Regioselective Mono-Deprotection of Di-*tert*-butylsilylene Acetal Derived from 1,3-Diol with Ammonium Fluoride

Masaki Ohtawa, Hiroshi Tomoda, and Tohru Nagamitsu*

Graduate School of Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641

Received August 26, 2013; E-mail: nagamitsut@pharm.kitasato-u.ac.jp

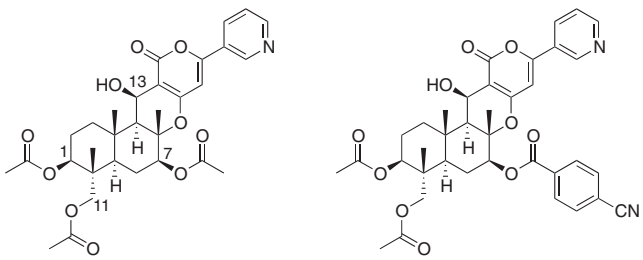
Here we report a novel and efficient method for the regioselective mono-deprotection of di-*tert*-butylsilylene acetals derived from 1,3-diols consisting of primary and secondary alcohols. The ammonium fluoride-mediated reactions of pyripyropene A derivative, thymidine and uridine derivatives, methyl β-D-glucofuranoside, and pyranoside derivatives each gave the corresponding primary alcohol with high regioselectivity.

Selective mono-silylation of the more hindered hydroxy group of 1,3-diols is frequently required in organic synthesis, but cannot be achieved by direct methods and generally requires a two-step sequence, i.e., disilylation of a 1,3-diol followed by selective mono-deprotection at the less hindered site,[1,2] or regioselective mono-deprotection of a di-*tert*-butylsilylene acetal derived from a 1,3-diol. Although the use of a silylene acetal in the latter case sometimes has the advantage of allowing selective protection of a 1,2- or 1,3-diol unit in a polyol compound,[3] the regioselective mono-deprotection usually needs strong acids ($BF_3 \cdot OEt_2$ or $BF_3 \cdot SMe_2$;[4a,4b] Scheme 1, eq 1) or bases (*n*-BuLi[4c] or *t*-BuLi;[4d] Scheme 1, eq 2) as cleavage reagents. The latter procedure is therefore problematic for acid- or base-labile substrates. In the present paper, we describe a novel method for the regioselective mono-deprotection of di-*tert*-butylsilylene acetals derived from 1,3-diols consisting of primary and secondary alcohols.

Results and Discussion

In recent years, structure–activity relationship (SAR) studies of pyripyropene A (PPPA, **1**), a potent and selective inhibitor toward acyl-CoA:cholesterol acyltransferase 2 (ACAT2) and a promising candidate for new cholesterol-lowering or anti-atherosclerotic agents, have been in progress in our laboratory.[5] We found that the 7-*p*-cyanobenzoyl PPPA derivative **2** has higher ACAT2 inhibitory activity than **1** (Figure 1).

We next focused on the synthesis of new 7-*p*-cyanobenzoyl PPPA derivatives with chemical modifications at the 1- and 11-positions, for further SAR studies. It was easy to synthesize derivatives with the same acyl groups at the 1- and 11-positions, but many attempts to prepare new derivatives with different acyl groups at the 1- and 11-positions were unsuccessful because



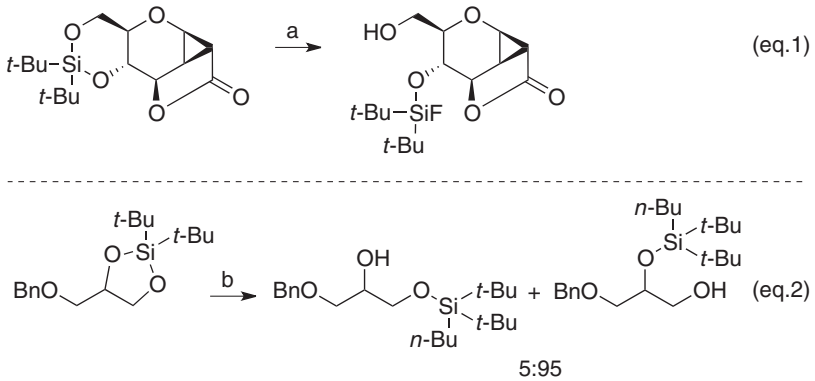
PPPA (1)

