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Ring Opening of a Resin-Bound Chiral Aziridine with Phenol Nucleophiles

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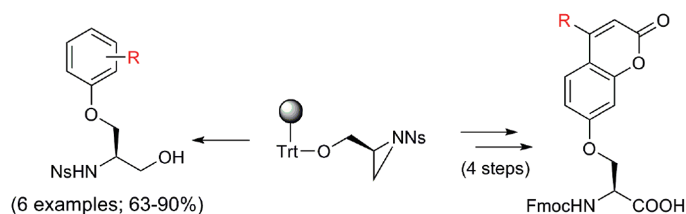

An efficient and versatile solid-phase route for the preparation of aryl-alkyl ethers is described. Regioselective ring opening of a resin-bound chiral aziridine with phenolic nucleophiles constitutes the key feature of the present protocol that allows incorporation of fluorescent moieties and subsequent on-resin protecting group interconversion. Initial experiments demonstrated that a competing oligomerization may occur by concomitant attacks of transient nosylamide anions on neighboring aziridines, resulting in formation of dimeric and trimeric byproduct. Expectedly, the significance of this alternative reaction pathway was strongly dependent on resin loading, and a low loading (<0.4 mmol g^{-1}) was required for obtaining high yields of the desired aryl-alkyl ethers. The developed methodology allowed preparation of novel *N*-Fmoc-protected coumaryl amino acid building blocks, which were incorporated into peptides by solid-phase peptide synthesis.

Introduction

Aziridines are important intermediates in organic synthesis as their highly strained ring system readily undergoes a range of ring-opening reactions with a variety of nucleophiles under mild conditions.[1−3] Although substantial progress in the general exploration of aziridines has been achieved during the past two decades, their utilization in solid-phase processes has been poorly investigated and limited to *N*- and *S*-nucleophiles.[4−9] In particular, solid-phase aziridinolysis with phenolic nucleophiles remains unexplored despite the emergence of several reports concerning the corresponding solution-phase conversions.[1,10−16]

As a part of our ongoing research in solid-phase synthesis (SPS) methodology involving ring opening of aziridines,[7−9] we here target functionalized aryl-alkyl ethers that are precursors of α-amino acids featuring aromatic structural motifs, thus contributing to the extension of the synthetic toolbox for aziridine-based SPS. Recently, we reported on the ring opening of resin-bound nosyl-activated aziridine-2-methanol with various 2-amino alcohols leading to chiral 2,5-disubstituted piperazine scaffolds.[9] Now, this resin-bound aziridine is investigated with respect to its ring opening with phenolic *O*-nucleophiles.

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The aim was to develop a versatile practical solid-phase protocol for the synthesis of aryl-alkyl ethers displaying amine and alcohol/carboxylic acid functionalities.

Previously, enantioselective syntheses of coumarin-bearing amino acids have been carried out by diastereoselective alkylation of chiral glycine equivalents.[17−19] In recent syntheses of coumaryl amino acids, protected aspartic and glutamic acids served as chiral starting materials that were converted to coumarylalanines and coumarylethylglycines.[20] These methods yielded optically pure amino acids; however, either multiple steps were required or the products were obtained in poor overall yields. Consequently, aziridinolysis with 7-hydroxycoumarin derivatives followed by on-resin protecting group manipulation and postcleavage oxidation were envisaged to constitute a novel four-step route to *N*-Fmoc-protected coumaryl amino acid building blocks.

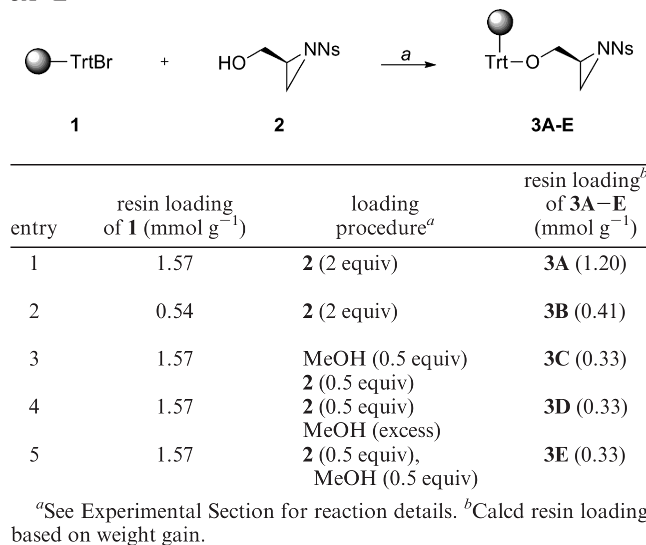
Results and Discussion

Preparation and Loading of Activated Aziridine onto the Solid Support. (*S*)-*N*-Nosylaziridine-2-methanol[9] (**2**), prepared from (*S*)-1-tritylaziridine-2-methanol,[21] was loaded onto a freshly prepared polystyrene trityl bromide (PS-TrtBr) resin[22] (**1**) in various ways to give resin-bound aziridines **3A−E** (Table 1). Activation by a *p*-nitrobenzenesulfonyl (nosyl = Ns) group has the advantage of being a readily removable protecting group during SPS.[23,24]

Optimization of Ring Opening of Resin 3A with Phenol. Initially, an optimization of the ring opening of resin **3A** was undertaken. First, nucleophilic ring openings of resin **3A** were performed at room temperature (rt) using 10 equiv of phenol while assessing the possible influence of base, solvent, and additive (Table 2).

Recently, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) were reported as suitable bases for ring opening of trisubstituted aziridines with phenol nucleophiles under solution-phase conditions.[12] However, when DBU (10 equiv) was employed in toluene, only a very low isolated yield of the desired aryl-alkyl ether **4** was obtained after a reaction time of 16 h (Table 2, entry 1). An attempted improvement by using TBD (10 equiv) led only to a slightly higher yield (Table 2, entry 2), and changing the solvent to DMF under otherwise similar conditions was likewise fruitless (Table 2, entries 3 and 4). Nevertheless, we found that these disappointing efforts to obtain aryl-alkyl ether **4** in acceptable yields was due mainly to competing aziridine ring-opening reactions with DBU and TBD serving as surprisingly efficient *N*-nucleophiles resulting in **5** and **6**, respectively, as the main products (Scheme 1).

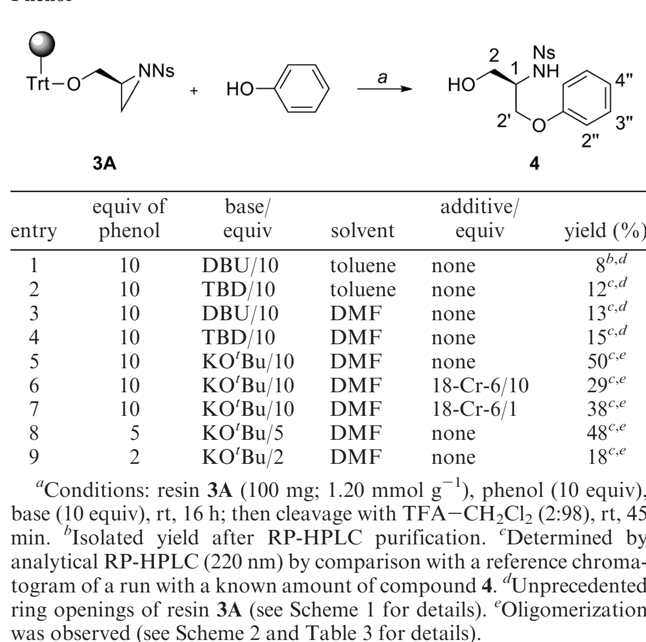
TABLE 1. Preparation of Nosyl-Activated Resin-Bound Aziridines 3A−E



entry	resin loading of **1** (mmol g^{-1})	loading procedure[a]	resin loading[b] of **3A−E** (mmol g^{-1})
1	1.57	**2** (2 equiv)	**3A** (1.20)
2	0.54	**2** (2 equiv)	**3B** (0.41)
3	1.57	MeOH (0.5 equiv) **2** (0.5 equiv)	**3C** (0.33)
4	1.57	**2** (0.5 equiv) MeOH (excess)	**3D** (0.33)
5	1.57	**2** (0.5 equiv), MeOH (0.5 equiv)	**3E** (0.33)

[a]See Experimental Section for reaction details. [b]Calcd resin loading based on weight gain.

