A Versatile Polymer-Supported 4-(4-Methylphenyl(chloro)methyl)phenoxy Linker for Solid-Phase Synthesis of Pseudopeptides

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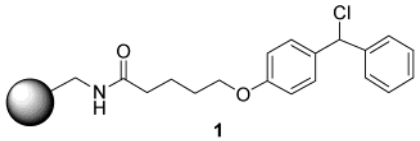
Solid-phase organic chemistry (SPOC) is now a mature science and is used extensively as a tool for drug discovery within the context of high throughput chemical synthesis.[1] A pivotal technology in any SPOC is the linker-resin; hence, a multitude of such linker-resins have been synthesized with the desired chemical properties in mind, encompassing not only the range of ligation methodologies, but also chemical orthogonality.[2]

Among the collection of linker-resins, the 2-chlorotrityl chloride polystyrene[3] and 4-[2,4-dimethoxyphenyl(hydroxy)methyl]phenoxymethyl polystyrene (Rink resin)[4] have been extensively used for anchoring a plethora of building blocks bearing nucleophilic functionalities. For example, we recently reported the anchoring of polyamines and *N*-Fmoc hydroxylamines, and following a series of synthetic transformations afforded polyamine peptide conjugates[5] and hydroxamic acids,[6] respectively. To extend the scope of the Rink resin, the linker-solid support is generally 'activated' by conversion to a halide[6b,7a] or trifluoroacetate.[7b,c] However, in our hands, these derivatives have to be prepared in situ, are unstable and particularly susceptible to hydrolysis. This prompted us to design and synthesize a comparatively more stable Rink chloride analogue.

Since the inherent instability of the Rink chloride resin is primarily due to the excessive number of electron-releasing aromatic methoxy groups, thus giving rise to a highly polarized C−Cl bond, we envisaged that a corresponding aromatic system containing a single *para*-butoxy group[8] would be sufficient to exhibit the desired chemical properties. Furthermore, this structural modification was anticipated to stabilize the benzhydryl cation through hyperconjugative effects and hence, contributed to an accelerating effect on the subsequent acidolytic cleavage reaction. To this end, the linker derivative 5-[4-(phenyl(chloro)methyl)phenoxy]pentanoyl aminomethyl polystyrene **1** was initially synthesized. Preliminary investigations into linker-resin **1** showed good stability and generic utility for anchoring a range of nucleophiles, e.g. carboxylates, alcohols and hydroxylamines. However, it was found that conditions such as 5% *v*/*v* TFA in CH_2Cl_2 for 1 h were necessary for complete acidolytic release of assembled hydroxamic acids and alcohols from the solid support. Such acidolytic cleavage conditions were harsher than we envisaged and this led to the design of the new linker-resin **2**.



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Structurally, the linker-resin **2** is analogous to the previously established **1** but with the introduction of a mildly electron-releasing methyl group at the *para* position on the second aromatic ring. Such *para*-methyl substituted aromatic systems have been similarly exploited,[9] e.g. in comparison to the trityl group, 4-methyltrityl[9a] as an amide-protecting group for the side-chain of asparagine and glutamine displays accelerated TFA-mediated deprotection kinetics.

Herein, we report a facile and robust approach for the synthesis of 5-[4-(4-methylphenyl(chloro)methylphenoxy]-pentanoyl aminomethylated polystyrene **2** and highlight its potential value for the synthesis of structurally diverse pseudopeptides, via a range of challenging chemical transformations. Thus, the synthesis of **2** involved first Friedel−Crafts acylation of toluene with *p*-methoxybenzoyl chloride in the presence of anhydrous aluminum chloride to yield **3** (Scheme 1).[10] The presence of only the *para*-substituted isomer was confirmed by both ^{1}H NMR and reversed-phase HPLC analysis. The aryl methyl ether cleavage of 4-methoxy 4′-methylbenzophenone **3** was efficiently accomplished using a solution of boron tribromide[11] in dichloromethane, to afford the deprotected handle 4-hydoxy 4′-methylbenzophenone. The desired linker derivative **4** was then readily obtained in two steps, specifically *O*-alkylation of 4-hydoxy 4′-methylbenzophenone with ethyl 5-bromopentanoate in the presence of anhydrous K_2CO_3, followed by saponification using methanolic aqueous NaOH. In summary, the synthesis of the desired handle **4** was accomplished in

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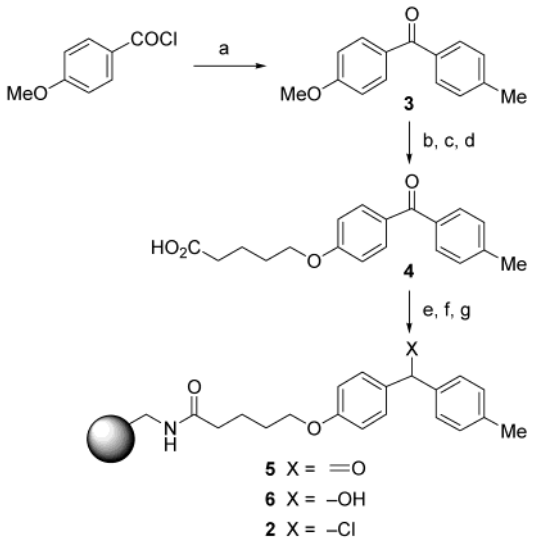
Scheme 1



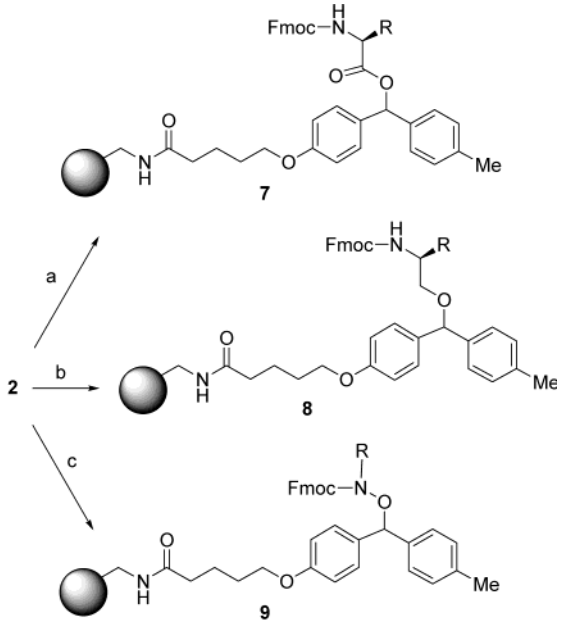
a. $AlCl_3$, $PhCH_3$, 2 h; b. BBr_3, CH_2Cl_2, 19 h; c. $Br(CH_2)_4CO_2Et$, K_2CO_3, DMF, 50°C, 72 h; d. NaOH, H_2O:MeOH, 15 h; e. *i*-PrN=C=N*i*-Pr, HOAt, aminomethyl polystyrene, DMF; f. $NaBH_4$, DMF, MeOH; g. $Ph_3P{\bullet}Cl_2$, CH_2Cl_2, THF.

four steps with an overall yield of typically 50%. Compound **4** was then conveniently coupled to a solid support, aminomethyl polystyrene, in quantitative yield. This was then followed by two versatile solid-phase reactions. First, sodium borohydride-mediated reduction of the resin-bound benzophenone functionality to yield the supported benzhydryl alcohol **6**, which on repeated treatment with excess $Ph_3P{\bullet}Cl_2$ furnished the reactive polymer-supported halide derivative **2**. Conversely, the resin-bound carbinol **6** was transformed to the chloride derivative **2** using excess acetyl chloride in CH_2Cl_2, though in marginally lower efficiency (ca. 90%). Moreover, in an approach similar to that outlined above and using the high-substitution poly(ethylene glycol)-modified aminomethyl polystyrene[12] (NovaGel), we have also readily achieved the synthesis of linker-derivatized solid support, 5-[4-(4-tolyl(chloro)methyl)phenoxy]-pentanoyl aminomethyl NovaGel.

The chloride substitution levels were initially estimated by exposing **2** to 0.05 M $NaOH_{(aq)}$ in 1,4-dioxane (2:3 *v*/*v*) followed by back-titration with 0.01 M $HCl_{(aq)}$, and using phenolphthalein as indicator. This typically indicated chloride levels of 0.85−1.0 mmol g^{-1}, which is ca. 30% higher than expected (0.64 mmol g^{-1}), hence suggesting the presence of noncovalently bound chloride. Based on subsequent experiments, we now routinely estimate the 'reactive' chloride levels in **2** by condensing with FmocAlaOH in the presence of DIEA, followed by determination of Fmoc-substitution;[6a] accordingly, 0.58−0.64 mmol g^{-1} chloride loading were typically obtained. Significantly, using the "reactive" chloride loading as a marker, the linker-resin **2** was observed to be stable when stored at −20 °C over a period of two-to-three months.

Having established a facile synthetic route to linker-resin **2**, we proceeded to tether a range of *O*-nucleophiles. Thus, in our initial investigations, a selection of *N*-Fmoc-amino acids (e.g., Ala, Arg(Pmc), Glu(O*t*-Bu), Trp(Boc), Thr(*t*-Bu)), in the presence of DIEA, readily condensed

Scheme 2



a. Fmoc-protected amino acid, DIEA, CH_2Cl_2, 24 h; b. *N*-Fmoc-amino alcohol, DIEA, $ClCH_2CH_2Cl$, THF, 48 h; c. *N*-Fmoc-substituted hydroxylamine, DIEA, CH_2Cl_2, THF, 72 h.

with **2** to yield amino acyl resins **7** in excellent yields (0.33−0.56 mmol g^{-1}; 72−100% based on theoretical chloride loading) (see Scheme 2). Furthermore, by employing a reversed-phase (RP)-HPLC based analytical procedure, it was established that FmocAlaOH could be released quantitatively by exposure of **7** (R = Me) to weakly acidic conditions, including 1% *v*/*v* TFA in CH_2Cl_2 within 10 min or 25% *v*/*v* 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) in CH_2Cl_2 within 1 h. This is in contrast to the Fmoc-amino acid-modified linker-resin **1**, which under identical conditions did not allow complete acidolysis of the benzhydryl ester bond. In addition, the derivatized resin **7** (R = Me) was effectively stable to conditions such as 20% or 50% *v*/*v* trifluoroethanol in CH_2Cl_2 (10−15% cleavage over 1 h), which are known to caused complete acidolysis of *O*-(*N*-Fmoc-aminoacyl)oxy 2-chlorotrityl polystyrene[3].

