# A New Fluoridolyzable Anchoring Linkage for Orthogonal Solid-Phase Peptide Synthesis: Design, Preparation, and Application of the *N*-(3 or 4)-[[4-(Hydroxymethyl)phenoxy]-*tert*-butylphenylsilyl]phenyl Pentanedioic Acid Monoamide (Pbs) Handle[†,1–3]

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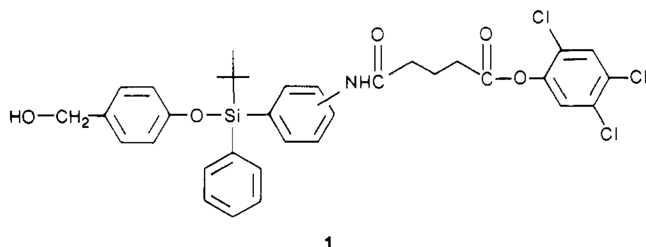
The silicon-containing bifunctional handle 2,4,5-trichlorophenyl *N*-(3 or 4)-[[4-(hydroxymethyl)phenoxy]-*tert*-butylphenylsilyl]phenyl pentanedioate monoamide (1) (Pbs) has been prepared and evaluated for use in a new mild approach to solid-phase peptide synthesis. The overall route to 1 entailed 10 steps starting from commercially available *tert*-butylchlorodiphenylsilane (2) and featured a novel electrophilic substitution of an arylsilane as well as a mild new method for converting silanols to chlorosilanes by use of oxalyl chloride in the presence of 4-(dimethylamino)pyridine. A "preformed handle" approach was used to attach $N^{\alpha}$-9-fluorenylmethyloxycarbonyl (Fmoc) amino acids via derivatives **16** to amino-functionalized supports. After chain assembly with standard Fmoc or dithiasuccinoyl (Dts) deprotection/coupling protocols, peptides could be cleaved from Pbs supports in >90% yields by brief treatment with tetrabutylammonium fluoride (1 equiv) in *N,N*-dimethylformamide, in the presence of appropriate scavengers when needed. Cleavage occurred without racemization, and in the case of C-terminal asparagine, without $\alpha$-aminosuccinimide formation. The efficacy of the Pbs handle was demonstrated by syntheses of methionine-enkephalin and a protected gastrin fragment, Fmoc-Glu(*O-t*-Bu)-Ala-Tyr(*t*-Bu)-Gly-OH.

The solid-phase method of Merrifield[4] is a powerful technique for the synthesis of polypeptide chains while they are covalently attached to an insoluble polymeric support. Generally, the C-terminal amino acid of the peptide is linked through its carboxyl group to a suitable functionalized support, usually by an ester or amide bond. Any improvements in synthetic methodology,[5] through introduction of milder reaction and cleavage conditions along lines pursued in this laboratory[6] and others,[7] must address the key issue of facile attachment of and removal at the terminal residue.

The present paper provides details on the design and execution of a new approach for anchoring in solid-phase peptide synthesis. The 2,4,5-trichlorophenyl *N*-(3 or 4)-[[4-(hydroxymethyl)phenoxy]-*tert*-butylphenylsilyl]phenyl pentanedioate monoamide (Pbs) *handle* derivative[2,3a] (1) is a bifunctional spacer, which on one end contains a site for attachment of the first residue and on the other end contains a site for linkage to a polymeric support. Most importantly, the peptide handle ester bond can be cleaved cleanly under exceptionally mild conditions based on the lability to *fluoridolysis*[8] of a silicon–oxygen bond built into the handle. Thus, this fluoridolyzable anchor is applicable to *orthogonal*[6c,d,9] schemes, with use of either the base-labile 9-fluorenylmethyloxycarbonyl (Fmoc)[10] or thiolyzable dithiasuccinoyl (Dts)[9,11] groups for temporary $N^{\alpha}$-amino protection. The anchor is also suitable for the preparation of side chain protected peptide segments.[12]

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## Results and Discussion

### Bifunctionalization of *tert*-Butyldiphenylsilanes.

Throughout this work to design appropriate silicon-containing handles, it was anticipated that the reactivity of

† This paper is dedicated to the memory of Professor Emil Thomas Kaiser, Jr., friend and mentor.

(1) Abbreviations used are: AA, amino acid; Boc, *tert*-butyloxycarbonyl; DCC, *N,N'*-dicyclohexylcarbodiimide; DCHA, *N,N*-dicyclohexylamine; DIEA, *N,N*-diisopropylethylamine; DMAP, 4-(dimethylamino)pyridine; DMF, *N,N*-dimethylformamide; Dts, dithiasuccinoyl; FABMS, fast atom bombardment mass spectrometry; Fmoc, 9-fluorenylmethyloxycarbonyl; HOBt, 1-hydroxybenzotriazole; HPLC, high-pressure liquid chromatography; MPLC, medium-pressure liquid chromatography; Pbs, title handle of this paper; Pyr·Tos, pyridinium tosylate; TEA, triethylamine; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; Z, benzyloxycarbonyl.

(2) Preliminary report: Mullen, D. G.; Barany, G. *Tetrahedron Lett.* **1987**, *28*, 491–494.

(3) (a) Taken in part from the Ph.D. Thesis of D. G. Mullen, University of Minnesota, 1987. (b) Present address: The Rockefeller University, New York, NY 10021. After December 1, 1988: Department of Chemistry, University of California, Berkeley, CA 94720. (c) Searle Scholar, 1982; National Institute of Health Research Career Development Award, 1982–1987.

(4) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154.

(5) Recent advances in solid-phase peptide synthesis have been reviewed: Barany, G.; Kneib-Cordonier, N. K.; Mullen, D. G. *Int. J. Peptide Protein Res.* **1987**, *30*, 705–739.

(6) (a) Albericio, F.; Barany, G. *Int. J. Peptide Protein Res.* **1984**, *23*, 342–349. (b) Albericio, F.; Barany, G. *Int. J. Peptide Protein Res.* **1985**, *26*, 92–97. (c) Barany, G.; Albericio, F. *J. Am. Chem. Soc.* **1985**, *107*, 4936–4942. (d) Albericio, F.; Barany, G. *Int. J. Peptide Protein Res.* **1987**, *30*, 177–205. (e) Albericio, F.; Barany, G. *Int. J. Peptide Protein Res.* **1987**, *30*, 206–216.

(7) (a) Matsueda, R.; Walter, R. *Int. J. Peptide Protein Res.* **1980**, *16*, 392–401. (b) Dangles, O.; Guibé, F.; Balovoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4984–4993. (c) Kirstgen, R.; Sheppard, R. C.; Steglich, W. *J. Chem. Soc., Chem. Commun.* **1987**, 1870–1871.

(8) Independent of our efforts, a new handle removable by fluoridolysis of a silicon–carbon bond has been reported recently: Ramage, R.; Barron, C. A.; Bielecki, S.; Thomas, D. W. *Tetrahedron Lett.* **1987**, *28*, 4105–4108.

(9) Barany, G.; Merrifield, R. B. *J. Am. Chem. Soc.* **1977**, *99*, 7363–7365.

(10) (a) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404–3409. (b) Meienhofer, J.; Waki, M.; Heimer, E. P.; Lambros, T. J.; Makofske, R. C.; Chang, C. D. *Int. J. Peptide Protein Res.* **1979**, *13*, 35–42. (c) Atherton, E.; Logan, C. J.; Sheppard, R. C. *J. Chem. Soc., Perkin Trans. 1* 1981, 538–546.

(11) (a) Barany, G.; Merrifield, R. B. *Anal. Biochem.* **1979**, *95*, 160–170. (b) Barany, G.; Merrifield, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 3084–3095. (c) Zalipsky, S.; Albericio, F.; Słomczyńska, U.; Barany, G. *Int. J. Peptide Protein Res.* **1987**, *30*, 740–783.

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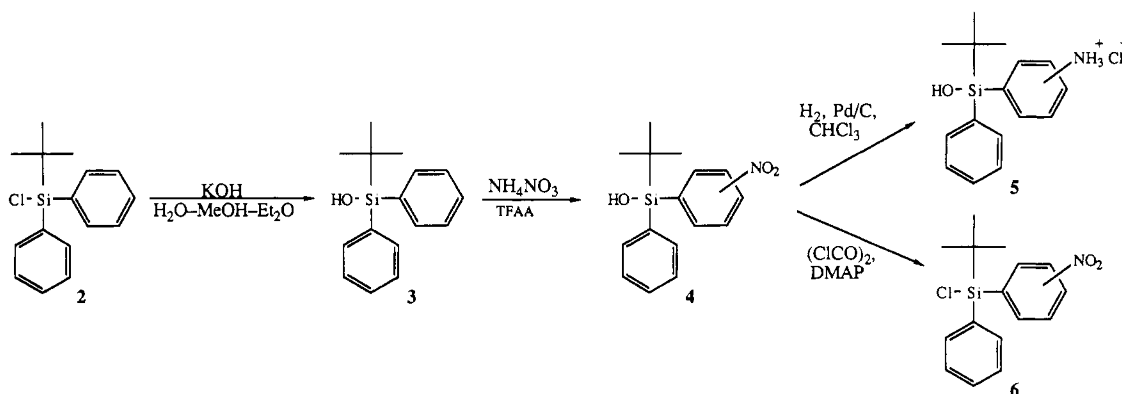
Scheme I




chlorosilanes could be exploited to create a direct or indirect linkage to the $C^{\alpha}$-carboxyl function of the anchored amino acid. However, it was also necessary to introduce onto the handle a second functional group that could be elaborated into a point of attachment to the polymeric support. Since the preferred anchoring reaction is amide formation between a handle carboxyl group and an amino-functionalized support,[5,6,13] chemistry was first sought to add a carboxyl side chain to one of the rings of *tert*-butylchlorodiphenylsilane.

Early experiments involved treatment of *tert*-butyldichlorophenylsilane with lithium or magnesium derivatives of 2-(3-bromophenyl)-5,5-dimethyl-2-oxazoline,[14] which can be viewed as a masked *m*-carboxyphenyl synthon. Unfortunately, the desired reactions did not proceed, presumably for steric reasons.

The next set of approaches that were explored involved direct functionalization of commercially available *tert*-butylchlorodiphenylsilane (2). The phenyl rings of 2 were thought to be possibly amenable to functionalization by electrophilic aromatic substitution reactions.[15] Specifically, it was anticipated that once a nitro group would be introduced into one of the rings, reduction would give an amino group that could further react with succinic anhydride to furnish the needed handle carboxyl functionality.

