UNIVERSITÉ
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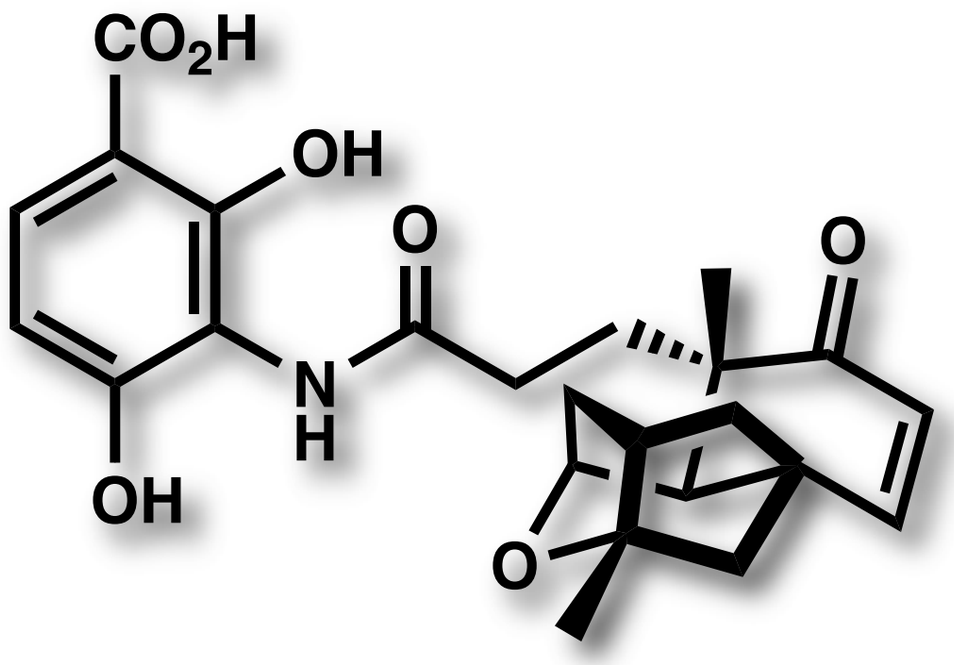
STeReO-selective Syntheses of Platensimycin



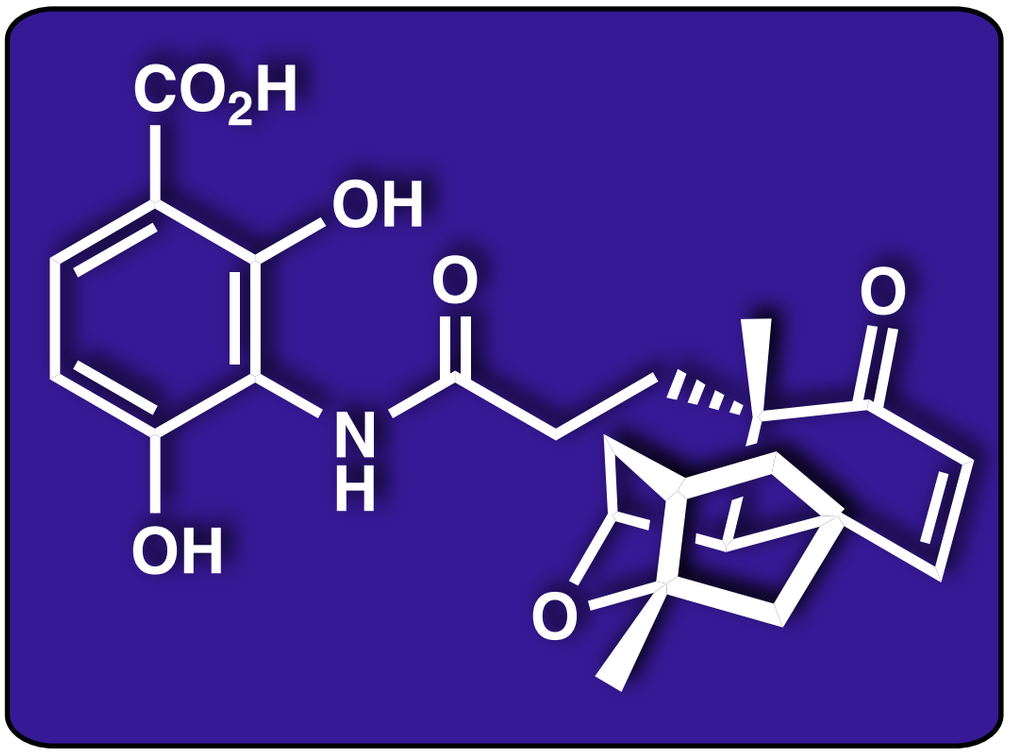
stéréo

27 mars 2008

Summary

- Presentation - Structure
- Total & formal syntheses : enantioselective & racemic pathways (chronological order)
- Syntheses of Analogs

Platensimycine: presentation

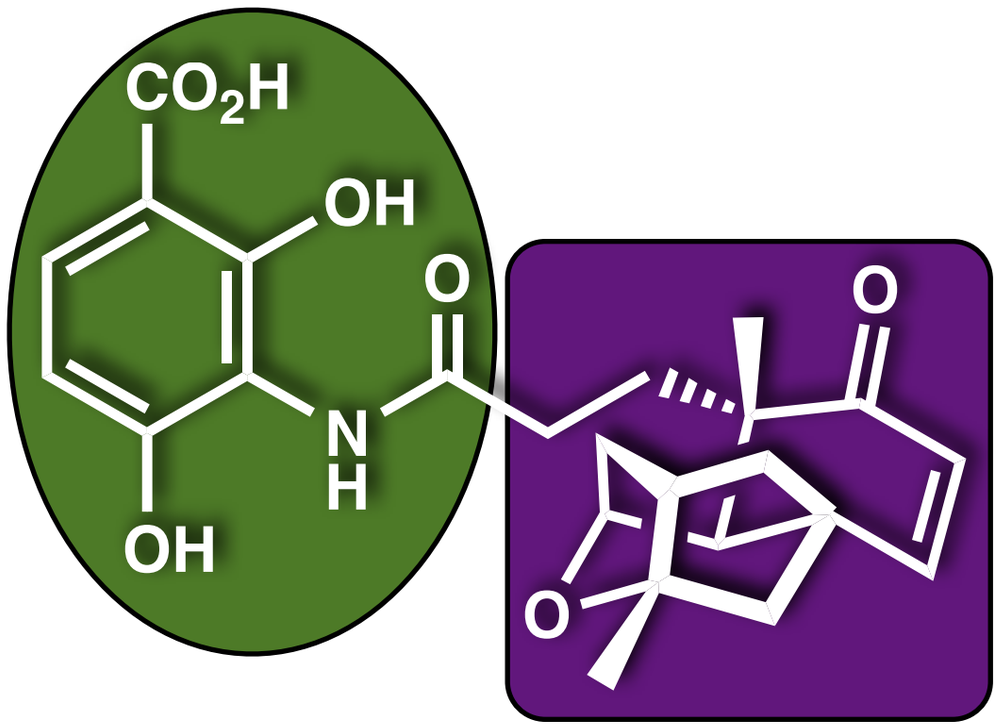


Isolated from *Streptomyces platensis*, in 2006, by Merck (*JACS* **2006**, 11916)

