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Synthesis of *C*-Fucopyranosyl Analogs of GDP-L-Fucose as Inhibitors of Fucosyltransferases

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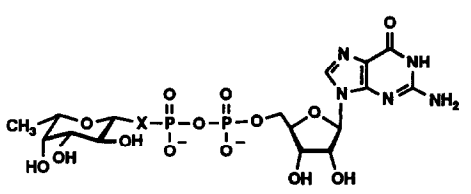
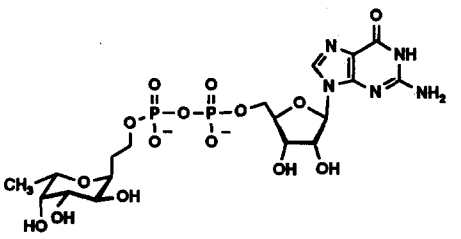
Abstract: The syntheses of the *C*-fucopyranosyl analogs of GDP-L-fucose **2** - **5** as potential inhibitors of fucosyltransferases are reported. The synthetic routes are based on the *C*-glycosidation of tetra-*O*-acetyl-α-L-fucopyranose **6** under conditions that provided either β- or α- *C*-fucosides with high stereoselectivity. Coupling to GMP was effected by Khorana's phosphomorpholidate method.

Fucosyltransferases incorporate α-L-fucopyranosyl residues into the oligosaccharides of membrane-bound glycoconjugates using GDP-L-fucose (**1**) as the carbohydrate donor. Early interest in these enzymes originated from the participation of fucose in blood-group determinants and other tissue antigens. Some of these determinants, such as the sialyl-Lewis X (SLe^x) that contains an unusual α(1-3) fucosyl linkage, were found to be associated with certain tumor cell lines.[1] More recently, fucosyltransferases have attracted considerable attention with the identification of the SLe^x epitope as the ligand of the E- and P-selectins, two members of the family of cell-adhesion proteins implicated in the recruitment of leukocytes to sites of inflammation.[2] The development of inhibitors for fucosyltransferases is therefore an area with broad therapeutic potential which will also provide powerful tools to study the role of individual carbohydrates in cell-recognition events.[3]

A key requirement for analogs of GDP-fucose (**1**) as competitive inhibitors of fucosyltransferases would be to inactivate the fucosyl ring toward the glycosyl transfer; this can be achieved using *C*-glycosides such as its corresponding phosphonate isostere **2**. In addition, since in the glycosylation reaction GDP effectively dissociates from the fucosyl unit, homologs **3** and **4**, which incorporate different distances between those two moieties, were synthesized. Finally, analog **5**, the axial epimer of **4**, was also synthesized to study the enzyme specificity and the contribution of the fucosyl ring to recognition of the analogs.



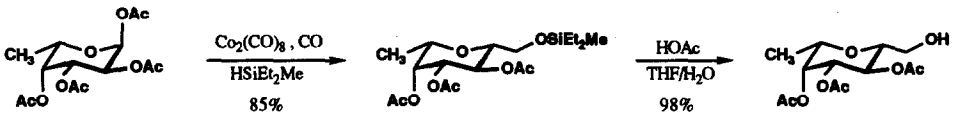
1 X = -O- **3** X = $-CH_2-O-$
2 X = $-CH_2-$ **4** X = $-CH_2-CH_2-O-$



