HETEROCYCLES, Vol. 77, No. 2, 2009, pp. 1089 - 1103. © The Japan Institute of Heterocyclic Chemistry
Received, 31st July, 2008, Accepted, 26th September, 2008, Published online, 29th September, 2008
DOI: 10.3987/COM-08-S(F)88

MILD AND EFFICIENT DEPROTECTION OF ACETAL-TYPE PROTECTING GROUPS OF HYDROXYL FUNCTIONS BY TRIETHYLSILYL TRIFLATE—2,4,6-COLLIDINE COMBINATION†

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Abstract – Deprotection of acetal-type protecting groups of hydroxyl functions has been studied in detail. The treatment of alcohol derivatives protected by acetal-type protecting groups with TESOTf—2,4,6-collidine followed by H_2O-treatment produces the corresponding hydroxyl compounds in good yields. The characteristic features of the method are very mild and chemoselective, and acid-labile functional groups can tolerate these conditions.

INTRODUCTION

The development of selective protection/deprotection methods is an important issue in synthetic organic chemistry.[1] Especially, in the syntheses of complex compounds with many functional groups such as natural products, the solution of such issues makes the synthetic route of these compounds more flexible. We have recently developed a new and efficient deprotection method of tetrahydropyranyl (THP) ethers.[2] Thus, the treatment of THP-ethers with triethylsilyl triflate (TESOTf)—2,4,6-collidine afforded the corresponding alcohols in good yields with high chemoselectivity under weakly basic conditions.[3,4] The reaction proceeds via the cationic collidinium salt formed by the selective attack of TESOTf to the oxygen atom in the oxacyclic ring, although there are two oxygen atoms in the THP-ethers (Scheme 1). During the reaction, acid-labile functional groups such as trityl (Tr)-ether and *tert*-butyldimethylsilyl (TBDMS)-ether can co-exist in the molecule. We then extended our method to various hydroxyl compounds with acetal-type protecting groups.

In this paper, we present the full details of our study on the deprotection of acetal-type protecting groups including THP-ethers.[5]

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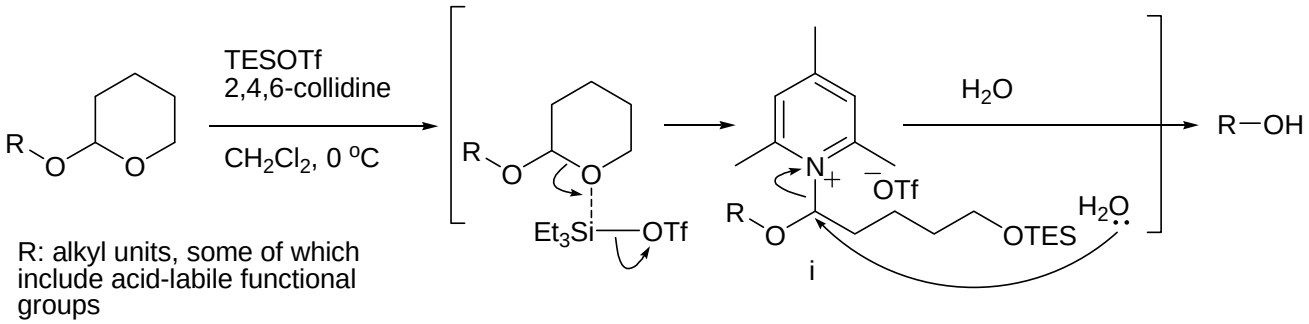
†*This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.*

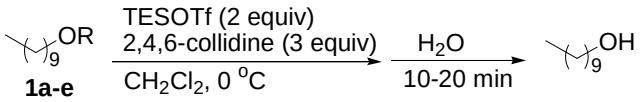


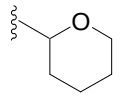
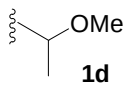
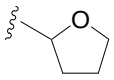
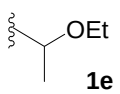
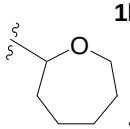
Scheme 1. Deprotection of THP-ethers

RESULTS AND DISCUSSION

We first examined the reactions of decanol derivatives **1a-e** with various acetal-type protecting groups. Thus, TESOTf (2 equiv.) was added to a solution of **1a-e** (1 equiv.) and 2,4,6-collidine (3 equiv.) in CH_2Cl_2 (0.1 M solution), then the mixture was stirred for 30 min at 0 °C. Treatment of the resulting solution with water for 10-20 min at rt, the usual work-up, and SiO_2 purification afforded decanol **2**. The results are shown in Table 1. The THP-ether **1a** gave **2** in 97% yield (entry 1). Similar results were obtained for the reactions of the oxacyclic-ethers **1b** and **1c**, and the deprotected **2** was obtained in high yields, 88% from **1b** and 88% from **1c** (entries 2 and 3). Compounds **1d** containing the acyclic methoxyethyl (ME) protecting group also gave the deprotected product **2** in 96% yield (entry 4). However, compound **1e** containing the ethoxyethyl (EE) protecting group needed excess reagents and a long reaction time, and **2** was obtained in moderate yield (56%) (entry 5).

