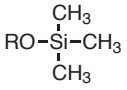
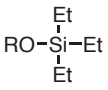
General Reference:

Greene, T. W.; Wuts, P. G. M. *Protective Groups In Organic Synthesis, 4th ed.* John Wiley & Sons: New Jersey, **2007**.

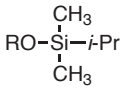
Important Silyl Ether Protective Groups:



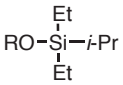
Trimethylsilyl (TMS)



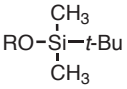
Triethylsilyl (TES)



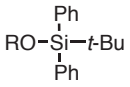
Isopropyldimethylsilyl (IPDMS)



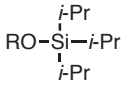
Diethylisopropylsilyl (DEIPS)



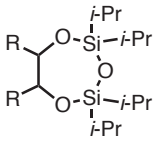
t-Butyldimethylsilyl (TBS)



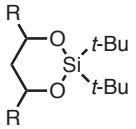
t-Butyldiphenylsilyl (TBDPS)



Triisopropylsilyl (TIPS)

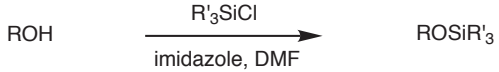


Tetraisopropyldisiloxanylidene (TIPDS)

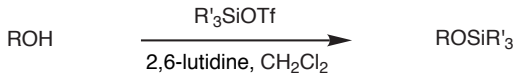


Di-*t*-butylsilylene (DTBS)

General methods for the formation of silyl ethers:



Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.



Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

- In general, the stability of silyl ethers towards acidic media increases as indicated:

  TMS (1) < TES (64) < TBS (20,000) < TIPS (700,000) < TBDPS (5,000,000)

- In general, stability towards basic media increases in the following order:

  TMS (1) < TES (10-100) < TBS ~ TBDPS (20,000) < TIPS (100,000)

Greene, T. W.; Wuts, P. G. M. *Protective Groups In Organic Synthesis, 3rd ed.* John Wiley & Sons: New York, **1991**.

Silyl Ether	Half Life (5% NaOH–95% MeOH)	Half Life (1% HCl–MeOH, 25 °C)
n-C_6H_{13}OTMS	≤1 min	≤1 min
n-C_6H_{13}OSi-*i*-Bu$(CH_3)_2$	2.5 min	≤1 min
n-C_6H_{13}OTBS	Stable for 24 h	≤1 min
n-$C_6H_{13}OSiCH_3Ph_2$	≤1 min	14 min
n-C_6H_{13}OTIPS	Stable for 24 h	55 min
n-C_6H_{13}OTBDPS	Stable for 24 h	225 min

Davies, J. S.; Higginbotham, L. C. L.; Tremeer, E. J.; Brown, C.; Treadgold, *J. Chem. Soc., Perkin Trans . 1* **1992**, 3043.

- A study comparing alkoxysilyl vs. trialkylsilyl groups has also been done:

Silyl Ether	Half Life $Bu_4N^+F^-$ (0.06 M, 6 equiv)	Half Life $HClO_4$ (0.01 M)
n-$C_{12}H_{25}$OTBS	140 h	1.4 h
n-$C_{12}H_{25}$OTBDPS	375 h	> 200 h
n-$C_{12}H_{25}OSiPh_2$(O*i*-Pr)	<0.03 h	0.7 h
n-$C_{12}H_{25}OSiPh_2$(O*t*-Bu)	5.8 h	17.5 h
n-$C_{12}H_{25}OSiPh$(*t*-Bu)(OCH_3)	22 h	200h

Gillard, J.W.; Fortin, R.; Morton, H. E.; Yoakim, C.; Quesnell, C. A.; Daignault, S.; Guindon, Y. *J. Org. Chem.* **1988**, *53*, 2602.

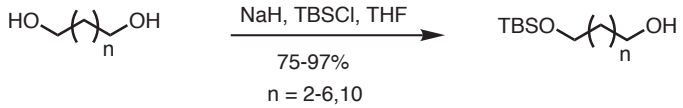
- Silyl groups are typically deprotected with a source of fluoride ion. The Si–F bond stength is about 30 kcal/mol stronger than the Si–O bond.

  Fluoride sources:

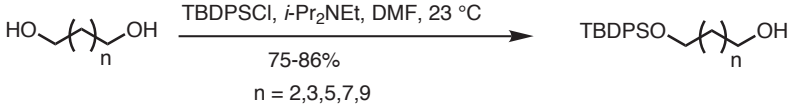
  Tetrabutylammonium fluoride, $Bu_4N^+F^-$ (TBAF)
  Pyridine•$(HF)_x$
  Triethylamine trihydrofluoride, Et_3N•3HF
  Hydrofluoric acid
  Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)
  Ammonium fluoride, $H_4N^+F^-$

P. Hogan

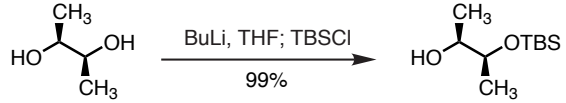
- Monosilylation of symmetrical diols is possible, and useful.



McDougal, P.G.; Rico, J.G.; Oh, Y.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.

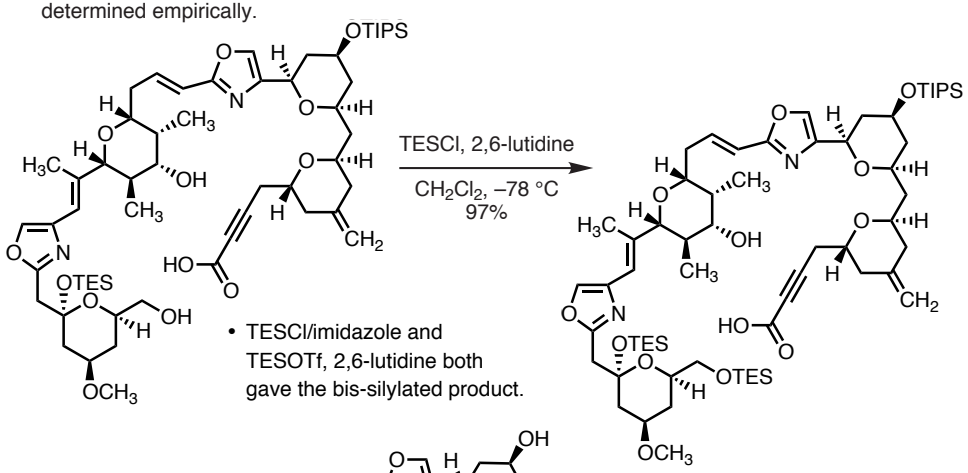


Hu, L.; Liu, B.; Yu, C. *Tetrahedron Lett.* **2000**, *41*, 4281.

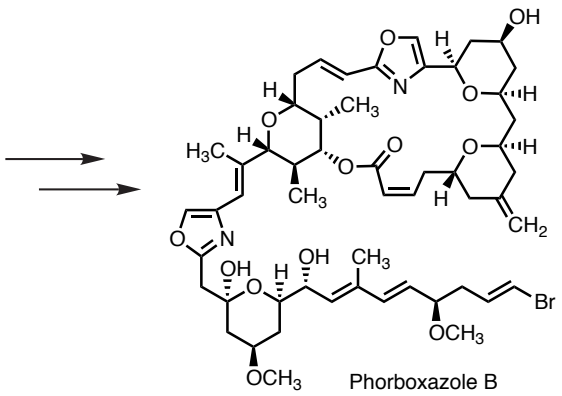


Roush, W. R.; Gillis, H. R.; Essenfeld, A. P. *J. Org. Chem.* **1984**, *49*, 4674.

- Selective protection of alcohols is of great importance in synthesis. Conditions often must be determined empirically.



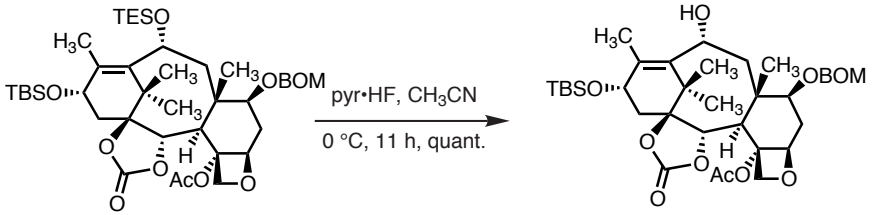
- TESCl/imidazole and TESOTf, 2,6-lutidine both gave the bis-silylated product.

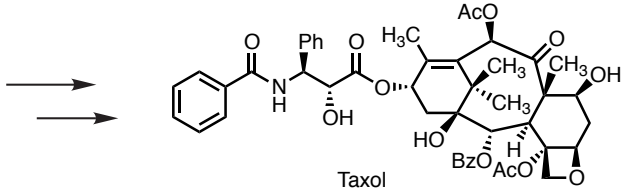


Phorboxazole B

Evans, D. A.; Fitch, D. M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2536.

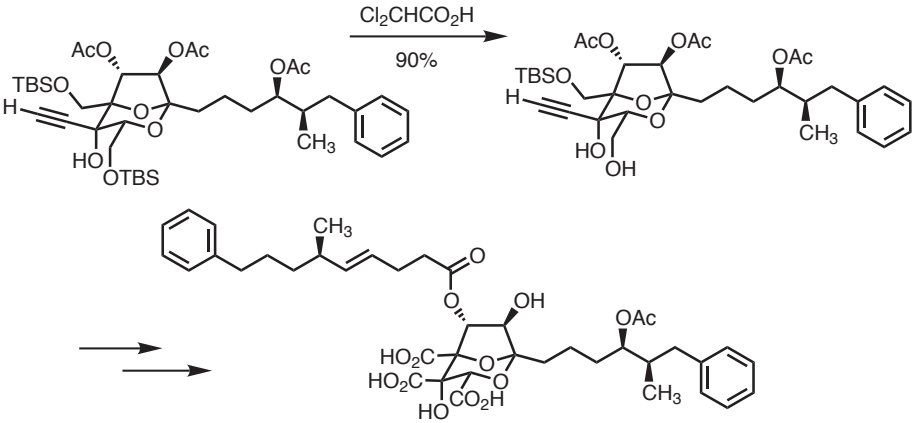
- Selective deprotection of silyl ethers is also important, and is also subject to empirical determination.





Taxol

Holton, R. A., et al. *J. Am. Chem. Soc.*, **1994**, *116*, 1599.



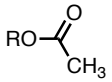
Zaragozic acid

Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106.

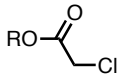
- Selective deprotections in organic synthesis have been reviewed: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1065.

P. Hogan

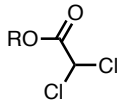
Esters and Carbonates



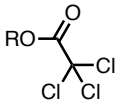
Acetate (Ac)



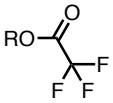
Chloroacetate



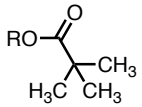
Dichloroacetate



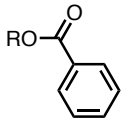
Trichloroacetate



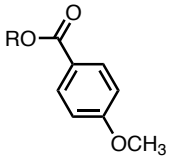
Trifluoroacetate (TFA)



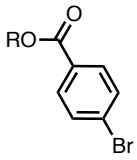
Pivaloate (Piv)



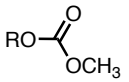
Benzoate (Bz)



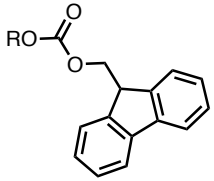
p-Methoxybenzoate



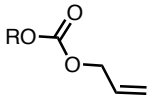
p-Bromobenzoate



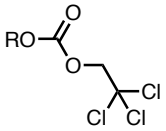
Methyl Carbonate



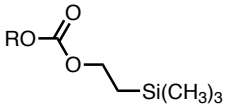
9-(Fluorenylmethyl) Carbonate (Fmoc)



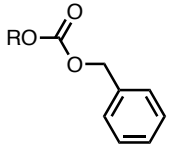
Allyl Carbonate (Alloc)



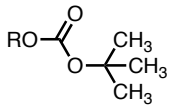
2,2,2-Trichloroethyl Carbonate (Troc)



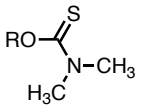
2-(Trimethylsilyl)ethyl Carbonate (Teoc)



Benzyl Carbonate (Cbz)

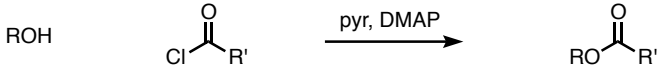


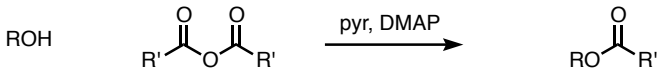
t-Butyl Carbonate (Boc)



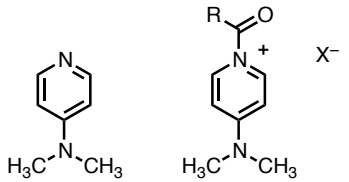
Dimethylthiocarbamate (DMTC)

General methods used to form esters and carbonates:





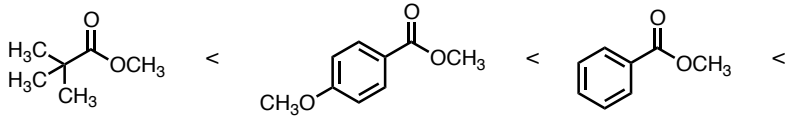
DMAP = 4-Dimethylaminopyridine:

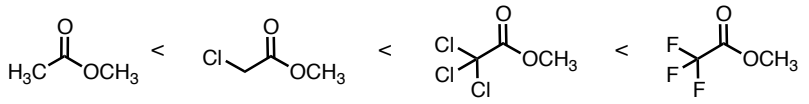


• Proposed intermediate

DMAP is used to accelerate reactions between nucleophiles and activated esters. Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

• In general, the susceptibility of esters to base-catalyzed hydrolysis increases with the acidity of the product acid.





