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A fast, efficient and stereoselective synthesis of hydroxy-pyrrolidines

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ABSTRACT

A five-step, protecting group free synthesis of 2,3-*cis* substituted hydroxy-pyrrolidines is presented. Key steps in the synthesis are the chemoselective formation of a primary amine via a Vasella reductive amination using ammonia as the nitrogen source, and the stereoselective formation of a cyclic carbamate from an alkenylamine. Improvement of the reductive amination, by way of the use of α-picoline borane as a more environmentally benign reducing agent, is also presented.

1. Introduction

The constant pressure to prepare compounds in a more efficient manner has placed the process by which traditional synthetic chemistry is conducted under scrutiny.[1] The 'ideal synthesis' has been described as one that uses readily available, inexpensive starting materials and proceeds in a simple, safe, environmentally acceptable and efficient manner.[2]

Key in improving the efficiency and atom economy of a synthesis is the omission of protecting groups in the synthetic plan.[1] Although the use of protecting groups has undoubtedly led to a surge in the successful completion of increasingly complex synthetic targets, and justifies the continual development of new and specialised protecting groups,[3] the incorporation and subsequent removal of a protecting group adds to the total number of steps in a synthetic sequence and leads to reductions in overall yield and atom economy.[4] In addition, the material that corresponds to the protecting group (and the reagents used for its introduction/removal) must be separated from the desired compound and discarded, leading to an increase in overall waste production.

There are a number of strategies that can be applied so as to achieve a total synthesis without the need for protecting groups, and a number of elegant reviews have been devoted to this topic.[1,4,5] Traditional methodologies have included the synthesis of compounds with few competing reactivities,[6] protection by protonation,[7] and biomimetic synthesis,[8] while more recent strategies have incorporated new chemistries involving the development of new chemoselective reagents and processes.[1,4,5] With an interest in developing efficient syntheses of iminosugars,[9] we turned our attention to the development of new synthetic methodologies that would enable pyrrolidines to be synthesised without the need for protecting groups. The initial focus of our work was the synthesis of 2,3-*cis*-substituted pyrrolidines (Fig. 1). Of these pyrrolidines, 1,4-dideoxy-1,4-imino-D-xylitol (**1**), isolated from the Pteridophyte *Arachniodes standishii*,[10] is a weak glycogen phosphorylase b inhibitor,[11] while its L-isomer, 1,4-dideoxy-1,4-imino-L-xylitol (**2**), and

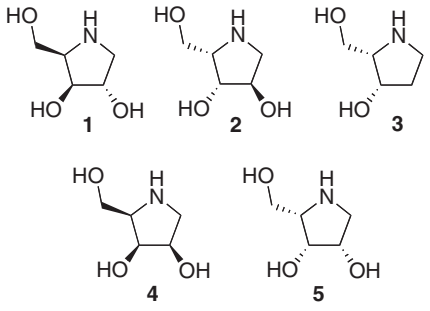

Figure 1. 2,3-*cis*-Substituted pyrrolidines.

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the trideoxy analogue, 1,2,4-trideoxy-1,4-imino-L-xylitol (**3**), are yet to be isolated or tested for biological activity. Of the lyxitol pyrrolidines, 1,4-dideoxy-1,4-imino-D-lyxitol (**4**), the structure tentatively assigned to a pyrrolidine found from *Raispalia* sp.,[12] is a potent α-galactosidase inhibitor,[13,14] while 1,4-dideoxy-1,4-imino-L-lyxitol (**5**) has not been isolated or assayed. A fast, efficient synthesis of pyrrolidines such as these will undoubtedly aid in a more thorough assessment of their therapeutic activities.

In the work presented herein, we report on the applicability of our novel protecting group free strategy[15,16] to the synthesis of L-xylitol **2** and D-lyxitol **4** and provide an explanation for the remarkable diastereoselectivity observed in our carbamate annulation methodology. Our efforts to improve the overall protecting group free strategy via the implementation of more environmentally favourable reductive amination protocols will also be presented. For a summary of other synthetic strategies that can be used to prepare pyrrolidines, there are a number of recent reviews published in this area.[17]

2. Results and discussion

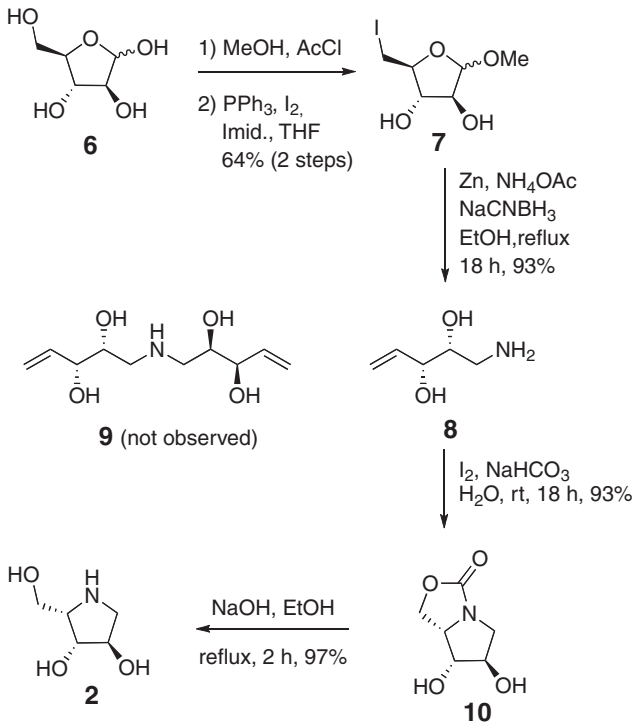
To achieve a protecting group free synthesis of 1,4-dideoxy-pyrrolidines, we envisioned a retrosynthetic analysis that involved three key synthetic transformations: carbamate hydrolysis (**A**→**B**), carbamate annulation (**B**→**C**) and Vasella reductive amination (**C**→**D**) (Scheme 1). Central to this work was the development of a novel tandem halo-cyclisation–carbonylation using sodium bicarbonate as the source of carbon dioxide (**B**→**C**).[15] An efficient reductive amination protocol that uses ammonia, instead of a protected amine, as the nitrogen source to directly yield a primary amine was also key in achieving this protecting group free strategy. Such a transformation has been difficult to effect in the past.[19]

