Syntheses Published in *Science* from 2001-2010 and Why They Made It In

MacMillan Group Meeting
12-08-2010
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What Makes a Synthesis Paper Important?

The Synthesis

New Reaction Methodology

New Application of Old Chemistry
to Make a Complex Motif in a Novel Way

The Molecule

Important Material or Pharmacological Properties

Structurally Profound

Both

The Synthesis Can Actually Produce an Important Molecule on Large Scale
Buckminsterfullerene

First observed in 1985 via laser vaporization of graphite,\(^2\) which lead to the 1996 nobel prize in chemistry

Isolated and fully characterized in 1990 via resistive heating of graphite electrodes\(^3\)

Global annual industrial production by such empirical synthetic methods exceeds 40 metric tons\(^4\)

Buckminsterfullerene Retrosynthetic Analysis

Synthesis of the Chlorinated Monomer

1. Mg, Et₂O
2. MeCHO 97%

Cl
Br

Me

Cl

OH

1. PBr₃, Benzene 86%

Cl

Me

Br

1. PPh₃
2. LiOCH₂CH₃, Naphthaldehyde 71%

Me

Cl

Me

Cl

I₂, hv 92%

Me

cyclohexane
Synthesis of the Chlorinated Monomer

1. Mg, Et₂O
2. MeCHO → 97%

PBr₃, Benzene → 86%

1. PPh₃
2. LiOCH₂CH₃, Naphthaldehyde → 71%

I₂ Oxidation

STILBENE PHOTOCYCLIZATION
6π photochemical electrocyclization

hv, I₂ → 92%

cyclohexane
Synthesis of the Chlorinated Monomer

1. KOH, H₂O
2. SOCl₂

51% for 3-steps

93% for 2-steps
Syntheses of the Trimer by Aldol Cyclotrimerization

\[
\text{TiCl}_4, \text{dichlorobenzene} \quad 100 \, ^\circ\text{C}, \, 85\% 
\]
Syntheses of the Trimer by Aldol Cyclotrimerization

The Aldol Cyclotrimerization Reaction

"Stitching Together" the Fullerene by Flash Vacuum Pyrolysis

FVP
1100 °C
-3Cl, -27H

0.1-1% Yield
Flash Vacuum Pyrolysis

Gas phase reaction minimizes bimolecular pathways
High temperature accentuates the entropic contribution to $\Delta G_{\text{rxn}}$

Scott, L.; Tsefikas, V. Chem. Rev. 2006, 106, 4868-4884
15 new C-C bonds
>60% yield per bond formation
16 new rings formed
~600 kcal/mol strain introduced

Why is this a Science Paper?

Not a preparatively useful way to make C60

No new chemical reactivity demonstrated

Buckminsterfullerene is a celebrity molecule at the height of its popularity during the disclosure of this synthesis

This demonstrates the feasibility of rationally synthesizing large fullerenes, which lays the groundwork for constructing novel fullerenes with superior material properties.
Buckminsterfullerene

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Ciguatoxin CTX3C

Structure elucidated in 1989 using sample from the marine dinoflagellate *Gambierdiscus toxicus*²

A ladderlike polyether with 30 stereocenters

LD₅₀ = 0.25 µg/kg in mice. Compare to brevetoxins > 100 µg/kg.

20,000 people suffer annually from ciguatera from eating contaminated seafood

Low natural availability has hampered preparation of anti-ciguatoxin antibodies for detecting ciguatoxin contamination in fisheries

Ciguatoxin CTX3C Retrosynthetic Analysis

Previously Reported Fragments
Preparing the Fragments for Coupling

\[ \text{39\% for 5-steps} \]
Coupling the Fragments by Acetal Formation

\[
\text{TMSSPh, TMSOTf, CH}_2\text{Cl}_2 \quad 61\% \\
\rightarrow \\
\text{single diastereomer}
\]

\[
\text{Sc(OTf)}_3 \text{ benzene} \quad 57\%
\]

4:1 mixture of epimers
Closing the 7-Membered G Ring by Radical Cyclization

NMM, CH$_2$Cl$_2$ \(\rightarrow\) 92%

AIBN, Bu$_3$SnH, Toluene \(\rightarrow\) 61%
Closing the Final 9-Membered F Ring by RCM

1. 1st generation Grubbs'
2. Na, NH₃, -90 °C
Why is This a Science Paper?

