



**Trip Report:  
Process Chemistry in the Pharmaceutical Industry  
Miami, Florida  
February 6– 9, 2005**

**Dean A. Frey, Ph.D., Peter Leeming, Ph.D. and Bernhard J. Paul, Ph.D.**

Chemical Development  
Albany Molecular Research, Inc.  
21 Corporate Circle  
Albany, NY 12212

**Abstract.** *Process chemistry in the pharmaceutical industry was held in Miami, Florida, February 6-9, 2005. This report highlights select material from the seminars presented at the conference.*

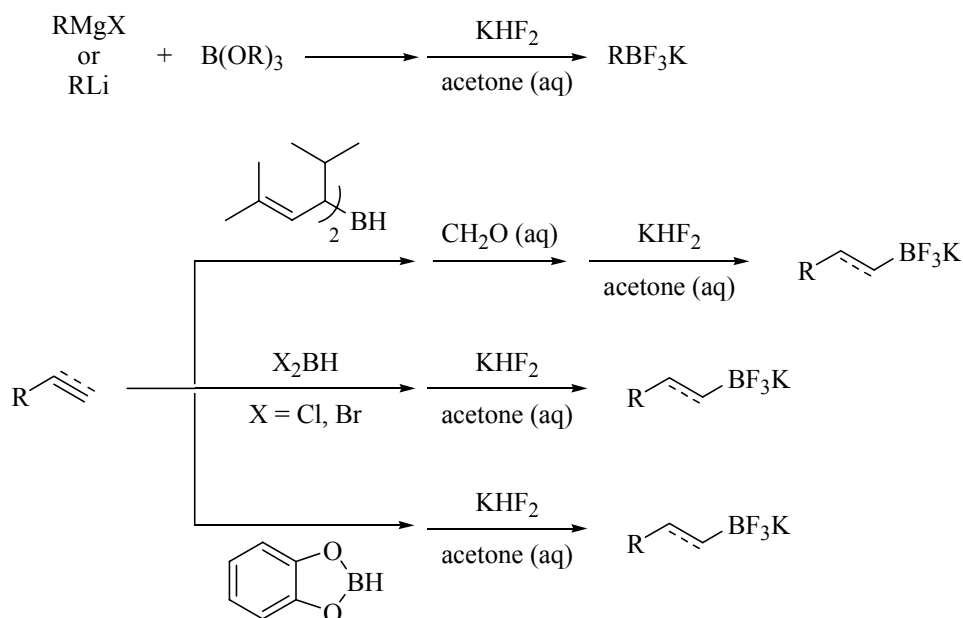
## Introduction

### “Organotrifluoroborates in Selective Organic Synthesis”

Gary Molander (University of Pennsylvania).

