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Synthesis and Properties of a Sterically Unencumbered δ-Silanediol Amino Acid

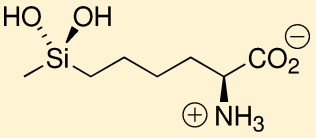
Jin Kyung Kim[†,‡] and Scott McN. Sieburth*[,†]

[†]Department of Chemistry, Temple University, 1901 North 13th Street, Philadelphia, Pennsylvania 19122, United States

[‡]Mail Stop E529, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, United States

Supporting Information

ABSTRACT: An amino acid carrying a 1-(4-dihydroxymethylsilyl)butyl side chain has been prepared in enantiomerically pure form as a potential inhibitor of the enzyme arginase, a pharmaceutical target. As a water-soluble silanediol, this compound was anticipated to be entropically stabilized against polymerization and siloxane formation. At 50 mM in D_2O, the degree of oligomerization was found to be pH dependent, with diastereomeric mixtures formed on condensation. Above pH 11 the silane is largely monomeric.



INTRODUCTION

Hydrolase enzymes come in many forms and mediate a vast array of biological processes. It is therefore not surprising that many hydrolytic enzymes are pharmaceutical targets.[1−5] Arginases I and II are enzymes that hydrolyze the guanidine of arginine, forming urea and ornithine, Scheme 1.[6,7] These enzymes play an important role in the urea cycle of the liver and in other tissues regulate the concentration of arginine. Arginine concentration can impact nitric oxide production by limiting availability of arginine to the enzyme NO synthase.[8] The important role of NO in biological processes has made inhibitors of this enzyme potential pharmaceutical targets.[9]

Design of inhibitors of arginase have largely focused on analogues of arginine and the hydrolysis intermediate **1**. Boronic acid **2**, with its moderately electrophilic boron atom, coordinates hydroxide at the arginase active site, forming a tetrahedral boron and inhibiting the enzyme by ligating/chelating both of the active site manganese ions as well as hydrogen bonding to both an aspartate residue and a peptide amide carbonyl.[7,10] Boronic acid **2** is the most potent inhibitor of arginase known, with a K_i of 110 nM against rat arginase I.[6] In the search for additional inhibitors, silanediol **3** was proposed. As a tetrahedral geminal diol, the silanediol group in **3** has been effectively used to simulate a hydrated carbonyl in peptidomimetic inhibitors of protease enzymes.[11] In the case of **3**, it was anticipated that this molecule could mimic the hydrated guanidine **1** and be an inhibitor of arginase.

Silanediols,[12] when embedded in a peptidomimetic, can act as hydrated carbonyl analogues and have been found to be effective inhibitors of protease enzymes.[11] Very recently, "geo-inspired" silanediol catalysts have been reported to facilitate organic reactions through hydrogen bonding.[13−16] Nanomolar inhibitors of the HIV protease, angiotensin-converting enzyme (ACE, inhibition of which is a treatment for hypertension), and thermolysin have been reported.[17−22] Design of an endoprotease inhibitor, where the enzyme cleaves a specific amide bond of a polypeptide sequence, is relatively straightforward: replacement of the scissile amide with hydrated amide mimics or chemical entities that intercept the hydrolytic machinery generally provide a starting point for inhibitor design.[23−25] Inhibition of the enzyme includes recognition of the hydrated amide surrogate as well as the amino acid side chains of the substrate flanking the active site. Multiple interactions in the binding site can be critical for target specificity.

The use of silanediols as transition state analogues requires consideration of silanediol reactivity. Silanediols are best known as monomers that will spontaneously undergo self-condensation, yielding silicones that are widely appreciated as robust polymers.[26] This truism, however, is based largely on the properties of simple unhindered dialkyl- and diarylsilanediols, especially dimethylsilanediol **5**, Scheme 2. Dimethylsilanediol **5** is not stable and undergoes condensation to form permethylsiloxane (silicone) **6**.[27] Self-condensation is inhibited by steric hindrance, with the liquid crystalline diisobutyl silanediol **7** being an outstanding example.[28,29] Design of silanediol protease inhibitors initially focused on structures with branched alkyl groups flanking the silanediol, such as ACE inhibitor **8**.[18] When steric shielding was removed to prepare thermolysin inhibitor **9**, some difficulties were encountered in its synthesis, attributed to oligomerization of the silanediol.[21] In the case of methylsilanediol **3**, the steric hindrance around the silanediol group resembles the intrinsically unstable **5**, and therefore polymerization of **3** was a concern. In contrast to **8** and **9**, proposed inhibitor **3** was expected to be highly water-soluble.

