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- [14] IR (KBr): $\tilde{\nu}$ = 3432, 3067, 1697, 1626, 1543, 1498, 1476, 1452, 1386, 1278, 1114, 1088, 748, 628 cm^{-1} ; elemental analysis (%) found: C 46.12, H 4.85, N 13.22, possibly corresponding to $[\text{Cu}_6(\text{Acntb})_6](\text{ClO}_4)_6 \cdot 22\text{H}_2\text{O} \cdot 6(\text{CH}_3\text{COCH}_3)$, calcd: C 46.34, H 4.74, N 13.04.
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Toward Fully Synthetic Homogeneous Glycoproteins: A High Mannose Core Containing Glycopeptide Carrying Full H-Type 2 Human Blood Group Specificity**

Zhi-Guang Wang, Xufang Zhang, Michael Visser, David Live, Andrzej Zatorski, Ulrich Iserloh, Kenneth O. Lloyd, and Samuel J. Danishefsky*

Carbohydrate domains in the context of glycolipids and glycoproteins carry significant messages. The definition of the full scope and impact of oligosaccharide-based bioinformatics, falls within the scope of the rapidly growing field of glycobiology.^[1] The sorting out of the diverse effects of glycosylation on phenomena ranging from protein folding^[2] to cascades with a bearing on fertilization,^[3] inflammation,^[4] and metastasis,^[5] constitutes a major challenge to glycobiology.^[6] Other phenomena that are communicated in the "grammar" of carbohydrate structure include aberrant glycosylation patterns, associated with tumorigenesis, and blood typing.^[7] The most widely known of the carbohydrate-centered serology systems, the ABO classification, is based on structural patterns of cell-surface glycoproteins on erythrocytes.^[8]

From the perspective of chemistry, one of the issues complicating molecular level understanding of the consequences of glycoarchitecture is the phenomenon of heterogeneity. While the various carbohydrate domains present on a glycoprotein may be isolated and purified, this tends to be feasible only after detachment of the oligosaccharide ensemble from its macromolecular setting. One method for dealing with the issue of the inhomogeneity of glycoproteins is through synthesis—either chemical, enzymatic, or a combination of both.^[9]

A long-term goal of our laboratory has been the development of methodology and strategies which would enable the synthesis of complex oligosaccharides bearing the inherent information in a context that simulates the natural glycoprotein setting. As will be shown below, advances in the field are

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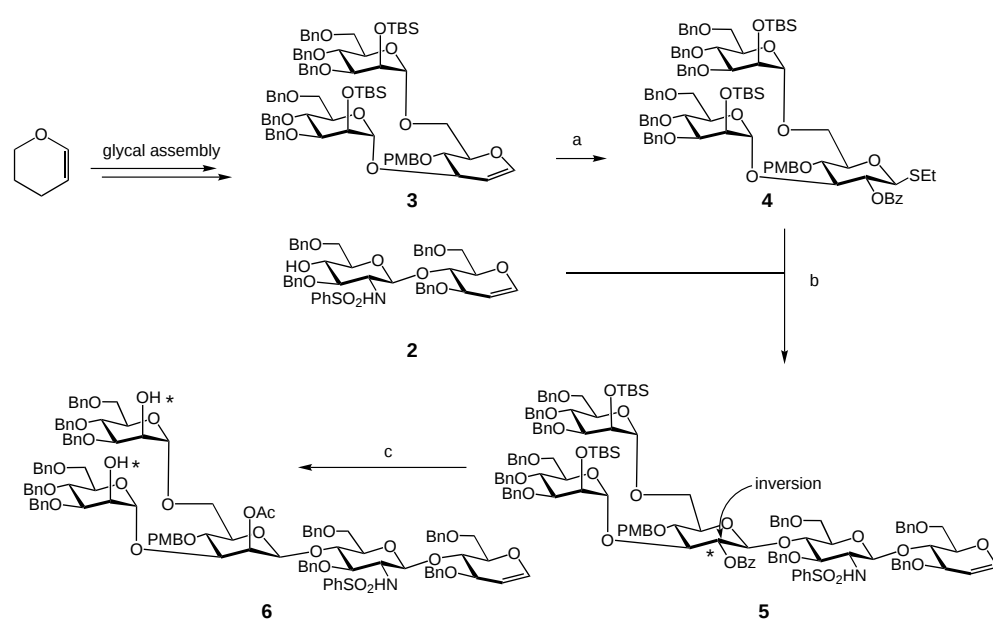
[**] This work was supported by the National Institutes of Health (Grant nos.: HL-25848 and CA-28824 (to S.J.D.), and CA-710506 (to K.O.L.)). Postdoctoral fellowship support is gratefully acknowledged by Z.-G.W. (US Army breast cancer grant no.: DAMD17-97-1-7119) and M.V. (NIH grant no.: CA-62948-04). We gratefully acknowledge Dr. George Sukenick of the Sloan–Kettering Institute's NMR core facility for mass spectral and NMR spectroscopic analyses (SKI core grant no.: CA-08748).