The synthesis of 1,4-dideoxy-1,4-imino-L-xylitol (**2**) commenced with the uneventful transformation of D-arabinose (**6**) to the corresponding iodinated methyl glycoside **7**,[19] although, with iodine, triphenylphosphine and imidazole used in excess, this represents the least environmentally benign aspect of the sequence (Scheme 2). Glycoside **7** was then treated with activated zinc, $NaCNBH_3$, a saturated solution of NH_4OAc in ethanol and aqueous NH_3. Following 18 hours at reflux and purification via Dowex H^+ resin, the corresponding linear alkenylamine **8** was isolated in an excellent yield (93%). When ammonia is used as a nucleophile during reductive amination, typically over-alkylation occurs, resulting in the dimeric product[20] (e.g., **9**). Our modified conditions, however, lead to the exclusive formation of monomer **8** and no trace of dimer **9**. Alkenylamine **8** was then subjected to our iodine-mediated carbamate annulation methodology, which gave carbamate **10** in an excellent yield (93%) and as the major product (>20:1 d.s., as determined by ^1H NMR of the crude reaction mixture). Hydrolysis of the carbamate and comparison of the NMR spectral data and optical rotation values of the hydrolysed product with those in the literature[21,22] confirmed the identity of the resulting pyrrolidine to be that of 1,4-dideoxy-1,4-imino-L-xylitol (**2**). With an overall yield of 54%, this five-step synthesis is remarkably efficient.

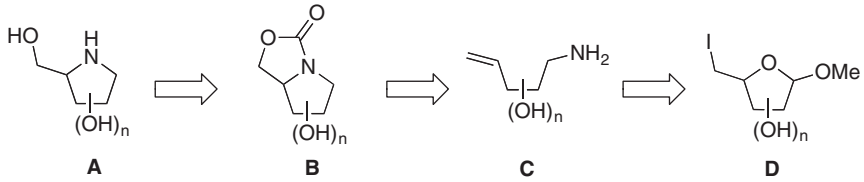
Given our success in preparing 1,4-dideoxy-1,4-imino-L-xylitol (**2**), we anticipated employing a similar synthetic strategy for the synthesis of 1,4-dideoxy-1,4-imino-D-lyxitol (**4**) (Scheme 3). However, unlike most other iodo-pentofuranosides,[18] literature precedent for the formation of the iodinated methyl glycoside **13** involved either a six-step synthesis commencing with D-mannose[23] or a five-step synthesis from 1,2-*O*-cyclohexylidene-α-D-xylofuranose.[24] Being keen to develop a shorter, and potentially more efficient synthesis, we subjected D-lyxose (**11**) to a solution of AcCl in MeOH and stirred the reaction for 18 h at room temperature (Scheme 3). Though a sometimes fickle reaction,[25] with the major impediment being the formation of the undesired thermodynamically more stable methyl pyranoside, these conditions nevertheless lead to the formation of the desired methyl glycoside **12** in 87% yield (with 8% of the pyranose isomer). Next, glycoside **12** was subjected to a solution of triphenylphosphine, iodine and imidazole in THF to install the iodide at the primary position. This transformation proceeded smoothly, with the iodo precursor **13** being prepared in good yield (76%).

With the iodinated methyl glycoside **13** in hand, this was then subjected to our reductive amination conditions. Again, transformation to the linear alkenylamine proceeded smoothly with alkenylamine **14** being prepared in 90% yield. The alkenylamine **14** was then treated with iodine and $NaHCO_3$ to give carbamate **15** in 99% yield (>20:1 d.s.). Following hydrolysis, 1,4-dideoxy-1,4-imino-D-lyxitol (**4**) was then obtained and NMR spectral data and optical rotation values were used to confirm the stereochemistry of the final product.[14]

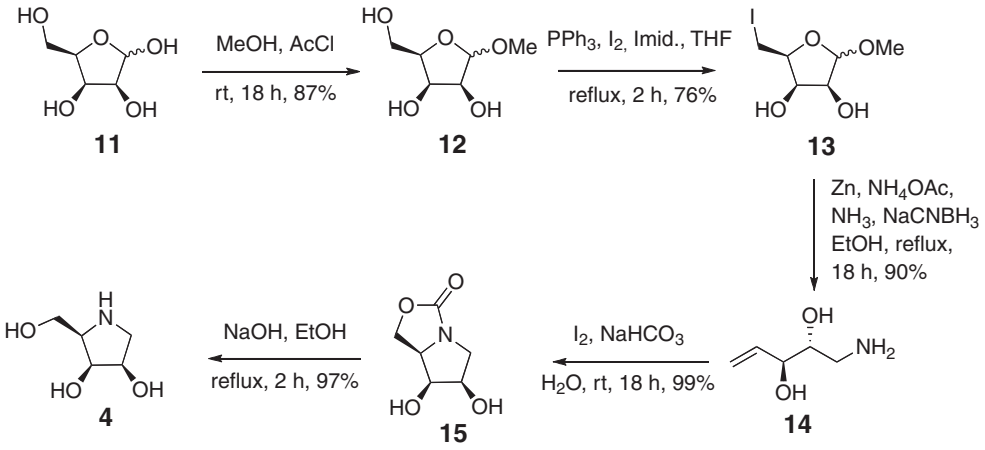
Having established a general procedure for the synthesis of iminopentitols, attempts were then made to improve the overall



Scheme 2. Protecting group free synthesis of 1,4-dideoxy-1,4-imino-L-xylitol.



