HIGHLIGHTS OF LEO PAQUETTE’S CAREER: BREAKTHROUGHS IN TOTAL SYNTHESIS

Christopher Parnell
Denmark Group Meeting
Brief Biography

Born Worchester, MA., July 15, 1934
Died January 21, 2019

B.S. Holy Cross College 1956
Ph.D., MIT, 1959 (Prof. Norman Nelson)
“Synthesis of azasteroids and the Regioselectivity in
Baeyer Villiger Oxidation”
Upjohn, medicinal chemist, 1959-1963
Professor of Organic Chemistry OSU 1969-2019

Research Interests:
Heterocyclic Chemistry
Natural Product Synthesis
Asymmetric Methodology
Synthesis of Complex Carbocycles
Overview

• Dodecahedrane (1974-1983)
• Select Syntheses
• Anionic Oxy-Cope (1989-1993)
• Squarate esters (1997-2002)
Platonic Solids

- Plato developed a theory that the “elements” were polyhedra

- First proposed balanced chemical reaction (Balanced by number of faces on each polyhedron)
Platonic Solids

- Only Tetrahedrane, Cubane, and Dodecahedrane are synthetically accessible

Peristylanes

- **Comes from the greek word “peristylion”, “peri” meaning around and “stylos” meaning column**

- **Interest in these compounds arises from their similarity to Platonic solids ([5] Peristylane being similar to Dodecahedrane)**

\[ \text{[3] Peristylane} \]
(Nickon and Pandit, 1968)

\[ \text{[4] Peristylane} \]
(Paquette, 1983)

\[ \text{[5] Peristylane} \]
(Eaton, 1972)

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[4]Peristylylene

\[ \text{PhH, } \Delta \]

98%

hv, acetone

95%

HIO\textsubscript{4}

10% MeOH (aq.)

95%

LiAlH(OtBu)\textsubscript{3}

90%

Li, EtNH\textsubscript{2}

68%

H\textsubscript{3}O\textsuperscript{+}

71%

Overview

• **Dodecahedrane (1974-1983)**
• Select Syntheses
• Oxy-Cope (1989-1993)
• Squarate esters (1997-2002)
Dodecahedrane

- $I_h$ Point group
- C-C bond length are 1.535-1.541 Å (1.546 Å for cyclopentane)
- C-C-C bond angles are 107.7-108.1°
- Transcavity space diameter is 0.91-0.93 Å
- Shown to be capable of encapsulating helium ions
- Synthesized in 1983 for it’s “exquisitely perfect symmetry”

We have shown that helium can penetrate the five-membered rings of dodecahedrane and that the resulting He@C$_{20}$H$_{20}$ is stable for weeks. In effect, we have made the world’s smallest helium balloons. Because of the very small

Retrosynthetic Analysis

Dehydrogenation

Norrish Type II

Wurtz/Acyloin Condensation

Annulation/Ring Expansion

Lactonization/Oxidation

Diels-Alder

Oxidative Dimerization
Road to Dodecahedrane

\[ \text{Na, I}_2 \rightarrow \text{THF, -78}^\circ \text{C} \]

\[ \text{MeO}_2\text{C} \equiv \text{CO}_2\text{Me} \rightarrow \text{THF} \rightarrow -78^\circ \text{C to RT} \]

23% 17%
Road to Dodecahedrane

i) KOH, H₂O
ii) I₂, NaHCO₃, DCM

CrO₃, H₂SO₄, H₂O, acetone

NaOMe, MeOH

Cu-Zn, MeOH

94%

68% from

Road to Dodecahedrane

allyl-TMS, s-BuLi
-45°C

MeO

O

MeO

OH

॥ TMS

“fair yield”

MeO

O

MeO

OH

॥ TMS

MeO

O

MeO

Al

॥

30% MeCO₃H
AcOH

MeO

O

MeO

Al

॥

8% P₂O₅
MsOH

83%

MeO

O

MeO

Al

॥

H₂, 10% Pd/C

MeO

O

MeO

Al

॥

Quant.
**Road to Dodecahedrane**

i) NaBH₄

ii) 2 N HCl

HCl
MeOH

62%

i) NH₃, Li

ii) PhOCH₂Cl

48%

Road to Dodecahedrane

\[
\text{hv, NEt}_3 \xrightarrow{\text{PhH, t-BuOH}} \quad \text{PhO}\text{COOMe} \quad 90\% \\
\text{hv} \xrightarrow{(9:1) \text{PhMe: EtOH}} \quad \text{PhO}\text{COOMe} \quad \text{92}\%
\]

\[
\text{N}_2\text{H}_2 \xrightarrow{\text{MeOH}} \quad \text{PhO}\text{COOMe} \quad \text{85}\% \text{ over 2 steps} \\
\text{i) DIBAL-H} \quad \text{ii) PCC} \quad \text{92}\%
\]

\[
\text{i) Li, NH}_3 \text{EtOH} \quad \text{ii) H}_3\text{O}^+ \xrightarrow{\text{H}_3\text{O}^+} \quad \text{HO}\text{OH} \quad \text{99}\%
\]

\[J. \text{Am. Chem. Soc.}, 1983, 105, 5446.\]
Road to Dodecahedrane

\[ \text{PCC, DCM} \rightarrow \text{O} \]

\[ \text{TsOH, PhH} \rightarrow \text{O} \]

\[ \text{i) KOH, MeOH, ii) hv} \rightarrow \text{OH} \]

\[ \text{H}_2\text{NNH}_2, \text{H}_2\text{O}_2 \rightarrow \text{37\% over 4 steps} \]

\[ \text{Pd/C, 250\°C} \rightarrow 50\% \]

