Total Synthesis of (−)-Sarain A


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Current Lit
Synthetic Approaches
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Outline

• Isolation
• Biosynthesis
• Syntheses from other groups
• Current route
• Overall picture
• Conclusions
Isolation

• In 1986, Cimino isolated Sarains A-C at the Bay of Naples from the marine sponge *Reniera sarai*. (Tetrahedron, 1989, 45, 3863)

![Structure of Sarain A](image1)

Sarain A

![Structure of Sarain B](image2)

Sarain B, \( R = -(Z)-\text{CH}_2\text{CH}=\text{CH-} \)

Sarain C, \( R = -(Z)-\text{CH}=\text{CHCH}_2 \)

• Products were characterized through MS, NMR, IR and 2D NMR: COSY, HETCOR, long range HETCOR. Structure was confirmed through X-ray of diacetate crystal (J. Nat. Prod. 1990, 53, 1519)

• Absolute conformation determined through Mosher ester analysis (Tetrahedron, 1996, 52, 8341)

• Sarains A-C display modest antibacterial, insecticidal and antitumor activities (Comp. Biochem. Physiol. B, 1992, 103B, 293)
Proposed Biosynthesis

Tet. Lett. 1995, 36, 707
Previous Synthetic Efforts

- **Weinreb**
  (J.O.C. 2006, 71, 2078)

- **Heathcock**
  (J.O.C. 1998, 63, 9616)

- **Cha**
  (J.O.C. 2003, 68, 2205)

- **Marazano**
Initial Retrosynthesis

Overman Communication: Angew.Chem.Int.Ed 2006, 45, 2912
First Models

- Seebach chemistry
  - Tet. Lett 1983, 24, 3311
- Benefit: Both enantiomers are accessible
- Early work done with unnatural enantiomer
- Model System: Z-enone needed
- 71% 20:1 dr
- Stereochem confirmed via derivatization

\[
\begin{array}{c}
\text{E} \quad \rightarrow \quad 26 \\
\text{Z} \quad \rightarrow \quad 28
\end{array}
\]
Model

\[
\begin{align*}
37 & \xrightarrow{1. \text{ DMSO, } 130 \, ^\circ \text{C}} \text{Ph} \xrightarrow{2. \text{ Me}_3\text{Al}} \text{Ph} \xrightarrow{\text{LHMDS, THF, DMPU, } -78 \, ^\circ \text{C}} \\
(\text{Ts}) \quad \text{N} & \text{N} \\
\text{EtO}_2\text{C} & \text{CO}_2\text{Me} \quad \text{Me} \\
\text{Ts} & \text{Ts} \\
\text{Boc} & \text{Boc} \\
\text{Ph} & \text{Ph} \\
\text{OTBDPS} & \text{OTBDPS} \\
\end{align*}
\]

\[
\begin{align*}
39 & \xrightarrow{\text{LHMDS, THF, DMPU, } -78 \, ^\circ \text{C}} \\
\text{Me} & \text{Me} \\
\text{Br} & \text{Br} \\
\end{align*}
\]

\[
\begin{align*}
40 & \xrightarrow{2 \, \text{N HCl}} \\
\text{Me} & \text{Me} \\
\text{Br} & \text{Br} \\
\text{NTs} & \text{NTs} \\
\text{OLi} & \text{OLi} \\
\end{align*}
\]

\[
\begin{align*}
41 & \xrightarrow{\text{H}_2\text{O}} \\
\text{Me} & \text{Me} \\
\text{Me} & \text{Me} \\
\text{NTs} & \text{NTs} \\
\text{BzO} & \text{BzO} \\
\text{HN} & \text{HN} \\
\text{CO}_2\text{Et} & \text{CO}_2\text{Et} \\
\text{NHTs} & \text{NHTs} \\
\text{OTBDPS} & \text{OTBDPS} \\
\end{align*}
\]

Model Findings

- Many Lewis Acids screened for cyclization to 49
  - SnCl₄, BF₃·OEt₂, Me₃Al
- Further exploration deemed necessary on real system
- 2 Plans
  - Plan A
    - Form macrocycle before cyclization
  - Plan B
    - Have larger C3 group on prior to cyclization
Plan A or Plan B

PLAN A: macrocycle then cyclize

PLAN B: cyclize with large C3 side chain
late stage macrocycle installation

no cyclization under a variety of conditions
Plan A & Problems

- Macrocycle formed prior to cyclization
- The synthesis commenced with:

- Converted to 65 in 8 steps
Plan B

1. LHMDS, allyl bromide
2. 2 N HCl
3. Boc₂O, DMAP (94%)

BocNTs

* Optimize!
Cyclization Optimization

Mechanistic studies:
Prins decomposition pathway
minor diastereomer

R=CO₂Me,
1. H₂
2. TIPSOTf

R=CO₂Me,
t-Butyl imine
or N-dimethyl hydrazone

1. DIBALH
2. NaCNBH₃, HOAc (93%)
3. DMSO 130 °C
4. TBAF
5. K₂CO₃ (68%)

Optimization

1. H₂ Pd/C
2. HCl (TBS removal)
3. PMBCl, NaHMDS (89%)
4. TAS-F
5. KOH
Finale

A. HF, 1.5 h (50-60%)

B. 1. HF, 10 min
B.2. TMSI complex mixture

Free aminal also used

messy reaction or loss of vinyl iodide

PMBO
OTES
N... 137
messy reaction
or loss of vinyl iodide
Free aminal also used

AcOH

1. K₂CO₃, MeOH (92%)
2. Dess-Martin
3. 144 (76%)

1. 138, (86%)
2. IBX, DMSO (71%)
3. 137 (68%), 3-4:1 dr
4. TBAF(85%)
5. TESCl (70%)

BrMg

SnBu₃

SnBu₃

1. Pd
2. DIBALH (64%)
3. Dess-Martin (70%)

A. HF, 1.5 h (50-60%)

B.1. HF, 10 min
B.2. TMSI complex mixture

sarain A
Conclusions

• After extensive optimization, the total synthesis of sarain A was completed in 45 steps and 0.13% overall yield from diethyl D-tartrate

• Weinreb, Heathcock, Cha and Marazano have independently developed methodology to synthesize the core

• The Highlights:
  – Seebach oxazoline chemistry sets three key stereocenters that influence all the remainder stereocenters in the molecule
  – Congested core constructed via novel enoxysilane addition to N-sulfonyliminium species
  – Ring closing metathesis sets western ring
  – Stille coupling on a sensitive substrate sets eastern ring