Total Synthesis, Assignment of the Relative and Absolute Stereochemistry,and Structural Reassignment of Phostriecin (aka Sultriecin)

Christopher P. Burke, Nadia Haq, and Dale L. Boger*

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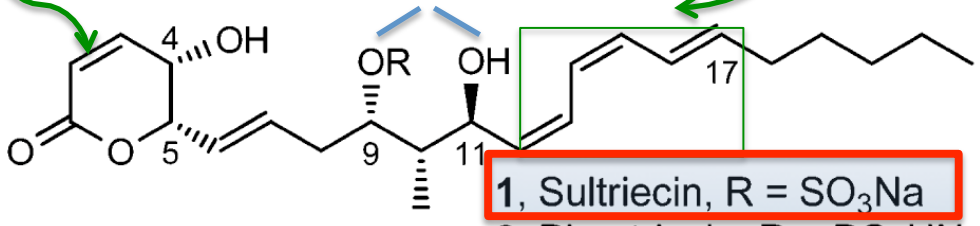
Structural features

Electrophilc α,β-unsaturated lactone

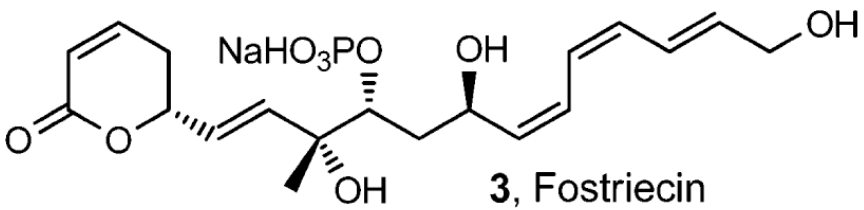
hydrophobic *Z,Z,E-triene capping*

Functionalized 1,3-diol

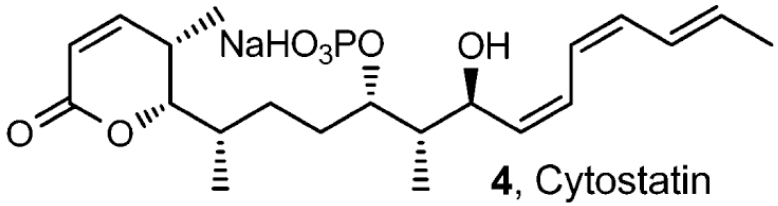


1, Sultriecin, R = SO_3Na

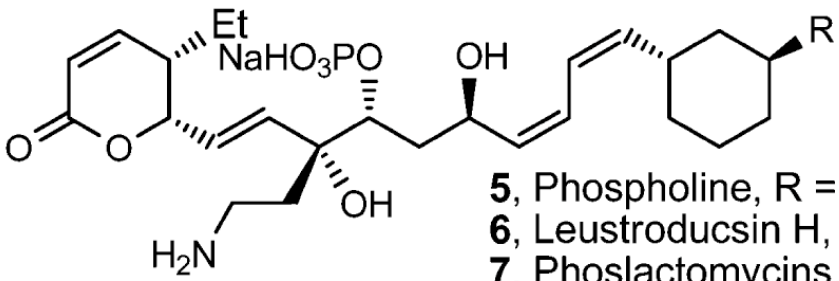
2, Phostriecin, R = PO_3HNa



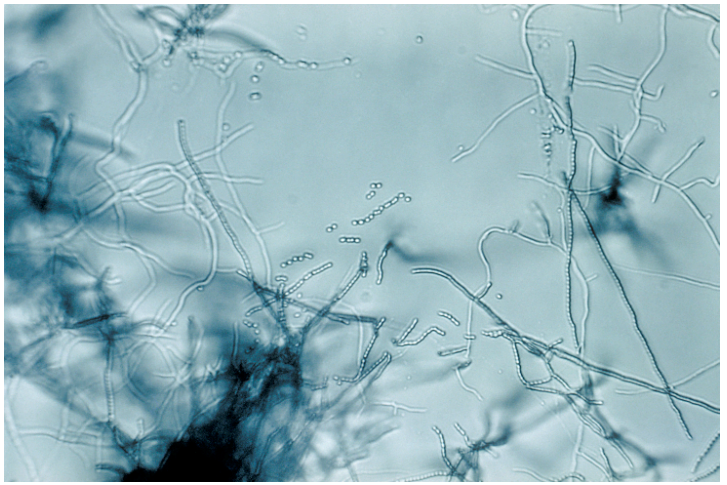
3, Fostriecin



4, Cytostatin



5, Phospholine, R = H
6, Leustroducsin H, R = OH
7, Phoslactomycins, R = OCOR'

