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Oral Presentation Abstracts

Plenary Sessions

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http://scg.ch/fallmeeting/2015

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Daring the Challenge and Thinking Big: the Value of Early Process Research (Sandmeyer Award Lecture 2015)

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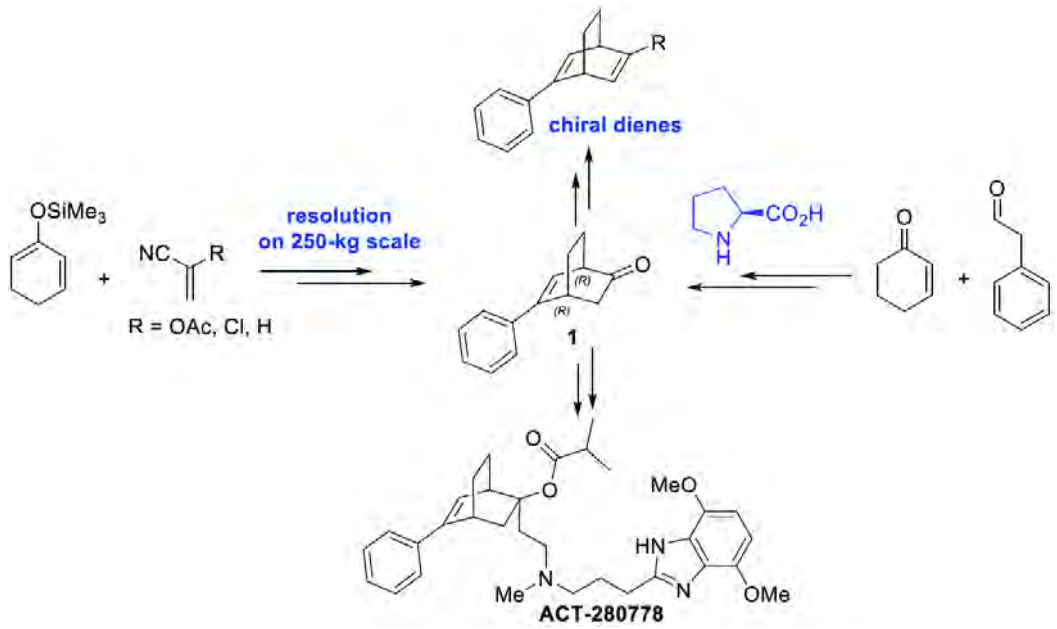
Enantiomerically pure phenylbicyclo[2.2.2]oct-5-en-2-one (1) was required in large quantities for the manufacturing of a L/T calcium channel antagonist ACT-280778[1] at Actelion Pharmaceuticals Ltd. Published routes delivered only gram amounts at exorbitant costs.
Two technologies that often defy scale-up have been successfully used to supply material at various stages of drug development: Diels–Alder reactions[2] and organocatalysis. Up to 90 kg of enantiomerically pure 1 were produced by a Diels–Alder approach[3] followed by a chiral separation of racemic 1. Early, thorough safety assessments enabled the scale-up of inherently hazardous chemistry in a safe manner. More than 14 kg of ACT-280778 were produced over 17 steps, ready for testing in clinical studies. An enantioselective route was required for larger scale. The 2nd generation route features an organocatalytic one-pot Michael addition–aldol reaction with cheap 2-cyclohexenone and phenylacetaldehyde, with L-proline as catalyst, thereby not only reducing the environmental burden but reducing the cost of goods by more than 90%.[4]

Just two steps were required to synthesize eleven novel chiral diene ligands (c.f. Hayashi's bod* ligands) from now readily available 1. As an efficient access to bod* ligands was still missing, this protocol should be beneficial for the widespread use of this new authoritative ligand class.[5] The courage to apply and safely scale up hazardous, rarely used, novel chemistry, and the use of expert knowhow by tactical outsourcing of special technologies have been crucial for the quick delivery of this Active Pharmaceutical Ingredient and in the quest for shorter routes at lower costs.



