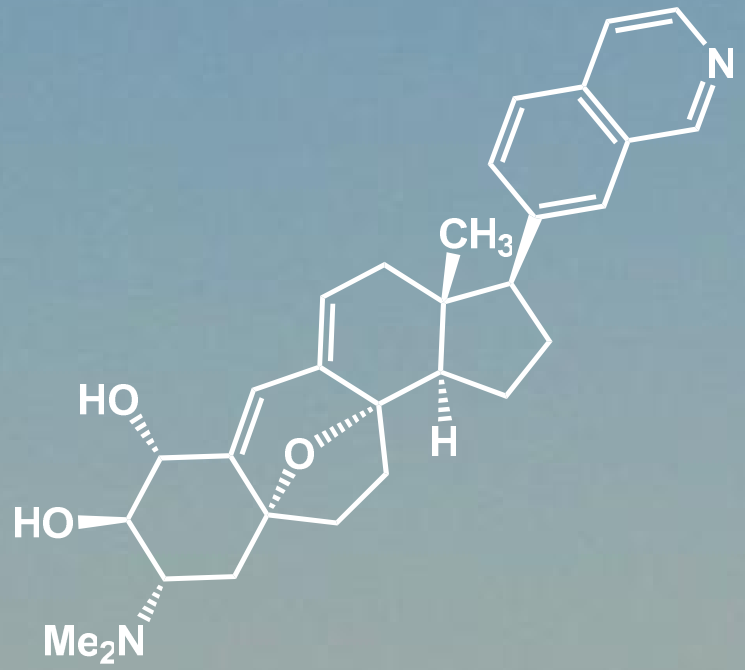
The total syntheses of (+)-Cortistatin A



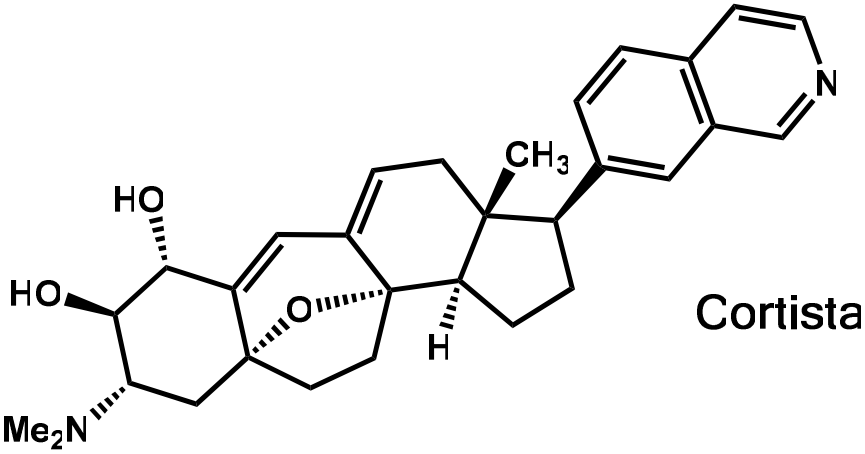
Dr. Tomas Loïc

10/01/2012 Biblio-Seminar

Synthèse Totale et Réactivité Organique

Cortistatin A : presentation

- Cytotoxic steroidal alkaloid extracted from a marine sponge called *Corticium simplex*
- Molecule discovered and isolated in 2006 by Kobayashi along 3 other closed related molecules



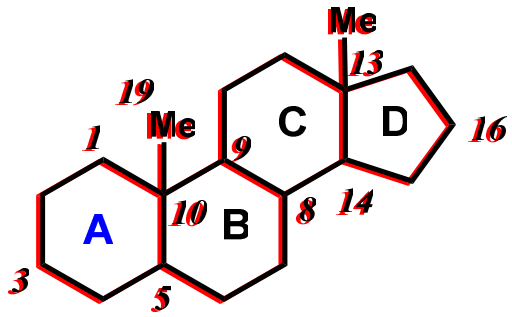
Cortistatin A

- The rest of the family was disclosed in 2007 by kobayashi

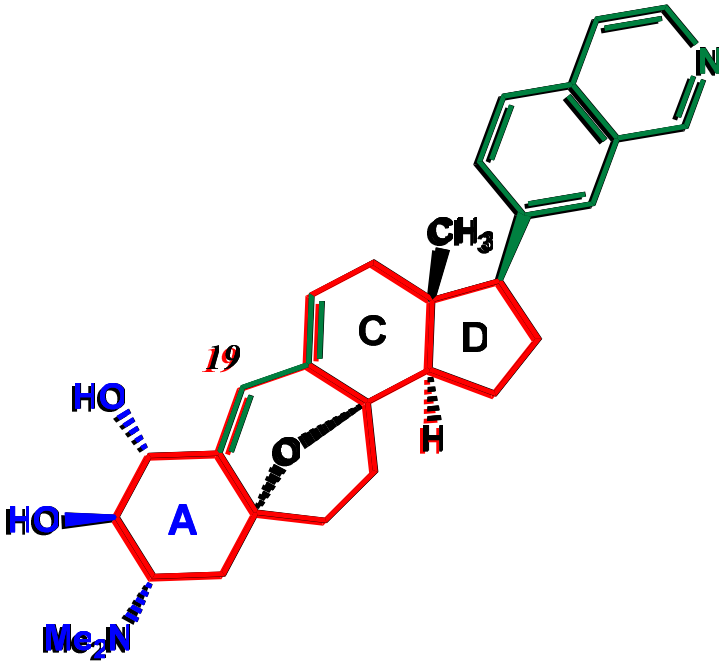
Cortistatins E, F, G, H, I, J, K, L

Cortistatin A : interest of the steroid

- Structural particularities :



Steroidal core



- Common rearranged steroidal core :
  C19 methyl group incorporated into the rare oxabicyclo[3.2.1]octane ring
- Original substitution of the A ring : two hydroxy groups and one dimethylamino group
- Isoquinoline substituant on the D ring and presence of a diene motif

Cortistatin A : interest of the steroid

- Biological properties :

- Important antiproliferative activity against human umbilical vein endothelial cells
  IC_{50} = 1.8 nM

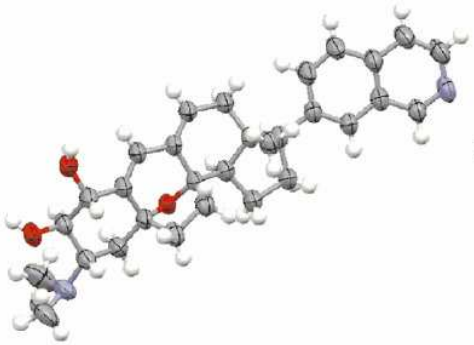
- A potent inhibitor of angiogenesis (processus of new blood vessels generation)

- Studies show no general toxicity toward either healthy or cancerous cell lines
  $IC_{50(testing\ cells)}/IC_{50(HUVECs)} > 3300$

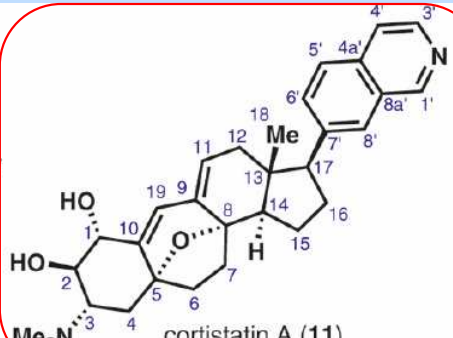
- Preliminary SAR's studies suggest isoquinoline moiety crucial for potent activity

Potential use in cancer treatment to reduce the growth of new blood capillaries to tumors

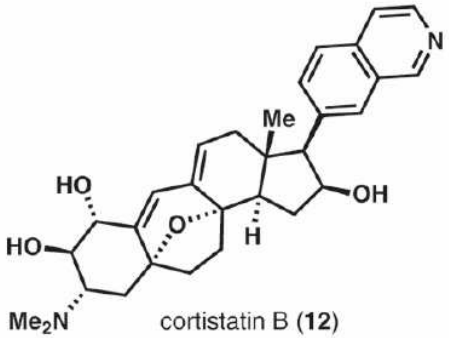
Cortistatin A : and its family



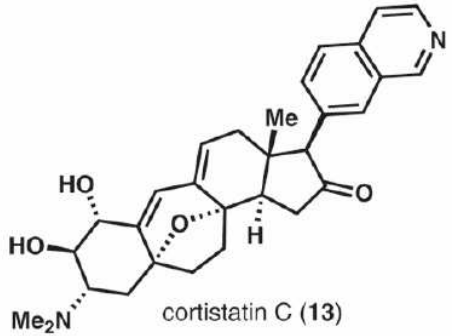
X-ray ≡



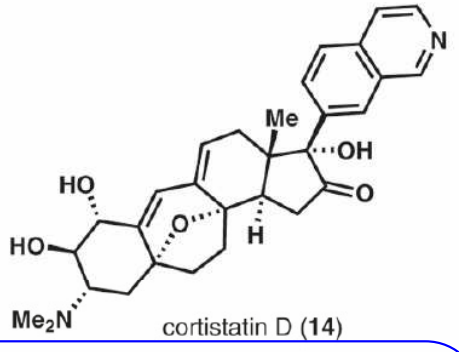
cortistatin A (**11**)



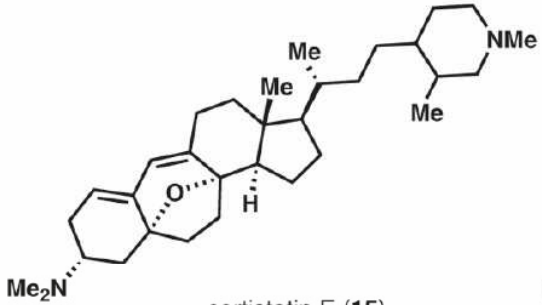
cortistatin B (**12**)



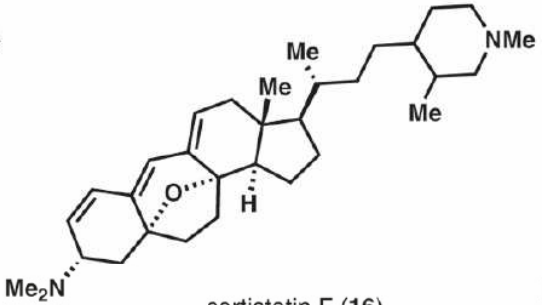
cortistatin C (**13**)



