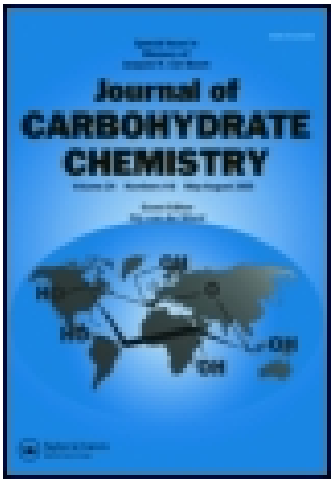


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lcar20

Epimerization of Carbohydrates via Stannylene Acetals. A Practical Synthesis of D-Talose

György Hodosi [a] & Pavol Kováč [a]
[a] NIDDK , National Institutes of Health , Bethesda, MD, 20892-0815, U.S.A.
Published online: 22 Aug 2006.

J. CARBOHYDRATE CHEMISTRY, 17(4&5), 557-565 (1998)

EPIMERIZATION OF CARBOHYDRATES *VIA* STANNYLENE ACETALS. A PRACTICAL SYNTHESIS OF D-TALOSE[1]

György Hodosi and Pavol Kováč*

NIDDK, National Institutes of Health, Bethesda, MD 20892-0815 (U.S.A.)

Final Form October 9, 1997

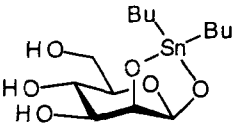
ABSTRACT

When treated with Bu_2SnO in a suitable solvent, reducing sugars preferentially form 1,2-*O*-stannylene acetals and, on prolonged treatment with a slight excess of the reagent at reflux temperature, they undergo epimerization. This allows simple preparation of rare monosaccharides from readily available, unprotected starting materials. The process is equilibrium driven, and the equilibrium is shifted largely in favor of structures having an axial hydroxyl group at position 2.

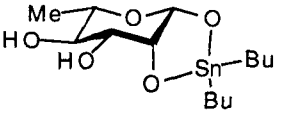
INTRODUCTION

Stannylene acetals are useful intermediates in synthetic carbohydrate chemistry, and extensive data are available on the utility of such derivatives of non-reducing sugars.[2] However, since the two reports in the past,[3,4] analogous derivatives of carbohydrates with the anomeric position unprotected have not received much attention. We have recently reported on the use of 1,2-*cis*-stannylene acetals of free sugars, such as **1** or **2**, for efficient, stereoselective preparation of some 1,2-*cis*-linked oligosaccharides[5] and of β-

per-*O*-acetyl derivatives[6] from carbohydrates having an axial hydroxy group at C-2. We have also shown,[6] by NMR spectroscopy, that the acetal largely predominating among the products of treatment of free sugars with Bu_2SnO under mild conditions is of the 1,2-*cis* type.



1



2

During our work on the β-per-*O*-acetates,[6] we observed that the preparation of stannylene acetals from free carbohydrates was occasionally accompanied by epimerization. We have managed to control the epimerization occurring during that process to the extent that, when desirable,[5,6] it could be virtually prevented from occurring or, when epimerization is the objective - as is the present case - it can become the main reaction. Here, we wish to report our results concerning the stannylation-mediated epimerization of some carbohydrates, and the application of the phenomenon to a simple, practical conversion of D-galactose into the rare sugar D-talose.

RESULTS AND DISCUSSION

A clue to increasing yields of the products of epimerization was provided by a series of experiments aimed at *minimizing* epimerization during the preparation[6] of β-acetates of carbohydrates possessing an axial OH group at C-2, where epimerization was the unwanted side reaction. There, epimerization could be suppressed when stannylation was performed under mild conditions. A similar investigation undertaken during this work revealed that the epimerization during the formation of stannylene acetals of free sugars is enhanced when the reaction is conducted at temperatures >60° C with a slight molar excess of Bu_2SnO, particularly when the reaction time is extended beyond that needed to form the 1,2-*O*-acetal. This indicates, perhaps, that the 1,2-*O*-dibutyltin group in the complex initially formed is continuously displaced by the excess reagent, from its opposite side, to form the product of epimerization, until an equilibrium is reached. Since the treatment of free sugars with excess of Bu_2SnO also results in discoloration of the

reaction mixture, the decision to terminate the process has to be based on a compromise. For the same reason, the use of more than a slight excess of the reagent, to push the equilibrium towards the product of epimerization, is impractical. The results of our epimerization studies with different monosaccharides are summarized in the Table.

