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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 7-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.

Keywords

lactam; oxazolidinone; drug delivery; poly(dimethylsiloxane) microchannel

1. Introduction

We disclose here a brief study on the propensity of amino ester and amino carbonate substrates of the type indicated in Figure 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 ($R' = \text{Ar}$) or an aniline derivative so that the intramolecular cyclization occurs rapidly at physiological temperature,⁵ generally with a half-life from minutes to one hour.⁶ Intramolecular cyclizations of this type also have been used to unmask aromatic hydroxyl,⁷ amine⁸ or thiol⁹ 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-

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Supplementary Data

Supplementary data (experimental details, ¹H and ¹³C NMR spectra) 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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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 prepared¹⁶ 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 (Figure 2).

2. Results and Discussion

2.1. Cyclization panel (Figure 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. To quantify release of the 'payload' (e.g., HO-R' in **1–3** and **5–6**, H₂N-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*, Figure 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-allylation¹⁸ of commercial Boc-protected amino acids **7** followed by carbodiimide-mediated esterification with 2-(9-anthracenyl)ethanol¹⁹ and Boc-deprotection furnished amino esters **1.1–3** (Scheme 1). Condensation of amino acid **8.1** with 2-(9-anthracenyl)ethanamine²⁰ 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 conditions²¹ then gave amino carbonates **2.1–2**.

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

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 -methylation¹⁰ of the ester derived from amino acid **8.1** (Scheme 5). Subsequent chemoselective ester reduction²² and carbonate formation using the established method gave desired substrate **6**.

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 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 5- and 6-membered lactams (**19**, Y = CH₂, n = 0, 1) and oxazolidinones (**19**, Y = O, n = 0, 1) at rates faster than from the progenitors of corresponding 7-membered rings (Figure 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 that lead to 7-membered rings. In regards to potential heat-triggered release applications, the high thermal responsiveness of esters **1.1–2** and carbonates **2.1–2** 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 (Figure 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 7-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 aminoxy ester **22** (Scheme 7) was hydrosilylated²⁵ to attach a terminal triethoxysilane group. The ammonium aminoxy substructure of ester **22** follows from our previously published work on ammonium aminoxy reagents for capture of aldehyde and ketone metabolites from aqueous cell extracts.^{26, 27} Subsequent condensation^{28, 29} with the PDMS microchannel (Figure 4a) covalently attached **23** to afford an aminoxy-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 aminoxy 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 (Figure 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 (CH₃CN) 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 Figure 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.

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 5- and 6-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 LiAlH₄. Acetonitrile was dried by distillation from CaH₂. 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 5mm z-axis gradient AutoX probe operating at the nominal ¹H frequency of 399.66 MHz and ¹³C 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 ¹³C 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 µm 60 Å 3.9×300 mm Prep Column and a Waters 2487 detector set at 254 nm.

4.2. Representative amino ester synthesis

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 one-hour 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 became transparent. The reaction 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 Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO₂, 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, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₃H₂₂NO₄[−] [*M* − *H*][−] *m/z* 256.1554, found 256.1555.

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 CH₂Cl₂ (8 mL) was 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 CH₂Cl₂. The combined filtrate was condensed *in vacuo* and the crude material was purified by column chromatography (SiO₂, 0:100 to 1:19 EtOAc:CH₂Cl₂ gradient) to give **9.2** (242 mg, 59%) as an oil; *R_f* 0.46 (1:19 EtOAc:CH₂Cl₂); FT-IR 3058, 2981, 1729, 1685 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₉H₃₅NNaO₄⁺ [*M* + Na]⁺ *m/z* 484.2458, found 484.2459.

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 CH₂Cl₂ (0.74 mL) at 0 °C. After stirring 1h, the volatiles were removed *in vacuo* and the remaining residue was diluted with Et₂O (10 mL) and washed with NaHCO₃ (3 × 5 mL). The organic phase was washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give **1.2** (53 mg, 100% yield) as an oil; *R_f* 0.20 (1:9 MeOH:CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₄H₂₈NO₂⁺ [*M* + *H*]⁺ *m/z* 362.2115, found 362.2141.

4.3. Representative amino carbonate synthesis

3-(Allyl(*tert*-butoxycarbonyl)amino)propyl 1*H*-imidazole-1-carboxylate (**12.2**)—

N,N-Diiso-propylethylamine (566 μL, 3.25 mmol) was added to a solution of alcohol **11.2** (399 mg, 1.85 mmol) in dry CH₂Cl₂ (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 to slowly warm to room temperature. After 24 h, the reaction was washed with water (2 × 20 mL), brine (20 mL), and then dried (Na₂SO₄). After filtration and concentration *in vacuo*, the residue was purified by column chromatography (SiO₂, EtOAc) to give **12.2** (543 mg, 95%) as a colorless oil; *R*_f 0.50 (EtOAc); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₅H₂₄N₃O₄⁺ [*M* + *H*]⁺ *m/z* 310.1761, found 310.1765.

