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A route to 1-deoxynojirimycin and 1-deoxymannojirimycin derivatives with quaternary centres adjacent to the ring nitrogen from methyl α-D-mannopyranoside

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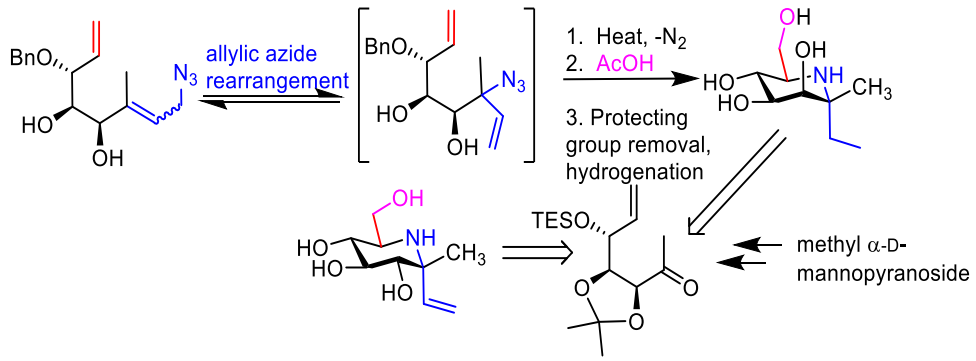
TOC graphic and TOC text: A cascade reaction incorporating the Winstein rearrangement and Huisgen cycloaddition in percursors derived from D-mannose gives iminosugars with quaternary centres



Key topic: Synthesis

Abstract

6-Alkylated-8-azido-1,6-octadiene derivatives were prepared from methyl α-D-mannopyranoside. The sequence to allylic azide precursors included a Horner-Wadsworth-Emmons reaction with a concomitant epimerization that ultimately enabled synthesis of 1-deoxynojirimycin as well as 1-deoxymannojirimycin derivatives. Thermally promoted allylic acid rearrangement followed by triazoline formation, then decomposition to aziridine and finally reaction with acetic acid was used to generate products that have quaternary anomeric centers adjacent to the piperidine ring nitrogen atom (cyclic α-tertiary amines). The stereoselectivity is accounted for based on minimization of steric interactions in the transition state structure, favouring the product where the larger methyl substituent is equatorial and the vinyl group prefers to be axial.

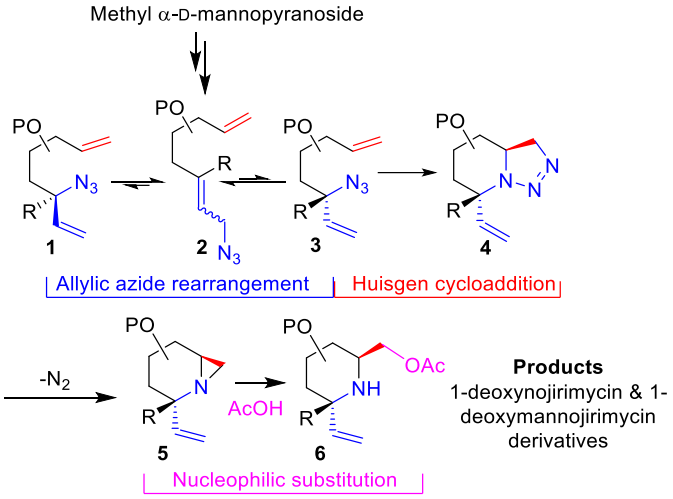
Introduction

α-Tertiary amines, which have a quaternary carbon atom with a nitrogen substituent, are of interest because of their bioactivity and relevance in medicinal chemistry. However, they are considered challenging to synthesise[1] and their preparation often involves a rearrangement to install nitrogen at the quaternary carbon.[2] Here we develop a strategy to generate such functionality in iminosugars, an important class of medicinal agents. Iminosugars are polyhydroxylated cyclic amines, where nitrogen replaces the ring oxygen in a monosaccharide, and such compounds are finding clinical use. Miglitol, miglustat, and migalastat (1-deoxynojirmycin derivatives or analogues) are used for treatment of type-2 diabetes,[3] Gaucher disease[4] and Fabry disease.[5] Other iminosugars have been, or are being, investigated in the clinic as potential new anti-viral agents.[6] The mechanism of action of iminosugars is related to their glycosidase inhibitory properties or for their ability to act as chaperones and they are classified as glycomimetics.[7]

It can be envisaged that new iminosugars with quaternary centres can be of interest in drug discovery as glycosidase inhibitors,[8] as immunological modulators,[9] as activity based probes[10] or to be used in peptidomimetic research, given they have found applicability as scaffolds in that area.[11] Despite a sustained interest in discovery of drugs based on glycomimetics,[12,13] there have been only a few syntheses of iminosugars with quaternary centers. One recent example by Py and co-workers, involved synthesis of aziridinyl iminosugars via nitrone-alkyne cycloaddition and subsequent Baldwin rearrangement.[14] Earlier, Dhavale and co-workers reported α-geminal dihydroxymethyl substituted piperidines by a route which included a variant of the Corey−Link reaction via suitably oxidized furanoses.[15] Fustero, Aceña and co-workers prepared chiral lactones using a carbon trifluoride rearrangement to an iminium ion in the quaternary center forming step and applied the methodology in iminosugar synthesis.[16]

The thermally promoted allylic azide rearrangement[17] of **2** is an equilibrium reaction that can generate α-tertiary azides **1** or **3**, which then undergo Huisgen azide-alkene cycloaddition (Scheme 1). This is

depicted for the reaction of **3** to give triazoline **4** (Scheme 1). The decomposition of the triazoline **4** to aziridine **5** can then occur and subsequent reaction with a nucleophile gives the substituted piperidine **6**. In this manuscript, we describe the application of this sequence for generating iminosugars with quaternary centers adjacent to the piperidine nitrogen, extending our earlier work using this cascade approach.[18,19]



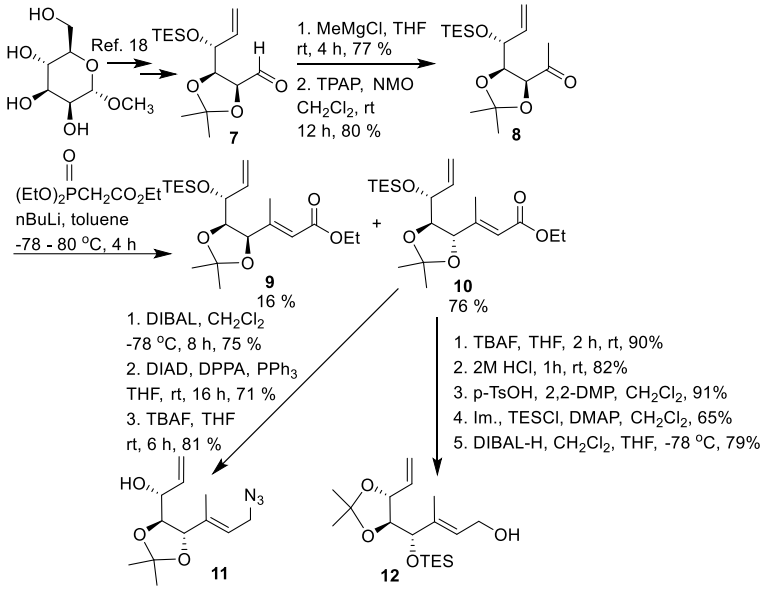
Scheme 1. Summary of synthetic approach to iminosugars with quaternary center adjacent to nitrogen.

2. Results and Discussion

2.1 Synthesis of allylic azides

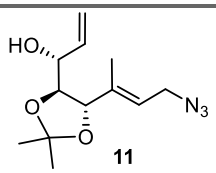
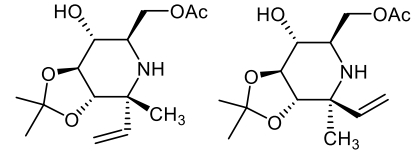
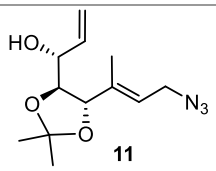
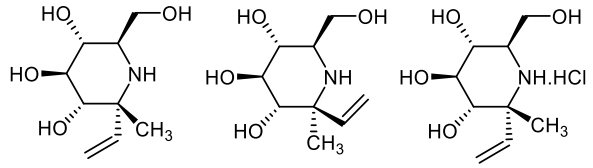
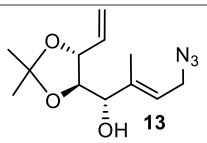
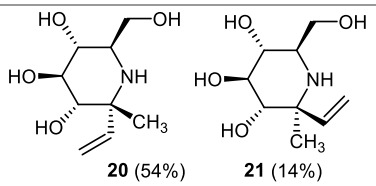
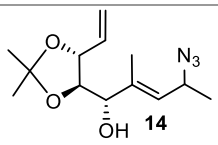
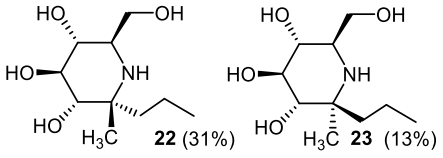
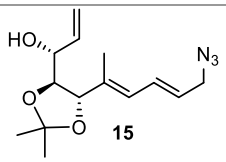
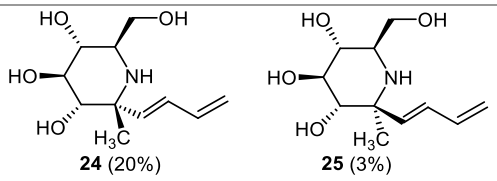
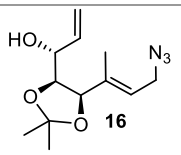
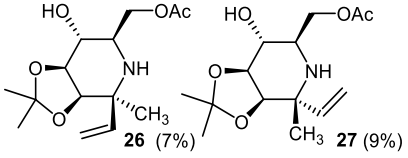
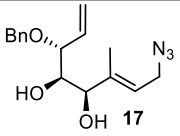
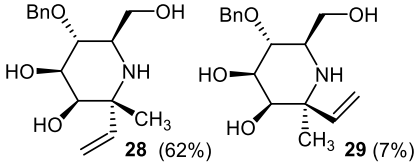
The preparation of the hydroxylated cyclic α-tertiary amines hinged firstly on the preparation of 6-substituted-8-azido-1,6-octadiene of general structure **2**. We commenced from readily available methyl α-D-mannopyranoside, which gave aldehyde **7** as previously described[17] and its subsequent Grignard reaction with MeMgCl and subsequent Ley-Griffith oxidation using TPAP-NMO gave ketone **8**. Next olefination of **8** was investigated. The required anion from the Horner-Wadsworth-Emmons precursor, ethyl 2-(diethoxyphosphoryl)acetate (Scheme 2), was generated using n-BuLi in toluene at -78 °C and its reaction with **8** gave **10** (76% yield) as the major product, as well as 16% of **9**. The formation of **10** requires epimerization at the carbon atom γ- to the carbonyl group under the reaction conditions. These