	IC_{50}/μM
ACAT2	0.07

2

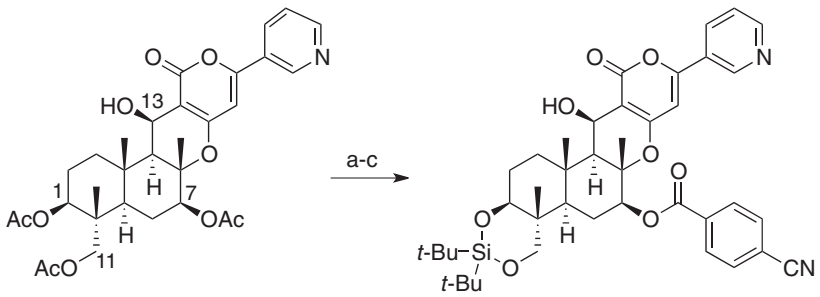
	IC_{50}/μM
ACAT2	0.0009

Figure 1. Structures of PPPA (**1**) and 7-*p*-cyanobenzoyl PPPA derivative **2**.



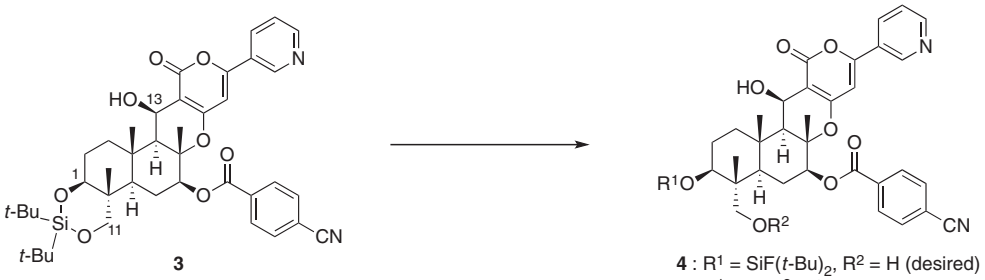
Scheme 1. Known procedures for regioselective mono-deprotection of di-*tert*-butylsilylene acetal. *Reagents and conditions*: (a) allyltrimethylsilane, $BF_3 \cdot OEt_2$, toluene, 85 °C, 95%; (b) *n*-BuLi, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, −78 °C, 83%.

Published on the web January 15, 2014; doi:10.1246/bcsj.20130237



Scheme 2. Synthesis of di-*tert*-butylsilylene acetal-protected PPPA derivative **3**. *Reagents and conditions*: (a) NaOMe, aq. MeOH, rt, quantitative; (b) $(t\text{-Bu})_2Si(OTf)_2$, 2,6-lutidine, DMF, 0 °C, quantitative; (c) *p*-cyanobenzoic acid, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, catalyst *N*,*N*-dimethylpyridin-4-amine, CH_2Cl_2, rt, 81%.

Table 1. Optimization of Reaction Conditions for Regioselective Mono-Deprotection of Di-*tert*-butylsilylene Acetal-Protected PPPA Derivative **3**



Entry	Conditions[a)]	Yield/%			
		4	**5**	**6**	Recovered **3**
1	TBAF (2.5 equiv), AcOH (2.5 equiv), THF, 10 min	—	—	quant.	—
2	TBAF (1.0 equiv), AcOH (1.0 equiv), THF, 2 h	trace[b)]	—	41	47
3	$Et_3N \cdot 3HF$ (1 equiv), THF, 10 min	—	—	quant.	—
4	$Et_3N \cdot 3HF$ (0.3 equiv), THF, 10 min	—	—	41	44
5	CsF (10 equiv), 10% aq. MeCN, 24 h	—	—	—	89
6	KF (10 equiv), 10% aq. THF, 24 h	—	—	—	92
7	NH_4F (1 equiv), MeOH, 5 h	18	1	2	49
8	NH_4F (5 equiv), MeOH, 5 h	50	8	21	3
9	NH_4F (10 equiv), MeOH, 3 h	81	5	11	—
10	NH_4F (10 equiv), DMF, 3 h	83	12	—	—
11	NH_4F (10 equiv), MeOH/DMF (1:1), 3 h	80	6	—	—
12	NH_4F (10 equiv), DMSO, 18 h	15	—	62	—
13	NH_4F (10 equiv), Et_2O, 24 h	—	—	—	95
14	NH_4F (10 equiv), THF, 24 h	10	—	9	75
15	NH_4F (10 equiv), MeCN, 8 h	63	7	21	—
16	NH_4F (10 equiv), acetone, 6 h	75	10	9	—

