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PAPER

A study of anhydrocelluloses – Is a cellulose structure with residues in a $^1C_4$-conformation more prone to hydrolysis?†

Vrushali Jadhav, Christian M. Pedersen* and Mikael Bols*

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A study of the effect of introduction of 3,6-anhydroglucose residues in the cellulose structure on glycoside hydrolysis rate was performed. A cellotetrose with an 3,6-anhydroglucose as the third residue was synthesised. Acidic hydrolysis of this tetrasaccharide showed that hydrolysis of the 3,6-anhydro-β-D-glucoside linkage was 31.400 times faster than hydrolysis of cellobiose. A series of different 3,6-anhydrocelluloses with different degree of substitution were prepared by tosylation of cellulose with varying amounts of tosyl chloride in dimethylacetamide and subsequent treatment with sodium hydroxide. Anhydrocelluloses with degrees of substitution of 0.02, 0.07, 0.31 and 0.74 were obtained. The anhydrocelluloses were subjected to acidic hydrolysis in 2.0 M aqueous HCl and the rate of hydrolysis monitored by ion chromatography analysis of the amount of glucose and/or cellobiose formed. All 3,6-anhydrocelluloses hydrolyzed with a faster rate than cellulose, but the anhydrocellulose with a low degree of substitution (ds = 0.07) hydrolyzed fastest which was 90 times faster than cellulose.

Introduction

Cellulose is the most abundant organic molecule in the biosphere constituting up to 50% of biomass such as wood and straw.[1] The tremendous amount of cellulose available makes it a highly interesting molecule for exploitation, be it conversion to food, energy or materials.[2] At present the use of cellulose for materials such as paper and clothes is well established, but the use of cellulosic biomass for chemicals is more difficult, but would nevertheless be of high interest.[3]

Cellulose's structure of β-1,4-linked glucose oligomers (Fig. 1) allow it to form parallel strands that through intermolecular hydrogen bonding form a strong and highly stable structure that is very difficult to dissolve even in water making both chemical and biological degradation troublesome. Ionic liquids[4] and dimethylacetamide/LiCl[5] can dissolve cellulose but are expensive, toxic and/or incompatible with many reagents. Thus many depolymerisation protocols are forced to work with insoluble cellulose. Aqueous acidic hydrolysis of cellulose requires treatment with concentrated acids or long reaction times at high temperature and even then the yield may be low due to decomposition and side reactions.[6] The reaction is complicated by the fact that the initial part takes place in the solid phase leading to a depolymerisation of insoluble cellulose that eventually results in soluble oligosaccharides and subsequent faster hydrolysis.[7] Both reversible and irreversible decomposition reactions occur with the former giving 1,6-anhydrides, or glycosides (from reglycosylation) and the latter leading to furfurals *etc*.[8]

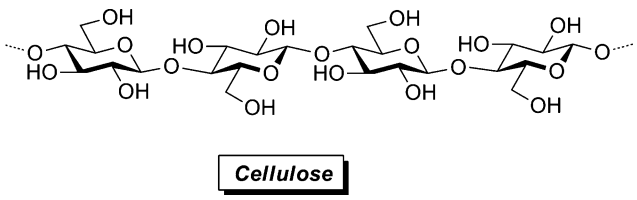

Fig. 1 The molecular structure of cellulose.

A fact that also makes cellulose very hard to depolymerise is that the 1,4-β-glucosidic bonds that link the glucose monomers together are extraordinary stable towards hydrolysis. Even when in solution, studies have shown that the half-life of spontaneous hydrolysis of a glycosidic bond is 5–8 million years,[9] and the hydrolysis catalysed by acid requires high temperatures and acid concentration. Making the glycosidic bonds more susceptible to acidic hydrolysis might be a way to make these compounds more readily degradable.

Our stimulus to the present study came from the exploration of stereoelectronic effects in carbohydrate and carbohydrate-like molecules.[10] We noticed an unexpected difference in the pK_a-value of two similar hydroxylated piperidines that we were studying as glycosidase inhibitors.[11] The all-*cis galacto*-isofagomine (**2**) was found to be 0.4 pK_a-units more basic than its corresponding *trans-trans gluco*-configured analogue, **1** (Fig. 2a). A more careful study of a wide range of piperidines with different electron-withdrawing groups revealed pK_a variations to be highly systematic. This

Department of Chemistry, University of Copenhagen, Universitetsparken 5, 2100, Copenhagen, Denmark. E-mail: bols@kemi.ku.dk

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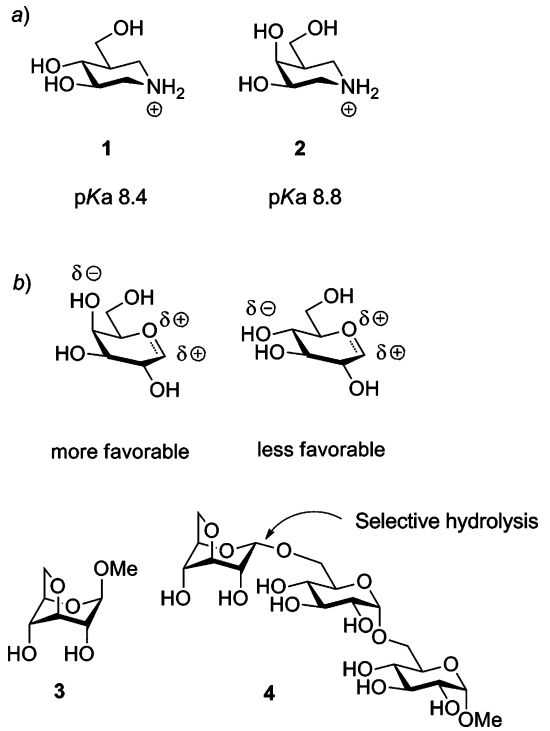


Fig. 2 Stereoelectronic effects make **1** a less basic piperidine than **2** (a). Similarly a *galacto*-configured oxacarbenium ion is more favorable than a *gluco*-configured ion (b). These effects make the 3,6-anhydro glucosides **3** and **4** more susceptible to hydrolysis than normal glucosides.

allowed us to assign specific values to each type of substituent that by means of a simple formula[11] with high accuracy could predict the pK_a value of a given protonated piperidine. Most striking was the fact that axially oriented electron-withdrawing groups were found to be less electron-withdrawing than their equatorially-placed counterparts. Charge–dipole interactions were found to be able to account for this phenomenon. Equatorially-oriented hydroxyl groups are hence more electron withdrawing than axially-placed hydroxyl groups much in the same way that F is more electron withdrawing than OH.

We soon realised that this effect could have bearing on other systems.[12] We used the substituent values to create a Hammett-type plot, to establish a one-to-one connection between the factors that determine the pK_a of a hydroxylated piperidine and the rate of hydrolysis of a corresponding glycoside.[13] This showed that the effects that govern piperidine basicity, which are expected to be electronic in nature, are the same that to a large degree influence glycoside reactivity. The common denominator in this case is the cationic structure of the protonated piperidine and the stability of the oxacarbenium ion-like transition state in glycoside hydrolysis (Fig. 2b). The presence of axially oriented hydroxyl groups would hence cause an enhancement of glycoside reactivity towards hydrolysis.[14]

The dehydrated 3,6-anhydrosugar **3** have undergone a ring flip from a $^4C_1$ to a $^1C_4$ conformation, which means that the hydroxyl substituents have moved from an equatorial to an axial orientation. This would, following the results mentioned above, be expected to be much more reactive than the corresponding glycoside in a relaxed $^4C_1$ conformation and this was in actual fact found experimentally. A reactivity increase of more than 400 fold was observed (Fig. 2).[15] We furthermore studied the reaction of a trisaccharide **4** (containing three glycosidic linkages) in acidic D_2O and found as expected the 3,6-anhydroglycosidic linkage to be the most labile due to the presence of more axially-oriented hydroxyl groups (Fig. 2).[15]

The latter research showed that glucose-containing saccharides could be activated towards hydrolysis by converting them into 3,6-anhydrosugars; in most of the cases studied conversion of a glucoside into the corresponding 3,6-anhydroglucoside led to a hydrolysis that occurred several hundred fold faster. For this reason it was suggested that this chemistry might be used to "activate" cellulose towards hydrolysis. If a few anhydrocellulose residues were introduced in cellulose this might conceivably lead to more readily degradable cellulose. Hydrolysis might proceed at a much faster pace at these modified sites and break the insoluble cellulose into smaller pieces that become soluble again leading to a faster overall rate (Fig. 3).

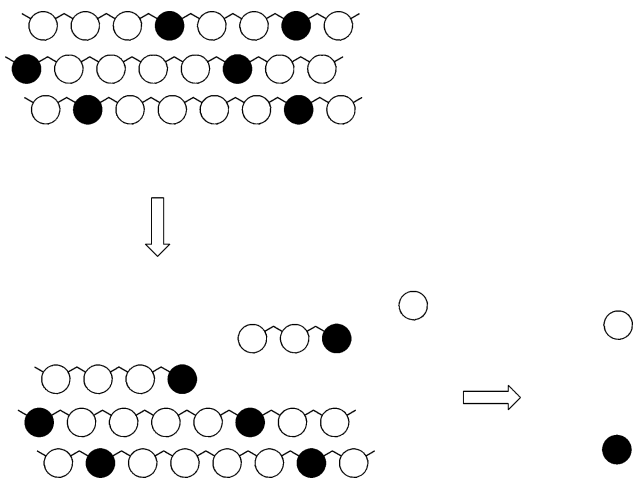


Fig. 3 Proposed depolymerisation of anhydrocellulose. ○ = glucose, ● = 3,6-anhydroglucose.

