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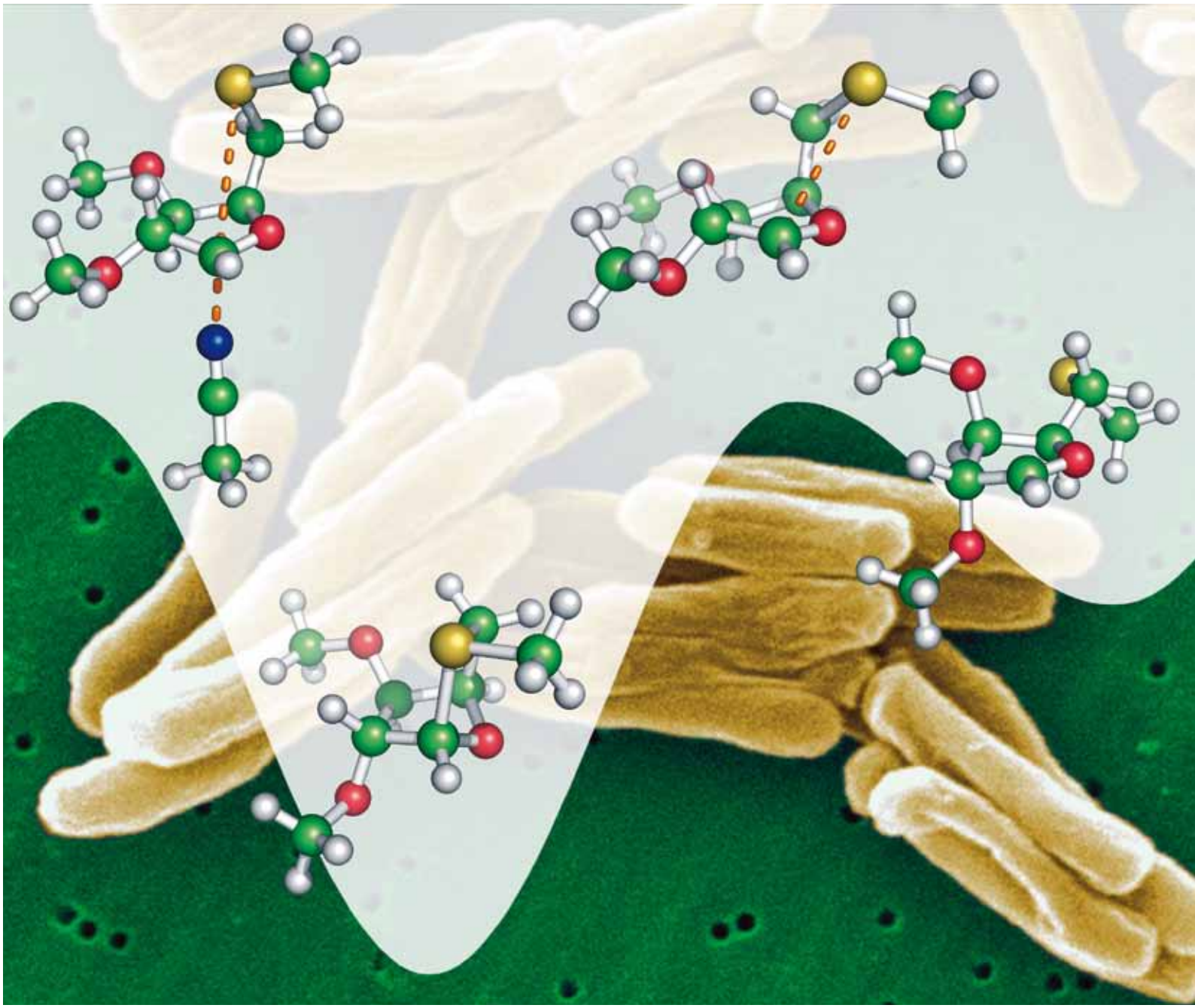

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FULL PAPER

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Neighbouring group participation *vs.* addition to oxacarbenium ions: studies on the synthesis of mycobacterial oligosaccharides†

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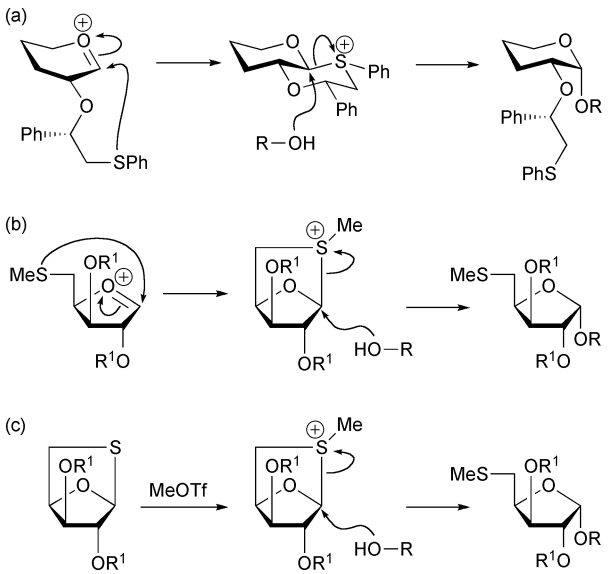
Neighbouring group participation is frequently used to control the stereoselectivity of chemical reactions. Herein, we investigate the use of neighbouring group participation for the synthesis of disaccharides incorporating the mycobacterial sugar methylthioxylose. A bicyclic thioglycoside was activated by methylation to generate a methylsulfonium group that would act both as the anomeric leaving group, and also provide the methylsulfide group in the product. Model reactions indicated that the bicyclic intermediate would also act as a participating group to direct the acceptor alcohol to the lower α-face of the sugar. While the key sulfonium intermediate could be detected in the reaction mixture, the glycosylation reaction proceeded with moderate stereoselectivity, apparently *via* an S_N1-type mechanism. Density functional theory calculations were used to compare our methylthioxylose sulfonium ion with a *trans*-decalin-like sulfonium ion described by Boons and co-workers to be an α-directing participating group (*J. Am. Chem. Soc*. 2005, **127**, 12090). Our studies show that even where a bicyclic sulfonium ion can be detected in the reaction mixture, caution should be applied before invoking it as an intermediate on the reaction pathway.

Introduction

Neighbouring group participation has long been used to control the stereochemistry of chemical reactions.[1] Nowhere is this concept more important than in the stereoselective synthesis of carbohydrates.[2-7] For example, glycosyl donors bearing an ester group adjacent to the anomeric carbon can provide 1,2-*trans*-β-glycosides with very high stereoselectivity.[3] Amino,[4] imido,[5] iodo,[6] and thio[7] groups at this position can also control stereochemistry effectively. More recently, the neighbouring group participation strategy has been extended to the synthesis of 1,2-*cis*-α-glycosides.[8,9] Boons and co-workers described an elegant strategy to make 1,2-*cis*-α-glycosides using a chiral auxiliary that contains a sulfide group (Scheme 1a).[9] Upon activation of the glycosyl donor, the oxacarbenium ion is trapped by the auxiliary group to form a *trans*-decalin-like sulfonium ion. The incoming nucleophile is thus directed to approach from the lower face of the sugar to yield a 1,2-*cis* glycoside. Functional groups at positions more distant from the anomeric centre can also influence stereoselectivity,[10,11] but the role of neighbouring group participation in these processes remains under debate.[12,13] Herein we report studies toward applying neighbouring group participation to the synthesis of mycobacterial oligosaccharides, and we use density functional theory (DFT) calculations to rationalise the scope and limitations of neighbouring group participation for stereoselective α-glycosylation.



Scheme 1 (a) Boons' 1,2-*cis* α-directing participating group; (b) NGP with a 5-methylthio substituent; (c) a bicyclic thioglycoside which is pre-organised for NGP.

Methylthioxylofuranose (MTX) is a natural thiosugar that is attached to the lipoarabinomannan polysaccharide from *Mycobacterium tuberculosis*.[14-16] The MTX-α-1,4-mannose disaccharide has been shown to inhibit production of the cytokine TNF-α,[16] and may also play a role in protecting *M. tuberculosis* from oxidative stress.[17] In the course of preparing some MTX-mannosyl oligosaccharides for biological studies, we wondered if a glycosyl donor containing the methylthio group could be

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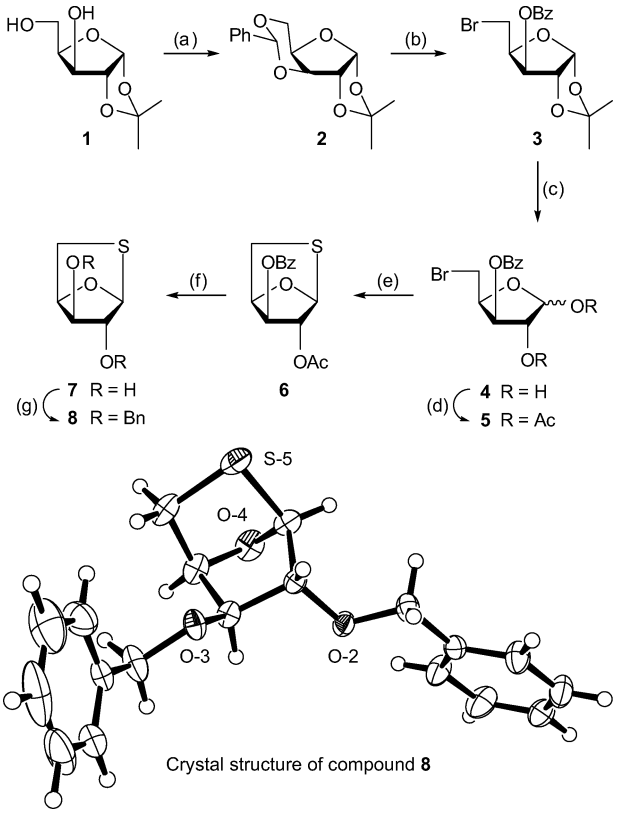
† Electronic supplementary information (ESI) available: Crystal structure details for compound **8**; coordinates for DFT structures; ^{1}H NMR spectra for novel compounds. CCDC reference number 735329. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b914417j

used to control the stereochemistry of the glycosylation reaction *via* neighbouring group participation (Scheme 1b). An oxacarbenium ion intermediate could be trapped intramolecularly by the methylthio group to give a 2.2.1 bicyclic sulfonium ion. If this intermediate was to undergo an S_N2 reaction with the acceptor alcohol, it would yield the desired α-glycoside. We reasoned that pre-organising the MTX glycosyl donor in the desired bicyclic configuration could maximise the probability of it reacting by neighbouring group participation. For example, activation of a bicyclic thioglycoside by methylation (Scheme 1c),[18] would lead directly to the desired sulfonium ion intermediate. As both the activating methyl group and the sulfide leaving group would form part of the target molecule, such a glycosylation reaction could also be considered to be atom efficient.[19]

Results and discussion

Glycosyl donor **8** was prepared from isopropylidene xylofuranose **1** in seven steps and 28% overall yield (Scheme 2). Benzylidene acetal **2** was prepared and subjected to oxidative bromination according to the method of Hollenberg *et al.*,[20] to provide bromide **3** in 83% yield. Hydrolysis of the acetonide gave hemi-acetal **4** which was acetylated to yield triester **5** in 68% yield over two steps. The bridging sulfur atom was introduced by activating the anomeric acetate group with TMSOTf in the presence of thiourea, followed by treatment with Et_3N to give the anhydrosugar **6** in 85% yield from **5**. Much lower yields of the product were obtained when $BF_3{\cdot}OEt_2$ was used to activate the anomeric acetate group. The ester protecting groups were removed under Zemplén conditions, and the resulting diol **7** was reprotected with benzyl ethers to yield glycosyl donor **8**. Single crystals of compound **8** were grown from aqueous MeOH and subjected to X-ray analysis to prove that the bicyclic ring system had been formed (Scheme 2).