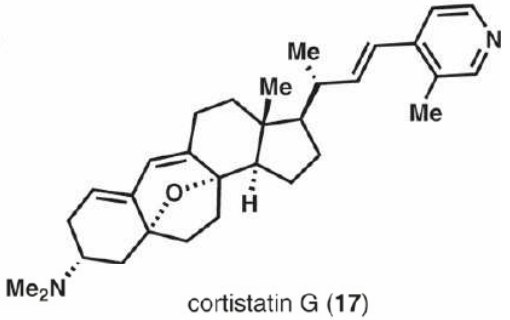
cortistatin D (**14**)



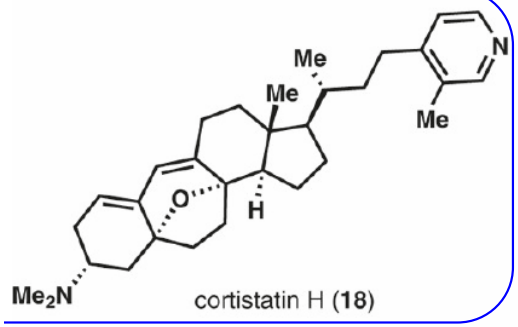
cortistatin E (**15**)



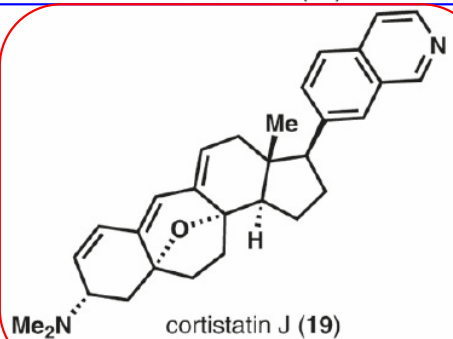
cortistatin F (**16**)



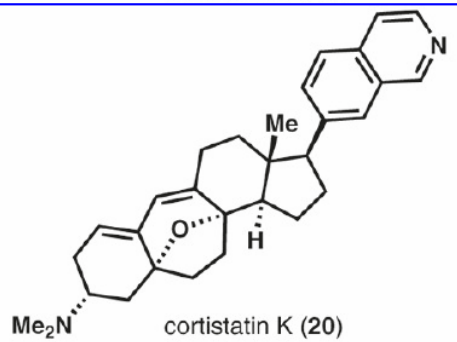
cortistatin G (**17**)



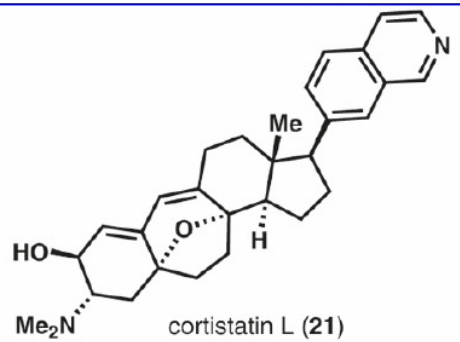
cortistatin H (**18**)



cortistatin J (**19**)



cortistatin K (**20**)



cortistatin L (**21**)

Growth inhibition of cortistatins against HUVECs

cortistatin	A	B	C	D	E	F	G	H	J	K	L
IC_{50}*	0.0018	1.1	0.019	0.15	0.45	1.9	0.80	0.35	0.008	0.04	0.023

*IC_{50} = μM.

Cortistatin A : synthetical studies

- 5 Total syntheses (one semisynthesis) :
  - **2008** : Baran (JACS, **2008**, *130*, 7241)

    Nicolaou – Chen (ACIE, **2008**, *47*, 7310)

    Shair (JACS, **2008**, *130*,1684)
  - **2010** : Myers (NCHEM, **2010**, *2*, 886)
  - **2011** : Hirama (JOC, **2011**, *76*, 2408)

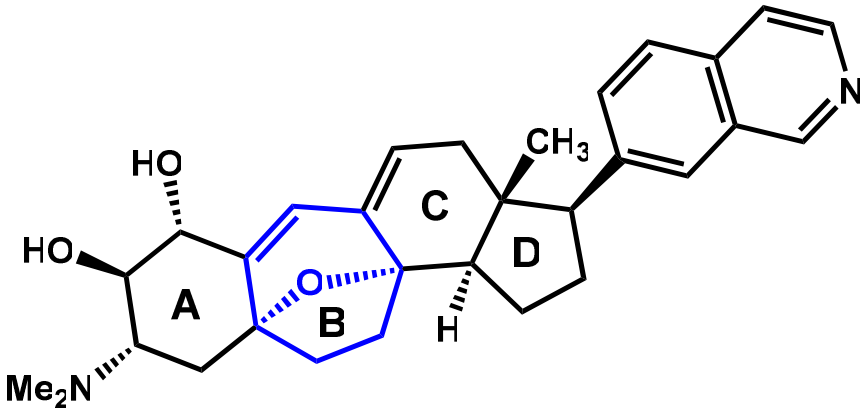
    Baran (JACS, **2011**, *133*, 8014)

- Over a dozen of papers about synthetic studies

  (Gung, Danishefsky, Sarpong, Corey, Sorensen, Stoltz, Magnus…)

Cortistatin A : today's talk

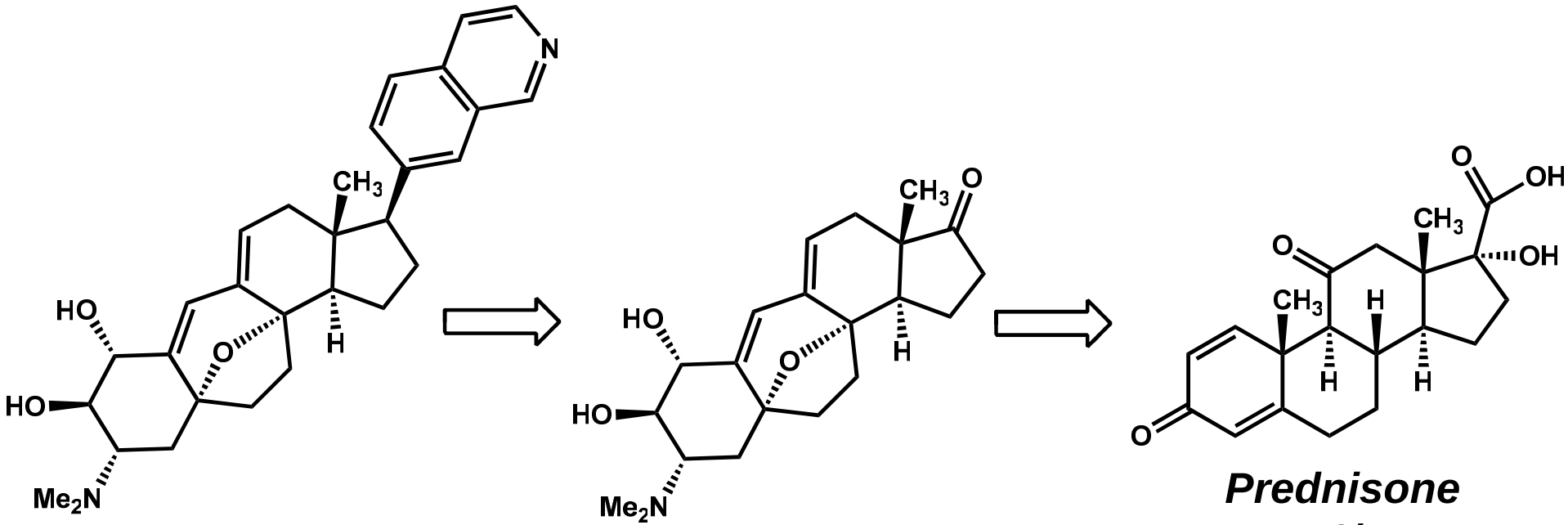
- Quick presentation of the 5 total syntheses of the natural alkaloid with emphasis on the B-ring formation and key steps



- The 5 total syntheses display the most recurrent approaches for the B-ring construction :
  - Ring expansion through cyclopropane fragmentation
  - Oxidative dearomatization
  - Domino sequence
  - Electrocyclisation

Cortistatin A : Baran's semisynthesis

- Retrosynthesis :

