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Thermally induced substrate release via intramolecular cyclizations of Amino esters and Amino carbonates

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ABSTRACT

The relative cleavage of an alcohol from a panel of amino esters and amino carbonates via intramolecular cyclization was examined as a mechanism for substrate release. Thermal stability at 37 °C was observed only for the seven-membered ring progenitors. Applicability of the approach was illustrated by δ-lactam formation within a poly(dimethylsiloxane) microchannel for release of a captured fluorescent probe.

1. Introduction

We disclose here a brief study on the propensity of amino ester and amino carbonate substrates of the type indicated in Fig. 1 to undergo intramolecular cyclization for purposes of releasing substrate HO-R′. Similar intramolecular cyclization modes of substrate release previously have been exploited as mechanisms for drug delivery.[1–4] In these cases, the released substrate is either a phenol (R′=Ar) or an aniline derivative so that the intramolecular cyclization occurs rapidly at physiological temperature,[5] generally with a half-life from minutes to 1 h.[6] Intramolecular cyclizations of this type also have been used to unmask aromatic hydroxyl,[7] amine[8] or thiol[9] moieties as mechanisms to initiate electron cascade reactions or for release of polymer-bound drugs.[10] Again the focus was to use the intramolecular cyclization for rapid drug release at physiological temperature, and this required R′ to be aromatic. Few examples have used this approach to release non-aromatic alcohols,[11,12] the most common being for the delivery of 5-halo deoxyuridine analogs.[13–15]

Our interest in control over heat-induced intramolecular cyclization as a mechanism for substrate release led us to investigate linkers that would expel HO–R′ at temperatures above 37 °C, such as in response to an externally triggered local hyperthermia. Consequently, we prepared[16] a panel of amino carbonyl substrates to determine factors that would minimize the rate of cyclization at 37 °C while allowing cyclization to proceed at higher temperature (Fig. 2).

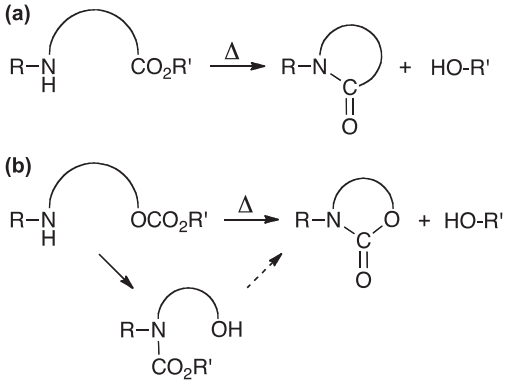

Fig. 1. Heat-induced cyclization via (a) lactamization or (b) carbamate formation.

2. Results and discussion

2.1. Cyclization panel (Fig. 2)

All substrates were prepared to contain an *N*-allyl moiety for convenient functionalization, such as hydrosilylation or thiol incorporation, for eventual covalent attachment to various supports.

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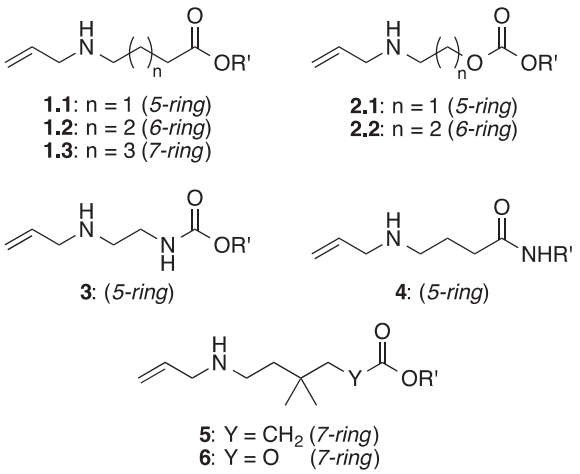
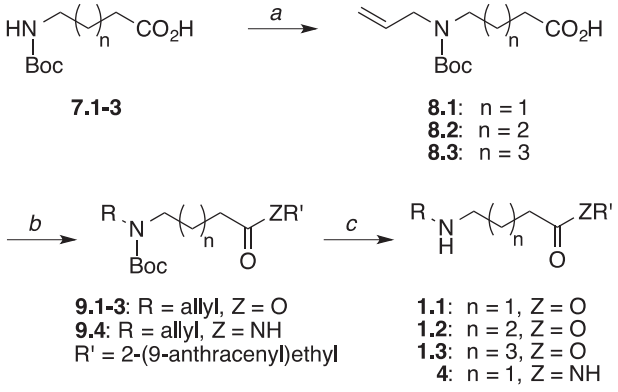


Fig. 2. Cyclization precursors (R=2-(9-anthracenyl)ethyl). Ring size after intramolecular cyclization given in parentheses.

To quantify release of the 'payload' (e.g., HO-R′ in **1**–**3** and **5**,**6**, H_2N-R′ in **4**) on heating, R′ was selected as a 9-substituted anthracene for ease of UV and fluorescent measurements. In addition to the cyclization ring size (italics, Fig. 2), we varied the carbonyl functionality to include ester, carbonate, carbamate, and amide examples. The influence of *gem*-dimethylation, as in seven-membered ring precursors ester **5** and carbonate **6**, also was examined as a means to enhance intramolecular cyclization via the Thorpe–Ingold effect.[17]

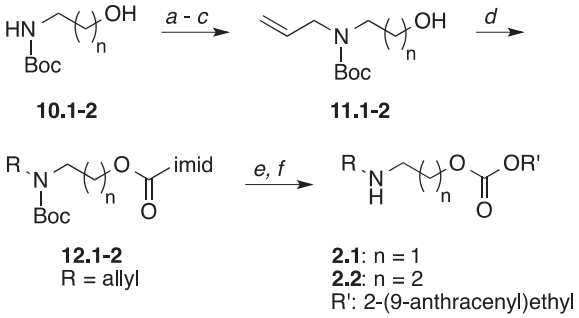
2.2. Syntheses (Schemes 1–5)

N-Allylation[18] of commercial Boc-protected amino acids **7** followed by carbodiimide-mediated esterification with 2-(9-anthracenyl)ethanol[19] and Boc-deprotection furnished amino esters **1.1**–**3** (Scheme 1). Condensation of amino acid **8.1** with 2-(9-anthracenyl)ethanamine[20] gave the amino amide substrate **4**. In similar fashion, N-allylation of Boc-protected alcohols **10** (Scheme 2), after necessary silylation and desilylation steps, gave alcohols **11**. The carbonate moiety was installed by first forming the corresponding acyl imidazole intermediates **12**. Reaction with anthracenyl ethanol under basic conditions[21] then gave amino carbonates **2.1** and **2.2**.

