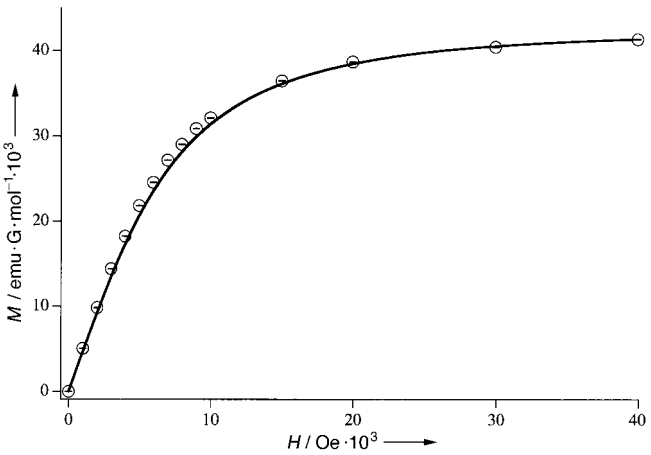

Figure 3. Dependence of the magnetization M of [{Mn(hfac)$_2$}$_2$(bnn)] on the field strength H at 2 K. The solid line indicates the theoretical curve for $S = 4$.

formal comparison of these systems with a Wheatstone bridge in an electric circuit (Scheme 1b). In a balanced Wheatstone bridge, no current flows through R_{13} even if R_{13} is very small. With respect to information processing at the molecular level, the mimicking of an electric circuit by molecular materials is instructive.[8]

We have succeeded in constructing a heterospin system which displays competing interactions between organic radicals and transition metal ions. In this system the large antiferromagnetic interaction was made ineffective by the butterfly spin configuration, and J and J_{13} are sufficiently large to realize the degeneracy of a ground-state spin-frustrated system.

Experimental Section

Preparation of the sample: A suspension of [Mn(hfac)$_2$]·2H$_2$O (165 mg, 0.32 mmol) in *n*-heptane (40 mL) was heated at reflux to remove H$_2$O by azeotropic distillation. The dark green solution obtained by adding bnn (50 mg, 0.16 mmol) in CH_2Cl_2 (20 mL) was concentrated on a rotary evaporator to remove CH_2Cl_2. The green precipitate was collected by filtration to afford dark green plates of [Mn$_2$(hfac)$_4$(bnn)] (153 mg, 76 %). The sample for X-ray crystallography was recrystallized from CH_2Cl_2/heptane: IR (KBr): $\tilde{\nu} = 1258, 1651, 3002\ cm^{-1}$.

Magnetic measurement: A fine-crystalline sample was mounted in a capsule and measured on a Quantum Design MPMS-5S SQUID susceptometer at 500 G. Corrections for the diamagnetic contribution were made with Pascal's constants.

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[7] Crystallographic data for [{Mn(hfac)$_2$}$_2$(bnn)]: $C_{34}H_{28}N_4O_{12}F_{24}Mn_2$, $M_r = 1250.45$, triclinic, space group $P\bar{1}$, $a = 13.305(1)$, $b = 18.617(1)$, $c = 11.0825(6)$ Å, $\alpha = 101.885(5)$, $\beta = 100.968(5)$, $\gamma = 103.359(6)^\circ$, $V = 2530.6(4)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.641\ g\,cm^{-3}$, $\mu(Cu_{K\alpha}) = 54.26\ cm^{-1}$. Data were collected on a Rigaku AFC7R diffractometer at 296 K with $Cu_{K\alpha}$ radiation ($\lambda = 1.54178$ Å). The structure was solved by direct methods and refined to $R = 0.082$, $R_w = 0.079$, for 3677 unique reflections with $|F_o| > 1.5\sigma(|F_o|)$ and 685 parameters. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100688. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Silanediols: A New Class of Potent Protease Inhibitors**

Scott McN. Sieburth,* Thomas Nittoli, Alfred M. Mutahi, and Luxuan Guo

Lower dialkylsilanediols, with their proclivity for self-condensation [Eq. (1)], are the cornerstone of the siloxane (silicone) industry, and siloxane polymers **2** have a reputation as stable and inert materials.[1] Dimethylsilanediol (**1**) is the best known siloxane monomer and the most prone to polymerization. In contrast, more sterically hindered silane-

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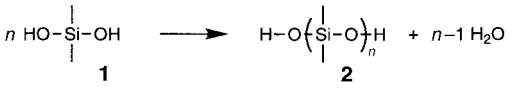
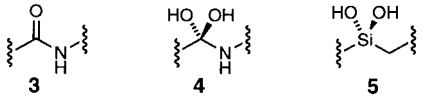


