# Stereoselective Template-directed *C*-Glycosidation. Synthesis of Bicyclic Ketooxetanes *via* Intramolecular Cyclization Reactions of (2-Pyridylthio)glycosidic Silyl Enol Ethers

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Bicyclic ketooxetanes **5a**, **5b** and **8** are formed with excellent stereoselectivity on treatment of (2-pyridylthio)glycosidic silyl enol ethers **1a**, **1b** and **2** with silver(I) trifluoromethanesulfonate.

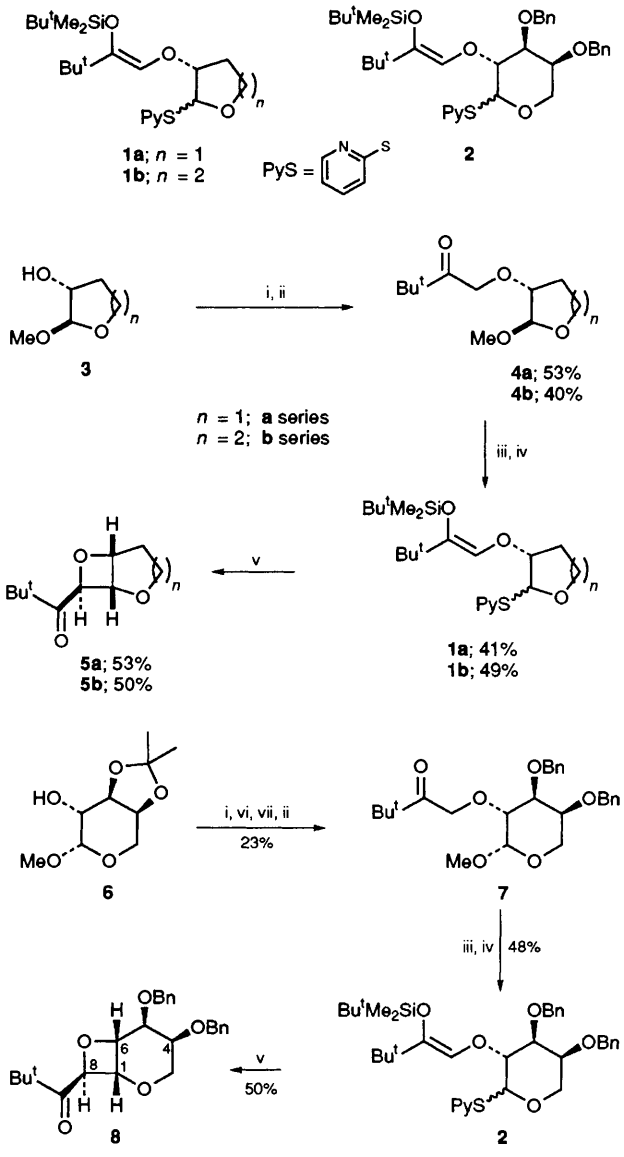
The importance of *C*-glycosides as structural sub-units of biologically active molecules is underlined by the increasingly wide range of methods for their assembly. Synthetic strategies mediated by carbanionic, carbocationic and carbon-centred radical intermediates have successfully been deployed for the formation of C–C bonds at the anomeric position, and such processes are often highly stereoselective.[1] We are seeking to develop a method for *C*-glycosidation in which this stereoselectivity arises from the intramolecular nature of the C–C bond-forming process. Thus, formation of five- and six-membered anomeric cations possessing nucleophilic silyl enol ether groups appended *via* ether linkages to the cyclic 'template' resulted in highly stereoselective intramolecular C–C bond formation between the anomeric position and the nucleophilic side-chain. This resulted in the formation of bicyclo[4.3.0] and -[4.4.0] *C*-glycosides.[2] This communication reports the application of this reaction to the formation of bicyclic ketooxetanes in a highly stereoselective manner by cation-mediated intramolecular *C*-glycosidation.

Compounds **1a**, **1b** and **2** were chosen as cyclization substrates. As with our previous study, it was considered important to demonstrate the non-dependence of cyclization stereochemistry on the configuration of the anomeric position. The *tert*-butyl group was incorporated into the side-chain both to control the regiochemistry of enol ether formation from the parent ketones, and to enhance on account of its steric bulk the prospects of high stereoselectivity during the ring-forming process. Also, substrate **2** would test the compatibility of the methodology with more highly oxygenated sugar-derived precursors.

The synthesis of **1a**, **1b** and **2** followed closely the strategy employed for the preparation of the cyclization substrates for six-membered ring formation (Scheme 1).† Thus, sequential (*tert*-butyl)allylation‡ and ozonolysis of secondary alcohols **3**[4] gave the *tert*-butylketonic lactol ethers **4**. Hydrolysis of **4**

† All yields reported herein are for isolated, pure materials, which had NMR, IR and high-resolution mass spectral characteristics in accord with the proposed structures.

‡ $H_2C{=}C(Bu^t)CH_2OTs$ was prepared in 68% yield by tosylation ($Bu^nLi$, THF, 1,10-phenanthroline indicator, −20 °C followed by TsCl, −20 °C, 30 min, then room temp., 1.5 h) of 2-(1,1-dimethylethyl)prop-2-enol.[3] For a related strategy for attachment of a ketone-containing side-chain involving $Pd^0$-mediated enolate ethallylation followed by ozonolysis, see: E. Piers and J. Renaud, *J. Org. Chem.*, 1993, **58**, 11.




