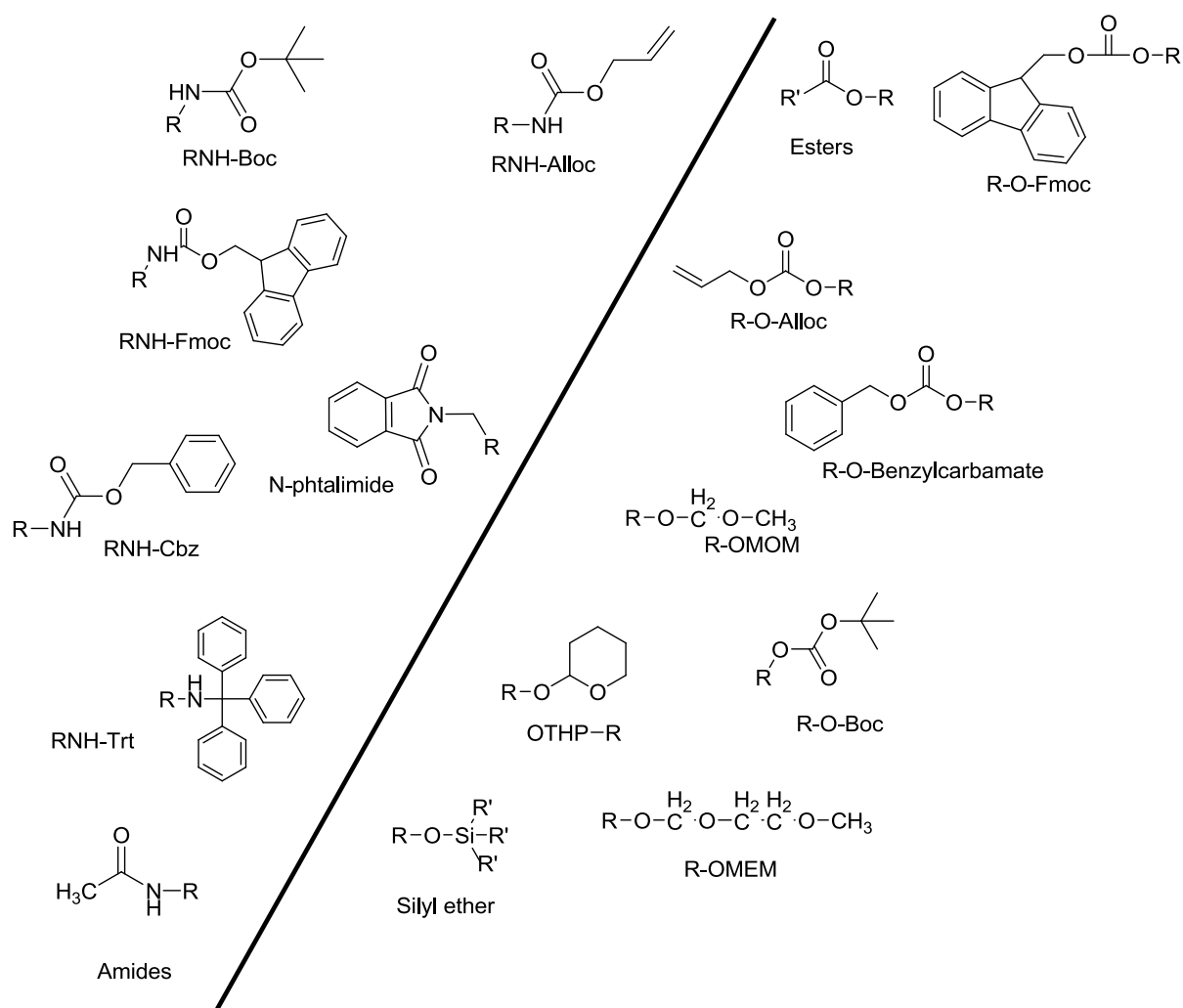


Protecting Groups



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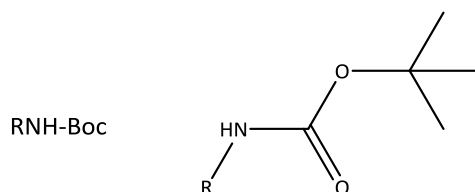
Protecting Groups

Amines

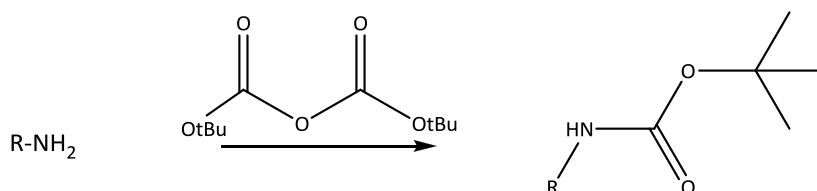
1. Carbamates

t-Butyl Carbamate (Boc)

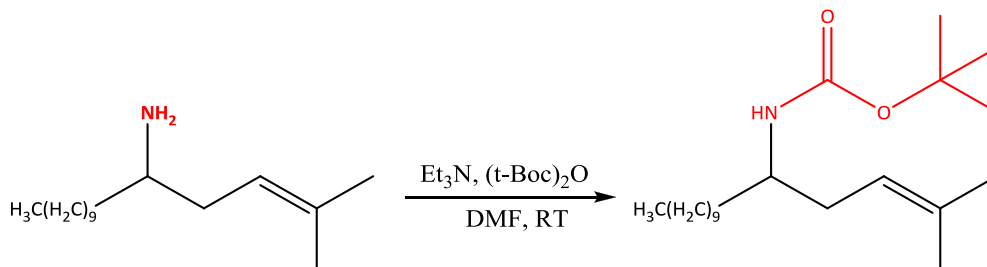
RNH-Boc



Synthesis



General procedure:

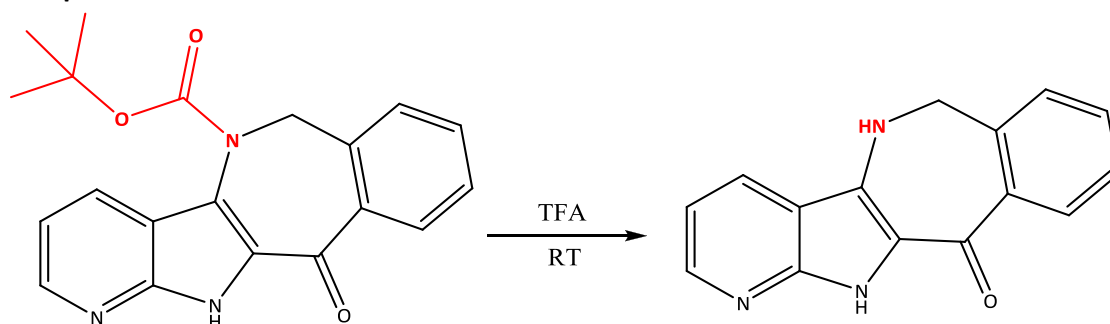


In a 50 ml 1-neck flask with a stirbar, a septum and N₂ inlet, 0.353 g (1.5 mmol, 1 eq) of amine is dissolved in 15 ml of dry DMF and stirred at RT. 0.168 g of Et₃N (1.7 mmol, 1.2 eq) followed by 0.356 g of (*t*-Boc)₂O (1.6 mmol, 1.1 eq) were added. After 45 min, TLC (10:90 EtOAc-hexanes, PMA) showed product spot at R_f 0.56. The reaction mixture was poured into H₂O and extracted with hexanes. The organic layer was dried over MgSO₄, filtered and the solvent was removed by rotary evaporation. The product was isolated by flash chromatography on silica gel using 10:90 EtOAc-hexanes as eluant. The product was a clear, yellow oil.

Cleavage

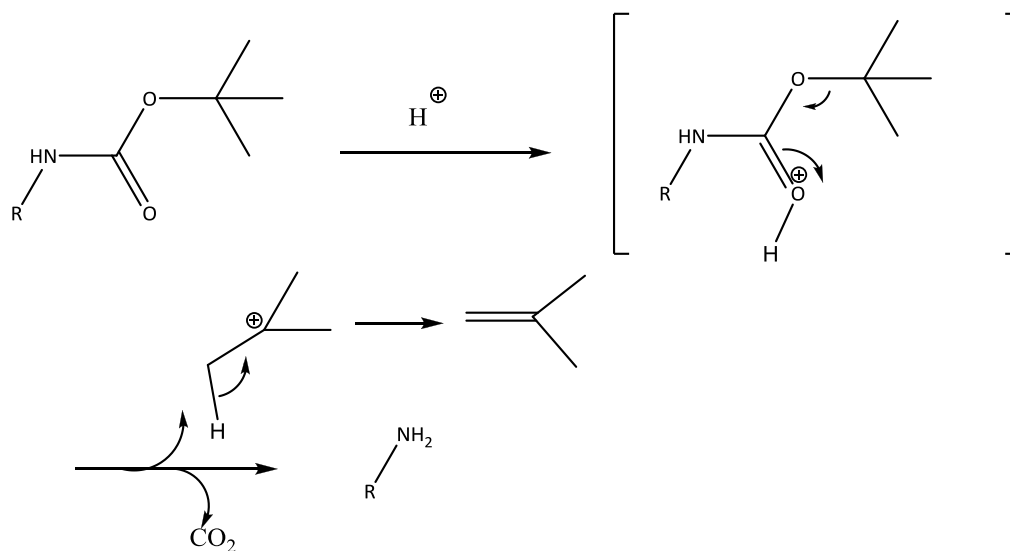
- TMSI
- Stable (Piperidine)
- Strong acid (HCl 3M); TFA (CF₃COOH)

General procedure:

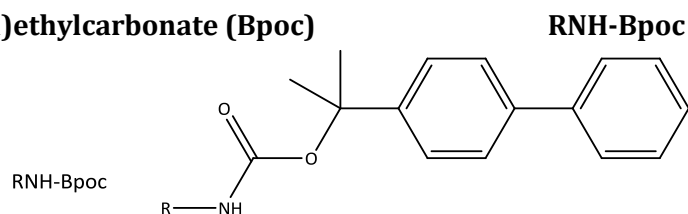


In a 250 ml 1-neck flask with a stirbar, a septum and N₂ inlet, 0.636 g (1.8 mmol, 1 eq) of the (*t*-Boc)amine were dissolved in 18.0 ml of TFA (99%) and stirred at RT. After 15 min, the reaction was quenched by carefully pouring it into 400 ml of saturated aqueous NaHCO₃. The product precipitated as a yellow solid which was washed with acetone and collected by filtration.

Mechanism

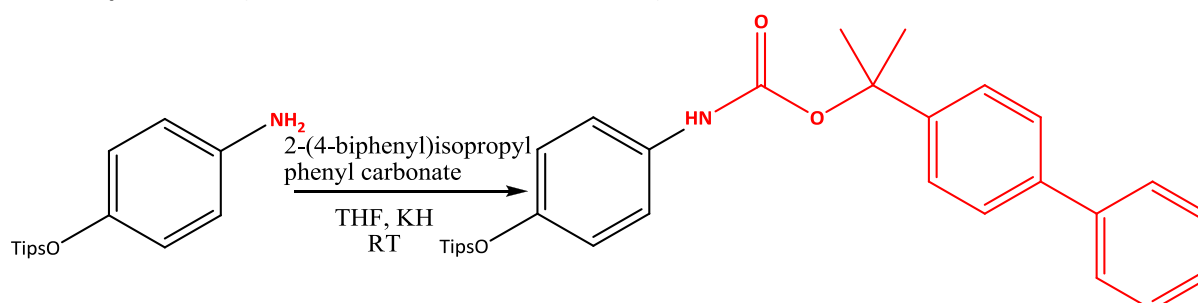


1-methyl-1-(4-biphenyl)ethylcarbonate (Bpoc)



Synthesis

General procedure (*J. Am. Chem. Soc.* **1995**, *117*, 3306):



To a schlenk flask under nitrogen, was added 2-(4-biphenyl)isopropyl phenyl carbonate (18.28 g, 55 mmol), O-triisopropylaminophenol (15.9 g, 59.9 mmol), THF (100 ml) and 35 % potassium hydride KH (18 g, 150 mmol). The reaction mixture was stirred overnight, than diluted with 100 ml of ethyl acetate and carefully quenched with water. The organic layer was washed with water (3 x 100 ml) and brine (100 ml), dried and concentrated. Column chromatography (eluting with 1:99 ethyl acetate/hexanes) followed by recrystallisation from hexanes gave 16.52 g (60 %) of the desired product as white crystals.

Cleavage

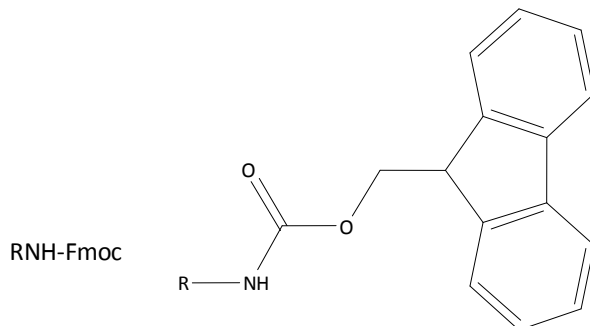
Comparison of cleavage rate

Group	K ^a rel	K ^b rel
Boc	1	1
Bpoc	2800	2000

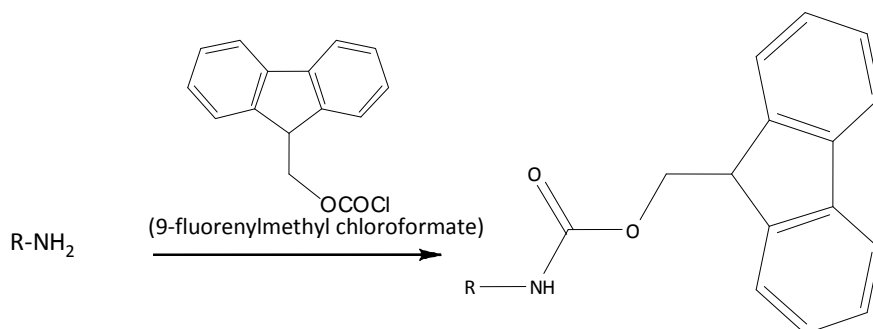
a) 80 % AcOH/H₂O; b) AcOH/HCO₂H/H₂O (7:1:2)

9-fluorenylmethyl (Fmoc)

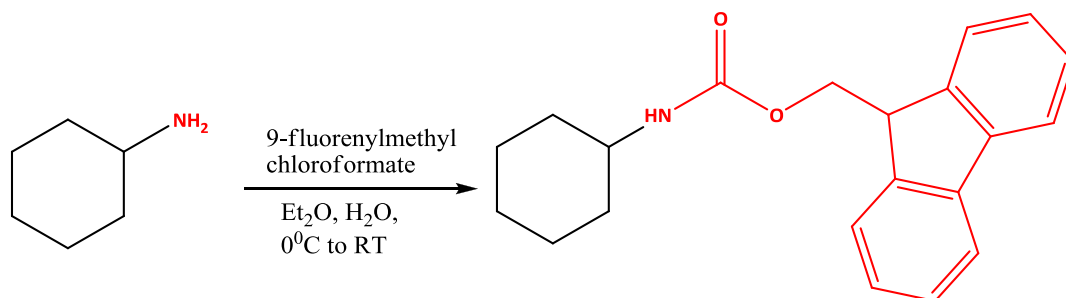
RNH-Fmoc



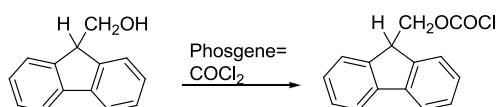
Synthesis



General procedure (*J. Org. Chem.* **1972**, 37, 3404):



A solution of 1 g of 9-fluorenylmethyl chloroformate* in 200 ml of ether was cooled in an ice bath and 0.769 g of cyclohexylamine in 100 ml of ether was added slowly. The mixture was stirred in the ice bath for 20 min and at room temperature for 20 min. after filtration to remove the amine salt, the ether solution was washed with H₂O, dried (MgSO₄), and evaporated and the residue was recrystallized from ether to give 1.2 g (97 %) of the carbamate.