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The Importance of Catalysis in the Synthesis of Active Pharmaceutical Intermediates (KGF-SCS Senior Industrial Science Award Lecture 2015)

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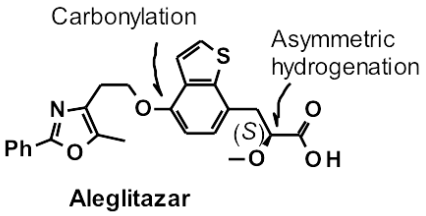
In recent years, a clear tendency towards increasing structural and stereochemical complexity of new drug candidates is observed. This factor, together with the limited amount of time and resources available to invent and develop more efficient syntheses, often lead to a critical issue regarding cost of the active pharmaceutical ingredient (API).

This presentation will illustrate how the early integration of catalysis in the synthesis plan of three new development compounds has not only been the condition to guarantee the timely supply of the amounts required for the planned preclinical and clinical investigations, but has also set the base for scalable and economical synthetic processes. Four reactions will be discussed as an example, three based on metal catalysis (carbonylation, asymmetric hydrogenation, ring-closing metathesis) and one on enzymatic catalysis (asymmetric keto reduction).



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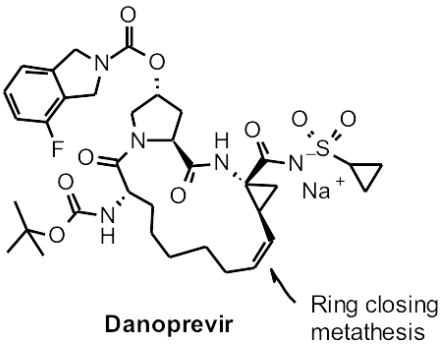

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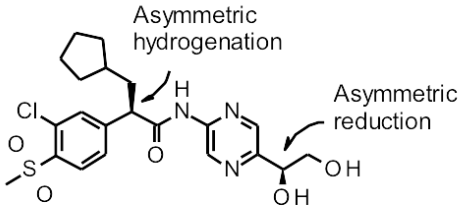

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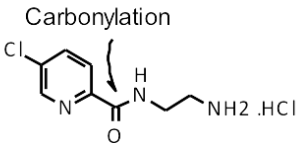

Lazabemide

Evolution in Medicinal Chemistry (KGF-SCS Distinguished Industrial Science Award Lecture 2015)

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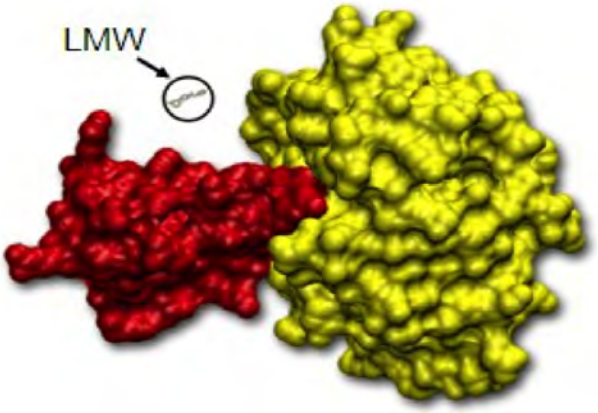
Medicinal chemistry is the chemistry discipline concerned with the design, development and synthesis of pharmaceutical drugs. It evolved from organic chemistry and its roots can be traced back at least hundred years to Ehrlich and others in Europe. Over the past 25 years, medicinal chemistry has gone through major changes as will be shown in the talk. Targets known as undrugable in the past are today the focus of modern medicinal chemistry. The molecular weight of the molecules synthesized increases significantly going from low-molecular weight heterocycles to antibodies, vaccines and proteins. In addition the batch mode is in some cases being replaced by flow-chemistry. Examples from our organizations will be presented and discussed.



In the above picture, a protein – protein interaction is shown with its huge interacting surface. The challenge for the rather small “LMW” to interrupt this interaction is clearly visible. Projects where the inhibition of these interactions is required are today the focus in many medicinal chemistry activities.