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# Chemistry of Pyruvate Enolates: *anti*-Selective Direct Aldol Reactions of Pyruvate Ester with Sugar Aldehydes Promoted by a Dinuclear Zinc Catalyst

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**Abstract:** A chiral dinuclear zinc complex can effectively catalyse the direct aldol reactions of pyruvic acid ester with various chiral sugar aldehydes, thus functionally mimicking the pyruvate-dependent type II aldolases. Application of sterically hindered aryl esters allows for the elusive aldol reaction of the pyruvate donor with controlled *anti*-selectivity *en route* to the short and efficient synthesis of 3-deoxy-2-ulosonic acids. Pyruvic acid ester is here used as a chemical equivalent of phosphoenol pyruvate (PEP) in imitation of the synthetic principle used in nature. The presented biomimetic methodologies use enol formation for the highly efficient and flexible formation of various $C_6$–$C_9$ ulosonic acids. Particularly, efficient and concise syntheses of 3-deoxy-D-*erythro*-hex-2-ulosonic acid (KDG, overall 50% yield), 3-deoxy-D-*ribo*-hept-2-ulosonic acid (DRH, overall 53% yield) and 3-deoxy-D-*glycero*-D-*talo*-non-2-ulosonic acid (4-*epi*-KDN, overall 78% yield) are described. This direct efficient application of pyruvic esters does not require additional demasking steps and thus surpassess previously methodologies utilising masked pyruvic synthons such 2-acetylthiazole and pyruvic aldehyde dimethyl acetal.

**Keywords:** aldol reaction; asymmetric synthesis; pyruvate esters; ulosonic acids; zinc catalysts

## Introduction

Asymmetric aldol reactions of biologically relevant substrates are of exceptional importance due to their usefulness in the synthesis of natural products and drugs in a way closely related to enzyme-promoted biotransformations.[1] Among known variants of asymmetric C–C bond forming reactions,[2] the pyruvate-dependent aldol reaction is particularly important for many life processes where pyruvic acid is used as a key $C_3$ donor unit.[3] Phosphoenol pyruvate (PEP), being the reactive form of pyruvic acid, is implicated as the intermediate in the biosynthesis of 3-deoxy-2-ketoaldonic acids (ulosonic acids) and sialic acids by way of the addition of PEP to aldoses.[4] Only enzymes – aldolases, which catalyse this reaction in nature, have recently been used to mimic the reaction between PEP and various aldehydes.[5]

Surprisingly, the enol form of pyruvic acid widely used as a nucleophile by nature has not been recognised as a suitable substrate in catalytic aldol reactions truly mimicking enzymatic transformations.[6] In general, our knowledge on catalytic asymmetric aldol reactions of puruvate acid and its derivatives remains restricted to a few examples despite the breakthroughs in many other fields of direct aldol reactions.[7] The first example of the direct use of a 1,2-dicarbonyl prenucleophile[8] was limited to the asymmetric homo-aldol reaction of ethyl pyruvate.[9] To achieve this goal, Jørgensen and co-workers, developed a chiral copper-bisoxazoline catalyst providing diethyl 2-hydroxy-2-methyl-4-oxoglutarate in high yield and 96% *ee* isolated as the more stable isotetronic acid. The authors postulated that the Cu-based chiral Lewis acid promotes both the formation of enol pyruvate and controls the stereochemistry of the reaction.[9] Interestingly, a similar homoaldol reaction of ethyl pyruvate leading to enantiomerically enriched isotetronic acid was observed by Dondoni under chiral pyrrolidine control, thus suggesting enamine-

based organocatalytic activation of the 1,2-dicarbonyl substrate.[10,11] On the other hand, the organocatalytic cross-aldol reaction of pyruvate ester has been limited to only one example of the highly active chloral hydrate. The proline-tetrazole catalyst presumably activates the ethyl pyruvate by formation of the corresponding enamine enhancing its reactivity to give the desired β-aldol in 55% yield and 86% *ee*.[12]

