Article:
Fascione, MA, Webb, NJ, Kilner, CA et al. (2 more authors) (2012) Stereoselective glycosylations using oxathiane spiroketal glycosyl donors. Carbohydrate Research, 348. 6 - 13 . ISSN 0008-6215

https://doi.org/10.1016/j.carres.2011.07.020

Published version: carbohydr. Res. 2012, 348, 6:
http://dx.doi.org/10.1016/j.carres.2011.07.020

Stereoselective glycosylation using oxathiane spiroketal glycosyl donors

Martin A. Fascione,[a] Nicola J. Webb,[a] Colin A. Kilner,[a] Stuart L. Warriner,[a,b] and W. Bruce Turnbull*[a,b]

[a]*School of Chemistry, University of Leeds, Leeds, LS2 9JT, UK. Fax: (+44) 11333436565; Tel: (+44) 1133437438; E-mail: w.b.turnbull@leeds.ac.uk*

[b]*Astbury Centre for Structural Molecular Biology, University of Leeds, Leeds, LS2 9JT, UK*

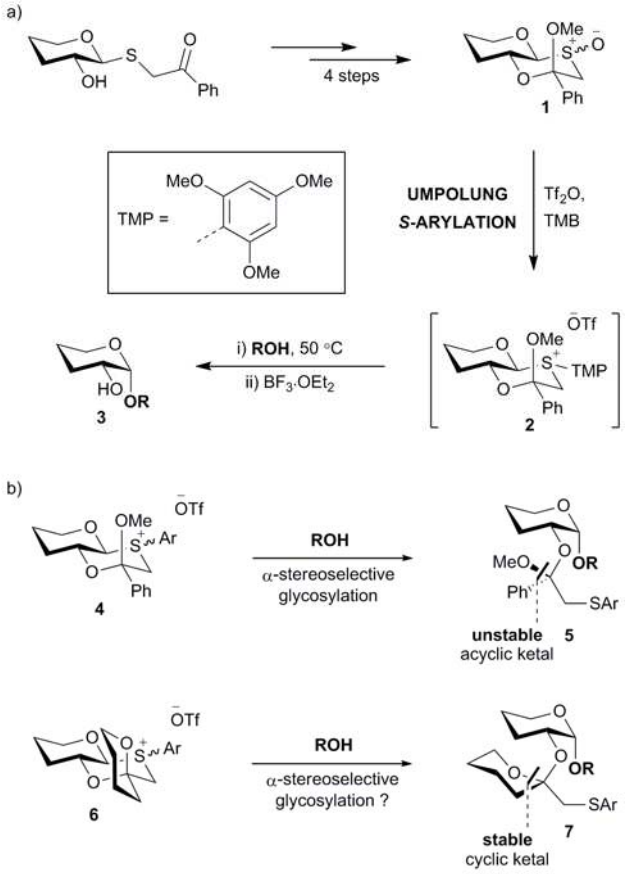
Abstract

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 are compared to the analogous TMP- and DMP-sulfonium ions derived from a oxathiane glycosyl donors 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 through 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, however, 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]



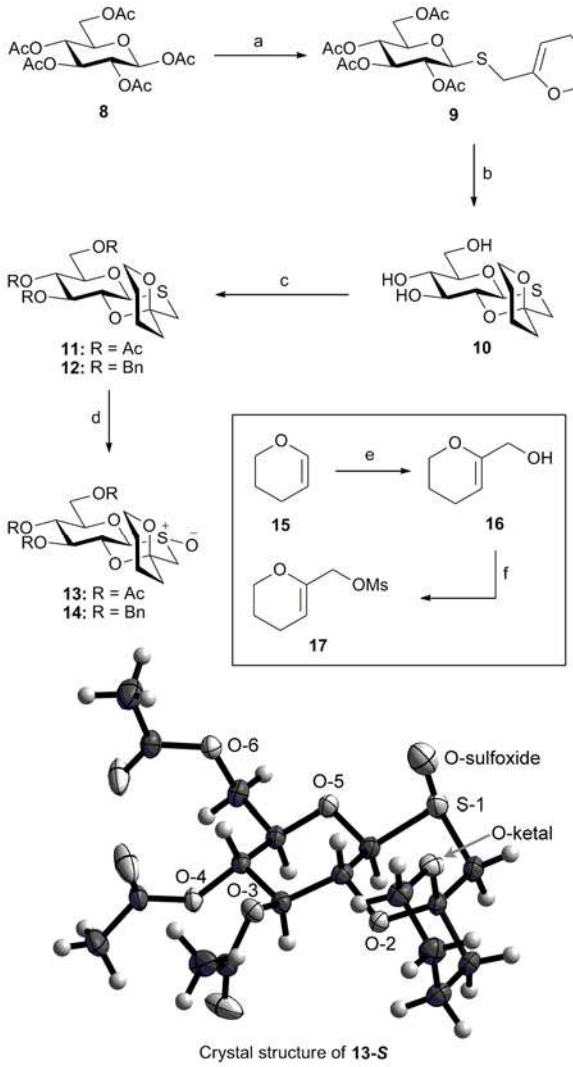
Scheme 1 a) Umpolung *S*-arylation strategy for oxathiane ketal-*S*-oxide donors **1**. b) Oxathiane ketal donor scaffold **4** and oxathiane spiroketal donor scaffold **6**.

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 which were sufficiently long-lived to undergo electrophilic aromatic substitution in the presence 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 reactivity and α-stereoselectivities 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 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*)→σ*(*C*-*O*) overlap.[28-30]



Crystal structure of **13-*S***

Scheme 2 *Reagents*: (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%, d.r. 97:3, only the major diastereomer is shown); **14** *m*-CPBA/CH_2Cl_2 (30% from **10**, d.r. 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%.

With spiroketal-*S*-oxide **13-*R*** in hand, umpolung *S*-arylation using triflic anhydride and TMB was attempted (Figure 1). Pleasingly, clean formation of the TMP-sulfonium ion **18** as

a single diastereomer was observed by 1H NMR. 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.

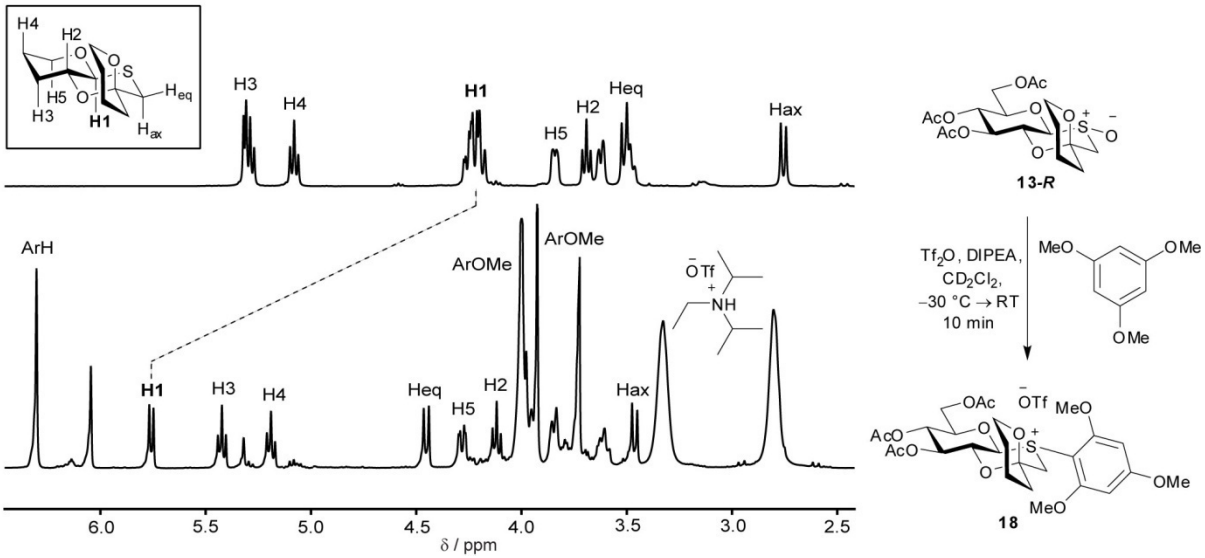
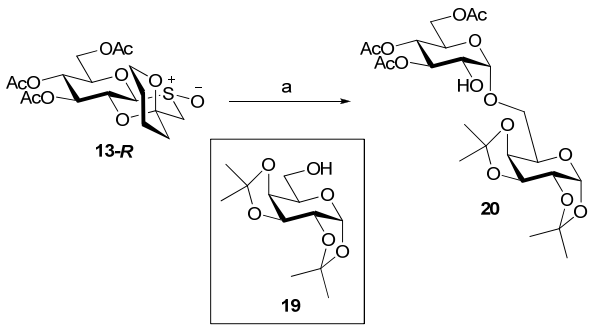


Figure 1 Formation of TMP-spiroketal **18**, observed by 1H NMR in CD_2Cl_2.