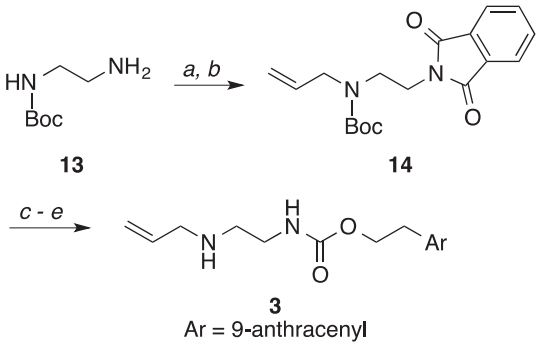


Scheme 1. Synthesis of amino esters **1** and amide **4**. Conditions: (a) allyl bromide, NaH, THF, 0 °C to rt, 81–98%; (b) 2-(9-anthracenyl)ethanol (or 2-(9-anthracenyl) ethanamine), DIC, cat. DMAP, CH_2Cl_2, 12 h, 59–97%; (c) TFA, CH_2Cl_2, 0 °C, 1 h, 72–100%.

Chloroformate acylation of *N*-allyl-*N*-Boc-ethanediamine provided a convenient route for synthesis of the amino carbamate substrate **3** (Scheme 3).

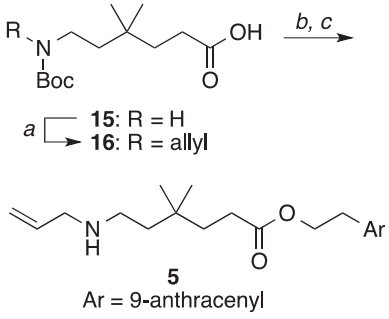


Scheme 2. Synthesis of amino carbonates **2**. Conditions: (a) TBSCl, Et_3N, imidazole, CH_2Cl_2, 0 °C to rt, 95–98%; (b) allyl bromide, NaH, THF, 0 °C to rt, 77–84%; (c) TBAF, THF, 0 °C to rt, 90–95%; (d). $(imid)_2C{=}O$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 0 °C to rt, 93–95%; (e) 2-(9-anthracenyl)ethanol, KOH, toluene, 60 °C, 34–45%; (f) TFA, CH_2Cl_2, 0 °C, 1 h, 96–100%.



Scheme 3. Synthesis of amino carbamate **3**. Conditions: (a) phthalic anhydride, toluene, reflux, 77%; (b) allyl bromide, NaH, THF, 0 °C to rt, 58%; (c) hydrazine monohydrate, 2:1 CH_2Cl_2/EtOH, 0 °C to rt, 92%; (d) $ArCH_2CH_2OC(O)Cl$, Et_3N, CH_2Cl_2, 0 °C to rt, 12 h, 41%; (e) TFA, CH_2Cl_2, 0 °C, 1 h, 88%.

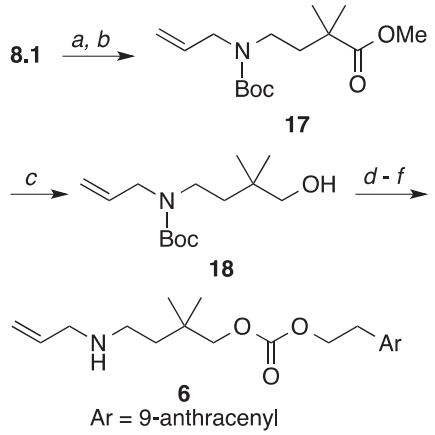
The *gem*-dimethyl amino ester **5** was prepared by applying the above-described three-step sequence of N-allylation, esterification, and Boc-deprotection to commercially available amino acid **15** (Scheme 4). Synthesis of *gem*-dimethyl amino carbonate **6** followed from bis-α-methylation[10] of the ester derived from amino acid **8.1** (Scheme 5). Subsequent chemoselective ester reduction[22] and carbonate formation using the established method gave desired substrate **6**.



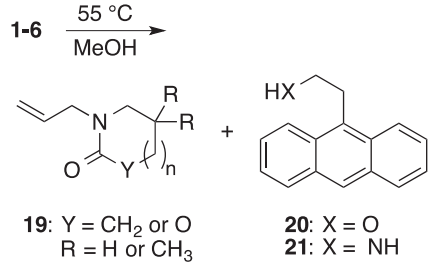
Scheme 4. Conditions: (a) allyl bromide, NaH, THF, 0 °C to rt, 68%; (b) 2-(9-anthracenyl)ethanol, DIC, cat. DMAP, CH_2Cl_2, 12 h, 87%; (c) TFA, CH_2Cl_2, 0 °C, 1 h, 85%.

2.3. Cyclization study

To determine the release rates of the 9-substituted anthracenes (e.g., **20**, Scheme 6) from the panel of amino carbonyl substrates, dilute methanol solutions of each compound were heated at 55 °C. Aliquots taken at various times were analyzed by normal phase HPLC for the appearance of **20** or **21**. Amino carbamate **3** and amino amide **4** were unreactive under the conditions and did not release



Scheme 5. Conditions: (a) MeOH, DIC, cat. DMAP, rt, 80%; (b) LiHMDS, MeI, THF, −78 °C to rt, 67%; (c) $LiBH_4$, THF, 0 °C to rt, 73%; (d) $(imid)_2C{=}O$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 0 °C to rt, 92%; (e) 2-(9-anthracenyl)ethanol, NaH, THF, −5 °C to rt, 48%; (f) TFA, CH_2Cl_2, 0 °C, 1 h, 92%.



Scheme 6. Heat-induced release of anthracene probes.

detectable **20** or **21**, respectively (Supplementary data, Table 1). As could be expected, anthracene alcohol **20** was released from the amino ester and amino carbonate progenitors of the five- and six-membered lactams (**19**, Y=CH_2, n=0, 1) and oxazolidinones (**19**, Y=O, n=0, 1) at rates faster than from the progenitors of corresponding seven-membered rings (Fig. 3). Control experiments indicated that ester or carbonate methanolysis did not occur under the conditions to yield **20**. Whereas dilute conditions were used to reduce the incidence of intermolecular reactions, these cannot be ruled out as a possible source of **20** particularly with the substrates