Table 1. Deprotection of acetal-type protecting groups

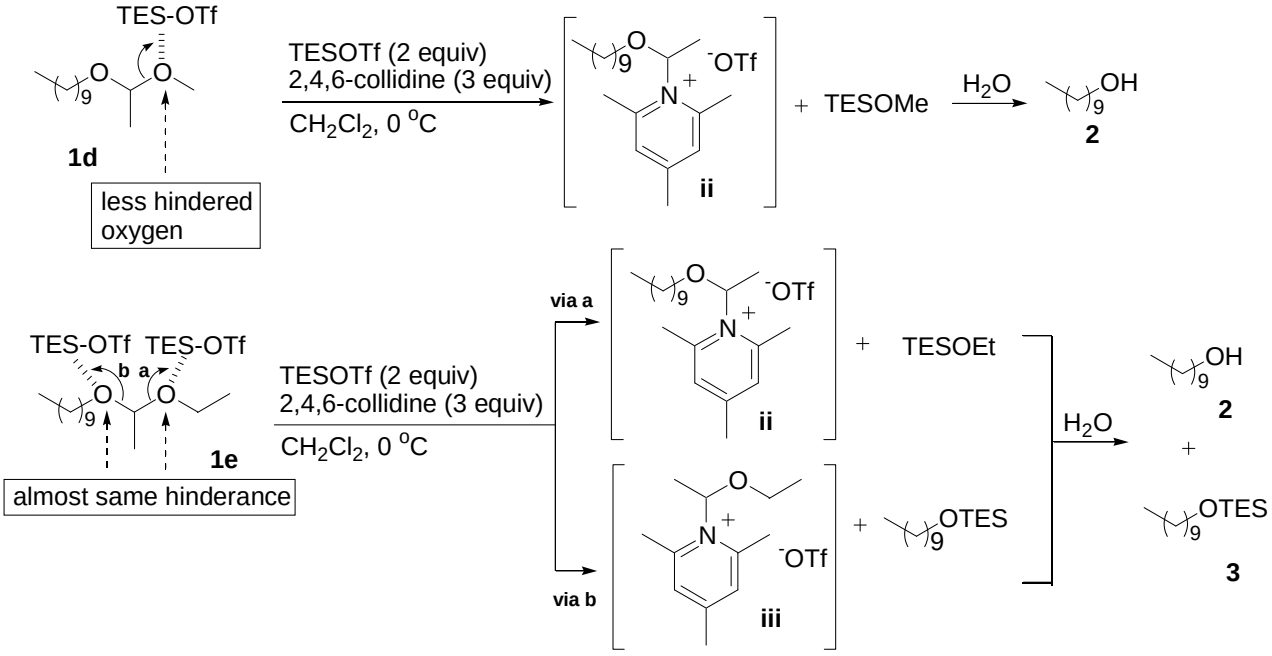


entry	R	time	yield	entry	R	time	yield
1	 **1a**	30 min	97%	4	 **1d**	30 min	96%
2	 **1b**	30 min	88%	5	 **1e**	2 h	56% [a),b)]
3	 **1c**	30 min	88%				

a) TESOTf (4 equiv) and 2,4,6-collidine (6 equiv) were used.
b) 20% of **3** was obtained (For the structure of **3**, see Scheme 2).

The desired results from **1a-c** can be rationalized by the fact that TESOTf can selectively attack the oxygen atom in the oxacyclic ring as shown in Scheme 1.[2] On the other hand, the results from **1d** and **1e**

might be rationalized as follows. There is still a difference between the two oxygen atoms in **1d**. The methoxy oxygen atom is less hindererd, and TESOTf can still attack the methoxy oxygen atom to selectively form the intermediate **ii**. This resulted in a high yield of **2** from **1d**. However, in the case of **1e**, a small difference is present between the two oxygen atoms, and TESOTf can not selectively detect the desired oxygen atom thus two intermediates **ii** and **iii** are formed. This reaction then gave **2** with a moderate amount of the TES-ether **3** (Scheme 2).

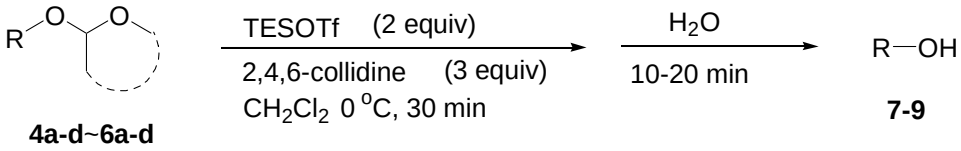


Scheme 2. ME ether **1d** *vs* EE ether **1e**

From the results of Table 1 and the consideration of Scheme 2, the acetal-type protecting groups, such as the oxacyclic ethers, and ME-ethers appear suitable for this method. The reactions of the substrates having various alcohol units with 5-7–membered oxacyclic and methoxyethyl acetal-type protecting groups were then examined. Since the reactions of decanol (**2**) as a simple primary alcohol were already studied in Table 1, benzyl alcohol (**7**), cinnamyl alcohol (**8**), and secondary alcohol **9** were chosen. These results are shown in Table 2. In every reaction, the desired deprotected alcohol was obtained in a moderate to good yield. In general, the yields from the secondary alcohol derivatives **6a-d**[6] to the alcohol **9** tend to be lower than those from the primary alcohol derivatives **4a-d** and **5a-d**. Deprotection of the allyl alcohol derivatives **5a-d** did not cause any problems when producing the corresponding alcohol **8** in good yields. This might be due to the weakly basic conditions of our reactions.

We next examined the chemoselectivity of the method using dodecane-1,12-diol derivatives **10a-d**~**13a-d**, which have acetal-type protecting group and another protecting group, such as the trityl

Table 2. Deprotection of acetal-type derivatives from various alcohols

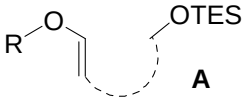


4a-d~6a-d **7-9**

(**4**, **7**: R = Bn; **5**, **8** : R = Ph ; **6**, **9**: R =)

substrate	product yield (substrate)		
	Bn—OH **7**	Ph OH **8**	OH **9**
RO O **4a-6a**	72% (**4a**)	86% (**5a**)	57%[b] (**6a**)
RO O **4b-6b**	90% (**4b**)	89% (**5b**)	69%[b] (**6b**)
RO O **4c-6c**	65%[a] (**4c**)	98%[a] (**5c**)	62%[b] (**6c**)
RO OMe **4d-6d**	83% (**4d**)	90% (**5d**)	62%[b] (**6d**)

a) TESOTf (5.0 equiv) and 2,4,6-collidine (6.0 equiv) were used.
b) Fairly large amount of enol ether (**A**) was formed.

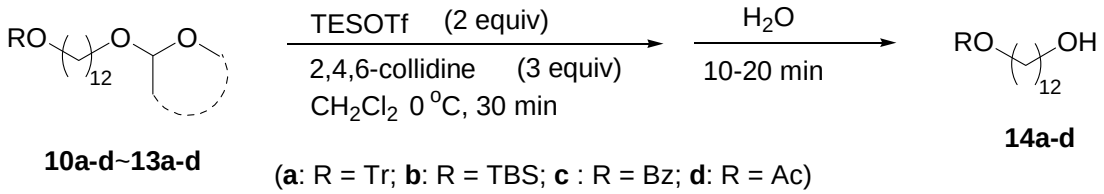


A

(Tr), *tert*-butyldimethylsilyl (TBS), benzoyl (Bz), or acetyl (Ac) function in the same molecule. These results are shown in Table 3. In every reaction, the corresponding alcohol **14a-d**, which was obtained by selective deprotection of the acetal-type protecting group of the substrate **10a-d**~**13a-d**, was obtained in high yields. It is noteworthy that the quite acid-labile Tr group can still tolerate these conditions (see the results of the reactions of the Tr-ethers **10a**, **11a**, **12a**, and **13a** to alcohol **14a**).

