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Synthesis of polysaccharides with 1,2-cis-glycosidic linkages by trityl-thiocyanate polycondensation. Stereoregular α-(1-6)-D-glucan

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Abstract. The completely stereoregular polysaccharide, α-(1-6)-D-glucan, has been synthesised using a new highly stereospecific type of polycondensation process - trityl-thiocyanate polycondensation.

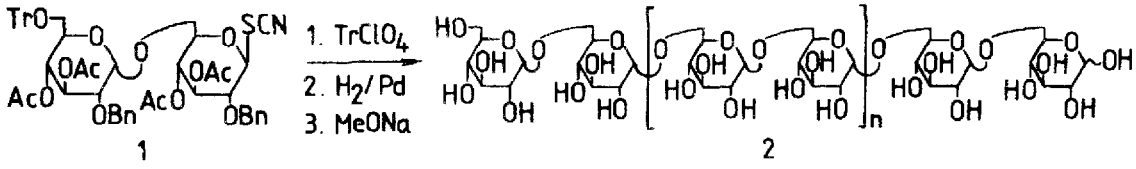
After chemical syntheses of polypeptides and polynucleotides, the synthesis of polysaccharides was a challenge to synthetic chemistry of new biopolymers. During last decade general approach to the synthesis of a regular polysaccharides consisting of mono- or oligosaccharide units connected by 1,2-*trans*-glycosidic linkages, has been developed[1] using stereospecific trityl-cyanoethylidene condensation[2].

There have been a few syntheses of simple 1,2-*cis*-linked homopoysaccharides performed by polymerisation of anhydroaldoses (for review see[1,3]), but a general approach to the synthesis of more complicated regular heteropolysaccharides built up of repeating oligosaccharide units with 1,2-*cis*-glycosidic linkages between them is still unknown.

This is due to the absence of a fully stereospecific method of formation of 1,2-*cis*-glycosidic linkages (cf., for example,[4]). Recently, we described a new reaction meeting this demand, that is glycosylation of 0-trityl ethers by 1-(1,2-*trans*)-glycosyl thiocyanates in the presence of triphenylmethylium perchlorate[5-7].

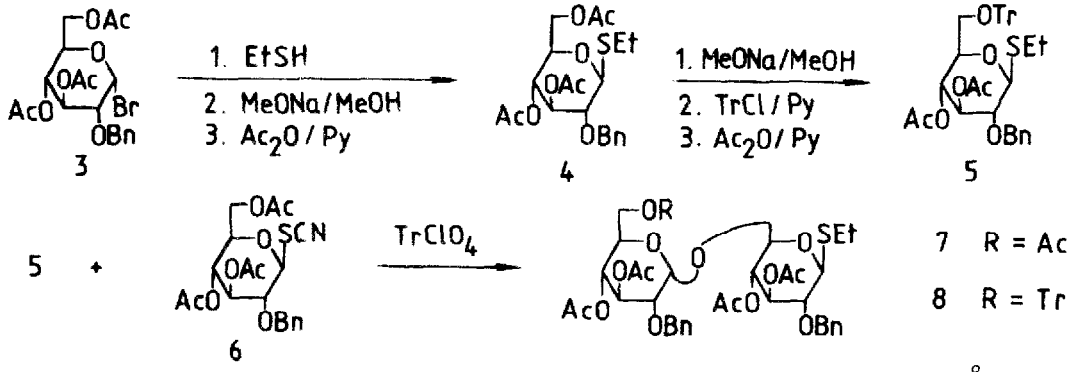
Here we report the development of a new highly stereospecific polycondensation process based on this reaction. This approach ("trityl-thiocyanate polycondensation") opens a real way to the synthesis of regular polysaccharides of complicated structure with 1,2-*cis*-linked repeating units, including many natural polysaccharides of biological significance. For this purpose the mono- or oligosaccharides containing both 0-trityl- and 1-(1,2-*trans*)-thiocyanate groups have to be used as monomers. In order to demonstrate the application of this approach for the synthesis of polysaccharides built up from repeating oligosaccharide units we describe here the polycondensation of a disaccharide monomer, namely isomaltose

derivative **1**, which should result in formation of the regular α-(1-6)-glucan **2**.



1 2

The monomer **1** containing a 6-O-trityl group at C-6 of the non-reducing glucose residue and a thiocyanate group at the reducing end was obtained according to the Scheme:



