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Stereoselective glycosylations using oxathiane spiroketal glycosyl donors

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ABSTRACT

Novel oxathiane spiroketal donors have been synthesised and activated via an umpolung S-arylation strategy using 1,3,5-trimethoxybenzene and 1,3-dimethoxybenzene. The comparative reactivity of the resulting 2,4,6-trimethoxyphenyl (TMP)- and 2,4-dimethoxyphenyl (DMP)-oxathiane spiroketal sulfonium ions is discussed, and their α-stereoselectivity in glycosylation reactions is compared to the analogous TMP- and DMP-sulfonium ions derived from an oxathiane glycosyl donor bearing a methyl ketal group. The results show that the stereoselectivity of the oxathiane glycosyl donors is dependent on the structure of the ketal group and reactivity can be tuned by varying the substituent on the sulfonium ion.

1. Introduction

The chemical synthesis of complex oligosaccharides presents many technical challenges ranging from lengthy reaction sequences to problematic purification steps.[1,2] But such is the biological importance of carbohydrates[3] that solutions for many of these difficulties are on the horizon, for example, through 'one-pot' glycosylations using orthogonally activated donors[4–6] and the advent of solid-phase automated oligosaccharide synthesis.[1,7–10] Despite these advances, stereocontrol over the formation of the glycosidic linkage still remains a challenge, particularly in the synthesis of 1,2-*cis*-glycosides.[11–15] Much recent work in this field has focussed on the study of stabilised glycosyl sulfonium ions and their stereodirecting ability,[16–22] including our recent report of oxathiane ketal-*S*-oxide glycosyl donors **1** for stereoselective 1,2-*cis* glycosylations (Scheme 1a).[19]

Attempts to arylate glycosyl oxathianes with benzyne led to the formation of glycosyl acetates.[21] However, oxidation of the oxathiane to give oxathiane ketal-*S*-oxides **1**, and subsequent treatment with Tf_2O, led to the formation of surprisingly stable activated intermediates that were sufficiently long-lived to undergo electrophilic aromatic substitution in the presence of 1,3,5-trimethoxybenzene (TMB). Therefore, conversion of the previously nucleophilic sulfide into an electrophilic S(IV) centre facilitated an 'umpolung' approach to S-arylation. The resulting 2,4,6-trimethoxyphenyl (TMP)-oxathiane ketal sulfonium ions **2** then afforded α-glycosides **3** with complete stereoselectivity following heating at 50 °C. However, although glycosylation reactions with oxathiane ketal sulfonium ions **4** are notable for the formation of glycosides with complete α-stereoselectivity,[19,21] the resulting O-2 acyclic ketal formed in the product **5** occasionally decomposed under the reaction conditions, diminishing yields in more challenging glycosylation reactions. Therefore, in an attempt to circumvent this issue, we set out to design a new oxathiane donor scaffold in which the axial methoxy group was replaced with an O-substituent constrained in a spirocyclic ring (Scheme 1b). It was anticipated that following glycosylation, spiroketal sulfonium ion **6** would afford glycosides **7** bearing an O-2 cyclic ketal which would be more stable than the corresponding O-2 acyclic ketal, but still sufficiently labile to be removed by Lewis acid catalysed cleavage. To this end, we present the synthesis and activation of oxathiane spiroketal-*S*-oxides via an umpolung S-arylation strategy, and compare their α-stereoselectivities in glycosylation reactions with the analogous oxathiane ketal sulfonium ions. We also demonstrate that the stability and α-stereoselectivity of oxathiane spiroketal sulfonium ions in glycosylation reactions can be modulated by changing the *S*-aryl appendage exogenous to the oxathiane ring. Both TMP and 2,4-dimethoxyphenyl (DMP) sulfonium ions are synthesised, and their reactivities and α-stereoselectivities are compared.

