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# Quantitative NMR Approach to Optimize the Formation of Chemical Building Blocks from Abundant Carbohydrates

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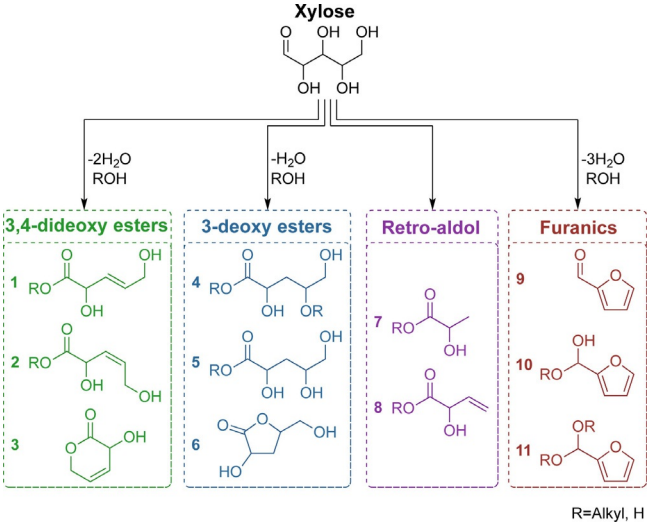
The future role of biomass-derived chemicals relies on the formation of diverse functional monomers in high yields from carbohydrates. Recently, it has become clear that a series of α-hydroxy acids, esters, and lactones can be formed from carbohydrates in alcohol and water solvents using tin-containing catalysts such as Sn-Beta. These compounds are potential building blocks for polyesters bearing additional olefin and alcohol functionalities. An NMR approach was used to identify, quantify, and optimize the formation of these building blocks in the Sn-Beta-catalyzed transformation of abundant carbohydrates. Record yields of the target molecules can be achieved by obstructing competing reactions through solvent selection.

The need to establish more sustainable methods of obtaining the chemicals needed by society for the production of food, materials, fuels, and energy is widely recognized. The current chemical industry is based on the availability of a small number of petroleum-derived building blocks. Biomass can be utilized to provide access to both existing and new types of building blocks, and research into this area has steeply increased during the last decade. It is important for these chemicals to be accessible at low cost and at the same time to have useful properties to be commercially utilized. Direct conversion of sugars to a target chemical by heterogeneous catalysis offers the best chance of lowering the process costs.[1–4] A plethora of reaction products have been identified in the acid-catalyzed conversion of C5 and C6 carbohydrates.[5] Amidst them acyclic α-hydroxy esters and acids have recently emerged as an attractive group of biomonomers (Scheme 1).

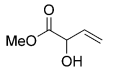
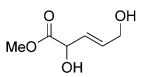
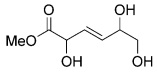
For potential use in biopolymer applications, the production, polymerization, and upgrading of the C3 building block lactate (**7**) and the C4 building block vinyl glycolate (**8**) has previously been demonstrated.[3,6–11] Recently, the production and polymerization of the C5 building block 2,5-dihydroxy-3-pentenoic acid methyl ester (Me-**1**) as well as the formation of the C6 building block *trans*-2,5,6-trihydroxy-3-hexenoic acid methyl ester (Me-**12**) have been described (Table 1).[12–14]

Conversions of C5 and C6 carbohydrates into the acyclic unsaturated α-hydroxy compounds **1** and **12** have been achieved using Sn-Beta in methanol[13,14] or in water[12] at temperatures




**Scheme 1.** Overview of major pathways in the catalytic conversion of xylose by Sn-Beta and the major products identified in the reaction mixtures at high temperatures (>100 °C). The products are shown for reactions in alcohol (R=alkyl) or water (R=H) and are grouped (from left to right) as 3,4-dideoxy esters, 3-deoxy esters, retro-aldol products, and furanics.

**Table 1.** Conversion of C4, C5, and C6 carbohydrates by Sn-Beta to homologous 3,4-dideoxy esters with declining yield.

| Carbon Backbone | Substrate | Compound | Structure | Yield [%] |
|---|---|---|---|---|
| C4 | Erythrulose | Me-**8** |  | 56[7] |
| C5 | Xylose | Me-**1** |  | 33[13] |
| C6 | Glucose | Me-**12** |  | 16[14] |

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above 100 °C in the absence of further additives. A Sn-Beta–zeolite synthesized under hydrothermal conditions using hydrofluoric acid as the mineralizing agent was the most efficient catalyst for this reaction.[12–14] C5 and C6 carbohydrates yield around 30% for C5-carbohydrate substrate Me-**1** and around 15% for C6-carbohydrate substrate Me-**12**, respectively. The yields for the formation of the C4 analogue vinyl glycolate methyl ester (Me-**8**) can exceed 50% (Table 1).[7,13,14] Alkali-salt additives were shown to reduce product yields and to strongly enhance the formation of smaller compounds such as methyl lactate.[8]

Optimizing carbohydrate conversion into new chemicals and detection of the products requires consideration of the analytical approaches employed. Methods that rely on the use of reference standards for identification and quantification, including liquid and gas chromatography, may be challenging to implement in work streams targeting new chemicals. In cases where commercial standards are unavailable, either production of standards or calculations to estimate response factors are necessary.[10] In contrast, methodologies that combine detailed structural information and the possibility of quantitatively detecting an accurate signal would be more valuable in the push toward bio-based economies.

