Total Synthesis of Antascomincin B

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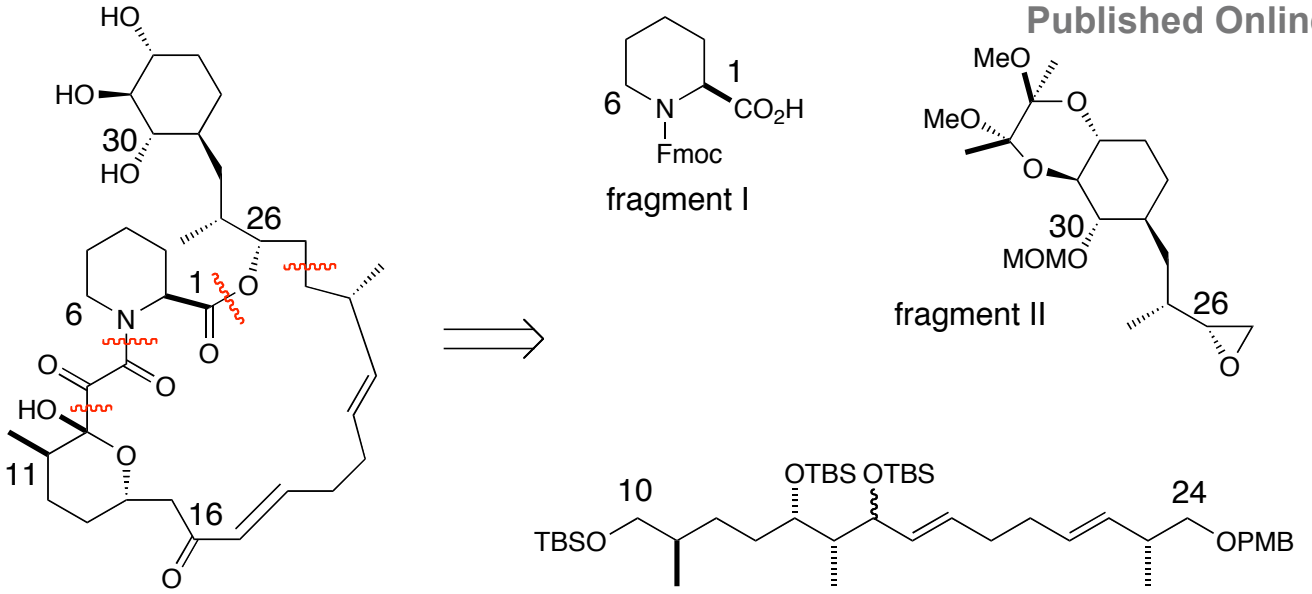
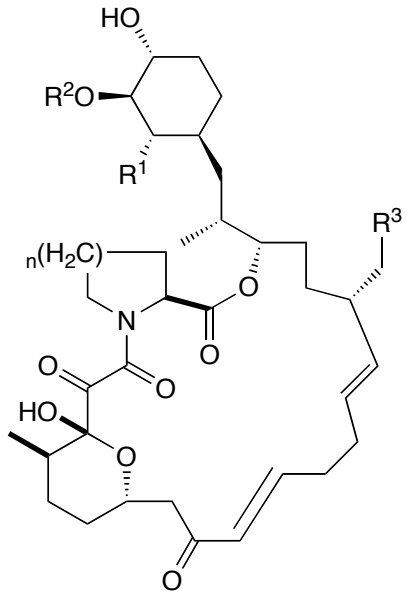


