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Synthesis of the C20–C32 Tetrahydropyran Core of the Phorboxazoles and the C22 Epimer via a Stereodivergent Michael Reaction

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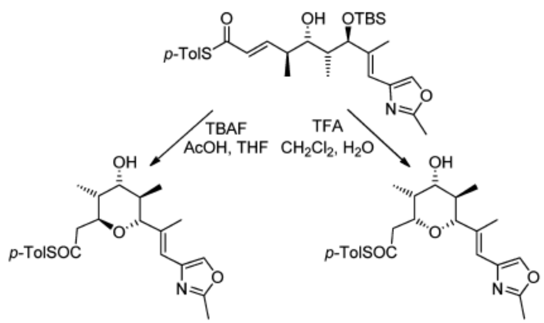
ABSTRACT



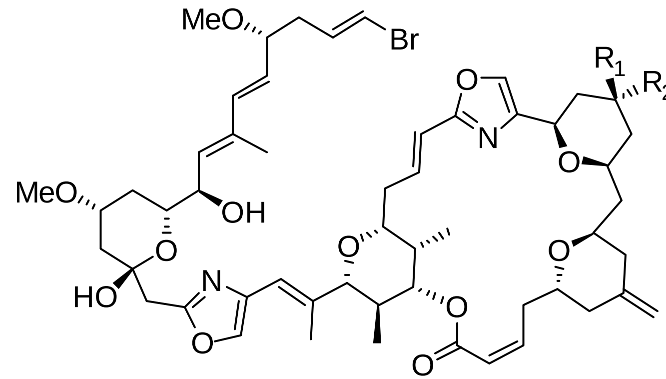
A stereoselective synthesis of the C20–C32 tetrahydropyran core of the phorboxazoles has been achieved in only seven steps and in a 31% overall yield. The C22 epimer was also synthesized. The key step was a silyl ether deprotection/oxy-Michael cyclization. When this step was conducted under Brønsted acid conditions, the C20–C32 core was formed with the desired 2,6-*cis*-stereochemistry. However, when the silyl ether deprotection/oxy-Michael cyclization was conducted under fluoride conditions buffered with acetic acid, the C22 epimer of the core was the sole product.

Benjamin R. Eyer
Wipf Group-Current Literature
November 2, 2012

Org. Let. **2012,** ASAP
DOI: 10.1021/ol302652q

Isolation and Biological Activity

- Isolated by Searle and Molinski in 1995
- The relative and absolute stereochemistries assigned by 2D NMR analysis, degradation studies, and synthetic correlation studies
- 4 different THP rings, two oxazole rings, and 15 stereocenters
- Subnanomolar activity against the NCI's 60 tumor cell lines



Phorboxazole A: R_1=H, R_2=OH
Phorboxazole B: R_1=OH, R_2=H

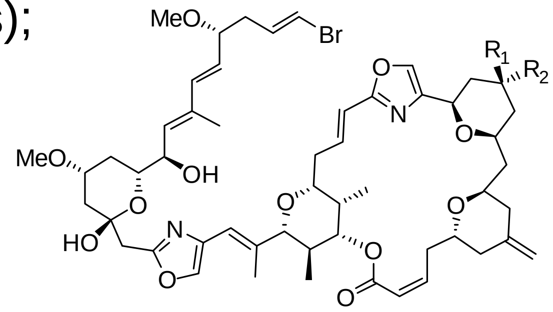
J. Am. Chem. Soc. **1995**, *117*, 8126.
J. Am. Chem. Soc. **1996**, *118*, 9422.
Tetrahedron Lett. **1996**, *37*, 7879.

Previous Synthetic Work on the Phorboxazoles

- Phorboxazole A (7 total syntheses)
  - **Forsyth**: *J. Am. Chem. Soc.* **1998**, *120*, 5597.

