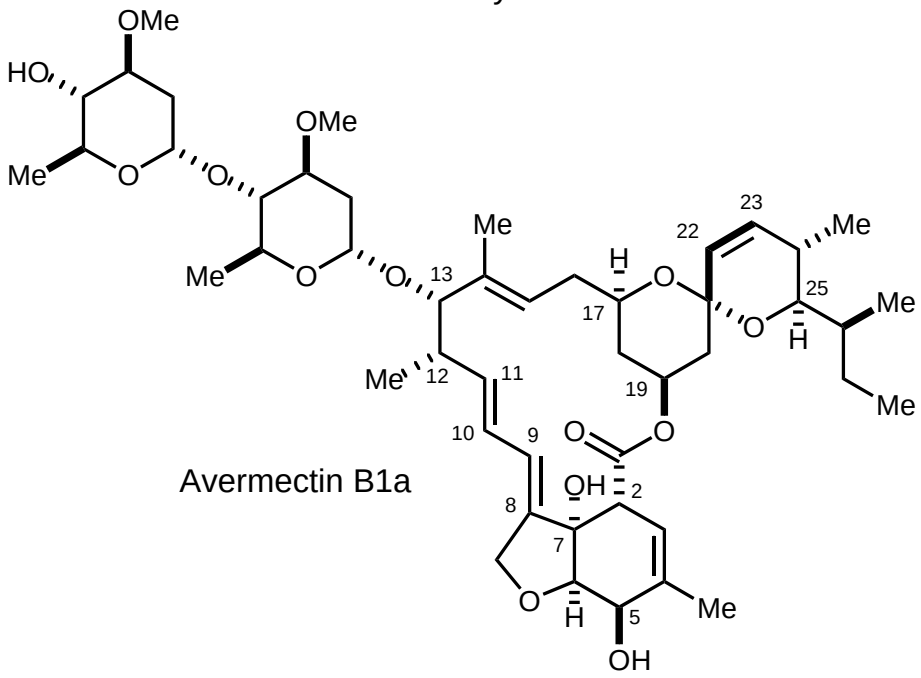
Approaches to the Total Synthesis of the Avermectins

December 8, 2000

Brian Raymer



Avermectin B1a

Structure Determination: Albers-Schonberg; *JACS* **1981**, *103*, 4216

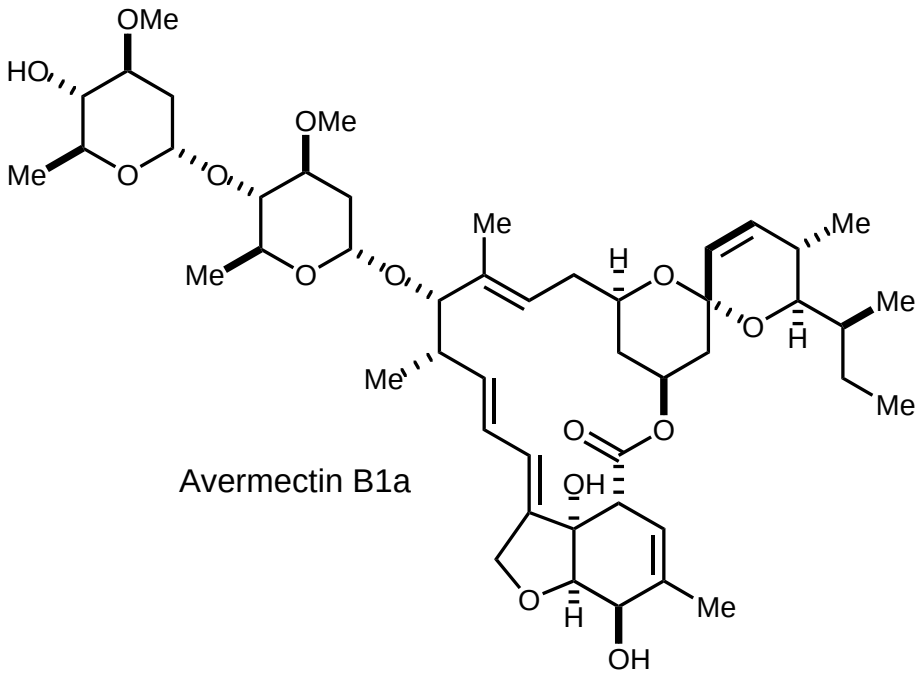
Absolute Configuration: Albers-Schonberg; *JACS* **1981**, *103*, 4221

Lead Reviews: Davies, Green; *NPR* **1986**, *13*, 87-121
Chem Soc. Rev. **1991**, *20*, 211-269
Chem Soc. Rev. **1991**, *20*, 271-339

Oxahydrindene Subunit Synthesis: Peak, Smith; Studies in Nat. Prod. Chem. **1993**, *12*, 3-31

Biosynthesis: Omura, Ikeda; *Chem. Rev.* **1997**, *97*, 2591

Avermectin B1a

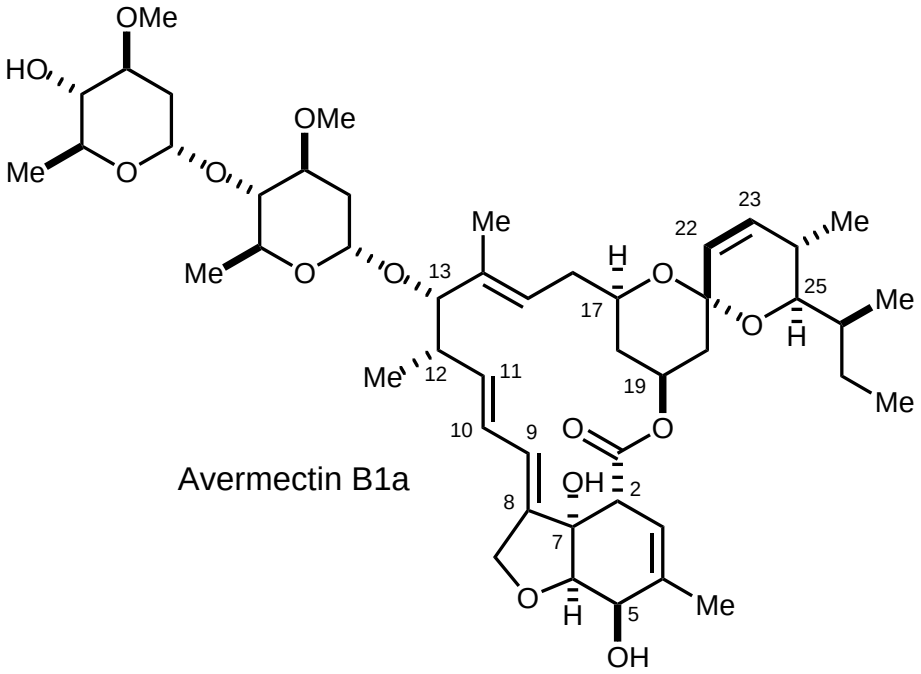


Avermectin B1a

- Discovered in soil sample from Japanese Golf Course (Kawana, Ito City; 1975)
- First therapeutic target: gastrointestinal worms in horses (Dr. W. Cambell, Merck)
- Broad spectrum anthelminic (worms), microfilaricide (heartworms), and miticide (mites) used for horses, cattle, pigs, household pets
- Commercial Avermectin Derivatives: Ivermectin (Merck), Dormectin (Pfizer)
- Ivermectin used in humans, especially for river blindness (onchocerciasis)
  Human dose: 9.1 mg/100 lbs., one injection

www.merck.com
topic: mectizan

Avermectin Structure

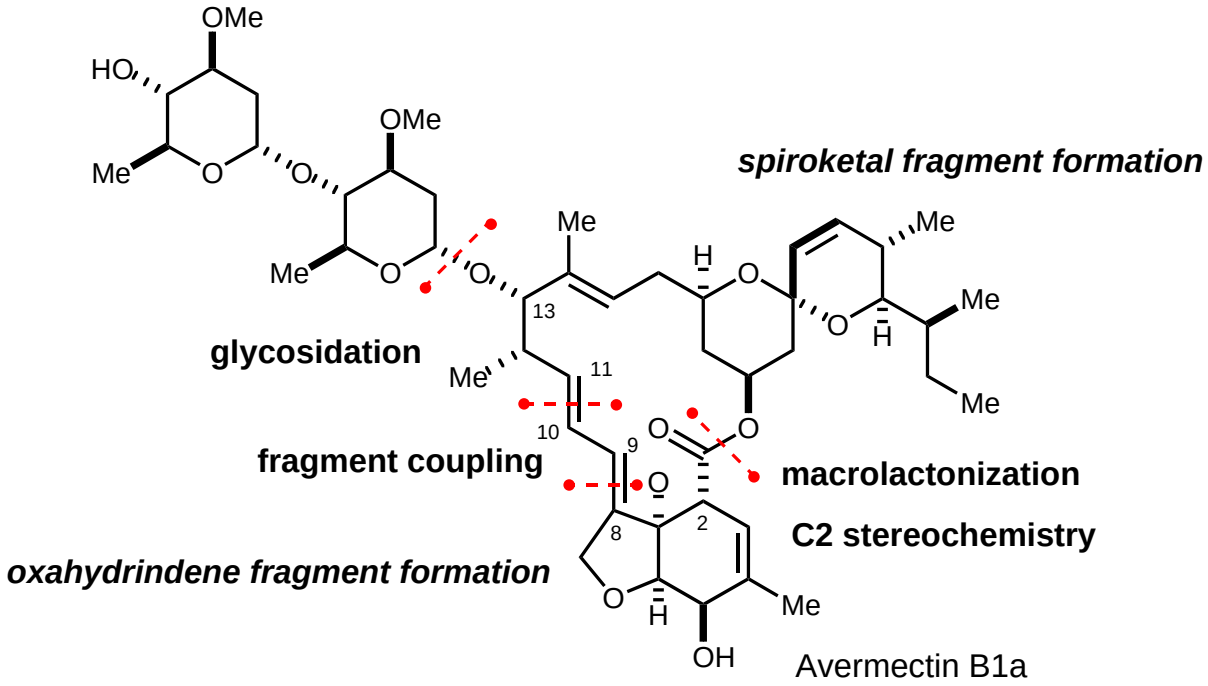


Avermectin B1a

- macrocycle
- oxahydrindene with stereogenic centers at 2, 5, 6, 7
- E, E diene from 8 to 11
- anti 12 and 13 stereocenters
- diglycoside (dioleandrose)
- trisubstituted alkene at 14 and 15
- thermodynamic spiroketal with stereogenic centers at 17, 19, (23), 24, 25
- alkyl substituent at 25

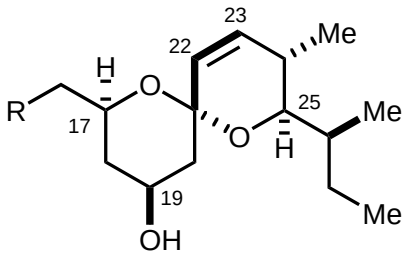
Contents

Major Synthetic Steps

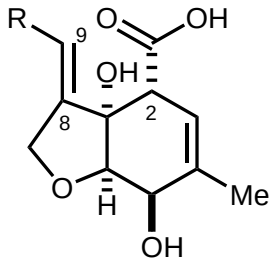


Order of Presentation

1. spiroketal fragment formation

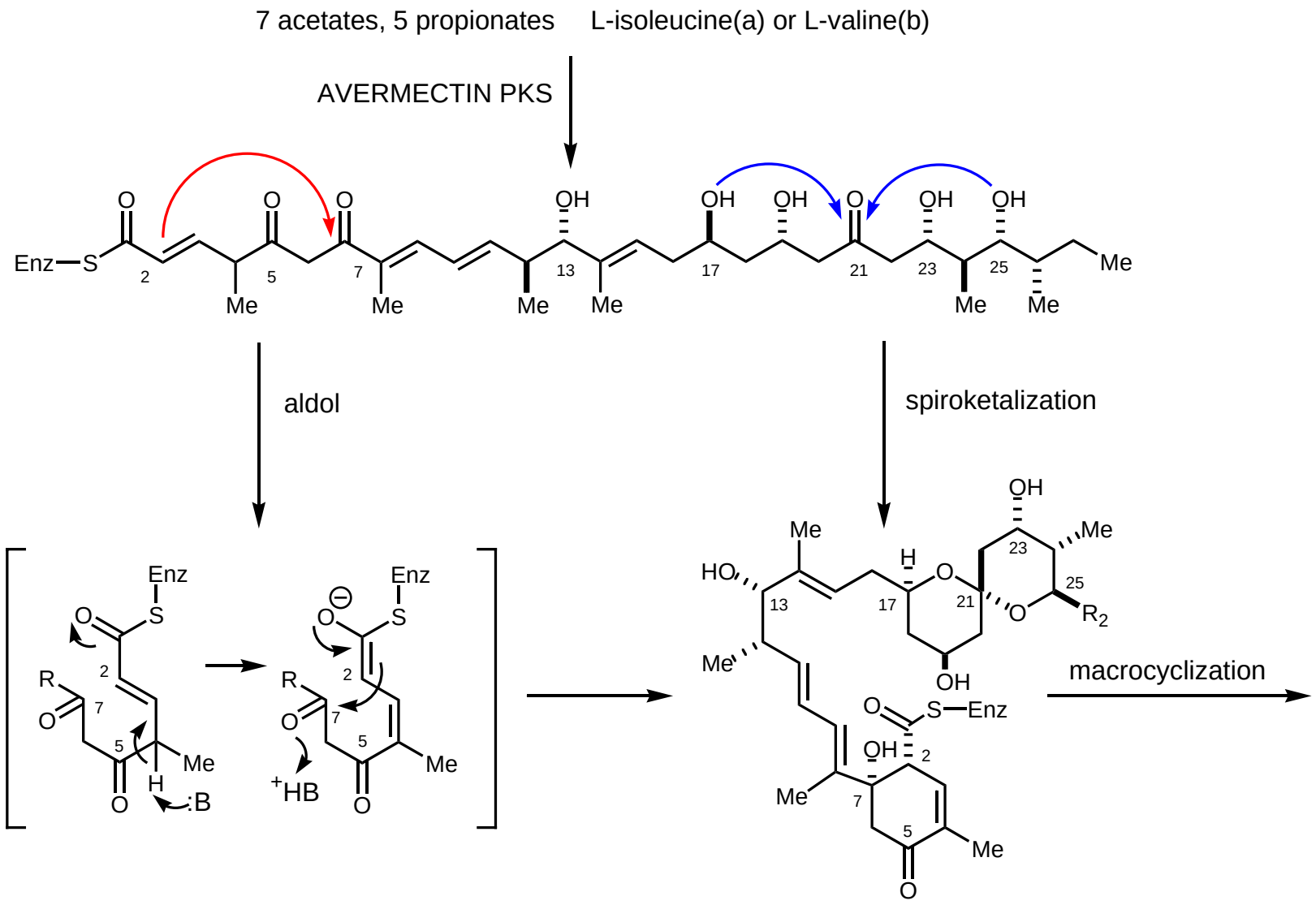


2. oxahydrindene fragment formation



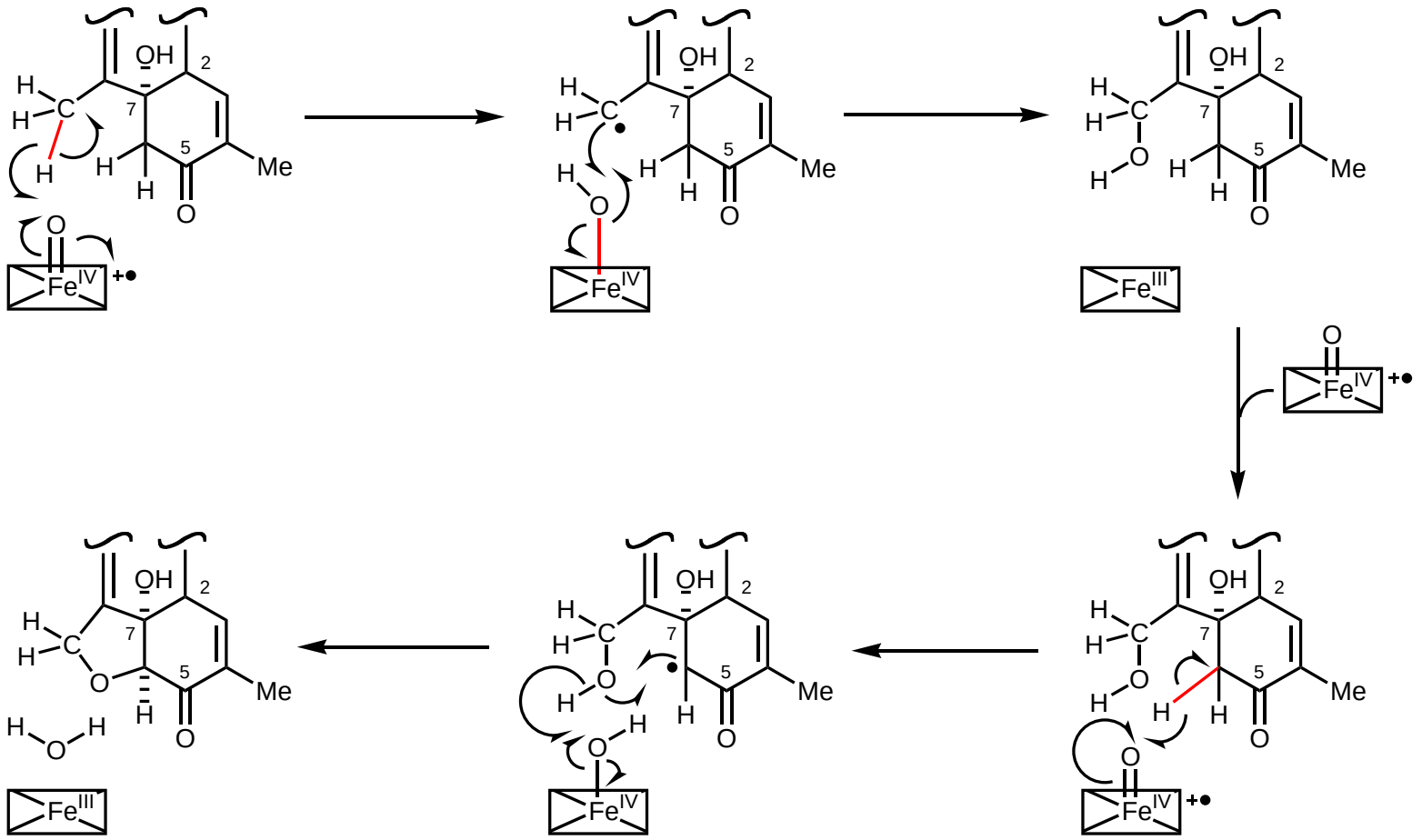
3. aglycone formation and glycosidation
   - fragment coupling
   - C_2 stereochemistry
   - macrolactonization
   - glycosidation
   - glycoside construction (appendix; Ley, Danishefsky)

Biosynthesis: Cyclohexenone and Spiroketal Formation



Chem Rev. **(1997)** 2591 - 2609

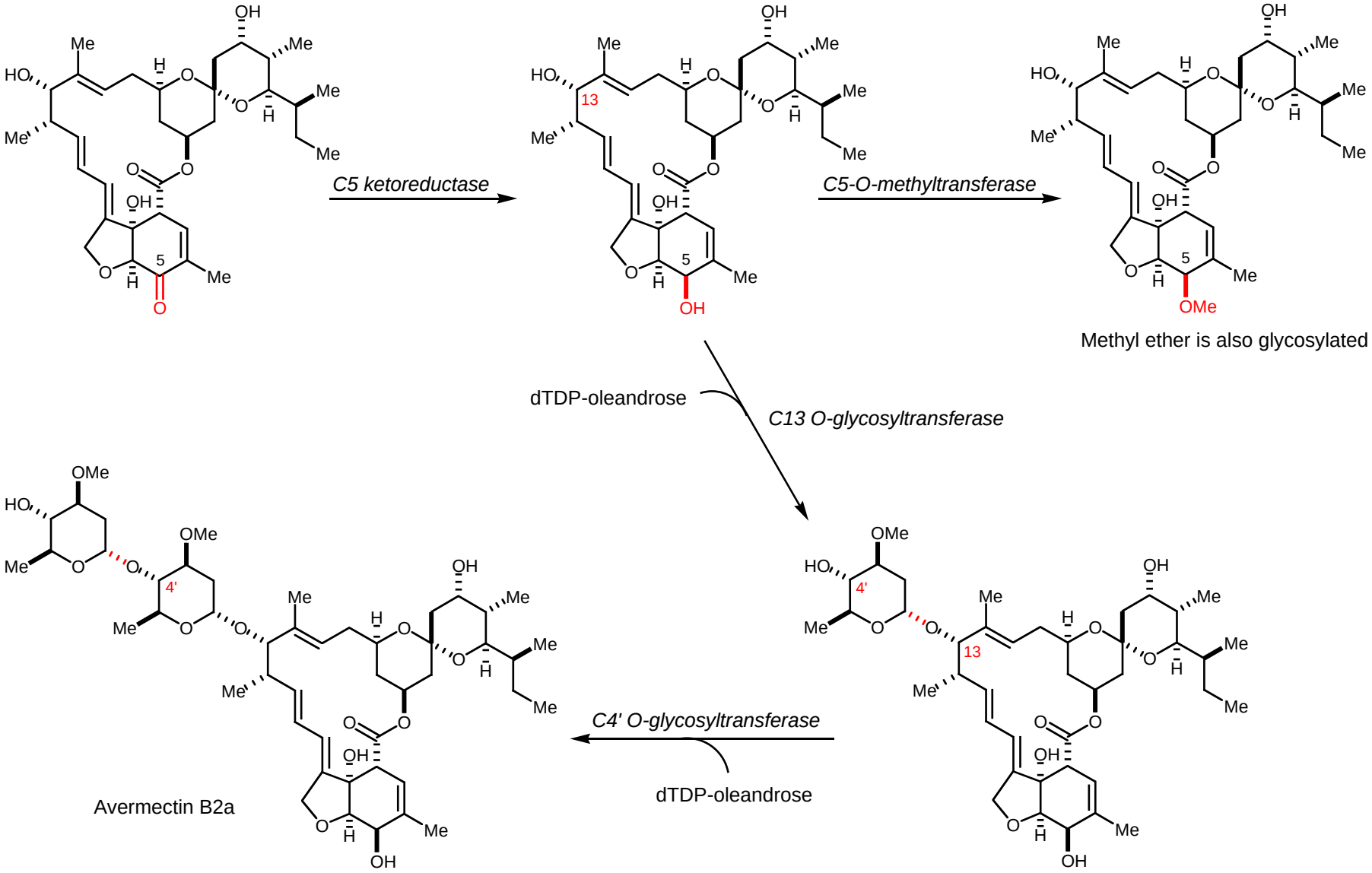
Biosynthesis: Oxahydrindene Formation



- oxygen derived from molecular oxygen
- amino acid sequence of protein resembles cytochrome P450

