Universität Konstanz

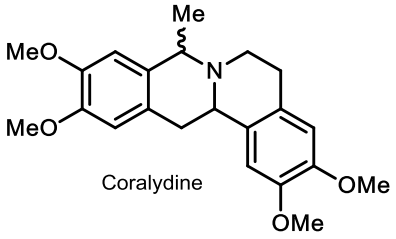
Angewandte Chemie International Edition 2009

Steve Karreman

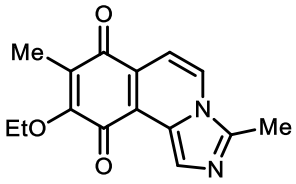
08/10/2016

Gaich Group Seminar

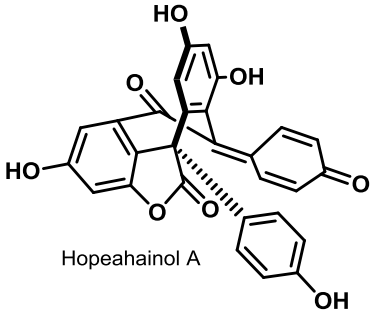
Total Synthesis



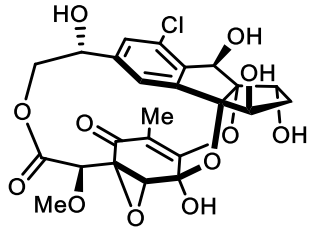
Coralydine



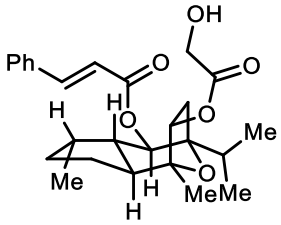
Cribrostatin 6



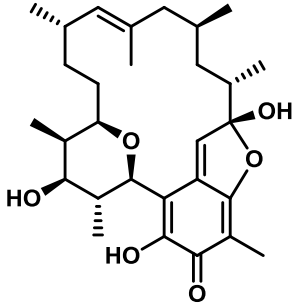
Hopeahainol A



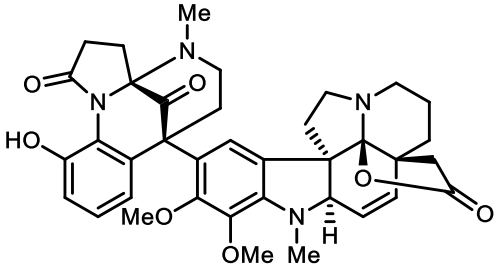
Sporolide B



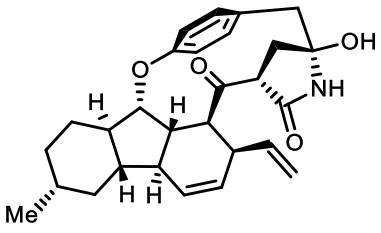
Englerin A



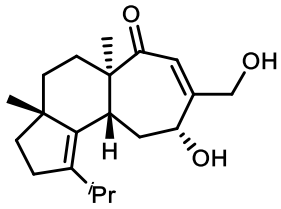
Kendomycin



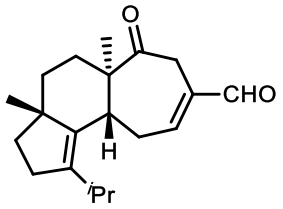
(+)-Haplophytine



Hirsutellone B

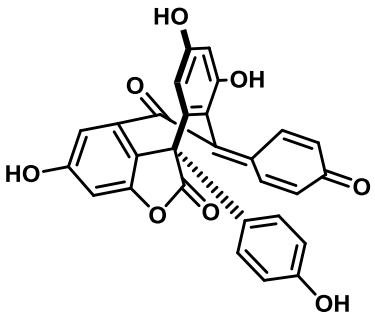


Cyathin B_2

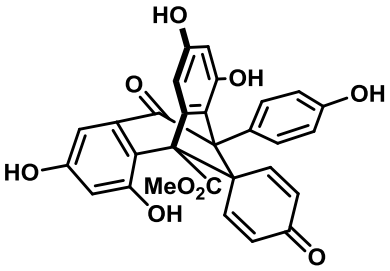


Cyathin A_3

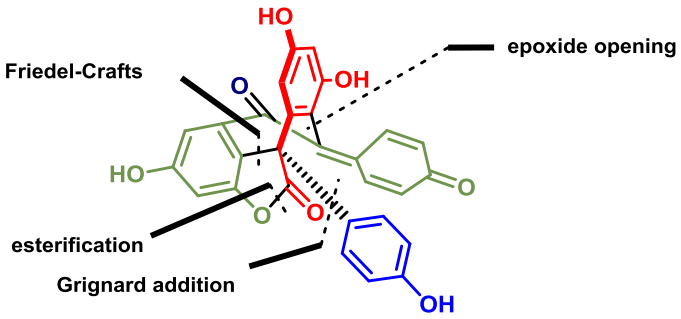
K. C. Nicolaou: Hopeahainol A and Hopeanol (Racemic!)

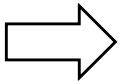


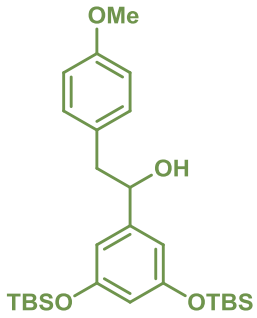
hopeahainol A

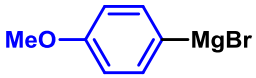


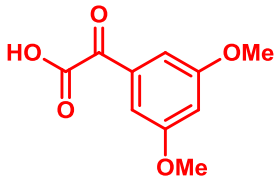
hopeanol
– biosynthetic precursor?







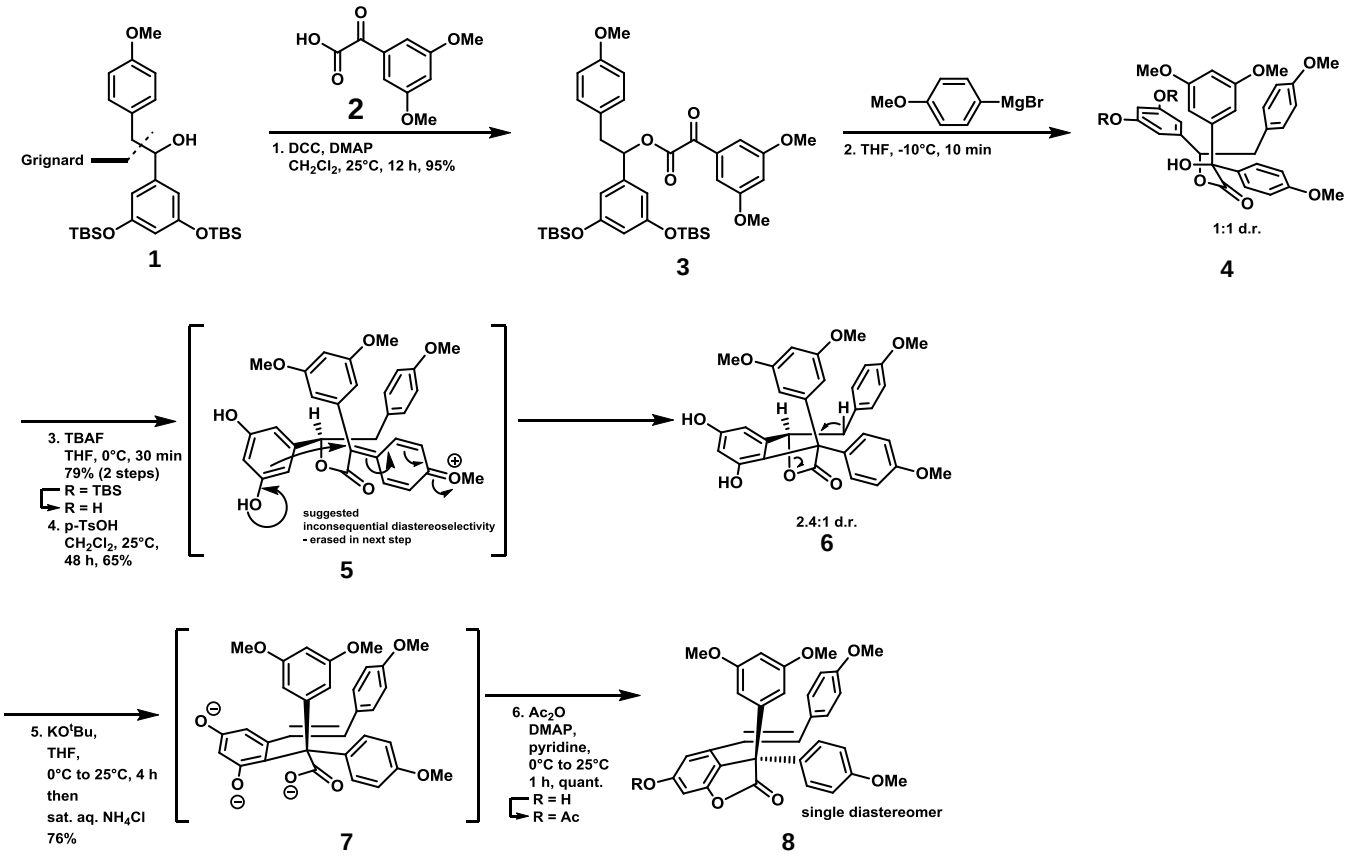




*m*CPBA

Nicolaou, K. C., et al. (2009). "Total Synthesis of Hopeahainol A and Hopeanol." Angewandte Chemie International Edition **48**(19): 3440-3443.

K. C. Nicolaou: Hopeahainol A and Hopeanol (Racemic!)



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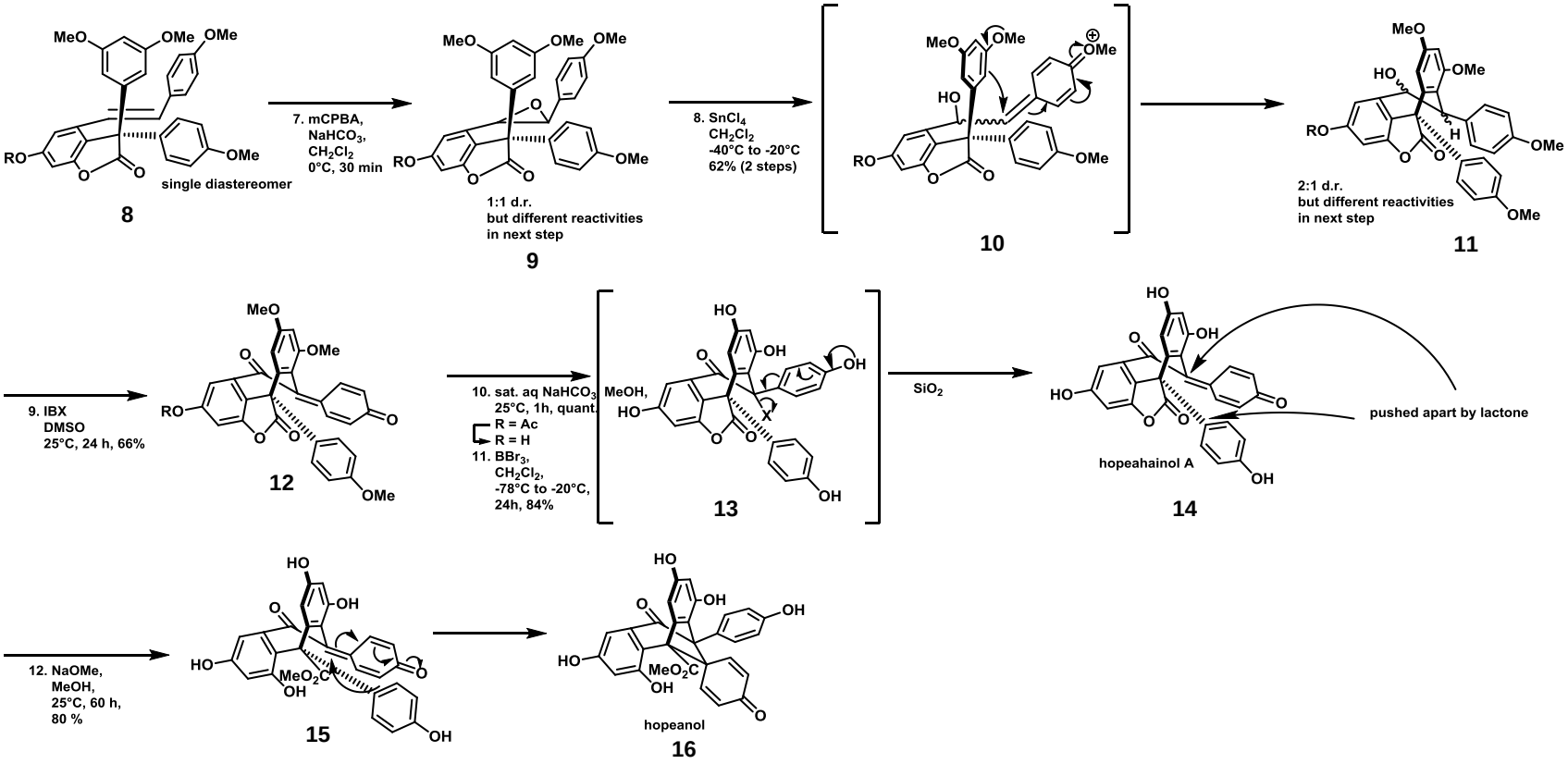
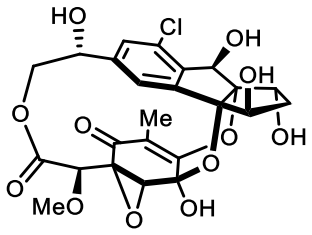
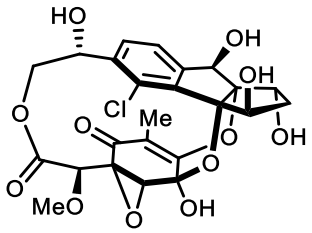


Nicolaou, K. C., et al. (2009). "Total Synthesis of Hopeahainol A and Hopeanol." Angewandte Chemie International Edition **48**(19): 3440-3443.