5

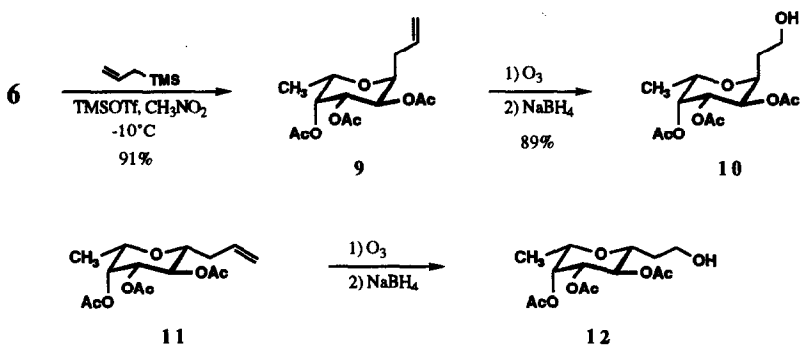
The synthetic schemes to compounds **2-5** center on the *C*-glycosylation of L-fucose. With tetra-*O*-acetyl-α-L-fucopyranose (**6**)[4] as substrate, we have studied this reaction in detail and found it to proceed with a stereoselectivity very dependent on the nature of the nucleophile and the reaction conditions. Highly efficient and complementary routes to both β-equatorial and α-axial *C*-fucopyranosides were thus developed.

Equatorial *C*-glycosylation took place in the cobalt-catalyzed siloxymethylation of **6** under the conditions reported by Murai (4% $Co_2(CO)_8$, $HSiEt_2Me$, 1 atm CO, CH_2Cl_2, 2 d, 22 °C),[5] the β-*C*-fucopyranoside **7** being obtained with excellent stereoselectivity (>20:1) in 85% yield; desilylation of **7** under mild conditions (THF/HOAc/H_2O, 0 °C) gave **8** cleanly without undesired acetyl migrations.



6 **7** **8**

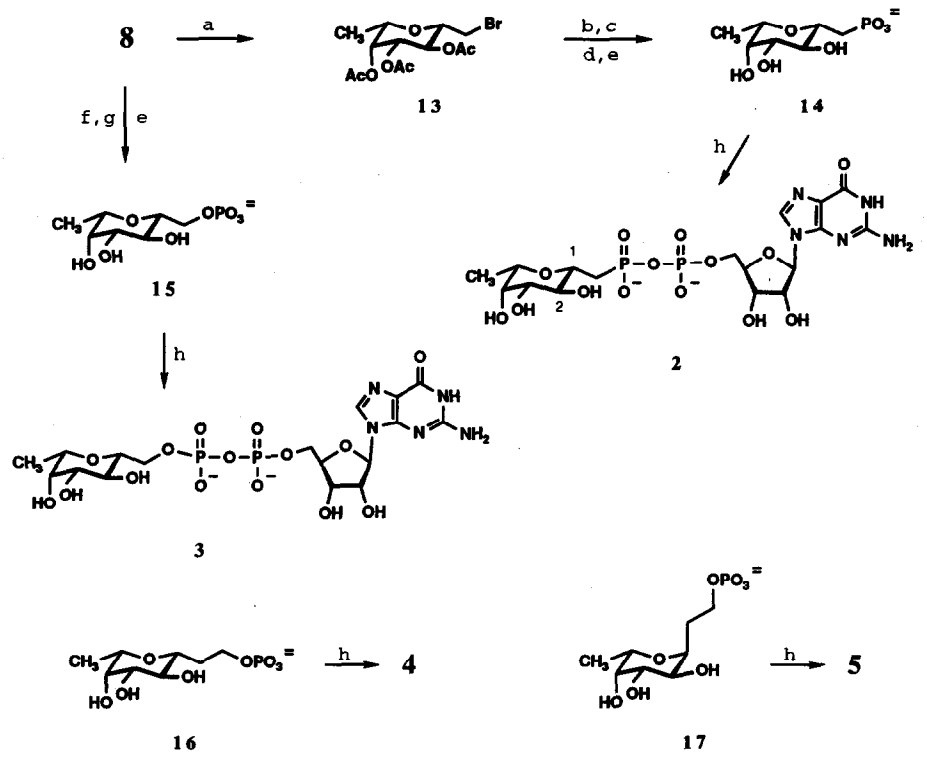
The opposite α-axial selectivity was obtained using alkenyl silanes with trimethylsilyl triflate as catalyst. Thus reaction of **6** with allyltrimethylsilane / TMSOTf in nitromethane[6] at -10 °C provided **9** in 91% yield with a 14:1 α:β stereoselectivity. Subsequent ozonolysis of the double bond followed by reduction with sodium borohydride led to **10**. Treatment of **6** under Kozikowski's conditions, zinc bromide in neat allyltrimethylsilane,[7] required higher temperatures (60 °C) and resulted in complete loss of stereoselectivity (1.1:1 mixture of **9**:**11** in 90% yield).[8]