TABLE 2. Optimization Studies of the Ring Opening of Resin 3A with Phenol[a]



entry	equiv of phenol	base/equiv	solvent	additive/equiv	yield (%)
1	10	DBU/10	toluene	none	8[b,d]
2	10	TBD/10	toluene	none	12[c,d]
3	10	DBU/10	DMF	none	13[c,d]
4	10	TBD/10	DMF	none	15[c,d]
5	10	KO^{t}Bu/10	DMF	none	50[c,e]
6	10	KO^{t}Bu/10	DMF	18-Cr-6/10	29[c,e]
7	10	KO^{t}Bu/10	DMF	18-Cr-6/1	38[c,e]
8	5	KO^{t}Bu/5	DMF	none	48[c,e]
9	2	KO^{t}Bu/2	DMF	none	18[c,e]

[a]Conditions: resin **3A** (100 mg; 1.20 mmol g^{-1}), phenol (10 equiv), base (10 equiv), rt, 16 h; then cleavage with TFA−CH_2Cl_2 (2:98), rt, 45 min. [b]Isolated yield after RP-HPLC purification. [c]Determined by analytical RP-HPLC (220 nm) by comparison with a reference chromatogram of a run with a known amount of compound **4**. [d]Unprecedented ring openings of resin **3A** (see Scheme 1 for details). [e]Oligomerization was observed (see Scheme 2 and Table 3 for details).

Relatively few examples have so far been reported on alkylation of DBU[25−29] and TBD,[30,31] respectively, and either very reactive alkylating agents (e.g., alkyl triflates) or forced reaction conditions (typically heating to reflux at 70−110 °C for several hours) have been utilized. Although DBU and TBU are indeed sufficiently strong bases to effect a high degree of deprotonation

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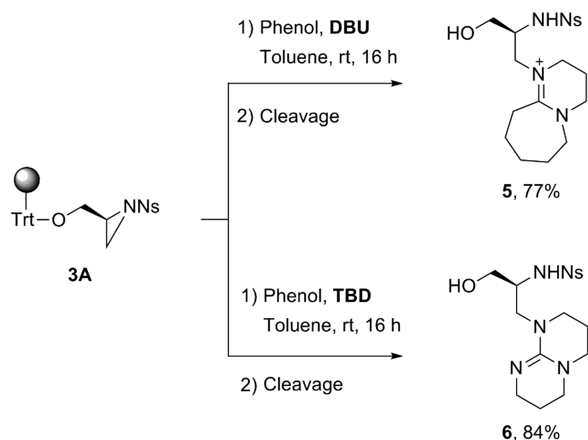
SCHEME 1. Unprecedented Ring Opening of Resin 3A with DBU and TBD



of phenols,[12] these observations indicated that the nucleophilicity of the phenolic anions were surpassed by these *N*-nucleophiles. Hence, a stronger and more hindered base (KO^{t}Bu) was applied to ensure both complete conversion of phenol into its anion and suppression of side reactions. Encouragingly, it was found that the use of 10 equiv of KO^{t}Bu afforded a significantly higher (but still moderate) yield of aryl-alkyl ether **4** (Table 2, entry 5). Notably, according to LC-MS and NMR analysis only the desired regioisomer was present in the crude product. The structure of **4** was confirmed by 2D NMR experiments (COSY and NOESY). Thus, correlations between the sulfonamide (NH) and the adjacent proton (H-1) as well as between the hydroxylic and the methylene protons (H-2) in the hydroxymethyl group were observed. In addition, the close proximity of the H-2′ and H-2″/H-6″ in the aryl alkyl ether moiety (Ph-O-CH_2-) was confirmed by the presence of the corresponding correlation in the NOESY spectrum (see Supporting Information for the spectra). Performing the ring opening in the presence of 10 equiv of 18-crown-6 in order to increase the nucleophilicity of the phenolic anion resulted unexpectedly in a decreased yield (Table 2, entry 6). This observation is tentatively explained by assuming that the entire, large potassium crown ether counterion complex must also enter the narrow resin pores, since macroscopic separation of charges would result in an electrostatic gradient at the resin surface. Hence, this bulky ion pair is less capable of entering the interior of the resin beads, where a large proportion of the reaction sites are located. This explanation was further corroborated by an additional experiment in which only 1 equiv of 18-crown-6 was used under otherwise similar conditions. In accordance with our hypothesis, this resulted in an intermediate yield of aryl-alkyl ether **4** (Table 2, entry 7). Noteworthy, attempts to decrease the excess of phenol and KO^{t}Bu afforded lower yields of **4** or extensive formation of byproduct (Table 2, entries 8 and 9). During the subsequent analysis of KO^{t}Bu-mediated ring openings of resin **3A** with phenol, it was found that additional peaks in the HPLC chromatogram were attributable to byproduct arising from a competing oligomerization. In Scheme 2 we propose a mechanism involving repeated attacks of transient nosylamide anions on neighboring aziridines that accounts for the formation of dimeric and trimeric byproduct **7** and **8**.

TABLE 3. Influence of Method of Resin Loading and Reaction Time on Aziridine Ring Opening[a]

entry	resin	*t* (h)	**4** (%)[b]	**7** (%)[b]	**8** (%)[b]
1	**3C**	16	76	5	0
2	**3D**	16	86	5	0
3	**3E**	16	88	7	0
4	**3E**	1	90	7	0

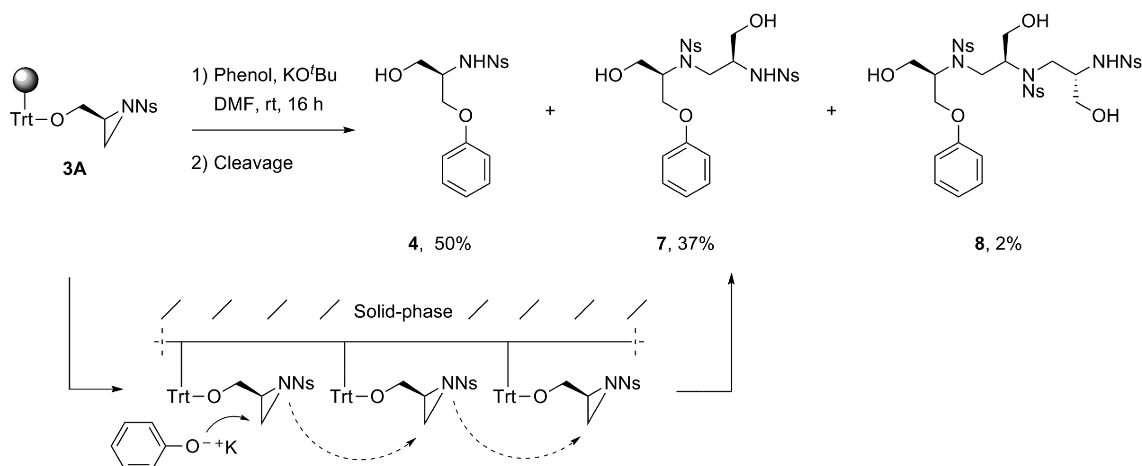
[a]Conditions: Appropriate resin **3C−E** (100 mg; 0.33 mmol g^{-1}), phenol (10 equiv), KO^{t}Bu (10 equiv), DMF, rt; then cleavage with TFA−CH_2Cl_2 (2:98), rt, 45 min. [b]Determined by analytical RP-HPLC (220 nm) by comparison with reference chromatograms of known amounts of compounds **4**, **7**, and **8**.

To overcome this obstacle, we decided to prepare a resin-bound aziridine on a low-loading resin ($\ll$1.20 mmol g^{-1}). In that case, it was anticipated that oligomerization would be diminished as the result of an increased physical separation of the aziridine moieties.

Evaluation of Low-Loading Resins with Phenol. Resin **3B** was prepared by attaching aziridine building block **2** to resin **1** (0.54 mmol g^{-1}) obtained from a commercial low-loading trityl alcohol resin (Table 1, entry 2). Subsequent ring opening of resin **3B** with phenol followed by cleavage afforded aryl-alkyl ether **4** in a good yield. Notably, no detectable amounts of oligomeric byproduct were present in the crude (Scheme 3).

With the intention to identify the most favorable distribution of the aziridine moieties on the solid support, we decided to evaluate different protocols leading to low-loading resins by partial

SCHEME 2. Proposed Mechanism for KO^{t}Bu-Mediated Cascade Ring Openings of Resin 3A Following Initial Attack of Phenolate



SCHEME 3. Ring Opening of Resin 3B with Phenol

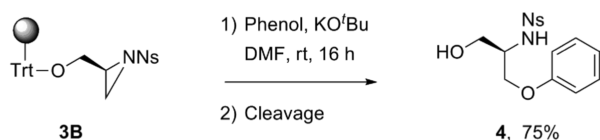


TABLE 4. Ring Opening of Resin 3E with an Array of Substituted Phenols[a]

entry	X	Y	product (% yield)[b]
1	CO_2Me	H	**9** (71)
2	CN	H	**10** (76)
3	Cl	H	**11** (81)
4	H	Cl	**12** (63)
5	H	CH_2OH	**13** (76)

[a]Conditions: resin **3E** (200 mg; 0.33 mmol g^{-1}), appropriate phenol nucleophile (10 equiv), KO^{t}Bu (10 equiv), DMF, rt, 1 h; then cleavage with TFA–CH_2Cl_2 (2:98), rt, 45 min. [b]Isolated yield after RP-HPLC purification.

