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SELECTIVE DEPROTECTION OF METHYLENE ACETAL AND MOM ETHER IN THE PRESENCE OF KETAL-TYPE PROTECTIVE GROUPS: REMARKABLE EFFECT OF TBSOTf†

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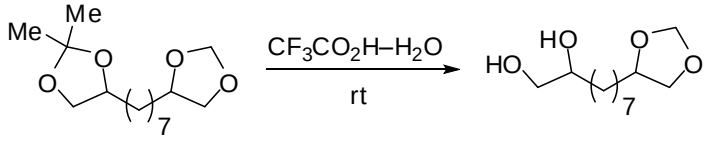
Abstract – A novel procedure for highly selective deprotection of methylene acetals and MOM (methoxymethyl) groups in the presence of ketal-type protective groups has been developed. The method, which utilizes a combination of TBSOTf and 2,2'-bipyridyl, displays a completely opposite selectivity compared with those of acid-mediated deprotection protocols.

INTRODUCTION

In the area of organic synthesis, acetals and ketals are among the most widely employed protective groups for aldehydes and ketones.[1] In addition, various acetal and ketal containing groups, such as MOM, BOM, acetonides and benzylidene acetals, have also been developed for protection of alcohols and diols. These protective groups are easily removed utilizing acidic conditions to produce the parent carbonyl and alcohol compounds. It is well-known that under these conditions ketals are deprotected more rapidly than acetals owing to the relative stabilities of the respective oxonium ion intermediates.[2] The reactivities of acetal and ketal protective groups display the same trend, and methylene acetals are more robust diol protecting groups under acidic conditions than their counterparts. In fact, acetonides are preferentially cleaved under acidic conditions in the presence of methylene acetals[3] (Scheme 1). In contrast, it is often difficult to cleave methylene acetals using mildly acidic conditions and, as a result, they are rarely used in organic synthesis because strong Lewis acids often need to be employed for their removal.[1]

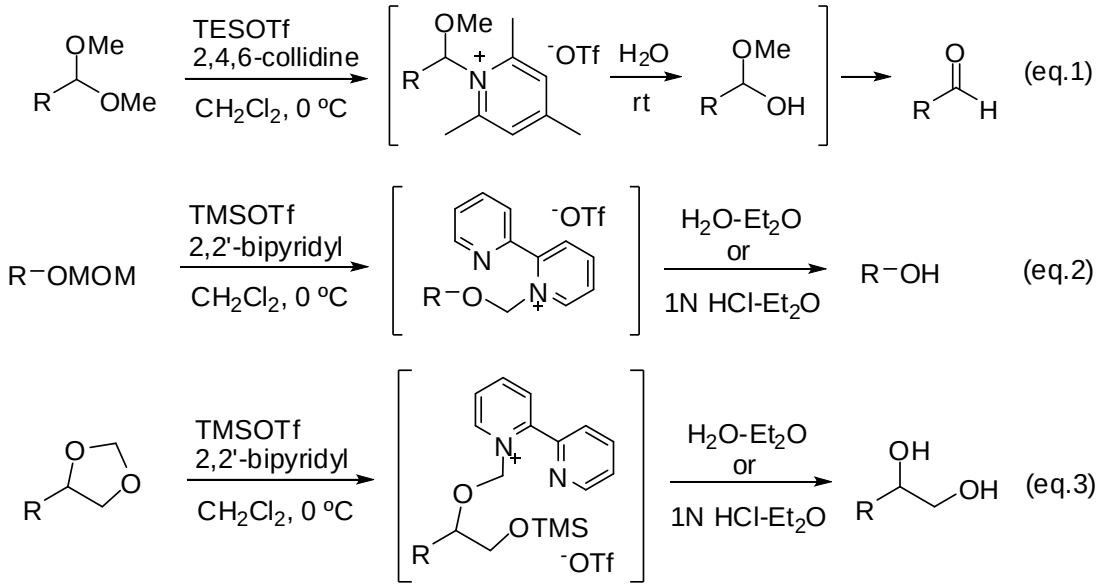


1a **2** (87%)

Scheme 1. Deprotection of **1a**, containing an acetonide and methylene acetal, under acidic conditions

† *This paper is dedicated to Professor Dr. Ei-ichi Negishi on the occasion of his 77th birthday.*

In recent studies, we investigated the reactivity of stable cationic species, including pyridinium-type salts generated by the reaction of acetals with TESOTf and 2,4,6-collidine. These salts were found to readily react with various nucleophiles including water (Scheme 2, eq. 1).[4]

