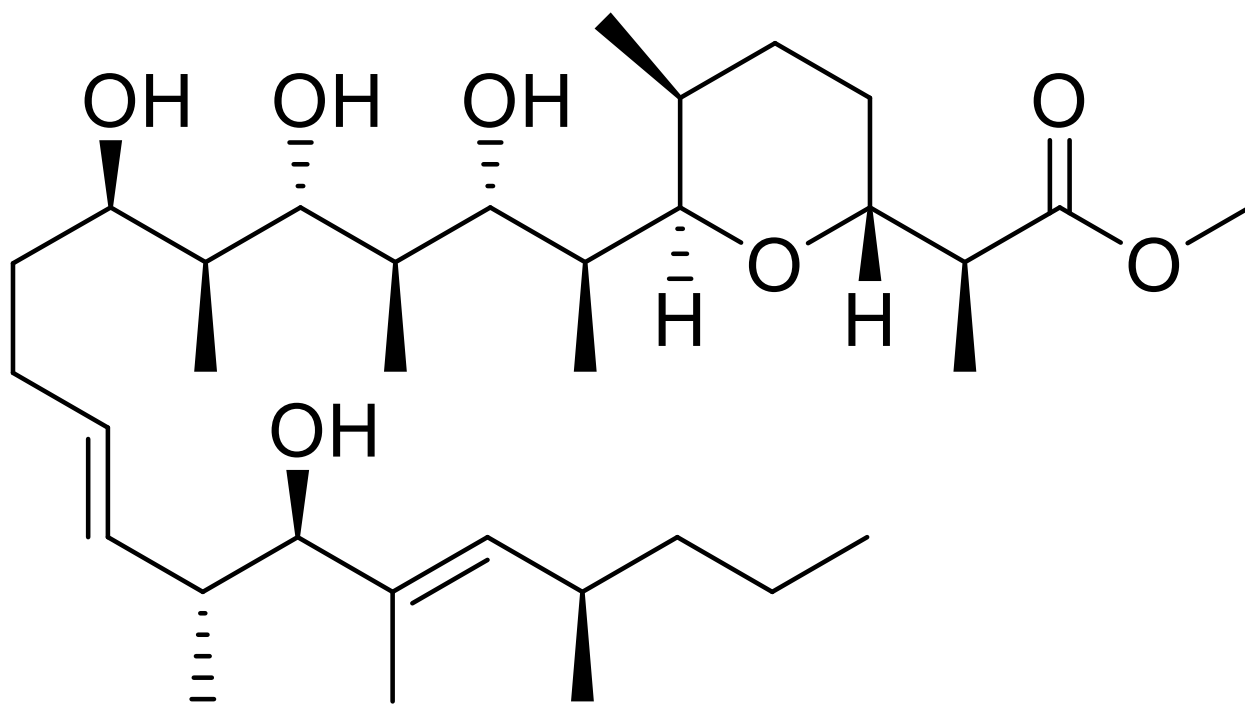


Total Synthesis of (+)- Zincophorin Methyl

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University of Texas at Austin, Department of Chemistry
and Biochemistry



Presented by:
Emmanuel W Maloba
Michigan State University
For CEM 852, SS18
04/21/2018

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- ❖ Zincophorin (one of the naturally occurring polyoxygenated ionophore) was isolated from a strain of *Streptomyces griseus*.
- ❖ These ionophores exhibit anti-infectious properties and have capacities to form lipophilic complexes with various cations, usually alkaline or alkaline-earth ones, which affect proton-cation exchange processes across biological membranes.
- ❖ Zincophorin and its calcium salt exhibited broad in vitro antibiotic activities against Gram-positive bacteria as well as *Clostridium welchii*.
- ❖ The ammonium and sodium salts of zincophorin showed significant anticoccidial activity against *Eimeria tenella* in chicken embryos.
- ❖ The methyl ester of zincophorin was reported to possess antiviral activity with reduced host cell toxicity compared to the free acid.
- ❖ Zincophorin has elicited considerable synthetic interest since 1987 and several total synthesis papers towards it have been published.

Gräfe, U.; Schade, W.; Roth, M.; Radics, L.; Incze, M.; Ujszaszy, K. *J. Antibiot.* **1984**, *37*, 8

Brooks, H. A.; Gardner, D.; Poyser, J. P.; King, T. J. *J. Antibiot.* **1984**, *37*, 1501 (Antibiotic

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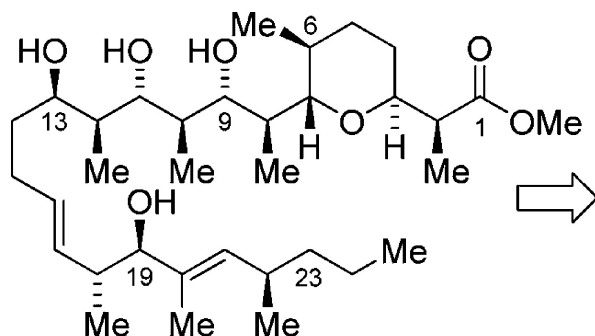
Reported Total Syntheses of Zincophorin Methyl Ester

Synthesis	Construction Steps	Strategic Redox	Non-Strategic Redox	Protecting Group Manipulations	Functional Group Interconversions	Total Steps (LLS)
Danishefsky (1987)	12	4	15	14	16	61 (35)
Cossy (2003)	13	3	18	10	12	56 (30)
Miyashita (2004)	21	1	13	12	5	53 (38)
Leighton (2011)	10	1	3	8	11	33 (21)
Guindon (2015)	12	2	21	18	17	70 (49)
Krische (2015)	10	0	3	3	9	25 (13)

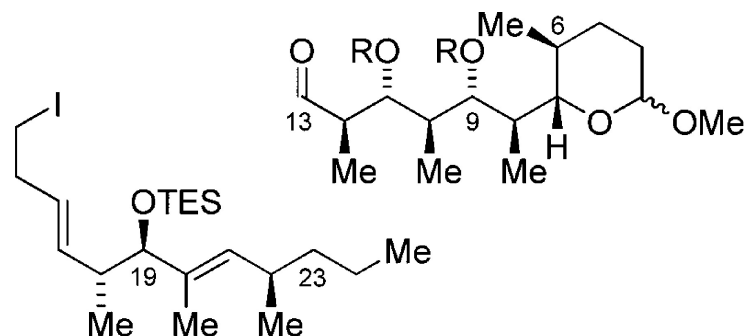
1. Danishefsky, *J. Am. Chem. Soc.* **1987**, *109*, 1572; *J. Am. Chem. Soc.* **1988**, *110*, 4368
2. Cossy, *Org. Lett.* **2003**, *5*, 4037; *J. Org. Chem.* **2004**, *69*, 4626
3. Miyashita, *Angew. Chem. Int. Ed.* **2004**, *43*, 4341
4. Leighton, *J. Am. Chem. Soc.* **2011**, *133*, 7308.
5. Guindon, *Tetrahedron* **2015**, *71*, 709
6. Krische *J. Am. Chem. Soc.* **2015**, *137*, 137–8903

