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Carbohydrate Research 303 (1997) 239–243

CARBOHYDRATE
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Note

Manipulation of free carbohydrates via stannylene acetals. Preparation of β-per-*O*-acyl derivatives of D-mannose, L-rhamnose, 6-*O*-trityl-D-talose, and D-lyxose

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Received 27 March 1997; accepted 22 May 1997

Abstract

A simple and high-yielding method for the preparation of 1-*O*-β-acyl derivatives of carbohydrates with an axial OH group at C-2 is described. It utilizes the property of unprotected carbohydrates to preferentially form 1,2-*O*-*cis* stannylene acetals, when treated with dibutyltin oxide. These acetals can be acylated with retention of configuration at the anomeric position. © 1997 Elsevier Science Ltd.

Keywords: Stannylene complexes; 1,2-*O*-*cis*-stannylene acetals; β-mannose; β-rhamnose, β-talose; β-lyxose

Per-*O*-acetyl and per-*O*-benzoyl derivatives of sugars are important intermediates in carbohydrate syntheses [1], including their role as glycosyl donors in glycosylation reactions [2,3]. General methods for direct, high yielding preparation of 1,2-*trans*-β-acetates of sugars are available [4], but analogous 1,2-*cis*-derivatives such as β-acetates of D-mannose, L-rhamnose, D-talose and D-lyxose have been obtained in poor yields only, either as byproducts (e.g. [5]), or via multistep procedures (e.g. [6]).

Here, we are introducing the first rational strategy for the synthesis of the not readily accessible, title derivatives. It is based on the reaction of dibutyltin oxide with *unprotected* sugars to preferentially form 1,2-*cis*-acetals. While this assertion was originally based on analogy with the formation of other cyclic acetals in carbohydrate chemistry, we have shown this to be the case by NMR spectroscopy: ^{1}H and ^{13}C NMR spectra (see Experimental; General procedure for acylations) of the stannylene acetals prepared from L-rhamnose showed presence of two compounds in a ratio of 5–6:1. The minor component was unchanged rhamnose (α anomer). The $J_{\text{C-1,H-1}}$ value found for the stannylene acetal (major component) confirmed its β-configuration and, consequently, that the acetal was of the 1,2-*cis* type. This is further supported by high yields of β-1-acetates obtained in this work, and β-manno and β-rhamno oligosaccharides [7] resulting from treatment of these species with carbohydrate trifluoromethanesulfonates. Clearly, glycosidic linkages would not have been formed in the latter reactions, were the anomeric center not part of the stannylene acetal. As we have found, 1,2-stannylene acetals can be acylated with

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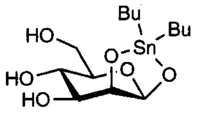
PII S0008-6215(97)00155-9

retention of configuration at the anomeric center using common acylating reagents. To the best of our knowledge [8,9], the only precedent for the preparation of this class of substances, is the use of 1,2-*O*-stannylene acetals of unprotected sugars, such as **1** and **2**, in our recent report [7] on a fundamentally new, stereospecific glycosylation.



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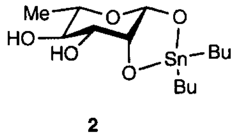
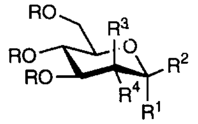
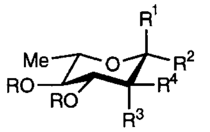


2

In the initial experiments, the stannylene acetals used in this work were prepared in the usual way (see Experimental, preparation of **4**(a), and acetylated with Ac_2O in pyridine. Chromatography of the products resulting from the foregoing treatment of D-mannose (**3**) and L-rhamnose (**8**) yielded, in addition to the expected *β*-1-acetates **4** (64.5%) and **9** (77.3%), also *β*-D-glucose pentaacetate (**5**, 25%) and 6-deoxy-*β*-L-glucose pentaacetate (**10**, 18%), respectively, resulting from epimerization [10] of the starting materials. Similarly, stannylation of D-mannose followed by benzoylation gave *β*-D-mannose pentabenzoate (**6**, 66.6%) and *β*-D-glucose pentabenzoate (**7**, 15.8%).

