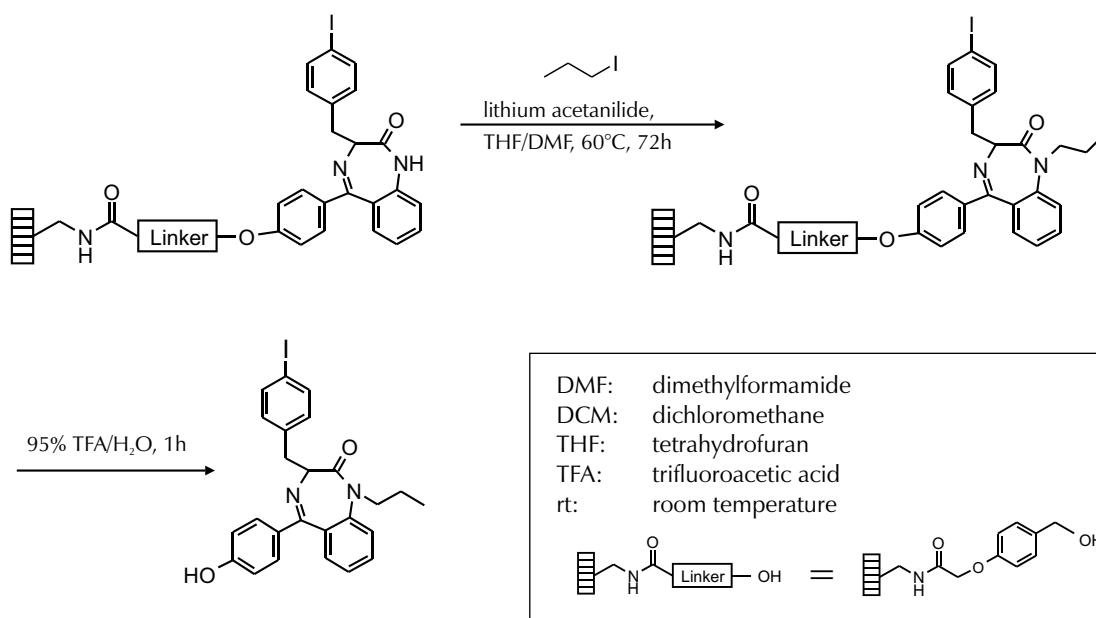




## Lithium Acetanilide Promoted Alkylation of a Support-Bound 1,4-Benzodiazepine

**1,4-Benzodiazepines of the general structure** shown below, may be further functionalized by alkylating the amide nitrogen. In the following example, a 1,4-benzodiazepine prepared on SynPhase™ Lanterns<sup>1</sup> is treated with lithium acetanilide then an alkyl halide to give the alkylated 1,4-benzodiazepine on cleavage.



### Preparation of Lithium Acetanilide Solution<sup>2</sup>

To a stirred solution of acetanilide (1.0g, 7.4mmol) in anhydrous THF (5mL) at -78°C under N<sub>2</sub> is slowly added *n*-butyl lithium (4mL, 1.6M, 6.4mmol). The mixture is then stirred at

-78°C for 30min, then the cooling bath is removed and anhydrous DMF (5mL) is added to give a 0.45M solution of lithium acetanilide.

### Alkylation of the 1,4-Benzodiazepine

Each D-Series Lantern<sup>1</sup> (initial specified loading: 35μmol) is treated with the above lithium acetanilide solution (0.75mL, 0.45M, 9.5 mole equivalents) and stood at rt for 1h. Iodopropane (31μL, 0.45M, 9.5 mole

equivalents) is then added and the mixture is heated at 60°C for 72h, cooled and reagent solution decanted. The Lanterns are washed with DMF (3×3min) and DCM (3×3min) then air dried.

## Cleavage

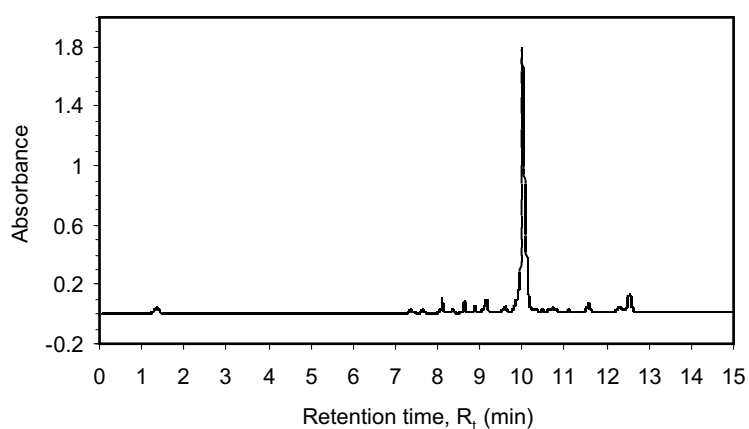
**Individual Lanterns are placed** in polypropylene tubes and treated with 95% TFA/H<sub>2</sub>O (0.6-0.8mL) for 1h. The Lanterns are removed and the cleavage solutions are concentrated using a centrifugal evaporator, then redissolved in 90%

CH<sub>3</sub>CN/H<sub>2</sub>O and freeze dried. Based on the initial Lantern loading, the yield of *N*-alkylated benzodiazepine is 78%. Samples are dissolved in 90% CH<sub>3</sub>CN/H<sub>2</sub>O for HPLC and ES-MS analysis.

## Analytical Data

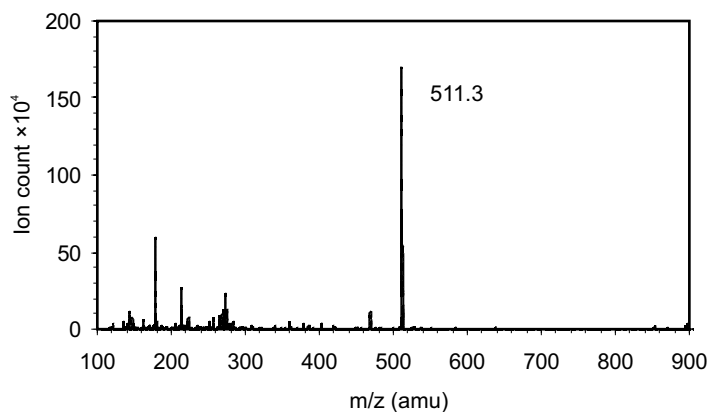
### Reverse phase HPLC trace of the crude *N*-propylbenzodiazepine

Detection at 214nm



### Electrospray MS trace of LC peak at R<sub>t</sub> = 10.06min

Molecular Formula: C<sub>25</sub>H<sub>23</sub>IN<sub>2</sub>O<sub>2</sub>  
Monoisotopic Mol. Weight: 510.1amu  
[M+H]<sup>+</sup> peak at 511.3amu



### References

- 1 See Mimotopes SynPhase Chemistry Note SCN 011-2.
- 2 Boojamra, C.G., Burow, K.M., Thompson, L.A. and Ellman, J.A., *J. Org. Chem.*, 1997, **62**, 1240-1256.



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