Career of Samuel J. Danishefsky

Bryon Simmons
MacMillan Group Meeting
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Key References:

Samuel Danishefsky: Biographical Notes

Birth & Education
- Born in 1936 (Bayonne, NJ)
- B.S. from Yeshiva University in 1956
- Ph.D. in chemistry from Harvard University in 1962 with Peter Yates
- National Institutes of Health postdoctoral fellowship in the laboratory of Gilbert Stork at Columbia University

Career
- 1963 to 1980, professor at the University of Pittsburgh (where he eventually attained the rank of University Professor)
- 1980 to 1993, professor at Yale University (where he rose to the rank of Sterling Professor of Chemistry)
- 1991 to present, Memorial Sloan-Kettering Cancer Center as director of the Laboratory for Cancer Research
- 1993 to present, Eugene Kettering chair and head of Columbia Laboratory of Bioroganic Chemistry

Notable Awards and Honors
- Shared the Wolf Prize in Chemistry with Gilbert Stork
- Arthur C. Cope Award
- Benjamin Franklin Medal in Chemistry
- National Academy of Science's award in Chemistry

Publications
> 480 publications (H-index of 62 as of 2009)
Samuel Danishefsky: Former Group Members

- Former students and postdocs include:

  Peter Seeberger
  Dalibor Sames
  Eric Sorensen
  David Gin
  Cholbum Lee
  Matt Shair
  Jon Clardy
  Rob Coleman
  Masahiro Hirama
  Takeshi Kitihara
  Raymond Funk
  William Pearson
  Jeffrey Aube
  James Panek

- Robert Zamboni
- Robert Volkman
- J. T. Link
- Mike Silvestri

- Mike Bednarski
- Margaret Chu Moyer
- R.C. A. Isaacs

- and many others...

- Roger Ruggeri
- Ray Cvetovich
- Dave Askin
- Gayle Schulte

- Dirk Trauner
- Robert Coleman
- Martin Maier
- Gary Sulikowski
- David Berkowitz
- Frank McDonald
- Ohyun Kwon
- Dionicio Siegel
- Tristan Lambert
- Ed Turos
- Randy Halcomb
- Jaqueline Gervay
- Jon Njardarson
- Alison Frontier
**Samuel Danishefsky: Selected Career Highlights**

- **Pittsburgh (1963-1980)**
  - Patchouli Alcohol
  - Activated Cyclopropanes
  - Vernolepin
  - Cascade Reactions

- **Yale (1980-1993)**
  - "Golden Era" of the Diene
  - 6a-Deoxy Erythronolide
  - Myrocin C
  - Enediyne Natural Products

- **Columbia (1993-present)**
  - Frondosin B
  - UCS 1025A
  - Taxol and Epothilone (*not covered*)
Pittsburgh: Patchouli—The Very First Synthesis

- Patchouli alcohol is used extensively in flavor and fragrance chemistry.

- The Diels-Alder reaction gave the endo isomer with respect to the ketone, and was epimerized with base to the endo isomer.

- A late-stage hydrogenation was envisioned that would set the methyl group.

\[ \text{J. Chem. Soc. 1963, 116, 11213} \]
Pittsburgh: Patchouli—The Very First Synthesis

Unfortunately, at the time, they were unable to produce the required Z-olefin system.

Using sodium metal, they anticipated what is now the widely used strategy of reductive cyclization (i.e. Molander-Kagan).

At that time contemporary reagents such as Sml₂ or surface active zinc-copper combinations were unavailable.

Pittsburgh: Interest in Electrophilic Cyclopropanes

■ Michael (1887)

\[ \text{EtO}_2C\text{C} = \text{Ph} + \text{EtO}_2C\text{C} = \text{CO}_2\text{Et} \xrightarrow{\text{NaOEt}} \text{EtO}_2C\text{C} = \text{CO}_2\text{Et} \]

1,4 add'n

\[ J. \text{Prakt. Chem. 1887, 35, 349} \]

■ Perkin (1895)

\[ \text{EtO}_2C\text{C} = \text{CO}_2\text{Et} \xrightarrow{\Delta} \text{EtO}_2C\text{C} = \text{CO}_2\text{Et} \]

1,5 add'n

\[ J. \text{Chem. Soc. 1895, 108} \]

■ Danishefsky (1969)

\[ \text{EtO}_2C\text{C} = \text{R} \xrightarrow{\Delta} \text{Nu} \]

\[ \text{Nu} = \text{amine, thiol, enolate, enamine, organocuprate} \]

\[ \text{Acc. Chem. Res. 1979, 12, 66} \]
Pittsburgh: Interest in Electrophilic Cyclopropanes

In almost every case the attack of the Nu was observed to occur at the more substituted carbon with clean inversion.