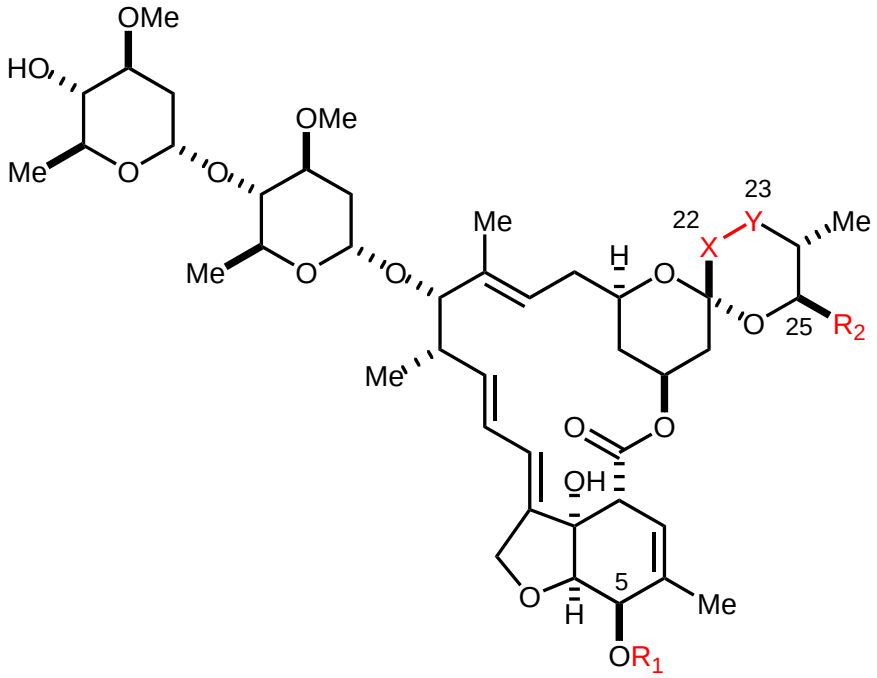
Chem Rev. **(1997)** 2591 - 2609

Biosynthesis: C_5 reduction and C_{13} Glycosidation



Chem Rev. **(1997)** 2591 - 2609

Avermectin Nomenclature



Avermectin		R1	R2	X–Y
(1)	A1a	Me	*s*-Bu	CH=CH
(2)	A1b	Me	*i*-Pr	CH=CH
(3)	A2a	Me	*s*-Bu	CH–CH(OH)
(4)	A2b	Me	*i*-Pr	CH–CH(OH)
(5)	B1a	H	*s*-Bu	CH=CH
(6)	B1b	H	*i*-Pr	CH=CH
(7)	B2a	H	*s*-Bu	CH–CH(OH)
(8)	B2b	H	*i*-Pr	CH–CH(OH)

Avermectin B1a

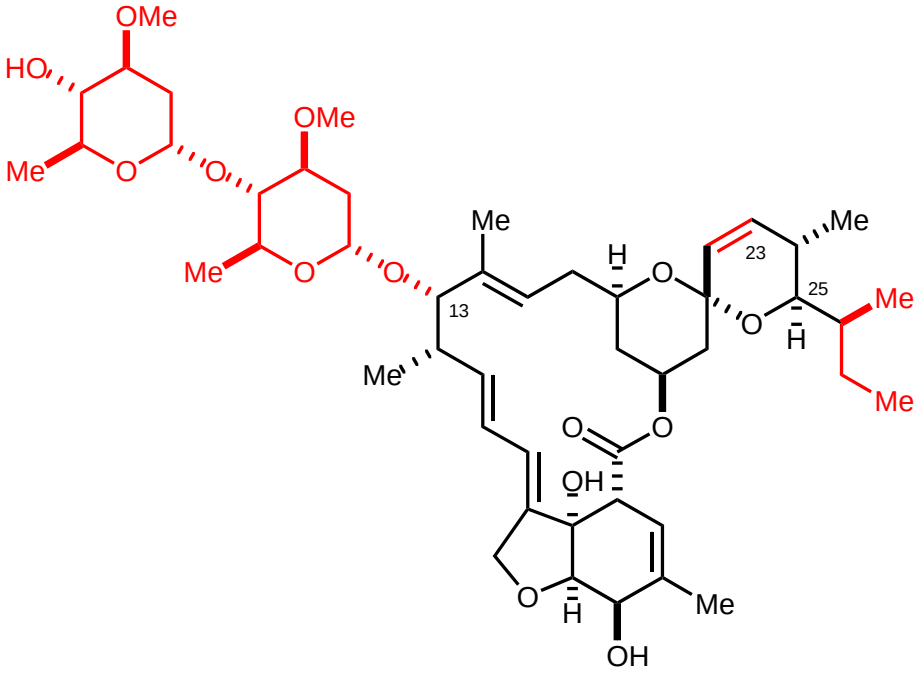
A: R_1 = Me ; **B**: R_1 = H

1: X-Y = CH=CH ; **2**: X-Y = CH–CH(OH)

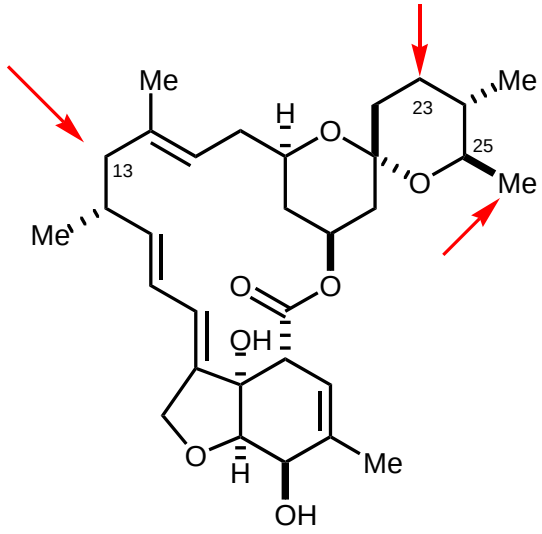
a: R2 = *s*-Bu ; **b**: R2 = *i*-Pr

- Hanessian, Ley, White: B1a
- Danishefsky: A1a

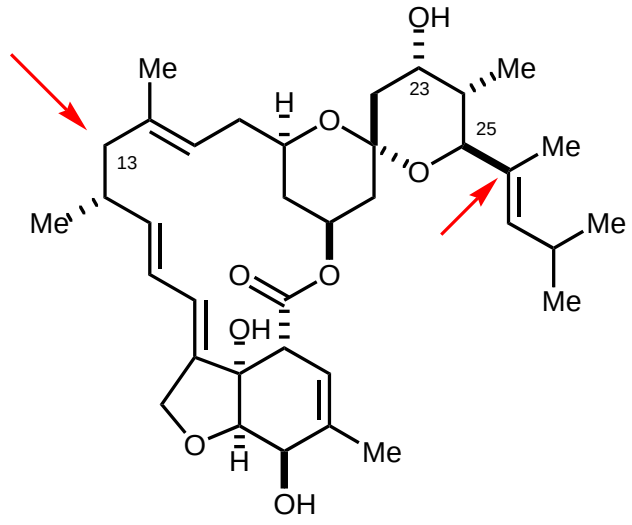
Avermectin is similar to Milbemycin and Nemadectin



Avermectin B1a

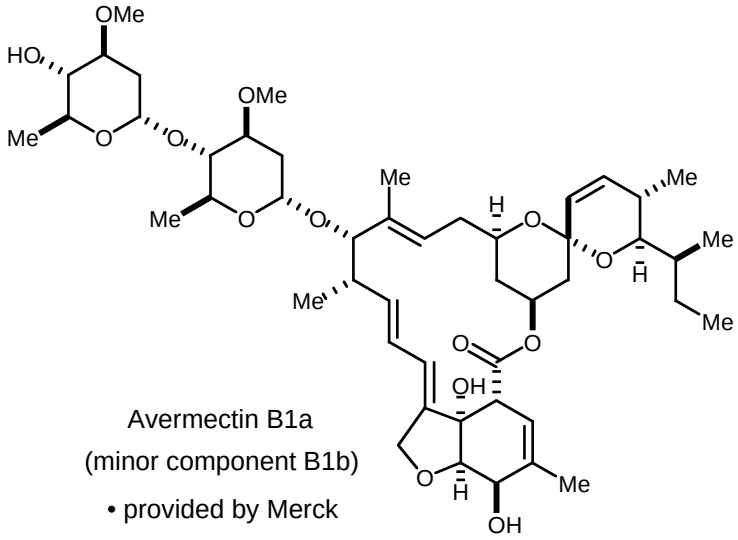


Milbemycin α1



Nemadectin

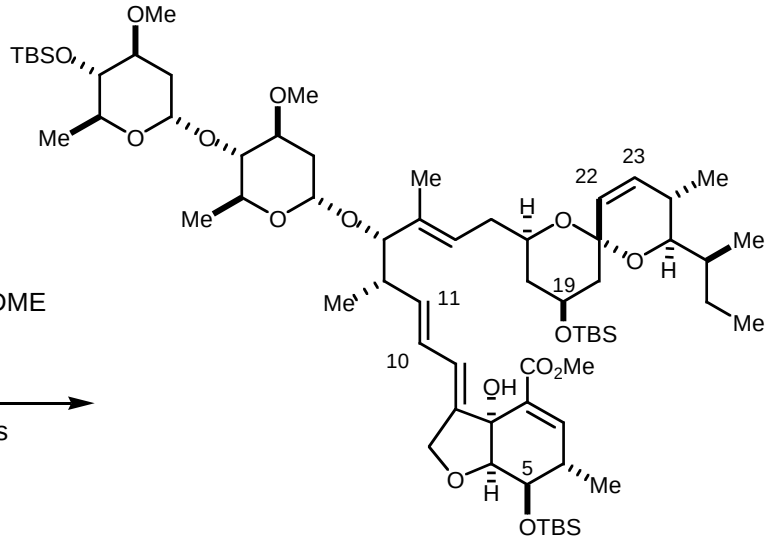
Hanessian: Avermectin Degradation



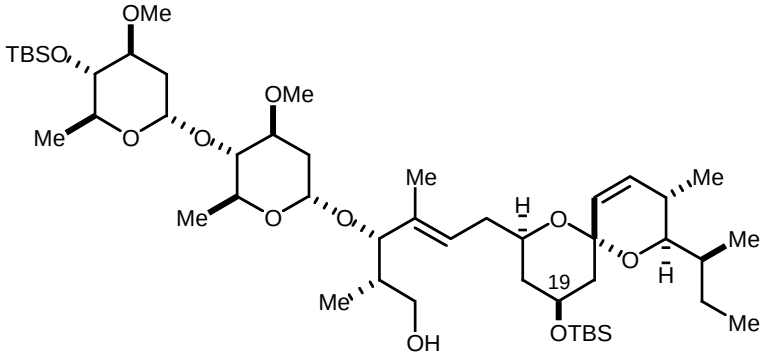
Avermectin B1a
(minor component B1b)
• provided by Merck

1. aq. KOH, DME
2. CH_2N_2
3. TBSCl

71%, 3 steps

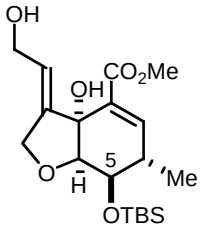


O_3; $NaBH_4$
(Sudan 7B)



92% yield
mixture of 1a and 1b

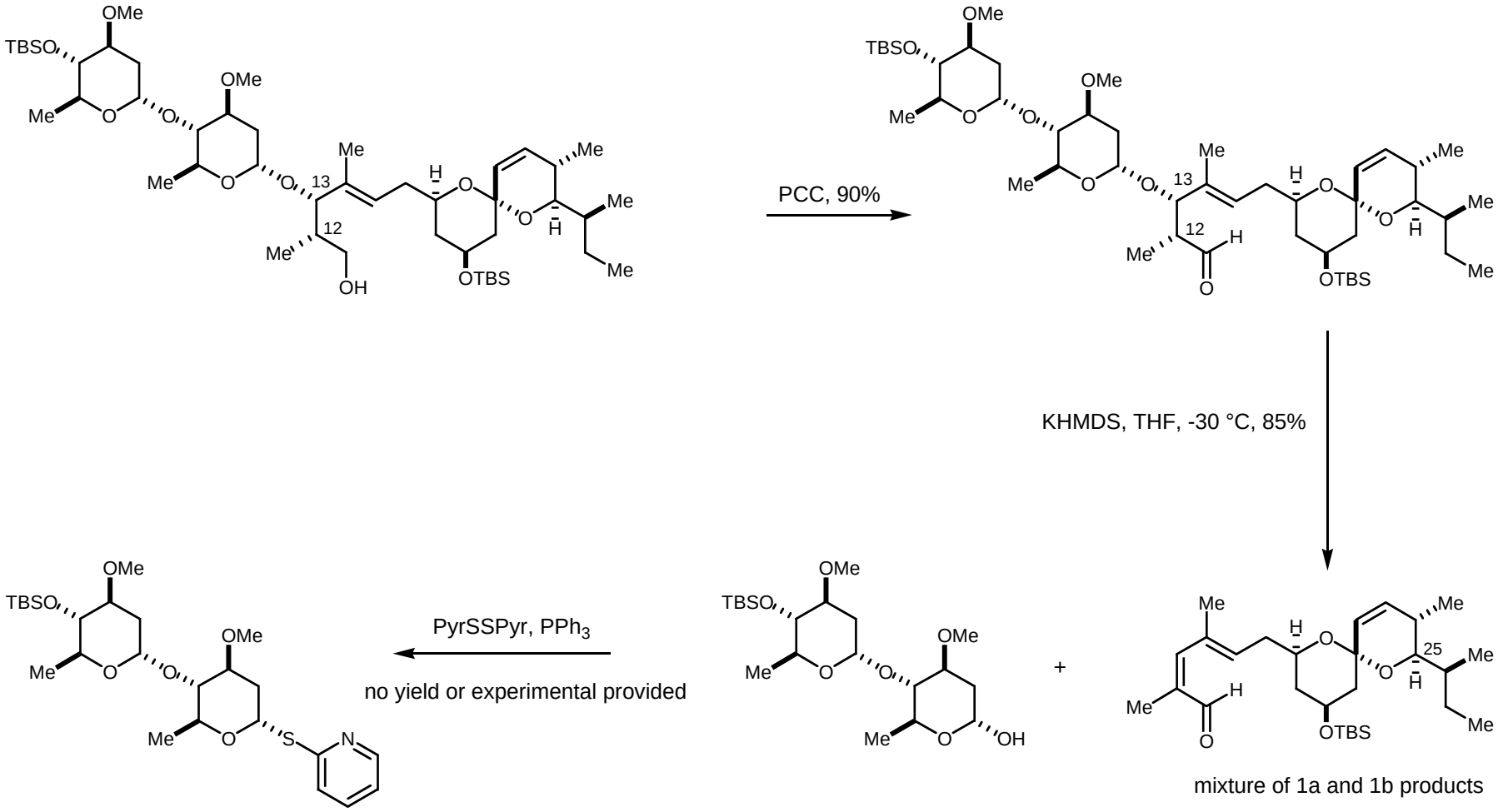
+



79% yield
used in fragment coupling

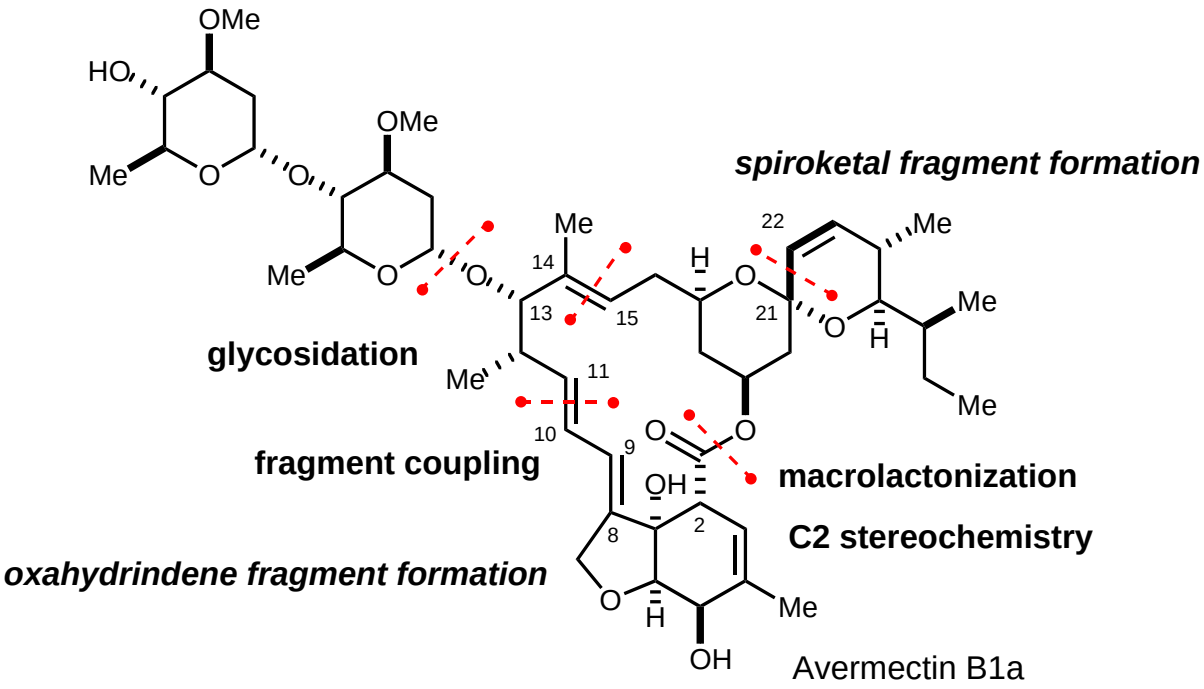
Hanessian, *TL* **1986**, *27*, 2699

Hanessian: Avermectin Degredation

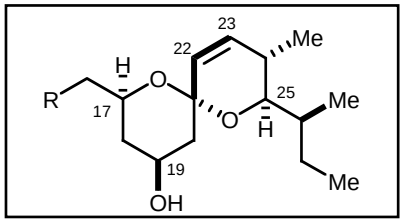


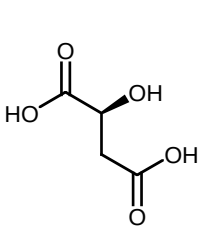
Hanessian, *TL* **1986**, *27*, 2699

Hanessian Disconnections



Hanessian: Lactone Synthesis

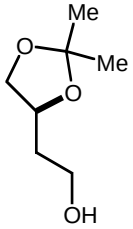




S - malic acid

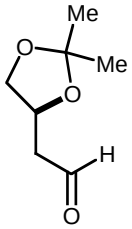
1. BH_3•DMS
2. acetone, TsOH

92%, 2 steps



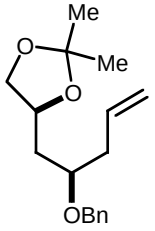
PCC

77%



1. BrMg
2. BnBr, NaH

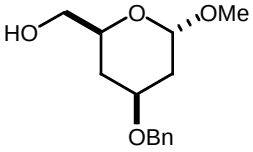
76%, 2 Steps



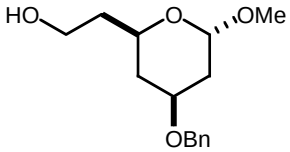
1:1 selectivity

1. H_3O^+
2. O_3, DMS
3. $BF_3 \bullet OEt_2$, MeOH

60%, 3 steps

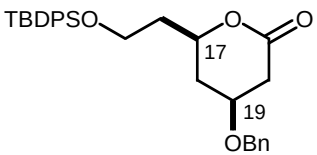


1. PCC, 81%
2. $Ph_3P{=}CH_2$, 71%
3. 9-BBN, 97%



1. aq. HOAc
2. TBDPSCl, pyr.
3. PCC

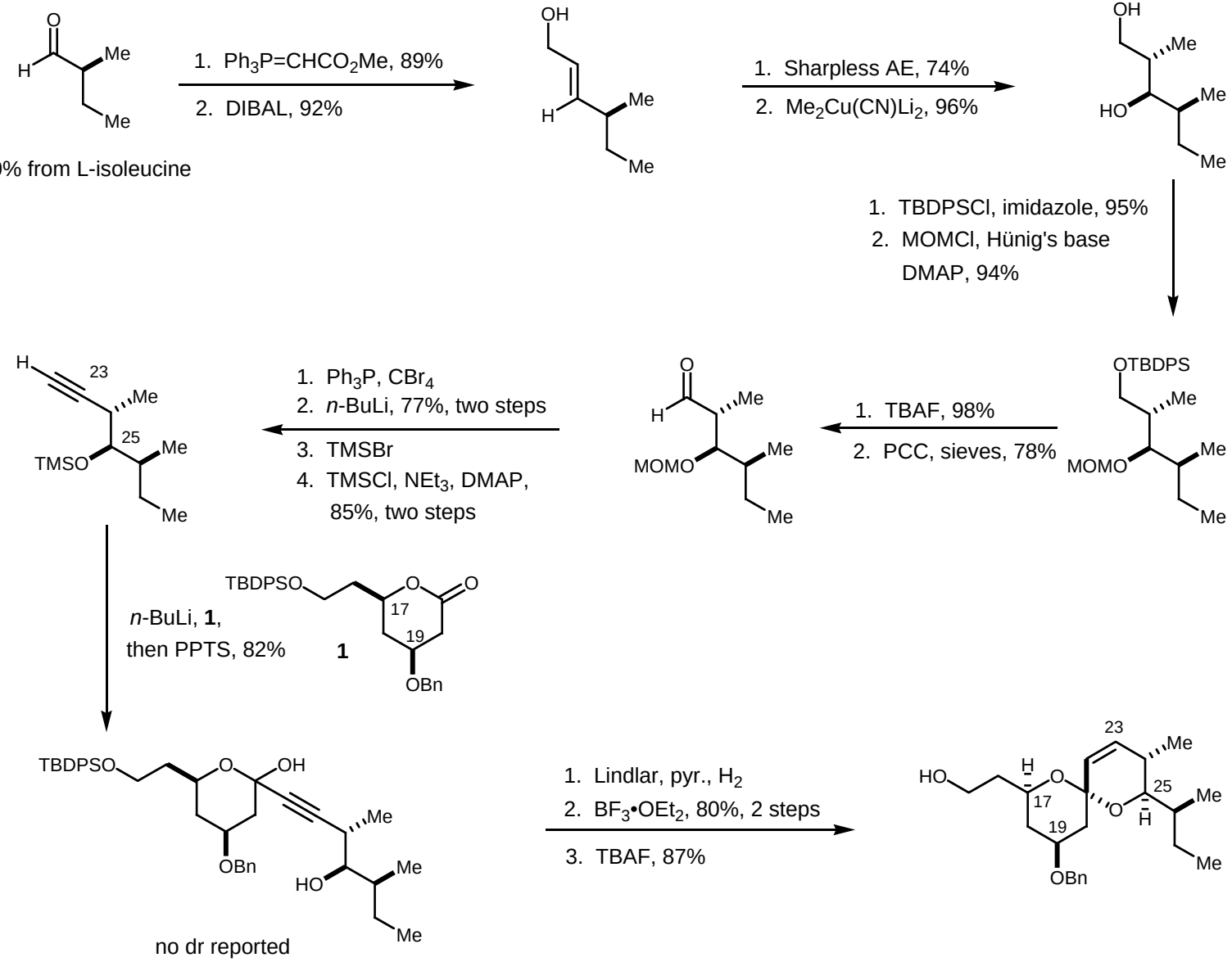
73%, 3 steps



"It should be noted that the unwanted diastereomer would be an ideal precursor to the lactone portion of the compactins and mevinolins" See JOC **(1990)** 5766.

