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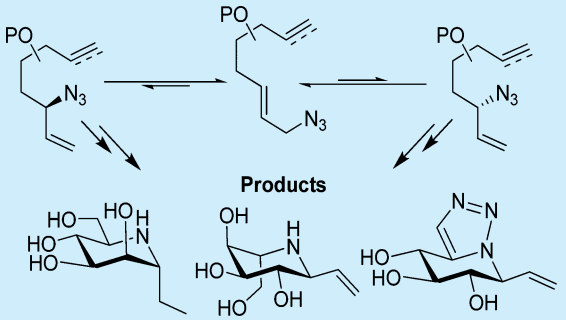
Allylic Azide Rearrangement in Tandem with Huisgen Cycloaddition for Stereoselective Annulation: Synthesis of *C*-Glycosyl Iminosugars

Lorna Moynihan, Rekha Chadda, Patrick McArdle, and Paul V. Murphy*

School of Chemistry, National University of Ireland Galway, University Road, Galway, Ireland

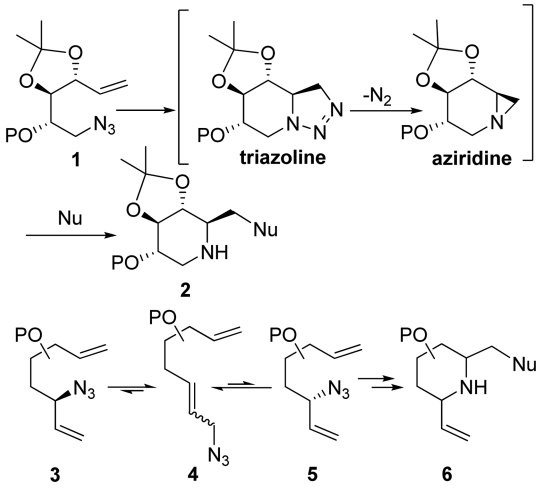
Supporting Information

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 stereocenters that 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 observed stereoselectivity, 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] Here we show that allylic azide rearrangement[4] can be used in tandem with triazoline formation and that subsequent decomposition of the triazoline leads to the formation of piperidines with controlled formation of two new stereocenters. 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] As interconversion between **4** and stereoisomers **3** and **5** through allylic azide rearrangement is possible, we considered that the rates of intramolecular cycloaddition in **3** and **5** would not be equal and that stereocontrolled ring formation 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 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, the primary azide **10** with the *E* configuration, was observed by ^{1}H NMR spectroscopy in $CDCl_3$ even though conversions to its *Z* isomer and secondary azides of types **3** and **5** are possible. The TES groups were next removed using TBAF to give **11**, which showed evidence for the presence of one major stereoisomer and minor amounts of other isomers. An acetonide group was next introduced to the 5- and 6-OH groups of **11** in a regioselective manner by reacting it with 2,2-dimethoxypropane in the presence of H_2SO_4 in dry acetone; this ketalization reaction led to acetonide **12** with 5,6-*trans* substituents, whereas the alternate acetonide would have had *cis* substituents and 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 upon 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 and H-4 in **13**.[14]

The 4,5-protected isopropylidene derivative **16** was also prepared (Scheme 3). Thus, the reaction of **7** with 2,2-