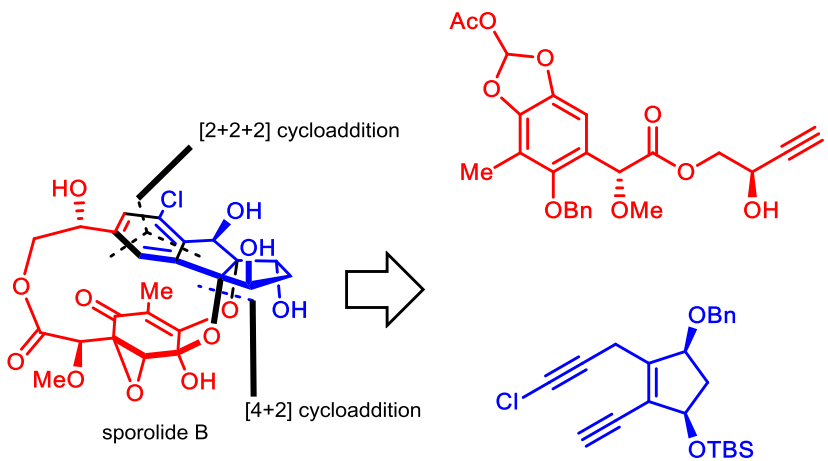
K. C. Nicolaou: Sporolide B



sporolide B

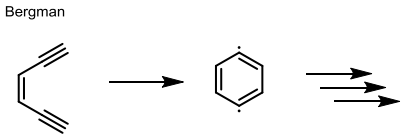


sporolide A



sporolide B

12 oxygen atoms
10 stereogenic centers
13-membered macrolide ring
Chlorobenzene nucleus
Indane structure
Cagelike-struktrure connected by 2 oxygen bridges and one ester bond
Biosynthesis: Bergman cycloaromatization?



Nicolaou, K. C., et al. (2009). "Total Synthesis of Sporolide B." Angewandte Chemie International Edition **48**(19): 3449-3453.

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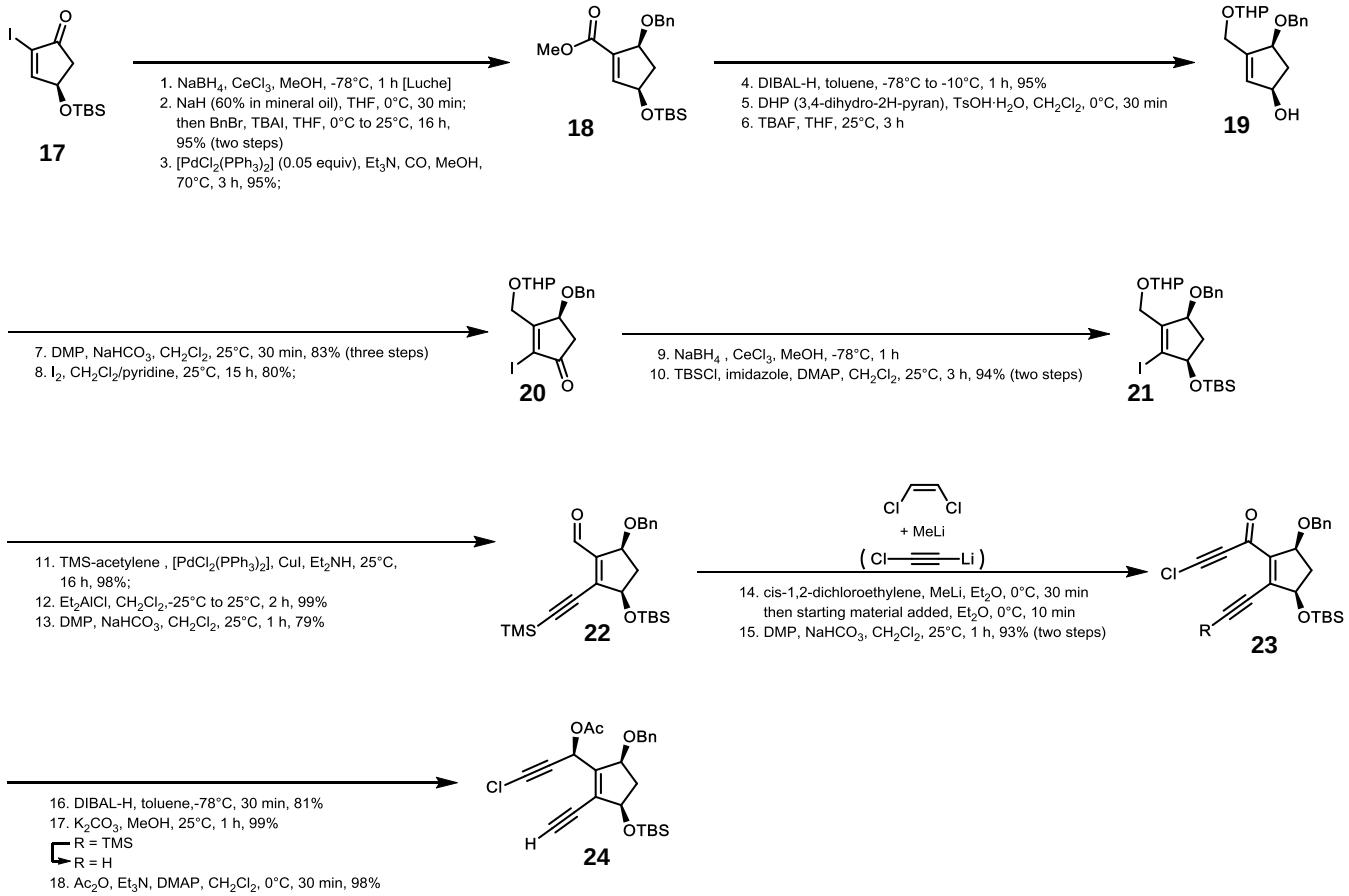

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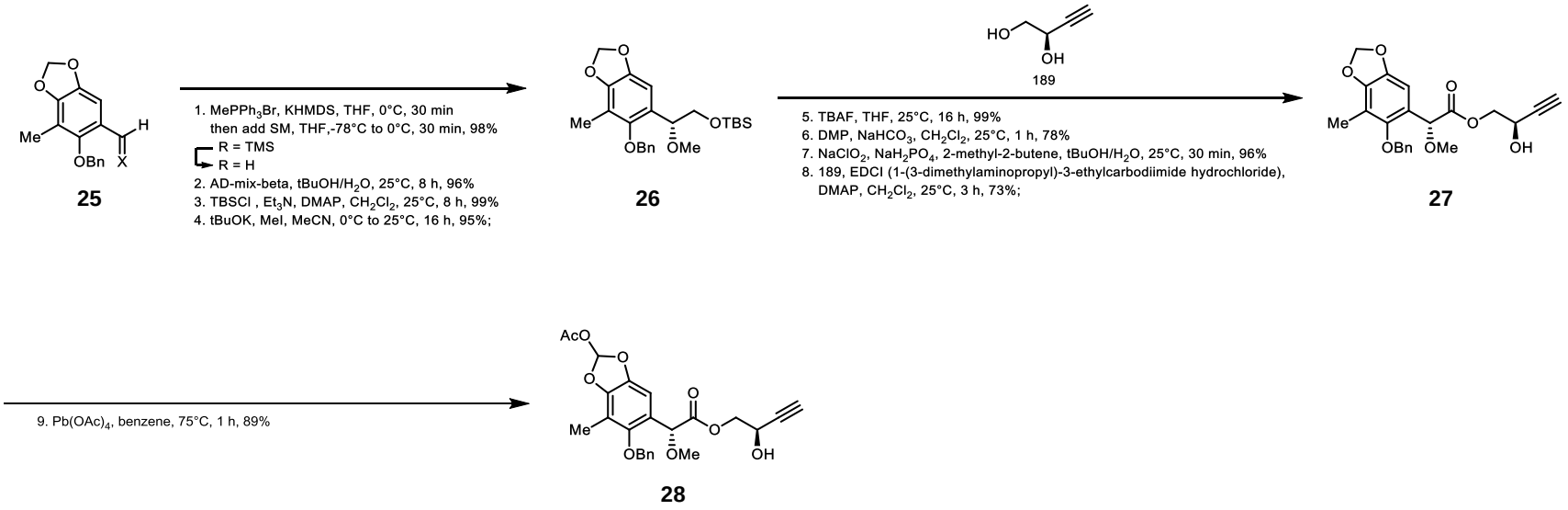

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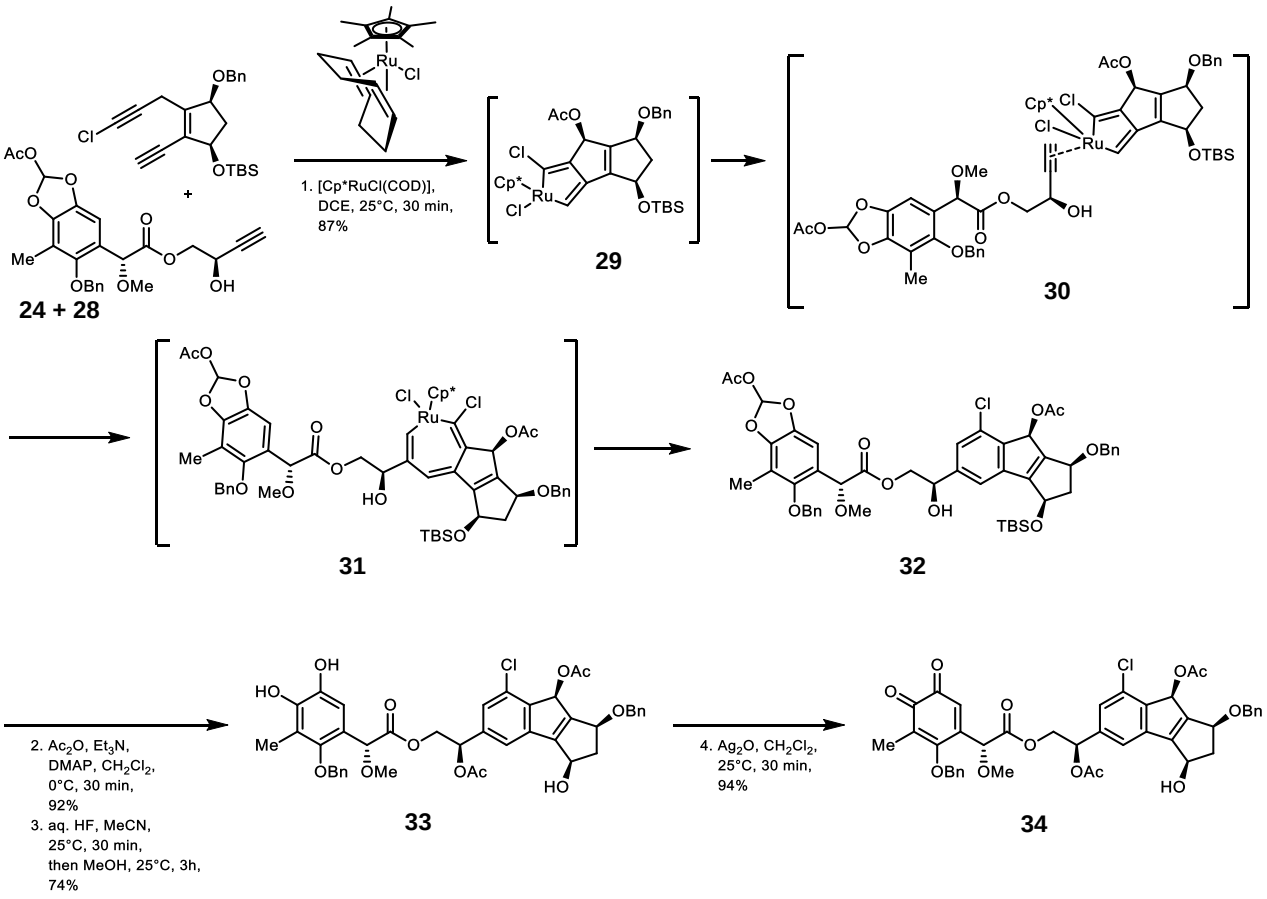

