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Tetraisopropyldisiloxane-1,3-diyl as a Versatile Protecting Group for Pentopyranosides

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Abstract

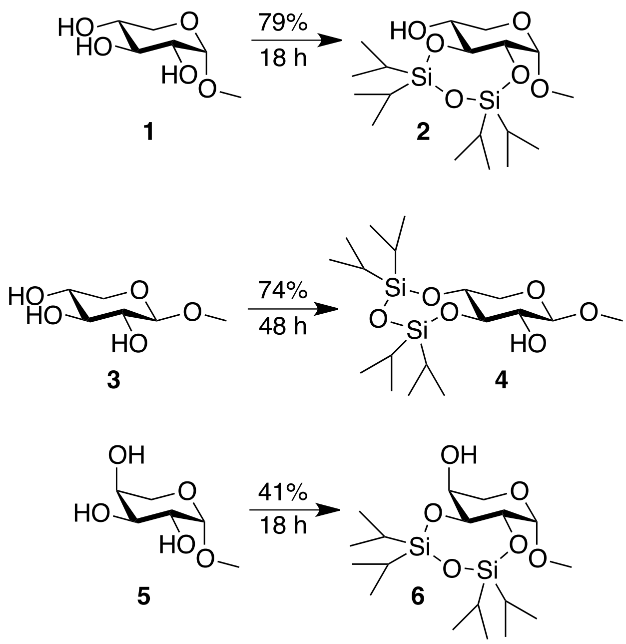
The protecting group tetraisopropyldisiloxane-1,3-yl has been investigated for simultaneous protection of two hydroxyls on pentopyranosides. Methyl α-D-xylopyranoside is protected in excellent regioselectivity and high yield to form the 2,3-protected xylopyranoside whereas methyl β-D-xylopyranoside gives the 3,4-protected product also with excellent regioselectivity.

Pentopyranosides have recently received attention in medicinal chemistry and for example, simple xylosides have shown to be interesting in cancer therapeutics.[1] Selective protection of xylose is complicated since all three hydroxyls are secondary and equatorial.[2] Several methods have been evaluated for regioselective protection, which can be achieved by stoichiometric benzoylation[3], benzylation[4] and tosylation[5]. Other methods for regioselective synthesis include phenylborate esters[6], isopropylidene acetals[4,7,8], butane-2,3-diacetals[9,10], cyclohexylidene acetals[4,11,12], tin acetals[13] and enzymatic deacetylation[14]. However, most of these methods give low selectivity, include toxic reagents or troublesome purifications. To find a versatile method for selective protection of pentopyranosides we decided to introduce tetraisopropyldisiloxane-1,3-diyl (TiPDS) to protect two hydroxyls simultaneously.

TiPDS is a cyclic protecting group that was introduced by Markiewicz in 1979 for protection of ribonucleosides.[15,16] The method gives a clean conversion to the 3',5' protected ribonucleoside, since the primary HO-5' reacts faster followed by the formation of the 8-membered ring. The method is still one of the preferred methods in nucleoside chemistry for modification on HO-2'.[17-19] One year later van Boom and co-workers introduced the TiPDS protection to hexopyranosides, showing that it simultaneously protected HO-4 and HO-6 and concluding that the protecting group rearranges by treatment with acid in DMF to generate the 3,4-protected glucoside.[20]

To investigate the use of TiPDS for pentopyranosides, methyl α-D-xylopyranoside (**1**) was dissolved in pyridine and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TiPDSCl_2$) was added and the reaction was followed by TLC. After 18 h, methanol was added to quench the excess of $TiPDSCl_2$ and the mixture was concentrated and chromatographed to give the 2,3-protected methyl α-D-xylopyranoside (**2**) in 79% yield (Scheme 1).

Methyl β-D-xylopyranoside (**3**) was subjected to the same reaction conditions and after 18 h reaction time the 3,4-protected methyl β-D-xylopyranoside was isolated in 59% yield. However, when the reaction time was increased to 48 h, **4** was isolated in 74% yield, indicating that the β-anomer reacts at a lower rate. In nucleoside chemistry the reaction proceeds at a higher rate if pyridine is exchanged for DMF using imidazole as base.[16] When methyl β-D-xylopyranoside was reacted under these conditions the starting material was consumed in just a couple of hours. However, the isolated yield of the desired product did not increase compared to the reaction in pyridine (59%) and the higher reaction rate also diminished the regioselectivity for the reaction (Scheme 1).



