Glycoconjugate J (1984) 1: 5—8

Synthesis of M and N Active Glycopeptides. Part of the N-Terminal Region of Human Glycophorin A

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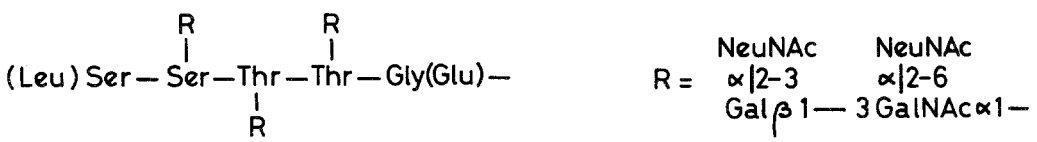
Received January 9, 1984.

The synthesis of two series of glycopeptides, part of the N-terminal region of human glycophorin A, was accomplished starting from derivatives of *O*-β-D-galactopyranosyl-(1-3)-*O*-(2-acetamido-2-deoxy-α-D-galactopyranosyl)-L-serine and -L-threonine.

The amino-terminal portion of glycophorin A, the major glycoprotein of the human red cell membrane [1], which is known to carry M and N blood group specificities, has the following primary structure [2]:



Two characteristic features are associated with this structure: the existence of an amino-acid polymorphism [3-5] (Ser/Leu and Gly/Glu) and the presence of clusters of *O*-glycosylic chains located at vicinal amino acid residues of the peptide chain.

Despite considerable investigation, the structure of the human M and N blood group antigenic determinants is still an open problem [6]. The NH_2-terminal amino acid residue is now considered to be responsible for the difference between the M (Serine) and N (Leucine) specificities [7], but the exact role of the clustered carbohydrate chains, together with the direct involvement of sialic acid residues are controversial [8]. As stated by Lisowska [6], we think that these questions "could be answered if model glycopeptides with controlled variations in the structure were available". Therefore, we would like to report the first chemical synthesis of such glycopeptides.

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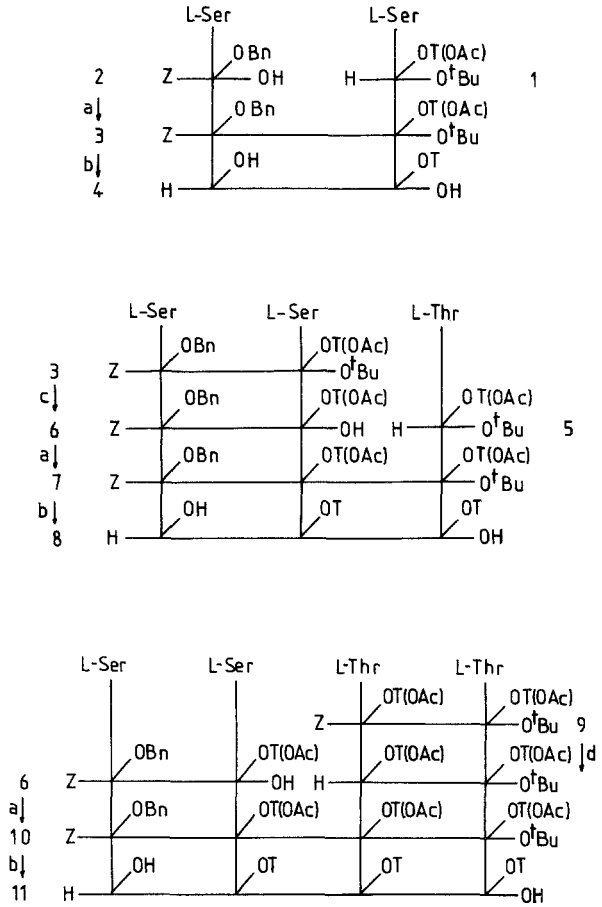
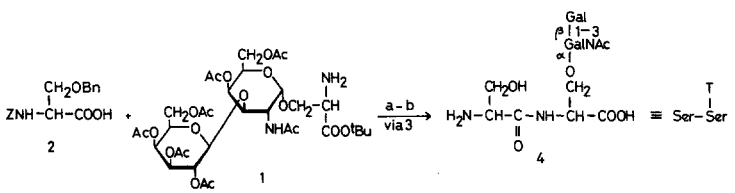


Figure 1. The synthesis of three "M-series" glycopeptides. Reagents [9, 10]: a) EEDQ, dichloromethane; b) (1) MeOH-Et_3, (2) CF_3COOH, (3) H_2 10% Pd/C; c) CF_3COOH; d) 10% Pd/C, cyclohexene-EtOH (1:2).

