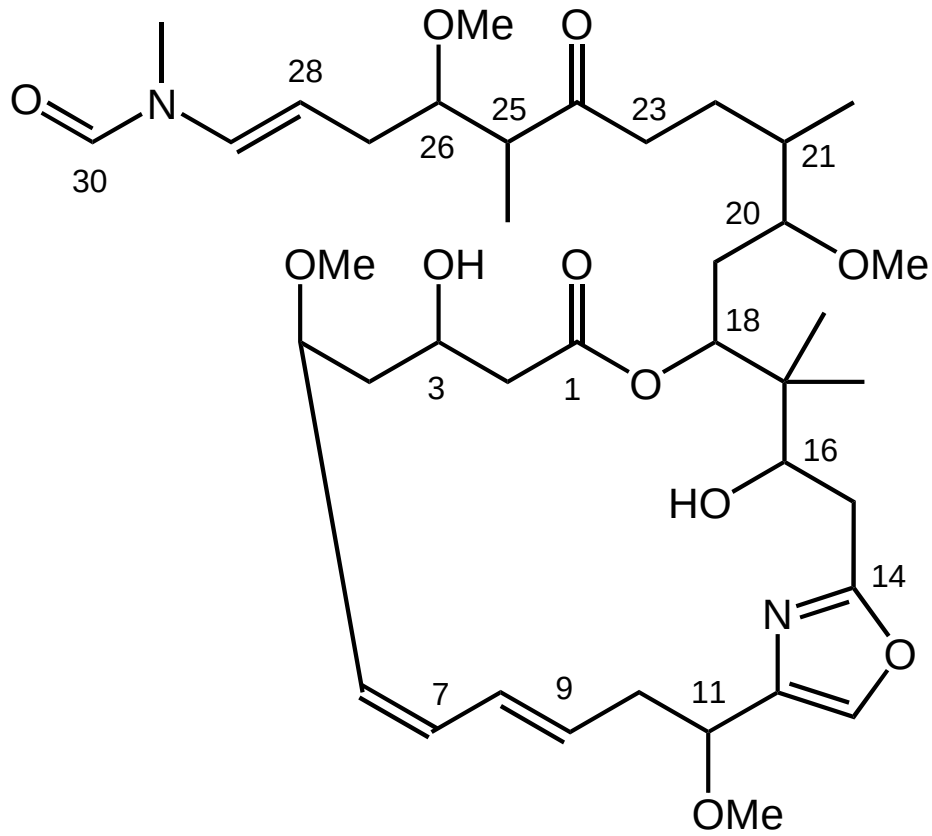
2010-05-25 Report: Duo-Sheng Wang
Checker: Jie Tang

Synthesis of the C9-C23 (C9'-C23') Fragment of the Dimeric Natural Product Rhizopodin

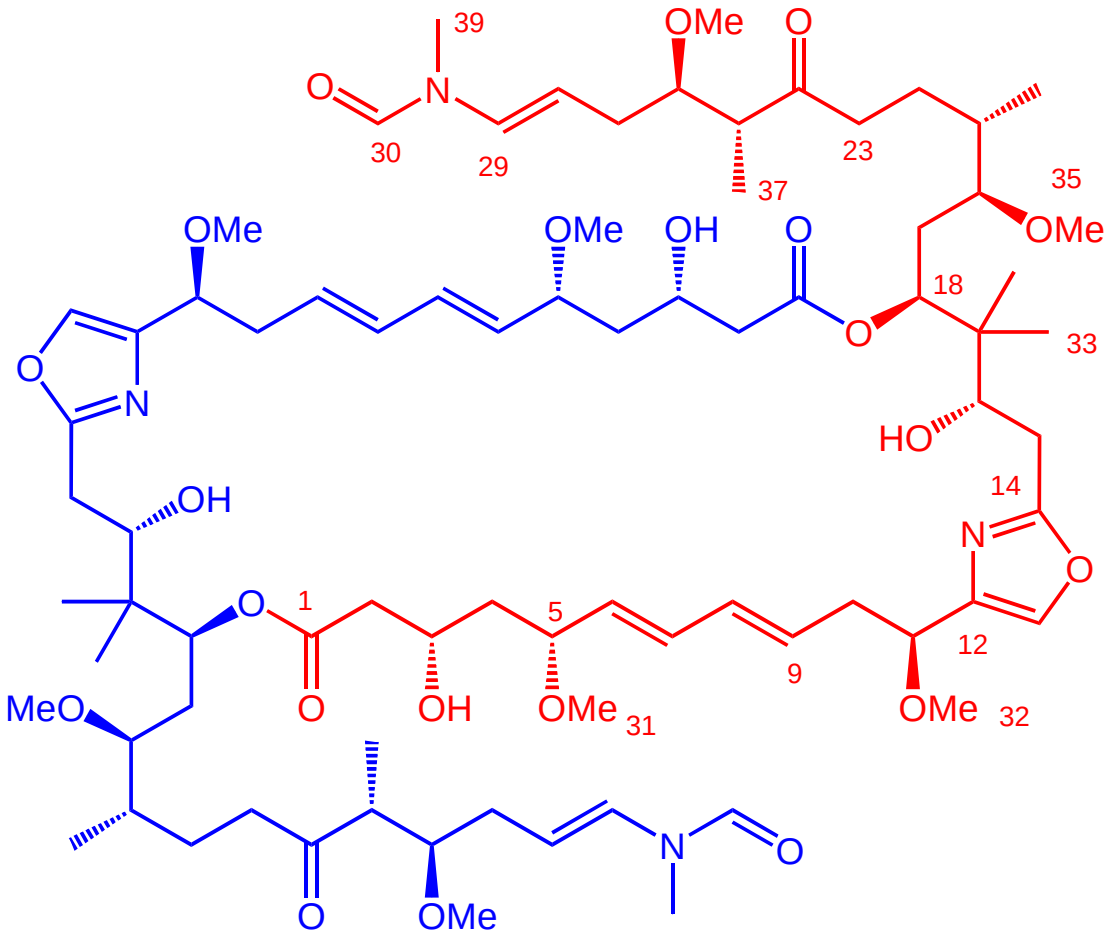
Ye, T.* *et al* *Org. Lett.* **2010**, *12*, 2036-2039.

Original Structure of Rhizopodin:



