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Stereoselective Template-directed *C*-Glycosidation. Silver(I)-mediated Intramolecular Reactions of (2-Pyridylthio)glycosidic Silyl Enol Ethers

Donald Craig* and V. Ranjit N. Munasinghe

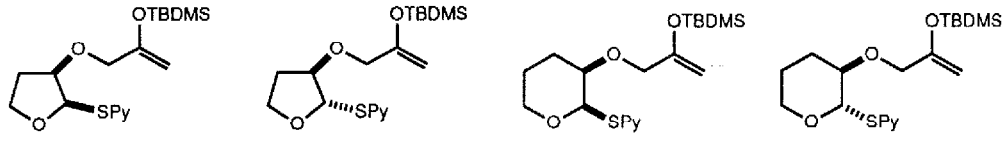
Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY, U.K.

Key Words: stereoselective cyclization; *C*-glycoside; intramolecular; (2-pyridylthio)ether; silyl enol ether

Abstract: *The synthesis and highly stereoselective intramolecular cyclization reactions of a series of (2-pyridylthio)glycosides possessing silyl enol ether-containing appended groups are described. The cyclizations are explained in terms of S_Ni-like reactions proceeding via anomeric cationic species.*

Intramolecular reactions are often attractive components of synthetic strategies because of the enhanced levels of regio- and stereocontrol associated with them. We have started a research programme aimed at the development of a general method for stereocontrolled *C*-glycosidation[1,2] *via* intramolecular cation-mediated cyclization. The strategy relies on the intramolecular delivery of an appended nucleophilic group to an electrophilic glycosidic 'template'.[3] We describe herein the synthesis and highly stereoselective ring-closure reactions of (2-pyridylthio)glycosides possessing silyl enol ether groups attached *via* ether linkages.

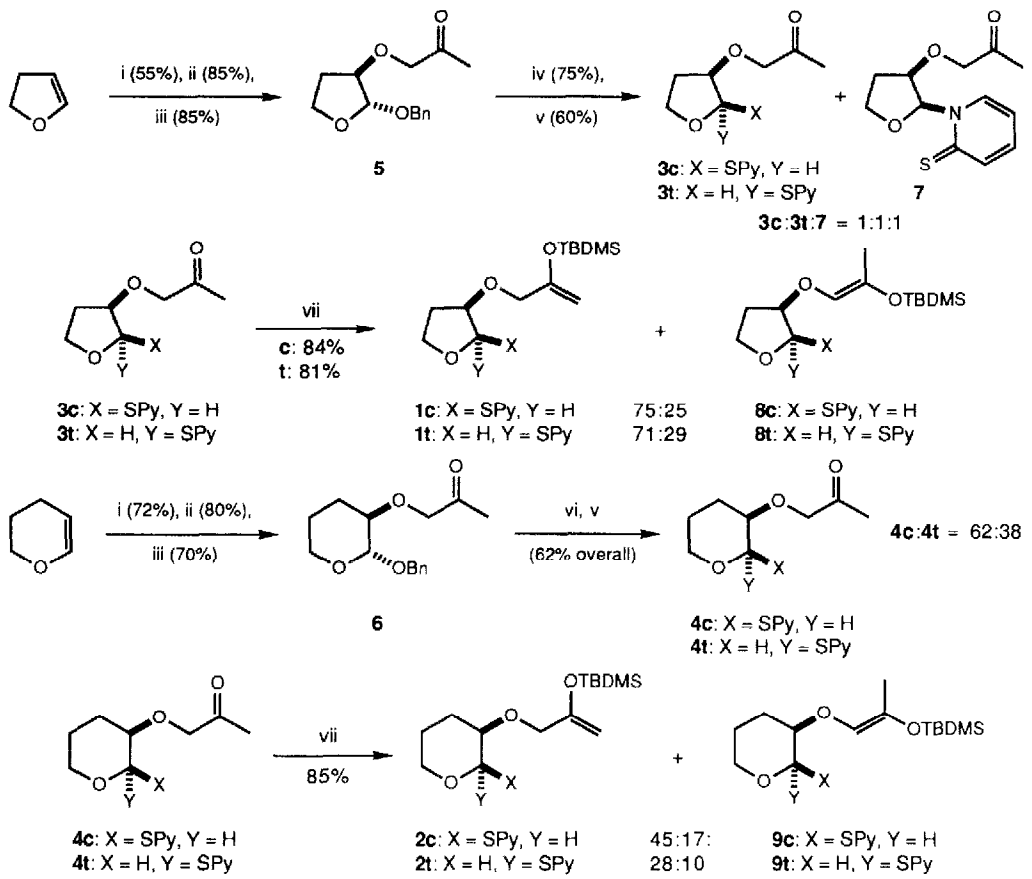
Intramolecular Mukaiyama-type[4] reactions of silyl enol ethers and ketene acetals with *O*-glycosides have been described.[5] In these examples the anomeric cationic intermediates were generated by reaction of the *O*-glycosides with oxaphilic Lewis acids. This approach is less attractive for sugar-derived *O*-glycosidic substrates because of the likelihood of unwanted interactions of the Lewis acid with oxygen substituents other than at the anomeric position. A published[6] solution to this problem lies in the use of *S*-glycosides in conjunction with thiaphilic metal additives. Silver(I)-induced inter*m*olecular reaction of (2-pyridylthio)-glycosides with silyl enol ethers, silyl ketene acetals, and electron-rich aromatics gave diastereomeric mixtures of *C*-glycosides. We sought to assess the viability of the intramolecular variant of this approach for stereocontrolled *C*-glycoside synthesis. Enol ethers **1** and **2** were chosen as cyclization substrates. It was felt that comparison of the cyclization stereochemistry of the *cis* compounds **c** with that of the corresponding *trans* isomers **t** would yield mechanistic information concerning the sequence of events leading to cyclization.