Novel and potent broad spectrum Gram-positive antibiotic

Found by high-throughput screening of 250 000 microbial extracts

Platensimycine : structure

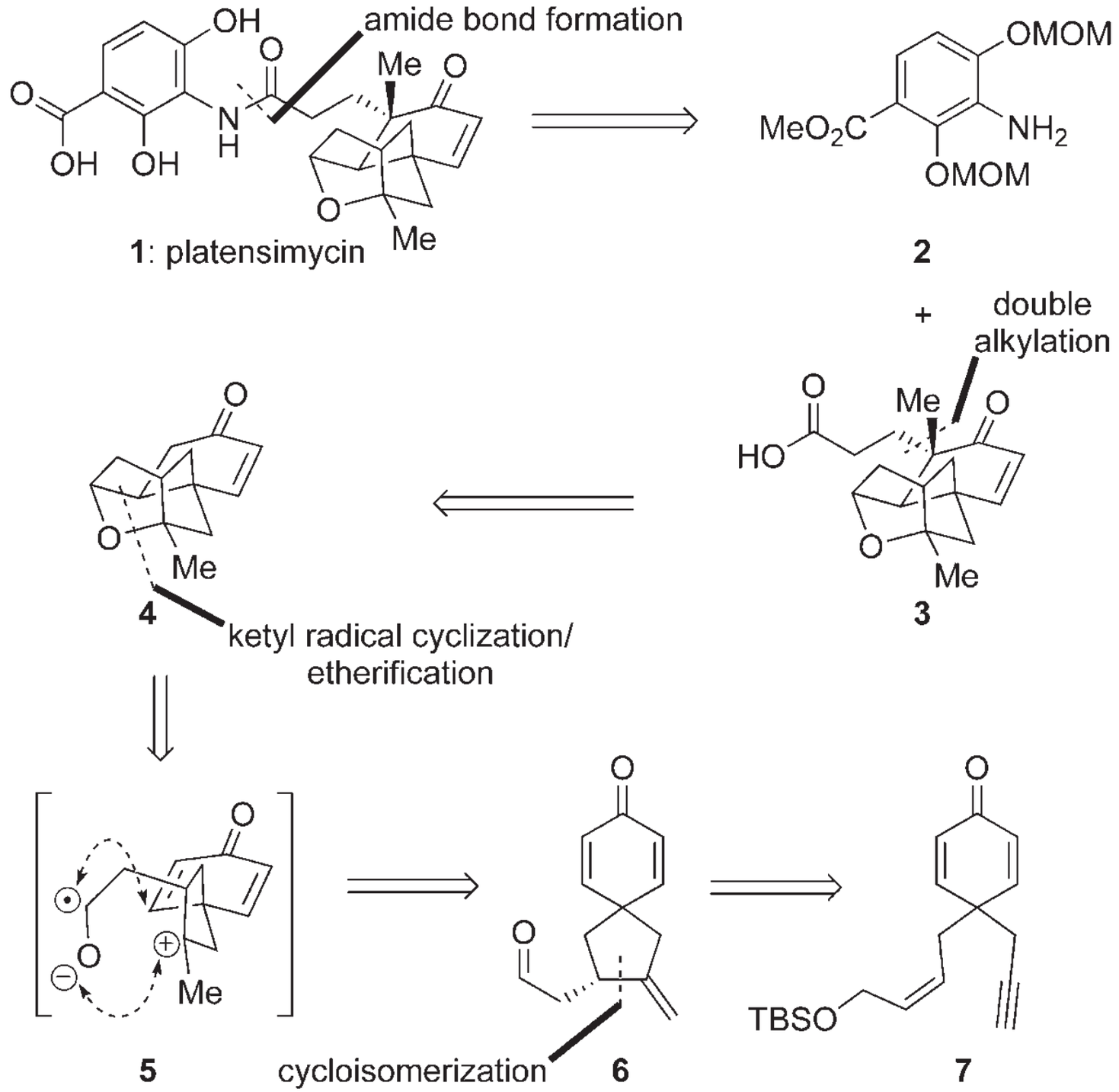


Apolar, complex pentacyclic core

Very polar unusual side chain, amide link

Syntheses of Platensimycin

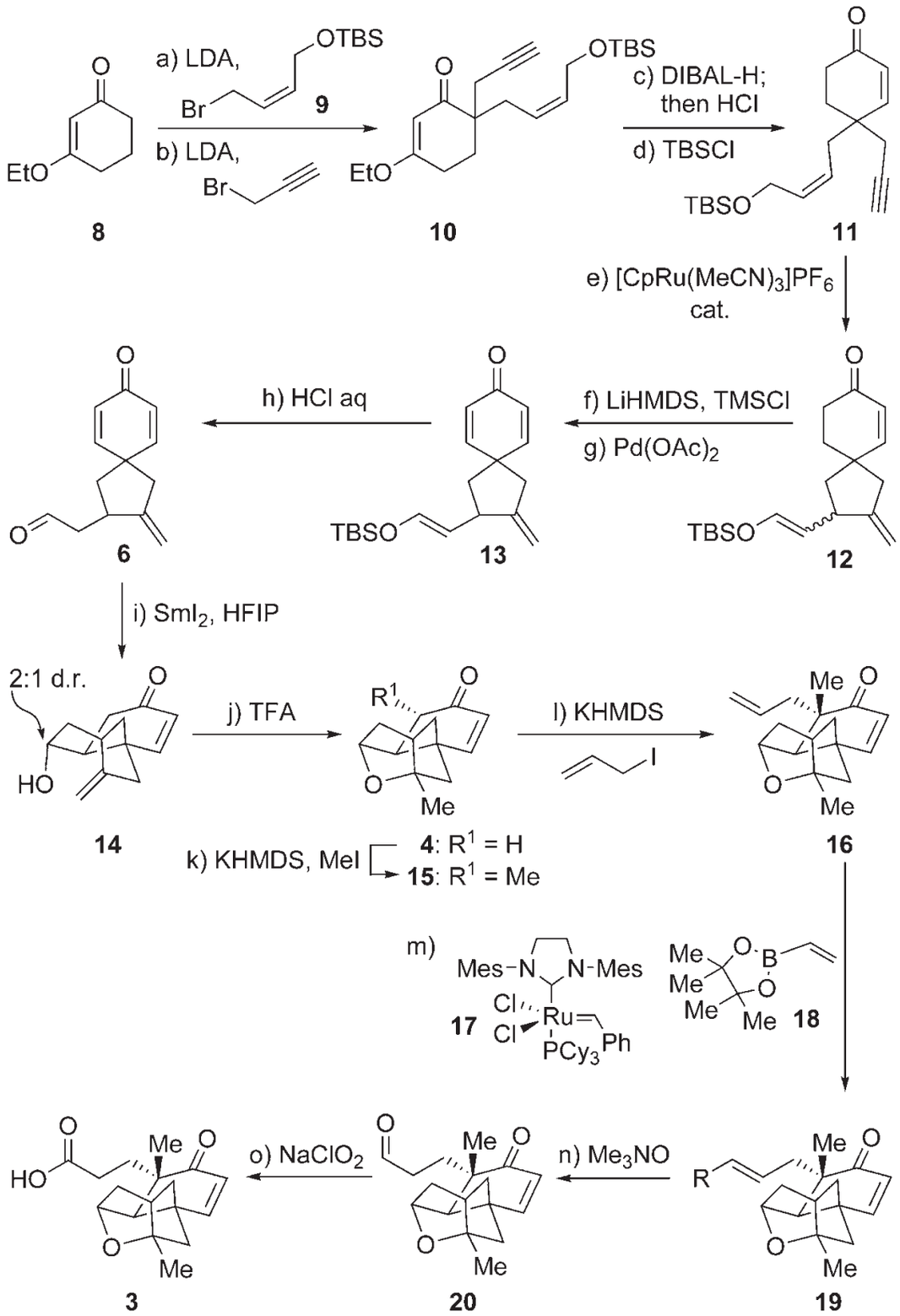
1st Synthesis: Nicolaou



total, racemic

ACIE **2006**, 7086

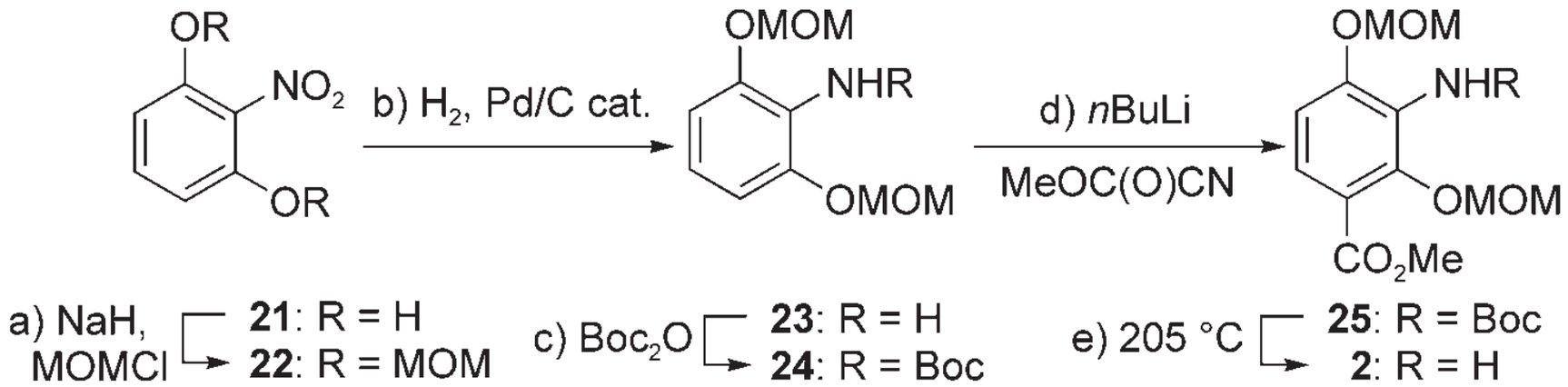
1st Synthesis: Nicolaou

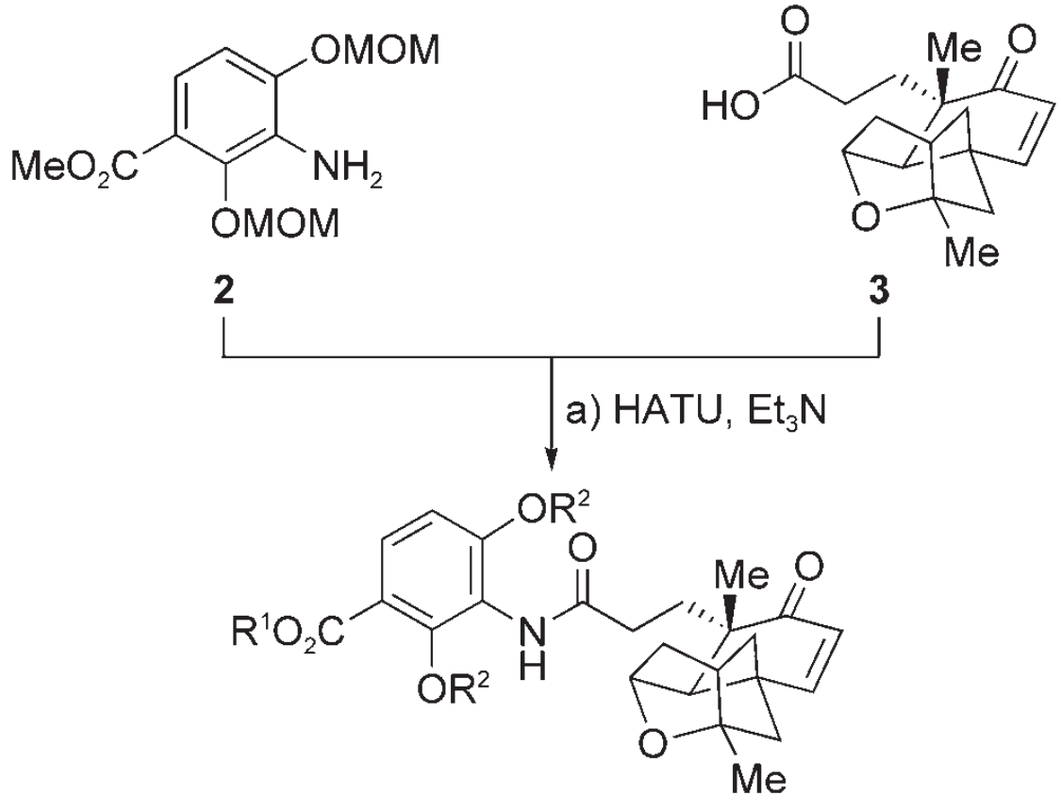


racemic

ACIE **2006**, 7086

1st Synthesis: Nicolaou

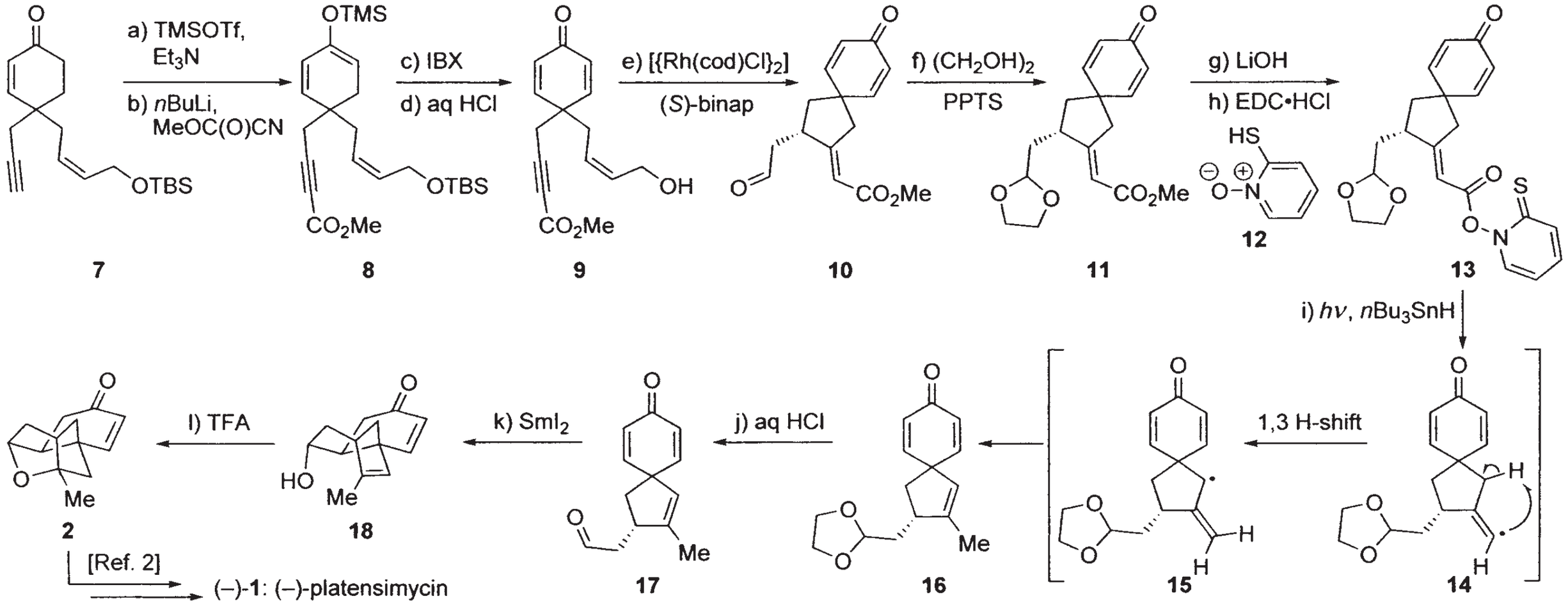




racemic

ACIE **2006**, 7086

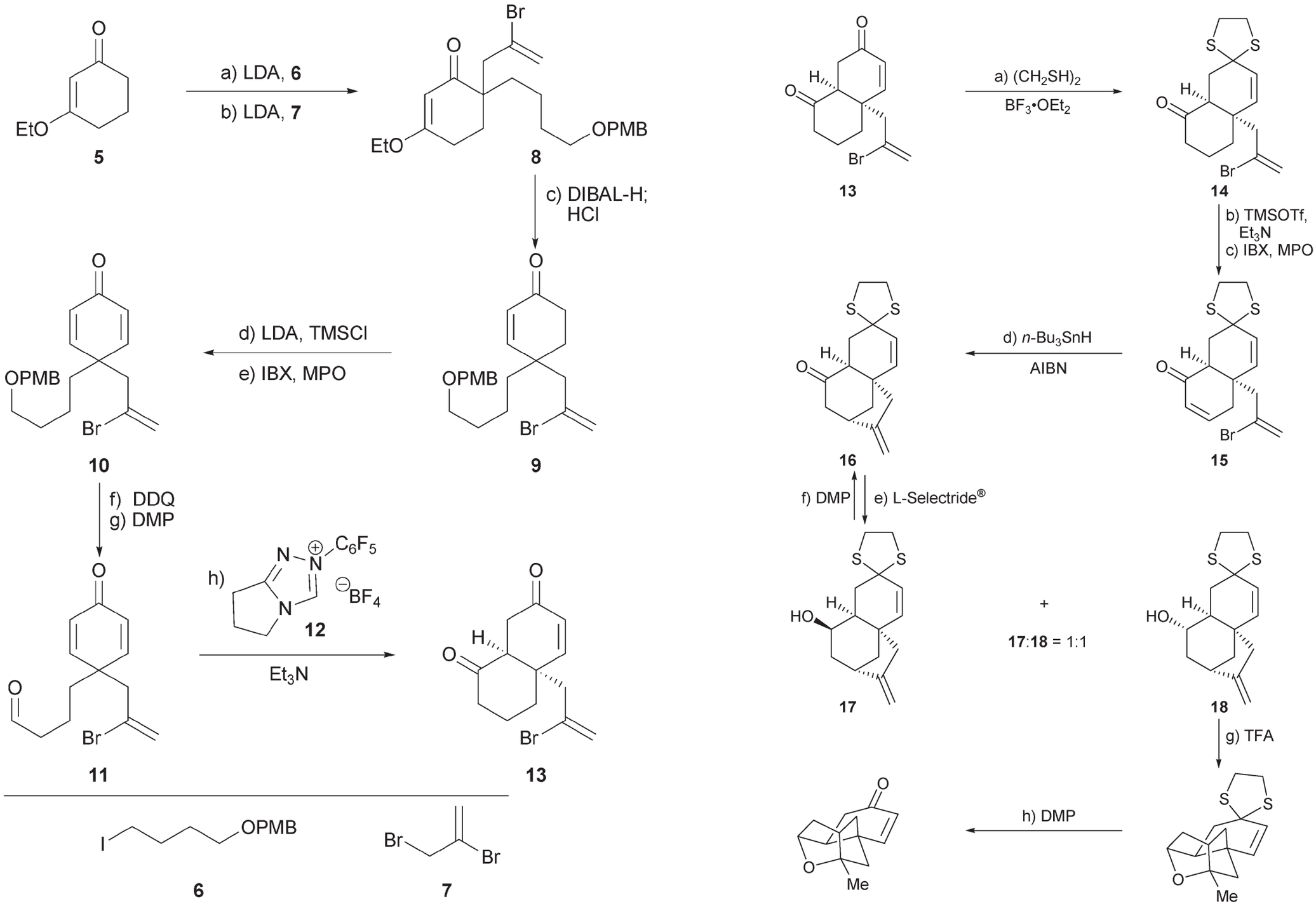
2007, February : Nicolaou



formal, enantioselective

ACIE **2007**, 3942

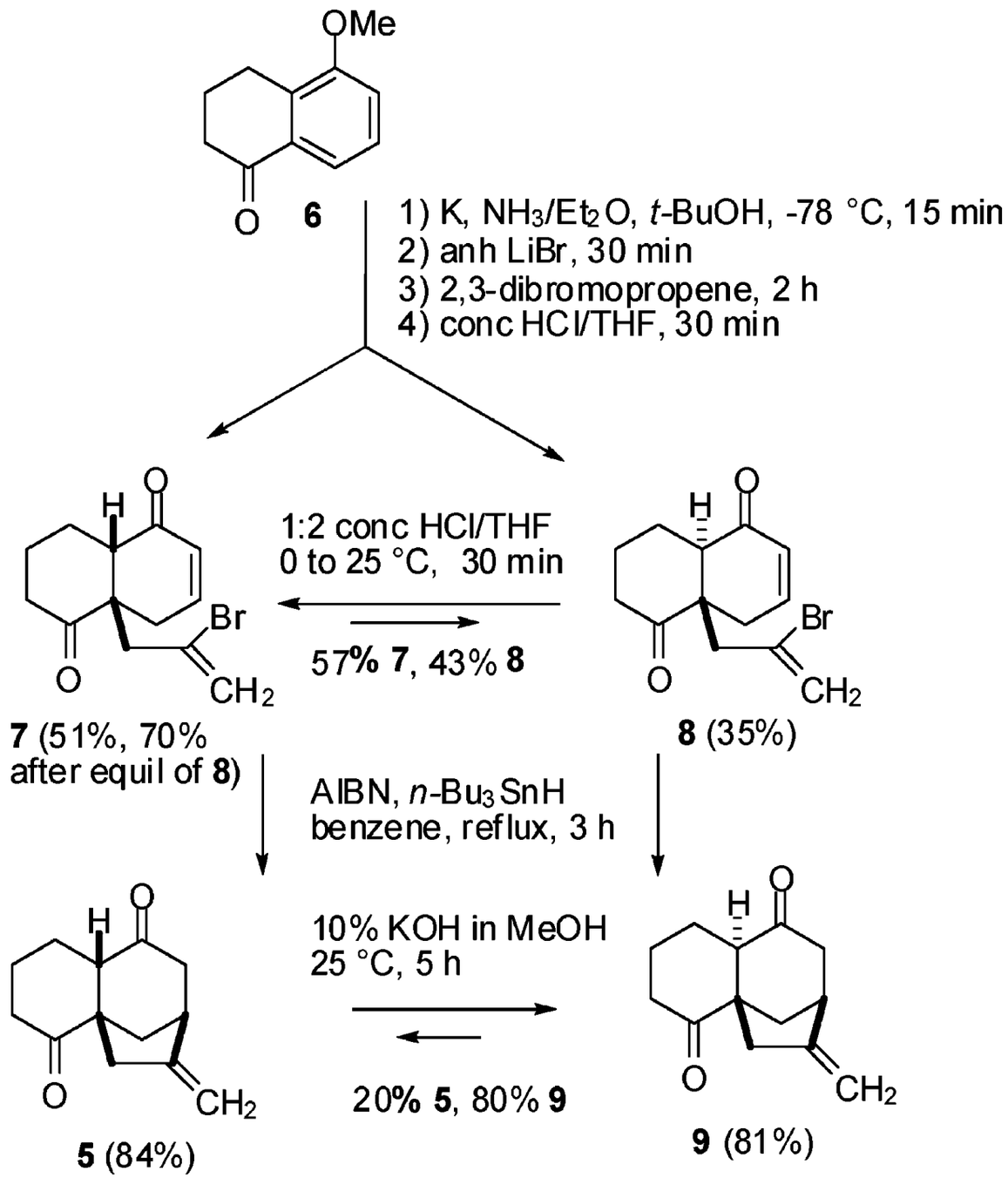
2007, March : Nicolaou



formal, racemic

Chem. Comm. **2007**, 1922