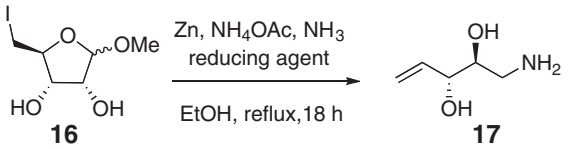
Scheme 1. Retrosynthesis for the formation of 1,4-dideoxy-pyrrolidines.



Scheme 3. Protecting group free synthesis of 1,4-dideoxy-1,4-imino-D-lyxitol.

strategy by modifying the choice of reducing agent used during the Vasella reductive amination. Given the toxicity of $NaCNBH_3$, which carries the risk of leaving residual cyanide in the product as well as in the work-up stream, it was desirable to substitute this reagent for a 'greener' reducing agent, such as sodium triacetoxyborohydride [$NaBH(OAc)_3$][26] or α-picoline borane.[27] Though $NaBH(OAc)_3$ selectively reduces imines over carbonyl compounds in 1,2-dichloroethane or THF, solvents such as ethanol lead to the rapid reduction of the carbonyl compound or the decomposition of the reducing agent and thus was not suitable for our purposes. α-Picoline borane, however, has been successfully used in the one-pot reductive amination of aldehydes and ketones in alcoholic solvents.[27] With methyl 5-deoxy-5-iodo-α/β-D-ribofuranoside (**16**) as our model substrate (Table 1), the reductive amination was repeated using $NaCNBH_3$ or α-picoline borane with varying equivalents of the reducing agent. The benchmark reaction was that with 3 equiv of $NaCNBH_3$, which gave the linear alkenylamine **17** exclusively and in 91% isolated yield (entry 1). The number of equivalents of $NaCNBH_3$ was then reduced to 1.1 equiv to determine the minimal amount of reducing agent that could be used to affect the transformation (entry 2). Here, the yield of alkenylamine **17** decreased to 82%, though only the primary amine product was observed, following purification by Dowex H^+ resin. With α-picoline borane as the reducing agent, similar results were observed. Gratifyingly, 3 equiv of α-picoline borane led to the smooth formation of alkenylamine **17** in 88% yield and with good chemoselectivity (entry 3). Decreasing the amount of reducing agent slightly lowered the reaction yield (entries 4 and 5) with α-picoline borane yielding similar results to $NaCNBH_3$. Though this methodology is not without fault, for stoichiometric amounts of α-picoline borane must still be used, this adaptation is nevertheless a step in the right direction for the development of a synthesis with reduced environmental impact.

Table 1
Optimisation of the Vasella eductive amination using α-picoline borane



Entry	Reducing agent	Equivalents	Yield (%)
1	$NaCNBH_3$	3	91
2	$NaCNBH_3$	1.1	82
3	α-Picoline borane	3	88
4	α-Picoline borane	2	81
5	α-Picoline borane	1.1	78

In sum, our reductive amination–carbamate annulation protocol has proven effective for the formation of a number of pyrrolidines, with each iminosugar being prepared in five steps, in good overall yield, and without the need for protecting groups. The overall yield for the formation of 1,4-dideoxy-1,4-imino-L-xylitol (**2**) was 54% and supersedes that of the next most efficient synthesis (three steps, 48% total yield, commencing from 2,3,5-tri-*O*-benzyl-D-arabinofuranose).[22] The total yield for the synthesis of D-lyxitol (**4**) was slightly higher at 57%. This synthesis is the shortest to date and is comparable with the most efficient published strategy—that by Blanco and Sardinia that commences with *trans*-4-hydroxy-L-proline (six steps, 57% yield).[28] We have previously reported on the preparation of 1,4-dideoxy-1,4-imino-D-xylitol (**1**) (57% total yield), 1,2,4-trideoxy-1,4-imino-L-xylitol (**3**) (48% total yield) and 1,4-dideoxy-1,4-imino-L-lyxitol (**5**) (55% total yield).[15,16] Again, all three syntheses were performed in five steps and with the highest reported yields to date.In addition to the high yields and short number of linear steps, another remarkable feature of our strategy is the high degree of diastereoselectivity observed in the carbamate annulation reaction. The reaction favours the formation of the 2,3-cis pyrrolidine, with the stereochemistry at the 3-position exerting stereocontrol on the cyclisation. This high diastereoselectivity can be explained by considering a transition state model originally proposed by Chamberlin et al.[29–31] and more recent theoretical studies presented by Gouverneur and co-workers.[32] In these models, attack of the amine on the I_2–ethylene complex is thought to take place via a five-membered ring transition structure in which the nitrogen approaches the double bond in an envelope conformation and follows a Bürgi–Dunitz-like trajectory[33] (Fig. 2). The hydroxyl substituent on the ring (depicted in blue) can now be positioned either in the plane of the double bond (A, O-in-plane), or almost perpendicular to that plane (B, H-in-plane). Of these two transition states, A has minimal overlap between the electron-withdrawing σ^*_{C-O} and reacting $\pi_{C=O}$

