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Template-directed Intramolecular *C*-Glycosidation. Stereoselective Synthesis of Bicyclic Ketooxetanes From Anomeric Sulfones

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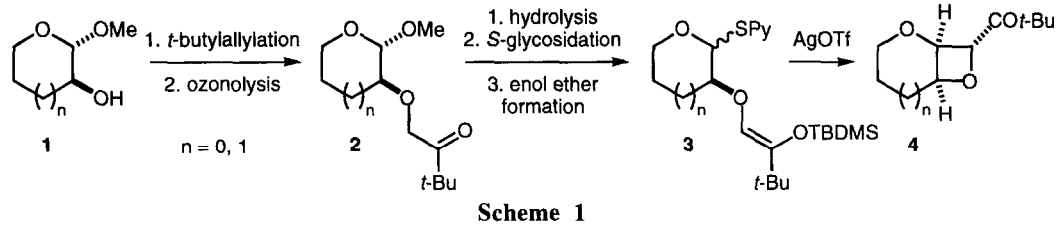
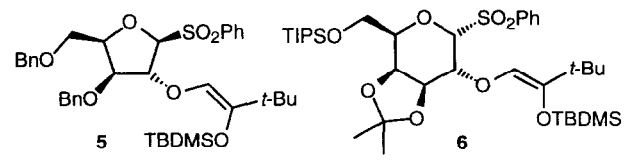
Abstract: The Lewis acid-mediated cyclisations of sugar-derived anomeric sulfone–enol ethers **5** and **6** to give respectively the bicyclic ketooxetanes **11/12** and **16/17** are reported. © 1997 Elsevier Science Ltd.

Over the past several years we have been seeking to develop a general strategy for stereoselective *C*-glycosidation. Underpinning our approach is the idea that stereoselectivity in the crucial anomeric C–C bond-forming step may be achieved by tethering a functional group which possesses a carbon nucleophile to a template containing the electrophilic anomeric cation. We have shown that by using ether linkages as the tethers, four-,[1] five-[2] and six-membered[3] rings may be made, often with high stereoselectivities.[4] For the synthesis of simple, model bicyclic ketooxetanes using this approach,[1] it was necessary to start from protected 'sugars' **1**, and to incorporate the requisite ketonic side-chain using an allylation–ozonolysis sequence, which gave **2**. Hydrolysis of the glycosidic linkage, activation of the anomeric centres by *S*-glycosidation, and silyl enol etherification completed the synthesis of the substrates **3**, which were formed as anomeric mixtures (Scheme 1).

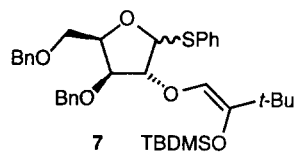


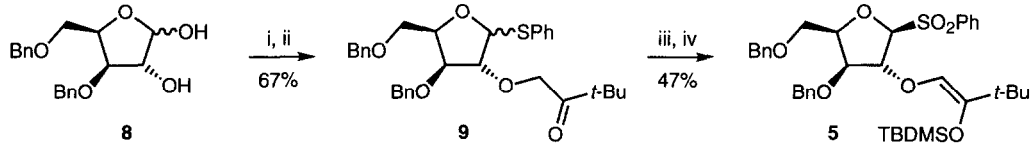
Scheme 1

We were keen to find out whether this kind of reaction would be viable on a sugar-derived template, and also to develop a new route to the ketooxetane precursors. In particular, we sought a sequence which would allow direct incorporation of the ketone group into a template which *already* contained the *S*-glycoside. We now report the synthesis and template-directed intramolecular *C*-glycosidation reactions of anomeric sulfone-containing substrates **5** and **6**.

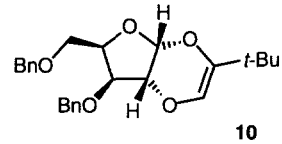


Assembly of the furanose substrate **5** began from 3,5-di-*O*-benzyl-D-xylofuranose **8** (Scheme 2).[5] This was readily accessed from commercially available 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose in 87% overall yield, by sequential regioselective 3,5-deprotection using 3:1 acetic acid–water, dibenzylation with benzyl chloride–potassium hydroxide,[6] and hydrolysis in acetonitrile containing aqueous sulfuric acid.[1] Given our intention to introduce the ketone side-chain after the *S*-glycosidic group, we were mindful of the possibility that the basic conditions anticipated for the necessary alkylation step might cause elimination of the arylthio function. We therefore elected to change from the pyridylthio group used previously to the phenylthio moiety, since it was considered that this would be a poorer leaving group. Hence, exposure of **8** to tri-*n*-butylphosphine–diphenyldisulfide[7] in dichloromethane gave a 6:1 anomeric mixture of thioglycosides,[8] which underwent smooth alkylation with bromopinacolone under phase-transfer conditions using Aliquat® 336 as catalyst to give **9** in high yield. Initially, we attempted to effect cyclisation of enol ether-containing substrates containing phenylthio as the anomeric leaving group. However, treatment of **7** with a variety of thiaphilic metal reagents[9] failed to give **10** in acceptable yields; mercuric triflate–*N*,*N*-dimethylaniline complex in acetonitrile[10] was identified as the most effective system. Since anomeric sulfones have been extensively deployed in *C*-glycosidation processes, most notably by Ley and co-workers,[11] an alternative strategy was adopted in which anomeric *S*-oxidation was carried out prior to 'arming' of the side-chain by silyl enol etherification. *S*-Oxidation of the mixture of **9** yielded a mixture of sulfone anomers, which was converted into a ca. 3:1 mixture of **5** and the *O*-cyclised by-product **10** in 78% combined yield using standard enol ether-forming conditions.[12] Interestingly, substrate **5** was formed as a *single*, β-diastereomer (Scheme 2).[13]