Indeed there are indications in the literature that this idea works. Gardner and Purves prepared an anhydrocellulose in 1943 and hydrolysis experiments indicated it hydrolysed readily.[16] Russian work from the 1960s also appear to show that an anhydrocellose is more susceptible to hydrolysis than ordinary cellulose.[17] Yet an anhydroglucose in an oligosaccharide is not always readily hydrolysed; an a mono 3,6-anhydrocyclodextrin did not undergo acidic hydrolysis preferentially at the 3,6-anhydro-residue.[15]

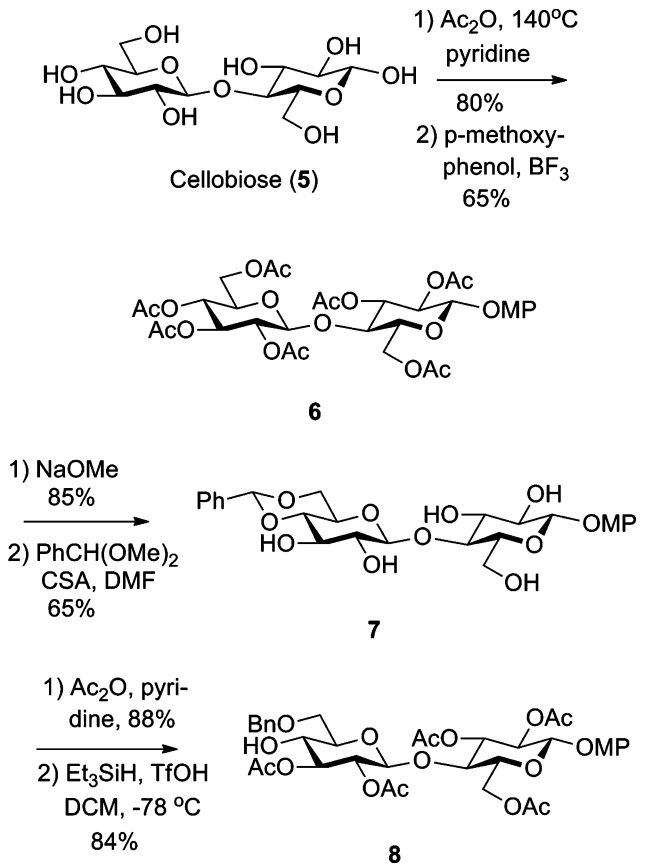
For this reason we wished to confirm these reports about the reactivity of anhydrocellulose. In this paper we have made a cellotetrose containing an 3,6-anhydroglucose residue and found that hydrolysis at the anhydroresidue is very fast. We also have prepared anhydrocelluloses with different degree of anhydro residues and show that depolymerisation is faster than cellulose.

Results and discussion

Synthesis of an anhydrocellotetrose

A suitable model compound for anhydrocellulose was judged to be a cellotetrose with a 3,6-anhydro ring at the 3rd residue *i.e.* 4′-*O*-[4-*O*-(β-D-glucopyranosyl)-3,6-anhydro-β-D-glucopyranosyl]cellobiose. Attempted preparation of this

compound is outlined in Schemes 1–3: Cellobiose **5** was acetylated with acetic anhydride/pyridine in 80% yield followed by glycosylation of *p*-methoxyphenol using $BF_3{\cdot}OEt_2$ as promoter (Scheme 1). This gave the β-glycoside **6** in 60% yield. After Zemplén deacetylation and reaction with dimethoxytoluene and camphorsulfonic acid, the 4′,6′-benzylidene derivative **7** was obtained in 51% yield over the two steps. Finally acetylation with acetic anhydride/pyridine followed by reductive opening of the benzylidene using triethylsilane and trifluoromethanesulfonic acid gave the disaccharide **8** in 84% yield.

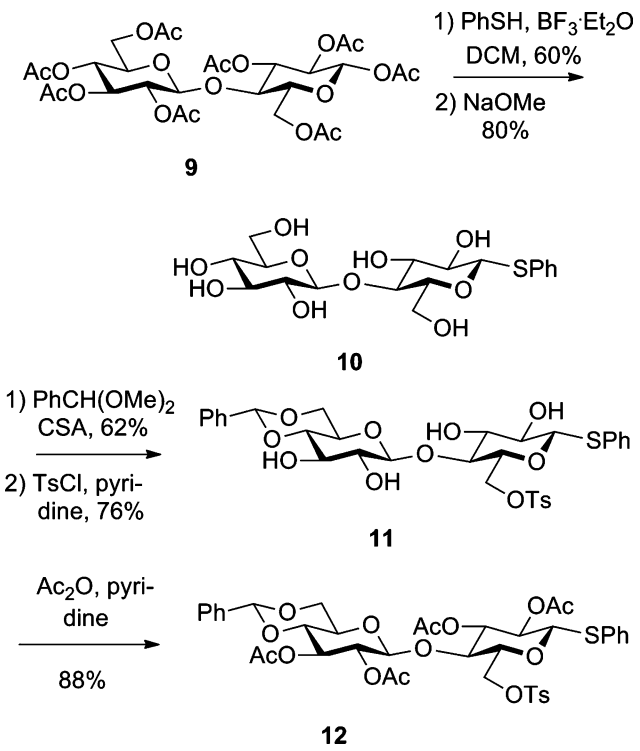


Scheme 1 Synthesis of the cellobiose acceptor **8**.

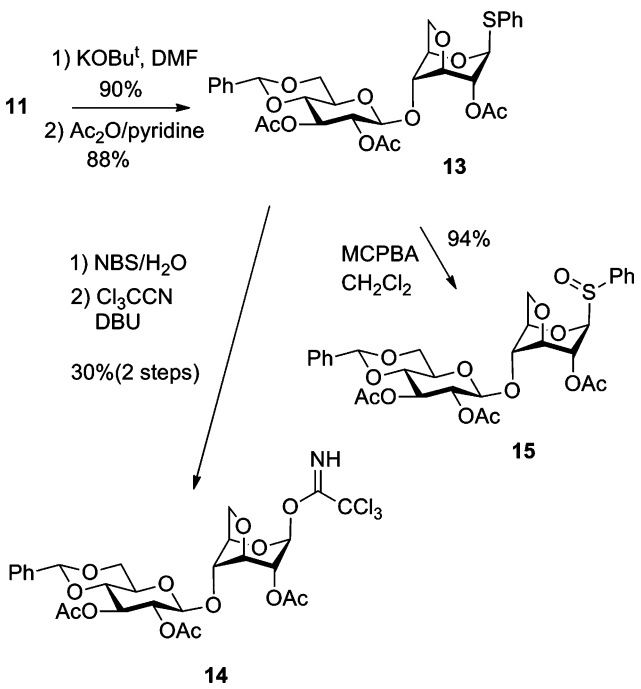
The glycosyl donor was prepared from cellobiose peracetate **9** that was reacted with thiophenol and $BF_3{\cdot}OEt_2$ in CH_2Cl_2, which after Zemplén deacetylation gave the thioglycoside **10** in 48% yield for the two steps (Scheme 2). Reaction with dimethoxytoluene and camphersulfonic acid led to the 4′,6′-*O*-benzylidene derivative that was selectively tosylated with tosyl chloride in pyridine to give the 6-*O*-tosyl derivative **11**. This compound was acetylated to give the donor **12**.

From **11** a series of anhydrocellobiose donors were prepared (Scheme 3). Reaction with potassium *tert*-butoxide in DMF followed by acetylation gave the anhydrothioglycoside **13** in 79% overall yield for the two steps. Oxidation of **13** afforded the sulfoxide **15** as one diastereoisomer. Hydrolytic cleavage of the thioglycoside **13** using NBS/H_2O[18] followed by reaction with trichloroacetonitrile gave the trichloroacetimidate donor **14**.

With the donors **13–15** in hand glycosylation with the acceptor **8** was attempted. Glycosylation with **13** using NIS/TfOH activation

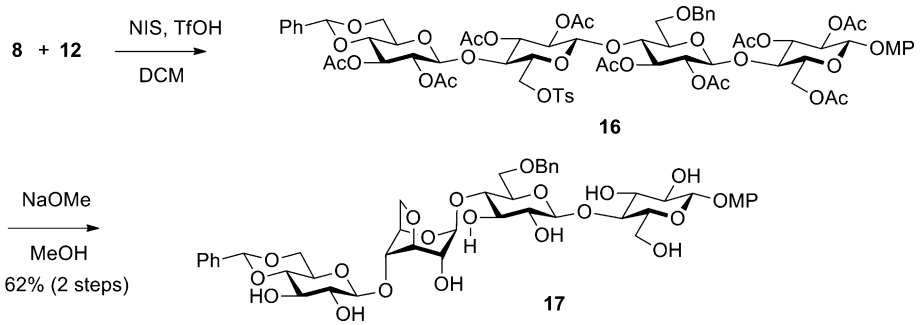


Scheme 2 Synthesis of cellobiose donor **12**.