It is noteworthy that compounds having an axial OH group at C-2 predominate among the products in a large number of cases. It appears, therefore, that the epimerization of carbohydrates *via* their 1,2-*cis*-*O*-stannylene acetals differs from that mediated by molybdenum salts.[7-9] In that process, the equilibrium of the conversion is shifted invariably towards the thermodynamically more stable compounds, *i.e.*, compounds with a larger number of equatorial OH groups.

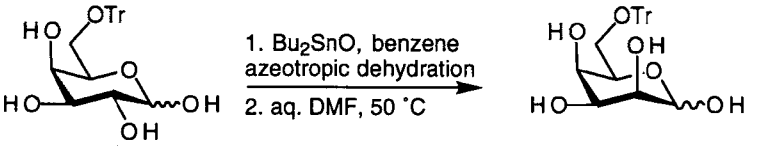
To apply this novel epimerization process to the preparation of the rare sugar D-talose, we first tried to prepare the 1,2-*O*-stannylene complex directly from D-galactose.

Table. Epimerization of various saccharides *via* 1,2-*O*-stannylene acetals[a]

Starting material	Product (~Yield, %)	Reaction time	Solvent
D-glucose	D-mannose (30)	1.25 h	MeOH
D-glucose	D-mannose (50)	24 h	MeOH
D-mannose	D-glucose (40)	1.25 h	MeOH
D-mannose	D-glucose (50)	24 h	MeOH
L-rhamnose	L-quinovose (10)	1.5 h	MeOH
L-rhamnose	L-quinovose (25)	20 h	MeOH
3-*O*-benzyl-D-mannose[b]		1.5 h	benzene
3-*O*-methyl-D-glucose	3-*O*-methyl-D-mannose (50)	4 h	EtOH
4,6-*O*-benzylidene-D-glucose[b]		2 h	benzene
6-*O*-trityl-D-glucose[c]	6-*O*-trityl-D-mannose (55)	2 h	benzene
6-*O*-trityl-D-talose[d]	6-*O*-trityl-D-galactose (≤20)	2.5	benzene

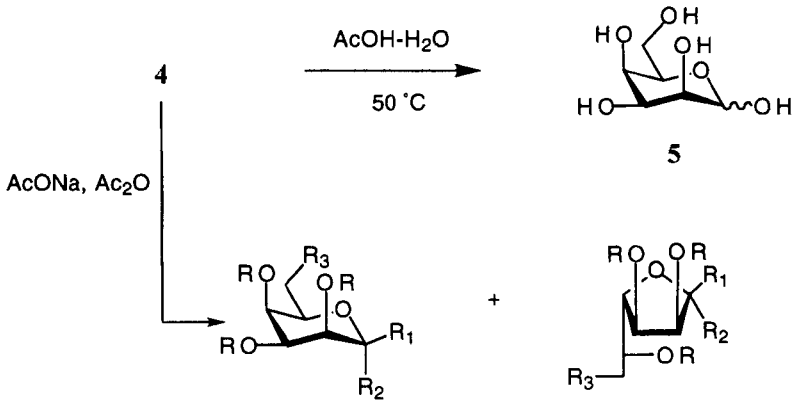
a. Stannylene complex was prepared at reflux temperature, using 1.1 equivalent of Bu_2SnO. Unless stated otherwise, the yields (not optimized) were determined after exhaustive acetylation by ^1H NMR spectroscopy.
b. Epimerization not observed.
c. The yield determined by weighing.
d. The yield determined by TLC.

While this was unsuccessful due to solubility problems, epimerization starting from 6-*O*-trityl-D-galactose[10] (**3**) gave 6-*O*-trityl-D-talose (**4**) consistently in yields of 60-70 %. Subsequent detritylation of **4** afforded D-talose (**5**, 90%, or ~60% overall). Thus, the present, simple method is an improvement over the D-galactose → D-talose conversions developed earlier.[11-13]



3 **4**

When crystallized according to the published procedure,[13] D-talose was obtained as a mixture of anomers. The observed ^{13}C NMR spectral data were in agreement with those in the literature.[14] The ^{1}H and ^{13}C NMR spectra of the intermediate 6-*O*-trityl-D-talose (**4**) were those of a mixture of four isomers (α,β-pyranoses and α,β-furanoses), and could not be fully interpreted. The compound was characterized by way of the acetates of its four isomeric forms **6-9**. Furanose structures for D-talose peracetates **8** and **9** followed from the down-field chemical shift for H-5 and C-4 found, respectively, in their ^{1}H and ^{13}C NMR spectra.



