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Biocatalytic Carbohydrate Analogues

Expedient Synthesis of *C*-Aryl Carbohydrates by Consecutive Biocatalytic Benzoin and Aldol Reactions

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Abstract: The introduction of aromatic residues connected by a C–C bond into the non-reducing end of carbohydrates is highly significant for the development of innovative structures with improved binding affinity and selectivity (e.g., *C*-aril-sLex). In this work, an expedient asymmetric "de novo" synthetic route to new aryl carbohydrate derivatives based on two sequential stereoselectively biocatalytic carboligation reactions is presented. First, the benzoin reaction of aromatic aldehydes to dimethoxyacetaldehyde is conducted, catalyzed by benzaldehyde lyase from *Pseudomonas fluorescens* biovar I. Then, the α-hydroxyketones formed are reduced by using $NaBH_4$ yielding the *anti* diol. After acetal hydrolysis, the aldol addition of dihydroxyacetone, hydroxyacetone, or glycolaldehyde catalyzed by the stereocomplementary D-fructose-6-phosphate aldolase and L-rhamnulose-1-phosphate aldolase is performed. Both aldolases accept unphosphorylated donor substrates, avoiding the need of handling the phosphate group that the dihydroxyacetone phosphate-dependent aldolases require. In this way, 6-*C*-aryl-L-sorbose, 6-*C*-aryl–L-fructose, 6-*C*-aryl–L-tagatose, and 5-*C*-aryl-L-xylose derivatives are prepared by using this methodology.

Introduction

Carbohydrates play essential roles in a broad range of signaling and recognition processes; for example, bacterial and viral infections, cancer metastasis, and inflammatory reactions.[1] The introduction of aromatic residues at the non-reducing end of carbohydrate structures, that is, *C*-aryl carbohydrates—different from the *C*-aryl glycosides, in which the C–C bond is connected to the reducing end—is highly significant for the development of innovative oligosaccharide structures to improve the binding affinity and the selectivity.[2] For instance, stabilization of the core of sLex by an intramolecular hydrophobic contact was found to be an important parameter in its affinity for E-selectin.[3] Moreover, *C*-aryl carbohydrates themselves exhibit interesting biological activities; for example, 5-*C*-aryl-L-xylose derivatives have been found to be selective inhibitors of the sodium-dependent glucose co-transporter 2 (SGLT2) with a potential medicinal use for the treatment of type 2 diabetes.[4]

The synthesis of *C*-aryl carbohydrate derivatives is a complex task that requires a number of cumbersome protection and deprotection steps.[3a,5] The stereoselective aldol addition reaction constitutes a straightforward and efficient bottom-up approach for the de novo construction of carbohydrate-like scaffolds.[1b,6] In that respect, biocatalytic carboligation reactions have been recognized as a powerful methodology for such transformations due to their high selectivity, their catalytic efficiency, and the often uncompromised stereoselectivity.[7] New and diverse structure types can be built up by a single or sequential combination of independent enzymatic carboligation reactions in which the product of one reaction becomes the substrate for the next one,[8] or even by convenient combination with chemical steps (e.g., Sharpless epoxidation).[9] Furthermore, the existence of stereocomplementary enzymes with similar substrate tolerance offers the potential of stereodivergent product generation from a common pair of synthetic precursors.[8j,10]

In this work, we endeavored to combine benzaldehyde lyase from *Pseudomonas fluorescens* biovar I (BAL) with D-fructose-6-phosphate aldolase (FSA) and L-rhamnulose-1-phosphate aldolase (RhuA) for the asymmetric synthesis of 6-*C* -aryl-L-sorbose, 6-*C*-aryl-L-fructose, 6-*C*-aryl-L-tagatose, and 5-*C*-aryl-L-xylose, including the deoxy derivatives.

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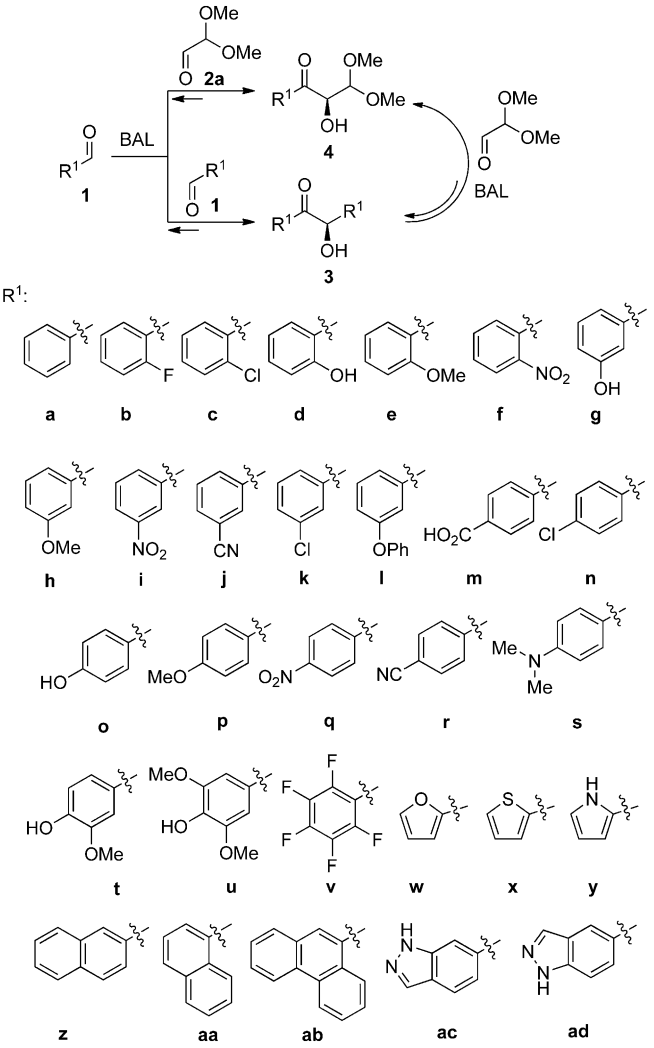
Results and Discussion

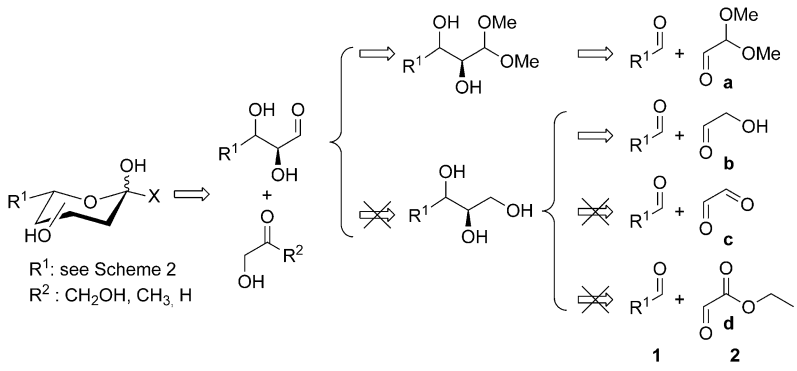
We first devised a strategy for the synthesis of the target compounds consisting of a cross-benzoin reaction of aromatic aldehydes **1** to derivatives of acetaldehyde **2a**–**d**, to furnish an aryl-α,β-dihydroxyaldehyde after reduction of the carbonyl group and hydrolysis of the acetal or oxidation of the primary alcohol (Scheme 1). This aldehyde was the acceptor in a subsequent aldol addition of dihydroxyacetone (DHA; Scheme 1, $R^2 = CH_2OH$), hydroxyacetone (HA; Scheme 1, $R^2 = CH_3$), or glycolaldehyde (Scheme 1, $R^2 = H$) catalyzed by FSA or RhuA to furnish the monosaccharide *C*-aryl derivatives (Scheme 1). FSA uses unphosphorylated DHA and analogues as donor substrates,[8h,l,11] which avoid the cumbersome and time-consuming need of handling the phosphate group that the dihydroxyacetone phosphate-dependent aldolases require.[8a,b,l,j] Moreover, the DHAP-dependent aldolase RhuA also accepts unphosphorylated DHA in the presence of borate buffer at practical rates.[12]

For the benzoin reaction step, only dimethoxyacetaldehyde (**2a**) and glycoladehyde (**2b**) were tolerated as acceptor substrates (Scheme 1). Nevertheless, in preliminary experiments, the oxidation of (1*R*,2*R*)-1-phenylpropane-1,2,3-triol (i.e., the cross-benzoin product of benzaldehyde with **2b**, after reduction with $Zn(BH_4)_2$) with 2-iodoxybenzoic acid (IBX), or (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO)/ClO^-, for example, gave a complex mixture of compounds and this strategy was therefore abandoned. Hence, dimethoxyacetaldehyde (**2a**) was the selected acceptor for the rest of this study. Dimethoxyacetaldehyde (**2a**) has been little exploited for synthetic purposes in benzoin reactions and it has only been employed as an acceptor in combination with benzaldehyde,[13] 2,4-difluorobenzaldehyde, 4-methoxybenzaldehyde,[13] furan-2-carbaldehyde,[14] and (benzyloxy)acetaldehyde donors[15] by using a variety of reactions conditions.

Thus, the reaction conditions for the benzoin reaction were investigated for the BAL-catalyzed cross-coupling of compounds **1a** and **1t**, respectively, to compound **2a** (Scheme 2). In an aqueous solution of Na_2CO_3 (0.1 M, pH 8.0)/dimethyl sulfoxide (DMSO) (4:1 *v/v*), the cross-coupling products **4a** (98%) and **4t** (95%), were formed after 24 and 72 h; respectively. In both reactions the formation of the benzoins **3a** and **3t** were observed immediately after the enzyme addition, which react to form the cross-coupling products within the given reaction times (Tables S1 and S2, as well as Figures S1 and S2, in the Supporting Information). This finding was consistent with earlier studies.[13] For practical purposes, an aqueous–organic two-phase system can be employed for the in situ product recovery, enabling the subsequent carbonyl reduction of compound **4** directly in the organic phase without need for its isolation and purification. In a 1:1 aqueous Na_2CO_3 (0.1 M, pH 8.0)/*tert*-butyl methyl ether (MTBE) two-phase system,[15b] the cross-coupling product was favored over the homo-coupling one from the beginning of the reaction in comparison to the aqueous Na_2CO_3 (0.1 M, pH 8.0)/DMSO



Scheme 2. BAL-catalyzed enantioselective cross C–C bond formation between aromatic aldehydes and dimethoxyacetaldehyde (**2a**).



Scheme 1. Multistep chemoenzymatic retrosynthesis of the monosaccharide aryl derivatives.

system (Tables S1–S4 and Figures S1–S4 in the Supporting Information). This could be due to the distribution of the substrates in the two phases: low concentration of the aromatic donor aldehyde in the water phase (i.e., $[\mathbf{1t}]_{total} = 50$ mM, distributed as $[\mathbf{1t}]_{aq} = 3$ mM and $[\mathbf{1t}]_{orgMTBE} = 47$ mM) and high concentration of compound **2a** in the water phase ($[\mathbf{2a}]_{aq} =$ 200 mM) where BAL is located. However, the reaction rate was slower than in the aqueous Na_2CO_3 (0.1 M, pH 8.0)/DMSO mixture (Tables S3 and S4 as well as Figure S3 and S4 in the Supporting Information). An optimization study of the benzoin reaction of compound **1t** to furnish compound **2a** with complete conversion in 24 h was conducted (Tables S5–S7 and Figures S5–S7 in the Supporting Information). A substrate ratio of [**1t**]/[**2a**] = 1:10, [**2a**] = 1 M, 500 U BAL mL^{-1}, $T = 25\,^{\circ}C$, and a 1:1 aqueous Na_2CO_3 (0.1 M, pH 8.0)/MTBE (1:1) solvent mixture gave the best results. These conditions were used for the rest of the examples selected (Scheme 2).