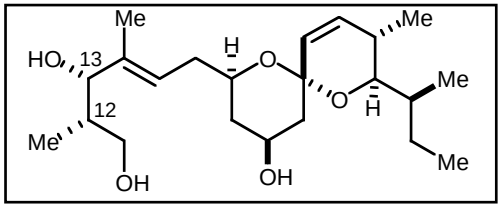
Pure & Appl. Chem. **1987**, *59*, 299 (full paper)

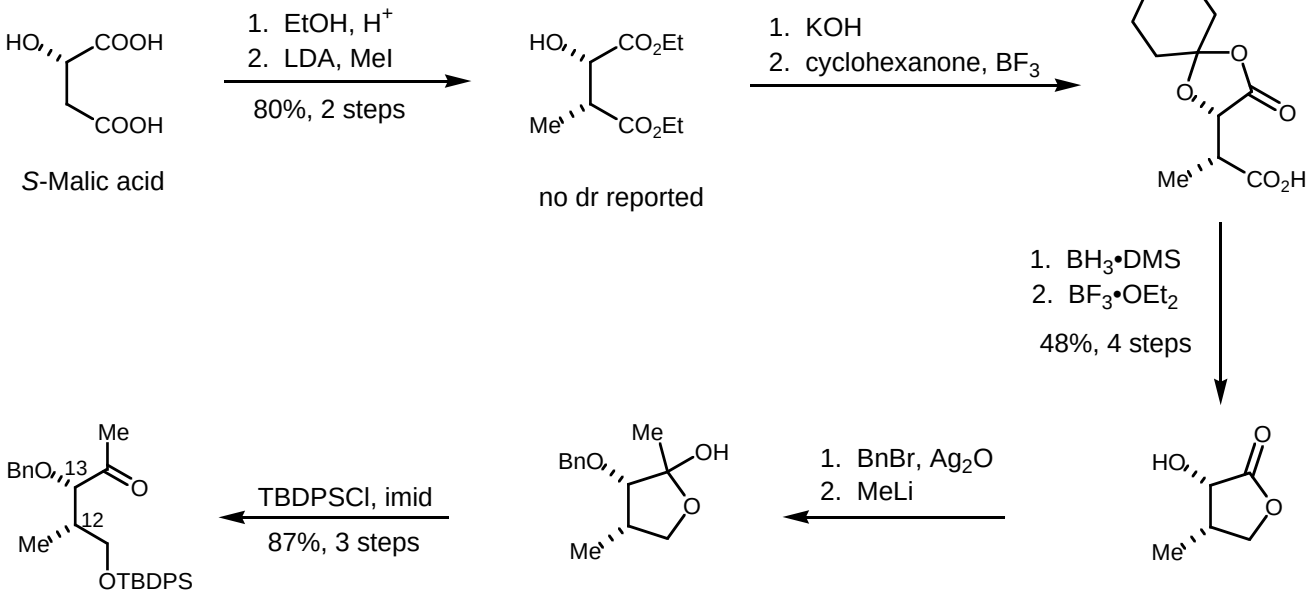
Hanessian: Spiroketal Formation



Pure & Appl. Chem. **1987**, *59*, 299 (full paper)

Hanessian: Skeleton Fragment



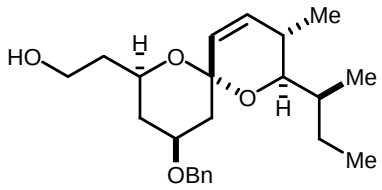


S-Malic acid

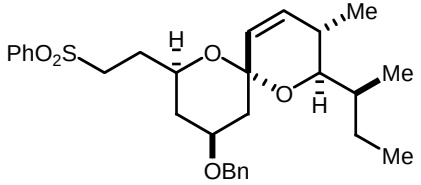
no dr reported

9 steps, 34% yield

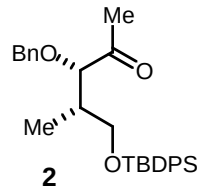
Hanessian: Aglycone Elaboration



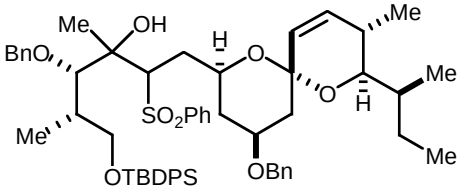
1. PhSSPh, Ph_3P, 85%
2. *m*-CPBA, -10 °C, 90%



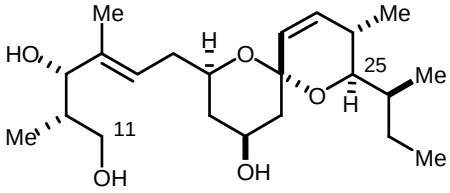
n-BuLi, THF, -78 °C, then **2**
40% (95% based on rec sm)



2

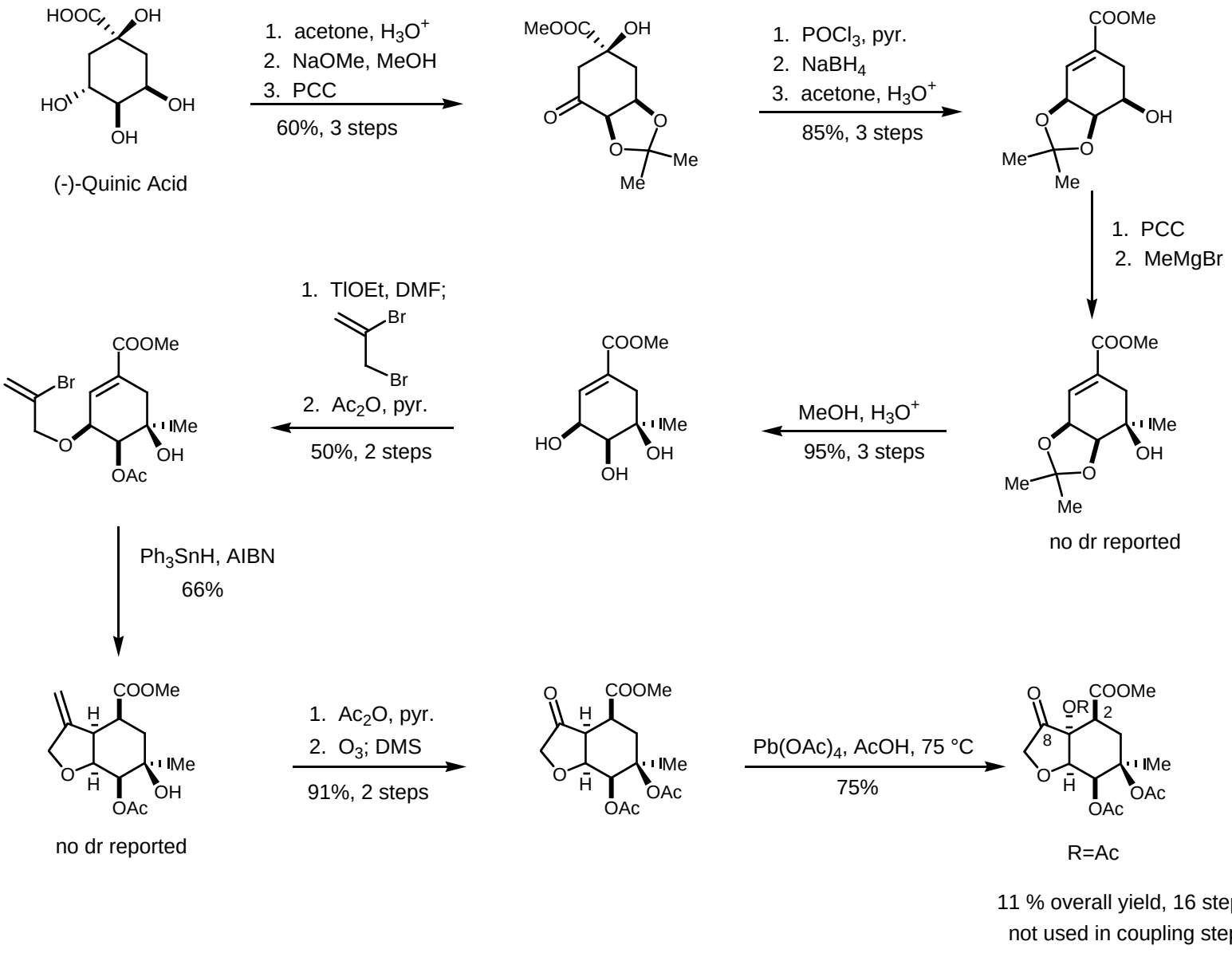


1. Na/Hg, MeOH, KH_2PO_4, 40%
2. TBAF, 95%
3. Li/NH_3, 75%

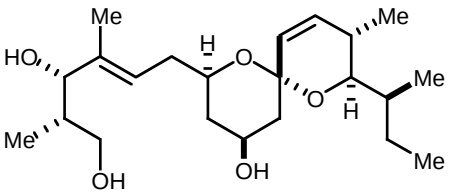


no E:Z reported

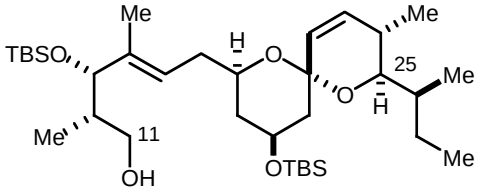
Hanessian: Oxahydrindene Partial Synthesis



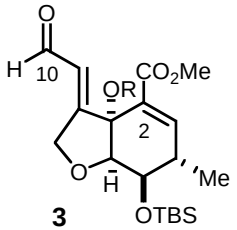
Hanessian: Aglycone Elaboration



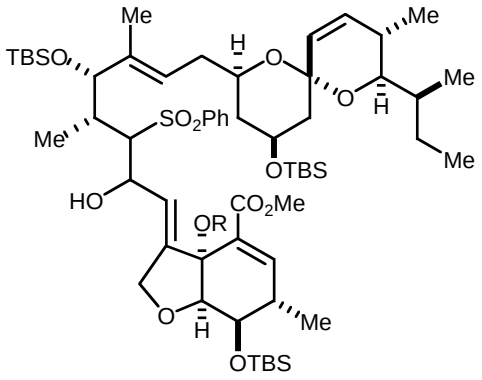
1. Me_3COCl, Et_3N, 78%
2. TBSCl, imidazole, DMAP, 91%
3. NaOMe, MeOH, 80%



1. Ph_2S_2, PBu_3, 83%
2. *m*-CPBA, 96%
3. *n*-BuLi, THF, -78 °C, then **3**, 77%

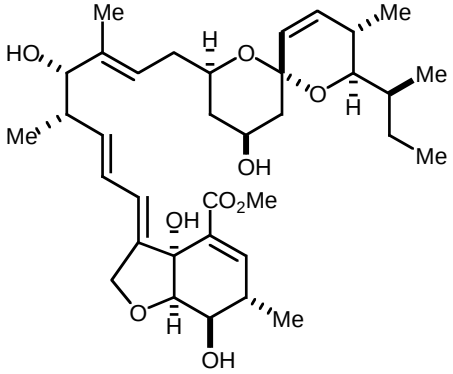


3
R=TMS
from degradation



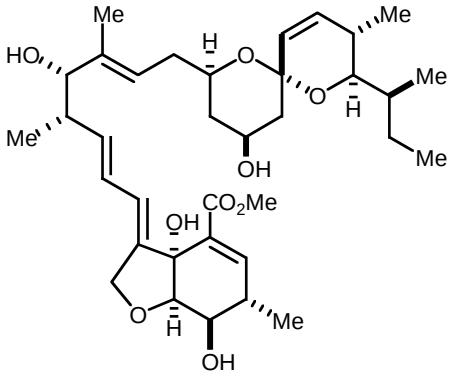
R=TMS

1. $SOCl_2$, pyr., then Na/Hg, MeOH
2. TBAF, 85%, 2 steps

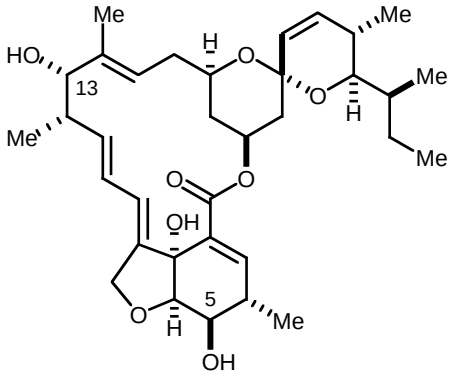


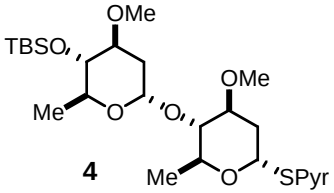
no E:Z ratio indicated

Hanessian: Macrocyclization and Glycosylation



1. aq. KOH, then Dowex 50, 72 %
2. DCC, DMAP, 30%

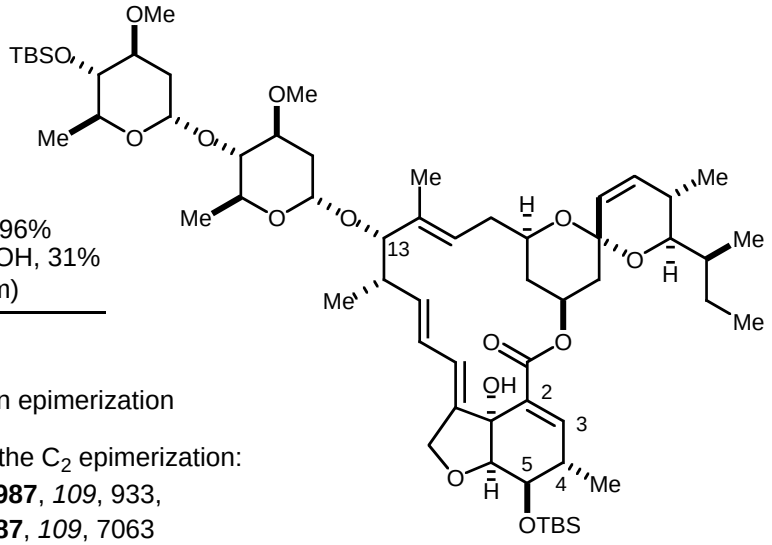




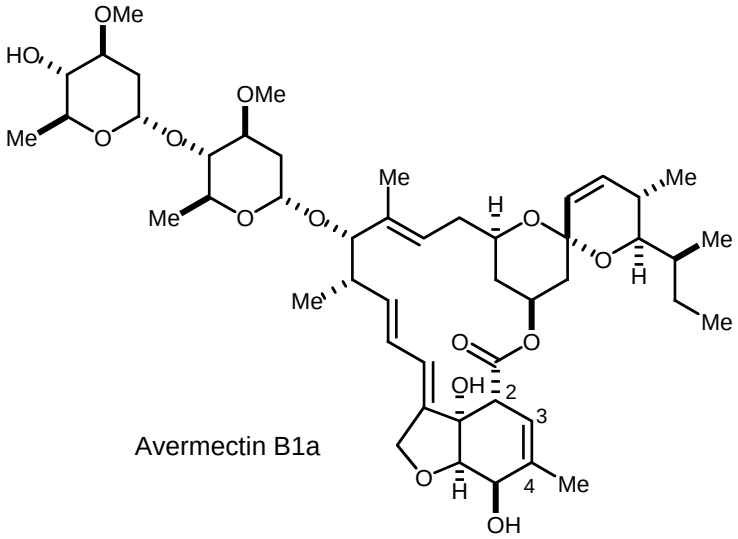
4

from degradation

1. TBSCl, imidazole, 91%
2. **4**, CH_2Cl_2, AgOTf, 72%



1. TMSCl, Et_3N, DMAP, 96%
2. LDA, TMSCl, then AcOH, 31% (72% based on rec. sm)
3. TBAF, 90%

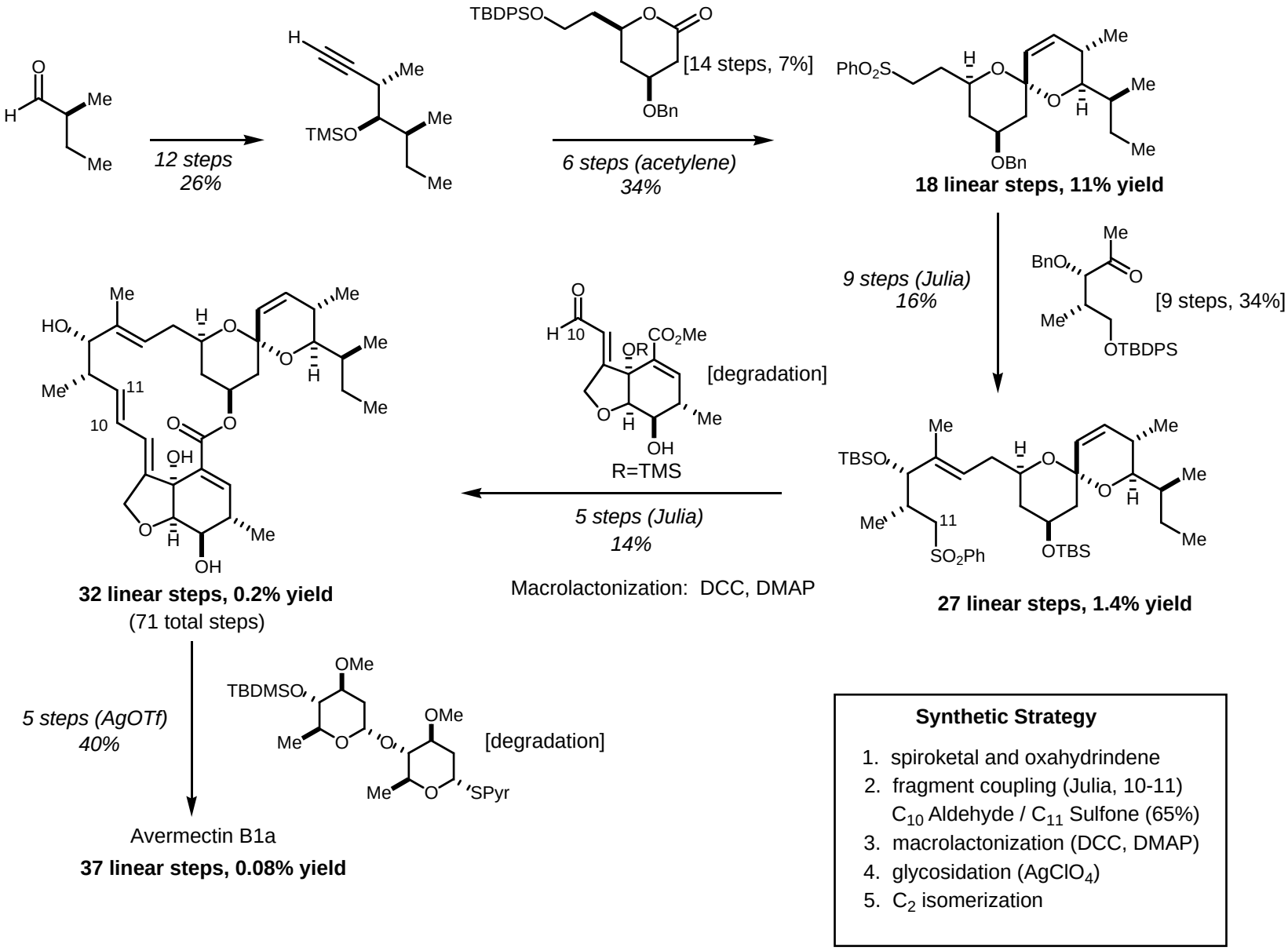


Avermectin B1a

- Deconjugation to epi-C_2, then epimerization

For a detailed discussion of the C_2 epimerization:
Fraser-Reid *JACS* **1987**, *109*, 933,
Hanessian *JACS* **1987**, *109*, 7063

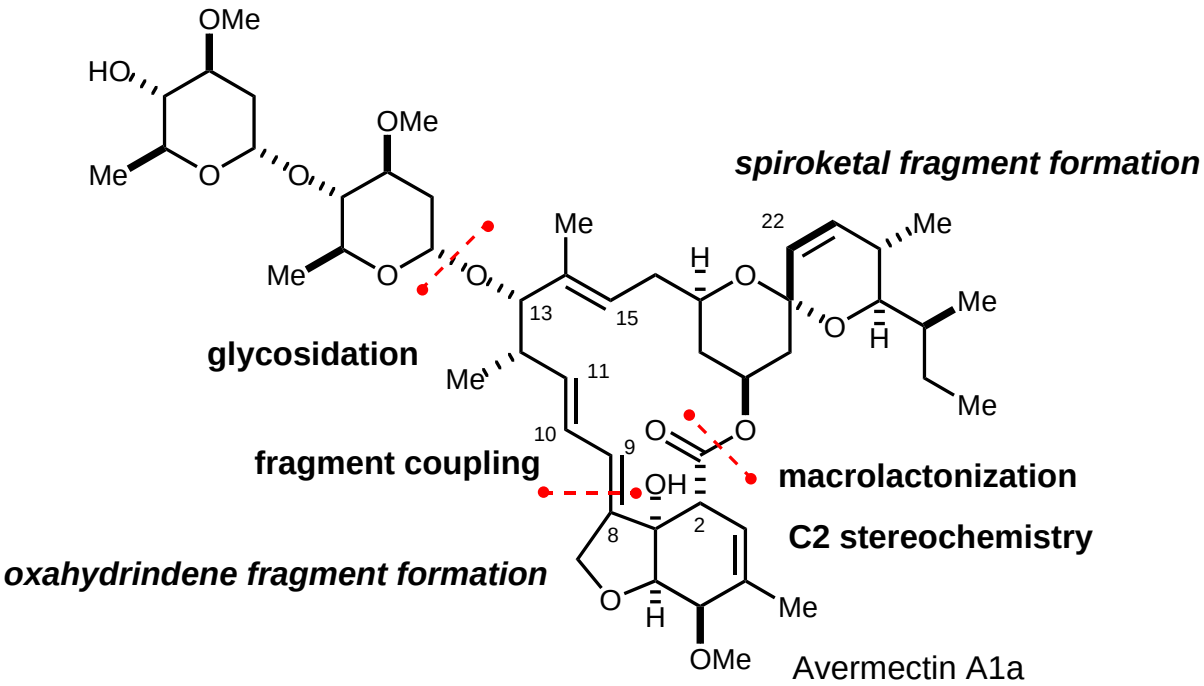
Hanessian: Route Summary



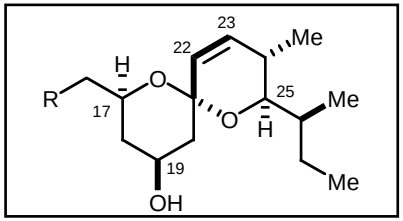
Synthetic Strategy

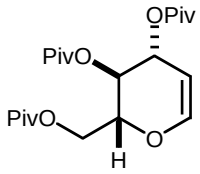
1. spiroketal and oxahydrindene
2. fragment coupling (Julia, 10-11)
   C_{10} Aldehyde / C_{11} Sulfone (65%)
3. macrolactonization (DCC, DMAP)
4. glycosidation ($AgClO_4$)
5. C_2 isomerization

Danishefsky Disconnections

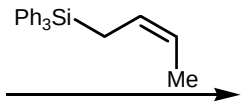


Danishefsky: Spiroketal Assembly

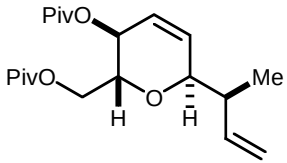




2 steps from
tri-O-acetyl-D-glucal



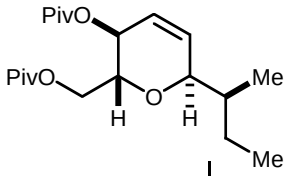
BF_3•OEt_2
90%



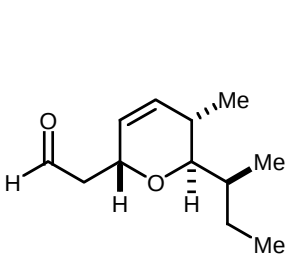
dr: 4.5:1
"...specific for
axial attack."