1

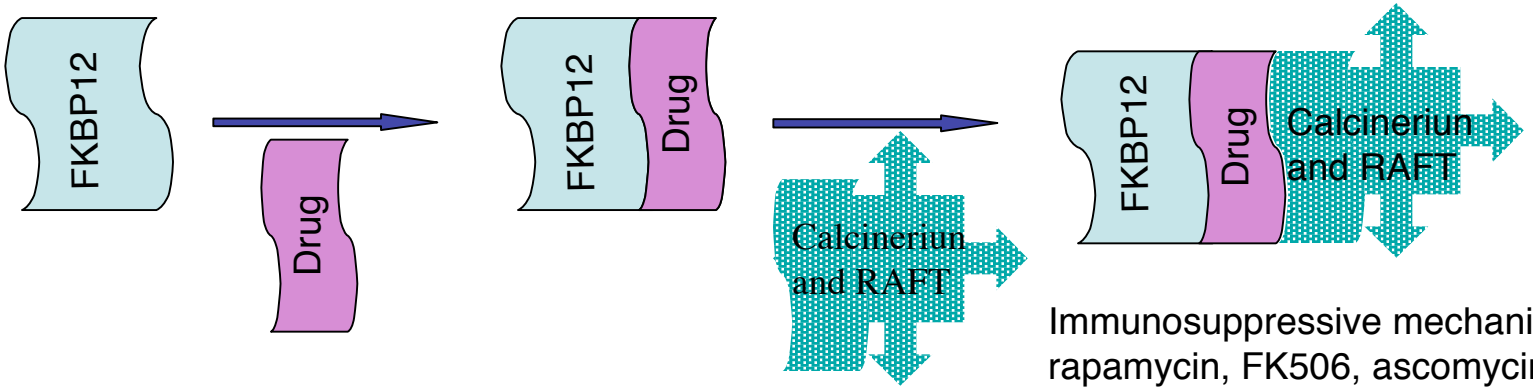
Antascomincin A - E and the FKBP12



- 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 peptydil 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.

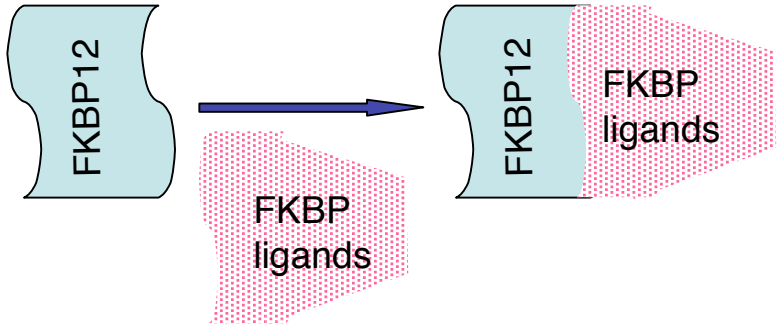
Antascomicin	R^1	R^2	R^3	n	FKBP12 binding IC_{50} (nM)
A	H	H	H	2	2.0
B	OH	H	H	2	0.7
C	OH	Me	H	2	1.0
D	H	H	H	1	5.2
E	H	H	OH	2	0.7

The Immunosuppressive Drug Action:



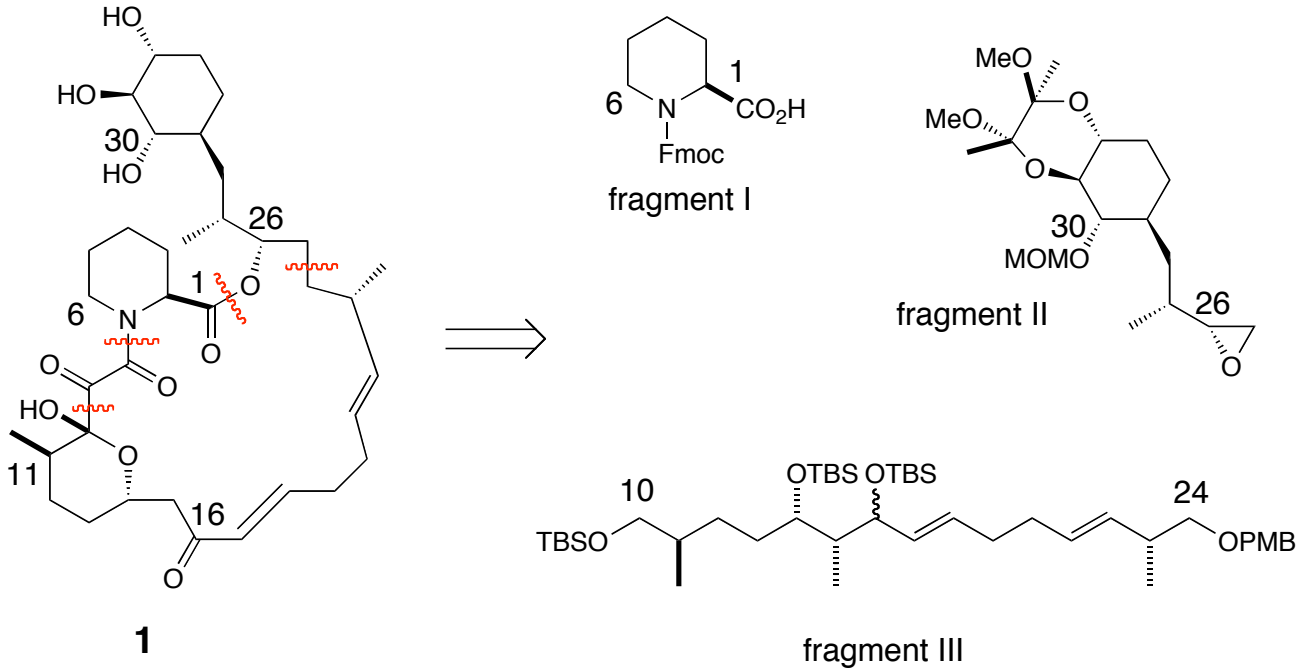
Immunosuppressive mechanism rapamycin, FK506, ascomycin and meridamycin.

