## Stereoselective glycosylation using oxathiane glycosyl donors†

Martin A. Fascione,<sup>*a*</sup> Sophie J. Adshead,<sup>*a*</sup> Susanne A. Stalford,<sup>*a*</sup> Colin A. Kilner,<sup>*a*</sup> Andrew G. Leach<sup>*b*</sup> and W. Bruce Turnbull<sup>\**a*</sup>

Received (in Cambridge, UK) 6th July 2009, Accepted 25th August 2009 First published as an Advance Article on the web 7th September 2009 DOI: 10.1039/b913308a

## A bicyclic glycosyl donor is activated as an arylsulfonium ion and used to synthesise $\alpha$ -glycosides with high stereoselectivity.

Carbohydrates form the most abundant class of biological molecules on Earth.<sup>1</sup> They play essential roles in energy storage, as structural materials and for molecular recognition to control processes as diverse as protein folding, fertilisation, inflammation and cancer metastasis.<sup>2</sup> Often synthetic chemistry provides the only source of pure oligosaccharides for biological studies. Both solid phase synthesis<sup>3</sup> and multi-component one-pot solution synthesis<sup>4</sup> can provide rapid access to complex oligosaccharides. However, if several glycosylation reactions are to be performed in sequence without separating the intermediate products, it is essential that each glycosylation reaction is highly stereoselective,<sup>5</sup> or complex mixtures of oligosaccharides will result. While 1,2-trans-glycosides can be formed easily through neighbouring group participation by an ester protecting group adjacent to the anomeric centre (Scheme 1a),<sup>6</sup> stereoselective synthesis of *cis*-1,2-glycosidic



Scheme 1 Strategies for controlling anomeric stereochemistry: (a) ester participating group leads to 1,2-*trans*-glycosides, while (b) non-participating benzyl ether often gives mixtures of  $\alpha$ - and  $\beta$ -glycosides; (c) Boons' 1,2-*cis*- $\alpha$ -directing group forms a bicyclic sulfonium intermediate.

linkages remains a significant challenge.<sup>7</sup> Although the anomeric effect favours the formation of  $\alpha$ -glycosides, in reality, mixtures of  $\alpha$ - and  $\beta$ -glycosides are often obtained when using glycosyl donors bearing non-participating ether protecting groups (Scheme 1b). Therefore, the precise control of anomeric stereochemistry remains a major challenge to be overcome.<sup>8</sup>

Recently Boons *et al.* described a participating group that could give 1,2-*cis*- $\alpha$ -glycosides (scheme 1c).<sup>9</sup> In this method, a chiral auxiliary adjacent to the anomeric carbon intercepts the oxacarbenium ion intermediate to form a sulfonium ion on the  $\beta$ -face of the sugar. The incoming nucleophile is thus directed to react on the lower face to give an  $\alpha$ -glycoside.<sup>10,11</sup> Although this elegant strategy gives excellent stereoselectivity, its implementation demands a significant amount of additional synthetic effort. The chiral auxiliary must first be synthesised with the correct stereochemistry to match the D- or L-configuration of the glycosyl donor. It must then be attached regioselectively to O-2 before finally introducing the anomeric leaving group. Incorporation of the participating group increases the number of protecting group manipulations and thus the length of the synthesis.

In this communication we present a novel class of thioglycoside donors that have an integral  $\alpha$ -directing group (Scheme 2). The oxathiane glycosyl donors are prepared by a concise route involving cyclisation of simple thioglycosides.<sup>12</sup> The stereochemistry of the participating group is thus determined by the absolute configuration of the parent thioglycoside. Activation of the glycosyl donor gives a bicyclic sulfonium ion intermediate which acts as a glycosylating agent with very high stereoselectivity.

A series of oxathiane glycosyl donors was prepared from glucose pentaacetate 1 (Scheme 3). Lewis acid activation of the anomeric acetate in the presence of thiourea provided a  $\beta$ -isothiouronium salt which was treated with Et<sub>3</sub>N and bromide 2 *in situ*.<sup>13</sup> The resulting thioglycoside 3 was de-esterified under Zemplén conditions to give tetraol 4. Upon exposure to acidic MeOH, the ketone cyclised regio- and



Scheme 2 Oxathiane glycosyl donors.

