Journal Years in Review: J. Am. Chem. Soc. 1996

Gaich-Group Seminar

Erik Stempel

09.12.2013

JACS

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Introduction / Analysis

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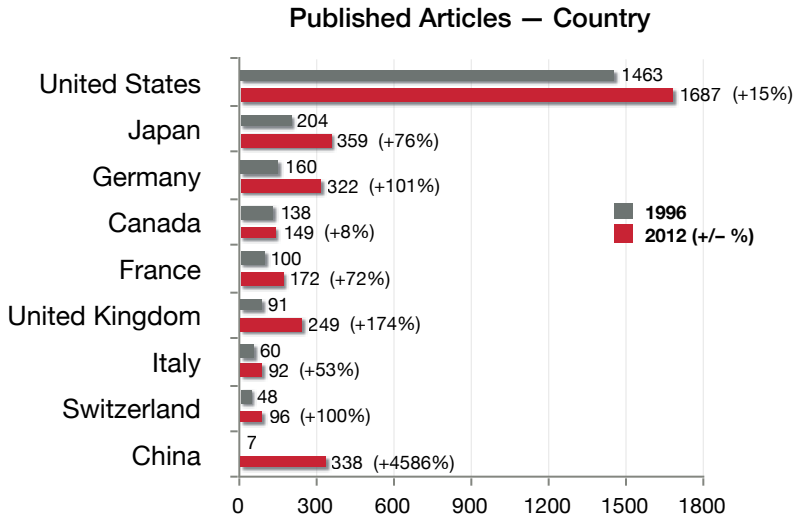
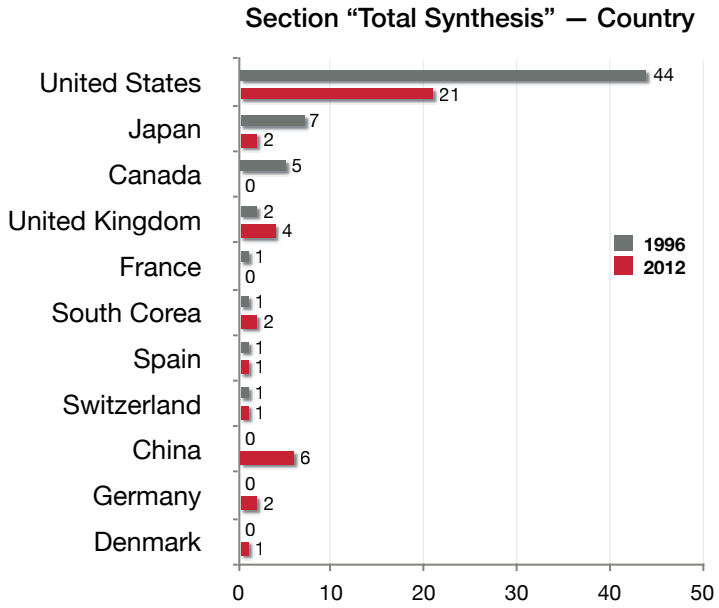
- JACS facts 1996 (2012 in parentheses):
  - Impact Factor: 5.948 (10.677, +80%)
  - 13 118 pages (20 858, +59%)
  - 2 236 published articles (3 170, +42%)
  - 52 “Total Syntheses” as topic (34, –35%)

- Most prolific authors of 1996:
  - P. v. R. Schleyer (11)
  - R. G. Bergman (11)
  - P. G. Schultz (9)
  - K. N. Houk (9)
  - S. L. Buchwald (9)
  - E. J. Corey (9)
  - B. M. Trost (9)
  - P. Beak (8)
  - B. M. Hoffman (8)
  - L. A. Paquette (8)





- Scopus / SciFinder

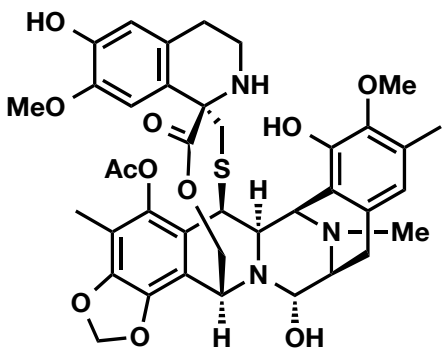
Introduction / Analysis (II)

- Most cited papers (general):
  - *Development and testing of the OPLS all-atom force field on conformational energetics and properties of organic liquids* (W. L. Jorgensen, pp. 11225-11236)
    - Number of citations: 3321
  - *Nucleus-independent chemical shifts: A simple and efficient aromaticity probe* (P. v. R. Schleyer, pp. 6317-6318)
    - Number of citations: 2423
  - *Synthesis and applications of $RuCl_2(=CHR')(PR_3)_2$: The influence of the alkylidene moiety on metathesis activity* (R. H. Grubbs, pp. 100-108)
    - Number of citations: 1609

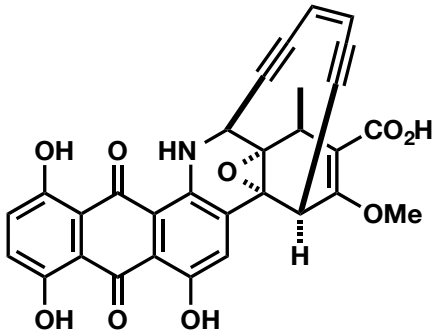
- Most cited papers (section „Total Synthesis“):
  - *Total synthesis of baccatin III and taxol* (S. J. Danishefsky, pp. 2843-2859)
    - Number of citations: 264
  - *Enantioselective total synthesis of ecteinascidin 743* (E. J. Corey, pp. 9202-9203)
    - Number of citations: 194
  - *Asymmetric total syntheses of pancratistatin and 7-deoxypancratistatin, promising antitumor agents* (T. Hudlicky, pp. 10752-10765)
    - Number of citations: 132

- Scopus / SciFinder

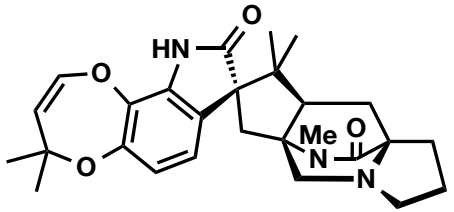
Selected Detailed Syntheses



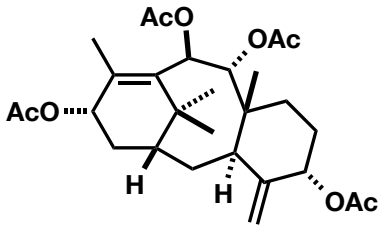
Ecteinascidin 743 (**38**)



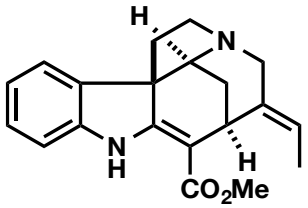
(±)-Dynemicin A (**72**)



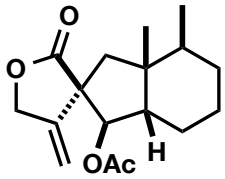
(+)-Paraherquamide B (**101**)



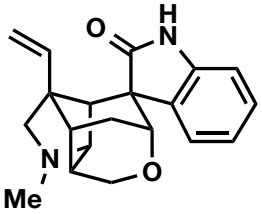
(±)-Taxusin (**117**)



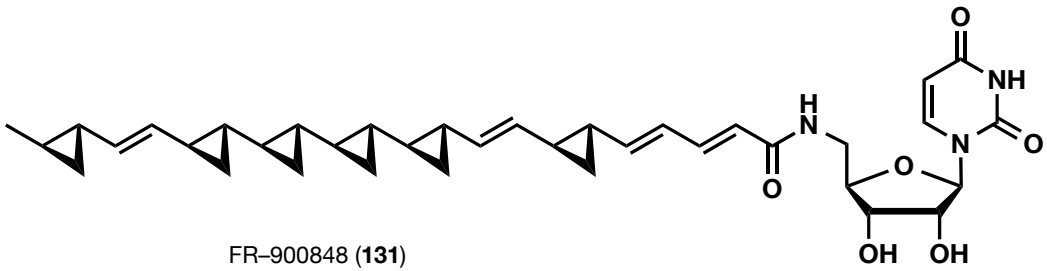
(±)-Akuammicine (**84**)



(±)-9-Acetoxyfukinanolide (**46**)

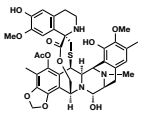


(±)-Gelsemine (**130**)



FR–900848 (**131**)

Ecteinascidin 743 — Corey (I)



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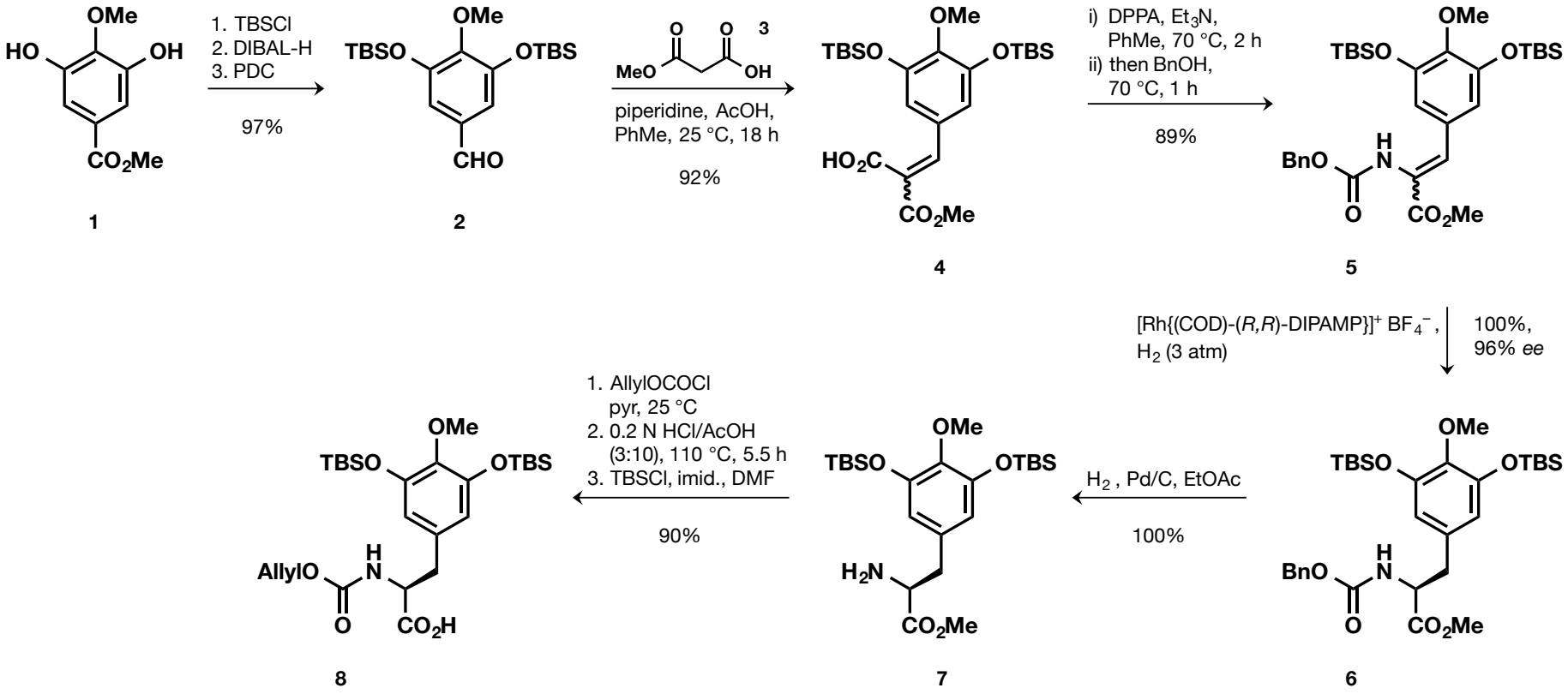
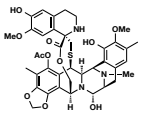


- E. J. Corey, *J. Am. Chem. Soc.* **1996,** *118*, 9202–9203.
- K. C. Nicolau, S. A. Snyder, *Classics in Total Synthesis II,* Wiley-VCH, **2003**.