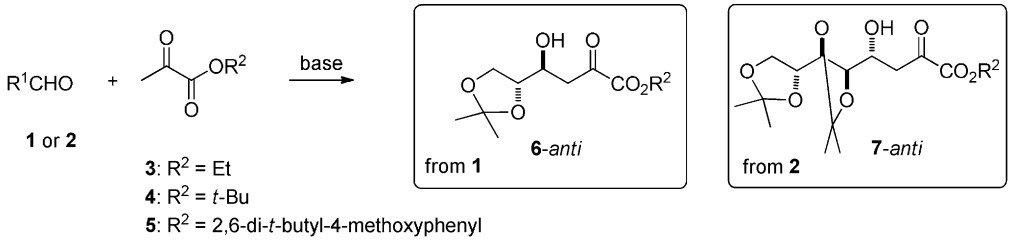
In spite of the presented efforts, the scope of the known pyruvate-dependent aldol methodologies is narrow and strictly limited to highly active non-enolisable aldehydes or self-condensation of pyruvate esters. Consequently there is a need for efficient catalysts for asymmetric cross-aldol reactions of pyruvate esters and aliphatic aldehydes, this being the realm of enzymes and thus remaining a challenging endeavour of great interest. Solving this problem would also constitute an excellent and biomimetic attempt to achieve the formation of 3-deoxy-2-ulosonic acids and sialic acids, which are essential sugar units for many biological processes and transformations.[4] In this paper we report that chiral zinc complexes can act as a pyruvate-dependent aldolase, i.e., a type II aldolase, to catalyse the direct asymmetric aldol reaction of pyruvate esters with chiral aldehyde electrophiles. It is important to mention that the direct catalytic aldol reaction of pyruvic esters with chiral aldehydes has not been reported so far.

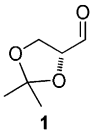
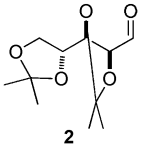
## Results and Discussion

Previously we showed that pyruvic derivatives such as dimethyl acetals or thiazole rings can be used as chemical equivalents of pyruvic esters in the metal enolate-based catalytic reaction with chiral aldehydes *en route* to ulosonic acid precursors.[13] Unfortunately, the elusive direct activation of pyruvate ethyl or methyl esters by using broad range of metal-based catalysts was unsuccessful.[6] Therefore, general methods for the generation of a metal enolate of pyruvic ester were explored to find the optimal conditions whereby a stereoselective aldol reaction between an enolate and a chiral glyceraldehyde could be performed.

As a starting point, a variety pyruvic esters was screened in the reaction with optically pure (*R*)-glyceraldehyde acetonide (**1**) to assess both reaction efficiency and stereoselectivity in the addition of lithium enolates controlled by a chiral aldehyde. Attempts to perform an aldol reaction by metallation of esters **3**–**5** with a solution of lithium *tert*-butoxide at −78 °C in THF and then introducing aldehyde (**1**) revealed that only the application of 2,6-di-*tert*-butyl-4-methoxyphenyl pyruvate (**5**) resulted in formation of the desired aldols, albeit in low yields (Table 1). Only aryl ester **5** was identified as a workable aldol donor due to steric hindrance preventing self-condensation of the corresponding enolate.[14] Under optimised conditions, *anti*-**6** and *syn*-configured aldols have been isolated in 28% overall yield (Table 1, entry 3). From the

**Table 1.** Aldol reactions of lithium enolates of pyruvic esters with sugar aldehydes.[a]

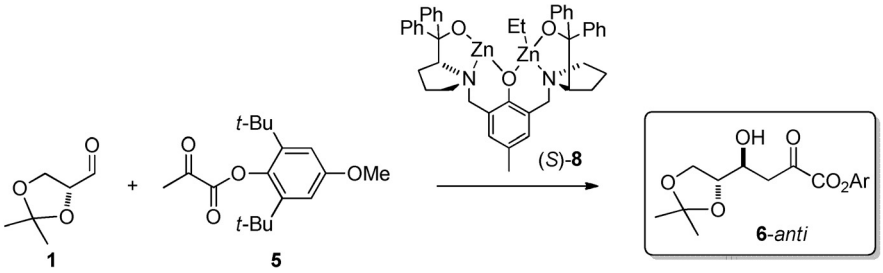



| Entry | Aldehyde | Pyruvate ester | Base | Yield [%] | *anti*/*syn*[b] |
|---|---|---|---|---|---|
| 1 |  | **3** | *t*-BuOLi | 0 | – |
| 2 | | **4** | *t*-BuOLi | 0 | – |
| 3 | | **5** | *t*-BuOLi | 28 | 1.5/1 |
| 4 | **1** | **5** | *t*-BuOLi, $ZnCl_2$[c] | 5 | 3/1 |
| 5 |  | **5** | *t*-BuOLi | 30 | 1/1 |
| 6 | **2** | **5** | *t*-BuOLi, $ZnCl_2$[c] | 8 | 4/1 |

