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# β-Rhamnosides from 6-thio mannosides†

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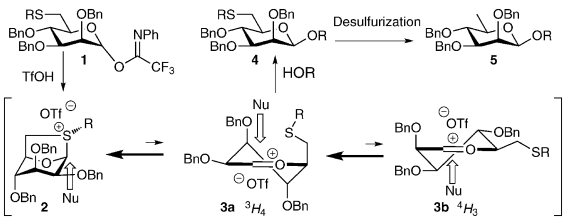
**Upon condensation of 6-thio-6-deoxy-mannosyl donors 1,2-*cis* products are obtained with a high degree of stereoselectivity. Subsequent reductive removal of the 6-thio functionality gives 1,2-*cis* rhamnosides. The 1,2-*cis*-selectivity can be rationalized with a product forming $^{3}H_{4}$-oxocarbenium, which is in equilibrium with a bridged sulfonium intermediate.**



Neighboring group participation is a powerful means to steer the stereochemical course of a synthetic transformation. Especially in the area of carbohydrate chemistry it takes up a prominent position and the placement of a participating *N*- or *O*-acyl function at the C-2 position is commonly used to secure the stereoselective formation of 1,2-*trans* glycosidic bonds.[1] C-2-thio- and C-2-seleno-ethers have also been exploited to direct the stereochemical outcome of glycosylation reactions and various groups have reported on their use for the construction of 1,2-*trans* linkages.[2–4] Recently, Boons and co-workers developed a chiral auxiliary for the stereoselective formation of 1,2-*cis* glucosyl and galactosyl linkages based on a participating chiral thioether grafted on the C-2-hydroxyl of the donor.[5] Turnbull and co-workers have reported on glycosylations of bicyclic methyl sulfonium xylofuranosides which, upon reaction with an acceptor nucleophile, provided the α-linked disaccharides with moderate selectivity.[6] The rate of success of participating thio functions seems to depend on the relative stability of the sulfonium species on the one hand and the corresponding oxocarbenium ions on the other, in combination with the ease of substitution of both species.[2,7] As Woerpel and co-workers have convincingly demonstrated, the intermediate sulfonium ions can serve as a reservoir for the corresponding oxocarbenium ions, which often are more reactive and react in a distinct stereochemical manner.[8]

Based on these precedents we reasoned that activation of a mannosyl donor (such as **1**, Scheme 1), equipped with a thio ether at C-6, can lead to the formation of a bicyclic sulfonium ion **2**. This sulfonium ion can serve as a reservoir for the structurally related but more reactive oxocarbenium ion–triflate anion pairs **3a** and **3b**. The $^{3}H_{4}$ oxocarbenium ion **3a** should be




**Scheme 1** Strategy for the synthesis of β-rhamnosides.

favored over its $^{4}H_{3}$ counterpart **3b**, because the former places all ring substituents in a favorable spatial orientation.[9] As indicated by Woerpel and co-workers, the C-2 alkoxy group preferentially takes up a *pseudo* equatorial position in a pyranosyl oxocarbenium ion half chair, thereby allowing for hyperconjugative stabilization of the cation by donation of electron density of the perpendicular $\sigma_{C-H}$ bond. Besides, alkoxy substituents at C-3 and C-4 prefer to occupy a *pseudo* axial orientation to minimize their electron-withdrawing effect,[10] and to allow for the donation of electron density from the heteroatom lone pairs to the electron-deficient oxocarbenium ion.[9] We hypothesize that the C-5 methylene thioether in a *pseudo* axial orientation contributes to the relative stability of **3a** with respect to **3b** by stabilizing the anomeric positive charge by the sulfur lone pair electrons. An incoming nucleophile preferentially attacks oxocarbeniums **3a** or **3b** on the diastereotopic faces leading to the chair product to give the β- or α-product, respectively. Like **3b**, nucleophilic attack on bicyclic sulfonium ion **2** will result in the formation of the α-product. Thus, although the product forming intermediates **2**, **3a** and **3b** occur in a dynamic equilibrium, the involvement of the C-5 methylene thioether in the stereochemical outcome can be deduced from the formation of β-product **4**. Desulfurization of this β-6-thio mannoside can then provide the corresponding β-D-rhamnoside **5** in a straightforward manner.[11,12]