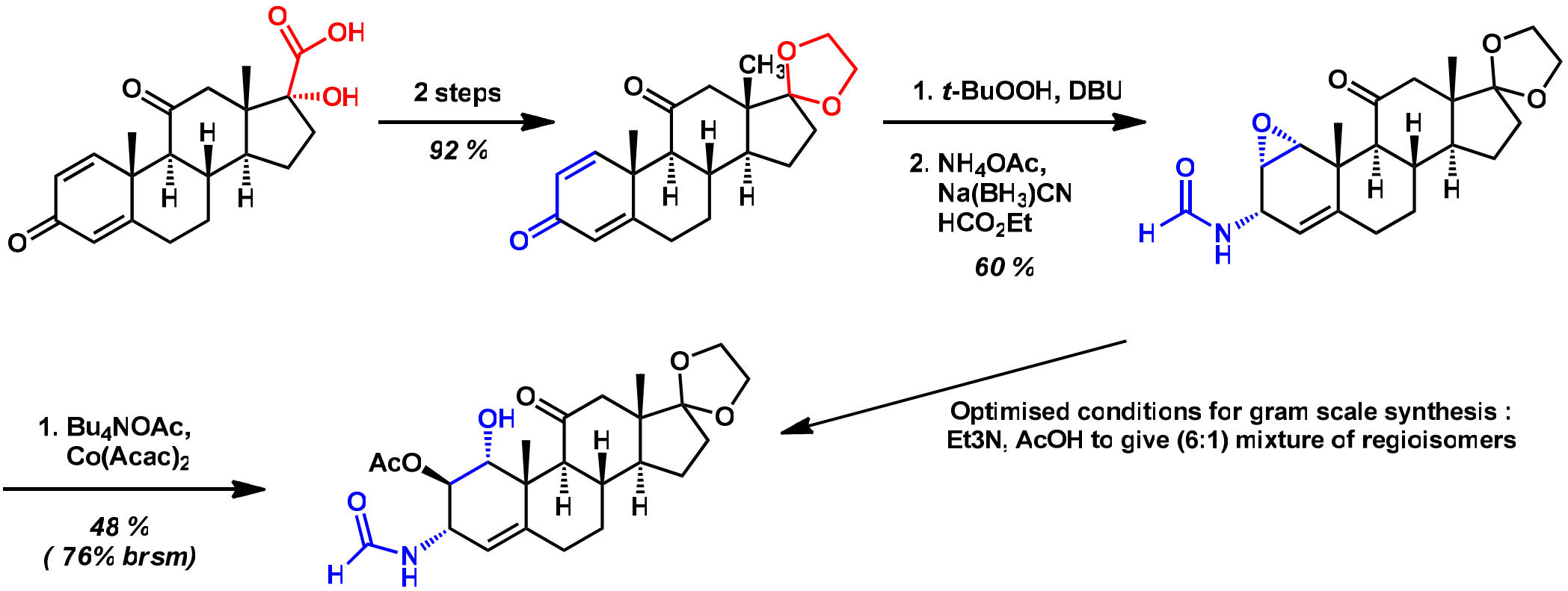


- Key steps : - cyclopropane fragmentation/ring expansion

  - Bridging bicyclic ether by conjugated displacement

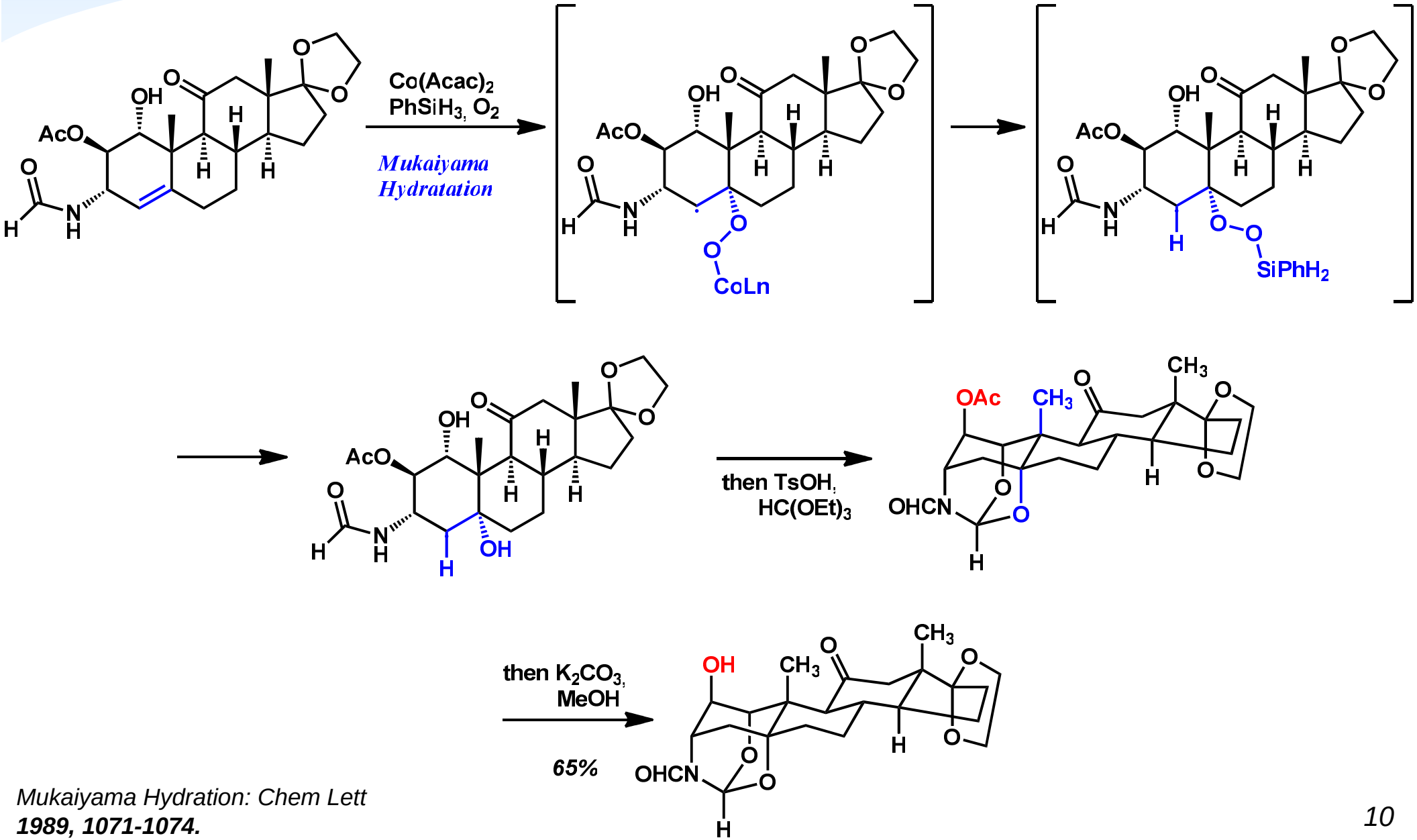
Cortistatin A : Baran's semisynthesis

- A-ring functionalization :



Cortistatin A : Baran's semisynthesis

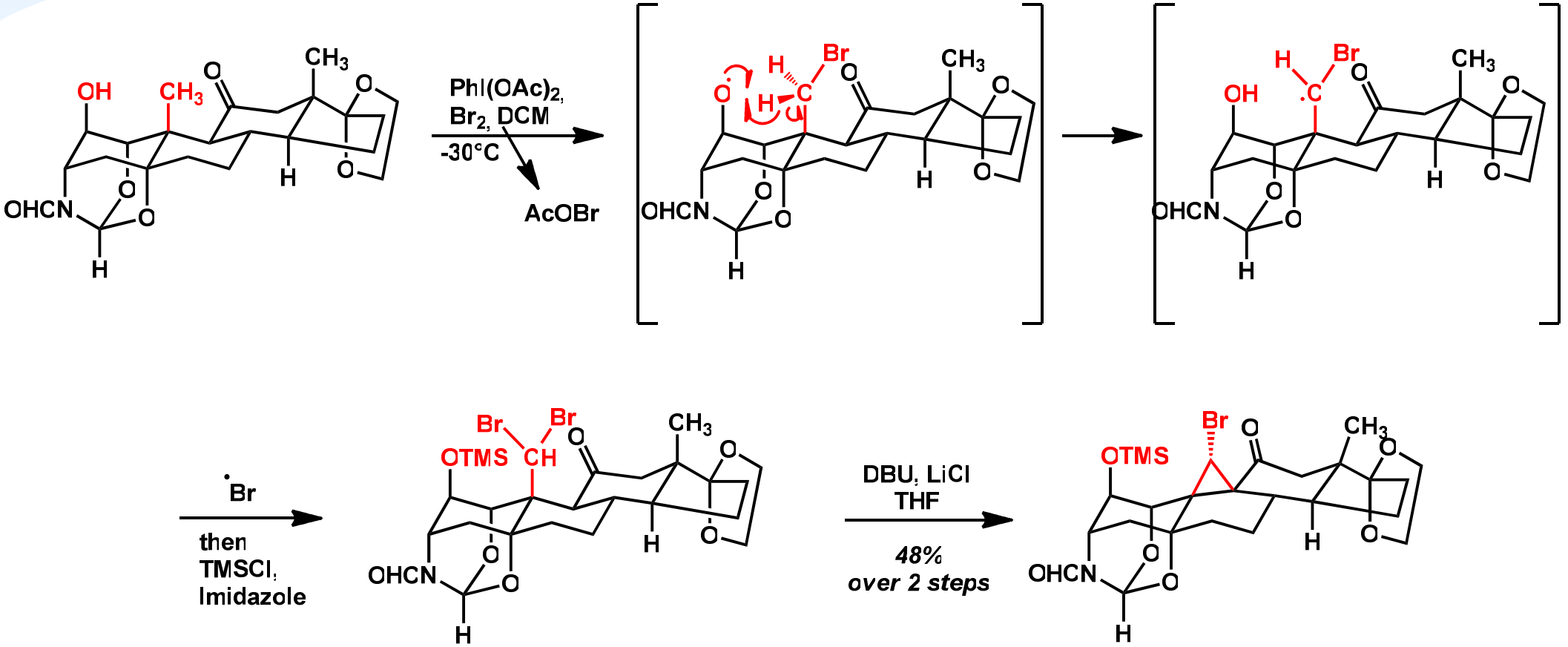
- Increasing of structural rigidity :



