Synthesis of Methyl 6-Deoxy-6-diphenylphosphino- α -D-glucopyranoside: Temperature-Dependence of the Primary O-Tosyl Cleavage Mode

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Z. Naturforsch. **51b**, 891–896 (1996); received November 29, 1995

Carbohydrates, Carbohydrate-Phosphines, O-Tosyl Cleavage (C-O/S-O),
Chiral Phosphine Ligand

Methyl α -D-glucopyranoside is converted to methyl 6-*p*-toluenesulfonyl-2,3,4-tris-O-trimethylsilyl- α -D-glucopyranoside **2** and then reacted with lithium diphenylphosphide in THF. When the reaction is carried out at room temperature and below, S-O cleavage dominates giving methyl 2,3,4-tris-O-trimethylsilyl- α -D-glucopyranoside **3**, whereas at 60°C in THF or at 35°C in diethyl ether, C-O cleavage occurs yielding the title carbohydrate-phosphine **4** in good yield after deprotection.

Introduction

The interest in water-soluble phosphines has risen dramatically since Kuntz pioneered the use of water-soluble rhodium complexes having sulfonated phosphine ligands in the Ruhrchemie/Rhône-Poulenc hydroformylation process [1a]. The separation of the water-soluble catalyst from the lipophilic products is so effective that the rhodium losses are only $<10^{-9}$ g Rhodium/kg of *n*-butanal [1b]. Apart from sulfonation, the other main approaches for obtaining water-soluble phosphines include the introduction of the most common hydrophilic groups such as carboxyl, hydroxyl, ethylene glycol or ammonium substituents [2].

Although there have been numerous reports of the synthesis of protected carbohydrate-phosphines [3], hitherto only one paper describes the attempt to prepare deprotected carbohydrate-phosphines [3 g]. The removal of the O-isopropylidene groups requires acidic conditions and this can cause difficulties in the presence of the basic phosphine moiety. Hence, the first reported deprotection of DIOP using hydrochloric acid in methanol/water gave impure product [4]. Kagan *et al.* [3i] only recently showed that methanesulfonic acid is a better catalyst for the hydrolysis of the DIOP

O-isopropylidene group and that purification by column chromatography is required. A pure dihydroxydiphosphine product is obtained from (S,S)-1,2:3,4-diepoxybutane, as no deprotection is needed [5].

In a project concerned with the synthesis of chiral water-soluble ligands, in particular phosphine-modified cyclodextrins [6], simple model carbohydrate phosphines were also prepared.

Below we report on the results obtained during work dealing with the conversion of methyl α -D-glucopyranoside, which served as a cyclodextrin model, to methyl 6-deoxy-6-diphenylphosphino- α -D-glucopyranoside.

Results and Discussion

Methyl α -D-glucopyranoside was first converted to methyl 6-O-tosyl- α -D-glucopyranoside **1** by treatment with tosyl chloride, in a reaction which was not as selective as expected [7].

As some mode of protection for **1** was required [10], O-trimethylsilyl protection was chosen, because this group is readily introduced and removed under slightly acidic conditions [12]. Previously OSiMe₃ protection had been successfully used in an extremely efficient synthesis of 1-[1,7-dicarba-*closo*-dodecaboran(12)-1-yl]- α,β -D-glucose by reaction of monolithiated *m*-carborane with 2,3,4,6-tetra-O-trimethylsilyl-D-glucono-1,5-lactone [13].

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Scheme 1. Reaction scheme: conversion of **1** to **5**.

Per-O-trimethylsilylation of **1** to give **2** in *ca.* 90% yield was achieved with a 2:1 mixture of hexamethyldisilazane and chlorotrimethylsilane [14]. The reaction of **2** with two equivalents of lithium diphenylphosphide was first attempted at 0 °C, since it was feared that cleavage of the OSiMe₃ group might occur to give O-lithiated derivatives of **1** and trimethylsilyl-diphenylphosphide. ³¹P NMR of the crude product mixture after hydrolysis revealed that tetraphenyldiphosphine was the major P-containing product and that only *ca.* 23% of the desired methyl 6-deoxy-6-diphenyl-

phosphino-2,3,4-tris-O-trimethylsilyl- α -D-glucopyranoside **4** had been formed, evidently because of S-O cleavage of the tosyl group [15].

Lowering the reaction temperature to -20 °C, resulted in a drop in the amount of **4** to only 10% with a concomitant increase in the proportion of tetraphenyldiphosphine. The NMR and mass spectra reveal that S-O cleavage of the O-tosyl group is the dominant reaction, resulting in the formation of the known methyl 2,3,4-tris-O-trimethylsilyl- α -D-glucopyranoside **3** [18].