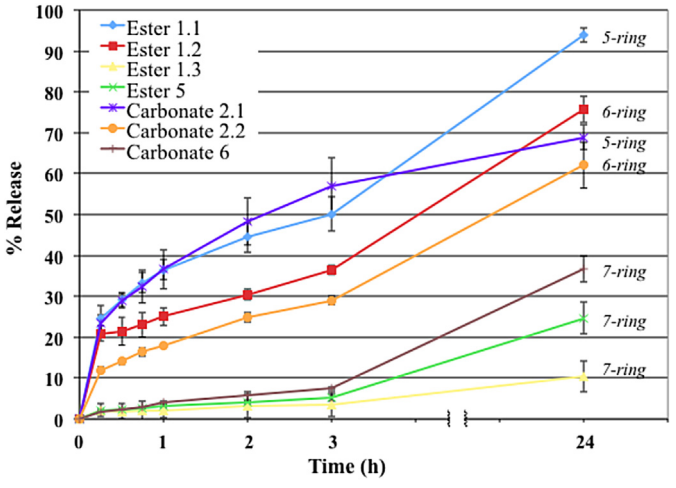


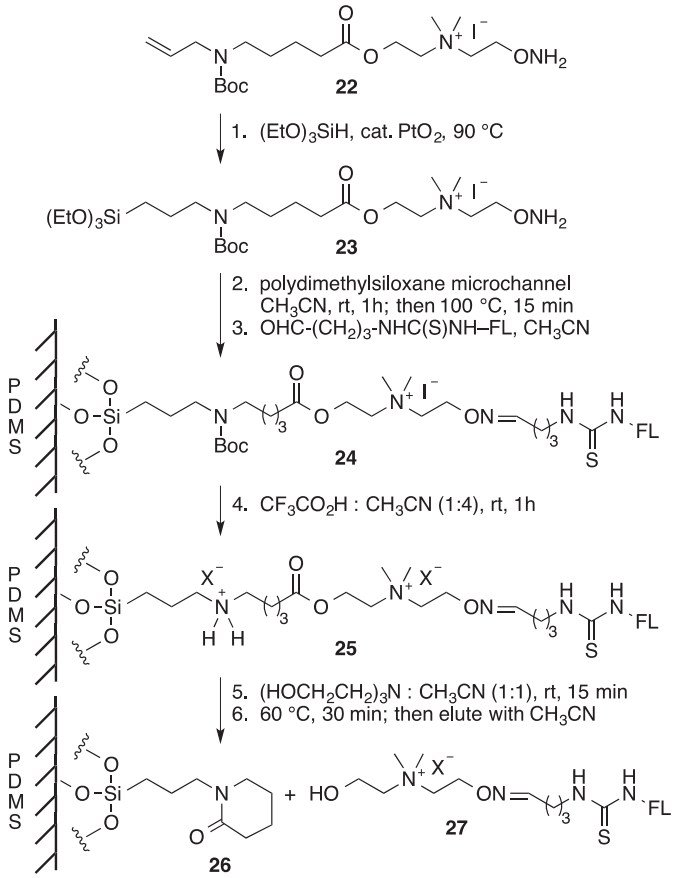
Fig. 3. Percent release of **20** from indicated substrates in MeOH at 55 °C. Shown are the standard deviations from the mean (n=3).

that lead to seven-membered rings. In regards to potential heat-triggered release applications, the high thermal responsiveness of esters **1.1** and **1.2** and carbonates **2.1** and **2.2** make these constructs ideal for applications involving thermally sensitive substrates, such as in cell studies involving triggered release at or below 37 °C. In contrast, the resistance to cyclization of the 7-ring progenitor ester **1.3** is promising for higher temperature applications (Fig. 3), although the overall release of **20** from **1.3** on heating at 55 °C was low. Comparison of amino esters **1.3** and **5** shows that *gem*-dimethylation more than doubled the heat-induced release of anthracene **20** after heating 24 h. The *gem*-dimethyl amino carbonate **6** provided an even higher thermal response than *gem*-dimethyl ester **5** with a nearly 40% release of payload at 55 °C over 24 h. Furthermore, the *gem*-dimethyl seven-ring carbonate motif resists cyclization at lower temperatures. Incubation of **6** at 37 °C for 24 h resulted in only 5.7±0.7% release of **20**.

2.4. Microchannel application

With these cyclization trends established, we set out to apply the approach toward mild heat-induced release of a substrate from a poly(dimethylsiloxane) (PDMS) microchannel using the ester **1.2** motif as a representative example (Scheme 7). Microchannels fabricated using PDMS have shown great utility for molecular and cellular separations due to their extremely high surface to volume ratio.[23] Further, small PDMS channel heights and incorporation of features, such as microfabricated grooves, enhance fluid mixing within the channel to increase interactions of functionalized surfaces with target molecules flowing through the channel.[24]

The *N*-allyl moiety of ammonium aminooxy ester **22** (Scheme 7) was hydrosilylated[25] to attach a terminal triethoxysilane group. The



Scheme 7. Poly(dimethylsiloxane) microchannel functionalization and heat-induced release study (FL=fluorescein, $X^- = CF_3CO_2^-$).

ammonium aminooxy substructure of ester **22** follows from our previously published work on ammonium aminooxy reagents for capture of aldehyde and ketone metabolites from aqueous cell extracts.[26,27] Subsequent condensation[28,29] with the PDMS microchannel (Fig. 4a) covalently attached **23** to afford an aminooxy-functionalized microchannel specific for reaction with aldehydes and ketones. Injection of an acetonitrile solution containing a fluorescent aldehyde probe, FITC (fluorescein isothiocyanate) reacted with a 4-aminobutanal equivalent,[30] anchored the fluorophore to the surfaces of the microchannel via oxime ether formation. The quaternary ammonium salt of **23** ensures availability of the aminooxy moiety for reaction with aldehydes since charged polar groups are repelled by the hydrophobic PDMS matrix. The capture and covalent attachment of the FITC-derived fluorophore to the microchannel was verified using fluorescent microscopy (Fig. 4b). Boc-deprotection using trifluoroacetic acid afforded trifluoroacetate salt **25**. Concerned that loss of captured aldehyde probe may occur at this stage, we verified that no fluorescent probe was released prior to neutralization and thermal triggering. Indeed, no fluorescence was observed in the microchannel effluent after heating **25** at 60 °C for 30 min. Injection of a dilute solution of triethanolamine into the microchannel neutralized the linker. After subsequent rinsing (CH_3CN) of the microchannel, we were gratified to observe that mild heating (60 °C, 30 min) promoted the intramolecular cyclization to release alcohol **27**. As can be seen in Fig. 4c, nearly complete release of the bound fluorophore was achieved. Further utilization of this release mechanism in microchannel studies of cell metabolites requiring hydroxide-free cleavage conditions are ongoing.

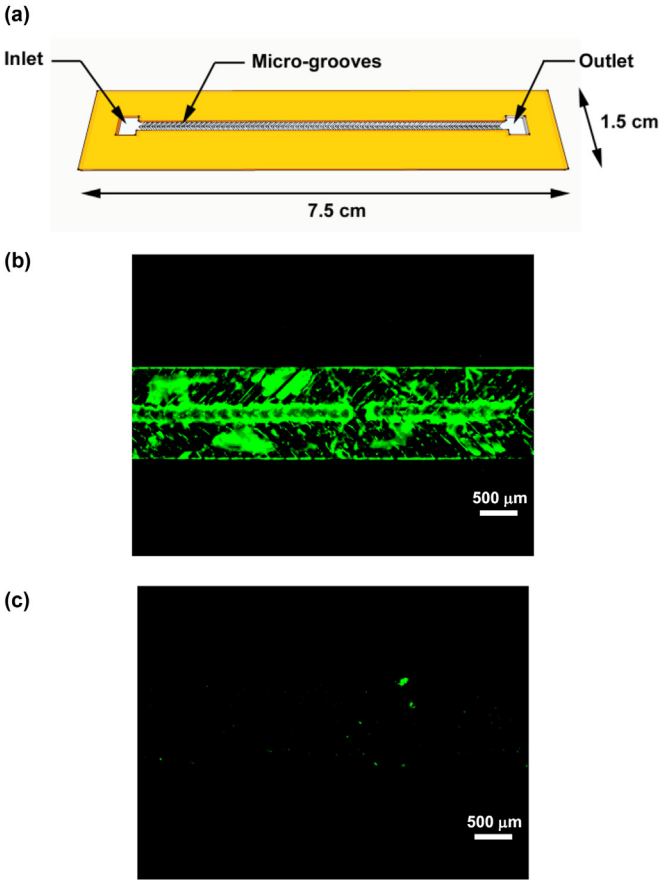


Fig. 4. (a) Schematic of poly(dimethylsiloxane) microchannel; (b) fluorescence microscopy image of FITC-derived substrate **12** within the microchannel and (c) same field of view showing microchannel fluorescence after heating neutralized **13**.

