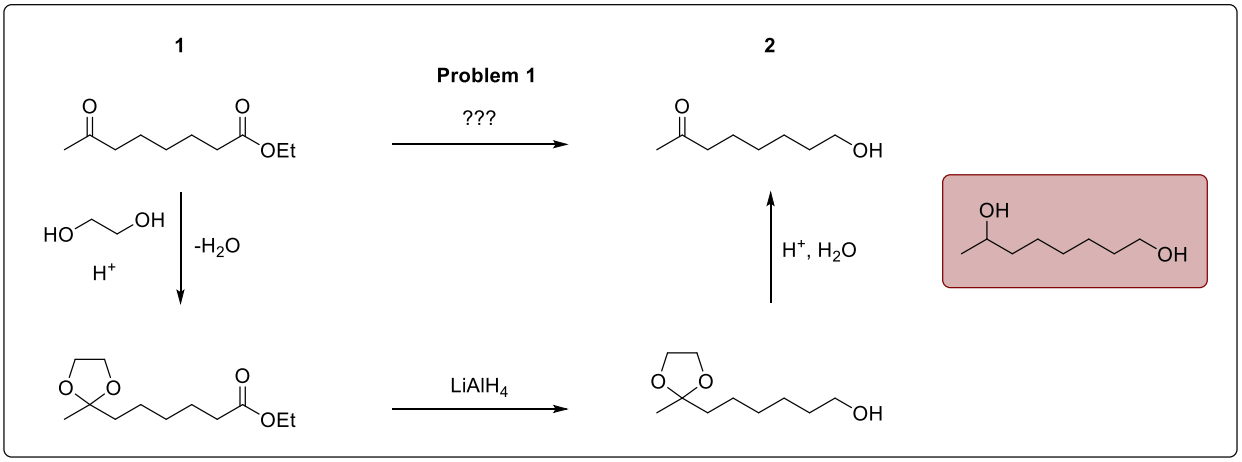
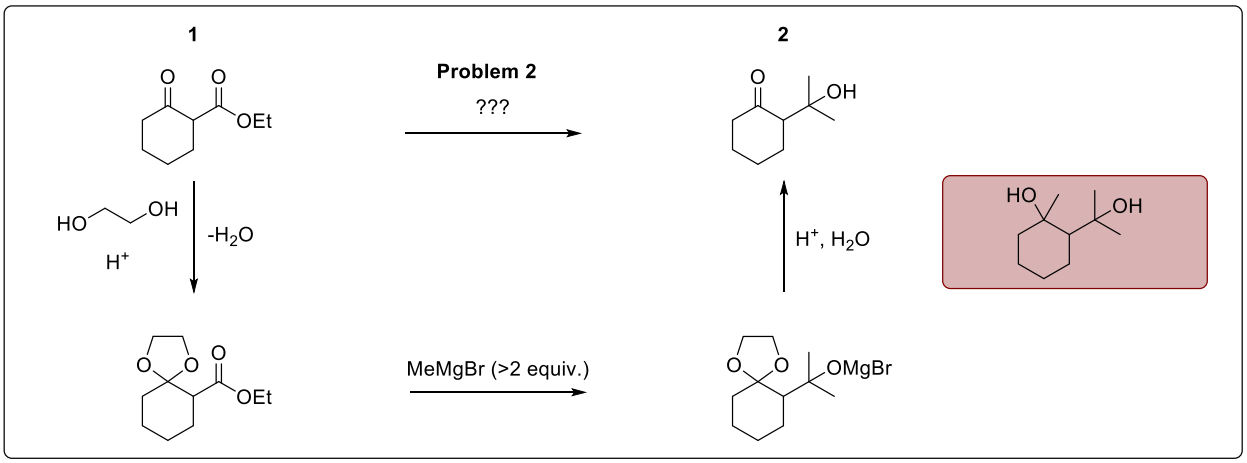
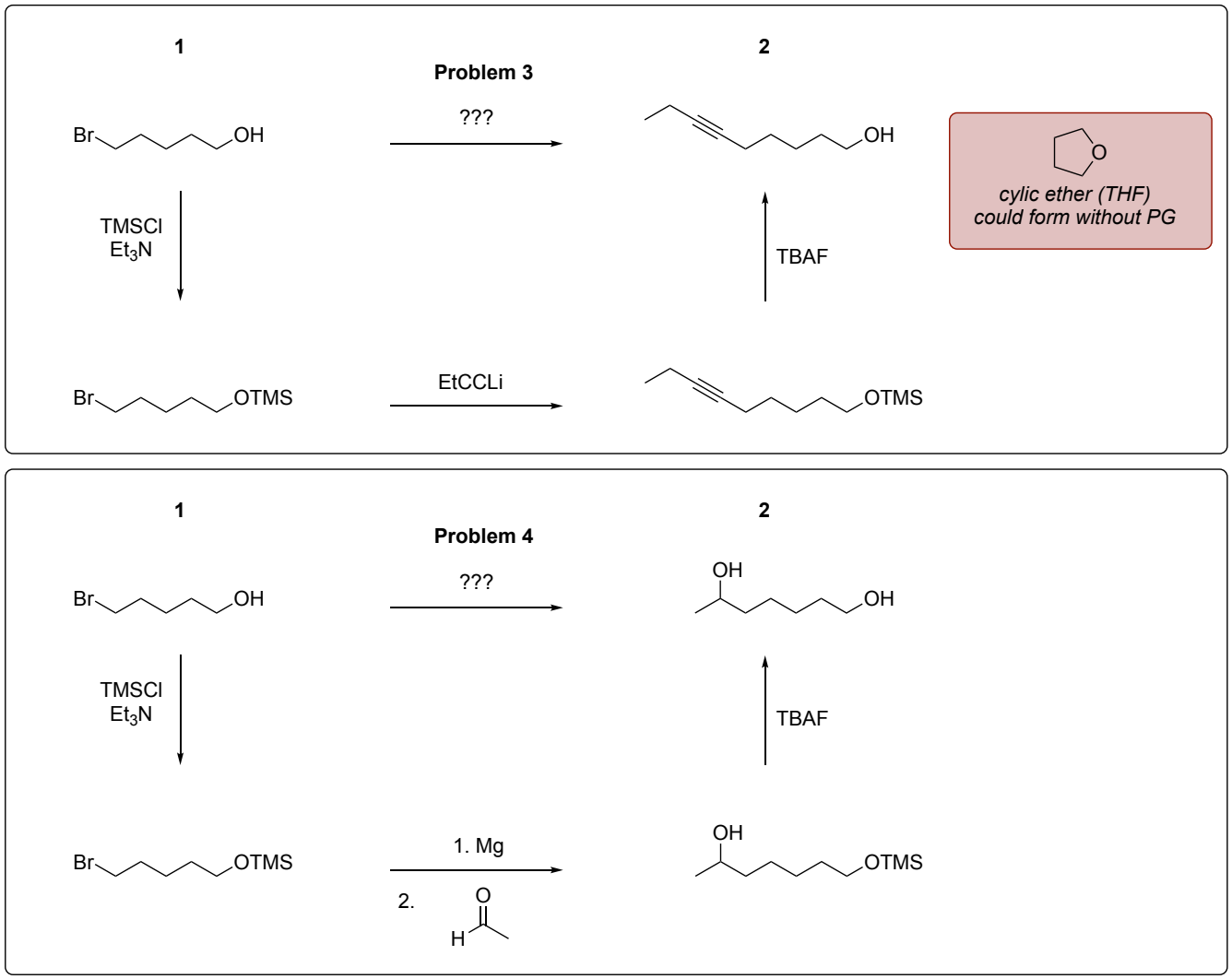
1. Propose a strategy to go from starting material **1** to final compound **2**. Make use of protecting groups and explain why they are necessary.