The Non-Immunosuppressive Ligand:



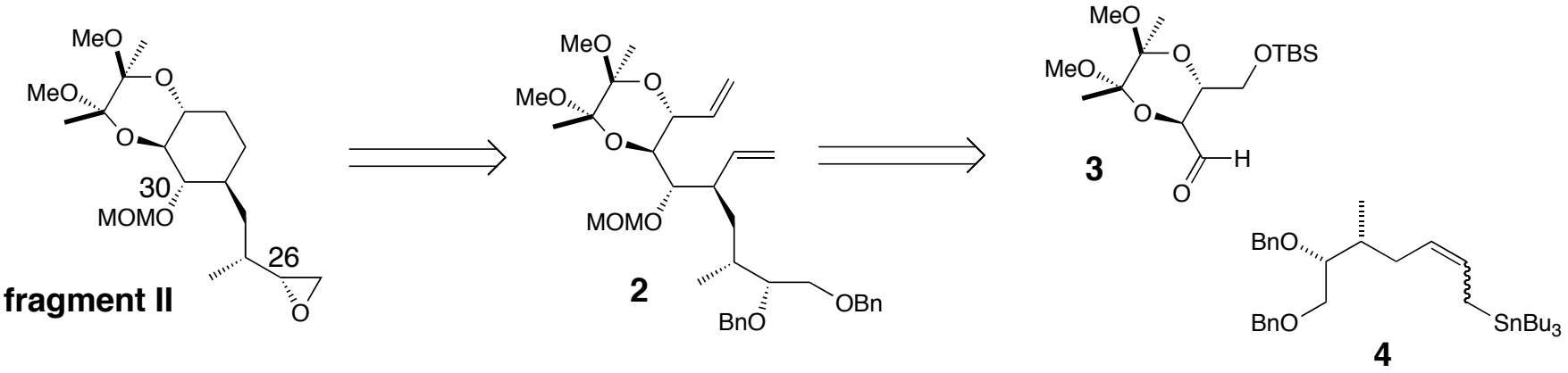
- Ligand-FKBP neurotropic non-immunosuppressant complexes: clinical use.
- Independent mechanisms.
- Attention returned to the strong FKBP's ligands with no immunosuppression activity.

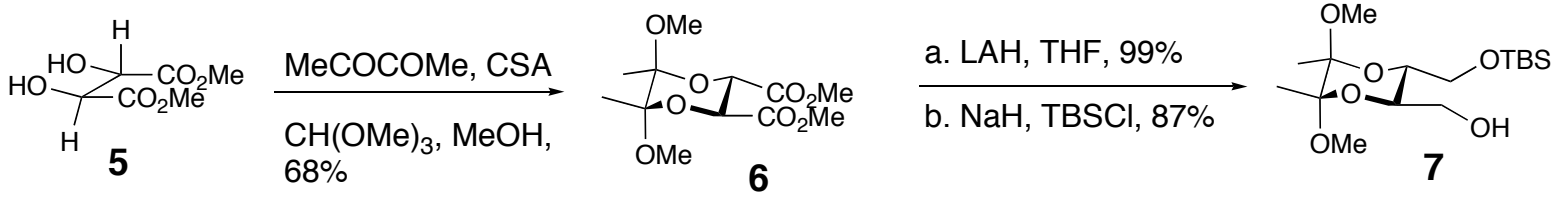
First Synthesis of an Antascomincin Member

