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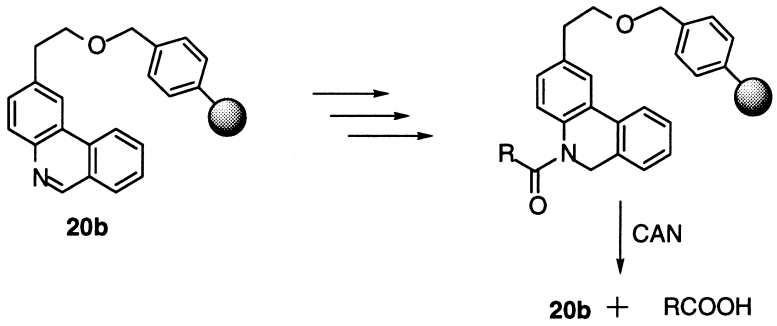

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New Phenanthridine Linkers for the Solid-Phase Synthesis of Acid-Containing Compounds

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Two novel, reusable phenanthridine linkers that use cerium ammonium nitrate as a cleavage reagent are described. These linkers are based on a disubstituted amide and are designed for the release of carboxylic acids but tolerate exposure to acidic, basic, and reductive reaction conditions. Application of these linkers to solid-phase organic synthesis affords products in excellent yields and high purities.

Introduction

Intensive research efforts have focused on the use of the combinatorial approach for the discovery of new compounds with desired properties.[1−6] The successful preparation of a combinatorial library of a class of compounds depends on the availability of suitable linkers and high-yielding strategies for synthesizing the compounds on solid supports.[7,8] To support the need for a variety of chemistries on solid phase, there is a great deal of interest in developing new linkers, which are stable during the solid-phase synthesis process and yet readily cleavable under mild conditions.[9−13]

The solid-phase synthesis of carboxylic acid containing structures is important to various fields of organic and medicinal chemistry because they are both valuable synthetic intermediates and often interesting target molecules.[14−22] Therefore, in almost all solid-phase peptide synthesis efforts and in a majority of small-molecule solid-phase synthesis approaches, the compound is linked to the solid support through the carboxylic acid functionality.[23−30] Although many linkers for the immobilization of carboxylic acids have been developed in recent years,[31−33] only the phenanthridine linker survives acid, base, reduction, and N-alkylation.[34] Following our initial success with the phenanthridine linker, we have also investigated (i) linkers (**1**−**3**, Figure 1) assembled on different solid supports, (ii) oxidative efficiency and kinetics on resin by substituent effects, (iii) the cleavage purities of different linkers, and (iv) the recycling yields of regenerated linkers. These studies now allow a more general and optimal utilization of the phenanthridine linkers (**1**−**3**).

The present paper provides details on the design of phenanthridine linkers (**1**−**3**) and execution of two approaches for anchoring them in solid-phase synthesis. Each of these phenanthridine linker derivatives (**1**−**3**) is a bifunctional spacer, which on one end contains a site for linkage to the first residue and on the other end contains a site for attachment of the resin. Most importantly, linkers **2** and **3** can be cleaved cleanly under mild oxidative conditions and give rapid cleavage kinetics (>95% purity in 5 min). Thus, these oxidatively removable linkers are applicable to orthogonal schemes, with use of either the base-labile or acid-labile protecting groups. These linkers are also suitable for the preparation of N- or O-alkylated compounds.

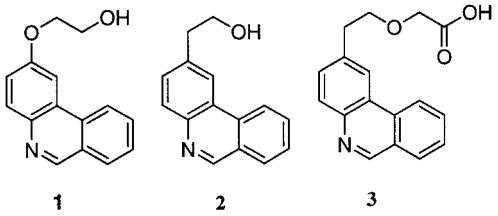

Figure 1.

Results and Discussion

Linker Design Strategy. Initial design efforts were directed toward linkers with various pendent chains attached to the phenanthridine moiety. On the basis of the mechanism for oxidative cleavage of the acylated phenanthridine linker, it was first anticipated that the introduction of a *p*-alkoxy group into an arylamide would increase the reactivity because of the electron-donating assistance of the alkoxy group during the oxidative cleavage. Unfortunately, the activated linker **1** was partially cleaved from the solid support under oxidative cleavage conditions. Accordingly, the alkoxy group in the phenanthridine linker **1** was changed to an alkyl group to obtain linker **2**. To extend the utility of the phenanthridine linker, a handle was introduced onto linker **2** using a carboxyl group. This handle could be used to link the resulting phenanthridine linker **3** to hydroxy- or amino-functionalized resins.

Preparation of Phenanthridine Linkers (1−3). Elaboration of the 4-aminophenol (**4**) to the desired linker **1** proceeded in seven steps (Scheme 1). Selective acylation of the amino group in 4-aminophenol with 2-iodobenzoic acid was accomplished using 1,3-diisopropylcarbodiimide (DIC) in THF. Treatment of phenol **5** in THF with ethyl bromoacetate and potassium carbonate at room temperature provided the alkylated product **6** in 91% yield. Attempts to perform a palladium-assisted internal biaryl cyclization of the amide **6** gave an undesired intermolecular coupling dimer.