Ecteinascidin 743 — Corey (II)



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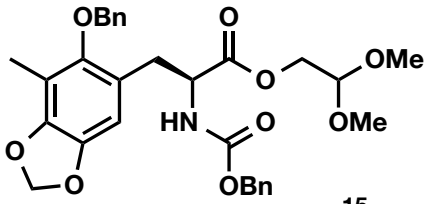
1. $BF_3 \cdot OEt_2$, H_2O, DCM
2. $BF_3 \cdot OEt_2$, DCM, 4 Å MS
3. H_2, Pd/C

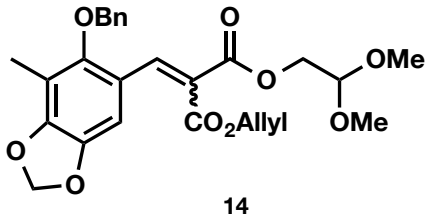
73%



15

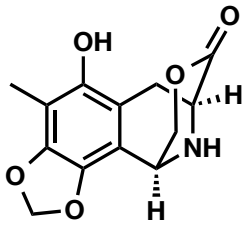
1. $Pd(PPh_3)_4$ (cat.), $Et_3N \cdot HCOOH$
   THF, 25 °C, 4 h
2. DPPA, Et_3N, PhMe, 70 °C, 4 h,
   then BnOH
3. $[Rh\{(COD)\text{-}(R,R)\text{-DIPAMP}\}]^+ BF_4^-$, H_2 (3 atm)

84%, 96% *ee*



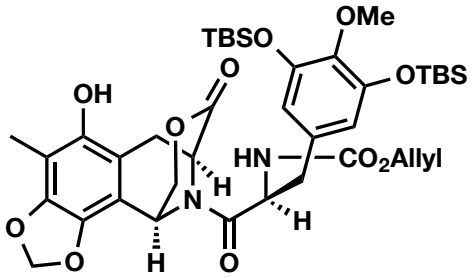
14

Intramolecular Pictet-Spengler



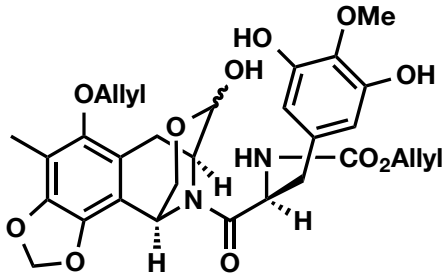
16

8 , CIP, HOAt, Et_3N,
0 °C → 25 °C, 6 h



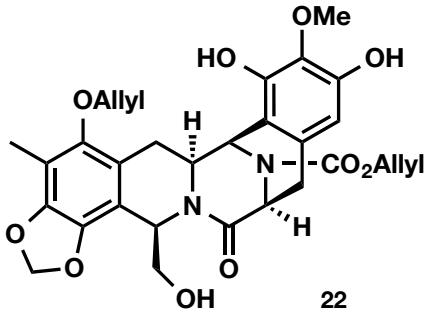
17

1. AllylBr, Cs_2CO_3 , DMF
2. $LiAlH_2(OEt)_2$, Et_2O, –78 °C
3. KF, MeOH



18

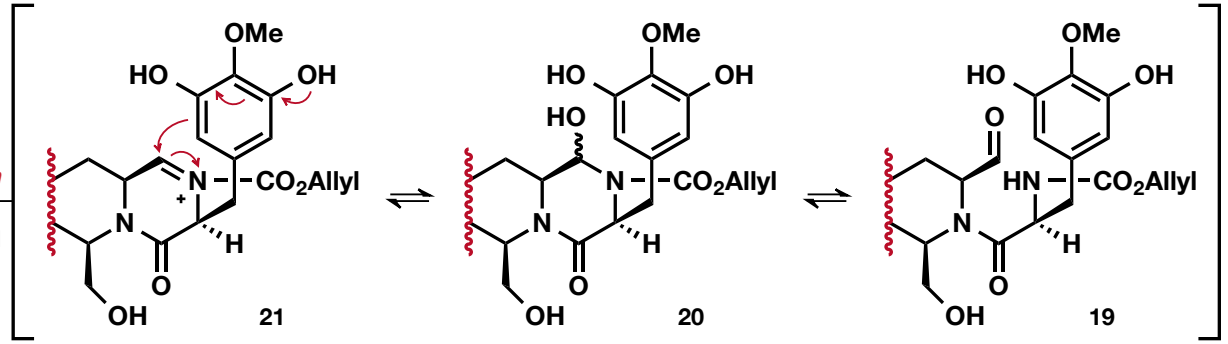
0.6 M TfOH, H_2O / CF_3CH_2OH (3:2),
BHT, 45 °C, 7 h



22

Mannich bisannulation

57 % overall
(5 steps)



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- E. J. Corey, *J. Am. Chem. Soc.* **1996,** *118*, 9202–9203.
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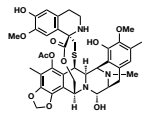
Ecteinascidin 743 — Corey (III)



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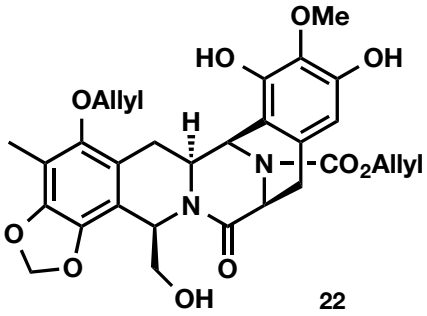
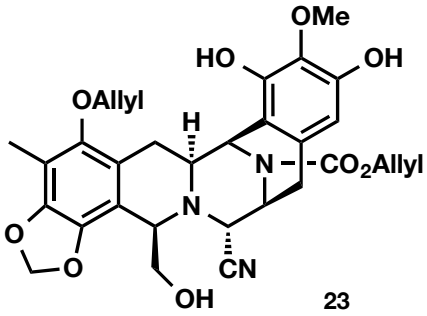


22

$LiAlH_2(OEt)_2$, THF, 0° C, 35 min, then AcOH, aq. KCN, 25 °C, 7 h

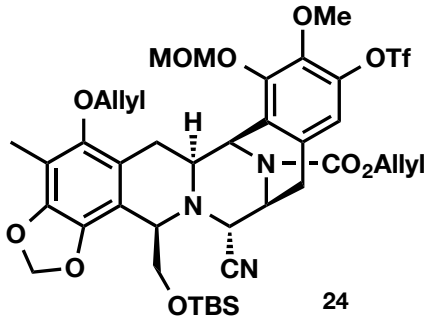
87%



23

1. Tf_2NPh, Et_3N, DMAP, DCM
2. TBSCl, imid., DMF then KF
3. MOMCl, $^iPr_2NEt$

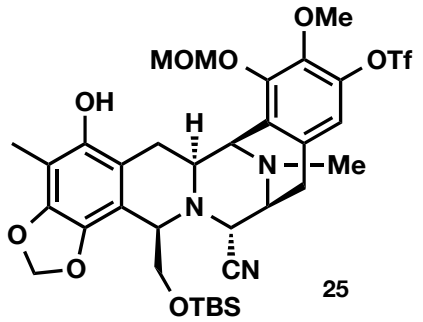
65%



24

95%

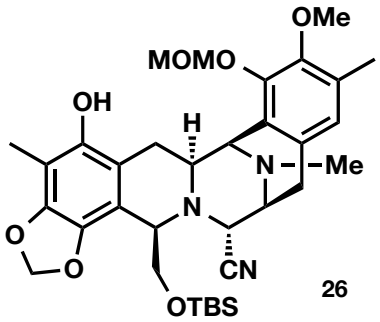
1. $^nBu_3SnH$, $PdCl_2(PPh_3)_2$, AcOH, DCM
2. CH_2O, $NaCNBH_3$, AcOH, MeCN



25

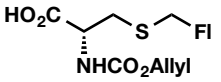
$PdCl_2(PPh_3)_2$ (cat.), LiCl, AcOH (cat.), Me_4Sn, NMP, 80 °C

94%

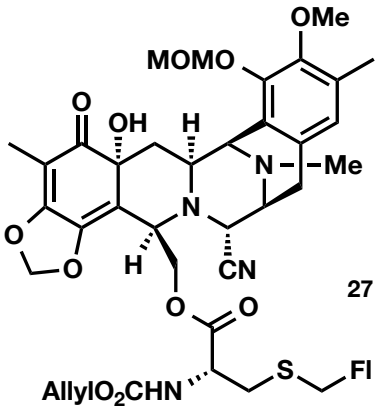


26

1. $(PhSeO)_2O$, DCM
2. TBAF
3. EDC, HOBt



78%



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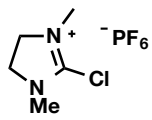
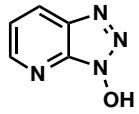
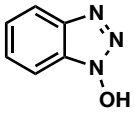


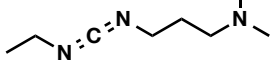
CIP



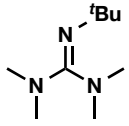
HOAt



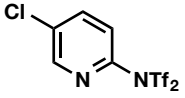
HOBt



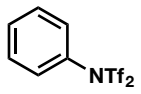
EDC



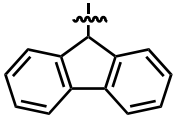
Barton's base



Comin's reagnet



McMurry–Hendrickson reagent



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- E. J. Corey, *J. Am. Chem. Soc.* **1996,** *118*, 9202–9203.
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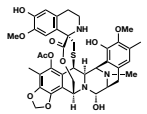
Ecteinascidin 743 — Corey (IV)



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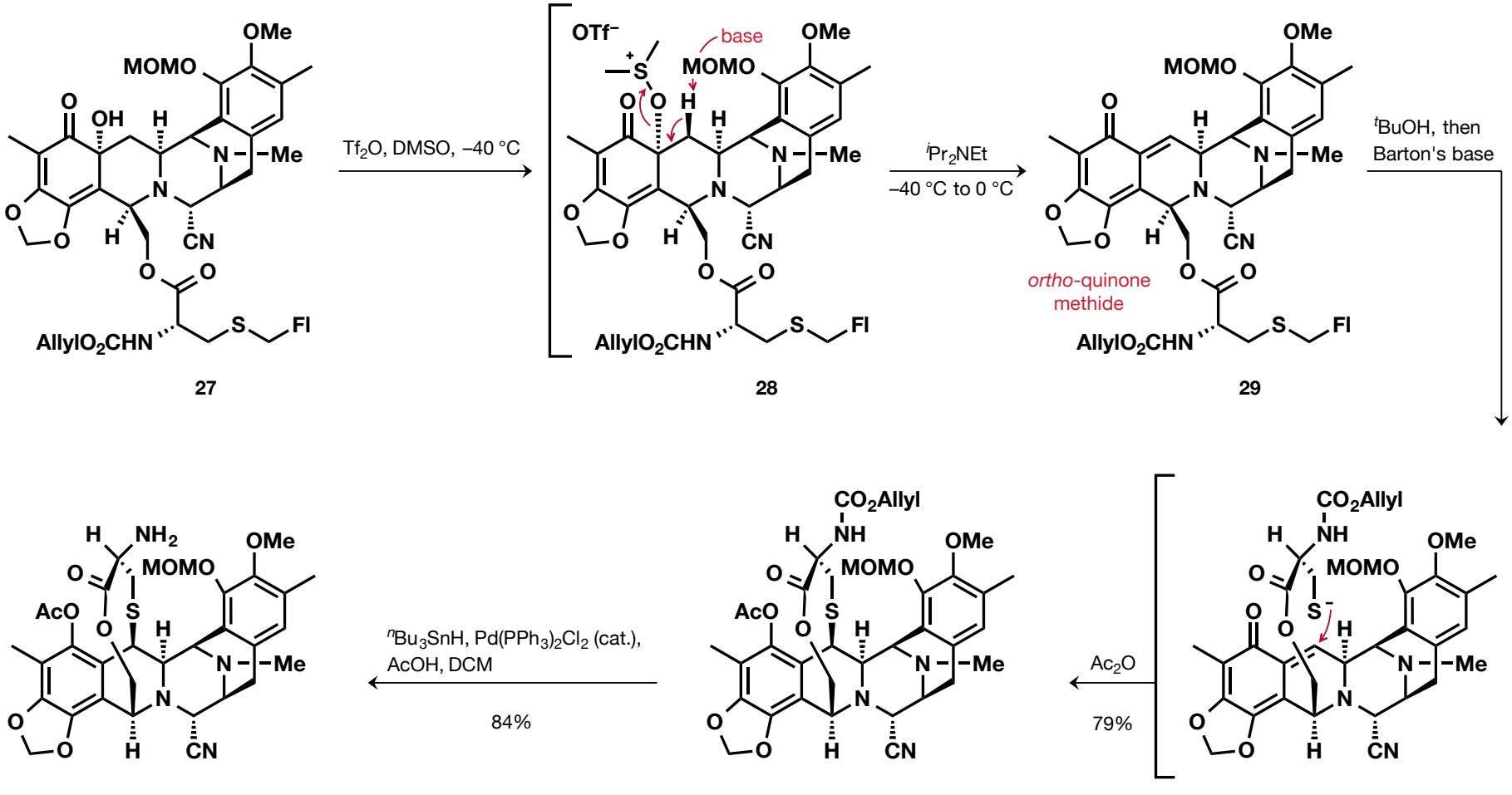

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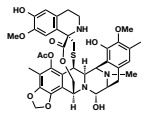
Ecteinascidin 743 — Corey (v)



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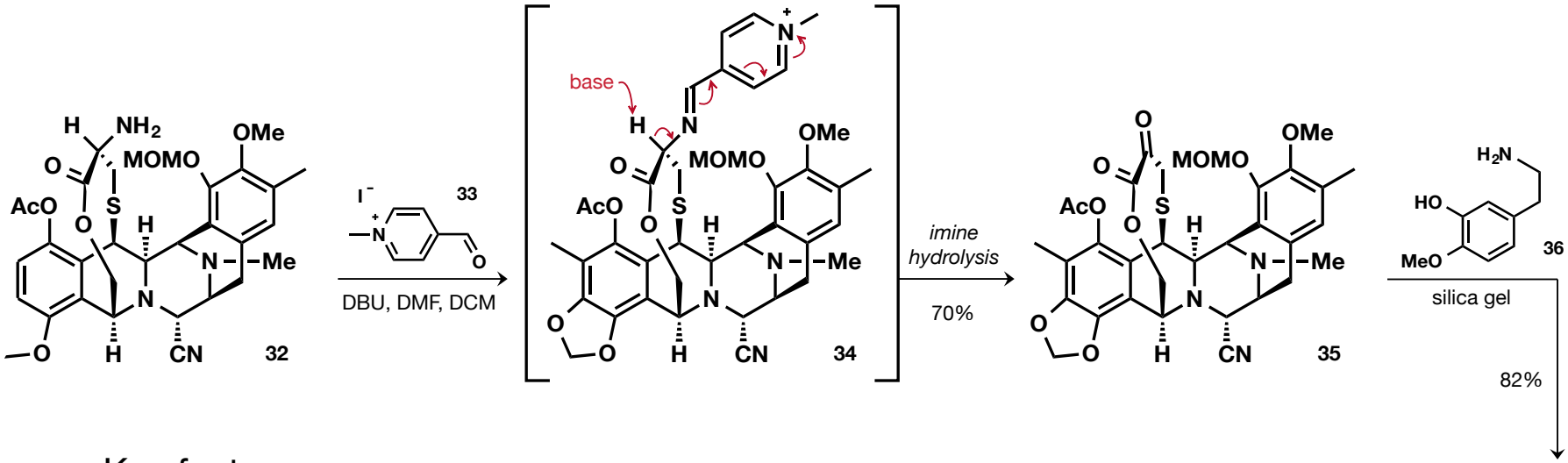
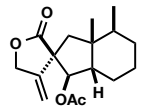


- Key features:
  - impressive cascade reactions to handle critical aspects of numerous synthetic problems
  - intramolecular Mannich bisannulation, two Pictet-Spengler reactions to stereoselectively create tetrahydroisoquinoline systems, and the *in situ* formation of quinone methide which sets the stage for intramolecular formation of 10-membered macrolactone (merely the noteworthy achievements)

- E. J. Corey, *J. Am. Chem. Soc.* **1996,** *118*, 9202–9203.
- K. C. Nicolau, S. A. Snyder, *Classics in Total Synthesis II,* Wiley-VCH, **2003**.