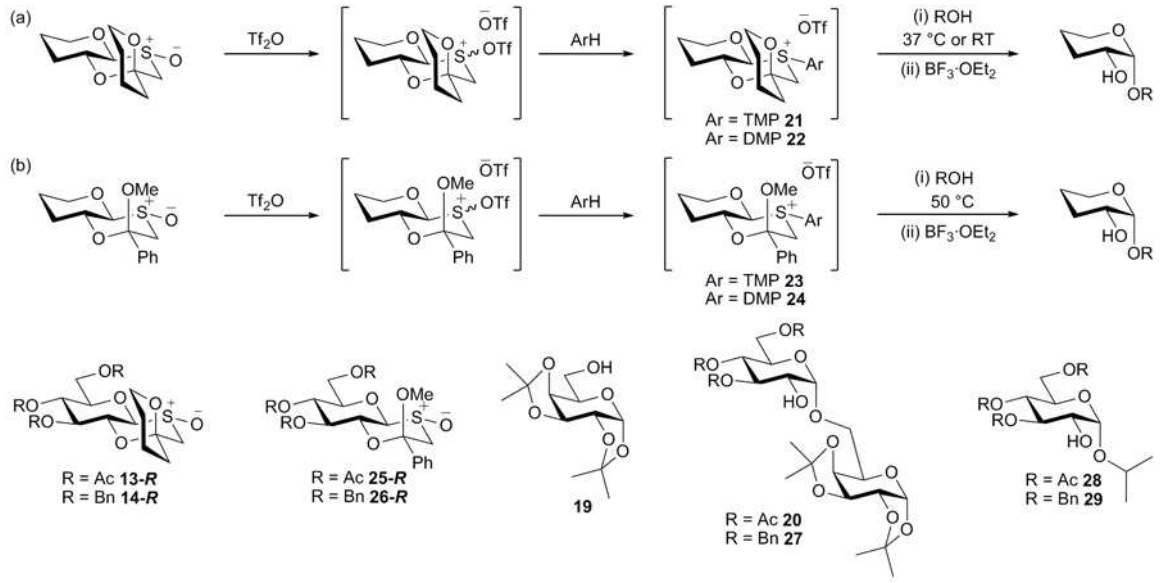
Content that the formation of TMP-spiroketal **18** occurred under the reaction conditions, glycosylation of diacetone galactose **19** was then attempted. As anticipated glycosylation reactions at room temperature proceeded very slowly, demonstrating the stability of sulfonium ion **18**. Therefore, 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-step (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).



Scheme 3 *Reagents*: (a) (i) Tf_2O/TMB/DIPEA/−30 °C →−10 °C (ii) **19** /$C_2H_4Cl_2$/−10 °C →50 °C (ii) $BF_3{\cdot}OEt_2/CH_2Cl_2$.

Table 1 Glycosylation reactions with a) oxathiane spiroketal sulfonium ions **21** and **22** and b) oxathiane ketal sulfonium ions **23** and **24**.



Entry	Donor	ArH	ROH	Product	Yield (%)[a]	α:β
1[b]	**13-*R***	TMB	**19**	**20**	60	93:7
2[b]	**13-*R***	TMB	*i*PrOH	**28**	61	98:2
3[c]	**14-*R***	TMB	**19**	**27**	58	92:8[d]
4[c]	**14-*R***	TMB	*i*PrOH	**29**	57	96:4[d]
5[b]	**13-*R***	DMB	**19**	**20**	50	86:14
6[b]	**13-*R***	DMB	*i*PrOH	**28**	52	95:5
7[e]	**25-*R***	TMB	**19**[f]	**20**	85	>98:2[g]
8[e]	**26-*R***	TMB	*i*PrOH[h]	**28**	77	>98:2[g]
9	**25-*R***	DMB	**19**[f]	**20**	62	>98:2[g]

[a]Isolated yield over two-steps. [b]Glycosylations were performed in CH_2Cl_2 at −30 °C, before being warmed to −10 °C, followed by ROH (1.5 equiv.) addition and stirring for 24 h at 37 °C. [c]After ROH (1.5 equiv.) addition reaction mixture was stirred for 24 h at RT. [d]Measured by 1H NMR, following purification on Sephadex LH-20 column. [e]Reproduced from reference 19 for comparison. [f]2.5 equiv ROH. [g]No β-anomer was detected in 1H NMR of crude mixture. [h]5 equiv ROH.

These conditions were then applied to the glycosylation of secondary alcohol isopropanol 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 reactivity that is expected on moving from the 'disarming' acetyl to the 'arming' benzyl ether protecting group.[31,32] Thus, glycosylation of primary alcohol **19** afforded α-glycoside **27** in 58% yield with an α:β ratio of 92:8 (Table 1, entry 3), and glycosylation of isopropanol afforded the desired α-glycoside **29** in 57% yield and an α:β ratio of 96:4 (Table 1, entry 4). Both reactions using the benzylated spiroketal **14-*R*** were therefore marginally less α-stereoselective than the comparable glycosylations using the acetylated spiroketal **13-*R***; a trend noted previously with oxathiane ether glycosyl donors.[21,33] It was pleasing to note that glycosylation reactions using spiroketal donors required significantly less glycosyl acceptor than analogous reactions Previously, it was found that the higher concentrations of acceptor were needed to avoid a competing glycosylation reaction involving MeOH that can be released from glycoside products bearing the methyl ketal protecting group on *O*-2.[19] This side reaction was found to be equally problematic at either 50 °C or room temperature. However, the increased stability of the *O*-2 cyclic ketal protecting group under the reaction conditions successfully avoids comparable side reactions. Although no quantitative comparison of the stability of the *O*-2 acyclic and cyclic ketal was performed, analysis of the crude reaction mixtures following glycosylation reactions using methyl ketal donors revealed significant loss of the *O*-2 acyclic ketal, while far less cleavage of the *O-2* cyclic ketal was observed following reactions employing oxathiane spiroketal donors. The lower yields in reactions using spiroketal donors **13-*R*** and **14-*R***, compared to the analogous reactions using the methyl ketal donors **25-*R*** and **26-*R*** (1.5 equiv. in entries 1-4 *vs.* 2.5 equiv. in entry 7, or 5 equiv. in entry 8) may be a result of competing intramolecular

glycosylation. However, no conclusive evidence for the formation of any resulting bicyclic-*O*-glycoside products could be obtained, even prior to the Lewis acid catalysed cleavage step.

Although still highly α-stereoselective, the spiroketal sulfonium ions **21** were less stereoselective than the corresponding methyl ketal sulfonium ions **23**.[19] This difference is intriguing considering both sulfonium ions appear to have comparable reactivity and both scaffolds contain a ketal substituent in the oxathiane ring. Recently, it has been proposed that the complete α-stereoselectivity of ketal sulfonium ions **23** may be a direct result of their inherent stability.[33] This theory is based on the assumption that ketal **23** can exist in either its bicyclic sulfonium ion form, or in a ring opened oxacarbenium ion form.[18,34-36] In a manifestation of the Thorpe-Ingold effect,[37,38] the ketal group is proposed to stabilise the cyclic sulfonium ion, thus promoting an 'S_N2-like' α-stereoselective glycosylation.[39-41] However, from a comparison of the results reported in table 1, it seems unlikely that the α-stereoselectivity of sulfonium ions **23** results simply from stabilising the oxathianium ion with a ketal group; instead it would appear that stereoselectivity may also be influenced by the other substituents on the oxathiane ring.

