

Selective Deprotection of Silyl Ethers

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This review focuses on the selective deprotection of silyl ethers in the presence of other like or unlike silyl ethers. Various examples are highlighted throughout the text, and these examples are compiled in tabular form at the end of the document (Tables 16–27). The abbreviations and structures for some of the more common silyl groups are given in Figure 1.

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1. Introduction

The protection/deprotection protocol of free hydroxyl groups has become commonplace in organic synthesis. When the protection of more than one hydroxyl group is necessary, the traditional methodology has been to carefully select protecting groups in a manner that allows selective removal at a later stage of the synthetic scheme. Thus, different protecting groups can be selectively re-

moved, allowing unlike transformations of various hydroxyl groups in the same molecule. More traditional protection schemes involved, for example, the protection of one alcohol as an ester and another as an ether. Due to their ease and recently developed selectivity of attachment, a host of di- and trialkylsilyl groups (Figure 1) have been commonly used as protection of free hydroxyl groups over the last 20 years.^{1–5}

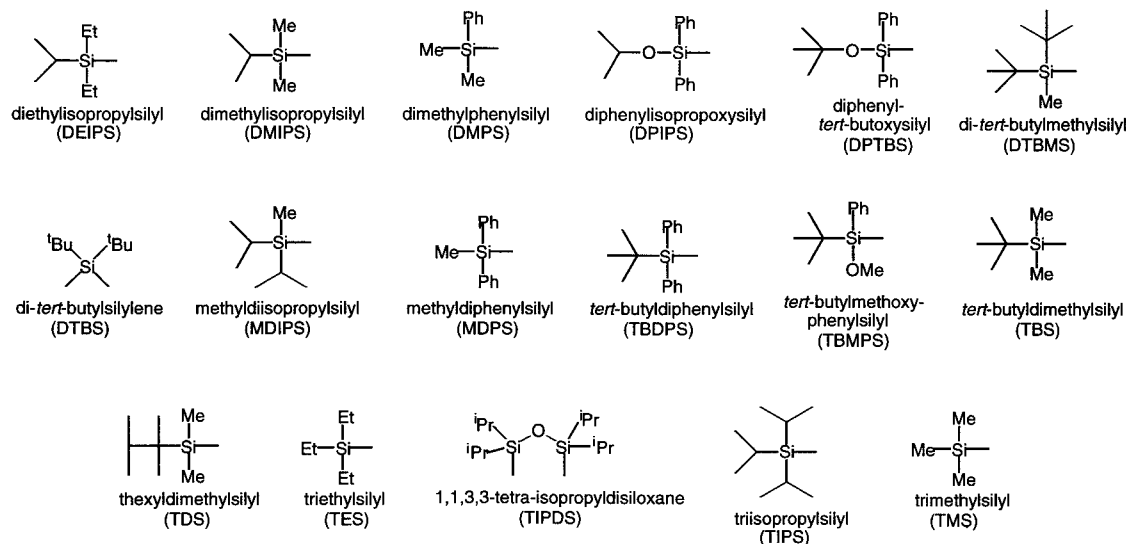
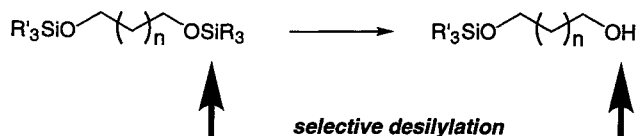


Figure 1⁵

As the complexity of synthetic targets has grown more demanding, selective discrimination of *different* silyl ethers in the same molecule has become increasingly important. The experimental conditions described in this review allow the selective deprotection of silylated alcohols in the presence of other silyl ethers. Differences in reactivity can be modulated by a variety of factors that include substrate control (e.g. the steric and electronic nature of the silyl substituents, the steric and electronic environment of the alcohol and the neighboring group effects within the substrate) and also by reagent control. Such selective differentiation of silyl ethers is illustrated in the recently published total syntheses of taxol,⁶⁻⁸ brevetoxin,^{9,10} rapamycin,¹¹ zaragozic acid,¹²⁻¹⁴ and avermectins.¹⁵



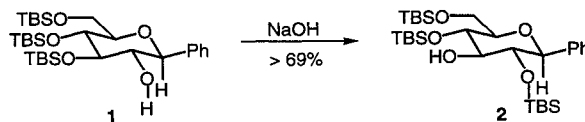
The purpose of this review is to serve as a compendium on the selective deprotection of silyl ethers. The focal point in this discussion will be on deprotection reactions that cleave a silicon-oxygen bond. Thus, silyl-containing protecting groups such as 2-(trimethylsilyl)ethoxymethyl (SEM), in which a carbon-silicon bond is broken, are not considered. While literature searches will provide an ample list of such methods, many more such procedures and conditions are included in papers describing lengthy total syntheses and receive only brief mention, despite their potential utility in other systems. The following

pages are organized according to the type of silylated carbinol (1°, 2°, etc.) that is deprotected in the presence of another silylated carbinol (1°, 2°, etc.). Hopefully, a compilation of this type will aid organic chemists in the design and execution of natural and unnatural product syntheses.

We have also chosen to preclude the in-depth discussion of selective deprotection of the following systems:

1. silyl enol ethers vs. silyl ethers (although a few examples of silyl enol ether differentiation are given in Section 7)
2. distinguishing C-Si bond cleavage from each other (some examples of selective protidesilylations are included in Section 9)
3. stability of O-Si bonds under conditions that oxidize C-Si bonds^{343,344}
4. O to O and O to C silyl migrations¹⁶⁻¹⁸

Although O to O silyl migrations will not be discussed in detail, this phenomenon nicely complements selective desilylation methodology. For example, treatment of the tris-silylated aryl glucal **1** with base initiated a 1,4-O to O silyl migration (Scheme 1).¹⁹ In terms of selective silyl deprotection, a 2° TBS ether was removed in the presence of both another 2° TBS ether and a 1° TBS ether.¹⁹ Marshall has reported a similar migration of a TBDPS group.²⁰

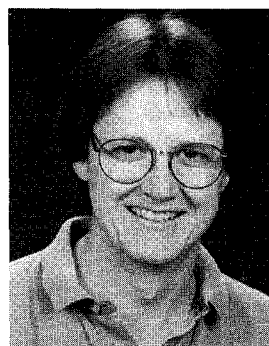


Scheme 1

Biographical Sketches

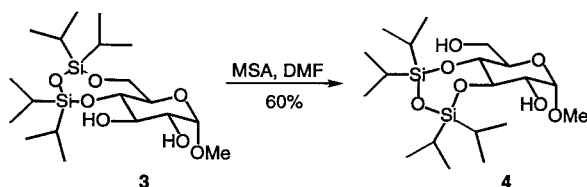


Todd D. Nelson received his Ph.D. in 1992 from The Johns Hopkins University, Baltimore, MD under the direction of Professor Gary H. Posner. He then conducted postdoctoral research in the laboratories of Professor A.I. Meyers at Colorado State University, Fort Collins, CO. until 1994. Todd is currently employed in the Process Research Group at Merck & Co., Rahway, NJ. His interests include synthetic methodology, functional group transformations and the synthesis of unnatural products.



R. David Crouch, born in 1956 in Durham, North Carolina, received his B.A. degree from Duke University. After 6 years of teaching science at the high school level, he received his M.S. degree from Shippensburg University in Pennsylvania in 1985 and his M.A. in 1988 and his Ph.D. in 1991 from The Johns Hopkins University, working under the direction of Professor Gary H. Posner. In 1991, he accepted a faculty position at Coker College in Hartsville, South Carolina and then moved to Dickinson College in 1994, where he is currently an Assistant Professor.

In addition, silyl migrations of this type can occur under acidic conditions.²¹ For example, mesitylenesulfonic acid (MSA)^{22,23} or TsOH²⁴ in DMF caused silyl migration from the C-1 alcohol of carbohydrate **3** to the C-3 alcohol of carbohydrate **4** (Scheme 2).

Scheme 2²²

2. Mechanistic Considerations

Although a number of possible mechanisms for the cleavage of silyl ethers have been proposed,²⁵ differences in the substituents on the silicon atom are known to result in dramatically different reactivity of these protecting groups.^{26,27} In many cases, these differences lie at the heart of selective deprotection. In general, the size of the substituent on the silicon atom is directly related to the rate of deprotection with smaller silyl substituents being more easily cleaved under acidic conditions.^{26–29} This steric effect is nearly additive, as illustrated by a comparison of the relative rates of cleavage of TIPS- and DMIPS-protected alcohols.²⁸

*Relative stabilities of trialkylsilyl ethers towards acid-catalyzed hydrolysis*²⁶

TMS $\approx$ DMPS $\approx$ MDPS $<$ TES $\approx$ DMIPS $\approx$ Pr₃Si $\approx$ Bu₃Si $<$ TPS $<$ MDIPS $<$ TBS $<$ TDS $<$ TIPS $<$ TBDPS $<$ DTBMS

Similarly, if the same protecting group is used to protect two or more hydroxyl groups, the silyl ether derived from the less sterically encumbered alcohol is usually the first to be deprotected. In general, an increase in substituent size on either the silicon or the alcohol carbon decreases the rate of desilylation.²⁹ Under acidic conditions, though, the steric environment around the silicon atom is more significant than that around the oxygen atom.²⁹

In recent years, methods have been developed that allow selective cleavage of bulkier silyl ethers in the presence of usually more labile and less hindered silyl ethers. These methods have relied, in part, on the electronic effect of substituents on the silicon atom. Sommer has shown that electron-withdrawing substituents on silicon accelerate base-catalyzed hydrolysis of silyl ethers while electron-donating groups accelerate acid-catalyzed hydrolysis.²⁸ In both cases, the effect is more significant for groups attached to the oxygen rather than to the silicon.²⁹

*Relative stabilities of trialkylsilyl ethers towards base-catalyzed hydrolysis*²⁶

DMPS $\approx$ MDPS $\approx$ TMS $<$ DMIPS $\approx$ TES $<$ Pr₃Si $<$ Bu₃Si $<$ MDIPS $<$ TBDPS $\approx$ TBS $<$ TDS $<$ TIPS $<$ DTBMS

Denmark has summarized the combined effect of steric and electronic influences on silyl ether cleavage.³⁰ While acid-catalyzed hydrolysis is decelerated by increased ligand size and by electron-withdrawing substituents, the rate is more strongly influenced by the electronic effect than by the steric effect. Under base-catalyzed conditions, the rate of hydrolysis is decelerated by large ligands on silicon and by electron-donating substituents.

Table 1. Effect of Silyl Substituents on Rates of Silyl Ether Hydrolysis

conditions	steric effect		electronic effect	
	large	small	electron withdrawing	electron donating
acidic	slow	fast	slow	fast
basic	slow	fast	fast	slow

Recently, the long range effects of through-bond orbital interactions on desilylation reactions have been investigated and indicate that the geometry of a substrate's carbon skeleton also plays a role in the rate at which desilylation occurs.³¹

3. Selective Deprotection of Silyl-Protected 1° Alcohols

3.1. In the Presence of a 1° Silyl Ethers

The selective deprotection of silyl-protected alcohols has been achieved by careful application of the “traditional” deprotecting agents as well as the use of more novel reagents. Silyl-protected 1° alcohols have been selectively deprotected in the presence of another 1° silyl ether by taking advantage of the variation in reactivity of silyl groups due to the size of the silyl substituents.^{26,27}

3.1.1. Under Acidic Conditions

Cunico³² and Davies³³ have compared the rates of acid-catalyzed hydrolysis of several silyl ethers of 1° alcohols (Table 2).

Table 2. Half-Lives of Hydrolysis of 1° Silyl Ethers³³

1 % HCl/MeOH, 25 °C	
<i>n</i> -C ₆ H ₁₃ OTMS	$\leq$ 1 min
<i>n</i> -C ₆ H ₁₃ OTBS	$\leq$ 1 min
<i>n</i> -C ₆ H ₁₃ OMDPS	14 min
<i>n</i> -C ₆ H ₁₃ OTIPS	55 min
<i>n</i> -C ₆ H ₁₃ OTBDPS	225 min

It is important to note that the steric environment of the silyl group alone does not dictate selectivity in deprotection. The steric requirements in the region of the oxygen-bearing carbon is also critical, and in many cases, determines which of two like silyl groups will be removed.

Aqueous HCl in THF has effected the selective deprotection of 1° TES ethers³⁴ and 1° TBS ethers³⁵ in the presence of TBDPS-protected 1° alcohols.

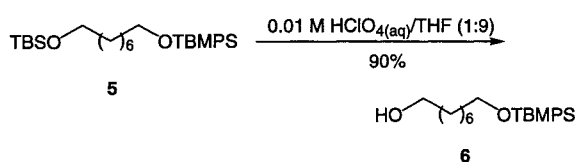
Ultrasonication of bis-silyl ethers in CH₃OH/CCl₄ has been reported to effect selective cleavage of a 1° TBS ether in the presence of a 1° TBDPS ether.³⁶ It is noteworthy that the pH of the CH₃OH/CCl₄ solution after sonification was 2.

In an attempt to exploit electronic effects in selective deprotections, a series of alkoxy-substituted silyl protecting groups has been introduced.^{37,38} The added influence of the electron-withdrawing alkoxy groups increases the difference in reactivity between these groups and the traditional trialkylsilyl groups with the alkoxy-substituted groups being more stable than trialkylsilyl groups under acidic conditions (Table 3).

Table 3. Half-Lives of Hydrolysis of 1° Trialkylsilyl vs. Alkoxysilyl Ethers with 0.01 M HClO₄³⁸

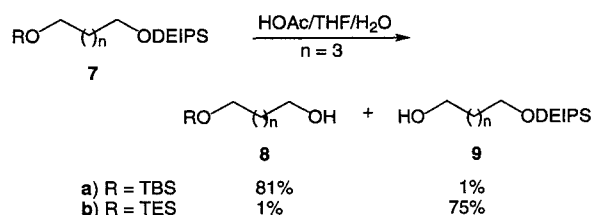
Trialkylsilyl Ethers		Alkoxysilyl Ethers	
<i>n</i> -C ₁₂ H ₂₅ OTBS	1.4 h	<i>n</i> -C ₁₂ H ₂₅ ODPIPS	0.7 h
<i>n</i> -C ₁₂ H ₂₅ OTBDPS	> 200 h	<i>n</i> -C ₁₂ H ₂₅ ODPTBS	17.5 h
		<i>n</i> -C ₁₂ H ₂₅ OTBMPs	200 h

The potential of selective deprotection of one 1° silyl ether in the presence of another using these protecting groups has been demonstrated with the selective cleavage of a 1° TBS group in the presence of a 1° TBMPs ether as demonstrated in the conversion of **5** to **6** (Scheme 3).³⁸ The widespread use of these alkoxy-substituted silyl protecting groups has not been observed, perhaps due to the limited commercial availability of the necessary silylating reagent; however, TBMPs-Br has recently been made commercially available (Aldrich catalog # 33,762-5).



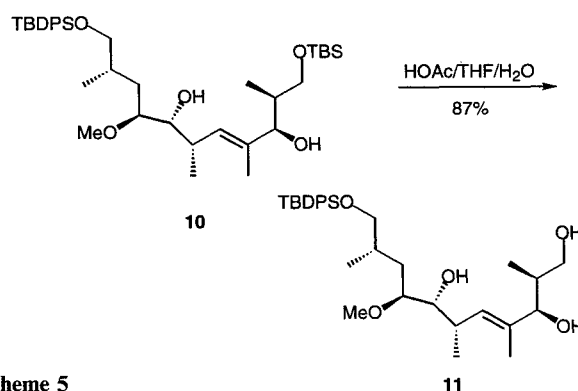
Scheme 3³⁸

With selectivity in deprotection as a goal, new silyl protecting groups have been developed. One such example is the introduction of the DEIPS group.³⁹ Traditional acid-catalyzed hydrolysis using acetic acid in THF/H₂O allowed the DEIPS group to be distinguished from the larger TBS group and the smaller TES group as illustrated in the deprotection of bis-silyl ether **7** (Scheme 4).



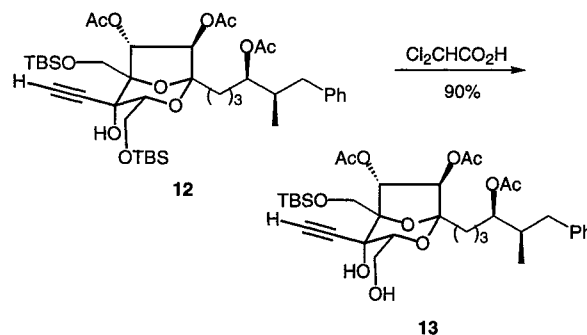
Scheme 4

Hanessian first employed acetic acid in the selective desilylation reactions of 1° TBS groups in the presence of 1° TBDPS-protected alcohols.⁴⁰ Similarly, Marshall has utilized a 3:1:1 mixture of acetic acid, THF and water to effect cleavage at 1° TBS ether in the presence of a 1° TBDPS ether in the conversion of silyl ether **10** to alcohol **11** (Scheme 5).⁴¹ Others have accomplished similar deprotections utilizing this same protocol.^{42–44}



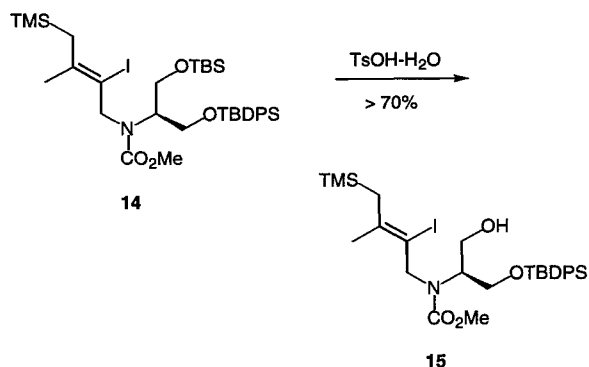
Scheme 5

In a recently described synthesis of (+)-zaragozic acid C, Carreira used dichloroacetic acid to effect the selective deprotection of one 1° TBS ether in the presence of another 1° TBS ether to afford diol **13** in 90 % yield (Scheme 6).^{12,13}



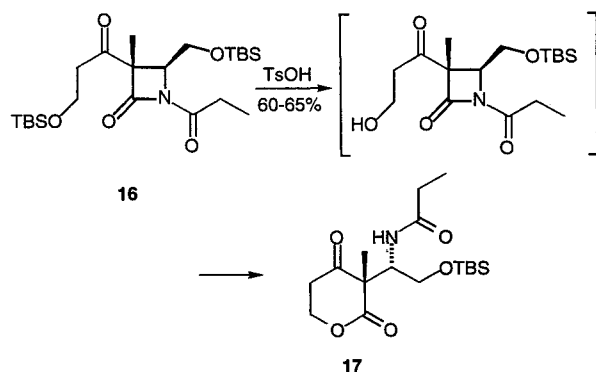
Scheme 6

The monohydrate of TsOH in methanol was used to deprotect a 1° TBS ether in the presence of a TBDPS-protected 1° alcohol to afford alcohol **15** (Scheme 7).⁴⁵



Scheme 7

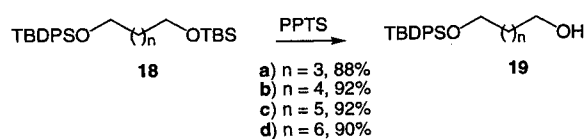
The accessibility of the 1° TBS ethers is significant in the selectivity of acid promoted hydrolysis reactions. Thomas has used 0.1 equivalents of TsOH in 20:1 THF/water to deprotect one TBS-protected 1° alcohol in the presence of another (Scheme 8).⁴⁶ Upon basic workup, lactone **17** was isolated in 60–65% yield.



Scheme 8

Camphorsulfonic acid has been used by Nicolaou in less than stoichiometric amounts to selectively deprotect a 1° TBS ether in the presence of a 1° TBDPS ether as part of work toward the synthesis of brevetoxin A⁴⁷ and brevetoxin B.⁴⁸

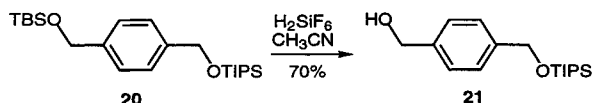
Other mildly acidic conditions have also been used to selectively deprotect silyl ethers. Prakash has reported a method that differentiates between TBS- and TBDPS-protected 1° alcohols in the same molecule.⁴⁹ Treatment of bis-silyl ethers **18** with 0.3 equivalents of PPTS (pyridinium *p*-toluenesulfonate) in ethanol at room temperature led to the selective removal of the TBS-protecting group, providing the monoprotected diols **19** in high yield (Scheme 9).⁴⁹ This protocol has recently been employed by Marshall.²⁰



Scheme 9

Fluoride has long been a key reagent in the deprotection of silyl ethers^{50–55} and delivery of fluoride under acid

conditions has been applied to the problem of selective deprotection of silyl ethers. DeShong has recently described a selective deprotection of TBS-protected 1° benzylic alcohols in the presence of TIPS-protected 1° benzylic alcohols by fluorosilicic acid (Scheme 10).^{56,57}



Scheme 10

In addition, Masamune has employed HF·pyridine to chemoselectively remove a 1° TES group in the presence of a 1° TBS ether.⁵⁸

3.1.2. Under Basic/Nucleophilic Conditions

Cunico³² and Davies³³ have measured the half-lives of a variety of 1° silyl ethers in methanolic NaOH (Table 4). The results indicate that a combination of steric and electronic factors contribute to the relative stability of these substrates.

Table 4. Half-Lives of Base-Catalyzed Hydrolysis of 1° Silyl Ethers³³

5% NaOH/MeOH, 25 °C	
<i>n</i> -C ₆ H ₁₃ OTMS	≤ 1 min
<i>n</i> -C ₆ H ₁₃ OIBDMS ^a	2.5 min
<i>n</i> -C ₆ H ₁₃ OTBS	^b
<i>n</i> -C ₆ H ₁₃ OMDPS	≤ 1 min
<i>n</i> -C ₆ H ₁₃ OTIPS	^b
<i>n</i> -C ₆ H ₁₃ OTBDPS	^b

^a IBDMS = isobutyltrimethylsilyl.

^b Stable over 24 h.

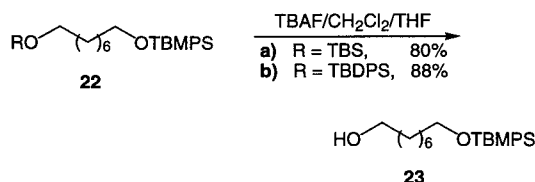
Electron-withdrawing substituents on the silicon atom of a silyl ether increase susceptibility to base-catalyzed cleavage. This effect serves as the basis for the selective deprotection of alkoxy-substituted silyl ethers in the presence of other silyl ethers.^{37,38} Alkoxy-substituted silyl groups are cleaved by TBAF more rapidly than trialkylsilyl ethers (Table 5).

