Tetrahedron 66 (2010) 1673–1677

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# A facile method for the rapid and selective deprotection of methoxymethyl (MOM) ethers

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ARTICLE INFO

*Article history:*
Received 8 December 2009
Received in revised form 24 December 2009
Accepted 4 January 2010
Available online 11 January 2010

ABSTRACT

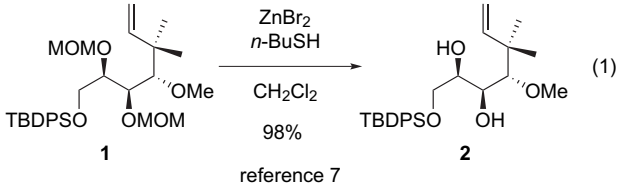
We describe a rapid and efficient method for selective deprotection of methoxymethyl (MOM) ethers using $ZnBr_2$ and *n*-PrSH, which completely removed MOM from diverse MOM ethers of primary, secondary, and tertiary alcohols or phenol derivatives. The deprotection takes less than ten minutes with both high yield and selectivity in the presence of other protecting groups. In addition, the rapid deprotection of MOM ethers of tertiary hydroxyls in high yield with no epimerization allows MOM to be a suitable protecting group for tertiary alcohols.



## 1. Introduction

Protection of functional groups in multistep organic syntheses is one of the key factors in the success of the synthesis. The protecting group should selectively react in good yield to give a protected substrate and should be selectively removed in good yield by readily available, preferably nontoxic reagents that do not attack the regenerated functional group.[1] One of the most abundant functional groups is the hydroxyl group, which is present in a number of compounds of biological and synthetic interest, including nucleosides, carbohydrates, steroids, macrolides, polyethers, and the side chain of some amino acids or in large numbers of intermediates in total syntheses of complex natural products.[2] Diverse protecting groups have been developed for hydroxyl groups, but it is hard to find an appropriate protecting group for each hydroxyl in the many cases where multiple hydroxyls are present in a molecule.[1,3]

The methoxylmethyl (MOM) group is widely used as a hydroxyl-protecting group because MOM ethers can be easily prepared and are stable under the removal conditions of protecting groups such as silyl, alkoxyacyl, or benzyl derivatives, as well as in strongly basic and weakly acidic conditions.[1] Many methods have been developed to cleave MOM ethers using Brønstead acids,[4] Lewis acids,[5] or other reagents,[6] but synthetic application of these methods has been limited, largely due to the high reactivity combined with long reaction times and low selectivity for MOM in the presence of other protecting groups. In 2005, one of these authors and Rawal reported a novel method for the selective removal of bis-MOM in the presence of TBDPS using $ZnBr_2$ and mercaptan in high yield, as applied to the total synthesis of mycalamide A (Eq. 1).[7] Since this efficient method has been used in the MOM removal from only compound **1**, it is essential to investigate the scope of the method for general use. Accordingly, we attempted to use the method for the selective removal of MOM groups from the corresponding ethers of primary, secondary, and tertiary alcohols and phenol derivatives in the presence of other hydroxyl-protecting groups.




(1)

## 2. Result and discussions

To investigate the scope of deprotection of MOM ethers with $ZnBr_2$ and mercaptan, we tested the cleaving of diverse MOM ethers. We optimized conditions for the removal of MOM by testing benzyl and phenethyl MOM ethers with variations of $ZnBr_2$ and mercaptan equivalents for different reaction times. Instead of using *n*-BuSH, we chose *n*-PrSH because its lower boiling point allowed for easier removal after completion of the reaction. Table 1 exhibits the results of the optimization studies. For both MOM ethers (0.5–1 mmol scale and 1 M concentration), one and two equivalents of $ZnBr_2$ and

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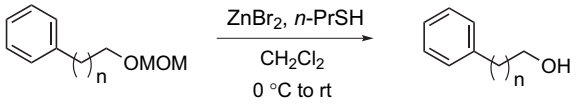
doi:10.1016/j.tet.2010.01.007

*n*-PrSH, respectively, in $CH_2Cl_2$ were needed to remove the MOM group. The reaction was not complete with less than two equivalents of *n*-PrSH or with less than one equivalent of $ZnBr_2$ (entries 2, 4, and 5). The reaction using one or two equivalents of $ZnBr_2$ with two equivalents of *n*-PrSH was completed cleanly in six min at 0 °C to room temperature (entries 1, 3, and 6).[8]