5

6 R = Ac; R_1 = H; R_2 = OAc; R_3 = OTr **8** R = Ac; R_1 = OAc; R_2 = H; R_3 = OTr
7 R = Ac, R_1 = OAc; R_2 = H; R_3 = OTr **9** R = Ac; R_1 = H; R_2 = OAc; R_3 = OTr

While a displacement with excess of the reagent, the 1,2-*O*-dibutyltin group in the complex initially formed might be a plausible explanation of the driving force for the observed epimerization, the process is not a simple nucleophilic substitution. This

follows from our observation that treatment (not described in the Experimental), of the 1,2-*O*-dibutyltin acetal prepared from D-mannose with sodium azide, potassium thioacetate, or sodium methoxide in DMF at elevated temperature does not lead to any product of nucleophilic substitution (TLC, NMR).

In another experiment aimed at clarifying the observed epimerization process, and ascertaining whether or not the hydrolysis of the stannylene complex is the primary driving force of the observed epimerization, we treated the complex prepared[15] from the D-galactose derivative **3** with $H_2{}^{18}O$. The reason for our choice of **3** for the mechanistic study was twofold. Firstly, the 1,2-*O*-stannylene complex prepared from compound **3** can be epimerized efficiently into the D-talose derivative **4** (see Experimental). Secondly, the preparation of the 1,2-*O*-stannylene complex from **3** could be done in benzene, thus assuring azeotropic removal of any H_2O present. After completing the preparation of 1,2-*O*-stannylene complex, it was hydrolyzed with $H_2{}^{18}O$. The resulting mixture of 6-*O*-trityl-D-talose and 6-*O*-trityl-D-galactose was resolved by chromatography, and the individual tritylated sugars were subjected to acetolysis. The detritylated, fully acetylated products were then analyzed by mass spectroscopy for the presence of ^{18}O. Mass spectra were taken of the major anomer present, as shown by GLC. Analyses showed that the ^{18}O was incorporated into both these monosaccharides, but the extent of the incorporation, and the extent of the distribution of ^{18}O between positions 1 and 2 in the individual sugars was different. The fragmentograms for D-galactose per-*O*-acetate showed that ~11.5% of the sugar contained ^{18}O, and from the intensities of A_1 and D ions (nomenclature of ions according to Kochetkov[16]) it was possible to deduce that ^{18}O was roughly equally distributed between positions 1 and 2. Similarly, it was possible to tell that about 50% of D-talose per-*O*-acetate contained ^{18}O, and that the amount of this isotope present at position 1 and 2 was in the ratio of 4:1. This result did not provide conclusive information regarding the reaction mechanism for the observed epimerization. It suggested, however, that hydrolysis of the 1,2-*O*-stannylene complex may contribute to the formation of D-talose from D-galactose in the extent of incorporation of ^{18}O at position 2 of D-talose (~10%). The ^{18}O-incorporation data indicate that the hydrolysis of the 1,2-*O*-stannylene complex is largely a random process and not significantly involved in the observed epimerization. In view of the experimentally demonstrated efficient

conversion (~60-70%) of 6-*O*-trityl-D-galactose → 6-*O*-trityl-D-talose, the incorporation of ^{18}O into position 2 of D-talose would be expected to occur to a much higher extent than observed (~10%), had the hydrolysis of the 1,2-*O*-stannylene complex been the main driving force for the epimerization.