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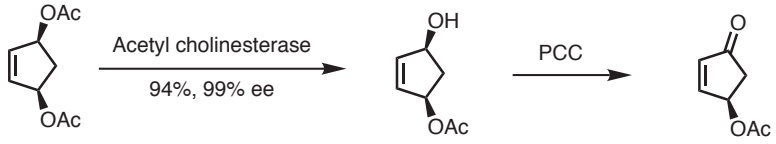
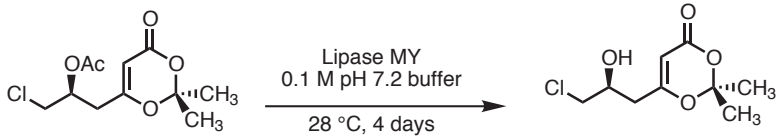
Acetate Esters:

- Several methods for forming and cleaving acetate esters have been developed. Lipases can often be used for the enantioselective hydrolysis of acetate esters. The enantioselective hydrolysis of meso diesters is an important synthetic transformation and racemic esters have been kinetically resolved using lipases.



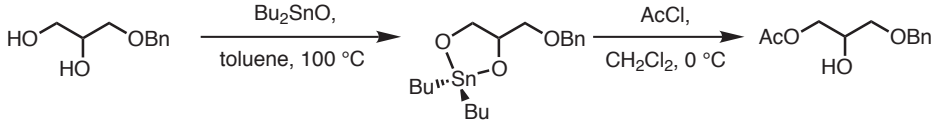
Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255.

- Lipases can also be effective for deprotection under very mild conditions, as in the case shown below, where conventional methods were unsuccessful.



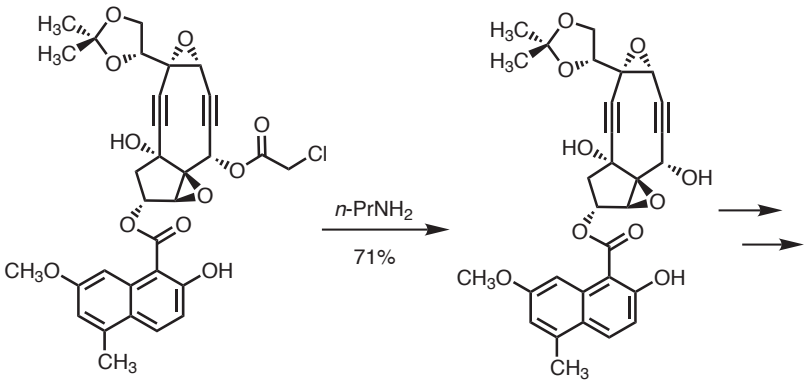
Sakaki, J.; Sakoda, H.; Sugita, Y.; Sato, M.; Kaneto, C. *Tetrahedron: Asymmetry*, **1991**, *2*, 343.

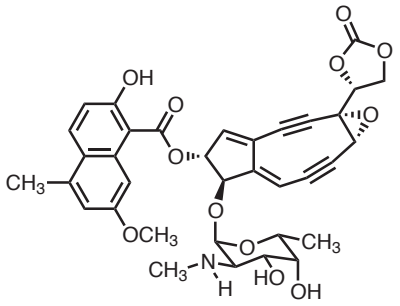
- A potentially general method for selectively acylating the primary hydroxyl group of a 1,2-diol makes use of stannylene acetals as intermediates:



Review: Hanessian, S.; David, S. *Tetrahedron* **1985**, *41*, 643.

- Good selectivity can often be achieved in the selective deprotection of different esters.





Neocarzinostatin Chromophore

Myers, A. G.; Liang, J.; Hammond, M.; Wu, Y.; Kuo, E. Y. *J. Am. Chem. Soc.* **1998**, *120*, 5319.

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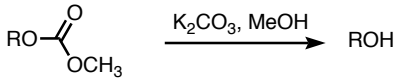
• When one protective group is stable to conditions that cleave another and the converse is also true, these groups are often said to bear an **orthogonal** relationship. This concept is illustrated well in the context of carbonates (and carbamates).

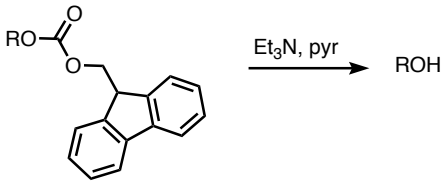
Summary of methods for deprotecting carbonates:

Methyl Carbonate:

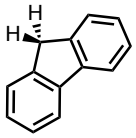


Meyers, A. I.; Tomioka, K.; Roland, D. M.; Comins, D. *Tetrahedron Lett.* **1978**, *19*, 1375.

9-Fluorenylmethyl Carbonate:

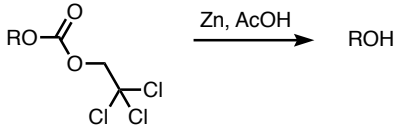


• The pKa of fluorene is ≈ 10.3

fluorene = 

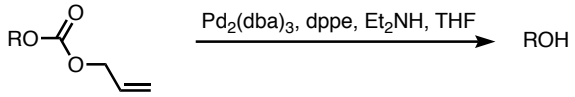
Chattopadhyaya, J. B.; Gioeli, C. *J. Chem. Soc., Chem. Comm.* **1982**, 672.

Trichloroethyl Carbonate:



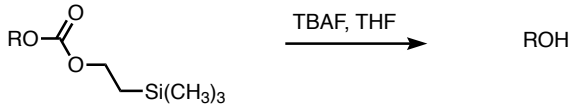
Windholz, T. B.; Johnston, D. B. R. *Tetrahedron Lett.* **1988**, *29*, 2227.

Allyl Carbonate:



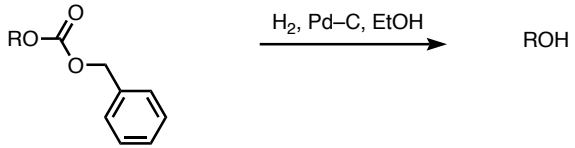
Genet, J.P.; Blart E.; Savignac, M.; Lemeune, S.; Lemaire-Audoire, S.; Bernard, J. *Synlett* **1993**, 680.

2-(Trimethylsilyl)ethyl Carbonate:



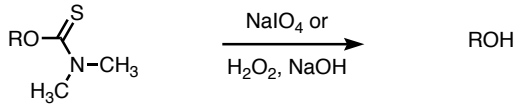
Gioeli, C.; Balgobin, S.; Josephson, S.; Chattopadhyaya, J. B. *Tetrahedron Lett.* **1981**, *22*, 969.

Benzyl Carbonate:



Daubert, B. F.; King, G. C. *J. Am. Chem. Soc.* **1939**, *61*, 3328.

Dimethylthiocarbamate (DMTC):



• The DMTC group is stable to a variety of reagents and reaction conditions (PCC oxidations, Swern oxidations, chromium reagents, Grignard and alkyllithium reagents, phosphorous ylides, LAH, HF, TBAF, and borane).

• The protecting group is introduced using thiocarbonyldiimidazole followed by treatment with dimethylamine, or by reaction with commercially available $ClCSN(CH_3)_2$.

Barma, D. K.; Bandyopadhyay, A.; Capdevilla, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4755.

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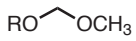
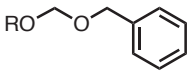
Acetals as Protective Groups:



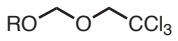
Methoxymethyl Ether

(MOM)

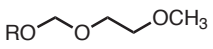


Benzyloxymethyl Ether

(BOM)

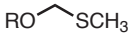


2,2,2-Trichloroethoxymethyl Ether



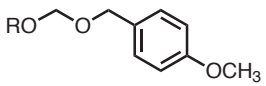
2-Methoxyethoxymethyl Ether

(MEM)



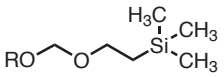
Methylthiomethyl Ether

(MTM)



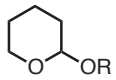
p-Methoxybenzyloxymethyl Ether

(PMBM)



2-(Trimethylsilyl)ethoxymethyl Ether

(SEM)



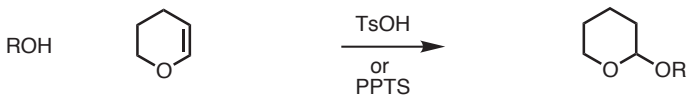
Tetrahydropyranyl Ether

(THP)

General methods for forming acyclic, mixed acetals:

Base-solvent combinations are often diisopropylethylamine-CH_2Cl_2, NaH-THF, or NaH-DMF. Sometimes a source of iodide ion is added to enhance the reactivity of the alkylating reagent. Typical sources include $Bu_4N^+I^-$, LiI, or NaI.

General methods for introducing 2-tetrahydropyranyl ethers:

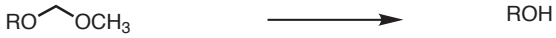


PPTS = Pyridinium *p*-toluenesulfonate

Grieco, P. A.; Yoshikoshi, A.; Miyashita, M. *J. Org. Chem.* **1977**, *42*, 3772, and references cited therein.

Cleavage of acetal protective groups:

Methoxymethyl Ethers:

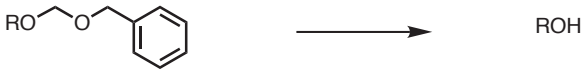


1. Conc. HCl, MeOH. Weinreb, S.; Auerbach, J. *J. Chem. Soc., Chem. Comm.* **1974**, 889.

2. Bromocatechol borane. This reagent cleaves a number of protective groups in approximately the following order: MOMOR ≈ MEMOR > *t*-BuO_2CNHR > BnO_2CNHR ≈ *t*-BuOR > BnOR > allylOR > *t*-BuO_2CR ≈ 2° alkylOR > BnO_2CR > 1° alkylOR >> alkylO_2CR. Boeckman Jr., R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.

3. $LiBF_4$, CH_3CN, H_2O. Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635.

Benzyloxymethyl Ethers:

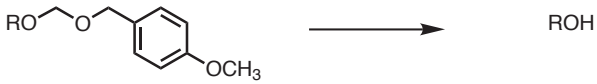


1. Na, NH_3. Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260.

2. H_2, Pd–C. D. Tanner, D.; Somfai, P. *Tetrahedron* **1987**, *43*, 4395.

3. Dowex 50W–X8, acidic ion exchange resin. Roush, W. R.; Michaelidies, M. R.; Tai, D. F.; Chong, W. K. M. *J. Am. Chem. Soc.* **1987**, *109*, 7575.

4-Methoxybenzyloxymethyl Ether:



1. DDQ, H_2O. Kozikowski, A. P.; Wu, J.-P. *Tetrahedron Lett.* **1987**, *28*, 5125.

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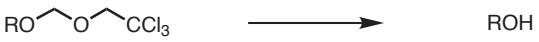
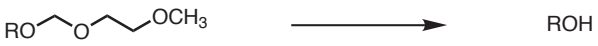
2,2,2-Trichloroethoxymethyl Ether:



1. Zn–Cu or Zn–Ag, MeOH. Jacobson, R. M.; Clader, J. W. *Synth. Commun*. **1979**, *9*, 57.

2. 6% Na(Hg), MeOH, THF. Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

2-Methoxyethoxymethyl Ether:

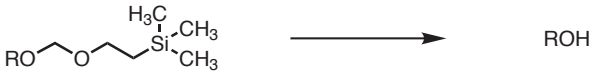


1. $ZnBr_2$, CH_2Cl_2. Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

2. Bromocatechol borane. Refer to the section on MOM ethers.

3. PPTS, *t*-BuOH, heat. Monti, H.; Leandri, G.; Klos-Ringuet, M.; Corriol, C. *Synth. Comm.* **1983**, *13*, 1021.

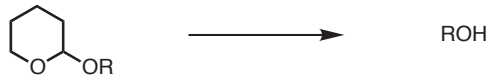
2-(Trimethylsilyl)ethoxymethyl Ether:



1. *n*-$Bu_4N^+F^-$, THF. Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.

2. TFA, CH_2Cl_2. Jansson, K.; Frejd, J.; Kihlberg, J.; Magnusson, G. *Tetrahedron Lett.* **1988**, *29*, 361.

Tetrahydropyranyl Ether:



1. PPTS, EtOH, 55 °C. Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.*, **1977**, *44*, 1438.

2. TsOH, MeOH, 25 °C. Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942.

Methylthiomethyl Ether:

1. $HgCl_2$, CH_3CN, H_2O. Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1976**, *17*, 3269.

2. $AgNO_3$, THF, H_2O, 2,6-lutidine. Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1976**, *17*, 3269.

