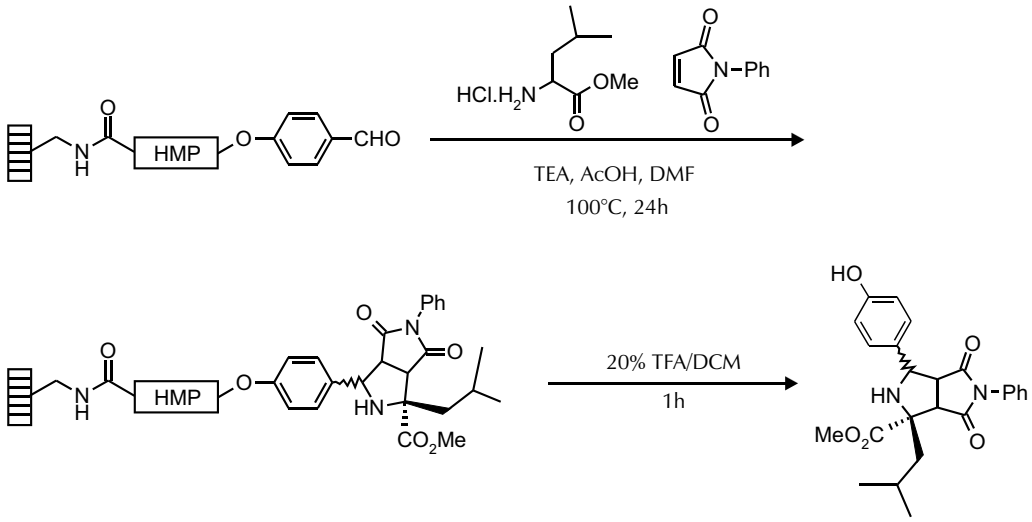
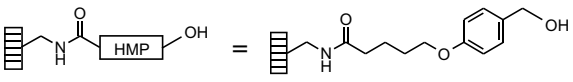
Preparation of a Bicyclic Pyrrolidine *via* a Three Component 1,3-Dipolar Cycloaddition

Pyrrolidines can be generated by trapping an azomethine ylide with a dipolarophile. In the following example, a three component 1,3-dipolar cycloaddition involving a solid-bound benzaldehyde,[1] an amino acid methyl ester and an *N*-substituted maleimide are used to prepare bicyclic pyrrolidines[2] on SynPhase™ PS HMP derivatized Lanterns.[3]



DMF: dimethylformamide
DCM: dichloromethane
TFA: trifluoroacetic acid
TEA: triethylamine
HMP: hydroxymethylphenoxy



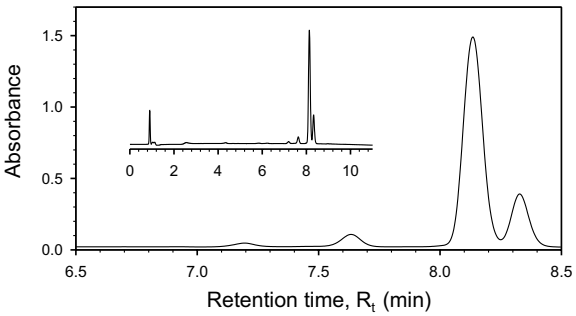
Three-Component 1,3-Dipolar Cycloaddition