(74% yield of desired diastereomer)

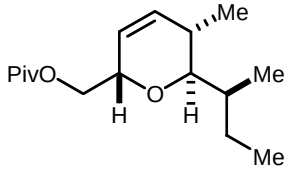
H_2, Pd/C
90%

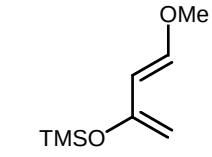


CuI, MeLi
73%

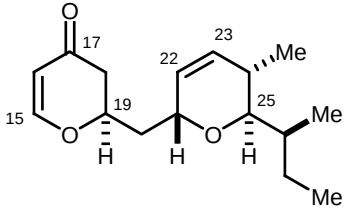


1. LiOH, 82%
2. Tf_2O, pyr.,
   then NaCN, 82%
3. DIBAL, 90%

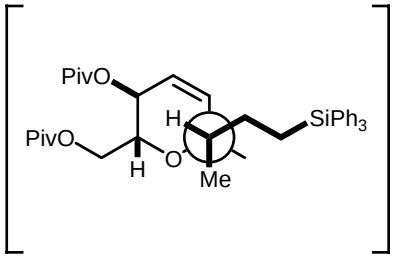


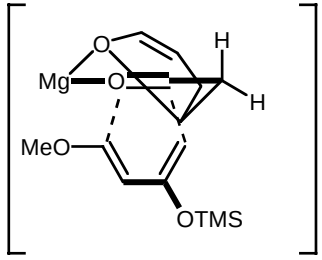


$MgBr_2$•OEt_2
then TFA
77%



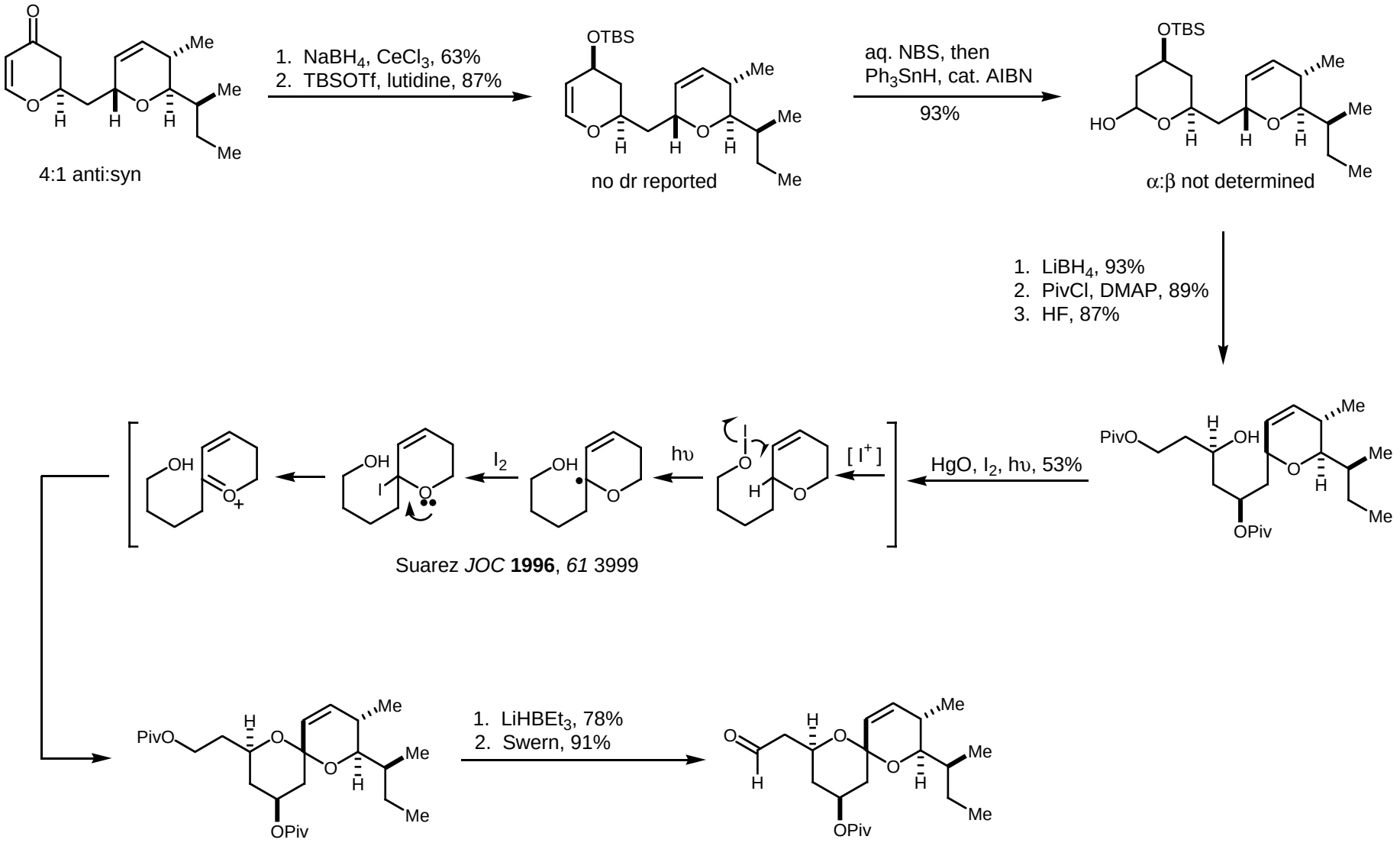
dr: 4:1





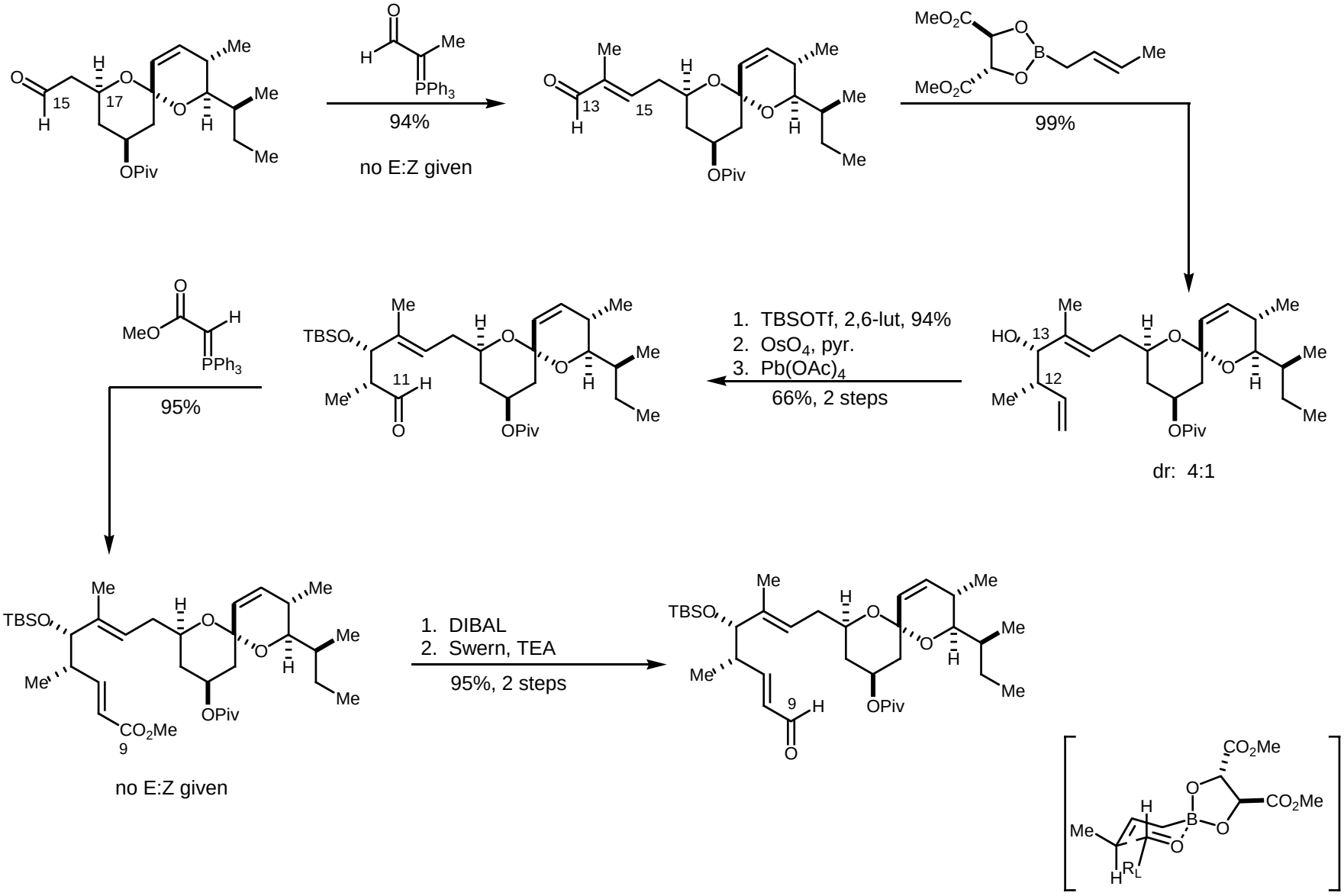
JACS **1989**, *111*, 2967 (full paper)

Danishefsky: Spiroketal Assembly

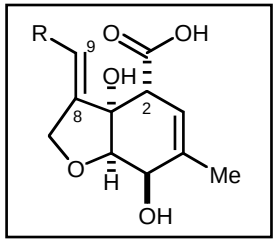


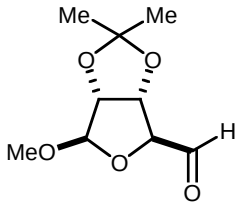
JACS **1989**, *111*, 2967 (full paper)

Danishefsky: Sidechain Elaboration

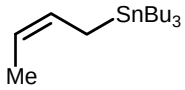


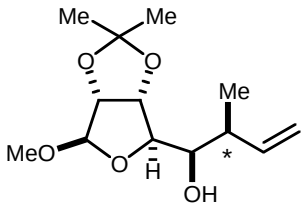
Danishefsky: Oxahydrindene Precursor





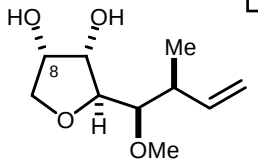
BF_3•OEt_2, 79%

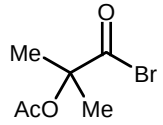




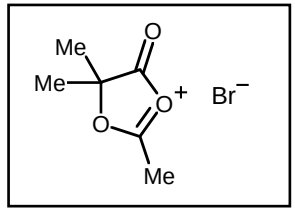
dr: 10:1

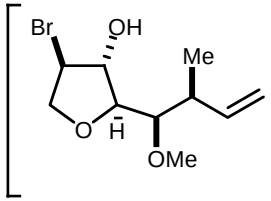
1. NaH, MeI, 86%
2. 1N HCl, then BF_3•OEt_2, Et_3SiH, 79%

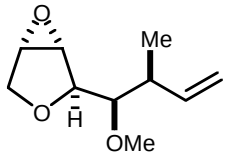




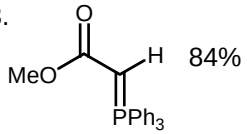
Amberlite IRA-400, 92%



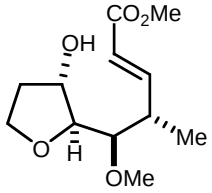




1. $LiBEt_3H$, 96%
2. O_3; Zn, HOAc
3.

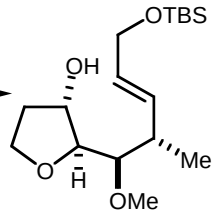


84%

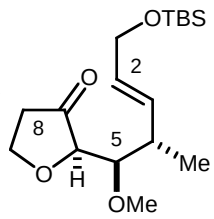


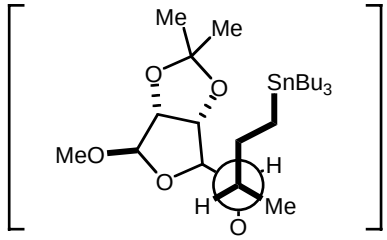
one isomer

1. DIBAL, 97%
2. TBSCl, TEA, DMAP, 97%

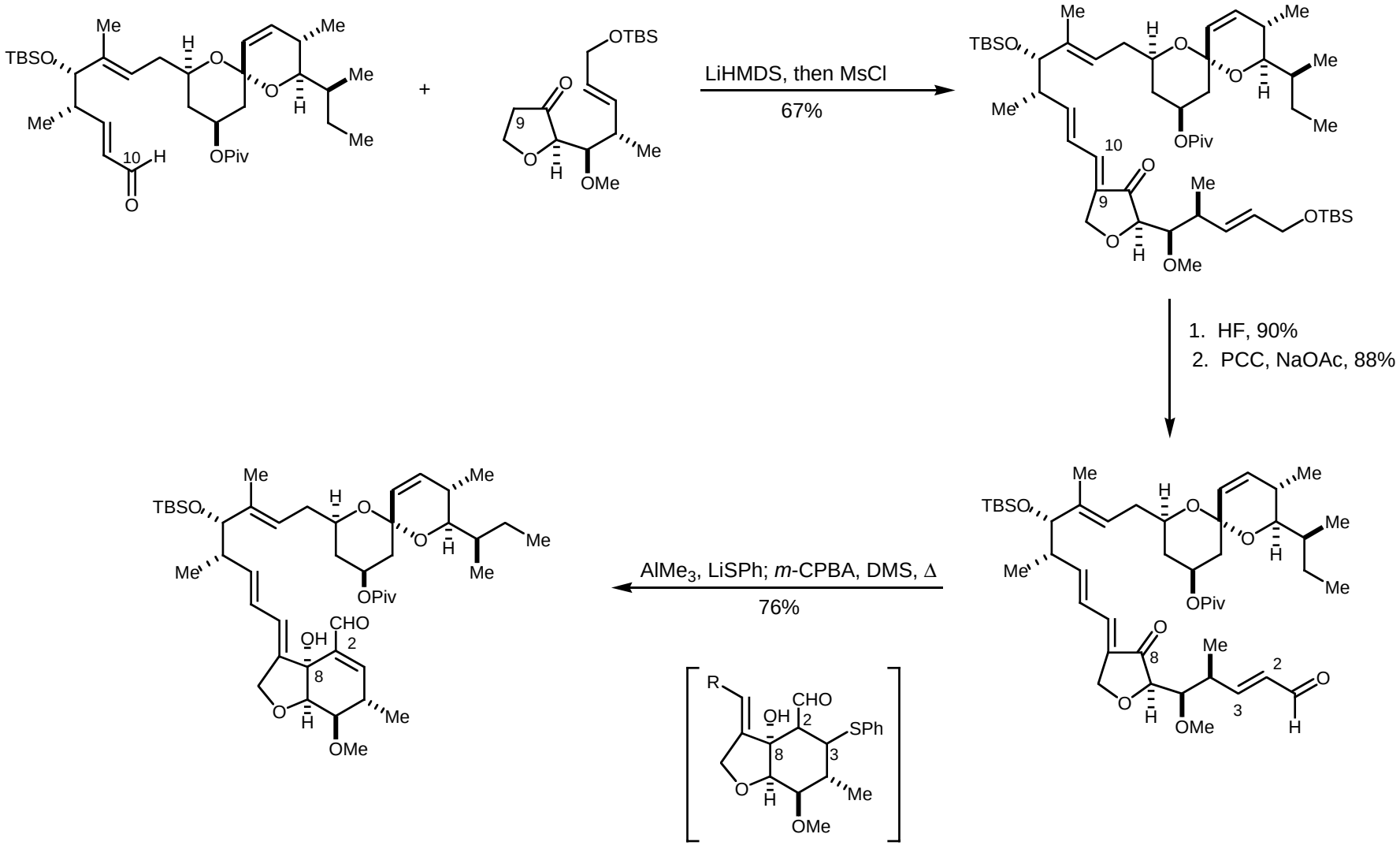


PCC, NaOAc, 89%

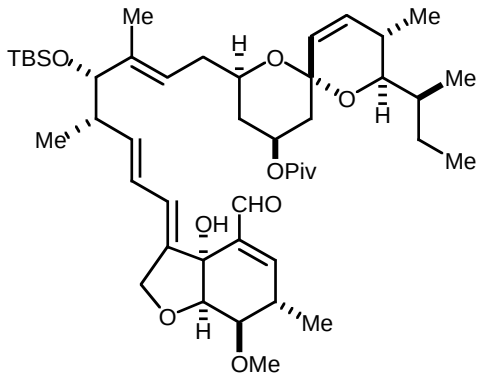




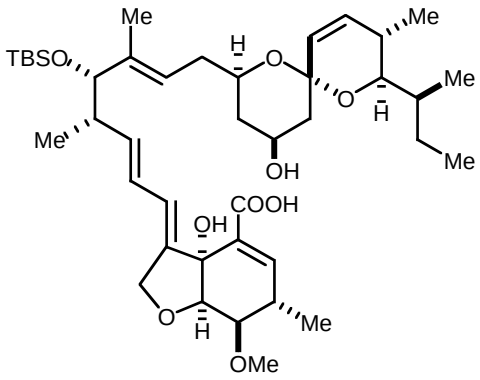
Danishefsky: Oxahydrindene Synthesis

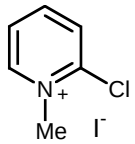


Danishefsky: Macrolactonization

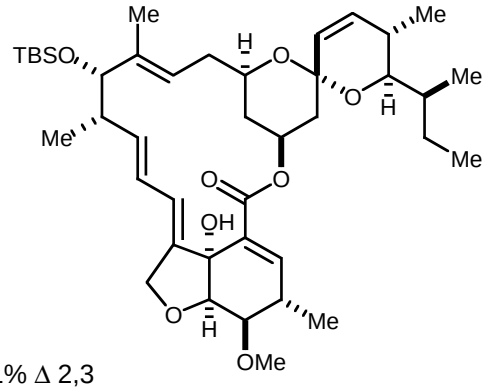


1. $NaClO_2$, NaH_2PO_4
2. CH_2N_2, 79%, 2 steps
3. LiOH, 95%





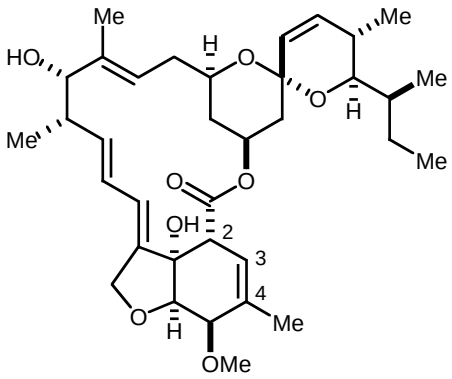
TEA
62%



Δ 2, 3

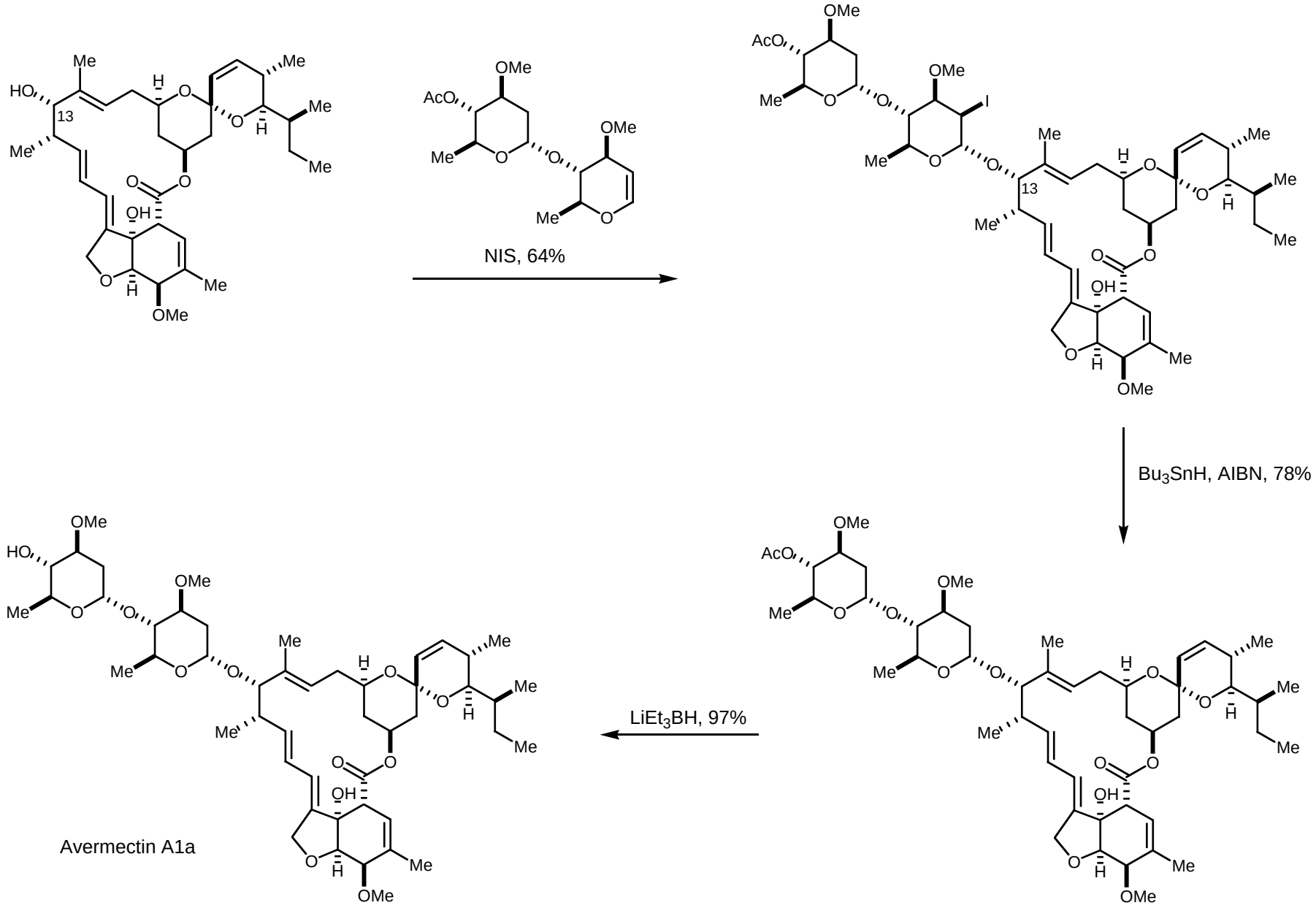
1. TBAF, 87%
2. LDA, 71%
3. imidazole, 32%

imidazole epimerization produced 21% Δ 2,3 and 33% epi-Δ 3,4 which could be reused.