Unexpectedly, in preliminary investigations, we noted the necessity of a higher acid concentration (5% *v*/*v* TFA in CH_2Cl_2, 75 min) for the release of FmocArg(Pmc)OH anchored to the linker resin **1**. It was hypothesized that during acid treatment, preferential protonation of the side-chain guanidino functionality of Arg occurred, thus retarding the rate of ester protonation that is close in proximity. Consequently, the rate of acidolysis was considerably retarded and is unique for the tethered FmocArg(Pmc)OH residue. It was anticipated that the new linker-resin **2**, by virtue of the introduced 4′-methyl group, would allow for a more rapid release of tethered FmocArg(Pmc)OH. Indeed, acidolytic cleavage was complete when the FmocArg(Pmc)-derivatized **7** was exposed to milder acidic conditions (1% TFA for 75 min), but the resin **7** was still relatively stable to 50% HFIP in CH_2Cl_2 (14% cleavage over 2 h). Intriguingly, we also found that the 4-[2,4-dimethoxyphenyl(FmocArg(Pmc)-oxy)methyl]phenoxymethyl polystyrene (derived from Rink resin[4]) on treatment with 50% *v*/*v* HFIP in CH_2Cl_2 for 2 h resulted in only 14% cleavage of the ester bond.

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The ability of the linker-resin **2** to anchor alcoholic functionality was then illustrated by the tethering of *N*-Fmoc-amino alcohols to yield derivatized resins **8** (R = H, *i*-Pr, Bn, *C,N*-cyclic[$-(CH_2)_3-$]; 0.46−0.56 mmol g^{-1}, 82−100%, based on theoretical chloride loading) (Scheme 2). However, initial studies indicated that during the TFA-mediated (1 or 5% TFA/CH_2Cl_2, in the presence of triethylsilane) release of resin-bound FmocNH$(CH_2)_2$OH, variable amounts of the byproduct FmocNH$(CH_2)_2$-OCOCF_3 were observed. Hence, following acidolytic release, either FmocNH$(CH_2)_2$OH reacts with the triethylsilyl trifluoroacetate intermediate in a nucleophilic manner to form the trifluoroacetate ester product, or the ester is obtained directly via an acid-catalyzed esterification reaction. The trifluoroacetylation of alcoholic products during TFA treatment has previously been observed, and a number of strategies have been devised to overcome this undesired side-reaction.[2,13] Thus, we systematically evaluated several mild HCl-based cleavage reagents and concluded that 0.2 M HCl in CH_2Cl_2 for 75 min was most effective.

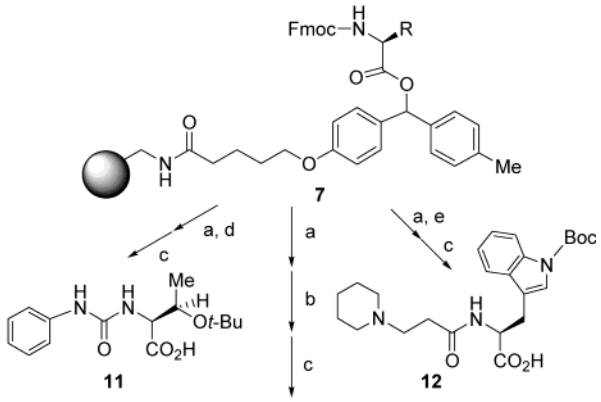
Furthermore, the ability of linker-resin **2** to anchor hindered primary alcohols was illustrated by the attachment of *N*-Fmoc-L-valinol to yield **8** (R = *i*-Pr; 0.42−0.54 mmol g^{-1}, 78−100%, based on a theoretical chloride loading of 0.64 mmol g^{-1}). This is in sharp contrast to the condensation of *N*-Fmoc-L-valinol with 2-chlorotrityl chloride polystyrene (0.46−0.51 mmol g^{-1}, 58−63%, based on an initial chloride loading of 1.05 mmol g^{-1}), which occurred in significantly lower efficiency and is comparable to observations reported by Wenschuh et al.[14]

Attention was then directed to the application of the linker-resin **2** for the selective *O*-anchoring of both *N*-substituted and *N*-Fmoc protected hydroxylamines. Thus, *N*-Fmoc protected hydroxylamines were tethered onto **2** in high efficiency to yield derivatized resins **9** (FmocNHOH, 88%; FmocN(Pr)OH, 71%; FmocN(Me)OH, 84%, FmocN(Bn)OH, 65%; FmocN(cyclobutyl)OH, 50%) (Scheme 2). Detailed evaluations established that FmocNHOH and FmocN(Pr)OH were released quantitatively from **9** on treatment with 1% *v*/*v* TFA in CH_2Cl_2 for 75 min at ambient temperature. Such mild acidolysis is advantageous, since strong acidic reagents are known to cause decomposition of the hydroxamic acid to the corresponding acid. It should be noted however, that upon exposure to 1% *v*/*v* TFA in CH_2Cl_2 for a shorter time period of 10 min, release of FmocNHOH and FmocN(Pr)-OH from the linker-resin **9** were 74% and 88%, respectively. In comparison, the FmocN(Pr)OH-derivatized Rink resin[4,6] upon treatment with 1% *v*/*v* TFA in CH_2Cl_2 for 10 min yielded the required hydroxamic acid in 78% yield.

Collectively, we are confident that our new benzhydryl-based linker retained many of the desired properties of the parent Rink linker, but with the added advantage of a highly stable and robust chloride intermediate **2**. Thus, we then subjected the derivatized linker-resins **7**, **8** and **9** to a range of chemical transformations. In the first instance, the resin **7** was successfully used for the synthesis of the *N*,*O*-protected nonapeptide **10**, using standard Fmoc/*t*-Bu solid-phase strategy,[15] in excellent yield (99%) and purity (>90%, determined by RP-HPLC). Such protected peptides per se are potentially useful molecular tools, as well as useful building blocks for convergent synthesis of proteins. The generic utility of the derivatized linker-resin **7** was further illustrated by the solid-phase synthesis of the acid-sensitive *N*-acyl amino acid derivatives **11** and **12** (Scheme 3) in excellent purities. Release of the protected peptide and derivatized amino acids from the solid support was typically accomplished using extremely mild acidic conditions, 25% *v*/*v* HFIP in CH_2Cl_2 for 1 h, under which a range of protecting groups, e.g. *N*-Boc and O*t*-Bu remained intact.

The resin-bound alcohols **8**, linked via the benzhydryl ether functionality, also proved to be ideal starting materials for the general solid-phase synthesis of various modified alcohols, including the protected pseudopeptides **13** and **14** (Scheme 4). Following solid-phase reactions, treatment of the resin products with 0.2 M HCl in CH_2Cl_2 for 75 min at ambient temperature afforded the

Scheme 3

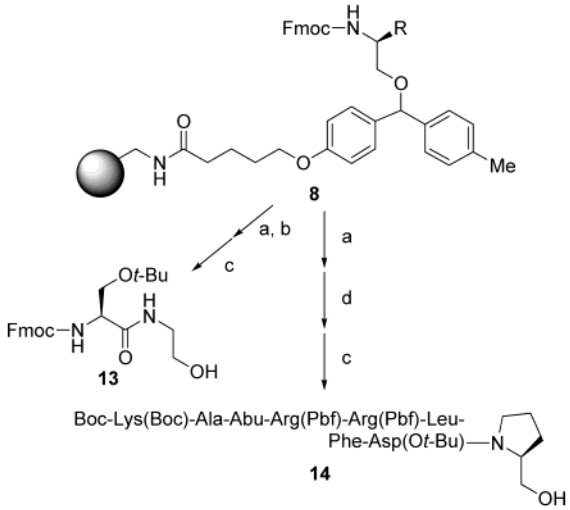


Boc-Lys(Boc)-Ala-Abu-Arg(Pmc)-Arg(Pmc)-Leu-Phe-Gly-Ala-OH

10

a. piperidine/DMF (1:4); b. peptide synthesis; c. $(CF_3)_2CHOH$/CH_2Cl_2 (2.5:7.5), 1 h; d. PhN=C=O, DIEA, 16 h; e. 1-piperidinepropionic acid, *i*-PrN=C=N*i*-Pr, HOAt, DMF.

Scheme 4



Boc-Lys(Boc)-Ala-Abu-Arg(Pbf)-Arg(Pbf)-Leu-Phe-Asp(O*t*-Bu)—N

14

OH

a. piperidine/DMF (1:4); b. FmocSer(*t*-Bu)OH, HATU, DIEA; c. 0.2 M HCl/CH_2Cl_2, 1.5 h; d. peptide synthesis.

