JOC*Note*

Stereospecific Uncatalyzed α-*O*-Glycosylation and α-*C*-Glycosidation by Means of a New D-Gulal-Derived α Vinyl Oxirane

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

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

crotti@farm.unipi.it

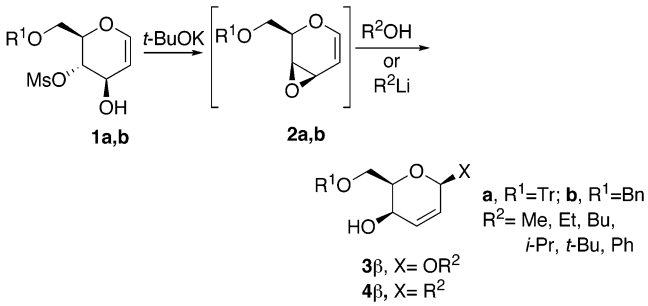
Received May 26, 2004

Abstract: The reaction of α vinyl oxirane **5**, prepared through a new route to the D-gulal system, with *O*-nucleophiles (alcohols and di-*O*-isopropylidene-α-D-monosaccharides) and *C*-nucleophiles (lithium alkyls) affords, in a completely stereoselective way, the corresponding 2-unsaturated α *O*- and *C*-glycosides having the same configuration as the starting epoxide.

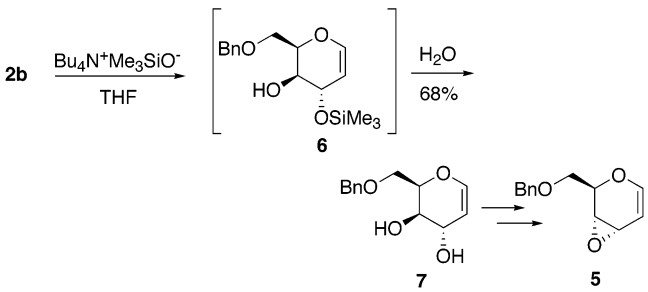
Alkyl 2,3-dideoxy-2-hexenopyranosides (pseudoglycals) are useful synthetic intermediates because the presence of the unsaturation allows the introduction of further functionalities.[1] One of the most common procedures for the synthesis of pseudoglycals is the Ferrier allylic rearrangement of glycals.[2] However, the drawbacks of this reaction are often its incomplete stereoselectivity (α/β ratio) and the use of a Lewis acid as the necessary catalyst.[2,3] As a consequence, methods for the stereoselective synthesis of *O*- and *C*-glycosides, whose importance in natural products synthesis and as mimics is well-documented, constitute an important synthetic challenge. Recently, we have found that vinyl oxiranes **2a** and **2b** simply prepared from D-glucal are useful intermediates for the synthesis of pseudoglycals and derivatives: the reaction of **2a** and **2b** (obtained in situ by cyclization of the corresponding hydroxy mesylates **1a** and **1b**) with alcohols (*O*-nucleophiles)[3a] and lithium alkyls (*C*-nucleophiles)[3b] afforded the corresponding 2-unsaturated β-*O*- (**3**β) and β-*C*-glycosides (**4**β) in a completely 1,4-regio- and β-stereoselective conjugate addition process (Scheme 1).[3,4]

The observation that the β-stereoselectivity obtained in the nucleophilic addition to epoxides **2a** and **2b** corresponded to the β-configuration of the oxirane ring led us to consider it interesting to prepare epoxide **5**, the α-diastereoisomer of the previously examined epoxide **2b**,

SCHEME 1



SCHEME 2



and to study the corresponding regio- and stereochemical behavior in nucleophilic addition reactions (Scheme 2).

