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A Versatile and Stereocontrolled Route to Pyranose and Furanose *C*-Glycosides

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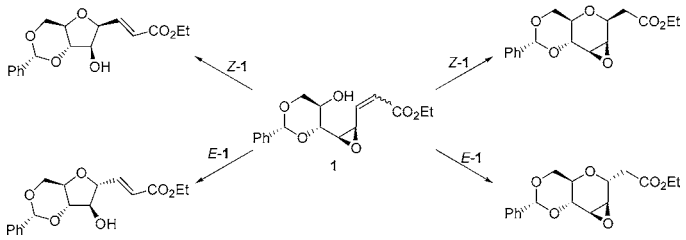
ABSTRACT



The α,*β*-unsaturated-*γ*,*δ*-epoxyester 1 is a novel and versatile precursor to a wide variety of *C*-glycosides. For instance, treatment of *Z*-1 or *E*-1 with palladium(0) affords, stereospecifically, *β*- or α-*C*-furanosides, respectively. In contrast, reaction of *Z*-1 or *E*-1 with base gives, stereoselectively, the *β*- or α-*C*-pyranosides, respectively.

C-Glycosides are important as analogues of naturally occurring heteroatom-linked glycosides as a result of their hydrolytic stability toward enzymes that normally catalyze cleavage of the anomeric bond. Such compounds can therefore act as small-molecule inhibitors of, inter alia, processes that involve cell-surface glycoside cleavage. The design of new *C*-glycosides is therefore driven by the need to probe the mode of action of enzymes that are implicated in disease and to inhibit these enzymes in the form of pharmaceutical drugs. *C*-Glycosides are also found in a number of natural products and, as such, represent attractive synthetic targets.[1] A number of routes to *C*-glycosides have been published,[1−3] but they are usually specific for a single type of product. We have previously described a synthetic route to *C*-glycosides, including *C*-disaccharides, using the Ramberg−Bäcklund reaction as a key step.[3,4] We now wish to report the preparation of building blocks *Z*- and *E*-**1** (Scheme 1), prepared from D-glucose in five steps, which can be utilized in a novel and particularly versatile approach to *C*-glycosides. Depending on the conditions used, *C*-furanosides or *C*-pyranosides can be synthesized in a chemoselective and stereocontrolled manner.

The key precursors for this approach, i.e. α,*β*-unsaturated-*γ*,*δ*-epoxyesters *E*- and *Z*-**1**, appeared to be accessible from D-glucose (Scheme 2). Thus, the known diol **3**[5] was prepared from D-glucose (**2**) in two steps, comprising anomeric allylation followed by 4,6-*O*-benzylidene acetal formation. The epoxide of compound **4** was installed by double deprotonation of the diol, followed by selective tosylation at O-2 and spontaneous displacement of the resulting leaving group.[6,7] Removal of the allyl group with $Pd(PPh_3)_4$, prepared in situ from $Pd(OAc)_2$ and PPh_3, in the presence of both

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(1) (a) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545−8599. (b) Postema, M. H. D. C-*Glycoside Synthesis*; CRC: Boca Raton, FL, 1995. (c) Levy, D. E.; Tang, C. *The Chemistry of* C-*Glycosides*; Pergamon: Oxford, 1995.

(2) For recent reviews of *C*-glycoside synthesis see: (a) Palomo, C.; Oiarbide, M.; Landa, A.; González-Rego, M. C.; García, J. M.; González, A.; Odriozola, J. M.; Martín-Pastor, M.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 8637−8643. (b) Zamojski, A. *Polish J. Chem.* **2002**, *76*, 1053−1084. (c) Vogel, P. *Chimia* **2001**, *55*, 359−365. (d) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077−3092. (e) Toshima, K. *Carbohydr. Res.* **2000**, *327*, 15−26. (f) Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4395−4421. (g) Spencer, R. P.; Schwartz, J. *Tetrahedron* **2000**, *56*, 2103−2112. (h) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913−9959. (i) Kozlowski, J. S.; Marzabadi, C. H.; Rath, N. P.; Spilling, C. D. *Carbohydr. Res.* **1997**, *300*, 301−313.

(3) McAllister, G. D.; Paterson, D. E; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1387−1391 and references therein.

(4) Paterson, D. E.; Griffin, F. K.; Alcaraz, M.-L.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2002**, 1323−1336.

(5) Mehta, S.; Jordan, K. L.; Weimar, T.; Kreis, U. C.; Batchelor, R. J.; Einstein, F. W. B.; Pinto, B. M. *Tetrahedron: Asymmetry* **1994**, *5*, 2367−2396.

