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Note

Glycosylation of acid sensitive acceptors. Synthesis of (2,3-epoxy-1-propyl) glycosides

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Abstract—Treatment of *O*-benzylated derivatives of glycosyl *N*-allyl thiocarbamate with racemic or enantiomerically pure glycidol and bromine provides the 1,2-*cis*-glycidyl glycosides. This protocol was mild, highly stereoselective and efficient.

Keywords: Glycidyl glycosides; Glycosides; Glycosylation; *N*-Allyl thiocarbamates

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It is now generally accepted that sugars, being information-rich molecules, are well suited for exploratory syntheses leading to new types of constructs with expected biological activity, including new drugs.[1] While glycosides are plentiful among secondary metabolites and many of them are exploited as medicinal compounds, synthetic drugs having complex glycosidic structure are relatively few.[2–4] This is at least in part due to intrinsic difficulties experienced by researchers seeking control over the anomeric centre chemistry, in terms of synthetic efficiency and desirable stereoselection.[5] Considering various possibilities of chemical glycoconjugation as a way to improve bioavailability and pharmacokinetics of poorly soluble active substances,[6] we have turned our attention to glycidyl (2,3-epoxy-1-propyl) glycosides of the general formula depicted in Figure 1.

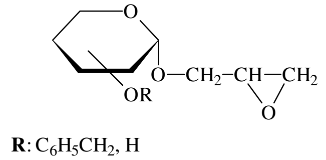

Figure 1.

Glycidyl glycosides combine desirable features of chemical reactivity in their structure. Both the glyceryl and glycosyl moieties of the molecule may act as substrate for selected enzymes, like lipases, glycosylases, kinases, etc., offering various pathways for bioprocessing, including targeting and biodegradation. Despite predicted high reactivity of the glycidyl glycosides, considerable degree of selectivity can be expected in reactions under both chemical and biological conditions. Indeed, it has been recently demonstrated that such compounds, named glycidol-carbohydrate hybrids, are capable of alkylating DNA selectively at the N-7 site of guanine residues.[7]

There are several approaches to the synthesis of (2,3-epoxy-1-propyl) glycosides. Epoxidation of allyl glycosides is efficient and operationally simple, but its diastereoselectivity is somewhat difficult to control.[8] We have observed that the alkylation of 1-OH sugars with glycidol derivatives containing a good leaving group usually leads to anomeric mixtures. Recent synthesis of glycidol-carbohydrate hybrids[7,9] involved glycerol derivative, rather than glycidol glycosylation. The glycosylation of epoxide is not a trivial task. This reaction is usually performed using strong acids (e.g., derivatives of trifluoromethanesulfonic acid, perchloric acid, trifluoroborate–etherate complex).[10] Due to the sensitive nature of oxiranes in acidic media, a complex

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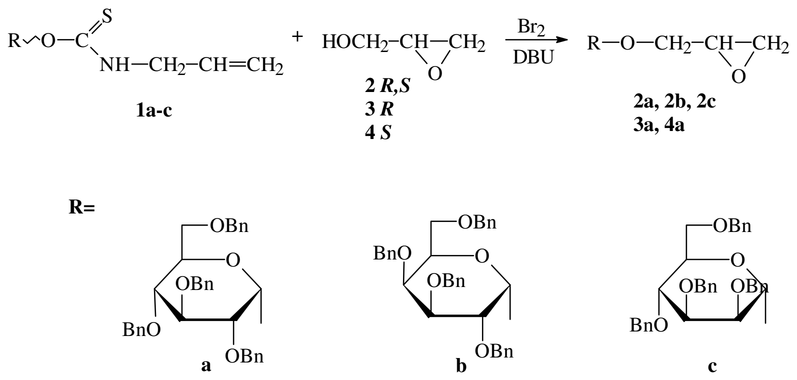

Scheme 1.

products mixture is usually formed. To our knowledge, no general procedure has been reported so far for glycosylation of compounds bearing an epoxide group.

