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Synthesis of an aza analogue of 2-deoxy-D-ribofuranose and its homologues

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Abstract

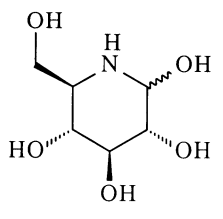
Azasugars were obtained in one-pot reactions by catalytic reduction reactions of amino group precursors in aldosugars followed by intramolecular reductive amino alkylation reactions. (3*R*,4*S*)-4-[(1*S*)-1,2-Dihydroxyethyl]pyrrolidin-3-ol was obtained from D-xylose by two different strategies through 3-*C*-cyano-3-deoxy-D-*ribo*-pentofuranose or 3-*C*-azidomethyl-3-deoxy-D-*ribo*-pentofuranose in 6 and 16% overall yields, respectively. The oxidative cleavage of the diol group in the corresponding Fmoc-azasugar followed by deprotection afforded (3*R*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol. (3*R*,4*S*)-4-[(1*S*,2*R*)-1,2,3-Trihydroxypropyl]pyrrolidin-3-ol was synthesized from diacetone-D-glucose through 3-deoxy-3-*C*-nitromethyl-D-allose and the overall yield was 7%.

Keywords: Azasugar; Iminosugar; 'Masked' 3-*C*-aminomethyl sugars; Reductive amination; (3*R*,4*R*)-4-(Hydroxymethyl)pyrrolidin-3-ol

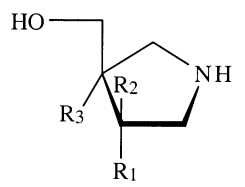
1. Introduction

The discovery of the glycosidase inhibitor activity of the natural product nojirimycin initiated the synthesis of various hydroxylated piperidines and hydroxylated pyrrolidines called azasugars or iminosugars.[1] This group of inhibitors are now finding application as anti-HIV, anticancer and antidiabetic agents[2] (Fig. 1).

Previous results have shown that pyrrolidine analogues of 2-deoxy-D-ribofuranose, having a nitrogen instead of the anomeric carbon, and a methylene group instead of the ring oxygen are inhibitors of glycosidases.[3] Jaeger and Biel[4] reported a synthesis of racemic 1-benzyl-4-(hydroxymethyl)pyrrolidin-3-ol which was used in the preparation of 1′-aza carbacyclic thymidine analogues[5] and aza-*C*-nucleosides.[6] Bols et al. published[7] a multistep synthesis of **1** from D-mannose and its inhibitory potency against purine nucleoside phosphorylase. Goskesen and Lundt prepared (3*S*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol (**2**) from D-xylose and found it a weak inhibitor of α-D, β-D glucosidase.[8]



nojirimycin



1: R_1 = OH; R_2 = H; R_3 = OH
2: R_1 = H; R_2 = OH; R_3 = H
3: R_1 = OH; R_2 = H; R_3 = H

Fig. 1. Examples of azasugars.

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Recently the synthesis of 2-deoxy-ribofuranose-type 1-azasugar was published by two groups. Bols and Hansen[9] synthesized triflouroacetic salt of *trans*-3-hydroxy-4-(hydroxymethyl)pyrrolidine (**3**) from (*Z*)-1,4-dichloro-2-butene in nine steps and attempted enzymatic purification of the enantiomers. Ichikawa and Makino[10] synthesized **3** in a multi-gram scale from fumaric acid monoethyl ester. The key step in this strategy included asymmetric epoxidation and epoxide-opening using cyanide anion (Yamamoto's aluminium reagent), with separation of regioisomers after tosylation of the ring-opened products.

There have also been reports on the synthesis of azasugars from aminosugars in reductive amination reactions.[11–13] In this work we also use a reductive amination reaction for formation of the heterocyclic ring (Fig. 2). It is believed that masking the aldehydo as a hemiacetal allows the use of an amino precursor, which can be reduced to an amino group prior to the reductive amination reaction in a one-pot reaction. Tedious chromatographic separation of anomers of pyranose and furanose forms prior to the reduction reaction is not needed, making this route more attractive. Retro synthetic analysis suggested the introduction of an amino group in the sugar from easily reducible precursor groups such as CN, N_3 and NO_2. As the key sugar synthones, we choose different types of furanos-3-uloses to obtain the corresponding azasugar homologues which can be cleaved to give **3**.

