ORGANIC LETTERS

2005
Vol. 7, No. 3
483−485

Silver(I)-Catalyzed Addition of Zirconocenes to Glycal Epoxides. A New Synthesis of α-*C*-Glycosides

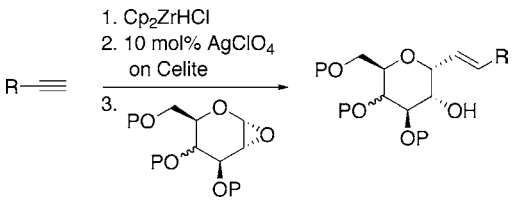
Peter Wipf,* Joshua G. Pierce, and Nian Zhuang[§]

Department of Chemistry and Center for Chemical Methodologies & Library Development, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

pwipf@pitt.edu

Received November 30, 2004

ABSTRACT



Hydrozirconation of terminal alkynes, followed by $AgClO_4$-catalyzed in situ addition of the resultant alkenylzirconocenes to 1,2-anhydrosugars (glycal epoxides) leads to α-*C*-glycosides in moderate to high yields.

The replacement of the anomeric oxygen atom in glycosides with carbon substitutents provides carbohydrate mimetics with improved stability toward glycosidases and hydrolytic conditions.[1] In principle, the greater chemical and enzymatic stability of these *C*-glycosides bodes well for their application as small molecule inhibitors of cell-surface recognition events and glycoside metabolism, but in practice the mimicry of conformational and electrostatic properties of the parent *O*-glycosides has been challenging to realize. Not surprisingly, biological activity is often critically dependent on solution conformation.[2] While most synthetic *C*-glycosides show diminished activity compared to the corresponding *O*-glycoside lead structures, considerable enhancement of activity has also been observed.[3] In this context, the development of new methods for the stereoselective synthesis of side-chain substituted *C*-glycosides continues to be of interest, not just for the preparation of analogues for biological assays but also for complex natural product synthesis.[4] We,[5] as well as others,[6,7] have investigated the use of 1,2-anhydrosugars for *C*-glycoside synthesis, and we now report a new protocol that allows the stereospecific C(1)-opening with unsaturated, functionalized nucleophiles derived from readily available terminal alkynes.

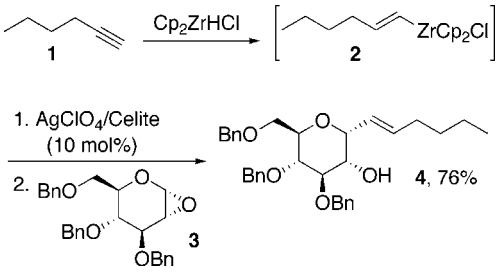
[§] Current address: PROD, Michigan Laboratories, Pfizer, Inc., 2800 Plymouth Rd., Ann Arbor, MI 48105.

