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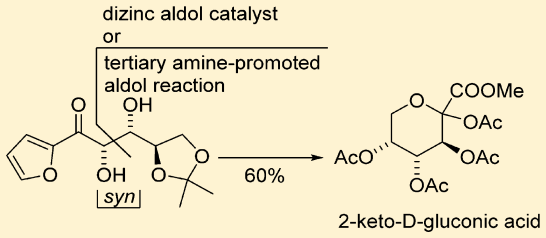
Synthesis of 2-Keto-D- and L-gluconic Acid via Stereoselective Direct Aldol Reactions

Sebastian Baś and Jacek Mlynarski*

Faculty of Chemistry, Jagiellonian University, Ingardena 3, 30-060 Krakow, Poland

Supporting Information

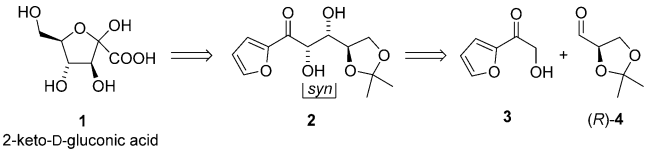
ABSTRACT: Stereoselective direct aldol reaction between optically pure D- or L-glyceraldehyde and hydroxyacetylfuran is demonstrated as an efficient and straightforward methodology for the synthesis of six-carbon atom D- and L-*arabino*-hex-2-ulosonic acids. *syn*-Selective aldol reactions realized by using either tertiary amines or a dizinc aldol catalyst constitute two parallel routes to the *de novo* synthesis of orthogonally protected biologically relevant 2-keto-D- and L-gluconic acids.



Stereoselective aldol reaction is a key carbon−carbon bond forming tool for organic synthesis and biotransformations.[1] In living organisms, enzyme-controlled aldol reactions are crucial for the biosynthesis of carbohydrates, keto acids, and some amino acids.[2] For example, the $C_3 + C_3$ strategy is most favored by nature for the synthesis of ketohexoses and is facilitated by the dihydroxyacetone phosphate family of aldolases.[3] Among the many possible aldol reactions that have been used to synthesize polyol architectures[4] and carbohydrates in the laboratory,[5] direct aldol reactions[6] promoted by small organic molecules have been recently demonstrated as a powerful and valuable variant.[7] To emulate aldolases' function, chemists developed efficient organocatalytic carbohydrate synthesis from dihydroxyacetone derivatives and chiral aldehydes. These studies have largely used 2,2-dimethyl-1,3-dioxan-5-one as a C_3 donor in an *anti*-selective aldol reaction catalyzed by (*R*)- or (*S*)-proline.[8] More recently, Barbas reported that a primary amino acid could catalyze a *syn*-aldol reaction of DHA and protected DHA leading to ketohexoses.[9] In contrast to well-studied direct aldol reactions of dihydroxyacetone with (*R*)-glyceraldehyde leading to four possible D-ketohexoses,[10] its stereoselective variants starting from other hydroxyketones have not been explored to date. This general lack in the field of organocatalysis is a considerable limitation in the synthesis of natural products where aromatic rings attached to the hydroxyketone donor can be used for masked carboxylic functionality.[11]

A valuable example of this concept could be the total synthesis of 6-carbon ulosonic acid (**1**) via the cross-aldolisation of chiral glyceraldehyde (*R*)-**4** with hydroxyacetylfuran (**3**) (Scheme 1). D-*arabino*-Hex-2-ulosonic acid **1** (sometimes referred to as 2-keto-D-gluconic acid) is an important metabolite derived from D-glucose. This acid is a component of polysaccharides obtained from a *Cyttaria* fungus,[12] and bacterial lipopolysaccharides found in *Acetobacter*.[13] It is also an important intermediate in the synthesis of D-*erythro*-hex-2-enono-1,4-lactone (D-erythorbic acid)[14] and isoascorbic acid.[15] 2-Keto-D-gluconic acid being a prominent

Scheme 1. Synthesis of 2-Keto-D-gluconic Acid by Means of Direct Aldol Reaction of (*R*)-Glyceraldehyde and Hydroxyketone 3



example of a broad family of sugar 2-keto acids has been prepared by chemical,[16] electrochemical,[17] and biochemical[18] oxidation of glucose or gluconic acid. Interestingly, stereoselective total synthesis of this compound has not been reported in the literature. Accordingly, we sought to develop a new route to the synthesis of D-*arabino*-hex-2-ulosonic acid (**1**) and its L-form, via direct aldol reaction of chiral aldehydes with hydroxyacetylfuran promoted by tertiary amines. We present also an alternative approach to the same molecule by using chiral zinc complexes to control the stereoselective direct aldol reaction, being that it is a crucial reaction step.