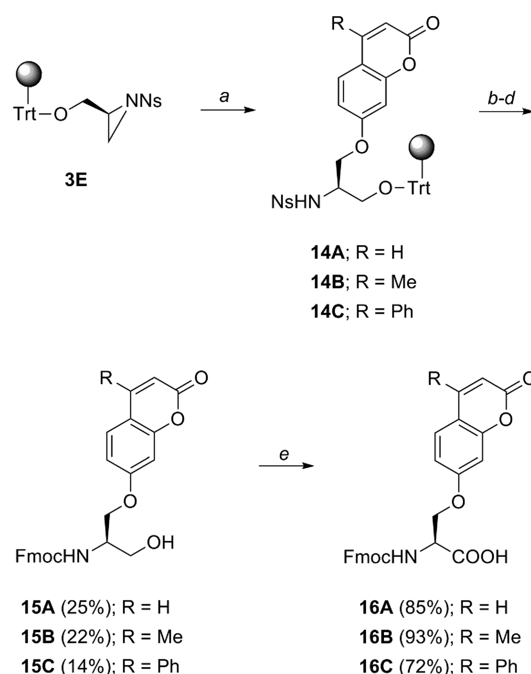
loading with aziridine **2** (Table 1, entries 3–5). Starting from high-loading resin **1** (1.57 mmol g^{-1}), aziridine building block **2** and methanol were loaded onto the solid support in various ways to give resins **3C–E** (0.33 mmol g^{-1}). Resin **3C** was obtained by first loading resin **1** with 0.5 equiv of methanol for 10 min and then adding 0.5 equiv of aziridine building block **2** (Table 1, entry 3), whereas resin **3D** was prepared by an initial loading of aziridine building block **2** (0.5 equiv) onto resin **1** for 10 min followed by treatment with excess MeOH/*i*Pr_2EtN/CH_2Cl_2 (5:10:85) for 5 min (Table 1, entry 4). Finally, simultaneous loading of a mixture of aziridine building block **2** (0.5 equiv) and methanol (0.5 equiv) onto resin **1** led to resin **3E** (Table 1, entry 5). With these differently loaded resins (all displaying similar loadings of 0.33 mmol g^{-1}) in hand, the optimal conditions for ring opening were further investigated (Table 3).

By using resin **3C**, the desired aryl-alkyl ether **4** was obtained in 76% yield with decreased formation of byproduct **7**, while byproduct **8** was not detectable (Table 3, entry 1). Even higher yields were obtained with resins **3D** and **3E** (Table 3, entries 2 and 3) indicating a more favorable distribution of the aziridine moiety on the solid support compared to the fully loaded as well as more expensive resin **3B**. Moreover, a very short reaction time (1 h) proved adequate to achieve full conversion of resin **3E** resulting in a high yield of aryl-alkyl ether **4** (Table 3, entry 4), and thus resin **3E** was employed in the subsequent experiments.

Ring Opening with Substituted Phenol Nucleophiles. A collection of *ortho*- and *para*-substituted phenols was employed in the ring opening of resin **3E** resulting in good to high yields of aryl-alkyl ethers **9–13** (Table 4).

Both *ortho*- and *para*-substituted phenols were examined in aziridine ring opening with resin **3E**, and in all cases satisfactory isolated yields of the desired aryl-alkyl ethers **9–13** were obtained. However, as expected, *o*-chlorophenol afforded a lower isolated yield of aryl-alkyl ether **12** (Table 4, entry 4) compared with that of *p*-chlorophenol (**11**; Table 4, entry 3), indicating sterical hindrance to be of some importance. Moreover, the presence of a benzyl alcohol functionality proved compatible as demonstrated in the ring opening with 2-hydroxybenzyl alcohol, which resulted exclusively in aryl-alkyl ether **13** (Table 4, entry 5).

SCHEME 4. Preparation of Novel Coumaryl Amino Acids[a]



[a]Conditions: (a) resin **3E** (4.0 g; 0.33 mmol g^{-1}), appropriate 7-hydroxycoumarin (10 equiv), KO^{t}Bu (10 equiv), DMF, rt, 1 h. (b) 2-Mercaptoethanol (10 equiv), DBU (5 equiv), DMF, rt, 2 h. (c) Fmoc-OSu (5 equiv), *i*Pr_2EtN (5 equiv), THF, rt, 2 h. (d) TFA–CH_2Cl_2 (2:98), rt, 45 min. (e) NaOCl (5 equiv), TEMPO (1 equiv), KBr (10 mol %), 5% $NaHCO_3$ (aq), acetone, 0 °C, 1 h.

Preparation of Novel Fluorescent Coumaryl Amino Acids. A number of coumarins are commercially available, and they constitute a group of fluorescent compounds having the advantage of possessing extended excitation and emission spectral ranges, high emission quantum yield, photostability, and solubility in many solvents.[18,32] Therefore, coumarins have been extensively used as fluorophores for labeling of amines, thiols, and acids,[33] thus being useful tools in chemical biology.[34] As C- and N-terminal domains of peptides often represent sites for biological interaction, the possibility of incorporating a fluorescence label at a well-chosen internal position is of considerable interest. Consequently, the use of an intact amino acid building block as a means for introducing a fluorescent chromophore offers two main advantages: (i) preparation by solid-phase peptide synthesis (SPPS) is straightforward, and (ii) terminals may be functionalized to improve other desired properties. Substituted coumarins are accessible by many pathways, including

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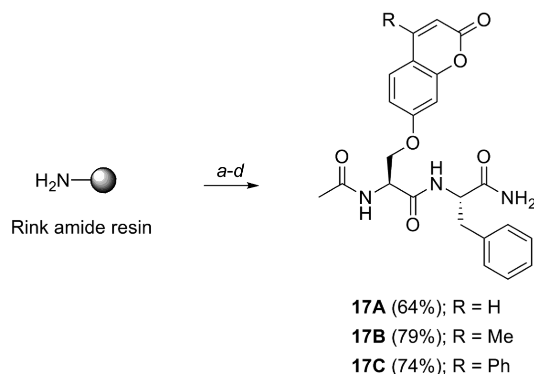
SCHEME 5. Preparation of Coumarin-Bearing Dipeptides 17A−C[a]



17A (64%); R = H
17B (79%); R = Me
17C (74%); R = Ph

[a]Conditions: (a) Rink amide resin (25 mg; 1.0 mmol g^{-1}), Fmoc-Phe-OH (2 equiv), PyBOP (2 equiv), HOAt (2 equiv), $i\mathrm{Pr_2EtN}$ (4 equiv), DMF, rt, 2 h, then Fmoc-deprotection with 20% piperidine in DMF, rt, 2 × 10 min. (b) Appropriate *N*-Fmoc-protected coumaryl amino acid **16A−C** (3 equiv), DIC (3 equiv), HOAt (3 equiv), MW irradiation, 60 °C, 30 min; then Fmoc-deprotection with 20% piperidine in DMF, rt, 2 × 10 min. (c) Ac_2O/$i\mathrm{Pr_2EtN}$/NMP (1:2:3), rt, 1 h. (d) TFA−CH_2Cl_2 (95:5), rt, 1 h.

von Pechmann, Perkin, Knoevenagel, Reformatsky, and Wittig reactions.[35−39]

To illustrate the efficiency of the developed solid-phase protocol a series of novel *N*-Fmoc-protected coumaryl amino acid building blocks **16A−C** were prepared (Scheme 4).

Regioselective ring opening of resin **3E** with three commercially available 7-hydroxycoumarin nucleophiles afforded resins **14A−C**. Standard removal of the nosyl group and subsequent Fmoc *N*-protection followed by cleavage under mild conditions furnished alcohol intermediates **15A−C** in acceptable yields after column chromatography. Finally, the desired coumarin-bearing building blocks **16A−C** were obtained upon oxidation with TEMPO/hypochlorite, and their utility in SPPS was validated by preparation of fluorescent dipeptides **17A−C** as depicted in Scheme 5.

