Title	Influence of acyl groups on glucopyranoside reactivity in Lewis acid promoted anomerisation
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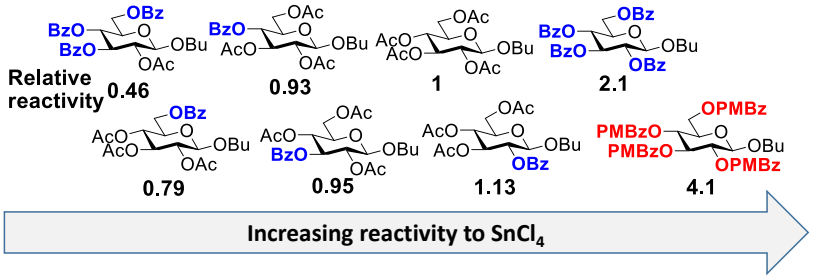
Publication Date	2018-05-26
Publication Information	Farrell, Mark P., Doyle, Lisa M., & Murphy, Paul V. (2018). Influence of acyl groups on glucopyranoside reactivity in Lewis acid promoted anomerisation. Tetrahedron Letters, 59(28), 2726-2731. doi: https://doi.org/10.1016/j.tetlet.2018.05.076
Publisher	Elsevier
Link to publisher's version	https://doi.org/10.1016/j.tetlet.2018.05.076
Item record	http://hdl.handle.net/10379/15195
DOI	http://dx.doi.org/10.1016/j.tetlet.2018.05.076

Graphical Abstract



Influence of acyl groups on glucopyranoside reactivity in Lewis acid promoted anomerisation

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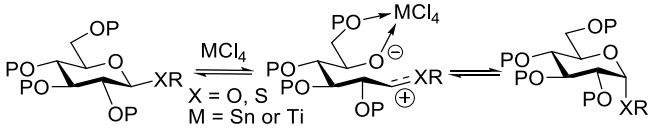
Abstract: Lewis acid promoted anomerisation has potential in *O*- or *S*-glycoside synthesis. Herein, the anomerisation kinetics of thirty one β-D-glucopyranosides was determined to determine how particular acyl protecting groups and their location influence reactivity towards a Lewis acid promoted reaction. The replacement of acetyl groups with benzoyl groups led to reduced reactivity when located at O-3, O-4 and O-6. However a reactivity increase was observed when the acetyl group was replaced by a benzoyl group at O-2. The 2,3,4,6-tetra-*O*-(4-methoxy)benzoate had an ~2 fold increase in rate when compared to the tetrabenzoate.

1. Introduction

Reactions at the anomeric centre are influenced by a variety of factors. For instance, in glycosylation, protecting groups on saccharide hydroxyl groups influence the stereochemical outcome as well as the reaction rate.[1] Differences in glycosylation rate can be exploited in reactivity based oligosaccharide synthesis in one pot.[2] Acyl protecting groups are considered 'disarming' in such glycosylation reactions when compared with ether protecting groups, such as benzyl ethers.[3] This is because the acyl group is more electron withdrawing than the ether and reduces the stability of transition states leading to cationic intermediates[4] resulting from exocyclic cleavage in these reactions.

Reactivity in Lewis acid promoted anomerisation[5,6,7] is also influenced by protecting groups,[8,9] a reaction that is believed to proceed via a cationic intermediate resulting from endocyclic cleavage[10,11] (Scheme 1). Acyl groups located on the saccharide oxygen atoms reduce the rate of these reactions compared to when ether groups are present.[6,8] Furthermore, there are differences between acyl groups. Tetra-*O*-benzoyl-β-D-glucopyranoside **2β** is more reactive than the corresponding tetraacetate **1β**. Based on inductive effects the presence of benzoyl groups would destabilize a cationic intermediate more than acetyl groups. However, the use of benzoylated reactants has been more successful, giving higher yields and shorter reaction times in equatorial to axial anomerisation reactions compared to reactions of the analogous acetylated reactants. This has been demonstrated in glycosphingolipid synthesis achieved *via* Lewis acid promoted anomerisation,[12,13] and more recently in the successful anomerisation of benzoylated glycosyl thiols.[14]