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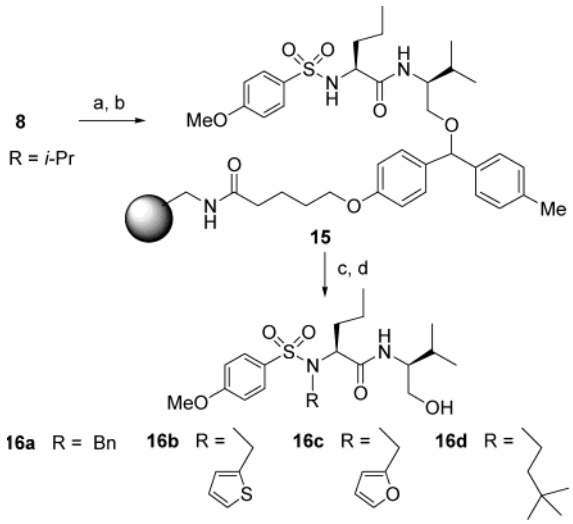
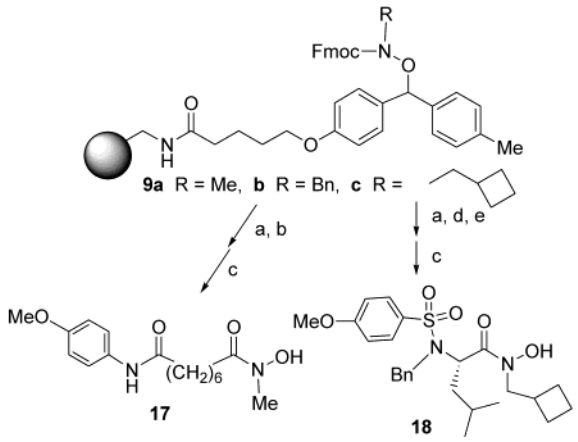
Scheme 5



a. *i*) piperidine/DMF (1:4), *ii*) FmocNvaOH, HATU, DIEA, DMF;
b. *i*) piperidine/DMF (1:4), *ii*) 4-MeOPhSO$_2$Cl, DIEA;
c. R–CH$_2$OH, Bu$_3$P, Me$_2$NCON=NCONMe$_2$, THF, 24 h;
d. 0.2 M HCl/CH$_2$Cl$_2$, 1.5 h.

Scheme 6



a. piperidine/DMF (1:4); b. *i*) MeOCO(CH$_2$)$_6$CO$_2$H, HATU, DIEA, *ii*) 0.5 M LiOH in MeOH/THF, *iii*) PyBOP, 4-MeOPhNH$_2$; c. 1% TFA/CH$_2$Cl$_2$, 75 min; d. *i*) FmocLeuOH, HOAt, *i*-PrN=C=N*i*Pr, *ii*) piperidine/DMF, *iii*) 4-MeOPhSO$_2$Cl, DIEA; e. BnOH, Bu$_3$P, Me$_2$NCON=NCONMe$_2$, THF, 24 h.

protected peptide alcohols in excellent yields and purities (>99%). The solid-phase syntheses of fully protected or acid-sensitive peptide alcohols, e.g., octreotide and peptaibols[14] have been the focus of recent research due to their unique biological properties. In summary, though a number of useful linker-resins for anchoring alcoholic functionality have been reported,[14,16] the versatility of our linker system makes it a valuable addition to the armory of chemical tools.

Moreover, the immobilized Fmoc-L-valinol derivative **8** was further elaborated to afford the sulfonamide intermediate **15**, via *N*-acylation with FmocNvaOH activated as the 7-azabenzotriazol-1-yl ester[17,18] and sulfonylation of the Fmoc-liberated amine with *para*-methoxybenzenesulfonyl chloride (Scheme 5). An aliquot of the resin **15** was cleaved to characterize the intermediate and assured the efficiency of the synthetic procedure. Subsequently, the solid-phase *N*-alkylation of the sulfonamide intermediate **15** was investigated extensively, and a generic approach based on the Mitsunobu reaction[19] was developed. Recently, several new azodicarboxamides have been introduced in order to improve the scope of the original combination of DEAD and Ph$_3$P in the Mitsunobu reaction. In our studies, facile *N*-alkylation was accomplished by employing Tsunoda's modified redox system[20] of *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD) and Bu$_3$P. A variety of aryl/heteroarylmethyl and alkyl alcohols as the alkylating component were investigated. Expectedly, we found the order of introduction of reagents and reaction temperature to be of utmost importance. Specifically, to the derivatized resin **15** in THF at 5 °C was added successively the alcohol, Bu$_3$P and TMAD. For the pseudopeptide derivatives **16a**−**c**, complete conversion of the starting material **15** to the desired resin-products were observed after 24 h (established by cleavage using 0.2 M HCl in CH$_2$Cl$_2$, and analysis by RP-HPLC). However, for the aliphatic derivative **16d**, ca. 10% of starting material remained even after 48 h reaction time.

Hydroxamic acid derivatives display a variety of pharmaceutical properties, in particular the inhibition of the matrix metalloproteinases (MMPs). These enzymes are mediators for the breakdown of structural proteins of the extracellular matrix and as such, have implications in a variety of inflammatory and degenerative conditions. Consequently, a number of solid-phase approaches for high throughput synthesis of hydroxamic acids have been reported.[6,21] In the main, these synthetic methodologies[21] are not adaptable for the synthesis of *N*-alkylhydroxamic acids. Thus, due to the flexibility of our linker system, we have also accomplished the solid-phase construction of various modified hydroxamic acids, including the hydroxamic acids **17** and **18** in good yields (Scheme 6).

The synthetic approach to the hydroxamic acid derivative **17** was developed to provide a framework for rapid access to structural analogues of the histone deacetylase inhibitors, trichostatin A and suberoylanilide hydroxamic acid,[22] which display potent anti-tumor properties. *N*-

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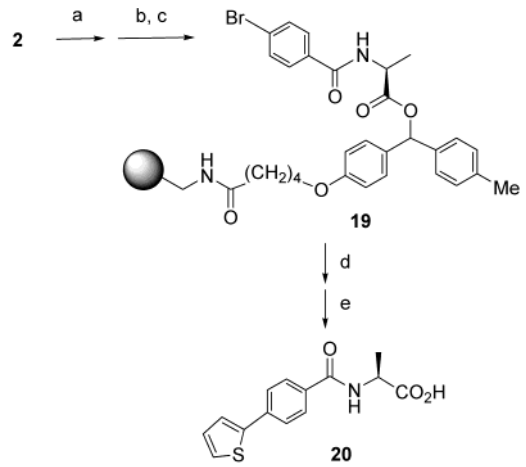
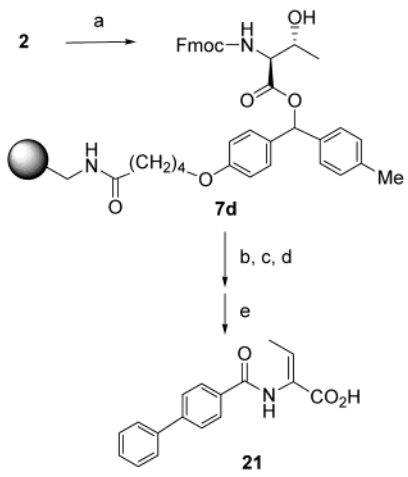
Scheme 7



a. FmocAlaOH, DIEA, CH_2Cl_2, 24 h; b. piperidine/DMF (1:4); c. $BrC_6H_4CO_2H$, HOAt, *i*-PrN=C=N*i*Pr; d. $Pd(Ph_3P)_4$, 2-thiopheneboronic acid, Na_2CO_3 (aq), DMF, 80°C, 24 h; e. 1% TFA/CH_2Cl_2, 75 min.

Scheme 8



a. FmocThrOH, DIEA, CH_2Cl_2, 24 h; b. piperidine/DMF (1:4); c. $PhC_6H_4CO_2H$, HOAt, *i*-PrN=C=N*i*Pr; d. $SOCl_2$, Et_3N, THF/CH_2Cl_2, -78°C to 5°C; e. 1% TFA/CH_2Cl_2, 15 min.

Fmoc-*N*-methyl hydroxamic acid was tethered onto **2** in good efficiency (83%), which on Fmoc-deprotection, was acylated with carboxy-activated monomethyl suberate. Saponification of the resin-bound ester intermediate with 0.5 M LiOH in MeOH/THF (cosolvent utilized to ensure optimal swelling of insoluble polystyrene support), followed by condensation with 4-methoxyaniline in the presence of PyBOP[18] yielded a resin product. Exposure of this material to 1% *v*/*v* TFA in CH_2Cl_2 furnished a crude compound in high yield (94%), which was readily purified to afford the hydroxamic acid **17** as a white solid.

The biaryl moiety, an important pharmacophore motif present in many biologically active molecules, is synthetically accessible through the well-established Suzuki palladium-catalyzed cross-coupling reaction.[23] Recently, the Suzuki reaction has been developed extensively for solid-phase organic chemistry as a method for parallel synthesis of potential medicinal compounds.[23c–h] Accordingly, we evaluated the robustness of our linker system to Suzuki reaction conditions. Thus, FmocAlaOH was condensed with the chloride linker-resin **2**, and following Fmoc-deprotection underwent acylation with activated 4-bromobenzoic acid (as the HOAt ester[18]) to yield the intermediate benzhydryl ester resin **19** (Scheme 7). The immobilized compound was then modified employing Suzuki coupling of 2-thiopheneboronic acid under standard conditions ($Pd(PPh_3)_4$, DMF, 80 °C, 24 h) and in a slight excess of base (2 M $Na_2CO_{3(aq.)}$), to afford upon release from the solid-support, the biaryl modified amino acid **20** in excellent crude yield and purity (>90%). Thus, these results confirmed the stability of our new linker system, in particular the 4-alkoxy 4′-methylbenzhydryl ester functionality to both Suzuki conditions and basic reagents.