2. Results and discussion

The synthesis of the oxathiane spiroketal donor began from pentaacetate **8**, which was activated with a Lewis acid in the presence of thiourea to afford an intermediate β-glycosyl isothiouronium salt.[23,24] Thioglycoside **9** was then isolated in 50% yield following treatment with Et_3N and mesylated dihydropyran **17**, which was synthesised from alcohol **16** (Scheme 2).[25] Subsequent deacetylation under Zemplén conditions afforded the unprotected

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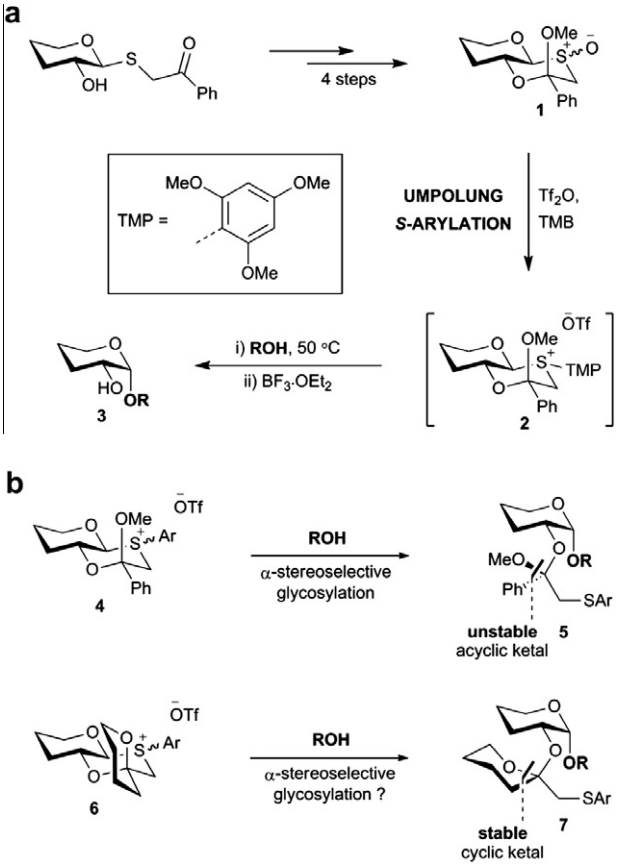
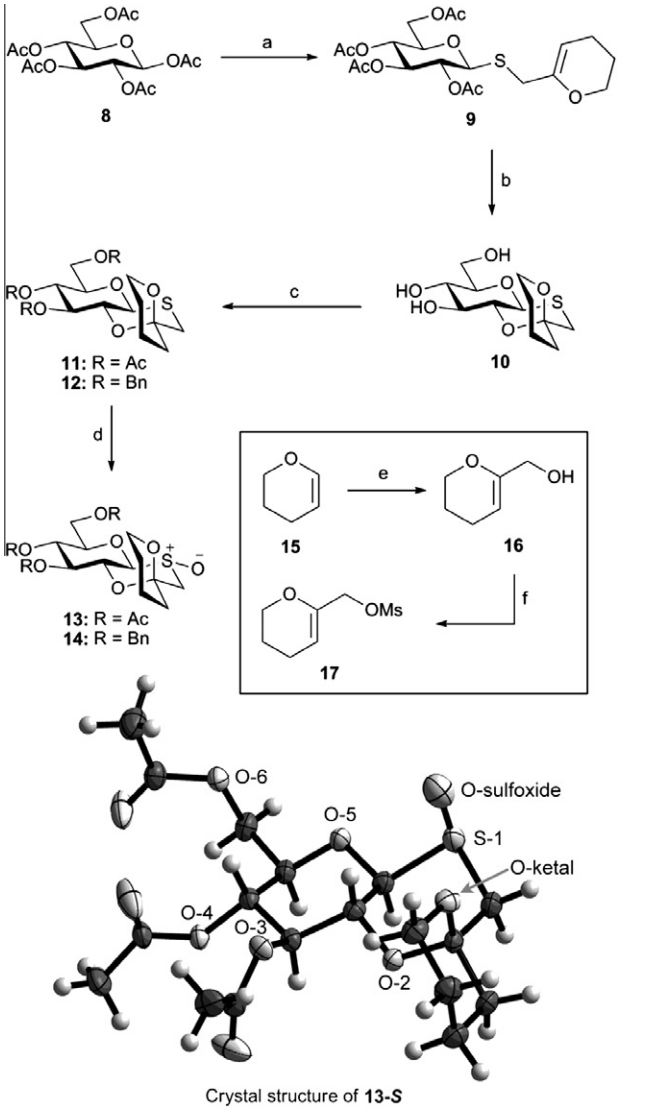


Scheme 1. (a) Umpolung S-arylation strategy for oxathiane ketal-*S*-oxide donors **1**. (b) Oxathiane ketal donor scaffold **4** and oxathiane spiroketal donor scaffold **6**.