Scheme 3 Synthesis of anhydrocellobiose donors **13–15**.

resulted in a complex mixture of products. Changing the activator system to DMSTS did not provide any cross coupling product, and the same was observed when using the TCA donor **14**. Activation of the sulfoxide donor **15** yielded a complex mixture as well, but MS indicated that the tetrasaccharide had been formed. Attempts to obtain the pure compound failed and neither debenzylation nor peracetylation proved to be helpful for the separation.



Scheme 4 Synthesis of cellobiosyl derivative **17**.

Due to the glycosylation problems with the variety of 3,6-anhydro-donors under different activation conditions, tactics had to be changed. The 6-*O*-tosyl-donor **12** was coupled to the acceptor **8** using TfOH and NIS giving the crude cellotetrose **16**, which was treated with sodium methoxide to give the anhydro derivative **17** in overall 62% yield (Scheme 4).

Final removal of the benzyl and benzylidene protective groups in **17** was tried under several different conditions: Catalytic hydrogenation with Pd/C and H_2(g), Pearlman's catalyst and H_2(g) and sodium in liquid ammonia was attempted, but neither reductive nor mildly acidic conditions could remove the benzyl and/or the benzylidene groups without also cleaving the glycosidic linkage at the anhydroglucoside. Acid scavengers in the Pd/C mediated hydrogenolysis inhibited the reaction. From the failed glycosylation attempts and the facile cleavage at the anhydro-glycoside to give the two disaccharides, it became evident that hydrolysis is indeed much faster at the anhydro-sugar than at a normal β-1,4-glucosidic residue. No cleavage of the benzylidene or any of the other glycosidic bonds was observed under these mildly acidic conditions. So in light of our problems in providing the unprotected target it was decided that **17** could act as a satisfactory replacement, since the acidic hydrolysis at the anhydro-linkage can be done selectively, and the *O*-benzylidene, which is quite remote, and the *O*-benzyl should have a minor influence on the reaction.

Acidic hydrolysis of 17

The hydrolysis of **17** was initially studied by NMR using 0.01 M DCl in D_2O. The reaction was finished after 4 h showing exclusive hydrolysis of the glycosidic linkage of the anhydro-sugar without cleavage of the benzylidene or any other glycosidic bonds. With the stability of the benzylidene established, kinetic measurements were carried out using optical rotation. As a reference compound for a β-glucosidic linkage was used cellobiose (**5**). The hydrolysis of **5** was however so sluggish compared with the 3,6-anhydro tetrasaccharide, that it became necessary to use Arrhenius plots in order to compare the data. The hydrolysis of cellobiose has been studied by Bobleter *et al.*[19] in diluted H_2SO_4, hence the acid was changed to H_2SO_4 (0.01 M). From the Arrhenius plot of these data the hydrolysis rates at 60 °C could be calculated for cellobiose (**5**) to be 1.1×10^{-6} min^{-1} and be compared to that of the tetrasaccharide **17**, which was 3.48×10^{-2} min^{-1} (Table 1). The hydrolysis products from the reaction of **17** under these conditions were analyzed by NMR and only the two disaccharide fragments, with intact protective groups, could be detected.

Table 1 Rate constants in min^{-1} for hydrolysis of **17** in 0.01 M H_2SO_4

	k (30 °C)	*k* (40 °C)	*k* (50 °C)	*k* (60 °C)
17	0.0016	0.005	0.0139	0.0348
Cellobiose (5)	—	—	—	1.11×10^{-6}[a]

[a] This rate constant was obtained from an Arrhenius plot of the data in Bobleter *et al.*[19]

These result mean that the anhydroglycosidic bond in **17** reacts 31400 times faster than an ordinary β-glucosidic bond. Thus introduction of an 3,6-anhydroresidue into a cellooligosaccharide has a profound effect its hydrolysability.

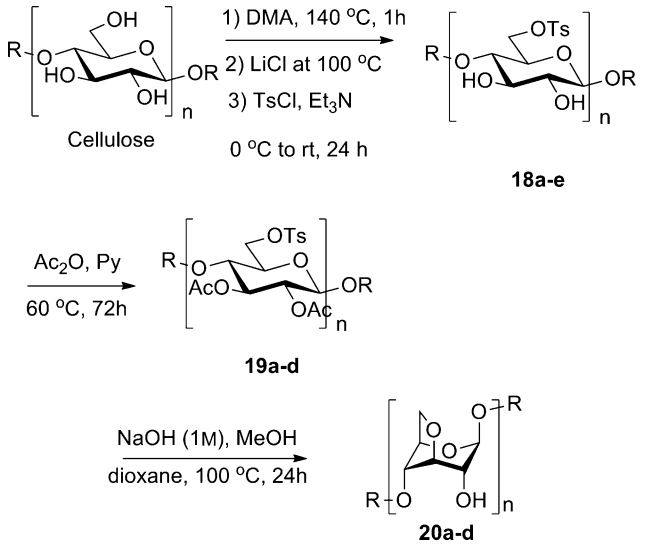
Preparation of the anhydro celluloses

We then decided to investigate if the effect observed in **17** could be reproduced in cellulose and if it would lead to a faster degradation of cellulose according to the scheme proposed in Fig. 3. Previous preparations of anhydrocelluloses[15,16] have used tosylation of the 6-OH groups with TsCl followed by treatment with base, and though such procedures have poor atom economy they were chosen to prove the concept. The procedure by Heinze and coworker was followed:[20] The cellulose was suspended in *N*,*N*-dimethylacetamide, which was heated to 140 °C where LiCl was added, followed by cooling to room temperature, which interrupted the hydrogen bond patters in the cellulose leading to a solution of cellulose (Scheme 5). Varying amounts of TsCl and Et_3N were added to the solution at 0 °C and it was allowed to react at rt for 24 h, where the tosylated celluloses **18a–d** were precipitated from ice water. The dried products were analyzed by elementary analysis and the degree of sulfur substitution (DSs) could be determined to be from 0.0 to 0.74 depending on the conditions (Table 2).

Table 2 Degree of substitution of tosylate (DSs) obtained in a series of celluloses made by reaction with varying amount of TsCl/Et_3N according to Scheme 5. Eq. is equivalents of reagent used per glucose residue

	TsCl (eq.)	Et_3N(eq.)	%S[a]	DSs[b]
18a	1.8	3.6	8.6	0.74
18b	0.9	1.8	4.8	0.31
18c	0.45	0.9	1.3	0.07
18d	0.2	0.4	0.4	0.02
18e	0.1	0.2	0.0	0.00

[a] Obtained from sulfur analysis. [b] The DSs is calculated from %S.



Scheme 5 Preparation of anhydrocelluloses **20a–d**.

Formation of the 3,6-anhydro linkage required some experimentation; neither NaH in DMF for 24 h, NaOH (2 M) at 100 °C for 24 h nor *t*-BuOK in DMF for 24 h provided any isolable product. The 3,6-anhydro celluloses (**20a–d**) could however be prepared in a two step procedure; first peracetylation followed by treatment with NaOH (1 M) in MeOH to give cellulose derivatives with varying amounts of 3,6-anhydro units. The sulfur content was estimated from elementary analysis before and after base treatment. Only in the case with the highly tosylated cellulose a significant sulfur residue was detected, the content was nearly 0 in all other cases *i.e.* the highly tosylated cellulose contained 2-*O* and 3-*O*-tosylates as well.

Acidic hydrolysis of anhydrocelluloses

Hydrolysis of cellulose and anhydrocelluloses were carried out using HCl (2 M) at 60 °C. Samples were taken from the reaction mixture and analyzed by ion chromatography, where glucose formation could be detected. These data do not directly tell us how fast the anhydroglucosidic bond are hydrolysed, because formation of glucose require cleavage of more than one glycosidic linkage of which at least one will be of 'normal' type. However the rate of glucose formation will be an indication of whether the presumed fast hydrolysis of the anhydroglucosidic bonds results in a breakdown in smaller pieces that are hydrolysed faster. The measurement of increase of glucose over time clearly showed that all the anhydro-celluloses produced glucose faster than cellulose itself (Fig. S1†). The start of the reaction is similar for all the derivatives investigated, and a linear formation of glucose is observed. The rate of these reactions are listed, in comparison to cellulose, in Table 3. **20c**, the cellulose with 7% anhydroresidues were found to the modified cellulose that was degraded to glucose fastest. This compound produced glucose 90 times faster than cellulose itself. (Table 3). This suggests that the optimal amount of anhydro-sugar units is around 7%. The anhydrocelluloses with a higher or lower content of anhydrosugars formed glucose more slowly (Table 3), yet faster than cellulose. For the more substituted celluloses (**20a** and **20b**) this may be due to the fact, particularly for **20a**, that they have less glucose in the polymer. When only

Table 3 Relative rate for the hydrolysis of anhydrocelluloses **20a–20d** in 2 M HCl at 60 °C

	No. of anhydro	$V/(\mathrm{mM\ h^{-1}})^a$	Relative rate
20a	74%	1.17×10^{-2}	9
20b	31%	2.19×10^{-2}	12
20c	7%	1.71×10^{-1}	90
20d	2%	1.36×10^{-2}	7
Cellulose	0%	1.9×10^{-3}	1

[a] Initial rate of formation of glucose as determined by IC.

