

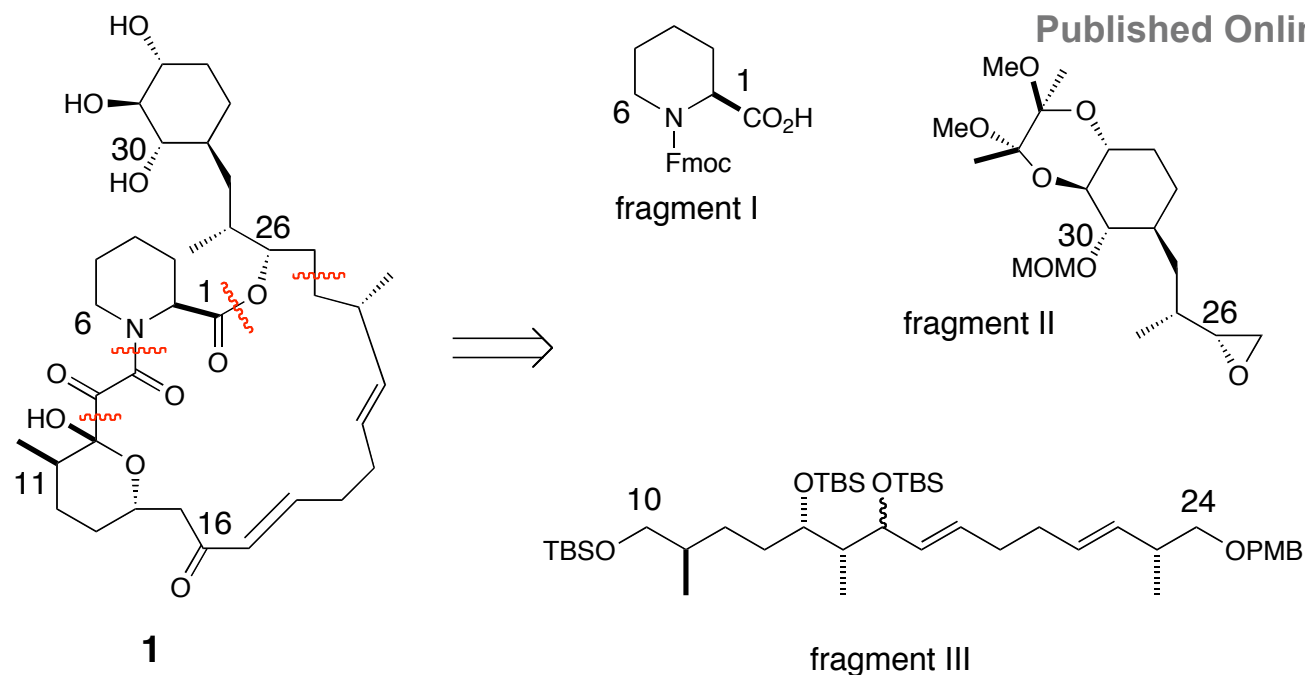
# Total Synthesis of Antascomincin B

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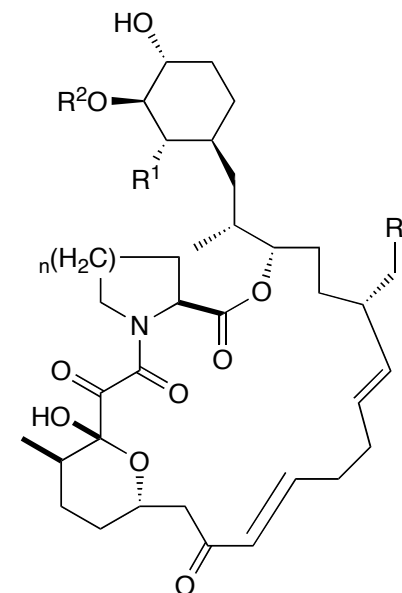
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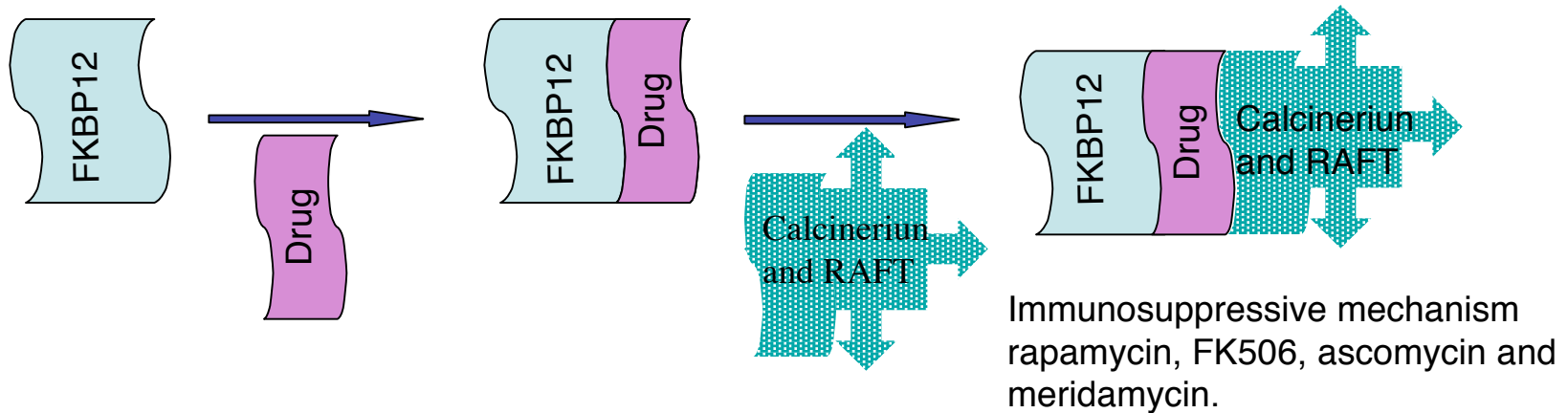
## Antascomincin A - E and the FKBP12

