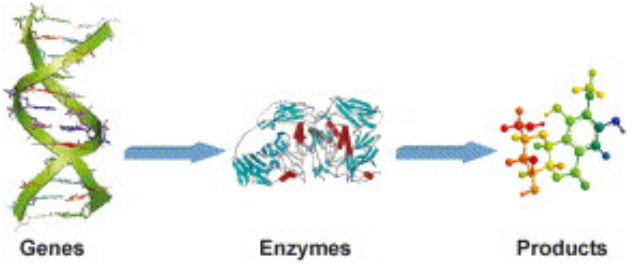
Introduction



API

Lead molecules

Natural products

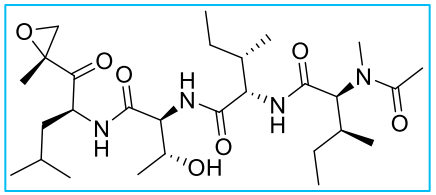
Sustainable building blocks

New scaffolds

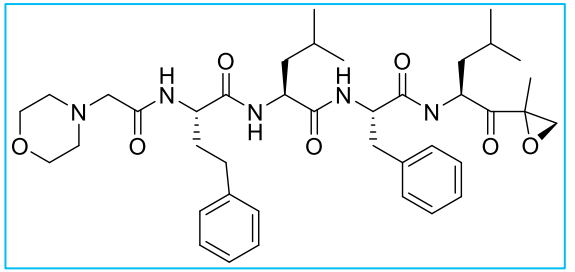
- Many natural products are great leads but poor API's.
- Toxicity/ADME/Stability/secondary manufacturing- formulation issues
- Also – maybe quality and supply chain issues
- Transformation into semi-synthetic molecules/ leads/building blocks needs chemical manipulations
- Complex, fragile structures are not always amenable to traditional stoichiometric transformations

