Simple Silyl Linker for the Solid Phase Organic Synthesis of Aryl-Containing Molecules

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We have designed a simple (dimethylsilyl)propionic acid linker for the solid phase synthesis of aryl-containing organic compounds. The linker is cleaved smoothly with trifluoroacetic acid either in solution or in the vapor phase to release the unsubstituted aryl moiety. Using this linker, we have successfully demonstrated the solid phase synthesis of a test compound which involved alkylation, acylation, and Mitsunobu reactions.

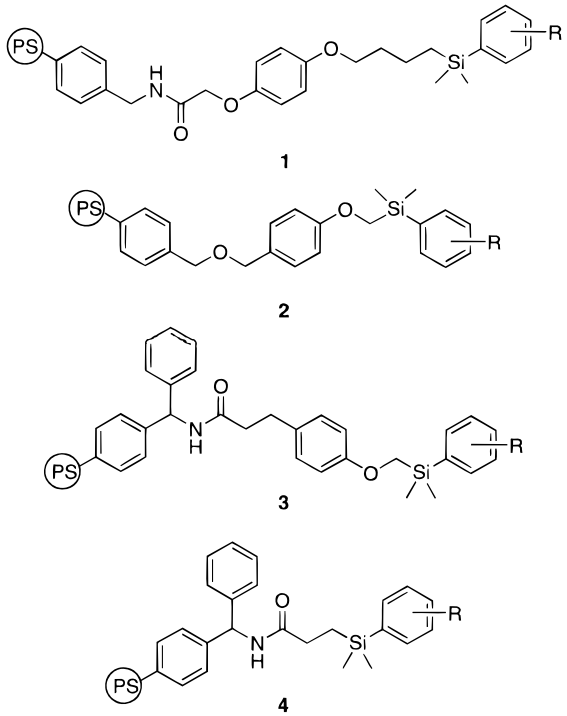
Introduction

There has been increasing interest in the application of solid phase synthesis to the preparation of organic compounds, especially in the contexts of combinatorial chemistry and multiple simultaneous synthesis. One of the limitations in the solid phase approach involves the linker by which the organic molecule is attached to the solid support. Most linkers are based on protecting group chemistry and require the presence of an appropriate functional group in the target molecules being synthesized. Recently Plunkett and Ellman[1] and Chenera et al.[2] have described arylsilane resin linkers (**1** and **2**, respectively, where PS represents the polystyrene matrix and R represents the rest of the organic molecule synthesized on the resin; Chart 1) which are designed to release the unsubstituted aryl moiety. Linker **1** is cleaved with hydrogen fluoride but is stable to TFA. Linker **2** is cleaved with either TFA at room temperature or cesium fluoride at elevated temperature.

We were interested in the solid phase synthesis of molecules of the general structure represented by **5** as a potential combinatorial library, and the use of an arylsilane linker provided an attractive synthetic route as shown in Scheme 1. We focused on linker **2** since we felt TFA cleavage would be more desirable than HF cleavage. We modified the design of linker **2**, which is attached to Merrifield resin via an ether linkage, to introduce a carboxylic acid functionality which could be coupled to benzhydrylamine (BHA) resin to give **3**. This strategy affords us several advantages. The silyl linker carboxylic acid **6** can be prepared in solution and can be rigorously purified and characterized before attachment to the resin. Attachment to the BHA resin is via an amide bond formation reaction, a highly optimized solid phase reaction which can easily be monitored by ninhydrin test[3] and can be driven to completion. The resulting resin construct should therefore be both homogeneous and of known loading, both of which facilitate analysis of the subsequent synthetic reactions performed.

During initial synthetic experiments, we encountered unexpected difficulties in isolating the expected intermediates after neat TFA cleavage from the resin and in fact were unable to isolate either benzyl alcohol from cleavage of **7a** or benzaldehyde from cleavage of **7b**. Since TFA cleavage offers considerable advantages in combinatorial synthesis, we investigated the cleavage chemistry in more detail. These results led us to design the simplified silyl linker **4**, on which we have successfully demonstrated all the requisite chemistry shown in Scheme 1.

Chart 1. Silyl Linkers



Results and Discussion

In order to evaluate cleavage conditions, we prepared the model compound **15** as shown in Scheme 2. 4-Bromobenzyl alcohol was protected as the triisopropylsilyl ether **9**, which was then converted to the Grignard reagent and reacted with (bromomethyl)chlorodimethylsilane to give the (bromomethyl)silane **10**. Treatment of **10** with methyl 3-(4-hydroxyphenyl)propionate and potassium carbonate in refluxing 2-butanone gave the silylmethyl phenyl ether **11**, which was deprotected to

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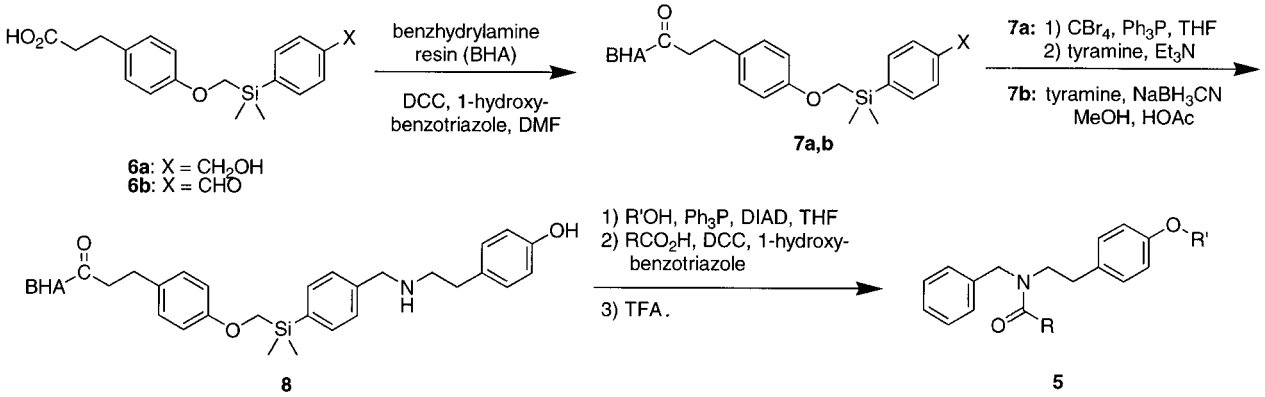
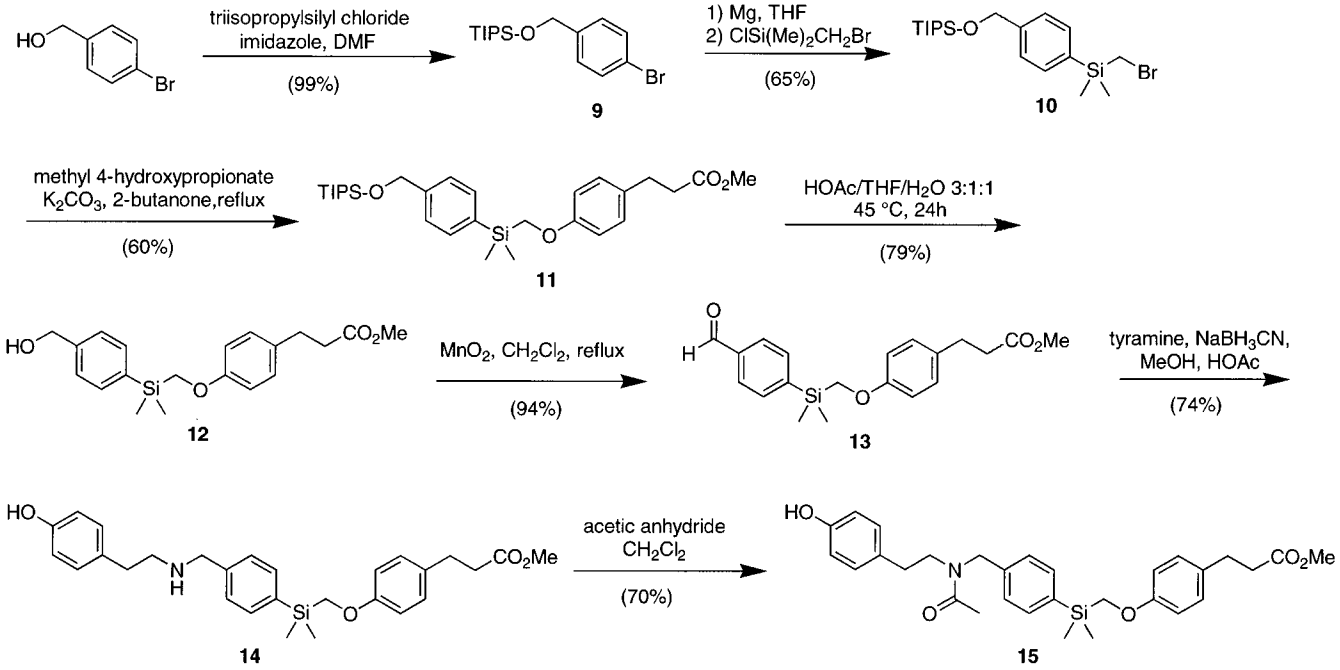
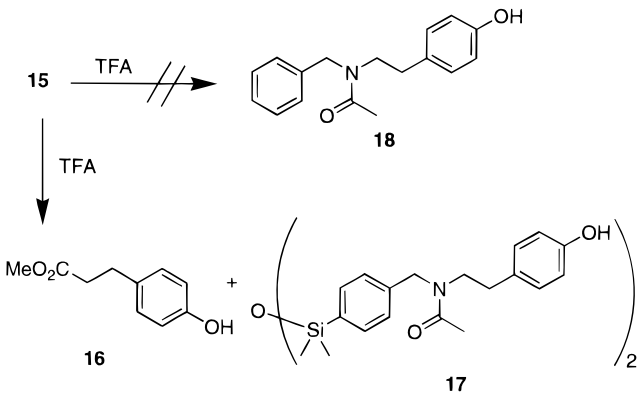
Scheme 1