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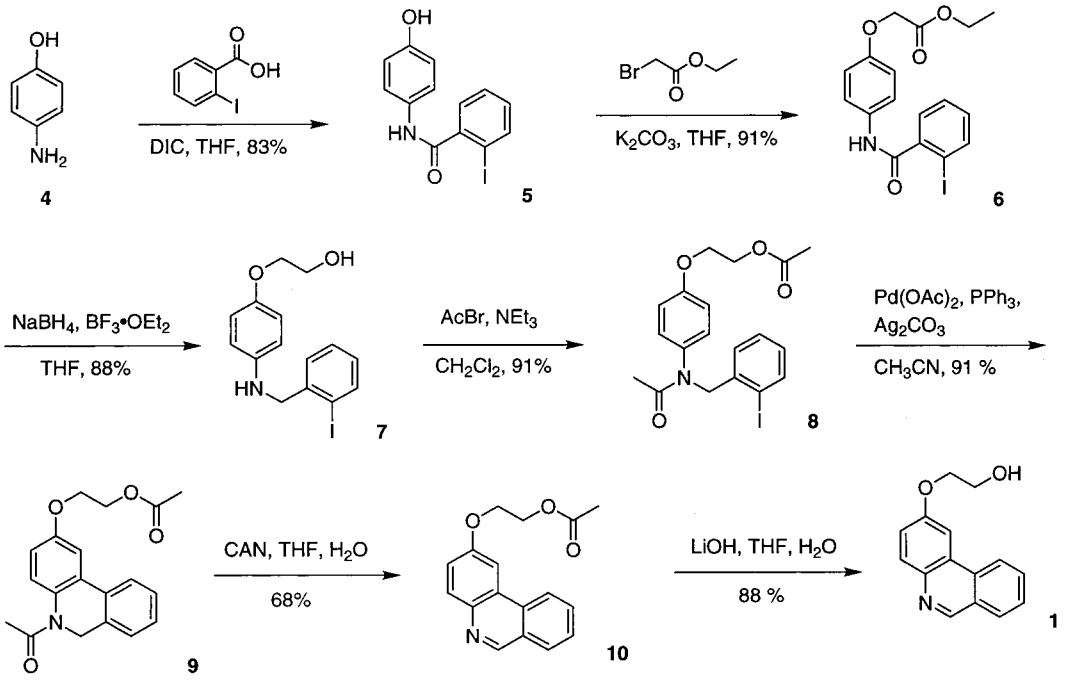
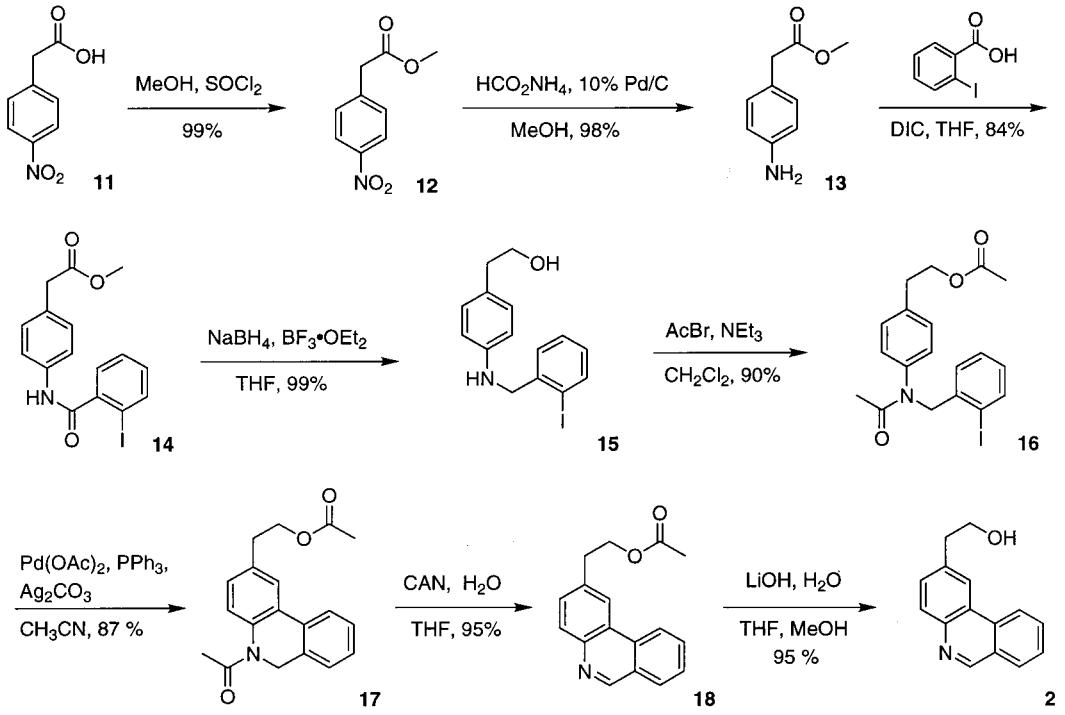
Scheme 1



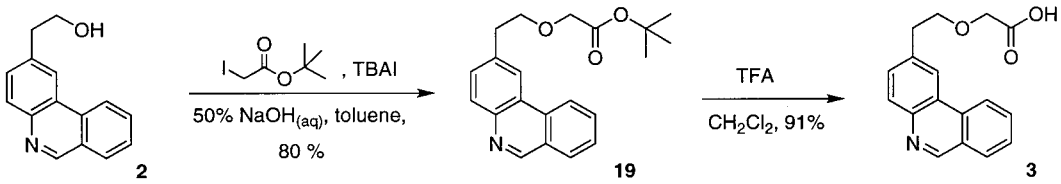
Scheme 2



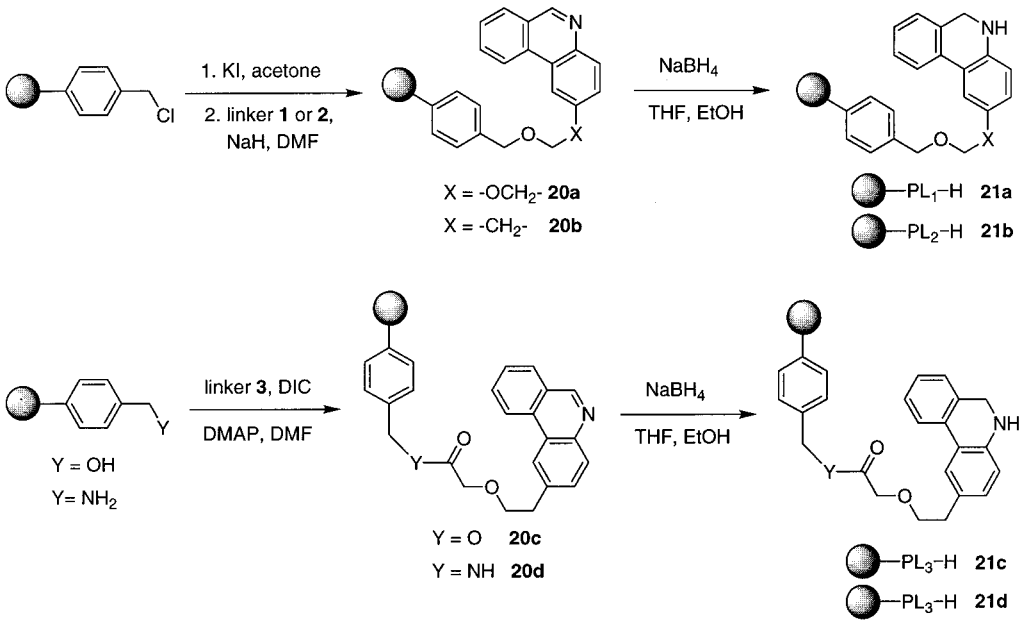
Failure of compound **6** to cyclize was attributed to the formation of a palladium complex with the amide of the benzamide unit (**6**) rather than the diaryl complex that would be expected to lead to the formation of desired product. Therefore, it was necessary to block the N−H function by reduction of the amide **6**, followed by acylation of the amino and hydroxy group of the resulting product **7**. Intramolecular Heck type cyclization of the amide **8**, employing $Pd(OAc)_2$, Ph_3P, and Ag_2CO_3 in CH_3CN, afforded the desired compound **9** in 91% yield.[35] Oxidative cleavage of the coupling product **9** with cerium ammonium nitrate (CAN) and subsequent hydrolysis of the acetate with LiOH in THF/H_2O provided the amine-masked phenanthridine linker **1**.

The synthesis of linker **2** (Scheme 2) began with protection of the acid group of 4-nitrophenylacetic acid (**11**) as its methyl ester (**12**). Reduction of the nitro group of the ester **12** was rapidly achieved by catalytic transfer hydrogenation with HCO_2NH_4 as the hydrogen donor over a Pd/C catalyst.[36] Coupling of the resulting amine **13** with 2-iodobenzoic acid using conventional conditions gave compound **14** in 84% yield. As shown in Schemes 1 and 2, treatment of amide **14** under conditions similar to those described for amide **6**