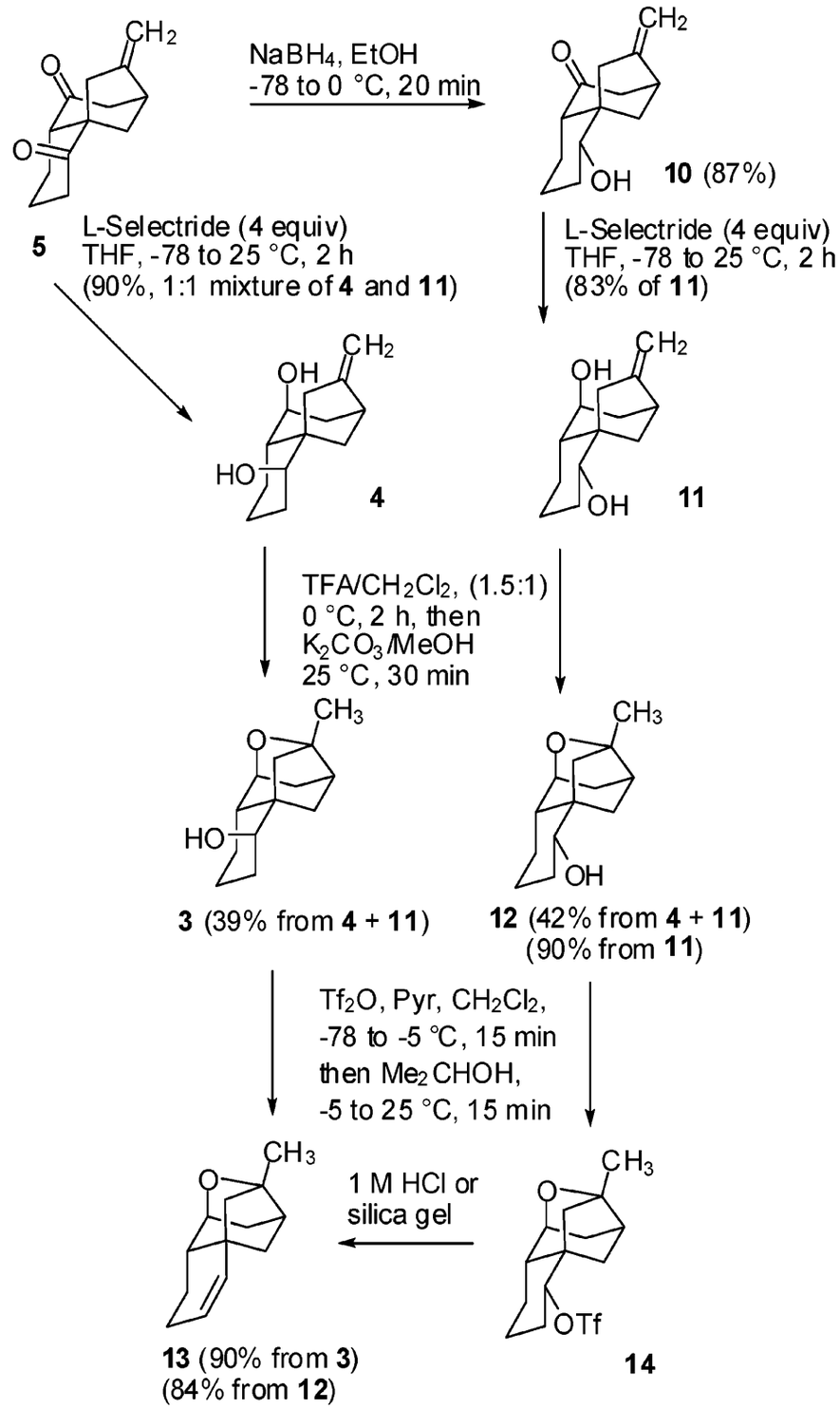
2007, March : Snider



formal, racemic

Org. Lett. **2007**, 1825

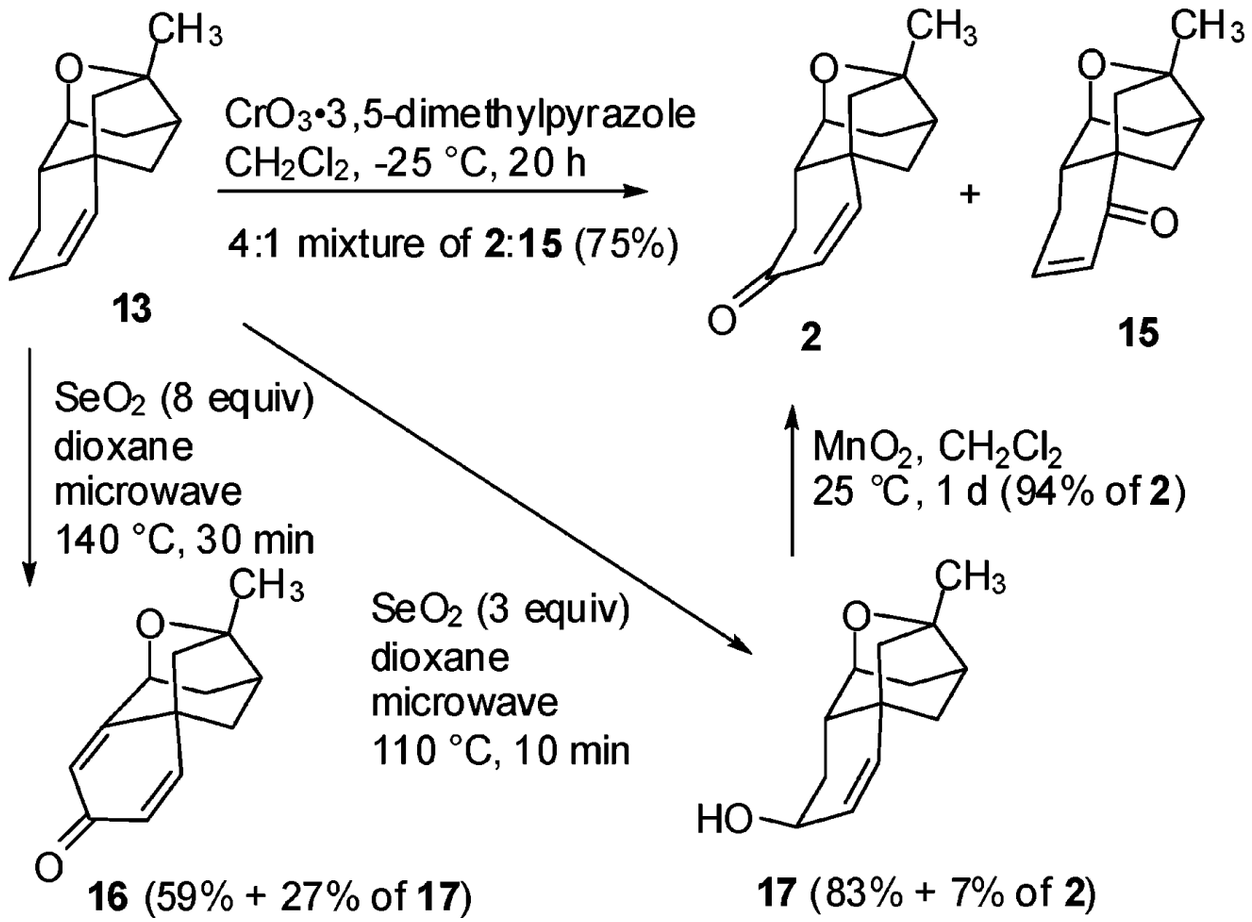
2007, March : Snider



formal, racemic

Org. Lett. **2007**, 1825

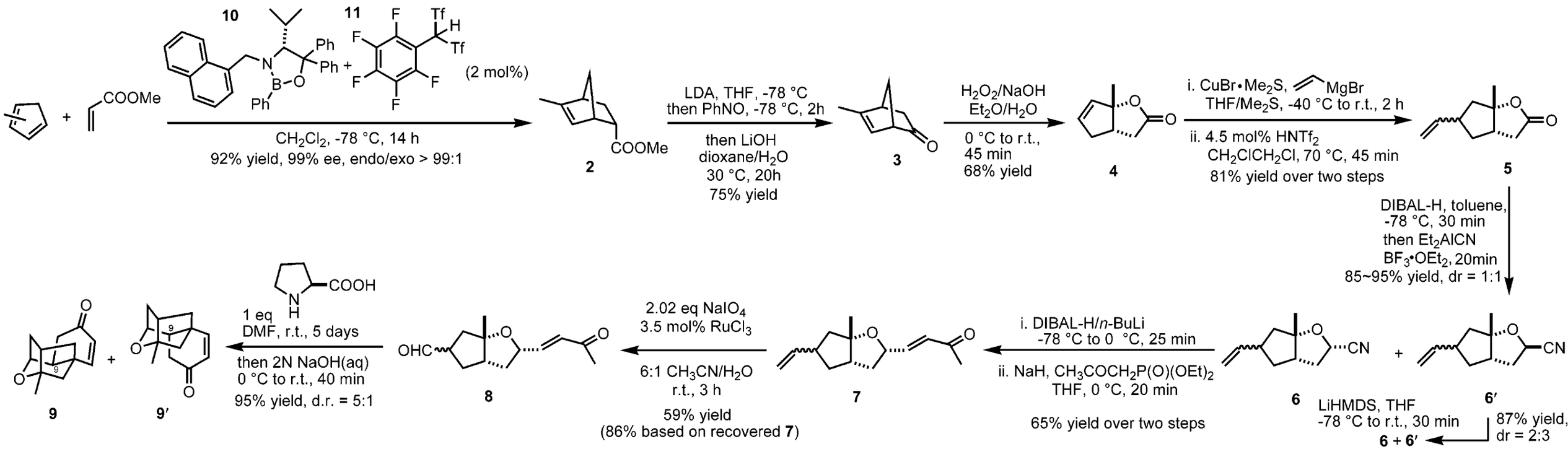
2007, March : Snider



formal, racemic

Org. Lett. **2007**, 1825

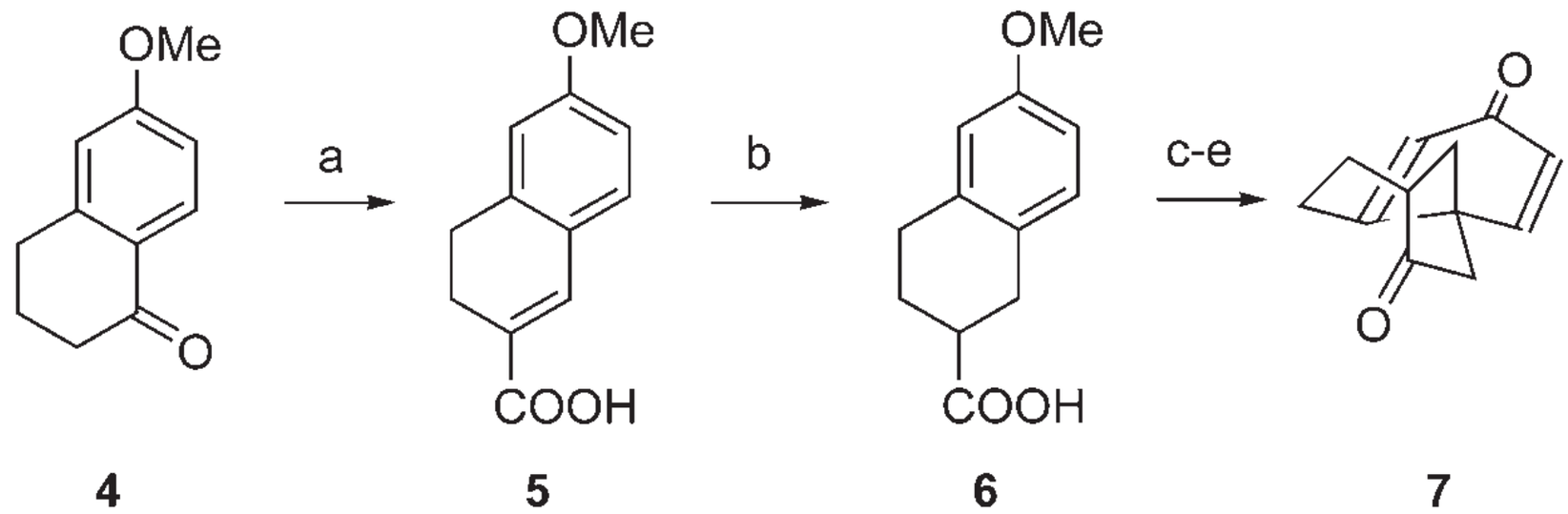
2007, May : Yamamoto



formal, enantioselective

JACS **2007**, 9534

2007, June : Mulzer

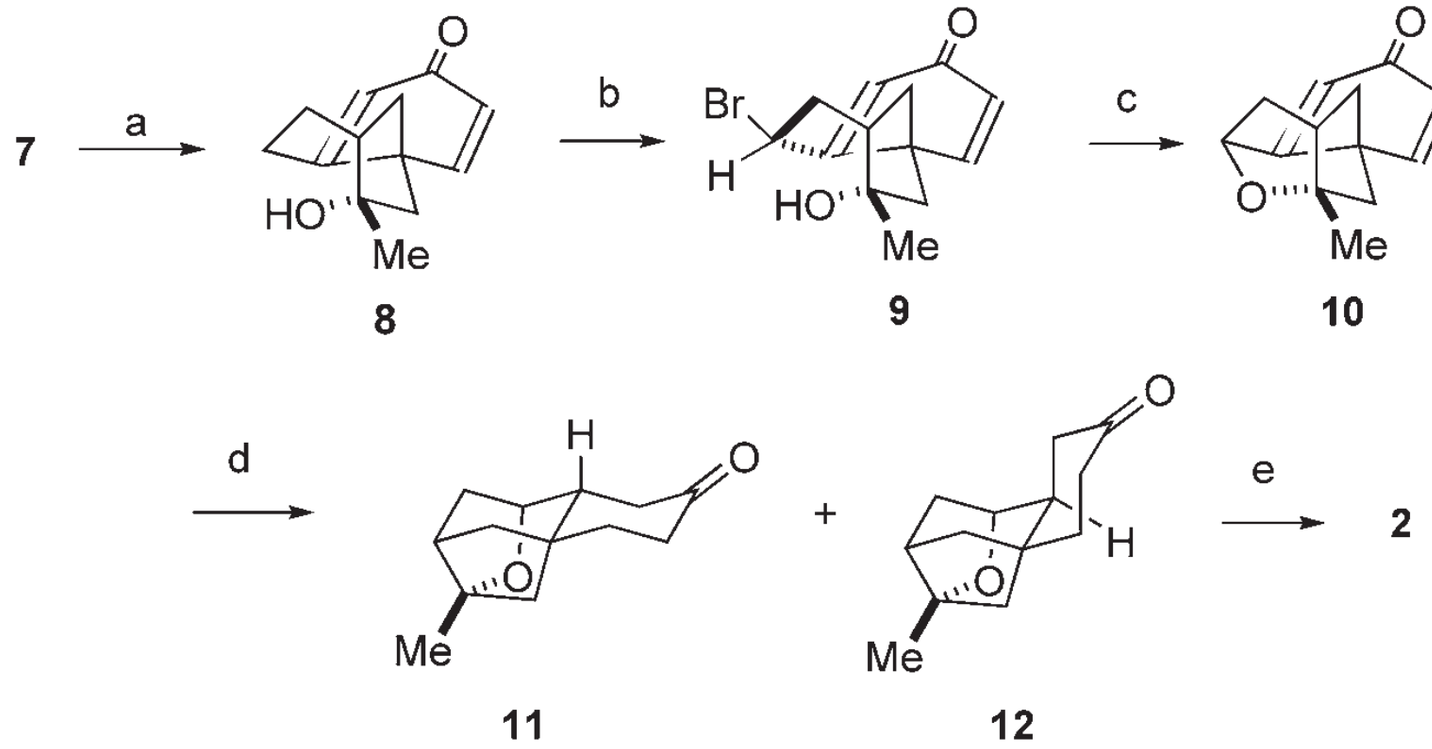


Scheme 2. Synthesis of tricycle **7**. Reagents and conditions: a) Three steps (86%; reference [7]: 54%); b) H_2, Pd/C, EtOH (99%; reference [7]: 92%); c) $SOCl_2$, DMF, toluene, RT, 3 h; d) $TMSCHN_2$, THF; hexane/EtOAc (10:1), SiO_2, RT, 12 h; e) TFA, −20 °C, 1 h (three steps, 59%). DMF = *N*,*N*-dimethylformamide, TMS = trimethylsilyl, THF = tetrahydrofuran, TFA = trifluoroacetic acid.