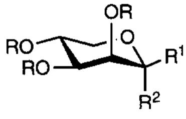


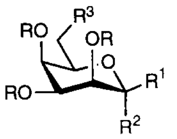
3 R= H; R^1,R^2= OH, H; R^3= OH; R^4= H
4 R = Ac; R^1, R^4= H; R^2, R^3= OAc
5 R= Ac; R^1, R^3= H; R^2, R^4= OAc
6 R= Bz; R^1, R^4= H; R^2, R^3 = OBz
7 R= Bz; R^1, R^3 = H; R^2, R^4= OBz



8 R= H; R^1, R^2= OH, H; R^3= OH; R^4=H
9 R= Ac; R^1, R^4= H; R^2, R^3= OAc
10 R= Ac; R^1, R^3= H; R^2, R^4 = OAc
11 R= Bz; R^1, R^4= H; R^2, R^3= OBz

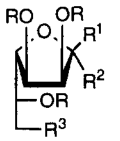
To avoid epimerization, we conducted a series of experiments aimed at optimizing the reaction conditions. We found that this unwanted side-reaction could be minimized when the stannylene acetals were prepared under milder conditions. Thus, when working with a more dilute solution of the reagents, the reaction could be conducted at lower temperature, without having to extend the reaction time. Subsequent acylation of the acetals isolated in the usual manner resulted in an increased yield of the targeted *β*-per-*O*-acyl derivatives. At the same time, the epimerization that had previously accompanied the formation of the acetals was minimal. Under the optimized conditions (see Experimental; General procedure for acylations), the yields of **4**, **9** and **6**, and **11** were 84.8, 94.5, 72 and 89.6%, respectively. In a similar way, acetylation of the 1,2-*cis* stannylene acetal prepared from D-lyxose (**12**) yielded the corresponding *β*-peracetate **13** in 84.5% yield. The chemical shifts and coupling constants we observed for H-1 and H-5a,b of **13** (see Experimental) matched those found among the incomplete NMR data reported [11] for the substance. Since in the conformationally flexible [12] D-lyxose molecule the $J_{C\text{-}1,H\text{-}1}$ coupling constant is not diagnostic of the anomeric configuration, our assignment of the *β*-configuration for **13** is based on its high negative value of $[\alpha]_D$. It is worth mentioning that our preparation of **13** shows an $[\alpha]_D$ value much more negative than that found [11,13] for materials previously described.



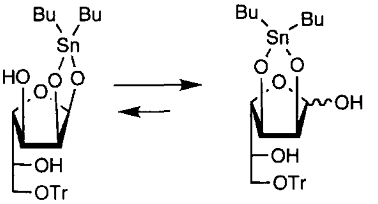


12 R= H; R^1, R^2= OH, H **14** R= H; R^1, R^2= OH, H; R^3= OTr
13 R= Ac; R^1= OAc; R^2= H **15** R= Ac, R^1= OAc; R^2= H; R^3= OTr