Scheme 3



Scheme 4



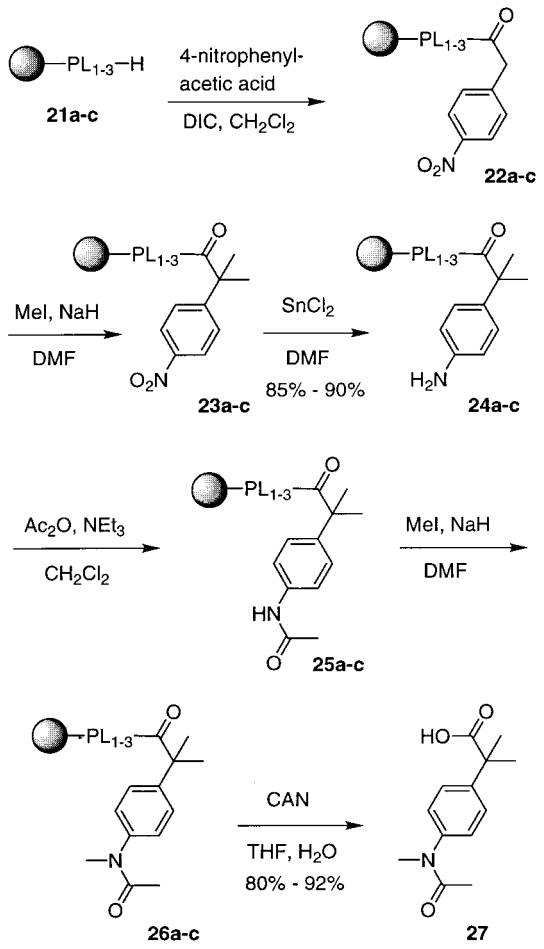
resulted in the formation of phenanthridine linker **2** in roughly 40% overall yield from 4-nitrophenylacetic acid.

Because the results obtained with linker **2** were encouraging, we proceeded to synthesize the analogous linker **3** (Scheme 3). Synthetic problems were encountered with the alkylation step designed to introduce a terminal carboxyl group for attachment to the solid support. The alkylation of linker **2** with bromoacetic acid using KOH in THF/H_2O at various temperatures failed to give the desired product. This result suggested the need to use a carboxylic acid protected haloacetic acid such as *tert*-butyl iodoacetate as the alkylating agent. However, treatment of linker **2** with *tert*-butyl iodoacetate under standard conditions (NaH, THF, or DMF) at room temperature afforded an acylated product instead of the desired alkylated compound. Finally, the carboxyl functionality needed for attachment to hydroxy- or amino-functionalized resins was provided by reaction of linker **2** with *tert*-butyl iodoacetate and 50% NaOH in the presence of a phase-transfer catalyst tetrabutylammonium iodide (TBAI).[37] Linker **3** was isolated as a crystalline compound after trifluoroacetic acid deprotection.

Loading of Resins with Linkers. As outlined in Scheme 4, linkers **1**−**3** were successfully anchored onto different polystyrene-based resins. Linkers **1** and **2** were attached to Merrifield resins (CM-PS) via each of the hydroxyl groups with the aid of sodium hydride in *N*,*N*-dimethylformamide (DMF) to afford compounds **20a** and **20b**, respectively. Linker **3** was loaded onto hydroxymethylpolystyrene (HM-PS) resin using conventional ester coupling conditions or onto aminomethyl polystyrene (AM-PS) resin using DIC and 1-hydroxybenzotriazole (HOBt), obtaining ester-linked or amide-linked derivatives **20c** or **20d**, respectively. Reduction of these functionalized resins (**20a**−**d**), afforded the resin-bound secondary amines (**21a**−**d**), which could be used to anchor the carboxylic acid for combinatorial solid-phase synthesis. To ensure complete reduction, initial experiments to reduce these amine-masked linkers (**20a**−**d**) involved reaction with $NaBH_4$, using EtOH as solvent for 3 h in the presence of BH_3·THF. Since the ester group of linker **20c** was cleaved under BH_3·THF reduction conditions, we tested various reduction conditions and found that $NaBH_4$ in THF and EtOH gave satisfactory results for all linkers. The loading of each linker was estimated through its (fluorenylmethoxy)-carbonyl (Fmoc) protection, deprotection with 20% piperidine/DMF, and UV−Fmoc quantitation.[38−40] The results (about 70−80% loading) were consistent with the expected weight gain.

Solid-Phase Synthesis with the Phenanthridine Linkers. Having established facile synthetic routes to tether linkers **1**−**3** to solid supports, we proceeded to investigate the scope and limitations of compounds **21a**−**c** and to select the best supported linker by two model syntheses. As shown in Scheme 5, the supported linkers are indicated with a generic linkage and the outcome of the significant experiments is reported in Table 1. In the first case, the supported compounds **21a**−**c** were used to synthesize a trimethylated derivative of actarit,[41] an immunomodulating agent (Scheme 5). Each of the three supported reagents **21a**−**c** was first derivatized with 4-nitrophenylacetic acid and then subjected to enolate alkylation, employing commonly used bases such

Scheme 5



as NaH or KH. The complete alkylation could also be accomplished using a strong base such as LDA at −78 °C when supported reagents **21a,b** were used.[42] Our first attempt to reduce the aromatic nitro group utilized conditions reported by Pavia and Goff using an aqueous 2 M $SnCl_2$ solution in DMF.[43,44] However, the reduction of resin-bound compound **23b** gave a mixture with low loading (<40% yield) estimated by UV−Fmoc quantitation. After the evaluation of several reducing reagents ($SnCl_2$, Na_2S, $Na_2S_2O_4$) and conditions, the aromatic nitro group could be fully reduced with $SnCl_2$ in oxygen-free DMF under an argon atmosphere. The resulting amines **24a**−**c** were then subjected to acetylation and N-alkylation to afford the trimethylated acid-bound resins **26a**−**c**, respectively. Treatment of each of the resulting resins with 1.2 equiv of CAN in THF and water resulted in complete cleavage of the desired acid **27** from the solid supports. After purification, the trimethylated actarit derivative **27** was isolated in 45−66% overall yield for eight steps (Table 1).

Next, the utility of these linkers was demonstrated by synthesizing an N-acylated dipeptide **33** (Scheme 6). The immobilized phenanthridine linkers **21a**−**c** were elaborated to afford the Boc-protected intermediates **30a**−**c**, via N-acylation with Fmoc-L-Ala-OH activated as its carbodiimide ester and coupling of the Fmoc-liberated amines **29a**−**c** with Boc-L-Phe-OH in the presence of 2-(1*H*-benzotriazo-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU).[45] Removal of the *tert*-butyloxycarbonyl protecting group in compounds **30a**−**c** by trifluoroacetic acid, and subsequent treatment with benzoyl chloride in the presence of *N*,*N*-diisopropylethylamine (DIPEA), afforded the dipeptide-bound resins **32a**−**c**. At each step, an aliquot of the resin was monitored by photometric Fmoc determination or the ninhydrin method to ensure the efficiency of the synthetic procedure.[38−40] After oxidative cleavage from resins **32a**−**c**, each sample of crude product was purified to give dipeptide **33** in 52−76% overall yield from chloromethylpolystyrene (CM-PS) or hydroxymethylpolystyrene (HM-PS) (Table 1).

