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REGIOSELECTIVE MONO-O-ALKYLATION OF DISACCHARIDE GLYCOSIDES THROUGH THEIR DIBUTYLSTANNYLENE COMPLEXES

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Summary : Allyl β-N-Acetyllactosaminide, methyl β-N-phthaloyllactosaminide, and methyl β-lactoside give with high selectivity and good yields the corresponding 3'-O-allyl derivatives by reaction of their dibutylstannylene complexes with allyl bromide and tetrabutylammonium bromide.

Most of the reports on the relative reactivities of hydroxyl groups in oligosaccharides have concerned selective esterifications,[1] and in this respect the use of trialkyltin derivatives has recently given interesting results with various disaccharides.[2] However the preparation of partially protected oligosaccharides for the block syntheses of longer saccharide chains[3] would be greatly facilitated by efficient methods of selective etherification. In earlier studies[4] we have reported that stannylation of benzyl β-D-galactopyranoside with one molar equivalent of dibutyltin oxide in refluxing benzene, followed by treatment with benzyl or allyl bromide, gave in a completely regiospecific way excellent yields of either the 3-O-benzyl or the 3-O-allyl derivative. Although it is not known which positions of the galactopyranoside cycle are spanned by the stannylene ring, it is quite remarkable that substitution occurs with such high selectivity on a secondary hydroxyl group of a polyhydroxy compound. Moreover the catalytic effect of quaternary ammonium halides upon the alkylation of tin alkoxides[4,5] makes the procedure very mild and convenient.

We now describe an extension of this work to disaccharides of biological interest, N-acetyllactosamine and lactose.

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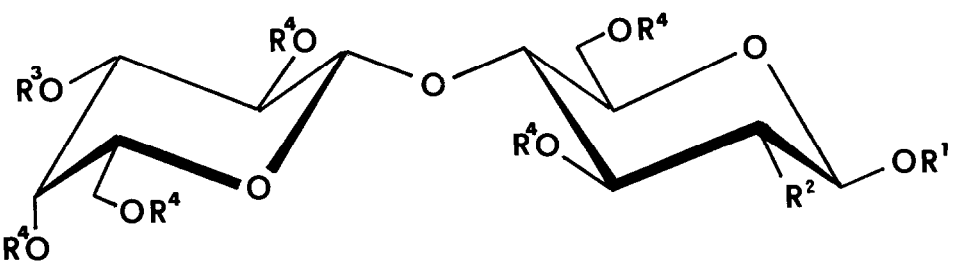
The impossibility of building any stannylene ring on the D-glucopyranose unit of N-acetyllactosamine (2-acetamido-2-deoxy-4-O-β-D-galactopyranosyl-D-glucopyranose) suggests a favourable outcome for the monoalkylation of the D-galactose residue. Indeed, when a mixture of allyl β-N-acetyllactosaminide 1[6] (1 mmol) and dibutyltin oxide (1.2 mmol) in benzene was boiled under reflux for 17 h with continuous removal of water, then treated under reflux for 2 h with allyl bromide (10 mmol) and tetrabutylammonium bromide (0.5 mmol), a 48% yield of the 3'-O-allylated disaccharide 2 could be obtained after silica gel column chromatography (CH_2Cl_2-CH_3OH, 4:1), m.p. 241-243°C, $|\alpha|_D^{20}$ -2° (c 1.01, water); 20% of starting material 1 was recovered. Acetylation of 2 with acetic anhydride in pyridine gave the penta-O-acetyl derivative 3, m.p. 147-149°C, $|\alpha|_D^{20}$ -8° (c 1.01, chloroform), ^1H NMR ($CDCl_3$) : δ 5.94-5.63 (m, 2H, -CH=CH_2), 5.78 (d, J 9.8 Hz, NH), 5.38 (d, $J_{3',4'}$ 3.2 Hz, H-4'), 5.29-5.15 (5H, H-3 and -CH=CH_2), 5.02 (dd, $J_{2,3}$ 9 Hz, H-2), 5.00 (dd, $J_{2',3'}$ 10 Hz, H-2'), 4.46 (d, $J_{1,2}$ 7.5 Hz, H-1), 4.40 (d, $J_{1',2'}$ 8.2 Hz, H-1'), 3.46 (dd, H-3'), 2.12, 2.10, 2.06, 2.05 and 1.95 (s, 18 H, $-COCH_3$). The pronounced upfield shift exhibited by H-3' on allylation of the 3'-hydroxyl group confirms the site of substitution in compounds 2 and 3.