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 was concentrated *in vacuo* and the residue was diluted with CH₂Cl₂ (5 mL). The solution was washed with water (3 × 5 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO₂, 1:19 EtOAc:CH₂Cl₂) to give Boc-protected **2.2** as an orange oil (93 mg, 34%). *R*_f 0.63 (1:19 EtOAc:hexanes); FT-IR: 3017, 2971, 1739, 1229 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₈H₃₃NNaO₅⁺ [*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 CH₂Cl₂ (0.50 mL) at 0 °C. After stirring 1h, the volatiles were removed *in vacuo* to afford the TFA salt of **2.2** (12 mg, 96%) as an oil; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₃H₂₆NO₃⁺ [*M* + *H*]⁺ *m/z* 364.1907, found 364.1911.

4.4. Synthesis of carbamate **3** (Scheme 3)

tert-Butyl allyl(2-(1,3-dioxoisindolin-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 1h, allyl bromide (2.23 mL, 25.8 mmol) was added dropwise. The slurry was stirred for three days and then quenched by addition into water (50 mL). The layers were separated and the aqueous phase was extracted with Et₂O (2 × 35 mL). The combined organic phase was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO₂,

1:19 EtOAc:CH₂Cl₂) 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, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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.

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 CH₂Cl₂:EtOH (6 mL) with stirring at 0 °C. The reaction was stirred for 18 h, allowing it to warm slowly to room temperature. The white precipitate was then filtered and the filter cake was washed with CH₂Cl₂ and concentrated *in vacuo*. The concentrate was diluted with CH₂Cl₂ and the precipitate was filtered, the cake washed with CH₂Cl₂ 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:NH₄OH:CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 28.6, 40.8, 50.1, 79.8, 116.4, 134.3, 156.0; FT-ICR-MS calcd for C₁₀H₂₁N₂O₂⁺ [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)OCH₂CH₂(9-anthracenyl) (303 mg, 1.06 mmol) in dry CH₂Cl₂ (3.5 mL) at 0 °C. After 10 minutes, Et₃N (148 μL, 1.06 mmol) was added dropwise to the reaction, causing the solution to darken. After stirring 17h, the reaction mixture was quenched by addition of sat. NH₄Cl (5 mL) and the aqueous phase was extracted with CH₂Cl₂ (5 mL). Combined organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO₂, 5:1:4 CH₂Cl₂:hexanes:EtOAc) to give Boc-protected **3** (171 mg, 41%) as a yellow gum; *R_f* 0.33 (1:19 EtOAc:CH₂Cl₂); FT-IR: 3449, 3058, 2971, 1724, 1514 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₇H₃₂N₂NaO₄⁺ [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 CH₂Cl₂ (0.50 mL) at 0 °C. After stirring 1h, the volatiles were removed *in vacuo* to afford the TFA salt of **3** (18 mg, 88%) as an oil; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₂H₂₅N₂O₂⁺ [M + H]⁺ *m/z* 349.1910, found 349.1913

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

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 1h, allyl bromide (913 μ L, 10.5 mmol) was added dropwise. After 24 h, the reaction mixture was cooled to 0 °C and quenched with water until the reaction became transparent. The reaction was acidified to pH ~3 by addition of 1 M HCl and the layers were separated. The aqueous phase was extracted with EtOAc (3 $\times$ 10 mL) and the combined organic phase was washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO₂, 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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₆H₂₈NO₄[–] [*M* – H][–] *m/z* 298.2024, found 298.2024.

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 CH₂Cl₂ (10 mL) at 0 °C was added DIC (264 μ L, 1.69 mmol) and DMAP (pinch). After 16 h, the precipitated white solids were filtered and the filter cake was washed with CH₂Cl₂. The combined filtrate was condensed *in vacuo* and the crude material was purified by column chromatography (SiO₂, 0:100 to 1:19 EtOAc:CH₂Cl₂ gradient) to give Boc-protected *gem*-dimethyl ester **5** as a yellow oil (494 mg, 87%); *R*_f 0.58 (1:19 EtOAc:CH₂Cl₂); FT-IR 3058, 2963, 1728, 1684 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₃₂H₄₁NNaO₄⁺ [*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 CH₂Cl₂ (0.50 mL) at 0 °C. After stirring 1h, the volatiles were removed *in vacuo* to afford the TFA salt of **5** (10 mg, 85%) as an oil; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₇H₃₄NO₂⁺ [*M* + H]⁺ *m/z* 404.2584, found 404.2588

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

Methyl 4-(allyl(*tert*-butoxycarbonyl)amino)-2,2-dimethylbutanoate (17)—DIC (837 μ L, 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 μ L, 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); ^1H 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 1 h, methyl iodide (772 μ L, 12.4 mmol) was added dropwise and the reaction was stirred overnight while slowly warming to rt. After 22 h, the reaction 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); ^1H 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 $\text{C}_{15}\text{H}_{27}\text{NNaO}_4^+$ [$\text{M} + \text{Na}$] $^+ m/z$ 308.1832, found 308.1836.