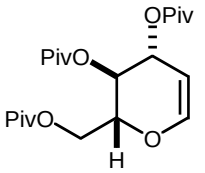


Δ 3,4

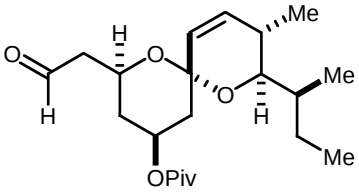
Danishefsky: Glycosylation



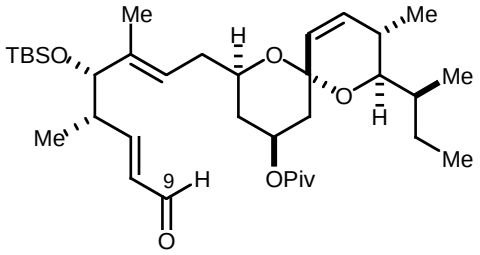
Danishefsky: Route Summary



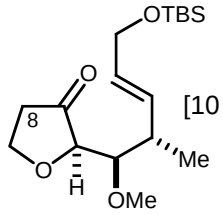
16 steps, (crotylsilane, cycloaddition)
3%



8 steps, (crotylboronate, 2 wittig)
52%



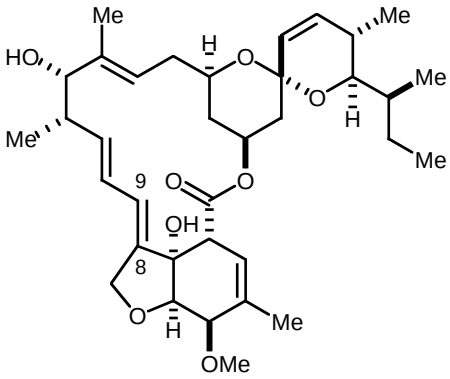
24 linear steps, 1.6% yield



[10 steps, 33%]

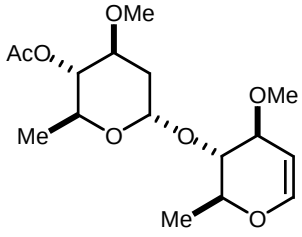
11 steps (aldol)
3.7%

Macrolactonization: Mukaiyama



35 linear steps, 0.06% yield
(44 total steps)

3 steps (NIS)
48%



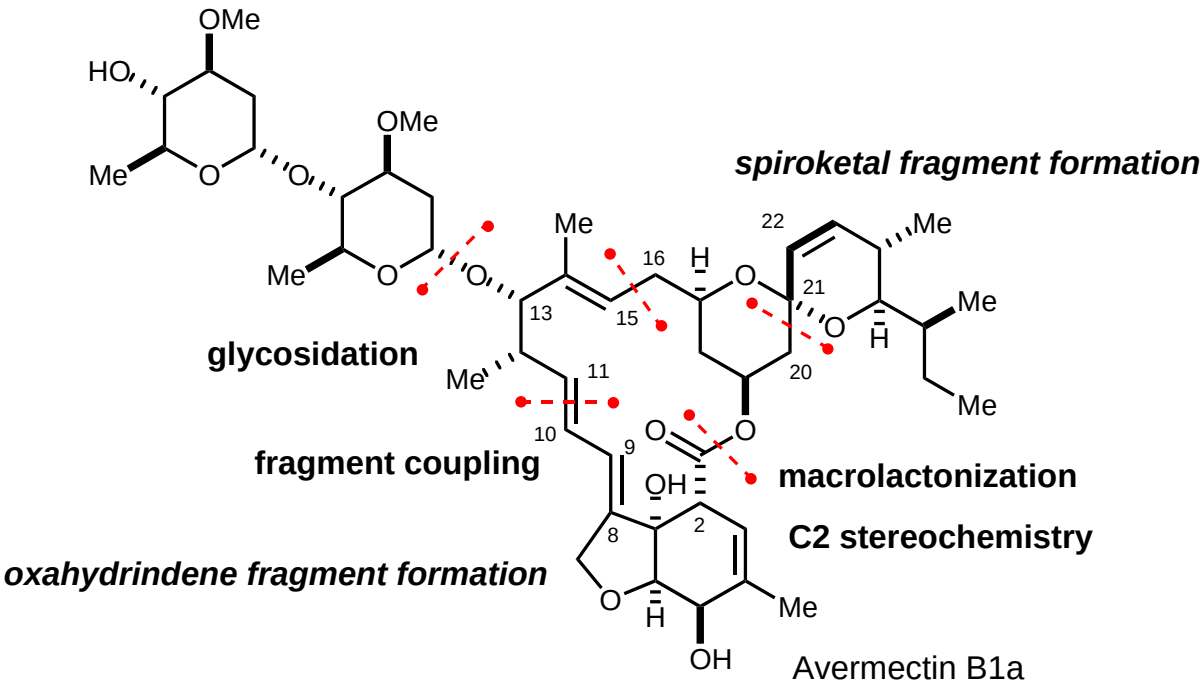
[9 steps, 18%]

Avermectin A1a
38 linear steps, 0.03%

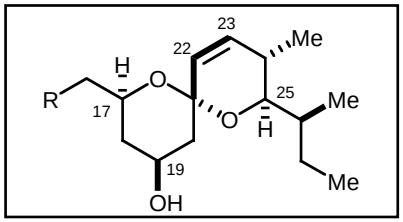
Synthetic Strategy

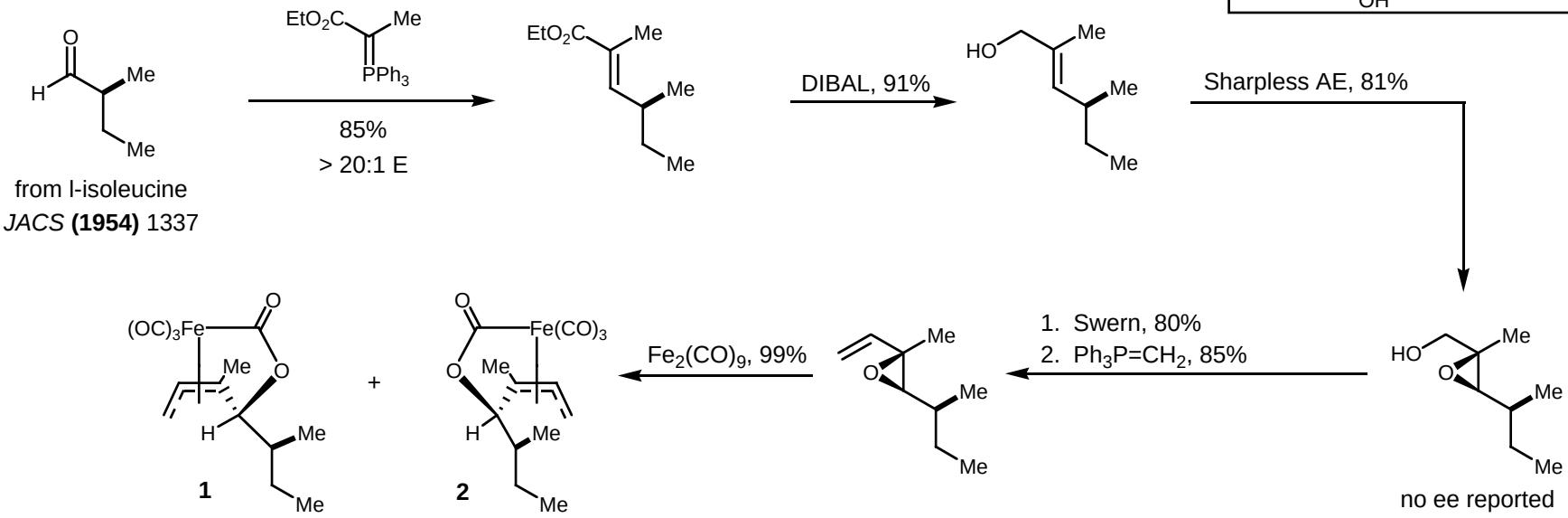
1. spiroketal
2. fragment coupling (aldol, 8-9)
   C_8 enol / C_9 aldehyde (67%)
3. oxahydrindene (Nozaki)
4. macrolactonization (Mukaiyama)
5. C_2 isomerization
6. glycosidation (NIS)

Ley Disconnections



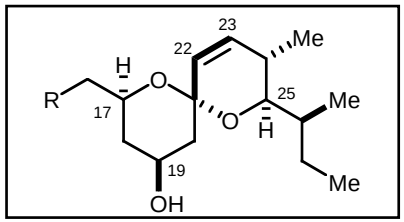
Ley: Spiroketal Precursor

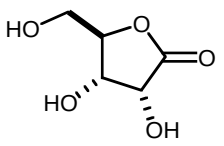




J. Chem. Soc., Perkin Trans. 1 **1991**, 667 (full paper)

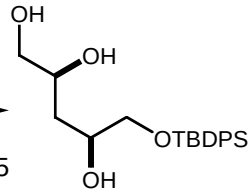
Ley: Spiroketal Precursor





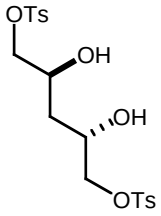
ribonic acid-γ-lactone

JCSPT1 **(1984)** 1315

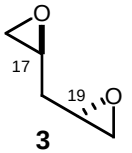


1. TBAF
2. TsCl, pyr.

65%, 2 steps



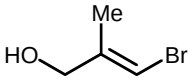
IR-400, 60%

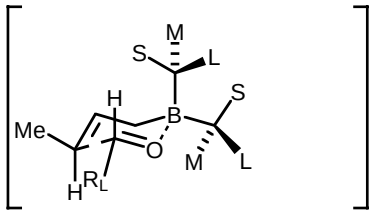


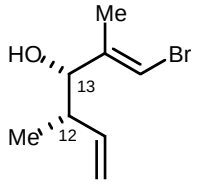
3

1. TPAP, NMO, mol. sieves, 94%
2. ((+)-IPC)$_2$B–Me

BF_3•OEt_2, 75%

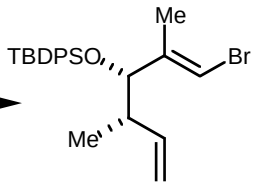




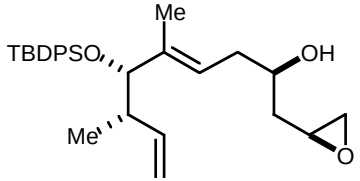


"excellent selectivity"

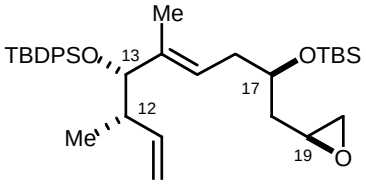
TBDPSCl, imidazole, DMAP, 92%



t-BuLi, Me_3Al, then **3**, 82%

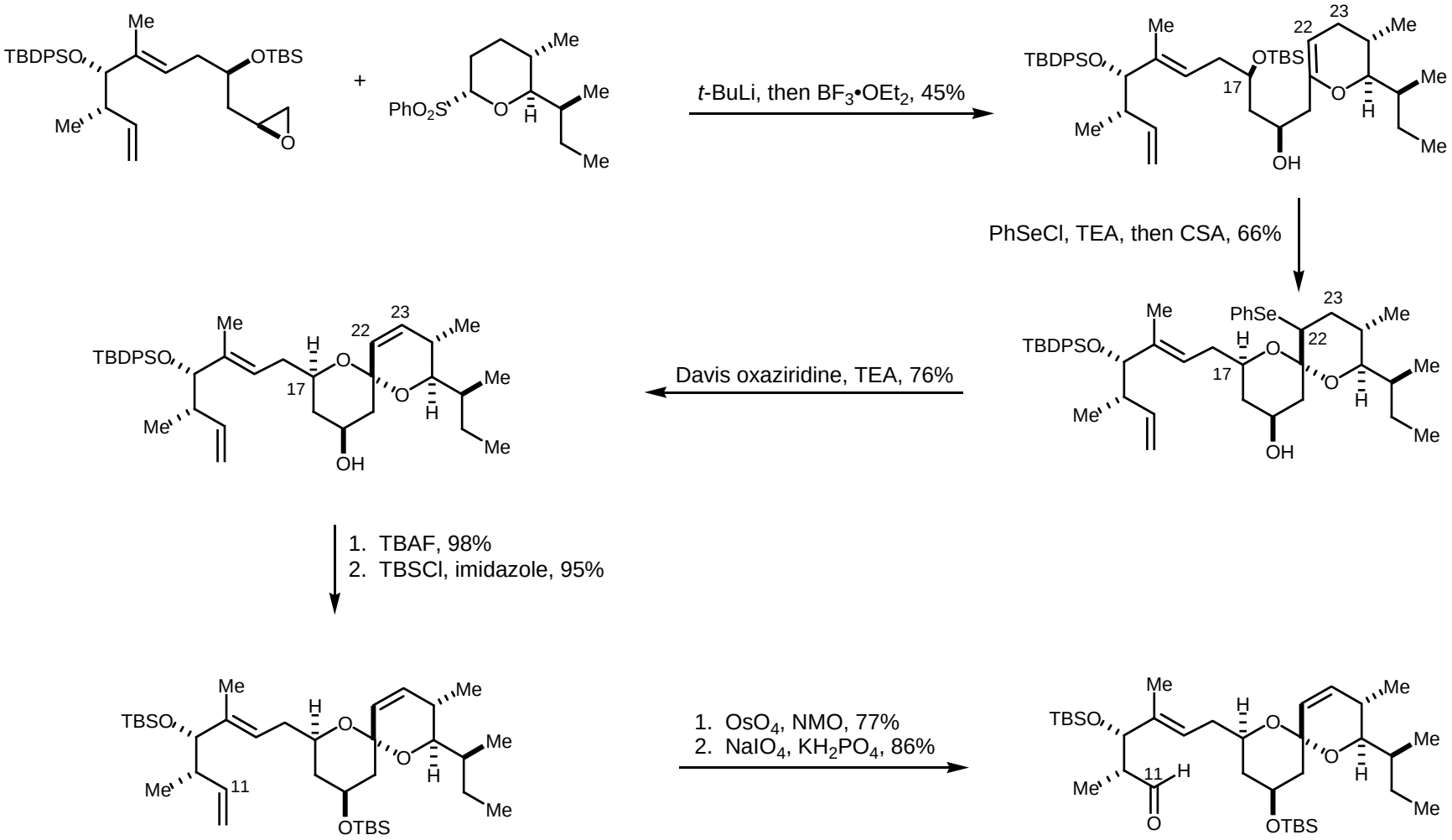


TBSCl, TEA, DMAP, 94%

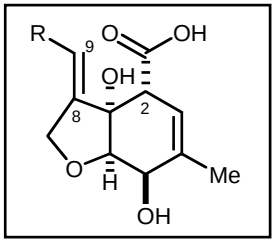


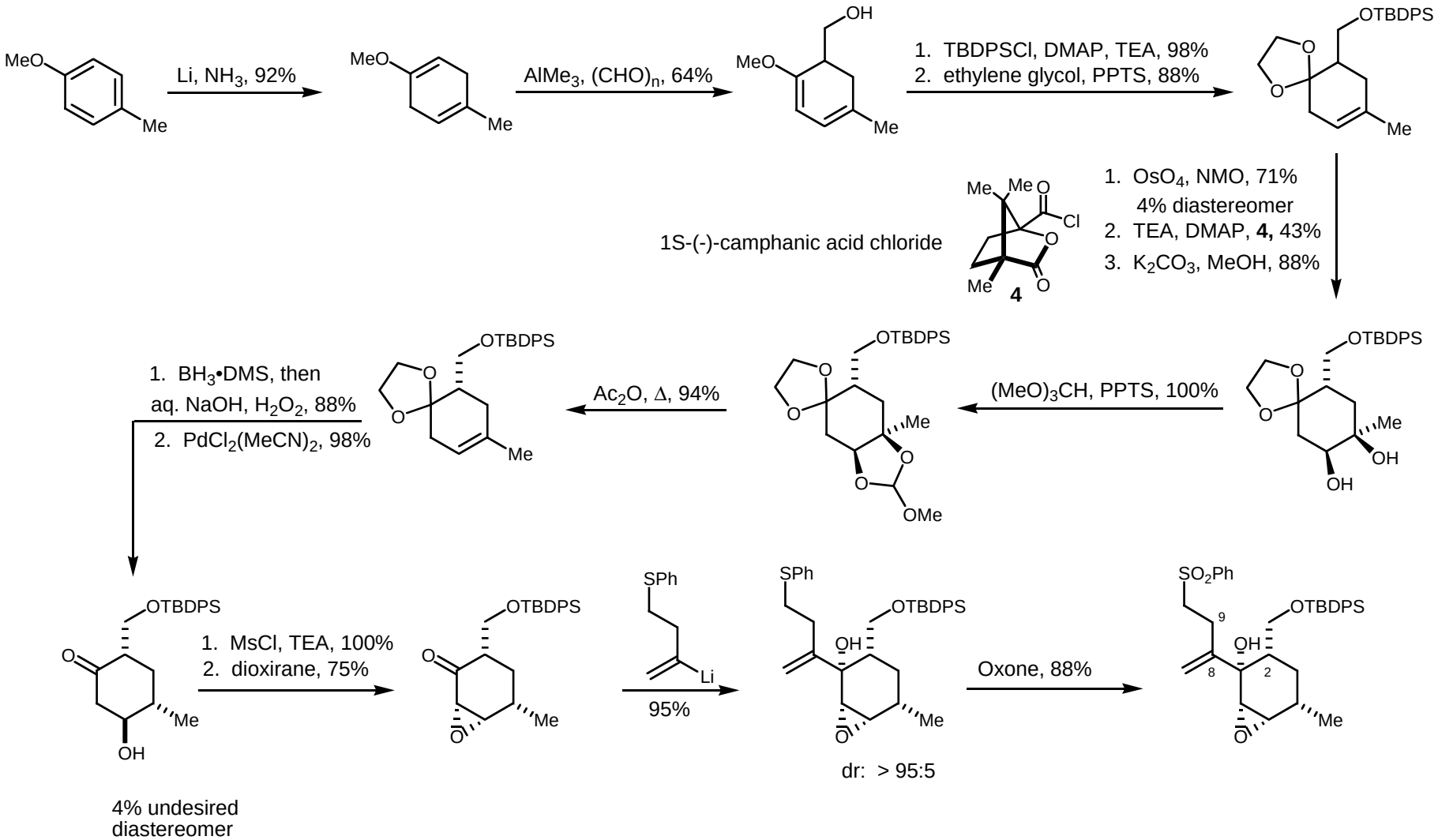
J. Chem. Soc., Perkin Trans. 1 **1991**, 667 (full paper)

