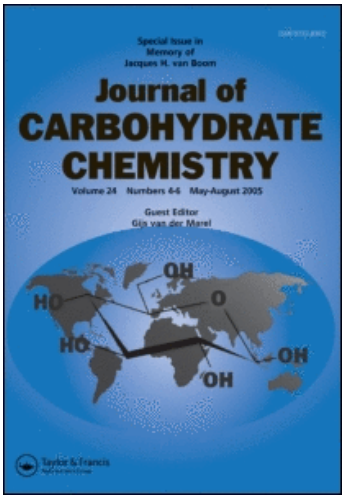

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COMMUNICATION

SYNTHESIS OF VINYL α-D-GLUCOPYRANOSIDES FROM MIXED ACETAL GLYCOSIDES[1]

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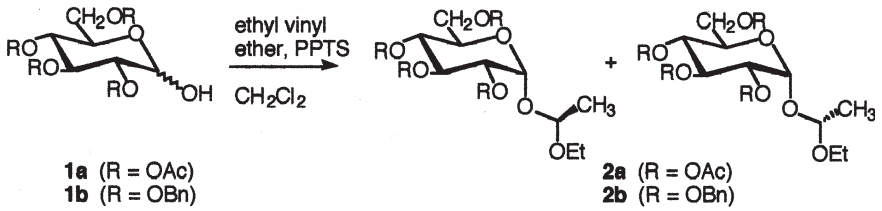
Vinyl D-glucopyranosides are useful intermediates in a wide variety of applications in synthetic carbohydrate chemistry. They have been utilized as chiral auxiliaries in the inverse-electron-demand cycloaddition with isoquinolinium salts, giving homochiral tetralins (Bradsher cycloaddition),[2] and as precursors to enantiomerically pure cyclobutanols by [2+2] cycloaddition with ketenes.[3] Vinyl glycosides that are unsaturated at C2-C3 undergo thermal Claisen rearrangement to give C-3 branched glycal derivatives.[4] Isopropenyl[5] and butenyl glycosides have been used as glycosyl donors in oligosaccharide synthesis.[6] Vinyl glycosides and mixed acetal glycosides have been studied as substrates for glycosidases.[7,8] In more recent studies, vinylated sugars, in which the vinyl group is attached to non-anomeric hydroxyl groups, have been utilized in the synthesis of cyclooctanoic mimetics of carbohydrates,[9] as precursors to *C*-glycosides,[10] and as intermediates in the synthesis of β-mannosides by intramolecular tethering and delivery.[11]

Vinyl glycosides are most often synthesized from glucopyranosides with an unblocked anomeric hydroxyl group by transvinylation with mercuric acetate[12] or from glycosyl halides by nucleophilic displacement with bis(acylmethyl)mercury reagents.[13]

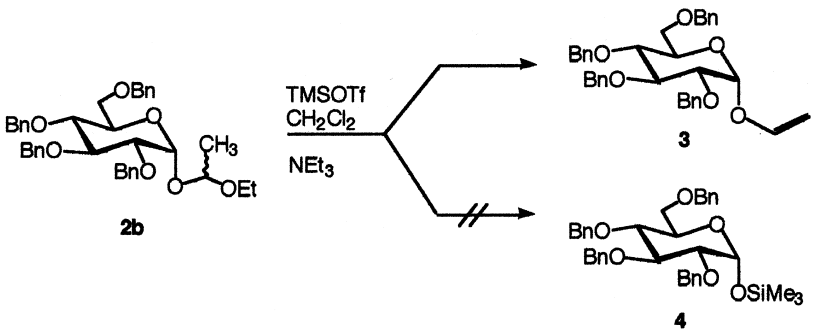
Elimination reactions of 2-(phenylselenyl)ethyl glycosides[14] and 2-(trimethylammonium)-ethyl glycosides,[12] and photolysis of 4-oxopentyl glycosides by Norrish Type II reactions also give vinyl glycosides.[15] Our studies of hetero-Diels-Alder reactions in carbohydrate synthesis required access to vinyl D-glucopyranosides. A mercury-free preparation of vinyl ethers derived from chiral alcohols has been reported,[16] in which treatment of mixed acetals with trimethylsilyl trifluoromethane sulfonate and an amine (Gassman method)[17] gave good yields of vinyl ethers. We were intrigued by the possibility of synthesizing vinyl glycosides by the Gassman method, since the required monosaccharides that

are unblocked at the anomeric center are readily available with both ether and ester protecting groups on the remaining hydroxyl groups. Treatment of these starting materials with vinyl ethers in the presence of an acid catalyst would provide the mixed acetal glycosides needed for the elimination reaction.[18] Mixed acetal glycosides are also available by the reaction of TMS glycosides and dialkyl acetals in the presence of TMS-triflate.[19] Herein, we describe the synthesis of vinyl and isopropenyl α-D-glucopyranosides by the Gassman method.

Both 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside and its corresponding tetra-*O*-acetyl derivative,[20] **1a** and **1b**, were treated with ethyl vinyl ether in dichloromethane in the presence of PPTS to give the mixed acetal α-D-glucopyranosides **2a**[7] and **2b**[8] in 85-90% yields as a 1:1 mixture of diastereomers that were not separated. The major products (~9:1) were the α-anomers in each case. Reduction of the quantity of acid catalyst and the use of no more than five equivalents of vinyl ether gave clean product that could be used directly in the elimination step (see Experimental).



