Organic & Biomolecular Chemistry

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DOI: 10.1039/C7OB02797D

Journal Name

ARTICLE

Total Synthesis of Pipecolic Acid and 1-*C*-Alkyl 1,5-Iminopentitol Derivatives by way of Stereoselective Aldol Reactions from (*S*)-Isoserinal

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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A short synthesis of iminosugars and pipecolic acid derivatives has been realized through aldol addition of a pyruvate, a range of ketones and (*S*)-isoserinal, followed by catalytic reductive intramolecular amination. The stereoselective aldol reaction was achieved successfully by using tertiary amines or di-zinc aldol catalysts, thus constituting two parallel routes to optically pure products with good yields and high diastereoselectivities. These carbohydrate analogues may be inhibitors of potent glycosidases and glycosyltransferases.

Introduction

Iminosugars refer to polyhydroxylated piperidines alkaloids, a group of synthetic and naturally occurring sugar derivatives in which the endocyclic oxygen is replaced by a nitrogen atom.[1] The lack of an acetal function in most iminosugar derivatives make them unable to undergo glycosidation reactions; instead of this, they act as transition state analogues of the glycosyl transfer process and manifest inhibitory activities against various glycosidases.[2] This feature has been exploited for the development of new antiviral and anticancer drugs as well as for the treatment of metabolic disorders such as type 1 Gaucher disease,[3] or type 2 diabetes mellitus.[4] Besides, iminosugars have been also investigated in agriculture to control insect and fungi population.[5] Among iminosugars, the group of hydroxylated pipecolic acids, which are non-proteinogenic α-amino acids often isolated from natural sources, display significant biological activity.[6] Hydroxypipecolic acids are useful scaffolds for the preparation of medicinally valuable compounds like the antibiotic tetrazomine,[7] the HIV-protease inhibitor palinavir[8] and antagonists of the cholecistokinin (CCK) hormone.[9] Owing to widespread presence of iminosugars in Nature and their significant medicinal potential, there is a strong demand for a practical route providing an easy access to the hydroxylated piperidine scaffold by asymmetric synthesis.[10] Most strategies, however, proceed through classical synthetic sequences starting from natural sugars, although enantioselective synthesis from non-sugar materials became also popular recently.[11] Enantiodivergent methods that result in optically pure iminosugars are thus especially interesting and could be of great advantage for the development of new glycosidase inhibitors as drugs as well as for the study of the iminosugars structure–bioactivity in interaction with glycosidases (SAR).[12] Despite its synthetic interest and potential, utilization of the direct catalytic aldol reaction in the realm of iminosugars has been limited to only few examples. What is more, an enzymatic approach for such aldol transformation was mainly investigated during last decades.[13] For example Class II aldolase activated aldol reaction of pyruvic acid has been exploited for the synthesis of pipecolic acid by Clapés et al quite recently.[14] A non-enzymatic protocol has been published by Majewski et al. for the synthesis of 1-deoxy-L-idonojirimycin (L-DIJ) and related iminoalditols through proline-catalysed *syn*-aldol reactions of protected dihydroxyacetone (DHA) and Cbz-protected (*S*)-isoserinal acetonide **11**; the latter compound is available from commercial L-malic acid in a short synthetic sequence.[15] More recently, we presented another example of application of **11** in *syn*-selective aldol reaction with hydroxyacetone **10** and 1-hydroxy-2-octanone **9** as enolate source and promoted by various amino acid-based catalysts.[16] As a part of our continuing effort towards the synthesis of natural products, we decided to investigate if a biomimetic approach which entails an organocatalytic or class II aldolase mimetic substrate activation could efficiently provide optically pure aldols which could serve as precursors of iminosugar skeletons. In this article we report the synthesis of pipecolic acid derivative **1**, iminosugars **3** and **4** by means of stereocontrolled aldol reaction between optically pure (*S*)-isoserinal acetonide **11** and appropriate hydroxyketones **8**–**10** or pyruvate **7** as a key step (Scheme 1).

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† Electronic supplementary information (ESI) available. Copies of NMR spectra (^{1}H and ^{13}C) for compounds **3**, **5**, **6a** and **19**. For ESI see DOI: 10.1039/x0xx00000x

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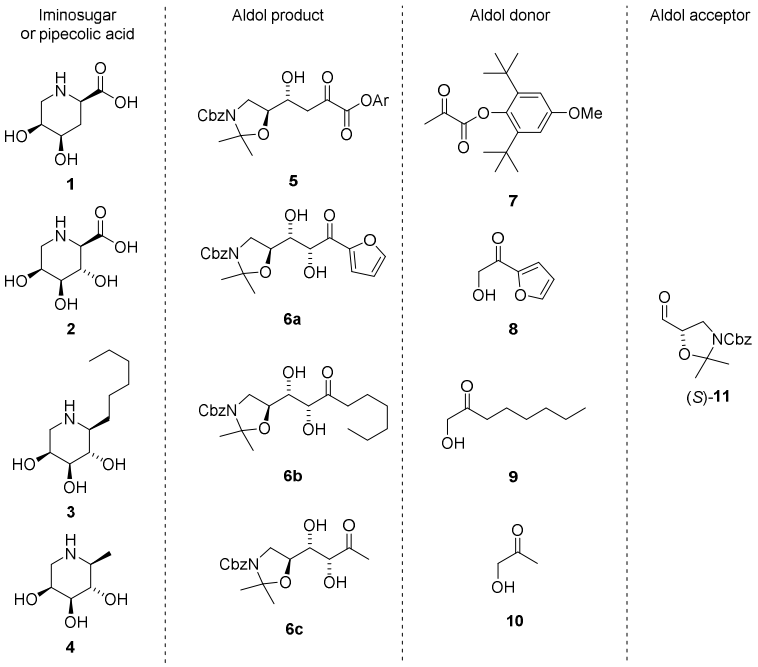

Scheme 1 General concept of de novo synthesis of selected iminosugars via aldol reactions of isoserinal (*S*)-**11**.