One of the driving forces for dehydration of **5** and formation of siloxane **6** is the hydrophobicity and insolubility of the polymer **6** in water.[30] The known reversibility of dimethylsilanediol polymerization, however, suggested that a water-soluble oligomer would have an enhanced tendency toward monomerization.[31] As a corollary to this analysis, Tacke has described the properties of β-dimethylsilyloxy alanine **10**, Scheme 3.[32] Novel amino acid **10** dimerizes to give siloxane **11**

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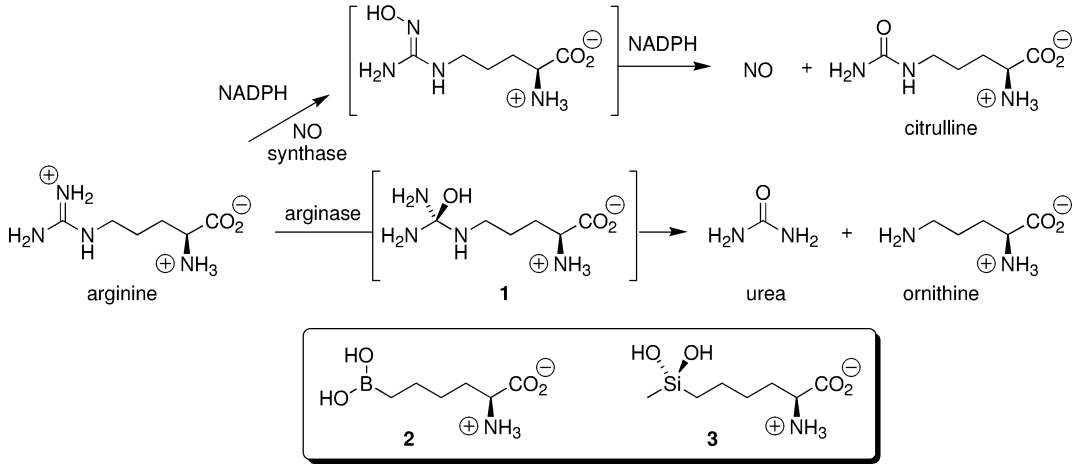
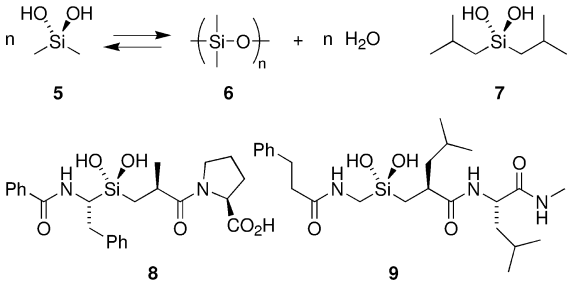
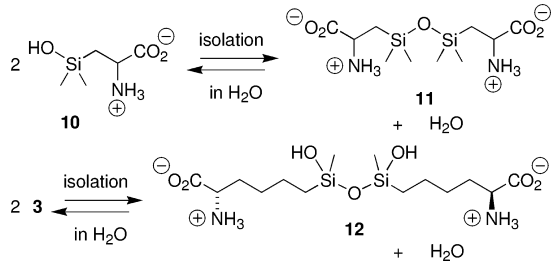
Scheme 1. Arginase and NO Synthase Reactions, Arginase Inhibitor 2 and Silane Analogue 3



Scheme 2. Silanediol Oligomerization Is Hindered by Steric Shielding



Scheme 3. Tacke's Silanol Amino Acid 10 and a Dimer of 3, with Two Stereogenic Silcon Atoms[32]