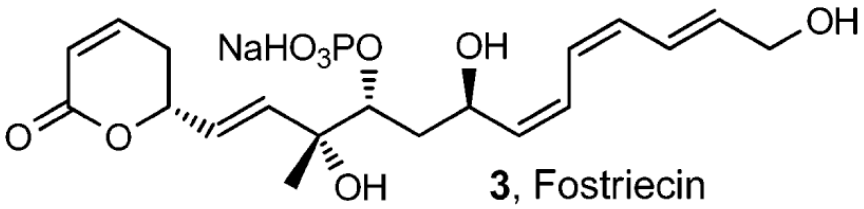


Streptomyces roseiscleroticus No. L827-7 (isolation 1983)

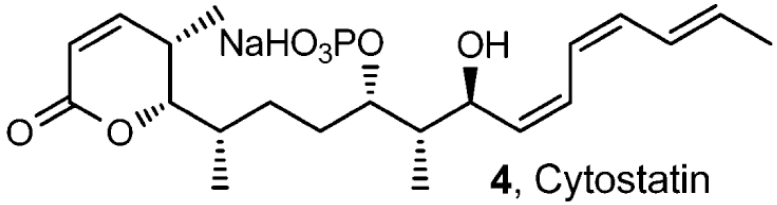
protein phosphatase 2A (PP2A) inhibitors

Ohkuma, H.; Naruse, N.; Nishiyama, Y.; Tsuno, T.; Hoshino, Y.; Sawada, Y.; Konishi, M.; Oki, T. *J.Antibiot.* ***1992, 45, 1239***

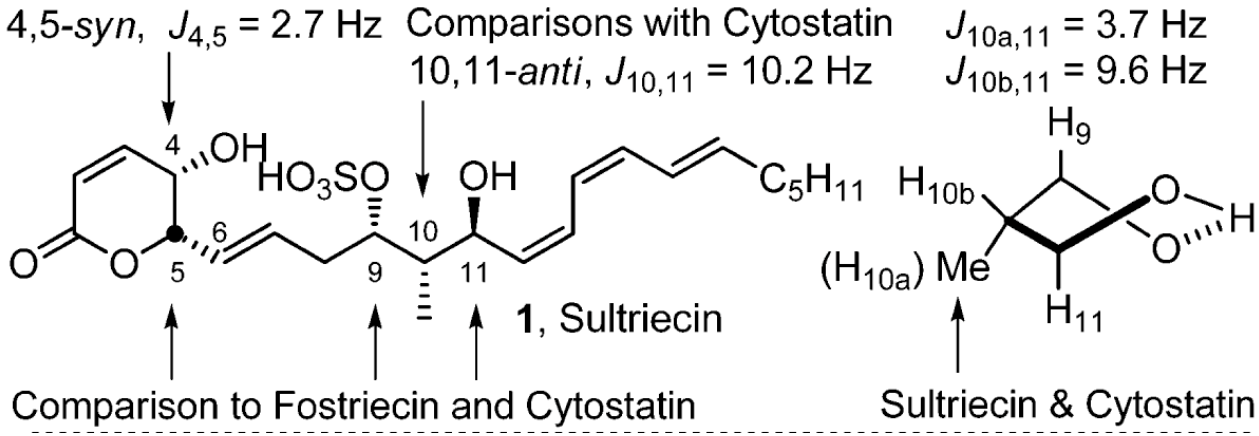
Relative and Absolute Stereochemistry



3, Fostriecin



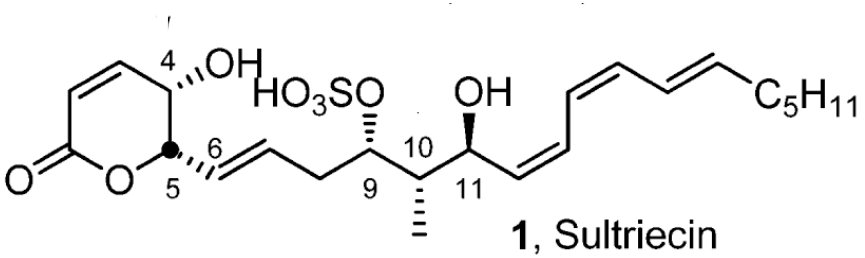
4, Cytostatin



(4S,5S,9S,10S,11S)- **Twist boat: H-bonding between SO_3H- C11-OH**

Lawhorn, B. G.; Boga, S. B.; Wolkenberg, S. E.; Colby, D. A.; Gauss, C.-M.; Swingle, M. R.; Amable, L.; Honkanen, R. E.; Boger, D. L. *J. Am. Chem. Soc.* **2006,** *128,* 16720.