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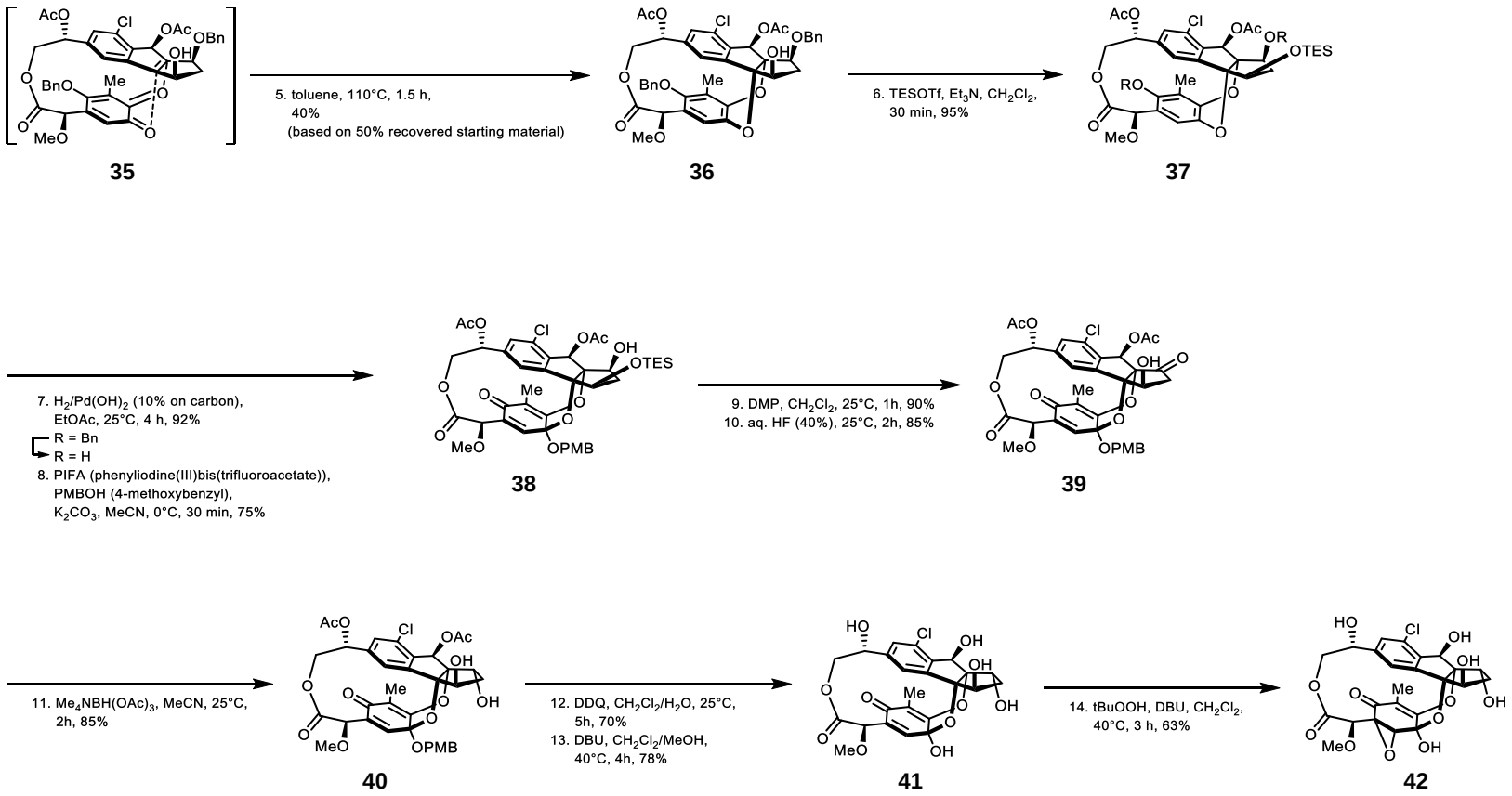
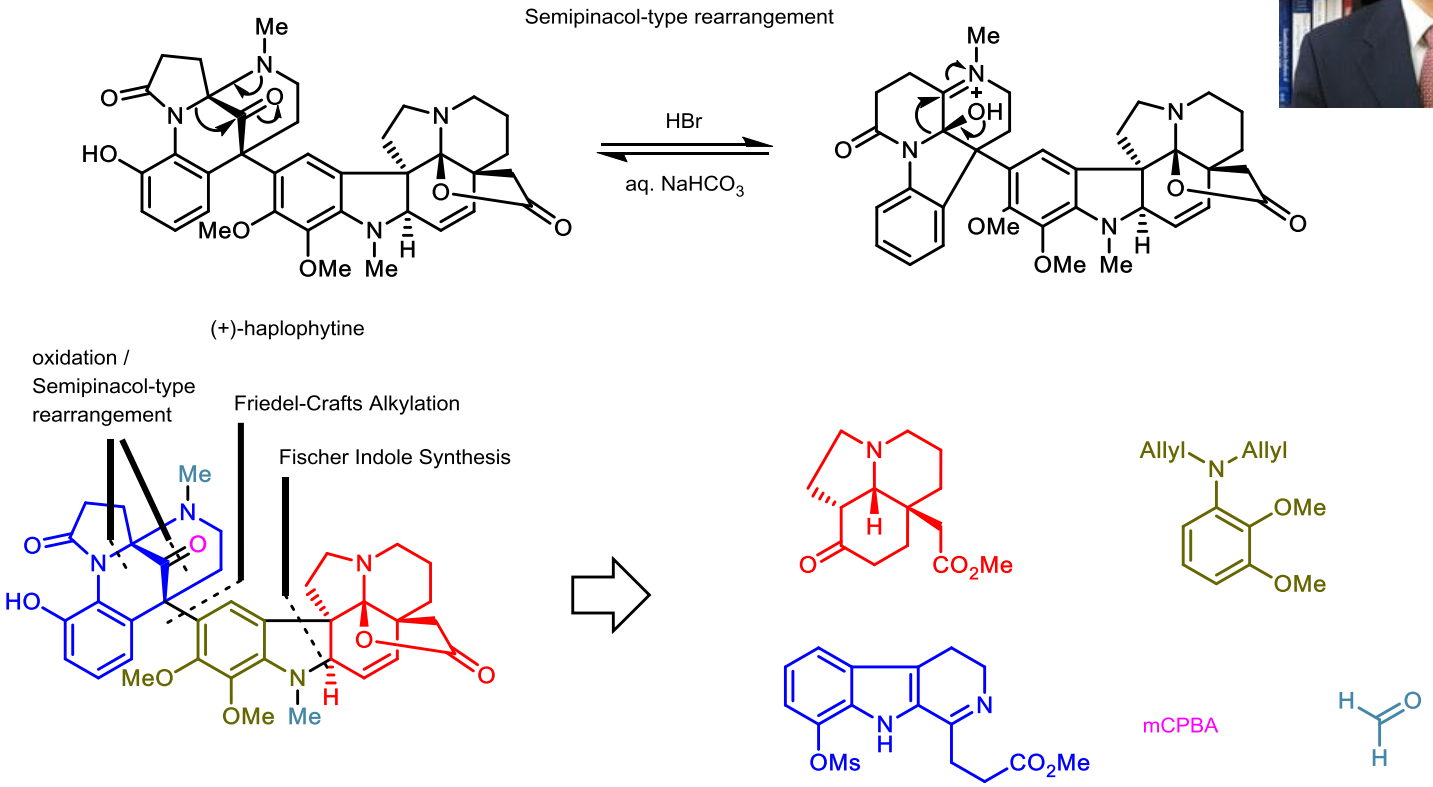


Nicolaou, K. C., et al. (2009). "Total Synthesis of Sporolide B." Angewandte Chemie International Edition **48**(19): 3449-3453.

H. Tokuyama: (+)-Haplophytine



6 stereocenters, 5 quaternary
Highly congested carbon-carbon bond adjoining the two halfves of the molecule
Bridged ketone structure (left)
Aspidosperma alkaloid (right)

Ueda, H., et al. (2009). "Total Synthesis of (+)-Haplophytine." Angewandte Chemie International Edition **48**(41): 7600-7603.

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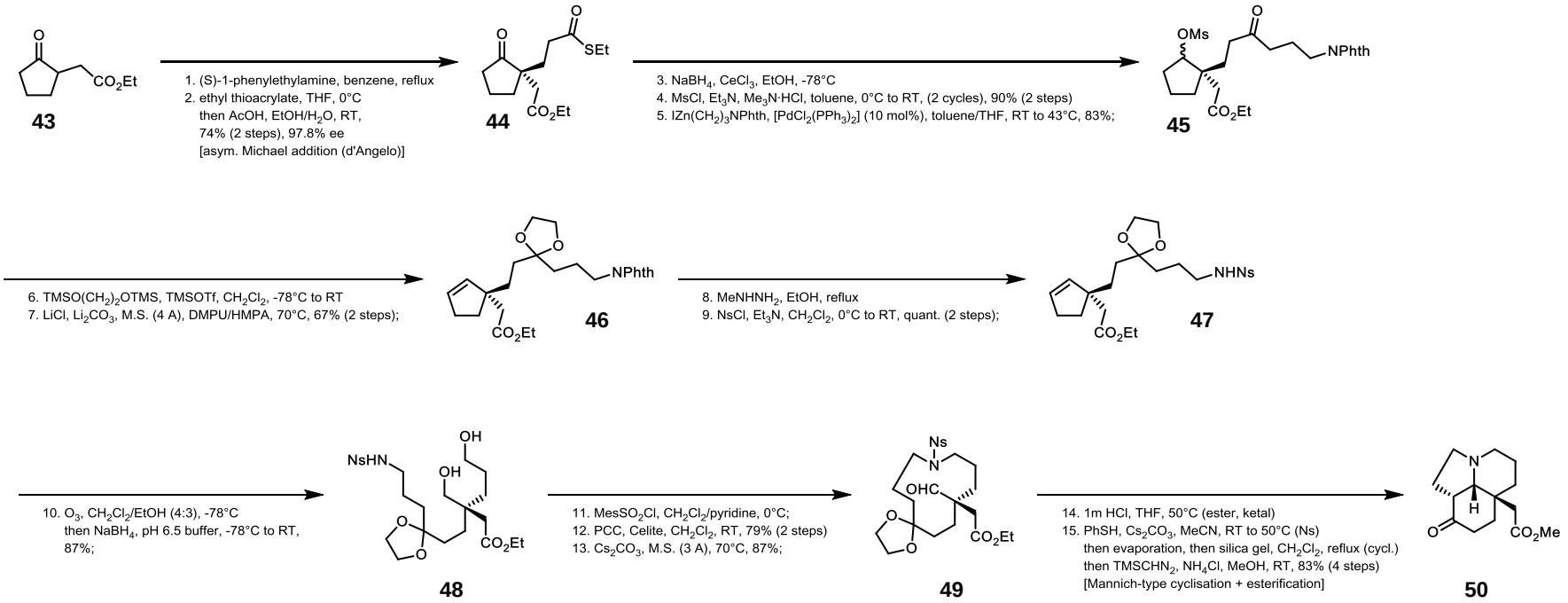

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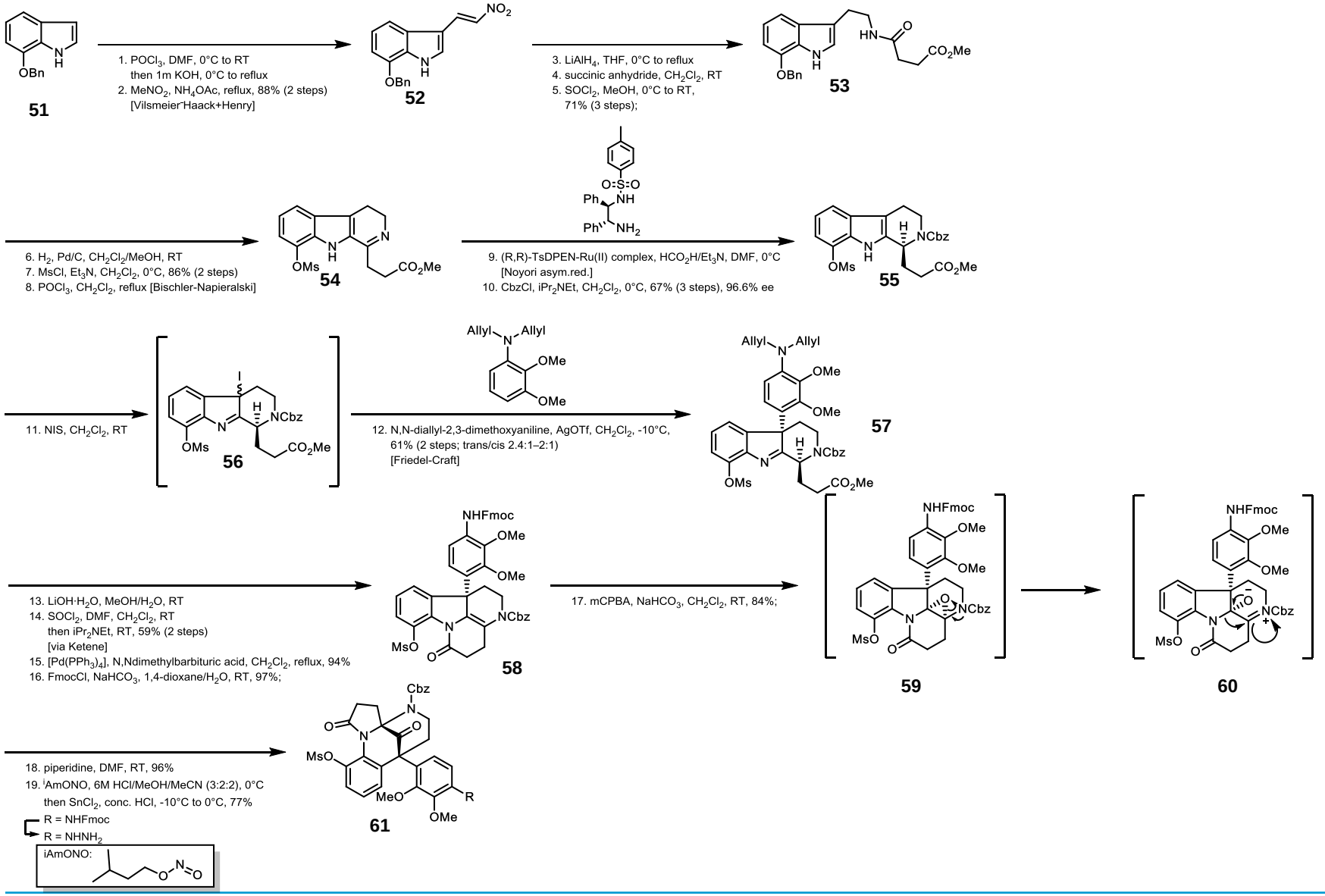