Our retrosynthetic analysis of the six-carbon skeleton of D-*arabino*-hex-2-ulosonic acid (**1**) illustrates that the structure could be reduced to simple starting materials such as hydroxyacetylfuran (**3**) and protected glyceraldehyde (**4**) using a stereocontrolled aldol reaction. Thinking in the forward direction, *syn*-selective formation of the diol **2** with internal *anti*-diastereoselectivity derived from a chiral aldehyde should be achieved. Such a C−C bond forming reaction is not possible by using an enamine-based organocatalytic protocol, but we have found a class of tertiary amine catalysts that work effectively with aromatic hydroxyketones as highly *syn*-selective aldol organocatalysts.[19] Application of tertiary amine catalysts to the said aldol reaction from Scheme 1 seems to be promising, as in all cases the relative stereochemistry of the

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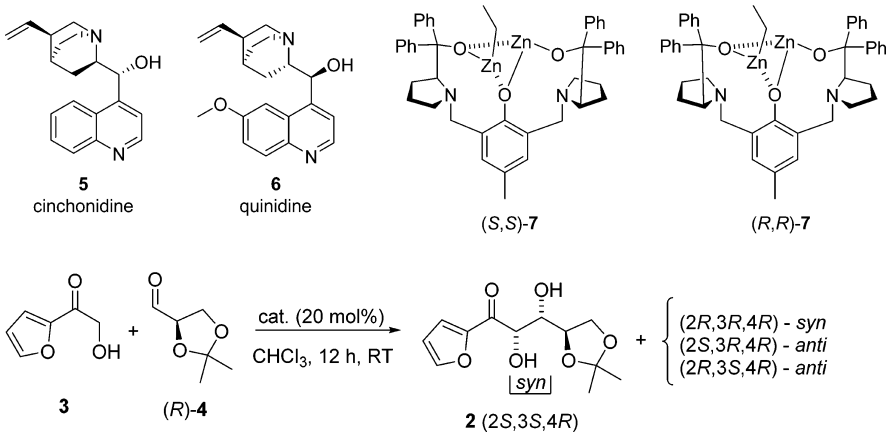
Table 1. Screening of Efficient Catalyst in the Direct Asymmetric Aldol Reaction of Glyceraldehyde and Hydroxyacetylfuran



entry	catalyst	isolated yield of **2** (%)[a]	total yield of all isomers (%)
1	**CD 5**	49	86
2	**QD 6**	50	78
3	quinuclidine	32	53
4	DBU	30	46
5	Et_3N	39	62
6	$iPrEt_2N$	36	53
7[b]	(*S*,*S*)-7	86	97
8[b]	(*R*,*R*)-7	41	85

[a]Isolated yield of *syn* isomers. Reaction conditions: **3** (1 mmol), (*R*)-**4** (1 mmol), catalyst (20 mol %) in $CHCl_3$ at rt for 12 h. [b]Reaction conditions: **3** (0.5 mmol), (*R*)-**4** (0.5 mmol), catalyst **7** (20 mol %) in dry THF at −20 °C for 12 h.

major aldol was *syn*, and the diastereoselectivity was good to excellent. It was not clear, however, if the desired stereoselectivity might be achieved by using a chiral tertiary amine, as it was demonstrated in our previous work,[19,20] or by simple 1,2-asymmetric induction controlled by chiral substrate **4**, as observed by others.[21]

For our first example we chose *Cinchona* alkaloids (Table 1) as the model tertiary amine catalysts for the aldol reaction with hydroxyacetylfuran **3** and optimized the reaction conditions in terms of chemical yield and stereoselectivity. The reaction of **3** and (*R*)-glyceraldehyde was explored as a catalyst test. The best reaction conditions include cinchonidine **5** (CD) and quinidine **6** (QD) alkaloids (20 mol %, Table 1, entries 1 and 2) as the catalysts, $CHCl_3$ as the solvent, and ambient temperature. Under these reaction conditions aldol adducts of hydroxyacetylfuran could be isolated with a good total yield of all possible stereoisomers (78−86%) for both tested catalysts (Table 1, entries 1 and 2). More importantly, the aldol adducts were formed with a high degree of relative *syn*-diastereoselectivity in all cases. To our delight, the overall ratio of *syn*- and *anti*-isomers was better than 9:1. Moreover, an internal diastereoselectivity controlled by the chiral aldehyde was also good, as reflected in preferential formation of isomer **2**-(2*S*,3*S*,4*R*) over (2*R*,3*R*,4*R*). Interestingly, the same level of diastereoselectivity was observed for a series of nonchiral tertiary amines (Table 1, entries 3−6) supporting the controlling effect of the Felkin−Ahn-type model instead of catalyst control. Application of other tertiary amines was possible yet less efficient. The influence of the solvent effect on the reaction output was rather negligible, and similar stereoselectivity was observed for all tested solvents (DCM, DME, DMSO, THF). Under the optimized conditions, a quinidine catalyst afforded the desired *syn*-aldol with good isolated yield (50%) (Table 1, entry 2). The observed diastereoselectivity was sufficient for practical application of the demonstrated methodology in light of the high simplicity of the elaborated one-step protocol.