3. Conclusion

In summary, a brief study on the cyclization of amino esters and amino carbonates as a mode for substrate release revealed that both ring size and carbonyl functionality significantly influence the release rate. The process is facile at mild temperatures in cases where five- and six-membered rings are formed, even for non-phenolic alcohols as illustrated in a PDMS microchannel application. In contrast, an amino carbonate motif leading to a seven-membered ring appears well suited for applications requiring thermal stability at 37 °C while still releasing the alcohol substrate at slightly elevated temperatures. This particular secondary amine–carbonate structural combination may be a promising linker for drug delivery vehicles relying on the generation of local hyperthermia.

4. Experimentals

4.1. General

Reagent grade solvents were used for extraction and flash chromatography. Tetrahydrofuran was dried by distillation from $LiAlH_4$. Acetonitrile was dried by distillation from CaH_2. All other commercial reagents were used as received without additional purification. The progress of reactions was checked by thin-layer chromatography (TLC, silica gel 60 Å F-254 plates). The plates were visualized first with UV illumination followed by staining using iodine, *p*-anisaldehyde, phosphomolybdic acid hydrate, or ninhydrin. Column chromatography was performed using silica gel (230–400 mesh). NMR spectra were obtained using a Varian/Agilent 400-MR NMR spectrometer equipped with a 5 mm *z*-axis gradient AutoX probe operating at the nominal ^1H frequency of 399.66 MHz and ^{13}C frequency of 100.49 MHz. All spectra are reported in parts per million (ppm) relative to the residual solvent peak in ^1H NMR and the deuterated solvent peak in ^{13}C NMR. High-resolution mass spectra were obtained using a Finnigan LTQ-FT spectrometer (Thermo Electron Corp). Release results were quantitated using a Waters Delta 600 HPLC fitted with a Waters Nova-Pak HR Silica 6 mm 60 Å 3.9×300 mm Prep Column and a Waters 2487 detector set at 254 nm.

4.2. Representative amino ester synthesis

*4.2.1. 5-(Allyl(tert-butoxycarbonyl)amino)pentanoic acid (**8.2**).* Boc-protected amine **7.2** (4.65 g, 21.4 mmol) was added to a slurry of 60% NaH (4.28 g, 107 mmol) in dry THF (140 mL) at 0 °C. After 1 h of stirring, allyl bromide (5.56 mL, 64.2 mmol) was added dropwise. After 24 h, the reaction mixture was cooled to 0 °C and quenched with water until the reaction mixture became transparent. The reaction mixture was acidified to pH ~3 by addition of 1 M HCl and the layers were separated. The aqueous phase was extracted with EtOAc (2×30 mL) and the combined organic phase was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 1:1 EtOAc/hexanes) to give **8.2** as an oil (4.77 g, 87%); R_f 0.36 (1:1 EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.51–1.64 (m, 4H), 2.35 (t, J=7.0 Hz, 2H), 3.17 (br s, 2H), 3.78 (br s, 2H), 5.09 (d, J=11.6 Hz, 2H), 5.70–5.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 27.8, 28.6, 33.9, 46.2, 49.7, 79.9, 116.5, 134.4, 155.8, 179.6; FT-ICR-MS calcd for $C_{13}H_{22}NO_4^-$ $[M-H]^-$ m/z 256.1554, found 256.1555.

*4.2.2. 2-(Anthracen-9-yl)ethyl 5-(allyl(tert-butoxycarbonyl)amino) pentanoate (**9.2**).* To amino acid **8.2** (255 mg, 0.99 mmol) and alcohol **20** (197 mg, 0.88 mmol) in dry CH_2Cl_2 (8 mL) were added DIC (211 μL, 1.35 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP,

pinch). After 3 h, the white solids were filtered and the filter cake was washed with CH_2Cl_2. The combined filtrate was condensed in vacuo and the crude material was purified by column chromatography (SiO_2, 0:100 to 1:19 EtOAc/CH_2Cl_2 gradient) to give **9.2** (242 mg, 59%) as an oil; R_f 0.46 (1:19 EtOAc/CH_2Cl_2); FTIR 3058, 2981, 1729, 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.50–1.61 (m, 4H), 2.33 (t, J=7.4 Hz, 2H), 3.16 (br s, 2H), 3.79 (br s, 2H), 3.97 (t, J=7.8 Hz, 2H), 4.48 (t, J=7.8 Hz, 2H), 5.11 (d, J=11.6 Hz, 2H), 5.72–5.82 (m, 1H), 7.45–7.49 (m, 2H), 7.51–7.59 (m, 2H), 8.01 (d, J=8.4 Hz, 2H), 8.34 (d, J=9.2 Hz, 2H), 8.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 27.5, 27.9, 28.6, 34.2, 46.3, 49.9, 64.3, 79.6, 116.2, 124.3, 125.1, 126.2, 127.0, 129.2, 129.4, 130.5, 131.7, 134.5, 155.7, 173.8; FT-ICR-MS calcd for $C_{29}H_{35}NNaO_4^+$ $[M+Na]^+$ m/z 484.2458, found 484.2459.

*4.2.3. 2-(Anthracen-9-yl)ethyl 5-(allylamino)pentanoate (**1.2**).* Trifluoroacetic acid (0.74 mL, 9.60 mmol) was added to a solution of **9.2** (68 mg, 0.15 mmol) in dry CH_2Cl_2 (0.74 mL) at 0 °C. After stirring for 1 h, the volatiles were removed in vacuo and the remaining residue was diluted with Et_2O (10 mL) and washed with $NaHCO_3$ (3×5 mL). The organic phase was washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give **1.2** (53 mg, 100% yield) as an oil; R_f 0.20 (1:9 MeOH/CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (dt, J=7.4 Hz, 2H), 1.64 (dt, J=7.6 Hz, 2H), 1.84 (br s, 1H), 2.32 (t, J=7.4 Hz, 2H), 2.59 (t, J=7.2 Hz, 2H), 3.24 (d, J=5.6 Hz, 2H), 3.97 (t, J=7.8 Hz, 2H), 4.48 (t, J=7.8 Hz, 2H), 5.11 (d, J=10.4 Hz, 1H), 5.18 (d, J=17.2 Hz, 1H), 5.86–5.96 (m, 1H), 7.47 (t, J=7.4 Hz, 2H), 7.55 (t, J=7.6 Hz, 2H), 8.01 (d, J=8.4 Hz, 2H), 8.34 (d, J=9.6 Hz, 2H), 8.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 27.5, 29.5, 34.3, 48.9, 52.5, 64.3, 116.4, 124.3, 124.6, 125.1, 126.2, 126.9, 129.4, 130.5, 131.7, 136.7, 173.9; FT-ICR-MS calcd for $C_{24}H_{28}NO_2^+$ $[M+H]^+$ m/z 362.2115, found 362.2141.