**Table 1**
Optimization of the MOM removal method[a,b]

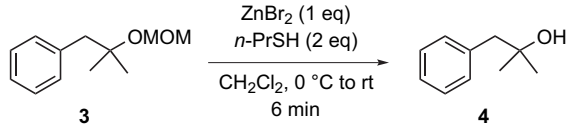



| Entry | *n* | $ZnBr_2$ (equiv) | *n*-PrSH (equiv) | Time (min) | Conversion (%) |
|---|---|---|---|---|---|
| 1 | 0 | 2.0 | 2.0 | 6 | 100 |
| 2 | 0 | 1.2 | 1.2 | 15 | 70 |
| | | +0.9 | +0.9 | +7 | 100 |
| 3 | 0 | 1.0 | 2.0 | 6 | 100 |
| 4 | 1 | 0.5 | 2.0 | 12 | 60 |
| | | +0.31 | | +5 | 85 |
| | | +0.22 | | +5 | 100 |
| 5 | 1 | 1.0 | 1.5 | 13 | 60 |
| | | | +0.53 | +13 | 100 |
| 6 | 1 | 1.0 | 2.0 | 6 | 100 |

[a] After $ZnBr_2$ and *n*-PrSH were added at 0 °C, the ice-bath was removed.
[b] Reaction was monitored using TLC.

We also tested the effects of the solvent and confirmed that $CH_2Cl_2$ was the best solvent for the MOM removal reaction, as compared to PhMe, $CH_3CN$, THF, and $CHCl_3$ (Table 2).

**Table 2**
Solvent effect of the MOM removal method



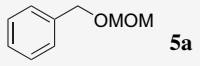
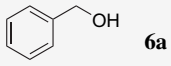
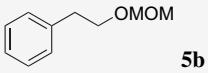
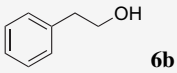
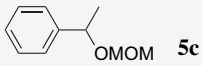
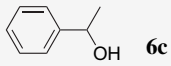
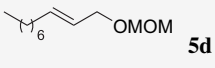
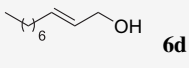
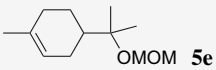
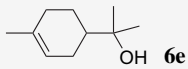
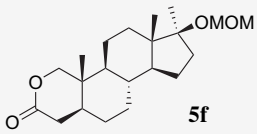
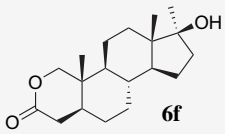
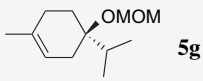
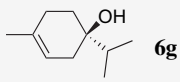
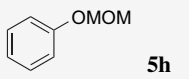
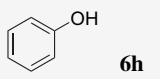
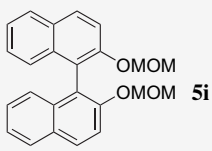
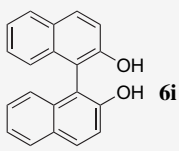

| Entry | Solvent | Scale (mmol) | Concentration (M) | Time (min) | Yield (%) |
|---|---|---|---|---|---|
| 1 | PhMe | 0.5 | 1.0 | 7.5 | 62 |
| 2 | $CH_3CN$ | 0.5 | 1.0 | 20 | 2[a] |
| 3 | THF | 0.5 | 1.0 | 10 | 1[a] |
| 4 | $CHCl_3$ | 0.5 | 1.0 | 6 | 77 |
| 5 | $CH_2Cl_2$ | 0.5 | 1.0 | 6 | 88 |

[a] Reaction was slow.

One of the notable advantages of this method is that it allows the MOM group to be utilized for the protection of a tertiary alcohol. Protection options are very limited for the multistep synthesis of a complicated molecule containing a tertiary hydroxyl that is present or generated at an early step in the synthesis. The limitation is due to difficulties in both protection and deprotection, or the viability of protecting groups such as TMS or acetate (Ac) that have been mostly used in the protection of tertiary hydroxyls.[1] As shown in Table 2, the removal of the MOM group from the MOM ethers of tertiary alcohols was achieved in good yield, in the same amount of time as for primary or secondary alcohols (entry 5).

After setting up the optimized conditions, we applied this method to the removal of the MOM group from a variety of MOM ethers. Table 3 summarizes some of our experimental results and illustrates the applicability and efficiency of the method. As with the primary alcohols, deprotection of MOM ethers in secondary, allyl, or tertiary alcohols was achieved rapidly and in high yield (entries 3–5).