Natural product

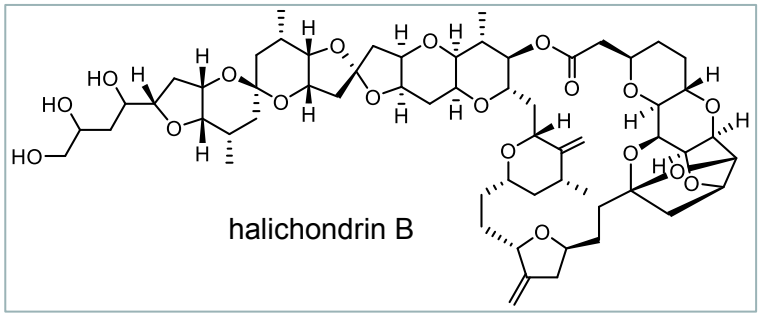
Drug/Candidate



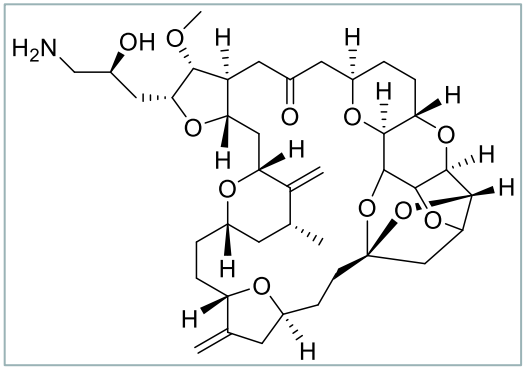
Epoxomicin



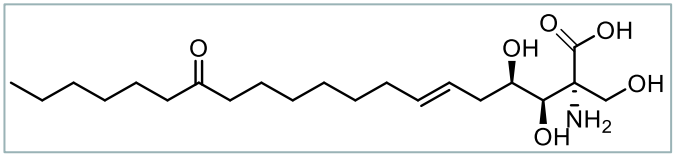
Carfilzomib Multiple myeloma



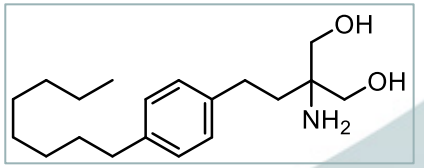
halichondrin B



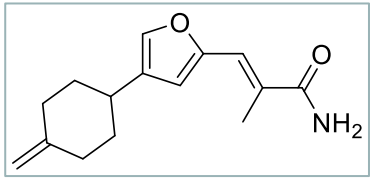
Eribulin



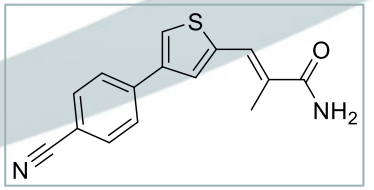
myriocin (ISP-1) metabolite



Fingolimod



Brasilamide E



Med. Chem. Lett. 26 (2016) 1885–1888

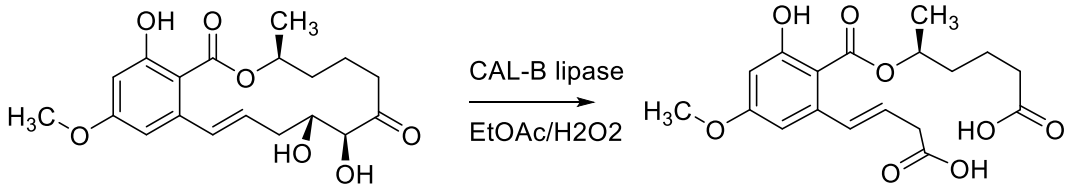
Advantages of biocatalysis – for lead discovery and manufacturing

- A wide range of possible reactions
  - number of transformations feasible for synthesis is growing rapidly
  - lipase/transaminase/keto-reductase/P450/nitrilase/aldolase, etc.
- High regioselectivity and stereoselectivity provide controlled, selective chemistry
- One-step reactions avoid the need for protection/deprotection
- Mild reaction conditions are suitable for complex fragile molecules
- High activity enables low catalyst concentrations
  - bespoke biocatalysts can be rapidly evolved
- Immobilized enzyme catalysts can be reused
  - suitable for use in continuous flow
- Safe to operate on scale – near ambient, pH 7 etc.
- Sustainable- enzymes made from glucose and completely degraded in the environment to innocuous materials

