Versatile intermediate for complete α/β stereocontrol in *O*-glycosidation reactions

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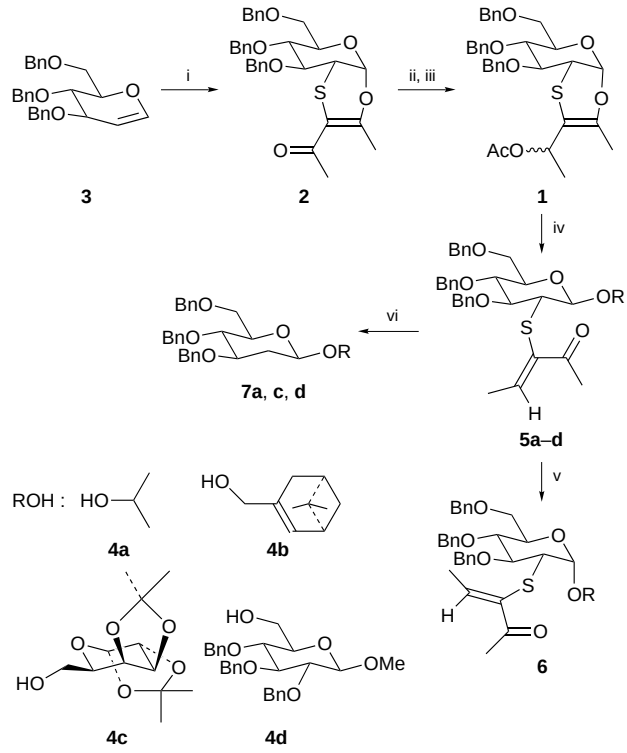
β-*O*-Glucosides 5, which can be completely converted to the α-anomers in the reaction medium, are obtained as single isomers by glycosidation of readily available donor 1 and are easily transformed into 2-deoxy-β-*O*-glucosides.

Stereocontrol in *O*-glycosidation is a central matter in carbohydrate chemistry. A wide number of biologically important molecules originate from an aglycone and a saccharide by formation of a glycosidic linkage, moreover entire classes of polysaccharides are generated in nature by glycosidation of simpler carbohydrates.[1] A great effort has been devoted to optimise the glycosidation reaction as an indispensable transformation in organic chemistry. The crucial aspect has always been the achievement of a good level of stereocontrol on the formation of the glycosidic linkage, which usually leads to mixtures of α and β anomers. Efforts in this area have met with varying degrees of success.[2] While methods affording the α anomer with good selectivity are available, preparation of the pure β anomer is still a rare achievement. The problem is more serious for 2-deoxyglycosides, a class of derivatives of biological relevance, where the lack of assistance from proximal substituents and the low stability of precursors make the preparation of pure anomers, particularly the β anomer, a real challenge.[3] Our approach to the stereoselective synthesis of 2-deoxyglycosides was based on the exploitation of intermediates like **1**. We report here a synthetic protocol for *O*-glycosidation of tri-*O*-benzylglucal derivative **1** with complete stereocontrol of the glycosidic linkage, affording in a single reaction either α- or β-2-deoxyglucosides by simply controlling the experimental conditions. To the best of our knowledge, among the very few methods available, there is only one report of a selective preparation of β-2-deoxyglucosides that follows a similar approach.[4] The substantial improvement of the present protocol is the preparation of the β anomer as a pure isomer by using the readily available acetate **1** and the complete transformation of the β into the α anomer in the same reaction medium. The procedure is outlined in Scheme 1.

The oxathiine **1** is obtained from **2** which in turn is prepared in high yield as a single regioisomer by cycloaddition of tri-*O*-benzylglucal **3** with 2,4-dioxopentane-3-thione in a 95 : 5 α : β diastereomeric ratio.[5,6] Subsequent reduction of the carbonyl group to the alcohol and acetylation with acetic anhydride under standard conditions gave quantitatively the acetate **1**, which is further reacted without purification after removal under vacuum of pyridine and excess acetic anhydride. The glycosidic donor **1** is reacted in dry nitromethane at room temperature with the appropriate acceptor **4a**–**d** in the presence of a catalytic amount of methyl trifluoromethanesulfonate and quenching the reaction with pyridine.‡ Timing of quench is crucial for the success of β glycosidation. Quenching the reaction at the turning of the colour of the mixture from pale yellow to red affords the β glycosides **5** exclusively (reaction times and yields are given in Table 1). The stereochemistry of products is readily assigned by the chemical shift (δ 4.3–4.4) and coupling constants ($J_{1,2}$ 7.6–8.4 Hz) of the anomeric proton in the ^{1}H NMR spectra.§ Chemically pure β-glycosides are obtained by flash column chromatography.

β-Glycosides **5** can be completely transformed into the α-anomers **6** by letting the product isomerise under the same reaction conditions; the isomerisation is presumably induced by acid catalysis. The aforementioned turning colour visually indicates the beginning of the isomerisation reaction, the time at which this occurs depends on the individual glycoside (from 0.5 h for **6a** to 1.5 h for **6d**¶). Thus, a single glycosidation reaction

