

Syntheses of Leucascandrolide A

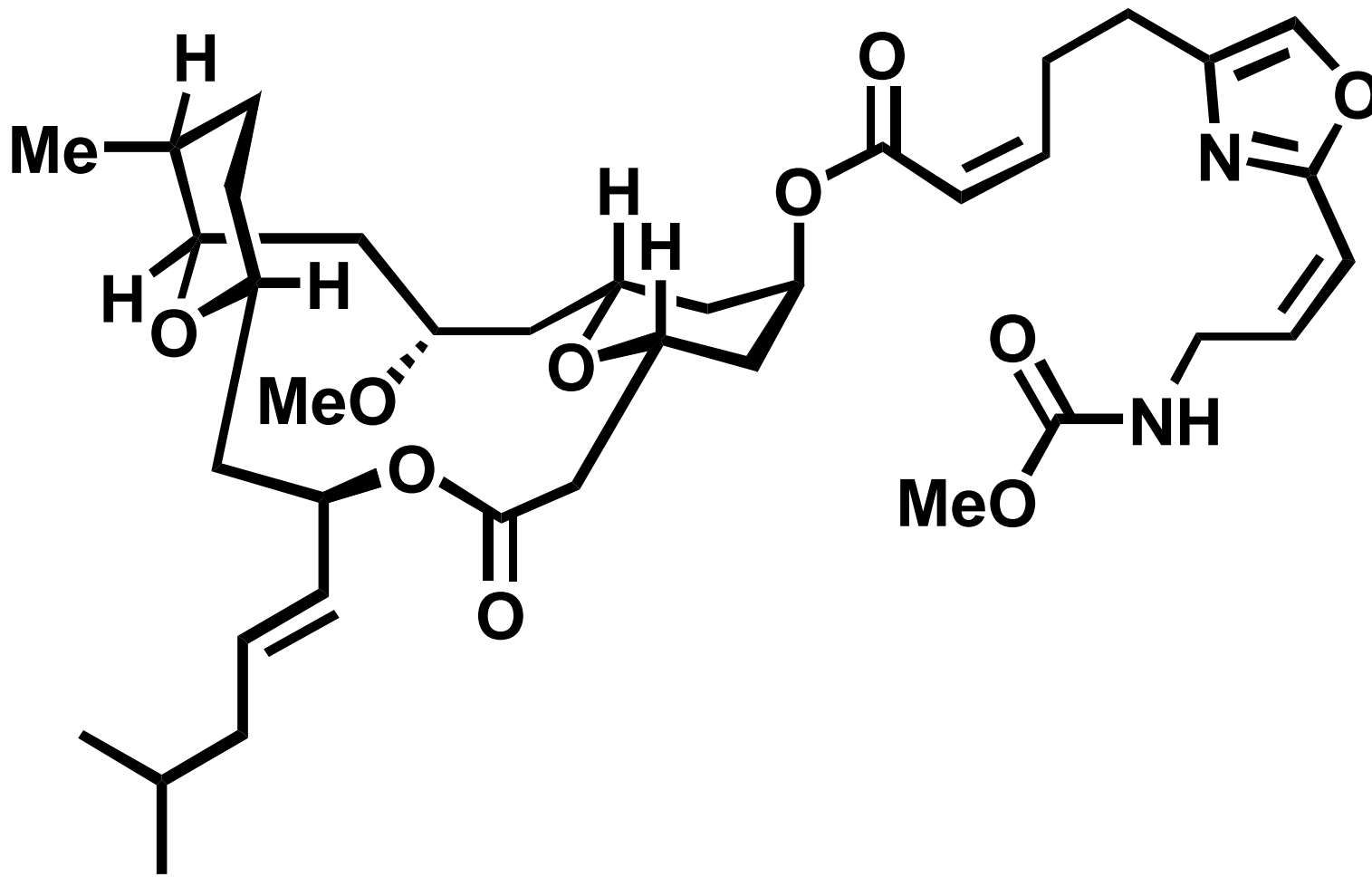


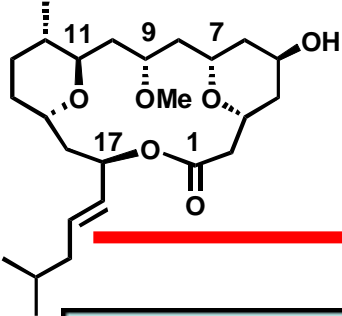
Supergroup Meeting

August 4th, 2004

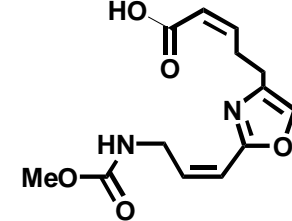
Yu Yuan

Leucascandrolide A





Isolation And Biology



Isolation:

The macrolide is isolated by Pietra and coworkers from the calcareous sponge *Leucascandra caveolata* along the east coast of New Caledonia.

Biology:

The macrolide displays strong cytotoxic activity

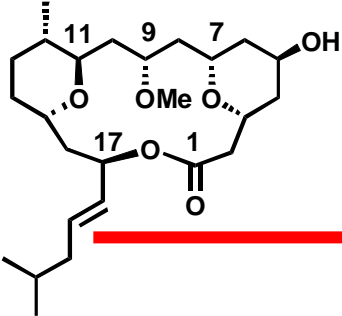
in vitro on human KB and P388 cancer cell lines

(IC₅₀ = 50 and 250 ng/mL) as well as antifungal activity.

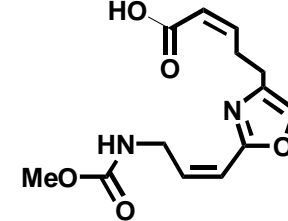
Origin:

The origin of Leucascandrolide A is not clear.

It may be a product of opportunistic microbial colonization of the sponge.



Synthetic Efforts



Total Synthesis:

J. L. Leighton

I. Paterson

E. M. Carreira

S. A. Kozmin

Formal Total Synthesis:

S. D. Rychnovsky

P. Wipf

M. T. Crimmins

D. R. Williams

Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* 2000, 122, 12894

Paterson, I.; Tudge, M. *Angew. Chem. Int. Ed.* 2003, 42, 343

Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* 2002, 124, 13670

Fettes, A.; Carreira, E. M. *Angew. Chem. Int. Ed.* 2002, 41, 4098

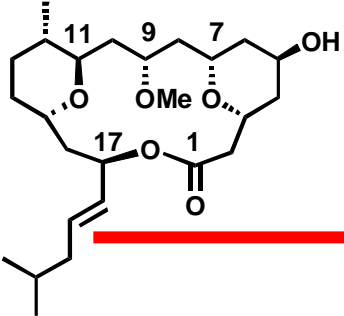
Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* 2001, 123, 8420

Wipf, P.; Reeves, J. T. *Chem. Comm.* 2002, 2066

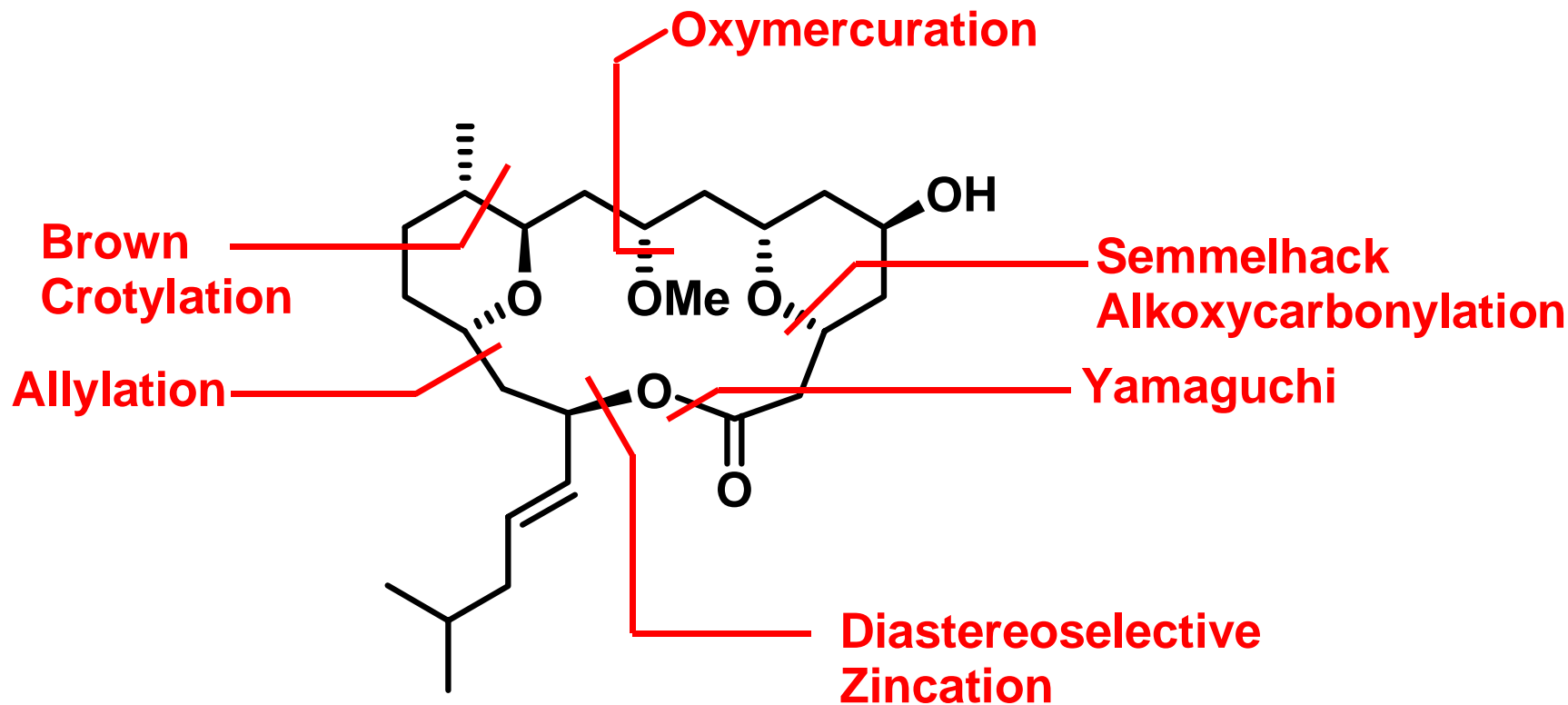
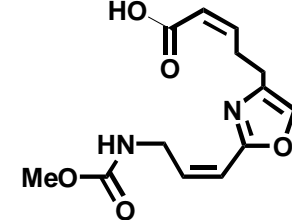
Crimmins, M. T.; Siliphalvanh, P. *Org. Lett.* 2003, 5, 4641