J. Am. Chem. Soc. **2015**, *137*, 137–8903

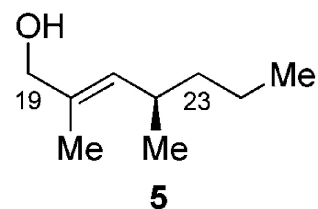
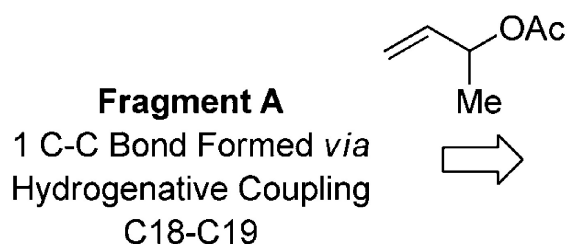
Retrosynthesis



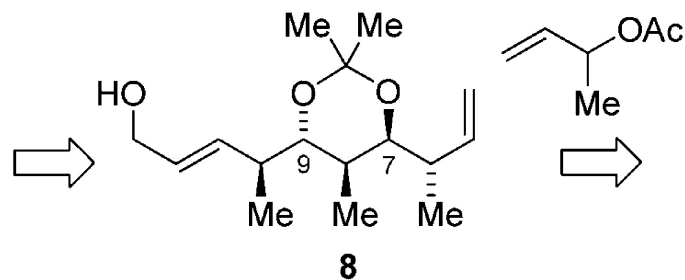
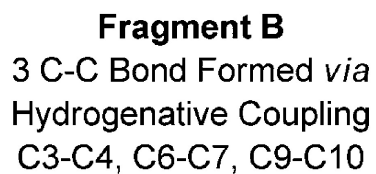
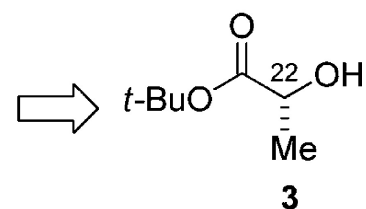
Zincophorin Methyl Ester
13 Steps (LLS), 25 Total Steps



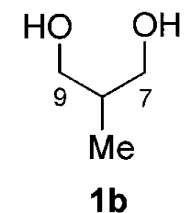
Fragment A **Fragment B** (R= Et₃Si)
8 Steps (LLS) 10 Steps (LLS)



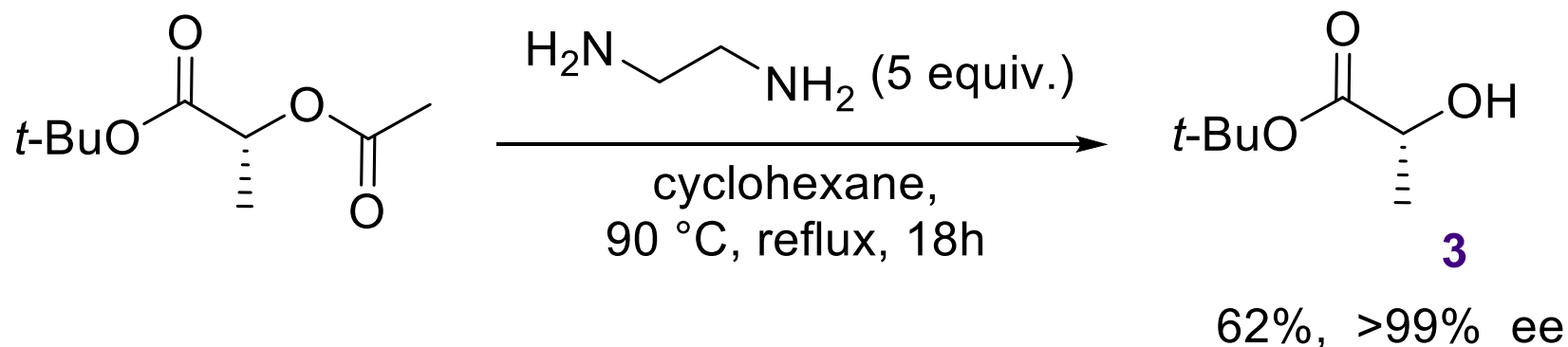
5 steps (LLS)



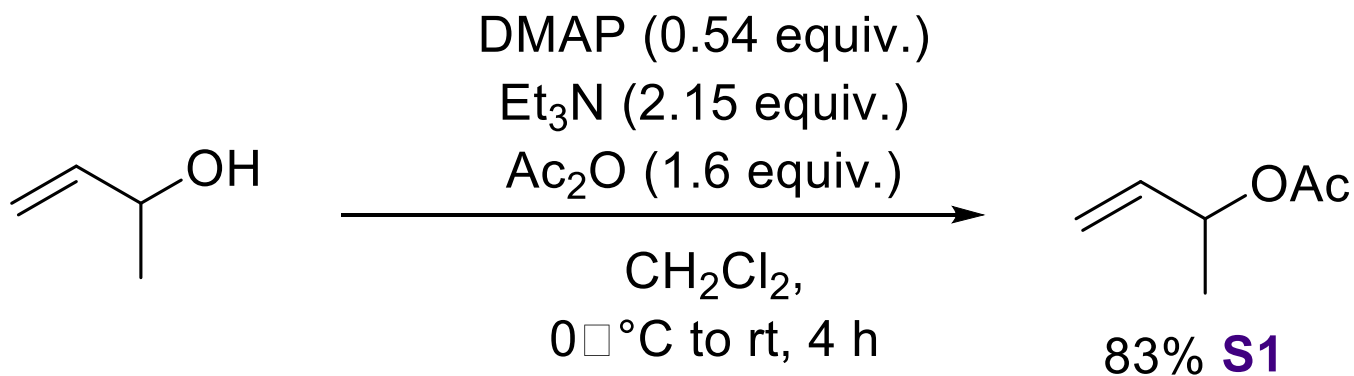
5 steps (LLS)



