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Synthesis of Seven-Membered Ring Glycals via *endo*-Selective Alkynol Cycloisomerization

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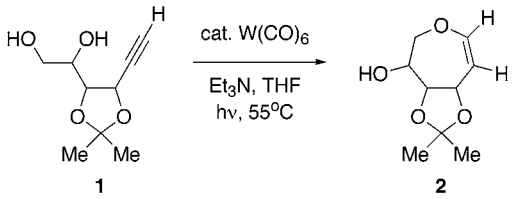
ABSTRACT



1 2

Alkynyldiols 1 undergo cycloisomerization to the corresponding seven-membered cyclic enol ethers 2 under tungsten carbonyl catalysis. This novel transformation proceeds with good yields and virtually complete regioselectivity for all diastereomers of 1, favoring the product 2 resulting from *endo*-mode cyclization. The unexpected regioselectivity may be dependent on the presence of the dioxolane structure tethering the terminal alkyne and diol functional groups.

Our laboratory has reported the synthesis of five- and six-membered ring glycals using group VI metal-catalyzed *endo*-regioselective cycloisomerizations of alkynyl alcohols.[1] This reaction type is similar to the formation of cyclic metal oxacarbenes via the intermediacy of transition metal vinylidenes,[2] arising from 1,2-migration of the terminal alkyne hydrogen. While the cyclic oxacarbene structures can be converted into metal-free cyclic enol ether structures (Figure 1), a more efficient transformation to cyclic enol ethers is accomplished in one step from the corresponding alkynyl alcohol. This novel reaction type is tolerant of many different functional groups and has been used in syntheses of several biologically active cyclic ether and polysaccharide structures.[3]

The current study began with the recognition that D-ribose could be easily converted into an alkynyl alcohol precursor, which would provide the hexopyranose glycal with the stereochemistry of D-allose. From the known ribofuranose acetonide **3** (Scheme 1),[4] the alkynyl alcohol substrate **4** was produced by Wittig chloromethylenation and dehydrohalogenation.[5] Alternately, the alkynyldiol **5** could be produced in one step using a diazophosphonate reagent for one-carbon homologation, with concomitant loss of the *tert*-butyldiphenylsilyl ether.[6]

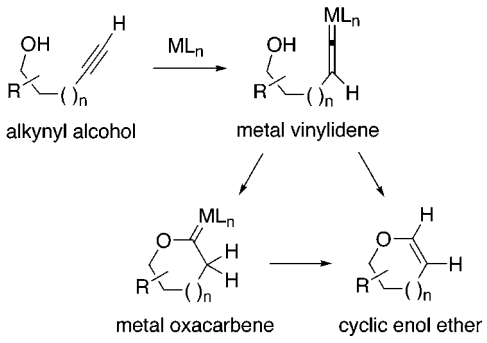


Figure 1. Metal-promoted alkynyl alcohol cyclizations.

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(2) (a) Chisholm, M. H.; Clark, H. C. *Acc. Chem. Res.* **1973**, *6*, 202. (b) Bruce, M. I.; Swincer, A. G. *Adv. Organomet. Chem.* **1983**, *22*, 59.

(3) (a) McDonald, F. E.; Reddy, K. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3653. (b) Cutchins, W. W.; McDonald, F. E. *Org. Lett.* **2002**, *4*, 749. (c) McDonald, F. E.; Wu, M. *Org. Lett.* **2002**, *4*, 3979. (d) Davidson, M. H.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 1601.

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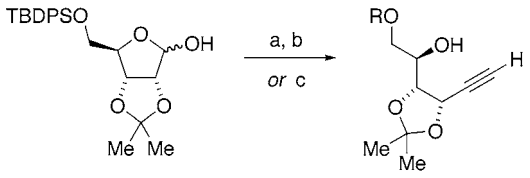
Scheme 1. Synthesis of Alkynyl Alcohol Substrates from D-Ribose[a]

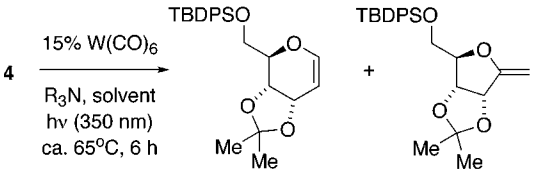


3 4 R = TBDPS 5 R = H

[a] Conditions: (a) $ClCH_2PPh_3Cl$/*n*-BuLi, TMEDA, THF (62% yield). (b) *n*-BuLi, THF, −78 °C (50% yield). (c) K_2CO_3, MeOH,$MeC(O)C(N_2)P(O)(OMe)_2$, 65 °C (50% yield).

