Tetrahedron Letters 54 (2013) 3831–3833

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Regioselective 6-detrimethylsilylation of per-O-TMS-protected carbohydrates in the presence of ammonium acetate

Yanli Cui [a,*], Zhaodong Cheng [a], Jianwei Mao [b], Yongping Yu [c]

[a] Department of Chemistry, Zhejiang University, Hangzhou 310027, PR China
[b] Zhejiang Provincial Key Lab for Chem. & Bio. Processing Technology of Farm Produces, Hangzhou 310023, PR China
[c] College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, PR China

ARTICLE INFO

Article history:
Received 23 February 2013
Revised 26 April 2013
Accepted 10 May 2013
Available online 18 May 2013

Keywords:
Carbohydrates
Regioselectivity
Desilylation
Glycosides
Protecting groups

ABSTRACT

A convenient methodology has been developed for the regioselective removal of primary trimethylsilyl group (TMS) of various per-*O*-TMS-protected carbohydrates by inexpensive ammonium acetate. After acetylation and trichloroacetimidation of 6-hydroxyl sugar **1b**, other TMS groups of **1d** and **1c** were inert to ammonium acetate in the same conditions, and this approach was also successfully applied in TMS-protected sphingosine.

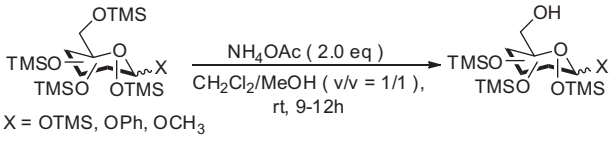
Regioselective modification of carbohydrates has always been a focus in research of glycochemistry and glycobiology.[1,2] However, the achievement of this goal is often complicated, because the carbohydrate molecules contain a number of hydroxyl units which are difficult to manipulate selectively.[3] Single hydroxyl sugar derivatives in 6-position and suitably protected 6-hydroxy sugars[4,5] are useful glycosyl acceptors for the preparation of several bioactive molecules[6] and some very important oligosaccharides.[7] In the early days, the synthetic routes of 6-hydroxy sugars need numerous, wasteful manipulation processes. Usually the bulky groups selectively hold up the 6-hydroxy position and are removed under certain conditions after the other hydroxies have been protected.[8] Therefore, an alternative approach is obligatory.

Per-*O*-TMS-protected glycosides were so sensitive to acid that they can be readily deprotected via acidic methanolysis.[9,10] The TMS group, which is an unusual protecting group, did not get much more attention for further research in earlier works. However, the value of TMS in carbohydrate research has been significantly increasing in recent years. Hung et al. have reported their regioselective one-pot protection of mono-saccharides from per-*O*-trimethylsilylated glycosides.[11] Witschi and Gervay-Hague revealed a method of regioselective nonenzymatic acetylation of monosaccharides.[12]

Currently we have applied considerable effort towards the construction of galactosylceramide (α-GalCer) with per-*O*-TMS galactosyl iodide.[13] We accidentally observed the removal of the TMS group at 6-position when per-*O*-trimethylsilylated galactose was treated with ammonium acetate in methanol. Concerning salt catalyst of detrimethylsilylation, Klaus and co-workers[14] reported that 6-*O*-TMS could be removed by potassium carbonate in methanol at 0 °C in 1994, but Hai and co-workers[15] stated that this method did not always work.

We herein disclose our findings on the detrimethylsilylation of carbohydrates under mild conditions (Scheme 1).

As a model system, per-*O*-trimethylsilylated α-D-galactose was treated with varying amounts of ammonium acetate and reaction solvent at room temperature. 2.0 equiv of NH_4OAc in co-solvent of CH_2Cl_2 and CH_3OH (v/v = 1/1) at rt afforded 6-detrimethylsilylated galactose **1b** in good to excellent yield.[16] In order to explore the application range, a series of TMS-protected mono and