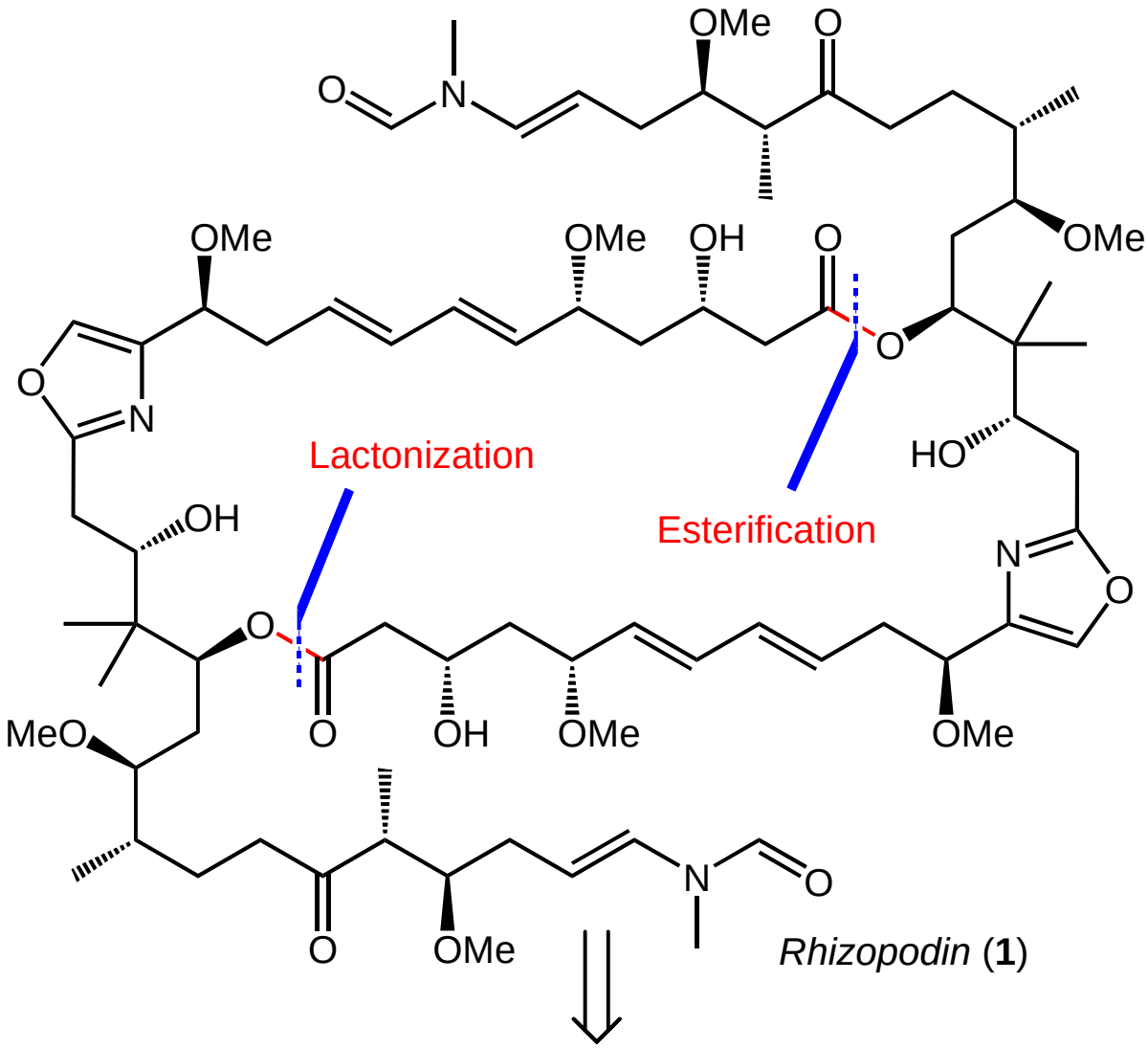
Reichenbach, H. et al *J. Antibiot.* **1993**, *46*, 741–748.

True Structure and Absolute Configuration of Rhizopodin:

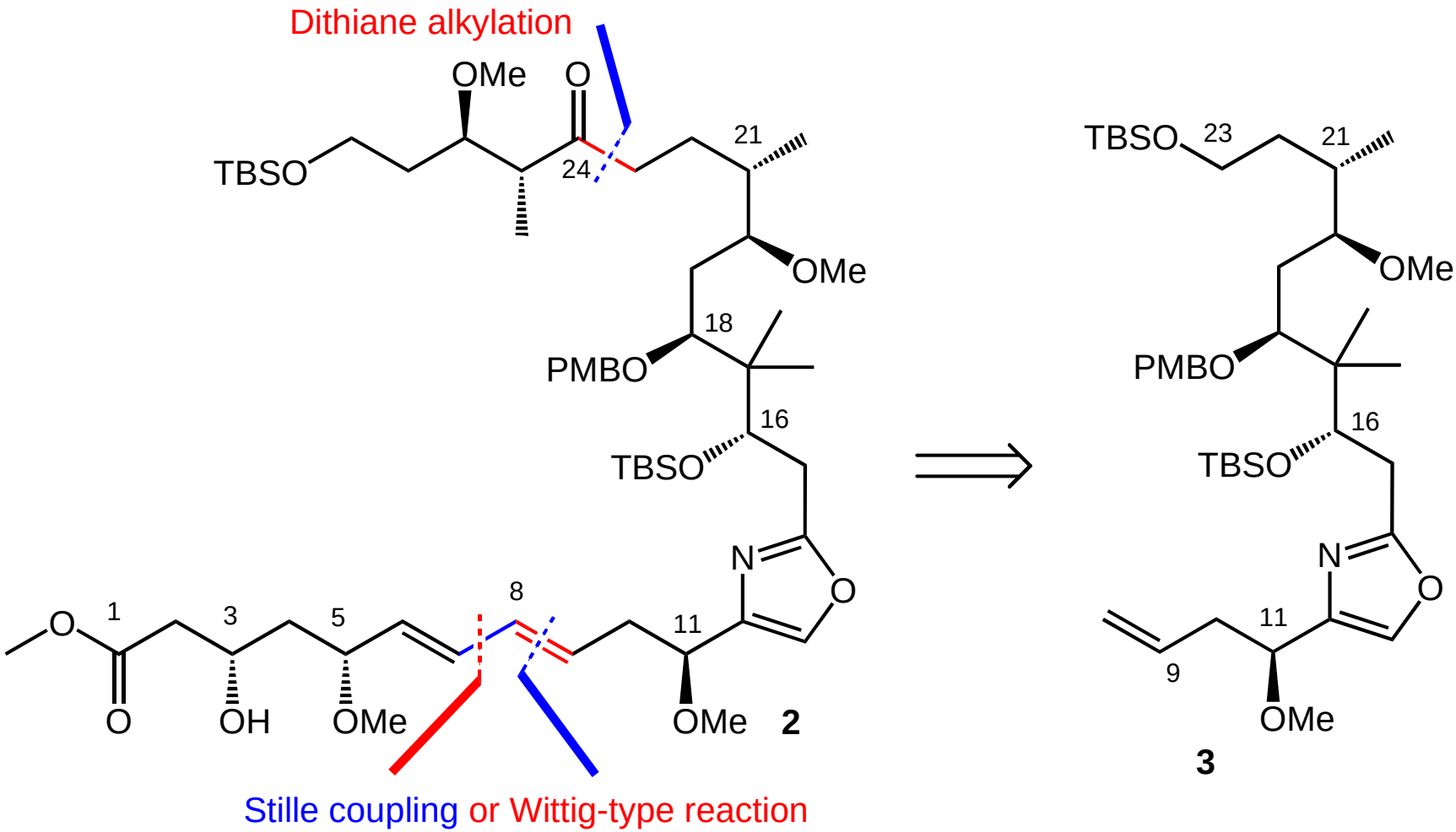


Jansen, R. et al *Tetrahedron Lett.* **2008**, *49*, 5796-5799.
Menche, D. et al *Chem. Commun.* **2008**, 5173-5175.
Schubert, W.-D. et al *Angew. Chem. Int. Ed.* **2009**, *48*, 595-598.