- Isolated from a strain of *Micromonospora* (China), 1996;  
*J. Antibiot.* **1996**, 49, 230.
- Immunophilin FKBP12, main target of rapamycin and FK506, used as binding to evaluate more than 12000 strains of *Actinomycetes*;
- FKBP's known as peptidyl prolyl *cis-trans* isomerases;
- Ligand-FKBP12 complex determines the immunosuppressant effect;  
*Science*, **1990**, 250, 556.  
*JACS*, **1991**, 113, 8045.
- The new family presented same degree of binding to the FKBP12 as rapamycin and FK506, but no immunosuppressive property;
- Antascomincins antagonize both immunosuppressants;
- FKBP12 found in high quantities in the brain;  
*Nature*, **1992**, 358, 584.

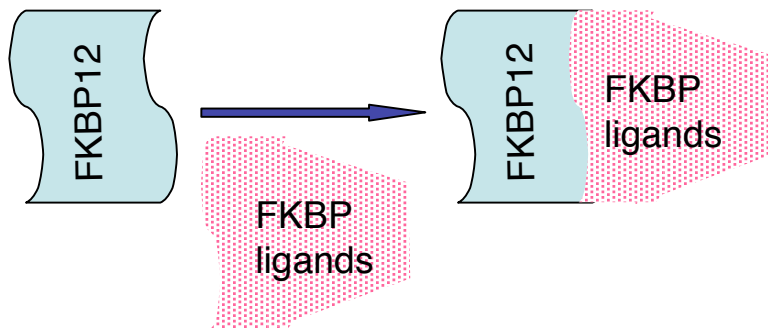


Antascomincin	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	n	FKBP12 binding IC <sub>50</sub> (nM)
A	H	H	H	2	2.0
B	OH	H	H	2	0.7
C	OH	Me	H	2	1.0
D	H	H	H	1	5.2
E	H	H	OH	2	0.7