conditions gave the highest yields, with the alternative, the Wittig reaction, giving lower yields. With **10** in hand it was then converted to the azide **11** in three steps (reduction with DIBAL-H to give a primary alcohol, then exchange of the OH of the alcohol for azide and removal of the TES group). Intermediate **10** was also used to prepare **12** via first removing both the TES and acetonide protecting groups to give a triol, then acetonidation that led to protection of a different diol than that of **10**, TES protection and reduction using DIBAL-H. With both **9** and **12** available then various other allylic azides **13-17** (Table 1) were synthesized. The details of the preparations of **13-17** from **9** and **12** are provided in the experimental section. The reasons for studying the behavior of **11** and **13-17** was to investigate influence of structure on the stereoselectivity as well as efficiency of the reaction. In our preliminary study on piperidine formation using this reaction, we found what appeared to be a requirement for conformational constraint brought about by incorporating the acetonide, which is presumed to enhance the probability of the intramolecular cycloaddition reaction after allylic azide rearrangement; **11** and **13-16** contain acetonide protection, whereas **17** does not contain this restraint. In advance of this work, that reaction of **16** would be expected to give rise to a less strained transition state than that from **13** was considered, with the former giving a 1,2-cis fused ring, whereas **13** would generate a more strained 1,2-trans (diequatorial) fused ring system. Also we wished to investigate whether the nature of the allylic azide would influence behavior, for example, whether **14** would show a more facile allylic azide rearrangement (2^o to 3^o) compared to **13** (1^o to 3^o) or whether **15** would still undergo rearrangement and cycloaddition as this would require breaking of the conjugation of its diene.



Scheme 2. Synthesis of **8-12**

Table 1 Iminosugars with quaternary centres from 6-methyl-8-azido-octa-1,6-dienes (allylic azides)

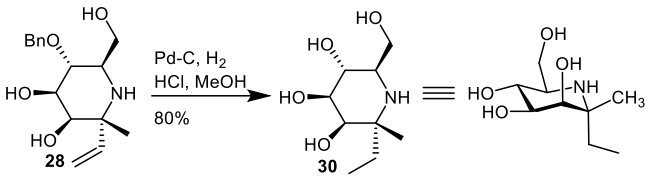
Entry	Reactant	Reagents & Conditions	Isolated Products (Yields)
1	 **11**	AcOH (5 equiv), solvent, 100 °C, 4.5 days	 Toluene **18** (30%) **19** (5%) DMF **18** (15%) **19** (5%)
2	 **11**	1. AcOH (5 equiv), toluene, 100 °C, 4.5 days 2. 2M HCl, 12 h	 Toluene **20** (43%) **21** (12%) **20.HCl** DMF **20** (24%) **21** (6%)
3	 **13**	1. AcOH, toluene, 100 °C, 4 days 2. 2M HCl, rt, 16 h	 **20** (54%) **21** (14%)
4	 **14**	1. AcOH (4 equiv), toluene, 100 °C, 4 days 2. Pd-C, MeOH, H_2, 2 h 3. 2M HCl, 16 h	 **22** (31%) **23** (13%)
5	 **15**	1. AcOH, toluene, 100 °C, 14 days 2. 2M HCl, 12 h	 **24** (20%) **25** (3%)
6	 **16**	AcOH, toluene, 100 °C, 14 days	 **26** (7%) **27** (9%)
7	 **17**	1. AcOH, toluene, 100 °C, 24 h 2. 2M HCl, 16 h	 **28** (62%) **29** (7%)

2.2 Study of cascade reactions and piperidine formation

The results from investigations with the various allylic azides are summarized in Table 1. The allylic azide was generally heated in the presence of acetic acid (nucleophile) for a time in DMF or toluene at ~100 °C to effect cycloaddition and decomposition of the triazoline and subsequent reaction with nucleophile; the conditions are summarized in Table 1. For **11** (entry 1) the reaction took 4-5 days with a mixture of **18** and **19** being isolated in low yields (20% from DMF, 35% from toluene). Acetic acid causes partial removal of the isopropylidene group during the reaction and this gives rise to lower yield of the acetonides **18**/**19**. Carrying out the reaction in absence of acetic acid from the beginning was investigated, but the triazoline generated was not stable and decomposed to different, unidentified products in its absence. The acetic acid may be required to promote the formation of the aziridine, but is certainly needed to trap the aziridine intermediate once generated. The isolated yield of piperidines is improved (entry 2) if the product mixtures were treated with aqueous HCl, ensuring full deprotection before chromatography, giving both **20** (43%) and **21** (12%). Further improvement in yield was observed from reaction of the regioisomeric precursor **13** (68% overall, entry 3). On the other hand, while **18** and **19** were separable, **20** and **21** were not, at least in our hands. A sample of the hydrochloride salt of **20** (**20**·HCl) was obtained from **18** for analytical purposes. The reaction of secondary allylic azide **14** (entry 4), gave **22** and **23**, with propyl substituents. The reaction of **15**, which involves a double allylic azide rearrangement, requiring breaking the conjugation of the diene during the rearrangement, gave **24** and **25** in low yield after a prolonged reaction time (14 days, entry 5). The products **18-25** are all 1-deoxynojirimycin (DNJ) derivatives and there was a general preference for the formation of the major products with the methyl group being equatorial and the vinyl group axial.

The formation of 1-deoxymannojirimycin (DMJ) derivatives was next investigated. The reaction of acetonide protected **16** gave rise to **26** and **27** but only in low yield (16%) after, again, a prolonged reaction time (14 days, entry 6). This contrasted with what had been anticipated in forming a more stable fused

ring product, with no improvement in yield compared to DNJ product formation. It is noteworthy however that a requirement for conformational restraint[17] provided by the acetonide was not observed in that the reaction of **17**, which had no acetonide and apparently reduced conformational bias, proceeded much more efficiently in 24 h, and gave the separable **28** and **29** (overall 69% yield, ratio ~9:1, entry 7). Some other work recently published showed that when five-membered rings fused to a triazoline are generated, that acetonide protection is not required,[19a] but the example herein is the first we have observed where the six-membered ring is fused to the triazoline is generated and can give rise to decomposition via aziridine. It is worth noting when lower yields arise it may be due to inefficient decomposition to the aziridine, where factors influencing this aspect are still not understood.[19a] As for the DNJ derivatives, the major product in the DMJ derivative had its methyl group in the equatorial orientation. Furthermore, the major isomer **28** was converted to DMJ derivative **30** after catalytic hydrogenolysis in the presence of HCl in methanol (Scheme 3).



Scheme 3. Formation of **30**

2.3 Use of NMR spectroscopy in structure determination

The use of both ^{3}J coupling constant analysis, 2D-NOESY and analysis of chemical shift trends, particularly for the C-1 substituent, supported the stereochemical assignments (see Figure 1). Firstly, ^{3}J values were generally consistent with chair conformers being predominantly adopted by the various piperidines and ^{3}J coupling constants between H-4 and H-5, for example, were consistent with the diaxial proton arrangement in the various products. For **19**, there were NOE crosspeaks observed between the methyl substituent (δ 1.25 ppm) at C-1 with H-3 (δ 3.68 ppm) and H-5 (δ 2.80 ppm), consistent with the axial orientation for the methyl group assigned to this stereoisomer. These NOE correlations were absent in the 2D NOESY spectrum of **18**, where instead there was a crosspeak between the methyl proton signal

and H-2 (δ 3.15 ppm). Examination of the ^{13}C-NMR data showed that the C-1 methyl group carbon atom is significantly shifted upfield in **19** (δ 16.50 ppm) compared with **18** (δ 28.19 ppm). This trend was also observed when comparing the chemical shift for the methyl carbon of **20** (δ 26.90 ppm) and **21** (δ 15.37 ppm) and other DNJ/DMJ derivatives prepared herein. For DMJ derivative **26** NOE correlations were observed between the signal for the anomeric methyl group (δ 1.29 ppm) with signals assigned to H-2, H-3 and H-5 (see supporting information), whereas **27** showed only correlation between the methyl proton signal and that of H-2.