**Table 3**
Scope of the MOM removal method

| Entry | R-OMOM | R-OH | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 |  **5a** |  **6a** | 6 | 92 |
| 2 |  **5b** |  **6b** | 6 | 90 |
| 3 |  **5c** |  **6c** | 6 | 90 |
| 4 |  **5d** |  **6d** | 7 | 89 |
| 5 |  **5e** |  **6e** | 6 | 93 |
| 6 |  **5f** |  **6f** | 7 | 91 |
| 7 |  **5g** |  **6g** | 7 | 87 |
| 8 |  **5h** |  **6h** | 5 | 86 |
| 9 |  **5i** |  **6i** | 7 | 95 |

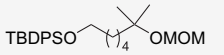
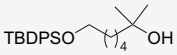
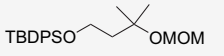
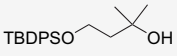
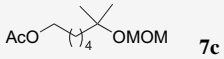
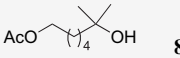
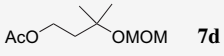
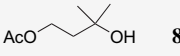
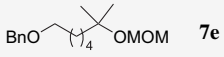
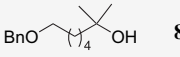
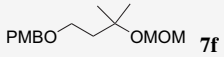
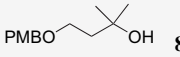
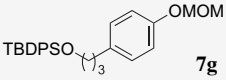
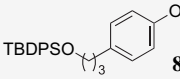
Since epimerization is possible in the deprotection of chiral tertiary MOM ethers under acidic conditions, we investigated our method in chiral tertiary alcohols. When the MOM ether of oxandrolone (**5f**) was reacted under the reaction conditions, there was no epimerization during the conversion of the ether to the corresponding alcohol (entry 6). Further studies were conducted with tertiary alcohols that could undergo elimination under acidic conditions. In the case of the MOM ether of (−)-terpinen-4-ol (**5g**) the removal of MOM was similar to that of primary or secondary alcohols, with no epimerization (entry 7).

We also tested phenolic MOM ether, which has been used infrequently for the protection of phenolic OH. The reaction conditions rapidly removed the MOM group in high yield (entries 8 and 9).[6a,b,d] In the case of BINOL, a methyl group has been generally employed for the protection of each of the two hydroxyls in the derivatization of the phenyl rings, for use in BINOL derivatives as chiral ligands in asymmetric reactions.[9] Our mild removal conditions converted the di-MOM ether of BINOL into BINOL within seven minutes, with a 95% yield.

To investigate the selective removal of MOM in the presence of other protecting groups, we tested a variety of protected diols (Table 4). We prepared MOM ethers of tertiary hydroxyls in the

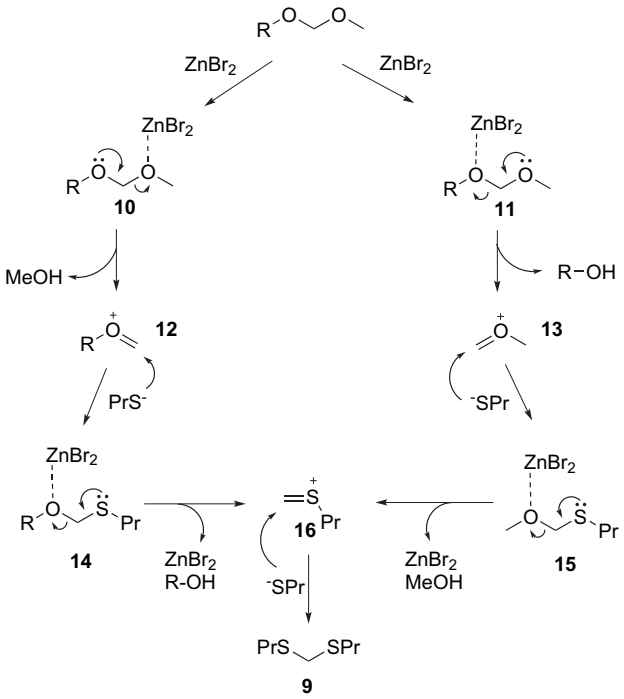
presence of protected primary hydroxyls so that the selectivity would be obvious, as deprotection of a tertiary hydroxyl often requires harsher reaction conditions than do those of primary or secondary hydroxyls. We tested tertiary MOM ethers containing primary hydroxyls that were protected with TBDPS, Ac, and Bn, as these groups are mostly used for the protection of hydroxyls. These compounds were prepared through a sequence of selective protection of the primary hydroxyl, followed by MOM protection of the remaining tertiary hydroxyl. These bis-protected compounds were treated with $ZnBr_2$ and *n*-PrSH in $CH_2Cl_2$ to obtain the corresponding tertiary alcohols in high yields, while maintaining the protected primary hydroxyls (entries 1–5).