9 **10** **11** **12**

As shown in the Scheme, alcohol **8** was converted to the bromide **13** by treatment with bromine, Ph_2PCl and imidazole in toluene (87% yield).[9] Subsequent Arbuzov reaction (triethyl phosphite, reflux) followed by reaction with bromotrimethylsilane[10] gave a bis(trimethylsilyl) ester which was hydrolyzed and deacetylated (K_2CO_3, MeOH) to provide the trihydroxy phosphonate **14** in 93% overall yield from **13**. Likewise, **8** was phosphorylated with $(PhO)_2POCl$ in pyridine (92% yield) and the resulting diphenyl phosphate subsequently converted to **15** by hydrogenolysis (PtO_2 in MeOH, 85%) followed by deacetylation. The same protocol, when applied to the epimeric alcohols **10** and **12**, resulted in their corresponding trihydroxy phosphates **16** and **17** in good overall yields (75-85%).

Synthesis of the nucleotides **2-5** was achieved by the phosphomorpholidate coupling of Moffatt and Khorana.[11] Thus compounds **14-17** were treated as their triethylammonium salts with the 4-morpholine-*N*,*N*'-dicyclohexylcarboxamidinium salt of guanosine 5'-monophosphomorpholidate in pyridine at 22 °C for 7 days; the resulting coupling products **2-5** were purified by column chromatography on DE-52 cellulose (elution with a linear



Scheme. Reagents and conditions: (a) Br_2, Ph_2PCl, imidazole, toluene, r.t., 87%; (b) $(EtO)_3P$, reflux, 1 d, 97%; (c) Me_3SiBr, 0 °C; (d) H_2O, r.t.; (e) K_2CO_3, MeOH, 0 °C; (f) $(PhO)_2POCl$, pyridine, r.t., 14 h, 92%; (g) H_2 (1 atm), PtO_2, MeOH, r.t., 36 h, 85%; (h) GMP morpholidate 4-morpholine-*N*,*N*'-dicyclohexylcarboxamidine salt, pyridine, r.t., 7 d.

gradient 0-0.1 M aqueous triethylammonium bicarbonate at pH 7.8).[12] The structures of compounds **2** to **5** were confirmed by their satisfactory elemental analyses, high resolution MS (FAB), ^{1}H-, ^{13}C- and ^{31}P-NMR spectra.[13] Particularly diagnostic was ^{31}P-NMR spectroscopy which showed the corresponding ^{31}P-^{31}P geminal coupling: δ -10.12, 14.51 (two doublets, ^2J = 26.0 Hz) for **2** and -10.15, -9.54 (two doublets, ^2J = 22.4 Hz) for **3**.

In summary highly efficient and stereocontrolled routes to the syntheses of GDP-Fuc analogs, based on *C*-glycosylation of tetra-*O*-acetyl-α-L-fucopyranose, **6**, were developed. Biological evaluation of compounds **2-5** is under current investigation. Results of these experiments will be presented elsewhere.