### The Immunosuppressive Drug Action:

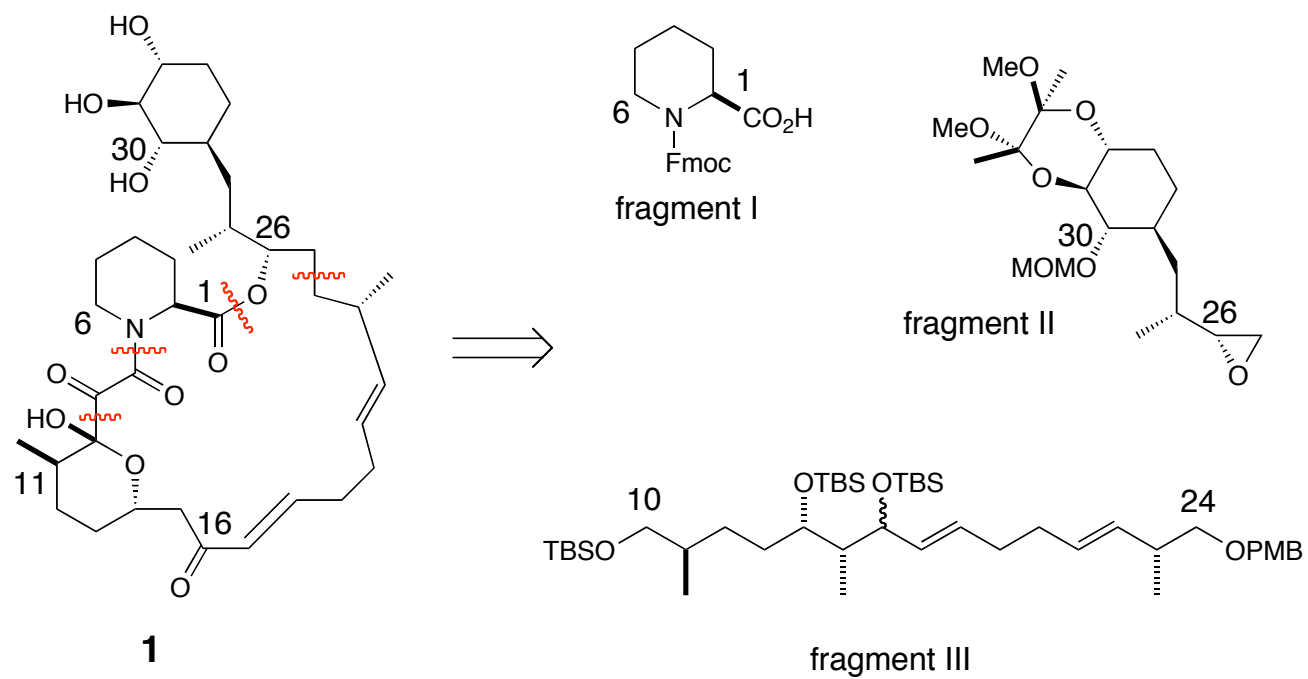


### The Non-Immunosuppressive Ligand:



- Ligand-FKBP neurotropic non-immunosuppressant complexes: clinical use.
- Independent mechanisms.
- Attention returned to the strong FKBP's ligands with no immunosuppression activity.

# First Synthesis of an Antascomincin Member

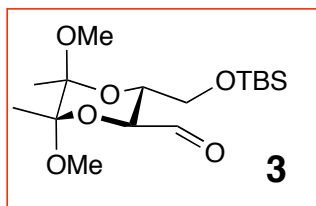
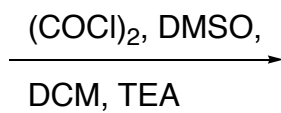
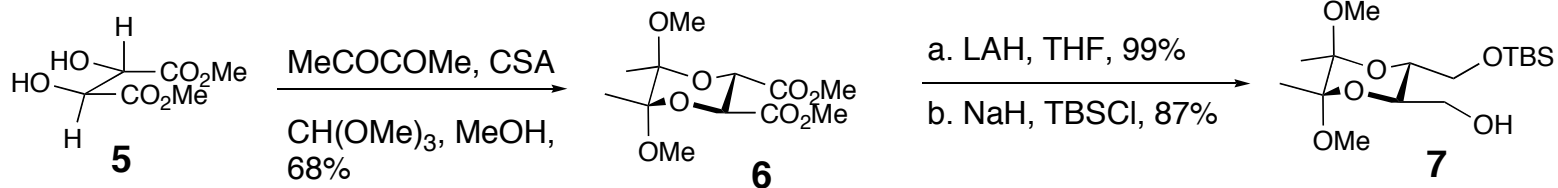
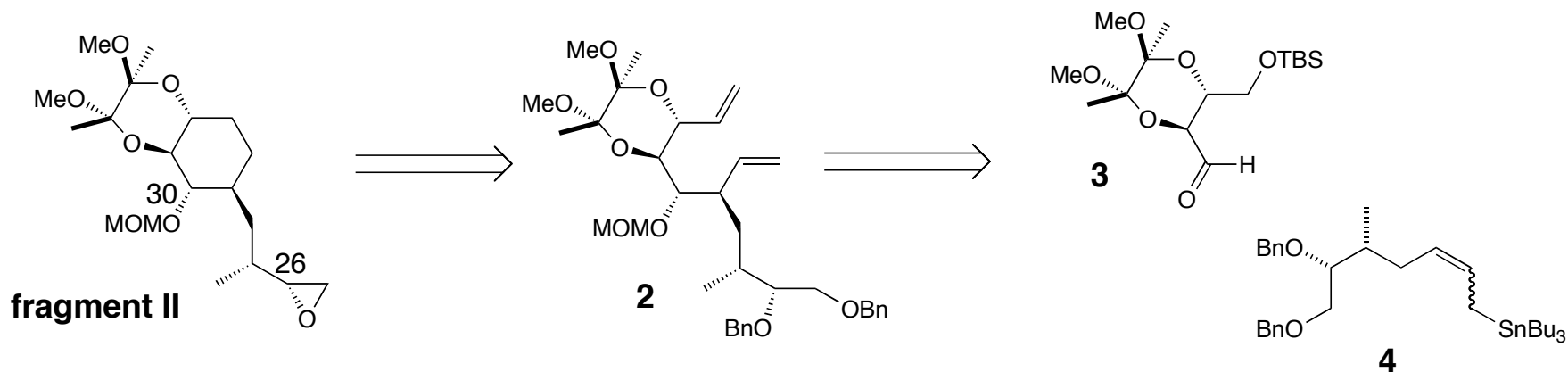