**Table 4**
Selective removal of MOM

| Entry | R-OMOM | R-OH | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 |  **7a** |  **8a** | 8 | 90 |
| 2 |  **7b** |  **8b** | 6 | 95 |
| 3 |  **7c** |  **8c** | 7 | 90 |
| 4 |  **7d** |  **8d** | 7 | 87 |
| 5 |  **7e** |  **8e** | 5 | 93 |
| 6 |  **7f** |  **8f** | 5 | 31 |
| 7 |  **7g** |  **8g** | 5 | 91 |

All reactions selectively removed the MOM group within eight min with no significant side-products. In the case of the *p*-methoxybenzyl ether, the desired tertiary alcohol was obtained in low yield along with side-products, presumably due to the electron-rich character of the phenyl ring (entry 6). We next investigated the selective removal of MOM from the phenolic MOM ether. The MOM ether of phenol with a primary TBDPS ether was prepared by selective protection of the primary hydroxyl with TBDPS, followed by formation of the MOM ether. Treatment of the bis-protected hydroxyl compound under the reaction conditions afforded the selective removal of MOM in an excellent yield (entry 7). This result, in combination with the results in Table 3, indicate that the MOM group is an adequate option for protection of phenolic OH.

To study the mechanism of cleavage of the MOM ether, we used $^1$H NMR and observed methanol and bis(propylthio)-methane (**9**)[5g] as by-products of the cleavage. This result led us to envision the mechanism of the MOM removal process shown in Scheme 1. There are two possible pathways for the removal of MOM and the generation of the by-products. Each pathway is initiated by the coordination of one of the oxygen atoms in the MOM ether to $ZnBr_2$ (compound **10** vs **11**), and the pathways merge at sulfonium ion **16**. The coordination of either oxygen to $ZnBr_2$ would be competitive with $CH_3CN$ or THF, which is why the reaction did not proceed well in those solvents (Table 2). Both routes required two equivalents of *n*-PrSH, as the reaction was not completed using less than two equivalents of *n*-PrSH (Table 1).




**Scheme 1.** Proposed mechanism of MOM removal by $ZnBr_2$ and PrSH.

## 3. Conclusions

We studied on the scope of a rapid and efficient method for the selective deprotection of MOM ethers using $ZnBr_2$ and *n*-PrSH. This protocol removed MOM from a variety of MOM ethers of primary, secondary and tertiary alcohols, and phenol derivatives. All reactions were complete within eight minutes, with both high yield and selectivity in the presence of other protecting groups such as TBDPS, acetyl or benzyl group. In addition, the rapid deprotection of the MOM ethers of tertiary hydroxyls in high yield with no epimerization allowed for the use of MOM as a suitable protecting group for tertiary alcohols. This rapid and efficient method for selective deprotection of MOM ethers could open a new horizon for MOM groups in hydroxyl protection.

## 4. Experimental

### 4.1. General experimental

Unless stated otherwise, reactions were carried out under a dry argon atmosphere in vacuum-flame dried glassware. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 $F_{254}$. Flash column chromatography was performed using E. Merck silica gel (40–60 μm particle size). $^1$H and $^{13}$C NMR spectra were recorded on a Varian at 300 MHz. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: $\delta$ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublet, qd=quartet of doublet, br=broad, m=multiplet), coupling constants (Hz), integration. Infrared spectra were recorded on a Nicolet 380. HRMS were recorded on JEOL JMS-700 mass spectrometer with EI, FAB resource. Optical rotations were determined on a Perkin-Elmer polarimeter model 343 plus at 589 nm. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane was distilled from calcium hydride.

*4.1.1. General procedure for the synthesis of MOM ether.* To a stirred solution of alcohol (1.0 equiv) in $CH_2Cl_2$ (0.1–0.5 M concentration) were added *i*-$Pr_2NEt$ (2.2 equiv) and MOMCl (1.5 equiv) at 0 °C, and the reaction mixture was stirred at room temperature to 60 °C until the reaction completed. After slow addition of satd $NH_4Cl$ at 0 °C, the mixture was extracted with $CH_2Cl_2$ (5 mL×3). The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography to afford MOM ether 3,[6e] **5a**–**5c**,[10,6b,11] **5d**, **5e**,[12] **5f**, **5g**, **5h**[13] or **5i**.[14]

*4.1.2. General procedure for the deprotection of MOM ether.* To a stirred solution of MOM ether (1 mmol, 1 M) in $CH_2Cl_2$ were added $ZnBr_2$ (1 equiv; **5a**–**5c**, **5e**, **5g**, **5h**, **7a**–**7f** or 1.5 equiv; **5d**, **5f**, **5i**, **7g**) and *n*-PrSH (2 equiv; **5a**–**5c**, **5e**, **5g**, **5h**, **7a**–**7f** or 3 equiv; **5d**, **5f**, **5i**, **7g**). After stirring for 5–8 min at room temperature, the resulting mixture was diluted with $CH_2Cl_2$ (10 mL). Satd $NaHCO_3$ (3 mL) was added slowly at 0 °C and the mixture was filtered through Celite. The aqueous layer was separated and further extracted with $CH_2Cl_2$ (5 mL×3). The combined organic layer was washed with brine (3 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography to afford corresponding alcohol.