1c **1t** **2c** **2t**

Py = 2-pyridyl

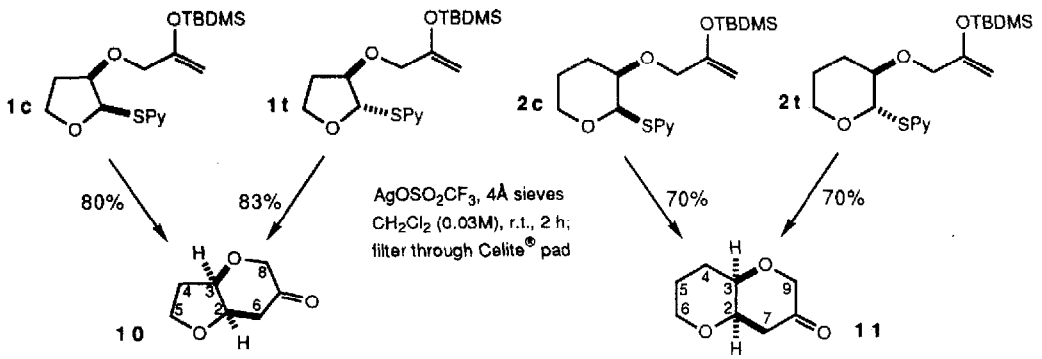
The ketone precursors **3** and **4** of cyclization substrates **1** and **2** were synthesized from 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran, respectively. The synthetic sequences began with oxidative alcoholysis of the cyclic enol ether starting material.[7] Methallylation of the resulting secondary alcohols, followed by ozonolysis gave ketones **5** and **6**. *O*-Glycoside cleavage and (2-pyridylthio)ether formation[6] completed the synthesis of **3** and **4**. Interestingly, ketones **3** were formed together with significant quantities of the *cis* thiopyridone **7**. This competing reaction pathway was not observed in the preparation of the higher homologues **4**. Treatment of ketones **3** and **4** with TBDMSOTf-Et_3N in diethyl ether gave regioisomeric mixtures of silyl enol ethers which were separated by HPLC to give pure samples of **1c**, **1t** and **2c**, **2t**, together with the regioisomers **8** and **9** as diastereomeric mixtures of single geometric isomers. In practice, it was found most convenient to separate **3c** and **3t** prior to enol ether formation. In the higher homologous series, a mixture of **4c** and **4t** was subjected to the silylation conditions, and the resulting mixture of **2** and **9** separated into its four components by HPLC. The syntheses of **1**, **2**, **8** and **9** are summarized in Scheme 1.