Absorption (λ_{abs}) and fluorescence (λ_{em}) wavelength maxima were measured for **17A−C** (Table 5). The coumarin-labeled dipeptides exhibited both higher absorption and emission maxima than the natural fluorescent amino acids tryptophan (λ_{abs} = 278 nm, λ_{em} = 352 nm) and tyrosine (λ_{abs} = 274 nm, λ_{em} = 303 nm).

Finally, coumaryl amino acid **16B** was used for N-terminal labeling of octaarginine (Scheme 6), a well-known cell-penetrating peptide (CPP) often used as a reference compound in cellular uptake studies relating to CPP-mediated drug delivery.[40]

Conclusion

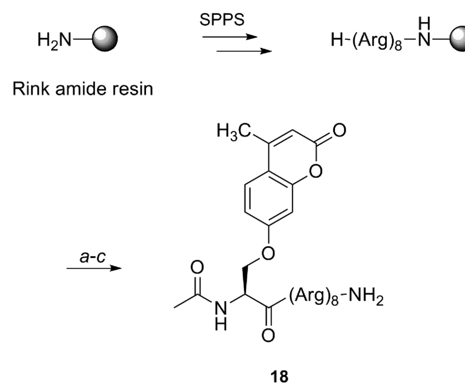
In the present work, an efficient solid-phase protocol for the preparation of aryl-alkyl ethers *via* regioselective ring opening of a resin-bound chiral aziridine with phenolic nucleophiles has been developed. Thorough studies revealed a strong correlation between the degree of resin loading and formation of oligomeric byproduct. It was found that resin loadings of 0.3−0.4 mmol g^{-1} were sufficiently low to allow formation of the desired aryl-alkyl ethers in high yields. The developed solid-phase protocol was further utilized for efficient preparation of novel *N*-Fmoc-protected coumaryl amino acid building blocks. On-resin *N*-protecting group exchange and a postcleavage oxidation constituted the last steps of these syntheses. Finally, the coumaryl amino acids were incorporated into peptides by SPPS.

TABLE 5. Fluorescence Properties of Coumarin-Bearing Peptides

compound	λ_{abs} (nm)[a]	λ_{em} (nm)[a]
17A	319	388
17B	320	381
17C	326	400

[a]Conditions: determined in HPLC-grade methanol.

SCHEME 6. Preparation of Fluorescently Labeled Octaarginine[a]



[a]Conditions: (a) **16B** (3 equiv), DIC (3 equiv), HOAt (3 equiv), MW irradiation, 60 °C, 30 min; then Fmoc-deprotection with 20% piperidine in DMF, rt, 2 × 10 min. (b) Ac_2O−$i\mathrm{Pr_2EtN}$−NMP (1:2:3), rt, 1 h. (c) TFA−TIS−H_2O (95:2.5:2.5), rt, 5 h.

The methodology presented here may readily enable preparation of an array of aryl-alkyl ether building blocks for combinatorial chemistry. In particular the corresponding unnatural amino acids may be obtained directly with an *N*-protection suitable for traditional solid-phase peptide synthesis, thus contributing to the continuous extension of the diversity of peptide analogues. The advantages of the protocol are those typical for relatively short solid-phase sequences: (i) near-quantitative conversion in the individual steps by using an excess of reagents, (ii) simple composition of the resulting crude product mixture, (iii) significant reduction of the number of chromatographic purification steps, and (iv) possibility of synthesis of many compounds in parallel.

Experimental Section

General. Starting materials were purchased from commercial suppliers and used without further purification. Trityl alcohol polystyrene resins with loadings of 1.75 and 0.60 mmol g^{-1} were obtained from IRIS Biotech and Matrix Innovation, respectively. Rink-amide-(aminomethyl)-polystyrene resin (1.0 mmol g^{-1}) was from Fluka. DMF dried over 4 Å molecular sieves (H_2O < 0.01%) was from Fluka, and anhydrous CH_2Cl_2 was distilled from P_2O_5 and kept over 4 Å molecular sieves. Water for reversed-phase HPLC was filtered through a 0.22 μm membrane filter (Millipak40, Millipore). Other solvents were analytical or HPLC grade and were used as received. Microwave-assisted coupling of **16A−C** in the

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syntheses of **17A–C** was carried out in an Initiator single mode microwave cavity producing controlled irradiation at 2.45 GHz (Biotage AB, Uppsala). The reactions were run in sealed vessels (0.5–2.0 mL), and magnetic stirring was used. Variable power was employed to reach the temperature desired (within 1–2 min) and then to maintain it during the period of time programmed. Temperature was monitored by an IR sensor focused on a point on the reactor vial; the sensor was calibrated to internal solution reaction temperature by the manufacturer. Preparation of resin-bound octaarginine was performed on a CEM Liberty microwave peptide synthesizer, and the final introduction of **17B** was performed manually as above. Analytical DAD-HPLC was performed by using a Phenomenex Luna (150 mm × 4.6 mm; C18(2); particle size 3 μm) column eluted at a rate of 0.8 mL/min. Injection volumes were 20 μL of a 1 mg/mL solution, and separations were performed at 40 °C. Solvent mixtures A (H_2O–MeCN–TFA 95:5:0.1) and B (MeCN–H_2O–TFA 95:5:0.1) were used in a gradient rising linearly from 0% to 100% of B during 30 min. Preparative HPLC separations were carried out on a Phenomenex Luna (250 mm × 21.2 mm; C18; particle size 5 μm) column. Solvent mixtures A (H_2O–MeCN–TFA 95:5:0.1) and B (MeCN–H_2O–TFA 95:5:0.1) were used in a gradient rising linearly from 0% to 100% of B during 30 min. Vacuum liquid chromatography (VLC) was performed using Merck silica gel 60 (particle size 0.015–0.040 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using $CDCl_3$, CD_3OD or DMSO-d_6 as solvents and TMS as internal standard. ^{1}H NMR and ^{13}C NMR spectra of compounds **17A–C** were recorded at 600 and 150 MHz, respectively. Multiplicities of ^{1}H NMR signals are reported as follows: s, singlet; br s, broad singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; m, multiplet. All target compounds were characterized by HRMS.

Preparation of Resins 3A and 3B. The resins were prepared using a previously reported procedure,[9] except that resin **3B** was prepared from a low-loading (0.60 mmol g^{-1}) polystyrene trityl alcohol resin.

Preparation of Resin 3C. A solution of MeOH (32 μL, 0.79 mmol) and iPr$_2$EtN (0.69 mL, 3.95 mmol) in anhydrous CH_2Cl_2 (5 mL) was added to a freshly prepared trityl bromide resin **1** (1.00 g; 1.57 mmol g^{-1}) preswollen in anhydrous CH_2Cl_2 (10 mL; in a 25 mL syringe equipped with a PP filter) under N_2 at rt. The resin was agitated for 10 min under N_2. The resin was drained, and a solution of **2** (204 mg, 0.79 mmol) and iPr$_2$EtN (0.69 mL, 3.95 mmol) in anhydrous CH_2Cl_2 (5 mL) was added. The resin was agitated for an additional 10 min under N_2. The resin was drained and washed with MeOH/iPr$_2$EtN/CH_2Cl_2 (5:10:85, 5 mL for 5 min). The resin was drained and washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 5 mL for 5 min). The resin was dried under vacuum to afford resin **3C** (1.09 g; calcd resin loading based on weight gain: 0.33 mmol g^{-1}).

Preparation of Resin 3D. A solution of **2** (204 mg, 0.79 mmol) and iPr$_2$EtN (0.69 mL, 3.95 mmol) in anhydrous CH_2Cl_2 (5 mL) was added to a freshly prepared trityl bromide resin **1** (1.00 g; 1.57 mmol g^{-1}) preswollen in anhydrous CH_2Cl_2 (10 mL; in a 25 mL syringe equipped with a PP filter) under N_2 at rt. The resin was agitated for 10 min under N_2. The resin was drained and washed with MeOH/iPr$_2$EtN/CH_2Cl_2 (5:10:85, 5 mL for 5 min). The resin was drained and washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 5 mL for 5 min). The resin was dried under vacuum to afford resin **3D** (1.09 g; calcd resin loading based on weight gain: 0.33 mmol g^{-1}).

Large-Scale Preparation of Resin 3E. A solution of **2** (3.10 g, 11.80 mmol), MeOH (0.95 mL, 11.80 mmol), and iPr$_2$EtN (12.3 mL, 70.80 mmol) in anhydrous CH_2Cl_2 (100 mL) was added to a freshly prepared trityl bromide resin **1** (15.00 g; 1.57 mmol g^{-1}) preswollen in anhydrous CH_2Cl_2 (100 mL; in a 250 mL reaction vessel equipped with a filter). The resin was agitated for 10 min using a 180° variable-speed flask shaker. The resin was drained and washed with MeOH/iPr$_2$EtN/CH_2Cl_2 (5:10:85; 100 mL for 5 min). The resin was drained and washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 100 mL for 5 min). The resin was dried under vacuum to afford resin **3E** (16.45 g; calcd resin loading based on weight gain: 0.33 mmol g^{-1}).

