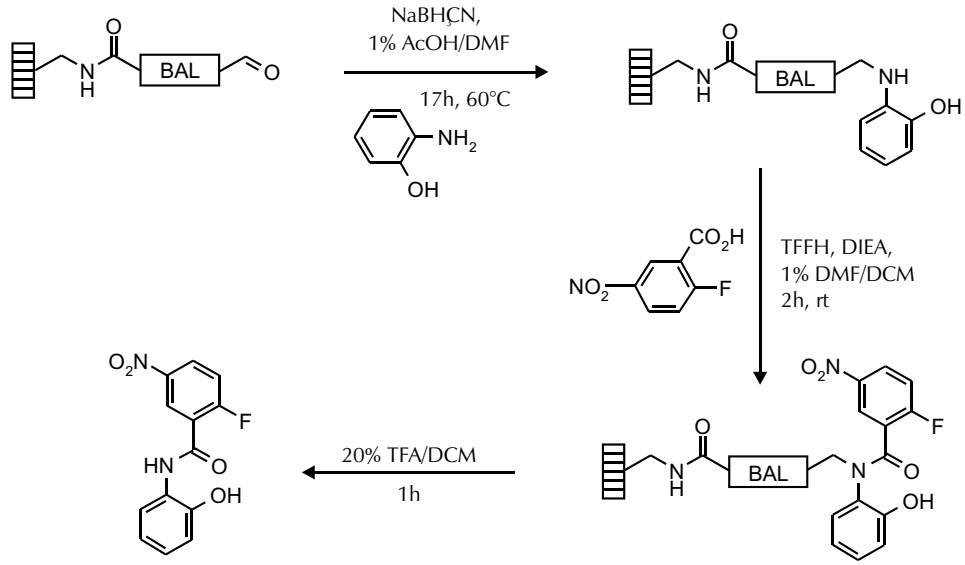
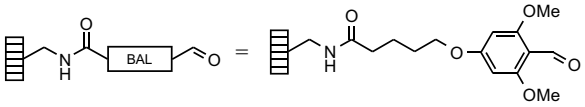
Preparation of Secondary Carboxamides on BAL Linker

A range of secondary carboxamides may be generated using the backbone amide forming Linker in a two step procedure.[1] In the following example, 2-aminophenol is reductively aminated to the linker on SynPhase™ PS Lanterns.[2] The resultant support-bound secondary amine is then acylated with a carboxylic acid such as 2-fluoro-5-nitrobenzoic acid using tetrafluoromethylformamidinium hexafluorophsophate.



BAL:	backbone amide linker
DMF:	dimethylformamide
DCM:	dichloromethane
rt:	room temperature
DIEA:	diisopropylethylamine
DCM:	dichloromethane
TFA:	trifluoroacetic acid



TFFH: fluoro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate

Reductive Amination

Each D-series Lantern (initial specified loading: 36μmol) is treated with 0.5mL of a solution of 2-aminophenol (0.5M, 250μmol, 7 mole equivalents) and sodium cyanoborohydride (0.05M, 25μmol, 0.7 mole equivalents) in 1% acetic acid/DMF at 60°C for 17h. After cooling to rt, the reagent solution is decanted and the Lanterns washed with DMF (3×3min) and DCM (3×3min).

Acylation

Each D-Series Lantern is treated with 0.5mL of a solution of 2-fluoro-5-nitrobenzoic acid (0.1M, 50μmol, 1.4 mole equivalents), TFFH (0.1M, 50μmol, 1.4 mole equivalents) and DIEA (0.2M, 100μmol, 2.8 mole equivalents) in 1% DMF/DCM at rt for 2h. The reagent solution is decanted, the Lanterns are washed with DMF (3×3min) and DCM (3×3min) then air dried.

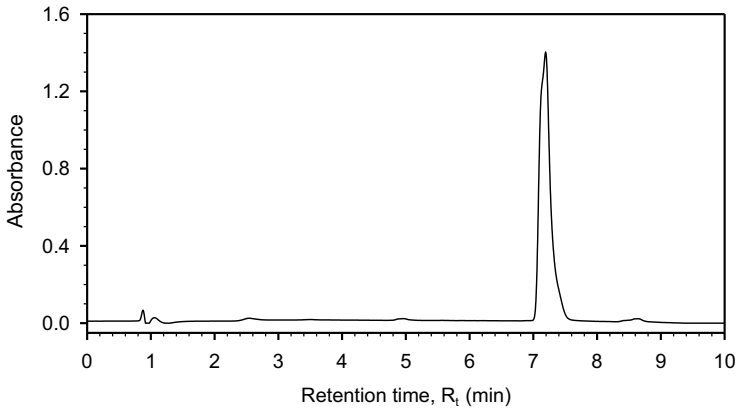
Cleavage

Individual Lanterns are placed in polypropylene tubes and treated with 20% TFA/DCM (0.6-0.8mL) for 1h. The Lanterns are removed and the cleaved products are concentrated using a centrifugal evaporator. The residue is freeze-dried from 90% CH_3CN/H_2O. The yield of carboxamide product is 54%, based on the initial loading. Samples are dissolved in 90% CH_3CN/H_2O for HPLC and ES-MS analysis.

Analytical Data

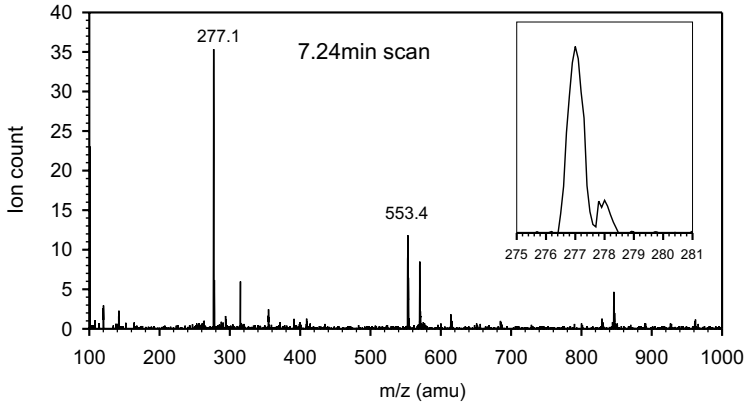
Reverse phase HPLC trace of the crude product

Detection at 214nm



Electrospray MS trace of LC peak at R_t=7.24min

Molecular Formula: $C_{13}H_9FN_2O_4$
Monoisotopic Mol. Weight: 276amu
$[M+H]^+$ peak at 277.1amu
$[2M+H]^+$ peak at 553.4amu



References and Notes

1 Ouyang, X., Tamayo, N. and Kiselyov, A.S., *Tetrahedron,* 1999, **55**, 2827-2834.
2 The chemistry described here was performed using SynPhase PS Lanterns but is readily adaptable to SynPhase PA Lanterns.

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