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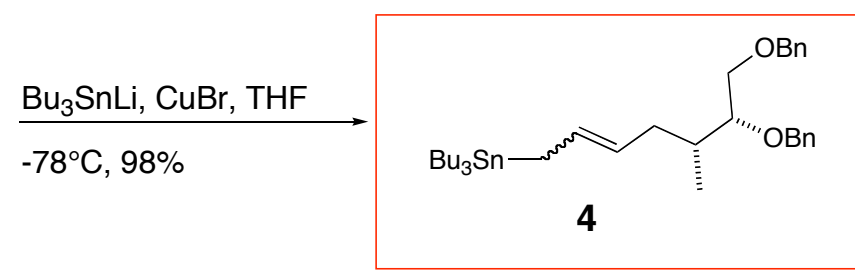
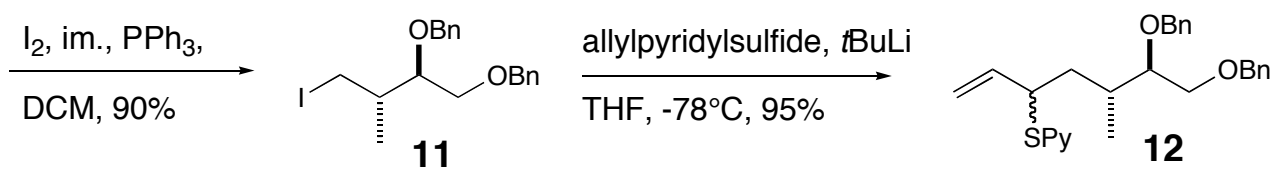
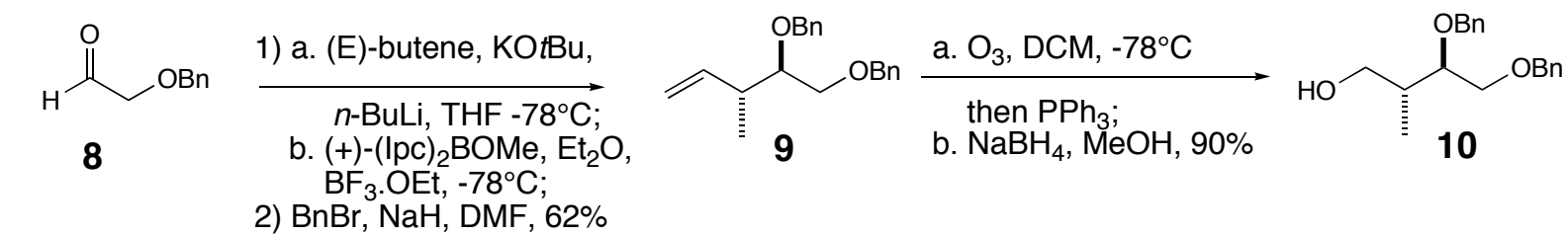
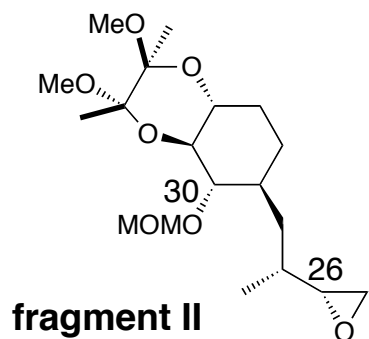
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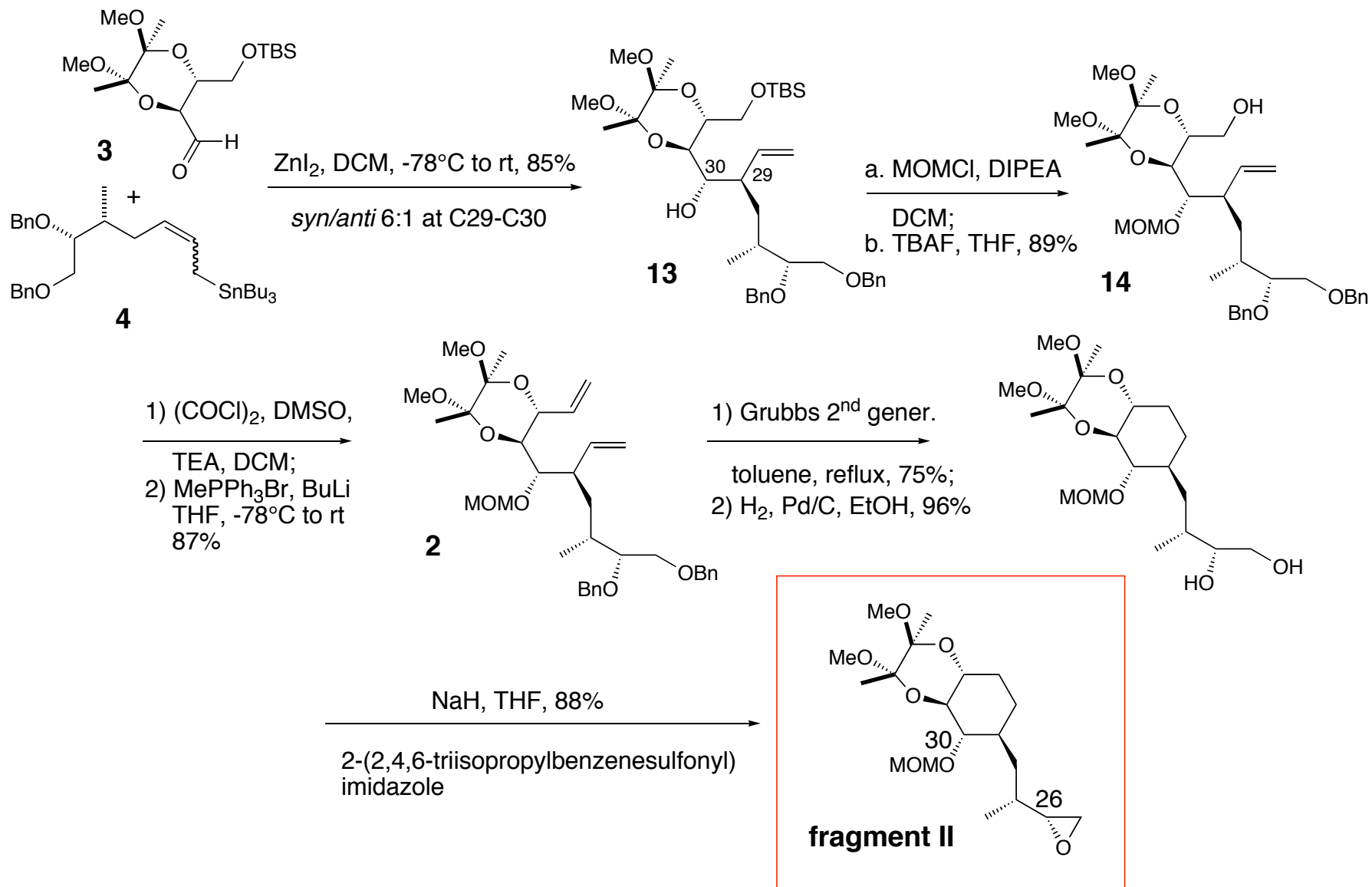
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## Fragment II