To investigate the stereodirecting effect of a mannosyl C-5 thioether, a panel of *N*-phenyltrifluoroacetimidate donors[13] **8–14** was combined with three acceptors (**15a,b,c**) in a series of condensation reactions.† A variety of C-6 thioethers, a C-6-selenoether, and a C-6-iodide[2,14] were probed, because all these functionalities have previously been used as participating groups. The perbenzylated mannosyl donor **6** and the C-6 deoxy donor **7** were included as reference donors. Table 1 records the outcome of the glycosylations. As expected perbenzylated imidate **6** provided little to moderate β-selectivity, depending on which acceptor was used.[15] Condensations of rhamnose donor **7** proceeded with low selectivity with all three acceptors, also in line with

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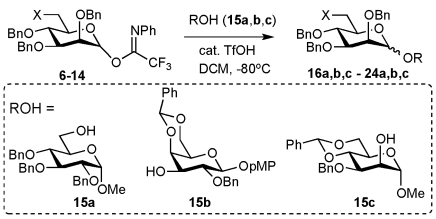
† Electronic supplementary information (ESI) available: Experimental procedures and full characterisation of all new compounds. See DOI: 10.1039/c2cc17623h

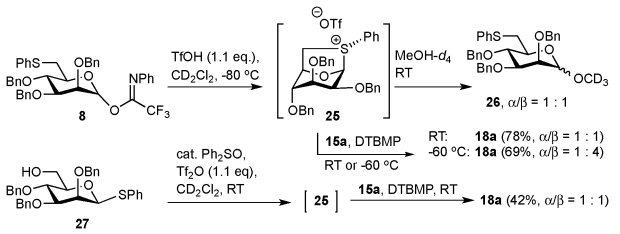
**Table 1** Condensations of donors **6–14**




| Entry | Donor | 15a Product (yield α/β)[a] | 15b | 15c |
|---|---|---|---|---|
| 1 | **6**, X = OBn | **16a** (94%, 1 : 3.5) | **16b** (88%, 1 : 1) | **16c** (99%, 1 : 4) |
| 2 | **7**, X = H | **17a** (91%, 1 : 2.5) | **17b** (87%, 1 : 1.5) | **17c** (90%, 1 : 1) |
| 3 | **8**, X = SPh | **18a** (90%, 1 : 7) | **18b** (89%, 1 : 11) | **18c** (87%, 1 : 5) |
| 4 | **9**, X = STol | **19a** (86%, 1 : 5) | **19b** (56%, 1 : 8) | **19c** (89%, 1 : 3.5) |
| 5 | **10**, X = *S*-*p*MeOPh | **20a** (85%, 1 : 5) | **20b** (58%, 1 : 7) | **20c** (88%, 1 : 4.5) |
| 6 | **11**, X = *S*-*p*$NO_2$Ph | **21a** (79%, 1 : 7) | **21b** (91%, 1 : 4) | **21c** (90%, 1 : 4) |
| 7 | **12**, X = SEt | **22a** (80%, 1 : 4) | **22b** (86%, 1 : 3.5) | **22c** (78%, 1 : 1.5) |
| 8 | **13**, X = SePh | **23a** (99%, 1 : 7) | **23b** (96%, 1 : 10) | **23c** (92%, 1 : 3) |
| 9 | **14**, X = I | **24a** (84%, 1 : 7) | **24b** (95%, 1 : 6) | **24c** (87%, 1 : 3) |

[a] Isolated yield after size exclusion chromatography. The anomeric ratio is based on $^1$H NMR of the diastereomeric mixture. The anomeric configuration of the mannosidic linkages has been established using C1′–H1′ coupling constants.