General Procedure A (*GP A*): Ring Opening of Resin-Bound Aziridine with Phenols. A solution of the appropriate phenol (10 equiv) and KO^{t}Bu (74 mg, 0.66 mmol; 10 equiv) in anhydrous DMF (1 mL) was added to resin **3E** (200 mg; 0.33 mmol g^{-1}; in a 10 mL syringe equipped with a PP filter). The resin was agitated at rt for 1 h under N_2 and then drained and washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 5 mL for 5 min). The product was cleaved with 2% TFA–CH_2Cl_2 (1.5 mL for 30 min, then 1.5 mL for 15 min), and finally the resin was washed with CH_2Cl_2 (2 mL). The eluates were pooled and the solvents were removed *in vacuo*. The crude material was purified by preparative reversed-phase HPLC.

(*R*)-*N*-(1-Hydroxy-3-phenoxypropan-2-yl)-4-nitrobenzenesulfonamide (4). Preparation according to *GP A* using phenol (62 mg, 0.66 mmol). Yield: 21 mg (90%) as a colorless syrup. $[\alpha]^{20}_D$ +11.1 (*c* 0.44, DMF). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.37 (d, J = 7.0 Hz, 1H), 8.33–8.29 (m, 2H), 8.06–8.03 (m, 2H), 7.20–7.15 (m, 2H), 6.88–6.83 (m, 1H), 6.64–6.61 (m, 2H), 4.97 (t, J = 5.5 Hz, 1H, OH), 3.95–3.83 (m, 2H), 3.53–3.40 (m, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 157.7, 149.1, 147.3, 129.2 (2C), 127.9 (2C), 124.2 (2C), 120.6, 114.1 (2C), 66.7, 61.1, 55.0. ν_{max} (KBr) cm^{-1} 3420, 3177, 2884, 1526, 1351, 1245, 1157. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{15}H_{16}N_2O_6S$, 353.0807; found, 353.0797.

(*S*)-1-[3-Hydroxy-2-(4-nitrophenylsulfonamido)propyl]-2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepin-1-ium (5). Preparation according to *GP A* using phenol (155 mg, 1.20 mmol). Note: resin **3A** (100 mg; 1.20 mmol g^{-1}) and DBU (179 μL, 1.20 mmol) were used instead of resin **3E** and KO^{t}Bu, respectively. Yield: 38 mg (77%) as a pale yellow oil. $[\alpha]^{20}_D$ +28.9 (*c* 0.54, DMF). ^{1}H NMR (CD_3OD, 300 MHz): δ 8.43–8.40 (m, 2H), 8.13–8.10 (m, 2H), 3.76–3.57 (m, 9H), 3.32–3.27 (m, 2H; hidden in part under the solvent peak), 3.01–2.96 (m, 2H), 2.23–2.15 (m, 2H), 1.93–1.77 (m, 6H). ^{13}C NMR (CD_3OD, 75 MHz): δ 169.0, 151.4, 148.2, 129.2 (2C), 125.4 (2C), 61.9, 56.3, 55.9, 55.7 (2C), 50.4, 29.6 (2C), 26.9, 24.3, 20.8. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{18}H_{27}N_4O_5S^+$, 411.1697; found, 411.1674.

(*S*)-*N*-[1-(2,3,4,6,7,8-Hexahydro-1*H*-pyrimido[1,2-*a*]pyrimidin-1-yl)-3-hydroxypropan-2-yl]-4-nitrobenzenesulfonamide (6). Preparation according to *GP A* using phenol (155 mg, 1.20 mmol). Note: resin **3A** (100 mg; 1.20 mmol g^{-1}) and TBD (167 mg, 1.20 mmol) were used instead of resin **3E** and KO^{t}Bu, respectively. Yield: 40.0 mg (84%) as a pale yellow oil. $[\alpha]^{20}_D$ +21.7 (*c* 0.59, DMF). ^{1}H NMR (CD_3OD, 300 MHz): δ 8.41–8.38 (m, 2H), 8.12–8.09 (m, 2H), 3.75–3.67 (m, 1H), 3.53–3.46 (m, 3H), 3.42–3.53 (m, 7H), 3.32–3.30 (m, 2H; hidden in part under the solvent peak), 2.12–1.99 (m, 4H). ^{13}C NMR (CD_3OD, 75 MHz): δ 152.6, 151.3, 148.5, 129.2 (2C), 125.3 (2C), 61.9, 54.5, 52.3, 49.2 (2C) (hidden in part under the solvent peak), 40.0 (2C), 21.9, 21.7. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{16}H_{23}N_5O_5S$, 398.1498; found, 398.1481.

***N*-[(*S*)-3-Hydroxy-2(4-nitrophenylsulfonamido)propyl]-*N*-[(*R*)-1-hydroxy-3-phenoxypropan-2yl]-4-nitrobenzenesulfonamide (7).** Preparation according to *GP A* using phenol (115 mg, 1.20 mmol) and KO^{t}Bu (135 mg, 1.20 mmol). Note: resin **3A** (100 mg; 1.20 mmol g^{-1}) was used instead of resin **3E**. Yield: 27 mg (37%) as a colorless syrup. $[\alpha]^{20}_D$ +45.9 (*c* 0.56, DMF). ^{1}H NMR (CD_3OD, 300 MHz): δ 8.36–8.33 (m, 2H), 8.25–8.22 (m, 2H), 8.14–8.11 (m, 2H), 8.05–8.02 (m, 2H), 7.14–7.09 (m, 2H), 6.87–6.82 (m, 1H), 6.54–6.51 (m, 2H), 4.08–4.01 (m, 3H), 3.83–3.79 (m, 1H), 3.70–3.47 (m, 5H), 3.34–3.27 (m, 1H; hidden in part under the solvent peak). ^{13}C NMR (CD_3OD, 75 MHz): δ 158.7, 151.2, 151.1, 148.4, 147.0, 130.2 (2C), 129.8 (2C), 129.4 (2C), 125.2 (2C), 125.1

(2C), 122.2, 115.1 (2C), 66.9, 62.3, 62.1, 61.8, 56.7, 48.4 (hidden in part under the solvent peak). HRMS (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{26}N_4O_{11}S_2$, 611.1118; found, 611.1126.

***N*-[(*S*)-3-Hydroxy-2-[4-nitrophenylsulfonamido]propyl]-*N*-[(*S*)-1-hydroxy-3-[*N*-[(*R*)-1-hydroxy-3-phenoxypropan-2-yl]-4-nitrophenylsulfonamido]propan-2-yl]-4-nitrobenzenesulfonamide (8).** Preparation according to *GP A* using phenol (115 mg, 1.20 mmol) and KO^{t}Bu (135 mg, 1.20 mmol). Note: resin **3A** (100 mg; 1.20 mmol g^{-1}) was used instead of resin **3E**. Yield: 2 mg (2%) as a colorless syrup. $[\alpha]^{20}_D$ +4.6 (*c* 0.26, DMF). ^{1}H NMR (CD_3OD, 300 MHz): δ 8.40−8.37 (m, 2H), 8.30−8.27 (m, 2H), 8.21−8.18 (m, 2H), 8.14−8.12 (m, 4H), 8.10−8.05 (m, 2H), 7.15−7.10 (m, 2H), 6.87−6.82 (m, 1H), 6.67−6.64 (m, 2H), 4.30−4.21 (m, 1H), 4.13−4.04 (m, 3H), 4.00−3.87 (m, 3H), 3.83−3.75 (m, 4H), 3.63−3.51 (m, 2H), 3.40−3.36 (m, 2H). ^{13}C NMR (CD_3OD, 75 MHz): δ 158.7, 151.3 (2C), 150.9, 148.4, 147.0, 145.8, 130.1 (4C), 129.7 (2C), 129.6 (2C), 125.3 (2C), 125.2 (2C), 125.0 (2C), 122.2, 115.3 (2C), 67.0, 63.2, 62.5, 61.7, 60.5, 59.7, 58.1, 48.4 (hidden in part under the solvent peak), 48.0 (hidden in part under the solvent peak). HRMS (*m/z*): $[M + H]^+$ calcd for $C_{33}H_{36}N_6O_{16}S_3$, 869.1428; found, 869.1375.