Attempts to synthesize the *β*-acetate of D-talose directly from the unprotected sugar failed because of solubility problems. However, per-*O*-acetyl-6-*O*-trityl-*β*-D-talose could be obtained from 6-*O*-trityl-D-talose (**14**) [10], via its stannylene acetal. Chromatography of the product of acetylation gave 6-*O*-trityl-*β*-D-talofuranose tetraacetate **16** (38.5%), 6-*O*-trityl-*β*-D-talopyranose tetraacetate **15** (40.1%), and 6-*O*-trityl-*α*-D-talofuranose tetraacetate **17** (12.8%). The presence of **17** among the product of the conversion suggests the likelihood of (reversible) isomerisation of **18** to **19**, whose treatment with the acetylation reagent would be expected to give a mixture of **16** and **17**. The putative isomerisation of a 1,2-acetal into a 2,3-acetal becomes quite plausible following another observation of ours. We have observed that the yield of the desired *β*-1-*O*-acyl derivatives decreased when the temperature of the exothermic acylation of the stannylene acetals was controlled by external cooling, lest the previously observed epimerization might become extensive. NMR spectra of products obtained in this way showed, in addition to the presence of the desired β-acetates, the presence of a relatively large proportion of α anomers. It appears that, in order to achieve a high yield of the 1,2-*cis*-acyl derivative, more important than to prevent the occurrence of epimerization, is to complete the acylation rapidly, whereupon neither isomerization of **18** to **19** nor epimerization can take place.



16 R= Ac; R^1= OAc; R^2=H; R^3= OTr
17 R= Ac; R^1= H; R^2= OAc; R^3 =OTr



18 **19**

Known compounds prepared independently during this work were identified by comparison of their physical characteristics with those previously reported, and the stereochemistry around the glycosidic linkage was corroborated by the observed $J_{\text{C-1,H-1}}$ coupling constants [14]. The determination of the β-configuration of substances which were hitherto unknown was based on the $J_{\text{C-1,H-1}}$ coupling constants found in their ^{13}C NMR spectra (see Experimental). Furanose structures of **16** and **17** were evidenced mainly by the low-field ^{13}C NMR chemical shift found for C-4. Since assigning the anomeric configuration to furanose structures is more reliable when based on the chemical shift for C-1 [15] than when based on $J_{\text{C-1,H-1}}$ coupling constants, the former method was applied for tentative α/β assignment in case of **16** and **17**, which was then corroborated by the specific optical rotation of the substances.

A practical application of the epimerization observed during this work is described in a separate communication [10].

1. 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*, 1:1 hexane–EtOAc; *B*, 2:1 hexane–EtOAc; *C*, 10:1 toluene–EtOAc; *D*, hexane–EtOAc–Et_3N 200:100:1. The detection was effected by charring with 5% H_2SO_4 in EtOH 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 ^{1}H 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 (CIMS) were measured using ammonia as the reactive gas. Solutions in organic solvents were dried with anhydrous Na_2SO_4, and concentrated at 40 °C/2 kPa.

General procedure for acylations.—A mixture of a sugar (5.55 mmol) and dibutyltin oxide (5.55 mmol) in anhydrous MeOH (50 mL) was vigorously stirred at 60 °C (bath) until a clear solution was obtained (80–100 min). Toluene (5 mL) was added, the solution was concentrated, and the residue was kept at 50 °C/ ~ 0.3 kPa for 2.5 h, to complete dehydration. The NMR spectra (in CD_3OD) of **2** taken at this stage showed the following characteristics for the major component present: ^{1}H NMR: δ 5.00 (bs, 1 H, H-1), 3.66 (m, 1 H, H-2), 3.42 (dd, 1 H, H-3, $J_{2,3}$ 3.4 Hz, $J_{3,4}$ 9.2 Hz), 3.15 (t, 1 H, H-4, $J_{4,5}$ 9.1 Hz), 3.05 (dd, 1 H, H-5, $J_{5,6}$ 6.1 Hz), 1.8–1.3 (m, 8 H, $SnCH_2$, $SnCH_2CH_2$), 1.24 (m, 4 H, CH_2CH_3), 1.12 (d, 3 H, H-6), 0.80 9 (m, 6 H, CH_2CH_3). ^{13}C NMR data of the major component: δ 95.90 (C-1, $J_{\text{C,H}}$ 161.8 Hz), 77.08 (C-2), 75.50 (C-3), 73.77 (C-4), 72.13 (C-5), 28.73, 28.18 and 28.06 (3 CH_2), 18.34 (C-6), 14.03 (CH_3). A mixture of anhydrous pyridine (8 mL) and the acylation reagent (1.6 equiv/OH group to be derivatized) was slowly added to the foregoing stannylene acetal, without external cooling during 5 min.