However, to explore further this concept, we tested also the possibility of a chiral metal complex protocol thus mimicking another group of aldolases. We turned our attention to zinc-promoted processes by using a catalyst capable of simultaneous activation of both the substrate donor and acceptor in a chiral environment thus possibly improving the stereoselectivity. This kind of catalysis could be compared mechanistically to the type II aldolases observed in Nature where a zinc cofactor activates the donor by coordination and facilitates enolate form creation.[22] We started our investigations with the Zn/ProPhenol **7** catalytic system which has been used for an array of enantioselective aldol reaction with aromatic hydroxyketones with success.[11,23] In this respect, we wished to extend the scope of the Zn/Prophenol-catalyzed aldol reactions in a diastereoslective manner with chiral aldehydes. To our delight the reaction of ketone **3** with (*R*)-glyceraldehyde acetonide promoted by the (*S*,*S*)-**7** catalyst resulted in the clean and nearly quantitative formation of desired aldol product **2** with a very high level of diastereoselectivity favoring product (2*S*,3*S*,4*R*)-**2** in 90% yield (Table 1, entry 7). In comparison, enantiomeric catalyst (*R*,*R*)-**7** also gave complete conversion, but the selectivity level was rather low (Table 1, entry 8). The opposite situation was observed in the case of enantiomeric aldehyde (*S*)-**4**, where the (*R*)-catalyst gave 96% of the total yield and the main product was isolated in 88% yield compared to (*S*,*S*)-**7** where the yield of (2*R*,3*R*,4*S*)-**2** was only 59% (94% total yield). Whereas, in the stereoselective reaction of enantiomeric (*S*)-glyceraldehyde activated by quinidine, *syn*-aldol ent-**2** was obtained in 39% yield (61% total yield), which confirmed substrate-based

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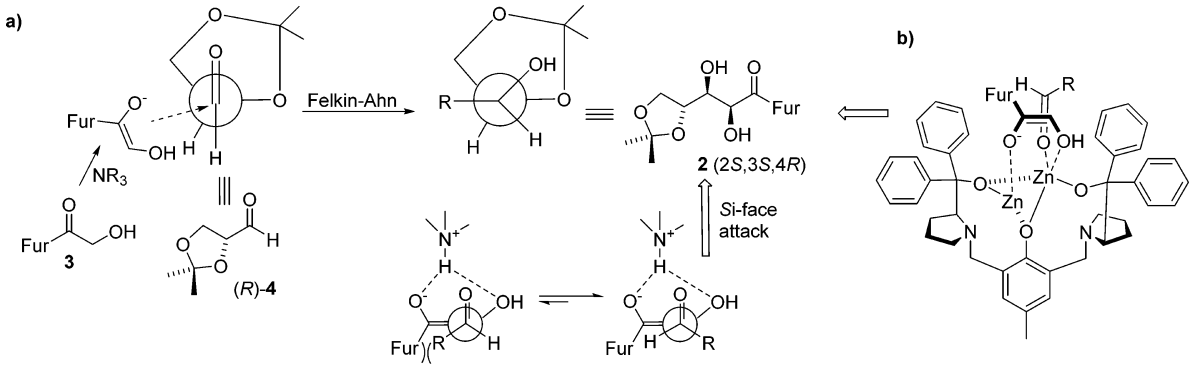
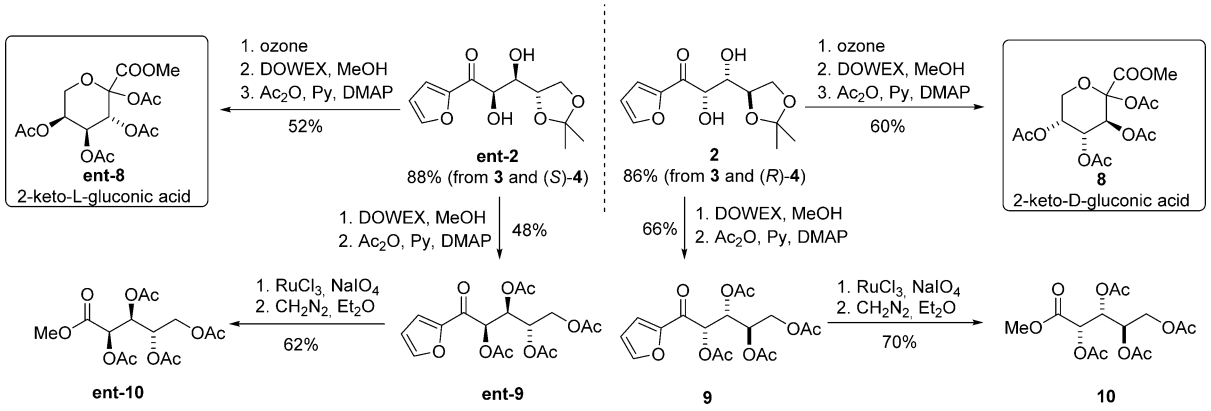
Scheme 2. Possible Structures of Transition States