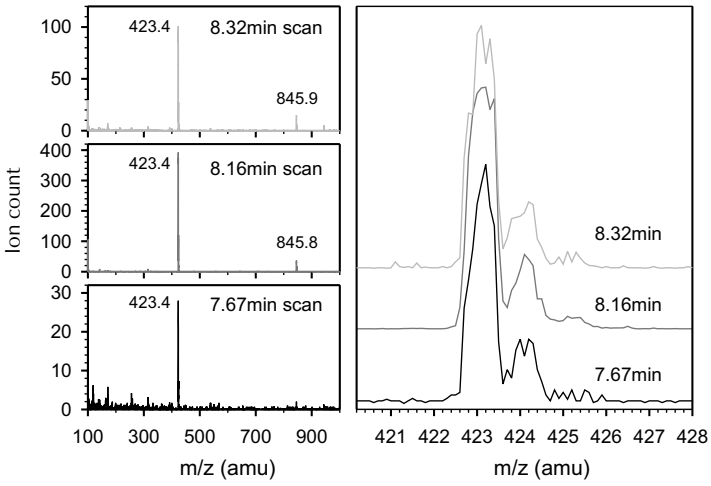
Each D-Series Lantern derivatized with 4-hydroxybenzaldehyde[1] (initial specified loading: 36μmol) is treated with 0.5mL of a solution of L-leucine methyl ester hydrochloride (0.2 M, 100μmol, 2.8 mole equivalents), *N*-phenyl maleimide (0.2M, 100μmol, 2.8 mole equivalents), TEA (0.2M, 100μmol, 2.8 mole equivalents) and acetic acid (0.5M, 250μmol, 7.0 mole equivalents) in DMF at 100°C for 24h. The reaction is allowed to cool to room temperature, the reagent solution is decanted and the Lanterns washed in turn with DMF (3x3min) and DCM (3x3min) then air dried.

Cleavage

Individual Lanterns are placed in polypropylene tubes and treated with 20% TFA/DCM (0.6-0.8mL) for 1h. Cleavage solutions are concentrated using a centrifugal evaporator. The crude yield is *ca.* 70%, based on the initial specified loading of the Lanterns. LC-MS analysis indicates three LC peaks with the required $[M+H]^+$ peak in the mass spectra. The purity of the crude diastereomeric mixture is 95%. Samples are dissolved in 95% CH_3CN/H_2O for LC-MS analysis.

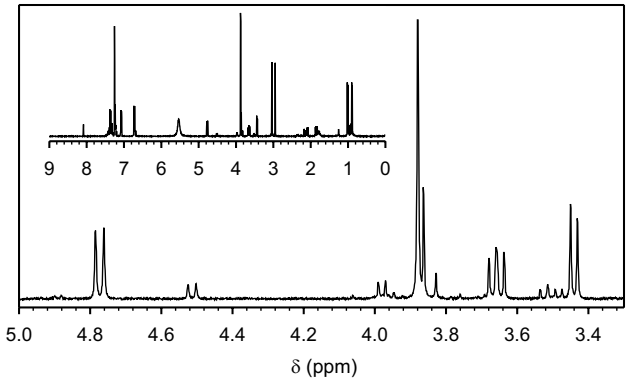
Analytical Data





Electrospray Mass spectra of LC peaks at R_t = 7.6, 8.1 and 8.3min

Molecular Formula: $C_{24}H_{26}N_2O_5$
Monoisotopic Mol. Weight: 422.5amu
$[M+H]^+$ peak at 423.4amu in each spectrum



400MHz ^{1}H NMR spectrum of crude pyrrolidine ($CDCl_3$)

References

1 See SynPhase Chemistry Note SCN 005-3.
2 Hamper, B.C., Dukesherer, D.R. and South, M.S., *Tetrahedron Lett.,* 1996, **37**, 3671-3674.
3 The chemistry described here was performed using SynPhase PS Lanterns but is readily adaptable to SynPhase PA Lanterns.

MIMOTOPES

International
Tel : + 61 3 9565 1111
Fax : + 61 3 9565 1199
mimotopes@mimotopes.com

France
Tel : + 33 1 5858 0002
Fax : + 33 1 5858 0006
europe@mimotopes.com

United Kingdom
Tel: +44 151 648 3343
Fax: +44 151 648 3328
uk@mimotopes.com

USA West
Tel : + 1 858 558 5800
Fax : + 1 858 558 5810
Tel : 800 644 1866
Fax : 800 655 1866
uswest@mimotopes.com

USA East
Tel : + 1 919 873 1123
Fax : + 1 919 873 1127
Tel : 800 633 8161
Fax : 800 424 3970
useast@mimotopes.com

http://www.synphase.com http://www.mimotopes.com