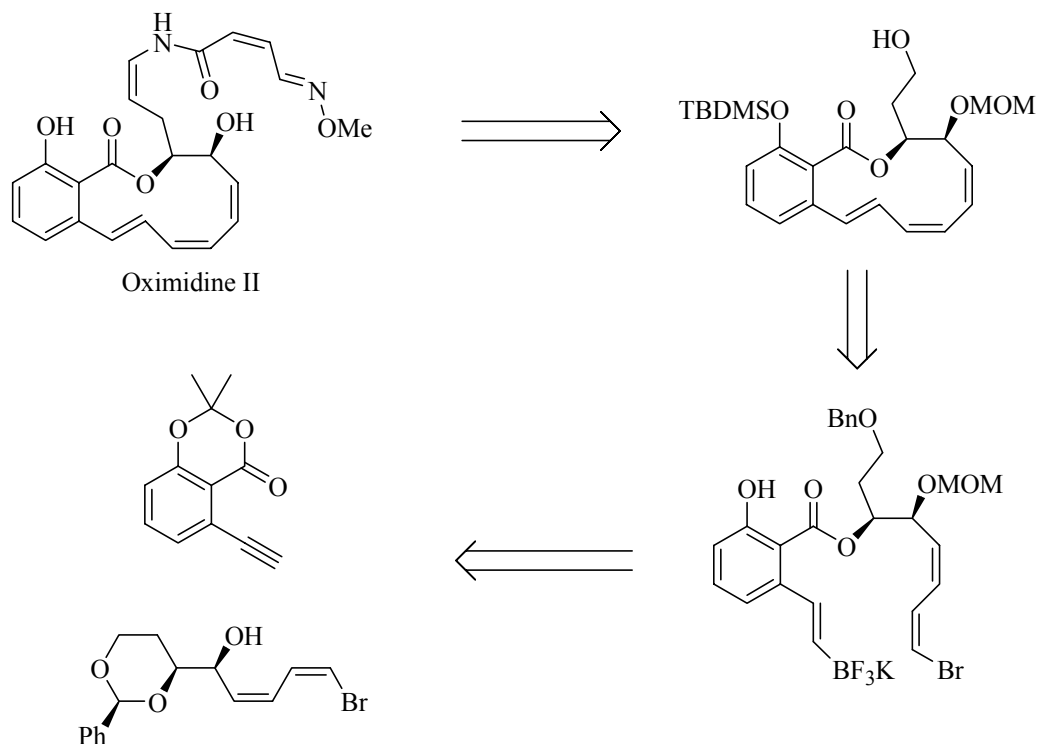
Professor Molander started his presentation by stating that the problems associated with most existing organoborons are that they can be difficult to purify (boronic acids), the starting diols can be expensive (boronate esters) and the reagents can be limited to hydroboration as well as usually being prepared *in situ* (organoboranes). However, organofluoroborates are easily accessible (Scheme 1), stable to air and moisture, environmentally sound and versatile coupling partners.

**Scheme 1: General Methods of Synthesis of Organofluoroborates**



The versatility of these organofluoroborates was clearly demonstrated by their use in alkyl/aryl cross coupling reactions, biaryl cross coupling reactions, heteroaryl halide couplings and vinyl cross couplings, as well as being able to tolerate silyl protecting groups during these cross coupling reactions. Professor Molander demonstrated the application of this methodology in the synthesis of Oximidine II, a salicylate enamide macrolide that inhibits mammalian vacuolar-type  $\text{H}^+$ -ATPase (see Scheme 2).

## Scheme 2: Retrosynthetic Analysis of Oximidine II

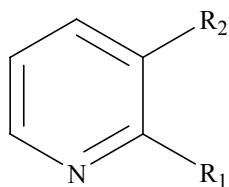


## “Impact of API Process Lots on Formulation Development”

*Sophie-Dorothee Clas (Merck Frosst Canada & Co.).*

Dr. Clas focused her talk on understanding the stability of the bulk API (see Figure 1) due to its significant scientific and regulatory concern. She discussed the polymorphic stability of an API with 5 anhydrous polymorphs and 2 hydrates.

## Figure 1: Selection of Form



Hydrophobic non-hygroscopic  
crystalline free base selected  
for development

two ionizable functional groups  
pK<sub>a1</sub> 4.6 and pK<sub>a2</sub> <1

practically insoluble in water  
(70 µg/mL)

Polymorphs!!!!

Hydrates!!!

Initially in pre-clinical development the medicinal chemistry route identified the first polymorph which was assigned as Form B. The first process chemistry lot gave two new polymorphs which were assigned as Form A and a metastable Form C. In the clinical development after 20 mid-scale syntheses another polymorph was identified and this assigned as Form D, and after 40 large scale syntheses Form E was identified. The question that now faced Dr. Clas was which form to develop.

