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SYNTHESIS OF INHIBITORS OF α-1,3-FUCOSYLTRANSFERASE

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Abstract: A new class of compounds **1**, structurally modified derivatives of the α-fucosidase inhibitor deoxyfuconojirimycin **2**, has been prepared and found to display activity as inhibitors of α-1,3-fucosyltransferase in the μM range. © 1997 Elsevier Science Ltd.

α-1,3-Fucosyltransferases are key enzymes in the biosynthesis of sialyl lewis X, Figure 1. The interaction between sialyl lewis X and the glycoprotein E-selectin is an important event in the cell adhesion process that occurs between leukocytes and endothelial cells.[1] Limiting this interaction by inhibiting α-1,3-fucosyltransferases, for example, may provide a useful therapy for controlling inflammatory processes such as arthritis or for combating tumour growth.[2]

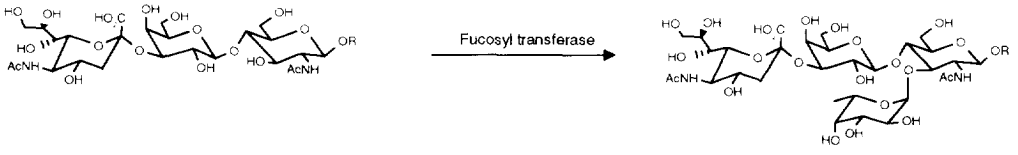
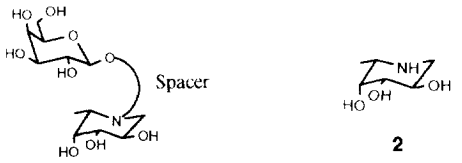


Figure 1 Sialyl Lewis X

Aza sugars have received considerable attention as inhibitors of glycosidase enzymes that are capable of cleaving specific carbohydrate linkages.[3] This class of compounds, polyhydroxylated piperidines and pyrrolidines, mimics electronic and geometric features associated with the transition state of cleavage of the glycosyl unit from the natural substrate.[4] In addition the glycosyl transferase reaction, which may be regarded as the reverse of the above process, has been targeted with aza sugars. Thus Wong has shown that fucosidase inhibitors can behave as inhibitors of fucosyltransferase.[5] In view of the low levels of inhibition of fucosyltransferase by deoxyfuconojirimycin **2** we believed that incorporating recognition elements of the natural carbohydrate acceptor substrate would give a structure more closely related to the transition state and would thus lead to a more powerful inhibitor. This approach considers events that occur in the vicinity of the fucose sugar during the transition state in contrast to the approaches of other groups who designed inhibitors based on an elaborated fucopyranose structure.[6] Herein we report the synthesis and activity of a new class of inhibitors **1** of α-1,3-fucosyltransferase IV, Figure 2.

