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Conversion of Unprotected Aldose Sugars to Polyhydroxyalkyl and C-Glycosyl Furans via Zirconium Catalysis

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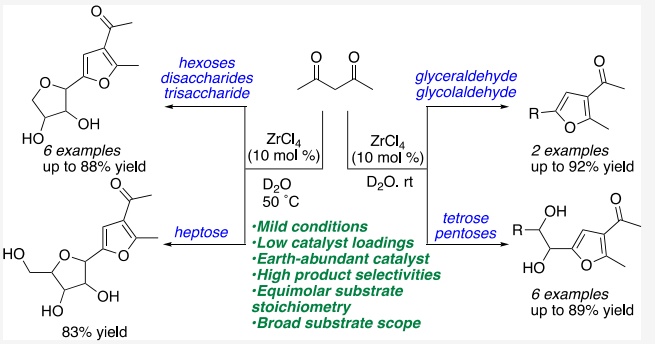
ABSTRACT: An efficient, zirconium-catalyzed conversion of unprotected aldose sugars with acetylacetone to polyhydroxyalkyl furans or C-glycosylfurans is reported. The furan products are formed in up to 93% yield using 5−10 mol % $ZrCl_4$. Pentoses are readily converted at room temperature, while hexoses and their oligosaccharides require mild heating (i.e., 50 °C). Efficient conversions of glycolaldehyde, glyceraldehyde, erythrose, a heptose, and glucosamine are also demonstrated. This approach outpaces each of the previous Lewis acid-catalyzed methods in at least one the following ways: (i) lower catalyst loadings; (ii) reduced reaction temperatures; (iii) shorter reaction times; (iv) equimolar substrate stoichiometry; (v) expanded sugar scope; (vi) higher selectivities; and (vii) the use of an Earth-abundant Zr catalyst.



INTRODUCTION

Biomass represents a variety of renewable feedstocks that, through upgrading, offer an important alternative to fossil resources for the production of chemicals, fuels, and materials.[1] A number of integrated technologies have been developed to upgrade biomass to biofuels and bio-based platform chemicals that can be further converted to a host of industrially relevant products.[2] Carbohydrates, one of the most abundant and common forms of biomass, have been the center of much of the research focused on finding new and efficient renewable feedstock upgrading technologies.[3] For example, levulinic acid, substituted furfurals, sugar alcohols, lactic acid, phenols, and succinic acid have been identified as low-cost platform chemicals that are derived from carbohydrates.[3,4] Despite these important examples, carbohydrate upgrading technologies have remained limited. A pressing need exists for the identification and development of technologies that offer new platform chemicals that can be utilized on a production scale.

The Garcia Gonzalez (GG) reaction is a biomass upgrading approach that takes simple sugars and converts them into polyhydroxyalkylated furans or C-glycosylfurans in the presence of 1,3-dicarbonyl compounds and Lewis acids (Scheme 1A).[5−7] Both furan products are considered underexplored platform chemicals that have potential for various therapeutic and industrial applications. For instance, GG reaction products have been explored as anticancer agents,[8] antimicrobials,[9] glycomimetics,[10] biological probes,[11] fuel-type molecules,[6a] gels,[12] and more.

The GG reaction has been largely overlooked for industrial-scale upgrading due to various limitations of published literature protocols that include:[6,13] (1) a high reaction temperature; (2) a high Lewis acid loading; (3) a long reaction time; (4) an excess of one substrate; (5) poor product selectivity; (6) a limited substrate scope; (7) inconsistent stereochemical assignments; or (8) irreproducibility. To tackle these issues and to make the reaction potentially viable in practical syntheses, we sought to establish milder and more generalizable conditions. Toward that goal, herein, we describe the development of a Zr-catalyzed GG reaction that addresses each of the limitations (Scheme 1B).

RESULTS AND DISCUSSION

As a starting point for our study, we chose the conversion of ribose **1a** with acetylacetone **2** (Table S1). This reaction does not proceed at room temperature without a catalyst and has precedent across the literature using different Lewis acids. For measures of success, we established the following screening criteria: (1) the reaction must be performed in water; (2) the reaction must be performed at room temperature; (3) the reaction must reach completion within 7 h; (4) the reaction must employ equimolar substrate stoichiometry; and (5) the Lewis acid loading must remain 10 mol % or less. Given these

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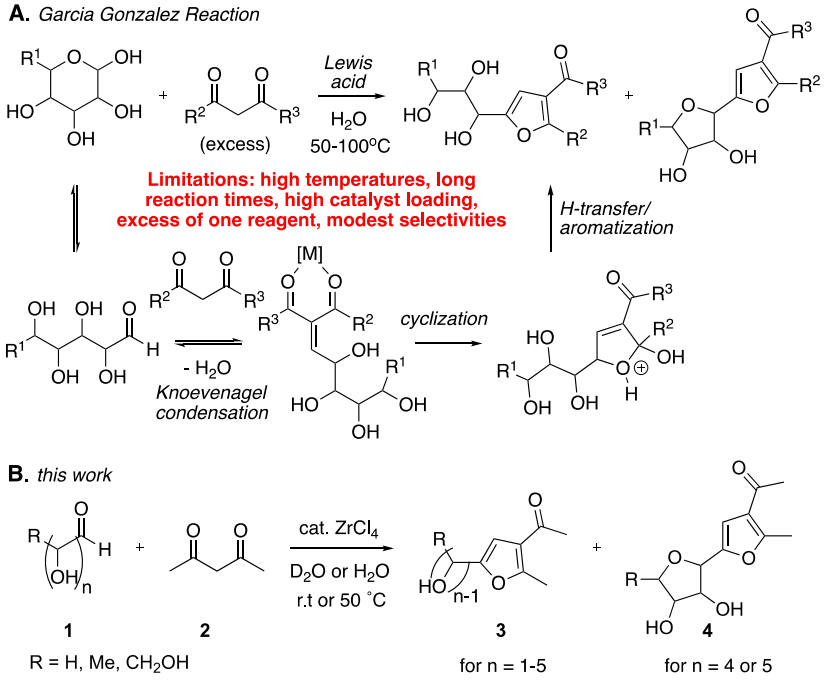
Scheme 1. Garcia Gonzalez Reaction (A) and the $ZrCl_4$-Catalyzed Variant (B)



criteria, we first screened Lewis acid salts (at 5 mol % loading and 2.4 M sugar concentration) that had been reported to promote any GG-type reaction.[14] Of the salts previously employed, $Sc(OTf)_3$[6h] offered promising results, as 47% yield of **3a** was obtained (see Table S1 in the Supporting Information for full catalyst screening).