Scheme 2



Scheme 3



give the benzyl alcohol **12**. Oxidation of **12** with manganese dioxide to the aldehyde **13** followed by reductive amination with tyramine and acetylation with acetic anhydride gave the desired model compound **15**. Compound **15** was then subjected to several different cleavage reactions. The results are summarized in Scheme 3.

Treatment of **15** with neat TFA at room temperature did not give the desired compound **18**. The phenol **16**, which arises from an alternative cleavage of the carbon−oxygen bond in the linker, was instead isolated in quantitative yield along with a second product which has been tentatively assigned the structure **17** based on ^{1}H NMR and mass spectral data. This cleavage pattern and distribution of products were unanticipated based on the previously published work[2] but has in fact been observed in the analogous cleavage of silylmethyl methyl ethers with trimethylsilyl iodide[4] and, in work reported subsequently to this investigation, in a related arylsilane linker.[5]

The use of TFA as a cleavage reagent is quite attractive for combinatorial or multiple simultaneous synthesis due to the ease of workup, especially compared with alternatives like HF or CsF. We therefore undertook to modify the silyl linker such that we could perform the cleavage with neat TFA.[6]

Since the presence of the heteroatom in the silylmethyl ether moiety provided a competing cleavage pathway, we decided to design a linker which did not contain a

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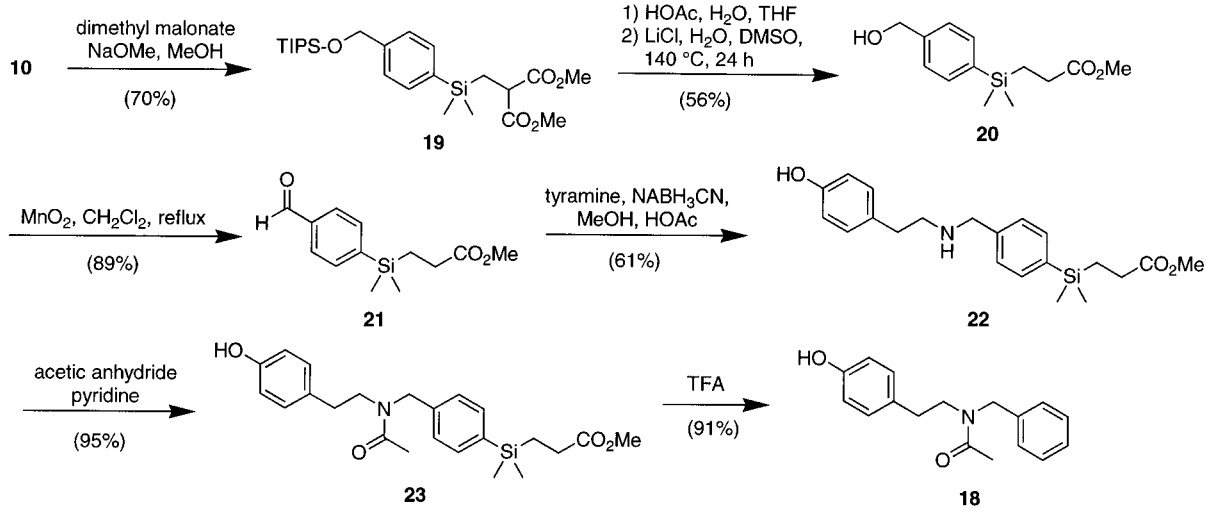
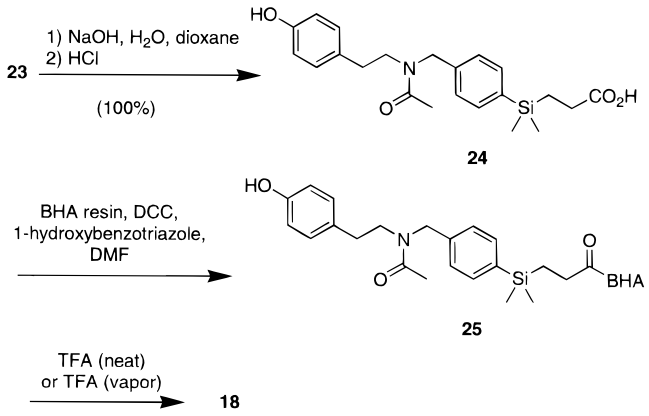
(5) Han, Y.; Walker, S. D.; Young, R. N *Tetrahedron Lett.* **1996**, *37*, 2703−2706.
(6) Subsequent experiments demonstrated that the desired product **18** could be obtained from **15** using conditions less suitable for combinatorial synthesis, such as HF or CsF (see ref 2).

Scheme 4



Scheme 5



heteroatom in the chain. Since the precedent for TFA-mediated cleavage of aryl−silyl bonds generally involve simple trialkylsilanes, we designed linker **4** (Chart 1), in which the linker is formally a (dimethylsilyl)propionate moiety. This would afford the same strategic advantages in being able to prepare, purify, and characterize the arylsilyl linker by traditional methods and then attaching it to an amine-containing resin using a high-yielding, easily monitored acylation step.