The high chemoselectivity and the mildness of the method are also ascertained from our previous results.[2] Although compound **15** has many functional groups such as *tert*-butyldimethylsilyl-ether (TBSO), triethylsilyl-ether (TESO), 4-methoxyphenylmethyl-ether (MPMO), olefin, and allyl TES-ether units in addition to the THP-ether, the reaction succeeded in the highly chemoselective deprotection of the THP protecting group, and the corresponding alcohol **16** was obtained in high yield from **15** (Scheme 3).

Table 3. Chemoselective Deprotection

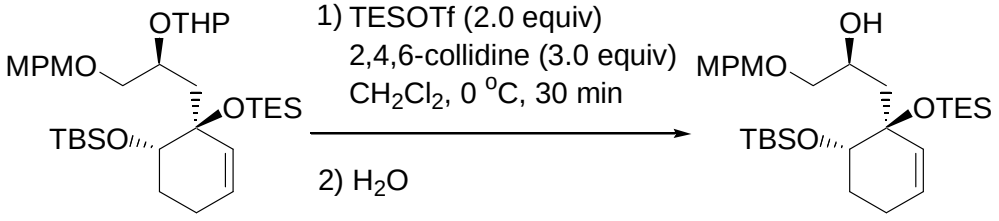


10a-d~13a-d

14a-d

(**a**: R = Tr; **b**: R = TBS; **c** : R = Bz; **d**: R = Ac)

substrate	product yield (substrate)			
	TrO(CH2)12OH **14a**	TBSO(CH2)12OH **14b**	BzO(CH2)12OH **14c**	AcO(CH2)12OH **14d**
RO(CH2)12O(CH2)3 **10a-d**	83% (**10a**)	86% (**10b**)	88% (**10c**)	88% (**10d**)
RO(CH2)12O(CH2)4 **11a-d**	87% (**11a**)	87% (**11b**)	90% (**11c**)	88% (**11d**)
RO(CH2)12O(CH2)5 **12a-d**	77% (**12a**)	81% (**12b**)	82% (**12c**)	84% (**12d**)
RO(CH2)12OCH(OMe)CH3 **13a-d**	80% (**13a**)	90% (**13b**)	80% (**13c**)	86% (**13d**)



15

16 (71%)

Scheme 3. Chemoselective deprotection of THP ether **15**

CONCLUSION

We have found that TESOTf—2,4,6-collidine combination can be applicable to various types of acetal-type protecting groups of the hydroxyl functions. The reaction is a mild, efficient, and highly chemoselective deprotection method. The reaction also can proceed in the presence of acid-labile protecting groups without affecting such functional groups because of the weakly basic conditions.

EXPERIMENTAL

General techniques

The ^{1}H and ^{13}C NMR spectra were measured by 500 MHz, 300 MHz or 270 MHz spectrometers with tetramethylsilane as an internal standard at 20-25 ^{o}C. IR spectra were recorded by a diffuse reflectance measurement of samples dispersed in KBr powder. Merck silica gel 60 was used for column chromatography.

General Procedure for Preparation of THF-ethers 1b, 4a-6a, THP-ether 5b, and EE-ether 1e

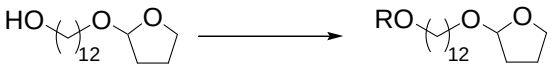
According to a literature,[7] a solution of an alcohol (1 equiv.), pyridinium *p*-toluenesulfonate (PPTS) (0.1 equiv.) and 2,3-dihydrofuran (for THF-ether), 3,4-dihydro-2*H*-pyran (for THP-ether) or ethyl vinyl ether (for EE-ether) (1.8-2 equiv.) in dry CH_2Cl_2 (0.1 M) was stirred at room temperature. After checking disappearance of the alcohol on TLC, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by flash SiO_2 column chromatography (neutralized SiO_2 purchased from Kanto Chemical) to give a THF-ether, THP-ether, or ethoxyethyl-ether. Alcohols **2**, **7-9** are commercially available. **1b**,[8] **4a**,[9] **5a**,[10] and **5b**[11] are known in the literatures.

1e: Colorless oil, IR (KBr) 2855, 2735, 1340, 1059, 912 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.6 Hz), 1.18-1.38 (20H, m), 1.51-1.61 (2H, m), 3.36-3.71 (4H, m), 4.68 (1H, q, *J* = 5.4 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.1, 15.3, 19.9, 22.7, 26.3, 29.4, 29.5, 29.6, 29.9, 31.9, 60.5, 65.2, 99.4; HRMS (FAB) calcd for $C_{14}H_{30}NaO_2$ (M^{+}+Na) 253.2143, found 253.2172.

6a: Colorless oil, IR (KBr) 2930, 2856, 1454, 1115, 1020 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.6 Hz), 1.10 (1.7H, d, *J* = 6.1 Hz), 1.17 (1.3H, d, *J* = 6.3 Hz), 1.27-1.41 (14H, m), 1.77-2.05 (4H, m), 3.61-3.75 (1H, m), 3.80-3.95 (2H, m), 5.20-5.25 (1H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.2, 19.5, 21.9, 22.8, 23.6, 23.7, 25.7, 25.9, 29.4, 29.7, 29.8, 29.9, 32.0, 32.6, 32.7, 36.9, 37.6, 66.4, 66.5, 70.9, 73.6, 100.7, 103.4; HRMS (FAB) calcd for $C_{14}H_{29}O_2$ (M^{+}+H) 229.2168, found 229.2157.

General Procedure for Preparation of THF-ethers 10a-d

THF-ether **10a-d** were prepared from THF-ether **10e** according to a literature.[2] THF-ether **10e** was obtained from 1,12-dodecanediol by the procedure described above.



