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Preliminary communication

The synthesis of derivatives of *O*-β-D-galactopyranosyl-(1→3)-*O*-(2-acetamido-2-deoxy-α-D-galactopyranosyl)-L-serine and -L-threonine

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The MN blood-group antigenic determinants are located[1,2] on an *N*-terminal octaglycopeptide of glycophorin A, a major protein of the human erythrocyte membrane[3]. Evidence is accumulating that the structural difference between the M and N antigens is represented by two amino acid polymorphisms at the first and fifth positions of this protein[4]. Also, considerable interest has been focused on the MN blood-group system, because one of its precursor substances, the T antigen, is expressed on malignant, but not on benign or normal, breast glandular tissue[5].

In order to elucidate the character and size of the M, N, and T specific immunodeterminants, we have launched a programme on the chemical synthesis of various model glycopeptides. One aim of this work is to study the influence of the "density" of carbohydrate haptens on a peptide backbone on the specificity of the corresponding antibodies or lectins. We now report the chemical synthesis of *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-4,6-di-*O*-acetyl-2-deoxy-α-D-galactopyranosyl)-*N*-(benzyloxycarbonyl)-L-serine *tert*-butyl ester (**9**) and *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-4,6-di-*O*-acetyl-2-deoxy-α-D-galactopyranosyl)-*N*-(benzyloxycarbonyl)-L-threonine *tert*-butyl ester (**11**), which are versatile monomeric units for subsequent syntheses of glycopeptides required to study the molecular basis of the expression of the T-antigen.

Treatment of benzyl 2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside[6] with tetra-*O*-acetyl-α-D-galactopyranosyl bromide [$Hg(CN)_2$, acetonitrile, room temperature, 24h] gave benzyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside** (**1**, 70%), m.p. 206° (from methanol), $[\alpha]_D$ −6°. Removal (aqueous 70% acetic acid, 90°, 2 h) of the benzylidene group from **1** afforded the diol **2**, m.p. 210–211° (from methanol), $[\alpha]_D$ −23°, which was acetylated (Ac_2O, pyridine) to give **3**, m.p. 108–109° (from methanol), $[\alpha]_D$ −17.5°. ^{13}C-N.m.r. data ($CDCl_3$): δ 100.0

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**Satisfactory elemental analyses and n.m.r. data were obtained for all intermediates and products. Optical rotations were measured for solutions in chloroform at 20°.

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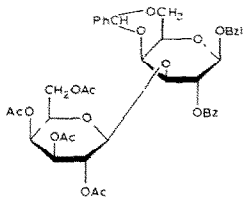
(C-1′β), 98.6 (C-1β). Catalytic hydrogenolysis (10% Pd/C, methanol–ethyl acetate, 24 h) of 3 followed by acetylation (Ac_2O–pyridine) gave **4** (92% from 1), m.p. 160–161° (from ethanol), $[\alpha]_D$ −53°. ^{1}H-N.m.r. data ($CDCl_3$): δ 4.59 (d, 1 H, $J_{1',2'}$ 8.5 Hz, H-1′).



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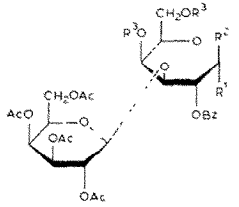
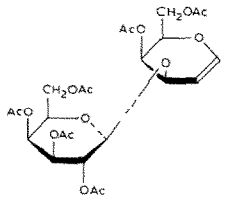


2 $R^1 = R^3 = H$, $R^2 = OBzl$
3 $R^1 = H$, $R^2 = OBzl$, $R^3 = Ac$
4 $R^1 = OAc$, $R^2 = H$, $R^3 = Ac$
5 $R^1 = Br$, $R^2 = H$, $R^3 = Ac$



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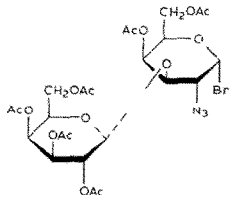

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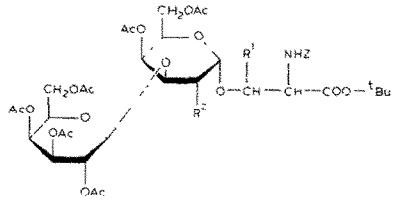

8 $R^1 = H$, $R^2 = N_3$
9 $R^1 = H$, $R^2 = NHAc$
10 $R^1 = Me$, $R^2 = N_3$
11 $R^1 = Me$, $R^2 = NHAc$

The glycosyl bromide **5** (87%), $[\alpha]_D$ +103°, was then prepared (HBr–acetic acid, 0°, 1 h) from **4** and transformed (Zn–acetic acid, 0°, 4 h) into the glycal **6** (92%), $[\alpha]_D$ −3°. ^{1}H-N.m.r. data ($CDCl_3$): δ 6.39 (d, 1 H, $J_{1,2}$ 6.6 Hz, H-1). Application of the well-established azidonitration–bromination sequence[7] to **6** gave the azido bromide **7** (41%), $[\alpha]_D$ +81°. ^{1}H-N.m.r. data ($CDCl_3$): δ 6.49 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1).