formal, racemic,
protecting-group-free

ACIE **2007**, 8074

2007, June : Mulzer



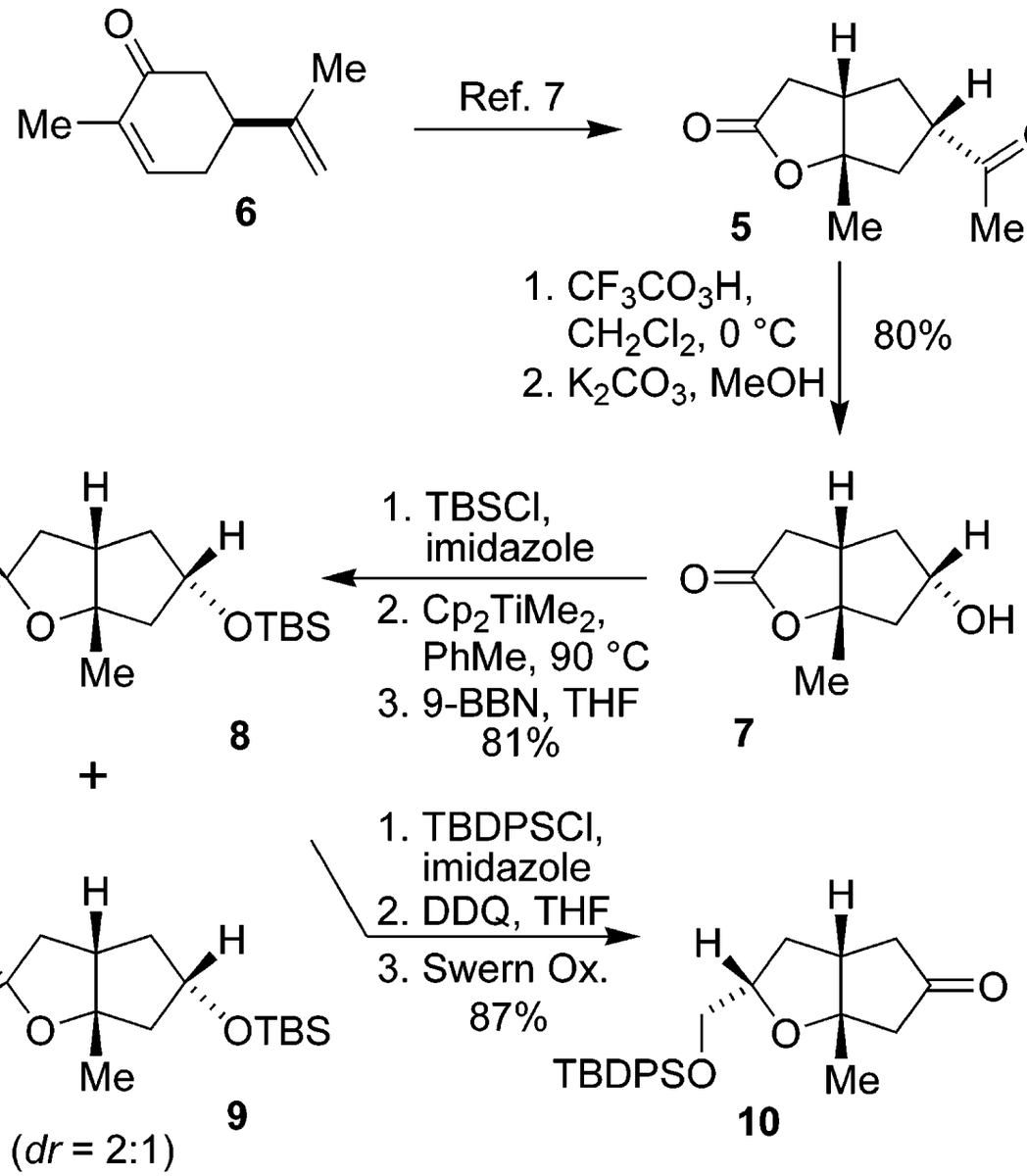
Scheme 3. Synthesis of Nicolaou's key intermediate (**2**). Reagents and conditions: a) MeMgI, THF, −78 °C, 4 h (71% brsm); b) NBS, $(BzO)_2$, CCl_4, reflux, 90 min (75%); c) NaOMe, THF, 0 °C, 30 min (80%); d) cat. $[Ir(cod)Py(PCy_3)]PF_6$, H_2 (1 bar), CH_2Cl_2, over night, (78% brsm), **12**/**11** = 1.3:1; alternatively: Pd/C (5%), KOH, EtOH, H_2 (1 bar), 3 h (90%), **12**/**11** = 1:2; e) HIO_3·DMSO, DMSO, cyclohexene, 50 °C, 8 h (60%). brsm = based on recovered starting material, NBS = *N*-bromosuccinimide, Bz = benzoyl, cod = cyclooctadiene, Py = pyridine, Cy = cyclohexyl, DMSO = dimethyl sulfoxide.

