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Selective cleavage of primary MPM ethers with TMSI/Et$_3$N

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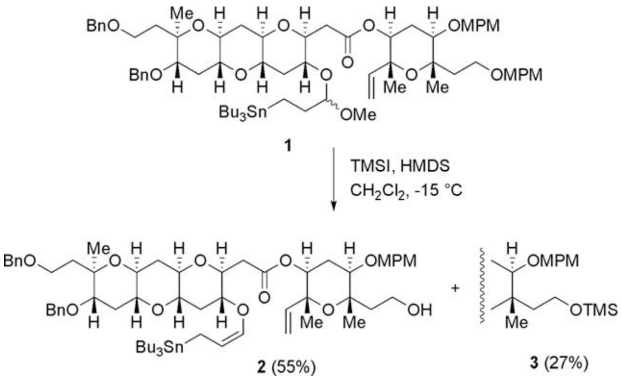
ABSTRACT

A useful method for the selective cleavage of primary MPM ethers by using TMSI/Et$_3$N is described. Other protective groups such as secondary MPM ethers, silyl ethers, and benzylidene acetal were stable under the reaction conditions.

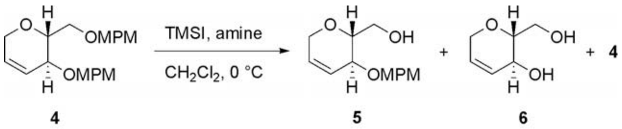
As well as the synthetic strategy, choice of the suitable protective group is very important for the multi-step synthesis of natural product. MPM (methoxyphenyl methyl) ether is well recognized as one of the most useful protective groups, and widely used because of its stability under the reaction conditions and ease of the deprotection. Various methods have been reported for the selective cleavage of MPM ethers.[1] Particularly, hydrogenolysis using Pd catalysts, oxidation with DDQ, and some Lewis acids are popularly used for this purpose. In the course of our synthetic study of yessotoxin, we found that the reaction of **1** with TMSI and HMDS (1,1,1,3,3,3-hexamethyldisilazane) gave a mixture of the primary alcohol **2** and its TMS ether **2** in 55% and 27% yields, respectively (Scheme 1).[2,3] Unexpectedly, the primary MPM ether was cleanly cleaved although the benzyl ethers and secondary MPM ether were not affected under the reaction conditions.[4,5] This result prompted us to investigate the generality of this reaction. In this Letter, we wish to report a new method for the selective cleavage of primary MPM ethers by using TMSI and amine base.[6]

In an initial experiment, to a mixture of bis-MPM ether **4** in CH$_2$Cl$_2$ at 0 °C were added TMSI (2 equiv) and HMDS (3 equiv).[7] After stirring for 1 h, the reaction mixture was treated with MeOH and K$_2$CO$_3$ to give the corresponding primary alcohol **5** in 83% yield (Scheme 2).[8] The use of Et$_3$N as a base provided the same result, and the product **5** was obtained in 83% yield.[9] On the other hand, the reaction in the absence of amine afforded a mixture of **5**, diol **6**, and unreacted **4**.[10] These results clearly indicate that the use of amine is essential for the selective cleavage of primary MPM ether.

On the basis of the results described above, we next examined the selective cleavage of primary MPM ethers of substrates having



Scheme 1.



amine	5	6	4
HMDS	83%	-	-
Et$_3$N	83%	-	-
none	32%	10%	14%

Scheme 2.

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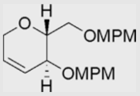
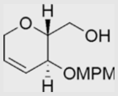
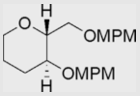
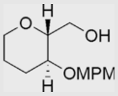
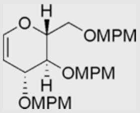
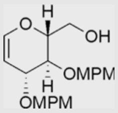
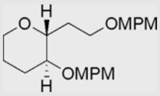
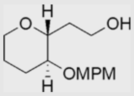
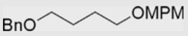
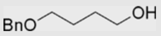
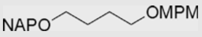
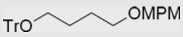
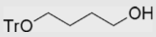
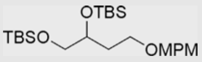
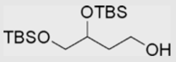
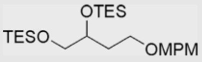
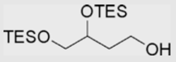
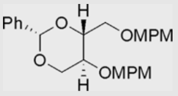
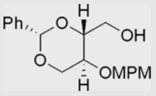
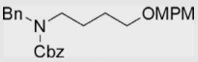
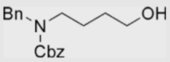
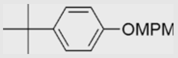
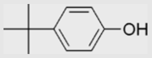
Table 1
Selective cleavage of primary MPM ethers[a]