Result and discussion

In our previous work we have successfully employed proline-based catalysts for the enantioselective aldol reaction of aliphatic ketones **9** and **10** to afford aldol products **6b** and **6c** with yield up to 43%, 67% and diastereoselectivity *syn/anti* (3.4:1) and (8:1), respectively. However, we were unable to activate by this method aromatic ketones like 2-hydroxy-acetophenone.[16] In an attempt to activate more demanding substrates such as aromatic ketones or pyruvates and further increase the yield and selectivity of the aldol reaction, we assessed various types of non-amino acid catalysts. Easley accessible optically pure tertiary amines: *Cinchona* alkaloids **12–16** were selected as first choice catalysts for efficient and selective aldol reaction of (*S*)-**11.** In our previous works *Cinchona* alkaloids have been exploited for the promotion of aldol reaction of aromatic ketones[17] and sterically hindered pyruvates[18] with various aldehydes. According to our published data we screened various *Cinchona* alkaloids in the reaction of optically pure (*S*)-**11** and pyruvate **7** to access both efficiency and stereoselectivity (Table 1, entry 1–6). Starting from the previously developed conditions[19] we found that pseudoenantiomeric pairs of *Cinchona* alkaloids showed a match/mismatch effect toward the chiral aldehyde (*S*)-**11**. A slightly higher yield and stereoselectivity in favour of the *anti*-isomer **5** was obtained by applying alkaloids with the stereochemistry of **12** and **15** (Table 1 entry 1, 4) in comparison to their pseudoenantiomers **13** and **14** which afforded nonselective mixture of diastereomers (Table 1, entry 2, 3). Alkaloids with phenol group **16** and **17** did not match to this general observation due to their weak solubility in chloroform (Table 1, entry 5, 6). Catalyst **17** stay undissolved during the whole reaction time, so obtained results cannot be compared with others. Interestingly, achiral tertiary amines were found to be inefficient in activation of this transformation and resulted in very low yield and selectivity (Table 1, entry 7, 8). Notably, the presence of 20 mol-% tertiary amine at room temperature was necessary to reach acceptable conversions in reasonable times wherein MTBE was the solvent of choice (Table 1, entry 9–13). After careful tuning of reaction conditions, catalyst **15** provided the desired *anti*-**5** product in 50% yield and a diastereoselectivity *syn/anti* ratio (1:7.5) (Table 1, entry 9). Next our target was shifted to an alternative route utilizing chiral zinc complexes as mimetics of Class II aldolases, wherein bimetal-catalyst activate both substrates donor and aldehyde in a chiral environment.[20] We chose the Zn/ProPhenol complex **18** developed by Trost which is an excellent catalytic system for an array of enantioselective aldol reactions.[21] In this approach, both enantiomers of complex **18** were investigated: they displayed a match/mismatch effect with respect to chiral aldehyde (*S*)-**11** similar to the *Cinchona* alkaloids. We were glad to observe that the reaction between **7** and (*S*)-**11** promoted by (*S*,*S*)-**18** catalyst proceeded smoothly and provided the aldol product in 40% yield with a selectivity comparable to that obtained for **15**, favouring the *anti*-product in a (1:7) ratio (Table 1, entry 14). It is noteworthy that the (*R*,*R*)-enantiomer afforded nearly the same yield (43%), but with a very low diastereoselectivity *syn/anti* (1:1.3) (Table 1, entry 15). Solvent switch from THF to Toluene intermit the side reaction of pyruvate **7** self-

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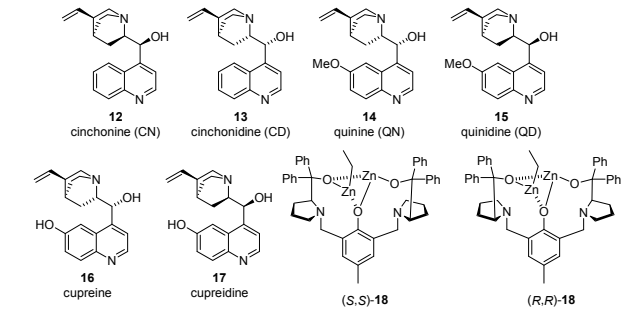
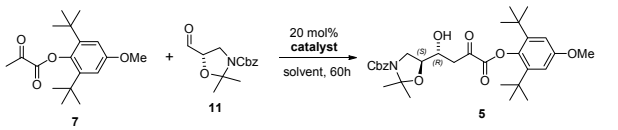
condensation a main source of impurities and side products, but result with significant selectivity decrease (Table 1, entry 16). Presence of triphenylphosphine sulphide, a typical additive used together with ProPhenol catalyst **18**[20] was beneficial for the selective product formation in Toluene which manifested also in an increase of the yield up to 56% (Table 1, entry 17).

Table 1. Catalyst screening for the aldol reactions of pyruvic ester **7** and isoserinal (*S*)-**11**.





entry	catalyst	solvent	yield (%)[a]	*syn*/*anti*[b]
1[c]	**12**(CN)	$CHCl_3$	27	1/4
2[c]	**13**(CD)	$CHCl_3$	20	1/2.6
3[c]	**14**(QN)	$CHCl_3$	23	1/1
4[c]	**15**(QD)	$CHCl_3$	30	1/7
5[c]	**16**	$CHCl_3$	16	1/7
6[c]	**17**	$CHCl_3$	7	1/1.5
7[c]	Quinuclidine	$CHCl_3$	24	1/2.4
8[c]	DBU	$CHCl_3$	6	1/1.5
9[c]	**15**	MTBE	50	1/7.5
10[c]	**15**	AcOEt	33	1/6
11[c]	**15**	THF	44	1/7
12[c]	**15**	Toluene	37	1/5
13[c]	**15**	1,4-Dioxane	47	1/4
14[d]	(*S*,*S*)-**18**	THF	40	1/7
15[d]	(*R*,*R*)-**18**	THF	43	1/1.3
16[d]	(*S*,*S*)-**18**	Toluene	42	1/2.5
17[e]	(*S*,*S*)-**18**	Toluene	56	1/6

[a]Isolated yield. [b] Diastereomeric ratio determined by ^{1}H NMR analysis of the product mixture. [c]Reaction conditions: **7** (0.5 mmol), **11** (0.5 mmol), catalyst (0.1 mmol) in solvent (1.0 mL) at rt. [d]Reaction conditions: **7** (0.5 mmol), **11** (0.5 mmol), catalyst **18** (20 mol%) in dry solvent (1.5 mL) under argon at -20 °C. [e]Reaction performed at -20 °C for 60 h in dry solvent (1.5 mL) with triphenylphosphine sulfide (0.15 mmol) and 4Å MS (100 mg) as additives.