[a] *Reaction conditions:* aldehyde (0.2 mmol), pyruvate ester (0.2 mmol), *t*-BuOLi (0.22 mmol, 110 mol%) in THF at −78 °C for 2 h and then 1 h at room temperature.
[b] Determined by $^1$H NMR spectroscopy.
[c] Reactions were performed with $ZnCl_2$ (0.22 mmol, 110 mol%).

**Table 2.** Direct aldol reaction of the pyruvic ester with protected (*R*)-glyceraldehyde.[a]




| Entry | Catalyst | Yield [%] | *anti/syn*[b] |
|---|---|---|---|
| 1 | (*R*)-**8** (5 mol%) | 62 | 8/1 |
| 2 | (*S*)-**8** (5 mol%) | 62 | 3/1 |

[a] Reactions were performed with **1** (0.1 mmol), **5** (0.1 mmol), catalyst **8** (5 mol%) in THF at room temperature for 12 h.
[b] Determined by $^1$H NMR spectroscopy.

chiral aldols, the corresponding *anti*-aldol **6** was obtained as a major isomer, albeit with poor diastereoselectivity (1.5:1). This result was consistent with a reaction *via* a non-chelation-controlled transition state matching the Felkin–Anh model for an asymmetric addition to chiral aldehydes,[15] however the observed diastereoselectivity was simply disappointing.

Similar *anti*-selectivity was previously reported for the addition of various ketone enolates to α-alkoxy aldehydes[16] including glyceraldehyde acetonide,[17] while stereoselective additions of the lithium enolate of pyruvic acid esters have not been previously documented, surprisingly. It is likely that the lithium ion coordinates to both carbonyl groups in pyruvate acid ester instead of the formyl oxygen in the aldehyde. Reactions promoted by LDA were unsuccessful. Application of the above reaction sequence to the aldol reaction of D-arabinose **2** and pyruvic ester **5** resulted in the unselective formation of *anti*- and *syn*-aldols (Table 1, entry 5) suggesting that a stereoselective addition of lithium enolates to chiral aldehydes could not be directly predicted by using the Felkin–Anh model. Surprisingly worse results in terms of yield were obtained when an attempt was made to prepare the corresponding zinc enolate, but the observed higher diastereoselectivity was noteworthy in both cases and encouraged a search for Zn-based catalysts (Table 1, entries 4 and 6).

Consequently, we turned our attention to metal-promoted processes by using catalysts capable of simultaneous activation of the donor and acceptor aldehyde in a chiral environment thus possibly improving the expected stereoselectivity. These catalysts can be compared mechanistically to the type II aldolases, which employ zinc ion to form an active enolate.[18] After many trials, we found Zn-(*R*)-ProPhenol **8**[19] to be the catalyst of choice for the enolisation of pyruvic acid ester **5**. Again, employing the bulky 2,6-di-*tert*-butyl-4-methoxyphenyl ester to avoid self-condensation of the ketone was decisive (Table 2).

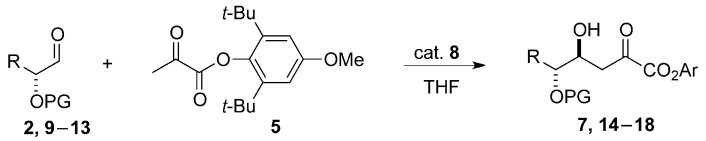
Finally, after careful tuning of solvent and temperature, the reaction of ester **5** with (*R*)-glyceraldehyde acetonide **1** promoted by only 5 mol% of (*R*)-ProPhenol catalyst **8** resulted in a clean and efficient formation of the desired cross-aldol products with a very good level of diastereoselectivity, favouring *anti* isomer **6** (Table 2, entry 1). Application of the (*S*)-configured catalysts resulted in the loss of stereoselectivity, apparently as a result of the formation of a mismatched pair between chiral catalyst and optically pure aldehyde (Table 2, entry 2).