In addition, we were also interested in the use of zirconium(IV) salts as Lewis acid catalysts. Zr(IV) salts have been shown to promote a wide range of transformations including condensations, cycloadditions, multicomponent reactions, and so on.[15] They are readily available, cheap, earth-abundant, nontoxic, moisture-stable, air-stable, easy to handle, and, in some cases, recoverable/reusable.[16] Of the available types of Zr(IV) species, $ZrCl_4$ and $ZrOCl_2{\cdot}8H_2O$ (the hydrolysis product of $ZrCl_4$) have been the most studied. Interestingly, $ZrCl_4$ gave 47% yield of furan **3a** after 6 h (Table 1, entry 1) and 89% yield when allowed to run for 16 h.[14,17] We chose to continue our GG study with $ZrCl_4$ due to its much lower relative cost as compared to $Sc(OTf)_3$ (~$0.40/g vs >$30/g).[18]

More concentrated reaction conditions led to improved yields of **3a** with $ZrCl_4$.[19] After further screening of reaction concentrations and $ZrCl_4$ loading, the following optimized conditions were obtained that ultimately met each of the five established screening criteria: 10 mol % $ZrCl_4$, D_2O (12 M sugar concentration), and 6 h (Table 1, entry 2). Trihydroxalkyl furan **3a** was formed in 93% NMR yield with these conditions, which translated to an 89% isolated yield following chromatography.[20] Although D_2O was used as the solvent, we felt it was important to ensure that H_2O was equally compatible given the goal of efficient scale-up (Table 1, entry 3). Running the reaction in H_2O for 6.5 h gave a comparable isolated yield of 88%. The H_2O reaction also scaled up to 12 mmol (1.8 g of ribose) without issue (Table 1, entry 4). To the best of our knowledge, these results represent the first known examples of an efficient GG reaction performed at room temperature.

Next, other pentoses were screened using the conditions optimized for the conversion of ribose. D-Xylose (**1b**) and D-lyxose (**1c**) both gave furan product **3b** with isolated yields of 83 and 81%, respectively (Table 1, entries 5 and 6). For D-arabinose (**1d**), the expected furan product **3a** was not observed and instead the fully C-1′-epimerized product **3b** was obtained in 85% yield (Table 1, entry 7). Arabinose has been shown to readily epimerize, providing varying mixtures of **3a** and **3b**, depending on the Lewis acid and the reaction temperature employed.[21] D-Rhamnose (**1e**), a 5-methylpentose, generated its product **3e** in good yield without incident (78%, Table 1, entry 8).

We then expanded the substrate scope to include D-erythrose (**1f**, an aldotetrose), glycolaldehyde (**1g**), and D-glyceraldehyde (**1h**). D-Erythrose (**1f**) afforded dihydroxyalkyl furan **3f** in 89% isolated yield (Table 1, entry 9). Both D-glyceraldehyde and glycolaldehyde similarly performed well under the reaction conditions, providing their respective furan products **3g** and **3h** in 92 and 90% isolated yields in 5 h (Table 1, entries 10 and 11).

Encouraged by these results, hexoses became the next focus. In accordance with the recognized increase in stability and literature precedents, the hexoses reacted less readily than the pentoses (Table 2).[22] When D-glucose (**1i**, a representative hexose) was subjected to the optimized conditions, a 3.2:1 mixture of tetrahydroxylalkyl furan **3i** and *β*-*C*-glycosylfuran **4i** was obtained in a 43% total NMR yield (Table 2, entry 1).[23] Conversely, at 50 °C, *C*-glycosylfuran **4i** (10:1 *β*:*α* ratio) was generated in 93% total NMR yield in a 1:10 uncyclized (**U**) to cyclized (**C**) ratio (Table 2, entry 2). In this instance, the reaction gave isolated yields of 80 and 8% for **4i** and **3i**, respectively. As with ribose, the glucose reaction could be performed in H_2O without issue, offering results comparable to the D_2O reaction (Table 2, entry 3). The H_2O reaction was also scalable to 12 mmol (2.16 g glucose) providing *C*-glycosylfuran **4i** in 82% isolated yield (Table 2, entry 4). Although our reaction did not specifically meet the room

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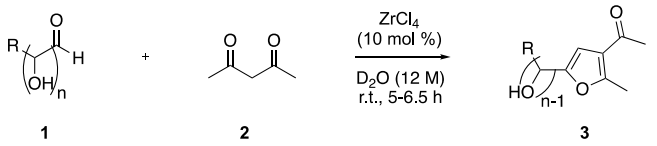
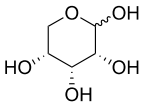
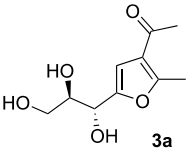
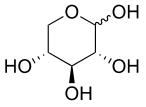
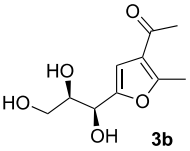
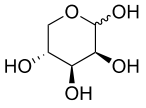
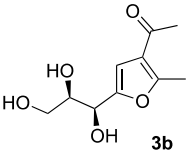
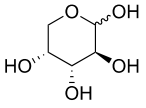
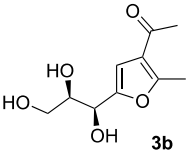
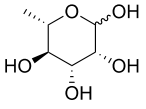
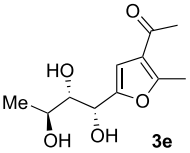
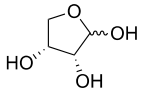
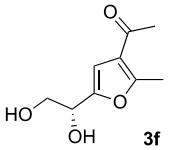
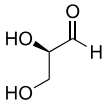
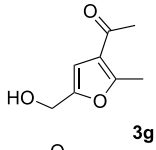
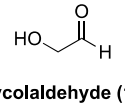
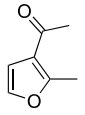
Table 1. Conversion of Pentoses, Erythrose, Glycolaldehyde, and Glyceraldehyde[a]



1 2 3

entry	sugar	product(s)	yield[b] (%)[c]
1[d]	 D-ribose (1a)	 3a	— (47)
2			89 (93)
3[e]			88 (92)
4[e,f]			84 (89)
5	 D-xylose (1b)	 3b	83 (74)
6	 D-lyxose (1c)	 3b	81 (70)
7	 D-arabinose (1d)	 3b	85 (91)
8	 L-rhamnose (1e)	 3e	78 (80)
9	 D-erythrose (1f)	 3f	89 (94)
10[g]	 D-glyceraldehyde (1g)	 3g	92 (94)
11[g]	 glycolaldehyde (1h)	 3h	90 (93)

[a]Reactions performed at 12 M with 1.2 mmol of sugar, 1.2 mmol of acetylacetone **2**, and 10 mol % $ZrCl_4$ in D_2O at room temperature for 6 h. [b]Isolated yields of the indicated products after column chromatography. [c]Yields in parentheses indicate NMR yields of the indicated products using EtOH as an internal standard. [d]Reaction performed at 2.4 M sugar concentration with 5 mol % $ZrCl_4$. [e]Reaction performed in H_2O for 6.5 h. [f]Reaction performed on a 12.0 mmol (1.80 g) scale (based on ribose). [g]Reaction time of 5 h.

temperature criterion,[24] it still outpaced most of the published literature, providing high selectivity for *C*-glycosylfuran **4i** at substantially lower reaction temperatures (50 vs >80 °C).[13]

Hexoses D-allose, D-altrose, and D-mannose are all expected to give the same product **4i** as glucose and thus were omitted from the substrate scope.[5a] Instead, we chose to use D-galactose (**1j**) as the representative for the other hexoses (D-gulose, D-idose, and D-talose), which should give the epimeric product **4j**. As expected, *C*-glycosylfuran **4j** was obtained from D-galactose in 80% yield with a 1.4:1 β:α anomeric ratio along with an 8:1 **C**:**U** ratio (Table 2, entry 5).

