Enantioselective Total Synthesis of (+)-Salvileucalin B

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![Molecule](image)

Tropylium Ion Mediated alpha-cyanation of Amines

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\[\text{t-Bu}_2\text{N} + \text{H} \rightarrow \text{CN} + \text{KBF}_4 \]

\[\text{KCN, MeCN, 23 }{\circ}\text{C, 3 hrs, 81% yield} + \text{t-Bu}_2\text{N} \text{Me} + \text{C}_4\text{H}_4\text{BF}_4\]
Sarah E. Reisman


2001 - 2006: Ph.D. Yale University (John Wood/Total Synthesis)

2006 - 2008: NIH Postdoctoral Fellow, Harvard University (Jacobsen, asymmetric catalysis)

2008 - current: Assistant Professor at Caltech University

Research Interests

**Natural product synthesis** - Emphasis on the development of catalytic asymmetric methods that facilitate the construction of complex molecules.

**Current areas of research** - Synthesis of alkaloid natural products, catalytic asymmetric methods for the synthesis of arylated indolines, and the development of catalysts for enantioselective electrophilic chlorination.
• Isolated in 2008 by Takeya and co-workers from *Salvia leucantha*

• Exhibits cytotoxicity against A459 (Human Lung) and HT-29 (Human Colon) cells with IC$_{50}$ of 5.23 and 1.88 µg/mL

• Norcaradiene core embedded within a caged polycyclic skeleton

• Five stereogenic centers, with 3 all carbon quaternary centers

• First reported enantioselective total synthesis

• The key step involves an intramolecular copper catalyzed arene cyclopropanation

• 18 steps longest linear sequence
Retroynthetic Approach to (+)-Salwinecalin B

\[
\begin{align*}
\text{salwinecalin B} & \quad \Rightarrow \quad \text{Intramolecular Arene Cyclopropanation} \\
& \quad \Rightarrow \quad \text{Metal-Catalyzed Cycloisomerization} \\
\end{align*}
\]
Construction of Triyne

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\[ \text{Me}_2\text{Zn, 8 (40 mol \%)} \]
\[ \text{PhMe, 70 °C; 3-furaldehyde 0 °C to 23 °C} \]
\[ 85 \% \text{ yield} \]

\[ \xrightarrow{\text{TBSO}} \]
\[ 93\% \text{ ee} \]

\[ \text{1) NaH, } \equiv \equiv \text{Br} \]
\[ \text{DMF, 23 °C} \]
\[ \text{2) 1M HCl, MeOH} \]
\[ \text{3) MsCl, Et}_3\text{N, THF, 23 °C, then LiBr} \]
\[ 80\% \text{ yield, 3 steps} \]

\[ \text{LHMDS, LiCl, THF, } -78 \text{ °C to 23 °C;} \]
\[ \text{then, } -78 \text{ °C} \]
\[ 90\% \text{ yield} \]
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Synthesis of (+)-Salvileucalin B

1) TBAF, DCM, 23 °C
2) RuCp*(Cod)Cl (8 mol %), DCM, 45 °C
3) n-Bu₄NOH, t-BuOH/H₂O, 90 °C
74% yield, 3 steps

1) (COCl)₂, cat. DMF then CH₂N₂, THF
2) AgTFA, MeOH, Et₃N
THF, −30 °C to 23 °C
69% yield, 2 steps

Arndt—Eistert homologation

1) NaCH₂CN
THF, −78 °C to 23 °C
2) (imid)SO₂N₃, pyr
78% yield, 2 steps

NaHMDS, −78 °C; then Tf₂NPh
90% yield

Cu(hfacac)₂ (10 mol %)
DCM, 120 °C
μwave, 1 min
65% yield

hexafluoroacetylacetonate
Continued Synthesis of (+)-Salvileucalin B

[Chemical reactions and structures are depicted, showing the synthesis process involving DIBAL, CrO3, Pd2(dba)3, and DIPEA in different solvent mixtures and temperatures.]
Tristan H. Lambert

1994 - 1998: B.S. University of Wisconsin at Platteville; Dwight Klaassen


2004 - 2006: NIH Postdoctoral Fellow, Sloan-Kettering Cancer Center;
(Danishefsky, total synthesis)

2006 - current: Assistant Professor at Columbia University

Research Interests

Aromatic Ions - The use of aromatic ions as catalysts/promoters for new synthetic methodologies

Multicatalysis - The use of catalysis to assemble complex molecules in a single pot.