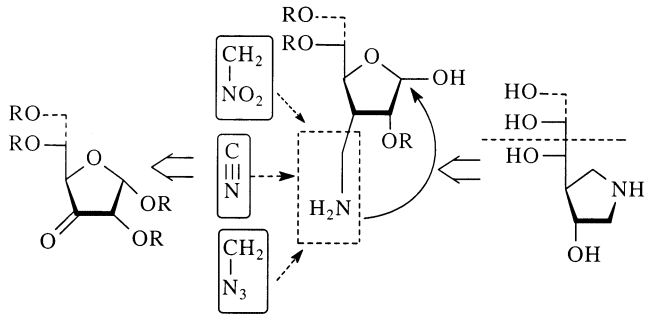


Fig. 2. Synthetic plan for the synthesis of azasugars by an intramolecular aminoalkylation reaction. Possible amino group precursors are shown in the rectangular forms.

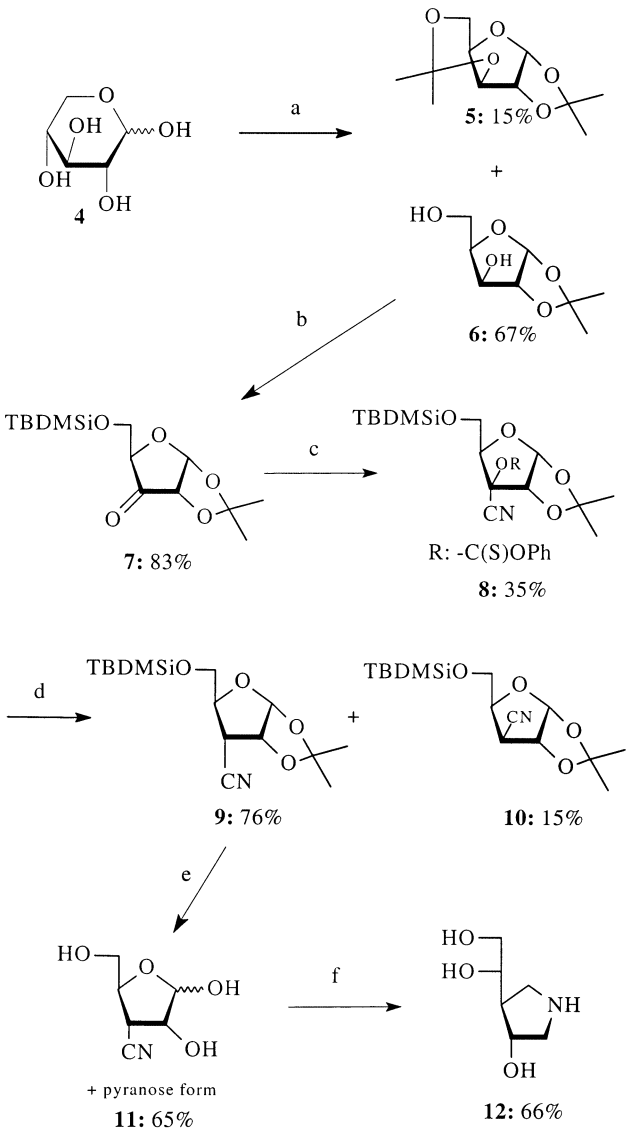
2. Results and discussion

The azasugar **12** was synthesized by two different strategies, both starting from 5-*O*-(*tert*-butyldimethylsilyl)-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose (**7**). This starting material was synthesized as earlier described[14,15] from D-xylose (**4**) via its 1,2-*O*-isopropylidene derivative **6** which was silylated and oxidized with a CrO_3–Py–Ac_2O complex. When applying the procedure of Moravcova et al.[14] to the synthesis of **6** from **4**, by an acid-catalyzed reaction with acetone, followed by partial hydrolysis, we found it difficult to avoid decomposition during work-up unless a larger amount of sodium carbonate was used in the hydrolysis step. In this way 1,2-*O*-isopropylidene-α-D-xylofuranose (**6**) and 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose (**5**) were obtained in 67 and 15% yield, respectively (Scheme 1).