Herein, we combine in situ NMR spectroscopy for the identification of reaction products with an accurate quantitative NMR (qNMR) methodology to assess solvent effects in the Sn-Beta-catalyzed conversion of abundant carbohydrates. The methodology operates on a timescale comparable to commonly used chromatography methods but avoids empirical instrument- and analyte-dependent response factors altogether. Instead, qNMR signals are simply proportional to the number of contributing atoms. Moreover, identifying new chemicals in situ makes intensive purification and characterization steps obsolete. Water and a series of short-chain alcohols are used as solvents that provide sufficient substrate solubility for the carbohydrates. The motivation for testing longer-chain alcohols as reaction solvents as opposed to methanol and water is to compare the physicochemical properties of the solvents and to investigate the stoichiometric participation of the solvent as a nucleophile in the reaction. Thus, the choice of solvent will affect the formation of alkyl-glycoside and acetal-type intermediates during the reaction, modulate the microenvironment and Lewis-acid properties of tin active sites in the stannosilicates, and alter molecular dynamics and energetics within the reaction pathway.[9,10] Hence, solvent variation is a means of optimizing operational conditions toward increased profitability of bioprocesses.

For the analysis of solvent effects, optimized spectra of complex reaction mixtures without prior purification or sample pre-treatment in protic, non-deuterated solvents were obtained. An advantage of this approach is that it does not rely on the availability of purified reference compounds. Changes in the product structures upon reaction with the solvent do not critically complicate product identification or quantification for the eleven main reaction products (Scheme 1).

## Results and Discussion

### Detection of products in reaction mixtures without relying on reference compounds

NMR spectroscopy is widely used for chemical structure elucidation and mixture analysis. The use of NMR spectroscopy for component identification and quantification is particularly well-developed for biological samples, including biofluids, extracts, and foods, but has also gained popularity within biomass conversion, for instance in the study of carbohydrate isomerization reactions[15–17] or for lignin structure and depolymerization reactions.[18] Herein, we use a suite of homo- and heteronuclear NMR experiments for the detection and identification of carbohydrate degradation products in situ. Specifically, DQF-COSY, TOCSY, $^{1}$H-$^{13}$C HMBC, conventional and edited $^{1}$H-$^{13}$C HSQC, as well as $^{1}$H-$^{13}$C HSQC-TOCSY spectra were employed for compound identification. Band-selective $^{13}$C excitation[19] and optimized decoupling sequences[20,21] were used to suppress non-informative signals and artefacts and to obtain higher quality $^{1}$H-$^{13}$C 2D NMR spectra. NMR spectroscopy has notorious shortcomings in the detection of heteroatoms, but this problem was negligible for reactions involving carbohydrate fragmentation or dehydration, as oxygen positions could be inferred from $^{13}$C chemical shifts. At the same time, the detection of discrete signals for individual atomic positions by NMR spectroscopy allows for the distinction of isomers. Such distinction of isomers is crucial, as several potential products in carbohydrate dehydration cannot be distinguished based on their mass alone.

Major products that were identified in reaction mixtures produced from xylose at 160 °C using a Sn-Beta–zeolite catalyst are shown in Scheme 1. These compounds were identified through de novo structure determination and $^{1}$H/$^{13}$C chemical shift assignments in unpurified reaction mixtures in six different protic solvents (water, methanol, ethanol, *n*-propanol, *iso*-propanol and *n*-butanol). This approach was aided by the use of high-field NMR instrumentation (18.7 Tesla magnets) equipped with cryogenically cooled detection electronics to reduce electronic noise approximately threefold. The identified reaction products are derived from pathways including C–C bond breakage in retro-aldol reactions to yield C2, C3, and C4 fragments, which may subsequently undergo dehydration to various α-hydroxy esters (**7**–**8**). Alternatively, direct dehydration of the C5 compound to α-hydroxy-, 3-deoxy-, or 3,4-dideoxy esters (**1**–**6**) or triple dehydration to furanics (**9**–**11**) can occur. The most interesting of these products may be the *trans*-2,5-dihydroxy-3-pentenoic acid alkyl ester (**1**). We recently showed that this prospective chemical building block could be co-polymerized enzymatically in a selective 1,5-polymerization reaction with ethyl 6-hydroxy-hexanoate, yielding polymers that could be specifically functionalized at the secondary alcohol group or at the olefinic bond of the monomer.[13] Thus, 2,5-dihydroxy-3-pentenoic acid alkyl esters could provide a platform for a vast variety of functional materials derived from C5 carbohydrates.