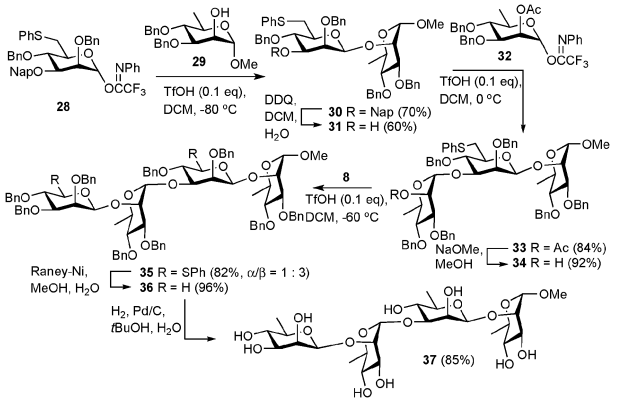
our previous results.[15] The C-6-thio, seleno and iodo mannosyl donors **8–14** on the other hand, all preferentially provided the 1,2-*cis* linked disaccharides, with the C-6-*S*-phenyl donor **8** performing best and the C-6-*S*-ethyl mannoside **12** showing least selectivity. Although, these results indicate that for these donors the $^3H_4$-oxocarbenium ion **3b** can be the main product forming intermediate, no simple correlation between the nature of the C-6-thio-, C-6-seleno, or C-6-iodo functionality and stereochemical outcome of the reactions can be distilled from Table 1. Small changes in the dynamic equilibrium of the reactive intermediates **2**, **3a** and **3b**, as a result of the different C-6 functionalities in combination with the different nucleophilicity of the three acceptors, contribute to the observed variation in stereoselectivity. Although direct $S_N2$ displacement of the activated imidate donors (having predominantly the α-configuration) by the acceptors is conceivable, this reaction mode is excluded as a major pathway because the variation in the amount of the β-product in the different glycosylations, including the role of the C-thio/iodo/seleno function, cannot be accounted for by this pathway. Illustrative of this is the finding that most condensations with secondary acceptor **15b** proceed with better β-selectivity than the corresponding couplings with primary alcohol **15a**. The same reasoning holds for the intermediacy of α-triflates that have been shown to be product forming intermediates in glycosylations using 4,6-*O*-benzylidene mannosyl donors[16] and mannosides equipped with electron withdrawing substituents.[17] Given the reactive (“armed”) and conformationally unconstrained nature of the mannosyl donors used here, triflate intermediates are probably not the major product forming species.[17b,c]




