A Glycosylation Driven Strategy for the Synthesis of Anomerically Pure Vinyl Sulfone-modified Pent-2-enofuranoses and Hex-2-enopyranoses

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Abstract: Both α- and β-anomers of vinyl sulfone-modified pent-2-enofuranosides have been synthesized for the first time by taking advantage of the formation of α- and β-methyl glycosides in almost equal ratio only from derivatives of D-xylose. The strategy was equally applicable in the synthesis of α- and β-anomers of vinyl sulfone-modified hex-2-enopyranosides where a D-glucose derivative was selected over a D-allose derivative as the starting material because the former almost exclusively produced the required methyl pyranosides.

Key words: modified carbohydrates, Michael acceptors, vinyl sulfone, pent-2-enofuranoside, hex-2-enopyranoside

The most common methods for the modification of monosaccharides involve the reactions of various reagents with sugar derived epoxides, tosylates and ketones although several other minor methods are also reported.[1] Nucleophilic addition (Michael) to double bonds activated by electron withdrawing groups as part of carbohydrates should serve as a useful methodology for the functionalization of monosaccharides. For example, studies on the Michael addition of nucleophiles to hex-2-enose[2–4] and 3-nitro-hex-2-enopyranosides[5–12] have been reported.

During the course of our studies on the synthesis and properties of carbohydrate modified monovinyl sulfone[13] and bisvinyl sulfone[14] substituted nucleosides, we envisaged that due to the high reactivities of vinyl sulfones towards various nucleophiles, vinyl sulfone-modified carbohydrates could be utilized to generate a wide variety of modified monosaccharides.

Vinyl sulfone-modified carbohydrates are expected to offer several additional advantages for synthetic chemistry, which have been detailed in earlier publications.[15,16a] Vinyl sulfone-modified pyranoses, such as, methyl 2,3 dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-α-D-*erythro*-hex-2-enopyranoside **22α** and methyl 2,3 dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-β-D-*erythro*-hex-2-enopyranoside **22β** have been subjected to reactions with various amines and the study has later been utilized for the synthesis of D-lividosamine (a component of aminoglycoside antibiotics) and its analogues by us.[16,17]

In order to broaden the scope of this study and also to gather information on the reaction patterns of *endo*cyclic mono-vinyl sulfones derived from pentofuranoses, we needed to develop a practical methodology for the synthesis of anomerically pure methyl 5-*O*-benzyl-2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-α-D-*erythro*-pent-2-enofuranoside **6α** and methyl 5-*O*-benzyl-2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-β-D-*erythro*-pent-2-enofuranoside **6β**. Anomerically pure vinyl sulfone-modified pent-2-enofuranoses were needed because we wanted to use the anomeric configuration as a tool to direct the diastereoselectivity of addition of nucleophiles to the 2-position of these enofuranoses. However, this particular requirement imposed greater restrictions on the choice of methodologies for the synthesis of compounds **6α** and **6β** starting from a single and easily accessible starting material.

A retrosynthetic analysis of the route to **6α** and **6β** necessitated the nucleophilic displacement of the *p*-tolylsulfonyl group of the easily accessible[18] starting material 5-*O*-benzyl-1,2-O-isopropylidene-3-*O*-tosyl-α-D-xylofuranose **1**. Thus, the synthesis was initiated by reacting **1** with *p*-thiocresol at 120 °C to produce the *ribo*-analogue **3** in 59% yield. The moderate yield of the *ribo*-product **3** can be partly explained on the basis of the repulsion caused by the 1,2-*O*-isopropylidene group to the incoming nucleophile.[1] Compound **3** on methanolysis produced the anomeric mixture of **4α** and **4β** in 78% yield. The anomers were separated at this stage over a silica gel (230–400 mesh) column using a mixture of acetone: chloroform:petroleum ether (1:1:8). Compounds **4α** and **4β** were oxidized separately to the corresponding sulfone derivatives **5α** and **5β** in high yields. The sulfones **5α** and **5β** on treatment with mesyl chloride and pyridine afforded smoothly the desired vinyl sulfone-modified carbohydrates **6α** and **6β** in excellent yields (Scheme 1).

Although at this stage the less efficient conversion of **1** to **3** was acceptable, the major drawback of this methodology was the unacceptable ratio of **4α** and **4β** (1:10) in the mixture. Lower ratio of α-anomer **4α** in the mixture of **4α** and **4β** contributed to the poor overall yield of the vinyl sulfone derivative **6α** (Scheme 1).