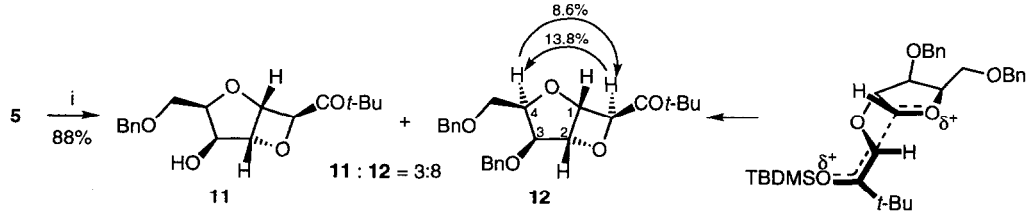


(i) *n*-Bu_3P, PhSSPh, CH_2Cl_2, 0°C
(ii) $BrCH_2CO$*t*-Bu, Aliquat® 336, 50% aq NaOH–CH_2Cl_2, rt
(iii) 36% CH_3CO_3H in AcOH, NaOAc, CH_2Cl_2, rt
(iv) TBDMSOTf, Et_3N, CH_2Cl_2, 0°C→rt



Scheme 2

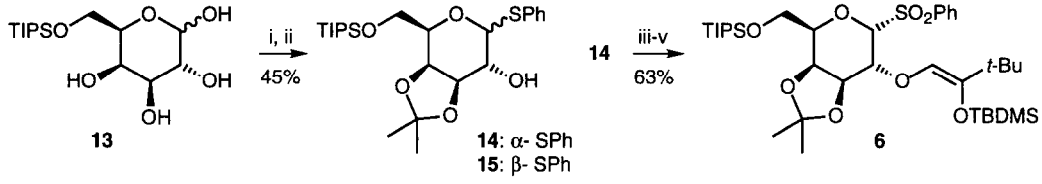
A range of Lewis acidic reagents was screened in order to identify optimum conditions for the cyclisation reaction of **5**. After extensive experimentation it was found that treatment of a dilute (0.04M) dichloromethane solution of **5** with two equivalents of tin(IV) chloride at -40°C afforded in 88% combined yield an 8:3 mixture of the bicyclic ketooxetane **12** and the debenzylated analogue **11**.[14] The assignment of **12** as possessing an exo-oriented *t*-butyl ketone moiety followed from the observation of substantial n.O.e.s between the ketone α-methine and H-4. This was expected on the basis of our previous work,[1] and is rationalised in terms of a more favoured exo-oriented enol ether side-chain intercepting the α-face of the anomeric cation (Scheme 3).



(i) $SnCl_4$ (2 eq), CH_2Cl_2, -40°C; aq $NaHCO_3$

Scheme 3

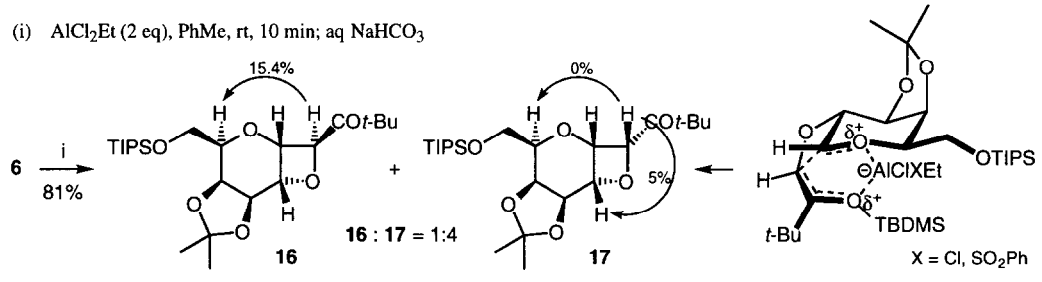
The hexopyranose substrate **6** was synthesised from 6-*O*-triisopropylsilyl-D-galactopyranose **13**[15] as depicted in Scheme 4. *S*-Glycosidation of **13** was achieved as before using *n*-Bu_3P–PhSSPh in dichloromethane, and gave a ca. 2:1 mixture of α- and β-anomers, which were protected to give the acetonides **14** and **15**. It was found that in the subsequent, phase-transfer alkylation step that anomer **14** was significantly more reactive than **15**, and therefore ways to improve the α:β ratio in the *S*-glycosidation reaction in favour of the α-anomer **14** were sought. In the event, addition of a large excess of pyridine to the dichloromethane used as solvent in this step resulted in a significantly slower reaction, but gave essentially complete (28:1) selectivity for the α-anomer.[16] Phase-transfer-catalysed alkylation of **14** proceeded smoothly to give the expected ketone, which was *S*-oxidised to the sulfone as before and similarly converted into the enol ether substrate **6**.



