Total Synthesis of Amphidinolide F

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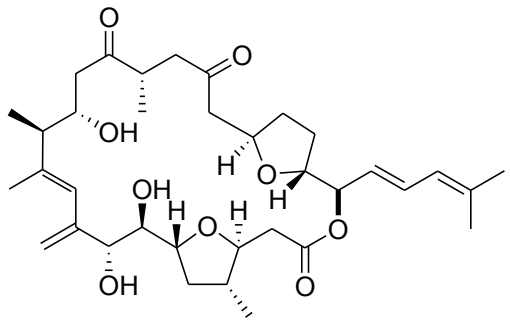
***Angew. Chem. Int. Ed.* 2013, 52, 9534-9538**



amphidinolide F

Feng Zhang

Wipf Group Current Literature

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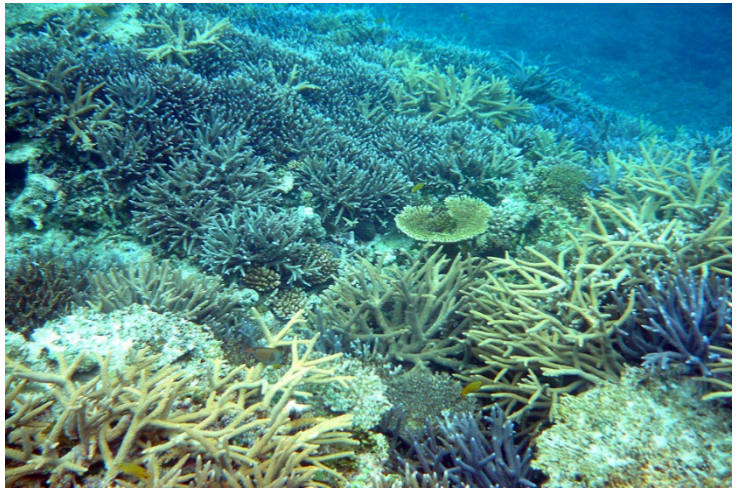
Feng Zhang @ Wipf Group Page 1 of 12 10/2/2013

Introduction



Okinawan marine organisms

Marine dinoflagellates

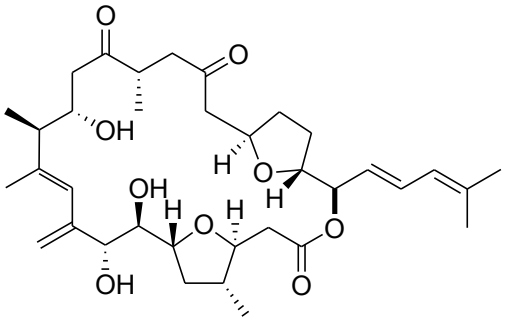
Marine dinoflagellates have proved to be a subject of considerable attention as a new valuable source of bioactive compounds.

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

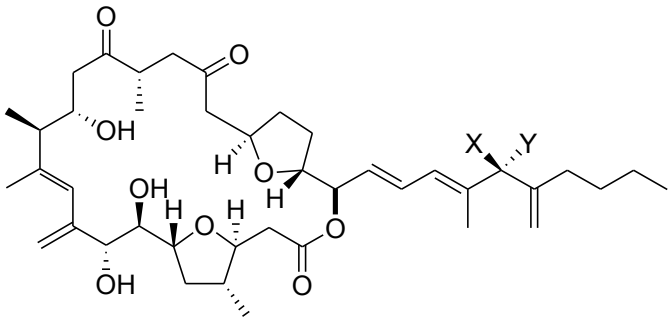
Most of them exhibiting a potent cytotoxicity against human cancer cell lines in micromolar, nanomolar, or even subpicomolar concentrations in vitro.