3 4 5 6

3,4,6-Tri-O-acetyl-2-O-benzyl-α-D-glucopyranosyl bromide **3**[8] was converted into the thioglucoside **4** (EtSH, MeOH, MeONa, 0°- 20°, 1 h, 52%, m.p. 81-81° (hexane-ether), $[\alpha]_D^{25}$ +23.4° (c 4.6, $CHCl_3$)[9]. Deacetylation of **4** (1 N MeONa - MeOH), followed by successive tritylation (Ph_3CCl-Py, 12 h), and acetylation (Ac_2O-Py, 3 h), and chromatography (SiO_2, C_6H_6-EtOAc) led to **5**, 85%, m.p. 150-151° (hexane-ether), $[\alpha]_D^{24}$ +0.4° (c 2, $CHCl_3$). Coupling of the thioglycoside **5** (2 mmol) and the thiocyanate **6**[7] (2 mmol) in the presence of $TrClO_4$ (10 mol.%, CH_2Cl_2, 20°, 4 h) gave **7**, 82%, syrup, $[\alpha]_D^{26}$ +76° (c 2, $CHCl_3$). The disaccharide **7** was deacetylated (1 N MeONa-MeOH, 1.5 h), then tritylated (Ph_3CCl-Py), acetylated (Ac_2O-Py), and purified by chromtography (SiO_2, gradient hexane-EtOAc) to give **8**, 70%, amorphous powder, $[\alpha]_D^{26}$ + 48° (c 2, $CHCl_3$). Treatment of **8** with Br_2 (mol. sieves 3 A, CH_2Cl_2, argon, 40 min) resulted in a bromide (homogeneous in HPLC), which on interaction with KSCN (dry acetone, 18-krown-6, 20°, 10 h) and purification by HPLC gave **1**, 25%, amorphous powder, $[\alpha]_D^{26}$ +80° (c 6.1, $CHCl_3$); the structure was supported by the ^{1}H-n.m.r. (H-1, δ 4.60 ppm, $J_{1,2}$ 9.5 Hz), and IR spectra (2160 cm^{-1}, S-C≡N).

Polycondensation of **1** was performed as follows: a solution of **1** (341 mg, 0.35 mmol) and $TrClO_4$ (12 mg, 0.035 mmol) in CH_2Cl_2 (3 ml) was kept at 20°. After 3 h, TLC showed the complete conversion of the monomer, Py (1 drop) and $CHCl_3$ (50 ml) were added to the mixture, which was then washed with H_2O and

evaporated. Chromatography (SiO_2, gradient of acetone in $CHCl_3$) of the residue gave the fraction of protected polysaccharide (141 mg, 60%) with R_f 0.0-0.2 (TLC, ether). Debenzylation of the polycondensation product (EtOH, 10% Pd/C, 2 h), followed by deacetylation ($CHCl_3$-MeOH, 1 N MeONa-MeOH, 12 h), neutralisation (AcOH), and chromatography on Bio-Gel P-4 gave the polysaccharide **2** (38 mg, 34%). Rechromatography on Fractogel TSK HW-40 (S) afforded the high-molecular-weight fraction of **2** as a white water-soluble powder, $[\alpha]_D^{28}$ 155° (c 1, water). The clean ^{13}C-N.m.r. spectrum (Fig. 1) contained six sharp signals (δ, ppm): 98.91 (C-1), 74.57 (C-3), 72.58 (C-2), 71.37 (C-5), 70.84 (C-4), and 66.94 (C-6) that confirmed the full regio- and stereoregularity of the synthetic polysaccharide. The presence of a signal at δ 98.91 and absence of signals in the region of δ 102-104 indicates unambigously that all new-born glycosidic linkages are α and proves the full stereospecificity of the new polycondensation procedure. The comparison of integral intensities of signals at δ 61.80 (C-6 of the nonreducing glucose residue) and at δ 66.44 (C-6 of the internal glucose residues) indicates that the polymer contains 20-22 glucose units, which corresponds to a mass of 3200-3500 D and a degree of polymerisation of the disaccharide monomer of 10-11.

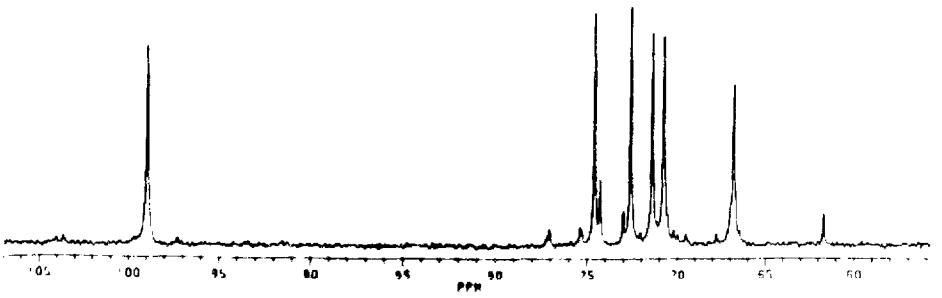


Fig. 1. ^{13}C-N.m.r. spectrum of α-(1-6)-D-glucan (D_2O).

The new approach to the synthesis of regular polysaccharides with 1,2-*cis*-glycosidic linkages by a new polycondensation process described in this communication has probably general character. The most important feature of the new method consists of the possibility of preparing regular polysaccharides from oligosaccharide monomers. It means that starting from a properly derivatized oligosaccharide it would be possible to synthesize a complicated heteropolysaccharides built up of repeating units, including natural polysaccharides with highly specific biological activities.

This method together with previously elaborated synthesis of regular polysaccharides with 1,2-*trans*-glycosidic linkages[1] opens real route to a synthetic polysaccharides of different types.

References and Notes

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9. Satisfactory ^{1}H NMR spectra and elemental analyses were obtained for this and all other new compounds.

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