An examination of the percentage compositions of methyl furanosides of D-ribose, D-arabinose, D-xylose and D-lyxose at equilibrium revealed that the ratios of α- and β-

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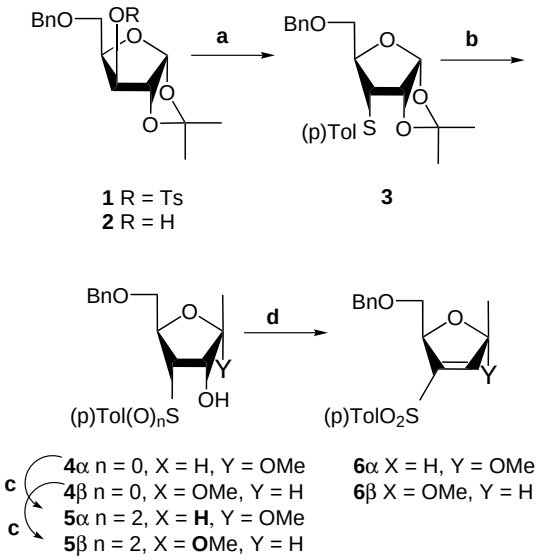
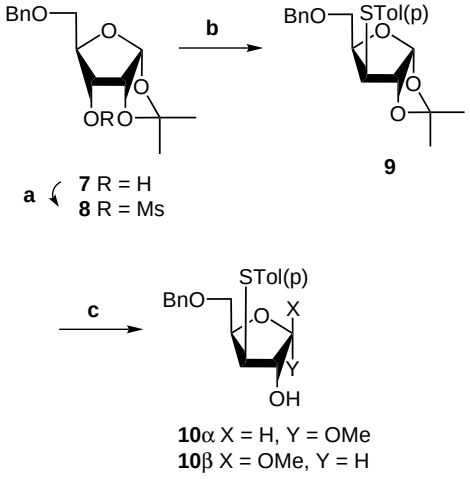


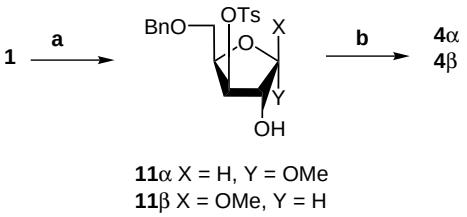
Scheme 1 Reagents and conditions: (a) *p*-thiocresol, NaOMe, DMF, 115–120 °C, 3.5–4.0 h, 59%; (b) MeOH, concd H_2SO_4, 65–70 °C, 3 h, 78% (**4α**:**4β** = 1:10); (c) MMPP, MeOH, r.t., 3 h, **5α** = 94%, **5β** = 93%; (d) MsCl, pyridine, 0 °C to r.t., 18–24 h, **6α** = 74%, **6β** = 92%.

furanosides present at equilibrium were 1:3.4, 3.1:1, 1:1.5 and only α, respectively.[19] Thus, the pattern of glycosylation of various pentose sugars dictated us to select a D-*xylo*-derivative based strategy for the synthesis of an anomeric mixture close to the ideal ratio of 1:1. Accordingly, it was possible to synthesize a *xylo*-derivative **9** from 5-*O*-benzyl-1,2-*O*-isopropylidene-3-*O*-mesyl-α-D-*ribo*furanose **8** in 79% yield. Compound **9** on methanolysis produced the mixture of anomers **10α** and **10β** in a ratio 1.5:1 (Scheme 2). Although this ratio was acceptable for the synthesis of both the anomers **6α** and **6β**, the overall yield again dropped due to the addition of two synthetic steps for converting **1** to the *ribo*-derivative **7** via a two-step oxidation-reduction process.



Scheme 2 Reagents and conditions: (a) MsCl, pyridine, 0 °C, 24 h, 98%; (b) *p*-thiocresol, NaOMe, DMF, 145 °C, 3 h, 79%; (c) MeOH, concd H_2SO_4, 65–70 °C, 3 h, 89% (**10α**:**10β** = 1.5:1).

It was, however possible to circumvent all these shortcomings by first converting the *xylo*-derivative **1** to an anomeric mixture of **11α** and **11β** in a ratio 1:1.3 in high yields (85–94% from several batches). In the absence of any steric hindrance, the nucleophilic displacement of the tosyl group of the mixture of **11α** and **11β** by *p*-thiocresol proceeded smoothly to afford a mixture of 3-deoxy-3-*C*-(*p*)-tolylsulfide-D-*ribo*furanosides **4α** and **4β** in 94% yield (Scheme 3). The anomers **4α** and **4β** were separated at this stage and were converted separately to **6α** and **6β** as described in Scheme 1.