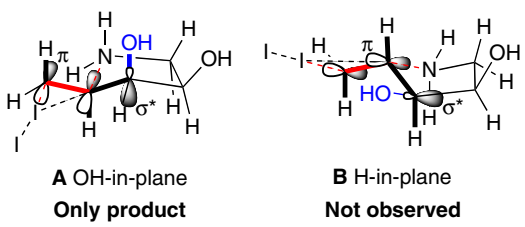


Figure 2. Proposed transition state for the iodo-cyclisation.

orbitals, thereby forming the lowest energy transition state. The H-in-plane structure (B) has overlapping hydroxyl σ^*_{C-O} and double bond $\pi_{C=O}$ orbitals, which destabilises the complex and is hence disfavoured.

3. Conclusion

Herein, we have reported on the expansion of our novel, stereoselective, five-step strategy for the synthesis of important pyrrolidines, namely 1,4-dideoxy-1,4-imino-L-xylitol (**2**) and 1,4-dideoxy-1,4-imino-D-lyxitol (**4**). Our strategy is not only competitive in terms of yield and number of steps but also allows for the achievement of total syntheses without the need for protecting groups. Improvements to the Vasella reductive amination reaction were also made, with $NaCNBH_3$ being substituted with the more environmentally benign α-picoline borane as the reducing agent. The expansion of our novel reductive amination and carbamate annulation methodologies towards the synthesis of other iminosugars is currently being explored in our laboratory.

4. Experimental

4.1. General methods

Unless otherwise stated all reactions were performed under atmospheric air. THF (Lab-Scan) was distilled from $LiAlH_4$ prior to use. H_2O, MeOH (Pure Science) and EtOAc (Pure Science) were distilled prior to use. EtOH (absolute, Pure Science), DCM (LabServ), 30% aqueous NH_3 (J. T. Baker Chemical Co.), arabinose (Sigma–Aldrich), lyxose (Sigma–Aldrich), AcCl (B&M), PPh_3 (Merck), imidazole (Aldrich), I_2 (BDH), $NaCNBH_3$ (Aldrich), α-picoline borane (Aldrich), NaOH (Pure Science) and NH_4OAc (AnalaR) were used as received. Zn dust was activated by the careful addition of concentrated H_2SO_4 washed with EtOH (3×) and hexanes (3×), and stored under dry hexanes. All solvents were removed by evaporation under reduced pressure. Reactions were monitored by TLC-analysis on Macherey–Nagel silica gel coated aluminium sheets (0.20 mm, Silica Gel 60) with detection by UV-absorption (254 nm), by spraying with 20% H_2SO_4 in EtOH followed by charring at ~150 °C, by dipping in I_2 in silica or by spraying with a solution of ninhydrin in EtOH followed by charring at ~150 °C. Column chromatography was performed on Pure Science silica gel (40–63 μm). Dowex® W50-X8 acidic resin (Sigma) and Dowex® 1X4-50 basic resin (Sigma) were used for ion exchange chromatography and HP-20 (Supelco) for reverse phase chromatography. High-resolution mass spectra were recorded on a Waters Q-TOF Premier™ Tandem Mass Spectrometer using positive electro-spray ionisation. Optical rotations were recorded using a Perkin–Elmer 241 polarimeter at the sodium D-line. Infrared spectra were recorded as thin films using a Bruker Tensor 27 FTIR spectrometer, equipped with an Attenuated Total Reflectance (ATR) sampling accessory, and are reported in wave numbers (cm^{-1}). Nuclear magnetic resonance spectra were recorded at 20 °C in D_2O, CD_3OD or $CDCl_3$ using either a Varian Unity-INOVA operating at 300 MHz or a Varian Unity operating at 500 MHz. Chemical shifts are given in parts per million (ppm) (δ) relative to tetramethylsilane. NMR peak assignments were made using COSY, HSQC and HMBC 2D experiments.

4.2. General procedure for the synthesis of methyl furanosides

To a solution of pentose (150 mg, 1 mmol) in MeOH (5 mL), AcCl (15 μL) was added and the reaction was stirred at room temperature for 18 h. The reaction was quenched by the addition of Dowex (OH^-), filtered and concentrated. The resulting oil was purified by flash chromatography (MeOH–EtOAc, 1:9, v/v) to give the pure methyl furanosides.

4.2.1. Methyl D-arabinofuranoside

By subjecting D-arabinose (**6**) (20.1 g, 134 mmol) to the general procedure for the synthesis of methyl furanosides, methyl D-arabinofuranoside was isolated as a colourless oil (19.1 g, 118 mmol, 88%). R_f = 0.48 and 0.36 for α and β, respectively (MeOH–EtOAc, 1:9, v/v); $[\alpha]_D^{19}$ +91.0 (*c* 1.0, MeOH); IR (film), 3356, 2924, 2481, 1455, 1119, 972, 824 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 4.88 (d, $J_{1,2}$ = 1.5 Hz, 1H, H-1α), 3.94 (dd, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3.5 Hz, 1H, H-2α), 3.91 (ddd, $J_{4,5a}$ = 3.3 Hz, $J_{4,5b}$ = 5.3 Hz, $J_{3,4}$ = 6.1 Hz, 1H, H-4α), 3.83 (dd, $J_{2,3}$ = 1.5 Hz, $J_{3,4}$ = 6.1 Hz, 1H, H-3α), 3.75 (dd, $J_{4,5a}$ = 3.3 Hz, $J_{5a,5b}$ = 11.6 Hz, 1H, H-5aα), 3.64 (dd, $J_{4,5b}$ = 5.3 Hz, $J_{5a,5b}$ = 11.6 Hz, 1H, H-5bα), 3.37 (s, 3H, OMe); ^{13}C NMR (75 MHz, CD_3OD) δ 109.2 (C-1), 84.1 (C-4), 82.0 (C-2), 77.3 (C-3), 61.6 (C-5), 53.9 (OMe); HRMS-ESI *m/z* calcd for $[C_6H_{12}O_5+Na]^+$: 187.0582, obsd: 187.0581.

