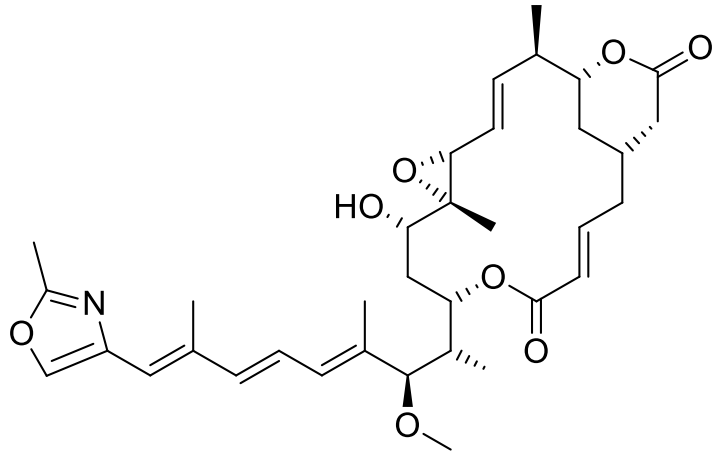
Total Synthesis of the Tubulin Inhibitor WF-1360F Based on Macrocycle Formation through Ring-Closing Alkyne Metathesis

Christian M. Neuhaus, Marc Liniger, Martin Stieger, and Karl-Heinz Altmann

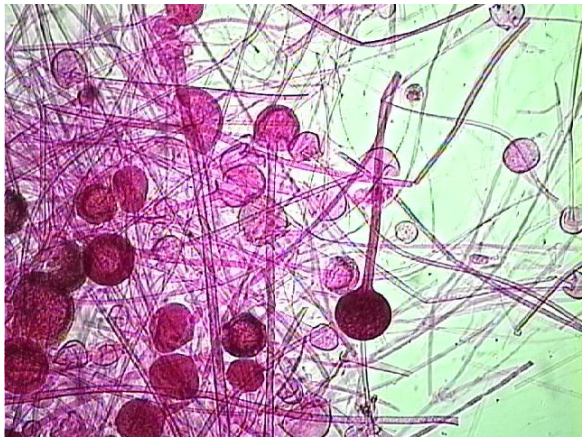
Angew. Chem. Int. Ed. **2013**, *52*, 5866-5870



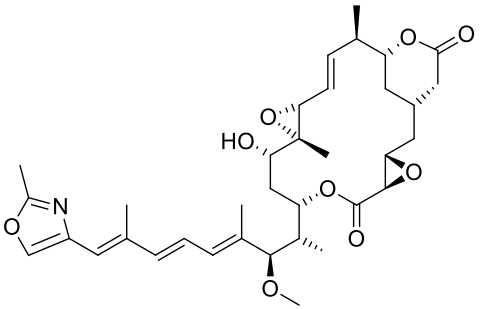
Nicholas Reed
Wipf Group Current Literature
June 8, 2013

Rhizoxin and Cogeners

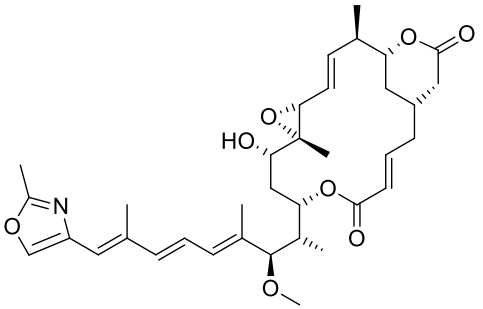
- Isolated from *Rhizopus chinensis* by Okuda and co-workers
  - -Cause of rice seedling blight[1]
  - -Later found to be produced by a bacterial endosymbiont [2]
- Inhibitor of eukaryotic tubulin polymerization
  - -Good in vivo and in vitro activity[3]
  - -Has gone to phase II clinical trials[4]