Preparation of Starting Materials

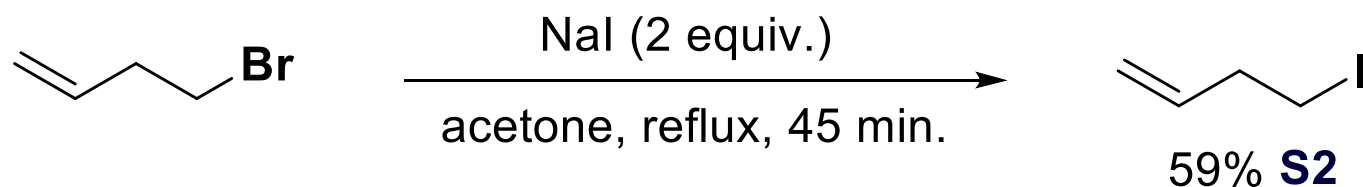


Angew. Chem. Int. Ed. **2008**, 47, 5451–5455

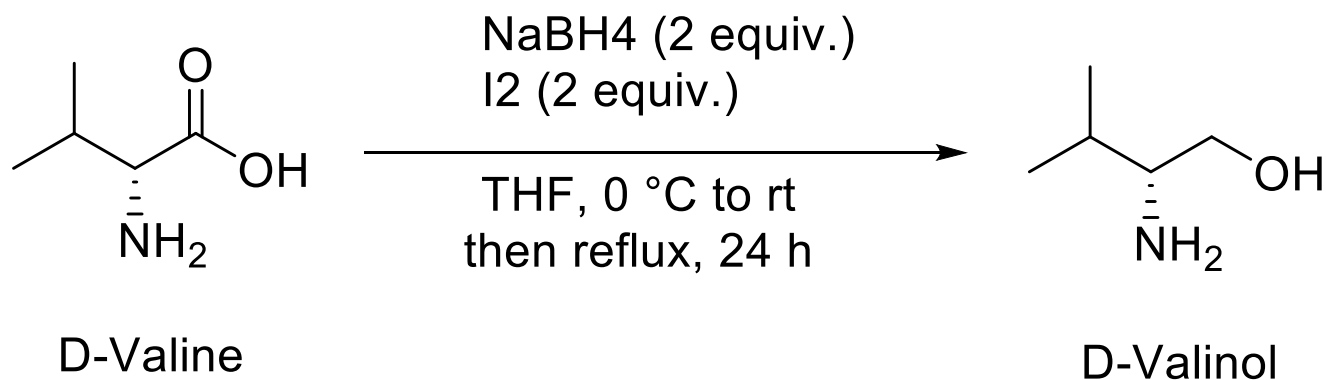


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Preparation of Starting Materials Cont...

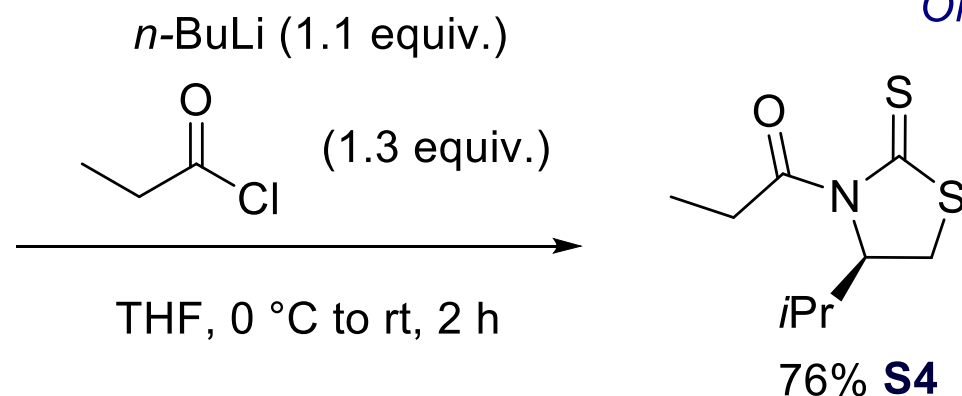
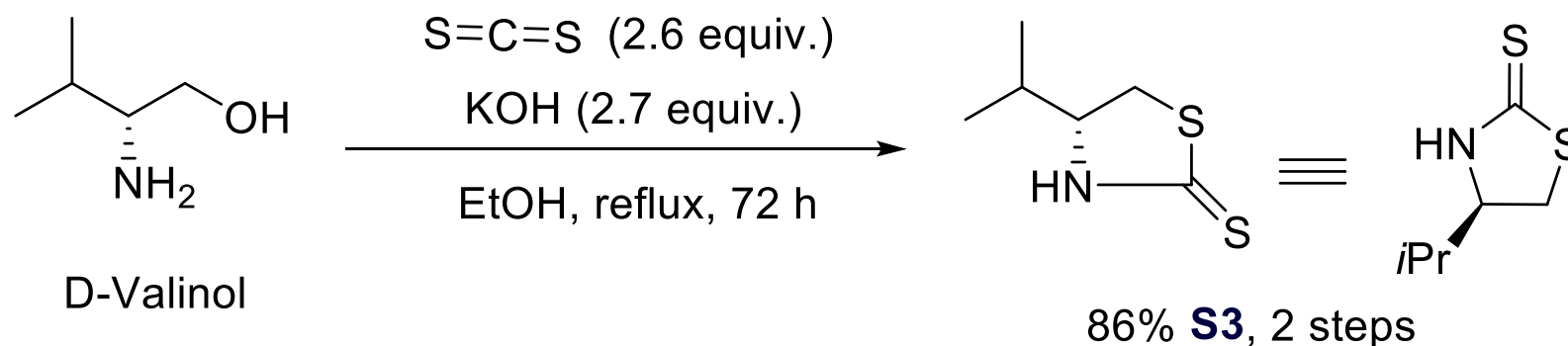