    2nd Generation: *J. Am. Chem. Soc.* **2011**, *133*, 1484 and *J. Am. Chem. Soc.* **2011**, *133*, 1506.
  - **Smith**: *J. Am. Chem. Soc.* **2001**, *123*, 4834;

    2nd Generation: *Org. Lett.* **2005**, *7*, 4399 and *J. Org. Chem.* **2008**, *73*, 1192.
  - **Pattenden**: *Angew. Chem., Int. Ed.* **2003**, *42*, 1255 and *Org. Biomol. Chem.* **2003**, *1*, 4173.
  - **Williams**: *Angew. Chem., Int. Ed.* **2003**, *42*, 1258.
  - **White**: *Org. Lett.* **2006**, *8*, 6039 and *Org. Lett.* **2006**, *8*, 6043.
- Phorboxazole B (3 total syntheses)
  - **Evans**: *J. Am. Chem. Soc.* **2000**, *122*, 10033 (Studies); *Angew. Chem., Int. Ed.* **2000**, *39*, 2533 and *Angew. Chem., Int. Ed.* **2000**, *39*, 2536.
  - **Zhou and Lin**: *Chem. Eur. J.* **2006**, *12*, 1185.
  - **Burke**: *Angew. Chem., Int. Ed.* **2007**, *46*, 769.



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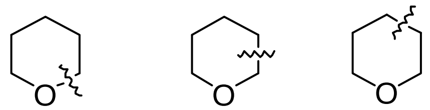
Tetrahydropyran and Tetrahydropyran synthesis

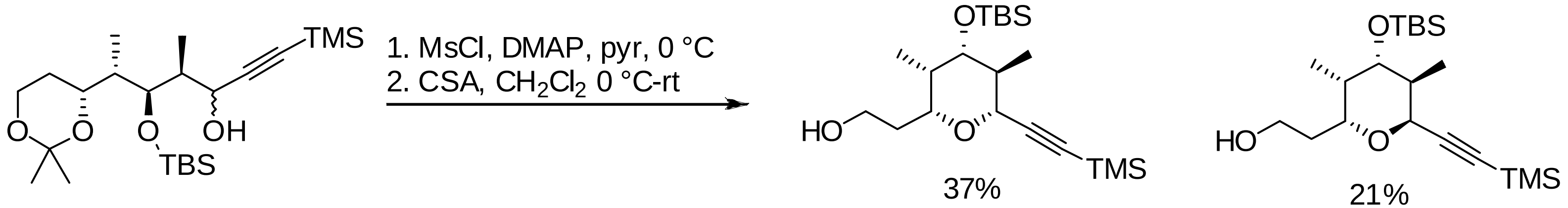


Type 1 Type 2 Type 3

- Six-membered oxygenated heterocycles (pyrans) range from glucose to complex metabolites like the Phorboxazoles
- Cyclization methods
  - Type 1: S_N2 and S_N1-mediated cyclizations, metal-promoted processes and Michael-like reactions
  - Type 2 and Type 3: Prins sequences, Petasis-Ferrier rearrangements and RCM reactions
  - Other: Maitland-Japp multicomponent reactions, Hetero-Diels-Alder cyclizations

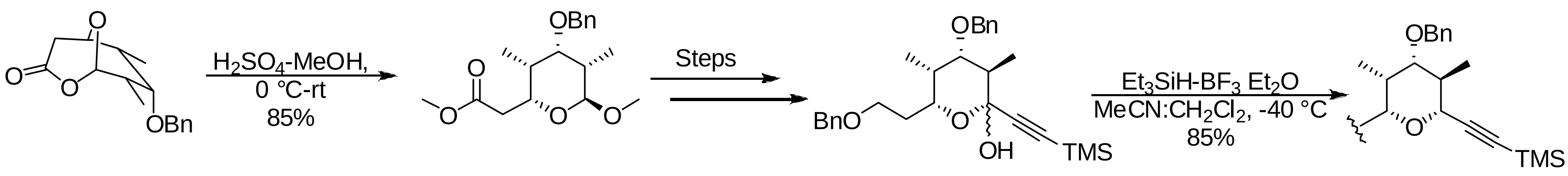
THP Reviews:
Eur. J. Org. Chem **2006**, 2045
Tetrahedron **2008**, *64*, 2683

