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First Stepwise Synthesis of Cellulose Analogs

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Abstract: The first synthesis of a homologous series of cellulose analogs, 3-*O*-benzyl-2,6-di-*O*-pivaloyl derivatives and 2,3,6-tri-*O*-acetyl derivatives up to an eicosamer was achieved based on highly stereoselective β-glycosylation and subsequent removal of the protective groups. Such homologous series will play an important role in the basic studies of cellulose.

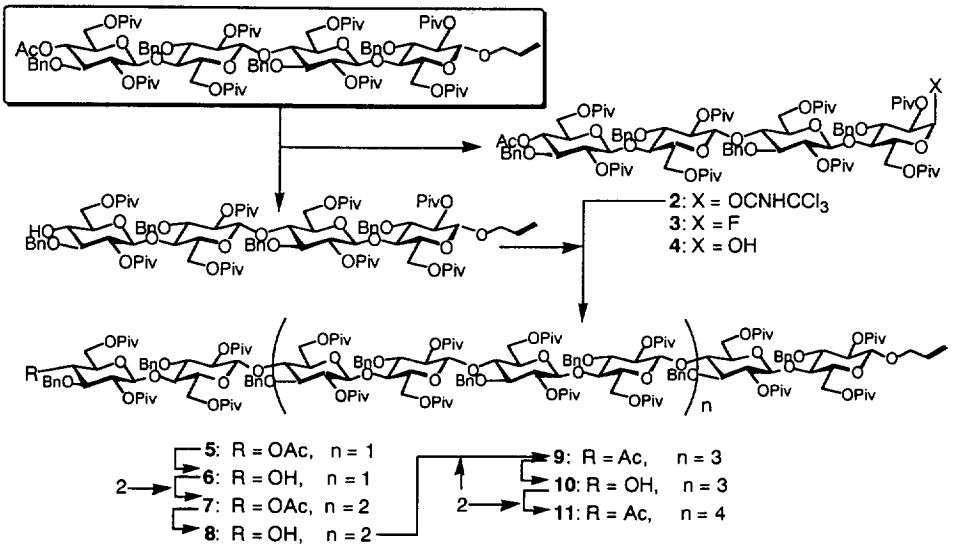
Cellulose is the most abundant natural organic polymer and very important as renewable organic material. For the basic studies of cellulose, a homologous series of the oligomeric compounds that asymptotically approach the polymer structure is very important, for example, for investigation of the macromolecule character of cellulose by increasing DP from glucose[1]. On the other hand, the current papers describe the importance of cellooligosaccharide with defined DP as a simple model of cellulose for the structural studies[2]. It is very difficult to prepare such products, especially the higher oligosaccharide, either by partial acetolysis of cellulose or chemical synthesis as reported previously[3]. We therefore attempted the stepwise synthesis of cellulose starting from glucose. Toward this challenging synthesis, we began with selection of the starting material for the convergent synthesis[4] and investigation of the substituent effect on stereoselective β-glycosylation[5,6,7]. Recently, we had succeeded in linear synthesis of acetyl cellooctaose from allyl 2,3,6,2',3',6'-hexa-*O*-benzyl-4'-*O*-(p-methoxybenzyl)-β-D-cellobioside[8] and convergent synthesis of cellooctaose from allyl 4-*O*-acetyl-3,3'-di-*O*-benzyl-2,6,2',6'-tetra-*O*-pivaloyl-β-D-cellobioside (**1**)[9,10] by the Schmidt method[11]. The protective system of the latter starting material **1** was especially suitable for high yield preparation of α-trichloroacetoimidate and the highly stereoselective β-glycosylation by a convergent synthesis[9]. Here, we report the successive elongation of the carbohydrate chain from cellooctaoside **5**.

In the initial experiment, convergent synthesis in the shortest reaction steps[4], that is, conversion of **5** into a cellooctaosyl donor and acceptor, and the subsequent β-glycosylation was tried. Deallylation of **5** with SeO_2 and AcOH[12] in dioxane at 80°C gave a 60% yield of the deallylated product, which was further treated with DBU and CCl_3CN in CH_2Cl_2[13]. But preparation of the cellooctaosyl donor was unsuccessful because the imidoylation reaction is extremely slow. For this reason, sugar chain elongation was carried out by stepwise additions of cellotetraosyl unit **2**.

