6

Protecting Groups

In his book, *Protecting Groups*, Philip J. Kocieński stated that there are three things that cannot be avoided: *death, taxes, and protecting groups*. Indeed, protecting groups mask functionality that would otherwise be compromised or interfere with a given reaction, making them a necessity in organic synthesis. In this chapter, for each protecting group showcased, only the most widely used methods for protection and cleavage are shown. Also, this section is not comprehensive and only addresses some of the most common blocking groups in organic synthesis. For a thorough review of protecting groups, the reader should consult the following references: (a) Wuts, P. G. M.; Greene, T. W.; *Protective Groups in Organic Synthesis*, 4th ed.; Wiley: Hoboken, NJ, 2007; (b) Kocienski, P. J. *Protecting Groups*, 3rd edition.; Thieme: Stuggart, 2004.

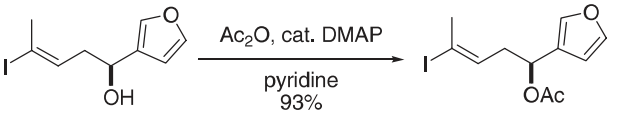
6.1 Alcohols and Phenols

In this section, the formation and cleavage of eight protecting groups for alcohols and phenols are presented: acetate; acetonides for diols; benzyl ether; *para*-methoxybenzyl (PMB) ether; methyl ether; methoxymethylene (MOM) ether; *tert*-butyldiphenylsilyl (TBDPS) silyl ether; and tetrahydropyran (THP).

6.1.1 Acetate

Acetate is a convenient protecting group for alcohols—easy on and easy off. Selective protection of a primary alcohol in the presence of a secondary alcohol can be achieved at low temperature. The drawback of this protecting group is its incompatibility with hydrolysis and reductive conditions.

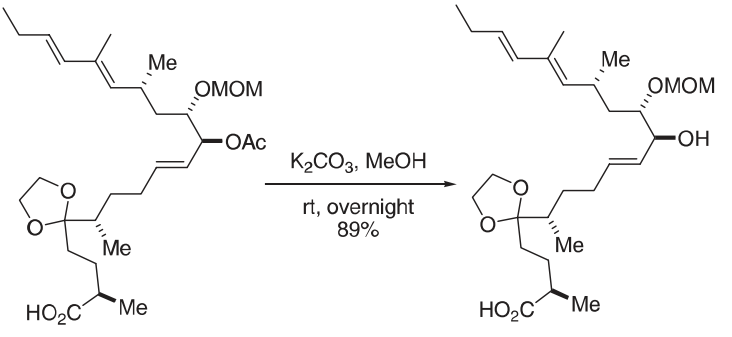
Protection



A solution of (+)-(*E*)-1-(3-furyl)-4-iodopent-3-en-1-ol (58 mg, 0.21 mmol), acetic anhydride (0.04 mL, 0.421 mmol), 4-(dimethylamino)pyridine (DMAP, 1.2 mg, 0.01 mmol), and pyridine (1 mL) was stirred until disappearance of the starting material. The mixture was quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether and the organic layers were washed with a saturated aqueous $CuSO_4$ solution and water, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (light petroleum/Et_2O, 9:1) to give (+)-(*E*)-1-(3-furyl)-4-iodopent-3-en-1-yl acetate at 93% yield.

Reference: Commeiras, L.; Parrain, J.-L. *Tetrahedron: Asymmetry* **2004**, *15*, 509–517.

Cleavage



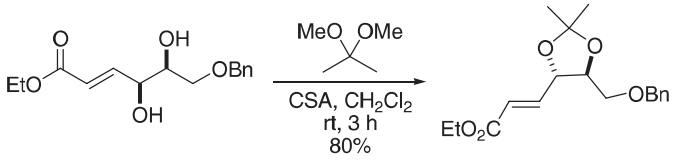
To a solution of the acetate starting material (78 mg, 0.145 mmol) in MeOH (4 mL) was added K_2CO_3 (400 mg, 2.9 mmol). The reaction was stirred at room temperature overnight. The mixture was poured into pH 4 buffer (aqueous solution of NaH_2PO_4 and $NaHSO_4$) and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (40% EtOAc/hexanes) afforded the corresponding alcohol (64 mg, 89%) as a clear oil.

Reference: Ghosh, A. K.; Gong, G. *J. Am. Chem. Soc*. **2004**, *126*, 3704–3705.

6.1.2 Acetonide

O,O-Isopropylidene acetal has been widely used in protecting 1,2- and 1,3-diols. They are resistant to very basic conditions, but are cleaved under acidic conditions.

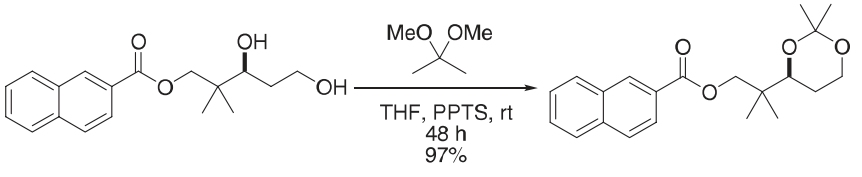
Protection



To a stirred solution of the diol starting material (0.8 g, 2.85 mmol) in CH_2Cl_2 (2 mL) at room temperature was added 2,2,-dimethoxypropane (0.52 mL, 4.2 mmol) and camphorsulfonic acid (CSA, 13 mg, 2 mol%). The reaction was stirred for 3 h and quenched with saturated aqueous sodium bicarbonate (10 mL) and the aqueous layer was extracted with ether (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography eluting with EtOAc/hexane (1:9) afforded the isopropylidene acetal (0.73 g, 80%) as a viscous oil.

Reference: Ahmed, M. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. *Org. Lett*. **2005**, *7*, 745–748.

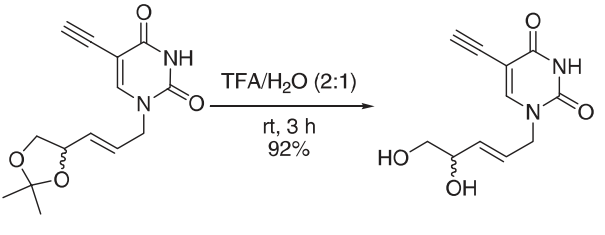
Protection of the 1,3-diol as an acetonide works similarly to the 1,2-diol.



A solution of this ester (8.35 g, 27.6 mmol, 1.0 equivalents) in tetrahydrofuran (THF 100 mL) was cooled to 0 ˚C, and pyridinium *p*-toluenesulfonate (PPTS, 500 mg, 2.00 mmol, 0.1 equivalents) and then 2,2-dimethoxypropane (20.0 mL, 163 mmol, 5.9 equivalents) were added. The cold bath was removed and the mixture was stirred at room temperature for 48 h, quenched with saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (3% ethyl acetate and 1% triethylamine in hexanes, and then 100% EtOAc) afforded the acetonide and a small amount of starting diol which was re-subjected and purified as above. The two batches were combined to afford naphthalene-2-carboxylic acid 2-[(4*S*)-2,2- dimethyl-[1,3]dioxan-4-yl]-2-methylpropyl ester (9.140 g, 97%) as a clear colorless syrup.

Reference: Wipf, P.; Graham, T. H. *J. Am. Chem. Soc*. **2004**, *126*, 15346–15347.