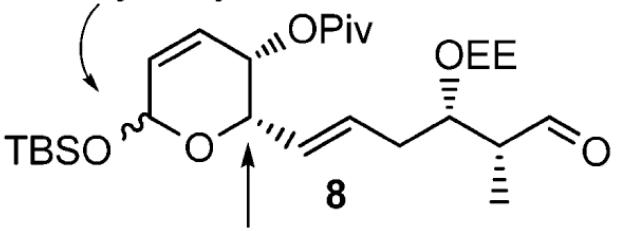
Retrosynthetic Analysis



1, Sultriecin

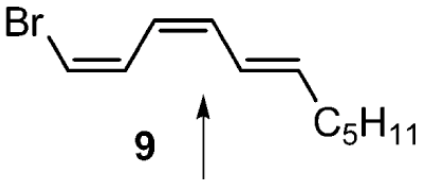
Chelation-Controlled
Addition to Aldehyde

Oxidative Ring Expansion
of α-Hydroxyfuran



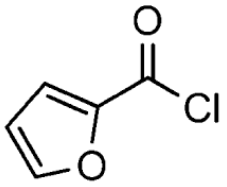
8

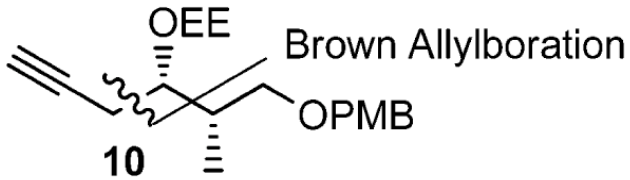
CBS Reduction



9

Electrocyclic Ring Opening

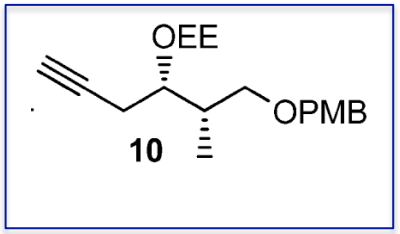


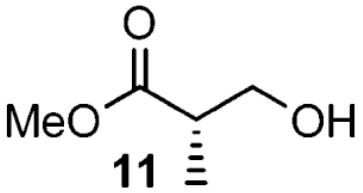


10

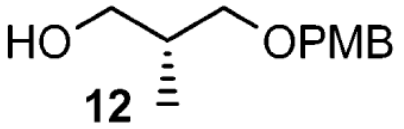
Brown Allylboration

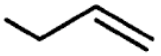
Synthesis of Alkyne 10

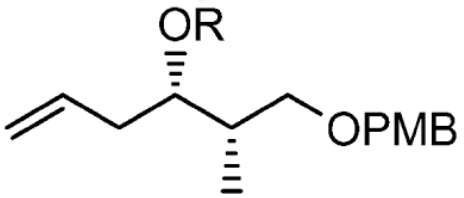




1. $PMBOC(=NH)CCl_3$
2. $LiAlH_4$ 91%, 2 steps

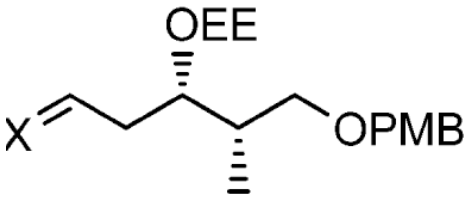


1. Swern
2. (–)-Ipc_2B 
–100 °C
14:1 dr



Ethyl vinyl ether
PPTS
13, R = H
14, R = EE

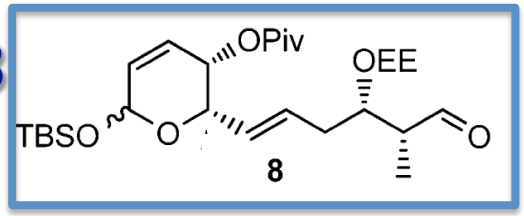
OsO_4, NMO
$NaIO_4$
73%, 4 steps

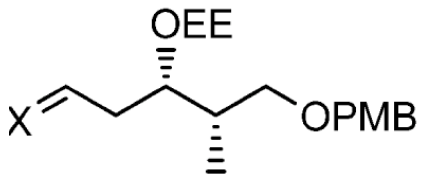


CBr_4, PPh_3, 71%
15, X = O
16, X = CBr_2

EE: direct chelation controll addition.
removal, mild acid

Synthesis of Fragment 8

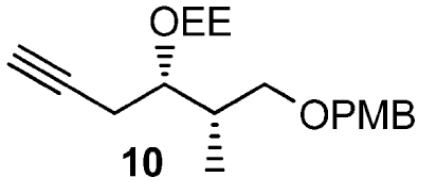




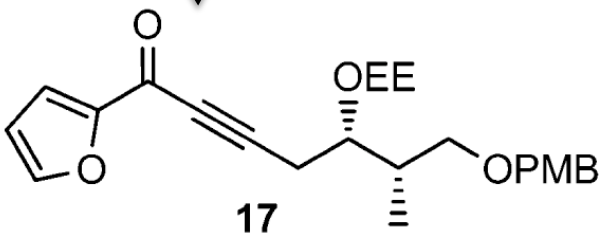
X= CBr_2

n-BuLi

93%

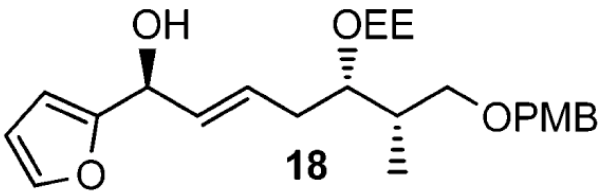


2-furoyl chloride
$Pd(PPh_3)_2Cl_2$
CuI, Et_3N, 85%



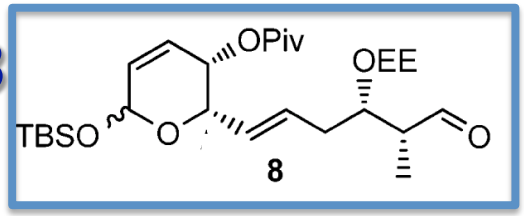
1. (*R*)-CBS cat., BH_3–Me_2S
–40 °C, 12.5:1 dr