Toward this end, *tert*-butylchlorodiphenylsilane (2) was first nitrated by the method of Coon and co-workers,[16] which uses nitric acid–trifluoromethanesulfonic acid. The crude reaction mixture was analyzed by mass spectrometry to reveal desired mononitrochlorosilane, as well as mononitrosilanol and dinitrated products. Further control of the chemistry (Scheme I) was achieved in two ways: (1) the substrate for nitration was changed to *tert*-butyldiphenylsilanol (3), obtained by hydrolysis of 2 in a two-phase reaction mixture with aqueous potassium hydroxide–diethyl ether according to the general procedure of Sommer and Tyler;[17] (2) switching to the nitration procedure of Crivello,[18] which uses ammonium nitrate–trifluoroacetic anhydride as the nitronium ion source. The yield of desired mononitrosilanol 4 was optimized by applying 1.15 equiv of ammonium nitrate (a convenient-to-use solid) at −23 °C for 5 h. The dinitro side products could not be totally eliminated and were separated from mononitrosilanol 4, which was isolated in 65% yield, by silica gel chromatography. It was established by two-dimensional COSY NMR spectroscopy at 300 MHz that the meta- and para-substituted isomers both formed (≈5:1 ratio).[3a,19]

The potential usefulness of intermediate 4 was demonstrated by its catalytic hydrogenolysis[20] to amine hydro-

**Table I. Conversion of *tert*-Butyldiphenylsilanol (3) to *tert*-Butylchlorodiphenylsilane (2)**

| reagent/conditions | convn,[a] % | literature precedent[b] |
|---|---|---|
| conc aqueous HCl, reflux, 12 h | 0[c] | 21 |
| acetyl chloride, reflux, 12 h | 0[c] | 22 |
| cyclohexyl-*o*-phenylene phosphorochloridate/sulfuryl chloride | 58 | 23 |
| thionyl chloride, neat, reflux, 24 h | 60 | this work |
| DMAP/thionyl chloride | 100 | 24 |
| DMAP/oxalyl chloride | 100 | this work[d] |

[a] The approximate percent conversion was determined by comparing the NMR peak heights of the *tert*-butylsilyl group of the chlorosilane (δ 1.15) to that of the unreacted silanol (δ 1.06). [b] Except for line 1, which refers to conversion of $Et_3SiOH$ to $Et_3SiCl$, and line 2, which refers to conversion of polymeric dimethylsilanols to polymeric dimethylchlorosilanes, the literature precedents are for conversion of alcohols to alkyl chlorides. [c] Quantitative recovery of starting material. [d] See ref 25 for use of oxalyl chloride–*N*-hydroxypyridine-2-thione to convert tertiary alcohols to the corresponding alkyl chlorides

(12) For examples of prior approaches to protected segments, see: (a) Barton, M. A.; Lemieux, R. U.; Savoie, J. Y. *J. Am. Chem. Soc.* **1973**, *95*, 4501–4506. (b) Wang, S. S. *J. Am. Chem. Soc.* **1973**, *95*, 1328–1333. (c) Wang, S. S. *J. Org. Chem.* **1975**, *40*, 1235–1239. (d) Hudson, D.; Kenner, G. W. *Int. J. Biol. Macromol.* **1980**, *2*, 63–67. (e) Tam, J. P.; Tjoeng, F. S.; Merrifield, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 6117–6127. (f) Tam, J. P.; DiMarchi, R. D.; Merrifield, R. B. *Int. J. Peptide Protein Res.* **1980**, *16*, 412–425. (g) DeGrado, W. F.; Kaiser, E. T. *J. Org. Chem.* **1980**, *45*, 1295–1300. (h) DeGrado, W. F.; Kaiser, E. T. *J. Org. Chem.* **1982**, *47*, 3258–3261. (i) Whitney, D. B.; Tam, J. P.; Merrifield, R. B. *Tetrahedron* **1984**, *40*, 4237–4244. (j) Lyle, T. A.; Brady, S. F.; Ciccarone, T. M.; Colton, C. D.; Paleveda, W. J.; Veber, D. F.; Nutt, R. F. *J. Org. Chem.* **1987**, *52*, 3752–3759.

(13) (a) Mitchell, A. R.; Erickson, B. W.; Ryabtsev, M. N.; Hodges, R. S.; Merrifield, R. B. *J. Am. Chem. Soc.* **1976**, *98*, 7357–7362. (b) Mitchell, A. R.; Kent, S. B.; Engelhard, M.; Merrifield, R. B. *J. Org. Chem.* **1978**, *43*, 2845–2852.

(14) Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787–2793.

(15) A few previous examples of electrophilic aromatic substitution reactions on silicon-functionalized compounds are known: (a) Speier, J. L. *J. Am. Chem. Soc.* **1953**, *75*, 2930–2931. (b) Chernyshev, E. A.; Dolgaya, M. E.; Petrov, A. D. *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk.* **1960**, 1424–1428; *Chem. Abstr.* **1961**, *55*, 429*h*. (c) Limouzin, Y.; Maire, J. C.; Llinas, J. R. *J. Organomet. Chem.* **1973**, *63*, 51–66. (d) Gvozdev, V. V.; Traven, V. F.; Knyazhevskaya, V. B.; Krasnova, T. L.; Chernyshev, E. A.; Stepanov, B. I. *Zh. Obshch. Khim.* **1979**, *49*, 2632–2633; *Chem. Abstr.* **1980**, *92*, 94484*k*. (e) Traven, V. F.; Knyazhevskaya, V. B.; Eismont, M. Yu.; Kudryavtsev, A. B.; Stepanov, B. I. *Zh. Obshch. Khim.* **1981**, *51*, 99–107; *Chem. Abstr.* **1981**, *94*, 208929*h*.

(16) Coon, C. L.; Blucher, W. G.; Hill, M. E. *J. Org. Chem.* **1973**, *38*, 4243–4248.

(17) Sommer, L. H.; Tyler, L. J. *J. Am. Chem. Soc.* **1954**, *76*, 1030–1033.

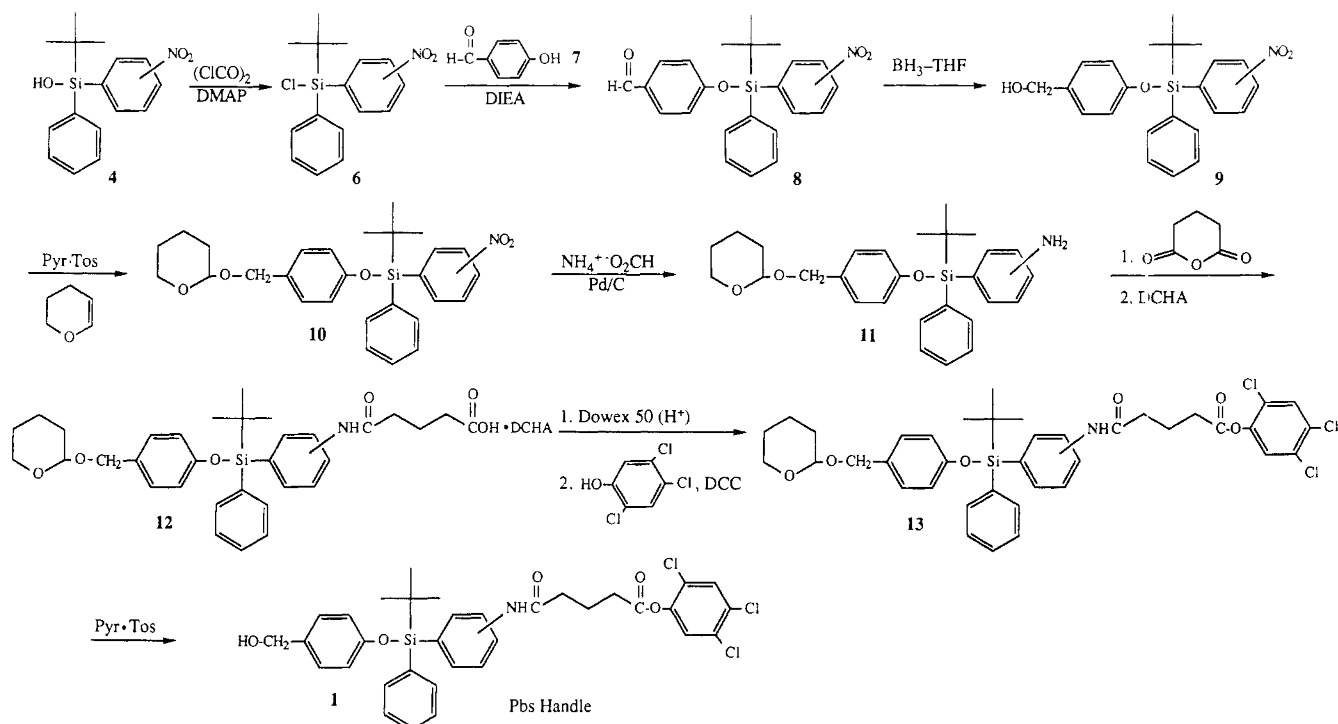
(18) Crivello, J. V. *J. Org. Chem.* **1981**, *46*, 3056–3060.

(19) (a) This ratio of isomers carried over for subsequent steps. (b) Table III (see the Experimental Section) contains detailed chemical shifts and coupling constants for both meta and para isomers. (c) A trace of the ortho isomer may also have formed, although positive identification could not be made by NMR analysis of the mixture.

(20) Secrist, J. A.; Logue, M. W. *J. Org. Chem.* **1972**, *37*, 335–336.

(21) Sommer, L. H.; Pietrusza, E. W.; Whitmore, F. C. *J. Am. Chem. Soc.* **1946**, *68*, 2282–2284.

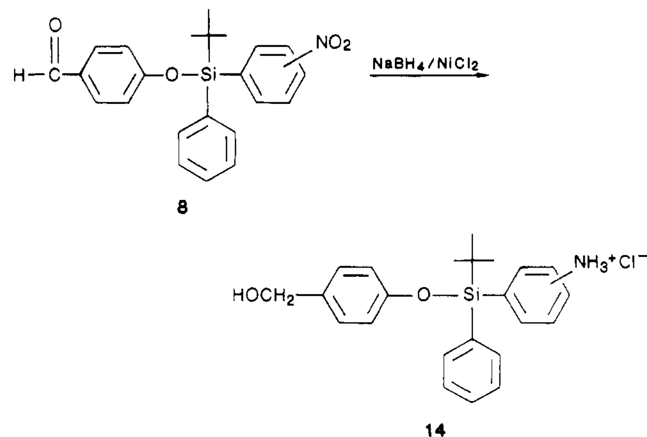
Scheme II




chloride **5** (Scheme I), in accordance with the original concept. However, in order to take **4** forward to appropriate handles (see earlier), the reduction step should be deferred until transformations at silicon are carried out. Specifically, it becomes necessary to convert the quite inert silanol function to a reactive chlorosilane. The desired chlorosilane **6** was obtained by the novel mild reaction of **4** with oxalyl chloride in the presence of 4-(dimethylamino)pyridine, which proved to be the best of several reagent combinations tested (Table I).

