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# Chain Extension of Sugar δ-Lactones with the Enolate of *tert*-Butyl Bromoacetate and Elaboration into Functionalized *C*-Ketosides, *C*-Glycosides, and *C*-Glucosyl Glycines

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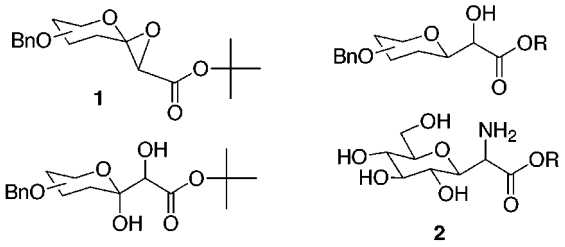
## ABSTRACT




**We describe the synthesis of a series of exocyclic sugar epoxides 1 prepared in a one-step procedure from sugar δ-lactones with the enolate of *tert*-butyl bromoacetate. Ring opening of the sugar oxiranes provides *C*-ketosides while reduction affords functionalized *C*-glycosides bearing an α-hydroxy ester moiety. The α-hydroxy ester can be converted into *C*-glucosyl glycine analogues 2.**

Glycoconjugates which are involved in several biological events such as tumor metastasis, inflammation, and immune response have a significant pharmaceutical potential.[1] Of particular interest are glycoproteins and glycopeptides containing modified glycosylamino acids, thus exhibiting new properties. *C*-Glycosylamino acids promise to be attractive building blocks due to their enhanced stability toward chemical and enzymatic degradation.[2] In a few cases *C*-glycopeptides have also been isolated from natural sources.[3]

We present here a novel method for the chain elongation of a series of aldono-lactones into exocyclic epoxides which can be used as precursors for the synthesis of functionalized *C*-glycosides and *C*-glycosylamino acids.

Our initial interest focused on the synthesis of *C*-glycosylamino acids where the α-*C*-atom of glycine is fused to a glucopyranoside, refered to as *C*-glycosyl glycines. Few reports deal with the synthesis of pyranoside-based *C*-glycosyl glycines.[4] Most of these have significant drawbacks such as low diastereoselectivity[4a−c] (α-carbon), unspecified stereochemistry[4b,c] (α-carbon), and multistep synthesis.[4a,c] Recently, we explored the Claisen condensation of *tert*-butyl acetate enolate with 2,3,4,6-tetra-*O*-benzyl-D-galactono-1,5-lactone and found that 2-deoxyoct-3-ulopyransonates could

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(1) (a) Varki, A. *Glycobiology* **1993**, *3*, 97. (b) Lee, Y. C.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 322.

(2) Marcaurelle, L. A.; Bertozzi, C. R. *Chem. Eur. J.* **1999**, *5*, 1384.

(3) (a) Hofsteenge, J.; Müller, D. R.; Beer, T.; Löffler, A.; Richter, W. J.; Vliegenhart, J. F. G. *Biochemistry* **1994**, *33*, 13524. (b) Beer, T.; Vliegenhart, J. F. G.; Löffler, A.; Hofsteenge, J. *Biochemistry* **1995**, *34*, 11785. (c) Löffler, A.; Doucey, M.-A.; Jansson, A. M.; Müller, D. R.; Beer, T.; Hess, D.; Meldal, M.; Richter, W. J.; Vliegenhart, J. F. G.; Hofsteenge, J. *Biochemistry* **1996**, *35*, 12005. (d) Doucey, M.-A.; Hess, D.; Blommers, M. J. J.; Hofsteenge, J. *Glycobiology* **1999**, *9*, 435.

(4) (a) Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Scherrmann, M.-C.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5484. (b) Simchen, G.; Pürkner, E. *Synthesis* **1990**, 525. (c) Rosenthal. A.; Brink, A. J. *J. Carbohydr. Nucleosides Nucleotides* **1975**, *2*, 343. (d) Colombo, L.; Casiraghi, G.; Pittalis, A. *J. Org. Chem.* **1991**, *56*, 3897.