Synthetic work on the THP core

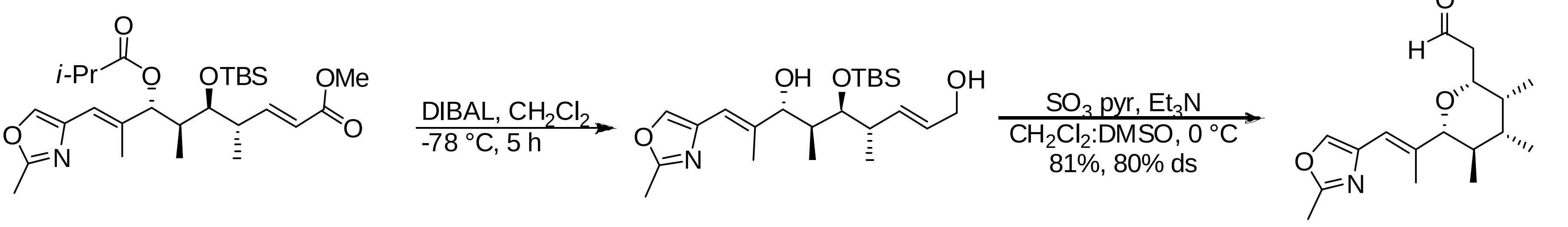


C20-C28 of phorboxazoles

Tetrahedron **2003**, 59, 8613.



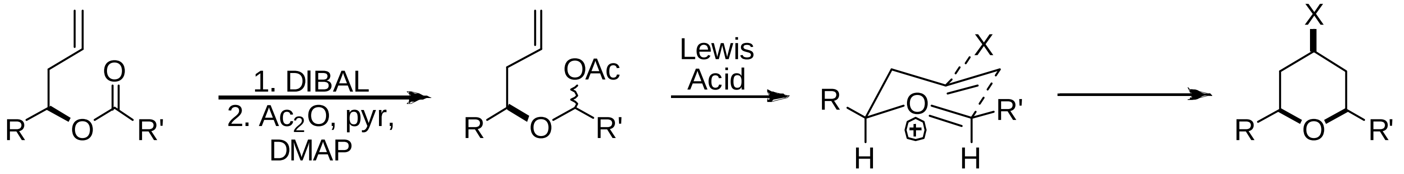
Synlett **2007**, *10*, 1577.

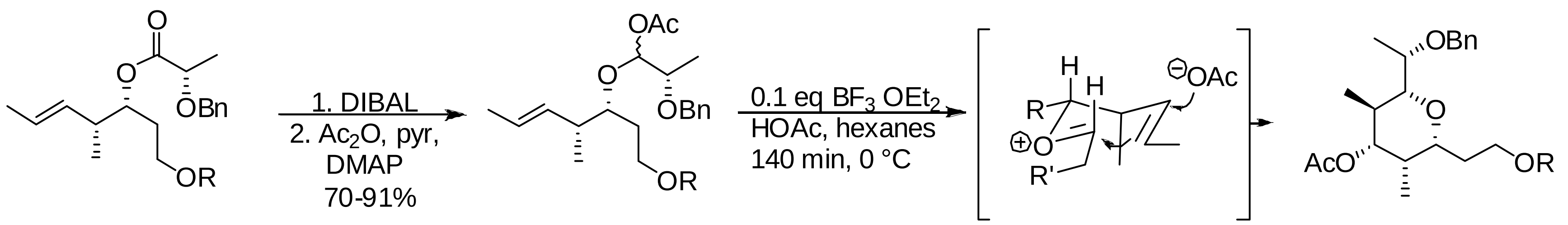


C20-C32 of phorboxazoles

Tet. Let. **1998**, *39*, 7185.