(*R*)-Methyl-4-[3-hydroxy-2-(4-nitrophenylsulfonamido)propoxy]-benzoate (9). Preparation according to *GP A* using methyl-4-hydroxybenzoate (100 mg, 0.66 mmol). Yield: 19 mg (71%) as a colorless syrup. $[\alpha]^{20}_D$ +26.7 (*c* 0.36, DMF). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.42−8.40 (br s, 1H, NH), 8.32−8.29 (m, 2H), 8.05−8.02 (m, 2H), 7.80−7.78 (m, 2H), 6.75−6.72 (m, 2H), 5.01 (t, J = 5.5 Hz, 1H, OH), 4.04−3.93 (m, 2H), 3.80 (s, 3H), 3.54−3.41 (m, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 165.5, 161.5, 149.1, 147.2, 130.9 (2C), 127.8 (2C), 124.2 (2C), 121.8, 114.1 (2C), 67.1, 61.0, 54.7, 51.8. ν_{max} (KBr) cm^{-1} 3433, 3147, 2906, 1730, 1529, 1348, 1244, 1169. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{17}H_{18}N_2O_8S$, 411.0862; found, 411.0890.

(*R*)-*N*-[1-(4-Cyanophenoxy)-3-hydroxypropan-2-yl]-4-nitrobenzenesulfonamide (10). Preparation according to *GP A* using 4-cyanophenol (79 mg, 0.66 mmol). Yield: 19 mg (76%) as a colorless syrup. $[\alpha]^{20}_D$ +27.1 (*c* 0.41, DMF). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.38 (d, J = 7.0 Hz, 1H, NH), 8.32−8.29 (m, 2H), 8.05−8.02 (m, 2H), 7.67−7.64 (m, 2H), 6.83−6.80 (m, 2H), 4.04−3.95 (m, 2H), 3.80−3.62 (m, 1H), 3.58−3.38 (m, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 161.1, 149.1, 147.1, 133.9 (2C), 127.8 (2C), 124.2 (2C), 118.9, 115.1 (2C), 102.9, 67.2, 60.9, 54.6. ν_{max} (KBr) cm^{-1} 3422, 3140, 2901, 2224, 1529, 1350, 1258, 1165. HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{16}H_{15}N_3O_6S$, 400.0579; found, 400.0578.

(*R*)-*N*-[1-(4-Chlorophenoxy)-3-hydroxypropan-2-yl]-4-nitrobenzenesulfonamide (11). Preparation according to *GP A* using 4-chlorophenol (84 mg, 0.66 mmol). Yield: 21 mg (81%) as a colorless syrup. $[\alpha]^{20}_D$ +22.1 (*c* 0.28, DMF). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.38 (d, J = 7.5 Hz, 1H, NH), 8.33−8.30 (m, 2H), 8.05−8.02 (m, 2H), 7.22−7.19 (m, 2H), 6.68−6.65 (m, 2H), 4.98 (t, J = 5.5 Hz, 1H, OH), 3.94−3.84 (m, 2H), 3.54−3.39 (m, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 156.5 (2C), 149.1, 147.2, 128.9 (2C), 127.8 (2C), 124.2 (2C), 115.8 (2C), 67.1, 60.9, 54.8. ν_{max} (KBr) cm^{-1} 3426, 3145, 2907, 1529, 1344, 1248, 1153, 1090. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{15}H_{15}ClN_2O_6S$, 387.0418; found, 387.0391.

(*R*)-*N*-[1-(2-Chlorophenoxy)-3-hydroxypropan-2-yl]-4-nitrobenzenesulfonamide (12). Preparation according to *GP A* using 2-chlorophenol (85 mg, 0.66 mmol). Yield: 16 mg (63%) as a colorless syrup. $[\alpha]^{20}_D$ +11.4 (*c* 0.51, DMF). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.40 (d, J=6.5 Hz, 1H, NH), 8.31−8.28 (m, 2H), 8.06−8.03 (m, 2H), 7.31 (dd, J = 1.5, 8.0 Hz, 1H), 7.22 (ddd, J=1.5, 7.0, 8.0 Hz, 1H), 6.99 (dd, J=1.5, 8.0 Hz, 1H), 6.89 (ddd, J = 1.5, 7.0, 8.0 Hz, 1H), 5.05−4.89 (br s, 1H, OH), 4.06−3.95 (m, 2H), 3.53−3.43 (m, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 153.1, 149.0, 146.9, 129.7, 128.1, 127.8 (2C), 124.2 (2C), 121.5, 121.1, 113.5, 67.6, 60.8, 54.7. ν_{max} (KBr) cm^{-1}3428, 3133, 2917, 1529, 1347, 1248, 1152, 1051. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{15}H_{15}ClN_2O_6S$, 387.0418; found, 387.0392.

(*R*)-*N*-[1-Hydroxy-3-[2-(hydroxymethyl)phenoxy]propan-2-yl]-4-nitrobenzenesulfonamide (13). Preparation according to *GP A* using 2-hydroxybenzyl alcohol (82 mg, 0.66 mmol). Yield: 19 mg (76%) as a pale yellow syrup. $[\alpha]^{20}_D$ +10.7 (*c* 0.41, DMF). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.33 (d, J = 7.0 Hz, 1H, NH), 8.31−8.28 (m, 2H), 8.06−8.03 (m, 2H), 7.28 (dd, J = 1.0, 7.5 Hz, 1H), 7.10 (ddd, J=1.0, 7.5, 8.5 Hz, 1H), 6.87 (ddd, J=1.0, 7.5, 8.5 Hz, 1H), 6.73 (dd, J=1.0, 8.5 Hz, 1H), 5.05−4.89 (m, 2H, OH), 4.33 (d, J= 14.5 Hz, 1H), 4.24 (d, J = 14.5 Hz, 1H), 3.89 (d, J = 4.5 Hz, 2H), 3.53−3.44 (m, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 154.5, 149.0, 147.1, 130.5, 127.7 (2C), 127.2, 126.6, 124.3 (2C), 120.1, 110.5, 66.4, 60.7, 57.7, 54.8. ν_{max} (KBr) cm^{-1} 3326, 2876, 1530, 1350, 1243, 1162. HRMS (*m/z*): [M + Na] calcd for $C_{16}H_{18}N_2O_7S$, 405.0732; found, 405.0745.

General Procedure B (*GP B*): Preparation of Coumaryl Amino Alcohols. A solution of the appropriate 7-hydroxycoumarin (10 equiv) and KO^{t}Bu (1.50 g, 13.20 mmol; 10 equiv) in anhydrous DMF (40 mL) was added to resin **3E** (4.00 g; 0.33 mmol g^{-1}; in a 60 mL syringe equipped with a PP filter). The resin was agitated at rt for 1 h under N_2 and then drained and washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 40 mL, for 5 min). Then a solution of 2-mercaptoethanol (0.90 mL, 13.20 mmol; 10 equiv) and DBU (1.00 mL, 6.60 mmol; 5 equiv) in anhydrous DMF (40 mL) was added to the resin. After gentle agitation at rt for 1.5 h under N_2, the resin was drained and then treated again with 2-mercaptoethanol (0.90 mL, 13.60 mmol; 10 equiv) and DBU (1.00 mL, 6.60 mmol; 5 equiv) in anhydrous DMF (40 mL) for 30 min under N_2. The resin was drained and washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 40 mL, for 5 min). Fmoc-OSu (2.20 g, 6.60 mmol; 5 equiv) in anhydrous THF (30 mL) was added to the resin preswollen in anhydrous THF (10 mL) and *i*Pr_2EtN (1.20 mL, 6.60 mmol; 5 equiv). The resin was gently stirred at rt for 2 h under N_2. The resin was drained and washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 40 mL, for 5 min). The product was cleaved with 2% TFA−CH_2Cl_2 (40 mL for 30 min, then 40 mL for 15 min), and finally the resin was eluted with CH_2Cl_2 (40 mL). The eluates were pooled, and the solvents were removed *in vacuo*. The crude material was purified by VLC (heptane/EtOAc 4:1 as eluent).

(*R*)-(9*H*-Fluoren-9-yl)methyl 1-Hydroxy-3-(2-oxo-2*H*-chromen-7-yloxy)propan-2-ylcarbamate (15A). Preparation according to *GP B* using 7-hydroxycoumarin (2.1 g, 13.2 mmol). Yield: 154 mg (25%; overall yield in 3 steps) as a white foam. $[\alpha]^{20}_D$ +15.2 (*c* 0.50, DMF). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75−7.73 (m, 2H), 7.62−7.57 (m, 3H), 7.41−7.29 (m, 5H), 6.84−6.80 (m, 2H), 6.24 (d, J = 9.5 Hz, 1H), 5.52−5.44 (br s, 1H, NH), 4.59−4.44 (m, 2H), 4.22−4.09 (m, 3H), 3.94−3.66 (m, 2H), 3.23−3.14 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.4, 161.3, 156.4, 155.6, 143.7 (2C), 143.5 (2C), 141.3, 128.9, 127.8 (2C), 127.1 (2C), 125.0 (2C), 120.1 (2C), 113.3, 112.9, 112.7, 101.8, 67.1 (2C), 61.8, 51.7, 47.3. HRMS (*m/z*): [M + Na] calcd for $C_{27}H_{23}NO_6$, 480.1423; found, 480.1423.

