



LUND UNIVERSITY

Tetraisopropylidisiloxane-1,3-diyl as a versatile protecting group for pentopyranosides.

Johnsson, Richard

Published in:
Carbohydrate Research

DOI:
[10.1016/j.carres.2012.03.016](https://doi.org/10.1016/j.carres.2012.03.016)

2012

[Link to publication](#)

Citation for published version (APA):

Johnsson, R. (2012). Tetraisopropylidisiloxane-1,3-diyl as a versatile protecting group for pentopyranosides. *Carbohydrate Research*, 353(Online 24 March 2012), 92-95. <https://doi.org/10.1016/j.carres.2012.03.016>

Total number of authors:
1

General rights

Unless other specific re-use rights are stated the following general rights apply: Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

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

Richard Johnsson

Center for Analysis and Synthesis, Lund University, P.O. Box 124, SE-221 00 Lund, Sweden

Corresponding author: richard.johnsson@organic.lu.se, Phone: +46 46-222 82 10, Fax: +46 46-222 82 09

Abstract

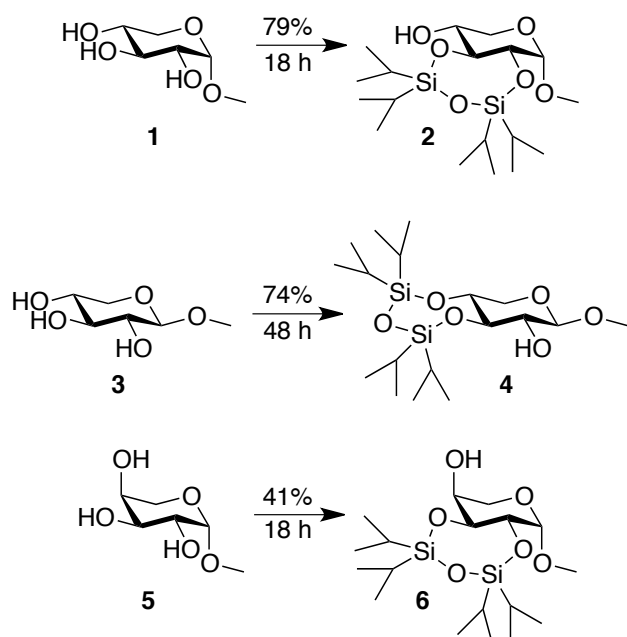
The protecting group tetraisopropyldisiloxane-1,3-yl has been investigated for simultaneous protection of two hydroxyls on pentopyranosides. Methyl α -D-xylopyranoside is protected in excellent regioselectivity and high yield to form the 2,3-protected xylopyranoside whereas methyl β -D-xylopyranoside 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 benzylation³, benzylation⁴ and tosylation⁵. Other methods for regioselective synthesis include phenylborate esters⁶, isopropylidene acetals^{4,7,8}, butane-2,3-diacetals^{9,10}, cyclohexylidene acetals^{4,11,12}, tin acetals¹³ and enzymatic deacetylation¹⁴. 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-tetraisopropylidisiloxane (TiPDSCl₂) was added and the reaction was followed by TLC. After 18 h, methanol was added to quench the excess of TiPDSCl₂ 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 $\text{HO-2} > \text{HO-4} > \text{HO-3}$.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 benzylation 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 $\text{HO-4} > \text{HO-3} > \text{HO-2}$.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.

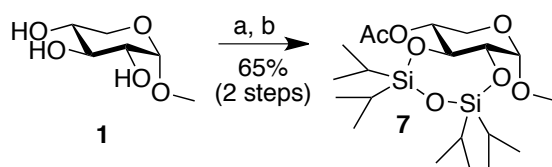
To investigate the difference in reaction rate between the α - and β -anomer, the consumption of the starting material was followed by NMR. The reaction was hence run over 10 h in an NMR-tube in pyridine- d_5 with 1 equivalent of toluene as internal

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-tetraisopropylidisiloxane-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 TiPDSCl₂. 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. ¹H-NMR spectra were assigned using 2D-methods (COSY, HMQC). Chemical shifts are given in ppm downfield from the signal for Me₄Si, with reference to residual C₆D₅H. 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 μ m,

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-tetraisopropylidisiloxane protections.

Methyl glycoside (56-116 mg, 0.34-0.71 mmol) was dissolved in pyridine (0.1 M) and stirred at r.t. under N₂. TiPDSCl₂ (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 (SiO₂ heptane/EtOAc 6:1) to give the product as an amorphous white solid.

1.3 Methyl 2,3-*O*-(1,1,3,3-tetraisopropylidisiloxane-1,3-diyl)- α -D-xylopyranoside

(2). Yield 79%. $[\alpha]_D^{20}$ 59.6 (*c* 0.8, C₆H₆). ¹H-NMR (C₆D₆): 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). ¹³C-NMR (C₆D₆): 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 C₁₈H₃₈O₆Si₂Na (M+Na): 429.2105, found: 429.2136.

1.4 Methyl 3,4-*O*-(1,1,3,3-tetraisopropylidisiloxane-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, C₆H₆). ¹H-NMR (C₆D₆): 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). ¹³C-NMR (C₆D₆): 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 C₁₈H₃₈O₆Si₂Na (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 N₂ and imidazole (110 mg, 1.62 mmol) was added. TiPDSCl₂ (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 (SiO₂ 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-tetraisopropylidisiloxane-1,3-diyl)- β -L-

arabinopyranoside (6). Yield 41%. $[\alpha]_D^{20}$ 88.0 (*c* 0.6, C₆H₆). ¹H-NMR (C₆D₆): 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). ¹³C-NMR (C₆D₆): 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 C₁₈H₃₈O₆Si₂Na (M+Na): 429.2105, found: 429.2119.

