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Efficient, Enantioselective Assembly of Silanediol Protease Inhibitors

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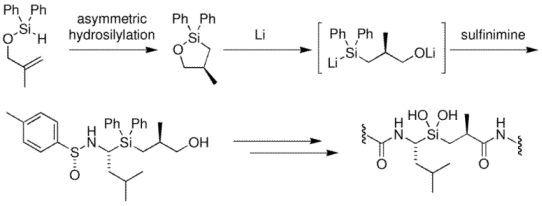
Abstract



A five-step assembly of silicon-protected dipeptide mimics from commercially available reagents is described. This methodology makes silanediol protease inhibitors readily available for the first time. The sequence features asymmetric hydrosilylation, a novel reduction of a silyl ether to a silyllithium reagent, and addition of this dianion to a sulfinimine, to produce the complete inhibitor skeleton with full control of stereochemistry. Oxidation of the primary alcohol to an acid completes the synthesis.

Inhibition of proteolytic enzymes remains a fundamental approach to the design of new pharmaceuticals, with recent examples including the treatment of cancer, anti-retrovirus diseases (HIV), treatment for Alzheimer's and hepatitis C.[1] Most protease inhibitors utilize now-standard functionality to mimic the transition state or to intercept the catalytic functional groups: hydroxamic, carboxylic and phosphinic acids (for metalloproteases), hydroxyls (for aspartic acids), and activated carbonyls (for serine proteases).2 Fundamentally different functional groups that can act as transition-state analogs have the potential to give enhanced enzyme binding and pharmacokinetic properties, as well as intellectual property novelty.3

Dialkylsilanediol dipeptide analogs (e.g. **1**, Scheme 1) are tetrahedral functional groups that can mimic hydrated carbonyls.[4] When silanediols are embedded in a peptide-like structure such as **1**, they are recognized by protease enzymes and, as hydrolytically stable entities, act as inhibitors. Tripeptide analog **1**, for example, is a 4 nM inhibitor of the metalloprotease angiotensin-converting enzyme, an important therapeutic target for hypertension.[5] A silanediol has also been shown to be a 3 nM inhibitor of the aspartic acid HIV-protease, an activity that translates to cell-protection assays.[6]

An impediment to utilization of these silanediol structures, however, has been the methodology for their assembly. In our original preparation of **1**, Scheme 1, diphenylsilane **2**

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Supporting Information Available Detailed experimentals, characterization data and proton NMR spectra for new compounds is available. This material is available free of charge via the Internet at http://pubs.acs.org.

was the direct precursor of the silanediol; the α-amino silane portion of **2** was prepared utilizing a dithiane nucleophile **3** and six synthetic steps, while Roche ester **5** was transformed to the β-silyl acid of **2** in seven steps. In this synthesis, the stereochemistry of the methyl substitution was purchased and the benzyl group stereochemistry relied on separation of diastereomers. While effective, this approach was 13 steps and technically challenging.[7]

We report here a short, general, asymmetric preparation of silanediol precursor **2**: one that employs intramolecular asymmetric hydrosilylation to set the β-silyl acid stereochemistry, a novel reduction of a silyl ether to a silyl anion, and addition of the resulting dianion to a sulfinimine. The resulting product requires only alcohol oxidation to give the fully functionalized dipeptide mimic.

Asymmetric intramolecular hydrosilylation of 2-alkyl allyl silyl ethers in the simple system **6a** was described by Bosnich, who found 25% ee was possible using BINAP–rhodium complexes.[8,9] We have reexamined this transformation, surveying a series of commercially available phosphine ligands.[10] (*S*,*S*)-Diethylferrotane[11] as a rhodium ligand (2 mol %) was found to fully convert 2 g of the methylallyl ether of diphenylsilane **6a** into (4*S*)-2-diphenylsilafuran **7a** with good enantiomeric excess within one hour.[12] Additional examples **b** – **d** indicate a useful breadth of utility for this ligand in these asymmetric hydrosilylations, which all proceed quantitatively.

Conversion of silafuran **7a** to a protease inhibitor was conveniently effected (Scheme 3) by treatment with 48% HF, protection of the alcohol as the MOM ether[13] and transformation of the fluoride to the hydride **8** by reduction with lithium aluminum hydride. Following the Skrydstrup protocol,[14] silane **8** was converted to the corresponding lithium reagent and then coupled with sulfinimine **12** to give sulfinamide **9** as a single stereoisomer. Mild acidic deprotection of both the amine and the alcohol, followed by Schotten-Baumann derivatization of the amine gave amide-alcohol **10**. Oxidation of the alcohol with TEMPO gave **11** in 72% yield.[15]

This seven-step sequence, Scheme 3, cut the number of steps required for preparation of **11** by nearly half while simultaneously controlling the stereochemistry. Nevertheless, the inclusion of protection-deprotection protocols suggested that further improvements were possible.

To explore a more direct conversion of **7a**, this substrate was subjected to standard lithiation conditions by stirring with lithium metal. To our delight, formation of the typical brown-green color of silyllithium reagents was observed. After 7 h, addition of chlorotrimethylsilane led to formation of **14**, indicating that dianion **13** had been produced.