Mukaiyama Hydration: Chem Lett ***1989, 1071-1074.***

Cortistatin A : Baran's semisynthesis

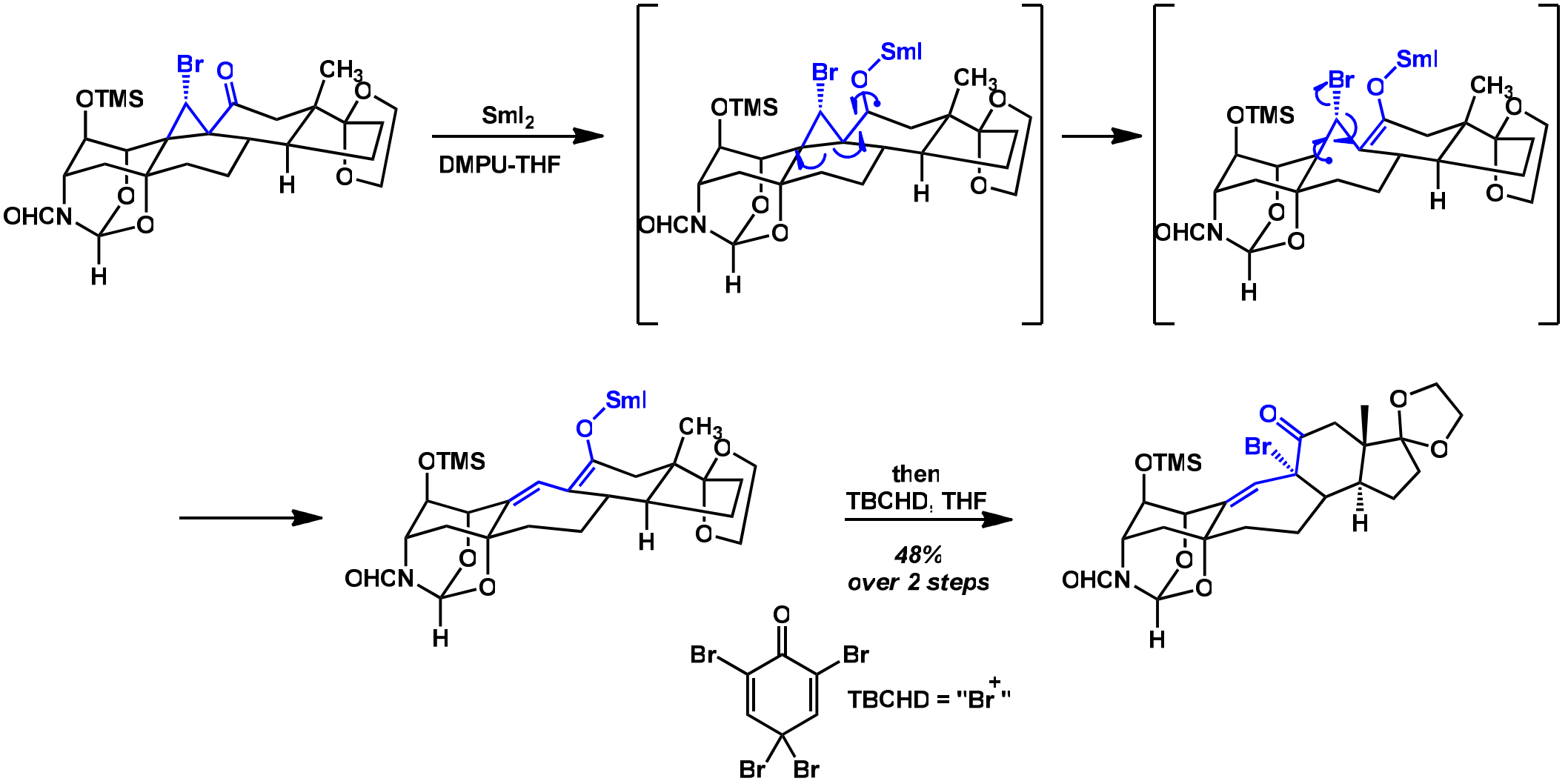
- Selective angular methyl oxidation :



Probably the first alcohol-directed geminal dihalogenation of unactivated hydrocarbon

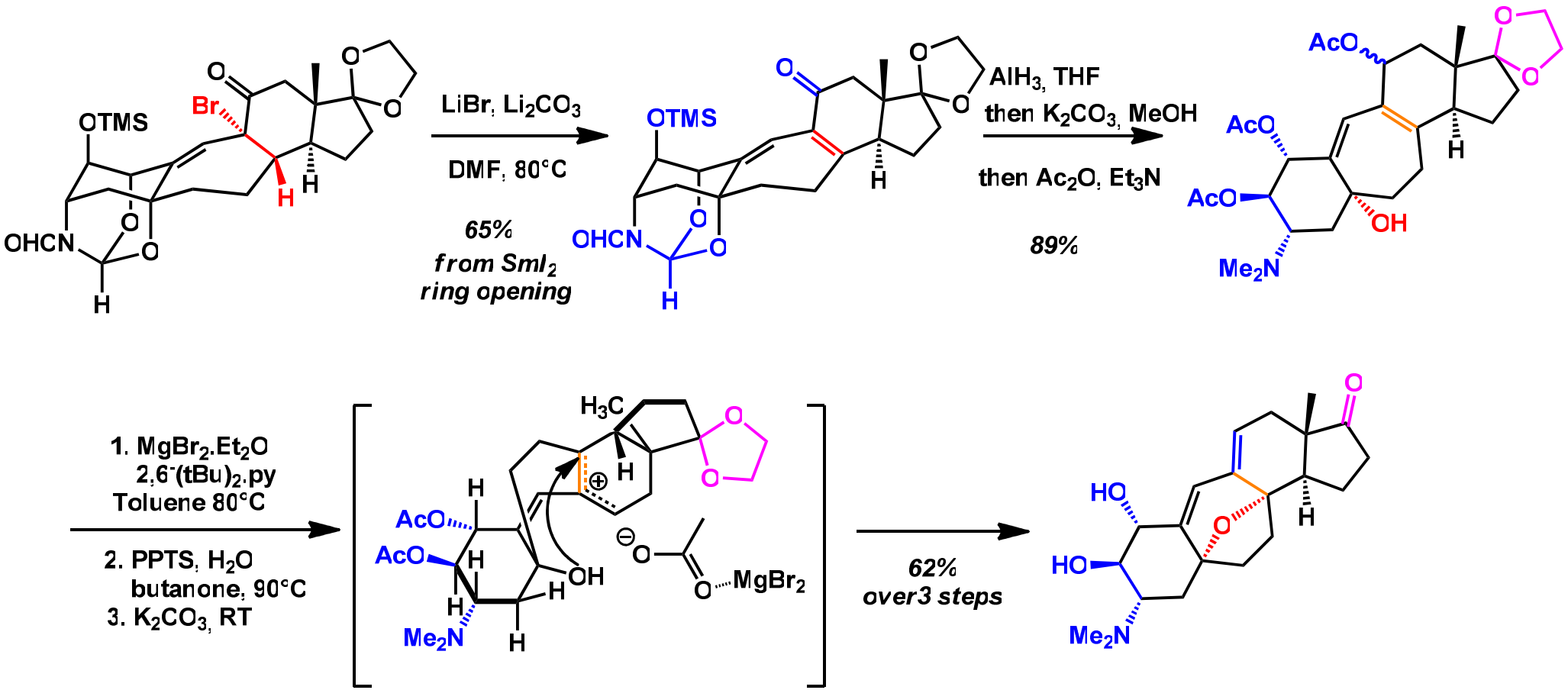
Cortistatin A : Baran's semisynthesis

- Ring expansion :



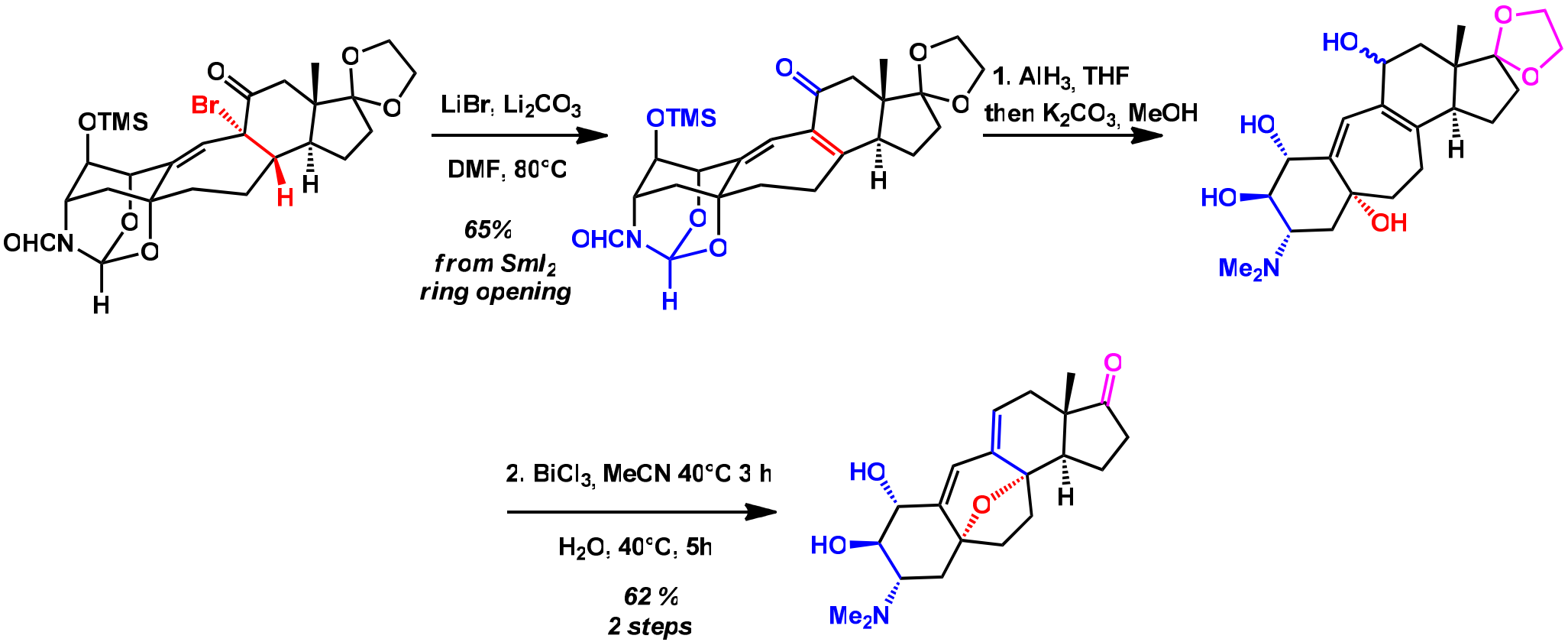
Cortistatin A : Baran's semisynthesis

- Bicyclic ether formation:



