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# Alpha-amino silanes via metalated imines as an approach to the synthesis of silanediol protease inhibitors

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ABSTRACT

Metalation of benzophenone imines for elaboration of the alpha-amino silane component of silanediol-based protease inhibitors allows for rapid diversification of targets. Coupling this chemistry with recently developed asymmetric hydrosilylation chemistry for preparing beta-silyl acids results in a streamlined process for drug design.



## 1. Introduction

Proteolytic enzymes mediate many biological processes. An improper level of protease activity can cause disease and many disease-causing organisms have proteases that play crucial roles in their life cycle.[1,2] Protease inhibitors are commercial pharmaceuticals, important in the treatments for hypertension, AIDS, cancer, and periodontal disease, to name a few.[3–7]

Design of protease inhibitors based on the protease substrate often begins with a suitable mimic of the tetrahedral intermediate **2** formed during protease-mediated hydrolysis of peptide **1**, Fig. 1.[8] Effective replacements for the hydrated amide **2** include hydroxyethylene **3**, which is found in nearly all HIV protease inhibitors. The choice of functional group to replace this tetrahedral intermediate is often specific to the class of protease (aspartic, metallo-, serine or cysteine) and the functional group carries with it the physical properties of the selected analog, which in turn affects the entire molecule and its pharmacokinetic properties. Our research seeks to add a new analog of **2** to the medicinal chemist's toolbox, the silanediol, exemplified by structure **4**, which has very different structure and properties.[9]

Silicon is the element most similar to carbon, and like carbon has no intrinsic toxicity. Unlike carbon however, silicon only forms double bonds under duress, and therefore silanediols can act as stable tetrahedral *gem*-diol analogs of hydrated carbonyls.[10]

To prepare silanediols like **4** we initially developed the chemistry outlined in Fig. 2.[11,12] At the outset of this endeavor, silanediols with acid or amino functional groups were unknown.

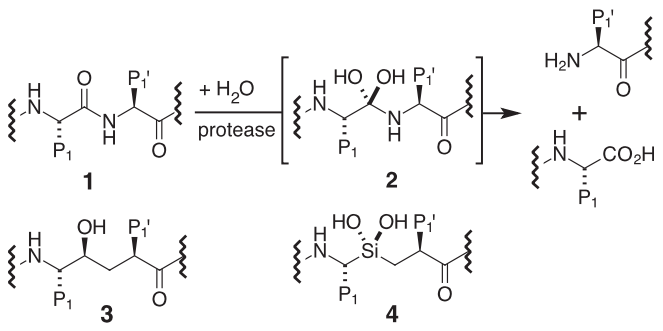


**Fig. 1.** Protease enzymes stabilize the hydrated amide hydrolysis intermediate. A typical aspartic protease inhibitor structure **3** and silanediol inhibitor **4**.[9]

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Similarly, stereochemistry was not present in known silanediols at that time. Silanediol **5** has two different structural subunits: a beta-silyl amide group and an alpha-amino silane, each carrying a stereogenic center. In this first solution to the structure **5**, the beta-silyl amide was constructed with enantiomerically pure lithium reagent **10**, with absolute stereochemistry derived from the commercially available Roche ester.[12] The alpha-amino silane component was prepared via the silyl ketone **7**. Overall the sequence was effective, but it was lengthy and not particularly general.

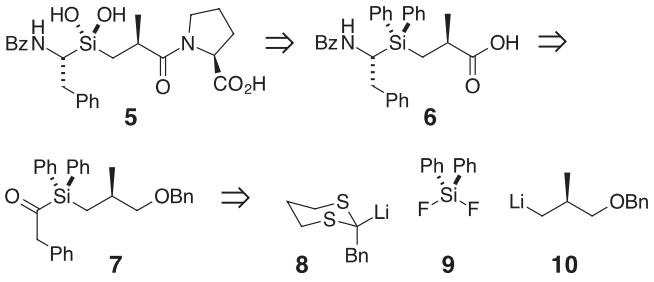

**Fig. 2.** The first preparation of a silanediol protease inhibitor.[12]

In the approach outlined in Fig. 2, installation of the alpha-amino silane component required five steps, with introduction of the benzyl substituent in the earliest stage (**8**). An intriguing alternative to this approach is the late introduction of the substituent between N and Si by metalation–alkylation of the parent aminomethylsilane, **12**, Fig. 3. This approach has the potential benefit of the well-known stabilization of carbanions alpha to silicon, as well as the potential for asymmetric metalation to control the stereochemistry. This approach has been investigated in the context of Y=Boc, but a suitably efficacious protocol did not emerge.[13] Late introduction of the aminomethylsilane substituent would lend itself to diversification of protease inhibitor structures for study.

