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TOWARD A TRANSITION STATE ANALOG INHIBITOR OF *N*-ACETYLGLUCOSAMINYL TRANSFERASE V

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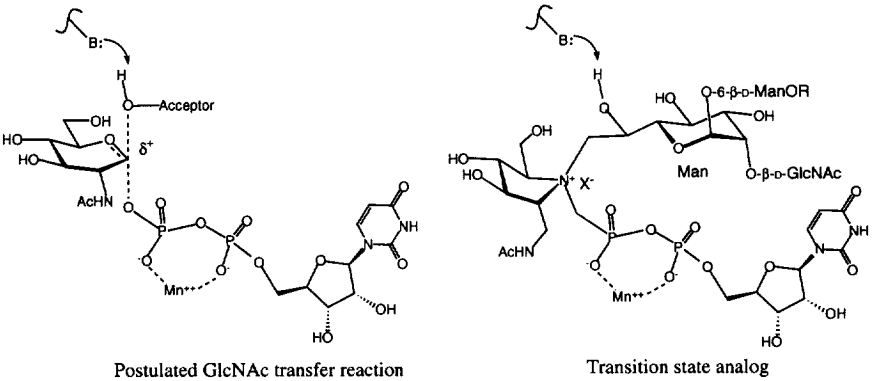
Abstract: The tumor related enzyme *N*-acetylglucosaminyltransferase V catalyzes the transfer of GlcNAc to OH-6 of branching Man to give complex oligosaccharide structures. A transition state analog inhibitor of this enzyme was designed and a model compound was synthesized to illustrate the feasibility of the synthetic strategy.