Feng Zhang @ Wipf Group Page 2 of 12 10/2/2013

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

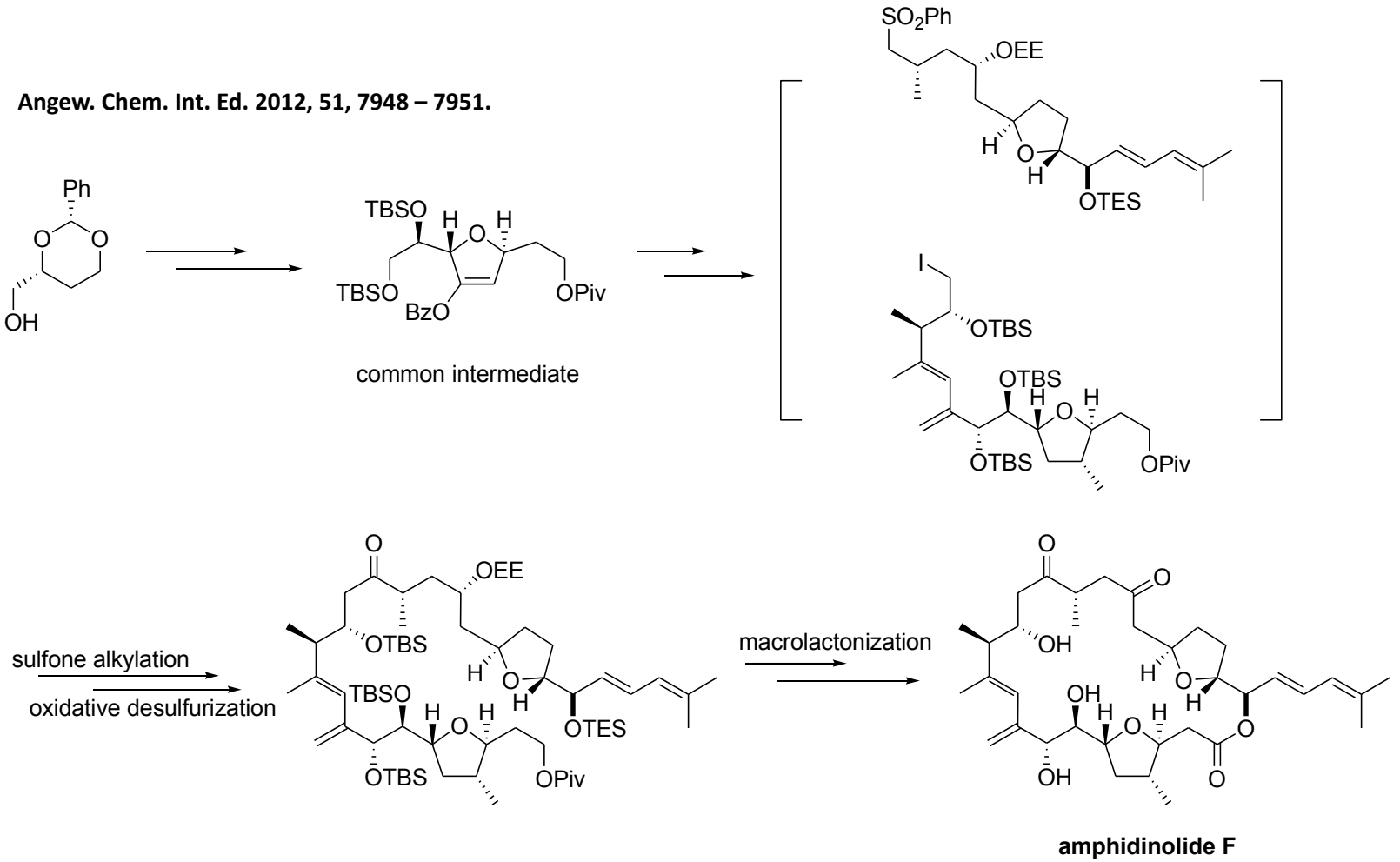
		cytotoxic activity (IC50)	
	Isolation yield (%)	murine lymphoma LI210 cells	human epidermoid carcinoma KB cells
Amphidinolide F	0.0006	1.5 µg/mL	3.2 µg/mL
Amphidinolide C	0.0015	5.8 ng/mL	4.6 ng/mL
Amphidinolide C 2	0.00015	0.8 µg/mL	3.0 µg/mL
Amphidinolide C 3	0.00006	7.6 µg/mL	10.0 µg/mL