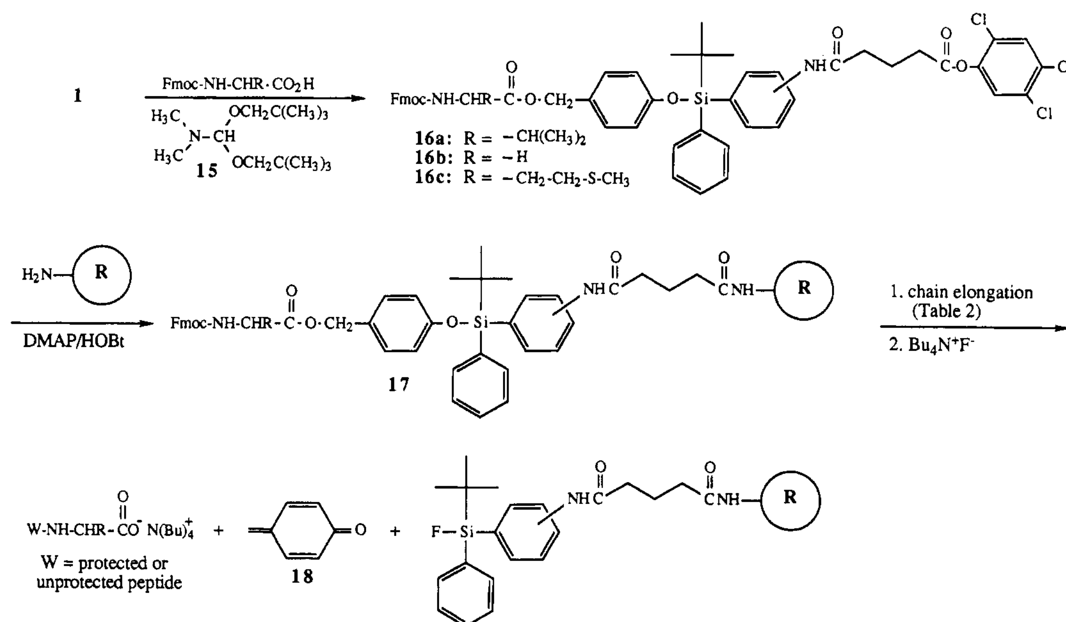
**Preparation of Pbs Handle.** Elaboration of the bifunctional silane derivative **4** to the desired handle **1** proceeded in eight steps (Scheme II). The silanol functionality was converted to the chlorosilane **6** according to the new method already mentioned (Table I), and this was followed by reaction with *p*-hydroxybenzaldehyde (**7**) in the presence of *N*,*N*-diisopropylethylamine (DIEA) to furnish silyl ether **8**. The aldehyde of **8**, which includes a labile silicon–oxygen bond,[26] was efficiently reduced to the stable benzyl alcohol **9** by use of borane–tetrahydrofuran complex. Pure **9** was protected[27] as the tetrahydropyranyl ether **10** and then reduced to amine **11** by catalytic transfer hydrogenation with ammonium formate as the hydrogen donor over a Pd/C catalyst.[28,29] The carboxyl functionality needed for attachment to amino-functionalized resins was provided by reaction of **11** with glutaric anhydride,[30] and the product was isolated as dicyclohexylammonium salt **12**. After neutralization, the acid was esterified to 2,4,5-trichlorophenol with *N*,*N*'-dicyclohexylcarbodiimide as the coupling reagent.[6a,b] The trichlorophenyl ester of the resultant **13** serves the dual roles of protecting the carboxyl group while amino acids are coupled to the handle and also activating the handle for attachment to amino-functionalized polymers. Finally, the tetrahydropyranyl group was removed with pyridinium tosylate[27] to give the silicon-functionalized Pbs handle **1**.

An attempt to shorten the Pbs handle synthesis involved simultaneous reduction of the aldehyde and nitro functons of **8** by use of $NaBH_4$–$Ni^{II}Cl_2$.[31] However, both functional groups of the resultant amino alcohol **14** were acylated by glutaric anhydride with approximately equal efficiencies. This result also points to the need to selectively protect the benzyl alcohol function (as is done in **10**).




(22) Fréchet, J. M.; Haque, K. E. *Tetrahedron Lett.* **1975**, 3055–3056.
(23) Corey, E. J.; Anderson, J. E. *J. Org. Chem.* **1967**, *32*, 4160–4161.
(24) Arrieta, A.; Garcia, R.; Palomo, C. *Synth. Commun.* **1982**, *12*, 1139–1146.
(25) Crich, D.; Fortt, S. M. *Synthesis* **1987**, 35–37.
(26) This lability was indicated in two ways: (a) crude **8** was contaminated with some silanol **4**; reduction to **9** was carried out directly without removal of **4**; (b) attempted reduction of **8** with sodium borohydride in methanol gave not only desired **9**, but also substantial amounts of methyl *tert*-butyldiphenylsilyl ether.
(27) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772–3774.
(28) Ram, S.; Ehrenkaufer, R. E. *Tetrahedron Lett.* **1984**, *25*, 3415–3418.
(29) The catalytic transfer hydrogenation was complete in 2 h. In contrast, if the procedure of Secrist and Logue (ref 20), namely Pd/C in ethanol–chloroform at 3 atm, was applied, complete reaction required 2 days. No ethyl silyl ether formed, indicating the stability of the silicon–oxygen bonds in **10** and **11** (compare to ref 26b).
(30) Earlier trials using succinic anhydride were abandonded when it was found that the subsequent esterification step with 2,4,5-trichlorophenol was accompanied by succinimide formation.
(31) Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1981**, *29*, 1159–1161.

Scheme III




**Anchoring of Amino Acids for Solid-Phase Peptide Synthesis.** The optimal strategy for attachment of amino acids to polymeric supports for peptide synthesis involves the coupling of pure preformed handles.[5,6,13,32] Toward this end, *N,N*-dimethylformamide dineopentyl acetal (15) was successfully applied to esterify Fmoc-glycine, methionine, and valine to 1 to provide preformed handle derivatives **16a–c** (Scheme III). The products were isolated in yields of 15–50% after silica gel chromatography. However, attempts to esterify Fmoc–phenylalanine and Fmoc-asparagine to 1 failed because the insolubility of the corresponding preformed handles made aqueous workup impossible.

Initial experiments to load preformed Pbs handles involved their reaction with "internal reference" amino acyl-aminomethyl-polystyrene resins, using DMF as solvent for 12–48 h in the presence of 1-hydroxybenzotriazole (HOBt).[6a,b] Incorporation of the first residue was occasionally quite high, but more often in the 30% range. Although free amino groups were clearly indicated by a positive qualitative ninhydrin test[33] and could be covered by acetylation, these amino groups did not react with Pbs handle after longer reaction times.[34] Consequently, improved anchoring conditions were optimized, using 4-(dimethylamino)pyridine (DMAP) (0.5 equiv) as a catalyst in addition to HOBt (3 equiv) in DMF. Incorporations were now reproducibly 60–80% after reaction times of only 2–4 h.

**Characterization of the Pbs Handle.** The stability of Pbs-anchored amino acid-residues was tested under a variety of conditions. Since the Pbs handle is similar to Wang's acid-labile *p*-alkoxybenzyl ester handle,[12b] the expected complete cleavage upon exposure to trifluoroacetic acid–$CH_2Cl_2$–dimethyl sulfide (5:4:1) for 1 h was indeed observed. This result rules out application of the Pbs handle in conjunction with stepwise incorporation of Boc-amino acids. However, when exposed to Fmoc deprotection conditions [piperidine–$CH_2Cl_2$ (1:1) for 3 h] or Dts deprotection conditions [$\beta$-mercaptoethanol–DIEA (0.5/0.5 M) in $CH_2Cl_2$ for 3 h], no loss of peptide from the resin was detected. The reaction time chosen represents approximately 30 deprotection cycles, so the Pbs handle should be suitable for the synthesis of large peptides using either Fmoc or Dts chemistries.

Gratifyingly, the Pbs anchor was very rapidly cleaved with tetrabutylammonium fluoride in DMF (Scheme III). Cleavage yields were routinely in excess of 90%, employing only 1 equiv of the fluoride reagent for a 2-min time period. Longer reaction times for fluoridolysis failed to release additional amino acids (or peptides; see later) from the support.

Because the 1,6-elimination mechanism for Pbs handle cleavage also generates the soluble quinone methide **18** (Scheme III), which might react to irreversibly modify good peptide products, the milieu for cleavage with fluoride routinely contained thiophenol (1.2 equiv) as a scavenger.[12f,35]

The overall anchoring/cleavage process (Scheme III) proceeded without racemization. This was demonstrated by assembly on the support of the dipeptide alanylvaline (see later for methods), which was cleaved by fluoridolysis and shown by Manning–Moore assay[36] to be exclusively the L,L-diastereomer (sensitivity limit 0.05%).

In solution studies on the fluoridolysis of asparaginyl and glutaminyl 2-(trimethylsilyl)ethyl esters, Sieber[37] reported that these rapidly undergo, respectively, succinimide and glutarimide formation.[38] To determine whether an analogous process might occur during fluoridolysis of the Pbs handle, the Pbs handle (1) was first coupled to the support. Fmoc-asparagine was then coupled,[39] with use

(32) Giralt, E.; Andreu, D.; Pons, M.; Pedroso, E. *Tetrahedron* **1981**, *37*, 2007–2010.

(33) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595–598.

(34) The acylation mixture was concentrated and washed with water to remove solvents and HOBt and then analyzed by NMR. The presence of diagnostic 2,4,5-trichlorophenyl ester singlets at $\delta$ 7.54 and 7.28 and a benzyl ester singlet at $\delta$ 5.04 (see the Experimental Section) indicated that the active acylating species was still present.