(±)-9-Acetoxyfukinanolide — Greene



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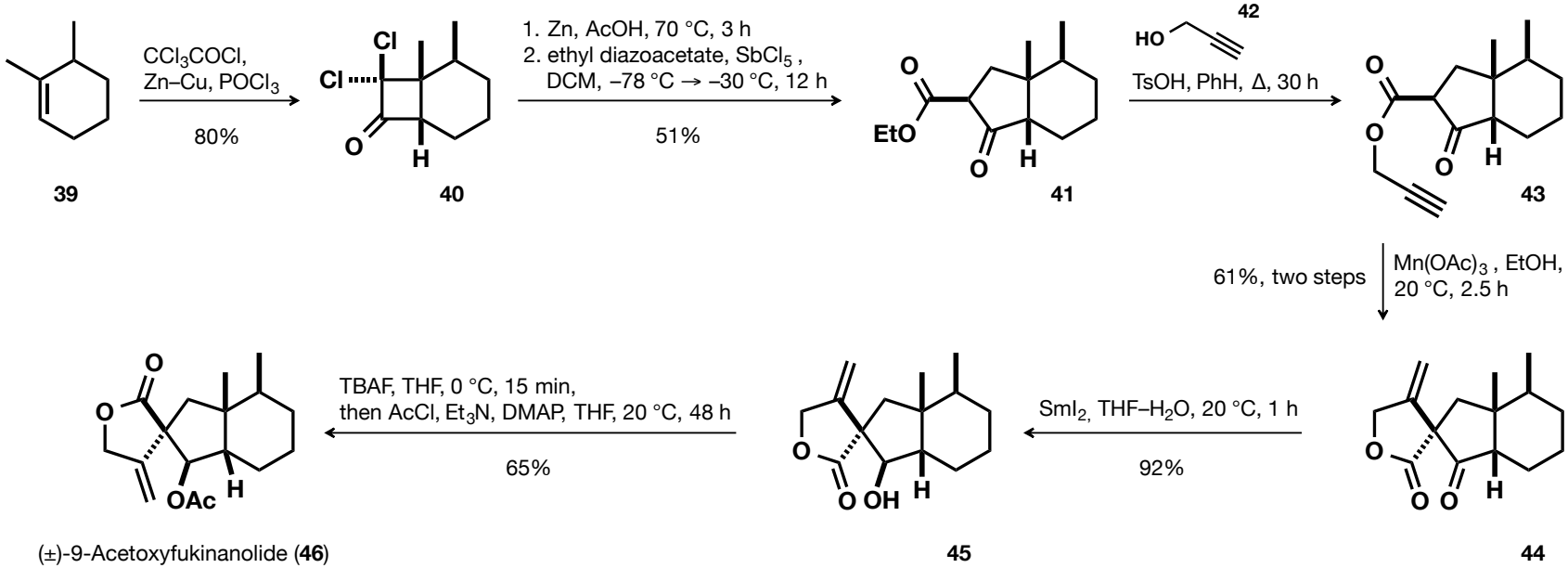
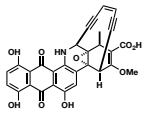


- Key features:
  - very concise synthesis, 15% overall yield
  - good transformations
  - Mn(III)-mediated radical 5-*exo*-*dig* ring closure
  - TBAF-mediated inversion of the C1 stereogenic center

▪ A. E. Greene, *J. Am. Chem. Soc.* **1996,** *118*, 9992–9993.

(±)-Dynemicin A — Danishefsky (I)



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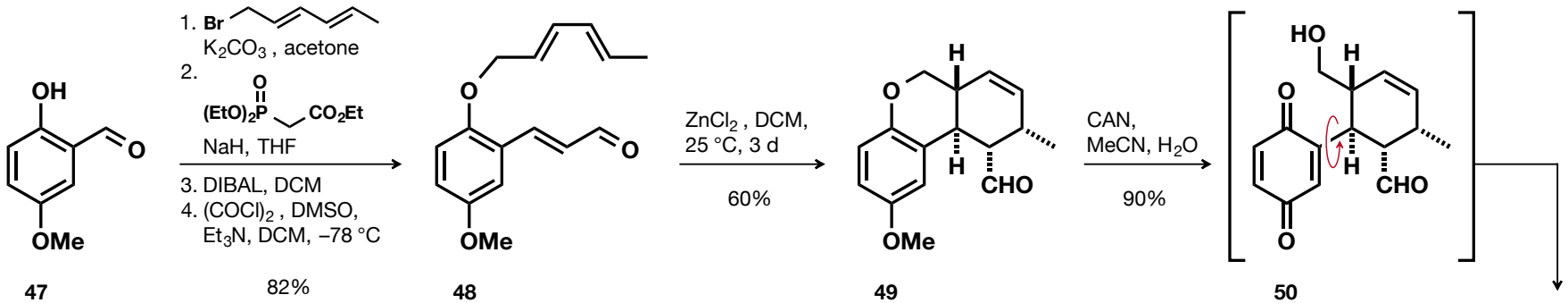
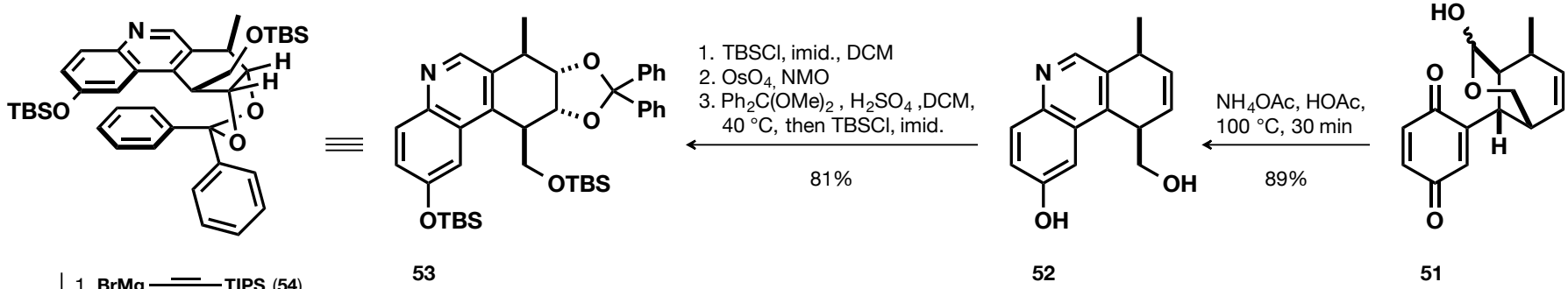
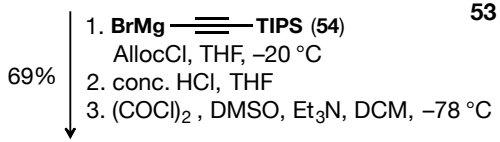
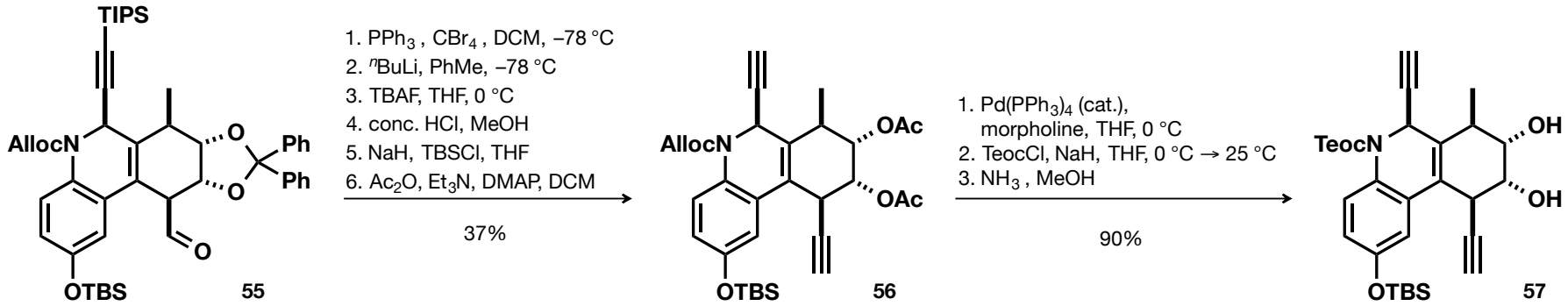


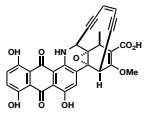






▪ S. J. Danishefsky, *J. Am. Chem. Soc.* **1996,** *118*, 9509–9525.

(±)-Dynemicin A — Danishefsky (II)



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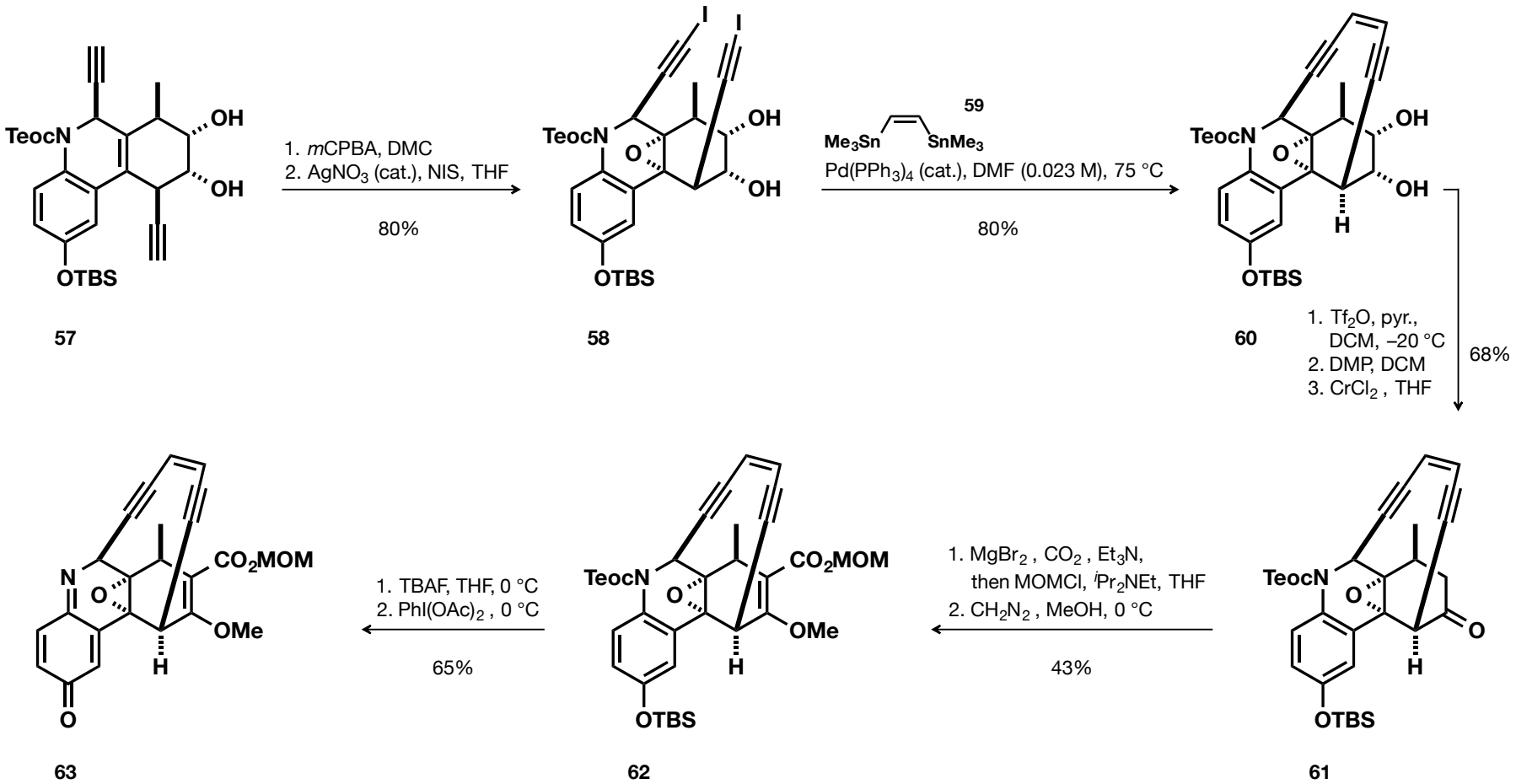
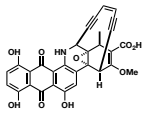


▪ S. J. Danishefsky, *J. Am. Chem. Soc.* **1996,** *118*, 9509–9525.

