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# A Useful Regioselective Approach to Episulfides *via cis*-Oriented Anhydro Triflate Sugars

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**Abstract:** An efficient method for the regioselective synthesis of episulfides, showing remarkable proteinase-inhibiting activity, from *cis*-oriented anhydro triflate sugars is decribed. 

*Keywords: Anhydro sugars, Episulfides, Proteinase inhibitors.*

Considerable interest has been focused on the synthesis of thioanhydro- and sulfur-containing sugar derivatives due to their potent glycosidase inhibitor activity and also their utility as chiral building blocks.[1-8] In the past, we have extensively used triflates of the 2,3-anhydroribopyranosides (**1** and **2**) as starting materials toward the syntheses of either new useful chiral building blocks or biologically active natural products.[9-13] Our strategy banks upon the difference in the reactivity between the *cis*-oriented triflate at C-4 as a powerful leaving group and the epoxide ring. This strategy enabled us to control the regioselective nucleophilic displacement of the triflate group forming *trans*-oriented systems which can be further modified by chemical transformations.

In this communication we describe a simple and efficient route for the syntheses of the episulfides **5** and **6** from the anhydro triflates **1** and **2** (Scheme 1). Reaction of **1** at -15°C with 2 equiv. of potassium thioacetate in DMF yielded within 0.5 h via a highly regioselective nucleophilic displacement of the triflate group at C-4 the 4-S-acetyl-4-thio derivative **3** in quantitative yield. Treatment of **3** with catalytic amounts of sodium methoxide at -20°C, gave within 5 min the corresponding episulfide **5** in 95% yield via deacetylation and intramolecular opening of the trans-oriented epoxide ring by the sulfur anion. The same reaction was carried out with the triflate **2**, producing the episulfide **6** in 90% overall yield. The structures of the episulfides were confirmed unequivocally by means of MS, elemental analyses, $^{1}H$ and $^{13}C$ NMR spectroscopy. For the $^{13}C$ NMR resonances of **5** (400 MHz, $CDCl_3$) the following chemical shifts were determined: $\delta$ = 33.8 (*C*-4), 36.6 (*C*-3), 64.9 (*C*-5), 69.3 (*C*-2), 70.3 (*C*H2Ph), 103.2 (*C*-1), 128.1-137.1 (6Ar-*C*). The optical rotation values for **5** and **6** are +49.9° ($c$ = 0.4, $CHCl_3$) and +130.0° ($c$ = 0.1, $CHCl_3$), respectively.

The episulfides **5** and **6** have remarkable inhibiting activity on a thermostable neutral proteinase, isolated recently by our groups from *Saccharomonospora canescens*.[14,15] The inhibition constant of the corresponding benzyl anhydropyranosides is one order of magnitude less compared to the thio analogues due to the decreased susceptibility to nucleophilic ring opening of the oxirane compared to the thiirane moiety. The epoxy ring of a recently new designed protease inhibitor, 2-benzyl-3,4-epoxybutanoic acid, is suggested to inhibit carboxypeptidase A activity by covalent modification of the enzyme's active site.[16] As demonstrated from our tests on the new neutral proteinase from *Saccharomonospora canescens*, we suggest that thiirane compared to oxirane analogues in general should increase the inhibition activity against proteinases. Further experiments to support this conclusion are under way in our laboratory.

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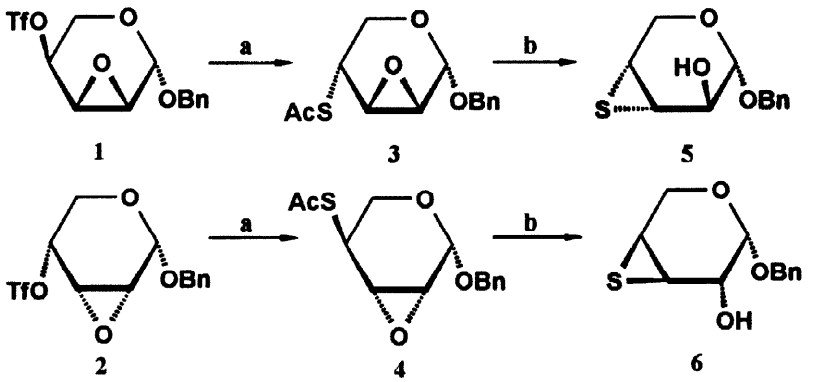
In summary our new templates **5** and **6** would allow further elaboration to other targets through nucleophilic ring opening of the episulfide residue.[10-12]




Scheme 1. a) KSAc/ DMF/ -15°C. b) NaOMe/ MeOH/ -20°C.

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