The chemical shift of C-6 at 60.9 is in the characteristic range for the carbon atom of a free primary hydroxyl group [19] and the mass spectrum has a *m/z* = 395, which is due to M-Me.

However, it is somewhat surprising that when the lithium diphenylphosphide is added dropwise to **2** at 60 °C, the desired sugar-phosphine **4** becomes the major product with only 10% of tetraphenyl-diphosphine in the reaction mixture.

Orientational experiments [20] with 6-O-tosyl-1,2:3,4-di-O-isopropylidene- α -D-galactopyranose had shown that the amount of lithium diphenylphosphide can be almost halved when carrying out the reaction in diethyl ether rather than tetrahydrofuran. This enabled the synthesis of 6-deoxy-6-diphenylphosphino-1,2:3,4-di-O-isopropylidene- α -D-galactopyranose in *ca.* 80% yield.

Scheme 2. Possible S-O cleavage mode of **2** by LiPPh₂ leading to **3** and Ph₂PPPPh₂.Table I. Reaction of **2** with LiPPh₂ at various temperatures.

2 [mmol]	Solvent	Molar ratio 2 : LiPPh ₂	Temperature [°C] ^b	Time [h]	4 ^a	Ph ₂ PPPPh ₂ ^a
1	THF	1:2	0	1	~23	~77
0.7	THF	1:2	-20	3	~10	~90
3.5	THF	1:2	60	1	~90	<10

^a Amounts of **4** and Ph₂PPPPh₂ estimated by ³¹P PMR after hydrolysis: **4** δ -20.2, Ph₂PPPPh₂ δ -14.3; ^b bath temperature.

In the case of **2**, the use of diethyl ether as a solvent also allowed a reduction in the amount of lithium diphenylphosphide required for complete reaction of the starting tosylate. The reaction of **2** with lithium diphenylphosphide in the ratio 1:1.2 gave **4** in high yield, with only 6 mol% of tetraphenyldiphosphine side-product being present in the crude product.

Deprotection of **4** was achieved with acidic methanol at room temperature, giving waxy **5** in *ca.* 90% yield. The ^{31}P NMR chemical shifts of both **4** and **5** are at *ca.* -20. These values are close to those found for DIOP and 2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane [4]. Hence, in these cases deprotection does not result in a remarkable low-field shift in the ^{31}P NMR spectra, as reported recently for two carbohydrate-phosphines [3 g].

Experimental

All experiments were carried out in dry deoxygenated solvents under argon.-MS: Finnigan MAT CH5.- ^1H , ^{13}C and ^{31}P NMR: Bruker AC-200, AMX-400. The ^{31}P NMR shifts are given in δ relative to external 85% phosphoric acid. Other chemical shifts are given relative to TMS.

Starting compounds

Methyl α -D-glucopyranoside was purchased from Fluka. Lithium diphenylphosphide was prepared by reaction of butyl lithium with diphenylphosphine (both obtained from Aldrich) in hexane at room temperature as described below.

HPLC conditions

For analytical measurements at 35 °C -Varian 5060, Shimadzu CTO-6A, Varian UV 100. Stationary phase: 250 mm Nucleosil 100-5- C_{18}/A , 4.5 mm internal diameter. Mobile phase: acetonitrile/water 30:70-10 min-80:20-10 min isocratic 80:20. Flow rate 0.8 ml/min with 10.6 MPa. Preparative conditions at room temperature.-Instrument: Shimadzu LC-8 gradient system.-Column: 230 mm Buchi MPLC, 36 mm. Stationary phase: LiChroprep Si 100-C18/Cl, 25-40 μm . Mobile phase: acetonitrile/water 60:40 for isolation of the ditosyl compound and 25:75 for isolation of the monotosylated compounds. Flow rate 20 ml/min at 1.4 MPa. Detection: UV, 238 nm.

Lithium diphenylphosphide

A 1.6 m solution of butyl lithium (80 ml, 128 mmol) is added dropwise in *ca.* 1.5 h to a stirred solution of diphenylphosphine (20.5 g, 110 mmol) in hexane (350 ml), so that the flask temperature does not exceed 38 °C. After stirring overnight, the lithium diphenylphosphide is filtered off, washed with hexane and dried *in vacuo* (10^{-3} Torr) to give yellow, powdery product (19.5 g, 92%). ^{31}P NMR (THF): δ = -20.7.