The model compound **23** was readily prepared according to Scheme 4. The benzyl alcohol silylpropionate **20** was prepared from the corresponding 4-bromobenzyl alcohol in six steps. Treatment of **10** with the sodium salt of dimethyl malonate gave **19**, which was deprotected to the benzyl alcohol and then demethoxycarbonylated with lithium chloride in DMSO and water to give **20**. Oxidation to the benzaldehyde **21** with MnO_2, reductive amination with tyramine, and acetylation of the secondary amine with acetic anhydride gave the silyl-linked model compound **23**. Gratifyingly, treatment of **23** with neat TFA for 24 h produced the desired model product compound **18** cleanly, with no evidence of any side reactions including reattachment of the linker to the unprotected phenol.

In order to evaluate the cleavage on the solid support, **23** was saponified and the resulting free acid **24** was coupled to BHA resin to give **25** as shown in Scheme 5. Treatment of **25** with neat TFA for 40 h at room temperature gave a quantitative yield of **18**. As is often the case with solid phase cleavage reactions, the crude product was quite clean, with no detectable impurities or contamination by starting material.

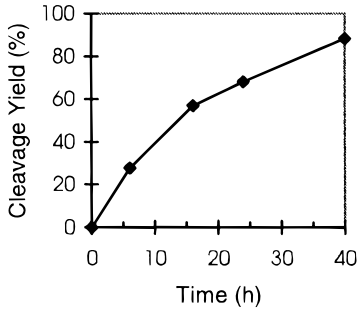


Figure 1. Time course of TFA vapor cleavage of **25**.

In addition to neat TFA, TFA vapor has also been used to cleave compounds from acid-labile resins and represents an effective method for interfacing bead-based combinatorial synthesis with subsequent biological screening.[7] The time course of vapor phase TFA cleavage of **25** is shown in Figure 1. Weighed aliquots of **25** were cleaved for various times and extracted with 2% MeOH in $CHCl_3$, and the amount of **18** obtained was quantitated by HPLC. The time course for vapor phase cleavage is quite similar to the solution cleavage results, with a $t_{1/2}$ of about 13 h and nearly quantitative cleavage occurring by 40 h at room temperature.

The time course of cleavage and the relatively substantial amount of cleavage, approximately 30%, which had occurred in the first 6 h of reaction suggested that this resin might be useful for controlled partial release of compound from the resin. Partial release is useful in single-bead-associated combinatorial screening.[7,8] A portion of the compound can be released from a single bead, eluted, and assayed as soluble material. Sufficient compound remains on the bead for subsequent identification.[9,10] Partial cleavage has been achieved in a rigorous fashion by the simultaneous use of orthogonally cleavable

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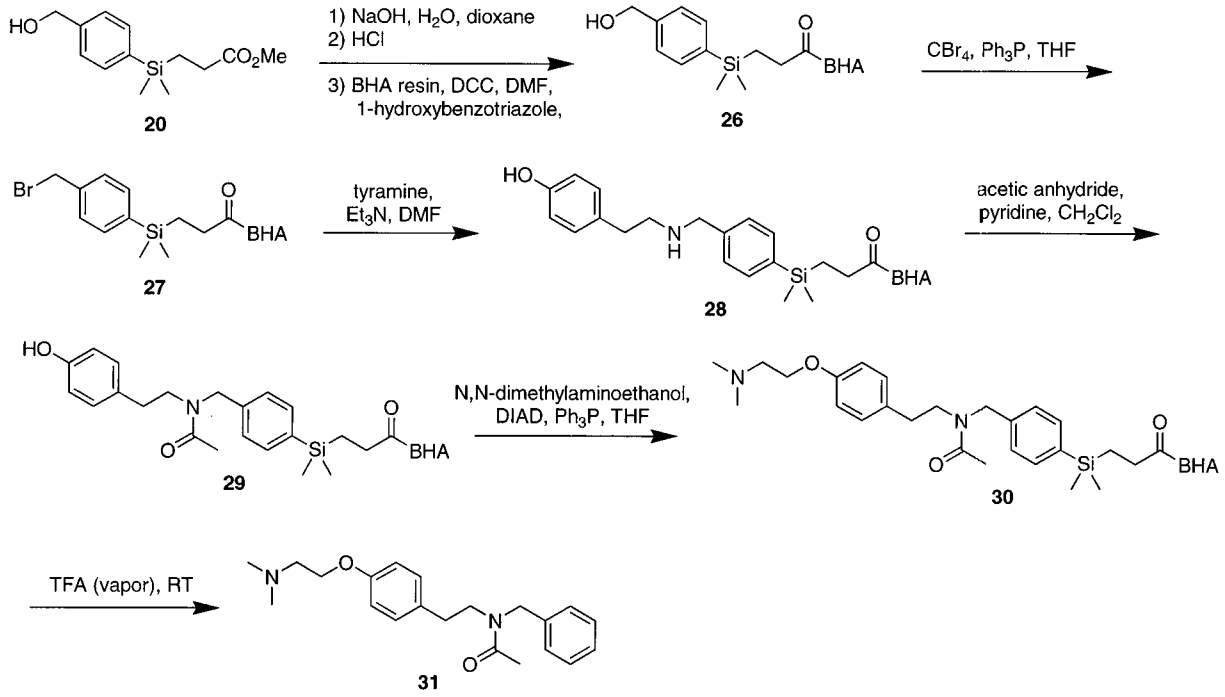
Scheme 6



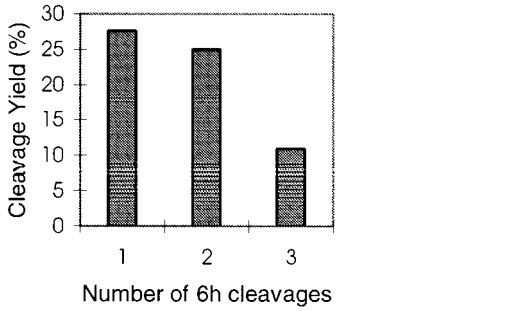


Figure 2. Repetitive partial cleavages of **25** with TFA vapor.

linkers, but it has also been effected by limited exposure of acid-labile linkers to TFA vapor.

In order to evaluate the utility of the silylpropionate linker for partial cleavage, an aliquot of **25** was subjected to several rounds of treatment with TFA vapor. After each partial cleavage, the released **18** was eluted from the resin and quantified by HPLC. The results are shown in Figure 2. Approximately 25% of the available **18** was released from the resin in each of the first two 6-h exposures to TFA vapor, and an additional 10% was released in the third partial cleavage. These numbers are in good agreement with the time course of cleavage in Figure 1 and indicate that this linker would perform suitably in a partial release strategy.

Having demonstrated the desired cleavage properties in the silylpropionate linker, we undertook a model synthesis, as shown in Scheme 6, incorporating all the chemistry which we had envisioned in Scheme 1. The chemistry was monitored by elemental analysis and magic angle spinning (MAS) proton NMR. The benzyl alcohol linker **20** was saponified, coupled to BHA resin, and smoothly converted to the benzyl bromide **27** with CBr_4 and triphenylphosphine. This resin-bound benzyl bromide was then used to alkylate tyramine to produce the secondary amine **28**. This reaction demonstrates the power of solid phase synthesis. In a solution reaction, one would expect to obtain a mixture of mono- and dialkylated tyramines. Using an excess of tyramine and a resin-bound alkylating agent, dialkylation is effectively suppressed and the desired product is obtained cleanly. Acetylation with acetic anhydride to give **29** followed by Mitsunobu reaction with (dimethylamino)ethanol using diisopropyl azidodicarboxylate (DIAD) instead of DEAD to avoid formation of any ethyl ether[11] gave the resin-bound model compound **30**. The final product **31** was obtained in quantitative yield based on starting resin **26** after cleavage with TFA vapor.

