Cortistatin A: A Strange Feeling of déjà vu...

Russell Smith
Denmark Research Group
November 25, 2008
Isolation and Activity of Cortistatins

- Isolated from marine sponge *Corticium simplex*
- Cortistatin A proved to have the most potent biological activity
- Shows cytostatic anti-proliferative activity against Human Umbilical Vascular Endothelial Cells (100 pM)

Synthetic Challenges Towards Cortistatin A

- 9(10->19)-abeo-androstane type steroidal skeleton
- Oxabicyclo[3.2.1]octene core
- Isoquinoline unit
- 8 stereocenters
- Contiguous \textit{trans} stereocenters about the A ring
- X-ray crystal structure provided relative stereochemistry
- CD - exciton chirality method provided absolute stereochemistry

Remember When - Team A

RCM

1,4-addition

enyne metathesis

Aryl

TBSO

TBSO

CO₂Me

CO₂Me

Br

 PgO

OPg

Br

OH

Me

N

Me

N

Me

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H

Me

N

Me

H
Way Back When - Team B

\[
\text{HO} \quad \overset{\text{Heck}}{\longrightarrow} \quad \text{HO}
\]

\[
\text{1,4-addition}
\]

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

\[
\text{HO} \quad \overset{\text{I}}{\longrightarrow} \quad \text{HO}
\]

\[
\text{Me} \quad \text{N} \quad \text{Me}
\]
A Blast from the Past - Team C

Synthesis of C,D - ring precursor

Hajos-Parrish Ketone
Back to the Future - Team D

\[
\begin{align*}
\text{Aldol} & \quad \implies \\
\text{[5 + 2]} & \quad \downarrow
\end{align*}
\]
Retrosynthetic Analysis - Danishefsky
Snieckus Lithiation/RAR

\[
\text{t-BuLi} \quad \text{80 °C} \quad \text{44%}
\]

Alkylative dearomatization provides a facile route to furan core.
Retroynthetic Analysis - Danishefsky II

Masamune Alkylation

\[ \text{TBSO} \text{MeH} \text{X} \text{Y} \text{LG} \rightarrow \text{TBSO} \text{MeH} \text{X} \text{Y} \text{LG} \]

\[ \text{X} \text{Y} \text{LG} \rightarrow \text{X} \text{Y} \text{LG} \]
Benzyne-Nitrone Cycloaddition

Attempts to use methylated or benzylated nitrone were ineffective.

\[
\text{9a-c} \quad + \quad \text{Br-TfO 10} \quad \xrightarrow{\text{nBuLi, THF}} \quad -78^\circ C \quad \text{11a-c}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>(-R)</th>
<th>Ratio 9:10</th>
<th>Yield (11)</th>
<th>RSM (9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(-t\text{Bu} (9a))</td>
<td>2:1</td>
<td>49% (11a)</td>
<td>54%</td>
</tr>
<tr>
<td>2</td>
<td>(-t\text{Bu} (9a))</td>
<td>1:1</td>
<td>47% (11a)</td>
<td>28%</td>
</tr>
<tr>
<td>3</td>
<td>(-t\text{Bu} (9a))</td>
<td>1:1.2</td>
<td>51% (11a)</td>
<td>37%</td>
</tr>
<tr>
<td>4</td>
<td>(-t\text{Bu} (9a))</td>
<td>1:2</td>
<td>74% (11a)</td>
<td>10%</td>
</tr>
</tbody>
</table>

Stereoselectivity of [3+2] cycloaddition

- Attempted to induce diastereoselectivity from resonant stereocenter

\[
\begin{align*}
\text{R}^2\text{=C=CH}^+\text{N-O}^+\text{tBu} & \quad + \quad \text{Br-Ph}^+\text{Tf}^- & \quad n\text{BuLi, THF} & \quad -78 ^\circ\text{C} & \quad \text{PhO=NN-tBu} \\
14a-c & \quad 10 & \quad 15a-c
\end{align*}
\]

- Found that regioselectivity dependent on steric of benzyne

Improved Selectivity in Reduction/Electrocyclization

Upon initial completion of reaction, NO diastereoselectivity observed
Application to the Cortistatin Core

\[ \text{CHO} \quad \text{OPMB} \quad \xrightarrow{t-\text{BuNHOH, HOAc}} \quad \text{OPMB} \quad \text{t-BuO}^- \quad + \quad \text{OMe} \quad \text{TfO} \quad \text{OTIPS} \]

1. \text{Zn, HOAc}
2. 170 °C

\[ \text{TIPS} \quad \text{OMe} \quad \text{N-t-Bu} \]

\[ \text{O} \quad \text{Br} \quad \text{OMe} \quad \text{TIPSO} \quad \text{TBAF, rt} \quad \text{then 50 °C} \quad \text{2 d} \]

52%
Retrosynthetic Analysis- Oxidative Dearomatization (Sarpong)
Preparation of Indene Enyne

- Synthesis performed in racemic form
- Aldehyde has been previously prepared in enantiopure form (53% yield)

Angew. Chem. Int. Ed. 2008, 47, 6650
Cycloisomerization of Indene Compounds

• Previously demonstrated GaCl$_3$ promotes cyclization
  – Competing deprotection of silyl group observed