No new chemistry, but the RCM was impressive for its time

First synthesis of an incredibly complex natural product

Material furnished from the study to be used for the preparation of anti-ciguatoxin antibodies

Ciguatoxin CTX3C

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Norzoanthamine

First isolated in 1995 from the zoanthids of the genus *Zoanthus*

Inhibits the growth of P-388 murine leukemia cell lines and also demonstrates promising anti-osteoporotic activity in mice

Novel and stereochemically dense structure attracted attention from the synthetic community

Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science, 2004*, 305, 495-499
Norzoanthamine Retrosynthetic Analysis
Synthesis of the Diels-Alder Precursor

\[
\text{Me} \xrightarrow{\text{LiCu} \left( \text{Me} \right) \text{OTIPS}} \text{THF, TMSCl} \xrightarrow{\text{Me}} \text{OTMS} \xrightarrow{\text{BuLi, ZnBr}_2,} \text{84\% for 2-steps} \xrightarrow{\text{OH} \text{C}} \text{O} \xrightarrow{\text{Me}} \text{Me} \xrightarrow{\text{OTIPS}} \text{Me} \xrightarrow{\text{OAc}} \text{H} \xrightarrow{\text{Me}} \text{Me} \xrightarrow{\text{Me}} \text{Me} \xrightarrow{\text{Me}} \text{Me}\]

71\% for 9-steps
Synthesis of the Diels-Alder Precursor

\[
\begin{align*}
\text{Ketone} & \xrightarrow{\text{LiCu(OTIPS)}_2} \text{Diene} \xrightarrow{\text{BuLi, ZnBr}_2} \text{Product} \\
\text{OAc} & \xrightarrow{\text{hv, O}_2} \text{Final Product}
\end{align*}
\]
Synthesis of the Diels-Alder Precursor

1. Reaction of a ketone with LiCu[(Me)C=CH(OTIPS)_2] in THF, TMSCl.

2. Reaction of an aldehyde with BuLi, ZnBr₂, yielding an alcohol in 84% for 2-steps.

3. Photodegradation of an aldehyde with hv, O₂, and rose bengal, yielding a ketone in 71% for 9-steps.

Photosensitized Oxidation of Furan
Synthesis of the Diels-Alder Precursor

1. TBAF, MeI
2. TBSOTf, Me₂NEt

THF, TMSCI

BuLi, ZnBr₂, 84% for 2-steps

hv, O₂, rose bengal

71% for 9-steps

Photosensitized Oxidation of Furan
Key Intramolecular exo-Diels-Alder

Synthesis of the Alkyne Segment

63% for 5-steps
Synthesis of the Alkyne Segment

63% for 5-steps

1. Ph₃PCD₃Br
   KHMDS
2. 9-BBN, THF
   then H₂O₂
**Synthesis of the Alkyne Segment**

1. **First Step:**
   - Start with the initial molecule.
   - Reaction: $\text{AcO} \rightarrow \text{TESO}$
   - Yields: 63% for 5-steps

2. **Second Step:**
   - Reaction: $\text{OTBS}$
   - Reagents: $\text{Ph}_3\text{PCD}_3\text{Br}, \text{KHMDS}$
   - Yields: 60% for 7-steps

3. **Third Step:**
   - Reaction: $\text{CHO}$
   - Reagents: 9-BBN, THF then $\text{H}_2\text{O}_2$
   - Yields: 60% for 7-steps
Synthesis of the Alkyne Segment

1. Ph₃PCD₃Br
   KHMDS
2. 9-BBN, THF
   then H₂O₂

63% for 5-steps

Tf₂O
2,6-di-iBuPy
then DBU
81%

60% for 7-steps
Synthesis of the Alkyne Segment

Kinetic Isotope Effect Exploited to Prevent 1,5-hydride Shift
Forming the Aminoacetal and Removing the Deuterium

1. BuLi, THF
2. DMP, CH₂Cl₂  

82%
Forming the Aminoacetal and Removing the Deuterium

1. BuLi, THF
2. DMP, CH₂Cl₂

82%

1. H₂, PtO₂
2. AcOH, 50 °C
Forming the Aminoacetal and Removing the Deuterium

1. BuLi, THF
2. DMP, CH$_2$Cl$_2$

82%

Deuterium Burned-Out
End Game

1. TMSCHN₂
2. TMSCl, LHMDS
3. Pd(OAc)₂, MeCN

96%
End Game

1. TMSCHN₂
2. TMSCl, LHMDS
3. Pd(OAc)₂, MeCN

AcOH, 100 °C

1. TFA, H₂O
2. Al₂O₃, MeOH
Why is This a Science Paper?

First synthesis of Norzoanthamine

Extremely high yielding despite non-convergent synthesis:
3.5% overall yield from a 41 step synthesis (92% per step)

Clever exploitation of kinetic isotope effect

A key exo-selective diels-alder sets the core

Norzoanthamine

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Prostratin

First isolated from *Pimelea prostrata* in 1976 in limited quantities

Protein kinase C activator capable of activating viral reservoirs in latently HIV infected CD4 T-cells

A combination therapy of prostratin and antiretroviral drugs offers a potential cure to HIV-AIDS by "flushing out" viral reservoirs