Hexose-based disaccharides were then explored for compatibility with the reaction conditions. After initial experiments, a more dilute sugar concentration (6 M) was found to be optimal for the reaction. Interestingly, although the reactions reach completion within 6 h, high selectivities were only observed after longer reaction times (i.e., 16 h). For instance, D-maltose (**5a**) readily converted into its *C*-glycosylfuran

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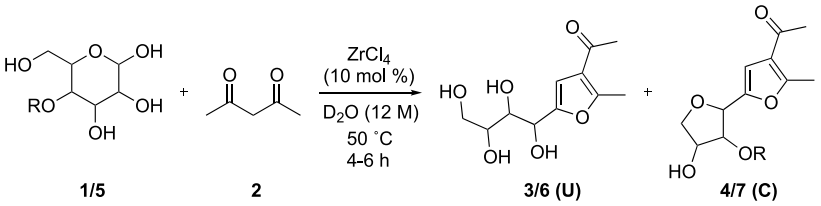
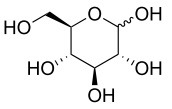
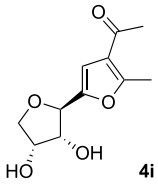
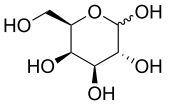
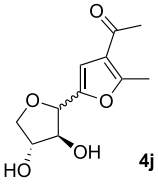
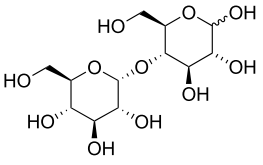
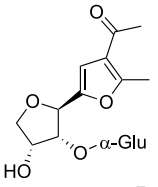
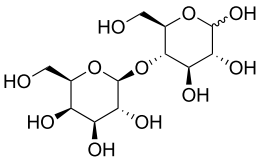
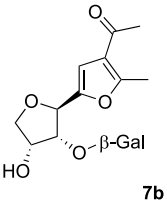
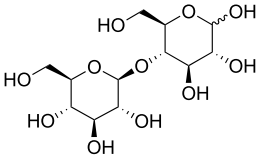
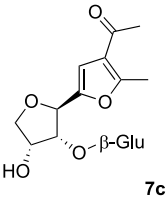
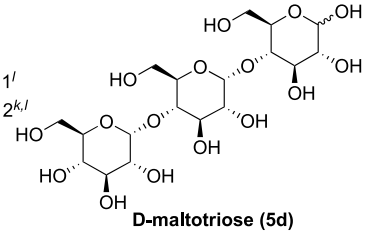
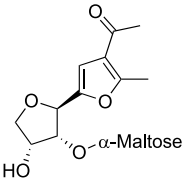
Table 2. Chemoselective Conversion of Hexoses and Oligosaccharides[a]



1/5 2 3/6 (U) 4/7 (C)

entry	sugar	product(s)[b]	yield (%)[c,d]	ratio[e] (C:U)
1[f]	 D-glucose (1i)	 4i	11 (43)[g]	1:3
2			80 (88)	10:1
3[h]			84 (92)	10:1
4[h,i]			82 (88)	10:1
5	 D-galactose (1j)	 4j (1.4:1 β:α)	80 (90)	8:1
6[j]	 D-maltose (5a)	 7a	51 (75)	2:1
7[j,k]			81 (85)	22:1
8[j]	 D-lactose (5b)	 7b	49 (70)	2:1
9[j,k]			67 (70)	20:1
10[j]	 D-cellobiose (5c)	 7c	38 (50)	3:1
11[l]	 D-maltotriose (5d)	 7d	61 (91)	2:1
12[k,l]			88 (92)	22:1

[a]Reactions performed with 1.2 mmol of sugar **1**, 1.2 mmol of acetylacetone **2**, and 10 mol % $ZrCl_4$ in D_2O (12 M) at 50 °C for 4−6 h. [b]Unless otherwise noted, the ratio of β-anomer/α-anomer is >10:1. [c]Isolated yields of the indicated products after column chromatography. [d]Numbers in parentheses represent total yield of cyclized and uncyclized products. [e]Ratio of cyclized (**C**) to uncyclized (**U**) products. [f]Reaction performed at room temperature. [g]NMR yield using EtOH as an internal standard. [h]Reaction performed in H_2O. [i]Reaction performed on 12.0 mmol (1.20 g) scale in H_2O. [j]Reaction performed at 6 M concentration. [k]Reaction run for 16 h. [l]Reaction performed at 4 M concentration.

product **7a** in 51% yield and a 2:1 **C**:**U** ratio after 6 h (Table 2, entry 6) but gave 81% yield and a 22:1 **C**:**U** ratio after 16 h (Table 2, entry 7). Similarly, D-lactose (**5b**) afforded *C*-glycosylfuran **7b** in 49% yield and a 2:1 **C**:**U** ratio vs 67% yield

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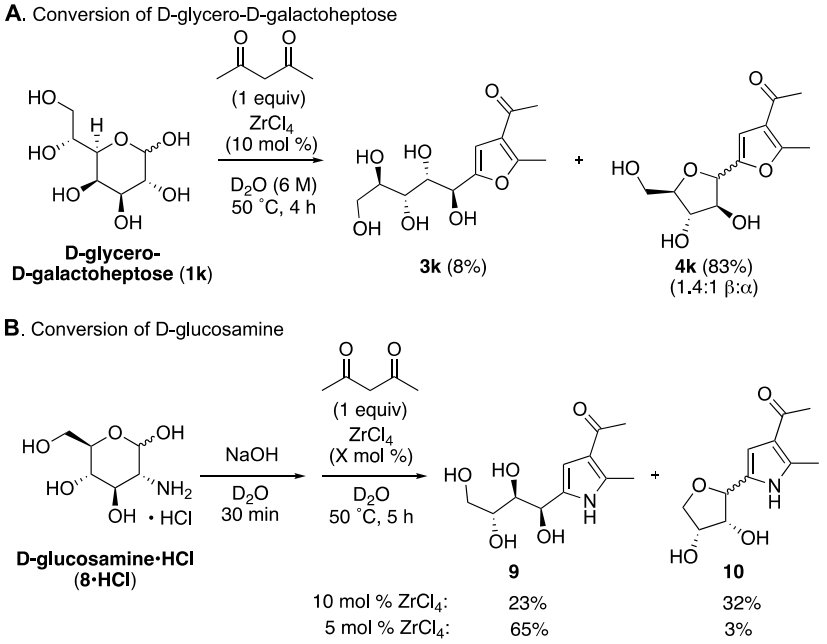
Scheme 2. Conversions of D-Glycero-D-galactoheptose (A) and D-Glucosamine·HCl (B)



and 20:1 **C**:**U** ratio at 6 and 16 h, respectively (entries 8 and 9). With D-cellobiose (**5c**), the reaction, unexpectedly, did not reach full conversion after 16 h and gave a reduced total product yield (50%) of **7c** along with a poor **C**:**U** selectivity (3:1, Table 2, entry 10). This outcome can be explained by cellobiose's reduced solubility.[25] Specifically, cellobiose has been shown to have a 9-fold lower solubility when directly compared to maltose (0.120 vs 1.08 g/mL). In addition, the solubility of cellobiose was reported to only change incrementally between room temperature and 50 °C (from 0.010 to 0.013 mol fraction solubilized).