EXPERIMENTAL

General methods. Unless stated otherwise, optical rotations were measured at 25 °C for solutions in $CHCl_3$ (*c* 1) with a Perkin Elmer automatic polarimeter, Model 241 MC. All reactions were monitored by thin-layer chromatography (TLC) on silica gel-coated glass slides (Whatman), performed with solvents of appropriately adjusted polarity consisting of *A*, 90:10:1 dichloromethane-MeOH-triethylamine; *B*, 3:1 dichloromethane-MeOH; *C*, hexane-EtOAc-triethylamine 200:100:1. Detection was effected by charring with 5% sulfuric acid in ethanol and, when applicable, by UV light. Preparative chromatography was performed by gradient elution from columns of Silica Gel 60 (Fluka, particle size 0.035-0.070 mm) using, at the onset of development, a solvent mixture slightly less polar than that used for TLC. Assignments of NMR signals, obtained at 300 MHz for ^1H and 75 MHz for ^{13}C at 25 °C, were made by first-order analysis of spectra and, when feasible, the assignments were supported by APT and/or DEPT experiments, homonuclear decoupling and/or homo- and heteronuclear 2-dimensional correlation spectroscopy. The commercial software supplied with the spectrometers (Varian Gemini or Varian XL 300) was used. Chemical ionization mass spectra (70 eV) were measured using pyridine[17] as the reactive gas. Electron impact mass spectroscopy (70 eV) was performed using Finnigan MAT SSQ 710 spectrometer. Samples were introduced from a gas-chromatograph, using a DB1, 60 m x 0.25 mm (i.d) column (J&W Scientific). The $H_2{}^{18}O$ (containing 90% of ^{18}O) used was purchased from Cambridge Isotope Laboratories. Solutions in organic solvents were dried with anhydrous sodium sulfate, and concentrated at 40 °C/2 kPa.

6-*O*-Trityl-D-talose (4). A mixture of 6-*O*-trityl-D-galactose[10] (**3**, R_f 0.3, solvent *A*, 20 g, 47.34 mmol) and dibutyltin oxide (12.9 g, 52.07 mmol, 1.1 eq) in benzene (500 mL) was heated under reflux, with azeotropic removal of water, for 2.5 h. After

concentration, the residue was dissolved in DMF (150 mL), and water (10 mL) was added. The reaction mixture was stirred overnight at 50 °C, then concentrated, and chromatography (solvent *A*) gave **4** (14 g, 70%), R*f*. 0.4 (solvent *A*). For characterization, a portion of **4** was acetylated, as described below.

1,2,3,4-Tetra-*O*-acetyl-6-*O*-trityl-α-D-talofuranose (9), 1,2,3,4-Tetra-*O*-acetyl-6-*O*-trityl-α-D-talopyranose (6) and 1,2,3,4-Tetra-O-acetyl-6-*O*-trityl-β-D-talopyranose (7). 6-*O*-Trityl-D-talose (**4**) (1.0 g, 2.36 mmol) was dissolved in acetic anhydride (5 mL) and sodium acetate (0.194 g, 2.36 mmol) was added. The reaction mixture was stirred at 25 °C for 20 h, and then at 100 °C (bath) for 2 h. Conventional processing and chromatography (solvent *C*) afforded first **9** (0.596 g, 42.6%), which was identical (mp, $[\alpha]_D$, NMR) with the independently synthesized substance.[6]

Eluted second was **6** (0.24 g, 17.1%), mp 87-88 °C (from EtOH, $[\alpha]_D$ +3.8°. ^{1}H NMR ($CDCl_3$): δ 7.2-7.4 (m, 15 H, aromatics), 6.07 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1), 5.56 (m, 1 H, H-4), 5.33 (t, 1 H, $J_{3,4}$ 3.7 Hz, H-3), 5.08 (dt, 1 H, $J_{2,3}$ 3.8 Hz, H-2), 4.15 (ddd, 1 H, $J_{4,5}$ ~2.0 Hz, H-5), 3.3 (dd, 1 H, $J_{5,6a}$ 5.4, $J_{6a,6b}$ 9.0 Hz, H-6a), 3.2 (t, 1 H, $J_{5,6b}$ 8.8 Hz, H-6b). ^{13}C NMR ($CDCl_3$): δ 91.47 (C-1, $J_{C1,H1}$ 175 Hz), 86.92 (*C*Ph), 70.12 (C-5), 66.55 (C-2), 65.55 (C-4), 65.38 (C-3), 60.86 (C-6).

Anal. Calcd for $C_{33}H_{34}O_{10}$: C, 67.10; H, 5.80. Found: C, 67.00; H, 5.83.

Eluted next was **7** (0.219 g, 15.6%), which was identical (mp, $[\alpha]_D$, NMR) with the independently synthesized substance.[6]

Eluted last was a very small amount of material, whose ^{1}H NMR spectrum showed[6] that it was 1,2,3,4-tetra-*O*-acetyl-6-*O*-trityl-β-D-talofuranose (**8**).

