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Synthesis of a Novel Analogue of Sialyl Lewis X

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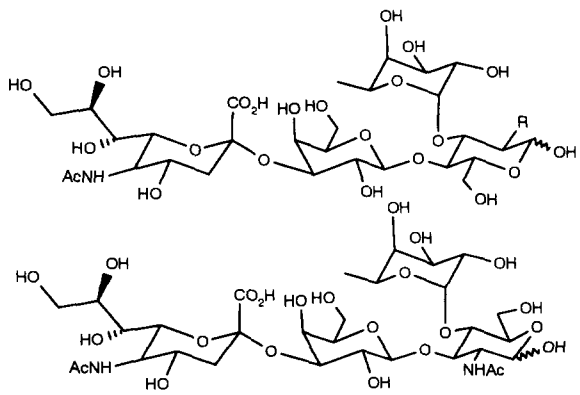
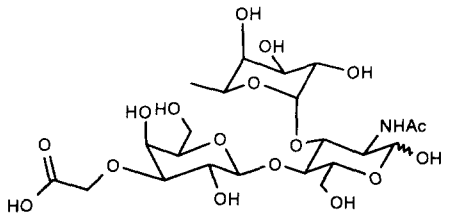
Abstract: Two different strategies have been developed in order to synthesise an analogue and potential mimic of sialyl Lewis X that incorporates a carboxymethyl group and a C_2-symmetric 2,3-butanediol unit as replacements for the sialic acid and the N-acetylglucosamine residues respectively.

Cell adhesion processes of the immune system are currently of particular interest in that they have implications in the therapeutic areas of infection, cancer, and inflammation. In particular, the role of neutrophil-endothelial cell interaction in inflammation is being extensively investigated. Neutrophil adhesion to the endothelium is a multistep process, the initial stage of which involves the rolling of the neutrophil along the cell surface.[1] A constitutive glycoprotein on the surface of the neutrophil possesses a terminal tetrasaccharide unit sialyl Lewis X (sLex) and this has been demonstrated to bind to the E-selectin protein on human endothelial cells and to mediate the rolling phenomenon.[2] Recent reports of *in vivo* experiments suggest that if the E-selectin/sLex interaction is antagonised then inflammation is substantially reduced.[3]



The key structural features of sLex that are required for recognition by E-selectin have been explored. Indeed, the synthesis of analogues of sLex that inhibit neutrophil rolling along the endothelium has been the goal of several research groups.[4] In studies on various oligosaccharides, it was shown that both the fucose and sialic acid residues of sLex were required for recognition by the protein.[5] Modifications to the sialic acid residue indicate that its key structural feature is simply the carboxylic acid moiety and the 3'-carboxymethyl substituted analogue **2** has similar antagonist affinity.[6] Sialyl Lewis A (sLea), a naturally occuring regioisomer of sLex, also binds to E-selectin with similar affinity and it has been shown that the N-acetylglucosamine unit of sLex can be replaced by glucose, **1**, with no apparent loss of affinity.[7] In addition, activity is retained if the glucose unit of this derivative is ring-opened by reduction.[8] It is apparent that the N-acetylglucosamine unit may be acting merely as a linker and to test this hypothesis we have designed and synthesised the novel sLex analogue **3** (**Scheme 1**). The analogue **3** has reduced glycosidic character and molecular weight. Furthermore, the C_2-symmetric nature of the 2,3-butanediol linker renders **3** a potential mimic for both sLex and sLea.