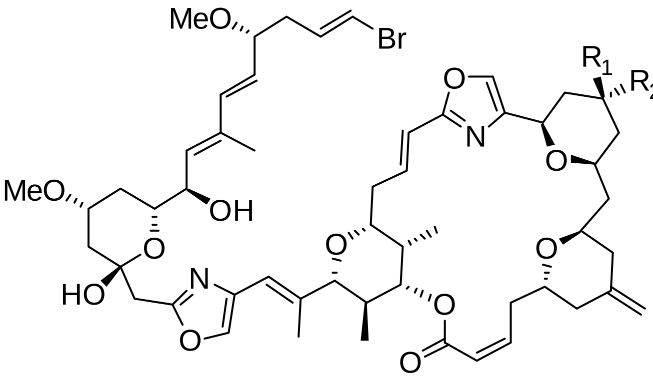
Rychnovsky and the Prins Reaction



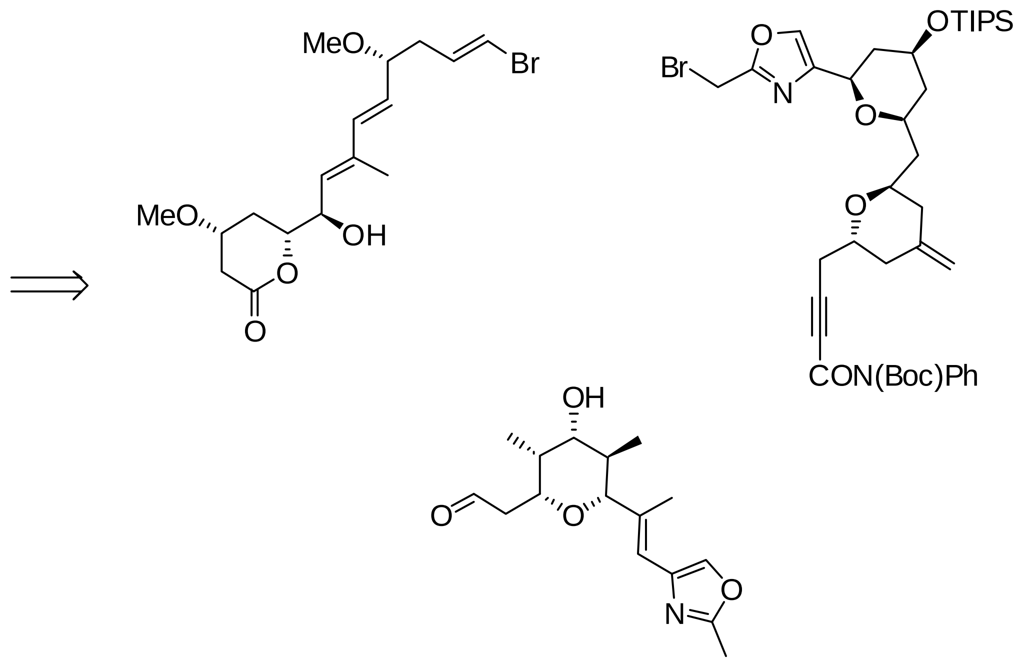


Org. Let. **2000**, 2(9), 1217.
Org. Let. **2005,** 7(15), 3255.

