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Alkynylation of Pentose Derivatives with Stereochemical Fidelity: Implications for the Regioselectivity of Alkynyl Diol Cycloisomerizations to Cyclic Enol Ethers

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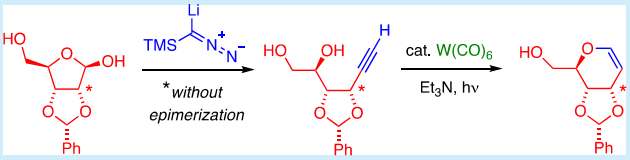
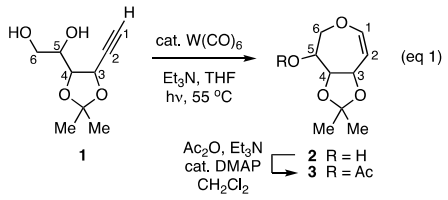
Supporting Information

ABSTRACT: This work characterizes a previously undetected epimerization in the preparation of alkynyl diols from pentose precursors utilizing the Ohira–Bestmann reagent. Lithium trimethylsilyldiazomethane (Colvin reagent) additions to the D-ribose and D-lyxose-derived benzylidene acetals provide the respective alkynyl diol stereoisomers, without epimerization. Regioselective tungsten-catalyzed cycloisomerizations of the D-ribose- and D-lyxose-derived alkynyl diols yield rigid bicyclic pyranose glycals, confirming the stereochemical fidelity of the Colvin alkynylation process.



Our laboratory previously described the synthesis of seven-membered cyclic enol ethers **2**, prepared by tungsten carbonyl-catalyzed cycloisomerizations of alkynyl diols **1** (eq 1).[1,2] The alkynyl diol substrates included

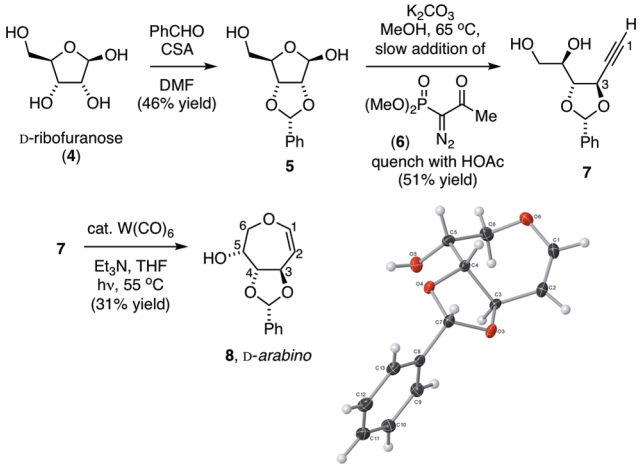


dioxolane spacers between the terminal alkyne and vicinal diol moieties as a necessary condition for seven-membered ring formation. We recently re-explored this work, aiming to extend its synthetic applications, but uncovered a previously undetected epimerization in the preparation of alkynyl diols closely related to **1**.

In our initial report,[1] we claimed that all four diastereomers of **1** gave the corresponding septanose glycals **2** with the assignment of regioselectivity for the seven-membered ring secured by *O*-acylation of secondary alcohols to the acetate esters **3** (eq 1). This manuscript describes how we identified epimerization of these compounds at carbon 3 (C3) and offers a reliable method for synthesizing alkynyl diols with stereochemical fidelity. We also discuss the implications of substrate stereochemistry on the regioselectivity of tungsten-catalyzed cycloisomerizations of alkynyl diols.

For several of the substrates reported earlier,[1] we prepared the alkynyl diols by the Ohira–Bestmann protocol[3] from pentose precursors protected as acetonides. In this extension of our work, we chose benzylidene acetal protection, intending late-stage chemoselective deprotection in the presence of acid-sensitive enol ether and/or glycoside functional groups. Beginning with D-ribofuranose **4** and the known benzylidene acetal **5**,[4] Ohira–Bestmann alkynylation with diazophosphonate **6** gave the alkynyl diol **7** (Scheme 1). *As this transformation yielded a single diastereomer*, we were initially unaware that the propargylic center at C3 of compound **7** had epimerized.[5] Tungsten carbonyl-catalyzed cycloisomerization[1,2] of the alkynyl diol **7** produced the septanose glycal **8**. In a serendipitous opportunity, we obtained a crystal structure of **8**, revealing that the chiral center at C3 was opposite to the configuration of the D-ribofuranose starting material. Thus, compound **8** corresponded to the D-*arabino* stereochemistry.