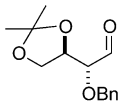
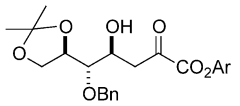
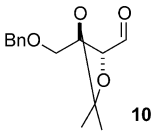
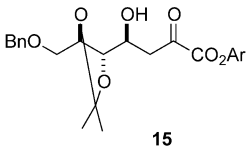
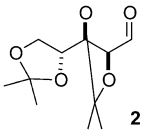
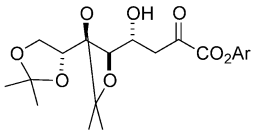
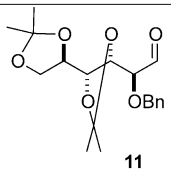
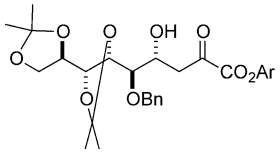
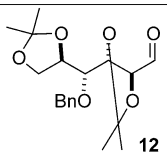
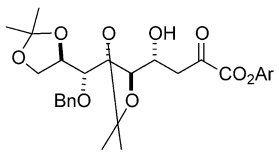
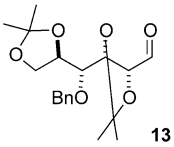
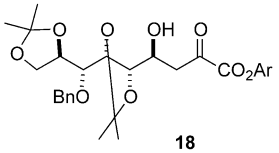
The *anti*-configured aldol **6** obtained from (*R*)-glyceraldehyde acetonide and pyruvic acid ester possess the configuration of natural 3-deoxy-D-*erythro*-hex-2-ulosonic acid (2-keto-3-deoxy-D-glucosonic acid, KDG).[20] Thus, the elaborated efficient $C_3+C_3$ strategy seems to be closely related to the biosynthesis of natural sugar by using ester **5** as a chemical equivalent of PEP (phosphoenol pyruvate). The observed high *anti*-stereoselectivity encouraged us to study the further transformation of the protected aldol into a natural sugar in hemiketal form, which will be described in the next part of the manuscript.

This methodology was successfully applied with various protected aldehydes derived from D-erythrose (**9**, **10**), D-arabinose (**2**), and D-hexoses (**11**-**13**) (Table 3). To our delight, the previously observed principle of *anti*-selectivity was maintained also for the reaction of protected D-erythrose (**9**). The corresponding *anti*-aldol **14** was formed as the major product by using optimal 20 mol% of (*R*)-configured catalyst **8** (Table 3, entry 2). The observed diastereoselectivity (7:1) could be improved by using a lower amount of the catalyst albeit at the expense of overall yield (entries 3 and 4). Interestingly, application of (*S*)-configured catalyst **8** resulted also in the selective formation

**Table 3.** Direct aldol reaction of the pyruvic ester with protected D-erythrose, D-arabinose, and D-hexoses.




| | Aldehyde | Aldol | Catalyst | Yield [%] | *anti/syn*[b] |
|---|---|---|---|---|---|
| 1<br>2<br>3<br>4 |  **9** |  **14** | (*S*)-**8** (20 mol%)<br>(*R*)-**8** (20 mol%)<br>(*R*)-**8** (10 mol%)<br>(*R*)-**8** (5 mol%) | 35<br>71<br>43<br>24 | 6/1<br>7/1<br>10/1<br>10/1 |
| 5<br>6 |  **10** |  **15** | (*S*)-**8** (20 mol%)<br>(*R*)-**8** (20 mol%) | 46<br>55 | 2/1<br>3/1 |
| 7<br>8 |  **2** |  **7** | (*S*)-**8** (20 mol%)<br>(*R*)-**8** (20 mol%) | 64<br>72 | 2/1<br>1/1 |
| 9<br>10 |  **11** |  **16** | (*S*)-**8** (20 mol%)<br>(*R*)-**8** (20 mol%) | 31<br>70 | 6/1<br>6/1 |
| 11<br>12 |  **12** |  **17** | (*S*)-**8** (20 mol%)<br>(*R*)-**8** (20 mol%) | 79<br>76 | only *anti*<br>only *anti* |
| 13<br>14 |  **13** |  **18** | (*S*)-**8** (20 mol%)<br>(*R*)-**8** (20 mol%) | 83<br>80 | 2/1<br>4/1 |

