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Toward partial fucosyl transferase transition state analogues: methylene sulfono sulfonamide as surrogate of pyrophosphate

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Abstract—Partial fucosyl transferase transition state analogues having sulfonoacetamido- and methylene sulfono sulfonamide links as a non-charged surrogate of the pyrophosphate moiety have been prepared from fructose and guanosine. The use of a MOM group at N1 and a formamidine group at the primary amine function for the protection of the guanine residue proved troublesome.

The inhibition of fucosyl transferases is well recognized as a potential way to interfere with some biological events such as tumor metastasis[1] and inflammation.[2] Several fucosyl transferases (FucT) have been identified,[3] and are 'Leloir enzymes', which make use of a nucleotide diphosphate donor, i.e. guanosyl diphospho fucose (GDP-fucose). A putative mechanism of fucose transfer from GDP-fucose to the glycosyl acceptor is shown in Figure 1.[4] The knowledge of this mechanism allow the design of new classes of carbohydrate analogues,[5] able to mimic transition states.[6] Another important point in the design of inhibitors is their biological availability. Non-charged derivatives are then requested to facilitate membrane crossing. In non functional analogues of GDP-fucose, the diphosphate link between the fucose and the guanosine residue constitue an obstacle to cell penetration, which could be circumvented by using surrogates of the diphosphate arrangement.[7] In the particular field of fucosyl transferase, some interesting non-charged links have been proposed to replace the diphosphate tether.[8]

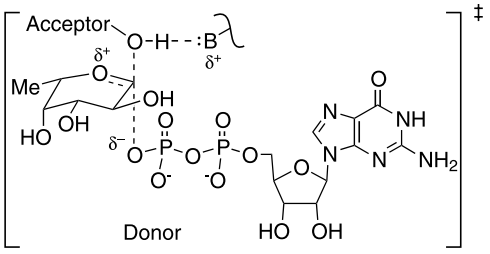

Figure 1. Postulated transition state of FucT.

In a previous paper, we reported the synthesis of analogues of GDP-fucose in which the diphosphate linkage was replaced by a methylene sulfono amide link.[9] This analogue was not an inhibitor of FucT. This failure should be attributed to the tether, which did not mimick correctly the diphosphate moiety but also to the absence of the saccharidic acceptor necessarily present at the catalytic site.

Another class of analogues, incorporating the hydroxyl group of the glycosyl acceptor, able to interact with a basic site of the enzyme was designed. Furthermore two different non-charged diphosphate surrogates were devised to connect the fucose mimic and the nucleoside.

Methylene disulfones are isosteric of pyrophosphate and are non-charged, 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 normally use as a cofactor.[10–12]

In this paper we report our efforts toward the synthesis of partial transition state analogues of the FucT reaction using a methylene sulfono sulfonamide link as surrogate of diphosphate.

In the design of these transition state analogues, we chose to link a mimic of the fucose residue by a non cleavable link, i.e. a carbon–carbon bond. We also reasoned that the oxygen group of the glycosyl acceptor, which lies in the α configuration with respect to the

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fucose ring should be mimicked by an additional hydroxyl group at the anomeric position (Fig. 2). The above requirements led us to use a ketose derivative.

A second approximation was done by assuming that the methyl group of fucose has a relatively unimportant role in recognition by the enzyme if any. Such a point has been clearly established by Wong et al. in a sound structure–activity relationship study of the E-selectin-sialyl Lewis X binding.[13] With these two prerequisites in mind, the use of fructose, having the required anomeric hydroxyl group and all the absolute configurations of fucose seemed appropriate. Finally, an amide bond was chosen to link the nucleoside moiety to the fucose mimic. This resulted in the design of **1** and **2** with a sulfonoamide and a methylene–sulfono sulfonamide linkage respectively, as surrogates of the pyrophosphate link.

