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An efficient and highly regioselective synthesis of 4-deoxy- and 2-acetamido-2,4-dideoxy-β-D-*threo*-hex-3-enopyranosides

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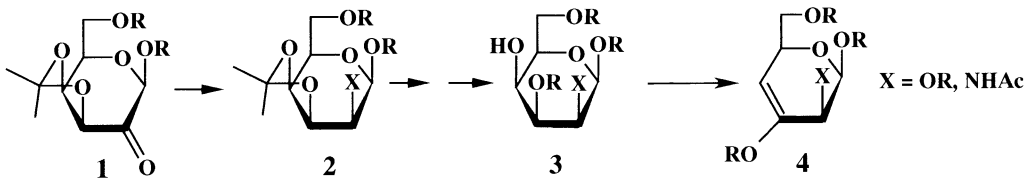
Abstract—The preparation of the previously undescribed class of 4-deoxy- and 2,4-dideoxy-2-acetamido-β-D-*threo*-hex-3-enopyranosides was accomplished with a very high yield and a complete regioselectivity by means of a simultaneous activation–elimination process of the OH-4 group of β-D-talopyranosides (**5a**,**b**) and 2-acetamido-2-deoxy-β-D-talopyranosides (**5c**,**d**) with NaH/*N*,*N*′-sulfuryldiimidazole. The same reaction of analogous β-D-galactopyranosides (**5e**,**f**) is not regioselective, leading to mixtures of 3- and 4-hexeno derivatives. This difference is evidently determined by the orientation of the C-2 substituent, which, in the *talo* series, is *anti* diaxially disposed to the H-3 eliminating group.

Unsaturated monosaccharides are one of the most useful classes of synthetic intermediates for the conversion of common sugars into more sophisticated glycides,[1] as well as for the synthesis of other types of natural compounds.[2] Glycals, cyclic vinyl ethers involving the ring oxygen atom, are by far the most popular unsaturated glycide derivatives,[3] but some other types of olefinic pyranosides have received great attention, such as for instance 2,3-dideoxy-hex-2-enopyranosides,[4] easily obtained by Ferrier rearrangement of glycals.[1] Much less studied are pyranose vinyl ethers not involving the anomeric centre, although their preparation is in principle very quick, requiring the activation of one hydroxyl group (e.g. a sulfonate) followed by a simple base-promoted elimination.[1] The major drawback of this approach is that a leaving group in a pyranose framework, with the exception of those in position 1 or 6, is flanked by two hydrogen atoms with approximately the same reactivity, with the result that the formation of a single enol ether is relayed only to favourable specific cases.[1]

We present here a very efficient and regiospecific formation of the title unsaturated pyranosides (**4**) through a simultaneous activation–elimination process with NaH/*N*,*N*′-sulfuryldiimidazole (Im_2SO_2) of 4-*O*-deprotected β-D-talopyranosides (**3**, X = OR) or 2-deoxy-2-acetamido-β-D-talopyranosides (**3**, X = NHAc), in turn obtained in very high yields by reduction[5] or oximation/reduction[6] of easily accessible 2-ulopyranosides **1**[6,7] (Scheme 1).

Compounds **4** have, to our knowledge, not been previously reported, whereas their *erythro* analogues have been obtained only in mixtures with other products during nucleophilic substitution[8a,b] or elimination reactions[8c] of 4-*O*-sulfonyl-D-galactopyranoside derivatives.

In the context of a general project on the chemical transformation of common glycides into more rare bioactive sugars, we started a study to determine useful conditions for the epimerization at C-4 of 2-acetamido-



Scheme 1.