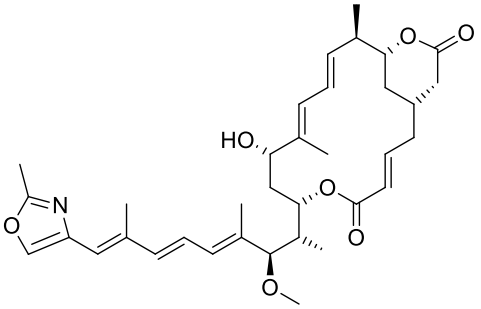
Rhizopus Sporangia



Rhizoxin



WF-1360F

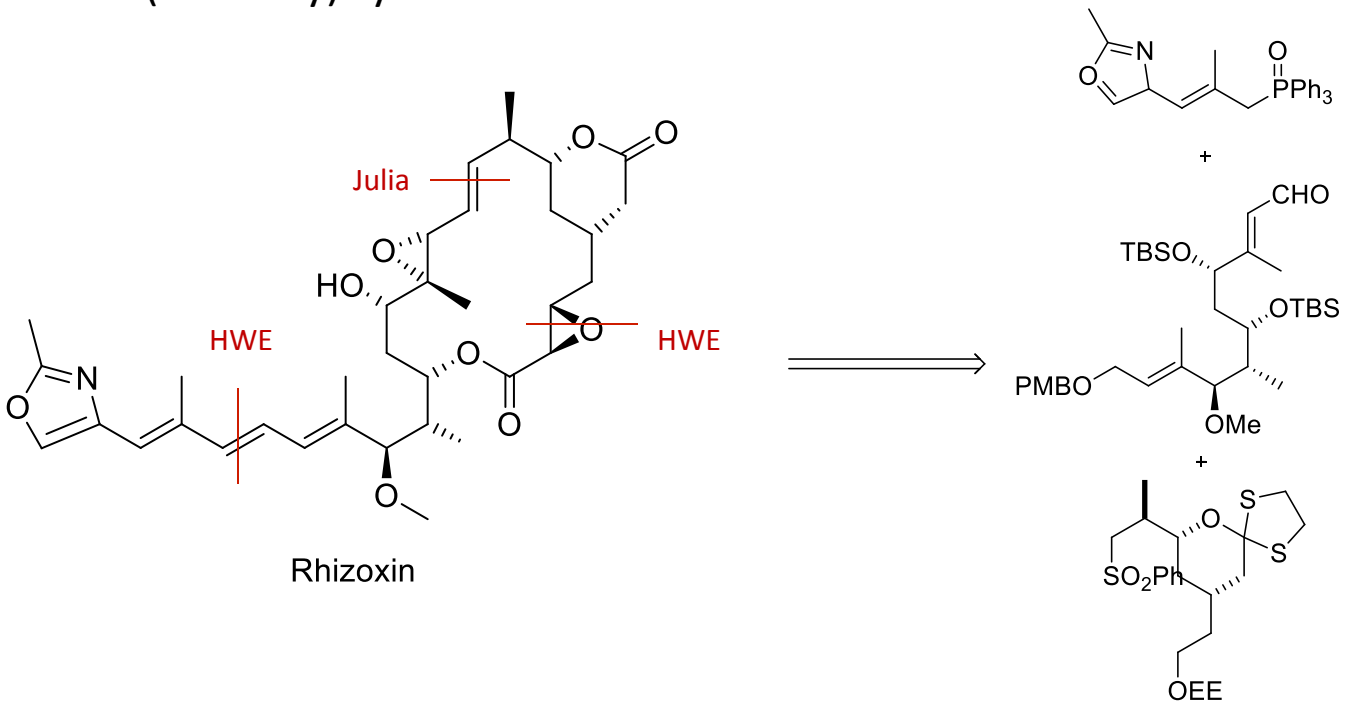


Rhizoxin D

[1] *J. Antibiot.* **1984**, *37*, 354-362
[2] *J. Antibiot.*, **1986**, *39*, 424-429
[3] *Cancer Res.* **1986**, *46*, 381-385
[4] *J. Cancer* **1996**, *73*, 397-399

Previous Syntheses of Rhizoxin (and derivatives)

- First (and only) synthesis of Rhizoxin

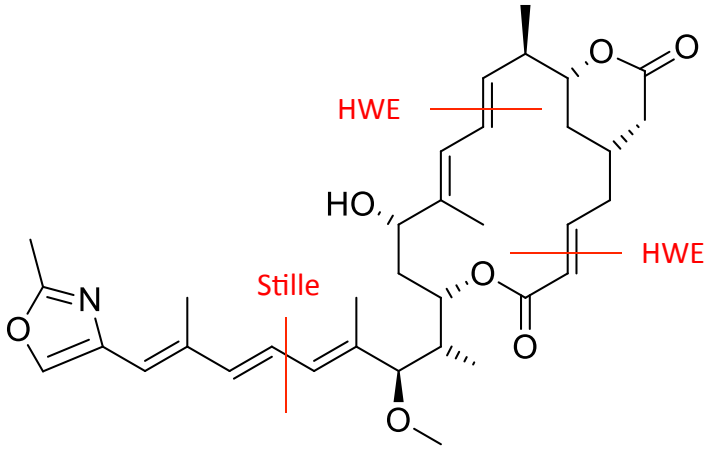


Ohno- .8%, 34 steps (LLS), 52 steps overall

Tetrahedron Lett. **1993**, *34,* 1035-1038
Tetrahedron Lett. **1993**, *34,* 1039-1042

Previous Syntheses of Rhizoxin (and derivatives)

- Most syntheses focus on Rhizoxin D



Rhizoxin D

[1]Kende- 1.7%, 29 steps (LLS), 39 steps overall

[1]*Tetrahedron Lett.* **1995**, *36*, 4741-4744

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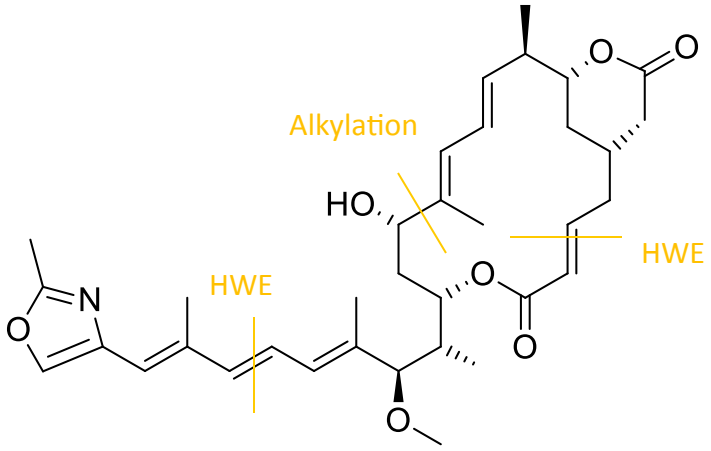

Rhizoxin D

[1]*Tetrahedron Lett.* **1995**, *36*, 4741-4744
[2]*Tetrahedron Lett.* **1997**, *39*, 6825-6828

[1]Kende - 1.7%, 29 steps (LLS), 39 steps overall
[2]Williams - 1.1%, 25 steps (LLS), 35 steps overall

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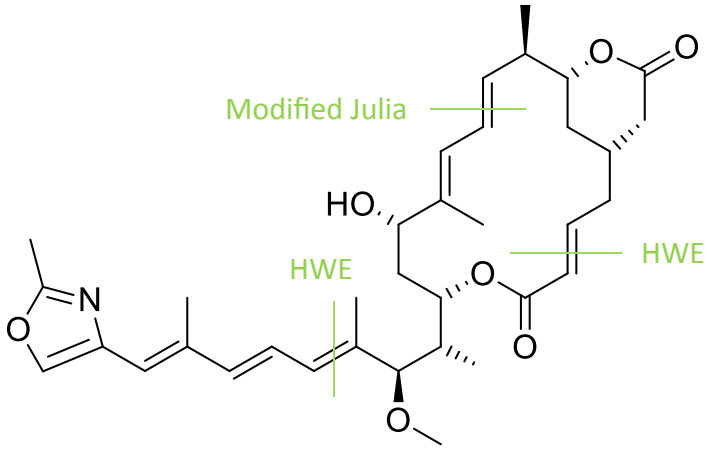

