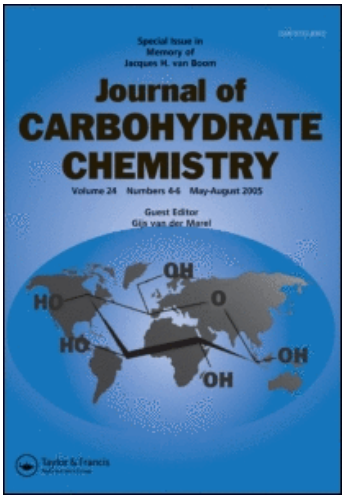

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Selective Removal of the Isopropylidene Group in 4-O-Protected 1,6-Anhydro-2,3-O-Isopropylidene-β-D-Mannopyranose and the Conformational Impact of it

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To cite this Article van Rijsbergen, Ronan , Anteunis, Marc J. O. and De Bruyn, André(1983) 'Selective Removal of the Isopropylidene Group in 4-O-Protected 1,6-Anhydro-2,3-O-Isopropylidene-β-D-Mannopyranose and the Conformational Impact of it', Journal of Carbohydrate Chemistry, 2: 4, 395 — 404
To link to this Article: DOI: 10.1080/07328308308057886
URL: http://dx.doi.org/10.1080/07328308308057886

J. CARBOHYDRATE CHEMISTRY, 2(4), 395-404 (1983)

SELECTIVE REMOVAL OF THE ISOPROPYLIDENE GROUP IN 4-O-PROTECTED 1,6-ANHYDRO-2,3-O-ISOPROPYLIDENE-β-D-MANNOPYRANOSE AND THE CONFORMATIONAL IMPACT OF IT

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Received July 21, 1983

ABSTRACT

Pyridinium p-toluenesulfonate (PPTS) is a reagent of choice for the selective removal of an O-isopropylidene group in a 1,6-anhydro-β-D-aldohexopyranose, where the remaining OH-group is protected.

INTRODUCTION

The choice of protecting groups is a major problem for the synthesis of multi-substituted sugar derivatives, mainly because of the necessity for selective deprotection. Pyridinium p-toluenesulfonate (PPTS) has been recognized to be a mild reagent for deacetylation of highly sensitive molecules.[1] It is also used for the formation and removal of tetrahydropyranyl (THP)[2, 3] and tetrahydrofuranyl (THF)[4] ether protecting groups.

In 1,6-anhydro-β-D-aldohexopyranoses the O-isopropylidene group is easily removed by a 0.1 N solution of HCl if no other protecting groups are present.[5] Aqueous trifluoroacetic acid is also used for the selective hydrolysis of an isopropylidene group from disaccharides.[6, 7] For the compounds in the present study, we have tried without success TFA and HOAc as well as

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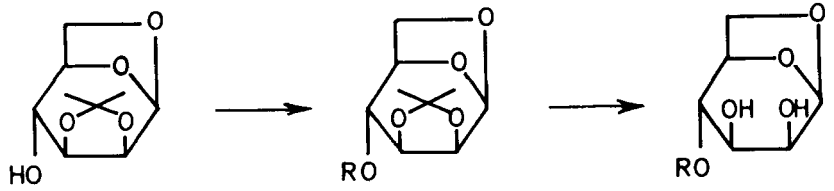
dilute inorganic acids at different concentrations and temperatures. We found that a selective removal of an O-isopropylidene group in 4-O-protected 1,6-anhydro-2,3-O-isopropylidene-β-D-mannopyranose can be performed with high yield with PPTS, leaving the 1,6-anhydro bridge as well as an O-tert-butyl, O-tert-butyldiphenylsilyl or O-allyl groups on C-4 untouched. However, a 4-O-trichloroacetyl group was cleared by handling with PPTS.