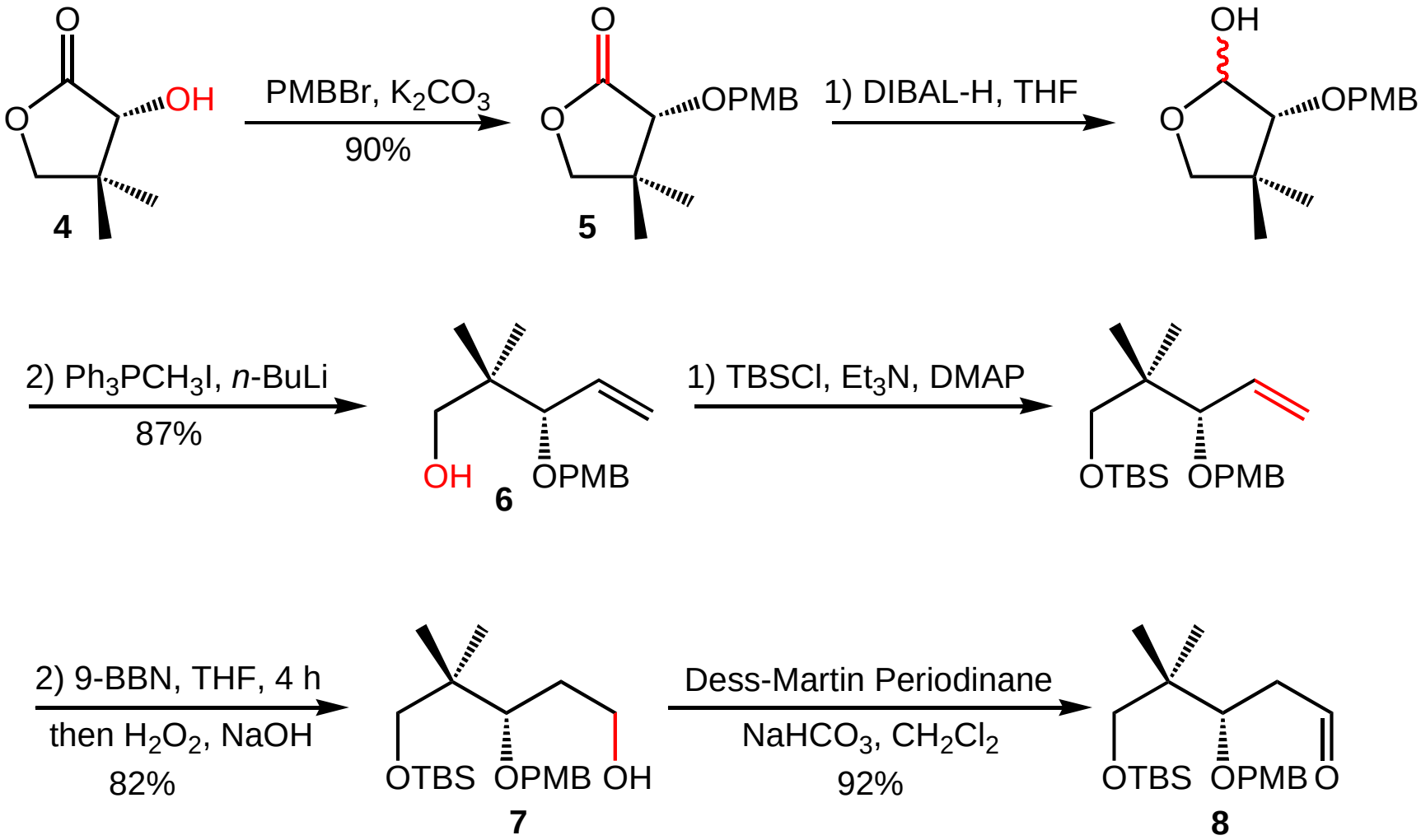
Synthetic strategy for the synthesis of Rhizopodin:



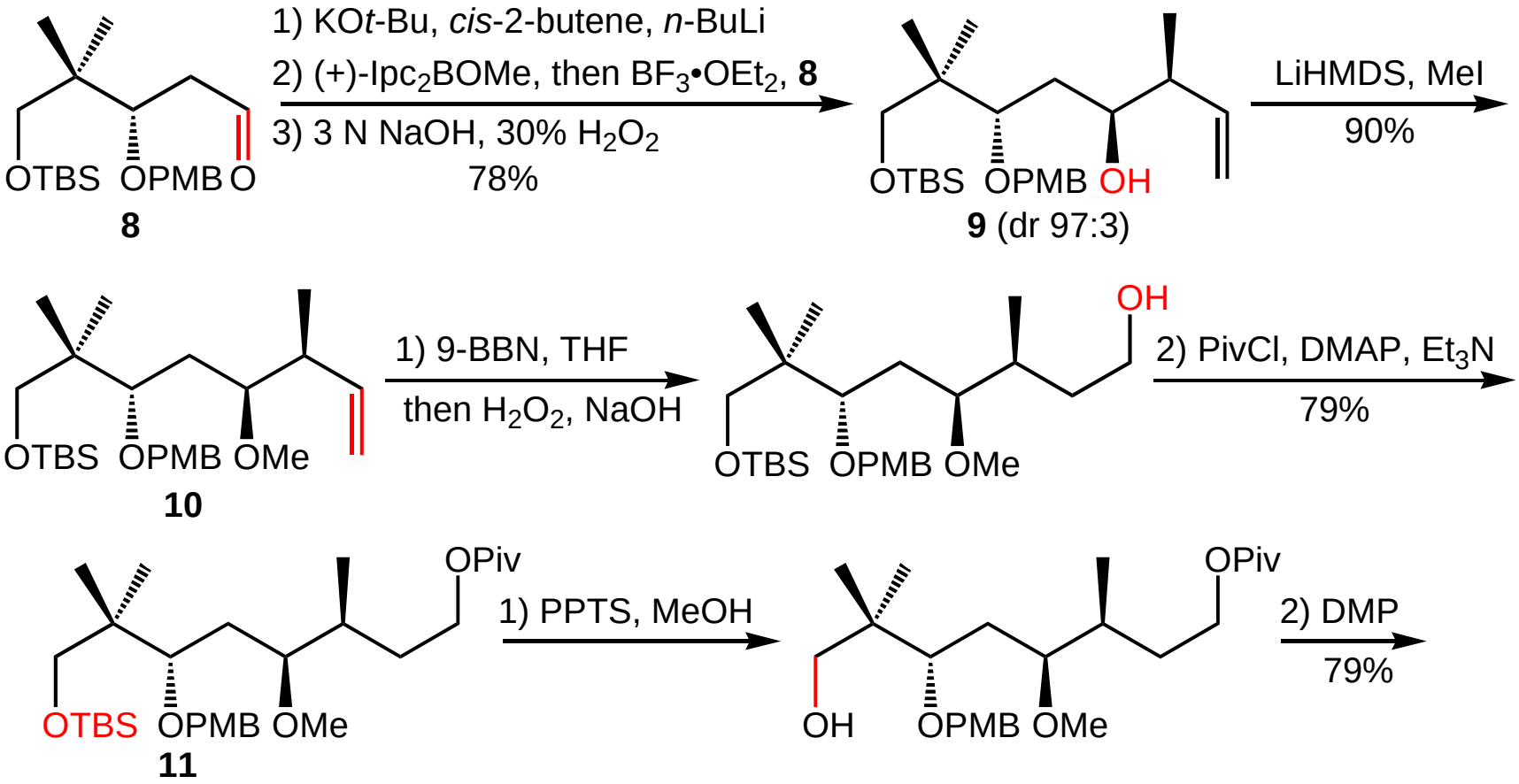
Synthetic strategy for the synthesis of Rhizopodin



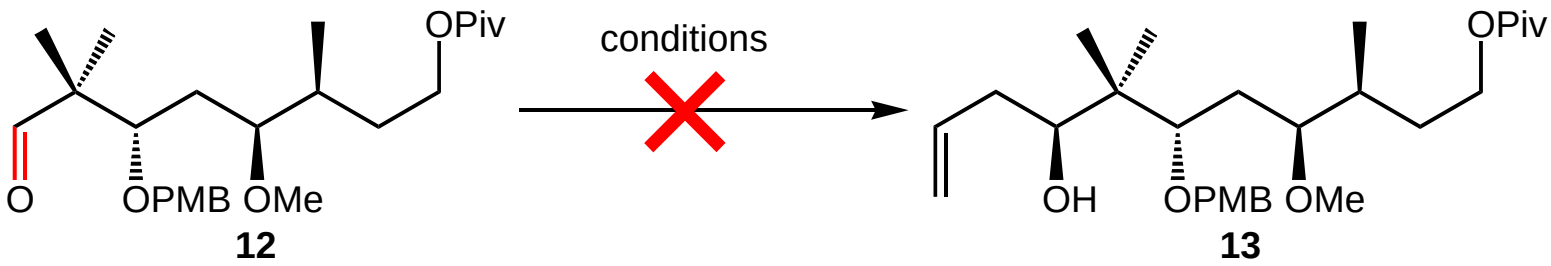
Synthesis of the C16-C23 Fragment:



Synthesis of the C16-C23 Fragment:



Allylation of Aldehyde **12:**



(1) allyltri(*n*-butyl)tin, (*S*)-BINOL, $Ti(O\text{-}i\text{-}Pr)_4$, CH_2Cl_2, -20 ^oC, 2 d

(2) allyltri(*n*-butyl)tin, $BF_3.Et_2O$, CH_2Cl_2, -78^oC ~ -45 ^oC, 4 h

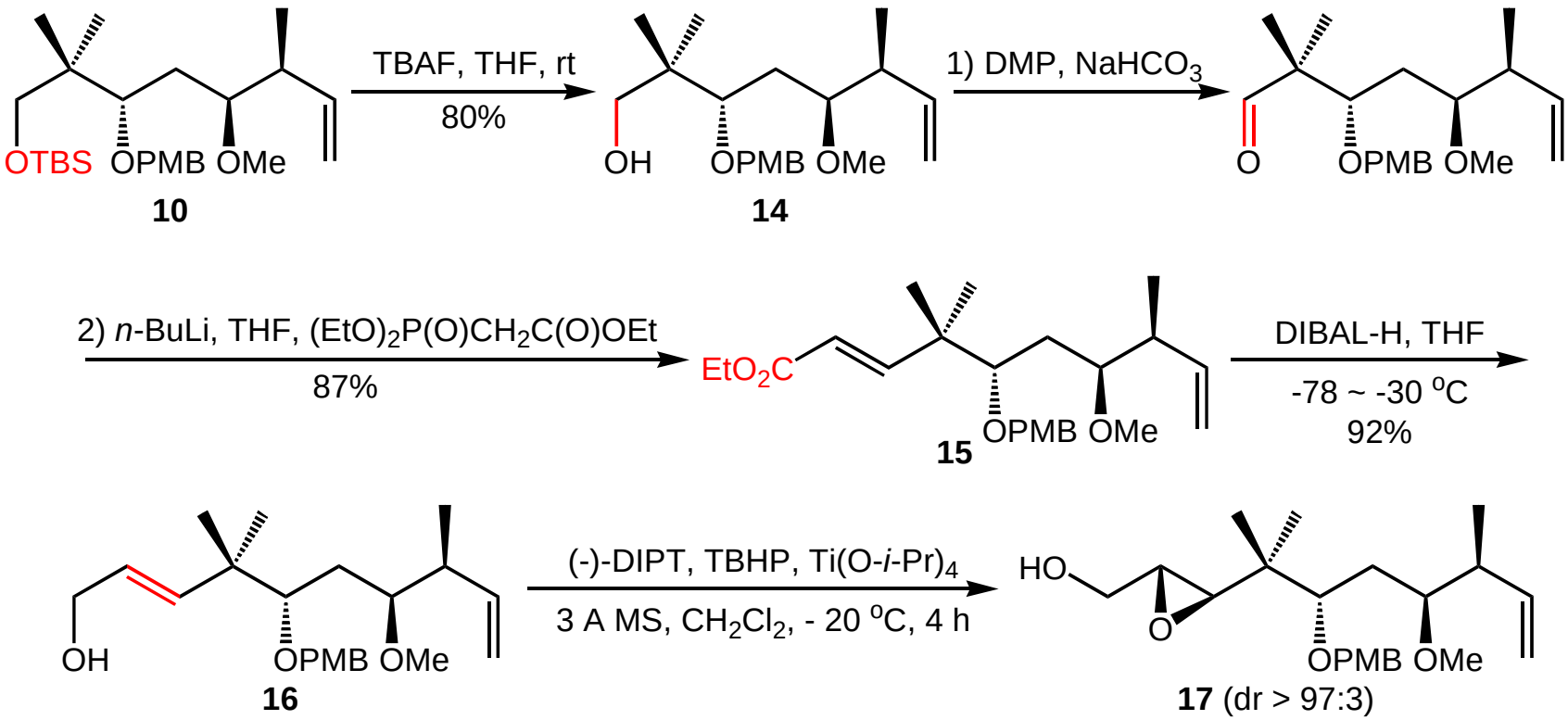
(3) allyltri(*n*-butyl)tin, $SnCl_4$, CH_2Cl_2, -78 ^oC, 4 h

(4) allyltrimethylsilane, TiF_4, (*S*)-BINOL, CH_2Cl_2:CH_3CN (97:3), -20 ^oC, 2 d

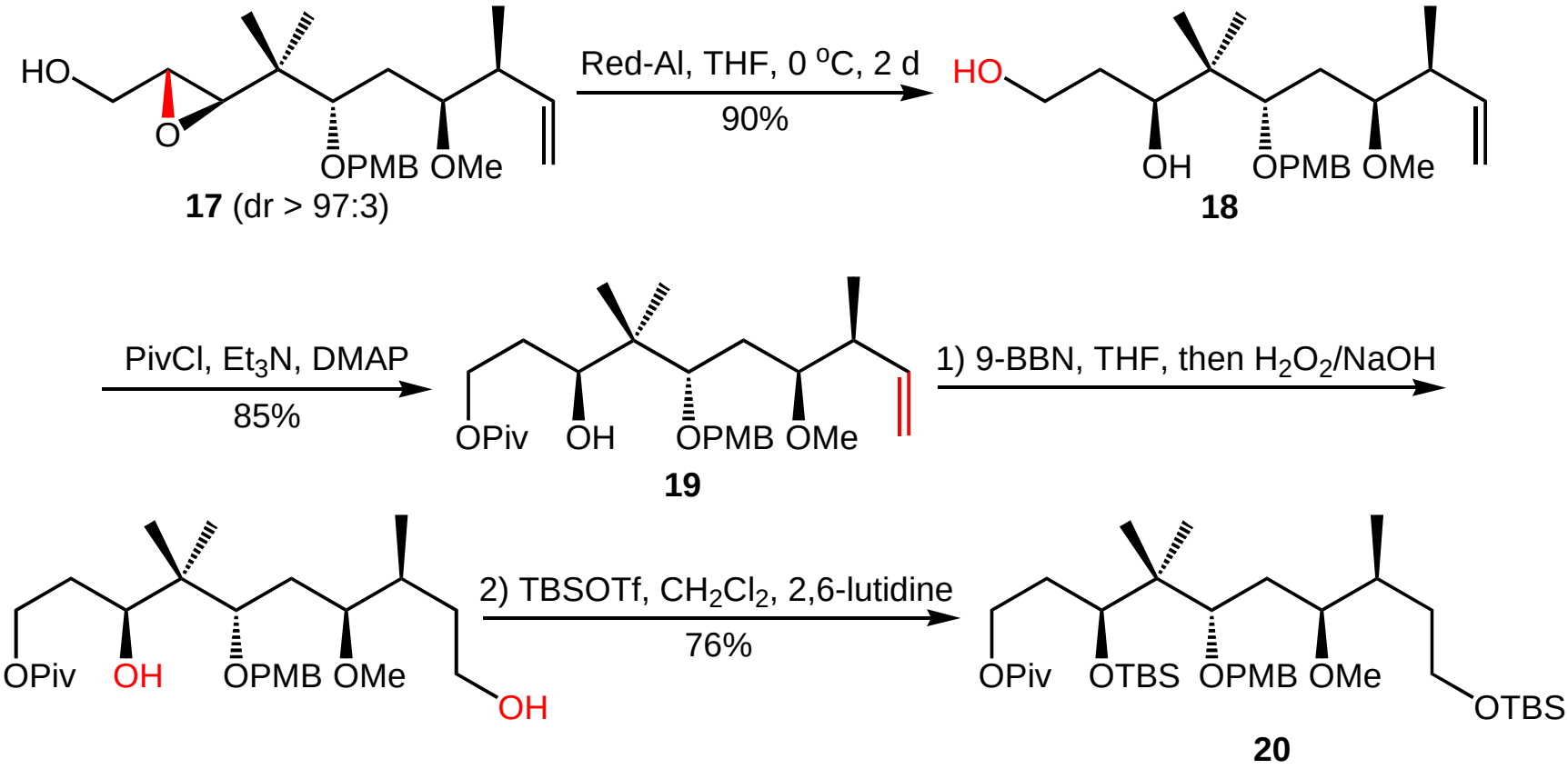
(5) allyltrimethylsilane, $BF_3.Et_2O$, CH_2Cl_2, -20 ^oC, 4 h