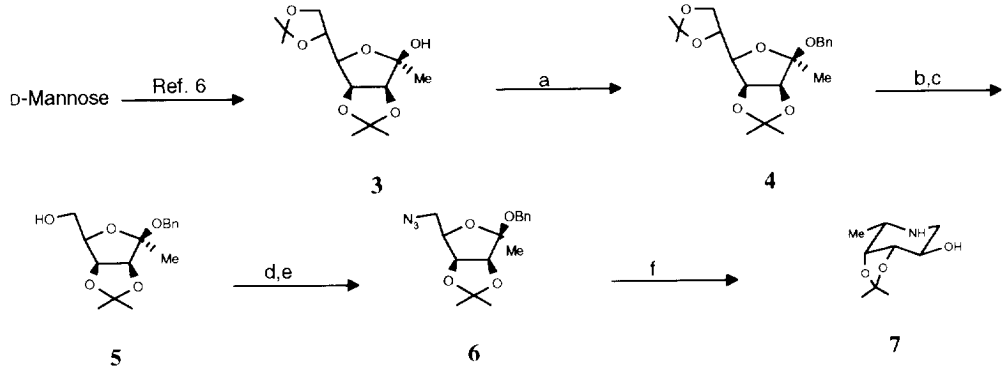


1 **2**

Figure 2

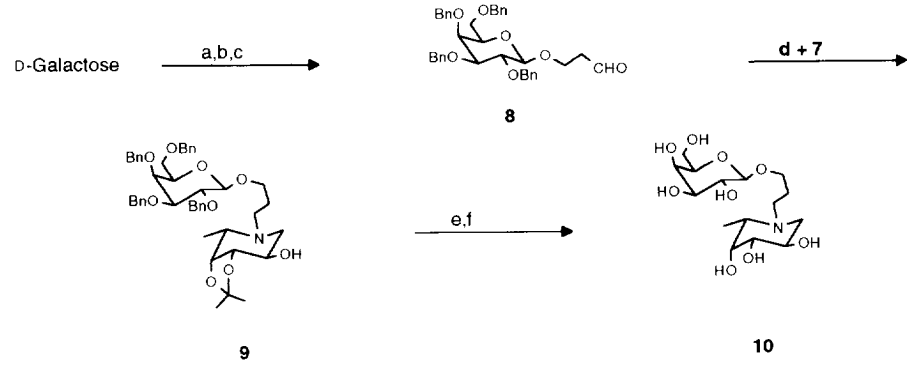
This class of inhibitors is based on tethering the amino sugar **2** to a D-galactose unit by a suitable spacing group. For these studies we developed an expedient synthesis of **7**, a precursor of deoxyfuconojirimycin **2**, Scheme 1, starting with **3**,[7] which was prepared from D-mannose. Benzylation under standard conditions provided **4**.[8] Oxidative cleavage with periodic acid,[9] and immediate reduction of the intermediate aldehyde with sodium borohydride gave the alcohol **5**.

This was converted to the azide **6** by formation of the triflate and azide displacement. Transfer hydrogenation using ammonium formate as hydrogen donor resulted in azide reduction, de-*O*-benzylation and cyclisation followed by reduction of the intermediate imine to give **7**.[10,11]



Scheme 1

Reagents: (a) NaH, BnBr, nBu_4NI, DMF, 70%; (b) H_5IO_6, THF, H_2O (2:1); (c) $NaBH_4$, MeOH, 68%; (d) Tf_2O, CH_2Cl_2, pyridine; (e) NaN_3, DMF, 0°C, 59% for 2 steps; (f) 10% Pd-C, $HCONH_4$, 60°C, 74%



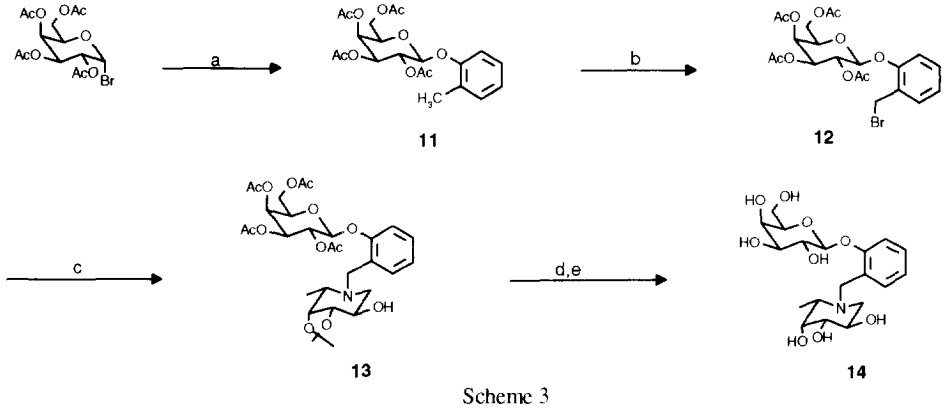
Scheme 2

Reagents: (a) 3-butenol, CSA, 53%; (b) BnBr, NaH, nBu_4NI, DMF, 23% beta-anomer; (c) O_3, CH_2Cl_2, -78°C then Me_2S, 50%; (d) *t*-BuOH, H_2O, 41%; (e) $HCONH_4$, 10% Pd-C, MeOH, 76%; (f) 50% TFA, Dowex 50Wx2, 75%

The D-galactose derivative **10** was prepared as shown in Scheme 2. Glycoside formation with 3-butenol, followed by perbenzylation gave a mixture of anomers from which the desired β-anomer could be isolated by chromatography. Ozonolysis provided the aldehyde **8** which underwent reductive amination with

7 to give **9**. Debenzylation was achieved under transfer hydrogenation conditions, subsequent acetonide removal and ion exchange chromatography gave **10**.