Initial studies on the cycloisomerization of alkynyl alcohol substrate **4** resulted in a mixture of products **6** and **7**, arising from *endo*- and *exo*-mode cyclizations, respectively (Scheme 2). The ratio of isomers was not significantly affected by

Scheme 2. Cycloisomerizations of Alkynyl Alcohol **4**



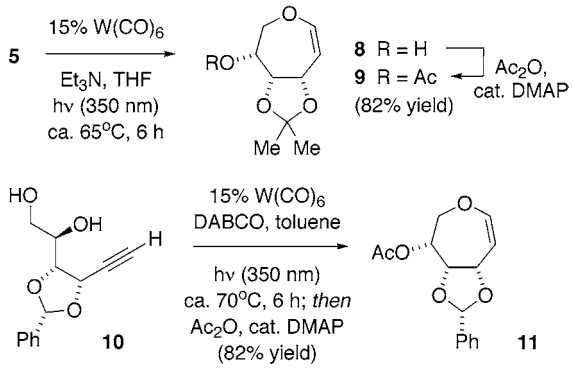
6 7

R_3N, solvent	ratio **6** : **7**	isolated yield (combined)
Et_3N, THF	55 : 45	81%
Et_3N, toluene	45 : 55	80%
DABCO, THF	95 : 5	76%
DABCO, toluene	95 : 5	80%

solvent effects, although changing the tertiary amine from triethylamine to DABCO resulted in nearly complete recovery of the desired *endo*-mode selectivity producing **6** in both THF and toluene, providing a successful synthesis of the protected D-allose glycal **6**.

Although alkynyl diol **5** could also be converted into **4** by selective silylation of the primary alcohol, we anticipated that the primary alcohol would be compatible and unreactive upon cyclization to the six-membered ring glycal, given the closer proximity of the secondary alcohol oxygen to the terminal alkyne carbon. To our surprise, tungsten-catalyzed cycloisomerization of **5** provided not the expected pyranose glycal analogue of **6** with an unprotected primary alcohol but rather gave the seven-membered ring glycal **8** in 68% isolated yield (Scheme 3). This compound was produced with

Scheme 3. Cycloisomerizations of Alkynyl Diols **5** and **10**



complete regioselectivity for *endo*-mode cyclization and virtually complete selectivity for reaction of the primary alcohol, with less than 2% of a probable six-membered ring glycal byproduct observed in the crude ^1H NMR spectrum. ^1H NMR resonances at 6.6 and 5.1 ppm were consistent with endocyclic glycal hydrogens 1 and 2, respectively (*exo*-methylenic hydrogens appear around 4.2−4.4 ppm, as in **7**). Furthermore, derivatization of product **8** as its acetate **9** resulted in deshielding of only one hydrogen, consistent with a secondary alcohol in **8**.[7] Compound **8** slowly decomposed upon standing (perhaps via oligomerization), but acylation of **8** prior to purification gave the septanose glycal acetate ester **9** in an isolated yield of 82% from **5**. The corresponding substrate **10** with benzylidene acetal protection also provided the seven-membered glycal **11**. As this work progressed, we found that isolated yields were improved in some cases by using DABCO as the base and toluene as the solvent.

Furthermore, formation of seven-membered ring glycals is general for all diastereomers of acetonide-protected alkynyldiol **5**, including **12** (from D-lyxose), **14** (from D-xylose), and **16** (from L-arabinose, Scheme 4).[7] Although seven-membered ring formation for **15** and **17** might be favored over six-membered ring formation due to the ring strain required for formation of the unobserved trans-fused bicyclic[4.3.0] structure, the cis-fused seven-membered ring products **9** and **13** are also favored even though the six-membered ring regioisomers are anticipated to be unstrained.