Form C was found to be the least stable form, while Form E was the most stable. Form B was less stable than Forms A, D and E. However, all the anhydrous polymorphs converted to the hemihydrate and Form C was a metastable form obtained principally by dehydration. This led Dr. Clas to ask the question of whether the hemihydrate should be developed. The hemihydrate contained 2.5% by weight of water and was chemically stable for at least six months at 40 °C with a relative humidity of 75%. However, the hemihydrate dehydrated with time (25 days) to the metastable Form (Form C), and then to Form A at relative humidities <32%, but was stable at relative humidities of >32%. Since the anhydrous Form E was the thermodynamically stable form and the bioavailability was similar to other anhydrous crystal Forms (A and D) these three forms were selected for formulation studies.

The effect of moisture on the drug product now had to be addressed to determine the correct packaging to use for the tablet. Upon exposure to 45 °C at 75% relative humidity for 12 and 21 weeks, conversion to the hemihydrate was seen when tablets were stored in packaging with a poor moisture barrier (i.e. PVC blister). Dr. Clas then went on to understand the factors that were contributing to the hydrate forming. A variety of detection methods were employed including X-ray powder diffraction, Raman spectroscopy, NIR and SSNMR. Another interesting problem that developed was that different lots of the same polymorph showed different rates of hydrate conversion with one lot hardly converting to the hemihydrate, while another lot rapidly converted to the hemihydrate. Thus Dr. Clas developed a hydrate screen test which involved mixing 200 mg of the API with 0.5 mL of water in a mortar a pestle for one minute and then analyzing the slurry by XRPD.

Her conclusions from these studies were that ball milling and compression resulted in the formation of some amorphous API which catalyzed hydrate conversion. It was found that approximately 1% amorphous API was sufficient to increase the hemihydrate conversion rate. Also a minor amount of the hemihydrate (0.1 to 0.5%) cooperatively accelerated the hemihydrate conversion, and the presence of amorphous API or hemihydrate seeds had a significant impact on the rate of hydration. It was also shown that hydrate conversion occurred in formulations stressed at 40 °C and 75% relative humidity in the open. Thus moisture ingress had to be minimized and was done so using the appropriate formulation process (RC, DC, dry blending), and by reducing the use of excipients with high moisture contents. Thus by carefully selecting the appropriate barrier package, to prevent hydrate conversion of the tablet, the shelf life of the product was increased and no conversion to the hydrate was observed.

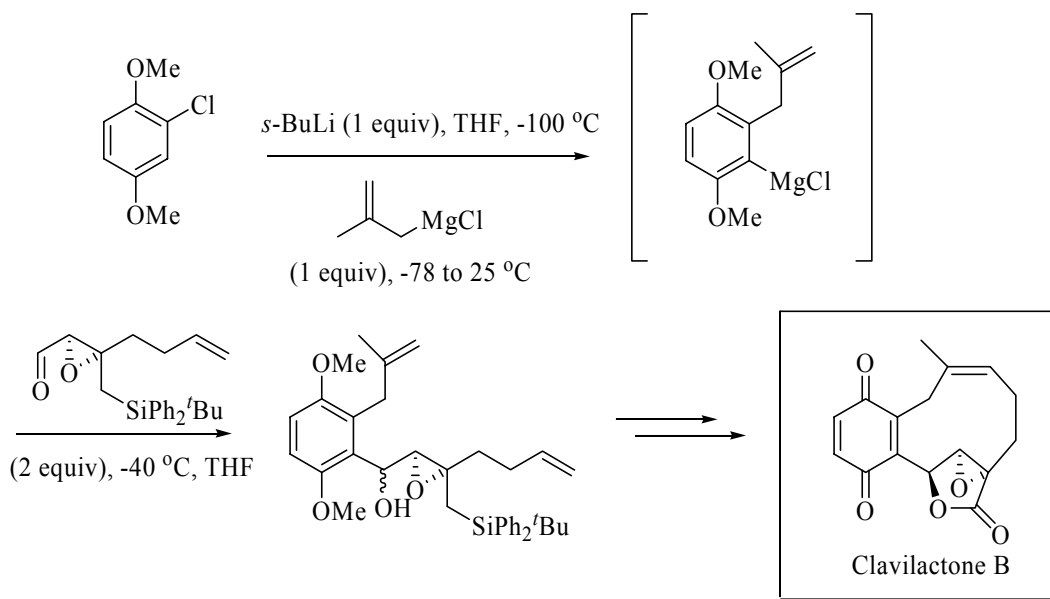
### **“Recent Advances in the Total Synthesis of Antibiotic Natural Products”**