(±)-Dynemicin A — Danishefsky (III)



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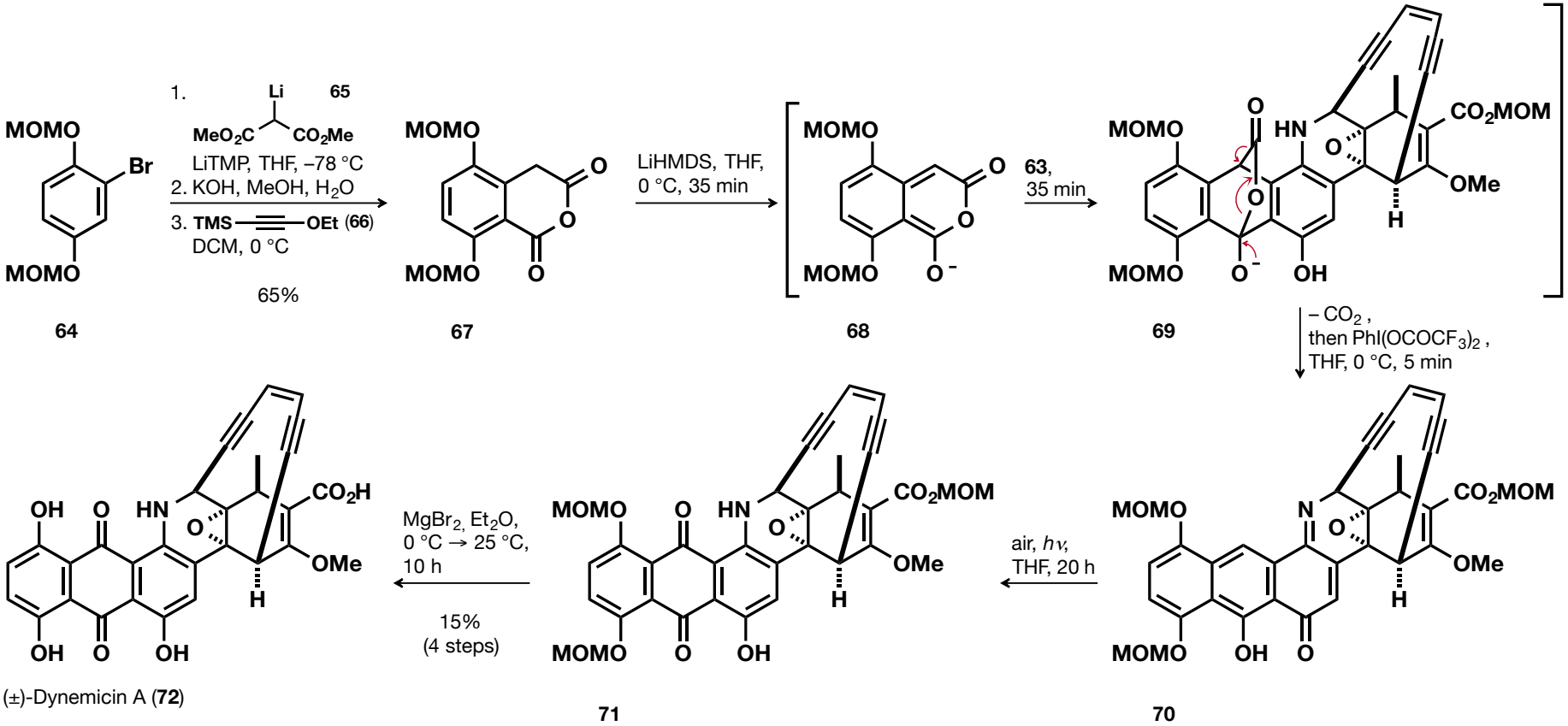
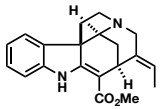


- Key features:
  - 35 steps, 0.13% overall yield
  - Yamaguchi alkynylation, Corey-Fuchs homologation, and double Stille reactions to complete ene-diyne system
  - Diels-Alder reaction of homophthalic anhydride enolate for anthraquinone ring system

- S. J. Danishefsky, *J. Am. Chem. Soc.* **1996,** *118*, 9509–9525.

(±)-Akuammicine — Martin



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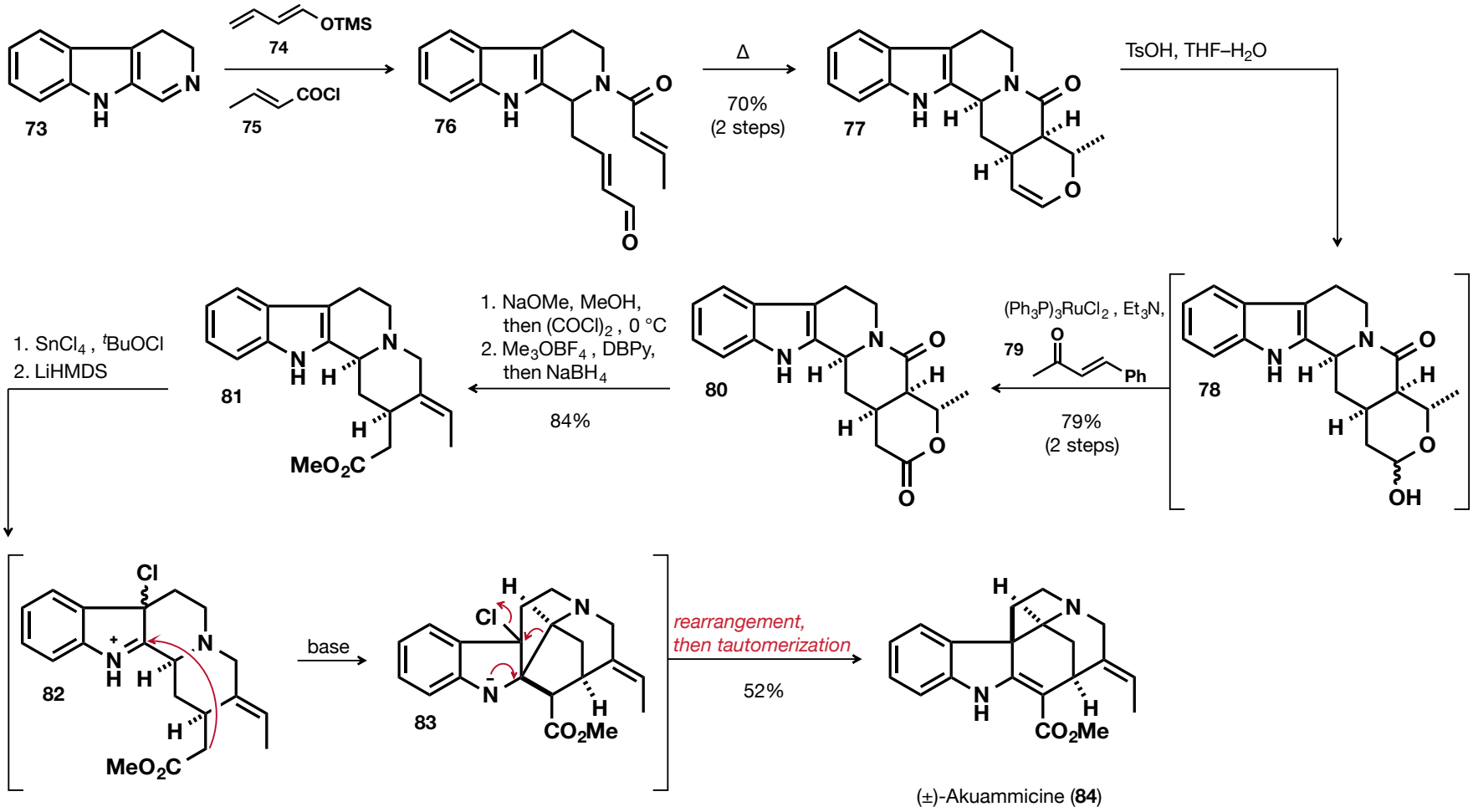
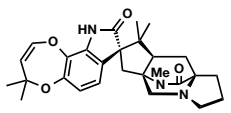


- Key features:
  - very concise synthesis, 10 steps from commercially available materials, 24% overall yield
  - vinylogous Mannich reaction, hetero Diels-Alder reaction

- S. F. Martin, *J. Am. Chem. Soc.* **1996,** *118*, 9804–9805.

(+)-Paraherquamide B — Williams (I)



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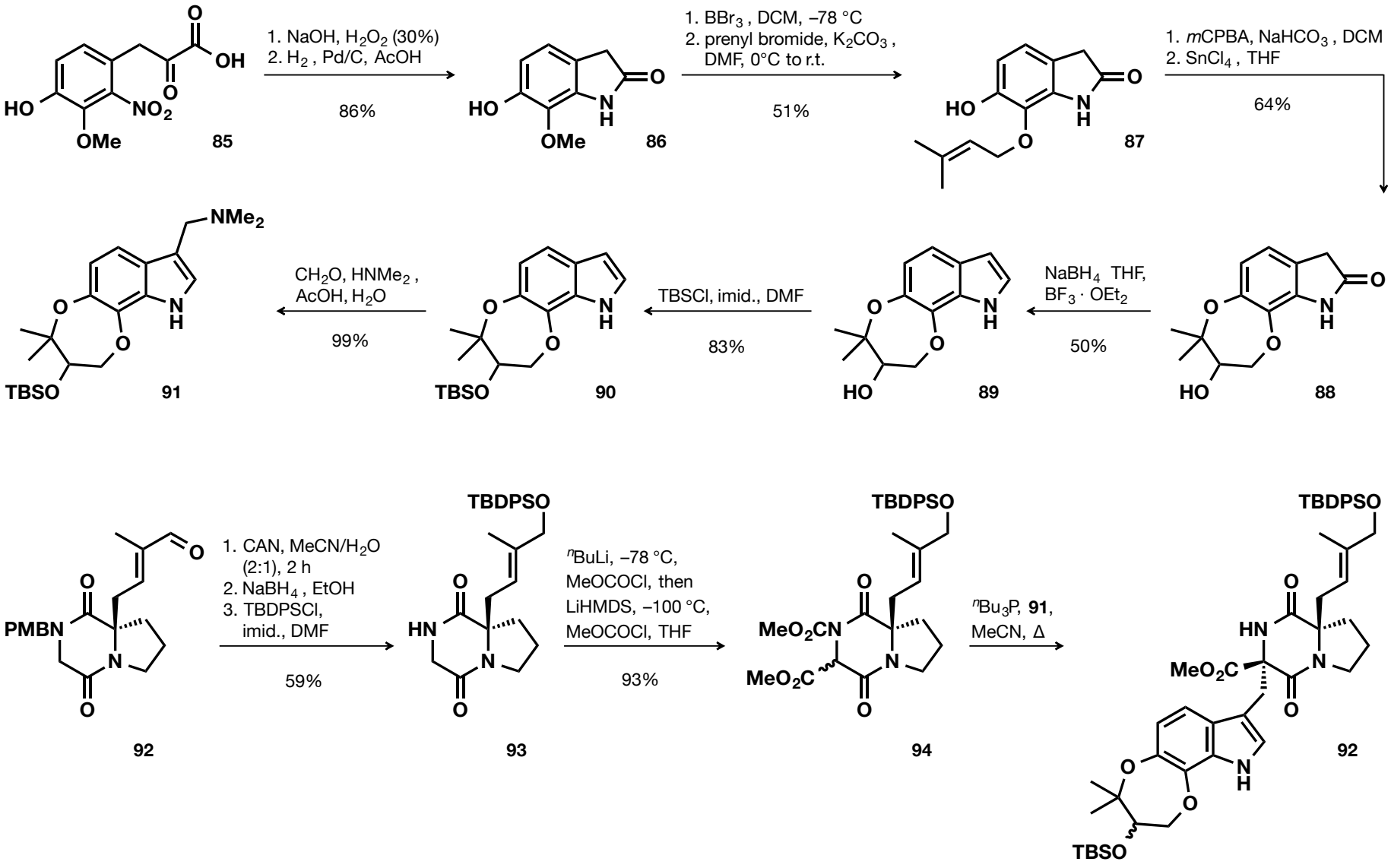
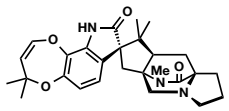


▪ R. M. Williams, *J. Am. Chem. Soc.* **1996,** *118*, 557–579.