Table 5. Half-Lives of Hydrolysis of 1° Trialkylsilyl vs. Alkoxysilyl Ethers with TBAF³⁸

Trialkylsilyl Ethers		Alkoxysilyl Ethers	
<i>n</i> -C ₁₂ H ₂₅ OTBS	140 h	<i>n</i> -C ₁₂ H ₂₅ ODPIPS	< 0.03 h
<i>n</i> -C ₁₂ H ₂₅ OTBDPS	375 h	<i>n</i> -C ₁₂ H ₂₅ ODPTBS	5.8 h
		<i>n</i> -C ₁₂ H ₂₅ OTBMPS	22 h

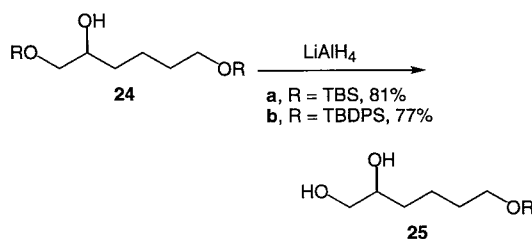
This effect has been demonstrated in the selective TBAF-promoted deprotection of a 1° TBMPs ether in the pres-

ence of a 1° TBS (**22a**) or TBDPS (**22b**) ether (Scheme 11).³⁷ TBAF has also been used to selectively deprotect one 1° TBS ether in the presence of another.⁵⁹



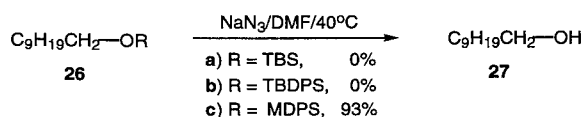
Scheme 11

Selective deprotection of one 1° TBS ether or one 1° TBDPS ether in the presence of a similarly protected 1° alcohol has been effected by treatment with an excess of LiAlH₄ (Scheme 12).⁶⁰ In this reaction, selectivity was attributed to the effect of a neighboring hydroxyl group, which presumably coordinates to aluminum and delivers the hydride exclusively to the neighboring silyl group.



Scheme 12

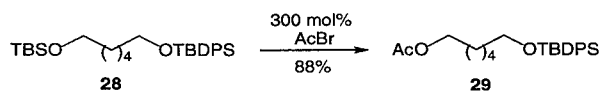
The importance of steric effects cannot be overlooked as evidenced by the selectivity of azide in deprotections. Excess azide (N₃⁻) has been employed to differentiate 1° MDPS ethers from 1° TBS and 1° TBDPS ethers (Scheme 13).⁶¹ The electron-donating effect of two phenyl groups is negated by the steric hindrance of the *t*-butyl group in TBDPS.



Scheme 13

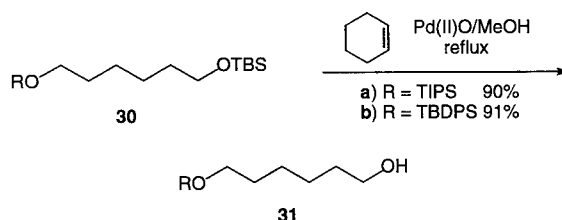
3.1.3. Miscellaneous Conditions

Primary alcohols protected as TBS and TBDPS ethers have been differentiated upon treatment with excess acetyl bromide to yield the monoacetate **29** in 88% yield (Scheme 14).⁶²



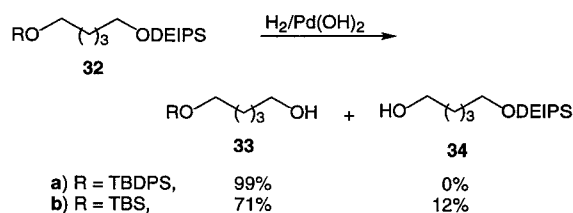
Scheme 14

Transfer hydrogenation has also been reported to be useful in distinguishing 1° TBS ethers from TIPS- and TBDPS-protected alcohols.⁶³ In studies on differentially protected 1° diols, bulkier silyl groups of bis-silyl ether **30** are removed more slowly (Scheme 15).



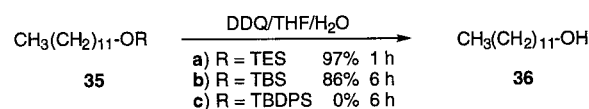
Scheme 15

The stability of the TBDPS group toward hydrogenolysis conditions has been exploited to selectively deprotect a 1° DEIPS ether in the presence of a TBDPS-protected 1° alcohol.⁶⁴ While the selectivity for cleavage of a DEIPS group over a TBDPS group is near 100% with no observed deprotection of the latter group (**32a** to **33a**), some removal of the TBS group (**34b**) was observed (Scheme 16).



Scheme 16

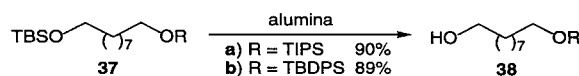
Tanemura and co-workers have applied a series of π -acceptors to selective desilylations of silyl-protected alcohols **35** (Scheme 17).^{65,66} 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) rapidly caused hydrolysis of TES-protected 1° alcohols. TBS ethers react slower while alcohols protected as TBDPS ethers are inert under these conditions.⁶⁵



Scheme 17

A similar trend in reactivity was observed with the other π -acceptors, 2,3,5,6-tetrafluoro-7,7,8,8-tetracyanoquinone dimethane (TCNQF₄), 7,7,8,8-tetracyanoquinodimethane (TCNQ), tetracyanoethylene (TCNE) and chloranil (CA).⁶⁶ Some evidence points to a single electron transfer mechanism for these deprotections but other work indicates that in situ acid production facilitates deprotection.⁶⁷

The Lewis acidity of activated alumina (3% H₂O) has shown a remarkable facility to selectively cleave 1° silyl ethers.^{68,69} Again, the bulkier TIPS and TBDPS groups remain intact while the TBS-protecting group was selectively removed from bis-silyl ethers **37** (Scheme 18).



Scheme 18

Silyl ethers of 1° alcohols have also been selectively cleaved with $\text{Cu}(\text{NO}_3)_2$ or $\text{Ce}(\text{NO}_3)_3$ in acetonitrile at room temperature (Table 6).⁷⁰ Again, the rate of deprotection decreases as the silicon substituent size increases.

Table 6. Rates of Cleavage of Various Silyl Ethers by Lewis Acids⁷⁰

	$\text{Cu}(\text{NO}_3)_2$	$\text{Ce}(\text{NO}_3)_3$
$n\text{-C}_{10}\text{H}_{21}\text{OTMS}$	1 min, 100 %	1 min, 100 %
$n\text{-C}_{10}\text{H}_{21}\text{OTBS}$	12 h, 90 %	15 h, 90 %
$n\text{-C}_{10}\text{H}_{21}\text{OTBDPS}$	2 d, 0 %	2 d, 0 %

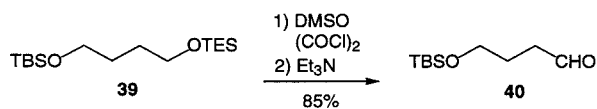
all reactions were run using 1 equivalent of Lewis acid in CH_3CN at room temperature

Such high selectivity, however, is not exhibited by all Lewis acids and in all substrates. For example, poor selectivity was observed in the incidental deprotection of one 1° TBS ether in the presence of another 1° TBS ether during a TBS-OTf mediated intramolecular cyclization–condensation.⁷¹

The novel 1,3-disubstituted tetrabutylstannoxanes, generated from the reaction of Bu_2SnCl_2 and Bu_2SnO , have also shown selectivity in the deprotection of a 1° TMS ether in the presence of a 1° TBS ether.⁷²

Corey reported that SiF_4 readily cleaved 1° TBS ethers, but 1° TDS or TBDPS ethers essentially remained intact under these same conditions.⁷³

A common transformation in organic synthesis is the deprotection of a silyl-protected alcohol followed by the oxidation of that alcohol. Deprotection under oxidative conditions streamlines the synthetic process, resulting in direct conversion of a silyl ether to a carbonyl moiety.⁷⁴ Recently, a number of such methods have been utilized that have differentiated between silyl ethers, thus allowing selective oxidation of silyl-protected alcohols. For example, primary alcohols protected as TMS or TES ethers underwent selective oxidation in the presence of TBS-protected 1° alcohols **39** under Swern conditions to afford aldehydes **40** (Scheme 19).^{74–76} 1° TMS and 1° TES ethers have also been oxidized to aldehydes by treatment with Collins reagent ($\text{CrO}_3\cdot\text{pyr}$) while 1° TBDPS and 1° TIPS groups remain unchanged.^{77–79}



Scheme 19

3.2. In the Presence of 2° and 3° Silyl Ethers

Selectively deprotecting a silyl-protected 1° alcohol in the presence of a similarly protected 2° alcohol is one of the most common and oldest selective desilylation reactions.

3.2.1. Under Acidic Conditions

Cunico has investigated the rates of acid- and base-catalyzed hydrolysis of 1° versus 2° silyl ethers (Table 7).³²

Table 7. Half-Lives of Acid-Catalyzed Hydrolysis of Various Silyl Protected 1° and 2° Alcohols³²

R	$n\text{-C}_4\text{H}_9\text{OR}$	$c\text{-C}_6\text{H}_{13}\text{OR}$
TBS	< 1 min	< 4 min
TIPS	18 min	100 min
TBDPS	244 min	360 min

all reactions were performed in 1% $\text{HCl}/95\% \text{EtOH}$ at 22.5°C

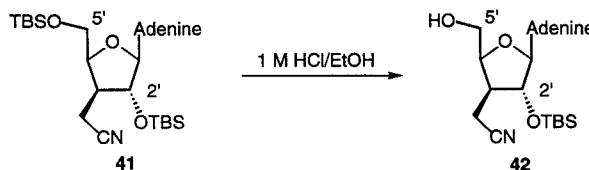
The introduction of the hexyldimethylsilyl (TDS) protecting group allows for differentiation of 1° and 2° alcohols under acidic conditions or upon treatment with fluoride.⁸⁰ As summarized in Table 8, the rates of acid-catalyzed deprotection of TDS-protected butanol is considerably faster than that of TDS-protected cyclohexanol.

Table 8. Half-Lives of Deprotection of TDS Ethers⁸⁰

	1% HCl/EtOH , r. t.
$n\text{-C}_4\text{H}_9\text{OTDS}$	3 min (30 min) ^a
$c\text{-C}_6\text{H}_{11}\text{OTDS}$	20 min (2.3 h) ^a

^a The time for complete deprotection.

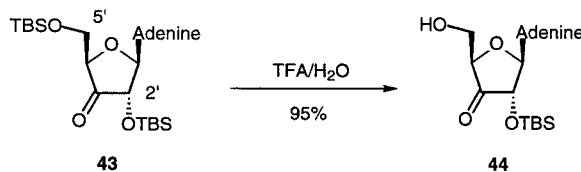
Alcoholic HCl has been used to selectively deprotect 1° TBS ethers in nucleoside **41** containing a 2° TBS ether (Scheme 20).⁸¹ The selectivity of this deprotection sharply contrasts the lack of selectivity observed upon treatment with TBAF.⁸¹



Scheme 20

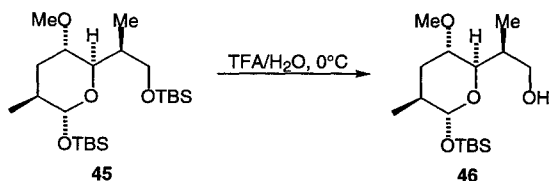
A host of other examples demonstrating the same selectivity in silyl deprotection of nucleosides under acid conditions exist.^{21,82–84} Poor selectivity was observed, however, in another example in which HCl was used to discriminate between 1° and 2° TBS-protected alcohols.⁸⁵

Aqueous TFA ^{86,87} in H_2O was the reagent of choice to selectively deprotect the 5'-OH of 2',5'-di-OTBS-3'-oxo-adenosine **43** (Scheme 21).⁸⁶



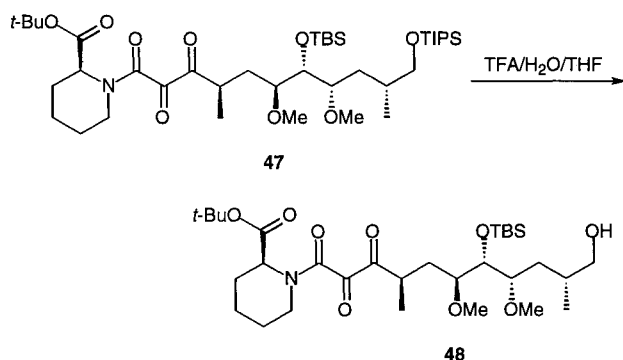
Scheme 21

These conditions were also used by Martin to remove a 1° TBS group without cleaving the 2° TBS group of pyran **45** en route to (+)-macbecin I (Scheme 22).⁸⁸



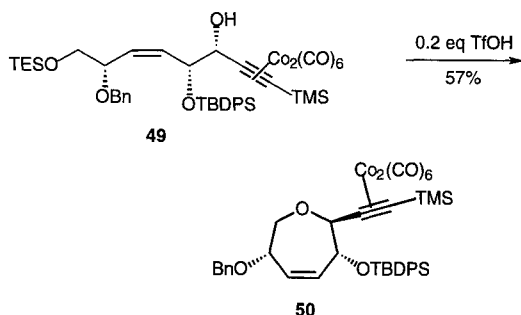
Scheme 22

TFA was also used in studies directed toward the total synthesis of (–)-FK-506.⁸⁹ In an unsuccessful attempt at complete deprotection of a differentially silyl-protected diol **47**, the selective removal of a TIPS-protecting group from a 1° alcohol was observed without affecting the TBS-protected 2° alcohol (Scheme 23).



Scheme 23

Likewise, Knochel has used TFA/H₂O/THF to desilylate a 1° TIPS ether in the presence of a 2° TBDPS ether.⁹⁰ Triflic acid has also been used to selectively deprotect the 1° TES ether of alkynyl cobalt complex **49** and effect cyclization to dehydrooxepane **50** (Scheme 24).⁹¹

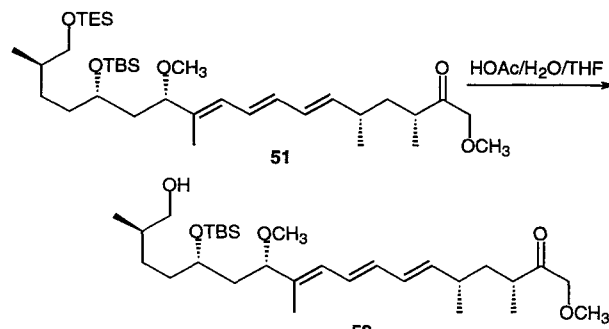


Scheme 24

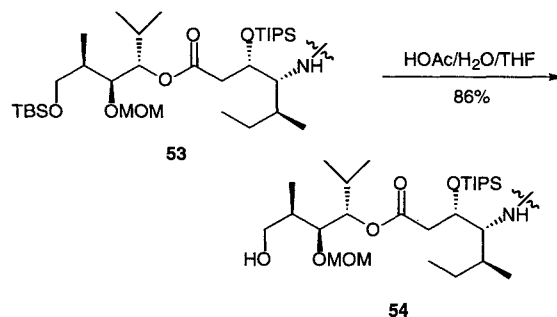
In one of the early uses of acidic conditions in selective deprotections of silyl ethers, Ogilvie and co-workers reported that, in competitive deprotection studies on silyl-protected deoxythymidines, the 5' or 1° position was always deprotected faster than the 3' or 2° position when treated with 80 % acetic acid.^{92,93} These studies compared the time required to achieve 100 % deprotection for a variety of silyl groups including the MDIPS, TBS and TIPS groups.

Aqueous acetic acid in THF has enjoyed widespread application in selective deprotection of 1° silyl ethers in the

presence of silyl-protected 2° and 3° alcohols. In the preparation of the C10–C27 segment **52** of rapamycin, deprotection of the TES-protected 1° alcohol **51** occurred readily under these conditions without reaction of the TBS-protected 2° carbinol (Scheme 25).^{94,95}

Scheme 25⁹⁴

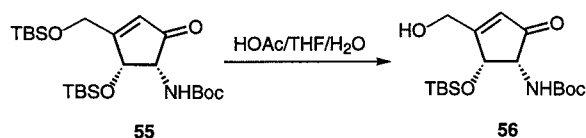
In Merck's degradation of FK-506, HOAc/THF/H₂O effected the selective deprotection of a 1° TES ether without affecting TES-, TBS- and TIPS-protected 2° alcohols.⁹⁶ Similarly, stirring with HOAc/THF/H₂O at room temperature allowed the successful deprotection of a TBS-protected 1° alcohol in the presence of a TIPS-protected 2° alcohol in the synthesis of didemnin B analogs (Scheme 26).⁹⁷



Scheme 26

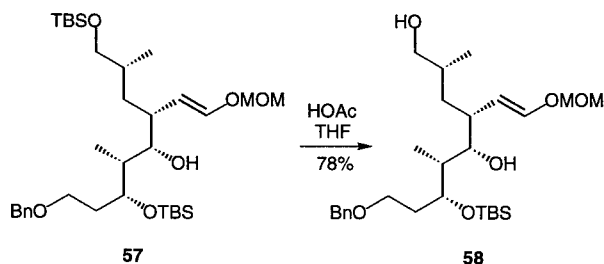
Slightly more vigorous conditions were needed to remove a 1° TBS ether in the presence of a 2° TIPS ether during the synthesis of substituted pyrrolidines⁹⁸ and didemnins.⁹⁹ Joullie and co-workers also used dilute acetic acid to selectively deprotect a 1° TBS ether in the presence of a TIPS-protected 2° alcohol¹⁰⁰ or a TBS-protected 2° alcohol.¹⁰¹ Note that the selectivity of the deprotection in the latter reaction was determined by the steric requirements of the oxygen-bearing carbon atoms.

Other examples of TBS-protected 1° alcohols being selectively cleaved in the presence of similarly protected 2° alcohols with acetic acid have been reported.^{102–104} These mild conditions allow for other protecting groups to be preserved. For example, 1° TBS ethers have been selectively deprotected in the presence of a 2° TBS group and a Boc-protected amine of cyclopentenone **55** (Scheme 27).¹⁰⁴



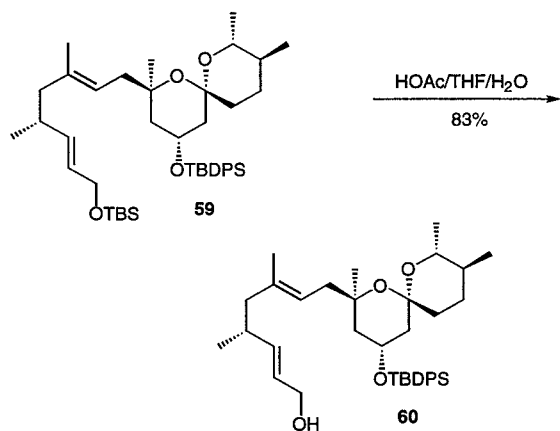
Scheme 27

Marshall has described the use of 70% acetic acid in THF to selectively deprotect a 1° TBS ether in the presence of a TBS-protected 2° carbinol (Scheme 28).¹⁰⁵



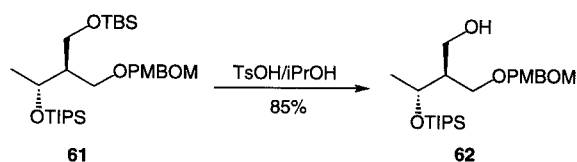
Scheme 28

Aqueous acetic acid in THF as a selective deprotecting agent was used in Barrett's total synthesis of (+)-milbemycin b₃ (Scheme 29).^{106,107}



Scheme 29

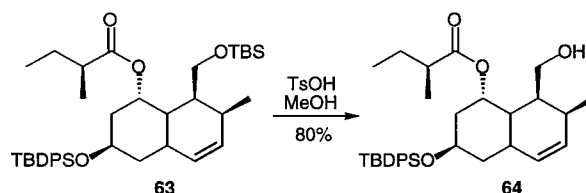
Acid-catalyzed deprotections are not limited to HCl, TFA and HOAc; a number of other acidic reagents have been introduced that allow for more subtle selective desilylation of silyl ethers. In a synthesis of carbapenam precursors, a 1° TBS ether **61** was deprotected in the presence of a TIPS-protected 2° alcohol in 85% yield using TsOH in anhydrous propan-2-ol (Scheme 30).¹⁰⁸ These conditions were also used to remove a 1° TBS ether without cleaving a 2° TIPS ether.¹⁰⁹



PMBOM = *p*-methoxybenzyloxymethyl

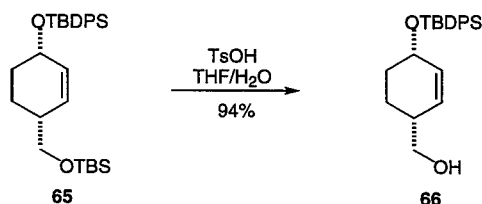
Scheme 30

In a similar procedure, as a part of the synthesis of dihydroepiastin, a 1° TBS ether **63** was deprotected in the presence of a 2° TBDPS ether using TsOH/MeOH (Scheme 31).¹¹⁰ However, diol formation from nonselective deprotection was observed, so careful monitoring was required.



