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A CONVENIENT AND GENERAL SYNTHESIS OF 5-VINYLHEXOFURANOSIDES FROM 6-HALO-6-DEOXYPYRANOSIDES[1]

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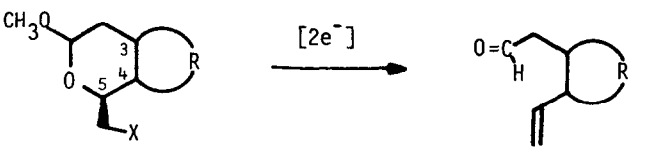
Abstract: The synthesis of five different 5,6-dideoxyhex-5-enofuranosides (5, 7, 9 and 11) proceeds in 30-60% overall yield in two steps from commercially available 1-O-methyl pyranosides by reductive β-elimination of the intermediate 6-bromo-6-deoxypyranosides.

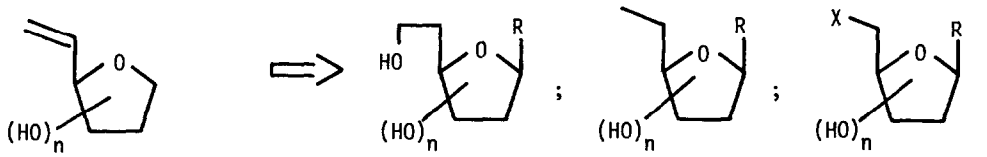
We desired a test of the idea that reductive β-elimination of CH_3OX from a 1-O-methyl-3,4-disubstituted-5-halomethyltetrahydropyrane (A) could lead to the formation of the δ,ε-unsaturated aldehyde functionality (B) present in masked form in A (eq 1). Realization of this transformation might enable us to use the chirality at C-5 of A to induce asymmetry in some other part of the molecule (— R* —) during its formation, then unmask the δ,ε-unsaturated aldehyde moiety to obtain the desired product in an optically active form.



(1)

The practicality of the above approach to the asymmetric synthesis of natural products in which we are interested depends on two things: (1) having an inexpensive and convenient source of C-5 chiral A and (2) establishing that annulation of the "— R —" portion onto a suitable 5-halomethyl-3,4-dehydropyrane to give A occurs with acceptable asymmetric induction. Since these two requirements can be satisfied, in principle, by the use of the D-pyranose form of carbohydrates and their simple derivatives, we examined the reductive β-elimination of a series of (D)-1-O-methyl-6-halo-6-deoxypyranosides as a model system for the transformation shown in eq 1.

We report now that our study has resulted in a convenient and general synthesis of 5,6-dideoxyhex-5-enofuranosides from readily available carbohydrates in two steps (30-60% overall yield). This synthetic development has general importance because of the current interest in 5,6-dideoxyhex-5-enofuranosyl nucleosides,[4] 5-deoxyhexofuranosyl glycosides[3] and various 5-substituted[5] analogues derivable from 5-vinylhexofuranosides (eq 2) as chemotherapeutic agents.[6] In particular, our new method is applicable to the preparation of L-5-vinylhexofuranosides and 2-deoxy-D or L-5-vinylhexofuranosides, which have been prepared previously by much less efficient routes.[4a]



(2)

The 6-bromo-6-deoxypyranosides required for the reductive β-elimination reaction can be prepared from 1-O-methyl pyranosides, many of which are commercially available, by the method of Hanessian et al. involving treatment of the O-methyl glycoside with NBS, Ph_3P and DMF.[7b] This reaction works well for most unprotected pyranosides (Table 1), except galactose, which must be converted to its 6-bromo-6-deoxy derivative via either the intermediate 1,2:3,4-di-O-isopropylidene pyranoside,[8] or the 1-O-methyl-4,6-benzylidene acetal.[9] The latter method worked best in our hands for the preparation of 1-O-methyl-6-bromo-6-deoxygalactoside (3). The analogous O-methyl 6-chloro-6-deoxypyranosides can be prepared by reaction of their methyl glycosides with mesyl chloride and DMF.[10]

Table 1. Preparation of 1-O-Methyl-6-Bromo-6-deoxypyranosides[a]

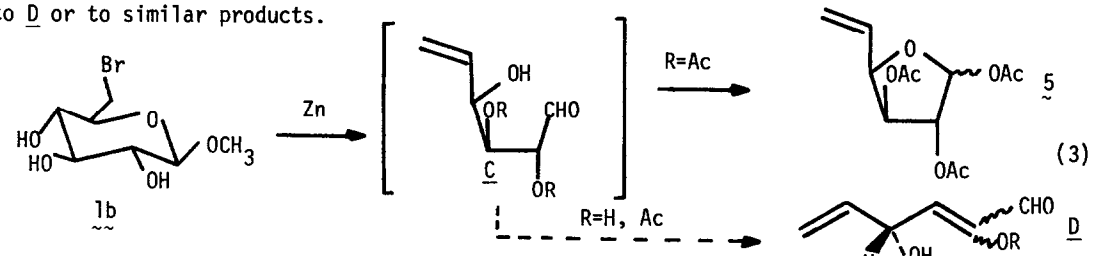
Starting glycoside	Product[b]	Yield (%)
Methyl-α-D-glucose	1(α)-O-Methyl-6-bromo-6-deoxyglucose (1a)[7b]	80
Methyl-β-D-glucose	1(β)-O-Methyl-6-bromo-6-deoxyglucose (1b)[9]	82
Methyl-α-D-mannose	1(α)-O-Methyl-6-bromo-6-deoxymannose (2)[11]	78
Methyl-α-D-galactose	1(α)-O-Methyl-6-bromo-6-deoxygalactose (3)[9]	45[c]
Methyl-α-D-2-deoxygalactose	1(α)-O-Methyl-6-bromo-2,6-dideoxygalactose (4)[d]	49

[a]All products had spectral and physical properties consistent with the literature data. [b]Literature preparation given by superscript. [c]Overall in three steps. [d]mp 79-87°C (EtOH, amorph crys); $[\alpha]_D^{24°}$ = +135° (CH_3OH).