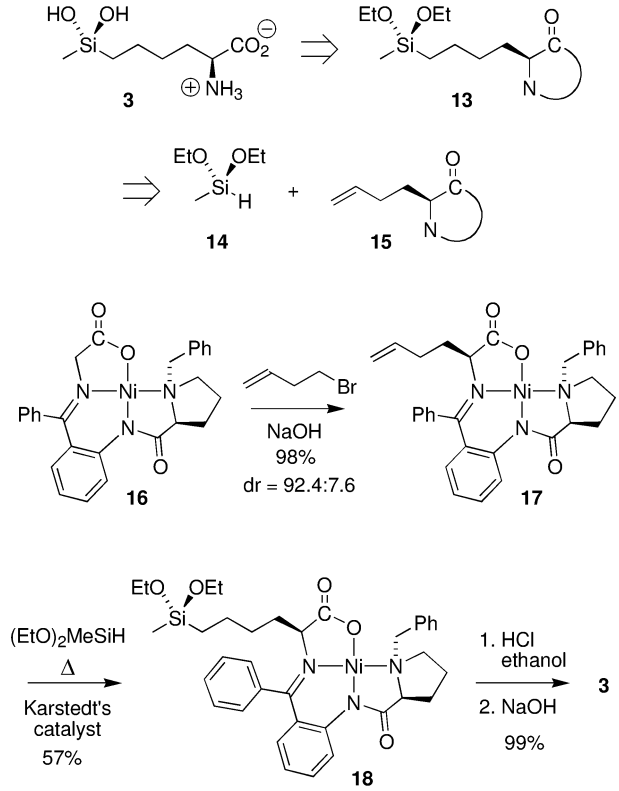


when isolated, but it quantitatively hydrolyzes to the monomer when **11** is dissolved in water.

The similarity of silanol **10** and silanediol **3** suggested that the they might share the propensity for monomerization in aqueous solution. As a potential enzyme inhibitor, the synthesis of **3** as a single enantiomer was undertaken. With a desire to introduce the silane in a form as close to the silanediol as possible, we elected to use hydrosilylation as the penultimate step to give **13**, Scheme 4. By introducing the silane at the correct oxidation level, completion of the silanediol synthesis would only require exchange of hydroxy groups for the ethoxy groups in **13**. The hydrosilylation substrate was to be an optically active 3-butenyl glycine, **15**.

One important consequence of an asymmetric synthesis of **3** related to the potential for diastereomers during siloxane formation. While Tacke's racemic silanol **10** dimerizes in both meso and *d,l* forms, the silicon is never a stereogenic center. In contrast, dimerization of silanediol **3** would result in **12** with *two* new stereogenic silicon atoms in the product, Scheme 3.

Scheme 4. Retrosynthesis and Synthesis of Amino Acid 3



Compound **12**, derived from a single enantiomer of **3**, would be expected to form three diastereomers, whereas seven diastereomers would result from dimerization of a racemic **3**. Higher oligomers would yield increasingly more complex mixtures.

RESULTS AND DISCUSSION

The straightforward preparation of **3** began with Belokon's nickel complex **16**, which functions as a diastereoselective equivalent of a glycine enolate, Scheme 4.[33] An advantage of **16** lies in its ready purification and facile hydrolysis to free the amino acid product.

Starting with commercially available **16**, alkylation with 4-bromo-1-butene gave a nearly quantitative yield of **17**. HPLC analysis indicated that the new stereogenic center was installed

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with greater than 92:8 diastereoselectivity. Hydrosilylation of **17** with diethoxy(methyl)silane in THF using Karstedt's catalyst gave excellent regioselectivity, and product **18** was isolated in acceptable yield after silica gel chromatography. Hydrolysis of the chiral auxiliary involved two stages. Initially, an anhydrous ethanol solution of **18** containing 10 equiv of hydrochloric acid was stirred at ambient temperature for 1 h and then concentrated. This served to free the amino acid from the nickel and the benzophenone derivative, presumably as the ethyl ester, without altering the diethoxysilyl group. Hydrolysis of this product was then accomplished by taking up the residue in refluxing 0.1 N NaOH. Under these conditions, the nickel is converted to an insoluble form and easily removed by filtration. The aqueous phase was washed with dichloromethane and then filtered through Celite. The resulting clear aqueous solution was diluted with water (or aqueous HCl) to give a 1.8 mM solution of **3**, assuming 100% conversion of **18**.

