Check for updates

View Article Online
View Journal

Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: M. Heuckendorff, L. Poulsen, C. Hedberg and H. H. Jensen, *Org. Biomol. Chem.*, 2018, DOI: 10.1039/C7OB02968C.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the author guidelines.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the ethical guidelines, outlined in our author and reviewer resource centre, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C7OB02968C

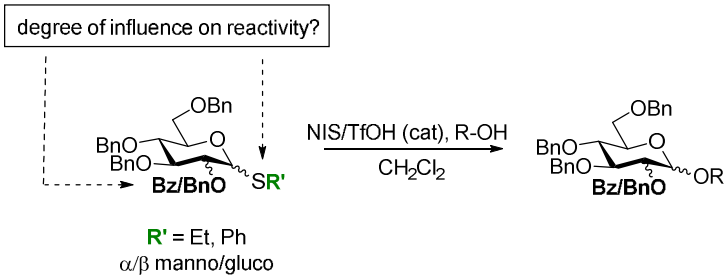
Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

Dissection of the Effects that Govern Thioglucoside and Thiomannoside Reactivity

Mads Heuckendorff, Lulu Teressa Poulsen, Christinne Hedberg and Henrik H. Jensen*

Department of Chemistry, Aarhus University, Langelandsgade 140, 8000 Aarhus C, Denmark,

hhj@chem.au.dk



Abstract: Neighboring group effects were investigated in *gluco*- and *manno*-configured thioglycosides under NIS/TfOH activation. Donors possessing a 2-*O*-benzoyl group that are capable (1,2-*trans*) and incapable (1,2-*cis*) of performing neighboring group participation were compared with donors possessing a participatory neutral 2-*O*-benzyl group. By using competition experiments between sets of glycosyl donors the direct effect of neighboring group participation and the electron withdrawing effect of the 2-*O*-benzoyl group could be separated. The study brings insight into how the stereochemistry of the 1 and 2 position and how the nature of the aglycon (Ph or Et) have a pronounced effect on glycosyl donor reactivity.

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

Introduction

Even with modern modelling techniques, the number of possible effects, being either electronical or sterical, makes it difficult to predict the reactivity of a given reaction in organic chemistry. One of these effects describe when a substituent stabilizes a transition state or an intermediate by becoming temporary covalently attached to the reaction center. This is known as neighboring group participation, which often implicates that the stereochemical outcome of the reaction is affected by the substituent's involvement.[1] In certain cases, a rate enhancement of the reaction can be observed due to neighboring group participation, and the effect is then referred to as anchimeric assistance.[2] Research into neighboring group participation was pioneered by Winstein in the 1940s,[3] whereas effects in carbohydrate chemistry was later led by Lemieux.[4] Aside from the earlier work on the solvolysis of glycosyl halides, acetolysis of glycosyl esters and hydrolysis of glycosides,[5] only little is known about the degree to which neighboring group participation influences the rate of modern, synthetically relevant glycosylation reactions.

From our recent work on the so-called electronically superarmed glycosyl donors,[6] having the 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl protecting group pattern,[7] we became surprised that the high reactivity reported for an SBox donor with DMTST activation was not general as anticipated.

The effect by the 2-*O*-benzoyl group is deactivating (disarming)[8] due to its electron withdrawing properties and its closeness to the reaction center. However, it can also have an accelerating effect due to anchimeric assistance. The balance between these two effects of opposite direction apparently varies depending on reaction conditions.[6]

By using reactivity measurements in a competition setting between various glycosyl donors, we here describe our attempts to dissect activating and deactivating effects caused by changes in the 2-*O*-protecting group and the anomeric configuration to obtain further in-depth insight into the intricate nature of glycosylation chemistry.

Competition Experiments and Discussion

To separate the deactivating effect from the activating effect of the electron withdrawing 2-*O*-benzoyl group, it was necessary to study both 1,2-*trans* and 1,2-*cis* configured donors of which the latter can only be expected to experience a deactivating effect, since anchimeric assistance is not possible. Specifically, the reactivity was studied in a series of competition experiments involving SPh and SEt functionalized gluco- and manno-pyranosyl donors with

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

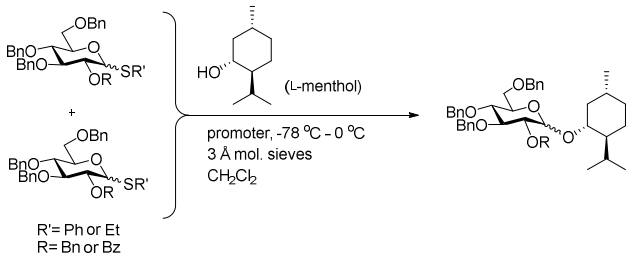
Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

NIS/TfOH activation, given the fact that these constitute an often-used set of reaction conditions and that the steric and electronic nature varies significantly between SPh and SEt. All donors were synthesized by standard methods and prior to performing the competition experiments, evaluated separately in reaction with L-menthol as acceptor to ensure that good and reproducible yields could be obtained.[9]

The competition experiments were performed by having two donors (1 equiv. of each) competing for the acceptor L-menthol (5 equiv.) in presence of triflic acid (TfOH, 10 mol%) with a limiting amount of NIS (1 equiv.). Prior to each reaction, the ratio of mixed donors was ensured to be 1.0:1.0 by recording a ^{13}C-NMR spectrum with a high signal-to-noise ratio and comparing the anomeric carbon intensities.[10] After ended reaction with NIS/TfOH and standard reaction work-up, another ^{13}C-NMR spectrum was recorded of the crude reaction mixture and the anomeric signals of the unreacted donors were again compared. The reported data were found to be highly reproducible.

The consumption of each donor is an expression of its reactivity related to the competing counterpart. The higher the proportion of unreacted donor, the less reactive it is. In the following, we treat the obtained ratio as a ratio of rate constants, however, in reality this is not entirely correct since there is a 'catching up effect' by the slower reacting donor due to the consumption of the faster reacting species. This imperfection inherent to the experimental protocol is also present in measurements conducted by Wong and co-workers in their much celebrated work with S-tolyl functionalized donors.[11]

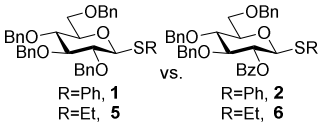
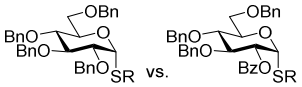
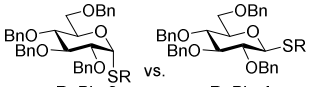
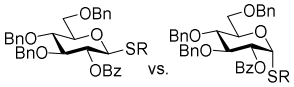
Table 1. Competition experiments with SPh and SEt glucopyranosyl donors (conditions: 1 equiv. NIS, 0.1 equiv. TfOH and 5 equiv. L-menthol).



Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

Entry	Competition experiment	Ratio of unreacted donors R'=Ph (left), R'=Et (right)	
1	 R=Ph, **1** R=Et, **5** vs. R=Ph, **2** R=Et, **6**	1 : 2	1 : 2
2	 R=Ph, **3** R=Et, **7** vs. R=Ph, **4** R=Et, **8**	1 : 12	1 : 60
3	 R=Ph, **3** R=Et, **7** vs. R=Ph, **1** R=Et, **5**	1 : 4	1 : 1.1
4	 R=Ph, **2** R=Et, **6** vs. R=Ph, **4** R=Et, **8**	1 : 2	1 : 20

Competition experiments in the glucopyranosyl series were initially performed. As seen from Table 1 (Entry 1) and as previously established,[6] there is a two-fold reactivity difference between SPh donors **1** and **2**, favoring the tetra-*O*-benzylated donor **1**, meaning that donor **2** is not superarmed let alone as reactive as **1**. The same result was observed for the analogous competition experiment between SEt functionalized donors **5** and **6**. This lower reactivity of 2-*O*-benzoylated donors **2** and **6** suggests that the rate acceleration achieved by anchimeric assistance is not large enough to override the deactivating effect originating from the electron withdrawing effect of the 2-*O*-benzoyl group. A competition experiment between the corresponding donors **3**/**4** and **7**/**8** in the α-series (Entry 2), shows an even greater reactivity difference (12-fold for SPh donors and 60-fold for SEt donors) in favor of the tetra-*O*-benzylated donors (**3** and **7**). This finding is in accordance with the fact that the 2-*O*-benzoyl group of **4** and **8** is incapable of performing neighboring group participation[12]/nucleophilic

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

push due to their 1,2-*cis* relationship.[13] The reason for the larger difference in reactivity between the SEt functionalized donors is not clear.

Next, the reactivity difference between α- and β-configured tetra-*O*-benzylated donors **1**/**3** and **5**/**7** were evaluated under the same conditions (Entry 3). To our surprise, the phenyl α-thioglycoside **3** was established to be four-fold more reactive its anomer (β-thioglycoside **1**), while the SEt anomers **5** and **7** were found to be almost equally reactive. We assumed that the equatorially oriented β-configured donors (**1** and **5**) would be more reactive than their α-anomers based on the expectation of **3** and **7** would have a lower ground state energy, due to stabilization by the endo anomeric effect,[14] as opposed to **1** and **5**. Bols and co-workers have earlier published an identical result for the SPh donors in a competition experiment without commenting on the reactivity difference.[15]

For acid catalyzed hydrolysis of *O*-methyl glucopyranosides the β-anomer is approximately 2-fold more reactive than its α-amomer[16] and the anomeric effect is typically given as an explanation of this fact.[17] A similar explanation has been given as the cause of the observed α-selectivity in the famous *in situ* anomerization procedure, where a β-halide is speculated to be the reactive intermediate.[18]

In contrast to *O*-methyl glucosides, however, the equatorial β-anomer of *O*-phenyl glucosides[19] is known to hydrolyze at a slower rate than its α-anomer in accordance with the order of reactivity measured for thioglucosides **1** and **3**.

The difference in reactivity between α and β configured donors possessing a 2-*O*-benzoyl group (**2**/**4** and **6**/**8**) is shown in Entry 4. In both cases the β-configured donors were the most reactive in accordance with the possibility of anchimeric assistance. In case of the SEt set of donors, however, the difference in reactivity was found to be far greater (1:20) than for the analogous set of SPh donors (1:2).

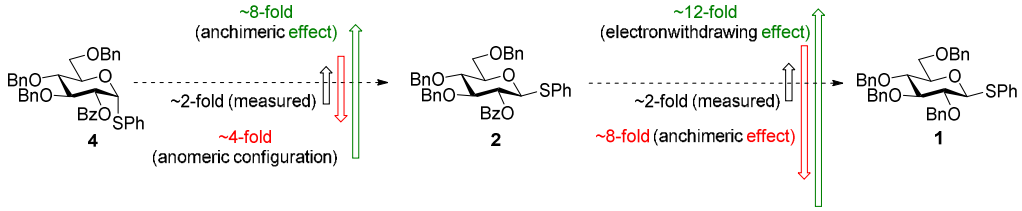
We assume that there are three major features that govern the reactivity of the studied donors: *i*) the anchimeric effect of a 1,2-*trans* oriented 2-*O*-benzoyl is activating, and *ii*) the presence of a strongly electron withdrawing 2-*O*-benzoyl group is deactivating, and *iii*) the effect of anomeric configuration. With the values reported in Table 1 in hand it ispossible to obtain intimate knowledge in relation to the balance between *i*), *ii*) and *iii*) for thioglucosides under NIS/TfOH activation.