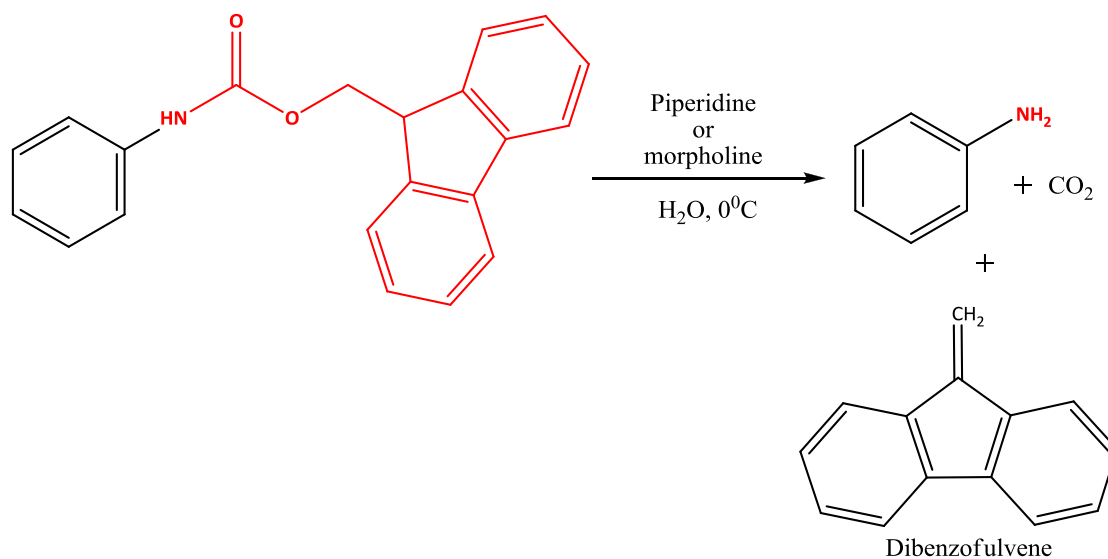
*Preparation of 9-fluorenylmethyl chloroformate: A

solution of 7.12 g of phosgene in 75 ml of CH₂Cl₂ was cooled in an ice bath and 1.28 g of 9-fluorenylmethanol was added slowly with stirring. The solution was stirred for 1 hour in the ice bath and then let stand for 4 hours at ice-bath temperature. Removal of solvent and excess phosgene under reduced pressure gave oil which crystallized after several hours to give 16 g (95 %) of the crude chloroformate.

Cleavage

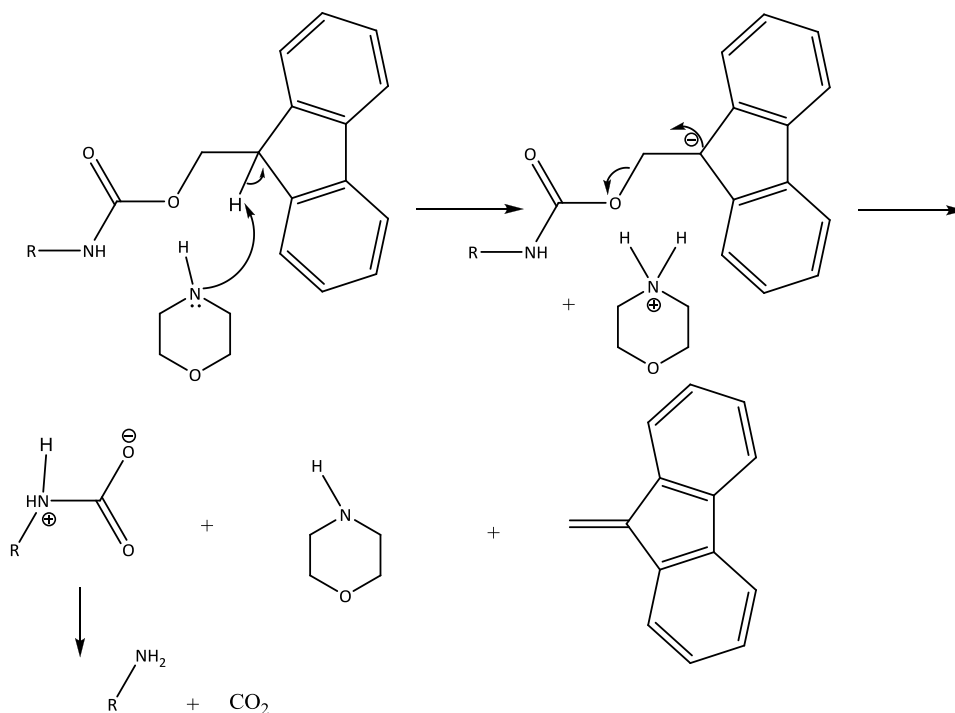
- ✚ Mild base (Piperidine, morpholine ...)
- ✚ Liquid ammonia
- ✚ Orthogonal to Boc

General procedure (*J. Org. Chem.* **1972**, *37*, 3404):



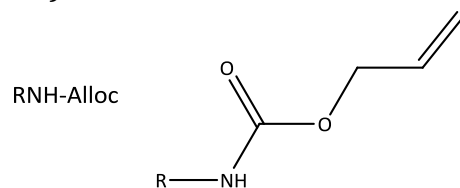
A solution of 0.5 g of Fmoc-NHC₆H₅ in 15 ml of piperidine or morpholine was stirred at room temperature for 40 min and poured into 250 ml of cold H₂O. The precipitated solid was removed by filtration and the filtrate was extracted with ether. The dried (MgSO₄) ether extracts were evaporated.

Mechanism

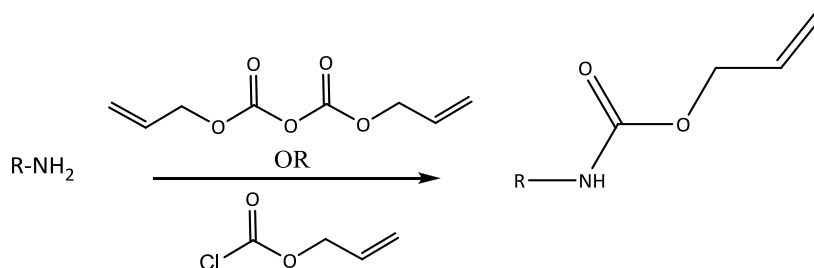


Allylcarbamate (Alloc)

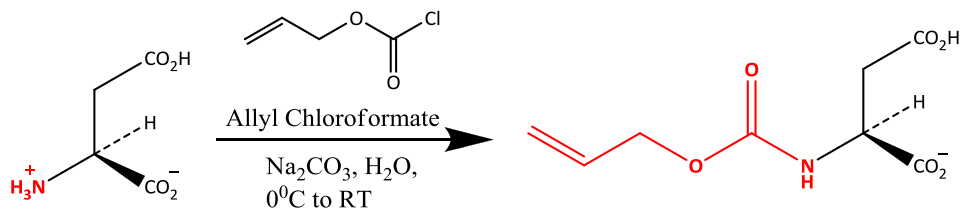
RNH-Alloc



Synthesis



General procedure (*Tetrahedron* **1996**, *52*, 12386):



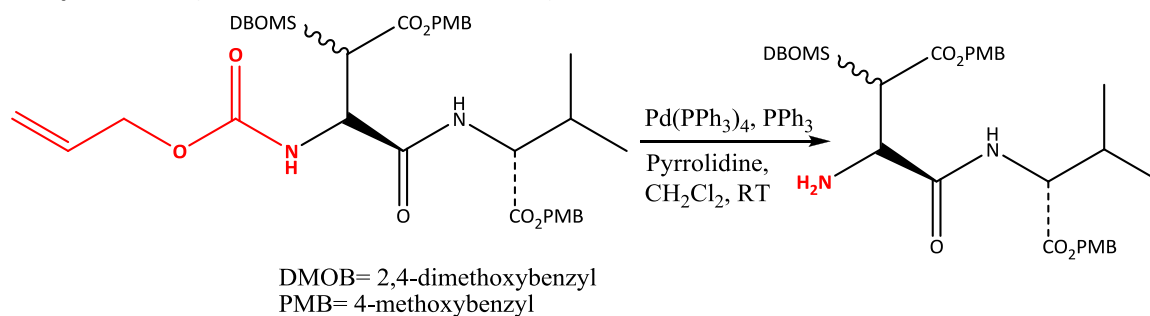
Allyl chloroformate (10.9 ml, 103 mmol, 0.9 eq) was added slowly to a stirred solution of L-aspartic acid (15.0g, 113 mmol) and sodium carbonate (31.8g, 300 mmol, 2.7 eq) in water (400ml) at 0°C. The mixture was stirred for 12 h during which time, it was allowed to slowly attain room temperature. The reaction mixture was washed with ethyl acetate (2 x 500 ml) and the separated aqueous phase

was acidified to pH 1 by addition of concentrated hydrochloric acid. The resulting suspension was extracted with several portions of ethyl acetate (1000 ml), the combined extracts being dried (Na_2SO_4), filtered and evaporated *in vacuo* to give N-allyloxycarbonyl-L-aspartic acid as a colourless solid (17.5 g, 79 % from allyl chloroformate).

Cleavage

- Removed with Pd(0) Tetrakis and a reducing agent (Bu_3SnH , Et_3SiH ...)
- Orthogonal to Boc and Fmoc

General procedure (*Tetrahedron* 1996, 52, 12386):

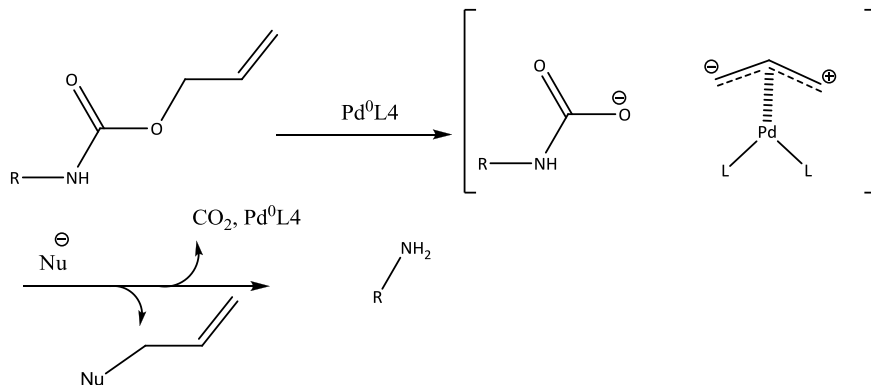


To a stirred solution of *(2R,3R)*-N-allyloxycarbonyl-S-(2,4-dimethoxybenzyl)-β-(4-methoxybenzyl)-3-mercaptoaspartyl-D-valine-(4-methoxybenzyl) ester (1.20 g, 1.63 mmol) and pyrrolidine (678 μl, 8.14 mmol, 5 eq) in dichloromethane (10 ml) at room temperature was added triphenylphosphine (85.4 mg, 0.33 mmol, 0.2 eq) and tetrakis(triphenylphosphine)palladium (0) (94.2 mg, 81.5 μmol, 0.05 eq). After stirring at this temperature for 15 min, the solvent was removed *in vacuo* and the residue was dissolved in acetonitrile (100 ml). The resulting solution was washed with 40-60 petroleum ether (3 x 250ml) and the separated acetonitrile phase was evaporated *in vacuo* the residue being purified by flash chromatography on silica gel (eluting with a gradient from 7:3v/v 60-80 petroleum ether : ethyl acetate to 2:3v/v 60-80 petroleum ether : ethyl acetate). This gave 2R-S-(2,4-dimethoxybenzyl)-[β-(4-

Protecting Groups By Jessy AZIZ and Abdallah HAMZE

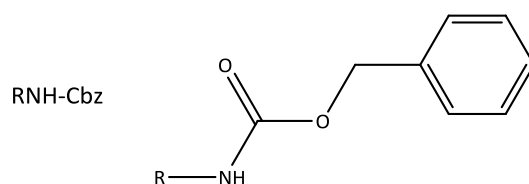
methoxybenzyl)-3-mercaptoaspartyl-D valine-(4-methoxybenzyl) ester as a 1:1 mixture of diastereoisomers (overall 987 mg, 93 %).

Mechanism

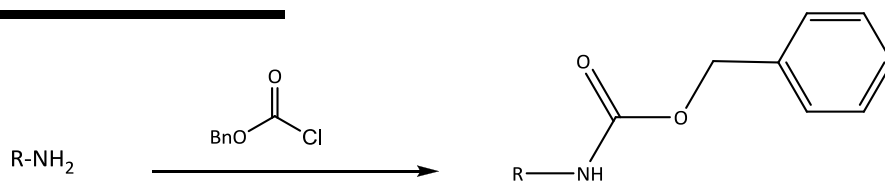


Benzylcarbamate (Cbz or Z)

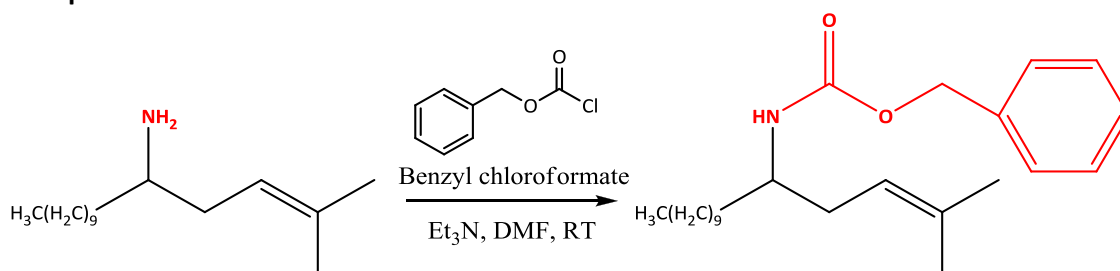
RNH-Cbz



Synthesis



General procedure:



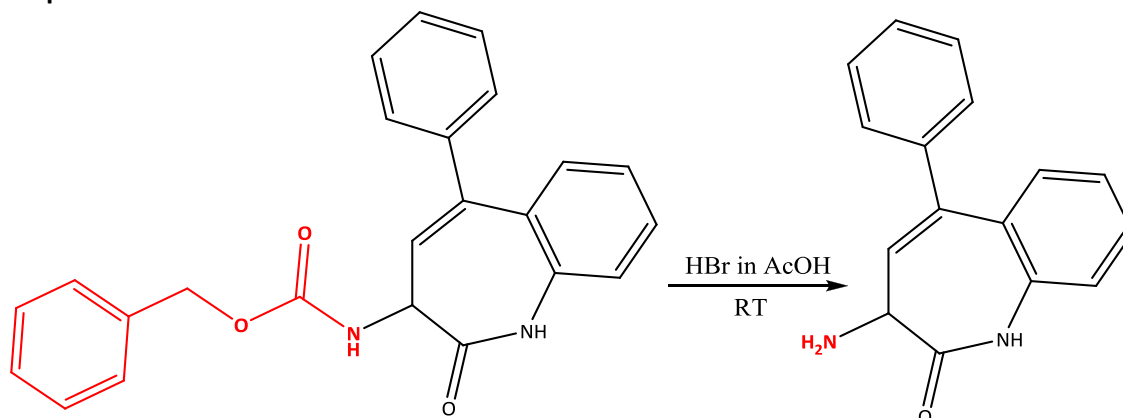
In a 50 ml 1-neck flask with a stirbar, septum and N₂ inlet, 0.342 g of the amine (1.4 mmol, 1 eq) was dissolved in 15 ml of dry DMF and stirred at RT. Then, 0.170 g of Et₃N (1.7 mmol, 1.2 eq) was added followed by 0.295 g (1.7 mmol, 1.2 eq) of benzyl chloroformate. The reaction mixture became cloudy.

After 45 min, the reaction mixture was poured into water and extracted with hexanes. The organic layer was dried over MgSO_4 , filtered and the solvent was removed by rotary evaporation. The product was isolated by flash chromatography on silica gel using 10:90 EtOAc-hexanes as eluant. The product was a white solid (64 %).

