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Steric control in Pd-mediated cycloisomerization of sugar alkynols: documentation of a rare allylic epimerization

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Abstract—Pd-mediated cycloisomerization of C3-alkynylated glucofuranosyl derivatives revealed a dominance of steric factors over electronic factors. However, the intermediate glycals were epimerized prior to the ketalization and afforded the more stable cis-fused bicyclic ketals.

Designing effective routes to complex cyclic structures through organo transition-metal catalyzed cyclization reactions has been recognized as an attractive strategy for delivering molecular diversity.[1] Transition-metal mediated cycloisomerization of alkynols was envisioned as a concise approach to fully functionalized oxygen-containing heterocycles encompassing functionalized furan, pyran, benzopyran and spiroketal skeletons.[2,3] During our ongoing studies on the Pd(II)-mediated cycloisomerization reactions of sugar alkynols, we recently documented a systematic investigation dealing with the influence of electronic factors on the regioselectivity of cyclization.[4] After examining Pd-mediated cycloisomerization of a set of 3-*C*-alkynyl-*allo*-furanosyl derivatives, we concluded that the regioselectivity of cyclizations is influenced by electronic factors, electron donating substituents on the aromatic ring favouring 6-*endo*-dig, while electron withdrawing groups favoured 5-*exo*-dig modes of cyclization. Along similar lines, an alkyl-substituted alkynol **1** (Fig. 1) also favoured 6-*endo*-cyclization and gave predominantly **2**.

In the early 80s Utimoto[5] and Schwartz[6] independently reported the highly regioselective cycloisomerization of cis- and trans-substituted 2-(hept-3-ynyl)cyclopentanols (**3** and **4**, respectively, Fig. 1) using either mercury or Pd(II), resulting exclusively in 5-*exo-dig* cyclization from cis-isomer **3** and 6-*endo-dig* cyclization from trans-isomer **4**. The exclusive 6-*endo* product formation from **4** was reasoned on strain grounds where the formation of a trans-fused 5,5-bicyclic ring system may not be feasible.[5,6]

This is a classical example of cycloisomerization influenced by steric factors. Hoping to take advantage of such an influence to synthesize 6-*endo* products having –M substituted aryl groups (5-*exo*-preferring), we extended our investigations to explore trans-configured sugar derived cycloalkynols. For this work, we designed a series of sugar alkynols (Fig. 1) and chose the alkyne **8** as our initial target molecule, which we hoped to prepare from the chloromethyleneoxirane **9** via a base mediated double elimination reaction.[7] The synthesis of the corresponding disubstituted alkynes is possible by means of Sonogashira reactions.[8]

The synthesis of the key 3-*C*-ethynyl-1,2:5,6-di-*O*-isopropylidene-D-glucofuranoside (**8**) started with the preparation of known allyl alcohol **11** from glucose diacetonide (**10**) following the literature procedure.[9] As anticipated, epoxidation of **11** gave a single diastereomer **12**. The spectral and analytical data of **12** were in agreement with the assigned structure.[10] Heating **12** with PPh_3 in CCl_4 in the presence of $NaHCO_3$ afforded the corresponding chloro derivative **9** in 68% yield.[11] After standardizing the reactions, we could prepare the requisite alkynol **8** in good yield by treating **9** with 3 equiv of *n*-butyllithium in THF at −78 °C for 2 h.[7] The spectral data of **8** showed characteristic chemical shift differences when compared with the corresponding known C-3 epi-

