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Synthesis of the Cellulose Model Compound Methyl 4″-*O*-Methyl-β-D-Cellotrioside

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Summary: A high-yield synthetic route towards methyl 4″-O-methyl-β-D-cellotrioside (**17**) *via* cellobioside acceptor **8** and glucosyl fluoride donor **15** was established. The former was synthesized from cellobiose peracetate in 7 steps and 21% overall yield, while the latter was obtained from methyl β-D-glucopyranoside in a 6-step-synthesis with 19% yield. Glycosidation afforded 13% of α-compound besides the desired β-isomer (31%). The target compound, being the higher homologue of the recently prepared 4′-O-methyl-β-D-cellobioside (**1**), is required to study by solid-state techniques the hydrogen bond network in cellodextrins and cellulose, and its changes upon swelling and dissolution.

Keywords: cellulose model compounds; cellodextrin; ^{13}C NMR spectroscopy; glycosidation; trisaccharide

Introduction

Cello-oligosaccharides are simple, yet useful cellulose model compounds with regard to the solid-state structural and analytical features.[1,2,3] Many synthetic efforts were thus directed towards step-wise or convergent chemical synthesis of cellooligosaccharides. For that, generally two synthetic tasks must be accomplished: regioselective 1,4-glycosidic bond formation with β-stereospecificity. In a stepwise approach, for instance, oligomers up to cellotetraose were synthesized.[4,5,6] Later, some cello-oligomers up to the octamer were obtained by a linear approach.[7] In an convergent approach, a benzyl and pivaloyl protected allyl cellooctaoside was obtained and deprotected into cellooctaose.[8] All these approaches provided either the free reducing sugars or corresponding alkyl glycosides.

In our general approach to cellulose model compounds, we use cellodextrins which represent sections of the cellulose chain rather than their proximal or terminal ends, i.e. model compounds with proximal protection of OH-4 and terminal protection of OH-1, such as methyl 4′-*O*-methyl-β-D-cellobioside (**1**), which was the first cellodextrin model compound for cellulose[9] found to crystallize in two distinct phases.[10] As supported by the allomorphism of **1**, these models are thought to resemble cellulose with regard to crystal structure and hydrogen bond patterns more closely than reducing cellodextrins or simple alkyl glucosides traditionally studied so far. Comprehensive characterization of both allomorphs of **1** by X-ray crystallography, ^{13}C CPMAS NMR, and FTIR, showed distinct differences in the hydrogen bond networks and indicated an unexpectedly high effect of the crystal packing on the chemical shifts.[11] The availability of complete solid-phase structural data of **1** prompted us towards the synthesis of ^{13}C-perlabeled material, which constitutes an ideal probe for CPMAS studies of the

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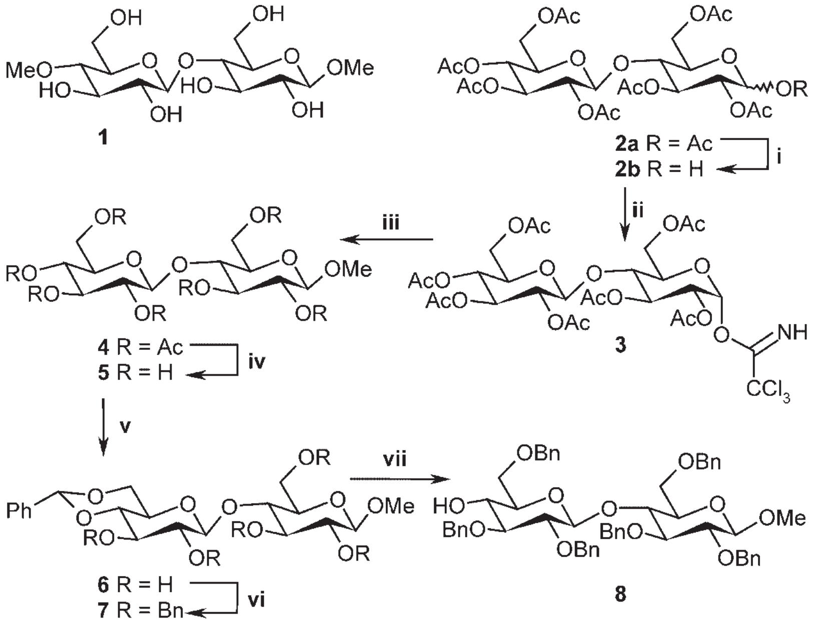
hydrogen bond network in cellodextrins and their changes upon swelling and dissolution processes.[12] Due to the considerable intensity gain in the ^{13}C domain, it appears reasonable that an eventual resolution of the H domain can be achieved. With the hydrogen bond pattern being known from X-ray studies, these data can be correlated with the CPMAS and FTIR results.