Ley: Spiroketal



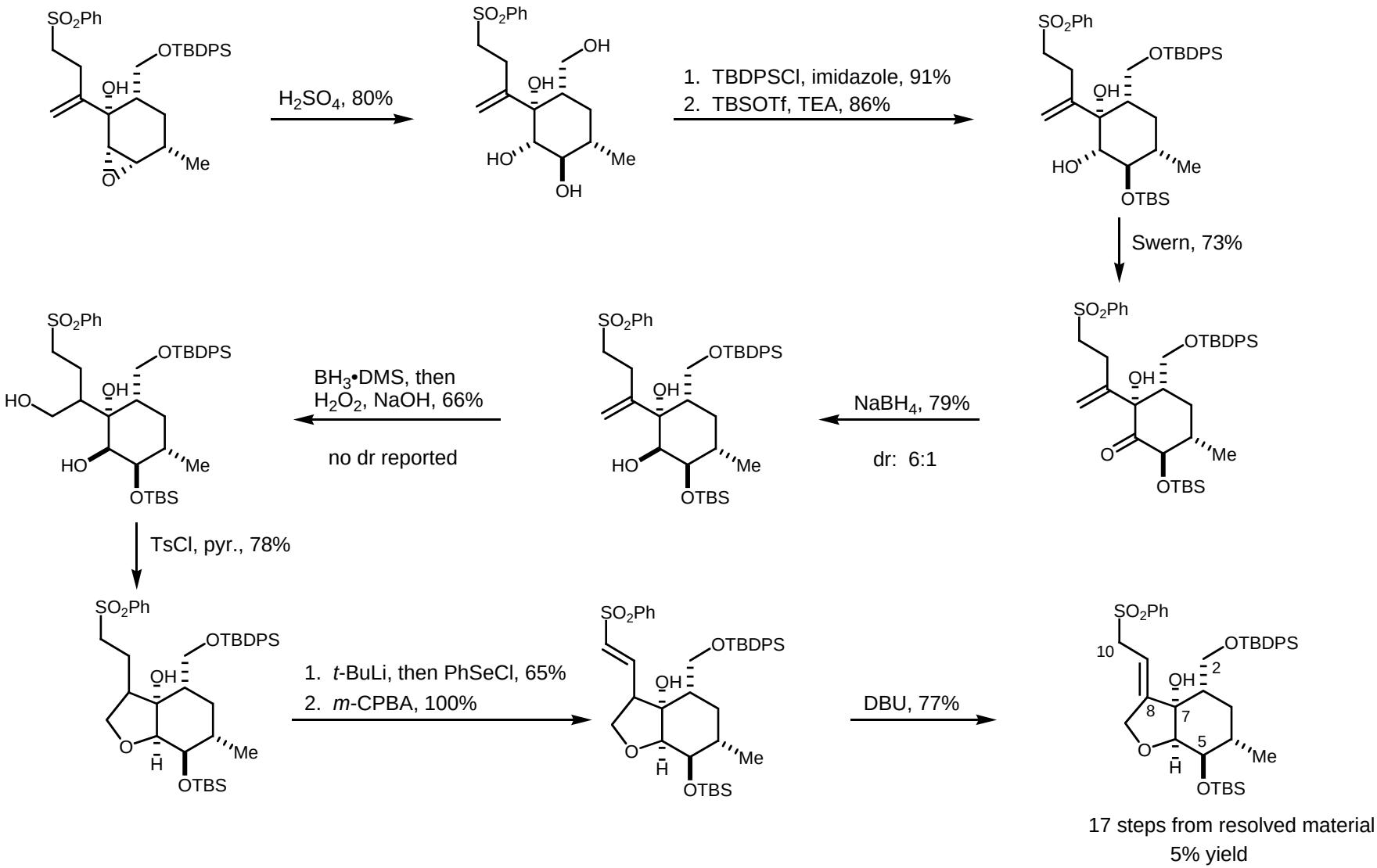
Ley: Oxahydrindene Precursor





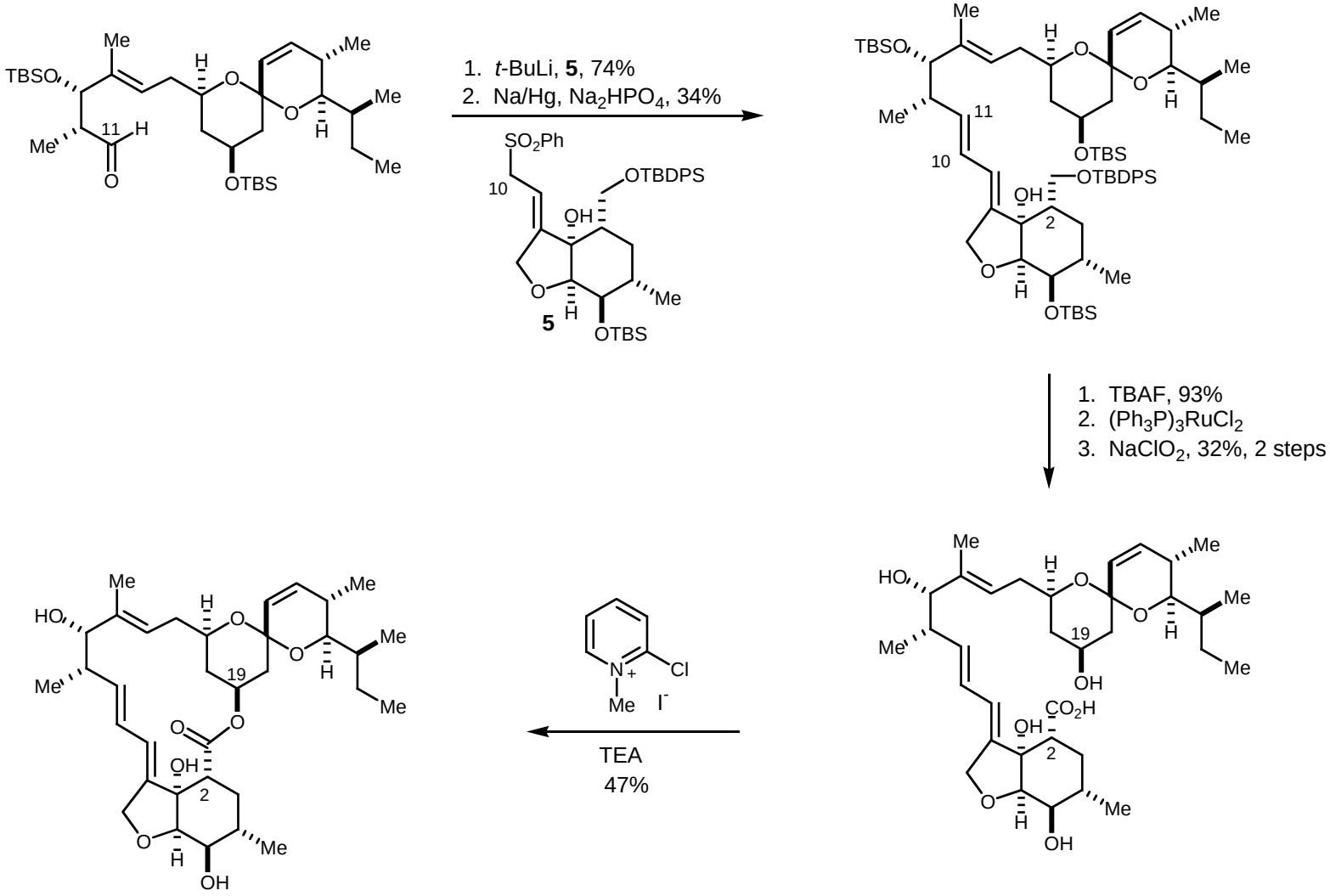
J. Chem. Soc., Perkin Trans. 1 **1991**, 667 (full paper)

Ley: Oxahydrindene

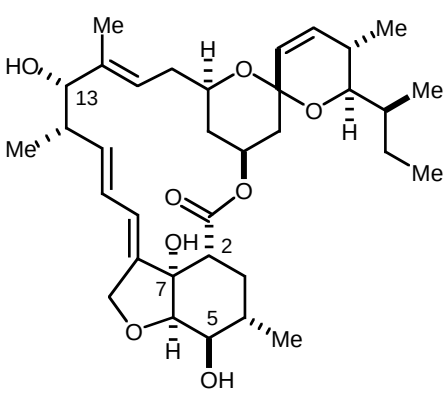


17 steps from resolved material
5% yield

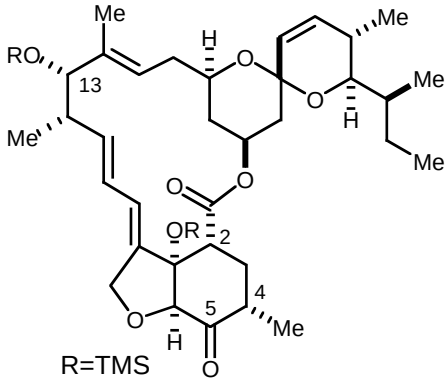
Ley: Macrolactonization



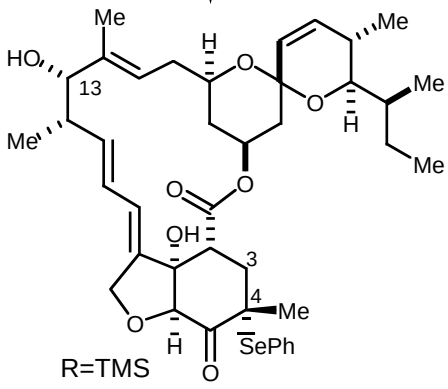
Ley: C_2 - C_4 Transformation



1. TPAP, NMO, mol. sieves, 61%
2. TMSOTf, TEA, 88%

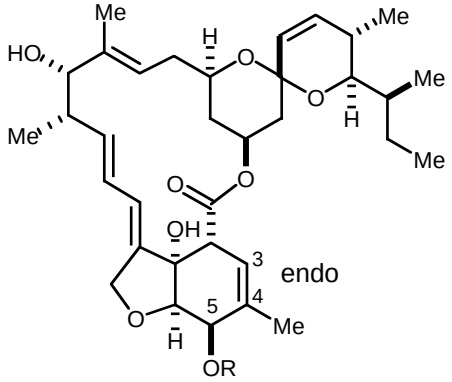


1. TEA, TMSOTf; PhSeCl; 91%, dr: 1:1
2. HF, pyr., 87%



1. Davis oxaziridine
2. $NaBH_4$, $CeCl_3$

92%, dr: 1:1, 2 steps

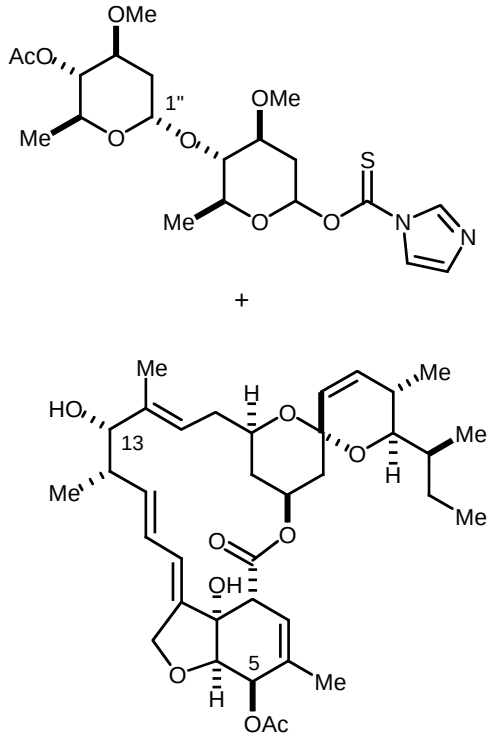


R = H

R = Ac

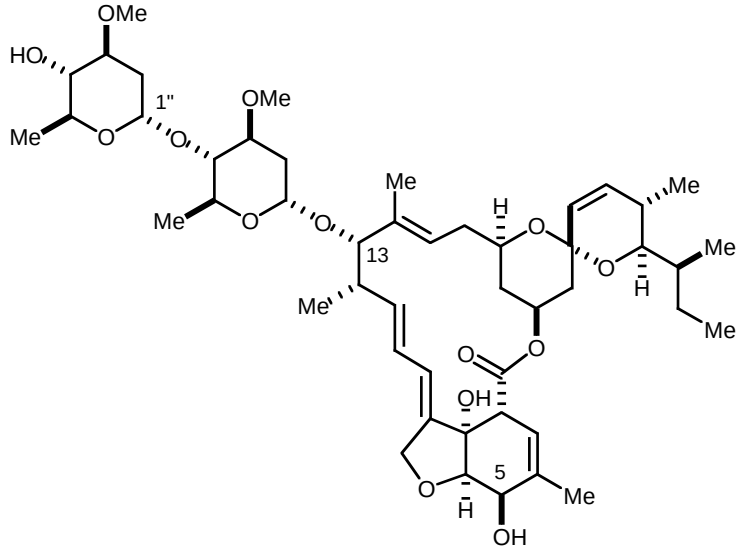
AcCl, pyr., DMAP, 97%

Ley: Glycoside Construction



+

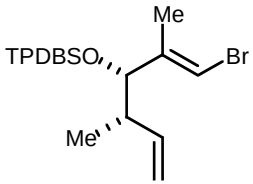
1. $CaCO_3$, $AgClO_4$, 64%
2. $LiBHEt_3$, 90%



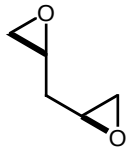
Avermectin B1a

27 linear steps, 0.01% yield

Ley: Route Summary

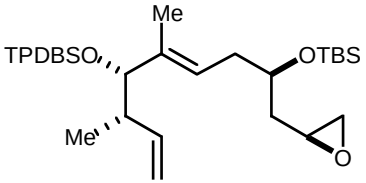


[3 steps, 65%]



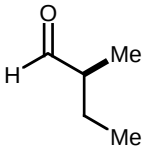
[3 steps, 39%]

2 steps (vinyl metal)
77%

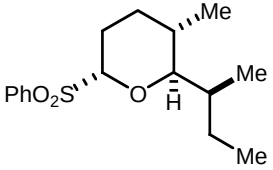


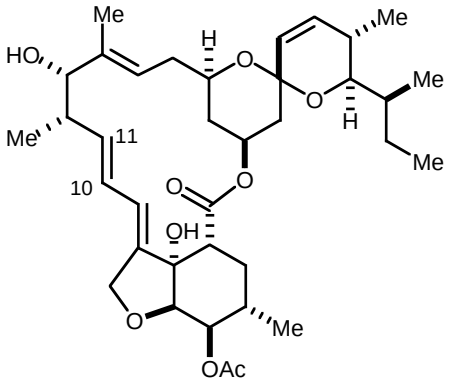
5 linear steps, 50% yield
(13 total steps)

7 steps (epoxide opening)
14%



10 steps
14%

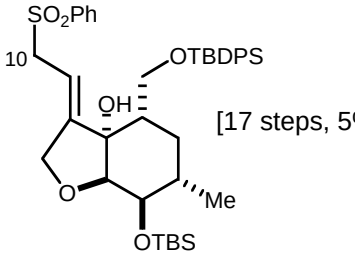




25 linear steps, 0.02% yield
(48 total steps)

2 steps (AgClO4)
50%

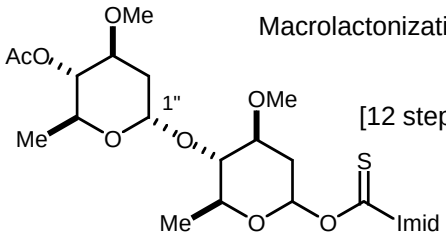
Avermectin B1a
27 linear steps, 0.01% yield



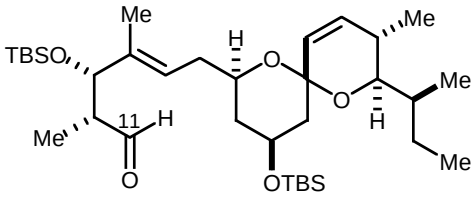
[17 steps, 5%]

13 steps (Julia)
0.3%

Macrolactonization: Mukaiyama



[12 steps, 2%]

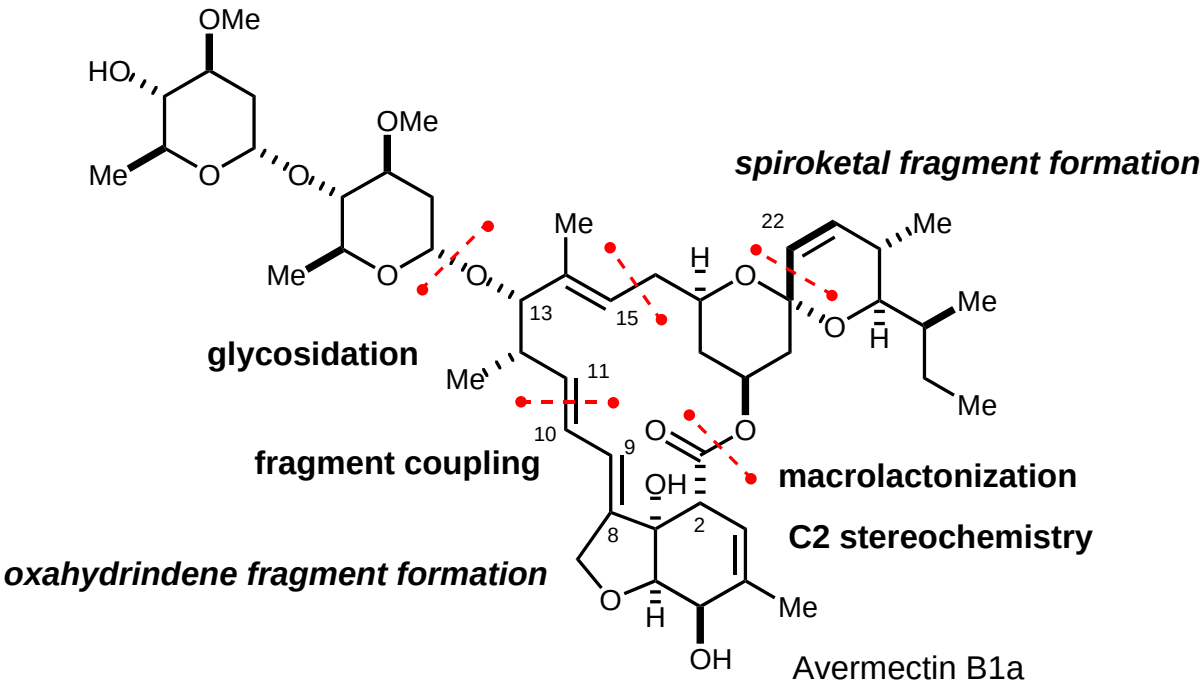


12 linear steps, 7% yield

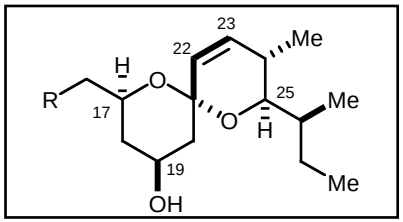
Synthetic Strategy

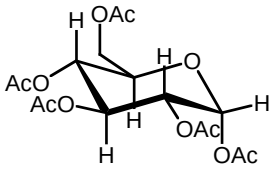
1. spiroketal and oxahydrindene
2. C_2 pre-formed
3. fragment coupling (Julia, 10-11)
   C_{10} Sulfone / C_{11} Aldehyde (25%)
4. macrolactionization (Mukaiyama)
5. glycosidation ($AgClO_4$)

White Disconnections



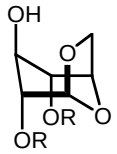
White: Spiroketal Precursor





glucose pentaacetate

Methods Carb. Chem **(1963)** II, 374



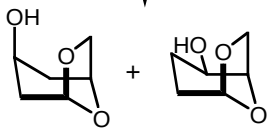
laevoglucosan

$LiBEt_3H$, 70%

R = H

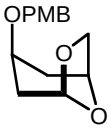
R = Ts

TsCl, pyr, 90%

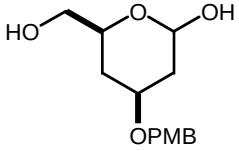


5:1

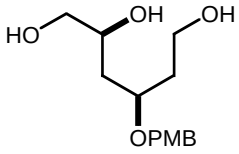
KH, PMBCl, 76%

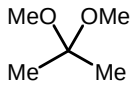


p-TsOH, 78%

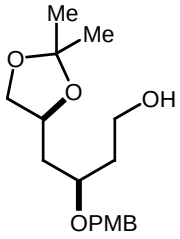


LAH, 94%

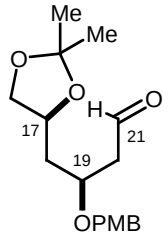




CSA, 60%



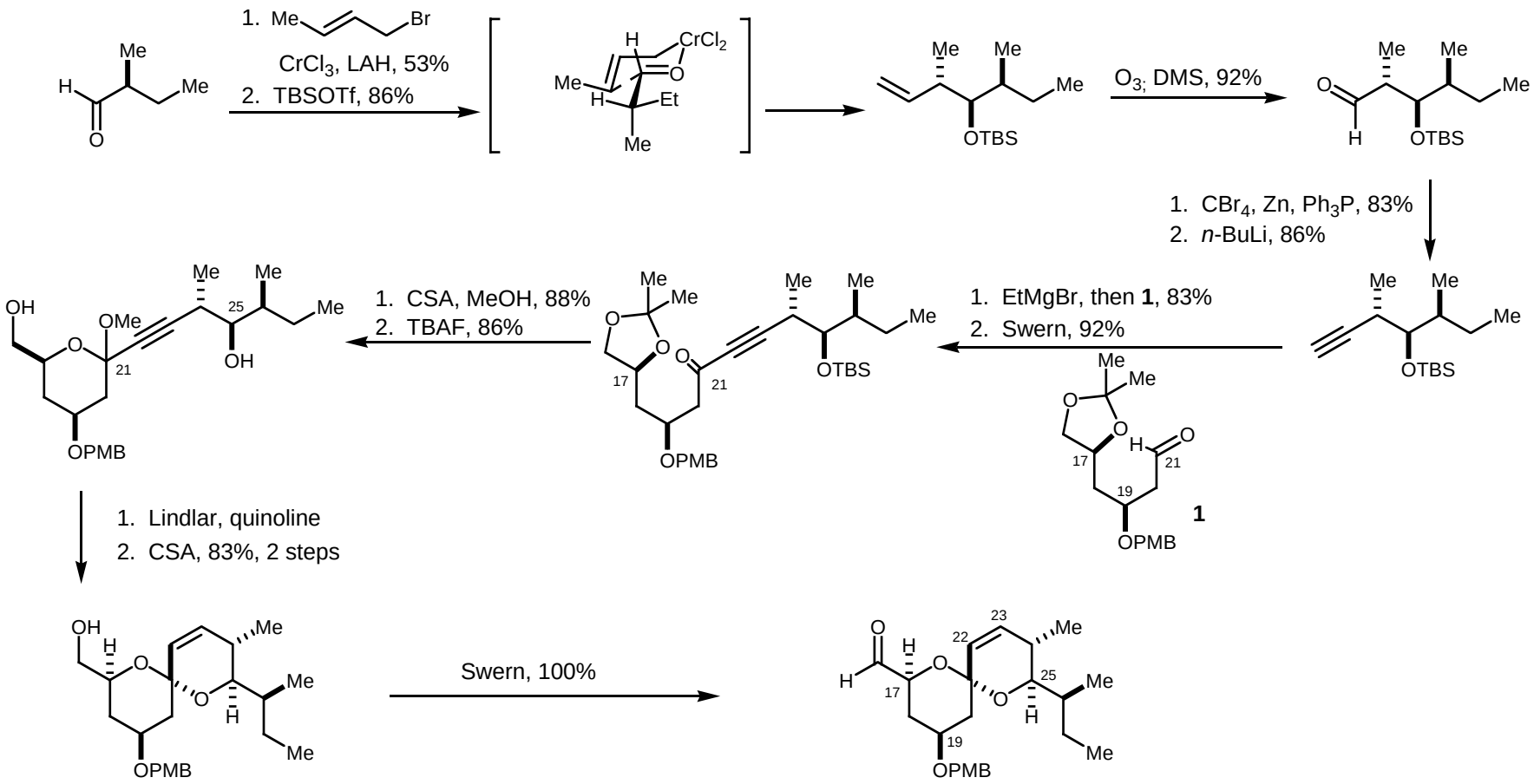
Swern, 92%



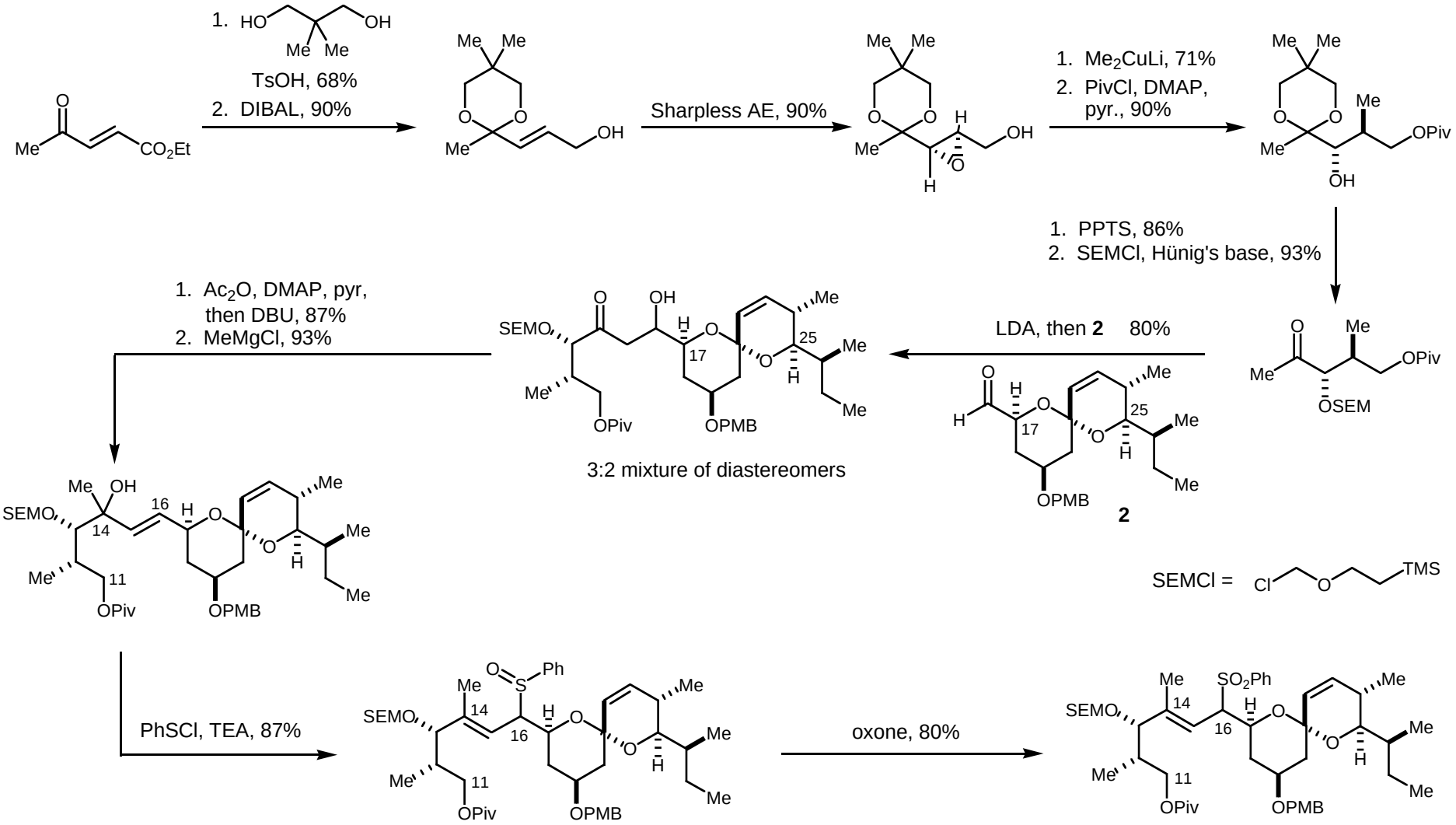
7 steps, 19% yield

JACS **1995**, *117*, 1908 (full paper)

