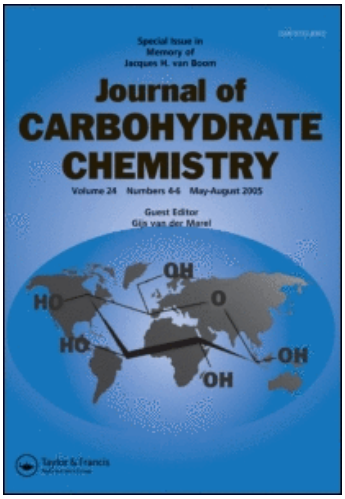

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Synthesis of Chitooligosaccharide Derivatives by Condensation Polymerization

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COMMUNICATION

SYNTHESIS OF CHITOOLIGOSACCHARIDE DERIVATIVES BY CONDENSATION POLYMERIZATION+

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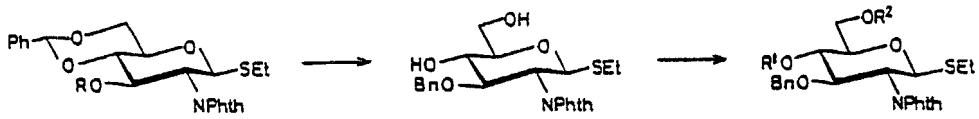
Oligomerization of mono- and oligosaccharide units can be an interesting methodology for synthesis of homooligosaccharides and oligosaccharides having repeating units, respectively. Recently, chitooligosaccharides, especially the hexamer, were shown to have an antitumor effect,[2] suppress metastasis[3] and protect against microbial infection.[4] For the synthesis of these oligomers the ring-opening polymerization of such monomers as 1,6-anhydro[5] and 1,2-cyanoethylidene[6] derivatives, which are the effective monomers for polycondensation, cannot be used.

In the present communication we report a direct synthesis of a series of chitooligosaccharide derivatives by oligomerization of a thioglycoside having a free hydroxyl group.

A monomer, ethyl 6-O-acetyl-3-O-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (4) was synthesized from ethyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside[7](1). Treatment of 1 with sodium hydride and benzyl bromide in 1,2-dimethoxyethane[8] gave, in 90% yield, the 3-O-benzyl derivative (2), which was then converted into a diol 3 with 60% aqueous acetic acid at 100 °C in 82% yield. A selective acetylation of 3 with 1 equiv. of

+ Presented at the 14th International Carbohydrate Symposium, Stockholm, Sweden, August 14-19, 1988.



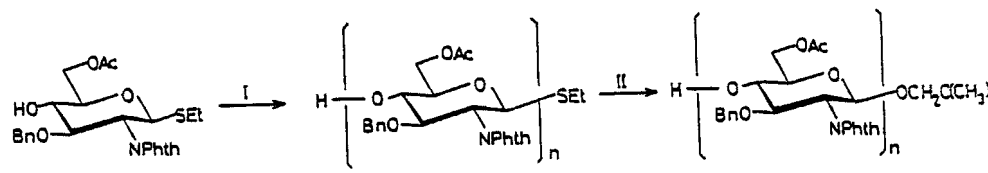
1 R=H
2 R=Bn

3

4 R^1=H, R^2=Ac
5 R^1=Ac, R^2=H
6 R^1=R^2=Ac

acetic anhydride in pyridine gave the 6-acetate 4,[9] 4-acetate 5 and 4,6-diacetate 6 in 59%, 6% and 18% yields, respectively.

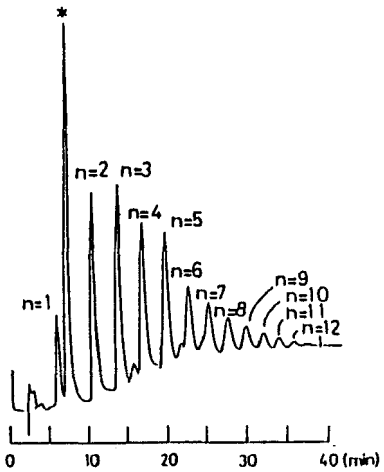
The self-condensation reaction of 4 was carried out in two steps as shown in the following scheme. The first step is oligomerization under conventional glycosylation conditions for thioglycoside and the second one is introduction of a marker in order to determine the degree of oligomerization by ^{1}H NMR.



I : MeOTf, MS4A/CH_2Cl_2, II : MeOTf, $HOCH_2C(CH_3)_3$

One of the best results is as follows: A solution of the monomer 4 (0.2 mmol) and methyl triflate (0.5 mmol) in dry dichloromethane (2.5 mL) was kept in the presence of molecular sieves 4A (2g) at -15 °C for 3 days, and then 2,2-dimethylpropanol (5.0 mmol) and methyl triflate (5.0 mmol) were added to the reaction mixture. Being kept at -15 °C for another 12h and at room temperature for 12h, the mixture was stirred with triethylamine (0.5 mL) for 5 min and filtered with the aid of celite. The filtrate was washed successively with 1M sulfuric acid, saturated aqueous sodium hydrogencarbonate and water, and dried. The chitooligosaccharide mixture obtained was analyzed by HPLC using 1,3,4,6-tetra-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose as an internal standard under conditions as shown in Fig. 1.