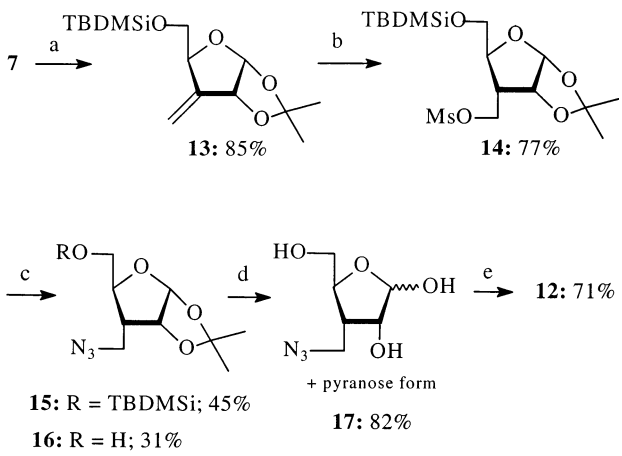
The reaction of **7** with KCN in 2:1 diethyl ether–water took place stereoselectively to give only the xylo cyanoisomer (previously obtained in a two step synthesis by treatment of **7** with NaCN–$NaHCO_3$ affording the ribo cyanohydrin and subsequent epimerization under basic condition with DBU–acetonitrile).[16] The cyano compound was treated with phenyloxythiocarbonyl chloride and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in acetonitrile to give **8**. From the reduction reaction of **8** using tributyltin hydride in the presence of α,α′-azobisisobutyronitrile (AIBN), Calvo-Mateo et al.[17] isolated 5-*O*-(*tert*-butyldimethylsilyl)-3-*C*-cyano-3-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-pentofuranose (**9**) contaminated with pentofuranos-3-ulose (**7**) which was described as an inseparable mixture. However, by column chromatography we isolated **9** and 5-*O*-(*tert*-butyldimethylsilyl)-3-*C*-cyano-3-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-pentofuranose (**10**). The assignment of the epimers was confirmed by NOE experiments. NOE (3–4%) was observed between 3-H and 4-H in **10** when each of them were irradiated, whereas no NOE was found between the same protons in **9**. The NOEs between 2-H and 3-H confirmed in a similar manner the assignment showing the greater NOE (3–5%) for **9** versus 2% for the same

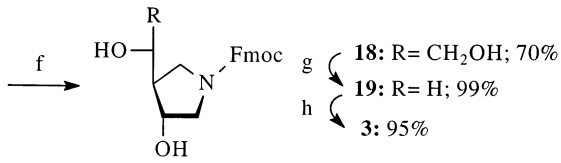
protons in **10**. Using 50% aqueous acetic acid[18] for the hydrolysis of protecting groups in **9**, did not in our results give complete hydrolysis of the isopropylidene group after 1 h. Instead, we found it preferable to use 70% aqueous acetic acid which led to 3-*C*-cyano-3-deoxy-D-*ribo*-pentofuranose (**11**) in 65% yield. The azasugar **12** was obtained by a reductive amination reaction using hydrogen over 10% Pd–C in water in an autoclave for 24 h.

An alternative way for the synthesis of **12** started from the 3-methylene analogue **13** which was obtained in 85% yield in a Wittig



Scheme 1. (a) $(CH_3)_2CO/H^+$; (b) (1) TBDMSiCl/Py; (2) $CrO_3/Py/Ac_2O/CH_2Cl_2$; (c) (1) $KCN/Et_2O/H_2O$; (2) PhOC(S)Cl/DMAP/acetonitrile; (d) $(n\text{-}Bu)_3SnH/AIBN$/toluene; (e) 70% AcOH; (f) H_2/200 psi/Pd–C/H_2O.



