Chemical Synthesis of 2-*O*-(α-L-Fucopyranosyl)-3-*O*-(2-acetamido-2-deoxy-α-D-galactopyranosyl)-D-galactose, the Terminal Structure in the Blood-group A Antigenic Determinant

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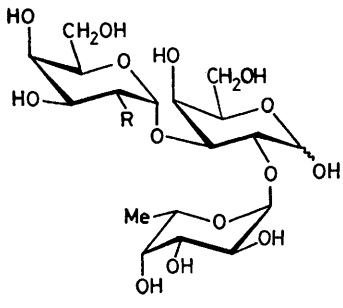
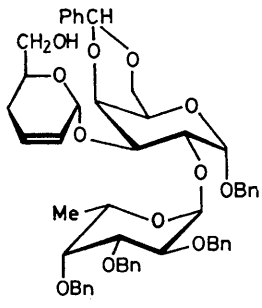
Summary The trisaccharide (**1**), the terminal structure in the blood-group A antigenic determinant, has been prepared from the trisaccharide (**4**) which was obtained from the product of a cycloaddition and seems to be a suitable precursor for synthesis of modified A and B blood-group antigens.

BLOOD-GROUP antigens from erythrocytes membranes are glycolipids which carry the A-, B-, H-, and Le-determinants on the outer part of their oligosaccharide chains. The terminal structures of the A and B antigens, the trisaccharides (**1**) and (**2**), differ only at C-2 of one of the non-reducing units.[1] The MeCO group in the trisaccharide (**1**) seems most important in this connection since treatment of normal A_1 erythrocytes with a bacterial *N*-acetylgalactosamine deacetylase leads to a pH-dependent B specificity, probably due to structure (**3**).[2] It was thus of interest to test modified A(B) trisaccharides as inhibitors in these systems,

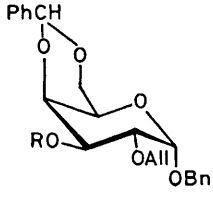
and we have prepared as precursor for such syntheses the trisaccharide (**4**), the usefulness of which is demonstrated by its conversion into the A determinant (**1**). We are not aware of any published synthesis of (**1**), but a preparation by coupling of a 2-azido-2-deoxy derivative[3] has been disclosed at a meeting.[4]



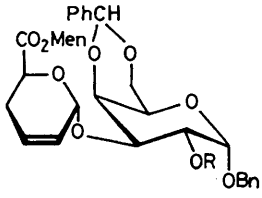
(1) R = NHAc
(2) R = OH
(3) R = NH_2



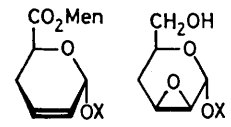
(4)



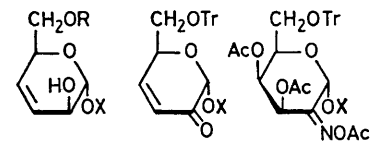
(5) R = H
(6) R = *trans*-CH=CHC≡CH
(7) R = *trans*-CH=CHCH=CH_2



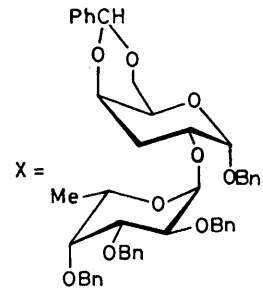
(8) R = Allyl
(9) R = H



(10) (11)



(12) R = H (14) (15)
(13) R = Trityl



Bn = benzyl; Men = (−)-menthyl; All = allyl; Tr = trityl.

Acetal formation (PhCHO, $ZnCl_2$) with benzyl 2-*O*-allyl-α-D-galactopyranoside[5] gave the starting material, benzyl 2-*O*-allyl-4,6-*O*-benzylidene-α-D-galactopyranoside (**5**) (86%) [m.p. 116 °C (from ether–light petroleum); α_D^{20} + 141°].† From the alcohol (**5**), by repetition of the described reaction sequence[6] were prepared in succession the *trans* enynyl ether (**6**) (36%)‡ [eluent, chloroform–ether–light petroleum (1:4:5); m.p. 126 °C (from ether–light petroleum; α_D^{20} +211°), the *trans* dienyl ether (**7**) (90%) [eluent, ether–light petroleum (1:1); oil; α_D^{20} + 195°], and then after cycloaddition with (−)-menthyl glyoxylate, a mixture of dihydropyrans (85%). Isomerization (0·1 ml of BF_3–Et_2O in 20 ml of ether per g of mixture) gave the 'α-D' compound (**8**) (43%) [eluent, toluene–ether–light petroleum (80:20:15) oil; α_D^{20} + 57°] the configuration of which was ascertained by the described procedure.[6] The allyl group was removed[7] and the resulting disaccharide (**9**) (62%) [eluent, ether–light petroleum (1:1); m.p. 137 °C; α_D^{20} + 64°] was fucosylated on its free OH by the common-ion procedure.[8] The protected trisaccharide (**10**) (85%) [eluent, toluene–ether–light petroleum (8:2:3); oil, α_D^{20} −41°] was reduced with $LiAlH_4$ to the primary alcohol (**4**) (90%) [eluent, ether–light petroleum (4:1); m.p. 140 °C (from ether–light petroleum; α_D^{20} + 15·6°].