**Scheme 2** Formation and reactions of bicyclic sulfonium ion **25**.

Because the C-6-*S*-phenyl donor **8** performed best in the model glycosylations, is easier to synthesize than its C-6-seleno counterpart **13** and more stable than 6-iodo mannoside **14** we continued our studies with donor **8**. The formation of the bridged sulfonium ion **25** from donor **8** and its reactivity was assessed in a variable temperature NMR experiment (Scheme 2). Treatment of **8** with an equimolar amount of triflic acid (TfOH) at −80 °C in $CD_2Cl_2$ led to the near instantaneous formation of **25**, tentatively assigned as the exo-sulfonium isomer. This species proved to be stable up to room temperature (decomposition set in after several hours at room temperature) and treatment of the mixture with excess MeOH-*d*4 led, after 16 hours, to the formation of methyl mannoside **26** as an anomeric mixture (α/β = 1 : 1). Interestingly, sulfonium ion **25** could also be generated from the C-6-OH β-*S*-phenyl mannoside **27** by treating this thiomannoside with a catalytic amount of diphenylsulfoxide ($Ph_2SO$) and equimolar triflic anhydride ($Tf_2O$).[18,19] The outcome of the latter experiment substantiated the result of the former pre-activation experiment. It also shows that the primary alcohol in **27** is more nucleophilic towards diphenylsulfonium bistriflate than the anomeric thiophenyl functionality[19] and that a catalytic amount of $Ph_2SO$ can be used for complete activation of donor **27**. Addition of acceptor **15a** and di-*tert*-butylmethylpyridine (DTBMP) to sulfonium ion **25**, generated from **27** at room temperature, provided disaccharide **18a** as a 1 : 1 α/β mixture in 42% yield. A similar stereochemical result was obtained when **8** was preactivated with an equimolar amount of TfOH at −80 °C followed by reaction with **15a** in the presence of DTBMP at room temperature.[20] Importantly, β-selectivity was restored when the coupling reaction was executed at low temperature: generation of **25** from **8** using an equimolar amount of TfOH at −80 °C, and ensuing reaction with acceptor **15a** at −60 °C delivered **18a** in a 1 : 4 α/β-ratio (67% yield). These results can be rationalized by the mechanistic proposal in Scheme 1. The equilibrium of bridged sulfonium ion **2** (with R = Ph) and oxocarbenium ions **3a** and **3b** lies to the side of the sulfonium ion. At low temperatures this species is not reactive enough to react with an incoming nucleophile, in line with the recent results obtained by Woerpel *et al.*[8] and Turnbull *et al.*[6] Reaction takes place from the more reactive oxocarbenium ion **3a**, the formation of which is favored over the alternative half chair oxocarbenium ion **3b**, to produce the β-linked product in a Curtin–Hammett type kinetic scenario. At higher temperatures sulfonium ion **2** and/or oxocarbenium ions **3a,b** can be attacked, leading to the demise of stereoselectivity.

To explore the use of C-6-*S*-phenyl mannosyl donors in the context of complex oligosaccharide synthesis, we undertook the assembly of tetrasaccharide **37**, containing alternating



**Scheme 3** Assembly of a *Xanthomonas campestris* tetrasaccharide.

α- and β-D-rhamnosides (Scheme 3). Tetrasaccharide **37** represents two repeating units of the O-specific polysaccharide of the LPS of the phytopathogen *Xanthomonas campestris pathovar campestris*,[21] the causative agent of a devastating disease affecting cruciferous crops such as cabbage and broccoli.[22] The synthesis of **37** started with the condensation of 6-*S*-Ph mannoside **28** and rhamnosyl acceptor **29**. To keep the stereoelectronic effects in building block **28** as similar as possible to those in donor **8**, we used a naphth-2-ylmethyl ether as a selectively removable protecting group at the C-3 of **28**. Disaccharide **30** was obtained in 72% yield, highlighting the β-directing capacities of the 6-*S*-phenyl group in donor **28**. Removal of the naphth-2-ylmethyl ether liberated the C-3″-OH, which was glycosylated with rhamnoside **32** to provide the α-linked trimer **33**, by virtue of the participating acetyl function in donor **32**. Deacetylation of **33** then set the stage for the introduction of the second β-mannosidic bond. Reaction of the trimer acceptor and mannosyl donor **8** at −60 °C led to the formation of the target tetramer **35**, which was obtained as a mixture of anomers, in which the desired β-isomer prevailed (82%, α/β = 1 : 3). This result shows that also elaborate acceptors can be β-mannosylated with productive selectivity. Desulfurization of tetramer **35** under the agency of Raney-nickel proceeded uneventfully to deliver the perbenzylated tetrarhamnoside **36** in 96% yield. Reductive removal of all benzyl ethers completed the synthesis of tetramer **37**.

In conclusion, the installation of a thiophenyl ether at C-6 of a mannosyl donor leads to a 1,2-*cis*-mannosylating agent, which can be used as a precursor in the synthesis of β-D-rhamnosides. The stereoselectivity in the *cis*-mannosylation reaction can be rationalized with a Curtin–Hammett kinetic scenario in which the quasi-stable bicyclic $^{1}C_{4}$-sulfonium ion intermediate is in equilibrium with the more reactive and β-selective mannosyl $^{3}H_{4}$-oxocarbenium, which places all ring-substituents in an electronically favorable position.

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