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Stereoselective Template-directed *C*-Glycosidation. Synthesis of 5-Membered Oxygen Heterocycles via Cation-mediated Intramolecular Cyclization Reactions

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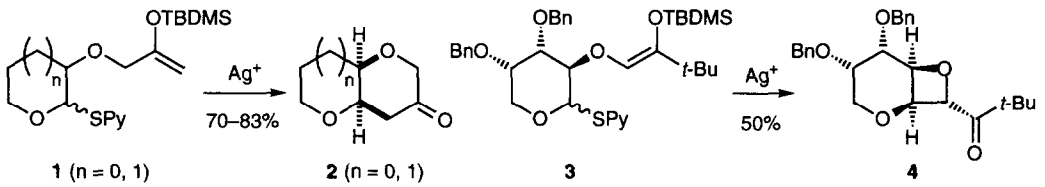
Abstract: Construction of 5-membered oxygen heterocycles by intramolecular template-directed *C*-glycosidation is described. Alkylation of thioglycoside **5** with enone **6** followed by enol etherification gave cyclization substrates **8**. Compound **8a** underwent silver(I) trifluoromethanesulfonate-mediated ring-closure to give a 1.7:1 mixture of **9**α and **9**β; isomer **8s** gave an 8.5:1 ratio. Some derivatization reactions of the bicyclic products are described.

We have been developing cation-mediated *C*-glycosidation[1] reactions in which the stereochemistry of formation of the new C–C bond is controlled by the intramolecular delivery of an appended nucleophilic group to an anomeric cationic centre.[2,3] Whilst the products of these transformations are bicyclic *C*-glycosides, cleavage post-cyclization of the tether which linked the nucleophilic and electrophilic groups would deliver the monocyclic products of overall formal in*ter*molecular *C*-glycosidation, with the stereochemical and reactivity advantages inherent in the in*tra*molecular processes.[4] Our studies to date have been concerned with assessing the viability of intramolecular cyclization of (2-pyridylthio)glycosidic[5] silyl enol ethers. Treatment of substrates **1** with silver(I) trifluoromethanesulfonate in dichloromethane gave bicyclic ketones **2** exclusively as the *cis*-fused diastereomers.[2] Exposure of L-arabinose-derived thioglycoside **3** to the same conditions resulted in formation of bicyclic ketooxetane **4**,[3] in which the configuration of the two new asymmetric centres is determined by that of the template atom to which the nucleophilic side-chain is attached, but is independent of the stereochemical relationship of the anomeric substituent and the side-chain (Scheme 1).

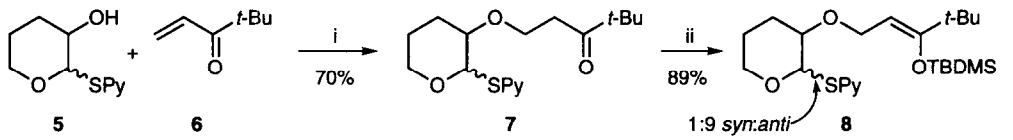


Scheme 1

Substrates **1** and **3** were prepared via reaction sequences in which the ultimately nucleophilic side-chains were incorporated into *O*-glycosidic templates as alkene groups. Ozonolytic cleavage to the corresponding ketones, conversion of the *O*-glycosides to the thioglycosides, and installation of the enol ether groups completed the synthesis. We are keen to develop alternative strategies for the assembly of thioglycosidic enol ethers in which the side-chain is introduced directly into the thioglycoside. This necessitates alkylation with a ketone-containing fragment, since the thioglycoside would not tolerate the oxidative conditions employed for the conversion of an alkene to a ketone. In light of the successful cyclization reactions of **1** and **3** giving respectively 6- and 4-membered rings we became interested in designing related materials which would undergo

cation-mediated C–C bond formation to give other ring sizes. We report herein the assembly of a new type of substrate which provides 5-membered oxygen heterocycles upon intramolecular *C*-glycosidation. We describe also some synthetically useful reactions of the bicyclic products.