Attention was then focused on an unique class of anomalous amino acid derivatives, namely the α,β-dehydroamino acids, which are found in many natural peptidic products that display interesting biological activities.[24] These unsaturated amino acid residues introduce elements of conformational rigidity, as well as reactive sites for Michael-type addition giving rise to potentially complex macrocyclic structures. In view of our particular interest in *C*-terminal dehydroamino acid peptides, we have adapted our linker system for solid-phase synthesis of these unique peptides. Our approach is based on a recent disclosure by Wandless and coworkers,[25] in which treatment of *threo*-*N*-acyl-β-hydroxyamino acids with thionyl chloride lead to the formation of cyclic sulfamidites that, under basic conditions, eliminated SO_2 stereospecifically to afford the corresponding (*Z*)-*N*-acyldehydroamino acids in high purity. Thus, Scheme 8 outlines a model study that was carried out to establish a mild solid-phase synthetic approach to (*Z*)-dehydroamino acid-containing pseudopeptides. The immobilized intermediate **7d** was produced via the attachment of FmocThrOH to linker-resin **2**, within 24 h, in high efficiency (98%). Since in a preliminary model experiment during which *N*-fluorenylmethoxycarbonylthreonylmorpholine amide reacted, over a period of 48 h, with linker-resin **2** in only ca. 10% efficiency, we were confident that FmocThrOH would react preferentially via the carboxylate and not the secondary alcohol functionality. Following Fmoc-deprotection of **7d**, acylation with activated 4-biphenylcarboxylic acid gave the resin-bound *N*-acylthreonine intermediate. Accordingly, in a one-pot procedure,[25] treatment of the resin-bound intermediate with $SOCl_2$ and Et_3N in THF/CH_2Cl_2 at −78 °C led first to the formation of the cyclic sulfamidite, followed by elimination at 5 °C to furnish an immobilized product, which on acidolysis provided the desired (*Z*)-4-phenylbenzoyl dehydroaminoalanine **21** (75% purity). The stereo-configuration of the purified pseudopeptide **21** was confirmed by ^1H NMR.

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In summary, we have developed a facile synthetic route to the 'fine-tuned' benzhydryl chloride linker-resin **2** and the robustness of the linker-resin to a range of advanced organic synthetic transformations has been comprehensively demonstrated. We envisaged that the linker described herein would fill a significant niche in the arsenal of chemical tools for solid-phase synthesis of both peptides and modified pseudopeptides.

Experimental Section

General Methods. See the Supporting Information for detailed information.

Aminomethylated polystyrene HL 200−400 mesh (AM resin), aminomethyl NovaGel 100−200 mesh were purchased from CN Biosciences UK Ltd., Nottingham, U.K Tetrahydrofuran (THF) and dichloromethane were redistilled prior to use. All glassware was oven-dried overnight prior to use. All resin products were dried in vacuo over KOH pellets for 15 h. Reversed-phase high performance liquid chromatography (RP-HPLC) was performed on a Hypersil Pep5-C_{18} column (4.6 × 150 mm). Eluent detection was monitored by UV absorbance at 220 nm. The linear elution gradient was either 50 to 100% **B** in 20 min, 20 to 60% **B** in 25 min or 30 to 70% **B** in 25 min at 1.20 mL min^{-1} (**A** = 0.06% aqueous trifluoroacetic acid (TFA), **B** = 0.06% TFA in 90% aqueous acetonitrile.

Preparation of 4-Methoxy 4′-Methylbenzophenone (3). Aluminum chloride (2.00 g, 0.015 mol) and toluene (5 mL) were placed in a two-necked flask, fitted with air-condenser and dropping funnel, in an ice-bath (5 °C). To the stirred suspension under argon was added dropwise *p*-methoxybenzoyl chloride (1.71 g, 0.010 mol) in toluene (10 mL) via the dropping funnel. The reaction mixture was stirred at 5 °C for a further 2 h, after which TLC analysis (ethyl acetate: hexane, 1: 4) indicated that the reaction had gone to completion. The reaction was quenched by pouring the mixture into ice−water, and then washed with 1 M aqueous sodium hydroxide (3 × 30 mL). The organic phase was separated and washed with aqueous potassium hydrogen sulfate (2 × 40 mL), aqueous sodium hydrogen carbonate (3 × 40 mL) and brine (2 × 40 mL). The organic extract was dried ($MgSO_4$) and evaporated to dryness in vacuo to afford the title compound as a white solid (2.12 g, 94%). Typically, this material was of sufficient purity: mp 91.3−91.9 °C (lit.[10] 92 °C); APcI-MS^+ *m*/*z* 227.1 (MH^+), calcd 227.3; TLC (ethyl acetate:hexane, 1:4) R_f = 0.32; RP-HPLC 50−100% B in 20 min, t_R 10.0 min; δ_H ($CDCl_3$, 250 MHz) 7.82 (2 H, d, *J* 9.0 Hz), 7.69 (2 H, d, *J* 8.2 Hz), 7.28 (2 H, d, *J* 8.4 Hz), 6.97 (2 H, d, *J* 9.0 Hz), 3.89 (3 H, s), 2.45 (3 H, s); δ_C ($CDCl_3$, 62.9 MHz) 195.33, 162.99, 142.59, 135.47, 132.40, 130.44, 129.97, 128.84, 113.45, 55.45, 21.59.

4-Hydroxy 4′-Methylbenzophenone. 4-Methoxy 4'-methylbenzophenone **3** (1.00 g, 4.4 mmol) was dissolved in CH_2Cl_2 (10 mL) under argon, and cooled to −78 °C. A solution of 1 M boron tribromide in CH_2Cl_2 (8.8 mL, 8.8 mmol) was added carefully to the stirred solution. The reaction mixture was allowed to attain room-temperature overnight (19 h) with stirring, during which a clear brownish yellow solution was obtained. A further quantity of boron tribromide (2.2 mL, 2.2 mmol) was added and the solution was stirred for a further 5 h. The reaction mixture was then quenched by the careful addition of ice−water (20 mL) and stirred for 15 min. A white solid was obtained, which was dissolved by the addition of *tert*-butyl methyl ether (60 mL). The organic phase was separated and extracted with 2 M aqueous sodium hydroxide (2 × 30 mL). The alkaline extract was washed with diethyl ether (2 × 30 mL), neutralized with 2 M aqueous hydrochloric acid and a white precipitate was formed, which was extracted into diethyl ether (2 × 40 mL). The organic phase was washed with brine (2 × 30 mL), dried and concentrated in vacuo to afford the crude product (0.90 g, 96%). The crude product was triturated with ice-cold toluene to afford the title compound (0.78 g, 83%) as an off-white solid: mp 167−169 °C (lit.[10] 175 °C); APcI-MS^+ *m*/*z* 213.2 (MH^+), calcd 213.3; TLC (ethyl acetate:hexane, 1:1) R_f = 0.51; RP-HPLC 50−100% B in 20 min, t_R 5.6 min; δ_H ($CDCl_3$, 250 MHz) 7.78 (2 H, d, *J* 8.8 Hz), 7.69 (2 H, d, *J* 8.2 Hz), 7.29 (2 H, d, *J* 8.5 Hz), 6.92 (2 H, d, *J* 8.8 Hz), 6.13 (1 H, br s), 2.45 (3 H, s); δ_C ($CDCl_3$, 62.9 MHz) 195.33, 159.81, 142.82, 135.31, 132.81, 130.36, 130.05, 128.91, 115.11, 21.62.

Ethyl 5-[4-(4-Toluoyl)phenoxy]pentanoate. 4-Hydroxy 4'-methylbenzophenone (0.75 g, 3.52 mmol) and anhydrous K_2CO_3 (0.24 g, 1.76 mmol) were placed in a round-bottomed flask and DMF (20 mL) was added. The reaction flask was sonicated for 15 min to aid the dissolution of K_2CO_3. Ethyl 5-bromopentanoate (668 μL, 4.22 mmol) was then added, and the resultant mixture was stirred at 50 °C for 72 h. TLC (ethyl acetate:hexane, 3:1) analysis indicated that the reaction had gone to completion. The reaction mixture was allowed to cool to room temperature and the suspension was filtered and washed with DMF (10 mL). The filtrate was evaporated to dryness in vacuo. The residue was then dissolved in ethyl acetate (40 mL) and washed with aqueous sodium hydrogen carbonate (2 × 30 mL), aqueous potassium hydrogen sulfate (2 × 30 mL) and aqueous brine (2 × 30 mL). The organic extract was dried and evaporated to dryness in vacuo to afford the crude product (1.13 g, 95%) as a pale yellow solid. Purification by flash column chromatography on silica gel, eluting with 30% ethyl acetate in hexane, yielded the title compound (0.89 g, 75%) as a white crystalline solid: mp 63−65 °C; APcI-MS^+ *m*/*z* 341.2 (MH^+), calc. 341.4; TLC (ethyl acetate: hexane, 1:4); R_f = 0.28; RP-HPLC 50−100% B in 20 min, t_R 14.0 min; δ_H ($CDCl_3$, 250 MHz) 7.80 (2 H, d, *J* 8.9 Hz), 7.68 (2 H, d, *J* 8.2 Hz), 7.28 (2 H, d, *J* 7.8 Hz), 6.94 (2 H, d, *J* 8.9 Hz), 4.14 (2 H, q, *J* 6.9), 4.06 (2 H, t, *J* 5.3 Hz), 2.44 (3 H, s), 2.41 (2 H, t, *J* 7.0 Hz), 1.80−1.92 (4 H, m), 1.27 (3 H, t, *J* 7.1 Hz); δ_C ($CDCl_3$, 62.9 MHz) 195.29, 173.31, 162.38, 142.51, 135.46, 132.36, 130.28, 129.93, 128.80, 113.85, 67.57, 60.31, 33.82, 28.47, 21.55, 21.52, 14.20. Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.10; H, 7.11%. Found: C, 73.98; H, 7.10%.