After the basic hydrolysis, silanediol amino acid **1** was obtained as an aqueous solution. Figure 1 shows the ^{1}H NMR

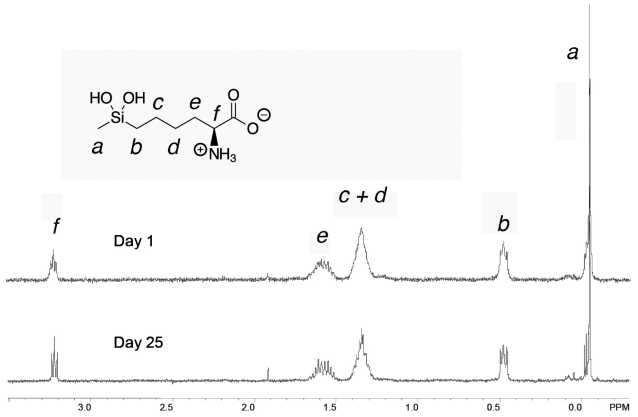

Figure 1. ^{1}H NMR study of silane **3** as a 9.2 mM solution in D_2O at pH 12.

spectrum of **3** in D_2O (1.9 mg/mL). In this spectrum, the sharp singlet at −0.08 ppm corresponds to the methyl group on silicon and is a sensitive indicator of purity. This singlet was accompanied by adjacent small peaks that presumably are associated with small quantities of oligomers derived from **1**. When the solution was concentrated, it gave an amorphous solid, assumed to be a siloxane. This amorphous solid could be redissolved in water after refluxing in basic solution (pH 12).

This solution of **3** was held at rt and pH 12 and evaluated by ^{1}H NMR spectroscopy over a period of nearly 1 month. There was no significant chemical shift change in the ^{1}H NMR spectra even after standing at ambient temperature for 25 days (Figure 1). Rather, the spectrum taken after 25 days had better defined coupling than the initial spectrum. Interestingly, a small quantity of a powder-like precipitate was observed at the bottom of the NMR tube. Although this precipitate could not be completely characterized, the precipitate was presumed to be either a high-molecular weight siloxane or a hydrogen−bonded silanediol species. Its precipitation appears to enhance the homogeneity of the sample, leading to better resolved spectra. Based on the signal-to-noise of these spectra, the concentration of the sample was essentially the same. This initial stability study suggested that the monomeric silanediol amino acid **1** is the major species in basic aqueous solution and that it is both soluble and stable under these conditions.

To probe the properties of silanediol **3** as a function of pH, four aliquots of a freshly prepared 0.53 M stock solution were pH adjusted by dilution with portions of 0.5 M NaOH and 0.5 M HCl in D_2O to produce 0.7 mL samples suitable for ^{1}H NMR. These samples were pH 11, 9, 6−7, and 3−4. NMR spectra were obtained within 3 h of sample preparation, Figure 2.

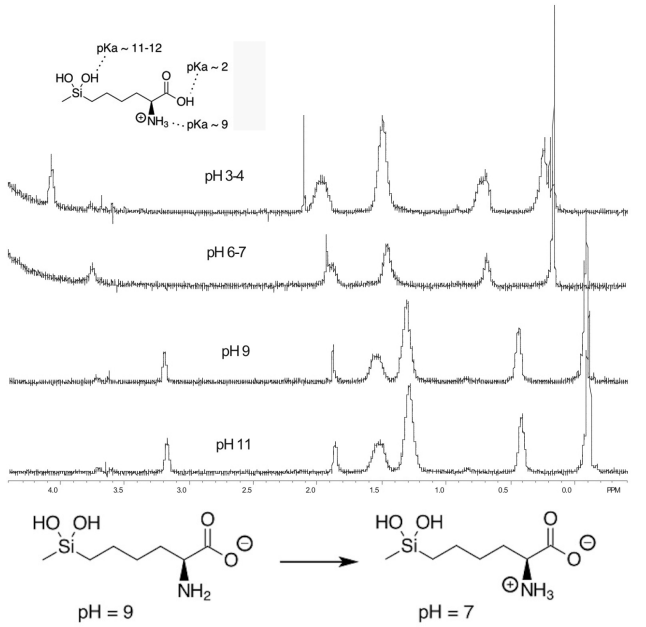

Figure 2. Expected pK_a values of **3** and the ^{1}H NMR spectra of **3** obtained at different pH.

As the pH of the solution became more acidic, chemical shifts changes were observed. The methine proton at approximately 3.2 ppm (pH 11) moved downfield the most, reaching ca. 4.1 ppm at pH 3−4. This shift is undoubtedly caused by protonation of the amine. Most notably, however, is the methyl singlet at −0.08 ppm (pH 11). This singlet moves downfield to ca. +0.2 ppm as the pH drops from 9 to 7. When the pH of the solution was adjusted to 3−4, the absorbance moves further downfield and becomes very broad.