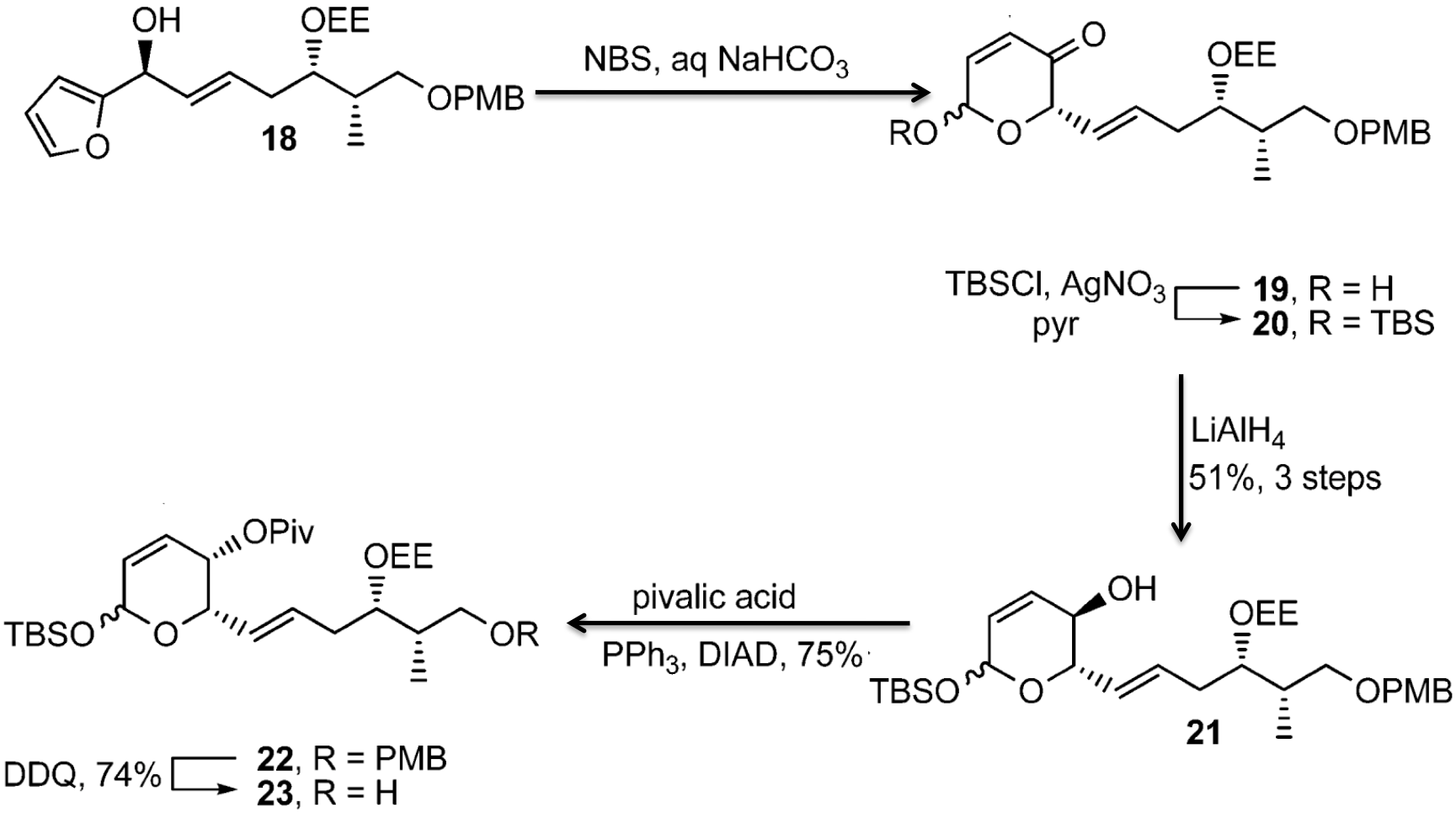
2. $LiAlH_4$
84%, 2 steps



CBS-reduction of α,β-unsaturated ketone: dr 2.5:1

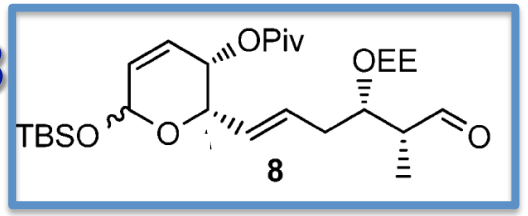