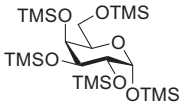
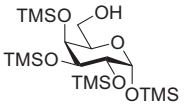
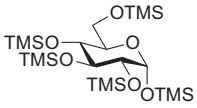
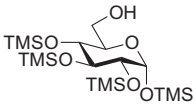
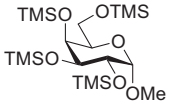
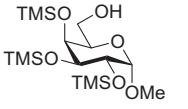
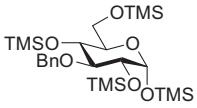
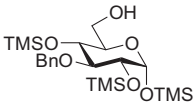
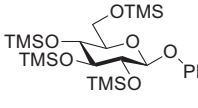
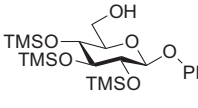
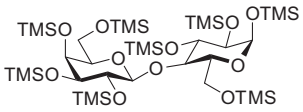
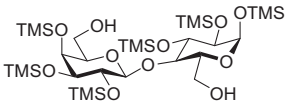
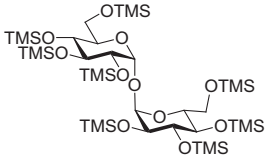
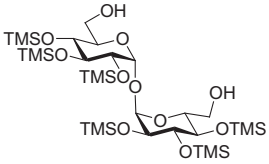
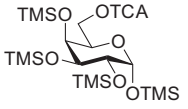
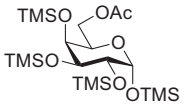
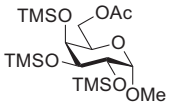
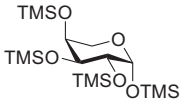


Scheme 1. 6-Detrimethylsilylation of carbohydrates.

* Corresponding author. Tel./fax: +86 571 88486676.
E-mail address: hnzzcyl@hotmail.com (Y. Cui).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.05.039

Table 1
6-Detrimethylsilylation of carbohydrates using NH_4OAc[a]

Entry	Substrates	Products	Time (h)	Yield[b] (%)
1	 **1a**	 **1b**	9	91
2	 **2a**	 **2b**	9	86
3	 **3a**	 **3b**	9	85
4	 **4a**	 **4b**	9	90
5	 **5a**	 **5b**	9	85
6	 **6a**	 **6b**	12	65
7	 **7a**	 **7b**	10	71
8	 [c] **1d**[c]	nr	24	0
9	 **1c**	nr	24	0
10	 **3c**	nr	24	0
11	 **8a**	nr	24	0

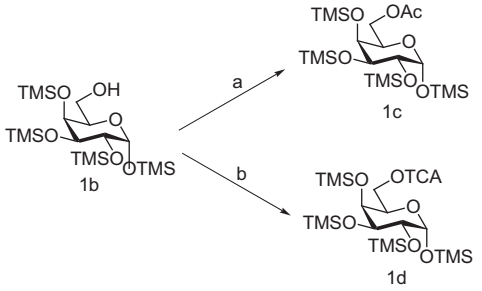
nr: No reaction.
[a] With 2.0 equiv of NH_4OAc in the co-solvent of CH_2Cl_2 and CH_3OH (v/v = 1/1) at rt.
[b] Isolated yield.
[c] TCA = trichloroacetimidate.

disaccharides were subjected to the detrimethylsilylation reactions and the results are presented in Table 1.

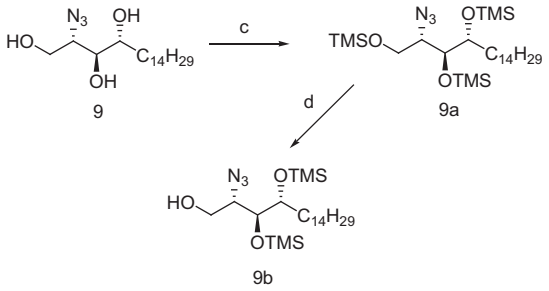
To our delight, only 6-*O*-TMS of per-*O*-trimethylsilylated mono-saccharides (entries 1–5) were selectively removed with good to excellent yields. Even the 3-*O*-Bn group (**3a**) did not have any influence on the selectivity of removing 6-*O*-TMS (entry 4). Additionally, we wanted to know whether the same results could be observed when disaccharides were treated under the same conditions. Per-*O*-trimethylsilylated lactose and trehalose (entries 6 and 7), both consist two primary *O*-TMS, were subjected to the same condition. Likewise, the primary *O*-TMS groups of disaccharides were selectively removed by ammonium acetate. Product **6b** and **7b** were separated in yield of 65% and 71%, respectively.