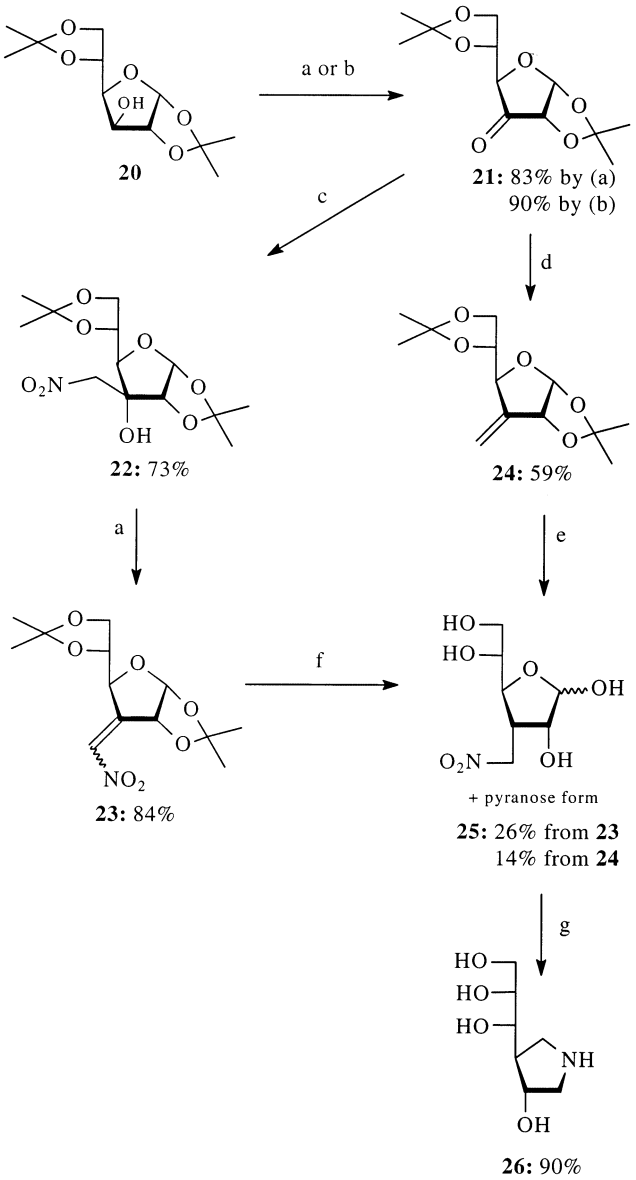


Scheme 2. (a) $CH_3P(C_6H_5)_3Br/n$-BuLi/THF; (b) (1) BH_3/THF; (2) $NaOH/H_2O_2$; (3) MsCl/Py; (c) $(CH_3)_2NH\cdots HN_3$ or NaN_3/DMF; (d) 70% AcOH; (e) H_2/200 psi/Pd–C/H_2O; (f) FmocCl/dioxane/10% aq $NaHCO_3$; (g) (1) $NaIO_4$; (2) $NaBH_4$; (h) NEt_3/acetonitrile.

reaction from **7** with CH_3PPh_3Br using *n*-BuLi in dry THF (Scheme 2). Sodium hydride in DMSO as earlier described[19] in this step was not used here in order to avoid contamination with sulfur compounds, which later on could poison the catalyst during the reductive amination reaction. Compound **14** was obtained in three steps from **13**[18] and for the preparation of **15** it was treated with ten equiv of sodium azide or 1.1 equiv of the DMF soluble dimethylammonium azide instead of lithium azide[18] which is no longer readily available. Dimethylammonium azide[20] was easily synthesized as previously described by treatment of an equal molar amount of sodium azide and dimethylammonium hydrochloride in DMF at 70 °C for 4 h, and subsequent removal of sodium chloride by filtration at 10 °C and crystallization of the product at −70 °C. In these two syntheses of azides, partial removal of the *tert*-butyldimethylsilyl protecting group was observed and compounds **15** and **16** were isolated in the ratio 3:2 with both reagents. Deblocking the mixture of **15** and **16** with 70% acetic acid afforded the azido sugar **17** in 82% yield. Reductive amination under the

same conditions as for compound **11** afforded the expected azasugar **12** in 71% yield as a brown oil.

The direct cleavage of the diol group in **12** to a hydroxymethyl derivative **3** by consecutive reactions with sodium periodate and sodium borohydride failed. *N*-Protection of the azasugar **12** by reaction with ethyl triflouracetate[21] was unsuccessful. However, the Fmoc-derivative **18** was obtained in 70% yield by treatment of the azasugar **12** with 9-fluorenylmethyl chloroformate (FmocCl) in 1:1 dioxane and 10% aqueous $NaHCO_3$ for 24 h.[22] Sodium periodate oxidation of **18** yielded an aldehydo sugar which was immediately reduced with sodium borohydride to give the expected Fmoc protected azasugar **19** in 99% yield, which in turn was deprotected by NEt_3 in acetonitrile for 15 h to yield the azasugar **3** in 95% yield.



Scheme 3. (a) $DMSO/Ac_2O$; (b) $CrO_3/Py/Ac_2O/CH_2Cl_2$; (c) $MeNO_2/t$-BuOK/DMF; (d) $CH_3P(C_6H_5)_3Br/n$-BuLi/THF; (e) (1) $AgNO_2/I_2/Et_2O$; (2) $NaBH_4$/EtOH; (3) Amberlite IR-120(H^+); (f) (1) $NaBH_4$/EtOH; (2) Amberlite IR-120(H^+); (g) H_2/200 psi/Pd–C/H_2O.

For the synthesis of (3*R*,4*S*)-4[(1*S*,2*R*)-1,2,3-trihydroxypropyl]pyrrolidin-3-ol (**26**) the target compound was obtained from **25** by catalytic reduction of a nitro group followed by reductive amination with the masked sugar aldehyde (Scheme 3). According to the literature, **25** could be obtained from diacetone-D-glucose which in the first step was oxidized with dry DMSO and acetic acid to give the furan-3-ulose **21**[23] which after conversion to **22**[24] was treated again with the same reagent for the elimination reaction to give **23**[24] prior to the conversion to **25**.[25,26] Although good yields were obtained of **25**, the main problem in this route was sulfur-by-products formed in the two steps where DMSO was used. The sulfur-by-products poisoned the catalyst in the reductive amination reaction and thereby inactivating it. The problem was partially solved by extensive-column chromatography after the synthesis of **22** and again after the synthesis of **23**. Even then, the Pd–C catalyst had to be exchanged several times in order to get a complete intramolecular reductive amination reaction. To avoid DMSO in the synthesis of **25**, diacetone-D-glucose (**20**) was oxidized by a complex of CrO_3–acetic anhydride and dry pyridine[27] and another route was followed to obtain **25** from **21**. The methylene derivative **24** was obtained in a Wittig reaction using $MePPh_3Br$ and *n*-BuLi in dry THF.[19] The nitro group was introduced in a radical reaction with $AgNO_2$ and I_2 and subsequent reduction of the resulting double bond[26] afforded **25**. Using this route for the synthesis of **25**, the azasugar **26** was obtained in 90% yield in the subsequent catalytic reduction reaction of the nitro group and reductive amino alkylation in the one-pot reaction using Pd–C and hydrogen.

