ORGANIC LETTERS

2003
Vol. 5, No. 12
2173−2176

New Stereoselective β-*C*-Glycosidation by Uncatalyzed 1,4-Addition of Organolithium Reagents to a Glycal-Derived Vinyl Oxirane

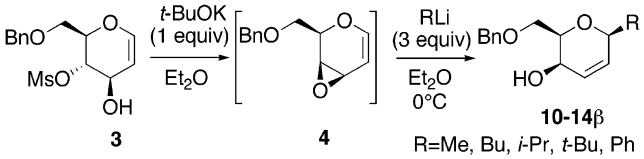
Valeria Di Bussolo, Micaela Caselli, Mauro Pineschi, and Paolo Crotti*

Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, I-56126 Pisa, Italy

crotti@farm.unipi.it

Received April 18, 2003

ABSTRACT



Epoxide 4 is generated in situ from D-glucal-derived hydroxy mesylate 3. Reaction of epoxide 4 with a series of alkyl- and aryllithium reagents affords 2,3-unsaturated β-C-glycosides with excellent 1,4-regioselectivity and complete stereoselectivity for the β-glycoside. Other organometallic reagents demonstrate more complex behavior in their reactions with epoxide 4.

C-Alkyl and *C*-aryl glycosides are carbohydrate analogues of *O*-glycosides in which the C−O glycosidic linkage is substituted by a C−C bond. This modification results in a greater stability of these compounds to both acid and enzymatic cleavage, compared with the corresponding O-derivatives, to the point that *C*-glycosides can be advantageously used as mimics of the corresponding more commonly encountered *O*-glycosides.[1] Moreover, the *C*-glycoside moiety occurs in several natural products with important pharmacological properties.[2] However, for an effective use of these compounds, methods for a complete stereoselective introduction of the C−C glycosidic bond are decidedly valuable.[3] In this framework, 2,3-unsaturated *C*-glycosides appear to be of interest because the presence of the unsaturation allows further functionalization.

Several synthetic methods to these unsaturated compounds by Pd- or Ni-catalyzed addition reaction of organometallics to a glycosyl donor have been described.[4] More recently, methods of C-glycosidation using arylboronic acids and Pd-$(AcO)_2$,[5]a nucleophilic addition of organozinc compounds to glycals,[6] and a Lewis acid mediated cross-coupling reaction between chiral titanium enolates and glycals have

(1) (a) Leavy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Oxford, 1995. (b) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545. (c) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55. (d) Weatherman, R. V.; Mortell, K. H.; Chervenak, M.; Kiessling, L. L.; Toone, E. J. *Biochemistry* **1996**, *35*, 3619. (e) Ravishankar, R.; Surolia, A.; Vijayan, M.; Lim, S.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 11297. (f) García-Herrero, A.; Montero, E.; Muñoz, J. L.; Espinosa, J. F.; Vián, A.; García, J. L.; Asensio, J. L.; Cañada, F. J.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **2002**, *124*, 4804.

(2) (a) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407. (b) Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1. (c) Townsend, L. B.; Devivar, R. V.; Turk, S. R.; Nassiri, M. R.; Drach, J. C. *J. Med. Chem.* **1995**, *38*, 4098. (d) Gudmundsson, K. S.; Drach, J. C.; Townsend, L. B. *J. Org. Chem.* **1997**, *62*, 3453

(3) (a) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1. (b) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913. (c) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700.

(4) (a) Kwok, D.-I.; Farr, R. N.; Daves, G. D., Jr. *J. Org. Chem.* **1991**, *56*, 3711. (b) Czernecki, S.; Dechavanne, V. *Can. J. Chem.* **1983**, *61*, 533. (c) Daves, G. D., Jr. *Acc. Chem. Res.* **1990**, *23*, 201. (d) Dunkerton, L. V.; Serino, A. J. *J. Org. Chem.* **1982**, *47*, 2812. (e) Yougai, S.; Miwa, T. *J. Chem. Soc., Chem. Commun.* **1983**, 68. (f) RajanBabu, T. V. *J. Org. Chem.* **1985**, *50*, 3642. (g) Brakta, M.; Le Borgne, F.; Sinou, D. *J. Carbohydr. Chem.* **1987**, *6*, 307. (h) Dunkerton, L. V.; Euske, J. M.; Serino, A. J. *Carbohydr. Res.* **1987**, *171*, 89. (i) Moineau, C.; Bolitt, V.; Sinou, D. *J. Org. Chem.* **1998**, *63*, 582.