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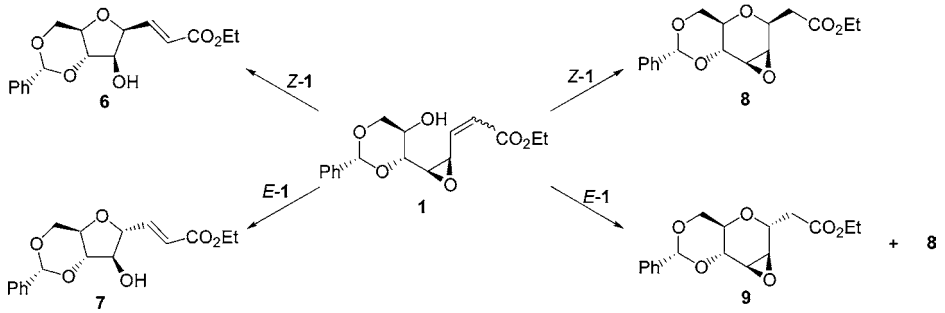
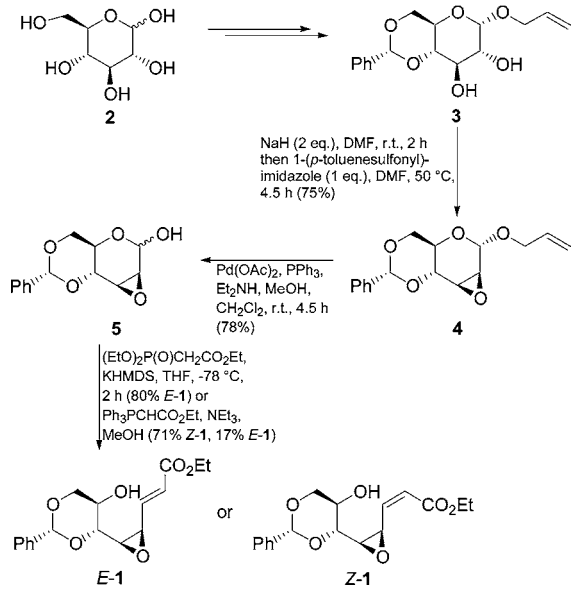
Scheme 1. Cyclization of *Z*-**1** and *E*-**1** to Afford *C*-Furanoside and *C*-Pyranoside Products



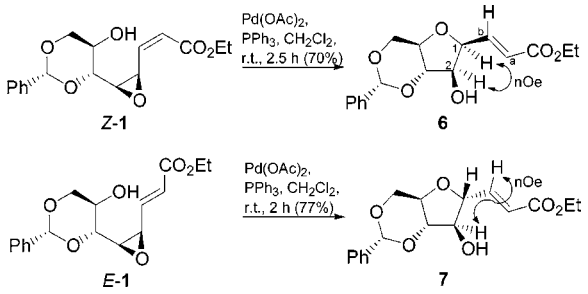
methanol and diethylamine afforded the hemiacetal **5** as a pale yellow solid in 78% yield. This common intermediate could be transformed either exclusively to the *E*-alkene *E*-**1** by Horner−Wadsworth−Emmons (HWE) reaction with triethyl phosphonoacetate and KHMDS or to the *Z*-alkene *Z*-**1** by *Z*-selective stabilized Wittig reaction[8] with (ethoxycarbonylmethylene)triphenylphosphorane in methanol in the presence of triethylamine (*Z*:*E* = 4:1).

Scheme 2. Preparation of Cyclization Precursors *Z*-**1** and *E*-**1**



The allyl epoxide functionality present within *E*- and *Z*-alkenes **1** undergoes reaction with Pd(0) to provide the corresponding palladium π-allyl intermediates, which can be trapped by the internal hydroxyl moiety to form a five-membered ring.[9] Although a 1.5:1 mixture of stereoisomers **6** and **7** (Scheme 3) was obtained upon treatment of

Scheme 3. Stereospecific Synthesis of *C*-Furanosides **6** and **7**



compound *Z*-**1** with a catalytic quantity of $Pd_2(dba)_3$/dppf, the use of $Pd(PPh_3)_4$, prepared in situ from $Pd(OAc)_2/PPh_3$, provided solely the β-*C*-furanoside **6** in 70% yield as the *E*-alkene ($^3J_{a,b}$ 15.7 Hz). The "anomeric" stereochemistry was established by NOE studies, which showed a through-space interaction between H-1 and H-2 (using furanoside numbering scheme).[10] Under identical conditions, the *E*-isomer also reacted stereospecifically to afford the α-*C*-furanoside **7** in 77% yield. The stereochemical assignment was confirmed by an NOE interaction between H-2 and H-b. Related compounds have been prepared before[2i] by a number of groups as precursors to, inter alia, *C*-nucleoside analogues,[11] the antibiotic elfamycins aurodox and efrotomycin,[12] and the antitumor polyether macrolide halichondrin B.[13] The novel

(6) Magnusson, G.; Ahlfors, S.; Dahmén, J.; Jansson, K.; Nilsson, U.; Noori, G.; Stenvall, K.; Tjörnebo, A. *J. Org. Chem.* **1990**, *55*, 3932−3946.