Methyl 6-*O*-*p*-toluenesulfonyl- α -D-glucopyranoside (**1**)

A solution of *p*-toluenesulfonyl chloride (10.5 g, 55.1 mmol) in pyridine (20 ml) is added dropwise to a stirred solution of methyl α -D-glucopyranoside (10 g, 51.5 mmol) in pyridine (20 ml) at room temperature so that the flask temperature reaches 35 °C. The clear, yellow solution is stirred for 2 d at room temperature and then concentrated *in vacuo* (10^{-3} Torr, 60-70 °C bath temperature). The residue is dissolved in chloroform (25 ml) and the so-

Compound	Formula [mol. mass]	Found m/z (% rel. intensity) ^a M Base mass	Other characteristic masses
1	$\text{C}_{14}\text{H}_{20}\text{O}_8\text{S}$ [348.4]	^b 60 ^c	317(<1), 245(19), 215(14) 173(14), 133(24), 91(64)
2	$\text{C}_{23}\text{H}_{44}\text{O}_8\text{SSi}_3$ [564.9]	564 (<1)	533(<1), 459(<1), 443(1) 317(26), 287(7), 217(30)
3	$\text{C}_{16}\text{H}_{38}\text{O}_6\text{Si}_3$ [410.7]	-	395(<1), 379(<1), 305(2) 290(4), 276(3), 217(48)
4	$\text{C}_{28}\text{H}_{47}\text{O}_5\text{PSi}_3$ [578.8]	578 (1)	563(7), 547(2), 488(17) 317(12), 243(23), 204(45)
5	$\text{C}_{19}\text{H}_{23}\text{O}_5\text{P}$ [362.4]	362 (5)	347(5), 331(3), 302(12) 285(40), 199(22), 108(56)

Table II. Formulae and mass spectrometric data of **1-5**.

^a EI-MS (70 eV);
^b $[\text{M}+\text{NH}_4]^+$ 366 found by CI with ammonia as the reactant gas;
^c above 140 °C decomposition occurs and the mass spectrum of *p*-toluenesulfonic acid is obtained.

lution is washed with saturated potassium hydrogen sulfate (10 ml) and potassium hydrogen carbonate (10 ml). The solid obtained after removal of the chloroform is treated with ethanol (10 ml) and dried *in vacuo* (10^{-3} Torr, <40 °C bath temperature) to give a white, amorphous solid mixture (12.3 g), which contains 46% **1**, 7% methyl 2-O-*p*-toluenesulfonyl- α -D-glucopyranoside and 31% methyl 2,6-di-O-*p*-toluenesulfonyl- α -D-glucopyranoside (HPLC analysis). Preparative HPLC separation yields 99.9% pure **1** (4.7 g, 26%) with m.p. 130 °C (Lit.[8] 124 °C) and $[\alpha]_D^{20}$ 100.7 (c 0.6, MeOH). The 2-O-tosyl isomer (0.5 g, 2.7%) and the 2,6-di-O-tosyl derivative (2.05 g, 8%) are also separated. The ditosylated compound can also be removed from the mixture by flash chromatography (silica gel, ethyl acetate).

Methyl 2,3,4-tris-O-trimethylsilyl-6-O-p-tolylsulfonyl- α -D-glucopyranoside (2)

A solution of **1** (4.7 g, 13.5 mmol) in pyridine (30 ml) is treated with hexamethyldisilazane (11.3 ml, 54.2 mmol) and trimethylsilyl chloride (3.4 ml, 27 mmol) is added dropwise to the stirred mixture at 0 °C. After 15 min. at 0 °C the mixture is stirred for 1 h at room temperature before adding pentane (*ca.* 30 ml), filtering and concentrating the filtrate *in vacuo* (10^{-3} Torr, <60 °C, bath). **2** (6.82 g, 89%) is obtained as a colourless, highly viscous residue.

Methyl 2,3,4-tris-O-trimethylsilyl- α -D-glucopyranoside 3 by reaction of 2 with lithium diphenylphosphide at 0 °C

A solution of **2** (0.55 g, ~ 1 mmol) in THF (10 ml) is added dropwise to lithium diphenylphosphide (2 mmol) in THF (5 ml) at 0 °C (bath). The mixture is stirred for 1 h, at which time the bath temperature has risen to 10 °C and TLC (diethyl ether / hexane 1:1) indicates that no more **2** is pre-

sent. Diethyl ether (10 ml) is added and the organic solution is washed with ice-water and then evaporated to dryness to give a P-containing mixture containing $\sim 23\%$ **4** and 77% tetraphenyldiposphine (by ^{31}P NMR) together with **3**.