3. $MgBr_2$, *n*-BuSH, Et_2O. Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *Synlett*, **1992**, 183.

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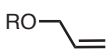
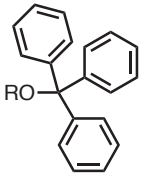
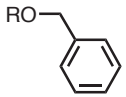
Ethers as Protective Groups:



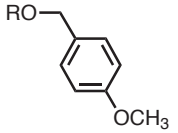
Allyl Ether



Trityl Ether



Benzyl Ether



p-Methoxybenzyl Ether

Allyl ether formation:

1. NaH, allyl bromide, benzene. Corey, E. J.; Suggs, W. J.; *J. Org. Chem.* **1973**, *38*, 3224.

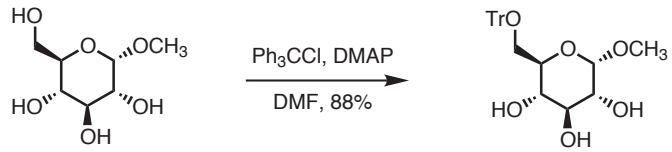
2. CH_2=$CHCH_2OC(=NH)CCl_3$, H^+. This procedure is useful for base-sensitive substrates. Wessel, H.-P.; Iverson, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.

Allyl ether cleavage:

1. The use of allyl ether protective groups in synthesis has been reviewed: Guibe, F. *Tetrahedron* **1998**, *54*, 2967.

2. $Pd(Ph_3P)_4$, RSO_2Na, CH_2Cl_2. Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932.

Formation of trityl ethers:



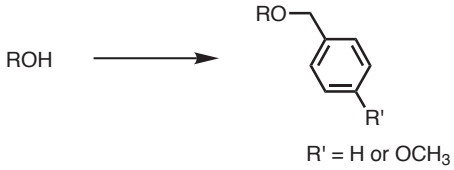
Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *19*, 95. In general, selective protection of primary alcohols can be achieved.

Cleavage of trityl ethers:

1. Amberlyst 15-H, MeOH. Malanga, C. *Chem. Ind.* **1987**, 856.

2. CF_3CO_2H, *t*-BuOH. MacCross, M.; Cameron, D. J. *Carbohydr. Res.* **1978**, *60*, 206.

Formation of benzyl ethers:



R' = H or OCH_3

1. NaH, benzyl bromide, THF. Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, *17*, 3535.

2. *p*-$CH_3OC_6H_4CH_2OC(=NH)CCl_3$, H^+. These are useful conditions for base-sensitive substrates. Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139. Similar conditions have been developed for benzyl ethers: White, J. D.; Reddy, G. N.; Spessard, G. O. *J. Am. Chem. Soc.* **1988**, *110*, 1624.

3. *p*-$CH_3OC_6H_4CH_2Cl$, NaH, THF. Marco, J. L.; Hueso-Rodriguez, J. A. *Tetrahedron Lett.* **1988**, *29*, 2459.

Cleavage of benzyl ethers:

1. H_2/ Pd-C, EtOH. Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746. Ammonium formate is often used as a source of H_2: Bieg, T.; Szeja, W. *Synthesis* **1985**, 76.

Cleavage of 4-methoxybenzyl ethers:

1. DDQ, CH_2Cl_2. Benzyl ethers are stable to these conditions. Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y. Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

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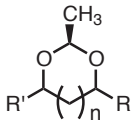
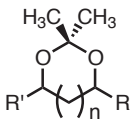
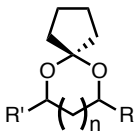
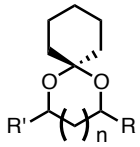
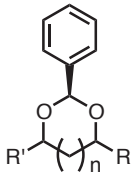
Protection of 1,2- and 1,3- Diols:

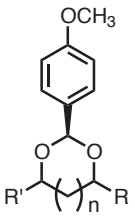

Ethylidene Acetal

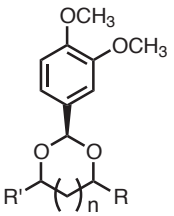

Acetonide

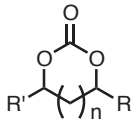

Cyclopentylidene Ketal


Cyclohexylidene Ketal


Benzylidene Acetal

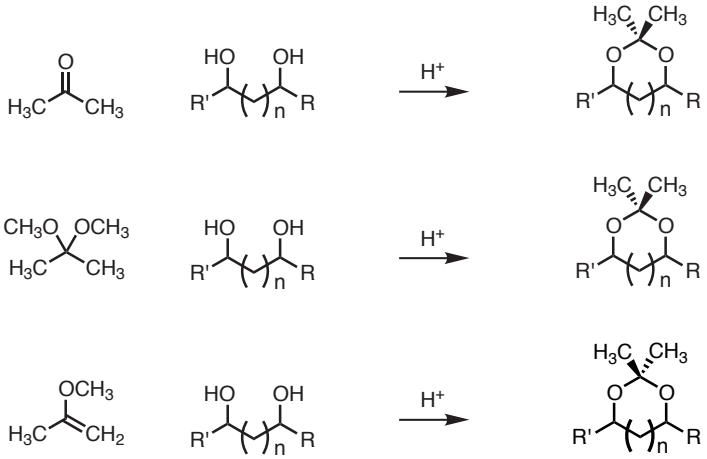

4-Methoxybenzylidene Acetal


3,4-Dimethoxybenzylidene Acetal

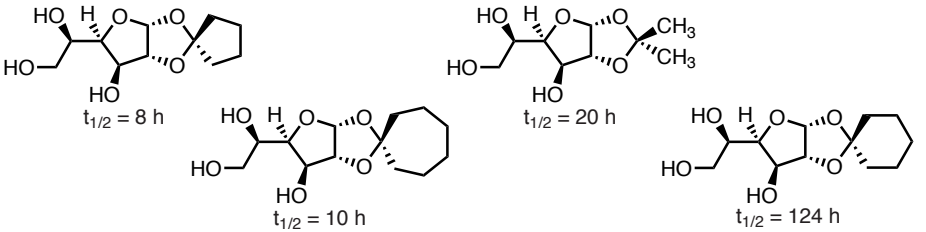

Cyclic Carbonate

- Generally, n = 0 or 1.

General methods used to form acetals and ketals (illustrated for acetonides):

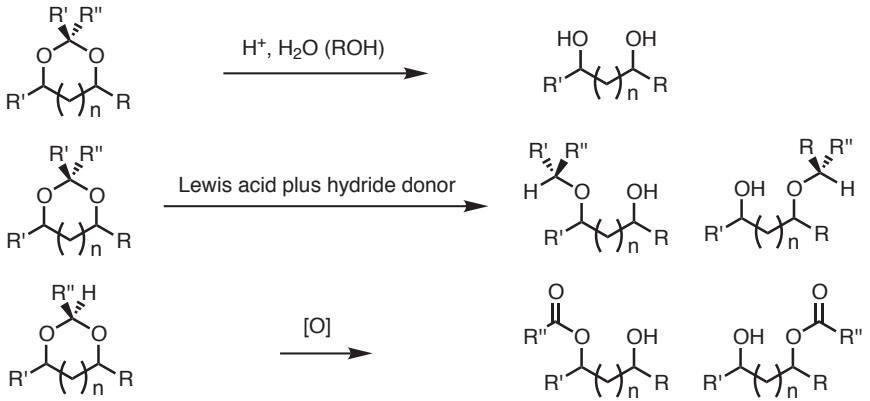


The relative rates of hydrolysis of 1,2-*O*-alkylidene-α-glucofuranoses have been studied.



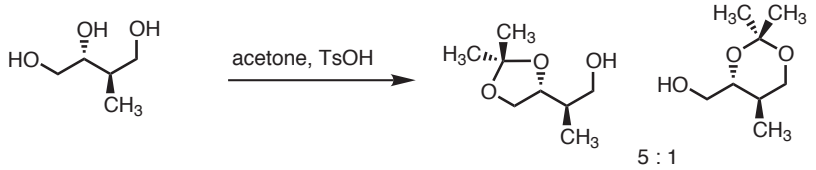
Van Heeswijk, W. A. R.; Goedhart, J. B.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1977**, *58*, 337.

General methods of cleavage:



Selective protection of polyols:

- In general, acetonide formation with 1,2-diols occurs in preference to 1,3-diols; benzylidene acetals display reversed selectivity. It is often possible to discriminate between 1,2- and 1,3-diols of a triol group.



Williams, D. R.; Sit, S.-Y. *J. Am. Chem. Soc.* **1984**, *106*, 2949.

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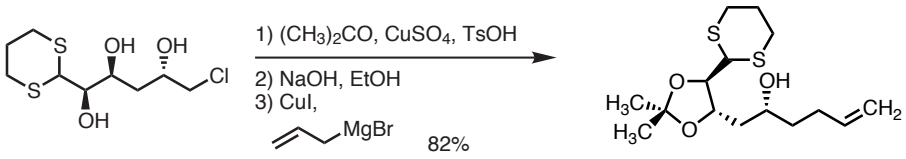
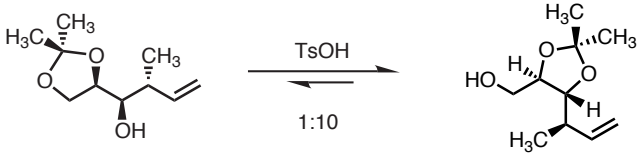
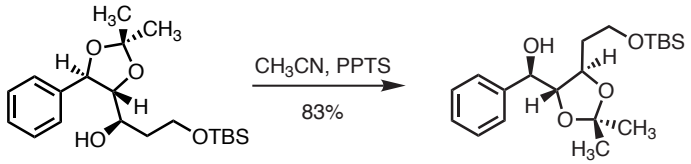


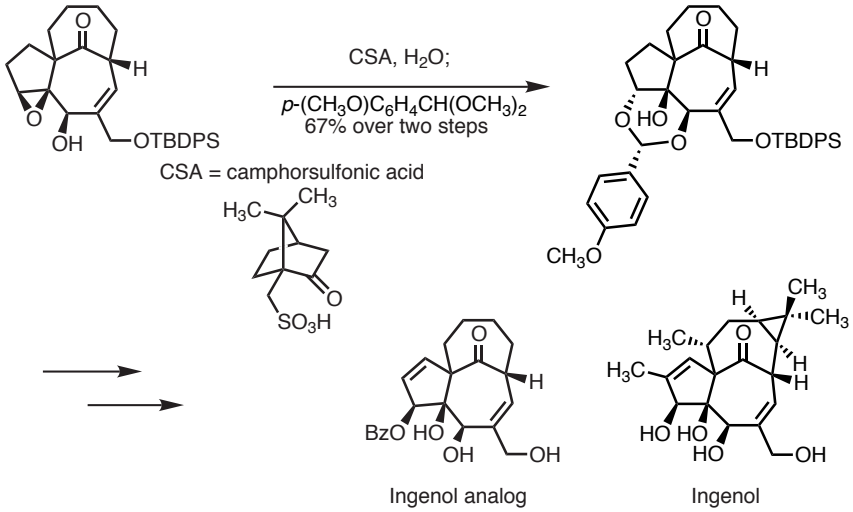
Mortlock, S. V.; Stacey, N. A.; Thomas, E. J. *J. Chem. Soc., Chem. Comm.* **1987**, 880.

- In the case of a 1,2,3-triol, careful analysis must be performed to accurately predict the site of acetonide formation. The more substituted acetonide will be favored in cases where the substituents on the resultant five-membered ring will be trans. If the substituents on the five-membered ring would be oriented cis, then the alternative, less substituted acetonide may be favored.

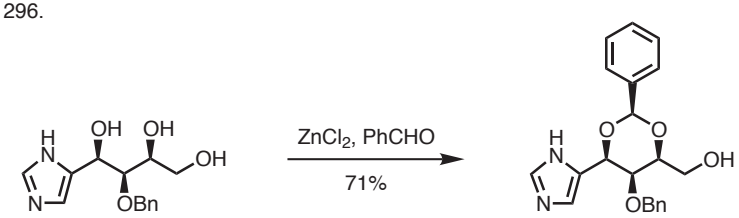




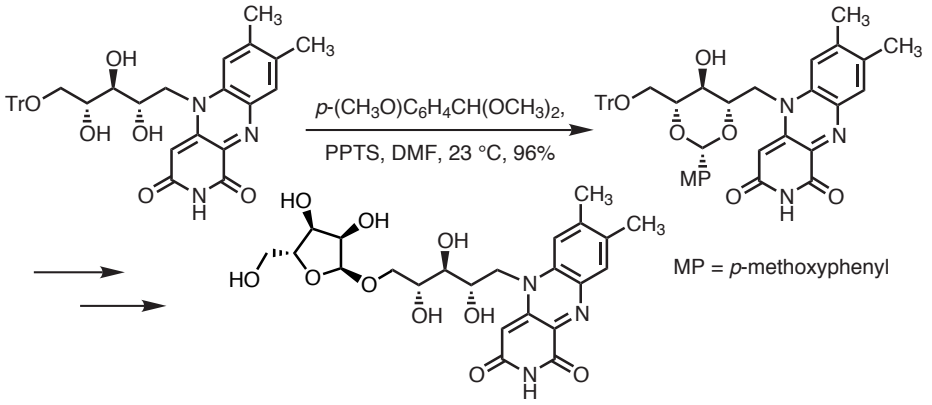
Roush, W. R.; Coe, J. W. *J. Org. Chem.* **1989**, *54*, 915. See also, Mukai, C.; Miyakawa, M.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 913.