Scheme 3. *De novo* Synthesis of 2-Keto-D- and L-gluconic Acid



selectivity control in case of tertiary amines activation. Since in that case complete separation of the desired isomer **2**-(2*S*,3*S*,4*R*) could be achieved by chromatography, this reaction was encouraging for further practical application of the elaborated methodology in the synthesis. In contrast, separation of the remaining isomers was tedious and inefficient.

Observed preferential formation of *syn*-isomer **2** (2*S*,3*S*,4*R*) from (*R*)-**4** could be explained by (*Z*)-enol formation from the hydroxyketone and its stereoselective addition to optically pure aldehyde. Considering Felkin−Anh transition state oxygen at C-2 of aldehyde, being electronegative, it will lie perpendicular to the carbonyl group in the most reactive conformer delivering *syn*-**2** (Scheme 2). This explains clearly formation of the (3*S*)-configured aldol while the controlled formation of the remaining stereocenter at C-2 to form *syn*-isomer **2** (2*S*,3*S*,4*R*) is more difficult. However, rational explanation for the formation of the *syn*-(2*S*,3*S*,4*R*) aldol is given by (*Z*)-enolate addition to the *Si*-face of (*R*)-aldehyde where steric hindrance is the main factor. In contrast, reaction at the *Re* face of the aldehyde leading to unfavored *syn*-(2*R*,3*R*,4*R*) is more difficult due to the steric repulsion between the two larger substituents.

This mechanism could be also used to explain results observed for catalyst **7**. The stereochemical outcome of these reaction could be rationalized by coordination of deprotonated **3** to the Zn/ProPhenol complex which creates a chiral pocket around generated (*Z*)-enolate (Scheme 2b). Thus, formed the zinc−enolate complex attacks the *Si* face of the chiral aldehyde; however, only the chiral pocket obtained from (*S*,*S*)-**7** complex matched (*R*)-glyceraldehyde acetonide, so that the aldol reaction occurred with high selectivity.

To complete the synthesis of target D-*arabino*-hex-2-ulosonic acid **1**, compound **2** was readily isolated and separated from other diastereomers by column chromatography. *syn*-Diol **2** isolated in 50% yield by using an organocatalytic protocol (or in an excellent 86% yield when the reaction was promoted by a Zn-based catalyst) was converted into the protected form of 2-keto-D-gluconic acid **1** according to Scheme 3. Direct ozonolysis of the furan residue and deprotection of the isopropylidene followed by acetylation delivered the protected form of D-*arabino*-hex-2-ulosonate (**8**) with an impressive 60% overall yield in three steps (Scheme 3). Ultimate evidence for the configuration of the final product (and also for the configuration of aldol **2**) was the comparison of ^{1}H and ^{13}C NMR spectra of compound **8** with those of the authentic sample of D-*arabino*-hex-2-ulosonic acid (compound **nat-8** in Experimental Part). The spectroscopic data for **nat-8** were in excellent agreement with those of the commercial compound.

With substantial amounts of **2** in hand, we decided also to use it in the parallel synthesis of arabonic acid derivative **10**.[24] This pathway required hydrolysis of acetonide residue in **2** and acetylation of tetraol to form **9** (Scheme 3). Subsequent transformation of the carbonyl into a carboxyl function was realized by using RuO_4-based oxidation, followed by esterification with diazomethane. This generated methyl D-*arabino*-hex-2-ulosonate (**10**) in 60% overall yield in three steps (Scheme 3).

The presented short synthesis of natural D-configured sugar **8** can be flexibly used for the preparation of its L-counterpart starting from L-glyceraldehyde. This expectation was based on the mentioned previously substrate-based strategy where chiral aldehyde controlled formation on the resulting aldol via the

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Felkin−Anh transition state. Thus, isolated **ent-2** (88% yield by using Trost catalyst) was converted into methyl ester of L-*arabino*-hex-2-ulosonic acid **ent-8** by using a previously elaborated protocol (52% yield, Scheme 3). Also synthesis of L-arabonic acid derivative **ent-10** was achieved by using the previously described protocol depicted in Scheme 3.