First, for the tetra-*O*-benzylated SPh donors **3** and **1** (Entry 3) there is a 4-fold reactivity difference caused by anomeric configuration in favor of the α-configured donor **3**. By

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

assuming that this difference also holds for comparing donors **2** and **4**, which both have the electron withdrawing 2-*O*-benzoyl group, the reactivity factor of 2 in favor of β-configured donor **2** then must mean that the rate acceleration due to the anchimeric effect is approximately 8-fold (Scheme 1).



Scheme 1. Overview of approximate magnitude of effects that are decisive for the level of reactivity of phenyl thioglucosides with NIS/TfOH activation.

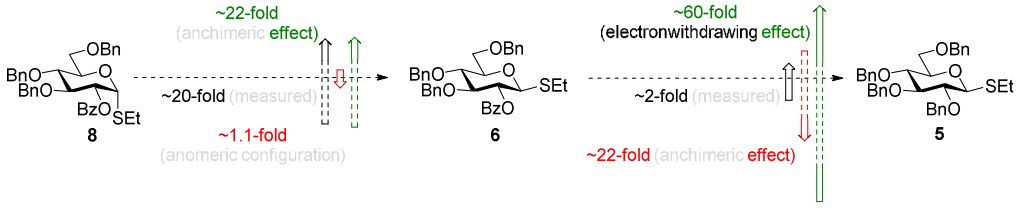
A comparison of the reactivity differences between the two α-configured donors **3** and **4** (Entry 2), where no achimeric assistance is possible and the major variation can be assumed to stem from the electron withdrawing power of the 2-*O*-benzoyl group, a factor of 12-fold was measured in favor of the tetra-*O*-benzylated donor **3**. The difference in reactivity between **1** and **2** (Entry 1), measured to be 2-fold, roughly agrees with an 8-fold rate enhancement due to achimeric assistance and a 12-fold reactivity decrease caused by the larger electron withdrawing power of a 2-*O*-benzoyl group (Scheme 1).

A similar analysis was performed for the SEt functionalized donors (**5**-**8**) with the results listed in Table 1. The tetra-*O*-benzyl donor **5** in competition with the 2-*O*-benzoyl counterpart **6** was found to be 2-fold more reactive, which is the identical ratio obtained for the analogous SPh functionalized donor pair **1** and **2** (Entry 1). Upon dissection of the cause of this reactivity difference, the SEt donors (**5** and **6**) clearly behave markedly different fromthe corresponding SPh donors (**1** and **2**).

For obtaining a value for the anchimeric effect for SEt donors, again the effect of anomeric configuration (a factor of 1.1, Entry 3) was multiplied by the effect of having anchimeric assistance, as opposed to not having this possibility (a factor of 20, Entry 4). Hereby, the value arrives at a 22-fold increase being much more pronounced than in the analogous SPh functionalized donor system (Scheme 2).

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.
Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

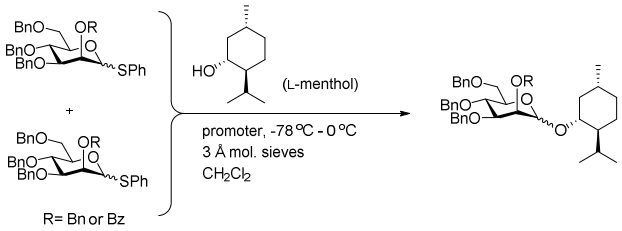


Scheme 2. Overview of approximate magnitude of effects that are decisive for the level of reactivity of ethyl thioglucosides with NIS/TfOH activation.

The large activating anchimeric effect (22-fold) is more than offset by an even larger deactivating effect (60-fold), caused by the presence of the electron withdrawing 2-*O*-benzoyl group compared to the less electron withdrawing 2-*O*-benzyl group, which largely accounts for an observed difference in reactivity of 2-fold between **5** and **6**.

Recently, Zhu and co-workers published a letter entitled: "Investigation of α-Thioglycoside Donors: Reactivity Studies toward Configuration-Controlled Orthogonal Activation in One-Pot Systems"[20] studying glycosylation rates of SEt functionalized thioglucosides. The authors used 2-*O*-acetylated donor analogues of donor **6** and **8** and obtained a difference in reactivity of 1:>19, which is in agreement with our result (cf. 1:20, Entry 4, Table 1). Given the great reactivity difference between α- and β-anomers in the SEt system, they were able to chemoselectively couple the 2-*O*-acetylated analogue of **6** to its anomer having a free 6-OH. Our results suggest that a similar coupling would have failed for SPh bearing glucosyl donors.

Table 2. Competition experiments with SPh mannopyranosyl donors (conditions: 1 equiv. NIS, 0.1 equiv. TfOH and 5 equiv. L-menthol).

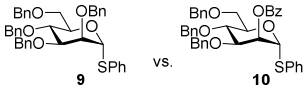
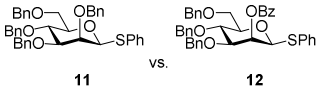
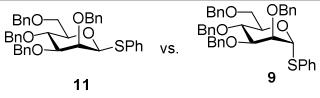
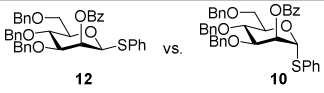


Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

Entry	Competetion Experiment	Ratio of unreacted donors
1	 **9** vs. **10**	1 : 13
2	 **11** vs. **12**	1 : 24
3	 **11** vs. **9**	1 : 2.5
4	 **12** vs. **10**	1 : 1.2

In the study by Zhu and co-workers,[20] the donor analogous to **6** is claimed to be superarmed[21] under activation by NIS/TMSOTf(cat). The authors, however, fail to demonstrate this statement and our present results brings this into question.

Having established the effect of a 2-*O*-benzoyl and 2-*O*-benzyl group on glucosylation rates a study of the behavior in the mannose system with its axial 2-*O* substituent was undertaken. We started out with comparing tetra-*O*-benzylated donor **9** and its 2-*O*-benzoyl protected analogue **10** both having a 1,2-*trans* relationship as in the study of thioglucosides. As in the glucose case, the tetra-*O*-benzylated donor (**9**) was found to be the most reactive, but this time the difference between the pair of donors had increased to 13-fold (cf. 2-fold) (Table 2, Entry 1). For the analogous β-case (Entry 2), devoid of the possibility of neighboring group participation from the 2-*O*-benzoyl functionality, the difference was even greater (24-fold) again in favor of the tetra-*O*-benzyl protected donor.

Studying the role of anomeric configuration by a competition experiment between the β- and α-configured tetra-*O*-benzylated donors (**11** and **9**, Entry 3) the equatorial thiomannoside **11** was established to be more reactive (by 2.5-fold) in opposition to the case for thioglucosides, where the axial thioglucoside was the most reactive. This reversed order of reactivity could be caused by a greater stabilization of the axial anomer in the thiomannoside ground state and possibly be a result of the Δ2-effect.[22] Lastly, it was found that the α-configured 2-*O*-benzoyl protected donor (**10**) was 1.2-fold less reactive than its corresponding β-anomer (**12**). (Entry 4).

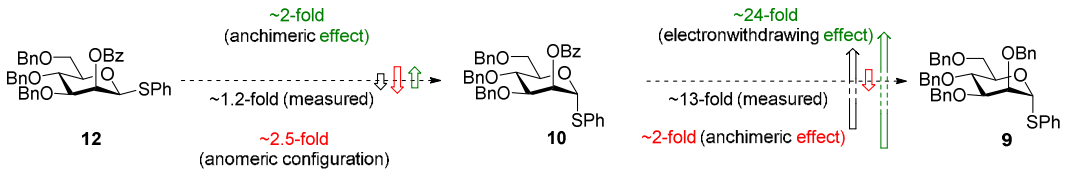
Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

For the two cases, where two anomeric donors are compared (Entry 3 and 4), there could be a dipole influence on the reactivity difference, which would be different compared to the glucopyranosyl case where the 1 and 2 substituents are arranged in a *gauche* relationship as opposed to being in an *anti* relationship for the α-anomeric mannopyranosyl cases. This effect is included in the effect of anomeric configuration.

Analyzing the overall results as above makes it evident, that the glucosyl- and mannosyl behavior is highly dissimilar (Scheme 3). From Entry 3, Table 2 the effect of anomeric configuration is 2.5-fold making the anchimeric effect only 2-fold, which is a factor of 4 less than for the phenyl thioglucosyl system. This means, that the electron withdrawing effect of the 2-*O*-benzoyl compared to that of a 2-*O*-benzyl is 12-fold, which is in good agreement with the measured factor of 13-fold (Entry 1).



Scheme 3. Overview of approximate magnitude of effects that are decisive for the level of reactivity of thiomannosides with NIS/TfOH activation.

In the above, the level of anchimeric assistance/neighboring group participation has been estimated using Entries 3 and 4 of Table 1 and Table 2. Alternatively, another number to estimate this effect can be obtained from Entries 1 and 2 of the same tables, as the latter entry is a measure of the electron withdrawing capacity of the 2-*O*-benzoyl substituent. The anchimeric effects then amounts to 6, 30 and 1.8-fold (cf. 8, 22 and 2.1-fold) for the phenyl glucopyranoside, ethyl glucopyranoside and phenyl mannopyranoside, respectively.

Disaccharide Synthesis

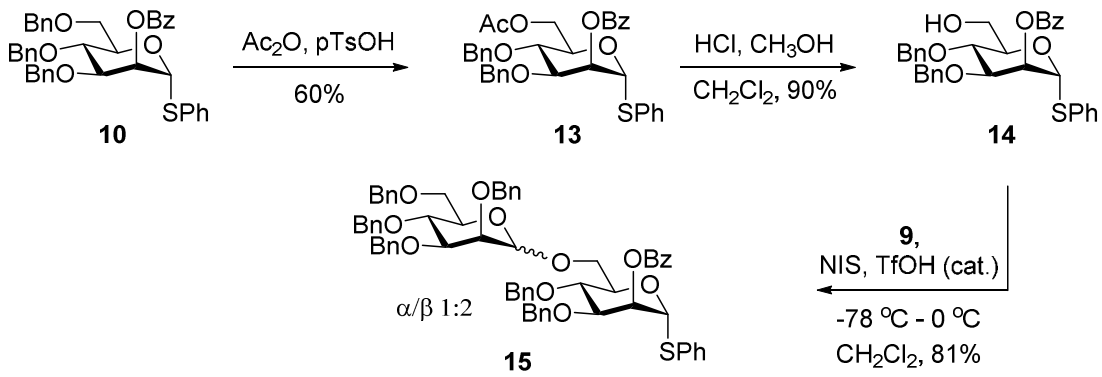
Given the significant reactivity difference between mannosyl donors **9** and **10** (a factor of 13) it was decided to demonstrate that a reactivity controlled chemoselective activation could be performed and attain a disaccharide in an acceptable yield. Removal of a benzyl ether is expected only to have little influence on the reactivity of the glycosyl donor.[11]

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

First, an analogue of the less reactive thiomannopyranoside **10** was prepared to act as an acceptor in coupling with donor **9**. Specifically, this was achieved by acetolysis[23] of **10** to obtain **13** in 60% yield, which was subsequently deacetylated under acidic conditions to obtain the acceptor **14** still possessing a donor function (Scheme 4). Glycosylation of **14** with the more reactive donor **9** indeed resulted in disaccharide **15** as a mixture of anomers (α/β 1:2) in 81% yield demonstrating how the determined reactivity values have synthetic utility. We note that a similar coupling most likely fail in the glucose series as a consequence of the much smaller reactivity difference in reactivity between **1**/**5** and a mono-deprotected derivative of **2**/**6**, respectively.