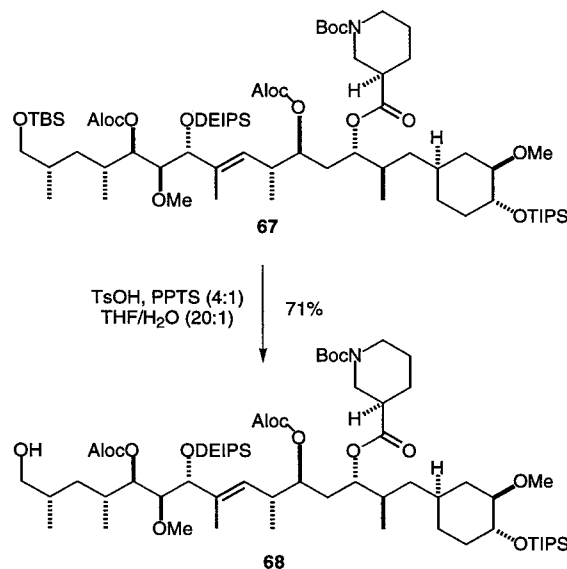
Scheme 31

Likewise, Baldwin selectively deprotected a 1° TBS ether in the presence of a 2° allylic TBDPS ether with catalytic TsOH during the synthesis of anticapsin (Scheme 32).¹¹¹



Scheme 32

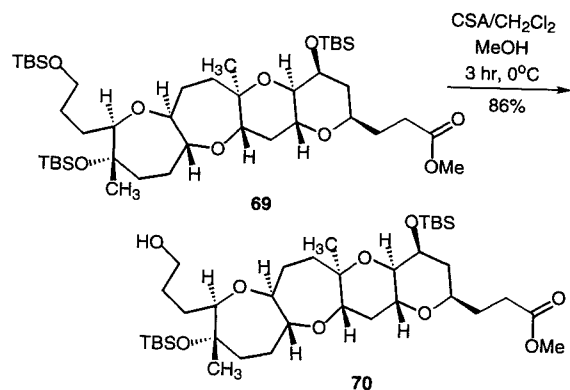
Selective deprotection of a 1° TBS ether in the presence of 2° DEIPS and TIPS ethers has been reported using TsOH that was buffered with PPTS in THF and water (Scheme 33).¹¹²



Scheme 33

CSA has been employed in less than stoichiometric quantities to deprotect a 1° TBS ether in the presence of a 2° and a 3° TBS ether en route to the total synthesis of hemibrevitoxin B (Scheme 34).¹¹³ These deprotections are noteworthy examples of the complexity of organic molecules to which the selective deprotection of silyl-protected alcohols has been applied. CSA was also utilized

in equimolar amounts to cleave TBS-protected 1° alcohols in the presence of 2° TBS ethers.^{10,48,114}

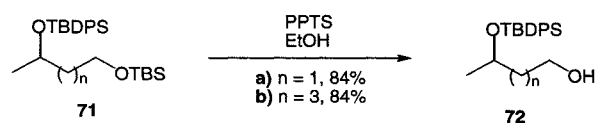


Scheme 34

Acid resins have also served as reagents for the selective deprotection of silyl ethers with some unusual selectivities.¹¹⁵ Rexyn 101 was shown to deprotect a 1° TMS ether in 19 hours but a 2° TMS ether required 80 hours for cleavage of the silyl group. However, when these same protected alcohols were treated with Amberlyst 15, the 2° TMS ether underwent deprotection more rapidly. Thus, judicious selection of acidic resin should allow selective deprotection of a 1° silyl ether in the presence of a 2° silyl ether and vice versa. Enholm has also utilized an acidic Amberlite resin to selectively remove a 1° TBS group in the presence of a 2° TBS ether.¹¹⁶

Ultrasonication of bis-silyl ethers in $\text{CH}_3\text{OH}/\text{CCl}_4$ has also resulted in selective desilylation of 1° TBS ethers in the presence of 2° and 3° TBS ethers.³⁶ This acid-promoted process is reported to result in yields in excess of 90%.

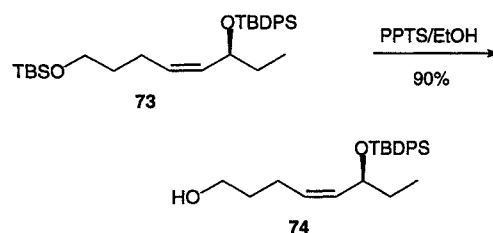
PPTS has been used for the deprotection of 1° TBS ethers in the presence of 2° TBS ethers. One equivalent of PPTS successfully removed a 1° TBS group without deblocking a 2° TBS ether.^{117–121} On the other hand, a copious amount of starting material was recovered and nonselective desilylation occurred when a catalytic amount of PPTS was used to distinguish a 1° TBS ether from a 2° TBS ether.¹²² Other conditions are better suited for this transformation, although PPTS efficiently monodesilylates 1° TBS ethers without removing silyl ethers that are more stable than 2° TBS groups. For example, discrimination between 1° TBS and 2° TBDPS ethers **71** has been achieved with 1 equivalent of PPTS in ethanol at room temperature (Scheme 35).⁴⁹



Scheme 35

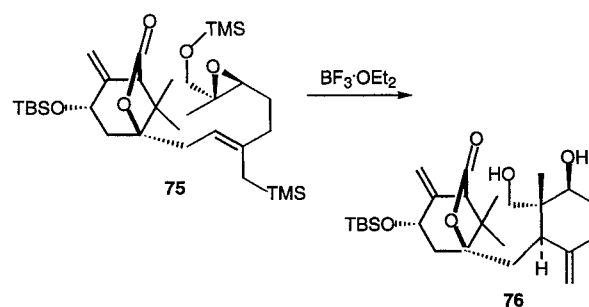
Snider has applied this methodology to a similar selective deprotection of 1° TBS ether **73** in the presence of an allylic 2° alcohol protected as a TBDPS ether (Scheme 36).¹²³ This method has been used by Posner in vitamin D analog work.¹²⁴ Nicolaou has reported the use of

catalytic PPTS to deprotect a 1° TMS ether in the presence of a 3° TMS ether.¹⁴



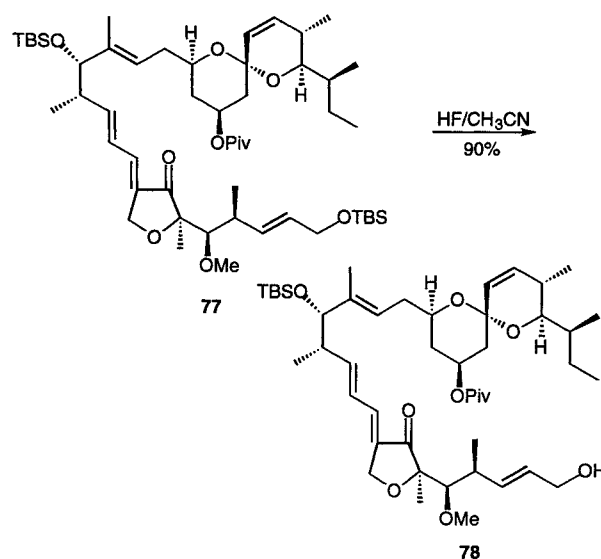
Scheme 36

Other mild conditions ($\text{BF}_3 \cdot \text{OEt}_2$) were used for the deprotection of the TMS-protected 1° alcohol **75** without deblocking a TBS-protected 2° allylic carbinol in a richly functionalized *seco*-taxane intermediate (Scheme 37).¹²⁵



Scheme 37

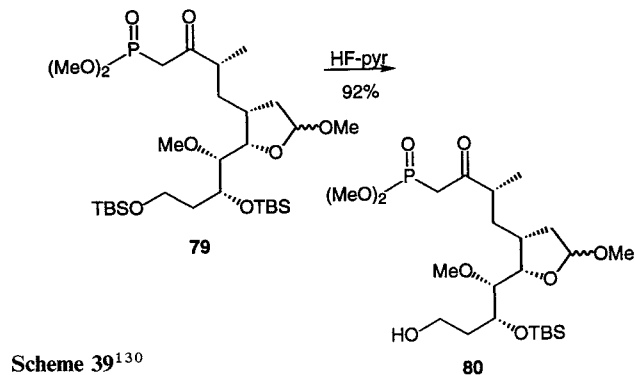
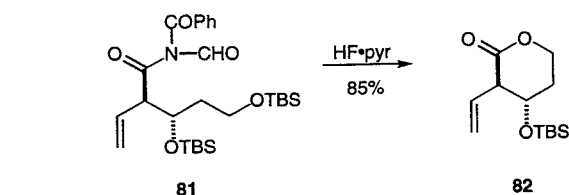
Typically, HF is the fluoride source of choice for selective desilylation of 1° silyl ethers in the presence of 2° and 3° silyl ethers. Danishefsky has used HF in CH_3CN to deprotect a 1° TBS ether in the presence of a 2° TBS ether in the synthesis of avermectin A_{1a} (Scheme 38).^{333,334}



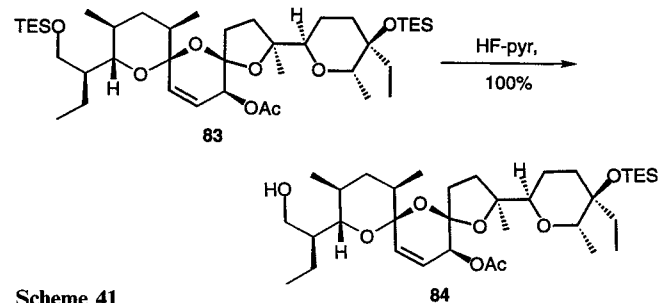
Scheme 38

Likewise, silyl-protected 1° alcohols have been deprotected in the presence of similarly protected 2° alcohols using $\text{HF} \cdot \text{pyridine}$ complex in the total or partial syntheses of such complex targets as (+)-macbecin I,¹²⁶ (+)-calyculin A,^{127,128} (–)-calyculin A,¹²⁹ (+)-carbonolide B (**79**

to **80**, Scheme 39),¹³⁰ avermectin and milbemycin subunits,¹³¹ the C1–C12 fragment of the calyculins,¹³² C-1 side chains for zaragozic acids,¹³³ rapamycin,^{134,135} and pimaricin⁵⁸ as well as for other target molecules (Scheme 40).^{136,137} In those instances where experimental details were included,^{126,127,130} HF was usually present in a large excess.

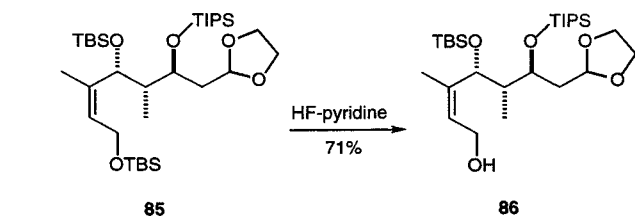
Scheme 39¹³⁰Scheme 40¹³⁶

Cleavage of a 1° TES ether without deblocking a 3° TES ether has also been accomplished using HF-pyridine. Kocienski used this methodology to selectively deprotect salinomycin intermediate **83** in quantitative yield (Scheme 41).¹³⁸



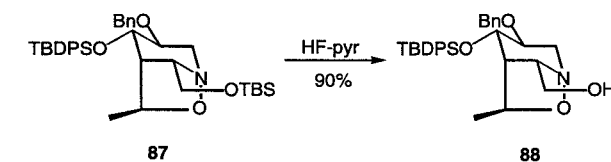
Scheme 41

Selective deprotection of 1° silyl ethers in the presence of 2° silyl ethers bearing different silyl moieties has also been commonly performed using HF-pyridine. Cleavage of a 1° TBS ether in the presence of 2° TIPS and TBS ethers by HF-pyridine was reported in the synthesis of fragment **86** en route to (+)-mycotrienin (Scheme 42).¹³⁹

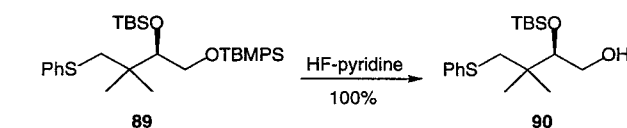


Scheme 42

As part of work directed toward the synthesis of rapamycin, Nicolaou used similar conditions to remove a 1° TBS group without deblocking a 2° TIPS ether.¹⁴⁰ Similarly, the TBS-protected 1° alcohol **87** was cleaved in the presence of a 2° TBDPS ether in 90% yield as part of the enantioselective synthesis of deoxynojirimycin (Scheme 43).¹⁴¹ and a 1° TBDPS ether was cleaved in the presence of a 2° TBDPS ether as part of the synthesis of ascidiatrienolide A.¹⁴²

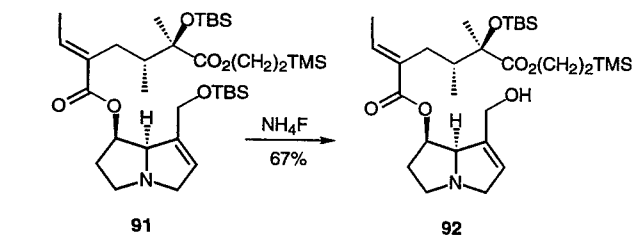
Scheme 43¹⁴¹

In a similar fashion, an excess of HF·NEt₃ was used to remove a 1° TBS group in the presence of a 2° TBS group.¹⁴³ The selective deprotection of a 1° TBMPS ether in the presence of a 2° TBS ether has also been effected via treatment with HF-pyridine (Scheme 44).¹⁴⁴



Scheme 44

An excess of ammonium fluoride in methanol has been shown to selectively cleave 1° TBS ethers¹⁴⁵ or 1° TBDPS ethers¹⁴⁶ in the presence of 2° TBS ethers in glycosyl units. White has also used ammonium fluoride to selectively cleave a 1° TBS ether in the presence of a 3° TBS ether in bis-silyl ether **91** in the synthesis of the alkaloids (–)-integerrimine and (+)-usaramine (Scheme 45).¹⁴⁷ White again used these conditions to discriminate a 1° TBS-protected alcohol from a 2° TBS-protected alcohol in work towards rutamycin B.¹⁴⁸



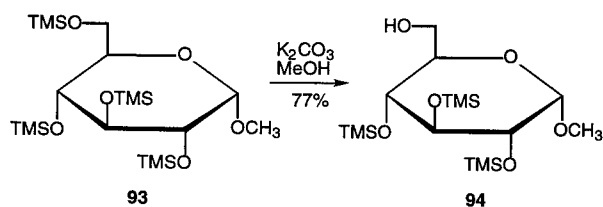
Scheme 45

The recent development of fluorosilicic acid, H₂SiF₆, as a deprotecting reagent has increased the arsenal of selective desilylating agents. DeShong has applied this reagent to the selective deprotection of 1°, 2° and 3° silyl ethers.⁵⁷ In competitive desilylation reactions, 1° TBS-protected alcohols were discriminated from 2° and 3° TBS ethers with excellent selectivity.

3.2.2. Under Basic/Nucleophilic Conditions

The earliest reported selective deprotection involves the treatment of a 1° TMS ether of methyl 2,3,4,6-tetra-*O*-

trimethylsilyl- α ,D-glucopyranose **93** with a solution of K_2CO_3 in anhydrous methanol to produce the mono-desilylated product **94** in 77% yield (Scheme 46).¹⁴⁹ In this instance, the characteristic of the substrate that determines selectivity is steric hindrance at the carbinol carbon.



Scheme 46

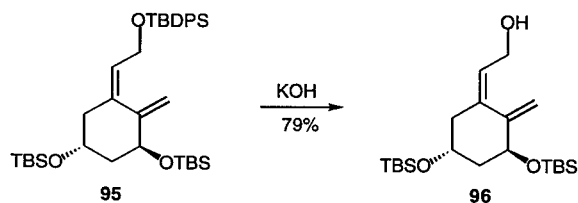
Cunico has reported the rates of hydroxide-promoted deprotection of 1° and 2° silyl ethers (Table 9).³² The results clearly indicate the potential for selective deprotection of 1° vs 2° silyl ethers.

Table 9. Half-Lives of 1° vs. 2° Silyl Ethers in Basic Solution³²

	$n\text{-C}_4\text{H}_9\text{OR}$	$c\text{-C}_6\text{H}_{11}\text{OR}$
R = TBS	1 h	26 h
R = TIPS	14 h	44 h
R = TBDPS	< 4 h	14 h

all reactions were performed in 5% NaOH/95% EtOH at 90°C

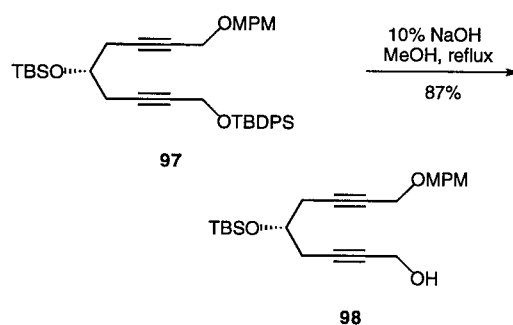
The primary alcohol in the A-ring synthon of vitamin D₃ **96** was prepared by selective deprotection of the 1° TBDPS ether in the presence of two 2° TBS ethers, which was brought about by treatment with 10% methanolic KOH at 70°C (Scheme 47).¹⁵⁰



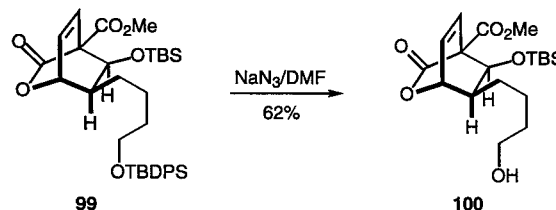
Scheme 47

A similar selective deprotection of a 1° TBDPS ether in the presence of a 2° TBS ether was reported as part of another synthesis of a vitamin D₃ A-ring synthon **98** (Scheme 48).¹⁵¹ In contrast, Marshall has reported the partial hydrolysis of a 1° TBS ether in the presence of a 2° TBDPS ether using NaOH in hot aqueous *t*-BuOH.²⁰

Roberts has described the use of 1 equivalent of NaN_3 in DMF⁶¹ to effect the selective desilylation of a 1° MDPS ether without cleavage of a 2° TBS ether. This method has recently been employed by Posner in the synthesis of bicyclic lactone **100** (Scheme 49).¹⁵²

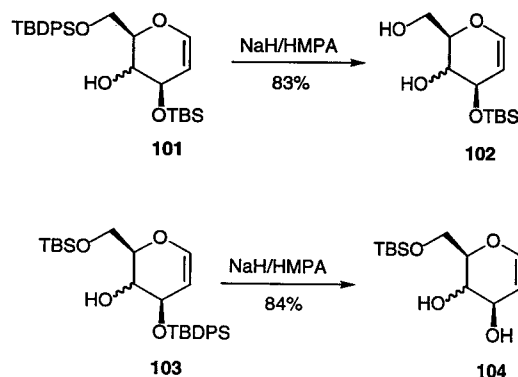


Scheme 48



Scheme 49

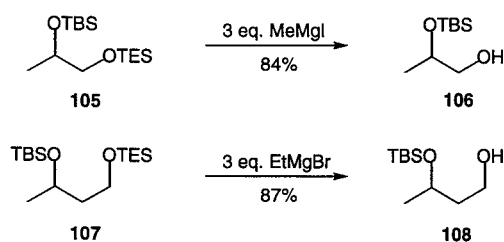
Other conditions have been applied that reverse the tendency of TBS ethers to cleave more easily than TBDPS ethers. When bis-silyl ether **101** was treated with 2.1 equivalents of NaH in HMPA, the monosilylated product **102** was isolated in 83% yield (Scheme 50).¹⁵³ The TBDPS ether was selectively cleaved under these conditions. The presence of a free alcohol on the substrate consumes one equivalent of NaH. To prove that this mode of cleavage was not due to steric crowding at the alcohol carbon, the order of alcohol protection was reversed to produce bis-silyl ether **103** and deprotection yielded monosilylated product **104** in 84% yield. The mechanism of this process remains unclear, although it is unlikely that hydride is acting as a nucleophilic species. These conditions have recently been employed by Smith as part of the synthesis of a rapamycin subunit, in which a 1° TBDPS group was removed in the presence of a 2° TIPS ether.¹⁵⁴



Scheme 50

One major hurdle in selectively removing a silyl ether from a bis-silylated 1,2-diol or 1,3-diol under basic conditions is the occurrence of silyl migrations.^{155,156} Grig-

nard reagents have been utilized to remove 1° TES ethers in the presence of 2° TBS ethers in bis-silyl ethers **105** and **107** (Scheme 51). The low nucleophilicity of the resulting magnesium alkoxide precludes silyl migration.¹⁵⁷



Scheme 51

Basic sources of fluoride have also been applied to the problem of selective deprotection. The half-lives of TBAF-mediated deprotection of TDS and TBS ethers have been measured and indicate that 1° TBS or TDS ethers can be cleaved with TBAF in the presence of 2° TDS ethers (Table 10).⁸⁰

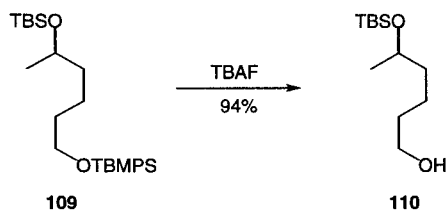
Table 10. Half-Lives of Deprotection of TDS vs. TBS Ethers⁸⁰

	<i>n</i> -C ₄ H ₉ OR		<i>c</i> -C ₆ H ₁₁ OR	
	R = TDS	R = TBS	R = TDS	R = TBS
2–3 equiv TBAF THF, r. t.	10 min (3 h) ^a	4 min	3 h (18 h) ^a	70 min

^a Time required for complete deprotection.

Nicolaou has employed 1.5 equivalents of TBAF to deprotect a TBDPS-protected 1° alcohol in the presence of a 2° TBS ether in the synthesis of hemibrevetoxin B¹⁵⁸ and 1.0 equivalent of TBAF deprotected a 1° TBDPS ether in the presence of a 2° TBS ether in the synthesis of brevetoxin B.⁹

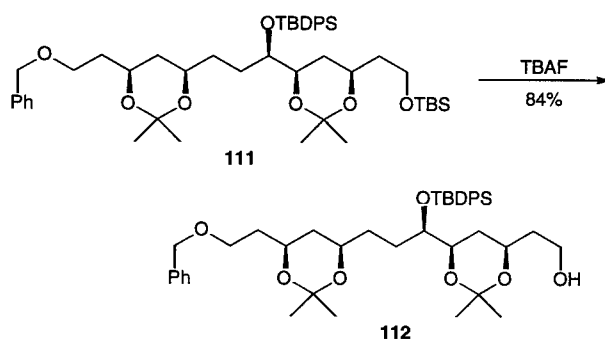
TBAF has shown useful selectivity in cleaving 1° TBMPs ethers in the presence of 2° TBS ethers.³⁷ Thus, bis-silyl ether **109** was treated with TBAF in 1,2-dichloroethane and alcohol **110** was isolated in 94% yield (Scheme 52). A low concentration (<10%) of F[−] was required to obtain this selectivity.³⁷ Similar selectivity has been achieved using other alkoxydiphenylsilyl protecting groups.³⁸



Scheme 52

Nicolaou has applied 1.1 equivalents of TBAF to selectively cleave the 1° TBS ether without reacting at the TBDPS-protected 2° alcohol of intermediate **111** in the

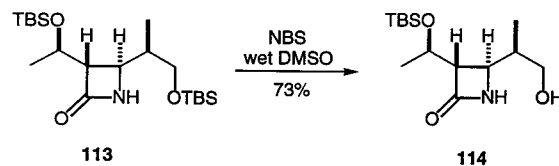
total synthesis of amphoteronolide B (Scheme 53).¹⁵⁹ TBAF was also used in Yamamoto's total synthesis of hemibrevetoxin B to selectively remove a 1° TIPS ether in the presence of both a 2° TIPS ether and a 3° TBS ether in a 73% yield.¹⁶⁰



Scheme 53

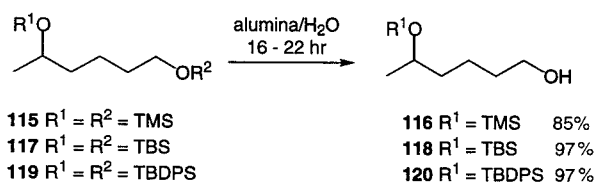
3.2.3. Miscellaneous Conditions

One equivalent of NBS in wet DMSO¹⁶¹ has been used to selectively deprotect the 1° TBS ether of azetidinone **113** in the presence of a 2° TBS ether (Scheme 54).¹⁶²



Scheme 54

The reactivity of moist alumina toward less sterically encumbered silyl ethers has been exploited in selectively deprotecting 1° silyl ethers.^{68,69} A series of 1°–2° bis-silyl ethers were stirred with moist alumina and the monodesilylated products **116**, **118** and **120** were isolated (Scheme 55). Although the initial report described only the selective deprotection of bis-TBS ethers,⁶⁸ this reaction has more recently been shown to be selective in the deprotection of 1° versus 2° silyl-protected alcohols, *if the same or smaller-sized silyl group protects the 1° alcohol*.⁶⁹



Scheme 55

In the same manner that allowed different 1° silyl ethers to be distinguished, differences in the rate of reaction of DDQ with 1° and 2° silyl ethers allows selectivity in their deprotection (Table 11).⁶⁶ Since all TBDPS ethers were unreactive with DDQ and all TES ethers reacted within one hour, DDQ should allow 1° TES groups to be removed without affecting the stable TBDPS-protected 2° alcohols.