(+)-Paraherquamide B — Williams (II)



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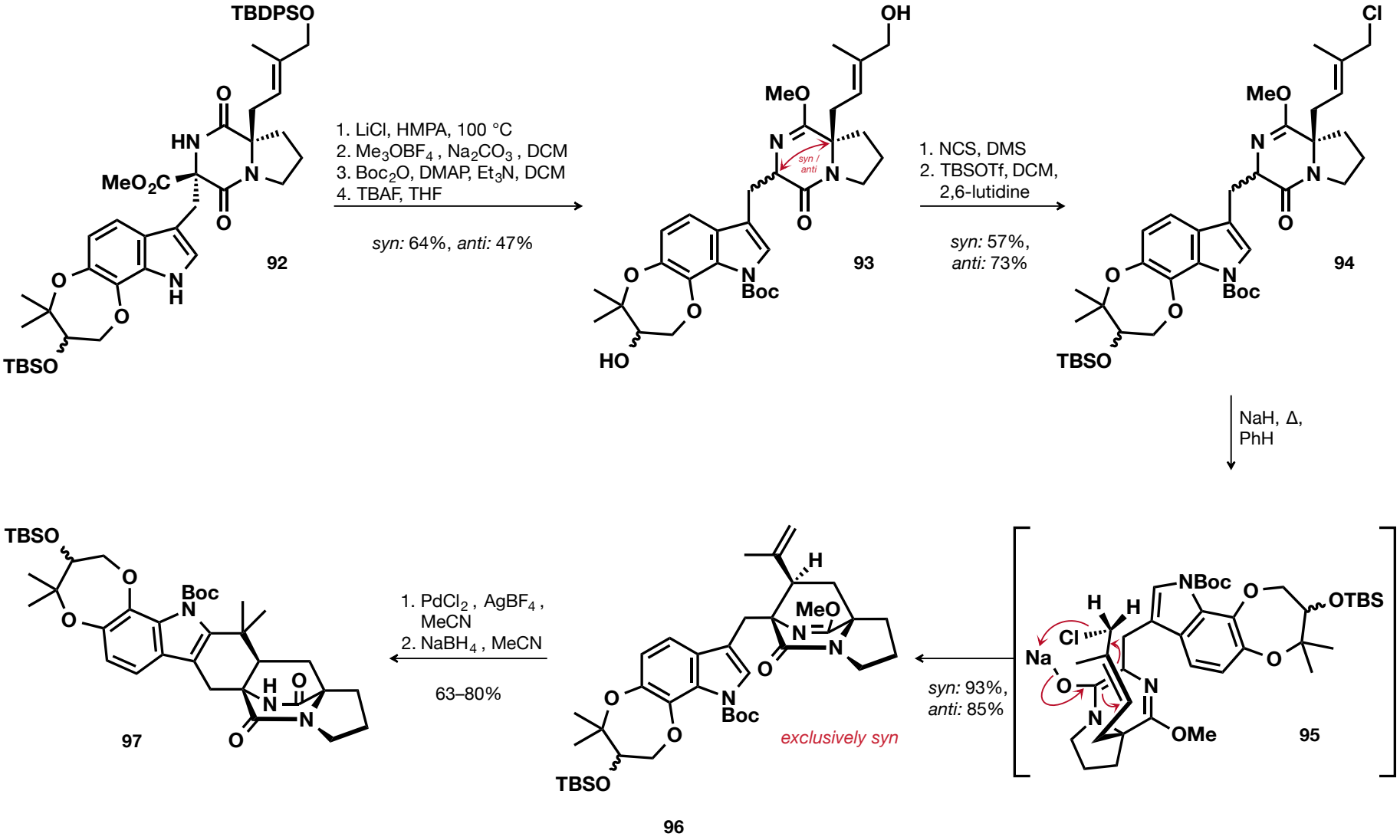
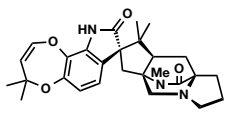


▪ R. M. Williams, *J. Am. Chem. Soc.* **1996,** *118*, 557–579.

(+)-Paraherquamide B — Williams (III)



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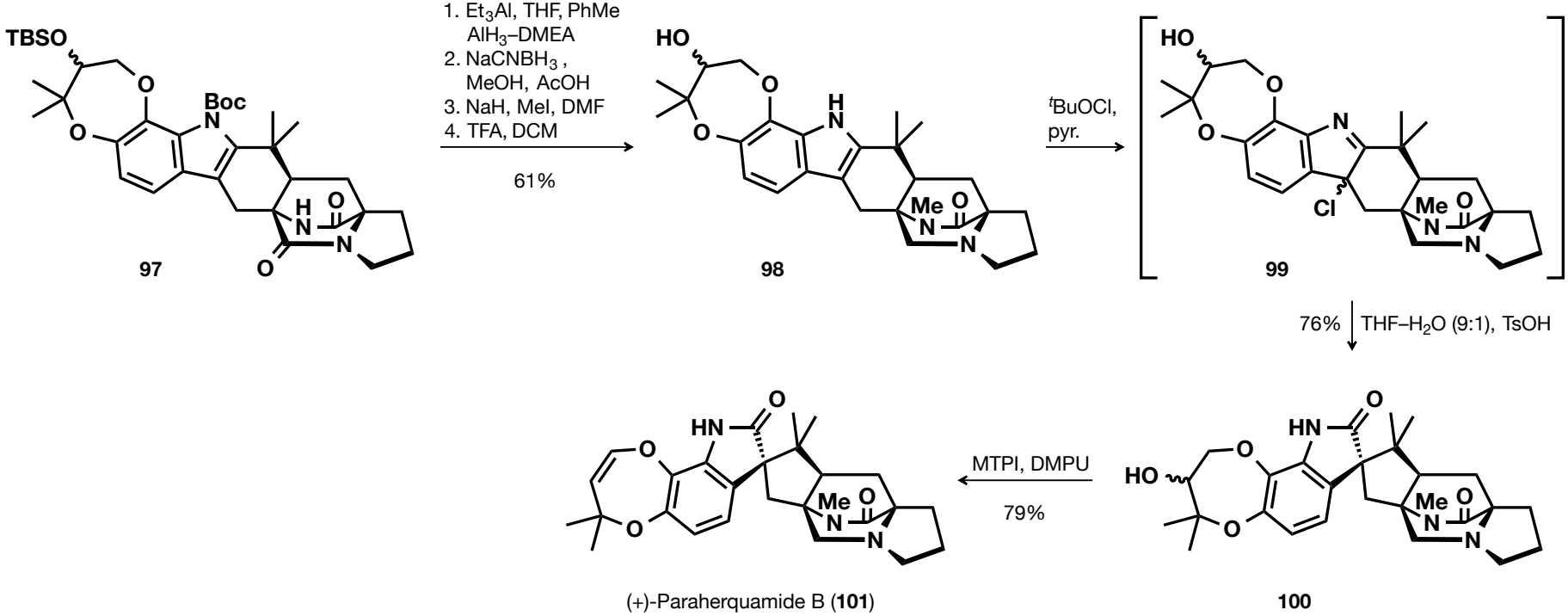
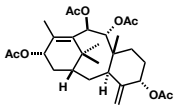


- Key features:
  - convergent synthesis, 1.4% overall yield (starting from *(S)*-proline)
  - reduction of unprotected oxindole to indole
  - application of the Somei-Kametani protocol with concomitant decarbomethoxylation
  - stereocontrolled intramolecular S_N2' cyclization reaction
  - Pd(II)-mediated cyclization with concomitant conversion of a lactim to a lactone

- R. M. Williams, *J. Am. Chem. Soc.* **1996,** *118*, 557–579.

(±)-Taxusin — Kuwajima (I)



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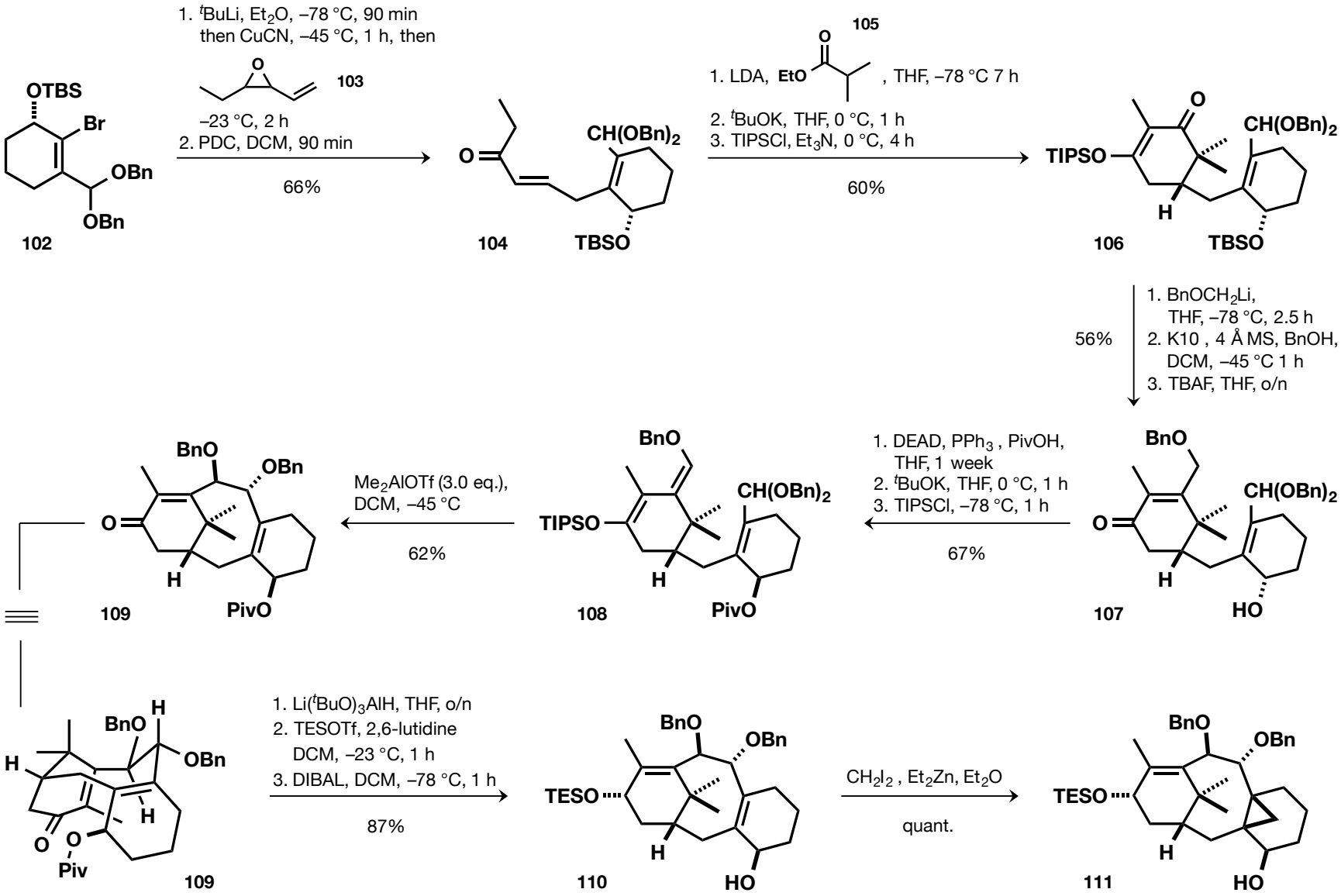
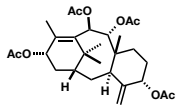


▪ I. Kuwajima, *J. Am. Chem. Soc.* **1996,** *118*, 9186–9187.

(±)-Taxusin — Kuwajima (II)



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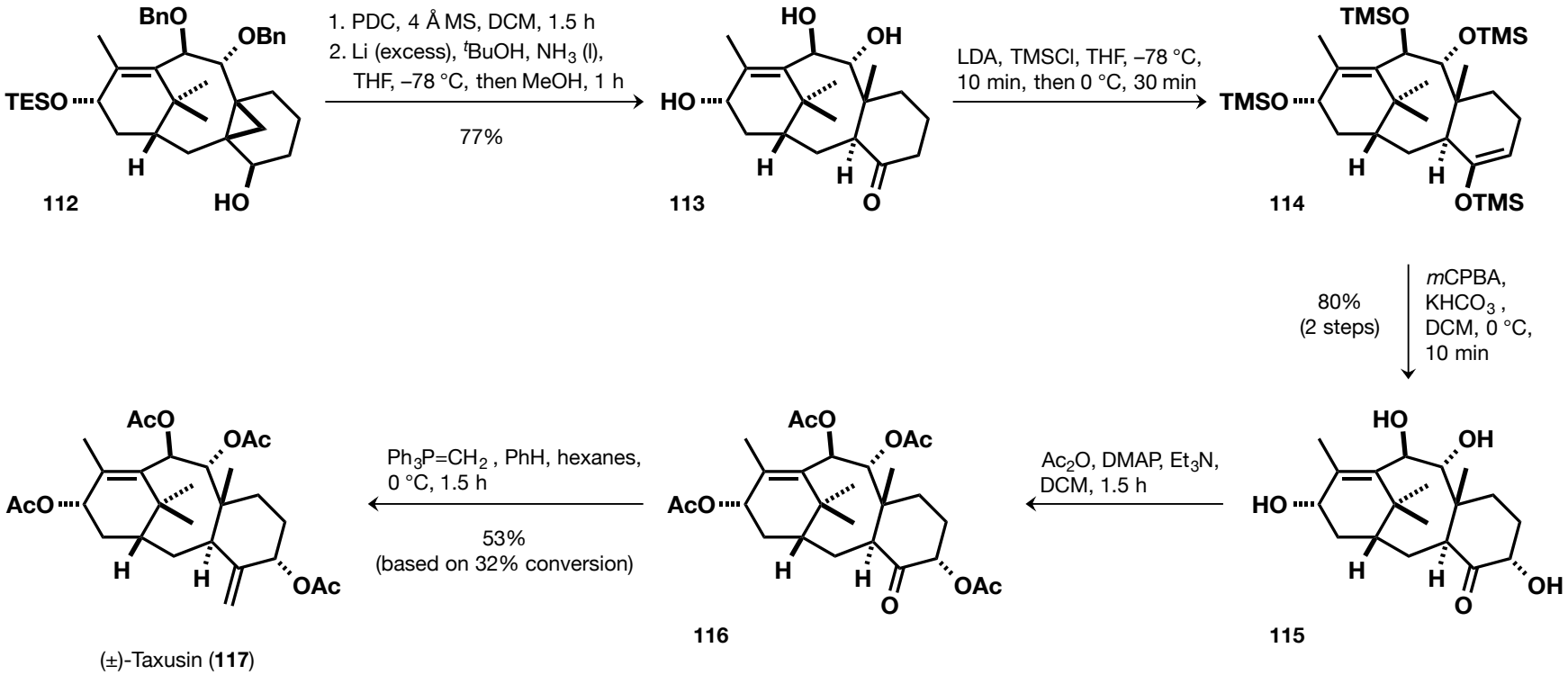
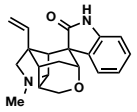


- Key features:
  - concise synthesis of the tricyclic taxane skeleton, 2% overall yield
  - effective eight-membered ring cyclization *via* extended Mukaiyama aldol reaction
  - reductive cyclopropane-opening to set angular methyl group with correct stereochemistry

- I. Kuwajima, *J. Am. Chem. Soc.* **1996,** *118*, 9186–9187.