(6) allyltrimethylsilane, $SnCl_4$, CH_2Cl_2, -78 ^oC, 6 h

Assembly of the C9-C23 Fragment **3**:



Assembly of the C9-C23 Fragment **3**:



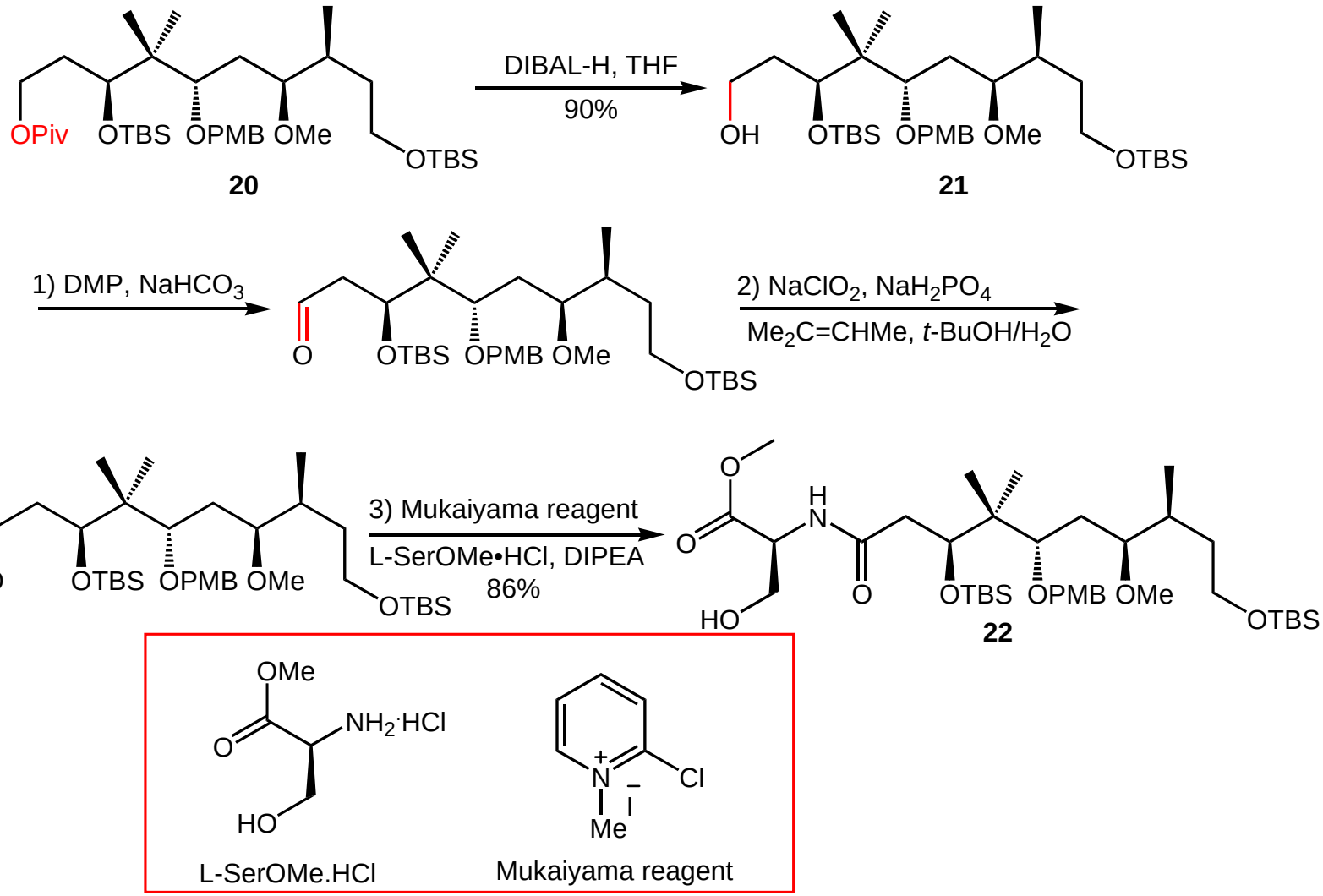
17 (dr > 97:3)

18

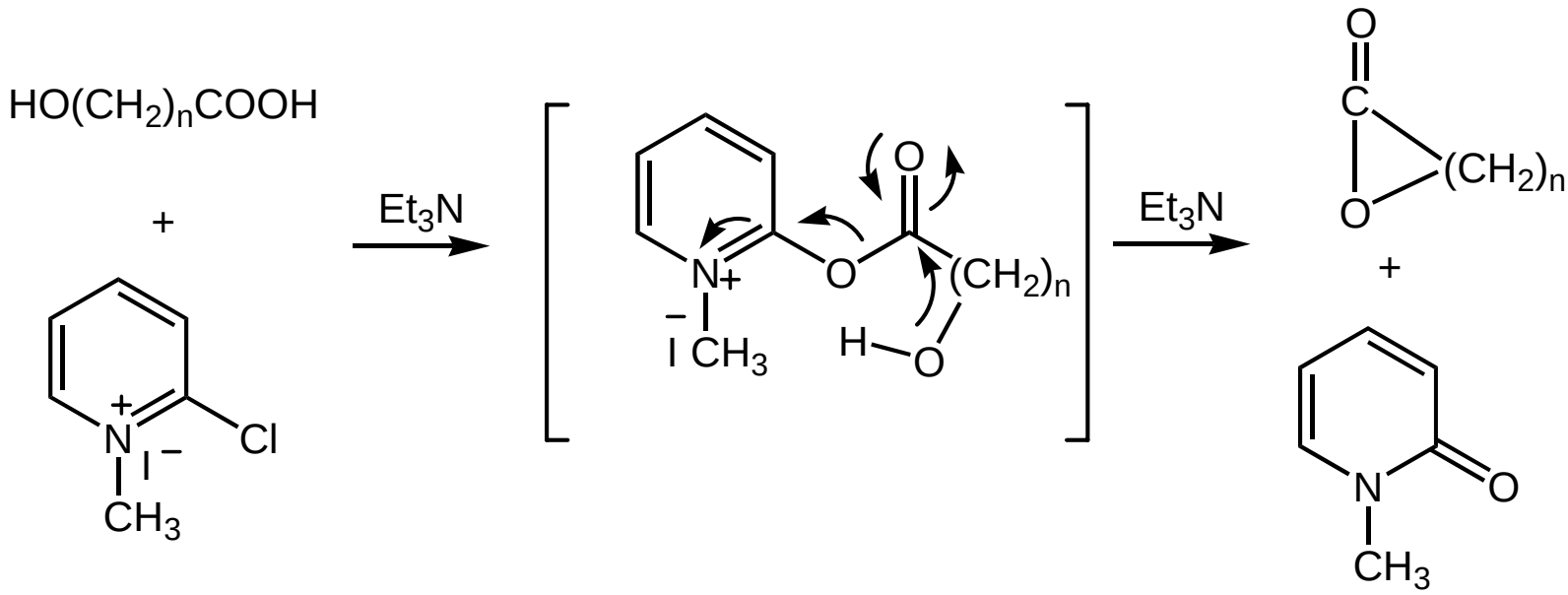
19

20

Assembly of the C9-C23 Fragment **3**:

