Allylic azide rearrangement in tandem with Huisgen cycloaddition for stereoselective annulation: synthesis of C-Glycosyl iminosugars
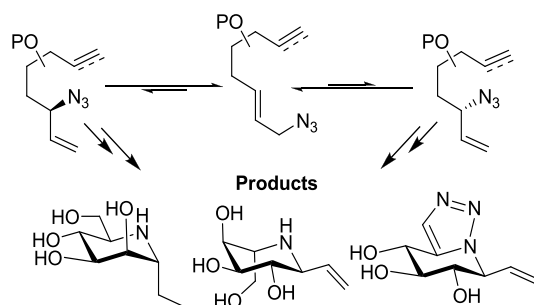
Allylic Azide Rearrangement in Tandem with Huisgen Cycloaddition for Stereoselective Annulation: Synthesis of C-Glycosyl Iminosugars

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*Supporting Information Placeholder*

Products

ABSTRACT: Allylic azide rearrangement is used in tandem with intramolecular azide-alkene cycloaddition to give a triazoline that when subsequently decomposed in the presence of a nucleophile gives piperidines. The tandem reaction gives two stereocentres which are generated with high control. The formation of the piperidines required the presence of innate conformational constraint. The applicability of the annulation reaction is demonstrated by the synthesis of iminosugars. A proposal is included to account for the stereoselectivity observed, which is influenced by the precursor structure.

Organic azides act as 1,3-dipoles in cycloaddition reactions (Huisgen cycloaddition[1]) and when reacted with an alkene give a triazoline that may decompose to form an aziridine, imine or different products.[2] The aziridine, if formed, can undergo further reaction with nucleophiles. This sequence has been used by our group for the synthesis of 1-deoxynojirmycin derivatives **2** from **1** (Scheme 1).[3] Now, we show that dynamic allylic azide rearrangement[4] can be used in tandem with triazoline formation, and where subsequent decomposition of the triazoline leads to the formation of piperidines with controlled formation of two new stereocentres. The intramolecular azide-alkyne variant was similarly successful.[5-10]
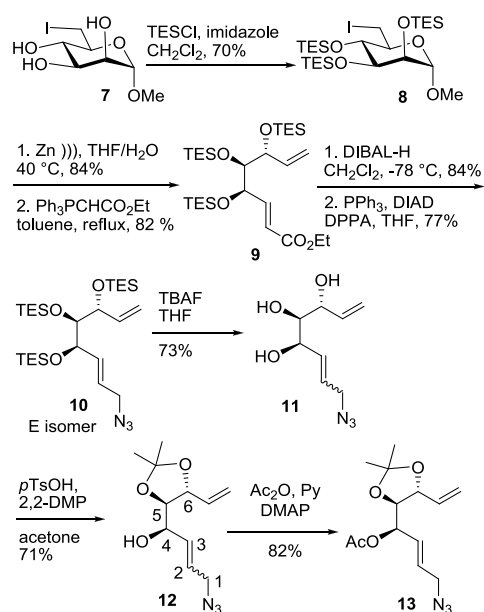
Scheme 1
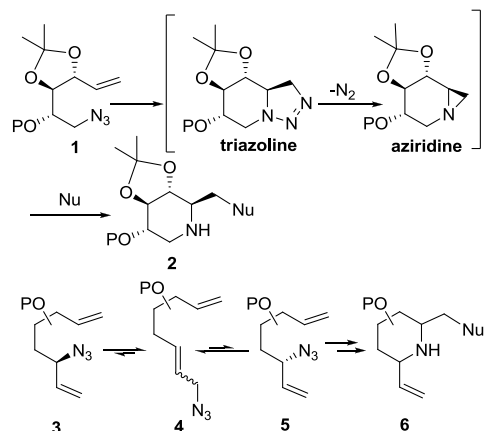
We set out to investigate the viability of the tandem reaction for the preparation *C*-glycosyl iminosugars, which are of synthetic, biological and medical interest.[11] Because of the dynamic interconversion between **4** and stereoisomers **3** and **5**, we considered it possible that rates of reaction of **3** and **5** would not be equal and that stereocontrolled cyclisation could be achieved.

