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cyclo - SEM: A New Carbonyl Protecting Group

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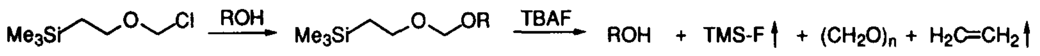
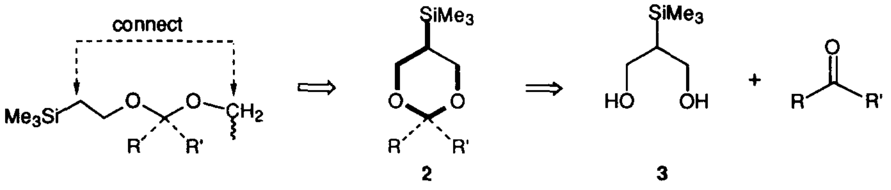
Summary. *Conversion of aldehydes and ketones to 1,3-dioxanes with 2-trimethylsilyl-1,3-propanediol affords carbonyl-protected products, ultimately susceptible to unmasking with $LiBF_4$ in THF.*

Protecting group chemistry[1] in organic synthesis remains a "fact of life", notwithstanding the recent push toward reactions that are classified as more environmentally friendly (*e.g.*, those run in H_2O). Most of the effort in this area focuses on either blocking of a hydroxyl moiety, or removal of the electrophilicity associated with an aldehyde or ketone carbonyl group. Several years ago we introduced SEM ethers **1**, derived from SEM-Cl, which afford the luxury of a chemospecific TBAF removal under neutral conditions.[2] An equivalent protecting group for the carbonyl was envisioned upon recognition of the SEM framework embedded within the 1,3-dioxane **2** (enboldened), which results from the hypothetical bond connection indicated below. We now describe the preparation of previously unknown 2-trimethylsilyl-1,3-propanediol (**3**) and its use as precursor to '*cyclo*-SEM' protected aldehydes and ketones (**2**, where *both* R and R' ≠ H).[3]

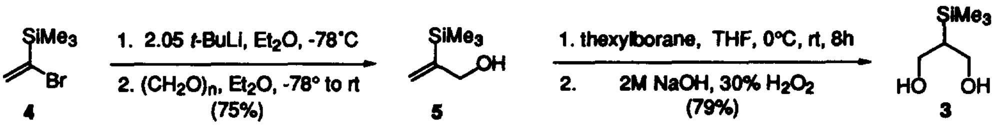


[SEM-Cl] **1**

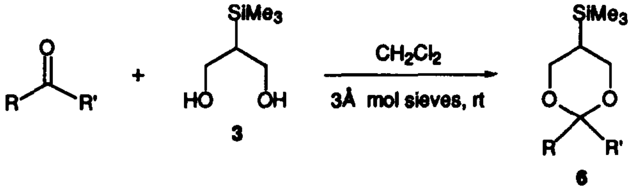


2 **3**

Diol 3 was originally conceived to arise by several straightforward routes ... at least on paper. However, suffice it to say that to date, of the *many* pathways examined, only one of any practicality has surfaced for this specific diol. Starting with 1-bromovinyltrimethylsilane (4), itself realizable *via* an *Organic Synthesis* procedure,[4] lithiation with 2*t*-BuLi[5] followed by inverse addition *via* cold (-78°) cannulation into a paraformaldehyde/THF slurry at -78° affords the volatile allylic alcohol 5. Treatment of 5 with thexylborane[6] (2.5 eq) and then basic peroxide gives 3 upon workup. After an initial flash chromatography, Kugelrohr distillation (bp 110-130° at 2 mm Hg) gives the diol as a white, low-melting solid (mp 36-38° C) which appears to be indefinitely stable to air on the benchtop at room temperature.



Carbonyl protection proceeds uneventfully at room temperature in dry CH_2Cl_2 (0.75-1.25M) using powdered and activated 3Å or 4Å molecular sieves and 1.5-2 eq of diol 3 in the presence of camphorsulfonic acid (0.25 eq). More sterically demanding cases may require 4-5 eq, but in all cases residual diol (R_f = 0.29 in 60% EtOAc/pet ether) can be recovered (*ca* 80%) by silica gel chromatographic separation from *cyclo*-SEM products 6. Forcing conditions, such as refluxing toluene in the presence of a Dean-Stark trap, consumes diol nonproductively and did not drive otherwise recalcitrant substrates to completion. Representative examples of *cyclo*-SEM acetals are shown in Table 1.



Key to the success of this new methodology is the selective removal of the *cyclo*-SEM residue, in particular under conditions where related (non-silylated) dioxanes and dioxolanes are unaffected, thereby highlighting the value of a fluoride-induced sequence. While $BF_3{\cdot}OEt_2$ in THF readily unravels acetals 6, our goal was to find strictly neutral, non-oxidative or reductive conditions for carbonyl regen-

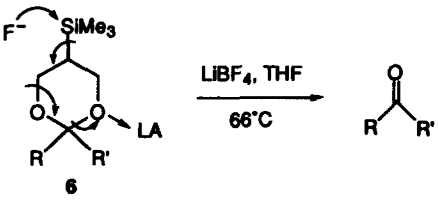
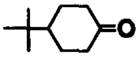
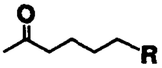
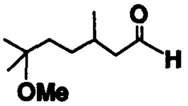
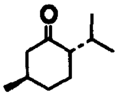
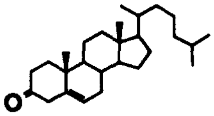
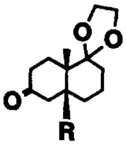
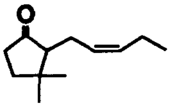
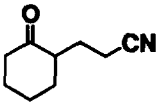


Table 1. Carbonyl protections and deprotections as *cyclo*-SEM derivatives.