4.3. Representative amino carbonate synthesis

*4.3.1. 3-(Allyl(tert-butoxycarbonyl)amino)propyl 1H-imidazole-1-carboxylate (**12.2**).* *N*,*N*-Diisopropylethylamine (566 μL, 3.25 mmol) was added to a solution of alcohol **11.2** (399 mg, 1.85 mmol) in dry CH_2Cl_2 (46 mL) at 0 °C. 1,1′-Carbonyldiimidazole (527 mg, 3.25 mmol) was then added to the cooled solution and the cooling bath was removed to allow the reaction mixture to slowly warm to rt. After 24 h, the reaction mixture was washed with water (2×20 mL), brine (20 mL), and then dried (Na_2SO_4). After filtration and concentration in vacuo, the residue was purified by column chromatography (SiO_2, EtOAc) to give **12.2** (543 mg, 95%) as a colorless oil; R_f 0.50 (EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.01 (dt, J=6.6 Hz, 2H), 3.34 (br s, 2H), 3.82 (br s, 2H), 4.43 (t, J=6.4 Hz, 2H), 5.09–5.14 (m, 2H), 5.74–5.81 (m, 1H), 7.06 (s, 1H), 7.41 (s, 1H), 8.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.6, 43.5, 50.3, 66.4, 80.2, 116.7, 117.3, 130.9, 134.2, 137.3, 148.8, 155.6; FT-ICR-MS calcd for $C_{15}H_{24}N_3O_4^+$ $[M+H]^+$ m/z 310.1761, found 310.1765.

*4.3.2. 2-(Anthracen-9-yl)ethyl 3-((allyl)amino)propyl carbonate (**2.2**, TFA salt).* Alcohol **20** (131 mg, 0.59 mmol) was added to a mixture of **12.2** (210 mg, 0.65 mmol) and KOH (s, 1 pellet) in dry toluene (3 mL) at 60 °C. After 5 h, the reaction mixture was concentrated in vacuo and the residue was diluted with CH_2Cl_2 (5 mL). The solution was washed with water (3×5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 1:19 EtOAc/CH_2Cl_2) to give Boc-protected **2.2** as an orange oil (93 mg, 34%). R_f 0.63 (1:19 EtOAc/hexanes); FTIR: 3017, 2971, 1739, 1229 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.92 (br s, 2H), 3.30 (br s, 2H), 3.83 (br s, 2H), 4.05 (t, J=8.0 Hz, 2H), 4.19 (t, J=6.2 Hz, 2H), 4.49 (t, J=8.2 Hz, 2H), 5.13 (d, J=11.2 Hz, 2H), 5.74–5.84 (m, 1H), 7.46–7.50 (m, 2H), 7.54–7.58 (m, 2H), 8.02 (d, J=8.0 Hz, 2H), 8.34 (d, J=8.8 Hz, 2H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 28.0, 28.6, 43.9, 49.8, 66.0, 67.3, 79.9, 116.8, 124.1, 125.2, 126.4, 127.2, 128.3, 129.5, 130.5, 131.7, 134.3, 155.5, 155.6; FT-ICR-MS calcd for $C_{28}H_{33}NNaO_5^+$ $[M+Na]^+$ m/z 486.2251, found 486.2251.

Trifluoroacetic acid (0.50 mL, 6.53 mmol) was added to a solution of Boc-protected **2.2** (12 mg, 0.026 mmol) in dry CH_2Cl_2 (0.50 mL) at 0 °C. After stirring for 1 h, the volatiles were removed in vacuo to afford the TFA salt of **2.2** (12 mg, 96%) as an oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (t, J=6.8 Hz, 2H), 3.00 (br s, 2H), 3.53 (br s, 2H), 4.02 (t, J=8.4 Hz, 2H), 4.23 (t, J=6.0 Hz, 2H), 4.50 (t, J=8.4 Hz, 2H), 5.12–5.48 (m, 2H), 5.83–5.96 (m, 1H), 7.45–7.56 (m, 4H), 8.00 (d, J=8.4 Hz, 2H), 8.30 (d, J=8.8 Hz, 2H), 8.39 (s, 1H), 9.64 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 27.4, 43.9, 50.1, 64.6, 67.7, 124.1, 124.3, 125.2, 126.4, 127.2, 127.6, 128.3, 129.5, 130.5, 131.7, 155.3; FT-ICR-MS calcd for $C_{23}H_{26}NO_3^+$ $[M+H]^+$ m/z 364.1907, found 364.1911.

4.4. Synthesis of carbamate 3 (Scheme 3)

*4.4.1. tert-Butyl allyl(2-(1,3-dioxoisoindolin-2-yl)ethyl)carbamate (**14**).* *tert*-Butyl *N*-(2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl) ethyl)carbamate phthalimide (5.76 g, 19.8 mmol) was added to a slurry of NaH (1.59 g of 60% in mineral oil, 39.7 mmol) in dry THF (83 mL) at 0 °C. After stirring for 1 h, allyl bromide (2.23 mL, 25.8 mmol) was added dropwise. The slurry was stirred for 3 days and then quenched by addition into water (50 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2×35 mL). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 1:19 EtOAc/CH_2Cl_2) to give **14** (3.77 g, 58%) as a white solid; R_f 0.55 (1:19 EtOAc/hexanes); mp=73–76 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 9H), 3.46 (br s, 2H), 3.81 (br s, 2H), 3.87 (br s, 2H), 5.01–5.13 (m, 2H), 5.71–5.77 (m, 1H), 7.70 (br s, 2H), 7.82 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 44.5, 49.3, 50.2, 80.1, 117.2, 123.4, 132.3, 133.9, 134.2, 155.3, 168.3.

*4.4.2. 2-(Anthracen-9-yl)ethyl N-(2-(allylamino)ethyl)carbamate (**3**, TFA salt).* Hydrazine monohydrate (147 μL, 3.03 mmol) was added to a solution of **14** (217 mg, 0.66 mmol) in 2:1 CH_2Cl_2/EtOH (6 mL) with stirring at 0 °C. The reaction mixture was stirred for 18 h, allowing it to warm slowly to rt. The white precipitate was then filtered and the filter cake was washed with CH_2Cl_2 and concentrated in vacuo. The concentrate was diluted with CH_2Cl_2 and the precipitate was filtered, the cake washed with CH_2Cl_2, and concentrated in vacuo again to give the crude amine (light yellow oil, 122 mg, 92%), which was used in the next step without further purification. R_f 0.47 (10:2:88 MeOH/NH_4OH/CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 2H), 1.43 (s, 9H), 2.79 (t, J=5.0 Hz, 2H), 3.22 (br s, 2H), 3.81 (br s, 2H), 5.09–5.12 (m, 2H), 5.74–5.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6, 40.8, 50.1, 79.8, 116.4, 134.3, 156.0; FT-ICR-MS calcd for $C_{10}H_{21}N_2O_2^+$ $[M+H]^+$ m/z 201.1598, found 201.1599.