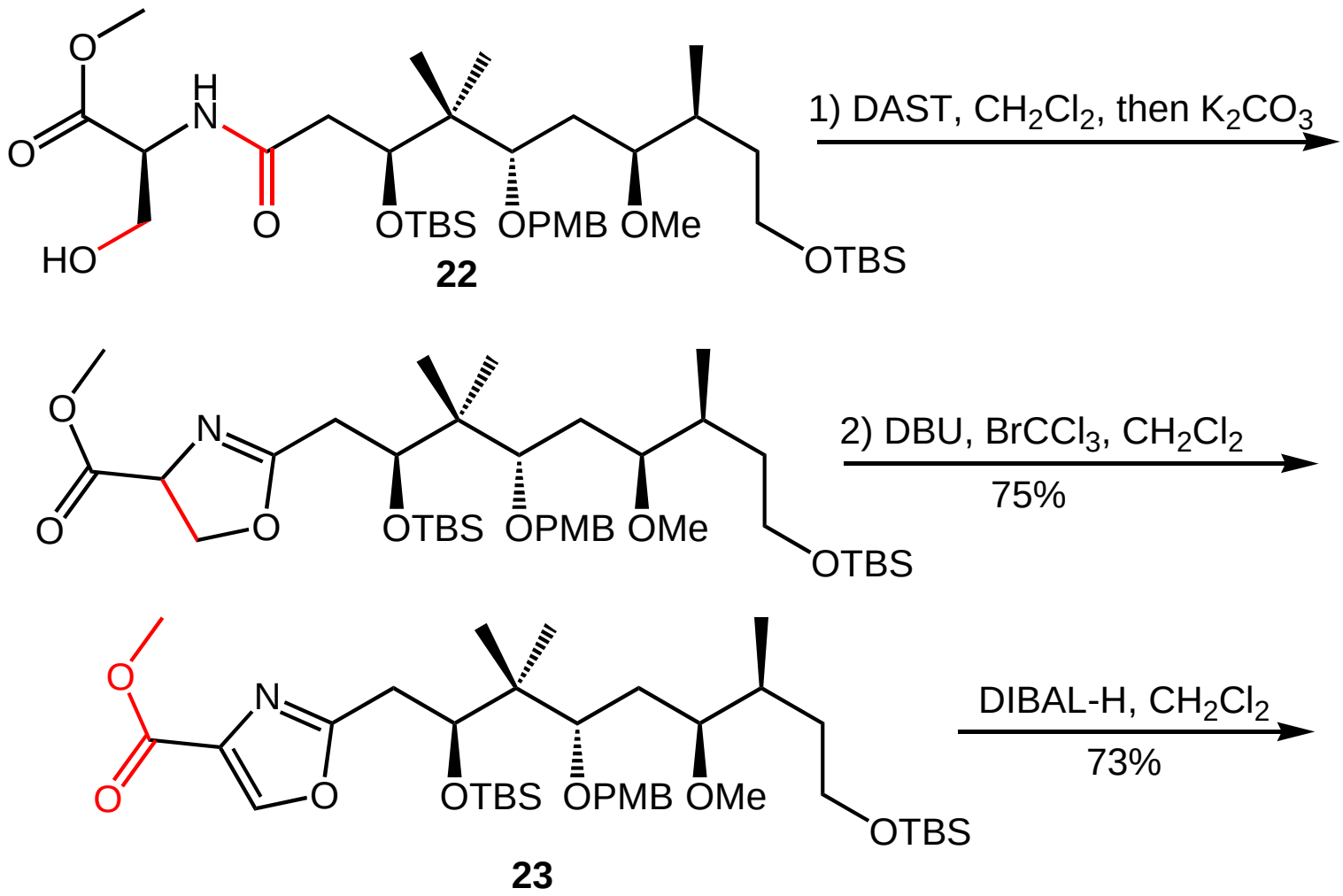


Mukaiyama reagent:

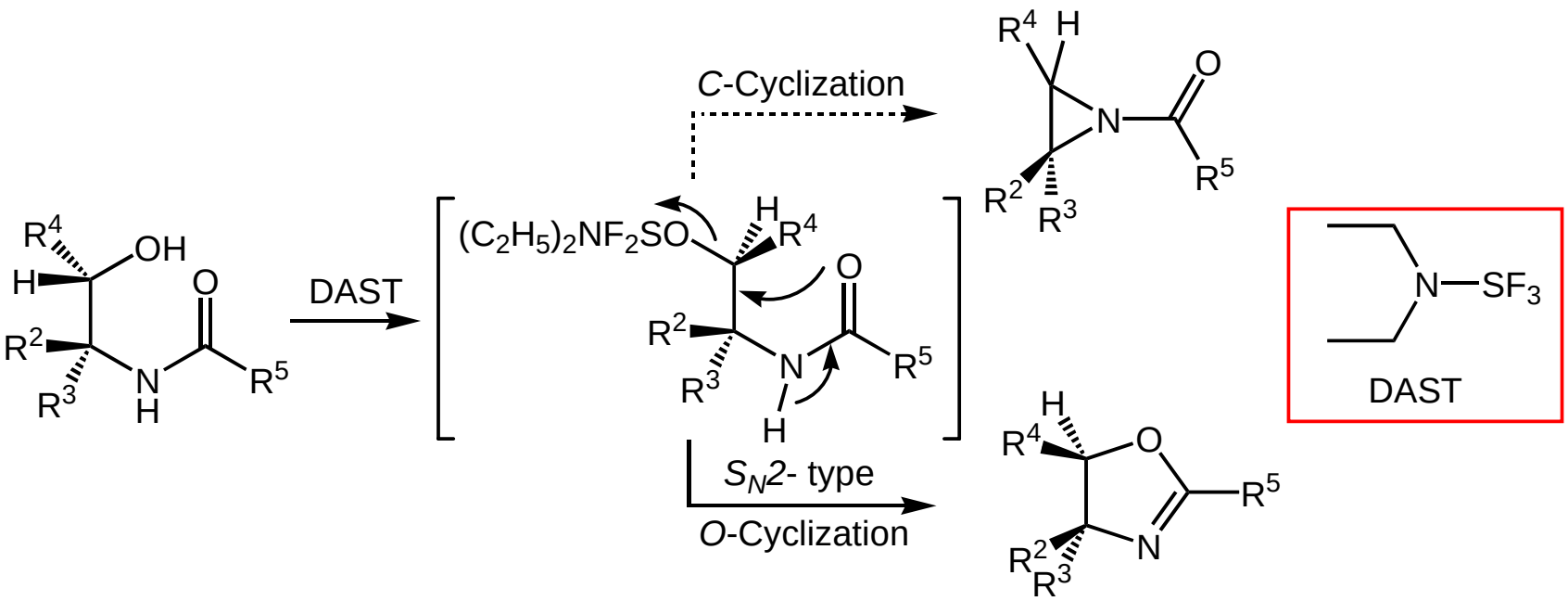


Mukaiyama, T. et al *Chem. Lett.* **1976**, 49-50.