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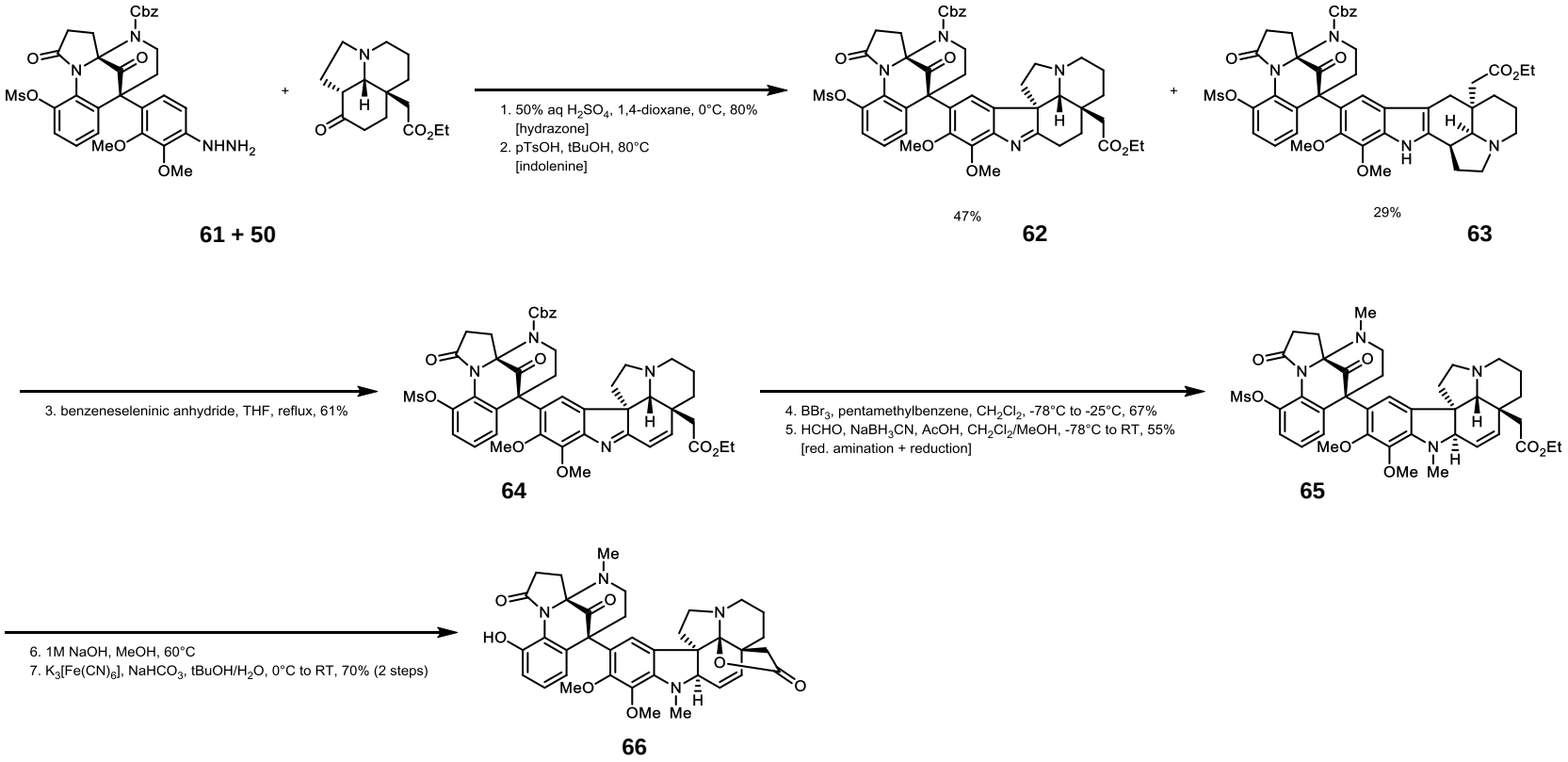
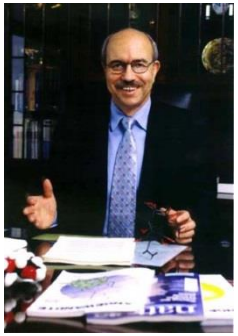
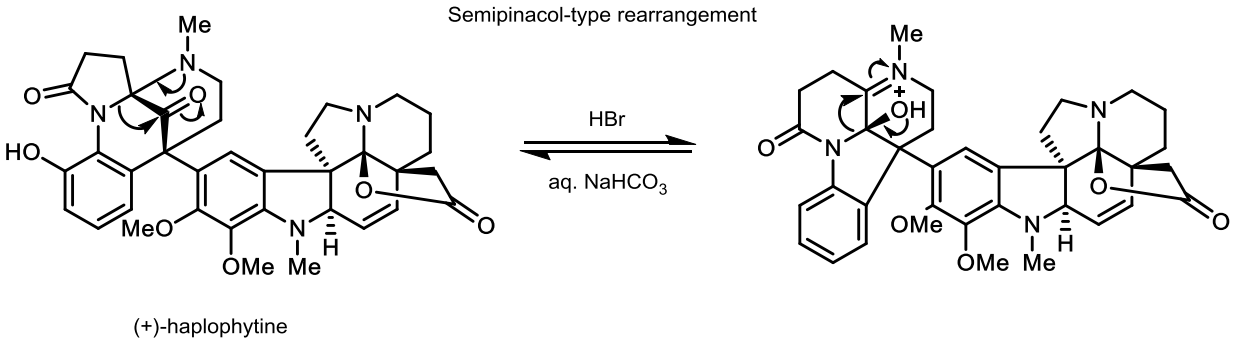


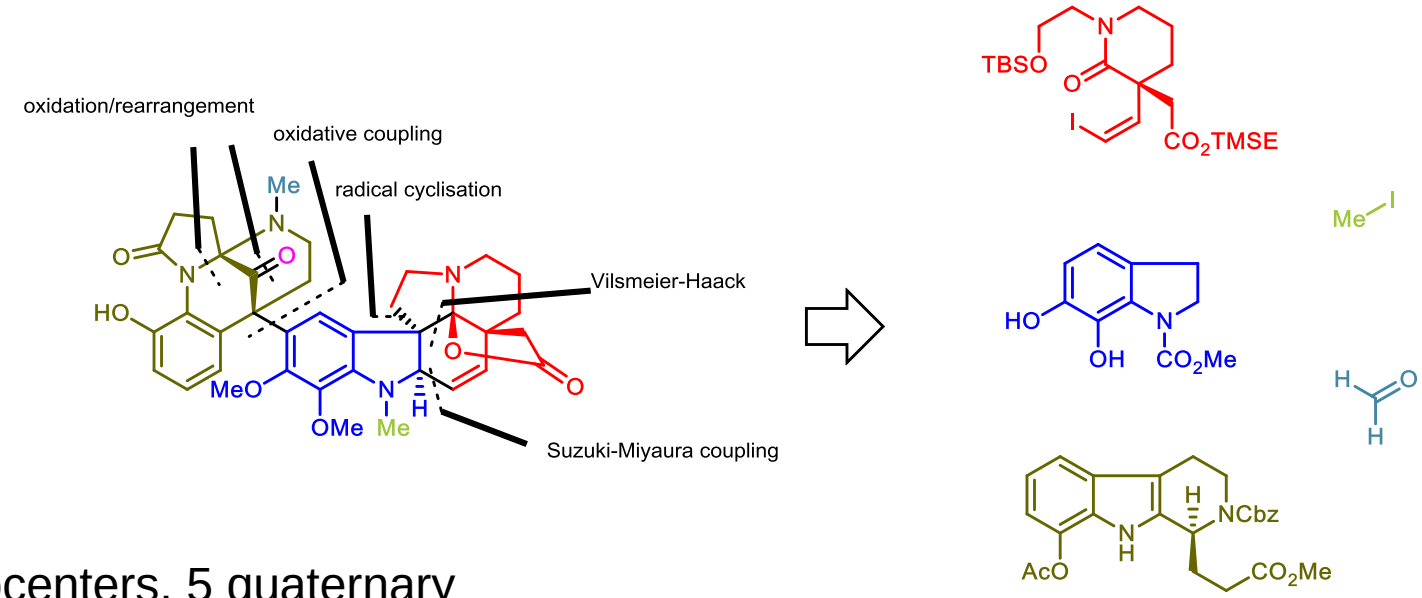
61 + 50 **62** **63** **64** **65** **66**

Ueda, H., et al. (2009). "Total Synthesis of (+)-Haplophytine." Angewandte Chemie International Edition **48**(41): 7600-7603.

K. C. Nicolaou: (+)-Haplophytine



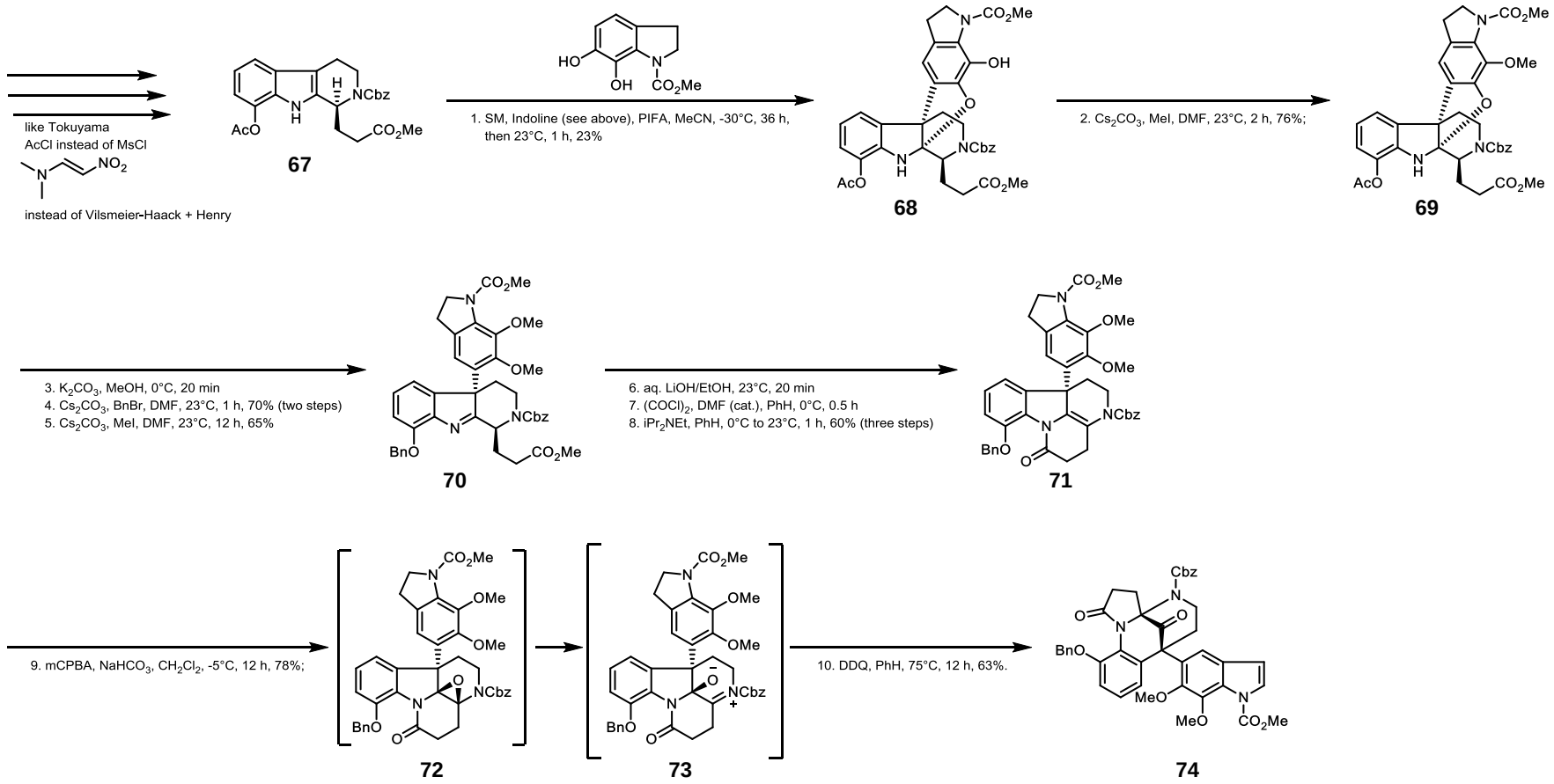




6 stereocenters, 5 quaternary
Highly congested carbon-carbon bond adjoining the two halfves of the molecule
Bridged ketone structure (left)
Aspidosperma alkaloid (right)

Nicolaou, K. C., et al. (2009). "Total Synthesis of (+)-Haplophytine." Angewandte Chemie International Edition **48**(41): 7616-7620.

K. C. Nicolaou: (+)-Haplophytine



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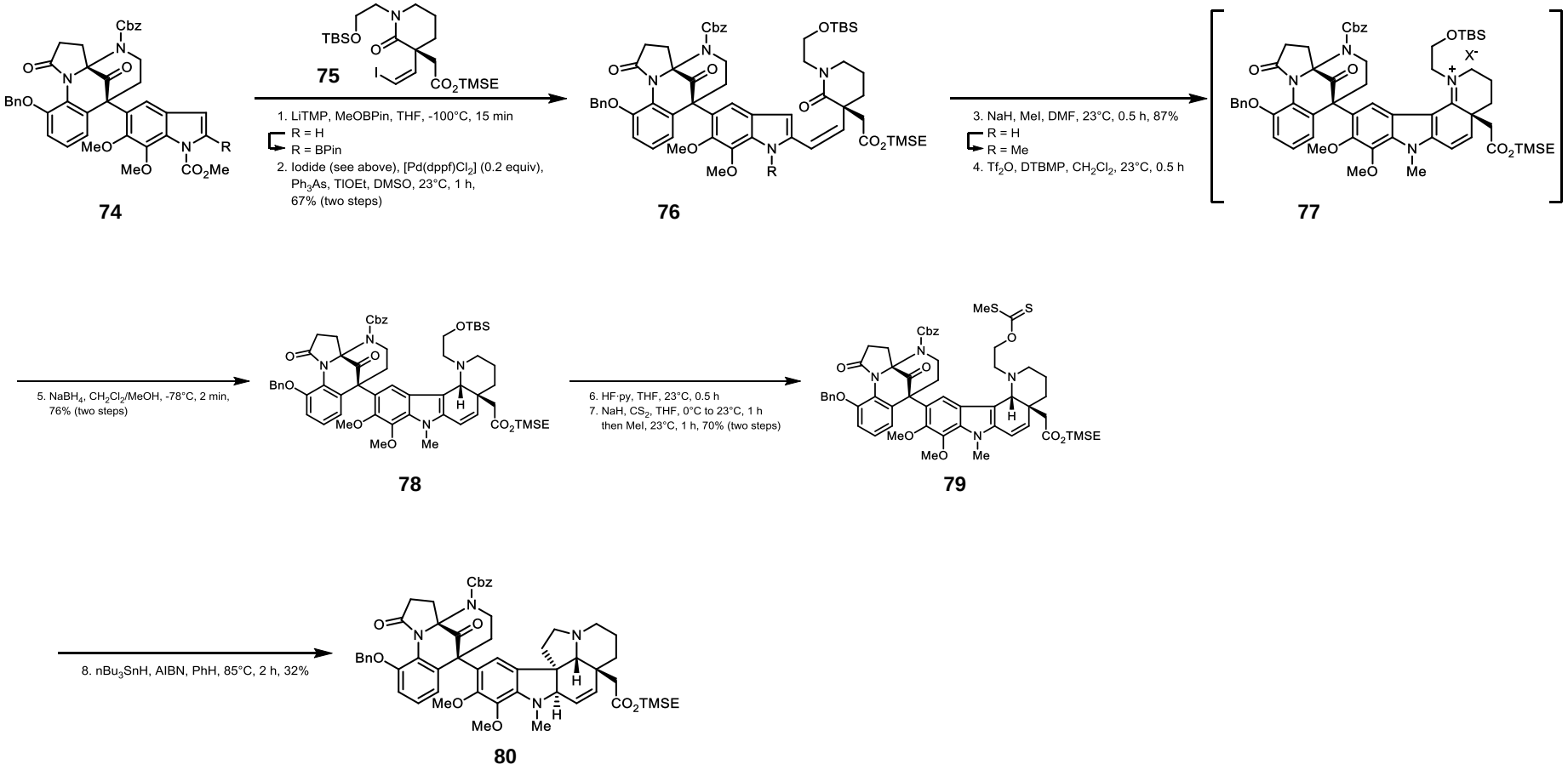

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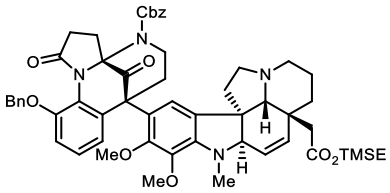
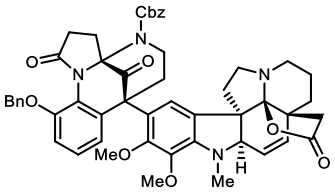