Standard reaction conditions were defined based on optimizations of *trans*-2,5-dihydroxy-3-pentenoic acid methyl ester (Me-**1**) formation in methanol.[13] In these studies, a Sn-Beta catalyst was found to be most effective for the formation of Me-**1**, and therefore Sn-Beta was also employed herein to probe the effects of different solvents.

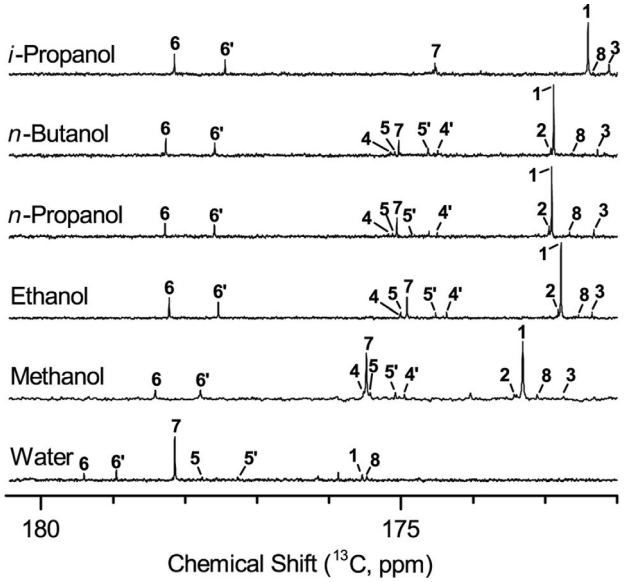


**Figure 1.** $^{13}$C NMR spectra from a reaction mixture containing D-xylose (360 mg) and Sn-Beta (180 mg) in the appropriate solvent (5 mL). The carboxyl spectral region is shown and signals are assigned to the molecules found in Scheme 1; an apostrophe denotes the diastereomer of a compound. Chemical shifts are relative to MeOH-$d_4$ (10% *v/v*) set at 47.85 ppm for all solvents.

1D $^{13}$C NMR spectra of reaction mixtures in various solvents were obtained and the carbonyl regions are shown in Figure 1. The spectral signals corresponding to compounds in Scheme 1 were assigned. In these reaction mixtures, careful inspection allowed for the identification of the minor *cis*-2,5-dihydroxy-3-pentenoic acid alkyl ester (**2**) as well as the dominant *trans*-form (**1**). The $^1$H-$^{13}$C HSQC spectral region showing chemical-shift assignments of **1** and **2** in methanol is displayed in Figure 2. Long-range correlations through $^2J_{CH}$ couplings across the double bond are indicated by white lines and serve to identify the signals connected within the same NMR spin system. The *cis*- and *trans*-configurations were identified by characteristic $^3J_{HH}$ scalar couplings across the olefinic bond and by the characteristic signal shifts to lower frequencies for carbon atoms adjacent to the *cis*-double bond. This *cis*-isomer was identified as the minor product in all solvents. Together with these products, six additional 3-deoxy ester/acid compounds were identified within the carbonyl region shown in Figure 1. These signals cluster within different spectral regions in accordance with their functionality: olefinic esters (**1**–**3**, **8**) at 172–174 ppm, alkyl esters (**4**, **5**, **7**) at 174–176 ppm, and lactones (**6**) downfield of 177 ppm. Further inspection of the $^{13}$C NMR spectra of Figure 1 indicates that rather dramatic compositional changes result upon changing the solvent from

