



**Trip Report:
Advanced Library Design and Organic Synthesis
San Diego, California
February 14– 17, 2005**

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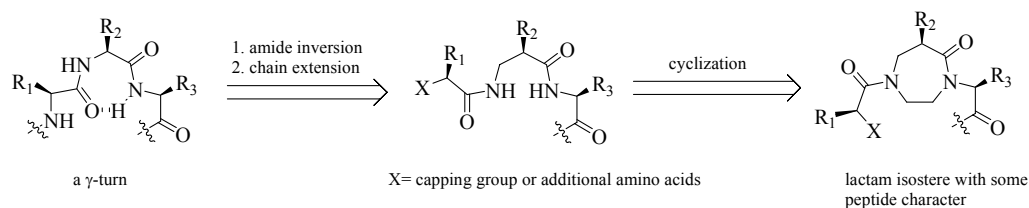
***Abstract.** Cambridge Healthtech Institute's "Advancing Library Design and Organic Synthesis" conference was held in San Diego, California, February 14-17, 2005. This symposium covered a wide range of topics including the use of microwaves for organic synthesis and diversity oriented synthesis. This report highlights select material from the seminars presented at the conference.*

“Multicomponent Synthesis of Libraries Inspired by Peptides and Alkaloids,”

Jeffery Aubé, (University of Kansas), USA.

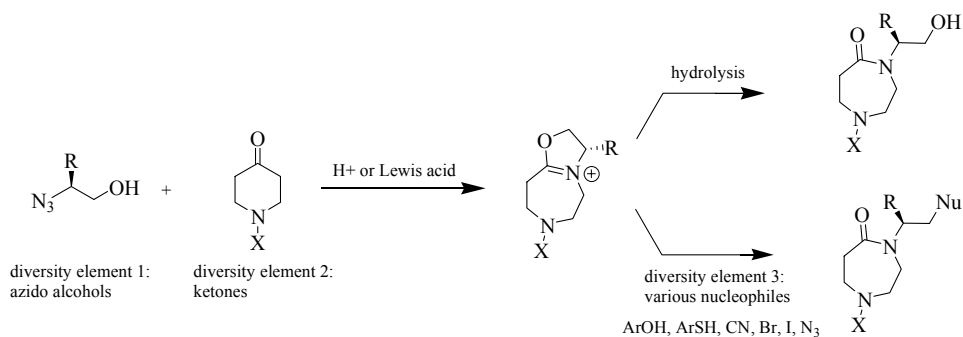
Dr. Aubé talked about a library of peptidomimetics inspired by γ -turns (Figure 1).

Figure 1



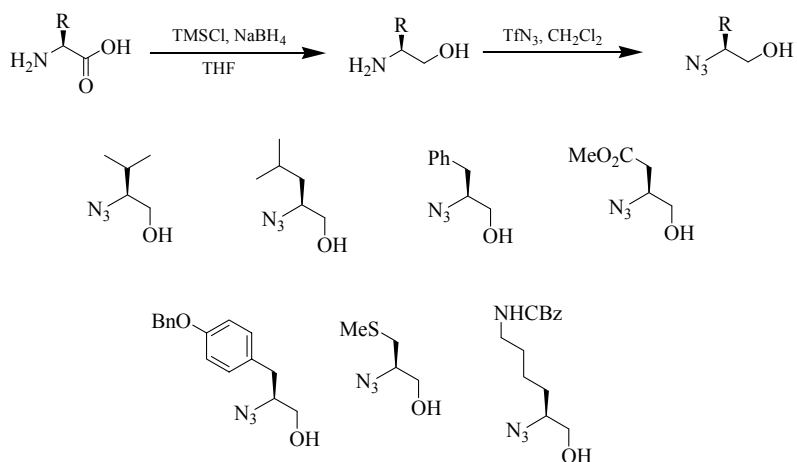
A three-component approach to substituted lactams was adopted allowing diversification with three separate elements (Figure 2).