The trisaccharide (**4**), which can be readily prepared in 10 g amounts, is a convenient precursor for the synthesis of modified A, B determinants. Extension of known procedures[9,10] gave the D-*lyxo* epoxide (**11**) (74%) (eluent, ether; foam; α_D^{20} + 38°), the allylic alcohol (**12**) (74%) [eluent, ether–methanol (95:5); foam; α_D^{20} + 58°], the trityl ether (**13**) (94%) [eluent, ether–light petroleum (1:1); powder; α_D^{20} + 4°] and the unsaturated ketone (**14**) (85%) [eluent, chloroform-ether-hexane (4:1:4); m.p. 106 °C (from ether); α_D^{20} + 5·5°].

Without isolation of intermediates, the ketone (**14**) was treated in succession with OsO_4 (1·1 equiv. in pyridine), hydroxylamine hydrochloride, and then acetic anhydride, to give the *NOO*-triacetate (**15**) (68%) [eluent, chloroform ether (20:3); amorphous; α_D^{20} + 18°]. $LiAlH_4$ reduction of (**15**), followed by selective *N*-acetylation in methanol, gave a mixture (58%) of *talo* (17%) and *galacto* (83%) compounds. The latter, a foam, was separated by chromatography (ether–methanol, 95:5), and the protective groups were removed by hydrogenolysis [1 week at room temperature in water–ethanol (5:95) solution, in the presence of an equal weight of 10% Pd on charcoal]. The trisaccharide (**1**) thus obtained was purified by cellulose column chromatography with eluent A (EtOAc–Pr^iOH–H_2O; 3:3:2) (91%) [m.p. 143—148 °C (from MeOH–EtOAc); α_D^{20} + 36·5° (H_2O); homogeneous by silica gel t.l.c. (eluent A) and paper chromatography (eluent A: $R_{lactose}$ 1·2, R_{fucose} 0·5; eluent, EtOAc–pyridine–H_2O, 10:4:3: $R_{lactose}$ 1·0, R_{fucose} 0·28)]. N.m.r. data (240 MHz; D_2O; Me_4Si in $CDCl_3$ as external reference) indicated the presence of a *ca.* 2:1 α,β-anomeric mixture: α-anomer: δ 5·40 (d, *J* 3·5 Hz, H-1 Gal), 5·14 (d, *J* 3·5 Hz, H-1 Fuc), 5·12 (d, *J* 3·7, H-1 GalNAc), 2·10 or 2·13 (s, NAc), and 1·26 or 1·30 (d, *J* 6 Hz, CMe); β-anomer: δ 4·73 (d, *J* 7·5 Hz, H-1 Gal), 5·30 (d, *J* 3·5 Hz, H-1 Fuc), 5·18 (d, *J* 3·7 Hz, H-1 GalNAc), 2·13 or 2·10 (NAc), and 1·30 or 1·26 (CMe). The presence of the *N*-acetyl galactosamine unit was confirmed by g.l.c. (SE 30 column at 180 °C) following acidic hydrolysis and trimethylsilylation.

The trisaccharide (**1**) inhibits hemagglutination of A_2 erythrocytes by human anti-A serum at the 80 μg/40 μl level. In this respect, and in its m.p., t.l.c., and paper

† When necessary, compounds were purified by silica gel column chromatography with the solvent mixture given as eluent. Optical rotations were determined for 1% solutions in CH_2Cl_2. All compounds exhibit satisfactory spectral and microanalytical properties.

‡ The alcohol (**5**) may be recovered from the *cis* ether.

chromatography behaviour, it was identical with a natural sample isolated from galactosemic urine.[11]

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