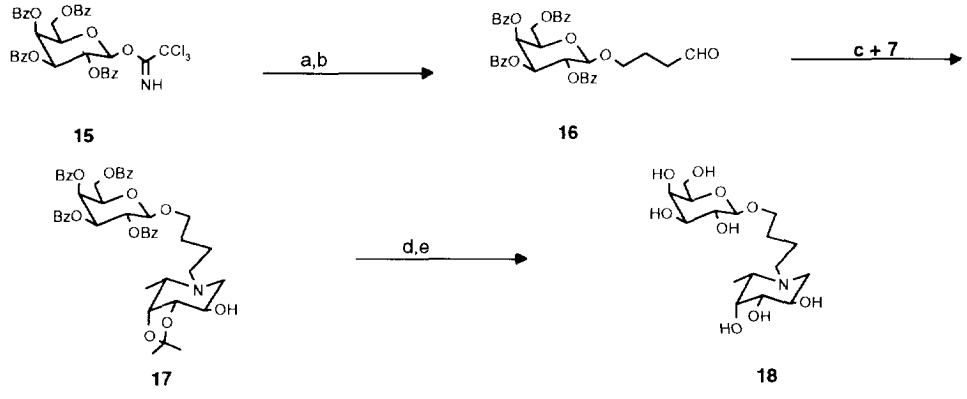
The effect of spacing the D-galactose unit and the amino sugar with an aromatic group was investigated, Scheme 3. Tetra-O-acetyl-α-D-galactopyranosyl bromide underwent phase transfer catalysed reaction with *o*-cresol,[12] to give the arylglycoside **11**. Benzylic bromination of **11** gave the bromide **12**, which reacted with the amino sugar **7** to give **13**. Two step deprotection provided the desired compound **14**.



Scheme 3

Reagents: (a) o-cresol, NaOH, $BnEt_3N^+Cl^-$, $CHCl_3$, 33%; (b) NBS, AIBN, CCl_4, 34%; (c) **7**, 45°C, 26%; (d) DBU, MeOH; (e) 50% TFA, 44% for two steps.

The spacing between the amino sugar and D-galactose unit was increased to a butylene chain **18**, Scheme 4. The trichloroacetimidate **15**,[13] was reacted with 1,4-butanediol using BF_3Et_2O catalysis followed by oxidation to give the aldehyde **16**. Reductive amination with **7** gave **17**, which was subsequently deprotected to give **18**.



Scheme 4

Reagents: (a) 1,4-butanediol, CH_2Cl_2, BF_3Et_2O, 62%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 81%; (c) H_2, Pd, *t*-BuOH, H_20, 77%; (d) 50% TFA; (e) 1% NaOH, MeOH, 62%

These compounds were examined as inhibitors of α-1,3-fucosyltransferase IV activity using a colorimetric assay patterned after that described by Palcic.[14]

Table 1. Inhibition of α-1,3-fucosyltransferase (at 8.5 μM GDP-fucose)

Compound	10	18	14	2	GDP
IC_{50}	>500 μM	233 μM	81 μM	3.5 mM	5 μM

The results in Table 1 show that compounds **18** and **14** display significantly enhanced inhibition of α-1,3-fucosyltransferase IV relative to deoxyfuconojirimycin **2**. We and others,[5] have observe that aza sugars including **2** synergize[15] with GDP to inhibit fucosyltransferases more potently than they do alone. The modified aza sugars discussed here also show synergistic inhibition with GDP. For example, at a concentration 2 μM GDP compound **14** shows an IC_{50} of 50 μM. Further information about the active site and mechanism of the enzyme is required in order to assist in the design of more potent inhibitors.

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