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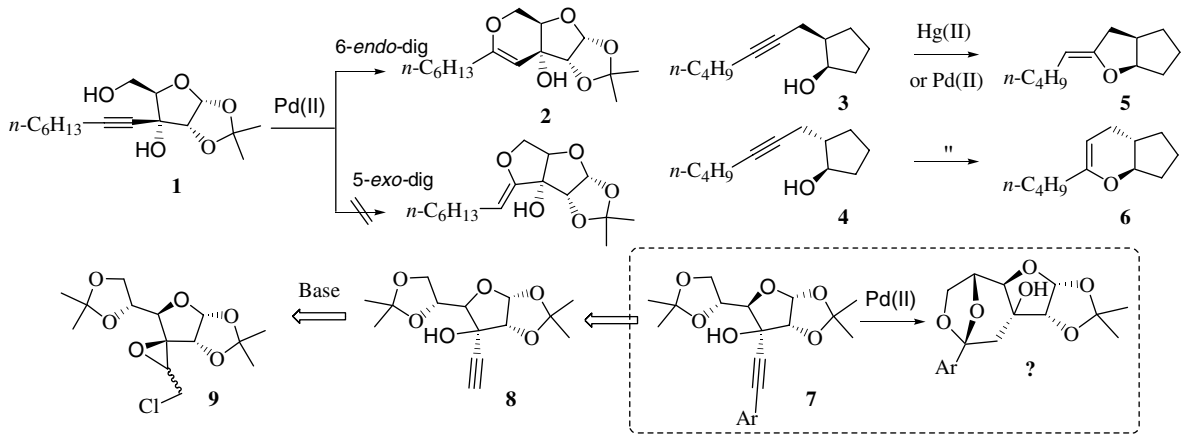
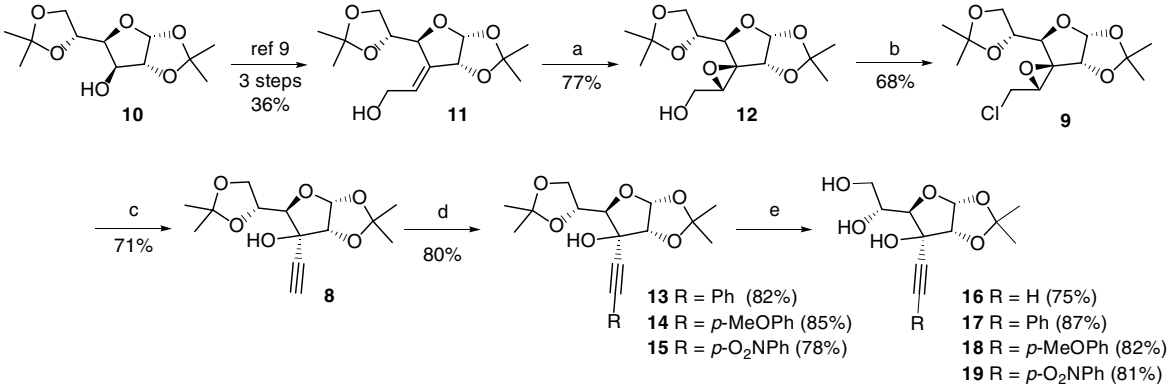


Figure 1. Influence of strain on Pd mediated cycloisomerization, model compound and intended synthesis.

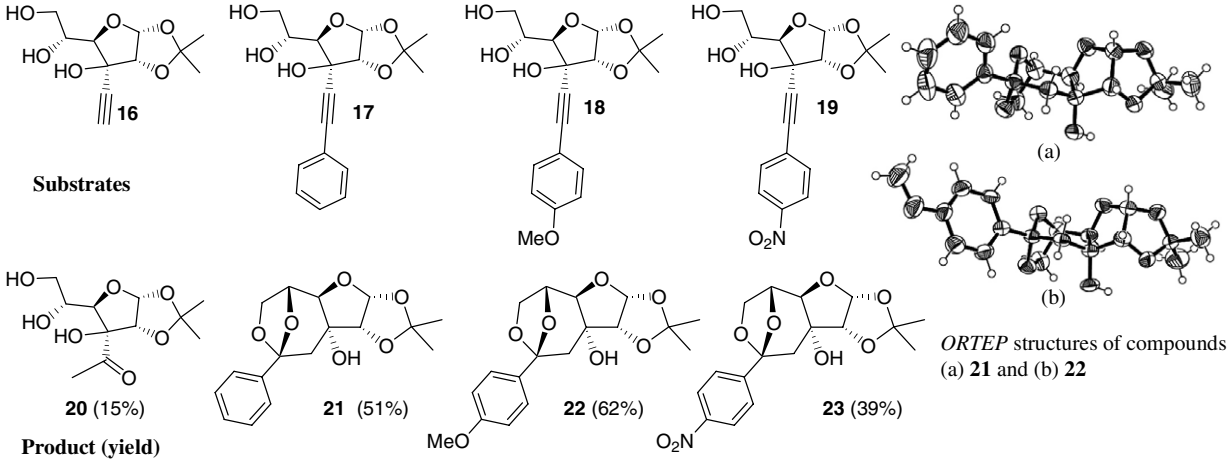
meric *allo* derivative thus confirming the assigned structure.[11] For example, in the ^{1}H NMR spectrum of **8**, H-4 (0.32 ppm) and H-1 (0.09 ppm) resonated downfield compared to the H-4 and H-1 of the *allo* derivative[12] (see Schemes 1 and 2).