Scheme 2 *Reagents*: (a) $PhCH(OMe)_2$/CSA/DMF (84%); (b) NBS/$BaCO_3$/CCl_4 (83%); (c) 60% aq. AcOH/H_2SO_4 (68%); (d) Ac_2O/pyr (100%); (e) (i) $CS(NH_2)_2$/TMSOTf/CH_3CN (ii) Et_3N (85%); (f) NaOMe/MeOH (77%); (g) NaH/DMF/BnBr (91%).

Methylation of sulfide **8** with MeOTf in CD_2Cl_2, or with either Me_3OBF_4 or MeOTf in nitromethane-d_3, led to a single product (Fig. 1). The ^1H NMR spectrum displayed a new methyl signal at 2.87 ppm and substantial downfield shifts for most of the xylose protons, in particular H-1[9,13] and the pro-*S* H-5.[21] Greater deshielding of the pro-*S* H-5 (compared to the pro-*R* H-5) would be consistent with the formation of the exo-(*S*)-sulfonium ion **9**. Density functional theory (DFT) calculations also indicated that the exo-(*S*)-isomer would be lower in energy than endo-(*R*)-isomer (2.8 kcal mol^{-1} in the gas phase; 3.0 kcal mol^{-1} with CH_2Cl_2 solvation); therefore, we would assign the *S*-configuration to sulfonium ion **9**. The spectrum in nitromethane-d_3 remained unchanged even after six days at room temperature indicating that the sulfonium ion was stable in a polar aprotic solvent.

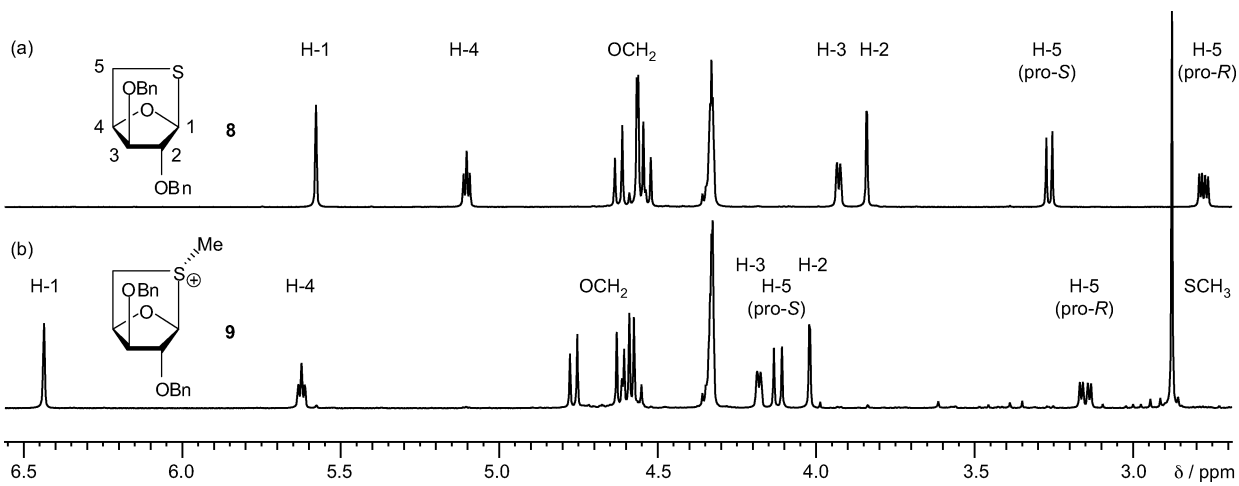


Fig. 1 ^1H NMR spectra (500 MHz, CD_3NO_2, 300 K) for (a) sulfide **8** and (b) methylsulfonium ion **9**·BF_4.

Methylation of sulfide **8** (87 mM) by Me_3OBF_4 in CD_3CN initially led to the same product as observed previously (Fig. 2a). However, over the course of a few hours at room temperature, the NMR spectrum changed dramatically, indicating that the sulfonium ion had been converted to a new species which was stable for several days (Fig. 2b-c). The signal for H-2 moved 1.7 ppm downfield, while that for H-4 moved 1.3 ppm upfield, suggesting that the compound had undergone a substantial change in conformation. Upfield shifts for H-5, H-5′ and the methyl signal were consistent with opening of the sulfonium ring to give a sulfide group.[15] The multiplicity of the anomeric proton signal changed from singlet to doublet ($J_{1,2}$ = 5.9 Hz) which is typical for an α-configured xylofuranosyl product.[15] The high chemical shift for H-1 indicated that there was still a strongly electron-withdrawing group at the anomeric centre which we presume to be the nitrilium ion **10** (Fig. 2d; R = Bn).[22]

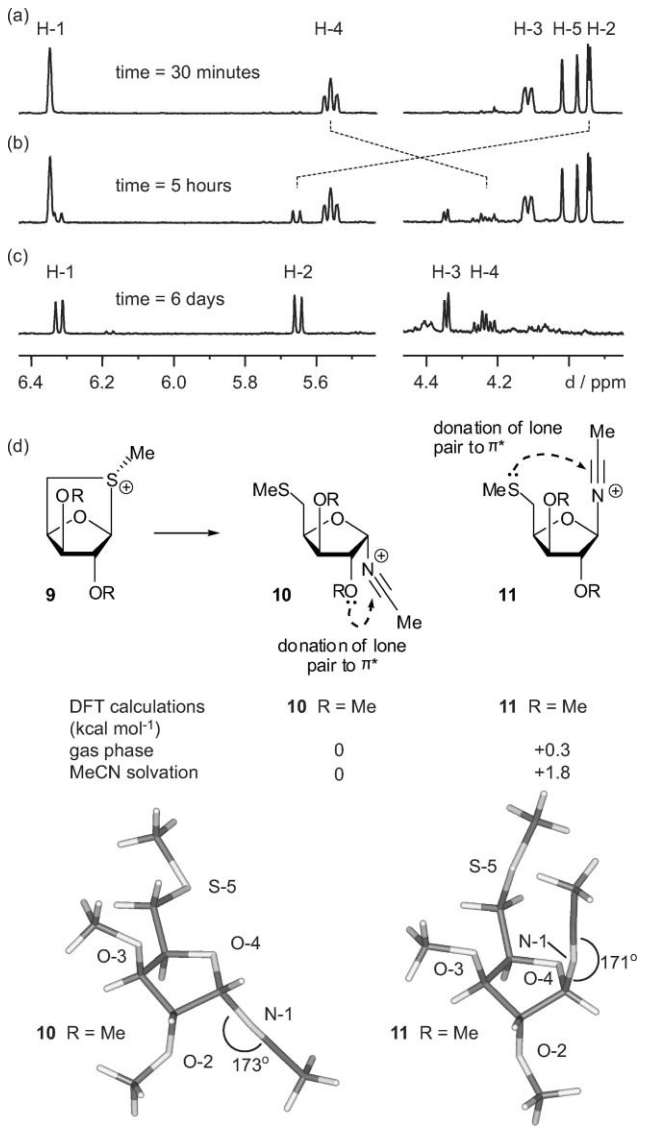


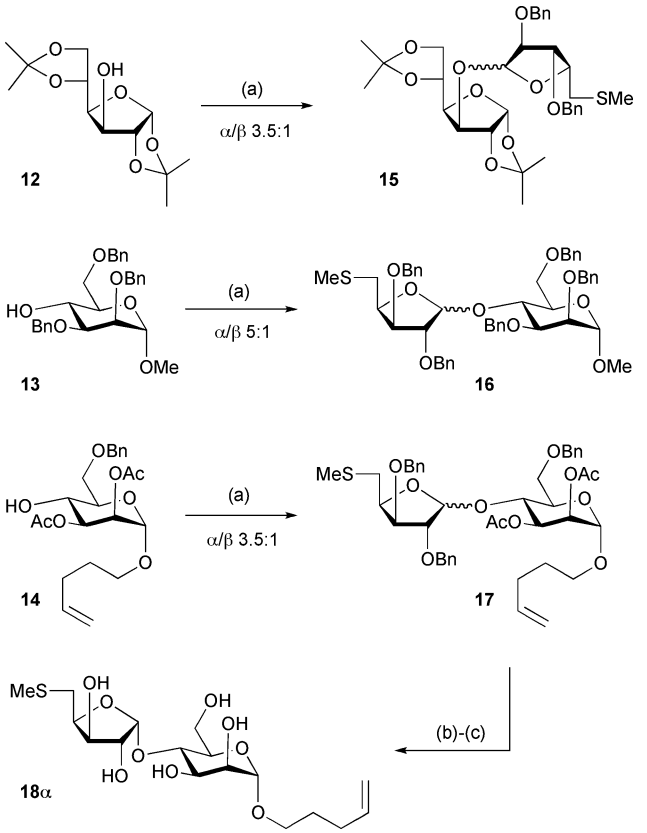
Fig. 2 ^{1}H NMR spectra (300 MHz, CD_3CN, 300 K) showing the conversion of methylsulfonium ion **9** (87 mM; R = Bn) into putative nitrilium adduct **10** (R = Bn) at different times after mixing sulfide **8** and Me_3OBF_4: (a) 30 minutes, (b) 5 hours and (c) 6 days. (d) structures for the two possible acetonitrile adducts (**10**, **11**; R = Me) with relative energies from DFT calculations (B3LYP/6-31+G*).

DFT calculations predict that the α-configured nitrilium ion **10** (R = Me) would be favoured in the gas phase by 0.3 kcal mol^{-1}, as O-2 can stabilise the adjacent cation. The C-N≡C angle is 173° in the lowest energy conformation suggesting that the stabilisation is not only electrostatic in nature, but there is also a hybridisation change which would be consistent with orbital overlap between O-2 and the nitrilium π* orbital. The lowest energy conformation of the β-configured nitrilium is similarly stabilized by interaction between the electron poor π system of the nitrilium group and the sulfur atom at C-5. This transannular interaction reduces the surface available for solvation and hence, when solvation is added to the model, the energy difference between the α- and β-isomers is increased to 1.8 kcal mol^{-1}. Repeating the reaction in a 1:1 mixture of CD_3CN and CD_3NO_2 led to the same intermediate, but the reaction rate was reduced by approximately a factor of two. As nitromethane and acetonitrile have essentially the same dielectric constant,[23] the change in rate may be attributed solely to the change in nucleophile concentration. Therefore, our data are consistent with an S_N2 mechanism. Alternatively, it is possible that the reaction could be stepwise if trapping the oxacarbenium ion by MeCN were slower than cyclisation onto the sulfur atom. The exclusive formation of the α-configured nitrilium ion may be under kinetic control, as has been reported for pyranosyl nitrilium ions,[24] although this configuration would also be expected were the reaction to run to equilibrium. As nitrilium intermediates are usually β-directing in glycosylation reactions,[25] all subsequent experiments were performed in dichloromethane.