Table 1. Performance Evaluation of Two Model Syntheses Using Phenanthridine Linkers **1**−**3**

entry	linker	resin	cleavage product	product purity, %[a]	product yield,[b] %	resin yield (first),[c] %	resin yield (second),[d] %
1	**1**	CM-PS	**27**	76	45	78	
2	**2**	CM-PS	**27**	95	62	90	84
3	**3**	HM-PS	**27**	95	66	91	83
4	**1**	CM-PS	**33**	75	52	76	
5	**2**	CM-PS	**33**	99	73	90	
6	**3**	HM-PS	**33**	99	76	92	

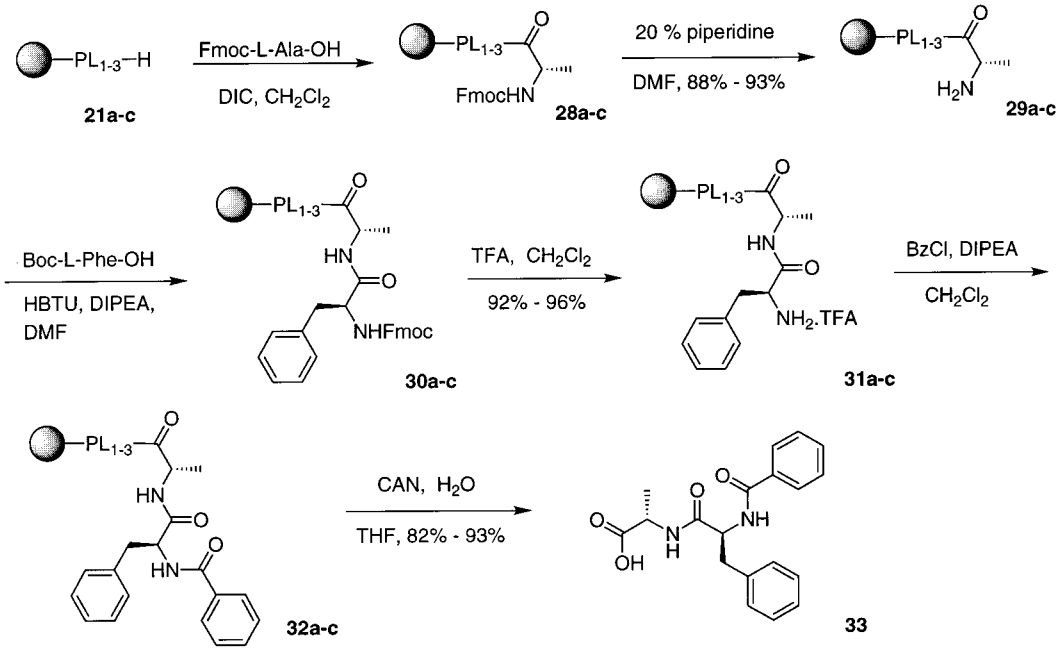
[a] Crude product purity. [b] Pure isolated product overall yield. [c] Yield of resin after one recycle. [d] Yield of resin after two recycles.

Characterization of the Phenanthridine Linkers. The amine-masked phenanthridine resins **20a**−**d** appeared to be indefinitely stable when stored at room temperature. Therefore, linker-bound resins should be kept in this form before they are derivatized with carboxylic acids.

The stability of phenanthridine linker-anchored resins **22a**,**b** was also examined under a variety of conditions. Resins **22a**,**b** were very rapidly cleaved with CAN in CH_3CN. However, we found that about 20% of linker **1** was also cleaved from resin **22a**, affording low product purity. Therefore, we turned our attention to kinetic studies of resin **22b**, and the rate of oxidative cleavage was measured using various equivalents of CAN in CH_3CN or THF. The best cleavage results were obtained in excellent yield (93%) and high purity (98%), employing only 1.2 equiv of CAN in THF/H_2O for a 5 min time period. Longer reaction times for oxidative cleavage of resin **22b** failed to release additional 4-nitrophenylacetic acid from the resin. None of linker **2** was cleaved from the solid support. Gratifyingly, when exposed to Fmoc deprotection conditions (50% piperidine in CH_2Cl_2 for 3 h) or Boc deprotection conditions (50% TFA in CH_2Cl_2 for 3 h), no loss of acid or linker from resin **22b** was detected. The reaction time chosen represents at least 20 deprotection cycles in the peptide synthesis, so linker **2** should be suitable for the synthesis of large peptides using Fmoc or Boc chemistries.

Resin **22b** was also stable upon treatment with 1 M HCl or NaOH in THF/H_2O solution for 24 h. No racemization was detected during either attachment or oxidative removal of the amino acid derivative **33** (Scheme 6) by HPLC and ^{1}H NMR analysis. As seen from Table 1, the yields of resins **20b**−**c** after one and two cycles are excellent and can be reused at least two times. It is also noteworthy that the cleavage reactions in both model syntheses proceeded cleanly

Scheme 6



and that the purity of each product (**27** and **33**) was greater than 95% when linker **2** or **3** was used.

Conclusions

We have successfully demonstrated the use of phenanthridine linkers **2** and **3** for the immobilization of carboxylic acids for solid-phase organic synthesis. These linkers were synthesized from an inexpensive, commercially available compound and can be prepared on a preparative scale in roughly 40% overall yield. The linker-derivatized resins **21b**−**d** can also be synthesized in two steps from different polymeric supports. Linker **2** is anchored to a C-terminal residue by a disubstituted amide and not an ester bond, ensuring stability to N-alkylation and avoidance of diketopiperazine formation at the dipeptide stage. Oxidative cleavage of linkers **2** and **3** occurs rapidly (∼5 min) under mild conditions (aqueous THF, room temperature), and compounds of high purity (95−99%) are obtained after a simple extraction and filtration protocol. While no linker can be stable to all conditions available to the synthetic chemist, the oxidative cleavage strategy promises to substantially increase the available options regardless of the long synthetic sequence of linkers **2** and **3**. These resins are also sufficiently robust to be recovered and recycled through the reaction sequence. Because oxidative cleavage is orthogonal to the Fmoc/Boc and Boc/Bn protecting group strategies, it is hoped that the phenanthridine linkers **2** and **3** will find broad application in the field of solid-phase combinatorial synthesis where tolerance to both strongly acidic and basic conditions is required.

Experimental Section

General. All solvents were reagent grade and distilled before use. Resins were obtained from Advanced ChemTech. All resins were dried by passing nitrogen through them for 20−30 min. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel (60 F 254) plates (0.25 mm). Visualization was effected with ultraviolet light or any of the following reagents: ninhydrin, phosphomolybdic acid, and anisaldehyde. Chromatography was carried out on Merck silica gel 60 (particle size 240−400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Brucker DRX-200 spectrometer. Chemical shifts were measured in parts per million (δ) relative to tetramethylsilane (TMS) or chloroform as the internal standard. Coupling constants (J values) are in hertz (Hz). Infrared spectra (IR) were obtained on a Bio-Rad FTS 155 spectrometer. Absorptions are reported in wavenumbers (cm^{-1}). The spectra taken were referenced to the 1601 cm^{-1} band of polystyrene, and only the most prominent or characteristic absorptions are noted. Optical rotations (in degrees) were recorded on a Perkin-Elmer Model 343 polarimeter at the sodium D line. Concentrations were reported in g/100 mL. High-resolution mass spectra (HRMS) were obtained on JEOL SX-102A, using either ammonia chemical ionization (CI) or electron impact (EI).

***N*-(4-Hydroxyphenyl)-2-iodobenzamide (5).** 2-Iodobenzoic acid (1.00 g, 4.03 mmol) was dissolved in THF (27 mL) in a flame-dried flask equipped with a magnetic stirrer. To this stirred solution were added 1,3-diisopropylcarbodiimide (DIC) (0.758 mL, 4.84 mmol) and 4-aminophenol (0.880 g, 8.06 mmol) under an argon atmosphere. The reaction mixture was stirred for 2 h and then concentrated under reduced pressure. The resulting crude material was dissolved in cold EtOAc (40 mL). The reaction mixture was filtered, and the collected solid was washed with cold EtOAc (5 mL). The organic layer was washed with 5% HCl (15 mL), 5% $NaHCO_3$ (15 mL), and saturated NaCl (15 mL) solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography, eluting with EtOAc/hexane (35:65). Compound **5** (1.12 g, 83%) was obtained as a white solid. IR (neat): 3272, 1644, 1508, 1429, 1241 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.66−7.85 (m, 8H), 9.94 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 1103.83, 113.34, 120.31, 126.53, 126.70,

129.21, 137.95, 142.03, 152.56, 165.77. HRMS Calcd for $C_{13}H_{10}INO_2$ (M^+): 338.9756. Found: 338.9761.