*J. Chem. Soc. Perkin Trans. 1*, **1999**, 1627, 1631  
*Chem Rev.* **2001**, 101, 53.



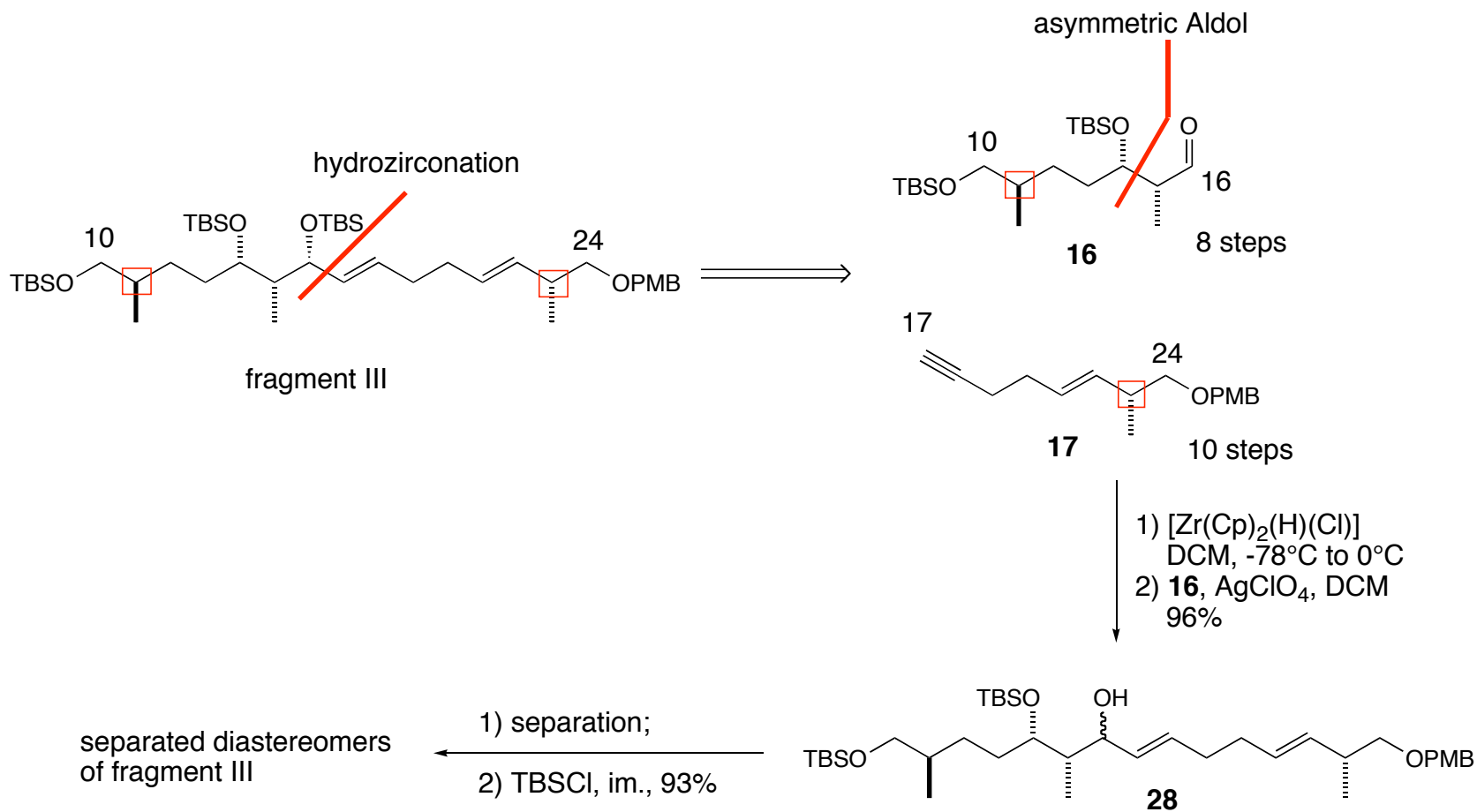


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# Fragment III



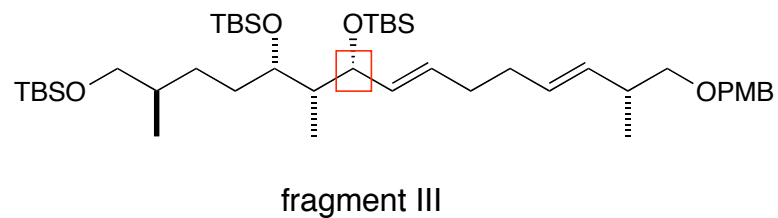