Synthesis of Fragment 8

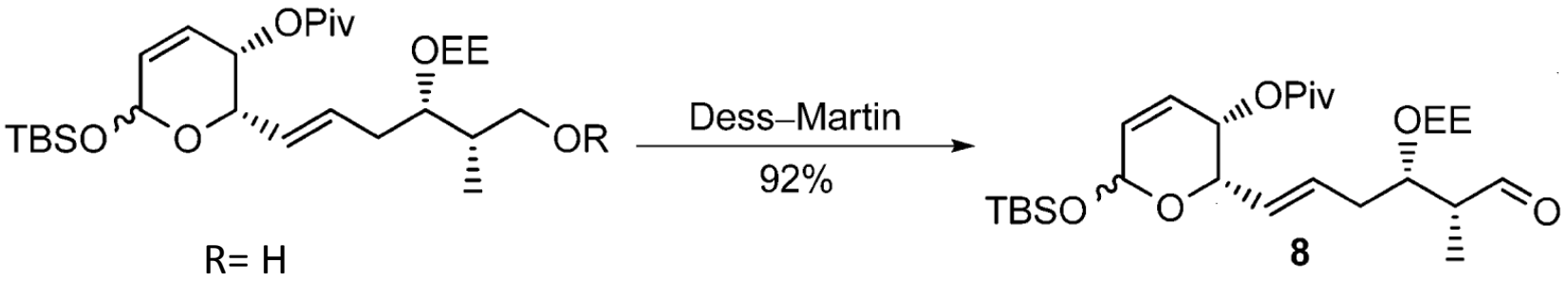




Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004,** *126,* 3428

