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Synthesis of a non-charged analogue of guanosyldiphosphofucose†

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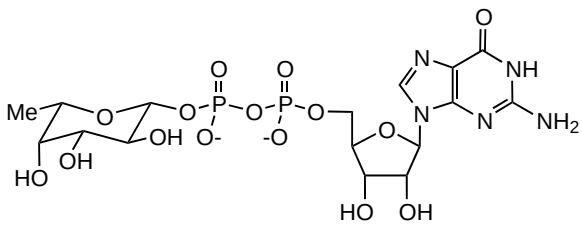
Abstract—Methylene sulfonoamide is used as a non-charged surrogate of the diphosphate moiety to prepare an analogue of the fucosyl donor guanosyldiphosphofucose of potential use as inhibitor of fucosyltransferases. © 2001 Published by Elsevier Science Ltd.

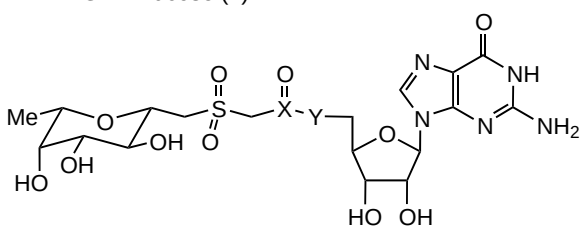
The inhibition of fucosyltransferases (FucT) has become of interest since it has been demonstrated that fucose-containing oligosaccharides are over-expressed in tumor cells. On the other hand fucosylated oligosaccharides such as sialyl Lewis^X are involved in the inflammatory process.[1] Thus, oligosaccharide biosynthesis blockade by inhibition of fucosyltransferases is a possible strategy for the intervention on these disorders. Fucosyltransferases have a substrate, guanosyldiphosphofucose **1** (GDP-fucose) from which the fucose residue is transfered in general to an *N*-acetyl glucosamine residue of the oligosaccharide. Non-functional analogues of this substrate,[2,3] transition state-multisubstrate analogues[4] have been proposed as candidates for the inhibition of FucT. In this context, we tried to devise new analogues of GDP-fucose in which the crucial diphospho linkage would be replaced by a non-charged isostere group,[3,5] the non-charged character being of help to penetrate the cells. Our attention was attracted by methylene disulfones which are isosteric of pyrophosphate and are non-charged.[6] Nevertheless the partial negative charge located on the oxygen atoms of the sulfone would allow complexation of these oxygen atoms with the manganese ion that FucTs use normally as a cofactor. Sulfur containing linkages have been used in the synthesis of nucleotide analogues.[7]

Compounds such as **2** with methylene disulfone bridge were therefore good targets,[8] but exploratory experiments on model compounds showed that this moiety was rather difficult to synthesize in an efficient way.

Here we report our preliminary results in the synthesis of a non functional analogue **3** of GDP-fucose (Scheme 1) in which the diphospho linkage is replaced by a methylene sulfono amide tether. In order to have a non-functional analogue of the donor **1** it was necessary to replace the anomeric oxygen by a carbon atom thus an efficient synthesis of a *C*-glycosyl fucose moiety was



GDP-Fucose (1)



2 X = SO, Y = O, NH

3 X = C, Y = NH

Scheme 1.

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† Warmly dedicated to Professor Gérard Descotes on the occasion of his retirement.

‡ Deceased on 21st May 2000.

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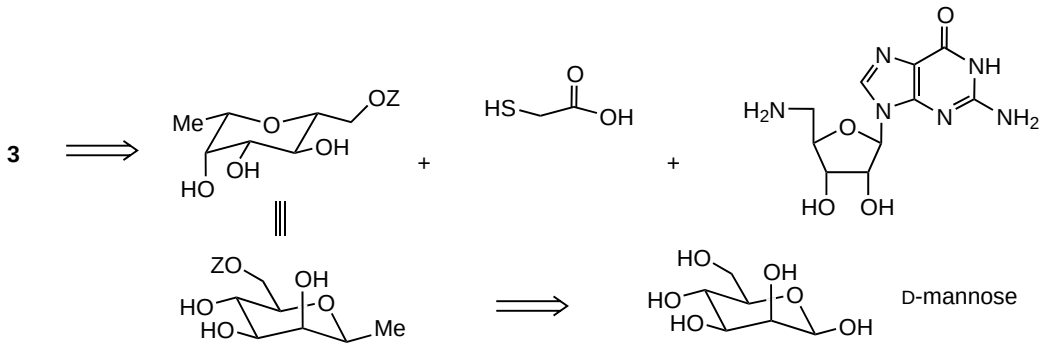


Scheme 2.

needed. This compound should be suitable for the construction of the carboxy methylene sulfonyl group.