Reaction Design - new transition metal catalyzed cycloadditions
Iminium Ion in Synthesis

• Traditional carbonyl-amine condensations are limited in terms of scope

• Iminium ion formation by amine oxidation typically carried out under harsh conditions (transition metals, DDQ, PhI(OAc)$_2$, or singlet oxygen).

• Trityl and tropylium ions are known to oxidize amines by hydride abstraction; synthetic utility under explored.

• Tropylium ion - 6π electron aromatic cation, shelf stable, commercially available

\[
\text{R}^+\text{N}^+\text{R} \xrightarrow{\text{Nu}^-} \text{R}\text{N}^+\text{R}^\text{Nu}
\]

- \(\text{BF}_4\) ion

\[
\begin{align*}
\text{i-Bu}_2\text{N} & \quad \text{MeCN} \quad 23^\circ\text{C}, 30 \text{ min} \\
\text{Me} & \quad \text{BF}_4^- \\
\text{i-Bu}_2\text{N} & \quad \text{BF}_4^- \\
\text{Me} & \quad \text{BF}_4^- \\
\text{H} & \quad \text{BF}_4^- \\
b.p. = 116^\circ\text{C}
\end{align*}
\]
**Alpha-cyanation of Amines**

\[
i-Bu_2NCHMe_2 + BF_4^- \xrightarrow{KCN, MeCN} \text{MeCN} \xrightarrow{81\% \text{ yield}} i-Bu_2NCHMe_2 + \text{Cyclopentadiene} + KBF_4
\]

Key is low solubility of KCN in MeCN

KCN added *before* oxidation

\[
\text{BF}_4^- + \text{Cyclopentadiene} \xrightarrow{KCN} \text{Cyclopentadienyl cyanide}
\]

Not observed

\[
i-Bu_2NCHMe_2 + BF_4^- \xrightarrow{KCN, MeCN, 18\text{-crown-}6} \text{MeCN} \xrightarrow{23 \, ^\circ C, 3 \, \text{hrs}} \text{No oxidation observed}
\]

\[
i-Bu_2NCHMe_2 + BF_4^- \xrightarrow{KCN, MeCN} \text{MeCN} \xrightarrow{23 \, ^\circ C, 3 \, \text{hrs}} \text{No oxidation observed}
\]

\[
i-Bu_2NCHMe_2 + BF_4^- \xrightarrow{TMSCN, MeCN} \text{MeCN} \xrightarrow{23 \, ^\circ C, 3 \, \text{hrs}} \text{No oxidation observed}
\]
**Substrate Scope**

\[
\begin{align*}
R^1_N R^2 & \overset{BF_4^-}{\xrightarrow{\text{KCN, MeCN}}} R^1_N R^2 \\
\end{align*}
\]

1. **120 °C, 12 h**
   - 78% yield
   - 5.9:1 regioselectivity

2. **120 °C, 12 h**
   - 77% yield
   - > 20:1 regioselectivity

3. **100 °C, 12 h**
   - 43% yield
   - 3.7:1 regioselectivity

4. **80 °C, 12 h**
   - 71% yield

5. **23 °C, 3 h**
   - 90% yield
   - 1 g scale

6. **23 °C, 0.25 h**
   - 73% yield

7. **80 °C, 12 h**
   - 42% yield
Proposed Mechanistic Pathway

- electron donor-acceptor complex
- might explain poor benzylic oxidations
One Final Transformation

Steric encumbrance by the gem-diphenyl group prevents alkylation of secondary amine.