1.6 Methyl 4-*O*-acetyl-2,3-*O*-(1,1,3,3-tetraisopropylidisiloxane-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 N₂. TiPDSCl₂ (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 CH₂Cl₂ and washed twice with brine. The water phase was extracted twice with CH₂Cl₂ and the combined organic phase was dried with MgSO₄ and concentrated to give **2**. Compound **2** was dissolved in pyridine (2.5 mL) and Ac₂O (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 (SiO₂, 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, C₆H₆). ¹H-NMR (C₆D₆): 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). ¹³C-NMR (C₆D₆): 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 C₂₀H₄₀O₇Si₂Na (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-d₅ (0.6 mL) and toluene (0.008 mL, 0.075 mmol) was added as an internal standard in an NMR tube. TiPDSCl₂ (0.028 mL, 0.086 mmol) was added. NMR spectra were taken immediately after addition of TiPDSCl₂ (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-d₅ (0.6 mL) and toluene (0.008 mL, 0.075 mmol) was added as an internal standard in an NMR tube. TiPDSCl₂ (0.026 mL, 0.080 mmol) was added. NMR spectra were taken immediately after addition of TiPDSCl₂ (t=0) and once every 60 min for 10 h.

Acknowledgments

The Swedish Research Council supported this work.

Supplementary data

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

References

1. Nilsson, U.; Johnsson, R.; Fransson, L.-Å.; Ellervik, U.; Mani, K. *Cancer Res.* **2010**, *70*, 3771-3779.
2. Siegbahn, A.; Aili, U.; Ochocinska, A.; Olofsson, M.; Rönnols, J.; Mani, K.; Widmalm, G.; Ellervik, U. *Bioorg. Med. Chem.* **2011**, *19*, 4114-4126.
3. Sivakumaran, T.; Jones, J. K. N. *Can. J. Chem.* **1967**, *45*, 2493-2500.
4. Morishima, N.; Koto, S.; Kusuhara, C.; Zen, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 631-632.
5. Buchanan, J. G.; Fletcher, R. *J. Chem. Soc., C* **1966**, 1926-1931.
6. Ferrier, R. J.; Prasad, D.; Rudowski, A.; Sangster, I. *J. Chem. Soc.* **1964**, 3330-3334.
7. Naleway, J. J.; Raetz, C. R. H.; Anderson, L. *Carbohydr. Res.* **1988**, *179*, 199-209.
8. Goodby, J. W.; Haley, J. A.; Watson, M. J.; Mackenzie, G.; Kelly, S. M.; Letellier, P.; Gode, P.; Goethals, G.; Ronco, G.; Harmouch, B.; Martin, P.; Villa, P. *Liq. Cryst.* **1997**, *22*, 497-508.
9. Jenkins, D. J.; Potter, B. V. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 41-50.
10. Oscarson, S.; Svahnberg, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 873-879.
11. Bissett, F. H.; Evans, M. E.; Parrish, F. W. *Carbohydr. Res.* **1967**, *5*, 184-193.
12. Koto, S.; Morishima, N.; Takenaka, K.; Uchida, C.; Zen, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1464-1468.
13. Tsuda, Y.; Haque, M. E.; Yoshimoto, K. *Chem. Pharm. Bull.* **1983**, *31*, 1612-1624.
14. Marek, M.; Medonos, I.; Kefurt, K.; Jary, J. *Biocatalysis* **1989**, *2*, 235-238.
15. Markiewicz, W. T. *J. Chem. Soc. (S)* **1979**, 24-25.
16. Markiewicz, W. T. *J. Chem. Soc. (M)* **1979**, 178-194.
17. Johnsson, R.; Lackey, J. G.; Bogojeski, J. J.; Damha, M. J. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3721-3725.

18. Dellinger, D. J.; Timár, Z.; Myerson, J.; Sierzchala, A. B.; Turner, J.; Ferreira, F.; Kupihár, Z.; Dellinger, G.; Hill, K. W.; Powell, J. A.; Sampson, J. R.; Caruthers, M. H. *J. Am. Chem. Soc.* **2011**, *133*, 11540-11556.
19. Hermann, C.; Kvassiouk, E.; Pflleiderer, W. *Helv. Chim. Acta* **2011**, *94*, 362-370.
20. Verdegaal, C. H. M.; Jansse, P. L.; de Rooij, J. F. M.; van Boom, J. H. *Tetrahedron Lett.* **1980**, *21*, 1571-1574.
21. Best, W. M.; Macdonald, J. M.; Skelton, B. W.; Stick, R. V.; Tilbrook, D. M. G.; White, A. H. *Can. J. Chem.* **2002**, *80*, 857-865.
22. Rio, S.; Beau, J.-M.; Jacquinet, J.-C. *Carbohydr. Res.* **1991**, *219*, 71-90.
23. Williams, J. M.; Richardson, A. C. *Tetrahedron* **1967**, *23*, 1369-1378.
24. Chalk, R. C.; Ball, D. H. *Carbohydr. Res.* **1973**, *28*, 313-325.
25. Reist, E. J.; Fisher, L. V.; Goodman, L. *J. Org. Chem.* **1967**, *32*, 2541-2544.