5-[4-(4-Toluoyl)phenoxy]pentanoic Acid (4). To a solution of ethyl 5-[4-(4-toluoyl)phenoxy]pentanoate (0.80 g, 2.35 mmol) in methanol (20 mL) was added 2 M aqueous sodium hydroxide (20 mL). It was noted that upon addition of the aqueous NaOH, the colorless solution turned cloudy and a precipitate was formed. A further quantity of MeOH (10 mL) was added to aid the dissolution of the ester. The mixture was vigorously stirred at room-temperature overnight; TLC (ethyl acetate:acetic acid, 99:1) analysis indicated that the reaction had gone to completion. The solution was evaporated to dryness in vacuo, and the resulting white solid was dissolved in water (50 mL) and washed with *tert*-butyl methyl ether (2 × 30 mL). The aqueous extract was acidified to pH 2 with 2 M aqueous HCl and a precipitate was obtained, which was extracted into *tert*-butyl methyl ether (3 × 40 mL). The organic extract was washed with brine (2 × 30 mL), dried and concentrated in vacuo to afford a crude product (0.69 g, 94%). The crude product was triturated with hexane to afford the title compound (0.63 g, 86%) as a white crystalline solid: mp 128−130 °C; APcI-MS^+ *m*/*z* 313.1 (MH^+), calcd 313.4; TLC (ethyl acetate:acetic acid, 99:1) R_f = 0.45; RP-HPLC 50−100% B in 20 min, t_R 7.2 min; δ_H ($CDCl_3$, 250 MHz) 7.80 (2 H, d, *J* 8.9 Hz), 7.68 (2 H, d, *J* 8.2 Hz), 7.27 (2 H, d, *J* 7.8 Hz), 6.94 (2 H, d, *J* 8.9 Hz), 4.06 (2 H, t, *J* 5.6 Hz), 2.47 (2 H, t, *J* 6.8 Hz), 2.44 (3 H, s), 1.81−1.89 (4 H, m); δ_C ($CDCl_3$, 62.9 MHz) 195.44, 179.21, 162.36, 142.61, 135.43, 132.43, 130.33, 129.98, 128.84, 113.87, 67.53, 33.50, 28.38, 21.59, 21.29; Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45%. Found: C, 73.21; H, 6.35%.

5-[4-(4-Toluoyl)phenoxy]pentanoyl Aminomethylated Polystyrene (5). Amino-methylated resin (0.5 g, 0.40 mmol, loading 0.80 mmol g^{-1}) was swollen in CH_2Cl_2 (3 mL) for 15 min. 5-[4-(4-Toluoyl)phenoxy]pentanoic acid **4** (0.375 g, 1.20 mmol), HOAt (0.163 g, 1.20 mmol) and *N*,*N*-diisopropylcarbodiimide (DIPCDI) (207 μL, 1.32 mmol) were then added to the resin suspension. DMF (3 mL) was added to aid stirring and the reaction mixture was stirred for 3 h at room temperature. A further quantity of aminomethylated resin (0.325 g, 0.26 mmol) was added to the reaction mixture and stirred for a further 24 h. The derivatized resin was filtered, washed successively with DMF, CH_2Cl_2 and hexane, and dried in vacuo to afford 5-[4-(4-toluoyl)phenoxy]pentanoyl aminomethylated polystyrene (1.25 g, quantitative yield): IR (KBr) 2922, 1651 and 1601 cm^{-1}.

5-[4-(4-Tolyl(hydroxy)methyl)phenoxy]pentanoyl Aminomethylated Polystyrene (6). 5-[4-(4-Toluoyl)phenoxy]pentanoyl aminomethylated polystyrene **5** (1.20 g, 0.78 mmol; expected loading 0.648 mmol g^{-1}) was swollen in DMF (10 mL)

and MeOH (2 mL). Sodium borohydride (0.295 g, 7.8 mmol) was added portionwise over a period of 30 min. The suspension was then stirred at room temperature overnight. The resin was filtered, washed successively with DMF, CH_2Cl_2 and MeOH, and dried in vacuo to yield the title compound (0.96 g, 80%): IR (KBr) 3322, 3025, 2921, 1657 and 1602 cm^{-1}.

5-[4-(4-Tolyl(chloro)methyl)phenoxy]pentanoyl aminomethylated polystyrene (2). 5-[4-(4-Tolyl(hydroxy)methyl)-phenoxy]pentanoyl aminomethylated polystyrene **6** (0.96 g, 0.62 mmol, expected loading 0.648 mmol g^{-1}) was suspended in CH_2Cl_2 (8 mL) and dichlorotriphenylphosphorane ($Ph_3P{\bullet}Cl_2$) (2.00 g, 6.20 mmol) was added portionwise over a period of 15 min. THF (2 mL) was added to aid the stirring of the resin. The reaction mixture was stirred at room temperature for 24 h. The resin was filtered and washed repeatedly with CH_2Cl_2 and hexane, and dried in vacuo (1.08 g). The resin was retreated with $Ph_3P{\bullet}Cl_2$ (1.00 g, 3.10 mmol) in CH_2Cl_2 (6 mL) and THF (2 mL). Following gently stirring for 24 h at room temperature, the resin was filtered, washed repeatedly with CH_2Cl_2 and hexane, and dried in vacuo to afford the desired title linker-resin (0.88 g, 91%): IR (KBr) 3025, 2922, 1657 and 1602 cm^{-1}. The chloride substitution level was estimated by exposing **2** to 0.05 M aqueous NaOH in 1,4-dioxane followed by back-titration using 0.01 M aqueous HCl. This typically indicated chloride levels of 0.85−1.0 mmol g^{-1}, which is ca. 30% higher than expected (0.64 mmol g^{-1}), hence suggesting the presence of noncovalent bound chloride. The chloride linker-resin **2** (100 mg) on treatment with FmocAlaOH (62 mg, 0.192 mmol) in the presence of DIEA, afforded 5-[4-(4-tolyl(*N*-Fmoc-Ala-O)-methyl)-phenoxy]pentanoyl amino-methylated polystyrene **7** (0.54 mmol g^{-1}). Based on a Fmoc-echo methodology, the chloride substitution was estimated to be 0.63 mmol g^{-1}.

Addition of *N*-Fmoc-Protected Amino Acids to the Benzhydryl Chloride Linker-Polystyrene 2. 5-[4-(4-Tolyl-(chloro)methyl)phenoxy]pentanoyl aminomethylated polystyrene **2** (0.064 mmol, theoretical loading 0.64 mmol g^{-1}) and *N*-Fmoc-protected amino acid (0.192 mmol) were suspended in DCM (2 mL). Following the addition of DIEA (0.128 mmol), the resultant mixture was stirred gently at room temperature for 24 h. The resin was filtered, washed successively with DMF, DCM and MeOH, and dried in vacuo.

Boc-Lys(Boc)-Ala-Abu-Arg(Pmc)-Arg(Pmc)-Leu-Phe-Gly-Ala-OH (10). 5-[4-(4-Tolyl(*N*-Fmoc-Ala-O)-methyl)phenoxy]pentanoyl aminomethylated polystyrene **7** (95 mg, 0.05 mmol; 0.54 mmol g^{-1}) placed in a reaction column was allowed to swell in DMF (1 mL) for 18 h, and then Fmoc-deprotected using 20% *v*/*v* piperidine in DMF (2.5 mL min^{-1}). The resin was washed with DMF (10 min, 2.5 mL min^{-1}) and the peptide sequence Boc-Lys(Boc)-Ala-Abu-Arg(Pmc)-Arg(Pmc)-Leu-Phe-Gly was assembled using the LKB Biolynx 4175 manual peptide synthesizer. Sequential acylation reactions were carried out at ambient temperature for 1.5 h using appropriate *N*-Fmoc-protected amino acids [Fmoc-Gly-OH, 74 mg; Fmoc-Phe-OH, 97 mg; Fmoc-Leu-OH, 88 mg; Fmoc-Arg(Pmc)-OH, 166 mg; Fmoc-Abu-OH, 81 mg; Fmoc-Ala-OH, 78 mg; Fmoc-Lys(Boc)-OH, 117 mg; 0.25 mmol] and carboxyl-activated using TBTU (80 mg, 0.25 mmol), HOBt (38 mg) and DIEA (87 μL, 0.50 mmol). Repetitive *N*-Fmoc-deprotection was achieved using 20% *v*/*v* piperidine in DMF (6 min, 2.5 mL min^{-1}). After the final *N*-Fmoc-deprotection, the terminal amine group was Boc-protected with di-*tert*-butyl dicarbonate (218 mg, 1.0 mmol). The assembled *N*-Boc-peptidyl-resin was filtered and washed successively with DMF, CH_2Cl_2 and MeOH and dried in vacuo (131 mg, 79%). The resin product was suspended in CH_2Cl_2 (3.75 mL) and HFIP (1.25 mL) was added. The mixture was left at room temperature for 1 h. The cleavage mixture was then filtered to remove residual resin and washed with CH_2Cl_2 (5 mL), CH_2Cl_2:MeOH (1:1, 10 mL) and MeOH (5 mL). The filtrate was evaporated to dryness in vacuo, the residual material redissolved in acetonitrile (10 mL) and the solution evaporated to dryness in vacuo; and the process was repeated twice. The peptide was precipitated with water, filtered, washed with water, air-dried overnight, and dried in vacuo to afford the title compound as a white crystalline solid (21 mg, 99%, purity >95%): mp 187−189 °C; RP-HPLC 50−100% B in 20 min, t_R 18.4 min; ES-MS$^+$ *m*/*z* 1736.8 (MH^+), calcd 1737.1. Anal. Calcd for $C_{83}H_{130}N_{16}O_{20}S_2{\cdot}^1/_4(CF_3)_2CHOH$: C, 52.86; H, 6.74; N, 11.27%. Found: C, 53.00; H, 6.96; N, 11.04%.

