Total Synthesis of Halipeptins A and D

Mariam Shamszad
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Isolation of the Halipeptin Family

- Halipeptins A and B were isolated in 2001 by the Gomez-Paloma group from the sponge *Haliclona sp*. Halipeptin C was isolated in 2002 also by Gomez and Paloma.

- Halipeptin D was isolated in 2003 by Faulkner and Manam from a different sponge, *Leiosella cf. arenifibrosa*.

- Halipeptin A is noted for its potent anti-inflammatory activity, rivaling in potency commercially available anti-inflammatory drugs, possibly without the side effects.

- Halipeptin D exhibits potent cytotoxic properties against an oncology diverse panel of tumor cell lines, particularly against the human colon cancer cell line.
Structural Determinations

- Initially, structure of halipeptin A was misassigned as containing an unusual oxazetidine-type structural motif:

  ![originally proposed structure of halipeptin A](image1)
  ![currently proposed structure of halipeptin A](image2)

- It was not until the isolation of halipeptin C that the structure was corrected.

- Neither Gomez-Paloma or Faulkner-Manam could assign with certainty the stereochemistries at C-3 and C-4, although the former group did conclude the stereochemistry at C-7 to be (S).
Synthetic Challenges of the Halipeptins

- Striking number of methyl groups situated on and around the periphery of the macrocyclic depsipeptide ring
- Constrains on the macrocycle by the thiazoline ring
- Potential for epimerization of the 3 stereocenters next to the carbonyl and thiazoline moieties
- Uncertainties in configurations of C-3, C-4, and C-7 demand flexible strategies for the construction of key intermediates
Synthetic Efforts

- Partial syntheses:
  - 2003: Snider and Duvall
  - 2003: De Riccardis and Izzo
  - 2004: De Riccardis and Izzo
  - 2004: Hamada and coworkers

- First total synthesis of halipeptin A in 2005 by Ma and coworkers
  

- Total synthesis of halipeptins A and D in 2006 by Nicolaou and coworkers
  
Ma’s Retrosynthesis

halipeptin A

macrocyclization

peptide formation

HTMMD fragment

NMeOHIle/Thiazoline fragment
HTMMD Fragment Assembly
NMeOHIle Fragment Assembly

1) MsCl, Et₃N, 82%
2) (R)-α-methylbenzylamine, 80%
3) BocNHCH₂CO₂H, EDCl, HOBT, DIEA, 96%

1) Lindlar catalyst, H₂, Et₂O, 91%
2) CF₃CO₂H, CH₂Cl₂, 96%

1) LiHMDS, THF
2) benzyl chloroformate, Et₃N
52% over 2 steps

1) TIPSCI, imidazole, DMAP, 89%
2) Pd/C, H₂, (Boc)₂O,
MeOH
3) Ag₂O, Mel, DMF
50 °C, 94% over 2 steps

LiOHₐq, THF, MeOH
then allyl bromide, K₂CO₃
DMSO, 92%
Thiazoline Formation and Coupling to NMeOHILe Fragment

Partial racemization at C\textsubscript{\alpha} of L-alanine residue
Completion of Synthesis

1) [Pd(PPh₃)₄], N-methylaniline, CH₂Cl₂
2) Et₂NH, MeCN
3) HATU, DIEA, DMF/CH₂Cl₂
4) TBAF, THF, 27% over 4 steps

halipeptin A
Nicolaou’s Retrosynthesis
Hydroxydecanoic Acid Fragment Assembly

1) EtMgBr, Cul
THF, 0 °C, 99%
2) TBSOTf, 2,6-lutidine,
0 °C, 99%

n-BuLi, LiCl, i-Pr₂NH
THF, -78 °C, then

1) NaH, Mel, THF, 95%
2) n-BuLi, i-Pr₂NH, BH₃ NH₃
THF, -78 °C to -25 °C, 82%
3) Swern oxidation

LiOHaq, MeOH/H₂O, 99%

10 steps, 44% overall yield
Hydroxy-isoleucine Methyl Ester Fragment Assembly

1) TBDPSCI, imidazole, CH$_2$Cl$_2$, 99%

2) n-BuLi, p-formaldehyde

Et$_2$O, -78 to 25°C, 72%

HO

OTBDPS

H$_2$, Pd/BaSO$_4$, quinoline

MeOH, 98%

HOOC

OTBDPS

AlMe$_3$, hexanes, 80%

Me

OTBDPS

Me

OTf

1) NaN$_3$, DMF, 75%

2) H$_2$, Pd/C, EtOH, 99%

In the case of halipeptin D, this fragment was constructed starting with

HOOC

OTBDPS

O
Assembly of Building Blocks into Thioamide

1) NaH, MeOTf
   THF, 0 °C, 83%
2) HCl, THF, 100%

1) PMe₃, toluene, 79%
2) H₂, Pd(OH)₂/C, EtOH, 100%
3) H₂S (excess), MeOH/Et₃N

In the case of halipeptin D, this fragment was used instead:
First Attempt at Synthesis of Halipeptin D

1. **1)** Me H2N S N MeO N Me O
   - PyAOP, DIEA, DMF, 92%
   - 2) TBSOTf, 2,6-lutidine
   - CH2Cl2, 0 °C, 99%
   - 3) Me3SnOH, 80 °C, 52%

2. **1)** Me H2N S N MeO N Me O
   - CH2Cl2, 0 °C, 99%
   - 2) DAST, CH2Cl2
   - -78 °C to 20 °C, 80%

3. **1)** Me H2N S N MeO N Me O
   - CH2Cl2, 38% over 2 steps

epi-isoleucine halipeptin D
Revised Completion of Synthesis of Halipeptin D

1) Me₃SnOH, 1,2-dichloroethane
   90 °C, 85%
2) PMe₃, THF/H₂O

18% of epi-halipeptin D obtained
Completion of Halipeptin A

1) Me₃SnOH, 1,2-dichloroethane
90 °C, 82%
2) PMe₃, THF/H₂O

DAST, CH₂Cl₂
-78 °C to 20 °C, 85%

PyAOP, DIEA, DMF, 71%

halipeptin A
5% epi-halipeptin A obtained
Synthesis of Halipeptin Analogue: *epi*-halipeptin D

- More stable than naturally occurring halipeptin D

![Chemical structure and reaction scheme]

1) CbzHN\(\text{OH}\) \(\xrightarrow{\text{CDI, CH}_2\text{Cl}_2, 69\%}\) \(\xrightarrow{\text{2) PMe}_3, \text{toluene, 80}\%}\) only *epi*-halipeptin D obtained
Biological Evaluations of Synthetic Halipeptins A and D and Analogues

  - None exhibited potent cytotoxic properties, despite previous report by Faulkner-Manam
  - Halipeptin A, halipeptin D and *epi*-oxazoline D had the most potent anti-inflammatory properties, with *epi*-oxazoline D exhibiting the most potency.