(±)-Gelsemine — Fukuyama (I)



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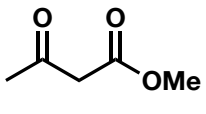
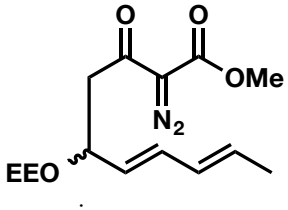


118

1. NaH, THF, 0 °C, then BuLi, then sorbic aldehyde, 0 °C to rt
2. ethyl vinyl ether, $POCl_3$, DCM 0 °C to rt.
3. TsN_3, Et_3N, DCM, 0 °C

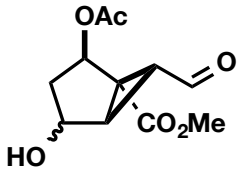
44%



119

1. $Cu(acac)_2$, $CuSO_4$, PhH, 85 °C, 3 h
2. $NaBH_4$, MeOH, 0 °C
3. Ac_2O, py., rt.
4. TsOH, $^iPrOH/H_2O$, rt.
5. O_3, MeOH–DCM (1:10), –78 °C, then Me_2S, –78 °C to rt.

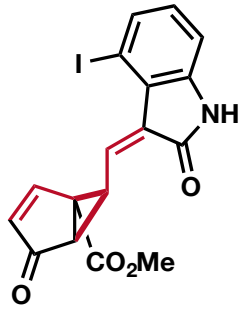
45%



120

1. 4-iodooxindole, piperidine (cat.), MeOH, rt.
2. DCC, DMSO, Py · TFA, rt.
3. Et_3N, DCM, rt.

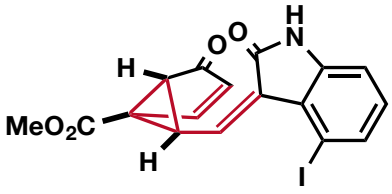
81%

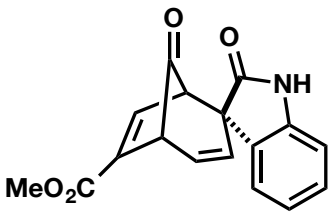


121

1. PhMe–MeCN (1:1), 90 °C, 45 min
2. Bu_3SnH, AIBN (cat.) PhMe, 95 °C, 1 h

83%

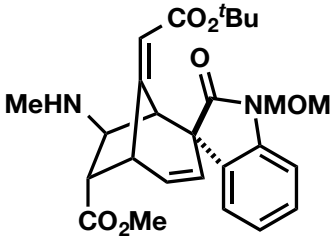




122

1. $(EtO)_2P(O)CH_2CO_2{}^tBu$, BuLi, THF, 65 °C, then MOMCl, ^tBuOK, rt.
2. $MeNH_2$, MeOH, rt.

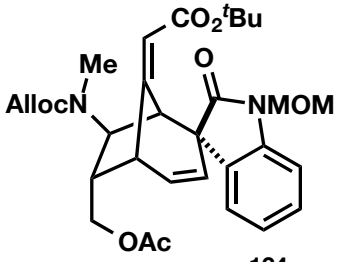
70%



123

1. AllocCl, py., DMAP, DCM, 0 °C
2. $LiBH_4$, cat. $LiBEt_3H$, THF, 23 °C
3. Ac_2O, py.

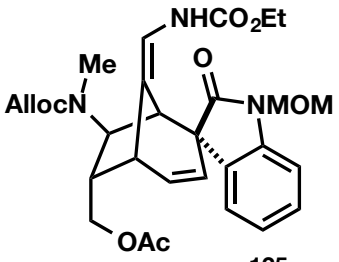
73%



124

1. HCO_2H, 23 °C
2. $ClCO_2Et$, Et_3N, THF, 0 °C
3. $^nBu_4NN_3$, PhMe, cat. Et_3N, reflux, then EtOH, 23 °C

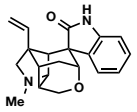
76%



125

▪ T. Fukuyama, *J. Am. Chem. Soc.* **1996,** *118*, 7426–7427.

(±)-Gelsemine — Fukuyama (II)



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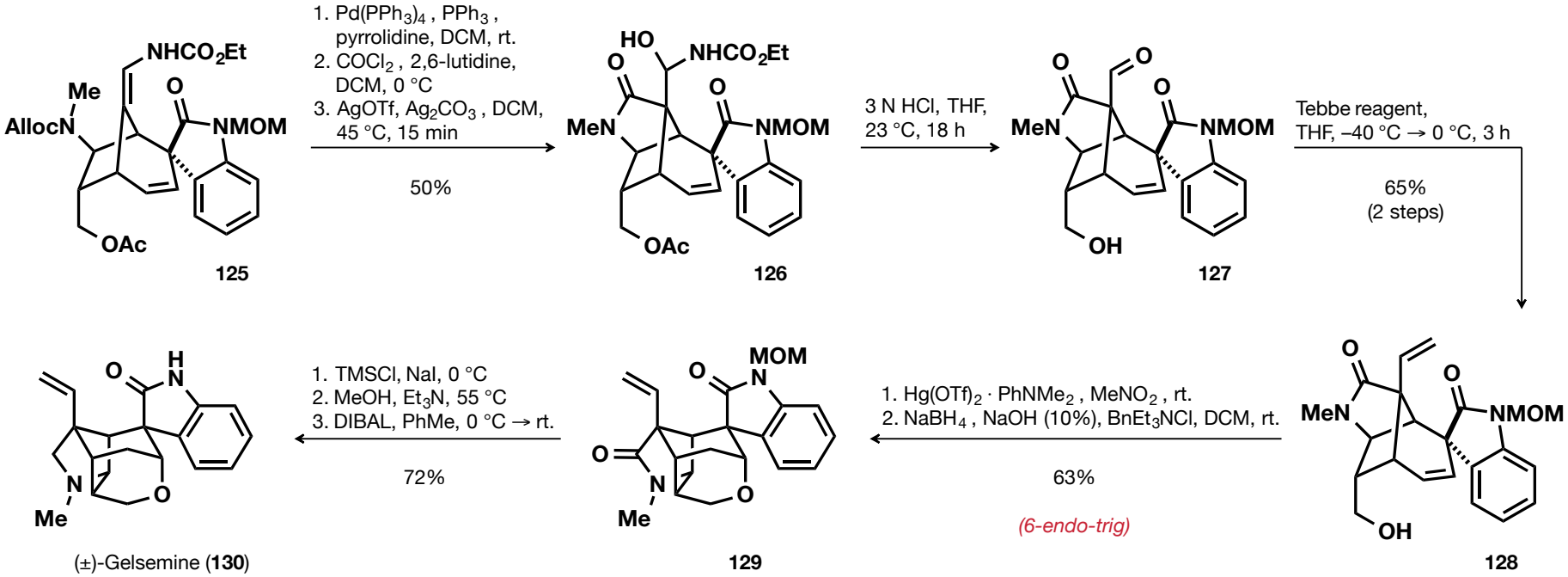
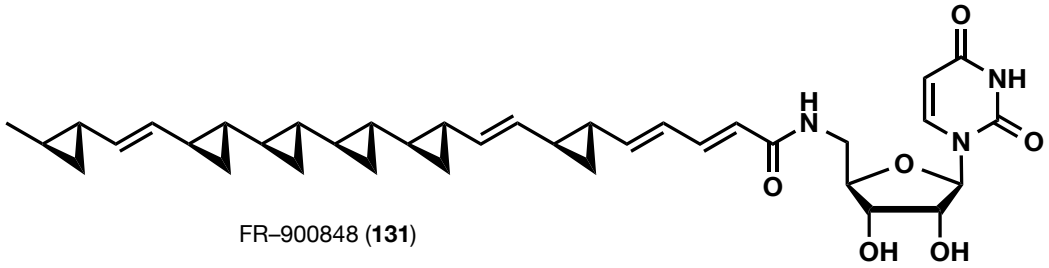


- Key features:
  - 31 steps, 0.8% overall yield
  - impressive use of the divinylcyclopropane rearrangement to set bicyclo[3.2.1]octane system—including a *spiro* connected oxindole (plus excellent yield—98%)
  - control of oxindole stereochemistry by use of 4–iodooxindole
  - reductive oxymercuration ring closure (adapted from Speckamp synthesis)

- T. Fukuyama, *J. Am. Chem. Soc.* **1996,** *118*, 7426–7427.

FR–900848 — Falck
U–106305 — Charette and Barrett (respectively)

- 1996 = synthetic year of polycyclopropane natural products
- Most notable synthesis: FR–900848 by Falck



FR–900848 (**131**)

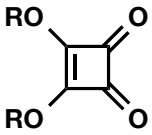
  - Charette–Juteau asymmetric cyclopropanation
  - Dimerization strategy
  - Horeau amplification principle
- U–106305
  - synthesized by Charette and Barrett, respectively, using the Charette–Juteau asymmetric cyclopropanation

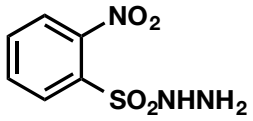
U–106305 (**132**)

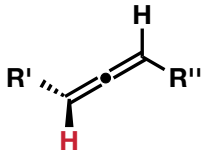
- For more information *cf.* presentation *Cyclopropanes in Total Synthesis (2013)*

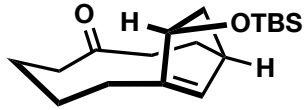
▪ T. Fukuyama, *J. Am. Chem. Soc.* **1996,** *118*, 7426–7427.

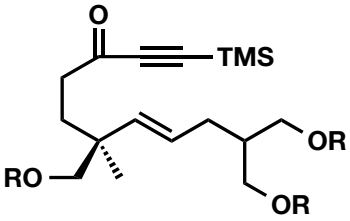
Selected Methodologies

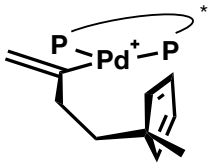


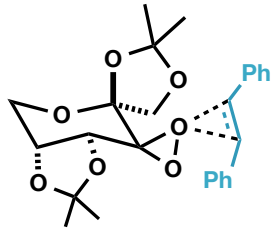


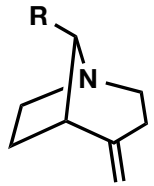












Formation of Highly Oxygenated [4,4]-Spirononenes — Paquette

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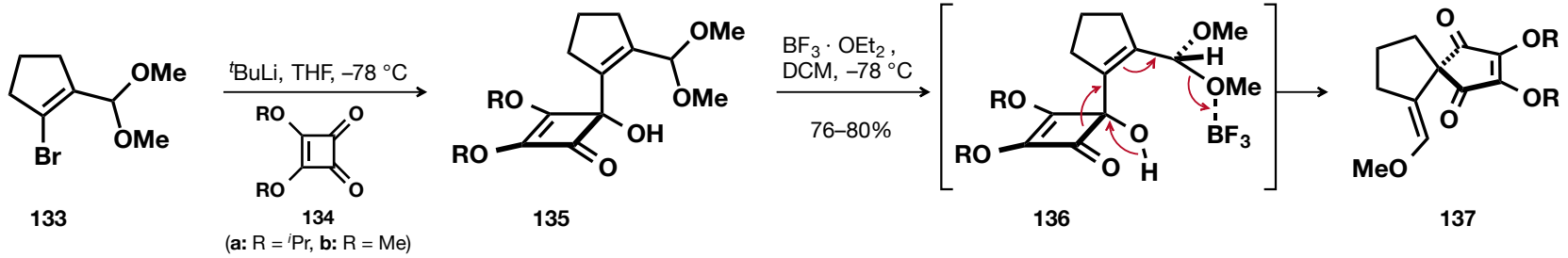
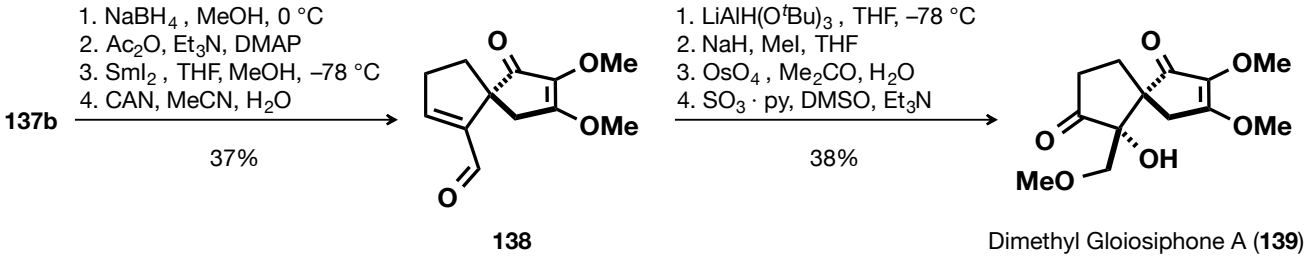
- Formation of highly oxygenated [4,4]-spirononenes *via* Lewis acid-catalyzed isomerization of adducts to squarate esters



  - condensation of bromide **133** with an equivalent of squarate ester and subsequent deployment of a regiocontrolled ring expansion to generate the spirocyclic center

- Off topic: synthesis of building block **133**?
- Applied in the total synthesis of Dimethyl Gloiosiphone A



- L. A. Paquette, *J. Am. Chem. Soc.* **1996,** *118*, 9456–9457.

