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Novel Deprotection of SEM Ethers: A Very Mild and Selective Method Using Magnesium Bromide

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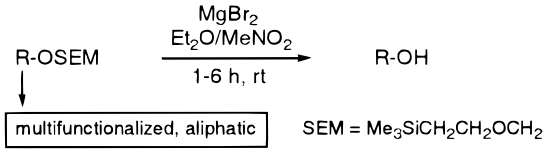
ABSTRACT



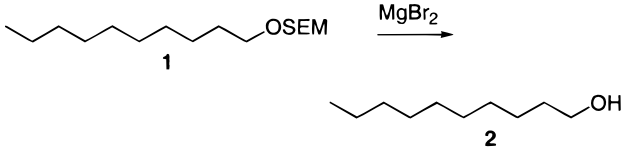
New lability and stability sequences have been established for multifunctional substrates containing SEM ether group(s) by a $MgBr_2/Et_2O/MeNO_2$ deprotection protocol.

Since its introduction by Lipshutz[1] in 1980, the trimethylsilylethoxymethyl ($Me_3SiCH_2CH_2OCH_2$) or SEM group has joined the ranks of silyl protecting groups in organic synthesis.[2] A Beilstein on-line search (February 2000) suggests there are more than 2000 SEM-protected ethers in the literature.

There have been reports on the difficulty of removing the SEM group which has in fact been characterized as "rugged".[2b] Typical deprotection conditions are TBAF in HMPA[3] (or nontoxic equivalents),[4] and activated fluoride ion (CsF) at elevated temperature.[5] Other deprotection protocols have been suggested.[6] However, for the synthesis multifunctionalized substrates, these conditions may be too vigorous and destructive.[7]

In the context of synthetic efforts in the polyketide field, we had occasion to investigate the deprotection of a variety of SEM ethers. Using $MgBr_2$ instead of the standard conditions was not promising in donor solvents (Table 1).

Table 1. Monofunctionalized SEM Ether



equiv of $MgBr_2$	solvent mixture	time [h], temp	yield [%]
6	Et_2O/DME (6 equiv)	4, rt	<5 insoluble precipitate
6	Et_2O/TMEDA (6 equiv)	4, rt	<5 insoluble precipitate

In the presence of DME and TMEDA, magnesium salts were precipitated.

A variation of solvent is shown in Table 2. $MgBr_2$ in anhydrous ether gave not only the fully deprotected aldol **4** but to our surprise also small amounts of hemiacetal **5** (entry 4), which survived under the mild experimental conditions. Addition of nitromethane gave a clear improvement: The

(1) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.
(2) (a) Greene, T. W.; Wuts, P. G. M.*Protective Groups in Organic Chemistry*, 2nd ed.; Wiley: New York, 1991. (b) Kocienski, P. J. *Protecting Groups*, 1st ed.; Thieme: Stuttgart, 1994. (c) Schelhaas, M.; Waldmann, H. *Angew. Chem.* **1996**, *108*, 2192; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2056.
(3) Kan, T.; Hashimoto, M.; Yanagiya, M. Shirahama, H. *Tetrahedron Lett.* **1988**, *29*, 5417.
(4) Lipshutz, B. H.; Miller, T. A. *Tetrahedron Lett.* **1989**, *30*, 7149.
(5) (a) Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279. (b) Suzuki, K.; Matsumoto, T.; Tomooka, K.; Matsumoto, K.; Tsuchihashi, G.-I. *Chem. Lett.* **1987**, 113.

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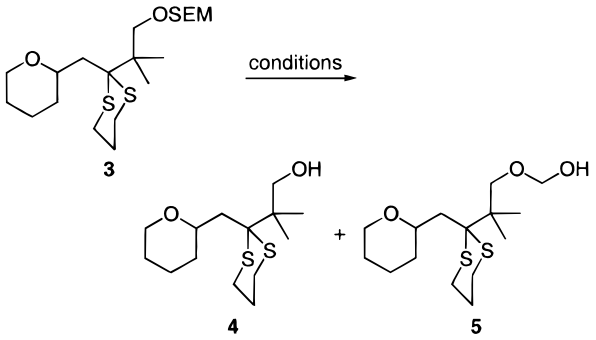
Table 2. Deprotection of Masked Aldol