(1)

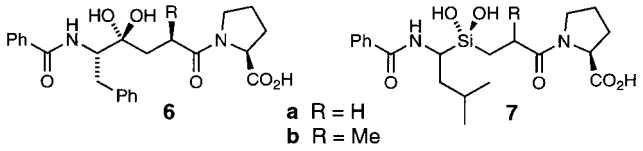
diols can be stable and in some cases will form oligomers only under forcing conditions.[2]

Organosilanes are inherently unnatural yet have no intrinsic toxicity.[3] As silicon is the element most similar to carbon, its derivatives have been the subject of many investigations in the search for bioactive materials.[4, 5] A dialkylsilanediol **5**[6, 7] should be an isosteric analogue of the tetrahedral hydrolysis intermediate **4** of a peptide amide **3**: The silicon atom of a



silanediol is most stable in a tetrahedral configuration, and the hydroxyl groups are excellent hydrogen bond donors and acceptors.[8, 9] Nevertheless, previous attempts to inhibit hydrolases with relatively simple silanediols[10] and silanetriols[11] found them to be inactive. Here we report the first synthesis of a silanediol-based dipeptide analogue and the discovery that these compounds can be potent inhibitors of the metalloproteases and, therefore, therapeutically important target molecules for medicinal chemistry.

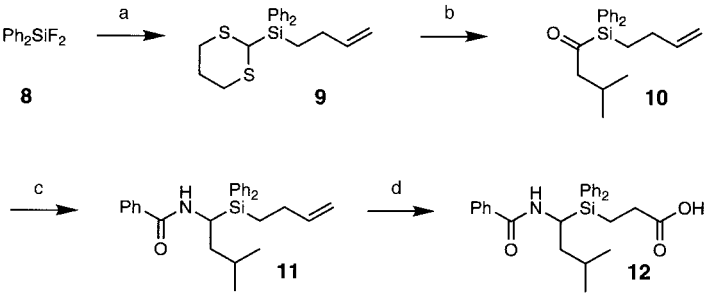
A ketone inhibitor (**6**, shown in the hydrated form) of angiotensin-converting enzyme (ACE) was used as a model for design of the silanediol inhibitor. This ketone is presumably hydrated at the active site of the enzyme.[12] The



silanediol analogue **7** differs from **6** in three significant ways: the central silicon atom, an isobutyl group in place of the benzyl group,[13] and the formation of **7** as a mixture of diastereomers.

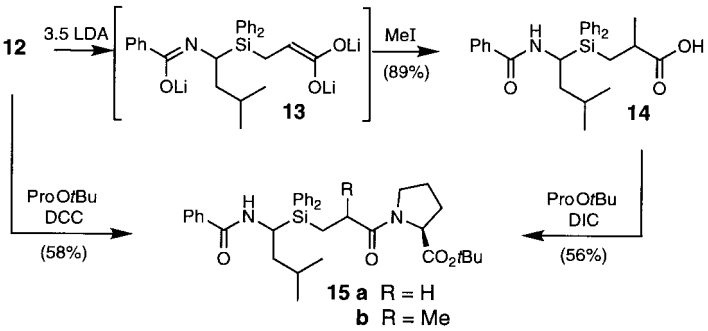
Synthesis of **7** required a silanol-protecting group. Phenyl groups were selected with the expectation that their hydrolysis with strong acid would be similar to standard peptide deprotection routines[14, 15] and would therefore be compatible with the amide groups in the molecule.

Preparation of **7** commenced with the sequential treatment of difluorodiphenylsilane[16] with 1-bromomagnesium-3-butene and 2-lithio-1,3-dithiane (Scheme 1).[17] The resulting 2-siladithiane **9** was deprotonated, alkylated with isobutyl bromide, and then hydrolyzed to yield the moderately stable silylketone **10**, which was reduced to the alcohol with lithium aluminum hydride. Mesylation of the alcohol and substitution with azide was followed by reduction with lithium aluminum hydride and benzoylation to give **11**. The alkene of **11** was then oxidatively cleaved under Weinreb conditions[18] to give



Scheme 1. Synthesis of diphenylsilane **12**. a) 1. C_4H_7MgBr (83%), 2. $C_4H_7S_2Li$ (96%); b) 1. *n*BuLi, *i*BuBr (92%), 2. $HgCl_2$, H_2O (88%); c) 1. $LiAlH_4$ (69%), 2. MsCl, NaN_3 (87%), 3. $LiAlH_4$, 4. PhCOCl (88%); d) OsO_4 (cat.), Jones reagent (96%). Ms = methanesulfonyl.