Donor **8** was treated with methyl triflate in the presence of the hindered base 2,6-di-*t*-butyl-4-methylpyridine (DTBMP), and the reaction was monitored by TLC until all of the starting material had been consumed. Addition of secondary alcohol acceptors **12-14** led to the formation of disaccharides **15-17**, respectively, in modest to good yields (Scheme 3). In contrast to the reaction with acetonitrile, mixtures of α- and β-glycosides were obtained in all cases. Lowering the reaction temperature gave little improvement to the anomeric ratio. If both the S_N1 and S_N2 pathways were to be in operation, one would expect an increase in flux down the S_N2 pathway upon increasing the concentration of the reactants. However, neither the product ratio, nor the reaction rate changed significantly on increasing the concentration of the reactants; therefore, the glycosylation reaction appears to proceed exclusively through an S_N1 mechanism. The acetyl groups were removed from disaccharide **17** under Zemplén conditions before Birch reduction of the benzyl ethers. The resulting disaccharides **18α** and **18β** were readily separated by flash chromatography, to provide an α-linked disaccharide that is suitable for further elaboration into glycoconjugates.

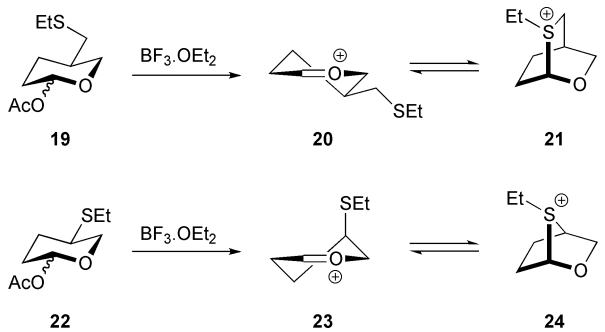
The synthetic strategy outlined above provides a convenient route to MTX-oligosaccharides, in which the methylthio substituent is introduced during the glycosylation step. However, the stereoselectivity of the glycosylation reaction was lower than anticipated, in particular when compared to the highly stereoselective ring opening of sulfonium ion **9** by acetonitrile.

So, why is the Boons system (Scheme 1a) more stereoselective than other bicyclic sulfonium ions, *e.g.*, our MTX system (Scheme 1c)? Woerpel and co-workers recently observed that the presence of a glycosyl sulfonium ion in a reaction mixture does



Scheme 3 *Reagents*: (a) donor **9**/DTBMP/CH_2Cl_2 (64% **15**; 48% **16**; 47% **17**); (b) NaOMe/MeOH (69%); (c) Na/NH_3 (l)/THF (46% **18α**; 17% **18β**).

not necessarily mean that it is an intermediate on the reaction pathway.[13] For example, sulfonium ion **21** (Scheme 4) could be detected by NMR spectroscopy; however, *C*-glycosylation products from this intermediate were consistent with an S_N1 mechanism that proceeded through oxacarbenium ion **20**. They also reported that donor **22** failed to react *via* neighbouring group participation. In this case, the authors were unable to detect the formation of the bicyclic intermediate **24** in the reaction mixture, even though modelling had predicted that the sulfonium ion should be 5-6 kcal mol^{-1} more stable than the oxacarbenium ion intermediate **23**. It is unclear if the lack of stereocontrol in this example results from a failure to form the sulfonium ion under the reaction conditions, or a Curtin-Hammett kinetic scenario proposed for the analogous 2.2.2. bicyclic system **21**.[13]



Scheme 4 Model systems studied by Woerpel and co-workers (ref. 13).

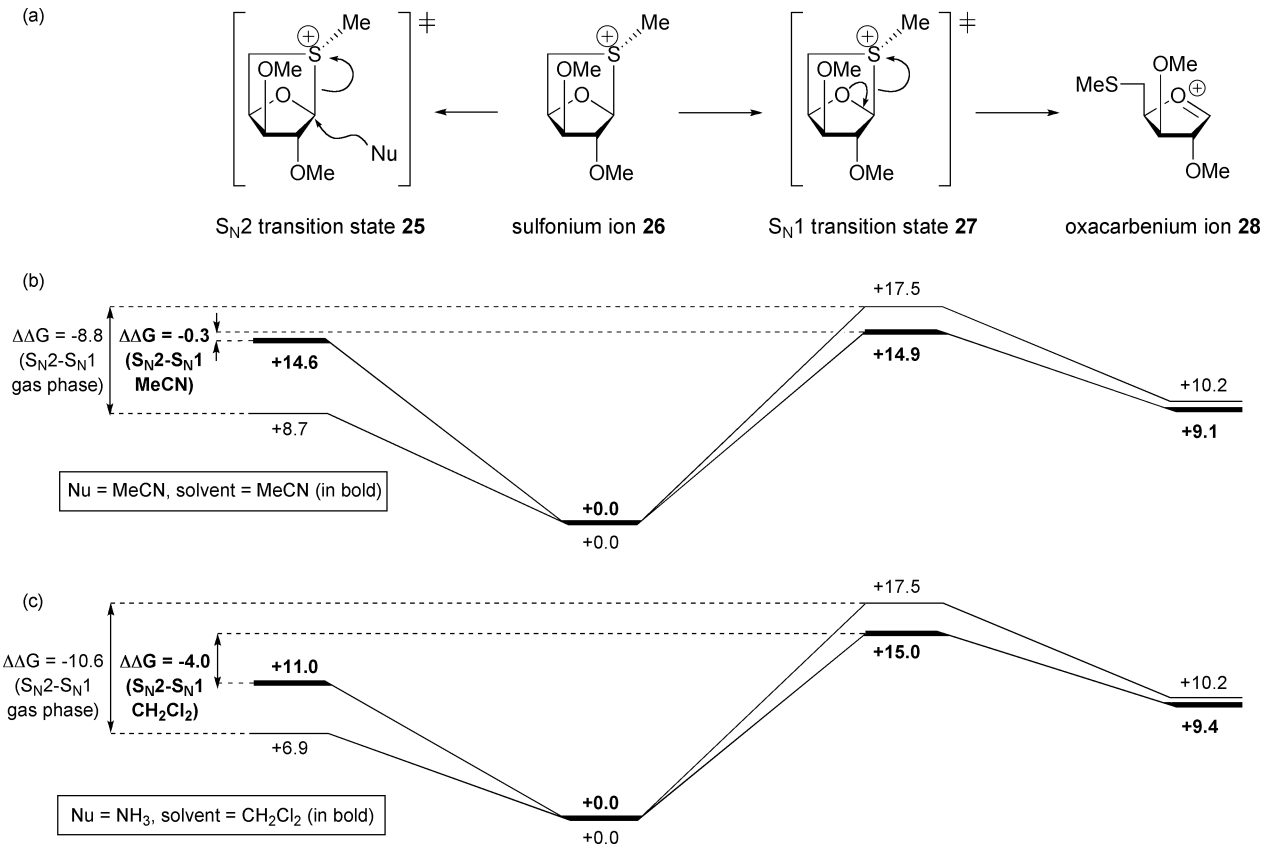
To address the question of stereoselectivity for our MTX donor and the Boons' system, we undertook DFT calculations on two model sulfonium ions **26** and **30** (Schemes 5 and 6). In order to reduce computational time, simplified structures were used in which benzyl protecting groups, the equatorial substituent on the oxathiane ring and primary carbon on the glucopyranosyl ring were all abbreviated to methyl groups. A correction for the energy of solvation was applied to each structure using parameters for MeCN or CH_2Cl_2, as appropriate. Generally, trapping of cations by nucleophiles is barrierless in the gas phase but in this intramolecular case, there is a conformational barrier between the sulfonium ion and the oxacarbenium ion. The S_N1 transition states are therefore those for an internal rotation. In general, the gap between S_N1 and S_N2 activation energies was reduced after inclusion of the correction for solvation; presumably, the S_N2 transition state benefited less from the solvation term than either the sulfonium ions or S_N1 transition states.

Calculations for the reaction of xylofuranosyl sulfonium ion **26** with MeCN indicated only a small preference for the S_N2 pathway (Scheme 5b; $\Delta\Delta G^{\ddagger}$ = -0.3 kcal mol^{-1} for S_N2 *vs.* S_N1; MeCN solvation parameters), suggesting that both mechanisms would be in operation under standard state conditions (*i.e.*, 1 M concentration). Therefore, we conclude that the S_N2 process observed when using MeCN as the solvent arises from the very high concentration of the nucleophile (*ca.* 19 M) that would increase the S_N2 reaction rate relative to that for the S_N1 mechanism.

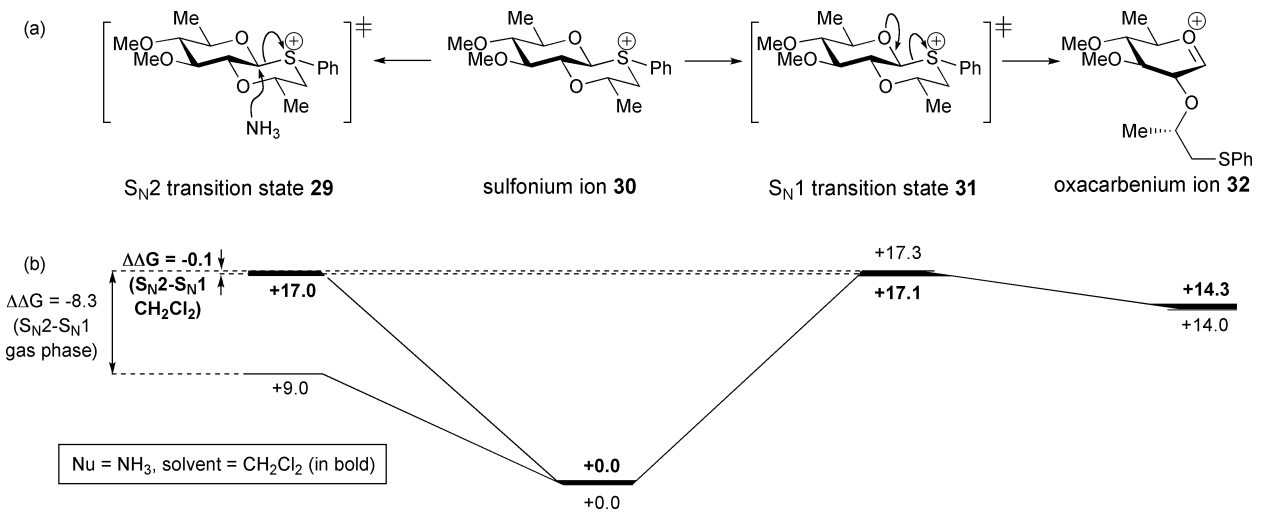
Ammonia was chosen as a model nucleophile for comparison of the Boons-type sulfonium ion **30** and our MTX model **26**. Ammonia has higher symmetry and basicity than an alcohol which remove the issues of (1) the directionality of the O-H bond vector as it approaches the glycosyl donor, and (2) the precise point at which the proton is removed during the reaction.[26] As the structures do not directly reproduce the reactions studied *in vitro*, it is important that one should apply caution when directly comparing the S_N1 and S_N2 activation barriers for a given glycosyl donor. Nevertheless, as the same nucleophile is used for reaction with ions **26** and **30**, general trends arising from the calculations should still be valid.

The S_N2 reaction of MTX sulfonium ion **26** (Scheme 5c) with ammonia is predicted to have a lower activation barrier than for reaction with MeCN (Scheme 5b). This observation is consistent with the greater nucleophilicity of ammonia. Both gas phase and solution calculations also suggest that sulfonium ion **26** should undergo a more facile S_N2 reaction than the Boons-type ion **30**. In this case, the lower activation energy for MTX ion **26** probably arises from release of ring strain in the S_N2 transition state,[13] and also a more optimal angle between the nucleophile, C-1 and sulfide leaving group (168° *vs.* 136° for transition states **25** and **29**, respectively). The difference between these activation energies is amplified further when solvation effects are added to the model.