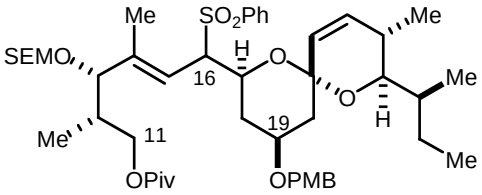
White: Spiroketalization



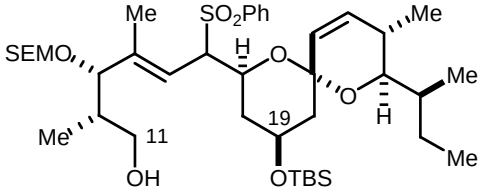
White: Sidechain Construction



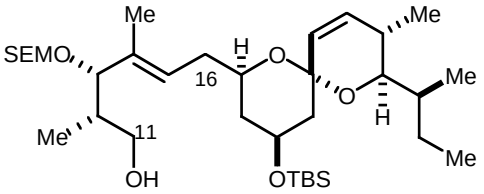
White: Sidechain Construction



1. CAN, 92%
2. TBSOTf, 2,6-lutidine, 75%
3. LAH, 77%

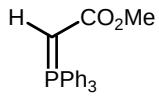


Na/Hg, Na_2HPO_4
MeOH, 35%



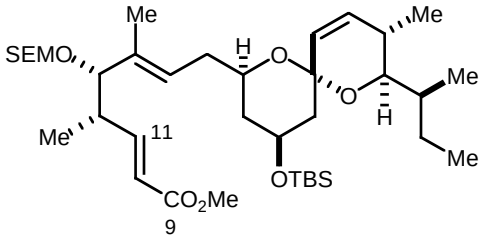
Low yield due to 1,4 elimination of -OSEM to form diene

convergent with degradation material

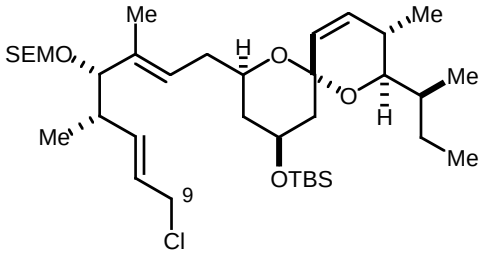
1. Swern, 90%
2. 

, 98%

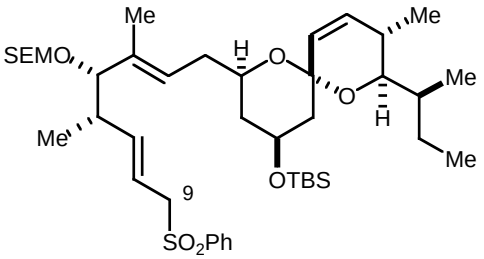
no E:Z given



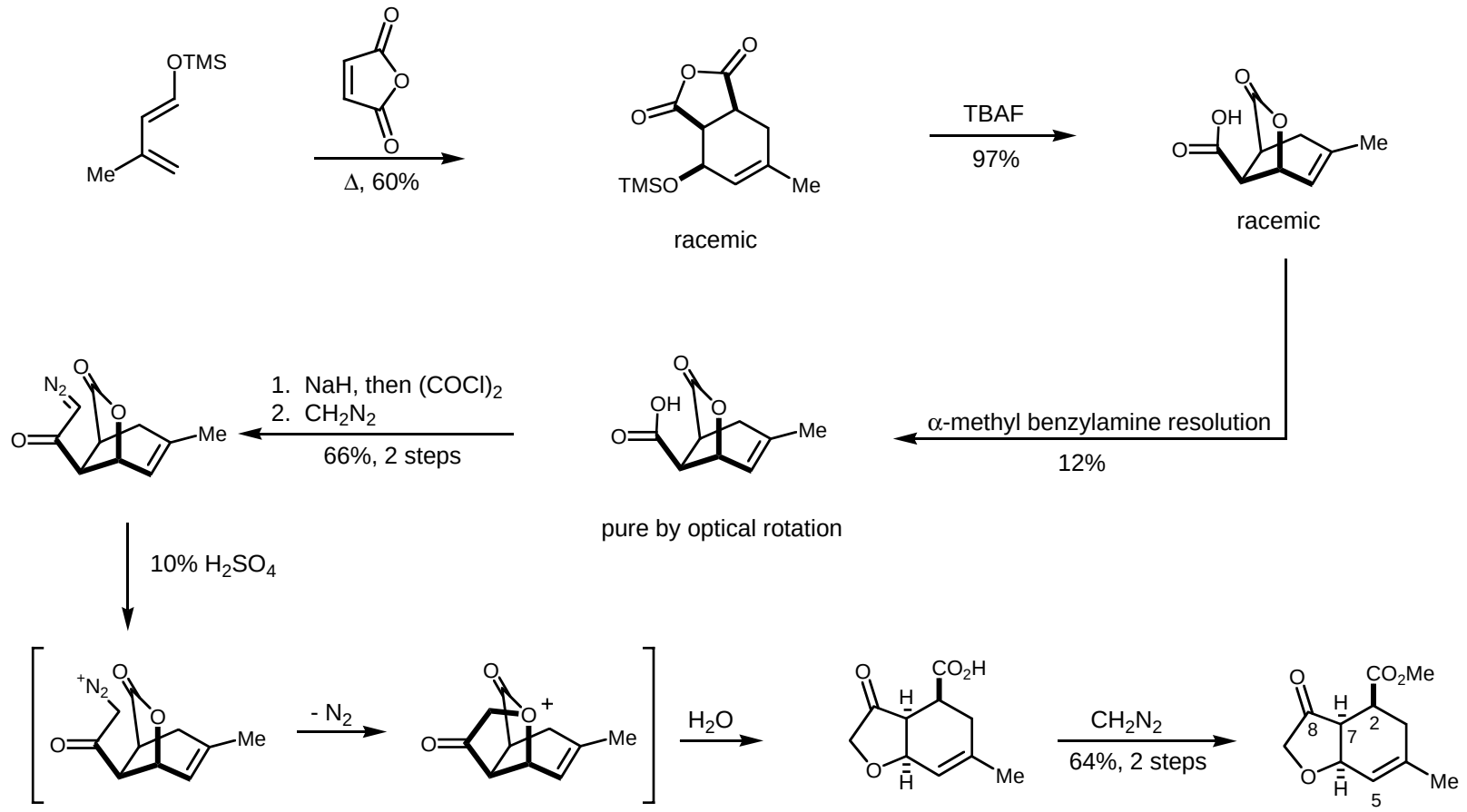
1. DIBAL, 94%
2. NCS, DMS, 93%



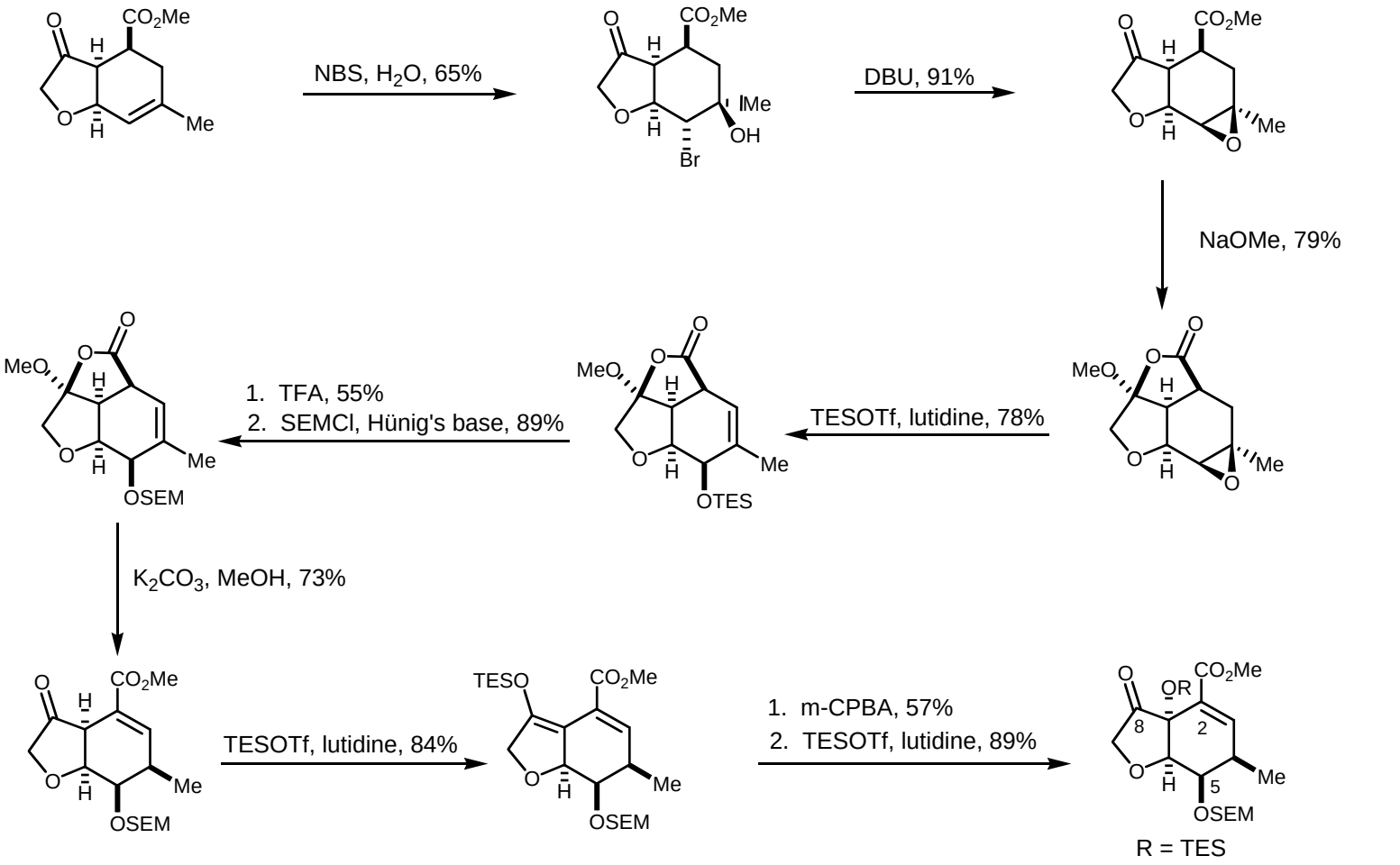
$PhSO_2Na$, 84%



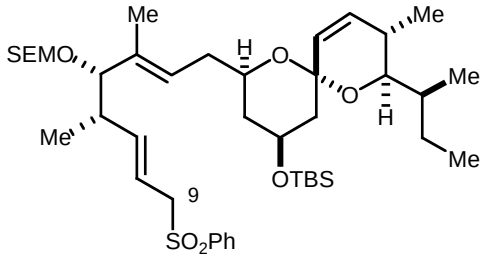
White: Oxahydrindene Synthesis



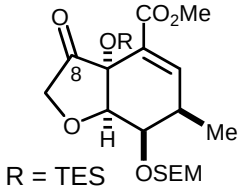
White: Oxahydrindene Synthesis



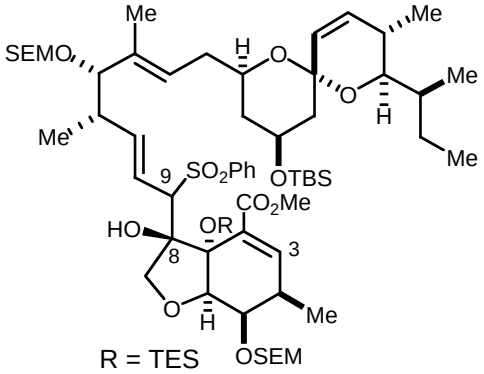
White: Fragment Coupling



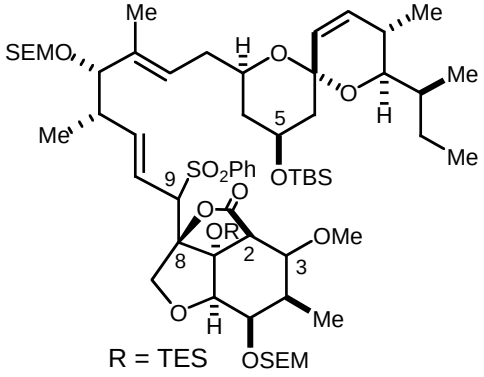
n-BuLi, then **3**, 51%



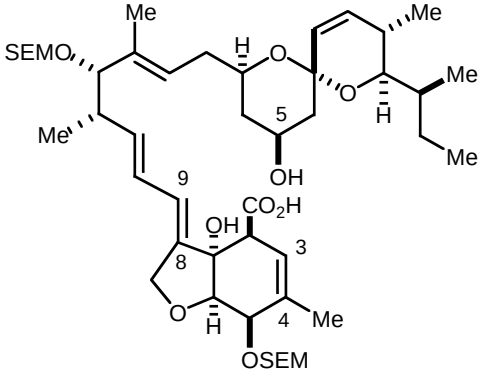
3



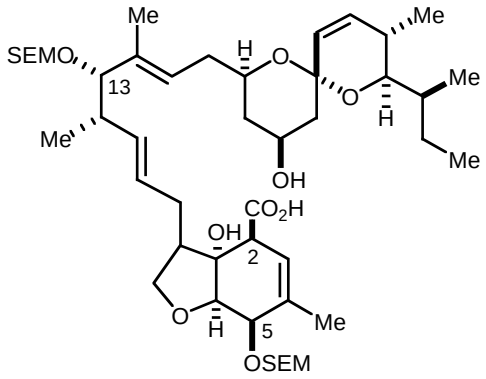
NaOMe, Na_2HPO_4, 42%

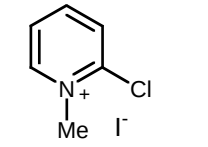


1. Na/Hg, Na_2HPO_4, MeOH, 71%
2. TBAF, 100%

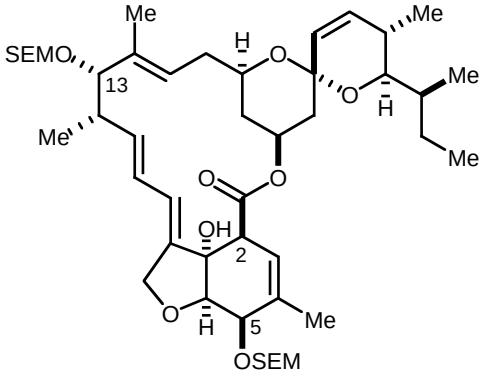


White: Macrocyclization and Glycosylation

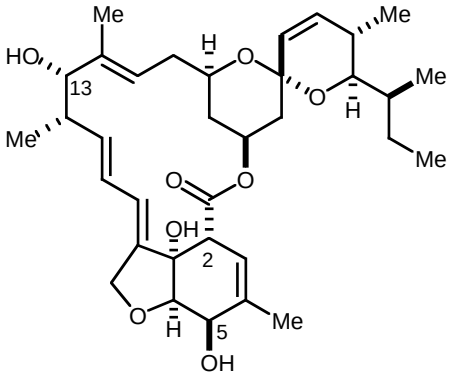




48%

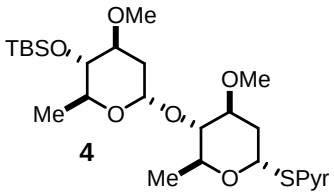


1. imidazole, benzene, Δ
   33% starting material
   46 % desired epimer
   15% 2,3 conjugated
   ] inseparable
2. HF, MeCN, 79%



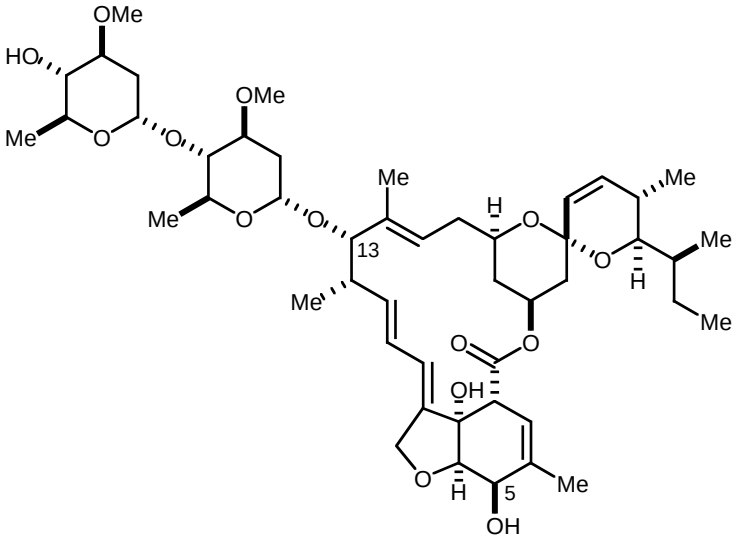
• alcohols are seperable

1. TBSCl, imidazole, 70%
2. AgOTf, **4**, mol. sieves, 35%
3. HF•pyr, 64%



4

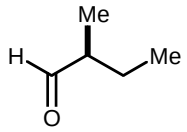
from Hanessian degradation
TL **(1986)** 2699



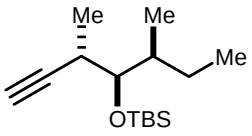
Avermectin B1a

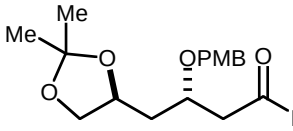
36 linear steps, 0.003% yield

White: Route Summary



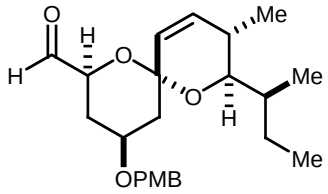
5 steps
30%





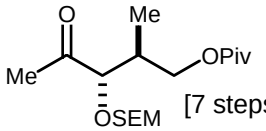
[7 steps, 19%]

7 steps (acetylene)
48%

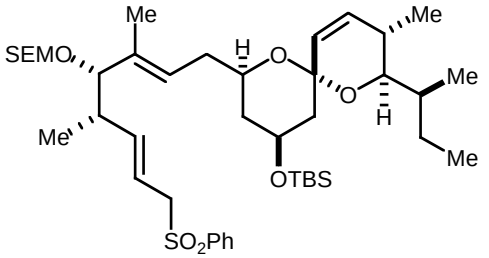


12 linear steps, 14% yield

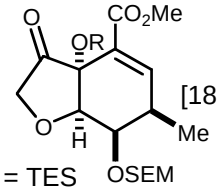
14 steps (aldol)
5%



[7 steps, 28%]



26 linear steps, 0.8% yield

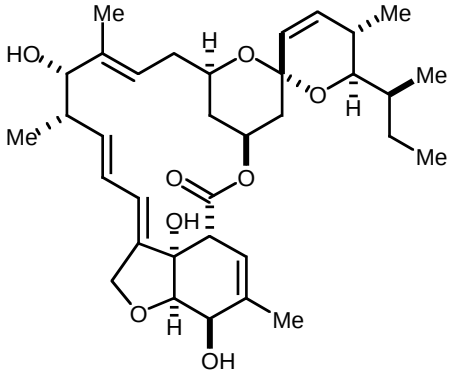


[18 steps, 0.02%]

R = TES

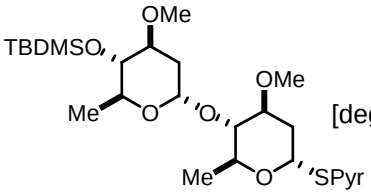
8 steps (Julia)
2.6%

Macrolactonization: Mukaiyama



34 linear steps, 0.02% yield
(65 steps total)

2 steps (AgOTf)
15%



[degradation]