10e **10a-d**

10e: White solid, Mp. 34 ^{o}C, IR (KBr) 3329, 2924, 2853, 1040, 920 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27-1.38 (16H, m), 1.51-1.63 (4H, m), 1.77-2.06 (4H, m), 3.36 (1H, dt, *J* = 11.7, 5.0 Hz), 3.60-3.68 (3H,

m), 3.87 (2H, m), 5.11 (1H, dd, *J* = 4.0, 1.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.4, 25.7, 26.0, 29.3, 29.4, 29.5, 29.6, 32.2, 32.7, 62.7, 66.6, 67.2, 103.6; HRMS (FAB) calcd for $C_{16}H_{33}O_3$ (M^++H) 273.2430, found 273.2419.

10a (R = Tr): Colorless oil, IR (KBr) 2930, 1448, 1090, 1034, 912 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24-1.38 (16H, m), 1.50-1.66 (4H, m), 1.79-2.05 (4H, m), 3.03 (2H, t, *J* = 6.6 Hz), 3.36 (1H, dt, *J* = 12.2, 4.7 Hz), 3.64 (1H, dt, *J* = 12.2, 4.7 Hz), 3.81-3.93 (2H, m), 5.11 (1H, dd, *J* = 3.9, 1.6 Hz), 7.17-7.32 (9H, m), 7.43-7.46 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 26.2, 29.4, 29.5, 29.6, 29.7, 30.0, 32.3, 63.6, 66.7, 67.3, 86.2, 103.7, 126.7, 127.6, 128.6, 144.5; HRMS (FAB) calcd for $C_{35}H_{46}NaO_3$ (M^++Na) 537.3345, found 537.3362.

10b (R = TBS): Colorless oil, IR (KBr) 2930, 2855, 1256, 1094, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.90 (9H, s), 1.21-1.29 (16H, m), 1.41-1.55 (4H, m), 1.72-1.99 (4H, m), 3.31 (1H, dt, *J* = 12.1, 4.8 Hz), 3.53-3.63 (3H, m), 3.77-3.88 (2H, m), 5.06 (1H, dd, *J* = 4.1, 1.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, 18.3, 23.5, 25.8, 25.9, 26.2, 29.4, 29.6, 29.7, 32.3, 32.8, 63.3, 66.7, 67.3, 103.7; HRMS (FAB) calcd for $C_{22}H_{46}NaO_3Si$ (M^++Na) 409.3114, found 409.3118.

10c (R = Bz): Colorless oil, IR (KBr) 2926, 2855, 1720, 1275, 1113 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28-1.99 (24H, m), 3.36 (1H, dt, *J* = 12.2, 4.8 Hz), 3.64 (1H, dt, *J* = 12.2, 4.8 Hz), 3.81-3.93 (2H, m), 4.31 (2H, t, *J* = 6.7 Hz), 5.11 (1H, dd, *J* = 2.0, 1.0 Hz), 7.41-7.59 (3H, m), 8.03-8.07 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 25.9, 26.1, 28.6, 29.2, 29.3, 29.4, 29.5, 29.7, 32.2, 65.0, 66.6, 67.2, 103.7, 128.2, 129.4 130.4,132.7,166.5; HRMS (FAB) calcd for $C_{23}H_{37}O_4$ (M^++H) 377.2692, found 377.2707.

10d (R = Ac): Colorless oil, IR (KBr) 2926, 2855, 1742, 1238, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26-1.36 (16H, s), 1.51-1.66 (4H, m), 1.78-2.04 (4H, m), 2.05 (3H, s), 3.36 (1H, dt, *J* = 12.1, 4.8 Hz), 3.64 (1H, dt, *J* = 12.1, 4.8 Hz), 3.82-3.93 (2H, m), 4.05 (2H, t, *J* = 6.8 Hz), 5.11 (1H, dd, *J* = 1.9, 0.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.0, 23.5, 25.9, 26.2, 28.6, 29.2, 29.4, 29.5, 29.6 29.7, 32.3, 64.5, 66.6, 67.2, 103.6, 170.9; HRMS (FAB) calcd for $C_{18}H_{35}O_4$ (M^++H) 315.2535, found 315.2556.

General Procedure for Preparation of Oxacyclic-Ether 1c, 4c-6c

DIBAL-H (1.1 equiv.) in hexane was added dropwise to a solution of ε-caprolactone (1.0 equiv.) in dry CH_2Cl_2 (0.2 M) at -78 °C under N_2. After checking disappearance of ε-caprolactone on TLC, the mixture was quenched with MeOH and H_2O, filtered through celite, and evaporated in vacuo gave crude 2-oxepanol. A solution of the crude 2-oxepanol (1.0 equiv.), pyridinium *p*-toluenesulfonate (PPTS) (0.1 equiv.) and alcohol (3.0 equiv.) in dry CH_2Cl_2 (0.2 M) was stirred at rt under N_2. After checking disappearance of the crude 2-oxepanol on TLC, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash SiO_2 column chromatography

(neutralized SiO_2 purchased from Kanto Chemical) to give a oxacyclic-ethers. This reaction is not optimized. **1c**[3] is known in the literatures.

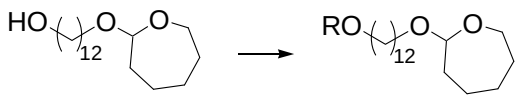
4c: Colorless oil, IR (KBr) 2859, 2247, 1454, 1026, 912 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.26-1.86 (7H, m), 2.04-2.14 (1H, m), 3.54-3.60 (1H, m), 3.82-3.91 (1H, m), 4.49 (1H, A in ABq, *J* = 11.9 Hz), 4.74 (1H, B in ABq, *J* = 11.9 Hz), 4.76-4.83 (1H, m), 7.26-7.35 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 29.6, 30.7, 34.9, 61.8, 68.7, 101.1, 127.4, 127.8, 128.3, 138.5; HRMS (FAB) calcd for $C_{13}H_{19}O_2$ (M^++H) 207.1385, found 207.1440.

5c: Colorless oil, IR (KBr) 2930, 2857, 2361, 1126, 964 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.25-1.75 (6H, m), 1.80-1.89 (1H, m), 2.04-2.15 (1H, m), 3.53-3.61 (1H, m), 3.85 (1H, ddd, *J* = 12.7, 10.4, 2.2 Hz), 4.14 (1H, ddd, *J* = 12.9, 6.6, 1.3 Hz), 4.35 (1H, ddd, *J* = 12.9, 5.6, 1.3 Hz), 4.82 (1H, dd, *J* = 8.7, 5.4 Hz), 6.30 (1H, ddd, *J* = 15.8, 6.6, 5.6 Hz), 6.61 (1H, d like, *J* = 15.8 Hz), 7.19-7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 29.5, 30.7, 34.9, 61.8, 67.4, 101.1, 126.1, 126.4, 127.5, 128.5, 132.2, 136.8; HRMS (FAB) calcd for $C_{15}H_{21}NaO_2$ (M^++H) 255.1361, found 255.1362.