Cleavage

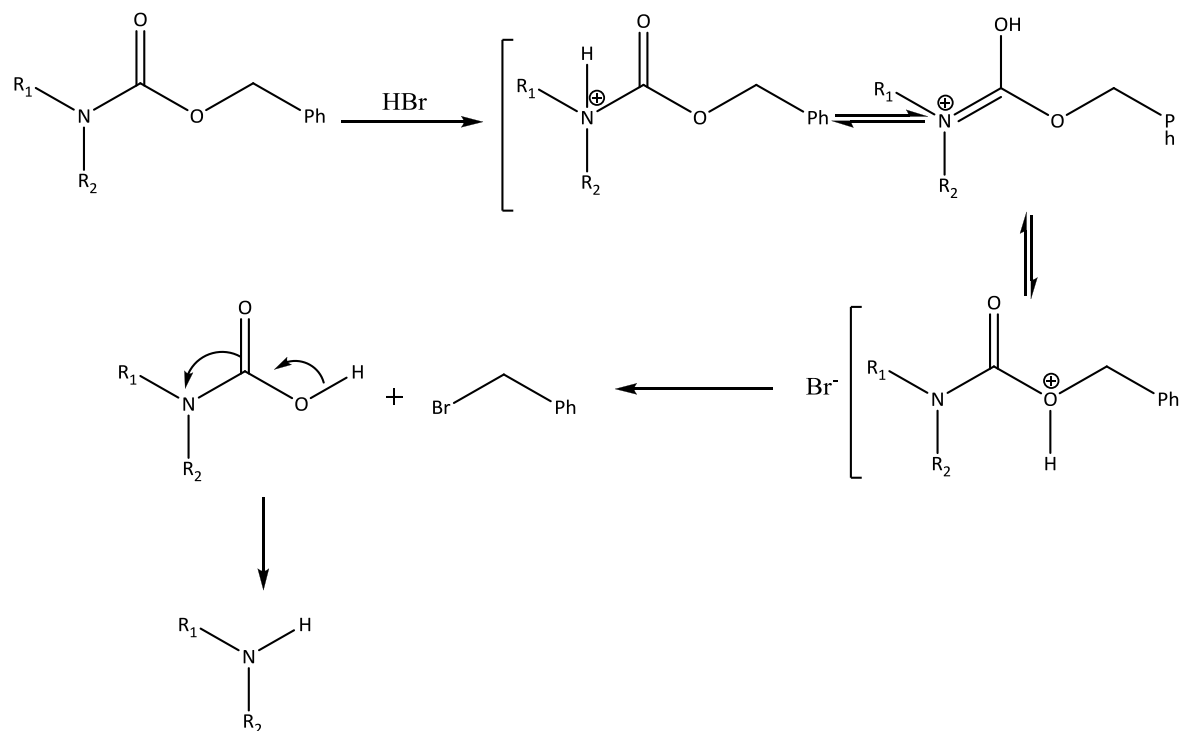
- Hydrogenolysis
- PdCl_2 , Et_3SiH
- TMS-I
- BBr_3
- Na/NH_3
- Orthogonal to Boc and Fmoc

General procedure:



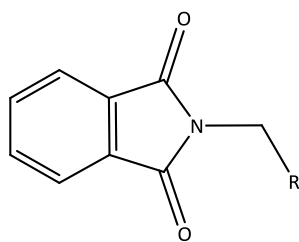
In a 10 ml 1-neck flask with a stirbar, septum and N_2 inlet, a mixture of 0.500 g of benzodiazepine (1.3 mmol, 1 eq) and 2.6 ml of 30 wt% Hbr in acetic acid (13.1 mmol, 10 eq) was stirred at RT. Bubbling was observed as the starting material slowly dissolved to give a yellow solution. After 2 h, TLC (10:90 MeOH- CH_2Cl_2 , UV) showed product at $R_f = 0.33$. The reaction mixture was carefully poured into sat. aq. NaHCO_3 . The mixture was saturated with NaCl and extracted with CHCl_3 . The organic layer was dried over Na_2SO_4 , filtered and concentrated by rotary evaporation. The product was isolated by flash chromatography on silica gel using 10% MeOH- CH_2Cl_2 as eluant. The product was a white solid (64 %).

Mechanism



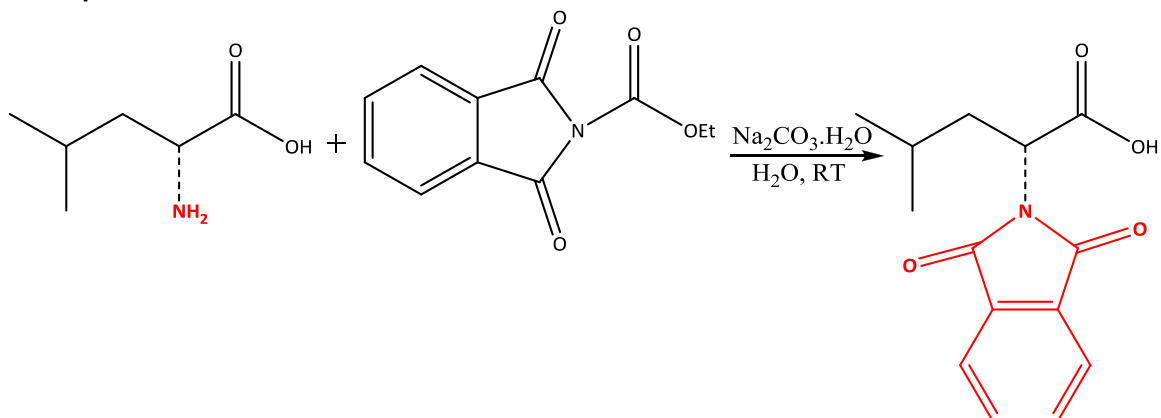
2. Imides

N-phthalimide



Synthesis

General procedure:



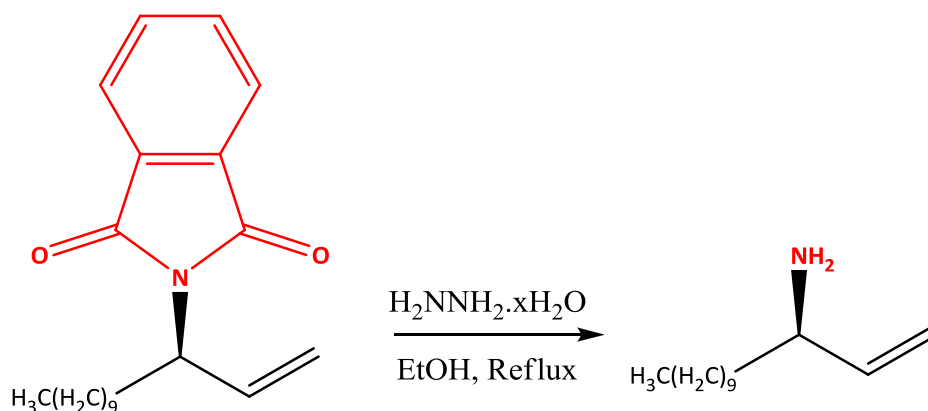
In a 50 ml 1-neck flask with a stirbar and a cap, 0.210 g (1.6 mmol, 1 eq) of L-leucine and 0.223 g (1.8 mmol, 1.2 eq) of $\text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}$ were dissolved in 16 ml of water and stirred at RT. Then, 0.423 g (1.9 mmol, 1.2 eq) of *N*-carboethoxyphthalimide was added. After 20 min, the undissolved solids were

removed by filtration and the filtrate was acidified to Ph = 2 with 1.0 N HCl. A white precipitate formed. The mixture was extracted with Et₂O and the organic layer was dried over MgSO₄, filtered and the solvent was removed by rotary evaporation to afford the product as a clear, colorless, viscous oil (70 %).

Cleavage

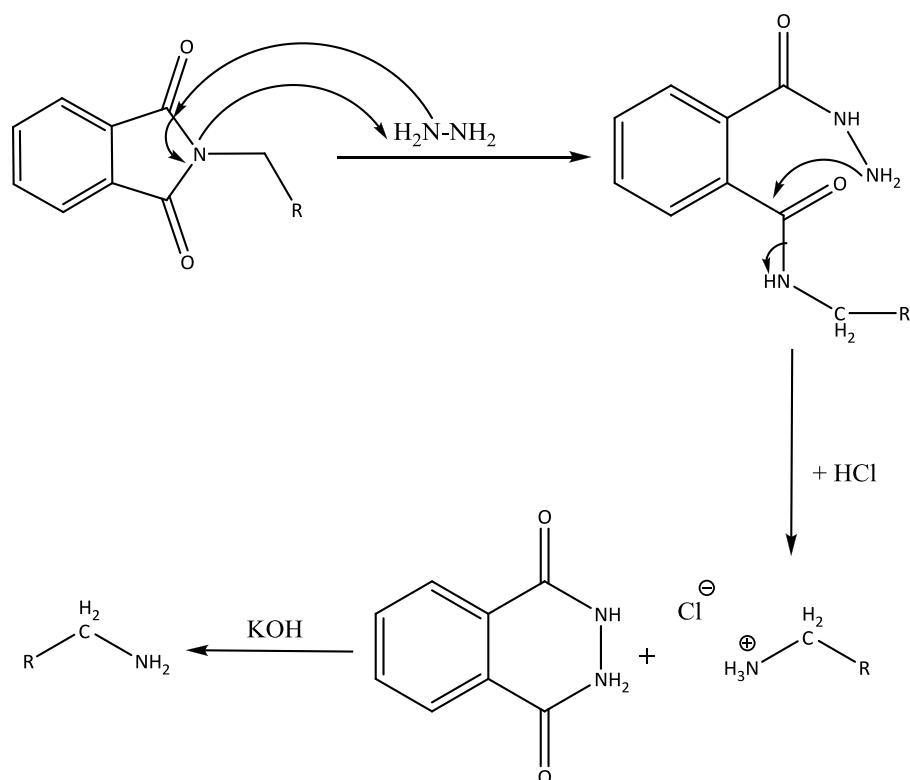
Hydrazine (NH₂-NH₂), EtOH

General procedure:

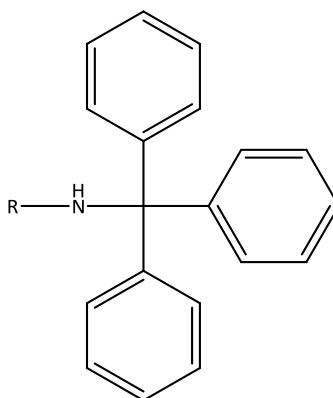


In a 50 ml 1-neck flask with a stirbar, condenser and N₂ inlet 0.602 g (1.8 mol, 1 eq) of phthalimide was dissolved in 20 ml of absolute EtOH and stirred at RT. Then, 0.275 ml (4.7 mmol, 2.5 eq) of H₂NNH₂·xH₂O (55% H₂NNH₂, Aldrich) was added and heated to reflux. After 3 h, TLC (20:80 EtOAc-hexanes, PMA) showed product at R_f = 0.73 and a white precipitate had been formed. 6 ml of conc. HCl were added, stirred and filtered through Celite. The solvent was removed by rotary evaporation to afford a solid. The solid was triturated with 2:1 EtOH-H₂O and filtered through Celite. The pH of the filtrate was raised to >10 with 1.0 N NaOH and extracted with Et₂O. The organic layer was dried over Na₂SO₄, filtered and the solvent was removed by rotary evaporation. At this point the product was sufficiently pure for further elaboration and was a clear, colorless oil (95 %).

Mechanism



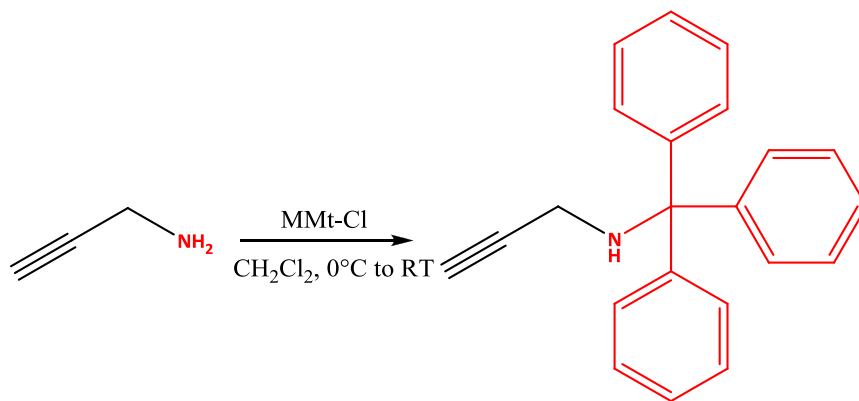
3. Trityls MMT (Methyltrityl)



Synthesis

MMt-Cl, Et_3N

General procedure (*Org. Lett.* **2011**, *13*, 1382):

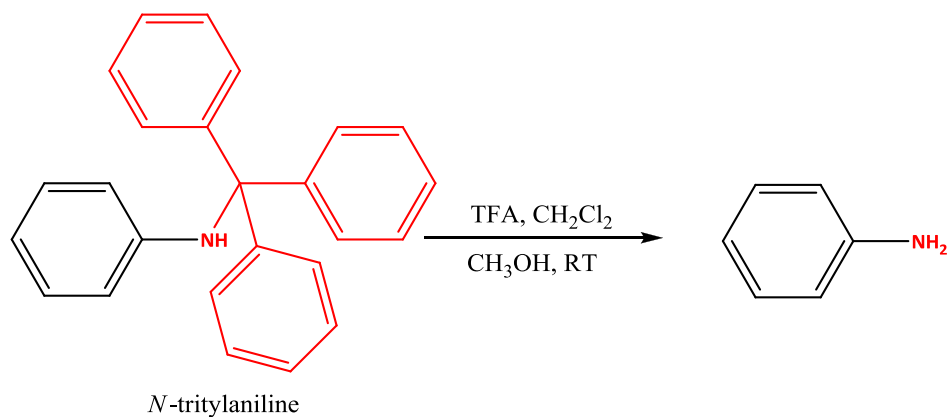


To a solution of propargylamine (14.78 g, 0.269 mmol) in dry CH₂Cl₂, the solution of trityl chloride (35.80 g, 0.128 mmol) in CH₂Cl₂ (75 ml) was added dropwise at 0°C. The solution was stirred at RT overnight. The reaction mixture was partitioned with water (50 ml), and the organic layer was washed with brine, dried (Na₂SO₄) and concentrated. The residue was crystallized from hexane to give the protected amine as a white solid (91 %).

Cleavage

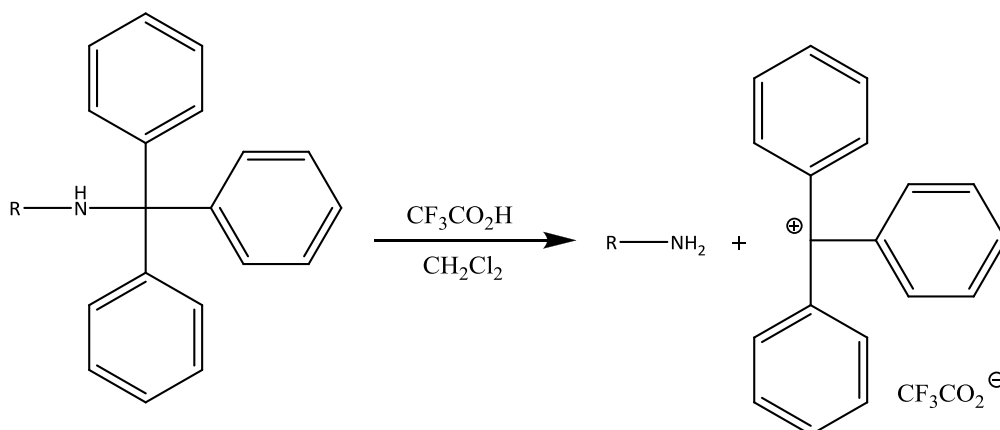
- ✚ CF₃CO₂H (1%) in CH₂Cl₂ (triphenylmethyl carbocation is stable)
- ✚ Orthogonal to BOC

General procedure (*Tetrahedron Lett.* **2005**, *46*, 1357):

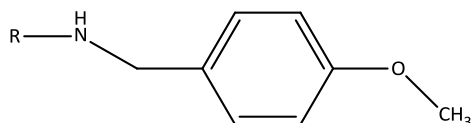


N-Tritylaniline (1 mmol) in a solution of 5 ml 60 % TFA in CH_2Cl_2 was stirred for 10 min at RT, then 2 ml of CH_3OH were added and the yellow colour immediately disappeared. After stirring for about 1 hour, the solvent was evaporated in vacuo and the hydrochloride salt ($\text{C}_6\text{H}_5\text{NH}_2\cdot\text{HCl}$) was precipitated by the addition of 10 ml 1N HCl in CH_3OH and subsequent concentrated to dryness. The salt was washed with dry ether.

