

## A MILD AND SELECTIVE DEPROTECTION OF *p*-METHOXYBENZYL (PMB) ETHER BY MAGNESIUM BROMIDE DIETHYL ETHERATE-METHYL SULFIDE

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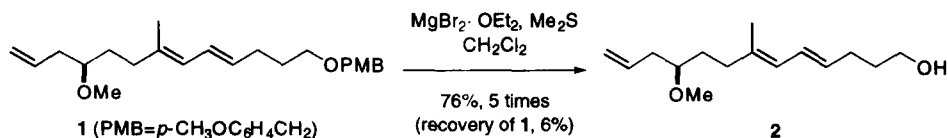
**Abstract:** The magnesium bromide diethyl etherate ( $\text{MgBr}_2 \cdot \text{OEt}_2$ )-methyl sulfide ( $\text{Me}_2\text{S}$ ) system is useful for the mild and chemo-selective deprotection of *p*-methoxybenzyl (PMB) ether in the presence of 1,3-diene, *t*-butyldimethylsilyl (TBDMS) ether, benzoate, benzyl ether and acetonide.

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Mild and selective removal of hydroxyl protecting groups is crucial for the synthesis of complex natural products such as carbohydrates and macrolide antibiotics.<sup>1</sup> Benzyl ether is frequently used as a protecting group because it shows suitable stability towards a variety of reactions and is easily removable by hydrogenolysis. However, benzyl protection can not be applied to alcohols possessing additional functional groups that are susceptible to reductive conditions. A number of benzyl-type protecting groups, which can be cleaved by mild, non-reductive methods, have been developed. *p*-Methoxybenzyl (PMB) ether is one of the most significant among them, and can be removed oxidatively with 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (DDQ)<sup>2</sup> and ceric ammonium nitrate (CAN)<sup>3</sup> in the presence of benzyl ether.

In the asymmetric synthesis of curacin A<sup>4</sup>, a novel marine antimitotic agent produced by a Caribbean cyanobacterium, we encountered difficulty in the deprotection of the PMB ether **1**. Deprotection of **1** with DDQ resulted in complete decomposition, and the desired alcohol **2** could not be obtained at all. Other reagents, such as CAN, trifluoroacetic acid (TFA)<sup>5</sup>, TFA-ethanethiol and  $\text{BBr}_3$  were also unsuccessful. During a survey of deprotection conditions, we found that the magnesium bromide diethyl etherate ( $\text{MgBr}_2 \cdot \text{OEt}_2$ )-methyl sulfide ( $\text{Me}_2\text{S}$ ) system, which is a combination of a hard Lewis acid and a soft nucleophile<sup>6</sup>, affords mild and chemo-selective deprotection of **1** (Scheme 1). Here we describe the selective deprotection of a variety of PMB ethers in the presence of 1,3-diene, *t*-butyldimethylsilyl (TBDMS) ether, benzoate, benzyl ether and acetonide by using this combined system.

### Scheme 1



First, deprotection of the PMB ether containing a 1,3-diene **3**<sup>7</sup> was examined (Table 1). The attempted deprotection of **3** with DDQ gave only a complex mixture and no starting material was recovered (Entry 1). Deprotection of **3** with  $\text{MgBr}_2 \cdot \text{OEt}_2$  in  $\text{CH}_2\text{Cl}_2$  was also unsuccessful (Entry 2). The addition of  $\text{Me}_2\text{S}$  to  $\text{MgBr}_2 \cdot \text{OEt}_2$  in  $\text{CH}_2\text{Cl}_2$ <sup>8</sup> at room temperature dramatically improved the reaction to give the desired alcohol **4**

in 37% yield along with the recovered PMB ether **3** (Entry 3).<sup>9</sup> The recovered **3** was subjected to the same procedure repeatedly (5 times) to give **4** in 65% total yield (Entry 6). Refluxing the reaction mixture in  $\text{CH}_2\text{Cl}_2$  (Entry 4), prolonging the reaction time or increasing the amount of reagents (Entry 5) had little effect on the chemical yield. Interestingly, the addition of  $\text{Me}_2\text{S}$  improved the deprotection with TFA and  $\text{BF}_3\cdot\text{OEt}_2$ ,<sup>10</sup> but isomerization of the 1,3-diene ( $E/Z=1.6/1$ ) in the recovered **3** and the product **4** took place to give the *E*-enriched diene (Entries 7 and 8). In the case of the  $\text{MgBr}_2\cdot\text{OEt}_2$ - $\text{Me}_2\text{S}$  system, isomerization was relatively suppressed.