Williams, D. R.; Patnaik, S.; Plummer, S. V. *Org. Lett.* 2003, 5, 5035

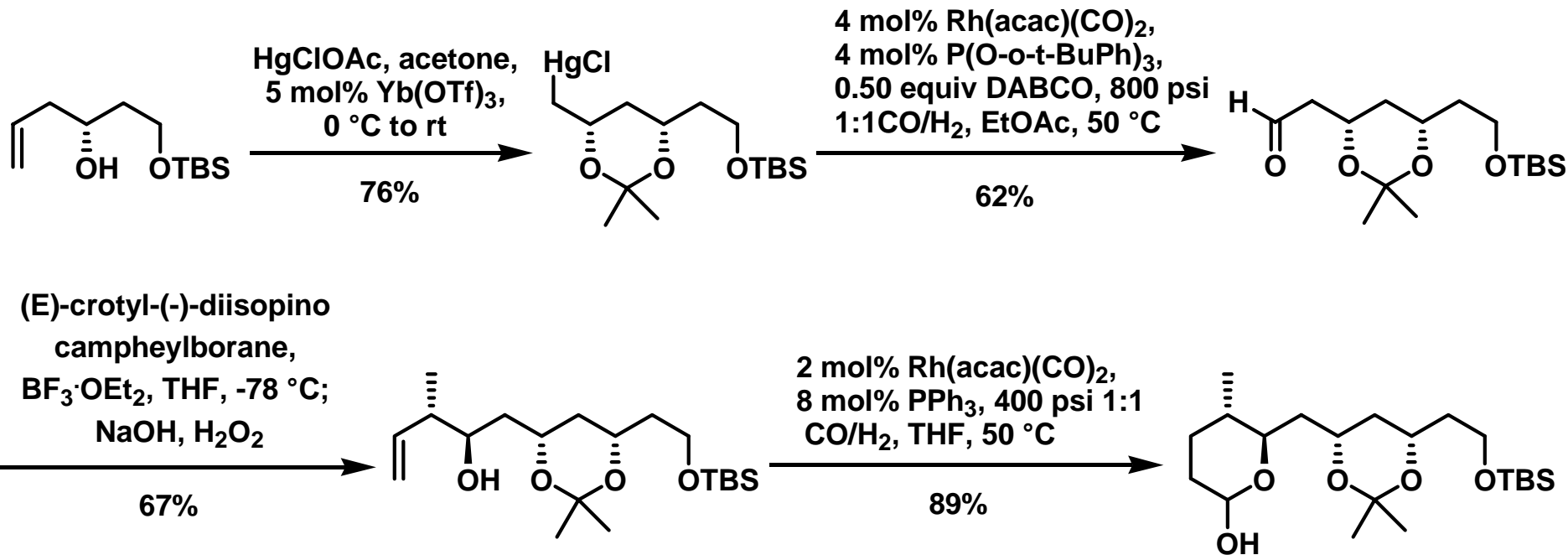
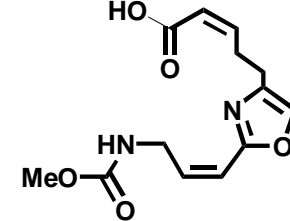
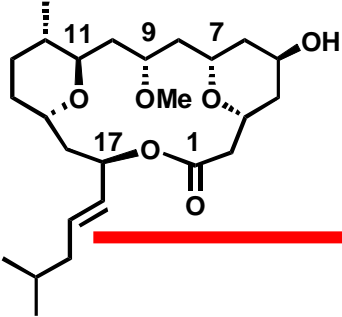
Dakin, L. A.; Panek, J. S. *Org. Lett.* 2003, 5, 3995-3998



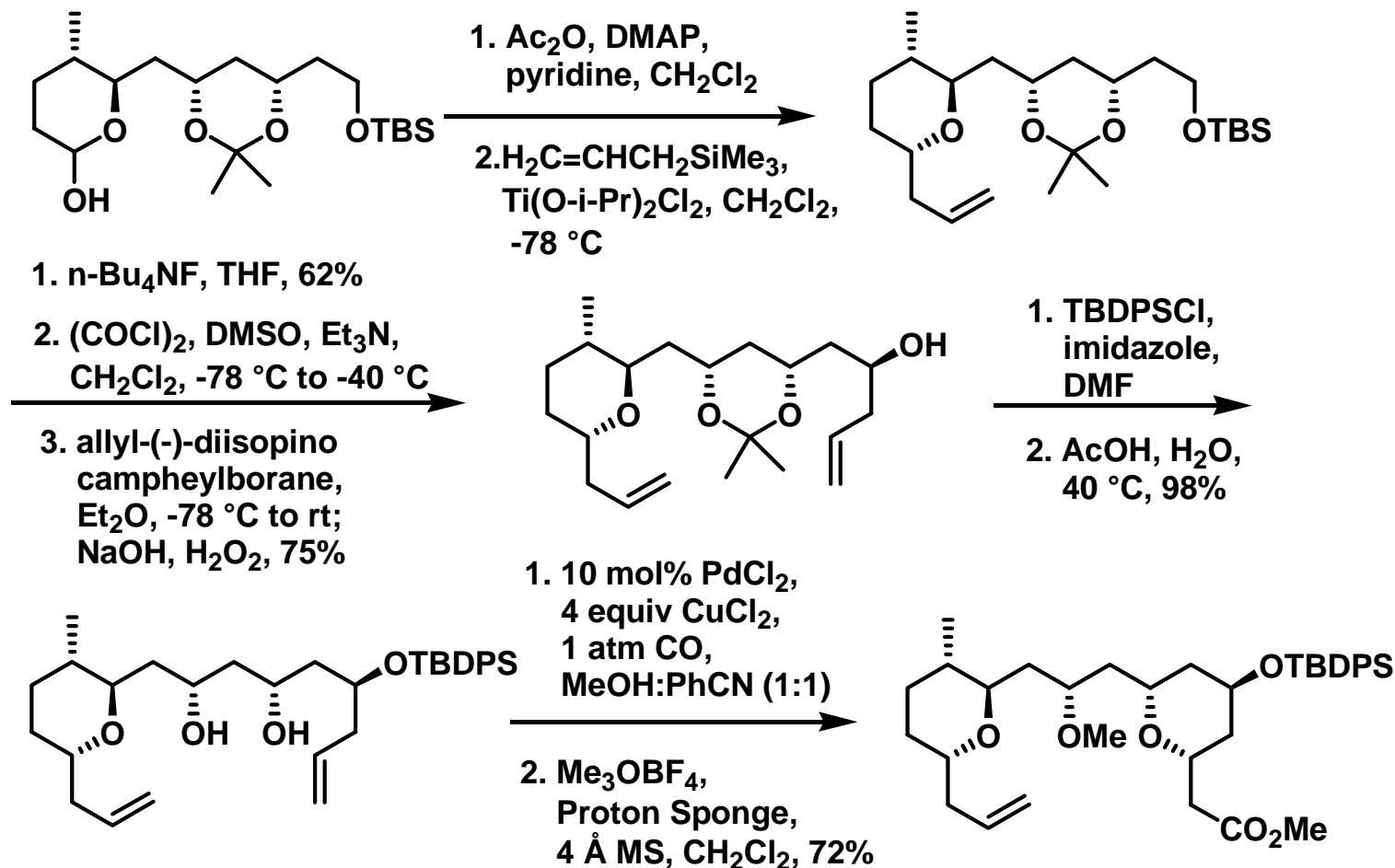
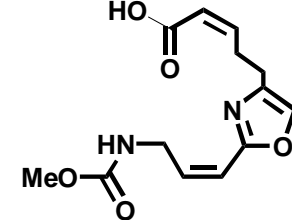
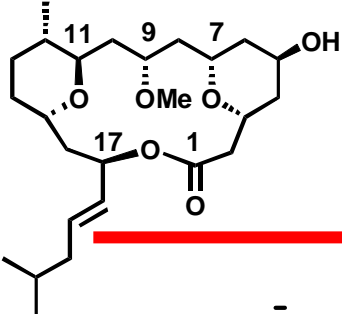
Leighton's Synthesis