Cortistatin A : Baran's semisynthesis

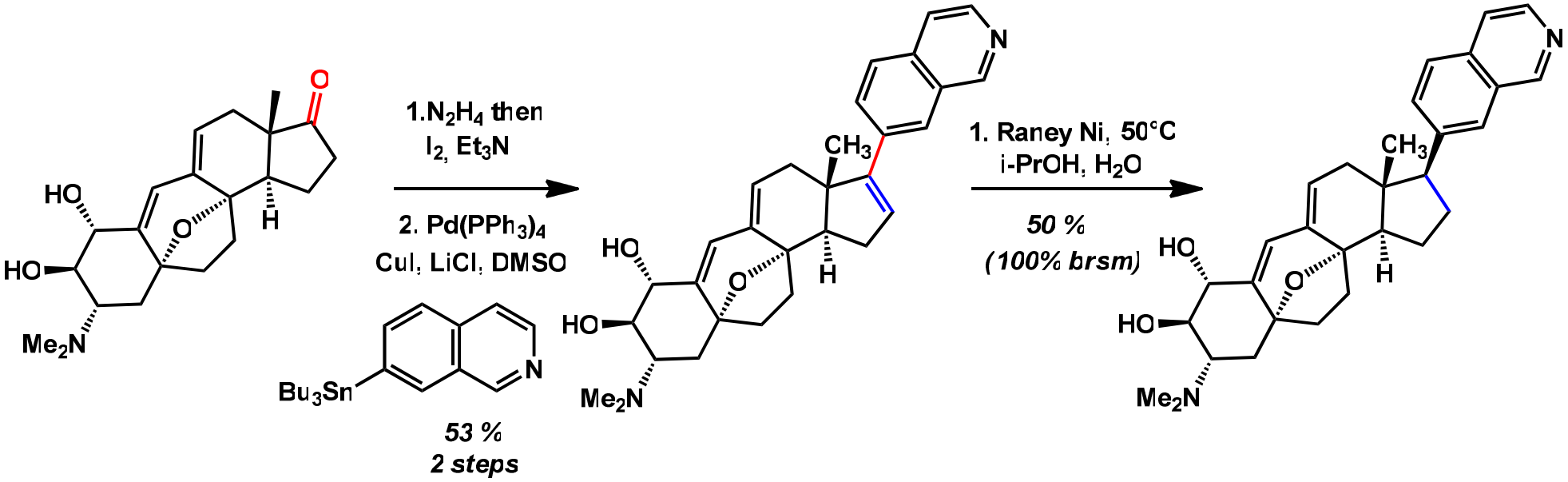
- Bicyclic ether optimized conditions for multigram-scale synthesis :



3 steps reduction and improved yield for total synthesis

Cortistatin A : Baran's semisynthesis

- Completion of the synthesis :

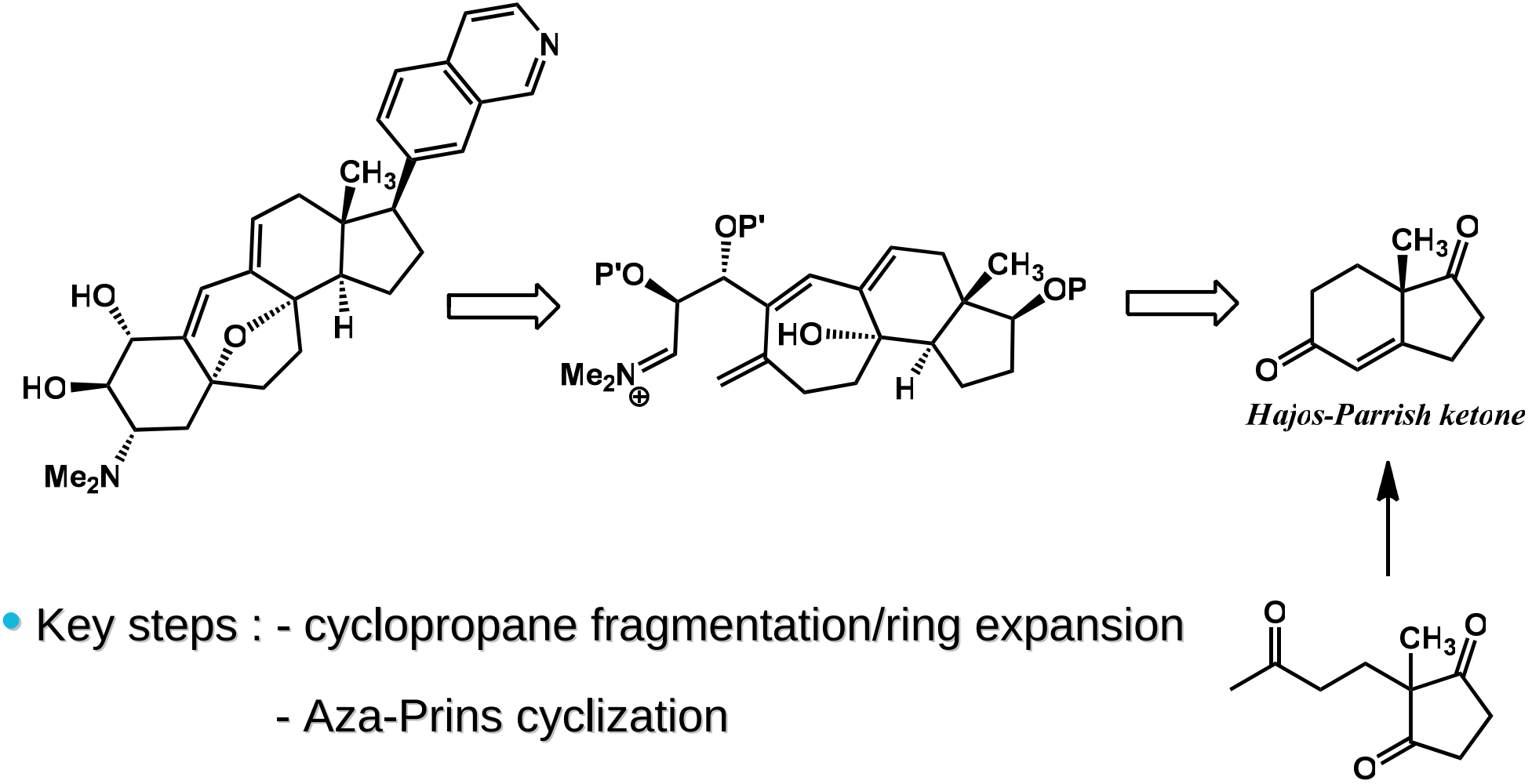


Earlier isoquinoline installation was not possible (makes dihalogenation impossible)

Late stage introduction allowed synthesis of various analogs

Cortistatin A : Shair's synthesis

- Retrosynthesis :

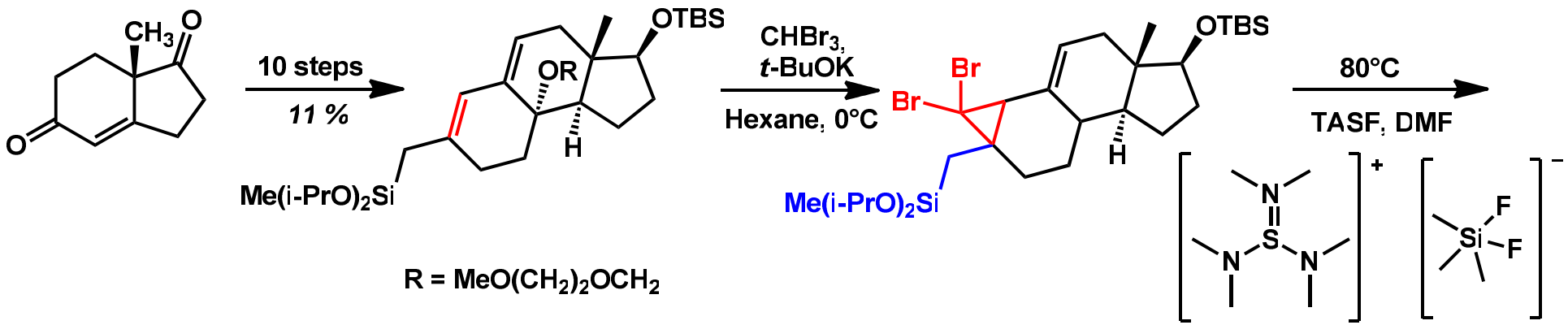


- Key steps : - cyclopropane fragmentation/ring expansion

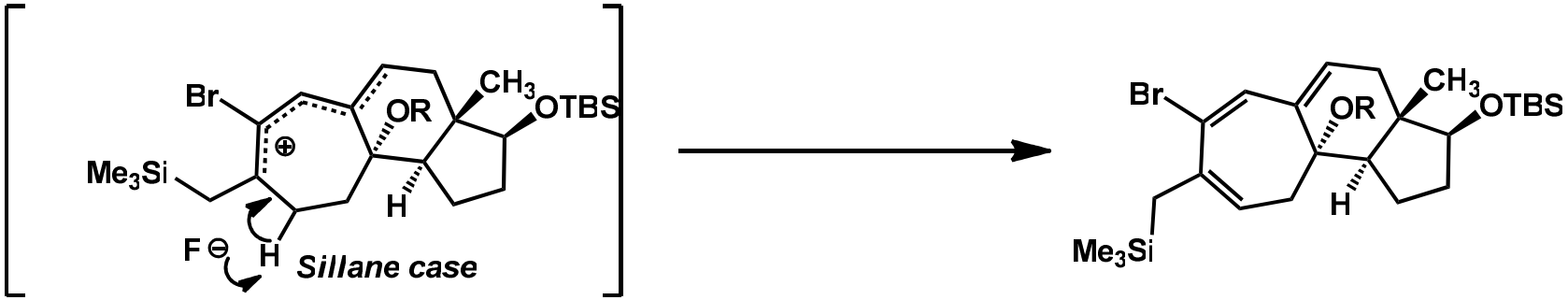
  - Aza-Prins cyclization

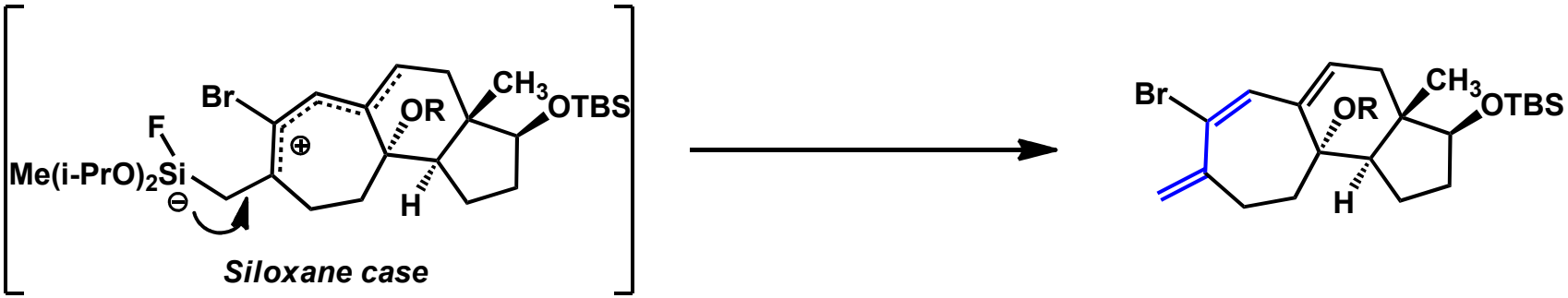
Cortistatin A : Shair's synthesis

- B ring expansion :



