The Amphidinolide T-Series

How a Total Synthesis Evolves Over Time

Jason M. Stevens
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**Amphidinolide Natural Products**

- Isolated in 2000 from marine dinoflagellates of the genus *Amphidinium* living in symbiosis with Okinowan acoel flatworm *Amphiscolops*

- Have exhibited significant antitumor properties and cytotoxicity against a variety of NCI tumor cell lines as well as human carcinoma KB cells

- Consist of highly oxygenated, stereochemically rich macrolactones ranging from 12 to 29 atoms with various degrees of unsaturation.
Total Synthesis of the T-Series

- Amphidinolides T1 and T3-5 have been synthesized to date
- The first total synthesis of T4 was reported by Fürstner in 2002 and T1, T3, T4, and T5 in 2003.
- The total synthesis of Amphidinolide T1 was first reported by Ghosh in 2003.
- The Jamison group reported the syntheses of Amphidinolide T1 and T4 in 2004 and 2005.
- In 2006 the Zhao group reported the total synthesis of Amphidinolide T3
- The library of the total synthesis of other Amphidinolides continues to grow steadily
A Glance at the T-Series
Fürstner’s Retrosynthesis

Assembly of the Mukaiyama Substrates

1. DIBAL-H, Toluene, -95 °C
2. (-)-Ipc2B-allyl, Et2O, -100 °C
70% over 2 steps

1. KCN, DMSO
2. DIBAL-H, CH2Cl2, -78 °C
3. PhSO2H, CaCl2, CH2Cl2, 0 °C
78% over 3 steps

HO- is Commercially Available

Me

SO2Ph

Me

Bu2BOTf, Et3N
90%

5 steps

60%

OMOM

OTBS Me

OTBS
Mukaiyama Selectivity

\[
\text{Me}\xrightarrow{\text{SnCl}_4, \text{CH}_2\text{Cl}_2, -78 \, ^\circ\text{C}} \text{Me} \xrightarrow{\text{Then silyl enol ether}} \text{Me} \\
\text{Nu} \xrightarrow{\text{OMOM}} \text{Nu} \\
\]
Negishi Coupling Partners

1. L-Selectride gives -OH down - 72%
   1b. LAH (5 eq) LiI (10 eq) gives -OH up - 70%

2. KHMDS, TBDPSCI, THF - 77%
3. p-TsOH, MeOH - 75%
4. PPh3, I2, Imidazole, toluene - 80%
Negishi Acyl Chloride Coupling

1. Zn/Cu Couple, TMSCl, Toluene, DMA
2. Pd$_2$(dba)$_3$ cat., P(2-furyl)$_3$ cat., 40-50%

THF is cleaved under these conditions.
Olefin Issues

1. Grubbs Catalyst, CH$_2$Cl$_2$, reflux*
2. H$_2$ (1 atm), Pd/C, EtOAc
2 steps 74%

CH$_2$Br$_2$, TiCl$_4$

OR

Nysted's Reagent

65%

PPh$_3$=CH$_2$

THF

quant

Peterson Olefination - complete failure

Nysted's Reagent
Endgame
What we learned...

- The Mukaiyama reaction is an efficient method of building the molecule up from the furan
- Protecting groups, if not chosen carefully, may alter the desired conformations of advanced intermediates and produce unfavorable reactivity
- The Negishi coupling is probably not the best coupling reaction
- Olefination is problematic after generation of the macrolactone
- Synthesizing the Northern Hemisphere of the molecule with differentiable protecting groups provides a template for synthesis of 4 of 5 T-Amphidinolides
Ghosh’s Retrosynthesis

Building the Furan

1. TiCl₄, i-Pr₂NEt; 90%
2. LAH, THF, r.t.; 91%
1. PhLi, TrisCl, THF -78 °C - rt; 86%
2. NaCN, DMSO 80 °C; 95%
3. aq. HCl, MeOH rt; 98%

DIBAL-H, -78 °C,
then TMS(CH₂)₂OH, p-TsOH
MgSO₄, r.t.