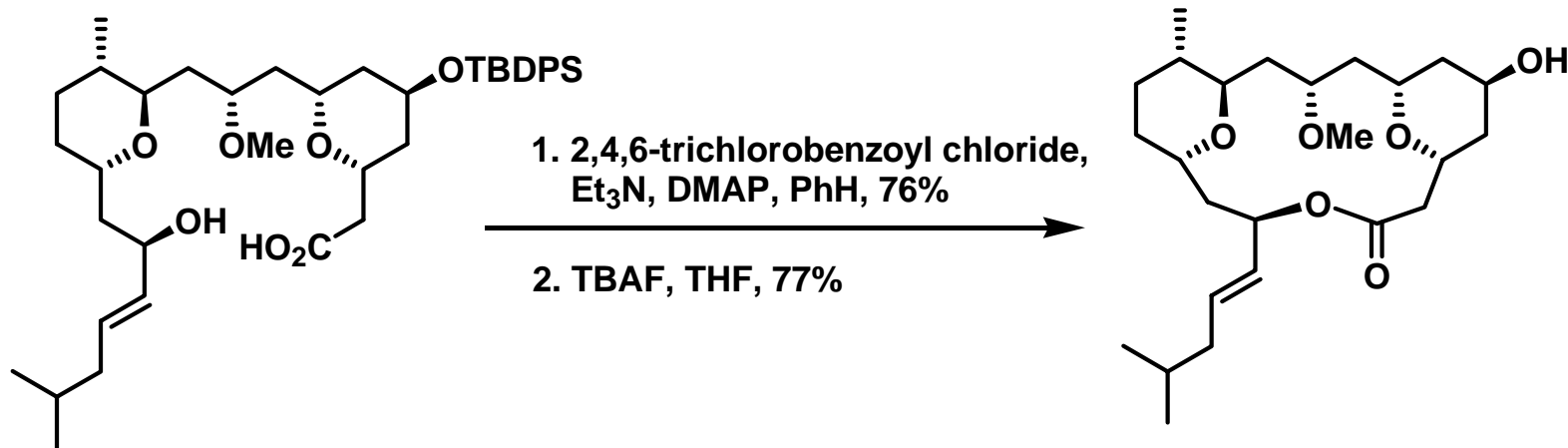
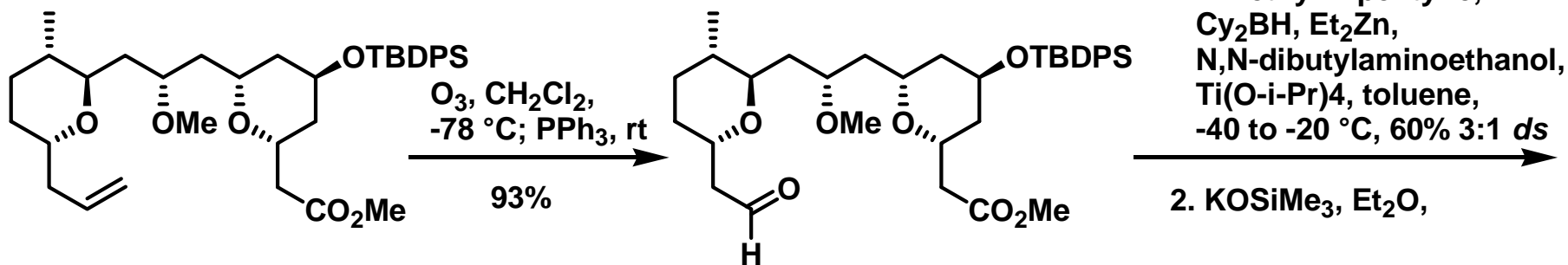
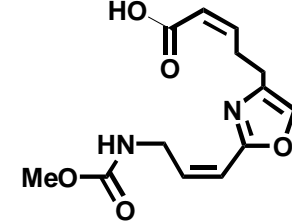
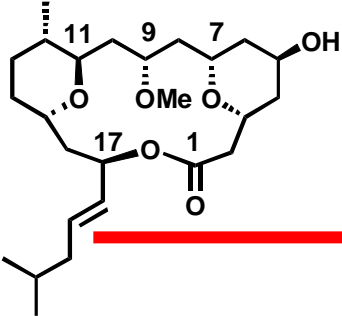
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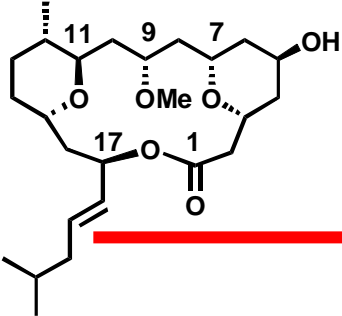


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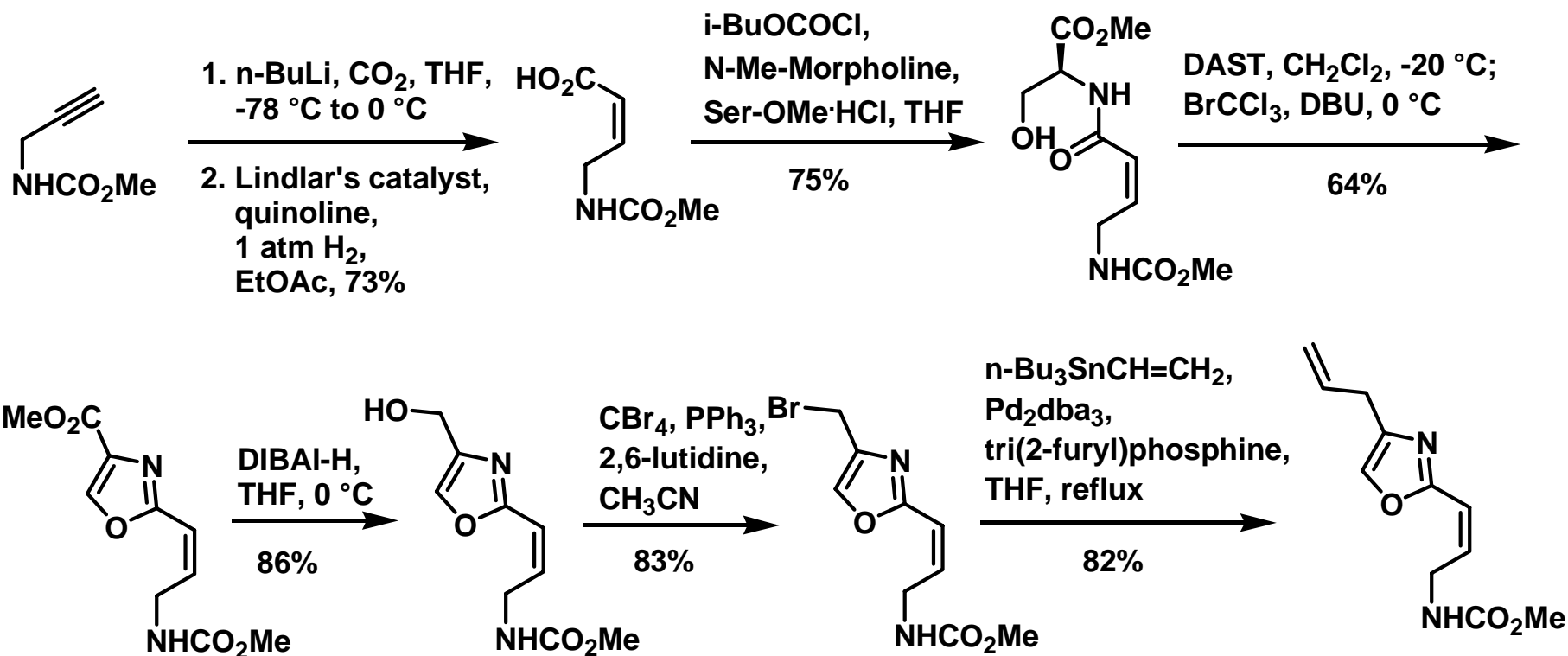
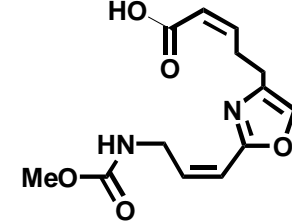


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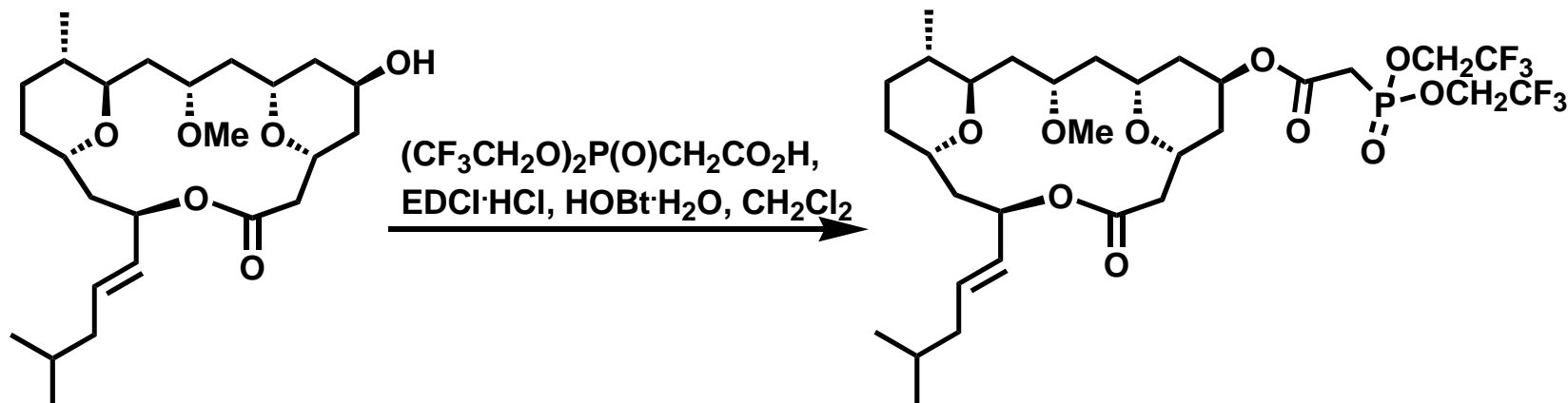
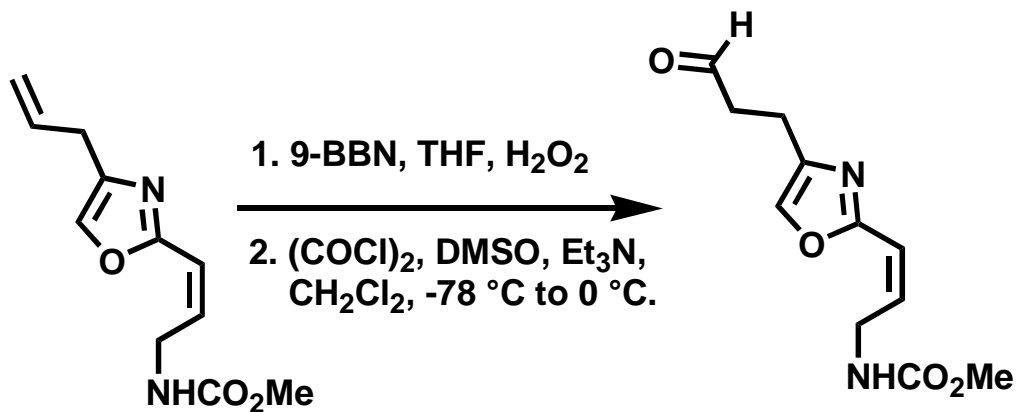
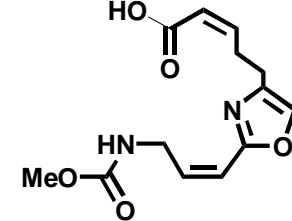
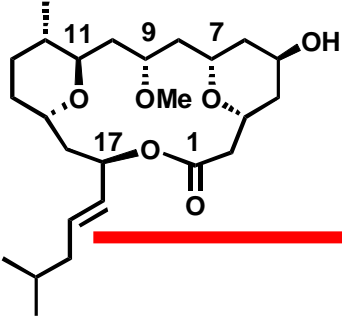