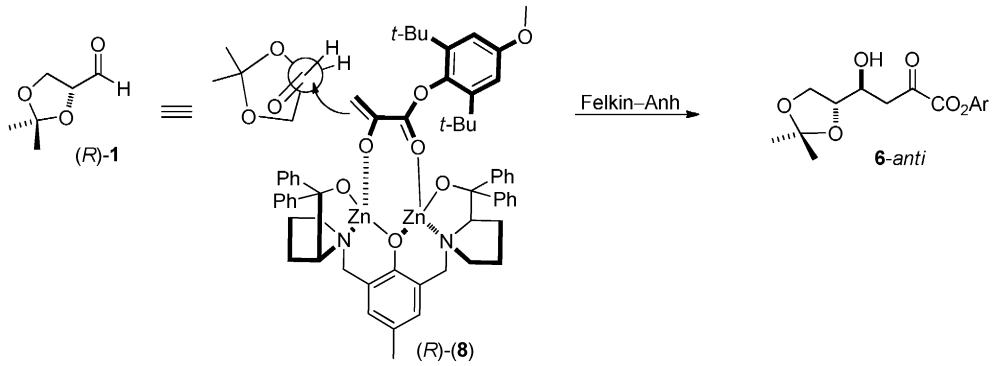
[a] *Reaction conditions:* aldehyde (0.1 mmol), **5** (0.2 mmol), aldehyde concentration 0.1 mmol mL$^{-1}$. Performed in dry THF, at −25 °C for 4 days.

[b] Determined by $^{1}$H NMR spectroscopy.

of the *anti*-aldol with inferior yield (Table 3, entry 1). This suggests that both features: chirality of zinc enolate (from catalyst) and Felkin–Anh principles (chiral aldehyde) play pivotal roles in controlling the sense of asymmetric induction.

Further analysis of the kind of protection groups used in the aldehyde revealed that substrate conformation plays an additional role in controlling stereoselectivity. Thus, application of more sterically rigid 2,3-*O*-isopropylidene derivative of the same D-eryth-




**Scheme 1.** Stereochemical rationalisation.

rose sugar **10** led to lower selectivity when compared to the more flexible 2-*O*-Bn isomer **9** (Table 3, entry 2 *vs.* entry 6).

Surprisingly, the reaction of D-arabinose diacetonide **2** was far less selective when compared to the above mentioned examples by using either (*R*)- or (*S*)-ProPhenol (Table 3, entries 7 and 8). Such an unselective formation of both aldols was similar to the reaction operating under Felkin–Anh control (Table 1). However, protected D-mannose **11** with the same configuration at C-2 exhibits a much higher *anti*-selectivity when promoted by (*R*)-catalyst (Table 3, entry 10). This time, switching to rigid isomer **12** improved yield and selectivity regardless of the catalyst antipode used (entries 11 and 12). Obtained as a sole isomer, *anti*-aldol **17** with the D-*glycero*-D-*talo*-configuration is a valuable C-4 epimer of natural 3-deoxy-D-*glycero*-D-*galacto*-non-2-ulosonic acid (KDN). In regards to the D-glucose, the use of a 2,3-*O*-isopropylidene derivative **13** along with the (*R*)-ProPhenol led to the best results in terms of yield and *anti*-selectivity (Table 3, entry 14).

Based on a previously described observation and the only slight influence of the chirality of the catalyst on the reaction stereoselectivity, we propose that the stereochemical outcome of these reactions can be rationalized by a dinuclear model in which zinc-ProPhenol catalyst is complexing the enol from pyruvic ester (**5**). The thus formed zinc-enolate attacks the chiral aldehyde according to Felkin–Anh principles (Scheme 1) resulting in *anti*-aldol **6**. Coordination of the aldehyde to the zinc atom is more speculative although it cannot be excluded. Combining chiral catalyst and chiral aldehydes with more than one stereogenic centre resulted in the formation of aldols in a less predictable way when compared to the classical addition of non-chiral enolates to chiral aldehydes, however. Nevertheless, such a scenario explains the predominant formation of *anti*-aldols in spite of the configuration of stereogenic centre in the α-position to the carbonyl group in the chiral aldehyde.