(5) Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013.

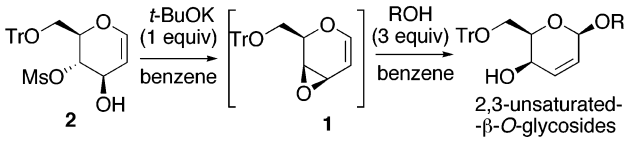
(6) Steinhuebel, D. P.; Fleming, J. J.; Du Bois, J. *Org. Lett.* **2002**, *4*, 293.

10.1021/ol034662f CCC: $25.00 © 2003 American Chemical Society
Published on Web 05/16/2003

been reported.[7] In these C-glycosidation methods involving the addition of carbon nucleophiles to anomeric carbon electrophiles, α-stereoselectivity is well documented.[4a−h,5,6] On the other hand, a general synthesis of *β*-*C*-glycosides that is not dependent on functionality in the substrate[7] or on the influence of a catalyst[4i] is still a significant challenge, especially in consideration of the importance of these compounds in naturally occurring glycoconjugates.[1a,8]

Recently, we have introduced into the synthesis a simple, completely *β*-stereoselective O-glycosylation by means of a regioselective 1,4-addition of O-nucleophiles (alcohols and phenol) to the previously undescribed 6-*O*-trityl vinyl oxirane **1**, derived from D-glucal (Scheme 1).[9]

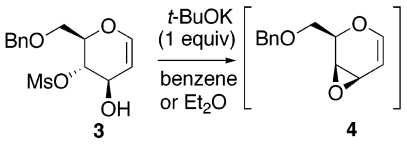
Scheme 1. *O*-Glycosylation of the in Situ-Formed Epoxide **1** with Alcohols and Phenol



This result prompted us to examine the possibility of obtaining similar regio- and stereoselectivity also with C-nucleophiles, to address the long-standing goal of synthesizing *β*-*C*-glycosides.

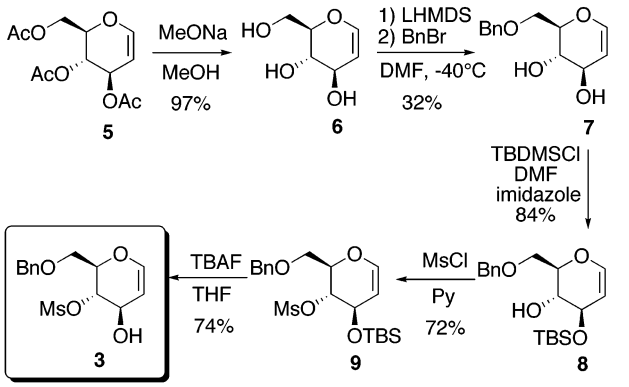
We now report a new process that allows direct synthetic access to *β*-*C*-glycosides from vinyl oxirane **4**, the 6-*O*-Bn analogue of **1**.[10] As in the case of **1**, vinyl oxirane **4** is not sufficiently stable to be isolated and can only be prepared in situ (*t*-BuOK/benzene or Et_2O) from the corresponding hydroxy mesylate **3**, immediately prior to use (Scheme 2).[11]

Scheme 2. In Situ Preparation of Epoxide **4**



Hydroxy mesylate **3** was prepared starting from tri-*O*-acetyl-D-glucal (**5**), which was initially deprotected to D-glucal (**6**). Monoalkylation of **6** with the LHMDS/BnBr protocol at −40 °C[12] afforded the monobenzyl derivative **7** with selective alkylation at the primary alcoholic functionality. Monoprotection of **7** with TBDMS-Cl gave the 3-*O*-TBS derivative **8**, which was treated with MsCl/Py to give the mesylate **9**. The 3-*O*-TBS group of **9** was removed by TBAF to give the hydroxy mesylate **3**, the necessary precursor of epoxide **4** (Scheme 3).