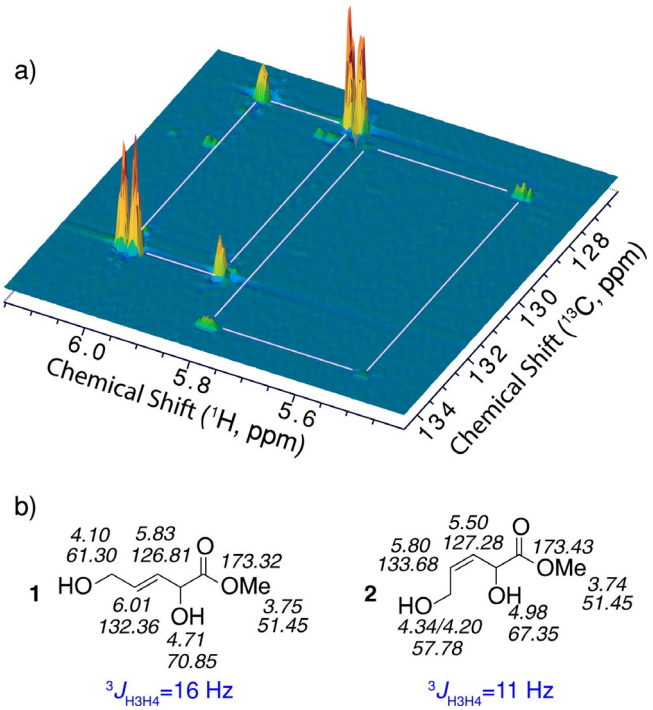


**Figure 2.** a) $^1$H-$^{13}$C HSQC spectral region displaying the olefinic signals of compound **1** (*trans*-isomer) and compound **2** (*cis*-isomer) in a reaction mixture. $^2J_{CH}$ correlations across the double bond are indicated by thin white lines. b) Chemical shift assignments of compound **1** (*trans*-isomer) and compound **2** (*cis*-isomer).

water to an alcohol. Furthermore, it was possible to distinguish the diastereomers of compounds **4**–**6** as signified by an apostrophe associated with the compound number in Figure 1.

## Quantification of bio-based chemicals in reaction mixtures

Reliable quantification of the compound series shown in Scheme 1 was subsequently pursued by quantitative NMR (qNMR) spectroscopy. As qNMR can operate at the highest level of quantitative measurement[22,23] the method is free of empirical factors in the uncertainty analysis of the experiment, and signal areas are directly proportional to the concentration of atoms contributing to the signal.

Cryogenically cooled detection electronics and high-field instrumentation enabled absolute quantification of reaction mixtures by quantitative 1D $^{13}$C NMR spectroscopy at natural $^{13}$C isotope abundance (1.11%). Inverse gated decoupling experiments were used exclusively to avoid enhancement of the $^{13}$C signals by the nuclear Overhauser effect.[24] Crude reaction mixtures analyzed by $^{13}$C qNMR spectroscopy contained dimethyl sulfoxide as an internal standard for absolute quantification. Dilute dimethyl sulfoxide showed good recovery after reactions without detectable degradation, was miscible with the solvents tested in this study, and did not result in $^1$H or $^{13}$C NMR signal overlap with analyte signals. Dimethyl sulfoxide was thus deemed preferable to compounds such as mesitylene, dioxane, glycerol, or other alditols screened as standards

for the spectroscopic characterization of reaction mixtures formed through catalytic carbohydrate conversion.

Quantitative 1D $^{13}$C NMR rather than the more commonly used $^{1}$H NMR spectroscopy was employed for quantification, as $^{13}$C NMR experiments provide excellent signal resolution and sharp, non-split signals. Protonated carbon positions were generally used for quantification owing to their shorter $T_1$-NMR relaxation times, yielding quantitative measurements for sub-minute-timescale inter-scan relaxation delays. Alternatively, improved $^{13}$C NMR spectra could be obtained by adding 1 mM of the relaxation agent $GdCl_3$ to the NMR sample, shortening the $^{13}$C-carbonyl $T_1$ relaxation time to about 1 s at room temperature and 18.7 T magnetic field. The reduced $^{13}$C $T_1$ relaxation time also permits accurate measurement of $^{13}$C NMR signal areas for quaternary carbons without the need for long inter-scan recycle delays. The signal-to-noise ratio obtained within 1 h of experiment time per sample translated into an estimated error of determination of 0.2–1.0% for product yields. This small experimental uncertainty was validated by performing the analyses for reaction mixtures in all six different solvents in duplicate, yielding near-identical $^{13}$C NMR spectra for repetitions in each solvent (Figure S1, see the Supporting Information).

### Solvent effects on the Sn-Beta-catalyzed reaction

Quantified yields of the eight major compounds in non-purified reaction mixtures in different solvents are displayed in Figure 3. Various trends become evident upon variation of the solvent. Increasing the length of the alkyl chain of alcohol solvents decreases the amount of retro-aldol products (**7**–**8**) formed, consistent with previously reported observations.[7] Simultaneously, an increased yield of 3,4-dideoxy esters (**1**–**3**) and related 3-deoxy esters (**4**–**6**) is observed. Notably, all of the longer-chain alcohols tested gave higher yields of 3,4-dideoxy esters than for methanol, even under conditions that were specifically optimized for reactions in methanol. The formation of 3,4-dideoxy esters was most pronounced in ethanol with yields of around 42% (38% of the *trans* compound (**1**) and 4% of the *cis* (**2**–**3**) forms), which were 1.2-fold higher than in methanol. Consistently increased yields were also found for the lactone (**6**), formed in 15% yield in ethanol as compared to 8% in methanol. Overall, the 3-deoxy and 3,4-dideoxy esters (**1**–**6**) account for 66% of the carbon balance in ethanol and in *iso*-propanol. Quantifications of these related compounds are summarized in Table 2. Furfural derivatization to alkyl acetals predominates for methanol and is less pronounced in larger alcohols and especially in *iso*-propanol. In all solvents, 3,4-dideoxy esters are primarily formed as the *trans* compound (**1**), with yields that are also higher than a combination of the *cis*-3,4-dideoxy forms (**2**–**3**) and the potentially related furfural forms (**9**–**11**).