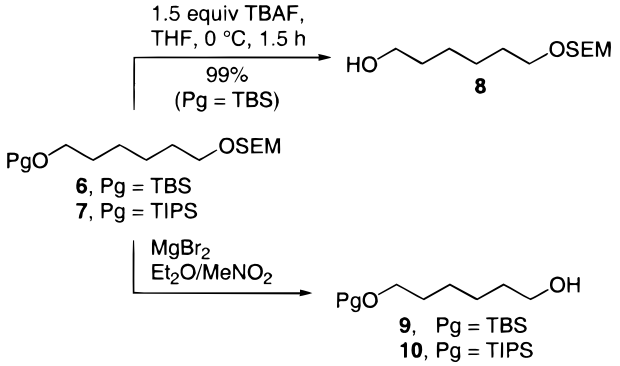


entry	Lewis acid	solvent mixture	time [h], temp [°C]	yield of **4** + **5** [%]
1	2 equiv of $MgBr_2 \cdot Et_2O$/2 equiv of TBAF	THF/DMPU (1:1)[a]	2, rt	0
2	2 equiv of $MgBr_2 \cdot Et_2O$/2 equiv of TBAF	DMF/MeOH (2:1)[a]	2, rt	0 insoluble precipitate
3	4 equiv of $MgBr_2 \cdot Et_2O$	Et_2O/MeOH (8 equiv)	2, rt	0 insoluble precipitate
4	5 equiv of $MgBr_2 \cdot Et_2O$	Et_2O	6, rt	28 + 9
5	6 equiv of $MgBr_2 \cdot Et_2O$	$Et_2O/MeNO_2$ (12 equiv)	6, rt	82 + 0

[a] Molecular sieves (4 Å) present.

two-phase reaction mixture turned into a homogeneous solution (entry 5). Encouraged by this finding, a variety of differentially substituted alcohols were prepared and subjected to the deprotection conditions (Table 3). Entry 4 shows that it was possible to remove the SEM group even without

Table 4. Traditional vs New Deprotection Method

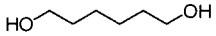
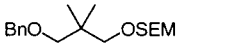
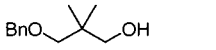
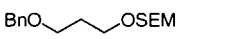
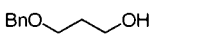
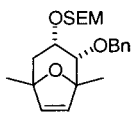
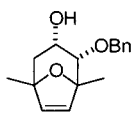
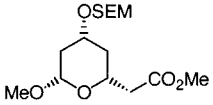
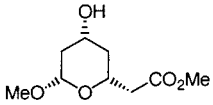
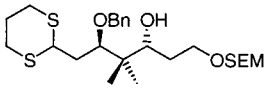
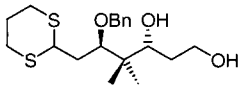
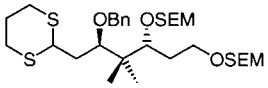
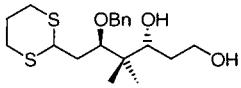


Pg	conditions	time [h]	yield [%]
TBS	6 equiv of $MgBr_2/Et_2O/MeNO_2$	16	40
TBS	10 equiv of $MgBr_2/Et_2O/MeNO_2$	10	74
TBS	14 equiv of $MgBr_2/Et_2O/MeNO_2$	5	87[a]
TIPS	14 equiv of $MgBr_2/Et_2O/MeNO_2$	5	96
TIPS	14 equiv of $ZnBr_2/CH_2Cl_2$/MeOH	5	53

[a] $ZnBr_2$ (14 equiv) in CH_2Cl_2/MeOH gives after 10 h the TBS-deprotected product (72%).

$MeNO_2$ as a cosolvent. Presumably, deprotection is facilitated by interaction of magnesium cation with the additional benzyloxygen heteroatom. The benzyloxy group also survived in a sterically hindered oxabicycle (entry 5). Methoxy acetals are tolerated, which is of interest in carbohydrate chemistry (entry 6). A free hydroxy group in a 1,3-functionality distance slows deprotection (entry 7), although a 1,6-distance is tolerated (entry 2). An excess of nitromethane is not helpful (entry 7b), but changing to $ZnBr_2$ as Lewis acid is effective in this case (entry 7c). Furthermore, double SEM deprotection was accomplished smoothly (entry 8).