Typical syntheses of allylic azide precursors required for this study are shown in Schemes 2 and 3. Thus, the 6-iodo derivative of methyl α-D-mannopyranoside **7**[12] was silylated to give **8**. Zinc mediated reductive fragmentation[13] converted **8** to an open chain aldehyde, which gave the ester **9** after Wittig reaction. Reduction of **9** to the primary alcohol followed by a Mitsunobu type exchange of the OH for azide gave **10**. One major isomer, which was the primary azide **10** with *E*-configuration was observed by ^{1}H-NMR spectroscopy in CDCl$_3$ even though dynamic conversion to its Z-isomer and secondary azides of the type **3** and **5** is possible. The TES groups were next removed using TBAF to give **11** which showed evidence again for one major stereoisomer and minor amounts of other isomers. An acetonide group was next introduced in a regioselective manner to the 5- and 6-OH groups of **11** by reacting it with 2,2-dimethoxypropane in the presence of H$_2$SO$_4$ in dry acetone, giving **12**. This ketalisation of **11** led to the acetonide **12** with 5,6-*trans*-substituents, whereas the alternate acetonide would have had *cis*-substituents with higher steric hindrance. Acetylation of the free 4-OH to give **13** helped to verify that the acetonide had been introduced at C-5 and C-6 as there was a significant downfield shift (~1 ppm) of the ^{1}H-NMR signal for the C-4 proton on acetylation of the adjacent OH group. In addition, the use of 2D-heteronuclear multiple bond correlation spectroscopy (HMBC) showed the

required three bond correlation between the carbonyl of the acetyl group with H-4 in **13**.[14]

Scheme 2 Synthesis of Precursors

The 4,5-protected isopropylidene derivative **16** was also prepared (Scheme 3). Thus the reaction of **7** with 2,2-dimethoxypropane under acidic conditions, and subsequent silylation gave **14**. Reductive fragmentation, Wittig reaction, reduction, followed by introduction of the azide and TES removal gave **16** via **15**.

With various substrates in hand (e.g. **10-13** & **16**) the tandem allylic azide rearrangement-Huisgen cycloaddition was investigated. A variety of conditions and solvents (e.g. MeCN, EtOH, THF, toluene, DMF, H_2O, MeOH, DMA, $CHOEt_3$) were explored. Reactions were achieved for acetonides but not acyclic derivatives, indicating that innate conformational constraint is required. The heating of the acetonide **12** in DMF at 100°C for 6 h gave the triazoline **17** (50-60%) after chromatography (Scheme 4), with a small amount of unreacted **12** (~10%) recovered from the reaction mixture. Given that triazolines such as **17** are often unstable, we investigated taking **12** and converting it directly to the piperidine in one pot. This was most effectively achieved from **12** by heating for 6 h in DMF at 100°C, which was followed by cooling the mixture and then adding acetic acid (5 eq) with subsequent heating at 50°C, which led to formation of **18α** which could not be separated from its anomeric product **18β** (~35%, 3:1) However, the subsequent reaction of the mixture with aq HCl, gave iminosugar **19α** (28% from **12**) after ion exchange chromatography. Catalytic hydrogenation of **19α** gave **20α**. The protocol was also investigated from **14** and in this case the triazoline **22α** could not be isolated. However, **22α** was clearly formed in a stereoselective manner as the heating of **14** in