Cleavage



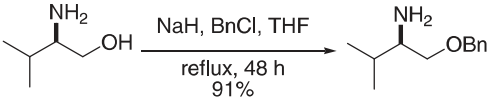
The acetal derivative (0.22 mmol) was stirred at room temperature for 3 h in a 2:1 mixture of trifluoroacetic acid (TFA)/H_2O (15 mL). After evaporation of volatiles, the crude residue was purified by flash chromatography (CH_2Cl_2/MeOH, 92:8) to give the corresponding diol (92% yield) as a pale yellow gum.

Reference: Amblard, F.; Aucagne, V.; Guenot, P.; Schinazi, R. F.; Agrofoglio, L. *Bioorg. Med. Chem*. **2005**, *13*, 1239–1248.

6.1.3 Benzyl ether

Benzyl chloride and benzyl bromide are strong lachrymators and therefore their usage should be carried out in the hood. When benzyl chloride is used in making the benzyl ether, addition of a catalytic amount of KI speeds up the reaction (Finkelstein reaction).

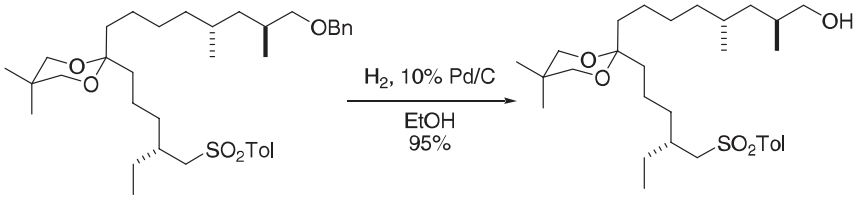
Protection



To a stirred solution of (*R*)-valinol (5.0 g, 48.5 mmol) in THF (50 mL) was added sodium hydride (60% dispersion, 1.94 g, 48.5 mmol) in 1 portion and the resultant suspension was refluxed for 30 min. Benzyl chloride (6.1 g, 48 mmol) was then added and the reaction mixture was refluxed for a further 48 h. On cooling, water (10 mL) was added and the solvent was removed in vacuo. The residue was treated with 6 N KOH until pH 12 was reached and then extracted with CH_2Cl_2. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow oil which on column chromatography over silica gel yielded the benzyl ether (8.55 g, 91%).

Reference: Patel, S. K.; Murat, K.; Py, S.; Vallée, Y. *Org. Lett*. **2003**, *5*, 4081–4084.

Cleavage



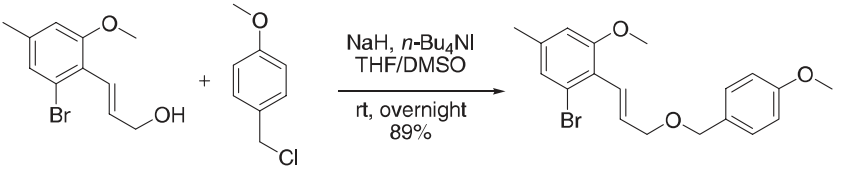
To a solution of the benzyl ether (762 mg, 1.44 mmol) in ethanol (10 mL) was added 10% palladium on activated carbon catalyst (50 mg). After stirring under an atmosphere of hydrogen for 2 h, the reaction mixture was filtered through a pad of Celite and concentrated to give the corresponding alcohol (603 mg, 95%) as a colorless oil.

Reference: Li, J., Ph.D. Thesis, *Total Synthesis of Myxovirescin A and Approaches Toward the Synthesis of the A/B Ring System of Zoanthamine*; Indiana University: Bloomington, Indiana, 1996; p. 174.

6.1.4 *para*-Methoxybenzyl

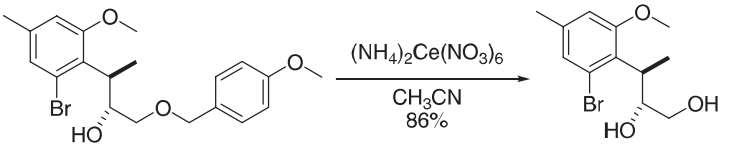
para-Methoxybenzyl (PMB) is a variant of the benzyl ether protective group. It can be differentiated from the benzyl ether because its cleavage can be accomplished by oxidation using ceric ammonium nitrate (CAN) or quinone.

Protection



To a solution of the cinnamyl alcohol (2.25 g, 8.75 mmol) in THF (100 mL) was added NaH (60% in mineral oil, 0.43 g, 10.5 mmol) followed by *p*-methoxybenzyl chloride, dimethylsulfoxide (5 mL), and a catalytic amount of *n*-Bu_4NI (0.20 g). The resulting suspension was stirred at room temperature overnight and quenched by slow addition of a saturated aqueous solution of NH_4Cl. After removal of THF in vacuo, the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography eluting with EtOAc/hexane (1:9) afforded the primary alcohol (2.00 g, 89%) as a yellow oil.

Cleavage



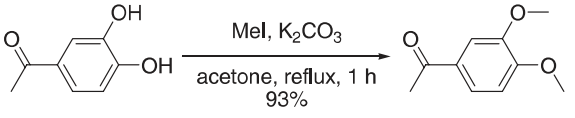
To a solution of the PMB ether (30 mg, 0.073 mmol) in acetonitrile (2 mL) was added CAN (80 mg, 0.15 mmol). The resulting yellow solution was stirred at room temperature overnight and then quenched by addition of a saturated aqueous solution of $NaHSO_3$. After removal of acetonitrile, the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography eluting with EtOAc/hexane (2:1) afforded the diol (18 mg, 86%) as white crystals.

Reference: Li, J., Ph.D. Thesis, *Total Synthesis of Myxovirescin A and Approaches Toward the Synthesis of the A/B Ring System of Zoanthamine*. Indiana University: Bloomington, Indiana, 1996; p. 174.

6.1.5 Methyl ether

The methyl ether is one of the most popular protecting groups for phenols. The resulting phenoxy methyl ether, however, sometimes requires harsh conditions for cleavage.

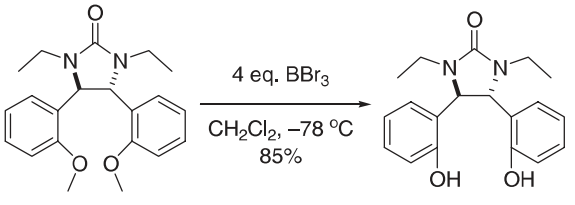
Protection



To a stirred mixture of 3′,4′-dihydroxyacetophenone (100 mg, 0.66 mmol) and anhydrous K_2CO_3 (5 g, 36 mmol) in dry acetone (10 mL) was added MeI (1 mL, 16 mmol). The mixture was heated at reflux for 45 min, cooled to room temperature, filtered, and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with 2 portions of water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The product was purified by flash chromatography (silica, hexane/EtOAc 4:1, v/v). Removal of the solvent gave a 93% yield of the product, 3′,4′-dimethoxyacetophenone (110 mg, 0.61 mmol).

Reference: Khatib, S.; Nerya, O.; Musa, R.; Shmuel, M.; Tamir, S.; Vaya, J. *Bioorg. Med. Chem*. **2005**, *13*, 433–441.

Cleavage



A solution of the bis-dimethyl ether (0.5 mmol) in dry CH_2Cl_2 (3 mL) was cooled to –78 ˚C and then BBr_3 (0.2 mL, 2 mmol) was added. After the mixture was stirred for 30 min at –78 ˚C, the cooling bath was removed and the stirring was continued for an additional 24 h at room temperature. The reaction was quenched by addition of water (3 mL), and the CH_2Cl_2 was removed in vacuo. The aqueous solution was neutralized by addition of aqueous NaOH and then extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica with EtOAc/hexane (30–50%) as eluent to give the corresponding diol at 85% yield.