In this paper the influence of acyl groups on the reactivity of a Lewis acid promoted anomerisation reaction of a series of *O*-glucopyranosides is probed further with a view to identification of protecting group strategies that would lead to wider application of anomerisation.[15,16,17,18,19,20,21,22] A variety of acyl protected glucopyranosides are prepared herein and a structure reactivity relationship is established. Here we report that the presence of benzoyl groups at C-2 of the β-glucopyranoside generally leads to a rate enhancement in the anomerisation reaction, while benzoyl groups at C-3, 4 or 6 lead to rate reduction when compared to the presence of acetyl groups at these positions. However, the replacement of all four acetyl groups with benzoyl groups gave the highest reactivity. Other tetra-*O*-acyl derivatives with improved reactivity compared to tetra-*O*-benzoyl groups are also reported.



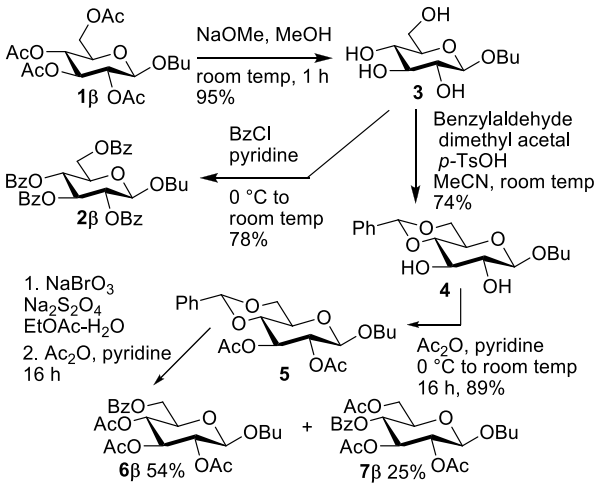
Scheme 1. Proposed mechanism for the Lewis acid promoted anomerisation of glucopyranosides

2. Results and Discussion

2.1 Synthesis of compounds for study

The preparation of monobenzoylated compounds was first investigated (Scheme 2). Thus Zemplén deacetylation of **1β**, which has been described previously[7] gave **3**. Reaction of **3** with benzaldehyde dimethyl acetal in the presence of *p*TsOH gave **4**. Acetylation gave **5**. The oxidative cleavage of the benzylidene group using $NaBrO_3$-$Na_2S_2O_4$ under bi-phasic conditions, followed by acetylation, resulted in the formation a separable mixture, giving **6β** (54%).and **7β** (25%). The application of biphasic $NaBrO_3$-$Na_2S_2O_4$, described by Adinolfi and co-workers,[23] was used frequently herein for the successful removal of benzyl groups as well as partial oxidative cleavage of benzylidene groups.

Next the benzylation of **4** (Scheme 3) under the biphasic alkali conditions previously reported by Garegg and co-workers[24] gave a mixture of **8** and **9** which were isolated in 39% and 17% yields, respectively. Benzoylation, followed by catalytic hydrogenolysis and subsequent acetylation gave **10β** and **11β** in 73% and 66% yields, respectively, over the three steps from **8** and **9**.



Scheme 2. Synthesis of **6β** and **7β**

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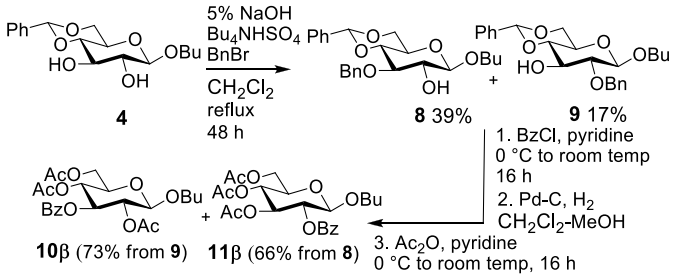
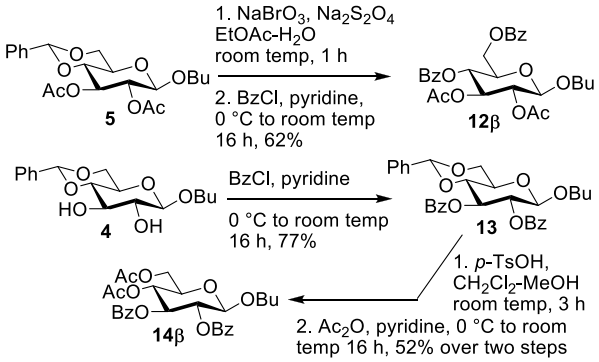