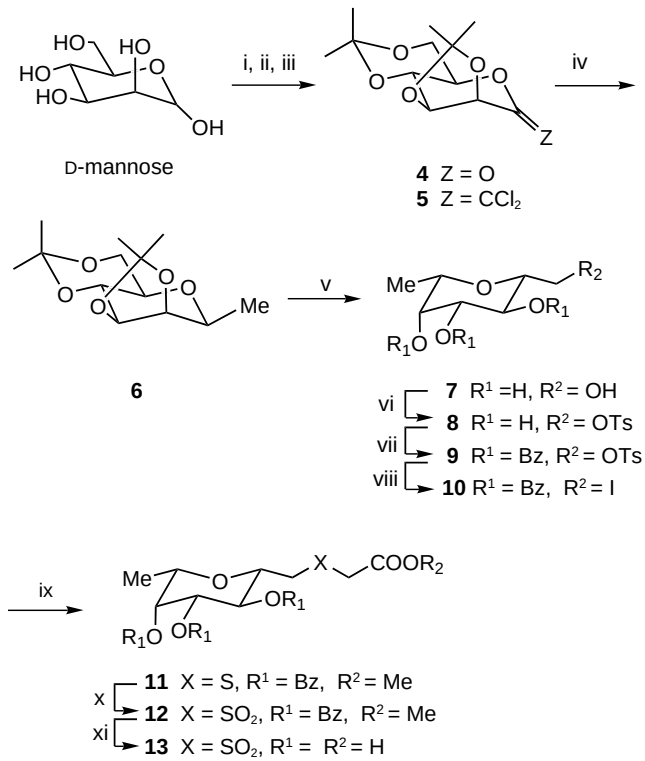
Finally a suitable derivative of the guanosine residue was required which would allow the formation of a stable amide linkage with the fucosyl residue. A retrosynthetic analysis of compound **3**, depicted on Scheme 2, shows three different building blocks. The synthetic plan was thus: (i) construction of the *C*-glycosyl moiety, (ii) coupling of this moiety with the mercapto acetic acid and (iii) coupling of the resulting fucosyl part with 5′-amino-guanosine.

Instead of starting from L-fucose to prepare a *C*-glycosyl derivative like **7**, we tried to exploit the strong analogy between L-fucose and D-mannose.[9] Thus, it turned out that branching an anomeric methyl group on a mannose derivative should provide a straightforward solution to our problem. Moreover we had previously described a short method for the synthesis of 1-*C*-methyl glycosyl derivatives by using the Wittig olefination of sugars.[10]

The known 2,3:4,6-di-*O*-isopropylidene *manno* derivative[11] was oxidized with CrO_3–pyridine into the lactone **4** in 70% yield (Scheme 3). Treatment of **4** according to our reported procedure gave the dichloroolefin **5** in 75% yield.[12] Hydrogenation of **5** gave the expected *C*-glycosyl derivative **6** as the single compound in 65% yield, the methyl group being in a *cis* relationship ($J_{2,3}$ 2.4 Hz) with the neighboring acetal group. Selective removal of the six-membered acetal of the L-*C*-fucosyl derivative **6** proved unsuccessful and led mainly to the free tetrahydroxy compound **7**. This compound was then selectively tosylated at the primary position to give **8**, which was subsequently acylated to give **9** in 80% overall yield. Substitution of the tosylate by iodide gave the iodo derivative **10** in 98% yield. The spacer was then grafted to the fucose unit by treatment of **10** with methyl mercaptoacetate in the presence of cesium carbonate to give almost quantitatively the ester **11**. The sulfone **12** was obtained from *m*CPBA oxidation in 92% yield. Finally saponification of all the ester groups with sodium methoxide in methanol gave the expected free acid **13** after acidification.[13] It is worthy of note, that the proton of the methylene group are relatively acidic as shown on the ^{1}H NMR spectrum which exhibited a signal at 8.3 ppm corresponding to the enolic form upon standing in D_2O. This should reinforce our hypothesis of a possible chelation of our analogue with manganese ions at the active site of FucT.

The guanosine part was prepared using modifications of the procedures developed by Sasaki for 8-bromoguanosine.[14] The diol function was first protected as an acetal and the guanidine group was protected as an amidine to provide **14**.

Introduction of a nitrogen atom at *C*-5′ by nucleophilic substitution required protection of the second nitrogen group at *N*-1 with a MOM group by treatment with