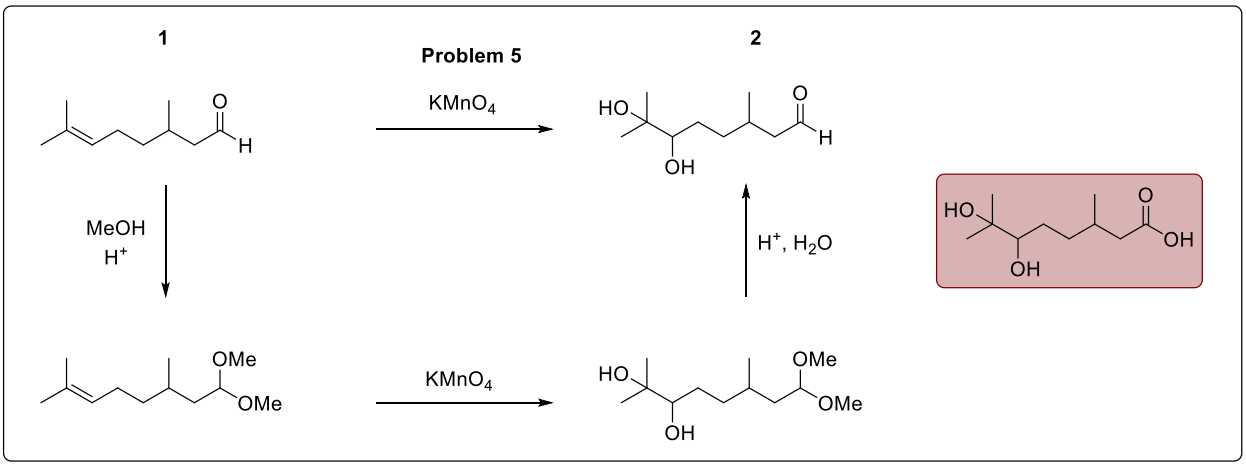
Problem 1: Reduction of the ester to the alcohol is desired. However, a direct reduction is not feasible since the ketone group would be reduced as well (product in the red square). The issue is solved by selective protection of the ketone, for example as an acetal, which does not undergo reduction. The acetal protecting group is easily removed in an aqueous acidic work up after reduction of the ester.

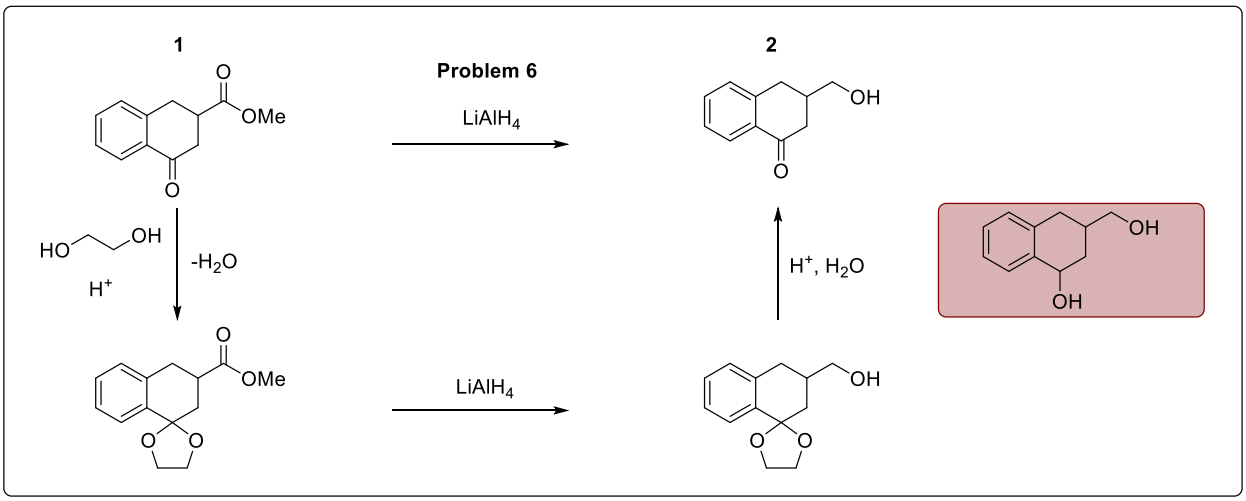
Problem 2: Addition of Grignard reagent to the ester is desired however a selective addition is not feasible since the ketone group will also react with the Grignard reagent (product in the red square). The issue is solved by selective protection of the ketone, again as an acetal for example. The acetal protecting group, after reaction of the ester, is easily removed in an aqueous acidic work up.



Problem 3: The acetylide is a strong base and thus would deprotonate the alcohol leading to the cyclic ether (red box). In this sequence trimethylsilane (TMS) is installed as protecting group since it is easily and selectively removed by tetrabutylammonium fluoride (TBAF) however other protecting groups (for example, other silanes or THP (tetrahydropyranyl) or as ether are also feasible).