Feng Zhang @ Wipf Group Page 3 of 12 10/2/2013

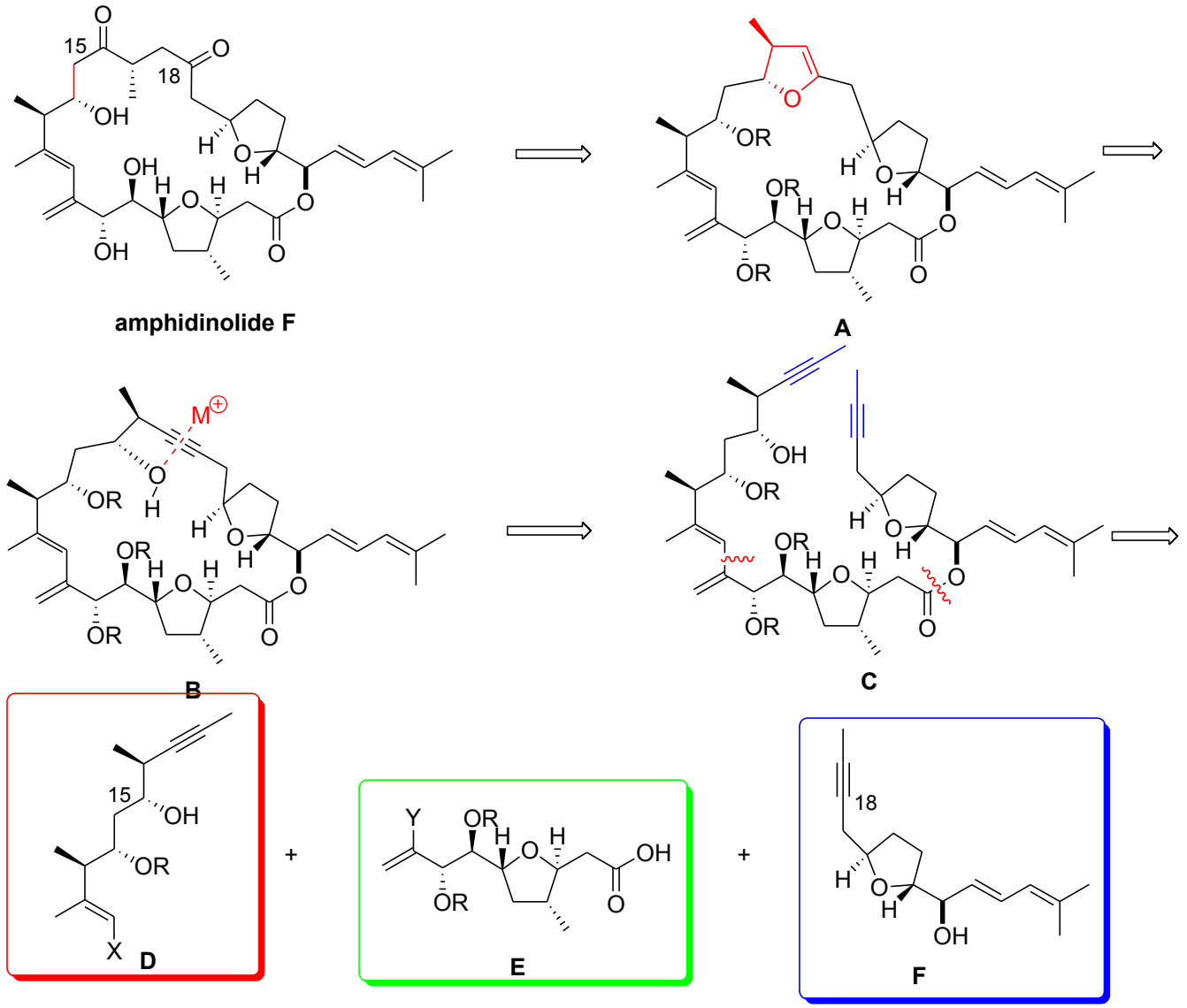
Due to their impressive potential bioactivity, unique structure, and low natural accessibility, total synthesis therefore becomes an important potential source.

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

Angew. Chem. Int. Ed. 2012, 51, 7948 – 7951.

