Proline organocatalysis as a new tool for the asymmetric synthesis of ulosonic acid precursors†

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PEP and aldolase mimicry is the key for a direct organocatalytic entry to precursors of ulosonic acids, biomolecules of enormous importance in biology, chemistry and medicine; in the key aldol reaction the dimethylacetal of pyruvic aldehyde is used as phosphoenolpyruvate (PEP) equivalent and the amino acid proline functions as an organocatalyst, imitating the enzyme.

The forthcoming advent of a post-antibiotic era has driven much research towards developing new tools to fight the emergence of devastating diseases and has prompted much effort to identify the biological functions of carbohydrates in physiological processes.[1] Naturally occurring 2-keto-3-deoxy-nonulosonic acids such as Neu5Ac (**1**) and KDN (**2**), generally known as sialic acids, have been significantly implicated in the pathogenesis of microorganisms and various disease states.[2,3] Likewise, pivotal biological roles are constantly ascribed to widely diffuse higher 3-deoxy-2-ulosonic acids.[4] For example, 3-deoxy-D-*manno*-2-octulosonic acid (KDO, **3**), present in the outer membrane lipopolysaccharide (LPS) of Gram-negative bacteria, is essential for their replication.[2,5] The 7-phosphate of the 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH, **4**) is a key intermediate in the biosynthesis of aromatic amino acids *via* the shikimate pathway.[6] The phosphorylated form of 2-keto-3-deoxy-D-glucosonic acid (D-KDG, **5**) is part of the Entner–Doudoroff pathway[7] (Fig. 1).

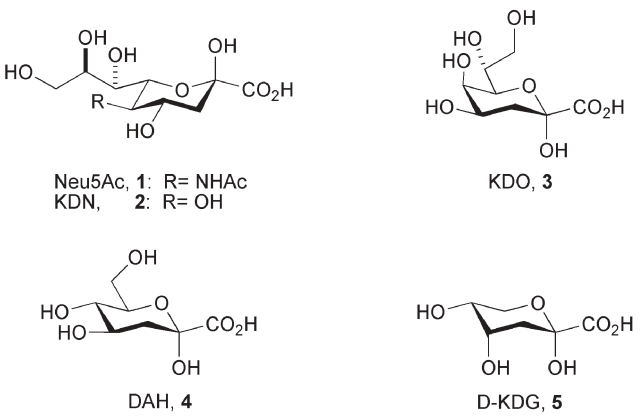

Fig. 1 Sialic and ulosonic acids.

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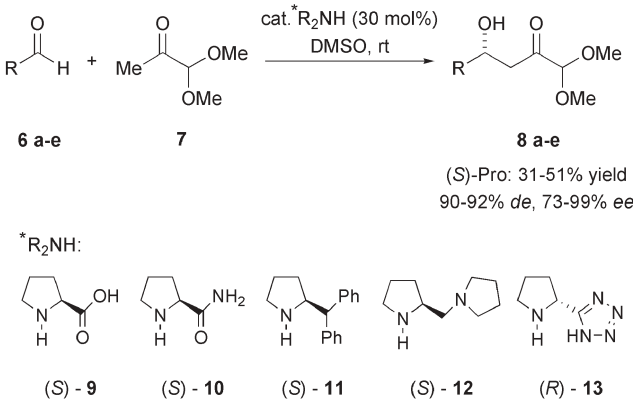
Over recent years a number of useful chemical and enzymatic methodologies have been reported and implemented to develop efficient syntheses of sialic and ulosonic acids[8,9] as well as of certain analogues.[10,11] However, in enzyme-catalyzed reactions the loss of stereocontrol regarding the substrate scope is often a problem[12] and the total synthesis approaches have suffered from long reaction sequences[13] due to protecting group manipulations. Consequently the need for short and practical synthetic routes remained a challenging endeavour of great interest, as proved by the most recent achievements.[14]