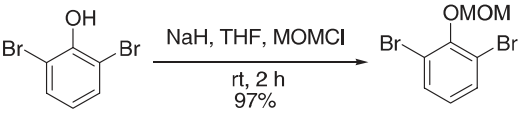
Reference: Liu, Y.; Ding, K. *J. Am. Chem. Soc*. **2005**, *127*, 10488–10489.

6.1.6 Methoxymethylene ether

The methoxymethylene (MOM) ether belongs to a class of substituted ether protecting groups. Unlike methyl ether, however, the MOM ether is actually an acetal, which is

cleaved under acidic conditions. The MOM ether is the most robust among all alkoxymethyl ether protecting groups.

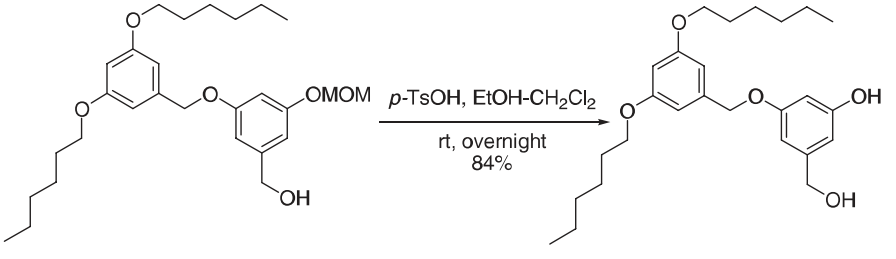
Protection



To a solution of 2,6-dibromophenol (58.0 g, 230.2 mmol) in THF (300 mL) at 0 ˚C was added NaH (13.8 g, 60% dispersion in mineral oil). After 5 min of stirring at 0 ˚C, MOMCl (22.5 mL, 300 mmol) was added via a syringe. The reaction mixture was then allowed to slowly warm to 25 ˚C, and following 2 h of additional stirring at that temperature the reaction mixture was poured into Et_2O (300 mL) and washed extensively with 3 M NaOH (3 × 75 mL) to remove any residual phenol starting material. The organic layer was then dried ($MgSO_4$) and concentrated to give MOM-protected 2,6-dibromophenol (66.2 g, 97%) as a yellow oil.

Reference: Nicolaou, K. C.; Snyder, S. A.; Huang, X.; Simonsen, K. B.; Koumbis, A. E.; Bigot, A. *J. Am. Chem. Soc*. **2004**, *126*, 10162–10173.

Cleavage



The MOM ether (0.63 g, 1.32 mmol) was dissolved in a mixture of ethanol and minimal amount of CH_2Cl_2. To this solution, *p*-toluenesulfonic acid (*p*-TsOH, 3–6 equivalents) was added and the reaction mixture was stirred at room temperature overnight. The reaction was then refluxed for 1 h to promote complete conversion, after which the solvent was removed in vacuo and the residue was partitioned between water and CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated to yield the crude product, which was then purified by silica gel chromatography using EtOAc/hexane (2:8) as the eluent to give the corresponding phenol (0.48 g, 84%).

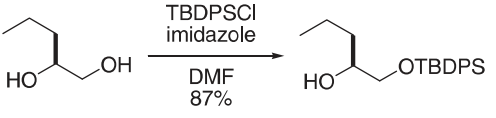
Reference: Sivanandan, K.; Aathimanikandan, S. V.; Arges, C. G.; Bardeen, C. J.; Thayumanavan, S. *J. Am. Chem. Soc*. **2005**, *127*, 2020–2021.

6.1.7 *tert*-Butyldiphenylsilyl ether

tert-Butyldiphenylsilyl (TBDPS) protection is one of the most popular alcohol protective groups. It is more stable than other silyl ethers under acidic conditions.

TBDPS ether is visible under UV light and thus it is more advantageous than the corresponding TBDMS ether if there is no chromophore present in the alcohol. Selective protection of the primary alcohol can be achieved as shown below. Silyl chloride and cleavage by-product silylol are both lachrymators and therefore the reactions should be carried out in the hood. The procedures for protection and cleavage are applicable to other silyl ethers such as *tert*-butyldimethylsilyl, trimethylsilyl, and tri-isopropylsilyl.

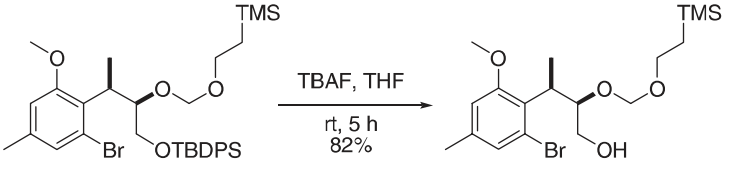
Protection



To a solution of (2*S*)-pentane-1,2-diol (86 mg, 0.83 mmol) in dimethylformamide (DMF, 95 mL) was added imidazole (84 mg, 1.2 mmol) followed by *tert*-butyldiphenylsilyl chloride (227 mg, 0.83 mmol, 0.22 mL). The resulting solution was stirred for 1 h, diluted with diethyl ether (40 mL), washed with water (3 × 5 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography eluting with EtOAc/hexane (1:9) afforded (2*S*)-1-(*tert*-butyldiphenylsilanyloxy)-pentan-2-ol (247 mg, 87%) as a colorless oil.

Reference: Li, J., Ph.D. Thesis, *Total Synthesis of Myxovirescin A and Approaches Toward the Synthesis of the A/B Ring System of Zoanthamine*. Indiana University: Bloomington, Indiana, 1996; p. 174.

Cleavage



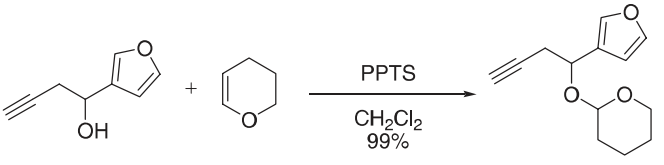
To a solution of the TBDPS ether (180 mg, 0.38 mmol) in THF (4 mL) was added a tetrabutylammonium fluoride solution (1.0 M in THF, 0.76 mL, 0.76 mmol). The resulting yellow solution was stirred at room temperature for 5 h and quenched by addition of a saturated aqueous solution of NH_4Cl. After removal of THF in vacuo, the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography eluting with EtOAc/hexane (1:9) afforded the primary alcohol (73 mg, 82%) as a colorless oil.

Reference: Li, J., Ph.D. Thesis, *Total Synthesis of Myxovirescin A and Approaches Toward the Synthesis of the A/B Ring System of Zoanthamine*. Indiana University: Bloomington, Indiana, 1996; p. 174.

6.1.8 Tetrahydropyran

Tetrahydropyranyloxy (THP) is an often-used and inexpensive protective group. The greatest disadvantage of this protecting group is that it creates an additional chiral center which can make the NMR spectra more complicated.