A similar experiment carried out at -20 °C bath temperature for 3 h gives a mixture of P-containing products with only $\sim 10\%$ **4** and 90% Ph_2PPPh_2 (by ^{31}P NMR).

When the experiment is carried out at 60 °C for 1 h $\sim 90\%$ **4** and $\leq 10\%$ Ph_2PPPh_2 is obtained.

Methyl 6-Deoxy-6-diphenylphosphino-2,3,4-tris-O-trimethylsilyl- α -D-glucopyranoside (4)

A solution of **2** (1.2 g, 2.1 mmol) in diethyl ether (10 ml) is added dropwise to a solution of lithium diphenylphosphide (0.47 g, 2.45 mmol) in diethyl ether (~ 15 ml) at 45 °C (bath temperature) and the stirred mixture is then heated under reflux. After 0.5 h, **2** can still be detected by TLC (ether/hexane 1:1) so a spatula tip of lithium diphenylphosphide is added and refluxing is continued for a further 0.5 h. The ether solution is shaken with water and the organic phase is concentrated *in vacuo* (10^{-3} Torr) to give **4** (1.18 g, 97%) with ^{31}P NMR (CDCl_3): $\delta = -20.2$. The crude product contains *ca.* 6 mol% of diphenylphosphine ($\delta_{31\text{P}} = -39.7$).

Methyl 6-deoxy-6-diphenylphosphino- α -D-glucopyranoside (5)

Methanol (10 ml) containing glacial acetic acid (0.1 ml) is added to **4** (2.8 g, 4.9 mmol) and the stirred mixture is heated under reflux for 6 h. Crude **5** (1.8 g, 102%) is obtained on removing the volatile components *in vacuo* (10^{-3} Torr, 60 °C bath temperature). **5** is treated with diethyl ether (20 ml) and heated under reflux before adding ethanol (~ 2 ml) to obtain a clear solution. On

Table III. ^1H NMR chemical shifts and coupling constants (in parentheses) for the methyl α -D-glucopyranosides **1**, **2** and **5**.

Compound	Solvent (MHz)	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6a}$)	H-6a ($J_{5,6a}$)	H-6b ($J_{6a,6b}$)	OMe
1	DMSO- d_6 (400)	4.28 (3.7)	3.21 (9.5)	3.41 (8.8)	3.07 (10)	3.56 (1.9)	4.28 (6.3)	4.12 (−10.7)	3.23
2	CDCl_3 (200)	4.36 (3.6)	3.25 (9.1)	3.57 (8.4)	3.22 (9)	3.53 (1.8)	4.15 (5.9)	3.94 (−10.5)	3.14
5 ^a	Pyridine- d_5 (400)	5.03 (3.7)	4.11 (9.6)	3.94 (8.9)	4.42 (10)	4.31 (2.4)	3.33 (10.4)	2.59 (−14.3)	3.38

^a Additional coupling constants: $J_{5,\text{P}}$ 10, $J_{6a,\text{P}}$ 3.8, $J_{6b,\text{P}}$ 2.

Compound	Solvent	C-1	C-2	C-3	C-4	C-5	C-6	OMe	Table IV. Characteristic ^{13}C NMR data for 1–5 .
1	DMSO- d_6	99.5	71.7	73.2	69.9	69.6	70.4	54.6	
2	CDCl_3	99.4	73.3	74.8	69.4	71.9	69.2	54.7	
3	CDCl_3	99.2	71.1 ^a	74.1 ^a	71.1 ^a	73.2 ^a	60.9	54.0	
4	CDCl_3	99.4	73.7 ^a	74.7 ^a	76.6 (7.1)	69.4 (13.2)	32.3 (13.7)	54.5 (4.3)	
5	Pyridine- d_5	101.1	73.5 ^a	74.9 ^a	76.7 (7.0)	70.6 (13.1)	32.2 (14.0)	54.7 (3.0)	^a Assignment may be interchanged; J_{PC} in brackets.

cooling, a waxy precipitate of **5** is formed and this is filtered off and dried to give white **5** (1.57 g, 89%) with ^{31}P NMR (pyridine- d_5): $\delta = -19.8$. Attempts to obtain crystalline material from either

diethyl ether, chloroform or hexane/ethanol always result in the formation of waxy product. **5** is poorly soluble in water (0.234 g/100 ml, 20 °C, *i.e.* ~6.5 mmol/l).

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