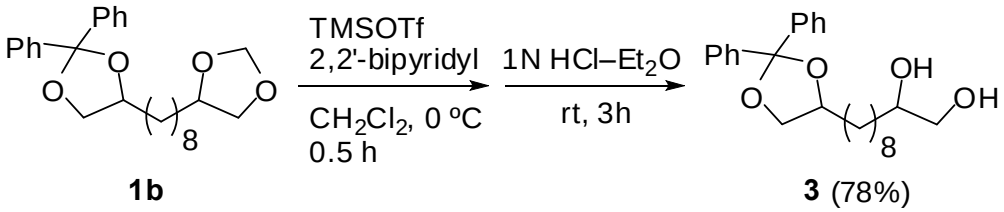


Scheme 2. Mild deprotection of acetals via the corresponding pyridinium salts

The results of this effort showed that the process, involving formation and hydrolysis of pyridinium salts, serves as a mild method for deprotection of acetal groups, THP and MOM ethers, as well as methylene acetals.[5-7] In the cases of MOM and related ethers, the combination of TMSOTf (or TESOTf) and 2,2'-bipyridyl can be used for effective deprotection.[6] In this process, 2,2'-bipyridylium salts are formed *in situ* and readily undergo hydrolysis to generate hemiacetals in routes to formation of parent alcohols (Scheme 2, eq. 2). The conditions employed are sufficiently mild to enable acid-labile groups, such as TBS and trityl (triphenylmethyl), to survive the reaction. It is noteworthy that, depending on the work-up conditions utilized to treat the intermediates, methylene acetals are also cleaved to afford the corresponding diols and their derivatives.[7] For example, employment of acidic work-up (*eg.*, 1N HCl) leads to formation of fully deprotected diols (Scheme 2, eq. 3), whereas basic work-up (satd. K_2CO_3 aq) can be employed to regioselectively generate monosilylated diols. Finally, methanolysis of cationic intermediates produces MOM protected diols in a regioselective manner.

The results of the studies described above indicate that TMSOTf (or TESOTf) would be capable of distinguishing between the different steric environments present in bis-acetals that contain the less crowded oxygen of methylene acetals. Initial work aimed at probing the selective deprotection process focused on the mixed ketal/acetal **1b**, possessing a bulky benzophenone ketal and unhindered methylene acetal. Benzophenone ketals are known to be cleaved using weakly acidic conditions, such as AcOH or

dilute HCl.[1] In contrast, the results of this study showed that the methylene acetal moiety in **1b** is selectively removed employing the TMSOTf based deprotection method (Scheme 3).[7b]

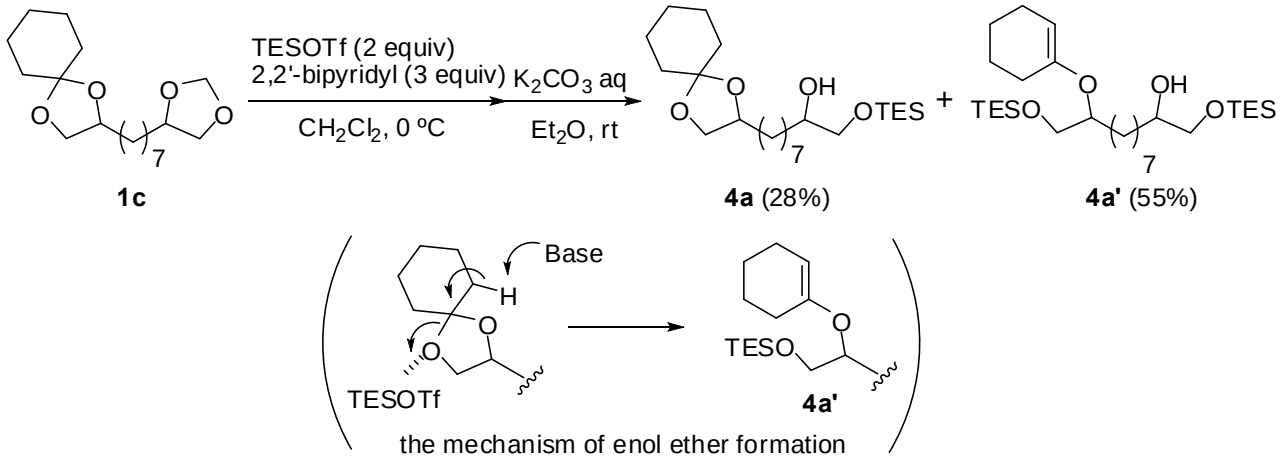


1b **3** (78%)

Scheme 3. Selective deprotection of a methylene acetal in the presence of a benzophenone ketal

RESULTS AND DISCUSSION

In a more thorough investigation, summarized below, we explored the scope and limitations of the novel method for highly selective deprotection of acetals in the presence of ketals that takes advantage of the remarkable properties of TBSOTf. In the initial phase of this effort, we investigated reactions of **1c**, which contains a methylene acetal and a cyclohexylidene ketal. An attempt to promote selective deprotection of **1c** using TESOTf and 2,2'-bipyridyl followed by base treatment led to formation of **4a** in a 28% yield. Moreover, enol ether **4a'** was produced as the major product (55%) in this process through β-elimination of the TESOTf activated cyclohexylidene acetal (Scheme 4).



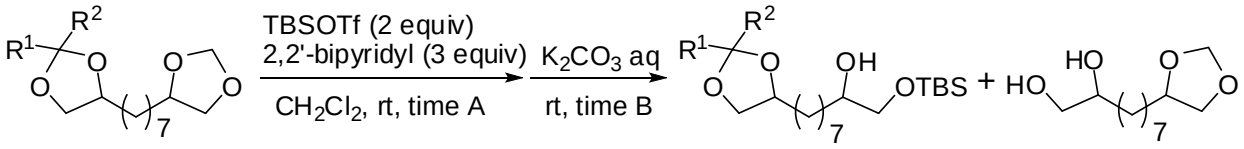
1c **4a** (28%) **4a'** (55%)

Scheme 4. Initial attempt to promote selective deprotection of methylene acetal in the presence of cyclohexylidene acetal by using the TESOTf–2,2'-bipyridyl combination

This observation indicated that the steric bulkiness of TESOTf was insufficient to discriminate between the oxygens in the methylene acetal and the cyclohexylidene ketal moieties. Consequently, we next

investigated the use of more bulky TBSOTf in this process and found that the selectively acetal-deprotected product **4b** is generated exclusively in a 92% (Table 1, entry 1). In addition, the results showed that the methylene acetal group can be preferentially cleaved when other ketal protective groups are present. This selectivity is observed even in bis-ketal/acetals containing cyclopentylidene ketals, which are typically more highly susceptible to acid-catalyzed hydrolysis than cyclohexylidene ketals and acetonides[8] (Table 1, entries 2 and 3). As expected, a contrastingly different reaction profile is observed when **1a** is subjected to an acid-catalyzed deprotection reaction, which leads to formation of ketal deprotected product **2** (Scheme 1, Table 1, entry 4).