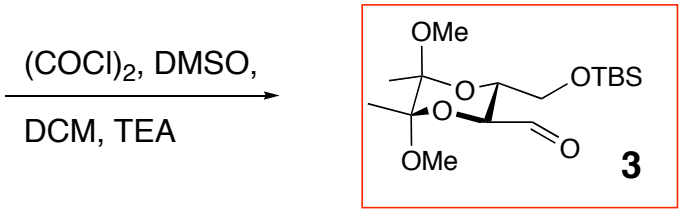


1

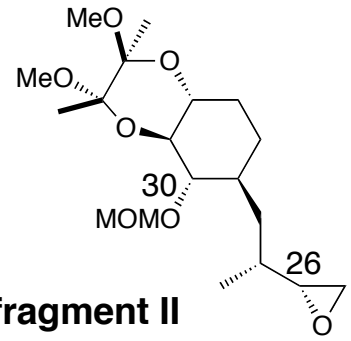
Fragment II



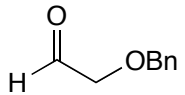




J. Chem. Soc. Perkin Trans. 1, **1999**, 1627, 1631
Chem Rev. **2001**, *101*, 53.



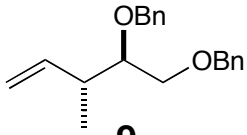
fragment II



8

1) a. (E)-butene, KO*t*Bu,

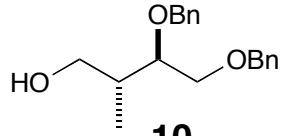
n-BuLi, THF -78°C;
b. (+)-$(Ipc)_2BOMe$, Et_2O, BF_3.OEt, -78°C;
2) BnBr, NaH, DMF, 62%