Therefore, our attention turned next to the *S*-aryl appendage on the sulfonium ions. 2,6-Dimethoxyphenyl (DMP) sulfonium ions **22** and **24** were prepared to study the effects of removing a methoxy group from the aromatic ring. Activation of the oxathiane ketal-*S*-oxide **25-*R*** in the presence of dimethoxybenzene (DMB) and addition of primary alcohol **19** afforded the desired α-glycoside **20** in 62% yield (Table 1, entry 9). The yield of the desired α-glycoside was lower than in the case of TMB activation (Table 1, entry 7), as a result of concomitant formation of the analogous α-methyl glycoside in 12% yield; nevertheless, both glycosides were still formed with complete α-stereoselectivity. However, when spiroketal-*S*-oxide **13-*R*** was activated in the same fashion, the resulting DMP-sulfonium ion afforded glycosides with lower α-stereoselectivity than observed for the TMP-sulfonium ion. For

example, glycosylation of primary alcohol **19** afforded the glycoside **20** in 50% yield with an anomeric ratio of α:β 86:14 (Table 1, entry 5), compared to α:β 93:7 for glycosylation using the analogous TMP-sulfonium ion (Table 1, entry 1). Also glycosylation of isopropanol afforded α-glycoside **28** in 52% yield with an anomeric ratio of α:β 95:5 (Table 1 , entry 6), which was less α-stereoselective than the corresponding glycosylation using the TMP-sulfonium ion (α:β 98:2, Table 1, entry 2).

We wondered if the reduction in α-stereoselectivity on moving from TMP sulfonium ions to DMP sulfonium ions would be accompanied by any differences in reactivity of the spiroketal sulfonium ions. To this end, the reaction of MeOH with equimolar amounts of TMP sulfonium ion **18** and DMP sulfonium ion **30** was monitored by ^{1}H-NMR spectroscopy in CD_2Cl_2 (Figure 2).

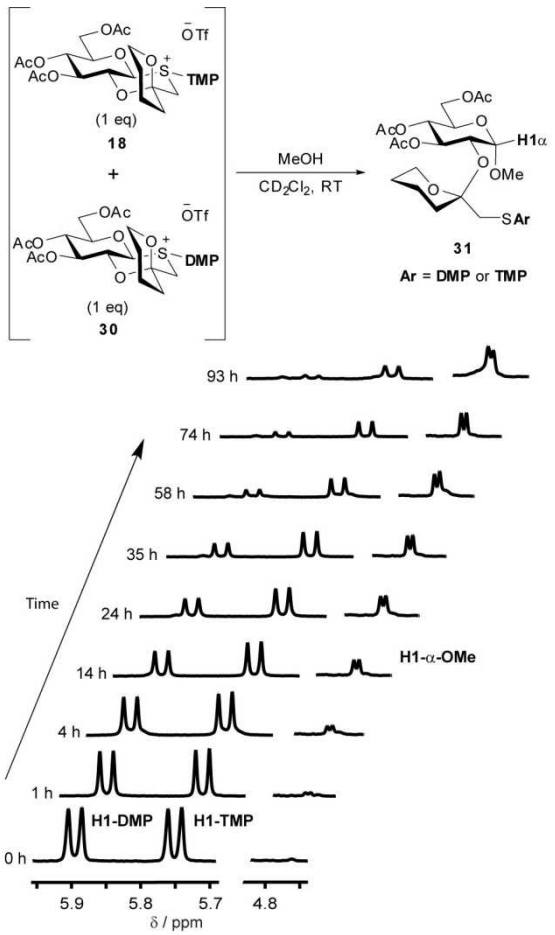


Figure 2. ^{1}H-NMR stackplot illustrating relative reactivities of TMP sulfonium ion **18** and

DMP sulfonium ion **30** in CD_2Cl_2 at room temperature.

After 35 h at RT, the H-1 signal of the TMP-spiroketal **18** was 48% of its original intensity (52% reacted), while the H-1 signal for the DMP-spiroketal **30** was only 24% of its original intensity (76% reacted). The reduction in H-1 signal intensities was also accompanied by the formation of methyl glycosides **31-TMP/DMP**, characterised by an H-1 doublet at ~4.8 ppm. The experiment demonstrated that DMP sulfonium ion **30** was approximately 1.5 times as reactive as the TMP sulfonium ion **18**. However, this experiment also illustrates the high stability of these spiroketal sulfonium ions as the glycosylation reaction was still not complete after 93 h at room temperature (4% DMP-spiroketal **30** and 10% TMP-spiroketal **18** remained). The increased reactivity of the DMP sulfonium ion **30** is perhaps unsurprising, as intuition would suggest that the more electron donating TMP aromatic group should stabilise the positively charged sulfonium ion more effectively.[18,42] This reactivity difference may also be reflected in the H-1 proton shifts for the sulfonium ions, as the more reactive and less stabilised DMP sulfonium ion **30** has the lowest field H-1 signal at 5.9 ppm compared to the more shielded TMP sulfonium ion H-1 signal at 5.75 ppm.

Therefore, the decrease in the α-stereoselectivity of glycosylation reactions using the DMP sulfonium ion **30** compared to the TMP sulfonium ion **18** is accompanied by an increase in reactivity of the sulfonium ion. A similar trend was observed when increasing the reactivity of the sulfonium ions by moving from ester to benzyl ether protecting groups.[33] However, due to the limited scope of this study, care must be taken not to over interpret this correlation between reactivity and α-stereoselectivity.

In conclusion, the synthesis and reactivity of new oxathiane spiroketal glycosyl donors have been described. The aryl sulfonium ions derived from the oxathiane spiroketal-*S*-oxides **13-*R*** and **14-*R*** have comparable stability to analogous sulfonium ions derived from

other oxathiane ketal donors, but afford glycosides with lower α-stereoselectivities than those reported previously.[19] Stereoselectivity could be improved by changing the protecting groups on the sugar ring (esters *vs.* benzyl ethers) or the *S*-aryl appendage (TMP-sulfonium ion *vs.* DMP-sulfonium ion). Although these changes in stereoselectivity appear to correlate with the stability of the sulfonium ions, the stabilising effect of an oxygen substituent on the oxathianium ring is not sufficient to explain the high α-stereoselectivity of the oxathiane ketal donors.[19] The difference in reactivity between TMP and DMP sulfonium ions in the spiroketal series potentially offers a strategy for 'arming' or 'disarming' oxathiane glycosyl donors without changing protecting groups.

3. Experimental

3.1 General Methods: All solvents were dried prior to use, according to standard methods.[43] Trifluoromethanesulfonic anhydride (Tf_2O) was distilled under a N_2(g) atmosphere. Boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$) was distilled over calcium hydride, and all other commercially available reagents were used as received. Where appropriate anhydrous quality material was purchased. All solvents used for flash chromatography were GPR grade, except hexane and EtOAc, when HPLC grade was used. All concentrations were performed *in vacuo,* unless otherwise stated. All reactions were performed in oven dried glassware under a N_2(g) atmosphere, unless otherwise stated. ^{1}H NMR spectra were recorded at 500 MHz on a Bruker Avance 500 instrument or at 300 MHz on a Bruker Avance 300 instrument. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker Avance 300 instrument. Chemical shifts are given in parts per million downfield from tetramethylsilane. The following abbreviations are used in ^{1}H NMR analysis: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, dt = double triplet, td = triple doublet, ddd = double double doublet. In ^{1}H NMR and ^{13}C-NMR of the oxathiane spiroketals, the spiroketal

ring is labelled “a” through to “e” starting from the position α to the axial oxygen and ending at the ketal carbon. Electrospray (ES+) ionisation mass spectra were obtained on a Bruker HCT Ultra Ion Trap mass spectrometer connected to an Agilent 1200 series HPLC system, and high resolution ES+ were perfomed on a Bruker Daltonics MicroTOF mass spectrometer. Infra-red spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. Melting points were obtained on a Reichert hot-stage apparatus and are uncorrected. Optical rotations were measured at the sodium D-line with an Optical Activity AA-1000 polarimeter. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Analytical T.L.C was performed on silica gel 60-F^{254} (Merck) with detection by fluorescence and/or charring following immersion in a 5% H_2SO_4/MeOH solution, unless otherwise stated.