Org. Lett. **2008**, *10*, 2781



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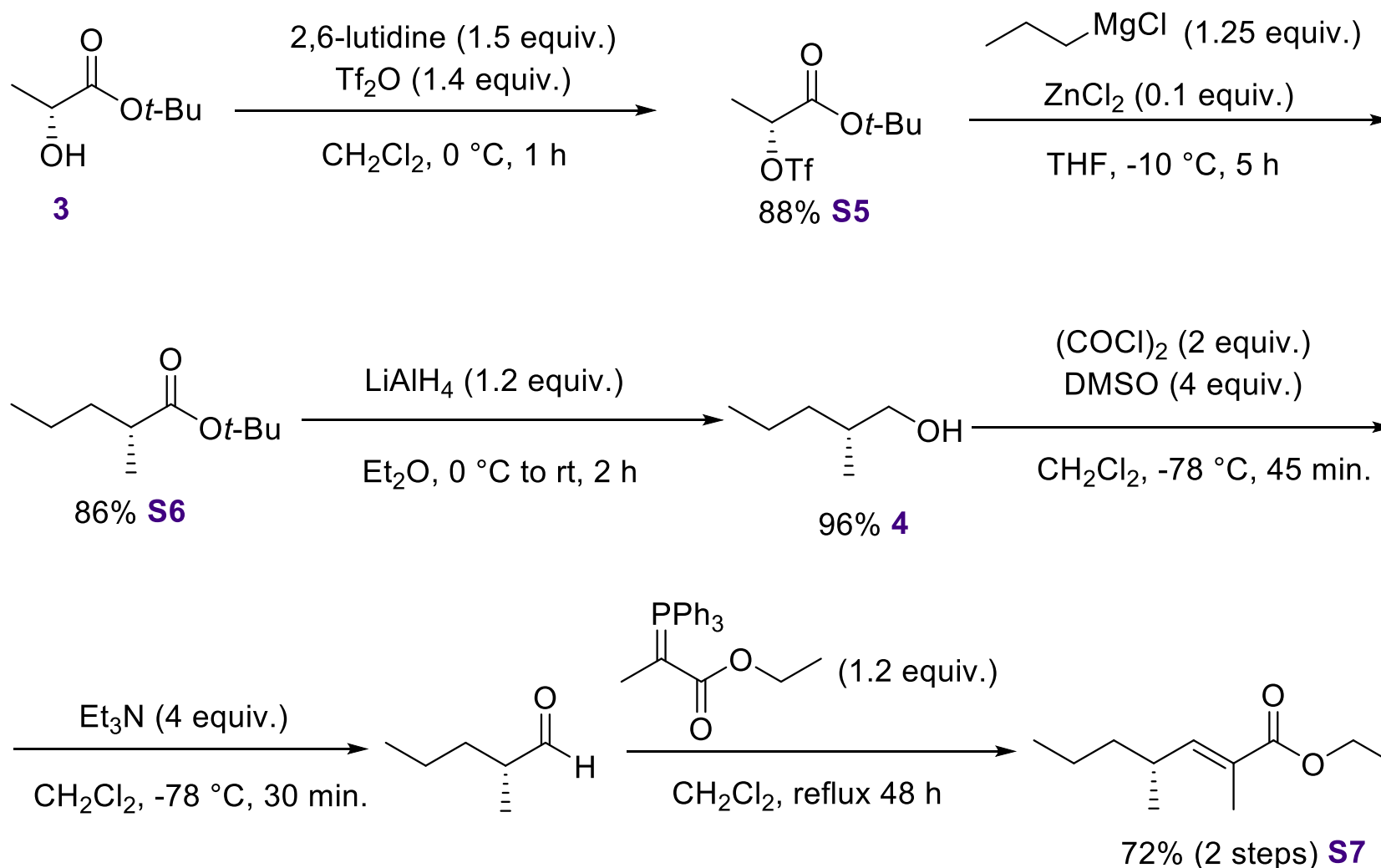
Preparation of Starting Materials Cont...



Organic Synthesis, **2009**, 86, 70

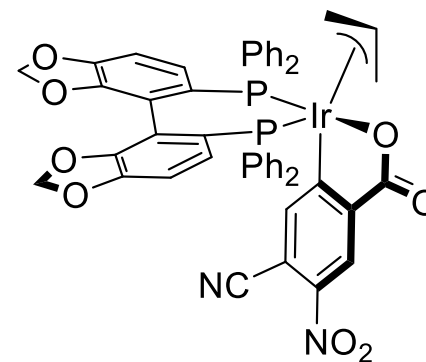
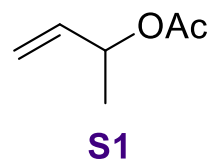
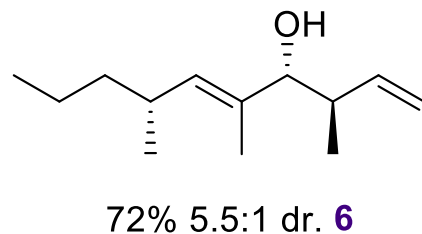
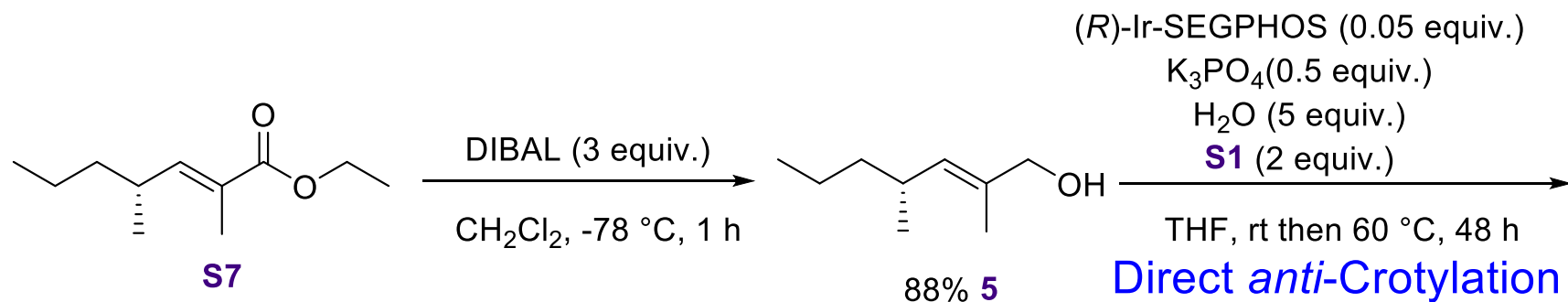
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Synthesis of Fragment A