(i) *m*-CPBA, BnOH; chromatography (SiO_2); (ii) KH (1.5 eq), THF; $ClCH_2C(CH_3)=CH_2$ (1.3 eq), $^nBu_4NI$ (0.05 eq); (iii) O_3, CH_2Cl_2, -78°C; Ph_3P (1 eq); (iv) H^+, 10% aq. MeCN; (v) $(PyS)_2$ (1.1 eq), $^nBu_3P$ (1.1 eq), CH_2Cl_2 (0.2M), 0°C - r.t., 1.5 h; (vi) H_2 (1 atm), 10% Pd(C) (13 mol%), EtOAc, H^+, r.t., 60 h; (vii) TBDMSOTf (1.2 eq), Et_3N (1.5 eq), Et_2O (0.13M), 0°C - r.t., 2h; HPLC.

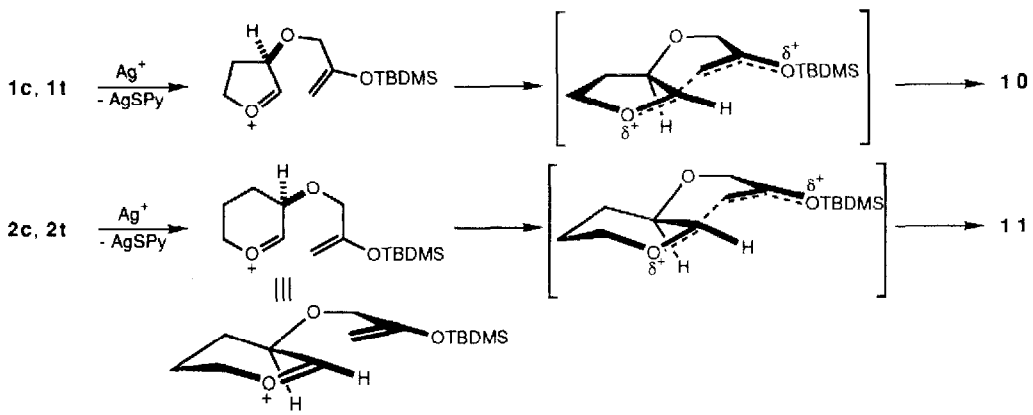
Scheme 1

Initial attempts to effect the crucial ring-closure of **1** and **2** by the action of silver(I) trifluoromethanesulphonate in dichloromethane always gave substantial amounts of the products of hydrolysis of both the enol ether and *S*-glycoside groups. This problem was overcome by the rigorous exclusion of moisture from reaction mixtures. Thus, addition of a dichloromethane solution of **1** or **2** to an anhydrous mixture of silver(I) trifluoromethanesulphonate and activated 4Å molecular sieves in dichloromethane effected smooth cyclization to give **10** and **11**, respectively.[8] In all cases studied, the bicyclic products were obtained as single diastereomers, regardless of the relative stereochemistry of the nucleophilic 'arm' and the 2-pyridylthio anomeric substituent. The cyclization reactions of **1** and **2** are depicted in Scheme 2.



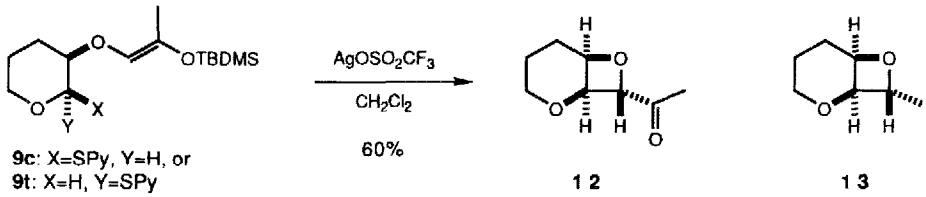
Scheme 2

The non-dependence of the stereochemical course of cyclization on substrate stereochemistry suggests the intermediacy of cyclic oxonium species, which are probably in equilibrium with the corresponding anomeric triflates.[6] For enol ethers **1** having a five-membered template the sense of intramolecular nucleophilic attack may readily be understood in terms of the prohibitive strain energy which would be associated with the unobserved *trans*-fused bicyclo[3.3.0] products. For substrates **2** possessing a six-membered ring one may envisage a degree of pyramidalization[9] of the oxonium intermediates because of the C-3 stereocentre. This distortion of the sp^2-hybridized anomeric carbon atom away from idealized trigonal geometry is such as to favour attack on the face *syn* to the oxygen atom bearing the nucleophilic side-chain, with formation of the new carbon-carbon bond taking place in the direction of pyramidalization (Scheme 3).