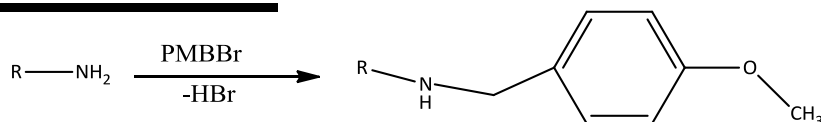
Mechanism



4. PMB (para-methoxybenzyl ether)



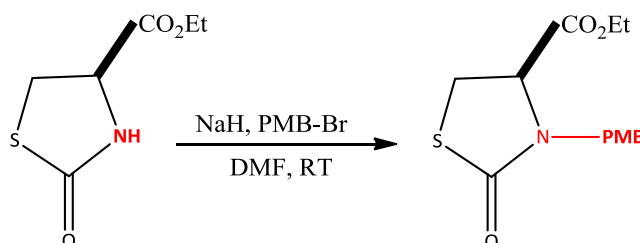
Synthesis



✚ Anisaldéhyde, Benzène then NaBH_4 , MeOH

✚ PMB-Br, NaH, DMF

General procedure (*J. Am. Chem. Soc.* 1992, 114, 2995):



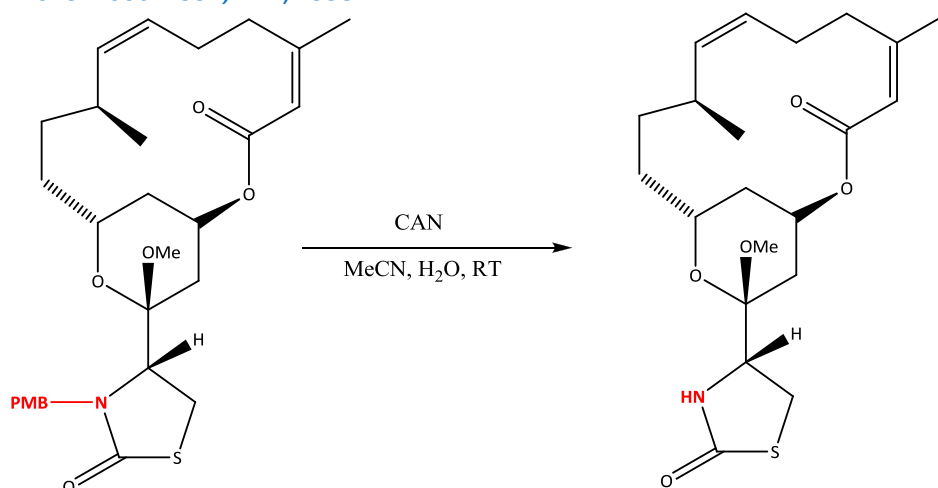
A suspension of sodium hydride (80% oil dispersion, 0.950 g, 31.7 mmol) in dry DMF (100 ml) was cooled to 0°C , and the amine (4.62 g, 26.4 mmol) dissolved in DMF (25 ml) was added slowly. The reaction was stirred for 30 min, and a solution of 4-methoxybenzylbromide (6.86 g, 34.3 mmol)

in DMF (7 ml) was added. The mixture was stirred for 1.5 h at room temperature, poured into ether, and washed with water. The aqueous phase was extracted with ether, and the combined organic layers were washed with brine, dried (MgSO_4), filtered, and concentrated. Flash chromatography (hexane:EtOAc, 4:1) gave the protected amine as a colorless oil (6.144 g, 78.9 %).

Cleavage

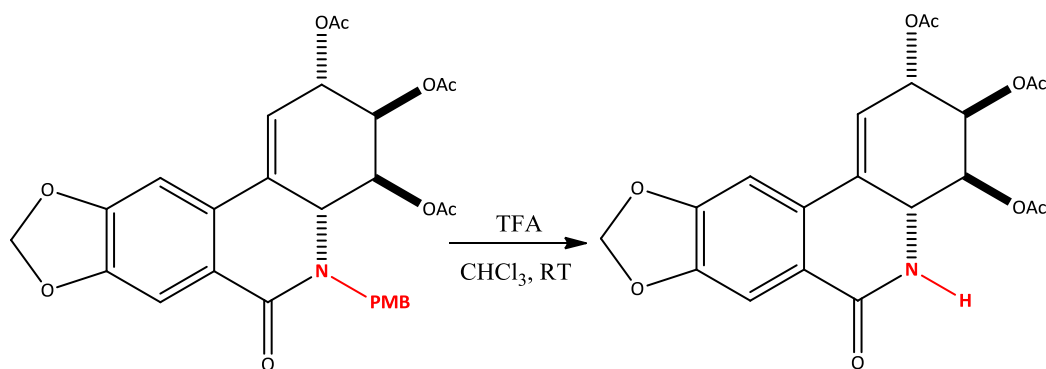
General procedure:

1- *J.Am.Chem.Soc.* **1992**, *114*, 2995:



A suspension of the protected amine (9.0 mg, 0.017 mmol) in acetonitrile/water (3:1, 85 μl) was treated with ceric ammonium nitrate [0.25 M in acetonitrile/water (3:1), 136 μl , 0.034 mmol]. As the resulting mixture was stirred at room temperature for 25 min, it became homogeneous. The solution was poured into brine and extracted with chloroform (3 X 40 ml), and the combined organic layers were dried (MgSO_4), filtered, and concentrated. Preparative thin-layer chromatography (hexane/EtOAc, 1:1; 0.25 mm X 20 cm X 20 cm plate, E. Merck, 1 development) afforded the amine as a colorless oil (3.3 mg, 48 %).

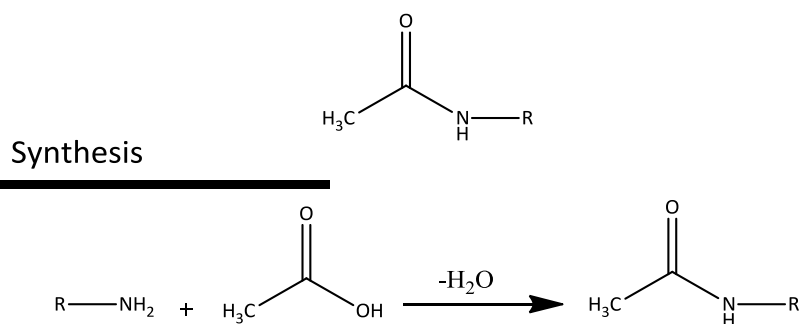
2- *J.Org.Chem.* **1993**, *58*, 4441:



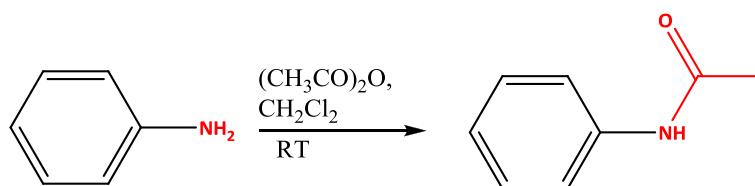
A solution of the protected amine (149 mg, 0.274 mmol) in TFA (0.75 ml) and CH₃Cl (0.75 ml) was stirred at rt for 1.5 h. The reaction mixture was concentrated, and the residual TFA was removed by

co-evaporation with several portions of chloroform to give a residue. Silica gel chromatography of the residue [6 g, EtOAc-toluene (1:4) eluent] gave the deprotected amine (90.5 mg, 79 %) as a crystalline residue.

5. Amides

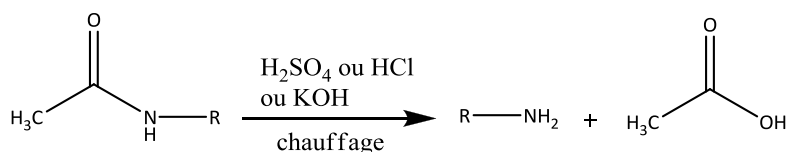


General procedure (*J. Am. Chem. Soc.* **2008**, *130*, 16474):



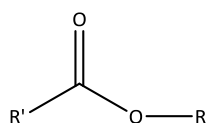
Aniline (10.1 ml, 109.7 mmol, 1 eq) was added to a round bottom flask via a syringe and fitted with a rubber septum. The flask was purged with argon and dry DCM (300 ml, 0.4 M) was added. Acetic anhydride (12.5 ml, 132.2 mmol, 1.2 eq) was added and the reaction was stirred at RT and monitored by TLC. Upon completion (generally a couple of hours, but as short as 20 minutes), the reaction mixture was washed with a saturated solution of sodium carbonate, the organic layer dried with MgSO_4 and the solvent removed under pressure. The product was obtained in quantitative yield (14.8 g). In most cases, analytically pure acetanilides can be obtained after extraction, however if necessary purification by flash chromatography with ethyl acetate/pet. ether was used.

Cleavage

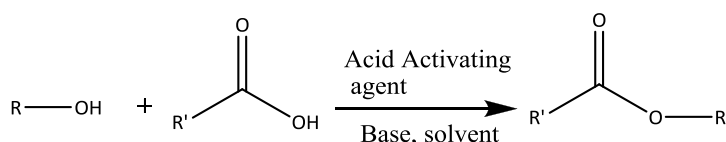


Hydroxyls

1. Esters



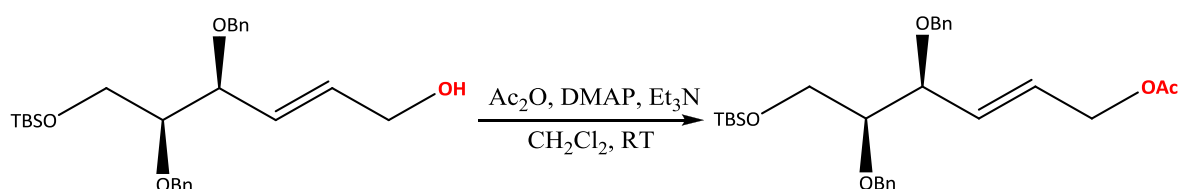
Synthesis



Acid Activating agent: 4-DMAP, Carbodiimide (DCC, DIC, EDAC, EDCI)



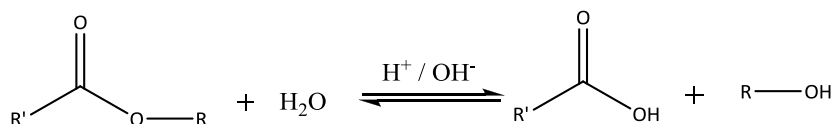
General procedure:



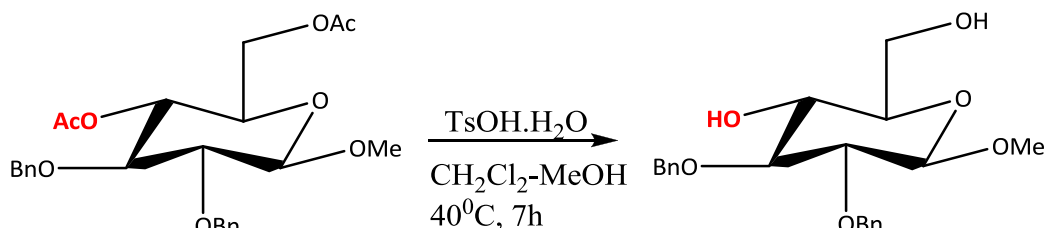
In a 1000 ml 1-neck flask with a stirbar, septum and N₂ inlet, 17.966 g (40.6 mmol, 1 eq) of alcohol were dissolved in 400 ml of dry CH₂Cl₂ and stirred at RT. Then, 19.10 ml (202.4 mmol, 5 eq) of Ac₂O were added followed by 22.6 ml (162.1 mmol, 4 eq) of Et₃N and 0.469 g (4.1 mmol, 0.1 eq) of DMAP. After 3 h, the reaction mixture was quenched with sat. aq. NH₄Cl and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄, filtered and the solvent was removed by rotary evaporation. The product was isolated by flash chromatography on silica gel using 10:90 EtOAc-hexanes as eluant. The product was a clear, colorless oil (94 %).

Cleavage

✚ Acid hydrolysis / Basic Saponification

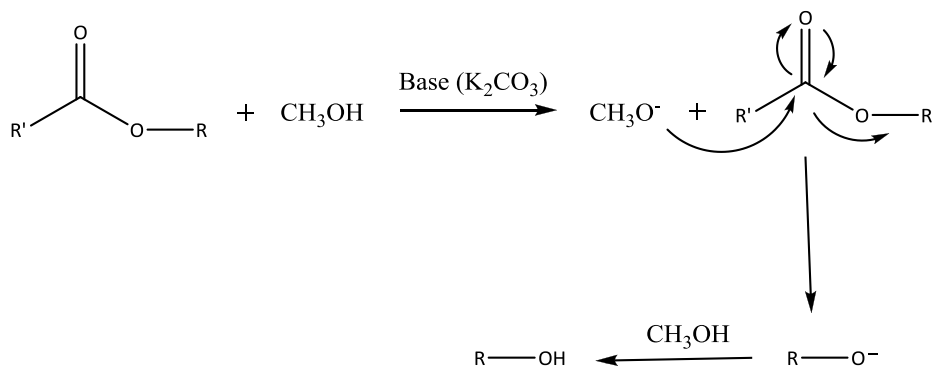


General procedure (*Tetrahedron Lett.* **2001**, 42, 3187):



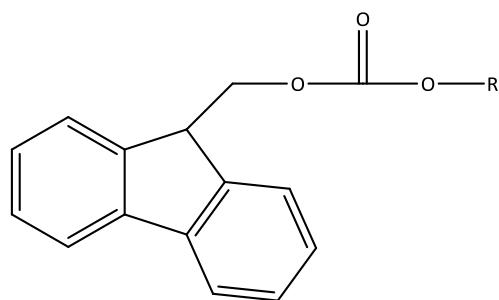
The substrate was dissolved in $CH_2Cl_2/MeOH$ (9:1) and then p -TsOH·H₂O (1.0 equiv. per acetate) was added. The resulting mixture was stirred at 40°C and the reaction was monitored by TLC. After the reaction was completed, the mixture was extracted with CH_2Cl_2 and the organic phase washed with aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4 , and evaporated in vacuo. The product was purified by flash column chromatography (Rdt = 91 %).

✚ Transesterification (MeOH/Base)

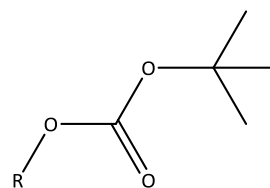


✚ Enzymatic cleavage (Lipases)

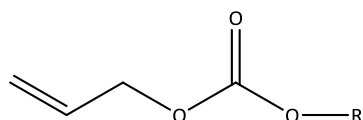
2. Carbamates



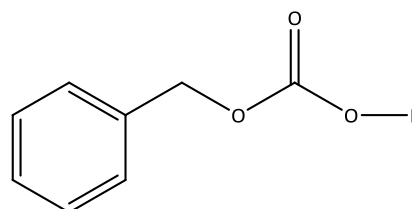
R-O-Fmoc



R-O-Boc



R-O-Alloc

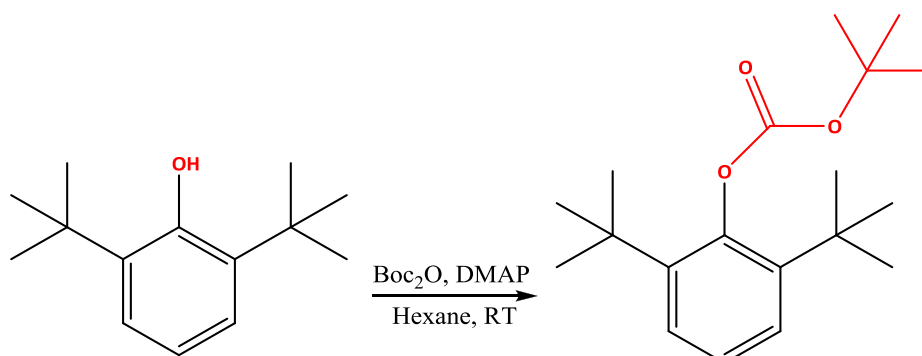


R-O-Benzylcarbamate

Synthesis

Ref. Amines section 1 (Carbamates)

General procedure: **Ex: R-OBoc**(*Tetrahedron Lett.* **1998**, *39*, 2705):

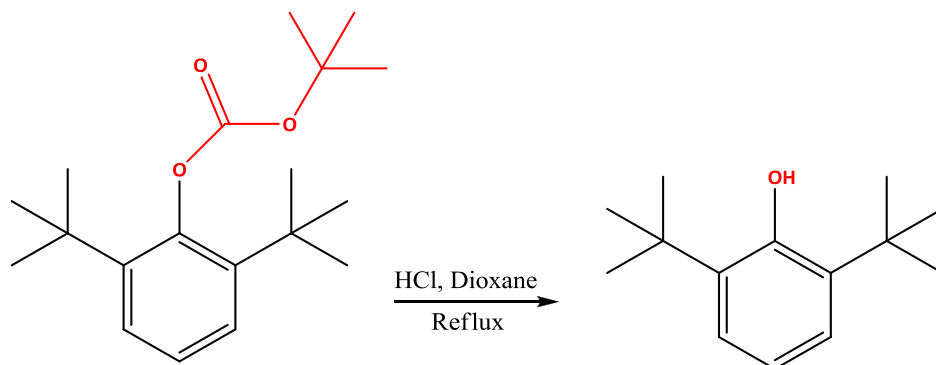


The phenol substrate and Boc_2O (1.02 eq) were dissolved in hexanes (0.7 M) and DMAP (0.05 eq) was added. When the reaction was complete as judged by TLC (19 h), the mixture was partitioned between ethyl acetate, brine and 1 N HCl. The layers were separated and the organic layer was washed with aqueous NaHCO_3 , dried (Na_2SO_4) and concentrated. The product was purified by chromatography on flash silica gel to give 93 % of the protected alcohol.

Cleavage

Ref. Amines section 1 (Carbamates)

General procedure: **Ex: R-OBoc**(*Tetrahedron Lett.* **1998**, *39*, 2705):



The substrate was dissolved in dioxane (10 ml per g of substrate) and an equivalent volume of 3 M HCl was added. The mixture was heated at reflux for 3 h, then partitioned between EtOAc and aqueous NaHCO₃. The organic layer was dried (Na₂SO₄) and evaporated to give the alcohol (89 %).