After this initial catalyst screening, we next explored the generality of the elaborated strategy with various hydroxyketones (i.e., **8**–**10**). We initiated this work by evaluating catalyst **15** and **18** for the reaction of the (2-hydroxyacetyl)furan **8** and aldehyde (*S*)-**11** (Table 2, entry 1–3). The experiments soon revealed that the developed catalysts were the key for successful activation of aromatic ketones with yields up to 83–92 %. Although catalyst **15** (30 mol%) afforded a yield above 80%, the content of the main isomer (2*R*,3*R*,4*S*)-**6a** did not exceed 50% in products mixture (Table 2, entry 1). Because of the presence of rotamers caused by the *N*-Cbz protecting group, it was difficult to determine the ratio of other isomers from the NMR spectra. A similar investigation was made for catalyst **18**, wherein both enantiomers of the catalyst resulted in yield above 90%. Application of the (*S*)-configured catalyst **18**, however, resulted in the loss of stereoselectivity, apparently as a result of a mismatched pair formed between the chiral pocket of catalyst and the aldol reaction undergoing substrates (Table 2, entry 2). Alternatively, (*R,R*)-**18** with the appropriate configuration promoted the formation of the aldol product **6a** having the expected configuration (2*R*,3*R*,4*S*), with a selectivity of (4:1) (Table 2, entry 3). Furthermore, we decided to investigate if an analogous approach could promote efficiently aldol reactions of ketones **9** and **10** which we have successfully employed in the past (Table 2, entry 4–9).[16] As anticipated, this methodology provided product **6b** in a much higher yield (79%) than that obtained using our previous route (43%) and, moreover, the diastereoselectivity was increased from 3.4:1 to 9:1 *syn*/*anti* (Table 2, entry 4–6). We were glad to observe the highest *dr* (9:1) for the quinidine (**15**)–activated reaction, although it required an extremely long reaction time (14 d) (Table 2, entry 4). For ketone **10** the reaction was faster (72 h), but resulted in lower selectivity (Table 2, entry 7).The match/mismatch effect of catalyst **18** enantiomers was maintained also for both ketones (Table 2, entry 5, 6, 8, 9). Surprisingly, aldol reaction of hydroxyacetone **10** exhibited higher selectivity for **6c** when promoted by (*S,S*)-**18** than its enantiomer (Table 2, entry 8, 9), whereas in case of ketone **9** mismatch effect was unaltered (Table 2, entry 5, 6).

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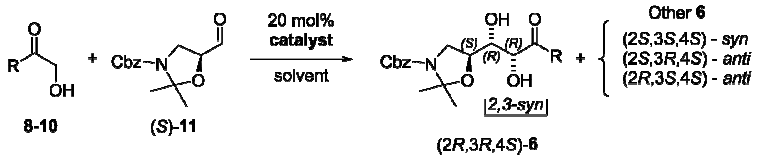
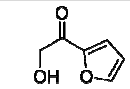
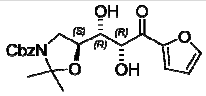
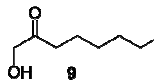
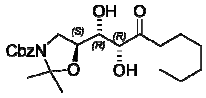
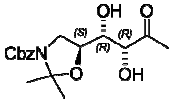
Table 2. Reactivity of Hydroxyketones **8**–**10**.

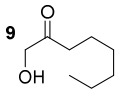


entry	ketone	main product	catalyst	yield (%)[a]	*dr*[b] (2*R*,3*R*,4*S*)-**6**:other **6**
1[c]	 **8**	 **6a**	**15**	83	1:1
2[d]			(*S*,*S*)-**18**	92	1:1
3[d]			(*R*,*R*)-**18**	92	4:1
4[e]	 **9**	 **6b**	**15**	41	9:1
5[d]			(*S*,*S*)-**18**	76	1.4:1
6[d]			(*R*,*R*)-**18**	79	4:1
7[c]	 **10**	 **6c**	**15**	48	3:2
8[d]			(*S*,*S*)-**18**	72	9:1
9[d]			(*R*,*R*)-**18**	58	1:1

[a]Isolated yield. [b]Diastereomeric ratio determined by ^{1}H NMR analysis of the product mixture. [c]Reaction conditions: ketone (0.5 mmol), **11** (0.5 mmol), catalyst **15** (30 mol%) in MTBE (1.0 mL) at rt for 72 h. [d]Reaction conditions: ketone (0.5 mmol), **11** (0.5 mmol), catalyst **18** (20 mol%) in dry THF (1.5 mL) under argon at 5 °C for 12 h. [e]Reaction time of 14 days with other conditions like in [c].

During our investigation on these aliphatic ketones, an unexpected solvent effect on the aldol reaction efficiency was observed. In dry THF, aldol reaction of **9** proceeded smoothly and provided **6b** in 79% yield with a (4:1) diastereoselectivity, whereas in dry toluene no product was observed (Table 3, entry 1, 2). An opposite situation was observed for ketone **10** (Table 3, entry 3, 4) wherein dry Toluene promoted the synthesis of aldol **6c** while THF prevented this process.

Table 3. Solvent Effect on Aldol Reactions.

entry	ketone	solvent	yield (%)[a]	*dr*[b] (2*R*,3*R*,4*S*)-**6**:other **6**
1[c]	 **9**	THF	79%	4:1
2[c]		Toluene	traces	n.d.
3[c]	 **10**	THF	traces	n.d.
4[c]		Toluene	76%	9:1

[a]Isolated yield. [b]Diastereomeric ratio determined by ^{1}H NMR analysis of the product mixture. [c]Reaction conditions: ketone (0.5 mmol), **11** (0.5 mmol), **18** (20 mol%) in dry solvent (1.5 mL) under argon at -20 °C for 12 h.

