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Note

Glycosides of 8-hydroxy-3,6-dioxaoctanal. A synthesis of a new spacer for synthetic oligosaccharides

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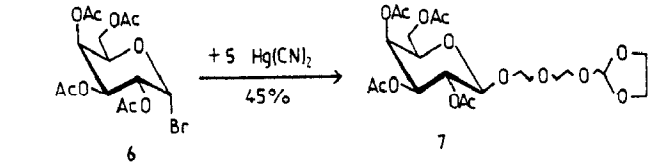
The preparation of a spacer-arm for synthetic oligosaccharides is now a common practice. The coupling of oligosaccharides with a carrier is performed through the active functional group of the spacer, currently the carboxymethyl group[1–4], which provides a convenient incorporation, but cannot be used for oligosaccharides containing acidic monosaccharide residues, such as for sialic acid, Kdo, or uronic acid. In our program for the development of new spacers, we recently[5] proposed the use of glycosides of monoallyldi(ethylene glycol) which, upon oxidation, were transformed into glycosides of 3,6-dioxaoctanal. Coupled with reductive amination, this procedure is excellent for the preparation of neoglycoproteins or immunoabsorbents. The main handicap, however, remains the incompatibility of using the benzyl protective group for compounds containing one allylic double bond. We report herein the use of 8-hydroxy-3,6-dioxaoctanal as a spacer group but having the aldehyde group protected as a dioxolane derivative. This new derivative is compatible with a wide range of protective groups and transformations used in synthetic carbohydrate chemistry.

Ethylene glycol mono(1,3-dioxolan-2-yl)ethyl ether (**5**) was obtained in four steps from tri(ethylene glycol) (**1**). Monobenzoylation of **1** with benzoyl chloride–triethylamine in dichloromethane gave the monobenzoate **2**, isolated in 41% yield without chromatographic separation. It was then oxidized with dimethyl sulfoxide and phosphorous pentaoxide in anhydrous dichloromethane[6] to give aldehyde **3**, which was immediately protected as the dioxolane derivative, **4**, by treatment with ethylene glycol in refluxing benzene in the presence of 4-toluenesulfonic acid. The ^{1}H-n.m.r. spectrum of **4** showed a characteristic triplet at δ 5.1. Debenzoylation by the Zemplén method afforded **5** in a 21% overall yield without chromatographic separation; ^{13}C-n.m.r.: δ 102.3, 71.9, 71.1, 71.4, 70.4, 68.6, and 65.0*.

* All new compounds gave satisfactory elemental analysis or n.m.r. spectra (or both) in accordance with the proposed structure. The configurations of the new glycosidic bonds were established by ^{13}C-n.m.r. spectroscopy.

$R^1OCH_2CH_2OCH_2CH_2OCH_2CHR^2R^3$

1 $R^1 = H; R^2 = H; R^3 = OH$
2 $R^1 = Bz; R^2 = H; R^3 = OH$
3 $R^1 = Bz; R^2, R^3 = O$
4 $R^1 = Bz; R^2, R^3 = OCH_2CH_2O$
5 $R^1 = H; R^2, R^3 = OCH_2CH_2O$



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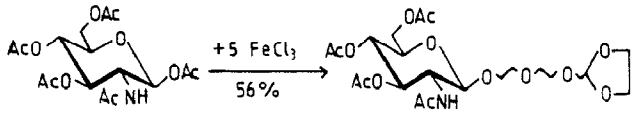

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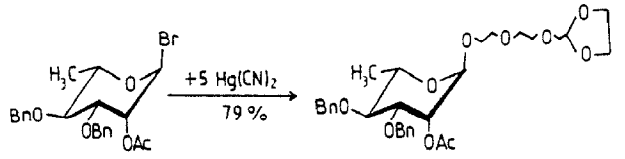

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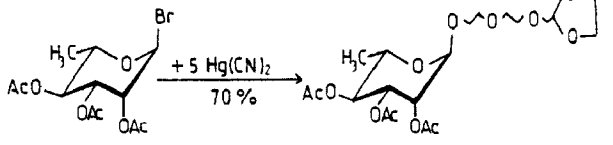