3. Summary

In the present investigation we have demonstrated a new methodology of synthesizing 1-aza analogues of furanose sugars. The key step is an intramolecular reductive aminoalkylation reaction of 3-*C*-aminomethyl aldosugars using hydrogen and Pd–C. The amino group in turn is obtained in the same reaction prior to the aminoalkylation by reduction of azido, cyano and nitro groups when the aldehydo group in the sugar is masked as a hemiacetal. It is believed this methodology of synthesizing azasugars will be generally applicable.

4. Experimental

General.—NMR spectra were recorded on a Bruker AC-300 FT NMR spectrometer at 300 MHz for ^{1}H NMR and at 75.5 MHz for ^{13}C NMR. Internal standards used in ^{1}H NMR spectra were Me_4Si (δ 0.00) for $CDCl_3$, CD_3OD, Me_2SO-d_6 and 1,4-dioxane (δ 3.75) for D_2O; in ^{13}C NMR were $CDCl_3$ (δ 77.0), CD_3OD (δ 49.0), Me_2SO-d_6 (δ 39.5) and 1,4-dioxane (δ 67.2) for D_2O. ^{1}H COSY experiment for compound **12** was recorded on an Varian Unity Inova at 500 MHz. ^{1}H NMR steady-state NOE difference spectroscopy experiments were carried out on compounds **9** and **10** with a Bruker AC-250 spectrometer. Accurate ion mass determination was performed on a Kratos MS-50-RF equipped with FAB source. The $[M+H]^+$ ions were peak-matched using ions derived from the glycerol matrix. Thin-layer chromatography (TLC) analyses were carried out using TLC plates 60 F_{254} purchased from Merck and were visualized in UV light (254 nm) and/or with a 5% solution of H_2SO_4 in MeOH for sugar derivatives and/or with a ninhydrin spray reagent (0.3 g ninhydrin in 100 mL butan-1-ol and 3 mL HOAc) for azasugars and its derivatives. The silica gel (0.063–0.200 mm) used for column chromatography was purchased from Merck. All solvents were distilled before use. The reagents used were purchased from Aldrich, Sigma or Fluka.

5-O-(tert-Butyldimethylsilyl)-3-C-cyano-3-deoxy-1,2-O-isopropylidene-α-D-ribo-pentofuranose (**9**).—A solution of 5-*O*-(*tert*-butyldimethylsilyl)-3-*C*-cyano-1,2-*O*-isopropylidene-3-*O*-(phenyloxythiocarbonyl)-α-D-*xylo*-pentofuranose[17] (**8**) (490 mg, 1 mmol), α,α′-azobisisobutironitrile (AIBN, 37.5 mg, 0.25 mmol) in dry oxygen free toluene (25 mL) was stirred for 15 min while N_2 was bubbled through the mixture. Then (n-Bu)$_3$SnH (0.53 mL, 2 mmol) was added. The flask was heated in an oil bath at 70 °C for 4 h under N_2. On cooling to rt, water (10 mL) was added and the emulsion was evaporated to dryness in vacuo. The residue was chromatographed on a silica gel column with EtOAc (5–10%, v/v) in cyclohexane to afford two compounds: **9** (239 mg, 76%): R_f 0.32 (50% EtOAc–cyclohexane); ^{1}H NMR ($CDCl_3$): δ 0.07, 0.09 (2s, 6 H, $[CH_3]_2Si$–), 0.90 (s, 9 H, –$[CH_3]_3$), 1.37, 1.59 (2s, 6 H, –$[CH_3]_2$), 3.35 (dd, 1 H, J 4.7, 9.5 Hz, H-3), 4.10 (m, 2 H, H-5), 4.55 (dd, 1 H, J 2.1, 9.8 Hz, H-4), 5.05 (t, 1 H, J 3.8 Hz, H-2), 6.05 (d, 1 H, J 3.3 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ −4.9 ($[CH_3]_2Si$–), 18.7 (–$C[CH_3]_3$), 26.3 (–$[CH_3]_3$), 26.8, 27.0 (–$[CH_3]_2$), 35.8 (C-3), 61.2 (C-5), 79.9 (C-4), 80.3 (C-2), 105.7 (C-1), 113.5 (–$C[CH_3]_2$), 115.8 (CN); and compound **10** (48 mg, 15%): R_f 0.41 (50% EtOAc–cyclohexane); ^{1}H NMR ($CDCl_3$): δ 0.07, 0.09 (2s, 6 H, $[CH_3]_2Si$–), 0.90 (s, 9 H, –$[CH_3]_3$), 1.37, 1.59 (2s, 6 H, –$[CH_3]_2$), 3.48 (d, 1 H, J 4.8 Hz, H-3), 4.05 (dd, 1 H, J 7.9, 10.2 Hz, H-5), 4.20 (dd, 1 H, J 4.8, 10.0 Hz, H-5), 4.58 (m, 1 H, H-4), 5.10 (d, 1 H, J 4.1 Hz, H-2), 6.20 (d, 1 H, J 3.6 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ −4.9 ($[CH_3]_2Si$–), 18.6 (–$C[CH_3]_3$), 26.2 (–$[CH_3]_3$), 26.8, 27.0 (–$[CH_3]_2$), 40.4 (C-3), 62.6 (C-5), 78.1 (C-4), 83.0 (C-2), 105.7 (C-1), 113.2 (–$C[CH_3]_2$), 116.5 (CN).