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{R}^3 & \quad \text{Me} \\
\text{OTBS} & \\
\hline
\text{PMBO} & \quad \text{Me} \\
\text{OMe} & \\
\text{Me} & \quad \text{OTBS}
\end{align*}
\]

\[
\begin{align*}
\text{24} & \quad (61\%) \\
\hline
\text{MeO} & \quad \text{Me} \\
\text{OMe} & \\
\text{Me} & \quad \text{OTBS}
\end{align*}
\]

\[
\begin{align*}
\text{25} & \quad (86\%) \\
\hline
\text{MeO} & \quad \text{Me} \\
\text{OMe} & \\
\text{Me} & \quad \text{OTBS}
\end{align*}
\]

\[
\begin{align*}
\text{26} & \quad (88\%) \\
\hline
\text{MeO} & \quad \text{Me} \\
\text{OMe} & \\
\text{Me} & \quad \text{OTBS}
\end{align*}
\]

\[
\begin{align*}
\text{27} & \quad (76\%) \\
\hline
\text{MeO} & \quad \text{Me} \\
\text{OMe} & \\
\text{Me} & \quad \text{OTBS}
\end{align*}
\]

*Angew. Chem. Int. Ed.* **2008**, *47*, 6650
Completion of Cortistatin Core

- Discovered that PMB phenol could not readily be scaled
- TES phenol proved to give more reproducible quantities of epoxide (46% over 3 steps)

*Angew. Chem. Int. Ed.* **2008**, *47*, 6650
• Found that storage of pyranyl iodide @ -30 °C increased dr to 20:1 via crystallization
• Epimerized at rt in CDCl₃
• Aza-Prins cyclization occurs via transannular cyclization
• Sets 2 stereocenters along with 2 ring systems
Elaboration of Hajos-Parrish Ketone

Chemical Formula: \( \text{C}_{25}\text{H}_{43}\text{BrO}_2\text{Si}_2 \)
Chemical Formula: \( \text{C}_{22}\text{H}_{35}\text{BrO}_2\text{Si} \)

- **QUESTION #1 (assume OR = OH for exercise)**
  - What two products were obtained upon treatment with fluoride? (Mechanism is helpful)
  - Suggest a method to prevent formation of X
Fluoride-Promoted Ring Expansion

8 steps

J. Am. Chem. Soc. 2008, ASAP.
Mechanistic Rationale for Elimination

**base-promoted elimination**

**silicate-directed elimination**

*J. Am. Chem. Soc. 2008, ASAP.*
Fluoride-Promoted Ring Expansion

- Found that use of “disiloxane” had greater propensity for hypervalency

*J. Am. Chem. Soc. 2008, ASAP.*
Diastereoselective Aza-Prins Cyclization

1. AD-mixβ
2. Ac₂O, TEA, DMAP
3. HF/pyr
4. Dess-Martin

> 95% diastereoselectivity @ amine carbon

1. TBAF
2. TPAP, NMO
3. N₂H₂, TEA, I₂
4. Bu₃Sn

Me₂NH, ZnBr₂

50 °C

d.r. = 10:1
Another Molecule to Change the World (Nicolaou)

1: cortistatin A

6: OTf

3: aldol dehydration cascade

4: 1,4-addition

Construction of Pentacyclic Dienone

Installation of Isoquinoline Fragment

- Isoquinoline subunit proves to be fairly robust; no epimerization observed
- Hydrogenation occurs from convex face

Completion of Ring A of Cortistatin A

Reduction of epoxy cyclohexanone results in a 1:1 diastereomeric mixture

Required separation and oxidation to recycle

Why not simply start with the complete core?

- Prednisone contains appropriate stereochemistry at C13 and C14
- Ring A contains desired oxidation for elaboration
- 70% carbon atoms present!

Synthesis of Cortistatinone from Prednisone

- Successfully elaborated ring A in 4 steps with all requisite stereochemistry
- Unprecedented alcohol directed dibromination

Mechanism for Isohypsic Cascade

\[ \text{Mechanism Diagram} \]

Revisiting Completion of Cortistatin A

- 15 linear steps from prednisone
- ca. 3% overall yield

1. $\text{N}_2\text{H}_4; \text{I}_2; \text{Et}_3\text{N}$
2. $\text{Pd(PPh}_3)_4$, (53\% over 2 steps)
3. Raney Ni (50\%, ca 100\% brsm)

Where have we been?
Where have we been?

[Chemical structures and reactions depicted]
Where have we been?
Where have we been?
Where have we been?

NHO MeOH

Danishefsky

O

OTBS

Danishefsky

OTBS

Sarpong

Yamashita

Shair

PMBO

Me

TBSO
Where have we been?
Where have we been?
Conclusions

• A number of semi-syntheses have been accomplished towards Cortistatin A
• The direct installation of stereochemistry at C8 is not essential; center can be epimerized fairly easily
• Installation of isoquinoline is facile; ease of hydrogenation with correct stereochemistry was observed in all cases
• Challenging oxabicyclo[3.2.1]octene core has been achieved using both nucleophilic and electrophilic methods
• Ability to use these synthesis to test actual biological requirements has not been realized
Potential Cycloisomerization Pathways

Pathway A

Pathway B
Preparation of Cyclopentyl alkyne

\[ S1 \rightarrow \text{ref. 5} \rightarrow S2 \]

1) OsO₄, NMO
2) NaIO₄

\[ S3 + \text{MeOH} \rightarrow S4 \rightarrow \text{LiAlH}_4 \rightarrow S5 \]

\[ \text{SO}_3 \text{pyr} \rightarrow \]

Angew. Chem. Int. Ed. 2008, 47, 6650