The pK_a values for the three types of acidic protons in amino acid **3** are shown in Figure 2. At pH 11, it is likely that the prevalent structure in solution would be the free amine-carboxylate, with most of the silanediol group un-ionized. Changing the pH of the solution from 9 to 7 would presumably protonate the amine to give the ammonium-carboxylate species. This protonation would lead to a substantial shift in the most downfield proton, as is seen in these spectra (proton f, Figure 1). Moreover, the solution for the pH 6−7 sample became cloudy. This is likely caused by the solution reaching the isoelectric point of the amino acid. Lowering the pH further to 3 is unlikely to result in significant protonation of the carboxylate as a typical pK_a for an amino acid carboxylic acid is 2 ± 0.2. The change in peak shape for this isolated methyl signal is possibly due to acid-catalyzed self-condensation of the silanediol and the formation of siloxane isomers. This would be consistent with the broadening of all of the signals in the pH 3 spectrum.

These NMR samples were aged and observed for 25 days. In the higher pH samples, significant precipitation was observed. In contrast, the pH 6−7 sample became a gel. Most

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surprisingly, the pH 3−4 remained clear and colorless, with no precipitation despite the broadness of the signals in the ^{1}H NMR spectrum.

To evaluate the monomer−dimer ratio at pH 12, both ^{1}H NMR and LC−MS were employed. The singlet at −0.06, corresponding to the monomer, and the two singlets at 0.02 and 0.04 ppm, assigned as the diastereomeric disiloxanes **12**, were integrated for samples with three different concentrations, 9 mM, 15 mM and 50 mM. The percentage of calculated dimer, 7%, 10%, and 29%, respectively, is graphed in Figure 3. The

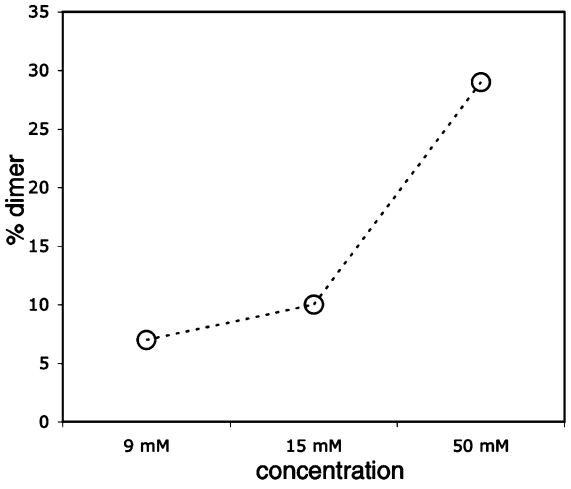

Figure 3. Calculated percentage of dimer present at pH 12 as a function of concentration of **3**, determined by ^{1}H NMR spectroscopy.

amount of dimer is strongly dependent on the sample concentration, as would be expected, and this presumably represents a monomer−dimer equilibrium under these basic conditions.

LC−MS was used to analyze the 9 and 50 mM samples, Figure 4. Using a mildly acidic eluant (0−25% acetonitrile in water with 0.075% formic acid), this analysis found the major species in both solutions to be the monomer (m/z = 207), with only small amounts of the disiloxane (m/z = 396). Significantly more of the dimer was observed in the 50 mM sample. Only traces of a trisiloxane was found (m/z = 585), and only at the higher concentration. These results are qualitatively consistent with the ^{1}H NMR analysis.

SUMMARY AND CONCLUSIONS

Oligomerization of silanols is catalyzed by both acid and base, and depolymerization is readily accomplished by hydroxide, driven by formation of silanolate products.[34] Polymerization of amino acid **3** would require bringing together ionized amino acids. Notably, the species giving rise to the broad methyl signal at pH 3 is readily converted back to the apparent monomer by changing the pH back to basic conditions.

Evaluation of amino acid **3** as an inhibitor of arginase found no significant level of inhibition, suggesting that the neutral silanediol moiety, as an amino acid side chain, does not adequately mimic the hydrated guanidine group, and the enzyme therefore does not recognize it.