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[3]Leahy - .4%, 28 steps (LLS), 40 steps overall

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[2]*Tetrahedron Lett.* **1997**, *39*, 6825-6828
[3]*Tetrahedron Lett.* **1995,** *36,* 6029-6032
Tetrahedron Lett. **1995,** *36*, 6033-6036

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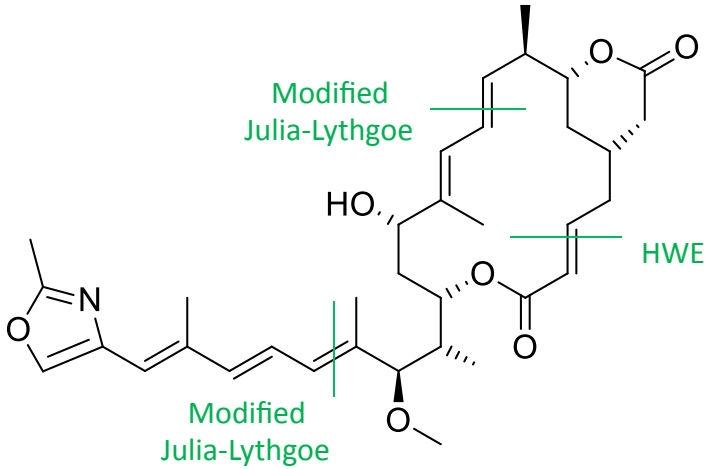

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[4]Keck - .5%, 35 steps (LLS), 44 overall

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[2]*Tetrahedron Lett.* **1997**, *39*, 6825-6828
[3]*Tetrahedron Lett.* **1995,** *36,* 6029-6032
Tetrahedron Lett. **1995,** *36*, 6033-6036
[4]*Angew. Chem. Int. Ed.* **2001**, *40*, 231–234

Previous Syntheses of Rhizoxin (and derivatives)

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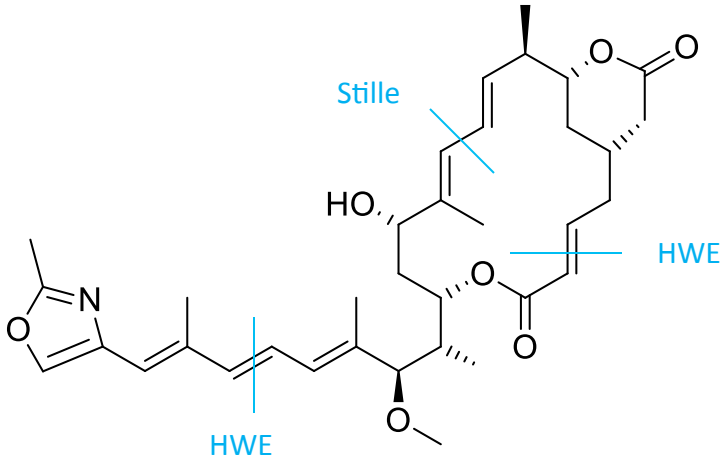

Rhizoxin D

[1]*Tetrahedron Lett.* **1995**, *36*, 4741-4744
[2]*Tetrahedron Lett.* **1997**, *39*, 6825-6828
[3]*Tetrahedron Lett.* **1995,** *36,* 6029-6032
Tetrahedron Lett. **1995,** *36*, 6033-6036
[4]*Angew. Chem. Int. Ed.* **2001**, *40*, 231–234
[5]*Tetrahedron Lett.* **2002**, *43*, 493–497

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[5]Pattenden - .5%, 20 steps (LLS), 28 overall

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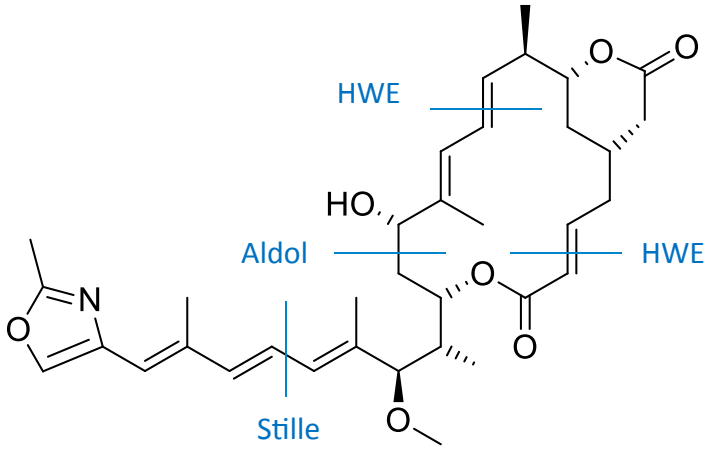

Rhizoxin D

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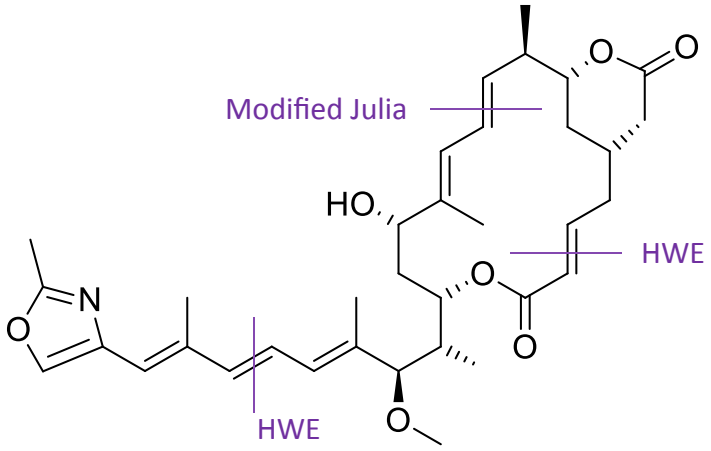
[3]Leahy - .4%, 28 steps (LLS), 40 steps overall
[4]Keck - .5%, 35 steps (LLS), 44 overall
[5]Pattenden - .5%, 20 steps (LLS), 28 overall
[6]White - .3%, 27 steps (LLS), 33 steps overall