Our experience with anomeric *N*-allyl thiocarbamates, which are storable, easily activated, efficient glycosylating reagents for various unstable substrates, encouraged us to try them as glycosyl donors for glycidols, which are acid and base sensitive acceptors.[11] We have found that glycosyl *N*-allyl thiocarbamates react with glycidol in the presence of non-nucleophilic bases and halogens, pseudohalogens or some thiophilic metal salts as activators, with formation of the expected glycidyl glycosides. The reaction is highly stereoselective and leads practically exclusively to α-glycosides. The stereochemical integrity of chiral glycidols is preserved under the applied conditions, affording pure single diastereoisomers as the reaction products (Scheme 1).

We have observed that introduction of lithium fluoride into the reaction mixtures improved the efficiency of these glycosylations. It seems likely that the fluoride ion, being strong and hard base, forms in the reaction mixture a complex with the hydroxyl group of the acceptor, letting it more nucleophilic[12] and thus facilitating the anomeric exchange.[13] The obtained glycidyl glycopyranosides are compounds designed for chemical conjugation, involving oxirane ring opening, primarily by a nucleophilic group of chosen pharmacophoric substrate, suitable also for parallel synthesis followed by high throughput screening.

The obtained products and their selected physicochemical data are collected in Table 1.

Table 1. Formation of glycidyl glycosides **2a**–**c**, **3a** and **4a**

Entry	Glycosides	Acceptor	$[\alpha]_D^{20}$	Yield (%)
1	**2a**	**2**	4.7 (*c* 0.8, $CHCl_3$)	94
2	**2b**	**2**	4.9 (*c* 0.9, $CHCl_3$)	88
3	**2c**	**2**	4.8 (*c* 0.9, $CHCl_3$)	85
4	**3a**	**3**	−10.0 (*c* 1.0, $CHCl_3$)	93
5	**4a**	**4**	9.8 (*c* 1.0, $CHCl_3$)	91

1. Experimental

1.1. General methods

Optical rotations were measured with a Perkin Elmer 141 polarimeter using a sodium lamp (589 nm) at room temperature. ^1H NMR spectra were recorded with a Varian 300 MHz spectrometer for solutions in $CDCl_3$ (internal TMS). TLC was performed on precoated plates of Silica Gel $60F_{254}$ (E. Merck), using 3:1 hexane–EtOAc or 2:1 toluene–EtOAc and the spots were visualized by spraying with H_2SO_4, followed by heating plates at 150 °C. Chromatographic purification was performed on Silica Gel 60 (E. Merck) 0.063–0.2 mm. All solns were concentrated under diminished pressure at 40 °C. Organic solns were dried over anhyd $MgSO_4$.

1.2. Starting materials

(*R*,*S*) Glycidol 97% (GC), (*R*) glycidol 97% (98% ee/GLC) and (*S*) glycidol 97% (98% ee/GLC) are commercially available (Aldrich). 2,3,4,6-Tetra-*O*-benzyl-1-*O*-[*N*-allylthiocarbamoyl]-β-D-glucopyranose (**1a**), 2,3,4,6-tetra-*O*-benzyl-1-*O*-[*N*-allylthiocarbamoyl]-β-D-galactopyranose (**1b**) and 2,3,4,6-tetra-*O*-benzyl-1-*O*-[*N*-allylthiocarbamoyl]-β-D-mannopyranose (**1c**) were prepared from 2,3,4,6-tetra-*O*-benzylated hexopyranose (0.2 g, 0.77 mmol) according to Ref. 14. Sugar was dissolved in a mixture of toluene/HMPA (3 mL\0.3 mL) containing micronized molecular sieves of 4 Å (0.05 g). Then, K_2CO_3 (0.10 g, 0.77 mmol), DBU (0.008 mL, 0.077 mmol) were added, the reaction mixture was stirred vigorously and *N*-allyl isothiocyanate (0.140 mL, 1.54 mmol) was added. The reaction was completed (TLC) in 4 h. The mixture was filtered, washed with 10% aq NaCl (3 × 5 mL), water (3 × 5 mL), dried (anhyd $MgSO_4$), filtered and concentrated. Column chromatography of the residue (8:1, 5:1, 3:1 hexane–EtOAc) gave the anomeric mixture of thiocarbamate. ^1H NMR in $CDCl_3$ showed a ratio of α:β = 3:1.