[4-(2-Iodobenzoylamino)phenoxy]acetic Acid Methyl Ester (6). To benzamide **5** (2.90 g, 8.55 mmol), at ambient temperatures, was added THF (42 mL). Finely powdered K_2CO_3 (3.59 g, 25.533 mmol) was then added in portions, followed by the addition of ethyl bromoacetate (8.53 g, 51.1 mmol). After 24 h, the reaction mixture was filtered and the collected solid was rinsed with EtOAc. The filtrate was concentrated under reduced pressure and diluted with EtOAc (200 mL). The organic layer was washed with 5% HCl (30 mL), 5% $NaHCO_3$ (30 mL), and saturated NaCl (20 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by column chromatography eluting with acetone/dichloromethane (5:95). Pure compound **6** (3.44 g, 91%) was obtained as a white solid. IR (neat): 3253, 3056, 2983, 1752, 1644, 1516, 1200 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.28 (t, J = 7.0 Hz, 3H), 4.18 (q, J = 4.2 Hz, 2H), 4.59 (s, 2H), 6.9−7.89 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 14.15, 61.42, 65.67, 92.48, 115.10, 121.82, 128.23, 128.43, 131.34, 131.66, 139.90, 142.06, 154.86, 167.20, 168.90. HRMS Calcd for $C_{17}H_{16}O_4N$ (M^+): 425.0124. Found: 425.0107.

2-[4-(2-Iodobenylamino)phenoxy]ethanol (7). Compound **6** (1.00 g, 2.35 mmol) was dissolved in THF (8 mL) and treated with $NaBH_4$ (0.793 g, 21.17 mmol) at 0 °C. After 10 min, a solution of $BF_3{\cdot}OEt_2$ (3.6 mL, 28.22 mmol) was added dropwise. After being stirred for 0.5 h at 0 °C, the reaction mixture was then brought to 60 °C. The reaction mixture was stirred for 24 h and then concentrated under reduced pressure. The resulting crude material was dissolved in EtOAc (60 mL) and washed with saturated $NaHCO_3$ (20 mL) and saturated NaCl (15 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography, eluting with acetone/dichloromethane (3:97). Pure alcohol **7** (0.77 g, 88% yield) was obtained as a white solid. IR (neat): 3291, 2915, 1516, 1449, 1260 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.18 (br s, 1H), 3.88 (t, J = 3.4 Hz, 2H), 3.96 (t, J = 4.5 Hz, 2H), 4.24 (s, 2H), 6.51−7.85 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 53.91, 61.48, 69.93, 98.53, 114.15, 115.84, 128.31, 128.75, 128.83, 139.35, 141.01, 142.14, 151.13. HRMS Calcd for $C_{15}H_{16}O_2N$ (M^+): 369.0226. Found: 369.0237.

Acetic Acid 2-{4-[Acetyl-(2-iodobenzyl)amino]phenoxy}-ethyl Ester (8). To compound **7** (0.130 g, 0.352 mmol), in CH_2Cl_2 (1.8 mL) at 0 °C, were added triethylamine (0.122 mL, 0.88 mmol) and acetyl bromide (0.065 mL, 0.88 mmol). After being stirred for 0.5 h at 0 °C, the solution was brought to room temperature. The reaction mixture was stirred for 1.5 h and then filtered, and the collected solid was rinsed with EtOAc (15 mL). The organic layer was washed with 5% HCl (5 mL), 5% $NaHCO_3$ (5 mL), and saturated NaCl (5 mL) solutions. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by column chromatography eluting with EtOAc/hexane (40:60). Ester **8** (0.15 g, 91% yield) was obtained as a white solid. IR (neat): 3064, 2936, 1738, 1657, 1509, 1381, 1227 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.92 (s, 3H), 2.09 (s, 3H), 4.13 (t, J = 4.8 Hz, 2H), 4.34 (t, J = 4.5 Hz, 2H), 4.96 (s, 2H), 6.81−7.76 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 20.66, 22.38, 56.73, 62.39, 65.84, 99.15, 115.10, 128.16, 128.74, 129.03 129.41, 135.43, 139.14, 139.22, 157.66, 170.62, 170.61. HRMS Calcd for $C_{19}H_{20}INO_4$ (M^+): 453.0437. Found: 453.0434.

Acetic Acid 2-(5-Acetyl-5,6-dihydrophenanthridin-2-yloxy)ethyl Ester (9). To a solution of compound **8** (0.140 g, 0.299 mmol) in dry CH_3CN (30 mL) were added $Pd(OAc)_2$ (0.168 g, 0.0749 mmol), triphenylphosphine (0.393 g, 0.1498 mmol), and Ag_2CO_3 (0.165 g, 0.599 mmol). The solution was refluxed under an argon atmosphere for 1 h. The reaction mixture was cooled and then concentrated under reduced pressure. The resulting crude material was dissolved in EtOAc (60 mL) and filtered, and the collected solid was washed with cold EtOAc (5 mL). The organic layer was washed with saturated NaCl (15 mL) solution, dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by column chromatography eluting with EtOAc/hexane (1:1). Pure **9** (0.88 g, 91% yield) was obtained as a white solid. IR (neat): 3448, 2936, 1732, 1649, 1495, 1235 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.87 (s, 3H), 2.09 (s, 3H), 4.14 (t, J = 4.46 Hz, 2H), 4.40 (t, J = 45.0 Hz, 2H), 4.84 (s, 2H), 6.87−7.76 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 20.75, 21.92, 44.95, 62.58, 66.17, 110.29, 113.61, 123.20, 125.53, 126.13, 127.90, 128.14, 130.86, 131.49, 135.26, 135.62, 156.62, 169.35, 170.79. HRMS Calcd for $C_{19}H_{19}O_4N$ (M^+): 325.1314. Found: 325.1307.

Acetic Acid 2-(Phenanthridin-2-yloxy)ethyl Ester (10). Compound **9** (0.60 g, 1.844 mmol) was dissolved in THF/H_2O (4:1, 9.2 mL). To this solution was added CAN (2.0 g, 4.06 mmol) at room temperature. After 10 min, the reaction was concentrated in vacuo. The resulting solid was dissolved with EtOAc (80 mL) and washed with 5% NH_4OH (10 mL), 5% HCl (5 mL), 5% $NaHCO_3$ (10 mL), and saturated NaCl (10 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography eluting with acetone/dichloromethane (5:95). Compound **10** (0.352 g, 68% yield) was obtained as a white solid. IR (neat): 2929, 1732, 1611, 1443, 1219 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.11 (s, 3H), 4.28 (t, J = 5.0 Hz, 2H), 4.50 (t, J = 5.0 Hz, 2H), 7.27−8.08 (m, 7H), 9.07 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.83, 62.67, 66.19, 118.55, 121.71, 125.03, 126.37, 127.48, 128.57, 130.48, 131.46, 131.85, 139.83, 151.23, 157.21, 170.92. HRMS Calcd for $C_{17}H_{15}NO_3$ (M^+): 281.1052. Found: 281.1056.