A hexose-based trisaccharide, D-maltotriose (**5d**), was subjected to more dilute reaction conditions to enhance solubility (4 M, Table 2, entry 11). At 6 h, *β*-*C*-glycosylfuran **7d** was formed in 61% yield with a 2:1 **C**/**U** ratio. Selectivity was high at 16 h giving a 22:1 **C**/**U** ratio with an 88% isolated yield of **7d** (Table 2, entry 12). These results represent the first known examples of the successful conversions of a trisaccharide in the GG reaction.

Given that this method is amenable to everything from glyceraldehyde to oligosaccharides, a representative aldoheptose was examined (Scheme 2A). When D-glycero-D-galactoheptose (**1k**) was subjected to the same reaction conditions as the disaccharides, a ∼10:1 mixture of *C*-glycosylfuran **4k** (1.4:1 *β*:*α*) and polyhydroxalkyl furan **3k** was obtained in a 91% total yield.

Finally, glucosamine (**8**) has been previously shown to be compatible with the GG reaction.[26] To determine glucosamine's amenability with our reaction method, we first treated D-glucosamine·HCl salt (**8·HCl**) with NaOH (1 equiv) then added in acetylacetone and $ZrCl_4$ (Scheme 2B). At 4 M sugar concentration[27] and 10 mol % catalyst loading, the reaction afforded a 1:1.4 mixture of uncyclized to cyclized products (**9**–**10**) in a 55% total yield. Small amounts of degradation products were also detected, so the catalyst loading was lowered to attempt to mitigate this issue. Unexpectedly, the reaction with 5 mol % $ZrCl_4$ preferentially gave the corresponding tetrahydroxyalkyl pyrrole **9** in 65% yield with a 20:1 **U**:**C** ratio.

To expand our scope further, we attempted our reaction conditions with additional dicarbonyl compounds other than acetylacetone. Through various optimizations, we determined our reaction conditions were less favorable with other diketones, such as ethyl acetoacetate, 1,3-cyclohexanedione, and 1-phenyl-1,3-butanedione (see Table S5 in the Supporting Information for details). Additionally, when we exposed fructose, a representative ketose to both sets of reaction conditions, only starting material was recovered. This was expected due to the less reactive nature of the ketoses vs aldoses.

■ CONCLUSIONS

In summary, we have developed a general method for the Garcia Gonzalez reaction with acetylacetone, utilizing a zirconium-based catalyst under mild conditions to obtain the desired products in good to excellent yields with short reaction times. The methodology is expandable to different classes of carbohydrates, such as pentoses, hexoses, and oligosaccharides. In addition, this new protocol also has great atom economy and very limited waste, with no detectable organic side products and water being the only byproduct of the reaction. The reaction could also be scaled up (∼2 gram-scale) with similar isolated yields, showcasing the potential for industry-scale production, especially given the simplicity of the setup. This low-cost and high-yielding methodology will allow more research to be focused on utilization of the Garcia Gonzalez products for use in materials, fuels, and other new areas.

■ EXPERIMENTAL SECTION

General Information. Chromatographic purification was performed as flash chromatography, utilizing a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture. For quantitative flash chromatography, technical grade solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on Silicycle SiliaPlate TLC silica gel F254 (250 *μ*m)

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TLC glass plates. Visualization was accomplished with UV light. Infrared (IR) spectra were obtained via attenuated total reflection (ATR) with a diamond plate using a Bruker α Fourier-transform infrared spectrophotometer. The IR bands are characterized as broad (br), weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 MHz spectrometer or a Bruker 700 MHz spectrometer. ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet, br = broad), coupling constants (Hz), and integration. Mass spectra were obtained through ESI on a Thermo Orbitrap XL.

General Procedure A. A 4 mL glass vial with a magnetic stir bar was charged with $ZrCl_4$ (10 mol %) and carbohydrate (1 equiv) and dissolved in 100 μL of D_2O (or H_2O). Acetylacetone (1 equiv) was added, and the reaction stirred at room temperature. The reaction was monitored via TLC, looking for disappearance of the acetylacetone and appearance of the desired product. Following disappearance of the starting material, ethanol (55 mg) was added as an internal standard and an aliquot was analyzed via quantitative NMR to obtain a product yield.

General Procedure B. A 4 mL glass vial with a magnetic stir bar was charged with $ZrCl_4$ (10 mol %) and carbohydrate (1 equiv) and dissolved in 100 μL of D_2O (or H_2O). Acetylacetone (1 equiv) was added and the reaction stirred at room temperature. The reaction was monitored via TLC, looking for disappearance of the acetylacetone and appearance of the desired product. The reaction mixture was then immediately loaded on a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column. A combination of water and acetonitrile was used as the eluting mixture, which were then removed in vacuo to yield the pure product(s).

Reaction of D-Ribose with Acetylacetone. General Procedure B was followed using D-ribose **1a** (0.180 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (100 μL, 12 M) at room temperature for 6 h. The reaction was then purified, as is, by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **3a** as a clear semisolid (0.229 g, 89% yield).

Large-Scale Reaction of D-Ribose with Acetylacetone. General Procedure B was followed with a slight variation to facilitate scaling up using D-ribose **1a** (1.80 g, 12.0 mmol), acetylacetone **2** (1.20 g, 12.0 mmol), $ZrCl_4$ (0.270 g, 12.0 mmol), and H_2O (1000 μL, 12 M) at room temperature for 6.5 h. The reaction was then purified by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **3a** as a clear semisolid (2.16 g, 84% yield).

*1-(2-Methyl-5-((1R,2R)-1,2,3-trihydroxypropyl)furan-3-yl)ethan-1-one (**3a**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.62 (s, 1H), 4.54 (d, J = 7.2 Hz, 1H), 3.88−3.91 (m, 1H), 3.69−3.73 (dd, J = 3.3 and 11.9 Hz, 1H), 3.57 (dd, J = 11.9 and 6.3 Hz), and 2.45 (s, 3H), 2.35 (s, 3H). **^{13}C {^{1}H} NMR** (126 MHz, D_2O) δ = 199.3, 160.1, 151.6, 121.8, 108.8, 72.6, 66.9, 62.4, 28.5, and 14.0. **IR:** 3365 (br), 1655 (m) cm^{-1}. **HRMS (ESI)** m/z: [M + Na]$^+$ calcd for $C_{10}H_{14}O_5Na$, 237.0733; found, 237.0728.

Reaction of D-Xylose with Acetylacetone. General Procedure B was followed using D-xylose **1b** (0.180 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (100 μL, 12 M) at room temperature for 6 h. The reaction was then purified, as is, by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **3b** as a clear semisolid (0.213 g, 83% yield).

*1-(2-Methyl-5-((1R,2R)-1,2,3-trihydroxypropyl)furan-3-yl)ethan-1-one (**3b**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.62 (s, 1H), 4.57 (d, J = 6.4 Hz, 1H), 3.88−3.91 (m, 1H), 3.50−3.53 (dd, J = 4.0 and 11.9 Hz, 1H), 3.40 (dd, J = 11.9 and 6.6 Hz, 1H), and 2.44 (s, 3H), 2.35 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.3, 160.1, 151.3, 121.8, 108.4, 73.0, 67.2, 62.2, 28.5, and 14.0. **IR:** 3370 (br), 1655 (m) cm^{-1}. **HRMS (ESI)** m/z: [M + Na]$^+$ calcd for $C_{10}H_{14}O_5Na$, 237.0733; found, 237.0729.