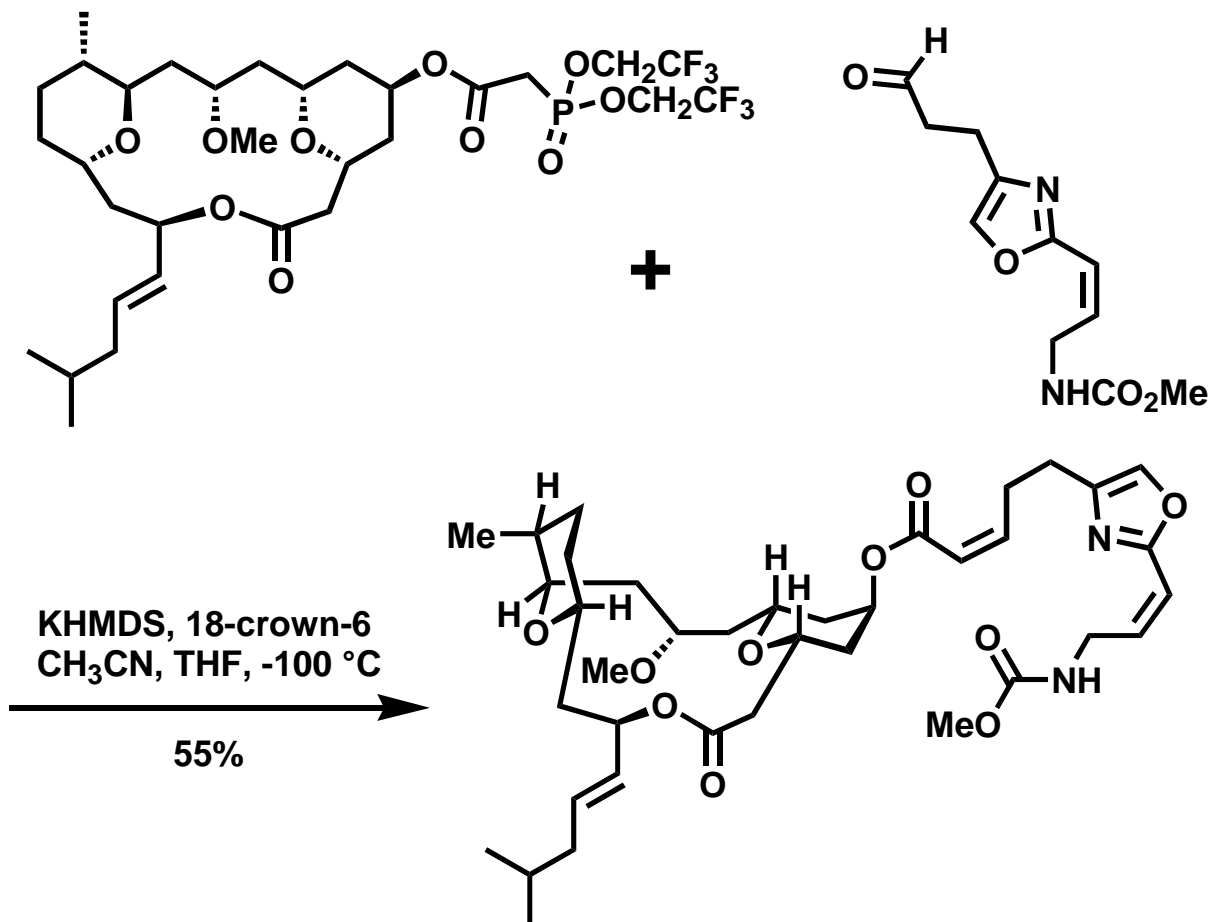
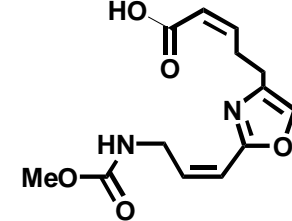
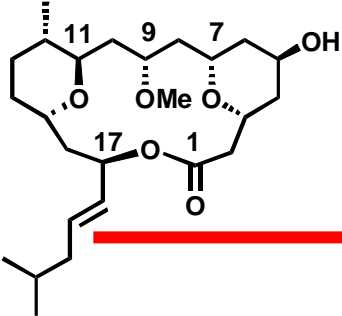
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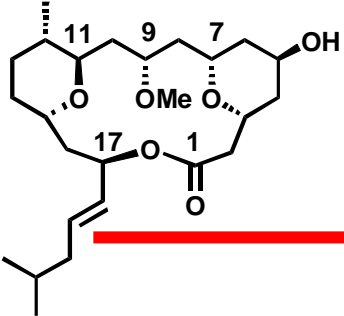


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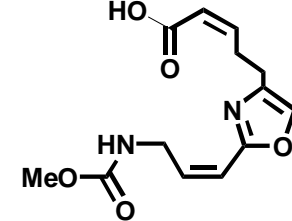


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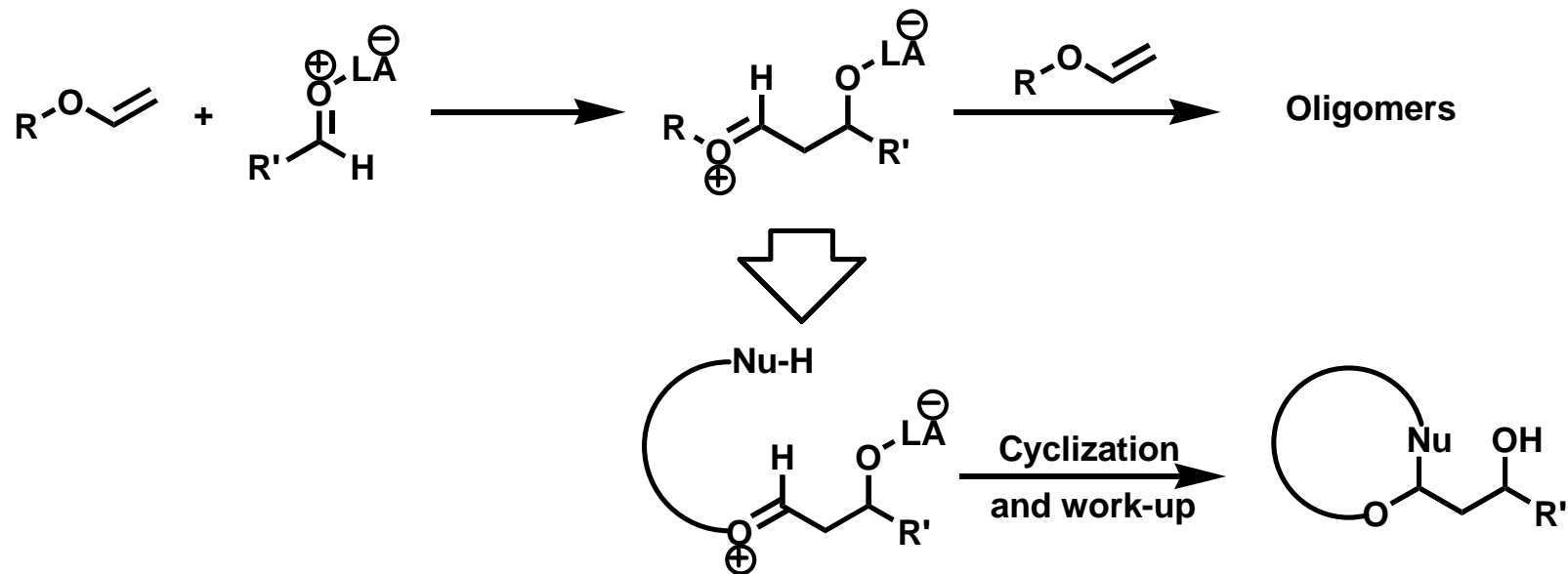


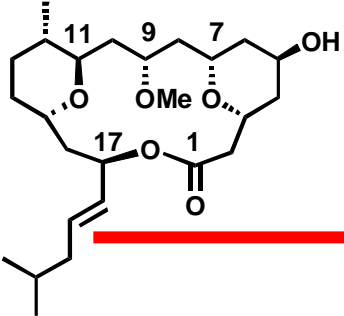


Rychnovsky's Synthesis

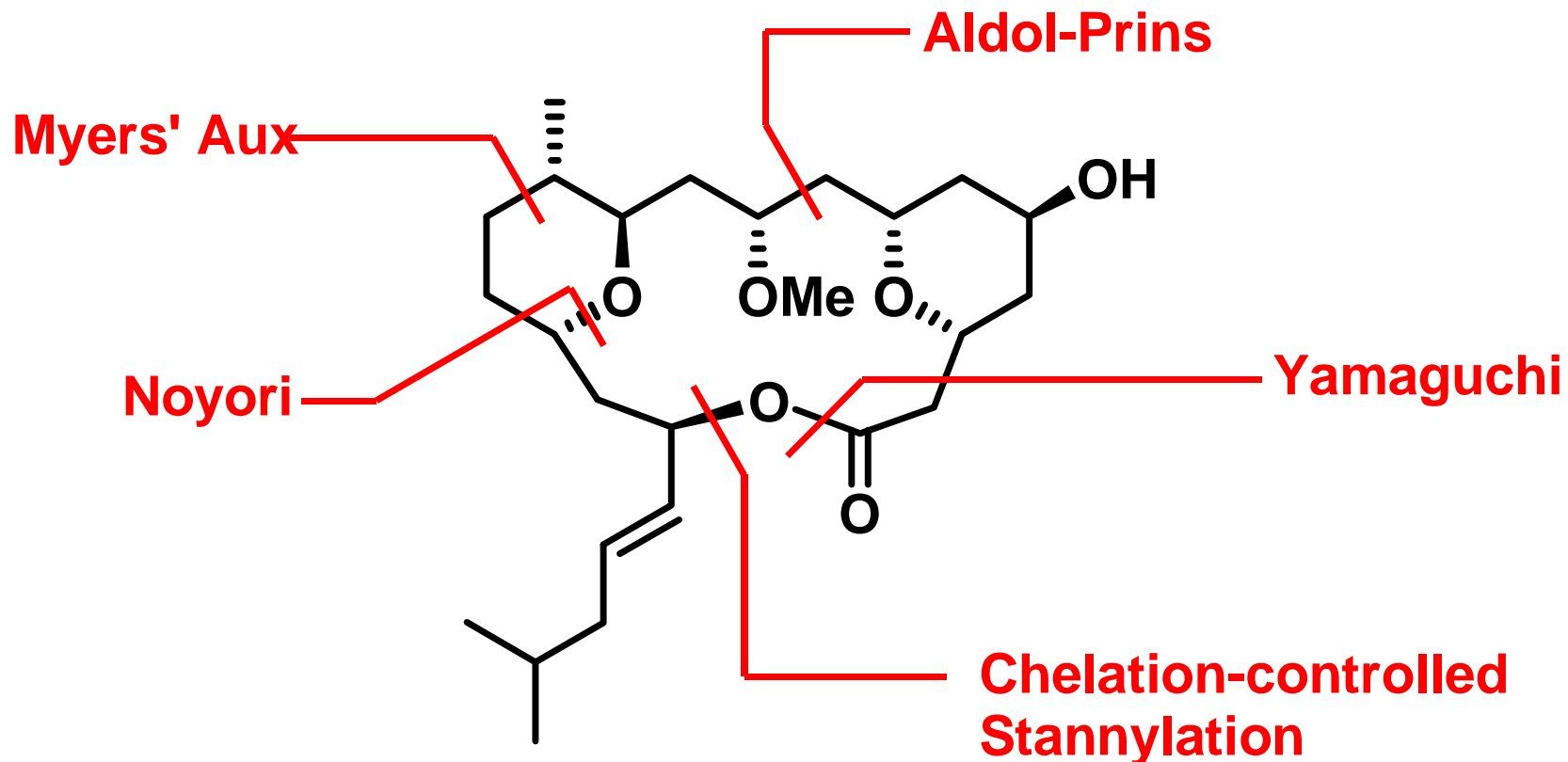
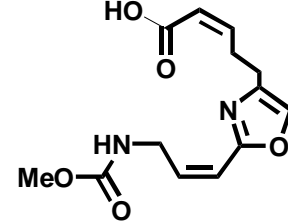