Scheme 1: TiPDSCl$_2$ protection of methyl D-glycosides. Reaction conditions: TiPDSCl$_2$ 1.1 eq. in pyridine 0.1 M.

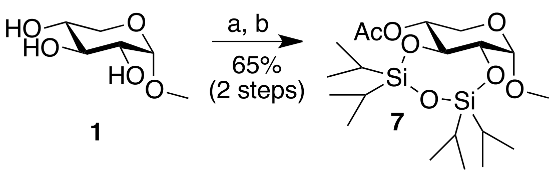
The difference in regioselectivity between the α- and β-anomer was expected based on previous literature. The reactivity for the secondary hydroxyls in methyl α-D-glucopyranoside towards benzoyl chloride was investigated by Williams *et. al.* and they concluded that the reactivity is HO-2 > HO-4 > HO-3.[23] The higher reactivity of HO-2 was reasoned to be due to activation by the anomeric substituent, probably through a hydrogen bond to the anomeric oxygen. In addition gauche effects between HO-2 and HO-3 as well as steric effects cause HO-4 to be more reactive than HO-3. Sivakumaran *et. al.* investigated benzoylation on benzyl α-D-xylopyranosides and concluded that the order of reactivity was the same as for methyl α-D-glucopyranoside. [3] The reactivity order for methyl β-D-xylopyranoside has been previously established to be HO-4 > HO-3 > HO-2.[24] The results from this study support these observations since methyl α-D-xylopyranoside forms the 2,3-cyclic product and methyl β-D-xylopyranoside forms the 3,4-cyclic product. See Table 1 for comparison of different cyclic protection groups on D-xylopyranosides.

To investigate the difference in reaction rate between the α- and β-anomer, the consumption of the starting material was followed by NMR. The reaction was hence run over 10 h in an NMR-tube in pyridine-d$_5$ with 1 equivalent of toluene as internal standard. The progress of the reaction was monitored by the disappearance of H-1. As expected, methyl α-D-xylopyranoside was consumed at a higher rate, in comparison to methyl β-D-xylopyranoside (Figure 1).

Figure 1: The consumption of methyl α-D-xylopyranoside (circles, ●) and methyl β-D-xylopyranoside (squares, ■) as a function over time. The disappearance of H-1 is followed by NMR.

The reducing form of xylose was also subjected to the reaction conditions. Unfortunately multiple products were formed and xylose is not suitable for this method.

Next, methyl β-L-arabinopyranoside (**5**) was also reacted under the same conditions but did not proceed as cleanly and several products were observed on TLC. However, the major product was the 2,3-protected methyl β-L-arabinopyranoside (**6**) that was isolated in 41% yield (Scheme 1). The reactivity of the hydroxyls of methyl β-L-arabinopyranoside has been suggested to be HO-2, HO-3 > HO-4, where the relative reactivity of HO-2, HO-3 is uncertain, and this reactivity is also supported by the silylation experiments in this study.[3,13,25]



Scheme 2: The selective acetylation of HO-4: Reaction conditions: a) $TiPDSCl_2$ 1.1 eq. in pyridine 0.1 M. 18 h b) Ac_2O/Pyridine 4:5 v:v 18h.

To confirm the usability of this protecting group, methyl α-D-xylopyranoside was protected with $TiPDSCl_2$ and with a short work-up, without column chromatography. The crude was treated with acetic anhydride in pyridine to give methyl 2,3-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-D-xylopyranoside (**7**) in 65% yield over two steps (Scheme 2).

Table 1: Comparison of yield and selectivity for cyclic protective groups on D-xylopyranosides.

Entry	*Anomeric configuration*	*Protective group*	*2,3-protected*	*3,4-protected*	*Ref.*
1	α-OMe	TiPDS	79%	-	This work
2	α-OMe	Isopropylidene acetal	39%	13%	4
3	α-OAll	Isopropylidene acetal	70%	-	8
4	α-OMe	Cyclohexylidene acetal	63%	13%	4
5	α-OBn	Cyclohexylidene acetal	42%	11%	12
6	β-OMe	TiPDS	-	74%	This work
7	β-OMe	Isopropylidene acetal	72%	-	7
8	β-OAll	Isopropylidene acetal	77%	6%	21
9	β-OBn	Isopropylidene acetal	78%	14%	22
10	β-OAll	Butane-2,3-diacetal	47%	47%	9

To summarize, we have developed a new methodology for regioselective protection of xylopyranosides to simultaneously protect HO-2 and HO-3 on methyl α-D-xylopyranosides and methyl β-L-arabinopyranosides as well as protection of HO-3 and HO-4 on methyl β-D-xylopyranosides by using $TiPDSCl_2$. The reaction proceeds cleanly and in high yield for the xylopyranosides although a lower yield was observed for the arabinopyranoside.