Asymmetric Entry to the 8,9-Secokaurene Diterpenoids — Paquette

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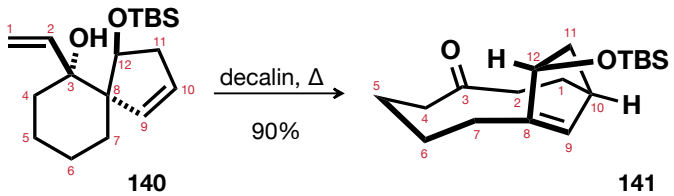
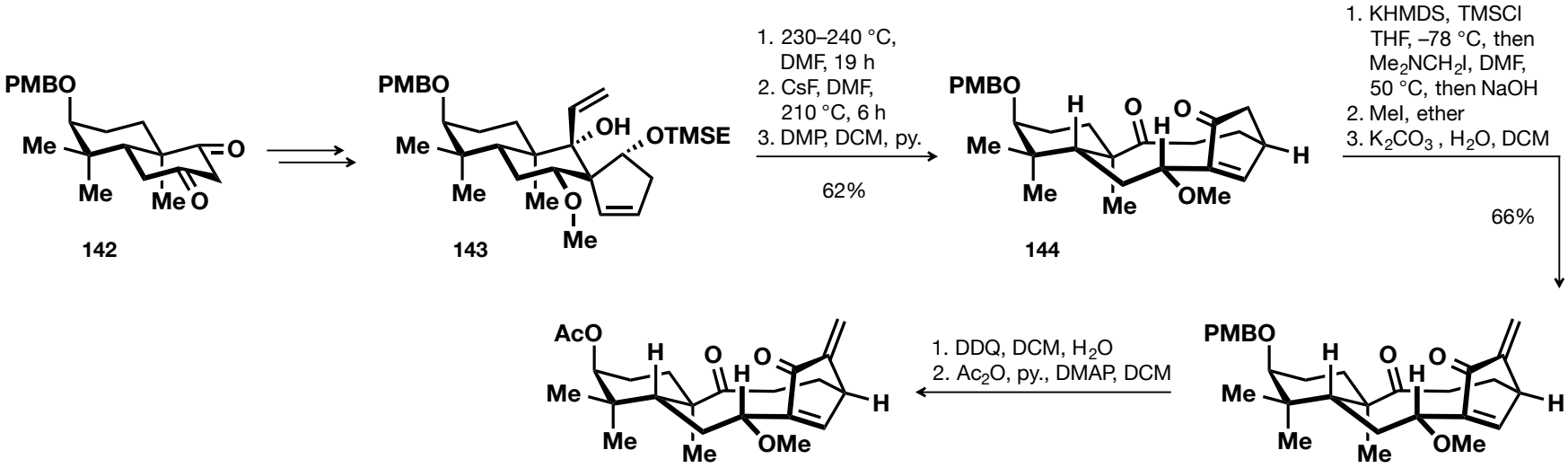
- Formation of oxygenated bicyclo[7.2.1]dodecene skeleton *via* oxy-Cope rearrangement of a *spiro*-cyclopentenol in high yield



140 **141**

- Application in the total synthesis of (–)-*O*-Methylshikoccin
  - model system **140** has conformational flexibility which is dramatically reduced in the natural product due to a *trans*-fused decalin system—nevertheless, the [3,3]-sigmatropic rearrangement proceeded with decent yield

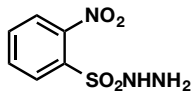


142 **143** **144** **145**

(–)-*O*-Methylshikoccin (**146**)

- L. A. Paquette, *J. Am. Chem. Soc.* **1996,** *118*, 11990–11991.

Synthesis of Allenes — Myers



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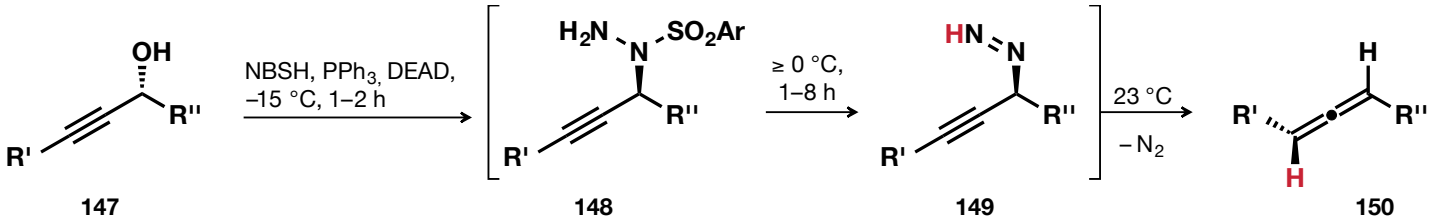
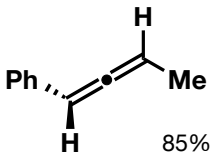
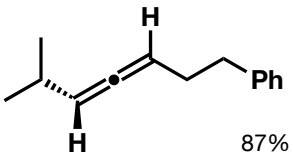
- stereospecific synthesis of allenes in a single step from propargylic alcohols



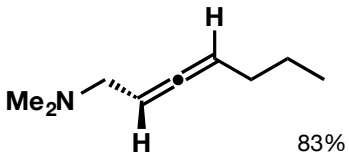
- wide reaction scope with decent to very good yields



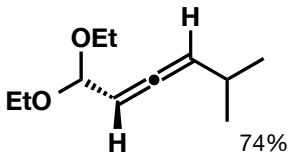
85%
(**151**)



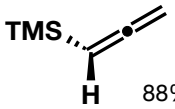
87%
(**152**)



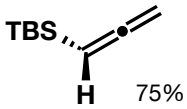
83%
(**153**)



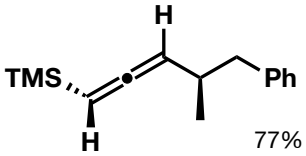
74%
(**154**)



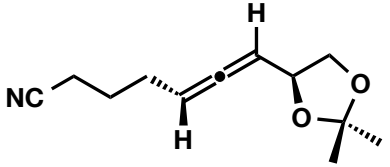
88%
(**155**)



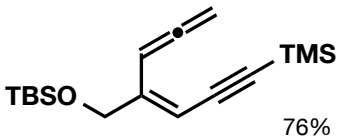
75%
(**156**)



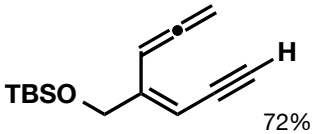
77%
(**157**)



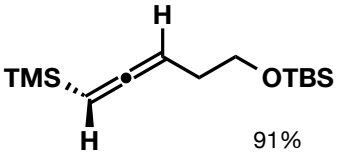
76%
(**158**)



76%
(**159**)



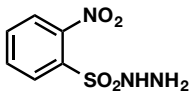
72%
(**160**)



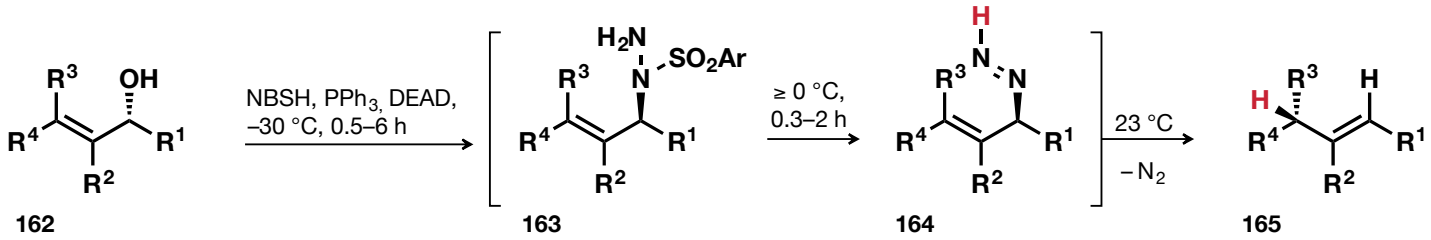
91%
(**161**)

- A.G. Myers, *J. Am. Chem. Soc.* **1996,** *118*, 4492–4493.

Excursus: NBSH (*o*-Nitrobenzenesulfonylhydrazide) — Myers

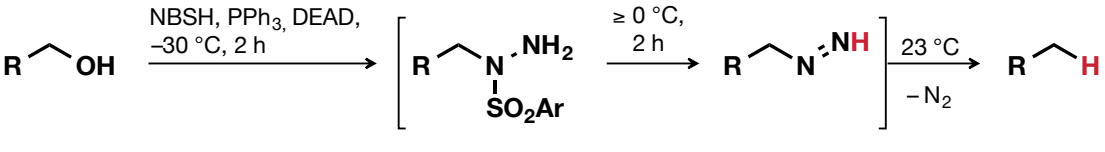


- *o*-Nitrobenzenesulfonylhydrazide has been shown to be a valuable reagent for the preparation of several useful compounds
- Preparation from hydrazine monohydrate and *o*-nitrobenzenesulfonyl chloride
- Synthesis of allenes from propargylic alcohols (*cf.* Slide 26)
- Reductive transposition of allylic alcohols



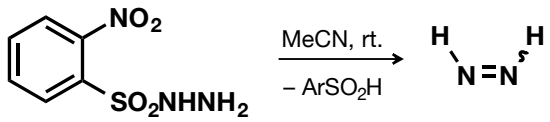
162 163 164 165

- Reductive deoxygenation of unhindered alcohols



166 167 168 169

- NBSH generates diimide in polar solvents at room temperature and neutral pH



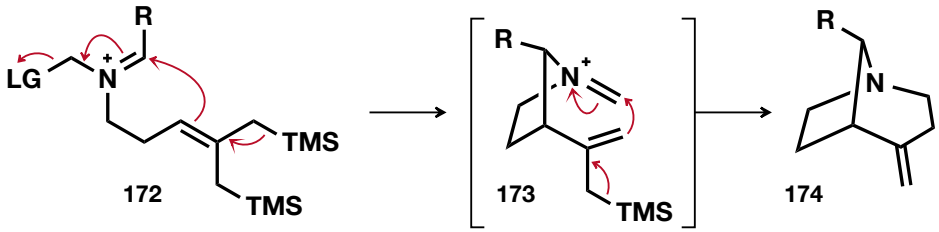
170 171

- (i) A.G. Myers, *J. Am. Chem. Soc.* **1996,** *118*, 4492–4493. (ii) A.G. Myers, *J. Org. Chem.* **1997,** *62*, 7507. (iii) A.G. Myers, *J. Am. Chem. Soc.* **1997,** *119*,8572–8573. (iv) A.G. Myers, *Tet. Lett.* **1996,** *37*, 4841–4844.