Retrosynthetic Analysis of the Phorboxazoles

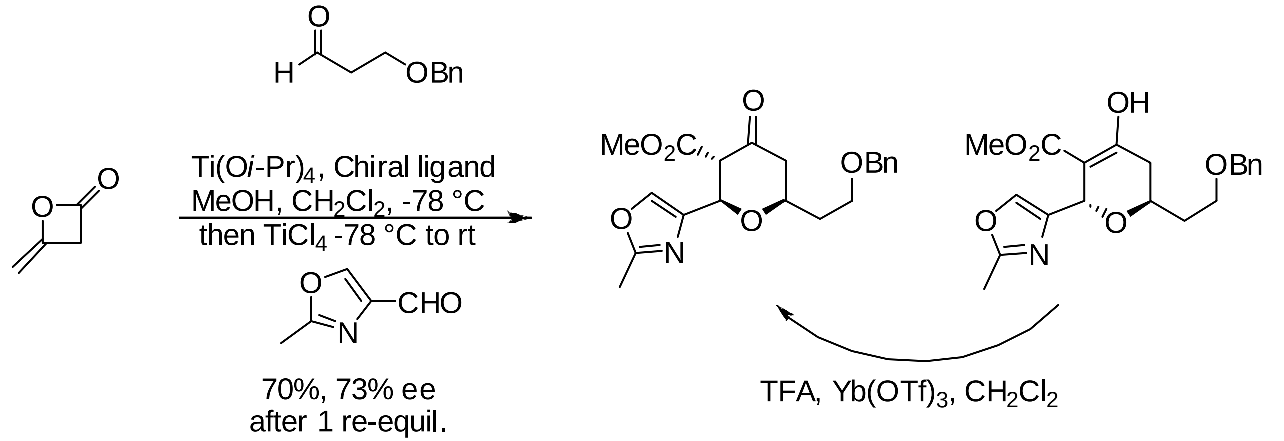


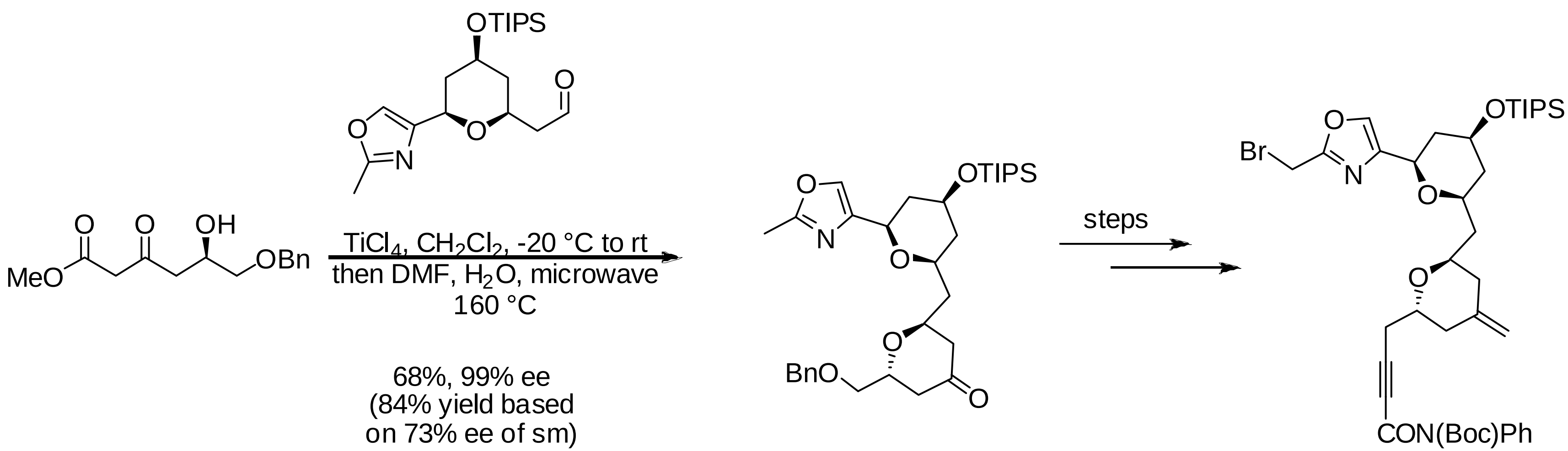
Phorboxazole A: R_1=H, R_2=OH
Phorboxazole B: R_1=OH, R_2=H



Org. Lett. **2012**, ASAP
DOI: 10.1021/ol3026523

Work within the Clarke Group





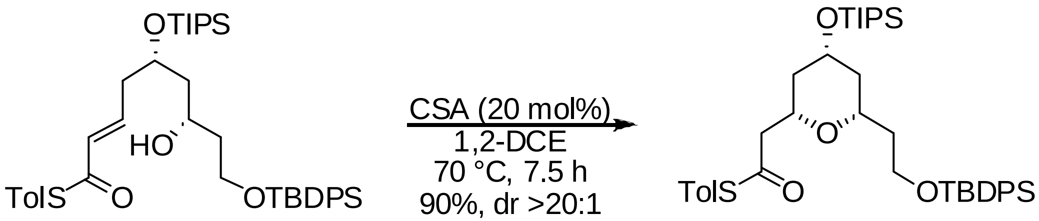
Org. Let. **2011,** 13(4), 624.

