Evolution of an Efficient and Scalable Nine-Step (Longest Linear Sequence) Synthesis of Zincophorin Methyl Ester

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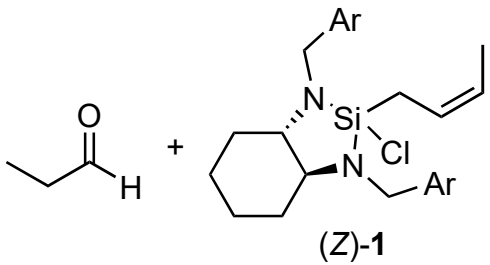
J. Am. Chem. Soc. **2017**, *139*, 4568-4573.



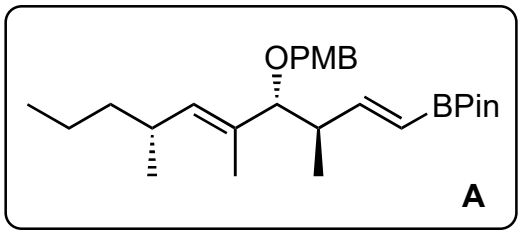
(*Z*)-**1**

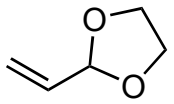
Ar = 4-Br-Ph

1) cat. $Sc(OTf)_3$
2) Methacrolein, Hoveyda-Grubbs 2
3) TsCl, Et_3N, cat. Me_3N•HCl
4) (*E*)-**1**, cat. $Sc(OTf)_3$
5) PMB-Br, Et_3N, KHMDS; then $LiBEt_3H$, Δ
6) Vinyl-BPin, Hoveyda-Grubbs 2

1) Product is (*S,S*)-configured

1-6



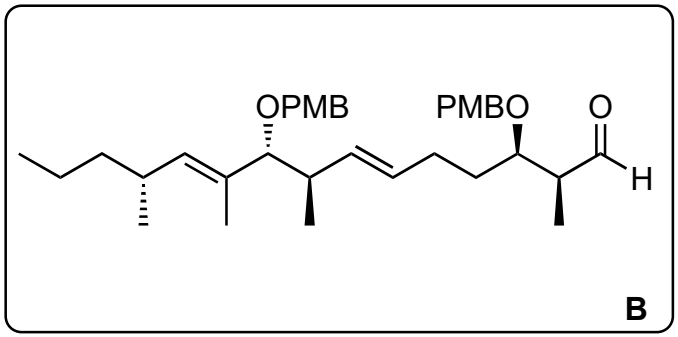


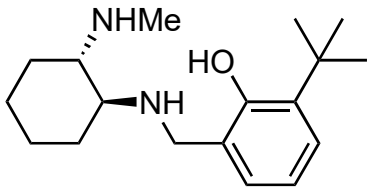
7) cat. $Rh(acac)(CO)_2$ / (*R,R*)-Ph-BPE, H_2, CO; then CH_2=$CHCH_2$–$SiCl_3$, DBU, **2**
8) PMB-Cl, Et_3N, KHMDS, 18-crown-6
9) cat. OsO_4, $NaIO_4$, 2,6-lutidine
10) $NaBH_4$
11) PPh_3, CBr_4, Et_3N
12) **A**, cat. $Pd(OAc)_2$ / P*t*-Bu_2Me, NaOH
13) TMSOTf, 2,2'-bipy

7) Product is (2*S*,3*R*)-configured

13) Acetal hydrolysis

7-13





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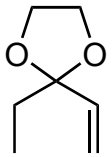
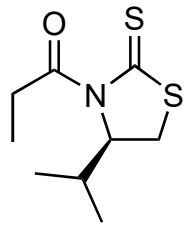


14-21

Zincophorin Methyl Ester

14) cat. $Rh(acac)(CO)_2$ / (*S,S*)-Ph-BPE, H_2, CO
15) *trans*-crotyl–BPin; then 2 M aq HCl
16) cat. $Rh(acac)(CO)_2$ / PPh_3, CO, H_2
17) Ac_2O, Pyridine, DMAP
18) {**3**, $TiCl_4$, DIPEA} added to previous, $SnCl_4$
19) MeOH, DMAP
20) Cy_2BCl, Et_3N, then add **B**
21) **4**, then DDQ, H_2O



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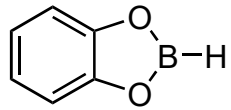
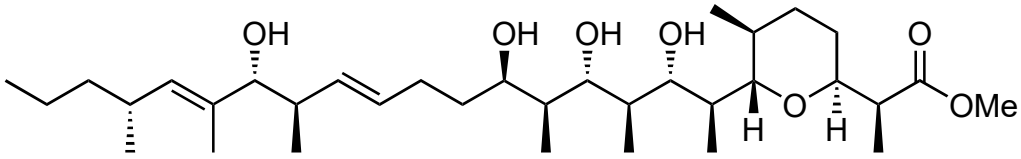


4

14) Product is (*R*)-configured
16) Product is a lactol



Zincophorin Methyl Ester