For the synthesis of **5** it was considered useful to have 6-(*O*-benzyl)-D-gulal (trans diol **7**) as the starting material (Scheme 2). Diol **7** could be reasonably prepared in a simple way by the opening reaction of epoxide **2b** with an alkaline hydroxide such as KOH (an *O*-nucleophile) through a S_N2 addition process and attack of the nucleophile on the allylic C(3) oxirane carbon. Actually, the reaction of **2b** with aqueous KOH afforded only a very complex reaction mixture not containing any trace of the desired diol **7**. Diol **7** could be prepared only by reaction of epoxide **2b** with a new reagent, tetrabutylammonium trimethylsilanolate ($Bu_4N^+Me_3SiO^-$), in which the nucleophilic alcoholate moiety is a synthetic analogue of OH^-. This reagent was prepared by exchange, in a THF solution, between Bu_4NBr and Me_3SiOK (commercially available) followed by filtration to eliminate KBr. The THF solution containing the new reagent was then added to epoxide **2b**. A clean reaction occurred and the trans diol **7** was obtained as the only reaction product. Reasonably, in these reaction conditions, the corresponding *O*-TMS derivative **6**, derived by an 1,2-anti attack of Me_3SiO^-, constitutes the primary reaction product, subsequently hydrolyzed to diol **7**, the reaction product, in the aqueous workup (Scheme 2). In this way, a new procedure for the synthesis of the D-gulal system has been found.[5]

Following the procedure previously utilized for the synthesis of epoxide **2b**, the reaction of diol **7** with

(1) (a) Takhi, M.; Abdel-Rahman, A. A.-H.; Schmidt, R. R. *Synlett* **2001**, 427 and references therein. (b) Linde, R. G., II; Egbertson, M.; Coleman, R. S.; Jones, A. B.; Danishefsky, S. J. *J. Org. Chem*. **1990**, *55*, 2771.

(2) (a) Ferrier, R. J.; Zubkov, O. A. In *Organic Reactions*; Overman, L. E., Eds.; Wiley: New York, 2003; Vol. 62, p 569. (b) Ferrier, R. J. *Top. Curr. Chem*. **2001**, *215*, 153.

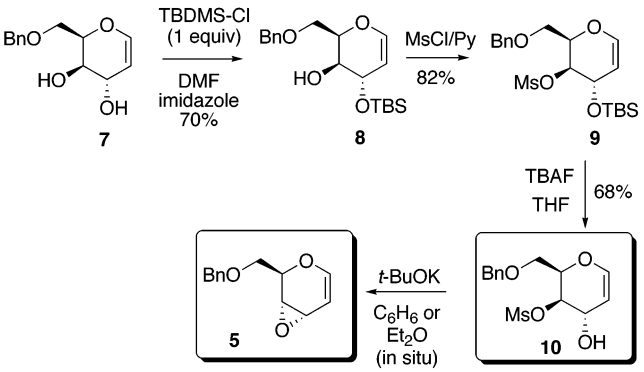
(3) (a) Di Bussolo, V.; Caselli, M.; Pineschi, M.; Crotti, P. *Org. Lett*. **2002**, *4*, 3695. (b) Di Bussolo, V.; Caselli, M.; Pineschi, M.; Crotti, P. *Org. Lett*. **2003**, *5*, 2173 and references therein.

(4) Control experiments carried out on epoxide **2b** with alcohols (MeOH and *i*-PrOH) and diacetone-D-glucose under protocol B showed that the regio- and stereoselective behavior of **2b** is superimposable to that of **2a**.[3a]

(5) For alternative procedures for the construction of the D-gulal system, see: (a) Engstrom, K. M.; Mendoza, M. R.; Navarro-Villalobos, M.; Gin, D. Y. *Angew. Chem., Int. Ed*. **2001**, *40*, 1128. (b) Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J.; Golik, J.; Vyas, D. *J. Org. Chem*. **1990**, *55*, 1979.