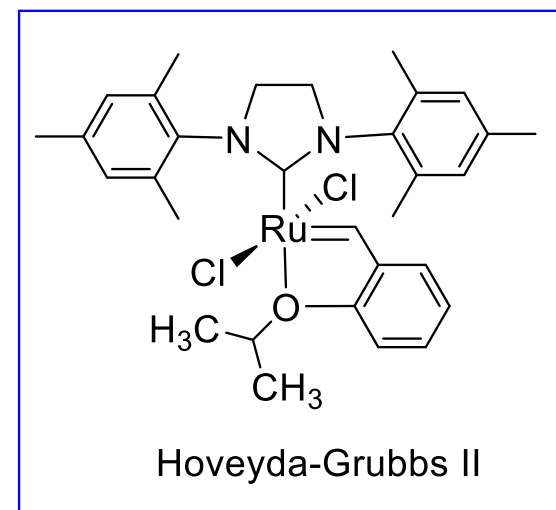
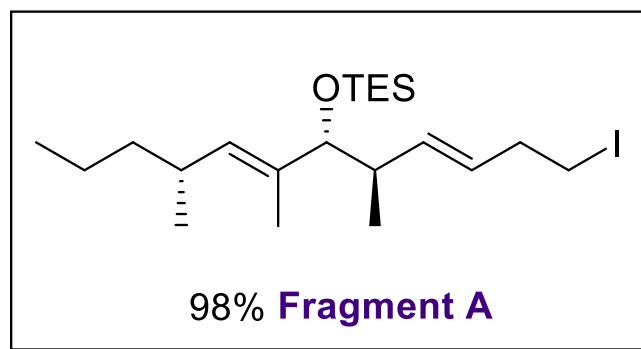
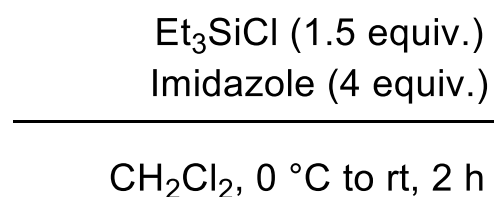
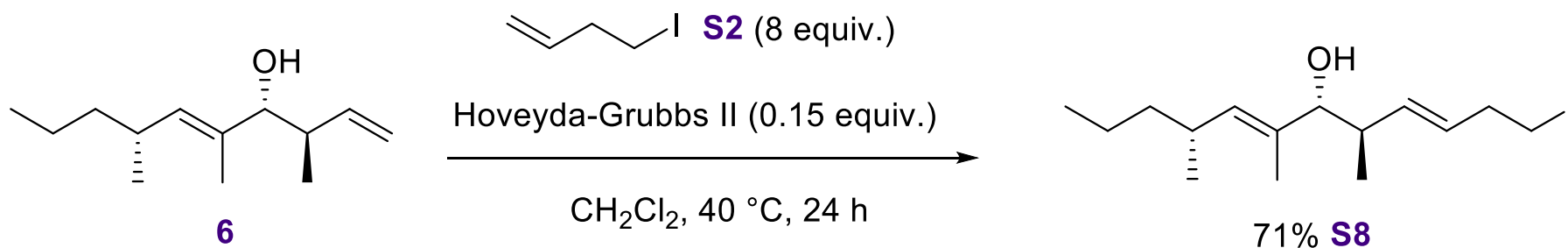


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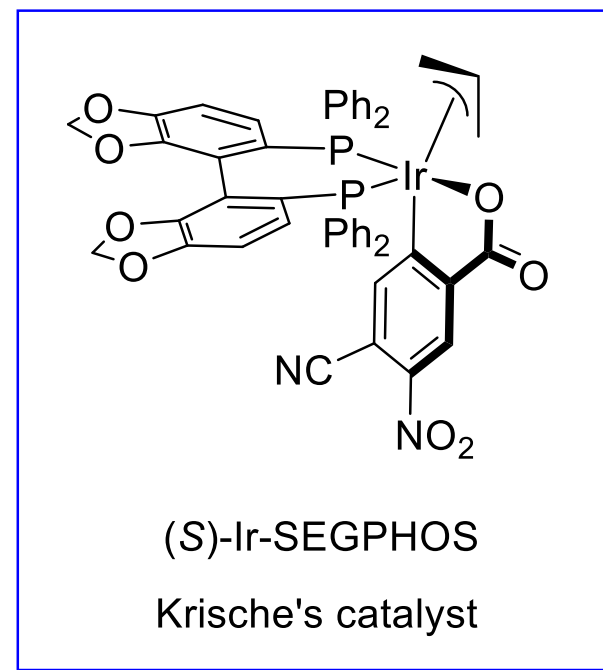
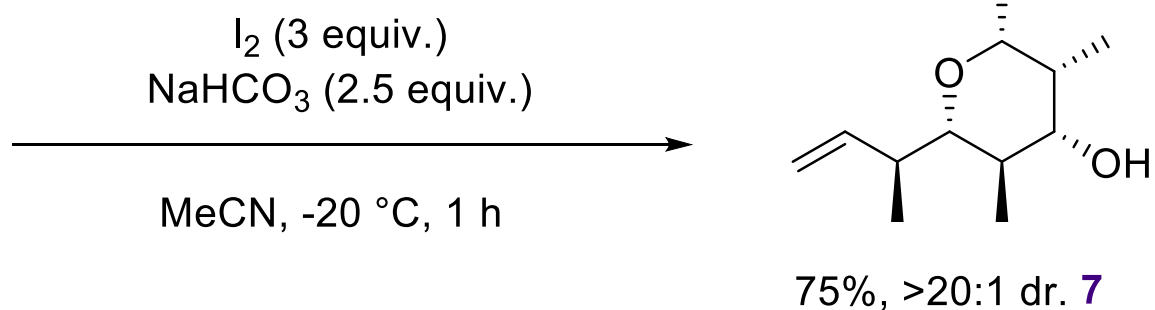
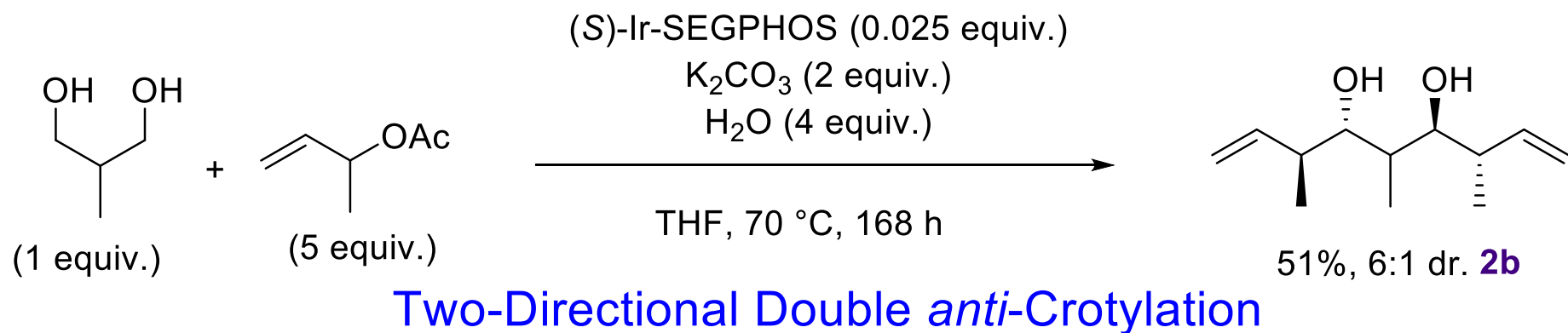
Synthesis of Fragment A Cont...



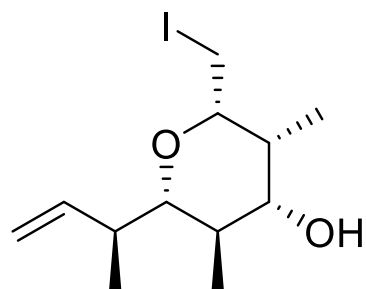
Synthesis of Fragment A Cont...



Synthesis of Fragment B



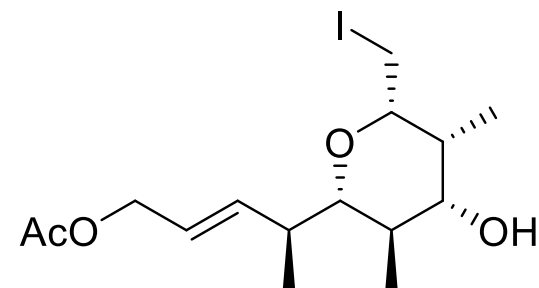
Synthesis of Fragment B Cont...