(7) A similar sequence had been used successfully on the corresponding 1-*O*-benzylglucoside, involving reaction at room temperature.[6] These conditions gave the epoxide **4** in only 31% yield (see also Pasetto, P.; Franck, R. W. *J. Org. Chem.* **2003**, *68*, 8042−8060.) By heating the reaction to 50 °C, the yield of **4** was improved to 75%. It is likely that the ring-flip necessary for epoxide formation occurs at ambient temperature for the bulky 1-*O*-benzylglucoside but is sluggish for the 1-*O*-allylglucoside unless heating is applied.

(8) Aldehydes bearing a substituent with a lone pair at the β-position give higher-than-expected amounts of the *Z*-isomer on treatment with stabilized ylids; see: Tronchet, J. M. J.; Gentile, B. *Helv. Chim. Acta* **1979**, *62*, 2091−2098. Fine-tuning of the solvent may then provide good *Z*-selectivity; see: Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265−276. Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109−1111.

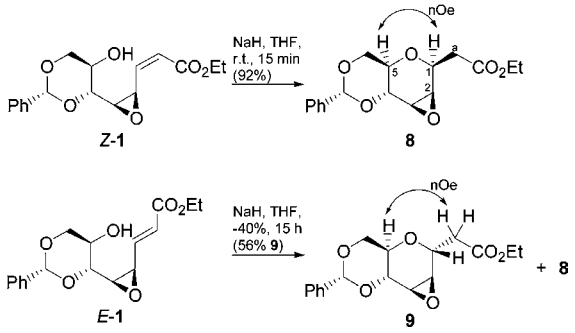
(9) Similar Pd(0)-catalyzed cyclizations have been carried out on simpler substrates: Suzuki, T.; Sato, O.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4747−4750. Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2927−2930. Using Rh(I) catalysis: Ha, J. D.; Shin, E. Y.; Kang, S. K.; Ahn, J. H.; Choi, J.-K. *Tetrahedron Lett.* **2004**, *45*, 4193−4195.

(10) The assignments made here were further confirmed by conversion of compound **6** to the *p*-bromobenzoate derivative, in which all of the NMR signals from the furanoside ring protons were well defined; there were NOE interactions between H-1 and H-2, H-1 and H-4, and H-2 and H-4, thus confirming the β-"anomeric" stereochemistry.

chemistry described in this Letter produces building blocks of this type in a particularly efficient and inexpensive manner. Furthermore, the ability to access, in a fully stereocontrolled manner, either anomer of the *C*-furanoside is noteworthy.[14]

We next investigated Michael-type cyclizations of the alkenes **1**.[15] When compound Z-**1** was treated with NaH, the *β*-*C*-pyranoside **8** (Scheme 4) was obtained in excellent yield.

Scheme 4. Stereoselective Synthesis of *C*-Pyranosides **8** and **9**

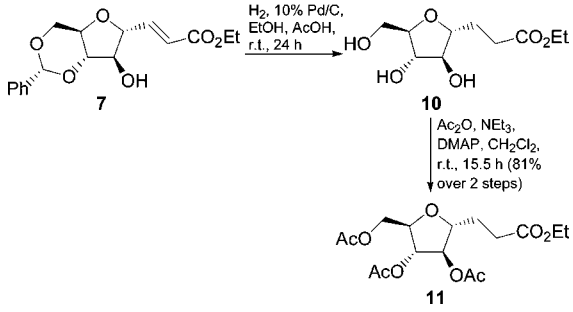


The stereochemistry at C-1 was assigned on the basis of a NOE interaction between H-1 and H-5. At lower temperature (0 °C), alkene *Z*-**1** reacted only extremely slowly with NaH, but the *E*-isomer *E*-**1** underwent conjugate cyclization to afford a 1:1.4 mixture of the novel epoxide-containing α- and *β*-*C*-pyranosides **9** and **8**. Chilling the reaction to −40 °C improved the α-selectivity to 2.5:1. The isomers were partially separable by chromatography, but the α-isomer **9** could be crystallized out of a mixture containing **8** using hot MeOH. An NOE between the exocyclic methylene protons (Ha) and H-5 confirmed the assignment of the product stereochemistry.