Scheme 4. Synthesis of disaccharide by chemoselective activation of 9 over 14.

Conclusion

By the use of competition experiments we have investigated the degree to which anomeric configuration, neighboring group participation/anchimeric assistance and electron withdrawing effects influence glycosyl donor reactivity for ethyl- and phenyl thioglucosides and phenyl thiomannosides with NIS/TfOH activation. Using rough estimations, it was possible to arrive at meaningful numbers with respect to reactivity differences suggesting that the above mentioned structural features are the main factors deciding thioglycoside reactivity under NIS/TfOH activation.

Of the three sets of donors investigated, the axial anomer was most reactive for the phenyl thioglucoside, while it was found to be the equatorial anomer for the phenyl thiomannoside. For the ethyl thioglucosides an almost equal reactivity was found between the two anomers.

A significant reactivity difference of a factor of 13 was noted for a set of mannopyranosyl donors that were not present in the analogous glucopyranosyl congeners. This insight was

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

used to perform a mannosylation of a derivative of the less reactive donor possessing an acceptor functionality.

The present study offers new detailed insight into the degree of glycosyl donors armament/disarmament, which is crucial for being able to perform chemoselective thioglycoside activation and thereby reactivity controlled one-pot glycosylations.

General Methods

All reagents were used as purchased without further purification. High purity NIS was bought from Chempur (004499, *N*-iodosuccinimide/98%+). Dry solvents were taken from a solvent purification system. Glassware used for water-free reactions were dried for 12 h at 120 °C before use. Columns were packed with silica gel 60 (230–400 mesh) as the stationary phase. TLC plates were visualized by 10% H_2SO_4 in EtOH and heating until spots appeared. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal. High-resolution mass spectral (HRMS) data were obtained on an electrospray (ES) mass spectrometer analyzing time-of-flight.

Experimental Section

General procedure for glycosylations

A mixture of glycosyl donor (0.10 mmol), glycosyl acceptor (0.15 mmol), and freshly activated molecular sieves (3 Å, 100 mg) in CH_2Cl_2 (2 mL) was stirred under argon for 1 h. The solution was cooled to –78 °C using a dry ice/acetone bath. NIS (0.11 mmol) and TfOH (0.1 mL of a 0.1 M solution of TfOH in CH_2Cl_2) were added. Lumps of dry ice were removed from the acetone bath and the reaction was slowly allowed to reach 0 °C (over approximately 3 hours). After having reached 0 °C, the solids were filtered off and the filtrate was washed with aqueous 10% $Na_2S_2O_3$ solution. The organic layer was separated, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford the corresponding glycoside. Anomeric ratios were measured by comparison of integral intensities of the anomeric protons and anomeric carbons from ^{1}H-NMR and ^{13}C-NMR spectra of crude reaction mixtures.

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

Competition Experiments

The two glycosyl donors (0.10 mmol each) were dissolved in $CDCl_3$ (1 mL) and the ratios of donors were checked to be 1.0:1.0 by ^{1}H NMR and ^{13}C NMR. The solvent was evaporated and dry CH_2Cl_2 (2 mL), L-menthol (0.5 mmol) and freshly activated molecular sieves (3 Å, 100 mg) were added. The mixture was stirred under argon for 1 h. The solution was cooled to −78 °C and NIS (0.10 mmol) and TfOH (0.1 mL of a 0.1 M solution of TfOH in CH_2Cl_2) were added. Lumps of dry ice were removed from the acetone bath and the reaction was slowly allowed to reach 0 °C (over approximately 3 h). Upon completion, the solids were filtered off and the filtrate was washed with aqueous 10% $Na_2S_2O_2$ solution. The organic layer was separated, dried over MgSO4, and concentrated *in vacuo*. The crude mixture was dissolved in $CDCl_3$ (1 mL) and ^{1}H NMR and ^{13}C NMR was measured. Anomeric ratios were measured by comparison of integral intensities of the anomeric protons and anomeric carbons from ^{1}H-NMR and ^{13}C-NMR spectra of crude reaction mixtures.

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (1)

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (21.8 g, 49.7 mmol, 1 equiv.) was dissolved in MeOH and sodium methoxide solution (25 wt. % in MeOH) was added until a pH-value of approximately 10 was reached. The reaction mixture was stirred for 30 h at rt, then neutralized with DOWEX® Acidic Cation Exchanger Resin in MeOH. The resin was filtered off by suction and the product mixture was concentrated *in vacuo*. The crude product was dissolved in anhydrous DMF (60 mL) and cooled to 0 °C. NaH (60 % (w/w) dispersion in mineral oil, 15.9 g, 397 mmol, 8 equiv.) was added and the mixture was stirred for 10 min prior to dropwise addition of BnBr (35.5 mL, 298 mmol, 6 equiv.). The resulting mixture was stirred for 18 h at rt then quenched by cautiously transferring the mixture into a large volume of H_2O at 0 °C. The aqueous phase was extracted with CH_2Cl_2 (three times) and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (pentane/EtOAc 4:1) to afford the product (19.9 g, 31.4 mmol, 63 %) as a white solid. R_f 0.66 (pentane/EtOAc 5:1). $[\alpha]_D^{295K}$ +3.2 (*c* 1.0, $CHCl_3$). lit. +3 ($CHCl_3$).[24] M_p (uncorr.) 91.5 – 92.5 °C. lit. 91 – 92 °C.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57 – 7.52 (m, 2H, Ar*H*), 7.37 – 7.14 (m, 23H, Ar*H*), 4.86 (d, *J* 10.9 Hz, 1H, C*H*HPh), 4.85 (d, *J* 10.2 Hz, 1H, C*H*HPh), 4.81 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.79 (d, *J* 10.8 Hz, 1H, C*H*HPh), 4.69 (d, *J* 10.3 Hz, 1H, CH*H*Ph) 4.63 (d, *J* 9.8 Hz, 1H, H1), 4.57 (d, *J* 12.0 Hz, 1H, C*H*HPh), 4.55 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.50 (d, *J* 12.0 Hz, 1H, CH*H*Ph) 3.75 (dd, *J* 9.8

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

Hz, 1H, H6a), 3.72 – 3.64 (m, 2H, H6b, H3/H4), 3.61 (t, *J* 9.2 Hz, 1H, H3/H4) 3.50 – 3.44 (m, 1H, H5), 3.47 (dd, *J* 9.5 Hz, 8.6 Hz, 1H, H2). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.4 (Ar*C*), 138.3 (Ar*C*), 138.0 (Ar*C*), 133.8 (Ar*C*), 132.0 – 127.5 (Ar*C*H), 87.5 (C1), 86.8 (C3/C4), 80.6 (C2/C5), 79.1 (C2/C5), 77.8 (C3/C4), 75.9 (*C*H_2Ph), 75.5 (*C*H_2Ph), 75.1 (*C*H_2Ph), 73.5 (*C*H_2Ph), 69.0 (C6). HRMS (ES): calcd. for $C_{40}H_{40}O_5SNa^+$ 655.2494; found 655.2488. Spectral values were in accordance with previously reported data.[25]

Phenyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucoyranoside (2)

Phenyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucoyranoside (100 mg, 0.18 mmol, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (3 mL) and DMAP (9 mg, 0.09 mmol, 0.5 equiv.), Et_3N (0.13 mL, 0.92 mmol, 5 equiv.) and BzCl (0.08 mL, 0.74 mmol, 4 equiv.) were added. The mixture was stirred at rt for 18 h. To quench excess BzCl the mixture was stirred with DMAPA[26] (0. 09 mL, 0.74 mmol, 4 equiv.) for 10 min. The reaction mixture was washed with aq. 1M HCl (x3), sat. aq. $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (pentane/EtOAc 10:1) yielding the product (86 mg, 0.14 mmol, 74 %) as a white solid. R_f 0.35 (pentane/EtOAc 5:1). $[\alpha]_D^{295K}$ +28.2 (*c* 1.0, $CHCl_3$), lit. +21.7 (*c* 1.1, $CHCl_3$).[27] M_p (uncorr.) 128.4 – 129.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.09 – 8.03 (m, 2H, Ar*H*), 7.63 – 7.09 (m, 23H, Ar*H*), 5.30 (t, *J* 9.5 Hz, 1H, H2), 4.82 (dd, *J* 10.8 Hz, *J* 10.8 Hz, 2H, C*H*HPh, CH*H*Ph), 4.75 (d, *J* 11 Hz, 1H, H1), 4.67 – 4.56 (m, 4H, 2xCH_2Ph), 3.86 (t, *J* 9.3 Hz, 1H, H3), 3.85 – 3.77 (m, 2H, H6a, H6b), 3.76 (t, *J* 8.8 Hz, 1H, H4), 3.67 – 3.60 (m, 1H, H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.2 (C=O) 138.2 (Ar*C*), 137.9 (Ar*C*), 137.6 (Ar*C*), 137.2 (Ar*C*), 133.2 –127.6 (Ar*C*H), 86.2 (C1), 84.3 (C3), 79.5 (C5), 77.8 (C4), 75.4 (*C*H_2Ph), 75.1 (*C*H_2Ph), 73.4 (*C*H_2Ph), 72.4 (C2), 68.9 (C6). HRMS (ES): calcd. for $C_{40}H_{38}O_6S$ [M+Na^+] 669.2281; found 669.2288. Spectral values were in accordance with previously reported data.[27]

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside (3)

1,2-di-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranose[28] (3.5 g, 6.55mmol) was dissolved in CH_2Cl_2 (20 mL). The solution was added PCl_5 (1.5 g, 7.21 mmol) and finally a drop of $BF_3{\cdot}Et_2O$ was added. After 5 minutes TLC analysis showed no more starting material and the reaction mixture was transferred to a separatory funnel. The reaction mixture was washed with ice water, cold saturated bicarbonate solution and finally with cold brine. The organic

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

layer was dried over Na_2SO_4, filtered and evaporated to dryness. The crude compound was dissolved in HMPA (5 mL) and added to a solution of thiophenol (1.34 mL, 0.013 mol) and NaH (0.79 g, 0.02 mol) in HMPA (10 mL) at 0 °C. The reaction was stirred for 1 hour and then quenched by addition of Ac_2O. The reaction mixture was diluted with EtOAc and then washed 5 times with water then brine followed by drying with $MgSO_4$. The solution was evaporated and the crude compound was subjected to column chromatography with pentane as eluent with a gradient to EtOAc giving phenyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-glucopyranoside as a waxy solid. (1 g, 26 %). R_f: 0.60 (pentane/EtOAc 5:1). $[\alpha]_D^{295K}$ +180 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.39 – 7.05 (m, 20H, Ar*H*), 5.80 (d, *J* 5.6 Hz, 1H, H1), 5.00 (dd, *J* 10.1, 5.6 Hz, 1H, H2), 4.81 – 4.68 (m, 4H, C*H*$_2$Ph), 4.52 (d, *J* 12.0 Hz, 1H, C*H*HPh), 4.45 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.36 (d, *J* 12.0 Hz, 1H, CH*H*Ph), 4.27 (dd, *J* 10.0, 2.0 Hz, 1H, H5), 3.86 (t, *J* 9.4 Hz, 1H, H3), 3.75 – 3.64 (m, 2H, H4, H6a), 3.56 (dd, *J* 10.8, 1.7 Hz, 1H, H6b), 1.96 (s, 3H, C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.2 (C=O), 138.5, 138.1, 138.0, 133.7, 131.9, 129.1, 128.6, 128.6, 128.5, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.5, 85.7 (C1), 81.0 (C3), 77.8 (C4), 75.7 (*C*H$_2$Ph), 75.3 (*C*H$_2$Ph), 73.6 (C2), 73.5 (*C*H$_2$Ph), 71.5 (C5), 68.5 (C6), 21.1 (*C*H$_3$). HRMS (ES): calcd. for $C_{35}H_{36}O_6SNH_4^+$ 602.2576; found 602.2575.