a) All reactions were carried out at room temperature. b) Detected by TLC and ESI-MS.

regioselective protection or acylation was difficult. Finally, the regioselective mono-deprotection of di-*tert*-butylsilylene acetal-protected PPPA derivative **3**,[5b] which was synthesized from **1** using silylene acetal, as described above (Scheme 2), was investigated (Table 1).

First, the di-*tert*-butylsilylene acetal **3** was subjected to basic conditions (*n*-BuLi[4c]) and acidic conditions ($BF_3 \cdot SMe_2$[4b]) reported previously. Consequently, only side reactions such as de-esterification and dehydration of the 13-hydroxy group under all conditions proceeded, without giving the desired corresponding primary alcohols. Therefore, we next embarked on the development of a novel method using a fluoride anion. Generally, the fluoride anion, with a high affinity toward silicon, is useful for desilylation reactions in organic chemistry. However, regioselective mono-deprotection of dialkylsilylene acetals with the fluoride anion seems to be difficult and has

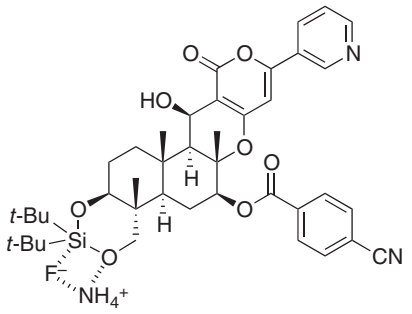


Figure 2. Proposed transition-state in regioselective mono-deprotection of di-*tert*-butylsilylene acetal.

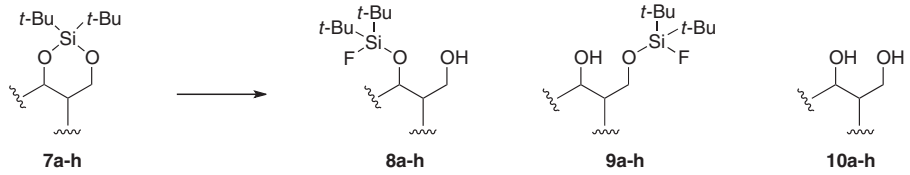
not been reported so far.[6] We expected that hydrogen-bond formation by the fluoride anion in the reaction would reduce its nucleophilicity to silicon and result in regioselective mono-deprotection. Initially, tetra-*n*-butylammonium fluoride, the most typical desilylating reagent, in the presence of acetic acid was examined (Entries 1 and 2). Consequently, triol **6** was obtained as the major product, without the desired primary alcohol **4**. Furthermore, treatment with $Et_3N \cdot 3HF$[7] also gave the same results (Entries 3 and 4). The use of inorganic fluoride reagents such as CsF[8] and KF[9] in aqueous solution led to no reaction (Entries 5 and 6). Subsequent treatment with NH_4F (1 equiv) in MeOH afforded the desired **4** (Entry 7), but in poor yield (18%), with recovered **3** (49%). Therefore, optimization of the reaction conditions using NH_4F was conducted. An increase in the number of equivalents of NH_4F improved the yield of the desired **4**, and the best yields were obtained by treatment with 10 equiv of NH_4F (Entries 8 and 9). Next, various solvents were investigated in the regioselective mono-deprotection of **3**. The use of dimethylformamide (DMF) and a 1:1 mixture of MeOH and DMF instead of MeOH gave almost the same results (Entries 10 and 11). In contrast, the reaction in dimethyl sulfoxide (DMSO) gave only a low yield of **4**, with a large amount of the undesired 1,3-diol **6** (Entry 12). Moreover, the use of ethers such as tetrahydrofuran (THF) and Et_2O led to no reaction and a very low yield (10%) of **4** with recovered **3** (75%) (Entries 13 and 14). Although the reactions in MeCN and acetone afforded the desired **4** in good yield regioselectively, the reactions proceeded a little more slowly than those in MeOH and DMF. As a result, MeOH and DMF proved to be the most suitable solvents for the regioselective mono-deprotection of di-*tert*-butylsilylene acetal.