In summary, we disclose the *de novo* synthesis of 2-keto-D-gluconic acid *via* the *syn*-selective aldol reaction of hydroxyacetylfuran to D-glyceraldehyde promoted by both tertiary amines and a Zn/Prophenol Trost catalyst. The methodology presented herein is an efficient direct entry to a one-step synthesis of orthogonally protected 2-keto-D- and L-gluconic acids. This is also an example of the valuable practical application of a direct asymmetric aldol reaction to the synthesis of natural products.

EXPERIMENTAL SECTION

General Information. Infrared (IR) spectra were recorded on a Fourier transform infrared (FT-IR) spectrometer. ^{1}H NMR spectra were measured at 300 and 600 MHz in $CDCl_3$. Data were reported as follows: chemical shifts in parts per million (ppm) from tetramethylsilane as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double−doublet, m = multiplet, br = broad), coupling constants (in Hz), and assignment. ^{13}C NMR spectra were measured at 75 and 150 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High resolution mass spectra (HRMS) were performed on an electrospray ionization time-of-flight (ESI-TOF) mass spectrometer. Optical rotations were measured on a digital polarimeter at room temperature. Reactions were controlled using TLC on silica [alu-plates (0.2 mm)]. All reagents and solvents were purified and dried according to common methods. All organic solutions were dried over anhydrous sodium sulfate. Reaction products were purified by flash chromatography using silica gel 60 (240−400 mesh). HPLC analysis was performed on an HPLC system equipped with chiral stationary phase columns, with detection at 254 nm.

General Method for Aldol Reactions of 3 with 4 Catalyzed by Tertiary Amines (Table 1 part 1). 2-Hydroxyacetylfurane **3** (20 mmol, 1.0 equiv) and glyceraldehyde acetonide **4** (20 mmol, 1.0 equiv) were dissolved in chloroform (10 mL), and then catalyst was added (0.2 equiv) and the mixture was stirred at rt for 12 h. After this time, mixture was diluted with ethyl acetate (50 mL) and washed by water (25 mL), saturated $NaHSO_3$ (2 × 25 mL), water (25 mL), and brine (25 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by column chromatography on silica gel with DCM−MTBE−hexane (5:1:2) to obtain a mixture of products as a yellow oil (total yield). Main diastereomer **2** was isolated by column chromatography on silica gel with hexane−diethyl ether−methanol (10:10:1).

General Method for Aldol Reactions of 3 with 4 Catalyzed by Zinc Complex (Table 1 part 2). The zinc/Prophenol catalyst was prepared as described in literature.[25] A solution of **7** (0.7 mL, 0.2 M in dry THF) was added to a mixture of **3** (0.5 mmol, 1.0 equiv) and **4** (0.5 mmol, 1.0 equiv) in dry THF (1 mL) at −20 °C. After 12 h at this temperature, the reaction was quenched by being poured into a saturated NH_4Cl solution. The water phase was extracted with ethyl acetate (4 × 25 mL). Combined organic phases were dried over anhydrous $MgSO_4$. Then the solvent was evaporated, and the residue was purified by column chromatography on silica gel with hexane−ethyl acetate (1:1) to obtain a mixture of products as a yellow oil (total yield). Main diastereomer **2** was isolated by column chromatography on silica gel with hexane−diethyl ether−methanol (10:10:1).

(2*S*,3*S*)-3-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-(furan-2-yl)-2,3-dihydroxypropan-1-one (2). The product was obtained from hydroxyacetylfurane **3**[19,26] and (*R*)-**4**[27] aldehyde as a yellowish oil (950 mg, 42% reaction catalyzed by CD). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (dd, J = 1.7, 0.6 Hz, 1H), 7.38 (dd, J = 3.6, 0.6 Hz, 1H), 6.62 (dd, J = 3.6, 1.7 Hz, 1H), 5.13 (d, J = 1.0 Hz, 1H), 4.22 (ddd, J = 8.2, 6.2, 4.4 Hz, 1H), 4.15 (dd, J = 8.9, 6.2 Hz, 1H), 4.07 (dd, J = 8.9, 4.4 Hz, 1H), 4.04 (d, J = 7.7 Hz, 1H), 3.83 (s, 1H), 2.30 (s, 1H), 1.53 (s, 3H), 1.40 (s, 3H) (ppm); ^{13}C NMR (151 MHz, $CDCl_3$) δ 188.2, 150.2, 147.4, 119.7, 112.9, 109.6, 75.8, 73.5, 73.4, 67.0, 27.1, 25.3. (ppm); IR (ATR) ν 3440, 3138, 2987, 2923, 2852, 1678, 1570, 1467, 1384, 1215, 1067 (cm^{-1}); $[\alpha]_D^{20}$ = +15.0 (c 1.04, $CHCl_3$); HRMS (ESI) [M + Na^+] calcd for $C_{12}H_{16}O_6$ 279.0845, found 279.0830.