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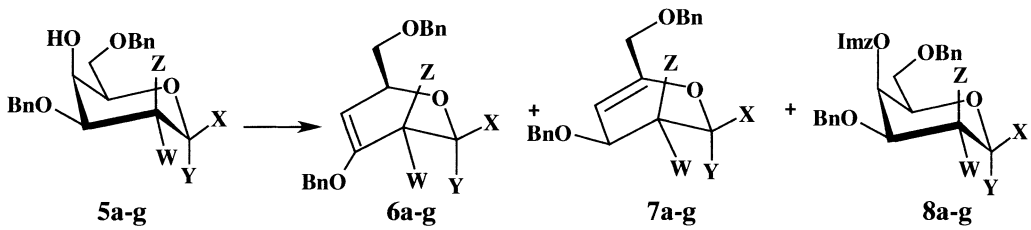
2-deoxy-β-D-talopyranosides, previously obtained[6] with high yields by 2-amination with inversion of the configuration of β-D-galactopyranosides, including lactose. However, all attempts to obtain 4-*O*-sulfonates (mesylate, tosylate, triflate) of methyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-talopyranoside (**5c**)[9] gave frustrating results, only starting material being recovered even in forcing conditions, probably because of the steric shielding exerted on OH-4 by the *syn*-diaxial 2-acetamido group. We thus tried to prepare 4-*O*-imidazole-1-sulfonate (4-*O*-imidazylate)[10] in accordance with a procedure based on the preliminary activaction of the hydroxyl group by salt formation with a large excess of NaH.[11] In the case of **5c**, a smooth reaction takes place leading with a high yield to a practically pure product, not corresponding to the structure of the expected 4-*O*-imidazylate, but identified as the 4-deoxy-hex-3-enopyranoside **6c** (Scheme 2).[12] The formation of **6c** is easily explainable, as determined by the transient formation of the imidazole-1-sulfonate (**8c**) followed by a β-elimination, favoured by the strongly alkaline medium and by the *anti* disposition between the imidazylate group and H-3. The elimination, probably following an E2 mechanism, appears to be a very fast process, the formation of the hypothesised intermediate **8c** not being confirmed, at least by TLC analysis, at any stage of the reaction. It is more difficult to explain the observed complete regioselectivity of the reaction, confirmed by the absence of product **7c** arising from a competitive β-elimination of H-5, despite its *anti* disposition with respect to the 4-leaving group (Scheme 2). Prompted by this interesting result, we extended the reaction to other pyranosides[15] of the D-talo and D-galacto series, having the same stereochemistry at C-3, C-4 and C-5. The results (Table 1) show interesting analogies and differences. The talosamine disaccharide **5d**, prepared starting from triacetonlactose derivatives,[6b] gives the 3-hexeno derivative **6d**[12,13] with a high yield, like its monosaccharide analogue **5c**; the only difference observed is a marked reduction in the reaction rate, requiring, for the complete transformation of the starting material, a higher reaction temperature (0°C instead −30°C), without, however, a significant influence on the final yield. Also in the cases of the neutral mono- and disaccharidic talopyranosides **5a** and **5b**, treatment with NaH and Im_2SO_2 led directly to the corresponding enol ethers **6a** and **6b**,[12,13] without the formation of isomeric enol ethers or other by-products, thus suggesting that the overall outcome of this reaction is independent from the type of substituent at C-2 and from the steric hindrance of the aglycon.

In the case of β-D-galactopyranosides **5e**,**f**, the reaction is not regioselective and a mixture of 3-hexeno- (**6e**,**f**) and 4-hexeno derivatives (**7e**,**f**) was obtained, with the former prevailing over the latter. The two disaccharide enol ethers **6f** and **7f** were separated over silica and their structure was definitively assigned through NMR analysis,[13] while in the case of the monosaccharide, the two products **6e** and **7e** proved to be unseparable, but their structure and the composition of the mixture were inferred by NMR.[14] The observed difference in the regioselectivity between the two stereochemical series is



Scheme 2.

Table 1. Product distribution in the reaction of some pyranosides of the D-talo- and D-galacto series with Im_2SO_2/NaH[a]

Compound	X	Y	Z	W	Temp (°C)	Reaction time (h)	Product distribution (%)[b]			Yield (%)[c]
							6	**7**	**8**	
5a	OMe	H	OBn	H	−30	3	100	–	–	95
5b	OGlc[e]	H	OBn	H	0	24	100	–	–	90
5c	OMe	H	NHAc	H	−30	3	100	–	–	93
5d	OGlc[e]	H	NHAc	H	0	24	100	–	–	79
5e	OMe	H	H	OBn	−30	4	65	35	–	75[d]
5f	OGlc[e]	H	H	OBn	0	29	60	40	–	46 (**6f**), 30 (**7f**)
5g	H	OMe	H	OBn	−30	3	–	10	90	75 (**8g**)

[a] All reactions were conducted in accordance with the procedure described in Ref. 11.
[b] Determined by NMR on the crude reaction products.
[c] Determined on analytically pure products (Ref. 12), fully characterised by NMR analysis (Ref. 13).
[d] Unseparable mixture of **6e**+**7e** (Ref. 14).
[e] Glc = 2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal.