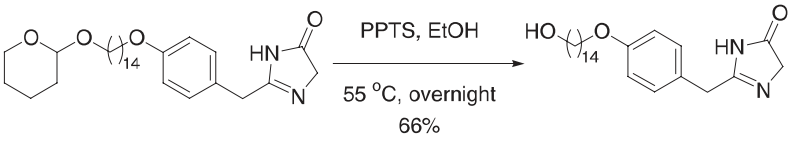
Protection



A mixture of 1-(3-furyl)but-3-yn-1-ol (500 mg, 3.68 mmol), CH_2Cl_2 (10 mL), dihydropyran (0.67 mL, 7.4 mmol), and PPTS (90 mg, 0.37 mmol) was stirred until the disappearance of the starting material. The solution was concentrated under vacuum and the crude product was purified by flash chromatography (light petroleum–Et_2O, 7/3) to give 1-(3-furyl)-1-(2-tetrahydropyranyl-oxy)but-3-yne, as a 1/1 mixture of diastereoisomers, at 99% yield.

Reference: Commeiras, L.; Parrain, J.-L. *Tetrahedron: Asymmetry* **2004**, *15*, 509–517.

Cleavage



The THP starting material (1.80 g) and PPTS (76 mg, 0.30 mmol) were heated at 55 °C in EtOH (30 mL) overnight. Water (about 40 mL) was added to the mixture while it was maintained at reflux overnight. The clear yellow solution was then kept at room temperature and the insoluble brown oil was separated from the supernatant by decantation. After drying under reduced pressure, the brown oil was purified by silica gel column chromatography (MeOH/CH_2Cl_2) and then recrystallized ($CHCl_3$) to afford the alcohol as white crystals (0.80 g, 66% yield).

Reference: Dong, C.-Z.; Ahamada-Himidi, A.; Plocki, S.; Aoun, D.; Touaibia, M.; Meddad-Bel Habich, N.; Huet, J.; Redeuilh, C.; Ombetta, J.-E.; Godfroid, J.-J.; Massicot, F.; Heymans, F. *Bioorg. Med. Chem*. **2005**, *13*, 1989–2007.

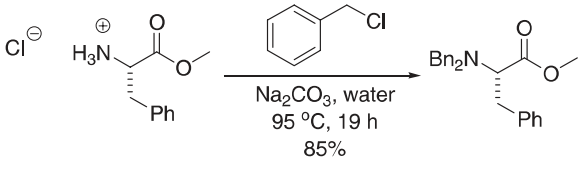
6.2 Amines and Anilines

In this section, the protections and cleavages of seven protecting groups for amines and anilines are presented: benzyl; BOC; Cbz; Fmoc; phthaloyl; sulfonamide; and trifluoroacetyl.

6.2.1 Benzyl

While the benzyl ether is readily removed via hydrogenolysis, the corresponding benzyl protected of amines is less readily cleaved.

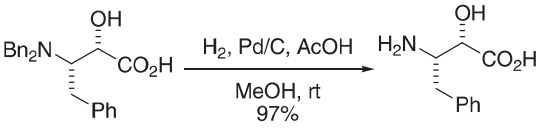
Protection



To a solution of *L*-phenylalanine methyl ester hydrochloride (25.0 g, 151 mmol) and Na_2CO_3 (66.7 g, 483 mmol) dissolved in water (100 mL) was added benzyl chloride (57.5 g, 454 mmol), and the mixture was heated at 95 ˚C with stirring for 19 h. After the reaction mixture was cooled to ambient temperature, water (50 mL) and *n*-heptane (67 mL) were added and extracted. The organic layer was separated and washed twice with a mixed solution of methanol/water (1:2, 50 mL) and then dried over anhydrous Na_2SO_4. Concentration of the solution in vacuo provided Bn_2-*L*-Phe-OMe (61.6 g, 85%) as a colorless oil.

Reference: Suzuki, T.; Honda, Y.; Izawa, K.; Williams, R. M. *J. Org. Chem.* **2005**, *70*, 7317–7323.

Cleavage



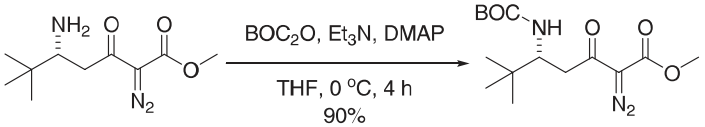
To a solution of the dicyclohexylamine salt of the dibenzylamine (2.8 g, 5.0 mmol) dissolved in a mixture of methanol (25 mL) and acetic acid (2.4 mL) was added 5% palladium on carbon (water content 53.3%, 1.2 g, 0.23 mmol Pd). The resulting mixture was stirred for 25 h under hydrogen at atmospheric pressure and ambient temperature. NaOH (2 M) aqueous solution (about 20 mL) was added to the reaction mixture in a water bath to adjust the pH to 5.1 at 30 ˚C. After the mixture was stirred for 40 min at ambient temperature, it was filtered to remove the catalyst. Filtration and concentration afforded the cleaved amine (949 mg, 97%). Recrystallization using EtOAc gave the sodium salt as white crystals (602 mg, 57% as a recovered yield in crystallization).

Reference: Suzuki, T.; Honda, Y.; Izawa, K.; Williams, R. M. *J. Org. Chem.* **2005**, *70*, 7317–7323.

6.2.2 *t*-Butyloxycarbonyl

t-Butyloxycarbonyl (BOC) is the most widely used protecting group for amines.

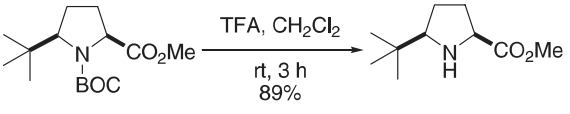
Protection



To a solution of the amine (1.4 g, 4.1 mmol) in THF (20 mL) at 0 °C was added Et_3N (3.4 mL, 2.5 g, 24.6 mmol), followed by DMAP (about 0.01 g). To the reaction mixture was added di-*tert*-butyl dicarbonate (0.95 g, 4.92 mmol) and the solution was stirred at this temperature for 4 h. At this time the reaction mixture was quenched with ice and water (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. Chromatography (5%–30% EtOAc/hexane) afforded the BOC-amine as a white solid (1.2 g, 90%).

Reference: Davis, F. A.; Yang, B.; Deng, J. *J. Org. Chem.* **2003**, *68*, 5147–5152.

Cleavage



In a 5-mL round-bottomed flask equipped with a stir bar and a rubber septum under an argon atmosphere was placed the BOC-pyrrolidine (0.033 g, 0.12 mmol) in CH_2Cl_2 (2 mL). The solution was cooled to 0 °C, and TFA (180 μL, 2.31 mmol) was added. The reaction mixture was stirred at room temperature for 3 h, quenched with saturated aqueous $NaHCO_3$ (2 mL), and stirred for 20 min. The organic phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Chromatography (1:1 EtOAc/hexane) afforded the pyrrolidine as a yellow low-melting solid (0.019 g, 89%).

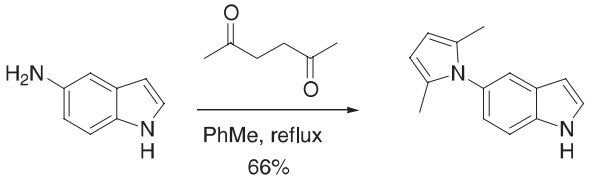
Reference: Davis, F. A.; Yang, B.; Deng, J. *J. Org. Chem.* **2003**, *68*, 5147–5152.

6.2.3 2,5-Dimethylpyrrole

The 2,5-dimethylpyrrole protecting group is a robust blocking group for the diprotection of primary amines. The protecting group is stable to a variety of nucleophiles (i.e., RLi, RMgX, etc.), reducing agents (i.e., $LiAlH_4$), and low reactivity

toward electrophiles (i.e., acid chlorides). Introduction of the protecting group is straightforward where an amine and acetonylacetone are condensed to form the pyrrole. The condensation is accelerated in the presence of acetic acid.