Our investigation into the substrate range of the BAL-catalyzed cross-coupling reaction (Table 1) revealed that *meta*-substituted benzaldehydes furnished high conversions to the cross-coupling products (>80%), the *para*-substituted products provided moderate to low yields (27–64%), whereas, with the *ortho*-substituted benzaldehydes, no cross-coupling product was observed, with the exception of compound **1b** (2-fluorobenzaldehyde), which is in agreement with the results obtained for other thiamine diphosphate (ThDP)-dependent lyases.[16] Aside from other electronic effects derived from the differently substituted benzaldehydes, this could be related to the steric limitations of the active-site cavity of BAL (Figure 1). The crystal structure of BAL (Figure 1A) shows a funnel-shaped entrance to its active site, which is narrower near the position that would be occupied by the *ortho* substituents. An energy-optimized molecular model of the **3c** adduct bound to the thiamine cofactor (Figure 1B and Figure S36 **IV** in the Supporting Information) shows that the adduct moiety could adopt a conformation with both *o*-chlorophenyl rings in an approximately parallel disposition, tightly packed against each other (π–π stacking interaction) and against the protein surface. Replacing the *o*-chlorophenyl moiety at the acceptor site by the bulkier dimethoxymethyl substituent (i.e., compound **2a**) would lead to steric clashes with the protein, which could render difficult or preclude the formation of the cross adduct. This steric effect would be more important for larger *ortho* substituents, which is consistent with the lack of reactivity observed for the cross-benzoin reaction. However, the model for the *meta*-chlorophenyl cross-adduct shows that the Cl substituent can fit in a subcavity located opposite to the acceptor side, which would leave the path to the incoming acceptor aldehyde free (Figure 1C). Alternatively, substituents at this position could be located on the more open side of the cavity without compromising the approach of the acceptor. Finally, the model for the *para*-chlorophenyl cross-adduct does not show any clash with the protein (Figure 1D), although steric restrictions can be expected for larger substituents. Concerning the rest of the donor aldehydes, **1z** (2-naphthaldehyde) was substrate, providing both homo- and cross-coupling products, whereas its isomer **1aa** (1-naphthaldehyde) and the more sterically demanding compound **1ab** (phenanthrene-9-carbaldehyde) did not react. Heterocycles such as compounds **1w** (2-furaldehyde), **1x** (thiophene-2-carbaldehyde), and **1ad** (1*H*-indazole-5-carbaldehyde) gave excellent results (Table 1). In contrast, compounds **1y** (1*H*-pyrrole-2-carbaldehyde) and **1ac** (1*H*-indazole-6-carbaldehyde) were ineffective as substrates for BAL. These results were in agreement with the reported substrate selectivity of BAL in homo-coupling reactions in aqueous buffer/DMSO mixtures.[13,19] In this study, the target reaction entails the aromatic aldehydes acting as donor substrates. Their quality as acceptors was not investigated and can be op-

Table 1. BAL-catalyzed cross-coupling of selected aromatic aldehydes **1** to products **2**[a].

1	Cross[b] 3	Homo[c] 4	1	Cross[b] 3	Homo[c] 4	1	Cross[b] 3	Homo[c] 4
a	*95*	–[d]	*k*	*98*	2	**u**	31	0
b	*80*	–[d]	**l**	28	–[d]	**v**	–[d]	–[d]
c	–[d]	31	**m**	–[d]	–[d]	*w*	*98*	–[d]
d	–[d]	20	**n**	27	39	*x*	*98*	–[d]
e	–[d]	–[d]	**o**	64	–[d]	**y**	–[d]	–[d]
f	–[d]	–[d]	**p**	52	7	**z**	27	34
g	*95*	–[d]	**q**	27	–[d]	**aa**	–[d]	–[d]
h	*98*	–[d]	**r**	–[d]	53	**ab**	–[d]	–[d]
i	*83*	11	**s**	–[d]	–[d]	**ac**	–[d]	–[d]
j	*98*	–[d]	*t*	*98*	–[d]	*ad*	*98*	–[d]

[a] Reaction conditions: ratio [**1**]/[**2a**] = 1:10, [**2a**] = 1 M, 500 U BAL mL^{-1}, $T = 25\,^{\circ}C$ and sodium carbonate buffer (0.1 M, pH 8.0, 2.5 mM $MgSO_4$, 0.2 mM ThDP)/MTBE (1:1). [b] Cross-coupling. [c] Homo-coupling. [d] Not detected by HPLC.

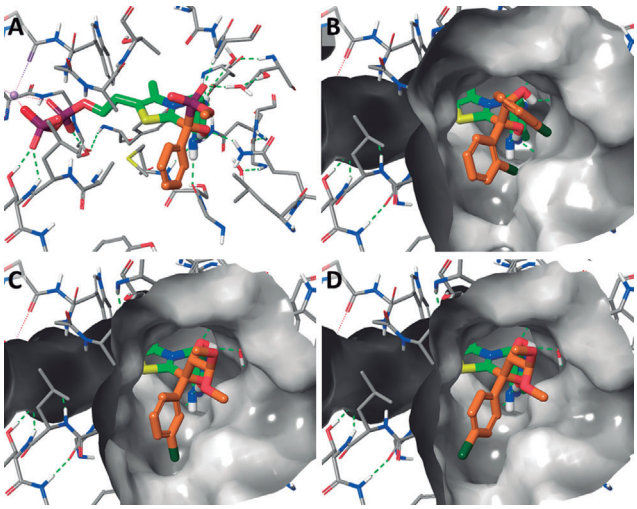


Figure 1. A) Crystal structure of the active site of BAL in complex with the inhibitor benzoylphosphonic acid methyl ester (PDB code 3D7K[17]). B–D) Energy-optimized models of the covalently bound BAL–thiamin diphosphate intermediates of the **3c** (B), **4k** (C), and **4n** (D) adducts. Residues conforming the active site of BAL (thin gray sticks), the thiamin diphosphate moiety (thick green sticks), and the adduct moieties (thick orange sticks) as well as the cavity accessible surface (gray, B–D) are shown. Models were built from the crystal structure (A) and were optimized with Macromodel.[18]

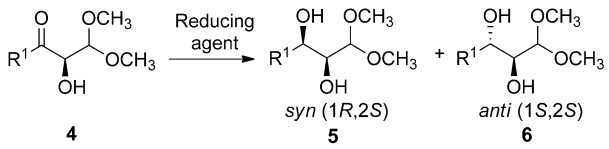
posite; for instance, compound **1v** was a good acceptor but not a donor substrate.[20]

The examples **4a**, **4b**, **4g**–**k**, **4t**, **4w**–**x**, and **4ad** were scaled up to 2 mmol. We assumed that the BAL-catalyzed reactions were stereoselective, providing cross-coupling products with absolute 2*R* stereochemistry, as reported for previous examples.[13] In the next step, different chemical reduction agents in MTBE (Table 2) were tested with compound **4a** (Scheme 3, $R^1 = C_6H_5$) as a model.

Table 2. Reduction of the acyloin product **4a** by using $NaBH_4$, $Zn(BH_4)_2$, and L-selectride in MTBE.

Reducing agent	Reaction conversion [%]	Ratio **5a**/**6a**[a] (1*R*,2*S*)/(1*S*,2*S*)
$NaBH_4$	>95	10:90
$Zn(BH_4)_2$[b]	48	6:94
L-selectride	–[c]	–

[a] Determined by HPLC (see Figure S8 in the Supporting Information). The relative stereochemistry was assessed by NMR spectroscopy upon formation of the corresponding 1,3-dioxolan-2-one derivatives (see Tables S8 and S9 as well as Figures S9 and S10 in the Supporting Information for products **S5a** and **S6a**). [b] Prepared from $ZnCl_2$ and $NaBH_4$ in THF.[21] [c] No reaction observed.



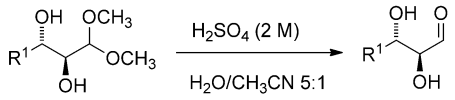
4 **5** **6**

Scheme 3. Chemical reduction of the acyloin products **4**.

$NaBH_4$ in MTBE provided the best results, with remarkably good stereoselectivity (from 26:84 to 3:97 (1*R*,2*S*)/(1*S*,2*S*)) and high conversion (Table 3). The internal asymmetric induction of the α-hydroxyketone **4** favored the *anti*-configured reduced product. Notably, the reduction of the cross-benzoin addition of benzaldehyde to glycoaldehyde with $Zn(BH_4)_2$ gave the *syn*-configured (1*R*,2*R*)-1-phenylpropane-1,2,3-triol as major product (10:90 *anti*/*syn*; see the Experimental Section and the Supporting Information). Reactions were performed directly in the organic phase (i.e., MTBE) from the benzoin reaction and previous drying over anhydrous Na_2SO_4.

Attempts to hydrolyze acetal **6** in HCl (pH 1.0) or Dowex 8W50 H^+ at 25 °C failed, leaving the starting material to be recovered intact. Increasing the temperature to 60 °C resulted in product decomposition. Finally, the hydrolysis was accomplished by using aqueous 2 M H_2SO_4/acetonitrile (5:1) at 25 °C (Table 4 and Figure S11 in the Supporting Information). Neutralization to pH 7.5 with $CaCO_3$ facilitated the removal of salt from the medium as a precipitate of $CaSO_4$. The product was used directly in the next step.

Table 4. Hydrolysis of the acetal group of compounds **5**/**6**.



5/6 **7**

Product	Yield[a]
7a	98
7b	80
7g	97
7h	97
7i	97
7j	59
7k	48
7t	78
7w	–[b]
7x	43
7ad	98

[a] Determined by HPLC. It was assumed that the *syn* (1*R*,2*S*)/*anti* (1*S*,2*S*) ratio was identical to the reduced mixture **5**/**6**. [b] The compound did not survive the deprotection conditions.

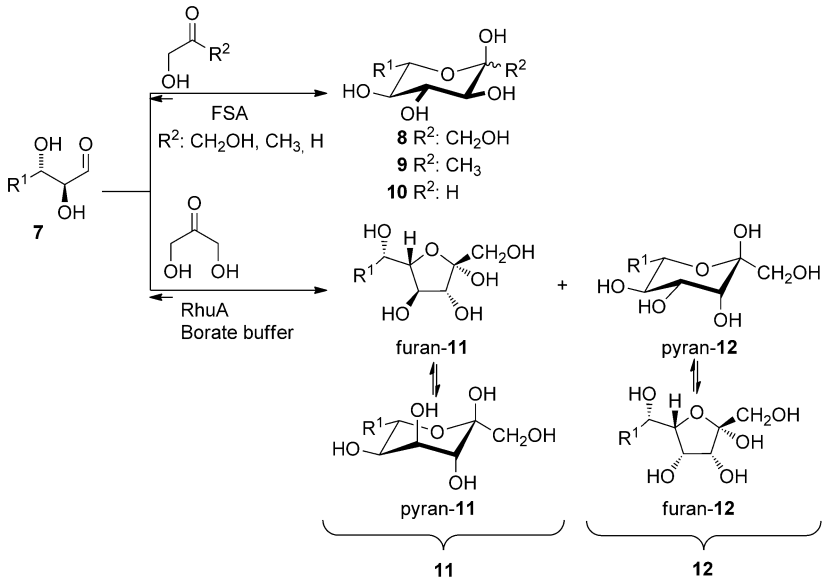
Table 3. Reduction of the acyloin product **4** with $NaBH_4$ in MTBE.

Starting material	Ratio **5**/**6**[a] (1*R*,2*S*)/(1*S*,2*S*)	Reduction yield[b]
4a	5:95	93
4b	4:96	89
4g	26:84	85
4h	3:97	98
4i	6:94	76
4j	4:96	98
4k	4:96	98
4t	23:87	98
4w	7:93	90
4x	8:92	93
4ad	6:94	96

[a] Determined by HPLC. [b] The products were obtained as a mixture of the diastereoisomers **5**/**6** with >90% purity by HPLC.

The last step was the enzymatic aldol addition reactions of DHA, HA, and glycolaldehyde to the dihydroxyaldehydes **7** (Scheme 4) by using FSA wild-type, FSA A129S, and A129T variants, and RhuA as catalysts.[8k,11a,22] As a result, twenty-four different carbohydrate derivatives (Table 5) were exemplarily obtained by using this methodology.