3-C-Cyano-3-deoxy-D-ribo-pentofuranose (**11**).—A solution of nitrile **9** (1.0 g, 3.2 mmol) in 70% HOAc (20 mL) was heated at 100 °C for 24 h. After allowing the mixture to cool, water was added (20 mL) and the aq solution was extracted with CH_2Cl_2 (3 × 15 mL). The water layer was evaporated under vacuum. The residue was purified by chromatography on a silica-gel column with 10% (v/v) MeOH in CH_2Cl_2 to give the mixture of pyranose and

furanose forms of **11** (331 mg, 65%) as a colorless oil: ^{1}H NMR (Me_2SO-d_6): δ 3.18 (dd, 1 H, *J* 5.0, 9.5 Hz, H-3), 3.25–3.80 (m, 5 H, 3 × OH, H-5), 4.08 (m, 1 H, H-4), 5.10 (m, 1 H, H-2), 5.90 (m, 1 H, H-1); ^{13}C NMR (Me_2SO-d_6): δ 40.0, 39.9 (C-3), 64.8, 64.3 (C-5), 68.3, 65.9 (C-4), 81.6, 76.6 (C-2), 103.3, 95.9 (C-1), 119.2, 119.4 (CN).

3-C-*Azidomethyl*-*3*-*deoxy*-*5*-O-*(*tert-*butyldimethylsilyl)*-*1,2*-O-*isopropylidene*-α-D-ribo-*pentofuranose* (**15**).—Compound **14**[18] (1.5 g, 3.8 mmol) and 10 equiv of NaN_3 or 1.1 equiv of dimethylammonium azide in DMF (20 mL) were heated with stirring at 95 °C for 1.5 h. The mixture was evaporated to dryness in vacuo. The residue was dissolved in a mixture of CH_2Cl_2 (20 mL) and water (20 mL). The organic layer was washed with water (3 × 15 mL), dried over Na_2SO_4 and evaporated to give a syrup which was purified on a silica-gel column with 10–50% (v/v) EtOAc in cyclohexane to yield **15** (540 mg, 45%); ^{1}H NMR ($CDCl_3$): δ 0.07, 0.09 (2s, 6 H, $[CH_3]_2Si$–), 0.90 (s, 9 H, –$[CH_3]_3$), 1.37, 1.59 (2s, 6 H, –$[CH_3]_2$), 2.51 (m, 1 H, H-3), 3.65 (dd, 1 H, *J* 5.5, 12.2 Hz, CH_2N_3), 3.80 (dd, 1 H, *J* 9.8, 12.2 Hz, CH_2N_3), 3.96 (dd, 2 H, *J* 3.9, 4.9 Hz, H-5), 4.08 (m, 1 H, H-4), 4.92 (t, 1 H, *J* 4.2 Hz, H-2), 6.05 (d, 1 H, *J* 3.8 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ −4.9($[CH_3]_2Si$–), 18.7 (–*C*$[CH_3]_3$), 26.2 (–$[CH_3]_3$), 26.8, 27.2 (–$[CH_3]_2$), 45.8 (C-3), 48.2 (CH_2N_3), 63.6 (C-5), 80.4 (C-2), 81.3 (C-4), 105.4 (C-1), 112.4 (–*C*$[CH_3]_2$); and 3-*C*-azidomethyl-3-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-pentofuranose (**16**, 270 mg, 31%); ^{1}H NMR ($CDCl_3$): δ 1.37, 1.59 (2s, 6 H, –$[CH_3]_2$), 1.98 (br,s, 1 H, OH), 2.32 (m, 1 H, H-3), 3.38 (dd, 1 H, *J* 6.5, 12.0 Hz, CH_2N_3), 3.65 (m, 2 H, CH_2N_3, H-5), 3.94 (m, 2 H, H-4, H-5), 4.73 (t, 1 H, *J* 4.2 Hz, H-2), 5.84 (d, 1 H, *J* 3.7 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 26.3, 26.6 (–$[CH_3]_2$), 43.8 (C-3), 47.7 (CH_2N_3), 61.9 (C-5), 80.4 (C-2), 80.9 (C-4), 104.8 (C-1), 112.2 (–*C*$[CH_3]_2$).