Figure 2



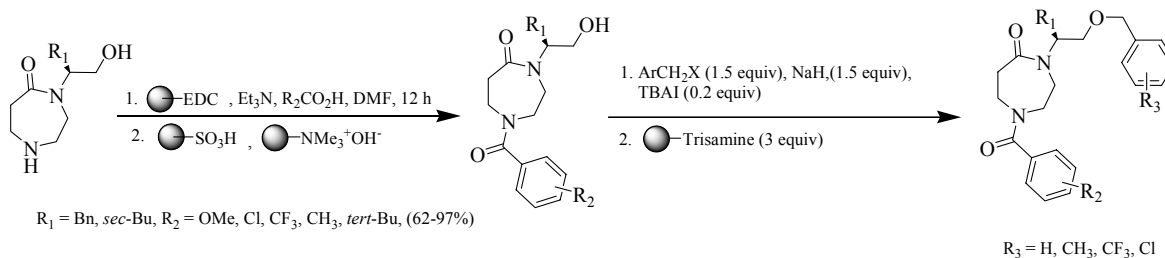
A “bookshelf” of azido alcohols was prepared in greater than 70% yield via a two step procedure starting from the corresponding amino acid (Figure 3).

Figure 3



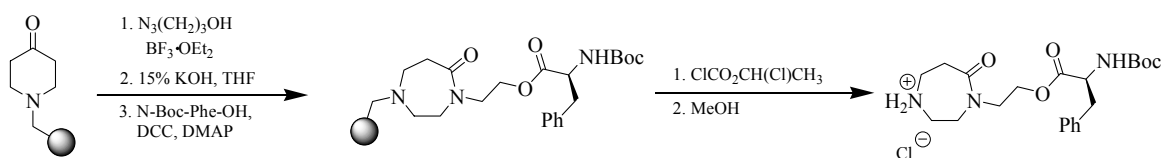
After a range of lactams had been prepared from the azido alcohols, a series of benzamides was prepared using resin-bound reagents and scavengers. The alcohol functionality was then alkylated with benzylic halides to produce the desired ethers (Figure 4).

Figure 4



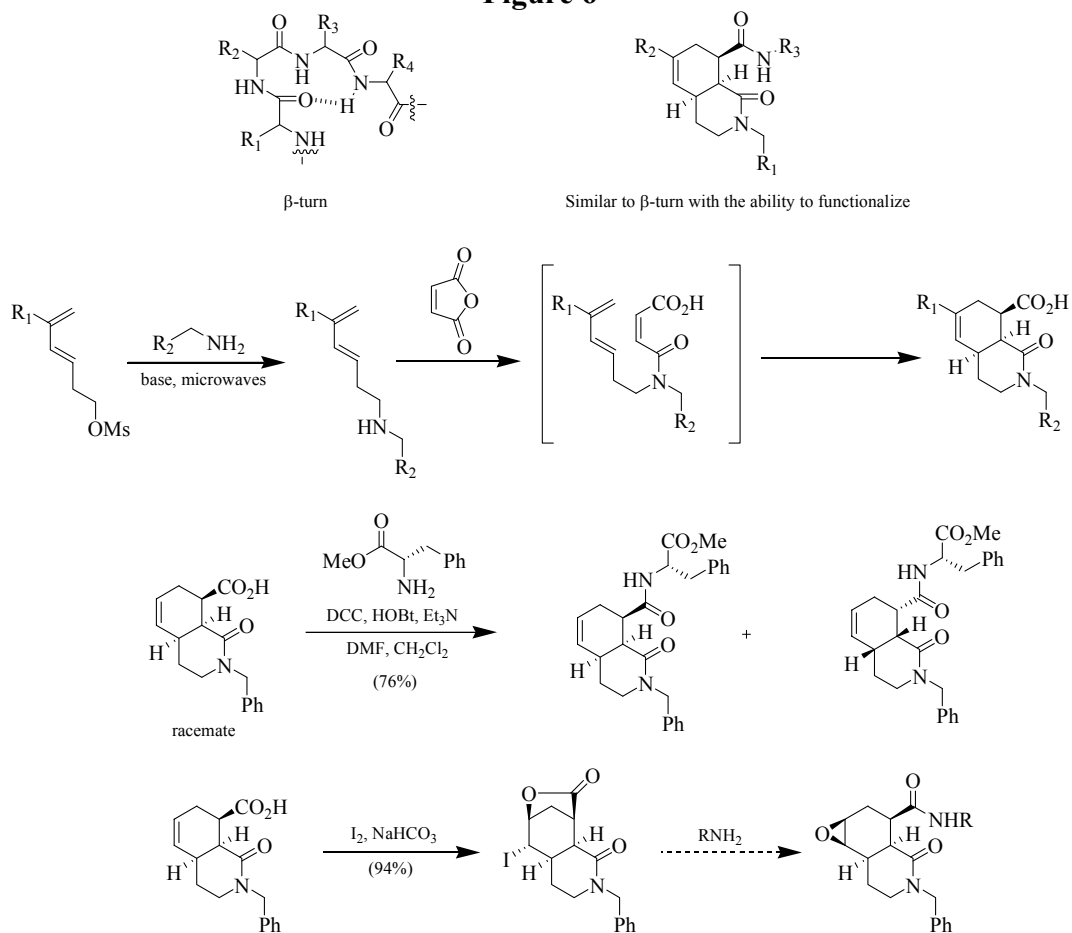
An approach where the starting material was resin-bound was also investigated. The overall yield was 33% from the starting piperidinone and was lower than obtained in the above examples (Figure 5).