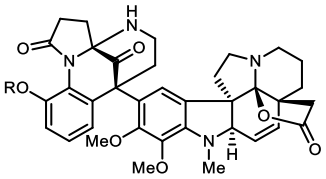
80

1. TBAF, THF, 23°C, 2 h
then $K_3[Fe(CN)_6]$, $NaHCO_3$, $tBuOH/H_2O$,
0.5 h, 71%;



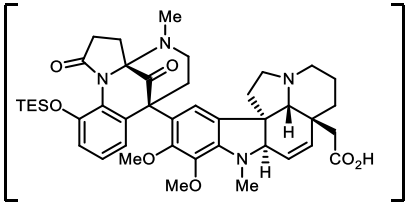
81

2. BCl_3, pentamethylbenzene, CH_2Cl_2, 0°C, 1 h, 58%;



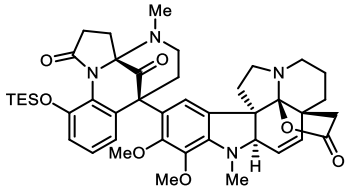
82

3. TESOTf, 2,6-lutidine, CH_2Cl_2, 23°C, 0.5 h, 68%
4. aq. CH_2O, $NaBH_3CN$, AcOH, MeOH, 238C, 0.5 h;



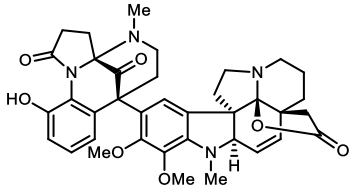
83

5. $K_3[Fe(CN)_6]$, $NaHCO_3$, $THF/tBuOH/H_2O$, 23°C, 15 min



84

6. TBAF, THF, 23°C, 0.5 h, 42% (three steps)

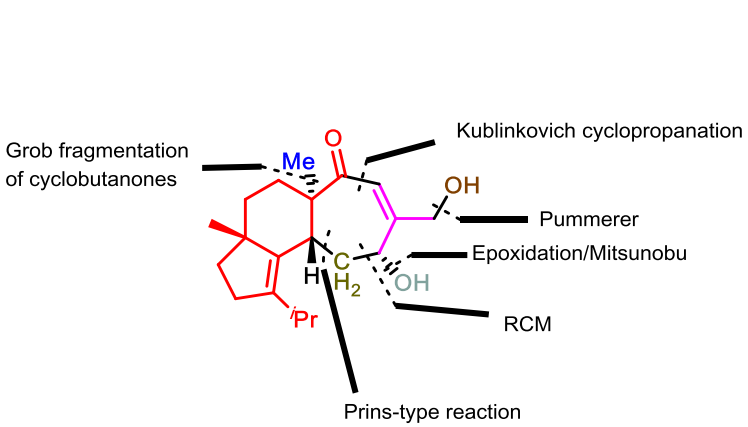


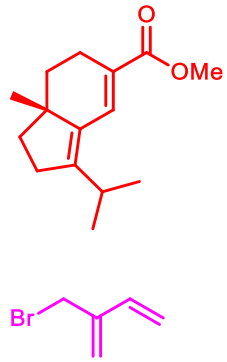
haplophytine

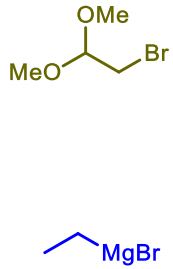
85

Nicolaou, K. C., et al. (2009). "Total Synthesis of (+)-Haplophytine." Angewandte Chemie International Edition **48**(41): 7616-7620.

J. K. Cha: Cyathin A_3 und Cyathin B_2



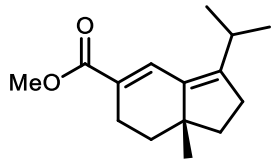


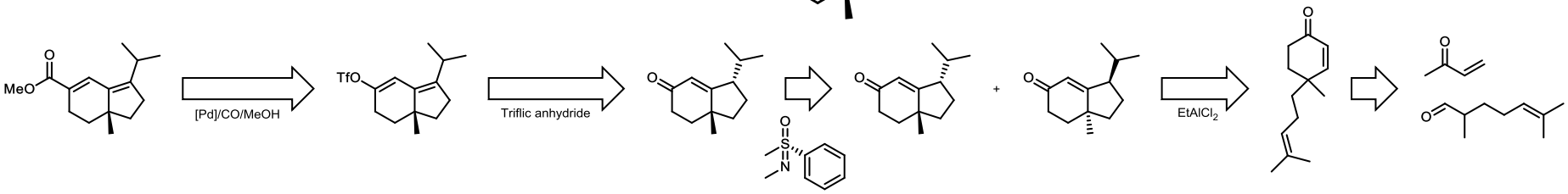


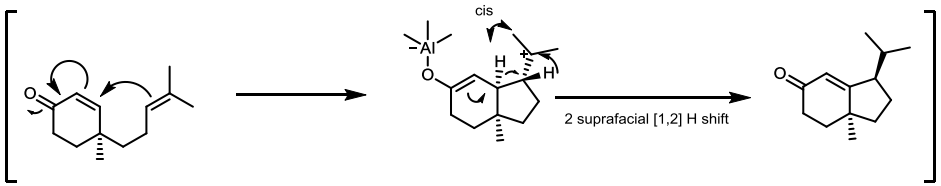
TFAA

$PhCO_2H$ [Mitsunobu after epoxidation]

Starting material

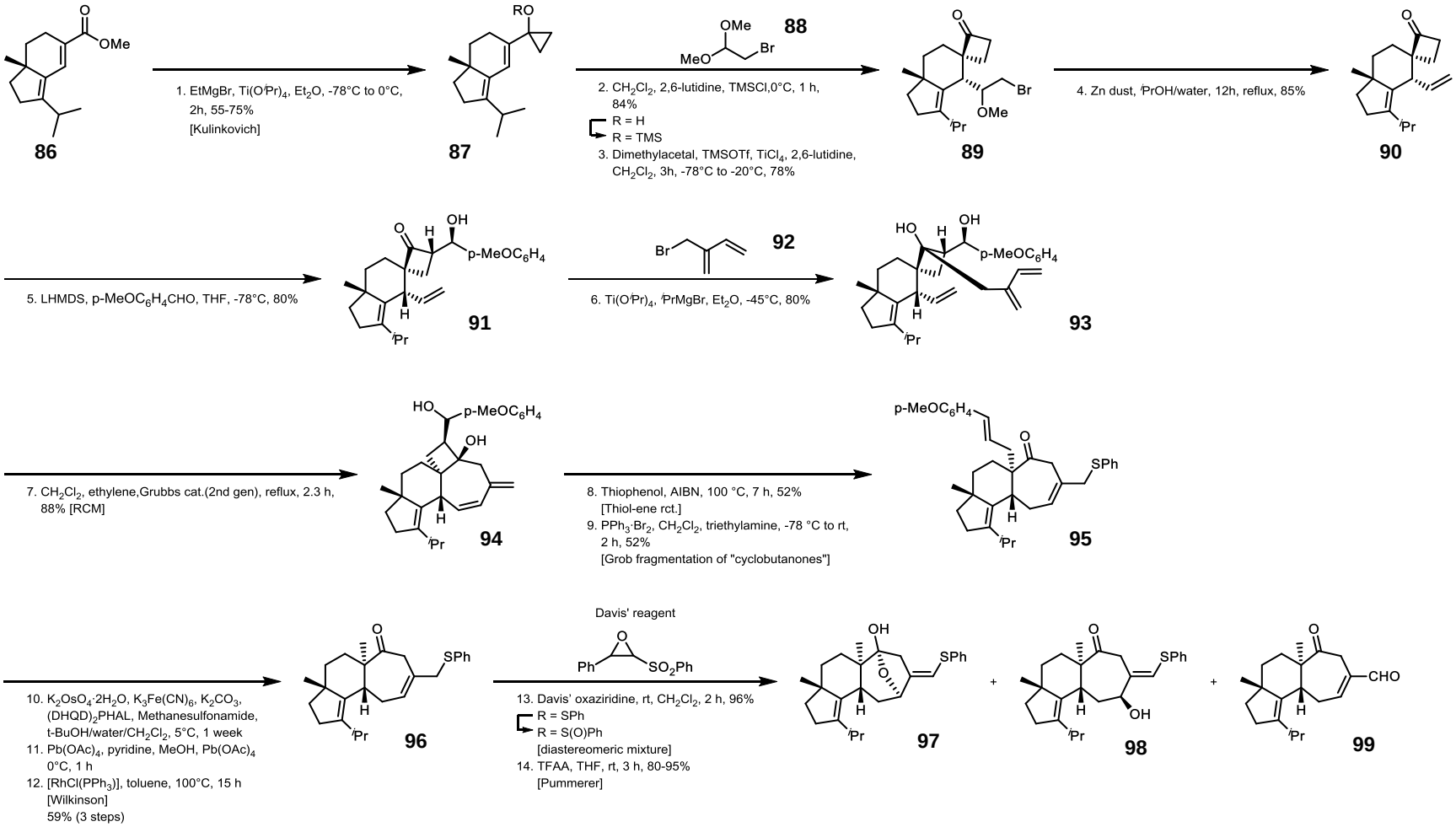






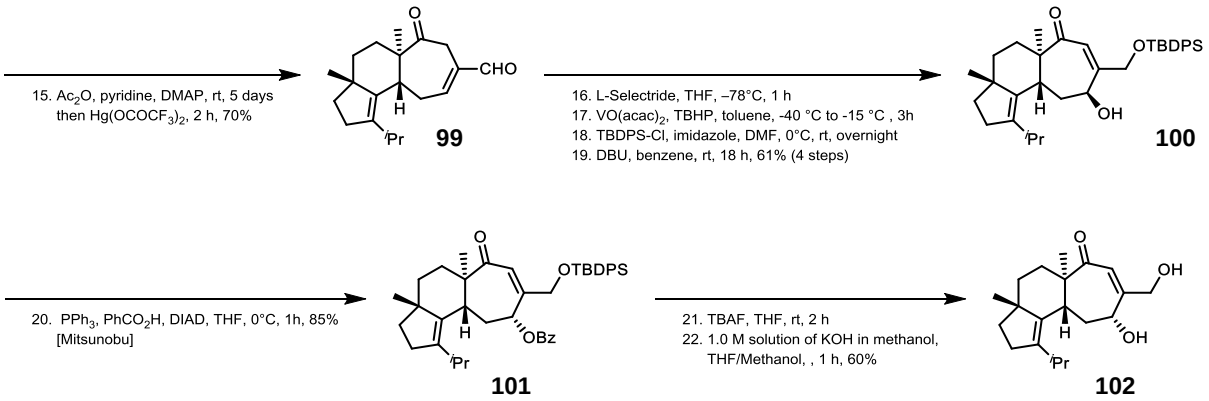
Kim, K. and J. K. Cha (2009). "Total Synthesis of Cyathin A3 and Cyathin B2." Angewandte Chemie International Edition **48**(29): 5334-5336.
Snider, B. B., et al. (1998). "Synthesis of (±)-Allocyathin B2 and (+)-Erinacine A." The Journal of Organic Chemistry **63**(14): 4732-4740.
Paquette, L. A. and T. M. Heidelbaugh (1998). "Studies directed to the synthesis of the antifungal antibiotic aleurodiscal. Enantioselective construction of an advanced beta-D-xyloside congener." Synthesis (Stuttgart): 495-508.
Snider, B. B., et al. (1980). "Lewis acid induced conjugate addition of alkenes to .alpha.,.beta.-unsaturated ketones or aldehydes." Journal of the American Chemical Society **102**(18): 5872-5880.

J. K. Cha: Cyathin A_3 und Cyathin B_2



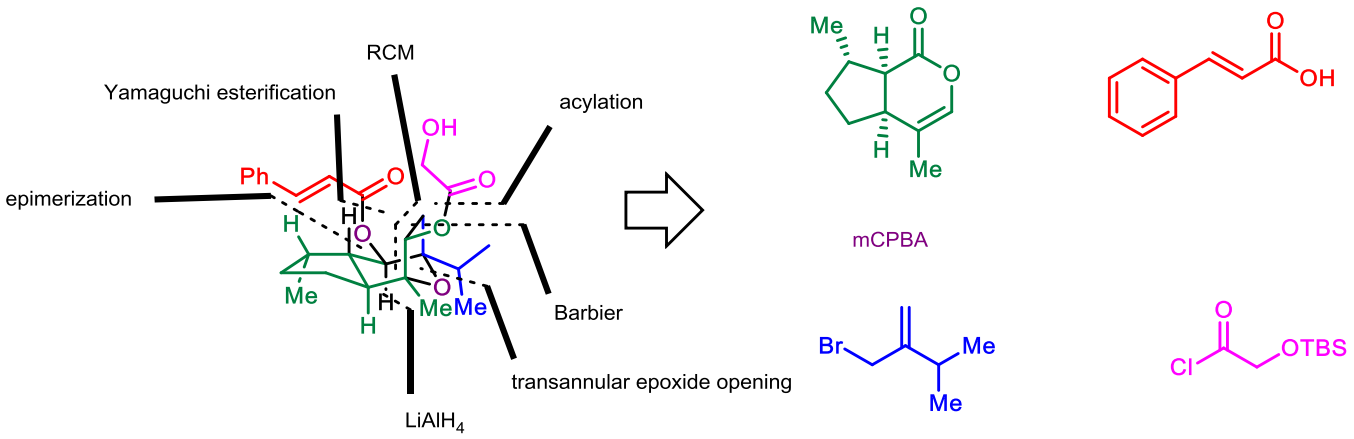
Kim, K. and J. K. Cha (2009). "Total Synthesis of Cyathin A3 and Cyathin B2." Angewandte Chemie International Edition **48**(29): 5334-5336.

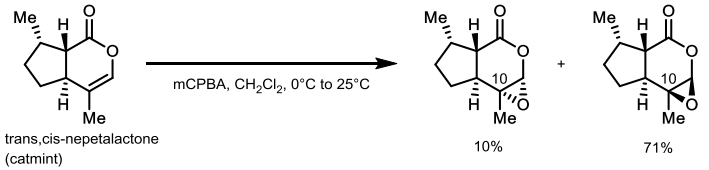
J. K. Cha: Cyathin A_3 und Cyathin B_2



Kim, K. and J. K. Cha (2009). "Total Synthesis of Cyathin A3 and Cyathin B2." Angewandte Chemie International Edition **48**(29): 5334-5336.