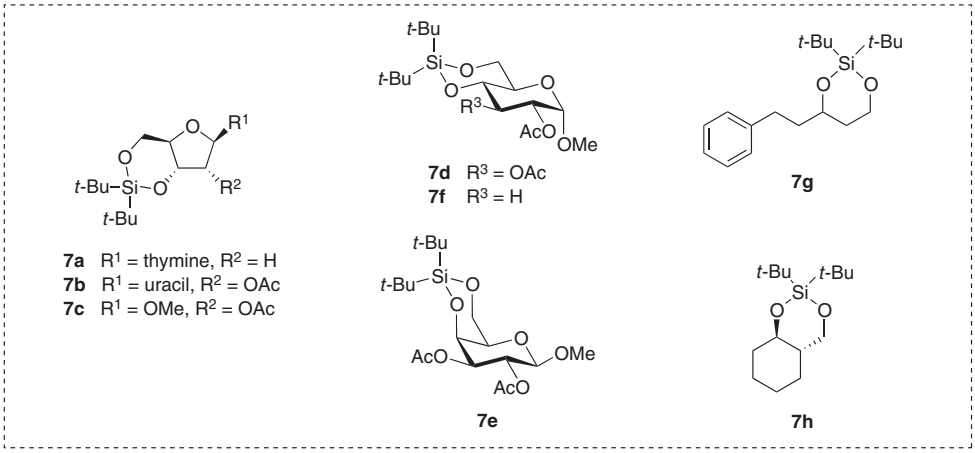
The regioselectivity observed in these reactions probably comes from kinetically controlled ring cleavage, in which the ammonium ion is located beside the more sterically accessible oxygen through Coulombic forces, prior to delivery of fluoride, as shown in Figure 2. In addition, reduction of the nucleophilicity of the fluoride anion toward silicon, caused by formation of strong hydrogen-bonds with ammonium ions in the reaction,[10] will contribute to the regioselective mono-deprotection.

