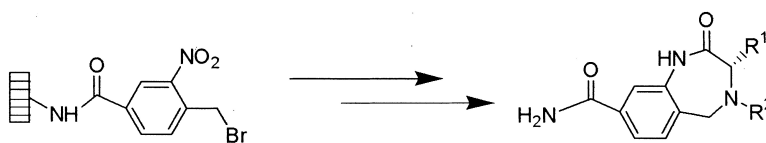Article

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Synthesis of Tetrahydro-1,4-Benzodiazepine-2-ones on Hydrophilic Polyamide SynPhase Lanterns

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Solid-phase synthesis is greatly dependent on the solid support. Here, we report the use of a new hydrophilic grafted surface on SynPhase lanterns in solid-phase organic chemistry. A convenient and facile solid-phase synthesis of disubstituted 1,4-benzodiazepine-2-ones on polyamide SynPhase lanterns is described. The key step of the synthesis involved a reduction−cyclization of a nitroaryl methyl ester with a mixture of tin(II) chloride dihydrate and ammonium acetate in water and ethanol at elevated temperature to give the desired target compounds. A library of 21 disubstituted 1,4-benzodiazepine-2-ones was prepared.

Introduction

Over the past 10 years, the solid-phase synthesis of small-molecule compounds has emerged from being a curiosity to being an ubiquitous tool for preparing large sets of compounds for lead finding and optimization in the pharmaceutical industry.[1] Since the mid 1980s, our group has been performing multiple solid-phase synthesis of both peptide and small-molecule compounds on grafted surfaces (SynPhase crowns and lanterns). The fundamental advantage of this technology, which is an alternative to beaded cross-linked resins, is the ease of handling large numbers in multiple parallel synthesis. There have been many improvements in the underlying system to allow for increased target diversity, purity, and loading. These improvements include the introduction of new graft polymers that are optimized for solid-phase organic synthesis.[2] There have been several generations, each with improved surface (hence, loading)/volume ratios. Graft polymers have been optimized on the basis of several factors, including reaction kinetics, loading, and compatibility with broad chemical and physical reaction conditions. SynPhase lanterns grafted with polystyrene have become popular for use by organic chemists for the synthesis of combinatorial libraries.[3] The lantern shape is designed to maximize loading to surface area. Importantly, there is very little lantern-to-lantern variation between batches, and thus, synthetic procedures are reproducible between batches.

Taking advantage of the multiple parallel handling efficiency and the knowledge gained from the last 15 years of research, a new hydrophilic surface in the shape of the SynPhase lantern has been developed. Here, we report the use of a new hydrophilic grafted surface in the form of SynPhase lanterns in solid-phase organic chemistry. The lanterns are specifically optimized for reactions carried out in polar media.

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Results and Discussion

Solid-phase synthesis is greatly dependent on the solid phase. We are interested in the development of a "pellicular" type of solid support in which a mobile polymer is grafted to a rigid plastic support. Compared to low-cross-linked microporous beads that dominate the field, this approach allows great flexibility of design, because plastics are available as sheets, films, or threads or can be moulded into any shape, as required. Many different polymers or copolymers can be grafted onto any particular shape to give a wide choice of options in the physicochemical characteristics of the actual solid support. The SynPhase lanterns are an example of such a solid support. In keeping with developments in resin technology during the early nineties, hydrophilic supports have historically been the main focus of our previous research and development.[4] Although polystyrene was successfully grafted, poly(hydroxyethyl methacrylate) HEMA and poly(methacrylic acid/dimethylacrylamide) MA/DMA yielded surfaces well-suited to peptide synthesis.[4] Presumably, more polar graft polymers minimized secondary structure formation, as with PEG-PS and polyamide gel resins. As reported by us previously, the hydrophilic MA/DMA surface was also the choice of graft for the solid-phase synthesis of peptide aldehydes via an oxazolidine linker system.[5] The graft is particularly suited to the hydrophilic cleavage conditions required.

Preparation of Polyamide Lanterns. The lanterns were designed to fulfill certain shape/size specifications and could be injection-molded from a number of polyolefins. The basic procedures to graft monomers to such base polymers have been previously described by us as well as other authors.[4,6] In optimizing the new hydrophilic surface, we investigated a number of parameters, such as type, concentration and ratio of monomers; radiation dose rate; and linker loading. A detailed discussion on the results derived from varying the parameters listed above will be presented elsewhere. Suffice to say, the polyamide graft is a copolymer of poly-

