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GLYCOSYLATION WITH HIGHLY REACTIVE GLYCOSYL DONORS: EFFICIENCY OF THE INVERSE PROCEDURE[1)]

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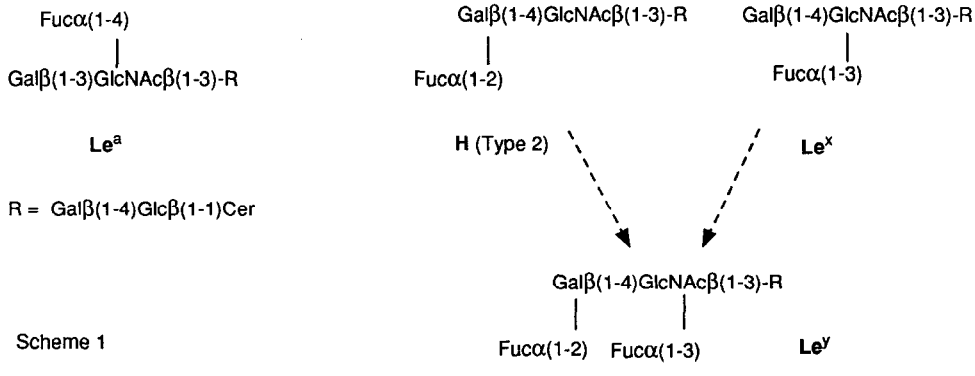
Abstract: α-Fucosylation with the reactive trichloroacetimidate **1** as donor and disaccharides **2** and **4** as acceptors led to a remarkable increase in yield under "inverse conditions", i.e. addition of the donor to an acceptor/catalyst solution. Thus, acceptor/catalyst complex formation enforcing the generation of the glycosylating species in the vicinity of the acceptor is favored yielding building blocks for antigen determinant synthesis

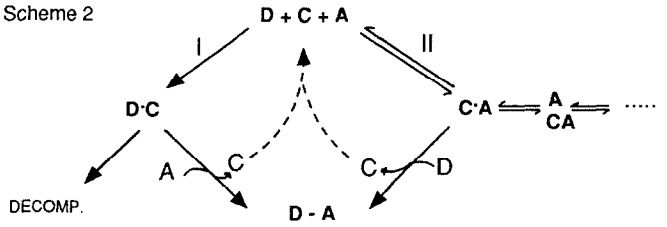
The biological importance of glycosphingolipids[2-5] has recently evoked great endeavours in chemical sphingosine and glycosphingolipid synthesis[1,4-9]. Of special interest is their function as cell-surface antigens, as for instance the Lewis antigen A-D (Le^a-Le^d) determinants or the well known H,A,B blood group determinants (see Scheme 1 for the Le^a and the H-determinant). Also glycosphingolipids which accumulate in the surface of cancer cell membranes being referred to as "tumor associated antigens" have gained great concern[5,10)]. Prominent tumor associated antigens are the Lewis antigen X (Le^x) and Y (Le^y) determinants (Scheme 1). Because most of the tumor associated blood-group glycosphingolipids were found to contain α-connected L-fucose[5], α-fucosylation constitutes an important task in glycosphingolipid synthesis.



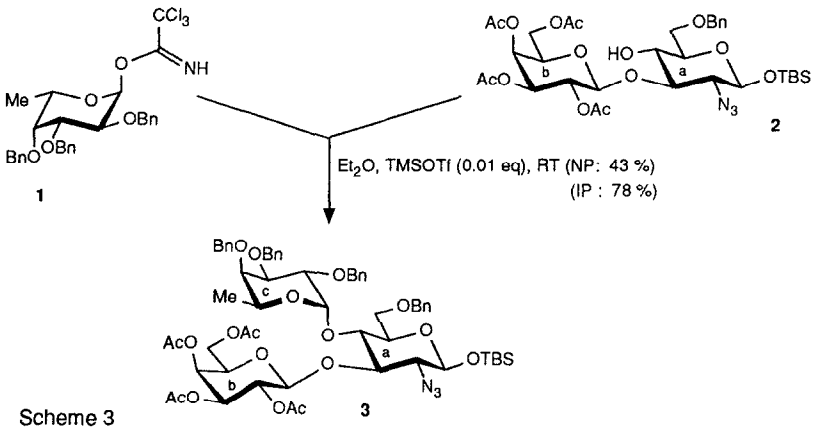
Scheme 1

Glycosylation and also fucosylation is generally carried out as formally termolecular reaction of donor (D), acceptor (A) and promotor or catalyst (C), respectively (depending on the amount required)[2,3]. Due to differences in the affinities, the reaction course is expected to be first DC interaction and then interaction of the DC-complex with A (Scheme 2, reaction course I). Obviously, for this sequence of interactions donors and acceptors are required with matching reactivities. Therefore, acceptor and donor reactivities are often varied by changing the protective group pattern and, in addition, the donor reactivity by the selection of leaving groups and catalysts[2,3]. However, this strategy is less successful for very reactive glycosyl donors which may decompose in the presence of the catalyst before awaiting reaction with the acceptor. Therefore, acceptor A complexation with the catalyst C prior to interaction with the donor D (Scheme 2, reaction course II) should overcome this problem[11].