Conclusion

We have designed a simplified arylsilyl linker for solid phase organic synthesis which cleanly releases the aryl moiety upon treatment with neat trifluoroacetic acid, in either the liquid or vapor phase, making it highly suitable for practical combinatorial or multiple synthesis. The amount of cleavage can be controlled by varying the reaction time, making controlled partial cleavage feasible. Finally, we have demonstrated the synthesis of a model compound for a combinatorial library, involving alkylation, acylation, and Mitsunobu reactions using our designed linker on a solid support.

Experimental Section

Reagent grade solvents and commercial reagents were used without additional purification. THF was distilled from sodium benzophenone ketyl. BHA resin (200−400 mesh, substitution 1.11 mmol/g) was prepared as previously reported.[12] Proton NMR spectra were obtained at 250 and 400 MHz. Magic angle spinning (MAS) proton NMR was obtained at 500 MHz on a spectrometer equipped with a magic angle spinning nanoprobe. Chemical shifts are reported relative to TMS.

***O*-(Triisopropylsilyl)-4-bromobenzyl Alcohol (9).** To a solution of 4-bromobenzyl alcohol (50.07 g, 268 mmol) in DMF (500 mL) was added with stirring, under argon, imidazole (40

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g, 588 mmol) followed by triisopropylsilyl chloride (TIPS-Cl; 57.3 mL, 268 mmol). After stirring for 24 h at room temperature the reaction mixture was evaporated to dryness, taken up in hexane (500 mL), washed with aq 1 N hydrochloric acid (500 mL) and brine (500 mL), dried ($MgSO_4$), and evaporated to give **9** as a clear oil (91.72 g, 99%): TLC R_f 0.71 (silica gel, 50:1 hexane:ethyl acetate); GC t_R 2.98 min (HP 530 μm × 20 m methylsilicone column, He carrier flow 20 mL/min, 150 °C initial temp, rate 10 °C/min, 250 °C final temp, 2 min final time); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (18H, d, J = 6.4 Hz), 1.14 (3H, m), 4.78 (2H, s), 7.22 (2H, d, J = 8.4 Hz), 7.45 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{16}H_{27}SiOBr$: C, 55.97; H, 7.93; Br, 23.37. Found: C, 55.82; H, 7.82; Br, 23.61.

[Dimethyl[4-[[(triisopropylsilyl)oxy]methyl]phenyl]silyl]methyl Bromide (10). To a stirred mixture of Mg turnings (2.22 g, 91 mmol) in THF (100 mL) was added 1,2-dibromoethane (300 μL, 3.5 mmol). The mixture was stirred under argon and heated to 70 °C (reflux). After 5 min the reaction mixture was cooled to room temperature, and a solution of **9** (30 g, 87.4 mmol) in THF (100 mL) was added in one portion. The reaction mixture was then slowly heated to reflux (slightly exothermic) and allowed to stir for another 5 h until all the Mg was consumed. The resultant pale brown solution was then cooled to −78 °C, and a solution of (bromomethyl)chlorodimethylsilane (15 mL, 110 mL) in THF (50 mL) was added slowly over 5 min. After stirring for 1 h the reaction mixture was allowed to warm to room temperature and stirred for an additional 16 h. The reaction mixture was evaporated to dryness, taken up in hexane (500 mL), washed with cold aq 1 N hydrochloric acid (500 mL) and brine (500 mL), dried ($MgSO_4$), and evaporated. Purification by Kugelrohr distillation (140−150 °C, 1 Torr) gave **10** as a clear oil (23.54 g, 65%): TLC R_f 0.53 (silica gel, 50:1 hexane:ethyl acetate); GC t_R 8.27 min (HP 530 μm × 20 m methylsilicone column, He carrier flow 20 mL/min, 150 °C initial temp, rate 10 °C/min, 250 °C final temp, 2 min final time); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.43 (6H, s), 1.12 (18H, d, J = 6.6 Hz), 1.18 (3H, m), 2.63 (2H, s), 7.38 (2H, d, J = 8.0 Hz), 7.51 (2H, d, J = 8.0 Hz). Anal. Calcd for $C_{19}H_{35}Si_2OBr$: C, 54.91; H, 8.49; Br, 19.23. Found: C, 54.88; H, 8.29; Br, 19.09.

Methyl 3-[[[Dimethyl[4-[[(triisopropylsilyl)oxy]methyl]phenyl]silyl]methoxy]phenyl]propionate (11). To a stirred solution of **10** (29.57 g, 71 mmol) and methyl 3-(4-hydroxyphenyl)propionate (12.80 g, 71 mmol) in 2-butanone (200 mL) was added K_2CO_3 (9.8 g, 71 mmol). The suspension was stirred under argon at reflux (80 °C) for 72 h, cooled to room temperature, and evaporated to dryness. The residue was taken up in ethyl acetate (500 mL), washed with aq 1 N HCl (500 mL) and brine (500 mL), dried ($MgSO_4$), and evaporated to dryness. Purification by flash chromatography (silica gel, 5% ethyl acetate/hexane) gave **11** (22.06 g, 60%) as a clear oil along with recovered starting material (10.43 g, 35%): TLC R_f 0.49 (silica gel, 10% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.41 (6H, s), 1.09 (18H, d, J = 6.5 Hz), 1.17 (3H, m), 2.58 (2H, t), 2.88 (2H, t), 3.66 (3H, s), 3.73 (2H, s), 4.84 (2H, s), 6.88 (2H, d, J = 8.7 Hz), 7.09 (2H, d, J = 8.7 Hz), 7.37 (2H, d, J = 8.0 Hz), 7.56 (2H, d, J = 8.0 Hz). Anal. Calcd for $C_{29}H_{46}O_4Si_2$: C, 67.65; H, 9.01. Found: C, 66.85; H, 8.36.

Methyl 3-[[[Dimethyl[4-(hydroxymethyl)phenyl]silyl]methoxy]phenyl]propionate (12). To compound **11** (29.76 g, 57.8 mmol) was added a solution of acetic acid:THF:water (3:1:1) (500 mL). The resulting mixture was stirred at 45 °C for 24 h under an Ar atmosphere, cooled to room temperature, and evaporated to dryness. Purification by flash chromatography (silica gel, 30% ethyl acetate/hexane) gave **12** as a white crystalline solid (16.47 g, 79%): TLC R_f 0.29 (silica gel, 30% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.41 (6H, s), 1.78 (1H, br s), 2.58 (2H, t), 2.88 (2H, t), 3.65 (3H, s), 3.74 (2H, s), 4.69 (2H, s), 6.88 (2H, d, J = 8.6 Hz), 7.08 (2H, d, J = 8.6 Hz), 7.38 (2H, d, J = 7.8 Hz), 7.60 (2H, d, J = 7.8 Hz); MS(ES) m/z 381.2 $[M + Na]^+$. Anal. Calcd for $C_{20}H_{26}O_4Si$: C, 67.01; H, 7.31. Found: C, 66.86; H, 7.41.