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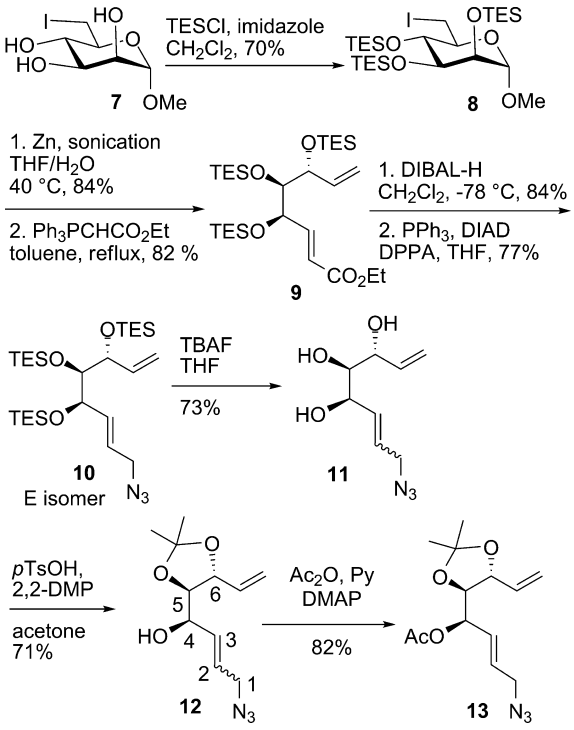
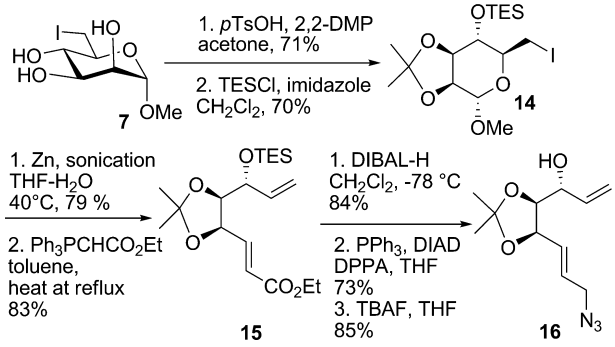
Scheme 2. Synthesis of Precursors



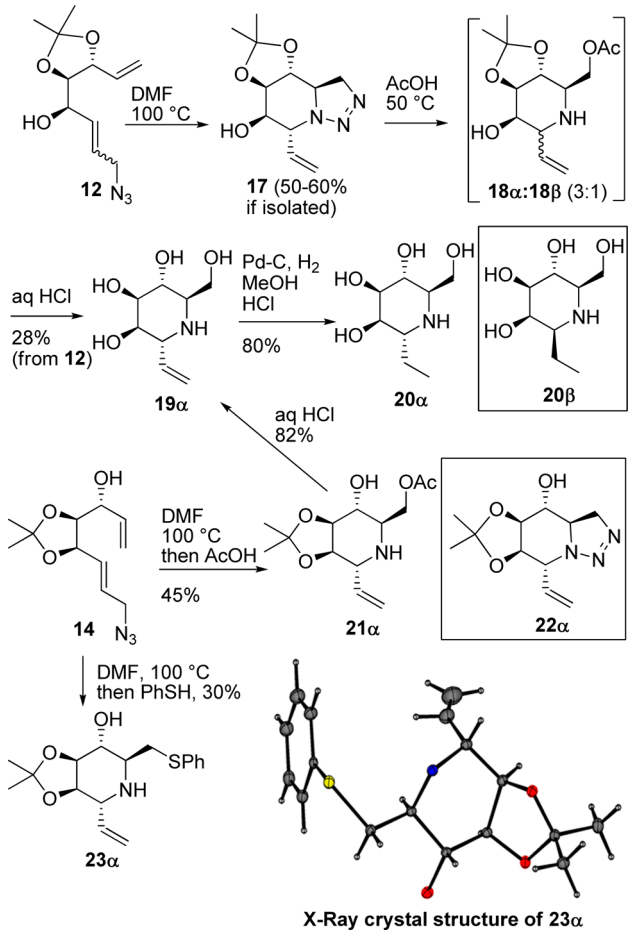
Scheme 3. Synthesis of 16



dimethoxypropane under acidic conditions and subsequent silylation gave **14**. Reductive fragmentation, Wittig reaction, and reduction followed by introduction of the azide and TES removal gave **16** via **15**.

With various substrates in hand (e.g., **10**−**13** and **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. Heating of acetonide **12** in DMF at 100 °C for 6 h gave triazoline **17** (50−60%) after chromatography (Scheme 4), and a small amount of unreacted **12** (~10%) was 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, cooling the mixture, and then adding acetic acid (5 equiv) with subsequent heating at 50 °C; this led to the formation of **18*α***, which could not be separated from its anomeric product **18*β*** (~35%, 3:1), However, subsequent