Figure 5



In another project, diversifiable bicyclic cores were synthesized using an intramolecular Diels-Alder cycloaddition (intramolecular Diels-Alder precedent, Garner *et al. J. Org. Chem.* **1991**, *56*, 5893), with these cores being designed to mimic β -turns (Figure 6). Ring opening of the anhydride with the alkylamine provided the requisite 4+2 π system which underwent concomitant cycloaddition to yield the bicyclic system as a single diastereomer (racemic). An iodolactonization sequence could also be used to further derivatize the system.

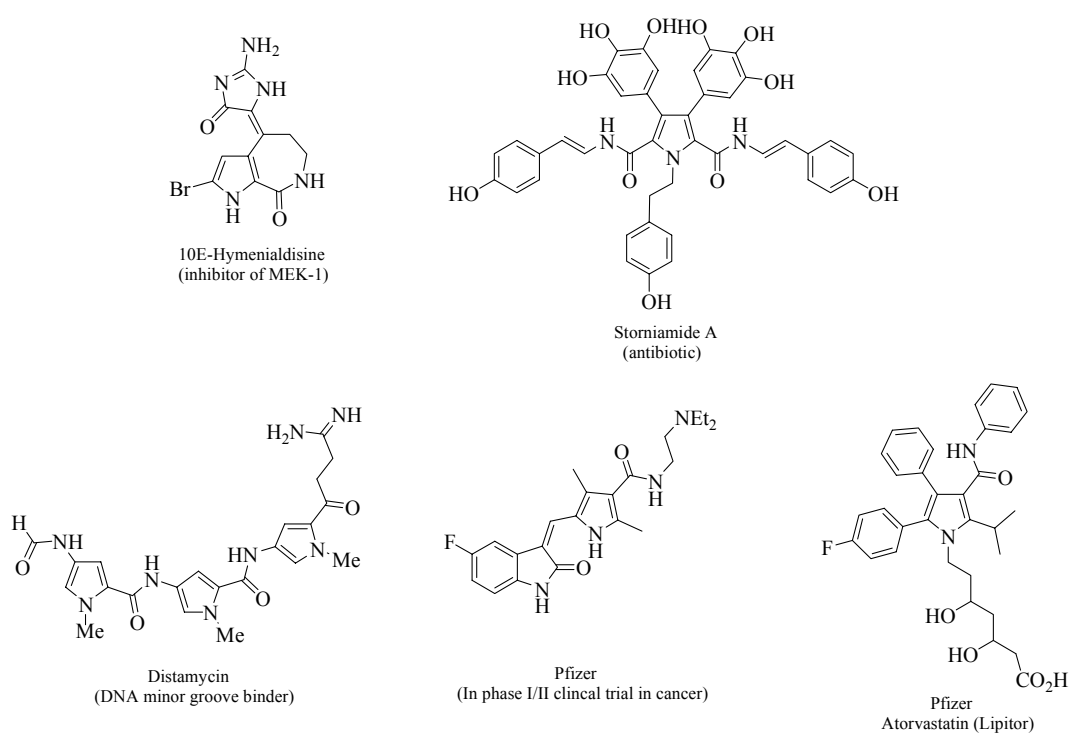
Figure 6



“Microwave Assisted Synthesis of Small-Molecule Libraries,”