Turning to the requisite disubstituted alkynols, the Sonogashira coupling[8] reactions of **8** were carried out with iodobenzene, 4-iodoanisole and 4-nitroiodobenze to afford alkynols **13**–**15** in 78–85% yields. Selective hydrolysis of the 5,6-acetonide group in **8**, **13**–**15** furnished the alkynols **16**–**19**, respectively.

Our initial attempt to bring about the cycloisomerization of alkynol derivative **16** in acetonitrile using $Pd(CH_3CN)_2Cl_2$ was sluggish, partially because of the



Scheme 1. Reagents and conditions: (a) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C–rt, 8 h; (b) TPP, $NaHCO_3$, CCl_4, reflux, 8 h; (c) *n*-Butyllithium, THF, −78 °C, 2 h; (d) Ar-I, CuI, TPP, $Pd(PPh_3)_2Cl_2$, Et_3N/DMF (1:2), rt, 3 h; (e) 0.8% aq H_2SO_4, MeOH–H_2O (10:1), 0 °C–rt, 14 h.



Scheme 2. Reagents and conditions: $Pd(CH_3CN)_2$, THF/CH_3CN (1:2), 6–7 h.

poor solubility of **16**. After experimenting with several solvent systems, the use of a 2:1 CH_3CN–THF mixed solvent system had substantial effect on the reaction time. However, we could only isolate **20** in low yield. In the ^1H NMR spectrum of **20**, a singlet corresponding to CH_3– was observed at δ 2.44, and H-4 (δ 4.60) resonated 0.3 ppm downfield compared to that of H-2 (δ 4.31) due to the anisotropic deshielding effect of the carbonyl group.

The cycloisomerization of **17** was carried out in the same solvent system to afford the cycloisomerized product **21** in moderate yield (Fig. 2). To our surprise, the spectral and analytical data of **21** were identical to the bicyclic ketal that we had previously synthesized from the *allo* derivative suggesting an inadvertent epimerization of the quaternary-OH during the cycloisomerization.[3] Single crystal X-ray analysis of compound **21** established the assigned structure.[13,14]

The cycloisomerization of alkynols **18** and **19** resulted in the epimerized bicyclic ketals **22** and **23**. The spectral and analytical data of compounds **22** and **23**[15] were in agreement with the assigned structure and the structure of **22** was further established by single crystal X-ray analysis.[13,14]

The formation of compounds **21**–**23** is obviously the consequence of an epimerization during the Pd-mediated cycloisomerization. The formation of **20** from **16** and of **23** from **19** ruled out the possibility of epimerization of the alkynol before the cyclization (since the epimer of **19** gave the 5-*exo*-dig product, exclusively).[16] Since the products **21**–**23** are expected to arise via a 6-*endo*-dig cyclization, a possible explanation would be competing formation of a π-allylpalladium complex from the intermediate σ-Pd-glycal and subsequent hydroxy approach from the less hindered pseudo-concave face (Fig. 2).[17] Indeed Matsumura and co-workers documented the C-3 epimerization of triacetyl glucal using a variety of metal salts but not with Pd.[18]

In summary, *gluco*-configured 3-*C*-alkynyl derivatives were prepared to examine the influence of strain over the regioselectivity of cycloisomerization reactions. As anticipated the dominance of steric factors over electronic factors favouring the 6-*endo*-dig mode of cyclization was observed. However, the intermediate cyclic enol derivatives were found to undergo a Pd-mediated epimerization prior to ketalization.

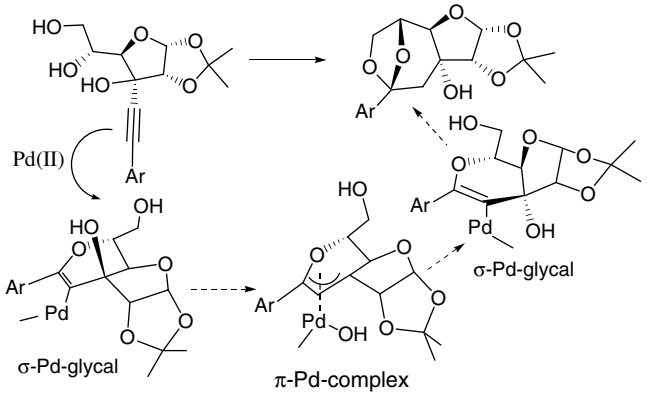


Figure 2. Tentative mechanism for the epimerization.