DMF for 6 h, followed by addition of acetic acid and further heating led to isolation of **21α** (45%). The improved reaction from **14**, when compared to that from **12**, is due to a lower degree of strain in the forming piperidine ring when it is fused to a *cis*-dioxolane, rather than to the more strained *trans*-dioxolane ring, the latter being the case from **12**. Removal of the protecting groups from **21α** and hydrogenation again gave **19α**. Thus, a stereoselective one-pot reaction to the C-glycosyl mannojirimycin derivatives occurred from **14**.
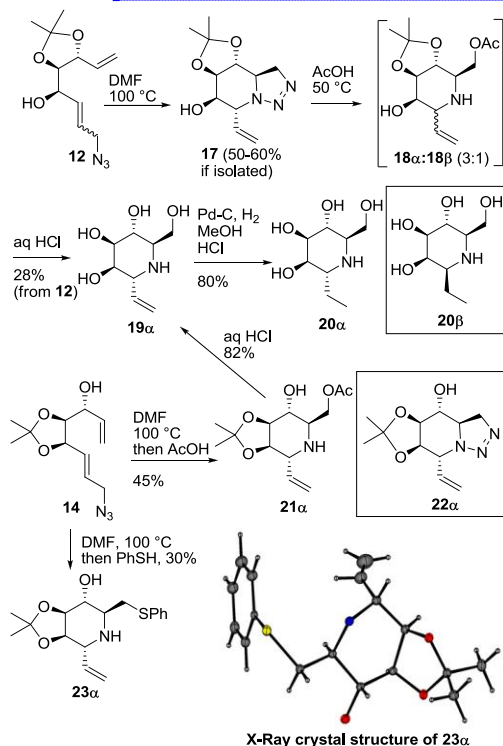
Scheme 3 Synthesis of 16
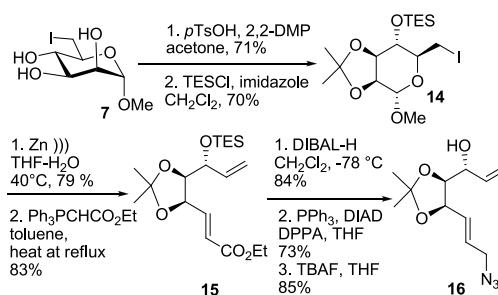
In our hands it was not possible to obtain crystals of **18α-21α** for X-ray crystal structure determination. However, when the reaction from **14** was carried out with thiophenol as nucleophile **23α** was obtained as in crystalline form, enabling the determination of its X-ray crystal structure**,** which confirmed its α-manno configuration, where the vinyl group is axially oriented. The formation of **23α** is consistent with the reaction proceeding via triazoline **22α**, which in turn provides the basis for confirmation of structures of **18α-21α**.. To further support this we observed strong NOE crosspeaks between the anomeric CH_2 group and ring protons H-3 and H-5 of the iminosugar ring for **20α** as would be expected. The α-anomer **20α** had ^{1}H-NMR and ^{13}C-NMR spectroscopic data which were in excellent agreement with NMR data reported for a natural product, which was isolated previously[15] and the coupling constants derived from ^{1}H-NMR indicate preference for a chair conformer. The evidence presented herein shows that the structure of this natural product was incorrectly assigned to **20β**, where the vinyl group is equatorial and should in our view be **20α**, assuming the D-mannose configured analogue is produced naturally. Independently, Fleet and co-workers have reported the synthesis of β-anomer **20β**[16] and they report significantly different ~~^{1}H NMR and~~ ^{13}C-NMR spectroscopic data for **20β** to that which we observed for **20α** and to that of data for the natural product.
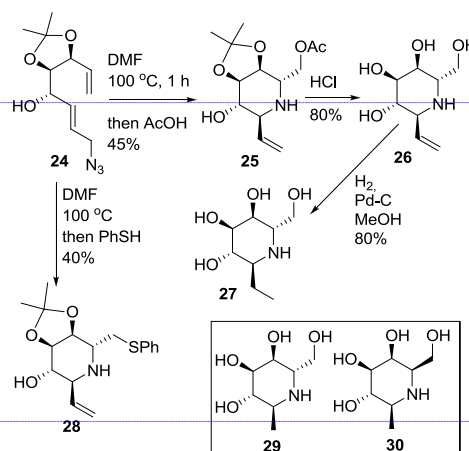
The reaction sequence was also investigated from substrates prepared from D-galactose. Hence reaction of acetonide **24** gave the altronojirimycin derivative **25**, in a highly stereoselective manner (45%) using acetic acid, whereas use of thiophenol gave **28** (40%). Removal of the protecting groups from **25** gave **26** and subsequent reduction of the alkene gave **27**. The altrose configuration (axial hydroxymethyl group at C-5) was assigned on the basis of comparing ^{13}C data obtained by Fleet and co-workers for the two known isomers **29** and **30**.[17] We found better agreement or less variance between ^{13}C ~~data~~

chemical shift data ~~reported~~ for **27** when compared with **29** than **30**, particularly for signals of C-4 to C-6 of the piperidine, in the environment of C-5. Evidence that there is a relationship between chemical shift and stereochemistry in ^{13}C-NMR data has been demonstrate in natural product fragments by Kishi and co-workers.[18] In addition NOE experiments with **28** supported the altrose configuration as there was a weak cross-peak between H-3 and one of the H-6 protons, but no cross-peak between H-3 and H-5, that latter being expected for a galactose configured isomer. In contrast with that observed from mannose substrates, the anomer with the vinyl group equatorially oriented was the major product in this case as supported by ^{1}H-NMR ($^3J_{1,2}$ = 9.1 Hz). The ^{1}H-NMR coupling constants indicate that a chair conformer is preferred for **27**.

Scheme 4   Reactions from 12 and 14 and X-ray crystal structure of 23α.