2-(Phenanthridin-2-yloxy)ethanol (1). To a solution of compound **10** (0.352 g, 1.25 mmol) in THF (3.5 mL) was added, dropwise, a cold lithium hydroxide solution (2.8 mL, 7.5 mmol) over a 5 min period. Stirring was continued for 6 h at ambient temperature. The solution was acidified to pH 7 with 10% HCl. After this time, the solution was concentrated to half its volume and washed with EtOAc (2 × 30 mL). The combined ethyl acetate layers were then washed with 5% HCl (5 mL), 5% $NaHCO_3$ (5 mL), and saturated NaCl (5 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude solid was purified by column chromatography, eluting with acetone/dichloromethane (20:80) to afford compound **1** (0.236 g) in 88% yield. IR (neat): 3332, 2929, 1611, 1449,

1227 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.85−3.10 (br s, 1H), 4.09−4.15 (t, J = 4.2 Hz, 2H), 4.28 (t, J = 4.0 Hz, 2H), 7.37−8.44 (m, 7H), 9.13 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 61.30, 69.73, 104.06, 118.60, 121.76, 125.12, 126.37, 127.53, 128.65, 130.57, 131.31, 131.93, 139.60, 151.13, 157.51. HRMS Calcd for $C_{15}H_{13}O_2N$ (M^+): 239.0946. Found: 239.0940.

(4-Nitrophenyl)acetic Acid Methyl Ester (12). To a solution of 4-nitrophenylacetic acid (6.0 g, 33.12 mmol) at 0 °C in MeOH (66 mL) was added thionyl chloride (2.54 mL, 34.78 mmol). The reaction mixture was brought to ambient temperature and stirred for 1.5 h. After this time, the reaction mixture was concentrated in vacuo. The resulting ester **12** (6.42 g, 99%) was used directly in the next step. IR (CH_2Cl_2): 3423, 2960, 1726, 1600, 1515, 1439, 1431, 1340 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.72 (s, 2H), 3.74 (s, 3H), 7.44−7.48 (d, 2H, J = 8.63 Hz), 8.16−8.21 (d, 2H, J = 8.68 Hz). ^{13}C NMR ($CDCl_3$): δ 40.75, 52.36, 123.72, 130.27, 141.21, 147.21, 170.55. HRMS Calcd for $C_9H_{11}NO_2$ (M^+): 195.0532. Found: 195.0531.

(4-Aminophenyl)acetic Acid Methyl Ester (13). To a solution of ester **12** (6.0 g, 30.74 mmol) in dried MeOH (60 mL) at 0 °C was added 10% Pd/C (1.5 g). The resulting mixture was stirred at 0 °C for 10 min, and anhydrous ammonium formate (9.692 g, 153.7 mmol) was added. After 20 min, the solution was filtered through Celite and concentrated. The resulting crude material was dissolved in EtOAc (300 mL). The ethyl acetate layer was washed with H_2O (50 mL) and saturated NaCl (15 mL) solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting ester **13** (4.98 g, 98%) was used directly in the next step. IR (CH_2Cl_2): 3453, 3367, 3010, 2950, 1725, 1624, 1435, 1260 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.49 (s, 2H), 3.59 (br s, 2H), 3.65 (s, 3H), 6.56−7.05 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 40.10, 51.74, 115.00, 123.40, 129.87, 145.40, 172.52. HRMS (EI) Calcd for $C_9H_{11}NO_2$ (M^+): 165.0790. Found: 165.0783.

[4-(2-Iodobenzoylamino)phenyl]acetic Acid Methyl Ester (14). According to the procedure used for the synthesis of compound **5**, starting from 4.24 g (25.67 mmol) of compound **13**, 7.00 g (28.234 mmol) of 2-iodobenzoic acid, 4.42 mL (28.234 mmol) of DIC, and 124 mL of THF, there was obtained 8.5 g (21.56 mmol, 84%) of ester **14**, as a white solid, after recrystallization (EtOAc). IR (CH_2Cl_2): 3278, 1725, 1652, 1516, 1322 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.60 (s, 2H), 3.66 (s, 3H), 7.06−7.88 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 40.52, 52.02, 92.37, 120.26, 128.19, 128.38, 129.85, 130.28, 131.34, 136.60, 139.87, 141.98, 167.25, 171.94. HRMS Calcd for $C_{16}H_{14}INO_3$ (M^+): 395.0018. Found: 395.0003.

2-[4-(2-Iodobenzylamino)phenyl]ethanol (15). According to the procedure used for the synthesis of compound **7**, starting from 4.36 g (11.03 mmol) of compound **14**, 5.43 g (143.43 mmol) of $NaBH_4$, 23.77 mL (187.56 mmol) of $BF_3 \cdot OEt_2$, and 27.6 mL of THF, there was obtained 3.86 g (10.92 mmol, 99%) of alcohol **15** as a white solid. IR (CH_2Cl_2): 3413, 3056, 2936, 1611, 1514 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.71 (t, 2H, J = 6.5 Hz), 3.74 (t, 2H, J = 6.4 Hz), 4.27 (s, 2H), 6.51−7.84 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 38.17, 53.26, 63.73, 98.44, 113.11, 127.29, 128.30, 128.66, 128.83, 129.74, 139.34, 140.88, 146.15. HRMS (EI) Calcd for $C_{15}H_{16}INO$ (M^+): 353.0277. Found: 353.0262.

Acetic Acid 2-{4-[Acetyl(2-iodobenzyl)amino]phenyl}-ethyl Ester (16). According to the procedure used for the synthesis of compound **8**, starting from 3.89 g (11.03 mmol) of compound **15**, 2.45 mL (33.10 mmol) of acetyl bromide, 4.60 mL (33.10 mmol) of Et_3N, and 56 mL of CH_2Cl_2, there was obtained 4.34 g (9.93 mmol, 90%) of ester **16** after flash chromatography (EtOAc/hexane 3:7). IR (CH_2Cl_2): 3056, 2950, 1725, 1671, 1516, 1376 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.88 (s, 3H), 2.02 (s, 3H), 2.92 (t, 2H, J = 6.9 Hz), 4.25 (t, 2H, J = 7.8 Hz), 4.97 (s, 2H), 6.88−7.76 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 20.89, 22.61, 34.47, 56.95, 64.43, 99.14, 128.03, 128.31, 128.87, 129.34, 129.96, 137.80, 139.30, 140.91, 170.61, 170.85. HRMS Calcd for $C_{19}H_{20}INO_3$ (M^+): 437.0488. Found: 437.0475.

Acetic Acid 2-(5-Acetyl-5,6-dihydrophenanthridin-2-yl)ethyl Ester (17). According to the procedure used for the synthesis of compound **9**, starting from 1.97 g (4.51 mmol) of compound **16**, 0.253 g (1.129 mmol) of $Pd(OAc)_2$, 0.592 g (2.257 mmol) of Ph_3P, and 90.3 mL of MeCN, there was obtained 1.22 g (3.93 mmol, 87%) of compound **17** as an oil after flash chromatography (acetone/CH_2Cl_2 1:9). IR (CH_2Cl_2): 3297, 2961, 2878, 1736, 1635, 1374 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.05 (s, 3H), 2.18 (s, 3H), 3.01 (t, 2H, J = 7.0 Hz), 4.34 (t, 2H, J = 7.0 Hz), 4.90 (s, 2H), 7.10−7.75 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 20.80, 22.5, 34.61, 44.81, 64.51, 123.07, 124.68, 126.01, 127.91, 128.02, 129.55, 131.51, 135.01, 135.76, 136.35, 169.17, 170.76. HRMS Calcd for $C_{19}H_{19}NO_3$ (M^+): 309.1365. Found: 309.1371.