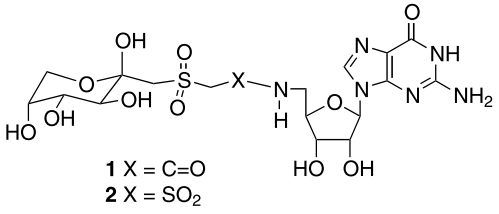
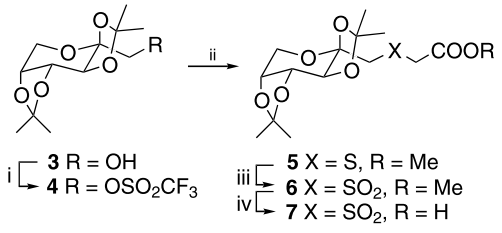


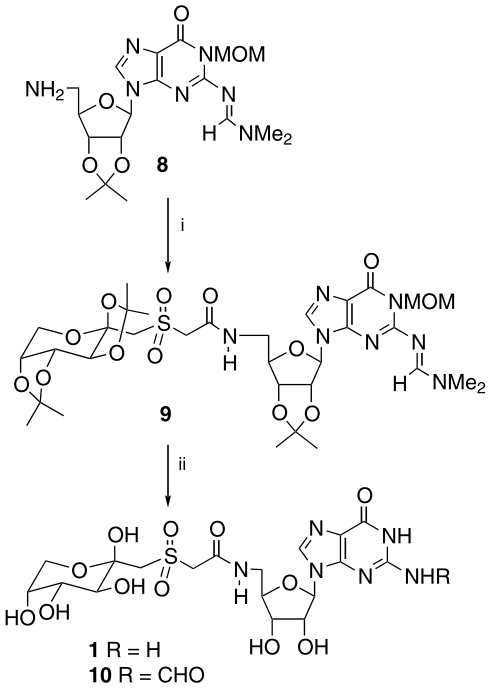
Figure 2. Potential transition state-based inhibitors of FucT.

The known di-*O*-isopropylidene-D-fructose derivative **3** was treated with trifluoromethane sulfonic anhydride to give the triflate **4**, which was used immediately without purification and substituted with methylthioglycolate in DMF in the presence of cesium carbonate (Scheme 1). The ester **5**, obtained in 81% for the two steps, was then treated with *m*CPBA to provide the sulfone **6** in 75% yield. Saponification of the ester function gave the carboxylic acid **7** in excellent yield.



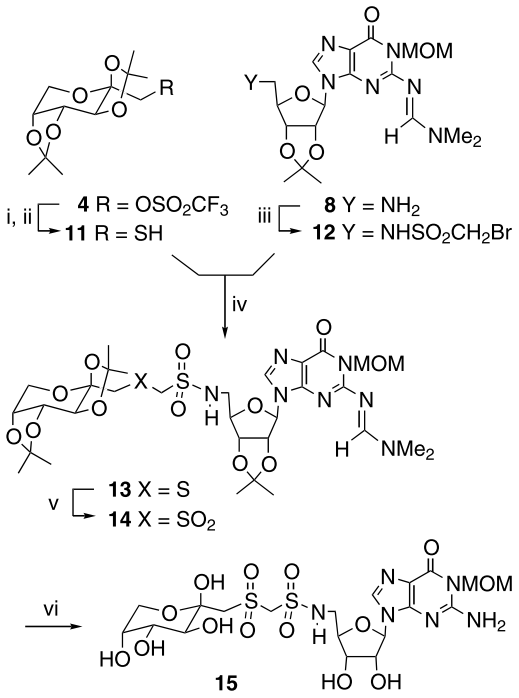
Scheme 1. *Reagents and conditions*: (i) $(CF_3SO_2)_2O$, pyridine/CH_2Cl_2, rt; (ii) $HSCH_2COOMe$, Cs_2CO_3, DMF, 81%, two steps; (iii) *m*CPBA, AcOEt, 75%; (iv) 1 M LiOH, THF, H_2O, 95%.

The protected 5′-amino-guanosine derivative **8**[9] was then coupled to **7** using the BOP reagent and gave the amide **9** in 79% yield[14] (Scheme 2). Deprotection of all protecting groups of the latter was achieved by acid hydrolysis. The expected free compound **1** was obtained together with the corresponding N2-formyl derivative **10** resulting from a abnormal cleavage of the formamidine residue.[15] **1** was obtained in 38% yield as a pure compound by preparative reverse phase column chromatography.[16]



Scheme 2. *Reagents and conditions*: (i) **7**, BOP, NEt_3, DMF, 79%; (ii) TFA, H_2O 8/2, rt.

