Larry Overman: Synthetic Highlights of an Amazing Chemist

Introduction:

1. Introduction to Larry Overman

2. Targets Achieved by Prins-Pinacol Rearrangement
   a. (−)-Magellanine
   b. (+)-Shahamin K
   c. (−)-7-Deacetoxyalcyonin Acetate
   d. Briarellins E and F

3. Targets Achieved by an Aza-Cope-Mannich Rearrangement
   a. (±)-Meloscine
   b. (±)-df-16-Methoxytabersonine
   c. (−)-Pancraine
   d. (−)-Strychnine

4. Targets Achieved via Asymmetric Heck Reaction
   a. (−)-Scopadulcic Acid A
   b. (−)-Chimonantheine
   c. (−)-Morphine

5. Misc. Targets achieved in the Overman Lab
   a. Adociasulfate 1
   b. (±)-Kumausallene

6. Conclusion
Who is Larry E. Overman??

The Boy:
- Born in Chicago, Illinois, in 1943
- Raised in Hammond Indiana, an industrial town in which he worked in local steel mills during summers to pay for college

The Chemist:
- Obtained B.A. from Earlham College in 1965
- Received his Ph.D. from University of Wisconsin in 1969
- NIH postdoctoral fellowship with Prof. Ronald Breslow (Columbia)
- Began at UC Irvine in 1971
- Currently a Distinguished Professor of Chemistry
- Awards/Honors include: ACS Arthur C. Cope Award (2003), ACS Creative Work in Synthetic Organic Chemistry (1995), and much more...
- Lab has completed syntheses of over 80 complex natural products and close to 260 publications in major journals

Larry on chemistry:
"I had absolutely no interest in chemistry until I was inspired by a great teacher in college. What ultimately intrigued me was not only the idea of studying the natural world but also creating things that didn't exist before."¹

"I hated chemistry in high school."²

"What my laboratory does is engineer and invent new chemical reactions that make structures that are by nature drug-like, and make them efficiently."¹


Gilbert Stork on Larry:
"The remarkable fact is that essentially every one of [his] papers contains either novel methodology or the imaginative application of methodology, more often than not arising from Overman's own research, to highly original total syntheses."²

Dave Evans on Larry:
"[he is] one of those scientists who are changing the way organic chemists build molecules, ... [he has] encompassed both the synthesis of complex molecular targets and the development of highly innovative synthesis methodology, has elevated the capabilities of our discipline,"²

Currently:
Larry is editor-in-chief of Organic Reactions, an editor for JACS, Org Lett, and others. He consults for many pharmaceuticals, including Pfizer, Roche, Cytokinetics, and Chiron. He is married to wife Joanne, a high school chemistry teacher, and they have two children.

He is, of course, still at UC Irvine.

And most importantly, what about life outside of chemistry:
"I decided early on that there would be at least one day a week that I would not do anything related to work."

Larry enjoys free-diving and spear fishing in Australia, Mexico, and the southern California coast.²

The Power of the Prins-Pinacol Rearrangement

- isolated in moss, Lycopodium magellanicum
- member of the Lycopodium alkaloids
- tetracyclic framework; one quaternary center

J. Am. Chem. Soc. 1993, 115, 2992
Total Synthesis of (–)-Magellanine

1. LiCH(SMe)₂
   THF, 0°C
2. Cu(OTf)-PhH, iPr₂NET, PhH, 50°C
   70%, >10:1 regioselectivity

Total Synthesis of (–)-Magellanine: Prins-Pinacol Cyclization

1. t-BuLi, Et₂O
   -110°C
2. 2; TBAF, THF
   71%, ds= 8:1
1. TIPSCI, imid., DMAP, DMF, 50°C
2. Swern
3. (MeO)₂CH, PPTS, CH₂Cl₂, rt
   85%
SnCl₄, CH₂Cl₂
-78°C to -23°C

57% 2:1 β:α
Total Synthesis of (–)-Magellanine:
End Game

```
1. OsO₄, NaIO₄, dioxane-H₂O, rt
2. Ph₂CHNH₂Cl, NaBH₃CN, i-PrOH, rt

(–)-Magellanine
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Total Synthesis of (+)-Shahamin K:
Retrosynthetic Analysis

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Shahmin K

Ring Expansion via Pb(OAc)₄
Stereocontrolled Michael Addn
Prins-Pinacol Rearrangement
Kinetic Resolution via CBS cat.
```