3. Ethers

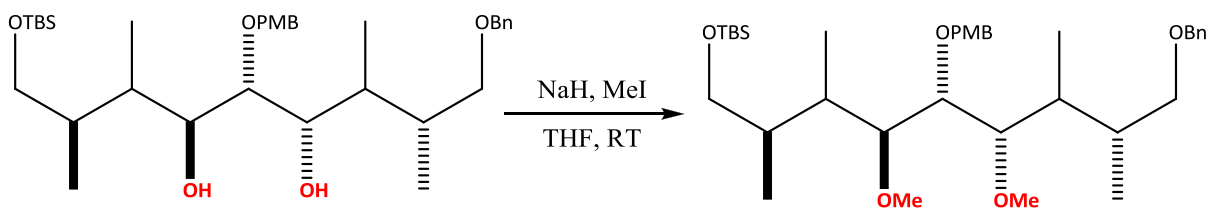
Methyl ethers

R—O—CH₃ Difficult to remove except for on phenols

Synthesis

- ✚ CH₂N₂, silica or HBF₄
- ✚ NaH, MeI, THF

General procedure (*J. Am. Chem. Soc.* **1990**, *112*, 2998):



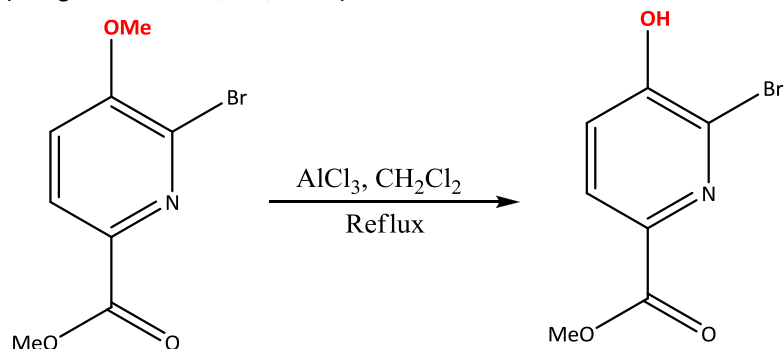
A 25 ml round-bottom flask fitted with a septum, nitrogen inlet and a magnetic stirring bar, was charged with 208 mg (5.19 mmol) of 60 % sodium hydride dispersion. The sodium hydride was washed with 4 x 2 ml of distilled tetrahydrofuran (THF) and then suspended in 2 ml of distilled THF. To the suspension were added 646 μ l (1.47 g, 10.38 mmol) of methyl iodide (MeI) and 970 mg (1.73 mmol) of the diol at 0 °C. The reaction was allowed to warm to RT over 30 min (an exotherm to 24 °C was observed) and then stirred at RT for 36 h. The reaction was cautiously quenched by the addition of 5 ml of saturated aqueous sodium thiosulfate followed by 10 ml of water. The reaction mixture was extracted with 3 x 20 ml of ethyl acetate. The organic layers were combined, dried over sodium

sulfate, filtered, concentrated and chromatographed (8:1 Hexane/Ethyl acetate) to provide 1 g (98 %) of the corresponding dimethyl ether.

Cleavage

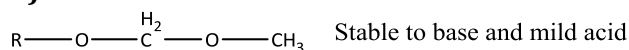
- AlBr₃, EtSH
- AlCl₃
- PhSe⁻
- Ph₂P-
- Me₃Si

General procedure (*J.Org.Chem.* **1996**, *61*, 4623):



To a solution of the methyl ether (3.34 g, 13.6 mmol) in 200 ml of freshly distilled CH₂Cl₂ under a nitrogen atmosphere was added AlCl₃ (22.0 g, 0.165 mol), and the cloudy solution was refluxed for 2 days. This mixture was slowly poured into 100 ml of 1 N HCl to destroy excess AlCl₃ (CAUTION!), extracted with CH₂Cl₂, and dried over Na₂SO₄. Evaporation of the solvent followed by silica gel chromatography (CH₂Cl₂: ethyl acetate = 3:1) gave 2.92 g (93%) of the alcohol as a white solid.

Methoxymethyl ethers (MOM)

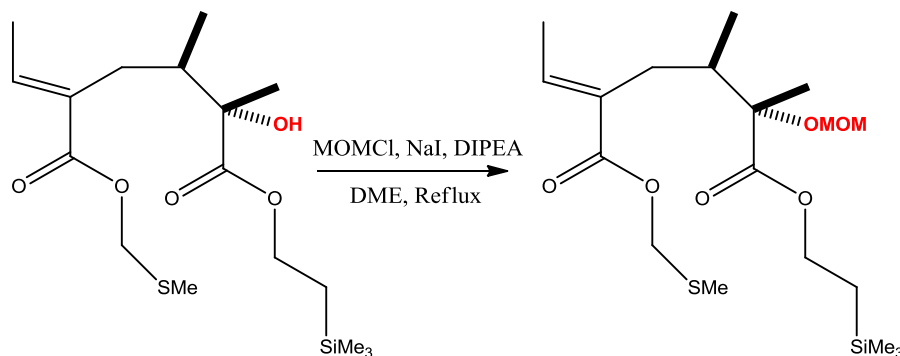


Synthesis

- MeOCH₂Cl, NaH, THF
- MeOCH₂Cl, CH₂Cl₂, *i*Pr₂EtN

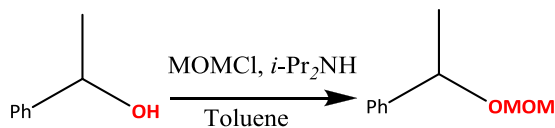
General procedure

1- *J. Am. Chem. Soc.* **1984**, *106*, 2954:



A mixture of sodium iodide (4.31 g, 28.7 mmol) and chloromethyl methyl ether (2.99 g, 37.1 mmol) in DME (10 ml) was stirred for 10 min at room temperature. Then, a solution of the alcohol (2.71 g, 7.21 mmol) and diisopropylethylamine (5.11 g, 39.6 mmol) in DME (30 ml) was stirred for 1 h at room temperature and for an additional 12 h under reflux. The reaction mixture was quenched with saturated Na_2CO_3 (40 ml) and water (30 ml) and extracted 4 times with methylene chloride. The combined extracts were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was chromatographed over silica gel with hexane-ether (7:1) as the eluting solvent to give the methoxymethyl ether (2.65 g, 88 %).

2- (*J. Org. Chem* **2005**, *70*, 9621):



R-Phenethyl alcohol (5 mL, 41.5 mmol, 1 equiv) and diisopropylethylamine (9.0 mL, 1.25 equiv) were added sequentially to a toluene solution of MOMCl (2.1 M, 40 mL, 83 mmol, 2 equiv)*. The reaction mixture was maintained at ambient temperature for 16 h. The light yellow solution was partitioned between EtOAc and a saturated aqueous NH_4Cl solution, and the biphasic mixture was stirred vigorously for a minimum of 5 min to ensure all residual starting material had been decomposed. The resulting clear, colorless organic layer was removed, washed with a saturated aqueous NaHCO_3 solution and then with brine, dried with MgSO_4 , and concentrated under reduced pressure.

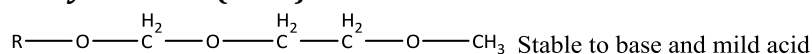
***Chloromethyl Methyl Ether as a Solution in Toluene.** A three-neck 500 mL flask fitted with a thermocouple thermometer, reflux condenser, and addition funnel was charged with dimethoxymethane (44.25 mL, 0.50 mol, 1 equiv), toluene (133 mL, 3 volumes), and $\text{Zn}(\text{OAc})_2$ (9.2 mg, 0.01%). Acetyl chloride (35.5 mL, 0.50 mol, 1 equiv) was placed in the addition funnel, and was then introduced into the reaction mixture at a constant rate over 5 min. The $\text{Zn}(\text{OAc})_2$ dissolved

shortly after addition of the AcCl was started. During the next 15 min, the reaction mixture warmed slowly to 45 °C, and then cooled to ambient temperature over 3 h, at which time analysis of an aliquot of the reaction mixture by NMR indicated complete consumption of DMM. Solutions of MOMCl in toluene prepared using this stoichiometry have a density of 0.91 g/mL, are approximately 2.1 M (18% w/w), and are stable for months if adequately sealed.

Cleavage

✚ Me₂BBr₂ (see cleavage MEM)

Methoxyethoxymethyl ethers (MEM)

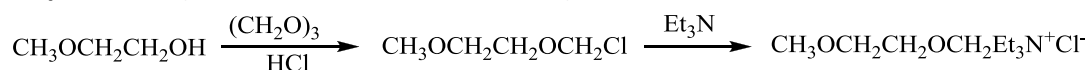


Synthesis

✚ MeOCH₂CH₂OCl, NaH, THF

✚ MeOCH₂CH₂OCl, CH₂Cl₂, Et₃N

General procedure (*Tetrahedron Lett.* **1976**, *11*, 809):

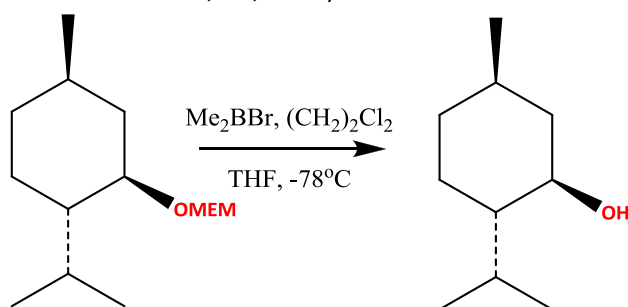


Reaction of MEM chloride in ether with 1.3 eq of triethylamine at 25 °C for 16 hrs affords the colorless, crystalline ammonium salt which is obtained pure (80% yield) simply by filtration and drying in vacuo. The salt is stable when kept in a sealed container, but must be protected from atmospheric moisture.

Cleavage

✚ Lewis acids such ZnBr₂, TiCl₄, Me₂BBr₂

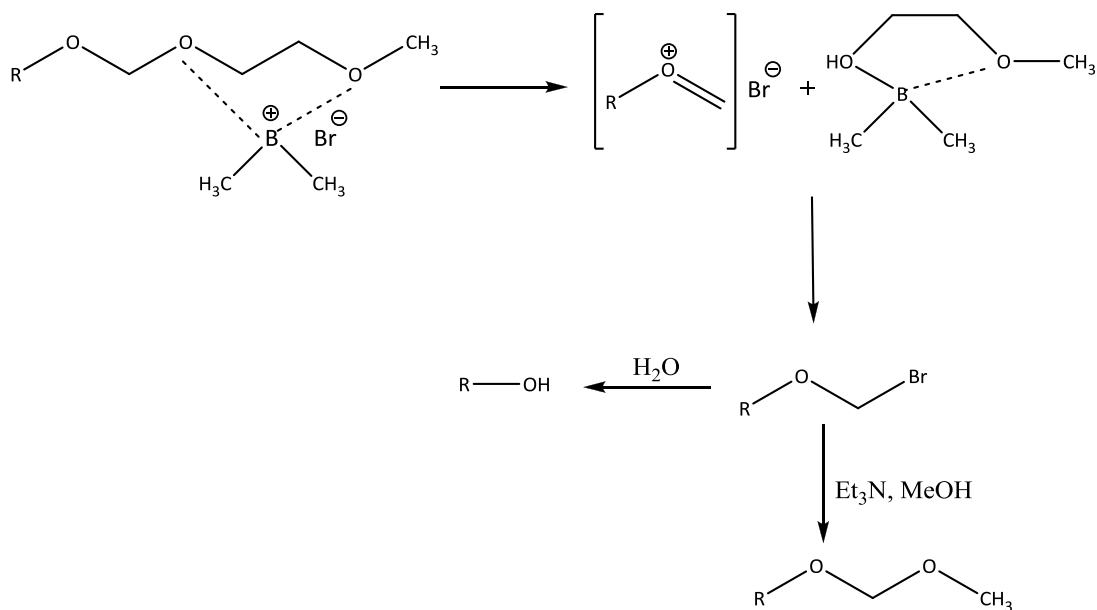
General procedure (*Tetrahedron Lett.* **1983**, *24*, 3969):



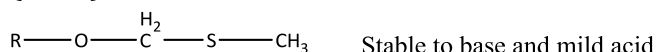
To a cold (-78 °C), stirred solution of menthol MEM ether (0.97 mmol), in 8.1 mL dry methylene chloride, under argon, was added dropwise, a solution of dimethylboron bromide (1.78 M, 1.63 mL)

in 1,2-dichloroethane. After 1 h the reaction mixture was cannulated into a vigorously stirred mixture of tetrahydrofuran 24 (10 mL) and saturated aqueous sodium bicarbonate (5 mL). The reaction vessel and cannula were rinsed with an additional 5 mL of methylene chloride. After a few minutes ether was added, the organic layer separated and washed successively with brine (3 mL), 10% aqueous sodium bisulphate (3 mL), and brine (3 mL). The aqueous layers were extracted with ether (10 mL) and the organic layers combined. After drying (Na_2SO_4), the resultant solution was concentrated and subjected to flash chromatography to afford after distillation (air-bath) pure menthol (91%).

Mechanism



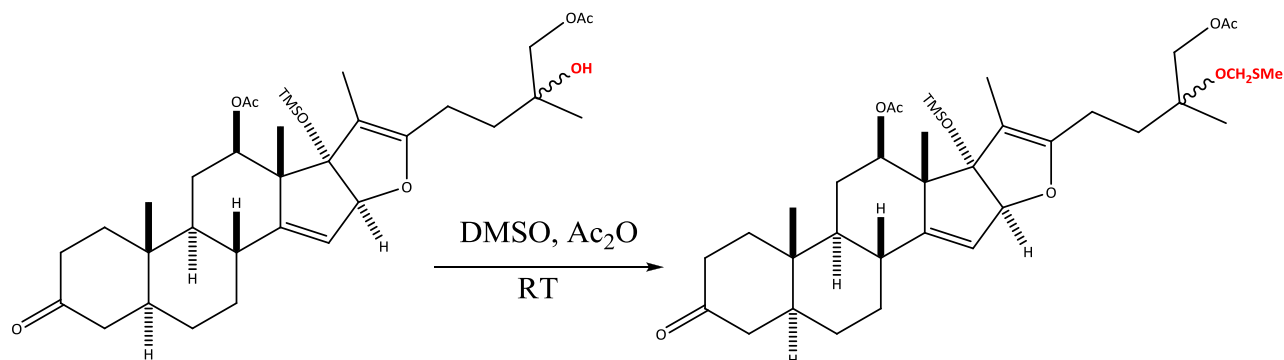
Methyl thiomethyl ethers (MTM)



Synthesis

- ✚ MeSCH₂Cl, NaH, THF
- ✚ DMSO, Ac₂O

General procedure (*J. Am. Chem. Soc.* **1999**, *121*, 2071):

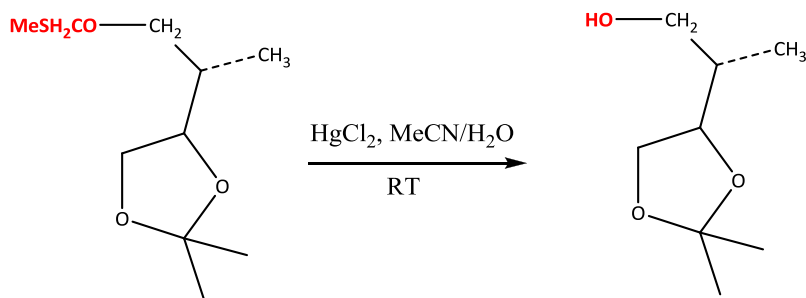


To a solution of keto alcohol (25 mg, 0.0435 mmol) in DMSO (0.25 ml) was added Ac_2O (0.18 ml) at 25 °C. After 19 h at 25 °C, the mixture was poured into cold saturated aqueous NaHCO_3 solution and extracted with ether. The combined extract was washed with saturated aqueous NaHCO_3 solution, H_2O and brine. After drying over MgSO_4 and concentration, flash column chromatography on silica gel (1:7 EtOAc/hexanes) provided 28 mg (96 %) of MTM ether.

Cleavage

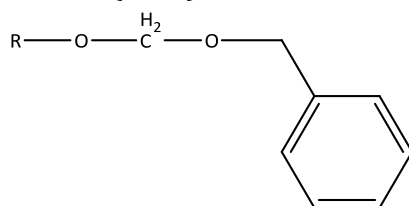
- ✚ HgCl_2 , $\text{CH}_3\text{CN}/\text{H}_2\text{O}$
- ✚ AgNO_3 , THF, H_2O , base
- ✚ MeI, K_2CO_3

General procedure (*Tetrahedron Lett.* **1978**, *38*, 3269):



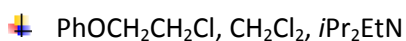
To a stirred solution of acetonitrile-water (4/1, v/v containing the protected alcohol) was added mercuric chloride (HgCl_2) (407 mg, 1.50 mmol) at RT. After 4 h, the reaction mixture was filtered through celite (ether elution) and washed with ammonium acetate solution. The aqueous layer was extracted with ether and the combined organic extracts were washed with brine, dried (K_2CO_3) and concentrated under reduced pressure. Chromatography on silica gel (3:1 Pentane/Ether) afforded the corresponding alcohol (94 mg, 94 %).