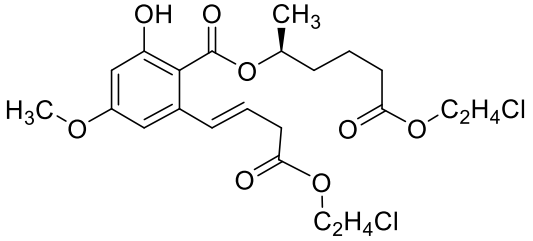
Hydrolase enzymes – Lipase

Oxidative cleavage
With *in situ* per acid

Replaces reagents
Like $KMnO_4$, IO_4^- etc

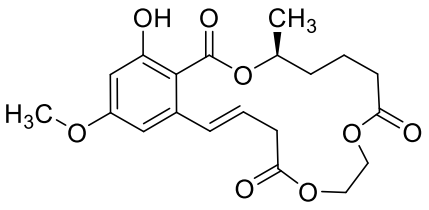


Dihydroxymethylzearalenone 1

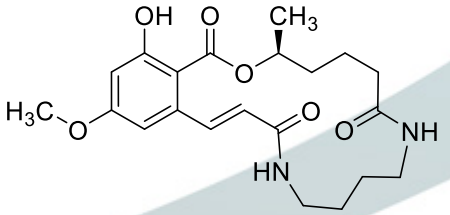


Efficient high yield
macrocyclisations
under mild conditions

Mucor miehei lipase
C2 -diol/MTBE



Mucor miehei lipase
C4-diamine/MTBE

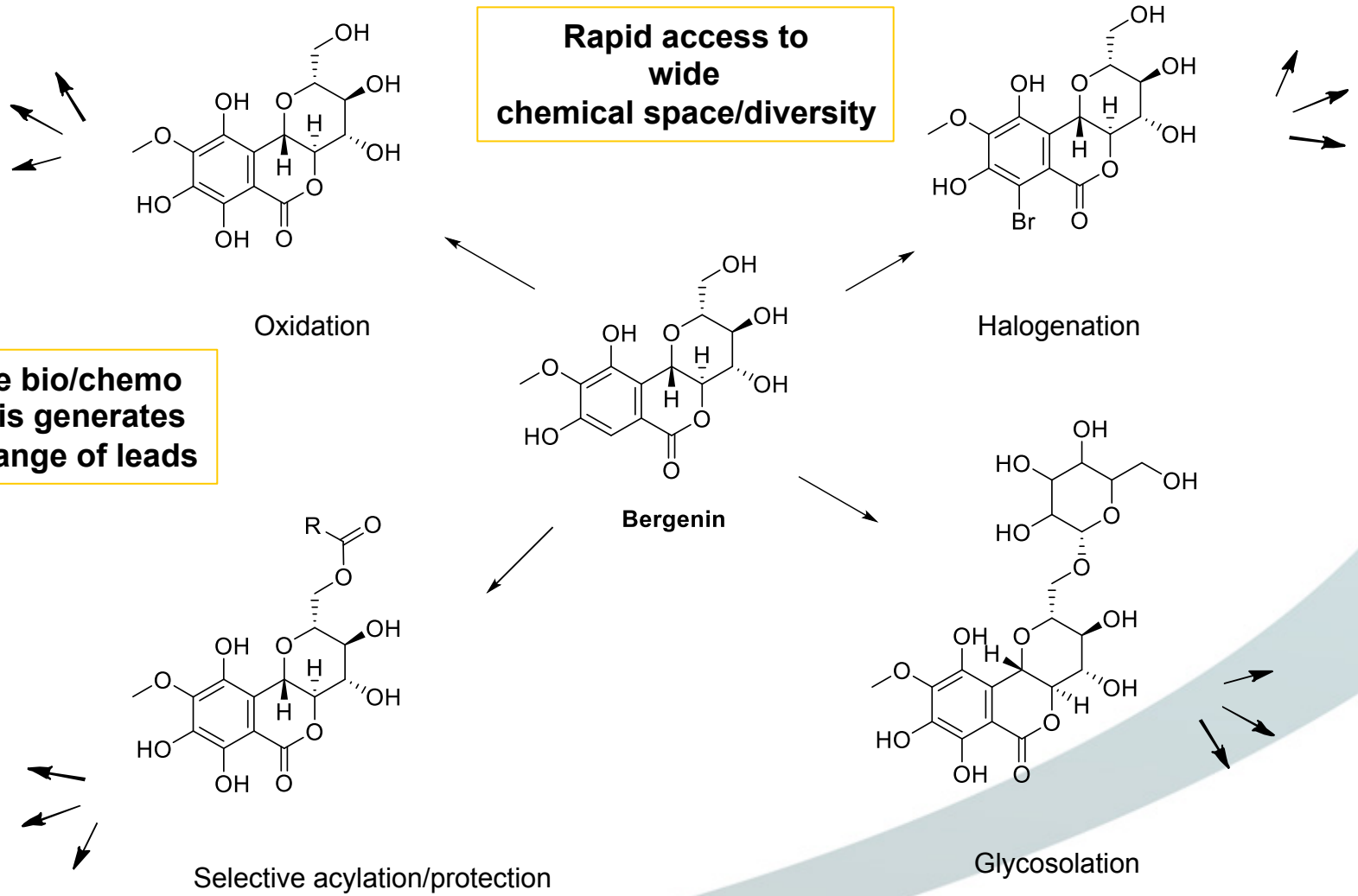


Bioorg. Med. Chem. Lett. 19 (2009) 3059–3062

Scanning the Biocatalysis tool box….