*Anthony G. M. Barrett, Imperial College London, London, UK.*

Prof. Barrett presented the synthesis of three antibiotic natural products:

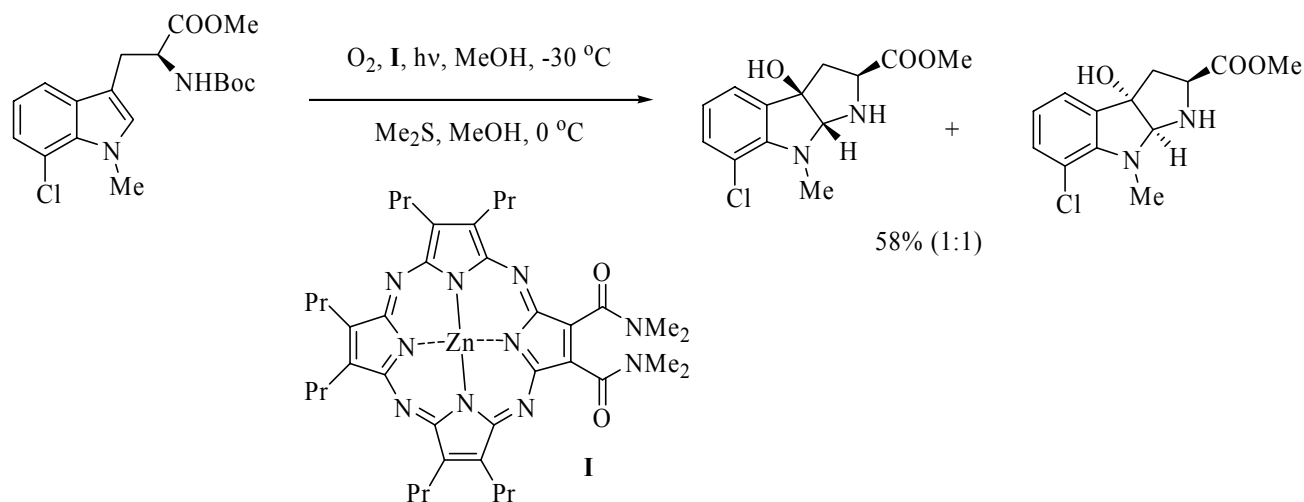
### Clavilactone B (Antifungal)

One of the key steps in the synthesis of clavilactone is shown below.

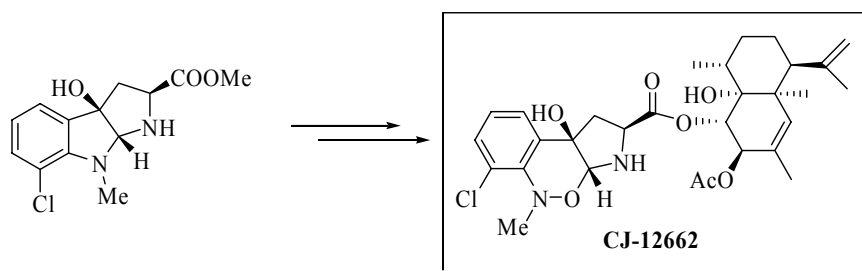


By making use of the three-component benzyne coupling developed by Meyers, the framework of clavilactone B could be assembled in one step. Subsequent functional group transformations and ring-closing by metathesis gave clavilactone B.