![Chemical Diagram]

The exact reason for the regioslectivity still requires further clarification.

*Acc. Chem. Res. 1979, 12, 66*
Pittsburgh: Interest in Electrophilic Cyclopropanes

- A major improvement in efficiency occurred when the diester was replaced with Meldrum's acid.

- Another benefit of the spiroacyl Meldrum's acids was exclusive attack on the more substituted carbon.

- According to Danishefsky, the spiroacyl linkage may confer greater charge separation in the transition state for ring opening, thereby favoring, more strongly attack at the most substituted center.

Acc. Chem. Res. 1979, 12, 66
**Pittsburgh: Interest in Electrophilic Cyclopropanes**

- **Intramolecular Opening:** *Spiro* vs *Fused* modes of attack.

  "Fused Mode"

  ![Fused Mode Diagram]

  "Spiro Mode"

  ![Spiro Mode Diagram]

  - The *Spiro* mode of attack was always exclusively observed for C, O, and N nucleophiles to make 3, 5 and 6 membered rings (vs 4, 6 and 7 in the *Fused* mode).

  ![Spiro Reaction Diagram]

  - Based on work by Linstead, they began to contemplate 1,7 additions as well, along with other research groups.
Pittsburgh: Interest in Electrophilic Cyclopropanes

- A cyclopropanation delivers the cyclopropane diastereoselectively.

- The Spiro mode of attack is observed, with inversion of stereochemistry.

- A second cyclization occurs to give the pyrrolizidine amide.

*JACS, 1977, 99, 4783*
Pittsburgh: Interest in Electrophilic Cyclopropanes

- Using the \( E \)-olefin, a trans relationship can be forged, leading to a related natural product.

\[ \text{NPh} \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{O} \quad \text{Me} \]

\[ \text{Cu} \quad 1) \quad \text{MeOH} \quad \text{NH}_2\text{NH}_2 \quad 2) \quad \text{steps} \]

\[ \text{isoretronecanol} \]

- This approach was also applied to the mitomycin core.

\[ \text{NPh} \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{O} \quad \text{Me} \]

\[ \text{NH}_2\text{NH}_2 \]

\[ \text{mytomycins} \]

- The \textit{Spiro} mode of attack is observed with inversion of stereochemistry.
Pittsburgh: The Total Synthesis of Vernolepin

- Vernolepin was complex for its time, and looking back, called by some "The Taxol of the 70's."

- Danishefsky's elegant and first ever synthesis of Vernolepin cemented his place as one of the top synthetic chemists in the world.

- The Danishefsky group employed for the first time its now famous diene as well as the then unknown reaction of an enolate (or silyl enol ether) with the Eschenmoser salt.
Pittsburgh: The Total Synthesis of Vernolepin

- Two consecutive Diels-Alder reactions are marshalled. First application of the "diene" to natural product synthesis.

- Additionally, 1-carbethoxycyclohexene had previously resisted all attempted Diels-Alder reactions due to its sluggish reactivity.

- Direct epoxidation of the lactone gave the β-epoxy-diastereomer so a 1-pot procedure was developed which utilized a Henbest type of stereocontrol to give the α-epoxide

*JACS, 1977, 99, 6066*
Pittsburgh: The Total Synthesis of Vernolepin

- A-ring enone is disassembled via oxidative cleavage to afford a valerolactone.

- A remarkable and facile orthoester formation of the A-ring allows work on the γ-lactone.