Reaction conversions by using FSA wild-type and the A129S variant for HA and DHA additions, respectively, were >95%. This is consistent with the fact that FSA wild-type has the best affinity for HA whereas FSA A129S has the best affinity for DHA and that α-hydroxyaldehydes are well tolerated by these biocatalysts.[8h,22] Moreover, as in *N*-Cbz-aminoaldehydes (Cbz = carboxybenzyl) and (benzyloxy)acetaldehyde, which are acceptor substrates for FSA wild-type and variants, the arene moiety could be oriented towards the entrance of the active-site cavity.[11a,23] Overall yields, that is, four reaction steps and the corresponding work-up steps and final purification, ranged from 18 to 58% (Table 5). The previous optimized FSA biocatalyst for cross-aldol additions of glycolaldehyde, FSA A129X (where X = T, V, and G variants),[11a] furnished overall yields of 11–50%. In this case, reaction conversions were not determined because of the presence of α- and β-anomers, which



Scheme 4. Aldol addition of DHA, HA, and glycolaldehyde to compounds **7** catalyzed by FSA wild-type, FSA A129S, and A129T variants, and RhuA. As examples, we performed the addition of DHA and glycolaldehyde to **7a**, **7b**, **7g**–**k**, **7t**, **7x**, and **7ad**, of HA to **7a** and **7h** and of DHA to **7a** and **7k**.

Table 5. *C*-Aryl monosaccharide derivatives obtained.

Product[a]	Overall yield[b]	Product[c]	Overall yield[b]	Product[d]	Overall yield[b]	Product[e]	Overall yield[b]
8a	49	**9a**	68	**10a**	25	**11a**[h]/**12a**[i] 74:26	54
8b	38	–[f]	–[f]	**10b**	8 (11)[g]	–[f]	–[f]
8g	49	–[f]	–[f]	**10g**	16	–[f]	–[f]
8h	58	**9h**	82	**10h**	22 (50)[g]	–[f]	–[f]
8i	20	–[f]	–[f]	**10i**	23	–[f]	–[f]
8j	48	–[f]	-[f]	**10j**	23	–[f]	–[f]
8k	39	–[f]	–[f]	**10k**	24	**11k**[h]/**12k**[i] 54:46	43
8t	25	–[f]	–[f]	**10t**	12	–[f]	–[f]
8x	18	–[f]	–[f]	**10x**	13	–[f]	–[f]
8ad	22	–[f]	–[f]	**10ad**	9 (32)[g]	–[f]	–[f]

[a] FSA A129S was used as catalyst. [b] Yields calculated from the starting aromatic aldehyde, four steps plus four work-up steps and final purification. All reactions were performed under the same experimental conditions unless noted otherwise. Individual optimization of the reaction conditions and purification steps was not performed. [c] FSA wild-type was used as catalyst. [d] FSA A129T was used as catalyst. Addition of glycolaldehyde by using a syringe pump (0.25 mL h^{-1}) unless noted otherwise. [e] RhuA was used as catalyst in the presence of 200 mM borate buffer. [f] Not synthesized. [g] Addition of glycolaldehyde in one portion. [h] Furanose-**11a/11k**/pyranose-**11a/11k** (2.5:1). [i] Furanose-**12a/12k**/pyranose-**12a/12k** (1:1.5).

overlapped with the acceptor substrate signal, making HPLC peak integration difficult. Introduction of glycolaldehyde in one portion gave in some instances better results than the slow addition with a syringe pump.[11c] This could be related to the instability of the dihydroxyaldehydes **7** under the reaction conditions. A decrease in the acceptor amount was noticed over time by HPLC, indicating a decomposition process probably due to water elimination of the benzylic alcohol. Consequently, the slow incorporation of glycolaldehyde might limit the rate of the aldol formation, compromising the stability of the aldehyde acceptor and limiting the final product yield.

RhuA wild-type-catalyzed aldol addition of DHA to compounds **7a** and **7k**, was performed in the presence of borate buffer (200 mM). The HPLC analysis of the reaction mixture after 24 h revealed two new peaks, which corresponded to the aldol adduct epimers at the C4 atom, that is, compounds **11** (i.e., L-fructose configured) and **12** (i.e., L-tagatose configured). Inversion of the stereochemistry at the C4 atom has already been reported during RhuA catalysis by using *N*-Cbz-aminoaldehyde acceptors with identical stereochemistry to compounds **7** at the C2 atom, either by using DHA or the natural dihydroxyacetone phosphate donor.[12b,24] We expected the formation of the L-tagatose-configured aldol adduct **12** as a major adduct owing to the thermodynamically unfavored diaxial configuration of compound **11** ($^1C_4$ conformation). However, the contrary was true, which was attributed to the equilibrium with the furanoid species that may favor the furan **11** with *trans* vicinal diol configuration.

The structural characterization of the carbohydrate derivatives **8**, **9**, and **10** (Figures S12–S35 in the Supporting Information) indicate that the enzymatic carboligation steps were fully stereoselective within the detection limits of NMR spectroscopy (i.e., >97%); BAL rendered the 2*R* acyloins and FSA catalysts the D-*threo* aldol adducts. This sequential two-step biocatalytic C–C bond formation furnished the corresponding (6*S*)-6-*C*-substituted-α-L-sorbose derivatives **8** and **9** and the (5*S*)-5-*C*-substituted-α/β-L-xylose derivatives **10** (Table 5). In contrast, RhuA gave mixtures of epimeric products at the C4 atom, furnishing the (6*S*)-6-*C*-substituted-L-fructose derivatives **11** and the (6*S*)-6-*C*-substituted-L-tagatose derivatives **12**.

In summary, we have developed a new strategy for the synthesis of uncovered *C*-aryl monosaccharide derivatives. Our study showed that complex carbohydrates can be constructed in four steps, starting with simple and achiral materials by using a combination of two enzymatic carboligation reactions and chemical reduction/deprotection steps.

Experimental Section

Materials

Synthetic oligonucleotides were purchased from MWG-Biotech. Aromatic aldehydes and dimethoxyacetaldehyde were purchased from Sigma-Aldrich. MTBE, sodium borohydride, and active charcoal were from Sigma-Aldrich. High-density IDA-Agarose 6BCL nickel charged was from GE Healthcare Life Science. Water for analytical and preparative HPLC and for the preparation of buffers and other assay solutions was obtained from an Arium pro ultrapure water purification system (SartoriusStedim Biotech). All other solvents used were of analytical grade. L-Rhamnulose-1-phosphate aldolase from *E. coli* (RhuA, 9.2 U mg^{-1}; 1 unit catalyzes the cleavage of 1 μmol of L-rhamnulose-1-phosphate per minute at 25 °C in 100 mM Tris-HCl buffer, pH 7.5, containing KCl (150 mM)), D-fructose-6-phosphate aldolase from *E. coli* (FSA) wild-type (0.22 U mg^{-1}), and the variants FSA A129S (9.4 U mg^{-1}) and FSA A129T (0.54 U mg^{-1}; 1 U of enzyme catalyzes the synthesis 1 μmol of D-fructose-6-phosphate per min from DHA and D,L-glyceraldehyde-3-phosphate at 25 °C in Gly–Gly buffer (50 mM, pH 8.0)) aldolases were obtained in our laboratory by using previously described procedures.[11a,12b,22]

Methods

Re-cloning of BAL: PCR amplification of the bal gene (1.7 kb) was performed by using the plasmid pKK233-2/BAL[25] as template and the primers bal (5–3) 5′-A***GAGGAG***AAATTAACCATGGCGATGATTACAGGCGG-3′ and bal (3–5) 5′-C***GGATCC***TGCGAAGGGGTCCATGCCGAT-3′, which introduced the appropriated restriction sites (BseRI and BamHI) for the subsequent cloning steps in a pQE-60.

Protein expression and purification: Expression and production of BAL was performed as follows: The plasmid was transformed into an *E. coli* strain M-15 [pREP-4] from QIAGEN and grown in LB medium with ampicillin (100 μg mL^{-1}) plus kanamycin (25 μg L^{-1}) at 37 °C on a rotary shaker at 250 rpm. A final optical density at 600 nm (OD_{600}) of 2–3 was usually achieved. An aliquot of the preculture (12 mL) was transferred into a shake-flask (2 L) containing LB (0.4 L) with ampicillin (100 μg mL^{-1}) plus kanamycin (25 μg mL^{-1}) and incubated at 37 °C with shaking at 250 rpm. During the middle exponential phase growth ($DO_{600} \approx 0.5$), Isopropyl β-D-1-thiogalactopyranoside (IPTG; 0.05 mM) was added and the temperature was decreased to 25 °C while reducing the shaking at 190 rpm to minimize potential inclusion bodies formation.

Cells from the induced-culture broths (4 L) were centrifuged at 12000 *g* for 10 min at 4 °C. The pellet was re-suspended with starting sodium phosphate buffer (50 mM, pH 8.0), containing NaCl (300 mM) and imidazole (10 mM) to a final cell density (OD_{600}) of ten. Cells were lysed by using a cell disrupter (Constant Systems). Cellular debris was removed by centrifugation at 12000 *g* for 10 min. The clear supernatant was collected and purified by affinity chromatography (IMAC) in an FPLC system (Amersham biosciences). The crude supernatant was applied to a cooled HR 16/40 column (GE Healthcare) packed with HiTrap chelating support (50 mL bed volume; Amersham Biosciences) and washed with the start buffer (150 mL). The protein was eluted with sodium phosphate buffer (50 mM, pH 8.0) containing NaCl (300 mM) and imidazole (500 mM) at a flow rate of 3 mL min^{-1}. Fractions containing the recombinant protein were combined and dialyzed against sodium phosphate buffer (10 mM, pH 7.0 containing ThDP (0.15 mM) and $MgSO_4$ (2.5 mM))[26] at 4 °C. The dialyzed solution was frozen at −80 °C and lyophilized. The white solid obtained was stored at −20 °C.

HPLC analyses: HPLC analyses were performed on a RP-HPLC XBridge C18, 5 μm, 4.6 mm × 250 mm column (Waters). The solvent system used was: Solvent A: 0.1% (*v/v*) trifluoroacetic acid (TFA) in H_2O; solvent B: 0.095% (*v/v*) TFA in CH_3CN/H_2O (4:1). The flow rate was 1 mL min^{-1}, detection was performed at $\lambda = 215$ nm and the column temperature was 30 °C. The amounts of products and substrates were quantified from the peak areas by using an external standard methodology.

NMR analysis: NMR spectra were recorded on Varian Mercury-400 spectrometer (400.13 MHz for ^1H and 100.62 MHz for ^{13}C) and Bruker Avance-III-600 (600.13 MHz for ^1H and 150.92 MHz for ^{13}C) spectrometers at 298 K. 1D (Conventional ^1H, ^{13}C, and selective 1D NOESY) and 2D (COSY, multiplicity-edited HSQC, and 2D NOESY) experiments were collected by using standard pulse programs under routine conditions. The residual solvent signal was used as the internal standard; chemical shifts (δ) are expressed in parts per million and coupling constants (*J*) in Hertz.

Activity assay of BAL: One unit of activity was defined as the amount of BAL, which catalyzes the formation of 1 μmol of benzoin per minute at 25 °C in 3-(*N*-morpholino)propanesulfonic acid (MOPS) buffer, (50 mM; pH 8.0), containing ThDP (0.15 mM) and $MgSO_4$ (2.5 mM). The assay mixture consisted of benzaldehyde (100 mM) dissolved in MOPS buffer (2.5 mL, 50 mM, pH 8.0) containing ThDP (0.15 mM), $MgSO_4$ (2.5 mM), and DMSO (25% *v/v*). Reactions were started by the addition of the enzyme (0.00875–0.28 mg of lyophilized powder dissolved in MOPS buffer (0.5 mL, 50 mM, pH 8.0) containing ThDP (0.15 mM) and $MgSO_4$ (2.5 mM)). Reaction monitoring was as follows: At appropriate time intervals (after 0, 2, 5, 8, 10, 15, and 20 min), samples (100 μL) were withdrawn, diluted with methanol (900 μL), and directly analyzed and quantified by HPLC; isocratic elution at 55% solvent B over 10 min.