Winkler, J. D.; Kim, S.; Harrison, S.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1999**, *121*, 296.



Frankowski, A.; Deredas, D.; Le Noen, D.; Tschamber, T.; Strieth, J. *Helv. Chim. Acta.* **1995**, *78*, 1837.



Lampteroflavin, a source of bioluminescence.
Isobe, M.; Takahashi, H.; Goto, T. *Tetrahedron Lett.* **1990**, *31*, 717.

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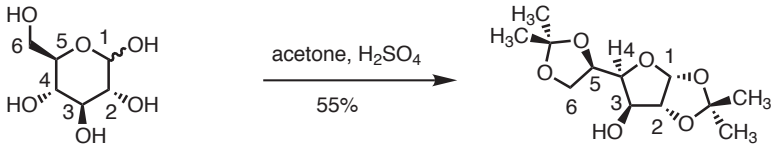
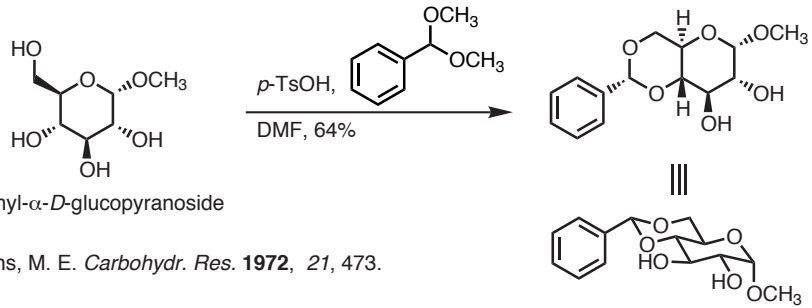
- Selective protection methods are central to carbohydrate chemistry. The most common protective groups in carbohydrate chemistry are acetonides, benzylidene acetals, and substituted benzylidene acetals. This subject has been reviewed: Calinaud, P.; Gelas, J. in *Preparative Carbohydrate Chemistry.* Hanessian, S. Ed. Marcel Dekker, Inc.: New York, **1997**.

Selective Protection: thermodynamic control



D-glucose 1,2:5,6-Di-O-isopropylidene-*D*-glucopyranose

Schmidt, O. T. *Methods Carbohydr. Chem.* **1963**, *2*, 318.

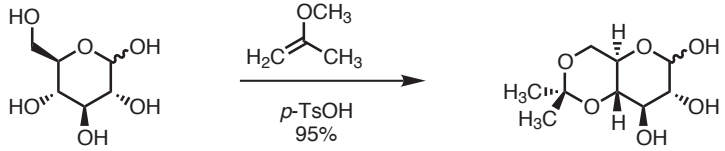


methyl-α-*D*-glucopyranoside methyl 4,6-benzylidene-α-*D*-glucopyranoside

Evans, M. E. *Carbohydr. Res.* **1972**, *21*, 473.

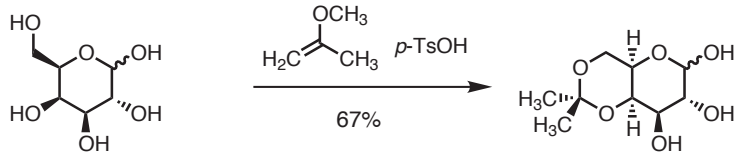
- Note the preference for 1,3-diol protection with the benzylidene acetal. The phenyl group is oriented exclusively as shown, in an equatorial orientation.

Selective Protection: kinetic control



D-glucose

Wolfrom, M. L.; Diwadkar, A. B.; Gelas, J.; Horton, D. *Carbohydr. Res.* **1974**, *35*, 87.

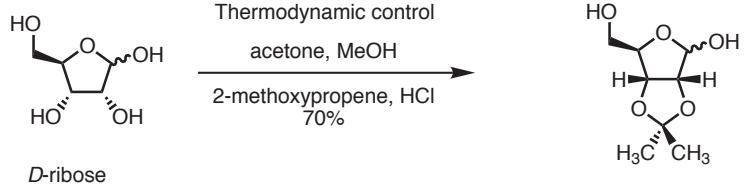


D-galactose

Gelas, J.; Horton, D. *Carbohydr. Res.* **1979**, *71*, 103.

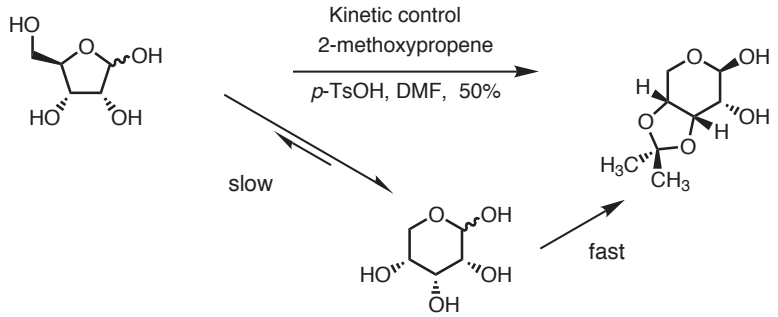
- Note that under kinetic control the most sterically accessible (primary) alcohol preferentially reacted.
- This reaction can be applied to many hexoses, including mannose, allose, and tallose

Kinetic vs. thermodynamic control with a pentose

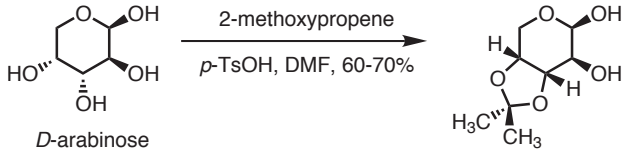


D-ribose

Leonard, N. J.; Carraway, K. L. *J. Heterocycl. Chem.* **1966**, *3*, 485.



The major isomer in solution is the pyranose form (≈ 80%). Under conditions that favor kinetic control, the least sterically encumbered alcohol in this form reacts preferentially. Isomerization is proposed to be slower than acetonide formation. This procedure also works well with arabinose:



D-arabinose

Gelas, J.; Horton, D. *Carbohydr. Res.* **1975**, *45*, 181.

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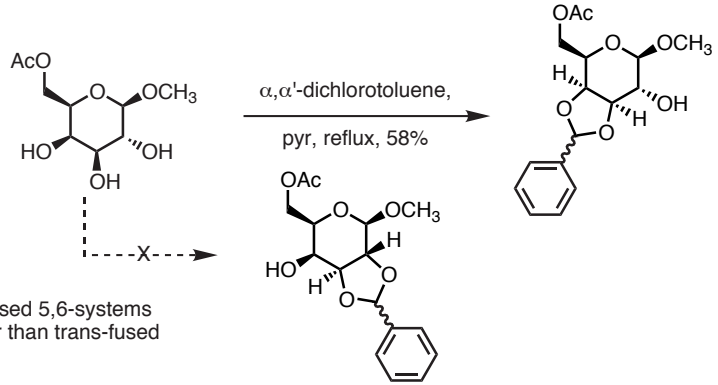
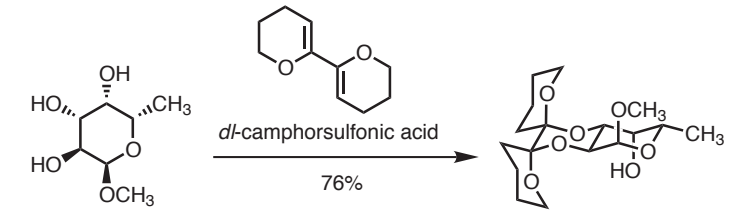
Protection of cis-vicinal diols:



- In general, cis-fused 5,6-systems are formed faster than trans-fused 5,6-systems.

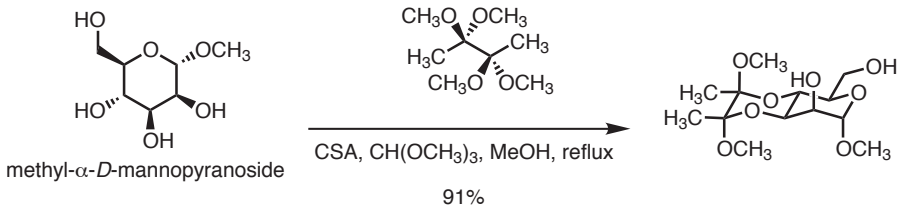
Garegg, P. J.; Maron, L.; Swahn, C. G. *Acta. Chem. Scand.* **1972**, *26*, 518.

Formation of dispiroacetals as a protective group for vicinal trans diequatorial diols:

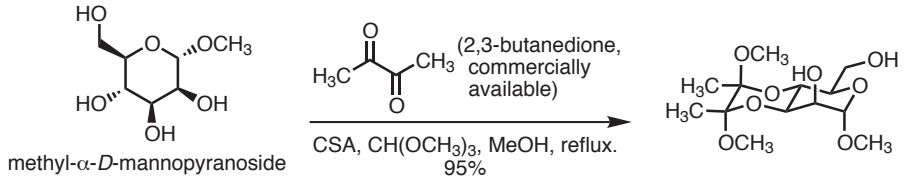


Ley, S. V.; Leslie, R.; Tiffin, P. D.; Woods, M. *Tetrahedron Lett.* **1992**, 4767.

A cheaper alternative has also been developed:



Montchamp, J.-L.; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 3897.

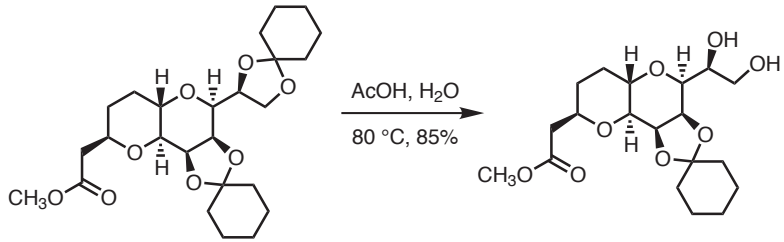


BF_3•OEt_2 is also an effective catalyst at 23 °C.

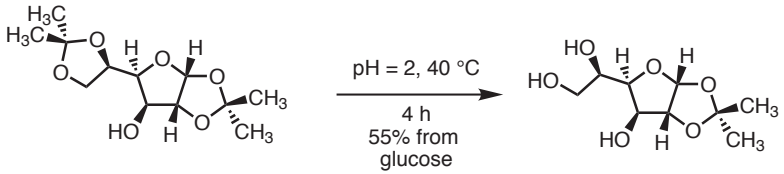
Hense, A.; Ley, S. V.; Osborn, H. M. I.; Owen, R. D.; Poisson, J.-F.; Warriner, S. L.; Wesson., K. E. *J. Chem. Soc., Perkins Trans. 1* **1997**, 2023.

Generalities concerning the selective removal of acetals and ketals:

- Hydrolysis of the less substituted dioxane or dioxolane ring occurs preferentially in substrates bearing two such groups.

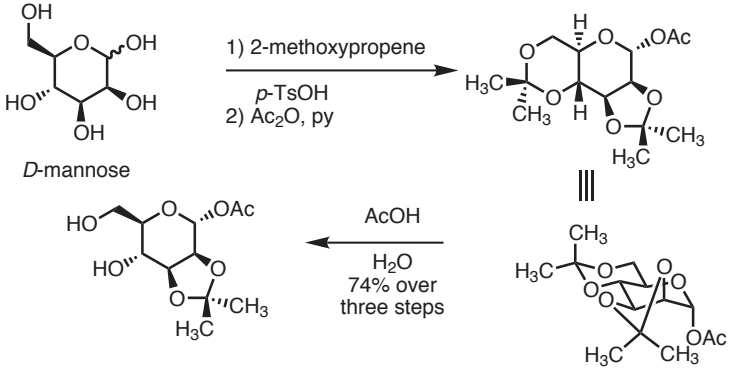


Kishi, Y.; Stamos, D.P. *Tetrahedron Lett.* **1996**, *37*, 8643



Schmidt, O. T. *Methods Carbohydr. Chem.* **1963**, *2*, 318.

- 2,2-disubstituted 1,3-dioxanes (6-membered rings) are generally hydrolyzed faster than the corresponding dioxolanes (5-membered rings).



Horton, D.; Gelas, J. *Carbohydr. Res.* **1978**, *45*, 181.