- Lactone was cleanly converted to the corresponding aldehyde and then to a vinyl group.
**Pittsburgh: The Total Synthesis of Vernolepin**

- A nucleophilic epoxide-opening was desired at C\textsubscript{7} using the Creger-Silbert dianion.

\[
\begin{align*}
\text{LiCCH}_2\text{CO}_2\text{Li} & \quad \text{LiCCH}_2\text{CO}_2\text{Li} \\
\text{then CH}_2\text{N}_2 & \quad \text{then CH}_2\text{N}_2 \\
\text{56\%} & \quad \text{55\%}
\end{align*}
\]

- The original substrate for epoxide opening could not be converted back to an aldehyde and was thus abandoned.

*JACS*, **1977**, *99*, 6066
Pittsburgh: The Total Synthesis of Vernolepin

- Simultaneous orthoester deprotection and lactonization

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{OH} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\quad \text{pTSA} \\
\Delta \\
\frac{61\%}{(+31\% \text{ regioisomer})}
\]

- Affords a 2:1 mixture of regioisomers, the minor is then converted to Vernomenin

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\text{O} & \quad \text{O} \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\quad \text{LDA, HMPA} \\
\frac{31\%}{(\text{minor})}
\]

- The first example of enolate methylenation using enolates. It also obviates the need for -OH protection.

*JACS*, **1977**, *99*, 6066
Pittsburgh: Exploration of Cascade Reactions

- Stereo selective Michael-Michael-Dieckman Reaction

- 1-step assembly of the epiclovane ring system

JACS, 1973, 95, 2410
**Pittsburgh: Exploration of Cascade Reactions**

- 2+2+2 annulation/epoxidation

- 4-bond forming reactions and 1 C-Br heterolysis.

_JACS, 1985, 107, 2474_
**Pittsburgh: Exploration of Cascade Reactions**

- The Danishefsky pyridine: Synthesis of (+) Estrone

\[
\begin{align*}
\text{Me} & \text{N} \text{Me} \quad \text{steps} \quad \text{Me} & \text{N} \text{Me} \\
& \quad \text{steps} \quad \text{Me} & \text{N} \text{Me} \\
& \quad \text{L-Phe} \quad \text{Na/NH}_3, \text{NaOEt} \quad \text{TsOH, Ac}_2\text{O}
\end{align*}
\]

- Pyridine is a masked dienolate & trisannelating agent.

*JACS, 1976, 98, 4975*
**Pittsburgh: Exploration of Cascade Reactions**

- The Danishefsky pyridine: Synthesis of (+) Estrone

\[
\begin{align*}
R &= \text{OCH}_2\text{CH}_2\text{O} \\
\text{Na/NH}_3 &\rightarrow \\
\text{NaOEt} &\rightarrow \\
\text{pTSA} &\rightarrow \\
\text{HCl} &\rightarrow \\
\end{align*}
\]

- Pyridine is a masked dienolate & trisannelating agent.

*JACS*, 1976, 98, 4975
Yale: The "Golden Era" of the Diene

- The synergistic diethoxy enol ether was known, and had been described as a diene in a single DA reaction with methyl glyoxylate.

- Its preparation involved the acid-catalyzed cracking of formyacetone diacetal. Preparation was not a trivial matter and several attempts to prepare it in bulk were unsuccessful.

- The use and preparation of silyl enol ethers had recently been described by Stork, House and Mukaiyama. A straight-forward silylation of a readily available methoxyenone gave birth to "Danishefky's Diene."

*Acc. Chem. Res. 1981, 14, 400*
Yale: The "Golden Era" of the Diene

The synergistic diene was next employed in the synthesis of the highly labile biosynthetic intermediate, prephenic acid.

\[
\text{OMe} \quad \text{CO}_2\text{Me} \quad \Delta \quad 76\%
\]

\[
X = \text{O} \quad X = \text{OH}, \alpha-\text{H}
\]

disodium prephenate

A new type of dienophile was employed, where a phenylsulfeny group activates the diene, but does not compete for regiocontrol. At some point an elimination of phenylsulfenate occurs to give a dienone.

\[
\text{MeO} \quad \text{Cl} \quad \text{MeO} \quad \Delta \quad 54\%
\]

The synthesis of griseofulvin involved further evolution of these concepts and employed a trioxy-diene which was even more reactive.

*Acc. Chem. Res. 1981, 14, 400*
Yale: The "Golden Era" of the Diene

In the synthesis of corilolin, a DA reaction occurred which gave the undesired regiochemistry. This may have been the consequence of the favorable energetics associated with early rehybridization of the bridgehead carbon from the sp² to the sp³ level.