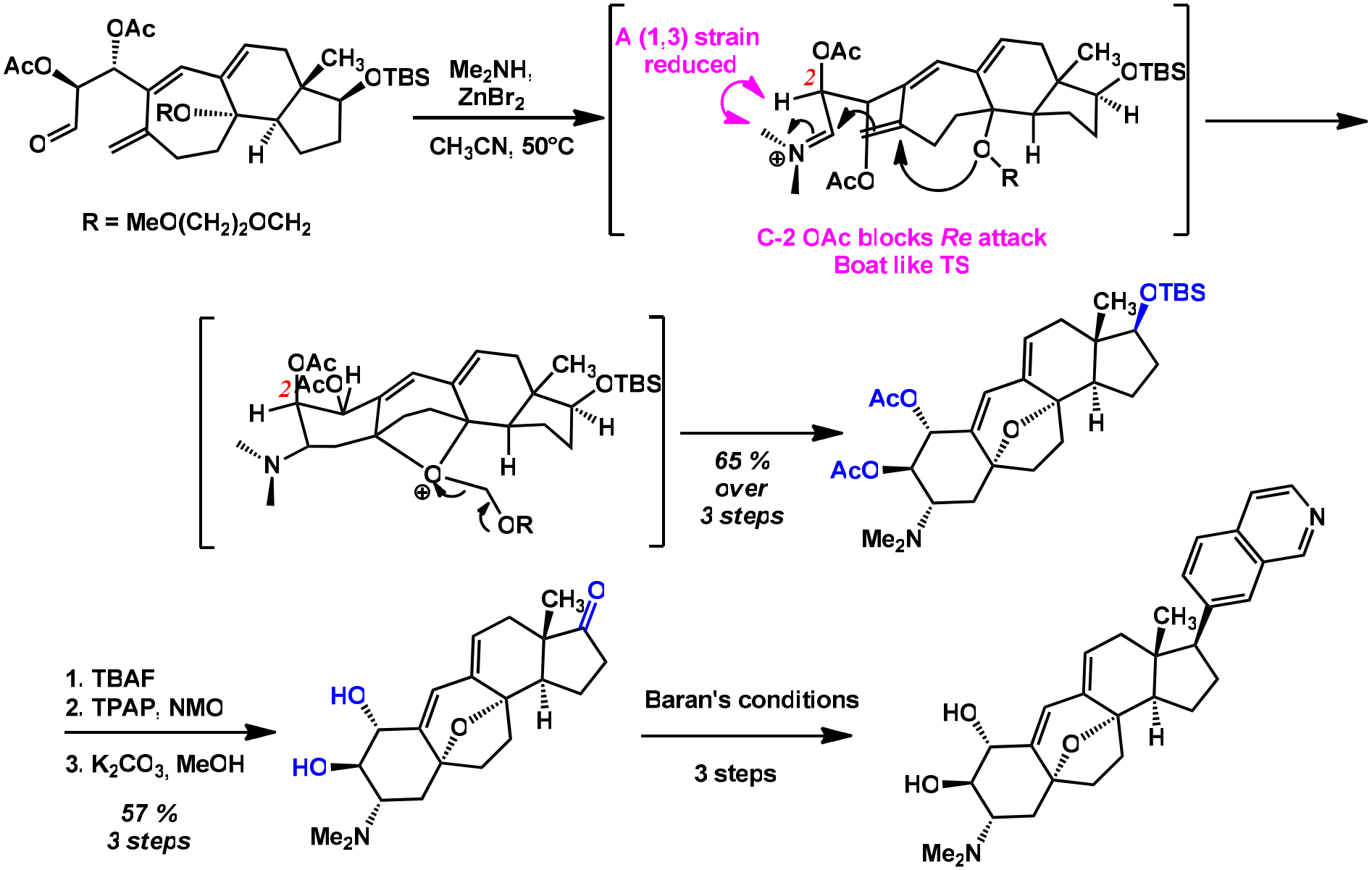
R = $MeO(CH_2)_2OCH_2$





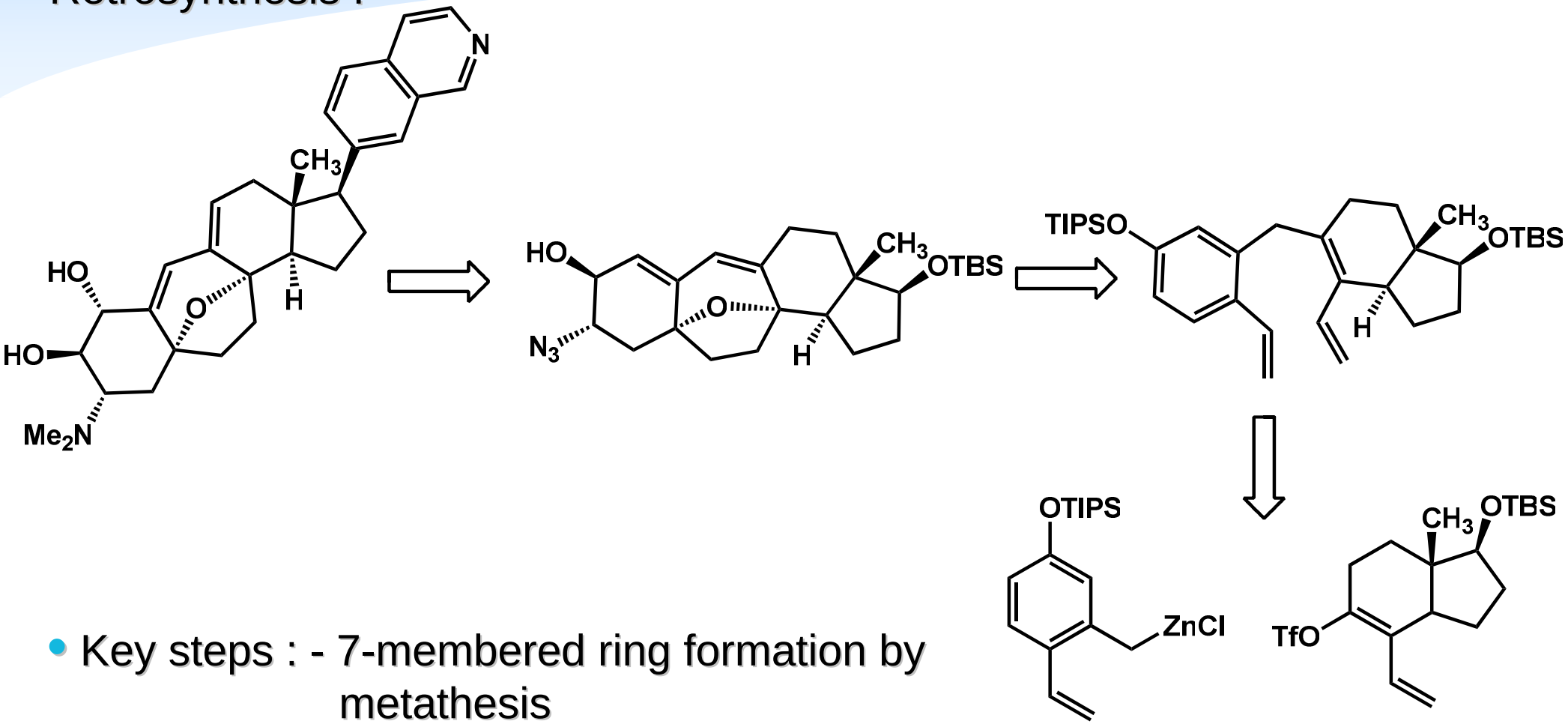
Cortistatin A : Shair's synthesis

- A-ring formation by Aza-Prins cyclization :



Cortistatin A : Myers' synthesis

- Retrosynthesis :