[1]*Tetrahedron Lett.* **1995**, *36*, 4741-4744
[2]*Tetrahedron Lett.* **1997**, *39*, 6825-6828
[3]*Tetrahedron Lett.* **1995,** *36,* 6029-6032
Tetrahedron Lett. **1995,** *36*, 6033-6036
[4]*Angew. Chem. Int. Ed.* **2001**, *40*, 231–234
[5]*Tetrahedron Lett.* **2002**, *43*, 493–497
[6] *Tetrahedron Lett*. **1997**, *38*, 7329–7332
Tetrahedron Lett. **1997,** *38*, 7333-7336
J. Org. Chem. **2002**, *67*, 7750-7760

Previous Syntheses of Rhizoxin (and derivatives)

- Most syntheses focus on Rhizoxin D



Rhizoxin D

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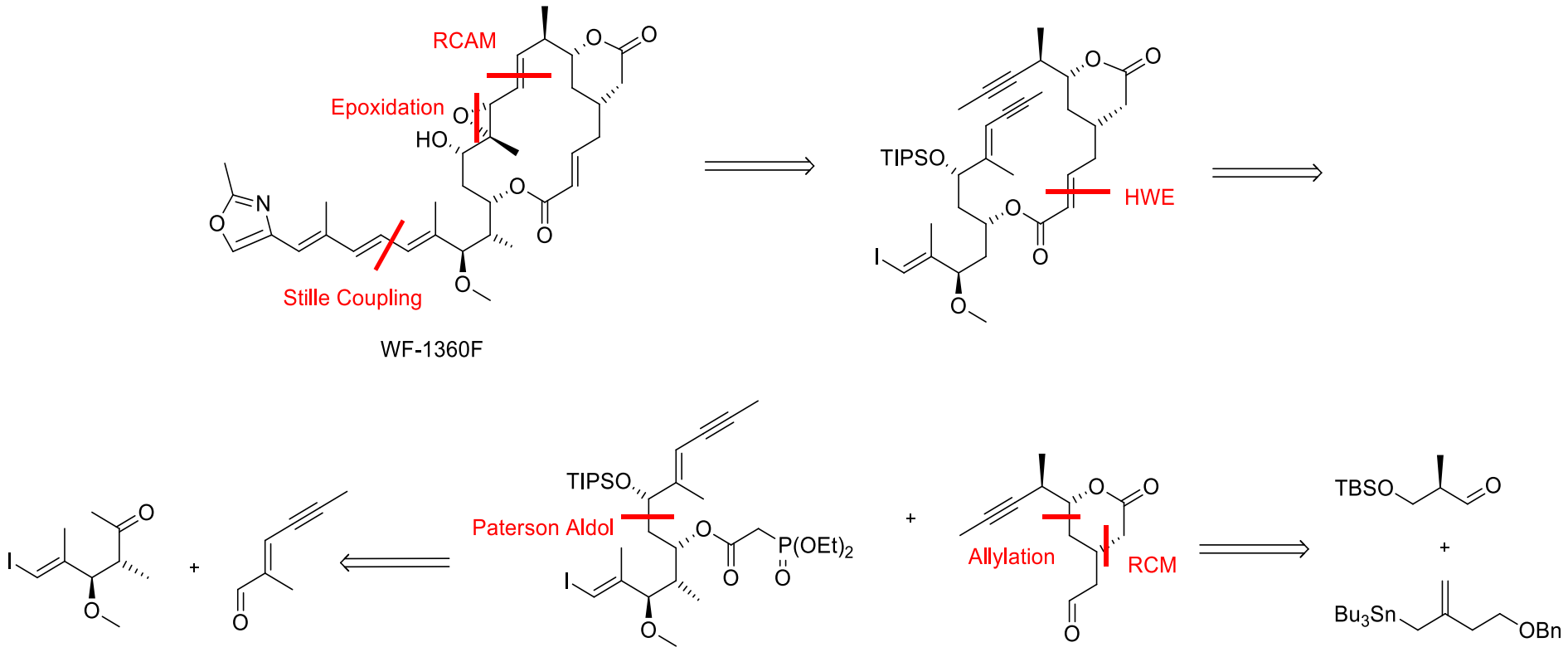
[2]Williams - 1.1%, 25 steps (LLS), 35 steps overall
[3]Leahy - .4%, 28 steps (LLS), 40 steps overall
[4]Keck - .5%, 35 steps (LLS), 44 overall
[5]Pattenden - .5%, 20 steps (LLS), 28 overall
[6]White - .3%, 27 steps (LLS), 33 steps overall
[7]Burke - .6%, 20 steps (LLS), 29 overall

[1]*Tetrahedron Lett.* **1995**, *36*, 4741-4744
[2]*Tetrahedron Lett.* **1997**, *39*, 6825-6828
[3]*Tetrahedron Lett.* **1995,** *36,* 6029-6032
Tetrahedron Lett. **1995,** *36*, 6033-6036
[4]*Angew. Chem. Int. Ed.* **2001**, *40*, 231–234
[5]*Tetrahedron Lett.* **2002**, *43*, 493–497
[6] *Tetrahedron Lett*. **1997**, *38*, 7329–7332
Tetrahedron Lett. **1997,** *38*, 7333-7336
J. Org. Chem. **2002**, *67*, 7750-7760
[7]*J. Org. Chem.* **1998**, *63*, 6952-6967
Org. Lett. **2004**, *6*, 1445-1448

Retrosynthesis



Key Steps: 1. Ring-Closing Alkyne Metathesis
2. Radical Reduction/Isomerization Sequence

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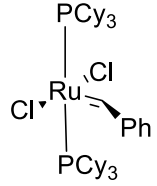
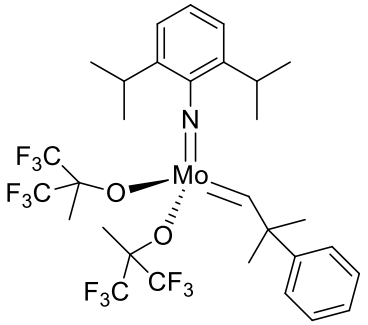
Why Ring-Closing Metathesis?

