Synthetic Ventures into the Lipstatins, Bielschowskysins, Platensimycins, and Enediynes

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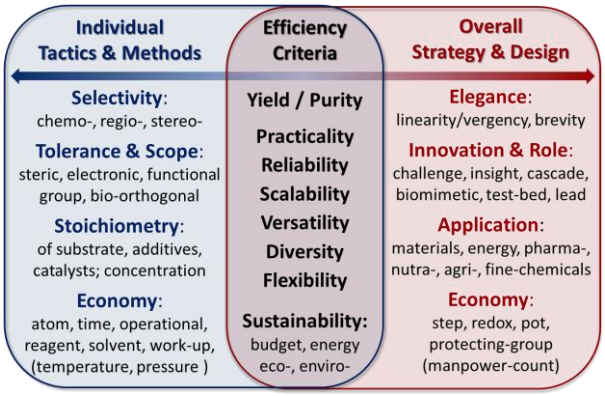
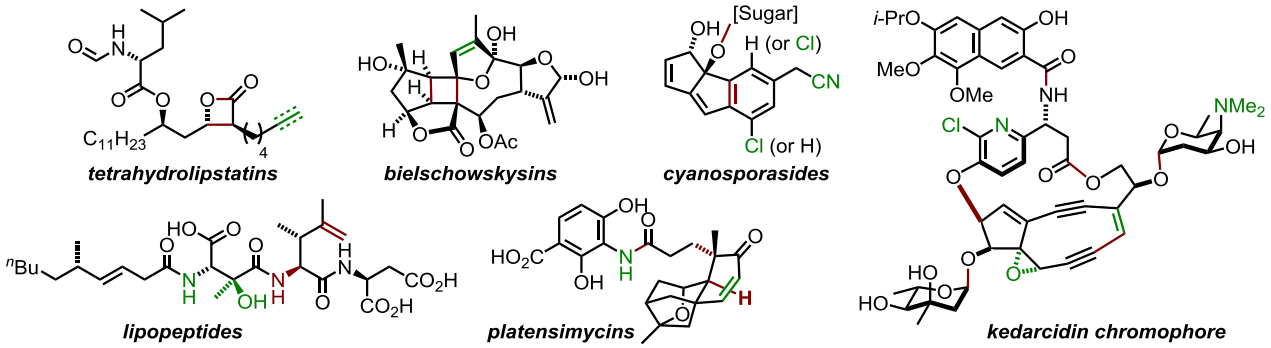
Natural products often unite structure and function in unforeseen ways. Such facets have long driven target-oriented synthesis and drug discovery campaigns. The concerted challenge for the organic chemist is not only to orchestrate a sequence of synthetic methods into a workable, clever strategy, but also to advance and develop methods and tactics in conceptually new ways.

Indeed, the complex multifunctionalized chemical environments of natural products frequently limit the effectiveness of a known method to achieve a desired reaction. Brønsted acids or bases, Lewis acids or bases, organometallics, carbocations, carbanions, radicals, carbenoids, ylids, and neutral and ionic species in general, will often experience competing interactions outside their designed or known roles as reactants or reagents. This is true whether they are being used (or generated) in a catalytic, additive, redox, spectator or stoichiometric sense. At each key step of a targeted synthesis, therefore, each chosen method often needs to be advanced and optimized, and may be scrutinized on the basis of several interrelated criteria (see opposite).

Such ideals need to be sensibly balanced within a multistep synthesis, whether a key building block is being constructed or a key coupling step is being optimized (or even devised). Herein, we present key methods and strategies that were advanced *en route* to uncovering the chemistry and biology of the (1) lipopeptides[1], (2) lipstatins[2], (3) platensimycins[3], (4) bielschowskysins[4], (5), cyanosporasides[5] and (6) the kedarcidin chrompohore[6]. Besides developing several new methods, the chemistry presented has challenged the frontiers of metal and amine catalysis, Lewis acid and organometallic couplings, and transannular tactics.





Selected References

1. With Butler et al. *Org. Lett.* **2012**, *14*, 1560; *Tetrahedron Lett.* **2012**, *53*, 2706.
2. With Yao et al. *Chem. Eur. J.* **2012**, *18*, 8403; *Chem. Asian J.* **2011**, *10*, 2762; *Chem. Commun.* **2010**, 8335; *J. Am. Chem. Soc.* **2010**, *132*, 656; featured by faculty-1000 as most promising method.
3. With Eey, S. T. C. *Org. Lett.* **2010**, *12*, 5510-5513; total synthesis submitted (PhD student with Scott Denmark).
4. With Yang, E. G. et al. *Tetrahedron Lett.* **2013**, ASAP; unpublished work (PhD students with Peter Seeberger).
5,6. With Yamashita, Sato, Hayashi, and Hirama et al.; unpublished work and manuscripts in preparation.

Martin J. Lear (マーティン ・リアー), b. April 2nd 1970 (British, UK), University of Glasgow, Scotland (B.Sc., 1991; Ph.D., 1996). Dr. Lear has over 8-years of independent research experience in the fields of organic chemistry and integrates applied or diversified synthesis with the molecular imaging and bio-targeting of natural products. Since Jan 2013, he has been a Lecturer at Tohoku University with Yujiro Hayashi (Sendai, Japan). During 2005 to 2012, he was an Assistant Professor and a core-member of the Medicinal Chemistry Group at the National University of Singapore (NUS). During 2000 to 2004, he was an Assistant Professor at Tohoku University with Masahiro Hirama (Sendai, Japan). He has also won several postdoctoral fellowships to work at Parke-Davis (Cambridge, UK, 1996), ICSN-CNRS (Gif-sur-Yvette, France, 1997) and Tohoku University (JSPS and CREST, 1997-2000). Dr. Lear is also the co-founder and Director of Chemistry of a biotech spin-off, BioLynx Technologies (**biolynxtech.com**).