We next investigated the scope of this reaction (Table 2). First, the regioselective mono-deprotection reactions of di-*tert*-butylsilylene acetal-protected D-glucofuranosides with NH_4F were examined. The thymidine derivative **7a**,[11] which is a deoxyribonucleoside, was treated with NH_4F in MeOH at 0 °C, and provided the desired primary alcohol **8a** in 81% yield, accompanied by a small amount of undesired secondary alcohol **9a** and diol **10a** (Entry 1). The reactions of uridine derivative **7b**,[12] which is a ribonucleoside, and methyl β-D-glucofuranoside **7c**[12] with NH_4F in MeOH at 0 °C also furnished the primary alcohols **8b** and **8c** in yields of 83% and 86%, respectively, with trace amounts of diols **10b** and **10c**[13] (Entries 2 and 3). The number of equivalents of NH_4F in Entries 1–3 was optimized to afford the corresponding primary alcohols in high yields.[14] In contrast, the reactions of methyl α-D-glucopyranoside **7d**[12] and methyl β-D-galactopyranoside **7e**[15] with NH_4F (10 equiv) in MeOH at room temperature afforded the desired primary alcohols **8d** and **8e** in moderate yields, with about 40% of recovered starting materials[16] (Entries 4 and 6). The starting materials were not consumed completely because the mono-deprotected **8d** and **8e** could be recyclized under the reaction conditions to provide the corresponding starting materials **7d** and **7e** with high thermodynamic stability.[17] To try to prevent recyclization, Dess–Martin periodinane (DMP) was added to the reaction mixtures to oxidize the resulting primary alcohols to the corresponding aldehydes (Entries 5 and 7). DMF was used as the solvent instead of MeOH. The corresponding aldehyde products were not obtained, but, surprisingly, the yields of the desired **8d** and **8e** increased, and only small amounts of the starting materials **7d** and **7e**, respectively, were recovered. It seems likely that temporary protection of the resulting hydroxy group with an active species originating from hypervalent iodine prevented recyclization; mechanistic studies of the effect of DMP in the NH_4F-mediated regioselective mono-deprotection reaction are currently in progress in our laboratory. In contrast, the reaction of 3-deoxyglucose derivative **7f**[12] with NH_4F (10 equiv) in MeOH at room temperature for 0.5 h gave the desired **8f** in 39% yield, accompanied by diol **10f** in 14% yield and recovered starting material in 42% yield (Entry 8). Prolonging the reaction time increased the yield of the corresponding diol **10f** and decreased the yields of the desired **8f** and recovered starting material **7f** (Entry 9). Moreover, the reactions of di-*tert*-butylsilylene acetals **7g**[4b] and **7h**,[12] derived from simpler 1,3-diols, with NH_4F (10 equiv) in MeOH or DMF at room temperature afforded only trace amounts of the desired **8g** and **8h**, regardless of the reaction time (Entries 10–13), and the yields of diols **10g** and **10h** and recovered starting materials **7g** and **7h** followed the same trends as those shown by **10f** and **7f**. These results indicate that moderate steric bulkiness around the secondary hydroxy group is important for avoiding over-deprotection of the desired primary alcohol with the fluorosilyl ether.

Next, we focused on the regioselective mono-deprotection of other types of di-*tert*-butylsilylene acetals (Table 3). Although treatment of di-*tert*-butylsilylene acetal **7i**,[12] consisting of primary and tertiary alcohols, with NH_4F (10 equiv) in MeOH at room temperature provided the desired primary alcohol **8i**, the reaction proceeded very slowly and gave **8i** in only low yield (35%), accompanied by unreacted **7i** (31%) and the diol **10i** (30%) (Entry 1). Formation of the primary alcohol **8i**, i.e., the di-*tert*-butylfluorosilyl ether of the tertiary alcohol, would probably be difficult because of its steric bulkiness. In contrast, the reaction of di-*tert*-butylsilylene acetal **7j**, derived from a 1,4-diol with NH_4F (10 equiv) in MeOH at room temperature, led to no reaction (Entry 2), even though the reaction of di-*tert*-

Table 2. Investigation of Scope of Regioselective Mono-Deprotection of Di-*tert*-butylsilylene Acetals