The lack of a response of the enzyme to the presence of this hydrated arginine mimic is disappointing; however, we are intrigued by the potential utility of these structures and the their incorporation into peptides. It is notable that even with the highly polarized and water-solubilizing amino acid group

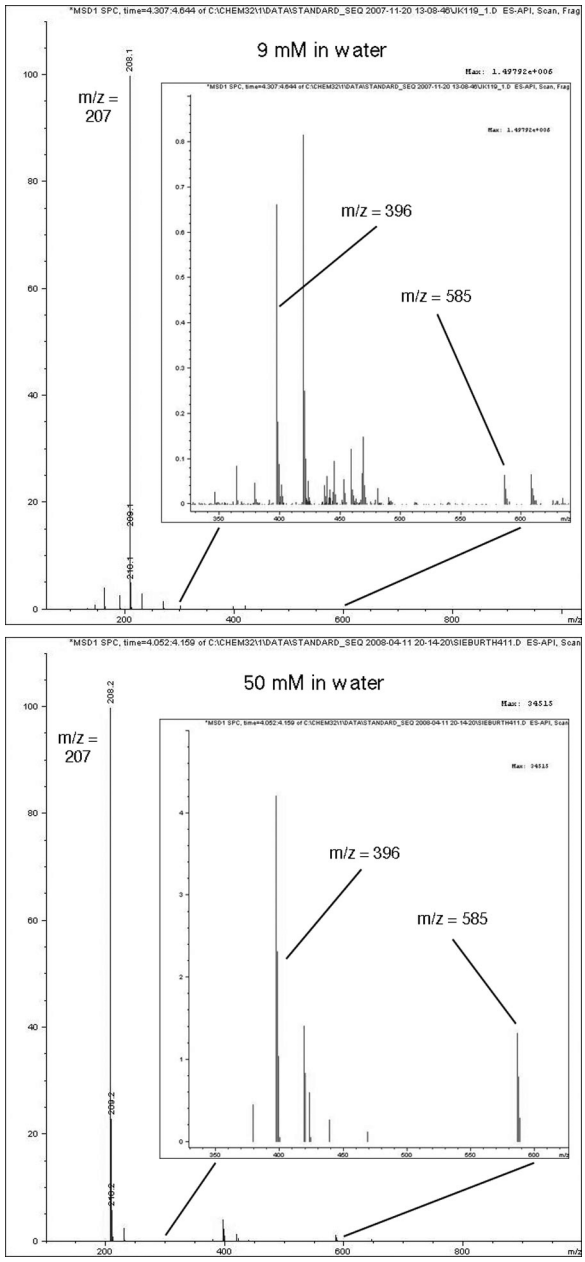

Figure 4. LC−MS of pH 12 solutions of **3** found mostly monomer (m/z = 297), with increasing amounts of disiloxane at higher concentrations.

connected to the silanediol, oligomerization and siloxane formation remains a favorable process.

EXPERIMENTAL SECTION

Compound 17. To a suspension of powdered NaOH (2.7 g, 67 mmol) in CH_3CN (50 mL) at rt was added **16**[33] (327 mg, 0.66 mmol). After the mixture was stirred for 1 h, 4-bromo-1-butene (0.20 mL, 2.0 mmol) was added, and the mixture was stirred for 24 h. The mixture was diluted with aq HCl (50 mL, 0.1 N), and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organics were washed with water (30 mL), dried over anhydrous $MgSO_4$, concentrated, and dried in vacuo to give **17** as a red amorphous solid (354 mg, 98%): mp 199−201 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.5 Hz, 1H), 8.07 (d, J = 7.1 Hz, 2H), 7.54 − 7.35 (m, 6H), 7.23 − 7.14 (m, 2H), 6.94 (d, J = 6.8 Hz, 1H), 6.66 (m, 2H), 5.55 (ddt, 1H), 4.98 (dd, J = 17.2 Hz, J = 1.6 Hz, 1H), 4.89 (dd, J = 10.2 Hz, J = 1.6 Hz, 1H), 4.46 (d, J = 12.4 Hz, 1H), 3.92

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(dd, 1H), 3.62 − 3.47 (m, 4H), 2.75 (m, 2H), 2.55 (m, 1H), 2.35 − 2.05 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 142.6, 136.8, 133.5, 131.8, 129.9, 129.2, 129.1, 127.8, 127.5, 124.0, 121.0, 116.0, 70.5, 70.0, 63.4, 57.3, 31.0, 29.7, 24.0; IR (thin film) 3059, 2925, 1668, 1589 cm^{-1}; exact mass (ESI/APCI TOF) MH^+ calcd for $C_{31}H_{31}N_3NiO_3$ 552.1797, found 552.1785.