The construction of the methylene sulfono sulfonamide tether needed a different strategy, which implied the formation of the sulfur methylene bond. Thus the sulfur atom was introduced on the fructose residue by nucleophilic substitution of the triflate group of **4** with thiourea followed by reduction of the resulting thiouronium salt with sodium bisulfite to give the thiol **11** in 65% overall yield (Scheme 3). On the other hand we attempted to form the bromo methyl sulfonamide from the amine **8** and bromomethyl sulfonyl chloride. Standard conditions for the formation of sulfonamide in the presence of a tertiary amine as the base or in pyridine failed to give any trace of the expected compound.[17] Extensive experimentation led us to the conclusion that the basic conditions destroyed the sulfonyl reagent . Formation of the sulfonamide bond was finally carried out by slow addition of the amine **8** and one equivalent of DMAP onto the solution of bromomethyl sulfonyl chloride in dichloromethane. The expected sulfonamide **12** was obtained in 56% yield. Subsequent reaction of the thiol **11** with **12** in the presence of cesium carbonate led to the desired compound **13**, which was immediately oxidized to the sulfone **14** using *m*CPBA in 50% overall yield.[18] In order to circumvent the problems related to formamidine cleavage, this group was removed first by catalytic hydrogenation. The other protecting groups were then hydrolyzed in acidic medium under our standard conditions (TFA/H_2O 8:2). However, under these conditions no cleavage of the *N*-methoxymethyl ether group was observed and only compound **15** was isolated.[19] To date all attempts to remove the MOM group even using harsh acidic conditions failed. This might be attributed to a facile protonation of the amino



Scheme 3. *Reagents and conditions*: (i) thiourea, 2-butanone, reflux; (ii) $Na_2S_2O_5$, H_2O, $CHCl_3$, reflux, 65%, two steps; (iii) $BrCH_2SO_2Cl$, DMAP, CH_2Cl_2, 56%; (iv) Cs_2CO_3, DMF; (v) *m*CPBA, AcOEt, 50%, two steps; (vi) (1) H_2, $Pd(OH)_2$, THF, MeOH, H_2O, 58%; (2) TFA, H_2O 8/2, rt.

group at C2 which precludes any further protonation of the MOM group needed to ensure its hydrolysis. It is interesting to note that although such protecting groups have been used in the 8-bromo-guanosine series,[20] no attempts to remove them has yet been described.

We described the synthesis of two compounds designed as partial transition state analogues of fucosyl transferases. The fucose residue was mimicked by fructose, the anomeric hydroxyl of this keto sugar being used to replace the hydroxyl group of the oligosaccharidic acceptor of FucT. The sulfono methylene sulfonamide moiety, a surrogate of the diphospho linkage of the natural substrate GDP Fucose, was prepared by nucleophilic substitution of a bromosulfonamide with a thiol function. This synthesis represents one of the first synthesis of a methylene disulfone linkage to replace the pyrophosphate linkage of glycosyl donors. The synthetic sequence described here opens the way to non-charged analogues of nucleoside diphospho-sugars, the natural substrates of the 'Leloir' enzymes involved in the biosynthesis of many oligosaccharides. One challenging task to achieve the synthesis of such compounds in the guanosine series would be to avoid the use of any protecting group at N1. Such a strategy toward these compounds is currently under investigation.