Two solutions were developed A) where the effect of the 1-Me group overrides the 2-OSi, and B), where sulfur is the more potent regiocontrol element relative to acetoxy.

Yale: The "Golden Era" of the Diene

adapted from Acc. Chem. Res. 1981, 14, 400
Dihydropyrans can serve as microenvironments to control stereochemistry and as polyketide synthons.

The synthesis is achieved using continuous asymmetric induction.

*JOC.* 1990, 55, 1636
Yale: Myrocin C

- Myrocin C was isolated from a soil fungus, *Myrothecium verrucaria*.

- Petacyclic primarane diterpene
- Broad spectrum antimicrobial
- Latent activated cyclopropane establishes biological activity

- Postulated bioactivation of Myrocin C.

- Nucleophilic attack upon a doubly activated cyclopropane.

*JACS. 1994, 116, 11213*
**Yale: Myrocin C**

- The synthesis commences with a DA reaction arising from an *endo* transition state.

- Luche reduction occurs from the convex face.

- The four oxygen atoms of this substance are differentiated.

*JACS* 1994, *116*, 11213
**Yale: Myrocin C**

- This substance and its derivatives were employed in studies to introduce the cyclopropane ring. In early experiments a cyclopropanation was achieved.

- However, efforts to extend this intramolecular alkylation to more relevant substrates were not successful.

- In fact, none of the above substrates could be converted into the desired cyclopropane.

_JACS. 1994, 116, 11213_
**Yale: Myrocin C**

- Conformational analysis of the enolate was revealing. The equitorial orientation of the C-Br bond does not permit good overlap with the enolate π-system.

- On the other hand, the enolate oxygen is well placed for an attack on the leaving group carbon. These failures gave rise to a new idea.

- If the R in a compound of type A is sufficiently large, then a strong tendency to minimize A^{1,3} strain would give an axial disposition of the leaving group carbon which would have meaningful overlap with the π-orbitals.

*JACS. 1994, 116, 11213*
Yale: Myrocin C

- A vinyl group was installed via Stille cross coupling.

- A mesylate was installed as the leaving group.

- Treatment with trialkyltin anion gave rise to the desired cyclopropane ring system.

*JACS. 1994, 116, 11213*
Yale: Myrocin C

Two mechanisms were proposed for this impressive transformation. The first has the tin adding into the diene with concomitant cyclopropanation.

A transient allyl tin would then open the epoxide. This mechanism was supported by the fact that t-BuLi was found to add to the diene in the same manner without the ensuing epoxide opening.

The bottom mechanism was supported by the finding that tin adds in this manner when -OMs is replaced by -OTBS.

*JACS. 1994, 116, 11213*
Yale: Myrocin C

- With the cyclopropane ring in place, the annulation of the C-ring could be addressed. The cycloadduct arises from a transition state which is endo with respect to the aldehyde.

- The preexisting C-7 stereocenter guides the formation of the C-13 quat center. Epimerization of the lactone carbonyl occurs in the Wittig reaction.

- Apparently the lactol at C-21 situated as it is with respect to the concave 6,6,5 tricyclic array is very hindered

*JACS. 1994, 116, 11213*
Yale: Myrocin C

- A 7:1 mixture of iodoformates were formed in favor of the β-diastereomer.

The epoxidation is preceded by olefin migration.

- Sulfoxide syn-elimination affords desoxymyrocin C which is then converted to the desires natural product.

*JACS.* 1994, 116, 11213
Yale: Enediyne Natural Products

- Calecheamycin γ1: a novel antitumor agent

- Sequence selective DNA scissor

- Among the most potent cytotoxic agents known

- Unusual tetrasaccharide is recognition element

- Bergman perceived the electronic feasibility of electronic reorganization to provide a 1,4 aryl diyl.

- Cleavage of the trisulfide sets the stage for a conjugate addition into an anti-Bredt double bond, which then triggers the cyclization.

*JOC. 1996, 61, 16*
A Becker-Adler reaction is used to supply the ketoaldehyde. Initially an endiyne dianion addition to that ketoaldehyde was attempted.

Due to the acidity of the intermediate formed that approach was not successful.

A solution was devised wherein the resident aldehyde was protected in situ.