*4.1.3. (E)-1-(Methoxymethoxy)dec-2-ene (**5d**).* IR (film): 2926, 1151, 1106, 1041, 969 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 0.88 (t, *J*=6.9 Hz, 3H), 1.22–1.40 (m, 10H), 2.02 (q, *J*=6.9 Hz), 3.37 (s, 3H), 4.00 (d, *J*=6.3 Hz, 2H), 4.64 (s, 2H), 5.53 (m, 1H), 5.73 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 14.3, 22.8, 29.2, 29.3, 32.0, 32.5, 55.3, 68.2, 95.5, 125.7, 135.5; HRMS (EI): calculated for $C_{12}H_{24}O_2$ ($M^+$) 200.1776; found 200.1773.

*4.1.4. (4aS,4bS,6aS,7S,9aS,9bR,11aS)-7-(Methoxymethoxy)-4a,6a,7-trimethyltetradeca-hydroindeno[4,5-h]isochromen-2(1H)-one (**5f**).* IR (film): 2913, 1746, 1726, 1099, 1041 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 0.87 (s, 3H), 1.00 (s, 3H), 0.80–1.00 (m, 2H), 1.22 (s, 3H), 1.17–1.38 (m, 6H), 1.40–1.63 (m, 6H), 1.66 (m, 4H), 3.63 (s, 3H), 3.92 (d, *J*=10.8 Hz, 1H), 4.23 (d, *J*=10.5 Hz, 1H), 4.70 (dd, *J*=6.6, 14.1 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 9.9, 14.0, 20.7, 22.2, 23.1, 26.9, 30.5, 31.6, 33.5, 34.4, 35.1, 35.2, 40.0, 46.3, 49.3, 49.4, 54.9, 80.7, 86.2, 92.0, 170.2; HRMS (EI): calculated for $C_{11}H_{34}O_4$ ($M^+$) 350.2457; found 350.2457.

*4.1.5. (4aS,4bS,6aS,7S,9aS,9bR,11aS)-7-Hydroxy-4a,6a,7-trimethyltetradeca-hydroindeno[4,5-h]isochromen-2(1H)-one (**6f**).* $[\alpha]_D^{20}$ −23.57 (*c*1.00, $CH_3Cl$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 0.87 (s, 3H), 1.01 (s, 3H), 0.80–1.00 (m, 2H), 1.21 (s, 3H), 1.17–1.38 (m, 6H), 1.40–1.63 (m, 6H), 1.66 (m, 6H), 3.92 (d, *J*=10.8 Hz, 1H), 4.24 (d, *J*=10.8 Hz, 1H).

*4.1.6. (R)-4-Isopropyl-4-(methoxymethoxy)-1-methylcyclo-hex-1-ene (**5g**).* IR (film): 2962, 2360, 1447, 1145, 1038 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 0.91 (dd, *J*=6.9, 2.7 Hz, 6H), 1.60 (m, 2H), 1.67 (s, 3H), 1.74–2.11 (m, 6H), 3.37 (s, 3H), 4.65 (d, *J*=7.5, 1H), 4.76 (d, *J*=7.5, 1H), 5.30 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 17.3, 17.6, 23.4, 27.6, 28.2, 30.9, 34.1, 55.9, 78.7, 90.8, 118.8, 133.8; HRMS (EI): calculated for $C_{12}H_{22}O_2$ ($M^+$) 198.1620; found 198.1621.

*4.1.7. (R)-1-Isopropyl-4-methylcyclo-hex-3-enol (**6g**).* $[\alpha]_D^{20}$ −21.07 (*c*1.24, $CH_3Cl$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 0.91 (t, *J*=6.9 Hz, 6H), 1.60 (m, 2H), 1.69 (s, 3H), 1.74–2.11 (m, 6H), 2.21 (br s, 1H), 5.30 (s, 1H).