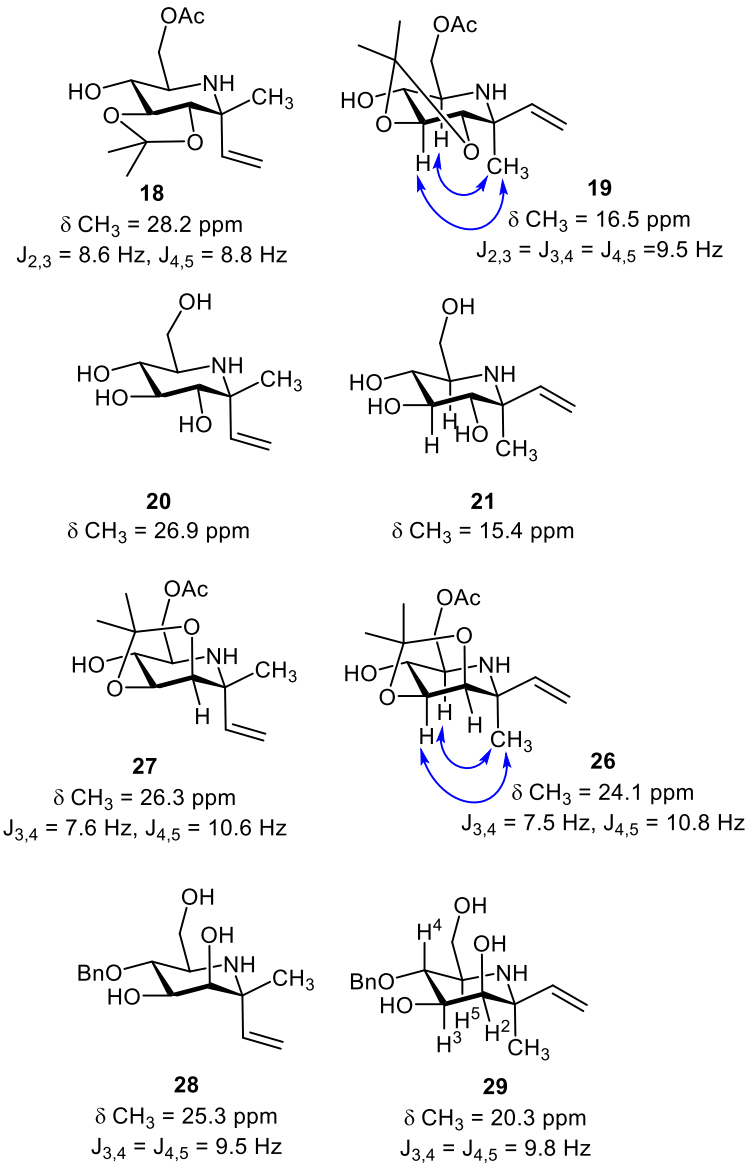


Figure 1 Selected NMR spectroscopic data (^{13}C signal for anomeric CH_3 and J values) and selected NOE correlations (indicated by blue curly arrows) observed for various piperidines that support structure assignments. The numbering for H-2 to H-5 is indicated on **29**. NOE correlations shown for **19** and **26** were not observed for **18** and **27**.

2.4 Mechanistic implications

The formation of the piperidines herein led to isolation of two of four possible stereoisomers, with all products having the H-5 axial. We have discussed previously that for piperidine formation, control at C-5 is presumably due to minimization of allylic strain in the transition state structure[19b,20], which applies herein also. The diastereoisomers isolated, thus, arise through incomplete control of stereoselectivity at C-1. Isomers with the methyl group equatorial are preferentially formed for both DNJ and for DMJ. In our earlier letter, we believed that minimization of gauche interactions, in the transition state influenced the stereochemical outcome. [14] Here, there are three substituents in the forming triazoline that need to be considered herein, CH_3, $CH{=}CH_2$ and OH or OR. Based on the use of cyclohexane A values, the methyl group is the bulkiest of these (A value for CH_3 = 1.7; for $CH{=}CH_2$ = 1.35; for OH = 0.87)[21] and the steric interaction between an axial CH_3 and the C-3 CH group will therefore give rise to the largest steric interaction (see Figure 1) and disfavor formation of products where the CH_3 is axial in formation of both DNJ and DMJ derivatives.

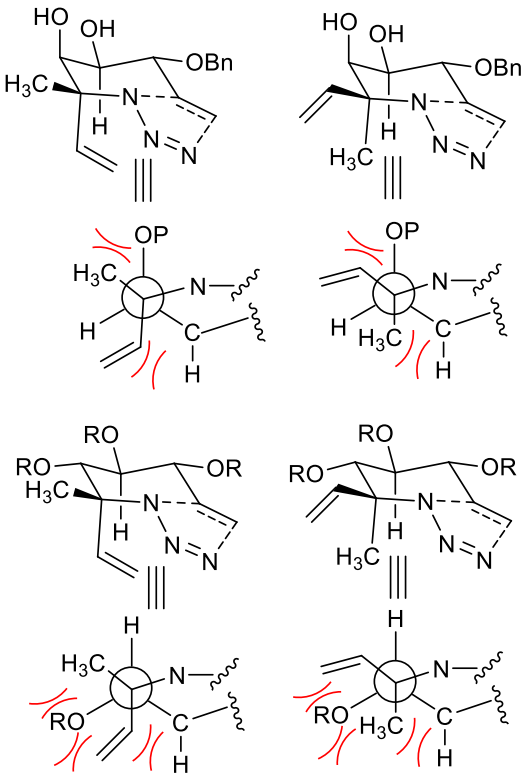


Figure 2. Possible transition states in the formation of **28** (top left) and **29** (top right) and also for DNJ derivatives (bottom structures). Largest steric interactions occur between the CH_3 group and other groups, in particular with the CH group at C-3 in transition state structures, and hence disfavor the formation of products where the methyl group is axial in the products.

4. Summary and Conclusions

Alkene-azide cycloaddition reaction combined with allylic azide rearrangement provides a new strategy for the preparation of iminosugars with quaternary centres.[22] Such iminosugars have been under explored to date in drug discovery, with potential in areas such as the development of new antiviral agents based on inhibition of glycosidases. The stereoselectivity observed from the reaction sequence is rationalized based on minimization of steric interactions in the cycloaddition transition state. We believe that competing pathways in the decomposition of the triazoline intermediate,[19a] which can proceed either to an aziridine that ultimately gives the iminosugars isolated herein, or to an imine that undergoes further decomposition is believed to influence the overall yield. However, the factors which influence the decomposition to the aziridine or imine are not understood and gaining a greater mechanistic insight could enhance the development of further applications of the reaction.

EXPERIMENTAL SECTION

GENERAL METHODS

The reagents (reagent grade) were used as obtained from Sigma-Aldrich, Fluka, Fluorochem or TCI, unless otherwise indicated. Dried organic solvents were obtained from a Puresolve purification system. During work-up procedures, organic solvents were dried over Na_2SO_4. ^{1}H-NMR spectra were recorded at 500 MHz using a Varian/Agilent spectrometer whereas ^{13}C-NMR spectra were recorded at 125 Hz. Chemical shifts in the ^{1}H-NMR spectra are reported with reference to internal Me_4Si (TMS) (δ 0.00) in $CDCl_3$; in ^{13}C-NMR spectra they are reported with reference to TMS. NMR spectra were processed and analysed using Mnova software. ^{1}H NMR signals were assigned with the aid of gDQCOSY (double quantum filtered correlation spectroscopy). ^{13}C NMR signals were assigned with the aid of gHSQCAD and gHMBC. Coupling constants are reported in Hertz and chemical shifts are reported in ppm. Mass spectral data were obtained using a Waters LCT Premier XE ESI-TOF Spectrometer, measured in either positive or negative mode, using MeCN (acetonitrile) as solvent.

1-((4S,5R)-2,2-Dimethyl-5-((R)-1-(triethylsilyloxy)allyl)-1,3-dioxolan-4-yl)ethenone 8. Aldehyde **7** (4.0 g, 13.3 mmol) was dissolved in THF (170 mL). The solution was cooled to 0 ºC and MeMgCl (13.3 mL, 3M in THF) charged slowly. The solution was allowed attain room temp and stirred for 4 h. The solution was then cooled to 0 ºC and reaction quenched with satd NH_4Cl. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were then dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Flash chromatography (EtOAc-Hexane, 1:20) afforded the intermediate alcohol (3.2 g, 77 %) as a mixture of diastereoisomers (0.45:0.55), and as a clear oil; R_f = 0.11 (EtOAc-Hexane, 1:20). This intermediate (4.5 g, 14.2 mmol) & NMO (2.5 g, 21.3 mmol) were dissolved in CH_2Cl_2 (300 mL) and stirred with 4 Å molecular sieves for 30 mins at room temp. The solution was cooled to 0 ºC, then TPAP (0.5 g, 1.4 mmol) was added and the mixture stirred while allowing to attain room temp for 12 h. The solution was filtered through celite and rinsed thoroughly with CH_2Cl_2. The solvent was removed under reduced pressure to yield the title compound **8** (3.6 g, 80 %) as a clear oil; R_f = 0.44 (hexane-EtOAc, 10:1); FTIR: 2954, 2914, 2878, 1716, 1458, 1417, 1380, 1353, 1241, 1211, 1166, 1123, 1063, 1000, 928, 906, 885, 841, 724, 671 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (ddd, *J* = 17.6, 10.3, 7.7 Hz), 5.27 (br d, *J* = 17.5, 1H), 5.17 (br d, *J* = 10.2 Hz, 1H), 4.45 (d, *J* = 7.6 Hz, 1H), 4.33 – 4.22 (overlapping signals, 2H), 2.30 (s, 3H, CH_3), 1.60 (s, 3H), 1.36

(s, 3H), 0.94 (overlapping signals, 9H), 0.57 (overlapping signals, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.7 (C=O), 137.9 (CH), 117.1 (CH_2), 109.8 ($C(CH_3)_2$), 82.7 (CH), 81.2 (CH), 72.9 (CH), 28.6 (CH_3), 26.4 ($C(CH_3)_2$), 25.0 ($C(CH_3)_2$), 6.7 ($Si(CH_2CH_3)_3$), 5.1 ($Si(CH_2CH_3)_3$); HRMS (ESI): *m/z* calc for $C_{16}H_{31}O_4Si$: 315.1992, found: 315.1980 $[M+H]^+$.