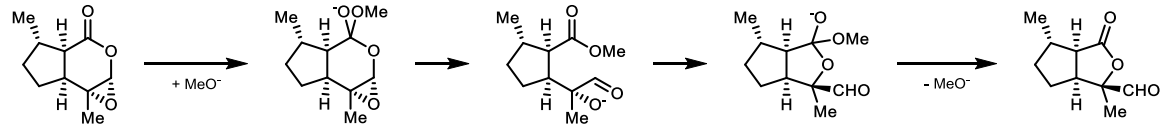
M. Christmann: Englerin A





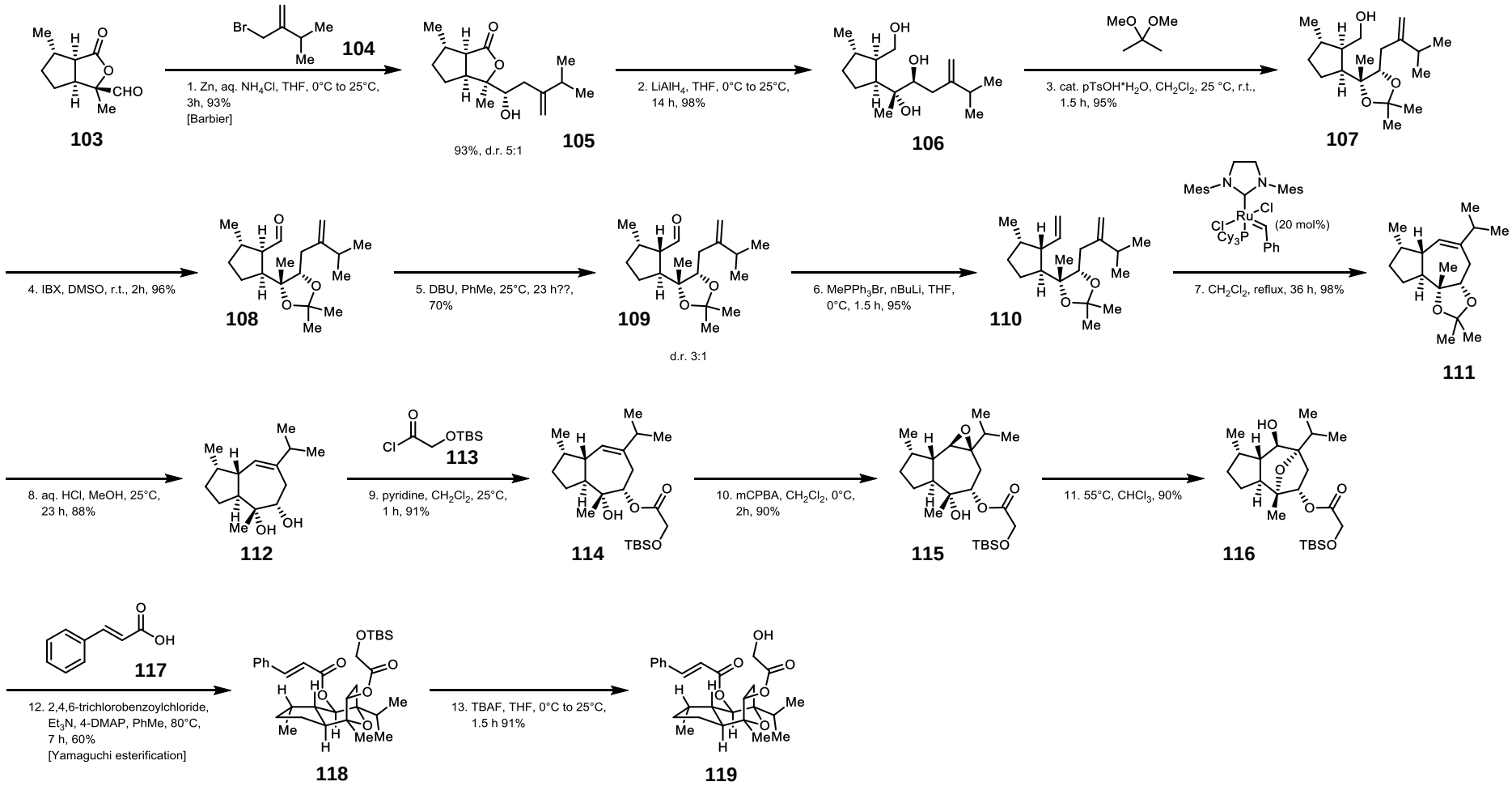
Correct configuration at C10, late-stage isomerisation at C5

Ring contraction of a epoxylactone into a formyl lactone



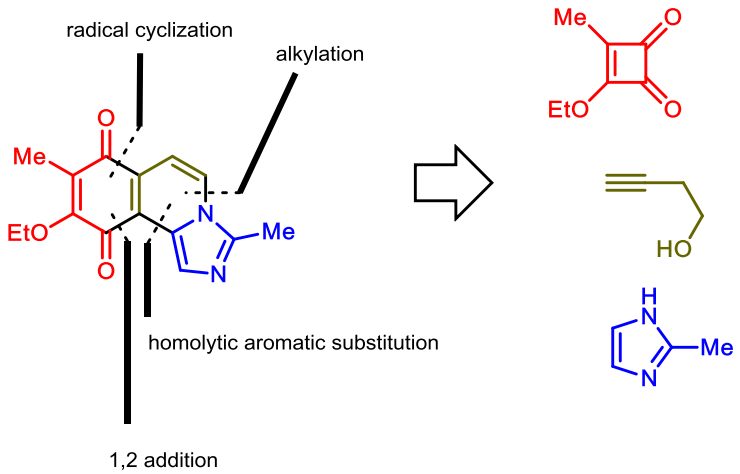
Willot, M., et al. (2009). "Total Synthesis and Absolute Configuration of the Guaiane Sesquiterpene Englerin A." Angewandte Chemie International Edition **48**(48): 9105-9108.

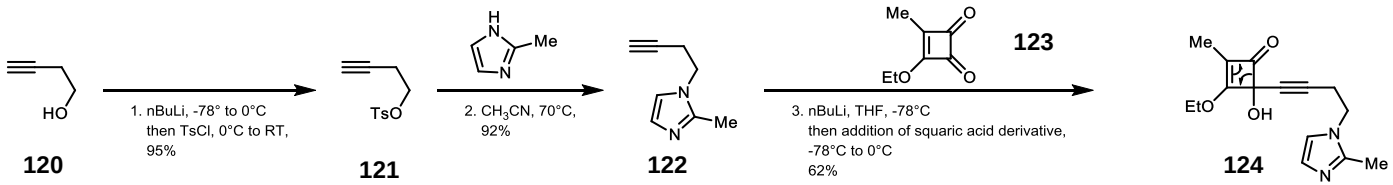
M. Christmann: Englerin A



Willot, M., et al. (2009). "Total Synthesis and Absolute Configuration of the Guaiane Sesquiterpene Englerin A." Angewandte Chemie International Edition **48**(48): 9105-9108.

S. F. Martin: Cribrostatin 6





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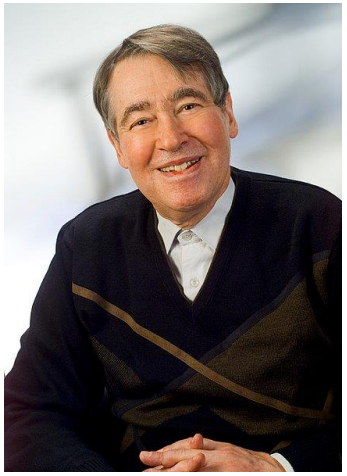
Knueppel, D. and S. F. Martin (2009). "Total Synthesis of Cribrostatin 6." Angewandte Chemie International Edition **48**(14): 2569-2571.

J. Mulzer: Kendomycin



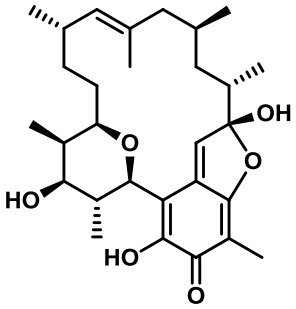
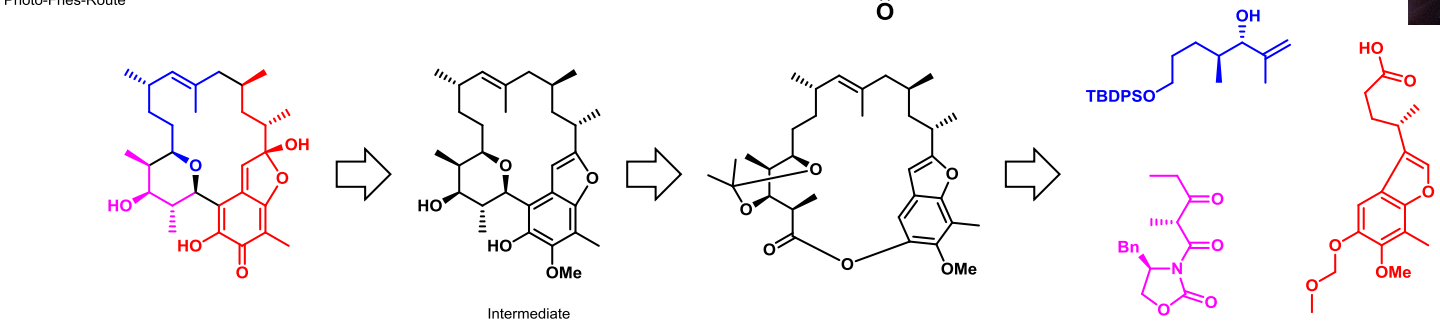
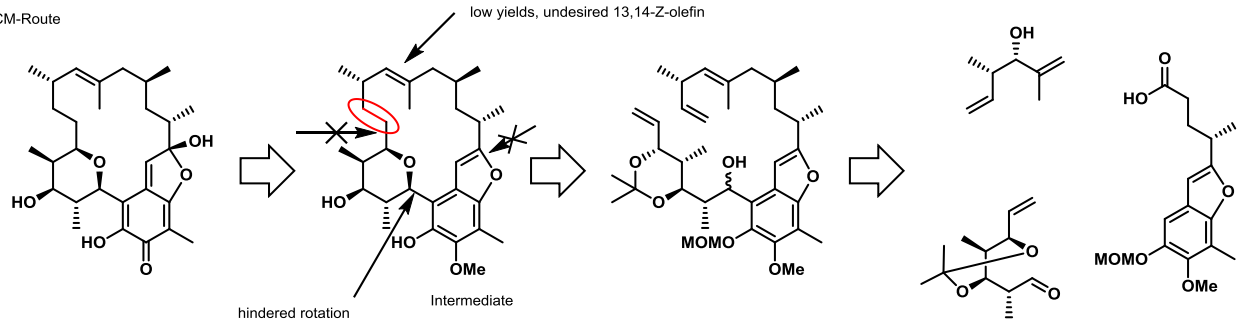