<sup>&</sup>lt;sup>a</sup> School of Chemistry, University of Leeds, Leeds, UK LS2 9JT. E-mail: w.b.turnbull@leeds.ac.uk; Fax: +44 (0)1133436565; rel: +44 (0)1133437438

<sup>&</sup>lt;sup>b</sup> AstraZeneca, Alderley Park, Macclesfield, Cheshire, UK

<sup>†</sup> Electronic supplementary information (ESI) available: Crystal structure of compound **8**, and synthetic procedures. CCDC 733122. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b913308a



Scheme 3 Reagents: (a) (i)  $S = C(NH_2)_2 - BF_3 \cdot OEt_2 - MeCN$ , (ii) 2–Et<sub>3</sub>N (64%); (b) NaOMe-MeOH (99%); (c) TsOH-MeOH (61%); (d) Ac<sub>2</sub>O-C<sub>5</sub>H<sub>5</sub>N (76%); (e) BnBr-NaH-DMF (87%); (f) mCPBA-CH<sub>2</sub>Cl<sub>2</sub> (8 95%, dr 91 : 9; 9 87% dr 96 : 4).

stereoselectively to give methyl ketal 5, in which the less bulky methoxy group adopts an axial position where it can also benefit from anomeric stabilisation. The remaining hydroxyl groups were then protected with acetate groups or benzyl ethers to provide compounds 6 and 7, respectively. Oxidation of these sulfides with *m*CPBA gave the corresponding sulfoxides 8 and 9, predominantly as the equatorial isomers. It was possible to prove the structure of sulfoxide 8 by X-ray crystallography (ESI<sup>†</sup>, Fig. S1).

Many methods have been developed for activating thioglycoside and sulfoxide donors.<sup>14</sup> However, as the leaving group would remain attached to the oligosaccharide following glycosylation, we decided to focus first on methods that would introduce an alkyl or aryl sulfide leaving group. Although alkylation can be used to activate strained bicyclic thioglycosides,<sup>15</sup> we found that methylation of donor 7 led to a surprisingly unreactive sulfonium ion.<sup>16</sup> The arylation of sulfides can be achieved with hypervalent iodonium reagents at high temperature,<sup>17</sup> but we anticipated that milder conditions might prove more suitable for a stereoselective glycosylation reaction. Therefore, we have adopted a novel strategy to activate the glycosyl donors based on electrophilic aromatic substitution,<sup>18</sup> which exploits the fact that triflyloxysulfonium salt 10 (Fig. 1) is more electrophilic at sulfur than at the anomeric carbon.

Oxathiane-S-oxide **8** (Fig. 1) was activated with triflic anhydride at 243 K in the presence of trimethoxybenzene. The <sup>1</sup>H NMR spectrum displayed the typical down-field shift of H-1 that is associated with the formation of cyclic glycosyl sulfonium ions.<sup>9,11</sup> Furthermore, H-1 maintained an 8 Hz coupling constant that was consistent with  $\beta$ -configured ion **11**. Concomitantly, the aromatic proton signal split in two and the aryl-methoxy group signal split in three. As the sample was warmed up to 278 K, both the aromatic signals and two of the methoxy signals coalesced and sharpened indicating the aryl group was starting to rotate more rapidly. Analysis of the NMR line-shapes above and below the coalescence temperature provided a value for the barrier to rotation of *ca*. 13 kcal mol<sup>-1</sup>. Density functional theory calculations (B3LYP/6-31+G\*) also gave an activation energy of



Fig. 1 <sup>1</sup>H NMR spectra (500 MHz,  $CDCl_3$ ) of (a) a mixture of sulfoxide 8 and 1,3,5-trimethoxybenzene. Addition of triflic anhydride at 243 K gave (b) sulfonium ion 11 which was gradually warmed (c)–(d) to 278 K.

13 kcal  $mol^{-1}$  for any group rotation (see ESI<sup>†</sup>). Therefore, the any sulfonium ion is the dominant species present in the reaction mixture at these temperatures.

Sulfoxide donors I (Table 1) were activated with triflic anhydride as before, and allowed to react with trimethoxybenzene to give sulfonium ions II.<sup>19</sup> A range of alcohols were glycosylated in good to excellent yields, and with essentially complete  $\alpha$ -stereoselectivity (Table 1).