10.1021/jo0491152 CCC: $27.50
Published on Web 09/14/2004

SCHEME 3



TBDMS-Cl (1 equiv) afforded the monoprotected derivative **8** in a completely regioselective way. Subsequent mesylation (MsCl/Py) of **8** afforded the *O*-protected mesylate **9**, which was then deprotected by the usual protocol (TBAF/THF) to give the hydroxy mesylate **10**, which constitutes the ultimate precursor of epoxide **5** (Scheme 3). As previously observed in the case of epoxides **2a** and **2b**, epoxide **5** is not sufficiently stable to be isolated, but can be prepared in situ by cyclization of hydroxy mesylate **10** under alkaline conditions (*t*-BuOK) and made to react immediately with a nucleophile.

To enable a direct comparison with the diastereoisomeric epoxide **2b** under the same conditions, the regio- and stereoselectivity of epoxide **5** in opening reactions with nucleophiles was examined in the addition reaction of simple *O*-nucleophiles and *C*-nucleophiles.[3] As for *O*-nucleophiles, MeOH, EtOH, *i*-PrOH, and *t*-BuOH were used following two protocols, A and B, which differ only in the amount of nucleophile (alcohol) present: in protocol A, the alcohol is the solvent of the reaction, and represents a large amount of the nucleophile present, whereas in the alternative procedure (protocol B), the alcohol is added in a very small amount (only 3 equiv) to epoxide **5**, previously formed from **10** in a benzene solution.

Under protocol A, the results obtained indicate that the addition reaction is completely 1,4-regioselective, but with an α/β stereoselectivity depending on the type of alcohol used: with MeOH and EtOH an 81:19 and a 97:3 mixture of the corresponding α- and β-glycosides, **11**α,β and **12**α,β, was obtained, respectively, whereas with *i*-PrOH and *t*-BuOH the corresponding α-glycosides **13**α and **14**α are practically the only reaction products (Table 1, entries 1, 3, 5, and 7).[6,7] In the alternative protocol B, a completely 1,4-regio- and α-stereoselective result is observed with the obtainment of the corresponding α-glycosides **11**−**14**α, as the only addition products, with all the alcohols examined (Table 1, entries 2, 4, 6, and 8).[8,9] The use of 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (diacetone-D-glucose) and 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose, as the glycosyl acceptors, showed that our protocol is also useful for the construction of disaccharides. Following protocol B, after 1 h at room temperature, the corresponding α-linked disaccharides **15**α and **16**α were obtained in a satisfactory yield (Table 1, entries 9 and 10).[11]

As for *C*-nucleophiles, lithium alkyls such as MeLi, BuLi, *s*-BuLi, *t*-BuLi, and PhLi (3 equiv) were added to epoxide **5**, previously prepared in Et_2O from hydroxy mesylate **10** (protocol C). In all cases, a complete 1,4-regioselective and α-stereoselective addition of the alkyl group occurred with the exclusive formation of the corresponding α-*C*-glycosides **17**−**21**α (Table 1, entries 11−15).[6,9]

The complete 1,4-regio- and α-stereoselectivity observed in the reaction of epoxide **5** with alcohols, di-*O*-isopropylidene monosaccharides, and RLi (the glycosyl acceptors) can be rationalized by a possible coordination between the oxirane oxygen and the nucleophile through a hydrogen bond, in the case of alcohols and di-*O*-isopropylidene monosaccharides, and of a coordination through the metal, in the case of RLi, as shown in structures **22** and **23** in Scheme 4. In this way, the nucleophile can be effectively transported onto the α-face of the vinyl oxirane system and appropriately disposed for a α-direct attack on the C(1) carbon to give the corresponding α-glycoside, as experimentally observed. A similar hydrogen bond or coordination with the nucleophile necessarily developed on the β-face was considered to be responsible for the complete 1,4-regio- and β-stereoselectivity observed with epoxides **2a** and **2b** under the same conditions.[3]

The comparison of the results obtained with α epoxide **5** and with previously studied β epoxides **2a** and **2b**[3,4] in their reactions with alcohols, di-*O*-isopropylidene-α-D-monosaccharides, and lithium alkyls indicates that, in these glycal-derived vinyl oxirane systems, the configuration α or β of the oxirane ring and the related coordination or chelation effects could be responsible for the complete α- or β-stereoselectivity respectively observed in the completely regioselective conjugate addition of *O*- and *C*-nucleophiles.[13] In this way, α- (from **5**) and β-*O*- and *C*-glycosides (from **2a**,**b**) can be stereospecifically obtained by a simple and efficient protocol that does not need a catalyst, but only smoothly basic conditions

(6) Under protocols A and C, the reaction crude products are particularly simple and clean, showing the exclusive presence of the corresponding 1,4-addition product(s).