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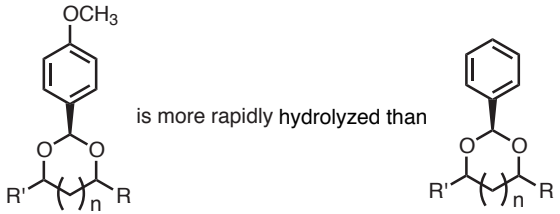
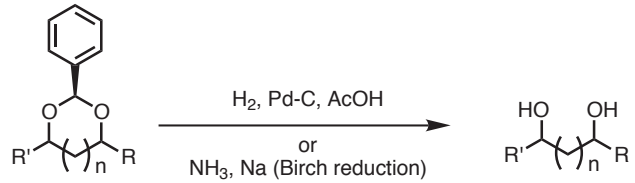
Special properties of benzylidene and substituted benzylidene acetals:

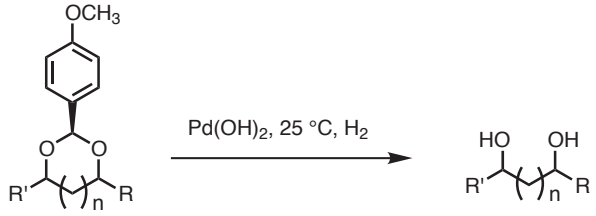
- In general, substitution of the ring of a benzylidene acetal with a *p*-methoxy substituent increases the rate of hydrolysis by about an order of magnitude.



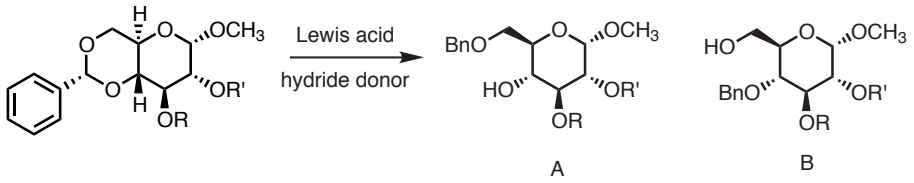
Smith, M.; Rammler, D. H.; Goldberg, I. H.; Khorana, H. G. *J. Am. Chem. Soc.* **1962**, *84*, 430.

- Benzylidene acetals can also be cleaved from the diol reductively.





- Methods have also been developed to cleave only one carbon-oxygen bond resulting in the formation of a benzyl ether. This reaction has been extensively studied in the context of carbohydrate chemistry.



R'	R'	Lewis acid	hydride donor	yield (regioisomer)
Ac	Ac	TFA	Et_3SiH	95% (A)
Bn	Bn	TFA	Et_3SiH	80% (A)
Bn	Bn	Bu_2BOTf	BH_3•THF	87% (B)
Bn	Bn	$AlCl_3$	BH_3•$N(CH_3)_3$	72% (A)
Bn	Bn	HCl, THF	$NaBH_3CN$	82% (A)

- The trifluoroacetic acid/triethylsilane reagent was ineffective with a galactose derivative, however the others appear to be general methods. Acetonides and other ketals and acetals can also be reduced, so care in synthetic planning must be exercised.

Trifluoroacetic acid, triethylsilane :
DeNinno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995**, *5*, 669.

Dibutylboron triflate, borane:
Chan, T. H.; Lu, J. *Tetrahedron Lett.*, **1998**, *39*, 355.

Aluminum trichloride, borane trimethylamine complex;
Garegg, P. J. *Pure. Appl. Chem.* **1984**, *56*, 845.

HCl, sodium cyanoborohydride:
Qiao, L.; Vederas, J. C. *J. Org. Chem.* **1993**, *58*, 3480.

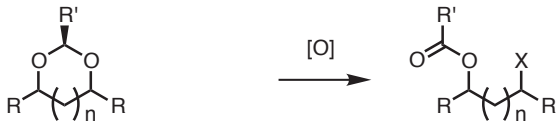
TfOH, sodium cyanoborohydride
Kiessling, L. L.; Pohl, N. L. *Tetrahedron Lett.* **1997**, *38*, 6985.

Diisobutyl aluminum hydride is also an effective reagent for regioselective reduction of benzylidene acetals. This reagent gives the more hindered ether.

Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593.

Oxidation of benzylidene and substituted benzylidene acetals:

- Acetals containing a methine group may be oxidized at that position resulting in the formation of hydroxy esters.



- This transformation can be effected under a variety of condtions, and some variants can be used to further functionalize a substrate.

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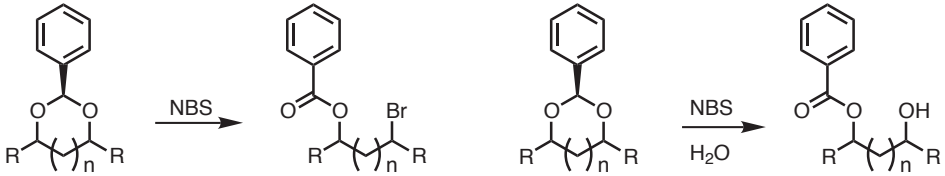
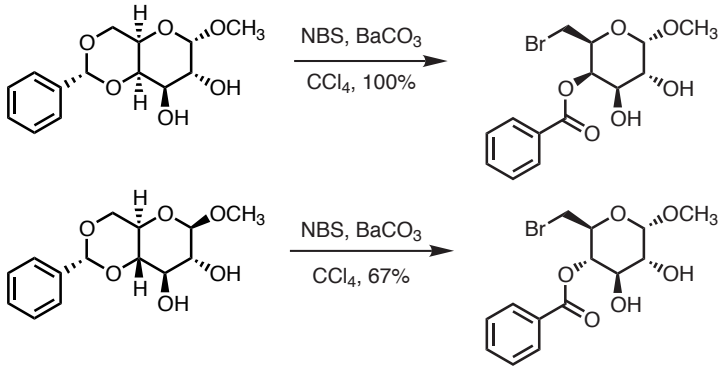
General Reactions:

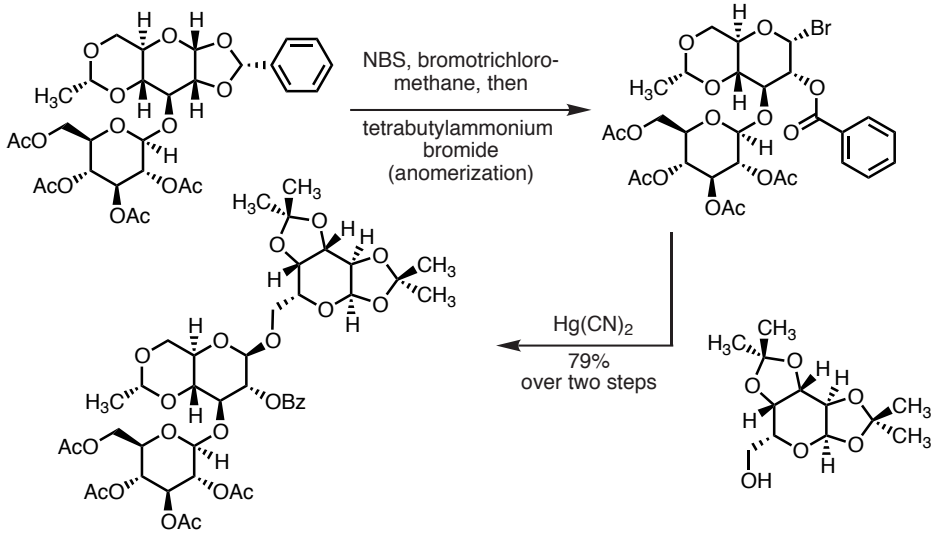


In the methyl 4,6-*O*-benzylidenehexopyranoside series, the oxidative formation of bromo benzoates is a general reaction:



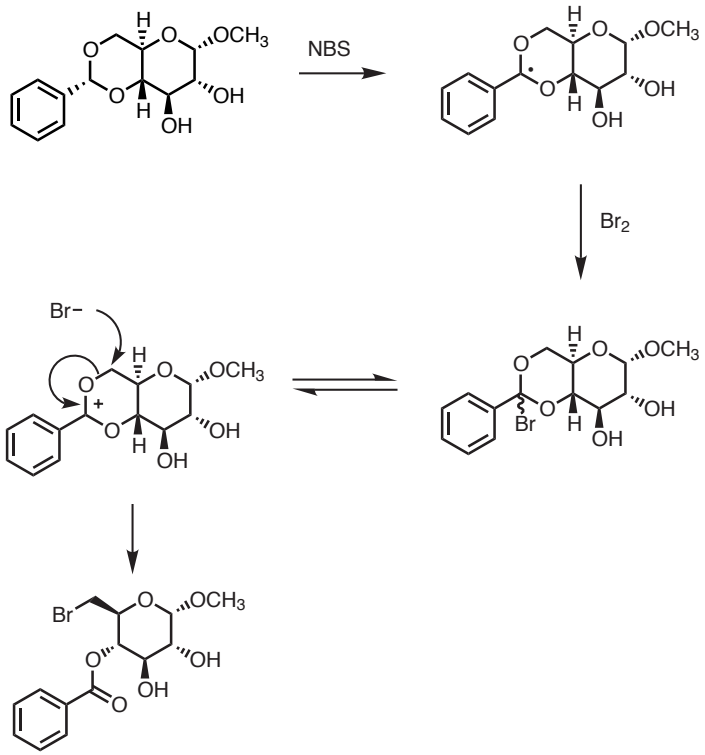
Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1035, 1045, and 1053.

- This reaction has also been used to generate glycosylating reagents

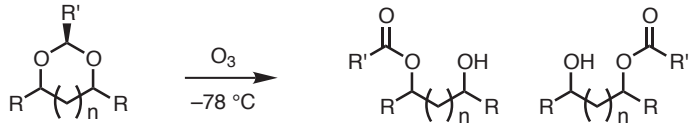


Collins, J. M.; Manro, A.; Opara-Mottah, E. C.; Ali, M. H.
J. Chem. Soc., Chem. Comm. **1988**, 272.

Proposed Mechanism:



- Ozonolysis also cleaves acetals to hydroxy esters efficiently. This reaction has been reviewed: Deslongchamps, P.; Atlani, P.; Frehel, D.; Malaval, A.; Moreau, C. *Can. J. Chem.* **1974**, *52*, 3651.



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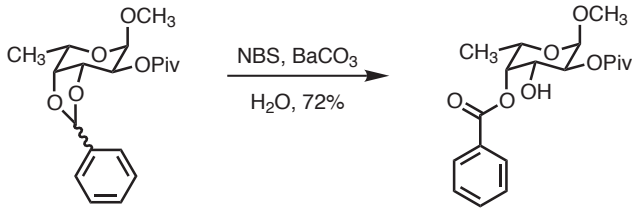
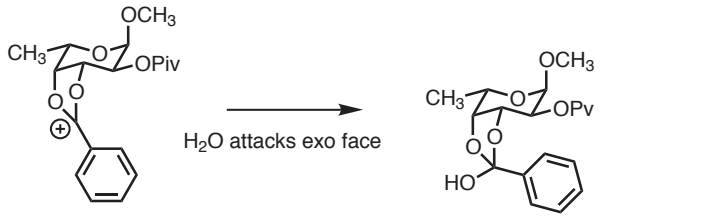
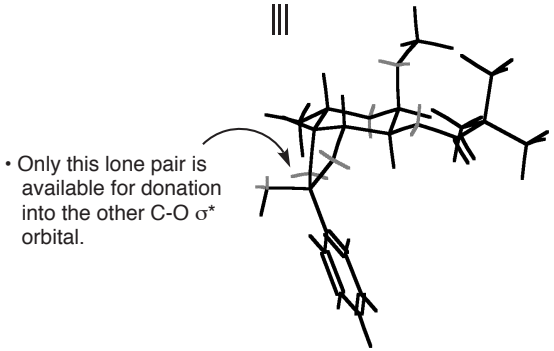
- Hydroxy benzoates are obtained in the presence of water.
- The axial benzoate is usually obtained.

Binkley, R. W.; Goewey, G. S.; Johnston, J. C. *J. Org. Chem.* **1984**, *49*, 992

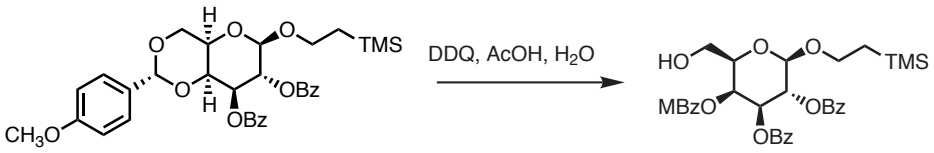




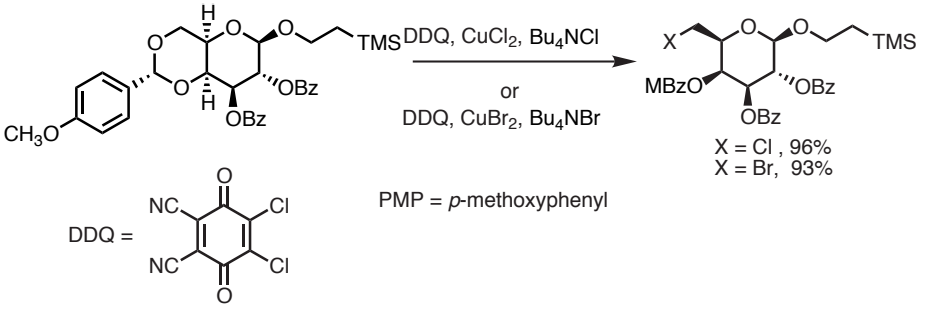


King, J. F.; Allbutt, A. D. *Can. J. Chem.* **1970**, *48*, 1754.