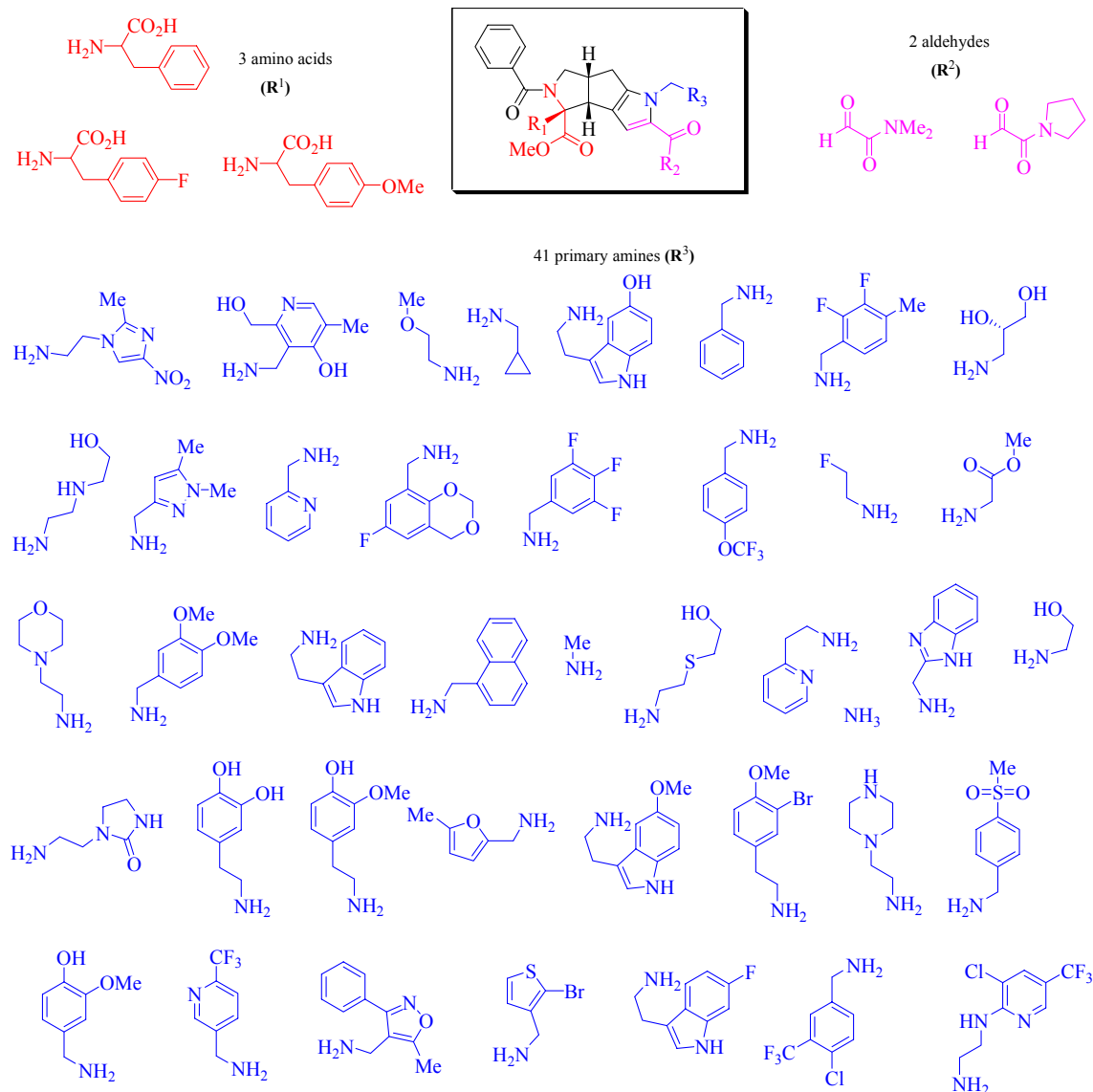
Stefan Werner, (University of Pittsburgh Center for Chemical Methodologies and Library Development), USA.

A 200 member discovery library was synthesized utilizing microwave irradiation to reduce reaction times and automated chromatography techniques to facilitate faster purification. It was intended that the library should have “drug-like” properties to enable the hit to lead process. The biological importance of pyrrololeucine derivatives was demonstrated by their prevalence in nature and in pharmaceuticals (Figure 1).