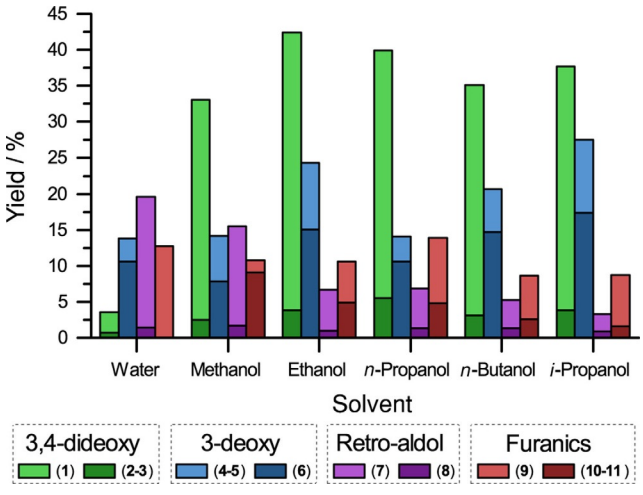


**Figure 3.** Product distribution of reactions in alcohols or water. The reactions were conducted with D-xylose (360 mg) and Sn-Beta (180 mg) in the appropriate solvent (5 mL) with dimethyl sulfoxide (50 mg) as an internal standard, and run for 2 h at 160 °C with 600 rpm stirring. An experimental uncertainty within ±1% was achieved in all cases. Legend numbers reference to the compounds in Scheme 1.

**Table 2.** Yield of 3,4-dideoxy compounds (**1**–**3**) and 3-deoxy compounds (**4**–**6**) from xylose in various solvents.

| Product mixture | Water [%] | Methanol [%] | Ethanol [%] | *n*-Propanol [%] | *n*-Butanol [%] | *iso*-Propanol [%] |
|---|---|---|---|---|---|---|
| **1**–**3** | 4 | 33 | 42 | 40 | 35 | 38 |
| **4**–**6** | 14 | 14 | 24 | 14 | 21 | 28 |
| Sum | 17 | 47 | 66 | 54 | 56 | 66 |

Reactions conducted in water exhibited a significantly altered composition compared to reactions conducted in alcohols, which also exhibited a greater tendency toward humin formation and catalyst discoloration. Thus, 3,4-dideoxy compounds are formed at lower levels than for retro-aldol products, furanics, and 3-deoxy compounds in water. A principal difference in the use of water and alcohol is brought about by the formation of free Brønsted acids as products in reactions conducted in water. Brønsted acids are known to catalyze a multitude of reactions including dehydration and acetalization.[3] The continuous formation of Brønsted acids during the reactions will have an impact on the catalytic system and alter the product distribution, thus rationalizing the principally different compositions of products in water and alcohol solvents. Especially in cases where the 3,4-dideoxy compounds are targeted, water is generally less useful as a solvent compared to the alcohols.

We finally note that reaction selectivity has been partially attributed to steric hindrance at the Sn active site in zeolite pores.[17] In the current analysis of solvent effects, the use of less nucleophilic and more bulky solvents increases the selectivity toward the formation of C5 lactones (compound **6**). This change in selectivity suggests that bulkier alcohols promote an intramolecular reaction rather than a reaction with the solvent inside the Sn-Beta–zeolite pores.

### Temperature effects in ethanol

As improved yields of 3,4-dideoxy esters were achieved in alcohols other than methanol (even under conditions that had been optimized for methanol) we evaluated the prospect for further improvements of the reaction system using ethanol as the solvent. In the range of 140–160 °C, the product selectivity was reasonably consistent, giving similar yields of 3,4-dideoxy esters (42%, see Table S2 in the Supporting Information). Overall, we find the formation of the 3-deoxy and 3,4-dideoxy dehydration products (**1**–**6**) to be only weakly sensitive toward temperature variation between 120 and 180 °C. Nevertheless, exploring solvent and temperature effects resulted in a combined yield above 40% for 3,4-dideoxy esters; an almost 10% increase relative to previously achieved yields in methanol (33%, Table 1).[13]

The product ratios of cyclic γ-lactone compound **6** and open-chain 3-deoxy compounds **4** and **5** are temperature-dependent (Figure 4). Lower temperatures favor the formation of compound **6** relative to the open-chain compounds **4** and **5**. This observation correlates with an increasing fraction of acyclic products following endothermic γ-lactone solvolysis forming compound **5**.[25] Tabulated yields of the variable-temperature experiments are collected in the Supporting Information (Table S2).