Our studies began with the hydroxylated thioglycoside **5**. This was prepared as a *ca.* 1:9 mixture of *syn*- and *anti*-diastereomers in 61% overall yield by oxidative hydration[6] of 3,4-dihydro-2*H*-pyran followed by treatment of the resulting hydroxylactol with 2,2'-dipyridyl disulfide–tributylphosphine.[5] As with the oxetane precursors,[3] it was important that the ketonic side-chain was substituted in such a way that enol ether formation would give rise to a single regioisomer. Attempted alkylation of the sodium salt of **5** with 2,2-dimethylpent-4-en-3-one **6**[7] gave very poor yields of the 1,4-adduct, and resulted in extensive decomposition of both starting materials. However, treatment of excess **5** with **6** under phase-transfer conditions rapidly gave the desired thioglycosidic ketones **7** in good yield. Unreacted **5** could efficiently be recovered and recycled.[8] Treatment of **7** with *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of excess potassium hexamethyldisilazide gave the cyclization precursors **8** in excellent yield exclusively as the *Z*-isomers (Scheme 2).[9]

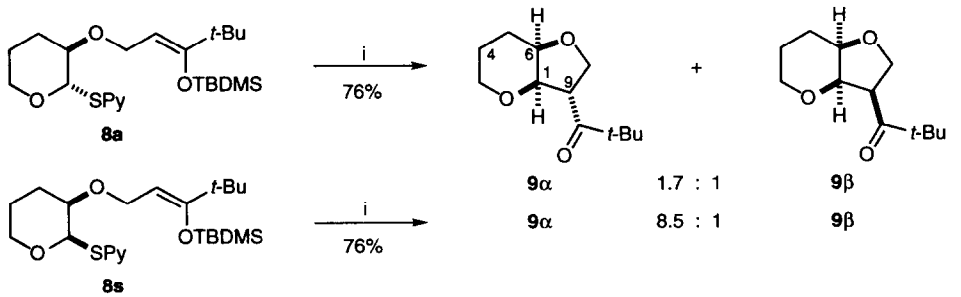


Reagents and conditions: (i) 1:1 50% aq NaOH–CH_2Cl_2 (0.25M in **5** (1.5 eq)), Aliquat® 336 (0.05 eq); add **6**, 20°C, 2 min; (ii) $TBDMSOSO_2CF_3$ (1.5 eq), THF (0.03M), -78°C, then add $KN(SiMe_3)_2$ (2.5 eq), PhMe, -78°C, 10 min.

Scheme 2

As with the previous work, the cyclization reactions of **8** were effected by treatment of dichloromethane solutions at ambient temperature with silver(I) trifluoromethanesulfonate in the presence of molecular sieves. Optimum yields were obtained when two equivalents of the thiaphilic reagent were used.[11] Two separable, diastereomeric bicyclic products were formed in a reproducible *ca.* 2:1 ratio. ^{1}H Nmr n.O.e. experiments[10,12] established that the major product **9α** had the *exo*-, or α-configured ketone side-chain. The modest selectivity observed for cyclization of the mixture of **8** prompted us to examine the cyclization selectivities of the individual diastereomers. Chromatographic separation of the mixture of **8** gave pure samples of **8s** and **8a** which were subjected to the standard cyclization conditions. Whilst the major, *anti*-component **8a** gave predominantly **9α** in a poorly selective reaction, cyclization of **8s** was highly selective for **9α** (Scheme 3).

The observed dependence of cyclization stereochemistry on the configuration of the anomeric substituent relative to the nucleophilic appendage was unexpected,[2,3] and might suggest that **8a** and **8s** undergo ring-closure via different mechanisms. Substrate **8a** may cyclize via an anomeric cation in an S_N1-like process, or by

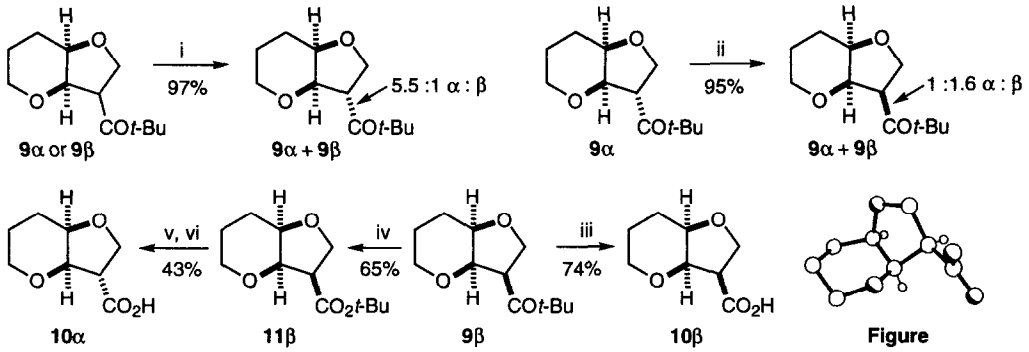


Reagents and conditions: (i) $AgOSO_2CF_3$ (2 eq), 4Å molecular sieves, CH_2Cl_2 (0.03M), 20°C, 20 min.