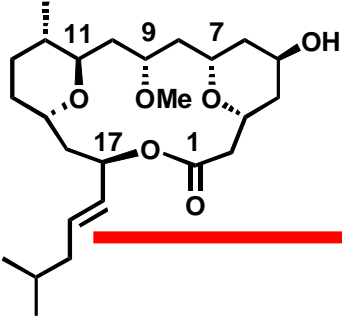
Conceptualization of the aldol-Prins reaction to avoid oligomerization:



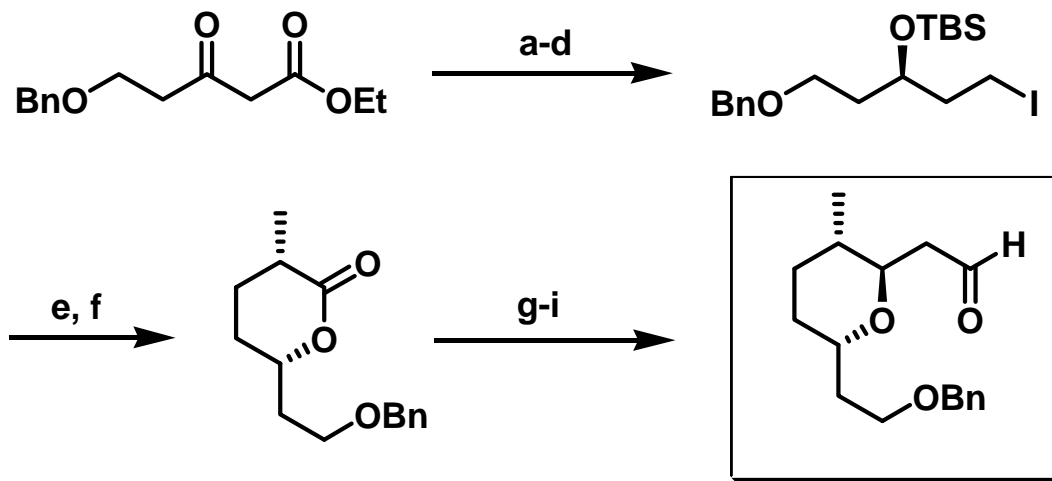
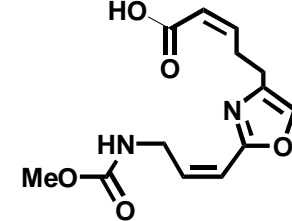


Rychnovsky's Synthesis

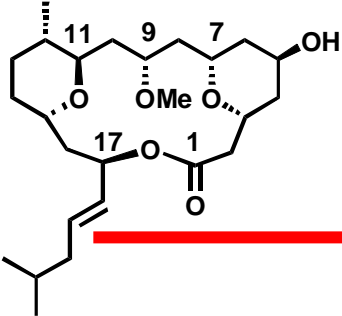




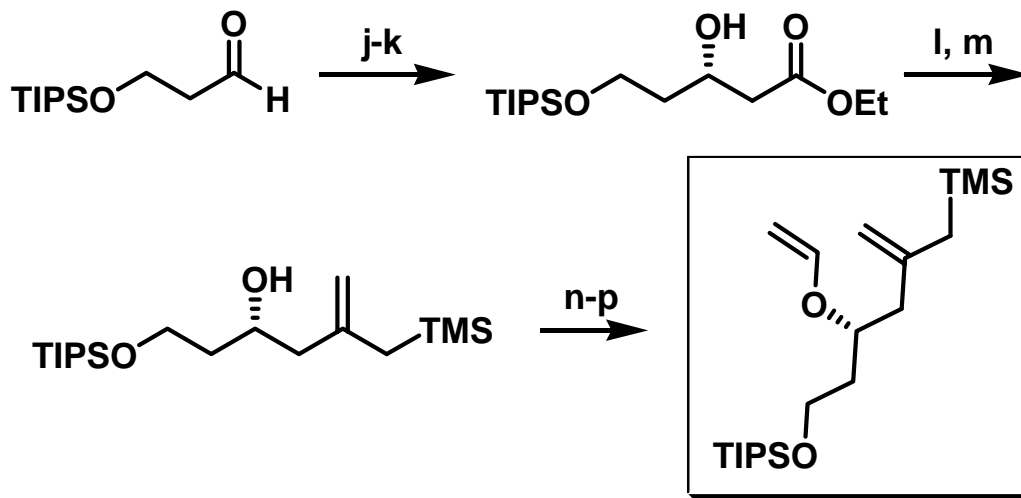
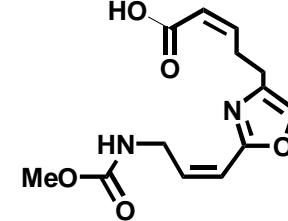
Rychnovsky's Synthesis



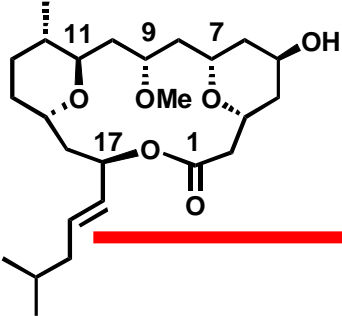
(a) [(R)-BINAP]-RuCl(C₆H₆), 80 atm H₂, EtOH, 96%, 94% ee; (b) TBSCl, imidazole, DMF, 86%; (c) DIBALH, THF, -25 °C, 88%; (d) PPh₃, I₂, imidazole, CH₂Cl₂, quant.; (e) combine LDA, (-)-pseudoephedrine propionamide, LiCl, then add the iodide, THF, -78 °C, 98%, ≥20:1 dr; (f) 2N H₂SO₄, dioxane, 95 °C, 77%; (g) i. DIBALH, CH₂Cl₂, -78 °C, ii. Ac₂O, DMAP, pyridine, 95%; (h) Allyltrimethylsilane, BF₃·OEt₂, CH₂Cl₂; -78 °C, 97%, ≥20:1 dr; (i) O₃, CH₂Cl₂, -78 °C, then PPh₃, 95%



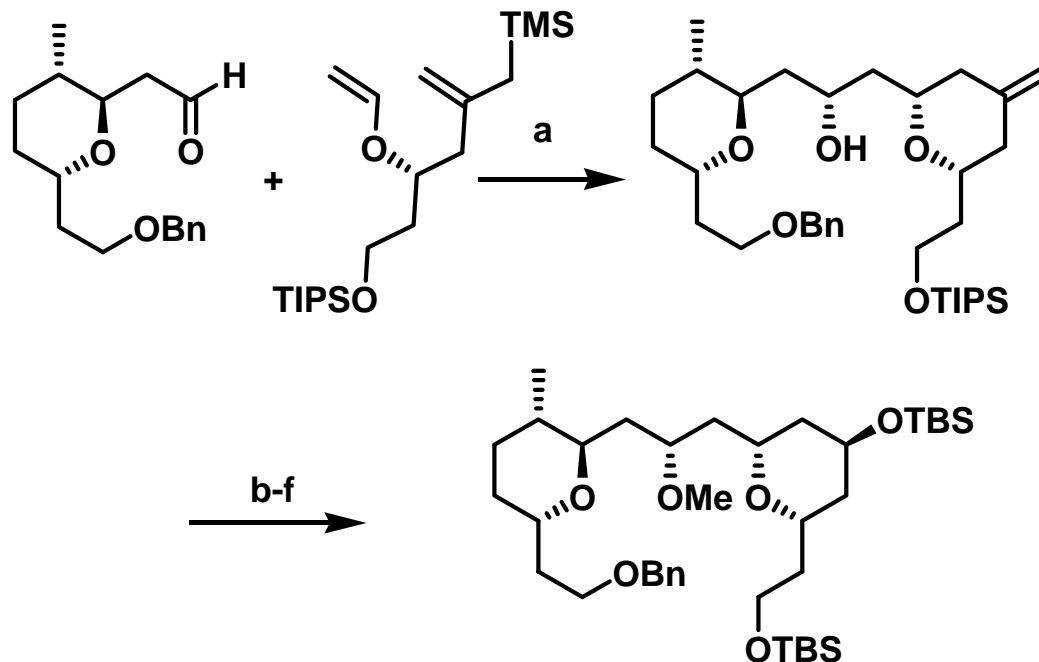
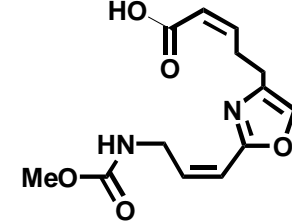
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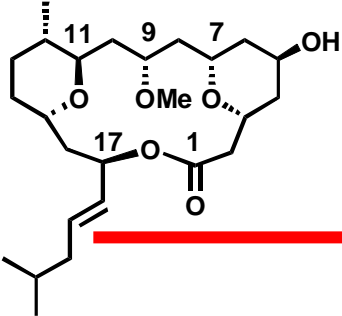
(j) $\text{N}_2\text{CHCO}_2\text{Et}$, SnCl_2 , CH_2Cl_2 , 72%; (k) [(S)-BINAP]- $\text{RuCl}(\text{C}_6\text{H}_6)$, 4 atm H_2 , EtOH , 100 °C, 51%, $\geq 95\%$ ee; (l) TMSCl , Et_3N , CH_2Cl_2 , 91%; (m) i. CeCl_3 , $\text{TMSCH}_2\text{MgCl}$, $\text{THF}/\text{Et}_2\text{O}$, -78 °C to 23 °C, ii. SiO_2 gel, CH_2Cl_2 , 87% (n) ClCH_2COCl , pyridine, CH_2Cl_2 , 95%; (o) i. DIBALH , CH_2Cl_2 , -78 °C, ii. Ac_2O , DMAP , pyridine, 95%; (p) Li° , NH_3 , THF , -78 °C, 65%