91%
Mukaiyama Precursor

1. H₂, Pd/C, EtOAc
2. (ClCO)₂, DMSO, Et₃N
3. Ph₃P=CH₂, THF

82% over 3 steps

Grubbs Cat
40 °C CH₂Cl₂

96%

1. H₂, Pd/C, EtOAc
2. BnOH, n-BuLi
3. HSO₂Ph, CaCl₂ CH₂Cl₂, rt

79% 3 steps
Silyl Enol Ether Construction

1. TiCl₄, i-Pr₂NEt
2. TIPSOTf, i-Pr₂NEt₂ 0 °C
3. DIBAL-H, -40 °C
4. I₂, PPh₃, Imidazole, rt

76% over 4 steps

1. TPAP, NMO, rt
2. Cp₂TiMe₂, THF 80 °C

84% over 2 steps

1. Li/NH₃ -33 °C, THF
2. LAH, THF, rt
3. NBS, 0 °C - rt

no yield for PG removal
82% 2 steps

1. TPAP, NMO, rt
2. MeMgBr -78 °C - rt
3. TPAP, NMO, rt
4. LiHMDS, TBSCI, HMPA -78 °C - rt

no yield reported for ox. or grignard addition
Endgame

1. HF-pyr, pyr
2. H₂, Pd/C
3. 2,4,6-(Cl₃)PhCOCl
   i-Pr₂NET, then DMAP toluene
4. Zn, NH₄Cl, EtOH, 80 °C

38% over 4 steps
no yield reported for hydrog.
Improvements?

• The olefin was protected in this synthesis although it seems the protection wasn’t very effective.
• The furan was used as the foundation for building up the molecule and its construction was more concise.
• RCM was an effective means of coupling for generation of the side chain prior to the macrocyclization.
• Yamaguchi conditions provided to be an effective means of completing the synthesis.

![Chemical structure diagram]
Jamison Retrosynthesis

Aldehyde Alkyne Coupling

\[ \text{Aldehyde Epoxide Coupling} \]
Lactone Precursor

1. LDA, LiCl
2. NaOH, t-BuOH, MeOH  
89% over 2 steps

AcO

(CH2)4OTBS

88%, > 95:5 dr

Bu3Sn

Et2OBF3, CH2Cl2

-78 °C - rt

PhI, cat CuI,
cat. Pd(PPh3)4
pyrrolidine

98%

PhI2, PPh3, imidazole

73%

1. LDA, LiCl
2. NaOH, t-BuOH, MeOH

89% over 2 steps
Epoxide-Alkyne Coupling

1. LDA, THF; PhCCCH$_2$Br
2. LAH, THF
3. TBSCl, imidazole, DMF

70% over 3 steps

Ni(COD)$_2$ (10 mol%) Bu$_3$P (20 mol%) Et$_3$B

81% yield 99% dr

Jamison, T.F.; Molinaro, C. J. Am. Chem. Soc. 2003, 125, 8076
Endgame

Key Steps in the T4 Synthesis

1. O\text{Me} \text{CB}_4, \text{PPh}_3 \rightarrow \text{Br} \text{Me} \text{CB} \text{Ph}_3 \rightarrow \text{MeLi, TMSCl} \rightarrow \text{Me}_3\text{Si}

2. O\text{Me} \text{Ni}(0) \rightarrow \text{LnNi} \text{O} \rightarrow \text{R} \text{Ni} \text{O} \rightarrow \text{Ph} \text{Ni} \text{O}

3. Ph \text{Ni} \text{O} \text{BEt}_2 \rightarrow \text{Ph} \text{Ni} \text{OBEt}_2 \rightarrow \text{Ph} \text{Ni} \text{OBEt}_2 \rightarrow \text{Ph} \text{Ni} \text{OBEt}_2

4. Ph \text{Ni} \text{OBEt}_2 \rightarrow \text{Ph} \text{Ni} \text{OBEt}_2 \rightarrow \text{Ph} \text{Ni} \text{OBEt}_2

5. \text{Ph}\text{Ni} \text{OBEt}_2 \rightarrow \text{Ph}\text{Ni} \text{OBEt}_2 \rightarrow \text{Ph}\text{Ni} \text{OBEt}_2