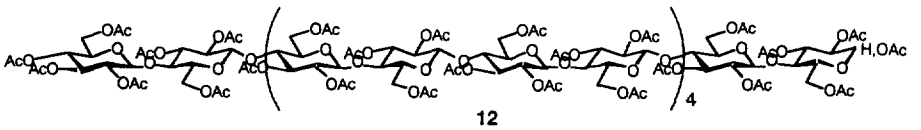
Selective elimination of the O-4 acetyl group of **5** with DBU (7.0 eq.)[14] in methanol at room temperature afforded celooctaosyl acceptor **6** in a 68% yield. Glycosylation between the glycosyl donor **2** (2.0

eq.) and acceptor **6** (1.0 eq.) was promoted with BF_3-Et_2O (0.3 eq.) in CH_2Cl_2 at room temperature and under the strict anhydrous conditions with a high vacuum system[15] to give a 97% yield of β(1→4)-linked cellododecaoside **7**. Configuration at C-1, the newly formed anomeric center of **7**, was assigned as a complete β-form from ^{13}C NMR data. Cellododecaoside **7** was further converted into glycosyl acceptor **8** in a 44% yield in a similar manner except that 20% MeOH/CH_2Cl_2 was used as the solvent because of the insolubility of **7** in CH_2Cl_2. Glycosylation between the glycosyl donor **2** (3.0 eq.) and acceptor **8** (1.0 eq.) was again performed with BF_3-Et_2O (0.45 eq.) in CH_2Cl_2 at room temperature using the high vacuum system to give a 95% of β(1→4)-linked cellohexadecaoside **9**. Sugar chain elongation by addition of **2** was repeated once more and finally, celloeicosaoside **11** was obtained (deacetylation: 53%, β-glycosylation: 85%). In each glycosylation step, the desired β(1→4)-linked product was obtained as almost the sole product and only a trace amount of glycosyl fluoride **3** and a small amount of hydrolysis product **4** was formed. A considerable amount of the glycosyl donor **2** remained unreacted. Very recently, we had already succeeded in the first synthesis of cellulose by cationic ring-opening polymerization making use of such substituent effect [16].

The four protective groups of celloeicosaoside **11** were removed stepwise as follows: 1) Deacylation with NaOMe in MeOH-ethylene glycol dimethylether (1:1, v/v) under reflux and subsequent acetylation with Ac_2O/Py. 2) Deallylation with SeO_2 and AcOH in dioxane at 80°C and subsequent acetylation with Ac_2O/Py. 3) Hydrogenolysis with Pd(OH)2-C in THF at room temperature for 4 h and subsequent acetylation (repeated three times for completely debenzylation). Finally, acetyl celloeicosaoside **12** was obtained in a 37% overall yield. The ^1H NMR data of **12** were in agreement with those of cellulose triacetate obtained by acetylation of natural cellulose[17], except that in the synthetic compound, H-1 at the reducing end unit clearly appeared (See Note 18, underlined signals). This deprotection procedure was also applied for the deprotection and conversion of cellododecaoside **7** into the peracetate derivative (overall 36.9%).



Scheme Convergent synthetic route for cellulose analogs.



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In summary, the first stepwise syntheses of cellulose analogs were achieved[18]. Our success implies the possibility of reaching polysaccharides by convergent synthesis[19]. Interestingly, from investigation of the changing properties with increasing DP such as molecular rotation, appearance of a polymer effect on higher order molecules structure may be suggested beyond the cellohexadecamer (DP = 16)[20]. Further sugar chain elongation and investigation of the chemical and physical properties of synthesized cellulose are in progress.

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18) Physical data for key compounds, celloeicosaoside **11**: Rf 0.30 (2% MeOH-CH_2Cl_2, c.f. Rf 0.27 for cellohexadecaosyl acceptor **10**); $[\alpha]_D$ -8.10° (c 1.6, in $CHCl_3$); ^{1}H NMR, (500 MHz, $CDCl_3$), δ 0.98-1.20 (360 H, $C(CH_3)_3$, strong two peaks appeared at 0.98 and 1.03 ppm, respectively), 1.89 (s, 3 H, CH_3), 3.35 (m, H-5), 3.47 (H-3), 3.63 (broad t, H-4), 3.82 (H-6), 4.08 (H-6), 4.27 (H-1) , 4.41 (broad d, benzyl-H), 4.82 (broad t, H-2), 4.95 (broad d, benzyl-H), 5.80 (m, 1 H, -C*H*=CH_2), 7.14-7.26 (m, 100 H, aromatic) ; ^{13}C NMR (125 MHz, $CDCl_3$), 27.1, 27.2 (-C(*C*H_3)$_3$), 38.6 (-*C*(CH_3)$_3$), 62.4 (C-6), 72.1 (C-2), 73.2 (C-5), 74.7 (benzyl-H), 76.7 (C-4), 80.7 (C-3), 100.1 (C-1), 126.7, 126.9, 127.1, 127.4, 128.0, 128.4, 138.6 (aromatic), 176.3, 177.6 (C=O); **12**: Rf 0.33 (5% MeOH-CH_2Cl_2), ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.95, 2.01, 2.14 (CH_3), 3.55 (m, H-5), 3.72 (t, H-4), 4.07 (broad dd, H-6), 4.37-4.48 (d, H-1 and dd, H-6), 4.80 (t, H-2), 5.07 (t, H-3), 5.62 (H-1, β-anomer), 6.24 (H-1, α-anomer); ^{13}C NMR (100 MHz, $CDCl_3$), 20.5, 20.6, 20.8 (CO*C*H_3), 62.0 (C-6), 71.8 (C-2), 72.5 (C-3), 72.8 (C-5), 76.1 (C-4), 100.5 (C-1), 169.3, 169.7, 170.2 (*C*OCH_3).

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