(i) PhSSPh, *n*-Bu_3P, C_5H_5N (20 eq), CH_2Cl_2, 0°C→rt; (ii) $Me_2C(OMe)_2$ (7 x 2.5 eq), cat. PPTS, CH_2Cl_2, rt; (iii) $BrCH_2CO$*t*-Bu, Aliquat® 336, 50% aq NaOH–CH_2Cl_2, rt; (iv) 36% CH_3CO_3H in AcOH, NaOAc, CH_2Cl_2, rt; (v) TBDMSOTf, Et_3N, CH_2Cl_2, 0°C→rt.

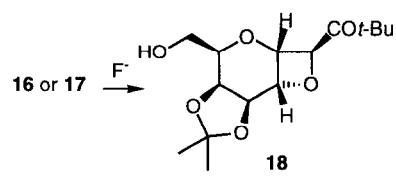
Scheme 4

As before, it was found that the choice of Lewis acid was crucial to the success of the cyclisation reaction of **6**. Unlike **5**, **6** was converted into cyclised product in only poor yield upon exposure to tin(IV) chloride. The use of aluminium chloride resulted in substantial hydrolysis of the enol ether function, together with anomeric substitution of the sulfonyl group with chloride; the anomeric chloride was the sole product obtained (84%) when diethylaluminium chloride was employed. It was finally established that brief treatment of **6** with two equivalents of ethylaluminium dichloride in toluene *at room temperature* effected clean cyclisation to give in 81% combined yield a separable 1:4 mixture of the exo and endo ketooxetanes **16** and **17**, whose structural assignments were inferred again from the observed n.O.e.s (Scheme 5).

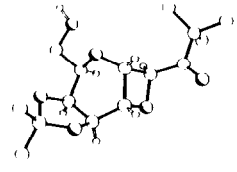


Scheme 5

The selectivity for the endo stereoisomer **17** is noteworthy, since both **3** (Scheme 1)[1] and **5** (Scheme 3) gave exclusively exo products on cyclisation. We speculate that this arises through coordination of the silyl enol ether and pyran oxygen atoms to the aluminium atom during formation of the anomeric C–C bond (Scheme 5). That **17** is the kinetically, but not thermodynamically preferred product was inferred from the observation that slow conversion into **16** occurred on exposure to $AlClEt_2$ in toluene. Also, lower **17**:**16** selectivity was observed if longer reaction times were used for the cyclisation of **6** using $AlCl_2Et$. Both **16** and **17** gave the crystalline alcohol **18** upon desilylation with tetra-*n*-butylammonium fluoride (Scheme 6, Figure).[17]



Scheme 6



X-ray structure of **18**

Figure

In summary, we have shown that sugar-derived anomeric sulfone–enol ethers **5** and **6** are readily available substrates for stereoselective template-directed intramolecular *C*-glycosidation processes, and that these novel transformations give bicyclic ketooxetanes in high yields. Current efforts are directed towards the development of precursors possessing electrophilic functionality within carbocyclic systems as triggers for the oxetane-forming process, and the results of these studies will be reported in due course.

ACKNOWLEDGEMENTS

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8. We have not assigned the major and minor *S*-glycoside anomers.
9. Mercuric acetate, mercuric trifluoroacetate and zinc chloride all failed to initiate the desired cyclisation.
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13. We speculate that the β-disposition of the sulfone moiety may arise via attack by $PhSO_2H$ or $PhSO_2^-$ on the anomeric cation in a fashion anti with respect to the neighbouring α-ketonic group.
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15. Compound **13** was prepared from D-galactopyranose in 53% yield by treatment with TIPS-Cl and imidazole in DMF (1M) containing 10 mol % DMAP (rt, 29 h).
16. We speculate that pyridine may intercept reversibly the anomeric cation formed on loss of *n*-Bu_3PO from the activated lactol, allowing formation of the anomerically stabilised α-stereoisomer.
17. We thank Professor David J. Williams and Dr Andrew J. P. White of this Department for the X-ray structure determination.

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