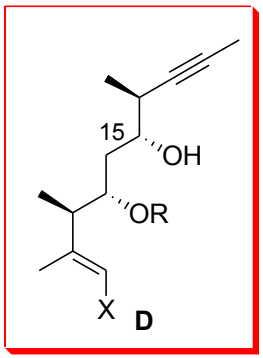


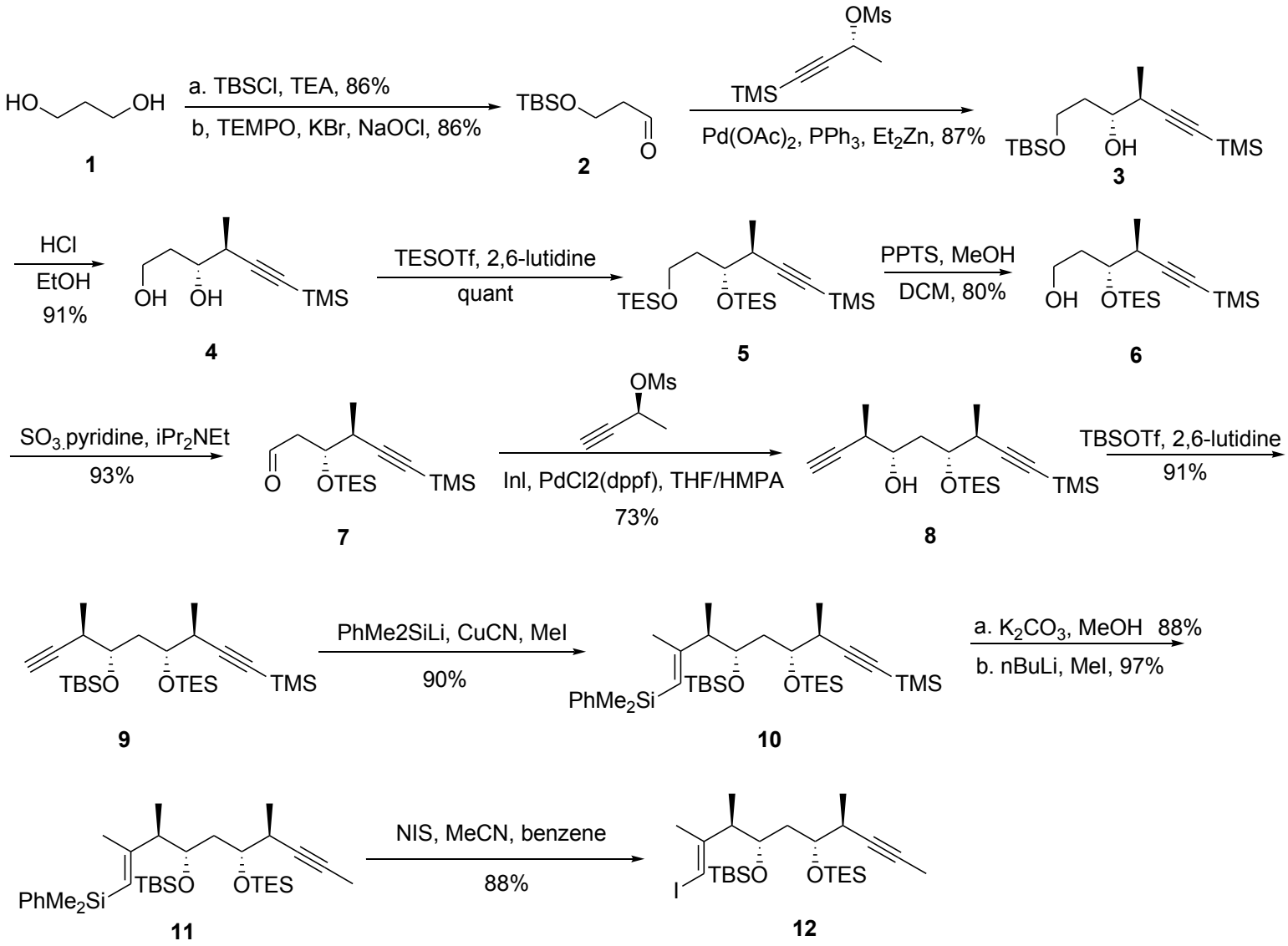
Retrosynthetic analysis



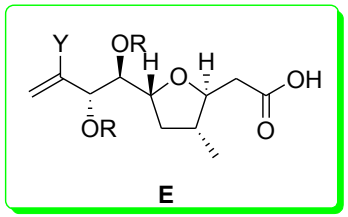
Feng Zhang @ Wipf Group Page 5 of 12 10/2/2013