To a stirred solution of phenyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-glucopyranoside (1 g, 1.71 mmol) in MeOH (10 mL) a catalytic amount of Na(s) was added until a pH-value of 10 was reached. The reaction mixture was stirred for 30 h at rt, then neutralized with DOWEX® Acidic Cation Exchanger Resin in MeOH. The resin was filtered off by suction and the product mixture was concentrated *in vacuo*, giving phenyl 3,4,6-tri-*O*-benzyl-1-thio-α-D-glucopyranoside as a white solid. (0.93 g, 100%). R_f: 0.27 (pentane/EtOAc 5:1). $[\alpha]_D^{295K}$ +217 (*c* 1, $CHCl_3$). Mp. 126.5-127.5 °C lit. 123-125 °C.[29] ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.61 – 7.18 (m, 20H, Ar*H*), 5.67 (d, *J* 5.4 Hz, 1H, H1), 4.94 (d, *J* 11.2 Hz, 1H, C*H*HPh), 4.90 (d, *J* 11.2 Hz, 1H, CH*H*Ph), 4.86 (d, *J* 10.8 Hz, 1H, C*H*HPh), 4.67 (d, *J* 12.0 Hz, 1H, C*H*HPh), 4.57 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.51 (d, *J* 12.0 Hz, 1H, CH*H*Ph), 4.37 (d, *J* 9.1 Hz, 1H, H5), 4.05 (dd, *J* 8.9, 5.4 Hz, 1H, H2), 3.86 (dd, *J* 10.8, 3.8 Hz, 1H, H6a), 3.79 – 3.67 (m, 3H, H3, H4, H6b). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 138.5, 138.1, 138.0, 134.2, 132.0, 129.2, 128.7, 128.6, 128.5, 128.1, 128.1, 128.0, 128.0, 127.9, 127.6 (Ar), 90.1 (C1), 83.6, 77.7, 75.6 (*C*H$_2$Ph), 75.1 (*C*H$_2$Ph), 73.6 (*C*H$_2$Ph), 72.5 (C2), 72.1 (C5), 68.6 (C6). HRMS (ES): calcd. for $C_{32}H_{34}O_5SNH_4^+$ 560.2571; found 560.2469. Spectral values were in accordance with those reported.[29]

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

Phenyl 3,4,6-tri-*O*-benzyl-1-thio-α-D-glucopyranoside (400 mg, 0.74 mmol, 1 equiv.) was dissolved in anhydrous DMF (15 mL) under N_2 atmosphere and NaH (60% dispersion in mineral oil, 59 mg, 1.11 mmol, 1.5 equiv.) was added at 0 °C. The mixture was stirred for 10 min prior to dropwise addition of BnBr (0.13 mL, 1.48 mmol, 2 equiv.). The reaction was allowed to reach rt while stirring for 5 h. To quench the reaction sat. aq. NH_4Cl was added until gas development ceased. The reaction mixture was extracted with EtOAc (three times) and the combined organic phases were washed with H_2O (five times), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (pentane/EtOAc 10:1) yielding the product (420 mg, 0.66 mmol, 90%) as a white solid. R_f (EtOAc/pentane 4:1) 0.40, $[\alpha]_D^{295K}$ +148 (*c* 1.0, $CHCl_3$), lit. +142.7 (*c* 0.33, $CHCl_3$).[30] M_p (uncorr.) 76.5 – 78.4 °C, lit. 77 – 78 °C.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72 (dd, *J* 8.0, 1.4 Hz, 2H, Ar*H*), 7.62 – 7.34 (m, 23H, Ar*H*), 5.89 (d, *J* 4.5 Hz, 1H), 5.23 (d, *J* 10.8 Hz, 1H, C*H*HPh), 5.08 (d, *J* 10.8 Hz, 1H, C*H*HPh), 5.03 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.96 (d, *J* 11.8 Hz, 1H, C*H*HPh), 4.87 (d, *J* 11.8 Hz, 1H, CH*H*Ph), 4.77 (d, *J* 12.0 Hz, 1H, C*H*HPh), 4.72 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.63 – 4.56 (m, 1H, H5), 4.59 (d, *J* 12.0 Hz, 1H, CH*H*Ph), 4.18 – 4.10 (m, 2H, H2, H3), 3.98 (dd, *J* 10.7, 3.8 Hz, 1H, H6a), 3.96 – 3.88 (m, 1H, H4), 3.81 (dd, *J* 10.6, 1.6 Hz, 1H, H6b). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 138.9, 138.5, 138.1, 137.9, 134.8, 131.8, 129.2 - 127.3 (Ar), 87.2 (C1), 82.8 (C2/C3), 80.0 (C3/C2), 77.6 (C4), 76.0 (*C*H_2Ph), 75.4 (*C*H_2Ph), 73.6 (*C*H_2Ph), 72.7 (*C*H_2Ph), 71.4 (C5), 68.7 (C6). HRMS (ES): calcd. for $C_{40}H_{40}O_5SNH_4^+$ 650.2935; found 650.2942. Spectral values were in accordance with those reported.[30]

Phenyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-glucoyranoside (4)

Phenyl 3,4,6-tri-*O*-benzyl-1-thio-α-D-glucopyranoside (400 mg, 0.74 mmol, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (10 mL) and DMAP (45 mg, 0.37 mmol, 0.5 equiv.), Et_3N (0.52 mL, 3.70 mmol, 5 equiv.) and BzCl (0.34 mL, 2.96 mmol, 4 equiv.) were added. The mixture was stirred at rt for 5 h under N_2 atmosphere. To quench excess BzCl the mixture was stirred with DMAPA[26] (0.37 mL, 2.96 mmol, 4 equiv.) for 10 min. The reaction mixture was washed with aq. 1M HCl (three times), sat. aq. $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. And the resulting residue purified by flash column chromatography (pentane/EtOAc 10:1) yielding the product (368 mg, 0.57 mmol, 77%) as a white solid. R_f (EtOAc/pentane 4:1) 0.39. $[\alpha]_D^{295K}$ +149 (*c* 1.0, $CHCl_3$). M_p (uncorr.) 56.6 – 58.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.27 – 8.24 (m, 2H, Ar*H*), 7.69 (t, *J*

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

7.4 Hz, 1H, Ar*H*), 7.62 – 7.54 (m, 4H, Ar*H*), 7.51 –7.31 (m, 18H, Ar*H*), 6.21 (d, *J* 5.6 Hz, 1H, H1), 5.63 (dd, *J* 10.0, 5.6 Hz, 1H, H2), 5.08 – 4.99 (m, 2H, C*H*HPh, CH*H*Ph), 5.04 (d, *J* 10.7, 1H, C*H*HPh), 4.78 (d, *J* 12.0 Hz, 1H, C*H*HPh), 4.74 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.68 – 4.62 (m, 1H, H5), 4.61 (d, *J* 12.1 Hz, 1H, CH*H*Ph), 4.33 (t, *J* 9.5 Hz, 1H, H3), 4.05 (t, *J* 9.5 Hz, 1H, H4), 4.01 (dd, *J* 10.8, 3.7 Hz, 1H, H6a), 3.85 (dd, *J* 10.7, 1.4 Hz, 1H, H6b). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.7 (C=O), 138.2, 138.0, 133.6, 133.6, 132.1, 130.1 – 127.6 (Ar), 86.1 (C1), 80.9 (C3), 77.9 (C4), 75.78 (*C*H_2Ph), 75.4 (*C*H_2Ph), 73.8 (C2), 73.6 (*C*H_2Ph), 71.6 (C5), 68.6 (C6). HRMS (ES): calcd. for $C_{40}H_{38}O_6SNH_4^+$ 664.2727; found 664.2732.

Ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-glucopyranoside (7)

A solution of ethyl 3,4,6-tri-*O*-benzyl-1-thio-α-D-glucopyranoside (0.738 g, 1.49 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (1 mL, 7.45 mmol), DMAP (90 mg, 0.75 mmol) and benzoyl chloride (0.7 mL, 6 mmol). The reaction mixture was stirred overnight and then quenched by addition of DMAPA[26] (0.75 mL, 6 mmol). The mixture was washed once with aq. 1M HCl solution then brine. The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness. The compound was further purified by column chromatography with pentane as eluent with a gradient to EtOAc giving the product as a syrup. (788 mg, 82%). R_f: 0.63 (pentane/EtOAc 7:1). $[\alpha]_D^{RT}$ +150 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.08 – 8.02 (m, 2H, Ar*H*), 7.59 (t, *J* 7.4 Hz, 1H Ar*H*), 7.46 (t, *J* 7.7 Hz, 2H, Ar*H*), 7.41 – 7.27 (m, 8H, Ar*H*), 7.23 – 7.15 (m, 7H, Ar*H*), 5.78 (d, *J* 5.7 Hz, 1H, H1), 5.35 (dd, *J* 10.0, 5.7 Hz, 1H, H5), 4.09 (t, *J* 10.0 Hz, 1H, H3), 3.88 – 3.80 (m, 2H, H4, H6a), 3.72 (dd, *J* 10.8, 1.9 Hz, 1H, H6b), 2.56 (m, 2H, S*CH*$_2$), 1.23 (t, *J* 7.4 Hz, 3H, *CH*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.6 (C=O), 138.2, 138.2, 138.0, 133.4, 129.9, 129.8, 128.6, 128.5, 128.4, 128.0, 128.0, 127.9, 127.8, 127.8 (Ar), 82.3 (C1), 80.9 (C3), 77.9 (C4), 75.7 (*C*H_2Ph), 75.2 (*C*H_2Ph), 73.8 (C2), 73.6 (*C*H_2Ph), 70.8 (C5), 68.5 (C6), 24.3 (S*C*H_2), 14.9 (*C*H_3). HRMS (ES): calcd. for $C_{36}H_{38}O_6SNH_4^+$ 616.2727; found 616.2737.