Benzyloxymethyl ethers (BOM)

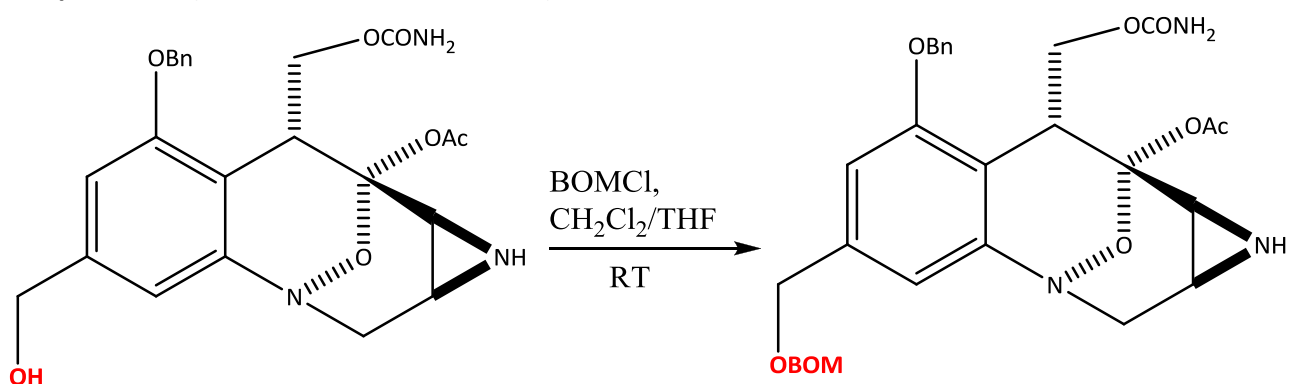


Stable to base and acid

Synthesis

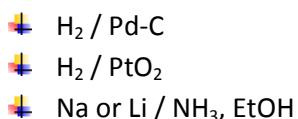


General procedure (*Tetrahedron* **1997**, 53, 10229):

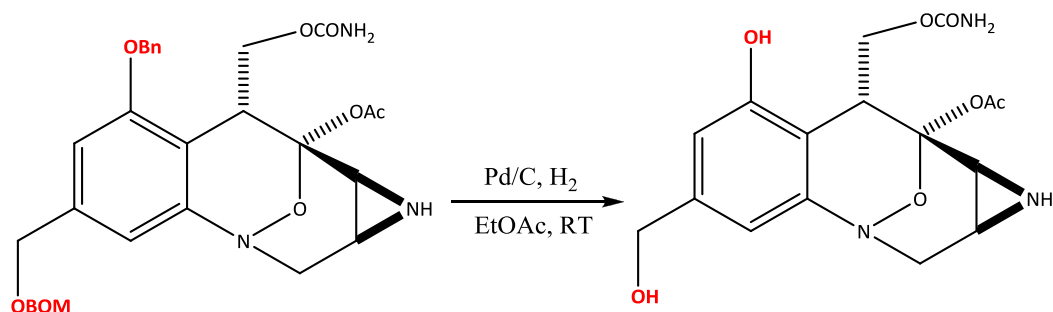


Benzyl chloromethyl ether (0.140 ml, 1.0 mmol) was added to a stirred solution of the alcohol (61 mg, 0.10 mmol) in dry tetrahydrofuran-dichloromethane (10:1) (6 ml) containing *N,N*-diisopropylethylamine (0.278 ml, 1.6 mmol) at room temperature under argon. After 15 h, the mixture was diluted with ethyl acetate (150 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine and then dried over Na₂SO₄. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:1) to give the protected alcohol (59.8 mg, 82 %) as a white solid.

Cleavage

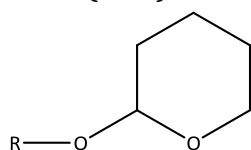


General procedure (*Tetrahedron* **1997**, 53, 10229):



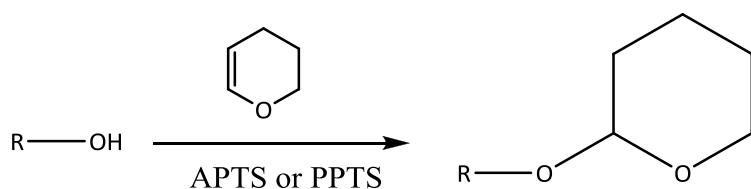
A mixture of the protected alcohol (35.8 mg, 62 μ mol) and 10% palladium on carbon (28 mg) in ethyl acetate (7 ml) was stirred for 5 h at room temperature under hydrogen atmosphere (1 atm). The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (chloroform-methanol, 10:1) to give the corresponding alcohol (19.8 mg, 87 %) as a white solid.

Tetrahydropyranyl ethers (THP)

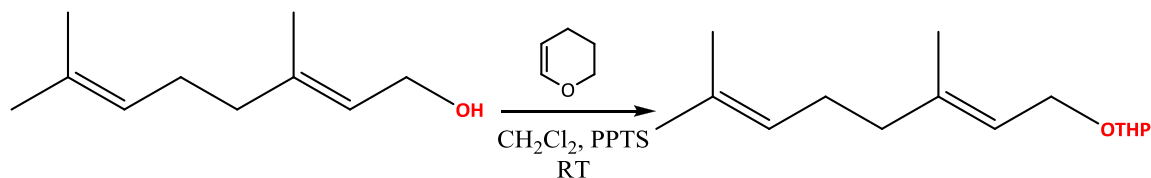


Stable to base, acid labile

Synthesis



General procedure (*J. Org.Chem.* **1977**, 42, 3772):

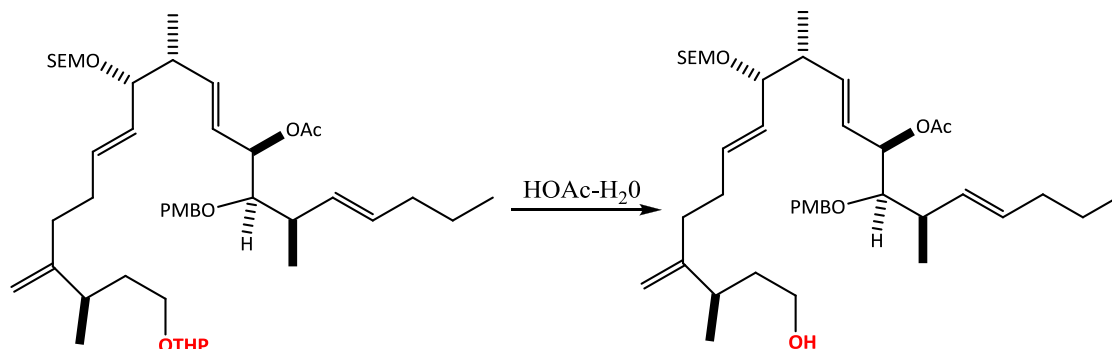


A solution of geraniol (154 mg, 1 mmol) and dihydropyran (126 mg, 1.5 mmol) in dry methylene chloride (7 ml) containing PPTS (*p*-toluenesulfonate) (25 mg, 0.1 mmol) is stirred for 4 h at room temperature. Then, the solution is diluted with ether and washed once with half-saturated brine to remove the catalyst. After evaporation of the solvent, distillation [bp = 140 $^{\circ}$ C (bath temperature)/ 10 mmHg] gives an essentially quantitative yield of geraniol THP ether (236 mg, 99 %).

Cleavage

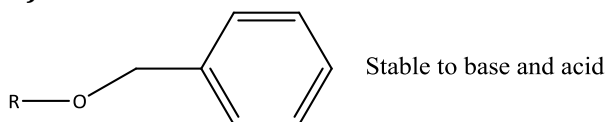
- ✚ AcOH, THF, H₂O
- ✚ Amberlyst H-15, MeOH

General procedure (*J. Am.Chem.Soc.* **1998**, *120*, 11198):



Tetrahydropyranyl ether (123 mg, 0.15 mmol) was dissolved in 50 ml of 80 % AcOH/H₂O. After 24 h, the AcOH was quenched by adding the reaction solution dropwise into saturated aqueous NaHCO₃ (300 ml). The solution was extracted with Et₂O (3 x 200 ml). The combined organic layers were washed with saturated aqueous NaHCO₃ (400 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified *via* flash chromatography (12 g of SiO₂, 15-20 % EtOAc/Hexanes) to provide 107 mg (97 %) of the C-1 primary alcohol as an oil.

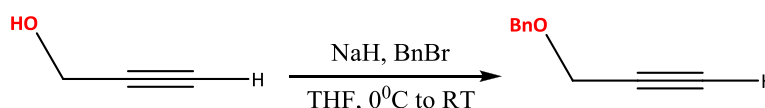
Benzyl ethers (R-OBn)



Synthesis

- ✚ KH, THF, PhCH₂Cl
- ✚ PhCH₂OC(=NH) CCl₃, F₃CSO₃H
- ✚ NaH, DMF, PhCH₂Br

General procedure:



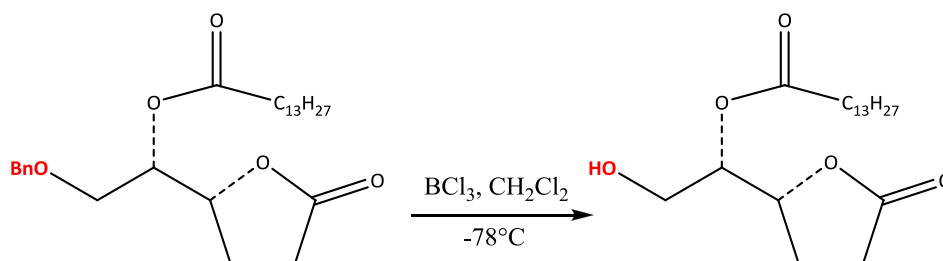
To a 100 ml 1-neck flask with a stirbar, septum and N₂ inlet, a suspension of 1.114 g (46.4 mmol, 1.1 eq) of powdered NaH in 40 ml of dry THF was prepared, stirred and cooled to 0 °C. Then, 2.46 ml (42.3 mmol, 1 eq) of propargyl alcohol were added dropwise. Hydrogen gas evolution occurred.

After 15 min of stirring, 5.20 ml (43.7 mmol, 1 eq) of BnBr were added. The reaction mixture was allowed to slowly warm to RT. After 24 h, the reaction was quenched with sat. aq. NH_4Cl and extracted with Et_2O . The organic layer was dried over MgSO_4 , filtered and the solvent was removed by rotary evaporation. The product was isolated by Kugelrohr distillation (15 mm, 100 C) as a clear, colorless oil (100 %).

Cleavage

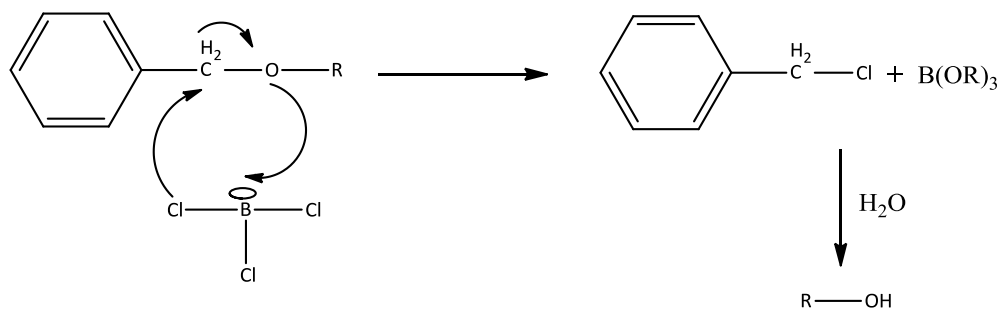
- H₂ / PtO₂
- Li / NH₃
- Lewis acid such BCl₃

General procedure (*J.Med.Chem.* 1996, 39, 4912):

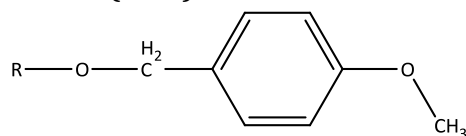


A solution of the protected alcohol (0.45 g, 1.0 mmol) in CH_2Cl_2 (20 ml) was cooled to -78°C and treated dropwise with boron trichloride (BCl_3) in CH_2Cl_2 (1 M, 3 ml, 3 mmol). After being stirred for 2.5 h at -78°C , the reaction mixture was quenched with saturated NaHCO_3 solution (3 ml) and immediately partitioned between ether and a pH 7 buffer solution. The organic layer was washed with the pH 7 buffer five times, dried (MgSO_4), and concentrated under reduced pressure to give the alcohol as a solid. The solid was dissolved in ether (3 ml), cooled over an ice bath, and crystallized by adding cold hexanes. The deposited solid was filtered to give pure alcohol as a white solid (92 %).

Mechanism



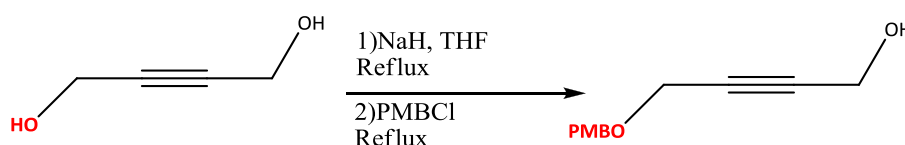
p-Methoxybenzyl ethers (PMB)



Synthesis

✚ *P*-MeOPhCH₂Cl, NaH ou KH, THF

General procedure:

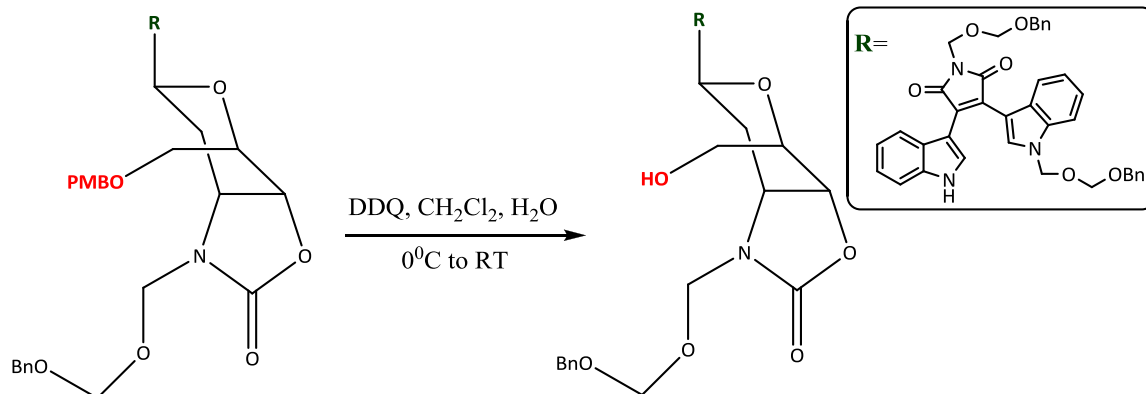


In a 100 ml 1-neck flask with a stirbar, septum, condenser and N₂ inlet, a suspension of 0.44 g (18.3 mmol, 1 eq) of NaH in 20 ml of dry THF was prepared and stirred at RT. Then, 4.789 g (55.6 mmol, 3 eq) of the diol were added and the reaction mixture was heated to reflux. After 2 h, the reaction was cooled back to RT and a solution of 2.5 ml (18.4 mmol, 1 eq) of PMBCl in 5.0 ml of THF was added. The reaction was heated back to reflux. After 48 h, TLC (20:80 EtOAc-hexanes, PMA) still showed some unreacted PMBCl. Then, the reaction mixture was quenched with sat. aq. NH₄Cl and extracted with Et₂O. The organic layer was dried over MgSO₄, filtered and the solvent was removed by rotary evaporation. The product was isolated by flash chromatography on silica gel using 30:70 EtOAc-hexanes as eluant. The product was a clear, pale yellow oil (69 %).