9

a. O_3, DCM, -78°C

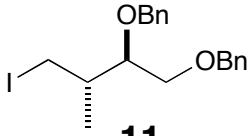
then PPh_3;
b. $NaBH_4$, MeOH, 90%



10

I_2, im., PPh_3,

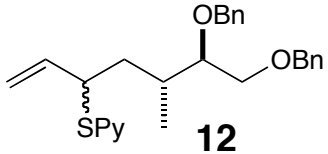
DCM, 90%



11

allylpyridylsulfide, *t*BuLi

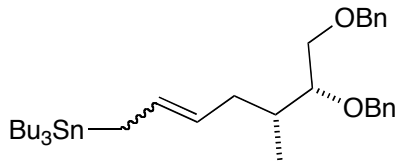
THF, -78°C, 95%



12

Bu_3SnLi, CuBr, THF

-78°C, 98%



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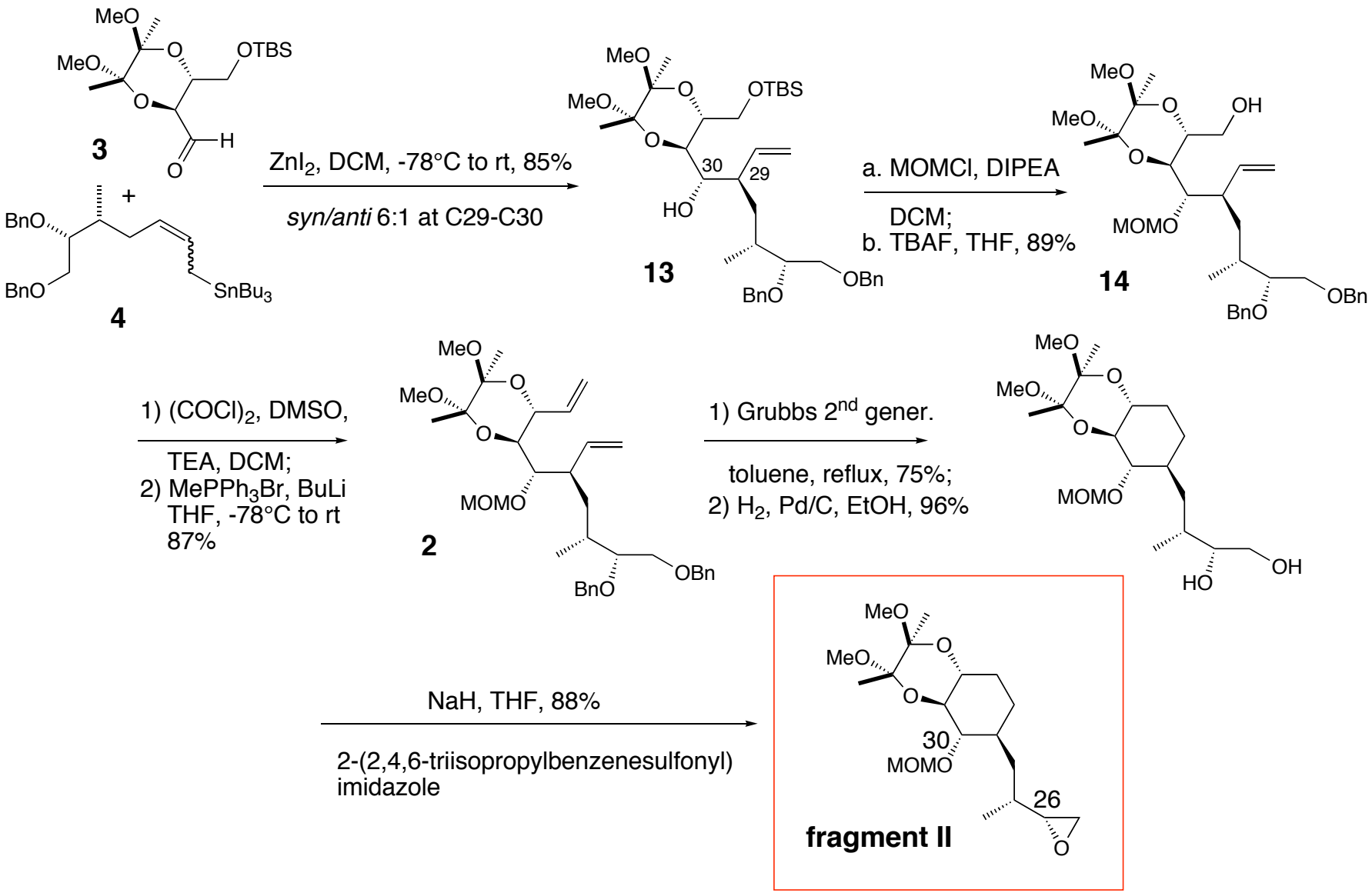
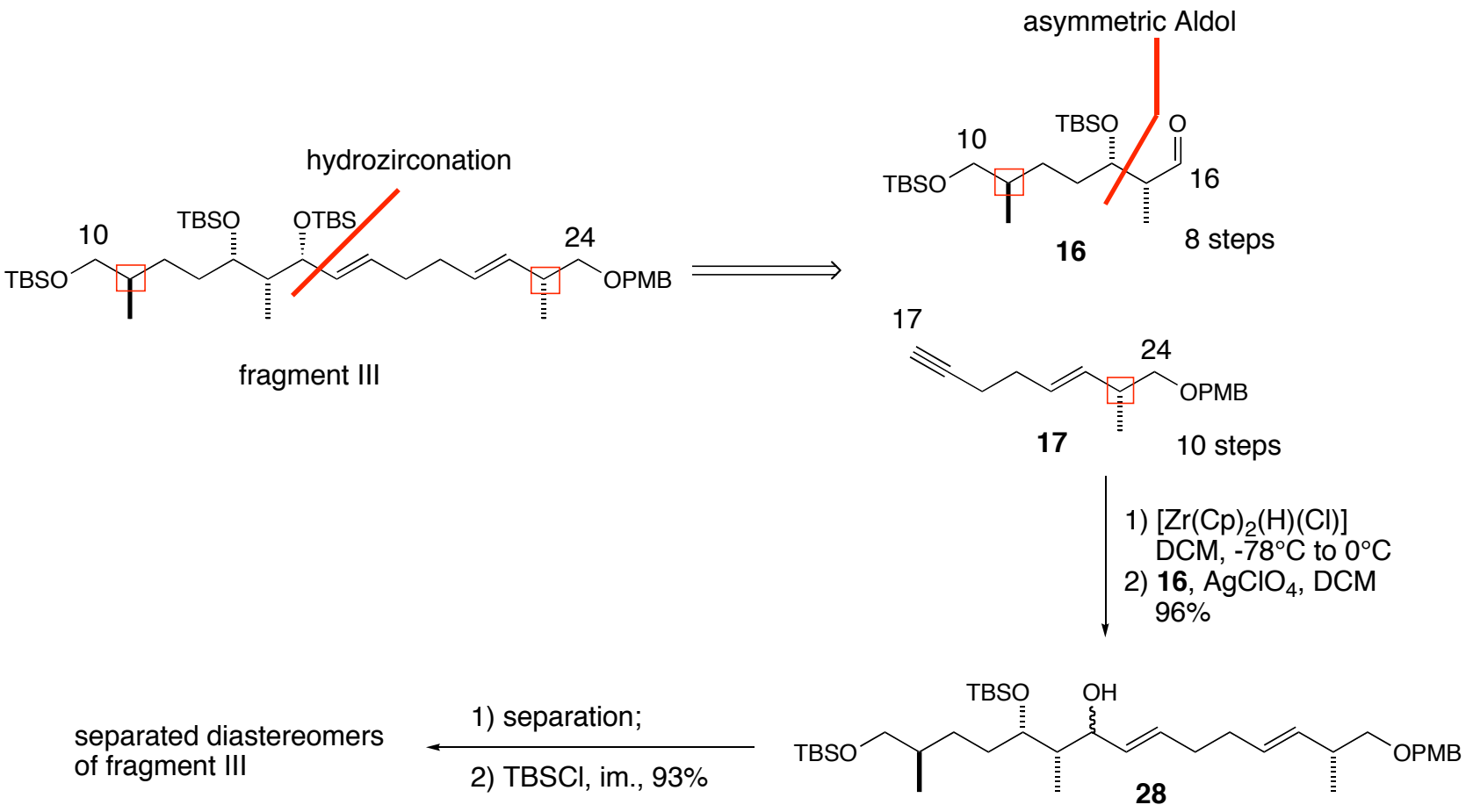
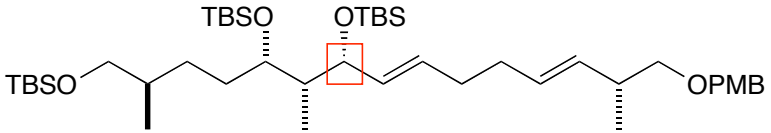