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8. Assignment of the configuration at the *C*-anomeric centers in the *C*-glycosides was based on the spin-spin coupling constants for the ring protons in their NMR spectra. Thus the β-isomers showed diaxial $J_{1,2}$ = 9-10 Hz whereas the α-epimers showed eq-ax $J_{1,2}$ = *ca.* 5.5 Hz.
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12. Yields of the isolated materials were not optimized and ranged from 35% to 50%; the actual conversions, however, are considerably higher if based on recovered starting materials, since most of the unreacted **14-17** separated cleanly in the chromatography step.
13. a) Selected data for **2** (bis(triethylammonium) salt): ^{1}H NMR (D_2O, 400 MHz) δ 1.002 (3H, d, *J* = 6.5 Hz), 1.110 (18H, t, *J* = 7.3 Hz), 1.794 (1H, ddd, *J* = 16.8 (P), 15.3, 8.7 Hz), 2.121 (1H, ddd, *J* = 19.5 (P), 15.3, 3.2 Hz), 3.032 (12H, q, *J* = 7.3 Hz), 3.223 (1H, t, *J* = 9.5 Hz), 3.358 (1H, dddd, *J* = 10.9 (P), 9.5, 8.7, 3.2 Hz), 3.404 (1H, dd, *J* = 9.5, 3.5 Hz), 3.461 (1H, q, *J* = 6.5 Hz), 3.540 (1H, d, *J* = 3.5 Hz), 4.032 (2H, dd, *J* = 5.3 (P), 3.4 Hz), 4.180 (1H, qd, *J* = 3.4, 2.0 (P) Hz), 4.369 (1H, dd, *J* = 5.2, 3.4 Hz), 4.647 (1H, dd, *J* = 6.2, 5.2 Hz,), 5.761 (1H, d, *J* = 6.2 Hz), 7.915 (1H, s). ^{13}C NMR (CD_3OD, 100.6 MHz) δ 9.15 (6C), 17.34, 34.52 (d, *J* = 137.4 Hz), 47.20, (6C), 66.61 (d, *J* = 5.6 Hz), 72.21, 73.59, 73.85 (d, *J* = 8.3 Hz), 75.06, 75.34, 76.56, 77.50, 85.36 (d, *J* = 8.9 Hz), 89.16, 117.77, 138.43, 153.26, 155.48, 159.50. ^{31}P NMR (CD_3OD, 145.8 MHz) δ -10.121 (d, *J* = 26.0 Hz), 14.515 (d, *J* = 26.0 Hz). FAB-MS *m/z* 588.1082 $(M+H)^+$, calcd for $C_{17}H_{28}N_5O_{14}P_2$ 588.1108.
b) Selected data for **3** (bis(triethylammonium) salt): ^{1}H NMR (D_2O, 400 MHz) δ 1.010 (3H, d, *J* = 6.5 Hz), 1.094 (18H, t, *J* = 7.3 Hz), 3.017 (12H, q, *J* = 7.3 Hz), 3.218 (1H, m), 3.431 (1H, dd, *J* = 9.7, 3.3 Hz), 3.486 (1H, t, *J* = 9.6 Hz), 3.509 (1H, qd, *J* = 6.5, 0.8 Hz), 3.553 (1H, dd, *J* = 3.3, 0.8 Hz), 3.912 (1H, ddd, *J* = 11.5, 6.4 (P), 5.1 Hz), 3.987 (1H, ddd, *J* = 11.5, 5.1 (P), 1.7 Hz), 4.027 (2H, dd, *J* = 5.0 (P), 3.6 Hz), 4.169 (1H, qd, *J* = 3.4, 2.0 (P) Hz), 4.349 (1H, dd, *J* = 5.2, 3.1 Hz), 4.645 (1H, dd, *J* = 6.4, 5.2 Hz), 5.743 (1H, d, *J* = 6.4 Hz), 7.929 (1H, s). ^{13}C NMR (CD_3OD, 100.6 MHz) δ 9.15 (6C), 17.37, 47.28 (6C), 66.46 (d, *J* = 5.1 Hz), 66.68 (d, *J* = 4.4 Hz), 67.69, 72.16, 73.55, 75.13, 75.69, 76.20, 80.94 (d, *J* = 8.9 Hz), 85.33 (d, *J* = 8.4 Hz), 89.08, 117.70, 138.39, 153.23, 155.38, 159.49. ^{31}P NMR (CD_3OD, 145.8 MHz) δ -10.155 (d, *J* = 22.4 Hz), -9.538 (d, *J* = 22.4 Hz). FAB-MS *m/z* 604.1057 $(M+H)^+$, calcd for $C_{17}H_{28}N_5O_{15}P_2$ 604.1057.

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