3.2 3,4-Dihydro-2H-pyran-6-(1-hydroxymethyl) (16)[25]

Commercially available 3,4-dihydro-2H-pyran **(15)** (13.3 mL, 145.45 mmol) and TMEDA (24.1 mL, 160 mmol) were stirred and cooled to 0 °C. *n*BuLi (100 mL, 160 mmol) was added slowly and the flask was cooled for a futher 45 min and then left for 20 h overnight at room temperature. The colour of the solution changed from a pale yellow to a burnt orange with a precipitate. Upon addition of tetrahydrofuran (100 mL) the precipitate dissolved to give an orange solution. The reaction mixture was cooled to 0 °C and paraformaldehyde (9.6 g, 320 mmol) was added portionwise (≈1 g per addition) over 1 h. The reaction mixture was held at 0 °C for 1 h and left to warm to room temperature slowly, and then stirred for a further 20 h. The reaction mixture was quenched with aq. NH_4Cl (100 mL) and then diluted with Et_2O (60 mL). The organic phase was poured over a solution of $CuSO_4.5H_2O$ (100 mL) and stirred for 30 min. The ether was then decanted off and washed with saturated aq. $NaHCO_3$ (2 x 100 mL), dried ($MgSO_4$) and concentrated to afford 3,4-dihydro-2H-pyran-6-(1-hydroxymethyl) **(16)** (7.85 g, 47%), as a yellow oil; R_F 0.4 (1:1 (v/v) hexane-EtOAc); ^{1}H

NMR: **δ_H** (500 MHz, C_6D_6); 4.59 (t, 1H, *J* 3.8 Hz, RC=C<u>H</u>$CH_2CH_2CH_2$), 3.88 (s, 2H, C<u>H</u>$_2$OH), 3.67 (t, 2H, *J* 5.1 Hz, RC=$CHCH_2CH_2C$<u>H</u>$_2$), 1.71 (dd, 2H, *J* 6.4, *J* 4.0 Hz, RC=$CHCH_2C$<u>H</u>$_2CH_2$), 1.38 (q, 2H, 6.0, *J* 5.1 Hz, RC=CHC<u>H</u>$_2CH_2CH_2$); ^{13}C-NMR: **δ_C** (75 MHz, C_6D_6); 154.7 (R<u>C</u>=$CHCH_2CH_2CH_2$), 97.1 (RC=<u>C</u>$HCH_2CH_2CH_2$), 66.7 (<u>C</u>H$_2$OH), 63.6 (RC=$CHCH_2CH_2$<u>C</u>H$_2$), 23.3 (RC=CH<u>C</u>$H_2CH_2CH_2$), 20.8 (RC=$CHCH_2$<u>C</u>H_2CH_2).

3.3 (3,4-Dihydro-2H-pyranyl)-methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (9)

Thiourea (1.35 g, 19.3 mmol) was added to a solution of 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose **(8)** (6.83 g, 17.5 mmol) in MeCN (60 mL) and heated to 85 °C. $BF_3{\cdot}OEt_2$ (4.66 mL, 36.8 mmol) was then added, and the reaction mixture was stirred for two hours at 85 °C. The solution was then cooled to room temperature and degassed before addition of Et_3N (7.62 mL, 54.3 mmol). Simultaneously, methanesulfonyl chloride (4.47 mL, 57.8 mmol) was added to a separate solution of 3,4-dihydro-2H-pyran-6-(1-hydroxymethyl) **(16)** (6.0 g, 52.5 mmol) and Et_3N (14.75 mL, 105 mmol) in CH_2Cl_2 (100 mL) at 0 °C before stirring for 10 min. This solution was then added to the reaction mixture, which was left to stir at room temperature for 18 h. The reaction mixture was then concentrated and redissolved in EtOAc (150 mL), washed with aq. NaCl (3 x 50 mL), dried and concentrated. The crude oil was purified by flash column chromatography (silica gel; 2:1 (v/v) hexane-EtOAc) to afford (3,4-dihydro-2H-pyranyl)-methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **(9)** (4.0 g, 50% yield) as an orange oil; R_F 0.19 (2:1 (v/v) hexane-EtOAc); **$[\alpha]_D^{21}$** 18.9 (*c* 0.7, $CHCl_3$); **FTIR** (ν_{max}/cm^{-1}) 1671 (C=C), 1750 (C=O); ^{1}H NMR: **δ_H** (500 MHz, $CDCl_3$); 5.23 (t, 1H, $J_{2,3}$ 9.4 Hz, $J_{3,4}$ 9.4 Hz, H-3), 5.09 (dd, 1H, $J_{1,2}$ 10.3 Hz, $J_{2,3}$ 9.4 Hz, H-2), 5.04 (t, 1H, $J_{3,4}$ 9.4 Hz, $J_{4,5}$ 9.4 Hz, H-4), 4.69 (t, 1H, *J* 3.4 Hz, RC=C<u>H</u>$CH_2CH_2CH_2$), 4.63 (d, 1H, $J_{1,2}$ 10.3 Hz, H-1), 4.25 (dd, 1H, $J_{5,6}$ 5.1 Hz, $J_{6,6'}$ 11.9 Hz, H-6), 4.14 (dd, 1H, $J_{5,6'}$

5.1 Hz, $J_{6,6'}$ 11.9 Hz, H-6'), 4.03 (m, 2H, RC=CHCH$_2$CH$_2$C<u>H$_2$</u>), 3.67 (m, 1H, H-5), 3.33 (d, 1H, *J* 13.6 Hz, SCH$_2$), 3.13 (d, 1H, *J* 13.6 Hz, SCH$_{2'}$), 2.08 (s, 3H, C(O)CH$_3$), 2.05 (s, 3H, C(O)CH$_3$), 2.02 (s, 3H, C(O)CH$_3$), 2.01 (s, 3H, C(O)CH$_3$), 2.07 (dd, 2H, *J* 3.4 Hz, *J* 5.1 Hz, RC=CHC<u>H$_2$</u>CH$_2$CH$_2$), 1.82 (dd, 2H, *J* 5.1, *J* 6.0 Hz, RC=CHCH$_2$C<u>H$_2$</u>CH$_2$); ^{13}C NMR: **δ_C** (75 MHz, CDCl$_3$); 171.0, 170.7, 169.8 (<u>C</u>(O)CH$_3$), 149.9 (R<u>C</u>=CHCH$_2$CH$_2$CH$_2$), 99.7 (RC=<u>C</u>HCH$_2$CH$_2$CH$_2$), 82.8 (C-1), 76.1 (C-5), 74.4 (C-4), 70.4 (C-2), 68.7 (C-3), 66.9 (RC=CHCH$_2$CH$_2$<u>C</u>H$_2$), 62.6 (C-6), 33.6 (S<u>C</u>H$_2$), 22.4 (RC=CHCH$_2$<u>C</u>H$_2$CH$_2$), 22.4 (C(O)<u>C</u>H$_3$), 21.4 (C(O)<u>C</u>H$_3$), 20.9 (C(O)<u>C</u>H$_3$), 20.7 (C(O)<u>C</u>H$_3$), 19.5 (RC=CH<u>C</u>H$_2$CH$_2$CH$_2$); **HRESIMS:** Found $[M+H]^+$ 461.1476 $C_{20}H_{29}O_{10}S$ requires 461.1481, $[M+Na]^+$ 483.1295 $C_{20}H_{29}O_{10}S$ requires 483.1301.