What factors are responsible for the unexpected but interesting regioselectivity for seven-membered ring formation? A primary alcohol is apparently not required for regioselective formation of the seven-membered ring product, as demonstrated for alkynyl diol substrate **18** with two secondary alcohols, obtained from L-rhamnose (Scheme 5).[6] At this stage, it appears likely that the cyclic 1,3-dioxolane protective group is responsible for *endo*-selective reaction of the distal hydroxyl group to give seven-membered ring products.

A control experiment changing the protective pattern from acetonide-protected substrate **5** was attempted by preparing

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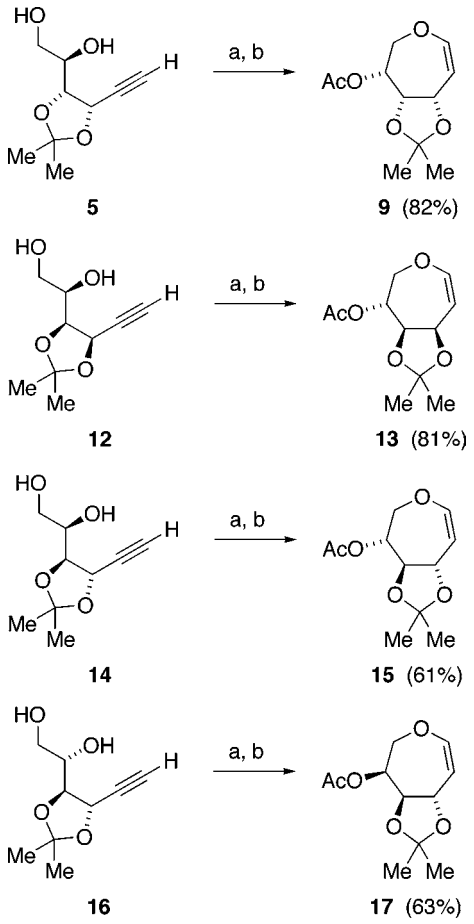
(5) Mella, M.; Panza, L.; Ronchetti, F.; Toma, L. *Tetrahedron* **1988**, *44*, 1673.

(6) Thiéry, J.-C.; Fréchou, C.; Demailly, G. *Tetrahedron Lett.* **2000**, *41*, 6337.

(7) See Supporting Information for substrate syntheses, cycloisomerization conditions, and detailed product characterization.

Scheme 4. Generality of Seven-Membered Ring Glycal Formation from Various Diastereomers[a]

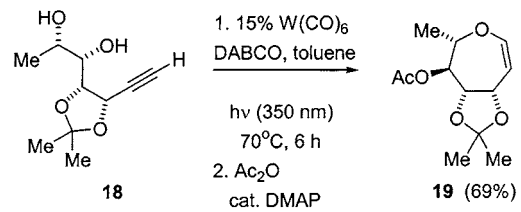


[a] Conditions: (a) 15% $W(CO)_6$, Et_3N, THF, h (350 nm) 55 °C, 6 h. (b) Ac_2O, cat. DMAP.

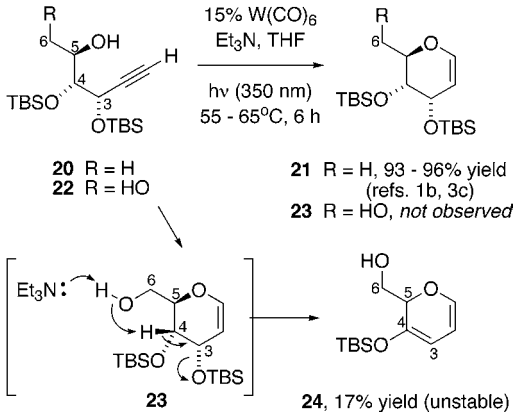
the bis-silyl ether substrate **22**[7] (Scheme 6), which is nearly identical to the 6-deoxy substrate **20** that we have previously established affords cycloisomerization product **21** in excellent yield.[1b,3a] Surprisingly, neither cycloisomerization product **23** nor the seven-membered ring isomer was observed as a product, and the only isolable compound was the unstable dienyl ether **24**.