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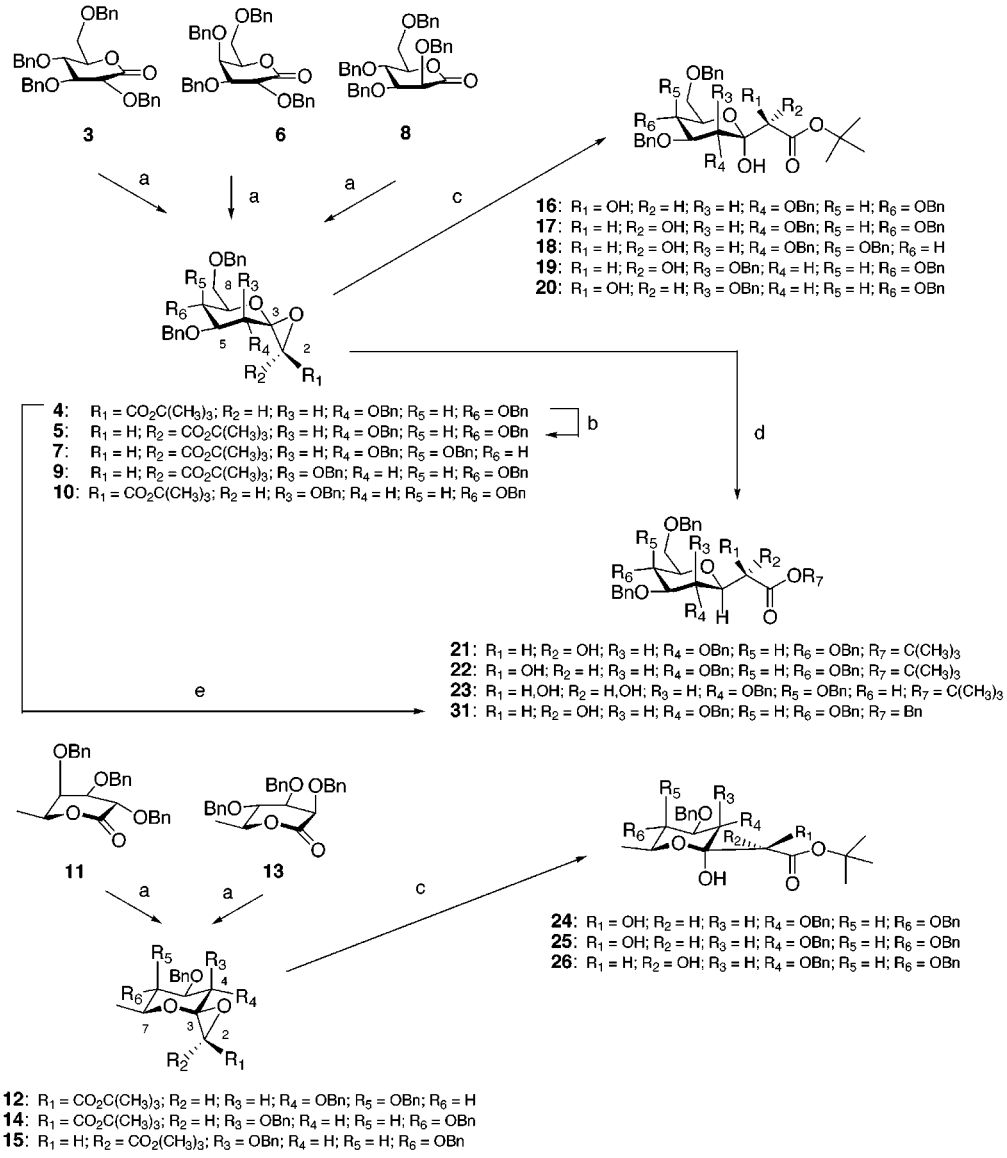
**Scheme 1**[a]




[a] Reagents and conditions: (a) $CHBrCO_2C(CH_3)_3$ (4.1 equiv), $LiN(SiMe_3)_2$ (4.0 equiv), THF, −78 °C; (b) 1. TFA (1 equiv), wet THF; 2. $Tf_2O$, pyridine, 0 °C, 2 h; (c) TFA (catalytic), wet THF, 1 d; (d) $SiEt_3H$ (2 equiv), TMSOTf (catalytic), $CH_2Cl_2$, −78 °C, 12 h; (e) 1. $SiEt_3H$ (3 equiv), TMSOTf (4 equiv), $CH_2Cl_2$, 0 °C; 2. $Cs_2CO_3$, BnBr.