Previous efforts from our laboratories led to structurally modified deoxygenated ulosonic acids *via* metalated SAMP-/RAMP-hydrazones as efficient chiral equivalents of phosphoenol pyruvate (PEP).[15] This strategy resembled the natural biosynthetic pathway, whereby PEP undergoes C–C linkage to aldehydes by means of class I aldolase catalysed reactions. Recently we have been utilizing an organocatalytic approach towards the asymmetric synthesis of various carbohydrates and amino sugars as well as phytosphingosines and polyoxamic acid starting from 2,2-dimethyl-1,3-dioxan-5-one as dihydroxyacetone equivalent.[16] Pursuing these biomimetic routes, we herein report the first results of our investigations towards the asymmetric organocatalytic synthesis of sialic and ulosonic acids that led us to obtain a direct precursor of D-KDG (**5**) as well as advanced intermediates of KDO (**3**) and analogues. In our biomimetic approach we chose the pyruvic aldehyde dimethyl acetal **7** as masked pyruvic acid in aldol reactions with various aldehydes **6** (Scheme 1).

Since a number of amine-catalytic systems gave different results[17] with respect to the employed substrates, we initially tested the enantiopure pyrrolidine derivatives **9–13** (30 mol%) in the reaction of **7** with 2-methyl propanal (**5a**, R = *i*Pr) as a model



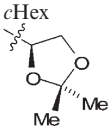
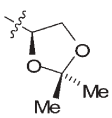
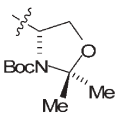
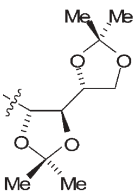
Scheme 1 Organocatalysed aldol reactions of the pyruvic aldehyde dimethyl acetal **7** with aldehydes **6**.

carbonyl component by performing the reaction in DMSO. In contrast with the results reported by Barbas *et al.*,[17a] the amine **12** did not yield the aldol product **8** in spite of the presence of CF_3CO_2H as additive. Likewise, the catalysts **10–11** predominantly afforded the corresponding aldol condensation product, which was always present in the tested reactions. Independent experiments performed by treating the aldol **8a** with each catalyst did not yield any of the corresponding dehydration compound, which is probably due to a Mannich-reaction-elimination sequence as also observed by List *et al.*[18] The best results were observed in the reactions with (*S*)-proline (**9**) and the tetrazole **13**[17e] affording the aldol **8a** in reasonable yield (51–53%) and good enantioselectivity (73–75% ee; Table 1).‡

As both catalysts produced comparable results, the optimisation of the reaction was performed with the much less expensive and proteinogenic amino acid proline. While screening diverse solvents of varying polarity failed to improve either the yield or the enantiomeric excess, cooling the reaction mixture to 4 °C and using an excess of **7** revealed that the aldol **8a** was obtained with a considerably higher enantioselectivity (93% ee). However, the Mannich-elimination side reaction could not be avoided, as well as the formation of the acetal self-aldolization product, which should lead to a decreasing efficiency of the catalyst towards the desired pathway.

Afterwards the developed conditions were evaluated using the α-branched aldehydes **6b–e** as carbonyl components. In spite of the modest yields, in all cases the expected aldol product was obtained

Table 1 (*S*)-Proline-catalyzed asymmetric aldol reaction of **7** with aldehydes **6** to afford **8**

8	R	Temp/°C	Time/ days	Yield (%)[a]	de (%)[b]	ee (%)
a	*i*Pr	rt	6	51	—	73[b]
a	*i*Pr	rt	6	53	—	75[b,c]
a	*i*Pr	4	8	48	—	93[b]
b	*c*Hex	4	10	37	—	85[b]
c		4	5	38	91	⩾99[d]
c[e]		4	5	45	90	⩾99[d]
d		4	7	31	90	⩾99[f]
e		4	9	35	92	⩾99[g]

[a] Yields of **8** isolated by flash chromatography on silica gel. [b] Determined by HPLC on chiral stationary phases (Chiralpak AD, Chiralpack IA 5 μ, Daicel IA, Daicel OJ, Whelk 01). [c] Tetrazole (*R*)-**13** was used as catalyst. [d] Based on the ee value of **6c**. [e] (*R*)-Proline was used as catalyst. [f] Based on the ee value of **6d**. [g] Based on the ee value of **6e**.