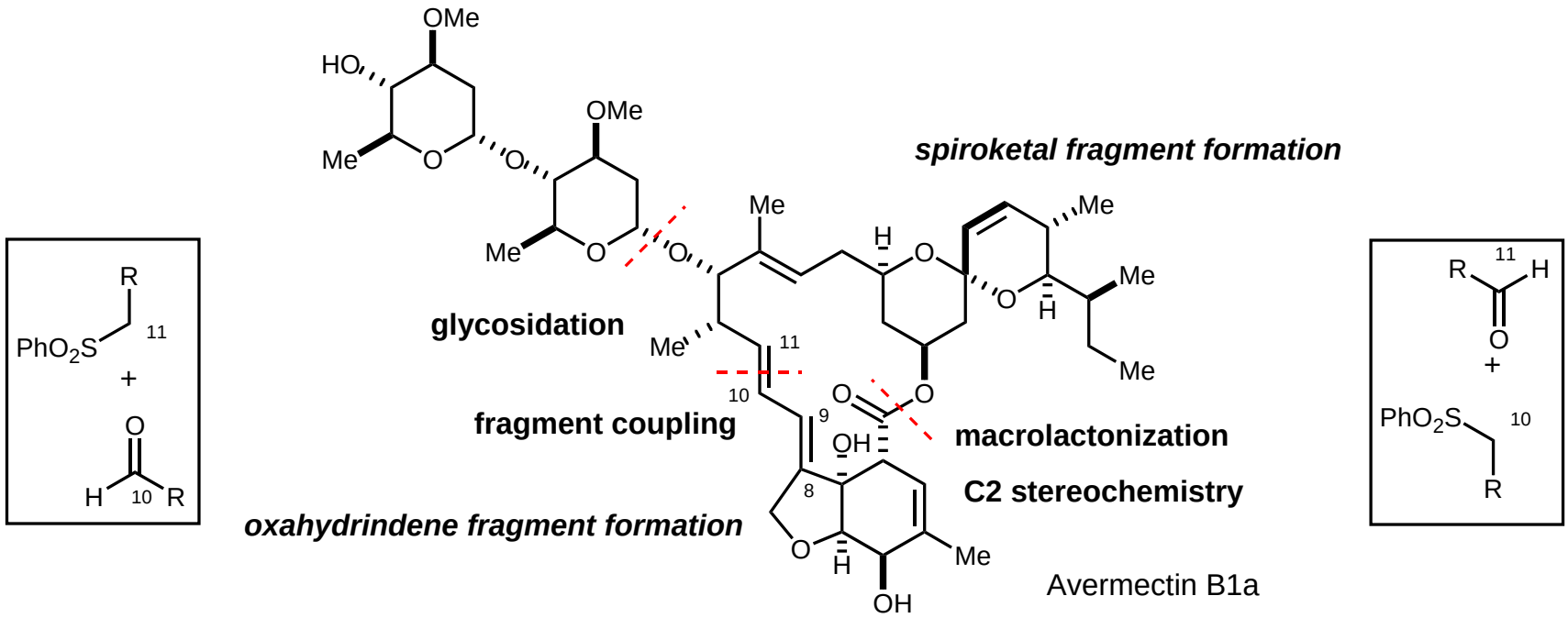
Avermectin B1a

36 linear steps, 0.003% yield

Synthetic Strategy

1. spiroketal and oxahydrindene
2. fragment coupling (Julia, 8-9)
   C_9 Sulfone / C_8 Ketone (15%)
3. macrolactonization (Mukaiyama)
4. C_2 epimerization
5. glycosidation ($AgClO_4$)

Synthetic Strategies



Hanessian Synthetic Strategy

1. spiroketal and oxahydrindene
2. fragment coupling (Julia, 10-11)
   C_{10} Aldehyde / C_{11} Sulfone (65%)
3. macrolactonization (DCC, DMAP)
4. glycosidation ($AgClO_4$)
5. C_2 isomerization

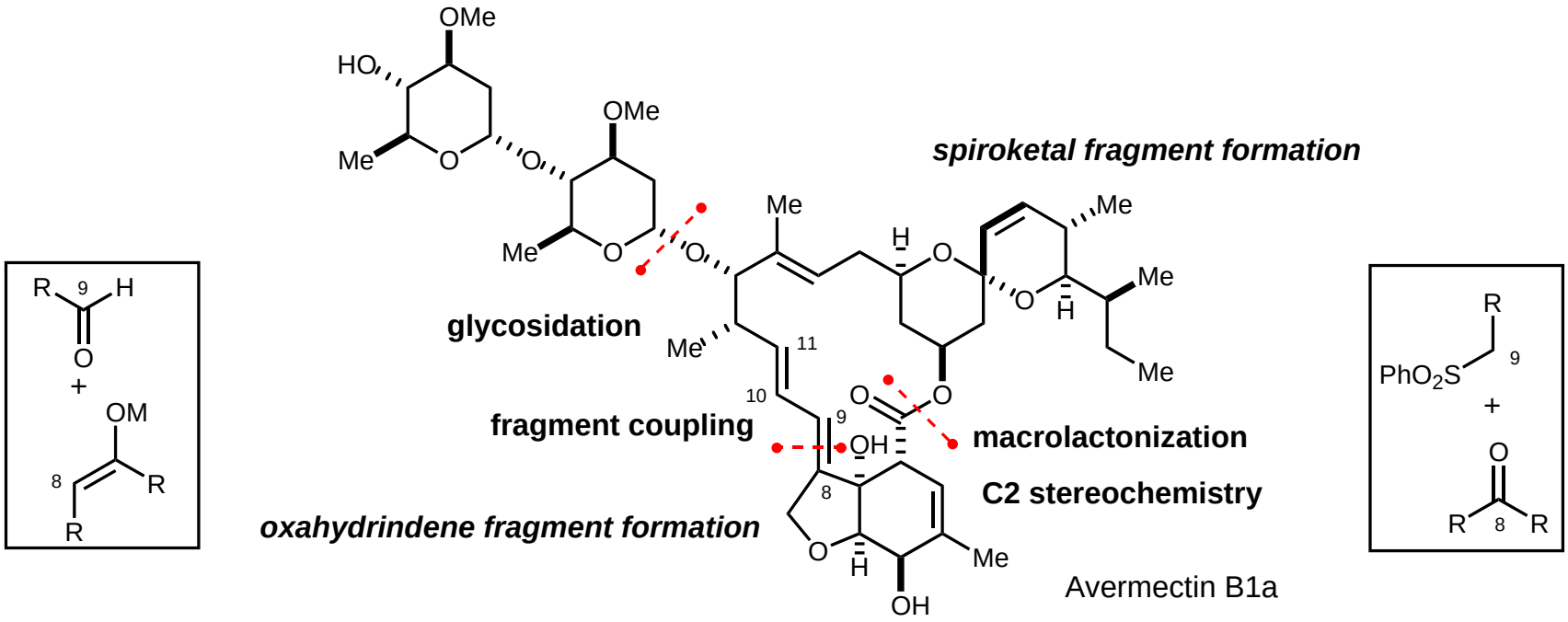
37 linear steps, 0.08% yield

Ley Synthetic Strategy

1. spiroketal and oxahydrindene
2. C_2 pre-formed
3. fragment coupling (Julia, 10-11)
   C_{10} Sulfone / C_{11} Aldehyde (25%)
4. macrolactionization (Mukaiyama)
5. glycosidation ($AgClO_4$)

27 linear steps, 0.01% yield

Synthetic Strategies



Danishefsky Synthetic Strategy

1. spiroketal
2. fragment coupling (aldol, 8-9)
   C_8 enol / C_9 aldehyde (67%)
3. oxahydrindene (Nozaki)
4. macrolactonization (Mukaiyama)
5. C_2 isomerization
6. glycosidation (NIS)

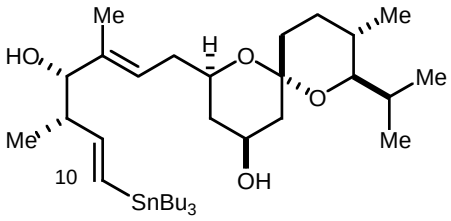
38 linear steps, 0.03% yield
Danishefsky: Avermectin A1a

White Synthetic Strategy

1. spiroketal and oxahydrindene
2. fragment coupling (Julia, 8-9)
   C_8 Ketone / C_9 Sulfone (15%)
3. macrolactonization (Mukaiyama)
4. C_2 epimerization
5. glycosidation ($AgClO_4$)

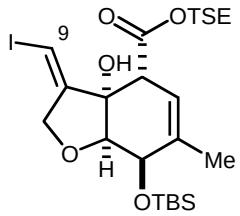
36 linear steps, 0.003% yield

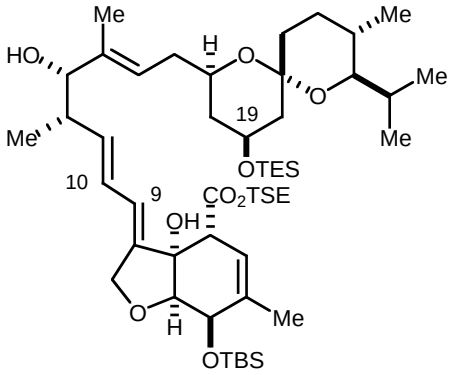
Julia: Ivermectin Aglycone



E/Z = 85:15

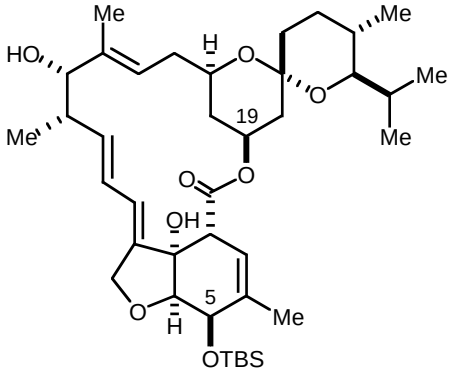
0.2 eq. $PdCl_2(ACN)_2$



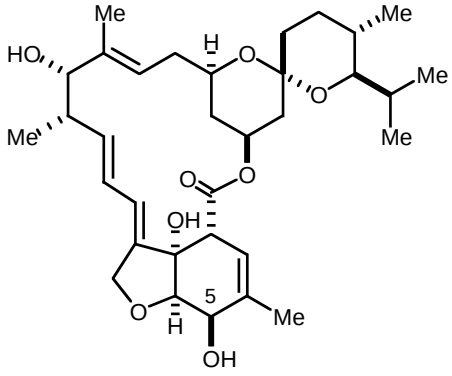


38% desired E/E

1. TBAF, *p*-TsOH
2. TEA, DMAP,
   trichlorobenzoylchloride, 30%, 2 steps



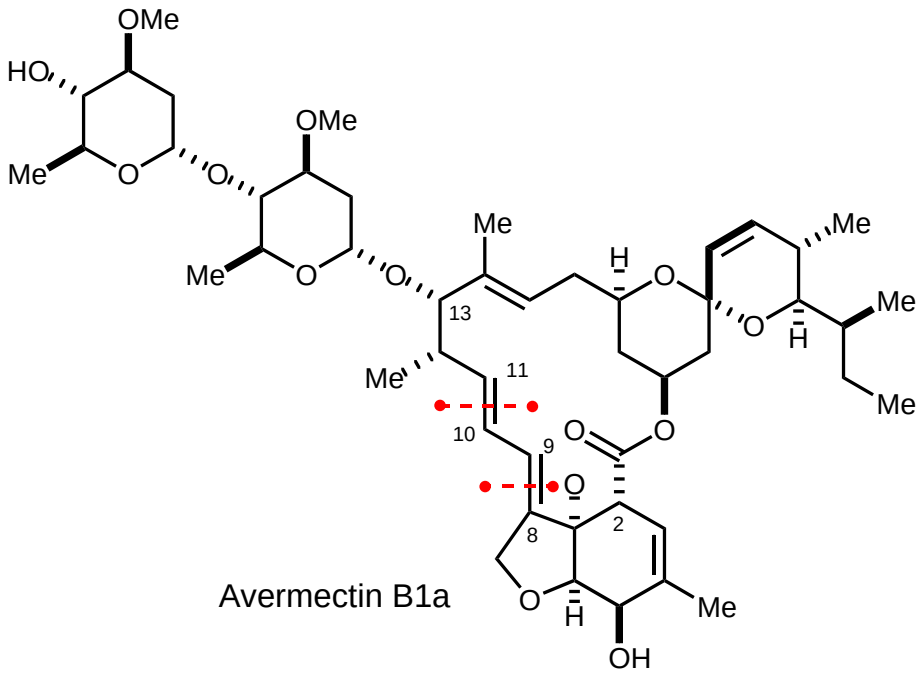
p-TsOH, 58%



Ivermectin Aglycone

Synlett **1991**, 614 (communication)
Bull. Soc. Chim. Fr. **1994**, *131*, 865 (full paper)
Bull. Soc. Chim. Fr. **1995**, *132*, 428 (full paper)

Parting Notes



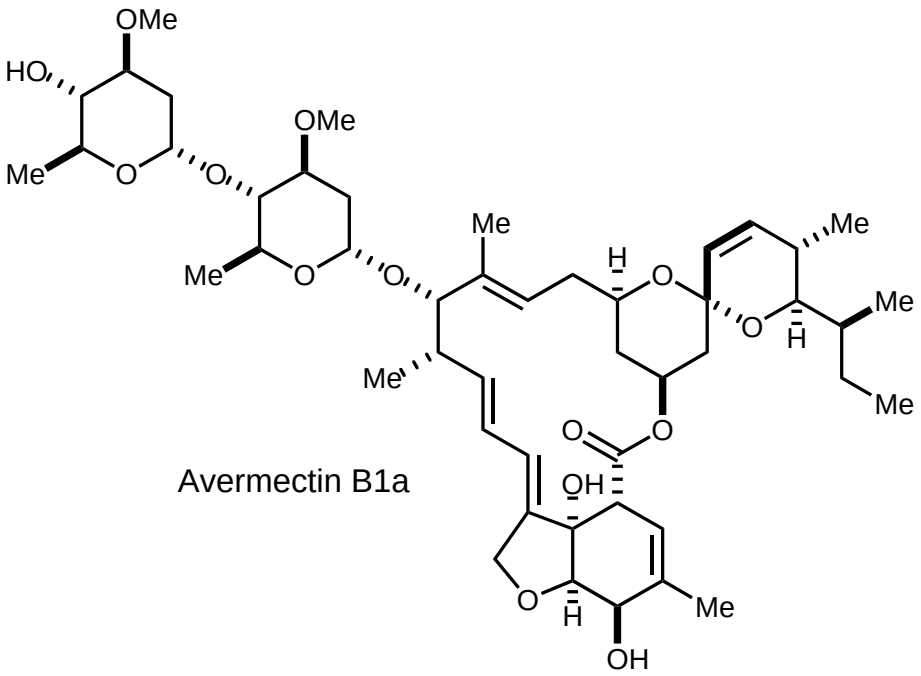
Avermectin B1a

- fragment coupling
- C_2 stereochemistry
- macrolactonization
- glycosidation

Yield of Glycosylated Avermectin from Fragment Coupling Step

Hanessian:	5.6%
Danishefsky:	1.8%
White:	0.39%
Ley:	0.15%

Parting Notes



Avermectin B1a

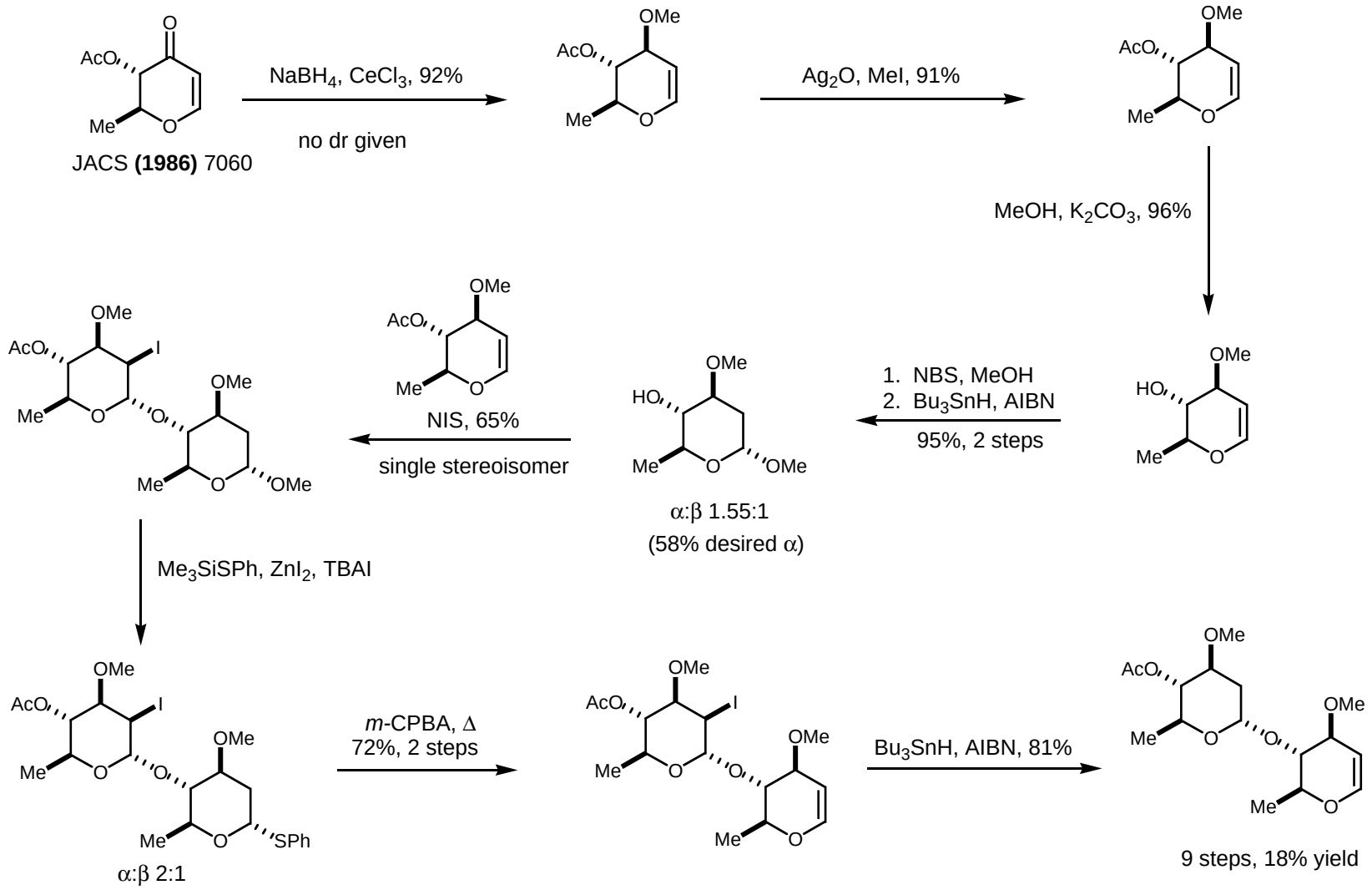
" The present syntheses detailed in this review are outstanding examples of the synthetic art but there may will be shorter, more efficient, methods to the natural avermectins and milbemycins which can be devised in the future."

Davies, Green; *Chem. Soc. Rev.* **(1991)** p. 339

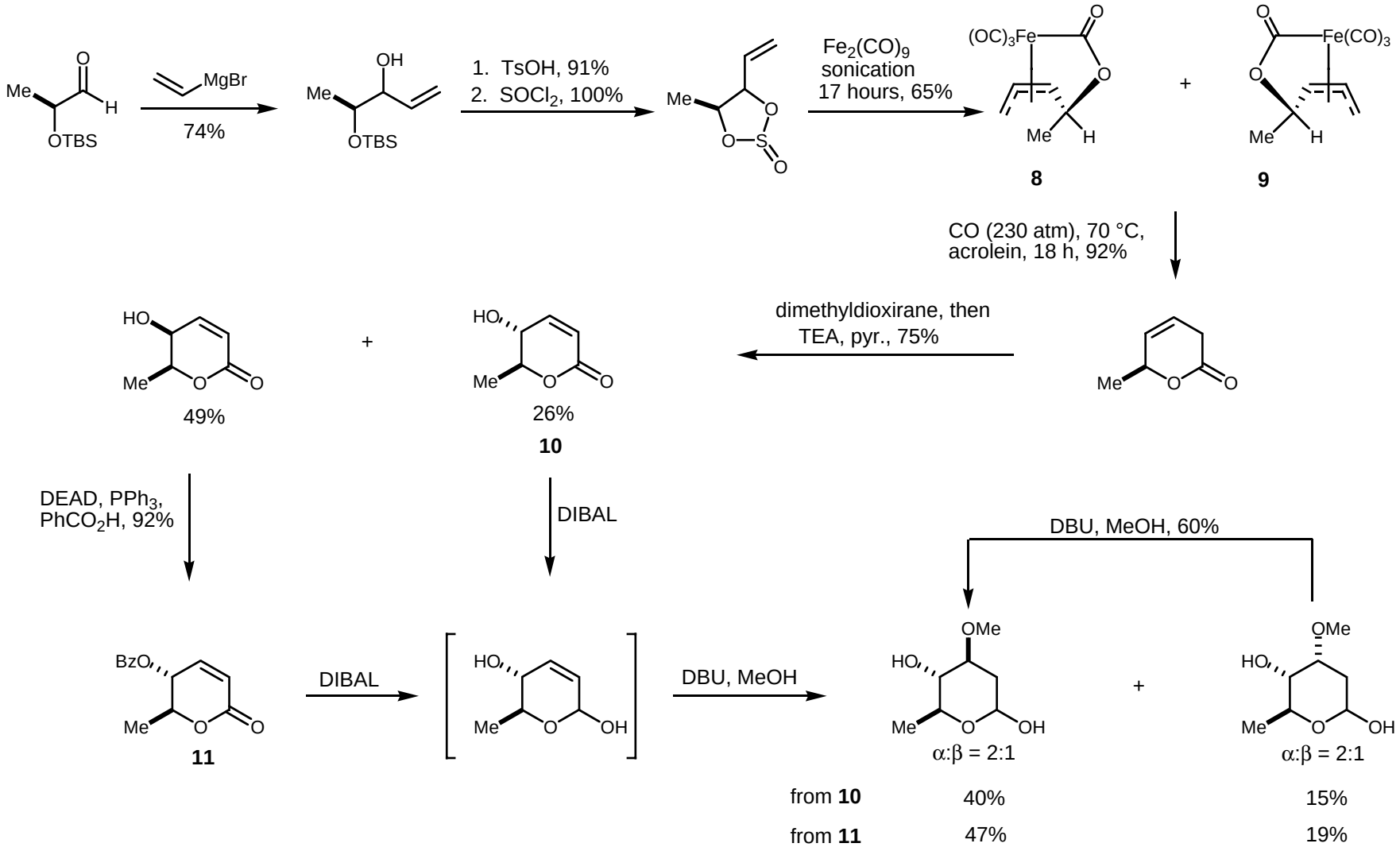
37 linear steps, 0.08% yield
27 linear steps, 0.01% yield
38 linear steps, 0.03% yield
36 linear steps, 0.003% yield

FIN

Danishefsky: Glycoside Formation



Ley: Glycoside Construction



Ley: Glycoside Construction