Scheme 1
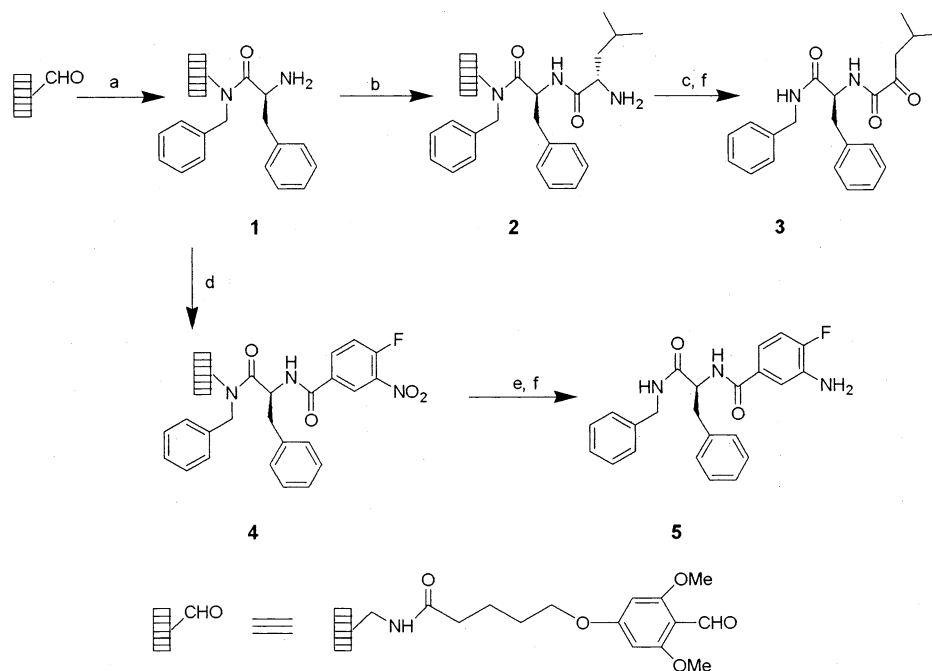
(a) (i) Bzl-NH$_2$ (1 M, 1% AcOH/DMF), NaCNBH$_3$ (0.1 M), 60 °C, 16 h; (ii) Fmoc−Phe−OH (0.1 M, 5% DMF/DCM), TFFH (0.1 M), DIEA (0.2 M), room temp, 4 h; (iii) 20% piperidine/DMF, 0.5 h. (b) (i) Fmoc−Leu−OH (0.120 M, 50% DMF/DCM), DIC (0.120 M), HOBt (0.144 M), room temp, 16 h; (ii) 20% piperidine/DMF, 0.5 h. (c) Sodium glyoxylate (0.5 M, in CH$_3$COONa/CH$_3$COOH buffer, pH 5.5−6.0), CuSO$_4$·5H$_2$O (0.06 M), room temp, 16 h. (d) 4-Fluoro-3-nitrobenzoic acid (0.15 M, 20% DMF/DCM), DIC (0.15 M), HOBt (0.075 M), room temp, 3 h. (e) SnCl$_2$·2H$_2$O/NH$_4$OAc (2 M, EtOH), room temp, 16 h. (f) 20% TFA/DCM, room temp, 1 h.

(methacrylic acid/dimethylacrylamide) but synthesized under different parameters (listed above) to the original MA/DMA graft described previously.[4]