(7) In the case of the reaction of epoxide **5** with *i*-PrOH under protocol A, a signal at δ 5.19 in the ^{1}H NMR spectrum of the crude reaction mixture, reasonably due to the isomeric β-anomer **13**β (0.6%), could be detected.

(8) Under protocol B, the reaction crude products obtained with all alcohols showed the presence, beside the corresponding α-glycosides (80−90%), of some amount (20−10%) of other products which, although not identified, turned out not to be the corresponding β-1,4- or anti 1,2-adducts (^{1}H NMR).

(9) The α-configuration of glycosides **11**−**21**α was established (i) by appropriate NOE experiments, where possible (**14**α and **20**α), (ii) by the presence of chemical shift values for C(5) lower than 75 ppm in the ^{13}C NMR spectra of *C*-glycosides **17**−**21**α, as a diagnostic tool for a 1,5-trans relationship between substituents at C(1) and C(5) (α anomer) in these 2-unsaturated *C*-glycopyranosyl compounds,[10] and (iii) by comparison of the chemical shift of the anomeric proton in both α- (**11**−**13**α and **15**−**16**α) and β-anomers (**11**−**13**β and **15**−**16**β),[7, 11] which indicate, in accordance with previously reported data,[12] that the value for H-1 in the α-anomer is upfield with respect to the value for the H-1 proton in the corresponding β-anomer.

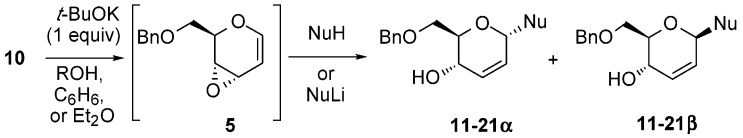
(10) Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013 and pertinent references therein.

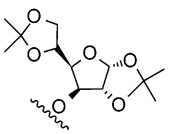
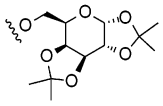
(11) In the case of the reactions of epoxide **5** with diacetone-D-glucose and 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (protocol B) a signal at δ 5.30 and 5.07 in the ^{1}H NMR spectrum of the respective crude reaction mixture, reasonably due to the corresponding isomeric β-anomer **15**β and **16**β (less than 3%), respectively, could be detected.

(12) Achmatowicz, O., Jr.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165.

(13) For a recent catalyzed reagent-controlled *O*-glycosylation, see: Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336.

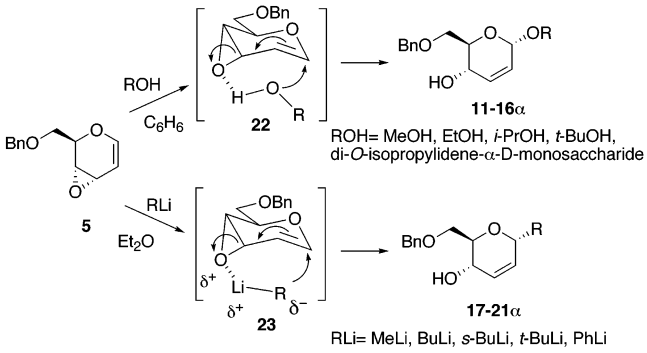
TABLE 1. Glycosylation of Alcohols and Lithium Alkyls by Epoxide 5



