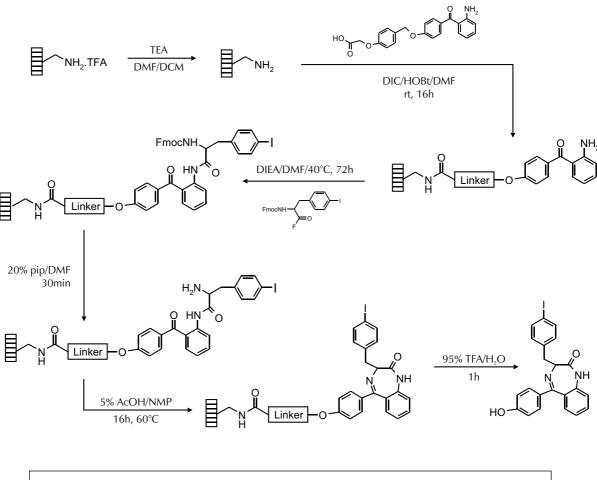


Preparation of 1,4-Benzodiazepines on SynPhase[™] Lanterns

1,4-Benzodiazepines exhibit a wide range of biological activities, are important therapeutically and show great potential as new drug candidates. In the following example, a 1,4-benzodiazepine is prepared in four steps on SynPhase[™] Lanterns. The synthesis involves the attachment of a pre-formed 2-aminobenzophenone hydroxymethylphenoxy compound to aminomethylated Lanterns. The solid supported primary aniline is then acylated with an Fmoc protected amino acid fluoride. Subsequent Fmoc deprotection followed by acid-catalysed intramolecular cyclisation generates a 1,4-benzodiazepine.



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Neutralisation of Aminomethylated Lanterns

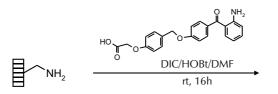
Each D-Series aminomethylated Lantern (supplied as TFA salt; initial specified loading: 35μmol) is covered with 5% TEA/1:1 DMF/DCM

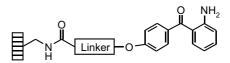
 $(2 \times 10 \text{min})$. The reagent solution is decanted and the Lanterns are washed with 1:1 DMF/DCM $(3 \times 3 \text{min})$, then DCM $(3 \times 3 \text{min})$.



Coupling Reaction

Each neutralised Lantern is treated with a 0.5mL solution of 4-[4-(2-aminobenzoyl)phenoxymethyl]phenoxyacetic acid¹ (0.1*M*, 50 μ mol 1.4 mole equivalents), HOBt.H₂O (0.1*M*, 50 μ mol 1.4 mole equivalents) and DIC (0.15M, 75 μ mol, 2.1 mole equivalents) in DMF at rt for 16h. The reagent solution is decanted and the Lanterns washed with DMF (3×3min), and DCM (3×3min).



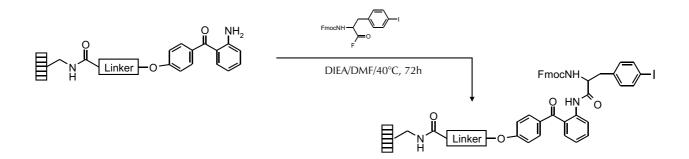


Acylation

To a suspension of TFFH (1.05g, 4.0mmol) and Fmoc-4-iodo-L-phenylalanine (2.1g, 4.1mmol) in DMF (1.5mL) is added DIEA (0.7mL, 4.0mmol). The mixture is stood at rt for 1h to afford a 0.8M solution of the amino acid fluoride.

Each aminobenzophenone coupled Lantern is

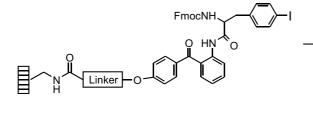
treated with 0.5mL of this acyl fluoride solution (400 μ mol, 11.4 mole equivalents) and heated at 40°C for 72h. The reagent solution is decanted and the Lanterns are washed with DMF (4×3min), and DCM (3×3min).

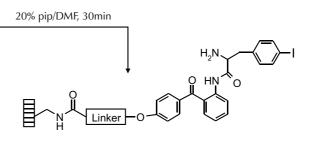


Fmoc Deprotection

Each acylated Lantern is covered with 20% pip/DMF and stood at rt for 30min. The reagent

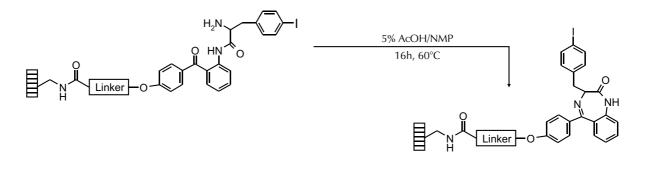
solution is decanted and the Lanterns are washed with DMF $(3 \times 3 \min)$, and DCM $(3 \times 3 \min)$.





1,4-Benzodiazepine Formation

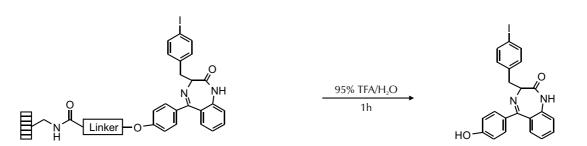
The Fmoc deprotected Lanterns are covered with a solution of 5% AcOH/NMP and heated at 60°C for 16h, then allowed to cool. The reagent solution is decanted and the Lanterns washed with DMF $(3 \times 3 \text{min})$, and DCM $(3 \times 3 \text{min})$.



Cleavage

Individual Lanterns are placed in polypropylene tubes and treated with 95% TFA/H $_2O$ (0.6-0.8mL) for 1h. The Lanterns are removed and the cleavage solutions are concentrated (centrifugal evaporator). Samples are dissolved in 90%

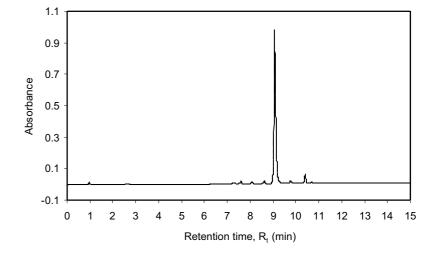
 CH_3CN/H_2O , analysed (HPLC and ES-MS analysis), and concentrated again. The yield of benzodiazepine based on the initial Lantern loading is 82%.

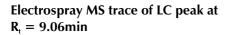


Analytical Data

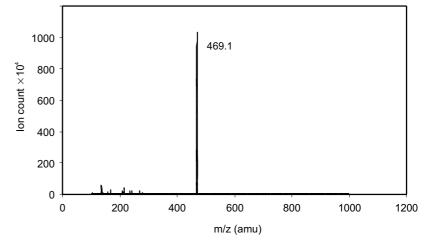
Reverse phase HPLC trace of the crude 1,4-benzodiazepine

Detection at 214nm





Molecular Formula: $C_{22}H_{17}IN_2O_2$ Monoisotopic Mol. Weight: 468.0amu $[M+H]^+$ peak at 469.1amu



Reference

1 Bunin, B. A., Plunkett, M. J. and Ellman, J. A., Proc. Natl Acad. Sci. USA, 1994, 91, 4708-4712.



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