Polyamide vs Polystyrene Lanterns. In a recent review of solid-phase synthesis, Gerritz raised the question of what is the chemical role of the solid support.[7] In the review, he revisits the contributions of Czarnik[8] and Janda,[9] who delve deeply into the microenvironment presented by the solid phase. Along with the many contributors in Hudson's Perspective on matrix assisted synthetic transformations,[10] the role of the solid phase is seen as critical to the success of a chemical reaction. As noted by Gerritz,[7] "... chemists know the structure of the 'business end' of the solid support (i.e., the linker) but do they take the polymeric matrix seriously in deciding the right solid phase for their chosen chemistry?" In assessing the polyamide lanterns performance in polar solvents, synthesis of compounds **3** and **5** as shown in Scheme 1 clearly demonstrates the importance of matching the correct solid phase to the conditions of chemistry. The two examples clearly demonstrate the difference between a hydrophobic polystyrene and hydrophilic polyamide grafted surface. Both examples used a scaffold constructed from the BAL linker, and in both examples, the two types of lanterns were reacted in the same vessel. The synthesis of the α-ketoamide **3** is adapted from work published by Meldal, who developed a new solid-phase oxidative deamination route.[11] In aqueous buffered solution, the terminal amino group of **2** undergoes a copper-catalyzed transamination with sodium glyoxylate to yield the α-ketoamide **3**. It is a remarkably efficient reaction on the hydrophilic surface, but it fails completely on a hydrophobic polystyrene matrix (see Figure 1). A similar result was obtained with the buffered
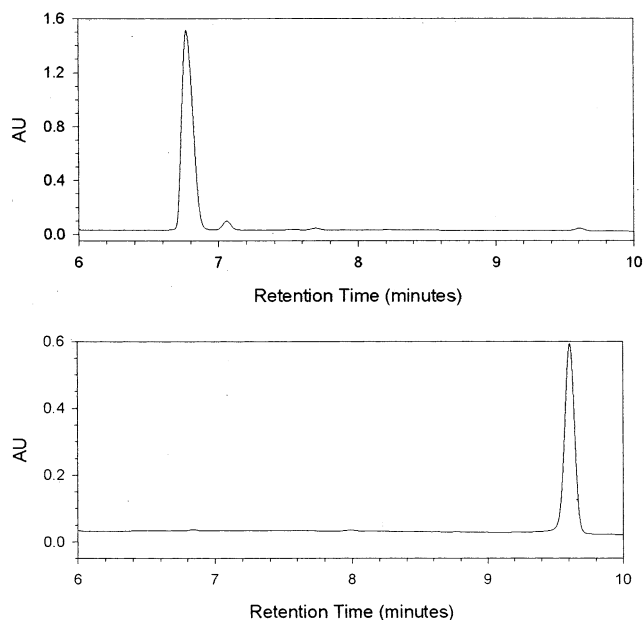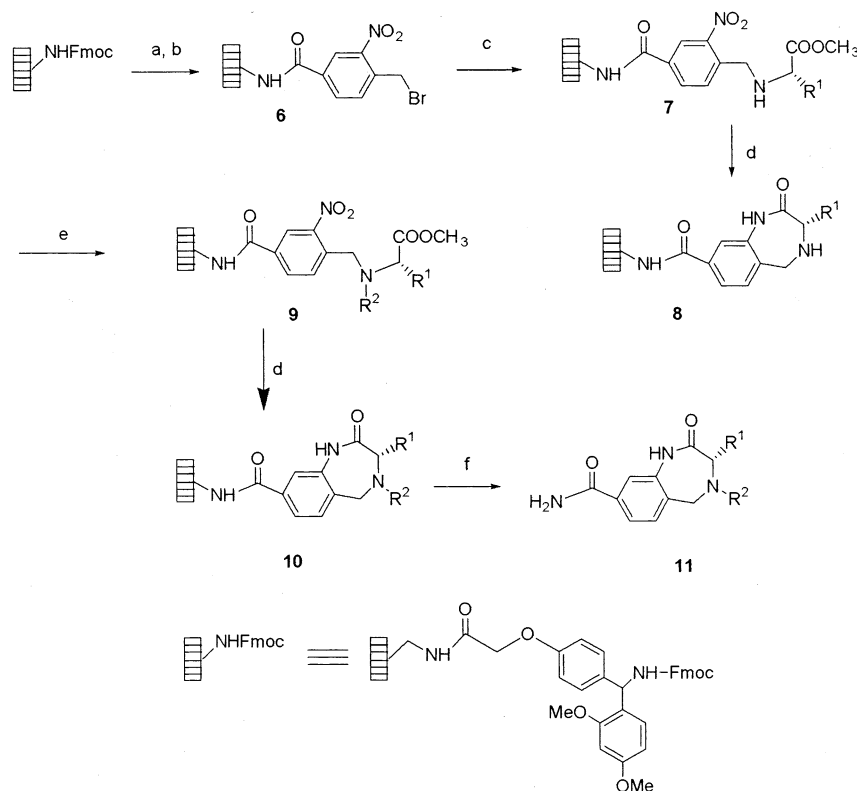

Figure 1. HPLC chromatogram (at 214 nm) of transamination product **3** synthesized on SynPhase polystyrene lanterns (top) and polyamide lanterns (bottom). By LCMS, peak at 6.80 min is starting material **2**, and peak at 9.61 min is product **3**.

tin reduction of the aryl nitro scaffold in Figure 2. The origin of this new buffered tin reduction is discussed in the next section.

Synthesis of Tetrahydro-1,4-benzodiazepine-2-ones. Benzodiazepines are an important class of compounds possessing a broad spectrum of biological activities, such as antihypertensive, anticonvulsive, and antimicrobial activity.[12] Many benzodiazepine derivatives have been used as therapeutic agents to treat a range of symptoms. Since Ellman and co-