Table 11. Rates of Cleavage of Silyl Ethers with DDQ⁶⁵

	TES	TBS	TBDPS
$n\text{-C}_{12}\text{H}_{25}\text{OR}$	1 h (97%)	6 h (86%)	6 h (0%)
4- <i>t</i> -butyl- $c\text{-C}_6\text{H}_{10}\text{OR}$	1 h (90–100%)	6 h (88–97%)	6 h (0%)

all reactions performed at room temperature using 0.1 equivalents of DDQ in 9 : 1 THF/ H_2O

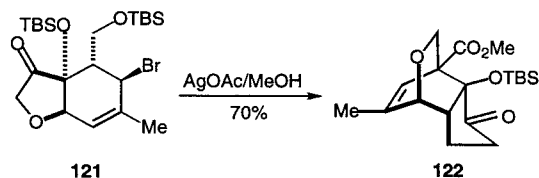
Similarly, differences in the rates of cleavage of various silyl ethers by Lewis acids allows a 1° TMS ether to be deprotected in the presence of a 2° TBS or TBDPS ether (Table 12).⁷⁰

Table 12. Cleavage of 1° vs. 2° Silyl Ethers by Lewis Acids⁷⁰

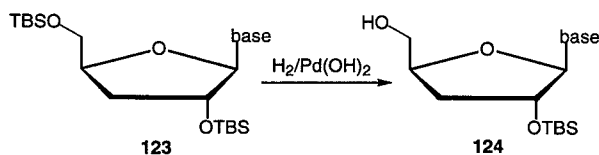
	$\text{Cu}(\text{NO}_3)_2/\text{CH}_3\text{CN}$	$\text{Ce}(\text{NO}_3)_3/\text{CH}_3\text{CN}$
$n\text{-C}_{10}\text{H}_{21}\text{OTMS}$	1 min, 100 %	1 min, 100 %
$n\text{-C}_{10}\text{H}_{21}\text{OTBS}$	12 h, 90 %	15 h, 90 %
$n\text{-C}_{10}\text{H}_{21}\text{OTBDPS}$	2 days, 0 %	2 days, 0 %
$c\text{-C}_6\text{H}_{11}\text{OTMS}$	1 min, 100 %	1 min, 100 %
$c\text{-C}_6\text{H}_{11}\text{OTBS}$	12 h, 94 %	15 h, 90 %
$c\text{-C}_6\text{H}_{11}\text{OTBDPS}$	2 days, 0 %	2 days, 0 %

all reactions were performed using 1 equivalent of Lewis acid at room temperature

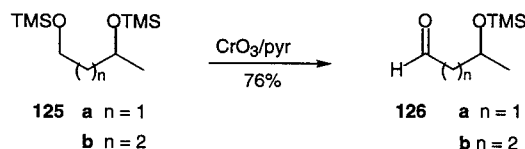
The system of AgOAc/MeOH has been used to effect the selective desilylation of a 1° TBS ether while not affecting a 3° TBS group to afford bicyclic lactone **122** in 70 % yield (Scheme 56).¹³¹

**Scheme 56**

Hydrogenation has been successfully applied to the problem of selectively deprotecting 1° TBS ethers in the presence of 2° TBS ethers. Cormier has reported that the 5'-TBS ether of bis-silylnucleoside **123** is selectively deprotected by hydrogenation with $\text{Pd}(\text{OH})_2$ (Scheme 57).¹⁶³ Weimer has obtained similar results with different nucleosides utilizing H_2 and wet Pd/C .¹⁶⁴

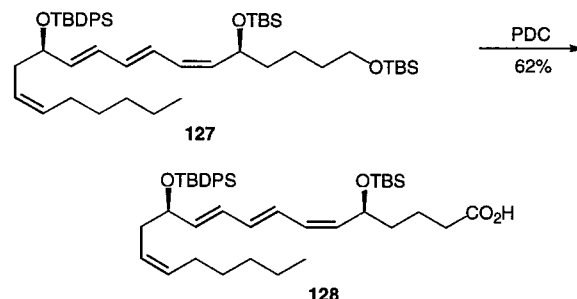
**Scheme 57**¹⁶³

Several instances of selective oxidation⁷⁴ of 1° silyl ethers in the presence of 2° and 3° silyl ethers have been reported. Treatment of bis-silyl ethers **125** with $\text{CrO}_3\cdot\text{pyridine}$ yielded aldehydes **126** in greater than 76 % yield (Scheme 58).^{74,165}

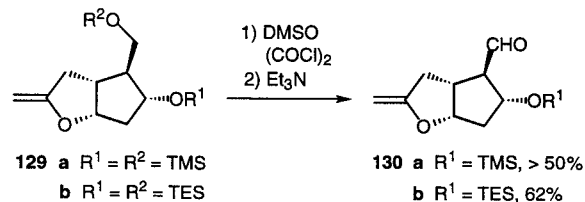
**Scheme 58**

Under similar conditions, a TES-protected 1° alcohol was oxidized to an aldehyde in the presence of both a TMS-protected 3° alcohol and a TBS-protected 2° alcohol.¹⁶⁶ Likewise, a 1° TMS ether has been selectively oxidized to an aldehyde in the presence of a 2° TMS ether.^{77–79,167} 1° TIPS and 1° TBDPS ethers are not affected under these conditions.⁷⁷

Pyridinium dichromate has been used to effect the selective oxidation of a 1° TBS ether to a carboxylic acid in the presence of 2° TBDPS ethers.¹⁶⁸ For example, under these conditions, the 2° TBS and 2° TBDPS ethers in polyene **127** were unaffected, while the 1° TBS ether was oxidized to the corresponding carboxylic acid in 62 % yield (Scheme 59).^{168a}

**Scheme 59**

Swern conditions¹⁶⁹ have been reported to selectively oxidize 1° and 2° silyl ethers while leaving more hindered silyl ethers unaffected.^{170,171} Application of Swern conditions to bis-silyl ethers **129** led to the formation of aldehydes **130** (Scheme 60).¹⁷¹ A 2° TMS ether remained unaffected while a 1° TMS ether in the same molecule was oxidized to an aldehyde with $\text{CrO}_3\cdot\text{pyridine}$.⁷⁹

**Scheme 60**

Differences in the reactivity of silyl ethers bearing ligands of differing size¹⁷⁰ illustrate the decisive role of steric factors in these selective oxidations.¹⁷¹ The significance

of the steric requirements of the parent alcohol are illustrated in the recent report of the oxidation of a TES-protected 1° alcohol in the presence of a 3° TES ether.¹⁷²

4. Selective Deprotection of Silyl-Protected 2° Alcohols

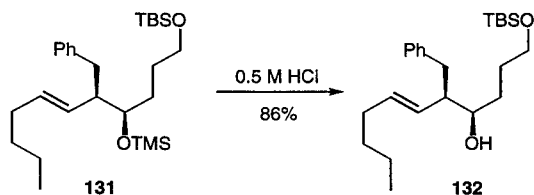
4.1. In the Presence of 1° Silyl Ethers

Since steric factors are the primary factor behind most selective deprotections of silyl ethers, deprotection of the silyl ether of a more sterically encumbered hydroxyl group without reaction at the less hindered site requires careful planning in the selection of protecting groups and deprotecting agents. The obvious solution has been to use more sterically crowded silyl groups to protect the 1° alcohol and silyl group bearing smaller substituents to protect the 2° alcohol.

4.1.1. Under Acidic Conditions

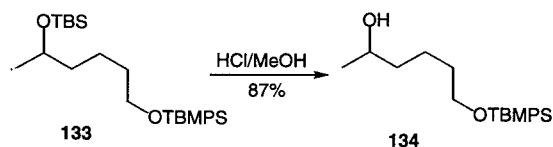
A variety of acidic conditions have been applied to the selective deprotection of 2° silyl ethers. In the synthesis of the C19–C29 fragment of rifamycin, the selective deprotecting agent was 1 M HCl/THF in removing a 2° TES without affecting a 1° TBDPS ether.¹⁷³ Kende has also used dilute HCl to discriminate between a 2° TBS group and a 1° TBDPS silyl ether in the synthesis of lankacidin C.¹⁷⁴

Aqueous HCl has been used to cleave a 2° TMS ether in the presence of a 1° TBS ether¹⁷⁵ (Scheme 61) or a 1° TBDPS ether.¹⁷⁶



Scheme 61¹⁷⁵

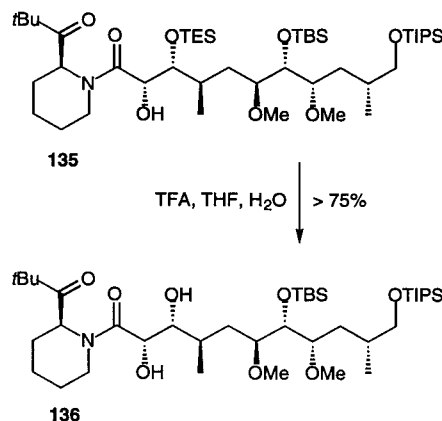
TBS and TBMPS ethers have shown differences in reactivity to cleavage under acidic conditions and have been used in the selective deprotection between 1° and 2° silyl ethers.³⁷ This protocol has also been extended to 2° versus 1° alcohols.³⁷ Thus, a 2° alcohol protected as a TBS ether has been deprotected in the presence of a 1° TBMPS ether by treatment with a 10% solution of 0.1 M aqueous HCl in methanol at room temperature to give the corresponding alcohol **134** in 87% yield (Scheme 62).^{37,38} This result complements the previously noted F⁻-promoted selective deprotection of the 1° TBMPS ether in the presence of a 2° TBS ether.³⁷ Use of other alkoxydiphenylsilyl protecting groups allows similar selectivity in deprotections.³⁸



Scheme 62

Methanolic HCl has been used to deprotect a 2° TBS in the presence of a 1° DTBS ether.³⁸

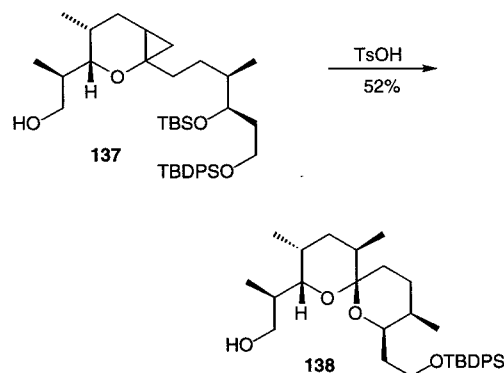
In Merck's total synthesis of (–)-FK-506, TFA was used to selectively deprotect a 2° TES ether in the presence of a TIPS-protected 1° alcohol and a TBS-protected 2° alcohol (Scheme 63).⁸⁹



Scheme 63

Corey has reported the removal of a 2° TES ether in the presence of a 1° TBDPS group using trichloroacetic acid in the synthesis of glycinoclepin A.¹⁷⁷ Likewise, aqueous acetic acid has been used in the selective deprotection of a 2° TES ether¹⁷⁸ and also a 2° TBS ether^{179,180} in the presence of a 1° TBDPS ether.

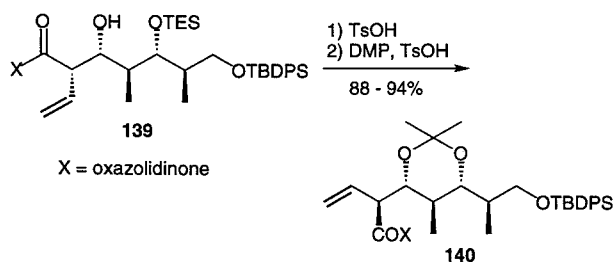
Methanolic TsOH has been used to cleave 2° TMS ethers in the presence of a 1° TBDPS ethers.¹⁸¹ Similarly, in studies leading to the synthesis of calcimycin,^{182,183} bis-silyl ether **137** was treated with TsOH to deprotect a 2° TBS ether in the presence of a 1° TBDPS ether (Scheme 64). The resulting intermediate 2° alcohol underwent spontaneous closure to the spiroketal **138**, which is a subunit common to ionophore antibiotics.¹⁸³



Scheme 64

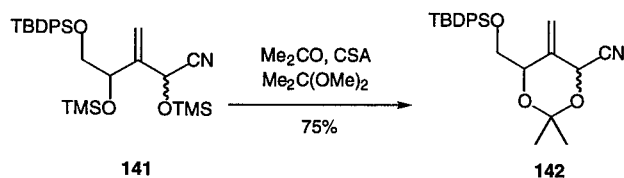
Roush has used two versions of acidic conditions in the selective deprotection of a 2° TES ether in the presence of a 1° TBDPS ether.^{173,184} In a synthesis of a segment of streptovaricin D, TsOH in THF/H₂O led to the selective cleavage of a 2° TES ether in bis-silyl ether **139**

in 88–94 % yield after reprotection of the diol as acetonide **140** (Scheme 65).¹⁸⁴



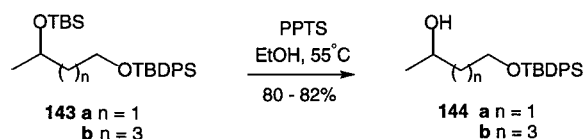
Scheme 65

The conditions developed by Rychnovsky to construct alternating polyol chains¹⁸⁵ have been shown to exhibit selectivity in deprotecting silyl ethers. In converting bis-silyl ether **141** to acetonide **142**, TMS groups were removed from the protected cyanohydrin and from the protected 2° alcohol but the 1° TBDPS ether was preserved (Scheme 66).¹⁸⁶



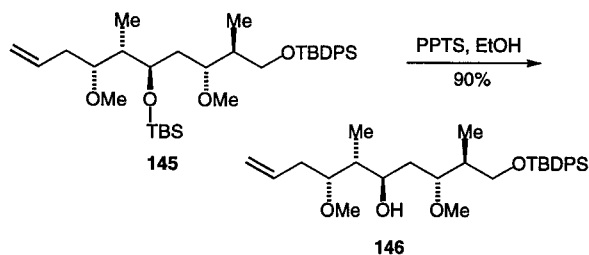
Scheme 66

PPTS, which proved effective in other selective desilylations,^{49,339} has also been applied to the selective deprotection of 2° silyl ethers in the presence of 1° silyl ethers. Treatment of bis-silyl ethers **143** with 1 equivalent of PPTS in ethanol and heating to 55°C produced the corresponding monodesilylated alcohols in 80–82 % yield (Scheme 67).⁴⁹



Scheme 67

These conditions were used to synthesize aliphatic alcohol **146** in Pattenden's route toward ulapualide A (Scheme 68).¹⁸⁷

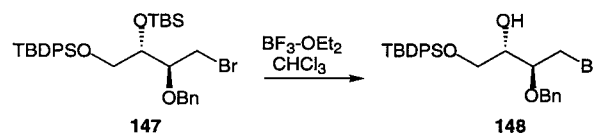


Scheme 68

A PPTS/MeOH system has been used to hydrolyze a 2° TMS ether without deblocking a 1° TBDPS-protected alcohol.^{188,189}

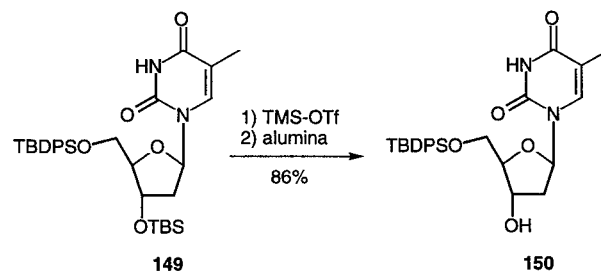
The ion exchange resin, Amberlyst 15, has also been reported to effect selective deprotection of 2° silyl ethers.¹¹⁵ TMS-protected 1° alcohols were deprotected in 86% yield in 3 hours while the similarly protected 2° alcohol was cleaved in slightly more than one hour.

A Lewis acid, $\text{BF}_3 \cdot \text{OEt}_2$, has effected the selective cleavage of a 2° TBS ether in the presence of a TBDPS-protected 1° alcohol (Scheme 69).¹⁹⁰ Thus, the differentially protected trihydroxybutane **147** was converted to alcohol **148**.



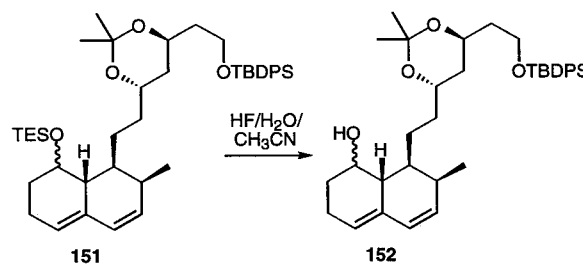
Scheme 69

The intermolecular exchange of silyl groups has also been used for the selective desilylation of TBS-protected alcohols in the presence of TBDPS-protected alcohols.¹⁹¹ Treatment of bis-silyl ether **149** with 3 equivalents of TMS-OTf at -20°C resulted in the overall selective cleavage of the 2° TBS ether (Scheme 70). A mechanism is described in which the TMS group selectively replaces the TBS protecting group. Upon workup, the more labile TMS ether is cleaved, resulting in an overall selective deprotection of a 2° TBS ether in the presence of a 1° TBDPS ether.



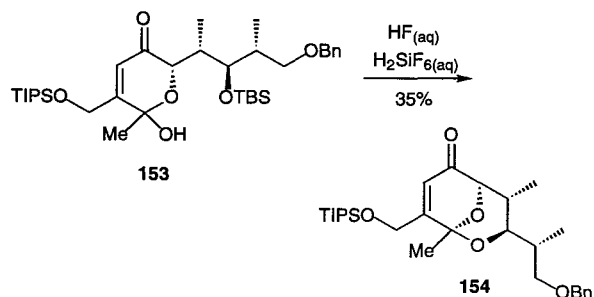
Scheme 70

The use of HF in selective deprotections of 2° silyl ethers was reported in the total synthesis of (+)-compactin and (+)-mevinolin.^{192,193} Using 48 % aqueous HF that had been diluted 50-fold with acetonitrile, intermediate **151** underwent cleavage of the 2° TES ether in the presence of a 1° TBDPS ether (Scheme 71).¹⁹³



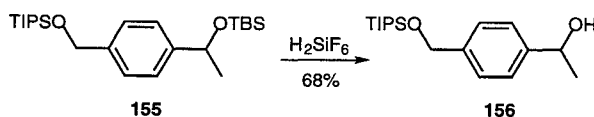
Scheme 71

In DeShong's synthesis of tirandamycin B, HF in the presence of catalytic aqueous H_2SiF_6 was used to deprotect a 2° TBS ether in the presence of a 1° TIPS ether with concomitant acid-catalyzed closure to form the bicyclic system **154** (Scheme 72).¹⁹⁴



Scheme 72

In an extension of this work, the TBS protecting group in bis-silyl ether **155** was selectively deprotected with H_2SiF_6 to afford alcohol **156** (Scheme 73).⁵⁷

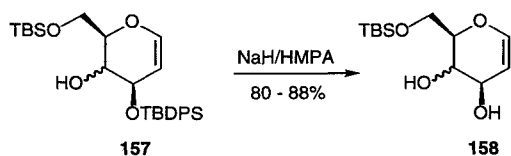


Scheme 73

4.1.2. Under Basic/Nucleophilic Conditions

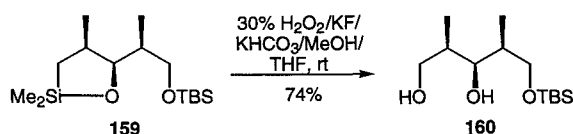
Although Cunico's measurements of the half-lives of 2° silyl ethers in basic media (see Table 9) does not point toward selective deprotection among 2° silyl ethers,³² several such examples have been reported. Schlessinger has described a base-promoted deprotection of a 2° TMS ether in the presence of a 1° TBS ether using K_2CO_3 in methanol.¹⁹⁵

An example of the selective cleavage of the more bulky ether employs NaH in HMPA at 0°C, in which the 2° alcohol **158** was liberated in 80–88% yield from the bis-silyl ether **157** (Scheme 74).¹⁵³

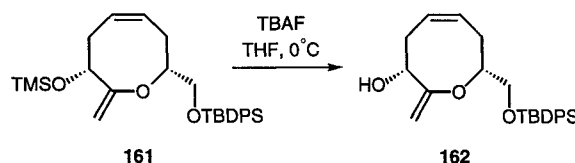


Scheme 74

Siloxanes and vinylsiloxanes have been removed utilizing a Tamao oxidation (30% $\text{H}_2\text{O}_2/\text{KF}/\text{KHCO}_3$) without affecting 1° TBS ethers (Scheme 75).^{196,197}

Scheme 75¹⁹⁶

Other examples of fluoride-based selective deprotections of 2° silyl ethers in the presence of 1° silyl ethers have also been reported. In the synthesis of (+)-laurencin, a TMS-protected 2° alcohol **161** was deprotected with TBAF in the presence of a TBDPS-protected 1° alcohol (Scheme 76).¹⁹⁸ Presumably, this deprotection was effected by treatment with only one equivalent of TBAF as later treatment with TBAF deprotects the TBDPS-protected alcohol.