### CJ-12662 (Anthelmintic and Ectoparasiticide)

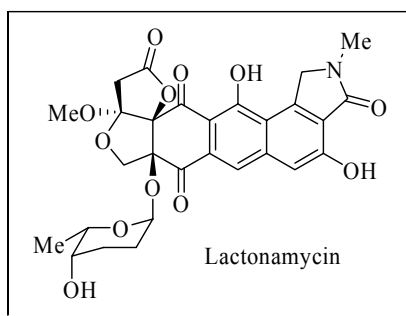


The key transformation in the synthesis of CJ-12662 was a double oxidation of a tryptophan derivative using *seco*-porphyrazines. One of the isomers from the double oxidation could then be converted to the natural product.

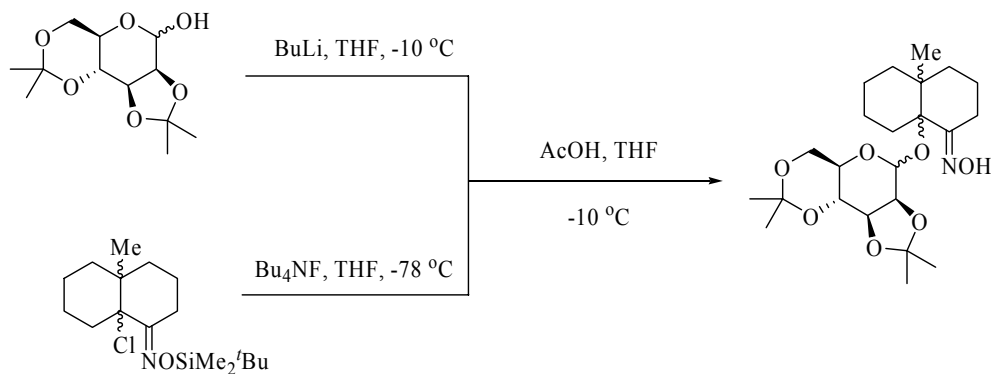


### Lactonamycin (Antibacterial)

Prof. Barrett presented two key synthetic concepts used in an approach towards lactonamycin.



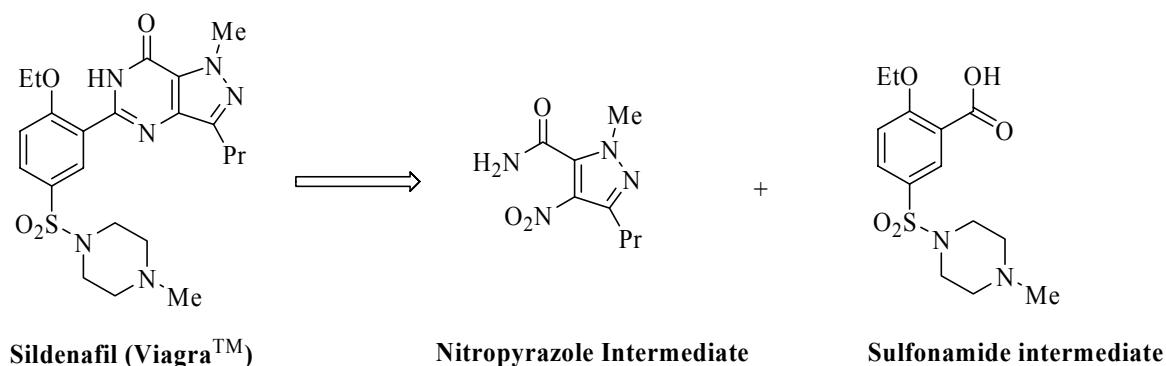
The use of iterative Michael addition reactions was presented as well as glycosidation using nitro- and nitroso- alkenes.