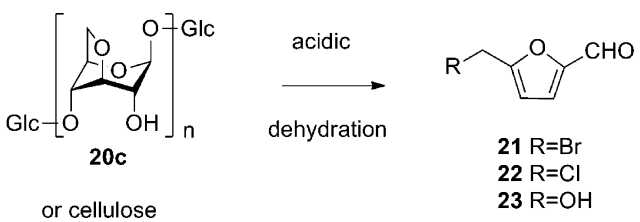
26% of the residues in the polymer is glucose residues it is obvious that the amount of glucose that is formed decreases. Yet glucose formation is still 9 times faster than for cellulose itself. With a lower content of anhydroresidues (**20d**) the number of strand breaking points is apparently too low to achieve a large increase. It may be argued the dissolution of the cellulose in DMA/LiCl and the subsequent precipitation could perceivably lead to a product that due to less crystallinity and less hydrogen bonding would hydrolyse faster. However this is contradicted by the observation that **20d** hydrolyse considerably slower than **20c**, because both compounds have been subject to similar conditions.

Another concern is that the substitution of glucose residues in cellulose with anhydrocellulose residues in the $^1C_4$ conformation perturb the crystalline strand-like structure and the hydrogen-bonding, and that this alone may increase the susceptibility of the cellulose to undergo hydrolysis. This can not be excluded, but an influence from the high reactivity of anhydroresidues is nevertheless better documented and thus more probable.

Overall these experiments are proof of concept for the idea that a cellulose, with a minor content of 3,6-anhydroglucose units, hydrolyse faster than cellulose itself.

Preparative experiments with 20c

To see if the anhydrocellulose could also advantageously be employed in furfural synthesis a series of experiments were performed with **20c** and compared to similar experiments done with cellulose. Synthesis of 5-hydroxymethylfurfural (**23**, HMF), 5-bromomethylfurfural (**21**, BMF) and 5-chloromethylfurfural (**22**, CMF) were performed, from either **20c** or microcrystalline cellulose, using literature procedures.[21,22] The anhydro cellulose **20c**, containing app. 7% anhydro residues, was used as the substrate and compared with pure cellulose as the reference compound (Scheme 6). The progress in the reactions was followed using HPLC to quantify the amount of product formed over time (Fig. S2–S4†). In Table 4 is shown the preparative yields and relative rates between initial rate of reaction.



Scheme 6 Synthesis of furfurals from anhydrocellulose **20c**.

Table 4 Yields and rates for formation of furfurals according to Scheme 6

Substrate	Reagents	Product	Yield	Rel. rate[a]
20c	HBr, LiBr, PhMe, 30 h	21	88%	1.3
Cellulose	HBr, LiBr, PhMe, 30 h	21	79%	1
20c	HCl, LiCl, PhMe, 30 h	22	71%	1.1
Cellulose	HCl, LiCl, PhMe, 30 h	22	62%	1
20c	HCl, LiCl, $CrCl_2$, 24 h	23	64%	5.2
Cellulose	HCl, LiCl, $CrCl_2$, 24 h	23	42%	1

[a] The relative start rate of formation of product from **20c** compared to cellulose determined by HPLC

It is seen from Table 4 that while **20c** is always a better starting material than unmodified cellulose, the difference in yield and rate of product formation is widely different. In synthesis of BMF (**21**) and CMF (**22**) the level of improvement is rather marginal. Yields are slightly better, and products are formed slightly faster. On the other hand for HMF (**23**) formation there is a clear improvement in terms of yield and rate.

The reason for this difference is comparatively easy to explain. In the synthesis of **21** and **22** concentrated acid is employed. This means that all glycosidic bonds are degraded rapidly regardless of whether they are modified or not. The conditions for preparations of HMF (**23**) on the other hand is much milder as a low concentration of acid is used. Therefore the lability of the glycosidic linkages is important in this synthesis.

Conclusions

In the present work we have shown that incorporation of anhydrosugars into the cellulose can enhance the hydrolysis of the saccharide. In a soluble cellulose-like tetrasaccharide the 3,6-anhydroglucosic linkage was hugely more labile (31.400 times) towards acid hydrolysis than an ordinary β-glucosidic linkage, which shows the potential of the incorporation of anhydroresidues.[23] In microcrystalline cellulose where some anhydro residues had been incorporated it was also found that the rate of hydrolysis, and the rate with which glucose was formed increased though the improvement was more modest (up to 90 times). An incorporation of approximately 7% anhydrosugars was found to be optimal for formation of glucose. Synthesis of furfurals from this anhydrocellulose gave slightly improved to superior yields and higher rate of reaction in some cases. The work shows that anhydrocelluloses are far more readily hydrolysed/degraded, and that they may pave the way for more efficient biomass conversion. In order to achieve this it will be necessary to find less expensive and economical ways of preparing the anhydrocelluloses.

Experimental

p-Methoxyphenyl 2,3,6-tri-*O*-acetyl-4-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-glucopyranoside (6)

A suspension of NaOAc (0.68 g, 10 mmol) in Ac_2O (11 mL, 100 mmol) was heated to reflux at 140 °C. To this was added D-cellobiose **5** (3 g, 10 mmol) in portions, and the reaction was heated at 140 °C for further 1 h. After completion of the reaction, the reaction mixture was concentrated to remove Ac_2O. Then H_2O (50 mL) was added to the reaction mixture, and the aqueous layer was extracted with $CHCl_3$ (2 × 75 mL). The $CHCl_3$ layer was washed with water 2–3 times, and the resulting organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to provide the crude per-acetylated cellobiose **9**. To a solution of this compound (2.5 g, 3.6 mmol) and 4-methoxyphenol (2.1 mL, 16.9 mmol) in dry CH_2Cl_2 (40 mL), Boron trifluoride ethyletherate (1.3 mL, 10.3 mmol) was added slowly at 0 °C under nitrogen atmosphere. After stirring for 6 h at 0 °C to room temperature, the reaction mixture was quenched with a solution of saturated $NaHCO_3$ (10 mL). The resulting organic layer was washed once with 1 M NaOH (20 mL), and water and the organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was loaded on an silica gel column and eluting with EtOAc/PE = 1 : 4 gave pure **6** (1.78 g, 65%) as a white solid; R_f 0.5 (EtOAc:PE = 3 : 2); mp = 176 °C; HRMS-ES $[M+Na]^+$: found 765.2360, calculated 765.2320.

p-Methoxyphenyl 4-*O*-(β-D-glucopyranosyl)-β-D-glucopyranoside (6a)

To a solution of **6** (1.5 g, 2.0 mmol) in MeOH (30 mL) was added a catalytic amount of NaOMe in MeOH at room temperature. After stirring for 2 h, the reaction mixture was concentrated *in vacuo* and the residue was loaded directly onto a silica gel column. Eluting with CH_2Cl_2/MeOH = 4 : 1 yielded pure **6a** (0.76 g, 85%) as a white solid; R_f 0.5 (CH_2Cl_2/MeOH = 5 : 5); mp = 197 °C; $[\alpha]_D^{20}$ −24.7 (*c* 1.9, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 7.13 (d, J = 9.1, 2H, C_6H_4), 6.98 (d, J = 9.1, 2H, C_6H_4), 5.02 (d, J = 7.9, 1H, H-1), 4.55 (d, J = 7.9, 1H, H-1′), 4.03–3.96 (m, 1H, H-6), 3.97 (dd, J = 12.3, 1.9, 1H, H-6′), 3.85 (dd, J = 12.3, 4.2, 1H, H-6), 3.82 (s, 3H), 3.76–3.70 (m, 4H, H-6′, H-4, H-4′, H-5), 3.60 (td, J = 7.9, 2.4, 1H, H-5′), 3.58–3.50 (m, 2H, H-2, H-3′), 3.49–3.42 (m, 1H, H-3), 3.36 (dd, J = 9.1, 8.1, 1H, H-2′); ^{13}C NMR (125 MHz, D_2O) δ 154.72, 150.87 (quaternary C of C_6H_4), 118.8, 118.2, 115.0 (C_6H_4), 102.6 (C-1′), 101.0 (C-1), 78.4, 75.9, 75.5, 74.8, 74.1, 73.1, 72.7, 69.4 (C2, C2′, C3, C3′, C4, C4′, C5, C5′), 60.6, 59.9 (C6, C6′), 55.7 (OCH_3). HRMS-ES [M+Na]+: found 471.1486, calculated 471.1581.

p-Methoxyphenyl 4-*O*-(4′,6′-*O*-benzylidiene-β-D-glucopyranosyl)-β-D-glucopyranoside (7)