The synthetic method for the fragment D

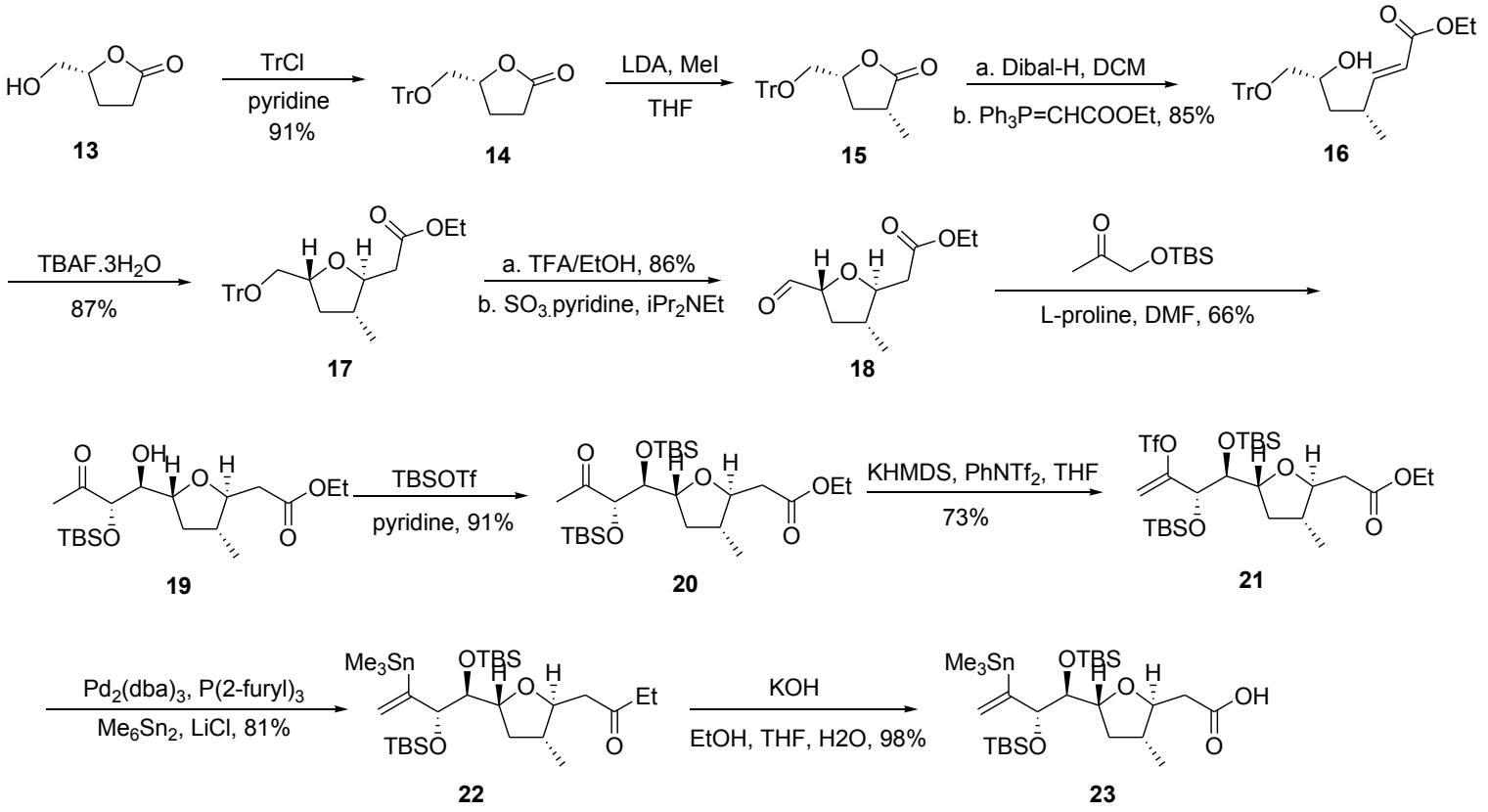




The synthetic method for the fragment E