Photo-Fries-Route



29 linear steps

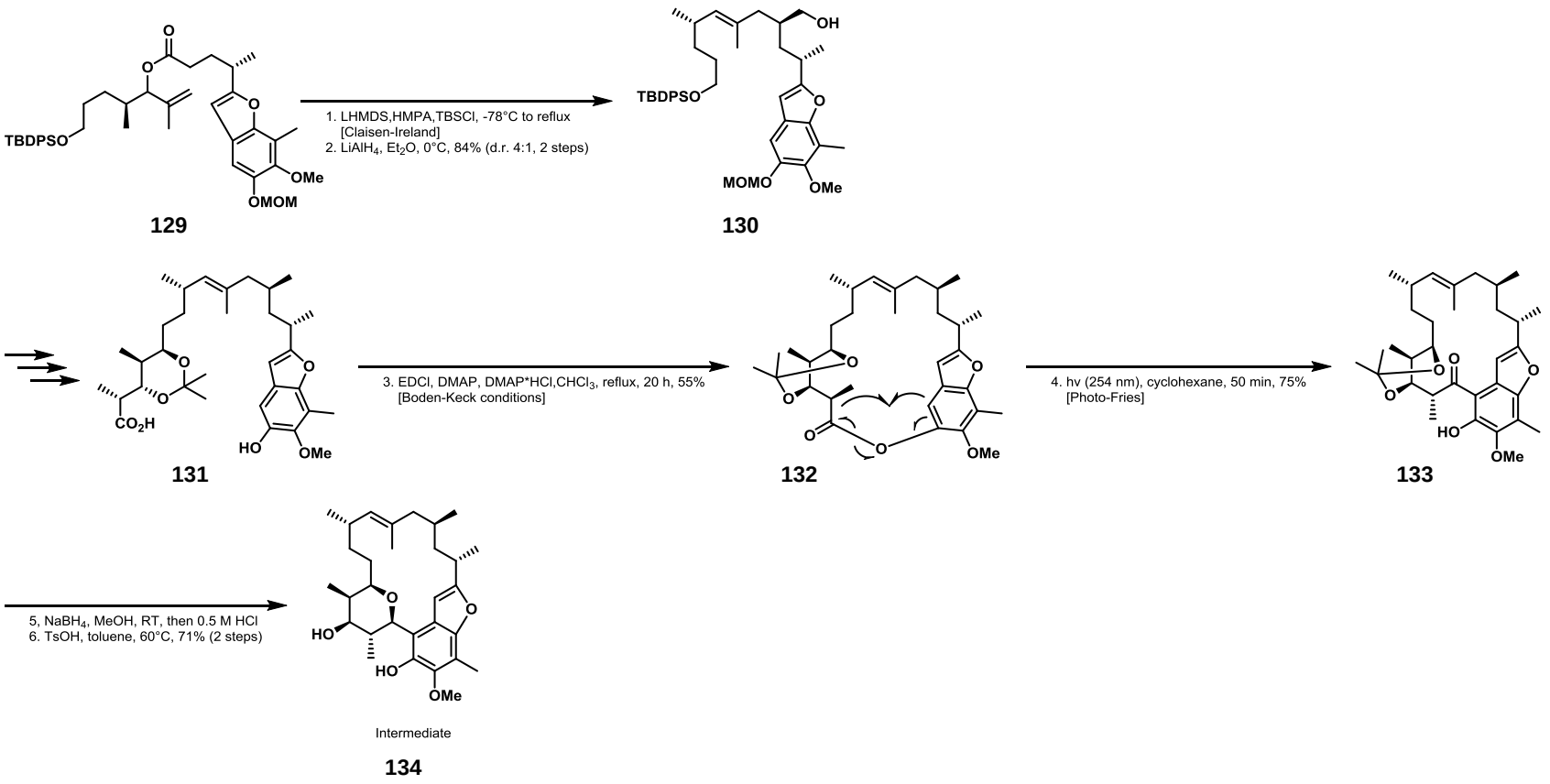
RCM-Route



23 linear steps

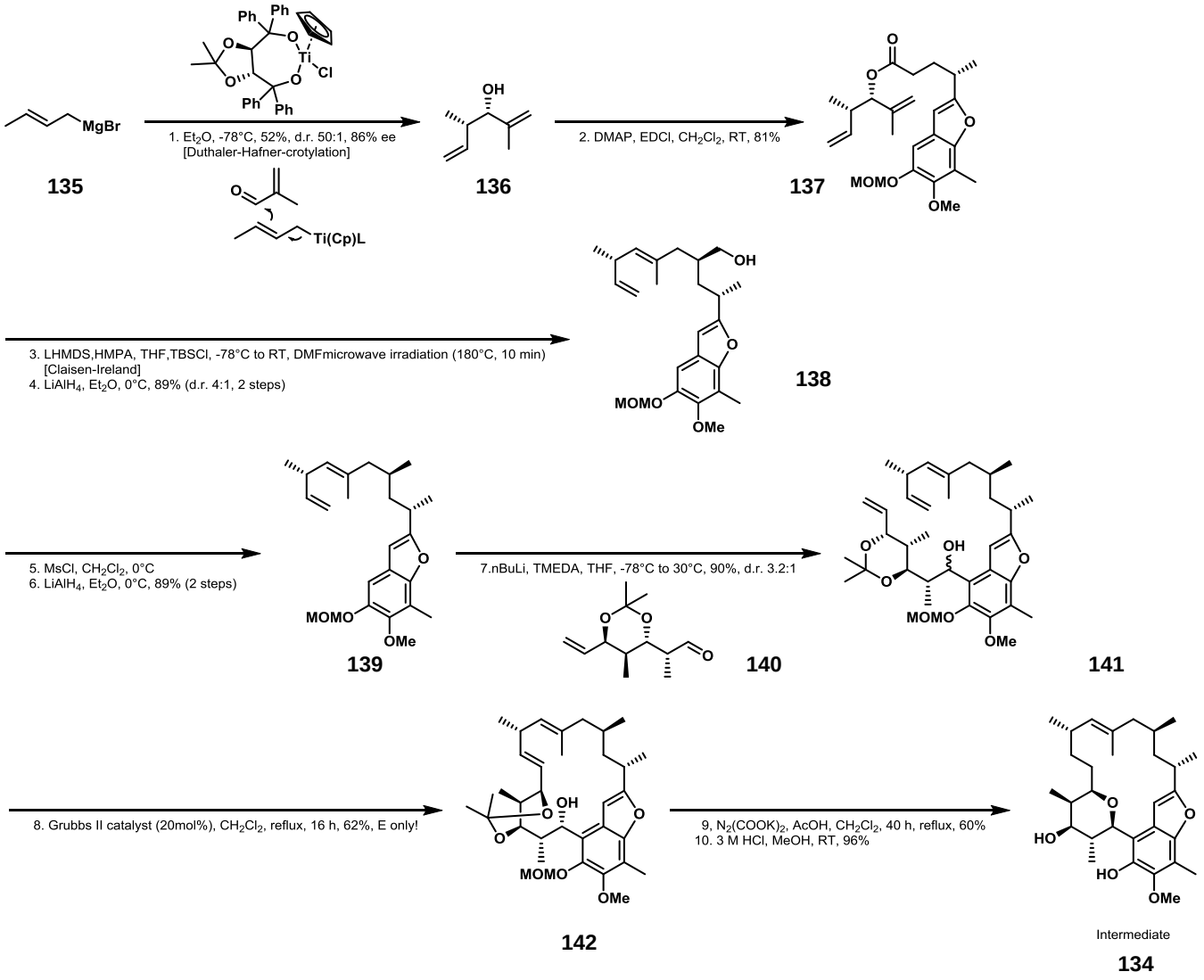
Magauer, T., et al. (2009). "Total Synthesis of the Antibiotic Kendomycin by Macrocyclization using Photo-Fries Rearrangement and Ring-Closing Metathesis." Angewandte Chemie International Edition **48**(33): 6032-6036.

J. Mulzer: Kendomycin



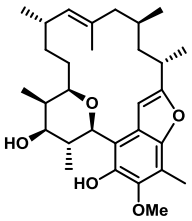
Magauer, T., et al. (2009). "Total Synthesis of the Antibiotic Kendomycin by Macrocyclization using Photo-Fries Rearrangement and Ring-Closing Metathesis." Angewandte Chemie International Edition **48**(33): 6032-6036.

J. Mulzer: Kendomycin



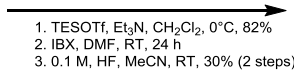
Magauer, T., et al. (2009). "Total Synthesis of the Antibiotic Kendomycin by Macrocyclization using Photo-Fries Rearrangement and Ring-Closing Metathesis." Angewandte Chemie International Edition **48**(33): 6032-6036.

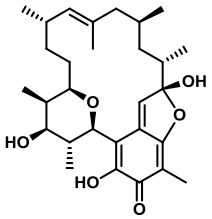
J. Mulzer: Kendomycin



Intermediate

134

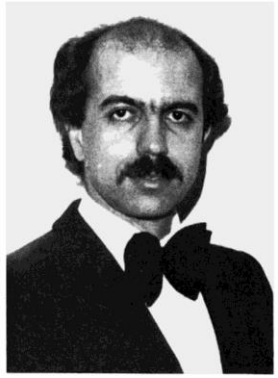


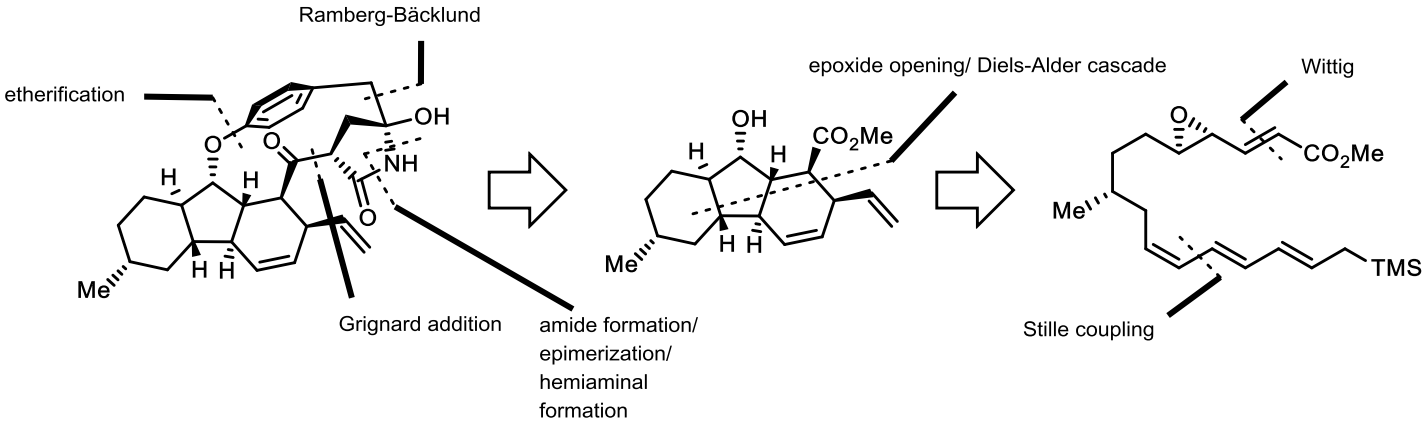


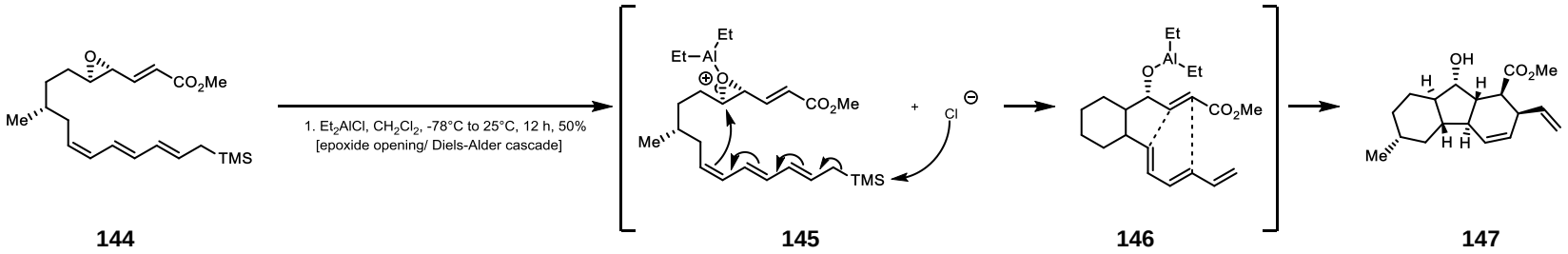
143

Magauer, T., et al. (2009). "Total Synthesis of the Antibiotic Kendomycin by Macrocyclization using Photo-Fries Rearrangement and Ring-Closing Metathesis." Angewandte Chemie International Edition **48**(33): 6032-6036.

K. C. Nicolaou: Hirsutellone B





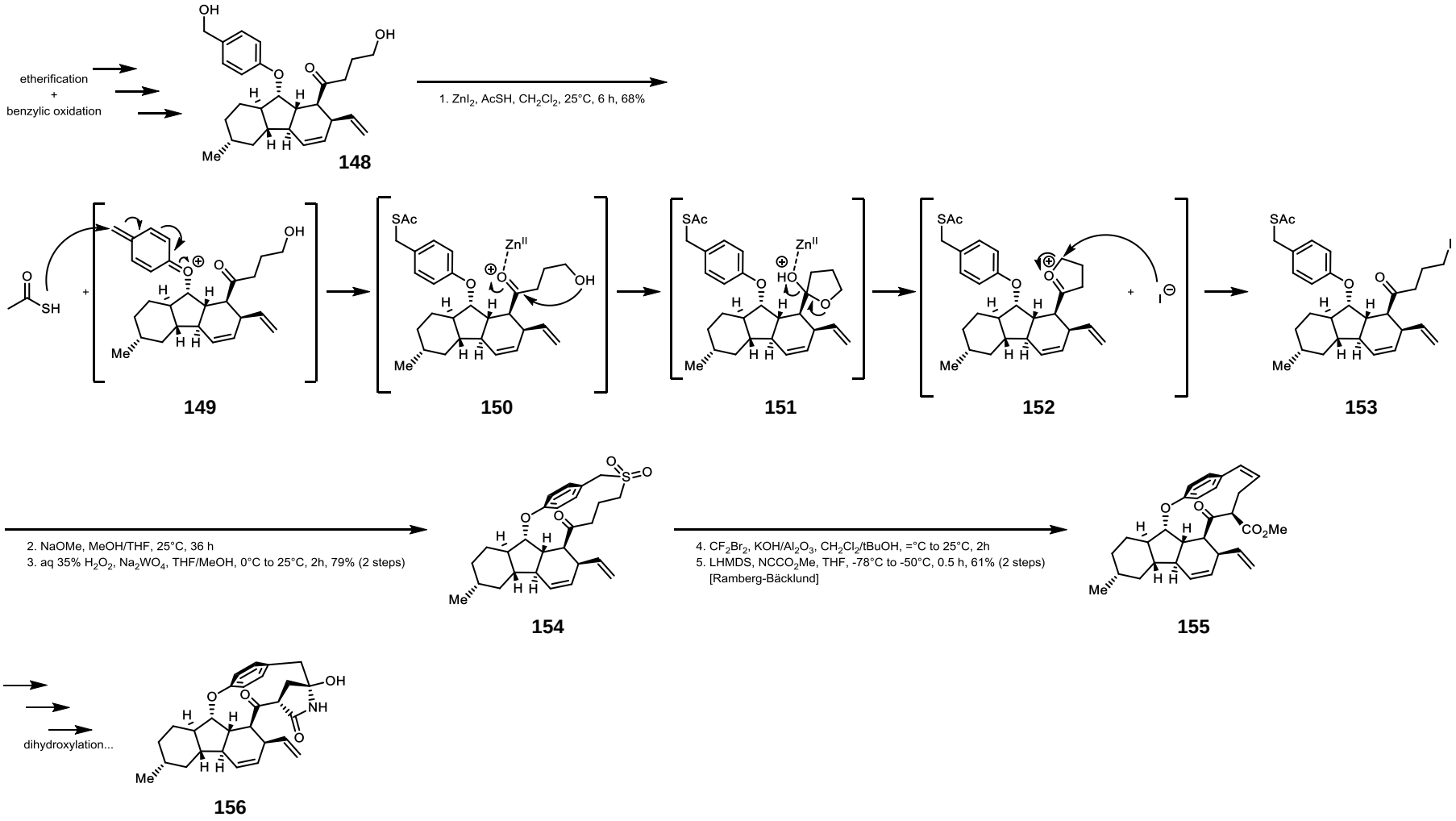


Synthetically challenging:

13-membered strained p-cyclophane

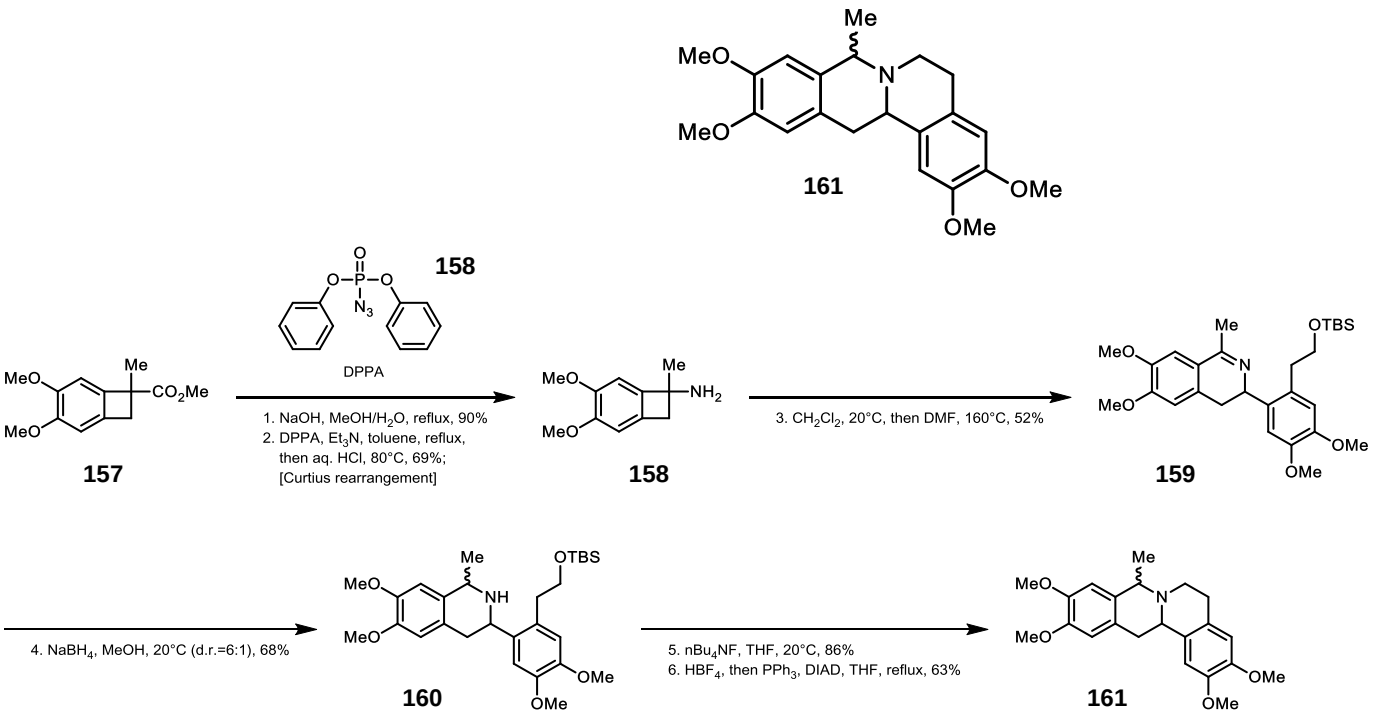
Nicolaou, K. C., et al. (2009). "Total Synthesis of Hirsutellone B." Angewandte Chemie **121**(37): 7002-7006.