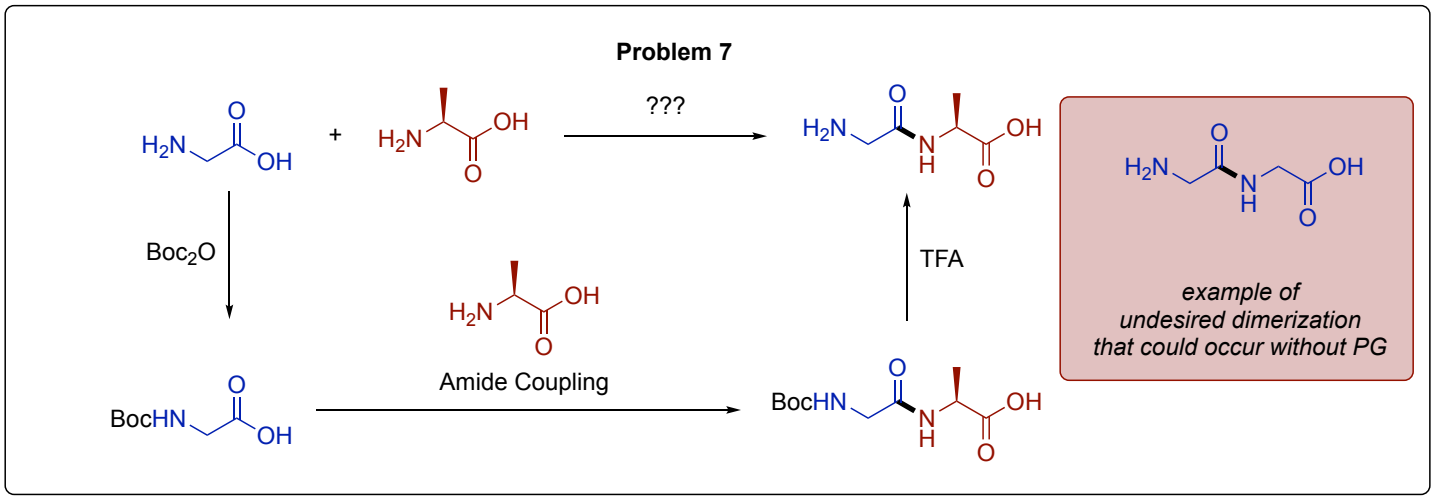
Problem 4: In the second a Grignard reagent is a plausible C-C bond formation strategy however the acidic proton of the hydroxyl would interfere thus protection is required. In this sequence again trimethylsilane (TMS) is installed since it is easily and selectively removed by tetrabutylammonium fluoride (TBAF) however other protecting groups (for example, other silanes or THP (tetrahydropyranyl) or as ether are also feasible).





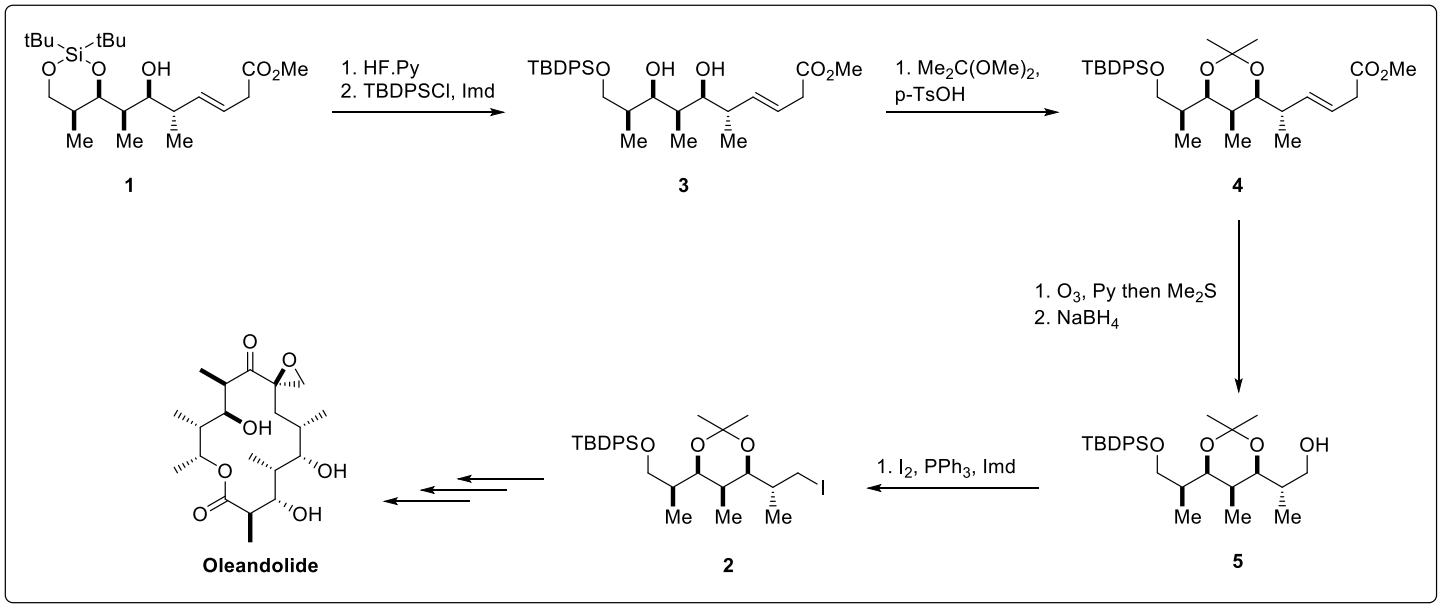
Problem 5: While selective oxidation is possible with other oxidants $KMnO_4$ will lead to the undesired carboxylic acid (red box) thus protection of the aldehyde is required.

Problem 6: The ketone is more easily reduced than the ester thus protection is required before reduction of the ester.



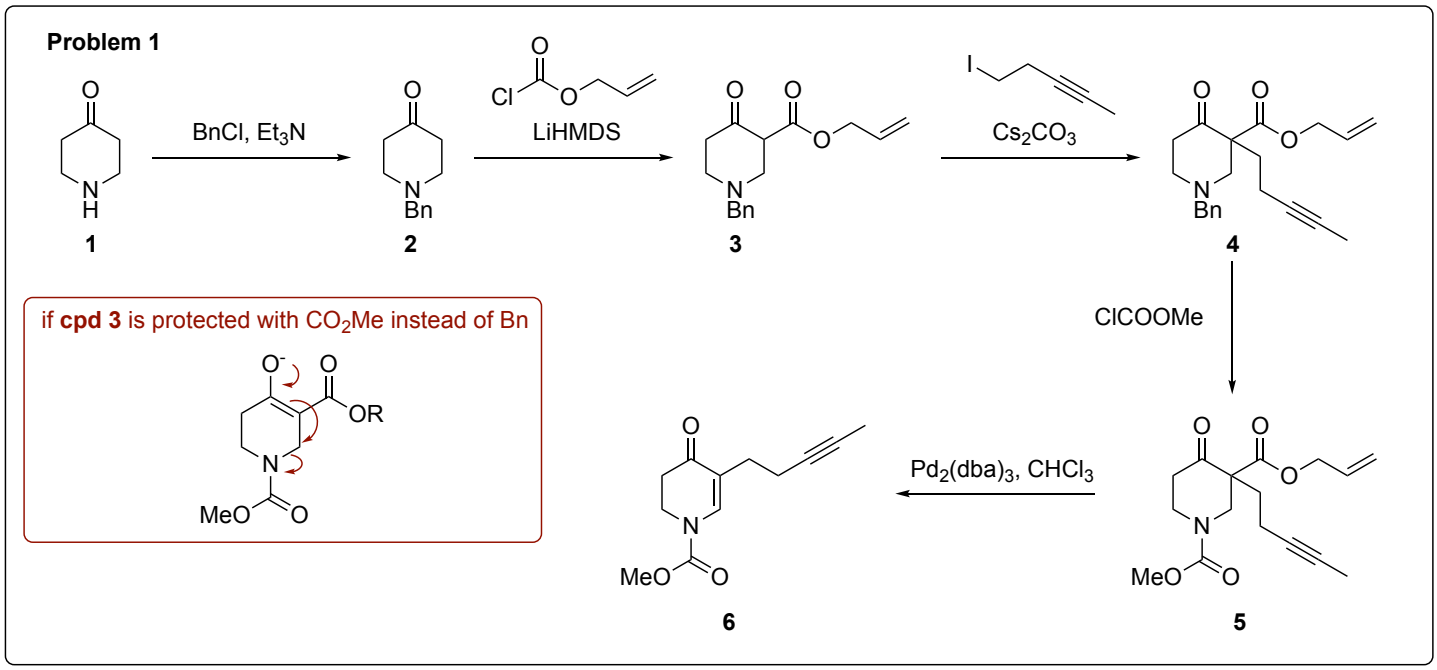
Problem 7: The target requires the coupling of two distinct amines. Since amino acids contain both an amine (nucleophilic) and carboxylic (electrophilic) site selective protection is required to avoid non-selective coupling or homocoupling. In this case a Boc carbamate group is first installed on Glycine (in blue), subsequent coupling with Alanine (in red) is now selective and finally the Boc group is removed by an acidic work-up.