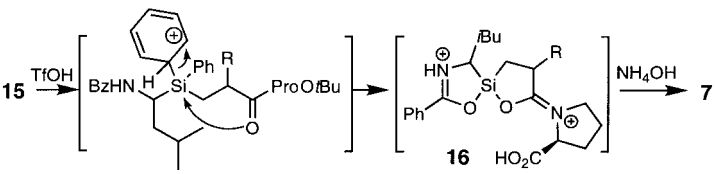
the carboxylic acid **12**. Introduction of the methyl group in the position α to the carboxyl group was achieved in good yield, albeit stereorandomly, by using the trianion **13** (Scheme 2).



Scheme 2. Synthesis of diphenylsilane **15**. LDA = lithium diisopropylamide, DCC = dicyclohexylcarbodiimide, DIC = diisopropylcarbodiimide.

Acids **12** and **14** were coupled with the *tert*-butyl ester of L-proline to give the silanediol precursors **15a** and **15b** as mixtures of two and four diastereomers, respectively.[17]

Reaction of phenyl groups on silicon with trifluoromethanesulfonic (triflic) acid is a routine method for the preparation of silyl triflates,[19, 20] and here it was combined with removal of the *tert*-butyl ester group. Consideration of the relative reactivities of the functional groups in **15** leads to the expectation that the protonated arylsilane will be intercepted by a nucleophilic neighboring amide carbonyl group rather than by triflate (Scheme 3). Therefore, a probable intermedi-



Scheme 3. Hydrolysis of **15** may be assisted by the amide carbonyl group. Tf = trifluoromethanesulfonyl, Bz = benzoyl.

ate in the acidic cleavage of the phenyl–silicon bond in nonnucleophilic solvents is the spirocyclic compound **16**. Hydrolysis of **16** was expected to be facile, as simple five-membered silyl ethers are strained.[21] In the event, treatment of **15a** and **15b** with triflic acid in dichloromethane at 0 °C for

30 min followed by addition of ammonium hydroxide led to **7a** and **7b** as diasteromeric mixtures that were very difficult to separate. Yields of isolated **7a** and **7b** after HPLC purification were 39% and 21%, respectively.

Silanediol mixtures **7a** and **7b** were tested as ACE inhibitors with use of the commercially available enzyme and substrate by the methods of Cushman[22] and Holmquist.[23] The measured IC_{50} values are listed in Table 1

Table 1. Inhibition of ACE by **6** and **7**.

	R	IC_{50} (**6**)[24]	IC_{50} (**7**)
a	H	3.2 nM	57 nM
b	Me	1.0 nM	14 nM

together with the reported values for **6a** and **6b**.[24] Notably for both **6** and **7**, introduction of the methyl group (R) in the position α to the amide carbonyl group increases the enzyme inhibition by a factor of 3–4. The more potent inhibitors **6b** and **7b** differ by a factor of 14. These differences in potency are likely to be due to the presence of low-activity diastereomers in the **7b** mixture and the replacement of an isobutyl group by a benzyl group in **6**.

Enantioselective synthesis of the isomers of **7** can be expected to improve the activity, and the chemistry reported here should be readily amenable to asymmetric control at all stereogenic centers. We have demonstrated the use of aryl groups as stable yet readily hydrolyzable protecting groups for silanols that are compatible with peptidomimetic silanediol synthesis. Silanediols **7a** and **7b** are the most complex silanediols reported to date and represent a new class of inhibitors for metalloproteases.

Experimental Section

Inhibition of ACE (EC 3.4.15.1, Sigma) was measured by monitoring the absorbance at 340 nm with a Perkin-Elmer Lambda 5 UV/Vis spectrophotometer. Samples were prepared in disposable polystyrene cuvettes and incubated at 37 °C. Each cuvette was charged with 1.0 mL of substrate (0.5 mM solution, pH 8.2, *N*-[3-(2-furyl)acryloyl]-L-phenylalanylglycylglycine, Sigma) and 0.1 mL of the porcine enzyme solution in a buffered human serum base (Sigma). Stock solutions of **7a** and **7b** were prepared in deionized water buffered with 0.3 M NaCl and 0.05 M Trizma (Sigma) to give a pH of 8.3 at 37 °C, and this solution was added to the cuvettes to achieve the desired concentration. Solutions with and without inhibitors were equilibrated at 37 °C for 5 min, and initial rates were measured. Captopril was used to calibrate the assay. Inhibition measurements were made three times at each concentration.

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