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Mild, selective deprotection of PMB ethers with triflic acid/1,3-dimethoxybenzene

Michael E. Jung *, Pierre Koch

Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095-1569, United States

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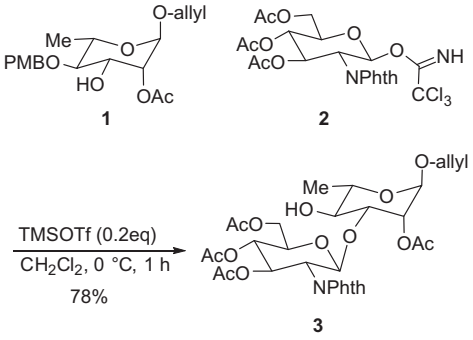
ABSTRACT

An efficient method for the cleavage of the *p*-methoxybenzyl protecting group of several alcohols in the presence of 0.5 equiv of trifluoromethanesulfonic acid and 1,3-dimethoxybenzene in dichloromethane at room temperature is described.

The *p*-methoxybenzyl (PMB) group is a very useful protecting group for alcohols since it is generally stable toward a variety of reaction conditions and can be selectively cleaved in the presence of unsubstituted benzyl ethers.[1] Numerous methods exist for the selective removal of the PMB group including oxidative removal with ceric ammonium nitrate (CAN)[2] or 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[3] Cleavage in the presence of a combination of a Lewis acid and a soft nucleophile, such as $AlCl_3$–EtSH, $MgBr_2$–Me_2S, $CeCl_3{\cdot}7H_2O$–NaI, $SnCl_4$–PhSH, $NaCNBH_3$–$BF_3{\cdot}Et_2O$, $ZrCl_4$–CH_3CN, or TMSCl–$SnCl_2$–anisole, has also been reported.[4] Although PMB ethers are stable under many acidic conditions, they may be cleaved in the presence of strong acids, for example, AcOH at 90 °C,[5] 10% trifluoroacetic acid (TFA) in dichloromethane,[6] TFA or methanesulfonic acid (MsOH) with 1,3-dimethoxybenzene in toluene,[7] or TFA-anisole in dichloromethane.[8] It has also been reported that the PMB group can be transferred from alcohols to sulfonamides in the presence of a catalytic amount of trifluoromethanesulfonic acid (triflic acid, TfOH).[9] However, when the sulfonamide was omitted from this reaction, no PMB cleavage occurred.[9]

During the course of our studies toward the synthesis of the carbohydrate moiety of Brasilicardin A,[10] we carried out the trimethylsilyl trifluoromethanesulfonate (TMSOTf)-catalyzed glycosidation reaction of the 3-OH-rhamnose donor **1** and imidate **2** (Scheme 1). To our surprise, the coupled alcohol **3** was isolated as the sole product of this reaction, in which the formation of the glycosidic bond took place, but the PMB group at the 4-OH position of the rhamnose unit was also cleaved.



Scheme 1. TMSOTf-promoted glycosidation of **1** and **2**.

Since Wolbers and Hoffmann had previously reported that the PMB group was unstable under the influence of the Lewis acid TMSOTf,[11] we wanted to explore the possibility of using TMSOTf as a general method to deprotect PMB ethers.

To check the generality of this novel process, we treated a solution of the PMB ether of the L-rhamnose derivative **1** in dichloromethane with a catalytic amount of TMSOTf (Table 1; all yields in Tables are isolated yields). Fair yields (50–54%) of the diol **4** were obtained with 0.05–0.2 equiv of TMSOTf, although the yield decreased when a larger amount (0.4 equiv) was used (entries a–d). The highest yield of the diol **4** (63%) was obtained by adding an additional 0.05 equiv of TMSOTf 5 min after the first addition (entry e). When undried dichloromethane was used, the yield of

* Corresponding author.
E-mail address: jung@chem.ucla.edu (M.E. Jung).