This unexpected phenomenon can be explained by the different solubility of the ketones in these solvents. The less polar ketone **9** is dissolved better in nonpolar Toluene in compare to THF whereas the opposite is true for ketone **10**. Of note, possible formation of aggregates between ketones and catalyst **18** in inappropriate solvents could result in aldol reaction acceleration.

All in all, the stereochemical outcome observed for both type of catalysts, which mainly produced adducts with the same configuration, might be consistent with similar mechanisms based on the generation of the enolate from pyruvic ester or ketone. In case of tertiary amines the tight complex between the enolate and the chiral catalyst is formed as an ions pair. The thus formed chiral enolate-catalyst pair attacks the chiral aldehyde according to Felkin–Anh principles (Scheme 2a). This model suggests also that the steric constraints imposed by larger substituents of reagents coordinated to catalyst and complex cavity determine which face of the aldehyde is preferentially exposed to the enolate nucleophile (Scheme 2b). Therefore, the asymmetric induction occurs during the approach of the nucleophile to the chiral acceptor electrophile which results in the formation of aldols having one precise configuration predominantly. The zinc catalysts **18** activation mode can be compared mechanistically to the type II

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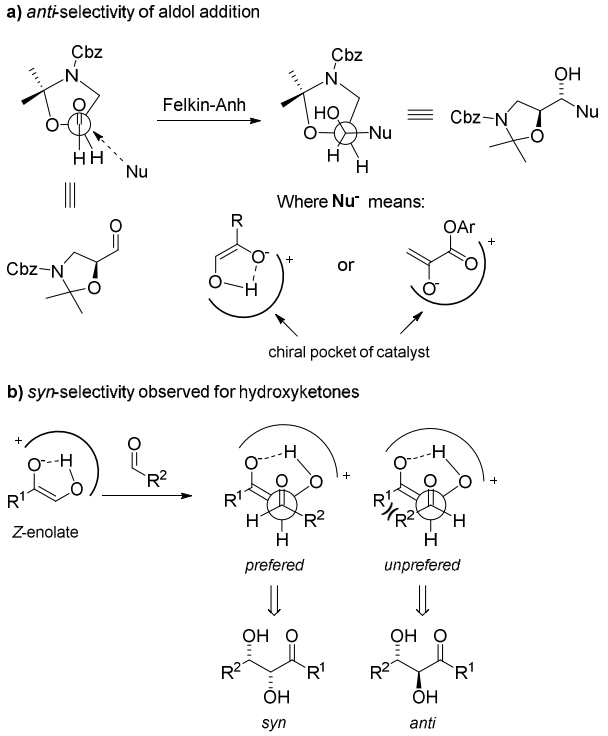
aldolases, which employ zinc ion to form an active enolate.[22] The role of two zinc species is to provide both a zinc to form the requisite enolate and a second zinc to function as a Lewis acid to coordinate the aldehyde (*S*)-**11**. In such scenario the surrounding chiral ligand effect the asymmetric aldol addition of zinc-enolate to the aldehyde both coordinated to zinc atoms.[21] Similar observations were described in our previous work and the present results are in good agreement with those published before.[19,23]



Scheme 2 Proposed model of observed stereochemistry explanation

Having decided the core of our strategy, we needed to select a convenient protocol for the preparation of iminosugars and pipecolic acid derivatives from aldol precursors. The corresponding adducts **5** and **6b–c** isolated by column chromatography were transformed into iminosugars **3** and **4** and pipecolic ester **19** in a three step sequence (Scheme 3). Deprotection with acidic ion–exchange resin was followed by intramolecular imine formation and reduction of the newly created C=N bond that could be done in a single flask by hydrogenolysis in the presence of palladium on carbon in acidic environment. This approach was successfully exploited for the synthesis of **3** in quantitative yield, a much better result than with our previously reported methodology (Scheme 2, part B).[16] An attempt to synthetize **4** was also made and resulted in an improvement of final product yield from 55% to 85% (Scheme 3, part C). High diastereoselectivity of products **3** and **4** is an outcome of a thermodynamic control obtain in acidic environment which accelerate formation of an isomer with aliphatic substituent in more preferred equatorial position (β-isomer). Unfortunately, this protocol failed in the case of synthesis of **2** which required additional oxidation of furan ring before reductive amination due to sensitivity of furan ring to reduction conditions. Various oxidation methods were investigated leading to mixtures of products from which we were unable to isolate desired product with reasonable yield. Starting from **5** the slightly modified protocol provided pipecolic ester **19** in 83% yield (Scheme 3, part A) and, moreover, it was easily scaled up (826 mg of **5**).Modification of the procedure was caused by the sensitivity of unprotected compound **5** for acidic condition of reductive amination, in which it undergoes elimination reaction. Less acidic conditions were introduce to the synthesis of **19**, nevertheless this result in decrease of final product diastereoselectivity (α/β anomers ratio 1:3.4). What is more, hydrolysis of the sterically hindered ester **19** turned out to be a more puzzling issue. Attempts using known methods failed in this case due to steric hindrance of the phenol moiety or because of sensitivity of the sugar-like region toward harsh conditions. Finally, we managed to remove the 2,6-di-*tert*-butyl-4-methoxyphenol ester by treatment with excess sodium hydride and *in situ* generation of sodium hydroxide through addition of H_2O to the reaction mixture. Compound **1** was obtained in 98% yield (45% overall yield after 3 steps from compounds (*S*)-**11** and **7**). The structure of **1** was unambiguously determined by comparison of the NMR of its hydrochloride spectra with the data reported in the literature, because there are no spectra of **1** as such in literature.[6a]