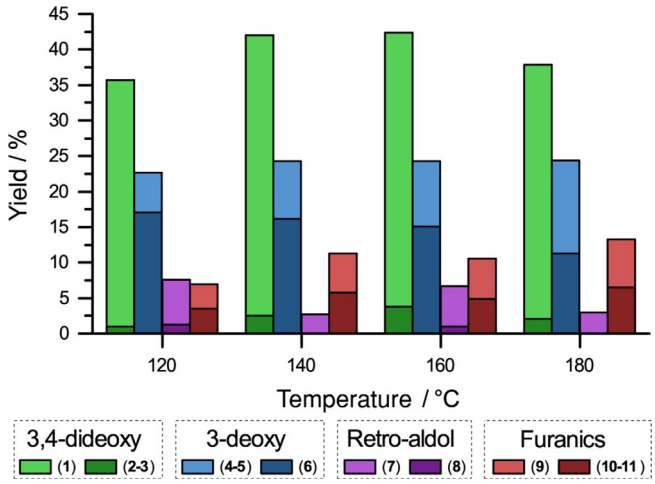


**Figure 4.** Product distribution of reactions run between 120 and 180 °C using ethanol as the solvent. The reactions were conducted with D-xylose (360 mg) and Sn-Beta (180 mg) in ethanol solvent (5 mL) with dimethyl sulfoxide (50 mg) as an internal standard, and run for 2 h at the selected temperature. An uncertainty within ±1% was achieved in all cases. Legend numbers reference to the compounds in Scheme 1.

### Time-resolved reaction analysis

Additional insight into solvent effects on the acyclic reaction of xylose to potential polyester building blocks was sought by tracking the reaction progress in water, methanol, and ethanol over time. Reactions were conducted under microwave heating for varying lengths of time and were subsequently analyzed by quantitative $^{13}C$ NMR spectroscopy (full datasets are provided in Table S3 in the Supporting Infomation). The experiments show that product formation continues even after full xylose conversion. This observation is attributed to the accumulation of glycoside intermediates,[14] some of which can be subsequently converted into the full range of products.

The formation of major product **1** in methanol and ethanol was tracked in an initial-rate experiment at 160 °C under quasi-steady state conditions as shown in Figure 5. Owing to the initial surplus of substrate, pseudo-first order kinetics were apparent, which resulted in a linear accumulation of product during the short initial period shown in Figure 5 (full kinetic data are provided in Figure S2). Although compound **1** formed with higher selectivity in ethanol (39%) than in methanol (31%) and water (approximately 5%) in the kinetic experiments, the initial rate of formation is lower in ethanol than in methanol. The formation of compound **1** is accompanied by higher rates of conversion of xylose in methanol than in ethanol and a lower rate of conversion in water (Table S3, Supporting Information).

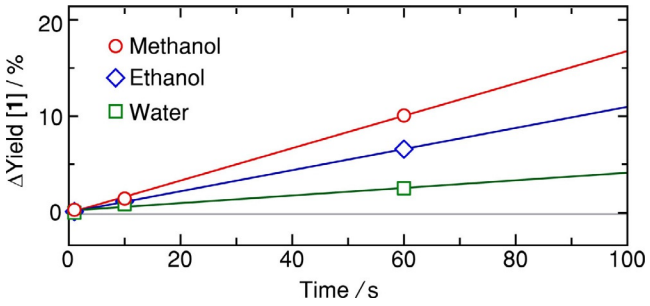


**Figure 5.** Initial-rate experiments for the formation of product **1** from D-xylose (360 mg), using Sn-Beta (180 mg) at 160 °C and 5 mL of methanol, ethanol, or water; initial rates: 0.85, 0.57 and 0.20 mmol $L^{-1}$ $min^{-1}$, respectively.