such that a construction is now possible. Our specific focus in this project was a maximally convergent, stereospecific synthesis of a homogeneous *N*-acetyllactosamine glycopeptide bearing an *N*-linked bidomainal high-mannose core, connected through lactosamine spacers to sectors carrying the carbohydrate-encoded information.^[10] For this demonstration, we focused on the total synthesis of a glycopeptide construct that presents human H-type2 specificity in a naturally occurring, glycan-like setting. Herein, we describe a solution to this problem in the context of the synthesis of **1** (see Scheme 5).

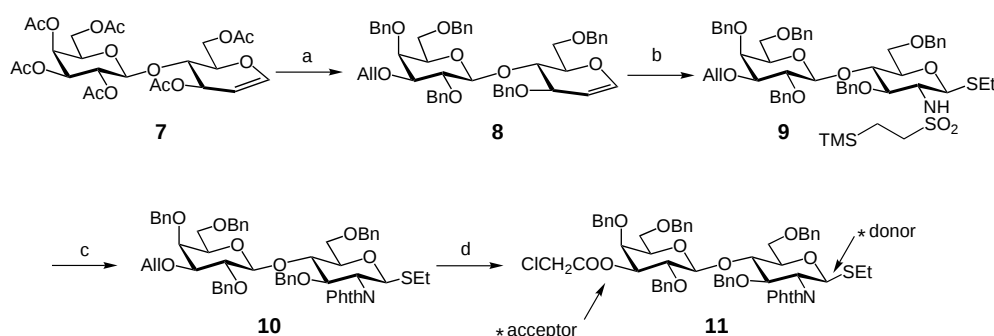
Glycal assembly logic had been used for the large-scale syntheses of **2** and **3** (Scheme 1).^[11, 12] Unfortunately, coupling of **2** with the glycal epoxide directly available from **3** occurs, at best, in poor yield. A body of chemistry to deal with just such a contingency had been developed (see **3** → **4** → **5**).^[13] System **5** had been organized such that a C-2 hydroxyl group in the C ring (see asterisk in **5**) could be exposed from a unique benzoate. Epimerization of the resultant alcohol (by oxidation/reduction),^[14] followed by acetylation at C-2 and deprotection of the unique ring D and ring E silyl ethers, gave rise to **6** with defined acceptor sites at the two "wing" mannose units (see asterisks in **6**).

We next concerned ourselves with fashioning the lactosamine spacer region, which characteristically intervenes between the bifurcated high mannose core sector and the bioinformation domains. For the purposes of this work, we focused on interpolation of an acetyllactosamine element on each wing of the mannose sector. Herein, we use the two-directional mannose building block **11** (see Scheme 2) as a single insertion unit in the two branching domains. However, the chemistry described here could be extended to the building of longer spacer sectors by controlled homocoupling of **11**.

Our synthesis of **11** commenced with peracetylated lactal **7**. This was converted into **8**, which bears a unique allyl protecting group at C-3' (Scheme 2).^[15] Following chemistry that we had developed with this type of application on the