The amine (188 mg, 0.94 mmol) was added dropwise with stirring to a solution of ClC(O)OCH_2CH_2(9-anthracenyl) (303 mg, 1.06 mmol) in dry CH_2Cl_2 (3.5 mL) at 0 °C. After 10 min, Et_3N (148 μL, 1.06 mmol) was added dropwise to the reaction mixture, causing the solution to darken. After stirring for 17 h, the reaction mixture was quenched by addition of satd NH_4Cl (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (5 mL). Combined organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 5:1:4 CH_2Cl_2/hexanes/EtOAc) to give Boc-protected **3** (171 mg, 41%) as a yellow gum; R_f 0.33 (1:19 EtOAc:CH_2Cl_2); FTIR: 3449, 3058, 2971, 1724, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 3.13 (br s, 2H), 3.36 (br s, 2H), 3.83 (br s, 2H), 3.97 (t, J=8.0 Hz, 2H), 4.43 (br s, 2H), 5.10–5.15 (m, 2H), 5.75–5.81 (m, 1H),

7.44–7.48 (m, 2H), 7.52–7.56 (m, 2H), 8.00 (d, J=8.4 Hz, 2H), 8.35–8.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 28.5, 40.5, 46.2, 50.6, 64.6, 80.3, 116.6, 124.4, 125.1, 126.1, 126.8, 129.3, 130.5, 131.7, 134.0, 155.3, 157.0; FT-ICR-MS calcd for $C_{27}H_{32}N_2NaO_4^+$ $[M+Na]^+$ m/z 471.2254, found 471.2256.

Trifluoroacetic acid (0.50 mL, 6.53 mmol) was added to a solution of Boc-protected **3** (20 mg, 0.045 mmol) in dry CH_2Cl_2 (0.50 mL) at 0 °C. After stirring for 1 h, the volatiles were removed in vacuo to afford the TFA salt of **3** (18 mg, 88%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (br s, 2H), 3.48–3.56 (m, 4H), 3.90 (t, J=8.0 Hz, 2H), 4.36 (t, J=8.0 Hz, 2H), 5.35–5.47 (m, 2H), 5.81–5.88 (m, 1H), 7.41–7.51 (m, 4H), 7.97 (d, J=8.4 Hz, 2H), 8.27 (d, J=8.8 Hz, 2H), 8.34 (s, 1H), 9.47 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 37.8, 47.2, 50.2, 65.1, 124.3, 124.6, 125.2, 126.2, 126.9, 127.5, 129.4, 130.5, 131.7, 134.3, 157.5; FT-ICR-MS calcd for $C_{22}H_{25}N_2O_2^+$ $[M+H]^+$ m/z 349.1910, found 349.1913.

4.5. Synthesis of *gem*-dimethyl ester 5 (Scheme 4)

*4.5.1. 6-(Allyl(tert-butoxycarbonyl)amino)-4,4-dimethylhexanoic acid (**16**).* Amino acid **15** (912 mg, 3.52 mmol) was added to a slurry of 60% NaH (703 mg, 17.6 mmol) in dry THF (18 mL) at 0 °C. After stirring for 1 h, allyl bromide (913 μL, 10.5 mmol) was added dropwise. After 24 h, the reaction mixture was cooled to 0 °C and quenched with water until the reaction mixture became transparent. The reaction mixture was acidified to pH ~3 by addition of 1 M HCl and the layers were separated. The aqueous phase was extracted with EtOAc (3×10 mL) and the combined organic phase was washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 1:1 EtOAc/hexanes with 0.5% AcOH) to give **16** (712 mg, 68%) as a light yellow oil; R_f 0.43 (1:1 EtOAc/hexanes with 0.5% AcOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 6H), 1.39–1.44 (m, 11H), 1.56 (t, J=8.0 Hz, 2H), 2.31 (t, J=8.2 Hz, 2H), 3.14 (br s, 2H), 3.80 (br s, 2H), 5.11 (d, J=11.6 Hz, 2H), 5.71–5.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 28.7, 29.5, 32.0, 36.4, 39.5, 42.8, 49.6, 79.8, 116.8, 134.6, 155.6, 180.2; FT-ICR-MS calcd for $C_{16}H_{28}NO_4^-$ $[M-H]^-$ m/z 298.2024, found 298.2024.

*4.5.2. 2-(Anthracen-9-yl)ethyl 4,4-dimethyl-6-(allylamino)-hexanoate (**5**, TFA salt).* To a mixture of carboxylic acid **16** (370 mg, 1.24 mmol) and **8** (249 mg, 1.12 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C were added DIC (264 μL, 1.69 mmol) and DMAP (pinch). After 16 h, the precipitated white solids were filtered and the filter cake was washed with CH_2Cl_2. The combined filtrate was condensed in vacuo and the crude material was purified by column chromatography (SiO_2, 0:100 to 1:19 EtOAc/CH_2Cl_2 gradient) to give Boc-protected *gem*-dimethyl ester **5** as a yellow oil (494 mg, 87%); R_f 0.58 (1:19 EtOAc/CH_2Cl_2); FTIR 3058, 2963, 1728, 1684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (s, 6H), 1.39 (br s, 2H), 1.46 (s, 9H), 1.51 (t, J=8.4 Hz, 2H), 2.28 (t, J=8.2 Hz, 2H), 3.12 (br s, 2H), 3.81 (br s, 2H), 3.98 (t, J=7.8 Hz, 2H), 4.48 (t, J=7.8 Hz, 2H), 5.12 (d, J=11.6 Hz, 2H), 5.73–5.82 (m, 1H), 7.46–7.49 (m, 2H), 7.53–7.57 (m, 2H), 8.02 (d, J=8.4 Hz, 2H), 8.34 (d, J=9.2 Hz, 2H), 8.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 27.5, 28.7, 29.8, 32.0, 36.6, 39.2, 42.8, 49.6, 53.6, 64.3, 79.6, 116.6, 124.3, 125.2, 126.2, 127.0, 129.5, 130.5, 131.7, 134.7, 155.5, 174.5; FT-ICR-MS calcd for $C_{32}H_{41}NNaO_4^+$ $[M+Na]^+$ m/z 526.2928, found 526.2927.

Trifluoroacetic acid (0.50 mL, 6.53 mmol) was added to a solution of Boc-protected **5** (11 mg, 0.022 mmol) in dry CH_2Cl_2 (0.50 mL) at 0 °C. After stirring for 1 h, the volatiles were removed in vacuo to afford the TFA salt of **5** (10 mg, 85%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 6H), 1.47 (t, J=8.4 Hz, 2H), 1.58 (t, J=8.6 Hz, 2H), 2.24 (t, J=8.4 Hz, 2H), 2.88 (br s, 2H), 3.54 (br s, 2H), 3.96 (t, J=7.6 Hz, 2H), 4.46 (t, J=8.0 Hz, 2H), 5.40–5.47 (m, 2H), 5.84–5.94 (m, 1H), 7.44–7.56 (m, 4H), 8.00 (d, J=8.8 Hz, 2H), 8.32 (d, J=9.2 Hz, 2H), 8.38 (s, 1H), 9.47 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 27.4, 29.4, 32.1, 36.1, 37.1, 43.2, 49.9, 64.4, 124.1, 124.3, 125.2, 126.2, 127.0, 127.9, 129.2, 129.5, 130.5, 131.7, 174.1; FT-ICR-MS calcd for $C_{27}H_{34}NO_2^+$ $[M+H]^+$ m/z 404.2584, found 404.2588.