However, methyl 4′-*O*-methyl-*β*-D-cellobioside (**1**) – despite its certainly intriguing features – is still the smallest of cellodextrin derivatives with terminal and proximal methyl caps which – as cellulose model compound – must naturally have a limited predictive power. Thus, we aimed at the next higher homologues, which would show better comparability to cellulose. Considering the basic cellobiose repeating units of cellulose, a cellotetraose derivative would follow as the next higher homologue to a single cellobiose unit. However, we considered the "intermediate" stage of a cellotriose especially interesting with regard to differences in length, angles and dihedrals of the interglucosidic linkages in solid state. Theoretically, target compound **17** could represent a composite of three equivalent glucose units having two largely identical interglucosidic bonds, whereas a "cellobiose + glucose" construct would translate into two differing interglucosidic linkages. The latter case would also occur for a cellotetraose homologue composed of two cellobiose units, if the central linkage was different from the two outer ones.

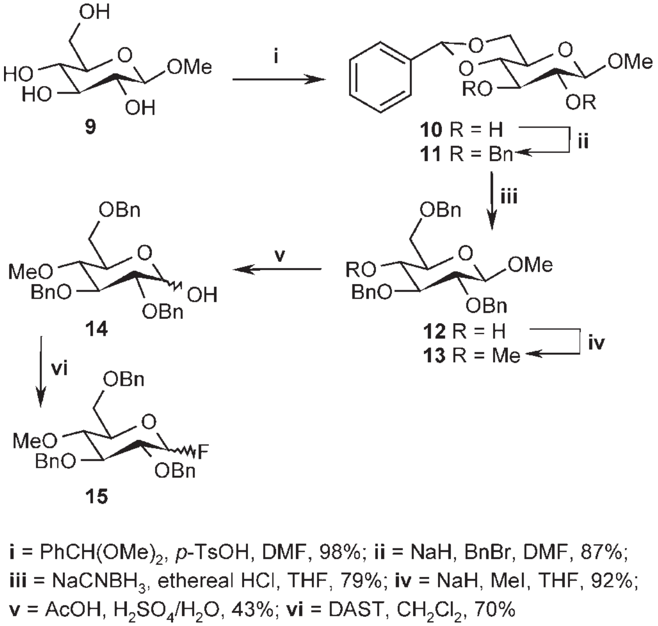
Results and Discussion

Taking into account increasing difficulties in separation of *α*/*β*-isomers and in the selective methylation of the proximal