Methyl 3-[[[Dimethyl(4-formylphenyl)silyl]methoxy]phenyl]propionate (13). To a stirred solution of **12** (4.0 g, 11.2 mmol) in CH_2Cl_2 (150 mL) was added MnO_2 (5.0 g, 57.5 mmol). The suspension was heated to reflux under argon and stirred for 16 h. After cooling to room temperature the reaction mixture was filtered through a pad of Celite and rinsed with CH_2Cl_2 (50 mL). The filtrate was evaporated to give **13** as a white crystalline solid (3.74 g, 94%): TLC R_f 0.47 (silica gel, 30% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.46 (6H, s), 2.59 (2H, t), 2.89 (2H, t), 3.66 (3H, s), 3.77 (2H, s), 6.88 (2H, d, J = 8.5 Hz), 7.09 (2H, d, J = 8.5 Hz), 7.78 (2H, d, J = 7.9 Hz), 7.86 (2H, d, J = 7.9 Hz), 10.03 (1H, s). Anal. Calcd for $C_{20}H_{24}O_4Si$: C, 67.38; H, 6.68. Found: C, 68.31; H, 6.68.

Methyl 3-[[[Dimethyl[4-[*N*-[2-(4-hydroxyphenyl)ethyl]aminomethyl]phenyl]silyl]methoxy]phenyl]-propionate (14). To a stirred solution of **13** (1.03 g, 2.9 mmol) in dry methanol (30 mL) were added tyramine (0.5 g, 3.6 mmol) and acetic acid (0.22 mL, 3.6 mmol). The reaction mixture was stirred for 2 h; then $NaBH_3CN$ (0.23 g, 3.6 mmol) was added portionwise over 15 min (foaming). After stirring for 16 h the reaction mixture was evaporated to dryness, taken up in $CHCl_3$ (100 mL), washed with brine (100 mL), dried (Na_2SO_4), and evaporated. Purification by flash chromatography (silica gel, 3−5% methanol/$CHCl_3$) gave **14** as a clear oil (1.02 g, 74%): TLC R_f 0.20 (silica gel, 5% methanol/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.40 (6H, s), 2.59 (2H, t), 2.75 (2H, t), 2.87 (4H, 2t), 3.66 (3H, s), 3.72 (2H, s), 3.80 (2H, s), 6.69 (2H, d, J = 8.4 Hz), 6.87 (2H, d, J = 8.6 Hz), 7.01 (2H, d, J = 8.4 Hz), 7.08 (2H, d, J = 8.6 Hz), 7.27 (2H, d, J = 7.8 Hz), 7.53 (2H, d, J = 7.8 Hz); MS(ES) m/z 478.3 $[M + H]^+$. Anal. Calcd for $C_{28}H_{35}NO_4Si$: C, 70.40; H, 7.39; N, 2.93. Found: C, 68.45; H, 7.19; N, 2.60.

Methyl 3-[[[Dimethyl[4-[*N*-[2-(4-hydroxyphenyl)ethyl]acetamidomethyl]phenyl]silyl]methoxy]phenyl]-propionate (15). To a stirred solution of **14** (2.0 g, 4.2 mmol) in CH_2Cl_2 (50 mL) was added acetic anhydride (0.47 mL, 5 mmol) followed by pyridine (0.81 mL, 10 mmol). After stirring for 16 h the reaction mixture was evaporated to dryness. Purification by flash chromatography (silica gel, 1−5% methanol/$CHCl_3$) gave **15** as a white solid (1.53 g, 70%): TLC R_f 0.41 (silica gel, 5% methanol/$CHCl_3$); HPLC (Altex Ultrasphere SI, 4.6 × 250 mm) 1−10% iPrOH/$CHCl_3$ linear gradient over 25 min, UV 280 nm, t_R 8.15 min, k' 2.2; ^{1}H NMR (400 MHz, MeOH-d_4) (amide rotamers) δ 0.37, 0.38 (6H, 2s), 1.91, 2.09 (3H, 2s), 2.55 (2H, t), 2.70, 2.74 (2H, 2t), 2.81 (2H, t), 3.43, 3.45 (2H, 2t), 3.61 (3H, s), 3.74, 3.75 (2H, 2s), 4.44, 4.57 (2H, 2s), 6.69, 6.70 (2H, 2d), 6.83 (2H, d, J = 8.6 Hz), 6.96, 6.97 (2H, 2d), 7.05 (2H, d, J = 8.7 Hz), 7.17, 7.24 (2H, 2d), 7.57, 7.60 (2H, 2d); MS(ES) m/z 520.2 $[M + H]^+$. Anal. Calcd for $C_{30}H_{37}NO_5Si$: C, 69.33; H, 7.18; N, 2.70. Found: C, 69.06; H, 7.13; N, 2.41.

TFA Solution Cleavage Reaction of 15. To an aliquot of compound **15** (300 mg, 0.58 mmol) was added TFA (10 mL). The reaction mixture was stirred for 16 h at room temperature and evaporated to dryness. HPLC analysis (Altex Ultrasphere SI, 4.6 × 250 mm, 1−10% iPrOH/$CHCl_3$ gradient over 25 min, 1.5 mL/min, UV at 280 and 254 nm) showed only trace amounts of starting material with two major products at t_R 3.89 and 15.15 min. The two major products were then isolated by flash chromatography (silica gel, 2% methanol/$CHCl_3$). The earlier eluting peak (t_R 3.89 min) was identified as methyl 3-(4-hydroxyphenyl)propionate (**16**) (95 mg, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (2H, t), 2.89 (2H, t), 3.68 (3H, s), 5.78 (1H, br s), 6.76 (2H, d), 7.04 (2H, d). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.83; H, 6.58. The later eluting peak (t_R 15.15 min) was isolated as a white solid and has a structure consistant with the siloxane dimer **17** (135 mg, 70%): MS(ES) m/z 669.4 $[M + H]^+$; IR (Nujol) 3162, 1616, 1252, 1045 cm^{-1}; ^{1}H NMR (400 MHz, MeOH-d_4) (amide rotomers) δ 0.29, 0.30 (6H, 2s), 1.91, 2.09 (3H, 2s), 2.71, 2.72 (2H, 2t), 3.45, 3.46 (2H, 2t), 4.43, 4.56 (2H, 2s), 4.86 (2H, s), 6.69, 6.71 (2H, d, J = 7.8 Hz), 6.95, 6.97 (2H, 2d, J = 7.8 Hz), 7.13, 7.20 (2H, 2d, J = 7.7 Hz), 7.47, 7.50 (2H, 2d, J = 7.7 Hz). Anal. Calcd for $C_{38}H_{48}N_2O_5Si_2 \cdot {}^1/_4H_2O$: C, 67.77; H, 7.26; N, 4.16. Found: C, 67.70; H, 7.26; N, 3.95.