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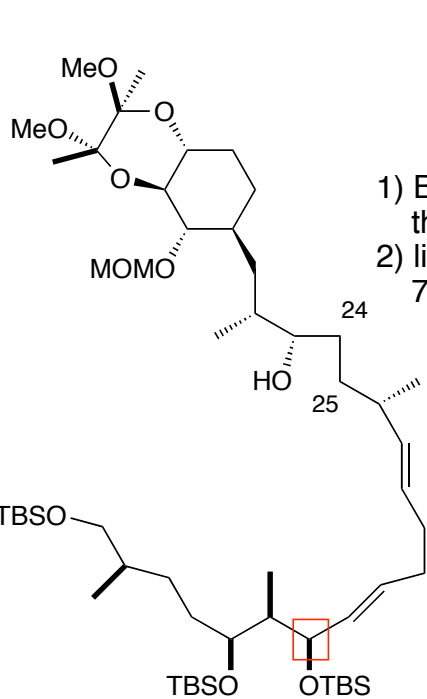
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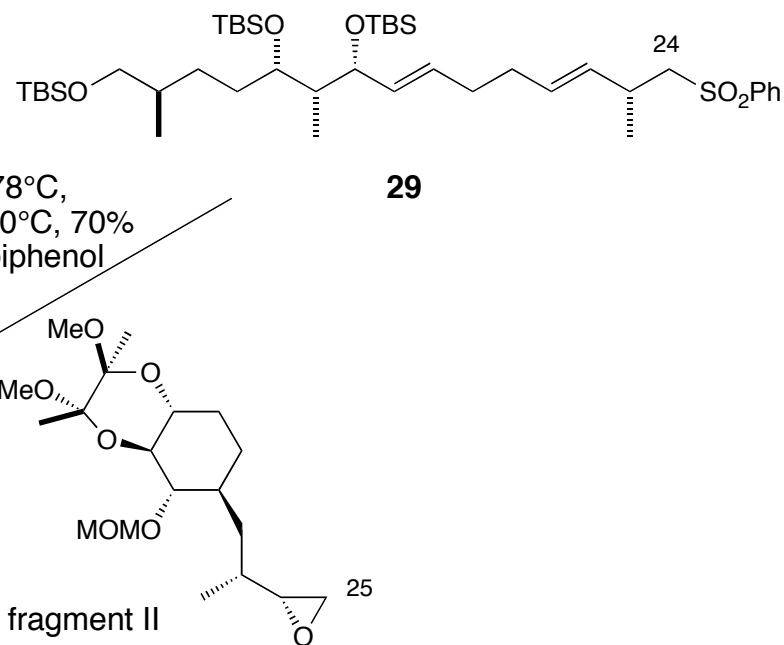
## Fragment III + Fragment II