The presence of the benzylidene acetal, hydroxyl, alkene, and ester in the *C*-furanosides **6** and **7** should enable further functionalization or differential protection, if required for future applications. Indeed, it was demonstrated that deprotection of **7** could be carried out by hydrogenation in the presence of acetic acid to afford the saturated triol **10** (Scheme 5), which was isolated as the peracetylated derivative **11**.

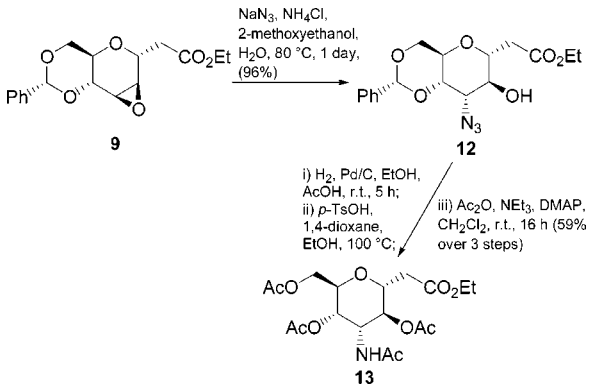
The presence of the epoxide in *C*-pyranoside products **8** and **9** also provides a useful synthetic handle, allowing further

Scheme 5. Deprotection of *C*-Furanoside **7**



functionalization. For instance, epoxide opening of α-isomer **9** with NaN_3 gave the azide **12** (Scheme 6) in excellent yield. Hydrogenolysis of the azide and benzylidene acetal removal followed by global acetylation afforded the novel 3-acetamido-3-deoxy-*C*-glycoside **13**.

Scheme 6. Deprotection of *C*-Pyranoside **9**



As the above results show, the versatility of alkenes of type **1** is particularly noteworthy in terms of the range of products accessible. Thus, α- and *β*-C-furanosides **7** and **6** and *β*-C-pyranoside **8** can be prepared in a stereocontrolled fashion from the *γ*,*δ*-epoxy-α,*β*-unsaturated esters *Z*- and *E*-**1**. The α-C-pyranoside **9** can be isolated by crystallization from a mixture containing the *β*-anomer **8**. Furthermore, the resulting products may be further functionalized at the ring and/or aglycon positions. Alternatively, it is proposed that reaction of hemiacetal **5** with other Wittig or HWE reagents would give a number of other interesting and useful alkenes whose cyclizations could be investigated. We plan to report our results in this area in due course, together with a fuller rationalization for the origin of the observed stereocontrol.

(11) Krishna, P. R.; Reddy, V. V. R.; Sharma, G. V. M. *Synlett* **2003**, 1619−1622. Dondoni, A.; Massi, A.; Minghini, E. *Synlett* **2002**, 89−92. Popsavin, M.; Torovič, L.; Spaić, S.; Stankov, S.; Kapor, A.; Tomić, Z.; Popsavin, V. *Tetrahedron* **2002**, *58*, 569−580. Fleet, G. W. J.; Seymour, L. C. *Tetrahedron Lett.* **1987**, *28*, 3015−3018.

(12) Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691−1694.

(13) Horita, K.; Hachiya, S.; Yamazaki, T.; Naitou, T.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1997**, *45*, 1265−1281.

(14) The α-*C*-furanoside, **7**, is presumably formed by overall retention in the Pd(0)-catalyzed cyclization, as is typical with *E*-allylic substrates. It is likely that the *β*-configuration of **6** is due to a *π*-*σ*-*π* rearrangement of the intermediate palladium complex prior to cyclization, with concomitant *Z*- to *E*-isomerisation. See: Vares, L.; Rein, T. *Org. Lett.* **2000**, *2*, 2611−2614 and references therein.

(15) Similar reactions, albeit without an epoxide group, are known; See ref 1 and Dawe, R. D.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 522−528. Betancort, J. M.; Martín, V. S.; Padrón, J. M.; Palazón, J. M.; Ramírez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570−4583. Martín, V. S.;. Nuñez, M. T.; Ramírez, M. A.; Soler, M. A. *Tetrahedron Lett.* **1990**, *31*, 763−766. Giannis, A.; Sandhoff, K. *Carbohydr. Res.* **1987**, *171*, 201−210.

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Supporting Information Available: Experimental procedures and spectral data for compounds *Z*-**1**, *E*-**1**, and **6**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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