***N*^{in}-*tert*-Butoxycarbonyl-*N*$^{\alpha}$-(3-piperidin-1-ylpropionyl)-L-tryptophan (12).** The amino acid derivative FmocTrp(Boc)-OH (0.158 g, 0.1 mmol) was reacted with **2** (0.156 g, 0.10 mmol, 0.64 mmol g^{-1}) to yield the derivatized resin **7** (0.184 g, 90%; Fmoc-substitution 0.45 mmol g^{-1}, 91% efficiency). The resin product was placed in a reaction column and swollen in DMF for 4 h. The resin was then washed with DMF (10 min, 2.5 mL min^{-1}), Fmoc-deprotected by treatment with 20% *v*/*v* piperidine in DMF and finally washed with DMF (10 min, 2.5 mL min^{-1}), after which excess DMF was removed. 1-Piperidinepropionic acid (0.05 g, 0.32 mmol), HOAt (0.04 g, 0.32 mmol) and DIPCDI (50 μL, 0.32 mmol) in DMF (1 mL) was added to the resin, and the mixture was gently stirred at room temperature for 16 h. The resin was then washed with DMF (10 min, 2.5 mL min^{-1}), followed by 20% *v*/*v* piperidine in DMF (5 min, 2.5 mL min^{-1}) and finally washed with DMF (10 min, 2.5 mL min^{-1}). The resin was filtered, washed successively with DMF, CH_2Cl_2 and MeOH, and dried in vacuo to yield the desired resin product (0.164 g, 93%), was suspended in CH_2Cl_2 (3.75 mL) and HFIP (1.25 mL) was added. The mixture was left at room temperature for 1 h. The cleavage mixture was then filtered, and washed with CH_2Cl_2 (5 mL), CH_2Cl_2:MeOH (1:1, 10 mL) and MeOH (5 mL). The filtrate was evaporated to dryness in vacuo to yield a crude product (0.033 g, 100%; >95% when analyzed by RP-HPLC). Purification by recrystallization from ethyl acetate:hexane afforded the title compound (0.026 g, 79%) as a white crystalline solid: mp 135 °C; ES-MS$^+$ *m*/*z* 444.4 (MH^+), calcd 444.5; RP-HPLC 50−100% B in 20 min, t_R 4.8 min; δ_H ($CDCl_3$, 250 MHz) 8.03 (1 H, d, *J* 8.2 Hz), 7.62 (1 H, d, *J* 7.4 Hz), 7.52 (1 H, d, *J* 7.1 Hz), 7.45 (1 H, s), 7.14−7.22 (2 H, m), 4.68 (1H, br m), 3.15−3.28 (2 H, m), 2.60−2.69 (14 H, m), 1.62 (9 H, s); δ_C ($CDCl_3$, 62.9 MHz) 176.10, 168.86, 149.88, 131.59, 123.89, 122.08, 119.63, 117.25, 114.98, 83.23, 54.86, 53.15, 31.83, 28.19, 28.15, 27.55, 22.53, 22.20. Anal. Calcd for $C_{24}H_{33}N_3O_5{\cdot}^1/_4(CF_3)_2CHOH$: C, 61.22; H, 6.95; N, 8.65%. Found: C, 61.07; H, 7.51; N, 8.75%.

2-(*N*-(9-Fluorenylmethoxycarbonyl)-*O*-*tert*-butyl-L-seri-nyl)aminoethanol (13). To a mixture of 5-[4-(4-tolyl(chloro)-methyl)phenoxy]pentanoyl aminomethylated polystyrene **2** (0.10 g, 0.06 mmol, expected loading 0.64 mmol g^{-1}) and *N*-Fmoc-aminoethanol (0.054 g, 0.192 mmol) in $ClCH_2CH_2Cl$ (DCE; 3 mL) and THF (1 mL) was added DIEA (0.10 mmol). The suspension was then gently agitated at room temperature for 24 h. The resin was filtered, washed successively with DMF, CH_2Cl_2 and MeOH, and dried in vacuo to yield the required resin **8** (0.096 g, 83%; Fmoc substitution 0.453 mmol g^{-1}, 82% efficiency). The derivatized resin product (0.065 g, 0.03 mmol) was placed in a reaction column and swollen in DMF for 3 h. The resin underwent Fmoc-deprotection by treatment with 20% *v*/*v* piperidine in DMF and finally washed with DMF (10 min, 2.5 mL min^{-1}), after which excess DMF was removed. FmocSer(*t*-Bu)OH (0.115 g, 0.30 mmol) and HATU (0.114 g, 0.30 mmol) were dissolved in DMF (1 mL) and DIEA (104 μL, 0.60 mmol) was added. After ca. 1 min, the mixture was added to the resin and the reaction mixture was stirred at room temperature for 3 h. The resin was then washed with DMF (10 min, 2.5 mL min^{-1}), filtered, washed successively with DMF, CH_2Cl_2 and MeOH, and dried in vacuo to give the desired functionalized resin (0.067 g, 94%; Fmoc-substitution 0.426 mmol g^{-1}, 100% efficiency). The derivatized resin product (17.7 mg) was suspended in CH_2Cl_2 (3 mL) and 0.5 M HCl in CH_2Cl_2 (2 mL) was added, followed by H_2O (50 μL) and triethylsilane (50 μL). The resin was vigorously stirred at room temperature for 1.5 h. The suspension was then filtered and the resin washed with CH_2Cl_2 (2 × 5 mL) and MeOH:CH_2Cl_2 (1:1, 5 mL). The combined filtrates were evaporated to dryness in vacuo to afford the title compound (4.1 mg, quantitative): RP-HPLC analysis (50−100% B in 20 min) estimated the purity to be >99%; ES-MS$^+$ *m*/*z* 449.6 (MNa^+), 427.7 (MH^+), calcd 427.5; RP-HPLC 50−100% B in 20 min, t_R 6.8 min; δ_H ($CDCl_3$, 250 MHz) 7.77 (2 H, d, *J* 6.9 Hz), 7.60 (2 H, d, *J* 7.1 Hz), 7.27−7.41 (4 H, m), 6.90 (1 H, br s), 5.73 (1 H, br s), 4.43 (2 H, d, *J* 6.8), 4.23 (2 H, m), 3.82 (1 H, dd, *J* 8.6, 3.6 Hz), 3.71−3.73 (2 H, m), 3.37−3.44 (3 H, m), 1.20 (9 H, s).

Boc-Lys(Boc)-Ala-Abu-Arg(Pbf)-Arg(Pbf)-Leu-Phe-Asp-(O*t*-Bu)-Pro[$\psi$$CH_2$OH] (14). The chloride resin **2** (0.10 g, 0.064 mmol, 0.64 mmol g^{-1}), suspended in DCE:THF (3:1; 4 mL), was derivatized with *N*-Fmoc-L-prolinol (0.062 g, 0.192 mmol; (*S*)-*N*-(9-fluorenylmethoxycarbonyl)-2-pyrrolidinylmethanol) in the

presence of DIEA (0.1 mmol) for 48 h, to yield the resin **8** (0.095 g, 81%; Fmoc-substitution 0.531 mmol g^{-1}, 98% efficiency). The resin product (0.094 g, 0.05 mmol) was placed in a reaction column, swollen in DMF for 18 h, and Fmoc-deprotected using 20% *v*/*v* piperidine in DMF. The resin was then washed with DMF (10 min, 2.5 mL min^{-1}) and the peptide sequence Boc-Lys(Boc)-Ala-Abu-Arg(Pbf)-Arg(Pbf)-Leu-Phe-Asp(O*t*-Bu) was then assembled using the LKB manual peptide synthesizer. Sequential acylation reactions were carried out at ambient temperature for 1.5 h using appropriate *N*-Fmoc-protected amino acids [Fmoc-Asp(O*t*-Bu)-OH, 103 mg; Fmoc-Phe-OH, 97 mg; Fmoc-Leu-OH, 88 mg; Fmoc-Arg(Pbf)-OH, 162 mg; Fmoc-Abu-OH, 81 mg; Fmoc-Ala-OH, 78 mg; Fmoc-Lys(Boc)-OH, 117 mg; 0.25 mmol] and carboxyl-activated using TBTU (80 mg, 0.25 mmol), HOBt (38 mg, 0.25 mmol) and DIEA (87 μL, 0.50 mmol). Repetitive *N*-Fmoc-deprotection was achieved using 20% v/v piperidine in DMF (6 min, 2.5 mL min^{-1}). After the final *N*-Fmoc-deprotection, the terminal amine group was Boc-protected with di-*tert*-butyl dicarbonate (218 mg, 1.0 mmol). The assembled *N*-Boc-protected peptidyl-resin was filtered, washed successively with DMF, CH_2Cl_2 and MeOH, and dried in vacuo (150 mg, 88%). The derivatized resin product was suspended in 0.2 M HCl in CH_2Cl_2 (10 mL) and vigorously stirred at room temperature for 1.5 h. The suspension was then filtered and the resin washed with CH_2Cl_2 (2 × 5 mL) and MeOH:CH_2Cl_2 (1:1, 5 mL). The combined filtrates were evaporated to dryness in vacuo to afford the title compound as a white solid (105 mg, quantitative yield; purity estimated using RP-HPLC >99%): mp 225−227 °C; ES-MS^+ *m*/*z* 1835.4 (MH^+), calcd 1835.3; RP-HPLC 20−60% B in 25 min, t_R 14.8 min. Anal. Calcd for $C_{89}H_{140}N_{16}O_{21}S_2$•HCl: C, 57.14; H, 7.60; N, 11.98%. Found: C, 57.21; H, 7.68; N, 11.41%.

***N*-(4-Methoxybenzenesulfonyl)-L-norvalinyl-L-valinol Derivatized Linker-Resin (15).** A solution of *N*-Fmoc-L-valinol (0.062 g, 0.19 mmol; (*S*)-*N*-(9-fluorenylmethoxy-carbonyl)-2-amino-3-methylbutanol) and DIEA (0.10 mmol) in DCE:THF (3:1; 4 mL) was reacted with the chloride linker-resin **2** (0.10 g, 0.064 mmol, 0.64 mmol g^{-1}) for 72 h to yield the derivatized resin **8** (0.105 g, 90%; Fmoc-substitution 0.50 mmol g^{-1}, 92% efficiency). It should be noted that after a 24 h reaction period, the Fmoc-substitution value of the derivatized resin was 0.42 mmol g^{-1} (78%). The derivatized resin product was placed in a reaction column and swollen in DMF for 4 h. The resin was then washed with DMF (10 min, 2.5 mL min^{-1}), Fmoc-deprotected by treatment with 20% *v*/*v* piperidine in DMF and finally washed with DMF (10 min, 2.5 mL min^{-1}), after which excess DMF was removed. FmocNvaOH (0.217 g, 0.64 mmol) and HATU (0.243 g, 0.64 mmol) were dissolved in DMF (1 mL) and DIEA (223 μL, 1.28 mmol) then added. After ca. 1 min, the mixture was added to the resin and the resultant mixture stirred at room temperature for 16 h. The resin was then washed with DMF (10 min, 2.5 mL min^{-1}) and dried in vacuo to afford the title resin.