2. Propose a strategy to go from starting material **1** to final compound **2**. Fill in the missing structures and reagents in the scheme and explain potential side reactions in the absence of protecting groups.

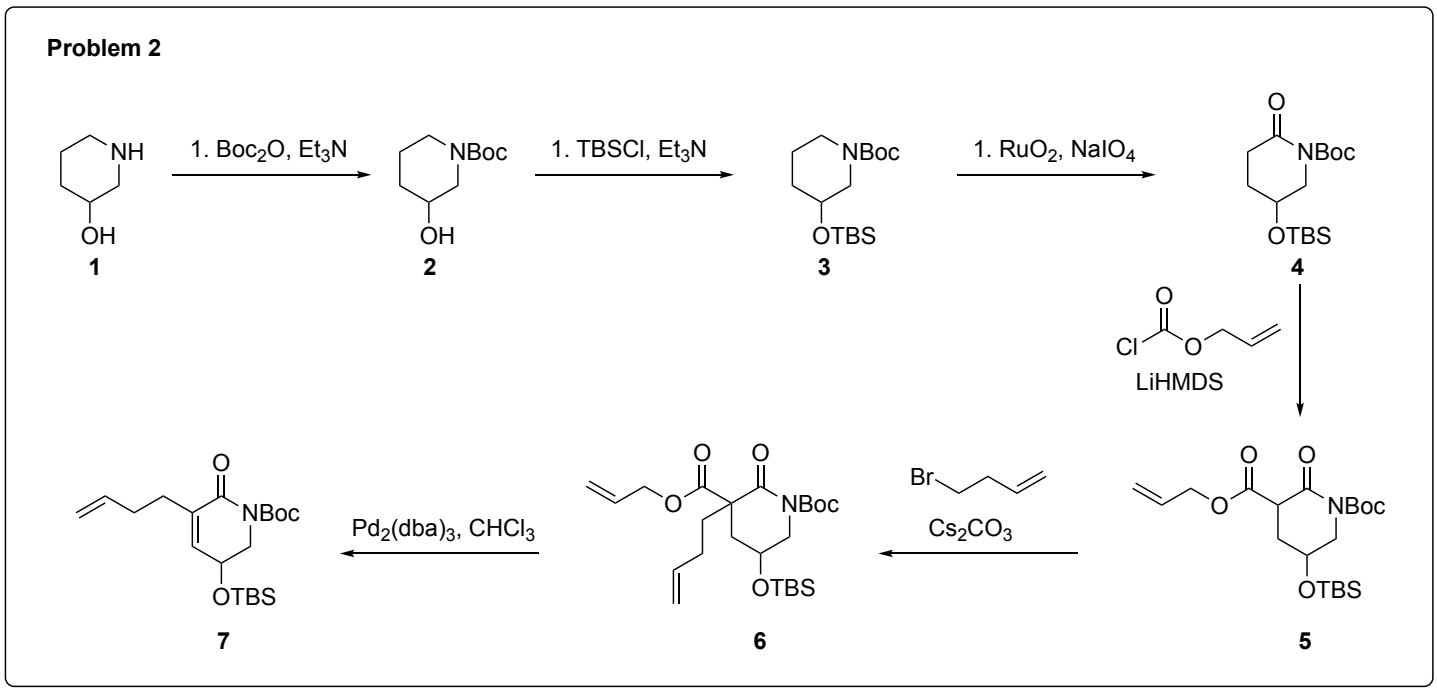


Panek and co-workers reported the total synthesis of the natural product Oleandolide in 2002 (JACS **2002**, 124, 12806-12815). Part of the C1-C7 subunit synthesis is shown in the scheme. Intermediate **1** was obtained from an α-methyl aldehyde in several steps. The first step is the deprotection of the silane and selective protection of the primary alcohol to obtain intermediate **3**. The C3 and C5 diol were converted to the acetonide **4**. Next with all alcohols protected oxidative cleavage (with ozone) and reduction provided compound **5**. Intermediate **5** was easily converted to the desired primary iodide **2**. Protection is necessary to achieve selective oxidative cleavage and selective conversion of the terminal alcohol to the corresponding iodide.

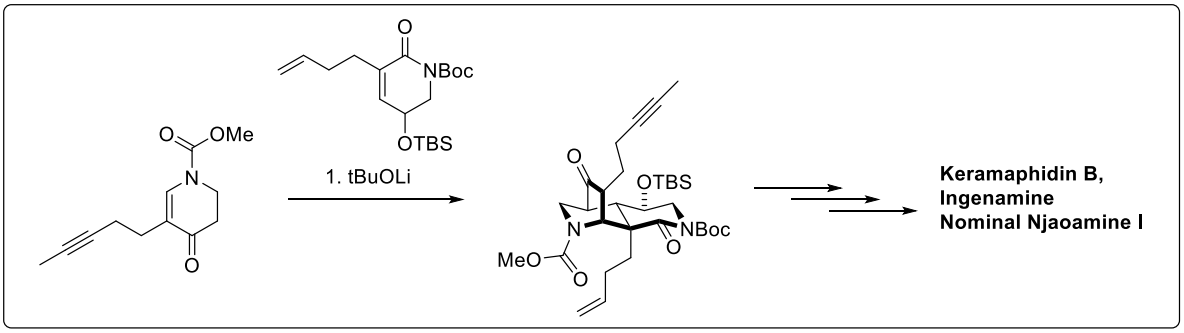
3. Propose a strategy to prepare intermediates **6** of **problem 1** and intermediates **7** of **problem 2.** Fill in the missing structures and reagents in the scheme and explain potential side reactions in the absence of protecting groups.