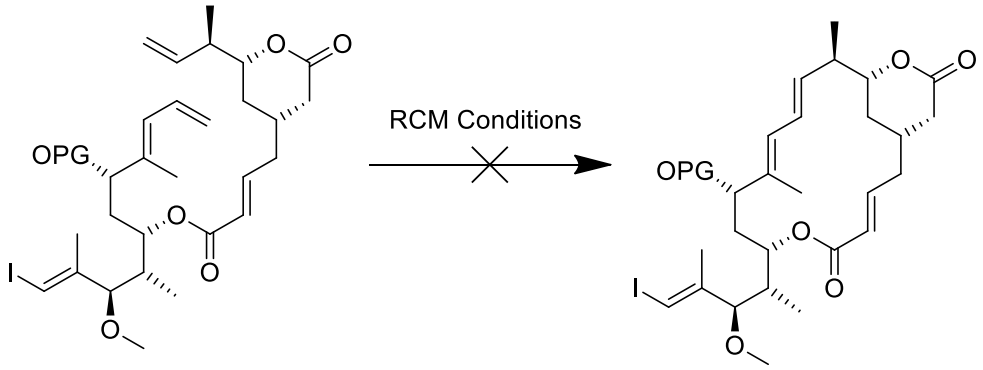
- Good generality, chemoselectivity, functional group tolerance, and predictability
- Utilizes relatively stable alkenes and alkynes instead of cross coupling partners or olefination precursors
- Catalysts are readily available (commercially available)
- Has not been used in the synthesis of these molecules



$112.50 / 1 g
Sigma-Aldrich



$120.00 / 100 mg
Strem Chemicals, Inc.



RCAM strategy utilizes most of the synthesis that had been developed

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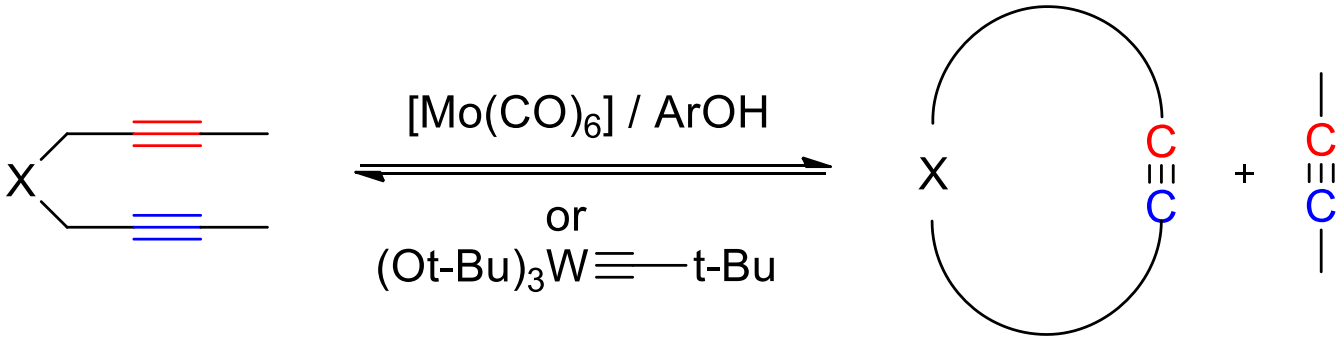
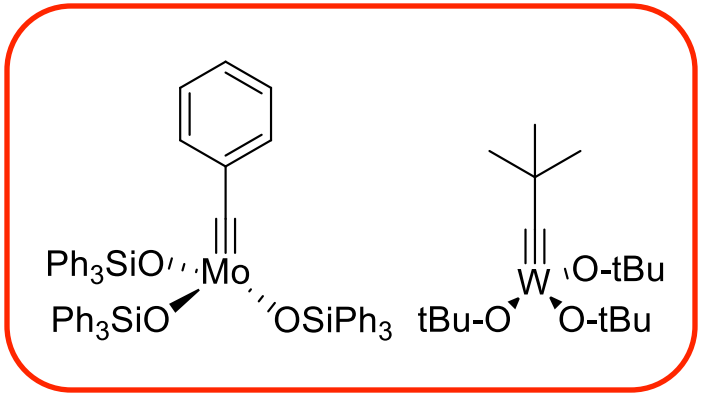
Chem. Comm. **2005**, 2307-2320

Ring-Closing Alkyne Metathesis





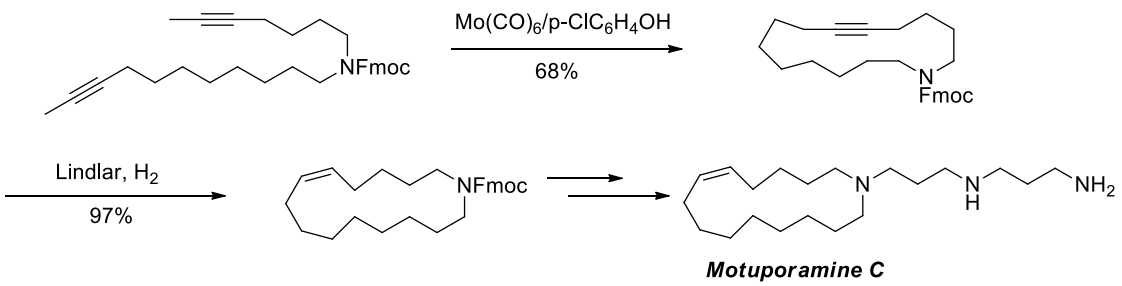
Representative catalysts

Features:
1. Schrock-type carbynes
2. Unreactive towards alkenes
3. Low functional group tolerance relative to Ru-based olefin metathesis catalysts
4. Relatively unstable
5. Limited to non-terminal alkynes*
6. Gives either (E) or (Z)-alkenes by hydrogenation