Protection

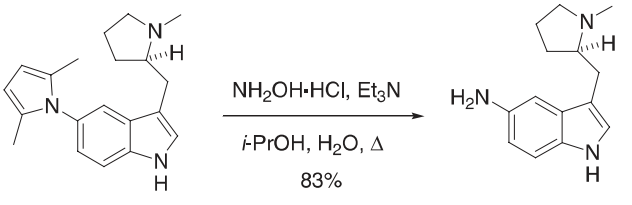


A mixture of 5-aminoindole (120.0 g, 0.908 mol), acetonylacetone (200.0 mL, 1.70 mol), and toluene (400 mL) was heated at reflux under nitrogen using a Dean-Stark trap for 6 h. The reaction was cooled and then poured through a silica gel filter (~ 2 kg) followed first by hexanes (4 L) and then by 6% ether in hexanes to afford 133.3 g of a pink solid. Recrystallization of this solid in ether/hexanes afforded 126.1 g (66%) of the 2,5-dimethylpyrrole as an off-white solid.

Reference: Macor, J. E.; Chenard, B. L.; Post, R. J. *J. Org. Chem.* **1994**, *59*, 7496–7498.

Cleavage

Cleavage of the 2,5-dimethylpyrrole has been achieved using $NH_2OH{\cdot}HCl$/base, TFA/H_2O, or singlet oxygen. The deprotection is normally done using $NH_2OH{\cdot}HCl$/Et_3N or KOH in a refluxing mixture of *i*-PrOH or EtOH and water. Despite the relatively harsh conditions for the removal of this protecting group, the cleavage has been achieved in highly functionalized molecules. See (a) Bowers, S. G.; Coe, D. M.; Boons, G.-J. *J. Org. Chem.* **1998**, *63*, 4570–4571. (b) Baker, R.; Castro, J. L. *J. Chem. Soc. Perkin Trans. 1* **1990**, 47–65.



A mixture of the 2,-5-dimethylpyrrole (81.5 g, 0.265 mol), hydroxylamine hydrochloride (368 g, 5.30 mol), and triethylamine (367 mL, 2.65 mol) in 2-propanol (800 mL) and water (200 mL) was heated at reflux under nitrogen for 4.5 h. The resulting reaction mixture was cooled in an ice bath, solid sodium hydroxide (212 g, 5.30 mol) was added, and the resulting reaction mixture was stirred at room temperature under nitrogen for 24 h. The reaction mixture was then filtered through Celite, and the filtrate was evaporated under reduced pressure. The residual oil was passed

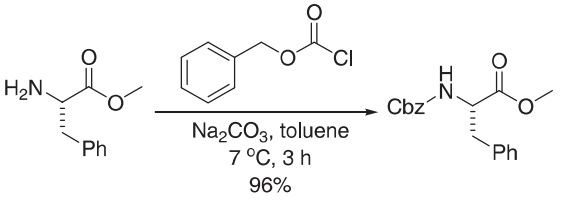
through a silica gel filter (~ 1 kg) followed by elution with EtOAc/MeOH/Et_3N (8:1:1) to afford 85 g of a pale yellow solid. The solid was dissolved in EtOAc (1 L), and this solution was washed with a saturated solution of sodium chloride (3 × 100 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to afford 50.55 g (83%) of the 5-aminoindole.

Reference: Macor, J. E.; Chenard, B. L.; Post, R. J. *J. Org. Chem.* **1994**, *59*, 7496–7498.

6.2.4 Carbobenzyloxy

Carbobenzyloxy (Cbz, *O*-benzyloxycarbonyl) may be removed by either hydrogenation or acid (e.g., TFA).

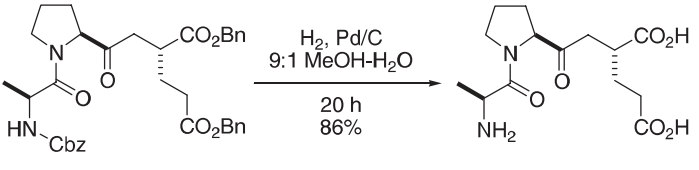
Protection



To a mixture of *L*-phenylalanine methyl ester hydrochloride (20.0 g, 93 mmol) suspended in toluene (93 mL) was added benzyl chloroformate (15.8 g, 93 mmol) with cooling in an ice bath. An aqueous solution of Na_2CO_3 (1 M, 130 mL) was added dropwise with vigorous stirring at 7 °C or lower. After this addition was complete, the mixture was stirred for 3 h. The organic layer was separated, washed with 0.1 M HCl (60 mL) and saturated $NaHCO_3$ solution (60 mL), and then dried over anhydrous Na_2SO_4. Concentration of the solution in vacuo provided Cbz-*L*-Phe-OMe (28.8 g, 96%) as a colorless oil.

Reference: Suzuki, T.; Honda, Y.; Izawa, K.; Williams, R. M. *J. Org. Chem.* **2005**, *70*, 7317–7323.

Cleavage



A mixture of the above-protected peptide (0.30 g, 0.48 mmol) and 10 wt% palladium on activated carbon (0.05 g, 0.13 mmol) in methanol (40 mL) was stirred under an atmosphere of hydrogen at room temperature for 20 h. The solution was filtered through a Celite pad and the pad was washed with methanol (2 × 25 mL). The filtrate was evaporated to dryness, dissolved in methanol (35 mL), and re-filtered through a Celite pad. The solution was evaporated to dryness, dried in vacuo, and triturated

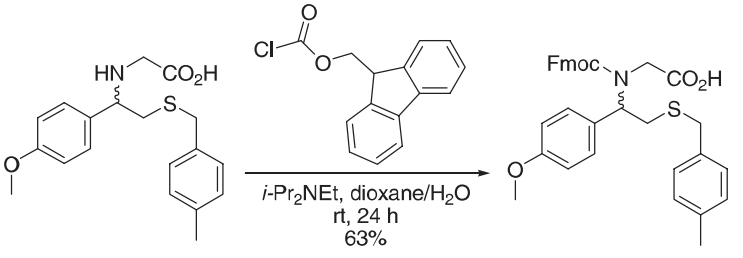
with anhydrous ether to give *D*-alanyl-*L*-prolyl-*L*-glutamic acid (0.13 g, 86%) as a white solid.

Reference: Lai, M. Y. H.; Brimble, M. A.; Callis, D. J.; Harris, P. W. R.; Levi, M. S.; Sieg, F. *Bioorg. Med. Chem*. **2005**, *13*, 533–548.

6.2.5 9-Fluorenylmethyl carbamate

9-Fluorenylmethyl carbamate (Fmoc) is widely used in peptide chemistry and solid-phase peptide chemistry. Fmoc is often uniquely cleaved by amines and is stable under acidic conditions.