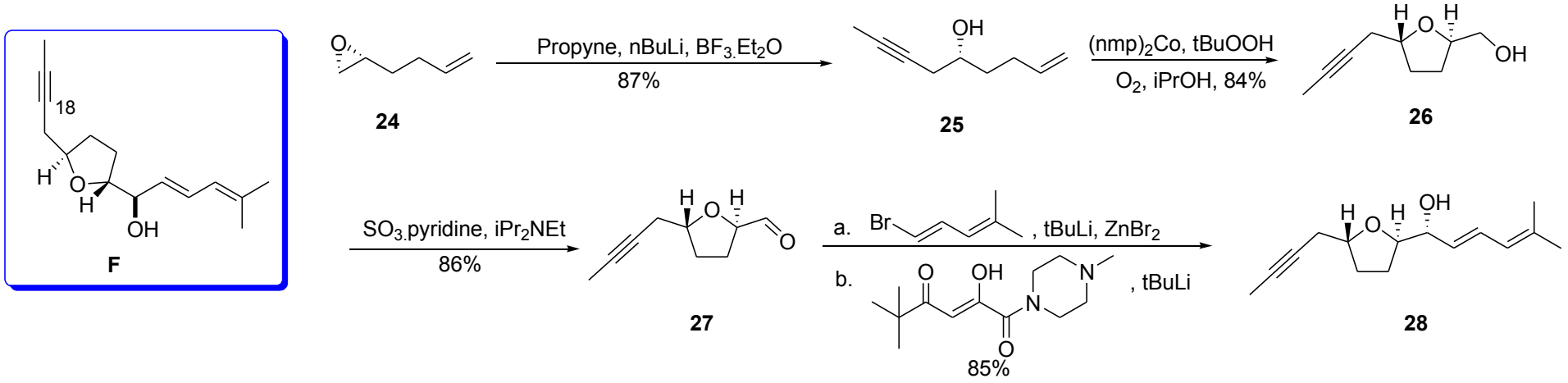


E



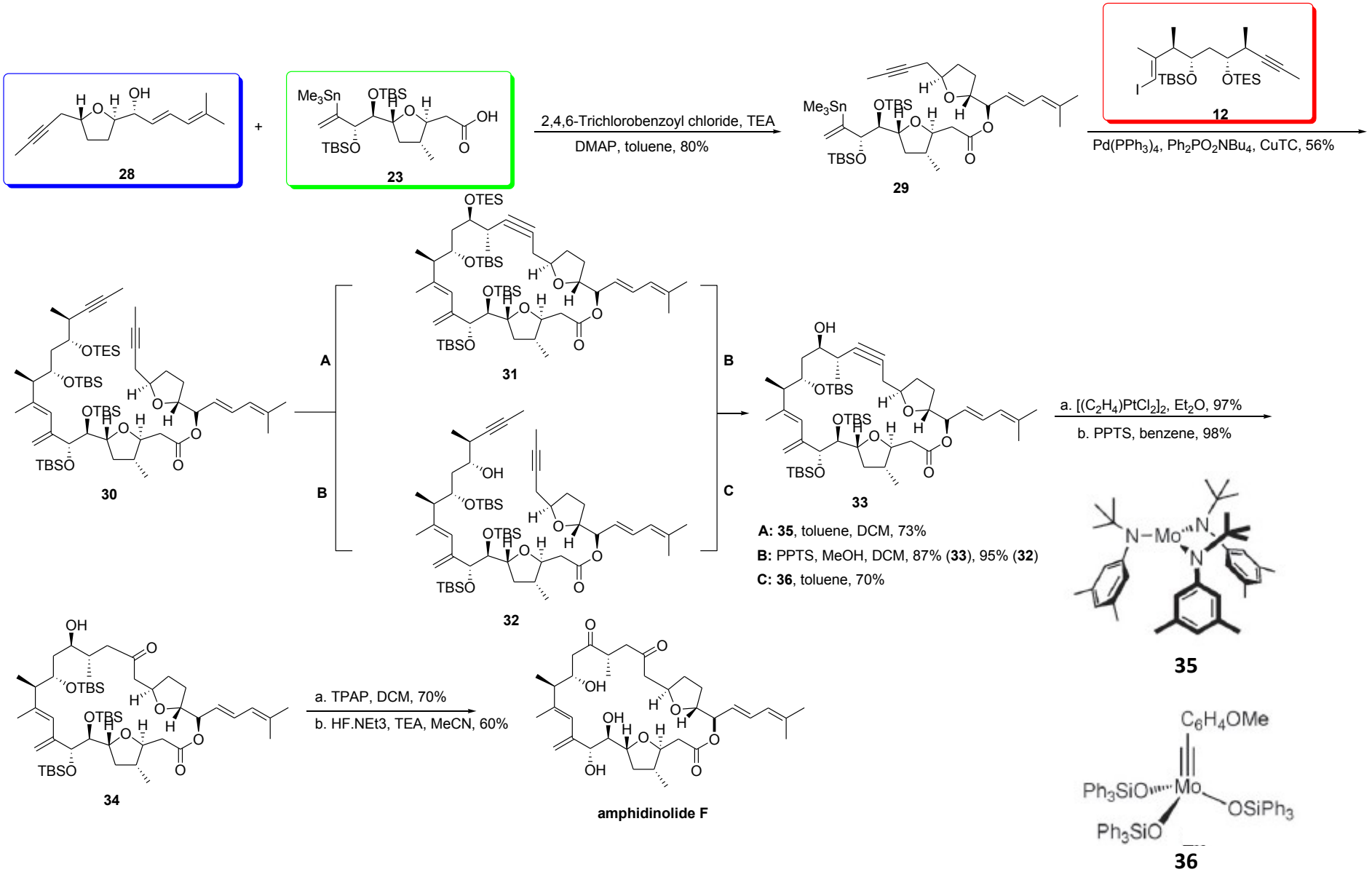
Feng Zhang @ Wipf Group Page 7 of 12 10/2/2013