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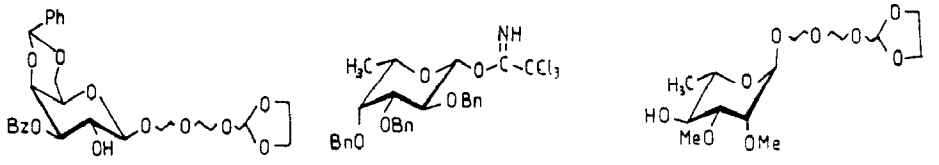

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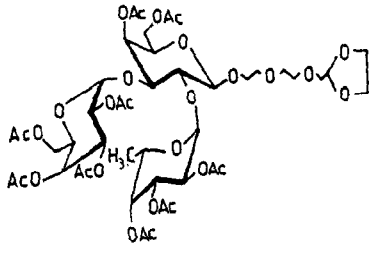
Several monosaccharide derivatives [**6**; **8**, obtained[7] in 56% yield, $[\alpha]_D$ +20°; ^{1}H-n.m.r., $J_{1,2}$ 8 Hz; ^{13}C-n.m.r., δ 101.7 (C-1); **10***; and **12**] were condensed with **5** to afford **7** (yield, 45%; $[\alpha]_D$ +16°; ^{1}H-n.m.r., $J_{1,2}$ 7 Hz), **9** {yield, 79%; $[\alpha]_D$ −13°, ^{1}H-n.m.r.,

* Prepared from the corresponding orthoester with acetyl bromide in the presence of tetraethylammonium bromide[8].

$J_{1,2}$ 1 Hz; ^{13}C-n.m.r., δ 99.2 (C-1)}, **11**, and **13** {yield, 70%; $[\alpha]_D$ −50°; ^{1}H-n.m.r., $J_{1,2}$ 2 Hz; ^{13}C-n.m.r., δ 97.6 (C-1)}, respectively. Derivative **7** was transformed into **14** {yield, 40%; $[\alpha]_D$ +68°; ^{13}C-n.m.r., δ 100.8 (C-1)} which was used for the synthesis of the human blood group B trisaccharide as follows. The α-L-fucopyranosyl and α-D-galactopyranosyl groups were introduced by use of the trichloroacetimidate procedure[10]; under our conditions (K_2CO_3) only the β-imidate **15** (^{1}H-n.m.r.: δ 5.72, J 9 Hz) was obtained, which is at variance with a previous report[11].

Compound **9** was deacetylated, and then benzylidenated to afford a useful synthon for the preparation of human Le^a blood group antigen. After the β-D-galactopyranosyl group had been introduced by use of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide and the Helferich method [yield, 79%; ^{1}H-n.m.r., $J_{1,2}$ 3 Hz; ^{13}C-n.m.r., δ 92.1 (C-1)], the benzylidene group was opened with sodium cyanoborohydride–HCl[12] and OH-4 was α-L-fucosylated with imidate **15** in oxolane to give **17** in 53% yield [^{1}H-n.m.r., $J_{1,2}$ 2 Hz; ^{13}C-n.m.r., δ 96.6 (C-1)].

For the synthesis of the tri-L-rhamnosyl antigen of streptococcal group B[13], deacetylated **11** was coupled in 90% yield with bromide **10** in the presence of mercuric bromide and molecular sieves to give a product having in ^{13}C-n.m.r. δ 99.4 (C-1) and 98.9 (C-1'). In the synthesis of **18** from *O*-deacetylated **9**, the yield of the β-D-galactosylation step was 62% [^{13}C-n.m.r., δ 100.8 (C-1)] and of the α-L-fucosylation step 33% [^{13}C-n.m.r., δ 97.2 (C-1)].