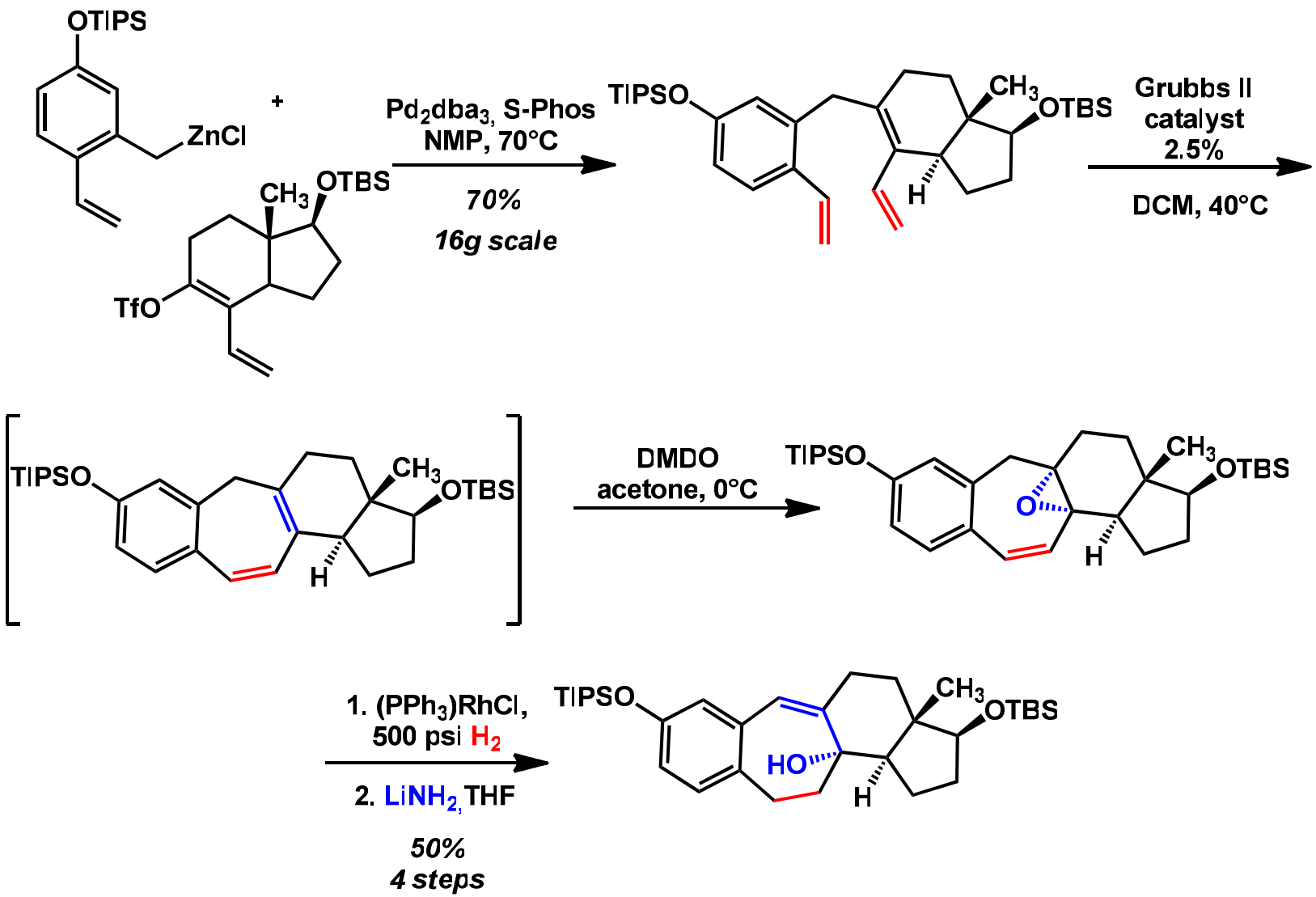


- Key steps : - 7-membered ring formation by metathesis

- Oxidative cyclization to oxabicyclic core synthesis

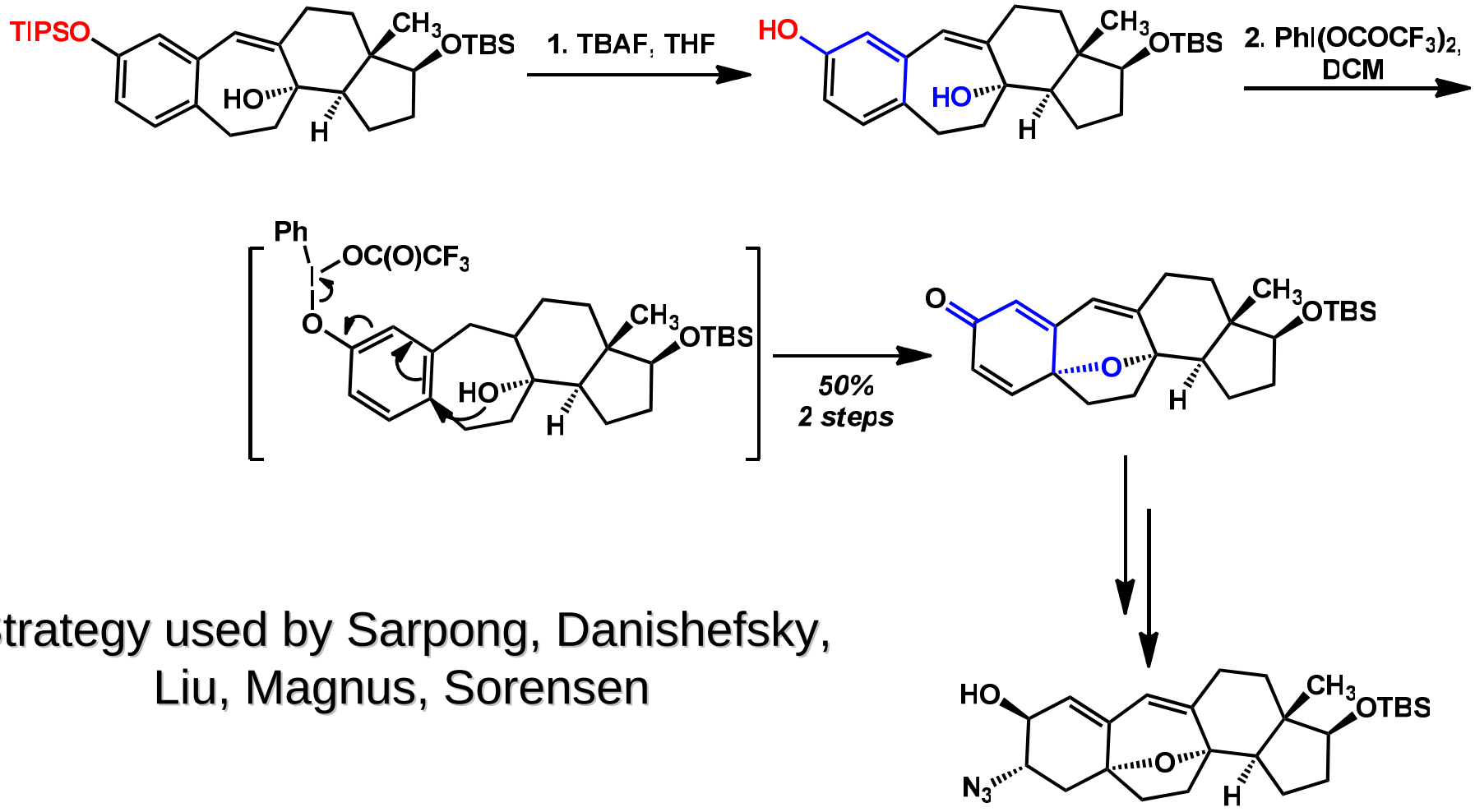
Cortistatin A : Myers' synthesis

- 7-membered ring set-up :



Cortistatin A : Myers' synthesis

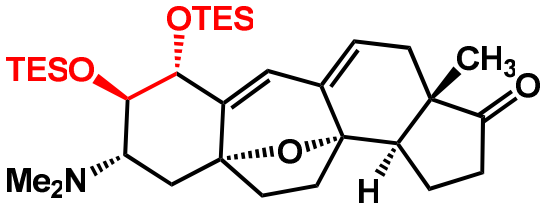
- B-ring installation :



- Strategy used by Sarpong, Danishefsky, Liu, Magnus, Sorensen

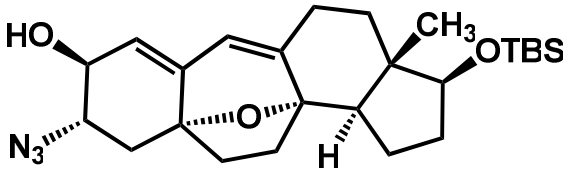
Cortistatin A : Myers' synthesis

- Versatility of the approach :



Cortisatin A series

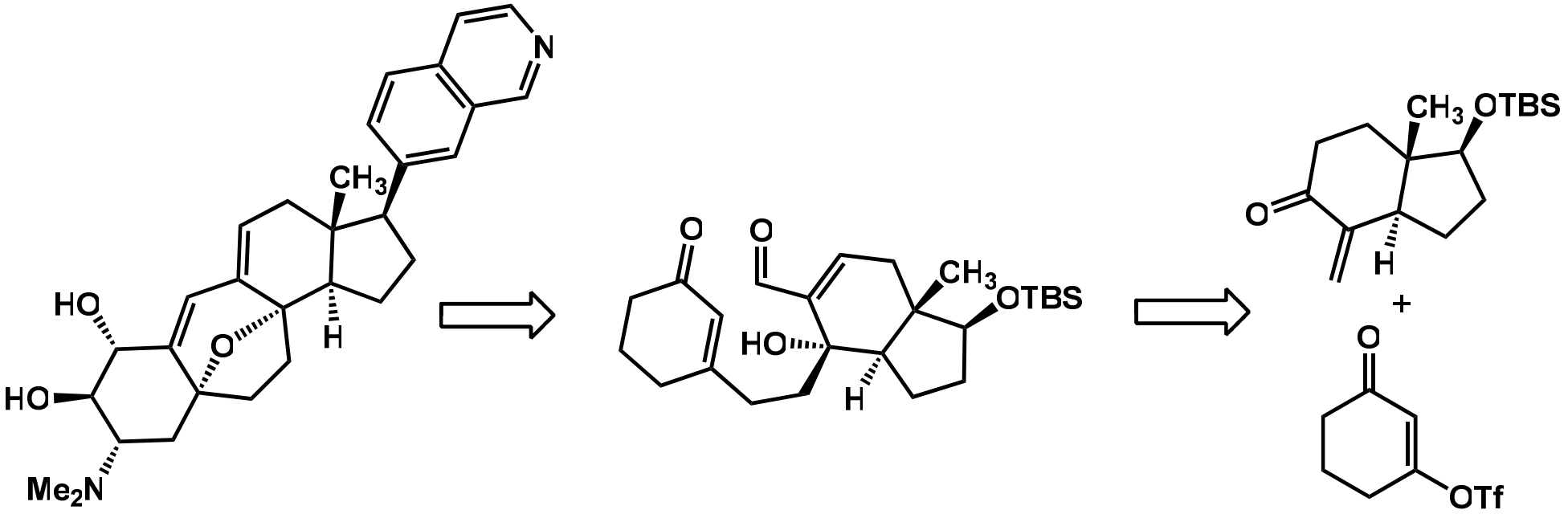
9 steps
17%



Addition of lithioquinoline and reductive deoxygenation lead to the total synthesis of the 4 steroids!!!

