 (d, $J_{5,6}$ = 7.3 Hz, H-5), 5.24-5.31 (m, H-2', H-3'), 4.26-4.35 (m, H-4'), 3.88-4.04 (m, H-5'$_a$, H-5'$_b$), 1.92, 1.98 (2s, 6 H, CH_3CO); **3b**: 8.58 (s, H-8), 8.51 (s, H-2), 6.32 (d, $J_{1',2'}$ = 5.8 Hz, H-1'), 5.63-5.70 (m, H-2'), 5.52-5.55 (m, H-3'), 4.49-4.52 (m, H-4'), 4.00-4.11 (m, H-5'$_a$, H-5'$_b$), 1.93, 2.09, 2.22 (3s, 9 H, CH_3CO); **3c**: 8.05 (s, H-8), 6.06 (d, $J_{1',2'}$ = 6.2 Hz, H-1'), 5.78 (dd, $J_{1',2'}$ = 6.2, $J_{2',3'}$ = 5.5 Hz, H-2'), 5.50 (dd, $J_{2',3'}$ = 5.5, $J_{3',4'}$ = 3.5 Hz, H-3'), 4.39 (m, H-4'), 4.00 (m, H-5'$_a$, H-5'$_b$), 1.19, 2.04, 2.10 (3s, 9 H, $COCH_3$); **4a**α,β: δ_H = 7.74-7.80 (m, 1 H, H-6α, H-6β), 5.77-5.81 (m, H-5, H-1'), 5.30 (dd, $J_{1'',2''}$ = 3.5, $J_{1'',P}$ = 6.6 Hz, 0.5 H, H-1'α), 4.62 (br.s, HOD, H-1'β), 4.15-4.25 (m, H-2', H-3'), 3.95-4.10 (m, H-4', H-5'$_a$, H-5'$_b$), 3.27-3.75 (m, H-2", H-3", H-4", H-5"), 3.03 (q, J = 7.3 Hz, NCH_2CH_3), 1.02-1.17 (m, H-6", NCH_2CH_3); δ_P = -0.92, -1.11; **4b**α: δ_H = 8.26 (s, H-8), 8.02 (s, H-2), 5.91 (d, $J_{1',2'}$ = 5.9 Hz, H-1'), 5.21 (br.d, $J_{1'',P}$ = 6.8 Hz, H-1"), 4.71 (dd, $J_{1',2'}$ = 5.9, $J_{2',3'}$ = 5.0 Hz, H-2'), 4.36 (dd, $J_{2',3'}$ = 5.0, $J_{3',4'}$ = 3.1 Hz, H-3'), 3.87-3.92 (m, H-5'$_a$, H-5'$_b$), 3.26-3.51 (m, H-2", H-3", H-4", H-5"), 3.00 (q, J = 7.3 Hz, NCH_2CH_3), 1.07 (t, J = 7.3 Hz, NCH_2CH_3), 0.75 (d, $J_{5",6"}$ = 6.5 Hz, H-6"); δ_P = -0.80; **4b**β: δ_H = 8.30 (s, H-8), 8.02 (s, H-2), 5.93 (d, $J_{1',2'}$ = 5.9 Hz, H-1'), 4.63 (br.s, HOD, H-2'), 4.54 (dd, $J_{1'',2''}$ = $J_{1'',P}$ = 7.7 Hz, H-1"), 4.34 (dd, $J_{2',3'}$ = 4.5, $J_{3',4'}$ = 3.2 Hz, H-3'), 4.18-4.23 (m, H-4'), 3.92-4.00 (m, H-5'$_a$, H-5'$_b$), 3.20-3.50 (m, H-2", H-3", H-4", H-5"), 3.01 (q, J = 7.3 Hz, NCH_2CH_3), 1.08 (t, J = 7.3 Hz, NCH_2CH_3), 0.81 (d, $J_{5",6"}$ = 6.3 Hz, H-6"); δ_P = -1.07; **4c**α: δ_H = 7.95 (s, H-8), 5.79 (d, $J_{1',2'}$ = 6.1 Hz, H-1'), 5.29 (dd, $J_{1'',2''}$ = 2.9, $J_{1'',P}$ = 7.1 Hz, H-1"), 4.75 (dd, $J_{1',2'}$ = 6.1, $J_{2',3'}$ = 4.8 Hz, H-2'), 4.40 (dd, $J_{2',3'}$ = 4.8, $J_{3',4'}$ = 3.3 Hz, H-3'), 4.19 (m, H-4'), 3.95-3.98 (m, H-5'$_a$, H-5'$_b$), 3.43-3.73 (m, H-2", H-3", H-4", H-5"), 3.06 (q, J = 7.3 Hz, NCH_2CH_3), 1.14 (t, J = 7.3 Hz, NCH_2CH_3), 0.86 (d, $J_{5",6"}$ = 6.5 Hz, H-6"); δ_P = -0.77; **4c**β: δ_H = 8.01 (s, H-8), 5.81 (d, $J_{1',2'}$ = 6.5 Hz, H-1'), 4.57-4.73 (m, HOD, H-2', H-1"), 4.38 (dd, $J_{2',3'}$ = 5.2, $J_{3',4'}$ = 3.2 Hz, H-3'), 4.21 (m, H-4'), 4.01 (m, H-5'$_a$, H-5'$_b$), 3.30-3.60 (m, H-2", H-3", H-4", H-5"), 3.07 (q, J = 7.2 Hz, NCH_2CH_3), 1.1 (t, J = 7.2 Hz, NCH_2CH_3), 0.94 (d, $J_{5",6"}$ = 6.4 Hz, H-6"); δ_P = -0.77.

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