- Oxidation of 4-methoxybenzylidene acetals has also been studied:



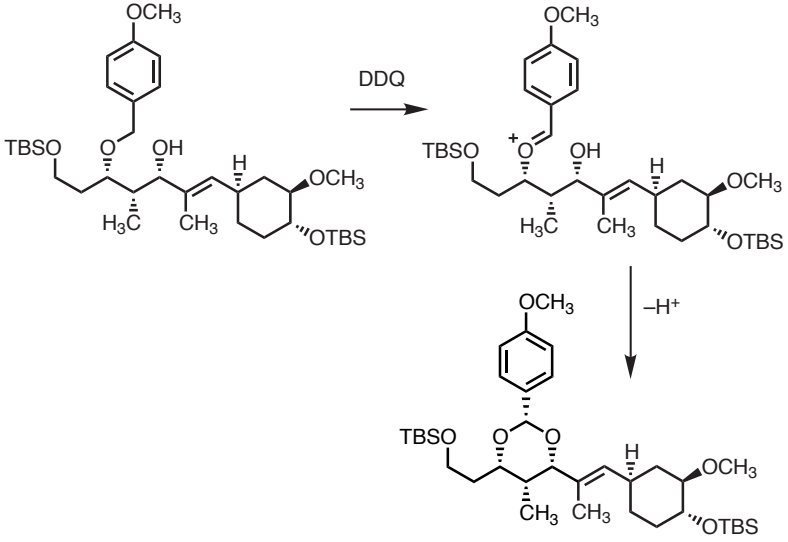
79% (19% of regioisomer)



PMP = *p*-methoxyphenyl

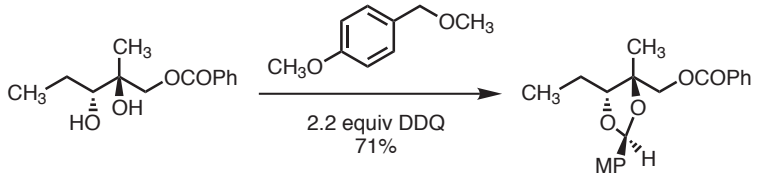
Zhang, Z.; Magnusson, G. *J. Org. Chem.* **1996**, *61*, 2394.

- 2-electron oxidation of 4-methoxybenzyl groups with DDQ is a general reaction.
- This has been used extensively to remove 4-methoxybenzyl ethers, and also to form 4-methoxybenzylidene acetals.



Jones, A. B.; Yamaguchi, M.; Patten, S.; Danishefsky, S. J.; Ragan, J. A.; Smith, D. B.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 17.

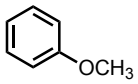
A useful extension of this reaction has been developed to protect diols directly:



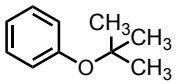
Oikawa, Y.; Nishi, T.; Yonemitsu, O. *Tetrahedron Lett.* **1983**, *24*, 4037.

P. Hogan

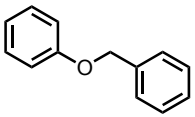
Phenolic Protective Groups:



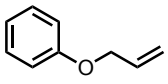
Methyl Ether



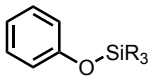
t-Butyl Ether



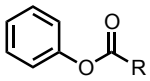
Benzyl Ether



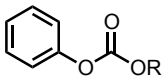
Allyl Ether



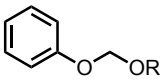
Silyl Ethers



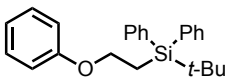
Phenyl Esters



Phenyl Carbonates

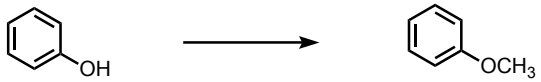


Acetals



t-Butyldiphenylsilylethyl Ether

Methyl Ether Formation:



1. MeI, K_2CO_3, acetone. Vyas, G. N.; Shah, N. M. *Org Synth., Collect. Vol. IV* **1963**, 836.

2. Diazomethane, Et_2O. Bracher, F.; Schulte, B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2619.

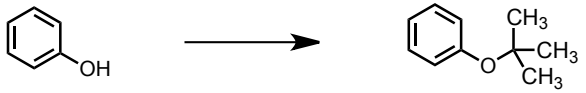
Methyl Ether Cleavage:

1. Me_3SiI, $CHCl_3$, 25-50 °C. This reagent also cleaves benzyl, trityl, and *t*-butyl ethers rapidly. Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

2. EtSNa, DMF, reflux. Ahmad, R.; Saa, J. M.; Cava, M. P. *J. Org. Chem.* **1977**, *42*, 1228.

3. 9-Bromo-9-borabicyclo[3.3.0]nonane, CH_2Cl_2. Bhatt, M. V. *J. Organomet. Chem.* **1978**, *156*, 221.

t-Butyl Ether Formation:



1. Isobutylene, CF_3SO_3H, CH_2Cl_2, –78 °C. Holcombe, J. L.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 11.

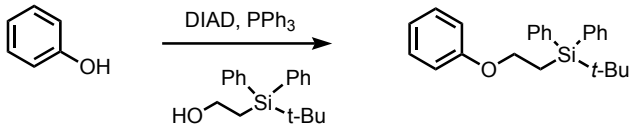
2. *t*-Butyl halide, pyr. Masada, H.; Oishi, Y. *Chem. Lett.* **1978**, 57.

t-Butyl Ether Cleavage:

1. CF_3CO_2H, 25 °C. Beyerman, H. C.; Bontekoe, J. S. *Recl. Trav. Chim. Pays-Bas.* **1962**, *81*, 691.

- For the other phenol protective groups, the sections describing these groups in the context of alcohols should be consulted. Most of the preparations used for alcohols are applicable to phenols. Hydroxyl protective groups that are cleaved with base are generally more labile with phenols.

t-Butyldiphenylsilylethyl (TBDPSE) ether formation:



- The TBDPSE group is stable to 5% TFA–CH_2Cl_2, 20% piperidine–CH_2Cl_2, catalytic hydrogenation, *n*-BuLi, and lead tetraacetate.
- The TBDPSE group has been cleaved using TBAF (2.0 equiv, 40 °C, overnight) or 50% TFA^- CH_2Cl_2.

Gerstenberger, B. S.; Konopelski, J. P. *J. Org. Chem.* **2005**, *70*, 1467.

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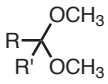
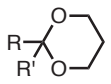
Carbonyl protective groups:

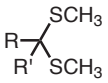


dimethyl acetal

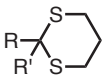


1,3-dioxane

1,3-dioxolane



S,S'-dimethylthioacetal



1,3-dithiane

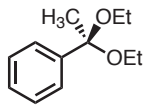
1,3-dithiolane

1,3-oxathiolane

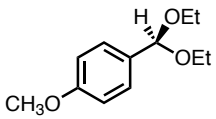
General order of reactivity of carbonyl groups towards nucleophiles:

aldehydes (aliphatic > aromatic) > acylic ketones ≈ cyclohexanones > cyclopentanones > α,β-unsaturated ketones ≈ α,α disubstituted ketones >> aromatic ketones.

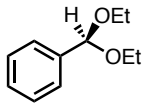
Approximate rates (L mol $^{-1}$s^{-1} at 25-30 °C) for proton-catalyzed (HCl, water or dioxane-water) cleavage of acetals and ketals.



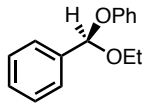
6 X 10^3



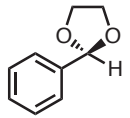
5 X 10^3



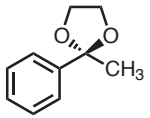
160



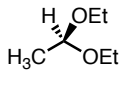
41



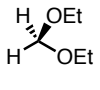
5



1.2



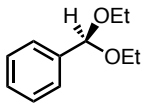
1.6



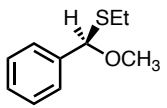
1.5 X 10^{-4}

- In general, cyclic acetals are cleaved more slowly than their open chain analogs
- In general, dithio acetals are not cleaved by Brønsted acids.

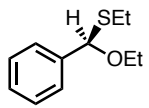
Rates of acid-catalyzed cleavage of mono thioacetals and acetals have been determined:



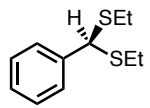
160



41



1.3



3.5 X 10^{-4}

Satchell, D. P. N.; Satchell, R. S. *Chem. Soc. Rev.* **1990**, *19*, 55.

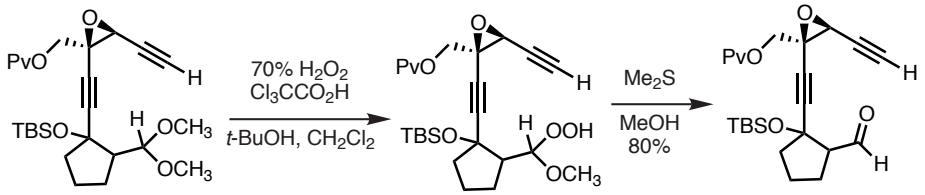
Preparation of dimethyl acetals and ketals:

1. MeOH, dry HCl. Cameron, A. F. B.; Hunt, J. S.; Oughton, J. F.; Wilkinson, P. A.; Wilson, B. M. *J. Chem. Soc.* **1953**, 3864.
2. MeOH, $LaCl_3$, $(MeO)_3CH$. Acetals are formed efficiently, but ketalization is unpredictable. Gemal, A. L.; Luche, J.-L. *J. Org. Chem.* **1979**, *44*, 4187.
3. Me_3SiOCH_3, Me_3SiOTf, CH_2Cl_2, –78 °C. Lipshutz, B. H.; Burgess-Henry, J.; Roth, G. P. *Tetrahedron Lett.* **1993**, *34*, 995.
4. $Sc(OTf)_3$, $(MeO)_3CH$, toluene, 0 °C. Ishihara, K.; Karumi, Y.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 839.

- Other dialkyl acetals are formed similarly.

Cleavage of dimethyl acetals and ketals:

1. TFA, $CHCl_3$, H_2O. These conditions cleaved a dimethyl acetal in the presence of a 1,3-dithiane and a dioxolane acetal. Ellison, R. A.; Lukenbach, E. R.; Chiu, C.-W. *Tetrahedron Lett.* **1975**, 499.
2. TsOH, acetone. Colvin, E. W.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Chem. Commun.* **1971**, 858.
3. 70% H_2O_2, Cl_3CCO_2H, CH_2Cl_2, *t*-BuOH; dimethyl sulfide. Myers, A. G.; Fundy, M. A. M.; Lindstrom, Jr. P. A. *Tetrahedron Lett.* **1988**, *29*, 5609.

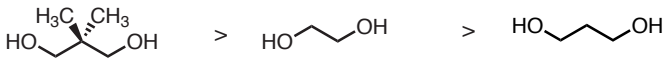


- Other methods resulted in cleavage of the epoxide.

P. Hogan

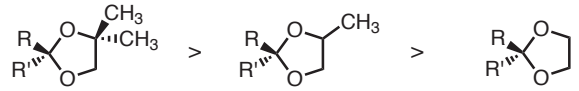
Cyclic acetals and ketals:

Relative rates of ketalization with common diols:



Cleavage of 1,3-dioxolanes vs. 1,3-dioxanes:

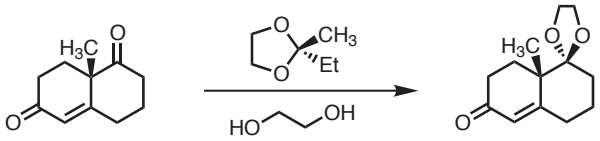
Relative rates of cleavage for 1,3-dioxolanes:



50,000 5000 1

Okawara, H.; Nakai, H.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 1087.

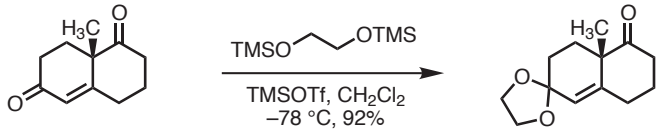
• In general, saturated ketones can be selectively protected in the presence of α,β-unsaturated ketones.



p-TsOH•H_2O, 95%

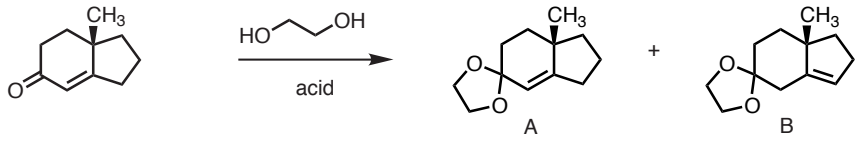
Bosch, M. P.; Camps, F.; Coll, J.; Guerrero, T.; Tatsuoka, T.; Meinwald, J. *J. Org. Chem.* **1986**, *51*, 773.

• Conditions have been developed to protect α,β-unsaturated ketones selectively.



Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

• When protecting α,β-unsaturated ketones, olefin isomerization is common.



Strong acids ($pK_a \approx 1$) tend to favor isomerization, while weaker acids ($pK_a \geq 3$) favor isomerization much less so, or not at all.

acid	pK_a	%A	%B	% conversion
fumaric acid	3.03	100	0	90
phthalic acid	2.89	70	30	90
oxalic acid	1.23	80	20	93
TsOH	< 1.0	0	100	100

De Leeuw, J. W.; De Waard, E. R.; Beetz, T.; Huisman, H. O. *Recl. Trav. Chim. Pays-Bas.* **1973**, *92*, 1047.