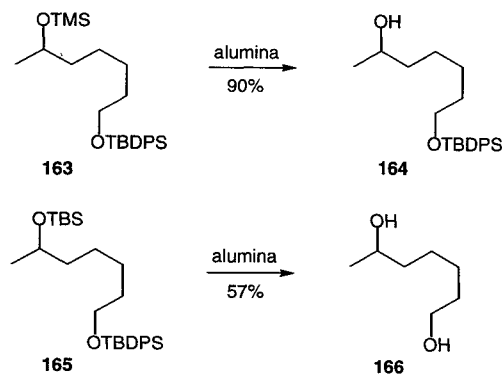
Scheme 76

Nicolaou used TBAF to selectively deprotect a 2° TES ether and 2° TBS ethers⁴⁷ without affecting a 1° TBDPS ether in work directed toward the synthesis of brevetoxin A. TBAF has also been used to selectively deprotect a 2° DPIPS ether in the presence of a 1° TBS ether.³⁸ A 2° TES group was cleaved in the presence of a 1° TBS ether with HCl -pyridine.³⁴²

4.1.3. Miscellaneous Conditions

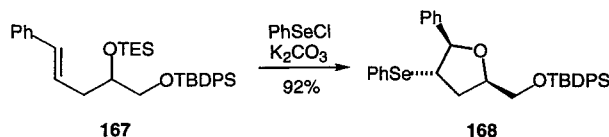
Differences in the rates of cleavage of various silyl ethers by DDQ (Table 11)⁶⁵ and metal nitrates such as $\text{Cu}(\text{NO}_3)_2$ and $\text{Ce}(\text{NO}_3)_3$ (see Table 12)⁷⁰ show utility in selectively deprotecting 2° silyl ethers in the presence of 1° silyl ethers.

Neutral alumina treated with 3% H_2O has been shown to selectively cleave a 2° TMS ether in a substrate containing a TBDPS-protected 1° alcohol **163**.⁶⁹ This method does not, however, extend to 2° TBS ethers **165** as significant diol **166** formation was observed (Scheme 77).



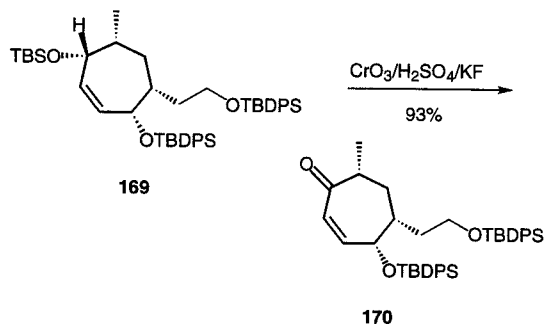
Scheme 77

$\text{PhSeCl}/\text{K}_2\text{CO}_3$ caused deprotection of a 2° TES-protected alcohol followed by cyclization to afford trisubstituted furan **168**, without affecting a 1° TBDPS group (Scheme 78).¹⁹⁹



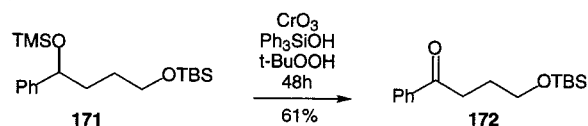
Scheme 78

Examples of selective oxidation of 2° silyl ethers in the presence of 1° silyl ethers have also been reported. The stability of TBDPS ethers of 1° and 2° alcohols to Jones oxidation conditions accompanied with aqueous KF was demonstrated by Liu and Han.²⁰⁰ This protocol was used to selectively oxidize 2° TBS ether **169** to ketone **170** in 93% yield without reaction of the 1° and 2° TBDPS ethers (Scheme 79).²⁰¹



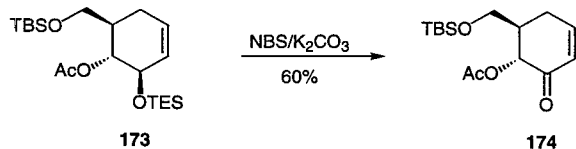
Scheme 79

Muzart has described the *t*-BuOOH-mediated oxidation of 2° benzylic silyl ethers in the presence of 1° TBS ethers.²⁰² In this reaction, which uses catalytic amounts of in situ generated $(\text{Ph}_3\text{SiO})_2\text{CrO}_2$, bis-silyl ether **171** was stirred at room temperature to yield a mixture of products, the major component being ketone **172** (Scheme 80).



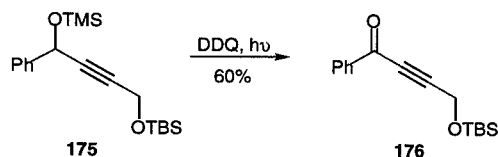
Scheme 80

Radical-induced selective oxidations of TES- and TBS-protected 2° allylic alcohols in the presence of TBS-protected 1° alcohols has also been described (Scheme 81).²⁰³ Treatment of bis-silyl ether **173** with 1 equivalent of NBS and K_2CO_3 in the presence of catalytic benzoyl peroxide yielded **174** in 60% yield. A significant decrease in yield was observed, however, when the 2° alcohol was protected as a TBS ether.



Scheme 81

Under irradiation in the presence of DDQ, 2° TMS ether **175** was selectively oxidized to ketone **176** without deprotecting the 1° TBS group (Scheme 82).²⁰⁴



Scheme 82

4.2. In the Presence of 2° Silyl Ethers

Deprotecting one silyl-protected 2° alcohol in the presence of another silyl-protected 2° alcohol has also been widely used.

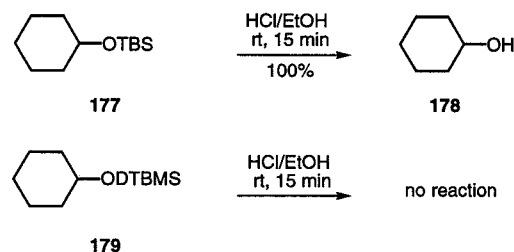
4.2.1. Under Acidic Conditions

Cunico has described the marked differences in the rate of acid-promoted hydrolysis of TBS-, TIPS- and TBDPS-protected cyclohexanols (Table 7).³² The rate of acid-promoted hydrolysis of 2° TBS ethers is approximately three times faster than that of the corresponding 2° TDS ether (Table 13).⁸⁰

Table 13. Half-Lives of Cleavage of 2° TDS vs. 2° TBS Ethers⁸⁰

1% HCl/EtOH, r. t.	
<i>c</i> -C ₆ H ₁₁ OTDS	20 min
<i>c</i> -C ₆ H ₁₁ OTBS	6 min

The reactivity of TBS-protected cyclohexanol has been compared with that of DTBMS-protected cyclohexanol in 1% HCl in 95% ethanol at room temperature.²⁰⁵ While the less sterically hindered 2° TBS ether **177** underwent 100% hydrolysis within 15 minutes, the 2° DTBMS ether **179** showed no decomposition after 3 days (Scheme 83).

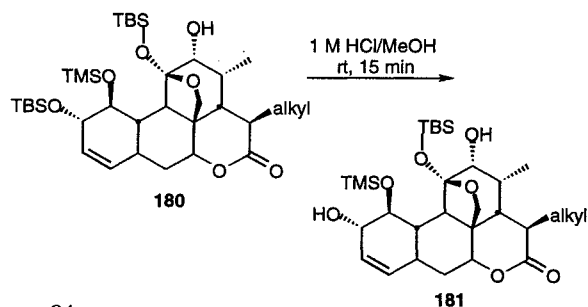


Scheme 83

Danishefsky has employed 0.01 M HCl in dioxane to selectively cleave a 2° TMS ether in the presence of a 2° TBS ether in the total synthesis of *N*-acetylactinobolamine.²⁰⁶ A reversal in the reactivity of silyl ethers has been described in the synthesis of quassinoid analogs.²⁰⁷ Selective deprotection of a 2° TBS ether was achieved by treating intermediate **180** with HCl in methanol over 15 minutes (Scheme 84). The time was critical to the survival of the usually more labile 2° TMS ether and the mixed ketal.

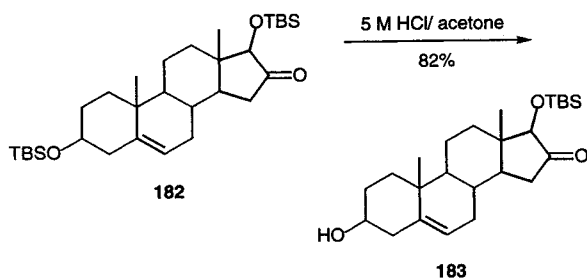
In contrast to the selectivity induced by the size of the alkyl substituents on the protecting silicon atom, structural differences in specific regions of the substrate can direct selective deprotections.

Under acidic conditions, TBS-protected 2° alcohols have been cleaved in the presence of another TBS-protected



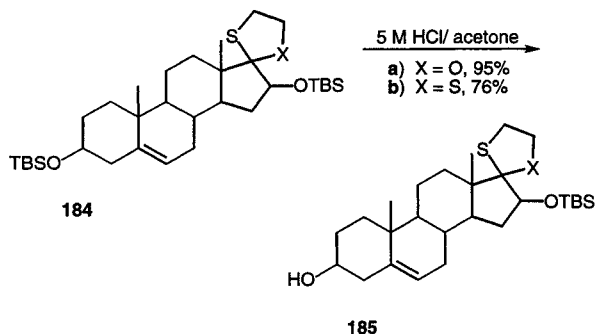
Scheme 84

2° alcohol which is α to a ketone.²⁰⁸ Thus, bis-silylated steroid derivative **182** was selectively converted into the mono-alcohol **183** in 82% yield (Scheme 85).



Scheme 85

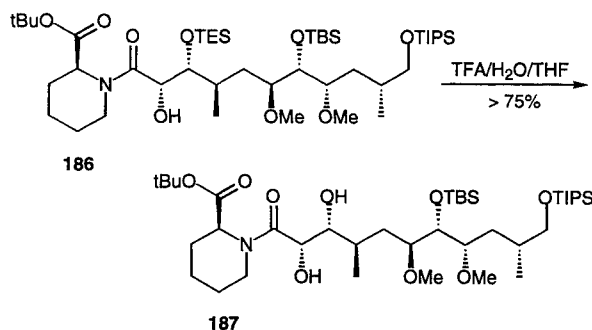
Similarly, TBS ethers at the α position of a protected ketone are stable, allowing selective deprotection of another remote 2° TBS ether.²⁰⁸ Steroid derivatives **184** were converted to the mono-deprotected product upon treatment with 5 M hydrogen chloride in acetone (Scheme 86). After selective deprotection occurred, the remaining TBS ether was hydrolyzed using TsOH in acetone at 40°C.



Scheme 86

TFA has also been employed to effect selectivity in the deprotection of 2° silyl ethers. As part of Merck's synthesis of FK-506, TFA/H₂O/THF was used to cleave the 2° TES ether of **186** without affecting TBS-protected 2° alcohol.⁸⁹ TFA was also used by this group to cleave a 2° TES ether without deblocking 2° TIPS and 2° TBS groups (Scheme 87).⁸⁹

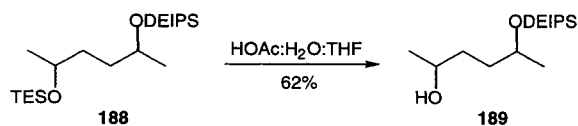
A similar selective deprotection scheme used by Schreiber employed TFA/H₂O to hydrolyze a TES-protected 2° alcohol in the presence of TIPS- and TBS-protected 2° alcohols.²⁰⁹



Scheme 87

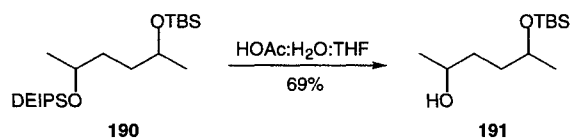
Kende has accomplished the deprotection of a 2° TBS in the presence of a 2° TBDPS ether with formic acid in the synthesis of didesepoxyrhizosin.²¹⁰

A 2° DEIPS ether in differentially silyl-protected diol **188** remained intact during the deprotection of the 2° TES ether upon treatment with HOAc/H₂O/THF (Scheme 88).³⁹



Scheme 88

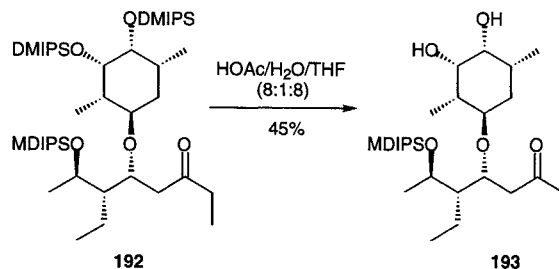
In a complementary fashion, the 2° DEIPS ether in protected diol **190** was selectively cleaved in the presence of a 2° TBS ether (Scheme 89).³⁹



Scheme 89

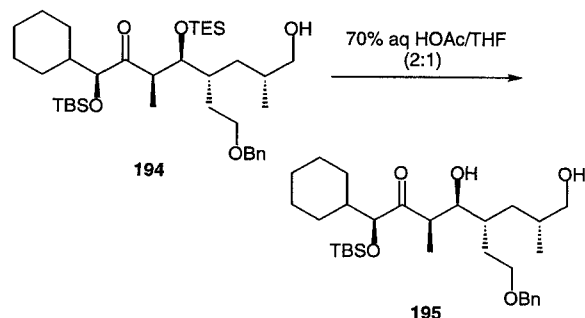
A similar mixture of HOAc, H₂O and THF was used to selectively deprotect a TMS-protected 2° alcohol in the presence of TBS-protected 2° and TES-protected 3° alcohols during the synthesis of analogs of 1 α ,25-dihydroxy-19-norvitamin D₃.²¹¹

Upon treatment with HOAc/H₂O/THF, the DMIPS ether of a 2° alcohol **192** was selectively deprotected in the presence of MDIPS ethers of 2° alcohols (Scheme 90).²¹² This result was unique in that a wide variety of other silyl protecting groups and deprotection conditions yielded the fully deprotected product.



Scheme 90

Aqueous HOAc in THF was the reagent of choice in deprotecting a 2° TES ether **194** in the presence of a 2° TBS ether (Scheme 91).²¹³



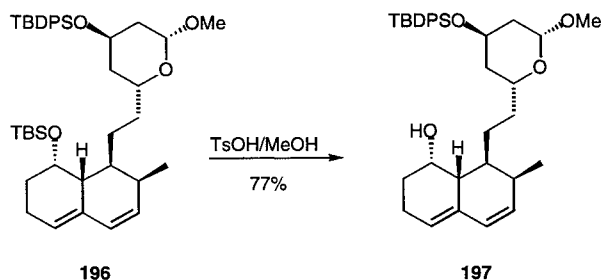
Scheme 91

Others have also used a mixture of HOAc/H₂O/THF to deprotect 2° TES ethers in the presence of 2° TBS ethers,^{214–216,218} 2° TBDPS ethers,²¹⁹ and 2° TIPS ethers.²²⁰ Evans used HOAc to remove both a 2° TES and 2° TBS ether without cleaving a 2° TIPS-protected alcohol during the synthesis of (+)-lepicidin A.^{221,222}

Ogilvie has described significant differences for the rate of HOAc-promoted hydrolysis of 3'-O-silylated nucleosides.⁹² In 80% aqueous HOAc, the MDIPS-protected 2° alcohol (3'-MDIPS-thymidine) was deprotected in 6 hours while the TBS-protected 2° position required 25 hours to achieve 100% hydrolysis.

A catalytic amount of TsOH has been used to selectively hydrolyze the less sterically hindered of two TBS protected carbinols during an avermectin subunit synthesis.²²³ However, a poor yield was obtained when TFA was used to discriminate between two TBS ethers.²²⁴

One equivalent of TsOH in methanol was used to cleave the 2° TBS ether in the presence of a 2° TBDPS ether of compactin intermediate **196** (Scheme 92).²²⁵



Scheme 92

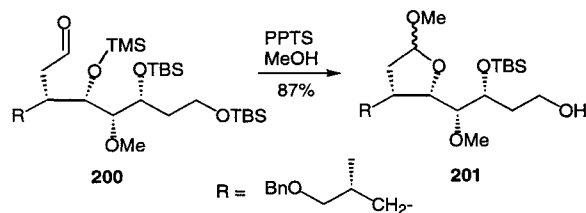
Johnson's group has used these conditions to discriminate between a 2° TMS ether and 2° TBS ether²²⁶ and also between a 2° TBS ether and a 2° TBDPS ether in cycloheptane **198** (Scheme 93).^{227,228}

TsOH was also used in Merck's work on avermectins to selectively deblock a 2° TMS ether in the presence of both a 2° TBS group and a 3° TMS group.²²⁹

Scheme 93^{227,228}

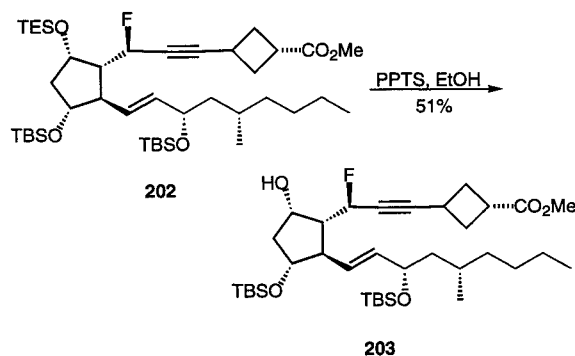
CSA has been used to selectively deprotect one 2° TBS ether in the presence of another 2° TBS ether²³⁰ or a 2° TBDPS ether²³¹ and also to remove a 2° TES ether in the presence of a 2° TBDPS ether.²³²

Citric acid has been used to discriminate between a 2° TMS ether and a 2° TBS ether^{233,234} or a 2° TIPS ether.²³⁵ In Keck's synthesis of (+)-carbonilide B, a 2° TMS ether of intermediate **200** was selectively cleaved in the presence of a 2° TBS ether using PPTS (Scheme 94).¹³⁰ In this same step a 1° TBS ether was also deprotected.



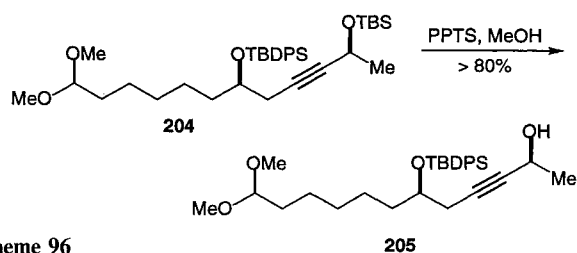
Scheme 94

Selective cleavage of a 2° TES ether in the presence of two 2° TBS ethers and two 2° TIPS groups was accomplished by using PPTS in MeOH/THF at room temperature.⁹⁶ Similar conditions were used in the synthesis of fluoroprostacyclin analog **203** (Scheme 95).^{236,237}



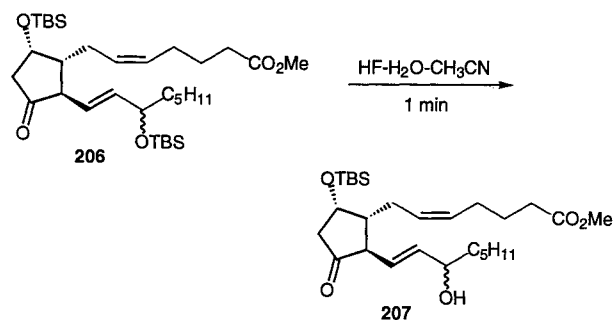
Scheme 95

Selective removal of a 2° TBS group in the presence of a 2° TBDPS ether with catalytic PPTS has also been reported.²³⁸ Hoyer has also utilized this protocol to synthesize alcohol **205** during the assembly of (+)-asimicin and (+)-bullatacin (Scheme 96).²³⁹

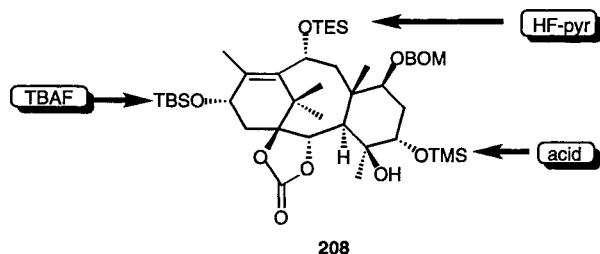


Scheme 96

Treatment with aqueous HF in CH_3CN has been reported to deprotect one 2° TBS ether in the presence of another 2° TBS ether.^{240,241} For example, bis-TBS ether **206** was converted to the mono-protected intermediate in nearly quantitative yield after exposure to an acetonitrile solution containing 30 % of a 40 % aqueous HF solution (Scheme 97).²⁴⁰ Longer exposure times resulted in slow disappearance of mono-silylated product **207**, although significant amounts remained after 1 week. Similar conditions were used by Merck in FK-506 analog work.²⁴² HF in CH_3CN was also used to deprotect a 2° TBS ether in the presence of a 2° TIPS-protected alcohol by Martin, en route to macbecin I.⁸⁸

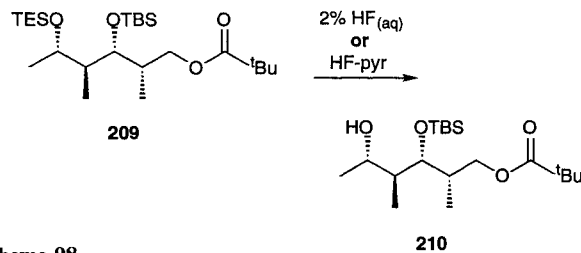
Scheme 97²⁴⁰

In Holton's synthesis of taxol,⁷ three different silyl groups were used to selectively protect three different 2° alcohols in intermediate **208**. The 2° TMS ether was selectively deprotected upon treatment with the Burgess reagent²⁴³ followed by acidic workup. The already-present 2° TES and 2° TBS ethers remained unaffected under these conditions. The 2° TES ether was selectively cleaved with HF-pyridine complex in acetonitrile. Removal of the remaining 2° TBS group was achieved with TBAF.