1. Experimental

1.1 General experimental details

NMR spectra were recorded with a Bruker Avance II 400 MHz and Bruker Avance 500 MHz. ^{1}H-NMR spectra were assigned using 2D-methods (COSY, HMQC). Chemical shifts are given in ppm downfield from the signal for Me_4Si, with reference to residual C_6D_5H. Reactions were monitored by TLC using alumina plates coated with silica gel and visualized using either UV light or by charring with *para*-anisaldehyde. Preparative chromatography was performed with silica gel (35-70 μm, 60 Å). DMF was distilled prior to use; pyridine (extra dry) and all other reagents were used as supplied from manufacturer.

1.2 General experimental for the 1,1,3,3-tetraisopropyldisiloxane protections. Methyl glycoside (56-116 mg, 0.34-0.71 mmol) was dissolved in pyridine (0.1 M) and stirred at r.t. under N_2. $TiPDSCl_2$ (1.1 eq.) was added dropwise during 5-10 min. Upon completion the reaction was quenched by addition of MeOH (1-2 mL) and the mixture was concentration to dryness by co-evaporation with toluene. Purified by column chromatography (SiO_2 heptane/EtOAc 6:1) to give the product as an amorphous white solid.

1.3 Methyl 2,3-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-D-xylopyranoside (2). Yield 79%. $[\alpha]_D^{20}$ 59.6 (*c* 0.8, C_6H_6). ^{1}H-NMR (C_6D_6): δ 4.60 (d, 1 H, *J* 3.6 Hz, H-1), 4.14 (t, 1 H, *J* 8.3 Hz, H-3), 3.76 (dd, 1 H, *J* 9.1, 3.6 Hz, H-2), 3.68-3.70 (m, 2 H, H-5, H-5'), 3.61 (dt, 1 H, *J* 8.1, 2.7 Hz, H-4), 3.12 (s, 3 H, OMe), 1.97 (d, 1 H, *J* 2.8 Hz, OH-2), 1.11-1.21 (m, 28 H, Silyl-H). ^{13}C-NMR (C_6D_6): δ 100.9, 77.9, 75.6, 71.6, 61.2, 55.2, 17.8, 17.73, 17.67, 17.61, 17.57, 17.54, 17.51, 17.48, 13.3, 13.2, 12.9, 12.6. HRMS calcd for $C_{18}H_{38}O_6Si_2Na$ (M+Na): 429.2105, found: 429.2136.

1.4 Methyl 3,4-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-xylopyranoside (4). Yield 59% (18 h reaction time), 74% (48 h reaction time). $[\alpha]_D^{20}$ -5.5 (*c* 0.8, C_6H_6). ^{1}H-NMR (C_6D_6): δ 3.98 (d, 1 H, *J* 7.6 Hz, H-1), 3.92 (dd, 1 H, *J* 11.5, 5.6 Hz, H-5), 3.79-3.85 (m, 1 H, H-4), 3.69 (t, 1 H, *J* 8.8 Hz, H-3), 3.55 (ddd, 1 H, *J* 8.8, 7.7, 2.4 Hz, H-2), 3.29 (s, 3 H, OMe), 3.12 (dd, 1 H, *J* 11.5, 10.0 Hz, H-5'), 2.17 (d, 1 H, *J* 2.4 Hz, OH-2), 0.97-1.26 (m, 28 H, Silyl-H). ^{13}C-NMR (C_6D_6): δ 104.9, 80.3, 74.6, 73.4, 66.2, 56.6, 17.7, 17.63, 17.60, 17.56, 17.5, 17.4, 13.4, 13.3, 12.60, 12.57. HRMS calcd for $C_{18}H_{38}O_6Si_2Na$ (M+Na): 429.2105, found: 429.2107. *DMF/Imidazole method:* Methyl β-D-xylopyranoside (57 mg, 0.35 mmol) was dissolved in DMF (3.5 mL) and stirred at r.t. under N_2 and imidazole (110 mg, 1.62 mmol) was added. $TiPDSCl_2$ (0.13 mL, 0.40 mmol) was added dropwise during 10 min. After 7 h the reaction was quenched by addition of MeOH (1 mL) and concentration to dryness by co-evaporation with toluene. Purified by column chromatography (SiO_2 heptane/EtOAc 4:1) to give **4** (84 mg, 59%) as an amorphous white solid.