• Generally, methods used for formation of 1,3-dioxolanes are also useful for formation of 1,3-dioxanes.

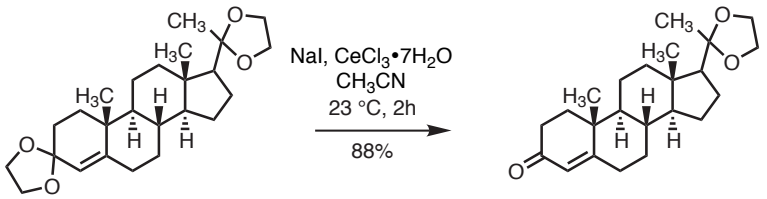
Cleavage of 1,3-dioxanes and 1,3-dioxolanes:

1. PPTS, acetone, H_2O, heat. Hagiwara, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1987**, 1351.

2. 1M HCl, THF. Grieco, P. A.; Nishizawa, M.; Oguri, T. Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *43*, 4178.

3. Me_2BBr, CH_2Cl_2, –78 °C. This reagent also cleaves MEM and MOM ethers. Guindon, Y.; Morton, H. E.; Yoakim, C. *Tetrahedron Lett.* **1983**, *24*, 3969.

4. NaI, $CeCl_3$•$7H_2O$, CH_3CN. Marcantoni, E.; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183. This method is selective for cleavage of ketals in the presence of acetals. It is also selective for ketals of α,β-unsaturated ketones over ketals of saturated ketones.



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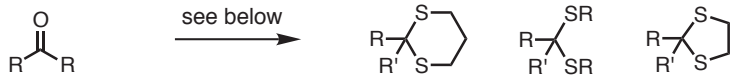
Dithioacetals:

General methods of formation of *S,S*''-dialkyl acetals:



1. RSH, HCl, 20 °C. Zinner, H. *Chem. Ber.* **1950**, *83*, 275.

2. $RSSi(CH_3)_3$, ZnI_2, Et_2O. Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.

3. RSH, BF_3•Et_2O, CH_2Cl_2. Marshall, J. A.; Belletire, J. L. *Tetrahedron Lett.* **1971**, 871. See also Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172. α,β-Unsaturated ketones are reported not to isomerize under these conditions. However, with any of the above mentioned conditions conjugate addition is a concern.

- A variety of methods has been developed for the cleavage of *S,S*''-dialkyl acetals, largely due to the fact that these functional groups *are often difficult to remove*.

General methods of cleavage of *S,S*''-dialkyl acetals:

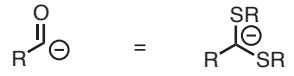
1. $Hg(ClO_4)_2$, MeOH, $CHCl_3$. Lipshutz, B. H.; Moretti, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15, and references therein.

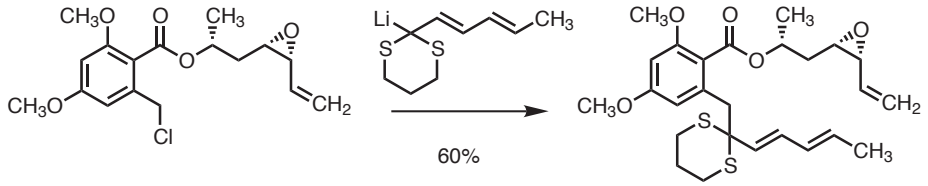
2. $CuCl_2$, CuO, acetone, reflux. Stutz, P.; Stadler, P. A. *Org. Synth. Collect. Vol.* **1988**, *6*, 109.

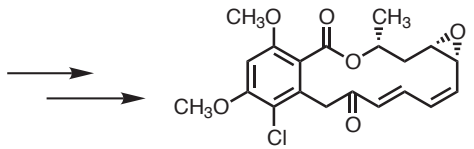
3. *m*-CPBA; Et_3N Ac_2O, H_2O. Kishi, Y.; Fukuyama, T.; Natatsuka, S. *J. Am. Chem. Soc.* **1973**, *95*, 6490.

4. $(CF_3CO_2)_2IPh$, H_2O, CH_3CN. Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.

In addition to serving as a protective group, *S,S*'-dialkyl acetals serve as an umpolung synthon in the construction of carbon-carbon bonds.





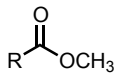


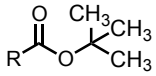
Radicicol dimethyl ether

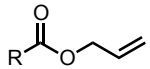
Garbaccio, R. M.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 3127.

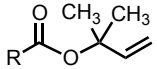
P. Hogan

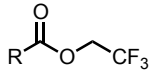
Carboxyl Protective Groups:

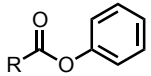

Methyl Ester

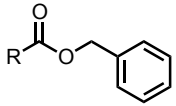

t-Butyl Ester

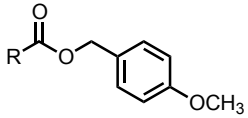

Allyl Ester

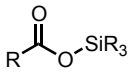

1,1-Dimethylallyl Ester

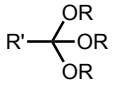

2,2,2-Trifluoroethyl Ester

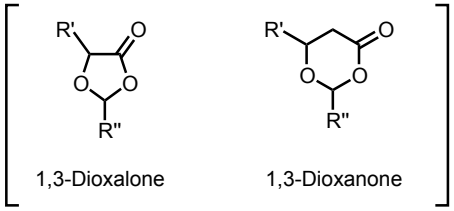

Phenyl Ester


Benzyl Ester


4-Methoxybenzyl Ester


Silyl Ester

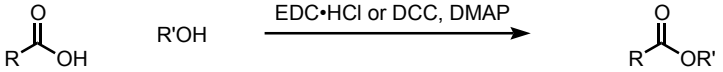

Ortho Ester


1,3-Dioxalone

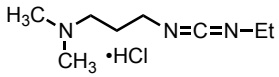
1,3-Dioxanone

Specific to α- and β-hydroxy acids

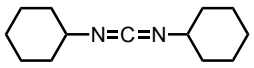
General preparations of esters:



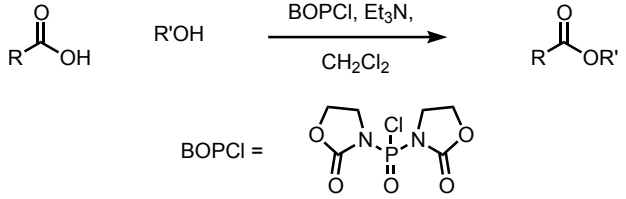
EDC•HCl = 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride



DCC = dicyclohexylcarbodiimide



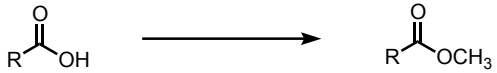
EDC•HCl is more expensive, but the urea by-product is water soluble and simplifies the purification of products



Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernandez-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis*, **1980**, 547.

Methyl esters:

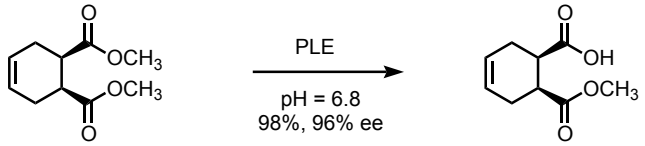
Formation:



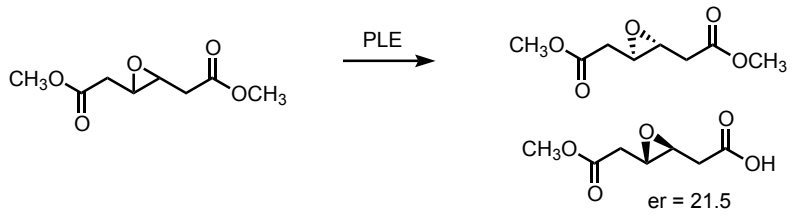
1. $TMSCHN_2$, MeOH, benzene. Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475. This is considered a safe alternative to using diazomethane.
2. MeOH, H_2SO_4. Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. *J. Am. Chem. Soc.* **1978**, *100*, 6536.

Cleavage:

1. LiOH, MeOH, 5 °C. Corey, E. J.; Szekely, I.; Shiner, C. S. *Tetrahedron Lett.* **1977**, 3529.
2. Pig liver esterase. This enzyme is often effective for the enantioselective cleavage of a meso diester.



Kobayashi, S.; Kamiyama, K.; Iimori, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 2557.



Mohr, P.; Rosslein, L.; Tamm, C. *Tetrahedron Lett.* **1989**, *30*, 2513.

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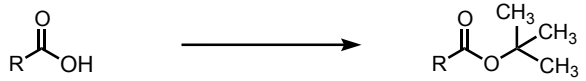
t-Butyl esters

Formation:



1. Isobutylene, H_2SO_4, Et_2O, 25 °C. McCloskey, A. L.; Fonken, G. S.; Kluiber, R. W.; Johnson, W. S. *Org. Synth., Collect. Vol. IV.* **1963**, 261.

2. 2,4,6-trichlorobenzoyl chloride, Et_3N, THF; *t*-BuOH, DMAP, benzene, 20 °C. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

3. *t*-BuOH, EDC•HCl, DMAP, CH_2Cl_2. Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962.

4. *i*-PrN=C(O-*t*Bu)NH-*i*-Pr, toluene, 60 °C. Burk, R. M.; Berger, G. D.; Bugianesi, R. L.; Girotra, N. N.; Parsons, W. H.; Ponpipom, M. M. *Tetrahedron Lett.* **1993**, *34*, 975.

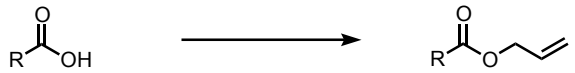
Cleavage:

1. CF_3CO_2H, CH_2Cl_2. Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 2353.

2. Bromocatechol borane. Boeckman Jr., R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.

Allyl esters

Formation:



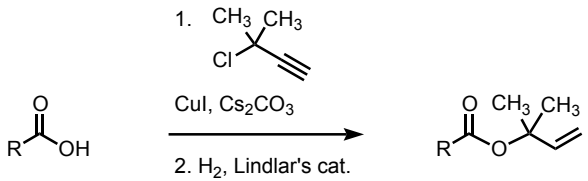
1. Allyl bromide, Cs_2CO_3, DMF. Kunz, H.; Waldmann, H.; Unverzagt, C. *Int. J. Pept. Protein Res.* **1985**, *26*, 493.
2. Allyl alcohol, TsOH, benzene, ($-H_2O$). Wladmann, H.; Kunz, H. *Liebigs Ann. Chem.* **1983**, 1712.

Cleavage:

1. The use of allyl esters in synthesis has been reviewed. Guibe, F.: *Tetrahedron* **1998**, *54*, 2967.
2. $Pd(Ph_3P)_4$, RSO_2Na, CH_2Cl_2. Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932.

1,1-Dimethylallyl esters

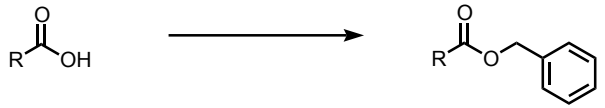
Formation:



• The 1,1-dimethylallyl ester is removed under the same conditions as an allyl ester, but is less susceptible to nucleophilic attack at the acyl carbon.

Sedighi, M.; Lipton, M. A. *Org. Lett.* **2005**, *7*, 1473.

Benzyl esters



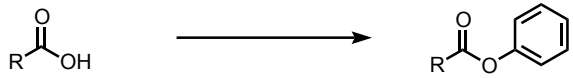
Benzyl esters are typically prepared by the methods outlined in the general methods section.

Cleavage:

1. H_2, Pd–C. Hartung, W. H.; Simonoff, R. *Org. React.* **1953**, *7*, 263.
2. BCl_3, CH_2Cl_2. Schmidt, U.; Kroner, M.; Griesser, H. *Synthesis* **1991**, 294.

Phenyl esters

Formation:



Phenyl esters are typically prepared by the methods outlined in the general methods section. They have the advantage of being cleaved under mild, basic conditions.

1. H_2O_2, H_2O, DMF, pH = 10.5. Kenner, G. W.; Seely, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 3259.

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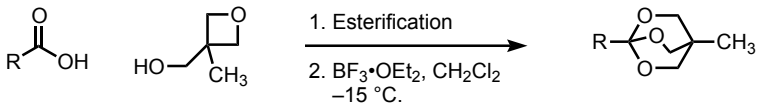
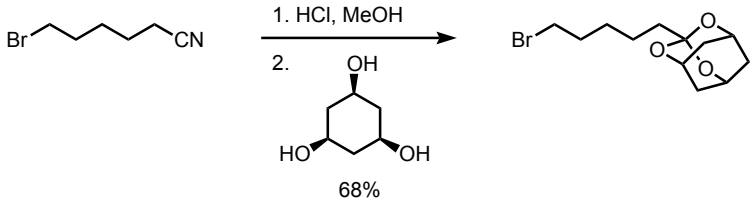
Ortho Esters:
The synthesis of simple ortho esters has been reviewed: Dewolfe, R. H. *Synthesis*, **1974**, 153.

OBO ester



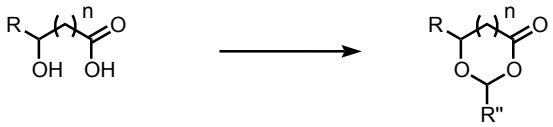
Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571.