The synthetic method for the fragment F

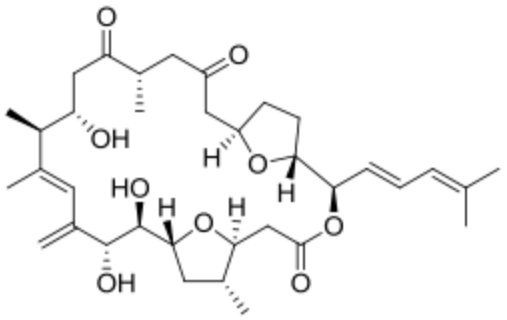


Feng Zhang @ Wipf Group Page 8 of 12 10/2/2013

Fragment Coupling and Completion of the Total Synthesis

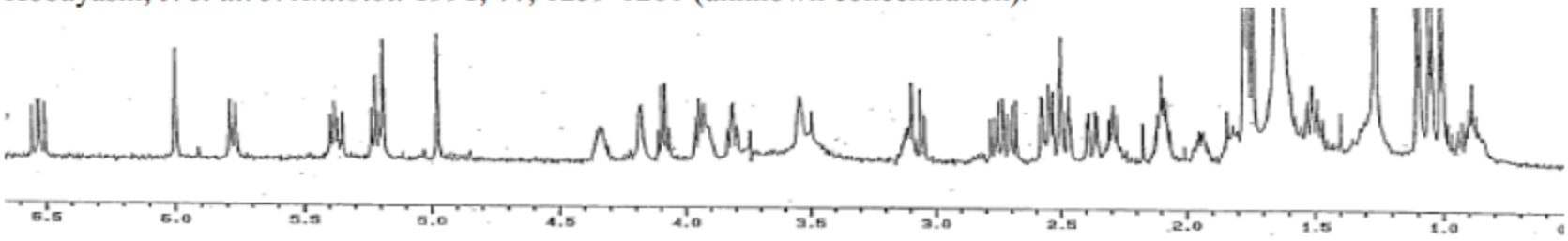


Comparison of ^{1}H spectra of amphidinolide F:

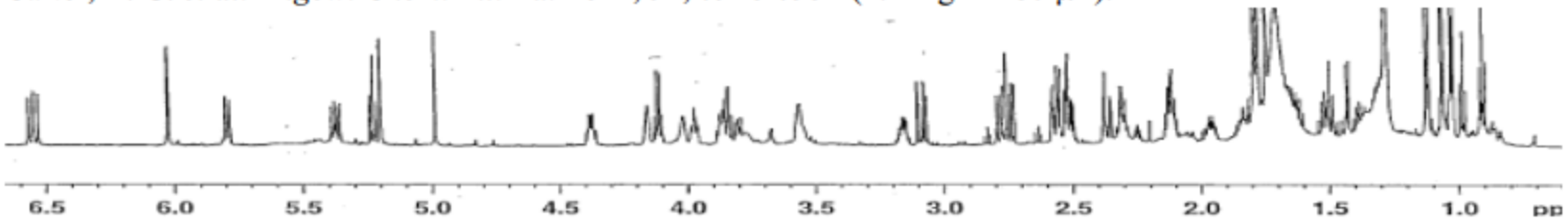


Fürstner *et al.* (1.4 mg in 180 μL).

Kobayashi, J. *et al. J. Antibiot.* **1991**, *44*, 1259-1261 (unknown concentration).



Carter, R. G. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 7948-7951 (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 π-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.

Feng Zhang @ Wipf Group Page 11 of 12 10/2/2013

Thanks!

Feng Zhang @ Wipf Group Page 12 of 12 10/2/2013