The compact representation used in Figs. 1 and 2 is classical in the field of peptide synthesis. It has also been used in references 9 and 10 dealing with similar problems. For instance, the upper part of Fig. 1 has the following meaning:



Abbreviations used: Z, benzyloxycarbonyl; Bn, benzyl; ^{t}Bu, tertio butyl; EEDQ, 2-ethoxy-*N*-(ethoxycarbonyl)-1,2-dihydroquinoline.

Fig. 1 illustrates the synthesis of three glycopeptides of the "M-series" — serine being the NH_2-terminal amino acid residue. In this figure, T is the disaccharide Galβ1-3GalNAcα-. During this work, it was found that the activation of the carboxylic group of a peptide with 'clustered' oligosaccharides was not possible, so that the glycopentapeptide (**19**) was synthesized as shown in Fig. 2.

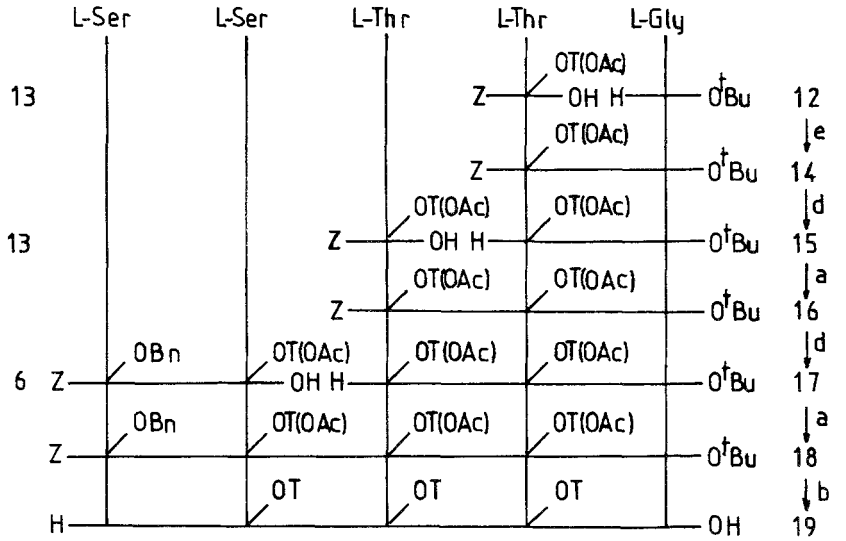


Figure 2. Synthesis of a glycopentapeptide. Reagents: (a-d) see Fig. 1; e) Morpholinethyl isocyanate, dichloromethane.

The following glycopeptides of the "N-series" were synthesized along the same lines:

(20) Leu-Ser(T)

(21) Leu-Ser(T)-Thr(T)

(22) Leu-Ser(T)-Thr(T)-Thr(T)

(23) Leu-Ser(T)-Thr(T)-Thr(T)-Glu

Although inhibition studies will be reported elsewhere, it is appropriate to mention here two results obtained with these synthetic glycopeptides, which may open up unexpected new vistas in the field: (**8**) caused inhibition of a human anti-M (2070170, South Florida Blood Service), whereas (**21**) failed to inhibit. On the other hand, both (**8**) and (**21**) caused inhibition of a human anti-N antibody (Queenan, South Florida Blood Service). These results suggest that sialic acid, although essential, in some cases is not part of the antigenic site of M and N substances, and that, although NH_2-terminal serine is probably part of the antigenic determinant of the M blood group substances, the same is not true for NH_2-terminal leucine, in the case of the N blood group substance.

Acknowledgements

We thank the Institute de la Santé et de la Recherche Médicale (C.R.L. No. 82 0127) for financial support, the Ministère des Relations Extérieures for a fellowship to one of us (VVB), Jacques Esnault for technical assistance, and Dr. Peter D. Issitt, South Florida Blood Service, for inhibition studies.

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