1.5 Methyl 2,3-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-L-arabinopyranoside (6). Yield 41%. $[\alpha]_D^{20}$ 88.0 (*c* 0.6, C_6H_6). ^{1}H-NMR (C_6D_6): δ 4.80 (d, 1 H, *J* 3.5 Hz, H-1), 4.28 (dd, 1 H, *J* 9.2, 3.5 Hz, H-2), 4.17 (dd, 1 H, *J* 9.2, 3.8 Hz, H-3), 3.82 (dd, 1 H, *J* 12.4, 1.6 Hz, H-5), 3.75-3.76 (m, 1 H, H-4), 3.59 (bd, 1 H, *J* 12.4 Hz, H-5'), 3.15 (s, 3 H, OMe), 2.72 (d, 1 H, *J* 1.7 Hz, OH-4), 1.00-1.19 (m, 28 H, Silyl-H). ^{13}C-NMR (C_6D_6): δ 101.2, 73.2, 72.6, 70.3, 61.6, 55.3, 17.71, 17.70, 17.64, 17.61, 17.57, 17.5, 17.4, 13.29, 13.28, 12.9, 12.5. HRMS calcd for $C_{18}H_{38}O_6Si_2Na$ (M+Na): 429.2105, found: 429.2119.

1.6 Methyl 4-*O*-acetyl-2,3-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-D-xylopyranoside (7). Methyl α-D-xylopyranoside (60 mg, 0.33 mmol) was dissolved in pyridine (3.5 mL) and stirred at r.t. under N_2. TiPDSCl_2 (0.12 mL, 0.37 mmol) was added dropwise during 5 min. After 18 h the reaction was quenched by addition of MeOH (1 mL) and concentration to dryness by co-evaporation with toluene. The residue was dissolved in CH_2Cl_2 and washed twice with brine. The water phase was extracted twice with CH_2Cl_2 and the combined organic phase was dried with $MgSO_4$ and concentrated to give **2**. Compound **2** was dissolved in pyridine (2.5 mL) and Ac_2O (2.0 mL) was added and the mixture was stirred at r.t. After 18 h the mixture was concentrated to dryness and purified by column chromatography (SiO_2, heptane/EtOAc 10:1) to give **7** (97 mg, 65%, 2 steps) as an amorphous white solid. $[\alpha]_D^{20}$ 81.9 (*c* 0.8, C_6H_6). ^{1}H-NMR (C_6D_6): δ 5.23 (ddd, 1 H, *J* 15.0, 9.0, 6.1 Hz, H-4), 4.64 (d, 1 H, *J* 3.6 Hz, H-1), 4.27 (t, 1 H, *J* 9.0 Hz, H-3), 3.74-3.78 (m, 2 H, H-2, H-5), 3.55 (t, 1 H, *J* 10.8 Hz, H-5'), 3.10 (s, 3 H, OMe), 1.73 (s, 3 H, OAc), 1.03-1.21 (m, 28 H, Silyl-H). ^{13}C-NMR (C_6D_6): δ 169.2, 100.5, 75.8, 74.5, 71.8, 58.6, 55.3, 20.3, 17.7, 17.63, 17.61, 17.58, 17.53, 17.48, 17.4, 17.3, 13.2, 12.8, 12.7. HRMS calcd for $C_{20}H_{40}O_7Si_2Na$ (M+Na): 471.2210, found: 471.2216.

1.7 Kinetics study, Methyl α-D-xylopyranoside (1).

Methyl α-D-xylopyranoside (**1**) (13 mg, 0.077 mmol) was dissolved in pyridine-d_5 (0.6 mL) and toluene (0.008 mL, 0.075 mmol) was added as an internal standard in an NMR tube. TiPDSCl_2 (0.028 mL, 0.086 mmol) was added. NMR spectra were taken immediately after addition of TiPDSCl_2 (t=0) and once every 30 min for 10 h.

1.8 Kinetics study, Methyl β-D-xylopyranoside (3).

Methyl β-D-xylopyranoside (**3**) (12 mg, 0.071 mmol) was dissolved in pyridine-d_5 (0.6 mL) and toluene (0.008 mL, 0.075 mmol) was added as an internal standard in an NMR tube. $TiPDSCl_2$ (0.026 mL, 0.080 mmol) was added. NMR spectra were taken immediately after addition of $TiPDSCl_2$ (t=0) and once every 60 min for 10 h.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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