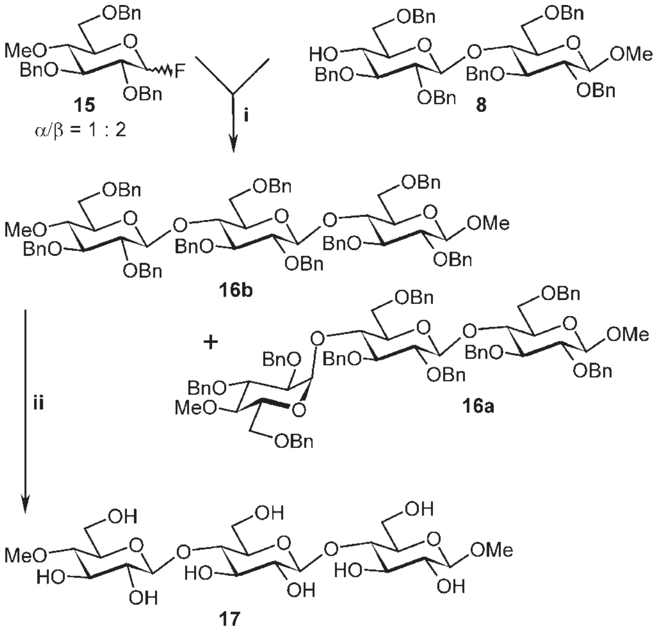
i = hydrazinium acetate, DMF, 98%, **ii** = CCl_3CN, $CsCO_3$, CH_2Cl_2, 80%;
iii = MeOH, TMS triflate, MeCN, 60%; **iv** = NaOMe, MeOH, 99%;
v = $PhCH(OMe)_2$, *p*-TsOH, DMF, 81%; **vi** = NaH, BnBr, DMF, 71%;
vii = $NaCNBH_3$, ethereal HCl, THF, 77%

Scheme 1.
Synthesis of glycosyl acceptor **8** from cellobiose octaacetate (**2a**).



i = $PhCH(OMe)_2$, *p*-TsOH, DMF, 98%; **ii** = NaH, BnBr, DMF, 87%;
iii = $NaCNBH_3$, ethereal HCl, THF, 79%; **iv** = NaH, MeI, THF, 92%;
v = AcOH, H_2SO_4/H_2O, 43%; **vi** = DAST, CH_2Cl_2, 70%

Scheme 2.
Synthesis of glucosyl donor 15 from methyl β-D-glucopyranoside (9).



i = $BF_3{*}Et_2O$, MeCN, 52% (**8**, 35% recovery);
ii = column separation, H_2/Pd-C, MeOH, 98%

Scheme 3.
Convergent synthesis of target trisaccharide 17.

4-OH group when going to higher cellodextrin congeners, we chose a convergent synthesis toward trisaccharide **17**, employing a glucosyl donor and a cellobiose-derived acceptor, which should additionally be usable for the synthesis of higher cellodextrins upon coupling with other donors. The synthesis of the acceptor, methyl 2,3,6-tri-*O*-benzyl-*β*-D-glucopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-*β*-D- glucopyranoside (**8**) started from cellobiose peracetate (**2a**), providing the product in 21% overall yield (Scheme 1). Glycosidation of trichloroacetimidate **3** was the key in the 7-step-sequence, which was thoroughly optimized. Usage of sufficiently activated molecular sieves, a reaction temperature of –30 °C and addition of TMS triflate in several small portions gave best results. Also, stopping the reaction by TEA addition after 30 min was a good compromise between incomplete consumption of the starting material and overly pronounced byproduct formation. Formation of benzylidene acetal **6**, benzyl protection of the remaining free hydroxyls and selective ring opening to provide the free 4′-OH group were standard procedures, performed as recently described for methyl 4′-*O*-methyl-*β*-D-cellobioside (**1**).

The glucosyl donor was synthesized in 6 steps starting from methyl *β*-D-glucopyranoside in 19% overall yield (Scheme 2). Demethylation of fully protected methyl glucoside **13** clearly was the yield-limiting step. For conversion into the fluoride, different reaction temperatures (0 °C to r.t.) in combination with different solvents, such as Et_2O, CH_2Cl_2 or THF, and different reaction times (15 min to 3 h) were tested,