1 R^1= CH_2-CH=CH_2, R^2= NHAc, R^3= R^4= H

2 R^1= R^3= CH_2-CH=CH_2, R^2= NHAc, R^4= H

3 R^1= R^3= CH_2-CH=CH_2, R^2= NHAc, R^4= Ac

4 R^1= CH_3, R^2= NPht, R^3= R^4= H

5 R^1= CH_3, R^2= NPht, R^3= CH_2-CH=CH_2, R^4= Ac

6 R^1= CH_3, R^2= OH, R^3= R^4= H

7 R^1= CH_3, R^2= OH, R^3= CH_2-CH=CH_2, R^4= H

8 R^1= CH_3, R^2= OAc, R^3= CH_2-CH=CH_2, R^4= Ac

Similarly, methyl β-N-phthaloyllactosaminide[7] 4 (1 mmol) was treated with dibutyltin oxide (1.1 mmol) in methanol for 4 h under reflux, then with allyl bromide (4 mmol) and tetrabutylammonium bromide (0.5 mmol) in toluene for 12 h

at 70°C. The main component of the reaction mixture was isolated by silica gel column chromatography ($CHCl_3$-CH_3OH, 19:1), 23% of starting compound 4 being recovered. Acetylation gave the penta O-acetyl derivative 5 in 56% overall yield, m.p. 158-160°C, $|\alpha|_D^{20}$ +41° (c 1.24, chloroform), ^{1}H NMR ($CDCl_3$) : δ 7.89-7.77 (m, 4H, phthaloyl), 5.85-5.73 (m, 2H, -CH=CH_2 and H-3), 5.37 (d, $J_{3',4'}$ 3.5 Hz, H-4'), 5.31 (d, $J_{1,2}$ 8.5 Hz, H-1), 5.27-5.17 (m, 2H, -CH=CH_2), 5.05 (dd, $J_{2',3'}$ 10 Hz, H-2'), 4.49 (d, $J_{1',2'}$ 8 Hz, H-1'), 3.47 (dd, H-3'), 3.44 (s, OCH_3), 2.18, 2.15, 2.11, 2.09 and 1.91 (s, 15 H, 5 OAc).

In those two examples, substitution was very selective, but not complete, as if the dibutylstannylene complex was not stable under the conditions of the reaction.

Then we turned to methyl β-lactoside, a disaccharide glycoside where another stannylene ring can span the 2,3 oxygen atoms of the glucopyranoside unit. However, we found that substitution occurs again preferentially upon the 3-position of the galactose residue, and by performing two successive stannylation-allylation sequences, we were able to drive the reaction nearly to completion with limited formation of further substituted compounds. Methyl β-lactoside[9] 6 (1mmol) was treated with dibutyltin oxide (1.2 mmol) in benzene under reflux for 17 h with azeotropic removal of water, then with allyl bromide (18.5 mmol) and tetrabutylammonium bromide (0.5 mmol) for 3 h under reflux. After evaporation of the solvent, the residue was dissolved into water, and the cloudy solution was extracted twice with ethyl acetate to remove tin by-products; water was evaporated, the residue dried and treated once more with dibutyltin oxide (1.1 mmol) in benzene under reflux for 17 h, then with allyl bromide (18.5 mmol) and tetrabutylammonium bromide (0.5 mmol) for 50 min under reflux. After evaporation of the solvent, the residue was taken up with methanol. After cooling, a crystalline precipitate was filtered off; its elemental analysis corresponds to the tetrabutylhydroxydistannoxane,[10] $BrBu_2Sn.O.SnBu_2(OH)$, m.p. 80-81°C, IR (nujol) 3480 cm^{-1}. The filtrate was evaporated, and ethyl acetate was added; the 3'-O-allylated disaccharide 7 crystallized rapidly and could be isolated without chromatography in 70% yield, m.p. 107-112°C, $|\alpha|_D^{20}$ +20° (c 1.00, water). The hexa-O-acetate 8 was amorphous, $|\alpha|_D^{20}$ +4.5° (c 1.11, chloroform), ^{1}H NMR ($CDCl_3$) : δ 5.76-5.61

(m, 1H, -C<u>H</u>=CH_2), 5.35 (d, $J_{3',4'}$ 3 Hz, H-4'), 5.25-5.14 (3H, H-3 and -CH=C<u>H_2</u>), 4.99 (dd, $J_{2',3'}$ 10 Hz, H-2'), 4.88 (dd, $J_{2,3}$ 9 Hz, H-2), 4.39 (2H, $J_{1,2}$ = $J_{1',2'}$ 8 Hz, H-1 and H-1'), 3.44 (dd, H-3'), 3.50 (s, OCH_3), 2.17-2.04 (s, 18 H, 6 OAc).

In conclusion, the use of dibutylstannylene derivatives has allowed a regioselective monoallylation of the disaccharides lactosamine and lactose, leading to compounds of high synthetic potential.

References and notes

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6. β-N-Acetyllactosaminide 1 was prepared from acetochlorolactosamine according to classical procedures, m.p. 255°C, $|\alpha|_D^{20}$ -22° (c, 0.99, water). All new compounds showed satisfactory elemental analysis.
7. β-N-phthaloyllactosaminide 4 was prepared from the corresponding phthalimido-chloride,[8] m.p. 283-285°C, $|\alpha|_D^{20}$ -67° (c 0.51, pyridine).
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10. R. Okawara and M. Wada, J.Organomet.Chem., 1, 81 (1963); the higher melting point (114-128°C) reported by these authors may correspond to a different dimeric structure.

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