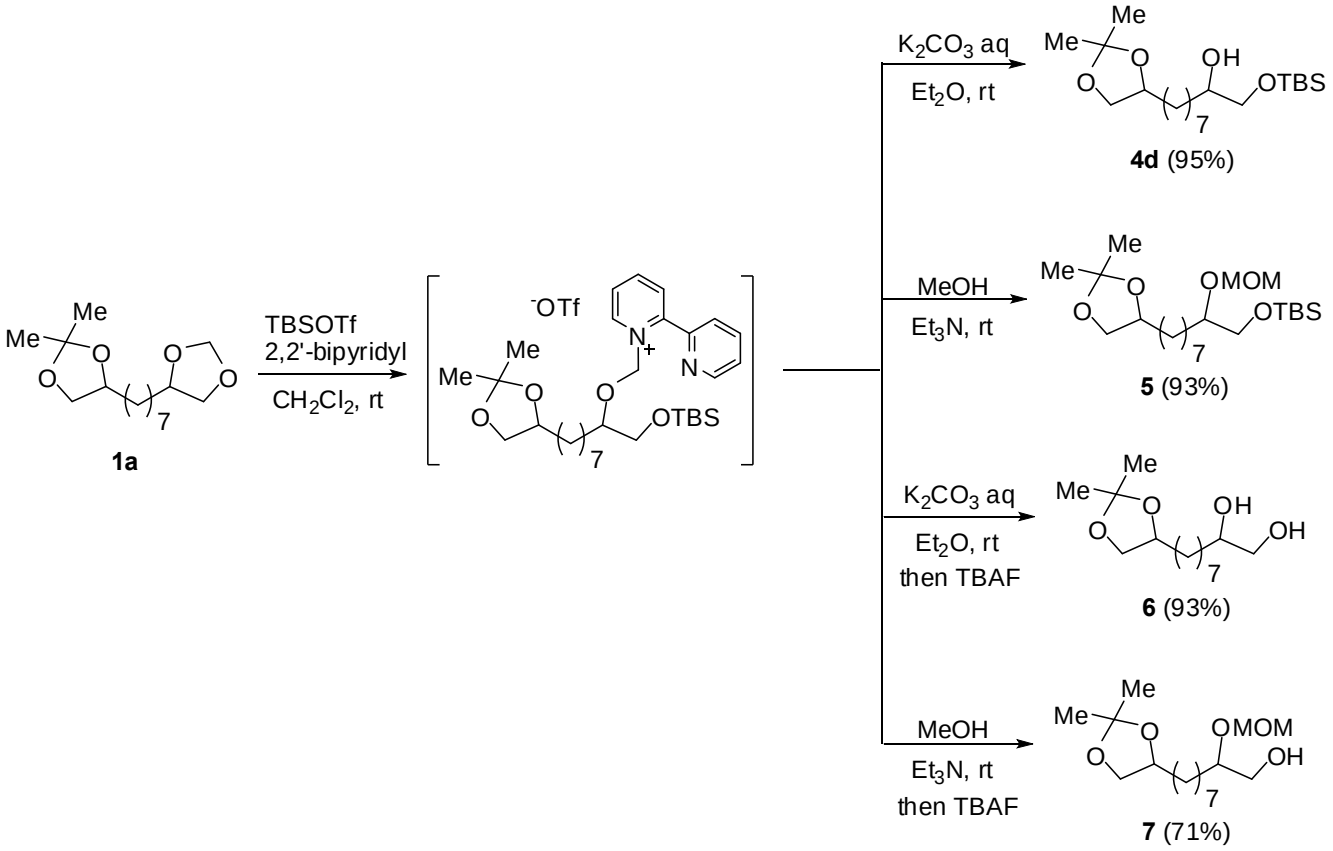
Table 1. Selective deprotection of a methylene acetal in the presence of ketal protective groups by using TBSOTf



entry	R^1	R^2	time A (h)	time B (h)	yield (%)
1	$-(CH_2)_5-$ (**1c**)		1.5	8	92 (**4b**)
2	$-(CH_2)_4-$ (**1d**)		0.5	7	96 (**4c**)
3	Me	Me (**1a**)	1.5	12	95 (**4d**)
4[a]	Me	Me (**1a**)	–	1.5	0 (87 (**2**))[b]

[a] The reaction was conducted under acidic conditions (CF_3CO_2H-H_2O). [b] The yield of **2** is indicated in the parenthesis.

Additional studies showed that the TBSOTf based method can be employed in a diverse array of selective deprotection reactions of methylene acetals (Scheme 5). For example, basic work-up of the intermediate, 2,2'-bipyridilium salt, formed by treatment of **1a** with the TBSOTf–2,2'-bipyridyl combination, affords the mono-TBS protected diol **4d** in 95% yield. In addition, treatment of the salt with methanol and triethylamine results in regioselective generation of the MOM and TBS protected diol **5** in high yield (93%). Finally, conversions of the salt derived from **1a** to diol **6** and mono-MOM protected diol **7** are achieved by using a one-pot protocol involving initial work-up with saturated K_2CO_3 aqueous solution and methanol, respectively, followed by treatment with TBAF/THF solution in one-pot.