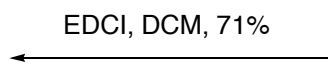
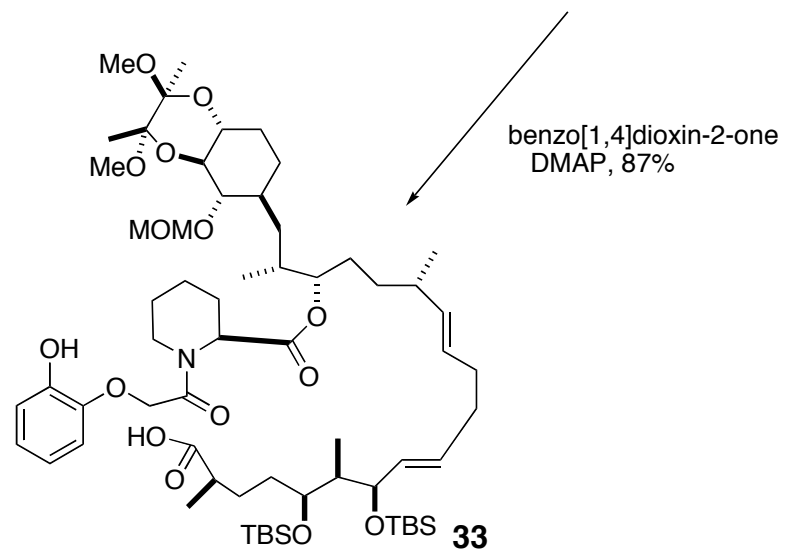
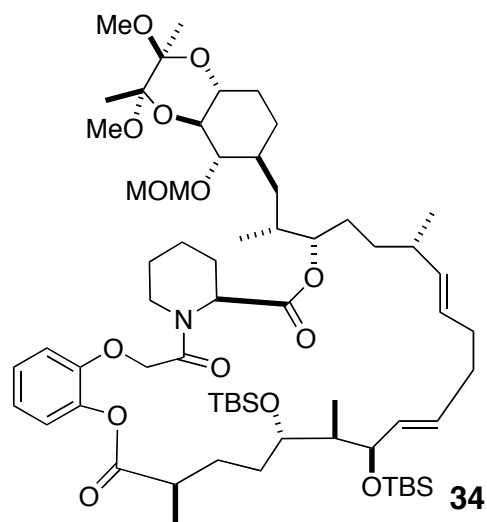
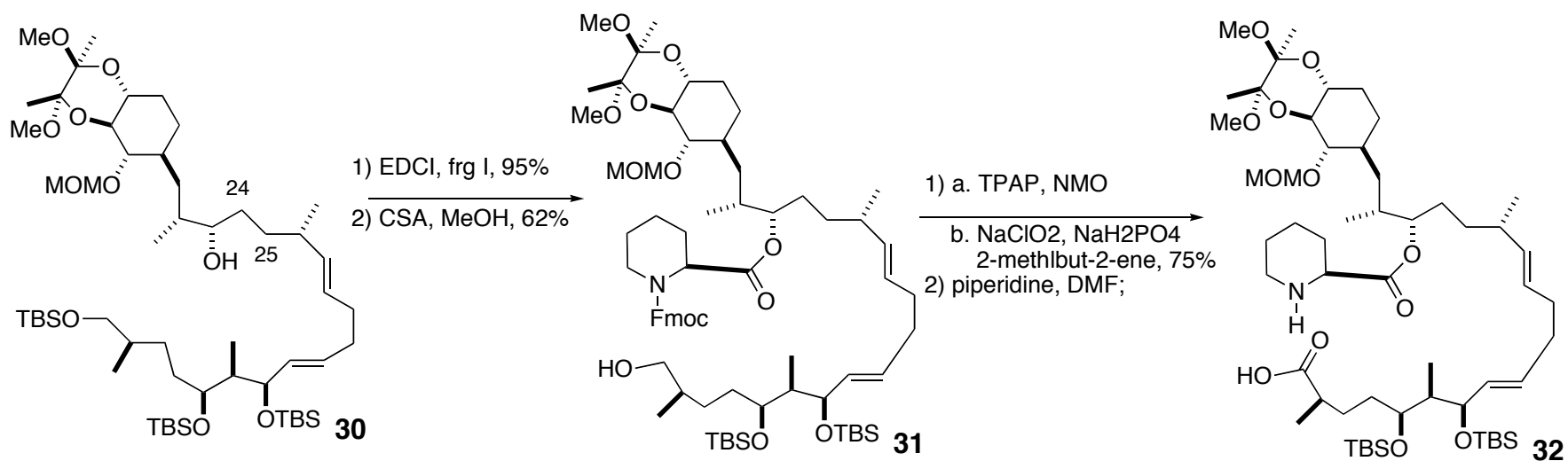


- 1) DDQ, DCM, H<sub>2</sub>O;  
 2) PhSSPh, PBU<sub>3</sub>, py, 95%  
 3) PhSeSePh, H<sub>2</sub>O<sub>2</sub>, Et<sub>2</sub>O  
 88%



- 1) BuLi, HMPA, THF, -78°C,  
 then fragment II at -20°C, 70%  
 2) lithium 4,4-di-*t*-butylbiphenol  
 78%