RESULTS AND DISCUSSION

1,6-Anhydro-2,3-O-isopropylidene-β-D-mannopyranose (1) can easily be isolated by treating the reaction product of the pyrolysis of ivory-nut kernels with acetone.[8] This compound is an interesting synthon for the preparation of 4-O-protected derivatives, if the isopropylidene group can be selectively removed. We have prepared the 4-O-tert-butyldiphenylsilyl, the tert-butyl, the trichloroacetyl, and the allyl derivative of 1.



1

2 R = $Si\emptyset_2$tert-butyl

3 R = tert-butyl

4 R = $COCCl_3$

5 R = allyl

6 R = $Si\emptyset_2$tert-butyl

7 R = tert-butyl

8 R = allyl

The 4-O-tert-butyldiphenylsilyl derivative 2 was obtained from 1 by treating it with tert-butyldiphenylsilyl chloride in DMF according to a method as described by Hanessian and Lavallee.[9] The 4-O-tert-butyl derivative 3 was obtained by treating 1 with 2-

methylpropene under acid catalysis according to the method described by Shapiro and co-workers.[10] The 4-O-trichloroacetyl derivative 4 was obtained by treating 1 with trichloroacetyl chloride following a modification of the method described by Lemieux and Huber.[11] We used chloroform instead of benzene, and the molar ratio of acid chloride: pyridine was >1. Finally, 4-O-allyl-1,6-anhydro-2,3-O-isopropylidene-β-D-mannopyranose (5) was prepared by treating 1 with NaH and allyl bromide in dry THF, following the procedure of Corey and Suggs,[12] except that we found THF to be a better solvent than benzene for our reaction.

For the selective removal of the O-isopropylidene group, a common procedure was used. The O-isopropylidene derivative and pyridinium p-toluene sulfonate were refluxed in an excess of methanol. Thus 1,6-anhydro-4-O-tert-butyldiphenylsilyl-β-D-mannose (6), its 4-O-tert-butyl (7) and 4-O-allyl analog (8) were obtained in high yield. Only the 4-O-trichloroacetyl analog was not obtained by this procedure, probably because of its high tendency to be removed by transesterification with methanol.

^{1}H-NMR Study.

The ^{1}H-NMR data of compounds 1-8 in $CDCl_3$ and benzene-d_6 solution are gathered in Table 1. In $CDCl_3$ solution the ^{1}H-NMR spectra of compounds 2 and 3 show degenerated spin systems (the protons on C-2 and C-3 are nearly isochronous, leading to second order effects resulting in possible erroneous interpretations[13]). Therefore we have measured all the compounds in a benzene-d_6 solution, where degenerations seem to be avoided. From the vicinal coupling constants it follows that the pyranose ring in the 4-O-substituted compounds 6-8 occurs in a $^1C_4$(D)chair form. In pyranose rings like those encountered in the present study, it is generally accepted[14] that they occur in a conformational equilibrium between $^1C_4$(D) and BO,3(D). The coupling value $J_{3,4}$ is in this case a sensitive reflection of interproton torsion angle $\tau(3,4)$. By conversion from conformation $^1C_4$(D) to B3,O(D), $\tau(3,4)$ varies between 60° and 180°. $J_{3,4}$ should accordingly

TABLE 1.

^{1}H NMR Data of Compounds 1-8 in $CDCl_3$ and C_6D_6 (Internal Me_4Si).

Chemical Shifts:

Compound	Solvent	H-1	H-2	H-3	H-4	H-5	H-6	H-6'	CH_3 isoprop.	CH_3 tert-butyl	allyl
1	$CDCl_3$	5.36	4.09	4.21	3.97	4.53	4.04	3.78	1.54; 1.33	—	—
2	$CDCl_3$	5.33	4.08	4.08	4.00	4.33	3.73	3.54	1.45; 1.18	1.12	—
	C_6D_6	5.41	4.05	4.25	4.09	4.27	3.55	3.21	1.57, 1.12	1.20	—
3	$CDCl_3$	5.33	4.09	4.09	3.78	4.39	3.97	3.72	1.46, 1.33	1.28	—
	C_6D_6	5.41	4.04	4.14	3.60	4.15	3.80	3.44	1.68, 1.25	1.05	—
4	$CDCl_3$	5.43	4.16	4.24	5.12	4.66	4.09	3.84	1.63, 1.36	—	—
	C_6D_6	5.24	3.76	3.93	4.78	4.04	3.73	3.21	1.54, 1.08	—	—
5	$CDCl_3$	5.35	4.09	4.22	3.64	4.60	3.94	3.76	1.55, 1.34	—	5.94; 5.35; 5.25; 4.13
	C_6D_6	5.38	3.96	4.20	3.34	4.16	3.70	3.41	1.65, 1.25	—	5.76; 5.20; 5.02; 3.74
6	$CDCl_3$	5.40	3.83	3.90	3.86	4.26	3.93	3.52	—	1.06	—
	C_6D_6	5.42	3.83	4.03	3.92	4.12	3.82	3.21	—	1.15	—
7	$CDCl_3$	5.37	3.79	3.86	3.71	4.37	4.17	3.71	—	1.27	—
	C_6D_6	5.38	3.69	3.79	3.48	4.11	4.03	3.44	—	1.07	—
8	$CDCl_3$	5.39	3.77	4.02	3.59	4.59	4.16	3.75	—	—	5.93; 5.32; 5.24; 4.17
	C_6D_6	5.41	3.70	3.96	3.24	4.15	3.98	3.44	—	—	5.79; 5.21; 5.03; 3.78

(continued)

TABLE 1 (Con't.)

Coupling Constants:

Compound	Solvent	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{1,3}$	$J_{1,5}$	$J_{2,4}$	$J_{3,5}$
1	$CDCl_3$	2.9	6.1	1.6	1.0	1.2	6.3	7.1	1.3	0.4	0.3	1.3
2	$CDCl_3$	- [a]	- [a]	- [a]	- [a]	1.2	6.2	7.2	- [a]	- [a]	- [a]	- [a]
	C_6D_6	2.9	6.1	1.6	1.0	1.1	6.2	7.2	1.4	0.5	0.3	1.5
3	$CDCl_3$	- [a]	- [a]	- [a]	- [a]	1.2	6.1	7.2	- [a]	- [a]	- [a]	- [a]
	C_6D_6	3.0	6.1	1.6	1.0	1.1	6.2	7.1	1.3	0.5	0.5	1.4
4	$CDCl_3$	2.9	6.3	1.6	0.9	1.2	6.2	7.4	1.2	0.5	0.5	1.4
	C_6D_6	2.9	6.2	1.6	1.0	1.1	6.1	7.4	1.3	0.5	0.5	1.6
5	$CDCl_3$	3.0	6.1	1.5	1.0	1.2	6.2	7.3	1.4	0.4	0.4	1.6
	C_6D_6	1.9	6.2	1.5	1.0	1.2	6.0	7.2	1.3	0.4	0.4	1.5
6	$CDCl_3$	1.5	5.0	1.8	1.2	0.7	5.7	7.2	1.3	0.5	0.5	1.5
	C_6D_6	1.6	5.1	1.8	1.2	0.7	5.7	7.1	1.4	0.4	0.4	1.5
7	$CDCl_3$	1.6	5.1	1.8	1.2	0.7	5.6	7.2	1.4	0.5	0.5	1.5
	C_6D_6	1.6	5.0	1.8	1.2	0.6	5.6	7.0	1.4	0.4	0.3	1.5
8	$CDCl_3$	1.5	5.0	2.0	1.2	0.9	5.7	7.1	1.2	0.4	0.3	1.5
	C_6D_6	1.5	5.0	1.9	1.2	0.9	5.7	7.0	1.3	0.4	0.3	1.5

[a] Could not be measured. Because of the width of the pattern, simulations were highly speculative.