Condensation of **7** (silver triflate, dichloromethane, −60° → 20°) with the *tert*-butyl ester of *N*-(benzyloxycarbonyl)-L-serine[8] gave **8** (61%), together with some β isomer (11%). Reduction ($NaBH_4$, $NiCl_2$, methanol) of **8** followed by acetylation (Ac_2O–methanol) gave **9** (83%), $[\alpha]_D$ +57.5°. ^{1}H-N.m.r. data ($CDCl_3$, 400 MHz): δ 7.34 (s, 5 H, Ph), 5.77 (d, 1 H, $J_{2,NH}$ 9 Hz, N*H*Ac), 5.63 (d, 1 H, NH), 5.34 (d, 2 H, H-4,4′), 5.12 (m, 3 H, C*H*$_2$Ph) and H-2′), 4.95 (q, 1 H, H-3′), 4.87 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.58 (d, 1 H, $J_{1',2'}$ 7.6 Hz, H-1′), 4.50 (m, 1 H, $J_{1,2}$ 3.6, $J_{2,3}$ 11 Hz, H-2), 1.95–2.20 (7 s, 18 H, 6 Ac), and 1.50 (s, 9 H, ^{t}Bu).

Condensation of **7** with the *tert*-butyl ester of *N*-(benzyloxycarbonyl)-L-threonine[8] gave exclusively the α-compound **10** (54%), $[\alpha]_D$ +58°, which was then transformed into **11** (80%), $[\alpha]_D$ +55°. ^{1}H-N.m.r. data ($CDCl_3$. 400 MHz): δ 7.36 (s, 5 H, Ph), 5.87 (d, 1 H, $J_{2,NH}$ 8 Hz, N*H*Ac), 5.48 (d, 1 H, NH), 5.33 (d, 2 H, H-4,4′), 5.13 (m, 3 H, C*H*$_2$Ph and H-2′), 4.91 (q, 1 H, H-3′), 4.80 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.55 (d, 1 H, $J_{1',2'}$ 8 Hz, H-1′), 4.53 (m, 1 H, H-2), 1.95–2.16 (7 s, 21 H, 7 Ac), 1.46 (s, 9 H, ^{t}Bu), and 1.35 (d, 3 H, Me).

The salient features of this work are the availability of the bromide **7**, which is a good chemical precursor of various T-antigen-containing structures, and the derivatives **9** and **11**, which are useful building units for the synthesis of various glycopeptides having potential T-activity. The preparation of such glycopeptides will be reported elsewhere.

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REFERENCES

1 W. Dahr and G. Uhlenbruck, *Hoppe-Seyler's Z. Physiol. Chem.*, 359 (1978) 835–843.
2 E. Lisowska and K. Waśniowska, *Eur. J. Biochem.*, 88 (1978) 247–252.
3 M. Tomita and V. T. Marchesi, *Proc. Natl. Acad. Sci. U.S.A.*, 72 (1975) 2964–2968.
4 O. O. Blumenfeld and A. M. Adamany, *Proc. Natl. Acad. Sci. U.S.A.*, 75 (1978) 2727–2731; W. Dahr, *Blood Transfusion Immunohaematol.*, 24 (1981) 85–95, and references therein.
5 G. F. Springer, P. R. Desai, and E. I. Banatwala, *J. Natl. Cancer Inst.*, 54 (1975) 335–339; G. F. Springer, P. R. Desai, M. S. Murthy, H. J. Yang, and E. F. Scanlon, *Transfusion (Philadelphia)*, 19 (1979) 233–249.
6 G. F. J. Chittenden and J. G. Buchanan, *Carbohydr. Res.*, 11 (1969) 379–385.
7 R. U. Lemieux and R. M. Ratcliffe, *Can. J. Chem.*, 57 (1979) 1244–1251.
8 H. Kinoshita, H. Ishikawa, and H. Kotake, *Bull. Chem. Soc. Jpn.*, 52 (1979) 3111–3112.