Scheme 2



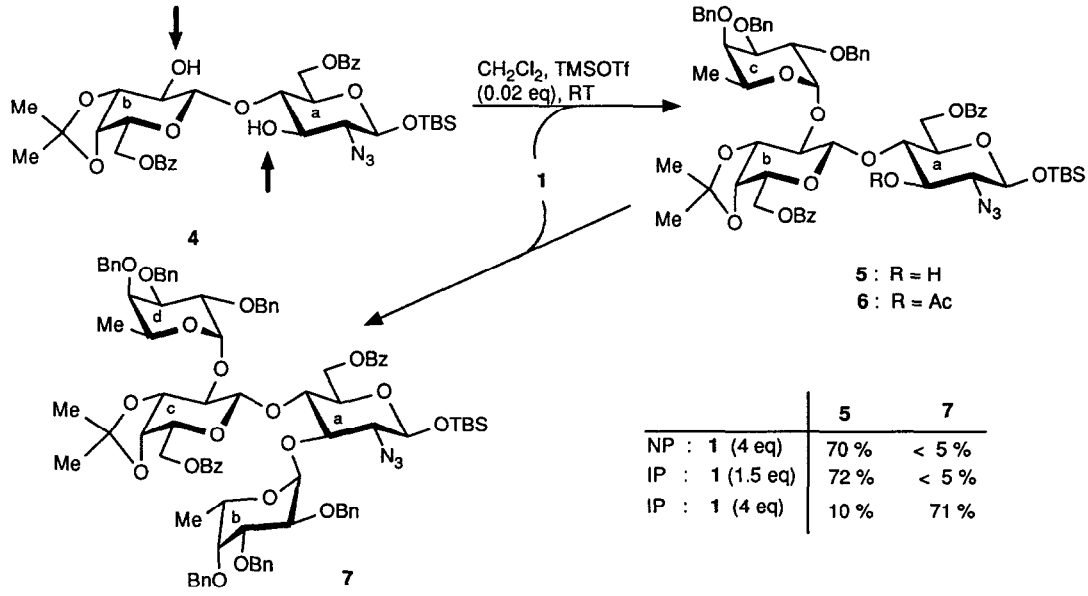
The efficiency of this approach could be proven in α-fucosylation with the highly reactive donor **1**[12] and the Galβ(1-3)GlcN and the Galβ(1-4)GlcN disaccharides **2** and **4**, respectively, as acceptors (Schemes 3 and 4). The 4a-O-unprotected disaccharide acceptor **2** was readily obtained from O-(tetra-O-acetyl-α-D-galactopyranosyl)trichloroacetimidate[13] and *tert*-butyldimethylsilyl 2-azido-6-O-benzyl-2-deoxy-β-D-glucopyranoside[14]. Attempts to carry out the fucosylation of **2** (1 eq) with donor **1** (1.5 eq) applying the normal procedure (NP), i.e. adding the catalyst trimethylsilyl trifluoromethanesulfonate (TMSOTf; 0.01 eq) to a solution of **1** and **2** in diethyl ether led to modest yields of the desired trisaccharide **3** (43 %). However, applying an inverse procedure (IP), i.e. dissolving firstly acceptor **2** (1 eq) and catalytic amounts of TMSOTf (0.01 eq) and then adding a solution of donor **1** (1.5 eq), thus enforcing reaction course II, yielded 78 % of **3** which is an important building block in Le^a synthesis[14]. The struc-



Scheme 3

ture of **3** was confirmed by the ^{1}H-NMR data[15]. Similarly, from a 3a-O-unprotected 2-azido-2-deoxy-lactose as acceptor and **1** as donor under NP-conditions a 35 % yield, however under IP-conditions an 89 % yield of an Le^x trisaccharide building block was obtained[1,16].

The 3a,2b-O-unprotected 2-azidolactose acceptor **4** exhibited even more striking results; **4** was readily obtained from *tert*-butyldimethylsilyl 2-azido-2-deoxy-β-lactoside[17] via selective 3b,4b-O-isopropylidenation and subsequent selective 6a,6b-O-benzoylation[18]. Treatment of a dichloromethane solution of acceptor **4** (1 eq) and donor **1** (4 eq) with TMSOTf (0.01 eq) under NP conditions resulted in selective formation of the H-trisaccharide precursor **5**. Neither the isomer from 3a-O attack (providing an Le^x building block) nor the Le^y derived tetrasaccharide **7** were found in appreciable amounts. Thus, by far the major part of fucosyl donor **1** was decomposed under the reaction conditions. However, carrying out the reaction under IP-conditions furnished a 71 % yield of **7** and only a small amount (10 %) of **5**. With lower amounts of donor **1** (1.5 eq) under IP-conditions highly selective formation of trisaccharide **5** (72 %) could be accomplished; unexpectedly, fucosylation in 2b-O-position of acceptor **4** is much faster than 3a-O attack. The structures of compounds **5** and **7** and the 3a-O acetylation product **6**, required for determining the regioselectivities, were assigned through their ^{1}H-NMR data[15].



	5	7
NP : 1 (4 eq)	70 %	< 5 %
IP : 1 (1.5 eq)	72 %	< 5 %
IP : 1 (4 eq)	10 %	71 %

Scheme 4

From these observations it is concluded that under IP-conditions AC-complex (or, due to the requirement of only catalytic amounts of C, AC-cluster formation) takes place first which then reacts with donor D to generate the glycosylating species in the vicinity of acceptor A (Scheme 2, II). Thus, higher product yields are obtained because the competing donor decomposition is not as effective as in reaction course I.

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