Reaction of D-Lyxose with Acetylacetone. General Procedure B was followed using D-lyxose **1c** (0.180 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (100 μL, 12 M) at room temperature for 6 h. The reaction was then purified, as is, by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **3b** as a clear semisolid (0.208 g, 81% yield).

*1-(2-Methyl-5-((1R,2R)-1,2,3-trihydroxypropyl)furan-3-yl)ethan-1-one (**3b**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.62 (s, 1H), 4.57 (d, J = 6.4 Hz, 1H), 3.88−3.91 (m, 1H), 3.50−3.53 (dd, J = 4.0 and 11.9 Hz, 1H), 3.40 (dd, J = 11.9 and 6.6 Hz, 1H), and 2.44 (s, 3H), 2.35 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.3, 160.1, 151.3, 121.8, 108.4, 73.0, 67.2, 62.2, 28.5, and 14.0. **IR:** 3370 (br), 1655 (m) cm^{-1}. **HRMS (ESI)** m/z: [M + Na]$^+$ calcd for $C_{10}H_{14}O_5Na$, 237.0733; found, 237.0728.

Reaction of D-Arabinose with Acetylacetone. General Procedure B was followed using D-arabinose **1d** (0.180 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (100 μL, 12 M) at room temperature for 6 h. The reaction was then purified, as is, by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **3b** as a clear semisolid (0.218 g, 85% yield).

*1-(2-Methyl-5-((1R,2R)-1,2,3-trihydroxypropyl)furan-3-yl)ethan-1-one (**3b**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.62 (s, 1H), 4.57 (d, J = 6.4 Hz, 1H), 3.88−3.91 (m, 1H), 3.50−3.53 (dd, J = 4.0 and 11.9 Hz, 1H), 3.40 (dd, J = 11.9 and 6.6 Hz, 1H), and 2.44 (s, 3H), 2.35 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.3, 160.1, 151.3, 121.8, 108.4, 73.0, 67.2, 62.2, 28.5, and 14.0. **IR:** 3370 (br), 1655 (m) cm^{-1}. **HRMS (ESI)** m/z: [M + Na]$^+$ calcd for $C_{10}H_{14}O_5Na$, 237.0733; found, 237.0727.

Reaction of D-Rhamnose with Acetylacetone. General Procedure B was followed using L-(+)-rhamnose monohydrate **1e** (0.219 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (100 μL, 12 M) at room temperature for 6 h. The reaction was then purified, as is, by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **3e** as a clear semisolid (0.214 g, 78% yield).

*1-(2-Methyl-5-((1R,2R,3S)-1,2,3-trihydroxybutyl)furan-3-yl)-ethan-1-one (**3e**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.63 (s, 1H), 4.64 (d, J = 6.0 Hz, 1H), 3.73 (m, 1H), 3.62 (m, 1H), 2.48 (s,3H), 2.37 (s, 3H), and 1.08 (d, J = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.5, 160.0, 151.7, 121.8, 108.2, 76.0, 67.0, 66.8, 28.5, 17.0, and 14.0. **IR:** 3380 (br), 1660 (m) cm^{-1}. **HRMS (ESI)** m/z: [M + Na]$^+$ calcd for $C_{11}H_{16}O_5Na$, 251.0890; found, 251.0884.

Reaction of D-Erythrose with Acetylacetone. General Procedure B was followed using D-(−)-erythrose **1f** (0.144 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (100 μL, 12 M) at room temperature for 6 h. The reaction was then purified, as is, by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **3f** as a clear semisolid (0.197 g, 89% yield).

*(R)-1-(5-(1,2-Dihydroxyethyl)-2-methylfuran-3-yl)ethan-1-one (**3f**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.63 (s, 1H), 4.66 (t, J = 6.0 Hz, 1H), 3.71−3.78 (m, 2H), 2.46 (s,3H), and 2.38 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.6, 160.0, 151.5, 121.8, 108.0, 76.0, 67.0, 63.1, 28.5, and 13.9. **IR:** 3380 (br), 1660 (m) cm^{-1}. **HRMS (ESI)** m/z: [M + Na]$^+$ calcd for $C_9H_{12}O_4Na$, 207.0633; found, 207.0640.

Reaction of DL-Glyceraldehyde with Acetylacetone. General Procedure B was followed using DL-glyceraldehyde **1g** (0.108 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (100 μL, 12 M) at room temperature for 5 h. The

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reaction was then purified, as is, by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **3g** as a clear semisolid (0.170 g, 92% yield).

*1-(5-(Hydroxymethyl)-2-methylfuran-3-yl)ethan-1-one (**3g**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.46 (s, 1H), 4.35 (s, 2H), 2.33 (s, 3H), and 2.23 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 198.6, 160.0, 151.8, 121.8, 108.4, 55.4, 28.3, and 13.9. **IR**: 3350 (br), 1660 (s), 1610 (m), and 1565 (s) cm^{-1}. **HRMS (ESI)** *m/z*: $[M + Na]^+$ calcd for $C_8H_{10}O_3Na$, 177.0522; found, 177.0518.

Reaction of Glycolaldehyde with Acetylacetone. General Procedure B was followed with slight variation using glycolaldehyde dimer **1h** (0.072 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (100 μL, 12 M) at room temperature for 5 h. The mixture was then added to 3 mL of H_2O and extracted by diethyl ether (3 × 5 mL). The organic layer was concentrated under reduced pressure and purified by silica column chromatography, using an eluent combination of hexane and diethyl ether. The fractions were then concentrated under reduced pressure to afford **3h** as a colorless liquid (0.134 g, 90% yield). Characterization information was found to correlate with literature values.[26] 1-(2-Methylfuran-3-yl)ethan-1-one (**3h**): **^{1}H NMR** (700 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 1.9 Hz, 1H), 6.63 (d, *J* = 1.9 Hz, 1H), 2.60 (s, 3H), and 2.42 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ = 194.2, 158.5, 140.2, 121.4, 110.5, 29.2, and 14.4. **IR**: 1655 (s) cm^{-1}. **HRMS (ESI)** *m/z*: $[M + H]^+$ calcd for $C_7H_9O_2$, 125.0597; found, 125.0591.

General Procedure C. A 4 mL glass vial with a magnetic stir bar was charged with $ZrCl_4$ (10 mol %) and carbohydrate (1 equiv) and dissolved in the indicated amount of D_2O (or H_2O). Acetylacetone (1 equiv) was added and the reaction stirred at 50 °C. The reaction was monitored via TLC, looking for disappearance of acetylacetone and appearance of the desired product. Following disappearance of the starting material, the reaction was allowed to cool to room temperature. At this point, ethanol (55 mg) was added as an internal standard and an aliquot was analyzed via quantitative NMR to obtain a product yield.

General Procedure D. A 4 mL glass vial with a magnetic stir bar was charged with $ZrCl_4$ (10 mol %) and carbohydrate (1 equiv) and dissolved in the indicated amount of D_2O (or H_2O). Acetylacetone (1 equiv) was added and the reaction stirred at 50 °C. The reaction was monitored via TLC, looking for disappearance of acetylacetone and appearance of the desired product. Following disappearance of the starting material, the reaction was allowed to cool to room temperature. The reaction was then immediately loaded on a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column. A combination of water and acetonitrile was used as the eluting mixture, which were then removed in vacuo to yield the pure product(s).