4.2.2. Methyl α-D-lyxofuranoside (12)

Subjection of D-lyxose **11** (1.00 g, 6.67 mmol) to the general procedure for the synthesis of methyl furanosides gave pure methyl α-D-lyxofuranoside (**12**) as a white crystalline powder (0.95 g, 5.81 mmol, 87%). R_f = 0.49 (MeOH–EtOAc, 1:9, v/v); mp 96.8–98.2 °C; $[\alpha]_D^{20}$ +131.2 (*c* 0.5, MeOH); IR (film), 3320, 2943, 2832, 1449, 1106, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.84 (s, 1H, H-1), 4.64 (br s, 1H, OH), 4.52 (dd, $J_{2,3}$ = 5.0 Hz, $J_{3,4}$ = 6.6 Hz, 1H, H-3), 4.19 (br s, 1H, OH), 4.16 (ddd, $J_{4,5b}$ = 2.9 Hz, $J_{4,5a}$ = 3.7 Hz, $J_{3,4}$ = 6.6 Hz, 1H, H-4), 3.99 (d, $J_{2,3}$ = 5.0 Hz, 1H, H-2), 3.85 (dd, $J_{4,5a}$ = 3.7 Hz, $J_{5a,5b}$ = 11.9 Hz, 1H, H-5a), 3.80 (dd, $J_{4,5b}$ = 2.9 Hz, $J_{5a,5b}$ = 11.9 Hz, 1H, H-5b), 3.36 (s, 3H, OMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.5 (C-1), 78.6 (C-3), 74.8 (C-4), 71.7 (C-2), 60.4 (C-5), 55.1 (OMe); HRMS-ESI *m/z* calcd for $[C_6H_{12}O_5+Na]^+$: 187.0582, obsd: 187.0578.

4.3. General procedure for the synthesis of methyl 5-deoxy-5-iodo-furanosides

To a solution of methyl furanoside (164 mg, 1 mmol) in dry THF (5.5 mL) under an atmosphere of N_2, PPh_3 (393 mg, 1.5 mmol) and imidazole (136 mg, 2 mmol) were added. I_2 (380 mg, 1.5 mmol) in dry THF (1.5 mL) was cannulated into the reaction vessel. The reaction was heated at reflux for 2 h, then cooled, filtered and concentrated. The product was taken up in hexanes–EtOAc, 3:1, v/v, and filtered through a silica plug to remove excess iodine, then purified using reverse phase HP-20 beads (MeOH–H_2O, 5:1, v/v) to give the methyl 5-iodo-D-furanosides.

4.3.1. Methyl 5-deoxy-5-iodo-D-arabinofuranoside (7)

By subjecting methyl D-arabinoside (4.20 g, 28 mmol) to the general procedure for the synthesis of methyl 5-deoxy-5-iodo-D-furanosides, arabinoside **7** was obtained as a colourless oil (5.62 g, 20.5 mmol, 73%). R_f = 0.60 (MeOH–EtOAc, 85:15, v/v); $[\alpha]_D^{20}$ +37.0 (*c* 2.2, $CHCl_3$); IR (film), 3435, 1216, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 4.96 (s, 1H, H-1α), 4.86 (d, $J_{1\beta,2\beta}$ = 4.6 Hz, 1H, H-1β), 4.17 (d, $J_{2\alpha,3\alpha}$ = 1.9 Hz, 1H, H-2α), 4.12 (dd, $J_{1\beta,2\beta}$ = 4.6 Hz, $J_{2\beta,3\beta}$ = 7.0 Hz, 1H, H-2β), 4.07 (dt, $J_{3\alpha,4\alpha}$ = 3.9 Hz, $J_{4\alpha,5\alpha}$ = 5.9 Hz, 1H, H-4α), 4.04 (ddd, $J_{3\beta,4\beta}$ = 3.2 Hz, $J_{4\beta,5a\beta}$ = 6.1 Hz, $J_{4\beta,5b\beta}$ = 7.0 Hz, 1H, H-4β), 3.95 (dd, $J_{3\beta,4\beta}$ = 3.2 Hz, $J_{2\beta,3\beta}$ = 7.0 Hz, 1H, H-3β), 3.91 (dd, $J_{2\alpha,3\alpha}$ = 1.9 Hz, $J_{3\alpha,4\alpha}$ = 3.9 Hz, 1H, H-3α) 3.48 (s, 3H, β-OMe), 3.42 (s, 3H, α-OMe), 3.41 (dd, $J_{4\alpha,5a\alpha}$ = 5.8 Hz, $J_{5a\alpha,5b\alpha}$ = 10.5 Hz, 1H, H-5aα), 3.37 (dd, $J_{4\alpha,5b\alpha}$ = 5.8 Hz, $J_{5a\alpha,5b\alpha}$ = 10.5 Hz, 1H, H-5bα), 3.33 (dd, $J_{4\beta,5a\beta}$ = 6.1 Hz, $J_{5a\beta,5b\beta}$ = 10.0 Hz, H-5aβ), 3.30 (dd, $J_{4\beta,5b\beta}$ = 7.0 Hz, $J_{5a\beta,5b\beta}$ = 10.0 Hz, H-5aα); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 108.9 (C-1α), 101.9 (C-1β), 84.7 (C-4α), 81.5 (C-3β), 81.0 (C-3α), 80.8 (C-2α), 80.6 (C-4β), 78.6 (C-2β), 55.6 (C-6β), 55.2