entry	glycosyl acceptor (protocol)[a]	reaction time (°C)	***α-1,4-adduct*** (%)	Nu	***β-1,4-adduct*** (%)	Yield (%)
1	MeOH (A)	18h (rt)	**11α** (81)	OMe	**11β** (19)	96[b]
2	MeOH (B)	18h (rt)	**11α** (>99)	OMe	**11β** (<1)	65[c]
3	EtOH (A)	18h (rt)	**12α** (97)	OEt	**12β** (3)	96[b]
4	EtOH (B)	18h (rt)	**12α** (>99)	OEt	**12β** (<1)	55[c]
5	*i*-Pr OH (A)	18h (rt)	**13α** (>99)	*i*-OPr	**13β** (<1)	96[b]
6	*i*-Pr OH (B)	18h (rt)	**13α** (>99)	*i*-OPr	**13β** (<1)	62[c]
7	*t*-Bu OH (A)	18h (rt)	**14α** (>99)	*t*-OBu	**14β** (<1)	89[b]
8	*t*-Bu OH (B)	18h (rt)	**14α** (>99)	*t*-OBu	**14β** (<1)	53[c]
9	1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (B)	1h (rt)	**15α** (>97)		**15β** (<3)	60[c]
10	1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (B)	1h (rt)	**16α** (>97)		**16β** (<3)	58[c]
11	MeLi (C)	0.5 h (0°C-rt)	**17α** (>99)	Me	**17β** (<1)	97[b]
12	BuLi (C)	0.5 h (0°C-rt)	**18α** (>99)	Bu	**18β** (<1)	87[b]
13	*s*-BuLi (C)	0.5 h (0°C-rt)	**19α** (>99)	*s*-Bu	**19β** (<1)	91[b]
14	*t*-BuLi (C)	0.5 h (0°C-rt)	**20α** (>99)	*t*-Bu	**20β** (<1)	97[b]
15	PhLi (C)	0.5 h (0°C-rt)	**21α** (>99)	Ph	**21β** (<1)	91[b]

[a] Protocol A: ROH as the solvent. Protocol B: benzene as the solvent, ROH = 3 equiv; Protocol C: Et_2O as the solvent, RLi = 3 equiv. [b] Crude product. [c] Purified product (flash chromatography or preparative TLC).

SCHEME 4



to generate epoxides **5** and **2a**,**b** from the corresponding hydroxy mesylates **10** and **1a**,**b**, respectively.

Studies are in progress to examine the chemical behavior of the new epoxide **5** also with other nucleophiles, other than alcohols and lithium alkyls, as *N*- and *S*-nucleophiles.

Experimental Section

Reaction of Epoxide 5 with an Alcohol as the Solvent/Nucleophile (Protocol A). General procedure: A solution of hydroxy mesylate **10** (0.042 g, 0.13 mmol) in anhydrous alcohol (2.5 mL) was treated with *t*-BuOK (0.017 g, 0.15 mmol) and the reaction mixture was stirred at room temperature for 18 h. Dilution with Et_2O and evaporation of the washed (saturated aqueous NaCl) solution afforded a crude oily product consisting of a mixture of the corresponding α- and *β*-glycosides **11**α,*β* and **12**α,*β*, in the case of the reaction in MeOH and EtOH, respectively, or containing only the corresponding α-glycoside **13**α and **14**α in the case of the reaction in *i*-PrOH and *t*-BuOH (^{1}H NMR) (Table 1), which was subjected to flash chromatography. Elution with a 6:4 hexane/AcOEt mixture afforded pure α-glycosides **11**−**14**α (only in the case of the reaction in MeOH did the 81:19 mixture of α- and *β*-glycosides **11**α and **11***β* turn out to be not separable under any chromatographic conditions).