*4.1.8. 5,5,13,13-Tetramethyl-12,12-diphenyl-2,4,11-trioxa-12-silatetradecane (**7a**).* To a solution of 6-methylheptane-1,6-diol[15] (0.40 g, 2.7 mmol) in $CH_2Cl_2$ (3.0 mL), were added *i*-$Pr_2NEt$ (0.71 mL, 4.1 mmol), DMAP (33 mg, 0.27 mmol) and TBDPSCl (0.85 mL, 3.3 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stir for 3 h. The resulting mixture was quenched with satd $NH_4Cl$ (8 mL) at 0 °C and extracted with $CH_2Cl_2$ (10 mL×3). The combined organic layer was washed with brine (15 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Flash column chromatography yielded 0.98 g (94%) of silyl ether **8a**: IR (film): 3368, 2933, 1471, 1109, 823 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.05 (s, 9H), 1.20 (s, 6H), 1.34 (m, 4H), 1.45 (m, 2H), 1.57 (m, 2H), 3.66 (t, *J*=6.3 Hz, 2H), 7.41 (m, 6H), 7.67 (m, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 19.4, 24.2, 26.5, 27.0, 29.3, 32.7, 44.1, 64.0, 71.2, 127.7, 129.6, 134.3, 135.7; LRMS (EI): calculated for $C_{24}H_{35}OSi$ ($M^+$−OH) 367; found 367. According to the general procedure, treatment of **8a** (0.87 g, 2.26 mmol) with *i*-$Pr_2NEt$ (0.86 mL, 4.96 mmol) and MOMCl (0.26 mL, 3.39 mmol) gave MOM ether **7a** (0.92 g, 95%): IR (film) 2937, 1427, 1145, 1108, 1039 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.04 (s, 9H), 1.20 (s, 6H), 1.34 (m, 4H), 1.45 (m, 2H), 1.57 (m, 2H), 3.36 (s, 3H), 3.65 (t, *J*=6.3 Hz, 2H), 4.70 (s, 2H), 7.40 (m, 6H), 7.67 (m, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 19.4, 24.0, 26.4, 26.5, 27.0, 32.7, 42.0, 55.2, 64.1, 91.1, 127.7, 129.6, 134.3; HRMS (FAB): calculated for $C_{26}H_{41}O_3Si$ ($M^+$+H) 429.2825; found 429.2829.

*4.1.9. 5,5,10,10-Tetramethyl-9,9-diphenyl-2,4,8-trioxa-9-silaundecane (**7b**).* To a solution of 3-methylbutane-1,3-diol (0.21 mL, 2.0 mmol) in $CH_2Cl_2$ (2.0 mL) were added *i*-$Pr_2NEt$ (0.52 mL, 3.0 mmol), DMAP (24 mg, 0.2 mmol), and TBDPSCl (0.63 mL, 2.4 mmol) at 0 °C, and the reaction mixture was warmed to room temperature and stirred for 3 h. The resulting mixture was quenched with satd $NH_4Cl$ (8 mL) at 0 °C and extracted with $CH_2Cl_2$ (10 mL×3). The combined organic layer was washed with brine (15 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Flash column chromatography yielded 0.65 g (95%) of **8b**.[16] According to the general procedure, treatment of **8b** (0.82 g, 2.4 mmol) with *i*-$Pr_2NEt$ (0.92 mL, 5.3 mmol) and MOMCl (0.27 mL, 3.6 mmol) gave **7b** (0.89 g, 95%): IR (film) 2933, 1088, 1048, 1032, 701 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.04 (s, 9H), 1.20 (s, 6H), 1.84 (t, *J*=7.2 Hz, 2H), 3.28 (s, 3H), 3.78 (t, *J*=7.2 Hz, 2H), 4.61 (s, 2H), 7.39 (m, 6H), 7.67 (m, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 19.3, 30.0, 44.1, 55.2, 60.5, 75.5, 91, 127.8, 129.7, 134.0, 135.7; HRMS (FAB): calculated for $C_{23}H_{35}O_3Si$ ($M^+$+H) 387.2355; found 387.2360.