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-mannopyranoside (9)

Phenyl 1-thio-α-D-mannopyranoside (872 mg, 3.20 mmol, 1 equiv.) was dissolved in anhydrous DMF (20 mL) under N_2 atmosphere and NaH (60% dispersion in mineral oil, 1.02 g, 25.60 mmol, 8 equiv.) was added at 0 ^{o}C. The mixture was stirred for 10 min prior to dropwise addition of BnBr (2.29 mL, 19.2 mmol, 6 equiv.). The reaction mixture was

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

allowed to reach rt while stirring for 18 h. To quench the reaction aq. sat. NH_4Cl was added until gas development ceased. The reaction mixture was then extracted with EtOAc (three times) and the organic phase was washed with H_2O (five times, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (pentane/EtOAc 25:1) affording the product (1.83 g, 2.89 mmol, 91%) as a colorless syrup. R_f (EtOAc/pentane 4:1) 0.63, $[\alpha]_D^{295K}$ +86.8 (*c* 1.0, $CHCl_3$), lit. +10 (*c* 1.1, $CHCl_3$)[31]. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 – 7.64 (m, 2H, Ar*H*), 7.58 – 7.37 (m, 23H, Ar*H*), 5.85 (d, *J* 1.3 Hz, 1H, H1), 5.13 (d, *J* 10.8 Hz, 1H, CP*H*HPh), 4.91 (d, *J* 12.3 Hz, 1H, C*H*HPh), 4.84 (d, *J* 12.1 Hz, 1H, C*H*HPh), 4.83 – 4.78 (m, 3H, CH_2Ph), 4.75 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.67 (d, *J* 12.0 Hz, 1H, CH*H*Ph), 4.53 (ddd, *J* 9.7, 4.9, 1.5 Hz, 1H, H5) 4.32 (t, *J* 9.5 Hz, 1H, H4), 4.22 (dd, *J* 2.8, 1.8 Hz, 1H, H2), 4.10 (dd, *J* 9.3, 3.0 Hz, 1H, H3), 4.06 (dd, *J* 11.0, 5.1 Hz, 1H, H6a), 3.95 (dd, *J* 10.8, 1.6 Hz, 1H, H6b). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 138.7, 138.6, 138.4, 138.2, 134.7, 131.9, 129.3, 128.7 - 127.6 (Ar), 86.0 (C1, $J_{C1\text{-}H1}$ 166.2 Hz (characteristic of the α-anomer)[7]), 80.4 (C3), 76.5 (C2), 75.4 (*C*H_2Ph), 75.2 (C4), 73.5 (*C*H_2Ph), 73.0 (C5), 72.3 (*C*H_2Ph), 72.1 (*C*H_2Ph), 69.4 (C6). HRMS (ES): calcd. for $C_{40}H_{40}O_5SNa^+$ 655.2489; found 655.2494. Spectral values were in accordance with previously reported data.[32]

Phenyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (10)

1,2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-D-mannopyranose (5.2 g, 9.74 mmol, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (50 mL) under inert atmosphere and thiophenol (2.00 mL, 19.5 mmol, 2 equiv.) and $BF_3{\cdot}OEt_2$ (3.61 mL, 29.2 mmol, 3 equiv.) were added at 0 °C. The ice bath was removed and the yellow mixture was stirred for 2 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$, diluted with CH_2Cl_2 and washed with H_2O and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* leaving the crude thiomannoside as an α/β-mixture. The thiomannosides were then dissolved in MeOH and sodium methoxide solution (25 wt. % in MeOH) was added until a pH-value of approximately 10 was reached. The reaction mixture was stirred for 18 h under inert atmosphere then neutralized with DOWEX® acidic ion exchanger. The solid was filtered off and filtrate was concentrated *in vacuo* leaving the crude 2-hydroxyl mannosides. The 2-hydroxyl mannoside was dissolved in anhydrous CH_2Cl_2 (35 mL) together with DMAP (287 mg, 2.34 mmol, 0.5 equiv.), Et_3N (3.26 mL, 23.4 mmol, 5 equiv.) and BzCl (2.18 mL, 18.7 mmol, 4 equiv.). The mixture was stirred for 18 h at rt under N_2 atmosphere. To quench

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

excess BzCl the mixture was stirred with DMAPA[26] (2.36 mL, 18.7 mmol, 4 equiv.) for 10 min. The reaction mixture was washed with aq. 1M HCl (three times), sat. aq. $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (pentane/EtOAc 10:1) yielding the product (2.33 g, 1.51 mmol, 37% over 3 steps) as a colorless syrup. R_f (EtOAc/pentane 4:1) 0.67. $[\alpha]_D^{295K}$ -18.8 (*c* 1.0, $CHCl_3$), lit. +69 (*c* 1.1, $CHCl_3$)[33], ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.10 – 8.04 (m, 2H, Ar*H*), 7.56 (t, *J* 7.4 Hz, 1H, Ar*H*), 7.53 – 7.46 (m, 2H, Ar*H*), 7.40 – 7.21 (m, 20H, Ar*H*), 5.88 (dd, *J* 2.7, 1.9 Hz, 1H, H2), 5.66 (d, *J* 1.5 Hz, 1H, H1), 4.92 (d, *J* 10.8 Hz, 1H, C*H*HPh), 4.83 (d, *J* 11.3 Hz, 1H, C*H*HPh), 4.72 (d, *J* 11.9 Hz, 1H, C*H*HPh), 4.62 (d, *J* 11.3 Hz, 1H, CH*H*Ph), 4.58 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.51 (d, *J* 11.9 Hz, 1H, CH*H*Ph), 4.40 (ddd, *J* 9.7, 3.5, 1.3, 1H, H5) 4.18 (t, *J* 9.5 Hz, 1H, H4), 4.07 (dd, *J* 9.3, 3.0 Hz, 1H, H3), 3.96 (dd, *J* 10.9, 4.0 Hz, 1H, H6a), 3.80 (dd, *J* 10.8, 1.6 Hz, 1H, H6b). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.6 (*C*=O), 138.4, 138.3, 137.7, 133.7, 133.3, 131.9, 130.0, 129.8, 129.1, 128.5 - 127.5 (Ar), 86.4 (C1, $J_{C1\text{-}H1}$ 167.2 Hz (characteristic of the α-anomer[34])), 78.6 (C3), 75.4 (*C*H_2Ph), 74.5 (C4), 73.4 (*C*H_2Ph), 72.6 (C5), 71.7 (*C*H_2Ph), 70.6 (C2), 69.0 (C6). HRMS (ES): calcd. for $C_{40}H_{38}O_6SNa^+$ 669.2281; found 669.2289.

Phenyl 2,3,4,6-tri-*O*-benzyl-1-thio-β-D-mannopyranoside (11)

A solution of phenyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (2.68 g, 5 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and Dess-Martin periodinane was added (2.50 g, 6 mmol). The reaction mixture was stirred for 3 hours while allowed to warm to rt. The reaction mixture was quenched by addition of saturated aq. $NaHCO_3$ and 10% $Na_2S_2O_2$ solution while stirring vigorously for 1 hour. The organic phase was separated and dried over $MgSO_4$ and evaporated to dryness. The crude compound was dissolved in a 1:1 mixture of MeOH and CH_2Cl_2 (30 mL). The solution was cooled to 0 °C and added $NaBH_4$ (2.5 g, 70 mmol). The reaction mixture was stirred for 2 hours while allowed to warm to rt. The mixture was diluted with CH_2Cl_2 and washed once with water, twice with aq. 1% citric acid solution and then brine. The solution was dried over $MgSO_4$ and evaporated to dryness. Crystallization from diisopropyl ether gave the Phenyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-mannopyranoside at colorless needles. (1.054 g, 39%). R_f: 0.59 (pentane/EtOAc 3:1). $[\alpha]_D^{295K}$ -44 (*c* 1, $CHCl_3$). Lit. -52, (*c* 1.5, $CHCl_3$)[35]. Mp. 113-114 °C lit. 109-110 °C.[35] ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.72 – 7.20 (m, 20H, Ar*H*), 4.95 (d, *J* 10.9 Hz, 1H, C*H*HPh), 4.87 (s, 1H, H1), 4.81 (d, *J* 11.6 Hz, 1H, C*H*HPh), 4.73 (d, *J* 11.6 Hz, 1H, CH*H*Ph), 4.71 –

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

4.58 (m, 3H, C*H*Ph), 4.36 (s, 1H), 3.90 (t, *J* 9.8 Hz, 2H), 3.79 (dd, *J* 10.9, 6.0 Hz, 1H), 3.72 – 3.66 (m, 1H), 3.63 – 3.54 (m, 1H), 2.77 (s, 1H, O*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 138.3, 138.1, 137.5, 135.1, 130.8, 129.0, 128.6, 128.4, 128.3, 128.1, 128.1, 128.0, 127.8, 127.8, 127.6, 127.2 (Ar), 86.7 (C1), 82.7, 79.6, 75.2, 74.2, 73.5, 71.9, 69.9, 69.5. HRMS (ES): calcd. for $C_{33}H_{34}O_5SNa^+$ 565.2019; found 565.2028. Spectral values were in accordance with those reported.[35]

A solution of phenyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-mannopyranoside (0.40 g, 0.74 mmol) in DMF was cooled to 0 °C and added NaH (60 % (w/w) dispersion in mineral oil (59 mg, 1.48mmol) and BnBr (0.18 mL, 1.48 mmol). The solution was stirred overnight and quenched by addition of water. The solution was diluted with EtOAc and washed 5 times with water, then brine. The organic phase was dried over $MgSO_4$ and evaporated to dryness. The crude compound was purified by column chromatography with pentane as eluent with a gradient to EtOAc giving the product as a white solid. (0.424 g, 91%). R_f: 0.4 (pentane/EtOAc 9:1). $[\alpha]_D^{295K}$ -44 (*c* 1, $CHCl_3$). Lit. -4.1 (*c* 1, $CHCl_3$).[36] Mp. 114-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.60 – 7.50 (m, 4H, Ar*H*), 7.43 – 7.18 (m, 21H, Ar*H*), 5.09 (d, *J* 11.5 Hz, 1H, C*H*HPh), 4.93 (d, *J* 10.8 Hz, 1H, C*H*HPh), 4.91 (d, *J* 11.5 Hz, 1H, CH*H*Ph), 4.82 (s, 1H, H1), 4.78 (d, *J* 11.8 Hz, 1H, C*H*HPh), 4.73 (d, *J* 11.8 Hz, 1H, CH*H*Ph), 4.64 (m, 2H, CH_2Ph), 4.59 (d, *J* 11.7 Hz, 1H, CH*H*Ph), 4.19 (d, *J* 2.5 Hz, 1H, H2), 3.98 (t, *J* 9.6 Hz, 1H, H4), 3.89 (dd, *J* 10.9, 1.7 Hz, 1H, H6a), 3.79 (dd, *J* 10.9, 6.6 Hz, 1H, H6b), 3.68 (dd, *J* 9.4, 2.9 Hz, 1H, H3), 3.61 – 3.55 (m, 1H, H5). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 138.6, 138.4, 138.3, 138.1, 135.8, 130.7, 129.0, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 127.9, 127.9, 127.9, 127.7, 127.5, 127.1 (Ar), 87.7 (C1), 84.5 (C3), 80.2 (C5), 77.6 (C2), 75.3, 75.2, 75.0, 73.6, 72.7 (*C*H_2Ph), 69.9 (C6). HRMS (ES): calcd. for $C_{40}H_{40}O_5SNH_4^+$ 650.2935; found 650.2933. Spectral values were in accordance with those reported.[36]

Phenyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-mannopyranoside (12)

A solution of phenyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-mannopyranoside (0.40 g, 0.74 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (0.51 mL, 3.7 mmol), DMAP (45 mg, 0.37 mmol) and benzoyl chloride (0.34 mL, 3 mmol). The reaction mixture was stirred overnight and then quenched by addition of DMAPA[26] (0.37 mL, 3 mmol). The mixture was washed once with aq. 1 M HCl solution then brine. The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness. The compound was further purified by column chromatography with pentane as eluent with a gradient to EtOAc giving the product as a syrup. (415 mg, 87%). R_f:

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

0.42 (pentane/EtOAc 8:1). $[\alpha]_D^{295K}$ -67 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.19 (d, *J* 7.2 Hz, 2H, Ar*H*), 7.70 – 7.19 (m, 23H, Ar*H*), 6.07 (d, *J* 3.1 Hz, 1H, H2), 4.99 (s, 1H, H1), 4.92 (d, *J* 10.8 Hz, 1H, C*H*HPh), 4.90 (d, *J* 10.1 Hz, 1H, C*H*HPh), 4.79 (d, *J* 11.9 Hz, 1H, C*H*HPh), 4.66 (d, *J* 11.9 Hz, 1H, CH*H*Ph), 4.61 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.59 (d, *J* 11.2 Hz, 1H, CH*H*Ph), 4.00 (t, *J* 9.3 Hz, 1H, H4), 3.92 (m, 2H, H6), 3.83 (dd, *J* 9.3, 3.3 Hz, 1H, H3), 3.67 (ddd, *J* 9.7, 4.2, 2.7 Hz, 1H, H5). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.8 (C=O), 138.5, 138.2, 137.5, 134.3, 133.2, 131.1, 130.2, 129.7, 129.0, 128.4, 128.4, 128.4, 128.4, 128.3, 128.0, 127.8, 127.8, 127.5, 127.5, 127.4 (Ar), 85.5 (C1), 81.5 (C3), 79.9 (C5), 75.3 (*C*H_2Ph), 74.1 (C4), 73.5 (*C*H_2Ph), 71.7 (*C*H_2Ph), 70.7 (C2), 69.5 (C6). HRMS (ES): calcd. for $C_{40}H_{38}O_6SNH_4^+$ 664.2727; found 664.2722.