Problem 1: The Michael donor **6** was prepared from 4-piperidone **1**. In this sequence the basic nitrogen needs protection to avoid downstream interfering in all the next steps. The benzyl protecting group of intermediate **4** is swapped to a carbamate to produce compound **5** since it plays a further role in the synthesis. Having the carbamate present from the beginning is not feasible because it acts as a leaving group under the basic conditions needed to go from intermediate **3** to **4** (shown in the red box).

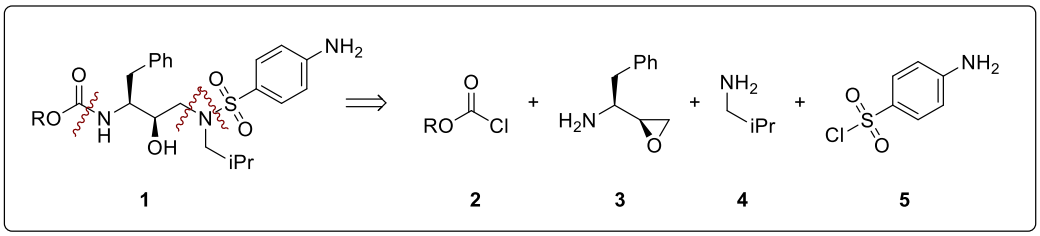


Problem 2: The next compound was prepared from 3-hydroxypiperidine **1**. Again, here the nucleophilic groups were protected (both OH and NH) to avoid downstream interference the next steps. The selective RuO_2 catalyzed C-H oxidation (from compound **3** to **4**) would not be feasible without a protecting group present on the alcohol.

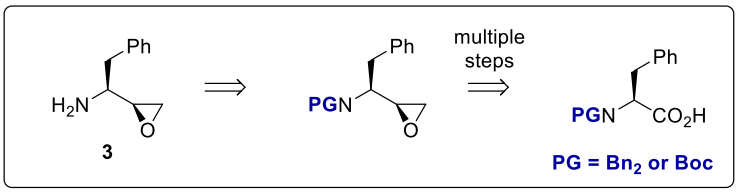


Both fragments where combined to generate the complex intermediate shown above. This intermediate was converted to Keramaphidin B, Ingenamine and Nominal Njaoamine I in multiple steps by Furstner and co-workers (JACS **2021**, 143, 14402 −14414).

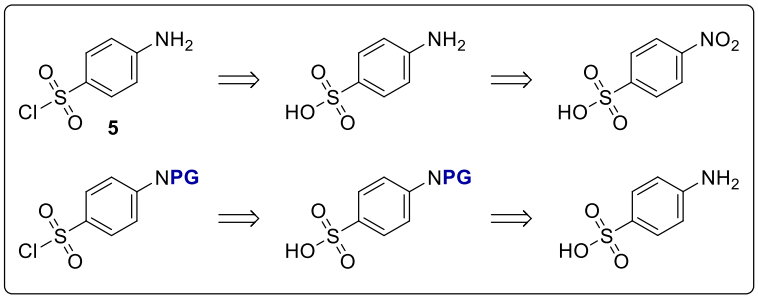
4. Based on the disconnections shown for compound **1** propose which reagents you would use and propose a synthetic strategy. If you make use of protecting groups, explain why they are necessary.



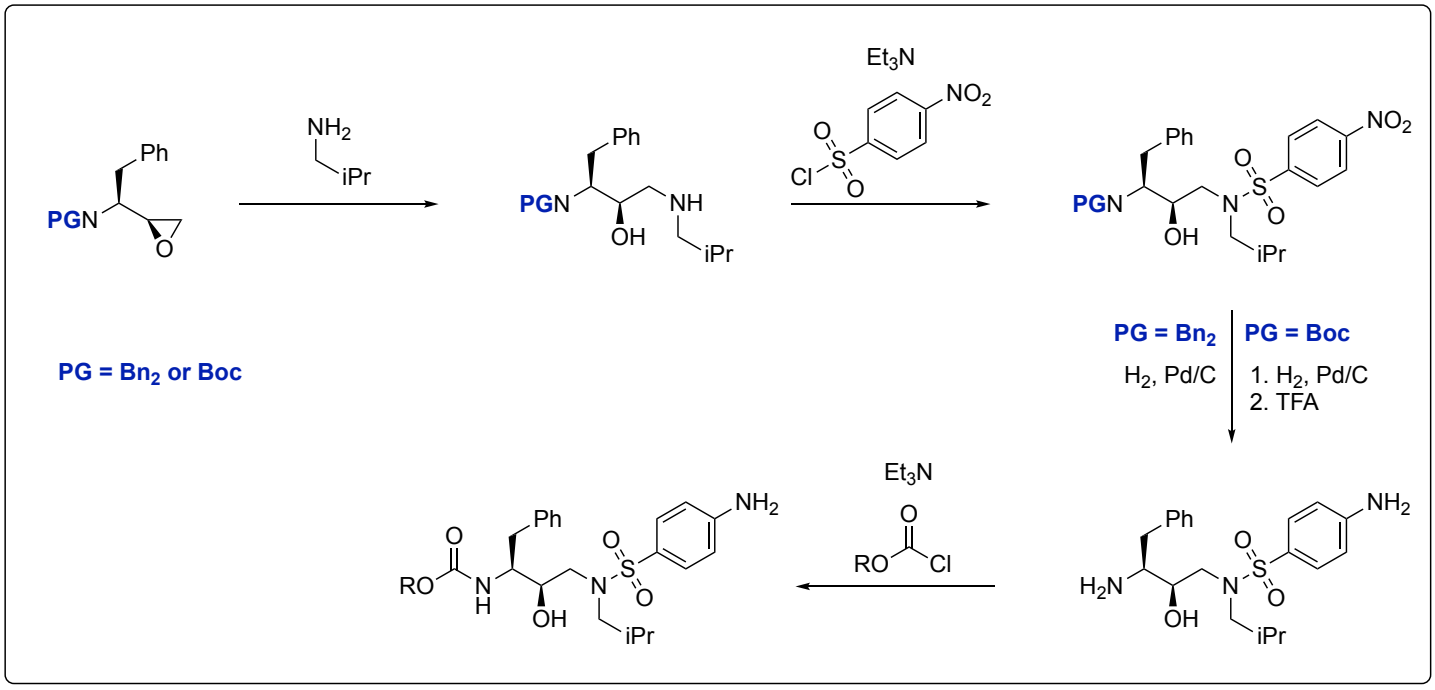
The disconnection of **1** gives four building blocks as shown in the scheme above. Compound **4** is commercially available.