Figure 1

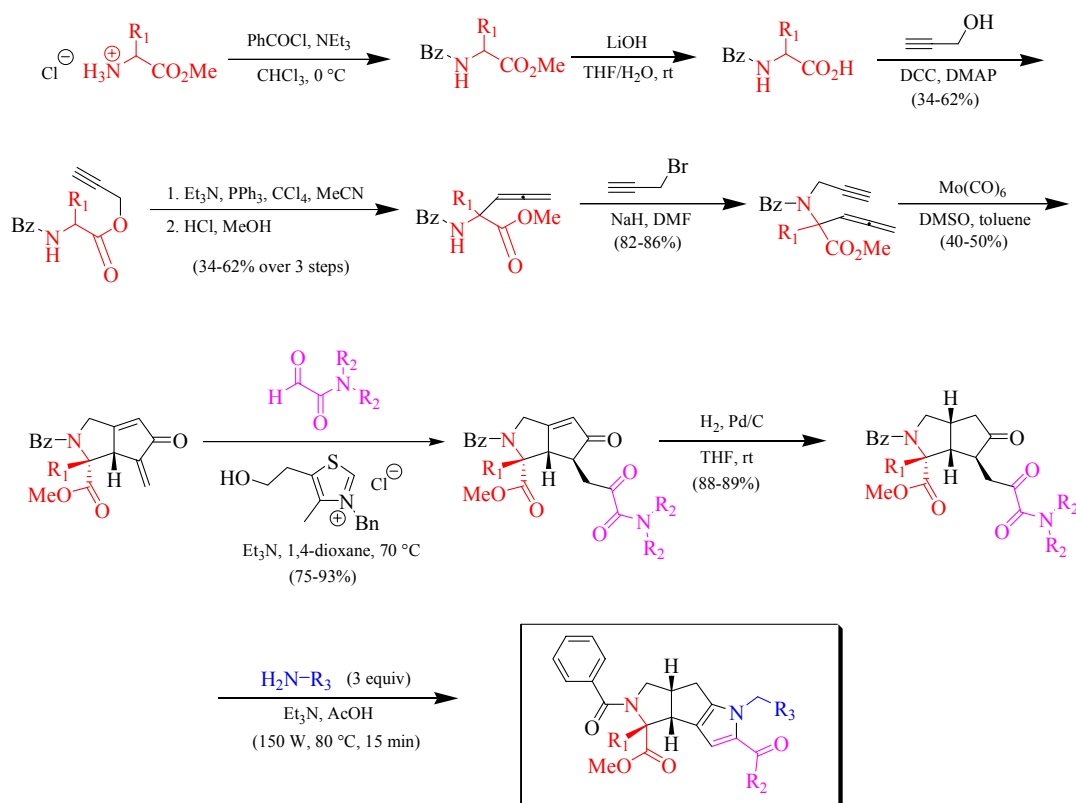
A tricyclic pyrrole core was selected for the library, to be constructed using 3 amino acids, 2 aldehydes and 41 primary amines to provide the required diversity (Figure 2).

Figure 2



The precursors to pyrrole formation were synthesized starting from the amino acids via a 9 step procedure using a Pauson-Khand reaction to construct the bicyclic ring system and a Stetter reaction to introduce the requisite 1,4-diketone functionality (Brummond, K.M.; Curran, D.P.; Mitasev, B.; Fischer, S. *J. Org. Chem.* **2005**, *In Press*). A Paal-Knorr reaction with the diverse amine set was used to introduce the pyrrole ring. Microwave irradiation (150 W, 80 °C) was found to provide the desired products 3-4 times faster and in 10% higher yields than the corresponding thermal oil bath reaction at 80 °C (Figure 3).