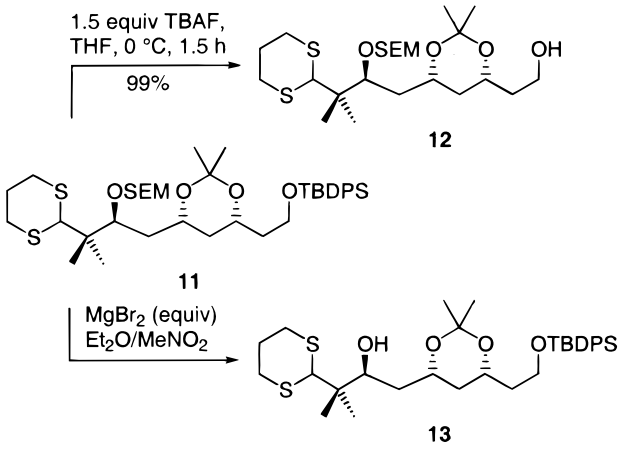
Table 3. Tolerance to Additional Functionality

entry	SEM-ether	product	conditions	time [h]	yield [%]
1	$C_{10}H_{21}OSEM$	$C_{10}H_{21}OH$	10 equiv $MgBr_2/Et_2O/MeNO_2$	5	99
2			10 equiv $MgBr_2/Et_2O/MeNO_2$	5	95
3			6 equiv $MgBr_2/Et_2O/MeNO_2$	5	99
4a			a: 6 equiv $MgBr_2/Et_2O/MeNO_2$	5	95
4b			b: 6 equiv $MgBr_2/Et_2O$	5	74
5			8 equiv $MgBr_2/Et_2O/MeNO_2$	4	92
6			8 equiv $MgBr_2/Et_2O/MeNO_2$	3	94
7a			a: 40 equiv $MgBr_2/Et_2O/MeNO_2$	24	90
7b			b: 40 equiv $MgBr_2$/85 equiv $Et_2O/MeNO_2$	24	64
7c			c: 40 equiv $ZnBr_2/CH_2Cl_2$/MeOH	24	99
8			30 equiv $MgBr_2/Et_2O/MeNO_2$	24	90

Conventional desilylating conditions (TBAF, 0 °C) removed the TBS group, leaving SEM intact as expected (Table 4). The new method allows preferential SEM deprotection under kinetic control to give the desired alcohol **9**. TIPS survived on deprotection with $MgBr_2$, but not with $ZnBr_2$.

Under conventional conditions (TBAF, THF) the terminal *O*-silyl group in **11** is removed and the SEM group remains intact (Table 5). Kinetically controlled reaction with $MgBr_2$

Table 5. Acetonide Tuning



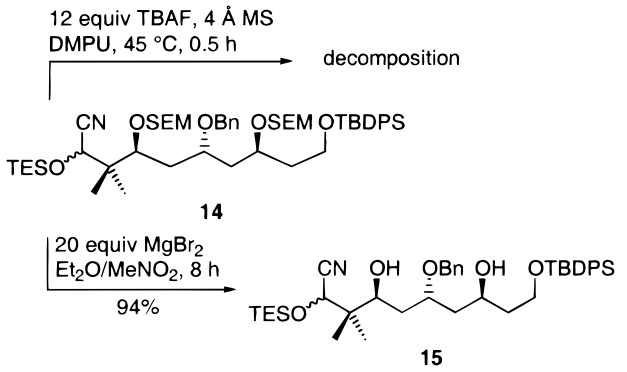
equiv of $MgBr_2$	time [h]	yield [%]
6	3	60
12	6	52[a]
14	1	81

[a] The use of $ZnBr_2$ (12 equiv) in CH_2Cl_2/MeOH gives after 6 h a complex product mixture.