(E)-Ethyl 3-((4R,5R)-2,2-dimethyl-5-((R)-1-(triethylsilyloxy)allyl)-1,3-dioxolan-4-yl)but-2-enoate 9 and (E)-ethyl 3-((4S,5R)-2,2-dimethyl-5-((R)-1-(triethylsilyloxy)allyl)-1,3-dioxolan-4-yl)but-2-enoate 10. Triethylphosphonoacetate (2.50 mL, 12.7 mmol) was dissolved in toluene and cooled to -78 ºC. Next, nBuLi (6.9 mL, 1.6 M in hexanes) was charged slowly and the mixture was stirred for 30 min. The ketone **8** (2.66 g, 8.46 mmol) in THF (12 mL) was then added and the reaction mixture was warmed to 80 ºC and heating was maintained at this temperature for 3 h. The solution was cooled to room temp and satd. NH_4Cl (aq) added and the mixture added to a separating funnel, the layers were separated, and the aqueous layer extracted with EtOAc. The organic portions were combined and then dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexane-EtOAc, 40:1) afforded diastereoisomers **9** (0.52 g, 16 %) and **10** (2.45 g, 76 %) both as clear oils. Analytical data for **9**: FTIR 2955, 2877, 1717, 1655, 1458, 1405, 1379, 136, 1324, 1219, 1151, 1072, 1039, 1004, 924, 867, 841, 811, 725 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (m, 1H), 5.87 (ddd, *J* = 17.2, 10.4, 6.7 Hz, 1H), 5.23 (dt, *J* = 17.1, 1.5 Hz, 1H), 5.14 (dt, *J* = 10.4, 1.2 Hz, 1H), 4.59 (dd, *J* = 6.9, 1.3 Hz, 1H), 4.22 – 4.14 (3H, overlapping signals), 4.09 (dd, *J* = 6.8, 5.5, 1.0 Hz), 2.19 (d, *J* = 1.3 Hz, 3H), 1.56 (s, 3H), 1.38 (s, 3H), 1.29 (m, 3H), 0.94 (overlapping signals, 9H), 0.59 (overlapping signals, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3 (C=O), 153.0 (C), 137.4 (CH), 117.8 (CH), 117.0 (CH_2), 108.8 (C), 81.4 (CH), 81.0 (CH), 73.5 (CH), 59.6 (CH_2), 26.4 (CH_3), 25.2 (CH_3), 17.4 (CH_3), 14.3 (CH_3), 6.7 ($Si(CH_2CH_3)_3$), 4.9 ($Si(CH_2CH_3)_3$); HRMS (ESI): m/z calc for $C_{20}H_{36}O_5SiNa$: 407.2230, found: 407.2239 $[M+Na]^+$. Analytical data for **10**: R_f = 0.14 (hexane-EtOAc, 40:1); FTIR 2956, 2878, 1718, 1655, 1458, 1406, 1379, 1370, 1314, 1219, 1150, 1074, 1040, 1004, 924, 868, 828, 810, 687 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 – 5.92 (2H, overlapping signals), 5.34 (dt, *J* = 17.4, 1.9 Hz, 1H), 5.25 (dt, *J* = 10.4, 1.6 Hz, 1H), 4.41 (d, *J* = 7.4 Hz, 1H), 4.34 (ddt, *J* = 5.6, 4.0, 1.4, 1.4 Hz, 1H), 4.17 and 4.18 (2 x q overlapping, *J* = 7.0, 7.0,

2H, OCH_2), 3.86 (dd, *J* = 7.7, 4.0 Hz, 1H, H-4), 2.17 (br s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.29 (m, 3H, CH_3), 0.95 (overlapping signals, 9H, $Si(CH_2CH_3)_3$), 0.61 (overlapping signals, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4 (C=O), 155.1 (C), 136.9 (CH), 117.8 (CH), 116.6 (CH_2), 109.7 (C), 82.7 (CH), 81.0 (CH), 72.8 (CH), 59.7 (CH_2), 27.0 (CH_3), 27.0 (CH_3), 14.6 (CH_3), 14.2 (CH_3), 6.7 ($Si(CH_2CH_3)_3$), 4.8 ($Si(CH_2CH_3)_3$); HRMS (ESI): m/z calc for $C_{20}H_{36}O_5SiNa$: 407.2230, found: 407.2223 $[M+Na]^+$

((R)-1-((4R,5S)-5-((E)-4-Azidobut-2-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)allyloxy)triethylsilane

11. Compound **10** (2.88 g, 7.48 mmol) was dissolved in CH_2Cl_2 and the mixture was cooled to -78 ºC and DIBAL-H (22.5 mL, 1M in CH_2Cl_2) added slowly and the mixture was stirred at -78 ºC for 8 h. MeOH was added slowly and the mixture allowed to attain room temp and was then stirred with aq satd potassium tartrate until clear. The layers were separated, and the organic portions combined and subsequently washed with H_2O, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to give a primary alcohol intermediate (1.92 g, 75 %) as a clear oil (R_f = 0.57 (EtOAc-hexane, 3:2)). This alcohol (2.32 g, 6.77 mmol) was dissolved in anhydrous THF (50 mL) and PPh_3 (3.0 g, 12 mmol) was added. The solution was cooled to 0ºC, followed by the addition of DIAD (2.27 mL, 11.5 mmol) and DPPA (2.47 mL, 11.5 mmol). The solution was allowed attain room temp and stirred for 16 h. The reaction mixture was concentrated and flash chromatography (hexane-EtOAc, 40:1) gave TES protected azide intermediate (1.64 g, 71 %) as a clear oil; R_f = 0.31 (EtOAc-hexanes, 1:20); FTIR 2955, 2877, 2094, 1457, 1415, 1379, 1369, 1239, 1167, 1132, 1068, 1033, 1055, 925, 880, 831, 726, 686 cm^{-1}. This intermediate (1.6 g, 4.4 mmol) was dissolved in anhydrous THF (30 mL) and TBAF (3.1 mL, 1 M in THF) charged slowly. The reaction mixture was stirred at room temp for 6 h and 3M NaOH added. After separation of layers, the aq layer was extracted with EtOAc and then the combined organic layers were then dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexane, 1:4) gave **11** (0.89 g, 81 %) as a clear oil; R_f = 0.59 (EtOAc-hexane, 1:1); FTIR 3472, 2987, 2935, 2095, 1644, 1456, 1371, 1218, 1165, 1135, 1106, 1060, 991, 928, 874, 825, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (ddd, J = 17.0, 10.5, 6.2 Hz, 1H), 5.71 (t, J = 7.2 Hz, 1H), 5.39 (d, J = 17.3 Hz, 1H), 5.25

(dt, J = 10.2 Hz, 1H), 4.45 (d, J = 8.1 Hz, 1H), 4.10 (m, 1H), 3.90 (dd, J = 14.0, 7.6 Hz, 1H), 3.75-3.85 (overlapping ms, 2H); 2.19 (d, J = 7.8 Hz, 1H), 1.76 (s, 3H, CH_3), 1.47 (s, 3H, $C(CH_3)_2$), 1.46 (s, 3H, $C(CH_3)_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5 (C), 137.4 (CH), 122.8 (CH), 117.0 (CH_2), 109.8 ($C(CH_3)_2$), 82.2, 81.4, 71.4 (each CH), 47.7 (CH_2N_3), 27.3 (2 x($C(CH_3)_2$), 12.1 (CH_3); HRMS (ESI): m/z calc for $C_{12}H_{20}N_3O_3$: 254.1505 found: 254.1515 $[M+H]^+$.

(S,E)-1-((4R,5R)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-methyl-4-triethylsilyloxy-but-2-ene-1-ol 12. Compound **10** (2.12 g, 5.51 mmol) was dissolved in anhydrous THF (40 mL) and TBAF (11.0 mL, 1 M in THF buffered with 20 % AcOH) charged slowly. The reaction mixture was stirred at room temp for 2 h, followed by the addition of pH buffer 7 solution (30 mL). The aqueous layer was extracted with EtOAc. The combined organic layers were then dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexane, 3:7) afforded the intermediate alcohol (1.34 g, 90 %) as a clear oil (R_f = 0.63 (EtOAc-hexanes, 3:7)). This alcohol (1.25 g, 4.62 mmol) was dissolved in 2M HCl (10 mL) and the mixture stirred at room temp for 1 h. The solution was extracted with EtOAc, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 7:3) afforded the required triol (0.88 g, 82 %) as a clear oil (R_f = 0.53 (hexanes-EtOAc, 7:3)). This triol (2.67 g, 11.6 mmol) was dissolved in CH_2Cl_2 (30 mL). The solution was cooled to 0 ºC and *p*-TsOH (0.4 g, 2.3 mmol) added. After stirring for 10 mins, 2,2-DMP (2.85 mL, 23.2 mmol) was added. The reaction mixture was subsequently stirred at room temp for 15 mins and triethylamine (1.60 mL, 11.6 mmol) charged. The solvent was then removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 7:3) afforded the required isopropylidene derivative (2.85 g, 91 %) as a clear oil (R_f = 0.72 (hexanes-EtOAc, 7:3); selected ^1H NMR data (500 MHz, $CDCl_3$): δ 5.97 (s, 1H), 5.82 (ddd, *J* = 17.3, 10.3, 7.4 Hz, 1H), 5.42 (d, *J* = 17.0 Hz, 1H), 5.32 (d, *J* = 10.4 Hz, 1H), 4.39 (t, *J* = 7.9 Hz, 1H), 4.18 (overlapping signals), 3.99 (dd, *J* = 8.4, 2.6 Hz, 1H), 3.82 (dd, *J* = 8.3, 2.6 Hz, 1H), 2.58 (d, *J* = 8.6 Hz), 2.15 (s, 3H, CH_3), 1.46 and 1.45 (each s, each 3H, $C(CH_3)_2$), 1.30 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3 (C=O), 156.5, 134.4, 119.9, 116.7, 109.9 ($C(CH_3)_2$), 80.8, 79.4, 73.6 (each CH), 59.8 (CH_2), 27.1 & 26.8 ($C(CH_3)_2$), 15.2 (CH_3), 14.2 (CH_3); HRMS (ESI): m/z calc for $C_{14}H_{22}O_5$

Na: 293.1365, found 293.1354 $[M+Na]^+$. This isopropylidene derivative (2.61 g, 9.65 mmol) was dissolved in CH_2Cl_2 (35 mL) followed by the addition of imidazole (1.25 g, 18.3 mmol), triethylsilane chloride (1.85 mL, 11.9 mmol) and DMAP (0.12 g, 0.97 mmol) and the mixture was stirred for 4 h. It was then diluted with CH_2Cl_2 (20 mL) and H_2O added (50 mL). The organic layer was separated & aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexane-EtOAc, 9:1) afforded silylated intermediate (2.41 g, 65%) as a clear oil. This intermediate (2.3 g, 6.0 mmol) was dissolved in CH_2Cl_2 and the mixture was cooled to -78 ºC and DIBAL-H (17.9 mL, 1M in THF) was added slowly and solution stirred at -78 ºC for 4 h. MeOH was carefully added and the mixture was allowed attain room temp and then aq satd potassium tartrate was added until clear. The organic layer was washed with H_2O, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford **12** (1.62 g, 79 %) as a clear oil (R_f = 0.57, EtOAc-hexane, 3:2); FTIR 3434, 2954, 2877, 1458, 1413, 1378, 1239, 1214, 1170, 1095, 1059, 1004, 927, 884, 834, 725, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.75 (ddd, J = 17.2, 10.3, 7.0 Hz, 1H), 5.62 (t, J = 6.4 Hz, 1H), 5.29 (d, J = 17.0 Hz, 1H), 5.19 (d, J = 10.1 Hz, 1H), 4.24 – 4.17 (overlapped signals, 2H, H-6 & H-1), 4.14 (dt, J = 12.7, 6.1 Hz, 1H), 4.04 (d, J = 6.0 Hz, 1H), 3.75 (dd, J = 8.1, 6.0 Hz, 1H), 1.63 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 0.95 (overlapped signals, 9H, TES CH_3), 0.60 (overlapped signals, 6H, TES CH_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.3 (alkene C), 136.0 (alkene CH), 126.5 (alkene CH), 118.2 (alkene CH_2), 109.0 ($C(CH_3)_2$), 83.1, 78.9, 78.5 (each CH), 59.1 (CH_2) 27.0 ($C(CH_3)_2$), 26.8 ($C(CH_3)_2$), 12.8 (CH_3), 6.7 (TES CH_3), 4.8 (TES CH_2); HRMS (ESI): m/z calc for $C_{18}H_{34}O_4SiCl$: 377.1915, found 377.1929 $[M+Cl]^-$.