L-Menthyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside

Appearance: Colorless oil. R_f 0.38 (pentane/EtOAc, 5:1). $[\alpha]_D^{295K}$ +31 (*c* 1.0, $CHCl_3$), lit. + 31.3 (*c* 1.1, $CHCl_3$).[37] ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.37 - 7.23 (m, 18H, Ar*H*), 7.15 - 7.11 (m, 2H, Ar*H*), 5.02 (d, *J* 3.6 Hz, 1H, H1), 4.98 (d, *J* 10.9 Hz, 1H, C*H*HPh), 4.84 (d, *J* 10.7 Hz, 1H, C*H*HPh), 4.82 (d, *J* 10.9 Hz, 1H, CH*H*Ph), 4.72 (d, *J* 11.8 Hz, 1H, C*H*HPh), 4.68 (d, *J* 12.3 Hz, 1H, CH*H*Ph), 4.64 (d, *J* 12.3 Hz, 1H, C*H*HPh), 4.47 (d, *J* 12.1 Hz, 1H, CH*H*Ph), 4.45 (d, *J* 10.7 Hz, 1H, CH*H*Ph), 4.02 (t, *J* 9.5 Hz, H3), 4.00 – 3.93 (m, 1H, H5), 3.75 (dd, *J* 10.5, 3.7 Hz, 1H, H6a), 3.64 (t, *J* 9.4 Hz, 1H, H4), 3.64 (dd, *J* 10.5, 1.6 Hz, 1H, H6b), 3.55 (dd, *J* 19.8, 3.6 Hz, 1H, H2), 3.35 (dt, *J* 10.6, 4.3 Hz, 1H, OC*H*), 2.42 (dsep, *J* 6.9, 1.9 Hz, 1H, C*H*$(CH_3)_2$), 2.16 – 2.08 (m, 1H), 1.65 - 1.57 (m, 2H), 1.40 – 1.25 (m, 2H), 1.08 – 0.75 (m, 3H), 0.86 (d, *J* 6.4 Hz, 3H, C*H*$_3$), 0.83 (d, *J* 7.1 Hz, 3H, C*H*$_3$), 0.71 (d, *J* 6.9 Hz, 3H, C*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 138.9, 138.4, 138.3, 138.0, 128.5 - 127.5 (Ar), 98.6 (C1), 82.0 (C3), 81.0 (O*C*H), 80.5 (C2), 78.1 (C4), 75.5 (*C*H_2Ph), 75.1 (*C*H_2Ph), 73.5 (*C*H_2Ph), 73.2 (*C*H_2Ph), 70.3 (C5), 68.6 (C6), 48.8, 43.1 (*C*H_2), 34.3 (*C*H_2), 31.7, 24.6 (*C*H$(CH_3)_2$), 22.9 (*C*H_2), 22.3 (*C*H_3), 21.1 (*C*H_3), 16.1 (*C*H_3). HRMS (ES): Calcd. for $C_{44}H_{54}O_6NH_4^+$ 696.4259; found 696.4273. Spectral values were in accordance with previously reported data.[37]

L-Menthyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside

Appearance: White solid. R_f 0.47 (pentane/EtOAc, 5:1). $[\alpha]_D^{295K}$ -16 (*c* 1.0, $CHCl_3$), lit. -17.2 (*c* 1.05, $CHCl_3$).[38] ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.57 – 7.53 (m, 1H, Ar*H*), 7.43 – 7.23 (m,

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

19H, Ar*H*), 5.01 (d, *J* 10.6 Hz, 1H, C*H*HPh), 4.98 (d, *J* 10.8 Hz, 1H, C*H*HPh), 4.88 (d, *J* 10.8 Hz, 1H, C*H*HPh), 4.85 (d, *J* 11.0 Hz, 1H, CH*H*Ph), 4.74 (d, *J* 10.9 Hz, 1H, CH*H*Ph), 4.67 (d, *J* 12.0 Hz, 1H, C*H*HPh), 4.64 (d, *J* 10.4 Hz, 1H, CH*H*Ph), 4.60 (d, *J* 12.2 Hz, 1H, CH*H*Ph), 4.53 (d, *J* 7.8 Hz, 1H, H1), 3.75 (d, *J* 3.2 Hz, 2H, H6a, H6b), 3.70 (t, *J* 8.5 Hz, H3/H4), 3.65 (t, *J* 9.0 Hz, H3/H4), 3.56 (td, *J* 10.7, 4.2 Hz, 1H, OC*H*), 3.50 – 3.44 (m, 1H, H5), 3.47 (t, *J* 8.2 Hz, 1H, H2), 2.46 – 2.35 (m, 1H, C*H*$(CH_3)_2$), 2.20 (d, *J* 12.1 Hz, 1H), 1.72 (m, 2H), 1.46 – 1.28 (m, 2H), 1.11 – 0.92 (m, 3H), 0.98 (d, *J* 7.1 Hz, 3H, CH_3), 0.96 (d, *J* 6.6 Hz, 3H, CH_3), 0.88 (d, *J* 6.9 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 138.9, 138.6, 138.4, 138.3, 129.1 – 127.2 (Ar), 100.8 (C1), 85.0 (C3/C4), 82.3 (C5/C2), 78.0 (C4/C3), 77.8 (O*C*H), 75.7 (*C*H_2Ph), 75.1 (*C*H_2Ph), 74.9 (*C*H_2Ph), 74.9 (C2/C5), 73.7 (*C*H_2Ph), 69.4 (C6), 48.2, 41.0 (*C*H_2), 34.5 (*C*H_2), 31.5, 25.3 (*C*H$(CH_3)_2$), 23.3 (*C*H_2), 22.3 (*C*H_3), 21.2 (*C*H_3), 16.0 (*C*H_3). Spectral values were in accordance with previously reported data.[38]

L-Menthyl 3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-β-D-glucopyranoside

Appearance: White solid. R_f 0.50 (pentane/EtOAc 4:1). $[\alpha]_D^{295K}$ -17 (*c* 1.0, $CHCl_3$). M_p (uncorr.) 68.0 – 70.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.95 -7.92 (m, 2H, Ar*H*), 7.51 – 7.39 (m, 1H, Ar*H*), 7.34 (t, *J* 7.7 Hz, 2H, Ar*H*), 7.28 – 7.13 (m, 10H, Ar*H*), 7.09 – 7.01 (m, 5H, Ar*H*), 5.14 (t, *J* 8.5 Hz, 1H, H2), 4.76 (d, *J* 10.6 Hz, 1H, C*H*HPh), 4.66 (d, *J* 11.0 Hz, 1H, C*H*HPh), 4.58 (d, *J* 10.6 Hz, 1H, CH*H*Ph), 4.56 (d, *J* 12.1 Hz, 1H, C*H*HPh), 4.55 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.49 (d, *J* 12.5 Hz, 1H, CH*H*Ph), 4.48 (d, *J* 8.3 Hz, 1H, H1), 3.72 (t, *J* 9.0 Hz, 1H, H3), 3.70 – 3.62 (m, 3H, H4, H6a, H6b), 3.47 – 3.40 (m, 1H, H5), 3.31 (td, *J* 10.8, 4.1 Hz, 1H, OC*H*), 2.23 (dsep, *J* 6.9, 2.5 Hz, 1H, C*H*$(CH_3)_2$), 1.82 – 1.75 (m, 1H), 1.52 – 1.41 (m, 2H), 1.24 – 1.11 (m, 2H), 1.10 - 1.00 (m, 1H), 0.89 - 0.78 (m, 1H), 0.77 (d, *J* 7.1 Hz, 3H, CH_3), 0.69 (d, *J* 6.8 Hz, 3H, CH_3), 0.64 (d, *J* 6.6 Hz, 3H, CH_3), 0.60 - 0.47 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.3 (*C*=O), 138.5, 138.2, 138.1, 133.0, 130.4, 129.9, 129.2, 128.6 - 127.3 (Ar), 99.3 (C1), 83.1 (C3), 78.8 (O*C*H), 78.3 (C4), 75.4 (C5), 75.2 (*C*H_2Ph), 74.9 (*C*H_2Ph), 74.2 (C2), 73.9 (*C*H_2Ph), 69.3 (C6), 47.5, 41.1 (*C*H_2), 34.3 (*C*H_2), 31.4, 25.1, 23.1 (*C*H$(CH_3)_2$), 22.2 (*C*H_3), 21.1 (*C*H_3), 15.9 (*C*H_3). HRMS (ES) Calcd. for C-$_{44}H_{52}O_7NH_4^+$ 710.4071 found; 710.4062.