(C-6α), 8.0 (C-5β), 6.6 (C-5α); HRMS-ESI *m/z* calcd for $[C_6H_{11}O_4I+Na]^+$: 296.9600, obsd: 296.9598.

4.3.2. Methyl 5-deoxy-5-iodo-D-lyxofuranoside (13)

By subjecting methyl D-lyxose **12** (1.60 g, 9.75 mmol) to the general procedure for the synthesis of methyl 5-deoxy-5-iodo-D-furanosides, lyxoside **13** was obtained as a colourless syrup (2.03 g, 7.41 mmol, 76%). R_f = 0.61 (MeOH–EtOAc, 1:9, v/v); $[\alpha]_D^{20}$ +68.0 (*c* 1.5, $CHCl_3$); IR (film), 3445, 1214, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.91 (d, $J_{1,2}$ = 2.9 Hz, 1H, H-1), 4.37 (dd, $J_{2,3}$ = 4.8 Hz, $J_{3,4}$ = 3.8 Hz, 1H, H-3), 4.30 (ddd, $J_{3,4}$ = 3.8 Hz, $J_{4,5a}$ = $J_{4,5b}$ = 6.2 Hz, 8.2 Hz, 1H, H-4), 4.17 (dd, $J_{1,2}$ = 2.9 Hz, $J_{2,3}$ = 4.8 Hz, 1H, H-2) 3.48 (br s, 1H, OH), 3.40 (s, 3H, OMe), 3.37 (dd, $J_{4,5a}$ = 8.2 Hz, $J_{5a,5b}$ = 9.7 Hz, 1H, H-5a), 3.27 (dd, $J_{4,5b}$ = 6.2 Hz, $J_{5a,5b}$ = 9.7 Hz, 1H, H-5b); ^{13}C NMR (125 MHz, $CDCl_3$): δ 108.4 (C-1), 79.6 (C-4), 76.3 (C-3), 70.5 (C-2), 55.0 (OMe), −0.8 (C-5); HRMS-ESI *m/z* calcd for $[C_6H_{11}O_4I+Na]^+$: 296.9600, obsd: 296.9604.

4.4. General procedure for the synthesis of alkenylamines

To a solution of iodo-pyranoside (274 mg, 1 mmol) in a saturated solution of NH_4OAc in EtOH (20 mL) were added activated Zn (327 mg, 5 mmol), reducing agent ($NaCNBH_3$ or α-picoline borane, 3 mmol) and 30% aqueous NH_3 (8 mL). The mixture was stirred at reflux for 18 h, cooled to room temperature, filtered to remove excess zinc and concentrated under reduced pressure. The residue was redissolved in H_2O, loaded onto a Dowex H^+ ion exchange resin and washed several times with H_2O to remove excess salt. The amine product was then eluted with 15–30% aqueous NH_3. The eluent was concentrated under reduced pressure then converted to the HCl salt using 1 m HCl. If necessary, further purification could be achieved using gradient flash chromatography (DCM–EtOH–MeOH–30% aqueous NH_3, 25:2:2:1→5:2:2:1, v/v/v/v).

4.4.1. (2*R*,3*R*)-1-Amino-pent-4-ene-2,3-diol hydrochloride (8)

By subjecting iodide **7** (274 mg, 1 mmol) to the general procedure for the synthesis of alkenylamines, alkenylamine **8** was obtained as the HCl salt (143 mg, 93 mmol, 93%). R_f = 0.61 (DCM–EtOH–MeOH–30% aqueous NH_3, 5:2:2:1, v/v/v/v); $[\alpha]_D^{20}$ +50.6 (*c* 1.0, EtOH); IR (film) 3412, 3252, 3045, 1632, 1432, 1013 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 5.74 (ddd, $J_{3,4}$ = 5.3 Hz, $J_{4,5\text{-}cis}$ = 10.5 Hz, $J_{4,5\text{-}trans}$ = 17.3 Hz, 1H, H-4), 5.23 (d, $J_{4,5\text{-}trans}$ = 17.3 Hz, 1H, H-5-*trans*), 5.17 (d, $J_{4,5\text{-}cis}$ = 10.5 Hz, 1H, H-5-*cis*), 3.99 (t, $J_{3,4}$ = $J_{2,3}$ = 5.3 Hz, 1H, H-3), 3.70 (ddd, $J_{1a,2}$ = 2.8 Hz, $J_{2,3}$ = 5.3 Hz, $J_{1b,2}$ = 9.9 Hz, 1H, H-2), 3.03 (dd, $J_{1a,2}$ = 2.8 Hz, $J_{1a,1b}$ = 13.1 Hz, 1H, H-1a), 2.87 (dd, $J_{1b,2}$ = 9.9 Hz, $J_{1a,1b}$ = 13.1 Hz, 1H, H-1b); ^{13}C NMR (75 MHz, D_2O) δ 135.4 (C-4), 118.2 (C-5), 73.7 (C-3), 69.7 (C-2), 41.5 (C-1); HRMS-ESI *m/z* calcd for $[C_5H_{11}O_2N+H]^+$: 118.0868, obsd: 118.0869.