**Scheme 1** *Reagents and conditions*: i, KH (1.1 equiv.), $H_2C{=}C(Bu^t)$-$CH_2OTs$ (1.1 equiv.), $Bu^n_4NI$ (0.05 equiv.), tetrahydrofuran (THF), 20 °C; ii, $O_3$, $CH_2Cl_2$, −78 °C; $Ph_3P$, 20 °C; iii, $H_2SO_4$, 40% aq. MeCN, 35 °C; PySSPy (1.05 equiv.), $Bu^n_3P$ (1 equiv.), $CH_2Cl_2$, 0–20 °C; iv, $Bu^tMe_2SiOSO_2CF_3$ (1.1 equiv.), $Et_3N$ (1.5 equiv.), $Et_2O$, 20 °C; v, $AgOSO_2CF_3$ (1.05 equiv.), 4 Å molecular sieves, $CH_2Cl_2$, 20 °C; vi, trifluoroacetic acid (20 equiv.), 20% aq. THF, 20 °C; vii, KH (3 equiv.), BnBr (2.5 equiv.), $Bu^n_4NI$ (0.05 equiv.), THF, 0–20 °C; Ts = $p$-$MeC_6H_4SO_2$, Bn = benzyl

followed by *S*-glycosidation[5] of the resulting crude lactols, and enol ether formation gave cyclization substrates **1** as single geometric isomers§ in *ca.* 20% overall yield for the five-step sequence from **3**. Enol ether **2** was synthesized from methyl 3,4-isopropylidene-β-L-arabinopyranoside[6] **6** in a similar fashion; after (*tert*-butyl)allylation the acetonide protecting group was exchanged for benzyl ethers[7] prior to the ozonolysis step giving **7**. The ratio of 2,3-*syn* and *anti* anomers in **1a**, **1b** and **2** was typically *ca.* 1 : 1.

§ $^1$H NMR NOE studies of an *S*-glycosidic enol ether related to **1b** (with a thiophenyl instead of a thiopyridyl group at the anomeric position) showed an enhancement of the ex-ketone *tert*-butyl resonance upon irradiation of the olefinic proton, suggesting *Z*-geometry. Preparation of this modified cyclization substrate using potassium hexamethyldisilazide instead of triethylamine as the base led to a more rapid reaction, but gave exclusively the same geometric isomer in similar yield: D. Craig and J. P. Tierney, unpublished results.

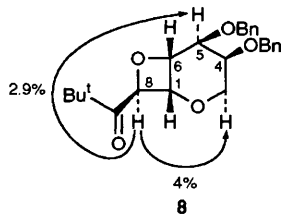
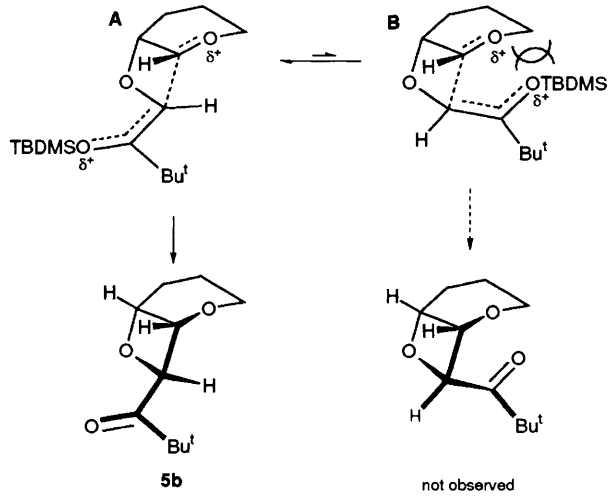



**Fig. 1**




**Scheme 2** TBDMS = *tert*-butyldimethylsilyl

Cyclization reactions were typically carried out at room temperature on dilute (0.03 mol $dm^{-3}$) solutions of enol ether. Addition of a dichloromethane solution of the substrate to a mixture of silver(I) trifluoromethanesulfonate and 4 Å molecular sieves¶ in dichloromethane at room temperature resulted immediately in the formation of a beige precipitate. TLC after *ca.* 1.5 h indicated complete reaction. Products were isolated by filtration through Celite followed by silica gel chromatography. In all three cases, high field (500 MHz) $^1$H NMR analysis of the crude reaction mixtures indicated the formation of a single diastereoisomer of bicyclic ketooxetane.‖ $^1$H NMR NOE experiments** carried out on **8** firmly established the *exo* orientation of the *tert*-butyl ketone side-chain (Fig. 1).

We rationalize the stereoselectivity of this remarkable cyclization reaction in terms of the transition-state conformation depicted in Scheme 2. Thus, following silver-mediated anomeric cation formation,[5] in transition-state conformation **A**, the bulky nucleophilic side-chain is oriented so as to minimize unfavourable steric interactions with the six-membered template. The steric crowding associated with the alternative conformation **B** possessing an *endo*-oriented side-chain has parallels in Claisen rearrangement reactions of cyclic substrates which proceed *via* boat-like rather than chair-like conformations in order to minimize such interactions.[8]

In summary, we have discovered a novel and highly stereoselective reaction for the generation of bicyclic ketooxetanes. This represents to our knowledge the first example of small-ring heterocycle synthesis *via* cation-induced intra-

¶ The use of molecular sieves minimized the formation of hydrolysis products arising from interception of the anomeric cation by adventitious moisture.

‖ All reaction mixtures were analysed by high field (500 MHz) $^1$H NMR prior to chromatographic purification.

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molecular C–C bond formation. Reactions for the direct introduction of the ketonic side-chain, and alternatives to the thiopyridyl–silver(I) trifluoromethanesulfonate combination for the cyclization process are under active investigation.

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