The mixture was shaken gently, to aid the solvation, and then stirred while the evolution of heat subsided. When TLC indicated that the reaction was complete (1–4 h), the mixture was processed in the usual manner, and the products were isolated by chromatography.

*1,2,3,4,6-Penta-O-acetyl-β-*D*-mannopyranose* (**4**) *and 1,2,3,4,6-penta-O-acetyl-β-*D*-glucopyranose* (**5**).—(a) A mixture of D-mannose (**3**, 1 g, 5.55 mmol) and dibutyltin oxide (1.38 g, 5.55 mmol) in anhydrous MeOH (20 mL) was vigorously stirred under gentle reflux (~ 80 °C, bath) until a clear solution was obtained (~ 90 min). The mixture was processed as described in the General method for acylations, using Ac_2O as acylating reagent, and chromatography (solvent $B \rightarrow A$) gave first **5** (0.55 g, 25%): mp 134–135 °C (from EtOH), lit. 132 °C [16]; $[\alpha]_D$ +3.8°, lit. +3.9° (*c* 1.0, $CHCl_3$) [16].

Eluted next was **4** (1.4 g, 64.5%): mp 118–119 °C (from EtOH), lit. 117.5 °C [17]; $[\alpha]_D$ −25.2°, lit. −24.9° (*c* 1.0, $CHCl_3$) [17]; $J_{C-1,H-1}$ 161.3 Hz.

(b) D-Mannose (**3**, 1 g, 5.55 mmol) was treated as described in the General procedure for acylations, using Ac_2O as acylating reagent, and chromatography afforded **4** (1.84 g, 84.8%).

*1,2,3,4-Tetra-O-acetyl-β-*L*-rhamnopyranose* (**9**) *and 6-deoxy-1,2,3,4-tetra-O-acetyl-β-*L*-glucopyranose* (**10**).—(a) L-Rhamnose monohydrate (1 g, 6.09 mmol) was treated as described above for the preparation of **4**(a), and chromatography (solvent *B*) first gave **10** (0.37 g, 18%): mp 148–149 °C (from diisopropyl ether), lit. 148–149 °C [18]; $[\alpha]_D$ −21.4°, lit. −21.6° (*c* 1.1, $CHCl_3$) [18].

Eluted next was **9** (1.57 g, 77.3%): mp 98–99 °C (from isopropyl ether), lit. 98.5–99 °C [19]; $[\alpha]_D$ +13.6°, lit. +13.3° (*c* 3.8, $CHCl_3$) [19]; $J_{C-1,H-1}$ 163.2 Hz.

(b) When L-rhamnose monohydrate (1 g, 5.49 mmol) was treated as described for the preparation of **4**(b), chromatography (solvent *B*) afforded **9** (1.72 g, 94.5%).

*1,2,3,4,6-Penta-O-benzoyl-β-*D*-mannopyranose* (**6**) *and 1,2,3,4,6-penta-O-benzoyl-β-*D*-glucopyranose* (**7**).—(a) D-Mannose (0.5 g, 2.74 mmol) was treated with dibutyltin oxide (0.682 g, 2.74 mmol) as described for the preparation of **4**(a), and the acetal formed was then treated with a mixture of BzCl–pyridine. When the benzoylation was complete (~ 4 h), EtOH was added, to decompose the excess of reagent. The mixture was partitioned between CH_2Cl_2 and water, the organic phase was concentrated, and the residue was purified by column chromatography (solvent *C*), to give first **7** (0.3 g, 15.8%): mp 188–190 °C (from EtOH), lit. 189–192 °C [20]; $[\alpha]_D$ +23.8°, lit. +24.2 (*c* 2.6, $CHCl_3$) [20].