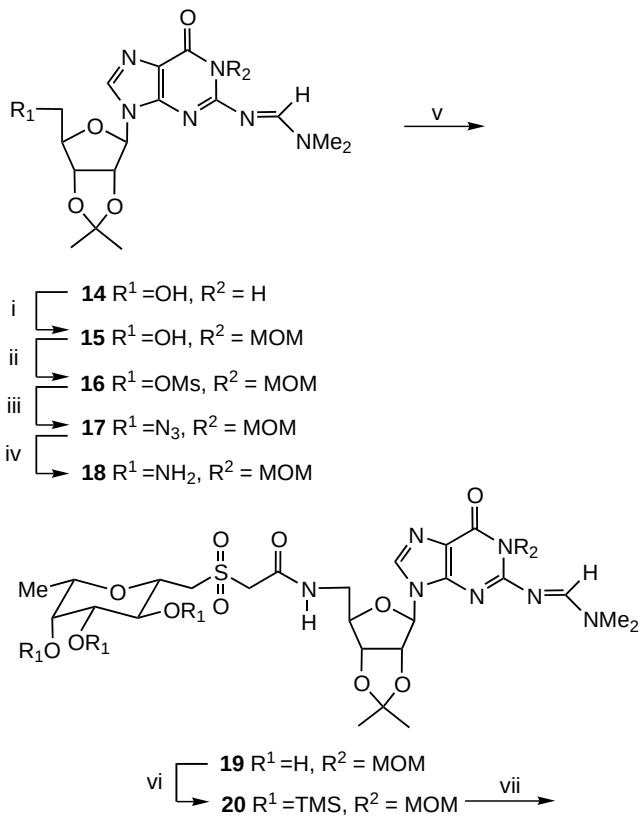


Scheme 3. *Reagents*: (i) methoxypropene, DMF, PTSA; (ii) CrO_3, pyridine; (iii) PPh_3, CCl_4, THF; (iv) Raney Ni, EtOAc; (v) AcOH, H_2O; (vi) TsCl, pyridine; (vii) BzCl, pyridine; (viii) NaI, butanone; (ix) $HSCH_2COOMe$, $CsCO_3$, DMF; (x) *m*CPBA, EtOAc; (xi) MeONa, MeOH.

methoxymethyl chloride in the presence of sodium hydride (1 equiv.) to give **15**. Finally the azido group was introduced at position 5′ using standard activation by a mesyl group. Reduction of the azido group using Staudinger conditions or better by catalytic hydrogenation with Pd/C 5% provided **18** in 65% yield. The last steps of the synthesis consisted in the coupling of the acid **13** with amine **18** using BOP to provide the protected derivative **19** in 48% yield. Silylation of the free OH groups of the fucose residue gave the less polar **20** which can be purified by standard column chromatography.[15] Final removal of all protecting group was achieved by treatment with trifluoroacetic acid gave the fully deprotected compound **3**.[16] Purification by column chromatography on reverse phase gave pure compound **3**[17] (Scheme 4).

This compound did not show any significant inhibition of fucosyltransferase using a soluble recombinant form of human FucT-III.[18]

In summary, we have prepared a non-functional analogue **3** of the natural fucosyl donor GDP-fucose having a methylene sulfono amide as a surrogate of the diphosphate link. One of the key features of our synthesis is the route developed for the preparation of a L-*C*-fucosyl unit from D-mannose. Different explanations can be invoked for the absence of inhibitory activity. The methylene sulfono amide tether is unable to mimic the diphosphate linkage because of the absence of formal negative charges like in the phosphate group. Moreover, the presence of an amide function in the tether used is this work may induce an improper spatial arrangement of the fucose and the guanosine residue. Compounds with significant affinity should be obtained by mimicking the transition state of the enzymatic reaction, tacking into account the presence of the acceptor and/or the planar geometry of the intermediate glycosyl cation.[19] This approach is currently under investigation in our group.



Scheme 4. *Reagents*: (i) NaH, MOMCl; (ii) MsCl, CH_2Cl_2, NEt_3; (iii) NaN_3, DMF; (iv) H_2, Pd/C 5%; (v) **13**, BOP, NEt_3; (vi) TMSCl, NEt_3, CH_2Cl_2; (vii) TFA/H_2O 8/2.

Acknowledgements

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13. Selected analytical data of 2,6-anhydro-1-deoxy-7-*S*-(carboxymethyl)-7-sulfonyl-D-glycero-D-galacto-heptitol (**13**): $[\alpha]_D$ +0.7 (*c* 0.6, H_2O); ^1H NMR (400 MHz), D_2O δ (ppm): 1.13 (d, 3H, H-1, $J_{1-2}=6.7$ Hz), 3.39 (dd, 1H, H-5, J_{5-6} 9.5 Hz), 3.54 (d, 1H, H-7, $J_{7-7'}$ 14.3 Hz), 3.56 (dd, 1H, H-4, J_{3-4} 3.5, J_{4-5} 9.4 Hz), 3.64 (d, 1H, H-7′), 3.65–3.73 (broad m, 3H, H-2, H-3, H-6), 3.98 (dd, 1H, H-8, $J_{8-8'}$ 15.1, *J* 1.4 Hz), 4.13 (d, 1H, H-8′) H-8 and H-8′ were shifted to 8.34 (s, 1H, H-8) after 48 h; ^{13}C NMR (62.9 MHz), D_2O δ (ppm): 18.5 (C-1), 57.4 (C-7), 71.8 (C-5), 74.5 (C-3), 76.6 (C-4), 77.1 (C-6), 77.3 (C-2), 171.0 (C-9), 172.75 (C-8) after 48 h. Anal. calcd for $C_9H_{16}O_8S$: C, 38.02; H, 5.67; S, 11.27. Found: C, 38.49; H, 5.58; S, 11.43.
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