The epoxide **3** can be prepared from the amino acid phenylalanine. However, the amino acid contains both a nucleophilic and electrophilic center thus protection is required.

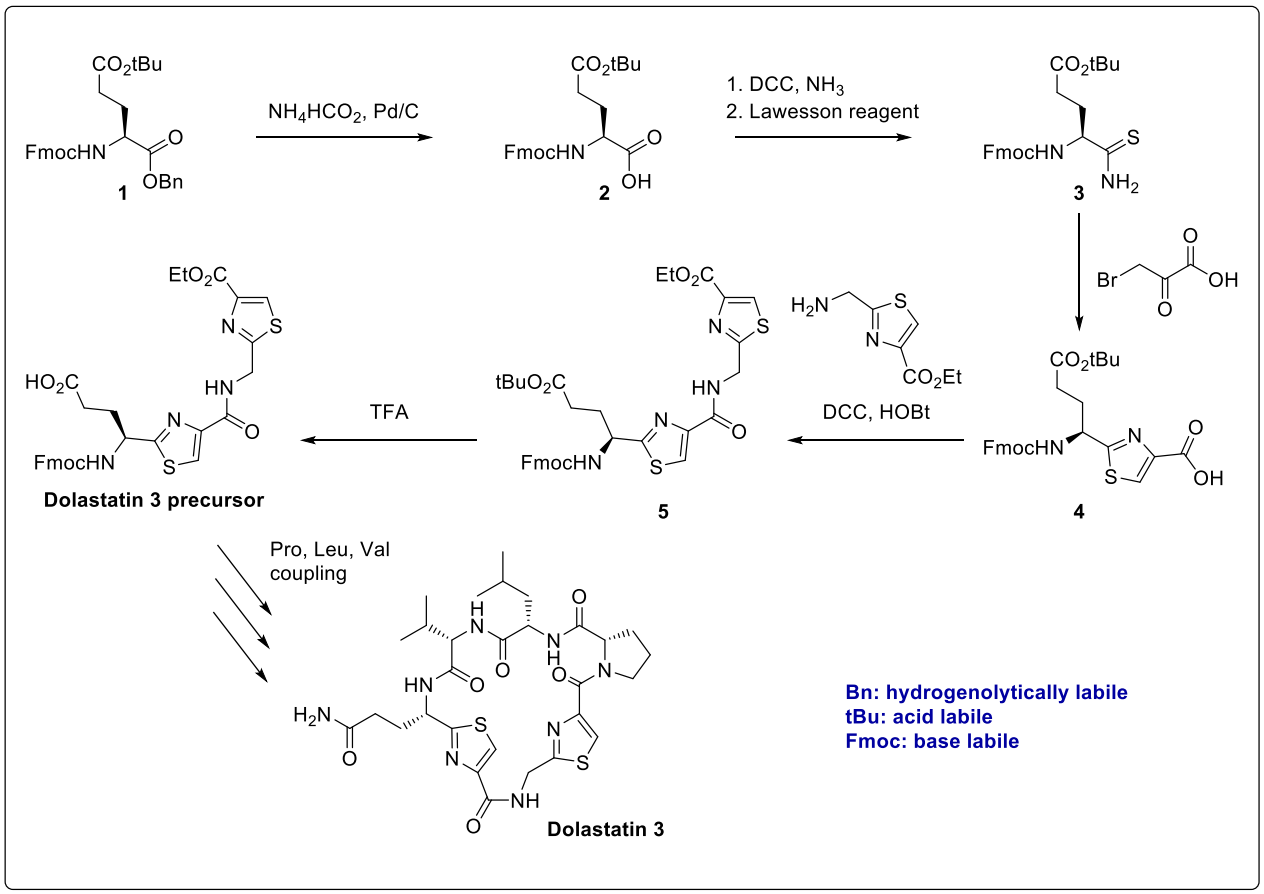


The reagent shown as **5** is unstable since the amine would rapidly react with the sulfonyl chloride and thus polymerize. This issue was avoided by working with either the nitro compound (reduced to the aniline later in the synthesis) or by installing a protecting group.



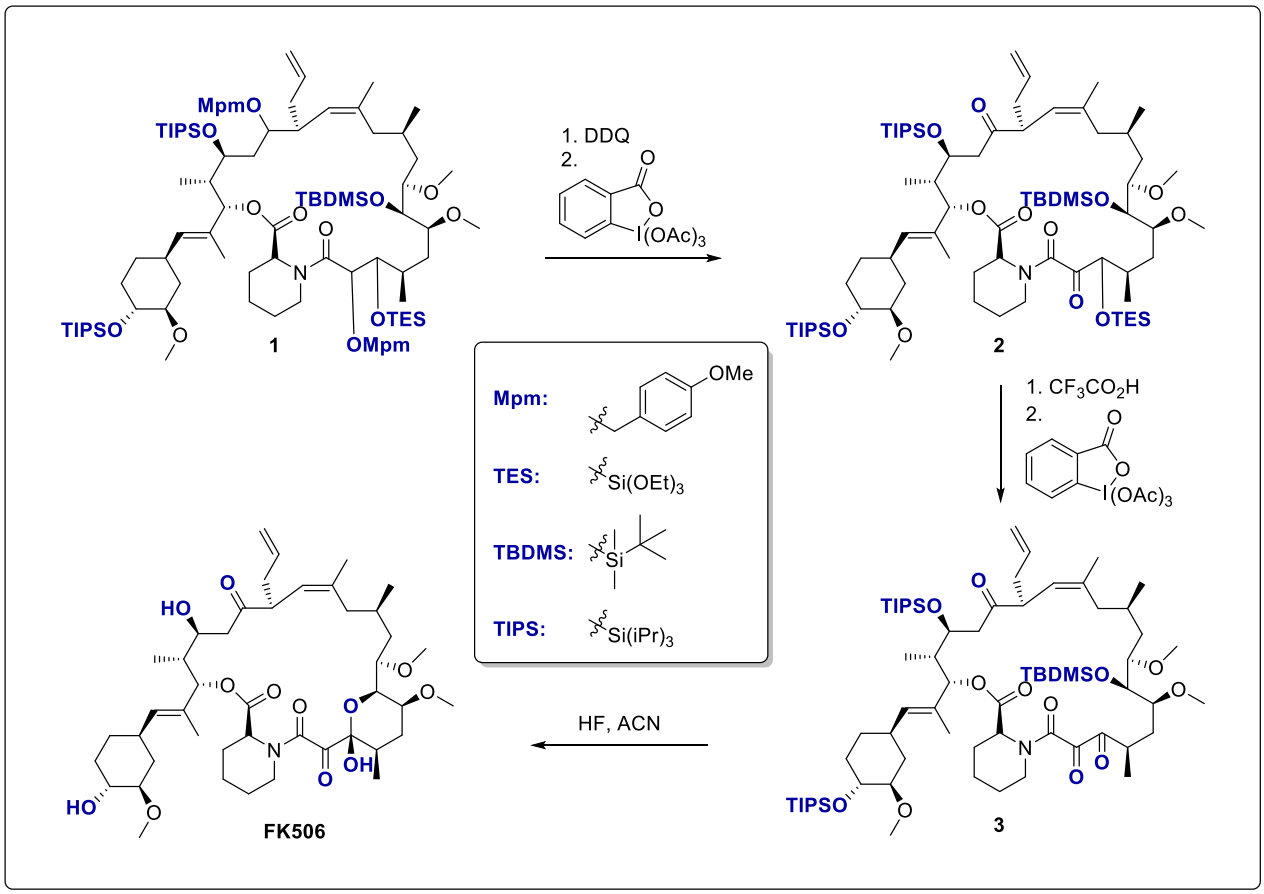
The order of assembling can vary but the approach of researchers at Tibotec is shown above (J. Med. Chem. **2005**, 48, 1813-1822). Two strategies, based on different protecting groups on the amine were devised. First, epoxide and amine were combined and next reacted with the sulfonyl chloride fragment. Protecting the amine functionality of the epoxide fragment is necessary to avoid side reactions of the amine as a competing nucleophile. Subsequent deprotection and reduction of the nitro can be combined when using Bn_2 or done stepwise when using Boc. Finally, the amine is reacted with an acyl chloride to obtain the final compounds.