HF Cleavage Reaction of 15. To compound **15** (300 mg, 0.58 mmol) in an HF reaction vessel containing anisole (1 mL) was distilled HF (9 mL) while cooling at −78 °C. The mixture

was stirred for 1 h at 0 °C in an ice bath and then evaporated under vacuum to dryness. The residue was placed under high vaccum for several hours to remove excess anisole and analyzed by HPLC. HPLC (Altex Ultrasphere SI, 4.6 × 250 mm, 1−10% iPrOH/$CHCl_3$ gradient over 25 min, 1.5 mL/min, UV at 280 and 254 nm) showed a major product with a retention time of 8.87 min as well as small amounts of the two products **16** and **17** isolated in the previous TFA reaction. Purification by flash chromatography (silica gel, 2% methanol/$CHCl_3$) gave the major product as a white solid, identified as the desired cleavage product **18** and identical with authentic material by TLC, HPLC, MS(ES), and ^{1}H NMR (108.5 mg, 69%): MS(ES) *m*/*z* 270.4 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) (amide rotomers) δ 1.88, 2.12 (3H, 2s), 2.74, 2.78 (2H, 2t), 3.41, 3.58 (2H, 2t), 4.39, 4.63 (2H, 2s), 6.78 (2H, 2d), 7.95, 7.01 (2H, 2d), 7.11−7.35 (5H, m). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.72; H, 7.01; N, 5.03.

Dimethyl [Dimethyl[4-[[(triisopropylsilyl)oxy]methyl]phenyl]silyl]methylmalonate (19). To a stirred solution of 0.5 M sodium methoxide in methanol (88 mL, 44 mmol) was added dimethyl malonate (10 mL, 85 mmol) followed by **10** (18.30 g, 44 mmol). The reaction mixture was heated at reflux to 70 °C, under argon, and stirred for 24 h. After cooling to room temperature, the reaction mixture was evaporated to dryness, taken up in ethyl acetate (250 mL), washed with cold aq 1 N hydrochloric acid (250 mL) and brine (250 mL), dried ($MgSO_4$), and evaporated. Purification by flash chromatography (silica gel, 5% ethyl acetate/hexane) gave **19** as a clear oil (14.37 g, 70%): TLC R_f 0.34 (silica gel, 10% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.29 (6H, s), 1.09 (18H, d, J = 6.5 Hz), 1.18 (3H, m), 1.41 (2H, d, J = 7.9 Hz), 3.36 (1H, t), 3.61 (6H, s), 4.83 (2H, s), 7.35 (2H, d, J = 7.9 Hz), 7.46 (2H, d, J = 7.9 Hz); MS(ES) *m*/*z* 489.2 $[M + Na]^+$. Anal. Calcd for $C_{24}H_{42}Si_2O_5$: C, 61.76; H, 9.07. Found: C, 61.84; H, 8.75.

Methyl 3-[Dimethyl[4-(hydroxymethyl)phenyl]silyl]propionate (20). Compound **19** (14.37 g, 30.8 mmol) was added to a solution of 3:1:1 acetic acid:water:THF (200 mL) and heated to 45 °C. The reaction mixture was stirred for 24 h, cooled, and evaporated to dryness. Purification by flash chromatography (silica gel, 35% ethyl acetate/hexane) gave the benzyl alcohol as a clear oil (8.31 g, 87%): TLC R_f 0.40 (silica gel, 40% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.30 (6H, s), 1.42 (2H, d, J = 7.7 Hz), 1.66 (1H, br s), 3.35 (1H, t), 3.62 (6H, s), 4.69 (2H, s), 7.36 (2H, d, J = 7.9 Hz), 7.49 (2H, d, J = 7.9 Hz); MS(ES) *m*/*z* 333.2 $[M + Na]^+$. Anal. Calcd for $C_{15}H_{22}O_5Si$: C, 58.04; H, 7.14. Found: C, 57.49; H, 7.03.

To a stirred solution the above alcohol (8.31 g, 26.8 mmol) in DMSO (50 mL) were added LiCl (2.27 g, 54 mmol) and water (1.4 mL). After flushing with argon the reaction mixture was heated to 140 °C and stirred for 24 h. The reaction mixture was then cooled to room temperature, taken up in ethyl acetate (250 mL), washed with brine (500 mL), dried ($MgSO_4$), and evaporated. Purification by flash chromatography (silica gel, 30% ethyl acetate/hexane) gave **20** as a clear oil (5.02 g, 74%): TLC R_f 0.41 (silica gel, 30% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.28 (6H, s), 1.09 (2H, ddd), 1.85 (1H, br s), 2.26 (2H, ddd), 3.62 (3H, s), 4.68 (2H, s), 7.36 (2H, d, J = 8.0 Hz), 7.50 (2H, d, J = 8.0 Hz); MS(ES) *m*/*z* 275.1 $[M + Na]^+$. Anal. Calcd for $C_{13}H_{20}O_3Si$: C, 61.87; H, 7.99. Found: C, 62.16; H, 7.81.

Methyl 3-[Dimethyl(4-formylphenyl)silyl]propionate (21). To a stirred solution of **20** (1.16 g, 4.6 mmol) in CH_2Cl_2 (50 mL) was added MnO_2 (2.0 g, 23 mmol). The reaction mixture was heated to reflux and stirred for 16 h. After cooling to room temperature the reaction mixture was filtered through a pad of Celite and washed with CH_2Cl_2, and the filtrate was evaporated to dryness to give **21** as a clear oil (1.03 g, 89%): TLC R_f 0.74 (silica gel, 30% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.35 (6H, s), 1.12 (2H, ddd), 2.32 (2H, ddd), 3.62 (3H, s), 7.68 (2H, d, J = 7.9 Hz), 7.85 (2H, d, J = 7.9 Hz), 10.02 (1H, s). Anal. Calcd for $C_{13}H_{18}O_3Si$: C, 62.36; H, 7.25. Found: C, 61.89; H, 7.07.

Methyl 3-[Dimethyl[4-[*N*-[2-(4-hydroxyphenyl)ethyl]aminomethyl]phenyl]silyl]propionate (22). To a stirred solution of **21** (1.00 g, 4 mmol) in MeOH (25 mL) was added tyramine (0.70 g, 5 mmol) followed by HOAc (0.30 mL, 5 mmol). After the mixture stirred for 2 h at room temperature, $NaBH_3CN$ (0.32 g, 5 mmol) was added in portions. The reaction mixture was stirred for 16 h and evaporated to dryness. Purification by flash chromatography (silica gel, 95:5 to 90:10 $CHCl_3$:MeOH) gave **22** as an oil (0.94 g, 61%): TLC R_f 0.25 (silica gel, 95:5 $CHCl_3$:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.28 (6H, s), 1.08 (2H, ddd), 2.28 (2H, ddd), 2.77 (2H, t), 2.89 (2H, t), 3.64 (3H, s), 3.81 (2H, s), 6.71 (2H, d, J = 8.4 Hz), 7.03 (2H, d, J = 8.4 Hz), 7.27 (2H, d, J = 7.8 Hz), 7.44 (2H, d, J = 7.8 Hz); MS(ES) *m*/*z* 372.3 $[M + H]^+$. Anal. Calcd for $C_{21}H_{29}NO_3Si$: C, 67.89; H, 7.87; N, 3.77. Found: C, 67.23; H, 7.69; N, 3.66.