12 N₃ → DMF 100 °C → **17** (50-60% if isolated) → AcOH 50 °C → **18α:18β** (3:1)

aq HCl 28% (from **12**) → **19α**

Pd-C, H₂ MeOH HCl 80% → **20α**   **20β**

aq HCl 82%

14 N₃ → DMF 100 °C then AcOH 45% → **21α**   **22α**

DMF, 100 °C then PhSH, 30% → **23α**

X-Ray crystal structure of 23α

Scheme 5   Reactions from galactose derived 24

The tandem rearrangement-cycloaddition approach was also extended to incorporate an alkyne as the dipolarophile. Thus acetonide **31** was heated in one pot to give **32** in a highly stereoselective manner, with the β-anomer being the only isolated product (63%) as confirmed in the X-ray crystal structure of **32**.   Removal of the protecting groups gave the 1-deoxynojirimycin analogue **33** ($^3J_{1,2}$ = 8.3 Hz).

Scheme 6.   Stereocontrolled azide-alkyne cycloaddition and X-ray crystal structure of 32

31 N₃ → DMF 100 °C 60-73 % → **32**

HCl MeOH 90% → **33**

X-ray crystal structure of 32
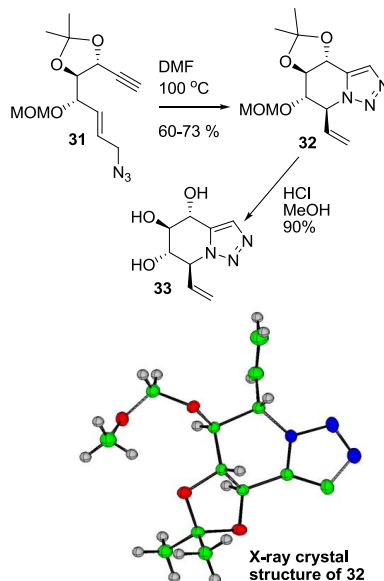
The stereochemical outcome of these reactions has been rationalized as summarized in Figure 1. Firstly, the azide-alkene cycloaddition of the mannose substrate gives ultimately a product also with mannose configuration; this contrasted with galactose which gives a product with altrose configuration. These differing outcomes are explained by minimization of

allylic strain in the reaction transition state.[19] Hence the orientation of the alkene involved in the dipolar cycloaddition depends on the configuration of the substituent at C-4 and this influences the stereoselectivity observed at the iminosugar C-5.

With regard to the anomeric selectivity, substrates from glucose and galactose give the C-glycosyl product where the vinyl group is equatorial, whereas substrates from mannose gave the product with the vinyl group axially oriented. The cycloaddition normally is a concerted process[20] between the azide and alkene and this may imply that the forming piperidine needs to adopt a boat or twist-boat conformation to enable the required orbital overlap in the transition state. In this situation substituents on the forming 6-membered ring could eclipse or be close to eclipsed. For the reaction from mannose substrates a reaction of the secondary allylic azide with *S*-configuration would place the vinyl group close to a C-H bond rather whereas reaction of the *R*-isomer would place the vinyl close to the 2-CO bond. Reaction of the *S*-isomer would be faster for steric reasons and this would give rise to the axially oriented anomer. Where galactose substrates are concerned the reaction from the *R* stereoisomer would be faster than the *S*-stereoisomer due to the configurational change at C-2 and thus the stereoselectivity is reversed. This rationale is summarized in Figure 1.
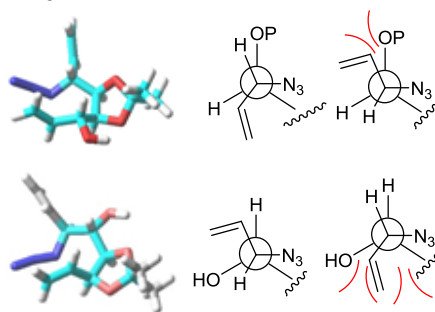

Figure 1. Possible geometries generated from **16** (top left) and **27** (bottom left). Newman projection formula viewing along for allylic azide stereoisomers are shown in the centre (corresponds to model on left) and right (corresponds to other stereoisomer to one in centre). In the top right and bottom right the vinyl group and 2-substituent are close to being eclipsed which disfavours pathways from these stereoisomers, which would give 1,2-cis configurations. Minimisation of allylic strain determines the C-4 to C-5 dihedral angle in the reacting conformer.

In summary, we have demonstrated that the allylic azide rearrangement when coupled to the Huisgen azide-alkene cycloaddition (or azide alkyne cycloaddition) can be used productively to define a highly diastereoselective annulation where two stereocentres are generated in a controlled manner. Application of the reaction is demonstrated for the synthesis of iminosugars (polyhydroxylated piperidines), which are of considerable biomedical interest.[11] Further study of this annulation approach is underway and the outcomes of this work will be reported in due course.

Supporting Information

Experimental procedures and analytical data for compounds. NMR Spectra. Crystallographic Information Files. The Supporting Information is available free of charge on the ACS Publications website.

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