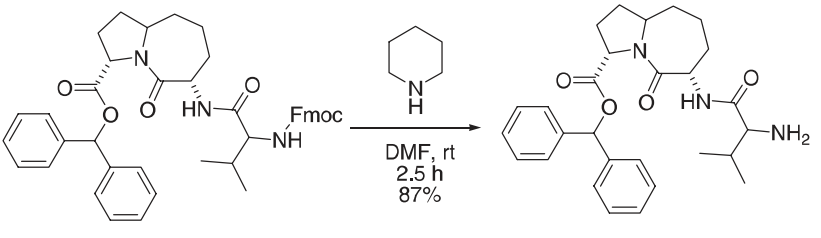
Protection



To a stirring solution of the amino acid (86.3 mg, 0.25 mmol) in a mixture of dioxane/H_2O (2:1, 3 mL) was added diisopropylethylamine (2.5 mmol) followed by a dioxane solution of Fmoc-Cl (1.1 mmol in 0.65 mL dioxane). The reaction mixture was stirred at room temperature for 24 h, poured into water (5 mL), and extracted with ether. The aqueous layer was then acidified with 1 M HCl solution and extracted with EtOAc. The combined organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (EtOAc/pentane, 30% to 50%) afforded the Fmoc protected amino acid as a white powder (89 mg, 63%).

Reference: Tchertchian, S.; Hartley, O.; Botti, P. *J. Org. Chem.* **2004**, *69*, 9208–9214.

Cleavage



The Fmoc-protected peptide (310 mg, 0.44 mmol) was dissolved in dry DMF (6 mL). Piperidine (1.2 mL, 20% by volume) was added and the solution was stirred at room temperature under nitrogen for 2.5 h. The solvent was removed in vacuo at < 50 ˚C to yield a white solid, which was purified by column chromatography on silica gel,

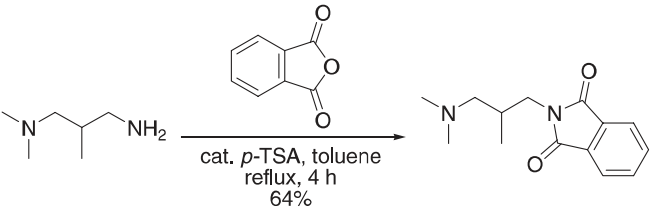
eluting with a gradient of methanol–dichloromethane (1:99 to 5:95). The deprotected peptide was collected as a yellow foam (182 mg, 87%).

Reference: Davies, D. E.; Doyle, P. M.; Hill, R. D.; Young, D. W. *Tetrahedron* **2005**, *61*, 301–312.

6.2.6 Phthaloyl

Phthalimides are relatively stable under both acidic and basic conditions but are easily cleaved by nucleophiles. Its cleavage is often accomplished using hydrazine according to the Ing–Manske procedure of the Gabriel reaction.

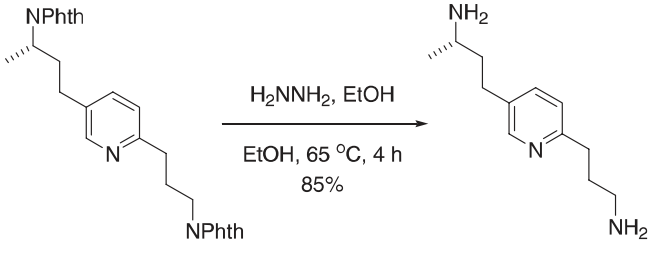
Protection



A mixture of phthalic acid anhydride (40 mmol), N^1,N^1,2-trimethylpropane-1,3-diamine (4.6 g, 40 mmol), and a catalytic amount of *p*-toluenesulfonic acid in toluene (100 mL) was refluxed using a water separator. After a reaction time of 4 h, the solvent was evaporated. The oily residues were purified by means of column chromatography (silica gel, eluent CH_2Cl_2:MeOH = 1:1). The obtained oils crystallized after a few hours at room temperature and the product was obtained at 64% yield.

Reference: Muth, M.; Sennwitz, M.; Mohr, K.; Holzgrabe, U. *J. Med. Chem.* **2005**, *13*, 2212–2217.

Cleavage



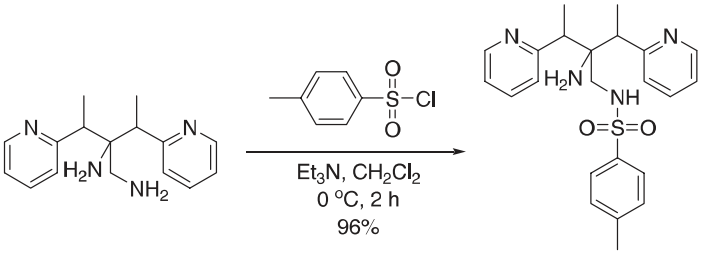
A mixture of the bis-phthaloyl starting material (16.6 g, 35.5 mmol), hydrazine hydrate (10.2 mL, 328 mmol), and ethanol (400 mL) was heated at 65 °C for 4 h. The mixture was filtered, and the cake was washed with toluene and azeotropically dried. The diamine was obtained at 85% yield.

Reference: Hartner, F. W.; Hsiao, Y.; Palucki, M. *J. Org. Chem.* **2004**, *69*, 8723–8730.

6.2.7 Sulfonamide

While sulfonamides are robust protecting groups for amines and anilines, their cleavage often calls for dissolving metal chemistry.

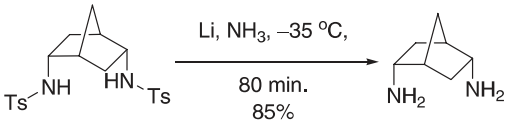
Protection



The diamine (2.99 g, 11.1 mmol) and Et_3N (1.7 mL, 12.2 mmol) were dissolved in CH_2Cl_2 (50 mL) and cooled in an ice bath. *p*-Toluenesulfonyl chloride (2.29 g, 12.0 mmol) was added slowly to the solution. The reaction mixture was stirred for 2 h, and then saturated aqueous $NaHCO_3$ (50 mL) was added and the solution was stirred overnight to quench excess sulfonic acid. The aqueous solution was drawn off and the CH_2Cl_2 layer was washed (2 × 50 mL) with saturated aqueous $NaHCO_3$ and water. The organic solution was dried (Mg_2SO_4) and decanted, and the solvent was removed in vacuo. The resulting amorphous white solid was recrystallized from EtOAc: hexane (3:1) to give the mono-protected product as colorless crystals (4.49 g, 96%).

Reference: Goodwin, J. M.; Olmstead, M. M.; Patten, T. E. *J. Am. Chem. Soc.* **2004**, *126*, 14352–14353.

Cleavage



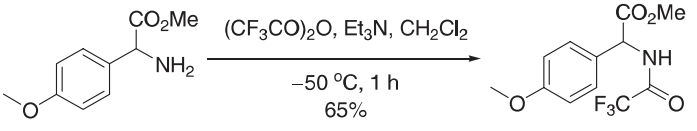
A flask was charged with the bis-sulfonamide (1.31 g, 3.00 mmol), and NH_3 was condensed at –78 °C with magnetic stirring. The mixture was allowed to warm to –33 °C and solid Li (220 mg, 31.7 mmol) was gradually added. The suspension turned blue and the reaction was quenched after 80 min by dropwise addition of brine (0.5 mL). NH_3 was evaporated and the residue was diluted with H_2O (10 mL) and concentrated in vacuo until the condensation of water was observed. The residue was diluted with water (10 mL), acidified with concentrated HCl, and extracted with CH_2Cl_2. The aqueous phase was concentrated in vacuo until a white precipitate formed. NaOH (25% aqueous, 15 mL) was added and the aqueous solution was extracted with CH_2Cl_2 in a liquid/liquid extractor for 42 h. Concentration of the organic phase yielded 2,5-diaminobicyclo[2.2.1]heptane as a colorless oil (321 mg, 85%).

Reference: Berkessel, A.; Schroeder, M.; Sklorz, C. A.; Tabanella, S.; Vogl, N.; Lex, J.; Neudoerfl, J. M. *J. Org. Chem.* **2004**, *69*, 3050–3056.