(35) (a) Turner, A. B. *Q. Rev.* **1964**, *18*, 347–366. (b) Wakselman, M. *Nouv. J. Chim.* **1983**, *7*, 439–447.

(36) Manning, J. M.; Moore, S. *J. Biol. Chem.* **1968**, *243*, 5591–5597.

(37) Sieber, P. *Helv. Chim. Acta* **1977**, *60*, 2711–2716.

(38) Asparagine and glutamine esters are known to rapidly form respectively $\alpha$-aminosuccinimide and $\alpha$-aminoglutarimide in the presence of base: (a) Sondheimer, E.; Holley, R. W. *J. Am. Chem. Soc.* **1954**, *76*, 2467–2470. (b) König, W.; Volk, A. *Chem. Ber.* **1977**, *110*, 1–11.

(39) As already stated, it was not possible to make the preformed handle of this amino acid because of solubility problems.

of DCC/DMAP/HOBt. Unfortunately, this reaction was found to be extremely sluggish. After six couplings, loading of asparagine was 52%, but this included a large amount of $\beta$-cyanoalanine formed from dehydration of the asparagine side chain during the coupling reactions.[40] Nevertheless, the resultant amino acyl-Pbs-resin was cleaved both by acidolysis and by fluoridolysis. In each case, ion-exchange chromatography revealed only asparagine and $\beta$-cyanoalanine but no $\alpha$-amino succinimide.[41] Although this experiment leaves unresolved the question of how best to incorporate asparagine as the C-terminal residue in a synthesis with the Pbs handle, it does prove that succinimide formation is not a problem with the fluoridolysis conditions used to cleave Pbs.

**Solid-Phase Synthesis with the Pbs Handle.** The efficacy of the Pbs handle was demonstrated by two model peptide syntheses. In the first case, the preformed Fmoc-Met-Pbs handle derivative **16c** was anchored to a leucyl "internal reference" *p*-methylbenzhydrylamine-resin in 77% yield by the methodology just described. Next, each appropriate Fmoc-amino acid of the methionine-enkephalin sequence[42] Tyr-Gly-Gly-Phe-Met was in turn incorporated by standard DCC/HOBt-mediated couplings.[43] After removal of the final Fmoc group, the peptide-resin was cleaved in three ways:

(1) Cleavage with fluoride (1 equiv) in DMF in the presence of thiophenol as a scavenger released 93% of the chains in 2 min. HPLC analysis under standard conditions of this laboratory[6d] revealed only the desired methionine-enkephalin and the corresponding sulfoxide, in a ratio of 3:1. Both peptide products were obtained analytically pure by preparative MPLC. Peptide sulfoxide presumably arose by oxidation during chain assembly, since starting handle was free of sulfoxide on the basis of NMR analysis. It is worth mentioning that no peptide eluted in the position[44] expected for D-methionine-enkephalin, proving again that the anchoring/fluoridolysis sequence proceeds without racemization.

(2) Cleavage with fluoride (1 equiv) in the *absence* of thiophenol revealed two further peaks in the HPLC trace on crude material. This result suggests that quinone methide (see structure **18** in Scheme III) reacts with the thioether side chain of methionine and that scavengers are needed to compete with this side reaction.

(3) Cleavage with TFA–$CH_2Cl_2$–dimethyl sulfide (5:4:1), with added thiophenol (1.2 equiv), 30 min, led to quantitative removal of peptide chains. Only desired methionine-enkephalin and the corresponding sulfoxide were noted, and the ratio of 3:1 agreed with the ratio from the fluoridolysis.

Because cleavage by fluoridolysis is orthogonal to conditions used to cleave the common acidolyzable and base-labile protecting groups used in peptide synthesis, it was hoped that the Pbs handle could be applied to the preparation of protected peptides. The feasibility of this idea was shown by the assembly of a gastrin fragment,[45]

**Table II. Fmoc Deprotection/Coupling Protocol**

| operation number | reagent, solvent | time, min |
|---|---|---|
| 1 | DMF wash | 3 × 1 |
| 2 | $CH_2Cl_2$ wash | 2 × 1 |
| 3 | piperidine–$CH_2Cl_2$ (1:1, v/v) | 3 × 2 |
| 4 | $CH_2Cl_2$ wash | 3 × 2 |
| 5 | DMF wash | 2 × 2 |
| 6 | Fmoc-amino acid and HOBt (3 equiv each) in DMF | 2 (no filtering) |
| 7 | DCC (3 equiv) in DMF | 60–90[a] |

[a] All couplings were monitored by the qualitative ninhydrin test (ref 33).

Fmoc-Glu(*O-t*-Bu)-Ala-Tyr(*t*-Bu)-Gly-OH. Cleavage with fluoride (1 equiv)–thiophenol (1.2 equiv)–DIEA (0.5 equiv) in DMF gave a 90% yield of a crude product that was ≈90% pure. MPLC purification readily gave the pure desired protected peptide, which had the predicted molecular ion upon FABMS.

## Experimental Section

Some of the materials and methods used in this study have been reported previously.[3a,6a,c,d] Melting points were determined on a Fisher-Johns apparatus and are uncorrected. $^1H$ NMR spectra were recorded at 300 MHz on either a Nicolet NT-300 WB or an IBM NR/300 instrument and at 200 MHz on an IBM NR/200 instrument with chloroform ($\delta$ 7.255) as the reference standard. In earlier work, a Varian HFT80 spectrometer was used at 80 MHz with tetramethylsilane ($\delta$ 0.00) as reference standard. Mass spectra were obtained on either a Finnigan 4000 or a VG 707E-HF instrument. IR spectra were obtained on either Beckman Accu-Lab or Beckman 4250 spectrometers. Elemental analyses were determined by M-H-W Laboratories.

Organic reactions were carried out at 25 °C unless otherwise stated, either under $N_2$ or protected from moisture with drying tubes containing Drierite ($CaSO_4$). Silica gel chromatography was performed with 60–300-mesh resin, and 30 g of silica gel per gram of compound to be purified was routinely used. Thin-layer chromatography was performed on Analtech silica gel GF plates (250 $\mu$, 10 × 20 cm), and compounds were observed by fluorescence quenching. The following solvent mixtures were used for development: A, diethyl ether–hexane (1:4); B, ethyl acetate–chloroform (1:9); C, chloroform. Amino acid analysis was performed on a Beckman 118BL instrument. Samples for amino acid analysis were hydrolyzed with 6 N HCl in acetic acid for 24 h with a drop of liquified phenol added as scavenger. Synthesized peptides were purified by MPLC with Lobar reversed-phase ($C_8$) columns. Flowrates of ≈1.75–2.0 mL/min were used. The eluant was monitored by UV detection at 214 nm. Analytical HPLC was performed on a Beckman-Altex 334 system with an Alltech Econosphere–ODS reversed phase ($C_{18}$) column (4.6 × 25 cm). Compounds were observed by UV detection at 210 nm.

Dry dichloromethane for organic synthesis was freshly distilled from $P_2O_5$ under $N_2$, dry methanol was obtained by sequential storing over 3-Å molecular sieves under $N_2$, and anhydrous diethyl ether was of analytical grade and was used without further drying. Solvents for peptide synthesis were purified as described earlier.[6a,46] All other solvents were analytical reagents and were used without further purification. *p*-Hydroxybenzaldehyde, glutaric anhydride, and 2,4,5-trichlorophenol were, respectively, recrystallized from water, absolute ethanol, and petroleum ether (bp 30–60 °C) prior to use. Ammonium formate was dried by storing over $P_2O_5$ in vacuo. Pyridinium tosylate was made by the procedure of Miyashita et al.[27] *N,N*-diisopropylethylamine (DIEA) was dried by storing over KOH. Dicyclohexylamine was distilled at reduced pressure (aspirator) prior to use. $\beta$-Cyanoalanine was purchased from Sigma. Carbonate buffer, pH 9.5, was made according to Tam et al.[47] Aminomethylcopoly(styrene-1%-di-

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vinylbenzene)-resin (0.17 or 0.62 mmol/g) was obtained according to Mitchell et al.[13b] or was purchased from Peptides International, and 4-methylbenzhydrylamine copoly(styrene-1%-divinylbenzene)-resin (0.42 mmol/g) was obtained from Biosearch Inc. The resins were first washed with TFA–$CH_2Cl_2$ (3:7) (3 × 10 min), $CH_2Cl_2$ (5 × 1 min), DIEA–$CH_2Cl_2$ (1:19) (3 × 2 min), and $CH_2Cl_2$ (3 × 1 min) before use. In all syntheses, an "internal reference" amino acid[48] was next attached to the resin before the preformed handle was loaded onto the resin. Loading and/or cleavage yields were calculated by hydrolyzing the resins after fluoridolysis and comparing the amount of internal reference amino acid present to the amount of C-terminal amino acid. Chain assembly with Fmoc-protected amino acids was carried out according to the deprotection/coupling protocol shown in Table II.

***tert*-Butyldiphenylsilanol (3).** A solution of *tert*-butylchlorodiphenylsilane (2) (10.0 g, 36.4 mmol) in diethyl ether (30 mL) was stirred for 24 h with a solution of KOH (2.24 g, 40.0 mmol) in $H_2O$–methanol (1:4) (20 mL). The aqueous layer was separated and washed with ether (2 × 30 mL), and the combined ether fractions were dried ($MgSO_4$) and concentrated to give a clear oil that solidified into a white solid (9.3 g, quantitative) upon standing. This solid, mp 61–62 °C, was pure by $^1H$ NMR and TLC [$R_f$(A) 0.32] analyses and was used without further purification. An analytical sample was recrystallized from petroleum ether (bp 30–60 °C): mp 62–64 °C; $^1H$ NMR ($CDCl_3$) δ 6.64–7.72 (m, 10 H, aromatic), 1.06 (s, 9 H, *tert*-butyl); CI MS ($NH_3$), *m/e* (relative intensity), positive 274 [$(M + NH_4)^+$, 100]; negative 255 [$(M - H)^-$, 100]. Anal. Calcd for $C_{16}H_{20}OSi$: C, 74.95; H, 7.86. Found: C, 75.05; H, 7.85.