(*R*)-(9*H*-Fluoren-9-yl)methyl 1-Hydroxy-3-(4-methyl-2-oxo-2*H*-chromen-7-yloxy)propan-2-ylcarbamate (15B). Preparation according to *GP B* using 7-hydroxy-4-methylcoumarin (2.3 g, 13.2 mmol). Yield: 122 mg (20%; overall yield in 3 steps) as a white foam. $[\alpha]^{20}_D$ +12.6 (*c* 0.31, DMF). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.92−7.86 (m, 2H), 7.72−7.66 (m, 3H), 7.46−7.28 (m, 5H), 7.02−6.96 (m, 2H), 6.22 (s, 1H), 4.40−4.30 (m, 2H), 4.28−4.20 (m, 3H), 4.19−4.06 (m, 2H), 3.54−3.48 (m, 2H), 2.40 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 162.3, 160.9, 156.7, 155.5, 154.2, 144.7 (2C), 141.5 (2C), 128.4 (2C), 127.9 (2C), 127.3, 126.0 (2C), 120.9 (2C), 114.1, 113.3, 112.0, 102.2, 68.4, 66.3, 61.2, 53.2, 47.7, 19.1. HRMS (*m/z*): [M + Na] calcd for $C_{28}H_{25}NO_6$, 494.1580; found, 494.1596.

(*R*)-(9*H*-Fluoren-9-yl)methyl 1-Hydroxy-3-(4-phenyl-2-oxo-2*H*-chromen-7-yloxy)propan-2-ylcarbamate (15C). Preparation

according to *GP B* using 7-hydroxy-4-phenylcoumarin (3.1 g, 13.2 mmol). Yield: 95 mg (14% overall yield) as a white foam. $[\alpha]^{20}_{D}$ +16.2 (*c* 0.37, DMF). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74−7.72 (m, 2H), 7.59−7.56 (m, 2H), 7.50−7.48 (m, 3H), 7.39−7.25 (m, 7H), 6.87−6.76 (m, 2H), 6.17 (s, 1H), 5.57 (d, *J* = 6.0 Hz, 1H, NH), 4.44−4.42 (m, 2H), 4.21−4.14 (m 4H), 3.98−3.77 (m, 2H), 2.87−2.64 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.5, 161.3, 156.4, 155.8, 155.7, 143.7 (2C), 141.3 (2C), 135.3, 129.7, 128.9 (2C), 128.4 (2C), 128.0, 127.8 (2C), 127.1 (2C), 125.0 (2C), 120.0 (2C), 112.8, 112.4, 112.0, 102.1, 67.0 (2C), 61.7, 51.8, 47.3. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{33}H_{27}NO_6$, 556.1736; found, 556.1755.

General Procedure C (*GP C*): Preparation of Coumaryl Amino Acids. To a stirred heterogeneous mixture of the appropriate coumaryl amino alcohol (1 equiv) in acetone (12 mL) and aqueous 5% $NaHCO_3$ (3 mL) were added KBr (0.1 equiv) and TEMPO (1 equiv) at 0 °C. An aqueous NaOCl solution (1.7 M; 5 equiv) was then added dropwise during 15 min, and the mixture was stirred vigorously at 0 °C for 1 h. Acetone was removed *in vacuo*, and the resulting aqueous mixture was acidified to pH 5−6 with 10% citric acid. After extraction of the aqueous layer with EtOAc (3 × 15 mL), the combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by VLC (heptane/EtOAc/HOAc 50:50:1 as eluent).

(*S*)-2[[(9*H*-Fluoren-9-yl)methoxy]carbonylamino]-3-(2-oxo-2*H*-chromen-7-yloxy)propanoic Acid (16A). Preparation according to *GP C* using **15A** (150 mg, 0.33 mmol), KBr (4 mg, 0.03 mmol), TEMPO (52 mg, 0.33 mmol), and NaOCl (~1.7 M; 0.97 mL, 1.65 mmol). Yield: 131 mg (85%) as a white foam. $[\alpha]^{20}_{D}$ +25.2 (*c* 0.50, DMF). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.00−7.94 (m, 2H), 7.87−7.84 (m, 2H), 7.74−7.72 (m, 2H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.42−7.37 (m, 2H), 7.33−7.26 (m, 2H), 7.00−6.93 (m, 2H), 4.56−4.50 (m, 1H), 4.40−4.32 (m, 4H), 4.25−4.20 (m, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 170.8, 161.1, 160.1, 156.1, 155.1, 144.1, 143.6 (2C), 140.6 (2C), 129.4, 127.6 (2C), 127.0 (2C), 125.2 (2C), 120.1 (2C), 112.7 (2C), 112.6, 101.4, 68.0, 66.0, 53.9, 46.7. HRMS (*m*/*z*): [M + Na] calcd for $C_{27}H_{21}NO_7$, 494.1216; found, 494.1198.

(*S*)-2[[(9*H*-Fluoren-9-yl)methoxy]carbonylamino]-3-(4-methyl-2-oxo-2*H*-chromen-7-yloxy)propanoic Acid (16B). Preparation according to *GP C* using **15B** (262 mg, 0.56 mmol), KBr (7 mg, 0.06 mmol), TEMPO (88 mg, 0.56 mmol), and NaOCl (~1.7 M; 1.60 mL, 2.80 mmol). Yield: 251 mg (93%) as a white foam. $[\alpha]^{20}_{D}$ +12.6 (*c* 0.31, DMF). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.95 (d, *J* = 8.0 Hz, 1H, NH), 7.89−7.87 (m, 2H), 7.74−7.66 (m, 3H), 7.42−7.40 (m, 2H), 7.33−7.28 (m, 2H), 6.99−6.95 (m, 2H), 6.21 (s, 1H), 4.49−4.41 (m, 1H), 4.38−4.30 (m, 4H), 4.24−4.20 (m, 1H), 2.38 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 170.7, 161.0, 159.9, 155.9, 154.4, 153.2, 143.6 (2C), 140.5 (2C), 127.5 (2C), 126.9 (2C), 126.4, 125.1 (2C), 119.1 (2C), 113.3, 112.3, 111.3, 101.4, 67.9, 65.8, 53.6, 46.6, 18.2. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{28}H_{23}NO_7$, 486.1553; found, 486.1568.

(*S*)-2[[(9*H*-Fluoren-9-yl)methoxy]carbonylamino]-3-(2-oxo-4-phenyl-2*H*-chromen-7-yloxy)propanoic Acid (16C). Preparation according to *GP C* using **15C** (85 mg, 0.16 mmol), KBr (2 mg, 0.02 mmol), TEMPO (25 mg, 0.16 mmol), and NaOCl (~1.7 M; 0.60 mL, 0.80 mmol). Yield: 63 mg (72%) as a white foam. $[\alpha]^{20}_{D}$ +15.0 (*c* 0.58, DMF). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.98 (d, *J* = 8.5 Hz, 1H, NH), 7.89−7.87 (m, 2H), 7.73−7.71 (m, 2H), 7.56−7.48 (m, 5H), 7.42−7.27 (m, 5H), 7.11 (d, *J* = 2.5 Hz, 1H), 6.95 (dd, *J* = 2.5, 9.0 Hz, 1H), 6.24 (s, 1H), 4.51−4.41 (m, 1H), 4.40−4.30 (m, 4H), 4.23−4.19 (m, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 170.7, 161.1, 159.8, 156.0, 155.2, 154.9, 143.6 (2C), 140.6 (2C), 134.8, 129.6, 128.8 (2C), 128.3 (2C), 127.8, 127.5 (2C), 126.9 (2C), 125.2 (2C), 120.0 (2C), 112.8, 112.2, 111.5, 101.9, 68.0, 65.8, 53.6, 46.6. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{33}H_{25}NO_7$, 548.1709; found, 548.1705.