5. Propose a synthetic approach for the synthesis of the **Dolastatin 3 precursor** shown in the scheme. Fill in the missing reagents and reactants and explain your choice of protecting groups.



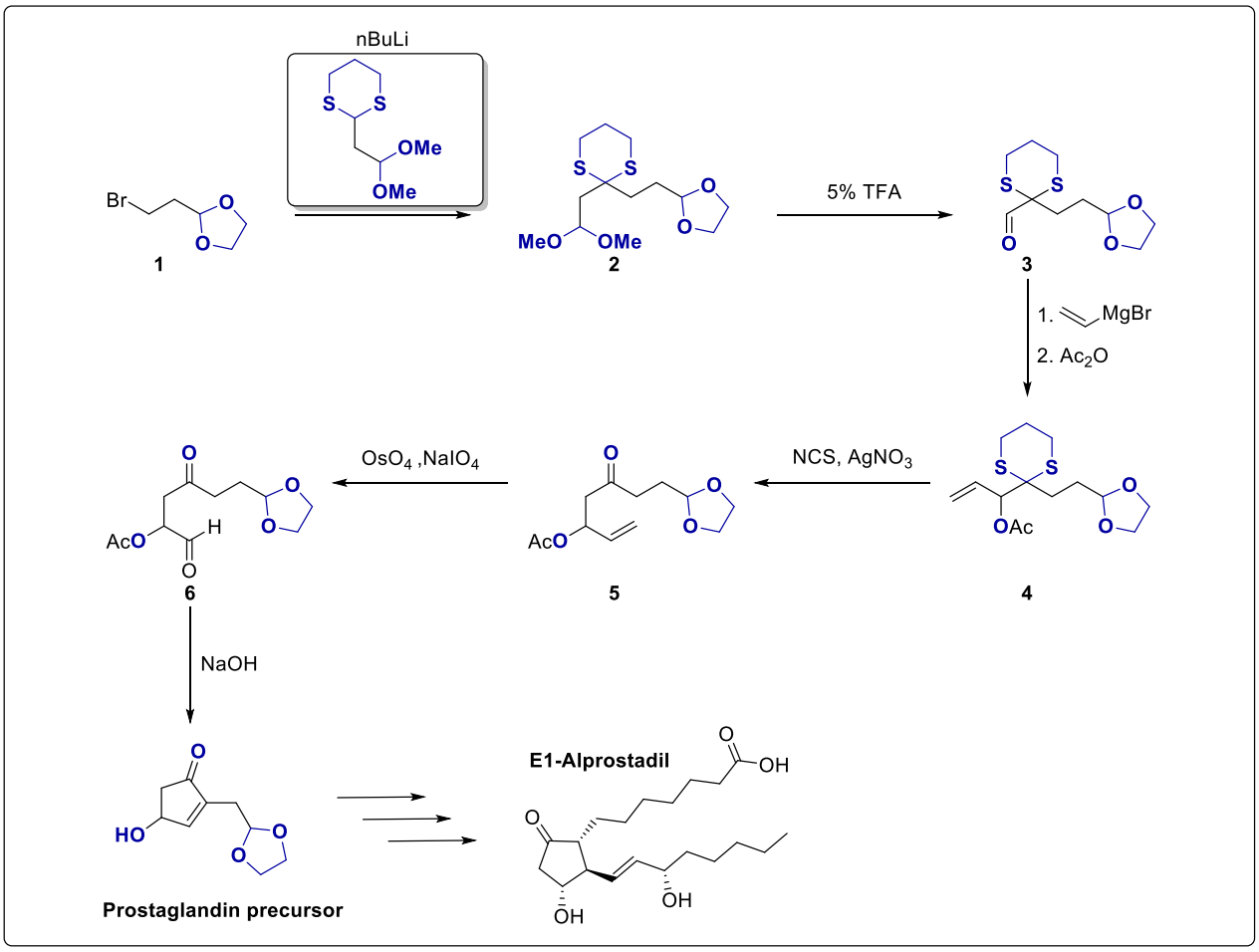
The synthesis of the **Dolastation 3 precursor** relies on acid-labile, base-labile and hydrogenolytically-labile protecting groups (JOC **1986**, 51, 4590-4594). All three types are present on the starting compound **1** (tBu, Fmoc and Bn). First the benzyl (Bn) is removed by hydrogenolysis to allow selective construction of the thiazole to reach compound **4** (the other COOH group remains protected as the tBu throughout). Compound **4** is selectively coupled to reach the bisthiazole compound **5** (the competing amine, on **4** as Fmoc, and carboxylic acid, on thiazole as ethyl ester, are blocked). Finally, selective acid-mediated cleavage of the tert-butyl (tBu) ester produces the free carboxylic acid in the **Dolastatin 3 precursor**. The free carboxylic acid can be converted to the amide (as in **Dolastatin 3**) or anchored to a solid support. The Fmoc group can be removed under basic conditions to allow extension on this side to reach **Dolastatin 3**.

6. The ultimate steps towards Immunosuppressant **FK506** are shown. The final steps involve selective oxidative cleavage, selective acid-mediated cleavage, and another final cleavage of a protecting group. Propose a structure for the protecting groups and suitable reagents for the different cleavage steps.