Rapid access to wide chemical space/diversity

Iterative bio/chemo catalysis generates a wide range of leads

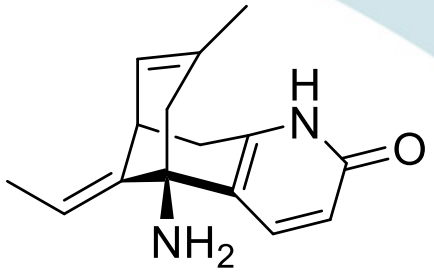


TIBTECH MAY 1998 (VOL 16) 215

Bioorg. Med. Chem. 12 (2004) 1817–1834

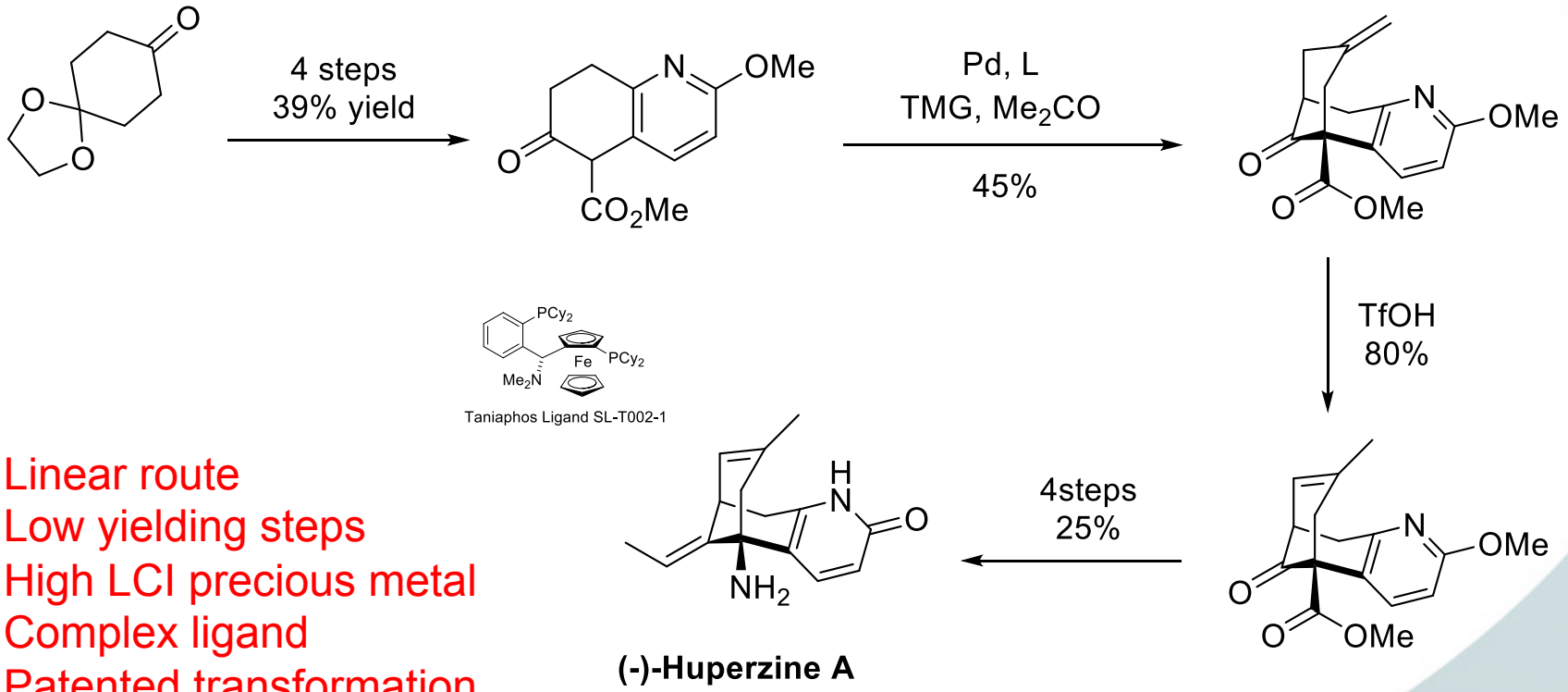
(–)-Huperzine A

(-)-Huperzine A



- Natural medicinal extract – of increasing clinical interest for CNS indications
- The primary obstacle to the clinical development of (-)-huperzine A is supply of clinical grade material
- The average yield from the dried herb is ~ 0.01%
- Slow growing ~ 20 years to reach maturity
- Increasing scarcity due to overharvesting in its native China
- Synthetic biology solution –maybe – it took $20,000,000 to establish Artemisinin pathway in yeast
- Still a need for synthetic/semi-synthetic routes….