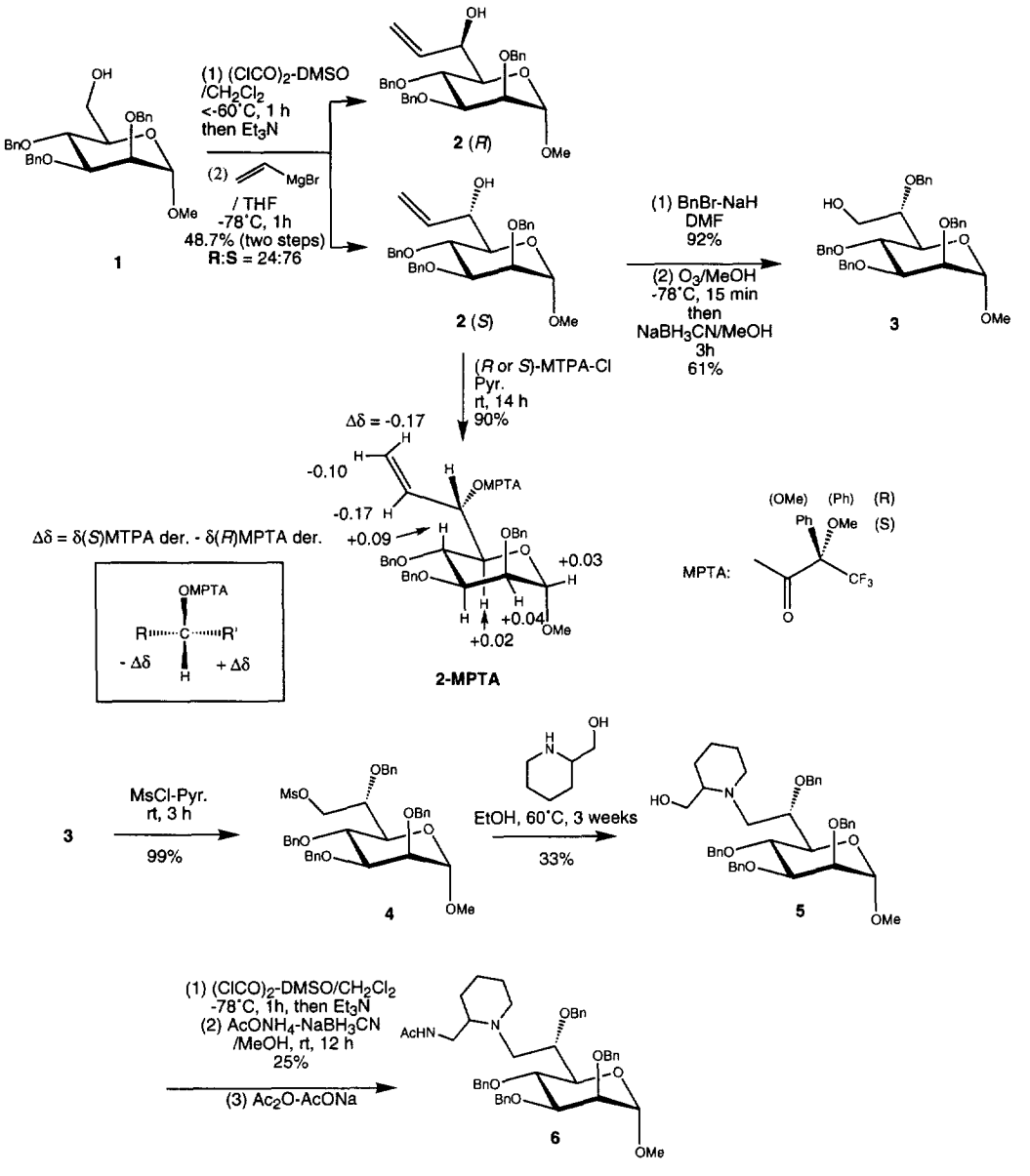
Glycosyltransferases are responsible for the biosynthesis of oligosaccharides of glycoproteins and glycolipids. Among this class of enzymes, *N*-acetylglucosaminyltransferase V (GnTase V, EC 2.4.1.155) is of particular interest as it is associated with the metastatic potential of tumor cells,[1] and inhibition of this enzyme could lead to a new cancer therapy. GnTase V catalyzes the transfer of β-GlcNAc from UDP-GlcNAc to the OH-6 of the branching Man residue in the *N*-linked oligosaccharide structure. Trisaccharide analogs in which the hydroxyl group is masked or removed have been found to have some inhibition against GnTase V with *Ki* in the 10~70 μM range.[2] To improve the inhibition potency, we have designed an inhibitor based on the postulated transition state of the enzymatic reaction (Fig. 1) and have reported the synthesis of a five-membered azasugar as a good mimic of the transition state of the *N*-acetylglucosamine moiety.[3] We have also shown that glucose could be used to replace the pyrophosphate part of the glycosyl donor.[4] In addition, an inhibitor consists of an azasugar and acceptor unit has been developed and shown to be a good inhibitor of α1,3-fucosyltransferase V.[5]



Postulated GlcNAc transfer reaction

Transition state analog

Figure 1


(1) (ClCO)2-DMSO /CH2Cl2 <-60°C, 1 h then Et3N
(2) MgBr / THF -78°C, 1h
48.7% (two steps)
R:S = 24:76
1
2 (R)
2 (S)
(1) BnBr-NaH DMF 92%
(2) O3/MeOH -78°C, 15 min then NaBH3CN/MeOH 3h 61%
3
(R or S)-MTPA-Cl Pyr. rt, 14 h 90%
Δδ = δ(S)MTPA der. - δ(R)MPTA der.
2-MPTA
MPTA:
MsCl-Pyr. rt, 3 h 99%
4
EtOH, 60°C, 3 weeks 33%
5
(1) (ClCO)2-DMSO/CH2Cl2 -78°C, 1h, then Et3N
(2) AcONH4-NaBH3CN /MeOH, rt, 12 h 25%
(3) Ac2O-AcONa
6

To establish a synthetic process for the synthesis of the designed transition state analog, we report here the synthesis of a model conjugate containing of *N*-acetamidomethylpiperidine and mannose moieties.