Treatment of the benzyl-protected mixed acetal glycoside **(2b)** with trimethylsilyl trifluoromethanesulfonate and triethylamine gave the vinyl α-D-glucopyranoside **3**[12] in 68% yield after purification by flash chromatography. Products resulting from ring-opening, glycals formed by elimination of the anomeric substituent, or the TMS glycoside **4** that would result from an alternative elimination were not detected. The regioselectivity observed is consistent with that reported by Dujardin, Rossignol, and Brown,[16] and it is assumed to result from complexation of the trimethylsilyl cation with the ethoxy group oxygen of the mixed acetal, rather than the oxygen at C-1.



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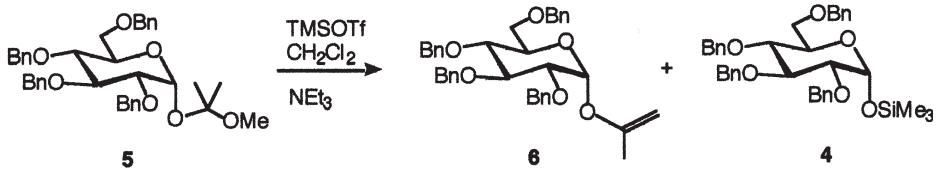
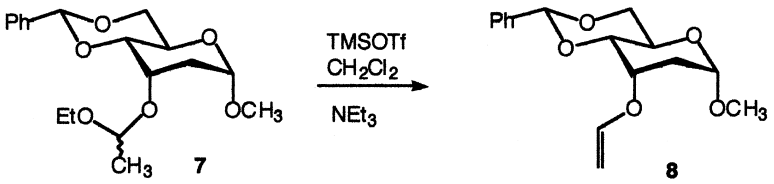
The synthesis of isopropenyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside by the Gassman method was also successful. Treatment of the mixed acetal glycoside **5** (prepared from **1b** using 2-methoxypropene) gave a product mixture containing a 2:1 ratio of isopropenyl glycoside **6**[5] to TMS glycoside **4**[8], from which **6** was isolated in 54% yield.



5 **6** **4**

The preparation of acetate ester-protected vinyl glycosides from mixed acetal glycosides **2a** by this procedure gave poor yields (20%) of vinyl glycoside, with decomposition being observed. Benzoate esters were not attempted, but these may be more suitable if competing enolization in the acetates is responsible for the low yields. In an example of the use of this method for the vinylation of other sites on the pyranose ring, the 3-*O*-vinyl ether **8** was obtained in 40% yield from mixed acetal **7**, which was readily prepared from methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside.[21]

In summary, a mercury-free synthesis of vinyl and isopropenyl glycosides was developed based on the Gassman method. Vinylation of hydroxyl groups at other positions also appears to be feasible. Further studies to test the scope of the reaction, the optimization of experimental conditions, and applications of the vinylated sugars are in progress.



7 **8**

EXPERIMENTAL

*Preparation of Mixed Acetal Glycosides **2a**, **2b**, **5**, and **7**.* A solution of the alcohol (1 mmol), vinyl ether (ethyl vinyl ether or 2-methoxypropene for **5**, 5 mmol), and PPTS (10 mg) in dry dichloromethane (20 mL) was stirred at room temperature until TLC (1:3 ethyl acetate-hexanes) showed that starting material was consumed (1-3 h). Solid sodium carbonate was added and after stirring for several minutes, the mixture was filtered and the filtrate concentrated under reduced pressure to give syrupy mixed acetal glycosides **2a**[7] and **2b**[8] in 85-90% yields, which were used without further purification. Compound **5** had $[\alpha]_D$ +60°

(*c* 1.1, chloroform); HRMS (ES+) Calcd. for $C_{38}H_{44}O_7Na$ [M+Na]: 635.3009. Found: 635.2985. Compound **7**: Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 63.55; H, 7.53.

*Preparation of Vinyl Glycosides **3**, **6** and Vinyl Ether **8***. To a solution of mixed acetal glycoside (1 mmol) in dichloromethane (3 mL) cooled to 0 °C was added triethylamine (1.6 equiv) followed by TMS- triflate (1.3 equiv). The reaction mixture was allowed to warm to room temperature and then stirred overnight. Additional triethylamine (0.4 equiv) and TMS-triflate (0.3 equiv) was added and stirring was continued until TLC (1:3 ethyl acetate-hexanes) showed the consumption of the starting material, usually another 18-24 h. Vinyl glycosides had slightly higher R_f values than mixed acetal glycosides, for example 0.38 and 0.54 for **5** and **6**, respectively (1:3 ethyl acetate-hexanes). Dilute sodium hydroxide solution (2 mL) was added slowly to the reaction, after which it was diluted with dichloromethane (20 mL). The organic phase was washed with saturated sodium chloride solution, dried (Na_2SO_4) and concentrated. Vinyl glycosides **3**[12] and **6**[5] were purified by flash chromatography using 10% ethyl acetate-hexanes. The same procedure was used for the preparation of 3-*O*-vinyl sugar **8**: R_f 0.20 (1:4 ethyl acetate/hexanes); $\alpha]_D$ +104° (*c* 1.0, chloroform); Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.43; H, 6.89.

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