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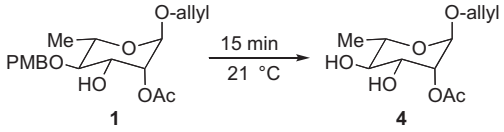
Table 1
Cleavage of the PMB ether of **1**



1 **4**

Entry	Reagent	Amount (equiv)	Solvent	Yield (%)
a	TMSOTf	0.05	CH_2Cl_2	50
b	TMSOTf	0.1	CH_2Cl_2	54
c	TMSOTf	0.2	CH_2Cl_2	51
d	TMSOTf	0.4	CH_2Cl_2	27
e	TMSOTf	2 × 0.05	CH_2Cl_2	63
f	TMSOTf	0.1	CH_2Cl_2[a]	36
g	TfOH	0.1	CH_2Cl_2	50
h	TfOH	2 × 0.05	CH_2Cl_2	59

[a] Not dried.

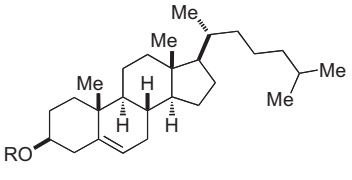
the diol **4** decreased significantly (entry f). In order to confirm whether the strong Brønsted acid triflic acid was generated during the reaction conditions and caused the PMB cleavage, we treated the PMB ether **1** with TfOH. Comparable yields of the diol **4** were obtained (compare entries b vs g, and e vs h). In these cases, the allyl ether, the anomeric acetal, and the acetate protecting groups of the rhamnose derivative remained intact.

Since we wanted to eliminate any neighboring group effects caused by the adjacent hydroxyl function in **1**, we chose the PMB ether of cholesterol **5** to investigate the cleavage of the PMB group (Table 2). The use of TMSOTf in this case resulted in the formation of side products, and the corresponding alcohol **6** was obtained only in poor yield (31%). An incomplete reaction was observed after 15 min when 0.1 equiv of TfOH was used (entry b), but no side products were detected. Increasing the amount of TfOH to 0.5 equiv increased the yield of cholesterol (**6**) to 85%. By using this amount of TfOH, we shortened the reaction time to 5 min and obtained an 82% yield of compound **6** (entry f). Lengthening the reaction time to 30 min resulted in a slight decrease in yield (entry g). Replacement of dichloromethane with toluene was tolerated, but when we performed the reaction in THF, a dramatic decrease in yield was observed (entries h and i). When we used TFA as the acid instead of TfOH, we could detect no cholesterol (**6**) after 15 min. After 48 h using this weaker acid, we were able to isolate only 16% of compound **6** (entry j).

The results of the removal of the PMB group of various substrates using 0.5 equiv of TfOH in dichloromethane as optimal reaction conditions are listed in Table 3.[12] All of the PMB ethers were prepared from the corresponding alcohol using the adapted protocol of Rai and Basu.[13] TfOH in dichloromethane cleaved the PMB ethers of primary and hindered secondary alcohols in excellent yields (88–94%, entries a–d). The PMB group could be chemoselectively removed in the presence of a simple benzyl ether (86%, entry e). These conditions are mild enough so that even substrates **17** and **19**, that have a phenolic TBS, an ester group, an allyl ether, an acetonide, and an anomeric acetal, were readily converted into the corresponding alcohols **18** and **20** in 79% and 83% yield, respectively (entries f and g). However, compounds that can easily generate carbocations could not be cleaved by this method (entries h and i). In neither case, could a clean product be isolated and only decomposition was observed.

Since yields of >50% can be achieved with only 10% of triflic acid in an aprotic solvent, there must be a way for additional protons to be generated during the reaction. We hypothesized that this pro-

Table 2
Cleavage of the PMB ether of **5**[a]

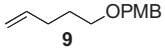
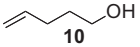
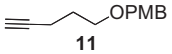
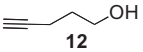
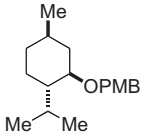
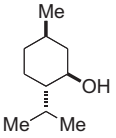
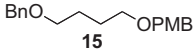
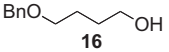
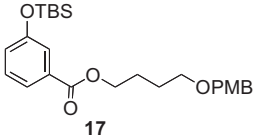
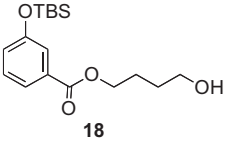
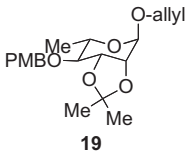
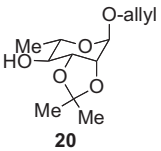
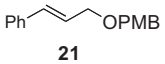
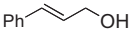
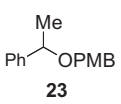
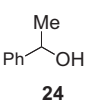