Conclusions

In conclusion, we have reported a short and facile synthesis of iminosugars **3**, **4** and pipecolic acid **1** based on the diastereoselective aldol reaction of aldehyde (*S*)-**11** with various donors promoted both by tertiary amines and Zn/Prophenol complexes. The synthetic approach developed for aromatic ketones and pyruvates activation in aldol reactions is a useful extension. In addition previously reported results have been significantly improved. The present methodology provides a concise and direct entry into the field of polyhydroxylated piperidines and iminosugars, in a simple and efficient way. In particular, it provides a new and short method of synthesis of 1-*C*-alkyl-1,5-iminopentitols, which are known as potent glycosidase inhibitors, especially for β-glucocerebrosidase.[24]

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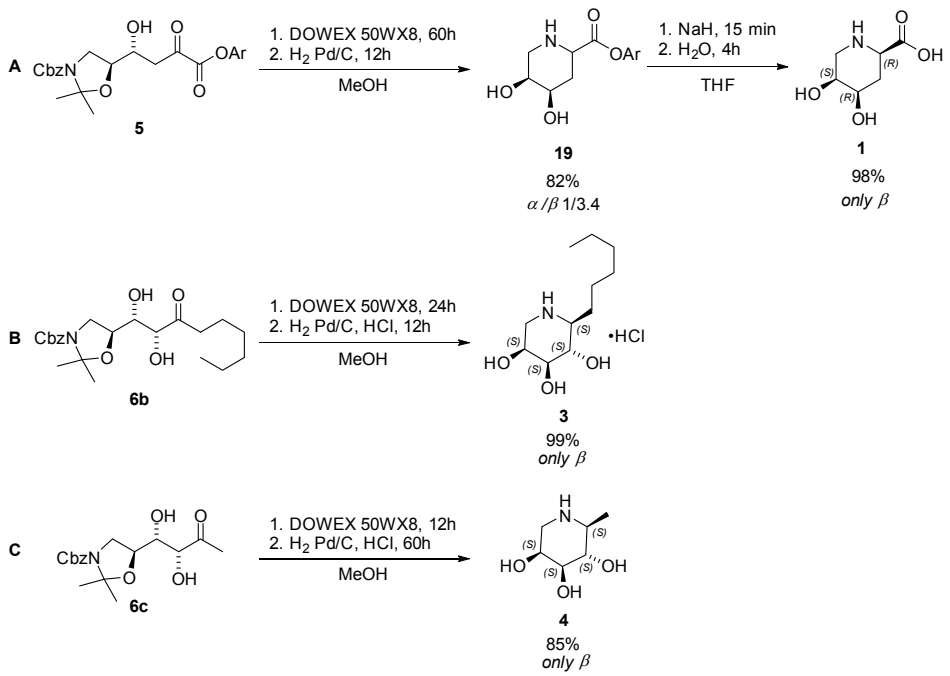

Scheme 3 Cyclisation of aldol products to give desired iminosugar and pipecolic acid derivatives.

Experimental section

General remarks

Infrared (IR) spectra were recorded with a Fourier transform infrared (FT-IR) spectrometer and are reported in wave numbers (cm^{-1}). ^1H NMR (600 MHz and 300 MHz) chemical shift values are listed in parts per million (ppm) downfield from TMS as the internal standard or relative to the corresponding nondeuterated solvent. Data are reported as follows: chemical shift (ppm on the δ scale), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, m = multiplet), coupling constant *J* (Hz), and integration. br meaning broaden. ^{13}C NMR (151 MHz and 75 MHz) chemical shifts are given in ppm relative to the corresponding nondeuterated solvent or TMS as the internal standard. High resolution mass spectra (HRMS) were recorded with an electrospray ionization time-of-flight (ESI-TOF) mass spectrometer. Specific optical rotations were measured with a digital polarimeter in a thermostated (20 °C) 1 dm long cell with high-pressure sodium lamp and are reported as follow: $[\alpha]_D^T$ [solvent, *c* (g/100 mL)]. Reactions were controlled using analytical thin-layer chromatographies (TLC) using Merck Silica Gel 60 F254 precoated plates. All reagents and solvents were purified and dried according to common methods.[25] All organic solutions were dried over anhydrous magnesium sulfate ($MgSO_4$). Reaction products were purified by normal phase flash chromatography, in air, using silica gel 60 (230–400 mesh) with *n*-hexane and ethyl acetate (EA) as eluents, unless otherwise stated. Hydroxyketones, such as (2-hydroxyacetyl)furane **8**[17] and 1-hydroxy-2-octanone 9[26] were synthesized using previously published protocols. The synthesis of 2,6-di-*tert*-butyl-4-methoxyphenyl pyruvate **7** was carried out using a method reported by Morin et al.[27] Aldehyde **11** was prepared according to a procedure described by J. Mlynarski and O. R. Martin.[16]

General Method for the Aldol Reactions Catalyzed by Tertiary Amines (GP A). The related hydroxyketones **8–10** or 2,6-di-*tert*-butyl-pyruvate **7** (0.5 mmol, 1.0 equiv.) and isoserinal (*S*)-**11** (0.5 mmol, 1.0 equiv.) were dissolved in MTBE (1.0 ml) and the tertiary amine catalyst was added (0.2 equiv.). The reaction mixture was then stirred at rt (ca. 20 °C) for an appropriate time (12 h to 12 d). The solvent was evaporated and the residue was purified by column chromatography to get mixture of products as oil. The main diastereomers were sometimes isolated and used in further reactions.

General Method for the Aldol Reactions Catalyzed by Zinc Complexes (GP B). The Zinc/Prophenol catalyst was prepared as described in the literature.[23] A solution of **18** (0.2 M in dry

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THF, 0.5 mL, 0.2 equiv.) was added to a mixture of compound **8–10** or pyruvate **7** (0.5 mmol, 1.0 equiv.) and (*S*)-**11** (0.5 mmol, 1.0 equiv.) in dry THF (1 mL) at -20 °C. The reaction mixture was then stirred for 12 h in case of ketones **8–10** or 60 h for pyruvate **7** at the same temperature and addition of aq. HCl (1M, 0.2 mL) was performed. Stirring was pursued for 5 min at 20 °C and the reaction mixture was poured in a mixture of EA (25 mL) and H_2O (25 mL). The aqueous phase was discarded and the organic phase was washed successively with H_2O (25 mL), saturated aq. NH_4Cl (25 mL), H_2O (25 mL) and brine (25 mL). The Organic phase was dried ($MgSO_4$), filtered over a cotton plug and concentrated under vacuum to afford a residue. The crude product was purified through column chromatography to give related aldol compound as a mixture of diastereomers. The main stereoisomer was isolated to carry further cyclization reactions.