Scheme 2

(a) 20% piperidine/DMF, room temp, 45 min. (b) 4-Fluoro-3-nitrobenzoic acid (0.1 M, 20% DMF/DCM), DIC (0.1 M), HOBt (0.005 M), room temp, 16 h. (c) L-Amino acid methyl ester hydrochloride salts (0.5 M), DIEA (1.0 M), DMF, room temp, 48 h. (d) SnCl$_2$·2H$_2$O/NH$_4$OAc (2.0 M, 50% EtOH/H$_2$O), 90 °C, 24 h. (e) Alkyl halides (R^{2}X, 1.0 M), DIEA (1.0 M), DMF, 100 °C, 24 h. (f) 20% TFA/DCM, room temp, 1 h.
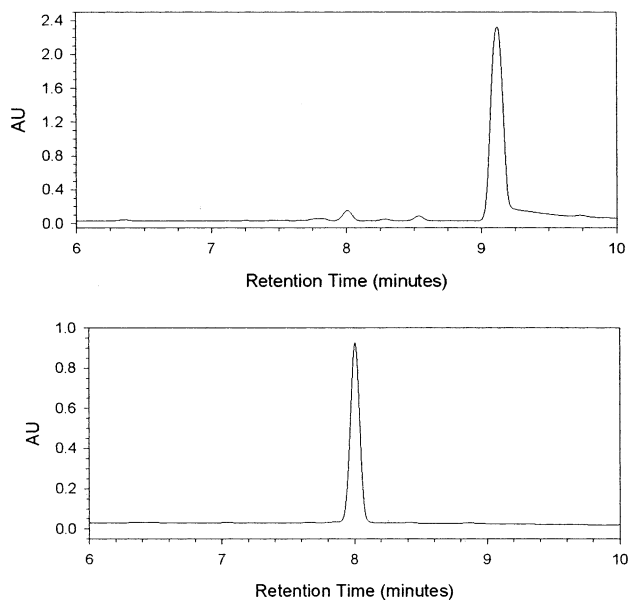

Figure 2. HPLC chromatogram (at 214 nm) of tin reduction product **5** synthesized on SynPhase polystyrene lanterns (top) and polyamide lanterns (bottom). By LCMS, peak at 9.11 min is starting material **4**, and peak at 8.02 min is product **5**.

workers published the landmark paper of solid-phase synthesis of 1,4-benzodiazepines in the early 1990s,[13] there has been increasing interest in solid-phase synthesis of both 1,4- and 1,5-benzodiazepines.[14] Among 1,4-benzodiazepines, a great deal of work has been directed toward the synthesis of 1,4-benzodiazepin-2,5-diones,[14] presumably as a result of relatively easy accessibility in comparison with the more

difficult 1,4-benzodiazepine-2-ones. Apart from Ellman and co-workers' articles, there have been very few publications on solid-phase syntheses of 1,4-benzodiazepine-2-ones.[15] Herein, we report a very convenient and facile solid-phase synthesis of tetrahydro-1,4-benzodiazepine-2-ones on the hydrophilic polyamide SynPhase lanterns.

As shown in Scheme 2, 4-bromomethyl-3-nitrobenzoic acid was initially attached to SynPhase Rink polystyrene lanterns[16a] using DIC/HOBt as coupling reagents. To avoid a side reaction caused by replacement of the bromine by HOBt, only 0.05 equiv of HOBt was employed in the coupling reaction. Both the yield and the purity of this attachment were above 90%. Nucleophilic displacement of the bromine of **6** with commercially available L-leucine methyl ester hydrochloride salt in the presence of DIEA in DMF at room temperature for 2 days was complete, giving the methyl ester **7** (R^1 = isobutyl) in good purity, as demonstrated by TFA cleavage. Krchnak et al.[17] reported that reduction of aromatic nitro compounds containing a methyl ester with tin(II) chloride dihydrate resulted in simultaneous intramolecular cyclization to give the quinox-alinones. It was hoped that a similar reduction−cyclization would occur on **7**, leading to the desired tetrahydro-1,4-benzodiazepine-2-one template **8**. Thus, **7** was treated with tin(II) chloride dihydrate in NMP at room temperature for 5 h. Surprisingly, apart from the reduced aniline along with the starting material, there was no trace of the desired tetrahydro-1,4-benzodiazepine-2-one **8** according to LC/MS analysis of the cleaved product. Combinations of changing

solvents, raising reaction temperature, and extending reaction time failed to offer any desired product.

