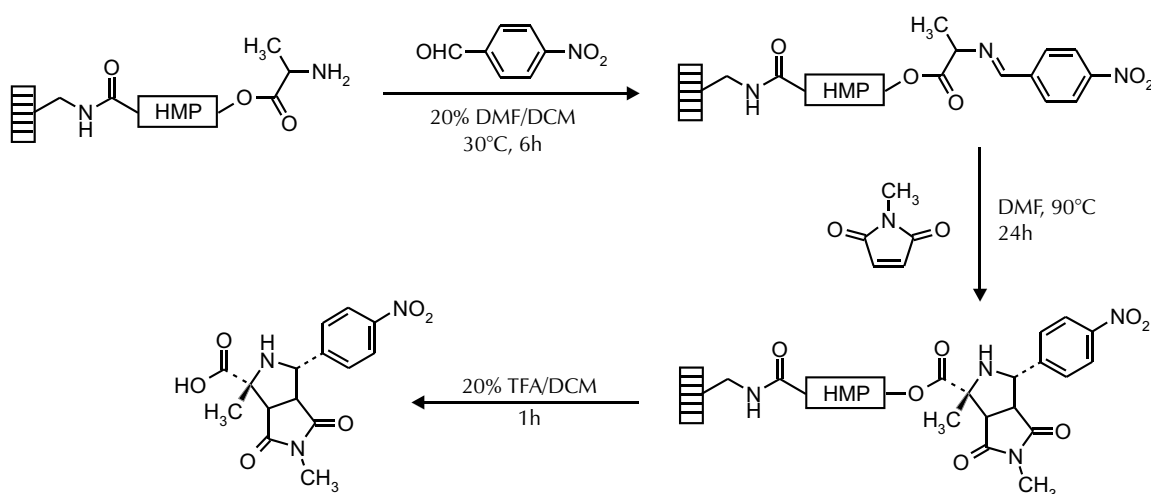




## Two Step Conversion of a Support Bound Amino Acid to a Bicyclic Pyrrolidine

The [3 + 2] cycloaddition of a support-bound azomethine ylide with an alkene is a useful route to pyrrolidines.<sup>1,2</sup> In the following example, a benzaldehyde is condensed with an  $\alpha$ -amino acid already attached<sup>3</sup> to HMP derivatized SynPhase™ PS Lanterns.<sup>4</sup> These Lanterns are then treated with an *N*-substituted maleimide at elevated temperature to produce a bicyclic pyrrolidine.<sup>1</sup>



DMSO: dimethylsulfoxide  
DMF: dimethylformamide  
DCM: dichloromethane  
TFA: trifluoroacetic acid  
HMP: hydroxymethylphenoxy



### Condensation Reaction

Each Fmoc-protected, alanine-coupled, D-Series Lantern (initial specified loading:  $36\mu\text{mol}$ )<sup>3</sup> is treated with 0.5mL of a solution of *p*-nitrobenzaldehyde (0.18M,  $90\mu\text{mol}$ , 2.5 mole equivalents) in 20% DMF/DCM at 30°C

for 6h. The Lanterns are washed with 20% DMF/DCM (3×3min) and DCM (3×3min) then dried in a vacuum oven at 40°C/ca. 1mmHg for 16h.

### Cycloaddition Reaction

Each Lantern is treated with 1.0mL of a solution of *N*-methylmaleimide (0.36M,  $360\mu\text{mol}$ , 10 mole equivalents) in DMF at 90°C for 24h. The reaction is allowed to cool to

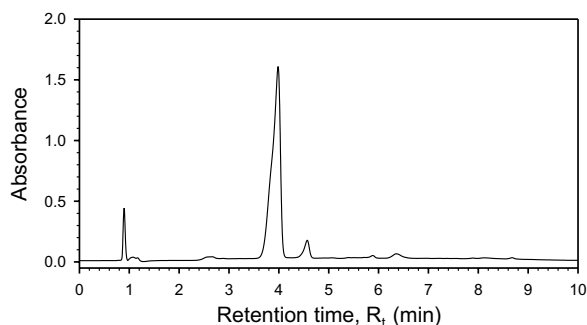
room temperature before the Lanterns are washed with DMF (3×3min) and DCM (3×3min) and dried in a vacuum oven at 40°C/ca. 1mmHg for 16h.