(1) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913.
(2) Wei, A.; Boy, K. M.; Kishi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9432.
(3) Yang, G.; Schmieg, J.; Tusji, M.; Franck, R. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 3818.
(4) (a) McGarvey, G. J.; Schmidtmann, F. W.; Benedum, T. E.; Kizer, D. E. *Tetrahedron Lett.* **2003**, *44*, 3775. (b) Harvey, J. E.; Raw, S. A.; Taylor, R. J. K. *Org. Lett.* **2004**, *6*, 2611. (c) Ben, A.; Yamauchi, T.; Matsumoto, T.; Suzuki, K. *Synlett* **2004**, 225. (d) Gardiner, J. M.; Mills, R.; Fessard, T. *Tetrahedron Lett.* **2004**, *45*, 1215. (e) Terauchi, M.; Abe, H.; Matsuda, A.; Shuto, S. *Org. Lett.* **2004**, *6*, 3751. (f) Steinhuebel, D. P.; Fleming, J. J.; Du Bois, J. *Org. Lett.* **2002**, *4*, 293. (g) Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2001**, *3*, 177.
(5) Zhuang, N. MS Thesis, University of Pittsburgh, 1997.
(6) (a) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545. (b) Parrish, J. D.; Little, R. D. *Org. Lett.* **2002**, *4*, 1439.
(7) (a) Grotenbreg, G. M.; Tuin, A. W.; Witte, M. D.; Leeuwenburgh, M. A.; Van Boom, J. H.; Van der Marel, G. A.; Overkleeft, H. S.; Overhand, M. *Synlett* **2004**, 904. (b) Xue, S.; Han, K.-Z.; He, L.; Guo, Q.-X. *Synlett* **2003**, 870. (c) Leeuwenburgh, M. A.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *J. Carbohydr. Chem.* **2003**, *22*, 549. (d) Boulineau, F. P.; Wei, A. *Org. Lett.* **2002**, *4*, 2281. (e) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997. (f) Bailey, J. M.; Craig, D.; Gallagher, P. T. *Synlett* **1999**, 132. (g) Rainier, J. D.; Allwein, S. P. *J. Org. Chem.* **1998**, *63*, 5310. (h) Evans, D. A.; Trotter, B. W.; Cote, B. *Tetrahedron Lett.* **1998**, *39*, 1709. (i) Manabe, S.; Ito, Y.; Ogawa, T. *Chem. Lett.* **1998**, 919. (j) Leeuwenburgh, M. A.; Timmers, C. M.; van der Marel, G. A.; van Boom, J. H.; Mallet, J.-M.; Sinay, P. G. *Tetrahedron Lett.* **1997**, *38*, 6251. (k) Best, W. M.; Ferro, V.; Harle, J.; Stick, R. V.; Tilbrook, D. M. G. *Aust. J. Chem.* **1997**, *50*, 463. (l) Bellosta, V.; Czernecki, S. *J. Chem. Soc., Chem. Commun.* **1989**, 199. (m) Klein, L. L.; McWhorter, W. W., Jr.; Ko, S. S.; Pfaff, K. P.; Kishi, Y.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7362.

10.1021/ol0475414 CCC: $30.25
Published on Web 01/05/2005

Hydrozirconation[8] of alkyne **1** provides a stoichiometric alkenyl zirconocene **2**,[9] which upon addition of 10 mol % of silver perchlorate on Celite followed by glucal epoxide **3**[10] gives α-*C*-glycoside **4** in 76% yield (Scheme 1).[11−13] Due

Scheme 1. Formation of α-Alkenyl-*C*-glycoside **4** from Alkyne **1**



to cationic zirconocene-assisted oxocarbenium ion formation and chelation-directed delivery of the alkenyl substituent, the reaction proceeds to give the α-epimer exclusively (Figure 1). After initial chloride ligand abstraction and initiation of the catalytic cycle by the silver(I) salt,[14] subsequent formation of the cationic zirconium species is a chain transfer process, in which the more Lewis-acidic cationic alkoxy zirconium(IV) species accepts the chloride anion from the alkenyl(chloro)zirconocene **2**. The α-*C*-glycoside configuration was assigned based on the coupling constant $^3J_{1,2} = 5.5$ Hz, which is characteristic for the 1,2-gauche relationship of the neighboring hydrogen atoms and compares well with literature values.[15]

The scope of the *C*-glycosylation reaction is illustrated in detail in Table 1.[16,17] In the absence of $AgClO_4$, no reaction between epoxides and organozirconocenes was detected. Systematic variation of the functional groups on the alkyne