Currently poised to enter phase I clinical trials conducted by the AIDS ReSearch Alliance using material furnished by this route

The Semi-Synthesis of Prostratin from Phorbol

Prostratin

Deoxygenation

Phorbol

Isolable from croton oil in kilogram quantities
Cyclopropane Complicates Radical Deoxygenation Strategy
Cyclopropane Complicates Radical Deoxygenation Strategy

3-steps

AIBN, Bu3SnH

0%
Cyclopropane Complicates Radical Deoxygenation Strategy

Intramolecular Ring Cleavage Outcompetes Intermolecular H Delivery
Deoxygenation by Hydrolysis Leaves Handles to Reform Cyclopropane

Deoxygenation by Hydrolysis Leaves Handles to Reform Cyclopropane

Cyclopropane Reestablished in 4-steps

H$_4$N$_2$H$_2$O, AcOH →

pyridine, DIPEA, 150 ºC →

Pb(OAc)$_4$

43% for 3-steps
Why is This a Science Paper?

No new chemical reactivity demonstrated, but the synthetic strategy is concise and non-obvious

The route is amenable to preparing various ether derivatives during the pyrazoline oxidation step

Preparatively useful way to make a very important substance
Prostratin

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(+)-11,11‘-Dideoxyverticillin A

Cytotoxic alkaloid isolated from marine *Penicillium* first reported in 1970

Inhibits tyrosin kinase activity of the epidermal growth factor receptor, and displays antiangiogenic activity

Densely functionalization with acid-, base-, and redox sensitive groups hampered synthesis of epidithioketopiperazine alkaloids

Kim, J.; Ashenhurst, J.; Movassaghi, M. *Science*, 2009, 324, 238-241
(+)-11, 11'-Dideoxyverticillin A Retrosynthetic Analysis
Synthesis of the Dimer Framework by Intermolecular Radical Coupling

\[
\text{PhSO}_2\text{N}_2\text{H}_{\text{Me}}\text{CO}_2\text{Me} \xrightarrow{\text{TFA, CH}_2\text{Cl}_2, 84\%} \text{PhSO}_2\text{N}_2\text{H}_{\text{Me}}\text{NMe} \xrightarrow{\text{Br}_2, \text{MeCN}, 76\%} \text{Br}_2\text{N}_{\text{SO}_2\text{Ph}}\text{O}_2\text{O} \xrightarrow{\text{CoCl}(\text{PPh}_3)_3, 46\%} \text{Me}_{\text{N}}\text{N}_{\text{SO}_2\text{Ph}}\text{O}_2\text{O} \xrightarrow{\text{MeI, 77\%}} \text{Me}_{\text{N}}\text{N}_{\text{SO}_2\text{Ph}}\text{O}_2\text{O}
\]
Synthesis of the Dimer Framework by Intermolecular Radical Coupling

Intermolecular Radical Coupling
Tetrahydroxylation and Tetrathiolation

Py$_2$AgMnO$_4$

CH$_2$Cl$_2$, 63%
Tetrahydroxylation and Tetrathiolation

\[
\text{Py}_2\text{AgMnO}_4 \xrightarrow{\text{CH}_2\text{Cl}_2, 63\%} \]

2-steps 55%
Tetrahydroxylation and Tetrathiolation

\[
\text{Py}_2\text{AgMnO}_4 \rightarrow \text{CH}_2\text{Cl}_2, 63\%
\]

\[
\begin{align*}
\text{SO}_2\text{Ph} & \rightarrow \text{SO}_2\text{Ph} \\
\text{Me} & \rightarrow \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{K}_2\text{CS}_3, \text{TFA} \rightarrow \text{CH}_2\text{Cl}_2, 56\%
\end{align*}
\]

\[
\begin{align*}
\text{Me,} & \rightarrow \text{Me,} \\
\text{Me} & \rightarrow \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{SOS} & \rightarrow \text{SOS} \\
\text{N} & \rightarrow \text{N}
\end{align*}
\]

\[
\begin{align*}
\text{2-steps} & \rightarrow 55\%
\end{align*}
\]
Oxidation to Form the Disulfides

\[
\text{ethanolamine, CH}_2\text{Cl}_2 \quad \text{then KI}_3, 62\%
\]
Why is This a Science Paper?

First synthesis of a dimeric epidithioketopiperazine alkaloid

Clever manipulation of sensitive, advanced-stage intermediates to generate the disulfide

Strategy should be amenable to synthesizing related compounds for further biological studies

Kim, J.; Ashenhurst, J.; Movassaghi, M. Science, 2009, 324, 238-241
11,11'-Dideoxyverticillin A

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Final Thought

The Synthesis

New Reaction Methodology

This is the only bullet point that was never colored red in this talk. Why is that?