Eluted next was **6** (1.2 g, 66.6%): mp 160–161 °C (from EtOH), lit. 160–161 °C [20]; $[\alpha]_D$ −80.5°; lit. −81° (*c* 1.0, $CHCl_3$) [20]; $J_{C-1,H-1}$ 163.8 Hz.

(b) D-Mannose (1 g, 5.55 mmol), when treated according to the general procedure, using BzCl as acylating reagent, afforded **6** (2.8 g, 72%).

*1,2,3,4-Tetra-O-benzoyl-β-*L*-rhamnopyranose* (**11**).—L-Rhamnose monohydrate (1.0 g, 5.49 mmol) was treated as described for the preparation of **6**(b). Chromatography gave **11** (2.85 g, 89.6%): $[\alpha]_D$ +139.0°, lit. +138.0° (*c* 1.0, $CHCl_3$) [21]; $J_{C-1,H-1}$ 163.0 Hz.

*1,2,3,4-Tetra-O-acetyl-β-*D*-lyxopyranose* (**13**).—D-Lyxose (1.0 g, 6.66 mmol), when treated as described in the General procedure for acylations, using Ac_2O as acylating reagent, afforded **13** (1.79 g, 84.5%): $[\alpha]_D$ −111°, lit. −70.6° (*c* 0.82, $CHCl_3$) [11], −83.4° (*c* 2.48) [13]. ^1H NMR ($CDCl_3$): δ 6.02 (d, 1 H, $J_{1,2}$ 2.8 Hz, H-1), 5.39 (t, 1 H, *J* 3.3 Hz, H-2), 5.23 (dd, 1 H, $J_{2,3}$ 3.0, $J_{3,4}$ 6.5 Hz, H-3), 5.04 (ddd, 1 H, $J_{4,5a}$ 3.3, $J_{4,5b}$ 5.3 Hz, H-4), 4.20 (dd, 1 H, $J_{5a,5b}$ 12.4 Hz, H-5a), 3.61 (dd, 1 H, H-5b), 2.13, 2.11, 2.10, 2.09 (4 s, 3 H each, 4 $COCH_3$); ^{13}C NMR ($CDCl_3$): δ 89.56 (C-1, $J_{C,H}$ 169 Hz), 67.65 (C-3), 67.52 (C-4), 66.18 (C-2), 61.25 (C-6), 20.82, 20.79, 20.64, 20.57 (4 $COCH_3$); CIMS: *m/z* 336 ($[M + 18]^+$): Anal. Calcd for $C_{13}H_{18}O_9$: C, 49.06; H, 5.70. Found: C, 49.17; H, 5.68.

*1,2,3,4-Tetra-O-acetyl-6-O-trityl-β-*D*-talopyranose* (**15**), *1,2,3,5-tetra-O-acetyl-6-O-trityl-β-*D*-talofuranose* (**16**), *and 1,2,3,5-tetra-O-acetyl-6-O-trityl-α-*D*-talofuranose* (**17**).—6-*O*-Trityl-D-talose [10] (**14**, 0.5 g, 1.18 mmol) and dibutyltin oxide (0.294 g, 1.18 mmol) in anhydrous benzene (25 mL) was vigorously stirred at 60 °C (bath) for 3 h. The mixture was concentrated, the residue was dissolved in anhydrous toluene (20 mL) and concentrated, to complete dehydration. Pyridine (3 mL) and Ac_2O (0.67 mL, 7.1 mmol) was added and, after 2 hours, when TLC (solvent *D*) showed that the reaction was complete, the mixture was concentrated, and chromatography gave first **17** (0.09 g, 12.8%): mp 68–69° (from EtOH); $[\alpha]_D$ +6.2°; ^1H NMR ($CDCl_3$): δ 6.09 (s, 1 H, H-1), 5.28 (bd, 1 H, $J_{2,3}$ 4.9 Hz, H-2), 5.21–5.13 (m 2 H, H-3,5), 4.43 (dd, 1 H, *J* 5.5 and 7.1 Hz, H-4), 3.31 (dd, 1 H, $J_{5,6a}$ 6.28, $J_{6a,6b}$ 10.2 Hz, H-6a), 3.24 (dd, 1 H, $J_{5,6b}$ 4.5 Hz, H-6b), 2.12, 2.09, 2.05, 1.93 (4 s, 3 H each, 4 $COCH_3$); ^{13}C NMR ($CDCl_3$): δ 97.75 (C-1, $J_{C,H}$ 184 Hz), 86.94 (*C*Ph), 79.65 (C-4), 74.07 (C-2), 71.72 (C-5), 70.41 (C-3), 62.44