(2*R*,3*R*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-(furan-2-yl)-2,3-dihydroxypropan-1-one (ent-2). The product was obtain from from hydroxyacetylfurane **3**[19,26] and (*S*)-**4**[28] aldehyde as a yellowish oil (98 mg, 39% reaction catalyzed by QD); all spectroscopic data have been in full agreement with those reported for compound **2**; $[\alpha]_D^{20}$ = −17.0 (c 1.00, $CHCl_3$); HRMS (ESI) [M + Na^+] calcd for $C_{12}H_{16}O_6$ 279.0845, found 279.0820.

General Procedure of Acyclic Acetylated Compound 9 Preparation. Compound **2** (1.285 g) was dissolved in MeOH (50 mL) followed by addition of DOWEX 50WX4 resin (0.5 g, 0.5 mass equiv). The reaction was stirred for 3 to 5 h, then filtrated, and evaporated under reduced pressure. The precipitate was dry under vacuum to remove traces of MeOH. Next the precipitate was dissolved in a mixture of pyridine (2.5 mL) and Ac_2O (2.5 mL) followed by the addition of a catalytic amount of DMAP. The reaction was stirred overnight. After the indicated time, the solution was diluted with ethyl acetate and washed with 1 M HCl (50 mL), saturated $NaHCO_3$ solution (2 × 50 mL), water (50 mL), and brine (50 mL). The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed by evaporation under reduced pressure. Product was purified by crystallization from hexane−ethyl acetate.

(2*R*,3*R*,4*S*)-5-(Furan-2-yl)-5-oxopentane-1,2,3,4-tetrayl Tetraacetate (9). The product was obtained from **2** as a white solid (1.276 g, 66%), mp = 130−132 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (dd, J = 1.7, 0.7 Hz, 1H), 7.30 (dd, J = 3.6, 0.7 Hz, 1H), 6.60 (dd, J = 3.6, 1.7 Hz, 1H), 5.92 (d, J = 2.3 Hz, 1H), 5.79 (dd, J = 8.8, 2.3 Hz, 1H), 5.36 (ddd, J = 8.8, 5.0, 2.5 Hz, 1H), 4.34 (dd, J = 12.6, 2.5 Hz, 1H), 4.20 (dd, J = 12.6, 5.0 Hz, 1H), 2.20 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 181.2, 170.7, 170.1, 169.8, 169.4, 150.8, 147.2, 118.8, 112.9, 73.2, 68.8, 68.6, 61.9, 20.9, 20.8, 20.6, 20.5 (ppm); IR (ATR) ν 3119, 2949, 1749, 1737, 1673, 1463, 1370, 1213, 1048 (cm^{-1}); $[\alpha]_D^{20}$ = +8.2 (c 1.00, $CHCl_3$); HRMS (ESI) [M + Na^+] calcd for $C_{17}H_{20}O_{10}$ 407.0954, found 407.0941.

(2*S*,3*S*,4*R*)-5-(Furan-2-yl)-5-oxopentane-1,2,3,4-tetrayl Tetraacetate (ent-9). The product was obtained from **ent-2** as a white solid (95 mg, 42%), mp = 133−135 °C; all spectroscopic data have been in full agreement with those reported for compound **9**; $[\alpha]_D^{20}$ = −8.3 (c 1.01, $CHCl_3$); HRMS (ESI) [M + Na^+] calcd for $C_{17}H_{20}O_{10}$ 407.0954, found 407.0926.

Synthesis of D- and L-Arabonic Acid Derivatives 10 and ent-10. $RuCl_3 \cdot 3H_2O$ (70 mg, 0.27 mmol, 0.08 equiv) was added in one portion to a stirred solution of $NaIO_4$ (5.1 g, 28 mmol, 8 equiv) in H_2O−CCl_4−CH_3CN 3:2:2 (70 mL) to give a yellowish brown colored solution. After stirring for 15 min, compound **9** (1.276 g, 3.32 mmol) in CH_3CN (5 mL) was added to the solution. The color of the solution turned instantaneously from brown to black. Then $NaIO_4$ (6.1 g, 32 mmol, 9.5 equiv) was added to the reaction to restore the brown color. The mixture was then partitioned with ethyl acetate (150 mL) and H_2O (50 mL). The aqueous phase was acidified with 20% $NaHSO_4$ to pH 1 and further extracted with ethyl acetate. The combined organic phases were washed with brine, dried with anhydrous $MgSO_4$, filtered through a pad of silica gel, and evaporated. The crude product (1.123 g, 3.1 mmol) was dissolved in diethyl ether (25 mL), and CH_2N_2 solution in Et_2O was added successively until a stable yellow color was obtained in the reaction mixture. Acetic acid was added to remove excess CH_2N_2. The reaction mixture was washed with water (10 mL), saturated $NaHCO_3$ solution (2 × 50 mL), water (50 mL), and brine (50 mL) and dried with anhydrous $MgSO_4$ and evaporated. The product was purified by column chromatography on silica gel with DCM−MTBE−hexane (5:1:2).