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14. Selected analytical data of 5′-[[[(1-deoxy-2,3:4,5-di-*O*-(1-methylethylidene)-α-D-fructopyranosyl)sulfonyl]acetyl]amino]-5′-deoxy-*N*-[(dimethylamino)methylene]-1-(methoxymethyl)-2′,3′-*O*-(1-methylethylidene)guanosine (**9**): $[\alpha]_D = -20.6$ (*c* 0.5, $CHCl_3$); IR (cm^{-1}) 3250 (NH), 1682 (CO), 1326, 1115 (SO_2); ^1H NMR (250 MHz), $CDCl_3$ δ (ppm) 1.32 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 3.13 (s, 3H, N-$(CH_3)_2$), 3.20 (s, 3H, N-$(CH_3)_2$), 3.41 (s, 3H, CH_3 mom), 3.54 (d, 1H, H-1″a, $J_{1''a-1''b}$ 15 Hz), 3.63 (ddd, 1H, H-5′a, $J_{NH-5'a} = J_{4'-5'a}$ 5, $J_{5'a-5'b}$ 13.5 Hz), 3.75 (d, 1H, H-6″a, $J_{6''a-6''b}$ 13 Hz), 3.77 (ddd, 1H, H-5′b, $J_{NH-5'}$ 5Hz), 3.88 (dd, 1H, H-6″b, $J_{5''-6''b}$ 1 Hz), 4.08 (d, 1H, H-1″b), 4.15–4.33 (m, 4H, H-4′, H-5″, H-2‴a, H-2‴b), 4.36 (d, 1H, H-3″, $J_{3''-4''}$ 2.5 Hz), 4.60 (dd, 1H, H-4″, $J_{4''-5''}$ 8 Hz), 4.91 (dd, 1H, H-3′, $J_{2'-3'}$ 6.5, $J_{3'-4'}$ 8 Hz), 5.21 (dd, 1H, H-2′), 5.73 (s, 2H, CH_2 MOM), 5;92 (s, 1H, H-1′, $J_{1'-2'}$ 3.5 Hz), 7.84 (s, 1H, H-8), 8.12 (t, 1H, NH), 8.51 (s, 1H, -N=CH-); ^{13}C NMR (62.9 MHz), $CDCl_3$ δ (ppm) 23.9, 24.9, 25.3, 25.8, 26.6, 27.2 (CH_3), 35.3, 41.4 (N-$(CH_3)_2$), 41.6 (C-5′), 57.6 (CH_3 mom), 60.2 (C-2‴), 61.0 (C-1″), 61.7 (C-6″), 69.9 (C-4″), 70.2 (C-5″), 72.8 (CH_2 MOM), 73.1 (C-3″), 81.4 (C-3′), 83.8 (C-2′), 84.1 (C-4′), 88.4 (C-1′), 99.8 (C-2″), 109.2, 110.1 (C″$(CH_3)_2$), 114.6 (C′$(CH_3)_2$), 119.5 (C-5), 137.3 (C-8), 148.0 (C-4), 157.4 (C-2), 157.8 (-N=CH-), 158.3 (C-6), 162.6 (C-1‴).
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16. 5′ - [[[(1 - Deoxy - α - D - fructopyranosyl)sulfonyl]acetyl]-amino]-5′-deoxy-guanosine (**1**): ^1H NMR (400 MHz) D_2O δ (ppm) 3.50–4.08 (m, 9H), 4.12 (m, 3H), 4.28 (dd, 1H, H-3, $J_{2'-3'}$ 4.8 Hz), 4.76 (m, 1H, H-2′), 5.77 (d, 1H, H-1′, $J_{1'-2'}$ 5 Hz), 7.85 (s, 1H, H-8); ^{13}C NMR (62.9 MHz, D_2O δ (ppm), 47.3 (C-5′), 58.7, 59.4 (C-1″, C-6″), 63.8 (C-1‴), 72.4, 73.7, 75.0, 75.6 (C-2′, C-3′, C-4′, C-4″, C-5″,), 86.2 (C-1′), 91.8 (C-3″), 99.9 (C-2″), 116.7 (C-5), 121.3 (C-6), 151.5 (C-8), 165.5 (C-3), 168.5 (C-1), 169.2 (CO); MS $(ES)^+$ *m*/*z* 574 $[M+H+Na]^+$
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19. 5′ - [[[(1 - Deoxy - α - D - fructopyranosyl)sulfonyl]methyl]-amino]-5′-deoxy-*N*-(methoxymethyl)guanosine (**15**): ^1H NMR (400 MHz) D_2O δ (ppm), 3.33 (s, 3H, CH_3 MOM), 3.05–4.05 (m, 9H), 4.10–4.18 (m, 2H), 4.19 (m, 1H, H-4′), 4.37 (dd, 1H, H-3′, $J_{2'-3'} = J_{3'-4'}$ 5Hz), 4.85 (dd, 1H, H-2′, $J_{1'-2'}$ 5.2 Hz), 5.42 (s, 2H, CH_2 MOM), 5.85 (d, 1H, H-1′), 7.82 (s, 1H, H-8); ^{13}C NMR (62.9 MHz, D_2O δ (ppm), 46.9 (C-5′), 59.0, 59.1, 59.2 (C-1″, C-6″, CH_3 mom), 66.76 (C-1‴), 71.6, 71.9, 72.8, 73.4, 75.3, 75.9 (C-2′, C-3′, C-4′, C-4″, C-5″, CH_2 mom), 86.0 (C-1′), 91.9 (C-3″), 99.5 (C-2″), 116.8 (C-5), 121.5 (C-6), 139.4 (C-8), 165.5 (C-3), 166.0 (C-1); MS $(ES)^+$ *m*/*z* 631 $[M+H]^+$.
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