***tert*-Butyl[(3 or 4)-nitrophenyl]phenylsilanol (4).** Silanol 3 (10.0 g, 39.1 mmol) was dissolved in acetonitrile (60 mL), and ammonium nitrate (3.60 g, 45 mmol) was added to form a suspension. The mixture was cooled to –23 °C in a dry ice–$CCl_4$ bath, and trifluoroacetic anhydride (22 mL, 155 mmol) was added all at once. After 5 h at –23 °C, the reaction was quenched by pouring into an ice/water mixture (60 mL). The aqueous solution was extracted with diethyl ether (3 × 60 mL), and the combined ether fractions were diluted with ice chips to control the subsequent exothermic neutralization. The organic phase was then washed with 2 N aqueous NaOH (100-mL portions) until the aqueous layer was basic (litmus paper), followed by brine (100 mL). The organic phase was then dried ($MgSO_4$) and concentrated to yield a yellow oil. The desired mononitrosilanol was separated from unreacted starting material and higher nitrated products by silica gel chromatography with diethyl ether–hexane (3:17) as eluant. Fractions were monitored by TLC, and the appropriate fractions [$R_f$(A) 0.14] were combined and concentrated: yield 8.1 g (69%); IR ($CDCl_3$) $NO_2$ stretches, 1350 and 1525 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.34–8.58 (m, 9 H, aromatic), 1.08 (s, 9 H, *tert*-butyl); CI MS ($NH_3$), *m/e* (relative intensity), positive 319 [$(M + NH_4)^+$, 36], 272 [$(MH - NO_2)^+$, 100]; negative 301 [$(M - H)^-$, 100]. The detailed $^1H$ NMR spectrum, with assignments and coupling constants verified by 2D COSY experiments, is shown in Table III. Anal. Calcd for $C_{16}H_{19}NO_3Si$: C, 63.76; H, 6.35; N, 4.65. Found: C, 63.92; H, 6.11; N, 4.75.

**[(3 or 4)-Aminophenyl]-*tert*-butylphenylsilanol Hydrochloride (5).** The corresponding nitro compound 4 (0.95 g, 3.2 mmol) was dissolved in absolute ethanol (50 mL) in a Parr vessel, 10% Pd/C (0.02 g) and $CHCl_3$ (0.5 mL) were added, and the mixture was reduced under $H_2$ (50 psi) overnight. The catalyst was then removed by filtration through a bed of diatomaceous earth, the solvent was removed, and the resultant brown oil was precipitated by treatment with diethyl ether (50 mL). The diethyl ether was removed by evaporation, and the solid residue was dissolved in the minimum amount of hot ethyl acetate that had been saturated with $H_2O$. Upon cooling overnight at 4 °C, white needles (0.25 g) formed that were collected and washed with cold $CH_2Cl_2$, mp 168–175 °C. Second (0.23 g) and third (0.21 g) crops were obtained each time by adding just enough $CH_2Cl_2$ to the mother liquor to create turbidity, followed by overnight cooling at 4 °C: total yield 0.69 g (70%); $^1H$ NMR (80 MHz, $CDCl_3$) δ 6.66–8.00 (m, aromatic), 1.06 (s, *tert*-butyl). Anal. Calcd for

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**Table III. Chemical Shifts and Coupling Constants for the Nitrated Phenyl Ring of the Meta and Para Mononitrosilanol Isomers[a,b]**

| | chemical shift[c] (coupling) |
|---|---|
| para (16%): $O_2N$–$C_6H_4$–Si ($H_B$, $H_A$, $H_{B'}$, $H_{A'}$) | $H_{A,A'}$: 7.90 (d, $J$ = 8.7 Hz)<br>$H_{B,B'}$: 8.20 (d, $J$ = 8.7 Hz) |
| meta (84%): $O_2N$–$C_6H_4$–Si ($H_C$, $H_D$, $H_E$, $H_F$) | $H_C$: 8.56 (dd, $J$ = 2.4, 0.7 Hz)<br>$H_D$: 8.25 (ddd, $J$ = 8.2, 2.4, 2.4 Hz)<br>$H_E$: 7.56 (t, $J$ = 7.8 Hz)<br>$H_F$: 8.02 (ddd forming 2 t, $J$ = 7.8, 1.1, 1.1 Hz) |

[a] Resolution-enhanced spectra recorded at 300 MHz. [b] A small amount of the ortho-substituted isomer may also be present (<1%). [c] Parts per million (ppm).

$C_{16}H_{22}ClNOSi$: C, 62.24; H, 7.20; N, 4.55; Cl, 11.51. Found: C, 62.31; H, 7.10; N, 4.36; Cl, 11.42.

***tert*-Butylchloro[(3 or 4)-nitrophenyl]phenylsilane (6).** A solution of silanol 4 (3.85 g, 12.8 mmol) and DMAP (2.34 g, 19.2 mmol) in $CH_2Cl_2$ (60 mL) was cooled in an ice bath, and oxalyl chloride (4.50 mL, 51.2 mmol) was added dropwise at a rate slow enough to maintain a gentle exotherm (*Caution*: The reaction of oxalyl chloride with DMAP is extremely exothermic). After addition was complete, the reaction mixture was allowed to warm to 25 °C and was further stirred for 36 h. The $CH_2Cl_2$ was removed by evaporation, diethyl ether (60 mL) was added, and the insoluble DMAP hydrochloride salt was filtered off. After removal of ether, a yellow oil resulted (3.84 g, 95%) that was pure by $^1H$ NMR and TLC [$R_f$(A) 0.61] analyses and was used in the next step without further purification. An analytical sample was prepared by bulb-to-bulb distillation, bp 170 °C (0.03 mmHg): $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.39–8.60 (m, 9 H, aromatic), 1.16 (s, 9 H, *tert*-butyl); CI MS ($NH_3$), *m/e* (relative intensity), positive 337 [$(M + NH_4)^+$, 100], 285 [$(MH - Cl)^+$, 21]; negative 319 [$M^-$, 100]. Anal. Calcd for $C_{16}H_{18}ClNO_2Si$: C, 60.08; H, 5.67; Cl, 11.08; N, 4.38. Found: C, 59.89; H, 5.87; Cl, 11.31; N, 4.26.

**4-[*tert*-Butyl[(3 or 4)-nitrophenyl]phenylsiloxy]benzaldehyde (8).** A solution of *tert*-butylchloro[(3 or 4)-nitrophenyl]phenylsilane (6) (3.82 g, 12.0 mmol) and 4-hydroxybenzaldehyde (7) (1.61 g, 13.2 mmol) in dry $CH_2Cl_2$ (120 mL) was stirred under nitrogen, and *N,N*-diisopropylethylamine (2.33 g, 18.0 mmol) was added. After overnight reaction, solvent was removed by evaporation to give a tan oil, which was taken up in diethyl ether (120 mL) and $H_2O$ (100 mL). The organic phase was separated and washed with 1 N HCl (3 × 100 mL), $H_2O$ (100 mL), pH 9.5 carbonate buffer (3 × 100 mL), and saturated NaCl (100 mL), followed by drying ($MgSO_4$). Concentration gave a tan oil (4.77 g), which was dissolved in $CH_2Cl_2$ and filtered through a 3.0 cm × 3.5 cm plug of silica gel, followed by rinsing with excess $CH_2Cl_2$, to remove colored impurities. The solvent was removed to yield 4.62 g (≈87%) of a light yellow oil that contained a trace of 4 as a contaminant. This contaminant was not easily separated from the desired 8, and the crude product was used without purification in the next step: IR ($CDCl_3$) carbonyl stretch 1700 $cm^{-1}$, $NO_2$ stretches 1530 and 1350 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 9.82 (s, 1 H, aldehyde), 7.42–8.58 (m, 11 H, aromatic), 6.85 (d, $J$ = 8.5 Hz, 2 H, *o*-phenoxy), 1.13 (s, 9 H, *tert*-butyl).

**4-[*tert*-Butyl[(3 or 4)-nitrophenyl]phenylsiloxy]benzenemethanol (9).** A solution of crude 8 (4.62 g, 11.4 mmol) in anhydrous diethyl ether (120 mL) was cooled in an ice/water bath under a nitrogen atmosphere, and 1.0 N borane–tetrahydrofuran complex (11.4 mL, 11.4 mmol) was added by syringe at a rate slow enough to maintain a gentle reflux. When the reflux had subsided, the reaction was allowed to equilibrate to 25 °C and stirred for an additional 2 h. The mixture was then cooled in an ice/water bath and quenched by the slow addition of water (75 mL) at a rate causing only a gentle reflux. After hydrogen evolution had ceased, the organic phase was separated, washed with 1 N HCl (75 mL) and saturated NaCl (75 mL), and dried ($MgSO_4$). The solvent was removed to yield an oil (4.93 g), which

was dissolved in ethyl acetate–hexane (3:7) (3 mL) and applied to a silica gel column with ethyl acetate–hexane (2:8) as eluant. The fractions were monitored by TLC, and the ones containing product [$R_f$(B) 0.48] were pooled and concentrated to give an analytically pure oil: yield 4.25 g (84% over three steps starting from 4); IR ($CDCl_3$) O–H stretch 3800 $cm^{-1}$, $NO_2$ stretches 1530 and 1350 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.36–8.57 (m, 9 H, aromatic), 7.17 (d, $J$ = 8.5 Hz, 2 H, *p*-phenoxy), 6.75 (d, $J$ = 8.5 Hz, 2 H, *o*-phenoxy), 4.55 (s, 2 H, benzylic $CH_2OH$), 1.12 (s, 9 H, *tert*-butyl); CI MS ($NH_3$), $m/e$ (relative intensity), positive 425 [$(M + NH_4)^+$, 12], 407 ($M^+$, 38), 390 [$(MH - H_2O)^+$, 100], 284 [$(M - C_7H_7O_2)^+$, 5]; negative 407 ($M^-$, 100). Anal. Calcd for $C_{23}H_{25}NO_4Si$: C, 67.78; H, 6.18; N, 3.44. Found: C, 68.03; H, 6.44; N, 3.31.

