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Minireview

Intramolecular aglycon delivery

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Abstract—A Minireview with 51 references covering the two-step tethering and intramolecular glycosylation process termed intramolecular aglycon delivery (IAD). Specifically, glycosylation reactions where the tethered oxygen acts as nucleophile are covered. In the majority of cases, tethering to O-2 of a glycosyl donor ensures formation of a 1,2-*cis* glycoside after intramolecular glycosylation.

Keywords: Intramolecular aglycon delivery; Glycosylation; Tethering; 1,2-*cis* Glycosides; Beta-mannosides

Contents

1. Introduction

The idea of using the stereochemistry at the 2-position to induce stereoselectivity in the glycosylation reaction is well established in carbohydrate chemistry: ester protecting groups at C-2 take part in a neighbouring group participation process in glycosylation reactions, resulting in 1,2-*trans* products. In a complementary approach, the stereochemistry at C-2 can be used to dictate a 1,2-*cis* outcome from a two-step tethering–glycosylation process called intramolecular aglycon delivery (IAD) (Fig. 1). In the first step, the aglycon is tethered to the glycosyl donor by a temporary tether; this Minireview covers specifically those intramolecular glycosylation reactions where the oxygen that is to be glycosylated is the same one as that used for tethering. The aglycon is normally tethered to the 2-position of the donor, ensuring a 5-membered ring transition state in a subsequent intramolecular glycosylation step, and complete stereocontrol for the formation of the 1,2-*cis* product. Loss of the tether gives the glycoside with OH-2 free. This Minireview brings together IAD reactions reported in the literature 1992 to date, ordered after tethering method. Some aspects have also been covered in earlier reviews.[1,2]

2. Acid-catalysed acetal tethering

Hindsgaul and Barresi introduced the concept of intramolecular aglycon delivery, demonstrating it for the

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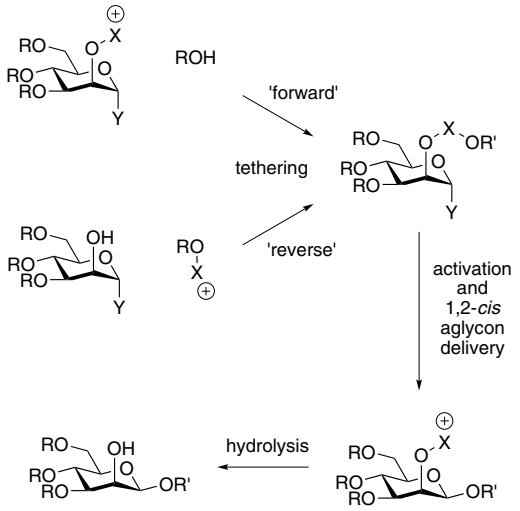
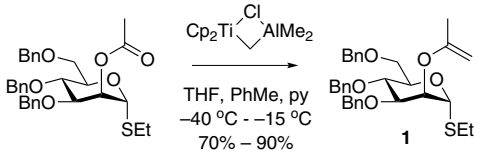


Figure 1. The intramolecular aglycon delivery concept for the formation of β-mannosides.

synthesis of β-mannosides using a mixed acetal tether.[3] Tethering was carried out using acid-catalysed (with CSA or TsOH) addition of the aglycon alcohol to an enol ether (e.g., **1**), which had been formed by the action of the Tebbe reagent on a mannose-2-*O*-acetate (Scheme 1).

Tethering under these conditions gave a reasonable yield of the mixed acetal from a primary alcohol **2** and an unhindered (i.e., monosaccharide) donor bearing the enol ether **1** (Table 1, entry 1). The reaction is very sensitive to steric effects, however, and increasing the bulk either of the alcohol (secondary alcohols **3**, **4** and disaccharide alcohols **5**) or of the enol ether component (di- **6** or trisaccharide **7** donors) caused significant decreases in the yield of mixed acetal formation (Table 1, entries 2–8).[3–5] The reaction time was also found to be critical: longer reaction times led to scrambling and formation of undesired symmetrical acetals, meaning that great care was needed to reproduce the optimum couplings. Furthermore, the stability of the mixed acetals was found to be rather low for the sterically hindered examples, meaning that they must be stored in basic solution to avoid decomposition.

Upon treatment with NIS, the mixed acetals underwent an intramolecular glycosylation to give the β-mannosides as sole glycosylated products in all cases. The isopropylidene tether was lost to give a free OH-group at C-2. No α-products were formed in any of the glycosylation reactions examined. Addition of a hindered base, 2,6-di-*tert*-butyl-4-methyl-pyridine (DTBMP), was found to increase the glycosylation yields, possibly by stopping the breakdown of mixed acetals. Other, less hindered, bases were not compatible with the glycosylation. More sterically hindered systems gave lower glycosylation yields, and also longer reaction times. Some competition experiments with the addition of external methanol (1 equiv) to glycosylation reactions were also carried out, from which it was concluded that the glycosylation was indeed intramolecular, and was S_N2-like.[5] Activation of mixed acetals **8** with NBS gave a major glycosylated product in which a presumed intermediate carbocation had been trapped by succinimide to give a mixed *N*,*O*-acetal **9**, along with a minor amount of the glycoside with OH-2 free **10** (Scheme 2).[5] Attempts at a convergent approach to the *N*-glycan core pentasaccharide with its key β-*manno* linkage were not successful with this early methodology.



Scheme 1.

3. Silicon tethering

Stork introduced silicon-tethered IAD using mannosyl sulfoxides as donors.[6] The tethering–glycosylation procedure was as follows: A dimethylchlorosilyl ether (2.5 equiv) derived from the aglycon alcohol was coupled to OH-2 of a mannose thioglycoside **12** (1 equiv), to give mixed silyl acetals in essentially quantitative yield after chromatography. The tethered intermediates were oxidised to the glycosyl sulfoxides, which, upon activation with triflic anhydride in the presence of the hindered base DTBMP underwent intramolecular glycosylation to give the β-mannosides. No α-anomers were seen, and this process was reported for methanol, isopropanol and two primary carbohydrate alcohols **2** and **11** (Scheme 3). The process gave β-mannosides in similar yields starting from either the α- or β-configured thiomannoside donor.

A subsequent article described a modified tethering procedure where equimolar amounts of the donor **13** and acceptor alcohols were mixed with 1 equiv Me_2SiCl_2 to give the tethered intermediates.[7] Oxidation of the thioglycoside to the sulfoxide was carried out prior to tethering in this procedure.

The tethering and glycosylation worked well for a number of primary **2** and secondary **4**, **14**–**16** carbohydrate alcohols (Table 2), but a limitation was found in the form of an O-4 glucose aglycon **3**. In this case, the major product from the glycosylation was formed by attack by O-6 at the anomeric position with concomitant 6-O-debenzylation to give a (β1→6)-linked glycoside **17** (Fig. 2) as the major product (82%) along with 12% of the (β1→4)-linked compound. The same side reaction was seen to a lesser extent with a glucosamine acceptor **4**.