K. C. Nicolaou: Hirsutellone B

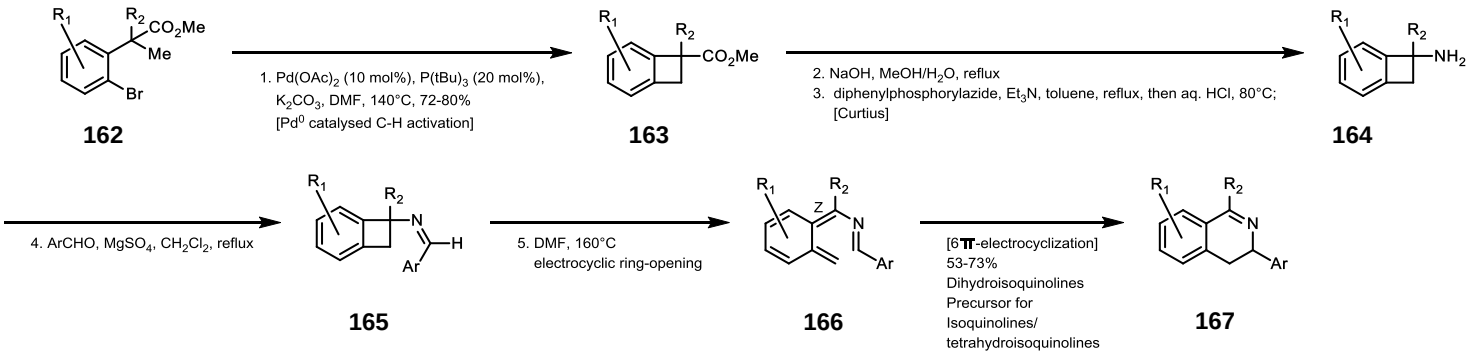


Nicolaou, K. C., et al. (2009). "Total Synthesis of Hirsutellone B." Angewandte Chemie **121**(37): 7002-7006.

O. Baudoin: Coralydine



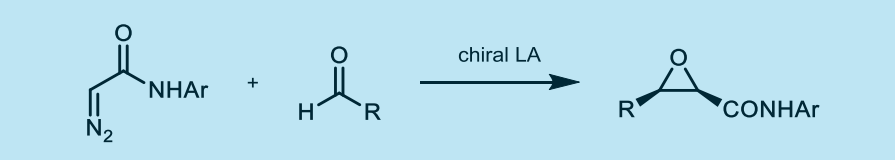
Alternative for Bischler Napieralski



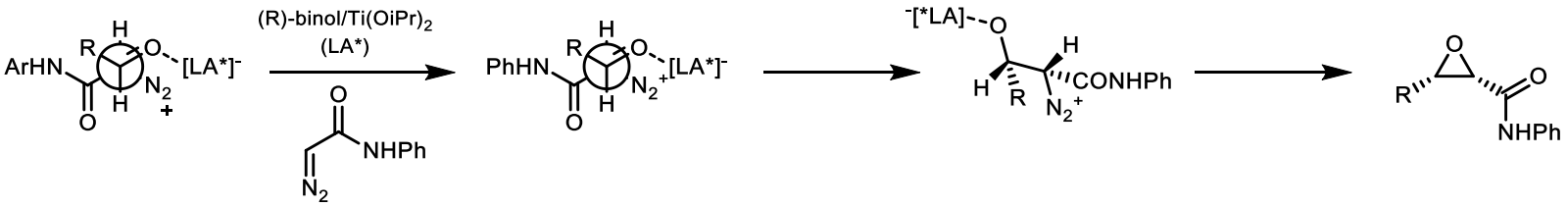
R_1= CF_3,OMe, H
R_2= Me, nPr
Ar = subst.
Ph, pyr, furan
Subst.: CF_3, Cl

Chaumontet, M., et al. (2009). "Synthesis of 3,4-Dihydroisoquinolines by a C(sp3)H Activation/Electrocyclization Strategy: Total Synthesis of Coralydine." Angewandte Chemie International Edition **48**(1): 179-182.

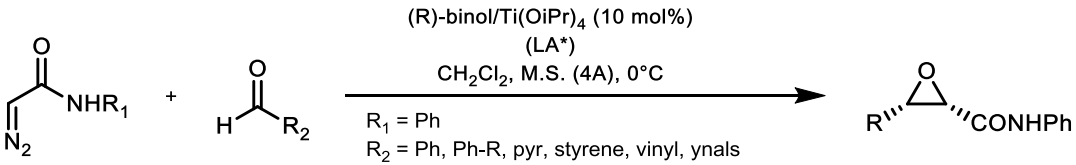
L.-Z. Gong: Asymmetric catalytic Darzens reaction



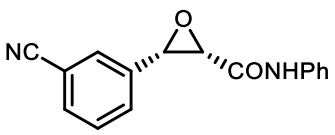
Proposed reaction mechanism:



Scope:

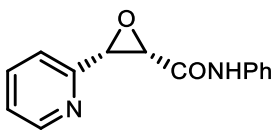


168 **169** **170**



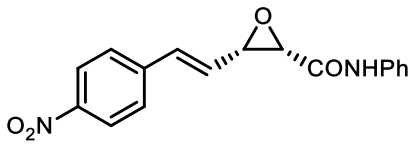
Yield: 95%, ee: 99%

171



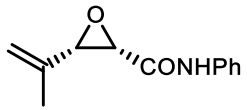
Yield: 81%, ee: 97%

172



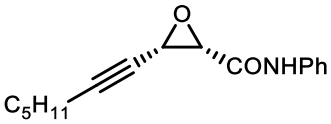
Yield: 52%, ee: 95%

173



Yield: 62%, ee: 98%

174

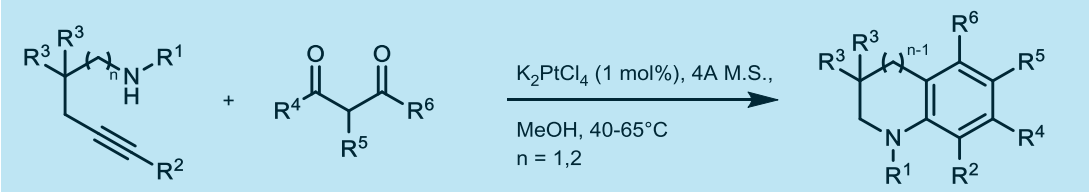


Yield: 66%, ee: 88%

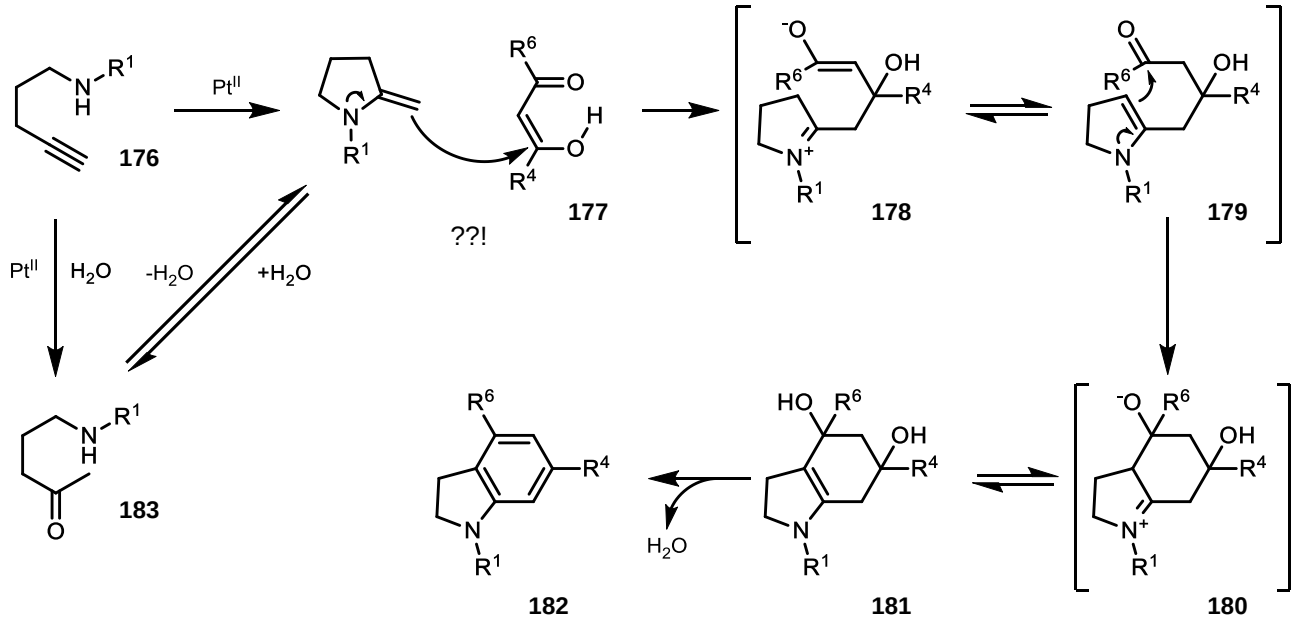
175

Liu, W.-J., et al. (2009). "An Asymmetric Catalytic Darzens Reaction between Diazoacetamides and Aldehydes Generates cis-Glycidic Amides with High Enantiomeric Purity." Angewandte Chemie **121**(35): 6625-6628.

C.-M. Che: Multiply substituted Indolines/ Tetrahydroquinolines by Pt(II) catalysed Tandem reaction



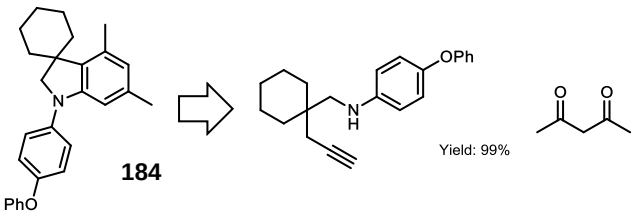
Proposed reaction mechanism:



Liu, X.-Y. and C.-M. Che (2009). "Highly Efficient and Regioselective Platinum(II)-Catalyzed Tandem Synthesis of Multiply Substituted Indolines and Tetrahydroquinolines." Angewandte Chemie International Edition **48**(13): 2367-2371.

C.-M. Che: Multiply substituted Indolines/ Tetrahydroquinolines by Pt(II) catalysed Tandem reaction

Scope:



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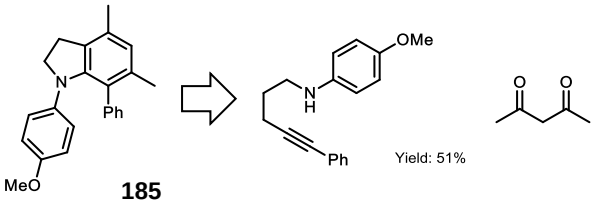

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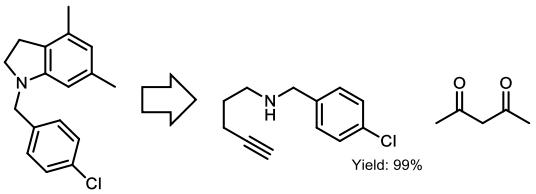

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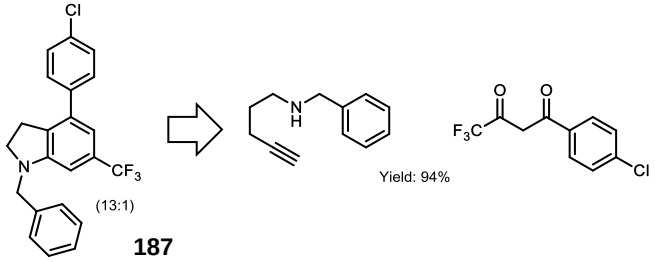

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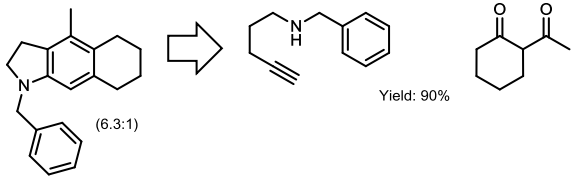

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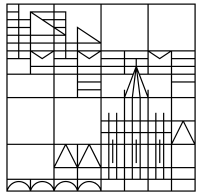
Liu, X.-Y. and C.-M. Che (2009). "Highly Efficient and Regioselective Platinum(II)-Catalyzed Tandem Synthesis of Multiply Substituted Indolines and Tetrahydroquinolines." Angewandte Chemie International Edition **48**(13): 2367-2371.

Universität
Konstanz



Thank you
For your attention!