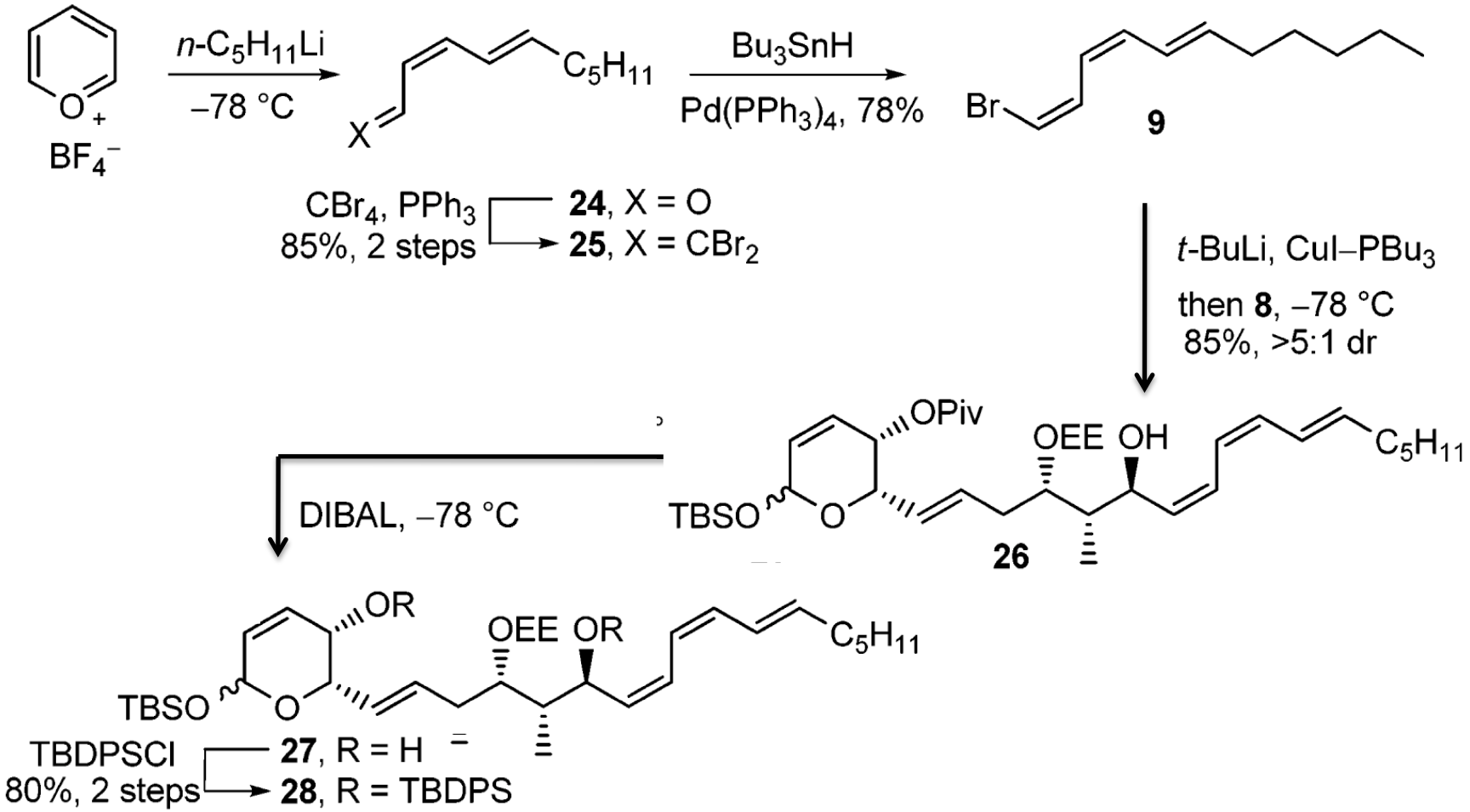
Synthesis of Fragment 8





R= H

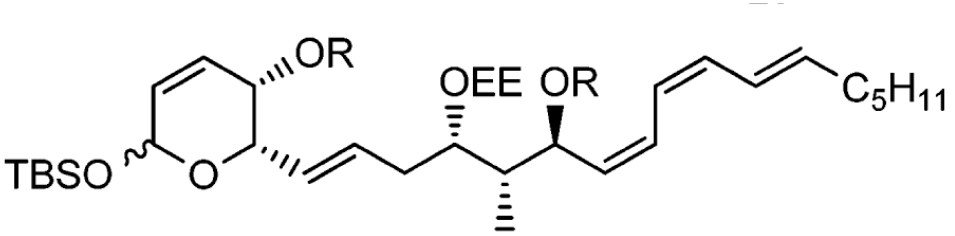
Synthesis of Final Skeleton : Chelation controlled addition