To confirm the position of free hydroxyl, **1b** was then added with Ac_2O in the presence of pyridine to afford **1c** in high yield (Scheme 2). All proton assignment was accomplished using COSY, and the position of Ac was determined via HMQC NMR data.

Now that ammonium acetate could selectively remove the primary *O*-TMS, what about secondary *O*-TMS? Firstly the free hydroxyl of **1b** reacted with Cl_3CCN in the presence of NaH to afford



Scheme 2. Reagents and conditions: (a) Ac_2O, pyridine, 2 h, rt 87%; (b) Cl_3CCN, NaH (60%), CH_2Cl_2, rt 2 h, 91%.



Scheme 3. Reagents and conditions: (c) TMSCl, HMDS, pyridine, 90%; (d) 2.0 equiv of NH_4OAc, $MeOH/CH_2Cl_2$, 10 h, rt, 82%.

1d. Compound **3c** was obtained with the same process of **1c**. Then **1c**, **1d** and **3c** (entries 8–10) were treated, respectively, in the co-solvent of CH_2Cl_2 and CH_3OH with ammonium acetate at rt for 24 h. To our surprise, no reaction was detected by TLC. As well, per-*O*-trimethylsilylated arabinose (**8a**) (entry 11) was stirred with ammonium acetate, and also no reaction was monitored via TLC.

Does this methodology selectively remove primary *O*-TMS in a molecule which is not a sugar? The experiment was extended to per-silylated sphingosine (**9a**) (Scheme 3). The sphingosine was per-silylated by trimethyl chlorosilane. Sequentially, only the primary *O*-TMS was removed in the presence of ammonium acetate in good yield to afford **9b**, which is known as a key intermediate for the preparation of α-GalCer.

In summary, we have developed a method for the regioselective removal of primary *O*-TMS from an array of mono and disaccharides in mild conditions and the new method has been successfully applied to the building of sphingosine intermediate (**9b**). The ammonium acetate could be easily removed by aqueous workup and the reaction is highly scalable due to the inexpensive cost of ammonium acetate. This approach offers high versatility that the deprotected free hydroxyl could be used as glycosyl acceptor or nucleophile for further chemical transformation.[9]

Acknowledgments

The work was supported financially by the National Natural Science Foundation of China (No. 30870553) and the Key International S&T Cooperation Project, China (No. 2010DFA34370).