It proved convenient to isolate the disaccharides as the 2-hydroxy derivatives III (Table 1), because the acyclic methyl ketal O-2-protecting group was occasionally lost on work-up. Therefore, the crude product mixture was treated with BF<sub>3</sub>·OEt<sub>2</sub> and MeOH in CH<sub>2</sub>Cl<sub>2</sub> prior to isolation of the product by column chromatography. While the benzylprotected glycosyl donors worked well with all acceptors tested, the less reactive acetyl-protected donors occasionally gave a poorer yield of the target glycoside (e.g., entry 3). In this case, MeOH was released from the acyclic protecting group during the glycosylation reaction, thus providing a competing nucleophile for  $\alpha$ -glycosylation. As no methyl glycoside formed prior to addition of the acceptor alcohol, we can rule out the possibility of intramolecular glycosylation, or cleavage of the methyl ketal from the oxathiane-sulfonium ion. Galactosyl oxathiane donors 12 and 13 also proved to be effective glycosylating agents (entries 7-8). C-Glycosylation of trimethoxybenzene predominated when 2-O-benzyl glycosyl sulfoxide donors were subjected to the same reaction 5

Table 1 Glycosylation reactions with oxathiane sulfoxide donors

$$\frac{\begin{pmatrix} 0 & 0 & 0 \\ 0 &$$

3 Aco 
$$OAc$$
  $OMe$   $BnO$   $BnO$   $OMe$   $44 > 98:2$   
8 Ph OMe

$$4 \qquad \begin{array}{c} BnO \\ BnO \\ g \\ g \\ g \\ Ph \end{array} \xrightarrow{OBn O Me}_{BnO \\ BnO \\ BnO \\ BnO \\ BnO \\ BnO \\ OMe \end{array} \xrightarrow{OH}_{BnO \\ OMe} 72 \qquad >98:2$$

-OBn

$$6 \qquad \begin{array}{c} \mathsf{BnO} & \mathsf{OBn} & \mathsf{OMe} \\ \mathsf{BnO} & \mathsf{OBn} & \mathsf{OMe} \\ \mathsf{g} & \mathsf{Ph} \\ \mathsf{g} & \mathsf{Ph} \\ \end{array} \qquad \begin{array}{c} \mathsf{BnO} & \mathsf{OBn} \\ \mathsf{g} & \mathsf{OBn} \\ \mathsf{g} & \mathsf{Ghom} \\ \mathsf{ghom$$

7 
$$AcO OAc OMe OF SO OF$$

<sup>*a*</sup> Unless stated otherwise, the sulfoxide was treated with 1.1 equiv. Tf<sub>2</sub>O, 2.2 equiv. 1,3,5-trimethoxybenzene, and 1.2 equiv. DIPEA at -30 °C. <sup>*b*</sup> The temp was raised to -10 °C, and a further 6 equiv. DIPEA and 2.5 equiv. ROH were added, before stirring at 50 °C for 18 h. <sup>*c*</sup> The crude reaction mixture was treated with a catalytic amount of BF<sub>3</sub>·OEt<sub>2</sub> to cleave the O-2 protecting group. <sup>*d*</sup> Isolated yields. <sup>*e*</sup> No β-isomers were detected by NMR spectroscopy of the crude reaction mixture prior to protecting group cleavage. <sup>*f*</sup> 7.2 equiv. DTBMP was used in place of DIPEA. <sup>*g*</sup> 5 equiv.

conditions. Therefore, it was not possible to conduct a directly comparable control experiment to test the importance of the oxathiane auxiliary group. Nevertheless, our results show substantial improvements in stereoselectivity when compared to literature examples with perbenzylated donors (see ESI<sup>†</sup>).

In conclusion, oxathiane glycosyl donors provide practical and highly stereoselective access to 1,2-*cis*- $\alpha$ -glycosides. A We thank the Royal Society and AstraZeneca for financial support. WBT is a Royal Society University Research Fellow.