Cleavage

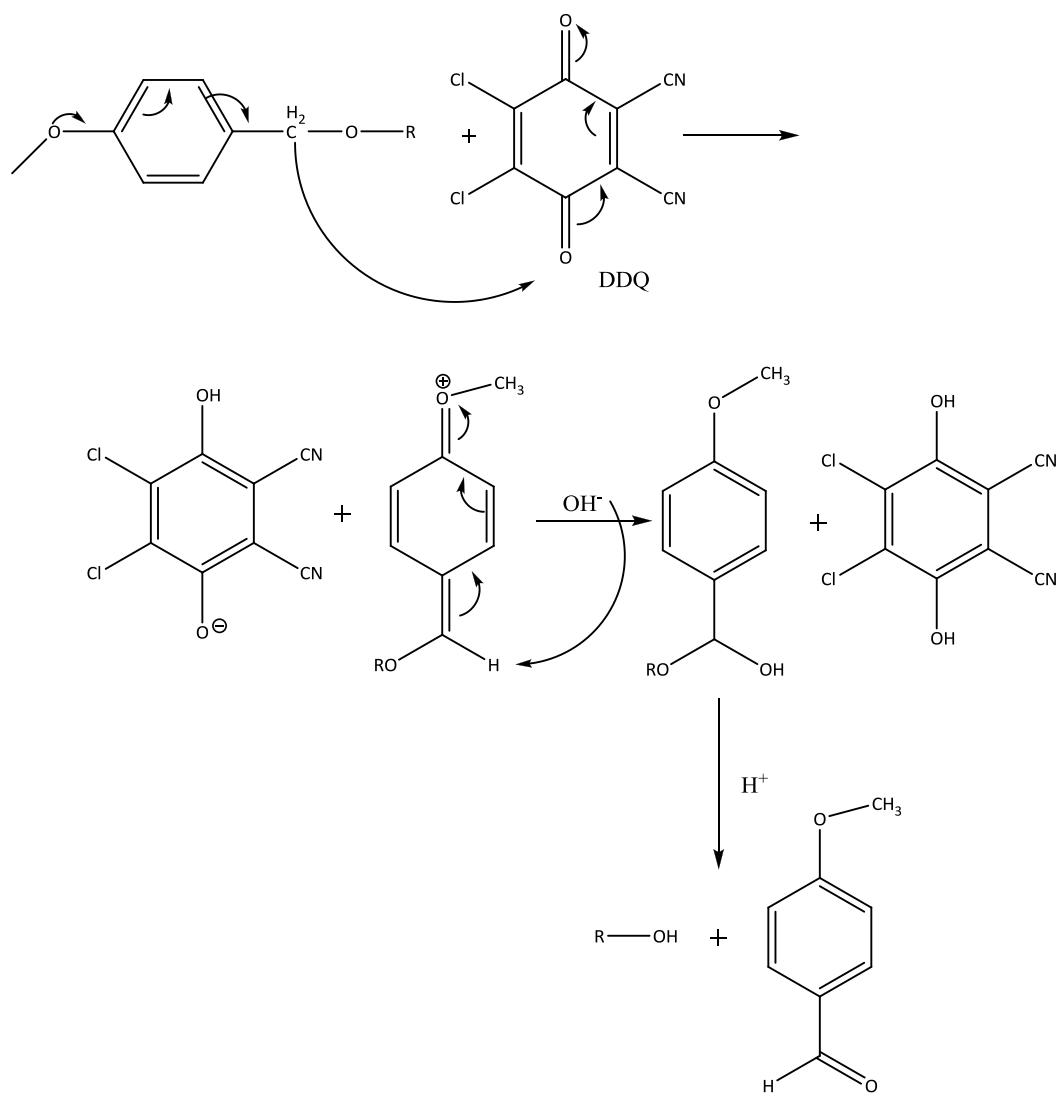
- ✚ H₂ / PtO₂
- ✚ Ce(NH₄)₂(NO₃)₆ (CAN)
- ✚ DDQ (DichloroDicyanoQuinone)

General procedure (*J. Am. Chem. Soc.* **1996**, *12*, 2825):

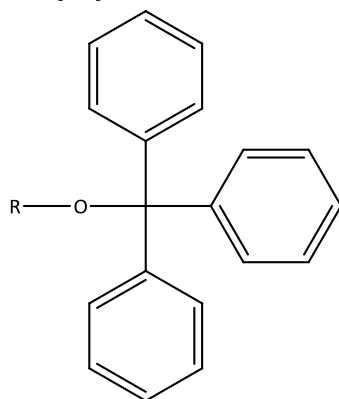


A red solution of 2.13 g (2.15 mmol) of indole glycoside in 180 ml of CH₂Cl₂ and 10 ml of H₂O at 0 °C was treated with 0.7316 g (3.22 mmol) of DDQ. The reaction was slowly warmed to ambient temperature and stirred vigorously overnight. The crude products were diluted with EtOAc, extracted with saturated NaHSO₃, rinsed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (3:1 EtOAc:hexane) on silica gel yielded 1.8110 g (97 %) of a red solid.

Mechanism



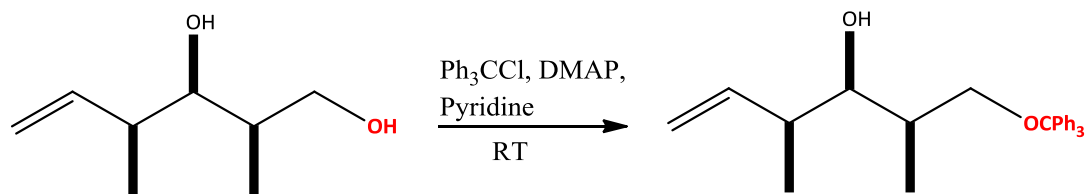
Triphenylmethyl ethers (Tr)



Synthesis

Ph_3CCl , pyridine, DMAP

General procedure (*J. Am. Chem. Soc.* **1991**, *113*, 910):

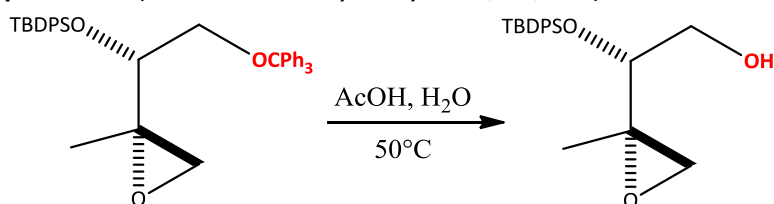


(2S, 3R, 4S)-2,4-Dimethyl-5-hexene-1,3-diol (50 g, 347 mmol) in pyridine (50 ml) was added to trityl chloride (106.3 g, 381 mmol) in pyridine (300 ml). DMAP (1 g) was added and the mixture was stirred at 22 °C for 2 days. Then, crushed ice (250 g) was added and the mixture was concentrated *in vacuo* to remove the pyridine. The residue was repeatedly extracted with dichloromethane. The combined organic phases were washed with water, dried over MgSO_4 , and evaporated. Flash chromatography (5:1 hexane/ethyl acetate) furnished the 1-trityl derivative (127 g, 95 %) as a clear colorless oil.

Cleavage

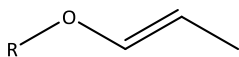
- ✚ AcOH, 50°C
- ✚ TFA
- ✚ $\text{H}_2/\text{Pd/C}$

General procedure (*Tetrahedron:Asymmetry* **2001**, *12*, 943):

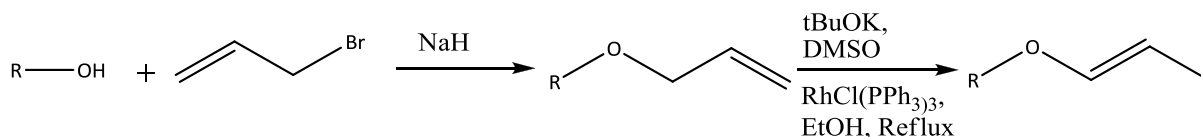


The protected alcohol (18 g, 30 mmol) was dissolved in acetic acid (200 ml) at 50 °C with stirring. Water (22 ml) was added to the solution, and the resultant cloudy mixture became clear after stirring at the same temperature for 3 h. Concentration of the solution gave an oily residue containing the powdery solid of triphenylmethanol (TrOH). After this mixture was diluted with 10 % diethyl ether in hexane, the TrOH was filtered off. Flash column chromatography (16 % ethyl acetate in hexane) of the concentrated filtrate afforded the primary alcohol as a colorless oil (7.85 g, 73 %).

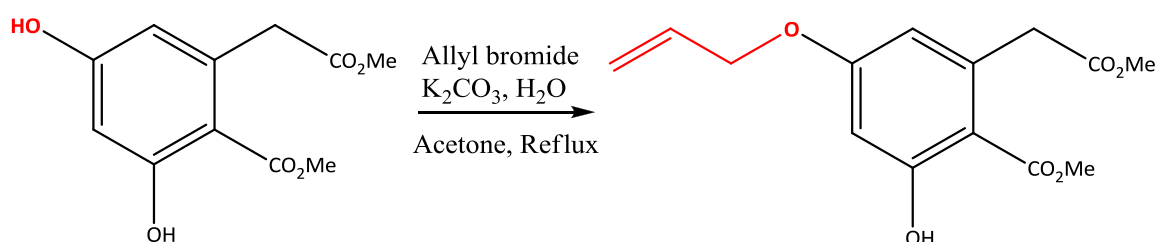
Vinyl ethers



Synthesis



General procedure (*J.Org.Chem.* **1992**, 57, 6622):

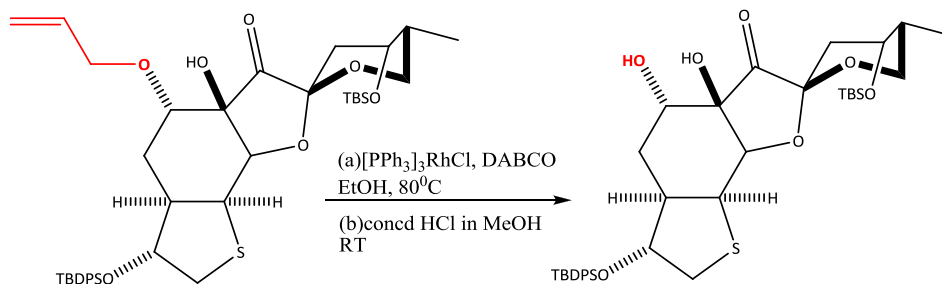


A mixture of diphenol (19.4 g, 81 mmol), $K_2CO_3 \cdot H_2O_{1.5}$ (53 g, 320 mmol), and allyl bromide (7.0 ml, 81 mmol) in acetone (575 ml) was heated at reflux for 6 h. The cooled reaction mixture was acidified with 1 N HCl, and the precipitate was collected by filtration and air-dried to give 23.1 g of crude protected alcohol. This material was crystallized from hexane to yield fluffy white needles, 19.0 g (83 %). The filtrate from the reaction mixture was extracted with ether (3 x). The combined extracts were dried ($MgSO_4$), combined with the mother liquor from the recrystallization, and concentrated to a white solid. Purification of this material by flash chromatography (silica gel, 10:1 hexane- ether, then 3:1 hexane-EtOAc) gave 1.6 g (6 %) of the diallyl ether.

Cleavage

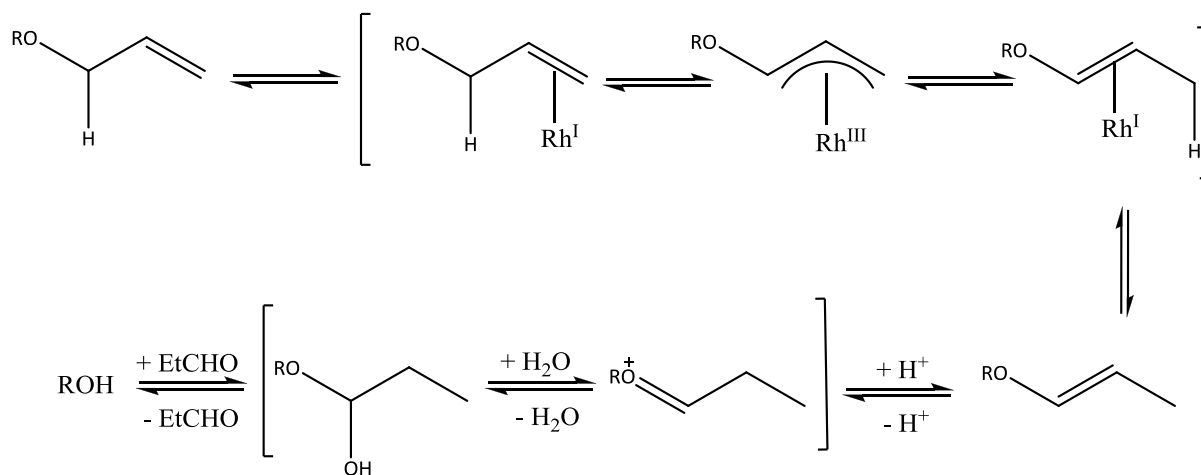
✚ Acid conditions

General procedure (*J. Am. Chem. Soc.*, 1992, 114, 9419):

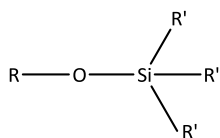


Allyl ether (3.1 mg, 4.2 μmol) was dissolved in 90% EtOH. DABCO (2 mg, 17.8 μmol , 4.2 eq) was added, and the mixture was warmed to 80 $^{\circ}\text{C}$. Following the introduction of $\text{RhCl}(\text{PPh}_3)_3$ (1.0 mg, 1.0 μmol , 0.26 eq), the reaction mixture was stirred for 15 min, cooled to room temperature, and quenched with pH 7.0 buffer solution. The aqueous phase was extracted with diethyl ether (3 x 10 ml), and the combined organic solutions were concentrated *in vacuo*. The crude enol ether was taken up in methanol (1 ml), and concentrated HCl (300 μl) was added. The resultant mixture was stirred at ambient temperature for 18 h and then concentrated *in vacuo*. HPLC with 1:11.5 methanol/chloroform as eluant furnished the alcohol (1.1 mg, 76 % yield) as an oil.

Mechanism



4. Silyl ethers

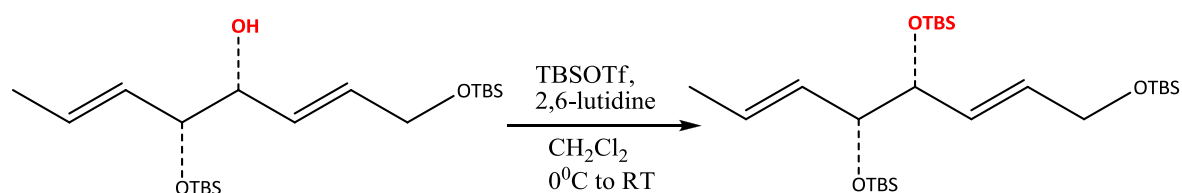


Synthesis

- ✚ R₃SiCl, Pyridine, DMAP
- ✚ R₃SiCl, CH₂Cl₂ (DMF, CH₃CN), Imidazole, DMAP
- ✚ R₃Si-OTf, DIPEA, CH₂Cl₂

Silyl ethers	R' =	Abbreviation (R' ₃ -Si-OR)	Properties
Trimethylsilyl ethers	Me	TMS-OR	- Very acid, water labile - Useful for transient protection
Triethylsilyl ethers	Et	TES-OR	- More stable than TMS - Can be selectively removed in the presence of more robust silyl ethers with F ⁻ or acid
Triisopropylsilyl ethers	<i>i</i> Pr	TIPS-OR	- More stable to hydrolysis than TMS
<i>t</i> -Butyldimethylsilyl ethers	<i>t</i> -Bu, Me ₂	TBS-OR	- Stable to base and mild acid - is selective for primary alcohols under controlled condition
<i>t</i> -Butyldiphenylsilyl ethers	<i>t</i> -Bu, Ph ₂	TBDPS-OR	- Stable to acid and base - Selective for primary alcohols - Me ₃ -Si- and <i>i</i> Pr ₃ -Si- groups can be selectively removed in the presence of TBDPS or TBS groups - TBS can be selectively removed in the presence of TBDPS by acid hydrolysis

General procedure: **Ex: TBS**

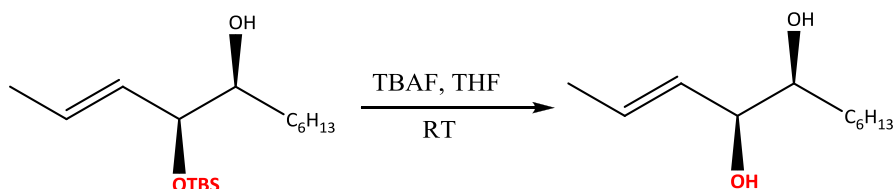


In a 250 ml 1-neck flask with a stirbar, septum and N₂ inlet, 1.498 g (3.9 mmol, 1 eq) of alcohol were dissolved in 40 ml of dry CH₂Cl₂, stirred and cooled to 0 °C. Then 0.50 ml (4.3 mmol, 1.1 eq) of 2,6-lutidine was added followed by 1.0 ml (4.4 mmol, 1.1 eq) of TBSOTf. The bath was removed and the reaction was allowed to warm to RT. After 30 min, TLC (5:95 EtOAc-hexanes, PMA) showed product spot at R_f 0.77. The solvent was removed from the reaction mixture by rotary evaporation. The product was isolated by flash chromatography on silica gel using 5:95 EtOAc-hexanes as eluant. The product was a clear, colorless oil (88 %).