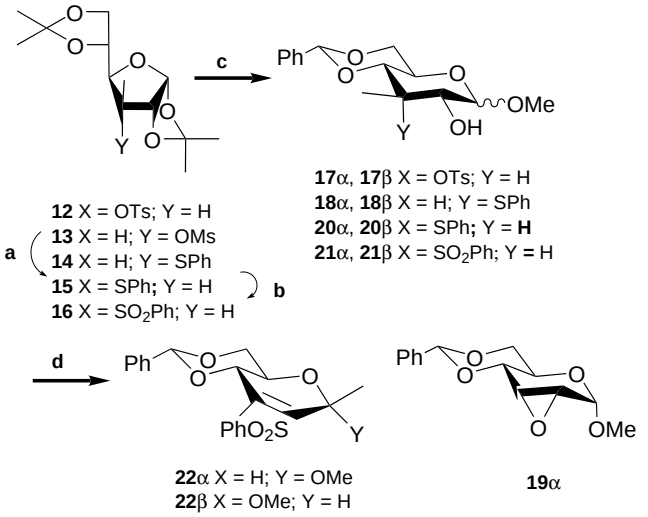


Scheme 3 Reagents and conditions: (a) MeOH, concd H_2SO_4, 65–70 °C, 3 h, 85–94% (**11α**:**11β** = 1:1.3); (b) *p*-thiocresol, NaOMe, DMF, 115–120 °C, 3.5–4.0 h, 94%.

After devising a route for the synthesis of hitherto unknown **6α** and **6β** using this novel approach, we turned our attention to the synthesis of known **22α** and **22β**. The existing routes for the synthesis of hex-2-enopyranose derivatives **22α** and **22β** are lengthy and each anomer requires separate starting material for its synthesis.[11,16a] However, for the continuation of research in this area we require relatively large amount of anomerically pure **22α** and **22β** through a shorter route. In order to achieve this target we applied the glycosylation driven strategy for the selection of starting sugar for the synthesis of **22α** and **22β**. It has been reported that the equilibrium mixture of methyl-D-allosides in methanol, contained more than 30% of furanosides[20,21] whereas D-glucose produced[19] methyl-D-pyranosides almost exclusively. Although the reported ratio of α- and β-anomers were not close to the ideal value of 1:1, in this case it was more important to get the methyl pyranosides without any contamination of the corresponding furanosides. This observation prompted us to study the feasibility of using the known tosylate **12** as a starting material,[22] which could be converted to an anomeric mixture of **17α** and **17β**[23] in a ratio 1:1.5. The α-anomer **17α**, on treatment with thiophenol did not produce the desired thiosugar **18α** due to the in situ formation of 2,3-*O*-anhydro-*allo*-derivative **19α**.[24]

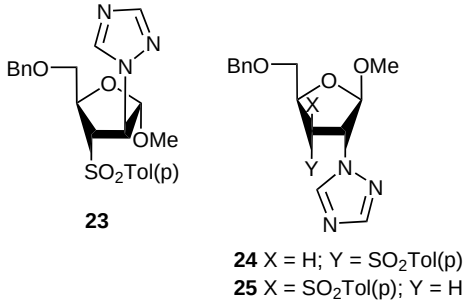
However, it was possible to incorporate thiophenyl group at the 3-position of the hexose sugar prior to pyranoside formation to get two possible starting materials **14** and **15** by displacing the leaving groups of **12** and **13** respectively by sodium thiophenolate. Here also, for reasons discussed above, the *gluco*-derivative **15** was the starting material of choice over the *allo*-derivative **14**. Oxidation of **15** produced **16** in excellent yield. Treatment of **16** with acetyl chloride in methanol afforded an anomeric mixture, which was isolated as the benzylidene derivatives **21α** and **21β** in

a ratio 1:1.8. The anomers **21α** and **21β** were separated and converted to the desired vinyl sulfone-modified hex-2-enopyranoses **22α** and **22β** respectively. It was also possible to access **22α** and **22β** by first converting **15** to **20α** and **20β** in a ratio 2.2:1 (Scheme 4).[26]



Scheme 4 Reagents and conditions: (a) PhSH, NaOMe, DMF, 125 °C, 2 h, 80%;(b) MMPP, MeOH, r.t., 3 h, 94%; (c) i. CH_3COCl, MeOH, 1 h, reflux, 24 h; ii. 1,1-dimethoxytoluene, *p*-TSA, DMF, 100 °C, 71% (in two steps; **21α**:**21β** = 1:1.8); (d) i. MsCl, pyridine, 0 °C 12 h; ii. DBU, CH_2Cl_2, r.t., 15 min, 96% (in two steps for **22α**), 96% (in two steps for **22β**).