formal, racemic,

protecting-group-free

ACIE **2007**, 8074

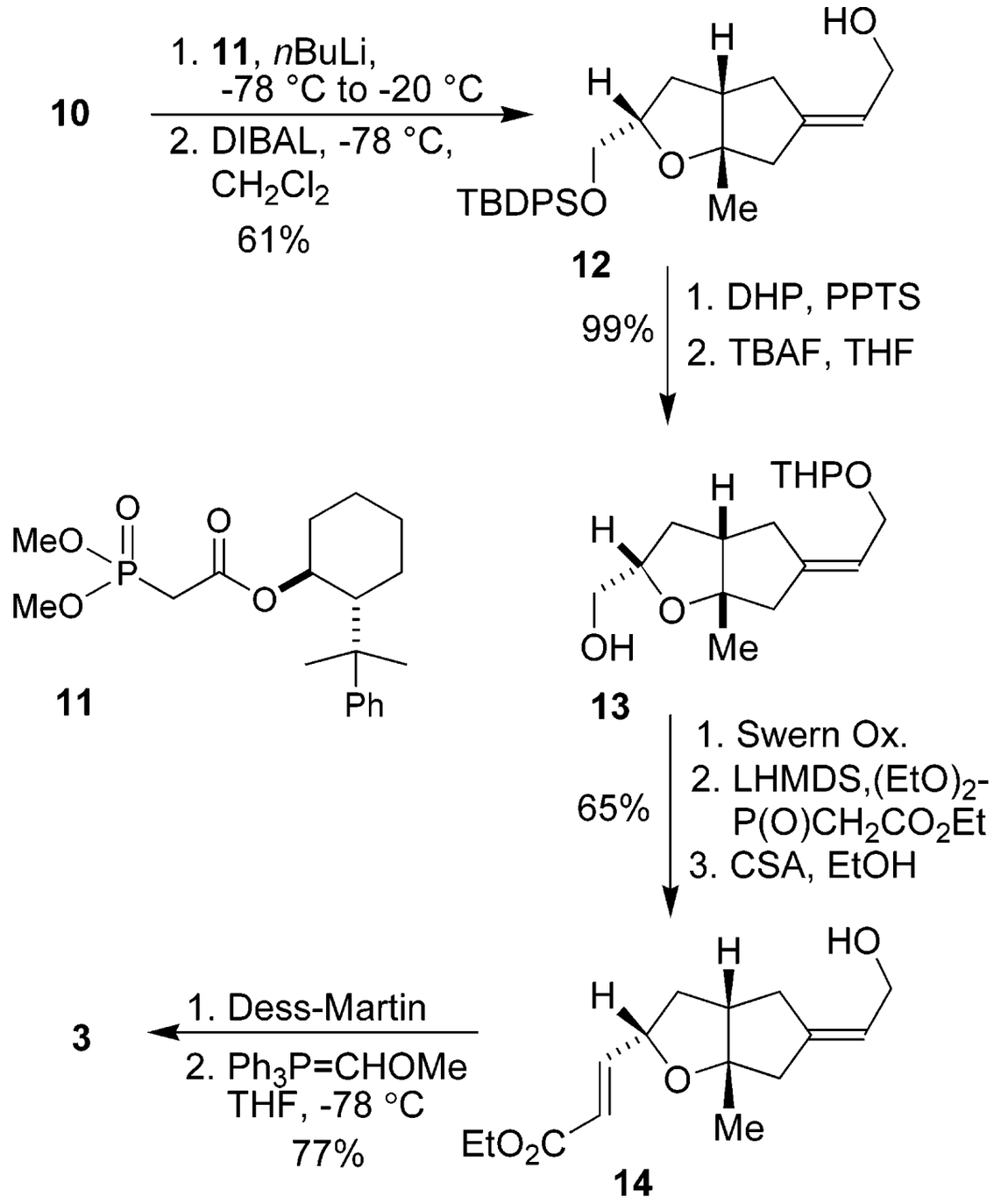
2007, July : Ghosh



formal, enantioselective

Org. Lett. **2007**, 4013

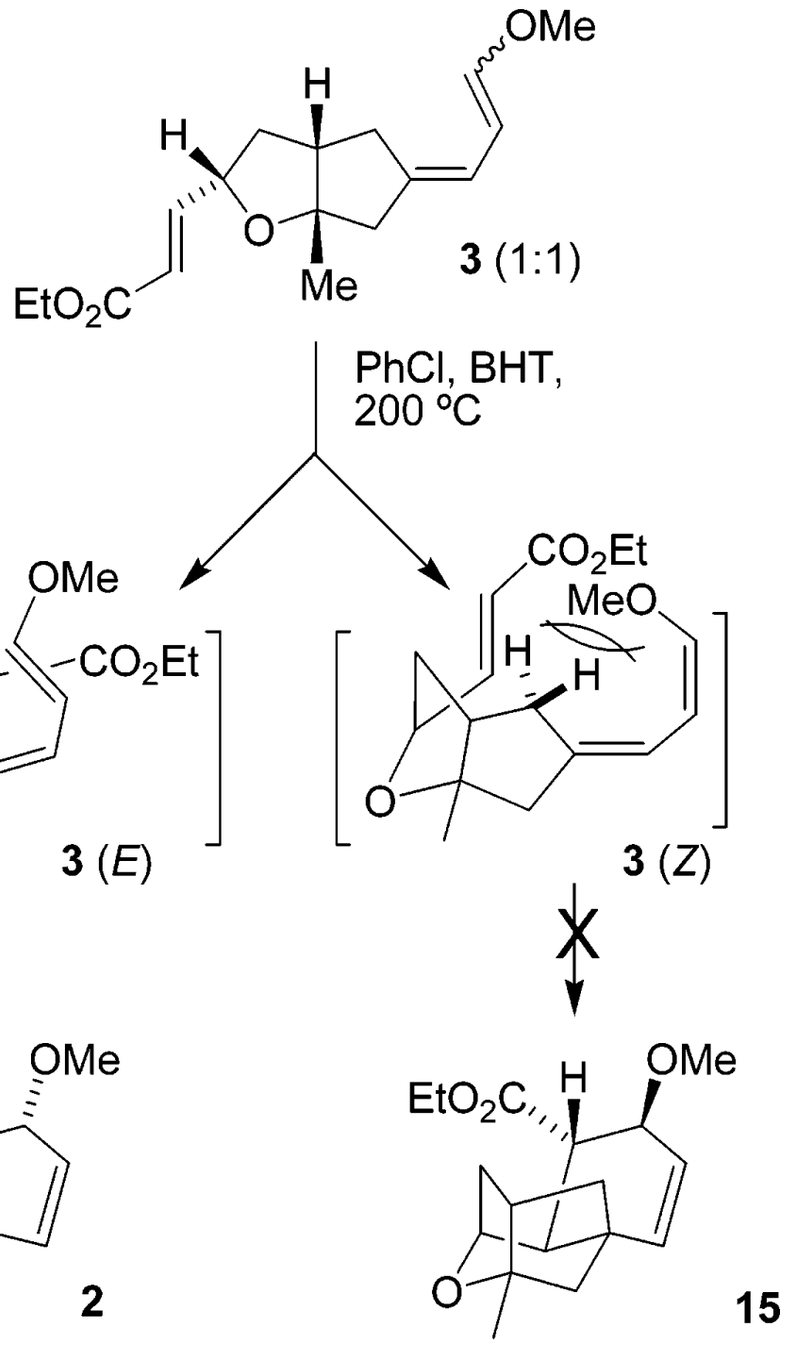
2007, July : Ghosh



formal, enantioselective

Org. Lett. **2007**, 4013

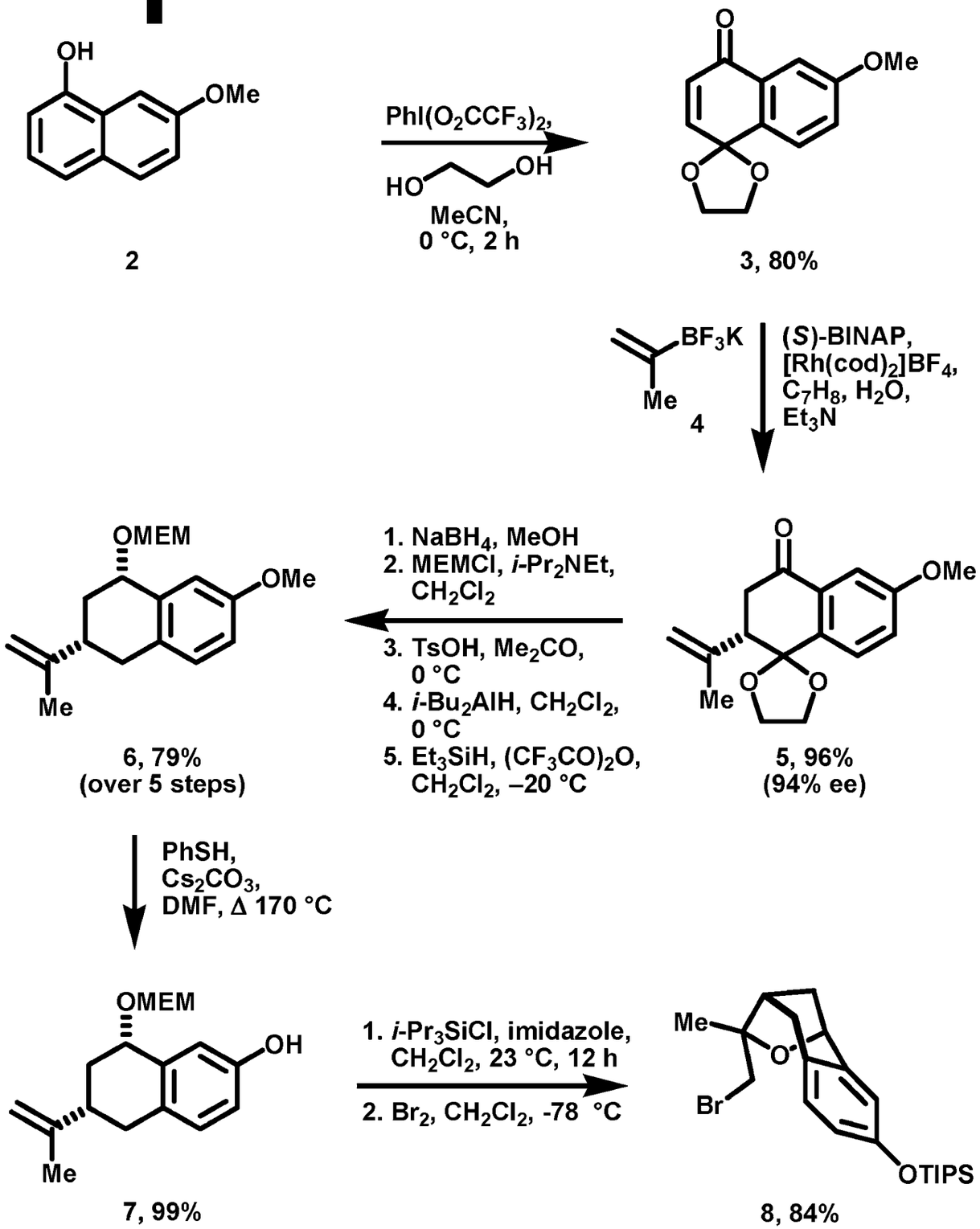
2007, July : Ghosh



formal, enantioselective

Org. Lett. **2007**, 4013

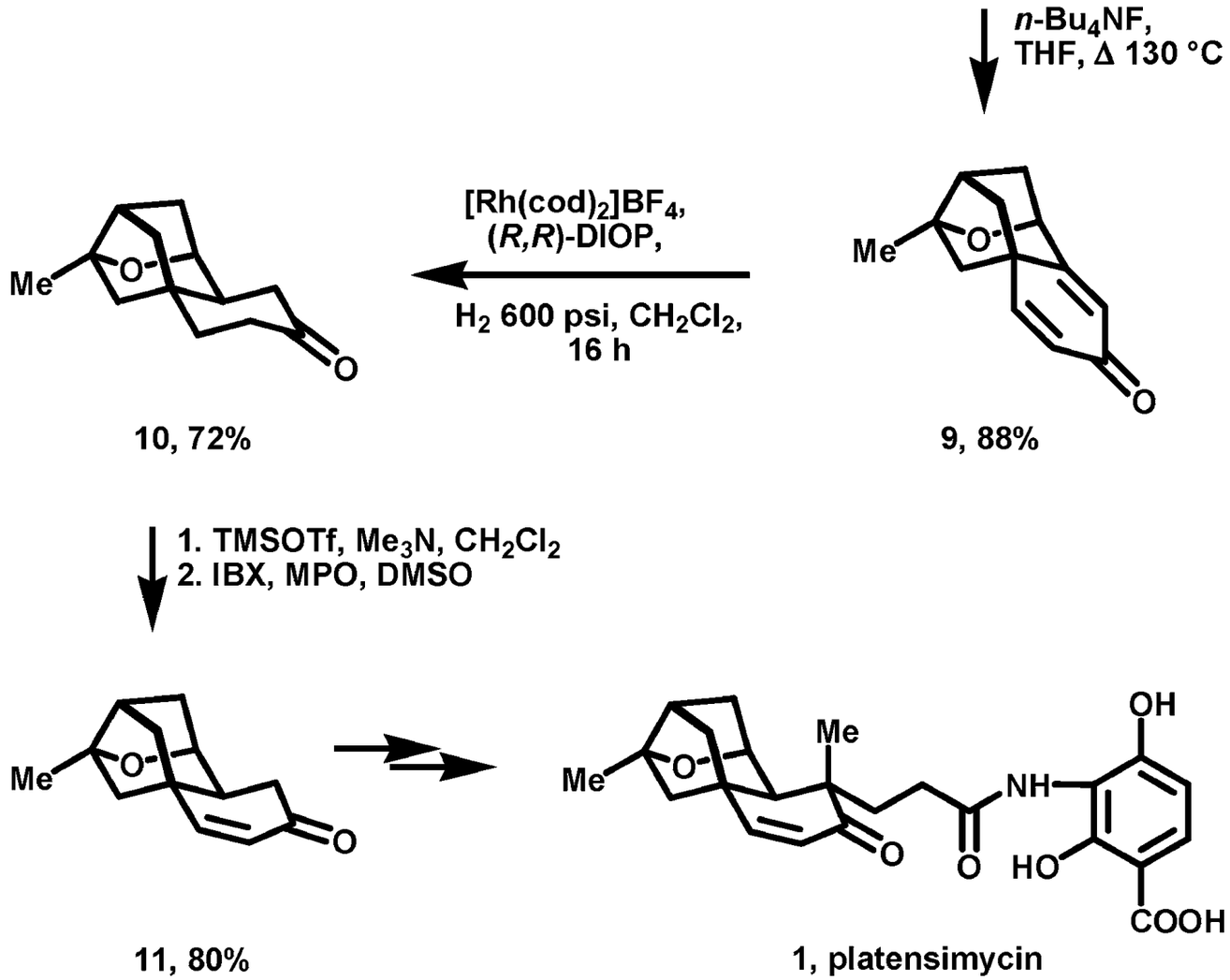
2007, September : Corey



formal, enantioselective

Org. Lett. **2007**, 4921

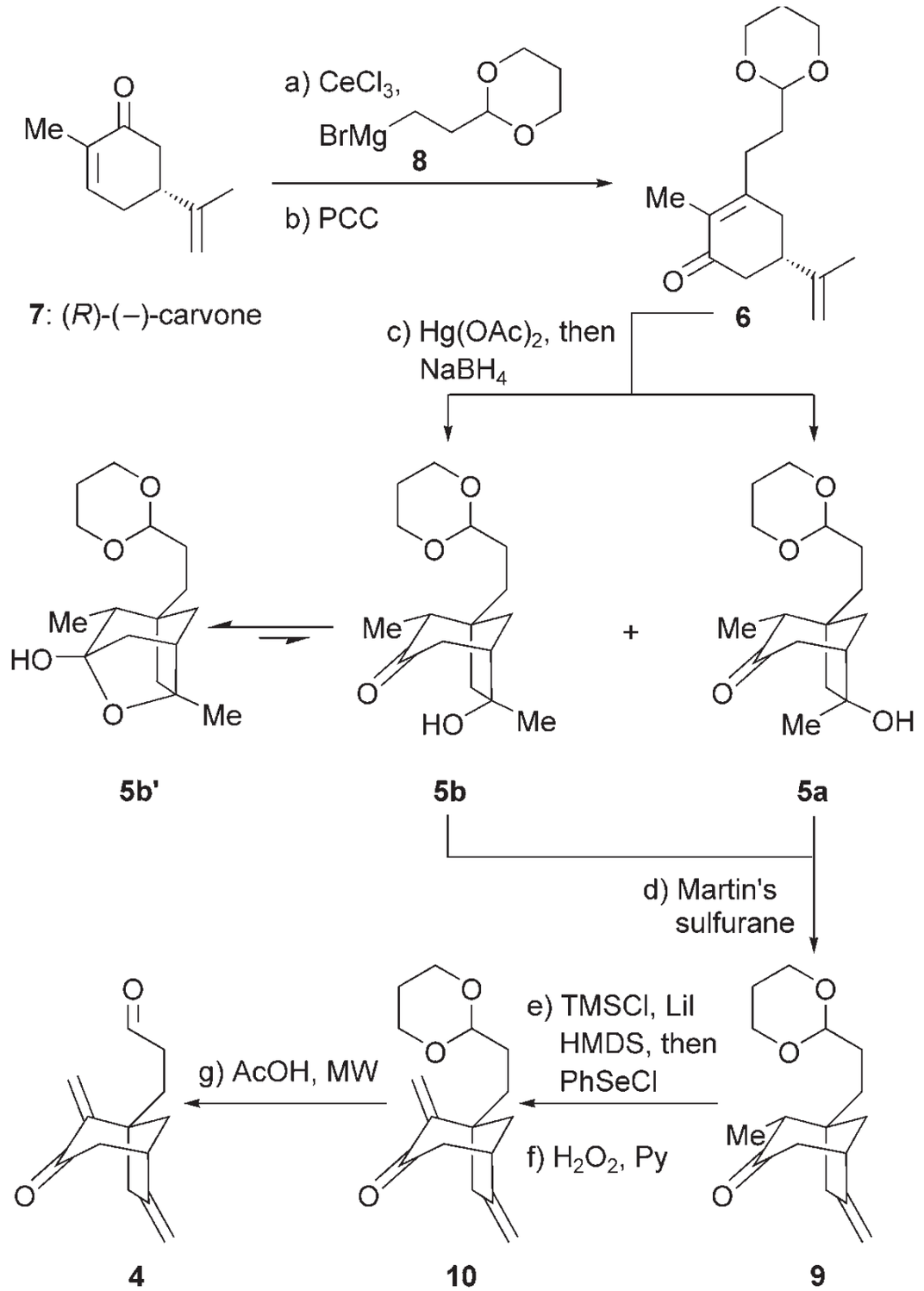
2007, September : Corey



formal, enantioselective

Org. Lett. **2007**, 4921

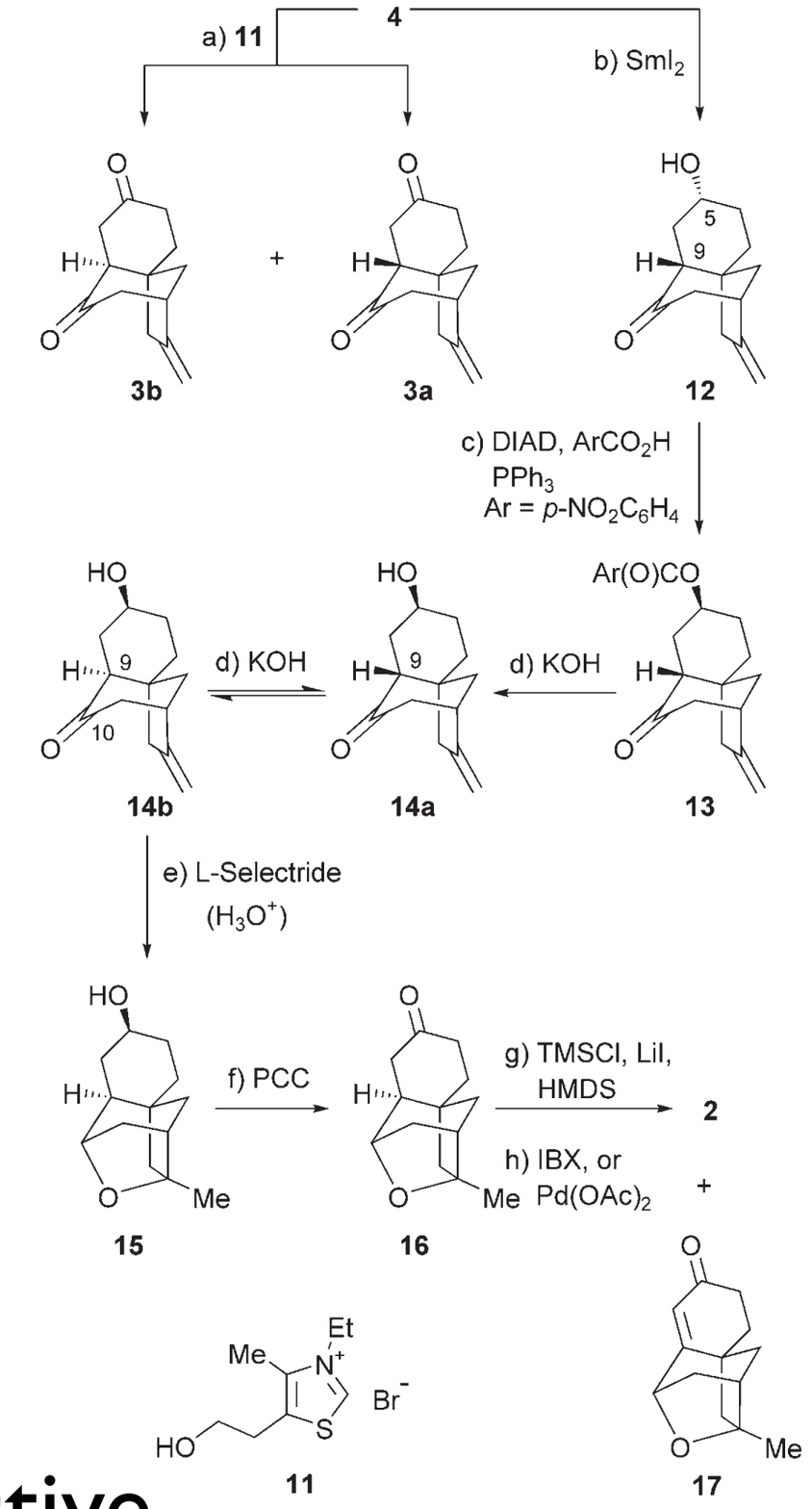
2007, November : Nicolaou



formal, enantioselective

ACIE **2008**, 944

2007, November : Nicolaou