Scheme 1. Synthesis and Crystal Structure of D-Arabinoseptanose Glycal 8, Arising from Epimerization at C3 in the Alkynylation Step



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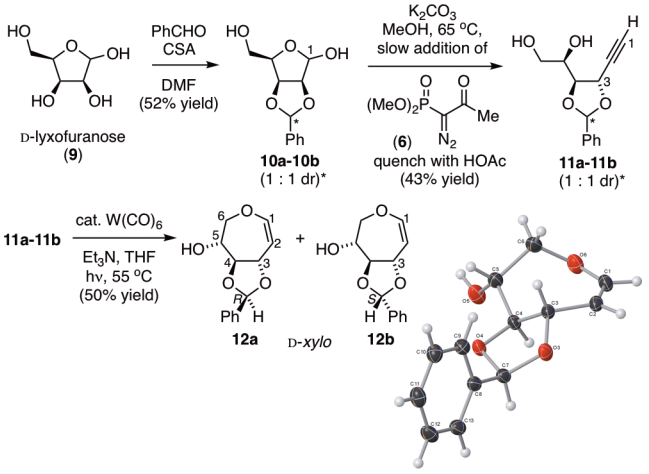
At the same time, we converted D-lyxofuranose **9** into the mixture of benzylidene acetal diastereomers **10a** and **10b**, followed by Ohira–Bestmann alkynylation, affording alkynyl diols **11a** and **11b** (Scheme 2). Although the acetal

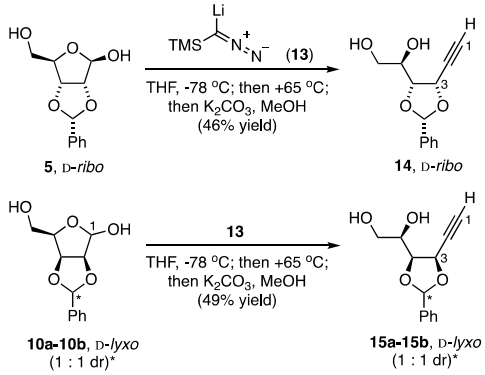
Scheme 2. Synthesis of D-Xyloseptanose Glycals 12a and 12b with Epimerization at C3 Confirmed by the Crystal Structure of 12a



diastereomers **11a** and **11b** were difficult to separate, tungsten carbonyl-catalyzed cycloisomerization of the mixture gave the chromatographically separable septanose glycals **12a** and **12b**. Crystallographic analysis of **12a** exhibited D-*xylo* stereochemistry, consistent with epimerization at C3, which we ultimately determined occurred in the alkynylation step.

Following precedents describing alkynylations of α-chiral aldehydes with lithium trimethylsilyldiazomethane (**13**) without epimerization,[6,7] we successfully applied this method (Colvin protocol) with benzylidene-protected furanoses **5** and **10a,b** (Scheme 3). In contrast with the Ohira–Bestmann

Scheme 3. Preparations of Alkynyl Diols 14 and 15a,b without Epimerization in the Alkynylation Steps



protocol, the reaction of **13** with ribose-derived furanose **5** proceeded without epimerization. A mixture of terminal alkyne and alkynyltrimethylsilane was initially produced, but basic methanolysis of the crude product mixture promoted protiodesilylation to provide the alkynyl diol **14**. We obtained similar results from the benzylidene-protected lyxofuranose **10a** and **10b**, producing **15a** and **15b**. ^{1}H NMR data for **14** and **15a,b** exhibited small but discernible differences in chemical shifts compared with **7** or **11a,b**, as expected for diastereomers.