(S,E)-4-Azido-1-((4R,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-methylbut-2-en-1-ol 13. The primary alcohol **12** (0.6 g, 1.8 mmol) was dissolved in anhydrous THF (10 mL) and PPh_3 (0.78 g, 2.98 mmol) was then added. The solution was cooled to 0ºC, followed by the addition of DIAD (0.59 mL, 2.98 mmol) and DPPA (0.64 mL, 2.98 mmol). The solution was allowed attain room temp and stirred for 12

h. The solvent was removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 40:1) afforded TES protected azide precursor to **13** (0.46 g, 73 %) as a clear oil. This precursor (0.49 g, 1.33 mmol) was dissolved in anhydrous THF (16 mL) and TBAF (4.0 mL, 1 M in THF) was charged slowly. The solution was stirred at room temp for 12 h. The mixture was then quenched with 3M NaOH and stirred for 15 min. The aqueous layer was extracted with EtOAc and the combined organic layers were then dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:1) afforded azide **13** (0.28 g, 85 %) as a clear oil; R_f = 0.8 (EtOAc-hexanes, 1:1); FTIR 3460, 2987, 2094, 1455, 1372, 1215, 1168, 1056, 988, 939, 878, 817 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ^1H NMR (500 MHz, Chloroform-d) δ 5.79 (ddd, J = 17.5, 10.3, 7.4 Hz, 1H), 5.64 (t, J = 7.1 Hz, 1H), 5.38 (d, J = 17.1 Hz, 1H), 5.28 (d, J = 10.3, 1H), 4.31 (dd, J = 8.3, 7.4, 1H), 4.00 (dd, J = 7.1, 4.1 Hz, 1H), 3.84 (d, J = 7.1 Hz, 2H), 3.79 (dd, J = 8.2, 4.1 Hz, 1H), 2.47 (d, J = 6.8 Hz, 1H), 1.71 (br s, 3H, CH_3), 1.46 (s, 3H, $C(CH_3)_2$), 1.44 (s, 3H, $C(CH_3)_2$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.7 (C), 134.8 (CH), 120.6 (CH), 119.5 (CH_2), 109.7 ($C(CH_3)_2$), 81.5, 79.4, 75.0 (each CH), 47.7 (C-1), 27.1 ($C(CH_3)_2$), 26.9 ($C(CH_3)_2$), 12.9 (CH_3); HRMS (ESI): m/z calc for $C_{12}H_{19}O_3N_3Cl$: 288.1115, found 288.1123 $[M+Cl]^-$

(S,E)-4-Azido-1-((4R,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-methylpent-2-en-1-ol 14

The alcohol **12** (1.32 g, 3.85 mmol, was dissolved in CH_2Cl_2 and the mixture was cooled to 0 ºC and Dess Martin periodinane reagent was added (2.45 g, 5.78 mmol). The reaction mixture was stirred at room temp for 1 h. The solution was subsequently diluted with Et_2O and stirred with aqueous $Na_2S_2O_3$ (1 g/L) containing $NaHCO_3$ (100 g/L). The organic layer was separated and washed with H_2O, brine, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to yield the desired aldehyde intermediate (1.11 g, 85 %) as a clear oil; R_f = 0.31 (EtOAc-hexanes, 1:20); ^1H NMR data (500 MHz, $CDCl_3$) δ 10.05 (d, *J* = 7.9 Hz, 1H), 6.07 (d, *J* = 8.0 Hz, 1H), 5.79 (ddd, *J* = 17.4, 10.3, 7.1 Hz, 1H), 5.33 (d, *J* = 17.1 Hz, 1H), 5.24 (d, *J* = 10.3 Hz, 1H), 4.29 (t, *J* = 7.6 Hz, 1H), 4.20 (d, *J* = 4.3 Hz, 1H), 3.78 (dd, *J* = 8.0, 4.4 Hz, 1H), 2.18 (d, *J* = 1.3 Hz, 3H, CH_3), 1.40 (s, 6H, 2 x $C(CH_3)_2$), 0.95 (overlapping signals, 9H, $Si(CH_2CH_3)_3$), 0.61 (overlapping signals, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.1 (C=O), 161.5, 135.4, 127.5, 118.9, 109.4 ($C(CH_3)_2$), 82.7, 78.3, 76.2, 27.0 ($C(CH_3)_2$), 26.6 ($C(CH_3)_2$),

14.5 (CH_3), 6.7 (Si(CH_2CH_3)$_3$), 4.7 (Si(CH_2CH_3)$_3$); HRMS (ESI): m/z calc for $C_{18}H_{32}O_4NaSi$: 363.1968, found 363.1958 $[M+Na]^+$. This aldehyde (0.65 g, 1.91 mmol) was dissolved in THF (50 mL) and methyl magnesium chloride (1.9 mL, 3M in Et_2O) added. The solution was stirred at room temp for 4 h. The reaction mixture was quenched with satd. NH_4Cl (aq), extracted with EtOAc, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 9:1) gave the desired secondary alcohol (0.55 g, 86 %) as a clear oil; R_f = 0.27 (hexanes-EtOAc, 9:1); FTIR 3420, 2955, 2877, 1457, 1413, 1369, 1239, 1213, 1170, 1053, 1005, 927, 886, 823, 803, 726, 671 cm^{-1}; HRMS (ESI): m/z calc for $C_{19}H_{36}O_4NaSi$: 379.2281, found 379.2287 $[M+Na]^+$. A mixture of this alcohol (0.54 g, 1.51 mmol) and PPh_3 (0.68 g, 2.57 mmol) in anhydrous THF (75 mL) was cooled to 0ºC, and this was followed by the slow addition of DIAD (0.51 mL, 2.57 mmol) and DPPA (0.55 mL, 2.57 mmol) and the mixture was allowed attainroom temp while being left for 16 h. The solvent was then removed under reduced pressure and flash chromatography (hexane-EtOAc, 80:1) gave the TES protected precursor to **14** (0.41 g, 62 %) as a clear oil; R_f = 0.16 (hexanes-EtOAc, 80:1); HRMS (ESI): m/z calc for $C_{19}H_{36}N_3O_3Si$: 382.2526, found 382.2539 $[M+H]^+$. To this precursor (0.41 g, 1.07 mmol) in THF (8 mL) and TBAF (2.15 mL, 1M in THF), 20% AcOH was added. The solution was stirred at room temp for 4 h and the mixture then quenched with slow addition of 3M NaOH, and stirred for a further 15 mins. The mixture was extracted with EtOAc, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:1) afforded azide **14** (0.21 g, 75 %) as a clear oil; R_f = 0.85 (EtOAc-hexanes, 1:1); FTIR 3454, 2986, 2097, 1454, 1373, 1217, 1168, 1038, 988, 928, 877, 813, 683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 – 5.70 (1H, m), 5.52 – 5.42 (1H, m), 5.41 (d, *J* = 17.5 Hz, 1H), 5.36 (d, *J* = 17.2 Hz, 1H), 5.30 – 5.25 (d, J = 10.5 Hz, 1H), 4.45 (d, J = 8.3 Hz), 4.10 (m, 1H), 3.90 (dd, *J* = 14.0, 7.6 Hz, 1H), 3.82 – 3.75 (2H, overlapping signals), 2.20 (d, *J* = 7.9 Hz, 1H), 1.47, 1.48 (each s, each CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.3, 137.3, 122.7, 116.8, 109.7, 82.0, 81.3, 71.3, 47.6, 27.1, 11.9; HRMS (ESI): m/z calc for $C_{13}H_{22}N_3O_3$: 268.1661, found 268.1675 $[M+H]^+$.