evidently due to their opposite configurations at C(2). It can be supposed that an axially disposed heteroatom at C(2), present in the talo series, co-operates on stereoelectronic grounds in the breaking of the C(3)–H bond during the elimination step, making this process easier than the competitive elimination involving the C(5)–H bond. The absence of this stereoelectronic factor in the galacto series reduces the energy difference between the two competitive pathways, leading to mixtures of enol ethers, as generally observed during the reactions of 4-*O*-sulfonyl-D-galactopyranosides with various kinds of nucleophiles.[8a,b]

The reaction of methyl α-D-galactopyranoside derivative **5g** with Im_2SO_2/NaH shows a further difference. A fast reaction takes place at −30°C giving, however, only 10% of the enol ether **7g**, the major product being, unexpectedly, the 4-*O*-imidazylate **8g**. When the reaction was prolonged for a further 4 h at room temperature, TLC analysis showed the disappearance of **8g** but without any appreciable increase in **7g**.

A tentative explanation for the inhibition of the elimination step registered in the α-galacto series, is that the attack of the hydride on the axially oriented H(3) or H(5) is hindered, probably because of steric or field factors, by the *syn*-1,3-diaxial α-aglycon. An analogous difference in reactivity between the two anomeric series of D-galactopyranosides has been previously reported[17] also in the case of the base-promoted acetone elimination of 2,6-di-*O*-protected 3,4-*O*-isopropylidene derivatives.

In conclusion, the reaction of an aldopyranoside having a single deprotected and axially orientated hydroxyl group with *N*,*N*′-sulfuryldiimidazole and NaH could represent, in selected stereochemical series like the β-D-talo one, a new, simple and very efficient way to obtain with a high yield sugar enol ethers of potential utility in glycide synthesis. Further studies on other favourable stereochemical series, as well on the synthetic uses of the enol ether products, are now planned in order to define the scope and limitations of the reaction.