Acetic Acid 2-(Phenanthridin-2-yl)ethyl Ester (18). According to the procedure used for the synthesis of compound **10**, starting from 1.40 g (4.51 mmol) of compound **15**, 3.71 g (6.77 mmol) of CAN, 4.5 mL of H_2O, and 18 mL of THF, there was obtained 1.14 g (4.29 mmol, 95%) of compound **18** as an oil after flash chromatography (EtOAc/hexane 45:55). IR (CH_2Cl_2): 2950, 1725, 1362, 1241 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.06 (s, 3H), 3.22 (t, 2H, J = 7.0 Hz), 4.44 (t, 2H, J = 7.0 Hz), 7.27−8.63 (m, 7H), 9.26 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.95, 35.33, 64.76, 121.72, 122.05, 123.99, 126.38, 127.48, 128.73, 129.71, 130.14, 130.92, 132.19, 136.77, 143.27, 153.16, 171.04. HRMS Calcd for $C_{17}H_{15}NO_2$ (M^+): 265.1103. Found: 265.1100.

2-(Phenanthridin-2-yl)ethanol (2). According to the procedure used for the synthesis of linker **1**, starting from 1.33 g (5.01 mmol) of compound **18**, 0.84 g (20.05 mmol) of LiOH, 5 mL of H_2O, 5 mL of MeOH, and 20 mL of THF, there was obtained 1.06 g (4.76 mmol, 95%) of linker **2**. IR (CH_2Cl_2): 3245, 2915, 1611, 1443, 1240 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.00 (t, 2H, J = 6.2 Hz), 3.97 (t, 2H, J = 6.3 Hz), 4.35 (br s, 1H, −OH), 7.37−8.20 (m, 7H), 8.77 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 39.53, 63.03, 121.36, 121.98, 123.44, 127.01, 128.26, 129.22, 130.54, 131.70, 138.15, 142.11, 152.20. HRMS Calcd for $C_{15}H_{13}NO$ (M^+): 223.0997. Found: 223.0994.

(2-Phenanthridine-2-yl-ethoxy)acetic Acid *tert*-Butyl Ester (19). To linker **2** (1.05 g, 4.72 mmol) at ambient temperatures were added toluene (23.6 mL) and TBAI (0.436

g, 1.18 mmol). A solution of 50% NaOH (23.6 mL) was then added in portions, followed by the addition of *tert*-butyl 2-iodoacetate (1.64 mL, 10.08 mmol). After 24 h, the solution was acidified to pH 7 with 10% HCl. After this time, the solution was concentrated to half its volume and washed with EtOAc (2 × 30 mL). The organic layer was washed with 5% $NaHCO_3$ (5 mL) and saturated NaCl (5 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by column chromatography, eluting with acetone/dichloromethane (5:95) to afford compound **19** (0.907 g) in 80% yield. IR (CH_2Cl_2): 2979, 2933, 1745, 1615, 1394, 1368, 1231, 1162, 1132, 755 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.46 (s, 9H), 3.19 (t, 2H, J = 6.8 Hz), 3.90 (t, 2H, J = 6.7 Hz), 3.99 (s, 2H), 7.59−8.61 (m, 7H), 9.20 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 28.059, 36.50, 68.93, 72.10, 81.62, 122.06, 122.18, 124.08, 126.20, 127.53, 128.88, 129.39, 130.06, 131.25, 132.55, 138.09, 142.35, 152.56, 169.63. HRMS Calcd for $C_{21}H_{23}NO_3$ (M^+): 337.1678. Found: 337.1680.

(2-Phenanthridine-2-yl-ethoxy)acetic Acid (3). Compound **19** (0.34 g, 1.01 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and treated with 30% TFA in CH_2Cl_2 (1.0 mL) solution. After 1.5 h, a solution of 5% HCl was added until the aqueous layer was pH 4−5. The aqueous layer was then extracted with CH_2Cl_2. The combined organic layers were washed with saturated NaCl (5 mL) solution, dried (Na_2SO_4), filtered, and concentrated to afford linker **3** (0.258 g, 0.918 mmol) in 91% yield. IR (CH_2Cl_2): 2914, 2849, 1734, 1670, 1200, 1134 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.15 (t, 2H, J = 6.5 Hz), 3.87 (t, 2H, J = 6.7 Hz), 4.08 (s, 2H), 7.73−8.91 (m, 7H), 9.46 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 35.42, 67.39, 70.85, 122.38, 122.61, 123.60, 125.54, 127.64, 128.12, 129.50, 130.52, 132.10, 132.33, 138.97, 140.35, 152.14, 171.69. HRMS Calcd for $C_{17}H_{15}NO_3$ (M^+): 281.1052. Found: 281.1056.

Resin-Bound Linkers 1 and 2 (20a,b). Each of the Merrifield resin (0.15 g, 0.158 mmol) was suspended in dry acetone (1 mL) and treated with KI (0.212 g, 1.26 mmol) under an argon atmosphere. The mixtures were agitated for 2 h at room temperature, flushed, and washed with DMF (2 mL × 2) and CH_2Cl_2 (2 mL × 2). Each of the resulting resin was then suspended in dry DMF (0.8 mL) and treated with linker **1** and **2** (0.473 mmol), respectively. After adding 60% NaH (0.019 g, 0.473 mmol) under an argon atmosphere, each of the mixtures was agitated for 24 h, filtered, and washed with DMF (2 mL × 2), MeOH (2 mL × 2), and CH_2Cl_2 (2 mL × 2) to afford the resin-bound linkers **1** and **2** (**20a**,**b**), respectively.

Resin-Bound Linkers 3 (20c−d). The hydroxymethyl resin and aminomethyl resin (100 mg, 0.16 mmol) were individually suspended in dry DMF (1.6 mL) and treated with linker **3** (0.135 g, 0.48 mmol), DIC (0.075 mL, 0.48 mmol), and DMAP (7.8 mg, 0.064 mmol) under an argon atmosphere. Each of the mixtures was agitated for 12 h at room temperature, flushed, and washed with DMF (2 mL × 2), MeOH (2 mL × 2), and CH_2Cl_2 (2 mL × 2). Each of the resulting resins was dried in vacuo to provide resin-bound linkers **3** (**20c** and **20d**).

General Procedure for Preparation of Resins 21a−d. To each of the resin-bound linkers **20a−d** (0.158 mmol) were added $NaBH_4$ (23.6 mg, 0.63 mmol), 0.18 mL of ethanol, and 0.8 mL of THF at room temperature. The mixtures were shaken for 4 h, and the resins were then filtered, washed thoroughly with DMF (2 mL × 2), MeOH (2 mL × 2), and CH_2Cl_2 (2 mL × 2), and dried by passing nitrogen through the resins. The overall yield of each resin was estimated to be in the range 70−80% through its Fmoc protection, deprotection with 20% piperidine/DMF, and UV−Fmoc quantitation.

General Procedure for Preparation of Resins 22a−c. To each of the resin-bound amines **21a−c** (0.130 mmol) were added 4-nitrophenylacetic acid (69.6 mg, 0.384 mmol), DIC (0.06 mL, 0.384 mmol), and 0.8 mL of CH_2Cl_2 at room temperature. The mixtures were agitated for 12 h, flushed, and washed with DMF (2 mL × 2), MeOH (2 mL × 2), and CH_2Cl_2 (2 mL × 2). Each of three resulting resins was dried in vacuo.