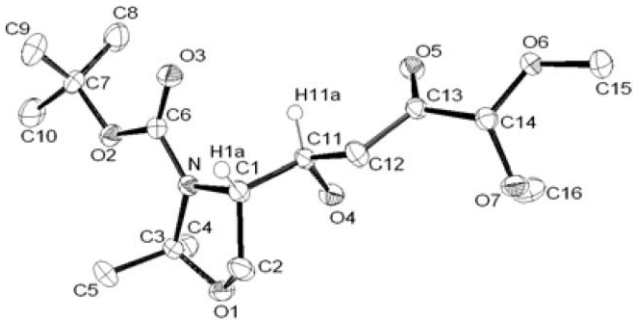


Fig. 2 X-Ray crystal structure of (*R*,*S*)-**8d**. Relative stereochemistry of the molecule is C1–(*S*), C11–(*R*). Certain hydrogen atoms have been omitted for clarity.

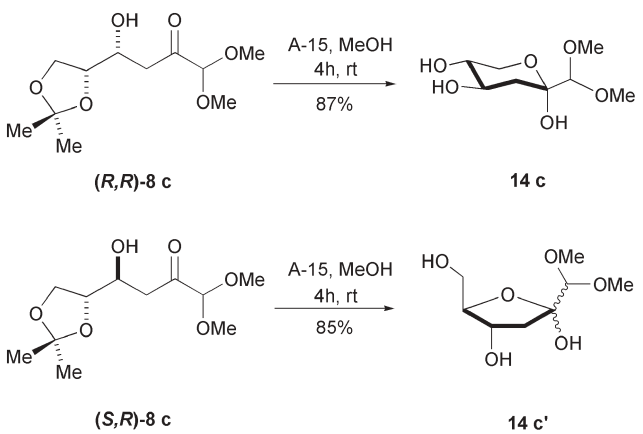
in very good diastereomeric excess (Table 1) with an increase in the reaction rate when aldehydes bearing a heteroatom in the β position were employed. As noted in our previous report, (*S*)-proline proved to be the most suitable catalyst when (*S*)-configured aldehydes (**6d,e**) were used, whilst with (*R*)-configured 2,3-*O*-(isopropylidene)-D-glyceraldehyde (**6c**) (*R*)-proline afforded the best results in terms of yield.

The given stereochemical assignments are based on the X-ray crystal structure analysis of the aldol product (*R,S*)-**8d** (Fig. 2),§ which proved an (*R*)-configuration at the newly formed stereogenic centre, and are confirmed by a polarimetric comparison with independently synthesized aldol products **8c**.[19]

The observed *R* configuration is in agreement with the transition state model for the proline-catalyzed aldol reaction.[20] The epimeric aldol products (*R,R*)-**8c** and (*S,R*)-**8c** were easily deprotected with an acidic ionic-exchange resin (Amberlyst® 15) to give the hemiketals **14** (Scheme 2).

Upon acidic treatment (*R,R*)-**8c** afforded only the pyranose form **14c** as a single anomer, which could be straightforwardly converted into the 4-*epi*-KDG. In contrast, the aldol (*S,R*)-**8c** provided only the furanose ring **14c′** in both possible anomeric forms (α : β, 1 : 1), whose stereogenic centres C(4) and C(5) have the correct configurations to make it a direct precursor of 2-keto-3-deoxy-D-glucosonic acid (D-KDG, **5**).

In conclusion, we have developed a direct entry to precursors of ulosonic and sialic acids by means of an organocatalytic approach closely resembling the natural pathway. Despite the modest yields,



Scheme 2 Deprotection of (*R,R*)-**8c** and (*S,R*)-**8c** to give **14c** and **14c′**.

the proline catalyzed aldol reaction might easily be scaled up to yield gram amounts of key intermediates for the synthesis of biologically challenging molecules. The high stereoselectivity of our protocol as well as the broad range of proline organocatalysis makes it suitable to a wide scope of substrates. Moreover, the availability of both enantiomeric forms of proline combined with the typically mild conditions and the exceedingly simple protocol avoid the use of protecting group manipulations and open a straightforward access for the synthesis of acid sugars.