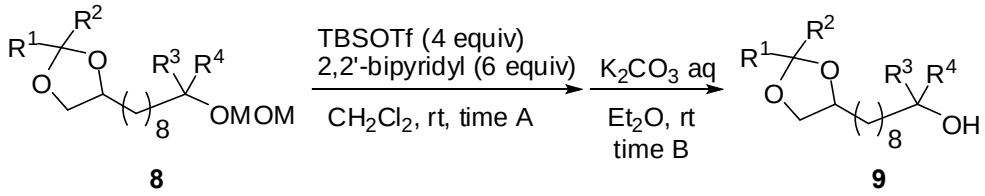


Scheme 5. Diverse deprotection reactions of the methylene acetal in the presence of acetonide function

Owing to the fact that MOM ethers also contain sterically unhindered acetal moieties, we presumed that they would be cleaved in preference to ketal protective groups. A method for selective deprotection of MOM ethers in the presence of acetonides and THP ethers, employing dimethylboron bromide and diphenylboron bromide at −78 ºC, has been described by Guindon and co-workers.[9] However, these reagents are also capable of cleaving a variety of ethers and potentially can have effects on acid-sensitive functionality.

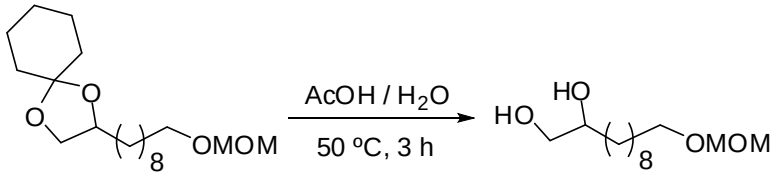
In studies probing the selective deprotection of MOM ethers **8a-c**, which also contain ketals, we observed that the use of increased quantities of TBSOTf and 2,2'-bipyridyl are required (Table 2). Under these conditions, selective deprotection of the MOM ether moieties was found to take place in high yields without adverse effects on cyclohexylidene, cyclopentylidene and acetonide ketal groups (entries 1-3). In addition, more bulky *sec*- and *tert*-MOM ethers **8d** and **8e** undergo the selective deprotection process under the optimized conditions to give the corresponding alcohols **9d** and **9e** in 93% and 91% yields, respectively (entries 4 and 5). In these cases, acid-promoted hydrolysis results in preferential deprotection of the ketal protective groups, leaving the MOM ethers intact (Scheme 6).

Table 2. Selective deprotection of MOM ethers in the presence of other ketal protective groups



8 **9**

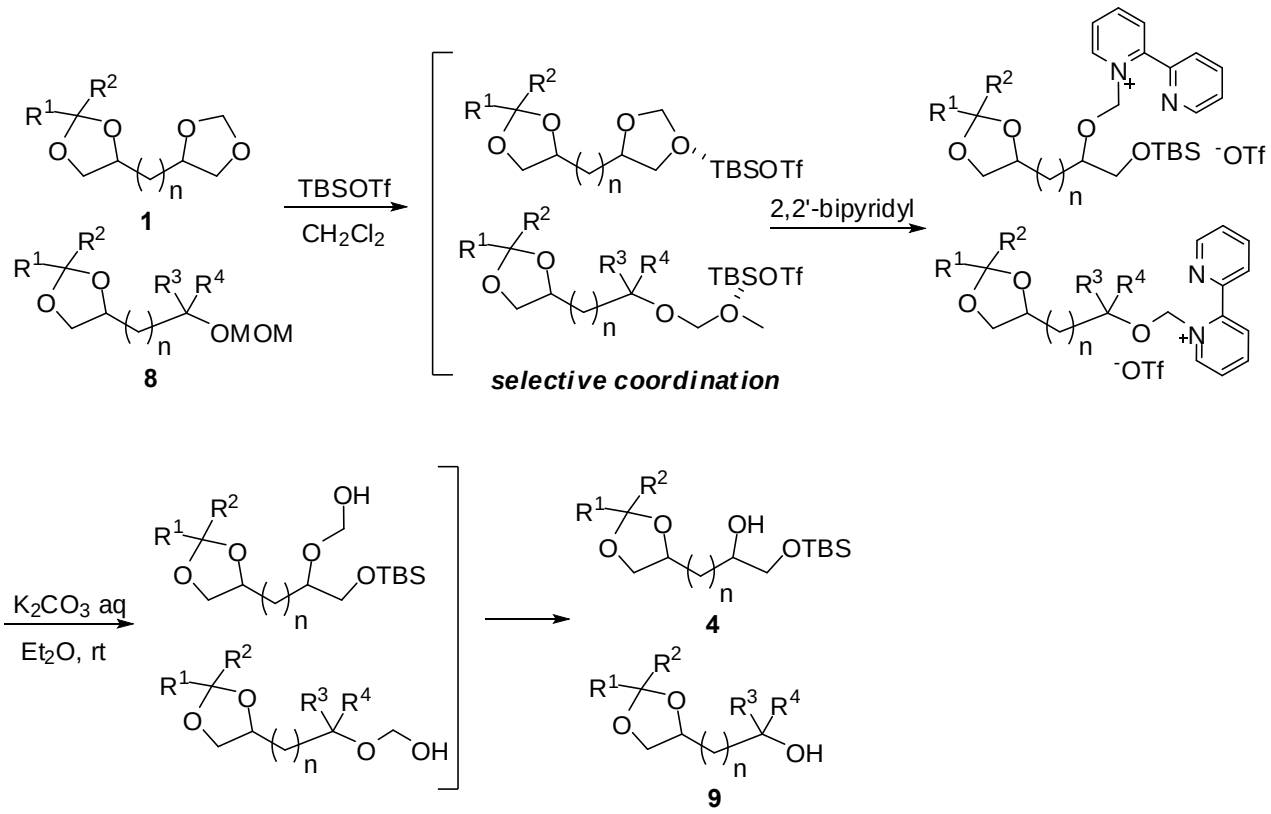
entry	R^1	R^2	R^3	R^4	time A (h)	time B (h)	yield (%)
1	$-(CH_2)_5-$		H	H (**8a**)	7	12	98 (**9a**)
2	$-(CH_2)_4-$		H	H (**8b**)	7	15	92 (**9b**)
3	Me	Me	H	H (**8c**)	6	9	96 (**9c**)
4	Me	Me	Me	H (**8d**)	6	14	93 (**9d**)
5	Me	Me	Me	Me (**8e**)	6	2	91 (**9e**)