***O*-(2-Tetrahydro-2*H*-pyranyl)-4-[*tert*-butyl[(3 or 4)-nitrophenyl]phenylsiloxy]benzenemethanol (10).** A solution of 9 (4.25 g, 10.4 mmol), dihydropyran (1.42 mL, 15.6 mmol), and pyridinium tosylate (0.26 g, 1 mmol) in $CH_2Cl_2$ (100 mL) was allowed to stir overnight. The solvent was then removed, and the resultant oil was taken up in diethyl ether (100 mL) and half-saturated aqueous NaCl (75 mL). The organic phase was separated and washed with another portion of half-saturated aqueous NaCl, followed by drying ($MgSO_4$). Concentration gave a light yellow oil (4.95 g, ≈100%) that was pure by $^1H$ NMR and TLC [$R_f$(B) 0.74] analyses. This oil was used without further purification in the next step. An analytical sample was obtained by silica gel chromatography [eluant ethyl acetate–hexane (1:19)]: IR ($CDCl_3$) $NO_2$ stretches 1510 and 1350 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.37–8.59 (m, 9 H, aromatic), 7.13 (d, $J$ = 8.6 Hz, 2 H, *p*-phenoxy), 6.74 (d, $J$ = 8.6 Hz, 2 H, *o*-phenoxy), 4.63–4.68 (overlapping d, $J$ = 11.7 Hz, and m; total 2 H; respectively, benzylic $CH_2O$ and THP anomeric H), 4.34 (d, $J$ = 11.7 Hz, 1 H, benzylic $CH_2O$), 3.82–3.87 (m, 1 H, $THPOCH_2$), 3.42–3.53 (m, 1 H, $THPOCH_2$), 1.11 (s, 9 H, *tert*-butyl); CI MS ($NH_3$), $m/e$ (relative intensity), positive 425 [$(M + NH_4)^+$, 12], 407 ($M^+$, 38), 390 [$(MH - H_2O)^+$, 100]; negative 407 ($M^-$, 100). Anal. Calcd for $C_{23}H_{25}NO_4Si$: C, 67.78; H, 6.18; N, 3.44. Found: C, 68.03; H, 6.44; N, 3.31.

***O*-(2-Tetrahydro-2*H*-pyranyl)-4-[*tert*-butyl[(3 or 4)-aminophenyl]phenylsiloxy]benzenemethanol (11).** Intermediate 10 (4.95 g, 12.2 mmol) and anhydrous ammonium formate (5.73 g, 91 mmol) were dissolved in dry methanol (100 mL) and vigorously stirred under a nitrogen atmosphere; 10% Pd/C (0.50 g) was added, and the reaction was stirred for 2 h. The catalyst was then removed by filtration through a bed of diatomaceous earth, the methanol was removed, and the resultant white solid was taken up in ethyl acetate (100 mL) and saturated aqueous NaCl (100 mL). The organic layer was separated, washed with saturated aqueous NaCl (2 × 100 mL), dried ($MgSO_4$), and concentrated to yield an oil (4.76 g, ≈85%) that was pure by TLC [$R_f$(B) 0.38] and $^1H$ NMR analyses and used in the next step without further purification. An analytical sample was obtained after silica gel chromatography [eluant ethyl acetate–hexane (2:8)]: $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 6.64–7.72 (m, 13 H, aromatic), 4.62–4.68 (overlapping d, $J$ = 11.5 Hz, and m; total 2 H; respectively, benzylic $OCH_2$ and THP anomeric H), 4.35 (d, $J$ = 11.5 Hz, 1 H, benzylic $OCH_2$), 3.83–3.92 (m, 1 H, THP $OCH_2$), 3.48–3.53 (m, 1 H, THP $OCH_2$), 1.08 (s, *tert*-butyl); CI MS ($NH_3$), $m/e$ (relative intensity) positive 462 [$(M + H)^+$, 16], 360 [$(MH - C_5H_9O_2)^+$, 100]. Anal. Calcd for $C_{28}H_{35}NO_3Si$: C, 72.84; H, 7.64; N, 3.03. Found: C, 72.65; H, 7.66; N, 2.95.

***N*-(3 or 4)-[[4-[[*O*-(2-Tetrahydro-2*H*-pyranyl)hydroxy]methyl]phenoxy]-*tert*-butylphenylsilyl]phenyl Pentanedioic Acid Monoamide, Dicyclohexylammonium Salt (12).** A solution of amine 11 (4.76 g, 10.1 mmol) and glutaric anhydride (1.27 g, 11.1 mmol) in $CH_2Cl_2$ (100 mL) was stirred overnight. The solution was then washed with aqueous 1 N HCl (3 × 100 mL), water (2 × 100 mL), and saturated NaCl (100 mL) and dried ($MgSO_4$). The solvent was removed to yield a resinous solid (5.16 g, 89%), which was dissolved in diethyl ether (100 mL) and cooled in an ice/water bath. Dicyclohexylamine (1.79 mL, 8.97 mmol) was then added dropwise over 1 min. A white precipitate formed after a few seconds, and petroleum ether (bp 30–60 °C) (100 mL) was then added into the ice-cold solution over a 10-min period. The crystals were collected and washed with excess petroleum ether to give analytically pure title product: yield 5.37 g (68% yield over three steps from 9); mp 115–117 °C; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 8.76 (s, 1 H), 7.29–7.81 (m, 9 H, aromatic), 7.07 (d, $J$ = 8.5 Hz, 2 H, *p*-phenoxy), 6.72 (d, $J$ = 8.5 Hz, 2 H, *o*-phenoxy), 4.61–4.67 (overlapping d, $J$ = 11.5 Hz, and m; total 2 H; respectively, benzylic $CH_2O$ and THP anomeric H), 4.33 (d, $J$ = 11.5 Hz, 1 H, benzylic $CH_2O$), 3.87 (m, 1 H, THP $OCH_2$), 3.53 (m, 1 H, THP $OCH_2$), 2.84 (m, 2 H, DCHA NC*H*), 2.42 [t, $J$ = 6.7 Hz, 2 H, $NH(C{=}O)CH_2$], 2.32 (t, $J$ = 6.7 Hz, 2 H, carboxyl salt $CH_2$), 1.18–1.30 (m, DCHA) 1.08 (s, 9 H, *tert*-butyl); FAB MS, $m/e$ (relative intensity), positive 757 [$[M_{(salt)} + H]^+$, 12], 474 [$[M_{(acid)} - C_5H_9O_2]^+$, 67], 182 (100); negative 574 [$[M_{(acid)} - H]^-$, 100]. Anal. Calcd for $C_{45}H_{64}N_2O_6Si$: C, 71.39; H, 8.52; N, 3.70. Found: C, 71.19; H, 8.66; N, 3.77.

**2,4,5-Trichlorophenyl *N*-(3 or 4)-[[4-[[*O*-(2-Tetrahydro-2*H*-pyranyl)hydroxy]methyl]phenoxy]-*tert*-butylphenylsilyl]phenyl Pentanedioate Monoamide (13).** Dicyclohexylammonium salt 12 (5.30 g, 7.00 mmol) and Dowex-50 × 8 strongly acidic ion-exchange resin (7 g, 2 equiv) were suspended in $CH_2Cl_2$ (100 mL). The suspension was vortexed for 5 min, by which time all of the 12 had dissolved. The resin was filtered off, and 2,4,5-trichlorophenol (1.52 g, 7.70 mmol) was added to the solution. Next, DCC (1.57 g, 7.70 mmol) dissolved in $CH_2Cl_2$ (5 mL) was added to the reaction, and stirring was continued overnight. The solvent was then removed to yield a solid, which was treated with ethyl acetate (100 mL) and filtered to remove solid *N,N'*-dicyclohexylurea. The organic solution was washed with pH 9.5 carbonate buffer (3 × 75 mL) and saturated NaCl (2 × 75 mL), dried ($MgSO_4$), and concentrated to yield an oil, which was crystallized by dissolving in 6 mL of hot $CHCl_3$, allowing to cool to 25 °C, and adding just enough petroleum ether (bp 30–60 °C) to promote turbidity. One or two drops of $CHCl_3$ was then added to clarify the solution, and after standing overnight at 25 °C, a white solid had formed. The mixture was then cooled to 4 °C, and the crystals were collected and washed with excess cold petroleum ether: yield: 4.12 g (78%), a granular white solid; mp 105–109 °C; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.54 (s, 2,4,5-trichlorophenolate), 7.28 (s, 2,4,5-trichlorophenolate), 7.32–7.91 (m, 11 H, aromatic including the defined singlets at 7.28 and 7.54), 7.09 (d, $J$ = 8.5 Hz, 2 H, *p*-phenolate), 6.72 (d, $J$ = 8.5 Hz, 2 H, *o*-phenolate), 4.62–4.67 (overlapping d, $J$ = 11.5 Hz, and m; total 2 H; respectively, benzylic $CH_2O$ and THP anomeric H), 4.33 (d, $J$ = 11.5 Hz, 1 H, benzylic $CH_2O$), 3.83–3.88 (m, 1 H, THP $OCH_2$), 3.48–3.53 (m, 1 H, THP $OCH_2$), 2.75 (t, $J$ = 7.1 Hz, 2 H), 2.50 (t, $J$ = 7.1 Hz, 2 H), 2.19 (q, $J$ = 7.0 Hz, 2 H, $CH_2CH_2CH_2$), 1.08 (s, 9 H, *tert*-butyl); CI MS ($NH_3$), $m/e$ (relative intensity), positive 652 [$(M - C_5H_9O_2)^-$, 100]; negative 788 [$(M + Cl)^-$, 63], 655 (51), 574 [$(M - C_6H_2Cl_3)^-$, 66], 195 [$(C_6H_2Cl_3O)^-$, 100]. Anal. Calcd for $C_{39}H_{42}Cl_3NO_6Si$: C, 62.03; H, 5.60; Cl, 14.08; N, 1.85. Found: C, 62.04; H, 5.70; Cl, 14.17; N, 1.91.

**2,4,5-Trichlorophenyl *N*-(3 or 4)-[[4-(Hydroxymethyl)-phenoxy]-*tert*-butylphenylsilyl]phenyl Pentanedioate Monoamide (1) (Pbs Handle).** A mixture of handle intermediate 13 (1.50 g, 1.99 mmol) and pyridinium tosylate (50 mg, 0.20 mmol) in absolute ethanol (50 mL) was heated at 50 °C for 4 h. The solvent was removed, and the residue was taken up in diethyl ether (50 mL) and half-saturated aqueous NaCl (50 mL). The organic phase was separated, washed twice more with half-saturated NaCl, dried ($MgSO_4$), and concentrated to yield a fluffy white solid (1.44 g, ≈100%), mp 53–56 °C, that was pure by TLC [$R_f$(B) 0.02] and $^1H$ NMR analyses. This solid was used without further purification, although an analytical sample was obtained by silica gel chromatography [eluant ethyl acetate–hexane (1:4)]: $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.54 (s, 2,4,5-trichlorophenolate), 7.27 (s, 2,4,5-trichlorophenolate), 7.27–7.87 (m, 11 H, aromatic including the defined singlets at 7.27 and 7.54), 7.08 (d, $J$ = 8.5 Hz, 2 H, *p*-phenolate), 6.73 (d, $J$ = 8.5 Hz, 2 H, *o*-phenolate), 4.52 (s, 2 H, benzylic $CH_2OH$), 2.74 (t, $J$ = 7.0 Hz, 2 H), 2.48 (t, $J$ = 7.0 Hz, 2 H), 2.18 (q, $J$ = 6.6 Hz, 2 H, $CH_2CH_2CH_2$), 1.09 (s, 9 H, *tert*-butyl); CI MS ($NH_3$), $m/e$ (relative intensity), positive 652 [$(MH - H_2O)^+$, 100]; negative 704 [$(M + Cl)^-$, 77], 670 [$(MH)^-$, 15], 195 [$(C_6H_2Cl_3O)^-$, 100]. Anal. Calcd for $C_{34}H_{34}Cl_3NO_5Si$: C, 60.85; H, 5.11; N, 2.09; Cl, 15.85. Found: C, 61.05; H, 5.35; N, 2.21; Cl, 15.67.