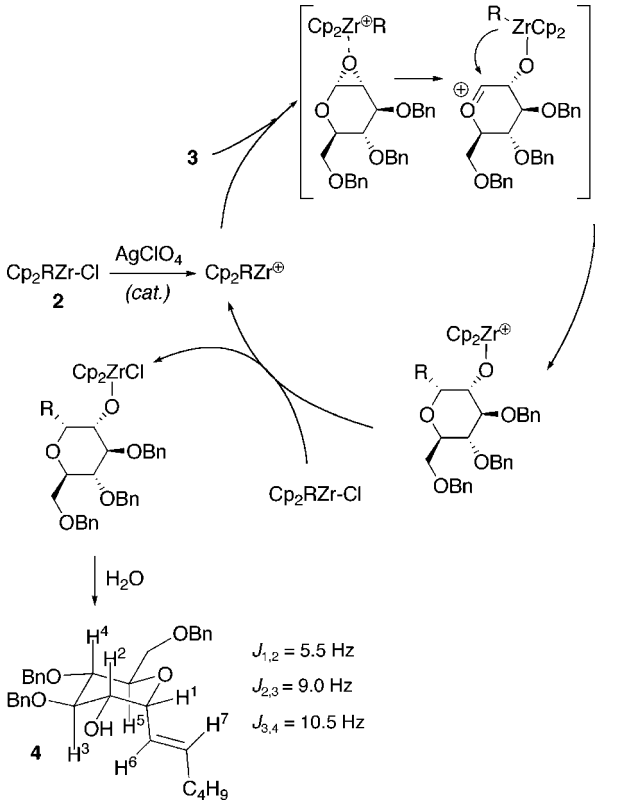


Figure 1. Proposed mechanism for regio- and stereoselective delivery of the alkenyl ligand on zirconium.

demonstrated the general tolerance of the process for a range of ether, ester, carbamate, and sulfonamide functions (entries 2−4). While terminal alkynes were very effective, internal alkynes such as 4-octyne yielded only trace amounts of the desired addition product (entry 9).[18] Presumably, the increase in steric hindrance at the zirconium-bearing carbon is sufficient to prevent the metal center from interacting with the Lewis-basic epoxide oxygen. Both benzyl and silyl ethers are feasible on the glycal epoxide (entries 1−8),[19] and the D-galactose derivative reacted analogously to the D-glucose epoxide (entries 1 and 2 vs 5 and 6). In all cases, $^3J_{H,H}$ analysis confirmed that the configuration of the newly formed glycosidic bond was exclusively α, i.e., syn to the C(2)-hydroxyl group.

In conclusion, the ability to combine relatively sensitive functional groups with the nucleophilic zirconocene under mild Ag(I) catalysis allows for rapid conversion of 1,2-anhydrosugars to complex α-*C*-glycosides that have previously not been readily available for synthetic or biological

(8) (a) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853. (b) Wipf, P.; Kendall, C. *Top. Organomet. Chem.* **2004**, *8*, 1.

(9) Wipf, P.; Nunes, R. L. *Tetrahedron* **2004**, *60*, 1269.

(10) Glycal epoxides were prepared by Danishefsky's protocol: (a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661. (b) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

(11) (a) Wipf, P.; Xu, W. *J. Org. Chem.* **1993**, *58*, 825. (b) Wipf, P.; Xu, W. *Tetrahedron* **1995**, *51*, 4551. (c) Wipf, P.; Xu, W.; Kim, H.; Takahashi, H. *Tetrahedron* **1997**, *53*, 16575. (d) Wipf, P.; Methot, J.-L. *Org. Lett.* **1999**, *1*, 1253.

(12) For the use of the $Cp_2ZrCl_2/AgClO_4$ system for glycosyl transfer reactions of anomeric sulfoxides, see: Wipf, P.; Reeves, J. T. *J. Org. Chem.* **2001**, *66*, 7910.

(13) Use of 1 equiv of silver perchlorate on Celite led to a fast conversion to give **4** in 85% yield.

(14) (a) Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* **1992**, *33*, 5965. (b) Ohmori, K.; Hatakeyama, K.; Ohrui, H.; Suzuki, K. *Tetrahedron* **2004**, *60*, 1365.

(15) (a) Bhagwatheeswaran, H.; Gaur, S. P.; Jain, P. C. *Synthesis* **1976**, 615. (b) Ramage, R.; Hopton, D.; Parrott, M. J.; Kenner, G. W.; Moore, G. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1357. (c) Desai, M. C.; Thadeio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831.