Benzyl-(*S*)-5-((*R*)-4-(2,6-di-tert-butyl-4-methoxyphenoxy)-1-hydroxy-3,4-dioxobutyl)-2,2-dimethyloxazolidine-3-carboxylate 5. Following GP B, 2,6-di-*tert*-butyl-4-methoxyphenyl pyruvate **7** and (*S*)-Isoserinal **11** were reacted with catalyst (*R,R*)-**18**. Column chromatography (*n*-hexane:EA 5:2) was performed on the crude mixture to give related aldol adduct (158 mg, 56%, yellow oil) as a 1:6 (*syn* : *anti*) mixture of diastereomers. The main diastereomer (130 mg, 46%) was separated (*n*-hexane:EA 4:1) and characterized. R_f 0.52 (*n*-hexane:EA 4:1). ^{1}H NMR (600 MHz, Acetone-d_6): δ 7.47–7.24 (m, 5 H), 6.90 (s, 2 H), 5.11 (s, 2 H), 4.52 (d, *J* = 4.5 Hz, 1 H), 4.36–4.26 (m, 1 H), 4.13 (dd, *J* = 14.2, 6.7 Hz, 1 H), 3.89–3.73 (m, 4 H), 3.60–3.45 (m, 1 H), 3.24 (dd, *J* = 17.1, 3.5 Hz, 1 H), 3.21–3.14 (m, 1 H), 1.54 (s, 3 H), 1.48 (s, 3 H), 1.29 (s, 18 H) ppm. ^{13}C NMR (75 MHz, Acetone-d_6): δ 192.7, 162.8, 158.1, 144.3, 129.5, 128.9, 112.7, 78.0, 69.0, 67.6, 67.0, 55.7, 48.5, 44.3, 36.4, 32.0 ppm. IR (ATR): ν 3338, 2961, 2929, 2871, 1751, 1592, 1418, 1170, 1062 cm^{-1}. $[\alpha]_D^{20}$ + 0.5 (*c* 1.00, $CHCl_3$). HRMS (ESI): *m/z* [M + Na^+] found 592.2871, $C_{32}H_{43}NNaO_8$ requires 592.2886.

Benzyl-(*S*)-5-((1*R*,2*R*)-3-(furan-2-yl)-1,2-dihydroxy-3-oxopropyl)-2,2-dimethyloxazolidine -3-carboxylate 6a. Following GP B, hydroxyacetylfurane **8** and (*S*)-**11** were reacted with catalyst (*R,R*)-**18**. Column chromatography (DCM:MTBE:*n*-hexane 5:1:2) was performed on the crude mixture to give related aldol compound as yellow oil (179 mg, 92%) as a mixture of diastereomers. The main diastereomer (115 mg, 60%) was separated (*n*-hexane:EA 1:1) and characterized. R_f 0.49 (*n*-hexane:EA 1:1). ^{1}H NMR (600 MHz, Acetone-d_6): δ 7.89 (d, *J* = 1.0 Hz, 1 H), 7.44 (d, *J* = 3.6 Hz, 1 H), 7.41–7.28 (m, 5 H), 6.71 (dd, *J* = 3.6, 1.7 Hz, 1 H), 5.12 (s, 2 H), 5.04–4.97 (m, 1 H), 4.38 (dd, *J* = 14.1, 7.1 Hz, 1 H), 4.15 (m, 2 H), 3.86–3.78 (m, 1 H), 3.59 (t, *J* = 8.6 Hz, 1 H), 1.62 (s, 3 H), 1.51 (s, 3 H) ppm. ^{13}C NMR (151 MHz, Acetone-6_6): δ 188.8, 153.2, 151.7, 148.4, 138.3, 129.4, 128.8, 128.6, 119.8, 113.4, 94.8, 75.4, 75.2, 74.6, 66.9, 48.8, 26.8, 24.8 ppm. IR (ATR): ν 3445, 2932, 1703, 1682, 1411, 1355, 1068 cm^{-1}. $[\alpha]_D^{20}$ - 8.4 (*c* 1.00, $CHCl_3$). HRMS (ESI): *m/z* [M + Na^+] found 412.1367, $C_{20}H_{23}NNaO_7$ requires 412.1372.

Benzyl-(*S*)-5-((1*R*,2*R*)-1,2-dihydroxy-3-oxononyl)-2,2-dimethyloxazolidine-3-carboxylate 6b.[16] Following GP B, 1-hydroxyoctan-2-one **9** and (*S*)-Isoserinal **11** were reacted with catalyst (*R,R*)-**18**. Column chromatography (*n*-hexane:EA 7:3) was performed on the crude mixture to give related aldol compound as colorless oil (160 mg, 79%) as a mixture of diastereomers. The main diastereomer (100 mg, 50%) was separated (*n*-hexane:EA 4:1) and characterized. R_f 0.45 (*n*-hexane:EA 7:3). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41–7.29 (m, 5 H), 5.12 (s, 2 H), 4.37 (s, 1 H), 4.19 (t d, *J* = 7.7, 6.4 Hz, 1 H), 3.98 (t, *J* = 8.3 Hz, 1 H), 3.84 (s, 1 H), 3.78 (d, *J* = 3.8 Hz, 1 H), 3.61–3.53 (m, 1 H), 2.60 (ddd, *J* = 17.1, 8.2, 6.7 Hz, 1 H), 2.52 (ddd, *J* = 17.1, 8.1, 6.9 Hz, 1 H), 2.21 (d, *J* = 9.7 Hz, 1 H), 1.74–1.47 (m, 8 H), 1.37–1.23 (m, 6 H), 0.88 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 210.2, 152.6, 136.7, 128.7, 128.2, 94.6, 76.2, 74.3, 72.7, 66.8, 48.3, 37.9, 31.6, 28.9, 23.6, 23.4, 22.6, 14.1 ppm.