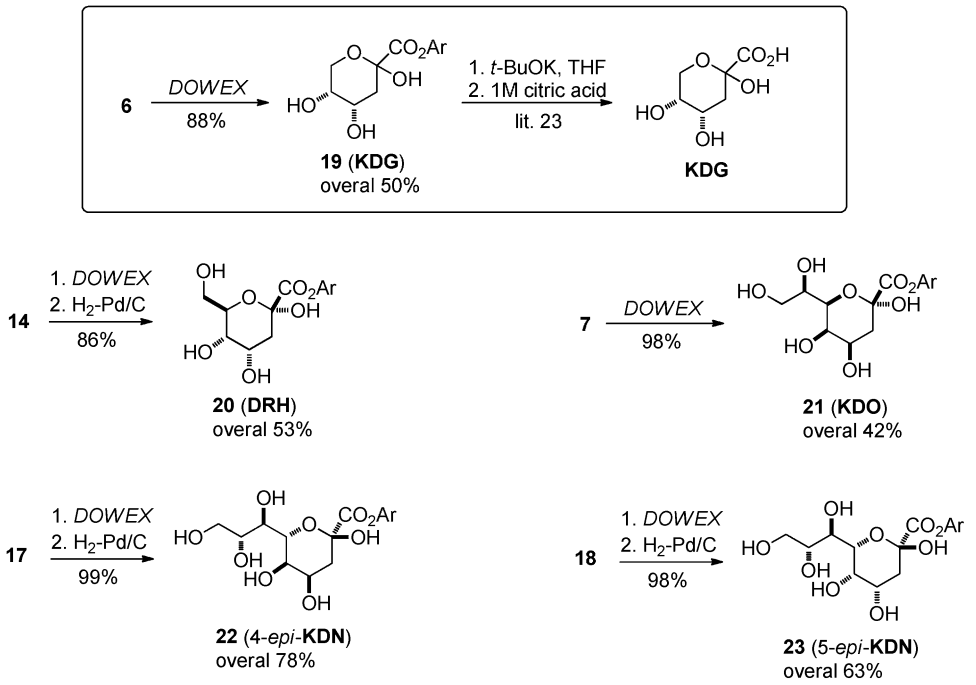
As was mentioned above, all obtained aldols could serve as intermediates in the synthesis of cyclic 3-deoxy-2-keto acids (ulosonic acids) *via* deprotection and hemiketalisation. In recent years, a number of chemical and enzymatic methodologies have been reported for the synthesis of sialic and ulosonic acids[21] but our attempt seems to be so far the simplest and closely related to the enzymatic pathway. In contrast to previously presented flexible synthesis of ulosonic acids utilising masked pyruvate synthons (i.e., 2-acetylthiazole, pyruvic aldehyde dimethyl acetal) this attempt uses only a stoichiometric amount of promoter and does not require tedious demasking of the thiazole ring.[22] To end-up the synthesis of ulosonic acid by using the thus elaborated efficient attempt, we carried out the necessary deprotections as depicted at Scheme 2.

Obviously the most valuable achievement is the direct stereoselective synthesis of protected 3-deoxy-D-*erythro*-hex-2-ulosonic acid KDG (**6**). *anti*-Configured linear aldol **6** possesses the configuration of natural KDG and can be easily transformed into this biomolecule. To end-up this $C_3+C_3$ protocol, *anti*-aldol **6** was easily deprotected when treated with an acidic ion-exchange resin (DOWEX) in methanol to give the mixture of cyclic forms of the KDG ester **19** (Scheme 2). For the reason of clarity the stereochemistry of this molecule was established by $^1$H NMR analysis of the cyclic furanose and pyranose forms of the ester.[20] Hydrolysis of the used aryl ester could be achieved by treatment of **19** with potassium *tert*-butoxide in THF at −30 °C, according to the Enders procedure.[23] It is noteworthy that KDG ester was achieved by using this concise two-step protocol in 50% overall yield, starting from protected glyceraldehyde (**1**).