The calculations also predict that the MTX sulfonium ion **26** would have a lower S_N1 activation barrier than *trans*-decalin sulfonium ion **30** in CH_2Cl_2 solution (Schemes 5c and 6b). Although one might attribute this difference to releasing ring strain in bicycle **26**, the gas phase energies for S_N1 transition states **27** and **31** are essentially the same. It is likely that the effect of ring strain is offset by the greater intrinsic stability of an alkyl sulfonium ion relative to an aryl sulfonium ion.[13] The more



Scheme 5 (a) Possible reaction pathways for sulfonium ion **26**. Energy profiles for reaction of sulfonium ion **26** with (b) MeCN or (c) NH_3 were determined using density functional theory calculations performed at the B3LYP/6-31+G* level of theory. $\Delta G^{\ddagger}$ and ΔG° values are quoted in kcal mol^{-1} relative to the lowest energy conformation of sulfonium ion **26**. Values for gas phase calculations are given in normal text, while values corrected for solvation effects are given in bold. Solvation correction employed the integral equation formalism polarisable continuum model (IEFPCM) with united atom Kohn–Sham (UAKS) radii.



Scheme 6 (a) Possible reaction pathways for sulfonium ion **30**. (b) Energy profiles for reaction of sulfonium ion **30** with NH_3 were determined as described in Scheme 5. Values for gas phase calculations are given in normal text, while values corrected for solvation effects (CH_2Cl_2) are given in bold.

facile S$_N$1 pathway calculated for ion **26** arises only from different effects of solvation when compared to the same reaction of ion **30**.

When taken together, our calculations would predict that MTX sulfonium ion **26** should be *more likely to react by an S$_N$2 mechanism* than the Boons-type ion **30** ($\Delta\Delta G^{\ddagger}$(S$_N$2 – S$_N$1) = –4.0 *vs.* –0.3 kcal mol^{-1} for ions **26** and **30**, respectively, in CH_2Cl_2 solution). However, neither the stereochemistry of the products nor the reaction kinetics observed experimentally are consistent with an S$_N$2 pathway (vide supra).

One additional factor that has not been considered thus far is the relative energy of the sulfonium ion reactants and their oxacarbenium ions **28** and **32**. The smaller this gap, the larger the concentration of oxacarbenium ion, and the more significant the contribution of an S_N1 reaction that would presumably be less stereoselective. The MTX oxacarbenium ions **28** (Fig. 3) are closer in free energy to the cyclised sulfonium ion **26** by about 5 kcal mol^{-1} in CH_2Cl_2 solution when compared to sulfonium ion **30** and oxacarbenium ion **32**. It may be that these systems operate at the borderline between S_N1 and S_N2 mechanisms and that small changes in the equilibrium concentration of the oxacarbenium relative to the sulfonium, or very high concentrations of the trapping nucleophile (*e.g.*, 19 M MeCN), can tip the balance one way or the other.

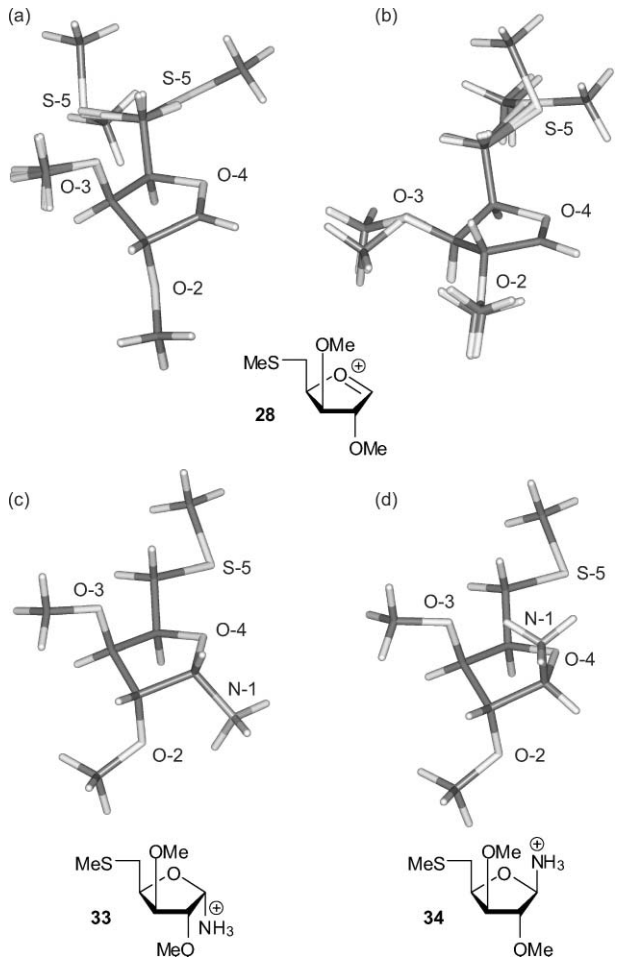
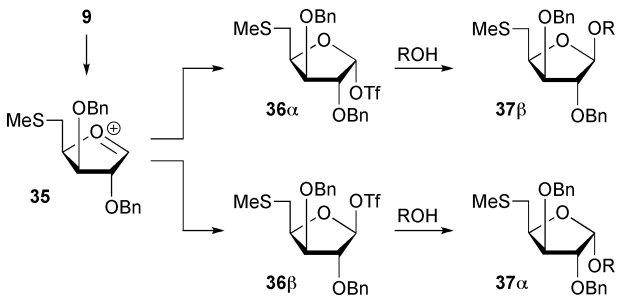


Fig. 3 Overlay of the five lowest energy conformations of oxacarbenium ion **28** having O-2 and O-3 substituents in (a) pseudoaxial and (b) pseudoequatorial positions. (c) Lowest energy conformation of α-ammonium adduct **33**. (d) Lowest energy conformation of β-ammonium adduct **34**.

Our experimental data would imply that MTX donor **9** reacts by an S_N1 mechanism *via* the oxacarbenium ion. MTX oxacarbenium ion **28** can adopt two distinct families of conformations in which O-2 and O-3 both adopt pseudoaxial or pseudoequatorial positions (Fig. 3a and b). The conformations with pseudoaxial methoxy substituents are on average favoured by 3 kcal mol^{-1} in the gas phase and 1.5 kcal mol^{-1} in CH_2Cl_2. This result is in line with Woerpel's observation that a furanosyl oxacarbenium ion conformation should be dictated by placing O-3 in a pseudoaxial position.[27]

While it is difficult to model the intermolecular addition of nucleophiles to oxacarbenium ions, covalent adducts of the nucleophile and cation may give some insight into the stereoselectivity of the addition step.[26] The lowest energy α- and β-ammonium adducts **33** and **34**, respectively, also adopted ring conformations in which the O-2 and O-3 substituents were in pseudoaxial conformations (Fig. 3c and d). The β-anomer was favoured by 1.2 kcal mol^{-1} in the gas phase and 0.6 kcal mol^{-1} in CH_2Cl_2. If we can assume that the ammonium ion adducts reflect the structures and relative energies of the transition states, then the model would suggest that the β-configured products would be favoured. This observation is in qualitative agreement with Woerpel's experimental observations that a nucleophile should add *cis* to a pseudoaxial O-3 group and *trans* to a pseudoaxial O-2 group on a furanosyl oxacarbenium ion.[27] However, we observe α-selectivity in all of our glycosylation reactions (Scheme 3).

One possible explanation is that the MTX donor reacts through neither the sulfonium ion **9**, nor the oxacarbenium ion **35** (Scheme 7). Instead, ion **35** is initially trapped as a glycosyl triflate **36α/β**,[11,28,29] and the stereoselectivity is governed by the relative stabilities (or reactivities) of the two triflates.[28] Alternatively, the α-glycoside **37α** could be formed principally from the β-triflate **36β**, while the β-glycoside **37β** could be formed from either the α-triflate **36α** or the oxacarbenium ion **35**. The major species present in the reaction mixture was always the sulfonium ion, and it was not possible to detect the presence of a glycosyl triflate. Therefore, if triflates **36α/β** are intermediates in the reaction, they always remain minor components of the reaction mixture.



Scheme 7 Putative glycosyl triflate intermediates.

Conclusions

We have demonstrated that a bicyclic thioglycoside provides a concise route to MTX oligosaccharides. NMR experiments in acetonitrile and DFT calculations would have predicted that bicyclic sulfonium ion **9** should react *via* an S_N2 mechanism to yield α-glycosides with high stereoselectivity. However, the glycosylation results demonstrate that such seductive predictions can not always be trusted. The observed stereoselectivity is more consistent with an S_N1 mechanism involving rate-limiting formation of an oxacarbenium ion which forms a contact ion pair with its triflate counterion. Our results support the observations of Woerpel[13] that the presence of a glycosyl sulfonium ion in the reaction mixture is not sufficient information to conclude that it will react *via* an S_N2 mechanism to yield the products.[39] The Boons

participating group (Scheme 1a)[9] is much more stereoselective than the bridged bicyclic system reported here; however, we note that our DFT calculations predict that the Boons-type sulfonium ion **30** is less likely to react *via* an S_N2 mechanism than MTX sulfonium ion **26**. Indeed, we have observed that *trans*-decalin sulfonium ions that are even more stable than Boons' compound do not necessarily lead to α-glycosides; these studies will be reported in due course.

Experimental section

All solvents were dried prior to use, according to standard methods.[30] Otherwise, commercial reagents were used without further purification. All concentrations and evaporations were performed *in vacuo* unless stated. Analytical TLC was performed on silica gel 60-F_{254} (Merck) with detection by fluorescence and/or by charring following immersion in 5% H_2SO_4/MeOH. Flash chromatography was performed with silica gel 60 (Merck). Melting points were determined on a Reichert hot stage apparatus. 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}. ^{1}H and ^{13}C NMR spectra were recorded at 300 K on either a Bruker Avance 500 spectrometer or a Bruker DPX 300 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were referenced using tetramethylsilane or residual solvent signals as internal standards.[31] Signals were assigned using a combination of COSY and HMQC experiments, and where appropriate NOESY experiments. The following abbreviations were used to explain the signal multiplicities or characteristics: s, singlet; bs, broad singlet; d, doublet; dd, double doublet; ddd, double double doublet; dt, doublet of triplets; m, multiplet; t, triplet. For disaccharides **15-18** the MTX is designated residue "a" and the glucosyl/mannosyl residue is designated ring "b". Mass spectra were acquired on a Micromass LCT-KA111 electrospray mass spectrometer, or Bruker MicroTOF electrospray mass spectrometer. Infra-red spectra were recorded on a Perkin Elmer Spectrum One FT-IR Spectrometer. Elemental analyses were performed by the School of Chemistry microanalysis service using a Carlo Erba 1108 Elemental Analyzer.