### “The Discovery and Development of the Commercial Route to Viagra™ and other Phosphodiesterase Inhibitors”

*Peter J. Dunn, Ph.D., Chemical Research and Development, Pfizer, Sandwich, UK.*

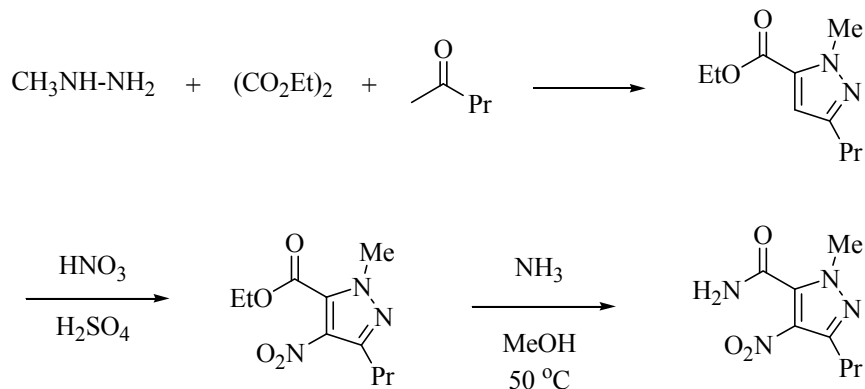
In the introduction, Dr. Dunn gave an analysis of the drugs selling more than \$0.5 billion in 2003. The drugs were grouped into biologics and small molecules and the latter analyzed by chiral complexity. The results showed that one in three small molecule drugs are achiral and that 40% of the top 25 small molecule drugs in 2003 were also achiral.



Dr. Dunn then gave a brief overview of biological mechanism of action of Sildenafil (Viagra™) and outlined the role of phosphodiesterases.

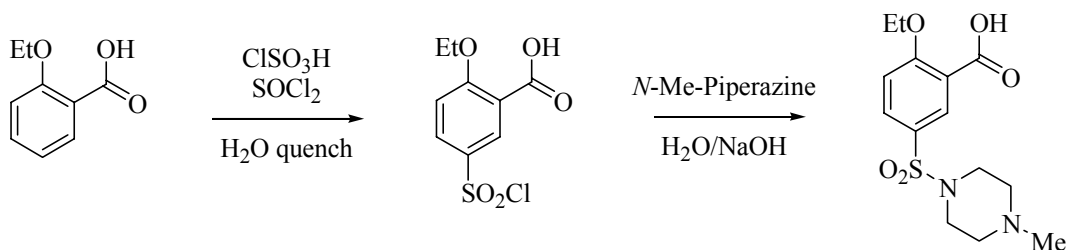
The medicinal chemistry route to Sildenafil was presented and potential scale-up issues (linearity, potential toxic intermediates, chlorosulphonation at the end of the synthesis) were discussed. A new three-step synthesis of the nitropyrazole intermediate was presented, which had several advantages over the original route.