Scheme 3. Synthesis of Hydroxy Mesylate **3**



To our delight, when vinyl oxirane **4** (the glycosyl donor) was exposed to organolithium reagents (the glycosyl acceptor, 3 equiv) in Et_2O at 0 °C, a clear, regioselective 1,4-addition reaction (conjugate addition) was obtained affording the corresponding *C*-glycosides in good yield and with complete *β*-stereoselectivity (compounds **10**−**14***β*, Table 1).[13] The reaction is amenable to a variety of alkyllithium reagents, and also a sterically hindered glycosyl acceptor like *t*-BuLi can be effectively used. It should also be noted that the sp^2 hybridization of the glycosyl acceptor, as in the case of PhLi, does not change the regio- or stereoselectivity of the addition process (entry 5, Table 1).

The protocol necessarily requires a separate generation in situ of the reacting species, the vinyl oxirane **4**, by independent cyclization of the corresponding hydroxy mesylate **3** with *t*-BuOK prior to the addition of the organometallic reagents (protocol A). In fact, when hydroxy mesylate **3** was left to react directly with alkyllithium and PhLi (3 equiv), with no pretreatment with *t*-BuOK (protocol B),[14] only complex reaction mixtures were obtained, indicating that no formation of the corresponding epoxide had occurred under these conditions.[15]

The *β*-*C*-glycoside configuration of the addition products **10**−**14***β* was firmly established by the presence in these

(7) Larrosa, I.; Romea, P.; Urpí, F.; Balsells, D.; Villarasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2002**, *4*, 4651.

(8) (a) Rohr, J.; Thiericke, R. *Nat. Prod. Rep*. **1992**, 103. (b) Hansen, M.; Hurley, L. H. *Acc. Chem. Res.* **1996**, *29*, 249.

(9) Di Bussolo, V.; Caselli, M.; Pineschi, M.; Crotti, P. *Org. Lett*. **2002**, *4*, 3695.

(10) In the present context, the 6-*O*-trityl group of the previous epoxide **1** was replaced with the benzyl group because of the greater stability of the latter to a wide range of reaction conditions.

(11) As previously performed in the case of epoxide **1**, the formation of epoxide **4** by *t*-BuOK cyclization of hydroxy mesylate **3** was established by running the reaction in C_6D_6 in an NMR tube and recording the ^1H NMR spectrum a few minutes after the addition of the base.

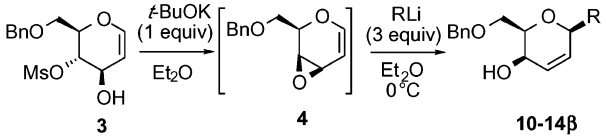
(12) Deshpande, P. P.; Kim, H. M.; Zatorski, A.; Park, T.-K.; Ragupathi, G.; Livingston, P. O.; Live, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 1600.

(13) Less than 5% of the corresponding anti 1,2-addition products were present in some cases. Products from an α-1,4 addition process were not observed at all.

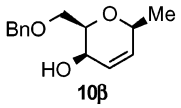
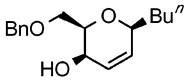
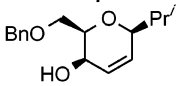
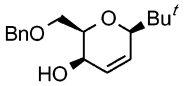
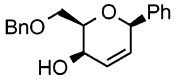
(14) Under protocol B, it was hoped that the organometallic reagents might behave as a base and thereby promote epoxide formation from hydroxy mesylate **3** and then undergo an addition reaction.

(15) This observation indicates that alkyllithium and PhLi do not behave, in the present case, as a base, which is necessary for the cyclization of hydroxy mesylate **3** to epoxide **4**.

Table 1. Regio- and Stereoselectivity of *C*-Glycosidation of the in Situ-Formed Epoxide **4** with Organolithium Reagents[13]