3-*O*-Benzoyl-5-bromo-5-deoxy-D-xylofuranose (4)

Sulfuric acid (100 μL) was added to a solution of bromide **3**[20] (1.0 g, 2.80 mmol) and 60% v/v aq. acetic acid (10 mL). The solution was heated at 70 °C for 2 hours, before cooling to room temp. The mixture was neutralised with sat. aq. $NaHCO_3$ solution and extracted with EtOAc (100 mL). The organic extracts were washed with sat. aq. NaCl solution (2 × 100 mL), dried (Na_2SO_4), filtered and evaporated to give an orange oil, which was purified by flash chromatography (silica gel; Hex-EtOAc, 3:2) to give *3-O-benzoyl-5-bromo-5-deoxy-D-xylofuranose* (**4**) (605 mg, 68%) as a colourless amorphous solid, α-β 81:19 (Found: C, 45.7; H, 4.3. $C_{12}H_{13}O_5Br$ requires C, 45.5; H 4.1%); ν_{max}/cm^{-1} 3425 (OH), 1718 (C=O); δ_H (500 MHz; $CDCl_3$); α-anomer 8.05-7.47 (5H, m, *Ph*CO), 5.61 (1H, dd, $J_{1,OH}$ 6.1, $J_{1,2}$ 4.3, H-1), 5.44 (1H, dd, $J_{3,4}$ 4.8, $J_{2,3}$ 2.8, H-3), 4.80 (1H, ddd, $J_{4,5}$ 6.9, $J_{4,5'}$ 6.5, $J_{3,4}$ 4.8, H-4), 4.38 (1H, ddd, $J_{2,OH}$ 4.6, $J_{1,2}$ 4.3, $J_{2,3}$ 2.8, H-2), 3.85 (1H, d, $J_{1,OH}$ 6.1, OH-1), 3.57 (1H, dd, $J_{5,5'}$ 10.4, $J_{4,5}$ 6.9, H-5), 3.53 (1H, dd, $J_{5,5'}$ 10.4, $J_{4,5'}$ 6.5, H-5′), 3.37 (1H, d, $J_{2,OH}$ 4.6, OH-2); β-anomer 8.05-7.47 (5H, m, *Ph*CO), 5.42 (1H, dd, $J_{1,OH}$ 5.8, $J_{1,2}$ 0.8, H-1), 5.39 (1H, dd, $J_{3,4}$ 5.1, $J_{2,3}$ 1.7, H-3), 4.78 (1H, ddd, $J_{3,4}$ 5.1, $J_{4,5}$ 2.0, $J_{4,5'}$ 1.8, H-4), 4.37 (1H, ddd, $J_{2,OH}$ 2.75, $J_{2,3}$ 1.7, $J_{1,2}$ 0.8, H-2), 3.69 (1H, d, $J_{4,5}$ 2.0, H-5), 3.67 (1H, d, $J_{4,5'}$ 1.8, H-5′), 3.01 (1H, d, $J_{1,OH}$ 5.8, OH-1), 2.75 (1H, d, $J_{2,OH}$ 3.6, OH-2); δ_C (75 MHz; $CDCl_3$); α-anomer 133.8-128.7 (*Ph*CO), 96.4 (C-1), 79.4 (C-3), 77.3 (C-4), 76.1 (C-2), 28.3 (C-5); β-anomer 133.8-128.7 (*Ph*CO), 103.3 (C-1), 80.7 (C-2), 80.3 (C-4), 78.7 (C-3), 29.3 (C-5); *m/z* (ES); 339.0, 341.0 ([M+Na]$^+$), 655.0, 657.0, 659.0 ([2M+Na]$^+$); Found: [M+Na]$^+$ 338.9842, $C_{12}H_{13}NaO_5Br$ requires 338.9839.

1,2-Di-*O*-acetyl-3-*O*-benzoyl-5-bromo-5-deoxy-D-xylofuranose (5)

Acetic anhydride (10 mL) was added to a stirred solution of *3-O-benzoyl-5-bromo-5-deoxy-D-xylofuranose* (**4**) (0.55 g, 1.73 mmol) in pyridine (10 mL). The reaction was stirred under a nitrogen atmosphere for 1 hour. The reaction mixture was diluted with EtOAc (100 mL) and washed with aq. 1M HCl solution (100 mL), sat. aq. $NaHCO_3$ solution (100 mL) and sat. aq. NaCl solution (100 mL). The organic extracts were dried (Na_2SO_4), filtered and evaporated to give an orange oil, which was purified by flash chromatography (silica gel; Hex-EtOAc, 2:1) giving the *acetylated bromide* **5** (696 mg, 100%) as a colourless syrup; α-β 59:41 (Found: C, 48.0; H, 4.4. $C_{16}H_{17}O_7Br$ requires C, 47.9; H 4.3%); ν_{max}/cm^{-1} 1755 and 1729 (C=O); δ_H (500 MHz; $CDCl_3$); α-anomer 8.08-7.47 (5H, m, *Ph*CO), 6.53 (1H, d, $J_{1,2}$ 4.6, H-1), 5.79 (1H, dd, $J_{3,4}$ 5.9, $J_{2,3}$ 5.0, H-3), 5.51 (1H, dd, $J_{2,3}$ 5.0, $J_{1,2}$ 4.6, H-2), 4.80 (1H, ddd, $J_{4,5}$ 6.3, $J_{4,5'}$ 5.5, $J_{3,4}$ 5.9, H-4), 3.54 (1H, dd, $J_{5,5'}$ 10.8, $J_{4,5}$ 6.3, H-5), 3.45 (1H, dd, $J_{5,5'}$ 10.8, $J_{4,5'}$ 5.5, H-5′), 2.23 (3H, s, *Me*CO), 2.16 (3H, s, *Me*CO); β-anomer 8.08-7.47 (5H, m, *Ph*CO), 6.21 (1H, s, H-1), 5.65 (1H, dd, $J_{3,4}$ 4.8, $J_{2,3}$ 0.9, H-3), 5.31 (1H, d, $J_{2,3}$ 0.9, H-2), 4.81 (1H, m, H-4), 3.59 (1H, s, H-5), 3.58 (1H, d, $J_{4,5'}$ 0.8, H-5′), 2.16 (3H, s, *Me*CO), 2.11 (3H, s, *Me*CO); δ_C (75 MHz; $CDCl_3$); α-anomer 133.9-128.7 (*Ph*CO), 93.3 (C-1), 77.7 (C-4), 76.8 (C-2), 75.9 (C-3), 28.0 (C-5), 20.9 (*Me*CO), 20.4 (*Me*CO); β-anomer 133.9-128.7 (*Ph*CO), 99.1 (C-1), 82.3 (C-4), 79.5 (C-2), 74.9 (C-3), 27.6 (C-5), 22.2 (*Me*CO), 20.7 (*Me*CO); *m/z* (ES); 423.0, 425.0 ([M+Na]$^+$), 823.0, 825.0, 827.0 ([2M+Na]$^+$); Found: [M+Na]$^+$ 423.0048, $C_{16}H_{17}NaO_7Br$ requires 423.0050.

2-*O*-Acetyl-1,4-anhydro-3-*O*-benzoyl-5-deoxy-5-thio-α-D-xylopyranose (6)

Trimethylsilyl trifluoromethanesulfonate (4.16 mL, 23.0 mmol) was added to a solution of diacetate **5** (6.15 g, 15.3 mmol) and thiourea (1.28 g, 16.8 mmol) in acetonitrile (100 mL) and stirred under a nitrogen atmosphere at 80 °C for 1 hour. The reaction mixture was cooled to RT while bubbling nitrogen gas through the solution. Triethylamine (6.41 mL, 46.0 mmol) was added and the solution was stirred for a further hour. The reaction mixture was diluted with EtOAc (250 mL) and washed with sat. aq. NaCl solution (100 mL). The organic extracts were dried (Na_2SO_4), filtered and evaporated to give a brown oil, which was purified by flash chromatography (silica gel; Hex-EtOAc, 3:1) to give the *epithiosugar* **6** (3.82 g, 85%) as a yellow syrup (Found: C, 57.2; H, 4.5. $C_{14}H_{14}SO_5$ requires C, 57.1; H 4.8%); $[\alpha]_D^{26}$ +142.4 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 1731 and 1725 (C=O); δ_H (500 MHz; $CDCl_3$); 8.06-7.46 (5H, m, *Ph*CO), 5.57 (1H, s, H-1), 5.40 (1H, dd, $J_{3,4}$ 5.5, $J_{4,5'}$ 4.3, H-4), 5.16 (1H, dd, $J_{3,4}$ 5.5, $J_{2,3}$ 1.2, H-3), 5.11 (1H, d, $J_{2,3}$

1.2, H-2), 3.11 (1H, d, $J_{5,5'}$ 9.9, H-5), 2.91 (1H, dd, $J_{5,5'}$ 9.9, $J_{4,5'}$ 4.3, H-5′), 2.12 (3H, s, CH_3CO); δ_C (75 MHz; $CDCl_3$); 134.0-128.9 (*Ph*CO), 85.8 (C-1), 82.4 (C-2), 79.4 (C-4), 78.9 (C-3), 30.3 (C-5), 21.1 (CH_3CO); *m/z* (ES); 317.0 ([M+Na]$^+$), 611.1 ([2M+Na]$^+$); Found: [M+Na]$^+$ 317.0450, $C_{14}H_{14}NaSO_5$ requires 317.0454.

1,4-Anhydro-5-deoxy-5-thio-α-D-xylopyranose (7)

Sodium methoxide in MeOH (9.5 mL, 4.76 mmol) was added to a solution of ester-protected epithiosugar **6** (3.5 g, 11.9 mmol) in anhydrous MeOH (35 mL) and stirred under a nitrogen atmosphere for 19 hours. The reaction mixture was neutralized with Amberlite IRC-50 H$^+$ ion exchange resin and diluted with MeOH (50 mL). The solution was filtered and evaporated to give an orange oil, which was purified by flash chromatography (silica gel; DCM-MeOH, 95:5) to give *1,4-anhydro-5-deoxy-5-thio-α-D-xylopyranose* (**7**) (1.359 g, 77%), as a colourless amorphous glass (Found: C, 40.6; H, 5.6. $C_5H_8SO_3$ requires C, 40.5; H 5.4%); $[\alpha]_D^{26}$ −12.3 (*c* 0.4 in MeOH); ν_{max}/cm^{-1} 3367 (OH); δ_H (500 MHz; D_2O); 5.44 (1H, s, H-1), 5.12 (1H, dd, $J_{3,4}$ 5.6, $J_{4,5'}$ 4.7, H-4), 4.04 (1H, d, $J_{3,4}$ 5.6, H-3), 3.94 (1H, s, H-2), 3.22 (1H, d, $J_{5,5'}$ 10.0, H-5), 2.81 (1H, dd, $J_{5,5'}$ 10.0, $J_{4,5'}$ 4.7, H-5′); δ_C (75 MHz; D_2O); 88.1 (C-1), 83.1 (C-2), 81.3 (C-4), 79.9 (C-3), 29.1 (C-5); *m/z* (EI); 148.0 ([M]$^+$); Found: [M]$^+$ 148.0191, $C_5H_8SO_3$ requires 148.0194.