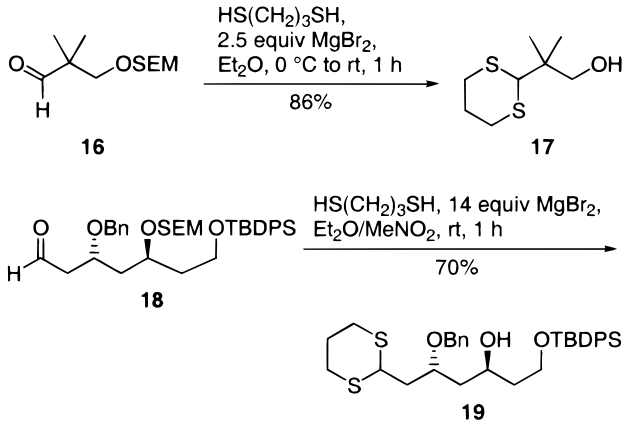
offers a turnaround of deprotection to afford **13**,[8] while the acetonide survives. A selective double SEM deprotection without compromising stereochemical integrity (see also Table 3, entry 8) is illustrated in Scheme 1. Even sensitive silylated cyanohydrin remained intact to give **15**, while traditional conditions (TBAF, DMPU) led to decomposition.

Treatment of SEM-protected aldols **16** and **18** with $MgBr_2$ and 1,3-propanedithiol allowed us to combine deprotection with protection of the sensitive aldehyde group (Scheme 2).

Scheme 1. Double Deprotection of *O*-Silylated Cyanohydrin

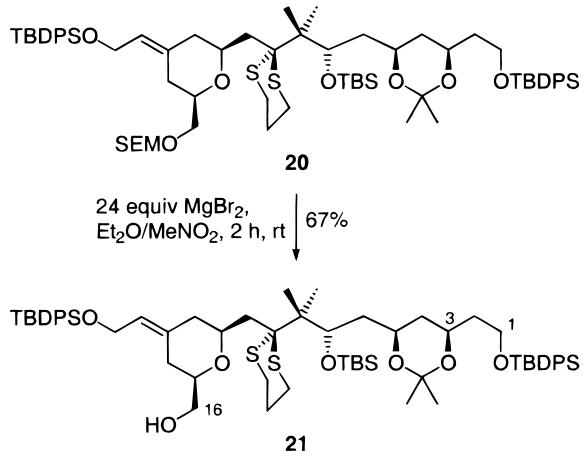


Scheme 2. One-Pot Thioketalization−SEM Deprotection



We have applied the deprotecting protocol in the synthesis of the northern C1−C16 segment **20** of 3-*epi*-bryostatins (Scheme 3). The desired C16-OH group was liberated,

Scheme 3. Orthogonal Deprotection in Polyketide Total Synthesis



leaving the three remaining *O*-silylated functions intact to give masked polyketide **21**.

In conclusion, a variety of functionalities are tolerated by the $MgBr_2$ deprotecting protocol including alcohols, esters, benzyl groups, dithians, and methoxy acetals (Table 1). In the presence of sensitive functionality such as acetonides, TBS and TIPS ethers, and especially *O*-silylated cyanohy-

(6) (a) HF/MeCN: White, J. D.; Kawasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4991. (b) $LiBF_4$/MeCN ($T > 70$ °C): Dittrich, K. *Liebigs Ann. Chem.* **1990**, 789. (c) BF_3·Et_2O, deprotection of the related β-trimethylsilylethyl ether group: Burke, S. D.; Pacofsky, G. J. *Tetrahedron Lett.* **1986**, *27*, 445. Jansson, K.; Frejd, T.; Kihlberg, J.; Magnusson, G. *Tetrahedron Lett.* **1986**, *27*, 753. (d) TFA: Schlessinger, R. H.; Poss, M. A.; Richardson, S. *J. Am. Chem. Soc.* **1986**, *108*, 3112. (e) I_2, *hν*: Karim, S.; Parmee, E. R.; Thomas, E. J. *Tetrahedron Lett.* **1991**, *32*, 2269.

(7) In the synthesis of bicyclic systems related to taxol, the SEM ether could not be removed and the [(*p*-methoxybenzyl)oxy]methyl (PMBM) group was used instead: Zeng, Q.; Bailey S.; Wang, T.-Z.; Paquette, L. A. *J. Org. Chem.* **1998**, *63*, 137.

drins, kinetically controlled deprotection is important and feasible. Since the experimental conditions are very mild and orthogonal to other deprotection strategies, modified SEM linkers[9] should also be useful in solid phase reactions and combinatorial chemistry.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for their support and Ulrike Eggert for her help.