In order to establish the influence of anomeric configuration on the diastereoselectivity of addition of various nucleophiles to these highly reactive Michael acceptors, **6α** and **6β** were reacted separately with 1,2,4-triazole in the presence of 1,1,3,3-tetramethylguanidine in DMF at ambient temperature. Compound **6α**[25] produced a single isomer **23** [82%;^{1}H NMR: δ = 5.12 (1 H, d, *J* = 2.0 Hz, H-1); Calcd for $C_{22}H_{25}N_3O_5S$: C, 59.58; H, 5.67; N, 9.47. Found: C, 59.77; H, 5.96; N, 9.33] where the nucleophile approached the C-2 position from the β-face. Compound **6β**, on the other hand produced a separable mixture (total yield 75% in a ratio of 1:1) of *ribo*-derivative **24** [^{1}H NMR: δ = 5.08 (1 H, s, H-1); Calcd for $C_{22}H_{25}N_3O_5S$: C, 59.58; H, 5.67; N, 9.47. Found: C, 59.48; H, 5.64; N, 9.66] and *xylo*-derivative **25** (^{1}H NMR: δ = 5.05 (1 H, d, *J* = 3.9 Hz, H-1); Calcd for $C_{22}H_{25}N_3O_5S$: C, 59.58; H, 5.67; N, 9.47. Found: C, 59.92; H, 5.29; N, 9.36]. For the formation of both **24** and **25**, the nucleophile attacked the C-2 position of **6β** exclusively from the α-face (Figure).[27] All new compounds were characterized by NMR spectroscopy and elemental analysis.



Figure

Acknowledgement

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(25) Analytical and spectroscopic data of selected compounds. **6α**: Gummy material. Found: C, 64.48; H, 5.90; S, 8.67. $C_{20}H_{22}O_5S$ requires C, 64.15; H, 5.91; S, 8.56%; ^{1}H NMR: δ = 6.59 (1 H, s), 5.88 (1 H, d, *J* = 4.4 Hz), 5.13 (1 H, m), 4.44 (2 H, s, $PhCH_2$), 3.85 (1 H, dd, *J* = 10.7, 2.4 Hz), 3.60 (1 H, dd, *J* = 10.7, 4.4 Hz), 3.39 (3 H, s, OMe), 2.42 (3 H, s, ArMe). **6β**: Gummy material. Found: C, 64.41; H, 6.36; S, 8.81. $C_{20}H_{22}O_5S$ requires C, 64.15; H, 5.91; S, 8.56%; ^{1}H NMR: δ = 6.60 (1 H, s), 5.72 (1 H, s), 4.95 (1 H, d, *J* = 6.3 Hz), 4.47 (2 H, s, $PhCH_2$), 3.83 (1 H, dd, *J* = 10.7, 2.4 Hz), 3.50 (1 H, m), 3.42 (3 H, s, OMe), 2.43 (3 H, s, ArMe). **16**: White solid, mp 158–159 °C. Found: C, 56.19; H, 6.90; S, 8.62. $C_{18}H_{24}O_7S$ requires C, 56.23; H, 6.28; S, 8.34%; ^{1}H NMR: δ = 5.96 (1 H, d, *J* = 3.9 Hz), 4.96 (1 H, d, *J* = 3.5 Hz), 1.49 (3 H, s, Me), 1.35 (3 H, s, Me), 1.29 (3 H, s, Me), 1.21 (3 H, s, Me).

(26) Compounds **22α** and **22β** have been synthesized earlier[11,16a] from D-glucose in 14 steps (7 steps for each anomer). The present method makes use of common intermediates upto compounds **21α** and **21β**, thereby drastically reducing the overall purification steps. Although overall yields for both the methods are comparable, methyl β-D-glucopyranoside, which has been used in the earlier synthesis,[11,16a] is far too expensive a starting material to be used in a large-scale multi-step synthesis.

(27) The configurations at the C-2 and C-3 positions of **23**–**25** have been established unambiguously. The data will be published as part of a full paper.