Scheme 4. Reactions from 12 and 14 and X-ray Crystal Structure of 23*α*



X-Ray crystal structure of 23α

reaction of the mixture with aqueous HCl gave iminosugar **19*α*** (28% from **12**) after ion exchange chromatography. Catalytic hydrogenation of **19*α*** gave **20*α***. The protocol was also investigated from **16**, and in this case triazoline **22*α*** could not be obtained; attempts to isolate it as for **17** gave an intractable mixture of products. However, **22*α*** was clearly formed in a stereoselective manner, as the heating of **16** in DMF for 6 h followed by addition of acetic acid and further heating led to the isolation of **21*α*** (45%). The improved reaction from **16** compared with that from **12** is due to a lower degree of strain in the forming piperidine ring when it is fused to a *cis*-dioxolane ring rather than to the more strained *trans*-dioxolane ring, the latter being obtained from **12**. Removal of the protecting groups from **21*α*** and hydrogenation again gave **19*α***. Thus, a stereoselective one-pot reaction to give *C*-glycosyl mannojirimycin derivatives occurred from **16**.

In our hands it was not possible to obtain crystals of **18*α***−**21*α*** for X-ray crystal structure determination. However, when the reaction from **16** was carried out with thiophenol as the nucleophile, **23*α*** was obtained in crystalline form. Determination of its X-ray crystal structure confirmed its *α*-manno configuration, where the vinyl group is axially oriented. The formation of **23*α*** is consistent with the reaction proceeding via triazoline **22*α***, which in turn provides the basis for confirmation of the structures of **18*α***−**21*α***. To further support this, we observed strong NOE cross-peaks between the anomeric CH_2 group and ring protons H-3 and H-5 of the

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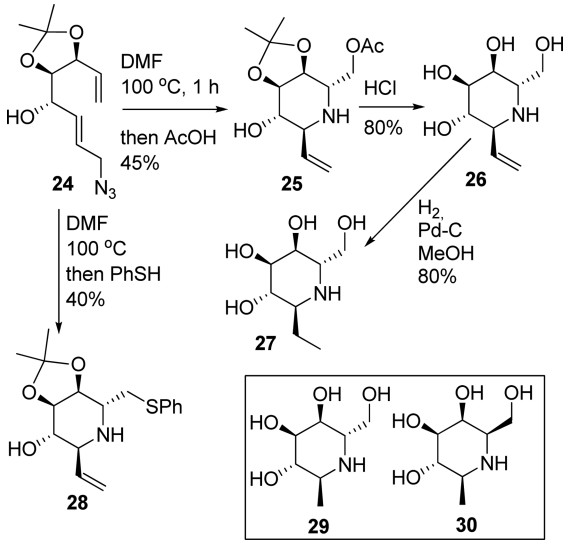
iminosugar ring for **20α**, as would be expected. The ^{1}H and ^{13}C NMR spectroscopic data for the α-anomer **20α** were in excellent agreement with those reported for a natural product that was isolated previously,[15] and the coupling constants derived from the ^{1}H NMR data indicate a preference for a chair conformer. The evidence presented herein shows that the structure of this natural product was incorrectly assigned as **20β** (where the vinyl group is equatorial) and should in our view be **20α**, assuming that the D-mannose-configured analogue is produced naturally. Independently, Fleet and co-workers reported the synthesis of the β-anomer **20β**,[16] and their ^{13}C NMR spectroscopic data for **20β** are significantly different from those we observed for **20α** and those for the natural product.

The reaction sequence was also investigated from substrates prepared from D-galactose (Scheme 5). Hence, reaction of

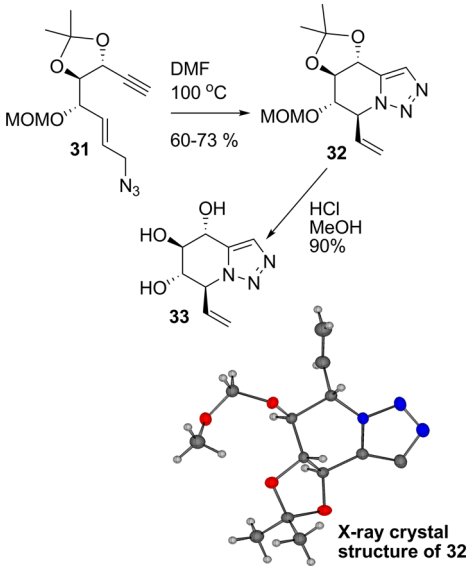
Scheme 5. Reactions from Galactose-Derived 24