Reactions catalyzed by BAL: General procedure

Analytical scale: Reactions (4 mL total volume) were conducted at 25 °C and magnetically stirred at 250 rpm. The aromatic aldehyde (0.2 mmol) was dissolved in MTBE (2 mL). Then, an aqueous sodium carbonate buffer (1.66 mL, 50 mM, pH 8.0) containing BAL (500 U mL^{-1}), $MgSO_4$ (2.5 mM), and ThDP (0.15 mM) was added. The reaction was started by adding dimethoxyacetaldehyde (2 mmol, 340 μL of a commercial aqueous solution, 5.8 M). Reaction monitoring was as follows: at 24 h of reaction time samples of the organic phase (10 μL) and the aqueous phase (10 μL) were withdrawn, placed in separate vials, diluted with methanol (500 μL), and directly analyzed and quantified by HPLC by using a gradient elution from 10 to 70% of solvent B over 30 min.

Scale-up: Reactions (40 mL total volume) were conducted at 25 °C under magnetic stirring at 250 rpm. The aromatic aldehyde (2 mmol) was dissolved in MTBE (20 mL). Then, sodium carbonate buffer (16.6 mL, 50 mM, pH 8.0) containing BAL (500 U mL^{-1}), $MgSO_4$ (2.5 mM), and ThDP (0.15 mM) was added. The reaction was started by the addition of dimethoxyacetaldehyde (20 mmol, 3.4 mL of a commercial aqueous solution, 5.8 M). Reaction monitoring was carried out by HPLC as described for the analytical scale reactions. After 24 h; NaCl was added to the reaction mixture up to saturation, and the phases were separated. The aqueous layer was extracted with MTBE (3 × 20 mL). The organic phases were combined and dried over anhydrous Na_2SO_4. The product dissolved in MTBE was used without further purification.

Synthesis of (1*S*,2*S*)-1-aryl-3,3-dimethoxypropane-1,2-diol (6): General procedure

(*R*)-1-Aryl-2-hydroxy-3,3-dimethoxy-propan-1-one (**4**; 2 mmol) dissolved in MTBE (100 mL) was stirred at 250 rpm and 25 °C. To this solution was added $NaBH_4$ (4 mmol). After 4 h, the conversion of the starting material was complete as determined by HPLC (as described previously). Then, the MTBE was removed under reduced pressure in a rotary evaporator. The residue containing the product was dissolved in water (50 mL) and purified by chromatography. The bulk stationary phase AMBERLITE XAD 1180 was packed into a gravity glass column (50×2 cm) to give a final bed volume of 110 mL. The crude material (50 mL in water, divided into three aliquots) was loaded onto the column. Impurities were washed away with H_2O (500 mL), and the product was eluted with ethanol (75 mL). Pure fractions were combined and the solvent was evaporated. The product was used in the next reaction without further purification.

Synthesis of (2*S*,3*S*)-3-aryl-2,3-dihydroxypropanal (7): General procedure

(1*S*,2*S*)-1-Aryl-3,3-dimethoxypropane-1,2-diol (**6**; 2 mmol) was dissolved in acetonitrile (2 mL). To this solution, H_2SO_4 (10 mL of a 2 M aqueous solution) was added. The reaction was stirred at 250 rpm and 25 °C. The formation of the aldehyde was monitored by HPLC, as described previously. After 3 h the reaction was stopped by addition of $CaCO_3$ powder to neutralize the acid. The solution was filtered to remove precipitated $CaSO_4$ and the aldehyde was used in the next step without further purification dissolved in water (50 mL).

Synthesis of (6*S*)-6-*C*-aryl-L-sorbose (8): General procedure

Dihydroxyacetone (4 mmol) was added to a solution of (2*S*,3*S*)-3-aryl-2,3-dihydroxypropanal (**7**) (2 mmol) dissolved in H_2O (50 mL) adjusted to pH 7.5 with $NaHCO_3$ (1 M, pH 8.0). The reaction was started by adding FSA A129S (47 U mL^{-1} reaction mixture). The reaction was conducted at 25 °C with magnetic stirring at 250 rpm and monitored by HPLC by using gradient elution from 0 to 60% of solvent B over 30 min. When the aldehyde was consumed, the reaction mixture was acidified to pH 3.0 with HCl (1 M) and the FSA started to precipitate. Then, K_2SO_4 was added up to saturation, which helped to complete precipitation of the enzyme. The mixture was filtered through Celite and the pellet was washed with water (200 mL). Purification of the product was carried out as follows: The product was adsorbed onto activated charcoal (60 mL), placed in a sintered glass funnel with a porosity of 3 μm (7× 4.5 cm), packed with water, and equipped with a vacuum system. Then, the activated charcoal was washed with distilled H_2O (1 L). The product was eluted with a stepwise elution from 5:95 to 60:40 acetonitrile/H_2O (i.e., twelve steps of 30 mL, increasing by 5% of acetonitrile in each step). Fractions containing the product were combined and concentrated to 40 mL under reduced pressure, frozen at −80 °C, and lyophilized.

(6*S*)-6-*C*-Phenyl-α-L-sorbopyranose (8a): The title compound was obtained according to the general procedure. Yield: 251.6 mg (white solid, 49%), >95% pure, as determined by HPLC; retention factor $k=2.1$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-43.3$ ($c=5$ in H_2O); ^{1}H NMR (400 MHz, D_2O): $\delta=$ 7.37–7.25 (m, 5H), 4.55 (d, $J=9.9$ Hz, 1H), 3.72 (t, $J=9.4$ Hz, 1H), 3.60 (d, $J=9.7$ Hz, 1H), 3.57 (d, $J=11.7$ Hz, 1H), 3.49 (dd, $J=9.9$, 9.2 Hz, 1H), 3.38 ppm (d, $J=11.8$ Hz, 1H); ^{13}C NMR (101 MHz, D_2O): $\delta=137.43$ (C7 arom), 128.57(C arom), 97.89 (C2), 74.69 (C6), 74.21 (C5), 73.59 (C4), 70.47 (C3), 63.62 ppm (C1); ESI-TOF: *m/z* calcd for $C_{12}H_{16}O_6Na$: 279.0845 [M+Na^+], $C_{24}H_{32}O_{12}Na$: 535.1791 [2M+Na^+]; found: 279.0840, 535.1793.

(6*S*)-6-*C*-(2-Fluorophenyl)-α-L-sorbopyranose (8b): The title compound was obtained according to the general procedure. Yield: 206.3 mg (white solid, 38%), >95% pure, as determined by HPLC; retention factor $k=3.4$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-44.0$ ($c=5$ in H_2O); ^{1}H NMR (400 MHz, D_2O): $\delta=7.46$–7.39 (m, 1H), 7.29 (dddd, $J=8.3$, 7.3, 5.4, 1.8 Hz, 1H), 7.13 (td, $J=7.6$, 1.2 Hz, 1H), 7.04 (ddd, $J=10.7$, 8.3, 1.2 Hz, 1H), 4.95 (d, $J=10.1$ Hz, 1H), 3.73 (d, $J=9.6$ Hz, 1H), 3.59 (d, $J=11.8$ Hz, 1H), 3.57 (d, $J=9.6$ Hz, 1H), 3.56 (dd, $J=9.1$ Hz, $J=9.9$ 1H), 3.38 ppm (d, $J=11.8$ Hz, 1H); ^{13}C NMR (101 MHz, D_2O): $\delta=162.11$ (C8 arom), 159.67 (C7 arom), 130.68 (C10 arom), 129.12 (C12 arom), 124.57 (C11 arom), 115.60 (C9 arom), 98.04 (C2), 73.58 (C5, C4), 70.43 (C3), 67.74 (C6), 63.52 ppm (C1); ESI-TOF: *m/z* calcd for $C_{12}H_{15}FO_6Na$: 297.0750 [M+Na^+], $C_{24}H_{30}F_2O_{12}Na$: 571.1603 [2M+Na^+]; found: 297.0747, 571.1607.

(6*S*)-6-*C*-(3-Hydroxyphenyl)-α-L-sorbopyranose (8g): The title compound was obtained according to the general procedure. Yield: 264.7 mg (white solid, 49%), >95% pure, as determined by HPLC; retention factor $k=0.4$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-55.3$ ($c=5$ in H_2O); ^{1}H NMR (400 MHz, D_2O): $\delta=7.17$ (t, $J=7.9$ Hz, 1H), 6.88 (dt, $J=7.7$, 1.2 Hz, 1H), 6.82 (dd, $J=2.5$, 1.6 Hz, 1H), 6.76 (ddd, $J=8.2$, 2.6, 1.0 Hz, 1H), 4.48 (d, $J=9.9$ Hz, 1H), 3.69 (t, $J=9.4$ Hz, 1H), 3.59 (d, $J=11.8$ Hz, 1H), 3.56 (d, $J=9.7$ Hz, 1H), 3.44 (dd, $J=9.9$, 9.2 Hz, 1H), 3.37 ppm (d, $J=11.8$ Hz, 1H); ^{13}C NMR (101 MHz, D_2O): $\delta=155.60$ (C9 arom), 139.35 (C7 arom), 130.06 (C11 arom), 120.28 (C12 arom), 115.79 (C10 arom), 114.76 (C8 arom), 97.47 (C2), 74.45 (C6), 73.75 (C5), 73.54 (C4), 70.23 (C3), 63.56 ppm (C1); ESI-TOF: *m/z* calcd for $C_{12}H_{16}O_7Na$: 295.0794 [M+Na^+], $C_{24}H_{32}O_{14}Na$: 567.1690 [2M+Na^+]; found: 295.0793, 567.1685.

(6*S*)-6-*C*-(3-Methoxyphenyl)-α-L-sorbopyranose (8h): The title compound was obtained according to the general procedure. Yield: 330.9 mg (white solid, 58%), >95% pure, as determined by HPLC; retention factor $k=3.7$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-48.0$ ($c=5$ in H_2O); ^{1}H NMR (400 MHz, D_2O): $\delta=7.25$ (dd, $J=8.3$, 7.5 Hz, 1H), 6.97 (t, $J=1.2$ Hz, 1H), 6.91–6.85 (m, 2H), 6.88 (ddd, $J=8.3$, 2.7, 1.0 Hz, 1H), 4.53 (d, $J=9.9$ Hz, 1H), 3.70 (s, 3H), 3.70 (t, $J=9.7$ Hz, 1H), 3.59 (d, $J=$ 11.9 Hz, 1H), 3.57 (d, $J=9.5$ Hz, 1H), 3.46 (dd, $J=9.9$, 9.2 Hz, 1H), 3.38 ppm (d, $J=11.8$ Hz, 1H); ^{13}C NMR (101 MHz, D_2O): $\delta=158.94$ (C9 arom), 139.24 (C7 arom), 129.93 (C11 arom), 120.95 (C12 arom), 114.50 (C10 arom), 113.51 (C8 arom), 97.91 (C2), 74.55 (C6), 74.11 (C5), 73.56 (C4), 70.44 (C3), 63.57 (C1), 55.30 ppm (C13); ESI-TOF: *m/z* calcd for $C_{13}H_{18}O_7Na$: 309.0950 [M+Na^+], $C_{26}H_{36}O_{14}Na$: 595.2003 [2M+Na^+]; found: 309.0952, 595.2005.

