**Approaches Towards... 1985 to 2005**

Criteria for selection:
- published within the time period of 1985 to 2005
- limited papers from the original group who published the approach
- group that published approach have yet to disclose full synthetic route to natural product
- approaches that led to formal synthesis are excluded

Main Journals covered:
- Journal of the American Chemical Society
- Angewandte Chemie International Edition
- Journal of Natural Products
- Helvetica Chimica Acta
- Organic Letters
- The Journal of Organic Chemistry
- Tetrahedron
- Tetrahedron Letters

**Disclaimer:**
The purpose of this group meeting is to highlight various synthetic approaches/methodologies to natural products which for one reason or another, did not lead to the completion of the target material. It is by no means exhaustive but designed to be comprehensive within the selected publications.

More often than not, failed routes are not disclosed in chemical literature and this seminar only serves to cover material that this presenter finds unusual or interesting.

Lastly, comments from the original papers are reproduced to provide appropriate context to each work. Highlights in these excerpts unless stated are absent from the original work.

Organization of material:
- material that were covered in previous Baran lab group meeting will be referenced accordingly
- organized by natural product families
- approaches published outside of the restricted time frame will not be discussed in detail, but references are provided
- approaches to polyketide natural products have been deliberately left out in this group meeting

Highly sought after targets/natural product class with numerous approaches towards:
- phorboxazole
- ingenanes
- taxol
- eleutherobin
- diazomamde A
- gambieric acid A
- azadirachtin
- manzamine A

**Main references -**
- Nicolaou: ACIE 2002, 2103
- Nicolaou: ACIE 2002, 2107
- Mura: Synlett 1995, 895
- Mura: Synlett 1997, 737
- Mura: ACIE 2003, 3637
- Watanabe: Synlett 1997, 4429
- Watanabe: ACIE 2007, 1512
- Watanabe: Tel. Lett. 1999, 4387
- Watanabe: Synthesis 2000, 1878
Approaches towards polyquinanes

Sieburth's Polyquinane Approach:

Approaches towards natural products with medium rings

Procter's Approach:

Approaches to steroid skeletons:

Mukai:

Deslongchamps:

Aubert & Malacria:

Ruveda:
Approaches Towards... 1985 to 2005

Sieburth's Fusicoccin Approach:

See Nathan's Group Meeting on Taxol for a more comprehensive coverage

See cover page for more selected examples of approach towards the taxanes

Snapper's approach to 5-8-5 systems:

Little's Approach:

1. vinyllithium
2. xylenes, reflux
3. CSA, MeOH

Approaches Towards... 1985 to 2005

Sieburth's Taxol Approach:

Kishi's approach:

"While the chemistry described herein did not culminate in the total synthesis of rudmollin (1), it did provide a useful and interesting forum for the exploration of new chemistry."
Zard's attempt 1:

\[
\begin{align*}
\text{HO-Cl} & \rightarrow \text{Me} \quad \text{N-hydroxythiopyridone, phenylvinylsulfone, } h_v \\
\text{COCl} & \rightarrow \text{Me} \quad 20\% \text{ if no acceptor}
\end{align*}
\]

Zard's attempt 2:

\[
\begin{align*}
\text{SePh} & \rightarrow \text{Me} \quad 55\% \\
\text{allylSbBu}_3 & \rightarrow \text{Me} \quad 4 \text{ steps} \\
\text{ACCN} & \rightarrow \text{Me} \quad \text{DLP}
\end{align*}
\]

Mechanistic Question:

\[
\begin{align*}
\text{TMS} & \text{Br} \quad \text{Br} \\
\text{cis} & \rightarrow \text{Br} \quad \text{anti} \\
\text{trans} & \rightarrow \text{Br} \\
\text{CHO} & \rightarrow \text{TMS}
\end{align*}
\]

2nd Generation:

\[
\begin{align*}
\text{MeO} & \quad \text{MeO}_2C \\
\text{OR} & \quad \text{OTBS} \\
\text{TMSCl} & \quad \text{TBSO}^\text{a}
\end{align*}
\]

25% 20% 60%

Baran Lab Group Meeting
01/23/2016

"It is hoped that the lessons learned in this series of experiments can be successfully applied to the acquisition of kalmanol and bioactive analogs thereof."
Approaches Towards… 1985 to 2005

Model Studies:
1. ClCH₂OCH₂CCH
2. iBuOCOCl; CH₃N₂
3. Rh₂(OAc)₄
4. 6 NHCl
5. NaH, MeI

Real tropolone system:
1. ClCH₂OCH₂CCH
2. iBuOCOCl; CH₃N₂
3. Rh₂(OAc)₄
4. 6 NHCl
5. NaH, MeI

Hoffmann’s approach:
1. LDA, allylBr
2. HBr, hv
3. NaI
4. Sml₂

Approaches towards alkaloids

Winkler’s approach:
1. DMP
2. AgNO₃
3. PhMe, A

Padwa’s Model System:

*Studies directed toward the isomerization of the C-3 exo-methylene to the Δ2,3 alkene present in eleutherobin are currently underway, and our results will be reported in due course*
Stork's Approach

We reported earlier our plan to synthesize gelsemine (1) by way, successively, of a diketone of the general structure (3), with the ketone group differentiated is some way, and a ketone of general structure (2). In each of the synthetic steps (3 -> 2) and (2 -> 1), a ketone group is to serve as the precursor of a quaternary centre, and it is the challenge of these steps that most excited our interest in the synthesis of gelsemine.

1st Generation

ketone group in 9 was at the wrong end of the three-carbon bridge, and this route had to be abandoned when we were unable to transpose the carbonyl group to the other side of the ring.

2nd Generation

- chirality transfer from THP ring indicated the possibility of using chiral sugar auxiliary for asymmetric approach

Fleming's Approach

"We chose the route involving spiroannulation onto a ketone precisely because there were no established methods for doing that. It forced us to invent and we did."

Oxindole Method 1:

works best with non-enolizable ketones

Oxindole Method 2:

18% from epoxide

Oxindole Method 3:


Oxindole Method 4:


"but in the end it was not completed, because no one would fund us to put the two pieces of work together"