Compound 18. To a solution of **17** (142 mg, 0.26 mmol) in THF (3 mL) at rt was added a solution of Karstedt's catalyst (0.02 mL, 2.3% Pt in xylene, 0.02 mmol) followed by diethoxy(methyl)silane (0.08 mL, 0.5 mmol). The reaction mixture was refluxed for 16 h and then cooled to rt. The mixture was filtered through Celite (2.5 cm thick) covered with a layer of activated carbon using absolute ethanol, and the pad was washed with ethanol (60 mL). The combined organics were concentrated and the residue was purified by flash column chromatography (9:1, then 5:1, then 1:1 CH_2Cl_2/acetone) to give **18** as a red amorphous solid (100 mg, 57%): mp 122−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 7.2 Hz, 2H), 7.50 − 7.10 (m, 10H), 6.91 (d, J = 7.2 Hz, 1H), 6.63 (m, 2H), 4.43 (d, J = 12.8 Hz, 1H), 3.90 (dd, 1H,), 3.73 (qd, J = 7.2 Hz, J = 1.6 Hz, 5H), 3.59 − 3.44 (m, 4H), 2.75 (m, 1H), 2.55 (m, 1H), 2.22 − 1.82 (m, 5H), 1.63 (m, 2H), 1.19 (td, J = 8 Hz, J = 1.6 Hz, 6H), 0.58 (t, J = 8.8 Hz, 2H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.2, 180.5, 179.5, 170.4, 142.5, 134.4, 134.0, 133.8, 133.6, 133.4, 133.3, 132.5, 132.2, 131.7, 129.8, 129.0, 127.8, 127.3, 126.6, 123.8, 120.8, 70.53, 70.45, 69.2, 63.3, 58.6, 58.2, 57.1, 54.0, 35.2, 30.9, 29.8, 29.4, 29.2, 23.8, 23.4, 22.9, 18.5, 14.0, 1.1, −4.8; IR (thin film) 2966, 2922, 1674, 1640 cm^{-1}; exact mass (ESI/APCI TOF) MH^+ calcd for $C_{36}H_{46}N_3O_5SiNi$ 686.2560, found 686.2551.

(*S*)-2-Amino-6-dihydroxymethylsilylhexanoic Acid (3). To a solution of **18** (30 mg, 0.04 mmol) in absolute ethanol (6 mL) at rt was added HCl (0.1 mL, 4 M in dioxane, 0.4 mmol). The mixture was stirred for 1 h, concentrated, and dried in vacuo to give a green solid. To this residue was added aq NaOH (10.0 mL, 0.1 N, 1.0 mmol). The reaction mixture was refluxed for 16 h. The mixture was allowed to cool to rt and then washed with CH_2Cl_2 (10 mL). The aqueous phase was filtered through a 2.5 cm pad of Celite in water. The pad was washed further with water. The final volume of the clear aqueous solution of **3** was 24 mL ([**3**] = 0. 37 mg/mL, 1.8 mM): ^{1}H NMR (400 MHz, D_2O) δ 3.23 (t, 1H), 1.65 (m, 2H), 1.38 (m, 4H), 0.48 (t, J = 6.8 Hz, 2H), −0.04 (s, 3H); ^{13}C NMR (400 MHz, D_2O) δ 182.8, 54.5, 33.0, 27.5, 21.6, 15.9, −2.8; LC-MS: (C18 5 mm ×250 mm, 0 to 25% H_2O/acetonitrile + 0.075% formic acid; then ES) calcd for monomer $C_7H_{18}NO_4Si$ 208.1005, found 208.1 (MH^+), calcd for dimer $C_{14}H_{33}N_2O_7Si_2$ 397.1821 found 397.1 (MH^+), calcd for trimer $C_{21}H_{48}N_3O_{10}Si_3$ 586.2642, found 586.2 (MH^+).

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimentals and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: scott.sieburth@temple.edu.

Notes

The authors declare no competing financial interest.

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