A novel donor for the synthesis of 2-deoxy-β-glycosides

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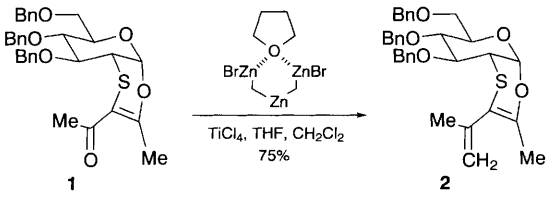
Vinyl glycoside 2, available in two steps from tribenzyl glucal, is found to be an excellent glycosyl donor for the synthesis of 2-deoxy-β-glycosides.

The most commonly used methods for glycosyl transfer involve formation of an electron-deficient anomeric carbon by electrophilic activation of a leaving group at C-1 of the glycosyl donor.[1] In the broad subcategory of methods that use leaving groups where C–O cleavage is the key step, the Schmidt trichloroacetimidate procedure is pre-eminent.[2] Four other modern methods, the Danishefsky glycal epoxidation–epoxide opening sequence,[3] the Fraser-Reid pentenyl glycoside concept,[4] an application of the Mitsunobu reaction by Roush,[5] and the phosphite (and phosphate) leaving group[6] have been used for some notable glycosylations. Recently, a new category of *O*-derivatives, vinyl (alkenyl) glycosides, have been successfully employed as transfer agents.[7–10] To achieve β-face transfer, neighbouring group participation is exploited to afford excellent 1,2-*trans* (β-glucosyl or galactosyl) stereoselection. However, none of the methods discussed above are particularly useful for the synthesis of the 2-deoxy-β-glycoside linkage,[11] a fairly common feature in natural products. Each of the methods mentioned would require extra steps to remove a β-directing participating group or would suffer poor stereoselection without such a group at C-2. Here we describe our studies of 2-deoxy-β-glycoside synthesis based on vinyl glycoside activation. Our method features (i) novel and facile synthesis of a vinyl glycoside moiety, (ii) excellent β-stereoselection and (iii) one-step post-glycosylation processing for production of the 2-deoxy species.

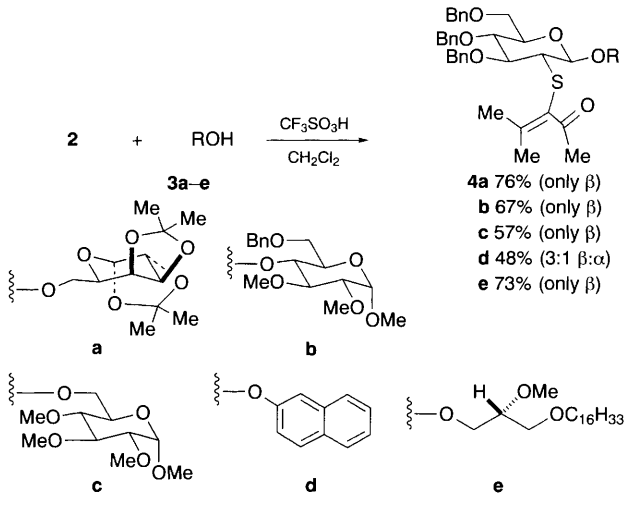
Our point of entry to a 2-deoxy-β-glycosyl transfer reagent is the bicyclic species **1**, readily available in high yield *via* cycloaddition chemistry of tribenzyl glucal.[12] Cyclodduct **1** may be viewed as a vinyl glycoside, and indeed with MeOH and *p*-TosH, it is cleanly but slowly (approx. 24 h) cleaved at C-1 to produce a methyl-β-glucoside. However, only MeOH and water are sufficiently nucleophilic to cleave the heterocyclic ring of **1**. We reasoned that replacement of the carbonyl oxygen of **1** with a methylene would enhance the rate of acid-catalysed cleavage of the anomeric C–O bond and concomitant glycosyl transfer. Thus, treatment of **1** with the Nysted reagent affords **2** in 75% yield (Scheme 1).[13] Vinyl glycoside **2** revealed excellent glycosyl donor properties, as summarized in Scheme 2. The reactions were performed at −20 °C in CH_2Cl_2, in the presence of molecular sieves, with 1 equiv. of CF_3SO_3H as the acid catalyst and 2 equiv.of the acceptor ROH.† Reaction times are 1 h or less. The reaction with 2-naphthol (**3d**) is the only case where the α-anomer product is detectable in the CF_3SO_3H-catalysed reaction. Among other catalysts examined (CF_3SO_3-$SiMe_3$, *p*-TsOH, $AlCl_3$) the most suitable is the Falck–Mioskowski catalyst, Ph_3P– HBr.[14] For example, when it is used in place of CF_3SO_3H for **3a**, the glycoside is obtained in 63% yield with a β : α ratio of 10 : 1. Other solvents including diethyl ether, toluene and acetonitrile served to decrease reaction rates and/or yields.



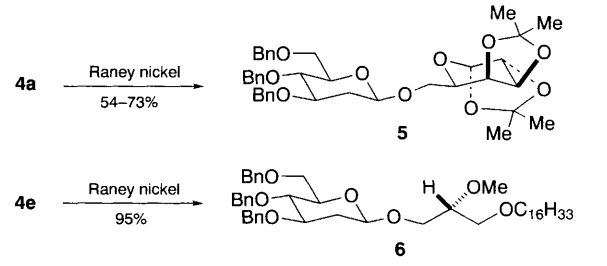
Scheme 1

Raney nickel desulfurization of the ring-opened products **4** is straightforward, but reaction times and isolated yields are very much batch-dependent, related to the age and quality of the Raney nickel. For example, when **4a** is treated with Raney nickel (W-2), O-(3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1-6)-1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose **5** is obtained in 54–73% yield with two different catalyst preparations (Scheme 3). In the case of **4e**, similar reductive removal of sulfur with the better batch of Raney nickel afforded the glyceride **6** in 95% yield. Glyceride **6** was previously prepared by Bittman using Schmidt glycosylation of a glucose derivative followed by removal of the 2-oxygen using Barton chemistry.[15] Bittman further describes debenzylation of **6** to yield a glucoside which has micromolar growth-inhibitory activity against a variety of tumour cells.

In conclusion, we have demonstrated that our 4-step method (cycloaddition, methylenation, acid-catalysed transfer and Raney nickel desulfurization) is competitive with earlier approaches to 2-deoxy-β-glycosides in terms of convenience, stereoselectivity and yield.[16] The extension of our method to



Scheme 2



Scheme 3

other cycloadducts‡ in our series and to 'latent/active' pairs[17] is underway and will be described in a full paper.[18]

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Footnotes

† In the absence of molecular sieves, 10 mol% of CF_3SO_3H catalyses glycosyl transfer to **3a**, but the donor is trapped by adventitious water as well as by the desired acceptor **3a**; whereas in the presence of sieves, less than 1 equiv. of CF_3SO_3H is not an effective catalyst. When 1 equiv. of acceptor **3a** is used with 1 equiv. of CF_3SO_3H, the isolated yield of glycoside is reduced to 22%.

‡ For example, preliminary application of our standard procedures to a 2-deoxygalactose donor affords results similar to the 2-deoxyglucose donor **2**.

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18 Aspects of this work have been presented at the American Chemical Society meeting, New Orleans, March, 1996, ORGN#300 and the MARM of the American Chemical Society, Villanova, May 1996, no. 52.

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