3.4 (6*S*)-1,7-Dioxa-4-thia-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*b*]-spiro[6.6]undecane (10)

A solution of sodium methoxide (380 mg, 6.95 mmol) in anhydrous MeOH (10 mL) was added to a solution of 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosyl-6-(1-hydroxymethyl)-3,4-dihydro-2H-pyran **(9)** (4.0 g, 8.69 mmol) in anhydrous MeOH (100 mL) and stirred overnight. The reaction mixture was then neutralised with Amberlite IRC H^+ resin and concentrated to leave a crude oil. The resulting oil was redissolved in chloroform (50 mL) and acidified with *p*-TSA (800 mg, 4.37 mmol) and left to stir for 45 min. The reaction mixture was then neutralised with Et$_3$N and concentrated to afford a crude oil. The crude oil was purified by flash chromatography (silica gel; 9:1 (v/v) CH$_2$Cl$_2$-MeOH) to afford (6*S*)-1,7-dioxa-4-thia-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*b*]-spiro[6.6]undecane **(10)** (1.5g, 60%) as a colourless foam; R_F 0.24 (9:1 (v/v) CH$_2$Cl$_2$-MeOH); **$[\alpha]_D^{21}$** +19.0 (*c* 2, CHCl$_3$); **FTIR** (ν_{max}/cm^{-1}) 3391 (OH), 2941 (C-H); 1H NMR: **δ_H** (500 MHz, CDCl$_3$); 4.39 (d, 1H, $J_{1,2}$ 8.5 Hz, H-1), 3.93 (dd, 1H, $J_{5,6}$ 1 Hz, $J_{6,6'}$ 12.8 Hz, H-6), 3.81 (dd, 1H, $J_{5,6'}$ 1 Hz, $J_{6,6'}$ 12.8 Hz,

H-6'), 3.76 (m, 2H, H-a, H-a'), 3.74 (m, 1H, H-4), 3.69 (dd, 1H, $J_{1,2}$ 8.5 Hz, $J_{2,3}$ 9.4 Hz, H-2), 3.59 (dd, 1H, $J_{2,3}$ 9.4 Hz, $J_{3,4}$ 9.4 Hz, H-3), 3.48 (m, 1H, H-5), 2.94 (d, 1H, $J_{SCHeq,SCHax}$ 13.6 Hz, SCHeq), 2.67 (d, 1H, $J_{SCHeq,SCHax}$ 13.6 Hz, SCHax), 1.81 (m, 2H, H-b, H-b'), 1.65 (m, 2H, H-c, H-c'), 1.53 (m, 2H, H-d, H-d'); ^{13}C NMR: $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$); 98.6 (C-e), 80.6 (C-1), 75.9 (C-5), 75.8 (C-4), 73.8 (C-2), 70.9 (C-3), 62.6 (C-6), 61.7 (C-a), 37.7 (SCH_2), 34.6 (C-d), 25.1 (C-b), 19.2 (C-c); **HRESIMS:** Found $[M+Na]^+$ 315.0873 $C_{12}H_{20}NaO_6S$ requires 315.0878.

3.5 (6*S*)-1,7-Dioxa-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-β-D-glucopyranoso)-4-thia-[1,2-*b*]-spiro[6.6]undecane (11)

Et_3N (1.18 mL, 8.48 mmol), acetic anhydride (810 μL, 8.48 mmol) and DMAP (5 mg, 0.05 mmol), were added to a solution of (6*S*)-1,7-dioxa-4-thia-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*b*]-spiro[6.6]undecane **(10)** (0.75 g, 2.57 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was left to stir for 1 h, before quenching with aq. $NaHCO_3$ (25 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated to leave a crude solid. The crude solid was purified by flash column chromatography (silica gel; 1:1 (v/v) hexane-EtOAc) to afford (6*S*)-1,7-dioxa-3,4,6-tri-O-acetyl-1,2-dideoxy-β-D-glucopyranoso)-4-thia-([1,2-*b*]-spiro[6.6]undecane **(11)** (1.07g, 100%) as colourless plates **mp:** 159.0-160.3 °C (from methanol); R_F 0.27 (2:1 (v/v) hexane-EtOAc); $\boldsymbol{[\alpha]_D^{21}}$ +16.9 (*c* 2.6, $CHCl_3$); **FTIR** (ν_{max}/cm^{-1}) 1747 (C=O), 2946 (C-H); 1H NMR: $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$); 5.14 (dd, 1H, $J_{2,3}$ 9.3 Hz, $J_{3,4}$ 9.3 Hz, H-3), 5.12 (dd, 1H, $J_{3,4}$ 9.3 Hz, $J_{4,5}$ 9.3 Hz, H-4), 4.40 (d, 1H, $J_{1,2}$ 9.3 Hz, H-1), 4.22 (dd, 1H, $J_{5,6}$ 4.6, $J_{6,6'}$ 12.3 Hz, H-6), 4.13 (dd, 1H, $J_{5,6'}$ 2.3, $J_{6,6'}$ 12.3 Hz, H-6'), 3.91 (dd, 1H, $J_{1,2}$ 9.3 Hz, $J_{2,3}$ 9.3 Hz, H-2), 3.75 (m, 1H, H-5), 3.65 (m, 2H, H-a, H-a'), 2.95 (d, 1H, $J_{SCHeq,SCHax}$ 13.7 Hz, SCHeq), 2.66 (d, 1H, $J_{SCHeq,SCHax}$ 13.7 Hz, SCHax), 2.08 (s, 3H, C(O)C$\underline{H}_3$), 2.06 (s, 3H, C(O)C$\underline{H}_3$), 2.03 (s, 3H, C(O)C$\underline{H}_3$), 1.56 (m, 6H, H-b, H-b', H-c, H-c', H-d, H-d'); ^{13}C

NMR: δ_C (75 MHz, $CDCl_3$); 171.2, 170.6, 169.9 ($\underline{C}(O)CH_3$), 93.1 (C-e), 77.2 (C-1), 76.2 (C-5), 73.4 (C-4), 72.0 (C-2), 68.8 (C-3), 62.4 (C-6), 61.6 (C-a), 37.6 (SCH_2), 34.5 (C-d), 25.1 (C-b), 21.2 ($C(O)CH_3$), 21.1 ($C(O)CH_3$), 21.0 ($C(O)CH_3$), 19.0 (C-c); **HRESIMS:** Found $[M+Na]^+$ 441.1190 $C_{18}H_{26}NaO_9S$ requires 441.1195.

3.6 (6*S*)-1,7-Dioxa-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-β-D-glucopyranoso)-4-thia-[1,2-*b*]-spiro[6.6]undecane (*R*/*S*)-*S*-oxide (13)