Reaction of D-Glucose with Acetylacetone. General Procedure D was followed using D-glucose **1i** (0.216 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (100 μL, 12 M) at 50 °C for 4 h. The reaction was then purified by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **3i** (0.023 g, 8% yield) and **4i** (0.217 g, 80% yield). Characterization information was found to correlate with literature values.[12]

Large-Scale Reaction of D-Glucose with Acetylacetone. General Procedure D was followed using D-glucose **1i** (2.16 g, 12.0 mmol), acetylacetone **2** (1.20 g, 12.0 mmol), $ZrCl_4$ (0.270 g, 1.20 mmol), and H_2O (1000 μL, 12 M) at 50 °C for 4 h. The reaction was then purified by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **3i** (0.233 g, 8% yield) and **4i** (2.17 g, 80% yield).

*1-(2-Methyl-5-((1S,2R,3R)-1,2,3,4-tetrahydroxybutyl)furan-3-yl)-ethan-1-one (**3i**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.63 (s, 1H), 4.80 (d, *J* = 4.1 Hz, 1H), 3.80 (dd, *J* = 7.4 and 4.2 Hz, 1H), 3.70 (dd, *J* = 11.9 and 3.1 Hz, 1H), 3.61−3.64 (m, 1H), 3.53 (dd, *J* = 11.8 and 6.7 Hz, 1H), and 2.48 (s, 3H), 2.39 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.5, 159.9, 152.1, 121.9, 107.8, 72.6, 71.1, 66.4, 62.6, 30.2, and 13.9. **IR**: 3390 (br), 1660 (m) cm^{-1}. **HRMS (ESI)** *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{16}O_6Na$, 267.0839; found, 267.0837.

*1-(5-((2S,3R,4R)-3,4-Dihydroxytetrahydrofuran-2-yl)-2-methylfuran-3-yl)ethan-1-one (**4i**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.69 (s, 1H), 4.61 (d, *J* = 7.9 Hz, 1H), 4.29−4.31 (m, 1H), 4.12 (dd, *J* = 10.3 and 4.3 Hz, 1H), 3.78 (dd, *J* = 10.3 and 2.3 Hz, 1H), and 2.39 (s, 3H), 2.29 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 198.7, 160.7, 149.4, 121.9, 110.1, 75.4, 74.2, 72.6, 70.9, 28.4, and 14.0. **IR**: 3385 (br), 1670 (m) cm^{-1}. **HRMS (ESI)** *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{14}O_5Na$, 249.0733; found, 249.0730.

Reaction of D-Galactose with Acetylacetone. General Procedure D was followed using D-galactose **1j** (0.216 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (100 μL, 12 M) at 50 °C for 4 h. The reaction was then purified, as is, by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **3j** (0.029 g, 10% yield) and **4j** (0.217 g, 80% yield).

*1-(2-Methyl-5-((1S,2S,3R)-1,2,3,4-tetrahydroxybutyl)furan-3-yl)-ethan-1-one (**3j**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.67 (s, 1H), 4.61 (d, *J* = 8.8 Hz, 1H), 3.88−3.91 (m, 1H), 3.84 (dd, *J* = 8.8 and 2.9 Hz, 1H), 3.58−3.64 (m, 2H), and 2.48 (s, 3H), 2.39 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.6, 160.2, 152.1, 121.9, 109.0, 71.2, 70.1, 66.0, 62.9, 28.5, and 14.0. **IR**: 3390 (br), 1660 (m) cm^{-1}. **HRMS (ESI)** *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{16}O_6Na$, 267.0839; found, 267.0835.

*1-(5-((2S,3S,4R)-3,4-Dihydroxytetrahydrofuran-2-yl)-2-methylfuran-3-yl)ethan-1-one (**4j**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.71 (s, 1H), 4.60 (d, *J* = 5.0 Hz, 1H), 4.29−4.31 (m, 1H), 4.24−4.26 (m, 1H), 4.02 (dd, *J* = 10.1 and 5.0 Hz, 1H), 3.84 (dd, *J* = 10.1 and 3.0 Hz, 1H), and 2.45 (s, 3H), 2.35 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.3, 160.8, 149.1, 121.9, 109.5, 79.8, 79.2, 76.7, 72.8, 28.5, and 14.0. **IR**: 3395 (br), 1670 (m) cm^{-1}. **HRMS (ESI)** *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{14}O_5Na$, 249.0733; found, 249.0729.

Reaction of D-Maltose with Acetylacetone. General Procedure D was followed using D-(+)-maltose monohydrate **1l** (0.432 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (200 μL, 6 M) at 50 °C for 16 h. The reaction was then purified, as is, by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **6a** (0.020 g, 4% yield) and **7a** (0.377 g, 81% yield). At 4 h, the reaction gave **6a** (0.120 g, 24% yield) and **7a** (0.237 g, 51% yield).

*1-(2-Methyl-5-((1S,2R,3R)-1,3,4-trihydroxy-2-(((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-butyl)furan-3-yl)ethan-1-one (**6a**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.68 (s, 1H), 4.95 (d, *J* = 3.8 Hz, 1H), 4.87 (d, *J* = 6.7 Hz, 1H), 4.05 (dd, *J* = 6.6 and 3.5 Hz, 1H), 3.75−3.80 (m, 1H), 3.72 (t, 1H), 3.67−3.71 (m, 2H), 3.64 (t, 1H), 3.56 (dd, *J* = 11.7 and 3.7 Hz, 1H), 3.42 (dd, *J* = 9.9 and 3.7 Hz, 1H), 3.39 (dd, *J* = 11.7 and 7.7 Hz, 1H), 3.34 (t, 1H), 2.48 (s, 3H), and 2.38 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.4, 160.1, 150.6, 122.0, 108.9, 100.0, 81.3, 72.9, 72.3, 72.2, 71.6, 69.3, 66.9, 61.9, 60.3, 28.6, and 14.0. **IR**: 3390 (br), 1665 (m) cm^{-1}. **HRMS (ESI)** *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{26}O_{11}Na$, 429.1367; found, 429.1356.

*1-(5-((2S,3R,4R)-4-Hydroxy-3-(((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)tetrahydrofuran-2-yl)-2-methylfuran-3-yl)ethan-1-one (**7a**).* [Contains 2.8% of acetylacetone as impurity] **^{1}H NMR** (700 MHz, D_2O) δ = 6.80 (s, 1H), 4.84 (d, *J* = 7.8 Hz, 1H), 4.75 (d, *J* = 3.8 Hz, 1H), 4.50 (dd, *J* = 7.8 and 4.6 Hz, 1H), 4.45−4.48 (m, 1H), 4.14 (dd, *J* = 10.3 and 3.8 Hz, 1H), 3.84 (d, *J* = 10.3 Hz, 1H), 3.65−3.69 (m, 2H), 3.73−3.78 (m, 2H), 3.37 (dd, *J* = 9.9 and 3.9 Hz, 1H), 3.30 (t, 1H), 2.47 (s, 3H), and 2.37 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.2, 161.0, 149.2, 122.0, 110.4, 98.5, 79.2, 73.8, 73.0, 72.6, 72.3, 71.2, 70.8, 69.4, 60.4, 28.5, and 14.0. **IR**: 3390 (br), 1670 (m) cm^{-1}. **HRMS (ESI)** *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{24}O_{10}Na$, 411.1262; found, 411.1258.