6c: Colorless oil, IR (KBr) 2926, 2855, 1452, 1126, 1049 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.5 Hz), 1.08 (1.8H, d, *J* = 6.1 Hz) , 1.17 (1.2H, d, *J* = 6.3 Hz),1.26-1.68 (20H, m), 1.82-1.86 (1H, m), 1.96-2.10 (1H, m), 3.47-3.55 (1H, m), 3.64-3.86 (2H, m), 4.76-4.84 (1H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.1, 19.5, 21.8, 22.7, 22.8, 25.6, 25.9, 29.3, 29.6, 29.7, 30.7, 30.8, 31.9, 35.2, 35.3, 36.8, 37.5, 61.3, 61.4, 70.7, 73.3, 98.7, 101.3; HRMS (FAB) calcd for $C_{16}H_{33}O_2$ (M^++H) 257.2481, found 257.2480.

General Procedure for Preparation of Oxacyclic-ethers 12a-d

Oxacyclic-ether **12a-d** were prepared from oxacyclic-ether **12e** according to a literature.[2] Oxacyclic-ether **12e** was obtained from 1,12-dodecanediol and crude 2-oxepanol by the procedure described above.



12e **12a-d**

12e: Colorless oil, IR (KBr) 3331, 2926, 2853, 1447, 1126 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24-1.68 (26H, m) 1.81-1.85 (1H, m), 2.01-2.10 (1H, m), 3.36 (1H, dt, *J* = 12.0, 4.9 Hz), 3.50-3.56 (1H, m), 3.62-3.72 (3H, m), 3.76-3.84 (1H, m), 4.70 (1H, dd, *J* = 8.5, 5.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 25.7, 26.1, 29.3, 29.4, 29.5, 29.6, 30.6, 32.7, 34.9, 61.5, 62.7, 67.2, 101.7; HRMS (FAB) calcd for $C_{18}H_{37}O_3$ (M^++H) 301.2743, found 301.2723.

12a (R = Tr): Colorless oil, IR (KBr) 2927, 2825, 1448, 1126, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24-1.48 (18H, m), 1.51-1.68 (7H, m), 1.79-1.86 (1H, m), 2.01-2.10 (1H, m), 3.03 (2H, t, *J* = 6.6 Hz),

3.35 (1H, dt, *J* = 12.0, 4.8 Hz), 3.49-3.55 (1H, m), 3.68 (2H, dt, *J* = 12.0, 4.8 Hz), 3.75-3.84 (1H, m), 4.69 (1H, dd, *J* = 8.6, 5.3 Hz), 7.19-7.31 (9H, m), 7.44 (6H, t, *J* = 4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 26.2, 29.4, 29.5, 29.6, 29.7, 30.0, 30.7, 35.0, 61.6, 63.6, 67.3, 86.2, 101.8, 126.7, 127.6, 128.7, 144.5; HRMS (FAB) calcd for $C_{37}H_{50}NaO_3$ (M^++Na) 565.3658, found 565.3662.

12b (R = TBS): Colorless oil, IR (KBr) 2928, 2855, 1070, 1030, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.90 (9H, s), 1.26-1.40 (18H, m), 1.44-1.67 (8H, m), 1.79-1.86 (1H, m), 2.00-2.10 (1H, m), 3.35 (1H, dt, *J* = 12.0, 4.9 Hz), 3.50-3.79 (5H, m), 4.69 (1H, dd, *J* = 8.5, 5.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7, 18.9, 23.3, 26.4, 26.6, 26.8, 30.0, 30.1, 30.2, 30.4, 31.3, 33.5, 35.6, 62.1, 63.9, 67.8, 102.4; HRMS (FAB) calcd for $C_{24}H_{50}NaO_3Si$ (M^++Na) 437.3427, found 437.3415.

12c (R = Bz): Colorless oil, IR (KBr) 2926, 2855, 1720, 1275, 1124 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21-1.85 (27H, m), 2.01-2.10 (1H, m), 3.35 (1H, dt, *J* = 12.0, 4.9 Hz), 3.49-3.56 (1H, m), 3.68 (1H, dt, *J* = 12.0, 4.9 Hz), 3.75-3.84 (1H, m), 4.31 (2H, t, *J* = 6.7 Hz), 4.69 (1H, dd, *J* = 8.6, 5.3 Hz), 7.42-7.59 (3H, m), 8.03-8.07 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.7, 26.0, 26.2, 28.7, 29.2, 29.4, 29.5, 29.7, 30.7, 35.0, 61.6, 65.1, 67.2, 101.8, 128.2, 129.5, 130.5, 132.7, 166.6; HRMS (FAB) calcd for $C_{25}H_{41}O_4$ (M^++H) 405.3005, found 405.3003.

12d (R = Ac): Colorless oil, IR (KBr) 2930, 2856, 1730, 1246, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26-1.71 (26H, m), 1.81-1.85 (1H, m) 2.01-2.12 (1H, m), 2.05 (3H, s), 3.36 (1H, dt, *J* = 12.1, 4.8 Hz), 3.50-3.56 (1H, m), 3.68 (1H, dt, *J* = 12.1, 4.8 Hz), 3.76-3.84 (1H, m), 4.05 (2H, t, *J* = 6.7 Hz), 4.70 (1H, dd, *J* = 8.5, 5.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 22.5, 25.7, 26.0, 28.4, 29.1, 29.2, 29.3, 29.4, 29.6, 30.5, 34.8, 61.3, 64.4, 67.0, 101.6, 170.9; HRMS (FAB) calcd for $C_{20}H_{39}O_4$ (M^++H) 343.2848, found 343.2849.