***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 minutes of stirring the reaction was warmed to rt and stirred overnight. The reaction 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); ^1H 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 $\text{C}_{14}\text{H}_{27}\text{NNaO}_3^+$ [$\text{M} + \text{Na}$] $^+ m/z$ 280.1883, found 280.1886.

2-(anthracen-9-yl)ethyl 2,2-dimethyl-4-(allylamino)butyl carbonate (6, TFA salt)—*N,N*-Diisopropylethylamine (304 μ L, 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 was washed with water (2 × 10 mL), brine (10 mL) and then dried over Na₂SO₄. After filtration and concentration *in vacuo*, the crude residue was purified by column chromatography (SiO₂, EtOAc) to give the imidazole carbamate as a colorless oil (316 mg, 92%); *R*_f 0.61 (EtOAc); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 minutes. 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 was stirred overnight, then the mixture was filtered through Celite and the filter cake was washed with Et₂O. The filtrate was washed with water (2 × 10 mL) and the combined aqueous layers were extracted with Et₂O (3 × 10 mL). The combined organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO₂, 1:19 EtOAc:CH₂Cl₂) to give Boc-protected **6** (207 mg, 48%) as a yellow oil; *R*_f 0.64 (1:19, EtOAc:CH₂Cl₂); FT-IR 3008, 2974, 1743, 1685, 1256 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₆H₃₂NO₃⁺ [M + Na]⁺ *m/z* 528.2928, 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 CH₂Cl₂ (0.50 mL) at 0 °C. After stirring 1h, the volatiles were removed *in vacuo* to afford the TFA salt of **6** (11 mg, 92%) as an oil; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₆H₃₂NO₃⁺ [M + H]⁺ *m/z* 406.2377, found 406.2379.

4.7. Synthesis of ester **22** and PDMS loading procedure

2-((5-(allyl(*tert*-butoxycarbonyl)amino)pentanoyl)oxy)-*N*-(2-((1,3-dioxoisindolin-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*-isindole-1,3-dione mono-*O*-phthalimide of *N*-methyl-diethanolamine²⁷ were dissolved in dry CH₂Cl₂ (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 CH₂Cl₂. The filtrate was condensed *in vacuo* and the crude

material was purified by column chromatography (SiO₂, 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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 CH₂Cl₂ (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:CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 CH₂Cl₂:EtOH (2 mL) at –40 °C. After 1.5h, the solution was concentrated *in vacuo* and diluted with CH₂Cl₂, causing a white precipitate to form. The solid was filtered and the filter cake was washed with CH₂Cl₂. 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:CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₉H₃₈N₃O₅⁺ [M]⁺ *m/z* 388.2806, found 388.2807.

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 PtO₂ 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 two days, the reaction was cooled to room temperature and the solution was filtered under nitrogen through Celite and the filter cake was washed with dry CH₂Cl₂. The filtrate was concentrated *in vacuo* to give a moisture-sensitive residue, triethoxysilane intermediate **23**, which was immediately loaded onto the PDMS microchannel without further purification by first dissolving in CH₃CN (0.8 M) and then injecting the solution (10 μL, 80 μmol) into the microchannel. After 1h, the microchannel was washed with CH₃CN (5 × 10 μL) and placed in 110 °C oven for 15 minutes. On cooling, the loaded microchannel was stored at room temperature in a sealed bag until needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

Figure 2.

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

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

Figure 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**.

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, CH₂Cl₂, 12h, 59–97%; *c.* TFA, CH₂Cl₂, 0 °C, 1h, 72–100%

Scheme 2.

Synthesis of amino carbonates **2**. Conditions: *a*. TBSCl, Et₃N, imidazole, CH₂Cl₂, 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-Pr)₂NEt, CH₂Cl₂, 0 °C to rt, 93–95%; *e*. 2-(9-anthracenyl)ethanol, KOH, toluene, 60 °C, 34–45%; *f*. TFA, CH₂Cl₂, 0 °C, 1h, 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 CH₂Cl₂:EtOH, 0 °C to rt, 92%; *d*. ArCH₂CH₂OC(O)Cl, Et₃N, CH₂Cl₂, 0 °C to rt, 12h, 41%; *e*. TFA, CH₂Cl₂, 0 °C, 1h, 88%.

Scheme 4.

Conditions: *a.* allyl bromide, NaH, THF, 0 °C to rt, 68%; *b.* 2-(9-anthracenyl)ethanol, DIC, cat. DMAP, CH₂Cl₂, 12h, 87%; *c.* TFA, CH₂Cl₂, 0 °C, 1h, 85%.

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.* $(\text{imid})_2\text{C}=\text{O}$, $(i\text{-Pr})_2\text{NEt}$, 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 , 1h, 92%.

Scheme 6.
Heat-induced release of anthracene probes.

Scheme 7.

Poly(dimethylsiloxane) microchannel functionalization and heat-induced release study (FL = fluorescein, $\text{X}^- = \text{CF}_3\text{CO}_2^-$)