4.4.2. (2*R*,3*S*)-1-Amino-pent-4-ene-2,3-diol hydrochloride (14)

By subjecting iodide **13** (50 mg, 0.18 mmol) to the general procedure for the synthesis of alkenylamines, alkenylamine **14** was obtained as the HCl salt (25 mg, 0.16 mmol, 90%). R_f = 0.41 (DCM–EtOH–MeOH–30% aqueous NH_3, 5:2:2:1, v/v/v/v); $[\alpha]_D^{20}$ −8.0 (*c* 0.1, EtOH); IR (film) 3345, 2946, 2835, 1651, 1450, 1018 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 5.88 (ddd, $J_{3,4}$ = 6.6 Hz, $J_{4,5\text{-}cis}$ = 10.5 Hz, $J_{4,5\text{-}trans}$ = 17.1 Hz, 1H, H-4), 5.35 (d, $J_{4,5\text{-}trans}$ = 17.1 Hz, 1H, H-5-*trans*), 5.31 (d, $J_{4,5\text{-}cis}$ = 10.5 Hz, 1H, H-5-*cis*), 4.12 (dd, $J_{2,3}$ = 5.6 Hz, $J_{3,4}$ = 6.6 Hz, 1H, H-3), 3.81 (ddd, $J_{1a,2}$ = 3.0 Hz, $J_{2,3}$ = 5.6 Hz, $J_{1b,2}$ = 9.7 Hz, 1H, H-2), 3.23 (dd, $J_{1a,2}$ = 3.0 Hz, $J_{1a,1b}$ = 13.2 Hz, 1H, H-1a), 2.95 (dd, $J_{1b,2}$ = 9.7 Hz, $J_{1a,1b}$ = 13.2 Hz, 1H, H-1b); ^{13}C NMR (125 MHz, D_2O) δ 135.4 (C-4), 118.3 (C-5), 74.0 (C-3), 69.8 (C-2), 41.1 (C-1); HRMS-ESI *m/z* calcd for $[C_5H_{11}O_2N+H]^+$: 118.0868, obsd: 118.0871.

4.5. General procedure for the iodo-cyclisation–carbamate formation

To a solution of the alkenylamine hydrochloride (154 mg, 1 mmol) in water (5 mL) were added $NaHCO_3$ (126 mg, 1.5 mmol) and I_2 (279 mg, 1.1 mmol). The solution was stirred 18 h at room temperature, filtered and concentrated under reduced pressure. The product was purified by silica gel chromatography (1–5% MeOH in EtOAc, v/v).

4.5.1. (6*R*,7*R*,7*aR*)-6,7-Dihydroxy-tetrahydro-pyrrolo[1,2-*c*]oxazol-3-one (10)

By subjecting alkenylamine **8** (40 mg, 0.26 mmol) to the general procedure for the iodo-cyclisation–carbamate formation, carbamate **10** was isolated as an amorphous white powder (38.5 mg, 0.24 mmol, 93%). $[\alpha]_D^{18}$ +20.1 (*c* 0.6, EtOH); IR (film) 3372, 2954, 2845, 1715, 1635, 1416, 1253, 1079, 955 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.51 (t, $J_{4,5a}$ = $J_{5a,5b}$ = 9.2 Hz, 1H, H-5a) 4.38 (dd, $J_{4,5b}$ = 2.9 Hz, $J_{5a,5b}$ = 9.2 Hz, 1H, H-5b), 4.27 (d, $J_{1a,2}$ = 5.1 Hz, 1H, H-2), 4.17 (dt, $J_{4,5a}$ = 9.2 Hz, $J_{4,5b}$ = $J_{3,4}$ = 2.9 Hz, 1H, H-4), 3.90 (d, $J_{3,4}$ = 2.9 Hz, 1H, H-3), 3.67 (dd, $J_{1a,2}$ = 5.1 Hz, $J_{1a,1b}$ = 12.5 Hz, 1H, H-1a), 3.01 (d, $J_{1a,1b}$ = 12.5 Hz, 1H, H-1b); ^{13}C NMR (75 MHz, D_2O) δ 164.4 (C=O), 76.5 (C-2), 74.3 (C-3), 64.0 (C-5), 62.0 (C-4), 52.2 (C-1); HRMS-ESI *m/z* calcd for $[C_6H_9O_4N+Na]^+$: 182.0429, obsd: 182.0424.