8a **10** (73%)

Scheme 6. Acid promoted hydrolysis of the mixed MOM and cyclohexylidene protected substance **8a**

A plausible mechanism for the selective deprotection process is depicted in Scheme 7. The initial and the most significant step in the pathway is Lewis acid coordination of TBSOTf to the acetal, which takes place in a highly discriminatory manner at the least sterically encumbered acetal. This conclusion is consistent with the observation that no selectivity is displayed in reactions promoted using the less sterically demanding TESOTf rather than TBSOTf. It is interesting to note that strict discrimination among four oxygen atoms is observed in these processes. Successive attack of 2,2'-bipyridyl on the complex then leads to formation of the salt intermediate in a chemo- and regioselective fashion. Finally, work-up with H_2O affords the corresponding deprotected substances via hemi-acetal intermediate.



Scheme 7. A plausible mechanism for the TBSOTf promoted selective deprotection reaction

In conclusion, in the effort described above, we developed a novel, selective procedure for methylene acetal deprotection in substances that also contain ketal protective groups. This method displays a selectivity that is opposite to that of acid-mediated hydrolysis reactions because the reactivity differences arise from steric and not electronic effects. The new method is also applicable to MOM ether selective deprotection of substances in the presence of ketal-type protective groups. We believe that the current study has provided useful information about acetal deprotection reactions that will benefit those involved in the area of synthetic organic chemistry.

EXPERIMENTAL

General Information

Melting point (mp) was measured by Büchi B-545. Infrared spectra (IR) were recorded by Shimadzu FTIR 8400 using a diffuse reflectance measurement of samples dispersed in KBr powder. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-LA 500, JNM-ECS 400, JNM-AL 300 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet), coupling constant (Hz) and integration. Mass spectra were obtained on a Shimadzu GCMS-QP 5000

instrument with ionization voltages of 70 eV. Column chromatography and TLC were carried out on Merck Silica gel 60 (230-400 mesh), Kanto Kagaku Silica gel 60N (40-50 μm, spherical, neutral), and Merck silica gel F_{254} plates (0.25 mm), respectively. The commercially available reagents were used without further purification. Compounds **9c**[9] is known compound.

Acidic hydrolysis of 1a (Scheme 1)

1a (39.5 mg, 0.145 mmol) was treated with CF_3COOH (0.7 mL) and H_2O (0.6 mL) for 1.5 h at room temperature. Then the mixture was extracted with CH_2Cl_2 (30 mL × 3) and the combined organic layers was dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes/AcOEt = 10/1) affording **2** as colorless oil (29.1 mg, 87%).

9-(1,3-Dioxolan-4-yl)nonane-1,2-diol (2)

White solid (mp 39-42 °C); IR (KBr): 3395, 2932, 2361, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.21-1.41 (m, 13H), 1.53-1.68 (m, 1H), 2.01 (brs, 1H), 2.12 (brs, 1H), 3.35-3.45 (m, 2H), 3.59-3.74 (m, 2H), 3.89-4.02 (m, 2H), 4.84 (s, 1H), 4.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.5, 25.8, 29.43, 29.47, 29.5, 32.9, 33.1, 66.8, 69.6, 72.2, 76.2, 94.8; HRMS (FAB) calcd for $C_{12}H_{25}O_4$ ($M+H^+$) 233.1753, found 233.1743.

The Selective Deprotection of 1b (Scheme 3)

TMSOTf (73.1 μL, 0.404 mmol) was added to a solution of **1b** (82.9 mg, 0.202 mmol) and 2,2'-bipyridyl (94.6 mg, 0.606 mmol) in CH_2Cl_2 (0.4 ml) at 0 °C under N_2. The reaction mixture was stirred for 30 min at 0 °C. After disappearance of **1b** on TLC, Et_2O (2 ml) and 1N HCl (2 ml) was added to the reaction mixture. The resulting solution was stirred until disappearance of the pyridinium salt (highly polar compound). The mixture was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes/AcOEt = 1/1) to give a diol **3** (63.1 mg, 78%).