Figure 3



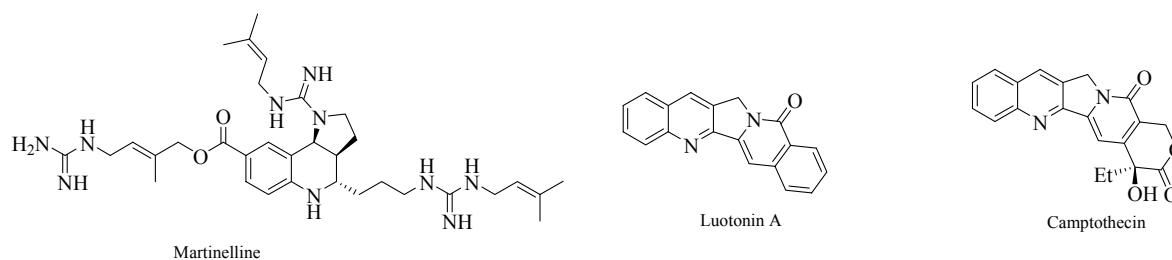
Of the 210 reactions carried out (out of a possible 246), 179 (85%) succeeded (>85% purity) and 31(15%) failed due to no reactivity or low purity. The products were analyzed by LCMS (210, 220 and 240 nm) and purified by semi-preparative HPLC using an automated set-up (Thermo Finnigan LCQ advantage/Gilson Serial HPLC). The library was screened against Mitogen-activated protein kinase phosphatase (MKP-1). Mitogen-activated protein kinases (MAPK) regulate proliferation, differentiation and apoptosis, and are dephosphorylated and inactivated by MKP-1. Evidence indicates that MPK-1 is oncogenic, with it being over-expressed in prostate, breast and ovarian cancer. Currently no inhibitor of MPK-1 is known. Seventeen compounds were found to have $\text{IC}_{50} < 25 \mu\text{M}$ and three compounds had $\text{IC}_{50} < 10 \mu\text{M}$. Seven compounds have been selected for further studies.

“Parallel Synthesis of Novel Heterocyclic Libraries as Peptidomimetics,”

Robert Batey, (University of Toronto), Canada.

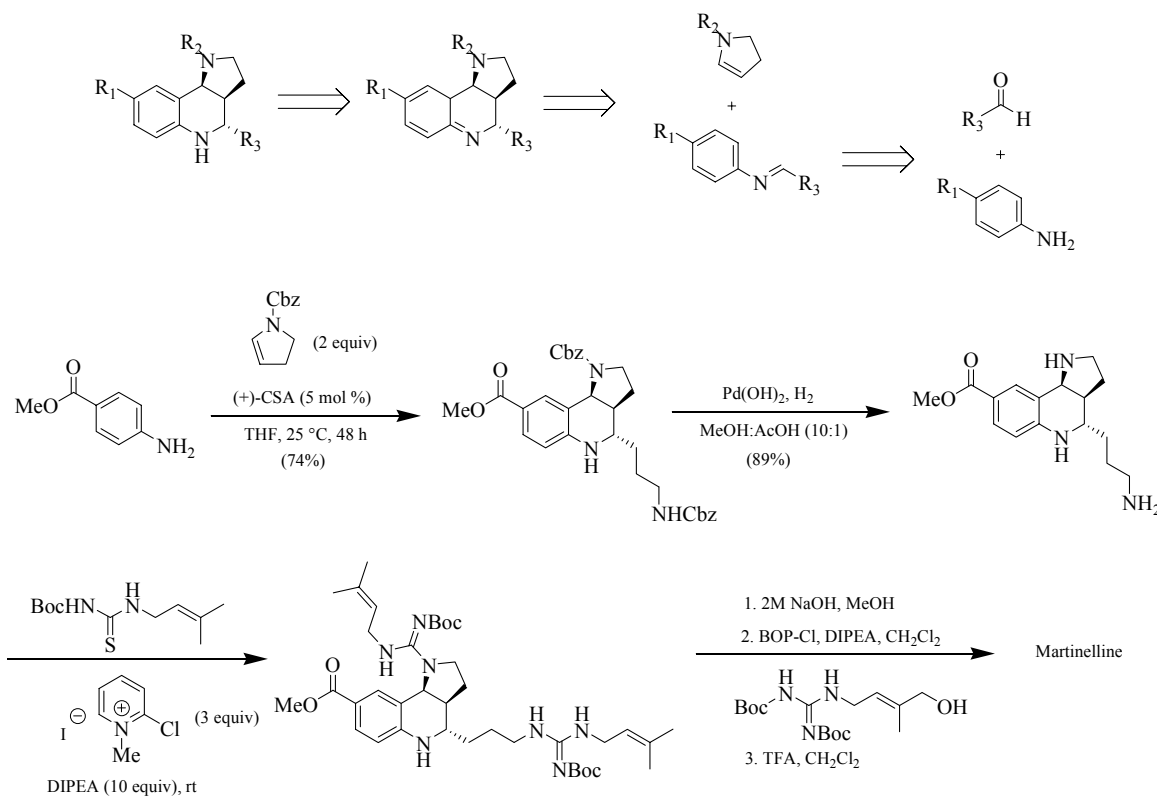
In the first part of his talk, Professor Batey talked about his group’s approaches to the natural products Martinelline, Luotonin A and Camptothecin (Figure 1).