***N*-Benzyl-*N*-(4-methoxybenzenesulfonyl)-L-norvalinyl-L-valinol (16a).** The above derivatized resin **15** (142 mg, 0.06 mmol) was swollen in dry THF (2 mL) for 16 h under nitrogen. To this suspension at 5 °C was added successively benzyl alcohol (124 μL, 1.2 mmol), tributylphosphine (148 μL, 0.6 mmol) and *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD; 103 mg, 0.6 mmol). The resultant mixture was then agitated at room temperature under nitrogen for 24 h. The resin was filtered, washed successively with THF, DMF, CH_2Cl_2 and MeOH, and dried in vacuo to yield the transformed resin product (139 mg, 88%). The resin product (119 mg) was treated with 0.2 M HCl in CH_2Cl_2 (10 mL) to afford the crude product (18.0 mg, 84%; >95% when analyzed by RP-HPLC), which was purified by preparative RP-HPLC to afford the title compound as a colorless oil (11.25 mg, 63% based on 18.0 mg crude compound, 52% theoretical): ES-MS^+ *m*/*z* 463.0 (MH^+), calcd 463.6; RP-HPLC 50−100% B in 20 min, t_R 8.8 min; δ_H ($CDCl_3$, 250 MHz) 7.72 (2 H, d, *J* 9.0 Hz), 7.27−7.38 (5 H, m), 6.96 (2 H, d, *J* 9.0 Hz), 6.62 (1 H, br d, *J* 6.6 Hz), 4.65 (1 H, d, *J* 15.3 Hz), 4.23 (1 H, d, *J* 15.3 Hz), 4.11 (1 H, dd, *J* 6.7, 8.1 Hz), 3.88 (3 H, s), 3.61 (1 H, dd, *J* 3.1, 11.3 Hz), 3.49 (1 H, dd, *J* 6.9, 11.3 Hz), 3.32−3.36 (1 H, m), 1.91−1.97 (2 H, m), 1.62−1.68 (1 H, m), 1.40−1.45 (2 H, m), 0.89 (3 H, d, *J* 6.8 Hz), 0.81 (3 H, d, *J* 6.8 Hz), 0.72 (3 H, t, *J* 7.2 Hz); δ_C ($CDCl_3$, 62.9 MHz) 171.61, 163.18, 136.63, 131.35, 129.36, 129.11, 128.61, 128.49, 128.01, 114.29, 114.22, 77.21, 64.37, 60.29, 58.38, 55.68, 52.93, 48.57, 30.47, 29.04, 19.63, 19.12, 18.67, 13.66; HRMS (FAB) calcd for $C_{24}H_{35}N_2O_5S$ (MH^+): 463.226669, found 463.228820.

***N*-(2-Thienylmethyl)-*N*-(4-methoxybenzenesulfonyl)-L-norvalinyl-L-valinol (16b).** The derivatized resin **15** (185 mg, 0.07 mmol) was swollen in dry THF (3 mL) for 16 h under nitrogen. To this suspension at 5 °C was added successively 2-thiophenemethanol (132.6 μL, 1.40 mmol), tributylphosphine (173 μL, 0.70 mmol) and TMAD (121 mg, 0.70 mmol). The resultant mixture was then agitated at room temperature under nitrogen for 24 h. The resin was filtered, washed successively with THF, DMF, CH_2Cl_2 and MeOH, and dried in vacuo to yield the transformed resin product (190 mg, 97%). The resin (190 mg) was treated with 0.2 M HCl in CH_2Cl_2 (10 mL) to afford the crude product (25.3 mg, 79%; >95% when analyzed by RP-HPLC), which was purified by preparative RP-HPLC to afford the title compound as a white semisolid (20.18 mg, 80% based on 25.3 mg crude compound, 63% theoretical): ES-MS^+ *m*/*z* 469.1 (MH^+), calcd 469.6; RP-HPLC 50−100% B in 20 min, t_R 8.0 min; δ_H ($CDCl_3$, 250 MHz) 7.68 (2 H, d, *J* 9.0 Hz), 7.24−7.27 (1 H, m), 7.06 (1 H, m), 6.94 (2 H, d, *J* 8.9 Hz), 6.92−6.96 (1 H, m), 6.68 (1 H, br d, *J* 6.9 Hz), 4.70 (1 H, d, *J* 16.0 Hz), 4.59 (1 H, d, *J* 16.0 Hz), 4.10 (1 H, dd, *J* 8.6, 6.2 Hz), 3.68 (3 H, s), 3.63−3.67 (1 H, m), 3.47−3.58 (2 H, m), 1.93−2.07 (2 H, m), 1.61−1.73 (1 H, m), 1.49−1.58 (2 H, m), 0.91 (3 H, d, *J* 6.8 Hz), 0.86 (3 H, d, *J* 6.8 Hz), 0.72 (3 H, t, *J* 7.1 Hz); δ_C ($CDCl_3$, 62.9 MHz) 171.65, 163.19, 139.57, 131.23, 129.41, 128.48, 126.78, 126.52, 114.22, 77.20, 64.30, 60.40, 58.23, 55.66, 42.76, 30.67, 29.05, 19.54, 19.21, 18.66, 13.60; HRMS (FAB) calcd for $C_{22}H_{33}N_2O_5S_2$ (MH^+): 469.183091, found 469.181357.

Suberoyl 4-Methoxyanilide *N*-Methylhydroxamic Acid (17). The chloride linker resin **2** (0.10 g, 0.064 mmol, 0.64 mmol g^{-1}), suspended in CH_2Cl_2:THF (2:1; 3 mL) was treated with *N*-Fmoc-*N*-methylhydroxylamine (0.069 g, 0.256 mmol) in the presence of DIEA (0.128 mmol) for 72 h to yield the required resin **9a** (0.093 g, 83%; Fmoc substitution 0.466 mmol g^{-1}, 84% efficiency). The resin product (0.092 g, 0.043 mmol) was placed in a reaction column and swollen in DMF for 5 h. The resin was then washed with DMF (10 min, 2.5 mL min^{-1}), Fmoc-deprotected by treatment with 20% *v*/*v* piperidine in DMF and finally washed with DMF (10 min, 2.5 mL min^{-1}), after which excess DMF was removed. To the resin was added a DMF (1 mL) solution containing monomethyl suberate (77 μL, 0.43 mmol), HATU (0.163 g, 0.43 mmol) and DIEA (150 μL, 0.86 mmol), and the mixture was stirred at room temperature for 18 h. Following washing the resin with DMF (10 mL), excess DMF was expelled, a solution of 0.5 M LiOH in MeOH/THF (3:5; 1 mL) was added and the resultant mixture was stirred at ambient temperature for 24 h. The resin product was extensively washed with DMF (20 min, 2.5 mL min^{-1}), and was then added a solution of benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP; 0.034 g, 0.065 mmol) in DMF (1 mL) followed by 4-methoxyaniline (0.053 g, 0.43 mmol). Following stirring at room temperature for 1 h, a further aliquot of PyBOP (0.022 g, 0.043 mmol) was added and the mixture was stirred for a further 20 h. The resin was filtered, washed successively with DMF, CH_2Cl_2 and MeOH, and dried in vacuo (0.085 g, 91%). Treatment of the derivatized resin (97 mg) with 1% TFA in CH_2Cl_2 (5 mL) for 75 min afforded the crude product as a beige solid (11.25 mg, 94%; >95% when analyzed by RP-HPLC). The crude compound was purified by preparative RP-HPLC to afford the title compound as a white solid (6.64 mg, 60% based on 11.25 mg compound purified, 55% theoretical): mp 135 °C; RP-HPLC 20−60% B in 25 min, t_R 11.6 min; δ_H ($CDCl_3$:CD_3OD, 250 MHz) 7.44 (2 H, d, *J* 9.1 Hz), 6.86 (2 H, d, *J* 9.1 Hz), 3.80 (3 H, s), 2.46 (2 H, t, *J* 7.4 Hz), 2.33 (2 H, t, *J* 7.5), 1.59−1.74 (4 H, m), 1.37−1.40 (4 H, m); δ_C ($CDCl_3$:CD_3OD, 62.9 MHz) 174.75, 172.60, 156.00, 131.21, 121.65, 113.78, 55.23, 36.61, 35.63, 31.66, 28.37, 28.32, 25.16, 24.16; HRMS (FAB) calcd for $C_{16}H_{25}N_2O_4$ (MH^+): 309.181433, found 309.183703.

***N*-(*N*-Benzyl-*N*-(4-methoxybenzenesulfonyl)-L-leucyl) *N*-Cyclobutylmethyl Hydroxamic Acid (18).** The chloride linker resin **2** (0.10 g, 0.064 mmol, 0.64 mmol g^{-1}) was treated with *N*-Fmoc-*N*-cyclobutylmethylhydroxylamine (0.083 g, 0.256 mmol) in the presence of DIEA (0.128 mmol) for 72 h to yield the required resin **9c** (0.094 g, 80%; Fmoc substitution 0.243 mmol g^{-1}, 50% efficiency). The derivatized resin product (0.092 g, 0.022