10-(2,2-Diphenyl-1,3-dioxolan-4-yl)decane-1,2-diol (3)

Colorless oil; IR (KBr): 3582, 2934, 2305 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.24-1.74 (m, 16H), 2.38 (brs, 2H), 3.39-3.42 (m, 1H), 3.61-3.69 (m, 3H), 4.08-4.16 (m, 2H), 7.24-7.34 (m, 6H), 7.48-7.52 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ:25.5, 25.7, 29.4, 29.47, 29.51, 33.1, 33.4, 66.8, 70.0, 72.3, 76.8, 109.3, 126.2, 127.8, 127.9, 128.1, 142.8; HRMS (EI) calcd for $C_{25}H_{34}O_4$ (M^+) 398.2457, found 398.2452.

The reaction of 1c with TESOTf and 2,2'-bipyridyl (Scheme 4)

TESOTf (94.5 μL, 0.42 mmol) was added dropwise to a solution of methylene acetal **1c** (65.4 mg, 0.21 mmol) and 2,2′-bipyridyl (98.0 mg, 0.63 mmol) in CH_2Cl_2 (0.42 mL) at 0 ºC under N_2. The reaction

mixture was stirred at the same temperature. After checking the disappearance of **1c** on TLC (1.5 h), satd. aq. K_2CO_3 (2 mL) and Et_2O (2 mL) were added to the reaction mixture, which was then stirred vigorously. After disappearance of the high polar component, monitored by TLC, the mixture was extracted with CH_2Cl (30 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexane/AcOEt = 8/1) to give **4a** as yellow oil; 24.4 mg (28%) and **4a'** as colorless oil; 60.8 mg (55%).

9-(1,4-Dioxaspiro[4.5]decan-2-yl)-1-(triethylsilyloxy)nonan-2-ol (4a)

Colorless oil; IR (KBr): 2936, 2251, 1462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.60 (q, *J* = 7.8 Hz, 6H), 0.94 (t, *J* = 7.8 Hz, 9H), 1.21-1.65 (m, 24H), 2.48 (brs, 1H), 3.30-3.37 (m, 1H), 3.44-3.49 (m, 1H), 3.57-3.66 (m, 2H), 3.97-4.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 4.3, 6.7, 23.9, 24.0, 25.2, 25.6, 25.7, 29.4, 29.58, 29.59, 32.7, 33.8, 35.3, 36.6, 66.9, 69.1, 71.8, 75.7, 109.1; HRMS (EI) calcd for $C_{23}H_{46}O_4Si$ (M^+) 414.3165, found 414.3156.

11, 14-Bis(triethylsilyloxy)-13-(cyclohex-1'-enyloxy)-dodecan-2-ol (4a')

Colorless oil, IR (KBr): 2936, 2251, 1664, 1456 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.53-0.63 (m, 12H), 0.89-0.97 (m, 18H), 1.23-1.65 (m, 18H), 1.97-2.04 (m, 4H), 2.44 (brs, 1H), 3.33-3.36 (m, 1H), 3.50-3.66 (m, 4H), 3.90-3.95 (m, 1H), 4.62-4.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 4.1, 4.3, 6.6, 6.7, 22.7, 23.0, 23.6, 25.4, 25.6, 28.1, 29.5, 29.7, 31.2, 32.7, 64.1, 66.9, 71.9, 75.8, 95.1, 153.3; HRMS (EI) calcd for $C_{29}H_{60}O_4Si_2$ (M^+) 528.4030, found 528.4027.

Typical procedure for selective conversion of methylene acetals to mono-TBS protected diols 4 (Table 1). TBSOTf (91.9 μL, 0.40 mmol) was added dropwise to a solution of methylene acetal **1c** (62.3 mg, 0.20 mmol) and 2,2′-bipyridyl (93.7 mg, 0.60 mmol) in CH_2Cl_2 (0.4 mL) at room temperature under N_2. After observing the disappearance of **1c** by using TLC (1.5 h), satd. aq. K_2CO_3 (2 mL) and Et_2O (2 mL) were added to the mixture, which was then stirred vigorously. After disappearance of the high polar component, monitored by using TLC (8 h), the mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes/AcOEt = 5/1) to give the mono-TBS protected alcohol **4b** (76.1 mg, 92%).

1-(*tert*-Butyldimethylsilyloxy)-9-(1,4-dioxaspiro[4.5]decan-2-yl)nonan-2-ol (4b): Colorless oil; IR (KBr): 2932, 1464 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.05 (s, 6H), 0.89 (s, 9H), 1.17-1.69 (m, 24H), 2.41 (brs, 1H), 3.32-3.39 (m, 1H), 3.44-3.49 (m, 1H), 3.57-3.61 (m, 2H), 3.99-4.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: -5.39, -5.44, 18.2, 23.8, 24.0, 25.2, 25.5, 25.7, 25.8, 29.4, 29.5, 29.6, 32.7, 33.7, 35.3, 36.6, 67.2, 69.1, 71.8, 76.7, 109.0; HRMS (FAB) calcd for $C_{23}H_{47}O_4Si$ (M^++H) 415.3244, found 415.3250.

1-(*tert*-Butyldimethylsilyloxy)-9-(1,4-dioxaspiro[4.4]nonan-2-yl)nonan-2-ol (4c): Colorless oil; IR (KBr): 3574, 2929, 2247, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.03 (s, 6H), 0.86 (s, 9H), 1.20-1.47 (m, 13H), 1.58-1.79 (m, 9H), 2.43 (brs, 1H), 3.32-3.37 (m, 1H), 3.42 (t, *J* = 6.8 Hz,1H), 3.56-3.62 (m, 2H), 3.92-3.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: -5.45, -5.38, 18.2, 23.3, 23.6, 25.5, 25.7, 25.8, 29.4, 29.53, 29.56, 32.7, 33.6, 36.3, 36.7, 67.2, 69.2, 71.7, 75.9, 118.5; HRMS (EI) calcd for $C_{22}H_{44}O_4Si$ (M^+) 400.3009, found 400.3011.