be prepared in high yields.[5] Encouraged by these results, we further investigated the reaction of a variety of α-substituted *tert*-butyl acetate enolates generated under two conditions (Table 1). Surprisingly, we found that the enolate of *tert*-butyl bromoacetate (4 equiv) generated from lithium bis-(trimethylsilyl)amide $[(CH_3)_3Si]_2NLi$ in THF at −78 °C reacted with the lactone **3** to form the exocyclic epoxide **4** in 81% isolated yield. It is noteworthy that the conditions for enolate generation, as well as the nature of the α-substituent, had a strong influence on the outcome of the reaction. For instance, attempts to use LDA as base (condition A) resulted in complete recovery of the starting lactone **3**. In addition, when the enolate of α-chloro *tert*-butyl acetate (condition B) was exposed to the lactone **3**, only starting material (70%) together with a small amount of *C*-ketoside **16** could be isolated after workup (aqueous $NH_4Cl$).

**Table 1.** Claisen Condensation of Sugar Lactone **3** with the Enolate of *tert*-Butyl Bromoacetate To Give Epoxide **4**[a]

| ester | cond. A | cond. B |
|---|---|---|
| $CH_3COOC(CH_3)_3$ | 91% | *c* |
| $CH_2N(Bn)_2COOC(CH_3)_3$ | X[b] | *c* |
| $CH_2ClCOOC(CH_3)_3$ | X[b] | X[d] |
| $CH_2BrCOOC(CH_3)_3$ | X[b] | 81% |

[a] Condition A: ester (4.1 equiv), THF, LDA (4 equiv), −78 °C, **3** (1 equiv), 1 h. Condition B: ester (4.1 equiv), THF, $LiN(SiMe_3)_2$ (4 equiv), −78 °C, **3** (1 equiv), 1 h. [b] Only starting material was recovered. [c] Reaction was not carried out. [d] Starting material (70%) and products (<15%) resulting from hydrolysis of the epoxide were isolated.

(5) Schweizer, F.; Lohse, A.; Otter, A.; Hindsgaul, O. *Synlett* **2001**, 1434.

**Table 2.** Characteristic (Un)Observed NOEs at 600 MHz NMR[i] and Reaction Yields for Compounds **4**, **5**, **7**, **9**, **10**, **12**, **14**, and **15**

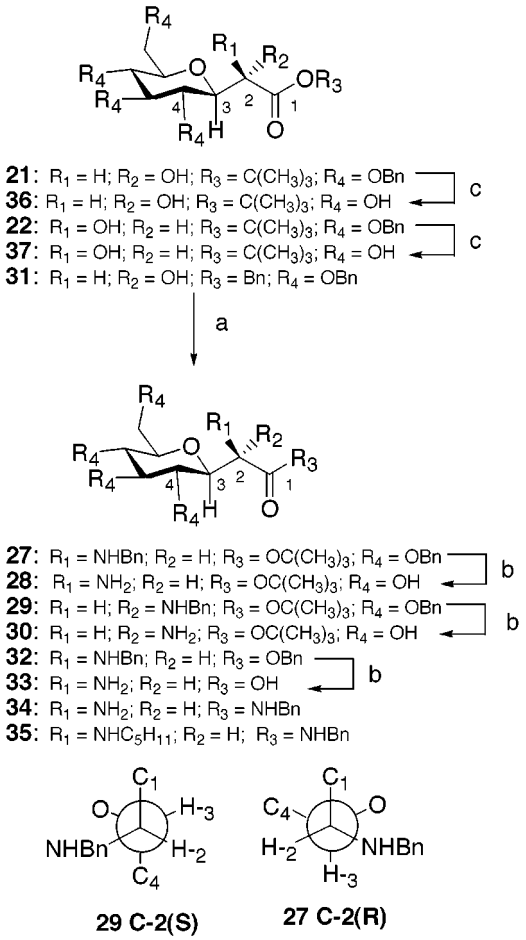
| cmpd | characteristic observed (obs) and unobserved (uobs) NOEs | yield |
|---|---|---|
| **4**[a] | obs: H-2/H-7; H-2/H-5; *tert*-butyl/H-7; *tert*-butyl/H-8a. uobs: H-2/C-4OC$H_2$Ph | 81% |
| **5**[b] | obs: H-2/H-5; *tert*-butyl/H-7; *tert*-butyl/H-8a; H-2/C-4OC$H_2$Ph. uobs: H-2/H-7 | 55%[d] |
| **7**[a] | obs: H-2/H-5; *tert*-butyl/H-7; *tert*-butyl/H-8a; H-2/C-4OC$H_2$Ph | 61%[e] |
| **9**[c] | obs: H-2/H-4; H-2/H-5; *tert*-butyl/H-7; *tert*-butyl/H-8a,b. uobs: H-2/H-7 | 42%[f] |
| **10**[b] | obs: H-2/H-7 (strong); H-2/H-4 (weak); H-2/H-5 (weak) | 10%[f] |
| **12**[c] | obs: H-2/H-5 (strong); H-2/H-7 (weak); *tert*-butyl/H-7; *tert*-butyl/Me | 50%[g] |
| **14**[c] | obs: H-2/H-4 (strong); H-2/H5. uobs: H-2/H-7 | 51%[h] |
| **15**[c] | obs: H-2/H-7 (strong); H-2/H-5 (weak). uobs: H-2/H-4 | 10%[h] |