(6*S*)-6-*C*-(3-Nitrophenyl)-α-L-sorbopyranose (8i): The title compound was obtained according to the general procedure. Yield: 118.0 mg (white solid, 20%), >95% pure, as determined by HPLC; retention factor $k=3.8$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-46.0$ ($c=5$ in H_2O); ^{1}H NMR (400 MHz, D_2O): $\delta=8.23$–8.19 (m, 1H), 8.11 (ddd, $J=8.3$, 2.4, 1.1 Hz, 1H), 7.75–7.69 (m, 1H), 7.51 (d, $J=8.0$ Hz, 1H), 4.69 (d, $J=9.9$ Hz, 1H), 3.74 (t, $J=9.5$ Hz, 1H), 3.63 (d, $J=11.9$ Hz, 1H), 3.60 (d, $J=9.9$ Hz, 1H), 3.43 (dd, $J=9.3$, 9.2 Hz, 1H), 3.42 ppm (d, $J=11.9$ Hz, 1H); ^{13}C NMR (101 MHz, D_2O): $\delta=147.90$ (C9 arom), 139.75 (C7 arom), 134.73 (C12 arom), 129.68 (C11 arom), 123.61 (C10 arom), 122.74 (C8 arom), 98.08 (C2), 74.34 (C5), 73.77 (C6), 73.38 (C4), 70.39 (C3), 63.53 ppm (C1); ESI-TOF: *m/z* calcd for $C_{12}H_{15}NO_8Na$: 324.0695 [M+Na^+]; found: 324.0693.

(6*S*)-6-*C*-(3-Cyanophenyl)-α-L-sorbopyranose (8j): The title compound was obtained according to the general procedure. Yield: 271.1 mg (white solid, 48%), >95% pure, as determined by HPLC; retention factor $k=3.0$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-52.7$ ($c=5$ in H_2O); ^{1}H NMR (400 MHz, D_2O): $\delta=7.73$ (ddt, $J=1.7$, 1.0, 0.5 Hz, 1H), 7.64 (d, $J=1.7$ Hz, 1H), 7.62 (d, $J=1.6$ Hz, 1H), 7.44 (ddd, $J=8.1$, 7.4, 0.6 Hz, 1H), 4.59 (d, $J=9.8$ Hz, 1H), 3.72 (t, $J=9.4$ Hz, 1H), 3.61 (d, $J=12.0$ Hz, 1H), 3.58 (d, $J=9.6$ Hz, 1H), 3.40 (d, $J=11.9$ Hz, 1H), 3.38 ppm (dd, $J=9.2$, 9.4 Hz, 1H); ^{13}C NMR (101 MHz, D_2O): $\delta=139.10$ (C7 arom), 133.01 (C12 arom), 132.58 (C10 arom), 131.77 (C8 arom), 129.43 (C11 arom), 119.33 (C13), 111.29 (C9 arom), 98.02 (C2), 74.30 (C5), 73.81 (C6), 73.36 (C4), 70.23 (C3), 63.53 ppm (C1); ESI-TOF: *m/z* calcd for $C_{13}H_{15}NO_6Na$: 304.0797 [M+Na$^+$]; found: 304.0800.

(6*S*)-6-*C*-(3-Chlorophenyl)-α-L-sorbopyranose (8k): The title compound was obtained according to the general procedure. Yield: 225.9 mg (white solid, 39%), >95% pure, as determined by HPLC; retention factor $k=4.9$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-3.3$ ($c=5$ in H_2O); ^{1}H NMR (400 MHz, D_2O): $\delta=7.42$–7.21 (m, 4H), 4.53 (d, $J=9.9$ Hz, 1H), 3.71 (t, $J=9.4$ Hz, 1H), 3.60 (d, $J=11.9$ Hz, 1H), 3.57 (d, $J=10.0$ Hz, 1H), 3.42 (t, $J=9.4$ Hz, 1H), 3.39 ppm (d, $J=11.9$ Hz, 1H); ^{13}C NMR (101 MHz, D_2O): $\delta=139.68$ (C7 arom), 133.75 (C9 arom), 130.07 (C11 arom), 128.76 (C8 arom), 127.84 (C12 arom), 126.49 (C10 arom), 97.96 (C2), 74.21 (C6), 74.09 (C5), 73.44 (C4), 70.24 (C3), 63.56 ppm (C1); ESI-TOF: *m/z* calcd for $C_{12}H_{15}ClO_6Na$: 313.0455 [M+Na$^+$], $C_{24}H_{30}Cl_2O_{12}Na$: 603.1012 [2M+Na$^+$]; found: 313.0452, 603.1015.

(6*S*)-6-*C*-(4-Hydroxy-3-methoxyphenyl)-α-L-sorbopyranose (8t): The title compound was obtained according to the general procedure. Yield: 135.1 mg (white solid, 22%), >95% pure, as determined by HPLC; retention factor $k=0.1$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-43.3$ ($c=5$ in H_2O); ^{1}H NMR (400 MHz, D_2O): $\delta=6.98$ (d, $J=1.9$ Hz, 1H), 6.85–6.78 (m, 2H), 4.48 (d, $J=9.9$ Hz, 1H), 3.74 (s, 3H), 3.69 (t, $J=9.5$ Hz, 1H), 3.59 (d, $J=11.3$ Hz, 1H), 3.56 (d, $J=9.4$ Hz, 1H), 3.47 (dd, $J=9.2$, 9.3 Hz, 1H), 3.37 ppm (d, $J=11.8$ Hz, 1H); ^{13}C NMR (101 MHz, D_2O): $\delta=147.39$ (C9 arom), 145.14 (C10 arom), 129.69 (C7 arom), 121.56 (C12 arom), 115.33 (C11 arom), 112.09 (C8 arom), 97.84 (C2), 74.54 (C6), 73.98 (C5), 73.53 (C4), 70.45 (C3), 63.59 (C1), 56.21 ppm (C13); ESI-TOF: *m/z* calcd for $C_{13}H_{18}O_8Na$: 325.0899 [M+Na$^+$], $C_{26}H_{36}O_{16}Na$: 627.1901 [2M+Na$^+$]; found: 325.0895, 627.1904.

(6*S*)-6-*C*-(2-Thiophene)-α-L-sorbopyranose (8x): The title compound was obtained according to the general procedure. Yield: 95.5 mg (white solid, 18%), >95% pure, as determined by HPLC; retention factor $k=2.3$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-41.3$ ($c=5$ in H_2O); ^{1}H NMR (400 MHz, D_2O): $\delta=7.37$–7.32 (m, 1H), 7.11–7.06 (m, 1H), 6.97–6.91 (m, 1H), 4.86 (d, $J=9.9$ Hz, 1H), 3.69 (t, $J=9.5$ Hz,1H), 3.57 (d, $J=11.9$ Hz, 1H), 3.54 (d, $J=9.5$ Hz, 1H), 3.46 (dd, $J=9.6$, 9.2 Hz, 1H), 3.38 ppm (d, $J=11.8$ Hz, 1H); ^{13}C NMR (101 MHz, D_2O): $\delta=140.34$ (C7 arom), 127.63 (C8 arom), 127.02 (C9 arom), 126.73 (C10 arom), 97.94 (C2), 74.87 (C5), 73.45 (C4), 70.33 (C6), 70.12 (C3), 63.45 ppm (C1); ESI-TOF: *m/z* calcd for $C_{10}H_{14}O_6SNa$: 285.0409 [M+Na$^+$], $C_{20}H_{28}O_{12}S_2Na$: 547.0920 [2M+Na$^+$]; found: 285.0404, 547.0915.

(6*S*)-6-*C*-[5-(1*H*-Indazole)]-α-L-sorbopyranose (8ad): The title compound was obtained according to the general procedure. Yield: 132.0 mg (white solid, 49%), >95% pure, as determined by HPLC; retention factor $k=1.3$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-35.3$ ($c=5$ in DMSO); ^{1}H NMR (400 MHz, [D_6]DMSO): $\delta=12.91$ (s, 1H), 7.99 (d, $J=1.2$ Hz, 1H), 7.68 (dt, $J=1.4$, 0.7 Hz, 1H), 7.41 (dt, $J=8.6$, 0.9 Hz, 1H), 7.35 (dd, $J=8.7$, 1.5 Hz, 1H), 5.44 (s, 1H), 4.68 (d, $J=4.8$ Hz, 1H), 4.64 (d, $J=5.8$ Hz, 1H), 4.59–4.51 (m, 2H), 4.44 (d, $J=6.7$ Hz, 1H), 3.55 (ddd, $J=9.4$, 8.7, 4.8 Hz, 1H), 3.48–3.37 (m, 2H), 3.31–3.23 (m, 2H), 3.11 ppm (ddd, $J=9.6$, 8.7, 5.8 Hz, 1H); ^{13}C NMR (101 MHz, [D_6]DMSO): $\delta=139.92$ (C13 arom), 133.82 (C10 arom), 133.07 (C7 arom), 127.05 (C11 arom), 122.92 (C9 arom), 119.88 (C8 arom), 109.42 (C12 arom), 98.19 (C2), 76.08 (C5), 74.74 (C4), 74.56 (C6), 71.23 (C3), 64.61 ppm (C1); ESI-TOF: *m/z* calcd for $C_{13}H_{17}N_2O_6$: 297.1087 [M+H$^+$]; found: 297.1083.

Synthesis of (6*S*)-1-deoxy-6-*C*-aryl-L-sorbose (9): General procedure

Hydroxyacetone (4 mmol) was added to a solution of (2*S*,3*S*)-3-aryl-2,3-dihydroxypropanal (**7**) (2 mmol) dissolved in H_2O (50 mL) adjusted to pH 7.5 with $NaHCO_3$ (1 M, pH 8.0). The reaction was started by adding FSA wild-type (1.1 U mL^{-1} reaction mixture). The reaction was conducted at 25 °C with magnetic stirring at 250 rpm and monitored by HPLC by using gradient elution from 0 to 60% of solvent B over 30 min. Reaction workup and purification was conducted as described in the general procedure for the synthesis of (6*S*)-6-*C*-aryl-L-sorbose.

(6*S*)-1-Deoxy-6-*C*-phenyl-α-L-sorbopyranose (9a): The title compound was obtained according to the general procedure. Yield: 328.5 mg (white solid, 68%), >95% pure, as determined by HPLC; retention factor $k=4.1$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-49.3$ ($c=5$ in H_2O); ^{1}H NMR (400 MHz, D_2O): $\delta=7.35$–7.25 (m, 5H), 4.53 (d, $J=9.9$ Hz, 1H), 3.64 (t, $J=9.3$ Hz, 1H), 3.54 (dd, $J=9.9$, 9.2 Hz, 1H), 3.34 (d, $J=9.5$ Hz, 1H), 1.33 ppm (s, 3H); ^{13}C NMR (101 MHz, D_2O): $\delta=137.16$ (C7 arom), 128.96, 128.76, 128.25 8 (C arom), 98.00 (C2), 75.09 (C3), 74.75 (C6), 74.08 (C5), 73.42 (C4), 24.56 ppm (C1); ESI-TOF: *m/z* calcd for $C_{12}H_{16}O_5Na$: 263.0895 [M+Na$^+$], $C_{24}H_{32}O_{10}Na$: 503.1893 [2M+Na$^+$]; found: 263.0897, 503.1895.

(6*S*)-1-Deoxy-6-*C*-(3-methoxyphenyl)-α-L-sorbopyranose (9h): The title compound was obtained according to the general procedure. Yield: 442.6 mg (white solid, 82%), >95% pure, as determined by HPLC; retention factor $k=5.0$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-46.0$ ($c=5$ in H_2O); ^{1}H NMR (400 MHz, D_2O): $\delta=7.24$ (ddd, $J=8.2$, 7.6, 0.5 Hz, 1H), 6.98–6.84 (m, 3H), 4.51 (d, $J=9.9$ Hz, 1H), 3.70 (s, 3H), 3.63 (t, $J=9.4$ Hz, 1H), 3.51 (dd, $J=9.9$, 9.2 Hz, 1H), 3.33 (d, $J=9.5$ Hz, 1H), 1.33 ppm (s, 3H); ^{13}C NMR (101 MHz, D_2O): $\delta=158.95$ (C9 arom), 139.21 (C7 arom), 129.91 (C11 arom), 121.07 (C12 arom), 114.56 (C8 arom), 113.50 (C10 arom), 97.98 (C2), 75.06 (C3), 74.75 (C6), 74.11 (C5), 73.40 (C4), 55.27(C13), 24.55 ppm (C1); ESI-TOF: *m/z* calcd for $C_{13}H_{18}O_6Na$: 293.1001 [M+Na$^+$], $C_{26}H_{36}O_{12}Na$: 563.2104 [2M+Na$^+$]; found: 293.1004, 563.2106.