Swern oxidation of compound **1**,[6] which is readily prepared from methyl α-D-mannopyranoside, followed by Grignard reaction with vinyl magnesium bromide provided C-2 extended compound **2**[7] (48.7% yield from **1**). Compound **2** was found as an inisolable diastereomixture and was separated after acetylation (*R*:*S* = 24:76). The stereochemistry was determined by Mosher's method.[8] Compound **2** (*S*) was first transformed into *R*- and *S*-methyltrifluoromethylphenylacetyl (MPTA) derivatives, of which ^{1}H NMR chemical shifts were compared. The Δδ values as designated in the scheme indicated that the major component was the *S*-isomer. Benzylation and ozonolysis followed by $NaBH_3CN$ treatment gave alcohol **3** (60%). The methanesulfonyl derivative of **3** was used for the coupling reaction with hydroxylmethylpiperidine, and yielded condensate **5** in 33% after 3 weeks at 60 °C. Other attempts, such as reductive amination of the intermediate aldehyde and the SN2 reactions in the presence of NaI and that using an iodide as the leaving group, failed to give **5** or related products. Swern oxidation of **5** followed by reductive amination (25%) and *N*-acetylation gave compound **6**.

Work is in progress to use this strategy to couple an acetamidoazasugar and a trisaccharide acceptor as inhibitor of the enzyme.

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7. Selected ^{1}H NMR data for key compounds which were recorded at 270 MHz (JEOL EX-270) on solution in $CDCl_3$ (internal Me_4Si, δ 0 ppm) are given below. **2**(*S*): δ 5.99 (ddd, 1H, *J* = 17.2, 10.5, 5.1Hz, C*H*=CH_2), 5.37 (dt, 1H, *J* = 17.2, 1.6Hz, CH=C*H*$_2$), 5.20 (dt, 1H, *J* = 10.5, 1.6Hz, CH=C*H*$_2$), 4.71 (d, 1H, *J* = 1.6Hz, H-1), 4.42 (broad s, 1H, OH), 4.22 (dd, 1H, *J* = 5.1, 3.0Hz, H-6), 4.14 (t, 1H, *J* = 9.6Hz, H-4), 3.90 (dd, 1H, *J* = 9.6, 3.0Hz, H-5), 3.78 (t, 1H, *J* = 1.6Hz, H-2), and 3.56 (dd, 1H, *J* = 9.6, 1.6Hz, H-3).

4: δ 4.82 (d, 1H, J = 1.7Hz, H-1), 4.46 (dd, 1H, J = 10.2, 6.6Hz, H-7a), 4.40 (dd, 1H, J = 10.2, 5.9Hz, H-7b), 4.18 (t, 1H, J = 9.2Hz, H-4), 4.17 (m, 1H, H-6), 3.92 (dd, 1H, J = 3.0, 1.6Hz, H-2), 3.71 (dd, 1H, J = 9.2, 1.6Hz, H-5), and 2.93 (s, 3H, SO_2CH_3). **6**: δ 6.29 (broad s, 1H, NH), 4.83 (d, 1H, J = 1.9Hz, H-1), 4.14 (t, 1H, J = 9.2Hz, H-4), 3.94 (m, 1H, H-6), 3.89 (dd, 1H, J = 9.2, 3.0Hz, H-3), 3.80 (dd, 1H, J = 3.0, 1.9Hz, H-2), 3.64 (broad d, 1H, J = 9.2Hz, H-5), 3.26-3.35 (m, 2H, CH_2NHAc), 3.33 (s, 3H, OCH_3), 2.86-2.98 (m, 3H, H-6' and H-7), 2.56 (m, 1H, H-2'), 2.42 (m, 1H, H-6'), 1.68 (s, 3H, NH*Ac*), and 1.32-1.63 (m, 6H, H-3', H-4', and H-5').

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