4.6. Synthesis of *gem*-dimethylcarbonate 6 (Scheme 5)

*4.6.1. Methyl 4-(allyl(tert-butoxycarbonyl)amino)-2,2-dimethylbutanoate (**17**).* DIC (837 μL, 5.34 mmol) and DMAP (pinch) were added to a mixture of amino acid **8.1** (631 mg, 2.59 mmol) and dry MeOH (173 μL, 4.28 mmol) in CH_2Cl_2 (32 mL) at rt. After 12 h, the precipitated solids were filtered and the filter cake was washed with CH_2Cl_2. The combined filtrate was concentrated in vacuo and the resulting residue was purified by column chromatography (SiO_2, 1:1:8, EtOAc/THF/hexanes) to give methyl 4-(allyl(*tert*-butoxycarbonyl)amino)butanoate as a pale yellow oil (532 mg, 80%); R_f 0.65 (1:1:8, EtOAc/THF/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.82 (dt, J=7.0 Hz, 2H), 2.30 (t, J=7.4 Hz, 2H), 3.20 (br s, 2H), 3.65 (s, 3H), 3.79 (br s, 2H), 5.10 (d, J=12.8 Hz, 2H), 5.72–5.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 28.6, 31.4, 45.9, 49.7, 51.8, 79.8, 116.7, 134.3, 155.7, 173.8.

The methyl ester (532 mg, 2.06 mmol) was dissolved in dry THF (10 mL) and cooled to −78 °C with stirring. A solution of lithium bis(trimethylsilyl)amide (LiHMDS) in THF (6.20 mL of 1 M solution, 6.20 mmol) was added dropwise to the reaction solution. After stirring for 1 h, methyl iodide (772 μL, 12.4 mmol) was added dropwise and the reaction mixture was stirred overnight while slowly warming to rt. After 22 h, the reaction mixture was cooled to 0 °C and quenched with water (5 mL), followed by 1 M HCl (5 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3×15 mL). The combined organic phase was washed with $NaHCO_3$ (10 mL) and brine (10 mL) and then dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 1:4 EtOAc/hexanes) to give a yellow oil **17** (397 mg, 67%); R_f 0.48 (1:4, EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 6H), 1.44 (s, 9H), 1.74 (br s, 2H), 3.11 (br s, 2H), 3.65 (s, 3H), 3.79 (br s, 2H), 5.10 (d, J=10.8 Hz, 2H), 5.70–5.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 28.6, 38.1, 41.1, 43.1, 49.4, 51.9, 79.7, 116.1, 134.2, 155.5, 178.0; FT-ICR-MS calcd for $C_{15}H_{27}NNaO_4^+$ $[M+Na]^+$ m/z 308.1832, found 308.1836.

*4.6.2. tert-Butyl allyl(4-hydroxy-3,3-dimethylbutyl)carbamate (**18**).* $LiBH_4$ (45 mg, 2.08 mmol) was added to a solution of **17** (265 mg, 0.93 mmol) in dry THF (21 mL) at 0 °C. After 5 min of stirring, the reaction mixture was warmed to rt and stirred overnight. The reaction mixture was then carefully quenched with NH_4Cl (25 mL) and extracted with Et_2O (3×10 mL). The combined organic phase was washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 1:1 EtOAc/hexanes) to give **18** (175 mg, 73%) as a colorless oil; R_f 0.47 (1:1, EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 6H), 1.43–1.49 (m, 11H), 2.89 (br s, 1H), 3.13–3.17 (m, 2H), 3.32 (s, 2H), 3.78 (br s, 2H), 5.09–5.13 (m, 2H), 5.71–5.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 28.6, 34.7, 36.5, 42.9, 50.4, 70.8, 79.8, 116.4, 134.6, 155.8; FT-ICR-MS calcd for $C_{14}H_{27}NNaO_3^+$ $[M+Na]^+$ m/z 280.1883, found 280.1886.

*4.6.3. 2-(Anthracen-9-yl)ethyl 2,2-dimethyl-4-(allylamino)butyl carbonate (**6**, TFA salt).* *N*,*N*-Diisopropylethylamine (304 μL, 1.74 mmol) was added to a solution of alcohol **18** (251 mg, 0.98 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C. 1,1′-Carbonyldiimidazole (283 mg, 1.74 mmol) was then added to the solution followed by warming to rt. After 24 h, the reaction mixture was washed with water (2×10 mL), brine (10 mL) and then dried over Na_2SO_4. After filtration and concentration in vacuo, the crude residue was purified by column chromatography (SiO_2, EtOAc) to give the imidazole

carbamate as a colorless oil (316 mg, 92%); R_f 0.61 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 6H), 1.42 (s, 9H), 1.56 (t, J=7.8 Hz, 2H), 3.21 (br s, 2H), 3.76 (br s, 2H), 4.12 (s, 2H), 5.07–5.09 (m, 2H), 5.70–5.79 (m, 1H), 7.07 (s, 1H), 7.42 (s, 1H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 28.6, 33.7, 36.7, 42.5, 50.0, 75.9, 79.8, 116.4, 117.2, 130.9, 134.5, 137.2, 148.9, 155.4.

A solution of alcohol **20** (191 mg, 0.86 mmol) in dry THF (1 mL) was added dropwise to a slurry of NaH (103 mg of 60% in mineral oil, 2.57 mmol) in dry THF (5 mL) at −5 °C and stirred for 30 min. A solution of the above imidazole carbamate (316 mg, 0.90 mmol) in dry THF (1 mL) was then added dropwise to the reaction mixture. The reaction mixture was stirred overnight, then the mixture was filtered through Celite and the filter cake was washed with Et_2O. The filtrate was washed with water (2×10 mL) and the combined aqueous layers were extracted with Et_2O (3×10 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 1:19 EtOAc/CH_2Cl_2) to give Boc-protected **6** (207 mg, 48%) as a yellow oil; R_f 0.64 (1:19, EtOAc/CH_2Cl_2); FTIR 3008, 2974, 1743, 1685, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 6H), 1.46 (s, 9H), 1.53 (t, J=7.8 Hz, 2H), 3.19 (br s, 2H), 3.77–3.82 (m, 2H), 3.90 (s, 2H), 4.05 (t, J=8.0 Hz, 2H), 4.50 (t, J=8.4 Hz, 2H), 5.10–5.13 (m, 2H), 5.74–5.80 (m, 1H), 7.45–7.49 (m, 2H), 7.53–7.57 (m, 2H), 8.01 (d, J=8.4 Hz, 2H), 8.34 (d, J=9.2 Hz, 2H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 27.6, 28.7, 33.5, 37.1, 42.5, 49.7, 67.3, 76.2, 79.7, 116.2, 124.1, 125.2, 126.4, 127.2, 128.3, 129.5, 130.5, 131.7, 134.5, 155.5, 155.7; FT-ICR-MS calcd for $C_{31}H_{39}NNaO_5^+$ $[M+Na]^+$ m/z 528.2720, found 528.2720.