Synthesis of (5*S*)-5-*C*-aryl-L-xylose (10): General procedure

To a solution of (2*S*,3*S*)-3-aryl-2,3-dihydroxypropanal (**7**) (2 mmol) dissolved in H_2O (50 mL) adjusted to pH 7.5 with $NaHCO_3$ (1 M, pH 8.0) and containing FSA A129T (2.7 U mL^{-1} reaction mixture), glycolaldehyde (4 mmol, dissolved in 5 mL of H_2O) was slowly added with a syringe pump (0.254 mL h^{-1}, 0.2 mmol h^{-1}).[11c] The reaction was conducted at 25 °C with magnetic stirring at 250 rpm and monitored by HPLC by using gradient elution from 0 to 60% of solvent B over 30 min. In some examples of this work, better results were obtained by adding the glycolaldehyde in one portion. Reaction workup and purification was conducted as described in the general procedure for the synthesis of (6*S*)-6-*C*-aryl-L-sorbose.

(5*S*)-5-*C*-Phenyl-α/β-L-xylopyranose (10a): The title compounds were obtained according to the general procedure. Yield: 95.5 mg (white solid, 25%), >95% pure, as determined by HPLC; retention

factor $k_1 = 1.8$, $k_2 = 2.4$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20} = -22.7$ ($c = 5$ in H_2O, α/β 37:67); ^{1}H NMR (400 MHz, D_2O): $\delta = 7.36$–7.25 (m, 5H), 5.14 (d, $J = 3.6$ Hz, 1H; α anomer), 4.65 (d, $J = 8.0$ Hz, 1H; β anomer), 4.59 (d, $J = 10.1$ Hz, 1H; α anomer), 4.20 (d, $J = 9.3$ Hz, 1H; β anomer), 3.69 (dd, $J = 9.8$, 9.1 Hz, 1H; α anomer), 3.59 (dd, $J = 9.8$, 3.8 Hz, 1H; α anomer), 3.51 (dd, $J = 9.8$, 9.1 Hz, 1H; α anomer), 3.55–3.42 (m, 3H), 3.27 ppm (dd, $J = 9.1$, 8.1 Hz, 1H; β anomer); ^{13}C NMR (101 MHz, D_2O): $\delta = 137.22$ (C6 arom, α anomer), 136.97 (C6 arom, β anomer), 128.44 (C arom), 96.21 (C1, β anomer), 92.41 (C1, α anomer), 78.21 (C5, β anomer), 75.43 (C4, β anomer), 74.27 (C2, β anomer), 74.07 (C4, α anomer), 73.90 (C3, β anomer), 73.81 (C5, α anomer), 72.61 (C3, α anomer), 71.59 ppm (C2, α anomer); ESI-TOF: *m/z* calcd for $C_{11}H_{14}O_5Na$: 249.0739 [M+Na$^+$], $C_{22}H_{28}O_{10}Na$: 475.1580 [2M+Na$^+$]; found: 249.0737, 475.1582.

(5*S*)-5-*C*-(2-Fluorophenyl)-α/β-L-xylopyranose (10b): The title compounds were obtained according to the general procedure. Yield: 54.1 mg (white solid, 11%), >95% pure, as determined by HPLC; retention factor $k_1 = 3.1$, $k_2 = 3.7$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20} = -32.0$ ($c = 5$ in H_2O, α/β 36:64); ^{1}H NMR (400 MHz, D_2O): $\delta = 7.41$–7.34 (m, 1H), 7.29 (dddd, $J = 8.3$, 7.3, 5.4, 1.8 Hz, 1H), 7.13 (tt, $J = 7.6$, 1.5 Hz, 1H), 7.04 (ddd, $J = 10.7$, 8.3, 1.2 Hz, 1H), 5.15 (d, $J = 3.9$ Hz, 1H; α anomer), 4.97 (d, $J = 10.0$ Hz, 1H; α anomer), 4.68 (d, $J = 8.0$ Hz, 1H; β anomer), 4.59 (d, $J = 9.8$ Hz, 1H; β anomer), 3.71 (dd, $J = 9.8$, 9.1 Hz, 1H; α anomer), 3.64–3.55 (m, 3H), 3.48 (t, $J = 9.2$ Hz, 1H; β anomer), 3.27 ppm (dd, $J = 9.4$, 8.0 Hz, 1H; β anomer); ^{13}C NMR (101 MHz, D_2O) $\delta = 162.18$ (C7 arom, α anomer), 161.86 (C7 arom, β anomer), 159.74 (C6 arom, α anomer), 159.41 (C6 arom, β anomer), 130.68 (C9 arom), 129.17 (C11 arom„ β anomer), 128.83 (C11 arom, α anomer), 124.71 (C10), 115.50 (C8), 96.31 (C1, β anomer), 92.48 (C1, α anomer), 75.42 (C3, β anomer), 74.19 (C2, β anomer), 73.31 (C4), 72.66 (C3, α anomer), 71.52 (C2, C5), 67.27 ppm (C5, α anomer); ESI-TOF: *m/z* calcd for $C_{11}H_{13}FO_5Na$: 267.0645 [M+Na$^+$], $C_{22}H_{26}F_2O_{10}Na$: 511.1392 [2M+Na$^+$]; found: 267.0640, 511.1393.

(5*S*)-5-*C*-(3-Hydroxyphenyl)-α/β-L-xylopyranose (10g): The title compounds were obtained according to the general procedure. Yield: 76.8 mg (white solid, 16%), >95% pure, as determined by HPLC; retention factor $k_1 = 1.9$, $k_2 = 2.4$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20} = -26.0$ ($c = 5$ in H_2O, α/β 37:63); ^{1}H NMR (400 MHz, D_2O): $\delta = 7.18$ (ddd, $J = 8.0$, 7.6, 0.5 Hz, 1H), 6.89–6.83 (m, 1H), 6.82–6.74 (m, 2H), 5.14 (d, $J = 3.8$ Hz, 1H; α anomer), 4.64 (d, $J = 9.5$ Hz, 1H; β anomer), 4.53 (d, $J = 9.9$ Hz, 1H; α anomer), 4.15 (d, $J = 9.4$ Hz, 1H; α anomer), 3.68 (dd, $J = 9.8$, 9.1 Hz, 1H; α anomer), 3.58 (dd, $J = 9.8$, 3.8 Hz, 1H; α anomer), 3.50–3.40 (m, 3H), 3.26 ppm (dd, $J = 9.4$, 8.0 Hz, 1H; β anomer); ^{13}C NMR (101 MHz, D_2O): $\delta = 155.60$ (C8 arom), 139.17 (C6 arom, α anomer), 138.89 (C6 arom, β anomer), 130.10 (C10 arom), 120.22 (C11 arom, α anomer), 119.99 (C11 arom, β anomer), 115.84 (C7 arom), 114.76 (C9 arom, α anomer), 114.51 (C9 arom, β anomer), 96.18 (C1, β anomer), 92.39 (C1, α anomer), 77.97 (C5, β anomer), 75.39 (C4, β anomer), 74.24 (C2, β anomer), 74.04 (C4, α anomer), 73.88 (C3, β anomer), 73.60 (C5, α anomer), 72.58 (C3, α anomer), 71.55 ppm (C2, α anomer); ESI-TOF: *m/z* calcd for $C_{11}H_{14}O_6Na$: 265.0688 [M+Na$^+$], $C_{22}H_{28}O_{12}Na$: 507.1478 [2M+Na$^+$]; found: 265.0689, 507.1475.

(5*S*)-5-*C*-(3-Methoxyphenyl)-α/β-L-xylopyranose (10h): The title compounds were obtained according to the general procedure. Yield: 256.4 mg (white solid, 50%), >95% pure, as determined by HPLC; retention factor $k_1 = 3.6$, $k_2 = 4.1$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20} = -26.0$ ($c = 5$ in H_2O, α/β 37:63); ^{1}H NMR (400 MHz, D_2O): $\delta = 7.25$ (ddt, $J = 8.1$, 7.5, 0.8 Hz, 1H), 6.96–6.86 (m, 3H), 5.15 (d, $J = 4.1$ Hz, 1H; α anomer), 4.63 (d, $J = 8.7$ Hz, 1H; β anomer), 4.57 (d, $J = 9.9$ Hz, 1H; α anomer), 4.19 (d, $J = 9.2$ Hz, 1H; β anomer), 3.70 (s, 1H), 3.68 (d, $J = 9.8$ Hz, 1H; α anomer), 3.59 (dd, $J = 9.8$, 3.8 Hz, 1H; α anomer), 3.50–3.43 (m, 3H), 3.28 ppm (dd, $J = 9.8$, 8.9 Hz, 1H; β anomer); ^{13}C NMR (101 MHz, D_2O): $\delta = 158.96$ (C8 arom), 139.08 (C6 arom, α anomer), 138.78 (C6 arom, β anomer), 129.98 (C10 arom), 120.88 (C11 arom, α anomer), 120.62 (C11 arom, β anomer), 114.54 (C7 arom), 113.87 (C9 arom, α anomer), 113.24 (C9 arom, β anomer), 96.20 (C1, β anomer), 92.41 (C1, α anomer), 78.05 (C5, β anomer), 75.41 (C4, β anomer), 74.24 (C2, β anomer), 74.08 (C4, α anomer), 73.68 (C5, α anomer), 72.59 (C3, α anomer), 71.56 (C2, α anomer), 55.29 ppm (C12); ESI-TOF: *m/z* calcd for $C_{12}H_{16}O_6Na$: 279.0844 [M+Na$^+$], $C_{24}H_{32}O_{12}Na$: 535.1791 [2M+Na$^+$]; found: 279.0840, 535.1790.

(5*S*)-5-*C*-(3-Nitrophenyl)-α/β-L-xylopyranose (10i): The title compounds were obtained according to the general procedure. Yield: 119.2 mg (white solid, 23%), >95% pure, as determined by HPLC; retention factor $k_1 = 4.0$, $k_2 = 4.7$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20} = -23.3$ ($c = 5$ in H_2O, α/β 40:60); ^{1}H NMR (400 MHz, D_2O): $\delta = 8.18$ (dddt, $J = 7.7$, 2.2, 1.7, 0.5 Hz, 1H), 8.12 (dddd, $J = 8.3$, 2.3, 1.7, 1.1 Hz, 1H), 7.74–7.67 (m, 1H), 7.52 (dddd, $J = 8.2$, 7.7, 2.4, 0.4 Hz, 1H). 5.20 (d, $J = 4.2$ Hz, 1H; α anomer), 4.72 (d, $J = 10.0$ Hz, 1H; α anomer), 4.69 (d, $J = 9.7$ Hz, 1H; β anomer), 4.37 (d, $J = 9.32$ Hz, 1H; β anomer), 3.72 (t, $J = 10.1$, 1H; α anomer), 3.62 (dd, $J = 9.8$, 4.2 Hz, 1H; α anomer), 3.53–3.43 (m, 3H), 3.30 ppm (t, $J = 9.5$, 1H; β anomer); ^{13}C NMR (101 MHz, D_2O): $\delta = 147.90$ (C8 arom), 139.58 (C6 arom, α anomer), 139.17 (C6 arom, β anomer), 134.68 (C11 arom, α anomer), 134.38 (C11 arom, β anomer), 129.82 (C10 arom), 123.76 (C9 arom), 122.79 (C7 arom, α anomer), 122.57 (C7 arom, β anomer), 96.27 (C1, β anomer), 92.54 (C1, α anomer), 77.16 (C5, β anomer), 75.25 (C4, β anomer), 74.25 (C4, α anomer), 74.15 (C2, β anomer), 73.99 (C3, β anomer), 72.93 (C5, α anomer), 72.42 (C3, α anomer), 71.48 ppm (C2, α anomer); ESI-TOF: *m/z* calcd for $C_{11}H_{13}NO_7Na$: 294.0590 [M+Na$^+$]; found: 294.0592.