Tetra-*O*-acetyl-D-arabonic Acid Methyl Ester (10). The product was obtained from **9** (1.276 g) as a white solid (926 mg,

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70%), mp = 126−128 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.59 (dd, J = 9.3, 2.1 Hz, 1H), 5.24 (d, J = 2.1 Hz, 1H), 5.21 (ddd, J = 9.3, 4.5, 2.5 Hz, 1H), 4.26 (dd, J = 12.6, 2.5 Hz, 1H), 4.12 (dd, J = 12.6, 4.6 Hz, 1H), 3.70 (s, 3H), 2.14 (s, 3H), 2.09−1.96 (m, 9H) (ppm); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 170.2, 169.7, 169.4, 167.6, 69.8, 68.8, 68.2, 61.8, 52.9, 20.8, 20.8, 20.6, 20.5 (ppm); IR (ATR) ν 2987, 2957, 1746, 1372, 1210, 1081, 1051 (cm^{-1}); $[\alpha]_D^{20}$ = +30.0 (c 0.99, $CHCl_3$); HRMS (ESI) [M + Na^+] calcd for $C_{14}H_{20}O_{10}$ 371.0954, found 371.0955.

Tetra-*O*-acetyl-L-arabonic Acid Methyl Ester (ent-10). The product was obtained from **ent-9** (96 mg) as a white solid (62 mg, 60%), mp = 126−128 °C; all spectroscopic data have been in full agreement with those reported for compound **10**; $[\alpha]_D^{20}$ = −24.0 (c 1.00, $CHCl_3$); HRMS (ESI) [M + Na^+] calcd for $C_{14}H_{20}O_{10}$ 371.0954, found 371.0927.

Synthesis of 2-Ketogluconic Acid Derivatives 8 and ent-8. Compound **2** (50 mg, 0.2 mmol) was dissolved in an anhydrous mixture of MeOH−DCM (10:1) and cooled to −78 °C. The O_3 gas was bubbled into the solution for 5 to 10 min until TLC showed the disappearance of substrate (DCM−MTBE−hexane 5:1:2). The excess of O_3 was purged by O_2 (5 min) and Ar (10 min). The solution was added by DOWEX 50WX4 resin (100 mg, 3.0 mass equiv) and stirred for 2 h. Afterward, DOWEX was removed by filtration, followed by evaporation of the reaction solvent. The obtained yellowish oil was dried under vacuum to remove traces of MeOH. Afterward, the residue was dissolved in a mixture of pyridine (0.5 mL) and Ac_2O (0.5 mL) followed by addition of a catalytic amount of DMAP. The reaction was stirred overnight, and then the solution was diluted with ethyl acetate and washed with 1 M HCl (50 mL), a saturated $NaHCO_3$ solution (2 × 50 mL), water (50 mL), and brine (50 mL). Organic phase was dried over anhydrous $MgSO_4$, and solvent was removed by evaporation under reduced pressure. The product was purified by column chromatography on silica gel with DCM−MTBE−hexane (5:1:2).

(3*S*,4*R*,5*R*)-2-(Methoxycarbonyl)tetrahydro-2*H*-pyran-2,3,4,5-tetrayl Tetraacetate or Methyl 2,3,4,5-Tetra-*O*-acetyl-α/β-D-arabino-hex-2-ulopyrano- and -furanosonate (8). The product was obtained from **2** as a yellow oil (44 mg, 60%) mixture of isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.73 (d, J = 7.0 Hz, 0.5H), 5.60 (d, J = 2.5 Hz, 1H), 5.50−5.33 (m, 2.8H), 5.09 (dd, J = 4.8, 2.5 Hz, 1H), 4.50−4.39 (m, 2.6H), 4.28 (m, 2H), 4.03 (dd, J = 13.4, 1.5 Hz, 0.5H), 3.91 (dd, J = 13.3, 1.2 Hz, 0.5H), 3.80 (s, 4H), 3.78 (s, 1.5H), 2.22 (s, 1.5H), 2.17 (m, 3H), 2.14 (s, 3H), 2.13 (s, 4H), 2.10 (s, 4H), 2.08 (s, 5.5H), 2.02 (s, 1.5H) (ppm); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 170.6, 170.5, 170.2, 170.1, 170.0, 169.8, 169.4, 168.9, 168.7, 168.5, 168.3, 165.8, 165.0, 164.9, 104.2, 99.6, 96.2, 82.6, 80.7, 79.9, 76.5, 76.0, 74.6, 67.9, 67.6, 66.8, 63.6, 62.8, 53.3, 53.2, 21.1, 20.9, 20.9, 20.8, 20.7, 20.64, 20.6 (ppm); IR (ATR) ν 2956, 1745, 1437, 1371, 1211, 1123, 1057, 602 (cm^{-1}); HRMS (ESI) [M + Na^+] calcd for $C_{15}H_{20}O_{11}$ 399.0903, found 399.0901.