[i] Solvents: [a]DMSO. [b]$CDCl_3$. [c]$C_6D_6$. [d] For conversion from **4** to **5**. [e] 35% starting material was recovered. [f] Compounds **9** and **10** were obtained as a mixture (ratio **9**:**10** = 4:1) together with 35% recovered starting material. [g] 40% starting material was recovered. [h] Compound **14** and **15** were obtained as a mixture (ratio **14**:**15** = 5:1) together with 30% recovered starting material.

The stereochemistry of compound **4** was deduced from the TROESY spectrum (600 MHz; DMSO, see Table 2). The observed NOEs between H-2 and H-5 and H-7 as well as the *tert*-butyl group and H-7 and one of the C-8 methylene protons are consistent with this structural assignment. By comparison, epimeric epoxide **5** was synthesized by a two-step procedure from epoxide **4** (epoxide opening: TFA (2 equiv) in 4:1 THF/$H_2O$ and activation of the resulting secondary hydroxyl function as the activated trifluoromethanesulfonate ester followed by concomitant intramolecular cyclization with trifluoromethanesulfonic anhydride in pyridine, Scheme 1) showed NOEs from H-2 to H-5 and H-4, respectively, but no NOE to H-7 was observed. In addition, an NOE between H-2 and the benzylic proton attached to the hydroxyl group at C-4 was observed which was absent in epoxide **4** (Table 2).

Encouraged by these results we then subjected the series of lactones **6**, **8**, **11**, and **13** to the enolate of α-bromo *tert*-butyl acetate (4 equiv) generated from lithium bis(trimethylsilyl)amide, $[(CH_3)_3Si]_2NLi$, in THF at −78 °C and isolated the epoxides **7**, **9**, **10**, **12**, **14**, and **15** in modest yields (41−61% for the major isomer after column chromatography, Table 2, and Scheme 1). The stereochemistry was assigned on the basis of observed (or not observed) characteristic NOEs shown in Table 2. In all cases, the epoxides **4**, **5**, **7**, **9**, **10**, **12**, **14**, and **15** could easily be opened by treatment with catalytic amounts of trifluoroacetic acid in wet THF, affording the *C*-ketosides **16**−**20** and **24**−**26** as a single stereoisomer, respectively, in quantitative yields (Scheme 1).[6] Treatment of the epoxides **4**, **5**, and **7** with triethylsilane (2 equiv) under TMSOTf-promoted conditions at −78 °C in $CH_2Cl_2$ afforded the functionalized *C*-glycosides **21**−**23**, respectively, in yields averaging 50% (Scheme 1).[7] Similarly, the α-hydroxybenzyl ester **31** was obtained by treatment with a mixture of TMSOTf and triethylsilane at 0 °C (reduction and ester cleavage) followed by treatment with $Cs_2CO_3$ and BnBr in DMF in 35% isolated yield (Scheme 1). The α-hydroxy esters **21**, **22**, and **31** were further selected for conversion into the *C*-glycosyl glycine esters (Scheme 2). At first, the alcohols **21**, **22**, and **31** were activated as trifluoromethanesulfonate esters using standard conditions ($Tf_2O$, pyridine), followed by subsequent inversion of the ester by primary amines (benzylamine and cyclopentylamine;