Figure 1



Martinelline is a potent non-peptidic bradykinin receptor antagonist ($B_2 > B_1$) which exhibits modest antibiotic activity and low cytotoxicity. It contains a novel tricyclic pyrroloquinoline core structure unprecedented in nature. A three component coupling strategy using the Povarov reaction was adopted to synthesize the core with the desired *exo*-stereochemistry. In this Lewis acid catalyzed reaction, an aniline reacts with the ring-opened version of the 2-pyrroline to form an intermediate imine which undergoes a formal hetero Diels-Alder reaction with another equivalent of 2-pyrroline to provide the *exo* and *endo*-products. It was subsequently discovered that the use of the Bronsted acid, camphorsulfonic acid, in THF increased the *exo:endo* ratio providing the core in 2 steps and 66% overall yield. The synthesis of the racemic natural product was completed in 6 steps and 8% overall yield (Figure 2).

Figure 2



A similar approach was used to prepare Luotonin A (Figure 3) and the Camptothecin core (Figure 4) again demonstrating the versatility of the Povarov reaction.

Figure 3

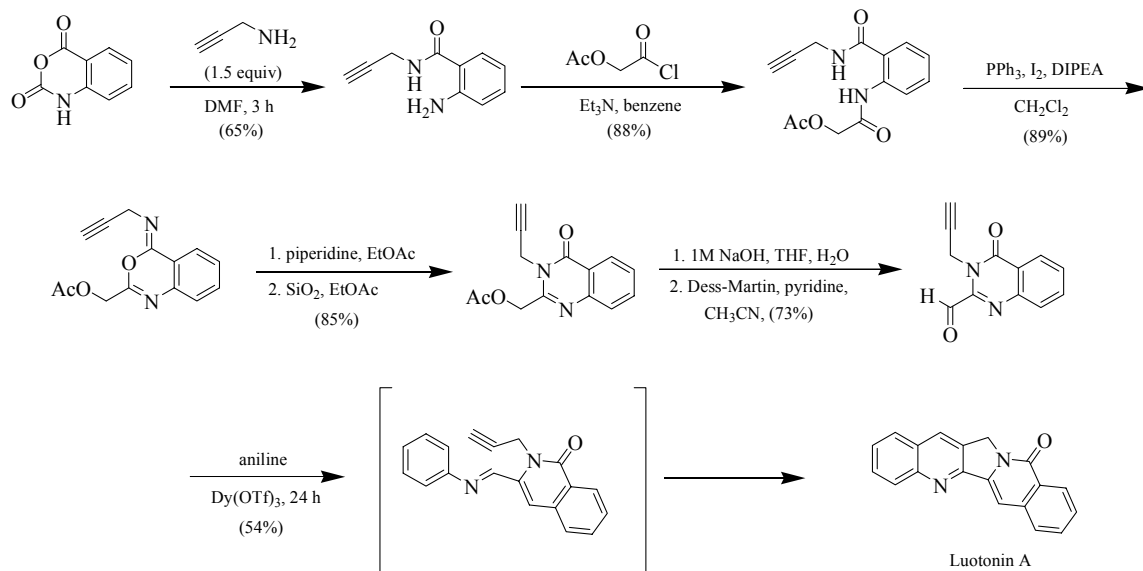
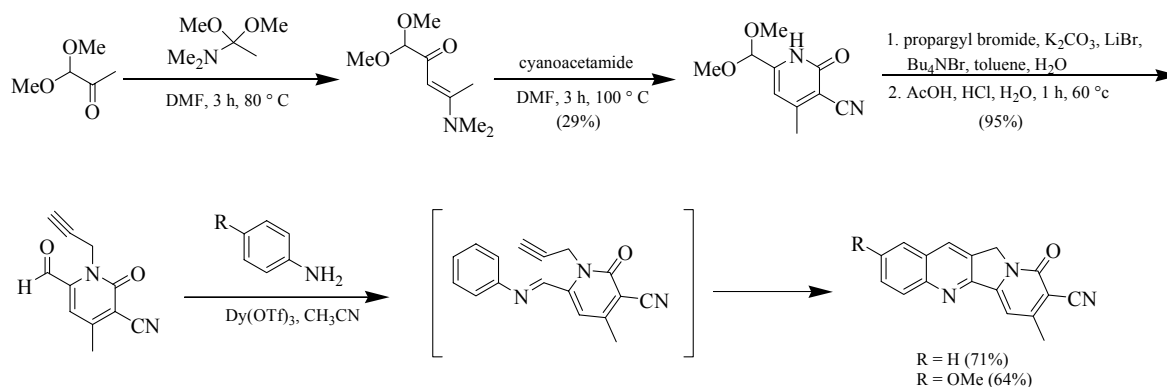
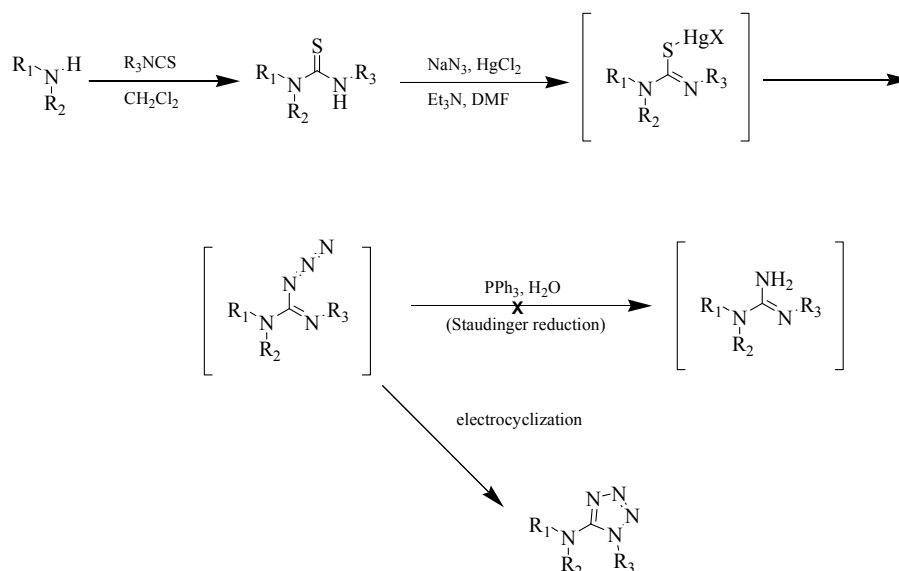