1-(*tert*-Butyldimethylsilyloxy)-9-(2,2-dimethyl-1,3-dioxolan-4-yl)nonan-2-ol (4d): Colorless oil; IR (KBr): 3572, 2930, 2249, 1464 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.05 (s, 6H), 0.88 (s, 9H), 1.23-1.66 (m, 20H), 2.40 (brs, 1H), 3.36 (m, 1H), 3.46-3.49 (m, 1H), 3.58-3.61 (m, 2H), 4.00-4.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: -5.44, -5.37, 18.3, 25.5, 25.72, 25.83, 26.9, 29.38, 29.54, 29.56, 32.7, 33.5, 67.2, 69.5, 71.7, 76.1, 108.5; HRMS (FAB) calcd for $C_{20}H_{43}O_4Si$ (M^+ +H) 375.2931, found 375.2948.

Typical procedure for the selective deprotection of methylene acetal 1a (Scheme 5)

Conversion of 1a to mono-TBS protected diol 4d. See the procedure for Table 1.

Conversion of 1a to MOM and TBS-protected diol 5. TBSOTf (114.0 μL, 0.49 mmol) was added dropwise to a solution of methylene acetal **1a** (64.4 mg, 0.24 mmol) and 2,2′-bipyridyl (116.0 mg, 0.74 mmol) in CH_2Cl_2 (0.5 mL) at room temperature under N_2. After observing the disappearance of **1a** by using TLC (1.5 h), Et_3N (98.0 μL, 0.71 mmol) and MeOH (2 mL) were added to the mixture, which was then stirred vigorously. After disappearance of the high polar component, monitored by using TLC (12 h), the mixture was extracted with AcOEt (20 mL × 3). The combined organic layers was washed with 3.5% aq. HCl (20 mL), H_2O (20 mL) and satd. aq. $NaHCO_3$ (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes/AcOEt = 10/1) affording product **5** (91.5 mg, 93%).

5-[7-(2,2-Dimethyl-1,3-dioxolan-4-yl)heptyl]-8,8,9,9-tetramethyl-2,4,7-trioxa-8-siladecane (5): Yellow oil; IR (KBr): 2929, 2249, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.02 (s, 6H), 0.85 (s, 9H), 1.19-1.64 (m, 20H), 3.34 (s, 3H), 3.45 (t, *J* = 6.8 Hz, 1H), 3.52-3.58 (m, 3H), 3.97-4.03 (m, 2H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.74 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: -5.46, -5.42, 18.2, 25.3, 25.7, 25.9, 26.9, 29.4, 29.57, 29.59, 31.6, 33.5, 55.4, 65.8, 69.5, 76.1, 78.1, 96.2, 108.5; HRMS (FAB) calcd for $C_{22}H_{46}O_5SiNa$ (M^++Na) 441.3012, found 441.3029.

Conversion of 1a to diol 6. TBSOTf (107.0 μL, 0.47 mmol) was added dropwise to a solution of methylene acetal **1a** (63.5 mg, 0.23 mmol) and 2,2′-bipyridyl (109.0 mg, 0.70 mmol) in CH_2Cl_2 (1.2 mL) at room temperature under N_2. After observing the disappearance of **1a** on TLC (1 h), satd. aq. K_2CO_3 (0.5 mL) and Et_2O (0.5 mL) were added to the mixture, which was then stirred vigorously. After

disappearance of the high polar component, monitored by using TLC (17 h), TBAF (1.0 M THF solution, 1.16 mL, 1.16 mmol) was added to the mixture, which was then stirred for 9 h. The mixture was extracted with CH_2Cl_2 (20 mL × 3) and the combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, AcOEt only) affording product **6** (56.2 mg, 93%).

9-(2,2-Dimethyl-1,3-dioxolan-4-yl)nonane-1,2-diol (6): Colorless oil; IR (KBr): 3402, 2931, 2250, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.23-1.50 (m, 19H), 1.56-1.66 (m, 1H), 1.99 (brs, 2H), 3.39-3.49 (m, 2H), 3.62-3.70 (m, 2H), 3.99-4.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.5, 25.68, 25.71, 26.9, 29.3, 29.47, 29.51, 33.1, 33.5, 66.8, 69.5, 72.2, 76.1, 108.6; HRMS (FAB) calcd for $C_{14}H_{29}O_4$ (M^++H) 261.2066, found 261.2090.

Conversion of 1a to mono-MOM protected diol 7. TBSOTf (127.0 μL, 0.55 mmol) was added dropwise to a solution of methylene acetal **1a** (73.9 mg, 0.27 mmol) and 2,2′-bipyridyl (130.0 mg, 0.83 mmol) in CH_2Cl_2 (0.55 mL) at room temperature under N_2. After observing the disappearance of **1a** by using TLC (1.5 h), MeOH (0.5 mL) and Et_3N (112 μL, 0.81 mmol) were added to the mixture, which was then stirred vigorously. After disappearance of high polar component, monitored by using TLC (4 h), TBAF (1.0 M THF solution, 1.35 mL, 1.35 mmol) was added to the mixture, which was stirred for 24 h. The mixture was extracted with AcOEt (20 mL × 3) and the combined organic layers was washed with 3.5% aq. HCl (20 mL), H_2O (20 mL) and satd. aq. $NaHCO_3$ (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes/AcOEt = 2/1) affording product **7** (58.5 mg, 71%).