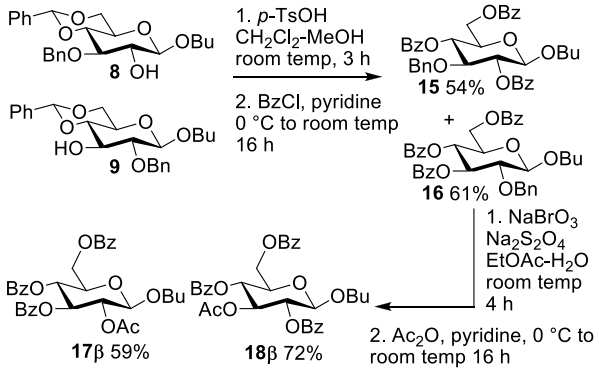
Scheme 3. Synthesis of **10β** and **11β**

Attention turned to the preparation of compounds with two or three benzoate groups (Schemes 4-6). Partial oxidative cleavage of **5** and subsequent benzoylation gave **12β (**62%). Benzoylation of **4** was followed by acid catalysed cleavage of the benzylidene acetal in CH_2Cl_2-MeOH and acetylation to give **14β**.



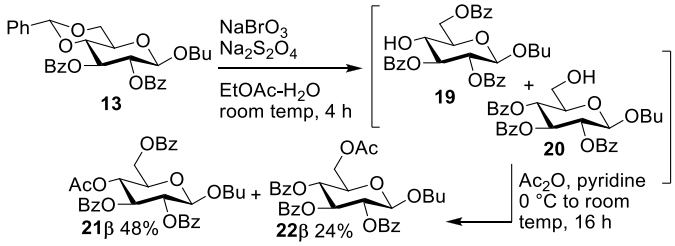
Scheme 4. Synthesis of **12β** and **14β**

Acid catalysed cleavage of the benzylidene group from both **8** and **9** and their subsequent benzoylation gave **15** and **16**. Oxidative removal of the benzyl groups with $NaBrO_3$-$Na_2S_2O_4$ proceeded smoothly and subsequent acetylation gave **17β** and **18β**.



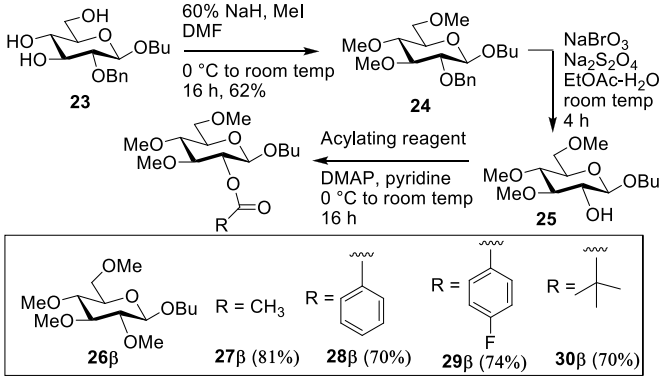
Scheme 5. Synthesis of **17β** and **18β**

Partial oxidative cleavage of the benzylidene group of **13** gave a mixture of **19** and **20**. Subsequent acetylation gave **21β** and **22β**.