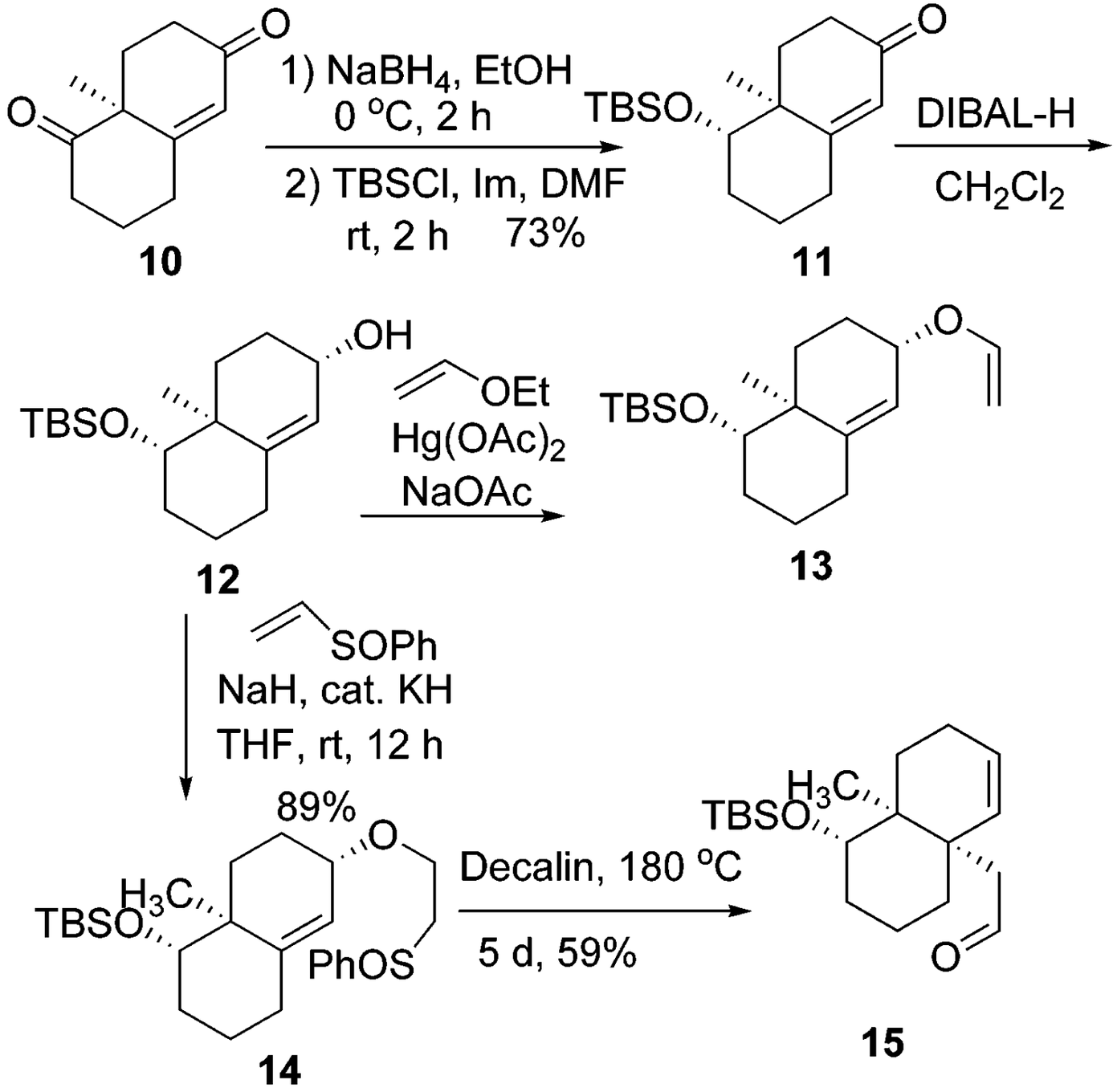


formal, enantioselective

ACIE **2008**, 944

Syntheses of Platensimycin Analogues

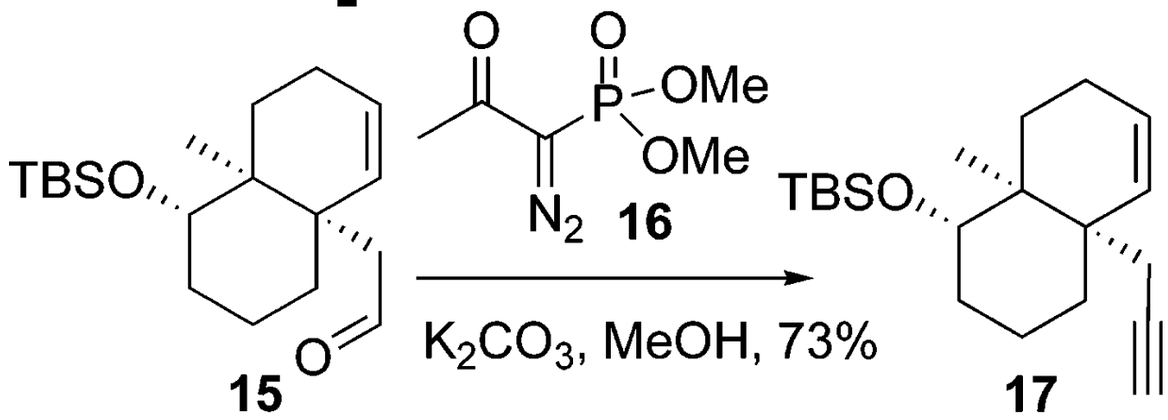
2007, April : Kaliappan

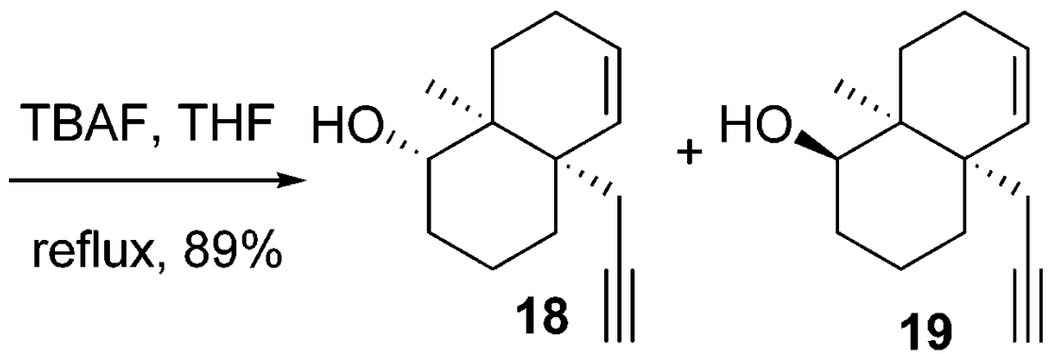


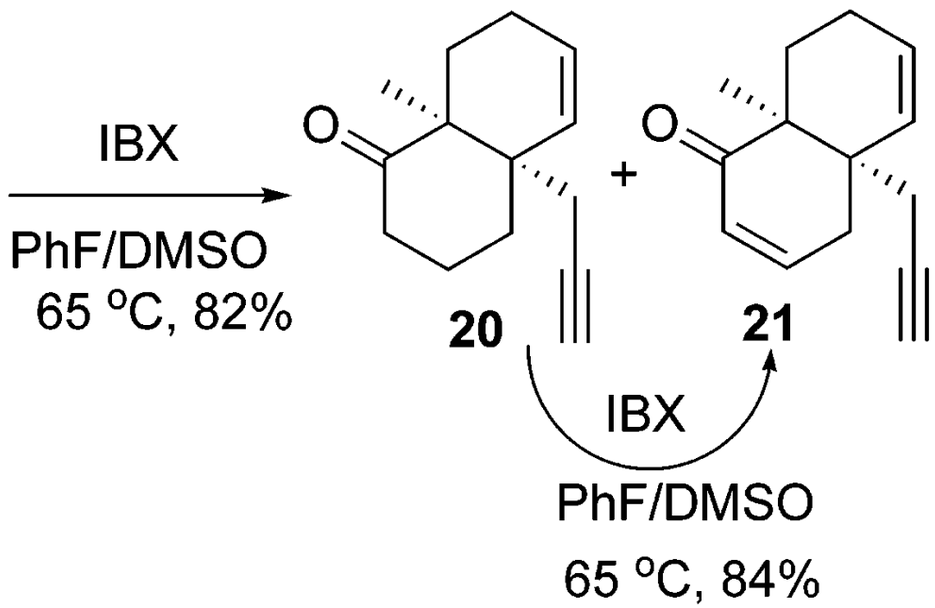
formal, enantioselective

Org. Lett. **2007**, 2417

2007, April : Kaliappan



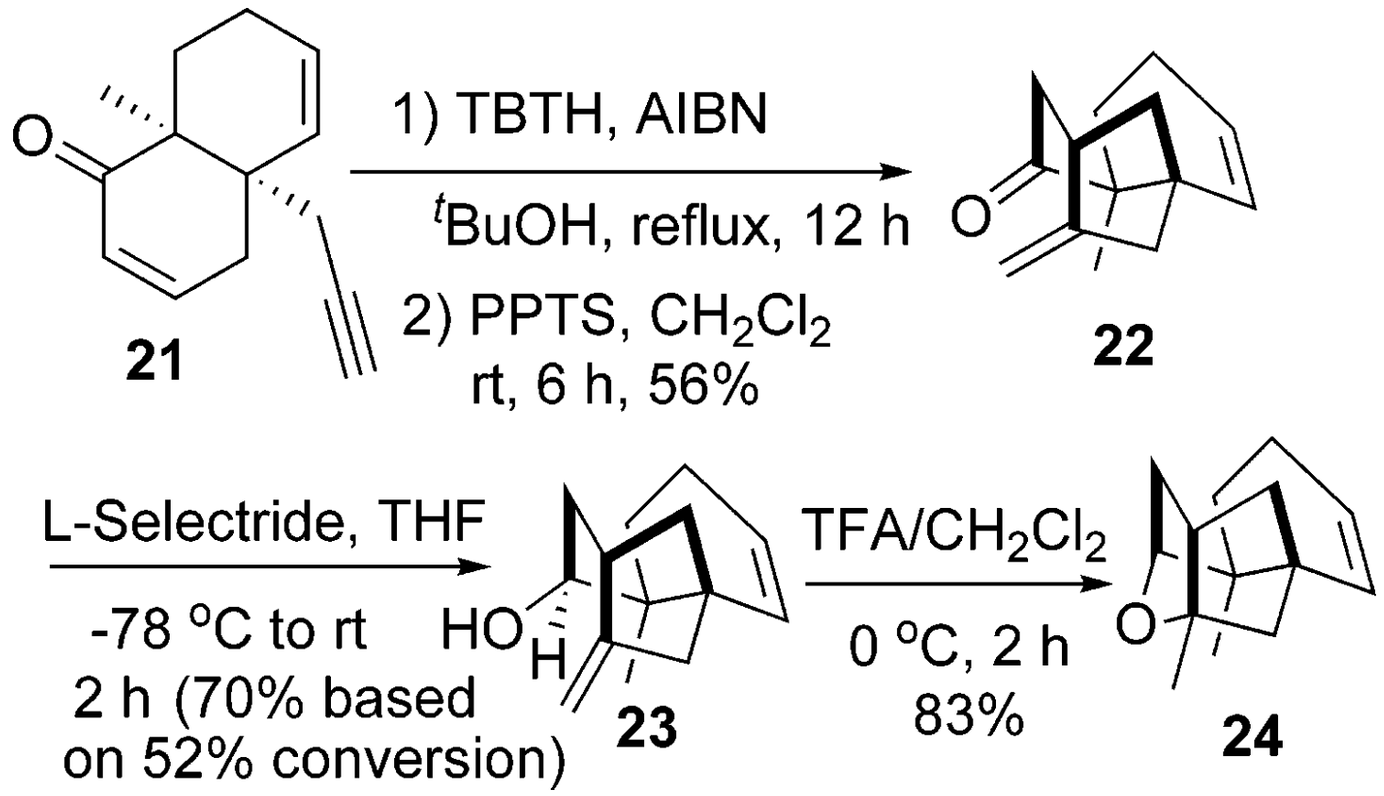




formal, enantioselective

Org. Lett. **2007**, 2417

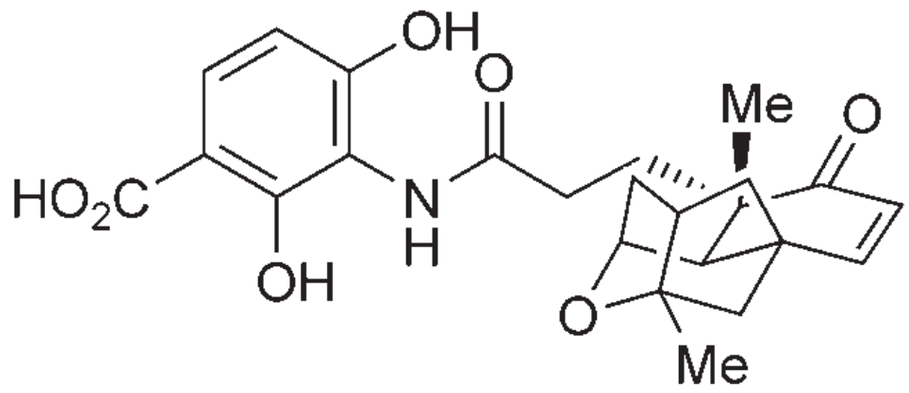
2007, April : Kaliappan



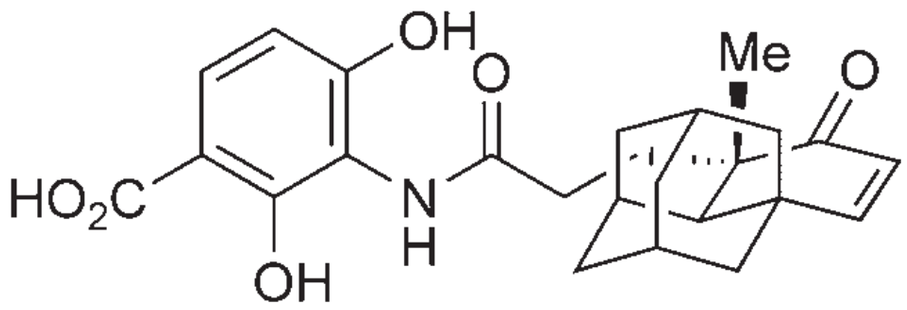
formal, enantioselective

Org. Lett. **2007**, 2417

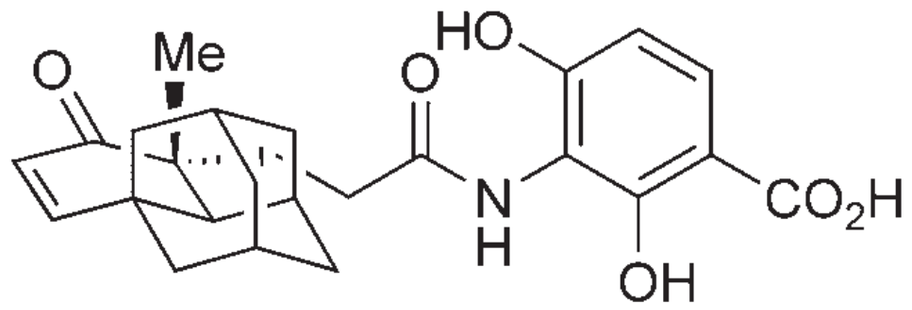
Adamentaplatensimycin



(–)-**1**: platensimycin



(–)-**2**



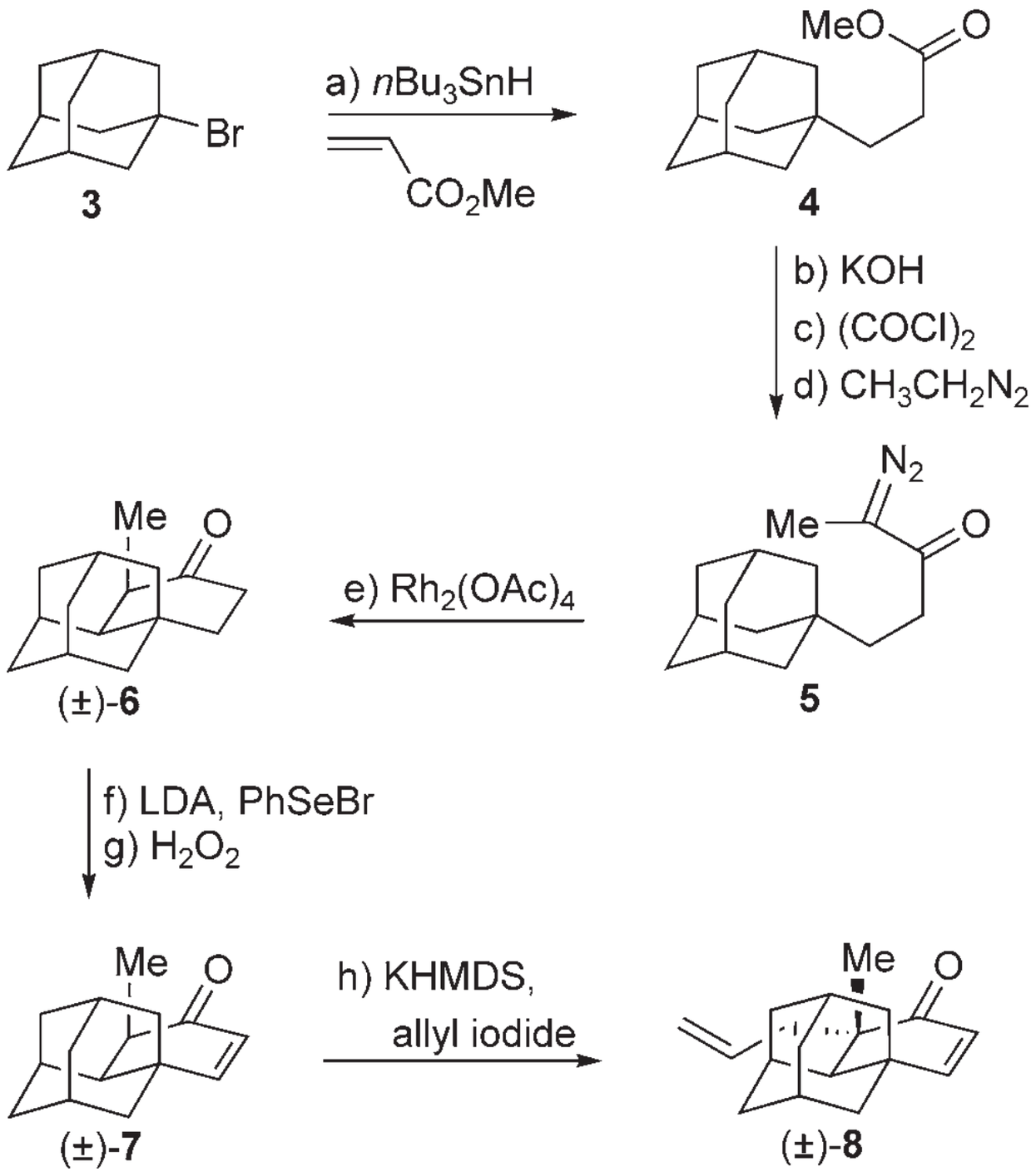
(+)-**2**

⇨ also bioactive !!!