Assembly of the C9-C23 Fragment **3**:

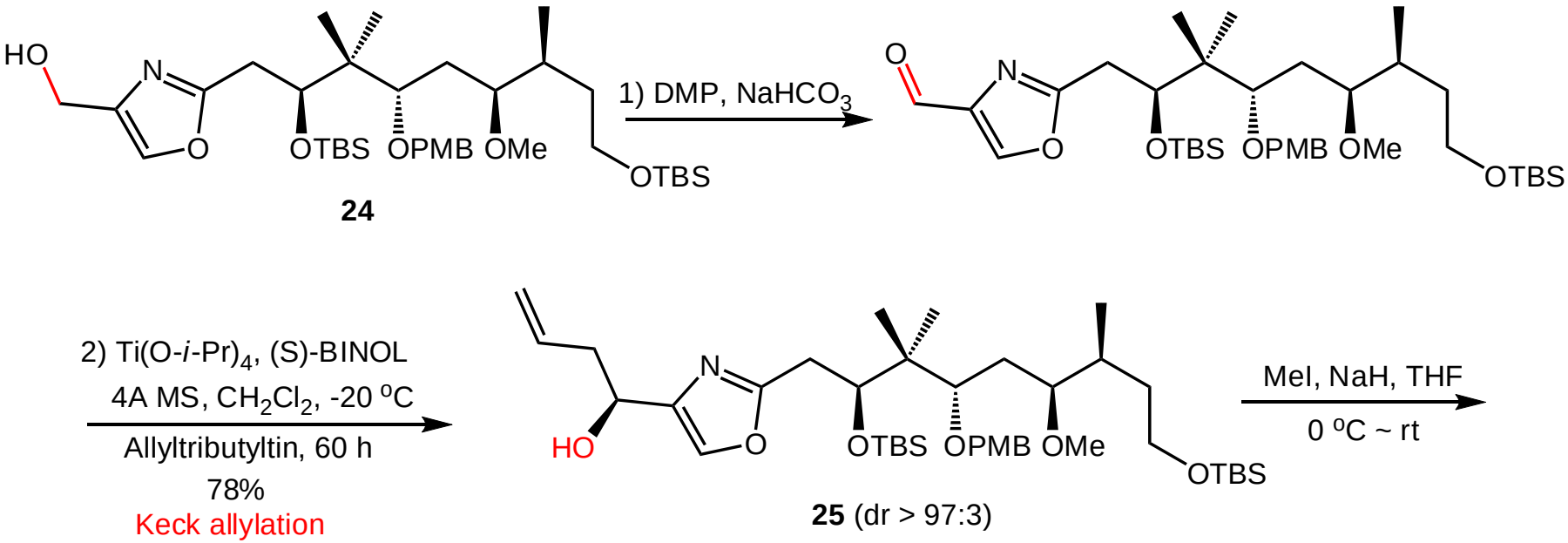


Ring-closing for Oxazoline:



Lellouche, J.-P. et al *Heterocycles* **1995**, *41*, 947-958.

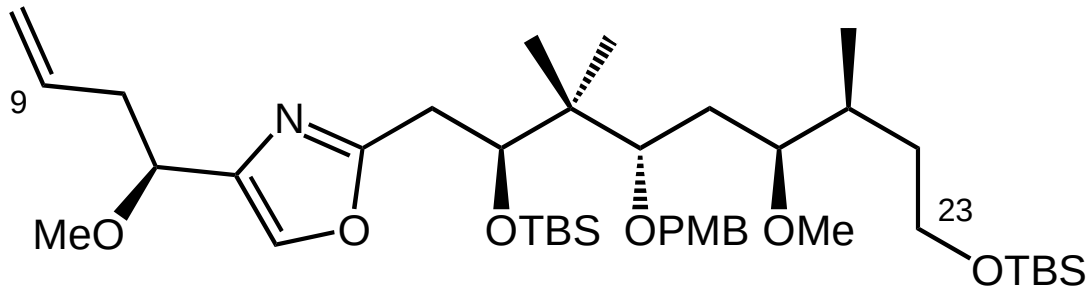
Assembly of the C9-C23 Fragment **3**:



24

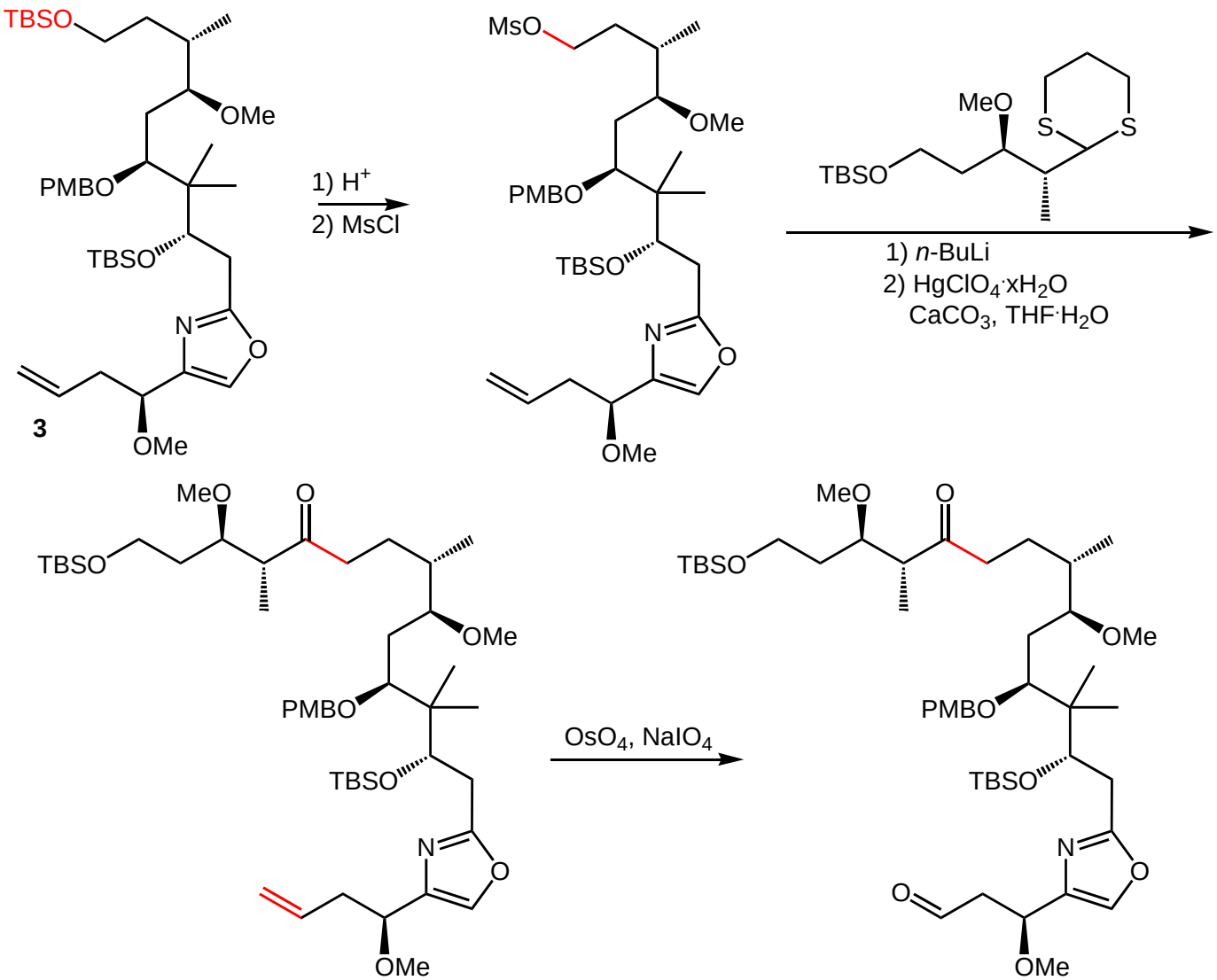
25 (dr > 97:3)