*4.1.10. 6-(Methoxymethoxy)-6-methylheptyl acetate (**7c**).* To a solution of 6-methylheptane-1,6-diol (0.17 g, 1.1 mmol) in $CH_2Cl_2$ (1.5 mL) were added pyridine (0.32 mL, 4.1 mmol) and $Ac_2O$ (0.18 mL, 1.9 mmol) at 0 °C, and the reaction mixture was warmed to room temperature and stirred for 8 h. The resulting mixture was quenched with 0.5 N HCl (3 mL) at 0 °C, and extracted with $Et_2O$ (10 mL×3). The combined organic layer was washed with brine (15 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Flash column chromatography yielded 0.19 g (74%) of acetate **8c**: IR (film): 3439, 2937, 1739, 1366, 1242 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.21 (s, 6H), 1.38 (m, 4H), 1.46 (m, 2H), 1.65 (m, 2H), 2.05 (s, 3H), 4.06 (t, *J*=6.6 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 21.1, 24.1, 26.6, 28.7, 29.4, 43.9, 64.7, 71.1, 171.3; HRMS (FAB): calculated for $C_{10}H_{21}O_3$ ($M^+$+H) 189.1491; found 189.1493. According to the general procedure, treatment of acetate **8c** (96.4 mg, 0.51 mmol) with *i*-$Pr_2NEt$ (0.20 mL, 1.1 mmol) and MOMCl (0.06 mL, 0.77 mmol) gave **7c** (0.11 g, 96%): IR (film): 2940, 1740, 1239, 1038 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.21 (s, 6H), 1.36 (m, 4H), 1.48 (m, 2H), 1.62 (m, 2H), 2.05 (s, 3H), 3.37 (s, 3H), 4.06 (t, *J*=6.6 Hz, 2H), 4.71 (s, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 21.1, 23.7, 26.4, 26.5, 28.7, 41.9, 55.2, 64.7, 76.2, 91.1, 171.3; HRMS (FAB): calculated for $C_{12}H_{25}O_4$ ($M^+$+H) 233.1753; found 233.1756.

*4.1.11. 6-(Methoxymethoxy)-6-methylheptyl acetate (**7d**).* To a solution of 3-methylbutane-1,3-diol (0.32 mL, 3.0 mmol) in $CH_2Cl_2$

(3.0 mL) were added pyridine (0.73 mL, 9.0 mmol) and $Ac_2O$ (0.34 mL, 3.6 mmol) at 0 °C, and the mixture was warmed to room temperature and stirred for 8 h. The resulting mixture was quenched with 0.5 N HCl (3 mL) at 0 °C, and extracted with $Et_2O$ (10 mL×3). The combined organic layer was washed with brine (15 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Flash column chromatography yielded 0.29 g (66%) of **8d**.[17] According to the general procedure, treatment of **8d** (0.24 g, 1.6 mmol) with *i*-$Pr_2NEt$ (0.63 mL, 3.6 mmol) and MOMCl (0.19 mL, 2.5 mmol) gave **7d**[18] (0.30 g, 97%): $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.26 (s, 6H), 1.87 (t, $J$=7.2 Hz, 2H), 2.04 (s, 3H), 3.37 (s, 3H), 4.20 (t, $J$=7.2 Hz, 2H), 4.71 (s, 2H).

*4.1.12. ((6-(Methoxymethoxy)-6-methylheptyloxy)methyl)-benzene (**7e**).* To a solution of diol **7** (0.35 g, 2.4 mmol) in THF (3.0 mL), were added NaH (60% wt in mineral oil, 87 mg, 3.6 mmol) and BnBr (0.43 mL, 3.6 mmol) at 0 °C, and the reaction mixture was allowed to warm to room temperature and stirred for 22 h. The resulting mixture was quenched with satd $NH_4Cl$ (8 mL) at 0 °C and extracted with $CH_2Cl_2$ (10 mL×3). The combined organic layer was washed with brine (15 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Flash column chromatography yielded 0.37 g (65%) of **8e**: IR (film): 3415, 2935, 1495, 1364, 1102, 1075 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.20 (s, 6H), 1.38 (m, 4H), 1.45 (m, 2H), 1.64 (m, 2H), 3.47 (t, $J$=6.6 Hz, 2H), 4.51 (s, 2H), 7.31 (m, 5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 24.3, 26.9, 29.3, 29.9, 44.0, 70.5, 71.1, 73.0, 127.6, 127.8, 128.5, 138.8; HRMS (FAB): calculated for $C_{15}H_{25}O_2$ ($M^+$+H) 237.1855; found 237.1856. According to the general procedure, treatment of **8e** (0.16 g, 0.7 mmol) with *i*-$Pr_2NEt$ (0.27 mL, 1.5 mmol) and MOMCl (0.08 mL, 1.04 mmol) gave **7e** (0.19 g, 96%): IR (film): 2938, 1496, 1382, 1097, 1039 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.20 (s, 6H), 1.35 (m, 4H), 1.47 (m, 2H), 1.64 (m, 2H), 3.36 (s, 3H), 3.47 (t, $J$=6.9 Hz, 2H), 4.50 (s, 2H), 4.70 (s, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 24.0, 26.5, 26.9, 41.9, 55.2, 70.5, 73.0, 76.4, 91.1, 127.6, 127.8, 128.5, 138.8; HRMS (FAB): calculated for $C_{17}H_{29}O_3$ ($M^+$+H) 281.2117; found 281.2112.