Entry	Substrate	Product	Yield[b] (%)
1			83
2			83
3			96
4			95
5			87
6			94
7			97
8			90
9			87
10			92
11			91
12[c]			91

[a] Reactions were carried out with TMSI (2 equiv) and Et_3N (3 equiv) in CH_2Cl_2 at 0 °C for 1 h. The reaction mixture was then treated with K_2CO_3 and MeOH.

[b] Isolated yield.

[c] The reaction was carried out at room temperature for 4 h.

various protective groups. The results are summarized in Table 1.[11] As expected, the reactions of substrates having secondary MPM ethers proceeded smoothly to give the corresponding primary alcohols in good yields (entries 1–4). Other primary benzylic protective groups, such as benzyl, NAP (2-naphthylmethyl), and Tr (triphenylmethyl) are stable under the reaction conditions (entries 5–7). The reaction proceeded smoothly in the presence of acid-sensitive protective groups such as TBS, TES, and benzylidene acetal (entries 8–10). The reaction conditions did not affect a Cbz-protected benzylamino group (entry 11). On the other hand, acyclic acetal protective groups such as MOM and THP groups were cleaved under the reaction conditions. Furthermore, the cleavage of phenolic MPM ether also proceeded cleanly to give the product in good yield although the reaction was much slower (entry 12).

In conclusion, we have demonstrated a simple and convenient method for the selective cleavage of primary MPM ethers with TMSI/Et_3N. Various protective groups, including secondary MPM ethers, can survive under the reaction conditions. We anticipate that the present method will be useful in natural product synthesis.

Acknowledgment

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References and notes

1. Wuts, P. G. M.; Greene, T. W. In *Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons: New Jersey, 2007; pp 121–130.
2. Kadota, I.; Ueno, H.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 8935–8938.
3. The reaction conditions were originally developed for the acetal cleavage giving enol ethers, see: (a) Miller, R. D.; McKean, D. R. *Tetrahedron Lett.* **1982**, *23*, 323–326; Also see: (b) Kadota, I.; Sakaihara, T.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 3195–3198.
4. For the use of TMSI to cleave a benzyl ether, see: Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761–3764.
5. For an example of the deprotection of secondary MPM ethers using TMSI, see: Gordon, D. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 659–663.
6. Direct conversion of MPM ethers into silyl ethers with R_3SiOTf/Et_3N has been reported, see: Oriyama, T.; Yatabe, K.; Kawada, Y.; Koga, G. *Synlett* **1995**, 45–46.
7. The amounts of the reagents used were found to be enough to complete the reaction although the precise optimization was not performed. The use of large excess of the reagents did not affect the selectivity.
8. The work up with MeOH and K_2CO_3 was carried out for the conversion of the TMS ether, contained in the reaction mixture, into the primary alcohol.
9. Although further investigation on the amine was not performed, other amines such as $^{i}Pr_2NEt$ and piperidine are expected to be applicable.
10. The reaction was carried out with 1.2 equiv of TMSI, and quenched after 0.5 h. The use of an excess amount of TMSI would complete the reaction leading to **6**. See Ref. 5.
11. The reaction of **4** is representative. To a stirring mixture of **4** (82 mg, 0.22 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C were added Et_3N (93 μL, 0.66 mmol) and TMSI (63 μL, 0.44 mmol). After 1 h, MeOH (2.0 mL) and K_2CO_3 (150 mg, 1.1 mmol) were added, and the stirring was continued for 0.5 h. The reaction mixture was then diluted with EtOAc, and then washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography to give **5** (46 mg, 83%).