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Hydroboration–oxidation: A chemoselective route to cellulose ω-hydroxyalkanoate esters

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ABSTRACT

We describe the first synthesis of hydroxy-functionalized polysaccharide esters via chemoselective olefin hydroboration–oxidation in the presence of ester groups. Cellulose esters with terminally olefinic side chains were first synthesized by esterification of commercially available cellulose esters (e.g., cellulose acetate) with undec-10-enoyl chloride or pent-4-enoyl chloride. Subsequent two-step, one-pot hydroboration–oxidation reactions of the cellulose esters were performed, using 9-borabicyclo[3.3.1]nonane as hydroboration agent, followed by oxidizing the intermediate borane to a hydroxyl group using mildly alkaline H_2O_2. Sodium acetate was used as a weak base to catalyze the oxidation, thereby minimizing undesired ester hydrolysis. Characterization methods including FTIR, ^1H, and ^{13}C NMR proved the selectivity of the hydroboration–oxidation pathway, providing a family of novel cellulose ω-hydroxyalkanoyl esters that were previously difficult to access.

1. Introduction

Polysaccharides are abundant, diverse, and renewable biomaterials which have an enormous range of structures and functions in nature. Selective chemical modification of these biopolymers is of great use to society, forming the basis of successful industries based on polysaccharide derivatives. These derivatives are typically more readily processed than the natural materials, and can be designed to possess properties fine-tuned for specific applications (Edgar et al., 2001). Among such derivatives, hydroxy-substituted polysaccharides, especially some of the hydroxy-substituted cellulose derivatives (e.g., hydroxypropyl methylcellulose, HPMC), possess important properties which have made them valuable materials in commerce (Edgar et al., 2001). The grafted hydroxyl groups enhance the hydrophilicity of the derivative, while the relatively randomly substituted cellulose hydroxyalkyl ethers are much less crystalline than the parent cellulose. The reduced crystallinity and enhanced hydrophilicity render these hydroxyalkyl ethers water-dispersible or water-soluble, allowing easy processing and also opening up additional applications, e.g., in aqueous rheology modification (Ford, 1999). Such properties have been exploited in fields like drug delivery, where ethers such as HPMC are used to modify release kinetics or amorphous/crystalline morphology of an incorporated drug (Siepmann & Peppas, 2001), and in water-borne coatings where hydroxyethyl cellulose for example is used to impart shear-thinning and enhanced pigment dispersion to latex house paints (Edgar et al., 2001). Hydroxy-substituted polysaccharides have the ability to interact with molecules such as drugs and other polymers via hydrogen bonding. Alone or paired with other suitable polymers, such cellulose derivatives are promising excipients for oral drug delivery. For example, HPMC and hydroxypropyl methylcellulose acetate succinate (HPMCAS) are frequently used in amorphous solid dispersion (ASD) formulations with hydrophobic drugs to enhance drug solution concentrations (Marks, Wegiel, Taylor, & Edgar, 2014; Sarode, Malekar, Cote, & Worthen, 2014). Furthermore, as the pendent hydroxyls tend to have less hindered approach angles than those of the native polysaccharide that are directly appended to the ring carbons, it makes them good sites for further reactions (Xu, Zhang, & Kadla, 2012).

Several methods have been developed for synthesis of hydroxy-substituted cellulose derivatives. Among these methods, ring-opening of epoxides (e.g., propylene oxide and ethylene oxide) by deprotonated cellulose hydroxyls (NaOH) is the most commonly used strategy to prepare hydroxyalkyl ethers of cellulose. Important cellulose derivatives synthesized in this way include 2-hydroxypropyl cellulose (HPC), 2-hydroxyethyl cellulose (HEC),

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and mixed cellulose ethers or ether–esters such as HPMC and HPMCAS (Edgar et al., 2001; Heinze, & Liebert, 2001). However, the epoxide ring-opening methods are imprecise in terms of product structure in two respects. First, reaction with an epoxide gives a new alkoxide distal from the main cellulose chain, less hindered and more reactive, thereby causing oligo(hydroxyalkyl) side chains of various lengths to be formed. Secondly, while ethylene oxide is symmetrical, many epoxides (e.g., propylene oxide) have two different sites for potential nucleophilic attack, leading to a mix of positional isomers. Therefore synthesis of hydroxyl-containing cellulose derivatives by classical epoxide ring-opening methods leads to complex mixtures of products that are very difficult to fully characterize; consequently, product structure and uniformity cannot be fully controlled.

Cellulose esters with pendant hydroxyl groups are interesting synthetic targets. Due to the hydrolytic instability of ester bonds, these polymers will have alternative biodegradability pathways (Buchanan et al., 1996) compared with their ether counterparts. However, for several reasons a simple synthetic pathway to cellulose ω-hydroxyalkanoates has not yet been created. As terminal alcohols are reactive towards acylation, direct esterification of cellulose using an activated acyl reagent that also possessed terminal alcohol functionality would more likely lead to formation of an oligo/polyester, either homopolymeric and/or grafted onto the cellulose backbone. While protecting group techniques may solve this issue, protection and deprotection can be expensive, laborious, and may be plagued by unwelcome reactivity of protected intermediates (Wang, Dong, & Tan, 2003). Cellulose ω-hydroxyalkanoates could in theory also be synthesized by ring-opening reactions between cellulose and lactones (Guo, Wang, Shen, Shu, & Sun, 2013; Teramoto, Ama, Higeshiro, & Nishio, 2004). However, the literature shows that in fact polylactones (e.g., polycaprolactone) become grafted onto cellulose under such conditions; thus the steric freedom and resulting higher reactivity of the initially formed ω-hydroxyl group are an issue in this approach as well. Generation of polyester homopolymers is a competing side reaction that also introduces complexity and inefficiency.