Scheme 3

an S_N2-like pathway in which formation of the anomeric C–C bond is initiated simultaneously with carbon–sulfur bond cleavage. Only the first of these two routes is available to **8s** because of the *syn*-disposition of the thiopyridyl and side-chain groups. The differing selectivities under identical reaction conditions provide strong evidence that the reactions are irreversible, kinetically-controlled processes. The markedly higher selectivity observed in the reaction of **8s** would indicate that steric effects are more pronounced in the transition-state for the reaction of the enol ether with an anomeric cationic centre than for concerted S_N2-type displacement of the thiopyridyl group.

We have investigated several derivatization reactions of the bicyclic *C*-glycosides **9** with a view to extending the utility of this strategy (Scheme 4). The thermodynamic favourability of **9α** was demonstrated by the formation of the same *ca.* 5.5:1 mixture of **9α** and **9β** on exposure of either single isomer to catalytic potassium *tert*-butoxide. Treatment of **9α** with potassium hexamethyldisilazide followed by kinetic proton quench gave in 95% yield a *ca.* 1.6:1 mixture of **9β** and **9α**. In order to render the ketone function more amenable to side-chain elaboration, we sought to convert it into a carboxyl group. Treatment of **9β** with trifluoroperacetic acid[13] gave directly the crystalline acid **10β** in good yield.[14] The X-ray crystal structure of **10β** confirmed the assignment of **9α** and **9β** (Figure).[15] Interestingly, **9α** was completely inert to these oxidation conditions. Acid **10α** was accessed via sequential Baeyer-Villiger reaction of **9β** under buffered conditions[13] to give the ester **11β**, followed by base-mediated epimerization as before and deprotection of the *tert*-butyl ester.[16]

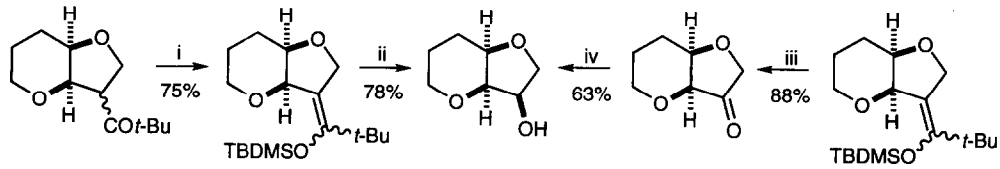


Reagents and conditions: (i) *t*-BuOK (0.3 eq), *t*-BuOH (3 eq), THF (0.1M), 20°C, 30 min; (ii) $KN(SiMe_3)_2$ (1.2 eq), THF (0.1M), -78°C, 5 min; 10%v/v AcOH–THF (1.4 eq); (iii) CF_3CO_3H (2.75 eq), CH_2Cl_2 (0.35M), 20°C, 12 h; (iv) CF_3CO_3H (1.8 eq), Na_2HPO_4 (12 eq), CH_2Cl_2 (0.3M), 20°C, 18 h (23% recovered **9β**); (v) *t*-BuOK (0.3 eq), *t*-BuOH (3 eq), THF (0.1M), 20°C, 4 h (53% **11α** + 26% recovered **11β**); (vi) CF_3CO_2H (excess), CH_2Cl_2 (0.5M), 20°C, 12 h (82% for step (vi)).

Scheme 4

We have pursued also a derivatization sequence which gives a hydroxylic product corresponding to formal delivery of an alcohol α-anion to the cationic anomeric centre. Treatment of a toluene solution of the 2:1 mixture of **9α** and **9β** obtained in the initial cyclization studies with *tert*-butyldimethylsilyl trifluoromethanesulfonate followed by potassium hexamethyldisilazide gave a mixture of enol ethers **12**. Low-temperature ozonolysis of **12** and direct reductive work-up gave a single isomeric alcohol **13** in 59% yield from **9**. Alcohol **13** could be prepared in similar overall yield by DIBAL-H reduction of ketone **14** obtained after neutral work-up of the ozonolysis reaction (Scheme 5). The highly stereoselective formation of **13** may be rationalized in terms of delivery of the reducing agent to the less hindered α-, convex face of the *cis*-fused bicycle.