Alternatively, ortho esters can be prepared from a nitrile:



Voss, G.; Gerlach, H. *Helv. Chim. Acta.* **1983**, *66*, 2294.

Special Carboxylates, α-Hydroxy and β-Hydroxy:



Formation:

1. Ketone or aldehyde, $Sc(NTf_2)_3$, CH_2Cl_2, $MgSO_4$. Ishihara, K.; Karumi, Y.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 839.
2. Pivaldehyde, acid catalyst. Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta.* **1986**, *70*, 448, and references cited therein.

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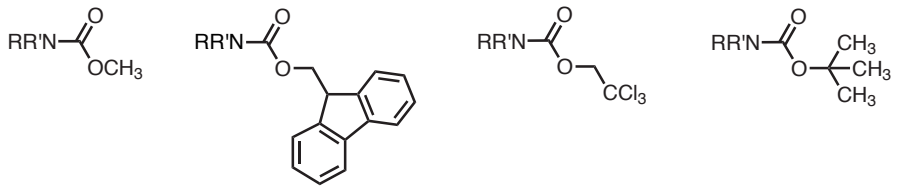
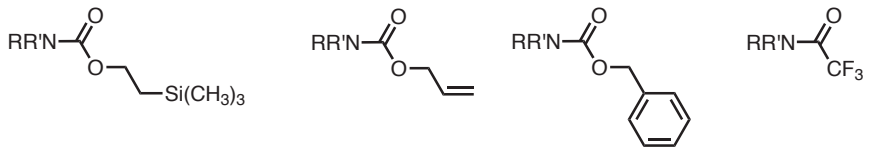
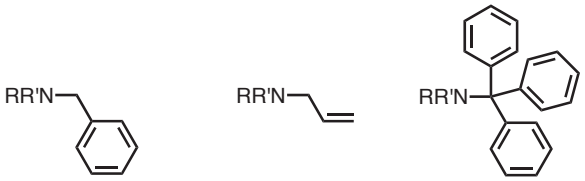
Protection of amines:



Methyl Carbamate | 9-Fluorenylmethyl Carbamate (Fmoc) | 2,2,2-trichloroethyl Carbamate (Troc) | *t*-Butyl Carbamate (Boc)

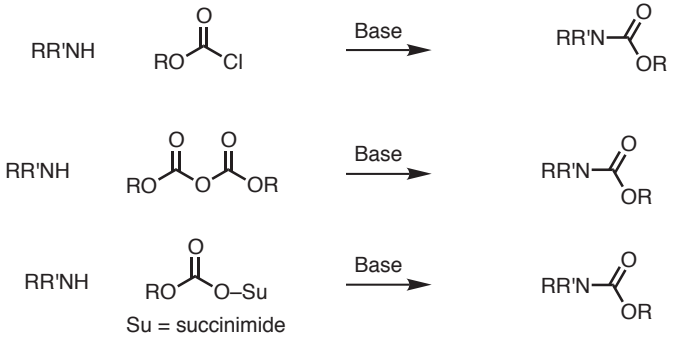


2-(Trimethylsilyl)ethyl Carbamate (Teoc) | Allyl Carbamate (Alloc) | Benzyl carbamate (Cbz) | Trifluoroacetamide



Benzylamine | Allylamine | Tritylamine

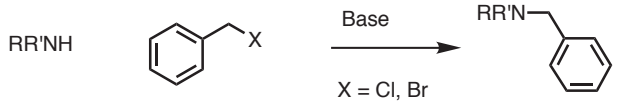
General preparation of carbamates:



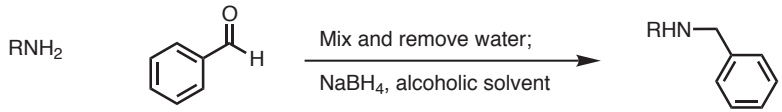
Su = succinimide

Bases that are typically employed are tertiary amines or aqueous hydroxide.

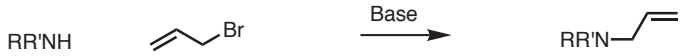
Formation of benzylamines:



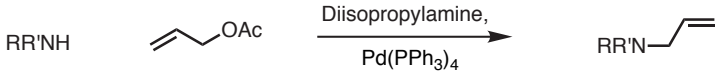
If primary amines are the starting materials, dibenzylamines are the products.



Formation of allylamines:

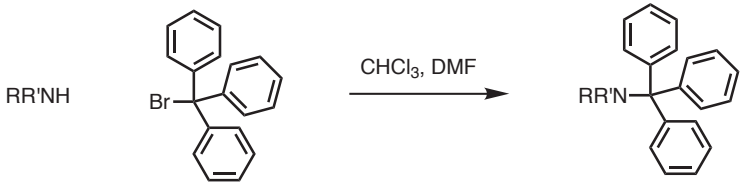


If primary amines are the starting materials, diallylamines are the products.



Garro-Helion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109.

Formation of tritylamines:

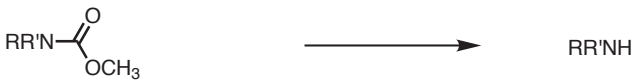


Mutter, M.; Hersperger, R. *Synthesis* **1989**, 198.

P. Hogan

Cleavage of carbamates:

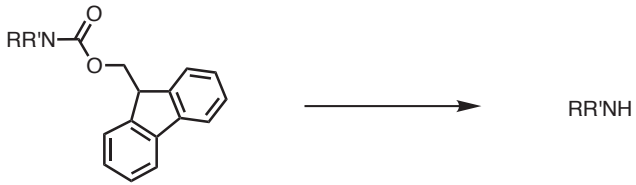
Methyl Carbamate:



1. TMSI, CH_2Cl_2. Raucher, S.; Bray, B. L.; Lawrence, R. F. *J. Am. Chem. Soc.* **1987**, *109*, 442.

2. MeLi, THF. Tius, M.; Keer, M. A. *J. Am. Chem. Soc.* **1992**, *114* , 5959.

9-Fluorenylmethyl Carbamate:



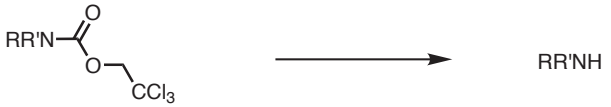
1. Amine base. The half-lives for the deprotection of Fmoc-ValOH have been studied: Atherton, E.; Sheppard R. C. in *The Peptides*, Udenfriend, S. and Meienhefer Eds., Academic Press: New York, **1987**, Vol. 9, p. 1.

Amine base in DMF	Half-Life
20% piperidine	6 s
5% piperidine	20 s
50% morpholine	1 min
50% dicyclohexylamine	35 min
10% *p*-dimethylaminopyridine	85 min
50% diisopropylethylamine	10.1 h

2. Bu_4NF, DMF. Ueki, M.; Amemiya, M. *Tetrahedron Lett.* **1987**, *28*, 6617.

3. Bu_4NF, *n*-$C_8H_{17}SH$. Thiols can be used to scavenge liberated fulvene. Ueki, M.; Nishigaki, N.; Aoki, H.; Tsurusaki, T.; Katoh, T. *Chem. Lett.* **1993**, 721.

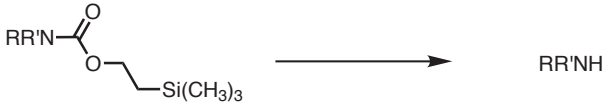
2,2,2-Trichloroethyl Carbamate:



1. Zn, H_2O, THF, pH = 4.2. Just. G.; Grozinger, K. *Synthesis*, **1976**, 457.

2. Cd, AcOH. Hancock, G.; Galpin, I. J.; Morgan, B. A. *Tetrahedron Lett.* **1982**, *23*, 249.

2-Trimethylsilylethyl Carbamate:

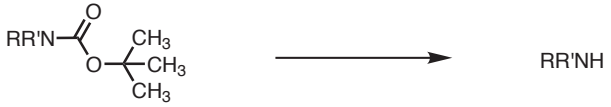


1. Bu_4NF, $KF{\bullet}H_2O$, CH_3CN, 50 ºC. Carpino, L. A.; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514.

2. CF_3COOH, 0 °C. Carpino, L. A.; Tsao, J. H,; Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc., Chem. Commun.* **1978**, 358.

3. Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF), DMF. Roush, W. R.; Coffey, D.S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *49*, 2325.

t-Butyl Carbamate



1. CF_3COOH, PhSH. Thiophenol is used to scavenge *t*-butyl cations. TBS and TBDMS ethers are reported to be stable under these conditions. Jacobi, P, A.; Murphree, F.; Rupprecht, F.; Zheng, W. *J . Org. Chem.* **1996**, *61*, 2413.

2. Bromocatecholborane. Boeckman Jr., R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.

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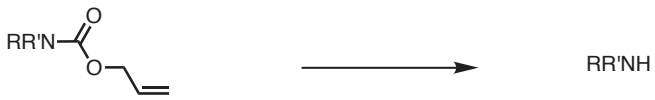
Allyl Carbamate:



1. $Pd(PPh_3)_4$, Bu_3SnH, AcOH, 70–100% yield. Dangles, O.; Guibe, F.; Balavoin, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4984.

2. $Pd(Ph_3P)_4$, $(CH_3)_2NTMS$, 89 – 100% yield. Merzouk A.; Guibe, F. *Tetrahedron Lett.* **1992**, *33*, 477.

Benzyl Carbamate:

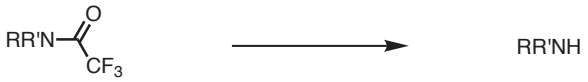
1. H_2/Pd–C. Bergmann, M.; Zervas, L. *Chem. Ber.* **1932**, *65*, 1192.

2. H_2/Pd–C, NH_3. These conditions cleave the benzyl carbamate in the presence of a benzyl ether. Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465.

3. BBr_3, CH_2Cl_2. Felix, A. M. *J. Org. Chem.* **1974**, *39*, 1427.

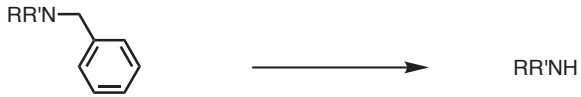
4. Bromocatecholborane. This reagent is reported to cleave benzyl carbamates in the presence of benzyl ethers and TBS ethers. Boeckman Jr., R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.

Trifluoroacetamide:



1. K_2CO_3, MeOH. Bergeron, R. J.; McManis, J. J. *J. Org. Chem.* **1988**, *53*, 3108.

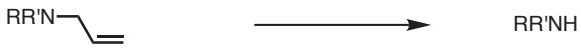
Benzylamine:



1. Pd–C, ROH, HCO_2NH_4. Ram, S.; Spicer, L. D. *Tetrahedron Lett.* **1987**, *28*, 515.

2. Na, NH_3. Bernotas, R. C.; Cube, R. V. *Synth. Comm.* **1990**, *20*, 1209.

Allylamine:



1. $Pd(Ph_3P)_4$, RSO_2Na, CH_2Cl_2. Most allyl groups are cleaved by this method, including allyl ethers and esters. Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932.

Tritylamine:

1. 0.2% TFA, 1% H_2O, CH_2Cl_2. Alsina, J.; Giralt, E.; Albericio, F. *Tetrahedron Lett.* **1996**, *37*, 4195.

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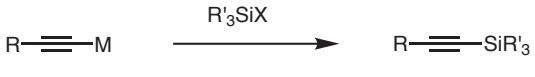
Alkyne protecting groups:

trialkylsilylalkyne

- Typical silyl groups include TMS, TES, TBS, TIPS, and TBDPS. Many silyl acetylenes are commercially available, and are useful acetylene equivalents.

General preparation of silyl acetylenes:



M = Li, Mg X= Cl, OTf

- Silyl chorides are suitable for smaller silyl groups, but the preparation of more hindered silyl acetylenes may require the use of the more reactive silyl triflate.

- In general, a strong fluoride source such as TBAF is used to cleave silylalkynes. In the case of trimethylsilylalkynes, milder conditions can be used.

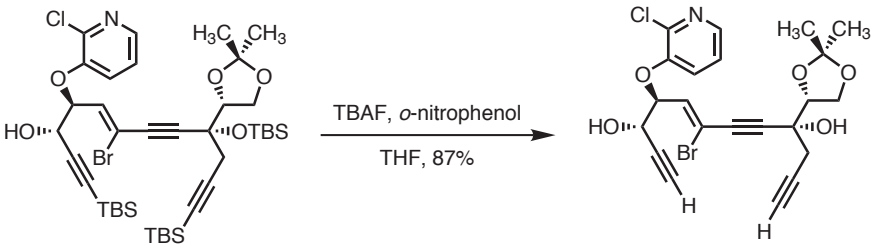
Cleavage of trimethysilylalkynes:

1. KF, MeOH, 50 °C. Myers, A. G.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1991**, *113*, 694.

2. $AgNO_3$, 2,6-lutidine. Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106.

3. K_2CO_3, MeOH. Cai, C.; Vasella, A. *Helv. Chim. Acta.* **1995**, *78*, 732.

- Buffered TBAF was used to deprotect the silylalkynes in the example shown below to prevent elimination of the sensitive vinyl bromide.



Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2732.

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