acetonide **24** gave altronojirimycin derivative **25** in a highly stereoselective manner (45%) using acetic acid, whereas the 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 a comparison to the ^{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, of the ^{13}C chemical shift data for the ring carbon atoms of **27** with those of **29** than with those of **30**, particularly for the signals of C-4 to C-6. Evidence that there is a relationship between chemical shift and stereochemistry in ^{13}C NMR data has been demonstrated in natural product fragments by Kishi and co-workers.[18] In addition, 1D 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, the 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 data ($^{3}J_{1,2}$ = 9.1 Hz). The ^{1}H NMR coupling constants indicate that a chair conformer is preferred for **27**.

The tandem rearrangement/cycloaddition approach was also extended to incorporate an alkyne as the dipolarophile (Scheme 6). Thus, acetonide **31** was heated in one pot to give **32** in a

Scheme 6. Stereocontrolled Azide−Alkyne Cycloaddition and X-ray Crystal Structure of 32



highly stereoselective manner, with the β-anomer being the only isolated product (63%), as confirmed by the X-ray crystal structure of **32**. Removal of the protecting groups gave the 1-deoxynojirimycin analogue **33** ($^{3}J_{1,2}$ = 8.3 Hz).

The stereochemical outcome of these reactions has been rationalized as summarized in Figure 1. First, the azide−alkene

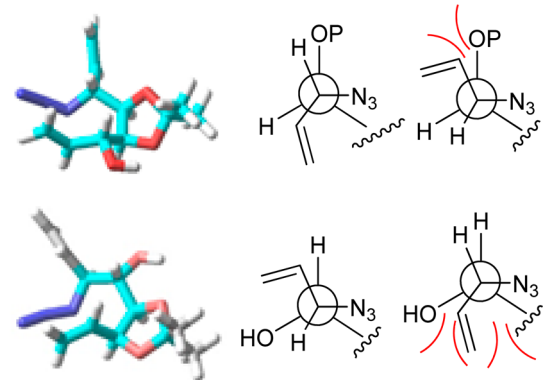


Figure 1. Possible geometries generated from **16** (top left) and **27** (bottom left). Newman projection formulas viewing along C-1 to C-2 for allylic azide stereoisomers are shown at the center (corresponding to the model on the left) and at the right (corresponding to the other stereoisomer). In the top right and bottom right, the vinyl group and 2-substituent are close to being eclipsed, which disfavors pathways from these stereoisomers. Minimization of allylic strain determines the C-4 to C-5 dihedral angle in the reacting conformer.

cycloaddition of the mannose substrate ultimately gives a product that also has a mannose configuration; this contrasted with galactose, which gives a product with an 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, giving a 4,5-*trans* product.

With regard to the anomeric selectivity, substrates from glucose and galactose give the *C*-glycosyl product where the

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vinyl group is equatorial, whereas substrates from mannose give the product with the vinyl group axially oriented; this can be summarized as giving a 1,2-*trans* product. The cycloaddition is normally 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 six-membered ring could be eclipsed or close to eclipsed. For the reaction from mannose substrates, a reaction of the secondary allylic azide with the *S* configuration would place the vinyl group close to a C−H bond, whereas reaction of the *R* isomer would place the vinyl group close to the C−O 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 is faster than that from the *S* stereoisomer because of the configurational change at C-2, and thus, the anomeric selectivity is reversed. This rationale is summarized in Figure 1.

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 in which two stereocenters are generated in a controlled manner. Application of the reaction has been demonstrated by the synthesis of iminosugars (polyhydroxylated piperidines), which are of biomedical relevance.[11] Further study of this ring-forming approach is underway, and the outcomes of that work will be reported in due course.[21]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03209.

Crystallographic data for **32** (CIF)
Crystallographic data for **23α** (CIF)
NMR spectra (PDF)
Experimental procedures and analytical data for compounds, schemes and experimental section for the preparation of **24** and **31**, tables of NMR data, and plots of chemical shift differences (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*paul.v.murphy@nuigalway.ie

Notes

The authors declare no competing financial interest.

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