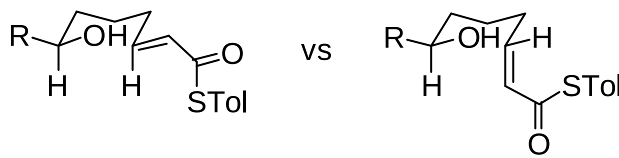
C1-C19 of phorboxazole

- When the Maitland-Japp reaction was used to synthesize the C20-C32 core, the THP was not obtained diastereomerically pure enough to continue or epimeric at C23

Tet. Let. **2010**, *51*, 4731.

Fuwa and mimicing acyl transfer proteins

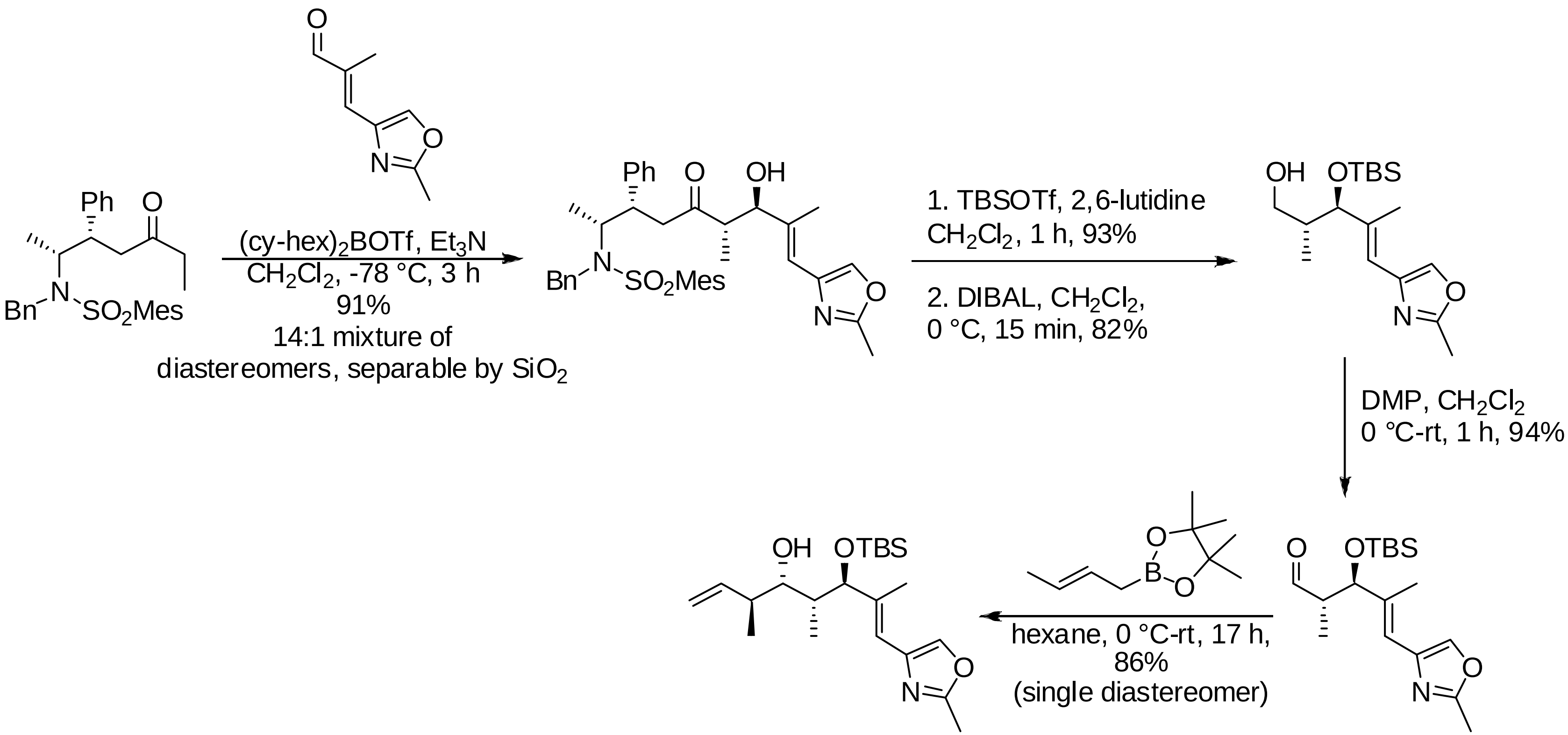


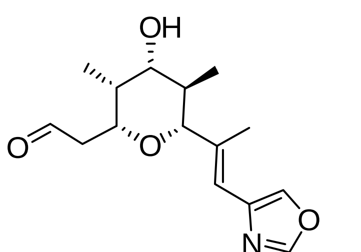


- 6-*exo*-trig cyclization often lead to 2,6-*trans* product where forcing conditions are required to form the 2,6-*cis*-THP
- Mimic thioester of acyl carrier protein (ACP) that would be activated by pyran synthase