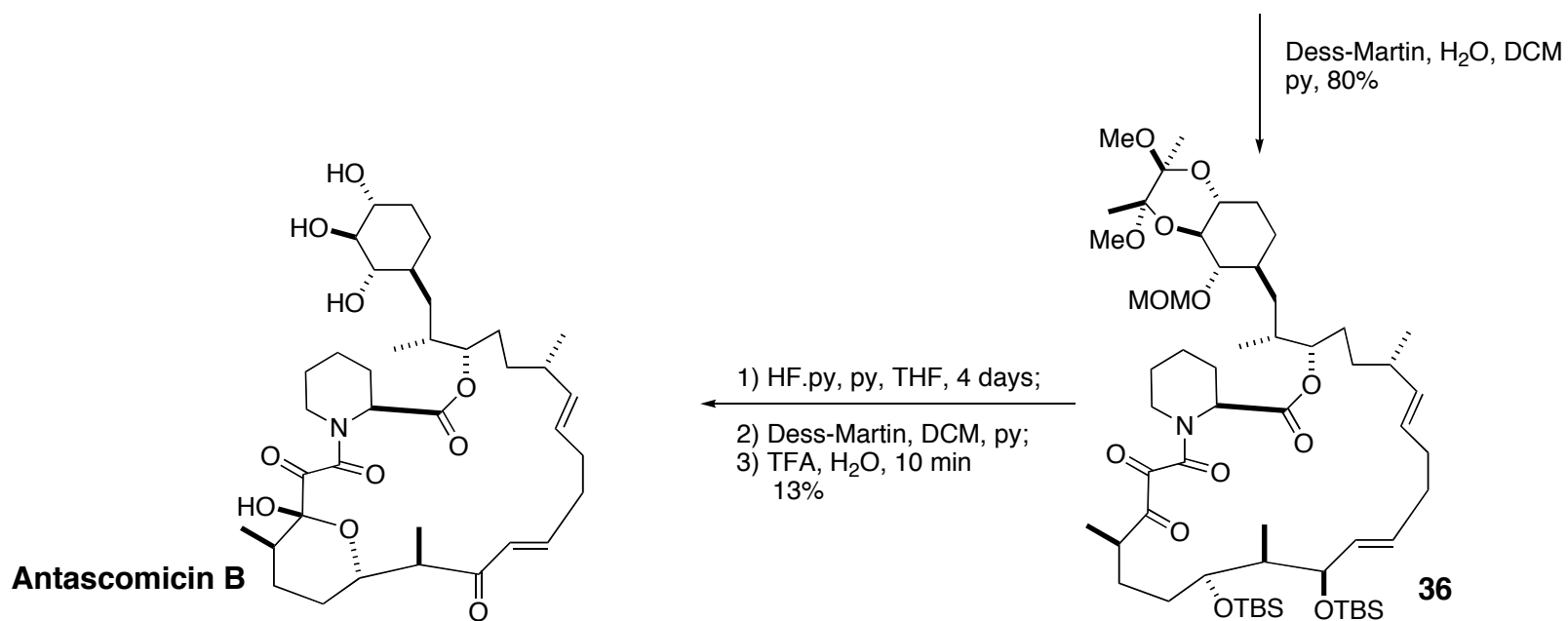
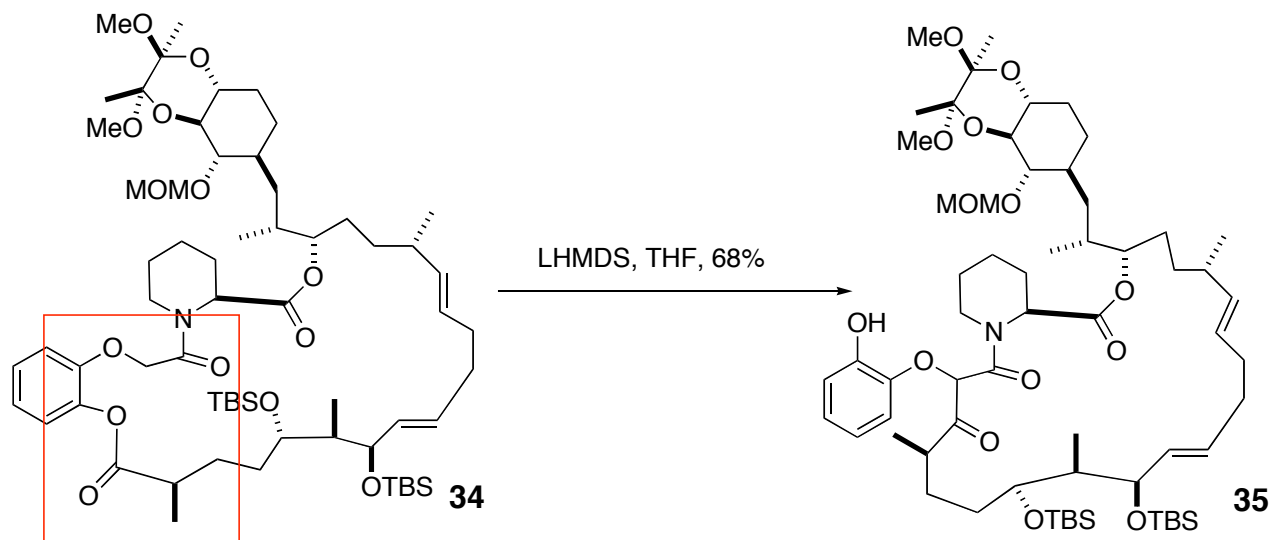




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## Conclusion

- First total synthesis of antascomicin family member;
- Butanediactal as protecting stereodirecting group;
- Transannular Dieckmann condensation - oxidation;
- Related approach used by Ohtsuka in 1983, in 1999 for a taxane skeleton;
- Vicinal tricarbonyls;
- 52 total steps from commercially available materials;
- Longest linear sequence of 23 steps;