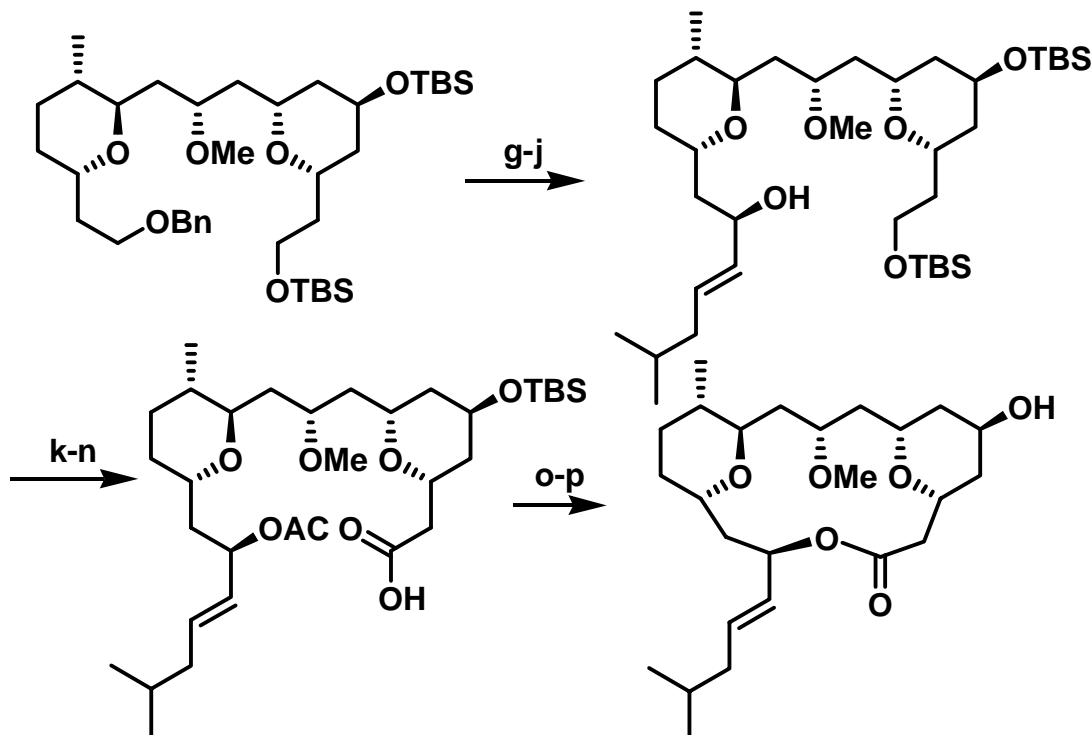
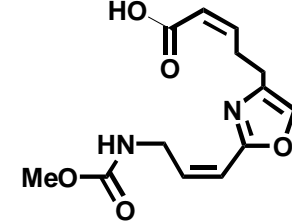
Rychnovsky's Synthesis



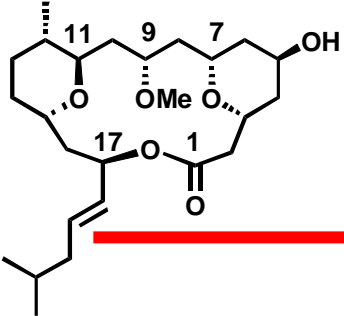
(a) i. $\text{BF}_3 \cdot \text{OEt}_2$, 2,6-di-tert-butylpyridine, CH_2Cl_2 , -78°C , ii. NaBH_4 , EtOH, 78%, 5.5:1 dr at C_9 ; (b) Me_3OBF_4 Proton Sponge, 4 Å M.S., CH_2Cl_2 , 79% (single epimer) plus C_9 epimer (15%), (c) i. OsO_4 , NMO, ii. NaIO_4 , 80%; (d) L-Selectride, THF, -90 to -60°C , 82% (single epimer) plus C_5 epimer (10%); (e) TBAF, THF, 92%; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2 , 89%



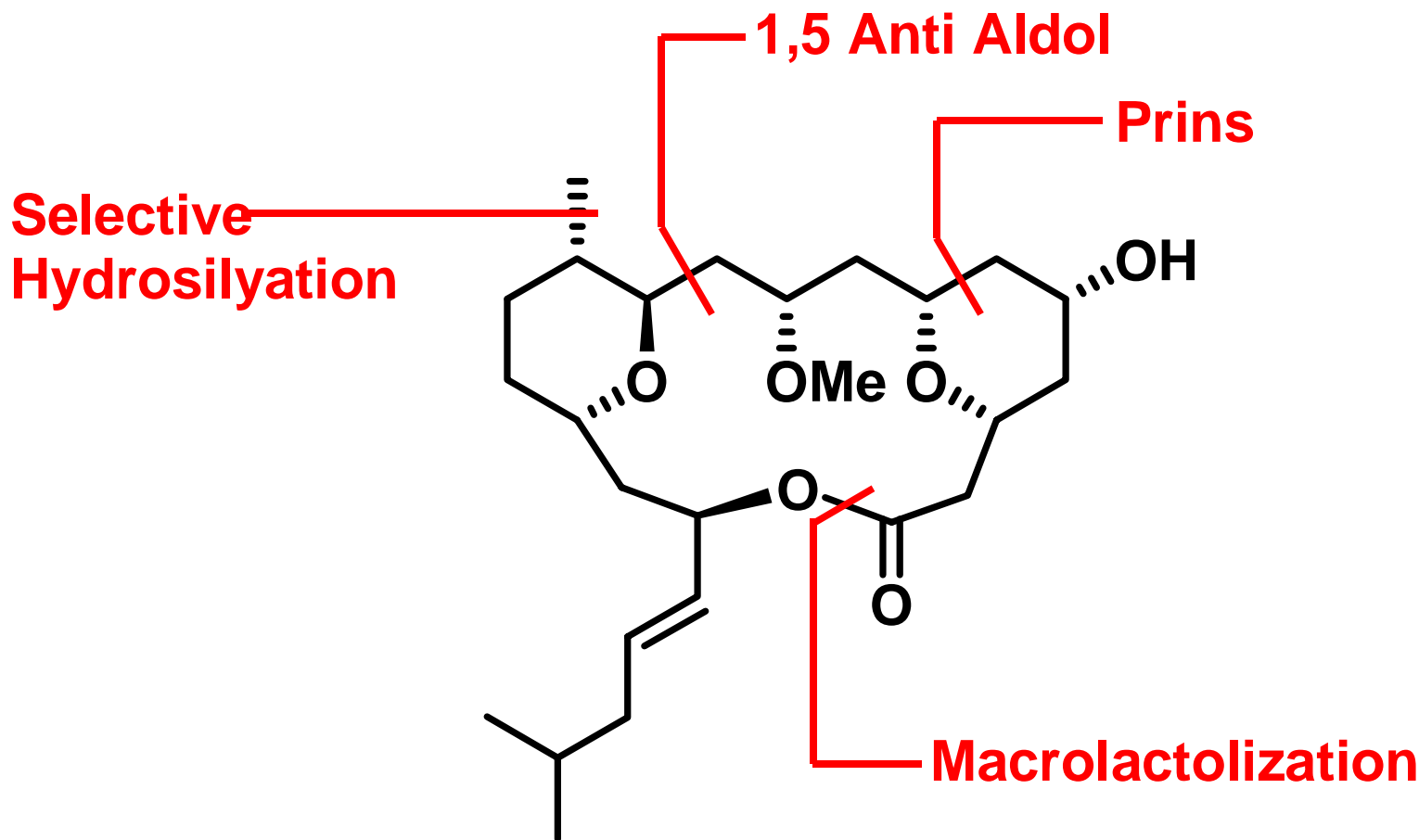
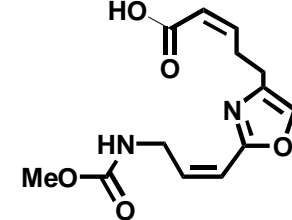
Rychnovsky's Synthesis

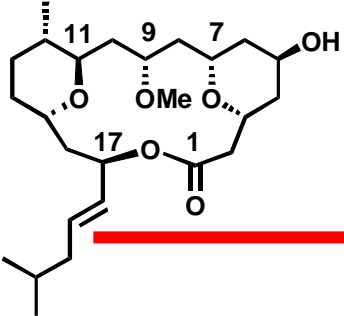


(g) H_2 , $\text{Pd}(\text{OH})_2$, EtOAc , 96%; (h) Swern, 94%; (i) Me_2AlCl , $\text{Me}_3\text{SnCCCH}_2\text{CH}(\text{CH}_3)_2$, PhCH_3 , -78°C , 80%, 3.5:1 dr at C_{17} ; (j) Red-Al, Et_2O , 60% (single epimer) plus recovered SM and C_{17} epimer; (k) Ac_2O , DMAP, pyridine, CH_2Cl_2 , 89%; (l) Neutral Al_2O_3 , hexanes, 96%; (m) Swern, 97%; (n) NaClO_2 , NaH_2PO_4 , 2-methyl-2-butene, 71%; (o) i. K_2CO_3 , MeOH , ii. $\text{Cl}_3\text{C}_6\text{H}_2\text{COCl}$, Et_3N , DMAP, C_6H_6 , 23°C , 56%; (p) HF/pyridine, THF, 96%