9-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(methoxymethoxy)nonan-1-ol (7): Colorless oil; IR (KBr): 3450, 2931, 2249, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.21-1.57 (m, 20H), 3.10 (brs, 1H), 3.39 (s, 3H), 3.42-3.54 (m, 4H), 3.97-4.04 (m, 2H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.4, 25.68, 25.69, 26.9, 29.3, 29.46, 29.51, 31.6, 33.5, 55.6, 65.6, 69.4, 76.1, 82.2, 96.9, 108.5; HRMS (FAB) calcd for $C_{16}H_{33}O_5$ (M^++H) 305.2328, found 305.2326.

Typical procedure for selective deprotection of MOM ether 8 (Table 2). TBSOTf (170.9 μL, 0.74 mmol) was added dropwise to a solution of MOM ether **8a** (61.2 mg, 0.19 mmol) and 2,2′-bipyridyl (174.3 mg, 1.12 mmol) in CH_2Cl_2 (0.93 mL) at room temperature under N_2. After observing the disappearance of **8a** by using TLC (7 h), satd. aq. K_2CO_3 (2 mL) and Et_2O (2 mL) were added to the mixture, which was then stirred vigorously. After disappearance of high polar component, monitored by using TLC (12 h), the mixture was extracted with AcOEt (20 mL × 3). The combined organic layer was washed with 3.5% aq. HCl (20 mL), H_2O (20 mL) and satd. aq. $NaHCO_3$ (20 mL). The organic layer was

dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes/AcOEt = 8/1) affording product **9a** (52.1 mg, 98%).

9-(1,4-Dioxaspiro[4.5]decan-2-yl)nonan-1-ol (9a): Colorless oil; IR (KBr): 2934, 2253, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.23-1.65 (m, 26H), 3.45-3.49 (m, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.98-4.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.8, 23.9, 25.1, 25.7, 29.31, 29.35, 29.4, 29.5, 32.7, 33.7, 35.2, 36.5, 62.8, 69.0, 75.7, 109.0; HRMS (FAB) calcd for $C_{17}H_{33}O_3$ (M^++H) 285.2430, found 285.2430.

9-(1,4-Dioxaspiro[4.4]nonan-2-yl)nonan-1-ol (9b): Yellow oil; IR (KBr): 3404, 2929, 2250, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.27-1.80 (m, 24H), 3.43-3.46 (m, 1H), 3.62 (t, *J* = 6.8 Hz, 2H), 3.94-3.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.3, 23.5, 25.6, 29.3, 29.36, 29.41, 29.5, 32.7, 33.5, 36.3, 36.7, 62.9, 69.2, 75.9, 118.5; HRMS (EI) calcd for $C_{16}H_{30}O_3$ (M^+) 270.2195, found 270.2208.

9-(2,2-Dimethyl-1,3-dioxolan-4-yl)nonan-1-ol (9c)[9]: Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.17-1.65 (m, 22H), 3.40-3.47 (m, 1H), 3.57 (t, *J* = 6.5 Hz, 2H), 3.94-4.05 (m, 2H)

10-(2,2-Dimethyl-1,3-dioxolan-4-yl)decan-2-ol (9d): Colorless oil; IR (KBr): 3616, 3465, 3155, 2931, 2250, 1456 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.15-1.49 (m, 23H), 1.59-1.65 (m, 2H), 3.46-3.49 (m, 1H), 3.74-3.77 (m, 1H), 3.99-4.07 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.4, 25.73, 29.75, 26.9, 29.41, 29.47, 29.58, 29.61, 33.5, 39.3, 68.1, 69.5, 76.2, 108.6; HRMS (FAB) calcd for $C_{15}H_{31}O_3$ (M^++H) 259.2273, found 259.2258.

10-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methyldecan-2-ol (9e): Colorless oil; IR (KBr): 3417, 2931, 2249, 1714, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.11-1.68 (m, 28H), 3.43-3.48 (m, 1H), 3.97-4.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.3, 26.0, 26.9, 29.1, 29.41, 29.45, 29.47, 29.55, 29.60, 30.1, 33.5, 43.9, 69.5, 71.0, 76.1, 108.5; HRMS (FAB) calcd for $C_{16}H_{32}O_3Na$ (M^++Na) 295.2249, found 295.2250.

Acidic hydrolysis of 8a (Scheme 6)

8a (39.7 mg, 0.121 mmol) was treated with AcOH (1.2 mL) and H_2O (0.3 mL) at 50 °C and stirred for 3 h. Satd. aq. $NaHCO_3$ was added to the reaction mixture and the mixture was extracted with AcOEt (30 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes/AcOEt = 10/1) affording **10** (21.9 mg, 73%).

11-(Methoxymethoxy)undecane-1,2-diol (10): white solid (mp 40-41 °C); IR (KBr): 3366, 2929, 2251, 1465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.26-1.40 (m, 14H), 1.52-1.59 (m, 2H), 2.20 (t, *J* = 5.6 Hz, 1H), 2.28 (t, *J* = 4.0 Hz, 1H), 3.33 (s, 3H), 3.37-3.42 (m, 1H), 3.49 (t, *J* = 6.8 Hz, 2H), 3.60-3.68 (m, 2H), 4.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.5, 26.1, 29.42, 29.45, 29.5, 29.6, 29.7, 33.1, 55.1, 66.8, 67.8, 72.3, 96.3; HRMS (FAB) calcd for $C_{13}H_{29}O_4$ ($M+H^+$) 249.2066, found 249.2061.

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