To a solution of *p*-methoxyphenyl 4-*O*-(β-D-glucopyranosyl)-β-D-*gluco*-pyranoside (**6a**, 0.7 g, 1.5 mmol) in DMF was added catalytic amount of CSA (0.036 g, 0.15 mmol) and benzylidienedimethylacetal (0.28 g, 1.8 mmol) followed by heating on rotary evaporator at 60 °C for 2 h. After 2 h, DMF was removed by raising temperature of water bath to 100 °C, and the residue was subjected to silica column chromatography (MeOH/$CHCl_3$ = 0.5 : 9.5) to yield pure **7** (0.54 g, 65%) as a white solid; R_f 0.5 (MeOH/$CHCl_3$ = 1 : 9); mp = 215 °C; $[\alpha]_D^{20}$ −27.5 (*c* 1.0, CH_3OH); ^{1}H NMR (500 MHz, CD3OD) δ 7.51–7.16 (m, 5H, C6H5), 6.92 (d, J = 9.1 Hz, 2H, C_6H_4), 6.72 (d, J = 9.1 Hz, 1H, C_6H_4), 5.45 (s, 1H, CH-Ph), 4.70 (d, J = 7.7 Hz, 1H, H-1), 4.51 (d, J = 7.8 Hz, 1H, H-1′), 4.19 (dd, J = 10.1, 4.0, Hz 1H, H-6), 3.75 (bd, J = 3.0 Hz, 2H, H-6, H-6′), 3.66 (s, 3H, OCH3), 3.60–3.33 (m, 8H, H-2, H-3, H-3′, H-4, H-4′, H-5, H-5′, H-6′), 3.22 (t, J = 8.2 Hz, 1H, H-2′); ^{13}C NMR (125 MHz, CD3OD) δ 153.2, 150.0 (quaternary C of C_6H_4), 136.0, 127.4, 126.5, 124.9, 116.4, 112.8 (C_6H_5, C_6H_4), 102.4 (CH-Ph), 100.2 (C-1′), 99.8 (C-1a), 79.0, 78.3, 73.6, 73.3, 72.9, 71.7, 71.5,

66.6 (C2, C2′, C3, C3′, C4, C4′, C5, C5′), 64.8, 58.9 (C6, C6′), 53.9 (OCH_3). HRMS-ES [M+Na]+: found 559.1832, calculated 559.1894.

p-Methoxyphenyl 2,3,6-tri-*O*-acetyl-4-*O*-(2′,3′-di-*O*-acetyl-4′,6′-*O*-benzylidiene-β-D-glucopyranosyl)-β-D-*gluco*-pyranoside (7a)

To a solution of compound **7** (0.5 g, 0.93 mmol) in pyridine (2 mL), Ac_2O (0.56 mL, 5.6 mmol) was added and the reaction mixture was stirred at 25 °C for 6 h. After completion, the reaction mixture was concentrated *in vacuo* to remove Ac_2O and pyridine and the residue was purified by silica gel column chromatography. Elution with EtOAc/PE = 2.5 : 7.5 gave compound **7a** (0.7 g, 88%) as a white solid; R_f 0.5 (EtOAc:PE = 5 : 5); mp = 243 °C; $[\alpha]_D^{20}$ −15.7 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.32 (m, 5H, C_6H_5), 6.92 (d, J = 9.0 Hz, 2H, C_6H_4), 6.79 (d, J = 9.0 Hz, 2H, C_6H_4), 5.48 (s, 1H, CHPh), 5.25 (td, J = 9.1, 6.7 Hz, 2H, H-3, H-2′), 5.16–5.08 (t, J = 15.0 Hz, 1H, H-3′), 4.97–4.88 (m, 2H, H-1, H-2′), 4.61 (d, J = 7.8 Hz, 1H, H-1′), 4.50 (dd, J = 11.9, 1.9 Hz, 1H, H-6), 4.36 (dd, J = 10.3, 4.8 Hz, 1H, H-6′), 4.17–4.08 (m, 2H, H-6, H-6′), 3.86 (t, J = 15.0 Hz, 1H, H-4), 3.78–3.63 (m, 2H, H-5, H-5′), 3.76 (s, 3H, OCH_3), 3.48 (td, J = 9.7, 4.9 Hz, 1H, H-4′), 2.09 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.3, 169.7, 169.6 (s, $COCH_3$), 156, 151.1 (quaternary C of C_6H_4), 136.7, 129.5, 128.5, 126.3, 118.9, 114.7 (C_6H_5, C_6H_4), 101.7 (C1′), 100.2 (C-1), 91.6 (CHPh), 78.1, 76.8, 73.3, 72.8, 72.7, 72.1, 71.7, 68.7 (C2, C2′, C3, C3′, C4, C4′, C5, C5′), 66.6, 62.1 (C6, C6′), 55.8 (OCH_3), 21.2, 21.1, 20.93, 20.9, 20.8 ($COCH_3$). HRMS-ES [M+Na]+: found 769.2334, calculated 769.2422.

p-Methoxyphenyl 2,3,6-tri-*O*-acetyl-4-*O*-(2′,3′-di-*O*-acetyl-6′-*O*-benzyl-β-D-glucopyranosyl)-β-D-glucopyranoside (8)

To a solution of *p*-methoxyphenyl 2,3,6-tri-*O*-acetyl-4-*O*-(2′,3′-di-*O*-acetyl-4′,6′-*O*-benzylidiene-β-D-glucopyranosyl)-β-D-glucopyranoside (**7a**, 0.55 g, 0.73 mmol) in CH_2Cl_2 at −78 °C was added TfOH (0.35 mL, 2.2 mmol). Then Et_3SiH (0.22 mL, 2.5 mmol) was added dropwise and the mixture was stirred at −78 °C for 0.5 h. After 0.5 h the reaction was quenched with Et_3N (0.5 mL) and MeOH (0.5 mL), $NaHCO_3$ (5 mL) was added to the reaction mixture followed by extraction with CH_2Cl_2 (2 × 10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* and the residue was loaded on silica gel column. Eluting with EtOAc/PE = 1 : 4 gave pure compound **8** (0.46 g, 84%) as a white solid; R_f 0.5 (EtOAc/PE = 6 : 4); mp = 176 °C; $[\alpha]_D^{20}$ −13.6 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.29 (m, 5H, Ph), 6.91 (d, J = 9.1 Hz, 2H, C_6H_4), 6.80 (d, J = 9.1 Hz, 2H, C_6H_4), 5.22 (t, J = 9.2 Hz, 1H, H-3), 5.13 (dd, J = 9.4, 7.8 Hz, 1H, H_2), 4.98 (t, J = 9.4, 1H, H-3′), 4.92–4.81 (m, 2H, H1, H-2′), 4.60–4.45 (m, 4H, H-1′, H-6, CH_2Ph), 4.11 (dd, J = 10.9, 5.4 Hz, 1H, H-6), 3.87–3.81 (m, J = 10 Hz, 1H, H-4), 3.75 (s, 3H, OCH_3), 3.80–3.62 (m, 4H, H-4′, H-5, H-6, H-6′), 3.47 (dt, J = 9.3, 4.5, 1H, H-5′), 2.08 (s, 3H, $COCH_3$), 2.06 (s, 6H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 1.99 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 170.3, 169.9, 169.6, 169.3 (COCH3), 155.7, 150.9 (quaternary C of C_6H_4), 137.2, 128.6, 128.1, 127.7, 118.7, 114.5 (C_6H_5, C_6H_4), 100.8 (C1′), 100.0 (C-1), 76.3, 75.7, 74.0, 73.7, 72.8, 72.7, 71.6, 71.5, 70.3 (C2, C2′, C3, C3′, C4, C4′, C5, C5′, CH_2Ph), 69.8, 61.9 (C6, C6′), 55.7 (OCH_3), 20.81(s), 20.70 (s), 20.61 ($COCH_3$). HRMS-ES [M+Na]$^+$: found 771.2454, calculated 771.2578.

1-Thiophenyl-2,3,6-tri-*O*-acetyl-4-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-glucopyranoside (9a)

A solution of boron trifluoride etherate (0.55 mL, 4.4 mmol) was added slowly at 0 °C to a solution of crude per-acetylated cellobiose **9** (2.5 g, 3.6 mmol) and thiophenol (0.45 mL, 4.4 mmol) in CH_2Cl_2 (40 mL) under nitrogen atmosphere. After stirring for 6 h where the reaction was allowed to reach room temperature, the reaction mixture was quenched with saturated $NaHCO_3$ (20 mL) solution and extracted with CH_2Cl_2 (2 × 50 mL). The organic layer was washed once with 1 M NaOH (20 mL) and water, and the resulting organic layer was dried over Na_2SO_4, concentrated *in vacuo*, and the residue was loaded on a silica gel column. Eluting with EtOAc/PE = 0.25 : 0.75 gave pure **9a** (1.60 g, 60%) as a white solid; R_f 0.5 (EtOAc/PE = 1 : 1); mp = 217 °C; $[\alpha]_D^{20}$ −13.2 (*c* 6.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.20 (m, 5H, Ph), 5.22–5.07 (m, 2H, H-3, H-3′), 5.02 (t, J = 8.9 Hz, 1H, H-4′), 4.93–4.82 (m, 2H, H-2, H-2′), 4.64 (d, J = 10.1 Hz, 1H, H-1), 4.53 (d, J = 11.8 Hz, 1H, H-6), 4.48 (d, J = 7.9 Hz, 1H, H-1′), 4.34 (dd, J = 12.5, 3.2 Hz, 1H, H-6′), 4.07 (dd, J = 11.9, 4.3 Hz, 1H, H-6), 4.00 (d, J = 12.9 Hz, 1H, H-6′), 3.69 (t, J = 9.5 Hz, 1H, H-4), 3.66–3.55 (m, 2H, H-5, H-5′), 2.07 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 1.99 (s, 3H, $COCH_3$), 1.97 (bs, 6H, $COCH_3$), 1.94 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.2 (s), 169.7, 169.5, 169.3, 168.9 ($COCH_3$), 132.9, 131.7, 128.8, 128.3 (C_6H_5), 100.7 (C1′), 85.4 (C-1), 76.7, 76.3, 73.5, 72.8, 71.9, 71.5, 70.1, 67.7 (C2, C2′, C3, C3′, C4, C4′, C5, C5′), 61.9, 61.5 (C6, C6′), 20.8, 20.7, 20.6, 20.5 (s), 20.5 (s) ($COCH_3$). HRMS-ES [M+Na]+: found 751.1877, calculated 751.1986.