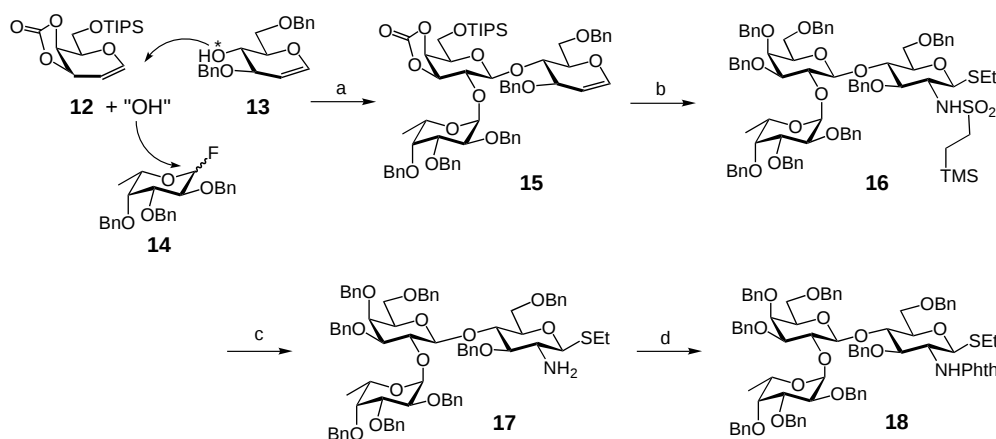
Scheme 1. Synthesis of core pentasaccharide **6**. a) 1. DMDO/CH₂Cl₂; 2. EtSH/TFA/CH₂Cl₂, 75 % (two steps); 3. BzCl/Py/DMAP, 90 %; b) MeOTf/CH₂Cl₂/DTBP, 75 %; c) 1. LiAlH₄/THF/−20 °C → 0 °C; 2. Dess–Martin periodinane/CH₂Cl₂/22 °C; 3. L-selectride/THF/22 °C; 4. Ac₂O/Py/DMAP/CH₂Cl₂, 82 % (four steps); 5. TBAF/THF, 77 %. Bn = benzyl, Bz = benzoyl, DMAP = 4-dimethylaminopyridine, DMDO = dimethyl dioxirane, DTBP = 2,6-di-*tert*-butylpyridine, PMB = *para*-methoxybenzyl, Py = pyridine, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, Tf = triflate = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.



Scheme 2. Synthesis of lactosamine building block **11**. a) 1. NH₃/MeOH; 2. Bu₂SnO/C₆H₆; 3. allyl bromide/Bu₄NBr; 4. BnBr/NaH/DMF, 50 % (four steps); b) 1. IDCP/TMSCH₂CH₂SO₂NH₂, 83 %; 2. EtSH/LiHMDS/DMF, 85 %; c) 1. CsF/DMF, 90 °C, 94 %; 2. phthalic anhydride/Py/22 °C; 3. Piv₂O, then Ac₂O, 100 % (two steps); d) 1. Ph₃RuCl/DABCO/THF; 1N HCl, 74 %; 2. (ClCH₂CO)₂O, DMAP/DTBP, 97 %. All = allyl, DABCO = 1,4-diazabicyclo[2.2.2]octane, DMF = dimethylformamide, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, IDCP = iodonium dicollidine perchlorate, Phth = phthaloyl, Piv = pivaloyl, TMS = trimethylsilyl.

horizon, *trans* diaxial addition of iodonium 2-(trimethylsilyl)ethanesulfonamide (SES) to the glycal double bond was followed by thiolysis, which triggered migration of the sulfonamide from C-1 → C-2 with concurrent ejection of iodide from C-2 to form **9**.^[16] Deprotection of the nitrogen and phthaloylation^[17] (to form **10**), followed by deallylation and reprotection at C-3, afforded **11**, which was equipped with activatable donor and acceptor sites (marked by asterisks in Scheme 2).

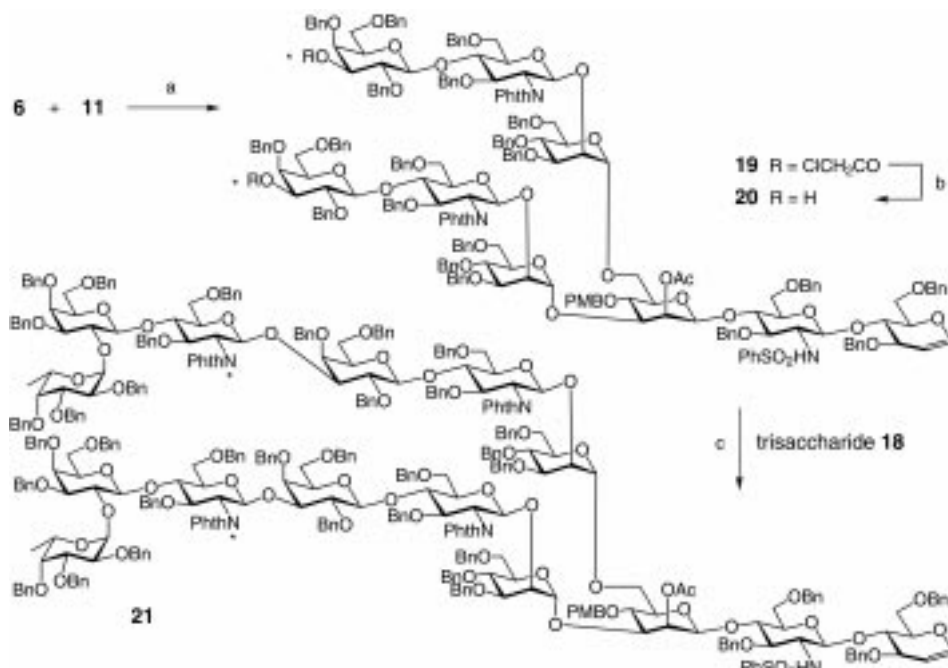
A concise fashioning of the H-type antigen is shown in Scheme 3. The galactal donor system **12** was actuated by strict α -face epoxidation. The α -epoxide coupled to **13**, notwithstanding the hindered nature of its acceptor site (marked with an asterisk). The C-2' alcohol specifically unveiled in the coupling step serves as the acceptor site for the L-fucosyl