75%, >20:1 dr. **7**

(Z)-but-2-ene-1,4-diyl diacetate **b** (7 equiv.)
Stewart–Grubbs catalyst (0.085 equiv.)

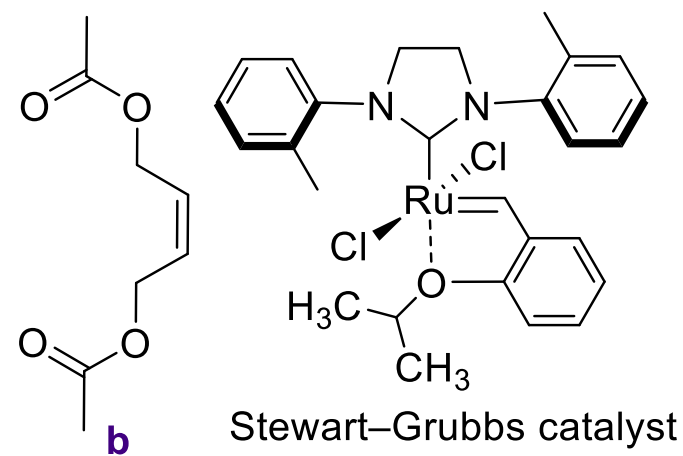
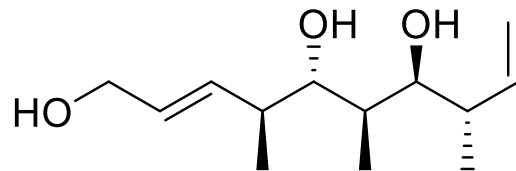
CH₂Cl₂, 40 °C, 24 h



81% **S9**

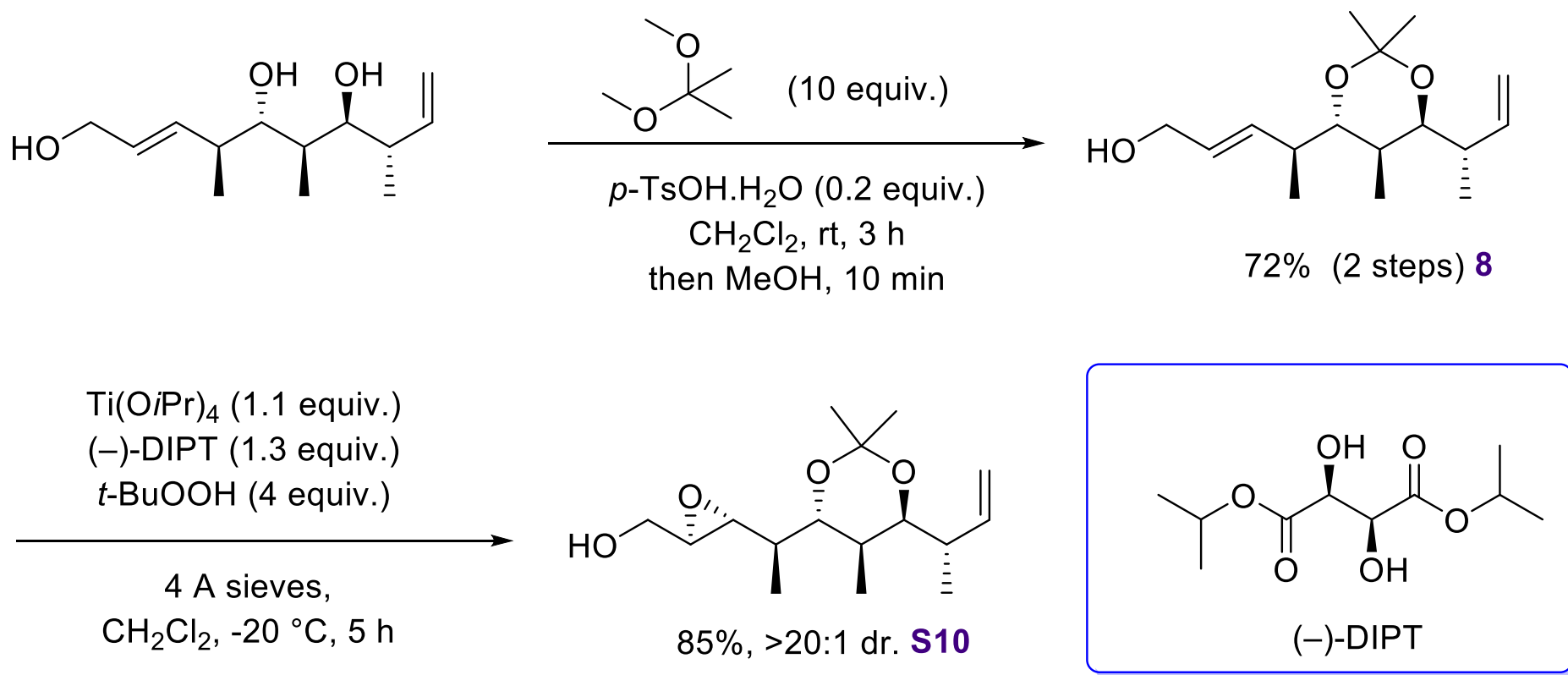
Zn (15 equiv.)
NH₄Cl (10 equiv.)

MeOH, 65 °C, 12 h



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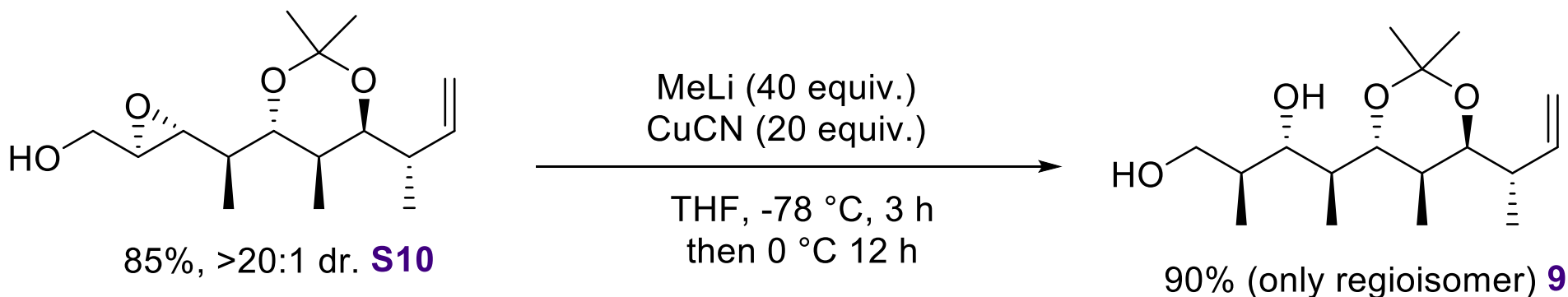
Synthesis of Fragment B Cont...



Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974

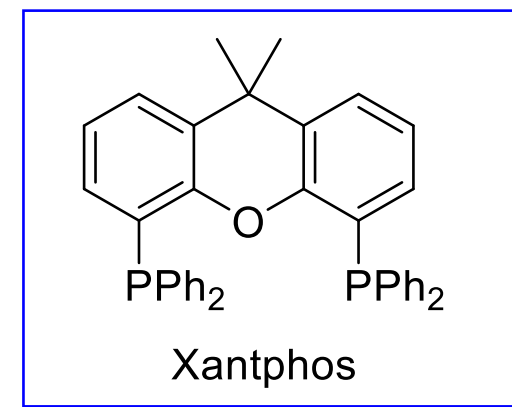
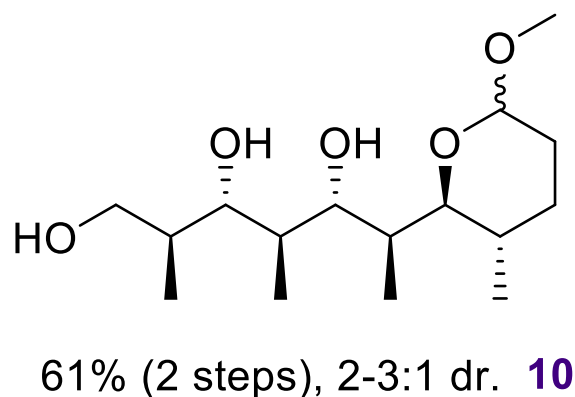
J. Am. Chem. Soc. **2015**, *137*, 137–8903

Synthesis of Fragment B Cont...

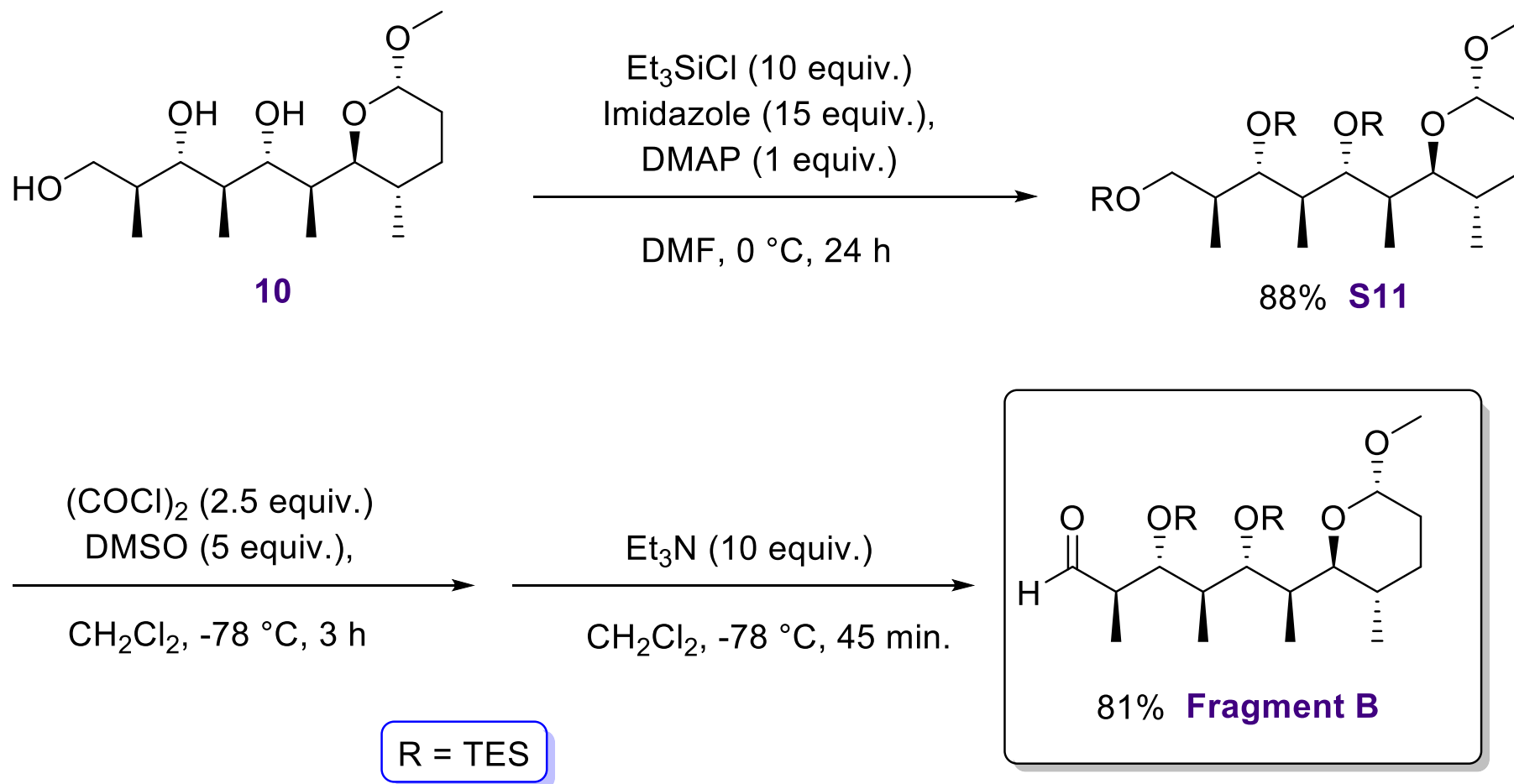


Rh(CO)₂acac (0.05 equiv.)
Xantphos (0.075 equiv.)
H₂/CO (1:1) 800 psi total
(Hydroformulation)