The reductive β-elimination of CH_3OX from compounds 1-4 proceeded well with only one reducing agent, the highly active Zn° made from the reduction of $ZnCl_2$ with metallic potassium in THF according to Rieke and Uhm.[12] The 6-bromo-6-deoxypyranosides were inert to all other activated forms of Zn dust [acid-washed; Hg, Cu, or Ag couples] in refluxing MeOH, although acid-washed Zn dust in aqueous ethanolic NH_4Cl[13] gave a low yield of the reductive β-elimination product from 1a after prolonged reaction time. Treatment of the 6-chloro-6-deoxy analogue of 1a with Cr(II) salts, a method that is known to be successful for reductive β-elimination,[14] gave very low yields of the desired elimination product, but the 6-chloro-6-deoxy analogues of 1-3 were inert to even the highly active Zn reagent. We note an independent report that the perbenzylated derivatives of 1 give the reductive β-elimination product analogous to those we obtain from 1-4 on treatment with acid-activated Zn (65-88% yield), or with n-butyl lithium.[15]

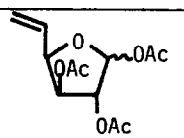
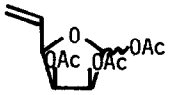
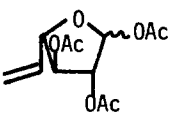
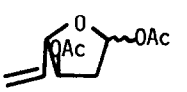
The results of the treatment of compounds 1-4 with Rieke's Zn are listed in Table 2. The product 5,6-dideoxyhex-5-enofuranosides were isolated as their peracetylated derivatives (5-11) for convenience only, and were always accompanied by small amount of the products (6-12)

resulting from C-6 reductive dehalogenation without accompanying β-elimination. [The latter are the sole product when 6-bromo-6-deoxypyranosides are treated with Zn in glacial AcOH.[16]] Acetates 5-11 were obtained as a mixture of C-1 anomers, reflecting the expected thermodynamic distribution of anomers resulting from cyclization of the intermediate δ,ε-unsaturated aldehyde C (eq 3).[15] We isolated this intermediate, obtained from the reductive β-elimination of peracetyl-1a, as its 2,3,4-triacetate, but the latter proved unstable to chromatography or aqueous base. This property is consistent with the expected ease of its β-elimination, e.g., to D or to similar products.



(3)

Table 2. Products from the Reductive β-Elimination of 1-O-Methyl-6-Bromo-6-deoxypyranosides

6-Bromo-6-deoxypyranoside	Products[a] β-elimination (% yield)		Reduction; % yield.
1a	5 	(70)	1(α)-O-Methyl-2,3,4-triacetyl-6-deoxy-glucose (6); 13.
1b	5	(73-75)	1(β) anomer of 6; 10.
2	7 	(65-69)	1(α)-O-Methyl-2,3,4-triacetyl-6-deoxy-galactose (8); 14-19.
3	9 	(68)	1(α)-O-Methyl-2,3,4-triacetyl-6-deoxy-mannose (10); 11.
4	11 	(70)	1(α)-O-Methyl-3,4-diacetyl-2,6-dideoxygalactose (12); 9.

[a]All new compounds had ir, ms, and nmr spectral data fully consistent with the assigned structure.

The results of our study reveal one point of mechanistic information about the reductive β-elimination reaction of compounds 1-4. Since the C-1 configuration of 1 did not affect the product distribution (or qualitative reaction rate, noticeably), it appears that the β-elimination reaction does not proceed in a concerted manner. That is, if this were true, 1b could have reacted much faster than 1a, or 1a not have given 5, only 6, since the orientation of the O^6-C^5 and C^1-OCH_3 bonds in 1b are anti and coplanar, but orthogonal in 1a.[17]

Our mechanistic conclusion rests on the presumption that even if the reductive β-elimination proceeds in two discrete steps, high stereoelectronic constraints would still have disfavored 1a going to 5.

A representative general procedure for the synthesis of compounds 5-12 is as follows: Freshly dried $ZnCl_2$ (1.8 g, 110°-130°C @ 1 Torr, 3 h) was partially fused by heating with a flame under a N_2 atmosphere. After cooling of the fused mass to rm temp, THF (20 mL freshly distilled from $LiAlH_4$) was added to the $ZnCl_2$ followed by the addition of K metal (0.8 g). The mixture was heated under N_2 at reflux with stirring until a vigorous reaction took place. The heat source was removed as necessary to control the reaction rate until the initial vigorous reaction had subsided, after which the mixture was refluxed another 3 h under N_2. After cooling the reaction mixture to rm temp, absolute MeOH (50 μL), then the 6-bromo-6-deoxypyranoside (200 mg) in absolute MeOH (0.5 mL) were added and the reaction mixture stirred at rm temp for 12-16 h. The resulting mixture was filtered through a Celite pad, the Celite washed with MeOH, and the combined filtrates were evaporated to dryness in vacuo. The resulting grayish-white oily residue was acetylated (Ac_2O, 3 mL; pyridine, 3 mL; rm temp; overnight). The yellowish oil resulting from work-up of the acetylation reaction (ice-Et_2O followed by washings with 1N HCl, aq. $NaHCO_3$, and water; drying (Na_2SO_4) and solvent removal) was purified by column chromatography on silica gel (60 g) using skellysolve B:EtOAc (5:1) as eluant.

References and Acknowledgements

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(2) Research Career Development Awardee of the National Cancer Institute (CA 00253), 1976-81.

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