Scheme 2. Reagents and conditions: (a) (i) $BF_3{\cdot}OEt_2/SC(NH_2)_2/CH_3CN$, (ii) Et_3N/**17** (50%); (b) (i) NaOMe/MeOH, (ii) *p*-TSA/$CHCl_3$ (60%); (c) **11** Ac_2O/Et_3N/DMAP/CH_2Cl_2 (100%); **12** NaH/BnBr/DMF; (d) **13** *m*-CPBA/CH_2Cl_2 (93%, dr 97:3, only the major diastereomer is shown); **14** *m*-CPBA/CH_2Cl_2 (30% from **10**, dr 99:1); (e) *n*-BuLi/TMEDA/THF/$(CH_2O)_n$ (47%); (f) Et_3N/MsCl/CH_2Cl_2—the crude product **17** was used without purification. The crystal structure depicts an ellipsoid probability of 50%.

thioglycoside, which was subjected to a regio- and stereoselective acid-catalysed cyclisation to afford key oxathiane spiroketal scaffold **10** in 60% yield over two steps. Acetylation then furnished protected spiroketal **11**, which was oxidised with *m*-CPBA to afford sulfoxide **13** in 93% yield with a diastereomeric ratio of 93:7. The equatorial sulfoxide **13**-*R* was unequivocally assigned as the major diastereomer based on analysis of the geminal coupling constants for the methylene protons adjacent to sulfur.[26,27] Benzylation of triol **10** similarly led to the protected oxathiane **12**, which was oxidised to sulfoxide **14** as virtually a single diastereomer in 30% yield over two steps. Importantly the structural integrity of the spiroketal ring was confirmed by X-ray crystallographic analysis. The X-ray structure of the acetylated axial sulfoxide **13**-*S* (Scheme 2) illustrates how the interlocked ring configuration benefits from stabilisation by double $n(O)\rightarrow\sigma*(C–O)$ overlap.[28–30]

With spiroketal-*S*-oxide **13**-*R* in hand, umpolung S-arylation using triflic anhydride and TMB was attempted (Fig. 1). Pleasingly, clean formation of the TMP-sulfonium ion **18** as a single diastereomer was observed by ^1H NMR spectroscopy. Assignment of sulfonium ion stereochemistry is tentative in the absence of both diastereomers of sulfonium ion **18**; however, comparison of the geminal coupling constant for the methylene protons adjacent to sulfur are consistent with analogous equatorial aryl sulfonium salts.[19] Following activation of sulfoxide **13**-*R* in CD_2Cl_2, a characteristic ~1.5 ppm downfield shift of the H-1 proton signal occurs,[16,19] indicative of the formation of sulfonium ion **18**. This is accompanied by similar downfield shifts for the H-axial and H-equatorial protons adjacent to the positively charged sulfur, and the appearance of signals corresponding to the aromatic protons and methoxy groups associated with the TMP *S*-appendage.

Content that the formation of TMP-spiroketal **18** occurred under the reaction conditions, glycosylation of diacetone galactose **19** was then attempted. As anticipated, glycosylation reactions at room temperature proceeded very slowly, demonstrating the stability of sulfonium ion **18**. Therefore, the glycosylation reaction was attempted at an elevated temperature of 50 °C (Scheme 3). It proved convenient to cleave the O-2 cyclic ketal protecting group with $BF_3{\cdot}OEt_2$ prior to isolation of glycoside product **20**, which was obtained in a yield of 38% over two steps (α:β 93:7). By reducing the temperature to 37 °C, it proved possible to increase the yield of the glycosylation reaction, affording glycoside **20** in an improved yield of 60%, but without change to the anomeric ratio (α:β 93:7; Table 1, entry 1).

These conditions were then applied to the glycosylation of the secondary alcohol, 2-propanol, with acetylated spiroketal **13**-*R*, which afforded α-glycoside **28** in 61% yield, on this occasion with an improved anomeric ratio of α:β 98:2 (Table 1, entry 2). Glycosylation reactions with the benzylated spiroketal **14**-*R* proceeded at room temperature, which is consistent with the increased reac-