(5*S*)-5-*C*-(3-Cyanophenyl)-α/β-L-xylopyranose (10j): The title compounds were obtained according to the general procedure. Yield: 116.2 mg (white solid, 23%), >95% pure, as determined by HPLC; retention factor $k_1 = 3.7$, $k_2 = 4.3$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20} = -18.7$ ($c = 5$ in H_2O, α/β 32:68); ^{1}H NMR (400 MHz, D_2O): $\delta = 7.72$–7.68 (m, 1H), 7.66–7.59 (m, 2H), 7.48–7.43 (m, 1H), 5.17 (d, $J = 4.2$ Hz, 1H; α anomer), 4.67 (d, $J = 8.0$ Hz, 1H; β anomer), 4.65 (s, 1H; α anomer), 4.28 (d, $J = 9.1$ Hz, 1H; β anomer), 3.70 (dd, $J = 9.8$, 9.1 Hz, 1H; α anomer), 3.60 (dd, $J = 9.8$, 3.8 Hz, 1H; α anomer), 3.52–3.38 (m, 2H), 3.28 ppm (dd, $J = 8.8$, 8.3 Hz, 1H; β anomer); ^{13}C NMR (101 MHz, D_2O): $\delta = 138.92$ (C6 arom, α anomer), 138.56 (C6, β anomer), 132.99 (C9, C11 arom, α anomer), 132.71 (C9, C11 arom, β anomer), 131.80 (C7 arom, α anomer), 131.52 (C7 arom, β anomer), 129.55 (C10 arom), 119.26 (C12), 111.39 (C8 arom), 96.25 (C1, β anomer), 92.50 (C1, α anomer), 77.23 (C5, β anomer), 75.24 (C4), 74.15 (C2, β anomer), 73.96 (C3, β anomer), 72.98 (C5, α anomer), 72.42 (C3, α anomer), 71.47 ppm (C2, α anomer); ESI-TOF: *m/z* calcd for $C_{24}H_{26}N_2O_{10}Na$: 525.1485 [2M+Na$^+$]; found: 525.1483.

(5*S*)-5-*C*-(3-Chlorophenyl)- α/β-L-xylopyranose (10k): The title compounds were obtained according to the general procedure. Yield: 126.9 mg (white solid, 24%), >95% pure, as determined by HPLC; retention factor $k_1 = 5.8$, $k_2 = 6.4$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20} = -26.0$ ($c = 5$ in H_2O, α/β 39:61); ^{1}H NMR (400 MHz, D_2O): $\delta = 7.38$–7.19 (m, 4H), 5.15 (d, $J = 3.8$ Hz, 1H; α anomer), 4.64 (d, $J = 9.0$ Hz, 1H; β anomer), 4.57 (d, $J = 9.7$ Hz, 1H; α anomer), 4.20 (d, $J = 8.9$ Hz, 1H; β anomer), 3.68 (t, $J = 9.8$, 1H; α anomer), 3.58 (dd, $J = 9.8$, 4.5 Hz, 1H;

α anomer), 3.50–3.39 (m, 3H), 3.27 ppm (dd, $J=9.1$, 8.1 Hz, 1H; β anomer); ^{13}C NMR (101 MHz, D_2O): $\delta=139.53$ (C6 arom, α anomer), 139.14 (C6 arom, β anomer), 133.71 (C8 arom), 130.13 (C10 arom), 128.87 (C11 arom), 127.89 (C7 arom, α anomer), 127.59 (C7 arom, β anomer), 126.45 (C9 arom, α anomer), 126.18 (C9 arom, β anomer), 96.21 (C1, β anomer), 92.45 (C1, α anomer), 77.54 (C5, β anomer), 75.30 (C4), 74.19 (C2, β anomer), 73.91 (C3, β anomer), 73.24 (C5, α anomer), 72.49 (C3, α anomer), 71.51 ppm (C2, α anomer); ESI-TOF: *m/z* calcd for $C_{11}H_{13}ClO_5Na$: 283.0349 [M+Na$^+$], $C_{22}H_{26}Cl_2O_{10}Na$: 543.0801 [2M+Na$^+$]; found: 283.0347, 543.0805.

(5*S*)-5-*C*-(4-Hydroxy-3-methoxyphenyl)-α/β-L-xylopyranose (10t): The title compounds were obtained according to the general procedure. Yield: 65.3 mg (white solid, 12%), >95% pure, as determined by HPLC; retention factor $k_1=0.1$, $k_2=0.2$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-20.0$ ($c=5$ in H_2O, α/β 35:65); ^{1}H NMR (400 MHz, D_2O): $\delta=6.96$–6.92 (m, 1H), 6.82–6.75 (m, 2H), 5.13 (d, $J=4.0$ Hz, 1H; α anomer), 4.63 (d, $J=$ 8.9 Hz, 1H; β anomer), 4.52 (d, $J=10.7$ Hz, 1H; α anomer), 4.14 (d, $J=9.6$ Hz, 1H; β anomer), 3.79 (s, 1H), 3.69 (t, $J=10.7$, 1H; α anomer), 3.57 (dd, $J=9.8$, 4.0 Hz, 1H; α anomer), 3.52–3.40 (m, 3H), 3.25 ppm (dd, $J=10.4$, 8.9, 1H; β anomer); ^{13}C NMR (101 MHz, D_2O): $\delta=147.39$ (C8 arom), 145.17 (C9 arom), 129.58 (C6 arom), 121.22 (C11 arom), 115.35 (C10 arom), 111.79 (C7 arom), 96.12 (C1, β anomer), 92.23 (C1, α anomer), 78.03 (C5, β anomer), 75.40 (C2, β anomer), 74.27 (C4, β anomer), 73.96 (C4, α anomer), 73.75 (C3, β anomer), 73.65 (C5, α anomer), 72.60 (C3, α anomer), 71.59 (C2, α anomer), 55.88 ppm (C12); ESI-TOF: *m/z* calcd for $C_{12}H_{16}O_7Na$: 295.0794 [M+Na$^+$], $C_{24}H_{32}O_{14}Na$: 567.1690 [2M+Na$^+$]; found: 295.0795, 567.1691.

(5*S*)-5-*C*-(2-Thiophene)-α/β-L-xylopyranose (10x): The title compounds were obtained according to the general procedure. Yield: 58.9 mg (white solid, 13%), >95% pure, as determined by HPLC; retention factor $k_1=2.4$, $k_2=3.1$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-33.3$ ($c=5$ in H_2O, α/β 40:60); ^{1}H NMR (400 MHz, D_2O): $\delta=7.38$–7.33 (m, 1H), 7.08 (tdd, $J=3.6$, 1.3, 0.5 Hz, 1H), 6.97–6.92 (m, 1H), 5.12 (d, $J=3.6$ Hz, 1H; α anomer), 4.91 (d, $J=9.9$ Hz, 1H; α anomer), 4.66 (d, $J=8.0$ Hz, 1H; β anomer), 4.55 (d, $J=9.4$ Hz, 1H; β anomer), 3.67 (dd, $J=9.8$, 9.1 Hz, 1H; α anomer), 3.55 (dd, $J=9.8$, 3.7 Hz, 1H; α anomer), 3.50–3.42 (m, 3H), 3.25 ppm (dd, $J=9.3$, 8.0 Hz, 1H; β anomer); ^{13}C NMR (101 MHz, D_2O): $\delta=140.20$ (C6 arom, α anomer), 139.55 (C6 arom, β anomer), 127.73 (C7 arom, α anomer), 127.53 (C7 arom, β anomer), 127.07 (C8 arom), 126.78 (C9, arom), 96.09 (C1, β anomer), 92.37 (C1, α anomer), 75.28 (C4, β anomer), 74.90 (C4, α anomer), 74.66 (C3, β anomer), 74.08 (C2, β anomer), 73.56 (C5, β anomer), 72.49 (C3, α anomer), 71.43 (C2, α anomer), 69.28 ppm (C5, α anomer); ESI-TOF: *m/z* calcd for $C_9H_{12}O_5SNa$: 255.0303 [M+Na$^+$], $C_{18}H_{24}O_{10}S_2Na$: 487.0709 [2M+Na$^+$]; found: 255.0305, 487.0706.

(5*S*)-5-*C*-[5-(1*H*-Indazole)]-α/β-L-xylopyranose (10ad): The title compounds were obtained according to the general procedure. Yield: 160.6 mg (white solid, 30%), >95% pure, as determined by HPLC; retention factor $k_1=0.8$, $k_2=1.4$ (HPLC analyses were performed as described previously); $[\alpha]_D^{20}=-46.7$ ($c=5$ in DMSO, α/β 44:56); ^{1}H NMR (400 MHz, [D_6]DMSO): $\delta=12.94$ (s, 1H), 8.00 (d, 1.2 Hz, 1H), 7.64 (ddd, $J=2.5$, 1.6, 0.8 Hz, 1H), 7.43 (ddt, $J=7.3$, 6.4, 1.0 Hz, 1H), 7.30 (dd, $J=8.7$, 1.5 Hz, 1H), 6.63 (d, $J=6.2$ Hz, 1H; β anomer), 6.34 (d, $J=4.5$, 1H; α anomer), 5.00 (t, $J=4.0$ Hz, 1H; α anomer), 4.92 (dd, $J=6.6$, 4.5 Hz, 2H; β anomer), 4.74—4.69 (m, 2H), 4.66 (d, $J=5.9$ Hz, 1H; α anomer), 4.60 (d, $J=9.7$ Hz, 1H; α anomer), 4.55 (d, $J=6.6$ Hz, 1H; α anomer), 4.46 (dd, $J=7.7$, 6.1 Hz, 1H; β anomer), 4.13 (d, $J=8.8$ Hz, 1H; β anomer), 3.59—3.51 (m, 1H; α anomer), 3.35–3.28 (m, 1H; α anomer), 3.27–3.18 (m, 2H; β anomer), 3.17–3.10 (m, 1H; α anomer), 3.06 ppm (ddd, $J=8.7$, 7.6, 4.5 Hz, 1H; β anomer); ^{13}C NMR (101 MHz, [D_6]DMSO): $\delta=139.94$ (C10 arom), 133.36 (C9 arom), 132.95 (C6, arom, α anomer), 132.41 (C6 arom, β anomer), 126.73 (C12 arom, α anomer), 126.51 (C12 arom, β anomer), 122.94 (C8 arom), 119.82 (C7 arom), 109.66 (C11 arom), 97.73 (C1, β anomer), 93.21 (C1, α anomer), 78.38 (C5, β anomer), 77.25 (C4, β anomer), 76.12 (C4, α anomer), 75.42 (C2, C3, β anomer), 73.77 (C3, C5, α anomer), 72.95 ppm (C2, α anomer); ESI-TOF: *m/z* calcd for $C_{12}H_{15}N_2O_5$: 267.0981 [M+H$^+$]; found: 267.0982.

Synthesis of (6*S*)-6-*C*-aryl-L-fructose (11) and (6*S*)-6-*C*-aryl-L-tagatose (12): General procedure

Dihydroxyacetone (4 mmol) was added to a solution of (2*S*,3*S*)-3-aryl-2,3-dihydroxypropanal (**7**) (2 mmol) dissolved in sodium borate buffer (50 mL, 0.2 M pH 7.5).[12b] Then, RhuA wild-type (46 U mL^{-1} reaction mixture) was added and mixed again. The reaction was conducted at 25 °C and stirred with a magnetic bar at 250 rpm. The reaction was monitored by HPLC by using gradient elution from 0 to 60% of solvent B over 30 min as indicated above, until the aldehyde was nearly consumed. Reaction workup and purification was conducted as described in the general procedure for the synthesis of (6*S*)-6-*C*-aryl-L-sorbose.

(6*S*)-6-*C*-Phenyl-L-fructose (11a) and (6*S*)-6-*C*-phenyl-L-tagatose (12a): The title compounds were obtained as a 76:26 mixture of **11a**/**12a** as a white solid according to the general procedure. Yield: 277.3 mg (54%), >95% pure, as determined by HPLC; retention factor $k_1=2.8$, $k_2=3.3$; $[\alpha]_D^{20}=-10.0$ ($c=5$ in H_2O). Compound **11a** exists as an equilibrium mixture of 71% as fructofuranose and 29% as fructopyranose. Compound **12a** exists of 40% as tagatofuranose and 60% as tagatopyranose. ESI-TOF: *m/z* calcd for $C_{12}H_{16}O_6Na$: 279.0845 [M+Na$^+$], $C_{24}H_{32}O_{12}Na$: 535.1791 [2M+Na$^+$]; found: 279.0846, 535.1795.