*JOC.* 1996, 61, 16
Yale: Enediyne Natural Products

A remarkably convergent glycosylation using maximally advanced domains allows a high level of convergency.

Global two-step deprotection of all blocking groups affords the natural product.

*JOC.* 1996, 61, 16
Yale: Enediyne Natural Products

- Dynemycin A: a novel antitumor agent
- Sequence selective DNA scissor
- Endiynne establishes biological activity
- Anthraquinone is recognition element

Semmelhack contibuted the basic idea that the quinone substructure provides the stabilizing element that protects dynemycin from spontaneous cyclization.

Reduction to the hydroquinone results in an epoxide opening, which then sets the stage for a conjugate addition which triggers the cyclization.

*JOC. 1996, 61, 16*
Yale: Enediyne Natural Products

- The product of the Diels-Alder reaction is the cycloadduct that is endo with respect to the aldehyde.

- The minor diastereomer of the IMDA is decomposed by CAN, suggesting the hemiacetal conveys stability.

- Os-Catalyzed dihydroxylation occurs away from the bulky alkyl groups.
A stereoselective Reissert reaction establishes the $\beta$-alkyne presumably due to the dibenzilidene acetal blocking the $\alpha$-face.

The acetal is removed and that allows $\alpha$-epoxidation from the convex face.

The defining step of the synthesis is a hybrid bis Sonagashira-Stille that delivers the enediyne in 81% yield.

*JOC.* 1996, 61, 16
Yale: Enediyn Natural Products

- A Rathke ketone carboxylation is employed to install acid moiety.

- Oxidation to the azaquinone delivers the dienophilic partner.

- A Tamura-Diels-Alder and oxidations round out the synthesis.

\[ \text{JOC. 1996, 61, 16} \]
Samuel Danishefsky: Columbia (1993-Present)
Columbia: Frondosin B

- Frondosin B was isolated from the sponge *Dysidea frondosa*.

  - Receptor antagonist of interleukin-8 (IL-8)
  - Benzofuran nor sequiterpenoid
  - Possible development as an anti-inflammatory agent

- Initially a racemic 12-step synthesis was conducted.

  - Sharpless epox.  63%, 84% ee
  - 1) NaO₄
  - 2) N₂CHPO(MeO₂)
    t-BuOK, 71% overall

- They then embarked upon an enantio-defined preparation of the natural product to define the absolute stereochemistry of the natural product.

  *JACS.* 2001, 123, 1878
Columbia: Frondosin B

- The benzofuran ring system was formed by a two-step Sonagashira-heterocyclization.

- The methyl stereocenter was prone to racemization.

- A Diels-Alder strategy forms the last ring.

*JACS. 2001, 123, 1878*
Columbia: UCS1025A

- UCS1025 was isolated from the fermentation broth of Acremonium sp. KY4917 fungus.
  - Antiproliferative in human cancer cell lines
  - Exists as three tautomeric isomers
  - Pyrrolizidine core connected to acyloctahydronaphthalene

- The original plan was to couple the two fragments by way of an aldol or Claisen condensation, then perform a series of late-stage oxidations.

- Unfortunately, all attempts to introduce functionality at the C-7 carbon were unsuccessful. To rationalize this they propose that a steric clash arises between the siloxy methyl and endo C-7a H protons.

*JACS. 2006, 128, 426*
The synthesis commences with the union of acetocly tataric anhydride and a commercially available amine salt.

Soft enolization conditions selectively afford the bicyclic pyrrolizidine ester.

Saponification and iodolactonization deliver the nucleophile fragment.
Columbia: UCS1025A

- Asymmetric organocatalysis delivers the aldol parter via asymmetric type 1 IMDA

\[\text{MeCN} \quad 20 \text{ mol\%} \quad 71\%, 90\% \text{ ee}\]

\[\text{JACS. 2005, 127, 11616}\]

- The key transformation is a boron Reformatsky coupling. Amazingly no β-elimination is observed.

\[\text{BEt}_3 \text{ PhMe} -78^\circ \text{C} \quad 99\%\]

- Oxidation and deprotection give the desired natural product as a tautomeric mixture which coalesced to a single product upon standing in CDCl$_3$.

\[\text{JACS. 2006, 128, 426}\]
Which synthesis did you like the best?