**Table 1.** Results of deprotection of the PMB ether **3**<sup>a)</sup>

1. reagents in  $\text{CH}_2\text{Cl}_2$ , r. t.  
2. work-up (sat. aq.  $\text{NH}_4\text{Cl}$ )  
3. silica gel chromatography and Kugelrohr distillation

Entry	Reagents (equiv.)	Reaction time (h)	Yield of <b>4</b> (%) <sup>b)</sup>	Recovery of <b>3</b> (%) <sup>b)</sup>
1	DDQ (x3)	3	trace	trace
2	$\text{MgBr}_2\cdot\text{OEt}_2$ (x1.5)	2	trace	trace
3	$\text{MgBr}_2\cdot\text{OEt}_2$ (x1.5), $\text{Me}_2\text{S}$ (x5)	4	37 ( $E/Z=2.2/1$ )	47 ( $E/Z=1.7/1$ )
4	$\text{MgBr}_2\cdot\text{OEt}_2$ (x1.5), $\text{Me}_2\text{S}$ (x5) <sup>c)</sup>	4	40 ( $E/Z=2.3/1$ )	35 ( $E/Z=1.7/1$ )
5	$\text{MgBr}_2\cdot\text{OEt}_2$ (x3), $\text{Me}_2\text{S}$ (x10)	16	45 ( $E/Z=2.7/1$ )	24 ( $E/Z=1.9/1$ )
6	$\text{MgBr}_2\cdot\text{OEt}_2$ (x3), $\text{Me}_2\text{S}$ (x10) <sup>d)</sup>	2	65 ( $E/Z=2.4/1$ )	8 ( $E/Z=2.1/1$ )
7	TFA (x5), $\text{Me}_2\text{S}$ (x5)	3	23 ( $E/Z=3.3/1$ )	32 ( $E/Z=4.6/1$ )
8	$\text{BF}_3\cdot\text{OEt}_2$ (x4.5), $\text{Me}_2\text{S}$ (x15) <sup>e)</sup>	3	49 ( $E/Z=4.0/1$ )	trace

a) All reactions were carried out on a 1 mmol scale, except Entry 6. b) The  $E/Z$  ratio of **3** and **4** was determined from the <sup>1</sup>H-NMR integration of the olefinic proton peak (500 MHz,  $\text{CDCl}_3$ ). c) Reaction was carried out under reflux. d) Reaction was carried out 5 times on a 4 mmol scale. e) Reaction was carried out at 0 °C.

Next, deprotection of a variety of PMB ethers was examined by the use of  $\text{MgBr}_2\cdot\text{OEt}_2$  (3 equiv.) and  $\text{Me}_2\text{S}$  (10 equiv.) in  $\text{CH}_2\text{Cl}_2$  at room temperature, and the results are shown in **Table 2**. PMB ethers containing an additional olefin **5** and an acid-sensitive acetonide **6** lost the PMB group selectively to give the corresponding alcohols in moderate yield, with recovery of the starting material (Entries 1 and 2). In the deprotection of **5** and **6**, prolonged reaction time caused decomposition of both the desired alcohol and the starting material. Deprotection of the PMB ether containing both a 1,3-diene and an acetonide **7** proceeded smoothly to give the desired alcohol in 64% yield (Entry 3). However, oxidative cleavage of **7** with DDQ was unsuccessful, as in the case of **1** and **3**. The PMB group was selectively removed from **8**, **9** and **10**, containing TBDMS, benzoyl and benzyl groups, to give the desired alcohol in high yield (Entries 4, 5 and 6). It should be noted that the PMB ether **10** was cleaved with high selectivity in the presence of benzyl ether with a combination of a hard Lewis acid and a soft nucleophile.<sup>11</sup> The PMB ether **11** also lost the PMB group to give the corresponding secondary alcohol (Entry 7). However, attempted deprotection of PMB ethers with acetal-type protecting groups such as methoxymethyl (MOM) and benzyloxymethyl (BOM) groups was unsuccessful (*data not shown*).

A representative procedure for the cleavage of **10** is as follows:  $\text{Me}_2\text{S}$  (740  $\mu\text{L}$ , 10.1 mmol) and powdered  $\text{MgBr}_2\cdot\text{OEt}_2$  (774 mg, 3.00 mmol) were added to a solution of **10** (300 mg, 1.00 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (15 mL). The reaction mixture was stirred vigorously for 90 h at room temperature, quenched by the

addition of saturated aqueous  $\text{NH}_4\text{Cl}$  (15 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (15 mL x2). The combined organic phases were washed with saturated aqueous  $\text{NaCl}$  (20 mL), dried over anhydrous  $\text{MgSO}_4$  and concentrated. Chromatography of the residue on silica gel (30 g, 10/1 to 2/1 hexane/EtOAc) gave 4-benzyloxybutanol (161 mg, 90%) as a colorless oil, with recovery of **10** (20 mg, 7%).