Scheme 3. Synthesis of "wing" trisaccharide **18**: a) 1. DMDO/CH₂Cl₂; 2. ZnCl₂; 3. SnCl₄/AgOTf/DTBP/CH₂Cl₂, 50 % (three steps); b) 1. TBAF/THF; 2. BnBr/NaH/DMF, 81 % (two steps); 3. IDCP/TMSCH₂CH₂SO₂NH₂; 4. EtSLi/DMF/−40 °C–0 °C, 75 % (two steps); c) CsF/DMF/100 °C, 5 days, 65 %; d) 1. phthalic anhydride/Py/22 °C; 2. Ac₂O, 97 % (two steps). TIPS = triisopropylsilyl.

donor **14**. This glycosylation leads to the α -L-fucoside **15**. The glycal found in **15** was advanced to **18** (through **16** and **17**) with chemistry previously developed on simple systems with such applications in mind.

We next turned to the assembly of these carefully crafted subunits. The program commenced with twofold coupling of **6** with **11** (Scheme 4). Fortunately, this goal could be accomplished in good yield to produce the 9-mer **19** through an apparently stereospecific sulfonamidoglycosylation reaction, modulated by the neighboring phthalamido linkages.^[18] The two positionally defined acceptor sites (marked with asterisks) of the nonasaccharide were unveiled as shown. Fortunately, coupling of **20** with H-type donor **18** occurs at each of the lactosamine moieties, again under mediation by methyl triflate, to afford 15-mer glycal **21**.



Scheme 4. Synthesis of the protected 15-mer glycal **21**. a) MeOTf/CH₂Cl₂/Et₂O/DTBP, 62 %; b) (NH₄)₂C=S/EtOH/NaHCO₃, 99 %; c) trisaccharide **18**/MeOTf/CH₂Cl₂/Et₂O/DTBP, 78 %.

Much planning and trial and error research went into accomplishing the global deprotection of the 15-mer (Scheme 5). The four phthaloyl groups of **21**, as well as the hindered acetate on the C ring, were deprotected concurrently. We next carried out the iodosulfonamidation of the glycal linkage at the reducing end of the 15-mer. This addition was followed by hydrolytic rearrangement (a four-step sequence). The critical massive deprotection step could now be realized. Thus, 37 benzyl groups and the sulfonamido function were all reductively cleaved through the agency of sodium/

ammonia.^[19] Remarkably, the terminal hemiacetal linkage was sufficiently robust such that there was no detectable reduction to an alditol under these conditions. Furthermore, selective acetylation of the lone amino function in the A ring was readily achieved in the polyhydroxyl substrate system. This remarkable sequence led to the free hemiacetal **22**, which was, in turn, converted into **23** by ammonolysis of the masked aldehyde.^[20] In the concluding step, the polyhydroxyl glycosylamine **23** coupled with differentiated pentapeptide **24** to produce the desired β -glycosyl N-linked glycopeptide target system **1** (m/z : calcd 3305 [M^+]; found 3328 [$M+Na$]).^[21]

While the yield of this compound may appear modest, detailed NMR spectroscopic analysis fully corroborates that compound **1** meets the standard of homogeneity while displaying its H-type2 serological determinant in the context

of an N-acetyllactosamine glycopeptide. The availability of such an advanced N-linked glycopeptide provides excellent opportunities for probing glycoarchitecture and its biological consequences. As seen in Figure 1, the ¹H NMR spectrum (800 MHz) of the 15-mer oligosaccharide system linked to the 5-mer peptide is extremely well resolved and suggestive of structural order. Detailed analysis of mutual conformational effects between the oligosaccharide and peptide domains using high level NMR spectroscopic techniques will be reported separately.

In addition to the critical nuclear magnetic resonance spectroscopic and mass spectrometric measurements that support our structural claim on behalf of compound **1**, it was



methyluronium hexafluorophosphate, HOBt = 1-hydroxy-1*H*-benzotriazole, Man = mannose.