### Synthesis of the Nitropyrazole Intermediate

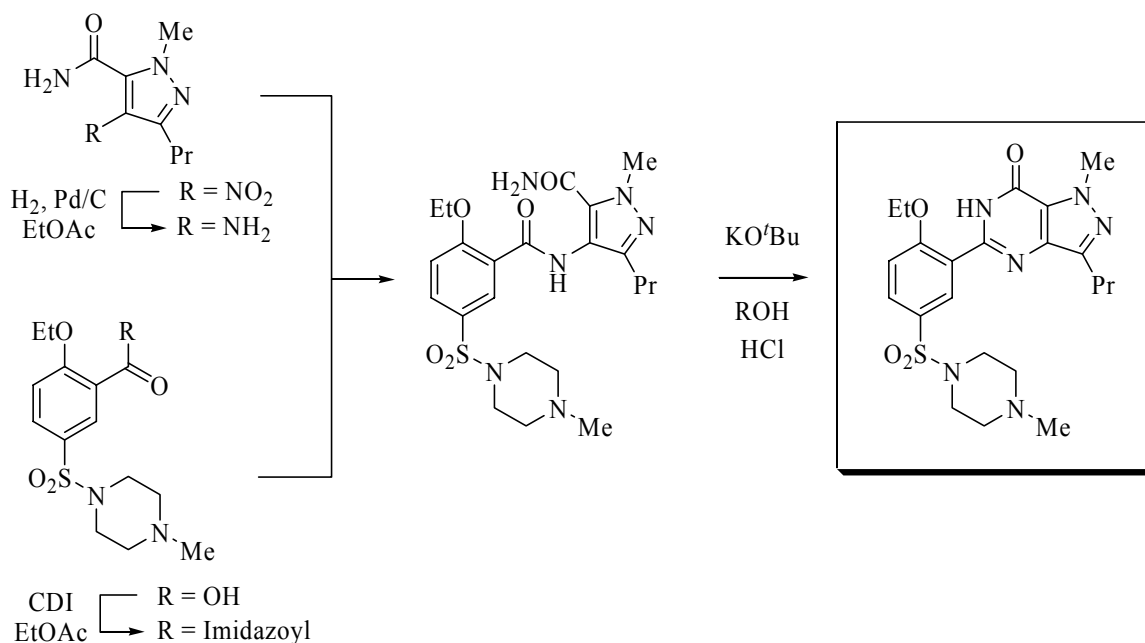


An improved preparation of the sulfonamide intermediate was also presented, in which isolation of a double salt was avoided.

### Synthesis of the Sulfonamide Intermediate



The final coupling of the two pieces was achieved as shown below.

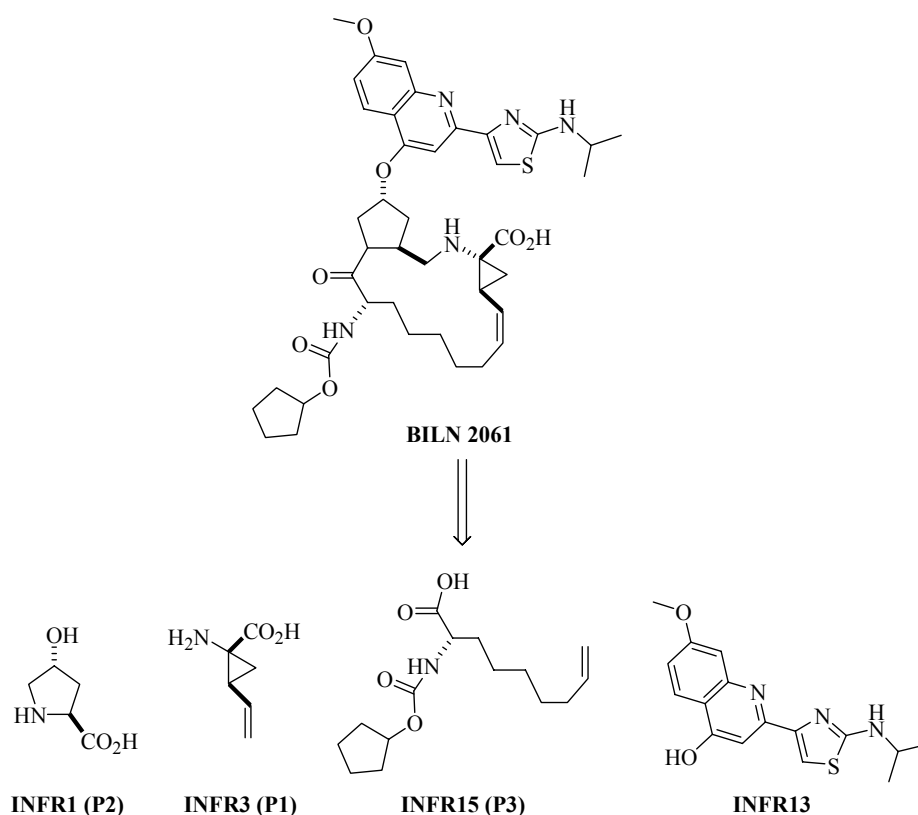


Overall goal of the chemical development efforts was to incorporate steps with potentially toxic material early in the synthesis and then have a clean crystallization at the end of the reaction sequence. The convergence of the route was also greatly improved. The overall yield of the process was improved by an order of magnitude and the commercial synthesis had an exceptionally low environmental impact.