Cleavage

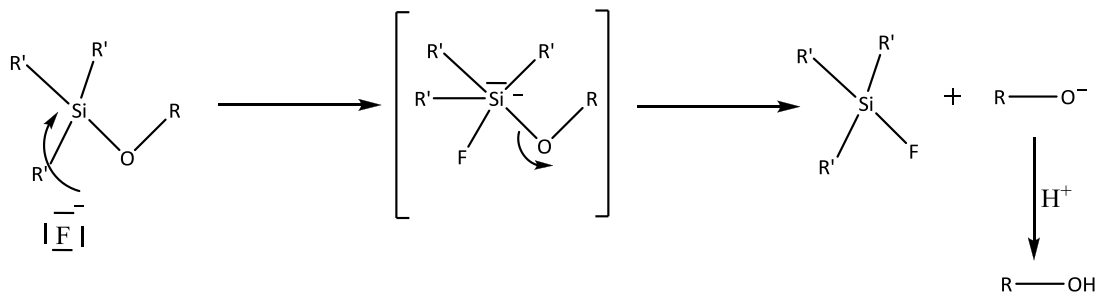
- ✚ Acid
- ✚ F⁻ (HF, nBu₄NF, CsF, KF)
- ✚ TBDPS: F⁻ (nBu₄NF, HF/H₂O/CH₃CN, HF/Pyridine, SiF₄/CH₂Cl₂)

General procedure: **Ex: TBS**



In a 100 ml 1-neck flask with a stirbar and a cap, 1.840 g (6.1 mmol, 1 eq) of alcohol were dissolved in 40 ml of THF and stirred at RT. Then, 18.3 ml (18.3 mmol, 3 eq) of TBAF (1.0 M in THF, water content ~5 wt. %, Aldrich) were added. After 3 h, the reaction mixture was quenched with sat. aq. NH₄Cl and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and the solvent was removed by rotary evaporation. The product was isolated by flash chromatography on silica gel using 75:25 Et₂O-hexanes. The product was a clear, pale yellow oil (91 %).

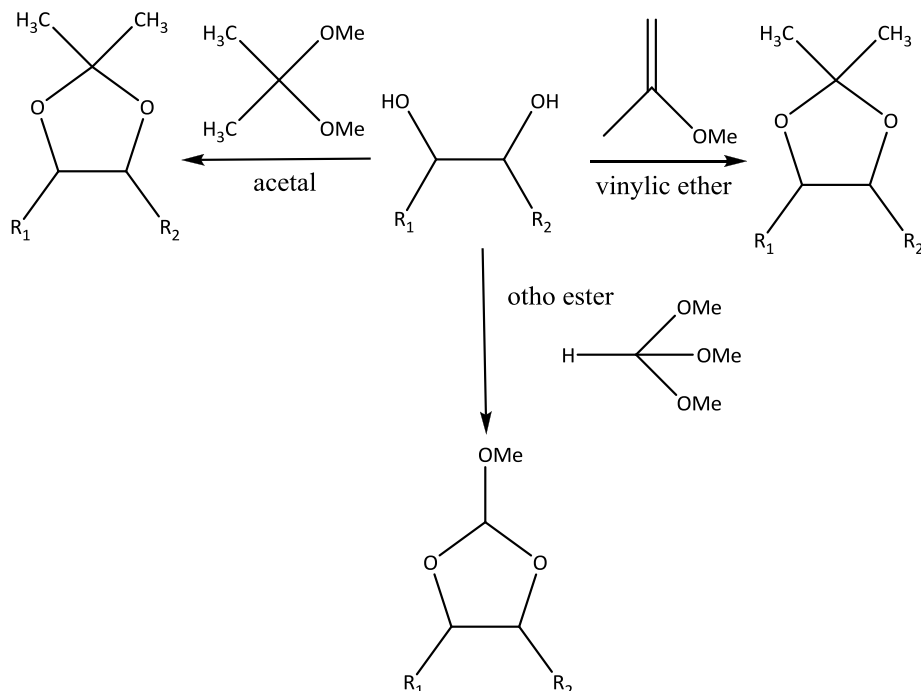
Mechanism



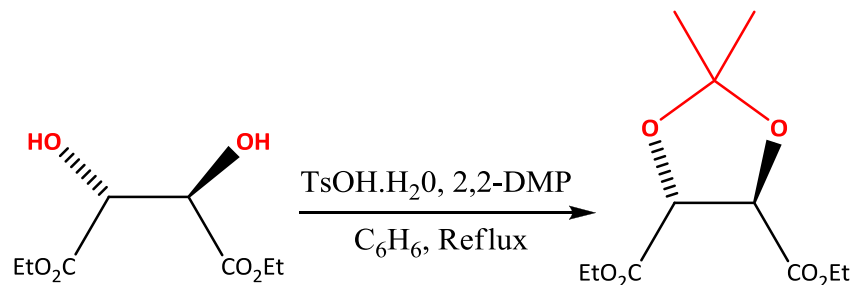
1,2 Diols

→ Acetal protection

Synthesis



General procedure:

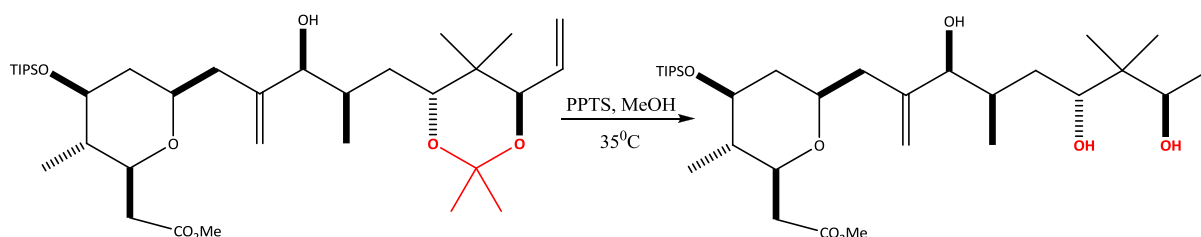


In a 100 ml 1-neck flask with a stirbar, Dean-Stark, condenser and N_2 inlet, 0.664 g 93.2 mmol, 1 eq) of diol was dissolved in 40 ml of benzene at RT. Then, 0.053 g (0.3 mmol, 0.1 eq) of $\text{TsOH} \cdot \text{H}_2\text{O}$ were added followed by 0.47 ml (3.8 mmol, 1.2 eq, $d = 0.847$) of 2,2-dimethoxypropane (2,2-DMP). The reaction mixture was heated to reflux. After 16 h, the reaction was cooled to RT, quenched with sat. aq. NaHCO_3 and extracted with Et_2O . The organic layer was dried over MgSO_4 , filtered and the solvent was removed by rotary evaporation. The product was isolated by flash chromatography on silica gel using 10:90 EtOAc -hexanes as eluant. The product was a clear, colorless oil.

Cleavage

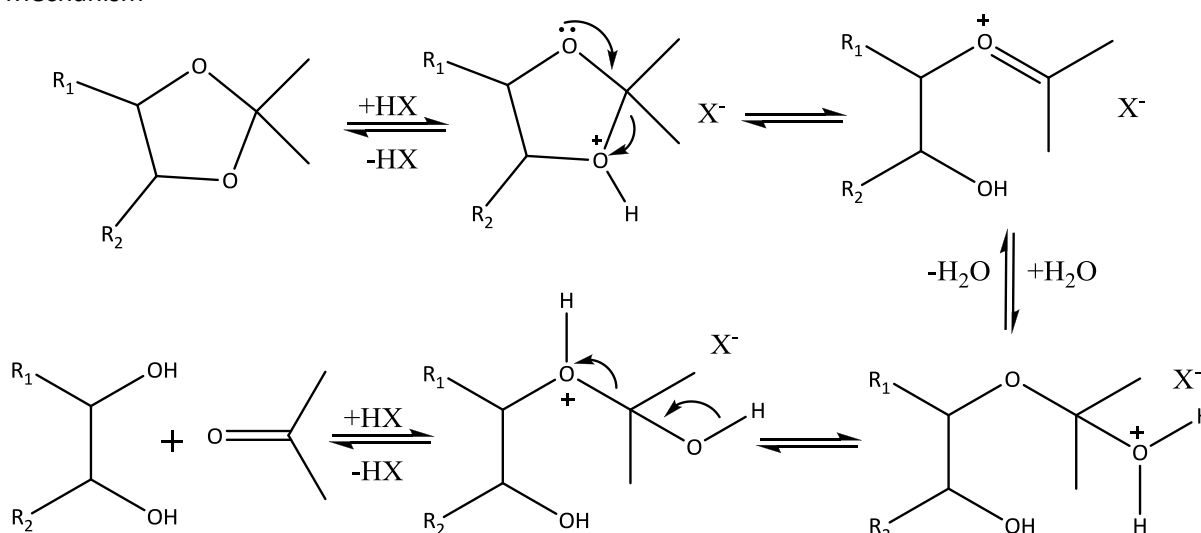
- ✚ Mild aqueous acid
- ✚ $\text{LiAlH}_4/\text{AlCl}_3, \text{Et}_2\text{O}$
- ✚ $\text{Na}(\text{CN})\text{BH}_3, \text{TiCl}_4, \text{CH}_3\text{CN}$

General procedure (*J. Am. Chem. Soc.*, 2001, 123, 8593):



A solution of the acetonide (230 mg, 36.8 μmol) in MeOH (3 ml) was treated with PPTS (pyridinium p-toluenesulfonate) (28 mg, 112 μmol) and stirred for 19 h at 35 °C. After this time, the mixture was allowed to cool to RT, treated with 10 % w/v aq. NaOH (2 ml, 5 mmol) and stirred for a further 6 h. the resulting mixture was diluted with H_2O (10 ml) and EtOAc (10 ml) and the pH of the aqueous layer adjusted to 2 by the careful addition of 1M aq. HCl. The layers were separated and the aqueous layer was extracted (2 x3 ml EtOAc). The combined organic extracts were washed with brine (3 ml), dried (Na_2SO_4) and concentrated in vacuo. The resulting residue was purified by column chromatography (eluting with 6- 10 % MeOH in CH_2Cl_2) to afford trihydroxyacid (18.1 mg, 31.7 μmol , 86 %) as a colorless oil.

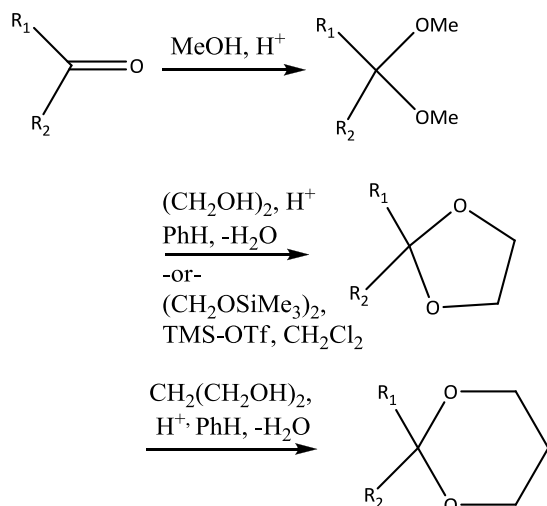
Mechanism



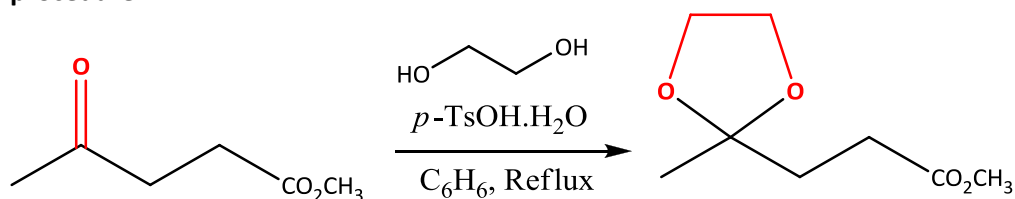
Ketones and aldehydes

→ ketals and acetals

Synthesis



General procedure:

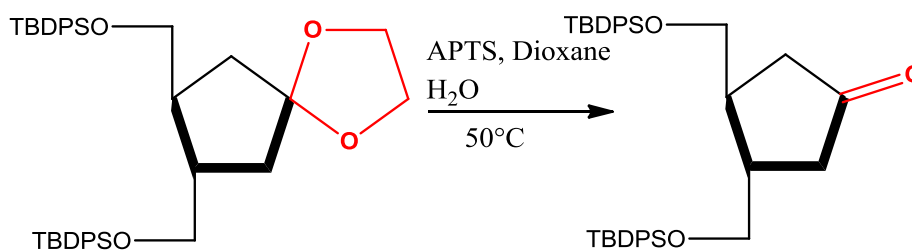


In a 2000 ml 1-neck flask with a stirbar, Dean-Stark, condenser, septum and N₂ inlet, 28.647 g (220.1 mmol, 1 eq) of methyl levulinate were dissolved in 500 ml of benzene. The reaction mixture was stirred at RT and added 25 ml (448.3 mmol, 2 eq, d = 1.113) of ethylene glycol followed by 0.569 g (3 mmol, 0.01 eq) of *p*-TSA-H₂O and heated to reflux. The water was collected in the Dean-Stark trap and was periodically removed. After 21 h, the reaction mixture was cooled to RT and washed with sat. aq. NaHCO₃. The organic layer was dried over MgSO₄, filtered and the solvent was removed by rotary evaporation. The product was isolated by short-path (fitted with a 3 in. vigreux) distillation (65 C, 0.25 mm) as a clear, colorless oil (55 %).

Cleavage



General procedure (*Tetrahedron*, 1995, 51, 2029):



To a solution of the ketal (7.45 g, 11.2 mmol) in dioxane (40 ml) and water (3 ml), p-toluene sulfonic acid (APTS) (0.2 g) was added. The mixture was stirred for 2 h at 50 °C, the neutralized with saturated aqueous NaHCO₃ (5 ml). Water (30 ml) was added and the mixture extracted with CHCl₃ (2 x 40 ml). The organic layer was dried and concentrated. The product was purified by flash chromatography (CHCl₃) to give 6 as a colourless syrup (6.39 g, 92%).

Mechanism (see **Cleavage 1,2-diol**)

Carboxylic acids

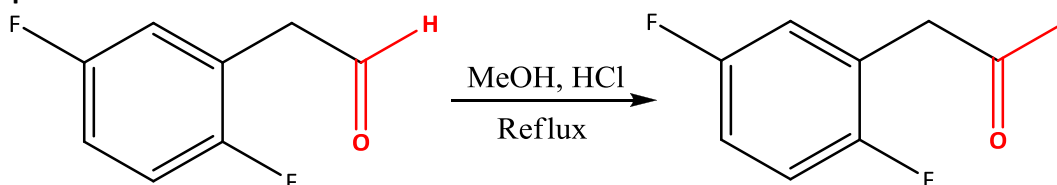
→ Esters



Synthesis

- ✚ Fisher esterification ($R-COOH + R'OH + H^+$)
- ✚ Acid chloride + $R'-OH$, Pyridine
- ✚ *t*-Butyl esters: isobutylene and acid
- ✚ methyl esters: diazomethane

General procedure:

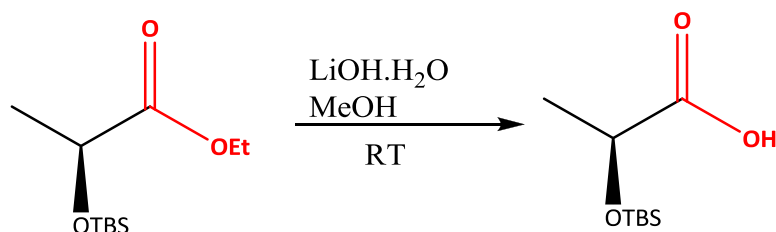


In a 500 ml 1-neck flask with a stirbar, condenser, septum and N_2 inlet, 15.362 g (89.2 mmol, 1 eq) were dissolved in 250 ml of absolute MeOH. HCl gas was then bubbled through the solution for 2 min. The reaction mixture was then refluxed for 4 h and cooled to RT. The solvent was removed by rotary evaporation and the material was extracted with sat. aq. $NaHCO_3$ and EtOAc. The organic layer was dried over $MgSO_4$, filtered and the solvent removed by rotary evaporation to afford 14.970 g of product as a yellow oil.

Cleavage

- ✚ LiOH, MeOH, H_2O
- ✚ Enzymatic hydrolysis
- ✚ *t*-Butyl esters are cleaved with aqueous acid
- ✚ Bu_2SnO , PhH, reflux

General procedure:



In a 50 ml 1-neck flask with a stirbar and a cap, 0.535 g (2.3 mmol, 1 eq) of ester were dissolved in 25 ml of absolute MeOH. Then, 0.523 g of LiOH-H₂O (12.5 mmol, 5 eq) was added and the reaction mixture was stirred at RT. After 24 h, 5 ml of water were added and stirred for 30 min. The reaction mixture was concentrated by rotary evaporation to about 5 ml and the pH was lowered to 3 with 1 M

Protecting Groups By Jessy AZIZ and Abdallah HAMZE

HCl. The mixture was extracted with EtOAc. The organic layer was dried over MgSO_4 , filtered and the solvent was removed by rotary evaporation. The product was a clear, colorless oil (75 %).

Mechanism