Scheme 3

We have found that it is possible also to construct four-membered rings using this intramolecular cyclization reaction. Exposure of either **9c** or **9t** to the cyclization conditions outlined in Scheme 2 gave in *ca.* 60% yield the bicyclic ketooxetane **12** as a single diastereomer (Scheme 4). The structure of **12** followed from high-field ^{1}H and ^{13}C nmr, ir, and high-resolution ms analysis. In addition, **12** showed ^{1}H and ^{13}C nmr characteristics very similar to those of the related bicyclic oxetane **13**.[10,11]



9c: X=SPy, Y=H, or
9t: X=H, Y=SPy

12 **13**

Scheme 4

In summary, we have demonstrated that bicyclic *C*-glycosides may efficiently be constructed in a highly stereoselective fashion *via* silver(I)-induced intramolecular cation-mediated cyclization reactions of *S*-glycosidic silyl enol ethers. We are currently designing modified cyclization substrates more amenable to regiocontrolled introduction of the nucleophilic double bond in the side-chain. We are also actively exploring the generality of the oxetane-forming reaction, and are developing modified routes to the requisite precursors.

Acknowledgements

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References and notes

1. For leading references, see footnote 1 of reference 2.
2. For a recently-published example of the use of radical-mediated reactions as part of a similar strategy to that reported herein, see: Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054.
3. For the use of templates in stereoselective intermolecular reactions, see: (i) Stork, G.; Rychnovsky, S. D.; *J. Am. Chem. Soc.* **1987**, *109*, 1564, 1565; Hanessian, S.; Cooke, N. G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276 (γ-lactones); (ii) Thomas, E. J.; Williams, A. C. *J. Chem. Soc., Chem. Commun.* **1987**, 992 (β-lactams).
4. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.
5. (i) Martin, O. R.; Prahlada Rao, S.; Kurz, K. G.; El-Shenawy, A. A. *J. Am. Chem. Soc.* **1988**, *110*, 8698; Martin, O. R. *Tetrahedron Lett.* **1985**, *26*, 2055; Martin, O. R.; Mahnken, R. E. *J. Chem. Soc., Chem. Commun.* **1986**, 497; Martin, O. R. *Carbohydr. Res.* **1987**, *171*, 211; (ii) Stork, G.; Krafft, M. E.; Biller, S. A. *Tetrahedron Lett.* **1987**, *28*, 1035.
6. Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289.
7. Cox, P.; Lister, S.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3151.
8. Nmr data ($CDCl_3$): **10**; δ_H (500 MHz) 4.35 (1H, ddd, J 7.5, 5.5, 2.5 Hz, H-3), 4.18 (1H, q, J 5.5 Hz, H-2), 4.08 (1H, d, J 17.5 Hz, H-8), 4.08-4.03 (1H, m, H-5), 3.82 (1H, d, J 17.5 Hz, H-8), 3.73-3.68 (1H, m, H-5), 2.84 (1H, dd, J 15.5, 5.5 Hz, H-6), 2.78 (1H, dd, J 15.5, 5.5 Hz, H-6), 2.32-2.25 (1H, m, H-4), 2.13-2.07 (1H, m, H-4); δ_C (125.8 MHz) 209.2, 77.7, 76.3, 71.2, 66.5, 40.9, 32.8. **11**; δ_H (500 MHz) 4.20 (1H, d, J 16 Hz, H-9), 4.05 (1H, d, J 16 Hz, H-9), 4.03-3.99 (1H, m, H-6_{eq}), 3.88 (1H, td, J 3.5, 0.5 Hz, H-3), 3.75 (1H, t, J 3 Hz, H-2), 3.48 (1H, ddd, J 12.5, 11.5, 2.5 Hz, H-6_{ax}), 2.63 (2H, m, H-7), 2.11-2.06 (1H, m, H-4_{eq}), 2.05-1.94 (1H, m, H-5_{ax}), 1.80-1.72 (1H, m, H-4_{ax}), 1.38-1.33 (1H, m, H-5_{eq}); δ_C (125.8 MHz) 205.2, 74.3, 73.9, 70.8, 68.3, 44.2, 28.2, 20.0.
9. Seebach, D.; Zimmerman, J.; Gysel, U.; Ziegler, R.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 4763.
10. We thank Dr H. A. J. Carless (Birkbeck College) for providing nmr spectra of **13**.
11. All new compounds reported herein had nmr, ir and high-resolution ms characteristics in accord with the proposed structures.

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