De novo chemical route to Hup A



- Linear route
- Low yielding steps
- High LCI precious metal
- Complex ligand
- Patented transformation

- Currently developing a new route to Hup A based on biocatalysis as a key enabling technology

Org. Process Res. Dev. 2012, 16, 635−642

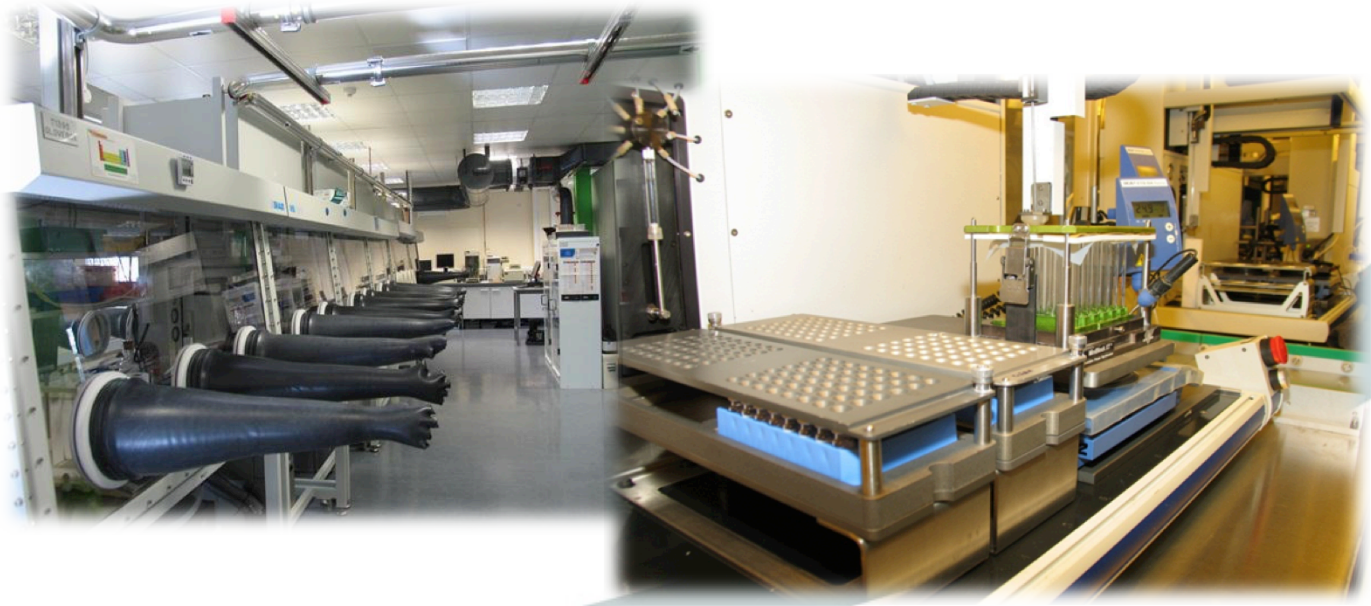
Acta Pharmacol Sin. 2006 Jan;27(1):1-26.

Conclusions

- Biocatalysis is highly compatible with the manipulation of complex natural products
- Combined with chemocatalysis, wide areas of chemical space can be accessed
- CatSci has the ability to deliver both bio and chemocatalysis to increase chemical diversity / identify better manufacturing routes
- CatSci has the expertise and equipment to isolate and identify products and impurities with their analytical suite

About CatSci Ltd

- CRO providing customised chemistry R&D services
- Privately owned business based in Cardiff, UK
- Spun out of AstraZeneca, trading since Q2 2011



About CatSci Ltd

- Services cover all aspects of synthetic and analytical chemistry
- Chemistry organised according to three technical divisions
  - *Applied Catalysis*
  - *Chemical Development*
  - *Custom Synthesis and Material Supply*
- Extensive knowledge and experience in a wide range of challenging chemistry
  - discovery through to commercial manufacturing
- Identification/Quantification of impurities by LC-MS