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EFFECTIVE DEPROTECTION OF 2-(TRIMETHYLSILYLETHOXY)METHYLATED ALCOHOLS (SEM ETHERS). SYNTHESIS OF THYRSIFERYL-23 ACETATE

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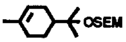
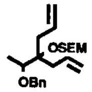
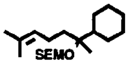
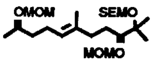
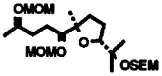
New conditions for effective cleavage of SEM ethers were developed (TBAF/HMPA in the presence of MS 4A) and usefulness of this reaction was demonstrated by the synthesis of thyrsiferyl-23 acetate.

The selection of a protective group is an important step for achievement of a multistep organic synthesis. 2-(Trimethylsilyl)ethoxymethyl (SEM) group was developed1) as a useful protective group which was stable over a wide range of conditions and could be cleaved in the presence of fluoride ion. A particular advantage of the SEM group is easy formation with hindered hydroxyl group, e.g. tertiary or neopentyl alcohol. However, the some difficulties in cleaving SEM ethers have prevented their wide use.2) Now, we wish to describe the new conditions for easy cleavage of SEM ethers and demonstrate its usefulness in the synthesis of thyrsiferyl-23 acetate.4)

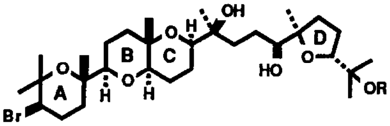
The cleavage of hindered SEM ethers by tetrabutyl ammonium fluoride

Table 1 Cleavage of Several SEM Ethers

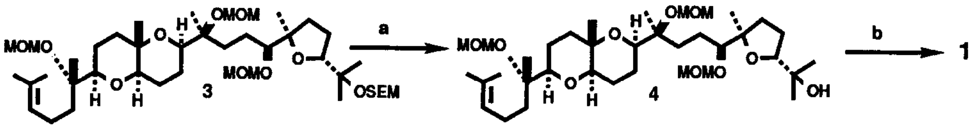
SEM ether R-OSEM	Conditions	Products (% yield) R-OR' 5)
	i) TBAF, HMPA, rt, 15 h	R'=SEM (63), R'=EOM (15), R'=H (15)
	ii) TBAF, HMPA, rt, MS 4A, 1 h	R'=H (94)
	i) TBAF, HMPA, rt, 15 h	R'=SEM (20), R'=EOM (24), R'=H (55)
	ii) TBAF, HMPA, rt, MS 4A, 1 h	R'=H (91)
	i) TBAF, HMPA, rt, 15 h	R'=SEM (20), R'=EOM (26), R'=H (52)
	ii) TBAF, HMPA, rt, MS 4A, 1 h	R'=H (90)
	i) TBAF, HMPA, 100 °C, 15 h	R'=SEM (18), R'=EOM (27), R'=H (53)
	ii) TBAF, HMPA, 100 °C, MS 4A, 1 h	R'=H (94)
	i) TBAF, HMPA, 100 °C, 15 h	R'=SEM (75), R'=EOM (20)
	ii) TBAF, HMPA, 100 °C, MS 4A, 1 h	R'=H (98)

(TBAF) in THF or HMPA always resulted in poor yield[5)] and TBAF in vacuum[3)] didn't give excellent results. Eventually, addition of molecular sieves 4A (MS 4A) to the reaction mixture, dramatically improved the deprotection yield, which was more than 90% in all the cases examined. Results were summarized in Table 1.

Among several thyrsiferol derivatives known to date, 23-acetate (**1**) exhibited exceptionally potent bioactivity. We synthesized thyrsiferol (**2**) previously[6)] and achieved preparation of the 23-acetate (**1**) this time. Key intermediate (**3**), discriminatingly protected by SEM group,[6)] was smoothly demasked under newly developed conditions to give an alcohol (**4**) in good yield (98%). Successive acetylation, removal of MOM ethers and bromonium ion induced cyclization of the A-ring afforded the acetate (**1**) which was identical with the natural product in all respects (400 MHz NMR, IR, HPLC-retention time and ORD).



1 R=Ac thyrsiferyl-23 acetate
2 R=H thyrsiferol



Conditions, a; (i) TBAF, HMPA, MS 4A, 100 °C (98%), b; (i) Ac_2O, DMAP, 120 °C (56%), (ii) HCl, MeOH (74%), (iii) TBCO,* CH_3NO_2(20%) *TBCO = 2,4,4,6-tetrabromocyclohexa-2,5-dienone

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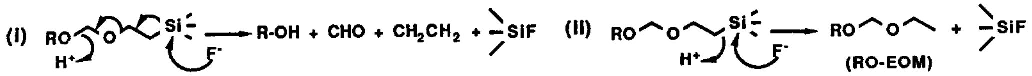
References and Notes

1) B. H. Lipshutz and J. J. Pegram, Tetrahedron Lett., **21**, 3343 (1980).
2) Removal of SEM ether often encountered sluggishness. Indeed, yields of demasking the hindered SEM ethers were not shown in original paper.[1)] Nevertheless, for the sake of particular usefulness of SEM group, improvement of the removing conditions has been attempted.[3)]
3) T. Sugimura and L. A. Paquette, J. Am. Chem. Soc., **109**, 3017 (1987).
4) T. Suzuki, M. Suzuki, A. Furusaki, T. Matsumoto, A. Kato, Y. Imanaka and E. Kurosawa, Tetrahedron Lett., **26**, 1329 (1985); T. Suzuki, S. Takeda, M. Suzuki, E. Kurosawa, A. Kato and Y. Imanaka, Chem. Lett., 361 (1987).
5) Occurring of the cleavage reaction (i) instead of (ii) made the deprotection poor.



6) M. Hashimoto, T. Kan. M. Yanagiya, H. Shirahama and T. Matsumoto, Tetrahedron Lett., **28**, 5665 (1987); M. Hashimoto, T. Kan, K. Nozaki, M. Yanagiya, H. Shirahama and T. Matsumoto, ibid., **29**, 1143 (1988).

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