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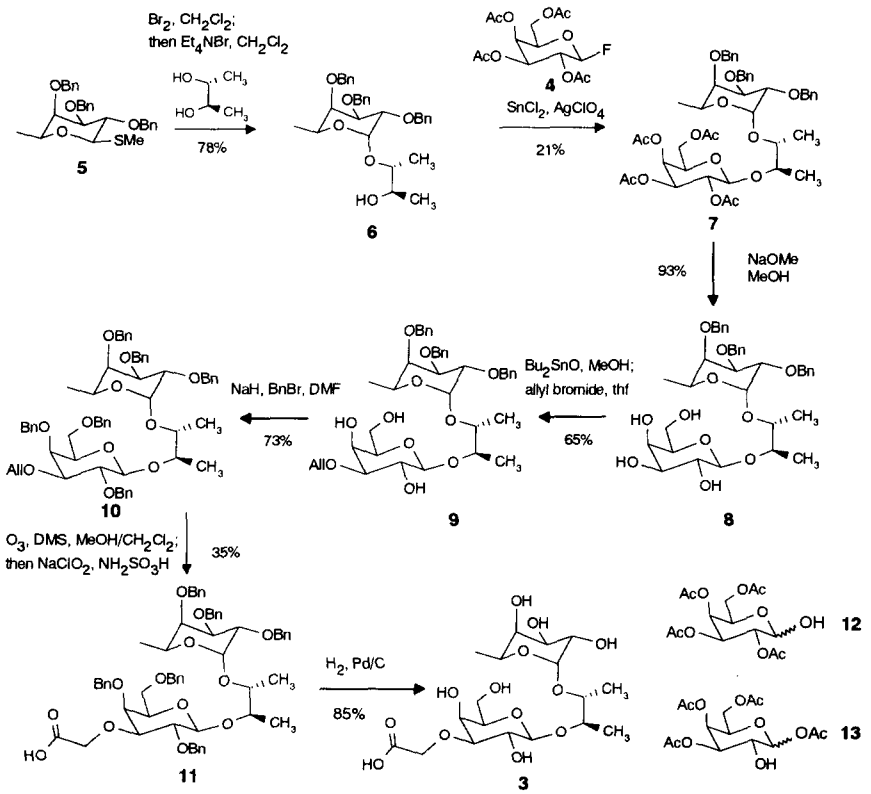
Retrosynthetic analysis of **3** furnishes a number of prospective synthetic routes. For example, an acid surrogate can be introduced into the 3-position of the galactose unit either prior to, or after, coupling to the fucose diol adduct **6**. The choice of acid surrogate will depend upon both its stability to glycosidic coupling reagents and its ease of conversion into the required acid functionality. In our initial synthetic strategy outlined in **Scheme 1** we chose to introduce an allyl group into the galactose unit as the masked acid functionality after the glycosidic coupling steps were complete. The galactose donor **4** was synthesised from β-D-galactose pentaacetate using standard literature methods.[9] In order to introduce the α-fucose unit we chose to use the well known fucose donor **5**.[7]

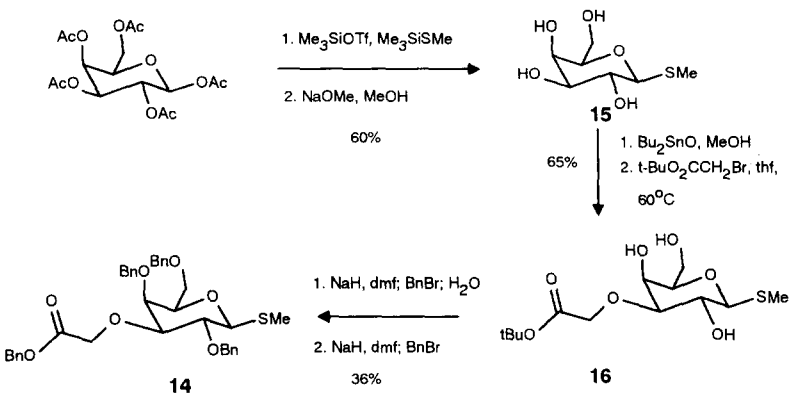


Scheme 1

The fucose donor **5** was converted into the bromide *in situ* and successfully coupled to (2R, 3R)-(-)-2,3-butanediol using a halide-catalysed glycosidation protocol[10] to give the α-fucose diol adduct **6** in 78% yield, none of the β-anomer was observed. The formation of the second glycosidic bond proved to be much more