2007, april

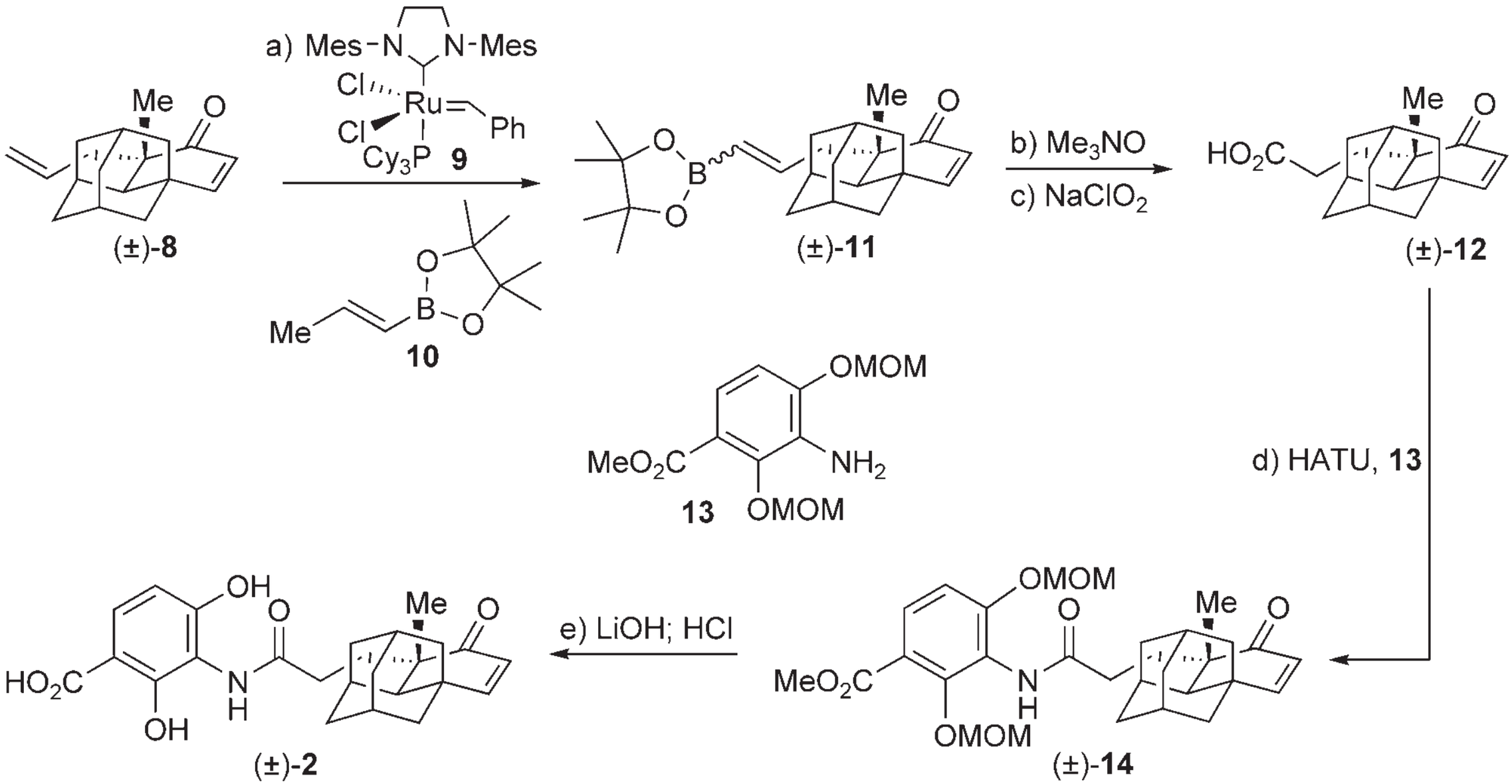
ACIE **2007**, 4712

Synthesis of Adamentaplatensimycin



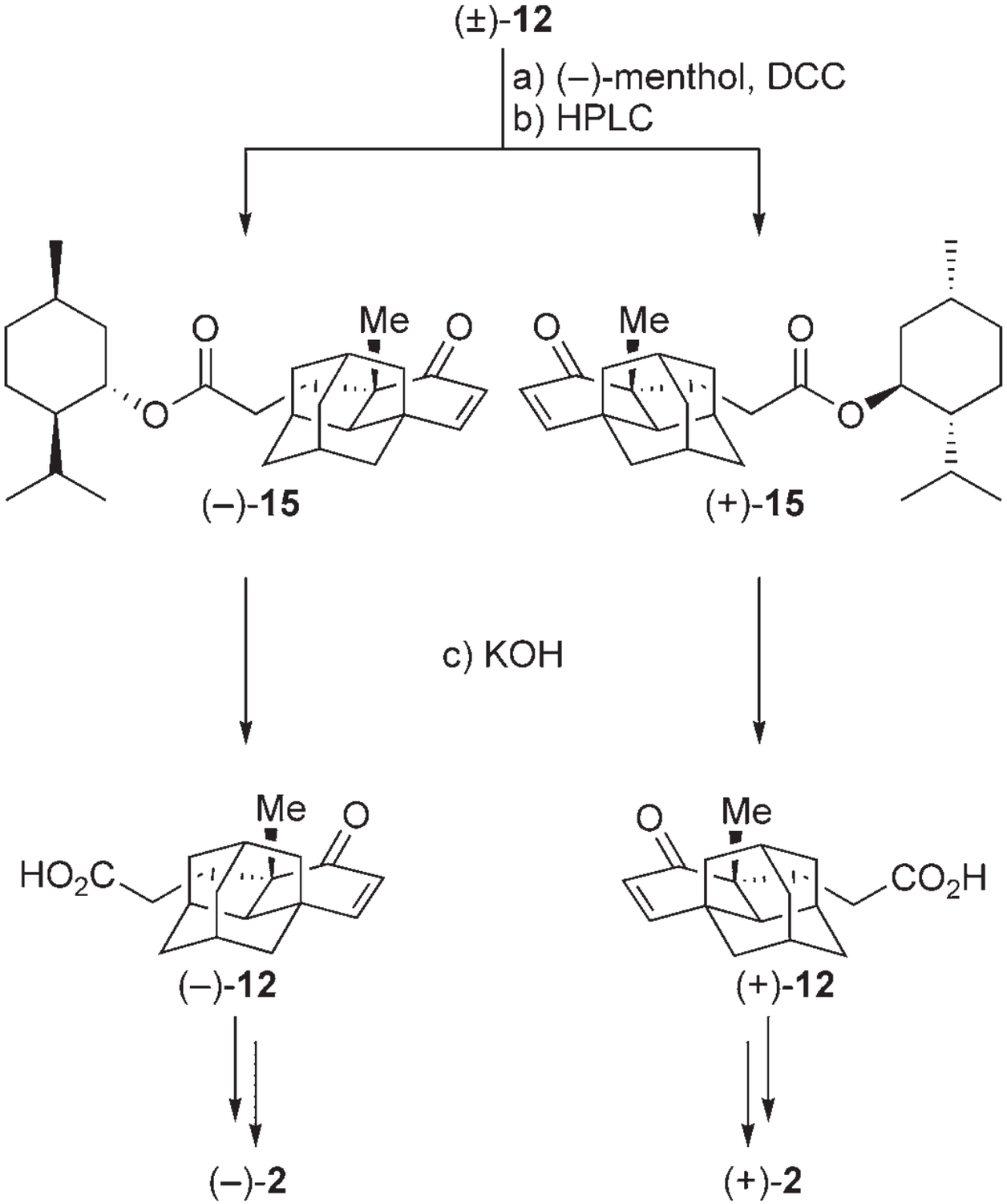
ACIE **2007**, 4712

Synthesis of Adamentaplatensimycin



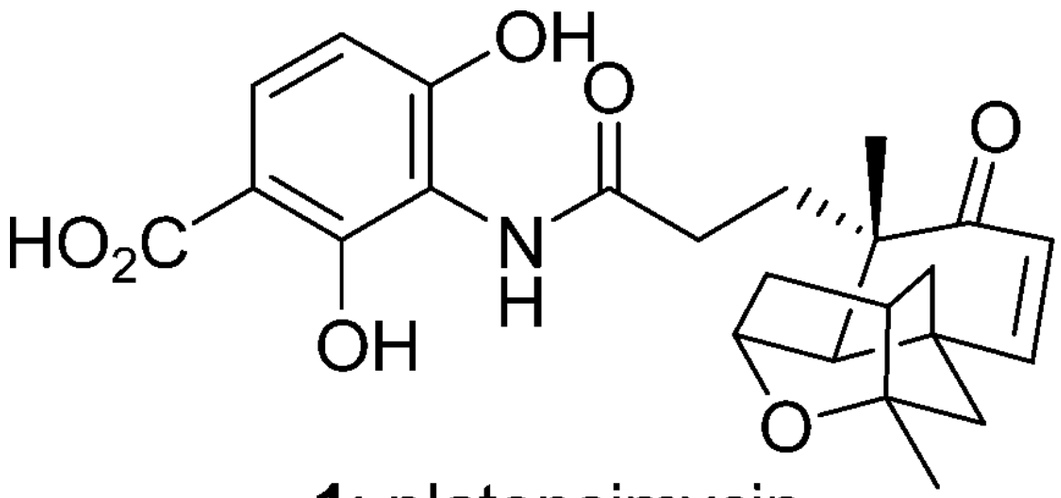
ACIE **2007**, 4712

Synthesis of Adamentaplatensimycin

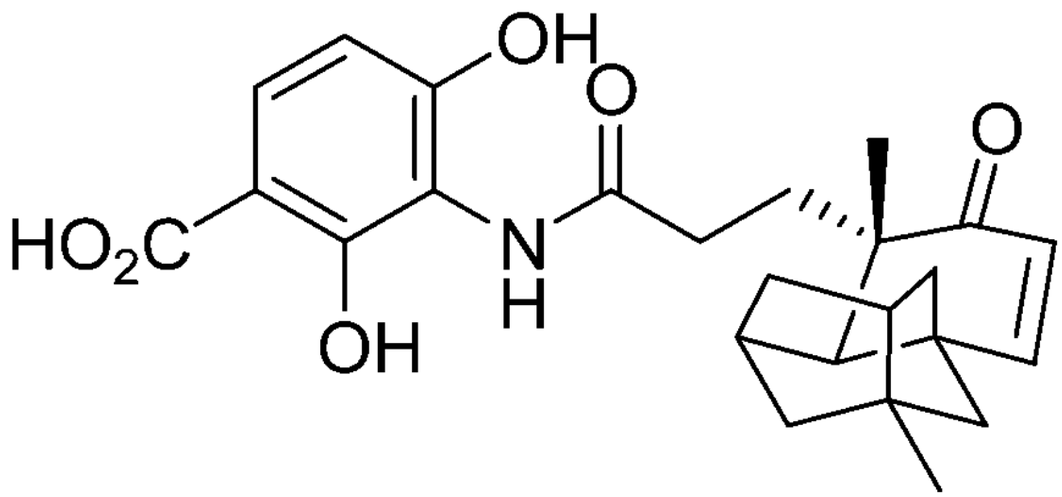


ACIE **2007**, 4712

Carbaplatensimycin



1: platensimycin

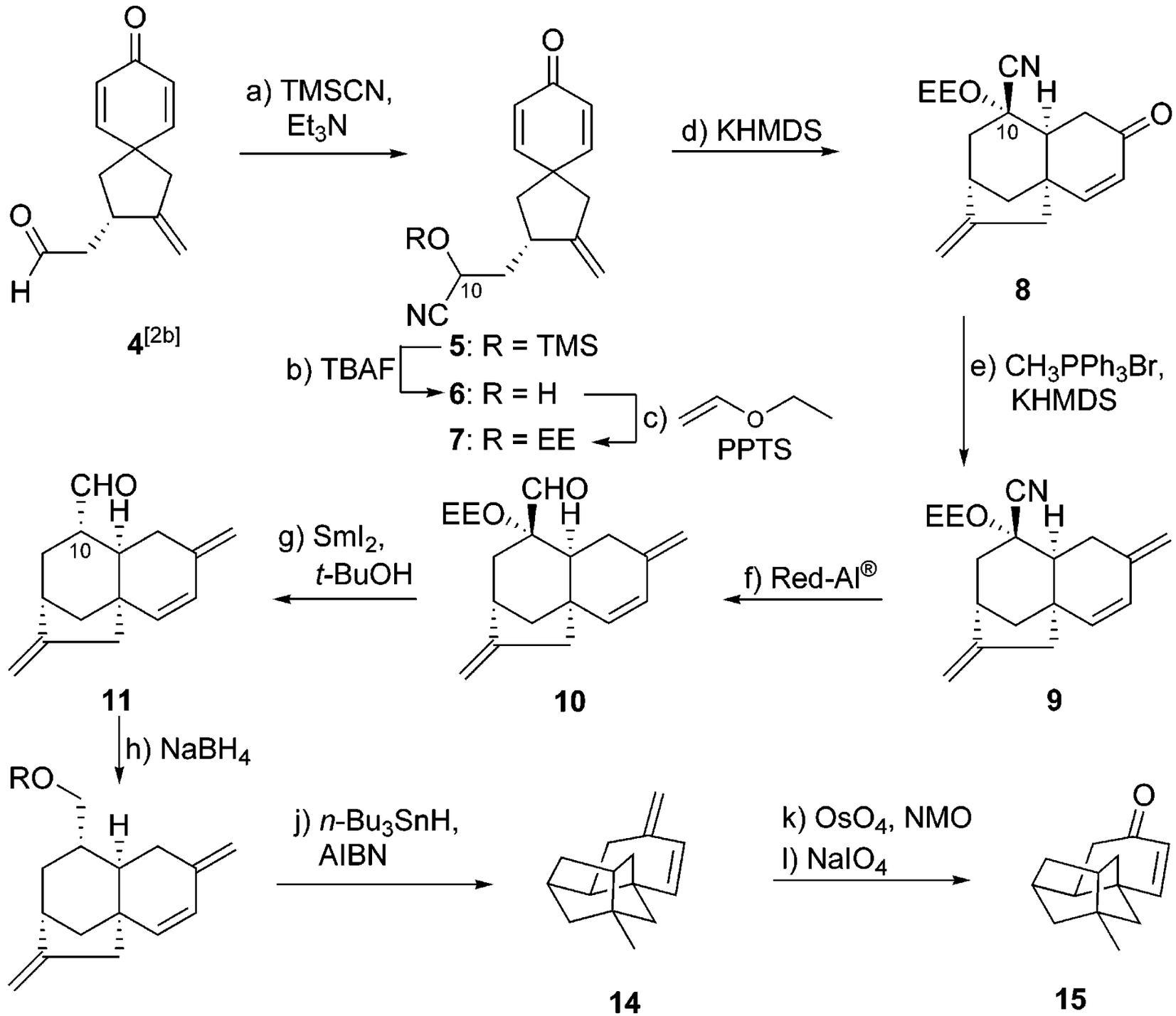


3: carbaplatensimycin

⇨ also bioactive

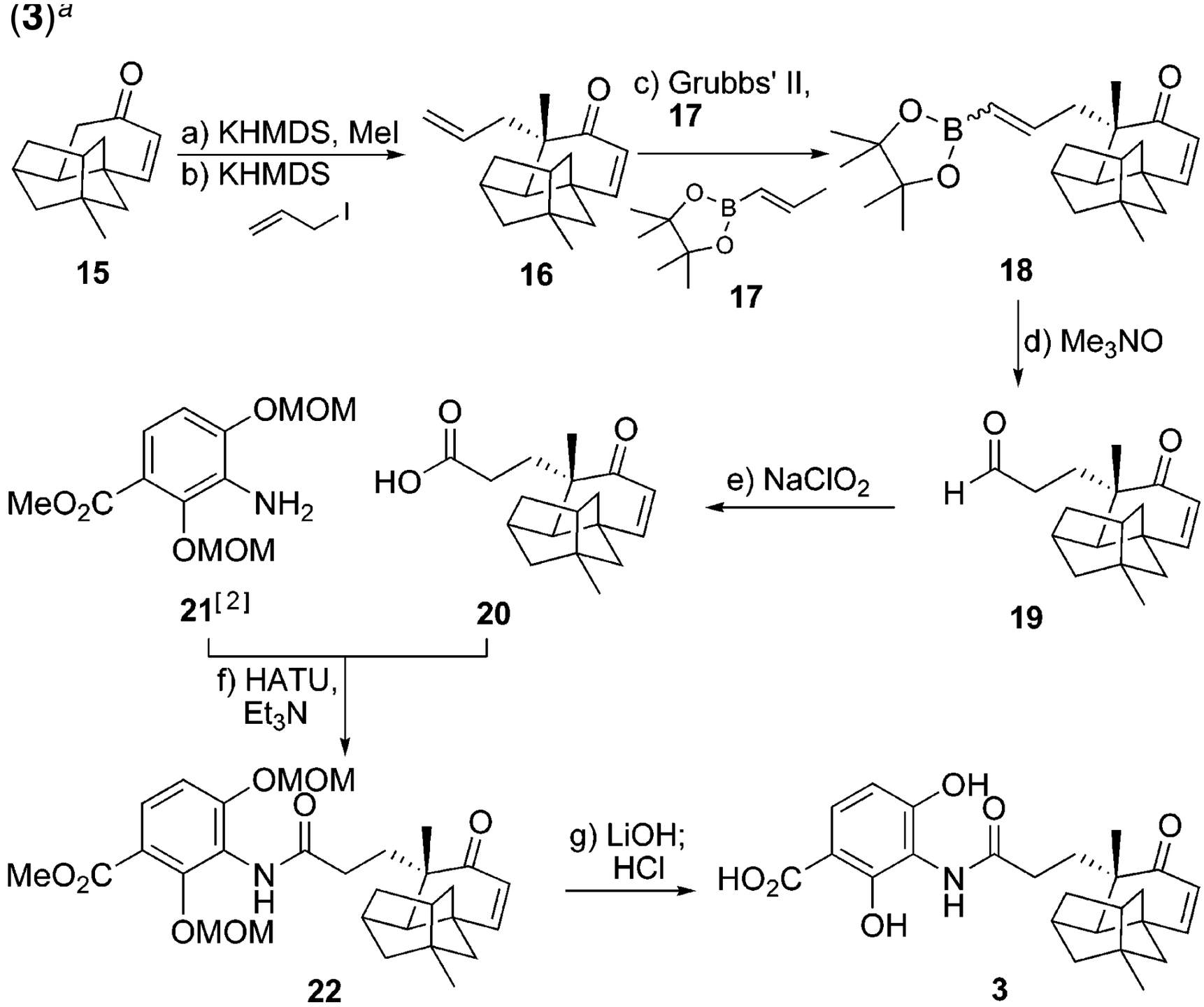
2007, August
JACS **2007**, 14850

Synthesis of Carbaplatensimycin



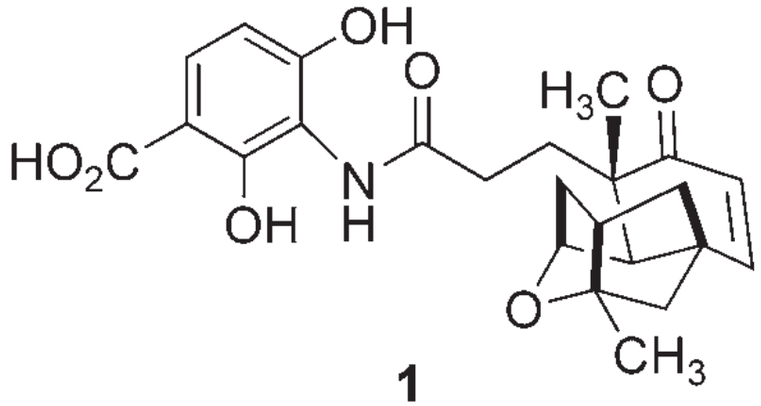
JACS **2007**, 14850

Synthesis of Carbaplatensimycin