(3*R*,4*S*,5*S*)-2-(Methoxycarbonyl)tetrahydro-2*H*-pyran-2,3,4,5-tetrayl Tetraacetate or Methyl 2,3,4,5-Tetra-*O*-acetyl-α/β-L-arabino-hex-2-ulopyrano- and -furanosonate (ent-8). The product was obtained from **ent-2** as a yellow oil (32 mg, 35%) mixture of isomers: all spectroscopic data have been in full agreement with those reported for compound **8**; HRMS (ESI) [M + Na^+] calcd for $C_{15}H_{20}O_{11}$ 399.0903, found 399.0897.

(3*S*,4*R*,5*R*)-2-(Methoxycarbonyl)tetrahydro-2*H*-pyran-2,3,4,5-tetrayl Tetraacetate or Methyl 2,3,4,5-Tetra-*O*-acetyl-α/β-D-arabino-hex-2-ulopyrano- and -furanosonate, Reference Compound nat-8. Commercially available 2-keto-D-gluconic hemicalcium salt hydrate **1** (250 mg, 0.6 mmol) was put into MeOH (10 mL). The heterogeneous mixture was added by DOWEX 50WX4 resin (500 mg, 2.0 mass equiv) and stirred for 3 days. Afterward DOWEX was removed by filtration, followed by evaporation of reaction solvent. The obtained white solid was dried under vacuum to remove traces of MeOH (210 mg, 86%). The crude product (60 mg, 0.3 mmol) was dissolved in a mixture of pyridine (0.5 mL) and Ac_2O (0.5 mL) followed by addition of a catalytic amount of DMAP. The reaction was stirred overnight, and then the solution was diluted with ethyl acetate and washed with 1 M HCl (50 mL), a saturated $NaHCO_3$ solution (2 × 50 mL), water (50 mL), and brine (50 mL). The organic phase was dried over anhydrous $MgSO_4$, and solvent was removed by evaporation under reduced pressure. The product was purified by column chromatography on silica gel with DCM−MTBE−hexane (5:1:2). Yellow oil (103 mg, 82%) mixture of isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.73 (d, J = 7.0 Hz, 0.5H), 5.60 (d, J = 2.5 Hz, 1H), 5.50−5.37 (m, 4H), 5.09 (dd, J = 4.8, 2.5 Hz, 1H), 4.50−4.39 (m, 2H), 4.34−4.25 (m, 2H), 4.04 (dd, J = 13.4, 1.5 Hz, 1H), 3.91 (dd, J = 13.3, 1.2 Hz, 1H), 3.80 (s, 4H), 3.78 (s, 3H), 2.22 (s, 3H), 2.18 (s, 3H), 2.17 (s, 1H), 2.14 (s, 3H), 2.13 (s, 4H), 2.10 (s, 4H), 2.09 (s, 1H), 2.08 (s, 6H), 2.02 (s, 3H) (ppm); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 170.6, 170.5, 170.2, 170.1, 170.0, 169.8, 169.4, 168.9, 168.7, 168.5, 168.3, 165.8, 165.0, 164.9, 104.2, 99.6, 96.2, 82.6, 80.8, 80.0, 76.5, 76.0, 74.6, 67.9, 67.6, 66.8, 63.7, 62.8, 53.7, 53.7, 53.7, 53.3, 53.2, 21.1, 20.9, 20.9, 20.8, 20.7, 20.6, 20.6 (ppm); IR (ATR) ν 2957, 1750, 1437, 1372, 1218, 1125, 1064, 603 (cm^{-1}); HRMS (ESI) [M + Na^+] calcd for $C_{15}H_{20}O_{11}$ 399.0903, found 399.0919.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01068.

^{1}H and ^{13}C NMR for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jacek.mlynarski@gmail.com; www.jacekmlynarski.pl.

Notes

The authors declare no competing financial interest.

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