*anti*-Aldol **14** prepared from D-erythrose could be transformed into unnatural 3-deoxy-D-*ribo*-hept-2-ulosonic acid ester (**20**, DRH, 4-*epi*-DAH)[24] with remarkable 53% overall yield (Scheme 2).

Non-selective synthesis of aldol **7** from D-arabinose seems to be only one example of an inconvenient




**Scheme 2.** Synthesis of various ulosonic acid esters.

methodology *en route* to natural 3-deoxy-D-*manno*-oct-2-ulosonic acid (KDO). Nevertheless, major protected *anti*-aldol **7** was liberated to form the natural octulosonic acid ester **21** (KDO) with lower, 42% overall yield. Apparently, in this particular case the parallel organocatalytic protocol seems to be more promising when compared to the discussed metal-promoted aldol reaction.[6]

In contrast, a highly stereoselective $C_6+C_3$ strategy leading to a nine-carbon chain from mannose (**12**) delivered *anti*-aldol **17**, exclusively. This, in turn, was transformed into the ester of the rare higher sugar: 3-deoxy-D-*glycero*-D-*talo*-non-2-ulosonic acid (**22**, 4-*epi*-KDN) by removal of the isopropylidene and *O*-benzyl residues (Scheme 2). Isomeric 3-deoxy-D-*glycero*-D-*gulo*-non-2-ulosonic acid (5-*epi*-KDN) **23** was easily reached after cyclisation of *anti*-aldol **18**, prepared from glucose. Final examination of the NMR spectra of ulosonic acids in their pyranose/furanose cyclic forms provided the ultimate confirmation of the structures of all *anti*-aldol precursors.[20]

## Conclusions

In conclusion, we have shown that Zn-based ProPhenol complexes (Trost's catalysts) can initiate stable enol formation from hindered pyruvate esters which can be further trapped by electrophilic aldehydes. This is the first example of an efficient catalytic *anti*-selective direct aldol reaction of pyruvate esters with sugar aldehydes closely resembling the biomimetic synthesis of ulosonic acids. Thus, a new synthetic route from protected acyclic optically pure aldehydes to cyclic ulosonic acid esters having six, seven, eight, and nine carbon atoms has been opened up. Based on this principle, we have provided practical protocols for the stereoselective synthesis of several six-, seven-, eight-, and nine-carbon 3-deoxy-2-ulosonic acids including the relevant 3-deoxy-D-*erythro*-hex-2-ulosonic acid (KDG, overall 50% yield), 3-deoxy-D-*ribo*-hept-2-ulosonic acid (DRH, overall 53% yield) and 3-deoxy-D-*glycero*-D-*talo*-non-2-ulosonic acid (4-*epi*-KDN, overall 78% yield) in their pyranose/furanose forms. This direct efficient application of pyruvic esters does not require additional demasking steps and thus surpasses previously methodologies utilising masked pyruvic synthons.

## Experimental Section

### Representative Procedure for Direct Aldol Reaction of the Pyruvic Ester 5 with Protected Sugar Aldehydes

Commercial Trost ProPhenol ligand (12.8 mg, 0.02 mmol) was dissolved in dry THF (0.5 mL) at room temperature under an argon atmosphere and treated with a solution of diethylzinc (1 M in hexane, 0.04 mL, 0.04 mmol). The reaction mixture was stirred for 30 min to give 0.02 mmol of the catalyst **8**. The thus prepared catalyst was added to a solution of aldehyde (0.1 mmol) and aryl pyruvate **5** in 0.5 mL of THF at −25 °C under an argon atmosphere. The reaction mixture was stirred for 4 days at −25 °C, then quenched by

saturated ammonium chloride, extracted with ethyl acetate, dried with sodium sulphate and evaporated. The crude product was purified on silica gel by column chromatography using hexane-ethyl acetate (4:1 or 9:1) as eluent to afford the desired *anti*-aldols. Isomeric *syn*-aldols have been isolated only in the case of more yielding and less selective reactions.

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