A solution of *m*-CPBA (250 mg, 1.26 mmol) in CH_2Cl_2 (1 mL) was added to a solution of (6*S*)-1,7-dioxa-(3,4,6-tri-O-acetyl-1,2-dideoxy-β-D-glucopyranoso)-4-thia-([1,2-*b*]-spiro[6.6]undecane **(11)** (500 mg, 1.20 mmol) in CH_2Cl_2 (12 mL) and stirred for ten min at −78°C. The reaction mixture was then quenched with aq. $NaHCO_3$ (25 mL) and diluted with CH_2Cl_2 (50 mL), and the organic phase was separated and concentrated to afford a crude syrup. The crude syrup was then purified by flash column chromatography (silica gel; 98:2 (v/v) CH_2Cl_2-MeOH) to afford (6*S*)-1,7-dioxa-(3,4,6-tri-O-acetyl-1,2-dideoxy-β-D-glucopyranoso)-4-thia-[1,2-*b*]-spiro[6.6]undecane (R/S)-S-oxide **(13)** (480 g, 93%, d.r: 97:3) as an amorphous solid; R_F 0.66 (9:1 (v/v) CH_2Cl_2-MeOH); $[\alpha]_D^{21}$ +6.5 (*c* 0.4, $CHCl_3$); (6*S*)-1,7-dioxa-4-thia-(3,4,6-tri-O-acetyl-1,2-dideoxy-β-D-glucopyranoso)[1,2-*b*]-spiro[6.6]undecane (*R*)-S-oxide **(13-*R*)**: **FTIR** (ν_{max}/cm^{-1}) 1740 (C=O), 2940 (C-H); 1H NMR: δ_H (500 MHz, $CDCl_3$); 5.23 (dd, 1H, $J_{2,3}$ 9.4 Hz, $J_{3,4}$ 9.4 Hz, H-3), 5.14 (dd, 1H, $J_{3,4}$ 9.4 Hz, $J_{4,5}$ 9.4 Hz, H-4), 4.35 (dd, 1H, $J_{5,6}$ 4.4, $J_{6,6'}$ 12.6 Hz, H-6), 4.22 (d, 1H, $J_{1,2}$ 10.2 Hz, H-1), 4.19 (dd, 1H, $J_{5,6'}$ 2.4, $J_{6,6'}$ 12.6 Hz, H-6'), 3.81 (m, 1H, H-5), 3.72 (dd, 1H, $J_{1,2}$ 10.2 Hz, $J_{2,3}$ 9.4 Hz, H-2), 3.68-3.65 (m, 1H, H-a), 3.54 (d, 1H, $J_{SCHeq,SCHax}$ 12.6 Hz, SCHeq), 3.50-3.46 (m, 1H, H-a'), 2.77 (d, 1H, $J_{SCHeq,SCHax}$ 12.6 Hz, SCHax), 2.08 (s, 3H, C(O)C$\underline{H}_3$), 2.06 (s, 3H, C(O)C$\underline{H}_3$), 2.05 (s, 3H, C(O)C$\underline{H}_3$), 1.58 (m, 6H, H-b, H-b', H-c, H-c', H-d, H-d'); ^{13}C NMR: δ_C (75 MHz, $CDCl_3$); 171.2, 170.7, 169.9 ($\underline{C}(O)CH_3$), 98.6 (C-e), 95.9 (C-1), 77.4 (C-

3), 73.3 (C-5), 67.9 (C-4), 67.5 (C-2), 61.9 (C-6), 60.2 (SCH_2), 33.9 (C-b), 24.5 (C-d), 24.5 ($C(O)CH_3$), 21.1 ($C(O)CH_3$), 21.1 ($C(O)CH_3$), 18.7 (C-c), 60.2 (C-a);); **HRESIMS:** Found $[M+Na]^+$ 457.1139 $C_{18}H_{26}NaO_{10}S$ requires 457.1144; (6S)-1,7-dioxa-(3,4,6-tri-O-acetyl-1,2-dideoxy-β-D-glucopyranoso)-4-thia-[1,2-b]-spiro[6.6]undecane (*S*)-S-oxide **(13-*S*)**: **mp:** 194.0-196.1°C (from hexane-EtOAc): 1H NMR: δ_H (500 MHz, $CDCl_3$); 5.36 (dd, 1H, $J_{2,3}$ 9.6 Hz, $J_{3,4}$ 9.6 Hz, H-3), 5.16 (dd, 1H, $J_{3,4}$ 9.0 Hz, $J_{4,5}$ 9.0 Hz, H-4), 4.27 (dd, 1H, $J_{5,6}$ 6.4, $J_{6,6'}$ 13.7 Hz, H-6), 4.09 (d, 1H, $J_{1,2}$ 9.9 Hz, H-1), 4.27 (dd, 1H, $J_{5,6'}$ 6.4, $J_{6,6'}$ 13.7 Hz, H-6'), 3.89 (m, 1H, H-5), 4.72 (dd, 1H, $J_{1,2}$ 9.9 Hz, $J_{2,3}$ 9.6 Hz, H-2), 3.68-3.65 (m, 1H, H-a), 3.50-3.46 (m, 1H, H-a'), 3.26 (d, 1H, $J_{SCHeq,SCHax}$ 14.9 Hz, SCHeq), 2.44 (d, 1H, $J_{SCHeq,SCHax}$ 14.9 Hz, SCHax), 2.08 (s, 3H, $C(O)CH_3$), 2.06 (s, 3H, $C(O)CH_3$), 2.05 (s, 3H, $C(O)CH_3$), 1.80 (m, 6H, H-b, H-b', H-c, H-c', H-d, H-d').

3.7 (6*S*)-1,7-Dioxa-(3,4,6-tri-*O*-benzyl-1,2-dideoxy-β-D-glucopyranoso)-4-thia-[1,2-*b*]-spiro[6.6]undecane (*R*)-*S*-oxide (14-*R*)

NaH (60% dispersion in oil, 107 mg, 4.45 mmol) was added in portions to a stirred solution of (6*S*)-1,7-dioxa-(1,2-dideoxy-β-D-glucopyranoso)-4-thia-[1,2-*b*]-spiro[6.6]undecane **(10)** (420 mg, 1.48 mmol) in *N,N*-dimethylformamide (10 mL) at 0°C, and stirred for 30 min while H_2(g) evolved. Benzyl bromide (616 μL, 5.18 mmol) was then added dropwise at 0 °C, and the reaction mixture stirred for a further 3 h. The reaction mixture was quenched with MeOH (10 mL) and concentrated. The crude solid was then redissolved in CH_2Cl_2 (20 mL) and washed with aq. NaCl (2 x 20 mL), dried ($MgSO_4$) and concentrated to leave a crude benzylated spiroketal **12**. The crude benzylated spiroketal **12** was redissolved in CH_2Cl_2 (5 mL) and cooled to −78 °C, and a solution of *m*-CPBA (350 mg, 1.73 mmol) in CH_2Cl_2 (5 mL) was slowly added over 5 min. The reaction mixture was stirred for 30 min at −78 °C and then quenched with aq. $NaHCO_3$ (10 mL) and diluted with CH_2Cl_2 (10 mL). The organic

phase was then separated, washed with aq. NaCl (2 x 10 mL), dried ($MgSO_4$) and concentrated to leave a crude colourless solid. The crude solid was purified by flash column chromatography (silica; 1:1 (v/v) hexane-EtOAc) to afford (6*S*)-1,7-dioxa-(3,4,6-tri-O-benzyl-1,2-dideoxy-β-D-glucopyranoso)-4-thia-[1,2-*b*]-spiro[6.6]undecane (*R*)-S-oxide **(14-*R*)** (243 mg, 30%, dr: 99:1) as a colourless syrup; R_F 0.19 (1:1 (v/v) EtOAc-hexane); $\mathbf{[\alpha]_D^{21}}$ +1.3 (*c* 1.5, $CHCl_3$); **FTIR** (ν_{max}/cm^{-1}) 2944 (C-H), 1099, 1051 (S=O); 1H NMR: $\mathbf{\delta_H}$ (500 MHz, $CDCl_3$); 7.35-7.14 (m, 15H, ArH), 5.02 (d, 1H, *J* 10.3 Hz, OC<u>H</u>$_2$Ph), 4.82 (d, 2H, *J* 10.3 Hz, *J* 10.3 Hz, OC<u>H</u>$_2$Ph), 4.66 (d, 1H, *J* 12.0 Hz, OC<u>H</u>$_2$Ph), 4.58 (d, 1H, *J* 10.3 Hz, OC<u>H</u>$_2$Ph), 4.52 (d, 1H, *J* 12.0 Hz, OC<u>H</u>$_2$Ph), 4.11 (d, 1H, $J_{1,2}$ 9.4 Hz, H-1), 3.87-3.83 (m, 3H, H-3, H-a, H-a'), 3.78-3.71 (m, 2H, H-5, H-6), 3.66 (dd, 1H, $J_{1,2}$ 9.4 Hz, $J_{2,3}$ 9.4 Hz, H-2), 3.60 (dd, 1H, $J_{5,6'}$ 5.1 Hz, $J_{6,6'}$ 11.1 Hz, H-6'), 3.57-3.53 (m, 2H, H-4, SCHeq), 2.75 (d, 1H, $J_{SCHeq,SCHax}$ 12.0 Hz, SCH_{ax}), 1.83-1.76 (m, 2H, H-d, H-c), 1.68-1.58 (m, 3H, H-b, H-c', H-d'), 1.47 (d, 1H, *J* 12.8 Hz, H-b'); ^{13}C NMR: $\mathbf{\delta_C}$ (75 MHz, $CDCl_3$); 138.2, 137.9, 128.5, 128.4, 128.4, 128.0, 127.9, 127.8, 127.7 (ArC), 98.1 (C-e), 95.8 (C-1), 83.6 (C-2), 80.3 (C-4), 76.6 (C-3), 75.8, 75.5, 73.7 (OCH_2Ph), 70.3 (C-5), 67.9 (C-a), 60.9 (C-6), 59.6 (SCH_2), 33.8 (C-d), 24.0 (C-b), 18.4 (C-c); **HRESIMS:** Found $[M+Na]^+$ 601.2238, $C_{33}H_{38}O_7SNa$ requires 601.2230.