*4.1.13. 1-Methoxy-4-((3-(methoxymethoxy)-3-methylbut-oxy)-methyl)benzene (**7f**).* To a solution of 6-methylheptane-1,6-diol (0.32 mL, 3.0 mmol) in DMF (3.0 mL) was added NaH (0.14 g, 60% wt in mineral oil, 3.6 mmol) at 0 °C, and the mixture was stirred for 20 min at room temperature. After addition of PMBCl (0.49 mL, 3.6 mmol) the reaction mixture was stirred for 18 h at room temperature. The mixture was poured into water (20 mL) and extracted with $Et_2O$ (20 mL×3). The combined organic layer was washed with brine (15 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Flash column chromatography yielded 0.46 g (79%) of **8f**: IR (film): 3441, 2968, 1612, 1513, 1247 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.22 (s, 6H), 1.78 (t, $J$=5.7 Hz, 2H), 3.32 (br s, 1H), 3.69 (t, $J$=5.7 Hz, 2H), 3.81 (s, 3H), 4.46 (s, 2H), 6.87 (d, $J$=5.7 Hz, 2H), 7.26 (d, $J$=8.7 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 29.4, 41.6, 55.4, 67.5, 70.7, 73.2, 114.0, 129.5, 130.0, 159.4; HRMS (FAB): calculated for $C_{13}H_{21}O_3$ ($M^+$+H) 225.1491; found 225.1482. According to the general procedure, treatment of **8f** (0.46 g, 2.4 mmol) with *i*-$Pr_2NEt$ (0.91 mL, 5.2 mmol) and MOMCl (0.22 mL, 2.8 mmol) gave **7f** (0.54 g, 96%): IR (film) 2974, 2361, 1613, 1514, 1248, 1092, 1033 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.24 (s, 6H), 1.87 (t, $J$=7.2 Hz, 2H), 3.34 (s, 3H), 3.58 (t, $J$=7.2 Hz, 2H), 3.80 (s, 3H), 4.43 (s, 2H), 4.70 (s, 2H), 6.87 (d, $J$=8.7 Hz, 2H), 7.26 (d, $J$=8.7 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 24.0, 26.5, 26.9, 41.9, 55.2, 70.5, 73.0, 76.4, 91.1, 127.6, 127.8, 128.5, 138.8; HRMS (EI): calculated for $C_{15}H_{25}O_4$ ($M^+$+H) 269.1753; found 269.1750.

*4.1.14. tert-Butyl(3-(4-(methoxymethoxy)phenyl)propoxy)-diphenylsilane (**7g**).* To a solution of 4-(3-hydroxypropyl)-phenol (0.30 g, 2.0 mmol) in DMF (1.5 mL) were added imidazole (0.20 mL, 3.0 mmol), DMAP (2.4 mg, 0.02 mmol), and TBDPSCl (0.62 mL, 2.4 mmol) at 0 °C, and the reaction mixture was warmed to room temperature and stirred for 3 h. The resulting mixture was quenched with satd $NH_4Cl$ (8 mL) at 0 °C and extracted with $CH_2Cl_2$ (10 mL×3). The combined organic layer was washed with brine (15 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Flash column chromatography yielded 0.73 g (94%) of **8 g**.[19] According to the general procedure, treatment of **8g** (1.00 g, 2.56 mmol) with *i*-$Pr_2NEt$ (1.01 mL, 5.63 mmol) and MOMCl (0.29 mL, 3.8 mmol) gave **7g** (1.09 g, 98%): IR (film): 2931, 1510, 1109, 1008 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.06 (s, 9H), 1.83 (m, 2H), 2.66 (t, $J$=8.1 Hz, 2H), 3.48 (s, 3H), 3.68 (t, $J$=6.0 Hz, 2H), 5.15 (s, 2H), 6.93 (d, $J$=8.7 Hz, 2H), 7.08 (d, $J$=8.7 Hz, 2H), 7.39 (m, 6H), 7.66 (m, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 19.4, 27.0, 31.3, 34.5, 56.1, 63.2, 94.7, 116.3, 127.7, 129.5, 129.7, 134.1, 135.7, 135.8, 155.4; HRMS (FAB): calculated for $C_{27}H_{35}O_3Si$ ($M^+$+H) 435.2355; found 435.2357.

## Acknowledgements

This work was supported by grants NRF-20090094024 (Priority Research Centers Program), NRF-20080058667 (Basic Science Research Program) and NRF-20090076108 (Basic Science Research Program).

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