General Procedure for Preparation of Resins 23a−c. Each of the above resins (0.130 mmol) was swelled with DMF (0.8 mL) and treated with methyl iodide (0.08 mL, 1.26 mmol) and 60% NaH (30.7 mg, 0.768 mmol) under an argon atmosphere. The mixtures were agitated for 24 h at room temperature, flushed, and washed with DMF (2 mL × 2) and CH_2Cl_2 (2 mL × 2). Each of the resins was dried in vacuo to provide resins **23a−c**.

General Procedure for Preparation of Resins 24a−c. To each of the above resins **23a−c** (0.130 mmol) were added oxygen-free DMF (0.4 mL) and $SnCl_2$ (149 mg, 0.788 mmol) at room temperature. The mixtures were agitated for 1.5 h, flushed, and washed with DMF (2 mL × 2), MeOH (2 mL × 2), and CH_2Cl_2 (2 mL × 2). Each of three resulting resins was dried in vacuo. UV−Fmoc quantitation of each of the three resins showed 85, 88, and 90% yields for three steps from resins **20a−c**, respectively.

General Procedure for Preparation of Resins 25a−c. To each of the resin-bound amines **24a−c** (0.102 mmol) were added 0.8 mL of CH_2Cl_2, acetic anhydride (0.045 mL, 0.384 mmol) and Et_3N (0.04 mL, 0.026 mmol) at room temperature. The mixtures were agitated for 12 h, flushed, and washed with DMF (2 mL × 2), MeOH (2 mL × 2), and CH_2Cl_2 (2 mL × 2). Each of the three resulting resins was dried in vacuo.

General Procedure for Preparation of Resins 26a−c. Each of the above resins (0.102 mmol) was swelled with DMF (0.8 mL) and treated with methyl iodide (0.08 mL, 1.26 mmol) and 60% NaH (18.9 mg, 0.474 mmol) under an argon atmosphere. The mixtures were agitated for 24 h at room temperature, filtered, washed thoroughly with DMF (2 mL × 2), MeOH (2 mL × 2), and CH_2Cl_2 (2 mL × 2), and dried by passing nitrogen through the resins.

General Procedure for Preparation of Resins 28a−c. To each of the resin-bound amines **21a−c** (0.130 mmol) were added Fmoc-L-Ala-OH (0.147 g, 0.473 mmol), DIC (0.074 mL, 0.473 mmol), and 0.8 mL of CH_2Cl_2 at room temperature. The mixtures were agitated for 12 h, flushed, and washed with DMF (2 mL × 2), MeOH (2 mL × 2), and

CH_2Cl_2 (2 mL × 2). Each of the three resulting resins was dried in vacuo.

General Procedure for Preparation of Resins 29a−c. To each of the resin-bound amides **28a−c** (0.130 mmol) was added 0.8 mL of a solution containing 20% piperidine in DMF at room temperature. The mixtures were agitated for 10 min and flushed, and the supernatants were collected for UV−Fmoc quantitation to estimate the loading of each of resins **29a−c**. The resins were then washed with DMF (2 mL × 2), MeOH (2 mL × 2), and CH_2Cl_2 (2 mL × 2). The resulting resins **29a−c** (88−93%) were used immediately in the next step.

General Procedure for Preparation of Resins 30a−c. Each of the above resins (0.115 mmol) was swelled with DMF (0.8 mL) and treated with Boc-L-Phe-OH (125 mg, 0.473 mmol), HBTU (179 mg, 0.473 mmol), and DIPEA (0.17 mL, 0.945 mmol) under an argon atmosphere. The mixtures were shaken for 2 h, and the resins were then filtered, washed thoroughly with DMF (2 mL × 2), MeOH (2 mL × 2), and CH_2Cl_2 (2 mL × 2), and dried by passing nitrogen through the resins.

General Procedure for Preparation of Resins 31a−c. To each of the resin-bound amides **30a−c** (0.115 mmol) was added 0.8 mL of a solution containing 0.24 mL of TFA and 0.56 mL of CH_2Cl_2 at ice-bath temperature. The mixtures were slowly warmed to room temperature and allowed to mix for 40 min at room temperature. After this time, the resins were then filtered and washed with DMF (2 mL × 2), MeOH (2 mL × 2), and CH_2Cl_2 (2 mL × 2). The overall yield of each resin was estimated to be in the range 92−96% through its Fmoc protection, deprotection with 20% piperidine/DMF, and UV−Fmoc quantitation. The resulting resins **31a−c** were used immediately in the next step.

General Procedure for Preparation of Resins 32a−c. Each of the above resins (0.105 mmol) was swelled with CH_2Cl_2 (0.75 mL) and treated with benzoyl chloride (0.055 mL, 0.473 mmol) and DIPEA (0.25 mL, 1.42 mmol) under an argon atmosphere. The mixtures were agitated for 24 h, and the resins were then filtered, washed thoroughly with DMF (2 mL × 2), MeOH (2 mL × 2), and CH_2Cl_2 (2 mL × 2), and dried by passing nitrogen through the resins.

General Procedure for Oxidative Cleavage of Resins 26a−c and Resins 32a−c. To each of the above resins (0.102 mmol) swelled in THF (0.64 mL) were added CAN (67 mg, 0.122 mmol) and H_2O (0.16 mL). The mixtures were stirred for 5 min at room temperature, and then the resins were collected by filtration. The filtrates were concentrated under reduced pressure and diluted with EtOAc (30 mL). The ethyl acetate layers were washed with 10% HCl (10 mL) and saturated NaCl (10 mL) solutions. Each of the organic layers was dried (Na_2SO_4), filtered, and concentrated to afford the desired product.

2-[4-(Acetylmethylamino)phenyl]-2-methylpropionic acid (27). IR (CH_2Cl_2): 2977, 1725, 1624, 1599, 1512, 1391, 1147, 846, 590 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.62 (s, 6H), 1.89 (s, 3H), 3.25 (s, 3H), 7.12−7.49 (m, 4H), 9.17 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 22.15, 26.32, 37.24, 46.04, 126.66, 127.28, 142.59, 144.12, 171.42, 180.68. HRMS Calcd for $C_{13}H_{17}NO_3$ (M^+): 235.1208. Found: 235.1207.

2-(2-Benzoylamino-3-phenylpropionylamino)propionic acid (33). $[\alpha]^{25}_D$ −25.8 (*c* 0.41, MeOH). IR (CH_2Cl_2): 3293, 2915, 1716, 1633, 1536, 694 cm^{-1}. ^1H NMR (CD_3OD): δ 1.17−1.20 (m, 1H), 1.32 (d, 3H, J = 7.4 Hz), 2.94−3.25 (m, 2H), 4.34 (q, 1H, J = 7.3 Hz), 7.09−7.60 (m, 12 H). ^{13}C NMR (CD_3OD): δ 17.74, 38.91, 56.32, 127.75, 128.41, 129.42, 129.47, 129.52, 130.43, 132.80, 135.22, 138.66, 170.10, 173.63, 175.78. HRMS Calcd for $C_{19}H_{20}N_2O_4$ (M^+): 340.1423. Found: 340.1419.

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Supporting Information Available. ^1H and ^{13}C NMR spectra for compounds **1−3**, **8**, **9**, **14−19**, **27**, and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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