3
4
ZnI_2, DCM, -78°C to rt, 85%
syn/anti 6:1 at C29-C30
13
a. MOMCl, DIPEA
DCM;
b. TBAF, THF, 89%
14
1) $(COCl)_2$, DMSO,
TEA, DCM;
2) $MePPh_3Br$, BuLi
THF, -78°C to rt
87%
2
1) Grubbs 2nd gener.
toluene, reflux, 75%;
2) H_2, Pd/C, EtOH, 96%
NaH, THF, 88%
2-(2,4,6-triisopropylbenzenesulfonyl)
imidazole
fragment II

Fragment III



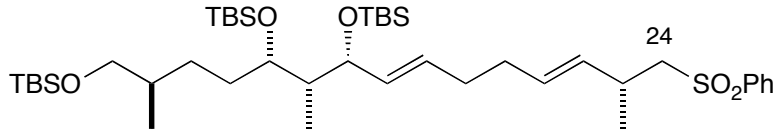
Fragment III + Fragment II



fragment III

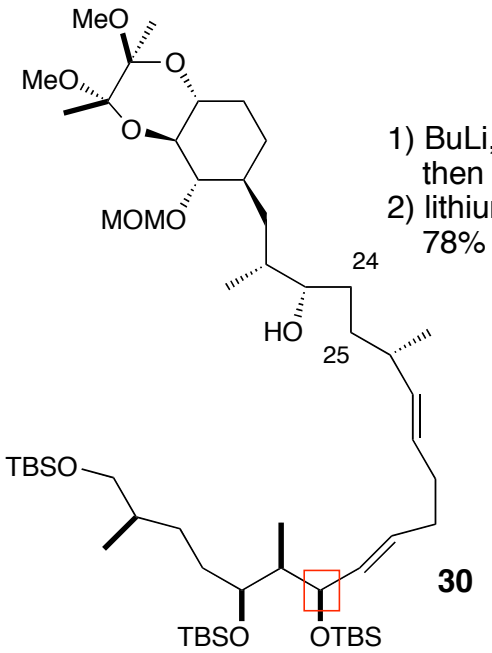
1) DDQ, DCM, H_2O;