The oligomers up to hexamer could be also isolated in a preparative scale on a Lobar column (Merck) and characterized by 500 MHz ^{1}H NMR.[10] The degree of oligomerization could be calculated easily



Column	HITACHI #3040 (Silica gel) 0.26 x 80 cm
Mobile Phase	To a 5:2 mixture of n-hexane and ethyl acetate (100 ml) was added ethyl acetate at the rate of 2.5 ml/min.
Elution Rate	2 ml/min
Detection	UV 290 nm

Fig. 1. Analysis of Chitooligosaccharide Mixture by HPLC

by comparison of the intensities for the signals of tert-butyl in the aglycon part with those for the signals of acetyl as well as aromatic protons of phthaloyl and benzyl groups. All glycosidic linkages were confirmed to be β by large coupling constants of anomeric protons.

Under the above conditions the total yield of oligomers was 70%,[11] and the oligomers were composed of dimer 12.6%, trimer 14.2%, tetramer 11.5%, pentamer 10.8%, hexamer 6.1%, heptamer 5.2%, octamer 4.4%, nonamer 2.6%, decamer 1.5%, and undecamer 1.1%. Yields of higher than hexamer were estimated by assuming the same molar extinction coefficient as that of the hexamer. In this case the average number of oligomerization was calculated to be 4.5. Although the average number increased with the reaction time of the step I, the total yield of the chitooligosaccharides decreased especially when the amount of the acid trapper was not enough. For example the same condensation as described above was carried out with one half of the molecular sieves for 2 and 4 days to give a chitooligosaccharide mixture with the average numbers of 2.4 and 4.0 in 84%[12] and 23%[12] total yield, respectively. Because a series of oligosaccharide by-products were detected by HPLC in the latter case and their formation could be avoided also with potassium carbonate instead of the molecular sieves, the acid formed during the condensation may prevent further oligomerization.

On the other hand, oligomerization of 6-O-acetyl-3-O-benzyl-2-deoxy-2-phthalimido-α,β-D-glucopyranosyl bromide[13] by the Koenigs-Knorr method using silver triflate as well as that of 1,6-di-O-acetyl-

3-O-benzyl-2-deoxy-2-phthalimido-4-O-trimethylsilyl-β-D-glucopyranose[14] with trimethylsilyl triflate gave the smaller average numbers (1.4 and 2.2) of oligomerization and the lower yields (26% and 32%).

In conclusion, the oligomerization of the thioglycoside derivative proved to be more effective than other glycosylation methods and may be suitable for preparation of a series of oligosaccharides by self-condensation of not only the monosaccharide but also the oligosaccharide unit.

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9. Spectroscopic data of 4: $[\alpha]_D$ + 21.6° (c 0.9, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, Ac), 3.07 (bs, 1H, OH), 4.52 and 4.74 (ABq, 2H, $PhCH_2$), 5.27 (d, 1H, $J_{1,2}$=1.0 Hz, H-1), 6.8-7.2 (m, 5H, aromatic in Bn), and 7.5-7.9 (m, 4H, aromatic in Phth).
10. As a typical example only ^1H NMR data of the hexamer measured at 500 MHz ($CDCl_3$) are given: δ 0.50 (s, 9H, t-Bu), 1.66, 1.68, 1.74, 1.78, 1.82 and 1.94 (s, each 3H, Ac), 2.96 (bs, 1H, OH), 2.67 and 3.30 (ABq, 2H, $tBuCH_2$), 4.53-4.84 (6 x ABq, 12H, J=12.2-13.2 Hz, $PhCH_2$), 6.6-7.0 (m, 30H, aromatic in Bn) and 7.4-7.9 (m, 24H, Phth) 3.38, 3.41, 3.42, 3.44, 3.56 and 4.13 (dd, 6H, $J_{5,6a}$ =3.5-3.9 Hz and $J_{6a,6b}$=11.7-12.2 Hz, H-6a), 3.94, 3.99, 4.01, 4.08, 4.10 and 4.61 (dd, 6H, $J_{5,6b}$ =2.0-2.2 Hz, H-6b), 3.15, 3.19,

3.21, 3.27, 3.29 and 3.47 (ddd, 6H, H-5), 3.51, 3.67(x2), 3.70, 3.74 and 3.92 (dd, 6H, $J_{4,5}$=9.6-10.2 Hz, H-4), 4.04(x2), 4.07(x2), 4.14 and 4.20 (dd, 6H, $J_{3,4}$=8.6-8.8 Hz, H-3), 3.92(x2), 3.93, 3.94, 4.04 and 4.10 (dd, 6H, $J_{2,3}$=10.5-10.7 Hz, H-2), and 4.76, 4.99, 5.01, 5.07(x2) and 5.22 (d, 6H, J=8.3-8.8 Hz, H-1).

11. The yields are calculated by subtracting the yield (4.2%) of the monomer.

12. These yields are caluculated in the same manner as above. The yield of the monomer after 2 days was 24.2%, and that after 4 days 1.3%.

13. The bromide was prepared by treatment of 4 with bromine in the presence of molecular sieves 4A in dichloromethane and a 1:9 mixture of α- and β-anomers.

14. Acetolysis of 4 with acetic acid and methyl triflate in the presence of molecular sieves 4A in dichloromethane gave the 1,6-diacetate, which was converted into the corresponding 4-O-trimethylsilyl derivative by a conventional method with chlorotrimethylsilane and imidazole in N,N-dimethylformamide.