As the Ohira–Bestmann conditions exposed the furanose substrates **5** and **10** to refluxing methanolic potassium carbonate, followed by slow addition of the diazophosphonate **6**, we realized that epimerization of the open-chain aldehyde–diol intermediate (Figure 1, **i** → **ii**) likely occurred

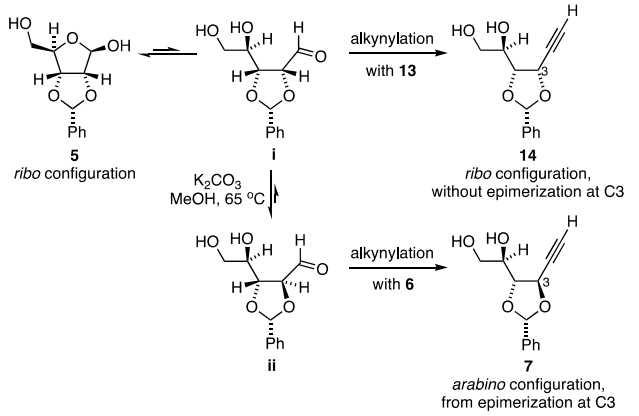
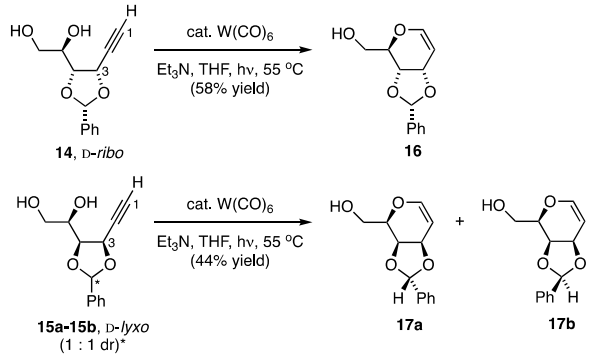


Figure 1. Competitive epimerization vs alkynylation depicted for alkynylation of benzylidene-protected D-ribofuranose **5**.

faster than alkynylation. In hindsight, we recognized that **ii** was probably thermodynamically favored over diastereomer **i**, minimizing *gauche* interactions between the aldehyde and diol substituents on the dioxolane ring. However, the Colvin protocol proceeded at low temperature in THF *under aprotic conditions that disfavored epimerization prior to carbon–carbon bond formation.*[8]

In contrast to our initial report, tungsten-catalyzed cycloisomerization of the *ribo*-alkynyl diol **14** gave the six-membered D-ribopyranose glycal **16** (Scheme 4). Similarly,

Scheme 4. Cycloisomerizations of *ribo*- and *lyxo*-Alkynyl Diols 14 and 15 Provide the Corresponding *Cis*-Fused Pyranose Glycals 16 and 17



the *lyxo*-alkynyl diols **15a,b** produced the D-lyxopyranose glycals **17a,b**, which were chromatographically separable. In both cases, the seven-membered ring septanose isomers were not observed.

We sought spectroscopic signatures to distinguish the relative stereochemistry of alkynyl diol diastereomers. Unfortunately, the coupling constants of the propargylic hydrogens (H3) of all alkynyl diol diastereomers were similar in magnitude, exhibiting $^3J_{H3,H4}$ coupling constants between

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5−8 Hz. However, the alkynyl diol diastereomers did exhibit regular differences *in the relative chemical shifts for the hydrogens at C5*: the *arabino*-**7** and *xylo*-**11a,b** diastereomers bearing a *trans*-relationship at H3 and H4 (arising from epimerization) had chemical shifts for H5 upfield of 4.0 ppm, whereas the *ribo*-**14** and *lyxo*-**15a,b** diastereomers bearing a *cis*-relationship of H3 and H4 (absence of epimerization) showed chemical shifts for H5 downfield of 4.0 ppm (Figure 2).