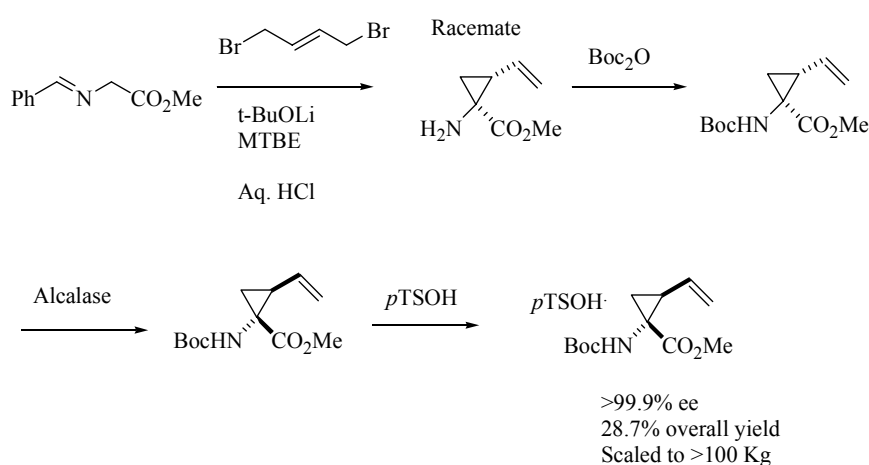
### “Efficient Synthesis of BILN 2061, a Potent HCV Protease Inhibitor, by a Convergent Approach Based on Ring-Closing Metathesis”

*Vittorio Farina, Ph.D., Boehringer Ingelheim Pharmaceuticals.*

Dr. Farina gave a brief overview of the Hepatitis C Virus (HCV) program and described the medicinal route to making **BILN 2061**. The convergent route was based on three unnatural amino acid residues (**P1**, **P2**, **P3**). The amino acids were strung together in a macrocycle and substituted with a very large hydrophobic heterocyclic moiety at **P2**. A practical process that could be scaled >100 kg amounts of the three amino acids had to be developed. The molecule features a 15-membered ring bearing a (*Z*)-1,2-disubstituted alkene subunit, as well as 5 stereocenters. The obvious disconnections involve scission of two amide bonds and an ether function, and closure of the macrocycle can be effected by a Ru-catalyzed Ring-Closing Metathesis (RCM) reaction, shown in Figure 2.

**Figure 2: Retrosynthetic Analysis**

The **P1** unit was prepared from the benzaldehyde Schiff base ester of glycine, shown in Figure 3. The racemate was resolved using Alcalase to give a greater than 99.9% *ee* after hydrolysis and tosylate salt formation.

**Figure 3: Scalable Process to P1**

The **P3** unit prepared from 1-chloro-4-bromobutane using a Grignard coupling. They resolved the acetamide to greater than 99% *ee* using Acylase 1, shown in Figure 4. The DHCA provided a crystalline solid for isolation of **P3** and the process was scaled to greater than 100 kg.



A new tool for profiling active species in transition metal catalyzed reactions is an *in situ* ATR UV/vis. An example of a palladium catalyzed Heck coupling was used to show the utility of following the catalyst cycle and the formation of palladium(0) nanoparticles by *in situ* ATR UV/vis. Palladium(0) nanoparticles are known to absorb in the UV-Vis region. The detection of palladium nanoparticles and stabilization prior to the aggregation of palladium and precipitation could be used to lower the overall catalyst loading, as shown in Figure 6. The tool could also be used for monitoring palladium removal at the end of a reaction.

**Figure 6: Catalytic Cycle of a Heck Coupling Reaction**