(R)-1-((4S,5S)-5-((2E,4E)-6-azidohexa-2,4-dien-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol 15 The alcohol **12** (3.0 g, 8.8 mmol) was dissolved in CH_2Cl_2 and the solution was cooled to 0 ºC and

Dess Martin periodinane (7.43 g, 17.5 mmol) was added. The reaction mixture was then stirred at room temp for 4 h, and then diluted with Et_2O and stirred with aqueous $Na_2S_2O_3$ (1 g/L) containing $NaHCO_3$ (100 g/L). The organic layer was separated and washed with H_2O, brine, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to yield the aldehyde intermediate (2.5 g, 84 %) as a clear oil; R_f = 0.81 (hexane-EtOAc, 3:2); HRMS (ESI): m/z calc for $C_{18}H_{33}O_4Si$: 341.2148 Found: 341.2153 $[M+H]^+$. This aldehyde (1.5 g, 4.4 mmol) was dissolved in THF (70 mL) and vinyl magnesium bromide (4.4 mL, 3M in Et_2O) charged. The reaction mixture was stirred at room temp for 4 h. Subsequently satd. NH_4Cl (aq) was added and the mixture extracted with EtOAc, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexane-EtOAc, 10:1) gave diastereoisomeric alcohols (1.4 g, 83 %), which were separable. The mixture of alcohols was dissolved in anhydrous THF (160 mL) and PPh_3 (1.43 g, 5.44 mmol) was added. The solution was cooled to 0ºC, followed by the addition of DIAD (1.1 mL, 5.4 mmol) and DPPA (1.17 mL, 5.55 mmol) and solution was stirred at room temp for 24 h. The solvent was removed under reduced pressure and flash chromatography (hexane-EtOAc, 160:1) afforded the TES protected precursor azide (0.8 g, 64 %) as a clear oil; R_f = 0.47 (EtOAc-hexane, 1:10); HRMS (ESI): m/z calc for $C_{20}H_{36}N_3O_3Si$: 394.2526 found: 394.2520 $[M+H]^+$. This intermediate (0.68 g, 1.73 mmol) was dissolved in anhydrous THF (20 mL), then TBAF (3.5 mL, 1 M in THF) was added. The reaction mixture was stirred at room temp for 16 h and subsequently 3M NaOH (10 mL) added and the mixture was stirred for 15 min. The aqueous layer was taken and extracted with EtOAc and all organic portions were combined and dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:1) afforded azide **15** (0.35 g, 73 %) as a clear oil; R_f = 0.7 (EtOAc-hexanes, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (dd, *J* = 14.8, 11.0 Hz, 1H), 6.16 (d, *J* = 11.0 Hz, 1H), 5.86 (ddd, *J* = 17.4, 10.5, 5.5 Hz, 1H), 5.74 (dt, *J* = 14.2, 6.6 Hz, 1H), 5.37 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.43 (d, *J* = 8.4 Hz, 1H), 4.07 (broad s, 1H), 3.85 (d, *J* = 6.7 Hz, 2H), 3.78 (dd, *J* = 8.6, 3.1 Hz, 1H), 2.19 (d, *J* = 7.9 Hz, 1H), 1.82 (s, 3H, CH_3), 1.47 (s, 3H, $C(CH_3)_2$), 1.45 (s, 3H, $C(CH_3)_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.4, 134.9, 129.8, 127.9, 126.9, 116.5, 109.5 ($C(CH_3)_2$), 82.5,

81.0, 71.1, 52.8, 27.1 (2s, C(*C*H_3)$_2$), 12.1 (CH_3); HRMS (ESI): m/z calc for $C_{14}H_{22}N_3O_3$: 280.1661, found: 280.1648 $[M+H]^+$

(R)-1-((4S,5R)-5-((E)-4-azidobut-2-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol 16. Ester **9** (0.86 g, 2.24 mmol) was dissolved in CH_2Cl_2. The solution was cooled to -78 ºC and DIBAL-H (6.7 mL, 1M in CH_2Cl_2) was added slowly. The reaction mixture was then stirred at -78 ºC for 7 h followed by quenching with the slow addition of MeOH. The solution was warmed to room temp and stirred with aq potassium tartrate until clear. The organic layer was separated and subsequently washed with H_2O, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to obtain the desired alcohol intermediate (0.57 g, 74 %) as a clear oil; R_f = 0.33 (EtOAc-hexanes, 3:7); HRMS (ESI): m/z calc for $C_{18}H_{34}O_4NaSi$: 365.2124, found: 365.2111 $[M+Na]^+$. This alcohol (0.58 g, 1.70 mmol) was dissolved in anhydrous THF (60 mL) and PPh_3 (0.76 g, 2.89 mmol) was added. The mixture was cooled to 0ºC, followed by addition of DIAD (0.57 mL, 2.89 mmol) and DPPA (0.62 mL, 2.89 mmol). It was allowed attain room temp and was stirred for 24 h. The solvent was removed under reduced pressure and flash chromatography (hexanes-EtOAc, 80:1) the TES protected azide (0.31 g, 50 %) as a clear oil; R_f = 0.35 (EtOAc-hexanes, 1:20); HRMS (ESI): m/z calc for $C_{18}H_{34}N_3O_3Si$: 368.2369, found 368.2357 $[M+H]^+$. This intermediate (0.42 g, 1.14 mmol) was dissolved in THF (25 mL) and TBAF (3.42 mL, 1M in THF) was subsequently charged. The reaction mixture was stirred at room temp for 4 h and subsequently quenched upon addition of 3M NaOH. The solution was diluted with EtOAc and organic layer separated, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:4) afforded the azide **16** (0.24 g, 83 %) as a clear oil; R_f = 0.41 (EtOAc-hexanes, 1:4); ^{1}H NMR (500 MHz, CDCl): δ 5.84 – 5.70 (overlapping ms, 2H), 5.35 (d, *J* = 17.4 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 4.63 (d, *J* = 6.4 Hz, 1H), 4.09 (t, *J* = 6.5 Hz, 1H), 4.04 (t, *J* = 6.3 Hz, 1H), 3.91 – 3.80 (overlapping ms, 2H), 2.17 (d, *J* = 0.7 Hz, 1H, OH signal), 1.74 (s, 3H, CH_3), 1.58 (s, 3H, C(CH_3)$_2$), 1.42 (s, 3H, C(CH_3)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.6, 136.4, 120.9, 117.7, 108.7 (*C*(CH_3)$_2$), 80.3, 80.3, 70.4, 47.7, 27.1 (C(*C*H_3)$_2$), 25.2 (C(*C*H_3)$_2$), 15.2 (CH_3); HRMS (ESI): m/z calc for $C_{12}H_{20}N_3O_3$: 254.1505, found 254.1516 $[M+H]^+$

(3R,4R,5R,E)-8-Azido-3-(benzyloxy)-6-methylocta-1,6-diene-4,5-diol 20. Compound **16** (0.18 g, 0.71 mmol) was dissolved in DMF (6 mL) and the solution was cooled to 0 ºC and NaH (31 mg, 60 % in mineral oil) added portion wise. The reaction mixture was stirred at 0 ºC for 30 min and this was followed by the addition of BnBr (0.25 mL, 2.13 mmol). The mixture was allowed attain room temp and stirred for 3.5 h. Water was added and the product was extracted into Et_2O (x 2). The combined organic layers were washed with satd. NH_4Cl (aq), dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:1) afforded the benzyl ether (0.21 g, 86 %) as a clear oil; R_f = 0.81 (EtOAc-hexanes, 1:1); HRMS (ESI): m/z calc for $C_{19}H_{25}N_3O_3Na$: 366.1794, found 366.1794 $[M+Na]^+$. To this ether (0.2 g, 0.6 mmol) in MeOH (2 mL) 2M HCl (10 mL) was added and the solution was stirred at room temp for 16 h and CH_2Cl_2 was then added. The organic layer was separated, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:1) afforded **17** (0.13 g, 73 %) as a clear oil; R_f = 0.61 (EtOAc-hexanes, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.22 (overlapping signals, 5H, aromatic H), 5.97 (ddd, *J* = 17.7, 10.4, 7.9 Hz, 1H), 5.62 (t, *J* = 7.3 Hz, 1H), 5.47 – 5.33 (2H, overlapping signals), 4.63 (d, *J* = 11.3 Hz, 1H), 4.33 (d, *J* = 11.4 Hz, 1H), 4.18 (t, *J* = 5.4 Hz, 1H), 4.05 (dd, *J* = 7.9, 3.1 Hz, 1H), 3.82 (2H, overlapping peaks), 3.64 (m, 1H), 2.99 (d, *J* = 6.2 Hz, 1H, OH), 2.57 (d, *J* = 7.6 Hz, 1H, OH), 1.71 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4 (C-3), 137.4 (Ar-C), 134.9 (C-7), 128.6 (Ar-CH x 2), 128.2 (Ar-CH x 2), 128.1 (Ar-CH), 120.1 (C-2), 119.8 (C-8), 79.9 (C-6), 77.7 (C-4), 73.3 (C-5), 70.5 (C-9), 47.6 (C-1), 13.0 (CH_3); HRMS (ESI): m/z calc for $C_{16}H_{21}N_3O_3Na$: 326.1481, Found 326.1480 $[M+Na]^+$.

(1*R*)-6-*O*-Acetyl-1,5-dideoxy-1-ethenyl-2,3-O-isopropylidene-1-methyl-1,5-imino-D-glucitol 18 & (1*S*)-6-*O*-acetyl-1,5-dideoxy-1-ethenyl-2,3-O-isopropylidene-1-methyl-1,5-imino-D-glucitol 19. Compound **12** (0.050 g, 0.197 mmol) was dissolved in toluene (20 mL) and acetic acid (56.0 µL, 0.98 mmol) was subsequently charged. The mixture was stirred at 98 ºC for 4.5 days. The solvent was then removed under reduced pressure. Flash chromatography (hexane-EtOAc, 1:1) gave in order of elution **18** (17 mg, 30%) and **19** (3 mg, 4 %) as clear oils.

Analytical data for **18**: R_f = 0.23 (hexane-EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.36 (d, *J* = 17.8 Hz, 1H), 5.23 (dd, *J* = 10.7 Hz, 1H), 4.52 (dd, *J* = 11.5, 4.6 Hz, 1H, H-6), 4.19 (dd, *J* = 11.4, 2.5 Hz, 1H, H-6), 3.55 – 3.44 (overlapping signals, 2H, H-3 & H-4), 3.15 (d, *J* = 8.6 Hz, 1H, H-2), 2.81 (ddd, *J* = 8.8, 4.4, 2.4 Hz, 1H, H-5), 2.12 (s, 3H, OAc), 1.45 (s, 3H, $C(CH_3)_2$), 1.41 (s, 3H, $C(CH_3)_2$), 1.25 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.48 (C=O), 136.85 (alkene CH), 114.85 (alkene CH_2), 110.21 ($C(CH_3)_2$), 83.27 (C-2), 79.13, 72.41 (each C-3, C-4), 63.85 (C-6), 57.04 (C-1) 55.71 (C-5), 28.19 (CH_3), 26.97 ($C(CH_3)_2$), 26.53 ($C(CH_3)_2$), 20.88 (OAc); HRMS (ESI): m/z calc for $C_{14}H_{24}NO_5$: 286.1654 found: 286.1663 $[M+H]^+$.