(6*S*)-6-*C*-Phenyl-α-L-fructopyranose (11a; pyran): ^{1}H NMR (400 MHz, D_2O): $\delta=4.81$ (d, $J=10.3$ Hz, 1H), 4.06—4.00 (m, 1H), 3.97 (dd, $J=3.3$, 0.5 Hz, 1H), 3.96–3.87 (m, 1H), 3.66 (d, $J=11.8$ Hz, 1H), 3.28 ppm (d, $J=11.6$ Hz, 1H); ^{13}C NMR (101 MHz, D_2O): $\delta=$ 104.85 (C2), 71.03 (C4), 70.98 (C6), 68.16 (C3), 67.78 (C5), 63.94 ppm (C1).

(6*S*)-6-*C*-Phenyl-β-L-fructofuranose (11a; furan): ^{1}H NMR (400 MHz, D_2O): $\delta=4.68$ (d, $J=6.3$ Hz, 1H), 4.16 (dd, $J=7.8$, 6.8 Hz, 1H), 3.93 (d, $J=7.8$ Hz, 1H), 3.87 (dd, $J=6.8$, 6.3 Hz, 1H), 3.37 ppm (d, $J=10.9$ Hz, 2H); ^{13}C NMR (101 MHz, D_2O): $\delta=101.55$ (C2), 83.04 (C5), 75.82 (C3), 75.78 (C4), 74.46 (C6), 62.34 ppm (C1).

(6*S*)-6-*C*-Phenyl-α-L-tagatopyranose (12a; pyran): ^{1}H NMR (400 MHz, D_2O): $\delta=4.55$ (d, $J=9.9$ Hz, 1H), 3.93–3.85 (m, 2H), 3.76 (t, $J=9.7$ Hz, 1H), 3.44 (d, $J=18.6$ Hz, 1H), 3.39 ppm (d, $J=17.4$ Hz, 1H); ^{13}C NMR (101 MHz, D_2O): $\delta=98.31$ (C2), 75.36 (C6), 70.98 (C5), 70.90 (C4), 69.83 (C3), 62.57 ppm (C1).

(6*S*)-6-*C*-Phenyl-β-L-tagatofuranose (12a; furan): ^{1}H NMR (400 MHz, D_2O): $\delta=4.72$ (d, $J=5.5$ Hz, 1H), 4.12 (t, $J=5.5$ Hz, 1H), 4.05–3.98 (m, 1H), 3.96–3.87 (m, 1H), 3.61 (d, $J=11.6$ Hz, 1H), 3.34 ppm (d, $J=17.8$ Hz, 1H); ^{13}C NMR (101 MHz, D_2O): $\delta=98.55$ (C2), 85.03 (C5), 81.35 (C3), 76.77 (C4), 73.12 (C6), 63.91 ppm (C1).

(6*S*)-6-*C*-(3-Chlorophenyl)-L-fructose (11k) and (6S)-6-*C*-(3-chlorophenyl)-L-tagatose (12k): The title compounds were obtained as a 54:46 mixture of **11k**/**12k** as a white solid according to the general procedure. Yield: 251.3 mg (43%), >95% pure, as determined by HPLC; retention factor $k_1=5.0$, $k_2=5.4$; $[\alpha]_D^{20}=-10.0$ ($c=5$ in H_2O). Compound **11k** exists as an equilibrium mixture of 71% as

fructofuranose and 29% as fructopyranose. Compound **12k** exists of 17% as tagatofuranose and 83% as tagatopyranose. ESI-TOF: *m/z* calcd for $C_{12}H_{15}ClO_6Na$: 313.0455 [*M*+Na^+], $C_{24}H_{30}Cl_2O_{12}Na$: 603.1012 [2*M*+Na^+]; found: 313.0457, 603.1010.

(6*S*)-6-*C*-(3-Chlorophenyl)-α-L-fructopyranose (11k; pyran): ^{1}H NMR (400 MHz, D_2O): δ = 4.79 (d, *J* = 10.3 Hz, 1H), 4.05–3.98 (m, 1H), 3.93–3.85 (m, 1H), 3.89–3.81 (m, 1H), 3.63 (d, *J* = 6.8 Hz, 1H), 3.29 ppm (d, *J* = 11.6 Hz, 1H); ^{13}C NMR (101 MHz, D_2O) δ = 104.88 (C2), 72.99 (C4), 70.48 (C6), 68.14 (C3), 67.88 (C5), 63.87 ppm (C1).

(6*S*)-6-*C*-(3-Chlorophenyl)-β-L-fructofuranose (11k; furan): ^{1}H NMR (400 MHz, D_2O): δ = 4.68 (d, *J* = 6.3 Hz, 1H), 4.14 (dd, *J* = 7.8, 6.8 Hz, 1H), 3.93 (d, *J* = 7.8 Hz, 1H), 3.83 (dd, *J* = 6.8, 6.2 Hz, 1H), 3.37 ppm (d, *J* = 9.4 Hz, 2H); ^{13}C NMR (101 MHz, D_2O): δ = 101.62 (C2), 82.89 (C5), 75.70 (C3), 75.66 (C4), 73.76 (C6), 62.30 ppm (C1).

(6*S*)-6-*C*-(3-Chlorophenyl)-α-L-tagatopyranose (12k; pyran): ^{1}H NMR (400 MHz, D_2O): δ = 4.53 (d, *J* = 9.8 Hz, 1H), 3.96–3.85 (m, 2H), 3.69 (t, *J* = 9.4 Hz, 1H), 3.43 (d, *J* = 9.1 Hz, 1H), 3.38 ppm (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (101 MHz, D_2O): δ = 98.60 (C2), 74.78 (C6), 71.11 (C5), 70.77 (C4), 69.80 (C3), 63.87 ppm (C1).

(6*S*)-6-*C*-(3-Chlorophenyl)-β-L-tagatofuranose (12k; furan): ^{1}H NMR (400 MHz, D_2O): δ = 4.76–3.68 (m, 1H), 4.08 (t, *J* = 5.5 Hz, 1H), 4.05–3.95 (m, 1H), 3.94–3.85 (m, 1H), 3.61 (d, *J* = 11.7 Hz, 1H), 3.34 ppm (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (101 MHz, D_2O): δ = 98.33 (C2), 84.83 (C5), 81.36 (C3), 76.63 (C4), 72.48 (C6), 62.57 ppm (C1).

Synthesis of (1*R*,2*R*)-1-phenylpropane-1,2,3-triol (Benzoin addition of benzaldehyde to glycolaldehyde; proof of concept)

Reactions (100 mL total volume) were conducted at 25 °C under magnetic stirring at 250 rpm. Benzaldehyde (10 mmol) was dissolved in MTBE (50 mL). Then, sodium carbonate buffer (50 mL, 50 mM, pH 8.0) containing BAL (500 U mL^{-1}), $MgSO_4$ (2.5 mM), and ThDP (0.15 mM) was added. The reaction was started by the addition of glycolaldehyde dimer (20 mmol equiv of monomer). Every 24 h, another fraction of BAL (25 000 U dissolved in 5 mL of sodium carbonate buffer (50 mL, 50 mM, pH 8.0) containing $MgSO_4$ (2.5 mM) and ThDP (0.15 mM)) was added. The reaction was monitored as follows: After 72 h, samples of the organic phase (10 mL) and the aqueous phase (10 mL) were withdrawn, placed in separate vials, diluted with methanol (500 mL), and directly analyzed and quantified by HPLC by using a gradient elution from 10 to 70% of solvent B over 30 min. After 72 h, NaCl was added to the reaction mixture up to saturation. The mixture was filtered through Celite and the pellet was washed with water (200 mL). The aqueous phase was extracted with AcOEt (5×50 mL), the organic fractions combined, dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The product, a yellow oil (1.55 g, 93%), was used without further purification. To a solution of (*R*)-2,3-dihydroxy-1-phenylpropan-1-one (1.55 g, 9.3 mmol) in THF (100 mL) a solution of $Zn(BH_4)_2$ (1.9 mol L^{-1} in THF, 6 mL, 11.4 mmol) at −80 °C was added. After 4 h the reaction mixture was allowed to warm up to RT and a solution of HCl (1 M 30 mL) was then added dropwise. The solvent was removed under vacuum and the pH value was adjusted to 7.0 with NaOH (1 M). The solution was frozen at −80 °C and lyophilized. Finally, the dry residue was extracted with AcOEt (3×30 mL), and the solvent was removed under vacuum affording a white solid, which was identified as the title compound (1.39 g, 89%, 10:90 (1*S*,2*R*)/(1*R*,2*R*), assessed by ^{1}H NMR spectroscopy). $[\alpha]_D^{20} = -13.3.0$ (*c* = 1.5 in $CHCl_3$; lit.[27] of the pure compounds: (1*S*,2*R*): $[\alpha]_D^{20} = +$ 89.73 (*c* = 0.66 in $CHCl_3$); (1*R*,2*R*): $[\alpha]_D^{20} = -20.92$ (*c* = 3.68 in $CHCl_3$)). NMR data matched the ones reported for (1*S*,2*R*) and (1*R*,2*R*).[27] ^{1}H NMR (400 MHz, D_2O): δ = 7.26-7.20 (m, 5H), 4.50 (d, *J* = 6.5 Hz, 1H; (1*S*,2*R*)), 4.47 (d, *J* = 7.1 Hz, 1H; (1*R*,2*R*)), 3.74 (td, *J* = 7.0, 3.2 Hz, 1H; (1*R*,2*R*)), 3.70 (d, *J* = 3.7 Hz, 1H; (1*S*,2*R*)), 3.62 (dd, *J* = 11.9, 3.3 Hz, 1H; (1*R*,2*R*)), 3.43 (dd, *J* = 11.8, 6.8 Hz, 1H; (1*R*,2*R*)), 3.35 (dd, *J* = 11.8, 3.7 Hz, 1H; (1*S*,2*R*)), 3.23 ppm (dd, *J* = 11.8, 6.9 Hz, 1H; (1*S*,2*R*)); ^{13}C NMR (101 MHz, D_2O): δ = 140.28 (C arom), 128.49 (C arom), 128.11 (C arom), 127.07 (C arom), 75.36 (-CHOH-, (1*S*,2*R*)), 74.54 (-CHOH-, (1*R*,2*R*)), 74.09 (Ph-CHOH-, (1*S*,2*R*)), 73.84 (Ph-CHOH-, (1*R*,2*R*)), 62.54 (-CH_2OH, (1*R*,2*R*)), 62.39 ppm (-CH_2OH, (1*S*,2*R*)).

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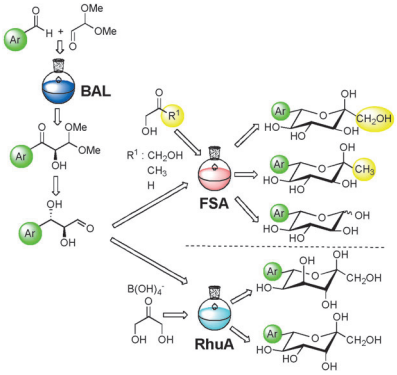
FULL PAPER

Bottom-up sugars: *C*-Aryl carbohydrates on the non-reducing end exhibit interesting biological activities. These molecules have been prepared in four synthetic steps combining cross-benzoin and aldol addition reactions with simple chemical transformation. By using this methodology, *C*-aryl carbohydrate analogues of L-sorbose, L-xylose, L-fructose, and L-tagatose are prepared (see figure).



Biocatalytic Carbohydrate Analogues

*K. Hernández, T. Parella, J. Joglar, J. Bujons, M. Pohl, P. Clapés**

■■ – ■■

Expedient Synthesis of *C*-Aryl Carbohydrates by Consecutive Biocatalytic Benzoin and Aldol Reactions