Kamal et al. reported that the solid-phase synthesis of pyrrolo[2,1-c][1,4]benzodiazepine-5-11-diones was achieved by indium/NH$_4$Cl-promoted reduction−cyclization of a solid-bound aryl nitro methyl ester.[18] This prompted us to investigate their reduction−cyclization conditions on the aryl nitro methyl ester **7** for the synthesis of tetrahydro-1,4-benzodiazepine-2-ones. However, treatment of **7** with indium/NH$_4$Cl in either DMF or ethanol did not produce any desired product **8**. Similarly, no reaction was observed after heating the mixture of **7** and SnCl$_2$·2H$_2$O/NH$_4$Cl in either DMF or ethanol after TFA cleavage. At that point, we considered using SnCl$_2$·2H$_2$O together with NH$_4$OAc, which had been reported by Harvey and Baell for nitro reduction in solution-phase chemistry.[19] However, after heating the mixture of SnCl$_2$·2H$_2$O/NH$_4$OAc and the nitro methyl ester **7** in ethanol at 80 °C for 16 h, a small percentage of the desired tetrahydro-1,4-benzodiazepine-2-one **8** was detected by LC/MS, along with a majority of unreacted nitro methyl ester **7**. We attributed the poor conversion to incompatibility of the hydrophobic solid supports of PS SynPhase lanterns with the hydrophilic solvent. Thus, the synthesis was undertaken on the hydrophilic polyamide SynPhase lanterns. The attachment of 4-bromomethyl-3-nitrobenzoic acid to the polyamide Rink lanterns[16b] and the subsequent displacement of the bromine with L-leucine methyl ester hydrochloride salt went smoothly, as expected. Treatment of **7** with SnCl$_2$·2H$_2$O/NH$_4$OAc in either EtOH or EtOH/H$_2$O (1:1) at 90 °C for 24 h gave the desired tetrahydro-1,4-benzodiazepine-2-one **8**. Subsequently, the secondary amine of the nitro methyl ester **7** was alkylated with 4-trifluoromethyl-benzylbromide in the presence of DIEA, thereby introducing the second point of diversity into the target molecule. Upon heating the mixture of the alkylated nitro methyl ester **9** (R^2 = 4-trifluoromethylbenzyl) and SnCl$_2$·2H$_2$O/NH$_4$OAc in EtOH/H$_2$O (1:1) at 90 °C for 24 h followed by TFA cleavage, the desired disubstituted tetrahydro-1,4-benzodiazepine-2-one **11** (R^1 = isobutyl, R^2 = 4-trifluoromethylbenzyl) was obtained in 71% purity.

To demonstrate the utility of the above-mentioned reduction−cyclization strategy for preparation of disubstituted 1,4-benzodiazepine-2-ones, we prepared a library of disubstituted 1,4-benzodiazepine-2-ones **11** using the reduction−cyclization conditions described above. Thus, 3 commercially available α-amino acid methyl ester hydrochloride salts (for R^1) along with 7 alkylating reagents (for R^2) were used for preparation of a 21-member disubstituted tetrahydro-1,4-benzodiazepine-2-one library on hydrophilic polyamide SynPhase lanterns. The purity of the library ranged from 60 to 86%, whereas the average mass yield of the library was ∼70%, as summarized in Table 1. The whole library was characterized by LC/MS, and selected members of the library gave satisfactory ^{1}H NMR spectra.

Conclusion

A new hydrophilic solid phase in the form of a SynPhase lantern has been developed for use in polar or aqueous reaction media. The importance of choosing the type of solid

Table 1. Product Distribution and HPLC Purity of 3 × 7 Tetrahydro-1,4-benzodiazepine-2-one Library[a]

R^2 (from alkylating reagents)	R^1 (from amino methyl ester)		
	H (Gly)	isobutyl (Leu)	benzyl (Phe)
4-fluorobenzyl	86 (75)	63 (65)	69 (65)
4-methylbenzyl	82 (85)	65 (70)	65 (64)
3-bromobenzyl	79 (66)	68 (70)	63 (70)
3-chlorobenzyl	83 (80)	70 (75)	65 (62)
4-trifluoromethylbenzyl	82 (80)	71 (68)	71 (75)
3-methoxybenzyl	75 (65)	67 (73)	65 (65)
3,5-difluorobenzyl	77 (60)	68 (65)	60 (61)

[a] Notes: (1) HPLC purities are given as area %, (2) all compounds gave the expected molecular ions in positive ion ESMS, (3) selected samples gave satisfactory 1H NMR spectra, and (4) figures in paratheses are crude yields, based on the initial loading of SynPhase lanterns.

phase to match the microenvironment generated during a chemical reaction was demonstrated by contrasting both polystyrene and polyamide grafted lanterns in highly polar reaction mixtures. Using the polyamide SynPhase lanterns, we have developed a facile and convenient method for solid-phase synthesis of disubstituted tetrahydro-1,4-benzodiazepine-2-ones. It is worth noting this is the first report of the reduction−cyclization strategy involving SnCl$_2$·2H$_2$O/NH$_4$OAc in H$_2$O and EtOH on a hydrophilic support.