Scheme 6. Synthesis of **21β** and **22β**

Intermediate **23**, prepared from **9** (Scheme 7) was treated with NaH and methyl iodide to give **24**. The benzyl group of **24** was then removed to give **25**. Acylation of **25** gave **27β-30β**. The tetra-*O*-methyl derivative **26β** was prepared as previously described.[8]



Scheme 7. Synthesis of **27β-30β**

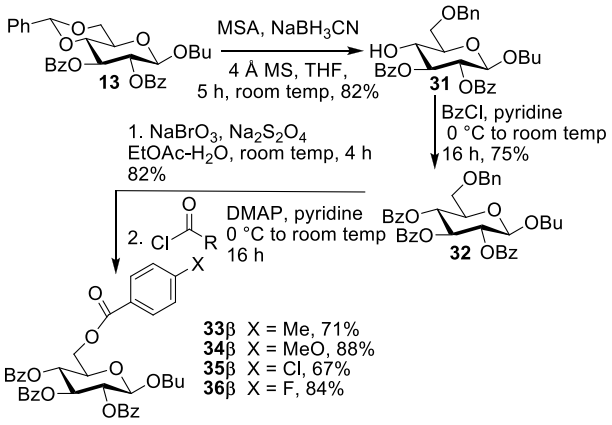
Partial reductive cleavage of the benzylidene group of **13** using methanesulfonic acid (MSA) and $NaBH_3CN$ resulted in the regioselective formation of **31**. Benzoylation gave **32**. Oxidative removal of the 6-*O*-benzyl ether followed by acylation gave **33β-36β** (Scheme 8) where as various peracylated compounds **37β-46β** were prepared by peracylation of **32** in pyridine-DMAP (Scheme 9).

2.2 Reactivity study

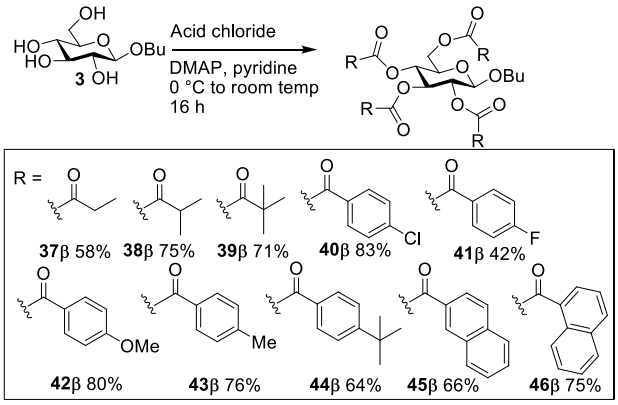
With various reactants in hand then Lewis acid catalysed anomerisations were investigated.[7] Reactions were carried out in NMR tubes with $CDCl_3$ as the solvent and using 1 equivalent of $SnCl_4$ as the promoter. Concentrations of reactant (β-anomers in Table 1) and the major product (α-anomer) were monitored as a function of time and were also measured at equilibrium (when no further change in the concentration of reactant and products were observed). The data obtained was used in equation (1) for equilibrium kinetics:[25]

$$\ln\left(\frac{[A]_0 - [A]_e}{[A]_t - [A]_e}\right) = -(k_f + k_r)t \quad (1)$$

where $[A]_0$ is the initial concentration of the β-anomer, $[A]_e$ is the concentration of the β anomer at equilibrium, $[A]_t$ is the concentration of the β-anomer at a time (t), k_f is the rate constant of the forward reaction (β → α) and k_r is the rate constant of the reverse reaction (α → β). Each reaction was carried out in triplicate and the data for all reactants in Table 1 gave linear plots with r^2 values of 0.97 or greater. The k_f+k_r value for each reactant was the slope and these values are given in Table 1 along with relative reactivities.



Scheme 8. Synthesis of **33β-36β**



Scheme 9. Synthesis of **37β**-**46β**

In this kinetic study the $SnCl_4$:reactant ratio used was 1:1. This differed from the earlier study from our laboratory where a ratio of $SnCl_4$:reactant of 0.5:1 was used.[8] The 1:1 ratio was used to reduce the overall reaction time so as to more rapidly obtain k_f+k_r values. This explains differences in the k_f+k_r values reported for **1β**, **2β** and **26β** in this study with those reported previously. In the previous study **2β** was ~4 fold faster than **1β** whereas it was ~2 fold faster using the current conditions. However, the trend in k_f+k_r values was consistent with those published earlier, with fully benzoylated reactant **2β** being faster than the acetylated **1β**. The fully methylated derivative **26β** was more than two orders of magnitude faster than both acylated compounds.