Benzyl-(*S*)-5-((1*R*,2*R*)-1,2-dihydroxy-3-oxobutyl)-2,2-dimethyloxazolidine-3-carboxylate 6c.[16] Following GP B, hydroxyacetone **10** and (*S*)-Isoserinal **11** were reacted with catalyst (*S,S*)-**18**. Column chromatography (*n*-hexane:EA 1:1) was performed on the crude mixture to give related aldol compound as white solid (128 mg, 72%) as a mixture of diastereomers. The main isomer (85 mg, 48%) was separated (*n*-hexane:EA 1:1) and characterized. R_f 0.41 (*n*-hexane:EA 1:1). M.p. 107–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (s, 5 H), 5.13 (s, 2 H), 4.38 (d, *J* = 1.2 Hz, 1 H), 4.27–4.12 (m, 1 H), 4.00 (d, *J* = 6.8 Hz, 1 H), 3.89–3.75 (m, 1 H), 3.56 (dd, *J* = 10.6, 8.0 Hz, 1 H), 2.30 (s, 3 H), 1.63 (s, 3 H), 1.53 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.7, 128.8, 128.2, 128.1, 76.7, 74.3, 72.7, 66.8, 48.1, 26.9, 25.3 ppm.

General procedure for the preparation of iminosugars 3, 4 and compound 19 (GP C). Aldol products **5, 6a–c** (100 mg) were dissolved in MeOH (10 mL) and resin DOWEX 50W×4 (H^+ form) (200 mg, 2 mass equiv.) was added. The suspension was stirred for a given reaction time (12–60 h, as followed by TLC analysis, *n*-hexane:EA 1:1) and the resin was filtered over a cotton plug. It was washed with MeOH and the solution was concentrated under reduced pressure. The precipitate was dissolved in MeOH (10 mL) and aq. HCl (1M, 0.5 mL only for ketones **6a–c**) was added, followed by Pd/C (1.9 equiv.). The reaction mixture was then stirred under hydrogen atmosphere (H_2-filled balloon) (12–60 h). The suspension was filtered over celite and the cake washed with MeOH (50 mL). The solution was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel to get the desired product as yellow oil or white solid (82–99%).

2,6-di-*tert*-Butyl-4-methoxyphenyl-(4*R*,5*S*)-4,5-dihydroxypiperidine-2-carboxylate 19. The titled product was obtained according to a scaled-up procedure of GP C, using compound **5** (860 mg, 1.5 mmol) dissolved in MeOH (50 mL), resin DOWEX 50W×4 (H^+ form) (1.6 g) and Pd/C (305 mg). The reaction mixture was stirred successively for 60 h and 12 h. Compound **19** (yellow oil, 470 mg, 82%) was obtained as a mixture of diastereomers (1:3.4 α,β) after purification over column chromatography ($CHCl_3$:MeOH 10:1). The main stereoisomer *β*-**19** (360 mg, 63%) was isolated after chromatography over silica gel ($CHCl_3$:MeOH 20:1 to 15:1). *β*-**19**. R_f 0.45 ($CHCl_3$:MeOH 15:1). ^{1}H NMR (600 MHz, MeOD-d_4):

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δ 6.87 (d, *J* = 4.3 Hz, 2 H), 3.80–3.74 (m, 5 H), 3.69 (dd, *J* = 12.3, 2.9 Hz, 1 H), 3.12 (dd, *J* = 14.1, 2.6 Hz, 1 H), 2.78 (dd, *J* = 14.0, 1.2 Hz, 1 H), 2.37–2.24 (m, 1 H), 1.92 (d, *J* = 1.0 Hz, 1 H), 1.33 (t, *J* = 2.0 Hz, 18 H) ppm. ^{13}C NMR (151 MHz, MeOD-d_4): δ 174.3, 158.0, 144.8, 144.7, 143.0, 112.7, 112.6, 70.9, 68.3, 59.8, 55.7, 50.5, 36.5, 36.5, 32.9, 32.0, 31.9 ppm. IR (ATR): ν 3338, 2961, 2928, 2871, 1751, 1592, 1170, 1062 cm^{-1}. $[\alpha]_D^{20}$ + 1.6 (*c* 1.00, MeOH). HRMS (ESI): *m/z* [M + H$^+$] found 380.2430, $C_{21}H_{34}NO_5$ requires 380.2432.

1-*C*-(1*S*)-1-*n*-Hexyl-1,5-dideoxy-1,5-imino-L-arabinitol hydrochloride 3. The titled product was obtained according to GP C using compound **6b**. The reaction mixture was stirred successively for 24 h and 12 h. Compound **3** (white solid, 64 mg, 99%) was obtained as a single diastereomer (β form) after purification over column chromatography (DCM:MeOH 4:1). M.p. 140–147 °C ^{1}H NMR (300 MHz, D_2O): δ 4.12 (td, *J* = 3.0, 1.5 Hz, 1 H), 3.61 (t, *J* = 9.7 Hz, 1 H), 3.52 (dd, *J* = 9.5, 3.0 Hz, 1 H), 3.25 (dd, *J* = 13.6, 3.1 Hz, 1 H), 3.08 (dd, *J* = 13.6, 1.4 Hz, 1 H), 2.90 (ddd, *J* = 9.8, 8.8, 3.5 Hz, 1 H), 1.88 (ddd, *J* = 9.4, 7.6, 4.4 Hz, 1 H), 1.53 (ddd, *J* = 23.6, 12.3, 6.7 Hz, 1 H), 1.43–0.98 (m, 9 H), 0.73 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, D_2O/Acetone-d_6): δ 63.0, 59.8, 56.4, 50.2, 38.4, 21.3, 19.6, 18.7, 15.0, 12.5, 3.9 ppm. IR (ATR): ν 3402, 3333, 3210, 3009, 2953, 2925, 2855, 1529, 1100 cm^{-1}. $[\alpha]_D^{20}$ + 3.5 (*c* 1.00, MeOH). HRMS (ESI): *m/z* [M + H$^+$] found 218.1751, $C_{11}H_{24}NO_3$ requires 218.1751.