Figure 4

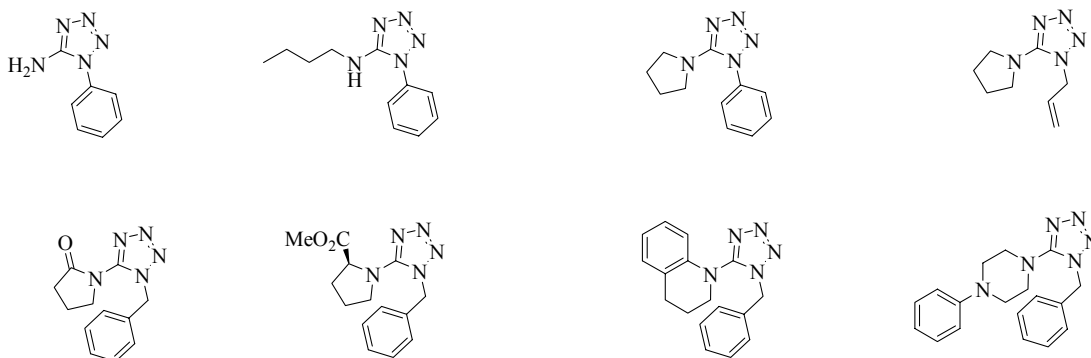


In the second part of his talk, Professor Batey talked about the development of a new route to 5-aminotetrazoles. Reaction of the activated thioguanidine species with the azide anion gave the expected intermediate, which underwent spontaneous electrocyclization to provide the unexpected aminotetrazole (Figure 5).

Figure 5



Examples of synthesized aminotetrazoles:



The methodology, in combination with solid phase techniques was used to generate a library of peptidotetrazoles. 2-Chlorotriyl chloride resin was used as the solid phase and after a series of amino acid couplings and deprotections, the requisite amines were obtained. Conversion to ureas with various isocyanates followed by activation and reaction with azide provided the desired library of aminotetrazoles after cleavage from the resin support.

Figure 6