5 **6**

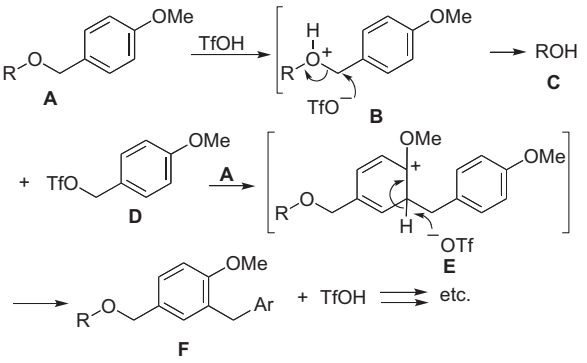
Entry	Reagent (amount)	Solvent	Time	Yield (%)
a	TMSOTf (0.1 equiv)	CH_2Cl_2	15 min	31
b	TfOH (0.1 equiv)	CH_2Cl_2	15 min	42
c	TfOH (0.2 equiv)	CH_2Cl_2	15 min	77
d	TfOH (0.5 equiv)	CH_2Cl_2	15 min	85
e	TfOH (1.0 equiv)	CH_2Cl_2	15 min	44
f	TfOH (0.5 equiv)	CH_2Cl_2	5 min	82
g	TfOH (0.5 equiv)	CH_2Cl_2	30 min	75
h	TfOH (0.5 equiv)	Toluene	15 min	79
i	TfOH (0.5 equiv)	THF	15 min	12
j	TFA (0.5 equiv)	CH_2Cl_2	48 h	16

[a] Conditions: PMB ether **5** (0.2 mmol), solvent (1 mL), 21 °C.

Table 3
Selective cleavage of the PMB group by triflic acid in dichloromethane[a]

Entry	Substrate	Product	Yield (%)
a	$Me(CH_2)_8CH_2OPMB$ **7**	$Me(CH_2)_8CH_2OH$ **8**	93
b	 **9**	 **10**	88
c	 **11**	 **12**	91
d	 **13**	 **14**	94
e	 **15**	 **16**	86
f	 **17**	 **18**	79
g	 **19**	 **20**	83
h	 **21**	 **22**	0
i	 **23**	 **24**	0

[a] Conditions: PMB ether (0.2 mmol), TfOH (0.1 mmol), CH_2Cl_2(1 mL), 21 °C, 15 min.



Scheme 2. Mechanism of deprotection.

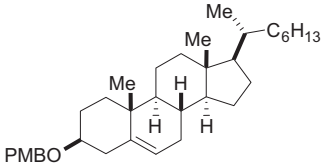
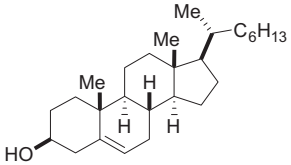
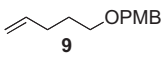
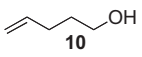
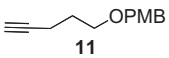
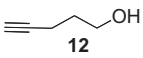
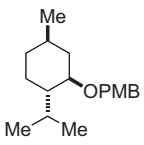
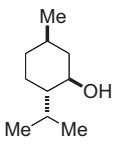
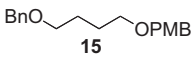
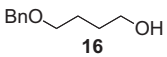
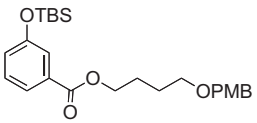
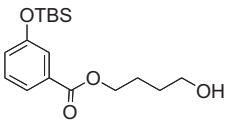
duction of protons occurred via an intermolecular Friedel–Crafts alkylation process (Scheme 2). Thus protonation of the PMB ether **A** with triflic acid would give the salt **B**, which could then be cleaved to the observed alcohol product **C** and the PMB triflate **D**. Under the reaction conditions, we propose that this very reactive species **D** (which could be in equilibrium with the PMB cation triflate salt) would react with the activated aromatic ring of another PMB ether **A** to generate the Friedel–Crafts intermediate **E**. Loss of a proton would generate an arylmethyl PMB ether **F** and regenerate an equivalent of triflic acid to continue the process. Thus the reaction is theoretically catalytic in triflic acid and therefore less than 1 equiv of the acid could generate >90% yield of the alcohols.