General Procedure for Preparation of Methoxy ethyl (ME)-ethers 1d, 4d-6d, 13a-d

According to a literature,[12] 2,4,6-collidine (3.0 equiv.) and TESOTf or TMSOTf (2.0 equiv.) were added to a solution of dimethylacetal (1.0 equiv.) in CH_2Cl_2 (0.1 M) at 0 °C under N_2. The reaction mixture was stirred for 30 min at the same temperature, and then alcohol (1.5-5.0 equiv.) was added to the reaction mixture. The resulting solution was stirred at rt until disappearance of the polar component was ascertained by TLC analysis. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash SiO_2 column chromatography (neutralized SiO_2 purchased from Kanto Chemical) to give a ME-ether.

1d: According to the general procedure, **1d** (499.4 mg, 25% based from decanol) was obtained from dimethylacetal (4.09 mL, 45.39 mmol), 2,4,6-collidine (2.39 mL, 18.16 mmol), TESOTf (1.64 mL, 9.08 mmol) and decanol (1.00 mL, 9.08 mmol). Eluent; hexanes-AcOEt (25/1). Colorless oil, IR (KBr) 2926,

2855, 1136, 1101, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.7 Hz), 1.26-1.37 (14H, m), 1.30 (3H, d, *J* = 5.3 Hz), 1.51-1.65 (2H, m), 3.31 (3H, s), 3.36-3.44 (1H, m), 3.52-3.60 (1H, m), 4.62 (1H, q, *J* = 5.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.2, 22.6, 26.2, 29.3, 29.4, 29.5, 29.6, 29.8, 31.9, 52.2, 65.4, 100.3. *Anal*. Calcd for $C_{13}H_{28}O_2$: C, 72.17; H, 13.04. Found: C, 72.23; H, 13.11.

4d: According to the general procedure, **4d** (101.0 mg, 18%) was obtained from dimethylacetal (0.35 mL, 3.30 mmol), 2,4,6-collidine (1.32 mL, 9.90 mmol), TMSOTf (1.19 mL, 6.60 mmol) and benzyl alcohol **7** (1.72 mL, 16.5 mmol). Eluent; hexanes-AcOEt (20/1). Colorless oil, IR (KBr) 2988, 2905, 2249, 1452, 1128 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (3H, d, *J* = 5.3 Hz), 3.35 (3H, s), 4.52 (1H, A in ABq, *J* = 11.7 Hz), 4.64 (1H, B in ABq, *J* = 11.7 Hz), 4.77 (1H, q, *J* = 5.3 Hz), 7.26-7.38 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 52.1, 67.1, 99.8, 127.5, 127.7, 128.3, 138.3. *Anal*. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.52; H, 8.65.

5d: According to the general procedure, **5d** (492.0 mg, 78%) was obtained from dimethylacetal (0.35 mL, 3.30 mmol), 2,4,6-collidine (1.32 mL, 9.90 mmol), TMSOTf (1.19 mL, 6.60 mmol) and cinnamyl alcohol (**8**) (2.21 g, 16.5 mmol). Eluent; hexanes-AcOEt (30/1 to 20/1). Colorless oil, IR (KBr) 2990. 2249, 1448, 1128, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, d, *J* = 5.3 Hz), 3.35 (3H, s), 4.16 (1H, ddd, *J* = 12.6, 5.7, 1.1 Hz), 4.28 (1H, ddd, *J* = 12.6, 5.7, 1.1 Hz), 4.75 (1H, q, *J* = 5.3 Hz), 6.30 (1H, dt, *J* = 15.9, 5.7 Hz), 6.63 (1H, d like, *J* = 15.9 Hz), 7.21-7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 52.8, 66.6, 100.5, 126.7, 127.2, 128.3, 129.2, 132.8, 137.4; HRMS (FAB) calcd for $C_{12}H_{16}NaO_2$ (M^++Na) 215.1048, found 215.1075.

6d: According to the general procedure, **6d** (414.0 mg, 58%) was obtained from dimethylacetal (0.35 mL, 3.30 mmol), 2,4,6-collidine (1.32 mL, 9.90 mmol), TESOTf (1.49 mL, 6.60 mmol) and 2-decanol **9** (1.26 mL, 6.60 mmol). Eluent; hexanes-AcOEt (20/1). Colorless oil, IR (KBr) 2925, 2855, 2247, 1462, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 5.6 Hz), 1.11 (1.6H, d, *J* = 6.2 Hz), 1.19 (1.4H, d, *J* = 6.2 Hz), 1.27-1.58 (17H, m), 3.30 (3H, s), 3.57-3.74 (1H, m), 4.64-4.74 (1H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.8, 20.7, 20.8, 21.7, 23.4, 26.2, 26.5, 30.0, 30.1, 30.4, 30.5, 32.6, 37.7, 38.2, 52.0, 72.3, 73.8, 98.8, 100.4. *Anal*. Calcd for $C_{13}H_{28}O_2$: C, 72.17; H, 13.04. Found: C, 72.39; H, 13.02.

13a (R = Tr): According to the general procedure, **13a** (470.2 mg, 45%) was obtained from dimethylacetal (0.22 mL, 2.08 mmol) with 2,4,6-collidine (0.82 mL, 6.23 mmol), TESOTf (0.94 mL, 4.15 mmol) and alcohol **14a**[2] (1.82 g, 4.09 mmol) in CH_2Cl_2 (6 ml) via cannula. Eluent; hexanes-AcOEt (10/1). Colorless oil, IR (KBr) 2930, 2855, 2359, 1489, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19-1.39 (16H, m), 1.29 (3H, d, *J* = 5.3 Hz), 1.53-1.66 (4H, m), 3.03 (2H, t, *J* = 6.7 Hz), 3.31 (3H, s), 3.36-3.60 (2H, m), 4.62 (1H, q, *J* = 5.3 Hz), 7.19-7.31 (9H, m), 7.44 (6H, d, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.2, 29.5, 29.6, 29.8, 30.0, 52.2, 63.6, 65.4, 86.2, 100.3, 126.7, 127.6, 128.6, 144.5; HRMS (FAB) calcd for $C_{34}H_{46}NaO_3$ (M^++Na) 525.3345, found 525.3331.