6.2.8 Trifluoroacetyl

Trifluoroacetyl amides are an easily installed and cleaved protecting group for amines and anilines.

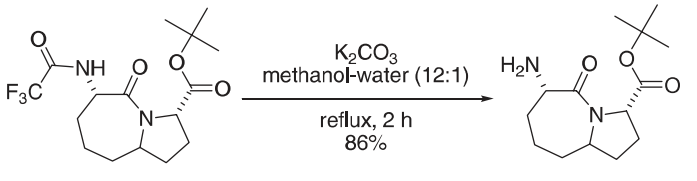
Protection



A dry, 3-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and a 200-mL addition funnel was charged with the HCl salt of the starting material amino ester (21.46 g, 92.7 mmol) and CH_2Cl_2 (134 mL). The solution was stirred while Et_3N (19.69 g, 195 mmol) was added in 1 portion. The solution was cooled to −50 ºC and trifluoroacetic anhydride (21.41 g, 102 mmol) was added dropwise to the reaction mixture through the addition funnel over 1 h. The solution was stirred at −50 ˚C for 1 h and then allowed to warm to 0 ˚C. Aqueous HCl (1.5%, 100 mL) was added to the solution in 1 portion, and the aqueous layer was separated by extraction. The organic extracts were washed with H_2O (100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give a pale yellow solid. The solid was dissolved in EtOAc and the resulting solution was purified by column chromatography (SiO_2, EtOAc/hexane, 1:1) to yield the trifluoroacetyl amide as a white solid (21 g). The solid was recrystallized from CH_2Cl_2/hexane to yield a white crystalline solid (17.6 g, 65%).

Reference: Itagaki, M.; Masumoto, K.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 3292–3295.

Cleavage



A suspension of trifluoroacetyl amide (158 mg, 0.434 mmol) and potassium carbonate (310 mg, 2.25 mmol) in methanol–water (12:1, 13 mL) was heated at reflux for 2 h. The solvent was removed in vacuo, the residue was dissolved in dichloromethane (30 mL), and water (20 mL) was added. The aqueous layer was extracted with a further 2 portions of dichloromethane (30 mL). The combined organic fractions were dried ($MgSO_4$) and the solvent was removed in vacuo to yield the deprotected amine as a yellow oil (100 mg, 86%).

Reference: Davies, D. E.; Doyle, P. M.; Hill, R. D.; Young, D. W. *Tetrahedron* **2005**, *61*, 301–312.

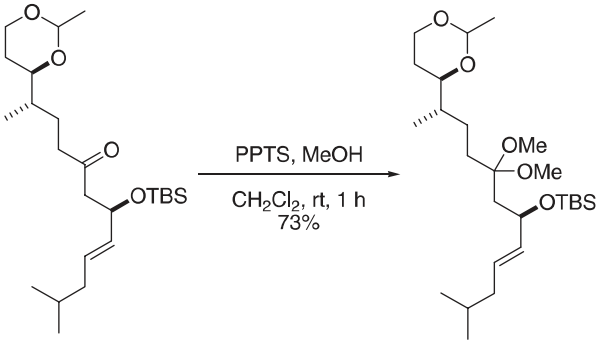
6.3 Aldehydes and Ketones

In this section, the protections and cleavages of four protecting groups for aldehydes and ketones are presented: dimethylketal; 1,3-dioxane; 1,3-dioxolane; and 1,3-dithiane.

6.3.1 Dimethylketal

Protection of a ketone as the corresponding dimethylketal is an older method. Dimethylketal are more readily cleaved under weakly acidic conditions compared with cyclic ketals.

Protection

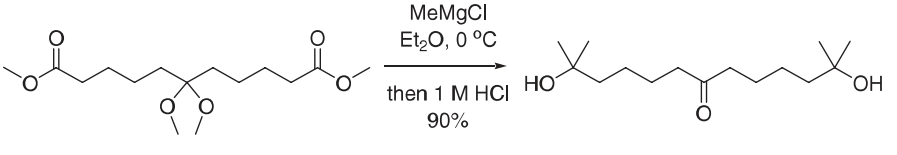


The ketone (0.33 g, 0.64 mmol) was diluted with anhydrous MeOH (7 mL) and catalytic amount of PPTS (0.008 g, 0.032 mmol) was added. The reaction mixture was stirred for 1 h and then diluted with CH_2Cl_2 and work up with saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography provided the dimethyl ketal (0.22 g, 73%).

Reference: Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, *5*, 4641–4644.

Cleavage

Even brief exposure to aqueous HCl is enough to cleave the dimethyl acetal, thus revealing the ketone functionality.



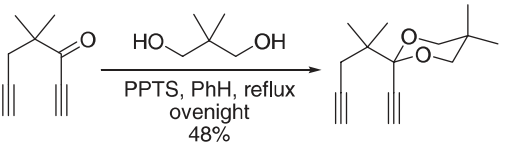
At 0 °C under a N_2 atmosphere, MeMgCl (22% (w/w) in THF (41.5 mL, 0.126 mol) was added dropwise to a solution of the bis-ester (8.5 g, 90% pure, 25.2 mmol) in Et_2O (100 mL) for 30 min. After stirring for 30 min, the reaction mixture was allowed to warm to room temperature, stirred for 2.5 h, and then cooled again to 0 °C. The reaction was quenched by careful addition of HCl (1 M, 125 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (50 mL) and the combined organic layers were washed with brine (2 × 25 mL) and dried. The remaining residue was purified by column chromatography (silica, EtOAc) to give 6.91 g of a brown oil, which was taken up in EtOAc (25 mL). Norrit (0.5 g) was added and the suspension was filtered through kieselguhr and washed with EtOAc (50 mL). The combined filtrate and washings were evaporated in vacuo to give 2,12-dihydroxy-2,12-dimethyl-7-tridecanone (6.73 g, 93%) as a dark yellow oil.

Reference: Bell, R. P. L.; Verdijk, D.; Relou, M.; Smith, D.; Regeling, H.; Ebbers, E. J.; Leemhuis, F. M. C.; Oniciu, D. C.; Cramer, C. T.; Goetz, B.; Pape, M. E.; Krauseand, B. R.; Dasseux, J.-L. *Bioorg. Med. Chem.* **2004**, *12*, 223–236.

6.3.2 1,3-Dioxane

1,3-Dioxane is one of the most popular protecting groups for carbonyls.

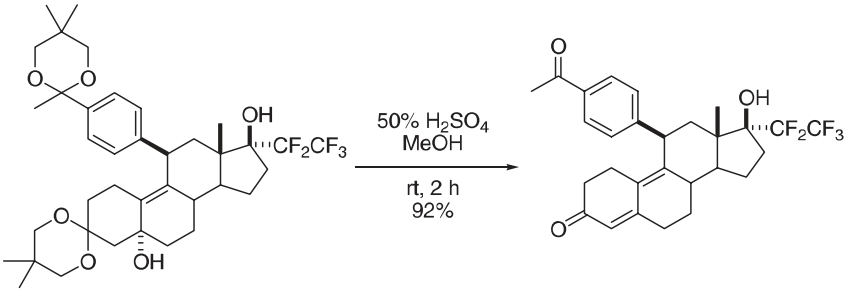
Protection



To a solution of the ynone (3.8 g, 28.3 mmol) in benzene (70 mL) was added PPTS (0.7 g, 2.83 mmol) and 2,2-dimethyl-1,3-propane diol (2.95 g, 28.3 mmol), and the resulting solution was refluxed overnight under Dean–Stark conditions. The reaction was cooled to room temperature and quenched with saturated $NaHCO_3$ solution. The product was extracted with CH_2Cl_2 and the organic layer dried over $MgSO_4$ and the solvent evaporated. Purification of the residue by flash chromatography (hexane/CH_2Cl_2 10:1 to 4:1) furnished the acetal (2.5 g, 48%).