2) PhSSPh, PBu_3, py, 95%
3) PhSeSePh, H_2O_2, Et_2O
88%



29

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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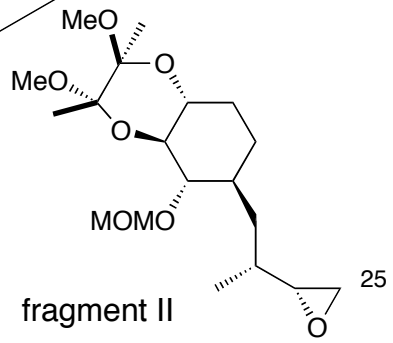
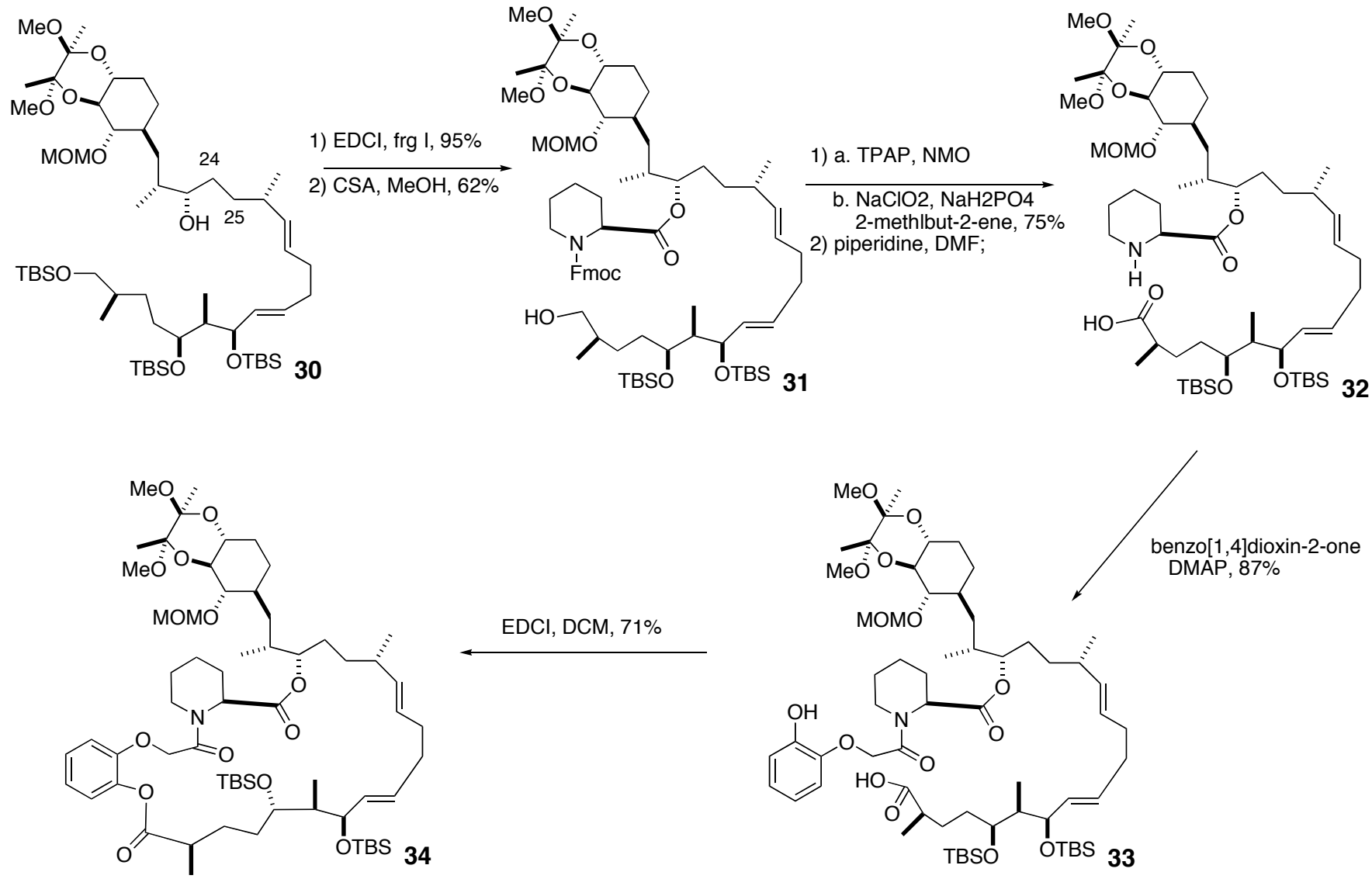
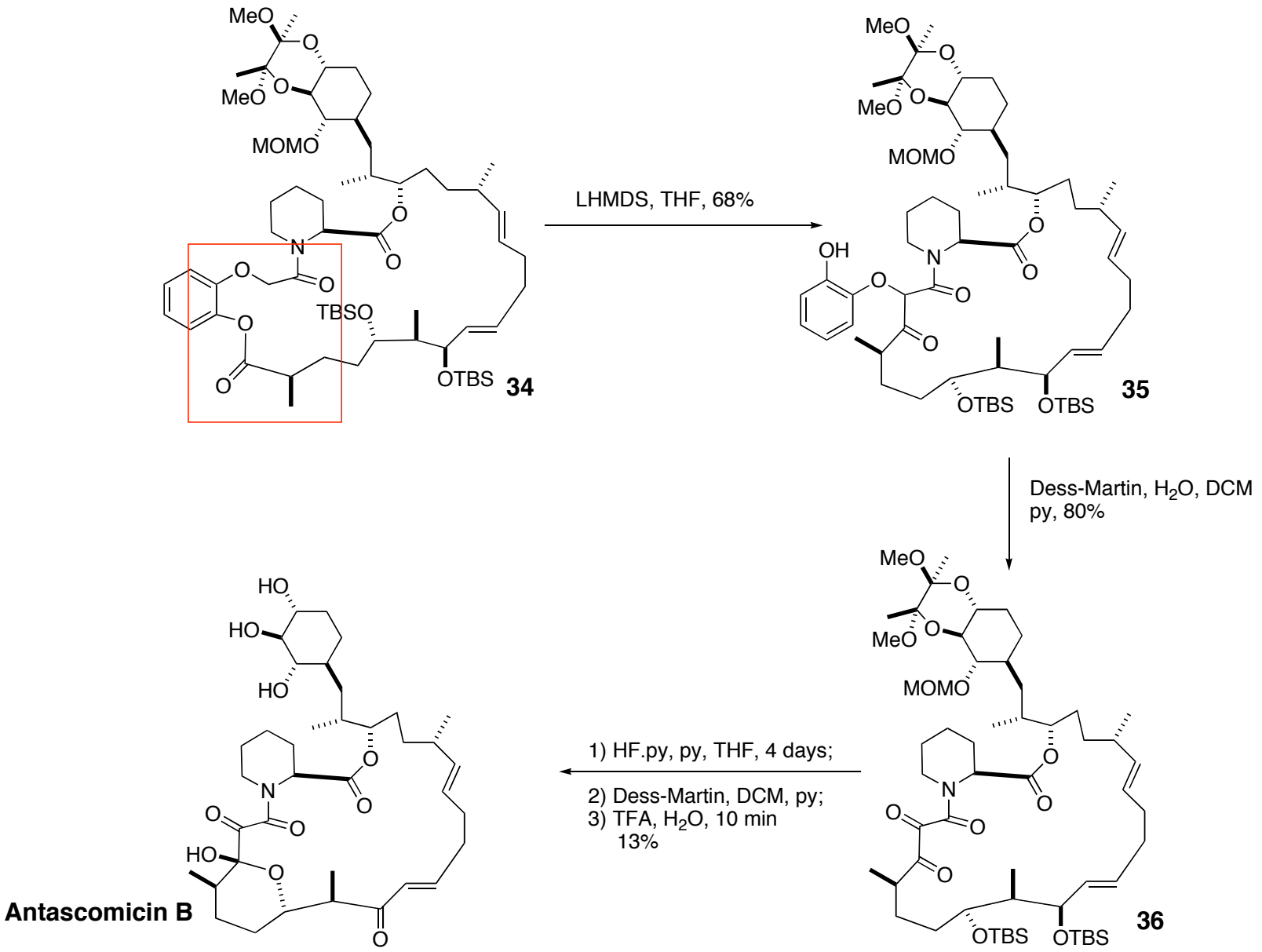


fragment II


MeO
MeO
MeO
MOMO
24
OH
25
TBSO
TBSO
OTBS
30
1) EDCI, frg I, 95%
2) CSA, MeOH, 62%
Fmoc
HO
TBSO
OTBS
31
1) a. TPAP, NMO
b. NaClO2, NaH2PO4
2-methlbut-2-ene, 75%
2) piperidine, DMF;
H
32
benzo[1,4]dioxin-2-one
DMAP, 87%
OH
33
EDCI, DCM, 71%
34


MeO
MeO
MOMO
TBSO
OTBS
34
LHMDS, THF, 68%
OH
OTBS
OTBS
35
Dess-Martin, H2O, DCM
py, 80%
36
1) HF.py, py, THF, 4 days;
2) Dess-Martin, DCM, py;
3) TFA, H2O, 10 min
13%
HO
HO
HO
HO
Antascomicin B

Conclusion

- First total synthesis of antascomicin family member;
- Butanediacetal 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;