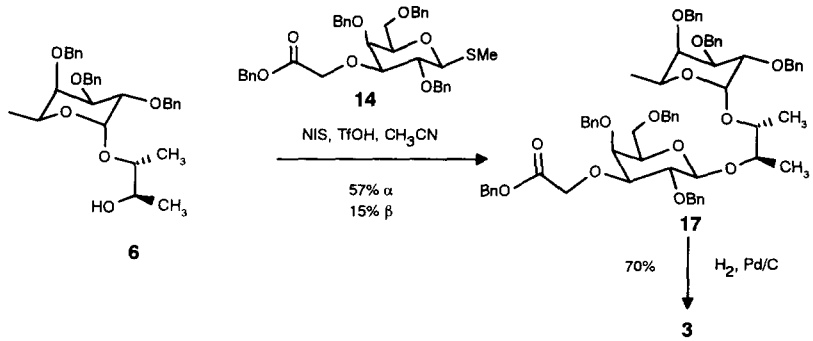
challenging. A variety of galactose donors with acetate protecting groups were used and the highest yield was obtained with the fluoride **4** using $SnCl_2/AgClO_4$ as promotor,[11] in this case a 21% yield of the β-galactoside **7** was obtained as the sole anomer. In many of the galactosylation reactions we obtained the galactose species **12** and **13** in addition to **7** and recovered fucose diol adduct **6**. Mechanistically the formation of **12** and **13** can be explained through an intermediate orthoester[12] which would be unstable to hydrolytic workup. The key step in our synthesis was the regioselective allylation of the C-3 hydroxyl group of the tetraol **8** and this was achieved using tin acetal chemistry in 65% yield.[13] The triol **9** was benzylated under standard conditions in 73% yield. We were pleased to find that the allyl group could be subsequently cleaved in two steps by ozonolysis with reductive work up followed by oxidation to give the acid **11** in 35% yield for two steps. Finally, debenzylation furnished the tetrasaccharide analogue **3** in 85% yield. Analogue **3** and all intermediates were subject to full characterisation, including elemental analysis. Although this route provides access to the target **3** it suffers from both linearity and a low yielding galactosylation reaction.

Another synthetic approach to the sLex analogue **3** would incorporate the acid surrogate into the galactose donor. The required galactose donor **14** was synthesised according to **Scheme 2** starting from β-D-galactose pentaacetate. Benzyl protecting groups were selected over acetate groups since they offer the advantage of a more reactive donor and avoid the formation of orthoesters in the glycosidation reaction. Conversion of β-D-galactose pentaacetate to the thiomethyl glycoside and subsequent Zemplen deacetylation to give **15** was achieved in high yield. The tin acetal prepared *in situ* from **15** could be selectively alkylated using a variety of electrophiles. Unfortunately, benzylbromoacetate gave low yields of alkylated product. Reaction with *tert*-butylbromoacetate gave **16** in reasonable yield. Treatment of **16** with sodium hydride and benzyl bromide followed by hydrolytic work-up alkylated the free hydroxyl groups but also surprisingly furnished the acid, which was converted into the required donor **14** in 36% yield for two steps.



Scheme 2

The fucose diol adduct **6** was successfully coupled to the galactose acid donor **14** (**Scheme 3**) using NIS/TfOH in acetonitrile solvent under conditions of kinetic control[14] to give the required β-galactoside **17** in 57% yield together with 15% of the α-anomer. Finally, deprotection of **17** furnished the required tetrasaccharide analogue **3** in 80% yield.



Scheme 3

In conclusion, we have described two synthetic routes to the novel sLex analogue **3**. Our initial route suffers from both linearity and an inefficient galactosylation procedure. In the second route a modified galactose donor is utilised which incorporates both the acid surrogate and benzyl protecting groups. The required β-galactose bond is formed using acetonitrile as solvent in the glycosidation reaction under conditions of kinetic control. The second route provides access to our required sLex analogue **3** in three steps from the requisite sugar donor units.

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