Reaction of Epoxide 5 with an Alcohol (3 equiv) in Anhydrous Benzene (Protocol B). General procedure: A solution of hydroxy mesylate **10** (0.042 g, 0.13 mmol) in anhydrous benzene (2.5 mL) was treated with *t*-BuOK (0.017 g, 0.15 mmol) and the reaction mixture was stirred at room temperature for 15 min. Alcohol (3 equiv) was added and the reaction mixture was stirred at room temperature for the time

shown in Table 1. Dilution with Et_2O and evaporation of the washed (saturated aqueous NaCl) solution afforded a crude oily product mostly consisting of the corresponding α-glycoside **11**−**14**α (^{1}H NMR) (Table 1), which was purified by flash chromatography with use of a 6:4 hexane/AcOEt mixture as the eluant.

Reaction of Epoxide 5 with a Di-*O*-isopropylidene-α-D-monosaccharide in Anhydrous Benzene (Protocol B). Typical procedure: A solution of hydroxy mesylate **10** (0.040 g, 0.13 mmol) in anhydrous benzene (2 mL) was treated with *t*-BuOK (0.016 g, 0.14 mmol) and the reaction mixture was stirred 15 min at room temperature. 1,2;5,6-Di-*O*-isopropylidene-α-D-glucofuranose (diacetone D-glucose) (0.102 g, 0.39 mmol) was added and the reaction mixture was stirred 1 h at room temperature. Dilution with CH_2Cl_2 and evaporation of the washed (saturated aqueous NaCl) organic solution afforded a crude reaction product (0.113 g) consisting of a mixture of disaccharide **15**α and unreacted diacetone-D-glucose (^{1}H NMR), which was subjected to preparative TLC (an 8:2 hexane/AcOEt mixture was used as the eluant). Extraction of the most intense band afforded **3-*O*-(6-*O*-benzyl-2,3-dideoxy-α-D-*erithro*-hex-2-enopyranosyl)-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose** (**15**α) (0.037 g, 60% yield): R_f 0.30 (6:4 hexane/AcOEt); FTIR ν 3458, 1454, 1373, 1072, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27−7.39 (m, 5H), 5.95 (d, 1H, J = 10.1 Hz), 5.86 (d, 1H, J = 3.5 Hz), 5.74 (dt, 1H, J = 10.1, 2.3 Hz), 5.20 (br s, 1H, H-1), 4.68 (d, 1H, J = 3.5 Hz), 4.62 (s, 2H), 4.27 (d, 1H, J = 2.6 Hz), 4.12−4.24 (m, 2H), 4.08 (dd, 2H, J = 8.3, 2.8 Hz), 3.97 (dd, 1H, J = 8.3, 5.3 Hz), 3.70−3.90 (m, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 137.8, 133.2, 128.7, 128.1, 127.9, 125.8, 112.1, 109.3, 105.6, 95.8, 84.3, 81.7, 81.5, 74.0, 72.8, 71.1, 70.4, 67.9, 66.0, 27.1, 27.0, 26.4, 25.6. Anal. Calcd for $C_{25}H_{34}O_9$: C, 62.75; H, 7.16. Found: C, 62.59; H, 7.03.

Reaction of Epoxide 5 with RLi (3 equiv) in Anhydrous Et_2O (Protocol C). General procedure: A solution of hydroxy mesylate **10** (0.034 g, 0.11 mmol) in anhydrous Et_2O (2 mL) was treated with *t*-BuOK (0.013 g, 0.12 mmol). After 15 min of stirring at room temperature, the reaction mixture was cooled at 0 °C and treated with a solution of commercially available RLi (0.33 mmol, Table 1) and the resulting reaction mixture was stirred at room temperature for 30 min. Dilution with Et_2O (20 mL) and evaporation of the washed (saturated aqueous NaCl) organic solution afforded a crude product consisting of the corresponding practically pure α-*C*-glycoside **17**−**21**α (^{1}H NMR), which was purified by flash chromatography, using a 7:3 hexane/AcOEt mixture as the eluant.

Acknowledgment. This work was supported by the University of Pisa and MIUR. P.C. gratefully acknowledges Merck Research Laboratories for the generous financial support derived from the 2002 ADP Chemistry Award.

Supporting Information Available: General information and experimental details, as well as spectral and analytical data for all compounds prepared in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0491152