1-Thiophenyl-4-*O*-(β-D-glucopyranosyl)-β-D-glucopyranoside (10)

To a solution of **9a** (1.5 g, 2.0 mmol) in MeOH (20 mL) was added a catalytic amount of NaOMe in MeOH at room temperature. After stirring for 2 h, the reaction mixture was concentrated *in vacuo* and the residue loaded directly onto a silica gel column. Eluting with MeOH/$CHCl_3$ = 2.5 : 7.5 yielded pure **10** (0.72 g, 81%) as a white solid; R_f 0.5 ($CH_3OH/CHCl_3$ = 1 : 1); mp = 168 °C; $[\alpha]_D^{20}$ −24.9 (*c* 2.5, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.66–7.21 (m, 5H, C_6H_5), 4.65 (d, J = 9.8 Hz, 1H, H-1), 4.44 (d, J = 7.9 Hz, 1H, H-1′), 3.95–3.84 (m, 2H, H-6, H-6′), 3.68 (dd, J = 11.9, 5.6 Hz, 1H, H-6), 3.64–3.53 (m, 3H, H-3, H-4′, H-6′), 3.49–3.44 (m, 1H, H-5′), 3.43–3.28 (m, 4H, H-2, H-2′, H-3′, H-5), 3.25 (dd, J = 9.1, 7.9 Hz, 1H, H-2′); ^{13}C NMR (125 MHz, CD_3OD) δ 134.9, 133.0, 129.9, 128.5 (C_6H_5), 104.5 (C1′), 89.2 (C-1), 80.5, 80.2, 78.1, 77.9, 77.8, 74.9, 73.5, 71.4 (C2, C2′, C3, C3′, C4, C4′, C5, C5′), 62.5, 61.9 (C6, C6′). HRMS-ES [M+Na]$^+$: found 457.1135, calculated 457.1247.

1-Thiophenyl-4-*O*-(4′,6′-*O*-benzylidiene-β-D-glucopyrano-syl)-β-D-glucopyranoside (10a)

To a solution of compound **10** (0.7 g, 1.61 mmol) in DMF was added a catalytic amount of CSA (0.04 g, 0.16 mmol) and benzylidienedimethylacetal (0.3 mL, 1.93 mmol), and the mixture was heated on rotary evaporator at 60 °C for 2 h. After 2 h, DMF was removed by raising temperature of water bath to 100 °C and

the residue was directly subjected to silica column chromatography and eluted with MeOH/$CHCl_3$ = 0.5 : 9.5 to yield **10a** (0.52 g, 62%) as a white solid; R_f 0.5 (MeOH:$CHCl_3$ = 1 : 9); mp = 192 °C; $[\alpha]_D^{20}$ −10.2 (*c* 3.6, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.63–7.21 (m, 10H, C_6H_5), 5.59 (s, 1H, CHPh), 4.64 (d, *J* = 9.8, 1H, H-1), 4.59 (d, *J* = 7.8, 1H, H-1′), 4.32 (ddd, *J* = 10.3, 6.4, 3.2, 1H, H-6), 3.94 (dd, *J* = 12.3, 2.4, 1H, H-6′), 3.88 (dd, *J* = 12.3, 4.2 Hz, 1H, H-6′), 3.83–3.77 (m, 1H, H-6), 3.70–3.44 (m, 6H, H-3, H-3′, H-4, H-4′, H-5, H-5′), 3.38–3.28 (m, 2H, H-2, H-2′); ^{13}C NMR (125 MHz, CD_3OD) δ 139.1, 134.9, 133.0, 129.9, 129.1, 128.5, 127.6 (2 × C_6H_5), 105.1 (CHPh), 102.9 (C1′), 89.1 (C-1), 82.0, 80.5, 80.3, 77.7, 75.8, 74.5, 73.6, 67.8 (C2, C2′, C3, C3′, C4, C4′, C5, C5′), 69.5, 61.9 (C6, C6′). HRMS-ES [M+Na]$^+$: found 545.1463, calculated 545.1560.

1-Thiophenyl-6-*O*-tosyl-4-*O*-(4′,6′-*O*-benzylidiene-β-D-glucopyranosyl)-β-D-glucopyranoside (11)

1-Thiophenyl-4-*O*-(4′,6′-*O*-benzylidiene-β-D-glucopyrano-syl)-β-D-*gluco*-pyranoside (**10a**, 0.25 g, 0.48 mmol) was dissolved in pyridine (1 mL) at room temperature and then tosylchloride (0.13 g, 0.71 mmol) was added and the reaction mixture was stirred at rt for 12 h. After completion of the reaction it was quenched with NH_4Cl, pyridine was then removed under vacuo and the reaction mixture was extracted with water and EtOAc. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* and the residue was loaded on silica gel column and eluted with EtOAc/PE = 3 : 7 to yield compound **11** (0.24 g, 76%) as a sticky solid; R_f 0.7 (EtOAc); $[\alpha]_D^{20}$ −36.0 (*c* 0.2, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.55–7.26 (m, 15H, Ar-H), 5.58 (s, 1H, CHPh), 4.58–4.49 (m, 2H), 4.38 (d, *J* = 7.9 Hz, 1H, H-1), 4.32 (dd, *J* = 10.8, 5.5 Hz, 1H), 4.27 (dd, *J* = 10.3, 4.9 Hz, 1H), 3.75 (t, *J* = 10.1 Hz, 1H), 3.70–3.63 (m, 1H), 3.59 (m, 2H), 3.55–3.40 (m, 4H), 3.22 (dd, *J* = 9.8, 8.5, 1H), 2.42 (s, 3H, $C_6H_4OCH_3$); ^{13}C NMR (125 MHz, CD_3OD) δ 146.5, 139.1, 134.4, 134.4, 133.5, 133.4, 131.2, 129.9, 129.8, 129.8, 129.2, 129.1, 128.6, 127.5 (Ar-C), 104.5 (C-1′), 102.9 (CHPh), 88.6 (C-1), 81.9, 79.0, 77.3, 77.2, 75.3, 74.4, 73.2, 67.9 (C2, C2′, C3, C3′, C4, C4′, C5, C5′), 70.2, 69.4, (C6, C6′), 21.6 (OCH_3). HRMS-ES [M+Na]+: found 701.4867, calculated 701.4898.

1-Thiophenyl-2,3-diacetyl-6-*O*-tosyl-4-*O*-(2′,3′di-*O*-acetyl-4′,6′-*O*-benzylidiene-β-D-glucopyranosyl)-(1→4)-β-D-glucopyranoside (12)

Compound **11** (202 mg, 0.29 mmol) was dissolved in pyridine (0.5 mL), Ac_2O (0.35 mL, 3.5 mmol) was then added, and the reaction mixture was stirred at 25 °C for 6 h. After completion of reaction, the reaction mixture was concentrated *in vacuo* to remove Ac_2O and pyridine The residue was loaded directly on silica and elution with EtOAc/PE = 2.5 : 7.5 gave compound **12** (0.22 g, 88%) as a semisolid. R_f 0.5 (EtOAc/PE = 5 : 5); $[\alpha]_D^{20}$ −19.0 (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16–7.08 (m, 15H), 5.38 (s, 1H, CHPh), 5.05 (t, *J* = 9.3, 2H, H-3, H-3′), 4.78 (dd, *J* = 9.1, 7.9, 1H, H-2′), 4.70 (t, *J* = 10.0 Hz, 1H, H-2), 4.52 (d, *J* = 10.1, 1H, H-1), 4.34 (dd, *J* = 10.7, 1.9, 1H, H-6), 4.27 (d, *J* = 7.8, 1H, H-1′), 4.24 (dd, *J* = 10.4, 5.0, 1H, H-6′), 4.10 (dd, *J* = 10.7, 4.0, 1H, H-6), 3.70–3.50 (m, 3H, H-4, H-4′, H-6′), 3.50–3.44 (m, 1H, H-5), 3.26–3.14 (td, *J* = 9.8, 5.0 Hz, 1H, H-5′), 2.35 (s, 3H, CH_3OPh), 1.99 (s, 3H, $COCH_3$), 1.96 (s, 3H, $COCH_3$), 1.95 (s, 3H, $COCH_3$), 1.90 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 169.4, 169.4, 169.3 ($COCH_3$), 145.5, 136.6, 133.4, 132.9, 131.1, 130.2, 129.2, 128.9, 128.5, 128.3, 128.1, 126.1 (2 × C_6H_5), 101.6 (CHPh), 101.1 (C1′), 85.2 (C1), 77.9, 76.1, 75.6, 73.8, 72.5, 71.8, 69.8, 66.2 (C2, C2′, C3, C3′, C4, C4′, C5, C5′), 68.4, 66.8 (C6, C6′), 21.6, 20.9, 20.7 (s), 20.6 (CH_3OPh, $COCH_3$). HRMS-ES: found 844.6915, calculated 844.6978

1-Thiophenyl-3,6-anhydro-4-*O*-(4′,6′-*O*-benzylidiene-β-D-glucopyranosyl)-β-D-glucopyranoside (11a)