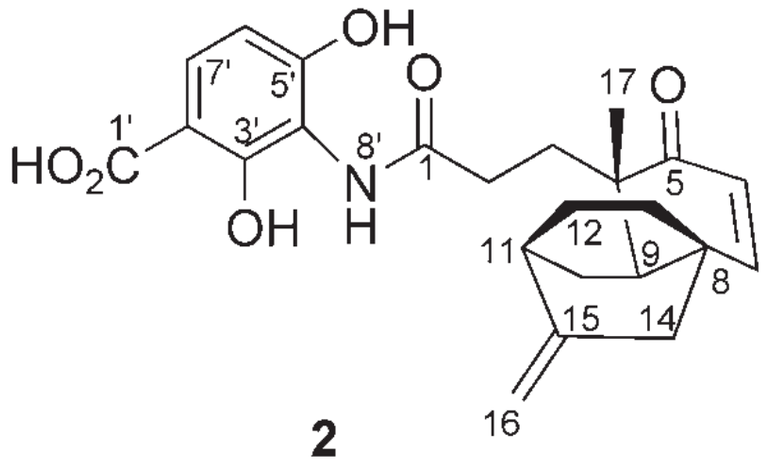


JACS **2007**, 14850

Platensin



1

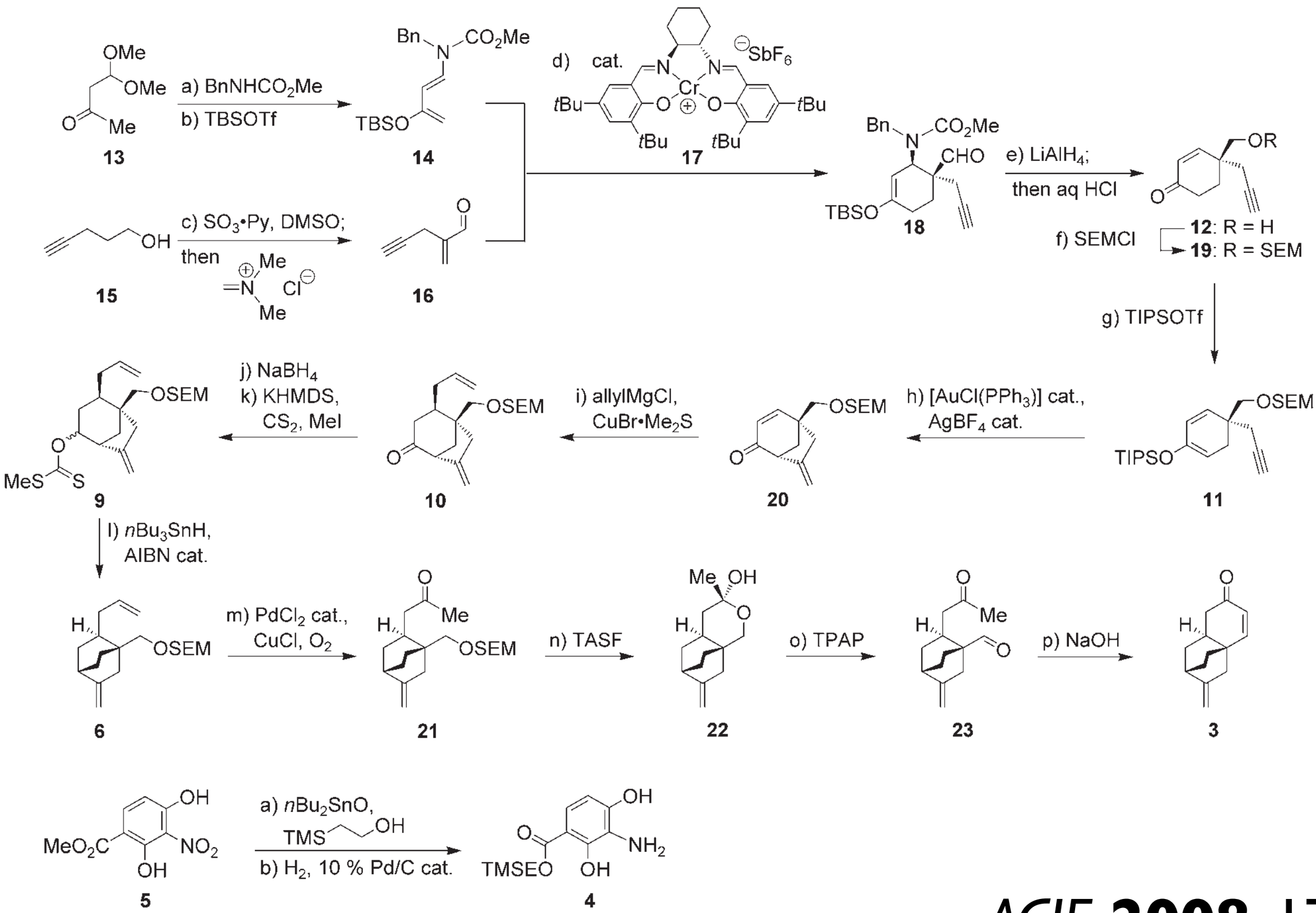


2

Isolated from another strain of *Streptomyces platensis*, by Merck (*ACIE* **2007**, 4684, sent in 2007, March)

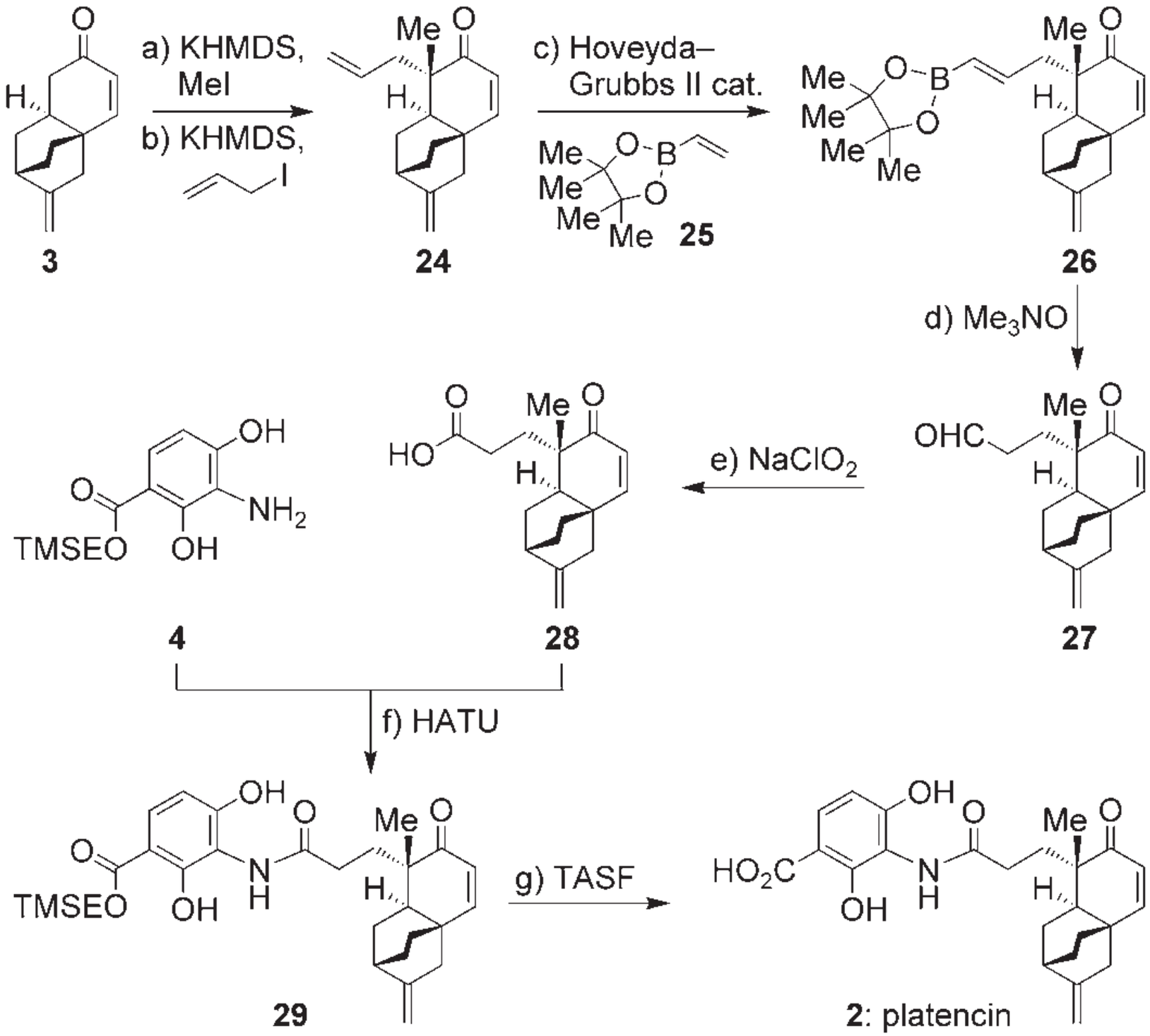
Less active, but less cytotoxic

Synthesis of platensin by Nicolaou



ACIE **2008**, 1780

Synthesis of platensin by Nicolaou



ACIE **2008**, 1780

Conclusion

- Novel unique antibiotic (architecture, mode of action, biological profile)
- Different ways for synthesizing the complex core structure
- Analogs show also biological activity

⇨ new lead compound of a valuable new class of antibiotics.