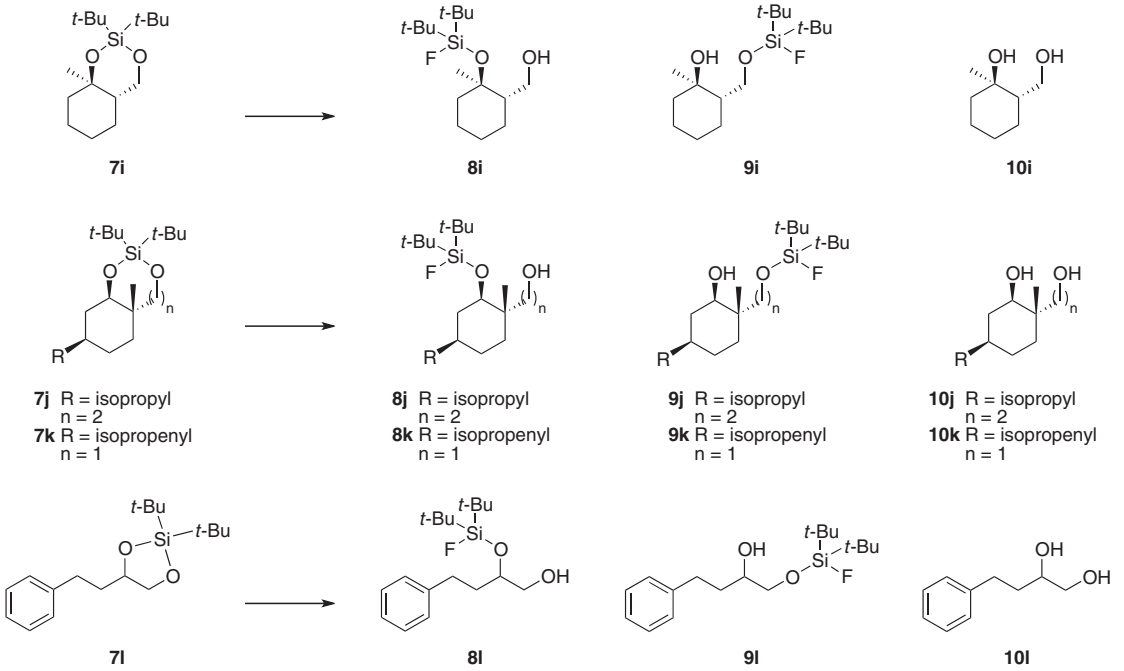
Entry	7	Conditions	Yield/%			
			8a–8h	**9a–9h**	**10a–10h**	**7a–7h**
1	**a**	NH_4F (5 equiv), MeOH, 0 °C, 3 h	81	4	13	—
2	**b**	NH_4F (7 equiv), MeOH, 0 °C, 2 h	83	—	trace	—
3	**c**	NH_4F (5 equiv), MeOH, 0 °C, 3.5 h	86	—	7	—
4	**d**	NH_4F (10 equiv), MeOH, rt, 6 h	58	—	—	37
5	**d**	NH_4F (10 equiv), DMP (2 equiv), DMF, rt, 2 h	85	—	—	7
6	**e**	NH_4F (10 equiv), MeOH, rt, 6 h	54	—	—	44
7	**e**	NH_4F (10 equiv), DMP (2 equiv), DMF, rt, 2 h	82	—	—	9
8	**f**	NH_4F (10 equiv), MeOH, rt, 0.5 h	39	—	14	42
9	**f**	NH_4F (10 equiv), MeOH, rt, 1 h	28	—	32	18
10	**g**	NH_4F (10 equiv), DMF, rt, 2 h	trace	—	9	82
11	**g**	NH_4F (10 equiv), DMF, rt, 24 h	trace	—	45	33
12	**h**	NH_4F (10 equiv), MeOH, rt, 2 h	5	—	4	77
13	**h**	NH_4F (10 equiv), MeOH, rt, 20 h	7	—	51	35

butylsilylene acetal **7k**, derived from a 1,3-diol, provided the desired primary alcohol **8k** in modest yield (Entry 3). Furthermore, the reaction of di-*tert*-butylsilylene acetal **7l**, derived from a simple 1,2-diol, with NH_4F (10 equiv) in MeOH at room temperature gave rise to the undesired diol **10l** in high yield, as expected (Entry 4); the reason could be the same as that used to explain the reactions of **7f**, **7g**, and **7h**. These results indicate that suitable substrates for NH_4F-mediated regioselective mono-deprotection reactions are di-*tert*-butylsilylene acetals derived from 1,3-diols consisting of a primary alcohol and a secondary alcohol with moderate steric bulkiness. This is one of the limitations of this reaction.