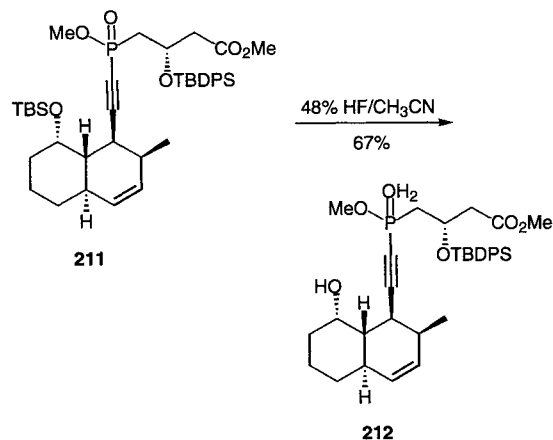
Scheme 98

in the presence of a 2° TBS ether with either 2 % aqueous HF in acetonitrile or HF·pyridine complex in THF (Scheme 98).²⁴⁴ Yamada has employed this same selective deprotection in the synthesis of aplyronine A.²¹⁷



Scheme 99

Evans has also removed a 2° TES ether with HF·pyridine without causing the removal other 2° TBS groups during the synthesis of rutamycin B,²⁴⁵ and in the total synthesis of rapamycin, Nicolaou used HF·pyridine to selectively remove two 2° TES ethers in the presence of a 2° allylic TIPS group, a 2° TIPS group and a 2° TBDPS group.^{134,246} Similarly, the selective cleavage of 2° TBS ether²⁴⁷ and 2° TES ether²³² in the presence of a 2° TBDPS ether has been effected by treatment with HF in acetonitrile. Under these conditions, bis-silyl ether **211**, an intermediate in the synthesis of an analog of mevinic acid, was converted into alcohol **212** in 67 % isolated yield (Scheme 99).²⁴⁷



Selective deprotection of a 2° DEIPS ether in the presence of a 2° TBS ether has been shown to occur upon treatment of the bis-silyl ether with a 3 : 1 : 3 mixture of acetic acid, aqueous 1 % $\text{KF}\cdot\text{HF}$, and aqueous HF.²⁴⁸

Boeckman has reported the selective desilylation of a 2° TMS ether in the presence of two 2° TBS ethers in > 86 % yield using an excess of $\text{Et}_3\text{N}\cdot\text{HF}$ complex.²⁴⁹

DeShong has reported the use of H_2SiF_6 in the selective deprotection of 2° silyl ethers.^{56,57,194} In competitive reactions, a 2° TBS ether was deprotected in the presence of a 2° TIPS ether with 63 % selectivity (Scheme 100).⁵⁷

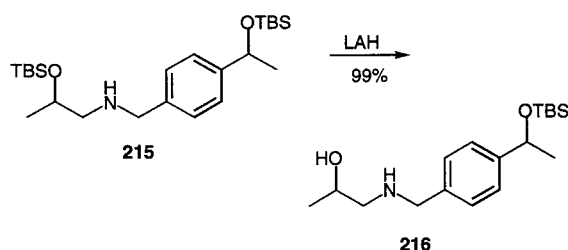
Other examples of fluoride-induced selective deprotection reactions have exploited the differing reactivities of silyl-protecting groups bearing alkyl groups of different sizes. As part of a synthesis of the C–D fragment of the aglycone of amphotericin B, Masamune has reported the selective deprotection of a TES-protected 2° alcohol **209**



Scheme 100

4.2.2. Under Basic/Nucleophilic Conditions

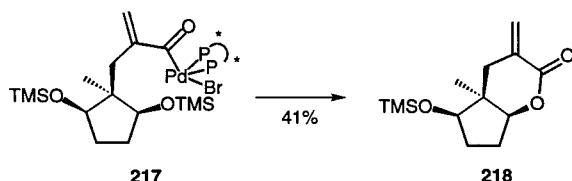
Bulky silyl ethers are generally considered to be stable to reductive conditions.¹ However, a few examples of deprotection of silyl ethers using hydride reagents have been reported.^{60,153,250,251,341} Other reports describe deprotections that are incidental to the reduction of another functional group in the same molecule.^{252,253} A recent detailed account describes the selective deprotection of 2° TBS ethers when the hydroxy group to be liberated is near an alcohol or amine (Scheme 101).⁶⁰ Thus, bis-silyl ether **215** was selectively converted into alcohol **216**.



Scheme 101

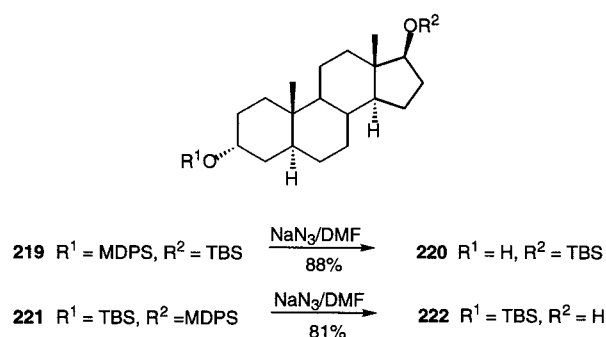
One explanation for this phenomenon is that LiAlH_4 deprotonates the neighboring group and the resultant anion binds the remaining AlH_3 . The hydride is preferentially delivered to the neighboring silyl group, resulting in selective deprotection. Another possible explanation would involve silyl migration. This protocol has also been used to remove a 3° TMS ether in the presence of a 2° allylic TBS ether.²⁵⁴

Another example of intramolecular assistance to accomplish selective desilylation has been reported in which the mode of desilylation has been attributed to an intermediate organopalladium species (Scheme 102).²⁵⁵ A 41% yield of **218** was obtained with partial resolution (39% ee) when catalytic (*S,S*)-chiraphos was used.



Scheme 102

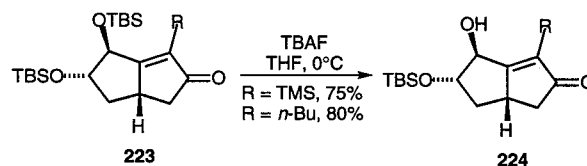
The selective affinity of the azide ion for MDPS protecting groups allows for selective deprotection of 2° MDPS ethers in the presence of 2° TBS ethers.⁶¹ This reaction has been applied to the selective deprotection of bis-silylated steroids **219** and **221** (Scheme 103).⁶¹ Treatment with one equivalent of NaN_3 in DMF at 40°C produced the mono-alcohols **220** and **222** in high yield.



Scheme 103

Basic sources of fluoride have been used extensively in selectively deprotecting one 2° silyl ether in the presence of another. The rates of TBAF-induced cleavage of the TDS- and TBS-protected cyclohexanols indicate that a 2° TBS ether can be selectively deprotected in the presence of a 2° TDS ether (see Table 10).⁸⁰ The more rapid TBAF-induced cleavage of 2° TBMPS ethers allows its selective deprotection in the presence of a 2° TBDPS ether.³⁷

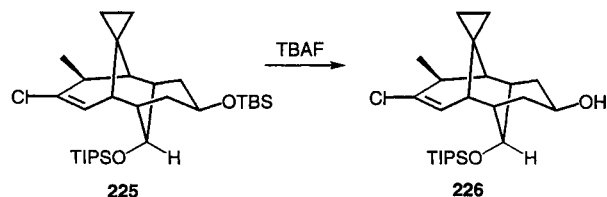
TBAF-mediated cleavage of a 2° TBS ether in the presence of a 2° TBDPS was used in the total synthesis of milbemycin α_1 .²⁵⁶ TBAF has been used to selectively deblock a 2° TMS ether without affecting other 2° TMS ethers present.²⁵⁷ The selective desilylation of 2° TES³⁴⁵ and 2° TBS ethers^{258,259} has been effected by treatment with TBAF (Scheme 104).

Scheme 104²⁵⁸

Although possibly not selective, a “net” regioselective discrimination between two TBS ethers with TBAF has been accomplished.²⁶⁰

In Danishefsky's work on rapamycin, a 2° TMS group was selectively removed from a molecule in the presence of a 2° TBS group using TBAF buffered with HOAc.²⁶¹ Selective desilylation of a 2° TBS-protected allylic alcohol in the presence of another 2° TBS ether has been reported to occur via sequential treatment with a chiral Rh-binap catalyst which selectively isomerizes one 2° allylic silyl ether into a silyl enol ether that is then cleaved with TBAF.^{262,263}

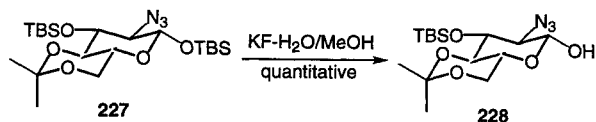
As part of the synthesis of aplasmomycin, Corey successfully removed a 2° TIPS group from different molecules that contained both two and four 2° TBS groups. This was accomplished by treatment with 1 equivalent of TBAF in THF for 30 minutes.²⁶⁴ On the contrary, in Cha's work on taxol, the sterically more accessible 2° TBS of **225** was deprotected in the presence of a 2° TIPS ether (Scheme 105).²⁶⁵



Scheme 105

Ireland required 5 equivalents of TBAF to accomplish the same task en route to FK-506.²⁶⁶ In another TBAF-mediated selective deprotection, Holmes found much better selectivity between a 2° TMS and a 2° TBDPS ether (99%) than between a 2° TBS and a 2° TBDPS ether (29–38%).²⁶⁷

Myers has described the use of $\text{KF} \cdot \text{H}_2\text{O}$ to effect the selective removal of the anomeric TBS group of carbohydrate **227** without deblocking another 2° TBS ether (Scheme 106).²⁶⁸



Scheme 106

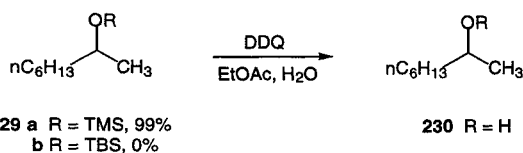
4.2.3. Under Miscellaneous Conditions

The variability in the rates of desilylation of 2° silyl ethers with the Lewis acids $\text{Cu}(\text{NO}_3)_2$ and $\text{Ce}(\text{NO}_3)_3$ also points toward applications in selective deprotection (see Table 12).⁷⁰ Cleavage of silyl ethers of cyclohexanol under these conditions show a reactivity trend in which TMS ethers cleave much faster than TBS ethers, with TBDPS ethers being unreactive.

Iron(III) chloride has been used to remove the more labile 2° TMS group in the presence of a 2° TIPS group.²⁶⁹ From this, it should be possible to directly form monoesters in a single transformation by stirring the parent bis-silyl ether with FeCl_3 and the corresponding acid chloride.²⁷⁰

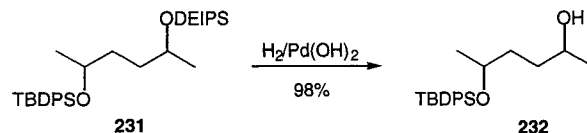
2° TES groups have been cleaved with $\text{MoO}_5 \cdot \text{HMPA}$ or $\text{WO}_5 \cdot \text{HMPA}$, but the corresponding 2° TBS and 2° TIPS ethers were unaffected.^{271,272}

Reactivity differences in single electron transfer (SET) reactions of silyl ethers is the basis for selective deprotection with DDQ (see Table 11).⁶⁵ TBDPS ethers are stable to DDQ while TES ethers are cleaved within one hour and TBS ethers required 3 to 7 hours. Thus, 2° TES ethers can be cleaved in the presence of 2° TBS or TBDPS ethers with DDQ. Note that the selectivity of this method of deprotection is due to the steric bulk of the silyl protecting agent but is independent of the steric environment of the parent alcohol. In similar work, 2° TBS ethers (e.g. **229b**) were unreactive toward DDQ in wet ethyl acetate while 2° TMS ethers (e.g. **229a**) hydrolyzed in 2.5 hours (Scheme 107).⁶⁷



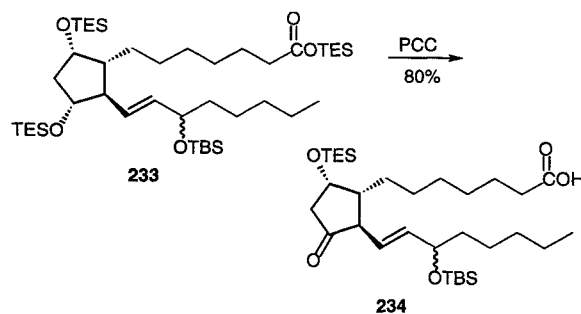
Scheme 107

Hydrogenolysis has been used to selectively deprotect a 2° DEIPS ether in the presence of a 2° TBDPS ether. Bis-silyl ether **231** was hydrogenated with $\text{Pd}(\text{OH})_2$ in MeOH to yield mono-protected product **232** in 99% yield (Scheme 108).⁶⁴ A decrease in selectivity was observed between DEIPS and TBS ether.⁶⁴



Scheme 108

Selective oxidations of 2° silyl ethers in the presence of other 2° silyl ethers have been reported.⁷⁴ In a total synthesis of (±)-prostaglandin D, tris-silyl ether **233** was converted into the 11-oxo derivative of PGD_1 **234** using a twofold excess of PCC (Scheme 109).²⁷³



Scheme 109

As noted earlier, Pearson has used a selective oxidation of a 2° TBS ether into a ketone with KF , CrO_3 and H_2SO_4 ²⁰¹ without hydrolysis of a 1° or 2° TBDPS ether.¹⁷² Under Swern oxidation conditions, 2° TMS ethers were oxidized to ketones, whereas the more stable 2° TBS ethers were unaffected.^{76,274,275} The reactivity of 2° silyl ethers with excess *t*-BuOOH and bis(triphen-

Table 14. Oxidation of Silyl Ethers of 1-Phenylpropan-1-ol²⁷⁶

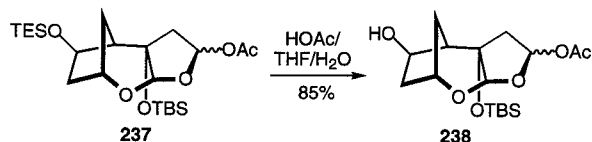
	Time (h)	Conversion (%)	Yield (%)
a , R = TMS	14	100	97
b , R = TBS	66	32	19
c , R = TDS	15	28	26
d , R = TPS	17	7	trace

ylsilyl)chromate shows selectivity for 2° TMS silyl ethers over the more sterically hindered 2° TBS, TDS, and triphenylsilyl ethers.²⁷⁶ Conversions of 100% were reported for 2° TMS ethers but, by contrast, 2° alcohols protected with TBS, TDS, and TPS moieties were deprotected in less than 26% yield (Table 14).

4.3. In the Presence of 3° Silyl Ethers

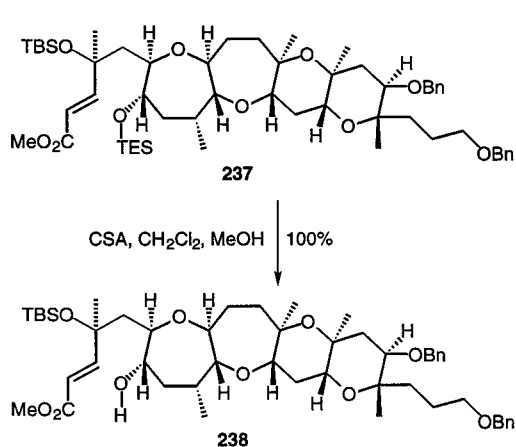
4.3.1. Under Acidic Conditions

Ley has described a selective deprotection reaction of a 2° TES ether in the presence of a 3° TBS ether of spiroketal **237** using acetic acid (Scheme 110).²⁷⁷ In the synthesis of a similar acetal, the selective deprotection of 2° TBS ethers in the presence of a 3° TBS ether was effected by heating in the presence of HOAc/THF/H₂O.²⁷⁸ Aqueous acetic acid in THF was also used to selectively deprotect a 2° TMS ether in the presence of a 3° TES ether as well as two TBS-protected 2° alcohols.²¹¹



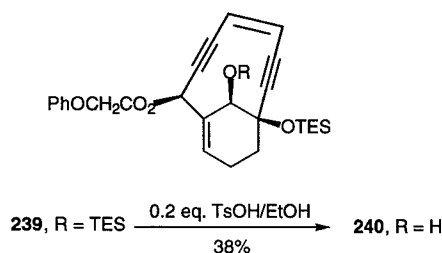
Scheme 110²⁷⁷

One equivalent of CSA was used in Nicolaou's recent synthesis of brevetoxin B intermediate **239** to selectively deprotect a 2° TES ether in the presence of 3° TBS ether (Scheme 111).¹⁰



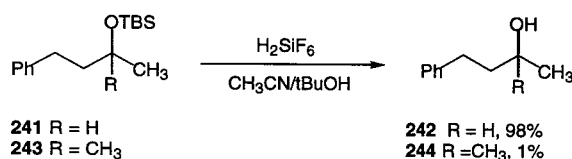
Scheme 111

Blizzard has used a catalytic amount of TsOH to hydrolyze a 2° TMS ether without cleaving a 3° TMS protected alcohol.^{229,279} Likewise, a Bristol-Myers Squibb group has done a selective deprotection, albeit in 38% yield, of a 2° TES-protected alcohol in the presence of a 3° TES-protected alcohol using catalytic TsOH to give alcohol **240** (Scheme 112).²⁸⁰



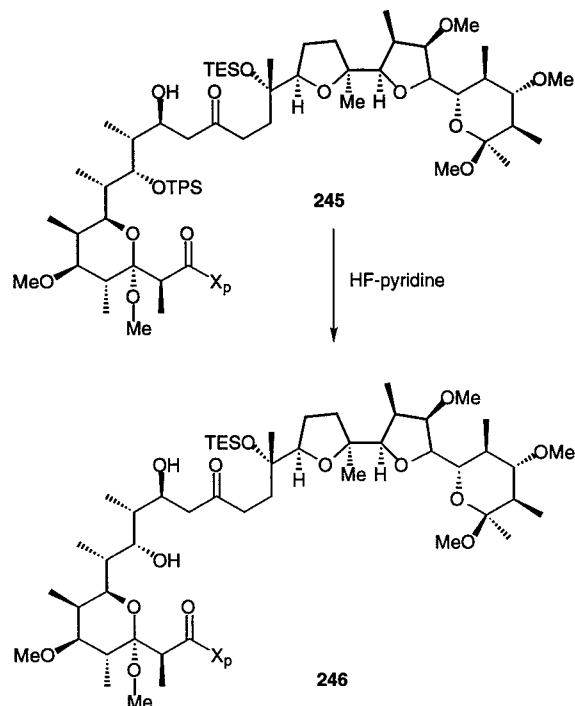
Scheme 112

DeShong has reported that fluorosilicic acid (H₂SiF₆) shows outstanding selectivity in the cleavage of a 2° TBS ether in the presence of a 3° TBS ether.⁵⁷ In competitive reactions in which a 1:1 mixture of TBS ethers **241** and **243** were treated with 0.25 equivalents of H₂SiF₆, the TBS group protecting the 2° alcohol was cleaved with 97% selectivity (Scheme 113).⁵⁷



Scheme 113

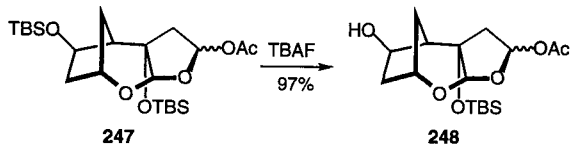
Selective cleavage of the 2° TPS ether in the presence of a 3° TES ether using excess HF·pyridine has recently been reported in a total synthesis of Ionomycin A (Scheme 114).²⁸¹ It is noteworthy that removal of both silyl groups occurred upon treatment with aqueous HF in acetonitrile at 0°C.



Scheme 114

4.3.2. Under Basic/Nucleophilic Conditions

Ley has used TBAF to selectively deprotect a 2° TBS ether in the presence of a 3° TBS ether in work directed toward the synthesis of insect antifeedant intermediate **248** (Scheme 115).²⁷⁷ Other examples of a 2° TBS ether being cleaved with TBAF in the presence of a 3° TBS ether have been reported.^{282,283}



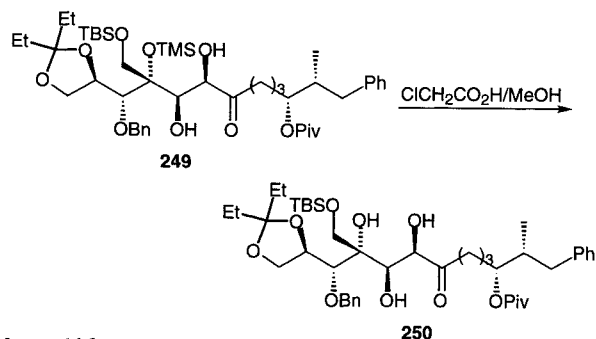
Scheme 115

5. Selective Deprotection of Silyl-Protected 3° Alcohols

5.1. In the Presence of 1° Silyl Ethers

5.1.1. Under Acidic Conditions

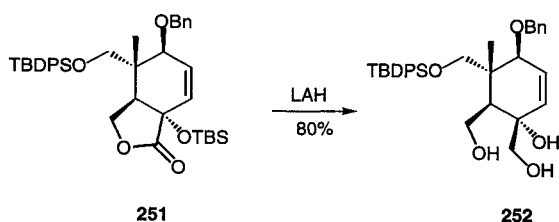
As part of studies directed toward the synthesis of zaragozic acid C, Carreira has described the selective deprotection of a 3° TMS ether in the presence of a 1° TBS ether (Scheme 116).¹² The reagent of choice for this deprotection was chloroacetic acid in MeOH, not dichloroacetic acid, which was used to discriminate between 1° TBS ethers in the same total synthesis.¹²



Scheme 116

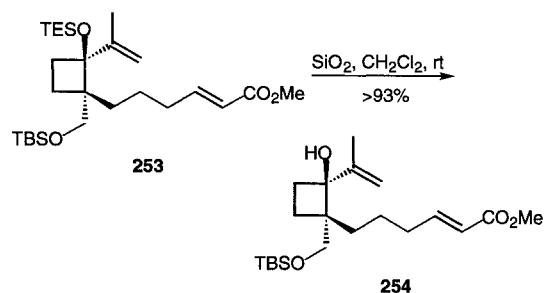
5.1.2. Under Basic/Nucleophilic Conditions

In Nicolaou's synthesis of taxol a TBS-protected 3° alcohol was cleaved in the presence of a 1° TBDPS ether with 3 equivalents of LiAlH₄ (Scheme 117).^{6,284} Reduction of the lactone probably occurs first followed by intramolecular assistance⁶⁰ from a newly formed 1° alkoxide yielding triol **252**.