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10. *Spectral data of Compound* **12**: $[\alpha]_D$ +60.9 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$): *v* 3492, 3020, 2991, 2938, 1455, 1384, 1216,

1163, 1117, 1073, 845, 755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.34 (s, 3H), 1.41 (s, 3H), 1.56 (s, 3H), 2.31 (br s, 1H), 3.53 (t, J= 5.5 Hz, 1H), 3.77 (dd, J = 12.5 Hz, 5.7 Hz, 1H), 3.90–4.07 (m, 4H), 4.32 (dd, J = 5.7 Hz, 1.5 Hz, 1H), 4.54 (d, J = 4.2 Hz, 1H), 5.95 (d, J = 4.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.3 (q), 26.5 (q), 26.8 (q), 26.9 (q), 57.1 (d), 62.0 (t), 66.9 (t), 68.7 (s), 72.7 (d), 76.4 (d), 82.6 (d), 104.3 (d), 109.6 (s), 112.5 (s) ppm; ESI-MS m/z: 325.187 $[M+Na]^+$. Anal. Calcd for $C_{14}H_{22}O_7$: C, 55.62; H, 7.33. Found: C: 55.86, H: 7.39.

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12. *Spectral data of Compound* **8**: $[\alpha]_D$ +96.6 (*c* 1, $CHCl_3$) IR ($CHCl_3$): ν 3390, 3306, 3019, 2990, 2937, 2234, 1455, 1384, 1375, 1216, 1073, 998, 759 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.38 (s, 3H), 1.50 (s, 3H), 1.56 (s, 3H), 2.68 (s, 1H), 3.69 (br s, 1H), 4.08–4.22 (m, 3H), 4.39–4.48 (m, 2H), 5.90 (d, J = 3.5 Hz, 1H) ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.4 (q), 26.6 (q), 27.0 (q), 66.6 (t), 74.3 (d), 75.4 (s), 76.3 (d), 80.5 (s), 82.4 (d), 86.9 (d), 104.7 (d), 109.9 (s), 112.8 (s) ppm. ESI-MS m/z: 307.598 $[M+Na]^+$. Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C: 59.31, H: 7.22.
13. (a) X-ray intensity data of compounds **20** and **21** were collected on a Bruker SMART APEX CCD diffractometer with omega and phi scan mode, $\lambda_{MoK\alpha}$ = 0.71073 Å at T = 297(2) K. All the data were corrected for Lorentzian, polarisation and absorption effects using Bruker's SAINT and SADABS programs. The crystal structures were solved by direct methods using SHELXS-97 and the refinement was performed by full matrix least squares of F^2 using SHELXS-97. Hydrogen atoms were included in the refinement as per the riding model except for the hydroxyl group, which is located in the difference Fourier map; (b) Sheldrick, G. M. SHELXS-*97 Program for Crystal Structure Solution and Refinement*; Unversity of Göttingen: Germany, 1997.
14. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as deposition Nos. CCDC 639467 (**21**) and CCDC 639468 (**22**). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk].
15. *Spectral data of Compound* **23**: $[\alpha]_D^{25}$ +3.2 (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.39 (s, 3H), 1.63 (s, 3H), 1.84 (d, J = 14.5 Hz, 1H), 2.26 (d, J = 14.5 Hz, 1H), 3.21 (br s, 1H), 3.87 (s, 1H), 4.01 (dd, J = 7.2, 5.6 Hz, 1H), 4.16 (d, J = 3.6 Hz, 1H), 4.42 (dd, J = 7.2, 0.9 Hz, 1H), 4.95 (d, J = 5.6 Hz, 1H), 5.96 (d, J = 3.6 Hz, 1H), 7.78 (d, J = 8.9 Hz, 2H), 8.25 (d, J = 8.9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.7 (q), 26.8 (q), 43.1 (t), 65.8 (t), 74.4 (d), 75.1 (s), 77.8 (d), 83.6 (d), 104.1 (d), 105.5 (s), 113.0 (s), 123.5 (d), 126.4 (d), 146.3 (s), 148.1 (s) ppm; ESI-MS m/z: 388.41 $[M+Na]^+$. Anal. Calcd for $C_{17}H_{19}NO_8$: C, 55.89; H, 5.24; N, 3.83. Found: C, 56.17; H, 5.44; N, 3.57.
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