Methyl 3-[Dimethyl[4-[*N*-[2-(4-hydroxyphenyl)ethyl]acetamidomethyl]phenyl]silyl]propionate (23). To a stirred solution of **22** (0.94 g, 2.4 mmol) in CH_2Cl_2 (25 mL) was added pyridine (250 μL, 3.1 mmol) followed by acetic anhydride (229 μL, 2.4 mmol). After stirring for 16 h the reaction mixture was taken up in $CHCl_3$ (50 mL), washed with cold aq 1 N HCl (50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated. Purification by flash chromatography (silica gel, 98:2 to 95:5 $CHCl_3$:MeOH) gave **23** as a clear oil (1.00 g, 95%): TLC R_f 0.41 (silica gel, 95:5 $CHCl_3$:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) (amide rotamers) δ 0.27, 0.28 (6H, 2s), 1.07 (2H, m), 1.73 (1H, s), 1.89, 2.11 (3H, 2s), 2.27 (2H, ddd), 2.76, 2.79 (2H, 2t), 3.41, 3.57 (2H, 2t), 3.62, 3.63 (3H, 2s), 4.38, 4.61 (2H, 2s), 6.76, 6.79 (2H, 2d, J = 8.4 Hz), 6.96, 7.01 (2H, 2d, J = 8.4 Hz), 7.11, 7.23 (2H, 2d, J = 7.9 Hz), 7.44, 7.46 (2H, 2d, J = 7.9 Hz); MS(ES) *m*/*z* 414.2 $[M + H]^+$. Anal. Calcd for $C_{23}H_{31}NO_4Si$: C, 66.79; H, 7.56; N, 3.39. Found: C, 63.37; H, 7.25; N, 2.97.

***N*-[2-(4-Hydroxyphenyl)ethyl]-*N*-benzylacetamide (18) from Cleavage of 23.** To compound **23** (300 mg, 0.7 mmol) was added trifluoroacetic acid (20 mL). The reaction mixture was stirred at room temperature for 36 h and concentrated to dryness. HPLC analysis (Zorbax SIL, 4.6 × 250 mm, 1−10% iPrOH/$CHCl_3$ gradient over 25 min, UV 280 nm) showed <8% starting material remained. The major product was purified by flash chromatography (silica gel, 98:2 $CHCl_3$:MeOH) to give **18** (172 mg, 91%): TLC R_f 0.36 (silica gel, 95:5 $CHCl_3$:MeOH); HPLC t_R 10.75 min, k' 4.4 (Zorbax SIL, 4.6 × 250 mm), 1−10% iPrOH/$CHCl_3$ over 20 min, UV 254 and 280 nm; MS(ES) *m*/*z* 270.4 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) (amide rotamers) δ 1.88, 2.12 (3H, 2s), 2.74, 2.78 (2H, 2t), 3.41, 3.58 (2H, 2t), 4.39, 4.63 (2H, 2s), 6.78 (2H, 2d), 7.95, 7.01 (2H, 2d), 7.11−7.35 (5H, m).

3-[Dimethyl[4-[*N*-[2-(4-hydroxyphenyl)ethyl]acetamidomethyl]phenyl]silyl]propionic Acid (24). To a stirred solution of **23** (0.67 g, 1.6 mmol) in dioxane (10 mL) was added aq 1 N NaOH (3.5 mL). After stirring for 16 h the reaction mixture was acidified with aq 1 N HCl (3.5 mL) and partially evaporated. The remaining material was taken up in $CHCl_3$ (75 mL), washed with brine (75 mL), dried ($MgSO_4$), and evaporated to give **22** as a white solid foam (0.66 g, 100%): TLC R_f 0.23 (silica gel, 95:4:1 $CHCl_3$:MeOH:HOAc); ^{1}H NMR (400 MHz, $CDCl_3$) (amide rotamers) δ 0.27, 0.28 (6H, 2s), 1.07 (2H, m), 1.94, 2.12 (3H, 2s), 2.28 (2H, ddd), 2.74, 2.77 (2H, 2t), 3.40, and 3.53 (2H, 2t), 4.36, 4.58 (2H, 2s), 6.76, 6.79 (2H, 2d, J = 8.4 Hz), 6.93, 6.99 (2H, 2d, J = 8.4 Hz), 7.10, 7.21 (2H, 2d, J = 7.9 Hz), 7.43, 7.46 (2H, 2d, J = 7.9 Hz); MS(ES) *m*/*z* 400.2 $[M + H]^+$. Anal. Calcd for $C_{22}H_{29}NO_4Si$: C, 66.13; H, 7.32; N, 3.51. Found: C, 65.94; H, 7.46; N, 3.23.

3-[Dimethyl[4-[*N*-[2-(4-hydroxyphenyl)ethyl]acetamidomethyl]phenyl]silyl]propionyl Benzhydrylamine Resin (25). To BHA resin (1.0 g, 1.06 mmol), which was washed with a solution of 10% Et_3N in CH_2Cl_2 followed by CH_2Cl_2 in a shaker vessel,[13] was added a solution of **24** (0.66 g, 1.59 mmol) in DMF (20 mL) followed by HOBt (0.42 g, 3.1 mmol) and DCC (0.36 g, 1.7 mmol). The reaction mixture was shaken for 16 h, washed with DMF (2 × 25 mL), 1:1 $CHCl_3$:MeOH (2 × 25 mL), and CH_2Cl_2 (2 × 25 mL), and dried under vacuum for 24 h to give **23** (1.36 g): EA %N = 2.3 found, 2.4 calcd (0.81 mmol/g).

***N*-[2-(4-Hydroxyphenyl)ethyl]-*N*-benzylacetamide (18) from the Solution Phase TFA Cleavage of 25.** To resin

(13) Stewart, J. M.; Young, J. D. *Solid Phase Peptide Synthesis*; Pierce Chemical Co.: Rockford, IL, 1984.

25 (301.5 mg, 244 μmol) was added TFA (20 mL). The reaction mixture was stirred for 40 h at room temperature, filtered through a sintered glass funnel, and washed with $CHCl_3$ (3 × 5 mL). The filtrate was evaporated to dryness and dried under vacuum for 24 h to give **21** as an off-white solid identical to the authentic material made in solution (77.6 mg, 100%, 96% by N analysis of recovered resin): TLC R_f 0.36 (silica gel, 95:5 $CHCl_3$:MeOH); HPLC t_R 10.75 min, k' 4.4 (Zorbax SIL, 4.6 × 250 mm), 1−10% iPrOH/$CHCl_3$ over 20 min, UV 254 and 280 nm; MS(ES) m/z 270.4 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) (amide rotomers) δ 1.88, 2.12 (3H, 2s), 2.74, 2.78 (2H, 2t), 3.41, 3.58 (2H, 2t), 4.39, 4.63 (2H, 2s), 6.78 (2H, 2d), 7.95, 7.01 (2H, 2d), 7.11−7.35 (5H, m).

Vapor Phase TFA Cleavage Reaction Studies. To each of four 2-mL sintered glass funnels was placed 100 mg of dried resin **25**. The samples were each washed with CH_2Cl_2 to swell the resin and then drained mostly dry by vacuum aspiration. Each was then placed into a 50-mL beaker, within a TLC chamber containing a layer of TFA on the bottom. At selected time periods (6, 16, 24, and 40 h) a sintered glass funnel with resin was removed and dried under vacuum to remove residual TFA. The resin in each sintered glass funnel was then washed twice with a 1-mL solution of 2% methanol in $CHCl_3$ filtered directly into separate vials under vacuum. A 5-μL aliquot of each filtrate was then injected into an HPLC, and the peak area of the product was obtained to determine the amount cleaved. The conversion factor for the peak area to percent cleaved was obtained from the peak area of the 40-h resin sample and the percent cleaved obtained from nitrogen analysis. For multiple TFA cleavages the washed resin after the 6-h reaction was reintroduced into the TFA chamber for another 6 h and reanalyzed as above. This was repeated a third time for another 6 h (see Figures 1 and 2).