3.8 General procedure for glycosylation reactions with oxathiane spiroketal-*S*-oxides

Tf_2O (1.1 equiv.) was added to a solution of oxathiane spiroketal-*S*-oxide **13-*R*** or **14-*R*** (1 equiv.), 1,3,5-trimethoxybenzene (1.1 equiv.) or 1,3-dimethoxybenzene (1.1 equiv.), DIPEA (1.2 equiv.) and 4 Å molecular sieves in CH_2Cl_2 or $C_2H_4Cl_2$ (initial donor concentration 0.26 M), cooled to −30 ºC. The reaction mixture was warmed to room temperature over 10 min and then DIPEA (1.3 equiv.), followed by a solution of the glycosyl acceptor (1.5 equiv.) in CH_2Cl_2 or $C_2H_4Cl_2$ (final donor concentration 0.11 M) was added and the reaction mixture

was stirred for 24 h at 37 °C or 50 °C (when using donor **13-*R***), or room temperature (when using donor **14-*R***). The reaction mixture was then diluted with CH_2Cl_2 (5 mL), washed with 1M HCl (2 x 5 mL), aq. $NaHCO_3$ (2 x 5 mL) and aq. NaCl (2 x 5 mL), dried ($MgSO_4$) and concentrated to afford the crude product. The crude product was then redissolved in CH_2Cl_2 (1 mL) and cat. $BF_3{\cdot}OEt_2$ and MeOH (1.5 equiv.) were added, after stirring for 30 min at room temperature the reaction mixture was diluted with CH_2Cl_2 (5 mL) washed with aq. NaCl (5 mL), dried ($MgSO_4$) and concentrated to afford the crude O-2 unprotected glycoside. The crude glycoside was purified by size exclusion chormatography (Sephadex LH-20 resin; eluted with MeOH (50 mL/h)) to afford the desired O-2 unprotected glycoside.

3.8.1 From 2,4,6-trimethoxyphenyl (TMP) oxathiane spiroketal sulfonium ions (21):

3,4,6-Tri-*O*-acetyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (20)[19]

24 h at 50 °C = 3,4,6-tri-O-acetyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose **(20)** as a colourless oil (49 mg, 38%, α:β 93:7); R_F 0.25 (1:1 (v/v) hexane-EtOAc). Analytical data was identical to that reported previously.

24 h at 37 °C = 3,4,6-tri-O-acetyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose **(20)** as a colourless oil (18 mg, 60%, α:β 93:7) (Table 1, entry 1). Analytical data was identical to that reported previously.

3.8.2 Isopropyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside (28) (Table 1, entry 2)

Isopropyl 3,4,6-tri-O-acetyl-α-D-glucopyranoside **(28)** as a colourless syrup (22 mg, 61%, α:β 98:2); R_F 0.38 (1:1 (v/v) hexane-EtOAc); $[\alpha]_D^{21}$ −56 (*c* 0.2, $CHCl_3$); **FTIR** (ν_{max}/cm^{-1}): 1738 (C=O); 1H NMR: δ_H (500 MHz, $CDCl_3$); 5.21 (dd, 1H, $J_{2,3}$ 9.7 Hz, $J_{3,4}$ 9.7 Hz, H-3), 5.01 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 5.00 (dd, 1H, $J_{4,5}$ 9.9 Hz, $J_{3,4}$ 9.7 Hz, H-4), 4.26 (dd, 1H, $J_{6,6'}$ 12.4 Hz,

$J_{5,6}$ 4.9 Hz, H-6), 4.09 (dd, 1H, $J_{6,6'}$ 12.4 Hz, $J_{5,6'}$ 2.0 Hz, H-6'), 4.05-4.03 (m, 2H, H-5, C<u>H</u>$(CH_3)_2$), 3.65 (ddd, 1H, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 9.7 Hz, $J_{2,OH\text{-}2}$ 11.5 Hz, H-2), 2.08 (s, 3H, C(O)CH_3), 2.03 (s, 3H, C(O)CH_3), 2.03 (s, 3H, C(O)CH_3), 1.96 (d, 1H, $J_{2,2\text{-}OH}$ 11.5 Hz, 2-OH), 1.22 (s, 3H, CH_3), 1.20 (s, 3H, CH_3); ^{13}C NMR: $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$); 170.0 (<u>C</u>(O)CH_3), 97.3 (C-1), 74.0, 72.1, 71.1, 68.5 (C-2, C-3, C-4, C-5), 62.5 (C-6), 30.1 (<u>C</u>H$(CH_3)_2$), 23.6, 22.3 (CH_3); **HRESIMS:** Found $[M+Na]^+$ 371.1323, $C_{15}H_{24}O_9Na$ requires 373.1313.

3.8.3 3,4,6-Tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (27)[19](Table 1, entry 3)

3,4,6-Tri-O-benzyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose **(27)** as a colourless syrup (28 mg, 58%, α:β 92:8); R_F 0.77 (1:1 (v/v) hexane-EtOAc). Analytical data was identical to that reported previously.

3.8.4 Isopropyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (29)[19] (Table 1, entry 4)

Isopropyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside **(29)** as a colourless oil (27 mg, 57%, α:β 94:6); R_F 0.70 (1:1 (v/v) hexane-EtOAc). Analytical data was identical to that reported previously.

3.8.5 From 2,4-dimethoxyphenyl (DMP) oxathiane spiroketal sulfonium ion (28): 3,4,6-Tri-*O*-acetyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (20)[19] (Table 1, entry 5)

3,4,6-Tri-O-acetyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose **(20)** as a colourless oil (19 mg, 50%, α:β 86:14). Analytical data was identical to that reported previously.

3.8.6 Isopropyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside (28) (Table 1, entry 6)

Isopropyl 3,4,6-tri-O-acetyl-α-D-glucopyranoside **(28)** as a colourless syrup (13 mg, 52%, α:β 95:5). For analytical data see **3.8.2**.

3.9 3,4,6-Tri-*O*-acetyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (20)[19] (Table 1, entry 9)

Tf_2O (20 μL, 0.117 mmol) was added to a solution of 2-methoxy-2-(*S*)-phenyl-(3,4,6-tri-O-acetyl-1,2-dideoxy-β-D-glucopyranoso)[1,2-e]-1,4-oxathiane (*R*)-S-oxide **(25-*R*)** (50 mg, 0.106 mmol), DTBMP (87 mg, 0.425 mmol), 1,3-dimethoxybenzene (15 μL, 0.117 mmol) and 4 Å molecular sieves (50 mg) in $C_2H_4Cl_2$ (400 μL) at −30 °C. The reaction mixture was warmed to −10 °C over 10 min, then a solution of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose **(19)** (69 mg, 0.265 mmol) in $C_2H_4Cl_2$ (100 μL) was added. The reaction mixture was then heated at 50 ºC for 2 h, allowed to cool and diluted with CH_2Cl_2 (10 mL), washed with 1M HCl (3 x 10 mL), aq. $NaHCO_3$ (2 x 10 mL) and aq. NaCl (2 x 10 mL) and concentrated to afford a crude oil. The crude oil was dissolved in DCM (1 mL), cat. $BF_3{\cdot}OEt_2$ and MeOH (0.163 mmol) was added, after stirring for 30 min at room temperature. the reaction mixture was diluted with CH_2Cl_2 (5 mL) washed with aq. NaCl (5 mL), dried ($MgSO_4$) and concentrated to afford a crude yellow oil. The crude oil was purified by size exclusion chormatography (Sephadex LH-20 resin; eluted with MeOH (50 mL/h)) to afford 3,4,6-tri-O-acetyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose **(20)** as a colourless oil (36 mg, 62%, α:β > 98:2). Analytical data was identical to that reported previously.