1,5,6-Trideoxy-1,5-imino-L-mannitol 4.[14] The titled product was obtained according to GP C using compound **6c**. The reaction mixture was stirred successively for 12 h and 60 h. Compound **4** (white solid, 37 mg, 85%) was obtained as a single diastereomer (β form) after purification over column chromatography ($CHCl_3$:MeOH:H_2O:$NH_{3\ (aq.)}$ 50:50:19:1). M.p. 140–143 °C. ^{1}H NMR (600 MHz, D_2O): δ 3.97 (dd, *J* = 4.6, 2.9 Hz, 1 H), 3.51 (dd, *J* = 9.7, 3.3 Hz, 1 H), 3.29 (t, *J* = 9.6 Hz, 1 H), 2.92 (dd, *J* = 14.5, 2.7 Hz, 1 H), 2.71 (dd, *J* = 14.5, 1.6 Hz, 1 H), 2.44 (dd, *J* = 9.6, 6.4 Hz, 1 H), 1.16 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (151 MHz, D_2O): δ 74.1, 73.9, 69.5, 55.1, 48.2, 17.0 ppm.

Hydrolysis of ester 19 to give 2*R*,4*R*,5*S*-dihydroxypipecolic acid 1. The piperidine-2-carboxylate β-**19** (130 mg, 0.35 mmol, 1 equiv.) was dissolved in dry THF (10 mL) and cooled to 0 °C. Sodium hydride (70 mg, 60% suspension in mineral oil, 1.70 mmol, 5 equiv.) was then added and the reaction mixture was stirred for 15 min at 0 °C. Water was added (20 µl, 1.00 mmol, 3 equiv.) and stirring was pursued for 30 min at the same temperature. The suspension was allowed to reach room temperature (ca. 30 min) and stirring was pursued until disappearance of the starting material (1.5–6 h, TLC analysis, $CHCl_3$:MeOH 10:1). Next, the reaction mixture was cooled to 0 °C and H_2O (1 mL) was added dropwise. The aqueous phase was washed successively with ethyl acetate (3 × 25 mL) and *n*-hexane (25 mL) and it was evaporated under reduced pressure. Compound **1** was obtained as a white solid (54 mg, 98%) after purification over column chromatography ($CHCl_3$:MeOH:H_2O:$NH_{3(aq.)}$ 100:300:20:1). M.p. >168 °C (decomposition) ^{1}H NMR (600 MHz, D_2O): δ 4.15 (d, *J* = 1.1 Hz, 1 H), 4.00 (ddd, *J* = 11.4, 4.7, 2.9 Hz, 1 H), 3.76 (dd, *J* = 12.8, 3.4 Hz, 1 H), 3.48 (dd, *J* = 13.6, 3.3 Hz, 1 H), 3.21 (dd, *J* = 13.6, 1.6 Hz, 1 H), 2.30 (dt, *J* = 13.6, 3.8 Hz, 1 H), 2.02 (td, *J* = 13.1, 11.6 Hz, 1 H) ppm. ^{13}C NMR (151 MHz, D_2O): δ 172.8, 67.4, 64.6, 57.5, 46.9, 28.2 ppm. IR (ATR): ν 3513, 3295, 2925, 2807, 2594, 2529, 2446, 2190, 2134, 1737, 1397, 1203, 1065, 1021 cm^{-1}. $[\alpha]_D^{20}$ + 11.2 (*c* 1.00, 2 M HCl). HRMS (ESI): *m/z* [M + H$^+$] found 162.0758 $C_6H_{12}NO_4$ requires 162.0761; (ESI): *m/z* [M + Na$^+$] found 184.0575, $C_6H_{11}NNaO_4$ requires 184.0586.

2*R*,4*R*,5*S*-dihydroxypipecolic acid hydrochloride (1•HCl).[6a] Compound **1** (34 mg, 0.34 mmol) was dissolved in D_2O (1 mL) and aq. HCl (1M, 0.5 mL) was added. The reaction mixture was stirred for 5 min and concentrated under reduced pressure. Absolute ethanol (1 mL) was added to the residue, that resulted in precipitation of white solid. The solvent was removed under reduced pressure. This procedure was repeat until water was removed. Later CD_3OD (1 mL) was added to the residue and the suspension was stirred for 5 min followed by solvent evaporation. The solid obtained was dried *in vacuo* to provide product **1•HCl** with 40 mg (96%). ^{1}H NMR (600 MHz, D_2O): δ 4.14 (s, 1 H), 4.10–3.97 (m, 2 H), 3.50 (dd, *J* = 13.5, 3.8 Hz, 1 H), 3.24 (dd, *J* = 13.5, 1.8 Hz, 1 H), 2.35 (dt, *J* = 13.7, 4.1 Hz, 1H), 2.20–2.06 (m, 1 H) ppm. ^{13}C NMR (151 MHz, D_2O): δ 170.5, 66.6, 64.2, 55.4, 46.4, 27.4 ppm.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support from the Polish National Science Centre (MAESTRO Grant Nr. 2013/10/A/ST5/00233) is gratefully acknowledged.

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DOI: 10.1039/C7OB02797D

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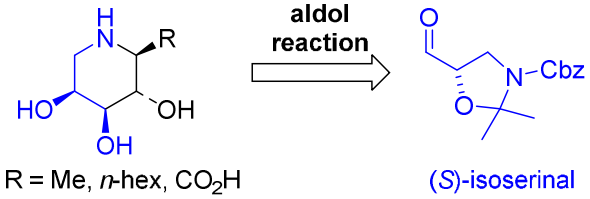

Asymmetric synthesis of iminosugars moiety *via* diastereoselective aldol addition of a pyruvate, a range of hydroxyketones with (*S*)-isoserinal, followed by catalytic reductive intramolecular amination.