1,4-Anhydro-2,3-di-*O*-benzyl-5-deoxy-5-thio-α-D-xylopyranose (8)

Sodium hydride (60% dispersion in oil, 297 mg, 3.4 mmol) was added to a solution of *1,4-anhydro-5-deoxy-5-thio-α-D-xylopyranose* (**7**) (0.5 g, 7.4 mmol) in DMF (10 mL) at 0 °C, and stirred under a nitrogen atmosphere for 30 minutes. Benzyl bromide (883 μL, 7.4 mmol) was added to the mixture and the reaction was stirred as before, warming to RT for 3 hours. MeOH (10 mL) was added to quench the reaction. The mixture was diluted with EtOAc (100 mL), and washed with sat. aq. NaCl solution (2 × 100 mL). The organic extracts were dried (Na_2SO_4), filtered and evaporated to give a yellow oil, which was purified by flash chromatography (silica gel; Hex-EtOAc, 6:1) to give the *dibenzylated epithiosugar* **8** (1.01 g, 91%) as colourless needles (Found: C, 69.5; H, 6.2. $C_5H_8SO_3$ requires C, 69.5; H 6.1%); m.p. 49-50 °C (from 1:1 H_2O-MeOH); $[\alpha]_D^{26}$ −8.6 (*c* 0.5 in $CHCl_3$); δ_H (500 MHz; $CDCl_3$); 7.37-7.28 (10H, m, *Ph*CH_2), 5.47 (1H, s, H-1), 4.97 (1H, dd, $J_{3,4}$ 5.5, $J_{4,5'}$ 4.5, H-4), 4.57-4.47 (4H, m, PhCH_2), 3.92 (1H, d, $J_{3,4}$ 5.5, H-3), 3.85 (1H, s, H-2), 3.30 (1H, d, $J_{5,5'}$ 9.3, H-5), 2.78 (1H, dd, $J_{5,5'}$ 9.3, $J_{4,5'}$ 4.5, H-5′); δ_C (75 MHz; $CDCl_3$); 128.7-128.0 (*Ph*CH_2), 88.6 (C-2), 86.0 (C-3), 85.6 (C-1), 79.3 (C-4), 73.2 and 71.8 (PhCH_2), 30.1 (C-5); *m/z* (ES); 351.1 ([M+Na]$^+$), 679.2 ([2M+Na]$^+$); Found: [M+Na]$^+$ 351.1035, $C_{19}H_{20}NaSO_3$ requires 351.1025.

Pent-4-enyl 2,3-di-*O*-acetyl-6-*O*-benzyl-α-D-mannopyranoside (14)

Acetic anhydride (25 mL) was added to a solution of *pent-4-enyl 4,6-O-benzylidene-α-D-mannopyranoside*[32] (4.45 g, 13.2 mmol) in pyridine (25 mL) and stirred under a nitrogen atmosphere for 24 hours. The reaction mixture was diluted with EtOAc (250 mL) and washed with aq. 1M HCl solution (2 × 250 mL), sat. aq. $NaHCO_3$ solution (250 mL) and sat. aq. NaCl solution (250 mL). The organic extracts were dried (Na_2SO_4), filtered and evaporated to give an orange oil, which crystallized on standing. Recrystallisation from EtOAc gave *pent-4-enyl 2,3-di-O-acetyl-4,6-O-benzylidene-α-D-mannopyranoside* (1.534 g, 36%) as colourless needles; m.p. 94-95 °C (from EtOAc); $[\alpha]_D^{25}$ +26.0 (*c* 1.1 in $CHCl_3$) (Found: C, 63.1; H, 6.7. $C_{22}H_{28}O_8$ requires C, 62.9; H 6.7%); ν_{max}/cm^{-1} 1750 (C=O), 1641 (C=C); δ_H (500 MHz; $CDCl_3$); 7.47-7.35 (5H, m, *Ph*C), 5.81 (1H, m, CH_2=*CH*), 5.58 (1H, s, PhC*H*), 5.42 (1H, dd, $J_{2,3}$ 3.4, $J_{3,4}$ 10.0, H-3), 5.35 (1H, dd, $J_{1,2}$ 1.3, $J_{2,3}$ 3.4, H-2), 5.07-4.99 (2H, m, CH_2=CH), 4.75 (1H, d, $J_{1,2}$ 1.3, H-1), 4.28 (1H, dd, $J_{5,6}$ 4.6, $J_{6,6'}$ 10.2, H-6), 4.03 (1H, dd, $J_{3,4}$ 10.0, $J_{4,5}$ 9.8, H-4), 3.97 (1H, ddd, $J_{5,6}$ 4.6, $J_{5,6'}$ 10.1, $J_{4,5}$ 9.8, H-5), 3.85 (1H, dd, $J_{5,6'}$ 10.1, $J_{6,6'}$ 10.2, H-6′), 3.72 (1H, m, OCH_2CH_2), 3.44 (1H, m, OCH_2CH_2), 2.17 (3H, s, CH_3CO), 2.12 (2H, m, CH_2CH_2CH), 2.03 (3H, s, CH_3CO), 1.72 (2H, m, OCH_2CH_2); δ_C (125 MHz; $CDCl_3$); 170.1 and 170.0 (CH_3CO), 138.0 (CH_2=*CH*), 129.3, 128.4 and 126.4 (*Ph*C), 115.4 (CH_2=CH), 102.1 (PhC*H*), 98.8 (C-1), 76.4 (C-4), 70.4 (C-2), 68.9 (C-6), 68.5 (C-3), 67.8 (OCH_2CH_2), 64.0 (C-5), 30.3 (CH_2CH_2CH), 28.6 (OCH_2CH_2) 21.1 and 21.0 (CH_3CO); *m/z* (ES); 443.2 ([M+Na]$^+$), 438.2 ([M+NH_4]$^+$), 421.2 ([M+H]$^+$); Found: [M+Na]$^+$ 443.1675, $C_{22}H_{28}NaO_8$ requires 443.1676.

Sodium cyanoborohydride (1.01 g, 16.1 mmol) was added to a solution of *pent-4-enyl 2,3-di-O-acetyl-4,6-O-benzylidene-α-D-mannopyranoside* (0.5 g, 1.2 mmol) and methyl orange (a few crystals) in tetrahydrofuran (10 mL). 1M HCl in ether was added dropwise to the mixture until the colour changed from yellow to pink and the mixture was stirred under a nitrogen atmosphere for 24 hours. The mixture was diluted with EtOAc (100 mL) and washed with sat. aq. $NaHCO_3$ solution (100 mL) and sat. aq. NaCl solution (100 mL). The organic extracts were evaporated to give red oil, which was purified by flash chromatography (silica gel; Hex-EtOAc, 3:2→1:1) giving the *4-hydroxy mannoside* **14** (355 mg, 71%) as a colourless syrup; $[\alpha]_D^{28}$ +30.8 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 3435 (OH), 1746 (C=O), 1641 (C=C); δ_H (500 MHz; $CDCl_3$); 7.36-7.28 (5H, m, *Ph*CH_2), 5.80 (1H, m, *CH*=CH_2), 5.22 (1H, m, H-3), 5.19 (1H, dd, $J_{2,3}$ 3.4, *J* 9.8 H-2), 5.05-4.96 (2H, m, CH=CH_2), 4.77 (1H, s, H-1), 4.62 (2H, m, PhCH_2), 4.02 (1H, m, H-4), 3.85-3.80 (2H, m, H-5 and H-6), 3.75 (1H, m, H-6′), 3.70 (1H, m, OCH_2CH_2), 3.43 (1H, m, OCH_2CH_2), 2.61 (1H, d, $J_{4,OH}$ 3.8, OH-4), 2.12 (3H, s, CH_3CO), 2.12 (2H, m, CH_2CH_2CH), 2.08 (3H, s, CH_3CO), 1.70 (2H, m, OCH_2CH_2); δ_C (75 MHz; $CDCl_3$); 171.0 and 170.3 (Me*CO*), 138.0 (CH_2=*CH*), 128.7-127.8 (*Ph*CH_2), 115.3 (CH_2=CH), 97.9 (C-1), 73.9 (PhCH_2), 72.1 (C-2), 71.0 (C-5), 70.4 (C-6), 70.1 (C-3), 67.7 (C-4), 67.6 (OCH_2CH_2), 30.4 (CH_2CH_2CH), 28.7 (OCH_2CH_2) 21.2 and 21.1 (CH_3CO); *m/z* (ES) 445.2 ([M+Na]$^+$), 867.4 ([2M+Na]$^+$), 440.2 ([M+NH_4]$^+$), 423.2 ([M+H]$^+$); Found: [M+Na]$^+$ 445.1820, $C_{22}H_{30}NaO_8$ requires 445.1833.

3-*O*-(2,3-Di-*O*-benzyl-5-deoxy-5-methylthio-D-xylofuranosyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (15)

Methyl trifluoromethanesulfonate (25.8 μL, 0.23 mmol) was added to a solution of *glycosyl donor* **8** (50 mg, 0.15 mmol), DTBMP (94 mg, 0.46 mmol) and molecular sieves (3Å) in DCM (0.25 mL) and stirred under a nitrogen atmosphere for three hours. *1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose* (79 mg, 0.30 mmol) and molecular sieves (3Å) in DCM (0.25 mL) was added to the reaction mixture and stirred for a further 20 hours. The reaction mixture was filtered through celite, diluted with DCM (25 mL) and washed with sat. aq. NaCl (25 mL). The organic extracts were

dried (Na_2SO_4), filtered and evaporated to give a colourless oil. Purification by flash chromatography (silica gel; Hex-EtOAc 3:1) gave *MTX-disaccharide* **15** (59 mg, 64%) as a colourless syrup; α:β 77:23 (Found: C, 64.0; H, 7.1. $C_{32}H_{42}SO_9$ requires C, 63.8; H 7.0%); δ_H (500 MHz; $CDCl_3$); α-anomer 7.36-7.27 (10H, m, *Ph*CH_2), 5.89 (1H, d, $J_{1b,2b}$ 3.5, H-1b), 5.28 (1H, d, $J_{1a,2a}$ 4.4, H-1a), 4.77-4.46 (4H, m, Ph*CH*$_2$), 4.76 (1H, m, H-2b), 4.38 (1H, m, H-4a), 4.32 (1H, m, H-5b), 4.21 (1H, m, H-3b), 4.19 (1H, dd, $J_{2a,3a}$ 6.3, $J_{3a,4a}$ 5.1, H-3a), 4.11 (1H, dd, $J_{4b,5b}$ 8.6, $J_{3b,4b}$ 2.9, H-4b), 4.02 (3H, m, H-2a, H-6b, H-6b'), 2.81 (1H, dd, $J_{5a,5a'}$ 13.9, $J_{4a,5a}$ 5.0, H-5a), 2.70 (1H, dd, $J_{5a,5a'}$ 13.9, $J_{4a,5a'}$ 7.7, H-5a'), 2.16 (3H, s, *CH*$_3$S), 1.50, 1.42, 1.32, 1.23 (12H, s, *CH*$_3$C); β-anomer 7.36-7.27 (10H, m, *Ph*CH_2), 5.81 (1H, d, $J_{1b,2b}$ 3.7, H-1b) 5.13 (1H, s, H-1a), 4.77-4.46 (4H, m, Ph*CH*$_2$), 4.45 (1H, m, H-4a), 4.39 (1H, m, H-2b), 4.27 (1H, m, H-5b), 4.21 (1H, m, H-3b), 4.11 (1H, m, H-4b), 4.02 (2H, m, H-2a, H-3a), 3.92 (2H, d, $J_{5b,6b}$ 6.1, H-6b, H-6b'), 2.91 (1H, dd, $J_{5a,5a'}$ 13.9, $J_{4a,5a}$ 6.5, H-5a), 2.84 (1H, dd, $J_{5a,5a'}$ 13.9, $J_{4a,5a'}$ 7.3, H-5a'), 2.16 (3H, s, *CH*$_3$S), 1.48, 1.37, 1.30, 1.22 (12H, s, *CH*$_3$C); δ_C (75 MHz; $CDCl_3$); α-anomer 128.7-127.8 (*Ph*CH_2), 112.0, 109.0 (2 × (Me)$_2$*C*O), 105.3 (C-1b), 104.5 (C-1a), 86.0 (C-2a), 84.0 (C-2b), 82.5 (C-3a), 82.2 (C-3b), 81.6 (C-4b), 77.3 (C-4a), 72.5 (C-5b), 72.5, 72.3 (2 × Ph*CH*$_2$), 66.9 (C-6b), 34.3 (C-5a), 27.1-25.5 (2 × (*Me*)$_2$CO); 16.8 (*Me*S); β-anomer 128.7-127.8 (*Ph*CH_2), 112.0, 109.2 (2 × (Me)$_2$*C*O), 105.5 (C-1b), 101.5 (C-1a), 84.0 (C-2a, C-2b), 81.9 (C-3a), 81.8 (C-3b), 81.4 (C-4b), 78.0 (C-4a), 72.6 (C-5b), 72.4 (2 × Ph*CH*$_2$), 67.6 (C-6b), 33.7 (C-5a), 27.0-25.4 (2 × (*Me*)$_2$CO); 16.3 (*Me*S); *m/z* (ES); 625.2 ([M+Na]$^+$); Found: [M+Na]$^+$ 625.2414, $C_{32}H_{42}NaSO_9$ requires 625.2442.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-5-deoxy-5-methylthio-D-xylofuranosyl)-α-D-mannopyranoside (16)[16]