J. Am. Chem. Soc. 2001, 123, 4851
Total Synthesis of (+)-Shahamin K: Prins-Pinacol Cyclization

Dimethyl Acetal:

\[
\text{TMSO} \quad \begin{array}{c}
\text{OMe} \\
\text{OMe}
\end{array} \quad \text{SnCl}_4 \quad \rightarrow \quad \begin{array}{c}
\text{TMSO} \\
\text{OMe}
\end{array} \quad \begin{array}{c}
\text{OMe} \\
\text{OMe}
\end{array}
\]

ThioPhenyl Acetal:

\[
\text{TMSO} \quad \begin{array}{c}
\text{SPh} \\
\text{SPh}
\end{array} \quad \text{DMTSF} \quad \text{CH}_2\text{Cl}_2, -45 \text{ to } 0^\circ \text{C} \quad \rightarrow \quad \begin{array}{c}
\text{TMSO} \\
\text{SPh}
\end{array} \quad \begin{array}{c}
\text{SPh} \\
\text{SPh}
\end{array}
\]

Total Synthesis of (–)-7-Deacetoxyalcyonin Acetate: Retrosynthetic Analysis

- isolated from soft coral
- class of Eunicellin diterpenes
- contains hydroisobenzofuran and oxonane ring

\[\text{J. Am. Chem. Soc. 1995, 117, 10391}\]
\[\text{Improved: Org. Lett. 2000, 2, 2683}\]

(S)-carvone

Enolate Addition
Total Synthesis of (−)-7-Deacetoxyalcyonin Acetate: Formation of the Hydroisobenzofuran System

Total Synthesis of (−)-7-Deacetoxyalcyonin Acetate: Formation of the Oxonane Ring
Briarellins E and F: A Similar Approach to Similar Molecules

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For (−)-7-Deacetoxyalcyonin:

For Briarellins E and F:
Target: (±)-Meloscine, a Pentacyclic Alkaloid

- member of the Melodinus alkaloids
- similar to Aspidasperma alkaloids (posses an indole ring rather than a quinoline)
- 2 quaternary centers


Key Transformations Towards (±)-Meloscine: Aza-Cope Mannich

1. Ph₃P=CH₂
2. KOH, EtOH/H₂O

78% 82%

(CH₂O)ₙ CSA, PhH, reflux

R = NHBOC

R =
Part II: A Similar Approach to a Similar Molecule

(-)-Pancracin: Another Alkaloid realized by the Aza-Cope Mannich Methodology

(-)-Pancracin

- isolated from various plant species
- member of Amaryllidaceae alkaloids
- pentacyclic structure

J. Org. Chem. 1993, 58, 4662

\[ (-)-\text{Pancracine} \rightarrow \text{Pictet-Spengler Cyclization} \rightarrow \text{Aza-Cope Mannich} \rightarrow \text{Reduction and Cyclization} \]

Carbonyl Addition via alkynylcerium reagent
Key Steps Towards the Total Synthesis of (−)-Pancrachine

1. [structure image]
2. [structure image]
3. [structure image]

Last, but surely not least, all hail to (−)-Strychnine

-isolated in 1818 from *Strychnos ignatii*
-1st total synthesis by Woodward in 1954
-extremely dense stereochemistry:
  7 rings in 24 atoms

References:
(-)-Strychnine: In the Forward Direction

1. Methyl chloroformate
   Pyr, CH₂Cl₂, rt, 97%
   2. NaN₃, i-PrNEt, CH₂Cl₂, -23°C
   NaH, 1% Pd₂(dba)₃
   15% PPh₃, THF, rt, 91%
   3. DIBAL, CH₂Cl₂, -78°C
   4. TIPSCI, tetramethylguanidine, NMP, -10°C
   65%

1. NaCNB₃, TiCl₄
   THF, -78°C, >20:1 (felkin)
   2. DCC, CuCl, PhH, 80°C
   89%

1. Jones ox., -5°C, 97%
   2. L-Selectride, PhN₃, THF
   -78°C to 0°C, 88%
   3. Me₈Sn₂, 10% Pd(PPh₃)₃, 80%

(-)-Strychnine: In the Forward Direction (cont'd)