## Cleavage

**Individual Lanterns are placed** in polypropylene tubes and treated with 20% TFA/DCM (0.6-0.8mL) for 1h. The cleavage solutions are concentrated using a centrifugal evaporator. The yield of bicyclic

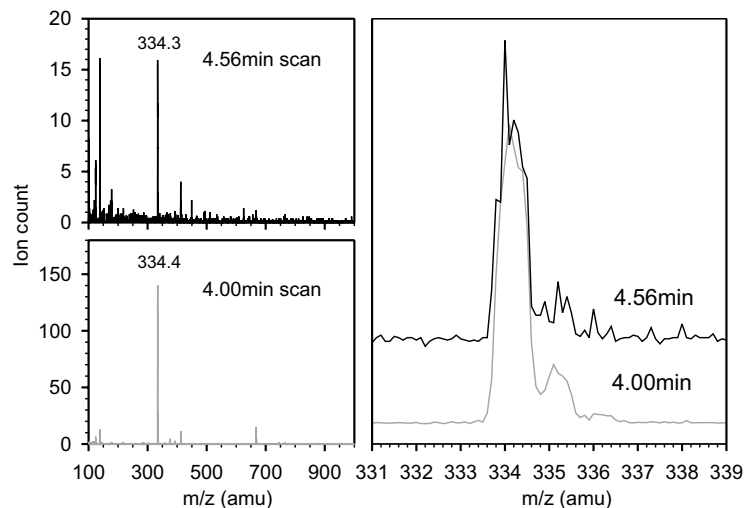
pyrrolidine product is 87% (based on the initial loading of 36 $\mu$ mol). The product is a 92:8 mixture of diastereoisomers. Samples are dissolved in 90% CH<sub>3</sub>CN/H<sub>2</sub>O for LC-MS analysis.

## Analytical Data



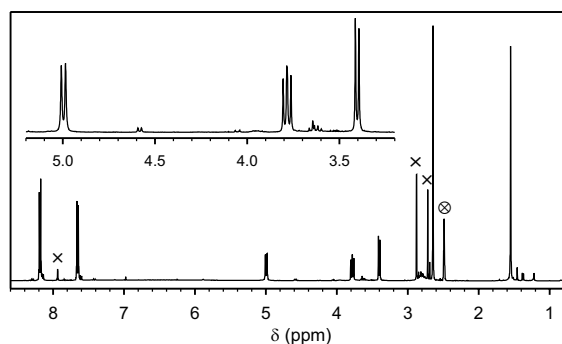
**Reverse phase HPLC trace of the crude bicyclic pyrrolidine**

Detection at 214nm



**Electrospray MS traces of LC peaks at R<sub>t</sub> = 4.00 and 4.56 min**

Molecular Formula: C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>O<sub>6</sub>  
Monoisotopic Mol. Weight: 333.3amu  
[M+H]<sup>+</sup> peak at 334amu in each spectrum.



**400MHz <sup>1</sup>H NMR spectrum of the crude bicyclic pyrrolidine (D<sub>6</sub>-DMSO)**

(⊗) DMSO  
(X) residual DMF

### References and Notes

- 1 Bicknell, A.J. and Hird, N.W., *Bioorganic and Medicinal Chemistry Letters*, 1996, **6**, 2441-2444.
- 2 Hamper, B.C., Dukeshner, D.R. and South, M.S., *Tetrahedron Lett.*, 1996, **37**, 3671-3674.
- 3 Refer to Mimotopes SynPhase Chemistry Note SCN 003-3.
- 4 The chemistry described here was performed using SynPhase PS Lanterns but is readily adaptable to SynPhase PA Lanterns.



**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