This compound can be envisioned to arise from hydroxyl-assisted β-elimination via the intermediacy of expected product **23**, especially given the syn relationship of the

Scheme 5. Cycloisomerization of Substrate **18** with Two Secondary Alcohols Also Gives Seven-Membered Ring Product **19**



Scheme 6. Attempted Cycloisomerization of Bis-silyl Ether Diol **22**



hydroxymethyl oxygen five atoms away from the C4-hydrogen, which in turn is anti to the allylic silyloxy substituent at C3. This previously unobserved limitation of the cycloisomerization methodology can be avoided by use of different protective group patterns, as described earlier with substrate **4**.

Classical methods for carbohydrate synthesis are well-known to favor furanose and/or pyranose structures over septanose (seven-membered ring sugar) isomers,[8,9] and seven-membered ring sugars can also be produced by multistep routes involving selective protection of hexose sugar secondary alcohols[10] or by rearrangement of partially protected furanoside derivatives.[11] Although other methods for the formation of oxepins (seven-membered cyclic enol ethers)[12,13]

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(11) Contour, M.-O.; Fayet, C.; Gelas, J. *Carbohydr. Res.* **1990**, *201*, 150.

(12) For formation of septanose glycals via ring-closing metathesis of alkenes tethered to *O*-vinyl ethers, see: (a) Peczuh, M. W.; Snyder, N. L. *Tetrahedron Lett.* **2003**, *44*, 4057. (b) Peczuh, M. W.; Snyder, N. L.; Fyvie, W. S. *Carbohydr. Res.* **2004**, *339*, 1163.

(13) For representative other methods for formation of oxepins via: ring-closing metathesis−isomerization: (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (b) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380. (c) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390. (d) Schmidt, B. *Eur. J. Org. Chem.* **2003**, 816. Oxidation−dehydration of 1,6-hexanediol: (e) Larkin, D. R. *J. Org. Chem.* **1965**, *30*, 335. (f) Oakes, F. T.; Yang, F.-A.; Sebastian, J. F. *J. Org. Chem.* **1982**, *47*, 3094. Via lactone enol phosphate or triflates: (g) Kane, V. V.; Doyle, D. L.; Ostrowski, P. G. *Tetrahedron Lett.* **1980**, *21*, 2643. (h) Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* **1989**, 1313. (i) Nicolaou, K. C. *J. Am. Chem. Soc.* **1997**, *119*, 5469. Via anionic cyclization of allyl glycidyl ether: (j) Ichikawa, Y.; Niitsuma, S.; Kato, K.; Takita, T. *J. Chem. Soc., Chem. Commun.* **1988**, 625. (k) Bird, C. W.; Hormozi, N. *Tetrahedron Lett.* **1990**, *31*, 3501. Oxidative expansion with peroxides: (l) Krafft, G. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459. (m) Goodman, R. M.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 5125. [3.3]-Rearrangements: (n) Wenkert, E.; Greenberg, R. S.; Kim, H. S. *Helv. Chim. Acta* **1987**, *70*, 2159. (o) Clark, D. L.; Chou, W.-N.; White, J. B. *J. Org. Chem.* **1990**, *55*, 3975. (p) Sugiyama, J.; Tanikawa, K.; Okada, T.; Noguchi, K.; Ueda, M.; Endo, T. *Tetrahedron Lett.* **1994**, *35*, 3111. (q) Hofmann, B.; Reissig, H.-U. *Chem. Ber.* **1994**, *127*, 2337. Conjugate oxacyclization

are known, our route is notable for its generality to produce a variety of septanose stereoisomers, ease of preparation for the alkynyl diol substrates from common pentose and hexose sugars, and the inexpensive nature of the tungsten carbonyl catalyst system. The availability of this family of septanose glycals may offer significant advances in the synthesis of structurally unusual hexoseptanose glycosides[14] as isomers of the more common hexopyranose glycosides ubiquitous in glycobiology.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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