Experimental Section

General Procedures. Starting materials and reagents were purchased from commercial suppliers and used without further purification, except for the following: DMF (dimethylformamide) was vacuum-distilled from ninhydrin, and TFA (trifluoroacetic acid) and DIEA (diisopropylethylamine) were distilled. TFFH (tetramethylfluoroformamidinium hexafluorophosphate) was purchased from Applied Biosystems (Warrington, U.K.). Lanterns were radiation-grafted with methacrylic acid/dimethylacrylamide as previously described.[4] The lanterns were coupled with (*tert*-butoxycarbonyl)-1,6-diaminohexane and Boc-deprotected with TFA. Fmoc-Gly-OH was coupled using DIC (*N,N'*-diisopropyl-carbodiimide) and HOBt (*N*-hydroxybenzotriazole), the unreacted amine was capped by acetylation, and the Fmoc protection was removed. The lanterns were coupled with either Rink (from Senn Chemicals) or BAL (5-(4-formyl-3,5-dimethoxyphenoxy)valeric acid) (from Advanced ChemTech) linkers using DIC/HOBt. Analytical HPLC was performed on a Waters 2690 chromatography system using a Monitor 5-μm C18 50 × 4.6 mm column (Column Engineering, CA); buffer A = water (0.1% TFA); buffer B = 90% acetonitrile/10% water (0.1% TFA); linear gradient A to B from 1 to 11 min; flow rate = 1.5 mL min^{-1}. Absorbances were recorded at 214 and 254 nm. HPLC purities were determined by peak area at 214 nm. LC/MS analyses were performed on a Perkin-Elmer Sciex API III mass spectrometer linked to a Shimadzu LC-10AD HPLC system. The following conditions were used: the column was a Monitor 5-μm C18 50 × 4.6 mm (Column Engineering, CA); buffer A = water (0.1% TFA); buffer B = 90% acetonitrile/10% water (0.1% TFA); linear gradient A to B from 0.5 to 11.5 min at a flow rate of 1.5 mL min^{-1}.

Absorbances were recorded at 214 and 254 nm. The flow rate to the mass spectrometer was 300 μL min^{-1} after being split, post UV-detector, from the column (1.5 mL min^{-1}). ^{1}H NMR spectra were recorded on a 400 MHz Varian $^{\text{UNITY}}$INOVA spectrometer using CDCl$_3$ or DMSO-d_6 as solvent.

Preparation of the Lantern-Bound 2. Each D-series BAL polyamide lantern (initial specified loading, 18 μmol) was treated with 0.5 mL of a solution of benzylamine (1.0 M, 500 μmol) and sodium cyanoborohydride (0.1 M, 50 μmol) in 1% glacial acetic acid in distilled DMF at 60 °C for 16 h. After cooling to room temperature, the reagent solution was decanted, and the lanterns were washed with DMF (3 × 3 min), 5% acetic acid in DMF (2 × 3 min), DMF (1 × 3 min), 5% DIEA in DMF (2 × 3 min), DMF (1 × 3 min), DMF (60 °C, 2 × 5 min), and DCM (2 × 3 min). Each D-series lantern was then treated with 0.5 mL of a solution of Fmoc-phenylalanine (0.1 M, 50 μmol), TFFH (0.1 M, 50 μmol) and DIEA (0.2 M, 100 μmol) in 5% DMF in DCM at 25 °C for 4 h. The reagent solution was decanted, and the lanterns were washed with DMF (2 × 3 min) and DCM (2 × 3 min) and then air-dried. Each lantern was treated with a 0.5-mL solution of 20% pip/DMF for 30 min. The reagent solution was decanted, and the lanterns were washed with DMF (3 × 3 min) and DCM (3 × 3 min) to give **1**. Each Fmoc-deprotected D-series lantern **1** was treated with 0.5 mL of a solution of DIC (0.120 M, 60 μmol), HOBt (0.144 M, 72 μmol), and Fmoc−leucine (0.120 M, 60 μmol) in 1:1 DCM/DMF at 25 °C overnight. The solution was decanted, and the lanterns were washed with DMF (2 × 3 min) and DCM (2 × 3 min) and then air-dried. Each lantern was treated with a 0.5-mL solution of 20% pip/DMF for 30 min. The reagent solution was decanted, and the lanterns were washed with DMF (3 × 3 min) and DCM (3 × 3 min) and air-dried to give **2**.