Chem. Comm. **2005**, 2307-2320
This is changing with recent advances, see Angew. Chem. Int. Ed.* **2012, *51*, 13019-13022

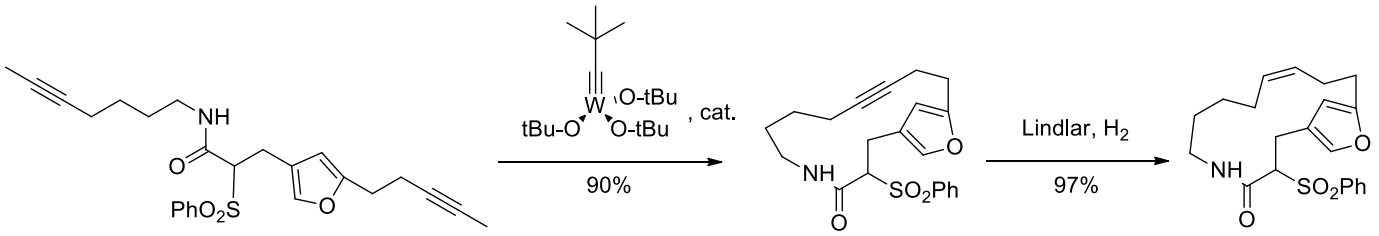
RCAM in Natural Product Synthesis

Motuporamine C



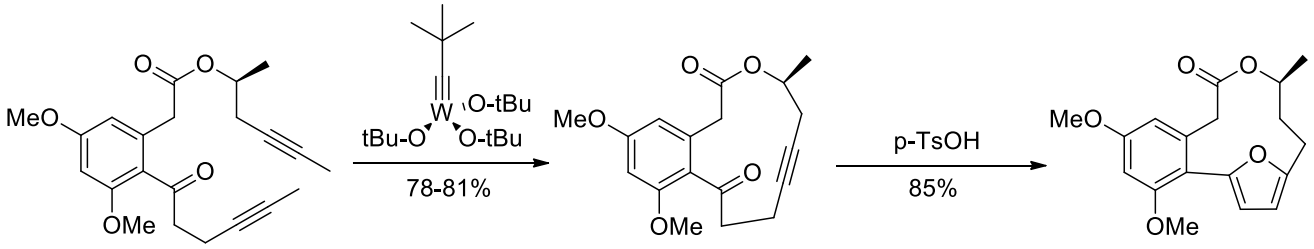
J. Org. Chem., **2000**, *65*, 2608

Nakadomarin



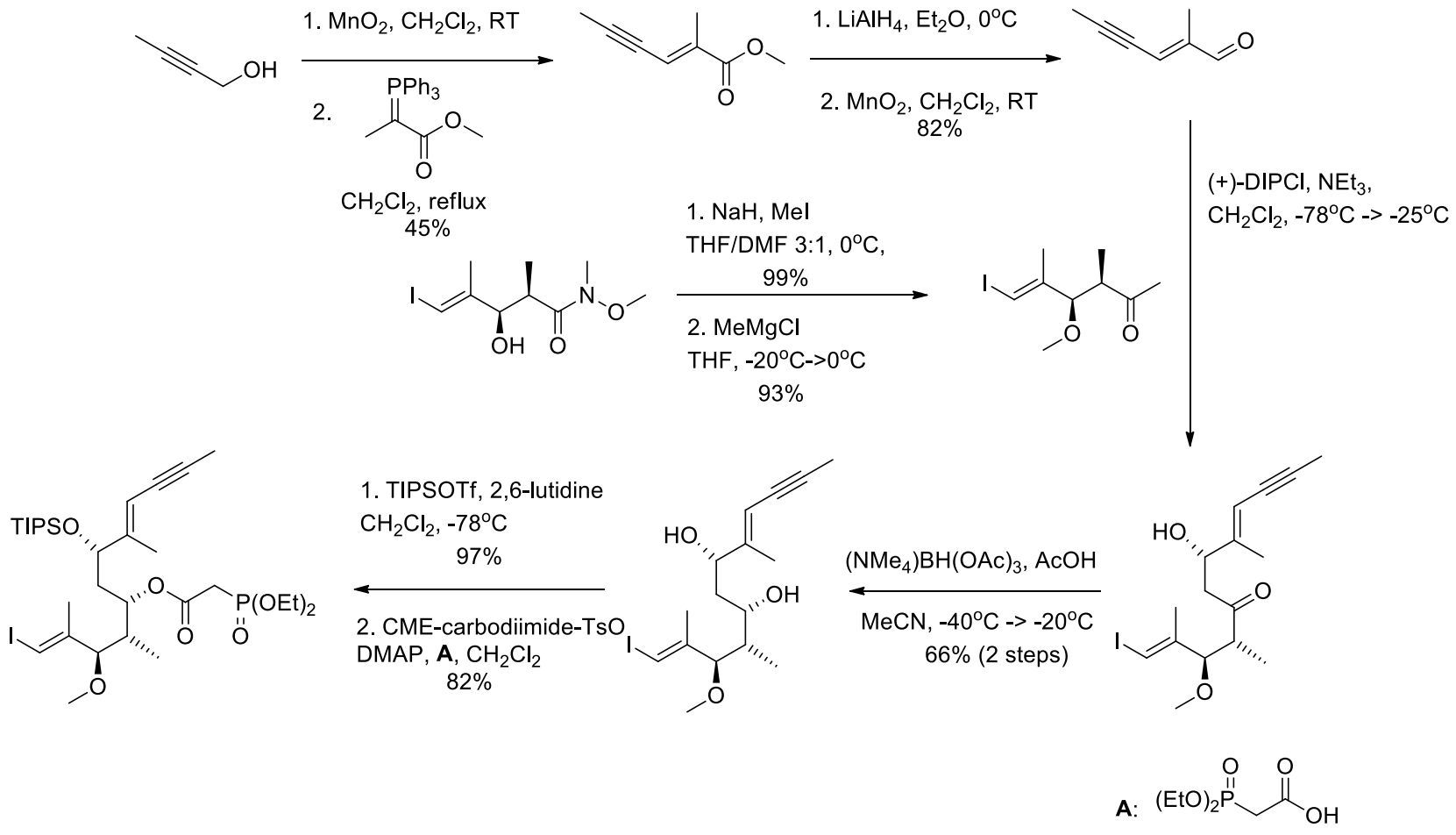
J. Am. Chem. Soc., **1999**, *121*, 11108