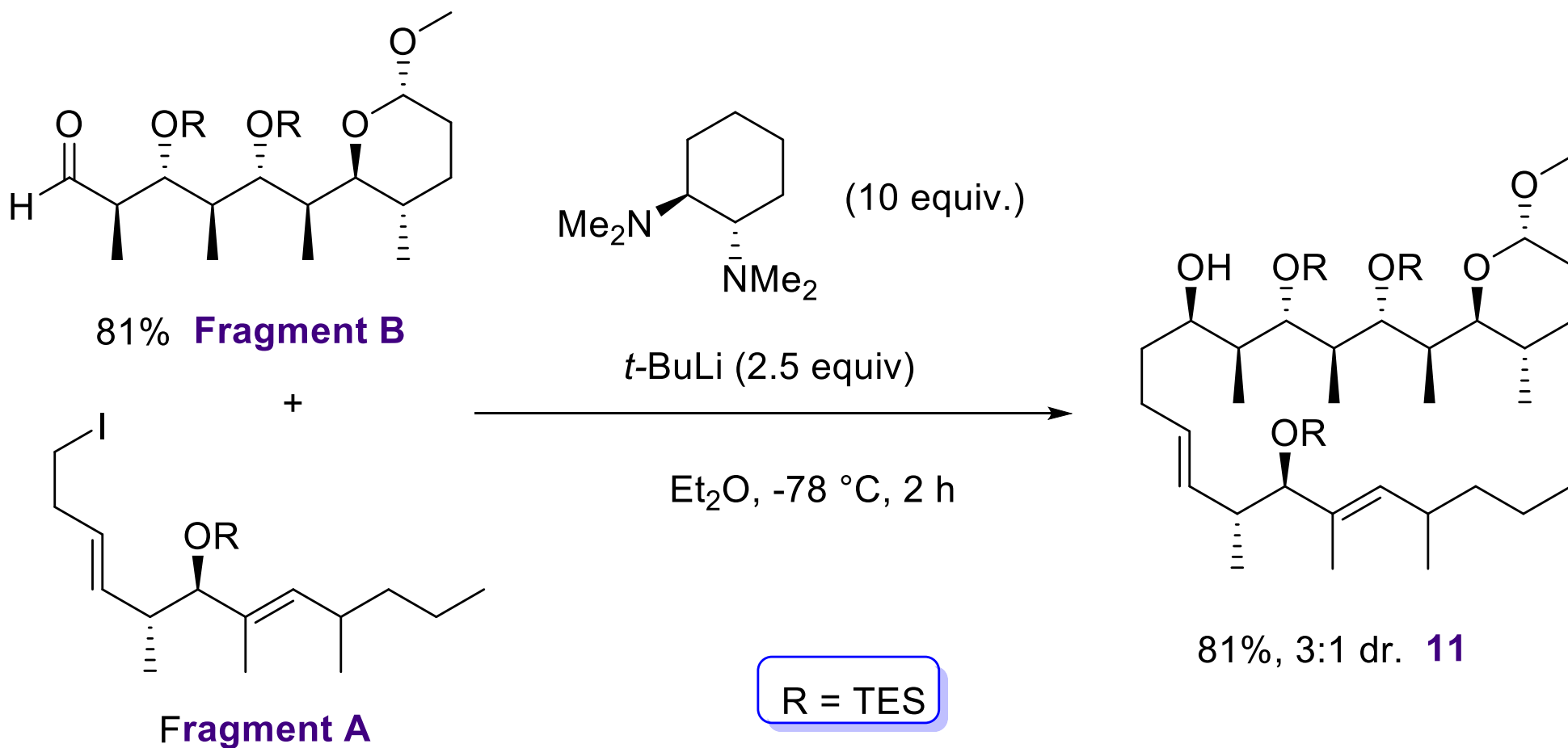
THF, 100 °C, 48 h
then p-TsOH (0.15 equiv.)
MeOH, rt, 6 h



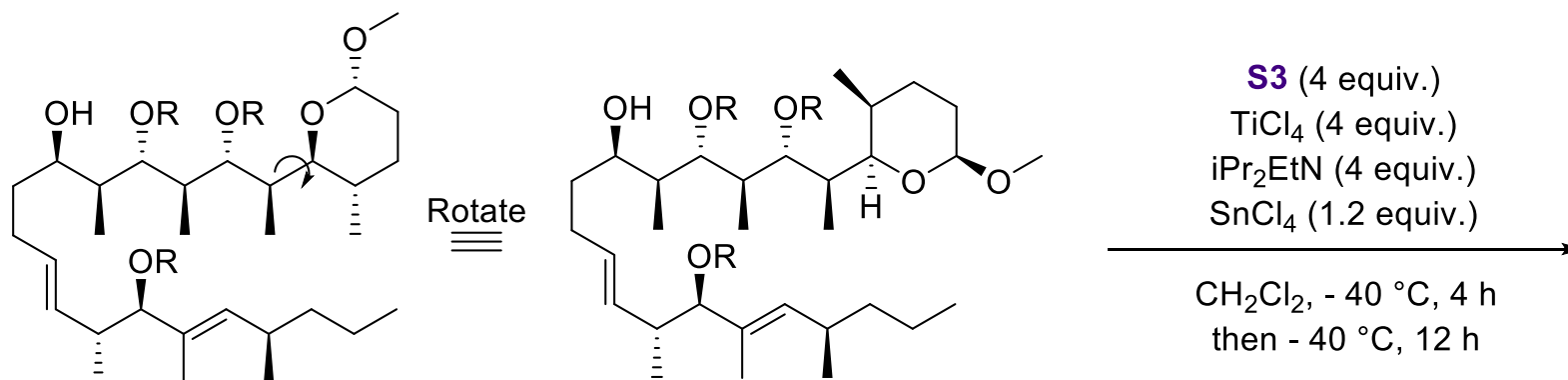
Synthesis of Fragment B Cont...



Union of Fragment A and Fragment B



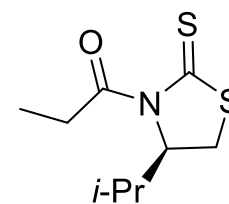
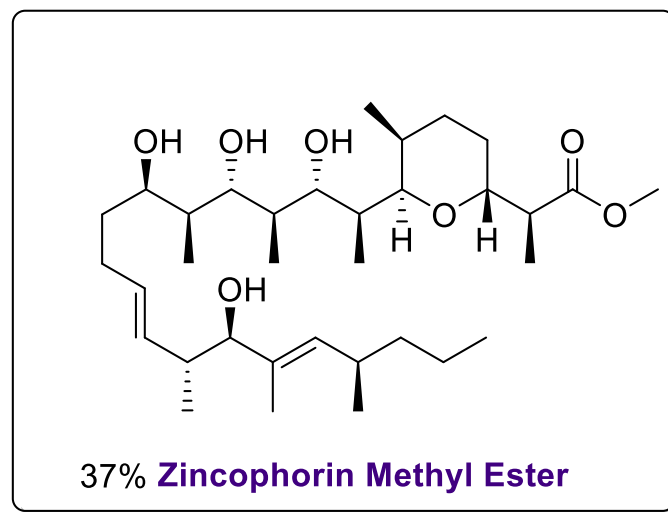
Total Synthesis of (+)- Zincophorin Methyl Ester



81%, 3:1 dr. **11**

DMAP (1 equiv.)

MeOH, rt, 24 h



Thiazole (**S3**)

R = TES

**Thank
You!!!**