Scheme 117^{6,284}

5.1.3. Miscellaneous Conditions

Treatment with silica gel allowed for the selective removal of a 3° TES protecting group in cyclobutane **253** without deblocking a 1° TBS ether (Scheme 118).²⁸⁵

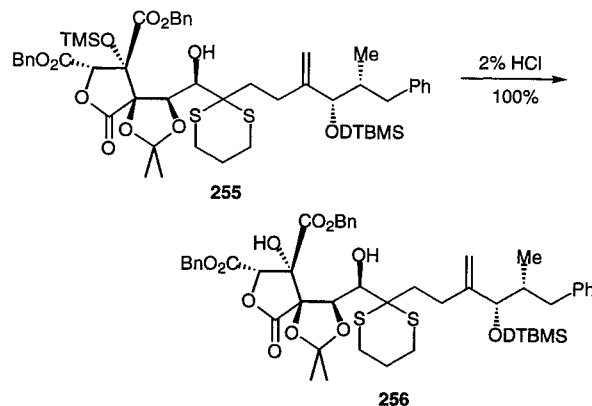


Scheme 118

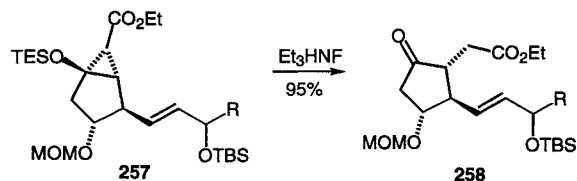
5.2. In the Presence of 2° Silyl Ethers

5.2.1. Under Acidic Conditions

In a total synthesis of zaragozic acid A, a 3° TMS ether was selectively cleaved in the presence of a 2° DTBMS ether by treatment of intermediate **255** with 2% HCl in 1:1 methanol/dichloromethane (Scheme 119).^{14,286} Selective deprotection occurred in 100% yield in 5 minutes at room temperature.²⁸⁶ Similarly, a 3° TMS ether was deprotected in the presence of a 2° TBDPS ether using 2% HCl/MeOH/CH₂Cl₂ in 5 minutes at room temperature.¹⁴ Hanessian also used HCl (2 M) to deblock a 3° TMS silyl ether in the presence of a 2° TBS ether.²⁸⁷

Scheme 119²⁸⁶

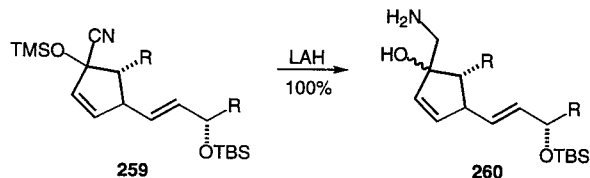
Triethylammonium fluoride has allowed for selective 3° TES silyl removal in the presence of a 2° allylic TBS ether (Scheme 120).^{288,289} The newly formed alkoxide initiated a cyclopropane ring opening to give substituted cyclopentanone **258**.



Scheme 120

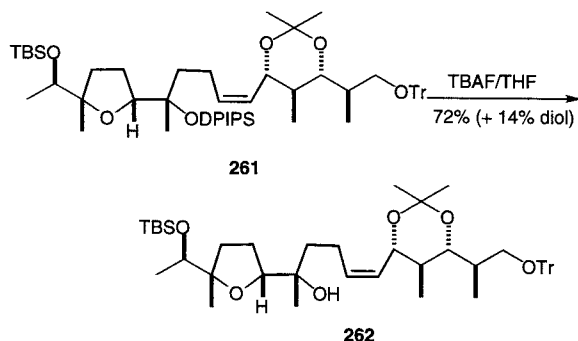
5.2.2. Under Basic/Nucleophilic Conditions

Amines and alcohols can be utilized to direct selective deprotections.⁶⁰ In the following example, the nitrile was first reduced to the corresponding amine (Scheme 121).²⁵⁴ This juxtaposition led to selective deprotection of the 3° TMS groups and left the 2° TBS unaffected.^{60,254}



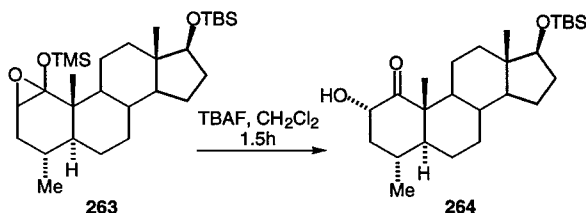
Scheme 121

Hanessian has, with fair selectivity, deprotected a 3° DPIPS ether³⁸ with TBAF to give alcohol **262** (Scheme 122).²⁹⁰ Partial removal of an accompanying 2° TBS ether occurred resulting in 14% diol formation.



Scheme 122

The initial product from a Rubottom oxidation **263** is a 3° silyl ether. Subsequent silyl deprotection affords the corresponding α -hydroxy ketone. The TBAF-mediated deprotection of a 3° TMS ether has been carried out in the presence of a 2° TBS group by Grieco to form steroid **264** (Scheme 123).²⁹¹



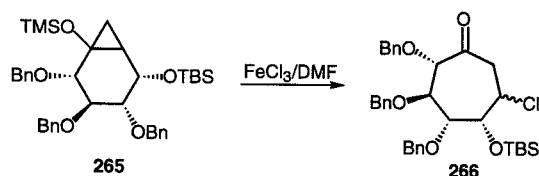
Scheme 123

Danishefsky's synthesis of rapamycin utilized TBAF buffered with acetic acid to cleave a 3° TMS group and 2° TBS group while leaving a 2° TIPS group intact.²⁹²

A 3° TBS group has also been selectively removed in the presence of a 2° TBS ether with TBAF.²⁷⁷

5.2.3. Miscellaneous Conditions

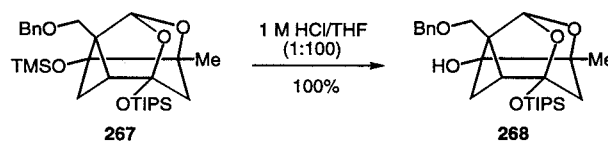
As part of a ring expansion, a 3° TMS ether was deprotected in the presence of a 2° TBS ether using FeCl_3 in DMF to afford cycloheptane **266** (Scheme 124).²⁹³



Scheme 124

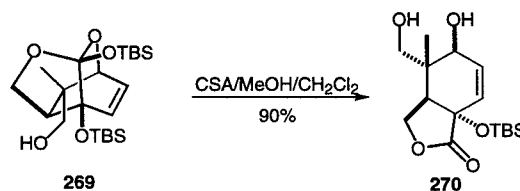
5.3. In the Presence of 3° Silyl Ethers

Corey has reported that a TMS-protected 3° alcohol **267** underwent selective desilylation in the presence of 3° TIPS ether, which was part of a mixed acetal (Scheme 125).²⁹⁴ Selective deprotection was effected by treatment with a 1:100 solution of 1 M HCl in THF at 0°C to afford the deprotected 3° alcohol in 100% yield. It is noteworthy that treatment of the bis-silyl substrate with aqueous HF in acetonitrile resulted in cleavage of both silyl groups.²⁹⁴



Scheme 125

Nicolaou's group made extensive use of silyl-protecting groups in their synthesis of taxol.²⁹⁵ At one point in the synthetic scheme, the TBS ether of a 3° alcohol was deprotected to yield diol **270** using catalytic CSA at room temperature, leaving a 3° TBS ether intact (Scheme 126).



Scheme 126

6. Selective Deprotection of Aryl Silyl and Alkyl Silyl Ethers

Aryl silyl ethers and alkyl silyl ethers can be selectively cleaved in the presence of one another. The techniques include an assortment of methods similar to those used for distinguishing among alkyl silyl ethers. Davies has measured the half-lives of acid and base catalyzed hydrolyses of 1° alkyl versus aryl silyl ethers (Table 15).³³ An important theme is illustrated by Davies' results. Acidic conditions generally favor the cleavage of the alkyl silyl ether while basic conditions favor deprotection of the aryl silyl ether.

Davies' results indicate that 5% NaOH/95% EtOH could be used to selectively hydrolyze ArOTES-, ArOTBS-, ArO-*i*-BuPh₂Si- and ArOTBDPS-protected phenols in the presence of 1° TBS, 1° TIPS and 1° TBDPS ethers.³³

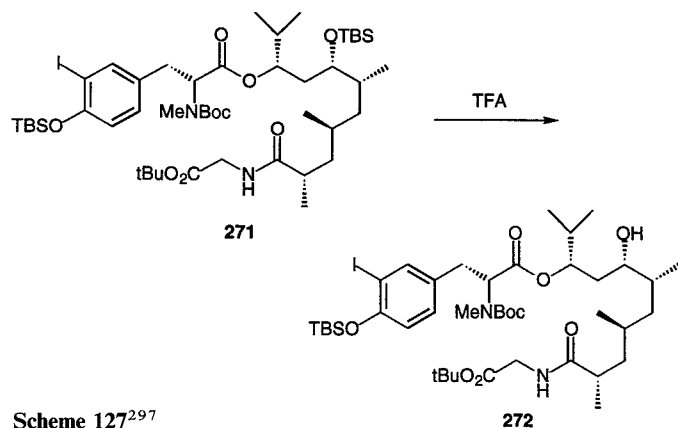
Table 15. Half-Lives of Hydrolysis of Alkyl vs. Aryl Silyl Ethers³³

	R	1 % HCl in 95 % MeOH	5 % NaOH in MeOH
ROTMS	<i>n</i> -C ₆ H ₁₃ —	≤ 1 min	≤ 1 min
	<i>p</i> -MeC ₆ H ₄ —	≤ 1 min	≤ 1 min
ROTBS	<i>n</i> -C ₆ H ₁₃ —	≤ 1 min	a
	<i>p</i> -MeC ₆ H ₄ —	273 min	3.5 min
ROTIPS	<i>n</i> -C ₆ H ₁₃ —	55 min	a
	<i>p</i> -MeC ₆ H ₄ —	100 h	188 min
ROTBDS	<i>n</i> -C ₆ H ₁₃ —	225 min	a
	<i>p</i> -MeC ₆ H ₄ —	100 h	6.5 min

all reactions were performed at 25 °C

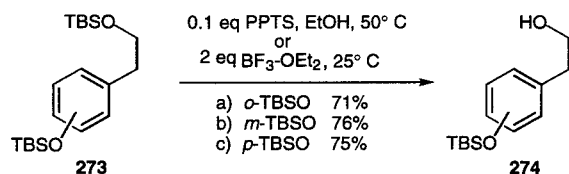
^a Half-life of 1 min represents the lower limit of sampling technique.

Evans used neat TFA to selectively deprotect a 1° TBS ether without cleaving two ArOTBS groups of **271** during the synthesis of cyanocycline.²⁹⁶ These conditions were also used to deprotect a 2° TBS ether in the presence of a phenol protected as a TBS ether en route to the cyclopeptide, dolicolide (Scheme 127).²⁹⁷

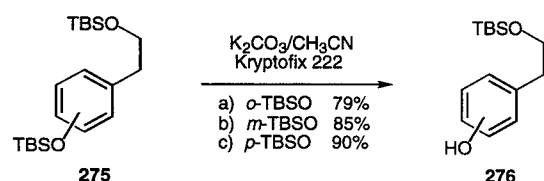
**Scheme 127**²⁹⁷

The acidic conditions during ultrasonication of CH₃OH/CCl₄ allows for the selective deprotection of TBS-protected 1° alcohols in the presence of TBS-protected phenols.³⁶

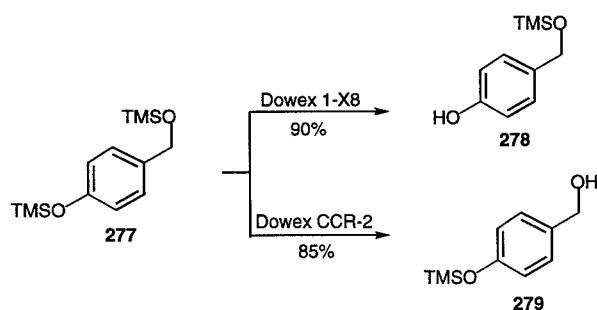
Primary and secondary TBS ethers have been selectively cleaved in the presence of silyl-protected phenols **273** using catalytic PPTS²⁹⁸ or 2 equivalents of BF₃·OEt₂³⁴⁰ (Scheme 128).²⁹⁸ This method worked equally well for alkyl silyl ethers derived from benzylic alcohols as well as alcohols that were remote from the aryl rings with yields ranging from 70–88 %.

**Scheme 128**

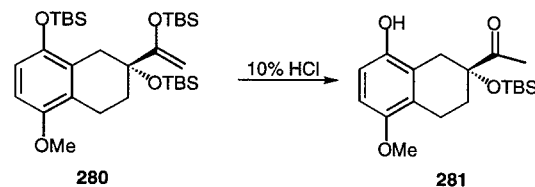
In a complementary reaction, the phenolic TBS groups of bis-silyl ethers (e.g. **275**) were selectively cleaved by treatment with excess K₂CO₃ and Kryptofix 222 in CH₃CN at 55 °C (Scheme 129).²⁹⁸

**Scheme 129**

Kawazoe has used a pair of Dowex resins to accomplish a similar selective deprotection scheme.²⁹⁹ A phenolic TMS ether underwent selective deprotection in the presence of TMS-protected carbinol to form phenol **278** when stirred with 0.1 equivalents of Dowex 1-X8, a quaternary ammonium resin (OH[−] form, Scheme 130). Again, a complementary reaction was developed in which treatment of the same substrate with 3.0 equivalents of Dowex CCR-2, a carboxylic resin (H⁺ form) deprotected the aliphatic silyl ether to form the corresponding alcohol **279** (Scheme 130).²⁹⁹ Barrett's synthesis of papulacandin D involved the selective removal of 1° and 2° aliphatic TMS ethers in the presence of two TIPS aryl ethers. This transformation was caused by Amberlite IR-120 (H⁺ form).³⁰⁰

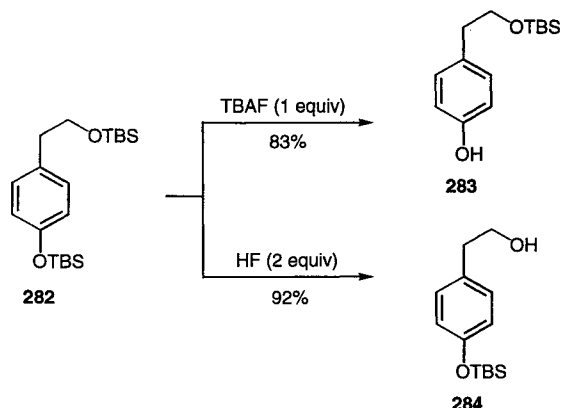
**Scheme 130**

In the synthesis of daunomycin and its 4-demethoxy analog, Davis has used acidic conditions to achieve the opposite selectivity in deprotection.³⁰¹ Addition of 10 % HCl to intermediate **280** selectively cleaved the TBS-protected phenol in the presence of the 3° TBS ether (Scheme 131).

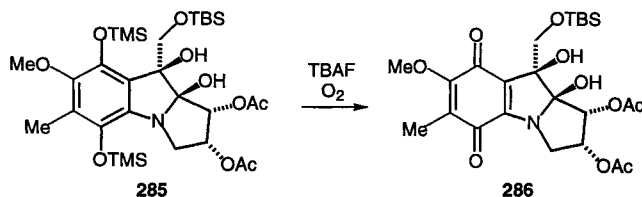
**Scheme 131**

In one of the earliest examples of selective deprotection of alkyl vs. aryl silyl ethers, carefully controlled conditions allowed 1° and 2° TBS ethers to be deprotected by HF in CH₃CN in the presence of silyl-protected phenols.³⁰² Danishefsky has utilized HF in CH₃CN³⁰³ or HCl/THF³⁰⁴ in selectively deprotecting a 1° TBS ether in the presence of a TBS-protected phenol in the synthesis of an ABC ring fragment of dynemicin A. Likewise, an excess of aqueous HF in CH₃CN has also been used in the selective deprotection of a 1° TBS ether in the presence

of two phenolic TBS ethers en route to the synthesis of erbstatin.³⁰⁵ In a complementary reaction, TBAF in THF allows cleavage of the aryl silyl ether in the presence of the silyl-protected carbinol **284** (Scheme 132).^{302,310} The deprotection of the protected aliphatic alcohol **282** was effected by treatment with 2 equivalents of HF while deprotection of the phenol occurred by treatment with 1 equivalent of TBAF.³⁰² Quantities of either reagent in excess of these amounts led to complete desilylation.

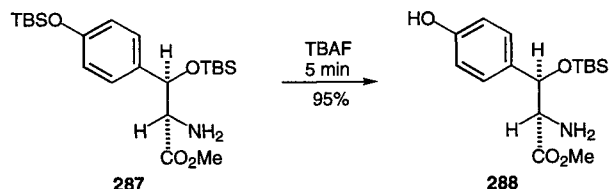
Scheme 132³⁰²

In a similar fashion, Danishefsky used TBAF to cleave two aryl TMS ethers of hydroquinone **285** in the presence of a 1° TBS ether (Scheme 133).^{306,307} The reaction was performed under oxidative conditions, so the quinone was produced.



Scheme 133

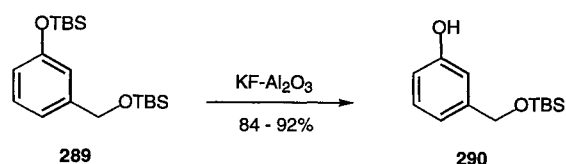
Likewise, Jung has employed TBAF to discriminate between aryl and alkyl silyl ethers (Scheme 134).³⁰⁸



Scheme 134

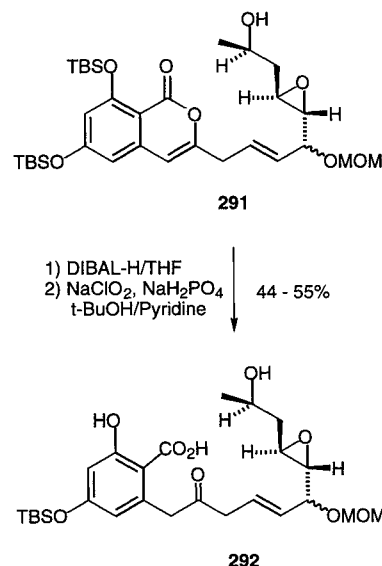
Alumina-supported KF has been used to selectively cleave TBS ethers of phenols in the presence of 1° TBS ethers (Scheme 135).³⁰⁹ For example, stirring bis-silyl ether **289** with 3 equivalents (by mass) of 37 % KF- Al_2O_3 in CH_3CN afforded the free phenol **290** in high yield. Both acidic alumina (4 hours, 92 % yield) and basic alumina (3 hours, 84 %) produced similar results, while ultrasonication of the latter reaction mixture resulted in marked acceleration (15 minutes, 86 %). In a similar fas-

hion, selective deprotection of an aryl TBS ether over a 1° TBS silyl ether was reported using 2 equivalents of KF and 0.3 equivalents of 18-crown-6.³¹⁰ Aliphatic 1° and 2° TBS ethers were cleaved with SiF_4 in dichloromethane whereas silyl-protected phenols were inert under identical reaction conditions.⁷³



Scheme 135

Few examples of selective deblocking of aromatic silyl ethers exist. In one case, during an oxidation of a bis-silylated isocoumarin lactol **291**, regioselective desilylation occurred (Scheme 136).³¹¹



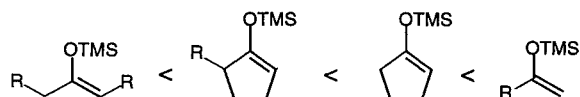
Scheme 136

In another example, TMS, TES, and TBS phenolic ethers have been cleaved with $\text{PdCl}_2(\text{CH}_3\text{CN})_2$, while phenolic TIPS and TBDPS ethers were inert to the reaction conditions.³¹² It should be possible to obtain similar results with dilute HCl ,³³ and some degree of selectivity with NaOH .³³

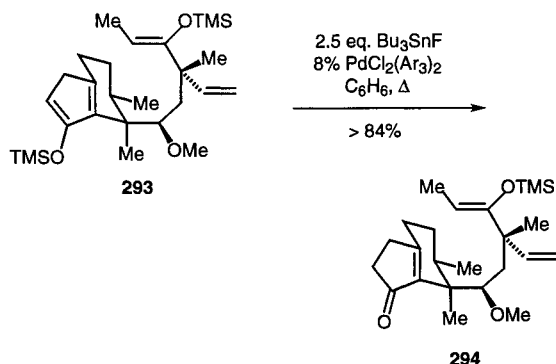
7. Selective Mono-Desilylation of Bis-Silylated Enol Ethers

Although not the focus of this review, deprotection protocols of silyl enol ethers are similar that of silyl ethers. Some of the following examples serve to illustrate this point. Dilute acetic acid has been used to hydrolyze a TMS enol ether to the corresponding ketone; however, under these conditions TBS and (2,4,6-tri-*tert*-butylphenoxy)dimethylsilyl enol ethers were inert.³¹³ Discrimination between two TMS enol ethers has been accomplished with a $\text{Bu}_3\text{SnF}/\text{Pd}$ catalyst system. The rate of reaction is dependent upon the steric environment of the silyl

groups, with the rate of reaction increasing in the following order:³¹⁴



An example by Paquette nicely illustrates the utility of this protocol (Scheme 137).³¹⁵

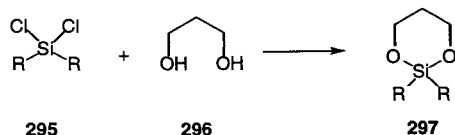


Scheme 137

MeLi has selectively removed a DMPS enol ether in the presence of a TBS enol ether.³¹⁶ Similarly, MeLi/TMEDA has been used to remove a TMS-protected enol in the presence of a TBS-protected enol.³¹⁶

8. Selective Deprotection of Silylene- and Disiloxane-Protected Diols

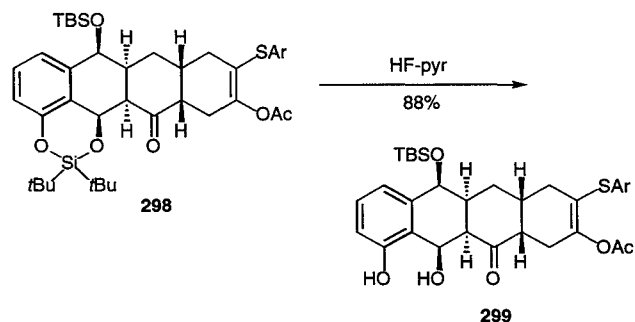
Dialkylchlorosilanes³¹⁷ **295** and dialkylsilylditriates³¹⁸ have been shown to react with 1,3 diols **296** under forcing conditions to form silylene derivatives **297** (Scheme 138).³¹⁷ In effect, one silyl group protects two hydroxy groups in much the same way that a cyclic ketal protects a diol.¹