Compound **11** (150 mg, 0.22 mmol) was dissolved in DMF (10 mL) and to it was added potassium-*t*-butoxide (37 mg, 0.33 mmol) at rt. After stirring for 2 h the reaction was quenched with saturated NH_4Cl solution (10 mL). DMF was then removed under *vacuo*, and the residue was extracted with water (30 mL) and $CHCl_3$ (2 × 30 mL) and the organic phase was concentrated *in vacuo* the residue was loaded directly on silica. Elution with EtOAc/PE = 5 : 5 gave compound **11a** (100 mg, 90%) as a sticky solid. R_f 0.5 (EtOAc); $[\alpha]_D^{20}$ −88.0 (*c* 2.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.14 (m, 10H, 2 × C_6H_5), 5.49 (d, *J* = 2.0, 1H, H-1), 5.44 (s, 1H, CHPh), 4.79 (d, *J* = 10.4, 1H, H6), 4.55 (d, *J* = 7.7, 1H, H-1′), 4.42 (t, *J* = 2.8, 1H, H-4), 4.34 (dd, *J* = 5.4, 2.8, 1H, H-5), 4.26 (dt, *J* = 7.8, 3.0, 2H, H-6′, H-4′), 3.97 (bd, 1H, H-2), 3.84–3.75 (m, 2H, H-3, H-6), 3.75–3.65 (m, *J* = 13.1, 9.6, 2H, H-3′, H-6′), 3.50–3.35 (m, 2H, H-2′, H-5′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 135.1, 131.2, 129.4, 129.0, 128.4, 127.3, 126.3 (Ar-C), 102.2 (CHPh), 102.0 (C1′), 87.5 (C-1), 87.5, 80.2, 74.6, 74.3, 73.1, 72.9, 72.8, 66.9 (C2, C2′, C3, C3′, C4, C4′, C5, C5′), 69.8, 68.4 (C6, C6b′). HRMS-ES [M+Na]$^+$: found 527.1337, calculated 527.1454.

1-Thiophenyl-2-*O*-acetyl-3,6-anhydro-4-*O*-(2′,3′-di-*O*-acetyl-4′,6′-*O*-benzylidiene-β-D-glucopyranosyl)-β-D-glucopyranoside (13)

1-Thiophenyl-3,6-anhydro-4-*O*-(4′,6′-*O*-benzylidiene-β-D-glucopyranosyl)-β-D-glucopyranoside (**11a**, 70 mg, 0.13 mmol) was dissolved in pyridine (0.2 mL), Ac_2O (0.07 mL, 0.69 mmol) was then added and the reaction mixture was stirred at 25 °C for 6 h. After completion of reaction the reaction mixture was concentrated on vacuo and the residue was loaded directly on silica. Elution with EtOAc/PE = 2.5 : 7.5 gave compound **13** (77 mg, 88%) as a semisolid. R_f 0.5 (EtOAc/PE = 5 : 5); $[\alpha]_D^{20}$ −9.25 (*c* 6.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.27 (m, 10H, 2 × C_6H_5), 5.52 (s, 1H, CHPh), 5.36 (t, *J* = 9.5, 1H, H-3′), 5.29 (d, *J* = 4.1, 1H, H-1), 5.09 (dd, *J* = 9.4, 7.9, 1H, H-2′), 5.04 (dd, *J* = 3.9, 2.5, 1H, H-2), 4.81 (d, *J* = 7.8, 1H, H-1′), 4.47 (m, 2H, H-5, H-6), 4.42–4.32 (m, 2H, H-3, H-6′), 4.29 (dd, *J* = 5.5, 2.4, 1H, H-4), 3.88 (dd, *J* = 10.3, 2.6, 1H, H-6), 3.80 (t, *J* = 10.3, 1H, H-6′), 3.73 (t, *J* = 9.6, 1H, H-4′), 3.57 (td, *J* = 9.7, 5.0, 1H, H-5′), 2.12 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 1.91 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 169.9, 169.4 ($COCH_3$), 136.6, 133.7, 132.4, 132.1, 129.2, 128.9, 128.3, 127.8, 126.1 (2 × C_6H_5), 101.5 (CHPh), 99.6 (C1′), 82.1 (C-1), 78.3, 74.8, 74.2, 72.4, 71.9, 71.7, 71.6, 66.6 (C2, C2′, C3, C3′, C4, C4′, C5, C5′), 71.0, 68.4, (C6, C6b′), 20.9, 20.7, 20.4 ($COCH_3$). HRMS-ES [M+Na]+: found 653.1711, calculated 653.1771.

1-Phenylsulfoxide-2-acetyl-3,6-anhydro-4-*O*-(2′,3′-di-*O*-acetyl-4′,6′-*O*-benzylidine-β-D-glucopyranosyl)-β-D-glucopyranoside (15)

$[\alpha]_D^{20}$ −16.6 (*c* 0.5, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.01 (m, 10H, 2 × Ph), 5.47 (s, 1H, CHPh), 5.38 (dd, *J* = 4.0, 1.9, 1H), 5.31 (t, *J* = 9.5, 1H), 5.08–4.97 (m, 1H), 4.75 (d, *J* = 7.8, 1H), 4.58 (d, *J* = 4.1, 1H), 4.46 (t, *J* = 2.9, 1H), 4.32 (dt, *J* = 8.4, 4.1, 2H), 4.25 (dd, *J* = 5.5, 2.0, 1H), 4.12 (t, *J* = 8.4, 1H), 3.98 (dd, *J* = 10.9, 2.9, 1H), 3.70 (dt, *J* = 19.0, 9.9, 2H), 3.58–3.43 (m, 1H), 2.03 (s, 4H), 1.94 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.22, 169.68, 169.22, 140.19, 136.81, 131.15, 129.45, 129.30, 128.49, 126.08, 124.77 (2xPh), 101.97 (CHPh), 100.02 (C1′), 93.31 (C1), 78.38, 75.06, 72.55, 72.24, 72.21, 72.12, 71.75, 68.57 (C2, C2′, C3, C3′, C4, C4′, C5, C5′), 67.03, 66.76 (C6, C6′), 20.94, 20.90, 20.54 ($COCH_3$). HRMS-ES [M+Na]$^+$: found 669.1754, calculated 669.1720.

Tetrasaccharide 17

Donor **12** (160 mg, 0.2 mmol) and acceptor **8** (100 mg, 0.13 mmol) were dissolved in dry DCM under nitrogen, and added was 3 A powdered molecular sieves (0.5 g). The reaction was stirred for 1 h. The reaction flask was cooled to −20 °C, to it was added *N*-iodosuccinamide (60 mg, 0.26 mmol), and it was then stirred for 15 min. Triflic acid (1.1 μL, 0.013 mmol) was added, and the reaction was stirred for an additional 2 h allowing to reach rt. The reaction was quenched with Et_3N (0.5 mL), filtered and washed with DCM (50 mL). The DCM layer was washed with water and concentrated to give the crude compound **16**, which was dissolved in methanol and treated with catalytic amount of NaOMe at rt for 2 h. After completion of the reaction the reaction mixture was concentrated *in vacuo* and loaded directly on silica. Elution with MeOH/$CHCl_3$ = 3 : 7 gave compound **17** (0.10 g, 62% over 2 steps) as a semisolid. R_f 0.5 (MeOH/$CHCl_3$ = 6 : 4); $[\alpha]_D^{20}$ −19.5 (*c* 0.5, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.53–7.20 (m, 10H, 2 × C_6H_5), 7.04 (d, *J* = 8.3, 2H, C_6H_4), 6.83 (d, *J* = 8.4, 2H, C_6H_4), 5.57 (s, 1H, CHPh), 5.31 (s, 1H, H-1″), 4.69 (d, *J* = 5.3, 1H, H-1‴), 4.64–4.52 (m, 4H), 4.42 (d, *J* = 7.8, 1H, H-1), 4.27 (dd, *J* = 10.2, 4.1, 1H), 4.07 (d, *J* = 7.2, 1H, H-1′), 3.93–3.84 (m, 2H), 3.84–3.57 (m, 13H), 3.57–3.44 (m, 5H), 3.44–3.20 (m, 4H); ^{13}C NMR (125 MHz, CD_3OD) δ 155.5, 151.9 (quaternary C at C_6H_4), 138.2, 137.8, 128.7, 128.6, 128.2, 127.8, 127.5, 126.3, 125.8, 118.1, 114.3 (ArH), 103.5 (CHPh), 102.4, 102.0, 101.9, 101.7 (C-1, C-1′, C-1″, C-1‴), 81.1, 79.9, 77.4, 76.6, 75.5, 75.2, 75.1, 74.5, 73.6, 73.5, 73.5, 73.3, 72.9, 72.3, 70.7, 70.5, 69.5 (C2, C2′, C2″, C2‴, C3, C3′, C3″, C3‴, C4, C4′, C4″, C4‴, C5, C5′, C5″, C5‴, CH2Ph), 68.5, 66.6, 65.0, 60.6 (C6, C6′, C6″, C6‴), 54.9 (OCH_3). HRMS-ES [M+Na]$^+$: found 975.3622, calculated 975.3601.