Reference: Rigby, J. H.; Laxmisha, M. S.; Hudson, A. R.; Heap, C. H.; Heeg, M. J. *J. Org. Chem.* **2004**, *69*, 6751–6760.

Cleavage



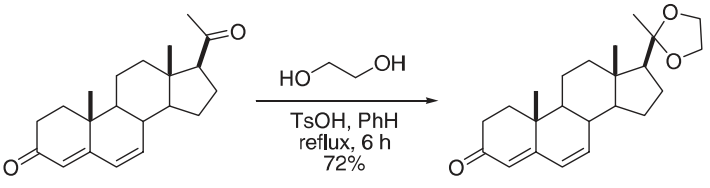
Aqueous sulfuric acid (50%, 0.4 mL) was added to a solution of the starting material (635 mg, 0.91 mmol) in methanol (9 mL). The reaction mixture was stirred at room temperature for 2 h. It was then cautiously poured into saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with EtOAc. The organic portions were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. Chromatography of the residue over silica gel using hexane/EtOAc afforded the bis-ketone (428 mg, 92%) as a colorless foam.

Reference: Fuhrmann, U.; Hess-Stumpp, H.; Cleve, A.; Neef, G.; Schwede, W.; Hoffmann, J.; Fritzemeier, K.-H.; Chwalisz, K. *J. Med. Chem*. **2000**, *43*, 5010–5016.

6.3.3 1,3-Dioxolane

Among all cyclic ketals, five-membered cyclic ketals (1,3-dioxolanes) are more readily hydrolyzed then the corresponding six-membered cyclic ketals (1,3-dioxanes) under acidic conditions.

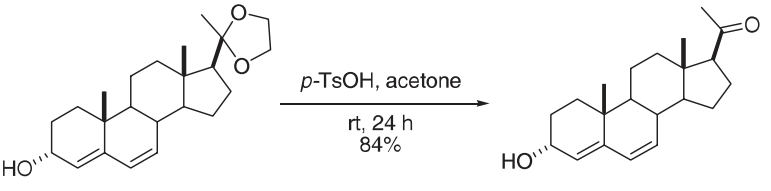
Protection



A mixture of pregna-4,6-diene-3,20-dione (2.70 g, 8.64 mmol), ethylene glycol (5.0 mL), *p*-TsOH (100 mg, 0.52 mmol) and benzene (150 mL) was stirred and heated under reflux for 6 h. Water formed during the reaction was removed by a Dean–Stark trap. The cooled reaction mixture was diluted with Et_2O (600 mL) and sequentially washed with saturated aqueous $NaHCO_3$, water, and brine. The Et_2O extract was stirred and dried over anhydrous $MgSO_4$ (35 g, 0.29 mol) for several hours until thin layer chromatography showed that the ketal group at C-3 was hydrolyzed completely. The mixture was filtered and the solvent was evaporated. The residue was purified by silica gel column chromatography to give the 1,3-dioxolane product (2.32 g, 75%) as a white solid.

Reference: Zeng, C.-M.; Manion, B. D.; Benz, A.; Evers, A. S.; Zorumski, C. F.; Mennerick, S.; Covey, D. F. *J. Med. Chem.* **2005**; *48*; 3051–3059.

Cleavage



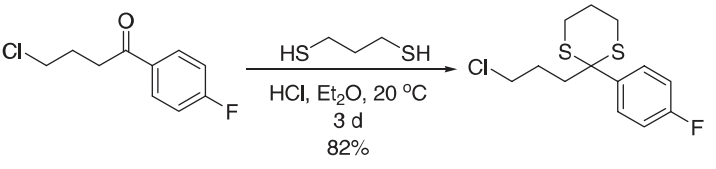
The ketal (70 mg, 0.19 mmol) was treated with *p*-TsOH (10.0 mg, 0.05 mmol) in acetone (15 mL). The mixture was stirred at room temperature for 24 h and extracted with Et_2O. The extract was washed with saturated aqueous $NaHCO_3$, water, and brine, and dried. The residue was purified by silica gel column chromatography to give (3α,5α,7α)-3-hydroxy-7-methylpregnan-20-one (52 mg, 84%) as a white solid.

Reference: Zeng, C.-M.; Manion, B. D.; Benz, A.; Evers, A. S.; Zorumski, C. F.; Mennerick, S.; Covey, D. F. *J. Med. Chem.* **2005**, *48*, 3051–3059.

6.3.4 1,3-Dithiane

1,3-Dithianes are very robust towards acidic hydrolysis. They have to be cleaved using mercury salts or oxidative procedure. One disadvantage is the stench of thiols, which may be alleviated by rinsing the reaction apparatuses with bleach.

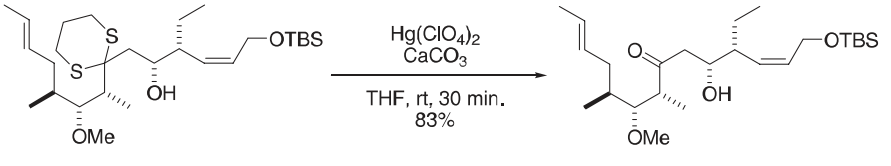
Protection



A mixture of 4-chloro-1-(4-fluorophenyl)butan-1-one (15.0 g, 74.8 mmol), propane-1,3-dithiol (10.0 g, 92.4 mmol), and a 2.0 M ethereal hydrogen chloride solution (90 mL, 180 mmol of HCl) was stirred at 20 ˚C for 3 days and then cooled to 0 ˚C, followed by the addition of water (100 mL). The organic phase was separated, washed with water (2 × 100 mL), and dried over anhydrous Na_2SO_4. The solvent and the excess propane-1,3-dithiol were removed under reduced pressure (crystallization of the residue on standing at 20 ˚C), and the resulting solid was washed with methanol (50 ml) and then recrystallized from *n*-pentane (slow cooling of a saturated boiling solution to 20 ˚C) to give 17.8 g (82%) of 2-(3-chloropropyl)-2-(4-fluorophenyl)-1,3-dithiane as a colorless crystalline solid.

Reference: Heinrich, T.; Burschka, C.; Penka, M.; Wagner, B.; Tacke, R. *J. Organomet. Chem*. **2005**, *690*, 33–47.

Cleavage



To a mixture of the 1,3-dithiane starting material (1.70 g, 3.2 mmol), $CaCO_3$ (500 mg, 5.0 mmol), and THF (200 mL) at room temperature was added mercury (II) perchlorate (167 mL of 0.025 M solution in water). After being stirred for 30 min,

the white precipitate was diluted with Et_2O (300 mL) and filtered through a Celite pad. The aqueous phase was separated and extracted with Et_2O (2 × 100 ml). The combined organic phase was successively washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (100 g) eluting with hexane/EtOAc (20:1) to give the ketone as a colorless oil (1.17 g, 83%).

Reference: Watanabe, H.; Watanabe, H.; Bando, M.; Kido, M.; Kitahara, T. *Tetrahedron* **1999**, *55*, 9755–9776.

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