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Propellane Synthesis

- Propellanes are hydrocarbons in which three ring systems share a single carbon-carbon bond.
- Some of Paquette’s early work involved using the Ramberg-Backlund Rearrangement in order to synthesize unsaturated propellanes en route to cyclophanes.
- Thermal retro-electrocyclizations were found to be unfavorable and other methods for we utilized for accessing cyclophanes.

\[ \text{Reaction Scheme:} \]

\[ \begin{align*}
\text{O} & \quad \text{O} \\
\text{S} & \quad \text{Cl} \\
\end{align*} \quad \overset{\text{KOTBu}}{\text{THF}} \quad \overset{i) \text{NBS}}{\text{ii) KOTBu}} \quad \begin{align*}
\end{align*} \]

*J. Am. Chem. Soc.*, 1971, 93, 4516
Cyclophane Synthesis

- Cyclophanes are hydrocarbons composed of aryl rings connected by alkyl linkers that hold them in a cage-like conformation.
- [n,n’]cyclophanes are thought to exhibit different reactivity based upon whether the aryl rings contained in the structure are [4n+2] or [4n] \( \pi \)-electron systems.

\[ \text{Cyclophane} \]

\[ \text{Cyclophane} \]

\[ \text{Cyclophane} \]

\[ \text{Cyclophane} \]
[2²](1,5)Cyclooctatetraenophane

[2²](1,5)Cyclooctatetraenophane

i) LiAlH₄

\[ \text{MeI; } \Delta \]

ii) NaH, CS₂

70%

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i) NBS

\[ \text{AIBN, CCl₄} \]

ii) 10% HCl, AcOH

85%

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Retro Electrocyclization

i) LiAlH₄

\[ \text{MeI; } \Delta \]

ii) NaH, CS₂

70%

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500 °C

Retro Electrocyclization

40%

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Overview

- Dodecahedrane (1974-1983)
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Anionic Oxy-Cope refresher

- Thermal [3,3]-sigmatropic rearrangement of a 1,5-dien-3-ol
- Thermodynamically driven by the enol-keto tautomerization following the rearrangement
- May proceed through a chair or boat transition state (chair favored unless system is conformationally locked)
- Rate acceleration occurs if the alkoxide is formed due to ground state destabilization

Conformational Analysis

Tandem Oxy-Cope

Anionic Oxy-Cope/α-Oxidation

\[ \text{Compound 1} \xrightarrow{\text{KN(SiMe}_3)_2, 18-c-6, O_2} \text{Compound 2} \]

\[ \text{Compound 3} \xrightarrow{} \text{Compound 4} \]

Anionic Oxy-Cope/ $S_N2'$

\[ \text{OMe} \quad \text{OH} \quad \text{OMe} \quad \xrightarrow{\text{KN(SiMe}_3)_2} \quad \text{MeO} \quad \text{O}^- \]

\[ \quad \xrightarrow{\quad} \quad \text{H} \quad \text{H} \quad \text{O} \quad \text{MeO} \quad \text{O}^- \quad \text{H} \]

\[ \quad \xrightarrow{\quad} \quad \text{H} \quad \text{H} \quad \text{O} \quad \text{MeO} \quad \text{O}^- \quad \text{H} \]

Anionic Oxy-Cope/ $S_N2'$

\[\text{HO} \quad \text{H} \quad \text{OMe} \quad \text{KN(SiMe}_3\text{)}_2 \quad 18\text{-c-6}\]

\[\begin{array}{c}
\text{OMe} \\
\text{OMe}
\end{array}\]

\[\text{H} \quad \text{H} \quad \text{OMe}\]

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Squarate Esters

Squarate Esters

\[ \text{BrCH(OMe)\textsubscript{2}} \xrightarrow{i) \text{tBuLi}} \text{MeO} \xrightarrow{\text{ii)} \text{MeO}} \text{CH(OMe)\textsubscript{2}} \]

\[ \text{MeO} \xrightarrow{\text{BF}_3\text{-OEt}_2} \text{MeO} + \text{MeO} \]

MeO\textsubscript{3}

Mechanism?
Mechanism

Squarate Esters

\[
\begin{align*}
\text{i) NaBH}_4, \text{MeOH} & \rightarrow \text{MeO} & \text{ii) Ac}_2\text{O, NEt}_3 & \rightarrow \text{MeO} \\
\text{DMAP} & \rightarrow \text{MeO} & \text{THF, MeOH} & \rightarrow \text{MeO} \\
& \text{73\%} & & \text{98\%} \\
\text{CAN} & \rightarrow \text{MeO} & \text{MeCN, H}_2\text{O} & \rightarrow \text{MeO} \\
& \text{52\%} & & \text{65\%} \\
\text{OsO}_4, \text{NaS}_2\text{O}_4 & \rightarrow \text{MeO} & \text{acetone, H}_2\text{O} & \rightarrow \text{MeO} \\
& \text{78\%} & & \text{80\%}
\end{align*}
\]

Concluding Remarks

- 55 Complete total Syntheses
- 1391 publications (111 reviews)
- 43 patents
- 17 books
- 38 book chapters
- Graduated ~150 students

Awards:
1965 Alfred P. Sloan Fellow
1971 Morley Medalist Cleveland Section
1976 Guggenheim Fellow
1979 Columbus Section Award
1980 Senior Research Award, OSU
1981 Kimberly Professorship in Chemistry
1984 National Award for Creative Work in Synthetic Organic Chemistry
1987 Arthur C. Cope Scholar
1989 Senior Humboldt Fellow
1990 Sullivant Award, OSU highest honor
1992 Awardee of the Japanese Society for the Promotion of Science
1992 Ernest Guenther Award
2002 S.T. Li Prize Science and Technology
Questions?