References and notes

1. *The Essentials of Glycobiology*; Varki, A., Cummings, R., Esko, J., Freeze, H., Hart, G., Marth, J., Eds.; Cold Spring Harbor Laboratory Press: New York, 1999.
2. (a) Lee, D.; Taylor, M. S. *Synthesis* **2012**, *44*, 3421–3431; (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235.
3. Pierre, C.; Isabel, H.; David, P. G.; Bo, L.; Rebecca, A. J.; Romano, T. K.; Lavina, C. S.; Anthony, J. F.; Benjamin, G. D.; John, P. S. *J. Am. Chem. Soc.* **2006**, *128*, 1976–1981.
4. Dulayymi, J. R.; Baird, M. S.; Maximiliano, M. I.; Beken, S. V.; Grooten, J. *Tetrahedron Lett.* **2009**, *50*, 3702–3705.
5. Lei, F.; Fan, W.; Li, X. K.; Wang, S.; Hai, L.; Wu, Y. *Chin. Chem. Lett.* **2011**, *22*, 831–834.
6. Veerapen, N.; Reddington, F.; Salio, M.; Cerundolo, V.; Besra, G. S. *Bioorg. Med. Chem.* **2011**, *19*, 221–228.
7. (a) Li, H.; Li, B.; Song, H.; Breydo, L.; Baskakov, L. V.; Wang, L. X. *J. Org. Chem.* **2005**, *70*, 9990–9996; (b) Deng, L. M.; Liu, X.; Liang, X. Y.; Yang, J. S. *J. Org. Chem.* **2012**, *77*, 3025–3027; (c) Mensah, E. A.; Azzarelli, J. M.; Nguyen, H. M. *J. Org. Chem.* **2009**, *74*, 1650–1657.
8. (a) Reynolds, D. D.; Evans, W. L. *Org. Synth.* **1942**, *22*, 56; (b) Haider, A.; Williams, C. K. *C.R. Chim.* **2011**, *14*, 736–744; (c) Latli, B.; Hrapchak, M.; Seetharama, R.; Krishnamurthy, D.; Senanayake, C. H. *J. Labelled Compd. Radiopharm.* **2011**, *54*, 337–339; (d) Zhang, Z.; Yu, B. *J. Org. Chem.* **2003**, *68*, 6309–6313.
9. Jervis, P. J.; Cox, L. R.; Besra, G. S. *J. Org. Chem.* **2011**, *76*, 320–323.
10. Du, W. J.; Kulkarni, S. S.; Gervay-Hague, J. *Chem. Commun.* **2007**, *23*, 2336–2338.
11. (a) Wang, C. C.; Lee, J. C.; Luo, S. Y.; Kulkarni, S. S.; Huang, Y. W.; Lee, C. C.; Chang, K. L.; Hung, S. C. *Nature* **2007**, *446*, 896–899; (b) Wang, C. C.; Kulkarni, S. S.; Lee, J. C.; Luo, S. Y.; Hung, S. C. *Nat. Protoc.* **2008**, *3*, 97–113; (c) Chang, K. L.; Zulueta, M. M. L.; Lu, X. A.; Zhong, Y. Q.; Hung, S. C. *J. Org. Chem.* **2010**, *75*, 7424–7427; (d) Huang, T. Y.; Zulueta, M. M. L.; Hung, S. C. *Org. Lett.* **2011**, *13*, 1506–1509; (e) Hu, Y. P.; Lin, S. Y.; Huang, C. Y.; Zulueta, M. M. L.; Liu, J. Y.; Chang, W.; Hung, S. C. *Nat. Chem.* **2011**, *3*, 557–563.
12. Witschi, M. A.; Gervay-Hague, J. *J. Org. Lett.* **2010**, *12*, 4312–4315.
13. Schombs, M.; Park, F. E.; Du, W.; Kulkarni, S. S.; Gervay-Hague, J. *J. Org. Chem.* **2010**, *75*, 4891–4898.
14. Ronnow, T. E. C. L.; Meldal, M.; Bock, K. *Carbohydr. Res.* **1994**, *260*, 323–328.
15. Fan, W.; Wu, Y.; Li, X. K.; Yao, N.; Li, X.; Yu, Y. G.; Hai, L. *Eur. J. Med. Chem.* **2011**, *46*, 3651–3661.
16. Ammonium acetate (185.9 mg, 2.41 mmol) was added to a solution of **1a** (653.0 mg, 1.21 mmol) in the co-solvent of CH_2Cl_2 (5.0 mL) and CH_3OH (5.0 mL) at rt. The mixture was stirred and monitored by TLC. Upon consumption of starting substrate, the solvent was evaporated and the residue was dissolved in hexane (50 mL) and the organic phase was washed with water (3 × 50 mL), brine, dried with $MgSO_4$ and concentrated in vacuum. The mixture was purified by flash column chromatography (petroleum ether/ethyl acetate = 20:1) on silica gel to afford the desired product **1b** as a white solid (515.3 mg, 91%). R_f = 0.38 (petroleum ether/ethyl acetate = 15:1). δ_H (400 MHz, $CDCl_3$) 5.01 (1H, d, J = 3.0), 3.82–3.64 (4H, m), 3.46 (1H, t, J = 9.1), 3.34 (1H, dd, J = 9.1, 3.0), 1.78 (1H, t, J = 6.1 Hz), 0.23–0.07 (36H, m). δ_C (101 MHz, $CDCl_3$) 93.88, 73.95, 73.49, 71.94, 71.67, 61.64, 1.08, 0.76, 0.47, 0.27, 0.03, −0.27. ESI-MS: m/z = 491.1 $[M+23]^+$.