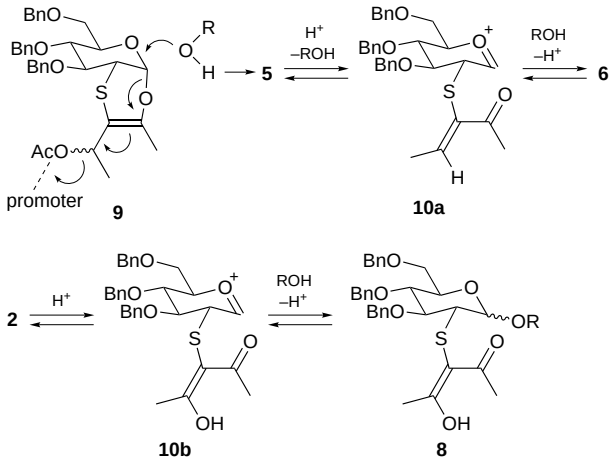


Scheme 1 *Reagents and conditions*: i, see ref. 5; ii, $LiAlH_4$ (0.5 equiv.), THF, 0 °C to room temp., 30 min, 92%; iii, Ac_2O, pyridine, room temp., 96%; iv, ROH (2 equiv.), MeOTf (0.2 equiv.), $MeNO_2$, room temp., v, MeOTf (0.2 equiv.), $MeNO_2$, room temp., 1 h, quantitative yield; vi, Raney-Ni, wet THF, 0 °C to room temp.

Table 1 Reaction times and yields of **5** and **7**

Entry	Compound	*t*/min	Yield[a] (%)
1	**5a**	5	82
2	**5b**	5	61
3	**5c**	35	40
4	**5d**	50	58
5	**7a**	45	72
6	**7c**	30	65
7	**7d**	30	68

[a] Isolated yield.



Scheme 2

provides both anomers in pure form by careful control of the reaction time. Glycosidation of the parent ketone **2** under acid catalysis is more sluggish than that of the acetate **1**, invariably providing mixtures of the α and β anomers **8** (Scheme 2). Since β-glycosidation of **1** is totally stereoselective we take this evidence as an indication of a different reaction pathway followed by **1** and **2**. In the former case, owing to the higher reactivity of the acetate, the developing positive charge induced on **1** by the catalyst might be trapped by the acceptor *before* ring-opening of the oxathiine, as shown in **9**, allowing for a β-stereospecific glycosidic linkage formation. Subsequent α–β equilibration might proceed through an oxonium intermediate **10a** analogous to that leading to product mixture in the glycosidation of the ketone **10b**.

Deprotection of the thiosubstituted glycosides **5a,c,d,** to the corresponding 2-deoxyglycosides **7a,c,d**‖ is readily achieved by desulfurisation with Raney-nickel[4,7] (Scheme 1). Reaction times and yield are reported in Table 1.

In conclusion these preliminary results clearly indicate that the aceate **1** is a readily available and effective new donor for the synthesis of 2-deoxy-β-*O*-glycosides and that the described procedure might represent a competitive protocol for an efficient α–β stereocontrol in the glycosidation reaction.

Footnotes and References

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‡ Running the reaction in the presence of molecular sieves causes an appreciable increase of reaction time (Table 1, entry 3: from 35 min to 2 h) without a significant increase in yield (entry 3: from 40 to 43%).

§ *Selected data* for **5d**: white solid, mp 98–100 °C; $[\alpha]_D$ −7 (*c* 0.3, $CHCl_3$); δ_H(200 MHz, $CDCl_3$, *J*/Hz) 2.05 (d, 3 H, *J* 6.6), 2.27 (s, 3 H), 2.37 (s, 3 H), 3.30–3.75 (m, 14 H), 3.94–3.99 (m, 1 H), 4.33 (d, 1 H, *J* 7.6), 4.47 (d, 1 H, *J* 8.2), 4.45–4.97 (m, 12 H), 6.81 (q, 1 H, *J* 7.0), 7.10–7.41 (m, 30 H); δ_C(50 MHz, $CDCl_3$) 16.7, 26.9, 52.1, 57.2, 68.2, 68.7, 73.5, 74.6, 74.7, 74.9, 75.6, 74.8, 75.1, 78.2, 78.6, 82.1, 83.3, 84.6, 104.3, 104.4, 127.5, 127.6, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 138.0, 138.1, 138.3, 138.5, 138.6, 138.9, 141.4, 196.7; ν_{max}(neat)/cm^{-1} 3032, 2874, 1676, 1602, 1452, 1068 (Calc. for $C_{60}H_{66}O_{11}S$: C, 72.40; H, 6.69; Found: C, 72.28; H, 6.88%).

¶ *Selected data* for **6d**: δ_H(200 MHz, $CDCl_3$, *J*/Hz) 5.50 (d, 1 H, *J* 3.2), 7.14 (q, 1 H, *J* 7.0).

‖ *Selected data* for **7d**: white solid, mp 96–98 °C; $[\alpha]_D$ −60.2 (*c* 0.8, $CHCl_3$); δ_H(200 MHz, $CDCl_3$, *J*/Hz) 1.64–1.75 (m, 1 H, H-2_{ax}), 2.22–2.30 (m, 1 H, H-2_{eq}), 3.37–3.73 (m, 13 H), 4.15–4.20 (m, 1 H), 4.30 (d, 1 H, *J* 7.8), 4.39 (m, 1 H), 4.37–4.97 (m, 12 H), 7.20–7.34 (m, 30 H); δ_C(50 MHz, $CDCl_3$) 36.5, 57.0, 68.4, 69.2, 74.5, 74.7, 74.8, 74.9, 75.2, 75.6, 71.4, 73.4, 78.0, 78.1, 79.2, 82.2, 84.6, 100.4, 104.6, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 138.1, 138.3, 138.4, 138.5 (Calc. for $C_{55}H_{60}O_{10}$. C, 74.96; H, 6.87. Found: C, 74.54; H, 6.92%).

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