Preparation of 4-Methyl-2-oxo-pentanoic Acid (1-Benzylcarbamoyl-2-phenyl-ethyl)-amide 3. Each Fmoc-deprotected D-series lantern **2** was treated with 1 mL of a freshly prepared aqueous solution of sodium glyoxylate (0.5 M, 500 μmol) and copper (II) sulfate pentahydrate (0.06 M, 60 μmol) in a buffer solution containing sodium acetate (2.0 M, 2000 μmol) and glacial acetic acid (0.5 M, 500 μmol). The pH of the resulting solution was 5.5−6.0. The lanterns were reacted at 25 °C overnight. The reagent solution was decanted, and the lanterns were washed with water (2 × 10 min), acetonitrile (2 × 10 min), and DCM (2 × 10 min). Cleavage with 20% TFA/DCM for 1 h yielded **3** (4.1 mg, 95% yield from **1**) after drying. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52−7.04 (m, 10H), 4.52 (dt, J = 6.4, 8.0 Hz, 1H), 4.36 (dd, J = 6.4, 14.8 Hz, 1H), 4.30 (dd, J = 6.4, 14.8 Hz, 1H), 3.14 (dd, J = 6.4, 13.6 Hz, 1H), 3.09 (dd, J = 8.4, 13.6 Hz, 1H), 2.76 (dd, J = 6.8, 16.8 Hz, 1H), 2.71 (dd, J = 7.2, 16.8 Hz, 1H), 2.13 (m,1H), 0.93 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H). HPLC: retention time 9.61 min; 99%. LC/MS: M + 1 peak 367 (calcd MW 366).

Preparation of 3-Amino-*N*-(1-benzylcarbamoyl-2-phenyl-ethyl)-4-fluoro-benzamide 5. Each D-series lantern **1** was treated with a 0.5-mL solution of 4-fluoro-3-nitrobenzoic acid (0.15 M, 75 μmol), DIC (0.15 M, 75 μmol), and HOBt (0.075

M, 37 μmol) in 20% DMF/DCM at room temperature for 3 h. The reagent solution was decanted, and the lanterns were washed in turn with DMF (3 × 3 min) and DCM (3 × 3 min) to give **4**. Each D-series lantern **4** was treated with 1 mL of a suspension of tin(II) chloride dihydrate (2.0 M, 2.0 mmol) and ammonium acetate (2.0 M, 2.0 mmol) in ethanol at 25 °C for 16 h. The lanterns were removed and washed with DMF (3 × 3 min), 20% H$_2$O/THF (60 °C, 3 × 30 min), MeOH (2 × 3 min), and DCM (2 × 3 min). Cleavage with 20% TFA/DCM for 1 h yielded **5** (3.9 mg, 85% yield from **1**) after drying. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.28−7.20 (m, 10H), 7.10 (dd, J = 2.0, 8.4 Hz, 1H), 7.05−7.02 (m, 1H), 6.96 (dd, J = 8.4, 10.8 Hz, 1H), 4.87 (t, J = 7.2 Hz, 1H), 4.41 (d, J = 14.0 Hz, 1H), 4.33 (d, J = 14.0 Hz, 1H), 3.18 (d, J = 7.2 Hz, 2H). HPLC: retention time 8.02 min; 98%. LC/MS: M + 1 peak 392 (calcd MW 391).

Preparation of the Lantern-Bound 4-Bromomethyl-3-nitrobenzoic Acid 6. Fmoc-protected Rink amide polyamide D-series lanterns were deprotected using 20% pip/DMF and stood at room temperature for 40 min. The solution was decanted, and the lanterns were washed with DMF (3 × 3 min) and DCM (3 × 3 min).

Each Fmoc-deprotected lantern was treated with 0.5 mL of a solution of 4-bromomethyl-3-nitrobenzoic acid (0.1 M, 0.05 mmol), DIC (0.1 M, 0.05 mmol), and HOBt (0.005 M, 0.0025 mmol) in 20% DMF/DCM at room temperature for 16 h. The solution was decanted, and the lanterns were washed with DMF (3 × 3 min) and DCM (3 × 3 min) and air-dried to give **6**.

Preparation of the Lantern-Bound 7. Each lantern **6** was treated with 0.5 mL of a solution of L-phenylalanine methyl ester hydrochloride salt or L-leucine methyl ester hydrochloride salt or glycine methyl ester hydrochloride salt (0.5 M, 0.25 mmol) and DIEA (1.0 M, 0.5 mmol) in DMF at room temperature for 48 h. The solution was decanted, and the lanterns were washed with DMF (3 × 3 min) and DCM (3 × 3 min), and air-dried to give **7**.

Preparation of the Lantern-Bound 9. Each lantern 7 was treated with 0.5 mL of a solution of one of the alkylhalides listed in the Table 1 (1.0 M, 0.5 mmol) and DIEA (1.0 M, 0.5 mmol) in DMF at 100 °C for 24 h. The solution was decanted, and the lanterns were washed with DMF (3 × 3 min) and DCM (3 × 3 min) and air-dried to give **9**.