**4-[*tert*-Butyl[(3 or 4)-aminophenyl]phenylsiloxy]-benzenemethanol Hydrochloride (14).** A solution of benzaldehyde 8 (4.75 g, 11.7 mmol) and $NaBH_4$ (1.93 g, 51 mmol) in methanol (150 mL) was cooled in an ice bath, and a solution of

$NiCl_2 \cdot 6H_2O$ (4.85 g, 20.4 mmol) in methanol (50 mL) was added dropwise at a rate slow enough to maintain a gentle reflux in the spontaneously exothermic reaction (*Caution*: the reaction of $NiCl_2$ with $NaBH_4$ is extremely exothermic). After the addition was complete, the reaction was allowed to equilibrate to 25 °C and stirred for a total of 2 h. Solvent was removed to give a black solid that was scraped from the sides of the flask and then taken up in ethyl acetate (200 mL) and aqueous 1 N HCl (300 mL). The organic layer was separated, the aqueous layer was extracted with ethyl acetate (2 × 100 mL), and the combined organic phases were dried ($MgSO_4$). Concentration gave a dark brown oil (5.22 g) that was purified by silica gel chromatography [eluant ethyl acetate–hexane (1:1)] to yield a light tan oil (2.01 g, 42%) that was pure by TLC [$R_f$(B) 0.14] and $^1$H NMR [(80 MHz, $CDCl_3$) δ 6.65–7.70 (m, aromatic), 4.54 (s, $HOCH_2$), 1.09 (s, *tert*-butyl)] analyses.

**Reaction of 14 with Succinic or Glutaric Anhydride.** Compound 14 (0.24 g, 0.58 mmol) and the anhydride (0.64 mmol) were dissolved in $CH_2Cl_2$ (15 mL), and DIEA (0.082 g, 0.64 mmol) was then added. After overnight stirring, the reaction was washed with aqueous 1 N HCl (2 × 10 mL) and saturated NaCl (15 mL), dried ($MgSO_4$), and concentrated to yield a tan solid that $^1$H NMR (80 MHz, $CDCl_3$) showed to be a mixture of ester [δ 5.05, (C=O)$OCH_2$] and amide (δ 4.56, $HOCH_2$) in an approximate ratio of 1:1.

**General Procedure for the Synthesis of 2,4,5-Trichlorophenyl *N*-(3 or 4)-[[4-[[[($N^{\alpha}$-Fmoc-amino)acyl]oxy]methyl]phenoxy]-*tert*-butylphenylsilyl]phenyl Pentanedioate Monoamides (Fmoc-AA-Pbs) (16).** A solution of 1 (0.90 g, 1.34 mmol), the Fmoc-amino acid (2.68 mmol), and *N,N*-dimethylformamide dineopentyl acetal (15) (0.62 g, 2.68 mmol) in $CH_2Cl_2$ (75 mL) was stirred for 3 days. The solvent was then removed and replaced with ethyl acetate–diethyl ether (1:1) (75 mL), and the organic solution was washed with pH 9.5 carbonate buffer (3 × 75 mL) and saturated NaCl (3 × 75 mL) and dried ($MgSO_4$). Concentration gave oils that contained the desired product and unreacted Pbs handle 1. The title preformed handles were isolated[49] after silica gel chromatography with ethyl acetate–hexane as the eluant.

**2,4,5-Trichlorophenyl *N*-(3 or 4)-[[4-[[($N^{\alpha}$-Fmoc-valyl)oxy]methyl]phenoxy]-*tert*-butylphenylsilyl]phenyl Pentanedioate Monoamide (16a).** The title compound was isolated in 51% yield as an oil after silica gel chromatography [eluant ethyl acetate–hexane (1:3)] [$R_f$(B) 0.52]: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 2,4,5-trichlorophenolate), 7.28 (s, 2,4,5-trichlorophenolate), 7.26–7.86 (m, aromatic including the defined singlets at 7.28 and 7.54), 7.09 (d, $J$ = 8.5 Hz, 2 H, *p*-phenolate), 6.73 (d, $J$ = 8.5 Hz, 2 H, *o*-phenolate), 5.03 (d, $J$ = 4.1 Hz, 2 H, $OCH_2C_6H_4$), 4.37 (d, $J$ = 7.3 Hz, 2 H, fluorenyl $CHCH_2O$), 4.21–4.31 (m, 2 H, α-$CH$ overlapping with fluorenyl $CHCH_2O$), 2.74 (t, $J$ = 7.1 Hz, 2 H), 2.48 (t, $J$ = 6.9 Hz, 2 H), 2.18 [br q, $J$ = 7.0 Hz, 3 H, $CH_2CH_2CH_2$ overlapping with valyl $CH(CH_3)_2$], 1.08 (s, 9 H, *tert*-butyl); high-resolution FAB MS calcd for $C_{54}H_{53}Cl_3N_2O_8Si$ $(M + Na)^+$ 1013.2534, found 1013.2549.

**2,4,5-Trichlorophenyl *N*-(3 or 4)-[[4-[[($N^{\alpha}$-Fmoc-glycyl)oxy]methyl]phenoxy]-*tert*-butylphenylsilyl]phenyl Pentanedioate Monoamide (16b).** The title compound was isolated in 16% yield after silica gel chromatography [eluant ethyl acetate–hexane (3:7)] [$R_f$(B) 0.38]: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 2,4,5-trichlorophenolate), 7.28 (s, 2,4,5-trichlorophenolate), 7.26–7.85 (m, aromatic including the defined singlets at 7.28 and 7.54), 7.08 (d, $J$ = 8.6 Hz, 2 H, *p*-phenolate), 6.73 (d, $J$ = 8.6 Hz, 2 H, *o*-phenolate), 5.04 (s, 2 H, $OCH_2C_6H_4$), 4.37 (d, $J$ = 7.1 Hz, 2 H, fluorenyl $CHCH_2O$), 4.22 (t, $J$ = 7.1 Hz, 1 H, fluorenyl $CHCH_2O$), 3.97 (d, $J$ = 5.6 Hz, 2 H, α-$CH_2$), 2.73 (t, $J$ = 7.1 Hz, 2 H), 2.48 (t, $J$ = 7.1 Hz, 2 H), 2.18 (br q, $J$ = 7.0 Hz, 2 H, $CH_2CH_2CH_2$), 1.08 (s, 9 H, *tert*-butyl); high-resolution FAB MS calcd for $C_{51}H_{47}Cl_3N_2O_8Si$ $(M + Na)^+$ 971.2065, found 971.2086.

**2,4,5-Trichlorophenyl *N*-(3 or 4)-[[4-[[($N^{\alpha}$-Fmoc-methionyl)oxy]methyl]phenoxy]-*tert*-butylphenylsilyl]phenyl Pentanedioate Monoamide (16c).** The title compound was isolated in 40% yield as an oil after silica gel chromatography [eluant ethyl acetate–hexane (3:7)] [$R_f$(B) 0.43]: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 2,4,5-trichlorophenolate), 7.28 (s, 2,4,5-trichlorophenolate), 7.26–7.86 (m, aromatic including the defined singlets at 7.28 and 7.54), 7.08 (d, $J$ = 8.4 Hz, 2 H, *p*-phenolate), 6.72 (d, $J$ = 8.4 Hz, 2 H, *o*-phenolate), 5.04 (d, $J$ = 4.3 Hz, 2 H, $OCH_2C_6H_4$), 4.43–4.48 (m, 1 H, α-$CH$), 4.38 (d, $J$ = 6.8 Hz, 2 H, fluorenyl $CHCH_2O$), 4.20 (br t, $J \approx$ 6.5 Hz, 1 H, fluorenyl $CHCH_2O$), 2.74 (t, $J$ = 7.1 Hz, 2 H), 2.39–2.51 [(2.48, t, $J$ = 7.1 Hz) overlapping with a multiplet, total 4 H], 2.16 (br q, $J$ = 6.9 Hz, 2 H, $CH_2CH_2CH_2$), 2.00 (s, 3 H, $SCH_3$), 1.08 (s, 9 H, *tert*-butyl); high-resolution FAB MS calcd for $C_{54}H_{53}Cl_3N_2O_8SSi$: $(M + Na)^+$ 1045.2255, found 1045.2241.

**General Procedure for Loading Preformed Pbs Handles onto Amino Group Containing Supports.** The appropriate Fmoc-AA-OPbs 16 (3 equiv) and HOBt (3 equiv) were dissolved in the minimal amount of DMF, furnishing an ≈0.1 M solution, which was added to the resin (1 equiv of free amino groups). This was following by DMAP (0.5 equiv), and the reaction mixture was shaken for 2 h. The resin was then washed with DMF (3×) and treated with acetic anhydride (3 equiv) and HOBt (3 equiv), both ≈0.1 M in DMF, for 1 h to cap unreacted amino groups. The resin was further washed with DMF, and an aliquot was shown to be negative to the ninhydrin test.[33]

**General Procedure for Fluoridolytic Cleavage of Peptidyl-Pbs-Resins.** The peptide-resin (1 equiv of peptide based on amino acid analysis) was treated with a solution of tetrabutylammonium fluoride trihydrate (1 equiv), thiophenol (1.2 equiv), and [for protected peptides] DIEA (0.5 equiv) in DMF (1 mL used per 100 mg of resin). After 2 min, the DMF solution was expressed under positive nitrogen pressure into a vessel containing both Dowex 50 × 8-400 strongly acidic cation-exchange resin (2 equiv) and Dowex 1 × 8-400 (hydroxide form) resin (2 equiv). Two further DMF washes of equal volume were also expressed into the mixed resin bed. After treatment for a total of 5 min, the resins were removed by filtration through a plug of glass wool. The DMF was removed at 2 mm and 35 °C, and the resultant residues were triturated with diethyl ether (3 × 5 mL, for 50-μmol scale of peptide). Afterwards, the products were often solids, and could be taken up in aqueous media for lyophilization.