13b (R = TBS): According to the general procedure, **13b** (995.0 mg, 60%) was obtained from dimethylacetal (0.47 mL, 4.40 mmol), 2,4,6-collidine (1.74 mL, 13.2 mmol), TESOTf (1.99 mL, 8.8 mmol) and alcohol **14b**[2] (4.18 g, 13.2 mmol). Eluent; hexanes-AcOEt (15/1 to 10/1). Colorless oil, IR (KBr) 2928, 2855, 1464, 1256, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.90 (9H, s), 1.22-1.32 (16H, m), 1.25 (3H, d, *J* = 5.3 Hz), 1.46-1.62 (4H, m), 3.26 (3H, s), 3.36-3.43 (1H, m), 3.52-3.61 (1H, m), 3.59 (2H, t, *J* = 6.5 Hz), 4.58 (1H, q, *J* = 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 18.3, 19.2, 25.7, 25.9, 26.2, 29.4, 29.5, 29.6, 29.8, 32.8, 52.1, 63.2, 65.4, 100.2; HRMS (FAB) calcd for $C_{21}H_{46}NaO_3Si$ (M^++Na) 397.3114, found 397.3102.

13c (R = Bz): According to the general procedure, **13c** (558.4 mg, 96%) was obtained from dimethylacetal (0.17 mL, 1.60 mmol), 2,4,6-collidine (0.63 mL, 4.80 mmol), TESOTf (0.72 mL, 3.20 mmol) and alcohol **14c**[2] (980.6 mg, 3.20 mmol). Eluent; hexanes-EtOH (5/1). Colorless oil, IR (KBr) 2928, 2855, 2251, 1715, 1277 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19-1.44 (16H, m), 1.29 (3H, d, *J* = 5.5 Hz), 1.53-1.61 (2H, m), 1.72-1.81 (2H, m), 3.31 (3H, s), 3.40 (1H, dt, *J* = 12.0, 4.7 Hz), 3.56 (1H, dt, *J* = 12.0, 4.6 Hz), 4.31 (2H, t, *J* = 6.7 Hz), 4.62 (1H, q, *J* = 5.4 Hz), 7.41-7.59 (3H, m), 8.03-8.06 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.0, 25.8, 26.0, 28.4, 29.0, 29.2, 29.3, 29.6, 51.8, 64.7, 65.1, 100.0, 128.0, 129.2, 130.3, 132.4, 166.1; HRMS (FAB) calcd for $C_{22}H_{36}NaO_4$ (M^++Na) 387.2511, found 387.2513.

13d (R = Ac): According to the general procedure, the treatment of dimethylacetal (0.16 mL, 1.50 mmol) with 2,4,6-collidine (0.50 mL, 4.50 mmol), TESOTf (0.93 mL, 3.00 mmol) and alcohol **14d**[2] (730 mg, 2.99 mmol, added as a solution of CH_2Cl_2 (3 ml)) gave **13d** (134.0 mg, 30%). Eluent; hexanes-AcOEt (20/1 to 10/1). Colorless oil, IR (KBr) 2928, 2855, 2251, 1732, 1244 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27-1.37 (16H, m), 1.29 (3H, d, *J* = 5.5 Hz), 1.53-1.59 (4H, m), 2.05 (3H, s), 3.31 (3H, s), 3.40 (1H, dt, *J* = 12.0, 4.6 Hz), 3.56 (1H, dt, *J* = 12.0, 4.6 Hz), 4.05 (2H, t, *J* = 6.8 Hz), 4.62 (1H, q, *J* = 5.3 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.3, 21.0, 25.9, 26.2, 28.5, 29.2, 29.4, 29.5, 29.8, 52.2, 64.5, 65.4, 100.2, 170.9; HRMS (FAB) calcd for $C_{17}H_{34}NaO_4$ (M^++Na) 325.2355, found 325.2336.

General Procedure for Deprotection of Acetal-type Protecting Groups by TESOTf–2,4,6-Collidine Combination

2,4,6-Collidine (3.0 equiv.) and TESOTf (2.0 equiv.) were added to a solution of the compound with acetal-type protecting group in CH_2Cl_2 (0.1 M) at 0 °C under N_2. The reaction mixture was stirred for 30 min at the same temperature. After checking disappearance of the substrate on TLC, H_2O was added to the reaction mixture and the solution was stirred for 10 min. Disappearance of the polar component was ascertained by TLC analysis. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash SiO_2 column chromatography to give an alcohol.

Experiments in Table 1

Entry 2: According to the general procedure, treatment of **1b** (27.1 mg, 0.119 mmol) with 2,4,6-collidine (47 μL, 0.357 mmol) and TESOTf (54 μL, 0.238 mmol) gave **2** (16.5 mg, 88%). Eluent; hexanes-AcOEt (4/1).

Entry 3: According to the general procedure, treatment of **1c** (51.0 mg, 0.199 mmol) with 2,4,6-collidine (79 μL, 0.597 mmol) and TESOTf (90 μL, 0.398 mmol) gave **2** (28.0 mg, 89%). Eluent; hexanes- AcOEt (10/1).

Entry 4: According to the general procedure, treatment of **1d** (51.6 mg, 0.239 mmol) with 2,4,6-collidine (94 μL, 0.717 mmol) and TESOTf (108 μL, 0.478 mmol) gave **2** (36.3 mg, 96%). Eluent; hexanes-AcOEt (6/1).

Entry 5: According to the general procedure, treatment of **1e** (108.7 mg, 0.472 mmol) with 2,4,6-collidine (373 μL, 2.830 mmol) and TESOTf (427 μL, 1.877 mmol) gave **2** (41.6 mg, 56%). Eluent; hexanes-AcOEt (50/1 to 5/1).

Experiments in Table 2

7 from 4a: According to the general procedure, treatment of **4a** (35.6 mg, 0.200 mmol) with 2,4,6-collidine (79 μL, 0.600 mmol) and TESOTf (90 μL, 0.400 mmol) gave **7** (15.6 mg, 72%). Eluent; hexanes- AcOEt (5/1).

7 from 4c: According to the general procedure, treatment of **4c** (28.9 mg, 0.140 mmol) with 2,4,6-collidine (111 μL, 0.840 mmol) and TESOTf (158 μL, 0.700 mmol) gave **7** (9.9 mg, 65%). Eluent; benzene- AcOEt (10/1).

7 from 4d: According to the general procedure, treatment of **4d** (30.1 mg, 0.181 mmol) with 2,4,6-collidine (72 μL, 0.543 mmol) and TESOTf (82 μL, 0.362 mmol) gave **7** (16.3 mg, 83%). Eluent; hexanes- AcOEt (3/1 to 2/1).