Trifluoroacetic acid (0.50 mL, 6.53 mmol) was added to a solution of Boc-protected **6** (12 mg, 0.024 mmol) in dry CH_2Cl_2 (0.50 mL) at 0 °C. After stirring for 1 h, the volatiles were removed in vacuo to afford the TFA salt of **6** (11 mg, 92%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 6H), 1.70 (t, J=8.4 Hz, 2H), 2.99 (br s, 2H), 3.86 (br s, 2H), 4.03 (t, J=8.0 Hz, 2H), 4.49 (t, J=8.0 Hz, 2H), 5.40–5.48 (m, 2H), 5.81–5.91 (m, 1H), 7.45–7.60 (m, 4H), 8.00 (d, J=8.4 Hz, 2H), 8.32 (d, J=8.4 Hz, 2H), 8.39 (s, 1H), 9.06 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 27.4, 33.6, 34.8, 43.3, 50.0, 67.5, 75.3, 124.1, 124.3, 125.2, 126.4, 127.2, 127.5, 128.3, 129.5, 130.5, 131.7, 155.5; FT-ICR-MS calcd for $C_{26}H_{32}NO_3^+$ $[M+H]^+$ m/z 406.2377, found 406.2379.

4.7. Synthesis of ester 22 and PDMS loading procedure

*4.7.1. 2-((5-(Allyl(tert-butoxycarbonyl)amino)pentanoyl)oxy)-N-(2-((1,3-dioxoisoindolin-2-yl)oxy)ethyl)-N,N-dimethylethanaminium iodide (**22**).* Amino acid **8.2** (98 mg, 0.38 mmol) and the 2-(2-((2-hydroxyethyl)(methyl)amino)ethoxy)-2,3-dihydro-1*H*-isoindole-1,3-dione mono-*O*-phthalimide of *N*-methyl-diethanolamine[27] were dissolved in dry CH_2Cl_2 (1.7 mL) with stirring. DIC (82 μL, 0.52 mmol) was added to the reaction solution followed by cat. DMAP. After 2 h, the white solids were filtered out and the filter cake was washed with CH_2Cl_2. The filtrate was condensed in vacuo and the crude material was purified by column chromatography (SiO_2, 3:1 to 1:0, EtOAc/hexanes gradient) to give the corresponding ester as a light yellow oil (96 mg, 55%). R_f 0.55 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.49–1.62 (m, 4H), 2.33 (t, J=7.4 Hz, 2H), 2.39 (s, 3H), 2.77 (t, J=6.0 Hz, 2H), 2.91 (t, J=5.6 Hz, 2H), 3.16 (br s, 2H), 3.78 (br s, 2H), 4.16 (t, J=5.8 Hz, 2H), 4.30 (t, J=5.4 Hz, 2H), 5.09 (d, J=11.2 Hz, 2H), 5.72–5.78 (m, 1H), 7.72–7.75 (m, 2H), 7.76–7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 28.0, 28.6, 34.1, 42.9, 46.3, 55.9, 60.6, 62.3, 76.1, 79.6, 116.5, 123.7, 129.2, 134.6, 155.7, 163.6, 173.6.

To the ester (96 mg, 0.19 mmol) in dry CH_2Cl_2 (1 mL) in a pressure tube was added iodomethane (24 μL, 0.38 mmol). The tube was sealed and heated to 60 °C for 18 h. The solution was then concentrated in vacuo to give a crude ammonium salt (yellow gum, 122 mg, 100%) that was used in the next step without further purification. R_f 0.20 (1:9, MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.50–1.56 (m, 4H), 2.40 (t, J=6.6 Hz, 2H), 3.12 (t, J=7.0 Hz, 2H), 3.66 (s, 6H), 3.73 (br s, 2H), 4.26 (br s, 2H), 4.39 (br s, 2H), 4.64 (br s, 2H), 4.77 (br s, 2H), 5.06 (d, J=12.0 Hz, 2H), 5.68–5.74 (m, 1H), 7.76–7.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 27.5, 28.5, 46.2, 49.9, 53.2, 57.8, 63.2, 64.9, 72.4, 79.5, 116.2, 124.1, 128.6, 134.3, 135.2, 155.6, 163.2, 172.5.

Methyl hydrazine (24 μL, 0.46 mmol) was added to a stirred solution of the crude ammonium salt (49 mg, 0.076 mmol) in 1:1 CH_2Cl_2/EtOH (2 mL) at −40 °C. After 1.5 h, the solution was concentrated in vacuo and diluted with CH_2Cl_2, causing a white precipitate to form. The solid was filtered and the filter cake was washed with CH_2Cl_2. The filtrate was concentrated in vacuo to give **22** (yellow gum, 39 mg, 100%) that was used in the next step without further purification; R_f 0.14 (1:9, MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.51–1.59 (m, 4H), 2.39 (t, J=7.0 Hz, 2H), 3.14 (t, J=6.4 Hz, 2H), 3.48 (s, 6H), 3.74 (br s, 2H), 4.02 (br s, 2H), 4.08 (br s, 2H), 4.19 (br s, 2H), 4.57 (br s, 2H), 5.07 (d, J=15.6 Hz, 2H), 5.70–5.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 27.6, 28.6, 33.8, 46.2, 49.9, 53.1, 57.8, 63.9, 64.2, 69.2, 79.7, 116.3, 134.3, 155.7, 172.6; FT-ICR-MS calcd for $C_{19}H_{38}N_3O_5^+$ $[M]^+$ m/z 388.2806, found 388.2807.

*4.7.2. Procedure for loading **22** onto PDMS microchannel.* Ester **22** (39 mg, 0.076 mmol) was placed into a pressure tube with a stir-bar and the headspace was purged with nitrogen. Catalytic PtO_2 was then added, followed by triethoxysilane (14 μL, 0.076 mmol). The headspace was purged with nitrogen and the pressure tube was sealed and heated to 80 °C. After 2 days, the reaction mixture was cooled to rt and the solution was filtered under nitrogen through Celite and the filter cake was washed with dry CH_2Cl_2. The filtrate was concentrated in vacuo to give a moisture-sensitive residue, triethoxylsilane intermediate **23**, which was immediately loaded onto the PDMS microchannel without further purification by first dissolving in CH_3CN (0.8 M) and then injecting the solution (10 μL, 80 μmol) into the microchannel. After 1 h, the microchannel was washed with CH_3CN (5×10 μL) and placed in 110 °C oven for 15 min. On cooling, the loaded microchannel was stored at rt in a sealed bag until needed.

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Supplementary data

Experimental details, ^{1}H and ^{13}C NMR spectra. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.03.092.

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