vary from a very small value (if $^1C_5$(D)) to about 9 Hz (if BO,3(D)). The experimental value 1.8-2.0 Hz suggests a conformation close to $^1C_4$(D) for all 4-O-substituted 1,6-anhydro-β-D-mannopyranose derivatives in the present study. Also the values of $J_{1,2}$ and $J_{2,3}$ agree with known coupling values for the proposed conformation.[14]

A deviation from the $^1C_4$(D) conformation is found in the 2,3-O-isopropylidene derivatives of the 4-O-substituted 1,6-anhydro-β-D-mannopyranoses. $J_{1,2}$ and $J_{2,3}$ are larger in the series 1-5 than in 6-8. Because H-1, -2 and -3 are mutually in a cis disposition, a change from the $^1C_4$(D) to the B3,O(D) conformation would cause these protons to become increasingly more eclipsed than in 6-8. Consequently, the torsion angles τ(3,4) and τ(4,5), where H-3 and H-4 as well as H-4 and H-5 are in trans dispositions, must approach 90° and the coupling constants $J_{3,4}$ and $J_{4,5}$ are expected to decrease, as observed. Thus, all the changes in the coupling constants disclose that the compounds 1-5 are more planar than 6-8. This conclusion is in accord with the suggestion of other authors[14] that the introduction of a 1,3-dioxolane ring on C-2 and C-3 in the 1,6-anhydro derivative of β-D-mannose causes a flattening of the pyranose ring. Also the influence of the planarity on $J_{5,6}$ as observed by these authors is found in the present study.

EXPERIMENTAL

General Methods.

Melting points were determined with a Koffler hot stage and are uncorrected. Specific rotations were determined with a Perkin-Elmer 141 polarimeter between 20 and 24 °C. NMR spectra were recorded on a Bruker WH360 spectrometer at 18 °C for 2% solutions (FT mode, pulse width 2 μsec, quadrature detection, resolution 0.208 Hz/point). All assignments were verified by double irradiation experiments. Because of the broadness of the peaks, all coupling constants values were extracted to the nearest 0.2 Hz. All evaporations were conducted under diminished pressure at temperatures below 40°.

1,6-Anhydro-4-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-β-D-mannopyranose (2). A solution of 1 (404 mg, 2 mmole) in dry N,N-dimethylformamide (2 mL), containing imidazole (300 mg, 4.4 mmole), was treated with tert-butyldiphenylsilyl chloride (600 mg, 2.2 mmole) and the reaction mixture stirred for 5 h at 35-40°. Water was added in small portions over a period of several hours until crystallization occurred (686 mg, 78%), mp 80-81 °C, $[\alpha]_D$ -17.0 °C (c 2.62 in chloroform).

Anal. Calcd for $C_{25}H_{32}O_5Si$: C, 68.15; H, 7.32. Found: C, 68.32; H, 7.39.

1,6-Anhydro-4-O-tert-butyl-2,3-O-isopropylidene-β-D-mannopyranose (3). Isobutene (5 mL, 53 mmole) was added at -10 °C to dry methylene chloride (18 mL) containing sulfuric acid (0.05 mL). After the mixture was stirred for a few minutes, 1 (404 mg, 2 mmole) was added in a single portion. Stirring was continued at -2-0 °C for 1 h and then overnight at room temperature. The cooled solution was shaken carefully with ice-cold 2.5% sodium hydrogen carbonate, washed with cold water to neutrality, dried over sodium sulfate, and concentrated. The residual amorphous product crystallized from ethyl acetate-hexane (244 mg, 47%), mp 103-105 °C, $[\alpha]_D$ -35.4° (c 0.94 in chloroform).

Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.53; H, 8.52.