Methyl trifluoromethanesulfonate (77.5 μL, 0.69 mmol) was added to a solution of *glycosyl donor* **8** (150 mg, 0.46 mmol), DTBMP (281.4 mg, 1.37 mmol) and molecular sieves (3Å) in DCM (0.5 mL) and stirred under a nitrogen atmosphere for three hours. *Methyl 2,3,6-tri-O-benzyl-α-D-mannopyranoside*[33] (424.3 mg, 0.92 mmol) and molecular sieves (3Å) in DCM (0.5 mL) was added to the reaction mixture and stirred for a further 25 hours. The reaction mixture was filtered through celite, diluted with DCM (50 mL) and washed with sat. aq. NaCl (50 mL). The organic extracts were dried (Na_2SO_4), filtered and evaporated to give a colourless syrup, which was purified by flash chromatography (silica gel; DCM-EtOAc 39:1→19:1) to give *benzylated MTX-disaccharide* **16** (178 mg, 48%) as colourless syrup; α:β 83:17; δ_H (500 MHz; $CDCl_3$); α-anomer 7.38-7.04 (25H, m, *Ph*CH_2), 5.55 (1H, d, $J_{1a,2a}$ 4.4, H-1a), 4.84 (1H, s, H-1b), 4.75-4.37 (10H, m, Ph*CH*$_2$), 4.05 (2H, m, H-4a, H-4b), 3.96-3.69 (6H, m, H-2a, H-2b, H-3a, H-3b, H-5b, H-6b), 3.39 (3H, s, *CH*$_3$O), 2.66 (1H, dd, $J_{5a,5a'}$ 13.8, $J_{4a,5a}$ 4.7, H-5a), 2.50 (1H, dd, $J_{5a,5a'}$ 13.8, $J_{4a,5a'}$ 7.2, H-5a'), 2.05 (3H, s, *CH*$_3$S); β-anomer 7.38-7.04 (25H, m, *Ph*CH_2), 5.39 (1H, s, H-1a), 4.84 (1H, s, H-1b), 4.75-4.37 (10H, m, Ph*CH*$_2$), 4.24 (1H, m, H-4a), 4.05 (1H, m, H-4b), 3.96-3.69 (6H, m, H-2a, H-2b, H-3a, H-3b, H-5b, H-6b), 3.32 (3H, s, *CH*$_3$O), 2.87 (1H, dd, $J_{5a,5a'}$ 13.5, $J_{4a,5a}$ 7.6, H-5a), 2.70 (1H, dd, $J_{5a,5a'}$ 13.5, $J_{4a,5a'}$ 6.3, H-5a'), 2.07 (3H, s, *CH*$_3$S); δ_C (75 MHz; $CDCl_3$); α-anomer only 128.6-126.9 (*Ph*CH_2), 100.8 (C-1a), 98.6 (C-1b), 82.7-76.9 (C-2a, C-2b, C-3a, C-3b, C-4a, C-4b), 73.3-70.2 (Ph*CH*$_2$, C-5b, C-6b), 54.9 (*CH*$_3$CO), 35.0 (C-5a), 16.8 (*CH*$_3$S); *m/z* (ES); 829.3 ([M+Na]$^+$); Found: [M+Na]$^+$ 829.3413, $C_{48}H_{54}NaSO_9$ requires 829.3381.

Pent-4-enyl 2,3-di-*O*-acetyl-6-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-5-deoxy-5-methylthio-D-xylofuranosyl)-α-D-mannopyranoside (17)

Methyl trifluoromethanesulfonate (129.2 μL, 1.14 mmol) was added to a solution of *glycosyl donor* **8** (250 mg, 0.76 mmol), DTBMP (469 mg, 2.28 mmol) and molecular sieves (3Å) in DCM (1 mL) and stirred under a nitrogen atmosphere for three hours. *Pentenyl mannoside* **14** (804 mg, 1.90 mmol) and molecular sieves (3Å) in DCM (1 mL) were added to the reaction mixture and stirred for a further 24 hours. The reaction mixture was filtered through celite, diluted with DCM (50 mL) and washed with sat. aq. NaCl (50 mL). The organic extracts were dried (Na_2SO_4), filtered and evaporated to give a colourless solid, which was purified by flash chromatography (silica gel; DCM-EtOAc 39:1) to give benzylated *MTX-disaccharide* **17** (274 mg, 47%) as a colourless syrup; α:β 77:23; ν_{max}/cm^{-1} 1750 (C=O), 1640 (C=C), 1599, 1454 (C=C aromatic); δ_H (500 MHz; $CDCl_3$); α-anomer 7.37-7.24 (15H, m, *Ph*CH_2), 5.81 (1H, m, CH_2=*CH*), 5.38 (1H, dd, $J_{3b,4b}$ 9.6, $J_{2b,3b}$ 3.3, H-3b), 5.32 (1H, d, $J_{1a,2a}$ 4.2, H-1a), 5.27 (1H, dd, $J_{2b,3b}$ 3.3, $J_{1b,2b}$ 1.5, H-2b), 4.99 (2H, m, *CH*$_2$=CH), 4.79 (1H, d, $J_{1b,2b}$ 1.5, H-1b), 4.71-4.39 (6H, m, Ph*CH*$_2$), 4.13-4.09 (3H, m, H-3a, H-4a, H-4b), 3.98 (1H, m, H-2a), 3.80-3.69 (3H, m, H-5b, H-6b, H-6b'), 3.68 (1H, m, O*CH*$_2$CH$_2$), 3.45 (1H, m, O*CH*$_2$CH$_2$), 2.72 (1H, dd, $J_{5a,5a'}$ 13.6, $J_{4a,5a}$ 4.8, H-5a), 2.56 (1H, dd, $J_{5a,5a'}$ 13.6, $J_{4a,5a'}$ 6.8, H-5a'), 2.12 (2H, m, CH$_2$*CH*$_2$CH), 2.10 (3H, s, *CH*$_3$S), 2.07 (3H, s, *CH*$_3$CO), 1.98 (3H, s, *CH*$_3$CO), 1.71 (2H, m, OCH$_2$*CH*$_2$); β-anomer 7.37-7.24 (15H, m, *Ph*CH_2), 5.81 (1H, m, CH_2=*CH*), 5.37 (1H, m, H-3b), 5.20 (1H, dd, $J_{2b,3b}$ 3.4, $J_{1b,2b}$ 1.5, H-2b), 5.07 (1H, d, $J_{1a,2a}$ 1.3, H-1a), 4.99 (2H, m, *CH*$_2$=CH), 4.76 (1H, d, $J_{1b,2b}$ 1.5, H-1b), 4.71-4.39 (6H, m, Ph*CH*$_2$), 4.26 (1H, m, H-4a), 4.13-4.09 (1H, m, H-4b), 3.92 (1H, dd, $J_{3a,4a}$ 4.7, $J_{2a,3a}$ 1.9, H-3a), 3.89 (1H, m, H-2a), 3.80-3.69 (3H, m, H-5b, H-6b, H-6b'), 3.68 (1H, m, O*CH*$_2$CH$_2$), 3.45 (1H, m, O*CH*$_2$CH$_2$), 2.88 (1H, dd, $J_{5a,5a'}$ 13.5, $J_{4a,5a}$ 7.4, H-5a), 2.69 (1H, dd, $J_{5a,5a'}$ 13.5, $J_{4a,5a'}$ 6.3, H-5a'), 2.12 (2H, m, CH$_2$*CH*$_2$CH), 2.12 (3H, s, *CH*$_3$S), 2.10 (3H, s, *CH*$_3$CO), 2.01 (3H, s, *CH*$_3$CO), 1.71 (2H, m, OCH$_2$*CH*$_2$); δ_C (75 MHz; $CDCl_3$); α-anomer 138.2 (CH_2=*CH*), 128.7-127.6 (*Ph*CH_2), 115.1 (*CH*$_2$=CH), 100.8 (C-1a), 97.5 (C-1b), 82.8 (C-2a), 81.9 (C-4a), 77.2 (C-3a), 73.4, 72.9, 72.6 (Ph*CH*$_2$), 72.7 (C-3b), 70.8 (C-4b), 70.6 (C-2b), 70.0 (C-5b), 69.5 (O*CH*$_2$CH$_2$), 67.7 (C-6b), 34.9 (C-5a), 30.4 (CH$_2$*CH*$_2$CH), 28.6 (OCH$_2$*CH*$_2$), 21.2, 21.1 (*CH*$_3$CO), 16.7 (*CH*$_3$S); β-anomer 138.1 (CH_2=*CH*), 128.7-127.6 (*Ph*CH_2), 115.2 (*CH*$_2$=CH), 108.3 (C-1a), 97.7 (C-1b), 86.5 (C-2a), 81.3 (C-4a), 80.9 (C-3a), 73.7, 73.0, 72.1 (Ph*CH*$_2$), 72.1 (C-4b), 71.3 (C-2b), 70.5 (C-3b), 70.1 (C-5b), 69.0 (O*CH*$_2$CH$_2$), 67.6 (C-6b), 33.6 (C-5a), 30.1 (CH$_2$*CH*$_2$CH), 29.2 (OCH$_2$*CH*$_2$), 21.3, 21.1 (*CH*$_3$CO), 16.6 (*CH*$_3$S); *m/z* (ES); 787.3 ([M+Na]$^+$); Found: [M+Na]$^+$ 787.3104, $C_{42}H_{52}NaSO_{11}$ requires 787.3123.