3-C-*Azidomethyl*-*3*-*deoxy*-D-ribo-*pentofuranose* (**17**).—This was synthesized as a mixture of pyranose and furanose forms from the mixture of 3:2 **15** and **16** (810 mg, 2.9 mmol) by the same methodology as described for the synthesis of **11**; yield 450 mg (82%) of a colorless oil: ^{1}H NMR (Me_2SO-d_6): δ 2.41 (m, 1 H, H-3), 3.40–3.95 (m, 7 H, 3 × OH, CH_2N_3, H-5), 4.08 (m, 2 H, H-2, H-4), 5.10 (s, 1 H, H-1); ^{13}C NMR (Me_2SO-d_6): δ 44.1, 36.7 (C-3), 50.8, 48.5 (CH_2N_3), 65.3, 64.6 (C-5), 76.1, 69.1 (C-4), 81.9, 76.1 (C-2), 103.0, 94.0 (C-1).

*(3*R,*4*S*)*-4*-*[(1*S*)*-1,2*-*Dihydroxyethyl]pyrrolidin*-*3*-*ol* (**12**).—The 10% Pd–C (315 mg) was suspended in a solution of water (25 mL) with **11** or **17** (2 mmol). The mixture was kept at 200 psi H_2 at rt for 24 h and filtered through Celite® which was further washed by 100 mL of water. The combined water solutions were evaporated in vacuo. The residue was purified by silica-gel column chromatography (0–30% (v/v) aq NH_3 in dioxane) to give **12** as a brownish oil, 194 mg (66%) from **11**, 209 mg (71%) from **17**: R_f 0.24 (50% aq NH_3–1,4-dioxane); ^{1}H NMR (D_2O): δ 2.15 (m, 1 H, H-4), 2.65 (dd, 1 H, *J* 7.3, 11.8 Hz, H-5), 2.89 (dd, 1 H, *J* 2.8, 12.5 Hz, H-2), 3.00 (dd, 1 H, *J* 5.4, 12.4 Hz, H-5), 3.20 (m, 1 H, H-2), 3.50–3.70 (m, 3 H, C*H*[OH]C*H*$_2$OH), 4.40 (dt, 1 H, *J* 3.2, 5.1 Hz, H-3), 4.79 (m, 4 H, 3 × OH, NH); ^{13}C NMR (D_2O): δ 48.0 (C-4), 50.5 (C-5), 54.1 (C-2), 64.9 (CH_2OH), 72.8 (CH), 74.1 (C-3); HRMS (FAB) *m*/*z* 148.0962 ($[MH]^+$ $[C_6H_{14}NO_3]$ = 148.0974).

N-*Fmoc*-*(3*R,*4*S*)*-4*-*[(1*S*)*-1,2*-*dihydroxyethyl]pyrrolidin*-*3*-*ol* (**18**).—(3*R*,4*S*)-4-[(1*S*)-1,2-Dihydroxyethyl]pyrrolidin-3-ol (**12**, 500 mg, 3.42 mmol) was dissolved in a suspension of 10% aq $NaHCO_3$ (15 mL) in dioxane (15 mL). 9-Fluorenylmethyl chloroformate (1.3 g, 5.1 mmol) was added. The resulting solution was stirred at rt for 18 h, treated with water (50 mL) and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under diminished pressure to give an oil which was purified by silica-gel column chromatography with cyclohexane–EtOAc (0–25%, v/v) followed by CH_2Cl_2–MeOH (25%) to afford **18** (880 mg, 70%): R_f 0.47 (10% MeOH–CH_2Cl_2); ^{1}H NMR (CD_3OD): δ 2.23 (br,s, 1 H, H-4), 3.25 (m, 2 H, H-5), 3.45–3.65 (m, 5 H, H-2, C*H*[OH]C*H*$_2$OH), 4.23 (m, 1 H, CH [Fmoc]), 4.40 (m, 3 H, CH_2 [Fmoc], H-3), 4.85 (br,s, 3 H, 3 × OH), 7.25–7.83 (m, 8 H, Fmoc); ^{13}C NMR (CD_3OD): δ 45.7, 45.9 (C-4), 46.3, 46.5 (C-5), 46.8 (Fmoc), 51.6, 51.8 (C-2), 63.9 (C-

3), 66.4 (Fmoc), 69.4, 70.1, 70.6, 70.7 ($CH[OH]CH_2OH$), 118.8, 123.9, 126.0, 126.6, 140.4, 143.0, 154.5 (Fmoc); FAB-MS m/z 370 $[M + H^+]$.