3.10 X-ray crystallography

CCDC ID: 805132 contains the supplementary crystallographic data for this paper. Copies of this information may be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (fax: +44-1223-336033, or via: http://www.ccdc.cam.ac.uk/products/csd/request/).

Measurements were carried out at 150 K on a Bruker-Nonius Apex X8 diffractometer equipped with an Apex II CCD detector and using graphite monochromated Mo-Kα radiation from a FR591 rotating anode generator. The structure was solved by direct methods and refined using SHELXL-97. Compound 13-*S* crystallises in the chiral space group C2. All non-hydrogen atoms were refined anisotropically. Most hydrogen atoms could be located in a difference Fourier map but, following refinement, their positions were unstable. In the final stages of the refinement, they were placed in calculated positions and refined using a riding model. C-H distances: CH_3, 0.98 Å; CH_2, 0.99 Å; CH, 1.00 Å. All Uiso(H) values were constrained to be 1.2 times (1.5 for methyl) Ueq of the parent atom. Anomalous dispersion effects were sufficient to determine the absolute configuration since the Flack parameter refined to 0.07(14). There is a high positive residual density of 1.45 e $Å^{-3}$ at a distance of 1.28 Å from S1. This is in the approximate position of the S1 lone pair. If this peak is modelled as an oxygen atom then the S1-O distance is 1.333 Å and the oxygen atom has an ellipsoid with an unreasonably large axis. The electron density associated with O1 is 5.15 e $Å^{-3}$ and the S1-O distance is 1.436 Å. Thus, the sulfoxide 13-*S* was considered to be the most reasonable model.

Supplementary Information

Supplementary data associated with this article can be found, in the online version, at doi: xxxx.

Acknowledgements

This work was supported by The Royal Society (UF051621/UF090025), EPSRC (EP/G043302/1) and the University of Leeds. WBT is the recipient of a Royal Society University Research Fellowship.

References

(1) Boltje, T. J.; Buskas, T.; Boons, G.-J. *Nature Chem.* **2009**, *1*, 611-622.
(2) Whitfield, D. M.; Douglas, S. P. *Glycoconjugate J.* **1996**, *13*, 5-17.
(3) *Essentials of Glycobiology*; 2nd ed.; Cold Spring Harbor Laboratory Press: Cold spring Harbor, N. Y., 2009.
(4) Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5221-5224.
(5) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734-753.
(6) Wang, Y.; Ye, X.-S.; Zhang, L.-H. *Org. Biomol. Chem.* **2007**, *5*, 2189-2200.
(7) Seeberger, P. H.; Haase, W.-C. *Chem. Rev.* **2000**, *100*, 4349-4394.
(8) Sears, P.; Wong, C.-H. *Science* **2001**, *291*, 2344-2350.
(9) Schmidt, R. R.; Jonke, S.; Liu, K.-g. *ACS Symp. Ser.* **2007**, *960*, 209-236.
(10) Seeberger, P. H. *Chem. Soc. Rev.* **2008**, *37*, 19-28.
(11) Demchenko, A. V. *Curr. Org. Chem.* **2003**, *7*, 35-79.
(12) Demchenko, A. V. *Synlett* **2003**, 1225-1240.
(13) Carmona, A. T.; Moreno-Vargas, A. J.; Robina, I. *Curr. Org. Synth.* **2008**, *5*, 33-60.
(14) Zhu, X.; Schmidt, R. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 1900-1934.
(15) Ishiwata, A.; Lee, Y. J.; Ito, Y. *Org. Biomol. Chem.* **2010**, *8*, 3596-3608.
(16) Kim, J.-H.; Yang, H.; Park, J.; Boons, G.-J. *J. Am. Chem. Soc.* **2005**, *127*, 12090-12097.
(17) Park, J.; Kawatkar, S.; Kim, J.-H.; Boons, G.-J. *Org. Lett.* **2007**, *9*, 1959-1962.
(18) Beaver, M. G.; Billings, S. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2082-2086.
(19) Fascione, M. A.; Adshead, S. J.; Stalford, S. A.; Kilner, C. A.; Leach, A. G.; Turnbull, W. B. *Chem. Commun. (Cambridge)* **2009**, 5841-5843.
(20) Nokami, T.; Shibuya, A.; Manabe, S.; Ito, Y.; Yoshida, J.-I. *Chem. Eur. J.* **2009**, *15*, 2252-2255.
(21) Fascione, M. A.; Turnbull, W. B. *Beilstein J. Org. Chem.* **2010**, *6*, No 19.
(22) Nokami, T.; Nozaki, Y.; Saigusa, Y.; Shibuya, A.; Manabe, S.; Ito, Y.; Yoshida, J.-I. *Org. Lett.* **2011**, *13*, 1544-1547.
(23) Ibatullin, F. M.; Shabalin, K. A.; Janis, J. V.; Shavva, A. G. *Tetrahedron Lett.* **2003**, *44*, 7961-7964.
(24) Tiwari, P.; Agnihotri, G.; Misra, A. K. *J. Carbohydr. Chem.* **2005**, *24*, 723-732.
(25) Lebouc, A.; Delaunay, J.; Riobé, O. *Synthesis* **1979**, 610-613.
(26) Lambert, J. B.; Mixan, C. E.; Johnson, D. H. *J. Am. Chem. Soc.* **1973**, *95*, 4634-4639.
(27) Lambert, J. B.; Featherman, S. I. *Chem. Rev.* **1975**, *75*, 611-625.
(28) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, G.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105-1121.
(29) Ley, S. V.; Priepke, H. W. M.; Warriner, S. L. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2290-2292.
(30) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press, Inc.: Boca Raton, FL., 1995.
(31) Fraser-Reid, B.; Lopez, J. C.; Radhakrishnan, K. V.; Nandakumar, M. V.; Gomez, A. M.; Uriel, C. *J. Chem. Soc., Chem. Commun.* **2002**, *18*, 2104-2105.
(32) Smoot, J. T.; Demchenko, A. V. *J. Org. Chem.* **2008**, *73*, 8838-8850.
(33) Boltje, T. J.; Kim, J.-H.; Park, J.; Boons, G.-J. *Org. Lett.* **2011**, *13*, 284-287.
(34) Beaver, M. G.; Billings, S. B.; Woerpel, K. A. *Eur. J. Org. Chem.* **2008**, 771-781.
(35) Walvoort, M. T. C.; Dinkelaar, J.; van den Bos, L. J.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *Carbohydr. Res.* **2010**, *345*, 1252-1263.

(36) Stalford, S. A.; Kilner, C. A.; Leach, A. G.; Turnbull, W. B. *Org. Biomol. Chem.* **2009**, *7*, 4842-4852.
(37) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc. Trans.* **1915**, *107*, 1080-1106.
(38) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735-1766.
(39) Sinnott, M. L. *Carbohydrate Chemistry and Biochemistry: Structure and Mechanism*; Royal Society of Chemistry: Cambridge, 2007.
(40) Crich, D. *Acc. Chem. Res.* **2010**.
(41) Mydock, L. K.; Demchenko, A. V. *Org. Biomol. Chem.* **2010**, *8*, 497-510.
(42) Markham, G. D.; Bock, C. W. *J. Phys. Chem.* **1993**, *97*, 5562-9.
(43) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; 4th edition ed.; Butterworth-Heinemann, 1996.