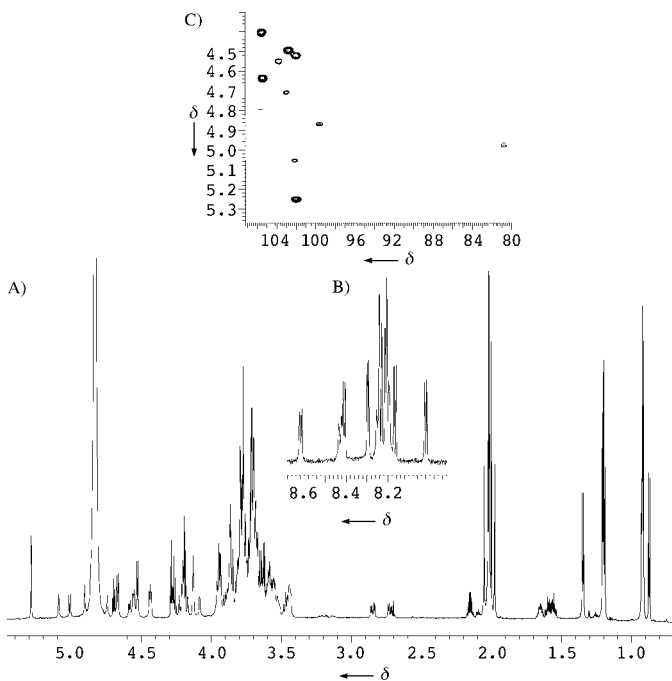


Figure 1. A) ^1H NMR (800 MHz) spectrum of **1** in D_2O at 20°C and pH 3.7 (phosphate buffer). B) Section of the spectrum of **1** in H_2O at 5°C and pH 3.7 (phosphate buffer) showing the secondary NH signals of amides from the peptide backbone, side chain, and GlcNAc sites. C) The anomeric region of the ^1H - ^{13}C HMQC spectrum at 800 MHz of **1** in D_2O at 20°C and pH 3.7 (phosphate buffer).

of interest to establish that the H-type constructs, so presented, maintain functionality. Indeed, the presence of operational H-type2 blood group determinants in the synthesized product was confirmed by demonstrating its reactivity with an antibody against H-type2 determinants (mAbSA) in an enzyme-linked immunosorbent assay (ELISA; Figure 2). This antibody is highly specific for H-type2 blood group determinants and does not react with H-type1, Le^a, or Le^x structures.^[22, 23]

This synthesis serves to illustrate the current reach of the glycal assembly method. More broadly it shows the extra-

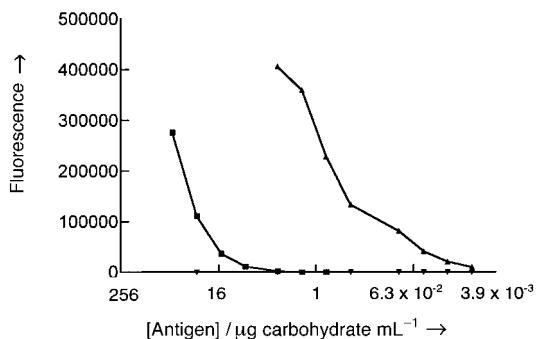


Figure 2. Reactivity of glycopeptide **1** (■), H-type2 active mucin (▲) as a positive control, and Le^x/Le^a-active mucin (▼) as a negative control with the antibody against H-type2 determinants (mAbSA) as determined with an ELISA. The mucin preparations have been previously described (see ref. [22]).

ordinary progress in the field of oligosaccharide and glycopeptide synthesis. Given the extendibility of this chemistry to virtually any type of saccharide presentation and the capacity, in principle, for ligation of the pentapeptide construct to larger polypeptide or protein domains,^[24] the synthesis of sequence-defined homogeneous glycopeptides, and thence glycoproteins, is at hand. Studies directed toward reaching fully functional glycoproteins by total synthesis are underway.

Received: January 22, 2001 [Z16470]

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Enhanced Physical Properties in a Pentacene Polymorph

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Pentacene is a highly promising material for application in thin film transistor devices because of its recently reported high mobilities and good semiconducting behavior.^[1] For this reason, we have carried out a program to grow single crystals of unusually high purity and crystalline perfection to study the intrinsic properties of organic semiconductors. We have produced millimeter-sized crystals with electrically active impurities at concentrations of the order of 10¹³ cm⁻³ (or one impurity molecule per 10⁸ pentacene molecules) by using a vapor-phase deposition technique. Such crystals were used for

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