Journal Club No.459 May 26, 2008

Build-couple-pair strategy meets fluorous tag technology: an ingenious way of diversity-oriented synthesis

Naoya Oku

No chemical biologists may argue against the idea that having an access to chemical library with high molecular shape diversity is a prerequisite for the successful outcome of chemical genetic screens. Nevertheless, the description on how the library was actually prepared is, unfortunately, often omitted from most of the biology papers, which prevents us from knowing what types of library we can expect to get better results. In this presentation, I would like to specifically focus on this rarely-described part and wish to introduce one of the latest progresses in the field of diversity-oriented synthesis.

References

(1) Synthesis of Natural-Product-Like Molecules with Over Eighty Distinct Scaffolds. Morton, D.; Leach, S.; Cordier, C.; Warriner, S.;Nelson, A. *Angew. Int. Ed.* **2009,** *48,* 104-109.

(2) Molecular diversity by design. Schreiber, S. L. *Nature,* **2009,** *457,* 153-154.

Summary

A key challenge in chemical biology is the design and synthesis of compound libraries spanning large tracts of biologically relevant chemical space. Despite this, organic chemistry is dominated by a remarkably small number of molecular scaffolds.

Diversity-oriented synthesis (DOS) aims the preparation of compound libraries with high substitutional, stereochemical, and/or scaffold diversity. Our approach to the combinatorial variation of molecular scaffolds involves 3 steps.

1) Attaching the internally unsaturated “propagating” building blocks to a fluorous-tagged linker, thus the removal of excess reagents allowed at each stage by fluorous-solid phase extraction (F-SPE) alone.

2) Attach the “capping” building blocks that incorporate a terminal alkene to the tagged products to produce metathesis substrates.

3) Initiate metathesis cascade at the terminal alkene to release cyclized products from the fluorous-tagged linker.

This approach allowed the preparation of 80 scaffolds from the building blocks in either four or five steps with the use of just six reaction types. Excitingly, the compounds had many of the broad structural features that are reminiscent of natural products.