Pent-4-enyl 4-*O*-(5-deoxy-5-methylthio-α-D-xylofuranosyl)-α-D-mannopyranoside (18α) and pent-4-enyl 4-*O*-(5-deoxy-5-methylthio-β-D-xylofuranosyl)-α-D-mannopyranoside (18β)

Sodium methoxide in MeOH (0.193 mL, 0.10 mmol) was added to a solution of *acetylated MTX-disaccharide* **17** (185 mg, 0.24 mmol) in anhydrous MeOH (2 mL) and stirred under a

nitrogen atmosphere for 19 hours. The reaction mixture was neutralized with Amberlite IRC-50 H^+ ion exchange resin and diluted with MeOH (50 mL). The solution was filtered and evaporated to give a colourless oil, which was purified by flash chromatography (silica gel; Hex-EtOAc, 1:1) to give *pent-4-enyl 6-O-benzyl-4-O-(2,3-di-O-benzyl-5-deoxy-5-methylthio-D-xylofuranosyl)-α-D-mannopyranoside* (114 mg, 69%), as a colourless syrup; α:β 77:23 (Found: C, 66.8; H, 7.0. $C_{38}H_{48}SO_9$ requires C, 67.0; H 7.1%); ν_{max}/cm^{-1} 3435 (OH), 1639 (C=C), 1593, 1453 (C=C aromatic); δ_H (500 MHz; $CDCl_3$); α-anomer 7.37-7.22 (15H, m, *Ph*CH_2), 5.80 (1H, m, CH_2=*CH*), 5.22 (1H, d, $J_{1,2}$ 4.5, H-1a), 4.99 (2H, m, *CH*$_2$=CH), 4.83 (1H, s, H-1b), 4.72-4.56 (6H, m, Ph*CH*$_2$), 4.35 (1H, m, H-4a), 4.26 (1H, dd, $J_{3a,4a}$ 6.5, $J_{2a,3a}$ 6.1, H-3a), 4.07 (1H, dd, $J_{2a,3a}$ 6.1, $J_{1a,2a}$ 4.5, H-2a), 3.91 (2H, m, H-2b, H-4b), 3.79-3.71 (4H, m, H-3b, H-5b, H-6b, H-6b'), 3.68 (1H, m, O*CH*$_2$CH$_2$), 3.42 (1H, m, O*CH*$_2$CH$_2$), 2.73 (1H, dd, $J_{5a,5a'}$ 13.9, $J_{4a,5a}$ 5.0, H-5a), 2.58 (1H, dd, $J_{5a,5a'}$ 13.9, $J_{4a,5a'}$ 7.4, H-5a'), 2.12 (2H, m, CH$_2$*CH*$_2$CH), 2.10 (3H, s, *CH*$_3$S), 1.67 (2H, m, OCH$_2$*CH*$_2$); β-anomer 7.37-7.22 (15H, m, *Ph*CH_2), 5.80 (1H, m, CH_2=*CH*), 5.07 (1H, d, $J_{1,2}$ 1.1, H-1a), 4.99 (2H, m, *CH*$_2$=CH), 4.87 (1H, s, H-1b), 4.72-4.40 (6H, m, Ph*CH*$_2$), 4.26 (1H, m, H-4a), 3.98 (1H, m, H-3a), 3.96 (1H, m, H-2a), 3.85-3.72 (5H, m, H-3b, H-4b, H-5b, H-6b, H-6b'), 3.68 (1H, m, O*CH*$_2$CH$_2$), 3.42 (1H, m, O*CH*$_2$CH$_2$), 2.88 (1H, dd, $J_{5a,5a'}$ 13.5, $J_{4a,5a}$ 6.4, H-5a), 2.80 (1H, dd, $J_{5a,5a'}$ 13.5, $J_{4a,5a'}$ 7.8, H-5a'), 2.13 (3H, s, *CH*$_3$S), 2.12 (2H, m, CH$_2$*CH*$_2$CH), 1.67 (2H, m, OCH$_2$*CH*$_2$); δ_C (75 MHz; $CDCl_3$); α-anomer 138.2 (CH_2=*CH*), 128.8-127.6 (*Ph*CH_2), 115.1 (*CH*$_2$=CH), 102.0 (C-1a), 99.6 (C-1b), 83.8 (C-2a), 81.9 (C-3a), 77.8 (C-4a), 77.2 (C-3b), 73.6, 73.3, 73.0 (Ph*CH*$_2$), 71.5 (C-2b), 71.0 (C-4b), 70.7 (C-5b), 69.2 (O*CH*$_2$CH$_2$), 67.3 (C-6b), 35.0 (C-5a), 30.5 (CH$_2$*CH*$_2$CH), 28.9 (OCH$_2$*CH*$_2$), 16.9 (*CH*$_3$S); β-anomer 138.2 (CH_2=*CH*), 128.8-127.6 (*Ph*CH_2), 115.1 (*CH*$_2$=CH), 108.0 (C-1a), 97.3 (C-1b), 85.7 (C-2a), 81.2 (C-4a), 80.9 (C-3a), 77.4 (C-3b), 73.7, 73.3, 72.3 (Ph*CH*$_2$), 70.5 (C-2b), 70.4 (C-4b), 70.2 (C-5b), 69.3 (O*CH*$_2$CH$_2$), 67.2 (C-6b), 33.7 (C-5a), 30.5 (CH$_2$*CH*$_2$CH), 28.8 (OCH$_2$*CH*$_2$), 16.3 (*CH*$_3$S); *m/z* (ES); 703.3 ([M+Na]$^+$); Found: [M+Na]$^+$ 703.2926, $C_{38}H_{48}NaSO_9$ requires 703.2911.

Ammonia (25 mL) was condensed into a flask containing *pent-4-enyl 6-O-benzyl-4-O-(2,3-di-O-benzyl-5-deoxy-5-methylthio-D-xylofuranosyl)-α-D-mannopyranoside* (90 mg, 0.13 mmol) in tetrahydrofuran (5 mL) at −78 °C. Shavings of sodium were added until a dark blue colour persisted and the solution was stirred under a nitrogen atmosphere for one and a half hours. MeOH (2 mL) was added and the mixture was left open to air at RT overnight. The solution was diluted with MeOH (20 mL) and neutralised with acetic acid, before evaporation to give a yellow residue, which was purified by flash chromatography (silica gel; DCM-MeOH, 9:1) to yield α-glycoside **18α** (25 mg) as colourless syrup and β-glycoside **18β** (9 mg) as colourless syrup (overall yield 63%).

α-Anomer 18α $[\alpha]_D^{26}$ +54.2 (*c* 3.1 in $CHCl_3$); ν_{max}/cm^{-1} 3350 (OH); δ_H (500 MHz; CD_3OD); 5.85 (1H, m, CH_2=*CH*), 5.38 (1H, d, $J_{1,2}$ 4.2, H-1a), 5.00 (2H, m, *CH*$_2$=CH), 4.74 (1H, d, $J_{1b,2b}$ 1.2, H-1b), 4.34 (1H, ddd, $J_{4a,5a'}$ 7.4, $J_{4a,5a}$ 5.7, $J_{3a,4a}$ 4.6, H-4a), 4.14 (1H, dd, $J_{3a,4a}$ 4.6, $J_{2a,3a}$ 4.1, H-3a), 4.08 (1H, dd, $J_{1a,2a}$ 4.2, $J_{2a,3a}$ 4.1, H-2a), 3.89-3.85 (2H, m, H-3b, H-6b'), 3.82-3.79 (3H, m, H-2b, H-4b, H-6b), 3.75 (1H, m, O*CH*$_2$CH$_2$), 3.62 (1H, m, H-5b), 3.44 (1H, m, O*CH*$_2$CH$_2$), 2.75 (1H, dd, $J_{5a,5a'}$ 13.8, $J_{4a,5a}$ 5.7, H-5a), 2.63 (1H, dd, $J_{5a,5a'}$ 13.8, $J_{4a,5a'}$ 7.4, H-5a'), 2.17 (3H, s, *CH*$_3$S), 2.15 (2H, m, CH$_2$*CH*$_2$CH), 1.69 (2H, m, OCH$_2$*CH*$_2$); δ_C (75 MHz; CD_3OD); 139.4 (CH_2=*CH*), 115.3 (*CH*$_2$=CH), 104.9 (C-1a), 101.6 (C-1b), 80.5 (C-4a), 78.9 (C-2a), 77.2 (C-3a), 76.1, 73.4, 72.5, 72.4 (C-2b, C-3b, C-4b, C-5b), 68.0 (O*CH*$_2$CH$_2$), 62.8 (C-6b), 34.5 (C-5a), 31.5 (CH$_2$*CH*$_2$CH), 29.9 (OCH$_2$*CH*$_2$), 16.3 (*CH*$_3$S); *m/z* (ES); Found: [M+Na]$^+$ 433.1514, $C_{17}H_{30}NaSO_9$ requires 433.1503.

β-Anomer 18β $[\alpha]_D^{26}$ +1.6 (*c* 1.5 in $CHCl_3$); ν_{max}/cm^{-1} 3350 (OH); δ_H (500 MHz; CD_3OD); 5.84 (1H, m, CH_2=*CH*), 5.01 (1H, s, H-1a), 5.00 (2H, m, *CH*$_2$=CH), 4.74 (1H, d, $J_{1b,2b}$ 1.4, H-1b), 4.36 (1H, ddd, $J_{4a,5a'}$ 7.5, $J_{4a,5a}$ 6.6, $J_{3a,4a}$ 3.9, H-4a), 4.07 (1H, d, $J_{2a,3a}$ 1.9, H-2a), 4.02 (1H, dd, $J_{3a,4a}$ 3.9, $J_{2a,3a}$ 1.9, H-3a), 3.86 (1H, m, H-2b), 3.84-3.75 (4H, m, H-3b, H-4b, H-6b, H-6b'), 3.73 (1H, m, O*CH*$_2$CH$_2$), 3.60 (1H, m, H-5b), 3.44 (1H, m, O*CH*$_2$CH$_2$), 2.91 (1H, dd, $J_{5a,5a'}$ 13.6, $J_{4a,5a}$ 6.6, H-5a), 2.80 (1H, dd, $J_{5a,5a'}$ 13.6, $J_{4a,5a'}$ 7.5, H-5a'), 2.18 (3H, s, *CH*$_3$S), 2.15 (2H, m, CH$_2$*CH*$_2$CH), 1.69 (2H, m, OCH$_2$*CH*$_2$); δ_C (75 MHz; CD_3OD); 139.4 (CH_2=*CH*), 115.3 (*CH*$_2$=CH), 110.4 (C-1a), 101.4 (C-1b), 83.6 (C-4a), 82.1 (C-2a), 76.7 (C-3a), 76.3, 73.2, 71.7, 71.4 (C-2b, C-3b, C-4b, C-5b), 68.0 (O*CH*$_2$CH$_2$), 62.3 (C-6b), 34.1 (C-5a), 31.5 (CH$_2$*CH*$_2$CH), 29.9 (OCH$_2$*CH*$_2$), 16.0 (*CH*$_3$S); *m/z* (ES); Found: [M+Na]$^+$ 433.1505, $C_{17}H_{30}NaSO_9$ requires 433.1503.

Density functional theory calculations

Conformations were generated in MacroModel using the OPLS forcefield.[34] For the MTX system, six low energy conformations of the reactant were obtained (sampling the six available conformations of the two OMe sidechains) each of which was used to generate the corresponding transition states for S_N1 and S_N2 reactions. For other species, a selection of 20-25 of the lowest energy conformations according to the forcefield were chosen. The geometries generated were subject to density functional theory calculations performed in Gaussian03[35] and using Becke's 3-parameter hybrid exchange functional[36] and the Lee-Yang-Parr exchange functional (B3LYP/6-31G*).[37] All stationary points were verified by frequency calculations. All energies are free energies quoted as differences between the species being referred to in its lowest energy conformation and the corresponding sulfonium ion in its lowest energy conformation. Solvation free energies were computed with the IEFPCM method in combination with B3LYP/6-31+G* and used UAKS radii.[38]

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