N-Fmoc-(3R,4R)-4-(hydroxymethyl)pyrrolidin-3-ol (**19**).—A cooled solution of compound **18** (724 mg, 1.96 mmol) in EtOH (10 mL) was added to a solution of $NaIO_4$ (461 mg, 2.16 mmol) in water (5 mL) while stirring. After 30 min, $NaBH_4$ (217 mg, 5.86 mmol) was added. After 30 min the resulting solution was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under diminished pressure to give pure **19** (660 mg, 99%): R_f 0.52 (10% MeOH–CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.30 (br.s, 1 H, H-4), 3.20 (m, 1 H, H-5), 3.32 (m, 1 H, H-5), 3.40–3.70 (m, 5 H, H-2, CH_2OH, CH [Fmoc]), 4.20–4.38 (m, 5 H, CH_2 [Fmoc], H-3, 2 × OH), 7.25–7.83 (m, 8 H, [Fmoc]). ^{13}C NMR ($CDCl_3$): δ 46.4, 46.6 (C-4), 47.2, 47.5 (C-5), 48.2 (Fmoc), 52.4, 52.8 (C-2), 62.4 (C-3), 67.4 (Fmoc), 71.8, 72.6 (CH_2OH), 119.9, 125.0, 126.0, 127.7, 141.2, 143.8, 155.2 (Fmoc); FAB-MS m/z 340 $[M + H]^+$.

(3R,4R)-4-(Hydroxymethyl)pyrrolidin-3-ol (**3**).—A mixture of compound **19** (520 mg, 1.53 mmol) and Et_3N (0.65 mL, 4.70 mmol) in MeCN (30 mL) was stirred at 60 °C for 15 h. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 (10 mL)–water (30 mL) and washed with CH_2Cl_2 (2 × 30 mL). The water layer was concentrated under diminished pressure to yield **3** (171 mg, 95%): R_f 0.41 (50% aq NH_3–1,4-dioxane); ^1H NMR (CD_3OD): δ 2.20 (m, 1 H, H-4), 2.74 (dd, 1 H, *J* 5.7, 11.4 Hz, H-5), 2.85 (dd, 1 H, *J* 3.1, 12.1 Hz, H-2), 3.10 (dd, 1 H, *J* 5.2, 12.0 Hz, H-5), 3.20–3.28 (m, 1 H, H-2), 3.45–3.60 (m, 2 H, CH_2OH), 4.15 (td, 1 H, *J* 3.3, 5.1 Hz, H-3), 4.79 (m, 3 H, 2 × OH, NH); ^{13}C NMR (D_2O): δ 73.5 (C-3), 61.9 (CH_2OH), 54.3 (C-2), 50.7 (C-5), 48.1 (C-4); HRMS (FAB) m/z 118.0868 ($[MH]^+$ $[C_5H_{12}NO_2] = 118.0864$).

(3R,4S)-4-[(1S,2R)-1,2,3-Trihydroxypropyl]pyrrolidin-3-ol (**26**).—3-Deoxy-3-*C*-nitromethyl-D-allose (**25**, 130 mg, 0.58 mmol) was dissolved in 10 mL of water, and 10% Pd–C (46 mg) was added. The solution was hydrogenated in an autoclave for 24 h at 200 psi. The solution was filtered through Celite® and washed thoroughly with water and evaporated in vacuo giving the title compound **26** (93 mg, 90%) as a brown foam, which could be purified by silica-gel column chromatography (0–30% (v/v) aq NH_3 in dioxane): R_f 0.10 (50% aq NH_3–1,4-dioxane); ^1H NMR (D_2O): δ 2.57 (sep, 1 H, *J* 3.7 Hz, H-4), 3.10 (dd, 1 H, *J* 7.0, 12.0 Hz, H-5), 3.16 (dd, 1 H, *J* 2.7, 12.5 Hz, H-2), 3.32 (dd, 1 H, *J* 5.4, 12.4 Hz, H-5), 3.50–3.70 (m, 5 H, H-2, –C*H*[OH]C*H*[OH]-CH_2OH), 4.57 (td, 1 H, *J* 3.1, 5.3 Hz, H-3), 4.78 (m, 5 H, NH, 4 × OH); ^{13}C NMR (D_2O): δ 47.9 (C-4), 48.5 (C-5), 53.6 (C-2), 63.3 (CH_2OH), 71.3, 71.4 (–CH[OH]CH[OH]–), 73.5 (C-3); HRMS (FAB) m/z 178.1078 ($[MH]^+$ $[C_7H_{16}NO_4] = 178.1079$).

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