Entry	Substrate	Protection[a]			Deprotection	
		Equiv[b]	Time (h)	Yield (%)[c]	Time (h)	Yield (%)[c]
1		2.0	1	97	18	78
2	 R = Cl	4.0	36	82	9.75	71
	R = SPh	5.0	16	93	6.25	86
3		2.5	10	83	3	76
4		4.0	18	81	7.5	92
5		5.6	19	65	10.5	79[d]
6	 R = *n*-Bu	5.0	18	83	[e]	[e]
	R = H	5.4	12	85	[f]	[f]
7		5.0	36	45	1.75	93
8		5.0	20	89	8	84

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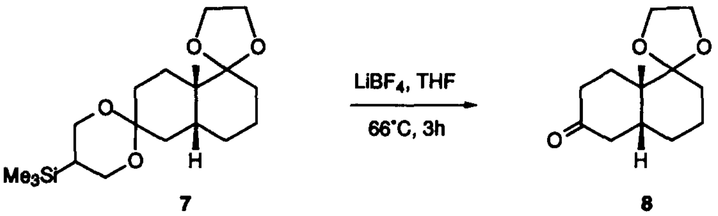
[a] All *cyclo*-SEM derivatives were fully characterized by spectral and MS data. [b] Amount of diol 3 used. [c] Isolated, chromatographically purified material. [d] The α,β-unsaturated ketone was obtained. [e] Not attempted. [f] See text.

eration. Ultimately, we found that $LiBF_4$ (1 eq), which contains both the 'push' (as a well-known source of fluoride ion[7]), and the 'pull' in the Lewis acidic (LA) lithium ion (or BF_3), in refluxing dry THF[8] (0.5M) cleanly returns the desired aldehyde or ketone. Under these conditions, non-silyated derivatives remain essentially intact.[9] Presumably, liberated BF_3 is tied up as the salt of by-product allyl alcohol.

The selectivity associated with *cyclo*-SEM deprotection could be further demonstrated by exposure of *bis* ketal **7** to our standard deprotection conditions. After three hours, keto ketal **8** was obtained in >80% yield (by glc); only 2-3% of the corresponding diketone was observed.



7 **8**

In summary, a structurally new carbonyl protecting group is reported which involves generation of 2-silylated 1,3-dioxanes, prepared from 2-trimethylsilyl-1,3-propanediol (**3**) and aldehydes or ketones. This cyclic acetal, a '*cyclo*-SEM' derivative, is susceptible to chemospecific unmasking under the influence of fluoride ion supplied by $LiBF_4$. The ready availability of precursor diol **3**, the good yields of protection and deprotection, and the mild and selective conditions[10] involved at each stage argue well for use of the *cyclo*-SEM group in synthetic chemistry.

Acknowledgements. We warmly acknowledge financial support provided by the NSF (CHE 93-03883).

References and Notes

1. Greene, T.W.; Wuts, P.G.M. in *Protective Grougs in Organic Synthesis*, Wiley, N.Y., 1991, 2nd Ed.; Kocienski, P.J. *Protecting Groups*, Thieme, Stuttgart, 1994.
2. Lipshutz, B.H.; Pegram, J.J. *Tetrahedron Letters*, **1980**, 21, 3343.
3. For a related protecting group, see Lillie, B.M.; Avery, M.A. *Tetrahedron Letters*, **1994**, *35*, 969.
4. Boeckman, R.K.; Blum, D.M.; Ganem, B.; Halvey, N. *Org. Syn. Coll. Vol. VI*, **1988**, 1033.
5. (a) The corresponding Grignard can be formed,[5b] although subsequent reaction with paraform-aldehyde leads to alcohol 5 in 35-71% yield; (b) Overman, L.; Renhowe, P.A. *J. Org. Chem.*, **1994**, *59*, 4138.
6. Use of alternative hydroborating agents, such as 9-BBN, led to inferior results.
7. Other sources of fluoride ion that did *not* effect deprotection include TBAF (in THF or DMPU), CsF (in DMF, CH_3CN, or THF), and Bu_4NBF_4 (in THF or DMPU).
8. Use of $LiBF_4$ in CH_3CN removes the *cyclo*-SEM group very easily, although in our hands, this reagent/solvent combination, in control experiments, also deprotects standard dioxane and dioxolane derivatives.
9. Both a dioxolane and dioxane derivative of 4-*t*-butylcyclohexanone, upon treatment with $LiBF_4$ in refluxing THF, gave only small percentages of ketone, presumably from traces of adventitious water.
10. For a recent alternative method for acetal unmasking under neutral conditions, see Johnstone, C.; Kerr, W.J.; Scott, J.S. *J. Chem. Soc., Chem. Commun.* **1996**, 341.

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