Analytical data for **19:** R_f = 0.17 (hexane-EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.31 (d, *J* = 17.4 Hz, 1H), 5.14 (d, *J* = 10.8 Hz, 1H), 4.62 (dd, *J* = 11.5, 4.0 Hz, 1H, H-6), 4.17 (d, *J* = 11.4 Hz, 1H, H-6), 3.69 (t, *J* = 9.5, 1H, H-3), 3.49 (t, *J* = 9.4 Hz, 1H, H-4), 3.24 (d, *J* = 9.4 Hz, 1H, H-2), 2.95 – 2.61 (broad signal, 1 or 2H, H-5), 2.11 (s, 3H, OAc), 1.45 (s, 3H, $C(CH_3)_2$), 1.43 (s, 3H, $C(CH_3)_2$), 1.24 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6 (C=O), 143.39 (alkene CH), 113.65 (alkene CH_2), 110.12 ($C(CH_3)_2$), 81.13 (C-2), 78.20 (C-3), 72.09 (C-4), 63.73 (C-6), 56.50 (C-1), 55.60 (C-5), 26.95 ($C(CH_3)_2$), 26.55 ($C(CH_3)_2$), 20.86 (OAc), 16.50 (CH_3); HRMS (ESI): m/z calc for $C_{14}H_{24}NO_5$: 286.1654 found: 286.1661$[M+H]^+$.

(1*R*)-1,5-Dideoxy-1-ethenyl-1-methyl-1,5-imino-D-glucitol 20 & (1*S*)-1,5-dideoxy-1-ethenyl-1-methyl-1,5-imino-D-glucitol 21 from azide 12. The azide **12** (50 mg, 0.19 mmol) was dissolved in toluene (20 mL) and acetic acid (56.0 µL, 0.98 mmol) subsequently charged. The reaction mixture was stirred at 98 ºC for 4.5 days and the solvent then removed under reduced pressure. The residue was subsequently treated with 1M HCl (5 mL) for 12 h. The volatile components were then removed under reduced pressure. Flash Chromatography (CH_2Cl_2-MeOH-aq NH_3-H_2O, 8:2:0.1:0.1) afforded **20** and **21** (21 mg, 55 %) as an inseparable 4:1 mixture of isomers and as a yellow foam; R_f = 0.11 (CH_2Cl_2-MeOH-aq NH_3-H_2O, 8:2:1:1); HRMS (ESI): *m/z* calc for $C_9H_{18}NO_4$: 204.1236 found: 204.1243 $[M+H]^+$. Selected ^{1}H-NMR data (500 MHz, CD_3OD) for major isomer **20**: δ 6.12 (dd, *J* = 18.0, 11.2 Hz, 1H), 5.22-5.29 (overlapping signals, 2H), 3.84 (dd, *J* = 10.9, 3.1 Hz, 1H), 3.55 (dd, *J* = 10.9, 6.9 Hz, 1H); ^{13}C NMR (126 MHz,

CD_3OD) δ 138.12 (alkene CH), 113.63 (alkene CH_2), 77.82 (CH, C-2), 75.59 (CH, C-3), 72.85 (CH, C-4), 61.99 (CH_2, C-6), 58.39 (CH, C-1), 55.86 (CH, C-5), 26.90 (CH_3). Selected ^{1}H-NMR (500 MHz, CD_3OD) for the minor isomer **21**: δ 5.98 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.13 (d, *J* = 10.9 Hz, 1H), 3.65 (dd, *J* = 10.9, 6.0 Hz, 1H), 3.45 (t, *J* = 9.3 Hz, 1H); ^{13}C NMR (126 MHz, CD_3OD) 143.84 (alkene CH), 112.40 (alkene CH_2), 76.28 (CH, C-2), 75.10 (CH, C-3), 72.33 (CH, C-4), 61.50 (CH_2, C-6), 57.74 (CH, C-1), 55.53 (CH, C-5), 15.37 (CH_3).

(1R)-1,5-Dideoxy-1-ethenyl-1-methyl-1,5-imino-D-glucitol hydrochloride 20.HCl . Compound **18** (25 mg, 0.088 mmol) was stirred in 1M HCl (1 mL) for 16 h. The volatile components were removed under reduced pressure to give the hydrochloride salt of **20** (18 mg, 86 %) as a white solid; ^{1}H-NMR (500 MHz, D_2O): δ 6.01 (dd, *J* = 17.6, 11.4 Hz, 1H, alkene H), 5.54 (d, *J* = 11.4 Hz, 1H, alkene H), 5.47 (d, *J* = 17.6 Hz, 1H, alkene H), 3.82 (dd, *J* = 12.8, 3.0 Hz, 1H, H-6), 3.77 (dd, *J* = 12.7, 5.3 Hz, 1H, H-6'), 3.59 – 3.49 (2H, overlapping signals, H-3 & H-4), 3.48 – 3.41 (m, 1H, H-2), 3.37 – 3.32 (m, 1H, H-5), 1.49 (s, 3H, CH_3); ^{13}C NMR (126 MHz, D_2O) δ 130.6 (CH), 122.0 (CH_2), 74.2 (C-2), 72.9, 68.2 (each C-3, C-4), 62.0 (C-1), 57.6 (C-6), 56.0 (C-5), 21.9 (CH_3); HRMS (ESI):m/z calc for $C_9H_{17}NO_4Cl$: 238.0846 found: 238.0843 $[M-H]^-$

(1R,2S,3S,4R,5R)-1,5-dideoxy-1-ethenyl -1-methyl-1,5-imino-D-glucitol 20 & (1S,2S,3S,4R,5R)-1,5-dideoxy-1-ethenyl-1-methyl-1,5-imino-D-glucitol 21 from azide 13. Azide **13** (50 mg, 0.20 mmol) was dissolved in toluene (20 mL) and acetic acid (56 µL, 0.98 mmol) subsequently charged. The reaction mixture was stirred at 98 ºC for 4 days. The solvent was then removed under reduced pressure and 2M HCl (5 mL) added to the resultant residue. This mixture was stirred for a further 16 h and then the solvent was then removed under reduced pressure. Flash chromatography (CH_2Cl_2-MeOH-aq NH_3-H_2O, 8:2:0.1:0.1) afforded an 84:16 mixture of the title compounds **20** & **21** (27 mg, 68 %) as a yellow foam; R_f = 0.11 (CH_2Cl_2-MeOH-aq NH_3-H_2O, 8:2:0.1:0.1); for HRMS and NMR spectral data see above.

(1R,2S,3S,4R,5R)-1,5-Dideoxy-1-methyl-1-propyl-1,5-imino-D-glucitol 22 and (1S,2S,3S,4R,5R)-1,5-Dideoxy-1-methyl-1-propyl-1,5-imino-D-glucitol 23. Compound **14** (40 mg, 0.15 mmol) was dissolved in toluene (20 mL) and acetic acid (43 µL, 0.75 mmol) added. The solution was stirred at

98 ºC for 4 days and solvent then removed under reduced pressure. The crude mixture was re-dissolved in MeOH (3 mL) and subsequently treated with Pd-C (10 %) under H_2 for 2 h. The reaction mixture was passed through celite and the solvent was removed. The residue was then treated with 2M HCl (5 mL) for 16 h and solvent subsequently removed under reduced pressure. Flash Chromatography (CH_2Cl_2-MeOH-aq NH_3-H_2O, 8:2:0.1:0.1) gave a 71:29 mixture of **22** and **23** (14 mg, 44 %) as a clear oil; R_f = 0.11 (CH_2Cl_2-MeOH-aq NH_3-H_2O, 80:20:1:1); HRMS (ESI): m/z calc for $C_{10}H_{22}NO_4$: 220.1549, found 220.1564 $[M+H]^+$. Selected NMR data for **22**: ^{1}H NMR (500 MHz, CD_3OD) δ 3.91 (dd, *J* = 11.3, 3.1 Hz, 1H, H-6a), 3.62 (dd, *J* = 11.3, 6.8 Hz, 1H, H-6b), 3.53 (t, *J* = 9.2 Hz, 1H, H-3), 2.87 (broad signal, 1H, H-5); 1.60-1.65 (broad signal, HNC(CH_3)CH_2), 1.29 (s, 3H, HNC(CH_3)CH_2); ^{13}C NMR (126 MHz, CD_3OD, mixture): 75.7 (CH, C-3), 61.4 (CH_2OH, C6), 58.2 (quaternary C, C-1), 57.4 (CH, C-5), 32.7 (CH_2, HNC(CH_3)CH_2), 23.6 (HNC(CH_3)); Selected NMR data for **23**: ^{1}H NMR (500 MHz, CD_3OD): δ 3.86 (dd, *J* = 11.3, 3.0 Hz, 1H, H-6a), 3.76 (dd, J = 11.3, 5.5 Hz, 1H, H-6b), 3.47 (t, *J* = 9.3 Hz, 1H, H-3), 2.91 (br signal, 1H, H-5), 1.52-1.60 and 1.66-1.75 (each m, CH_2); 1.29 (s, 3H, HNC(CH_3)CH_2); ^{13}C NMR (126 MHz, CD_3OD): δ 75.5 (CH, C-3), 61.4 (CH_2OH, C6), 57.3 (CH, C-5), 43.1 (CH_2, HNC(CH_3)CH_2), 16.7 (HNC(CH_3)).