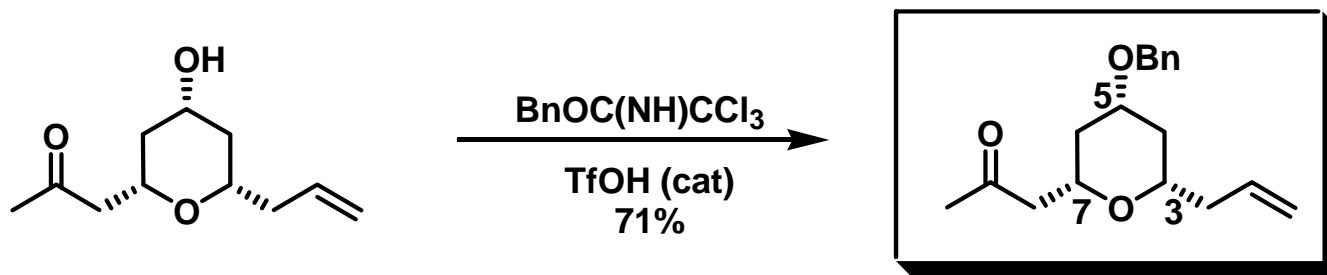
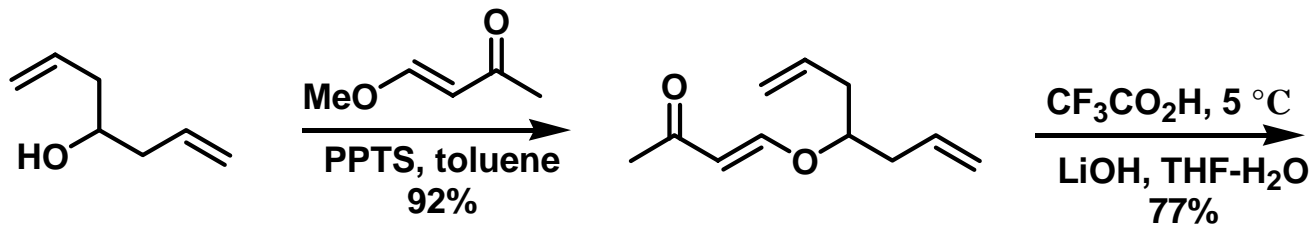
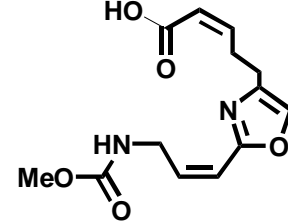


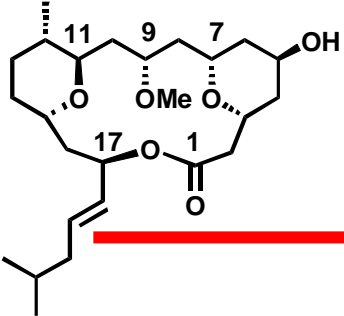
Kozmin's Synthesis



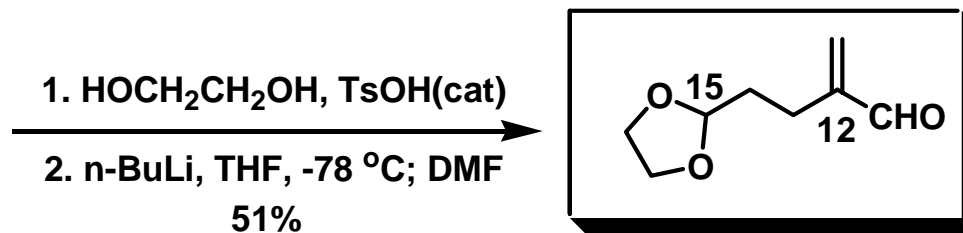
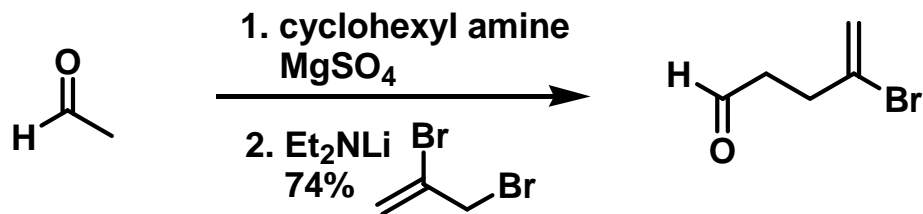
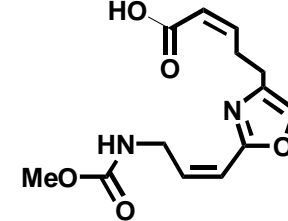


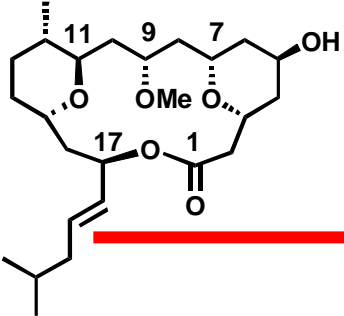
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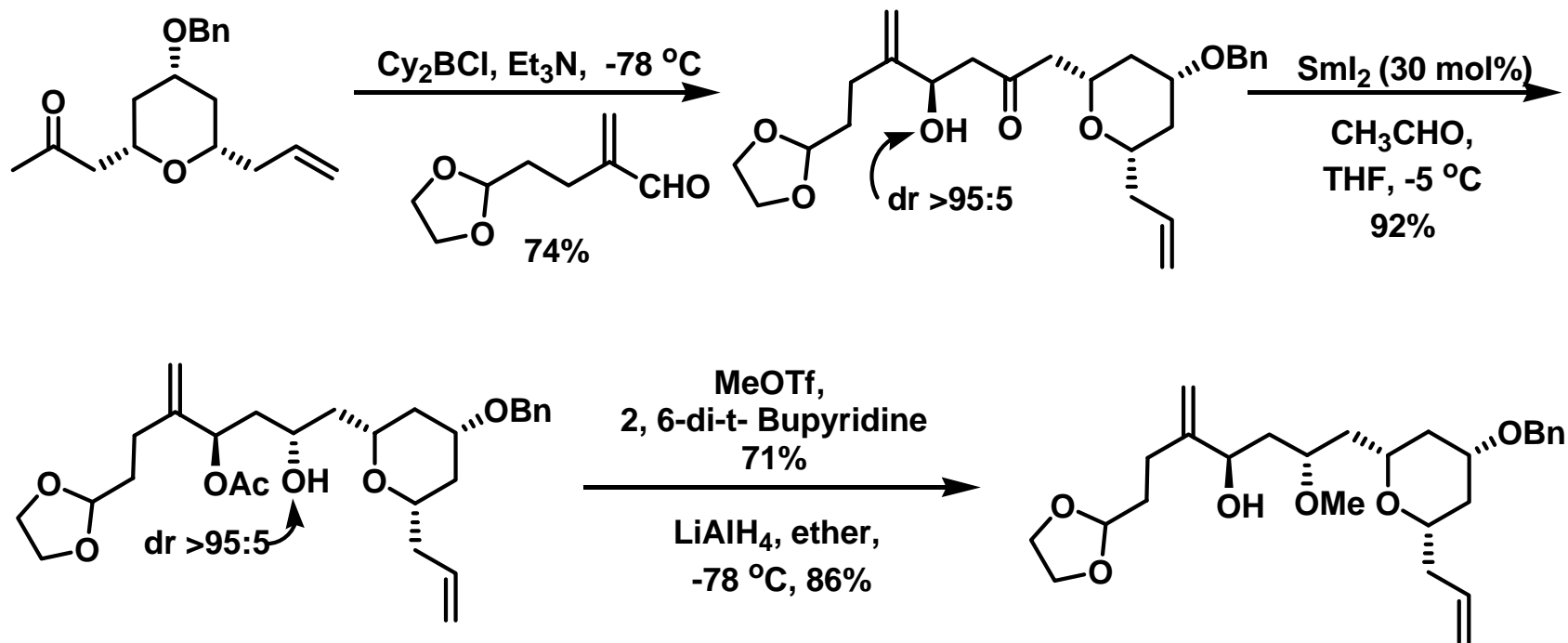
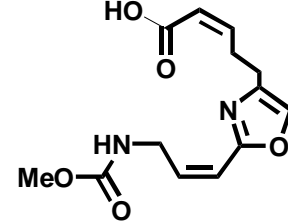