8 from 5a: According to the general procedure, treatment of **5a** (38.4 mg, 0.188 mmol) with 2,4,6-collidine (74 μL, 0.564 mmol) and TESOTf (85 μL, 0.376 mmol) gave **8** (21.6 mg, 86%). Eluent; benzene- AcOEt (10/1).

8 from 5b: According to the general procedure, treatment of **5b** (43.7 mg, 0.200 mmol) with 2,4,6-collidine (79 μL, 0.600 mmol) and TESOTf (90 μL, 0.400 mmol) gave **8** (24.0 mg, 89%). Eluent; benzene- AcOEt (10/1).

8 from 5c: According to the general procedure, treatment of **5c** (23.7 mg, 0.102 mmol) with 2,4,6-collidine (81 μL, 0.612 mmol) and TESOTf (115 μL, 0.510 mmol) gave **8** (13.4 mg, 98%). Eluent; benzene- AcOEt (10/1).

8 from 5d: According to the general procedure, treatment of **5d** (38.2 mg, 0.199 mmol) with

2,4,6-collidine (79 μL, 0.597 mmol) and TESOTf (90 μL, 0.398 mmol) gave **8** (24.0 mg, 90%). Eluent; benzene- AcOEt (10/1).

9 from 6a: According to the general procedure, treatment of **6a** (39.2 mg, 0.172 mmol) with 2,4,6-collidine (68 μL, 0.516 mmol) and TESOTf (78 μL, 0.344 mmol) gave **9** (15.4 mg, 57%). Eluent; hexanes-AcOEt (5/1).

9 from 6c: According to the general procedure, treatment of **6c** (51.3 mg, 0.200 mmol) with 2,4,6-collidine (79 μL, 0.600 mmol) and TESOTf (90 μL, 0.400 mmol) gave **9** (19.2 mg, 62%). Eluent; hexanes-AcOEt (4/1).

9 from 6d: According to the general procedure, treatment of **6d** (40.2 mg, 0.186 mmol) with 2,4,6-collidine (73 μL, 0.558 mmol) and TESOTf (84 μL, 0.372 mmol) gave **9** (18.2 mg, 62%). Eluent; hexanes-AcOEt (4/1).

Experiments in Table 3

14a from 10a: According to the general procedure, treatment of **10a** (83.1 mg, 0.161 mmol) with 2,4,6-collidine (64 μL, 0.483 mmol) and TESOTf (73 μL, 0.322 mmol) gave **14a** (59.6 mg, 83%). Eluent; hexanes-AcOEt (4/1 to 3/1).

14a from 12a: According to the general procedure, treatment of **12a** (102.1 mg, 0.188 mmol) with 2,4,6-collidine (74 μL, 0.564 mmol) and TESOTf (85 μL, 0.376 mmol) gave **14a** (64.3 mg, 77%). Eluent; hexanes-AcOEt (3/1).

14a from 13a: According to the general procedure, treatment of **13a** (100.0 mg, 0.199 mmol) with 2,4,6-collidine (79 μL, 0.597 mmol) and TESOTf (90 μL, 0.398 mmol) gave **14a** (74.2 mg, 80%). Eluent; hexanes-AcOEt (4/1).

14b from 10b: According to the general procedure, treatment of **10b** (77.0 mg, 0.199 mmol) with 2,4,6-collidine (79 μL, 0.597 mmol) and TESOTf (90 μL, 0.398 mmol) gave **14b** (54.0 mg, 86%). Eluent; hexanes- AcOEt (5/1).

14b from 12b: According to the general procedure, treatment of **12b** (82.0 mg, 0.198 mmol) with 2,4,6-collidine (78 μL, 0.594 mmol) and TESOTf (89 μL, 0.396 mmol) gave **14b** (50.9 mg, 81%). Eluent; hexanes- AcOEt (4/1).

14b from 13b: According to the general procedure, treatment of **13b** (65.6 mg, 0.175 mmol) with 2,4,6-collidine (69 μL, 0.525 mmol) and TESOTf (79 μL, 0.350 mmol) gave **14b** (49.7 mg, 90%). Eluent; hexanes- AcOEt (5/1).

14c from 10c: According to the general procedure, treatment of **10c** (71.6 mg, 0.190 mmol) with 2,4,6-collidine (75 μL, 0.570 mmol) and TESOTf (86 μL, 0.380 mmol) gave **14c** (51.0 mg, 88%). Eluent; hexanes- AcOEt (3/1).

14c from 12c: According to the general procedure, treatment of **12c** (80.9 mg, 0.200 mmol) with 2,4,6-collidine (79 μL, 0.600 mmol) and TESOTf (90 μL, 0.400 mmol) gave **14c** (50.2 mg, 82%). Eluent; hexanes- AcOEt (3/1 to 2/1).

14c from 13c: According to the general procedure, treatment of **13c** (70.3 mg, 0.193 mmol) with 2,4,6-collidine (76 μL, 0.579 mmol) and TESOTf (87 μL, 0.386 mmol) gave **14c** (47.2 mg, 80%). Eluent; hexanes- AcOEt (3/1).

14d from 10d: According to the general procedure, treatment of **10d** (59.7 mg, 0.190 mmol) with 2,4,6-collidine (75 μL, 0.570 mmol) and TESOTf (86 μL, 0.380 mmol) gave **14d** (40.8 mg, 88%). Eluent; hexanes-AcOEt (3/1 to 2/1).

14d from 12d: According to the general procedure, treatment of **12d** (63.5 mg, 0.186 mmol) with 2,4,6-collidine (73 μL, 0.557 mmol) and TESOTf (84 μL, 0.371 mmol) gave **14d** (38.0 mg, 84%). Eluent; hexanes-AcOEt (3/1).

14d from 13d: According to the general procedure, treatment of **13d** (60.5 mg, 0.200 mmol) with 2,4,6-collidine (79 μL, 0.600 mmol) and TESOTf (90 μL, 0.400 mmol) gave **14d** (42.4 mg, 86%). Eluent; hexanes-AcOEt (2/1).

ACKNOWLEDGEMENTS

This work was supported by a Grant-in-Aid for Scientific Research (S) and a Grant-in-Aid for Scientific Research for Exploratory Research from the Japan Society for the Promotion of Science and by a Grant-in-Aid for Scientific Research on Priority Areas (17035047) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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