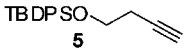
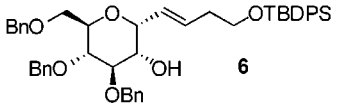
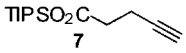
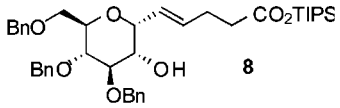
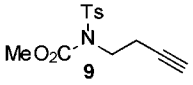
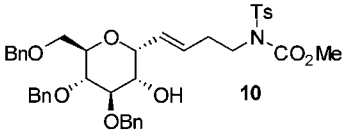
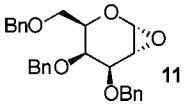
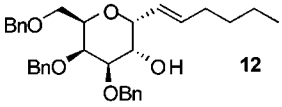
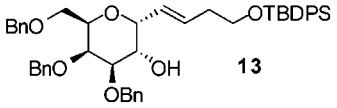
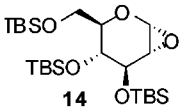
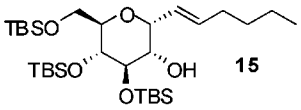
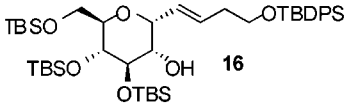
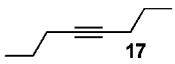
(16) **Typical Procedure:** To a suspension of zirconocene hydrochloride (38 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) was added 1-hexyne (17 μL, 0.15 mmol). The yellow reaction mixture was stirred at room temperature for 10 min, treated with $AgClO_4$ on Celite (15.5 mg, 15.0 μmol), stirred for 5 min, and treated dropwise with a solution of glycal epoxide **3** (44 mg, 0.10 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 1 h, quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (8:2, EtOAc:hexanes) to yield 39 mg (76%) of **4** as a colorless oil.

(17) In all reactions, a minor side product was derived from decomposition of the glycal epoxide under the Lewis acidic conditions. At lower temperatures (0 °C), the conversion was similar, but the side product was also formed to a comparable extent.

(18) Both 4-octyne and 6-dodecyne were used under the typical reaction conditions, but no significant product formation was observed. The reaction with these substrates was not further optimized.

(19) Deactivating carbohydrate protecting groups such as acetates have proven unsatisfactory in previous work with glycal epoxides and were not explored in the present studies; see refs 10 and 7l.

Table 1. Conversion of Glycal Epoxides to *C*-glycosides by Addition of in Situ Prepared Alkenylzirconocenes

entry	alkyne	glycal epoxide	product	yield [%][a]
1	**1**	**3**	**4**	76
2	 **5**	**3**	 **6**	74
3	 **7**	**3**	 **8**	67
4	 **9**	**3**	 **10**	70
5	**1**	 **11**	 **12**	73
6	**5**	**11**	 **13**	72
7	**1**	 **14**	 **15**	74
8	**5**	**14**	 **16**	71
9	 **17**	**3**	NR	-

[a] Yields are based on glycal epoxide.

studies. Prior organometallic protocols for glycal epoxide ring opening used Al(III)-,[7e,f] B(III)-,[7e] Cu(I)-,[7d,e,f,h,l,m] Li(I)-,[7c,e,h,i] Mg(II)-,[7c,e,g,h,k] Sn(IV)-,[7h] Ti(IV)-,[7c] and Zn(II)-mediated processes.[7a,b,c,e,j] Many of these reactions have proven to be substrate- and nucleophile-dependent, and mixtures of α- and *β*-*C*-glycosides were obtained.[7e] Despite the synthetic potential of vinyl-*C*-glycosides,[20] currently there is no effective method available for the addition of functionalized alkenyl organometallics to glycal epoxides. The Ag(I)-catalyzed addition of terminal alkyne-derived zirconocenes addresses this shortcoming and provides a versatile stereospecific access to substituted α-*C*-glycosides.

Acknowledgment. This work has been supported by the National Science Foundation (CHE-0315205).

Supporting Information Available: Experimental procedures and spectral data for all new compounds, including copies of ^{1}H and ^{13}C NMR spectra for **4**, **6**, **8**, **10**, **12**, **13**, **15**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0475414

(20) (a) Durrat, F.; Xie, J.; Valery, J.-M. *Tetrahedron Lett.* **2004**, *45*, 1477. (b) Caputo, R.; Festa, P.; Guaragna, A.; Palumbo, G.; Pedatella, S. *Carbohydr. Res.* **2003**, *338*, 1877. (c) Dondoni, A.; Giovannini, P. P.; Marra, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2380.