If this mechanism (or a similar one) were active, we argue that we could improve the process by adding a more electron-rich aromatic ring to react with the triflate **D** and generate additional triflic acid more rapidly. This turned out to be the case. Addition of 3 equiv of 1,3-dimethoxybenzene to the reaction mixture shortened the reaction time to 10 min and gave very good yields of the alcohols, up to 98%, as shown in Table 4.[14] For almost all of the substrates, the yield increased upon addition of the 1,3-dimethoxybenzene when compared to the yields given in Tables 2 and 3. In all the cases, 1,3-dimethoxy-4-(4-methoxybenzyl)benzene could be isolated, as expected.

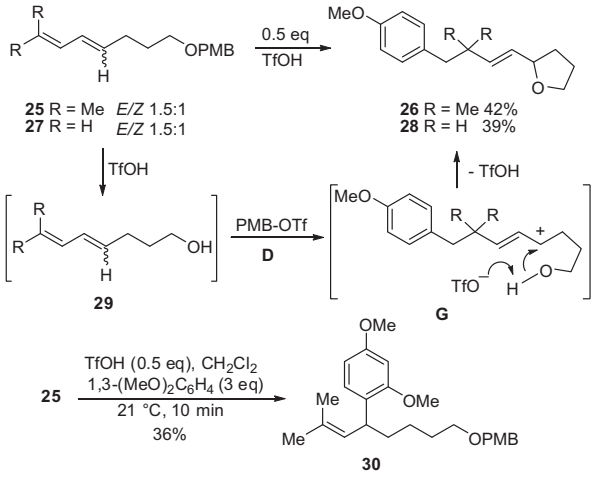
We tried to adapt our method to the cleavage of PMB ethers containing a conjugated diene system. Onoda, et al., reported this cleavage using $MgBr_2{\cdot}OEt_2$–Me_2S, but other reagents like DDQ, CAN, TFA, TFA-ethanethiol, and BBr_3 were unsuccessful.[4b] We worried that the conjugated diene would suffer an electrophilic attack by the PMB triflate under our conditions. Indeed, the PMB group of the two dienyl ethers **25** and **27** could not be cleaved by TfOH in dichloromethane (Scheme 3). Instead, the alkenyl tetrahydrofurans **26** and **28** were obtained in 42% and 39% yield, respectively. We believe that under these acidic conditions, the alcohol **29** and the PMB triflate (or carbocation) **D** are generated. The triflate **D** is then attacked by the diene system to form the relatively stable allylic carbocation **G**. Cyclization with the loss of triflic acid would produce the observed tetrahydrofurans **26** and **28**. When the reaction of **25** was carried out in the presence of 1,3-dimethoxybenzene, the adduct **30** was obtained in 36% yield, presumably via simple protonation of the diene and trapping.

In conclusion, we have reported a fast and efficient method for the selective removal of PMB ethers to generate alcohols, in which the deprotection proceeds smoothly by treatment of the PMB ether

Table 4
Selective cleavage of the PMB group with triflic acid/1,3-dimethoxybenzene in dichloromethane[a]

Entry	Substrate	Product	Yield (%)
a	 **5**	 **6**	91
b	$Me(CH_2)_8CH_2OPMB$ **7**	$Me(CH_2)_8CH_2OH$ **8**	97
c	 **9**	 **10**	93
d	 **11**	 **12**	89
e	 **13**	 **14**	98
f	 **15**	 **16**	94
g[b]	 **17**	 **18**	85

[a] Conditions: PMB ether (0.2 mmol), TfOH (0.1 mmol), 1,3-dimethoxybenzene (0.6 mmol), CH_2Cl_2 (1 mL), 21 °C, 10 min.
[b] Reaction time: 1 min.



Scheme 3. Attempted deprotection of dienyl PMB ethers.

with 0.5 equiv of TfOH and 3 equiv of 1,3-dimethoxybenzene in dichloromethane at room temperature.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.102.

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