On the basis of inductive effects (p*K*a benzoic acid = 4.20 vs p*K*a acetic acid = 4.76) the anomerisation of benzoylated reactant **2β** would be expected to be slower than **1β**.[26] The presence of benzoyl groups at C-3, C-4 and C-6, instead of acetates, in various monobenzoylated, dibenzoylated and tribenzoylated reactants, consistently led to a reduction in the rate of anomerisation (compare each of entries 3-5, 7 and 9 with 1). In contrast, the presence of a benzoyl group at C-2 generally led to rate increases (compare entry 6 with 1; 8 with 5; 10 with 7 and 9 with 2). The replacement of the 2-*O*-acetate of **17β** (Entry 9) to give **2β** led to the highest increase (four fold) in reactivity (Table 1, entries 1-12).

The tetra-*O*-methylated **26β** is over 600 times more reactive than fully acylated **1α** under these conditions. Replacement of the 2-*O*-methyl group with an acyl group led to a reduction in the rate of anomerisation (Entries 13-17). However, the 2-*O*-benzoate **28β** (Entry 15) was 1.3 times more reactive than 2-acetate **27β** (Entry 14). The more electron withdrawing *p*-fluorobenzoate **29β** reduced the rate (Entry 16) whereas the 2-*O*-pivalate **30β** was most reactive of the 2-*O*-acyl-3,4,6-tri-*O*-methyl-β-D-glucopyranosides **27**-**30β**.

The next series of compounds give insight into the effect of substituents at C-6, chosen for investigation due to its proximity to the proposed site of coordination to $SnCl_4$ (Entries 18-21). There was no clear trend apparent based on electronic properties, although the *p*-methoxy derivative was the most reactive. Finally, the study of homoacyl glucopyranosides (Entries 22-31) revealed the most improvement in reactivity for the 2,3,4,6-tetra-*O*-(4-methoxy)benzoate **42β** (Entry 27), which is associated with the greater electron releasing properties of the *p*-methoxy benzoyl group, compared to the benzoyl group.

Table 1 Reactivity of compounds in $SnCl_4$ promoted anomerisation[a]

Entry	Reactant (β-anomer)	Major product (α-anomer)	$10^6(k_f + k_r)$ (s^{-1})	Relative Reactivity	Ratio α:β	Yield α-anomer (%)

3. Summary and Conclusions

Relatively low reactivity differences (e.g. 2 fold) between fully acetylated or fully benzoylated glycosides can influence reaction progression and yields from anomerisation reactions. This is more noticeable during the preparation glycosphingolipids, where the aglycon is more complex. Hence, synthetic routes have been developed herein that have enabled regioselective acylation of glucopyranosides in order to gain insight how the location of the acyl group influences reactivity. The study showed that placement of benzoyl groups at O-2 led to an increase in reactivity, but to reduction when placed elsewhere, the exception being that the presence of four benzoates gave the highest reactivity. The latter could be influenced by steric hindrance with more crowding in the **2β** than for examples in entries 1 and 3-12 in Table 1. This crowding pushes the 2-carbonyl group closer to the carbocation centre where it can stabilize the forming cation.

While this study has focused on anomerisation, a 2-*O*-benzoyl group was shown to increase reactivity in a glycosylation reaction,[27] this being explained by the benzoyl group being involved in neighboring group participation. However, a rate enhancing effect for a 2-*O*-benzoate group may not be a general phenomenon in glycosylation.[1] In anomerisation involving a cationic intermediate, the 2-*O*-benzoyl group could also participate as a neighboring group. The degree of participation could be increased, as mentioned due to increased steric hindrance. The presence of the phenyl group also enables a resonance contribution from the 2-*O*-benzoyl group. This might explain why **2β** is faster than the sterically hindered tetra-*O*-pivalylated derivative **39β.** The use of a more electron releasing *p*-methoxybenzoyl group increased reactivity, which is consistent with increased stabilization of carbocation formation in a rate influencing step.[28]

A further study which has the aim to increase the understanding of why benzoates are more reactive in anomerisation reactions is in progress and this study will be reported in due course.