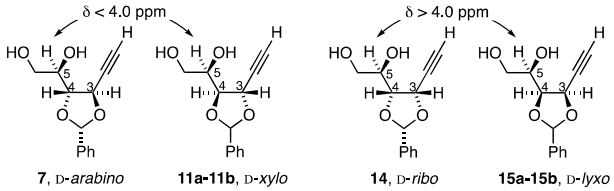

Figure 2. Diagnostic chemical shift trends for the hydrogens at C5 distinguish *trans*- vs *cis*-diastereomers at C3 and C4.

For the bicyclic glycals **16** and **17a,b**, the coupling constants confirmed the stereochemistry at C3 and C4, due to the rigidity of the bicyclic structures (Figure 3).

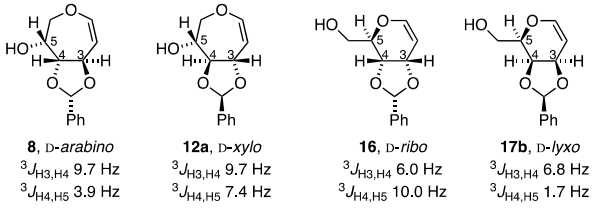

Figure 3. Consistent trends in the coupling constants distinguish the cyclic glycal products.

Specifically, the *arabino*-**8** and *xylo*-**12a,b** septanose glycal diastereomers bearing a *trans*-relationship of H3 and H4 exhibited relatively large $^{3}J_{H3,H4}$ of 9.7 Hz, consistent with *anti*-orientations of H3 and H4. In contrast, the *ribo*-**16** and *lyxo*-**17a,b** pyranose glycal diastereomers bearing *cis*-relationships of H3 and H4 (absence of epimerization) displayed smaller $^{3}J_{H3,H4}$ ranging from 5.8 to 6.8 Hz, in the range expected for *gauche* orientations of H3 and H4. Consistent with these assignments, the *ribo*-**16** pyranose glycal gave larger $^{3}J_{H4,H5}$ of 10.0 Hz as expected for *trans*-diaxial hydrogens, whereas the *lyxo*-**17a−17b** pyranose diastereomers showed very small or nonobservable $^{3}J_{H4,H5}$ < 2 Hz.

These results demonstrate that only dioxolane-protected alkynyl diols leading to *trans*-ring fusions produce the septanose glycals by tungsten-catalyzed cycloisomerization. As depicted for the *arabino*-diastereomer **7** (Figure 4), ring strain disfavors formation of a *trans*-fused [4.3.0]-bicyclic isomer, allowing the alternative pathway to the seven-membered ring [5.3.0]-bicyclic isomer **8**. However, both pathways are now possible from the *ribo*-diastereomer **14**: not surprisingly, the six-membered ring isomer **16** forms faster than the seven-membered ring.

These findings require corrections to two of our earlier publications.[1,9]

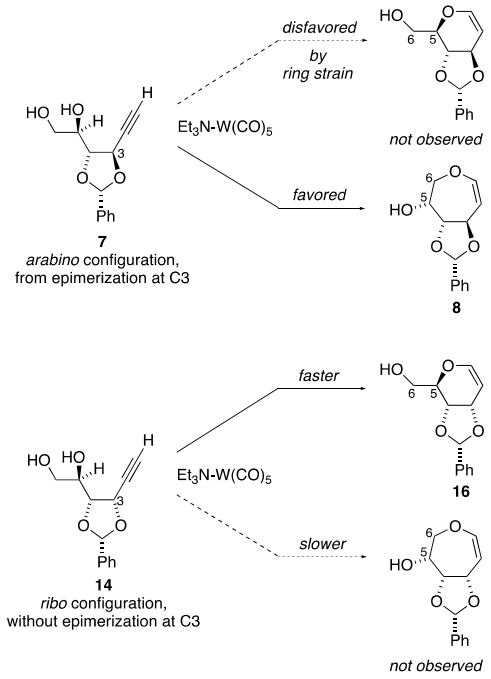

Figure 4. Regioselectivity of tungsten-catalyzed cycloisomerization depends upon the relative stereochemistry of the C3 and C4 oxygens when protected as cyclic acetals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01024.

Experimental procedures and characterization data, data comparison between structures from ref 1 and this work (PDF)

^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1902792−1902793 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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