4.5.2. (6*R*,7*S*,7*aR*)-6,7-Dihydroxy-tetrahydro-pyrrolo[1,2-*c*]-oxazol-3-one (15)

By subjecting alkenylamine **14** (6.5 mg, 55 μmol) to the general procedure for the iodo-cyclisation–carbamate formation, carbamate **15** was isolated as an amorphous white powder (8.5 mg, 55 μmol, 99%). $[\alpha]_D^{20}$ −30.5 (*c* 0.1, EtOH); IR (film) 3332, 2977, 1717, 1474, 1411, 1250, 1130, 1068 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.52 (m, 3H, H-2, H-5a and H-5b), 4.14 (ddd, $J_{3,4}$ = 3.1 Hz, $J_{4,5a}$ = 5.0 Hz, $J_{4,5b}$ = 7.9 Hz, 1H, H-4), 4.01 (dd, $J_{3,4}$ = 3.1 Hz, $J_{2,3}$ = 3.3 Hz, 1H, H-3), 3.51 (dd, $J_{1a,2}$ = 8.1 Hz, $J_{1a,1b}$ = 10.8 Hz, 1H, H-1a), 3.15 (dd, $J_{1b,2}$ = 7.9 Hz, $J_{1a,1b}$ = 10.8 Hz, 1H, H-1b); ^{13}C NMR (75 MHz, D_2O) δ 164.1 (C=O), 73.2 (C-2), 70.6 (C-3), 64.3 (C-5), 61.5 (C-4), 48.6 (C-1); HRMS-ESI *m/z* calcd for $[C_6H_9O_4N+Na]^+$: 182.0429, obsd: 182.0433.

4.6. General procedure for the synthesis of 2-hydroxymethyl-pyrrolidine-3,4-diols

To a solution of carbamate (159 mg, 1 mmol) in EtOH (5 mL) was added NaOH (400 mg, 10 mmol). The solution was stirred at reflux for 2 h then cooled and purified directly using Dowex (H^+). The product was eluted in 5–15% aqueous NH_3 and the eluent concentrated under reduced pressure then converted to the HCl salt using 1 M HCl.

4.6.1. (2*S*,3*R*,4*R*)-2-Hydroxymethyl-pyrrolidine-3,4-diol (2)

By subjecting cyclic carbamate **10** (13 mg, 0.082 mmol) to the general procedure for the synthesis of 2-hydroxymethyl-pyrrolidine-3,4-diols, L-imino-xylitol **2** was isolated as the HCl salt (13 mg, 0.077 mmol, 97%). R_f = 0.21 (DCM–EtOH–MeOH–30% aqueous NH_3, 5:2:2:1, v/v/v/v); $[\alpha]_D^{20}$ +8.2 (*c* 0.5, H_2O); IR (film) 3317, 2944, 2832, 1654, 1449, 1415, 1113, 1021 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.26 (d, $J_{1a,2}$ = 4.5 Hz, 1H, H-2), 4.19 (d, $J_{3,4}$ = 3.8 Hz, 1H, H-3), 3.89 (dd, $J_{4,5a}$ = 5.5 Hz, $J_{5a,5b}$ = 11.5 Hz, 1H, H-5a), 3.77 (dd, $J_{4,5b}$ = 7.7 Hz, $J_{5a,5b}$ = 11.5 Hz, 1H, H-5b), 3.62 (ddd, $J_{3,4}$ = 3.8 Hz, $J_{4,5a}$ = 5.5 Hz, $J_{4,5b}$ = 7.7 Hz, 1H, H-4), 3.46 (dd, $J_{1a,2}$ = 4.5 Hz, $J_{1a,1b}$ = 12.8 Hz, 1H, H-1a), 3.04 (d, $J_{1a,1b}$ = 12.8 Hz, 1H, H-1b); ^{13}C NMR (75 MHz, D_2O) δ 74.6 (C-2), 74.5 (C-3), 62.5 (C-4), 57.6 (C-5), 50.4 (C-1); HRMS-ESI *m/z* calcd for $[C_5H_{11}O_3N+H]^+$: 134.0817, obsd: 134.0817.

4.6.2. (2*R*,3*S*,4*R*)-2-Hydroxymethyl-pyrrolidine-3,4-diol (4)

By subjecting cyclic carbamate **15** (3.0 mg, 19 μmol) to the general procedure for the synthesis of hydroxymethyl-pyrrolidine-3,4-diols, D-imino-lyxitol **4** was isolated as the HCl salt (3.1 mg, 18 μmol, 97%). R_f = 0.89 (DCM–EtOH–MeOH–30% aqueous NH_3, 5:2:2:1, v/v/v/v); $[\alpha]_D^{20}$ +20.8 (*c* 0.1, H_2O); IR (film) 3369, 3198, 2956, 2857, 1456, 1266, 1127, 1056 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.47 (dt, $J_{2,3}$ = 4.1 Hz, $J_{1a,2}$ = $J_{1b,2}$ = 7.4 Hz, 1H, H-2), 4.32 (t, $J_{2,3}$ = $J_{3,4}$ = 4.2 Hz, 1H, H-3), 3.96 (dd, $J_{4,5a}$ = 5.0 Hz, $J_{5a,5b}$ = 12.1 Hz, 1H, H-5a), 3.86 (dd, $J_{4,5b}$ = 8.4 Hz, $J_{5a,5b}$ = 12.1 Hz, 1H, H-5b), 3.71 (ddd, $J_{3,4}$ = 4.2 Hz, $J_{4,5a}$ = 5.0 Hz, $J_{4,5b}$ = 8.4 Hz, 1H, H-4), 3.50 (dd, $J_{1a,2}$ = 7.4 Hz, $J_{1a,1b}$ = 12.2 Hz, 1H, H-1a), 3.18 (dd, $J_{1b,2}$ = 7.4 Hz, $J_{1a,1b}$ = 12.2 Hz, 1H, H-1b); ^{13}C NMR (75 MHz, D_2O) δ 69.9 (C-2), 69.7 (C-3), 62.4 (C-4), 57.6 (C-5), 46.9 (C-1); HRMS-ESI *m/z* calcd for $[C_5H_{11}O_3N+H]^+$: 134.0817, obsd: 134.0813.

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Supplementary data

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