Kinetic profiles underline the complexity of the reaction pathway and suggest that several solvent effects are important. Solvent molecules compete with the substrate for binding to Sn active sites. A weaker binding behavior is expected for alcohols relative to water, leading to better active-site availability for the substrate in alcohols compared to water.[26,27] This rationalization may explain the lower rate of formation of compound **1** and the consequent lower rate of xylose conversion observed in water. For the Sn-Beta-catalyzed conversion of xylose in alcohol, the alcohol enters the catalytic cycle as a nucleophilic reactant. The lower rate of production of compound **1** in ethanol compared to methanol is consistent with previous reports for C4 carbohydrate conversion, which suggests that lower nucleophilicity and steric limitations may direct product selectivity toward the 3,4-dideoxy compound.[9]

In methanol and ethanol the formation of **1**–**6** is continuous during the course of the reaction (Figure S2, Supporting Information). In contrast, the yield of compound **1** in water rises to a maximum and subsequently decreases during the reaction while maintaining a consistent increase of all 3-deoxy and 3,4-dideoxy compounds (**1**–**6**). This finding indicates that some rehydration of compound **1** can occur in water, especially in the presence of accumulating Brønsted acids. Formation of com-

pound H-**7** occurs more rapidly in water than formation of compounds Me-**7** and Et-**7** in alcohols (Figure S3). Accumulation of compound **7** in water is accompanied by an increase in formation of compound **7**, indicative of an alteration of the mechanism induced by increased Brønsted acidity. The final levels of furanics decrease slightly from water compared to methanol and ethanol (Figure 3). Observations of a lower carbon balance in water and the discoloring of the reaction mixture also suggest the formation of undetected polymeric species (humins). The distinct selectivity of Sn-Beta-catalyzed xylose conversion in water relative to alcohols can be ascribed to lower reactivity at the Sn active sites owing to competing solvent absorption and to mechanistic effects of Brønsted acid formation. The formation of alkyl lactates is largely suppressed in longer alcohols, consistent with previous studies under conditions that were optimized for lactate formation. Maximum alkyl lactate yields have been reported to decrease from 65% in methanol to approximately 35% in ethanol and 25% in *iso*-propanol.[7] Overall, the beneficial effect of ethanol relative to methanol in the formation of **1**–**3** can be ascribed to the less nucleophilic nature and larger molecular size of ethanol disfavoring side reactions.

### Improved yield of chemical building blocks from glucose

The abundance of glucose in biomass is even greater than that of xylose, and glucose is the most abundant carbohydrate in nature. Glucose is available from starch and cellulose, which are both homopolymers composed of glucopyranose subunits. Hexoses are able to form compound **12** (*trans*-2,5,6-trihydroxy-3-hexenoic acid methyl ester; Figure 6a), the C6 analogue of compound **1**, although in lower yields than the analogues obtained from C4 and C5 sugars (Table 1). To substantiate that the solvent effect discussed herein is also applicable to the formation of chemical building blocks from C6 carbohydrates, reactions using glucose as the substrate were performed.

The beneficial effect of ethanol relative to methanol in the formation of compound **12** is also valid for glucose, as can be seen from the NMR spectra of the olefinic region (Figure 6b). The solvent change from methanol to ethanol increases the formation of compound **12** approximately 1.2-fold (from 13.8 to 16.0% under the standard reaction conditions used herein). The formation of the hexono-lactone equivalent of compound **6** also increases, from 16.6 to 19.4%, whereas the formation of alkyl lactate **7** decreases from 31.5 to 12.6%. All of these effects closely follow trends observed for the conversion of xylose and are consistent with previous studies using homogeneous and heterogeneous Sn catalysts for conversion of the less-abundant acyclic C4 carbohydrate erythrulose.[9,10] A shift toward improved selectivity for the formation of commercially interesting 3,4-deoxy esters at the expense of retro-aldol cleavage can be achieved for a series of carbohydrates using a Sn-Beta catalyst in alcohols with a longer chain length than methanol.

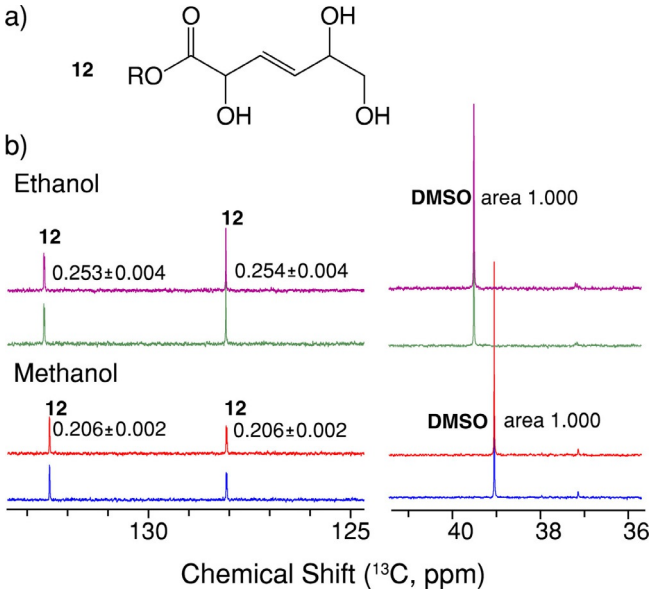


**Figure 6.** a) Structure of the C6 analogue of compound **1**, *trans*-2,5,6-trihydroxy-3-hexenoic acid methyl ester (**12**). b) Spectral comparison of the areas of the olefinic carbon shifts of compound **12** in ethanol (top) and methanol (bottom) reaction solvents. Duplicate samples are shown in different colors, including the errors of determination of signal areas relative to DMSO as an internal quantification standard.