**Scheme 2.**[a] Synthesis of *C*-Glucosyl Amino Acids by Displacement of Triflates with Primary Amines. The Newman Projection of the Predominant (>90%) Conformers of **27** and **29** Are Also Shown




[a] Reagents and conditions: (a) 1. $Tf_2O$, pyridine, 0 °C; 2. $RNH_2$, $CH_2Cl_2$, 3 d; (b) $Pd(OH)_2$, $H_2$, HCl, MeOH; (c) $Pd(OH)_2$, $H_2$, MeOH.

(6) The stereochemistry at C-2 of compounds **16**−**20** and **24**−**26** was assigned by assuming that the epoxide opening proceeds via a carboxonium ion intermediate with retention at C-2. The *C*-ketosides **16**−**20** and **24**−**27** exist as a single conformer with an axial hydroxy group at C-3 in $CDCl_3$ on the basis of NOE contacts between H-2 and H-4 and absent NOEs between H-2 and H-5 or H-7.

(7) The starting material and hydrolysis products resulting from ester hydrolysis and epoxide opening were isolated in a total yield of 35%. The stereochemistry at C-2 in **23** has not been determined yet.

5 equiv, rt, $CH_2Cl_2$, 3 d) to afford the amino esters **27**, **29**, and **35** as single stereoisomers respectively in isolated yields averaging 80% without detectable epimerization at C-2 (Scheme 2).[8] In the case of the benzyl ester **31**, the amino ester **32** (52%) and the amide **34** (25%) were isolated as products. Subsequent deblocking of the amino esters **27**, **29**, and **32** was achieved by hydrogenation using Pearlman's catalyst ($Pd(OH)_2$) in acidified (HCl) methanol to afford the *C*-glycosyl glycines **28**, **30**, and **33** in quantitative yield.

The present Claisen condensation of sugar lactones with the enolate of *tert*-butyl bromoacetate generated from lithium bis(trimethylsilyl)amide is an effective route toward exocyclic sugar epoxides. Ring opening of the oxiranes provides entry to novel *C*-ketosides, while reduction affords functionalized *C*-glycosides (α-hydroxy esters) in modest yields. Activation of the α-hydroxy esters as trifluoromethanesulfonate esters and subsequent inversion with primary amines yields *C*-glucosylamino acids without epimerization.

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**Supporting Information Available:** Characteristic spectroscopic and analytical data for compounds **4**, **5**, **7**, **9**, **10**, **12**, **14**, **15**, **27**, and **29** and experimental procedures for the synthesis of oxiranes, *C*-ketosides, and *C*-glycosides. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The absolute stereochemistry at C-2 in compounds **27** and **29** was deduced by MM2 calculations and CD and HMBC measurements. MM2 calculations on compounds **27** and **29** revealed that both compounds exist as single rotamers with antiperiplanar orientation C-1/H-3 (for **27**) and antiperiplanar orientation for C-1/C-4 (for **29**) (see Scheme 2). NMR in conjunction with HMBC measurements (500 MHz, $C_6D_6$) revealed the following homo- and heteronuclear coupling constants. **27**: $^3J_{H-2,H-3} = 1.7$ Hz; $^3J_{C-4,H-2} = 2.0$ Hz, $^3J_{C-1,H-3} = 5.5$ Hz. **29**: $^3J_{H-2,H-3} = 2.2$ Hz; $^3J_{C-4,H-2} = 1.4$ Hz, $^3J_{C-1,H-3} = 2.5$ Hz. In addition, **27** showed a negative Cotton effect, while **29** displayed a positive Cotton effect in MeOH which is consistent with reported values for this class of amino acids (see: Rosenthal, A.; Shudo, K. *J. Org. Chem.* **1972**, *37*, 4391). By comparison, the unprotected α-hydroxy ester **36** showed a positive Cotton effect while ester **37** exhibited a negative Cotton effect in $H_2O$.