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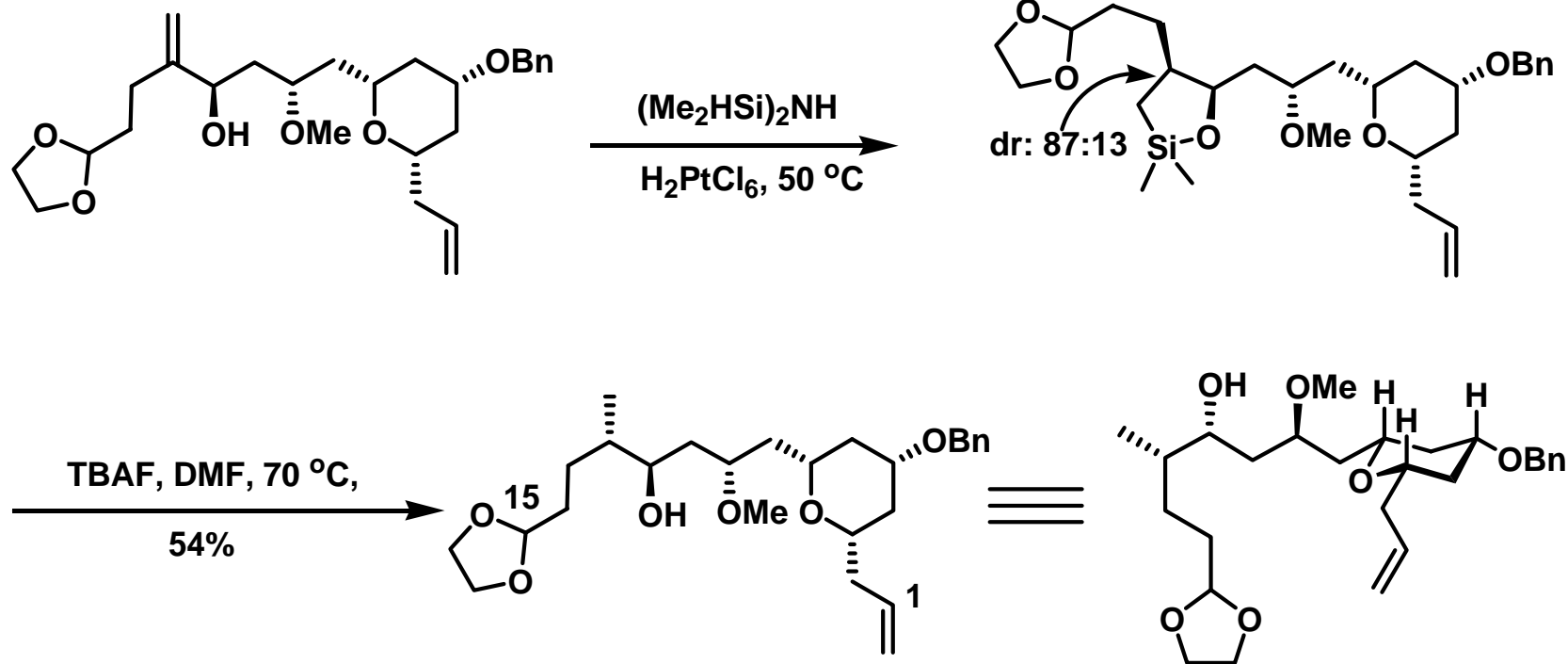
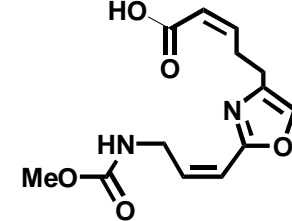
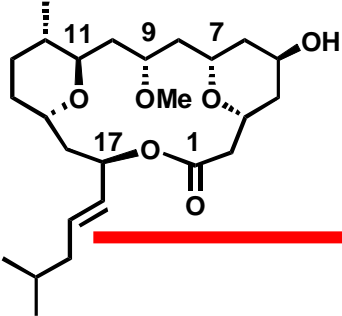




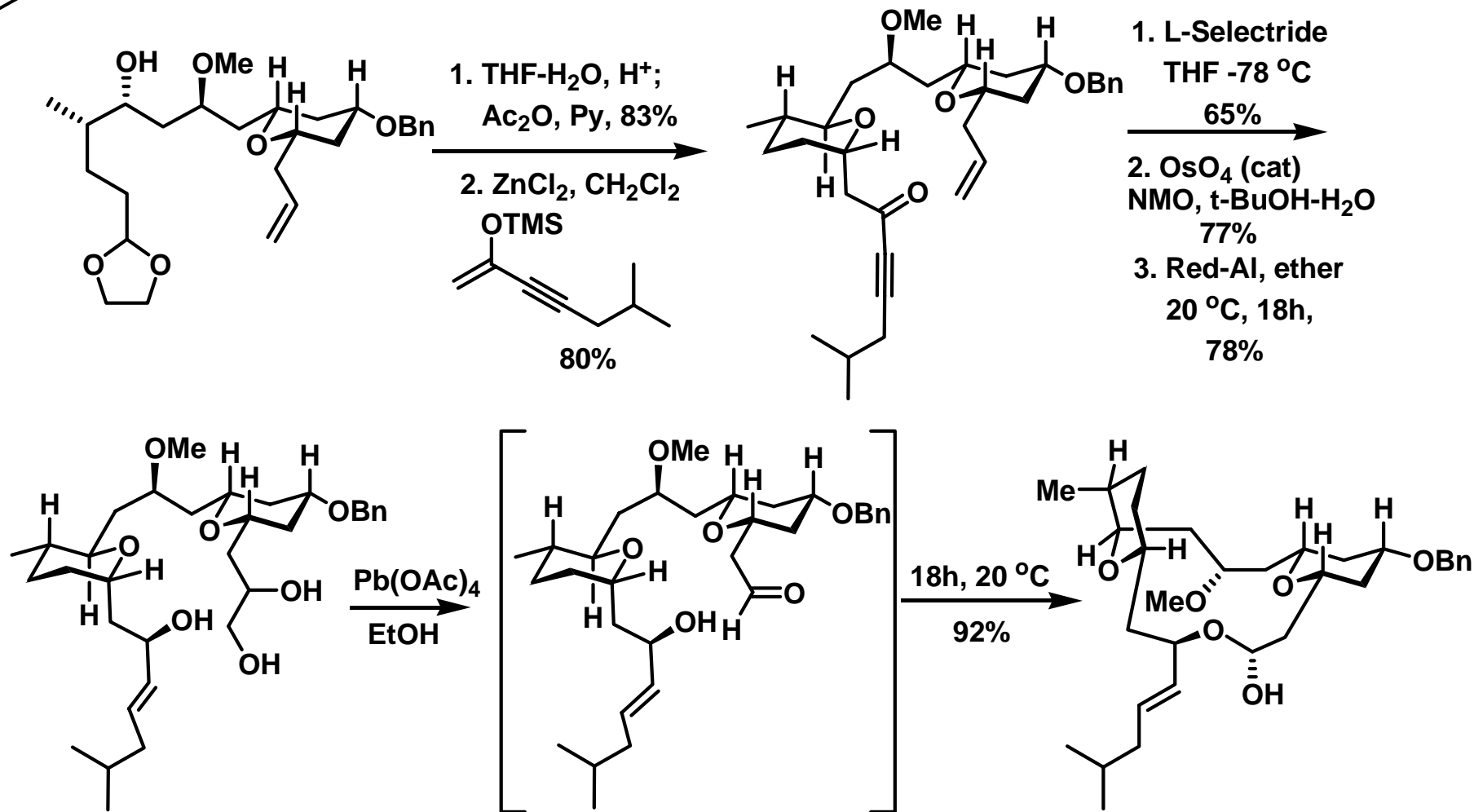
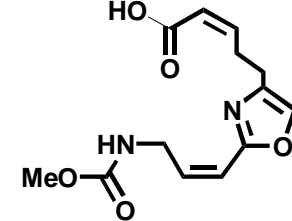
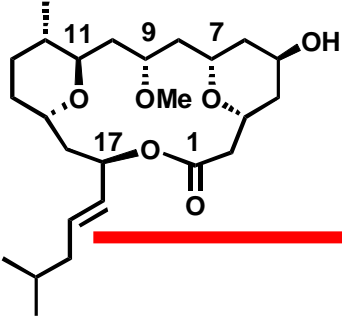
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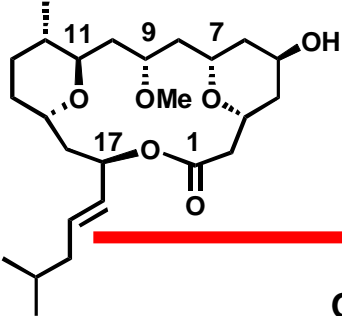


Kozmin's Synthesis

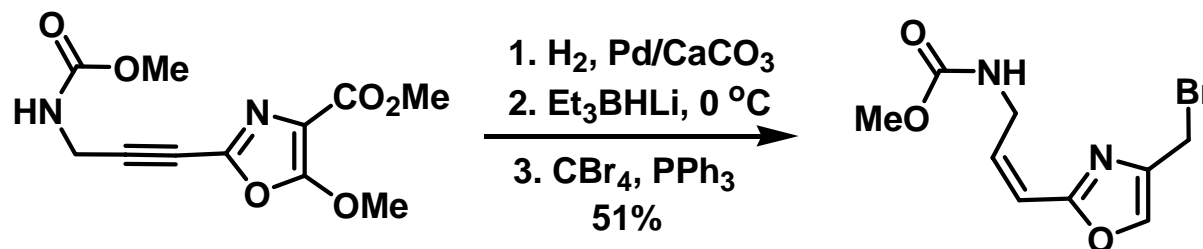
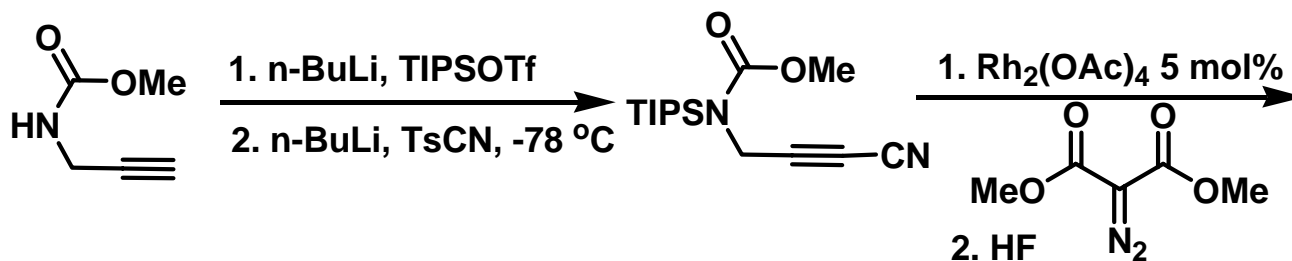
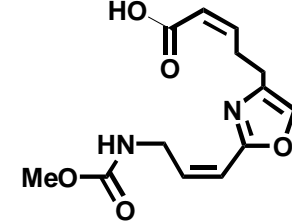


Kozmin's Synthesis

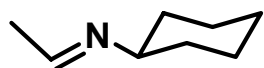




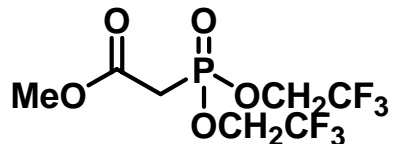
Kozmin's Synthesis



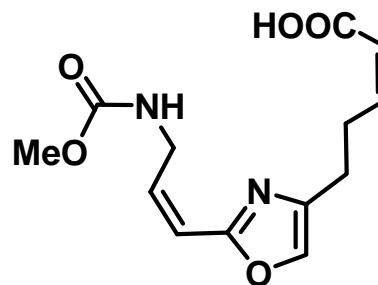
1. Et₂NLi, HMPA, 86%



2. KHMDS, 75%



3. LiOH 89%



Kozmin's Synthesis