A different method for generating a primary aminomethyl anion is the benzophenone *N*-methylimine **14**.[14] This readily available imine is easily deprotonated to form a nucleophilic aminomethyl anion. Indeed, metalation and alkylation of **14** has been reported repeatedly over the last 43 years and silylation of this anion was first performed 40 years ago.[15,16] The resulting silylmethyl imines have also been hydrolyzed to the free amine.[17]

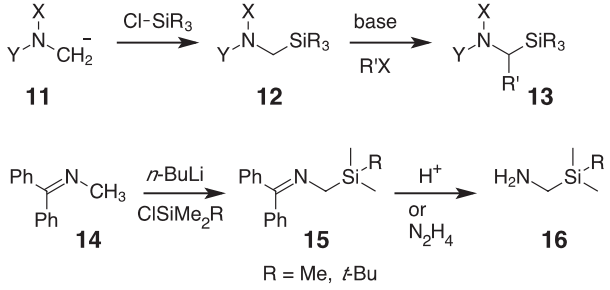

**Fig. 3.** Alpha-amino silane synthesis by metalation–alkylation.

On the other hand, *N*-silylmethyl imines are also well known precursors of azomethine ylides. Compound **17** has been found to desilylate under a variety of conditions, including simply stirring with water–acetic acid in a polar solvent at ambient temperature, Fig. 4.[18] Nevertheless, the anticipated simplicity of generating structures, such as **15,** and the precedent for hydrolysis to the free amine, stimulated our interest in this approach.

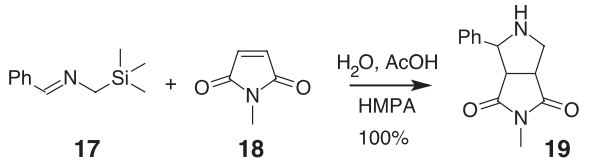

**Fig. 4.** *N*-Trimethylsilylmethyl imines can desilylate under mild conditions.[18]

## 2. Results and discussion

Assembly of the protease inhibitor was envisioned to use the sequence outlined retrosynthetically in Fig. 5. The protected inhibitor precursor **20** would come from the imine **22** after hydrolysis of the imine and oxidation of the protected alcohol, or an equivalent. Compound **22** would be prepared by alkylation of **23** after deprotonation between the silicon and imine, and **23** would derive from silylation of lithiated imine **24** and a suitable silane precursor of the beta-silyl acid unit **25**.

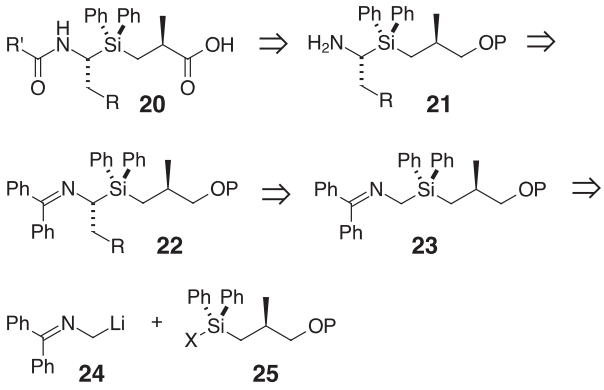

**Fig. 5.** *N*-Diphenyl(alkyl)silylmethyl imine approach to the protease inhibitors.

Two beta-silyl acid precursors were used in this study, Fig. 6. Fluorosilane **26** is generated by fragmentation of **27**, prepared by asymmetric hydroboration of **28**, the latter a product of magnesium-mediated cyclization of isoprene with dichlorodiphenylsilane.[19] Fluorosilane **29** is readily derived from **30** by asymmetric hydrosilylation of **31**.[20]

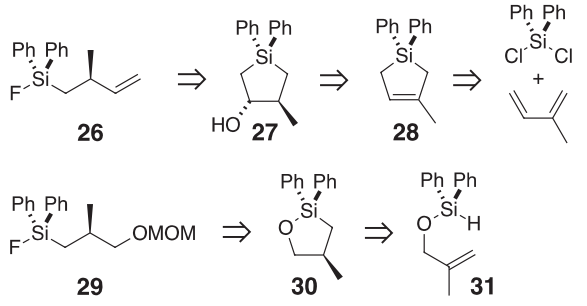

**Fig. 6.** Electrophilic fluorosilane precursors of beta-silyl acids.[19,20]

In the event, coupling of the lithiated imine derived from **14** with **26** and **29** proceeded in very good yield. In the case of **26**, racemic fluorosilane was used (Fig. 7).

In contrast, hydrolysis of the imine of **33**, using oxalic acid conditions described by Silverman[17] led to cleavage of the just-formed C–Si bond and isolation of silanol **34** in 58% yield