(1R,2S,3S,4R,5R)-1,5-Dideoxy-1-methyl-1-(butadienyl)-1,5-imino-D-glucitol 24 & (1S,2S,3S,4R,5R)-1,5-dideoxy-1-methyl-1-(butadienyl)-1,5-imino-D-glucitol 25 Azide **15** (76 mg, 0.27 mmol) was dissolved in toluene (30 mL), and acetic acid (75 µL, 1.4 mmol) was added. The solution was stirred at 100 ºC for 14 days and solvent was then removed under reduced pressure. The residue was treated with 1M HCl (5 mL) for 12 h. The volatile components were removed under reduced pressure and flash chromatography afforded a 9:1 mixture of **24** and **25** (17 mg, 23 %, clear oil); R_f = 0.23 (CH_2Cl_2-MeOH, 4:1); HRMS (ESI): m/z calc for $C_{11}H_{20}NO_4$: 230.1392, found: 230.1387 $[M+H]^+$; ^{1}H NMR (500 MHz, CD_3OD, major isomer **24**) δ 6.43 – 6.25 (4H, overlapping alkene proton signals), 5.98 (d, *J* = 15.6 Hz, 1H, alkene H), 5.17 (d, *J* = 14.5 Hz, 1H), 5.03 (dd, *J* = 10.0 Hz, 1H), 3.84 (dd, *J* = 10.8, 3.2 Hz, 1H), 3.56 (dd, *J* = 10.8, 6.8 Hz, 1H), 3.26 (1H, t, J = 10 Hz), 3.17 (2H, overlapping signals), 2.78 (ddt, *J* = 10.0, 6.8, 3.4 Hz, 1H), 1.25 (s, 3H, CH_3); ^{13}C NMR (126 MHz, CD_3OD) δ 137.1, 134.4, 130.6, 115.2,

78.0, 75.7, 72.9, 62.0, 57.9, 56.0, 26.8 (CH_3). Selected NMR spectrum data for **25** (minor isomer): ^{1}H NMR (500 MHz, CD_3OD) δ 5.84 (d, *J* = 15.3 Hz, 1H), 3.65 (dd, *J* = 11.5, 6.2 Hz, 1H), 3.45 (t, *J* = 9.3 Hz, 1H); ^{13}C NMR (126 MHz, CD_3OD): 137.0, 116.0, 76.5, 75.5, 75.1, 72.3, 55.6, 15.8 (CH_3).

(1S)-6-*O*-acetyl-1,5-dideoxy-2,3-O-isopropylidene-1-methyl-1-(ethenyl)-1,5-imino-D-mannitol 26 & (1R)-6-*O*-acetyl-1,5-dideoxy-2,3-O-isopropylidene-1-methyl-1-(ethenyl)-1,5-imino-D-mannitol 27

Compound **16** (40 mg, 0.16 mmol) was dissolved in toluene (20 mL), followed by the addition of acetic acid (45.0 µL, 1.06 mmol) The reaction mixture was stirred at 100 ºC for 14 days. The solvent was then removed under reduced pressure. Flash chromatography (hexane-EtOAc, 3:7) gave the title compounds **26** (4 mg, 7 %) and **27** (3 mg, 9 %) as clear oils. Analytical data for **26**: R_f = 0.23 (hexanes-EtOAc, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.31 (d, *J* = 17.3 Hz, 1H), 5.17 (d, *J* = 11.2 Hz, 1H), 4.56 (dd, *J* = 11.3, 4.0 Hz, 1H, H-6a), 4.17 (dd, *J* = 11.3, 2.8 Hz, 1H, H-6b), 4.07 (dd, *J* = 7.5, 4.7 Hz, 1H, H-3), 3.96 (d, *J* = 4.8 Hz, 1H, H-2), 3.40 (ddd, *J* = 10.6, 7.5 Hz, 1H, H-4), 2.85 (dt, *J* = 10.7, 3.5 Hz, 1H, H-5), 2.63 (d, *J* = 3.5 Hz, 1H, OH), 2.10 (s, 3H, OAc), 1.50 (s, 3H, ($C(CH_3)_2$)), 1.36 (s, 3H, ($C(CH_3)_2$)), 1.29 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5 (C=O), 142.3 (CH), 113.1 (CH_2), 109.4 ($C(CH_3)_2$), 79.9 (C-2), 77.2 (C-3), 71.3 (C-4), 64.7 (C-6), 55.3 (C-1), 52.5 (C-5), 28.5 ($C(CH_3)_2$), 26.6 ($C(CH_3)_2$), 24.1 (CH_3), 20.8 (OAc); HRMS (ESI): m/z calc for $C_{14}H_{24}NO_5$: 286.1654, found 286.1648 $[M+H]^+$. Analytical data for **27**: R_f = 0.13 (hexane-EtOAc, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.26 – 5.17 (2H, overlapping signals), 4.48 (dd, *J* = 11.3, 4.3 Hz, 1H, H-6), 4.15 – 4.10 (2H, overlapping signals, H-6b & H-2), 3.95 (dd, *J* = 7.6, 4.7 Hz, 1H, H-3), 3.38 (dd, *J* = 10.6, 7.5 Hz, 1H, H-4), 2.75 (dt, *J* = 10.6, 3.7 Hz, 1H, H-5), 2.11 (s, 3H, OAc), 1.52 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$), 1.27 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5 (C=O), 142.6 (CH), 114.8 (CH_2), 108.7 ($C(CH_3)_2$), 79.5 (C-3), 79.0 (C-2), 71.4 (C-4), 64.6 (C-6), 56.1 (C-1), 52.8 (C-4), 28.6 ($C(CH_3)_2$), 26.6 ($C(CH_3)_2$), 26.3 (CH_3), 20.8 (OAc); HRMS (ESI): m/z calc for $C_{14}H_{24}NO_5$: 286.1654, found 286.1642 $[M+H]^+$.

(1R)-4-*O*-benzyl-1,5-dideoxy-1-methyl-1-(ethenyl)-1,5-imino-D-mannitol 28 and (1S)-4-*O*-benzyl-1,5-dideoxy-1-methyl-1-(ethenyl)-1,5-imino-D-mannitol 29. Compound **17** (45 mg, 0.15 mmol) was dissolved in toluene (20 mL) and acetic acid (43 µL, 0.75 mmol) charged. The reaction mixture was stirred at 100 °C for 24 h. The solvent was then evaporated under reduced pressure and 2M HCl (5 mL) added to the crude residue. The solution was stirred at room temp for 16 h. The solvent was then removed under reduced pressure and flash chromatography (CH_2Cl_2-MeOH-H_2O-aq NH_3, 20:1:0.1:0.1) afforded **28** (27 mg, 62 %) and **29** (3 mg, 7 %) as clear oils. Analytical data for **28**: R_f = 0.13 (CH_2Cl_2-MeOH-H_2O-aq NH_3, 200:10:1:1); ^{1}H NMR (500 MHz, CD_3OD) δ 7.36 (overlapping signals, 2H, aromatic H), 7.31 (overlapping signals, 2H, aromatic H), 7.25 (m, 1H), 5.89 (dd, J = 17.9, 11.2 Hz, 1H, alkene H), 5.23-5.27 (overlapping signals, 2H, alkene protons), 4.92 (d, *J* = 11.0, 1H, benzyl CH), 4.61 (d, *J* = 11.2, 1H, benzyl CH), 3.71-3.80 (4H, overlapping signals), 3.64 (t, *J* = 9.5 Hz, 1H, H-4), 2.76 (broad d, 1H, H-5); 1.24 (s, 3H, CH_3); ^{13}C NMR (126 MHz, CD_3OD) δ 141.2 (alkene CH), 138.9 (C aromatic), 127.8 (CH aromatic x 2), 127.6 (CH aromatic x 2), 127.1 (CH aromatic), 114.0 (alkene CH_2), 76.8 (C-4), 75.5 (C-2) 73.1 (C-3), 60.6 (C-6), 58.7 (C-1), 55.8 (C-5), 25.3 (CH_3); HRMS (ESI): m/z calc for $C_{16}H_{24}NO_4$: 294.1705, found 294.1716 $[M+H]^+$. Analytical data for **29**: R_f = 0.21 (CH_2Cl_2-MeOH-H_2O-aq NH_3, 200:10:1:1); ^{1}H NMR (500 MHz, CD_3OD) δ 7.39 (overlapping signals, 2H, aromatic H), 7.32 (overlapping signals, 2H, aromatic H), 7.26 (t, *J* = 7.1 Hz, 1H, aromatic H), 5.96 (dd, *J* = 17.6, 11.1 Hz, 1H, alkene H), 5.24 (d, *J* = 17.6 Hz, 1H, alkene H), 5.16 (d, *J* = 11.1 Hz, 1H, alkene H), 4.97 (d, *J* = 10.9 Hz, 1H, benzyl CH), 4.63 (d, *J* = 10.9 Hz, 1H, benzyl CH), 3.92 (dd, *J* = 9.4, 3.0 Hz, 1H, H-3), 3.83 (dd, *J* = 11.1, 3.9 Hz, 1H, H-6a), 3.74 (dd, *J* = 11.0, 2.6 Hz, 1H, H-6b), 3.69 (t, *J* = 9.8 Hz, 1H, H-4), 3.60 (d, *J* = 2.9 Hz, 1H, H-2), 2.78 (broad d, *J* = 10.1 Hz, 1H, H-5), 1.26 (s, 3H, CH_3); Selected ^{13}C NMR (126 MHz, CD_3OD, obtained indirectly by gHSQC & gHMBC): δ 129.1 (CH), 78.3 (CH), 76.6 (CH, C-2), 76.2 (benzyl CH_2), 74.1 (CH), 61.7 (CH_2, C-6), 59.7 (C-1), 56.5 (CH, C-5), 20.3 (CH_3); HRMS (ESI): m/z calc for $C_{16}H_{24}NO_4$: 294.1705, found 294.1711 $[M+H]^+$.

(1R)-1,5-Dideoxy-1-methyl-1-(ethyl)-1,5-imino-D-mannitol 30. Benzyl ether **29** (15 mg, 0.051 mmol) was dissolved in MeOH (5 mL), followed by addition of Pd-C and the mixture was stirred under the

presence of H_2 at room temp for 24 h. The mixture was filtered through celite and the solvent removed under reduced pressure. Flash chromatography gave the title compound **30** (8 mg, 80 %) as a clear oil; ^{1}H NMR (500 MHz, D_2O) δ 3.85 (2H, overlapping signals), 3.79 (d, J = 2.9 Hz, 1H, CH), 3.77 – 3.69 (2H, overlapping signals), 3.22 (broad signal, 1H), 1.80 (dq, J = 14.8, 7.3 Hz, 1H), 1.65 (dq, J = 15.1, 7.7 Hz, 1H), 1.31 (s, 3H, -CH_3), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, D_2O) δ 71.1 (C-H), 69.8 (C-H), 65.6 (C-H), 63.3 (C-1), 58.1 (C-6), 55.8 (C-H), 25.1 (C-7), 19.4 (CH_3), 6.6 (C-8); HRMS (ESI): m/z calc for $C_9H_{20}NO_4$: 206.1392, found 206.1385 $[M+H]^+$

SUPPORTING INFORMATION

NMR Spectra (Word document)

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