mmol) was placed in a reaction column and swollen in DMF for 3 h. The resin underwent Fmoc-deprotection by treatment with 20% *v*/*v* piperidine in DMF and finally washed with DMF (10 min, 2.5 mL min^{-1}), after which excess DMF was removed. A solution of FmocLeuOH (0.078 g, 0.22 mmol), HOAt (0.03 g, 0.22 mmol) and DIPCDI (34.4 μL, 0.22 mmol) in DMF (1 mL) was then added to the resin, and the mixture was gently stirred at room temperature for 24 h. The resin was then washed with DMF (10 min, 2.5 mL min^{-1}), followed by 20% *v*/*v* piperidine in DMF (5 min, 2.5 mL min^{-1}), and finally washed with DMF (10 min, 2.5 mL min^{-1}). A solution of 4-methoxybenzenesulfonyl chloride (0.036 g, 0.176 mmol) in DMF (1 mL) was added to the resin, followed by DIEA (7.6 μL, 0.44 mmol) and the resultant suspension was gently agitated at room temperature for 24 h. The resin was filtered, washed successively with DMF, CH_2Cl_2 and MeOH, and dried in vacuo to yield the desired resin product (0.088 g, 95%). A batch of the derivatized resin (0.079 g, 0.017 mmol) was allowed to swell in dry THF (2 mL) for 16 h in a round-bottomed flask under nitrogen. To this suspension was added benzyl alcohol (35 μL, 0.34 mmol) and tributylphosphine (42 μL, 0.17 mmol) at 0 °C, followed by TMAD (0.03 g, 0.17 mmol). The mixture was allowed to reach ambient temperature and stirred under nitrogen for 24 h. The supernatant was removed and the resin was washed with THF (2 × 3 mL). The resin in THF (2 mL) was re-alkylated in the same manner with the above quantities of reagents and stirred for 16 h at room temperature. The resin was filtered, washed successively with THF, DMF, CH_2Cl_2 and MeOH, and dried in vacuo to give the required resin (0.074 g, 84%). Treatment of the derivatized resin (74 mg) with 1% TFA in CH_2Cl_2 (5 mL) for 75 min afforded the crude product as a colorless oil (6.2 mg, 83%; >80% when analyzed by RP-HPLC). The crude compound was purified by preparative RP-HPLC to afford the title compound (5.3 mg, 85% based on 6.2 mg compound purified, 71% theoretical): ES-MS^+ *m*/*z* 474.9 (MH^+), calcd 475.62; RP-HPLC 50−100% B in 20 min, t_R 13.6 min; δ_H ($CDCl_3$, 250 MHz) Mixtures of *Z*/*E* isomers 7.70 (0.67 H, d, *J* 8.7 Hz), 7.64 (1.33 H, d, *J* 8.8 Hz), 7.24−7.33 (5 H, m), 6.96 (0.67 H, d, *J* 8.6 Hz), 6.93 (1.33 H, d, *J* 8.7 Hz), 4.95 (0.67 H, dd, *J* 5.2, 9.2 Hz), 4.85 (0.33 H, m), 4.57, 4.78 (0.67 H, 2 × d, *J* 16.3 Hz), 4.37, 4.75 (1.33 H, 2 × d, *J* 16.2 Hz), 3.87 (3 H, s), 3.53−3.59 (1.33 H, m), 3.46, 3.97 (0.67 H, m), 2.59−2.68 (1 H, m), 1.82−1.92, 2.02−2.09 (6 H, m), 1.69−1.79 (1 H, m), 1.25 (1 H, m), 0.88−1.16 (1 H, m), 0.65, 0.83 (2.4 H, 2 × d, *J* 6.6 Hz), 0.60, 0.73 (3.6 H, 2 × d, *J* 6.6 Hz); δ_C ($CDCl_3$, 62.9 MHz) 163.11, 129.57, 128.29, 128.16, 127.21, 114.18, 77.20, 55.65, 53.13, 52.74, 52.18, 48.64, 47.71, 38.35, 33.21, 26.02, 24.79, 22.64, 21.71, 18.44; HRMS (FAB) calcd for $C_{25}H_{35}N_2O_5S$ (MH^+): 475.226669, found 475.225401.

4-(2-Thienyl)benzoyl-L-alanine (20). The FmocAlaOH-derivatized resin **7** (105 mg, 0.054 mmol; Fmoc-substitution 0.541 mmol g^{-1}, 100% efficiency) was placed in a reaction column and swollen in DMF for 4 h. The resin was then washed with DMF (10 min, 2.5 mL min^{-1}), Fmoc-deprotected by treatment with 20% *v*/*v* piperidine in DMF and finally washed with DMF (10 min, 2.5 mL min^{-1}), after which excess DMF was removed. A mixture of 4-bromobenzoic acid (0.043 g, 0.216 mmol), HOAt (0.029 g, 0.216 mmol) and DIPCDI (34 μL, 0.216 mmol) in DMF (1 mL) was added to the resin and the mixture was gently stirred at room temperature for 16 h. The resin was then washed with DMF (10 min, 2.5 mL min^{-1}). The resin was filtered, washed successively with DMF, CH_2Cl_2 and MeOH, and dried in vacuo to yield the desired resin product **19** (102 mg, 98%). The resin **19** (102 mg, 0.05 mmol) was allowed to swell in DMF for 1 h in a round-bottomed flask. To the resin suspension was added 2-thiopheneboronic acid (21.0 mg, 0.165 mmol) and 2 M aqueous Na_2CO_3 solution (103 μL, 0.206 mmol) and the mixture was deoxygenated under a stream of nitrogen for 5 min. Recently prepared tetrakis(triphenylphosphine)palladium(0) (6.4 mg, 0.0055 mmol) was then added, and the resultant mixture was stirred under nitrogen at 80 °C for 24 h. The mixture was filtered when hot, the resin washed sequentially with DMF (20 mL), DMF/H_2O (1:1, 40 mL), DMF (20 mL), THF (20 mL) and MeOH (20 mL), and dried in vacuo to afford the required resin product (101 mg, 98%). Treatment of the derivatized resin (100 mg) using 1% TFA in CH_2Cl_2 (5 mL) for 75 min yielded the crude product as a pale yellow solid (13.61 mg, 90%; >95% when analyzed by RP-HPLC). The crude compound was purified by preparative RP-HPLC to afford the title compound as a white solid (10.45 mg, 77% based on 13.6 mg compound purified, 70% theoretical): mp 191−193 °C; RP-HPLC 50−100% B in 20 min, t_R 3.6 min; δ_H ($CDCl_3$:CD_3OD, 250 MHz) 7.84 (2 H, d, *J* 8.6 Hz), 7.69 (2 H, d, *J* 8.6 Hz), 7.42 (1 H, dd, *J* 1.1, 3.6 Hz), 7.36 (1 H, dd, *J* 1.1, 5.1 Hz), 7.12 (1 H, dd, *J* 3.6, 5.1 Hz), 4.72 (1 H, br q, *J* 7.2 Hz), 1.56 (3 H, d, *J* 7.2 Hz); δ_C ($CDCl_3$:CD_3OD, 62.9 MHz) 166.97, 142.82, 137.55, 132.11, 128.12, 127.69, 125.90, 125.55, 124.12, 48.26, 17.92; HRMS (FAB) calcd for $C_{14}H_{14}NO_3S$ (MH^+): 276.069440, found 276.069310.

(*Z*)-2-(4-Phenylbenzoylamino)but-2-enoic Acid (21). Fmoc-ThrOH (66 mg, 0.192 mmol) was reacted with **2** (100 mg, 0.064 mmol, 0.64 mmol g^{-1}) to yield the derivatized resin **7d** (106 mg, 90%; Fmoc-substitution 0.525 mmol g^{-1}, 98% efficiency). The resin product was placed in a reaction column and swollen in DMF for 16 h. The resin was then washed with DMF (10 min, 2.5 mL min^{-1}), Fmoc-deprotected by treatment with 20% *v*/*v* piperidine in DMF and finally washed with DMF (10 min, 2.5 mL min^{-1}), after which excess DMF was removed. A DMF (1 mL) solution containing 4-biphenylcarboxylic acid (44 mg, 0.22 mmol), HOAt (30 mg, 0.22 mmol) and DIPCDI (34.4 μL, 0.22 mmol) was added to the resin (105 mg, 0.055 mmol), and the mixture was gently stirred at room temperature for 4 h. The resin was then washed with DMF (10 min, 2.5 mL min^{-1}), 20% *v*/*v* piperidine in DMF (6 min, 2.5 mL min^{-1}) and finally DMF (10 min, 2.5 mL min^{-1}). The resin was filtered, washed successively with DMF, CH_2Cl_2 and MeOH, and dried in vacuo to yield the desired resin product (101 mg, 98%). A portion of the β-hydroxyamino acid derivatized resin (87 mg, 0.046 mmol) was swollen in CH_2Cl_2 (0.5 mL) and THF (0.5 mL) in a two-necked round-bottomed flask for 1 h under a nitrogen atmosphere. The solution was cooled to −78 °C, and triethylamine (192 μL, 1.38 mmol) followed by thionyl chloride (16 μL, 0.184 mmol) were carefully added to the resin suspension. The mixture was stirred at −78 °C for 1 h, after which a further quantity of thionyl chloride (16 μL, 0.184 mmol) was added, and the stirred mixture was gradually warmed to −50 °C over a period of 1.5 h. The mixture was then stirred at 5 °C for 2.5 h. The resin was filtered, washed successively with DMF, CH_2Cl_2 and MeOH, and dried in vacuo to afford the required resin (84 mg, 96%). Treatment of the derivatized resin (84 mg) with 1% TFA in CH_2Cl_2 for 15 min afforded the crude product as an off-white solid (14.04 mg; >75% when analyzed by RP-HPLC). The crude compound was purified by preparative RP-HPLC to afford the title compound as a white solid (6.59 mg, 52%): mp 204−206 °C (dec); RP-HPLC 50−100% B in 20 min, t_R 4.4 min; δ_H ($CDCl_3$:CD_3OD, 250 MHz) 7.98 (2 H, d, *J* 8.5 Hz), 7.71 (2 H, d, *J* 8.5 Hz), 7.64 (2 H, m), 7.45 (3 H, m), 6.98 (1 H, q, *J* 7.2 Hz), 1.87 (3 H, d, *J* 7.2 Hz); δ_C ($CDCl_3$:CD_3OD, 62.9 MHz) 166.55, 166.06, 144.72, 139.76, 134.55, 132.29, 128.79, 127.95, 127.90, 127.13, 127.05, 14.62; HRMS (CI) calcd for $C_{17}H_{15}NO_3$ (M^+): 281.105194, found 281.105881.

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Supporting Information Available: Experimental details and spectral data for aminomethyl NovaGel derivatization studies, **11**, **16c**, **16d** and intermediate compounds; general procedures for attachment of *O*-nucleophiles to **2**; general procedures for cleavage experiments and RP-HPLC analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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