Acknowledgments

This publication has partly emanated from research supported by Science Foundation Ireland (SFI, grant number 12/IA/1398) and is co-funded under the European Regional Development Fund under Grant Number 14/SP/2710. The authors thank the Irish Research Council and Roche Ireland Ltd for an Enterprise Partnership postgraduate scholarship to MPF.

Supplementary Material

Experimental section including analytical data for compounds and selected NMR spectra.

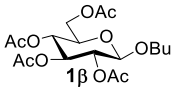
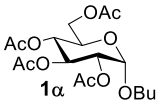
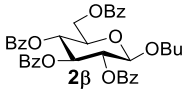
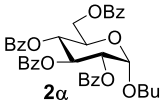
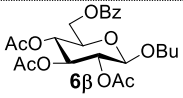
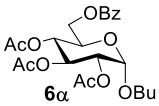
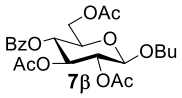
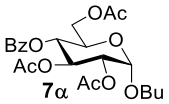
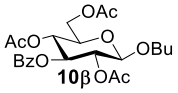
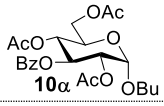
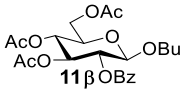
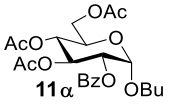
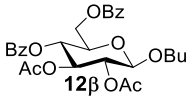
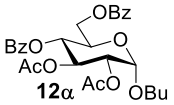
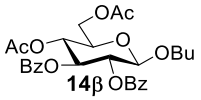
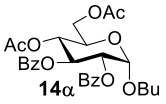
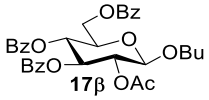
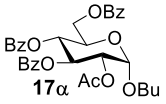
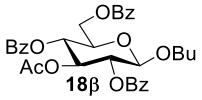
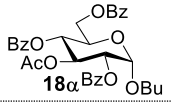
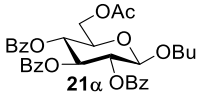
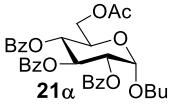
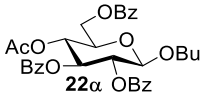
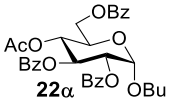
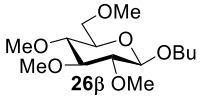
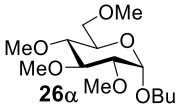
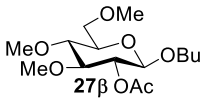
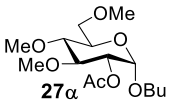
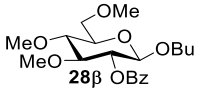
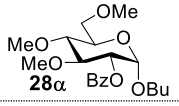
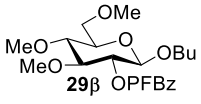
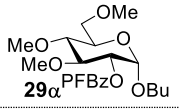
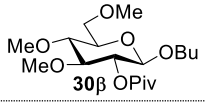
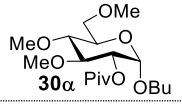
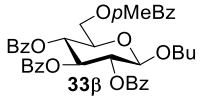
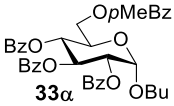
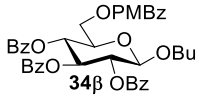
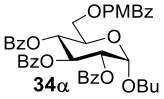
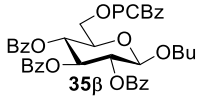
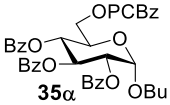
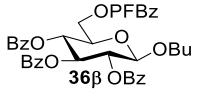
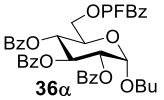
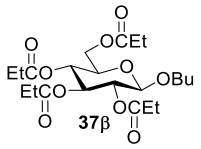
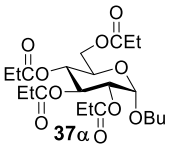
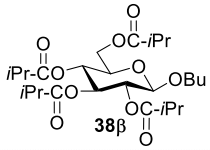
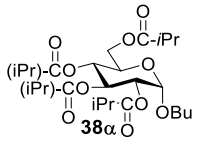
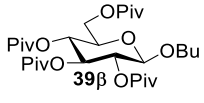
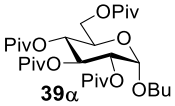
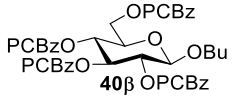
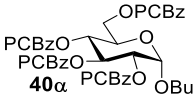
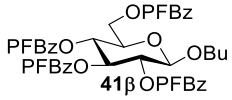
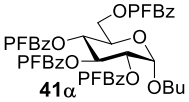
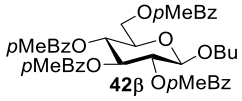
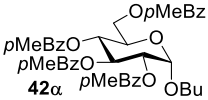
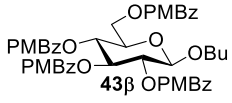
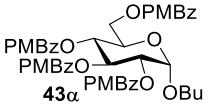
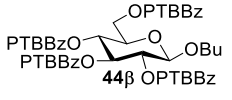
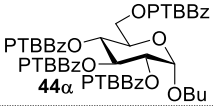
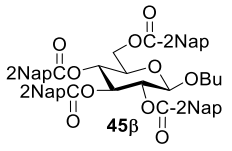
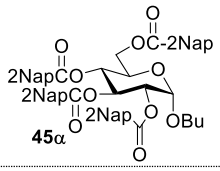
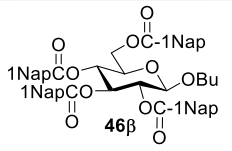
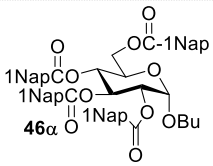
1			7.6	1	9:1	64
2			15.7	2.07	95:5	72
3			6	0.79	92:8	81
4			7.1	0.93	89:11	76
5			7.2	0.95	93:7	73
6			8.6	1.13	9:1	61
7			4.6	0.61	92:8	84
8			8.5	1.12	88:12	61
9			3.7	0.49	9:1	54
10			6.2	0.82	91:9	67
11			6.6	0.87	9:1	83
12			5.6	0.74	89:11	70
13			4676	615	96:4	72
14			3088	406	92:8	74
15			4088	538	95:5	71
16			1854	244	95:5	52
17			4386	577	94:6	84