## Notes and references

- 1 D. Peters, Biotechnol. J., 2006, 1, 806.
- 2 Essentials of Glycobiology, Cold Spring Harbor Laboratory Press, Cold spring Harbor, NY, 2009.
- 3 P. H. Seeberger, *Chem. Soc. Rev.*, 2008, **37**, 19; R. R. Schmidt, S. Jonke and K.-G. Liu, *ACS Symp. Ser.*, 2007, **960**, 209.
- 4 Y. Wang, X.-S. Ye and L.-H. Zhang, Org. Biomol. Chem., 2007, 5, 2189.
- 5 D. B. Werz, B. Castagner and P. H. Seeberger, J. Am. Chem. Soc., 2007, 129, 2770.
- 6 R. U. Lemieux, Advances in Carbohydrate Chemistry, 1954, 9, 1.
- 7 A. V. Demchenko, *Synlett*, 2003, 1225; A. V. Demchenko, *Curr. Org. Chem.*, 2003, **7**, 35; A. T. Carmona, A. J. Moreno-Vargas and I. Robina, *Curr. Org. Synth.*, 2008, **5**, 81.
- 8 Strategies for achieving stereoselective 1,2-cis glycosylation include: displacement of β-leaving groups; R. U. Lemieux, K. B. Hendriks, R. V. Stick and K. James, J. Am. Chem. Soc., 1975, 97, 4056; D. Crich and W. L. Cai, J. Org. Chem., 1999, 64, 4926; solvent optimisation; A. Ishiwata, Y. Munemura and Y. Ito, Tetrahedron, 2008, 64, 92; conformational constraints; R. E. J. N. Litjens, L. J. Van den Bos, J. D. C. Codée, H. S. Overkleeft and G. A. Van der Marel, Carbohydr. Res., 2007, 342, 419; S. Manabe, K. Ishii and Y. Ito, Trends Glycosci. Glycotechnol., 2008, 20, 187; J. D. M. Olsson, L. Eriksson, M. Lahmann and S. Oscarson, J. Org. Chem., 2008, 73, 7181; Y. Geng, L.-H. Zhang and X.-S. Ye, Chem. Commun., 2008, 597; remote group effects; A. Imamura, H. Ando, H. Ishida and M. Kiso, Heterocycles, 2008, 76, 883; D. Crich, T. S. Hu and F. Cai, J. Org. Chem., 2008, 73, 8942; O. J. Plante, E. R. Palmacci, R. B. Andrade and P. H. Seeberger, J. Am. Chem. Soc., 2001, 123, 9545; intramolecular aglycone delivery; A. J. Fairbanks, Synlett, 2003, 1945; Y. J. Lee, A. Ishiwata and Y. Ito, J. Am. Chem. Soc., 2008, 130, 6330; I. Cumpstey, Carbohvdr. Res., 2008, 343, 1553.
- 9 J. H. Kim, H. Yang, J. Park and G. J. Boons, J. Am. Chem. Soc., 2005, 127, 12090.
- 10 It is generally assumed that the sulfonium ion undergoes an  $S_N^{2-1}$  like reaction with the acceptor alcohol; however, it has been noted (see ref. 11) that the presence of a sulfonium ion intermediate in the reaction mixture does not exclude the possibility of an  $S_N^{1-1}$  type mechanism leading to the products.
- 11 M. G. Beaver, S. B. Billings and K. A. Woerpel, J. Am. Chem. Soc., 2008, **130**, 2082; S. A. Stalford, C. A. Kilner, A. G. Leach and W. B. Turnbull, Org. Biomol. Chem., 2009, DOI: 10.1039/b914417j.
- 12 Report of a natural gluco-oxathiane; B.-M. Feng, L.-X. Duan, L. Tang, Y.-H. Pei and Y.-Q. Wang, *Heterocycles*, 2008, 75, 173.
- 13 P. Tiwari, G. Agnihotri and A. K. Misra, J. Carbohydr. Chem., 2005, 24, 723.
- 14 K. P. R. Kartha and R. A. Field, *Carbohydrates*, 2003, 121; D. Crich and L. B. L. Lim, *Org. React.* (N. Y.), 2004, 64, 115.
- 15 I. Lundt and B. Skelbaek-Pedersen, Acta Chem. Scand., Ser. B, 1981, 35b, 637.
- 16 A thiazepane glycosyl donor has been reported to be unreactive to NIS–AgOTf and DMTST, and to give no isolable products on activation with methyl triflate; R. Slaettegard, D. W. Gammon and S. Oscarson, *Carbohydr. Res.*, 2007, 342, 1943.
- 17 A. Krief, W. Dumont and M. Robert, Synlett, 2006, 484.
- 18 Previous synthesis of sulfonium ions by electrophilic aromatic substitution: E. Schaumann and S. Scheiblich, *Tetrahedron Lett.*, 1985, 26, 5269.
- 19 If the alcohol was added before the arylsulfonium salt had formed, only reduction to the parent oxathiane resulted. Therefore the reaction does not proceed via the Kahne glycosyl sulfoxide method; D. Kahne, S. Walker, Y. Cheng and D. Vanengen, J. Am. Chem. Soc., 1989, 111, 6881; B. W. Skelton, R. V. Stick, D. M. G. Tilbrook, A. H. White and S. J. Williams, Aust. J. Chem., 2000, 53, 389.