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9. Compound **5c** was obtained from methyl 2-acetamido-2-deoxy-3,4-*O*-isopropylidene-β-D-talopyranoside,[6a] through the following sequence: (a) 6-*O*-benzylation (KOH, 18-crown-6, THF+0.5% H_2O, 84% yield); (b) 3,4-de-*O*-isopropylidenation (80% aq. AcOH, 40°C, 2 h, quant.); (d) 3-*O*-benzylation (1. Bu_2SnO, toluene, reflux, 2. BnBr, Bu_4NBr, toluene, 5 h, 80% yield).
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11. Sodium hydride (5.0 mmol), suspended in dry DMF (5 mL), was treated at room temperature with a solution of the appropriate sugar (1.0 mmol) in 20 mL of dry DMF. The mixture was stirred at rt for 30 min, cooled, treated with Im_2SO_2 (290 mg, 1.46 mmol) and further stirred (see Table 1). Excess of NaH was destroyed with MeOH (5 mL) and, after routine work-up, the residue was purified by flash chromatography on silica.
12. **6a**: syrup, $[\alpha]_D$ −1.6 (*c* 1.1, $CHCl_3$); **6b**: syrup, $[\alpha]_D$ +3.9 (*c* 1.2, $CHCl_3$); **6c**: syrup, $[\alpha]_D$ +2.1 (*c* 1.1, $CHCl_3$); **6f**: syrup, $[\alpha]_D$ −30.3 (*c* 0.9, $CHCl_3$); **7f**: syrup, $[\alpha]_D$ +9.8 (*c* 1.2, $CHCl_3$); **8g**: syrup, $[\alpha]_D$ +39.6 (*c* 1.4, $CHCl_3$).
13. Selected NMR data ($CDCl_3$, ^1H, 200 MHz ^{13}C, 50 MHz). **6a**: δ_H 3.55 (dd, 1H, $J_{5,6a}=5.6$ Hz, $J_{6a,6b}=9.7$ Hz, H-6a), 3.72 (dd, 1H, $J_{5,6b}=6.2$ Hz, H-6b), 4.51 (d, 1H, $J_{1,2}=2.0$ Hz, H-1), 4.92 (d, 1H, $J_{4,5}=1.7$ Hz, H-4), δ_C 98.6 (C-4), 101.6 (C-1), 152.1 (C-3); **6b**: δ_H 3.46 (dd, 1H, $J_{5',6'a}=5.3$ Hz, $J_{6'a,6'b}=9.5$ Hz, H-6′a), 3.68 (dd, 1H, $J_{5',6'b}=6.5$ Hz, H-6′b), 4.90 (d, 1H, $J_{1',2'}=1.9$ Hz, H-1′), 4.99 (d, 1H, $J_{4',5'}=1.5$ Hz, H-4′), δ_C 99.4 (C-4′), 101.6 (C-1′), 152.4 (C-3′); **6c**: δ_H (CD_3CN) 3.50 (dd, 1H, $J_{5,6a}=4.9$ Hz, $J_{6a,6b}=9.9$ Hz, H-6a), 3.57 (dd, 1H, $J_{5,6b}=6.1$ Hz, H-6b), 4.58 (d, 1H, $J_{1,2}=1.9$ Hz, H-1), 4.86 (d, 1H, $J_{4,5}=1.8$ Hz, H-4), δ_C (CD_3CN) 97.3 (C-4), 100.1 (C-1), 152.6 (C-3); **6d**: δ_H 4.77 (d, 1H, $J_{1',2'}=1.6$ Hz, H-1′), 4.99 (d, 1H, $J_{4',5'}=2.2$ Hz, H-4′), δ_C 97.6 (C-4′), 99.3 (C-1′), 152.5 (C-3′); **6f**: δ_H 3.39 (dd, 1H, $J_{5',6'a}=5.3$ Hz, $J_{6'a,6'b}=9.5$ Hz, H-6′a), 3.58 (dd, 1H, $J_{5',6'b}=6.5$ Hz, H-6′b), 4.92 (d, 1H, $J_{4',5'}=1.2$ Hz, H-4′), 5.00 (d, 1H, $J_{1',2'}=6.2$ Hz, H-1′), δ_C 97.6 (C-4′), 102.2 (C-1′), 153.0 (C-3′); **7f**: δ_H 3.91 (s, 2H, H-6′a, and H-6′b), 5.07 (d, 1H, $J_{3',4'}=3.1$ Hz, H-4′), 5.31 (d, 1H, $J_{1',2'}=6.9$ Hz, H-1′), δ_C 98.7 (C-1′), 101.0 (C-4′), 149.6 (C-5′); **8g**: δ_H 3.45 (tb, 1H, $J_{5,6b}=8.5$ Hz, $J_{6a,6b}=9.0$ Hz, H-6b), 3.54 (dd, 1H, $J_{5,6a}=5.7$ Hz, H-6a), 4.56 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 6.98 and 7.88 (2s, 2H, H-4′, and H-2′), δ_C 83.5 (C-4), 98.6 (C-1), 118.2, 130.2 and 137.1 (Im).
14. **6e**: δ_H ($CDCl_3$, 200 MHz) 3.44 (dd, 1H, $J_{5,6a}=6.0$ Hz, $J_{6a,6b}=9.4$ Hz, H-6a), 3.61 (dd, 1H, $J_{5,6b}=6.7$ Hz, H-6b); 4.76 (d, 1H, $J_{1,2}=3.6$ Hz, H-1); 4.92 (d, 1H, $J_{4,5}=2.3$ Hz, H-4); δ_C ($CDCl_3$, 50 MHz) 96.9 (C-4); 102.1 (C-1); 151.4 (C-3); **7e** δ_H ($CDCl_3$, 200 MHz) 3.96 (s, 2H, H-6a, and H-6b); 4.87 (d, 1H, $J_{1,2}=5.6$ Hz, H-1); 5.07 (d, 1H, $J_{3,4}=3.3$ Hz, H-4); δ_C ($CDCl_3$, 50 MHz) 99.0 (C-4); 101.3 (C-1); 149.2 (C-5).
15. The preparation of previously unreported derivatives **5**,**a**,**b**,**d** was performed by classic manipulation of protect-

ing groups, as exemplified for **5c** in Ref. 9, and will be reported in detail in the full paper. **5f** was prepared with a good yield by stannylidene-mediated benzylation of known (Ref. 16) 2′6′-di-*O*-benzyl-2,3:5,6-di-*O*-isopropylidenelactose dimethyl acetal. Derivatives **5e**,**g** have previously been reported (Ref. 18).

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