Citreofuran



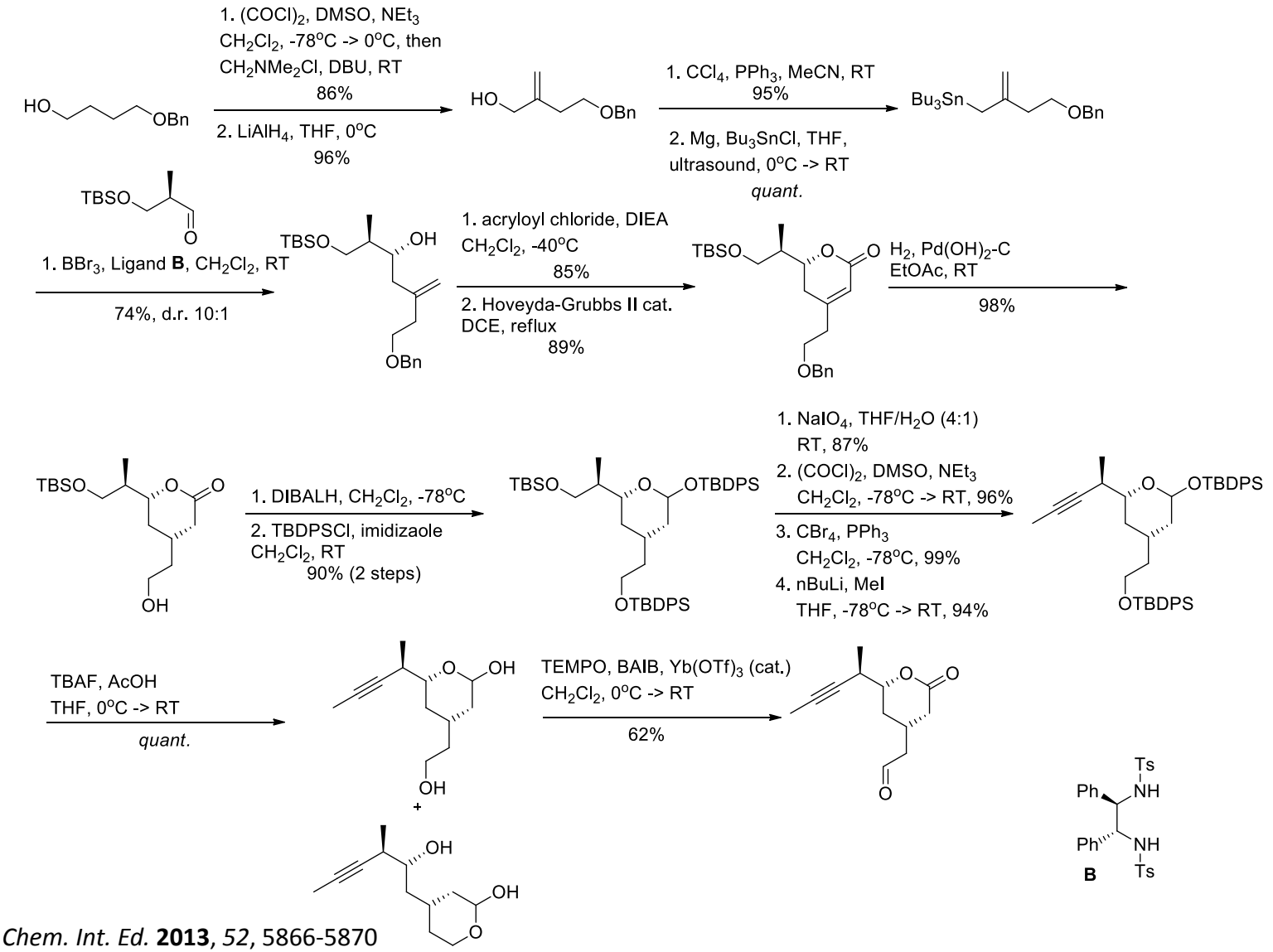
J. Org. Chem., **2003**, *68*, 1521

Synthesis of the Left-Hand Portion of WF-1360F



Angew. Chem. Int. Ed. **2013**, *52*, 5866-5870

Synthesis of the Right-Hand Portion of WF-1360F



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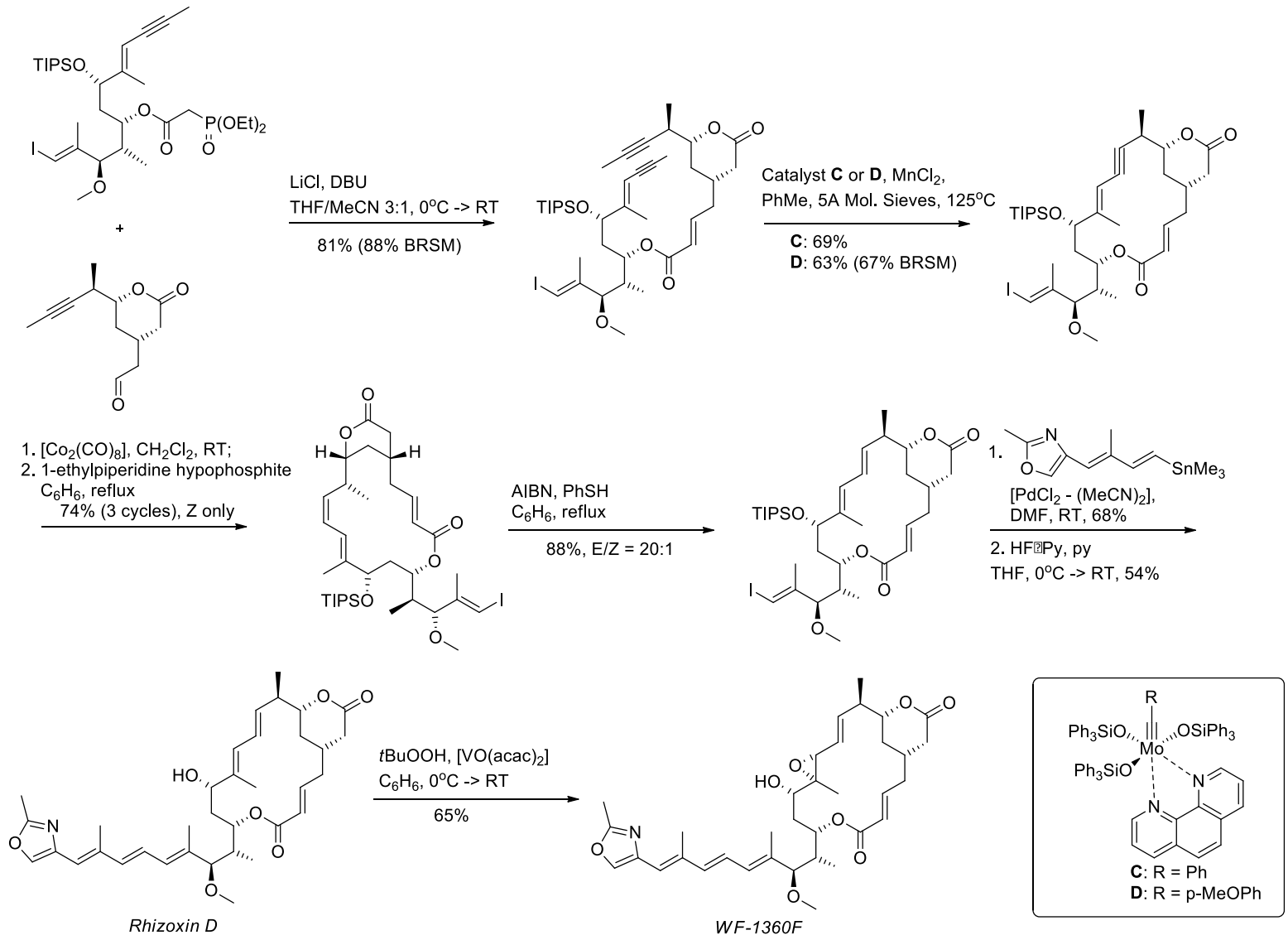
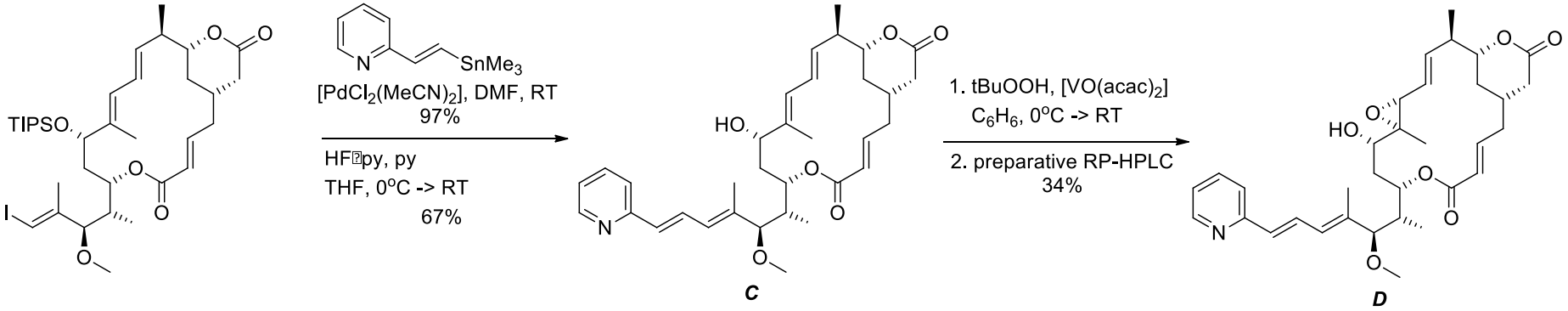
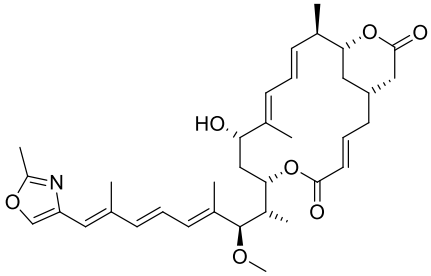
Coupling and Elaboration to WF-1360F



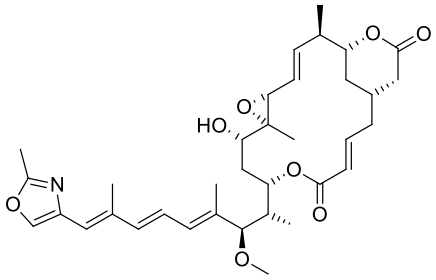
Angew. Chem. Int. Ed. **2013**, *52*, 5866-5870

Side-Chain Replacement and Biological Activity





Rhizoxin D



WF-1360F

Compd.	MiaPaCa (nM)	HCT116 (nM)
WF-1360F	5.1 ± 0.74	4.5 ± 0.38
Rhizoxin D	75 ± 6.9	49 ± 6.6
D	45 ± 1.8	29 ± 6.1
C	1432 ± 246	297 ± 2.4

Unstable side chains can potentially be replaced with only small loss in activity

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Conclusions

- First enantioselective total synthesis of WF-1360F
  - 2.1% to WF-1360F, 23 steps (LLS), 33 steps overall
  - 3.2% to Rhizoxin D, 22 steps (LLS), 32 steps overall

- Utilized ring-closing alkyne metathesis and radical reduction/ isomerization sequence

- Side-chain analogues show better stability and only slightly decreased activity compared to parent compounds (WF-1306F and Rhizoxin D)