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Reactions of D-Lactose with Acetylacetone. General Procedure D was followed using D-lactose monohydrate **1n** (0.432 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (200 μL, 6 M) at 50 °C for 16 h. The reaction was then purified, as is, by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **6b** (0.015 g, 3% yield) and **7b** (0.312 g, 67% yield). At 7 h, the reaction gave **6b** (0.105 g, 21% yield) and **7b** (0.228 g, 49% yield).

*1-(2-Methyl-5-((1S,2S,3R)-1,3,4-trihydroxy-2-(((2S,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-butyl)furan-3-yl)ethan-1-one (**6b**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.68 (s, 1H), 4.84 (d, J = 5.8 Hz, 1H), 4.41 (d, J = 7.8 Hz, 1H), 4.10 (t, 1H), 3.80 (d, J = 3.4 Hz, 1H), 3.69−3.73 (m, 1H), 3.59 (dd, J = 11.9 and 3.5 Hz, 1H), 3.44−3.57 (m, 6H), 2.48 (s, 3H), and 2.39 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.4, 160.0, 150.7, 122.0, 108.7, 103.0, 81.2, 74.9, 72.6, 71.6, 71.1, 68.4, 66.3, 61.8, 60.8, 28.5, and 14.0. **IR**: 3390 (br), 1665 (m) cm^{-1}. **HRMS (ESI)** m/z: $[M + Na]^+$ calcd for $C_{17}H_{26}O_{11}Na$, 429.1367; found, 429.1362.

*1-(5-((2S,3R,4R)-4-Hydroxy-3-(((2S,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)tetrahydrofuran-2-yl)-2-methylfuran-3-yl)ethan-1-one (**7b**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.79 (s, 1H), 4.85 (d, J = 7.4 Hz, 1H), 4.62 (dd, J = 7.3 and 4.6 Hz, 1H), 4.49−4.52 (m, 1H), 4.37 (d, J = 7.8 Hz, 1H), 4.09 (dd, J = 10.4 and 4.0 Hz, 1H), 3.82 (dd, J = 10.3 and 2.3 Hz, 1H), 3.79 (d, J = 3.4 Hz, 1H), 3.36−3.54 (m, 5H), 2.47 (s, 3H), and 2.37 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.0, 160.7, 149.3, 122.0, 110.2, 103.1, 81.8, 74.7, 74.6, 72.6, 72.1, 70.7, 70.2, 68.2, 60.2, 28.5, and 14.0. **IR**: 3390 (br), 1670 (m) cm^{-1}. **HRMS (ESI)** m/z: $[M + Na]^+$ calcd for $C_{17}H_{24}O_{10}Na$, 411.1262; found, 411.1250.

Reaction of D-Cellobiose with Acetylacetone. General Procedure D was followed using D-(+)-cellobiose **5c** (0.411 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (200 μL, 6 M) at 50 °C for 16 h. The reaction was then purified, as is, by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **6c** (0.059 g, 12% yield) and **7c** (0.177 g, 38% yield).

*1-(2-Methyl-5-((1S,2R,3R)-1,3,4-trihydroxy-2-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-butyl)furan-3-yl)ethan-1-one (**6c**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.65 (s, 1H), 4.85 (d, J = 5.1 Hz, 1H), 4.44 (d, J = 7.9 Hz, 1H), 4.08 (t, 1H), 3.71−3.75 (m, 1H), 3.58−3.66 (m, 2H), 3.46−3.53 (m, 2H), 3.37 (t, 1H), 3.17−3.28 (m, 3H), and 2.48 (s, 3H), 2.38 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.5, 159.8, 151.0, 122.0, 108.4, 102.4, 81.1, 75.5, 75.5, 73.3, 71.4, 69.3, 66.1, 61.8, 60.6, 28.5, and 14.0. **IR**: 3390 (br), 1665 (m) cm^{-1}. **HRMS (ESI)** m/z: $[M + Na]^+$ calcd for $C_{17}H_{26}O_{11}Na$, 429.1367; found, 429.1358.

*1-(5-((2S,3R,4R)-4-Hydroxy-3-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)tetrahydrofuran-2-yl)-2-methylfuran-3-yl)ethan-1-one (**7c**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.80 (s, 1H), 4.83 (d, J = 7.7 Hz, 1H), 4.64 (dd, J = 7.5 and 4.7 Hz, 1H), 4.49−4.52 (m, 1H), 4.43 (d, J = 7.9 Hz, 1H), 4.09 (dd, J = 10.3 and 3.8 Hz, 1H), 3.82 (dd, J = 10.3 and 4.7 Hz, 1H), 3.52 (dd, J = 12.3 and 4.4 Hz, 1H), 3.44 (dd, J = 12.3 and 1.9 Hz, 1H), 3.36 (t, 1H), 3.30 (t, 1H), 3.22 (t, 1H), 3.11−3.15 (m, 1H), 2.48 (s, 3H), and 2.38 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.2, 160.7, 149.1, 122.0, 110.3, 102.6, 82.0, 75.6, 75.5, 74.5, 73.0, 72.2, 70.2, 69.0, 60.1, 28.5, and 14.0. **IR**: 3390 (br), 1670 (m) cm^{-1}. **HRMS (ESI)** m/z: $[M + Na]^+$ calcd for $C_{17}H_{24}O_{10}Na$, 411.1262; found, 411.1246.

Reactions of D-Maltotriose with Acetylacetone. General Procedure D was followed using D-maltotriose **5d** (0.605 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (300 μL, 4 M) at 50 °C for 16 h. The reaction was then purified, as is, by a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford and **6d** (0.027 g, 4% yield) and **7d** (0.581 g, 88% yield). At 6 h, the reaction gave **6d** (0.203 g, 30% yield) and **7d** (0.403 g, 61% yield).

*1-(5-((1S,2R,3R)-2-(((2S,3R,4R,5S,6R)-3,4-Dihydroxy-6-(hydroxymethyl)-5-(((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)oxy)-1,3,4-trihydroxybutyl)-2-methylfuran-3-yl)ethan-1-one (**6d**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.68 (s, 1H), 5.31 (d, J = 3.4 Hz, 1H), 4.96 (d, J = 3.4 Hz, 1H), 4.87 (d, J = 6.7 Hz, 1H), 4.05 (dd, J = 6.4 and 3.4 Hz, 1H), 3.71−3.78 (m, 3H) 3.90 (t, 2H), 3.54−3.71 (m, 6H), 3.47 (dd, J = 9.9 and 3.7 Hz, 1H), 3.46 (dd, J = 9.9 and 3.7 Hz, 1H), 3.40 (dd, J = 11.6 and 7.8 Hz, 1H), 3.32 (t, 1H), 2.48 (s, 3H), and 2.38 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.4, 160.1, 150.5, 122.0, 108.9, 99.7, 99.6, 81.3, 76.5, 73.3, 72.8, 72.6, 72.2, 71.7, 71.5, 70.9, 69.2, 66.9, 61.9, 60.4, 60.3, 28.5, and 14.0. **IR**: 3390 (br), 1650 (w) cm^{-1}. **HRMS (ESI)** m/z: $[M + Na]^+$ calcd for $C_{23}H_{36}O_{16}Na$, 591.1880; found, 591.1901.