Repeating the lithiation step and addition to sulfinimine **17** gave alcohol **15** (0.2 g, 76%, Scheme 5). Exchange of the sulfinamide for a Boc group and oxidation of the alcohol with ruthenium chloride gave **16** in 43% yield (three steps). Acid **16** is ideally configured for use in silanediol inhibitor investigations. Addition of dianion **13** to other sulfinimines gave **18** (0.37 g, 56%) and **19** (0.10 g, 71%).

The reduction of diphenylsilyl ether **7a** to a diphenylsilyl lithium reagent has little precedent. Silyl anions are typically prepared from silanes carrying at least one phenyl and a chloride, a fluoride, a hydride or another silane.[16] Benkeser reported reduction of methoxytriphenylsilane with sodium-potassium alloy in 1952 and a similar reaction was reported by Gilman in 1953.[17] These appear to be the only examples of this transformation.

The addition of dianion **13** to the sulfinimine follows the seminal contributions of Nielsen and Skrydstrup.[14] The use of this silyl-alkoxy dianion, however, has a potential complication arising from competition of two different basic and nucleophilic groups. The alcohol, in particular, appears to be far less sterically encumbered. Nevertheless, even with the difficult substrate **12** the silane addition product **18** is isolated in good yield.

We have found the use of the sulfinimines developed by Davis[18] (*p*-toluene, e.g. **17**) and by Ellman[19] (*tert*-butyl, e.g., **12**) to be essentially interchangable, with only slight differences in diastereoselectivity. In some cases slight differences in stability or crystallinity may be advantageous.

An additional streamlining of this sequence could, in principle, be achieved by oxidizing the alcohol of **15** to an acid without oxidizing the easily removed sulfinamide to a more robust sulfonamide. This remains under study.

This scalable, short sequence for building silicon-based protease inhibitors makes these structures routinely available for the first time, with complete control of stereochemistry. Investigations into the use of silyl ethers as silyllithium reagent precursors and asymmetric intramolecular hydrosilylation will be reported elsewhere.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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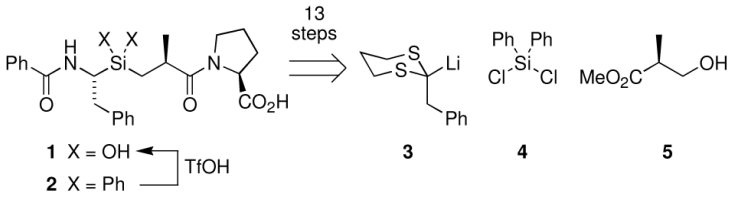
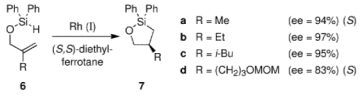


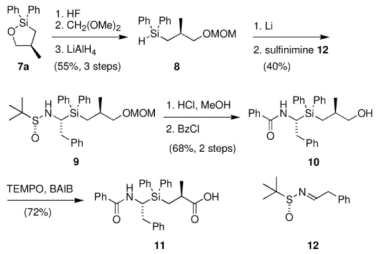
Scheme 1.
Protease inhibitor **1**, originally prepared via **2** from **3**-**5**.



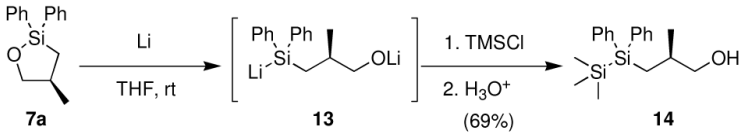
Scheme 2.

Asymmetric hydrosilylation of 2-alkyl diphenylsilyl ethers.[a]

[a.] Compound **7a** was correlated with a known compound; **7d** was assigned using the Mosher ester method; **7b** and **7c** were assigned by analogy. See Supporting Information.

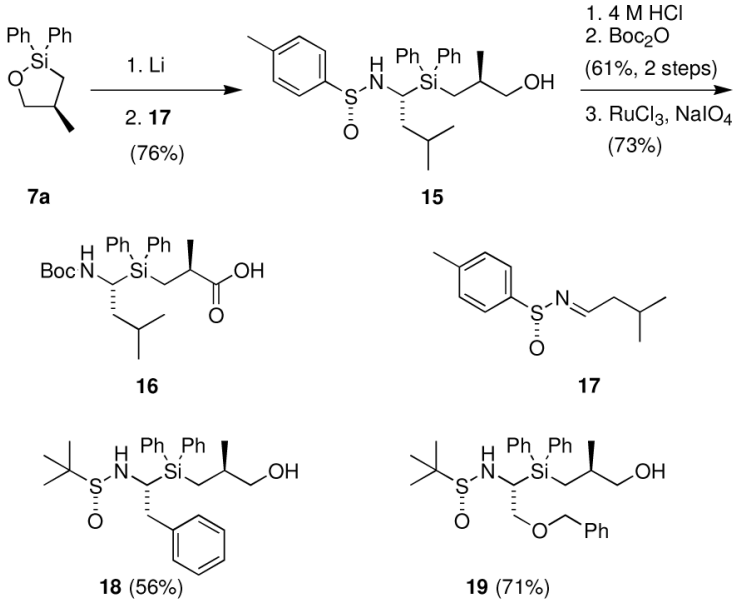


Scheme 3.
Conversion of the silafuran to an advanced intermediate.



7a 13 14

Scheme 4.
Lithiation of silyl ether **7a**.



Scheme 5.
Four-step assembly of **16** from **7a**