Total Synthesis of Amphidinolide F

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*Angew. Chem. Int. Ed. 2013, 52, 9534-9538

amphidinolide F

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Wipf Group Current Literature
Sep. 21, 2013
Introduction

Marine dinoflagellates have proved to be a subject of considerable attention as a new valuable source of bioactive compounds.

More than thirty macrolides have been isolated from different strains, which are collectively called amphidinolides.

Most of them exhibiting a potent cytotoxicity against human cancer cell lines in micromolar, nanomolar, or even subpicomolar concentrations in vitro.
In 1991, a new natural product Amphidinolide F was isolated from a dinoflagellate of the genus Amphidinium which was associated with the Okinawan flatworm Amphiscolops magniviridis and a different species from those reported previously.

Amphidinolide F

Amphidinolide C: X = OH, Y = H
Amphidinolide C2: X = OAc, Y = H
Amphidinolide C3: X, Y = O

Cytotoxic activity (IC50)

<table>
<thead>
<tr>
<th></th>
<th>Isolation yield (%)</th>
<th>murine lymphoma LI210 cells</th>
<th>human epidermoid carcinoma KB cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphidinolide F</td>
<td>0.0006</td>
<td>1.5 µg/mL</td>
<td>3.2 µg/mL</td>
</tr>
<tr>
<td>Amphidinolide C</td>
<td>0.0015</td>
<td>5.8 ng/mL</td>
<td>4.6 ng/mL</td>
</tr>
<tr>
<td>Amphidinolide C 2</td>
<td>0.00015</td>
<td>0.8 µg/mL</td>
<td>3.0 µg/mL</td>
</tr>
<tr>
<td>Amphidinolide C 3</td>
<td>0.00006</td>
<td>7.6 µg/mL</td>
<td>10.0 µg/mL</td>
</tr>
</tbody>
</table>
Due to their impressive potential bioactivity, unique structure, and low natural accessibility, total synthesis therefore becomes an important potential source.

20 years passed since Amphidinolide F was isolated, no total synthesis was reported until 2012 (totally 34 steps).

Retrosynthetic analysis

amphidinolide F

A

B

C

D

E

F
The synthetic method for the fragment D

1. TBSCI, TEA, 86%
2. Pd(OAc)₂, PPh₃, Et₂Zn, 87%
3. TBSCI, TEA, 86%
4. TEMPO, KBr, NaOCl, 86%
5. PPTS, MeOH, DCM, 80%
6. TBSOTf, 2,6-lutidine
7. SO₃, pyridine, iPr₂NEt
8. TBSOTf, 2,6-lutidine
9. PhMe₂SiLi, CuCN, MeI
10. K₂CO₃, MeOH, 88%
11. NIS, MeCN, benzene
12. PhMe₂Si, nBuLi, MeI, 97%
The synthetic method for the fragment E

1. **13**
   - Reaction: \( \text{TrCl, pyridine} \)
   - Yield: 91%

2. **14**
   - Reaction: \( \text{LDA, MeI, THF} \)

3. **15**
   - Reaction:
     - a. \( \text{Dibal-H, DCM} \)
     - b. \( \text{Ph₃P=CHCOOEt, 85\%} \)

4. **16**
   - Reaction: \( \text{OTBS, pyridine, 91\%} \)

5. **17**
   - Reaction:
     - a. \( \text{TrO, TFA/EtOH, 86\%} \)
     - b. \( \text{SO₃/pyridine, iPr₂NEt} \)

6. **18**
   - Reaction:
     - a. \( \text{L-proline, DMF, 66\%} \)

7. **19**
   - Reaction: \( \text{TBSOTf, pyridine, 91\%} \)

8. **20**
   - Reaction: \( \text{KHMD, PhNTf₂, THF, 73\%} \)

9. **21**
   - Reaction: \( \text{TfO, OTBS, TBSO} \)

10. **22**
    - Reaction:
        - \( \text{Pd₂(dba)₃, P(2-furyl)₃, Me₃Sn, LiCl, 81\%} \)

11. **23**
    - Reaction:
        - \( \text{KOH, EtOH, THF, H₂O, 98\%} \)
The synthetic method for the fragment F

\[
\begin{align*}
24 & \xrightarrow{\text{Propyne, nBuLi, BF}_3\text{Et}_2\text{O}} 25 & \text{(nmp)}_2\text{Co, tBuOOH} \quad 87\% \\
& \xrightarrow{\text{SO}_3\text{pyridine, iPr}_2\text{NEt}} 27 & \text{Br, tBuLi, ZnBr}_2 \quad 86\% \\
& \xrightarrow{\text{O}_2, \text{iPrOH}} 26 & \text{a. } \text{Br, tBuLi, ZnBr}_2 \quad 84\% \\
& \text{b. } \text{amine, tBuLi} & \text{85\%} \\
\end{align*}
\]
Fragment Coupling and Completion of the Total Synthesis

\[ \text{28} + \text{23} \xrightarrow{2,4,6-	ext{Trichlorobenzoyl chloride, TEA, DMAP, toluene, 80\%}} \text{29} \]

\[ \text{30} \xrightarrow{\text{A}} \text{31} \]

\[ \text{31} \xrightarrow{\text{B}} \text{32} \]

\[ \text{32} \xrightarrow{\text{a. TPAP, DCM, 70\%; b. HF,NEt3, TEA, MeCN, 60\%}} \text{amphidinolide F} \]

\[ \text{a. } [\text{C}_2\text{H}_2\text{PtCl}_2]_2, \text{Et}_2\text{O, 97\%} \]

\[ \text{b. PPTS, benzene, 98\%} \]

\[ \text{12} \xrightarrow{\text{Pd(PPPh}_3)_4, \text{Ph}_3\text{PO}_{2}\text{NBu}_4, \text{CuTC, 56\%}} \text{33} \]

\[ \text{A: 35, toluene, DCM, 73\%; B: PPTS, MeOH, DCM, 87\% (33), 95\% (32); C: 36, toluene, 70\%} \]
Comparison of $^1$H spectra of amphinidal F:

Fürstner et al. (1.4 mg in 180 μL).


Conclusions

• No more than 21 steps and therefore compares favorably with the only other completed approach known in the literature.

• A late-stage interplay of ring-closing alkyne metathesis (RCAM) and $\pi$-acid catalysis nicely solved the selectivity issue arising from the unusual 1,4-dioxygenation pattern decorating the targets polyfunctional backbone.

• The success of this strategy showcases the maturity of these methods and augurs well for future applications.
Thanks!