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

L-Menthyl 2,3,4,6-tetra-*O*-benzyl-2-*O*-benzoyl-α-D-mannopyranoside

Appearance: Colorless oil. R_f (pentane/EtOAc 6:1) 0.55. $[\alpha]_D^{295K}$ -89.2 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.31 – 7.16 (m, 18H, Ar*H*), 7.12 – 7.07 (m, 2H, Ar*H*), 4.82 (d, *J* 10.7 Hz, 1H, C*H*HPh), 4.80 (d, *J* 1.4 Hz, 1H, H1), 4.66 (d, *J* 12.6 Hz, 1H, C*H*HPh), 4.61 (d, *J* 12.8 Hz, 1H, CH*H*Ph), 4.59 (d, *J* 12.2 Hz, 1H, C*H*HPh) 4.58 (d, *J* 12.0 Hz, 1H, C*H*HPh), 4.53 (d, *J* 11.8 Hz, 1H, CH*H*Ph), 4.45 (d, *J* 12.8 Hz, 1H, CH*H*Ph), 4.42 (d, *J* 10.9 Hz, 1H, CH*H*Ph), 3.91 – 3.77 (m, 3H, H3, H4, H5), 3.72 (dd, *J* 10.6, 4.5 Hz, 1H, H6a), 3.65 (dd, *J* 10.8, 1.0 Hz, 1H, H6b), 3.62 – 3.58 (m, 1H, H2), 3.17 (td, *J* 10.6, 4.3 Hz, 1H, OC*H*), 2.07 (d, *J* 12.0 Hz, 1H), 1.69 (dsep, *J* 7.0, 2.3 Hz, 1H, C*H*$(CH_3)_2$), 1.55 – 1.43 (m, 2H), 1.31 – 1.18 (m, 1H), 1.06 – 0.99 (m, 1H), 0.91 – 0.64 (m, 3H), 0.75 (d, *J* 7.0 Hz, 3H, CH_3), 0.74 (d, *J* 6.5 Hz, 3H, CH_3), 0.56 (d, *J* 6.9 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 138.6, 138.6, 138.5, 138.3, 128.4 – 127.4 (Ar), 99.9 (C1, $J_{C1\text{-}H1}$ 166.6 Hz (characteristic of the α-product)[7]), 81.1 (O*C*H), 80.1 (C3), 75.3 (C4/C5), 75.2 (*C*H_2Ph), 74.4 (C2), 73.3 (*C*H_2Ph), 72.4 (*C*H_2Ph), 72.3 (*C*H_2Ph), 71.8 (C5/C4), 69.5 (C6), 48.7, 42.9 (*C*H_2), 34.3 (*C*H_2), 31.6, 25.7 (*C*H$(CH_3)_2$), 23.2, 22.2 (*C*H_3), 21.1 (*C*H_3), 16.3 (*C*H_3). HRMS (ES): calcd. for $C_{44}H_{54}O_6Na^+$ 701.3813; found 701.3832.

L-Menthyl 2,3,4,6-tetra-*O*-benzyl-2-*O*-benzoyl-β-D-mannopyranoside

Appearance: Colorless oil. R_f (pentane/EtOAc 6:1) 0.65. $[\alpha]_D^{295K}$ -23.4 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.44 – 7.40 (m, 2H, Ar*H*), 7.31 – 7.18 (m, 18H, Ar*H*), 4.94 (d, *J* 12.4 Hz, 1H, C*H*HPh), 4.88 (d, *J* 10.8 Hz, 1H, C*H*HPh), 4.81 (d, *J* 12.4 Hz, 1H, CH*H*Ph), 4.64 (d, *J* 11.9 Hz, 1H, C*H*HPh), 4.54 (d, *J* 11.0 Hz, 1H, C*H*HPh), 4.52 (d, *J* 11.9 Hz, 1H, CH*H*Ph), 4.48 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.47 (s, 1H, H1), 4.43 (d, *J* 11.5 Hz, 1H, CH*H*Ph), 3.84 (t, *J* 9.6 Hz, 1H, H4), 3.80 – 3.70 (m, 3H, H2, H6a, H6b), 3.56 – 3.47 (m, 2H, OC*H*, H3), 3.42 – 3.36 (m, 1H, H5), 2.38 (dsep, *J* 7.0, 2.3 Hz, 1H, C*H*$(CH_3)_2$), 1.95 (d, *J* 12.0 Hz, 1H), 1.67 – 1.57 (m, 2H), 1.38 – 1.27 (m, 1H), 1.26 – 1.17 (m, 1H), 1.03 – 0.81 (m, 2H), 0.87 (d, *J* 6.6 Hz, 3H, CH_3), 0.86 (d, *J* 7.2 Hz, 3H, CH_3), 0.79 (d, *J* 6.8 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 139.1, 138.7, 138.5, 138.4, 128.4 – 127.3 (Ar), 98.0 (C1, $J_{C1\text{-}H1}$ 154.1 Hz (characteristic of the β-product)[7]), 82.7 (C3), 76.3 (O*C*H), 76.1 (C5), 75.2 (C4), 75.1 (C2), 74.9 (*C*H_2Ph), 73.9 (*C*H_2Ph), 73.7 (*C*H_2Ph), 71.3 (*C*H_2Ph), 70.1 (C6), 48.3, 40.5 (*C*H_2), 34.5 (*C*H_2), 31.4, 25.3 (*C*H$(CH_3)_2$), 23.1 (*C*H_2), 22.4 (*C*H_3), 21.3 (*C*H_3),16.0 (*C*H_3). HRMS (ES): calcd. for $C_{44}H_{54}O_6Na^+$ 701.3813; found 701.3842.

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

L-Menthyl 3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-β-D-mannopyranoside

Colorless oil, 59 mg, 79%.

R_f (pentane/EtOAc 5:1) 0.60. $[\alpha]_D^{295K}$ -18.8 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.12 – 8.07 (m, 2H, Ar*H*), 7.59 – 7.53 (m, 1H, Ar*H*), 7.43 – 7.20 (m, 17H, Ar*H*), 5.53 (d, *J* 1.7 Hz, 1H, H2), 5.05 (d, *J* 1.4 Hz, 1H, H1), 4.91 (d, *J* 10.7 Hz, 1H, C*H*HPh), 4.81 (d, *J* 11.5 Hz, 1H, C*H*HPh), 4.76 (d, *J* 12.0 Hz, 1H, C*H*HPh), 4.62 (d, *J* 11.5 Hz, 1H, CH*H*Ph), 4.55 (d, *J* 11.6 Hz, 1H, CH*H*Ph), 4.16 – 4.01 (m, 3H, H3, H4, H5), 3.92 (dd, *J* 10.6, 3.9 Hz, 1H, H6a), 3.79 (dd, *J* 10.6, 1.2 Hz, 1H, H6b), 3.43 – 3.34 (m, 1H, OC*H*), 2.21 (d, *J* 11.8 Hz, 1H), 2.14 – 2.02 (m, 1H), 1.68 – 1.58 (m, 2H), 1.44 – 1.30 (m, 1H), 1.30 – 0.80 (m, 3H), 0.94 (d, *J* 7.0 Hz, 3H, CH_3), 0.87 (d, *J* 6.4 Hz, 3H, CH_3), 0.80 (d, *J* 6.9 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.9 (*C*=O), 138.5, 138.4, 138.1, 133.1, 130.1 – 127.5 (Ar), 99.4 (C1, J_{C1-H1} 164.8 Hz (characteristic of the α-product)[7]), 81.9 (O*C*H), 78.0 (C3/C4), 75.4 (*C*H_2Ph), 74.6 (C3/C4), 73.4 (*C*H_2Ph), 71.7 (C5), 71.5 (*C*H_2Ph), 69.6 (C2), 69.2 (C6), 48.5, 42.7 (*C*H_2), 34.3 (*C*H_2), 31.6, 26.0, 23.4 (*C*H_2), 22.3 (*C*H_3), 21.0 (*C*H_3), 16.4 (*C*H_3). HRMS (ES): calcd. for $C_{44}H_{52}O_7Na^+$ 715.3605; found 715.3617.

Phenyl 6-*O*-acetyl-2-*O*-benzoyl-3,4-di-*O*-benzyl-1-thio-α-D-mannopyranoside (13)

Thioglycoside **10** (0.963 g, 1.49 mmol) was dissolved in Ac_2O (8.5 mL). TsOH*H_2O (0.370 g, 1.95 mmol, 1.3 equiv.) was added. The reaction mixture was stirred at 70 °C for 2.5 h before it was poured into H_2O. The mixture was extracted thrice with EtOAc and the resulting organic phase was washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (pentane/AcOEt 20:1→6:1) to give **13** (0.538 g, 0.90 mmol, 60%) as a colorless oil. R_f (pentane/AcOEt 8:1) 0.30. $[\alpha]_D^{298K}$ +106.5 (*c* 2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.14-8.10 (m, 2H, Ar*H*), 7.62 (tt, J_{ortho} 7.4 Hz, J_{meta} 1.3 Hz, 1H, Ar*H*), 7.55-7.45 (m, 4H, Ar*H*), 7.42-7.21 (m, 13H, Ar*H*), 5.90 (dd, $J_{2,3}$ 2.9 Hz, $J_{2,1}$ 1.8 Hz, 1H, H2), 5.64 (d, 1H, H1), 4.96 (d, J_{gem} 10.9 Hz, 1H, C*H*HPh), 4.87(d, J_{gem} 11.2 Hz, 1H, C*H*HPh), 4.67 (d, J_{gem} 10.9 Hz, 1H, CH*H*Ph), 4.65 (d, J_{gem} 11.2 Hz, 1H, CH*H*Ph), 4.49 (ddd, $J_{5,4}$ 9.6 Hz, $J_{5,6a}$ 4.6 Hz, $J_{5,6b}$ 2.4 Hz, 1H, H5), 4.44 (dd, $J_{6a,6b}$ 11.7 Hz, 1H, H6a), 4.39 (dd, 1H, H6b), 4.13 (dd, $J_{3,4}$ 9.2 Hz, 1H, H3), 4.00 (t, 1H, H4), 2.06 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 170.7, 165.5 (*C*=O), 137.9, 137.5 (Ar*C*), 133.4 (Ar*C*H), 133.3 (Ar*C*), 132.3, 129.9 (Ar*C*H), 129.8 (Ar*C*), 129.2, 128.5-128.0 (Ar*C*H), 86.3 (C1), 78.7 (C3), 75.3 (*C*H_2Ph), 73.9 (C4), 71.7

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

(*C*H_2Ph), 70.8 (C5), 70.4 (C2), 63.4 (C6), 20.9 (*C*H_3). HRMS (ES): calcd. for $C_{35}H_{34}O_7SNH_4^+$ 616.2363; found 616.2374.

Phenyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-1-thio-α-D-mannopyranoside (14)

Acetate **13** (0.125 gm 0.21 mmol) was dissolved in dry CH_2Cl_2 (4 mL) and dry MeOH (4 mL). AcCl (0.2 mL, 2.8 mmol, 13 equiv.) was added. The reaction mixture was stirred at 6 h at rt before removal of volatiles under reduced pressure. The crude residue was purified by flash column chromatography (pentane/AcOEt 5:1→3:1) to give **14** (0.105 g, 0.19 mmol, 90%) as a colorless oil. R_f (pentane/AcOEt 3:1) 0.47. $[\alpha]_D^{298K}$ +87.8 (*c* 1.0, $CHCl_3$), lit. +82 (*c* 1.72, $CHCl_3$).[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.12-8.07 (m, 2H, Ar*H*), 7.61 (tt, J_{ortho} 7.5 Hz, J_{meta} 1.2 Hz, 1H, Ar*H*), 7.54-7.44 (m, 4H, Ar*H*), 7.42-7.23 (m, 13H, Ar*H*), 5.88 (t, $J_{2,1/3}$ 1.5 Hz, 1H, H2), 5.63 (d, 1H, H1), 4.98 (d, J_{gem} 10.9 Hz, 1H, C*H*HPh), 4.84 (d, J_{gem} 11.4 Hz, 1H, C*H*HPh), 4.72 (d, J_{gem} 10.9 Hz, 1H, CH*H*Ph), 4.65 (d, J_{gem} 11.4 Hz, 1H, CH*H*Ph), 4.30-4.25 (m, 1H, H5), 4.13-4.06 (m, 2H, H3, H4), 3.93-3.85 (m, 2H, H6a, H6b), 1.88 (s, 1H, O*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.7 (*C*=O), 138.2, 137.7 (Ar*C*), 133.5 (Ar*C*H), 133.3 (Ar*C*), 132.3, 130.0 (Ar*C*H), 129.8 (Ar*C*), 129.3 (Ar*C*H), 128.6-127.9 (Ar*C*H), 86.5 (C1), 78.5 (C3), 75.5 (*C*H_2Ph), 74.1 (C5), 73.1 (C4), 71.8 (*C*H_2Ph), 70.8 (C2), 62.0 (C6). Spectral values were in accordance with earlier reported.[39] HRMS (ES): calcd. for $C_{33}H_{32}O_6SNH_4^+$ 574.2258; found 574.2267.

Phenyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-mannopyranosyl)-2-*O*-benzoyl-3,4-di-*O*-benzyl-1-thio-α-D-mannopyranoside (15)

Acceptor **14** (0.056 g, 0.10 mmol, 1 equiv.) and donor **9** (0.081 g, 0.13 mmol, 1.3 equiv.) were dissolved in dry CH_2Cl_2 (2 mL). 3 Å molecular sieves (0.100 g) were added and the reaction mixture was stirred 1 h at rt before it was cooled to -78 °C in an acetone-dry ice bath. NIS (0.030 g, 0.13 mmol, 1.3 equiv.) and TfOH (0.13 mL of a 0.1 M solution in CH_2Cl_2, 0.013 mmol, 0.1 equiv.) were added. Lumps of dry ice were removed, and the cooling bath was allowed to reach 0 °C over 3 h and 15 min. The reaction mixture was filtered and 10% aq. $Na_2S_2O_3$ was added. The mixture was extracted with CH_2Cl_2 (x3). The resulting organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (CH_2Cl_2/Et_2O 200:1→100:1) to give **15** (0.088 g, 0.082 mmol, 81%, α/β 1:2) as a colorless oil.

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

R_f (Pentane/EtOAc 4:1) 0.61. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.06-8.00 (m, 4H, 2Ar*H*-α, 2Ar*H*-β), 7.51-7.43 (m, 6H, 3Ar*H*-α, 3Ar*H*-β), 7.40-7.10 (m, 70H, 35Ar*H*-α, 35Ar*H*-β), 5.85 (dd, $J_{2,3}$ 3.1 Hz, $J_{2,1}$ 1.7 Hz, 1H, H2-β), 5.82 (dd, $J_{2,3}$ 3.0 Hz, $J_{2,1}$ 1.7 Hz, 1H, H2-α), 5.64 (d, 1H, H1-β), 5.56 (d, 1H, H1-α), 4.99 (d, $J_{1',2'}$ 1.5 Hz, 1H, H1'-α), 4.96-4.84 (m, 5H, 2xC*H*HPh-α, 3xC*H*HPh-β), 4.81 (d, J_{gem} 11.3 Hz, 1H, C*H*HPh-β), 4.79 (d, J_{gem} 11.0 Hz, 1H, C*H*HPh-α), 4.73 (d, J_{gem} 12.3 Hz, 1H, C*H*HPh-β), 4.69-4.31 31 (m, 20H, 9xC*H*HPh-α, 7xC*H*HPh-β, 2xH-α, 2xH-β), 4.28 (s, 1H, H1'-β), 4.08 (dd, $J_{3,4}$ 9.2 Hz, $J_{3,2}$ 3.2 Hz, 1H, H3-β), 4.05-3.66 (m, 13H, 6xH-β, 8xH-α), 3.62 (dd, J_{gem} 10.7 Hz, $J_{6b/b',5/5'}$ 1.4 Hz, 1H, H6b/b'-α), 3.44-3.38 (m, 1H, H5'-β), 3.38 (dd, $J_{3',4'}$ 9.4 Hz, $J_{3',2'}$ 3.3 Hz, 1H, H3'-β). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.8 (*C*=O, β), 165.7 (*C*=O, α), 102.3 (C1'-β), 98.3 (C1'-α), 86.5 (C1-β), 86.4 (C1-α), 82.3 (C3'-β), 80.1 (C3'-α), 78.8 (C3-α), 78.8 (C3-β), 76.1 (C5'-β), 75.3 (*C*H_2Ph-α), 75.2 (*C*H_2Ph-β), 75.2 (*C*H_2Ph-β), 75.2 T, 75.1 (*C*H_2Ph-α), 75.0 (C-α), 75.0 (C-β), 74.9 (C-β), 74.6 (C-α), 74.2 (*C*H_2Ph-β), 74.1 (C-β), 73.6 (*C*H_2Ph-β), 73.3 (*C*H_2Ph-α), 72.7 (C-β), 72.7 (*C*H_2Ph-α), 72.2 (C-α), 72.1 (*C*H2Ph-α), 72.1 (C-α), 71.8 (*C*H_2Ph-β), 71.8 (*C*H_2Ph-α), 71.4 (*C*H_2Ph-β), 71.0 (C2-β), 70.9 (C2-α), 69.9 (C6/C6'-α), 69.2 (C6+C6'-β), 66.4 (C6/C6'-α). HRMS (ES): calcd. for $C_{67}H_{66}O_{11}SNH_4^+$ 1096.4664; found 1096.4679.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the publications website: Glycosylation results under a non-competitive setting and ^{1}H and ^{13}C spectra of compounds.

Corresponding Author

*Email: hhj@chem.au.dk

ACKNOWLEDGMENT

We are grateful for financial support from The Villum Foundation (VKR023110)

References

[1] Definition of neighboring group participation see http://goldbook.iupac.org/N04100.html (visited 1.2.2018)
[2] Capon, B. *Q. Rev. Chem. Soc*. **1964**, *18*, 45-111.
[3] Winstein, S.; Buckles, R. E. *J. Am. Chem. Soc.* **1942**, *64*, 2780-2786.
[4] For a selection of this massive work see: a) Lemieux, R. U.; Brice, C. *Can. J. Chem.* **1955**, *33*, 109-119. b) Lemieux, R. U.; Huber, G. *Can. J. Chem.* **1955**, *33*, 128-133. c) Lemieux, R. U.; Shyluk, W. P.; Huber, G. *Can. J. Chem*. **1955**, *33*, 148-162.
[5] Heuckendorff, M.; Pedersen, C. M.; Bols, M. *Org. Lett.* **2011**, *13*, 5956-5959.
[6] Poulsen, L. T.; Heuckendorff, M.; Jensen, H. H. "On the Generality of Superarmament of Glycosyl Donors" *submitted and accepted by Org. Biomol. Chem.*

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB02968C

Published on 15 February 2018. Downloaded by University of New England on 15/02/2018 19:27:22.

[7] a) Mydock, L. K.; Demchenko, A. V. *Org. Lett.* **2008**, *10*, 2103-2106. b) Mydock, L. K.; Demchenko, A. V. *Org. Lett.* **2008**, *10*, 2107-2110. c) Premathilake, H. D.; Mydock, L. K.; Demchenko, A. V. *J. Org. Chem.* **2010**, *75*, 1095-1100.
[8] Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583-5584.
[9] Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331-1334.
[10] ^{13}C NMR spectroscopic integration is a valid method for obtaining product ratios of diastereomeric pairs, see: Otte, D. A. L.; Borchmann, D. E.; Lin, C.; Weck, M.; Woerpel, K. A. *Org. Lett.* **2014**, *16*, 1566-1569.
[11] Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734-753.
[12] Paulsen, H.; Meyborg, H. *Tetrahedron Lett.* **1972**, *13*, 3973-3976.
[13] Sinnott, M. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 2026-2032.
[14] Gerber-Lemaire, S.; Vogel, P. In *Carbohydrate Chemistry: Chemical and Biological Approaches Volume 35*; The Royal Society of Chemistry, 2009; Vol. 35, 13–32.
[15] Heuckendorff, M.; Pedersen, C. M.; Bols, M. *J. Org. Chem.* **2013**, *78*, 7234-7248.
[16] Overend, W. G.; Rees, C. W.; Sequeira, J. S. *J. Chem. Soc.* **1962**, 3429-3440. Jensen, H. H.; Bols, M. *Org. Lett.* **2003**, *5*, 3419-3421.
[17] Boons, G.-J.; Hale, K. J. *Organic Synthesis with Carbohydrates*, Sheffield Academic Press, 2000.
[18] Lemieux, R. U.; Hendriks, K. B.; Stick, R. V. James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056-4062.
[19] Capon, B. *Chem. Rev.* **1969**, *69*, 407-498.
[20] Smith, R.; Müller-Bunz, H.; Zhu, X. *Org. Lett.* **2016**, *18*, 3578-3581.
[21] In our definition 'superarmed' is not synonymous with 'more reactive'. (See reference 6). Our present results suggest that the 2-*O*-acetylated donor by Zhu and co-workers is less reactive than the tetra-*O*-benzylated counterpart.
[22] Reeves, R. E. *J. Am. Chem. Soc.* **1950**, *72*, 1449-1506.
[23] Cao, Y.; Okada, Y.; Yamada, H. *Carbohydr. Res.* **2006**, *341*, 2219-2223.
[24] Ferrier, R. J.; Hay, R. W.; Vethaviyasar, N. *Carbohydr. Res.* **1973**, *27*, 55–61.
[25] Buda, S.; Gołębiowska, P.; Mlynarski, J. *Eur. J. Org. Chem.* **2013**, *19*, 3988–3991.
[26] Andersen, S. M.; Heuckendorff, M.; Jensen, H. H. *Org. Lett.* **2015**, *17*, 944–947.
[27] Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Bando, T.; Hughes, R.; Winssinger, N.; Natarajan, S.; Koumbis, A. E. *Chem. Eur. J.* **1999**, *5*, 2648–2667.
[28] Shi, L.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 6939-6940.
[29] Carpintero, M.; Nieto, I.; Fernández-Mayoralas, A. *J. Org. Chem.* **2001**, *66*, 1768–1774.
[30] Lázár, L.; Csávás, M.; Hadházi, Á.; Herczeg, M.; Tóth, M.; Somsák, L.; Barna, T.; Herczegh, P.; Borbás, A. *Org. Biomol. Chem.* **2013**, *11*, 5339–5350.
[31] Vidadala, S. R.; Thadke, S. a.; Hotha, S.; Kashyap, S. *J. Carbohydr. Chem.* **2012**, *31*, 241–251.
[32] Frihed, T. G.; Walvoort, M. T. C.; Codée, J. D. C.; van der Marel, G. A.; Bols, M.; Pedersen, C. M. *J. Org. Chem.* **2013**, *78*, 2191–2205.
[33] Zhang, Y. M.; Mallet, J. M.; Sinaÿ, P. *Carbohydr. Res.* **1992**, *236*, 73–88.
[34] Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293–297.
[35] Lichtenthaler, F. W.; Schneider-Adams, T. *J. Org. Chem.* **1994**, *59*, 6728–6734.
[36] Lee, Y. J.; Baek, J. Y.; Lee, B.-Y.; Kang, S. S.; Park, H.-S.; Jeon, H. B.; Kim, K. S. *Carbohydr. Res.* **2006**, *341*, 1708–1716.
[37] Imagawa, H.; Kinoshita, A.; Fukuyama, T.; Yamamoto, H.; Nishizawa, M. *Tetrahedron Lett.* **2006**, *47*, 4729–4731.

[38] Koide, K.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1991**, *32* (48), 7065–7068.

[39] Ainge, G. D.; Compton, B. J.; Hayman, C. M.; Martin, W. J.; Toms, S. M.; Larsen, D. S.; Harper, J. L.; Painter, G. F. *J. Org. Chem.* **2011**, *76*, 4941–4951.

Organic & Biomolecular Chemistry Accepted Manuscript