- Biomimetic acid catalyzed oxa-Michael cyclization proceeding through a late transition state favoring 2,6-*cis*-THP
- Several multi-substituted examples in the paper cyclized in high diastereoselectivity and good yields
  - Thioester easily elaborated to further analogues

Org. Let. **2011,** 13(7), 1820

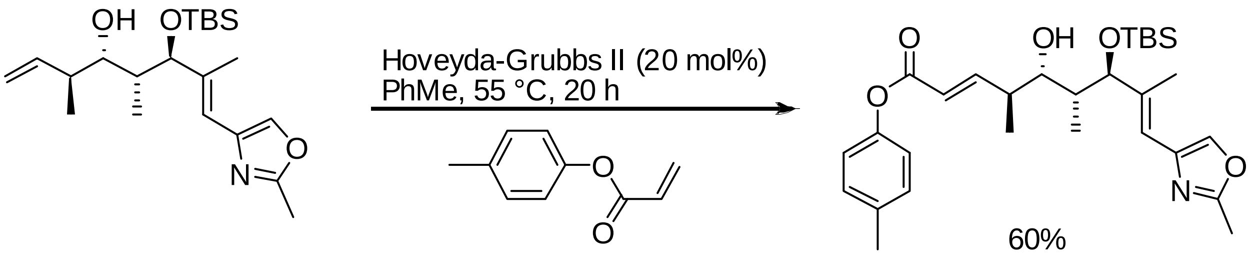
Construction of the Stereochemical Tetrad

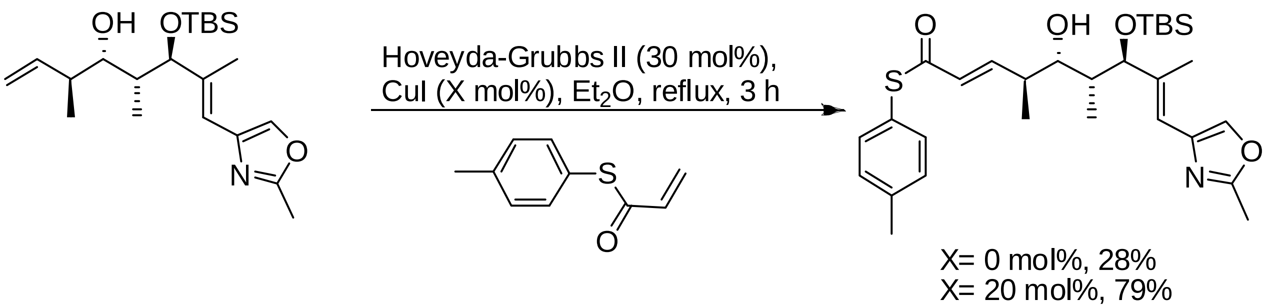




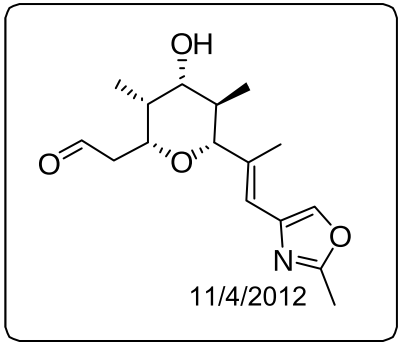
Org. Let. **2012**, ASAP
DOI: 10.1021/ol3026523