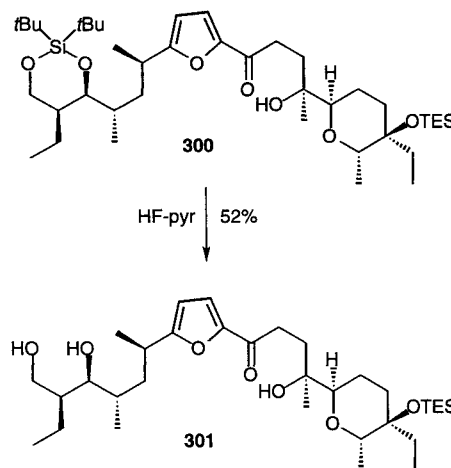
Scheme 138

Trost has reported that di-*tert*-butylsilylenes of 1,3 diols can be selectively cleaved in the presence of 2° TBS ethers.^{319,320} As a part of studies directed toward the synthesis of deoxypillaromycinone, silylene derivative **298** was converted into diol **299** in 88 % yield upon treatment with HF·pyridine (Scheme 139).^{319,320}

More recently, a silylene-protected 1,3-diol **300** was selectively cleaved in the presence of a 3° TES ether with HF·pyridine (Scheme 140).¹³⁸ Similar conditions were used by Paterson to remove a silylene without affecting several 2° TBS ethers.^{321,322}

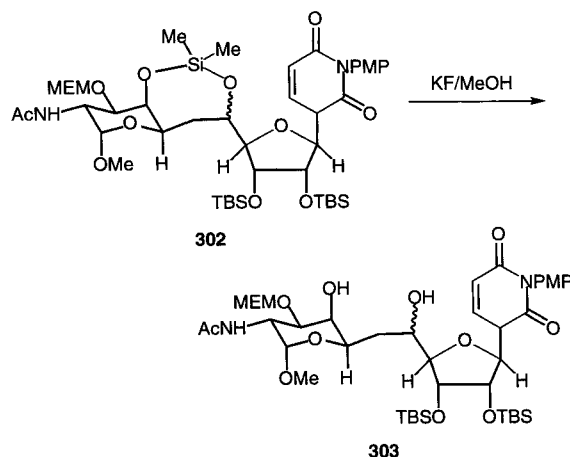


Scheme 139



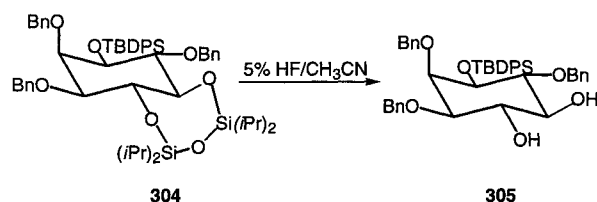
Scheme 140

Myers has accomplished a similar hydrolysis^{323,324} to release 1,4-diol **303** with KF/MeOH (Scheme 141).^{268,323}



Scheme 141

Disiloxanes have proven useful in the protection of diols and selectivity in their removal has also been demonstrated. Bruzik has reported that 5 % HF in CH₃CN selectively removes a TIPDS group in the presence of a 2° TBDPS ether affording carbohydrate **305** (Scheme 142).³²⁵

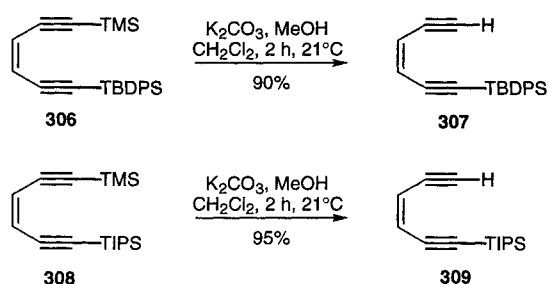


Scheme 142

Dilute aqueous NH_4OH has been used to selectively cleave a 2° TMS ether in the presence of a TIPDS-protected diol.³²⁶

9. Selective Protidesilylations

Although not a focus of this review, selective protidesilylations have been accomplished and a few examples are included. Fallis has taken advantage of the differences in silyl group size to selectively protidesilylate bis-silylated terminal alkynes (Scheme 143).³²⁷



Scheme 143

A few additional examples of selective protidesilylations are given in Schemes 144–147.

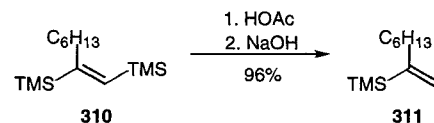
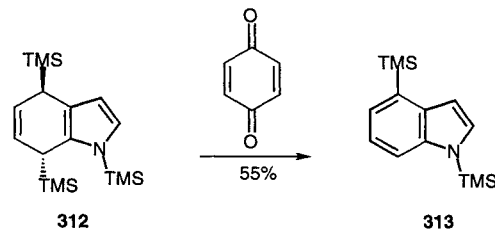
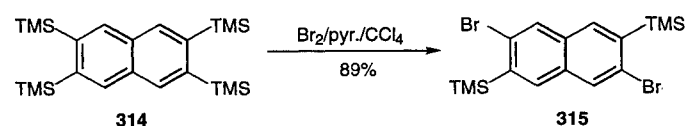
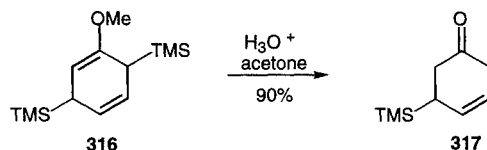
Scheme 144³²⁸Scheme 145³²⁹Scheme 146³³⁰Scheme 147³³¹

Table 16. Deprotection of 1° Silyl Ethers in the Presence of Another 1° Silyl Ether

Deprotection of:	In the Presence of:		1° DEIPS	1° TIPS	1° TBS	1° TBDPS
1° TMS	1° TMS	1° TES		NaOH/EtOH ³³	NaOH/EtOH ³³ Cu(NO ₃) ₂ ⁷⁰ Ce(NO ₃) ₃ [Bu ₂ (NCS)Sn] ₂ O ⁷²	NaOH/EtOH ³³ Cu(NO ₃) ₂ ⁷⁰ Ce(NO ₃) ₃ ⁷⁰ HCl ³³ HCl ³⁴
1° TES			HOAc/THF/ H ₂ O ³⁹		HF · pyr ⁵⁸ TCNQ/MeCN/H ₂ O ⁶⁶ DDQ/MeCN/H ₂ O ^{65,66} H ₂ /Pd(OH) ₂ ⁶⁴ HOAc/H ₂ O/THF ³⁹	SiF ₄ /CH ₂ Cl ₂ ⁷³ DDQ/MeCN/H ₂ O ^{65,66}
1° DEIPS						H ₂ /Pd(OH) ₂ ⁶⁴
1° TIPS				HCl/EtOH ^{32,33} H ₂ SiF ₆ (aq)/ <i>t</i> -BuOH ^{56,57} NaOH/EtOH ³² cyclohexene/PdO ⁶³ alumina ⁶⁹	TsOH/THF/H ₂ O ⁴⁶ Cl ₂ CHCO ₂ H ^{12,13} TBAF ⁵⁹ TBS-OTf ⁷¹	HCl ^{32,33,35} HOAc/THF/H ₂ O ^{40–44} CSA/MeOH ^{47,48} PPTS ^{20,49} TsOH ⁴⁵ MeOH/CCl ₄ ³⁶ Cu(NO ₃) ₂ ⁷⁰ Ce(NO ₃) ₃ ⁷⁰ cyclohexene/PdO ⁶³ alumina ⁶⁹ SiF ₄ /CH ₂ Cl ₂ ⁷³ DDQ/MeCN/H ₂ O ^{65,66} AcBr/CH ₂ Cl ₂ ⁶² TMS-OTf ⁹¹ LiAlH ₄ ⁶⁰
1° TBS						
1° TBDPS						

Biphenyldimethylsilyl (BPDMS) and biphenyldiisopropylsilyl (BPDIPS) groups are new entries into the arsenal of terminal alkyne silyl groups.³³² These groups should also be applicable to silyl ether deprotection, with the advantage of the corresponding silyl ether being a solid.

10. Summary

Methods (especially acidic) that selectively remove a smaller silyl ether in the presence of a larger silyl ether will generally be applicable to the selective removal of even smaller silyl ethers. In the same vein, even larger

silyl groups will be stable under these conditions. As well as reagent choice, modification.

Exploitation of differences in the steric requirements of the silicon atom of a protecting group and/or the alcohol carbon atom allow selective removal of one silyl protecting group in the presence of another. The commercial availability of the necessary silylating reagents along with a variety of methods for their selective attachment adds to the popularity of these protecting groups. From the vast number and variety of trialkylsilyl groups studied, it would seem that the majority of permutations on the theme of adjusting reactivity by changing the steric environment of the silicon atom have been investigated.

Table 17. Deprotection of 1° Silyl Ethers in the Presence of 2° Silyl Ethers

Deprotection of:	In the Presence of:					
	2° TMS	2° TES	2° DEIPS	2° TIPS	2° TBS	2° TBDPS
1° TMS	Rexyn 101 ¹¹⁵ K ₂ CO ₃ / MeOH ¹⁴⁹ alumina ⁶⁹				BF ₃ · OEt ₂ ¹²⁵	
1° TES		HOAc ⁹⁶		HOAc ⁹⁶	HOAc/H ₂ O/THF ⁹⁴⁻⁹⁶	TfOH ⁹¹
1° DEIPS				TBAF ¹⁶⁰	RMgX ¹⁵⁷	
1° TIPS				HCl ³²	TFA/H ₂ O/THF ⁸⁹	TFA/H ₂ O/THF ⁹⁰
1° TBS			TsOH/ PPTS ¹¹²	HOAc ^{92,97-100}	HCl, ⁸¹ HOAc ^{96,97,101-105}	HOAc/H ₂ O/THF ^{106,107}
				TsOH/PPTS ¹¹²	TFA/THF/H ₂ O ⁸⁶⁻⁸⁸	TsOH ^{110,111,335}
				HF · pyr ^{139,140,246}	CSA/MeOH ^{10,48,113,114}	PPTS ^{49,123,124}
				NaOH ³²	PPTS, ¹¹⁷⁻¹²²	TBAF ¹⁵⁹
				cyclohexene/ PdO ⁶³	Amberlite (H+) ¹¹⁶	HF · pyr ¹⁴¹
				TsOH ^{108,109}	NH ₄ F ^{145,148}	HF · Et ₃ N ¹⁴³
					HF/CH ₃ CN ^{333,334}	
					H ₂ SiF ₆ (aq)/ <i>t</i> -BuOH ⁵⁷	
					HF · pyr ^{58,126-129,132,133,135-137,139,140}	
					H ₂ /wet Pd, ¹⁶⁴ AgOAc ¹³¹	
					NBS/DMSO ¹⁶²	
					MeOH/CCl ₄ /))) ³⁶	
					NaOH, ³² TBAF ⁹	
					cyclohexene/PdO ¹⁶³	
					alumina ^{68,69}	
1° TBDPS				NaH/HMPA ¹⁵⁴	NaH/HMPA ¹⁵³	HF · pyr ¹⁴²
					NaOH, ¹⁵¹ KOH/MeOH ¹⁵⁰	alumina ⁶⁹
					TBAF, ^{9,158,336} NH ₄ F ¹⁴⁶	

Table 18. Deprotection of 1° Silyl Ethers in the Presence of 3° Silyl Ethers

Deprotection of:	In the Presence of:					
	3° TMS	3° TES	3° DEIPS	3° TIPS	3° TBS	3° TBDPS
1° TMS	PPTS ¹⁴					
1° TES		HF · pyr ¹³⁸				
1° DEIPS						
1° TIPS					TBAF ¹⁶⁰	
1° TBS					CSA ^{113,158}	
					NH ₄ F ¹⁴⁷	
					H ₂ SiF ₆ ⁵⁷	
					SiF ₄ /CH ₂ Cl ₂ ⁷³	
					MeOH/CCl ₄ /))) ³⁶	
1° TBDPS						

Table 19. Deprotection of 2° Silyl Ethers in the Presence of 1° Silyl Ethers

Deprotection of:	In the Presence of:					
	1° TMS	1° TES	1° DEIPS	1° TIPS	1° TBS	1° TBDPS
2° TMS	Amberlyst 15 ¹¹⁵				HCl ¹⁷⁵ K ₂ CO ₃ /MeOH ¹⁹⁵	HCl, ¹⁷⁶ TsOH ¹⁸¹ acetone, Me ₂ C(OMe) ₂ /CSA ¹⁸⁶ PhSeCl/K ₂ CO ₃ ¹⁹⁹ TBAF ¹⁹⁸ PPTS, ^{188,189} alumina ⁶⁹ HCl ^{34,173} HOAc ¹⁷⁸ Cl ₃ CCO ₂ H ¹⁷⁷ TsOH ¹⁸⁴ HF/MeCN ^{192,193} PhSeCl/K ₂ CO ₃ ¹⁹⁹ TBAF, ⁴⁸ DDQ/MeCN/H ₂ O ⁶⁵ SiF ₄ /CH ₂ Cl ₂ ⁷³
2° TES				TFA ⁸⁹ H ₂ SiF ₆ / HF/H ₂ O ³³⁹	DDQ/MeCN/H ₂ O ⁶⁵ HCl · pyr ³⁴²	
2° DEIPS						
2° TIPS						
2° TBS				H ₂ SiF ₆ /HF/ H ₂ O ^{57,194}	DIBAL-H ³³⁸	HCl ^{32,174} HOAc/H ₂ O/THF ^{179,180} TsOH ^{182,183} PPTS, ^{49,187} BF ₃ · OEt ₂ ¹⁹⁰ TMS-OTf ¹⁹¹ HF/MeCN ⁸⁸ TBAF ⁴⁷ SiF ₄ /CH ₂ Cl ₂ ⁷³
2° TBDPS					NaH/HMPA ¹⁵³	

Table 20. Deprotection of 2° Silyl Ethers in the Presence of Another 2° Silyl Ether

Deprotection of:	In the Presence of:					
	2° TMS	2° TES	2° DEIPS	2° TIPS	2° TBS	2° TBDPS
2° TMS	TBAF ²⁵⁷			citric acid/MeOH ²³⁵ TBAF/HOAc ^{261,292} FeCl ₃ ²⁶⁹	HCl, ²⁰⁶ TsOH, ^{226,229} HOAc/THF/H ₂ O ²¹¹ PPTS, ¹³⁰ HF · NEt ₃ ²⁴⁹ citric acid/MeOH ^{233,234} Cu(NO ₃) ₂ , ⁷⁰ Ce(NO ₃) ₃ ⁷⁰ DDQ/wet EtOAc ⁶⁷	TBAF ²⁶⁷ Cu(NO ₃) ₂ ⁷⁰ Ce(NO ₃) ₃ ⁷⁰
2° TES		HOAc ²⁷³ TBAF ³⁴⁵	HOAc ³⁹	TFA ^{89,209,337} HOAc ^{220–222} PPTS ⁹⁶ MoO ₅ · HMPA ^{271,272} WO ₅ · HMPA ^{271,272}	HOAc/THF/ H ₂ O ^{213–216,218} TFA ^{89,209,337} PPTS ^{96,236,237} HF/MeCN ²⁴⁴ HF · pyr ^{7,217,244,245} DDQ/MeCN/H ₂ O ⁶⁵ MoO ₅ · HMPA ^{271,272} WO ₅ · HMPA ^{271,272} HOAc/THF/H ₂ O ³⁹ HOAc/KF · HF/THF/ H ₂ O ²⁴⁸ H ₂ /Pd(OH) ₂ ⁶⁴ TBAF ²⁶⁴	HOAc/THF/H ₂ O ²¹⁹ CSA ²³² TBAF ⁴⁷ SiF ₄ /CH ₂ Cl ₂ ⁷³ DDQ/MeCN/H ₂ O ⁶⁵ DDQ/MeCN/H ₂ O ⁶⁵ HF/MeCN ²³² HF · pyr ^{134,246}
2° DEIPS					HOAc/KF · HF/THF/ H ₂ O ²⁴⁸ H ₂ /Pd(OH) ₂ ⁶⁴ TBAF ²⁶⁴	H ₂ /Pd(OH) ₂ ⁶⁴
2° TIPS						
2° TBS	HCl ²⁰⁷			HCl ³² H ₂ SiF ₆ (aq) ⁵⁷ HOAc ^{221,222} HF/MeCN ⁸⁸ TBAF ^{265,292}	HCl ^{32,208} CSA, ²³⁰ TsOH ²²³ HF/MeCN ^{88,240–242} LiAlH ₄ ⁶⁰ KF · H ₂ O ²⁶⁸ TBAF ^{258–260,267}	TsOH ^{225,227,228} HCO ₂ H/THF/H ₂ O ²¹⁰ CSA, ²³¹ PPTS ^{238,239} HF/MeCN ²⁴⁷ TBAF ^{256,266} SiF ₄ /CH ₂ Cl ₂ ⁷³ Cu(NO ₃) ₂ , ⁷⁰ Ce(NO ₃) ₃ ⁷⁰ DDQ/MeCN/H ₂ O ⁶⁵
2° TBDPS						

In recent years, the assistance of neighboring groups in selectively delivering reagents for deprotection to silyl protecting groups has been reported. As this is a relatively recent observation, systematic studies of such neighboring group effects have yet to be conducted and will likely be an important area of future study.

Differences in electronic effects of the substituents on the silicon atom have a profound impact on the reactivity

of the silyl group and allow for their selective removal as well. Interestingly, with the exception of the phenyl substituted silyl groups, only a handful of examples^{37,38} of modifications of the electronic environment of the silicon atom have been investigated, partially due to the commercial unavailability of most of the necessary silylating reagents. This would, however, seem to be an important area that remains open to study.

Table 21. Deprotection of 2° Silyl Ethers in the Presence of 3° Silyl Ethers

Deprotection of:	In the Presence of:		3° DEIPS	3° TIPS	3° TBS	3° TBDPS
	3° TMS	3° TES				
2° TMS	TsOH ^{229,279}	HOAc ²¹¹ TsOH ²⁸⁰				
2° TES					HOAc ²⁷⁷ CSA ¹⁰	
2° DEIPS						
2° TIPS						
2° TBS				H ₂ SiF ₆ / <i>t</i> -BuOH/H ₂ O ⁵⁷	HOAc ²⁷⁸ CSA ⁶ TBAF ^{282,283}	
2° TBDPS						

Table 22. Deprotection of 3° Silyl Ethers in the Presence of 1° Silyl Ethers

Deprotection of:	In the Presence of:		1° DEIPS	1° TIPS	1° TBS	1° TBDPS
	1° TMS	1° TES				
3° TMS					ClCH ₂ CO ₂ H/MeOH ¹² SiO ₂ ²⁸⁵	
3° TES						
3° DEIPS						
3° TIPS						
3° TBS						LiAlH ₄ ^{6,284}
3° TBDPS						

Table 23. Deprotection of 3° Silyl Ethers in the Presence of 2° Silyl Ethers

Deprotection of:	In the Presence of:		2° DEIPS	2° TIPS	2° TBS	2° TBDPS
	2° TMS	2° TES				
3° TMS				TBAF/HOAc ²⁹²	HCl ²⁸⁷ LiAlH ₄ ²⁵⁴ TBAF ²⁹¹ FeCl ₃ ²⁹³ Et ₃ NHF ^{288,289}	HCl ¹⁴
3° TES						
3° DEIPS						
3° TIPS						
3° TBS					TBAF ²⁷⁷	
3° TBDPS						

Table 24. Deprotection of 3° Silyl Ethers in the Presence of 3° Silyl Ethers

Deprotection of:	In the Presence of:		3° DEIPS	3° TIPS	3° TBS	3° TBDPS
	3° TMS	3° TES				
3° TMS				1 % 1 M HCl(aq)/THF ²⁹⁴		
3° TES						
3° DEIPS						
3° TIPS						
3° TBS					CSA ²⁹⁵	
3° TBDPS						

Table 25. Deprotection of Phenolic Silyl Ethers in the Presence of Alkyl Silyl Ethers

Deprotection of:	In the Presence of: 1° TMS	1° TBS	2° TBS	3° TBS
ArOTMS ArOTBS	Dowex 1-X8 (OH ⁻ form) ²⁹⁹	TBAF ^{306,307} NaOH ³³ K ₂ CO ₃ /Kryptofix 222/ MeCN ²⁹⁸ TBAF ^{302,310} KF/18-crown-6 ³¹⁰ KF/Al ₂ O ₃ /MeCN ³⁰⁹ NaOH ³³	TBAF ³⁰⁸ K ₂ CO ₃ /Kryptofix 222/ MeCN ²⁹⁸ TBAF ^{302,308}	10% HCl ₆ (aq) ³⁰¹
ArOTES ArOTBDPS		NaOH ³³		

Table 26. Deprotection of Alkyl Silyl Ethers in the Presence of Phenolic Silyl Ethers

Deprotection of:	In the Presence of: ArOTMS	ArOTBS	ArOTIPS	ArOTBDPS
1° TMS	Dowex CCR-2 (H ⁺ form) ²⁹⁹	HCl ³³	HCl ³³ Amberlite IR-120 (H ⁺ form) ³⁰⁰ Amberlite IR-120 (H ⁺ form) ³⁰⁰	HCl ³³
2° TMS 1° TBS		HCl ^{33,304} TFA ²⁹⁶ PPTS ²⁹⁸ HF/MeCN ^{302,303,305} BF ₃ · OEt ₂ ^{298,340} SiF ₄ /CH ₂ Cl ₂ ⁷³ MeOH/CCl ₄ /))) ³⁶ TFA ²⁹⁷ BF ₃ · OEt ₂ ^{298,340} HF/MeCN ³⁰² PPTS ²⁹⁸ SiF ₄ /CH ₂ Cl ₂ ⁷³	Amberlite IR-120 (H ⁺ form) ³⁰⁰ HCl ³³ Amberlite IR-120 (H ⁺ form) ³⁰⁰	HCl ³³
2° TBS				
1° TBDPS 1° TIPS			HCl ³³ HCl ³³	HCl ³³ HCl ³³

Table 27. Deprotection of Silylene- and Disiloxane-Protected Diols in the Presence of 2° Alkyl Silyl Ethers

Deprotection of:	In the Presence of: 2° TMS	2° TES	2° DEIPS	2° TIPS	2° TBS	2° TBDPS
DTBS silylene					HF · pyr ^{319–322} KF/MeOH ^{268,323,324}	
TIPDS siloxane						HF/MeCN ³²⁵

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