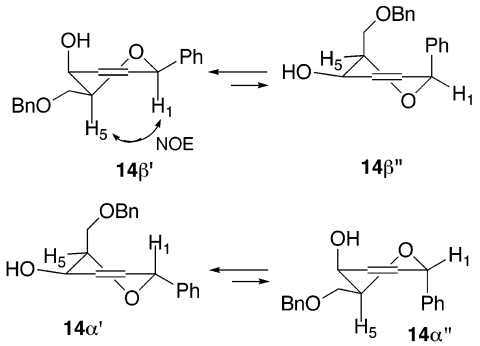


R=Me, Bu, *i*-Pr, *t*-Bu, Ph

entry	glycosyl acceptor	time (h)	product	yield (%)
1	MeLi	0.5	 **10β**	80
2	BuLi	3	 **11β**	81
3	*i*-PrLi	1	 **12β**	78
4	*t*-BuLi	0.5	 **13β**	80
5	PhLi	0.5	 **14β**	93

compounds of a clear NOE between protons H(1) and H(5), which is completely absent in the corresponding α-stereoisomer, as demonstrated in the case of the phenyl-substituted pair **14***β* and **14**α (Scheme 4). Moreover, the presence of

Scheme 4. NOE in *β*-*C*-Glycoside **14*β*** Compared with α-*C*-Glycoside **14**α.

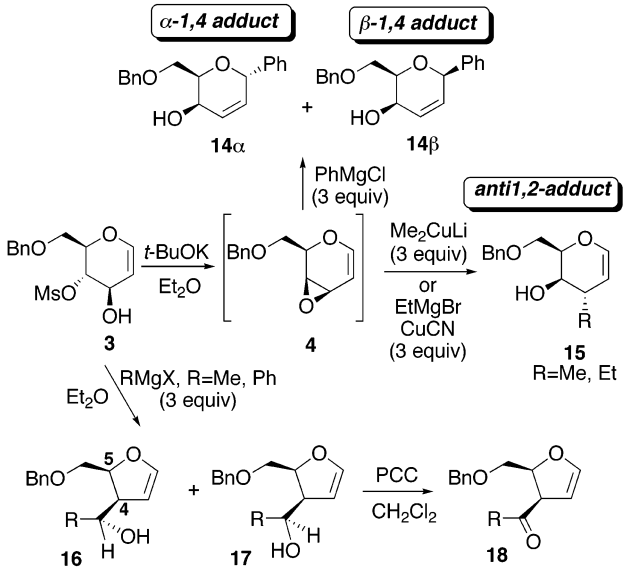


chemical shift values for C(5) higher than 75 ppm in the ^{13}C NMR spectra of compounds **10**−**14***β* is diagnostic for a 1,5-cis relationship between substituents at C(1) and C(5) in 2,3-unsaturated *C*-glycosides.[5,16]

Other organometallics, such as Grignard reagents and cuprates, showed a more complex behavior with epoxide **4**, affording completely different results as regards the regio- and stereoselectivity. In some cases (phosphoramidite-catalyzed addition of dialkylzinc reagents[17] and Pd-catalyzed addition of boronic acids),[5] only very complex mixtures were obtained that did not contain traces of the corresponding addition products.

As for the Grignard reagents, their behavior depends on the protocol (A or B). In the presence of a preventive cyclization (*t*-BuOK) of hydroxy mesylate **3** to epoxide **4** (protocol A), the use of MeMgBr and PhMgBr (3 equiv) resulted in an exclusive 1,4-addition of *t*-BuOH,[18] whereas the use of PhMgCl led to a 3:7 mixture of the corresponding α- (**14**α) and *β*-*C*-glycosides (**14***β*) (1,4-adducts). On the contrary, when the Grignard reagents (MeMgBr and PhMgBr, 3 equiv) were directly brought into contact with hydroxy mesylate **3** (protocol B), an almost 1:1 mixture of the corresponding diastereoisomeric 4,5-dihydrofuran-derived alcohols **16** and **17** turned out to be the only reaction product (Scheme 5).

Scheme 5. Regio- and Stereoselectivity of the Addition Reaction of Grignard Reagents and Cuprates to Hydroxy Mesylate **3** and Epoxide **4**



Alcohols **16** and **17** reasonably derive from an isomerization process, with ring contraction, of epoxide **4**, formed under the basic reaction conditions of the reagent (RMgX), to the intermediate aldehyde **20** (Scheme 6).[19] This isomerization is reasonably promoted by the oxophilic character of the magnesium salts present in the reaction mixture

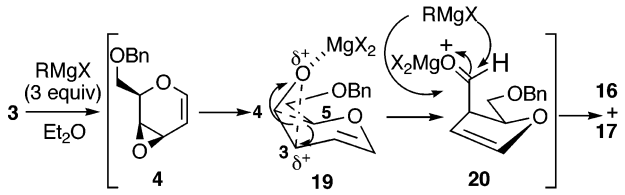
(16) The only exception is given by the *β*-methyl derivative **10***β* [*δ* C(5) = 73.79 ppm]. However, the *β*-*C*-glycosidic configuration for this compound was firmly established by corresponding NOE experiment.