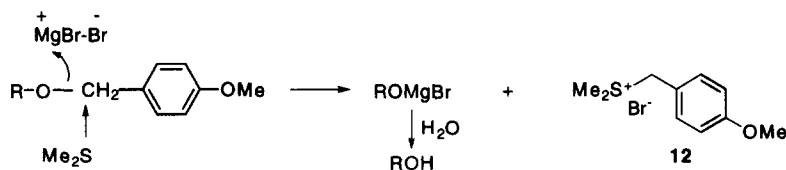
**Table 2.** Results of deprotection of PMB ethers<sup>a)</sup>

Entry	Starting material (S.M., $R_2$ =PMB)	Reaction time (h)	Yield of the alcohol (% , $R_2$ =H)
1	<b>5</b>	8	35 (75) <sup>b)</sup>
2	<b>6</b>	4	41 (75) <sup>b)</sup>
3	<b>7</b> ( $Z/E=12.6/1$ ) <sup>c)</sup>	20	64 (72) <sup>b)</sup> ( $Z/E=8.4/1$ ) <sup>c)</sup>
4	<b>8</b>	45	86 (93) <sup>b)</sup>
5	<b>9</b>	90	82 (95) <sup>b)</sup>
6	<b>10</b>	90	90 (96) <sup>b)</sup>
7	<b>11</b>	94	61 (93) <sup>b)</sup>

a) All reactions were carried out on a 1 mmol scale. b) Yields based on substrate reacted. c) The  $Z/E$  ratio of **7** and the deprotected alcohol was determined from the  $^1\text{H-NMR}$  integration of the olefinic proton peak (500 MHz,  $\text{CDCl}_3$ ). Abbreviations: TBDSM=tert-butyl dimethylsilyl, Bz=benzoyl, Bn=benzyl.

Our procedure was devised in the expectation that  $\text{MgBr}_2\cdot\text{OEt}_2$ , a hard Lewis acid having a high affinity for oxygen, would coordinate with the ether oxygen to assist the cleavage of carbon-oxygen bond and the benzylic carbon atom would be attacked by  $\text{Me}_2\text{S}$  in an  $\text{S}_{\text{N}}2$  fashion, as depicted in **Scheme 2**. This mechanism is supported indirectly by the observation of the sulfonium ion **12** ( $(\text{M}-\text{Br})^+$ ,  $m/z$ : 183) in FAB-MS of the reaction mixture.<sup>12</sup>

**Scheme 2**



In conclusion, we have found that the  $\text{MgBr}_2\cdot\text{OEt}_2\text{-Me}_2\text{S}$  system cleaved *p*-methoxybenzyl ethers under mild conditions to give the corresponding alcohols. The features of this system are 1) ease of handling of the reagent and of removal of the by-product; 2) suitability for 1,3-diene compounds, in contrast to DDQ

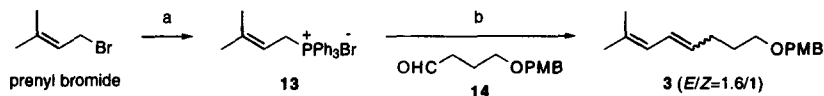
oxidation; 3) excellent selectivity between the PMB group and other common protecting groups such as TBDMS, benzoyl and benzyl. This system should provide a new approach to the removal of *p*-methoxybenzyl ether used as a hydroxyl protecting group during the synthesis of complex natural products.

### Acknowledgement

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- The PMB ether **3** was prepared as follows:



**Reagents and conditions:** (a) PPh<sub>3</sub>, benzene, 20°C, 20 h (96%); (b) **13**, *n*-BuLi, THF, -78°C, 1 h, then **14**, THF, -78-20°C, 15 h (85%)

- Other additives such as ethanethiol, anisole, thioanisole and *N,N*-dimethylaniline, and solvents such as CHCl<sub>3</sub>, CCl<sub>4</sub>, ether, tetrahydrofuran and toluene were examined for the deprotection of the PMB ether **3**. Me<sub>2</sub>S and CH<sub>2</sub>Cl<sub>2</sub> were the most suitable.
- In deprotection of the PMB ether **3**, a commercially available MgBr<sub>2</sub>·OEt<sub>2</sub> was used. The use of MgBr<sub>2</sub>, freshly prepared from magnesium and dibromoethane in ether, gave a similar result.
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- The structure of the salt **12** was supported by HRFAB-MS spectral data. Calcd. for C<sub>10</sub>H<sub>15</sub>OS (M-Br)<sup>+</sup> 183.0844, found 183.0861.

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