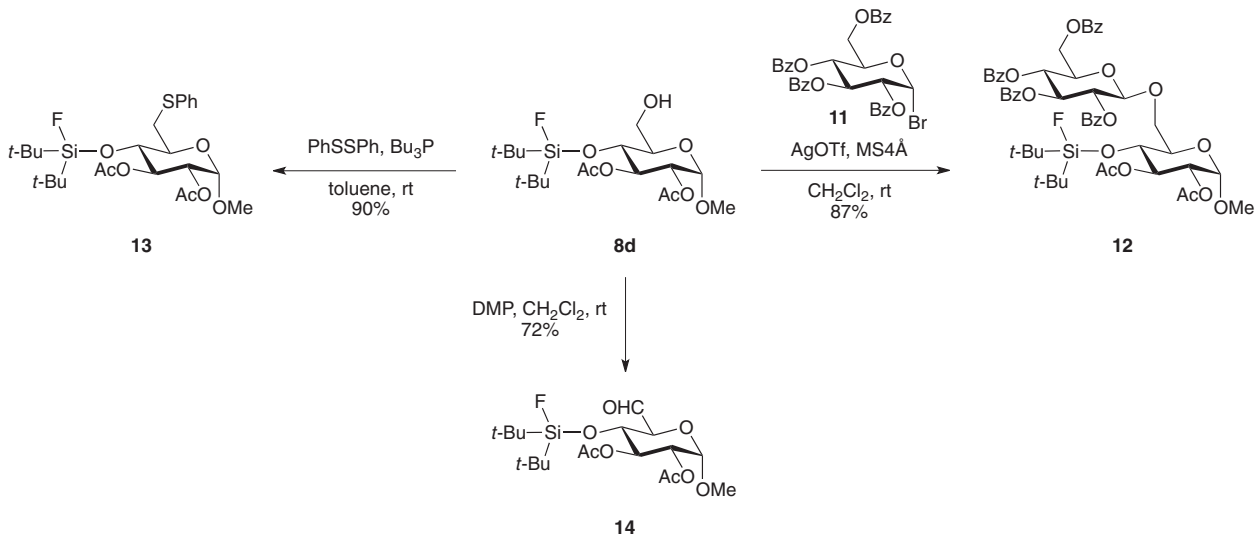
Although they have some limitations, NH_4F-mediated regioselective mono-deprotection reactions of suitable di-*tert*-butylsilylene acetals are very useful for preparation of the corresponding primary alcohols bearing fluorosilyl ethers under mild conditions. Furthermore, the primary alcohols are relatively stable, except under basic conditions,[4c] and are useful compounds for further chemical transformations. Pagenkopf reported that the simple fluorosilane derivatives are stable under weakly acidic conditions and in several transformations, including Jones oxidation, PCC oxidation, and the Finkelstein reaction.[4b] In our previous SAR studies, the syntheses of various new PPPA derivatives were achieved by chemical modifications of primary alcohol **4**.[5b]

To investigate further applications of the NH_4F-mediated regioselective mono-deprotection reaction, chemical transformations of the sugar **8d**, which is one of the products easily prepared by the reaction, were attempted in various reactions such as glycosylation, phenyl sulfenylation by an S_N2 reaction, and Dess–Martin oxidation (Scheme 3). The glycosylation of **8d** as an acceptor with donor **11** in the presence of $AgOTf^6$ as an activator proceeded smoothly to give the desired disaccharide **12** in 87% yield (β only). Phenyl sulfenylation of **8d** was also achieved by treatment with diphenyl disulfide and tributylphosphine,[18] producing **13** in 90% yield. Finally, **8d** was converted to aldehyde **14** in 72% yield by Dess–Martin oxidation.[19]

Table 3. Investigation of Scope of Regioselective Mono-Deprotection of Di-*tert*-butylsilylene Acetals



Entry	7	Conditions	Yield/%			
			8i–8l	9i–9l	10i–10l	7i–7l
1	**i**	NH_4F (10 equiv), MeOH, rt, 20 h	35	—	30	31
2	**j**	NH_4F (10 equiv), MeOH, rt, 24 h	—	—	5	91
3	**k**	NH_4F (10 equiv), MeOH, rt, 4 h	56	—	trace	35
4	**l**	NH_4F (10 equiv), DMF, rt, 14 h	trace	—	88	—



Scheme 3. Chemical transformations of primary alcohol **8d** obtained by regioselective mono-deprotection of di-*tert*-butylsilylene acetal.

Conclusion

We have developed a novel and efficient method for the regioselective mono-deprotection of di-*tert*-butylsilylene acetals derived from 1,3-diols consisting of a primary alcohol and a secondary alcohol with moderate steric bulkiness. This NH_4F-mediated reaction allows easy access to the corresponding primary alcohol bearing a fluorosilyl ether. Investigations of further applications of this reaction using other di-*tert*-butylsilylene acetals are in progress in our laboratory.