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Notes and references

‡ Unless otherwise stated, all chemicals are commercially available and were used without further purification. All new compounds were fully characterized (IR, NMR, MS, elemental analysis, optical rotation). (*S*,*R*)-**8c**: To a suspension of (*R*)-proline (172.5 mg, 1.5 mmol, 30 mol%) in DMSO (2.0 mL) the pyruvic aldehyde dimethyl acetal **7** (2.95 g, 25 mmol) was added. The suspension was stirred at 4 °C for 2 h after which freshly distilled aldehyde **6c** (650 mg, 5 mmol) was slowly added. The mixture became completely clear within *ca.* 30 min. After 5 days at 4 °C (*R*)-proline precipitated, the reaction was quenched with sat. ammonium chloride solution (5 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated and purified by flash chromatography (silica gel, pentane : ethyl acetate, 6 : 4). The product (*S*,*R*)-**8c** (533.2 mg, 43%) was obtained as a colourless solid. Mp = 45 °C (Et_2O:pentane); $[\alpha]_D^{24}$ −19.5 (*c* 1.13 in $CHCl_3$); Found C, 53.0; H, 8.1. Calc. for: $C_{11}H_{20}O_6$: C, 53.2, H, 8.11; IR ($CHCl_3$): ν_{max}/cm^{-1} 3471, 2986, 2938, 2361, 2335, 1733, 1376, 1254, 1214, 1068, 852; ^1H NMR δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.30 (s, 3H, CCH_3), 1.36 (s, 3H, CCH_3), 2.69 (dd, 1H, COC*H*H, *J* 17.8 Hz, *J* 9.0 Hz), 2.92 (dd, 1H, COCH*H*, *J* 17.8 Hz, *J* 2.7 Hz), 3.03 (bs, 1H, OH), 3.44 (s, 6H, OCH_3), 3.93–4.05 (m, 2H, OCH_2), 4.04–4.12 (m, 2H, CH_2CHOH, $OCHCH_2O$), 4.45 (s, 1H, $CH(OCH_3)_2$; ^{13}C NMR δ_C (125 MHz; $CDCl_3$) 25.1 (CCH_3), 26.6 (CCH_3), 41.1 (CCH_2), 54.7 (OCH_3) 54.7(OCH_3), 66.5 (CH_2O), 68.3 (CCH_2CHO), 77.6 (OCH_2CHO), 103.7 ($CHOCH_3$), 109.3 ($C(CH_3)_2$), 205.4 (CO); *m*/*z* (CI, methane): 249 (M^+ + 1, 1), 231 (M^+ − 17, 100), 217 (M^+ − 31, 37), 185 (M^+ − 63, 78) 159 (M^+ − 89, 86).
§ Crystal data for (*R*,*S*)-**8d**: $C_{16}H_{29}NO_7$, *M* = 347.40 g mol^{-1}, monoclinic, space group *P*21, *a* = 10.7551(14) Å, *b* = 6.1499(5) Å, *c* = 13.849(3) Å, α = 90°, β = 96.077(10)°, γ = 90°, *V* = 910.8(2) $Å^3$, *Z* = 2, calculated density ρ = 1.267 mg m^{-3}, μ = 0.099 mm^{-1}, *F*(000) = 376, crystal size = 0.55 × 0.50 × 0.14 mm, *T* = 159(2) K, λ = 0.71073 Å. Total reflections collected 16581 ($1.90 < \theta < 33.52°$), 3651 unique [*R*(int) = 0.0301]. Final *R* indices [$I > 2\sigma(I)$]: R_1 = 0.0314, wR_2 = 0.0788; *R* indices (all data): R_1 = 0.0366, wR_2 = 0.0829. The structure was refined on F^2 value using program SHELXL-97. CCDC 617147. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b611265j

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