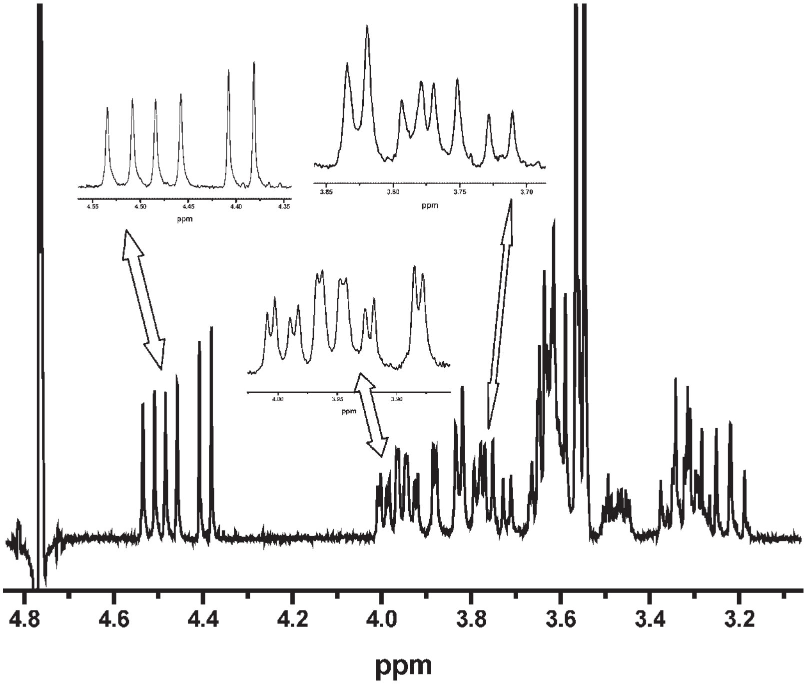


Figure 1.
^{1}H NMR spectrum of **17** recorded in D_2O. The regions of H-1′/H-1″/H-1 (upper left inset), H-6a/H-6a′/H-6a″(upper right inset), and H-6b/H-6b′/H-6b″ (lower inset) being zoomed out. Listing of the proton resonances: ^{1}H NMR (D_2O): δ 4.52 (d, 1 H, $J_{1',2'} = 7.9$ Hz, H-1′), 4.47 (d, 1 H, $J_{1'',2''} = 7.9$ Hz, H-1″), 4.39 (d, 1 H, $J_{1,2} = 8.0$ Hz, H-1), 4.00 (dd, 1 H, $J_{5,6b} = 1.9$ Hz, $J_{6a,6b} = 5.9$ Hz, H-6b), 3.95 (dd, 1 H, $J_{5',6b'} = 1.3$ Hz, $J_{6a',6b'} = 5.9$ Hz, H-6b′), 3.90 (dd, 1 H, $J_{5'',6b''} = 2.3$ Hz, $J_{6a'',6b''} = 12.4$ Hz, H-6b″), 3.84–3.77 (m, 2 H, H-6a, H-6a′), 3.74 (dd, 1 H, $J_{5'',6a''} = 5.3$ Hz, H-6a″), 3.68–3.55 (m, 7 H, H-5, H-5′, H-4, H-4′, H-3, H-3′, H-3″), 3.57 (s, 3 H, 1-OMe), 3.55 (s, 3 H, 4″-OMe), 3.51–3.44 (m, 1 H, H-5″), 3.38–3.21 (m, 4 H, H-2, H-2′, H-2″, H-4″).