Belosludtsev, Y. Y.; Borer, B. C.; Taylor, R. J. K. *Synthesis* ***1991,*** 320**.**

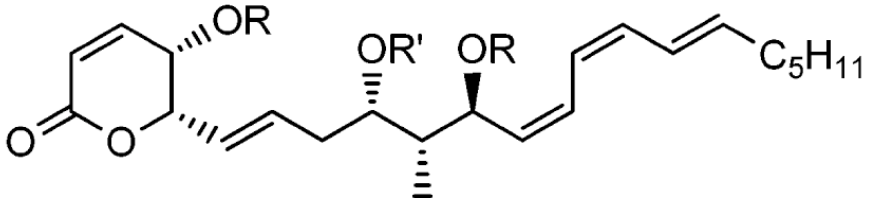
Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998,** *63,* 8965

Synthesis of Sultriecin 1



1. aq HCl, THF
   71%

2. Ag_2CO_3, PhH
   80 °C, 91%



SO_3–pyr, 80%

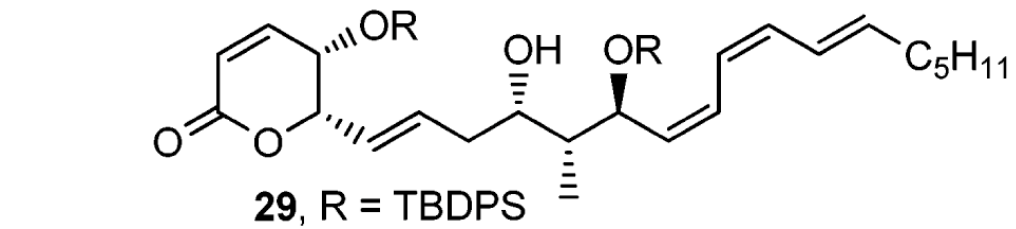
HF–pyr, 60%

29, R = TBDPS, R' = H

30, R = TBDPS, R' = SO_3Na

1, R = H, R' = SO_3Na

Synthesis of Phostriecin 2

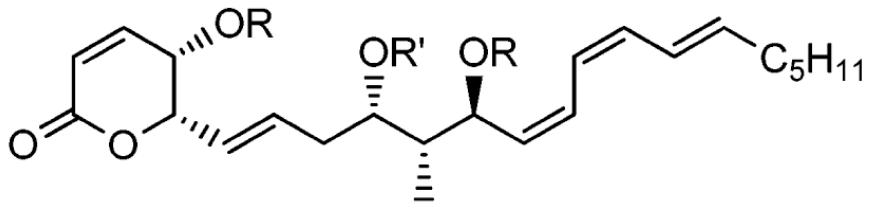


29, R = TBDPS

i-$Pr_2NP(OFm)_2$

tetrazole; H_2O_2

96%



HF–pyr

Et_3N; Dowex Na^+

63%, 2 steps

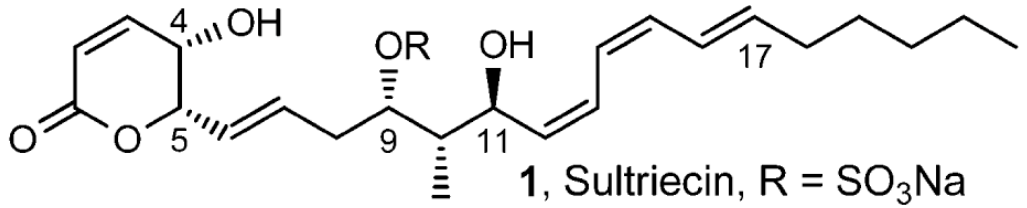
31, R = TBDPS, R' = $PO(OFm)_2$

32, R = H, R' = $PO(OFm)_2$

2, R = H, R' = PO_3HNa

Synthesis : Key Features

- Brown allylation with controlled introduction of C9 stereochemistry
- CBS reduction to establish the lactone C5-stereochemistry
- Diastereoselective oxidative ring expansion of α-hydroxyfuran to the pyran lactone precursor
- Singlestep installation of the sensitive triene unit through a chelationcontrolled cuprate addition.



1, Sultriecin, R = SO_3Na
2, Phostriecin, R = PO_3HNa