In summary, the present work demonstrates that five-membered oxygen heterocycles may efficiently be constructed via intramolecular template-directed *C*-glycosidation. We are currently investigating strategies for the cleavage of the newly-formed ring in order to generate monocyclic materials, including higher-order sugars. The results of these studies will be reported in due course.



Reagents and conditions: (i) $TBDMSOSO_2CF_3$ (1.5 eq), PhMe (0.2M), -78°C, $KN(SiMe_3)_2$ (2.5 eq), -78°C, 10 min; (ii) O_3, CH_2Cl_2 (0.01M), -78°C, 10 min; $BH_3{\cdot}SMe_2$ (4 eq), -78°C → 20°C, 12 h; (iii) O_3, CH_2Cl_2 (0.04M), -78°C, 10 min; Ph_3P (1 eq), -78°C → 20°C, 12 h; (iv) DIBAL-H (1.5 eq), PhMe (0.15M), -78°C, 5 min; H_2O.

Scheme 5

Acknowledgements

We thank SERC and ZENECA Pharmaceuticals[17] (CASE studentship to M. W. P.) for financial support.

References and notes

1. For a recent review of *C*-glycoside chemistry, see: Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545.
2. Craig, D.; Munasinghe, V. R. N. *Tetrahedron Lett.* **1992**, *33*, 663.
3. Craig, D.; Munasinghe, V. R. N. *J. Chem. Soc., Chem. Commun.* **1993**, 901.
4. For related strategies, see footnotes 2 and 5 of reference 2.
5. For intermolecular *C*-glycosidation reactions of (2-pyridylthio)glycosides, see: Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289.
6. Adapted from the method of Gallagher *et al.*, replacing methanol with water-saturated diethyl ether. See: Cox, P.; Lister, S.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3151. All yields cited herein are for isolated, pure materials, characterized by ^1H nmr, ir, ms and elemental combustion analysis or high-resolution ms.
7. 2,2-Dimethylpent-4-en-3-one was prepared via reaction of vinylmagnesium bromide with pivalaldehyde (THF, 0°C; 85%), followed by Swern oxidation of the product alcohol (50%).
8. The use of excess **6** in these reactions was precluded by difficulties encountered in recovering unreacted material. Formation of **7** apparently is an equilibrium process, and optimum conditions involved addition of **6** to 1.5 equivalents of **5** under phase-transfer conditions. The yield of 70% cited is based on **6**; 90% of unreacted **5** could be recovered by silica gel chromatography.
9. The use of triethylamine as base for this transformation (1M in diethyl ether, 20°C, 18 h) typically gave *ca.* 10:7 mixtures of *E*- and *Z*-geometric isomers. The *Z*- double bond geometry of **8** was established by the observation of 23% and 24% n.O.e.s between the *tert*-butyl and alkene hydrogen atoms in respectively the 2,3-*anti* and 2,3-*syn* diastereomers of **8**.[10]
10. We thank Mr R. N. Sheppard of this department for these experiments.
11. The yield of **9** was observed to vary markedly according to the quality of the silver(I) trifluoromethanesulfonate; with freshly-opened bottles of the reagent smaller quantities could be used. The use of two equivalents always ensured complete consumption of starting material.
12. For example, no n.O.e. was observed between H-6 and H-9 in compound **9**α; in **9**β a 2.3% effect was observed. A 1.8% n.O.e. was observed between H-1 and H-9 in **9**α; the corresponding value for **9**β was 4.5%.
13. Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.
14. For a recent review of the Baeyer-Villiger reaction, see: Krow, G. R. in *Comprehensive Organic Synthesis*, Trost, B. M., ed.; Pergamon: Oxford, 1991; Vol. 7, pp 671–688.
15. We thank Dr D. J. Williams and Ms A. M. Z. Slawin of this department for this determination.
16. Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 2353.
17. ZENECA Pharmaceuticals in the UK is part of ZENECA Limited.

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