6. T4
**Improvements?**

- Demonstrated that the molecule can tolerate a fair amount of manipulation during the late stages
- The conformation of the molecule in the late stages can terminate both internal and external means of stereocontrol
- Selective oxidative cleavage can be a useful means of protection
Zhao’s Retrosynthesis

1,3-Dithiane Addition

Macrolactonization

Building the Furan

1. LAH, THF
2. TBSCI, Imidazole, DMF 0 °C
3. Ac₂O, DMAP, Et₃N
4. TBAF
5. DMP, CH₂Cl₂

86% over 5 steps

(R,R)-2-diamino-1,2-diphenylethanebis(sulfonamide), BBr₃, CH₂Cl₂, then allyltributylstannane rt 6h, then -CHO -78 °C 2 h

85%, dr > 99:1

1. TsCl, pyr, rt
2. KOH, diglyme, glycol, 40 °C
3. BH₃Me₂S, THF then 30% H₂O₂, NaOH
4. I₂, PPh₃, imidazole, THF

99%, 99%, 83%, 95%

1. n-BuLi, HMPA, THF, -78 °C then R-I
2. Na-Hg, EtOH

80% over 2 steps

D-Glutamic acid
Generating the Aldehyde

1. 80% HOAc
2. PPh₃, I₂, imidazole, THF
3. 1,3-dithiane, THF/HMPA then R-OH
4. NaHCO₃, CH₃I, CH₃CN-H₂O (4:1)
   rt 16 h 95%

95%, 91%, 83%, 95%
Umpoles Everywhere!

1. [(R)-BINAP-RuCl₂](DMF), H₂, MeOH, 20 atm, 100 °C
2. TBSCI, imidazole, DMF
3. DIBAL-H, CH₂Cl₂, -78 °C
4. HS(CH₂)₃SH, BF₃Et₂O

all steps ~92%

1. i-PrNEt₂, BOMCI
2. LAH
3. PPh₃, I₂, imidazole

90% over 3 steps

1. I₂, NaHCO₃, acetone/H₂O (5:1) 0 °C
2. Cp₂TiMe₂, toluene 110 °C

82%, 86%

1. Li/NH₃, THF, -78 °C
2. DMP, CH₂Cl₂
3. ZnCl₂, Me₃SiS(CH₂)₃SSiMe₃

Et₂O, 0 °C - rt

99%, 95%, 92%
Back to Asymmetric Reductions

1. t-BuLi, HMPA/THF (1:9)
2. DMP, NaHCO₃, CH₂Cl₂
80% 1:1.7 dr, 90%

NaBH₄ - No selectivity
L- Selectride - N.R.
LiBH₄ - 88% down
CBS Red. - 68% up
isolated yields
1. Ac$_2$O, DMAP, pyridine
2. DDQ, CH$_2$Cl$_2$/H$_2$O (10:1), 30 h

92%, 95%

1. PCC, NaOAc, CH$_2$Cl$_2$, 4 A MS 0 °C
2. AgNO$_3$, NaOH, THF, H$_2$O, 0 °C
3. HF-pyr THF, rt
4. LiOH, MeOH/H$_2$O (5:1) 40 °C

96%, 81%, 94%, 95%

1. 2,4,6-Cl$_3$PhCOCl, i-PrNEt$_2$ 45 °C
then DMAP, toluene
2. PhI(CF$_3$CO$_2$H)$_2$, MeOH/H$_2$O (10:1) 15 °C

66%, 82%
Improvements?

• The olefin was installed early to prevent future problems and carried through successfully
• The furan was again used as a foundation for building the molecule although it was prepared in a different way
• The macrolactonization that was demonstrated by Ghosh was effectively used
• The current synthesis provides a template for preparation of future amphidinolides
Final Thoughts

• After several total syntheses the reactivity has been sufficiently investigated
• Of the four syntheses each has its own highlights and drawbacks with the “best” synthesis probably as a blend of each
• The broad scope and report by Fürstner provided future researchers a template to follow and improve upon
• The evolution is apparent in that each subsequent synthesis drew upon what was learned from previous efforts to continuously improve how the target molecule is prepared