1,6-Anhydro-2,3-O-isopropylidene-4-O-trichloroacetyl-β-D-mannopyranose (4). A solution of trichloroacetyl chloride (0.34 mL, 3 mmole) in dry chloroform (2 mL) was added dropwise to a stirred solution of 1 (404 mg, 2 mmole) and dry pyridine (0.21 mL, 2.6 mmole) in dry chloroform (10 ml) at 0 °C. After 3 h stirring at room temperature, TLC (silica gel, chloroform-ethyl acetate 8:2) showed complete conversion of 1 (R_F = 0.16) into a compound with R_F = 0.70. The reaction mixture was shaken with ice-cold 2.5% sodium hydrogen carbonate, washed with cold water to neutrality, dried over magnesium sulfate and concentrated. Crystallization from chloroform-hexane gave pure 4 (519 mg, 75%), mp 164-165 °C, $[\alpha]_D$ -59.6° (c 0.76 in chloroform).

Anal. Calcd for $C_{11}H_{13}O_6Cl_3$: C, 38.01; H, 3.77; Cl, 30.60. Found: C, 38.16; H, 3.74, Cl, 30.42.

4-O-Allyl-1,6-anhydro-2,3-O-isopropylidene-β-D-mannopyranose (5). An excess of sodium hydride was added in portions to a stirred solution of 1 (404 mg, 2 mmole) and allyl bromide (968 mg, 8 mmole) in dry tetrahydrofuran (5 mL). After 5 h stirring TLC (silica gel, chloroform-ethyl acetate 8:2) showed almost complete conversion of the starting compound (R_F : 0.15) into a compound with R_F = 0.59. The reaction mixture was neutralized with acetic acid, filtered and the filtrate concentrated. The residue was dissolved in chloroform, shaken with saturated sodium hydrogen carbonate, washed with water to neutrality, dried over magnesium sulfate and the chloroform evaporated. Chromatography on silica gel with 10:1 chloroform-ethyl acetate gave compound 5 as a colorless syrup (437 mg, 90%), $[\alpha]_D$ -34.7° (c 1.36 in chloroform).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.36; H, 7.43.

Common Procedure for Hydrolysis of Isopropylidene Acetals. A mixture of the 2,3-O-isopropylidene derivative (1 mmole), pyridinium p-toluenesulfonate (250 mg, 1 mmole) and methanol (250 mL) was gently refluxed. The reaction was followed by TLC (silica gel, chloroform-ethyl acetate 1:1). After 2-3 days less than 5% starting material was generally present. The solution was cooled, neutralized with a weak anion exchange resin, and the solvent evaporated. The last traces of pyridine were removed by several co-distillations with toluene. Chromatography of the residue on silica gel with 15:1 chloroform-methanol gave the pure deacetylated compounds.

1,6-Anhydro-4-O-tert-butyldiphenylsilyl-β-D-mannopyranose (6). Compound 2 (441 mg, 1 mmole) was hydrolyzed and the product purified as described in the common procedure to give compound 6 as a colorless syrup which refused to crystallize (354 mg, 88%), $[\alpha]_D$ -48.8° (c 1.12 in chloroform).

Anal. Calcd for $C_{22}H_{28}O_5Si$: C, 65.97; H, 7.05. Found: C, 66.25; H, 7.18.

1,6-Anhydro-4-O-tert-butyl-β-D-mannopyranose (7). Compound 3 (130 mg, 0.5 mmole) was hydrolyzed and the product purified as described above to give compound 7 as white crystals (90 mg, 82%), mp 128-130°°C, $[\alpha]_D$ -95.5° (c 0.86 in chloroform).

Anal. Calcd for $C_{10}H_8O_5$: C, 55.03; H, 8.31. Found: C, 55.29; H, 8.26.

4-O-Allyl-1,6-anhydro-β-D-mannopyranose (8). Compound 5 (242 mg, 1 mmole) was hydrolyzed and the product purified as described above to give compound 8 as a colorless syrup which refused to crystallize (168 mg, 83%), $[\alpha]_D$ -51.5° (c 2.05 in chloroform).

Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.44; H, 6.90.

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