3-[Dimethyl[4-(hydroxymethyl)phenyl]silyl]propionic Acid. To a solution of **20** (2.50 g, 9.9 mmol) in dioxane (30 mL) was added aq 1 N NaOH (15 mL). After stirring for 4 h the reaction mixture was acidified with aq 1 N hydrochloric acid (15 mL) and evaporated to near dryness. The residue was taken up in ethyl acetate (100 mL), washed with cold aq 1 N HCl (100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated to give the free acid as a clear oil (2.36 g, 100%): TLC R_f 0.45 (silica gel, 95:4:1 $CHCl_3$:MeOH:HOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.30 (6H, s), 1.08 (2H, ddd), 2.30 (2H, ddd), 4.68 (2H, s), 7.36 (2H, d, J = 7.9 Hz), 7.50 (2H, d, J = 7.9 Hz). Anal. Calcd for $C_{12}H_{18}O_3Si$: C, 60.47; H, 7.61. Found: C, 59.72; H, 7.42.

3-[Dimethyl[4-(hydroxymethyl)phenyl]silyl]propionyl Benzhydrylamine Resin (26). To BHA resin (7.0 g, 7.77 mmol), washed first with 10% Et_3N in CH_2Cl_2 followed by CH_2Cl_2, was added a solution of the above 3-[dimethyl[4-(hydroxymethyl)phenyl]silyl]propionic acid (2.36 g, 9.9 mmol) in DMF (30 mL). To this were added 1-hydroxybenzotriazole (HOBt; 2.7 g, 20 mmol) and DCC (2.1 g, 9.9 mmol). The reaction mixture was shaken for 16 h, washed with DMF (2 × 30 mL), 1:1 $CHCl_3$:MeOH (2 × 30 mL), CH_2Cl_2 (2 × 30 mL), and hexane (30 mL), and dried under vacuum for 24 h to give resin **26** (8.66 g, 0.90 mmol/g): negative ninhydrin test;[3] MAS ^{1}H NMR (500 MHz) δ 0.20 (6H), 1.05 (2H), 2.10 (2H), 2.80 (1H), 4.52 (2H), 7.22, 7.40 (4H).

3-[Dimethyl[4-(bromomethyl)phenyl]silyl]propionyl Benzhydrylamine Resin (27). To resin **25** (1.60 g, 1.44 mmol) in a shaker vessel were added THF (30 mL), CBr_4 (0.96 g, 2.88 mmol), and Ph_3P (0.76 g, 2.88 mmol). The reaction mixture was shaken for 16 h, washed with THF (2 × 30 mL), ethanol (2 × 30 mL), CH_2Cl_2 (2 × 30 mL), and hexane (30 mL), and dried under vacuum for 16 h to give resin **27** (1.76 g, 0.84 mmol/g): EA %N found 1.18, calcd 1.22; %Br found 6.62, calcd 6.95.

3-[Dimethyl[4-[*N*-[2-(4-hydroxyphenyl)ethyl]aminomethyl]phenyl]silyl]propionyl Benzhydrylamine Resin (28). To resin **27** (1.50 g, 1.26 mmoL) in a shaker vessel were added DMF (20 mL), tyramine (1.7 g, 12.4 mmol), and Et_3N (1.8 mL, 12.9 mmol). The reaction mixture was shaken for 16 h, washed with DMF (2 × 20 mL), MeOH (2 × 20 mL), CH_2Cl_2 (2 × 20 mL), and hexane (20 mL), and dried under vacuum for 16 h to give resin **28** (1.52 g, 0.72 mmol/g): EA %N found 2.01, calcd 2.33; MAS ^{1}H NMR (500 MHz) δ 0.20 (6H), 1.10 (2H), 2.20 (2H), 2.70 (2H), 2.82 (2H), 3.74 (2H), 6.71, 6.90, 7.18, 7.40 (8H).

3-[Dimethyl[4-[*N*-[2-(4-hydroxyphenyl)ethyl]acetamidomethyl]phenyl]silyl]propionyl Benzhydrylamine Resin (29). To resin **28** (1.0 g, 0.72 mmol) in a shaker vessel were added CH_2Cl_2 (20 mL), pyridine (60 μL, 0.74 mmol), and acetic anhydride (70 μL, 0.74 mmol). The reaction mixture was shaken for 16 h, washed with CH_2Cl_2 (2 × 20 mL), MeOH (2 × 20 mL), CH_2Cl_2 (20 mL), and hexane (20 mL), and dried under vacuum for 16 h to give resin **29** (1.07 g): MAS ^{1}H NMR (500 MHz) (amide rotamers) δ 0.19 (6H), 1.02 (2H), 1.80, 1.95 (3H), 2.15 (2H), 2.63, 2.70 (2H), 3.29, 3.45 (2H), 4.22, 4.49 (2H), 6.70, 6.81, 6.89, 7.3 (8H). TFA vapor cleavage of this resin **29** for 72 h at room temperature gave a 72% isolated yield of **12**, identical by HPLC, TLC, MS(ES), and ^{1}H NMR with authentic material. A small amount (<5%) of the diacetylated material was also obtained after cleavage.

3-[Dimethyl[4-[*N*-[2-[4-[(*N*′,*N*′-dimethylamino)ethoxy]phenyl]ethyl]acetamidomethyl]phenyl]silyl]-propionyl Benzhydrylamine Resin (30). To resin **29** (0.87 g, 0.58 mmol) in a shaker vessel were added dry THF (15 mL), (*N*,*N*-dimethylamino)ethanol (0.58 mL, 5.8 mmol), Ph_3P (0.76 g, 2.9 mmol), and DIAD (0.57 mL, 2.9 mmol). The reaction mixture was shaken under an argon atmosphere for 4 h and filtered to dryness under argon. The reaction was repeated an additional time for 16 h; the mixture was washed with THF (2 × 15 mL), MeOH (2 × 15 mL), CH_2Cl_2 (2 × 15 mL), and hexane (15 mL) and dried under vacuum for 16 h to give resin **30** (0.94 g, 0.67 mmol/g): MAS ^{1}H NMR (500 MHz) (amide rotamers) δ 0.21 (6H), 1.08 (2H), 1.95, 2.05 (3H), 2.19 (2H), 2.32 (6H), 2.72 (2H), 2.80 (2H), 3.36, 3.52 (2H), 4.02 (2H), 4.30, 4.58 (2H), 6.80, 6.90, 7.14, 7.47 (8H).

***N*-[2-[4-*N*′,*N*′-Dimethylamino)ethoxy]phenyl]ethyl]-*N*-benzylacetamide (31).** Resin **30** (200 mg, 134 μmol) was exposed to TFA vapor at room temperature for 72 h and dried under vacuum. Extraction with 1:1 $CHCl_3$:MeOH (4 × 2 mL), evaporation of the filtrate, and drying under vacuum for 24 h gave **31** as its TFA salt (67.2 mg, 100%): TLC R_f 0.23 (silica gel, 9:1 $CHCl_3$:MeOH); MS(ES) m/z 341.0 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) (amide rotamers) δ 1.92, 2.12 (3H, 2s), 2.77, 2.82 (2H, 2t), 2.98 (6H, s), 3.49 (2H, t), 3.58 (2H, m), 4.33 (2H, t), 4.53, 4.60 (2H, 2s), 6.94, 6.97 (2H, 2d, J = 8.5 Hz), 7.13, 7.14 (2H, 2d, J = 8.5 Hz), 7.19−7.38 (5H, m). Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.78; H, 8.15; N, 8.29.

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Supporting Information Available: NMR spectra for all compounds described (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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