D-Talose (5). 6-*O*-Trityl-D-talose **4** (12 g, 28.4 mmol) was dissolved in acetic acid (120 mL), water (10 mL) was added at 60 °C, and the mixture was kept at ~60 °C for 3 h, when the TLC showed complete disappearance of starting material. After concentration, chromatography (solvent *B*) gave **15** (4.7 g, 92%). Crystallization from EtOH (twice) gave material (a mixture of anomers) melting at 126-127 °C, lit.[13] mp. 133-134 °C for α-D-talopyranose. The ^{13}C NMR data agreed with those published[14] for D-talose.

Hydrolysis with ^{18}O of the 1,2-*O*-stannylene complex prepared from D-galactose. 6-*O*-Trityl-D-galactose[10] (0.5 g) was treated with dibutyltin oxide for 1 h as described for the preparation of **4**. After concentration, the residue was dissolved in DMF (1 mL), and $H_2{}^{18}O$ (0.5 mL) was added. The reaction mixture was stirred overnight at 50 °C, and then concentrated. The residue was chromatographed, to give 6-*O*-trityl-D-talose and 6-*O*-trityl-D-galactose (0.23 and 0.20 g, respectively). Each of the tritylated monosaccharides (~0.1 g) was dissolved in 50:20:0.5 (v/v) Ac_2O-AcOH-H_2SO_4 (1 mL), and kept at room temperature overnight. After conventional processing and chromatography, to remove noncarbohydrate material, a sample of each of the per-*O*-acetylated monosaccharides was subjected to mass spectral analysis.

ACKNOWLEDGMENTS.

The authors thank Dr. Vladimír Kováčik and Mr. Vladimír Pätoprstý of the Institute of Chemistry, Slovak Academy of Sciences, Bratislava, Slovakia, for the mass spectral analysis.

REFERENCES AND NOTES

1. Dedicated to the memory of Professor Akira Hasegawa
2. T. B. Grindley. in *ACS Symposium Series 560. Synthetic Oligosaccharides: Indispensable Probes for the Life Sciences* (eds. Kováč, P.), American Chemical Society, Washington, D.C., 1994.
3. V. K. Srivastava and C. Schuerch, *Tetrahedron Lett.*, 3269 (1979).
4. A. Dessinges, A. Olesker, G. Lukacs, and T. T. Thang, *Carbohydr. Res.*, **126**, C6 (1984).
5. G. Hodosi and P. Kováč, *J. Am. Chem. Soc.*, **119**, 2335 (1997).
6. G. Hodos, and P. Kováč, *Carbohydr. Res., xxx* (1997).
7. M. Hayes, N. J. Pennings, A. S. Serianni, and R. Barker, *J. Am. Chem. Soc.*, **104**, 6764 (1982).
8. V. Bílik, *Chem. Listy*, **77**, 496 (1983).
9. V. Bílik, L. Petruš, and V. Farkaš, *Chem. Zvesti*, **29**, 690 (1975).
10. A. K. Bhattacharjee, E. Zissis, and C. P. J. Glaudemans, *Carbohydr. Res.*, **89**, 249 (1981).
11. V. Bílik, W. Volter, and E. Bayer, *Liebigs Ann. Chem.*, 1162 (1974).
12. H. Paulsen, F. G. Espinosa, and W.-P. Troutwein, *Chem. Ber*, **101**, 186 (1968).

13. R. S. Tipson, and H. S. Isbell, *Methods in Carbohydrate Chemistry,* **1**, 157 (1962).
14. K. Bock and C. Pedersen, *Adv. Carbohydr. Chem. Biochem.* **41**, 27 (1983).
15. The objective of this experiment was not necessarily to achieve the highest yield of D-talose but to investigate the incorporation of ^{18}O. Thus, the reaction time for treatment of D-galactose with dibutyltin oxide applied in this experiment is in variance with that applied in the preparation of D-talose (see Experimental).
16. N. K. Kochetkov, N. S. Wulfson, O. S. Chizhov, and B. M. Zolotarev, *Tetrahedron,* **19**, 2209 (1963).
17. V. Pätoprstý, V. Kováčik, and S. Karácsonyi, *Rapid Commun. Mass Spectrom.,* **9**, 840 (1995).