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(8) **Represenitive Experimental Procedure. Synthesis of 13.** $MgBr_2$ (140 mg, 0.76 mmol) was treated with 0.5 mL of anhydrous Et_2O. After dissolution of the solid, the resulting two phases were treated with $MeNO_2$ (85 μL, 1.52 mmol, ACROS, p.a., water < 0.5%). The resulting solution (one phase) was added to a stirred mixture of SEM ether **11** (40 mg, 0.054 mmol) in 0.5 mL of Et_2O. The mixture was stirred for 1 h at room temperature and then diluted with MTB ether and washed with water (20 mL). The aqueous layer was extracted with MTB ether (2 × 10 mL), the combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4), and the solvent was removed. The crude product was purified by column chromatography (SiO_2; MTB/PE, 1:10 → 1:3) to afford **13** (26 mg, 81%), colorless oil: IR ($CHCl_3$) ν 3672, 3482, 3072, 2996, 2932, 2900, 1472, 1428, 1380, 1164, 1112, 956, 820 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.75−7.62 (m, 4 H, o-Ar-*H*), 7.44−7.31 (m, 6 H, Ar-*H*), 4.28 (s, 1 H, SC*H*S), 4.24−3.99 (m, 3 H, C*H*OH, $CH_2CHO(C(CH_3)_2)CH_2$, C*H*OC$(CH_3)_2)CH_2CH_2$OTPS), 3.91−3.76 (m, 1 H, CH_2OTPS), 3.75−3.61 (m, 1 H, CH_2OTPS), 3.05−2.91 (bs, 1 H, O*H*), 2.90−2.82 (m, 4 H, SCH_2-CH_2CH_2S), 2.17−2.02 (m, 1 H, $SCH_2CH_2CH_2$S), 1.95−1.51 (m, 7 H, $SCH_2CH_2CH_2$S, CH(OH)CH_2, CHCH_2CH, CH_2CH_2OTPS), 1.43/1.37 (s, 3 H, OC$(CH_3)_2$O), 1.05 (s, 9 H, $SiPh_2C(CH_3)_3$), 1.08/1.02 (s, 6 H, C$(CH_3)_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.52/134.80 (3°, o-Ar-*C*), 135.36/133.90 (4°, Ar-*C*), 129.54 (3°, p-Ar-*C*), 127.64 (3°, m-Ar-*C*), 98.73 (4°, *C*O_2-$(CH_3)_2$), 71.40 (3°, *C*HOH), 67.42 (3°, $CH_2CHOC(CH_3)_2)CH_2$), 65.72 (3°, C*H*OC$(CH_3)_2)CH_2CH_2$OTPS), 59.62 (2°, *C*H_2OTPS), 59.21 (3°, S*C*HS), 42.35 (4°, *C*$(CH_3)_2$), 39.26 (2°, *C*H_2CH_2OTPS), 36.66 (2°, CH(OH)*C*H_2), 36.49 (2°, CH*C*H_2CH), 31.50/31.39 (2°, S*C*$H_2CH_2CH_2$S), 30.22 (1°, OC-$(CH_3)_2$O), 26.57 (1°, $SiPh_2C(CH_3)_3$), 26.38 (2°, $SCH_2CH_2CH_2CH_2$S), 21.05 (1°, OC$(CH_3)_2$O), 19.95/19.68 (1°, C$(CH_3)_2$), 19.18 (4°, $SiPh_2C(CH_3)_3$); MS *m*/*z* 603 (M^+ + 1, 1.0), 602 (2.0, M^+), 588 (2.7), 526 (2.4), 487 (12.4), 469 (3.5), 437 (2.6), 379 (1.4), 350 (4.9), 326 (7.0), 256 (21.4), 225 (12.0), 199 (30.7), 183 (10.2), 161 (10.8), 134 (11.3), 119 (100), 107 (8.7), 91 (13.0), 81 (5.9), 75 (5.0); HRMS calcd for $C_{27}H_{45}O_4S_2Si_1$ ($M^+ - C_6H_5$) 525.2317, found 525.2308.

(9) β-Silylethyl group as an anomeric linker in saccharide chemistry: Weigelt, D.; Magnusson, G. *Tetrahedron Lett.* **1998**, *39*, 2839. For a general review on linkers in solid phase organic synthesis, see: James, I. W. *Tetrahedron* **1999**, *55*, 4855.