Olefin Cross Metathesis to Precursors





- Thioester metathesis issues
  - Same conditions: low yielding
  - Incresing temperature: 70 ºC- 20%, 90 ºC- 0%
  - CH_2Cl_2 and higher loading: 50%
  - Hypothesis: self-dimeriztion of thioester



Org. Lett. **2012**, ASAP
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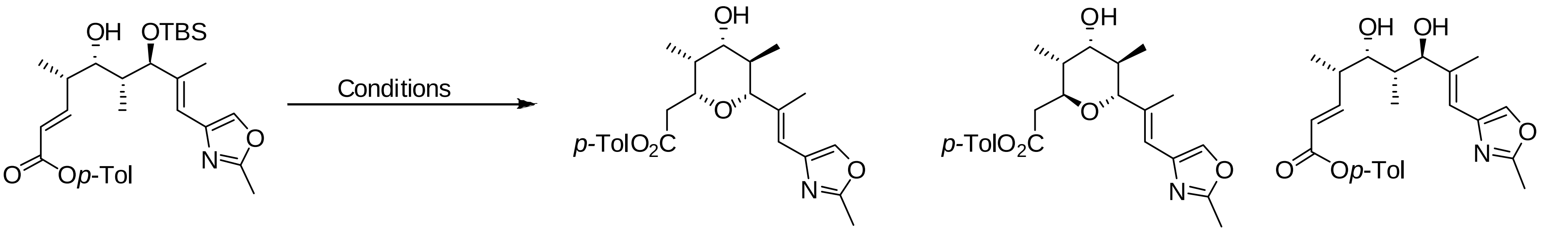
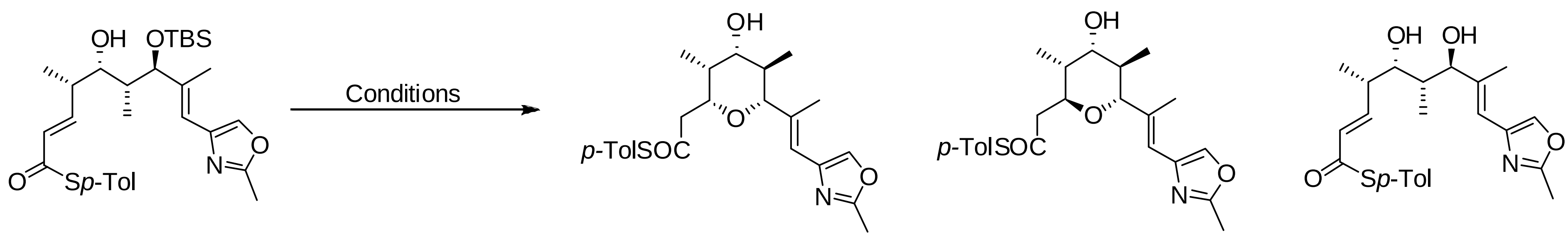
Cyclization of esters



Conditions			
CSA, 10:1 DCE/MeOH, rt to 70 °C	---	---	---
TBAF, AcOH, THF, rt	---	71%	---
TFA/CH_2Cl_2/H_2O, rt	---	---	68%



Conditions			
CSA, 3:1 DCE/MeOH, rt to 30 °C	trace	---	56%
CSA, 3:1 DCE/MeOH, rt to 55 °C	20%	---	---
TBAF, AcOH, THF, rt	---	35%	---
TFA/CH_2Cl_2/H_2O, rt (13:1 ratio crude)	71%	see conditions	---

Org. Lett. **2012,** ASAP
DOI: 10.1021/ol3026523

Summary

- 7 steps, 31% overall yield to C20-C32 phorboxazole core
- Selective Michael cyclization with thioester electrophile to
  - 2,6-*cis*-THP
  - 2,6-*trans*-THP
- More complete examination of the switch in selectivity *in progress*
- Completion of Phorboxazole B *in progress*