This research was partly supported by a Grant-in-Aid for Young Scientists from the ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan (MO). We

thank Ms. N. Sato and Dr. K. Nagai (Kitasato University) for kindly measuring NMR and MS spectra.

Supporting Information

The experimental procedure and spectroscopic data of newly synthesized compounds are included in the Supporting Information. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

References

1 P. G. M. Wuts, T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, 4th ed., Wiley-Interscience, New York, **2006**, p. 16.

2 P. J. Kocienski, *Protecting Groups*, 3rd ed., Thieme, Stuttgart, **2003**, p. 187.

3 B. M. Trost, C. G. Caldwell, E. Murayama, D. Heissler, *J. Org. Chem.* **1983**, *48*, 3252.

4 a) M. Yu, V. Lynch, B. L. Pagenkopf, *Org. Lett.* **2001**, *3*, 2563. b) M. Yu, B. L. Pagenkopf, *J. Org. Chem.* **2002**, *67*, 4553. c) K. Tanino, T. Shimizu, M. Kuwahara, I. Kuwajima, *J. Org. Chem.* **1998**, *63*, 2422. d) T. Mukaiyama, I. Shiina, K. Kimura, Y. Akiyama, H. Iwadare, *Chem. Lett.* **1995**, 229.

5 a) M. Ohtawa, H. Yamazaki, S. Ohte, D. Matsuda, T. Ohshiro, L. L. Rudel, S. Ōmura, H. Tomoda, T. Nagamitsu, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1285. b) M. Ohtawa, H. Yamazaki, D. Matsuda, T. Ohshiro, L. L. Rudel, S. Ōmura, H. Tomoda, T. Nagamitsu, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2659. c) M. Ohtawa, H. Yamazaki, S. Ohte, D. Matsuda, T. Ohshiro, L. L. Rudel, S. Ōmura, H. Tomoda, T. Nagamitsu, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3798.

6 The regioselective mono-deprotection reaction of 4,6-tetra-isopropyl-1,3-disiloxane-1,3-diyl-protected pyranoside by treatment with HF·pyridine was reported. T. Ziegler, R. Dattmann, M. Duszenko, *Carbohydr. Res.* **2000**, *327*, 367.

7 M. C. Pirrung, S. W. Shuey, D. C. Lever, L. Fallon, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1345.

8 P. F. Cirillo, J. S. Panek, *J. Org. Chem.* **1990**, *55*, 6071.

9 J. N. Kremsky, N. D. Sinha, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2171.

10 a) A. F. Wells, *Structural Inorganic Chemistry*, 4th ed., Oxford University Press, Oxford, **1975**, p. 640. b) B. Barbiellini, Ch. Bellin, G. Loupias, T. Buslaps, A. Shukla, *Phys. Rev. B: Condens. Matter Mater. Phys.* **2009**, *79*, 155115.

11 K. Furusawa, K. Ueno, T. Katsura, *Chem. Lett.* **1990**, 97.

12 The synthesis of **7b**–**7d**, **7f**, and **7h**–**7l** are described in the Supporting Information.

13 S. Iñigo, M. T. Porro, J. M. Montserrat, L. E. Iglesias, A. M. Iribarren, *J. Mol. Catal. B: Enzym.* **2005**, *35*, 70.

14 The reactions of **7a**–**7c** with 10 equiv of NH_4F decreased the yields of the desired primary alcohols **8a**–**8c**.

15 D. Kumagai, M. Miyazaki, S.-i. Nishimura, *Tetrahedron Lett.* **2001**, *42*, 1953.

16 The reactions for longer reaction times, at higher temperatures, and by addition of further NH_4F, each gave rise to the corresponding diol as a major product.

17 The retreatment of compound **8d** with NH_4F (10 equiv) in MeOH at room temperature gave the recyclized acetal **7d** in 19% yield, accompanied by diol **10d** (44%) and starting material (23%). Recyclization of **8d** and **8e** in the regioselective mono-deprotection reaction of di-*tert*-butylsilylene acetals **7d** and **7e** could therefore also proceed.

18 F. S. González, H. H. Baer, *Carbohydr. Res.* **1990**, *202*, 33.

19 D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155.