General Procedure for Determining the Rate of Glycoside Hydrolysis

A solution of 10 mg mL^{-1} of tetrasaccharide **17** in 0.01 N H_2SO_4 was added to a cuvette preheated to the desired temperature, and the optical rotation was measured as a function of time until a constant value. Analysis of the hydrolysate showed that **17** had been converted to 3,6-anhydro-4-*O*-(4′,6′-*O*-benzylidine-β-D-glucopyranosyl)-β-D-glucopyranose (**17a**) and *p*-methoxyphenyl 4-*O*-(6′-*O*-benzyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**17b**). 3,6-anhydro-4-*O*-(4′,6′-*O*-benzylidine-β-D-glucopyranosyl)-β-D-glucopyranose (**17a**): $[\alpha]_D^{20}$ −20.0 (*c* 0.6, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.54–7.28 (m, 5H, C_6H_5), 5.58 (s, 1H, CHPh), 4.67–4.61 (m, 2H, H1), 4.47 (ddd, *J* = 14.6, 7.0, 4.7 Hz, 1H), 4.33–4.23 (m, 3H), 3.87 (dd, *J* = 9.5, 4.8 Hz, 1H, H-6), 3.78 (ddd, *J* = 9.4, 7.6, 3.5 Hz, 2H, H-6, H-6′), 3.71–3.63 (m, 2H), 3.50–3.45 (m, 2H), 3.39 (t, *J* = 8.2 Hz, 1H, H-2); ^{13}C NMR (125 MHz, CD_3OD) δ 137.5, 128.4, 127.5, 126.0 (C_6H_5), 103.6 (CHPh), 101.5 (C1′), 97.1 (C-1), 80.6, 79.1, 77.8, 74.6, 72.9, 71.7 (C6), 71.2, 70.5, 68.1 (C6′), 66.4 (C2, C2′, C3, C3′, C4, C4′, C5, C5′). HRMS-ES [M+Na]$^+$: found 435.1401, calculated 435.1369. *p*-Methoxyphenyl-4-*O*-(6′-*O*-benzyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**17b**): $[\alpha]_D^{20}$ −12.6 (*c* 0.6, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.44–6.56 (m, 10H, 2 × C_6H_5), 4.71 (d, *J* = 7.8 Hz, 1H, H-1), 4.54–4.44 (q, *J* = 10 Hz, 2H, CH_2Ph), 4.33 (d, *J* = 7.9 Hz, 1H, H-1′), 3.79 (dd, *J* = 6.5, 3.3 Hz, 1H, H6′), 3.72 (dd, *J* = 10.8, 2.0 Hz, 1H, H6), 3.65 (s, 3H, OCH_3), 3.53 (m, 3H), 3.48–3.48 (m, 3H), 3.30–3.17 (m, 3H), 3.14 (t, *J* = 8.5 Hz, 1H, H2′); ^{13}C NMR (125 MHz, CD_3OD) δ 156.7, 153.2 (C_6H_4OMe), 139.4, 129.4, 129.1, 128.7, 119.3, 115.5 (C_6H_5, C_6H_4), 104.7 (C1′), 103.2 (C-1), 81.1, 77.8, 76.7, 76.4, 76.3, 74.8, 74.7, 74.5, 71.6 (C2, C2′, C3, C3′, C4, C4′, C5, C5′, CH_2Ph), 70.7, 61.8 (C6, C6′), 56.0 (OCH_3). HRMS-ES [M+Na]$^+$: found 561.2010, calculated 561.2050.

Dissolution of cellulose

Microcrystalline cellulose (1 g) was suspended in DMA (23 mL) and was heated at 140 °C and stirred for 1 h. In order to replace water bound to cellulose 2 mL of DMA was removed by distillation under nitrogen atmosphere. The solution was then allowed to cool to 100 °C and then anhydrous LiCl (2 g) was added at 100 °C. The solution was then gradually cooled to room temperature with stirring thus completely dissolving the cellulose to form a clear solution.

Tosylcellulose 18a

To a solution of cellulose (1 g, 6.17 mmol) in DMA/LiCl (21 mL) prepared as above was added Et_3N (2.97 mL, 22.2 mmol) under stirring at room temperature. After cooling the solution to about 0 °C TsCl (2.03 g, 11.1 mmol) was added and the reaction mixture was stirred for 24 h at rt. After 24 h, the reaction mixture was poured on ice water. The precipitate formed was filtered off and washed with 750 mL distilled water and 250 mL of ethanol to yield tosyl cellulose **18a** (1.7 g, 92%); Elemental analysis shows 8.6% of S with a DSs of 0.74.

Tosylcellulose 18b

Cellulose (1 g, 6.17 mmol) in DMA/LiCl, Et_3N (1.48 mL, 11.1 mmol) and TsCl (1.01 g, 5.55 mmol) were reacted as described above to give tosyl cellulose **18b** (1.75 g, 95%); Elemental analysis shows 4.8% of S with a DSs of 0.31.

Tosylcellulose 18c

Cellulose (1 g, 6.17 mmol) in DMA/LiCl, Et_3N (0.74 mL, 5.55 mmol) and TsCl (0.5 g, 2.8 mmol) were reacted as described above to give tosyl cellulose **18c** (1.73 g, 94%); Elemental analysis shows 1.3% of S with a DSs of 0.07.

Tosylcellulose 18d

Cellulose (1 g, 6.17 mmol) in DMA/LiCl, Et3N (0.37, 2.8 mmol) and TsCl (0.25 g, 1.4 mmol) were reacted as described above to give tosyl cellulose **18d** (1.68 g, 91%); Elemental analysis shows 0.4% of S with a DSs of 0.02.

3,6-anhydrocellulose 20a

The tosylated cellulose **18a** (1 g, 3.16 mmol) was dissolved in pyridine (2.6 mL, 31.6 mmol) and Ac_2O (1.6 mL, 15.8 mmol) was added and the reaction mixture was heated at 60 °C for 72 h, after which Ac_2O and pyridine was evaporated from reaction mixture to get the crude acetylated cellulose, which was further washed with water, ethanol and dried to get acetylated cellulose. In the next step, this crude compound was dissolved in dioxane (10 mL) at 100 °C and 1 N NaOH (10 mL) in methanol was added to the reaction mixture and the reaction was further stirred for 24 h. After 24 h, the reaction mixture was poured over ethanol to get precipitation of the anhydrocellulose product. The anhydrocellulose was further purified by passing it over a Dowex Marathon MR-3 hydrogen and hydroxide form mixed bed resin column and washing the column with water to get pure anhydrocellulose **20a** in (0.24 g, 50%) yield. Elemental analysis shows sulfur to be 2.5%.

3,6-anhydrocellulose 20b, 20c, 20d

Same procedure was followed for preparation of anhydrocellulose **20b**, **20c** and **20d** as for anhydrocellulose **18a** from tosyl cellulose **18b**, **18c** and **18d** respectively to give a yield of 50%. Sulfur content is nearly 0% in all cases.

Hydrolysis of 3,6-anhydrocellulose 20a–d

3,6-anhydrocellulose **20a–d** (0.1 g) was hydrolysed with 2 M HCl (10 mL) at 60 °C and the amount of glucose and cellobiose formed were recorded every hour on a Dionex 3000 Ion exchange chromatography system. The eluent system used was 33% 0.15 M NaOH, 20% 0.50 M NaOAc, 47% H_2O. The column used was carbo pac PA01 4 × 250 mm and the detector used was a gold electrochemical cell. Hydroxyl compounds are oxidized and detected with D-glucose showing a retention time of 2 min.

HPLC experiments. Conversion of cellulose or 20c to 5-bromomethyfurfural (BMF)

Cellulose or **20c** (100 mg) and LiBr (500 mg) was mixed with HBr (55%, 7.5 mL), toluene (7.5 mL) was also added to the reaction mixture. At different time intervals 20 μL of toluene layer was taken out and diluted to 1 mL of toluene and the concentration of BMF was determined by HPLC. The HPLC column used was Microsorb MV 100-5 Si 150 × 4.6 mm and eluent EtOAc/Heptane (1 : 9, 1 mL min^{-1}). BMF was monitored by UV at 254 nm and the retention time was 12 min. **Conversion of cellulose or 20c to 5-chloromethyfurfural (CMF):** Cellulose or **20c** (100 mg) and LiCl (500 mg) was mixed with HCl (55%, 7.5 mL), toluene (7.5 mL) was also added to the reaction mixture. At different time intervals 20 μL of toluene layer was taken out and diluted to 1 mL of toluene and the concentration of CMF was determined by HPLC. The HPLC column used was Microsorb MV 100-5 Si 150 × 4.6 mm and eluent EtOAc/Heptane (1 : 9, 1 mL min^{-1}). CMF was monitored by UV at 254 nm and the retention time was 12 min. **Conversion of cellulose or 20c to 5-hydroxymethyfurfural (HMF):** Cellulose or **20c** (100 mg) was heated in DMA (2.3 mL) at 140 °C for 1h. Then the solution was cooled down to 100 °C and LiCl (0.2 g) was added. The solution was then gradually cooled to rt with stirring thus completely dissolving cellulose to form clear solution. To this solution $CrCl_2$ (20 mg), HCl (5 μL) and toluene (10 mL) was added at 100 °C and the reaction mixture was stirred at 100 °C. At different time intervals 20 μL of toluene layer was taken out and the concentration of HMF was determined by HPLC. The HPLC column used was Microsorb MV 100-5 Si 150 × 4.6 mm and eluent EtOAc/Heptane (3 : 7, 1 mL min^{-1}). HMF was monitored by UV at 254 nm and the retention time was 16 min.

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