In previous studies (Dong & Edgar, 2015; Meng, Matson, & Edgar, 2014a,b), our group discovered that olefin cross-metathesis chemistry (CM) can be successfully applied to polysaccharides to synthesize discrete, non-crosslinked derivatives, enabling mild and modular side-chain modification of polysaccharides to afford products with carboxylic acid and a variety of other terminal functionalities. In the CM approach, terminally olefinic cellulose esters react with other functionalized alkenes under ruthenium catalysis (Meng et al., 2014b), and thus incorporate the corresponding functional group onto the cellulose side-chain. However, the CM approach for synthesis of cellulose ω-hydroxyalkanoates may be inefficient since the required allyl alcohol CM substrates may be prone to self-metathesis, leading to low CM conversion (Meng et al., 2014b).

Therefore investigation of potentially efficient methods for synthesis of discrete cellulose ω-hydroxyalkanoates is appealing. Hydroboration followed by oxidation is a well-known method in small molecule chemistry that can convert terminal olefins to primary alcohols by the net addition of H_2O across the double bond (Brown, 1980). Hydroborating agents such as diborane add to alkenes to form organoboranes in an anti-Markovnikov manner (Dhillon, 2007). Subsequent oxidation with hydrogen peroxide (usually under alkaline conditions) gives the corresponding anti-Markovnikov alcohols in which boron has been replaced by OH. Among such borane derivatives, 9-borabicyclo[3.3.1]nonane (9-BBN) exhibits remarkable thermal stability and also excellent regioselectivity, providing almost exclusively primary alcohols in hydroboration–oxidation of simple terminal alkenes (Dhillon, 2007). Standard hydroboration–oxidation conditions involve reacting a terminal alkene with an organoborane reagent in THF, and subsequent oxidation of the intermediate borane by the addition of H_2O_2 under alkaline conditions (e.g., NaOH). Schumann, Pfeifer, & Heinze (2009) synthesized 3-allylcellulose by reaction of a regioselectively protected 3-hydroxycellulose with allyl halide, then converted the allyl group to a 3′-hydroxypropyl group by reaction with 9-borabicyclo[3.3.1]nonane (9-BBN), and subsequent alkaline oxidation. This approach teaches us how to efficiently synthesize ω-hydroxyalkylcellulose ethers. However, we face additional challenges when considering a similar approach to synthesis of cellulose ω-hydroxyalkanoates. First, it is unknown whether cellulose esters would be reduced by 9-BBN. Hydroboration pioneer H.C. Brown, Heim, & Yoon (1970) has shown that small molecule esters are reduced, albeit slowly, to primary alcohols by diborane. Ester reduction by 9-BBN was also studied by Brown, who showed that 9-BBN will also reduce esters slowly (Brown, Krishnamurthy, & Yoon, 1976); Brown has described selective reductions of ketones in the presence of esters by taking advantage of the faster reduction rate by 9-BBN of ketones vs. esters (Krishnamurthy, & Brown, 1975). Secondly, an alkaline reagent (usually NaOH) is used in typical oxidation steps of hydroboration–oxidation reactions. Cellulose esters are quite labile to alkaline hydrolysis, with saponification usually occurring very rapidly under even the mildest conditions (Zheng, Gandour, & Edgar, 2014). Therefore there were at least two good reasons to be skeptical that this approach to cellulose ω-hydroxyalkanoates would prove successful. Herein, we report efforts to employ hydroboration–oxidation of terminally olefinic cellulose esters in the synthesis of cellulose 5′-hydroxypentanoate and 11′-hydroxyundecanoate esters. We also describe our efforts to suppress ester hydrolysis during both the hydroboration and oxidation steps.

2. Experimental

2.1. Materials

Cellulose acetate (CA-320S, M_n 38.0 kDa, DS(Ac) 1.82), cellulose acetate propionate (CAP-504-0.2, M_n 15.0 kDa, DS(Pr) 2.09, DS(Ac) 0.04), and cellulose acetate butyrate (CAB-553-0.4, M_n 20.0 kDa, DS(Bu) 1.99, DS(Ac) 0.14) were from Eastman Chemical Company. The molecular weight information was reported by the supplier and the DS values were previously measured by our group (Kar, Liu, & Edgar, 2011). Triethylamine (TEA) and 1,3-dimethyl-2-imidazolidinone (DMI) were purchased from Acros Organics. Sodium acetate (NaOAc), anhydrous tetrahydrofuran (THF), hydrogen peroxide solution (30% w/w in H_2O), 9-borabicyclo-[3.3.1]-nonane (9-BBN, 0.5 M in THF), and methyl ethyl ketone (MEK) were purchased from Sigma–Aldrich. DMI was dried over 4 Å molecular sieves before use. All other purchased reagents were used as received.

2.2. Preparation of terminally olefinic cellulose esters

The synthesis of terminally olefinic cellulose esters was according to our previous publications (Meng et al., 2014a,b) with slight modification.

(1) Example procedure of the synthesis of cellulose acetate undec-10-enoate (**1**, **CA-Un067**)

Cellulose acetate (CA-320S, 1.00 g, 4.19 mmol AGU) was dissolved in DMI (30 mL), and the solution was heated to 90 °C with mechanical stirring under N_2. Triethylamine (1.29 mL, 9.22 mmol, 2.2 eq/AGU) was added. A condenser was used to avoid evaporative loss of the base catalyst. Undec-10-enoyl chloride (1.70 g, 8.36 mmol, 2.0 eq/AGU) was added dropwise and allowed to react at 90 °C for 20 h. The reaction mixture was then cooled to room temperature, filtered, and the filtrate was precipitated in 300 mL of