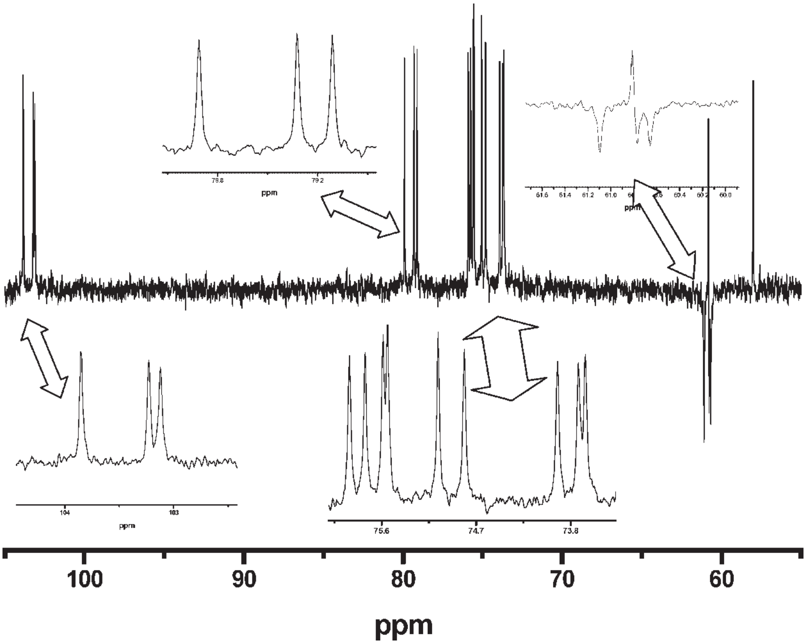


Figure 2.

Proton-decoupled ^{13}C NMR spectrum of **17** recorded in D_2O. Different signal groups are being zoomed out: C-1/C-1′/C-1″ (lower left inset), C-4″/C-4′/C-4 (upper left inset), C-3″/C-5″/C-5′/C-5/C-3′/C-3/C-2″/C-2′/C-2 (lower right inset), C-6″/4″-OMe/C-6′/C-6 (upper right inset). Listing of the carbon resonances: ^{13}C NMR (D_2O): $\underline{\delta}$ 103.85 (C-1), 103.23 (C-1′), 103.12 (C-1″), 79.91 (C-4″), 79.32 (C-4′), 79.11 (C-4), 75.91 (C-3″), 75.76 (C-5″), 75.59 (C-5′), 75.54 (C-5), 75.06 (C-3′), 75.06 (C-3), 73.93 (C-2″), 73.73 (C-2′), 73.66 (C-2), 61.10 (C-6″), 60.81 (4″-OMe), 60.77 (C-6′), 60.66 (C-6), 58.01 (1-OMe).

optimum yield of the fluoride donor **15** being obtained by treatment of reducing sugar **14** with 1.5 equivalents of DAST in CH_2Cl_2 at 0 °C and 20 min reaction time. While the 1:2 α/β-ratio, as determined by ^{1}H-NMR, was largely invariant, the overall reaction yield proved to be highly sensitive towards changes of the reaction conditions.

Optimization of the reaction between equimolar amounts of acceptor **8** and donor **15** (Scheme 3) showed the glycosylation to proceed best at 0 °C with 1.5 equivalents of BF_3 etherate catalyst being added gradually, using the beneficial effect of the solvent acetonitrile. After 5 h, the donor was completely consumed, giving 52% of trisaccharide product **16a** and **16b** ($\alpha/\beta = 1{:}2.5$) and 35% of recovered acceptor **8**. All attempts to further boost the yield by using excess donor or to increase the α/β-ratio were unsuccessful. Chromatographic separation of the cellotriose derivative **16b** and debenzylation provided the target compound methyl 4″-*O*-methyl-β-D-cellotrioside (**17**) in 35% yield relative to acceptor **8**.

Compound **17** was thoroughly characterized by solution NMR techniques. The proton and carbon spectra are given in figures 1 and 2, respectively. While the proton trace showed severe overlap, the carbon signals were fully assigned. Signal assignment, as given in the captions to figures 1 and 2, was based on correlated NMR techniques and on comparison to the NMR data of **1**.

A comprehensive characterization of the solid state features of **17** – and their comparative evaluation with regard to cellulose model compounds and cellulose allomorphs as outlined in the introduction - will be reported in due course.

Conclusion

A high-yield synthesis of the trisaccharide cellulose model compound methyl 4″-*O*-methyl-β-D-cellotrioside (**17**) *via* cellobioside acceptor **8** and glucosyl fluoride donor **15** was established. The target compound, being the higher homologue of the recently prepared 4′-*O*-methyl-β-D-cellobioside (**1**), is required to study by solid-state techniques the hydrogen bond network in cellodextrins and cellulose, and its changes upon swelling and dissolution.

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