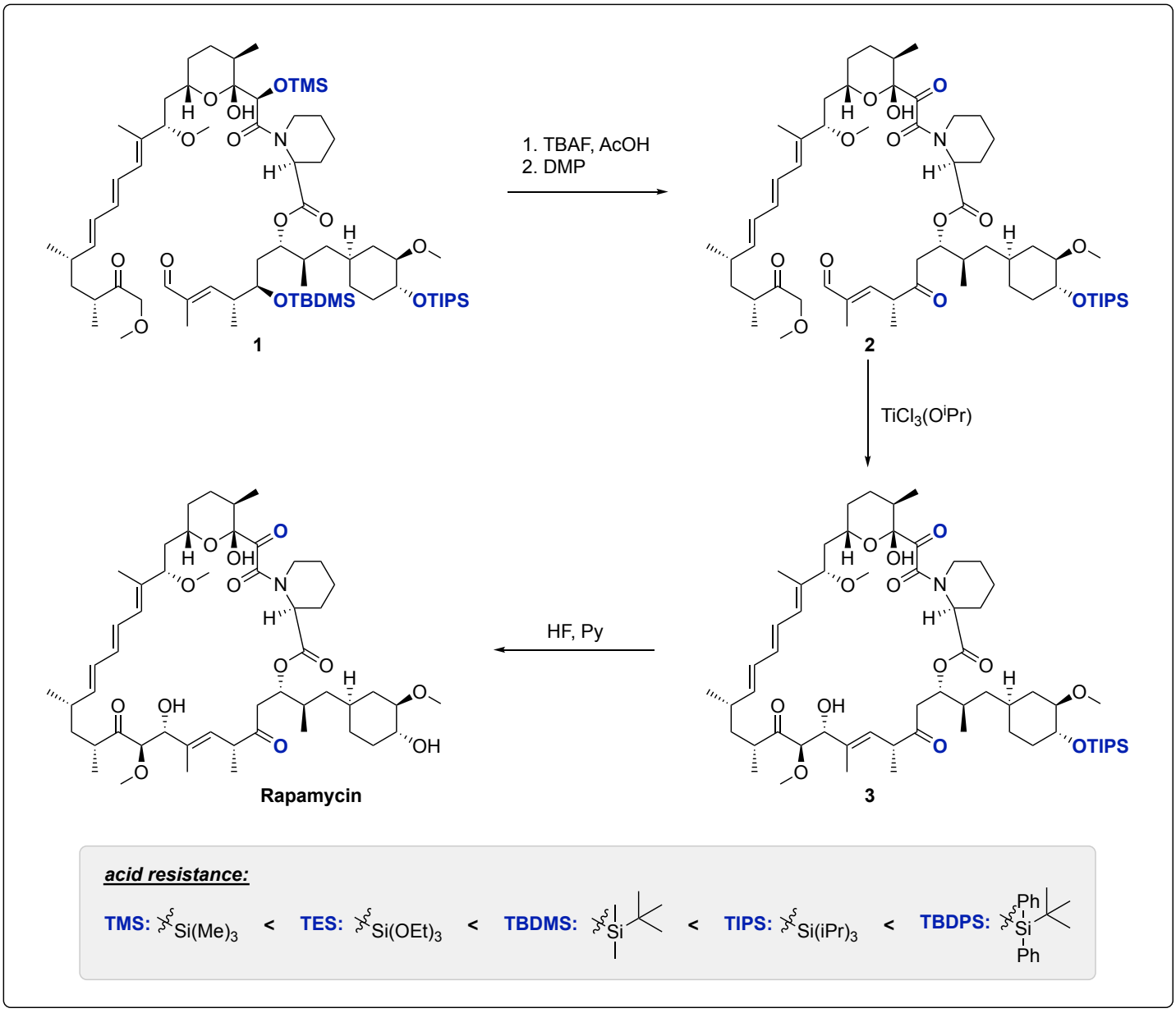
The sequence from advanced intermediate **1** to Immunosuppressant **FK506** was reported by Scheiber and co-workers (JACS **1990**, 112, 5583–5601). The first oxidative cleavage removes selectively the two Mpm (4-methoxybenzyl) protecting groups (most likely CAN can also be used instead of DDQ but the authors did not comment on this). Important is to select other protecting groups that are stable under oxidative conditions (for example TMS would be risky and to labile as protecting group for the other alcohols). The liberated alcohols were oxidized with Dess-Martin periodinane (DMP) to reach intermediate **2**. Next a selective acid cleavage of the triethoxysilane (TES) followed by again DMP oxidation results in the triketone **3**. The more stable tert-butyldimethylsilane (TBDMS) and triisopropylsilane (TIPS) are simultaneous cleaved with HF in ACN to complete the synthesis of **FK506**. The lability of silyl groups towards acid, base and fluoride ions varies depending on the substituents present (in general the bulkier the substituents the higher the stability) thus selective (de)protection is feasible (for more information see T. W. Greene Protective Groups in Organic Synthesis fourth edition **2006**).

7. A **prostaglandin precursor** was prepared from readily available starting materials. Fill in the missing reagents and reactants and explain your choice of protecting groups.



The **prostaglandin precursor** was prepared by Ellison and co-workers (Tetrahedron Lett. **1975**, 8, 499-502) according to the scheme shown above and relies on selective deprotection of non-cyclic vs cyclic acetals. Metalation of the dithiane followed by substitution results in intermediate **2**. Selective removal of the non-cyclic dimethyl acetal results in the aldehyde intermediate **3**. Subsequent Grignard addition and acylation result in intermediate **4**. The dithiane was removed by reaction with *N*-chlorosuccinimide (NCS) and silver nitrate (AgNO3) to give intermediate **5**. Oxidative generation of the aldehyde from the alkene and basic ring closure resulted in the desired **prostaglandin precursor**.

8. The final steps towards **Rapamycin** are shown below. Propose a structure for the protecting groups, intermediates, and suitable reagents for the cleavage of the protecting groups. In this exercise you are only allowed to use one type of protection group commonly used for alcohols.



The final sequence to **Rapamycin** was reported by Danishefsky and co-workers (JACS **1993**, 115, 9345–9346). A selective deprotection of two of the three alcohols is required to complete the total synthesis of **Rapamycin**. Danishefsky and co-workers employed the difference in reactivity between a TMS, a TBDMS and a TIPS ether to achieve selective (de)protection. As mentioned before, the lability of silyl groups towards acid, base and fluoride ions varies depending on the substituents present (in general more bulky substituents increase the stability thus selective (de)protection is feasible, see T. W. Greene Protective Groups in Organic Synthesis fourth edition **2006**). The TMS and TBDMS ether were removed with TBAF while the TIPS remained unreacted. Oxidation with Dess-Martin periodinane (DMP) resulted in intermediate **2.** A titanium-mediated aldol macrocyclization resulted in intermediate **3**. Finally, the remaining TIPS ether was removed with HF in pyridine to complete the total synthesis of **Rapamycin**.