Assembly of the C9-C23 Fragment **3**:

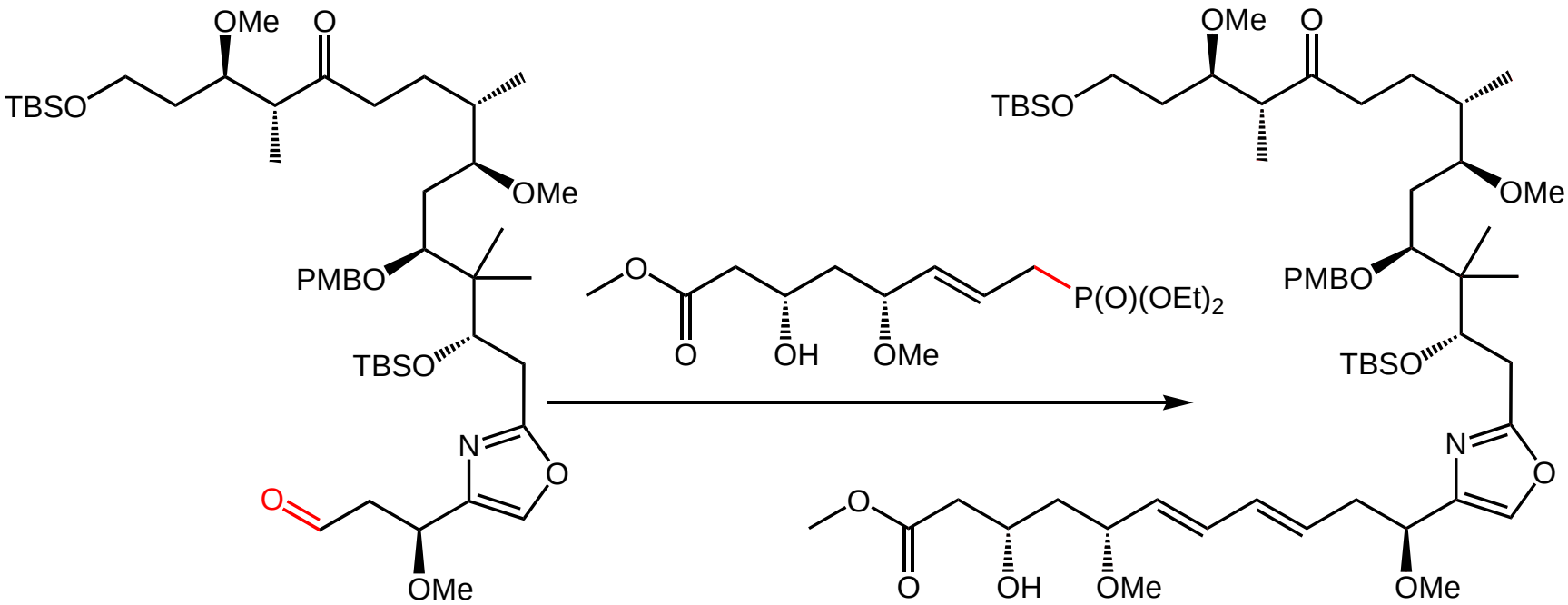


3

Proposed Route for Completed Synthesis of **Rhizopodin**:

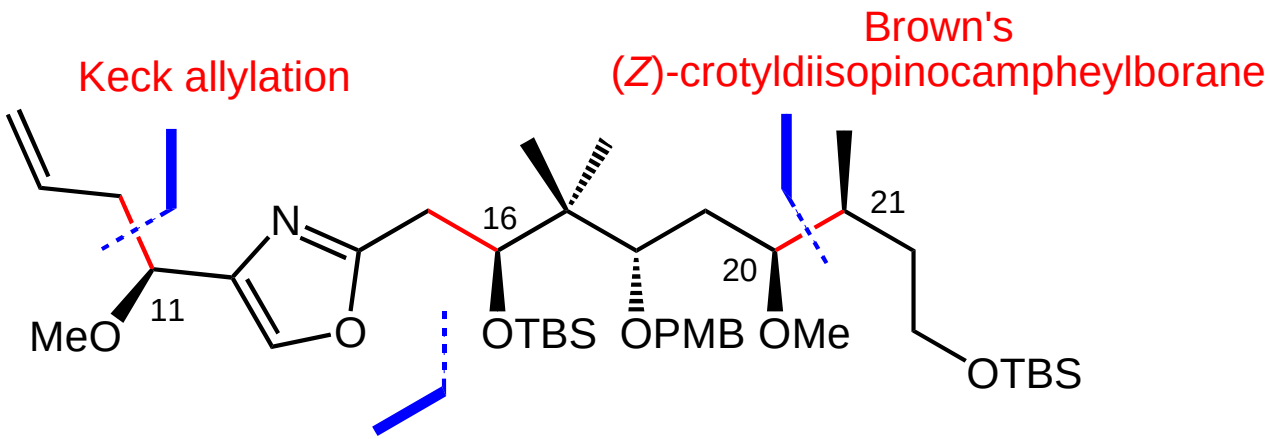


Proposed Route for Completed Synthesis of **Rhizopodin**:



Rhizopodin (**1**)

Summary:


Keck allylation
Brown's
(Z)-crotyldiisopinocampheylborane
MeO
11
N
O
16
OTBS
OPMB
20
OMe
21
OTBS
Sharpless asymmetric epoxidation
Williams' oxazoline dehydrogenation protocol

Introduction:

Rhizopodin is a structurally unique polyketide that was isolated from the myxobacterium *Myxococcus stipitatus* in 1993. Being originally considered as a monomeric lactone, its structure and absolute stereochemistry were recently revised as shown in Figure **1**. The planar structure of rhizopodin is distinguished by a C2-symmetric, 38-membered dilactone exhibiting 18 stereogenic centers, two conjugated diene systems in combination with two disubstituted oxazoles, and two enamide side chains. Rhizopodin displays impressive biological properties including potent cytostatic activity against a range of tumor cell lines in the low nanomolar range. It bears two enamide side chains, each of which binds a single G-actin molecule, resulting in a ternary rhizopodin/G-actin complex. The ability of rhizopodin to interfere with actin cytoskeleton dynamics has allowed it to play important roles as a probe molecule for chemical biology. The low supply of rhizopodin, together with its interesting biological activity and intriguing structure, makes it an attractive target for total synthesis. As part of our research program directed toward the total synthesis, stereochemical and structural studies, and biological evaluation of natural products, we have embarked on the synthesis of rhizopodin. Herein we report a highly stereocontrolled synthesis of fragment **3**, corresponding to the C9-C23 (C9'-C23') fragment of the natural product

Conclusion:

In summary, we have accomplished an efficient and highly stereoselective synthesis of **3** corresponding to the C9-C23 fragment of rhizopodin (28 steps, 4.1% overall yield). Key transformations in the sequence include installation of the C(20) and C(21) stereogenic centers via asymmetric crotylboration and hydroxyl-directed reductive opening of an epoxide, construction of the oxazole via Williams' oxazoline dehydrogenation protocol, and introduction of the C(11) stereogenic center via an asymmetric Keck allylation. Progress toward the development of an efficient total synthesis of rhizopodin will be reported in due course.