1. t-BuOOH, Triton B, THF, -15°C
   2. Ph₃P=CH₂
   THF, 0 to rt; TBAF, THF, -15°C
   80%

1. MsCl, i-PrNEt, CH₂Cl₂, -23°C
   2. LiCl, DMF, rt;
   NH₂COCF₃, NaH, DMF, rt
   83%

1. NaH, PhH, 100°C
   2. EtOH-H₂O, 60°C
   43% from 2

(-)-Strychnine: In the Forward Direction (cont'd)

[3, 3] Aza-Cope
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Natural Products Arising from the Asymmetric Heck Reaction: Part I
(−)-Scopadulcic A

- isolated from *Scoparia dulcis* L. (herb)
- tetracyclic diterpene acid
- 4 quaternary centers

Rapid Ring Formation via Divinyl Cyclopropane Rearrangement and the Asymmetric Heck

A Closer Insight into the Asymmetric Heck Cascade
Formation of Vicinal Quaternary Carbon Centers using Intramolecular Heck Cascade

(-)-chimonanthine

meso-chimonanthine

For Acetonide:

Meyer's Theory of Vicinal Quaternary Center Formation

For OTBS:

R =
Asymmetric Synthesis of My favorite Analgesic: 
(−)-Morphine

J. Am. Chem. Soc. 1993, 115, 11028

The Rapid Synthesis of the Morphine Core
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Retrosynthesis of (−)-Adociasulfate 1

- isolated in sea sponges off of Australia
- kinesin inhibitors (slows cell division)
- proton pump inhibitors

J. Am. Chem. Soc. 1999, 121, 12206
Epoxide-initiated polyene tetracyclization to Form the Pentacyclic system of (−)-Adociasulfate 1

Rearomatization

Yield for single step = 15%
Yield per Ring Formation = 62%

Retrosynthesis of (±)-Kumausallene

- isolated from red algae
- nonisoprenoid sesquiterpene
- family contains cis-dialkyltetrahydrofuran unit

J. Org. Chem. 1993, 58, 2468
The Total Synthesis (most of it) of (+)-Kumausallene

\[
\begin{align*}
&\text{OH} \quad \text{O} \quad \text{OBz} \\
&\text{BF}_3 \cdot \text{OEt}_2 \to -23^\circ \text{C} \quad 71\% \\
&\text{MeO}_2\text{C} \quad \text{O} \quad \text{OBz} \\
&\text{dr} = 10:12:1 \\
&\text{1. Swern Oxidation} \\
&\text{2. SiMe}_3 \quad \text{TiCl}_4 \quad -78^\circ \text{C} \to \text{rt} \quad 77\% \\
&\text{1. TiCl}_4 \quad -78^\circ \text{C} \to \text{rt} \\
&\text{TMS} \quad \text{Ti(O(OR))}_3 \quad 77\% \\
&\text{2. K}_2\text{CO}_3 \quad \text{MeOH} \quad 92\% \\
&\text{Felkin Addition, } >3:1:1 \\
&\text{R}^1 = 2,4,6-trisopropylphenyl
\end{align*}
\]

To Conclude with Larry Overman

Goals of the Talk:

1. The power of the Prins-Pinacol Rearrangement to form highly substituted tetrahydrofurans with high stereo-control
2. The power of the Aza-Cope Mannich to form highly substituted pyrrolidine rings and fused ring systems in a highly controlled manner
3. The power of the Heck Reaction to form isolated, and vicinal quaternary centers in an asymmetric manner
4. The amazing variety of natural products that have been synthesized by the latter methodologies, and more importantly, by a creative, thoughtful, and elegant mind of Larry Overman

Acknowledgements: There is one man to acknowledge: Larry Overman

Other Molecules that are worth looking at:

(+) physostigmine
J. Org. Chem. 1993, 58, 6949

(±)-Gelsemine
ACIEE, 1999, 38, 2934

Quadrigemine C and Psycholeine

(+)pumiliotoxin B
J. Am. Chem. Soc. 1984, 106, 4192