General Procedure D (*GP D*): Preparation of Coumarin-Bearing Dipeptides. A solution of Fmoc-Phe-OH (20 mg, 0.05 mmol; 2 equiv), PyBOP (26 mg, 0.05 mmol; 2 equiv), HOAt (6 mg, 0.05 mmol; 2 equiv), and *i*Pr_2EtN (18 μL, 0.10 mmol; 4 equiv) in anhydrous DMF (0.50 mL) was added to Fmoc-deprotected Rink amide resin (25 mg; 1.00 mmol g^{-1}) preswollen in anhydrous DMF (0.50 mL) in a Teflon reactor. The resin was gently agitated at rt for 2 h, drained, and washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 5 mL, for 5 min). The resin was then treated with a mixture of Ac_2O−*i*Pr_2EtN−NMP (1:2:3; 2 mL) for 10 min, drained, and washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 5 mL for 5 min). Next, the resin was treated with 20% piperidine−DMF (5 mL; 2 × 10 min), drained, and washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 5 mL for 5 min). A solution of the appropriate *N*-Fmoc-protected coumaryl amino acid (0.075 mmol; 3 equiv), DIC (13 μL, 0.075 mmol; 3 equiv), and HOAt (10 mg, 0.075 mmol; 3 equiv) in anhydrous DMF (1 mL) was added to the resin in a sealed microwave reactor (0.5−2 mL) in which the mixture was heated to 60 °C for 30 min under MW irradiation (Biotage). The resin was transferred to a Teflon reactor, drained, and washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 5 mL, for 5 min). After treatment with 20% piperidine−DMF (2 × 10 min), the resin was drained and washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 5 mL, for 5 min). The resin was treated with a solution of Ac_2O−*i*Pr_2EtN−NMP (1:2:3; 2 mL) for 1 h at rt, drained, and washed with DMF, MeOH and CH_2Cl_2 (each 3 × 5 mL for 5 min). The product was cleaved with 95% TFA−CH_2Cl_2 (2 mL for 1 h), and then the resin was eluted with CH_2Cl_2 and MeOH (each 2 mL upon shaking for 5 min). Finally, the resin was eluted with TFA (2 mL upon shaking for 5 min). The eluates were pooled, and the solvents were removed *in vacuo*. The crude material was purified by preparative reversed-phase HPLC.

(*S*)-2-Acetamido-*N*-[(*S*)-1-amino-1-oxo-3-phenylpropan-2-yl]-3-(2-oxo-2*H*-chromen-7-yloxy)propanamide (17A). Preparation according to *GP D* using **16A** (35 mg, 0.075 mmol). Yield: 7 mg (64%) as a white foam. $[\alpha]^{20}_{D}$ −9.4 (*c* 0.50, DMF). ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.32 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.32 (br s, 1H), 7.24−7.18 (m, 5H), 7.16 (br s, 1H), 6.95 (d, *J* = 2.5 Hz, 1H), 6.90 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.31 (d, *J* = 9.0 Hz, 1H), 4.67−4.64 (m, 1H), 4.47−4.43 (m, 1H), 4.19−4.15 (m, 2H), 3.05 (dd, *J* = 5.0, 14.0 Hz, 1H), 2.86 (dd, *J* = 9.0, 14.0 Hz, 1H), 1.87 (s, 3H). ^{13}C NMR (DMSO-d_6, 150 MHz): δ 172.4, 168.8, 168.6, 161.1, 160.1, 155.1, 144.2, 137.7, 129.4, 129.1 (2C), 127.9 (2C), 126.1, 112.6 (3C), 101.4, 68.0, 53.8, 52.3, 37.1, 22.4. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{23}H_{23}N_3O_6$, 460.1485; found, 460.1500.

(*S*)-2-Acetamido-*N*-[(*S*)-1-amino-1-oxo-3-phenylpropan-2-yl]-3-(4-methyl-2-oxo-2*H*-chromen-7-yloxy)propanamide (17B). Preparation according to *GP D* using **16B** (36 mg, 0.075 mmol). Yield: 9 mg (79%) as a white foam. $[\alpha]^{20}_{D}$ −9.3 (*c* 0.50, DMF). ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.33 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.33 (br s, 1H), 7.25−7.17 (m, 5H), 7.16 (br s, 1H), 6.93 (dd, *J* = 2.5, 8.0 Hz, 1H), 6.91 (d, *J* = 2.5 Hz, 1H), 6.23 (s, 1H), 4.67−4.64 (m, 1H), 4.47−4.43 (m, 1H), 4.19−4.14 (m, 2H), 3.05 (dd, *J* = 5.0, 14.0 Hz, 1H), 2.86 (dd, *J* = 9.5, 14.0 Hz, 1H), 2.40 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (DMSO-d_6, 150 MHz): δ 172.4, 169.8, 168.6, 161.0, 160.0, 154.5, 153.3, 137.7, 129.1 (2C), 127.9 (2C), 126.4, 126.1, 113.3, 112.3, 111.3, 101.4, 68.0, 53.8, 52.3, 37.1, 22.4, 18.0. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{24}H_{25}N_3O_6$, 474.1641; found, 474.1653.

(*S*)-2-Acetamido-*N*-[(*S*)-1-amino-1-oxo-3-phenylpropan-2-yl]-3-(2-oxo-4-phenyl-2*H*-chromen-7-yloxy)propanamide (17C). Preparation according to *GP D* using **16C** (41 mg, 0.075 mmol). Yield: 9 mg (70%) as a white foam. $[\alpha]^{20}_{D}$ −9.0 (*c* 0.10, DMF). ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.33 (d, *J* = 7.0 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.58−7.52 (m, 5H), 7.36 (d, *J* = 9.0 Hz, 1H), 7.32 (br s, 1H), 7.25−7.17 (m, 5H), 7.15 (br s, 1H), 7.06 (d, *J* = 2.5 Hz, 1H), 6.90 (dd, *J* = 2.5, 9.0 Hz, 1H), 6.26 (s, 1H), 4.68−4.65 (m, 1H), 4.47−4.43 (m, 1H), 4.21−4.16 (m, 2H), 3.05 (dd, *J* = 5.0, 14.5 Hz, 1H), 2.85 (dd, *J* = 9.0, 14.5 Hz, 1H), 1.87 (s, 3H). ^{13}C NMR

(DMSO-d_6, 75 MHz): δ 172.3, 169.7, 168.5, 161.2, 159.9, 155.2, 155.0, 137.7, 134.9, 129.6, 129.1 (2C), 128.8 (2C), 128.3 (2C), 127.9 (2C), 127.8, 126.1, 112.7, 112.0, 111.5, 101.9, 68.1, 53.8, 52.2, 37.2, 22.4. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{29}H_{27}N_3O_6$, 514.1978; found, 514.1996.

Preparation of Coumarin-Labeled Octaarginine (18). Resin-bound octaarginine (100 mg, 0.025 mmol) was prepared with a Rink amide linker by using Fmoc chemistry on a CEM Liberty Microwave Peptide Synthesizer. Loading as well as chain elongation were performed as double-couplings each with Fmoc-Arg(Pbf)-OH (5 equiv), TBTU (5 equiv), and *i*Pr_2EtN (5 equiv) at 60 °C for 15 min. Fmoc-deprotection was carried out with 20% piperidine−DMF. Compound **16B** (30 mg, 0.075 mmol) was introduced by using a coupling with DIC (12 μL, 0.075 mmol) and HOAt (10 mg, 0.075 mmol) in anhydrous DMF (2 mL) under microwave irradiation (Biotage) at 60 °C for 30 min in a sealed microwave reactor (0.5−2 mL). Final Fmoc-deprotection was performed at rt with 20% piperidine−DMF (2 × 10 min), while acetylation (Ac_2O−*i*Pr_2EtN−NMP; 1:2:3 in volume) was performed at rt for 1 h. The product was cleaved with TFA−TIS−H_2O (2 mL; 95:2.5:2.5) at rt for 5 h, and then the resin was eluted with CH_2Cl_2 and MeOH (each 2 mL upon shaking for 5 min). Finally, the resin was eluted with TFA (2 mL upon shaking for 5 min). The eluates were pooled, the solvents were removed *in vacuo*, and the crude material was purified by preparative reversed-phase HPLC. Yield: 10 mg (26%; overall yield in 9 steps) as a white foam. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.73 (d, *J* = 9.5 Hz, 1H), 7.04−7.01 (m, 2H), 6.22 (s, 1H), 4.60−4.57 (m, 1H), 4.43−4.41 (m, 2H), 4.34−4.22 (m, 8H), 3.23−3.19 (m, 16H), 2.46 (s, 3H), 2.09 (s, 3H), 1.87−1.70 (m, 32H). HRMS (*m*/*z*): $[M + 3H/3]^+$ calcd for $C_{29}H_{27}N_3O_6$, 518.6383; found, 518.6381.

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Supporting Information Available: Procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.