Table 1 (contd). Reactivity of compounds in $SnCl_4$ promoted anomerisation

Entry	Reactant		$10^6(k_f + k_r)$ (s^{-1})	Relative Reactivity	Ratio α:β	Yield of α-anomer (%)
18	 **33β**	 **33α**	6.9	0.91	9:1	41
19	 **34β**	 **34α**	10.4	1.37	96:4	66
20	 **35β**	 **35α**	8.2	1.08	93:7	73
21	 **36β**	 **36α**	5.8	0.76	85:15	62
22	 **37β**	 **37α**	8.3	1.09	90:10	66
23	 **38β**	 **38α**	9.4	1.24	92:8	76
24	 **39β**	 **39α**	10.1	1.3	95:5	81
25	 **40β**	 **40α**	6.2	0.82	95:5	61
26	 **41β**	 **41α**	7.2	0.95	90:10	49
27	 **42β**	 **42α**	27.9	3.67	92:8	57
28	 **43β**	 **43α**	31.1	4.1	95:5	61
29	 **44β**	 **44α**	27.0	3.55	94:6	51
30	 **45β**	 **45α**	12.5	1.64	9:1	48
31	 **46β**	 **46α**	21.6	2.84	95:5	45

[a] The yield reported is the isolated yield after chromatographic separation. PMBz = *p*-methoxybenzoyl; 2-Nap = 2-naphthyl; 1-Nap = 1-naphthyl; PTBBz = *p*-(*tert*-butyl)benzoyl; *p*-MeBz = *p*-methylbenzoyl; PFBz = *p*-fluorobenzoyl; PCBz = *p*-chlorobenzoyl; Piv = trimethylacetyl or pivalate.

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