(C-6); CIMS: m/z 608 ($[M+18]^+$). Anal. Calcd for $C_{33}H_{34}O_{10}$: C, 67.1; H, 5.8. Found: C, 66.92; H, 5.82.

Eluted next was **15** (0.22 g, 40.1%): mp 168–169 °C (from EtOH); $[\alpha]_D$ −30.0° (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.80 (bd, 1 H, $J_{1,2}$ ~ 1.2 Hz, H-1), 5.56 (bd, 1 H, $J_{3,4}$ ~ 3.5 Hz, H-4), 5.37 (bd,1 H, $J_{2,3}$ ~ 3.5 Hz, H-2), 5.18 (bt, 1 H, J ~ 3.7 Hz, H-3), 3.97 (bdd, 1 H, H-5), 3.45 (dd, 1 H, $J_{5,6}$ 5.3, $J_{6a,6b}$ 8.8 Hz, H-6a), 3.20 (t, J 8.8 Hz, H-6b), 2.12, 2.05, 2.01, 1.85 (4 s, 3 H each, 4 $COCH_3$); ^{13}C NMR ($CDCl_3$): δ 90.70 (C-1, $J_{C,H}$ 162 Hz), 86.93 (*C*Ph), 73.64 (C-5), 67.74 (C-3), 66.83 (C-2), 64.67 (C-4), 60.35 (C-6), 20.71, 20.62, 20.50, 20.47 (4 CO*C*H_3); CIMS: m/z 608 ($[M+18]^+$). Anal. Calcd for $C_{33}H_{34}O_{10}$: C, 67.1; H, 5.8. Found: C, 67.0; H, 5.83.

Eluted last was **16** (0.09 g, 12.8%): mp 68–69 °C (from EtOH), $[\alpha]_D$ −67°; ^1H NMR ($CDCl_3$): δ 7.45–7.20 (m, 15 H, aromatics), 6.34 (m, 1 H, H-1), 5.25 (td, 1 H, $J_{4,5}$ ~ 3.3 Hz, H-5), 5.20 (m, 2 H, H-2,3), 4.58 (dd, 1 H, $J_{3,4}$ 2.2 Hz, H-4), 3.31 (dd, 1 H, $J_{5,6a}$ ~ 6.1 Hz, $J_{6a,6b}$ ~ 9.7 Hz, H-6a), 3.25 (dd, 1 H, $J_{5,6b}$ ~ 5.7 Hz, H-6b), 2.13, 2.1, 2.03 (3 s, 12 H, 4 $COCH_3$); ^{13}C NMR ($CDCl_3$): δ 93.79 (C-1, $J_{C,H}$ 181 Hz), 87.0 (*C*Ph), 81.87 (C-4), 71.26 (C-5), 69.92, 69.76 (C2,3), 61.67 (C-6), 21.0, 20.88, 20.56, 20.22 (4 CO*C*H_3); CIMS: m/z 608 ($[M+18]^+$). Anal. Calcd for $C_{33}H_{34}O_{10}$: C, 67.1; H, 5.8. Found: C, 66.95; H, 5.82.

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