Preparation of the tetrahydro-1,4-benzodiazepine-2-one library 11. Each alkylated aryl nitro methyl ester D-series lantern **9** was treated with 1 mL of a suspension of 2.0 M SnCl$_2$·2H$_2$O/NH$_4$OAc in the mixture of H$_2$O/EtOH (1:1) at 90 °C for 24 h. The reagent solution was decanted. The lanterns were washed with H$_2$O (3 × 3 min), 20% H$_2$O/THF (60 °C, 3 × 30 min), MeOH (2 × 3 min), and DCM (2 × 3 min) and air-dried. Each lantern was cleaved in a polypropylene tube with 0.7 mL of 20% TFA/DCM for 1 h. The lanterns were removed, and the cleavage solution was evaporated to give a crude residue **11**.

3-Isobutyl-2-oxo-4-(4-trifluoromethyl-benzyl)-2,3,4,5-tetrahydro-1H benzo[*e*][1,4]diazepine-8-carboxylic acid amide. (R^1 = *iso*-butyl, R^2 = 4-trifluoromethylbenzyl) (4.3 mg, yield 68%), ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (d, J = 7.6 Hz, 2H), 7.59 (s, 1H), 7.52 (d, J = 8.8 Hz, 2H),

7.32−7.15 (m, 2H), 3.83 (s, 1H), 3.79 (s, 1H), 3.70 (d, J = 14.4 Hz, 1H), 3.62 (d, J = 14.4 Hz, 1H), 3.41 (t, J = 6.8 Hz, 1H), 1.65−1.47 (m, 3H), 0.79 (d, J = 6.0 Hz, 3H), 0.76 (d, J = 6.0 Hz, 3H). HPLC: retention time 7.20 min; 71.4%. LC/MS: M + 1 peak 420 (calcd MW 419).

2-Oxo-4-(4-trifluoromethyl-benzyl)-2,3,4,5-tetrahydro-1H benzo[*e*][1,4]diazepine-8-carboxylic acid amide. (R^1 = H, R^2 = 4-trifluoromethylbenzyl) (4.4 mg, 80%), ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (d, J = 7.6 Hz, 1H), 7.60 (s, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.26−7.17 (m, 3H), 4.06 (s, 2H), 4.02 (s, 2H), 3.42 (s, 2H). HPLC: retention time 5.71 min; 81.7%. LC/MS: M + 1 peak 364 (calcd MW 363).

2-Oxo-4-(4-methyl-benzyl)-2,3,4,5-tetrahydro-1H benzo-[*e*][1,4]diazepine-8-carboxylic acid amide. (R^1 = H, R^2 = 4-methyl-benzyl) (3.9 mg, 85%), ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 (s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 4.35 (s, 2H), 4.32 (s, 2H), 3.62 (s, 2H), 2.38 (s, 3H). HPLC: retention time 4.96 min; 82.4%. LC/MS: M + 1 peak 310 (calcd MW 309).

3-Benzyl-2-oxo-4-(4-trifluoromethyl-benzyl)-2,3,4,5-tetrahydro-1H benzo[*e*][1,4]diazepine-8-carboxylic acid amide. (R^1 = benzyl, R^2 = 4-trifluoromethylbenzyl) (5.1 mg, yield 75%), ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51−7.14 (m, 12H), 3.96 (d, J = 14.4 Hz, 1H), 3.94 (d, J = 14.4 Hz, 1H), 3.88 (t, J = 7.2 Hz, 1H), 3.75 (d, J = 14.4 Hz, 1H), 3.66 (d, J = 14.4 Hz, 1H), 3.32 (dd, J = 6.8, 14.4 Hz, 2H). HPLC: retention time 7.99 min; 71.4%. LC/MS: M + 1 peak 454 (calcd MW 453).

2-Oxo-4-(3-chloro-benzyl)-2,3,4,5-tetrahydro-1H benzo-[*e*][1,4]diazepine-8-carboxylic acid amide. (R^1 = H, R^2 = 3-chlorobenzyl) (3.9 mg, 80%), ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.50 (s, 1H), 7.40−7.34 (m, 4H), 4.15 (s, 2H), 4.12 (s, 2H), 3.62 (s, 2H), 3.55 (s, 2H). HPLC: retention time 5.10 min; 83.0%. LC/MS: M + 1 peak 330 (calcd MW 329).

2-Oxo-4-(3-bromo-benzyl)-2,3,4,5-tetrahydro-1H benzo-[*e*][1,4]diazepine-8-carboxylic acid amide. (R^1 = H, R^2 = 3-bromobenzyl) (3.7 mg, 66%), ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68−7.63 (m, 4 H), 7.54 (d, J = 7.6 Hz, 1H), 7.43 (dt, J = 1.2, 7.6 Hz, 1H), 7.31 (dt, J = 1.2, 8.4 Hz, 1H), 4.51 (s, 2H), 4.30 (s, 2H), 3.74 (s, 2H). HPLC: retention time 4.96 min; 78.7%. LC/MS: M + 1 peak 374 (calcd MW 373).

Supporting Information Available. Twelve representative spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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