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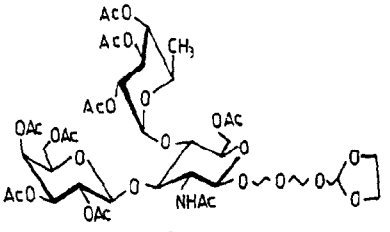

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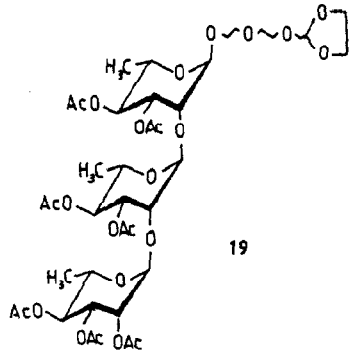

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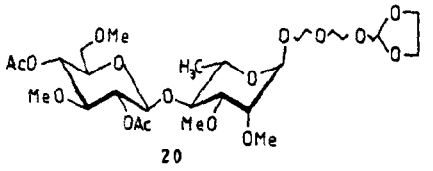

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By a sequence of deacetylation, formation of 2,3-orthoester with ethyl orthoacetate, benzylation, acidic opening of the orthoester, deacetylation, methylation, and hydrogenolysis, L-rhamnoside **13** was transformed into **16** in a 23% yield. Coupling of **16** ($[\alpha]_D$ −26°; ^{1}H-n.m.r., $J_{1,2}$ 2 Hz), as previously described, gave disaccharide **20** (yield, 90%; $[\alpha]_D$ −17°; ^{13}C-n.m.r., δ 97.0 (C-1) and 100.9 (C-1'), which contains the terminal disaccharide of a glycolipid from *Mycobacterium leprae*[14].

After the usual deprotection, the oligosaccharides were acetylated and then the dioxolane group was split off by treatment with formic acid for 2 h at room temperature. Under these conditions, the acid-sensitive α-L-fucosyl group was not affected and the aldehyde was obtained quantitatively (^{1}H-n.m.r., δ 9.70–9.80). The aldehydes were deacetylated by careful treatment with 0.02M sodium methoxide in anhydrous methanol (1 h, 0°); under these conditions, even after 12 h, the decomposition of aldehyde was minimal. The direct treatment with formic acid of deacetylated oligosaccharides is also possible, but the reaction is more complex owing to the partial formylation of hydroxyl groups.

The oligosaccharide derivatives were coupled with BSA by reductive amination with sodium cyanoborohydride. A molar ratio of aldehyde-to-cyanoborohydride-to-BSA of 3:6:1 gave neoglycoproteins having 25–30 mol of oligosaccharides/mol BSA. The use of the 8-hydroxy-3,6-dioxooctanal spacer is also useful for coupling to aminopropyl-silica gel, thus providing a specific immunoabsorbent.

The preparation of monosaccharide derivatives, such as **7**, could be simplified by starting from an *O*-acetylglycosyl bromide and di- or tri-(ethylene glycol)[15], followed by an oxidation similar to that applied to **2**, and then treatment with ethylene glycol in dichloromethane in the presence of 4-toluenesulfonic acid.

EXPERIMENTAL

Ethylene glycol mono(1,3-dioxolane-2-yl)ethyl ether. — To a solution of tri(ethylene glycol) (**1**; 25 mL) in dry dichloromethane (137 mL) and triethylamine (36.7 mL) was added a solution of benzoyl chloride (30.6 mL) in dichloromethane (58.2 mL). The mixture was stirred overnight, washed with water (88 mL), dried, and evaporated. The residue was dissolved in toluene (111 mL), diluted with hexane (225 mL), and extracted twice with 1:2 ethanol–water (336 mL). The aqueous layer was evaporated to 225 mL and extracted with chloroform to yield monobenzoate **2** (17 g). After oxidation performed according to Taber *et al.*[6], the aldehyde **3** was immediately treated with 4-toluenesulfonic acid (8.6 g) and ethylene glycol (5.4 mL) in benzene at reflux for 1 h. The mixture was then washed with $NaHCO_3$ solution and with water, dried, evaporated, and the residue (**4**) directly debenzoylated with sodium methoxide under usual conditions. After evaporation, the product was dissolved in water (260 mL), extracted twice with 4:1 toluene–hexane to remove impurities, and then extracted with chloroform in a continuous extractor to yield **5** (12 g); ^{1}H-n.m.r.: δ 5.1 (t, 1 H), 4.0 (m, 10 H), and 3.9 (d, 4 H); ^{13}C-n.m.r.: δ 102.3, 71.9, 71.2, 71.4, 70.4, 68.6, and 65.0.

Anal. Calc. for $C_8H_{16}O_5$: C, 49.99; H, 8.39. Found: C, 50.20; H, 8.21.

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