## Conclusions

In conclusion, quantitative $^{13}C$ NMR was employed for the detection and accurate quantification of previously unknown products in the conversion of abundant C5 and C6 carbohydrates by Sn-Beta, without using reference standard compounds. Identification and quantification are feasible in different solvents, thus permitting the elucidation of solvent effects on reaction selectivity. Exchanging methanol for longer-chain alcohols results in increased yields of C5 3,4-dideoxy esters from 33% in methanol to 42% in ethanol. This increase in yield can be ascribed to the less-nucleophilic and larger ethanol disfavoring competing reactions. The improved yield of C5 3,4-dideoxy esters in ethanol relative to methanol and water correlates with a lower rate of formation, although the pathway forming 3,4-dideoxy acids or esters is assumed to progress under kinetic control.[9] The formation of retro-aldol-derived products is diminished in ethanol and alcohols of longer chain length. Nonetheless, the reaction pathways forming 3-deoxy and 3,4-dideoxy compounds remain viable in various protic solvents.

Simple alcohols have been considered as environmentally preferable solvents and ethanol has been described as preferable to methanol in terms of environmental, health, and safety regulations.[28,29] Hence, the formation of 2,5-dihydroxy-3-pentenoic acid esters in 42% yield and formation of the related 3-deoxy esters in combined yields of nearly 66% from xylose in ethanol is encouraging for the development of environmentally benign processes in a future bio-based chemical industry.

## Experimental Section

Reactions were conducted with a Biotage Initiator$^+$ microwave reactor in 5 mL glass reaction vials. Reactions were typically performed with Sn-Beta (180 mg, Si/Sn = 200, hydrothermally synthesized), D-xylose (360 mg), solvent (5 mL) and dimethyl sulfoxide (50 mg) as internal standard.

Catalyst material Sn-Beta was produced according to the synthesis procedure described in the Supporting Information, based on a modification of the procedure described by Valencia and Corma,[30,31] yielding the Sn-Beta catalyst with a Si/Sn ratio of 200. The product composition and structure was confirmed by ICP (inductively coupled plasma; Si/Sn = 200), XRD (*BEA zeolite framework, Figure S4) and $N_2$-adsorption (see the Supporting Information for details).

To discern effects of solvent upon product composition and pathway usage, each sample was heated to 160 °C for 2 h. Aliquots of 500 μL were taken from each sample, MeOH-$d_4$ (50 μL; Sigma–Aldrich) was added, and the mixture transferred to a 5 mm NMR tube for immediate analysis. In kinetic experiments, samples in water, methanol, or ethanol were prepared in the same manner detailed above and heated to 160 °C for an allotted time (1 s, 10 s, 1 min, 10 min, 1 h, or 2 h). Samples were rapidly cooled with compressed air and 500 μL aliquots were taken from each sample, mixed with MeOH-$d_4$ (50 μL), and transferred to 5 mm NMR tubes. All NMR spectra were acquired on an 800 MHz Bruker Avance III NMR spectrometer equipped with a TCI CryoProbe and a SampleJet sample changer. 1D $^{13}$C NMR spectra were acquired by sampling 64k complex data points during an acquisition time of 1.36 s, and using an inter-scan recycle delay of 45 s. A pulse sequence with $^1$H irradiation only applied during signal acquisition was used to minimize distortions of signal integrals by the nuclear Overhauser effect. Protonated $^{13}$C carbon atoms were used for quantification and several carbon sites per molecule were used to improve the statistics of the signal area, using integration values from Bruker Topspin 3.5 pl5 (see for example, Figure 6). Standard DQF-COSY, TOCSY, $^1$H-$^{13}$C HMBC, standard and edited $^1$H-$^{13}$C HSQC, as well as $^1$H-$^{13}$C HSQC-TOCSY experiments were employed for compound identification in samples following solvent evaporation overnight in a fume hood and re-dissolution in deuterated solvents. Figure S6 (Supporting Information) demonstrates the accuracy of this method by comparison of a reaction sample with readily available standard compounds. Standard $^1$H-$^{13}$C HSQC, edited HSQC, as well as $^1$H-$^{13}$C HSQC-TOCSY were used in protic solvents to validate the assignments. All spectra were processed with ample zero filling in all spectral dimensions using Bruker Topspin 3.5 pl5.

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## *Conflict of interest*

*The authors declare no conflict of interest.*

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