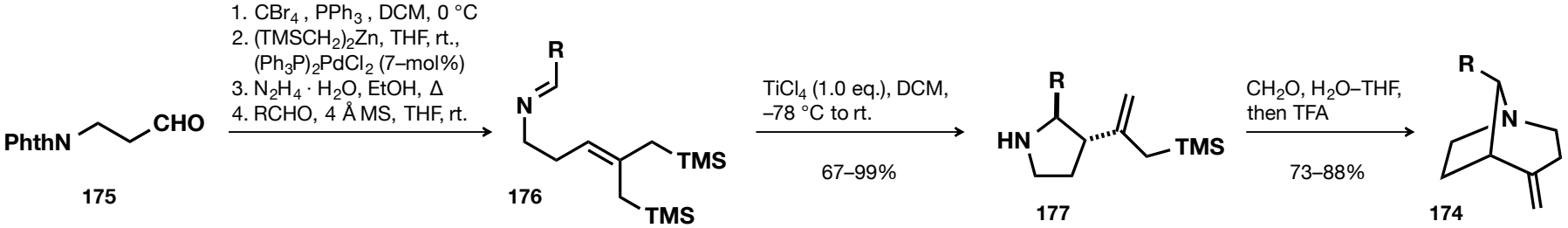
Intramolecular (Bis)silane Imine Cyclizations — Livinghouse

Gaich-Group Seminar
Erik Stempel

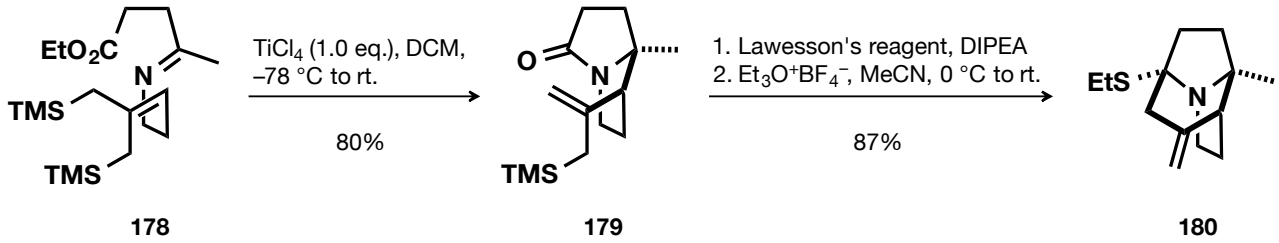
- General idea for the synthesis of isotropanes:



- Synthesis of substituted pyrollidines and subsequent formation of isotropanes



- Synthesis of bridged pyrrolizidines

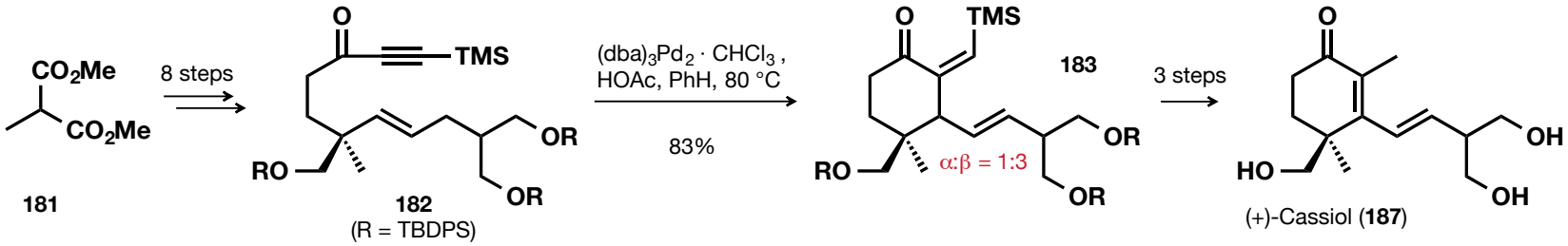


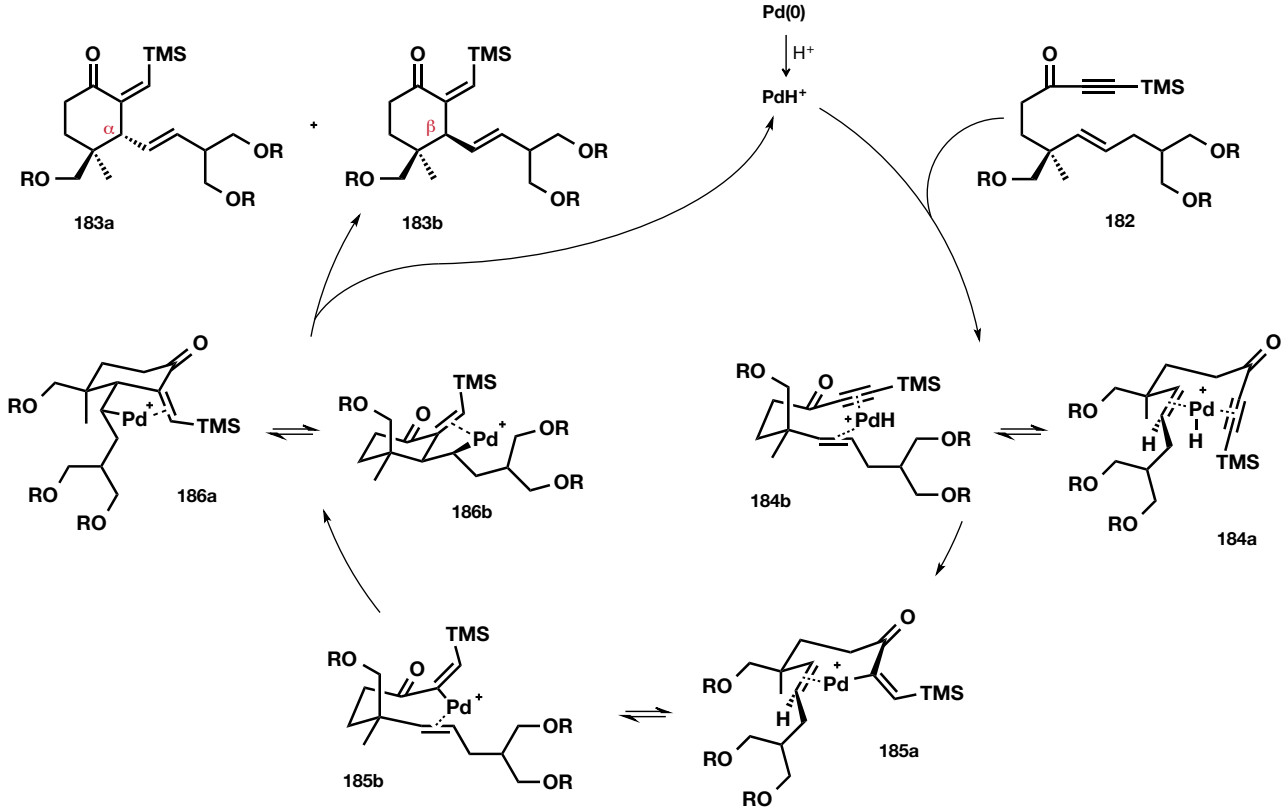
- T. Livinghouse, *J. Am. Chem. Soc.* **1996,** *118*, 4200–4201.

Pd Catalyzed Alder–Ene Reaction — Trost

Gaich-Group Seminar
Erik Stempel

- Pd catalyzed Alder-ene type reaction as powerful 6-membered ring forming process

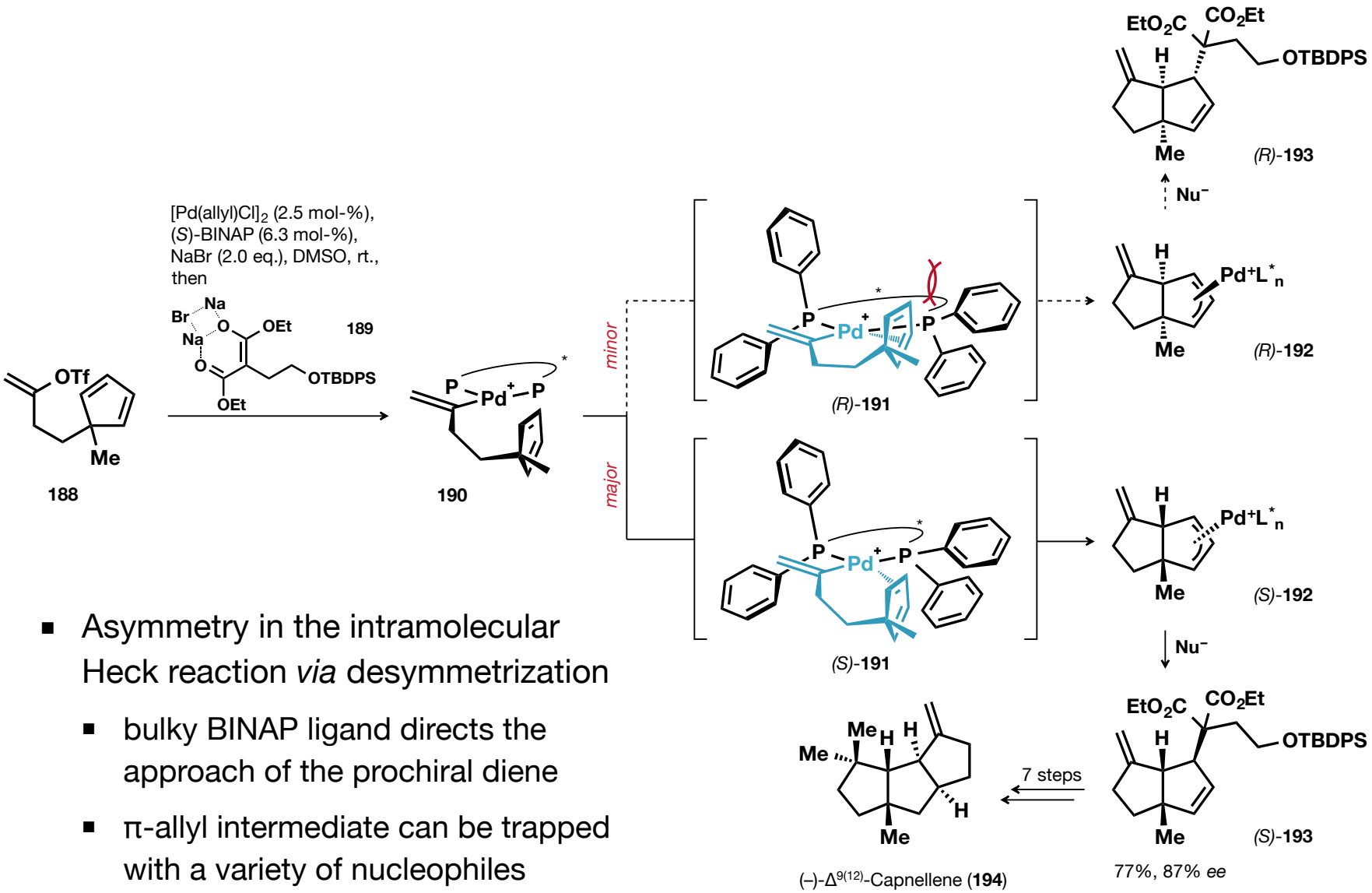




- B. Trost, *J. Am. Chem. Soc.* **1996,** *118*, 6625–6633.

Asymmetric Heck Reaction — Shibasaki

Gaich-Group Seminar
Erik Stempel

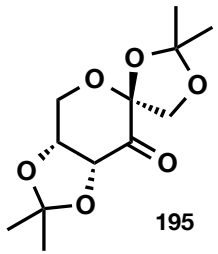


- Asymmetry in the intramolecular Heck reaction *via* desymmetrization
  - bulky BINAP ligand directs the approach of the prochiral diene
  - π-allyl intermediate can be trapped with a variety of nucleophiles

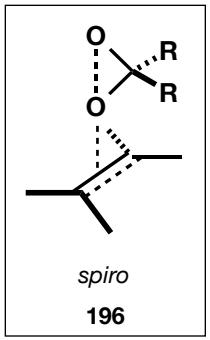
- M. Shibasaki, *J. Am. Chem. Soc.* **1996**, *118*, 7108–7116.

Asymmetric Epoxidation Method for *trans*-Olefins — Shi

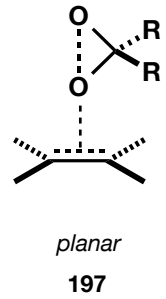
- Y. Shi: Introduction of the nowadays known *Shi Epoxidation*
- Mediated by a fructose-derived ketone (**195**)
- In general: *chiral DMDO*
- Transition state in dioxirane epoxidations is important, two mechanistic extremes are supposable: *spiro* and *planar*
  - *spiro* transition state is favored (Baumstark, 1987)
- Excellent methodology for epoxidation of *trans*-olefins bearing no allylic alcohol group
- Chiral catalysts are easy accessible
- 1997–2013: Methodology has been extended to a broader substrate scope



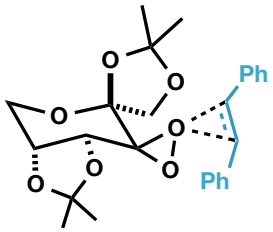
195



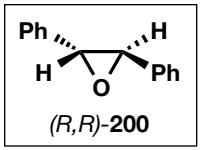
spiro
196
favored



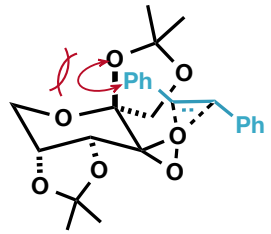
planar
197



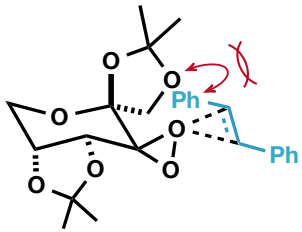
spiro-1 (favored)
198a



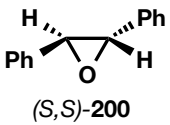
(R,R)-**200**
major product,
up to 99% *ee*



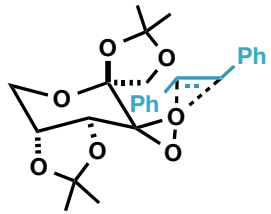
planar-1 (disfavored)
199a



spiro-2 (disfavored)
198b



(S,S)-**200**



planar-2 (favored)
199b

- Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807.
- A.L. Baumstark *Tet. Lett.* **1987**, *28*, 3311–3314.

Thanks for your attention.

Questions?