(17) Bertozzi, F.; Crotti, P.; Feringa, B. L.; Macchia, F.; Pineschi, M. *Synthesis* **2001**, 483 and pertinent references therein.

(18) From *t*-BuOK used for the cyclization of **3** to epoxide **4**.

(19) As suggested by a Rewiever, epoxide **4** is not a necessary intermediate for the generation of **16** and **17**, via protocol B. A Grob fragmentation process on hydroxy mesylate **3** could lead directly to the observed products.

Scheme 6. Formation of the Intermediate Aldehyde **20**



(Schlenk equilibrium) and proceeds through a typical concerted, highly stereocontrolled mechanism with migration of the C(4)−C(5) bond to the developing C(3)-carbocationic center, as shown in structure **19** (Scheme 6).[20] Subsequent nonstereoselective nucleophilic addition of the reagent (RMgX) to the intermediate aldehyde **20** affords alcohols **16** and **17**, as found experimentally. Oxidation of the separated alcohols **16** and **17** by PCC/CH_2Cl_2 yielded the same ketone **18**, indicating that **16** and **17** have the same configuration at C(4) and C(5), as independently suggested by examination of the reasonable reaction mechanism relative to their formation (Schemes 5 and 6).

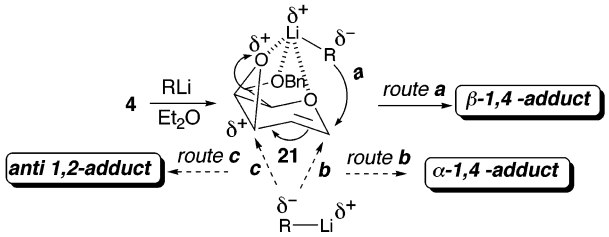
Under protocol A reaction conditions, cuprates such as Me_2CuLi or EtMgBr in the presence of CuCN afforded only the corresponding anti 1,2-adduct **15** (Scheme 5). Interestingly, this result is in contrast with the 1,4-regioselectivity normally observed with cuprates in their addition reactions to vinyl oxiranes.[21]

The regio- and stereoselective result obtained with organolithium reagents (RLi, R = alkyl, Ph) in their reaction with epoxide **4**, under protocol A, may be tentatively rationalized by admitting the incursion in the reaction pathway of a coordination of the lithium counterpart of the organometallic compound with the oxirane oxygen, probably followed by a bidentate chelation of the metal with both the endocyclic and exocyclic oxygen, as shown in structure **21** (Scheme 7). In this way, the reagent (RLi) is effectively

(20) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon: Oxford, 1991; Vol 3, pp 733−775.

(21) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503.

Scheme 7. Rationalization of the 1,4-Regio- and β-Stereoselectivity of the Addition Reaction of RLi (R = Alkyl and Ph) to Epoxide **4**



brought to the β-face of the glycal system and appropriately disposed to nucleophilically attack C(1) to give the 1,4-regio- and β-stereoselective result observed. The β-1,4-attack on C(1) by the reagent engaged in the chelated structure **21** (internal nucleophile) (route **a**), rather than an α-1,4-attack (route **b**) or an anti 1,2-attack (route **c**, Scheme 7) by an external nucleophile, appears to be favored by entropic factors to the point that products arising from routes **b** and **c** are consequently not observed.[13]

Studies are underway to obtain more evidence in favor of the proposed mechanism and to verify how the nature of the nucleophile and changes in the branched chain of vinyl oxiranes of type **4** can modify the regio- and stereoselective result so far obtained both in the O-glycosylation and in the present C-glycosidation reaction.

Acknowledgment. This work was supported by the University of Pisa and MIUR (Ministero dell'Istruzione, dell'Università e della Ricerca), Roma. P.C. gratefully acknowledges Merck Research Laboratories for the generous financial support derived from the 2002 ADP Chemistry Award.

Supporting Information Available: Experimental details and spectral and analytical data for all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034662F