*1-(5-((2R,3R,4R)-3-(((2S,3R,4R,5S,6R)-3,4-Dihydroxy-6-(hydroxymethyl)-5-(((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)oxy)-4-hydroxytetrahydrofuran-2-yl)-2-methylfuran-3-yl)ethan-1-one (**7d**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.81 (s, 1H), 5.31 (d, J = 3.5 Hz, 1H), 4.85 (d, J = 7.9 Hz, 1H), 4.50 (dd, J = 7.6 and 4.7 Hz, 1H), 4.46 (s, 1H), 4.15 (dd, J = 10.2 and 3.5 Hz, 1H), 3.94 (t, 1H), 3.82−3.89 (m, 2H), 3.77 (t, 2H), 3.72 (dd, J = 12.3 and 4.7 Hz, 1H), 3.67 (dd, J = 12.3 and 5.3 Hz, 1H), 3.61−3.64 (m, 1H), 3.59 (t, 1H), 3.54 (t, 1H), 3.48 (dd, J = 9.9 and 3.7 Hz, 1H), 3.40 (dd, J = 9.9 and 3.7 Hz, 1H), 3.32 (t, 1H), and 2.48 (s, 3H), 2.38 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.3, 161.0, 149.2, 122.0, 110.5, 99.6, 98.3, 79.2, 76.5, 73.8, 73.1, 72.9, 72.8, 72.6, 71.6, 71.0, 70.8, 70.8, 69.3, 60.4, 60.4, 28.5, and 14.0. **IR**: 3390 (br), 1650 (w) cm^{-1}. **HRMS (ESI)** m/z: $[M + Na]^+$ calcd for $C_{23}H_{34}O_{15}Na$, 573.1795; found, 573.1772.

Reaction of D-Glycero-D-galactoheptose with Acetylacetone. General Procedure D was followed using D-glycero-D-galactoheptose **1k**[28] (0.252 g, 1.20 mmol), acetylacetone **2** (0.120 g, 1.20 mmol), $ZrCl_4$ (0.027 g, 0.120 mmol), and D_2O (200 μL, 6 M) at 50 °C for 4 h. The reaction was then loaded onto a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column. Using a combination of water and acetonitrile as the eluent mixture, **3k** and **4k** (0.282 g, 91% yield) were afforded as an ∼1:10 mixture. A small fraction of **4k** was able to be isolated, free from **3k**. This fraction was then columned again using a Teledyne ISCO Combiflash Rf in conjunction with a RediSep Rf Gold C8 150 g column, at which point a small portion of β-**4k** was successfully isolated. **^{1}H NMR** (700 MHz, D_2O) δ = 6.72 (s, 1H), 5.04 (d, J = 5.4 Hz, 1H), 4.11 (dd, J = 4.1 and 5.4 Hz, 1H), 3.82−3.85 (m, 1H), 3.75 (dd, J = 3.8 and 12.3 Hz, 1H), 3.69 (dd, J = 6.3 and 12.3 Hz, 1H), 2.48 (s, 3H), and 2.38 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 215.3, 160.8, 148.20, 121.9, 110.3, 83.5, 77.1, 76.6, 75.7, 61.6, 28.5, and 14.0. **IR**: 3390 (br), 1650 (w) cm^{-1}. **HRMS (ESI)** m/z: [M]+ calcd for $C_{12}H_{16}O_6Na$ $[M + Na]^+$ 279.0839; found 279.0837. Note: In addition to ^{1}H and ^{13}C{^{1}H} NMR experiments, the structure of the β anomer of **4k** was confirmed using COSY and 1-D ROE studies.[29] In the 1-D ROE, the anomeric proton at 5.04 ppm was chosen to be irradiated.

Reactions of D-Glucosamine with Acetylacetone. General Procedure D was followed with a slight variation. D-Glucosamine hydrochloride 8·HCl (0.259 g, 1.20 mmol) and NaOH (0.048 g, 1.20 mmol) were stirred in 150 μL of D_2O for 30 min. A stirred solution of acetylacetone 2 (0.120 g, 1.20 mmol), $ZrCl_4$ (0.014 g, 0.060 mmol), and D_2O (150 μL) was then added. The reaction was then heated to 50 °C for 5 h. The reaction was then loaded onto the Teledyne ISCO Combiflash Rf equipped with a RediSep Rf Gold C8 150 g column, using a combination of water and acetonitrile as the eluent mixture to afford **9** (0.190 g, 65% yield) as a white solid.

*1-(2-Methyl-5-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-pyrrol-3-yl)ethan-1-one (**3k**).* **^{1}H NMR** (700 MHz, D_2O) δ = 6.48 (s, 1H), 4.78 (d, J = 4.1), 3.65−3.70 (m, 2H), 3.59−3.63 (m, 1H), 3.51 (dd, J = 11.8 and 6.8 Hz, 1H), 2.39 (s, 3H), and 2.35 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, D_2O) δ = 199.9, 137.9, 130.5, 119.8, 108.0, 73.8, 71.2, 66.3, 62.4, 27.5, and 13.1. **IR**: 3385 (br), 1640 (m) cm^{-1}. **HRMS (ESI)** m/z: $[M + H]^+$ calcd for $C_{11}H_{17}NO_5$, 244.1185; found, 244.1191. The reaction using 10 mol % $ZrCl_4$ gave a 1:1.4 ratio of **9** (0.067 g, 23%) to **10** (0.086 g, 32%).

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■ ASSOCIATED CONTENT

Supporting Information

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^{1}H NMR spectra for known compounds and NMR (^{1}H, ^{13}C, COSY, and ROESY, where applicable) spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(18) Pricing obtained from Strem Chemicals, Inc. and Millipore Sigma.
(19) The reaction is performed above the maximum concentration of acetylacetone in water. The control reaction performed without the zirconium chloride precatalyst is biphasic. However, when the reaction is run with zirconium chloride precatalyst, the reaction is monophasic. We believe this has to do with the interaction of the catalyst coordinating to acetylacetone, thus making the acetylacetone more water-soluble.
(20) Side products were not able to be identified or isolated in the crude reaction mixture. Other than the desired products, very minor amounts of unreacted acetylacetone (<5%) were isolated only in certain cases.
(21) Epimerization was confirmed by ^{1}H NMR and comparison with the products obtained from ribose, xylose, and lyxose. Based on a series of control experiments, epimerization does not happen when the sugars and $ZrCl_4$ are stirred together without acetylacetone. The epimerization seems to be unique to arabinose. No epimerization of the products occurs upon stirring under the reaction conditions. Therefore, we can assume epimerization is happening earlier in the mechanism, either during the Knoevenagel step or during the cyclization step. For a discussion of the observed epimerization with arabinose in the GG reaction, see: Molina, L.; Moreno-Vargas, A. J.; Carmona, A. T.; Robina, I. Stereoselective synthesis of chiral furan amino acid analogues of D- and L-serine from D-sugars. *Synlett* **2006**, 1327−1330.
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