**Racemization Test: L-Alanyl-L-valine.** Preformed Fmoc-Val-OPbs **16a** was loaded onto a Phe-aminomethyl-resin (50 mg, 9.5 μmol of Phe) by the general procedure already stated. One deprotection/coupling cycle (Table II) was carried out to incorporate Fmoc-alanine, the Fmoc group was removed, and the general fluoridolysis procedure (without scavengers) was performed. The oil obtained after evaporation of DMF was taken up in pH 2.2 sodium citrate buffer and injected onto the 9-mm column of the amino acid analyzer. The chromatogram developed at 75 °C with pH 3.49 sodium citrate buffer showed only L-alanyl-L-valine (106 min; under these conditions L-alanyl-D-valine elutes at 100 min) (sensitivity limit 0.05%).

**Loading and Cleavage of Asparagine with Pbs-Resin.** Handle 1 (310 mg, 0.411 mmol), HOBt (63 mg, 0.41 mmol), and leucylaminomethyl-resin (0.62 mmol of Leu/g) (221 mg, 0.14 mmol Leu) were shaken overnight in DMF (4 mL). The resin was then washed with DMF (6 × 3 mL) and found to be slightly ninhydrin positive. A solution of Fmoc-asparagine (146 mg, 0.411 mmol) and HOBt (63 mg, 0.41 mmol) in DMF (2 mL) was added to the resin, followed 5 min later by a solution of DCC (85 mg, 0.41 mmol) in DMF (1 mL). This coupling was carried out for 3 × 2 h, after which amino acid analysis of a hydrolyzed sample of resin showed the asparagine loading to be only 0.046 mmol of Asn/g (7%). The coupling was then carried out additionally for 3 × 2 h, except that DMAP (5.0 mg, 0.041 mmol) was present along with DCC and HOBt. The final loading was 0.32 mmol of Asn/g, but considerable β-cyanoalanine had formed. This was shown by taking a sample of resin (14 mg), removing Fmoc, and treating with TFA/$CH_2Cl_2$/dimethyl sulfide (5:4:1) for 1 h. After removal of the solvents, the residue was expressed on the 6-mm column of a standard amino acid analyzer. The ratio of β-cyanoalanine (retention 23 min) to asparagine (retention 28 min) was found to be ≈3:2.

The Asn-Pbs-Leu-resin (23 mg, 7.5 μmol) obtained as just described was treated according to the general fluoridolysis conditions. The precipitate obtained after diethyl ether trituration

(49) When this procedure was carried out for Fmoc-Asn and Fmoc-Phe, the resultant preformed handle products were not soluble. Consequently, the desired products could not be isolated.

was taken up in pH 2.2 citrate buffer and injected onto the 6-mm column of the amino acid analyzer to reveal only asparagine and β-cyanoalanine in the 3:2 ratio seen earlier. No α-aminosuccinimide (retention 69 min; authentic standard made by the procedure of Sondheimer and Holley[38a]) was observed.

**Methionine-Enkephalin (H-Tyr-Gly-Gly-Phe-Met-OH).** Preformed Fmoc-Met-OPbs **16c** was loaded onto a leucyl-MBHA resin (186 mg, 78 μmol Leu) by the general procedure already stated; amino acid analysis of the resin showed 0.32 mmol of Met/g (77%). The appropriate Fmoc-amino acids were introduced by the general protocol (Table II), and all couplings were found to be ninhydrin negative after 60 min. After the final coupling of Fmoc-Tyr(*t*-Bu)-OH and Fmoc deprotection, a portion of the peptide-resin (150 mg) was cleaved (93% cleavage yield) by the general fluoridolysis procedure already stated. The resultant material was treated with $TFA/CH_2Cl_2$/dimethyl sulfide (5:4:1) (2 mL) for 30 min to remove the *tert*-butyl protection of the tyrosine phenolic hydroxyl. Solvents were evaporated to provide an oil, which was again washed with diethyl ether (3 × 3 mL). A light tan solid remained, which was taken up in water and lyophilized to yield a white solid (33.9 mg); amino acid analysis: Gly, 1.79; Met, 0.7; Tyr, 1.00; Phe, 1.00. HPLC analysis [C-18 column; eluant 0.01 N aqueous $HCl-CH_3CN$ (3:1), flow 0.9 mL/min; detection 210 nm] revealed desired product ($t_R$ 12.6 min) and the corresponding sulfoxide ($t_R$ 8.2 min), in a ration of ≈3:1. Fluoridolytic cleavage in the absence of scavengers gave additional peaks ($t_R$ 10.7 min, ≈15%; $t_R$ 19.3 min ≈20%). Cleavage of peptide-resin (24 mg) with $TFA/CH_2Cl_2$/dimethyl sulfide (5:4:1) containing thiophenol (1.2 μL, 12 μmol), 30 min, gave a white solid (4.5 mg, cleavage yield >99% by amino acid analysis of cleaved resin) that was methionine-enkephalin and the corresponding sulfoxide in a ratio of ≈3:1, with no other products present.

Methionine-enkephalin and the corresponding sulfoxide were each obtained in pure form from the same preparative MPLC run and matched authentic standards from this laboratory.[6d,44] Methionine-enkephalin FAB MS, *m/e* (relative intensity), positive 574 ($MH^+$, 21), 185 (43), 136 (48), 120 (100); negative 572 [$(M - H)^-$, 100], 557 [$(M - CH_3)^-$, 20], 153 (64), 127 (50); methionine enkephalin sulfoxide FAB MS, *m/e* (relative intensity), positive: 590 ($MH^+$, 18), 185 (100), 136 (40), 120 (82); negative 588 [$(M - H)^-$, 42], 573 [$(M - CH_3)^-$, 14], 183 (100), 127 (55).

**Fmoc-Glu(*O*-*t*-Bu)-Ala-Tyr(*t*-Bu)-Gly-OH.** Preformed Fmoc-Gly-OPbs **16b** was loaded onto a leucyl-MBHA resin (200 mg, 84 μmol of Leu) by the general procedure; amino acid analysis of the resin showed 0.28 mmol of Gly/g (67%). Chain assembly was performed by the general protocol (Table II), and all couplings were ninhydrin negative after 60 min. A sample of resin (34.4 mg) was cleaved by the general procedure (both thiophenol and DIEA were added as scavengers) (cleavage yield 90%) to give a solid, which was dissolved in $CH_3CN$–water (3:1) and lyophilized. A light tan powder resulted (9.9 mg); amino acid analysis: Glu, 0.93; Gly, 1.00; Ala, 0.95; Tyr, 0.94. HPLC analysis [C-18 column; linear gradient taken from 0.01% aqueous $HCl-CH_3CN$ (9:1) to neat $CH_3CN$ over 40 min, flow 1.5 mL/min; detection 210 nm] of the crude peptide showed one large peak eluting at 23.5 min with small contaminants eluting at 17.6 (≈10%) and 19.3 min (<1%). The peptide was purified by MPLC (≈6 mg crude peptide), eluting with $CH_3CN$/0.01 N HCl (5:95) (flowrate ≈1.75 mL/min) for ≈15 min to elute the polar impurities, followed by a gradient to neat $CH_3CN$ over ≈6 h. The fractions containing the 23.5 min (HPLC) product were pooled and lyophilized to yield 1.7 mg of a white powder; amino acid analysis: Glu, 0.79; Gly, 1.00; Ala, 0.96; Tyr, 0.95; FAB MS, *m/e* (relative intensity), positive 773 ($MH^+$, 10), 423 {[Fmoc-Glu(*O*-*t*-Bu)-(CO)NH]$^+$, 10}, 179 [(fluorenyl-$CHCH_2$)$^+$, 100]; negative 807 [$(M + Cl)^-$, 8], 771 ($M^-$, 15), 715 [$(M - t\text{-Bu})^-$, 6], 549 [$(M - \text{Fmoc})^-$, 51], 107 (100). The impurities were also collected (the 17.6- and 19.3-min impurities eluted together off the MPLC column) and lyophilized to yield 0.7 mg (total recovery from MPLC was 40%) of a white powder; amino acid analysis: Glu, 1.00; Gly, 0.11; Ala, 2.94; Tyr, 0.90.

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**Supplementary Material Available:** Discussion and documentation of preliminary studies directed at the preparation and evaluation of the following classes of compounds: silyl esters cleaved by direct fluoridolysis of Si–O bond, 2-silylethyl esters fluoridolyzed by a β-elimination, and a model *p*-siloxybenzyl ester cleaved by a 1,6-elimination (5 pages). Ordering information is given on any current masthead page.

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# The MM2 Force Field for Silanes and Polysilanes[1]

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The MM2 force field has been extended so as to be able to deal with silanes, alkenyl derivatives of silanes, and polysilanes. Parameters have been chosen so that the available experimental structural and heat of formation data were fit as well as possible. The results are good and make possible molecular mechanics calculations on compounds of these classes.

## Introduction

The MM2 force field[1-3] has been extended to include silanes. A large volume of data (both experimental and ab initio) has appeared in the literature since our previous paper was published on silanes,[4] and most of these data have been taken into account in the development and parameterization of this new force field. An improvement in the MM2 force field that is important here was the introduction of the electronegativity correction for bond lengths.[5] Since silicon is electropositive with respect to carbon, when a silicon atom is attached to a $C_{sp^3}$–$C_{sp^3}$ bond, it causes the bond to stretch out. This elongation of a $C_{sp^3}$–$C_{sp^3}$ bond due to an attached silicon atom has been

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(1) Most of the material in this paper was taken from the dissertation submitted by Manton R. Frierson to the University of Georgia in partial fulfillment of the requirements for the Ph.D. degree, March 1984.

(2) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982.

(3) The MM2 force field for hydrocarbons was first described by Allinger: Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Extensions to functionalized molecules and all other sorts of special problems have been described in subsequent papers, which are summarized in ref 2. The original version of the program (MM2(77)) is available from the Quantum Chemistry Program Exchange, University of Indiana, Bloomington, IN 47405, Program 395. The latest version of the MM2 program, which is referred to as MM2(85), is available from the Quantum Chemistry Program Exchange, and also from Molecular Design Limited, 2132 Farallon Drive, San Leandro, CA 94577.

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