Cortistatin A : Nicolaou-Chen's synthesis

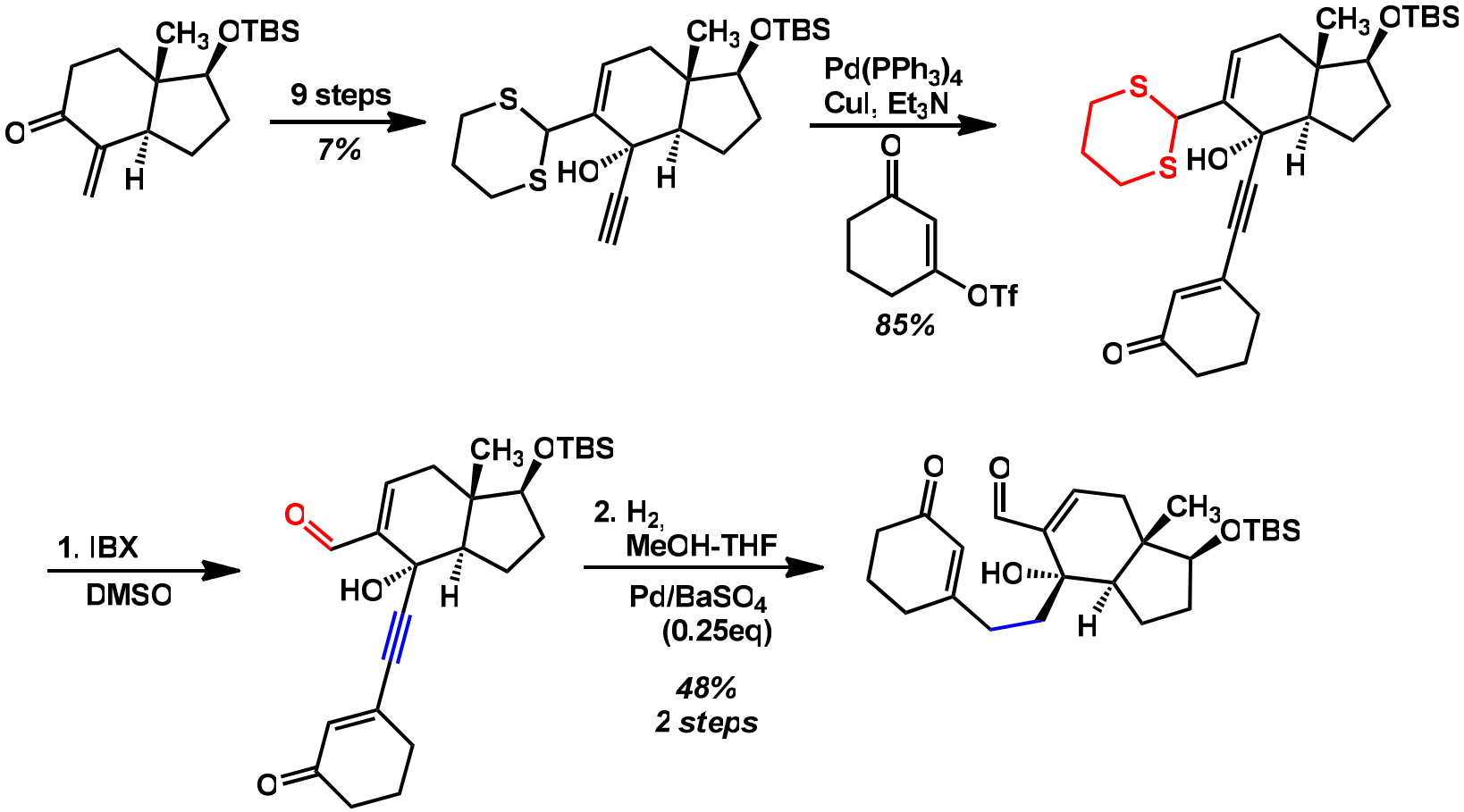
- Retrosynthesis :



- Key steps : - 1,4-addition / aldol / dehydratation cascade

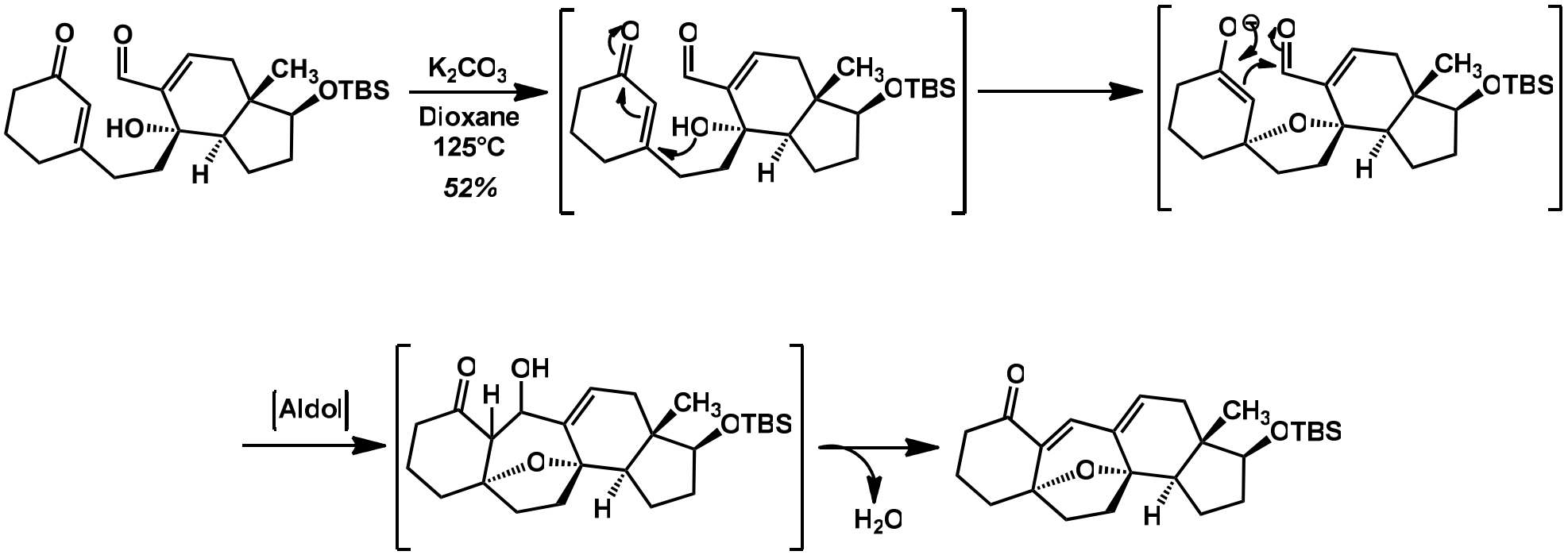
Cortistatin A : Nicolaou-Chen's synthesis

- Cascade precursor preparation :



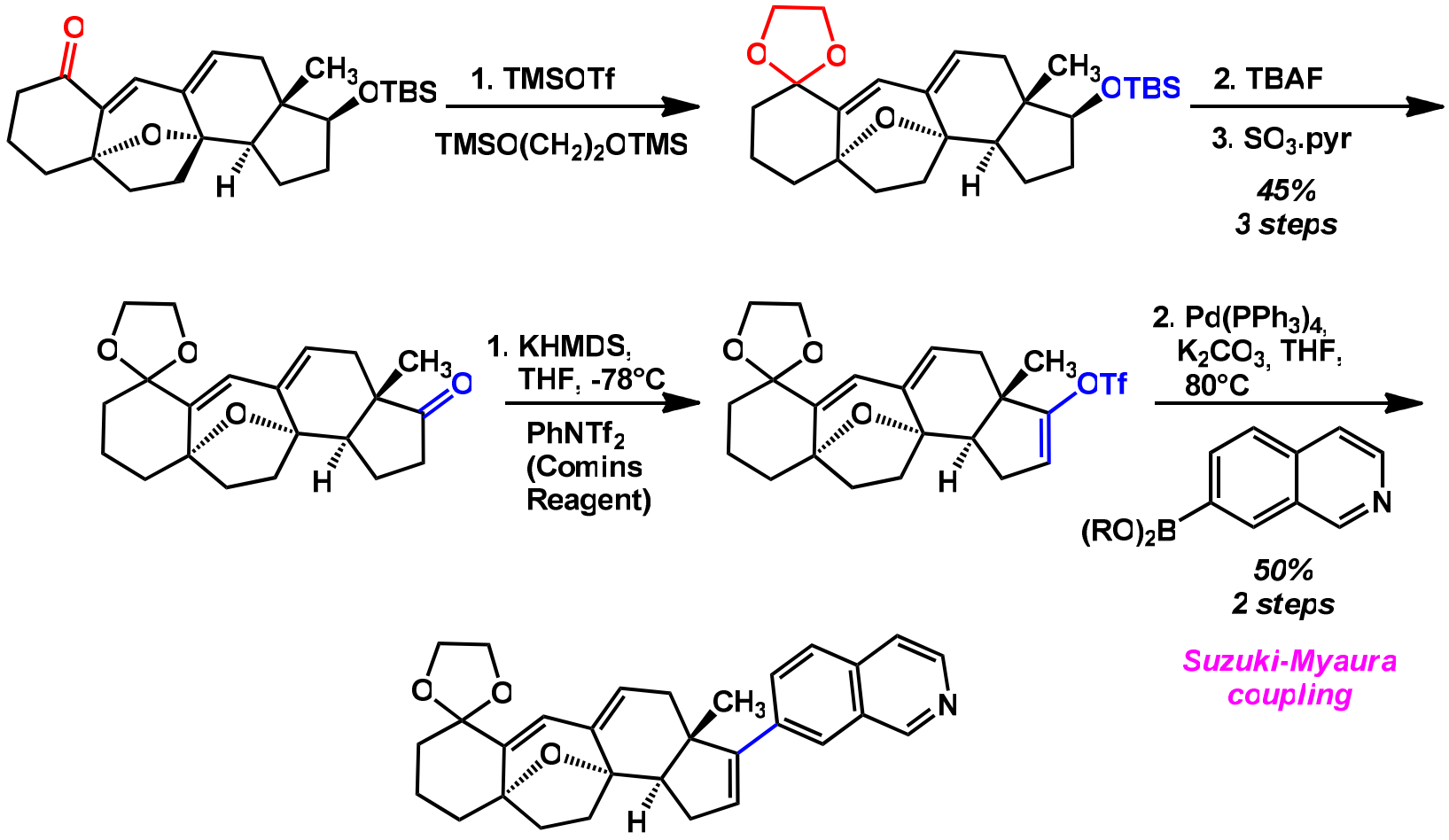
Cortistatin A : Nicolaou-Chen's synthesis

- Cascade and B-ring complete formation :



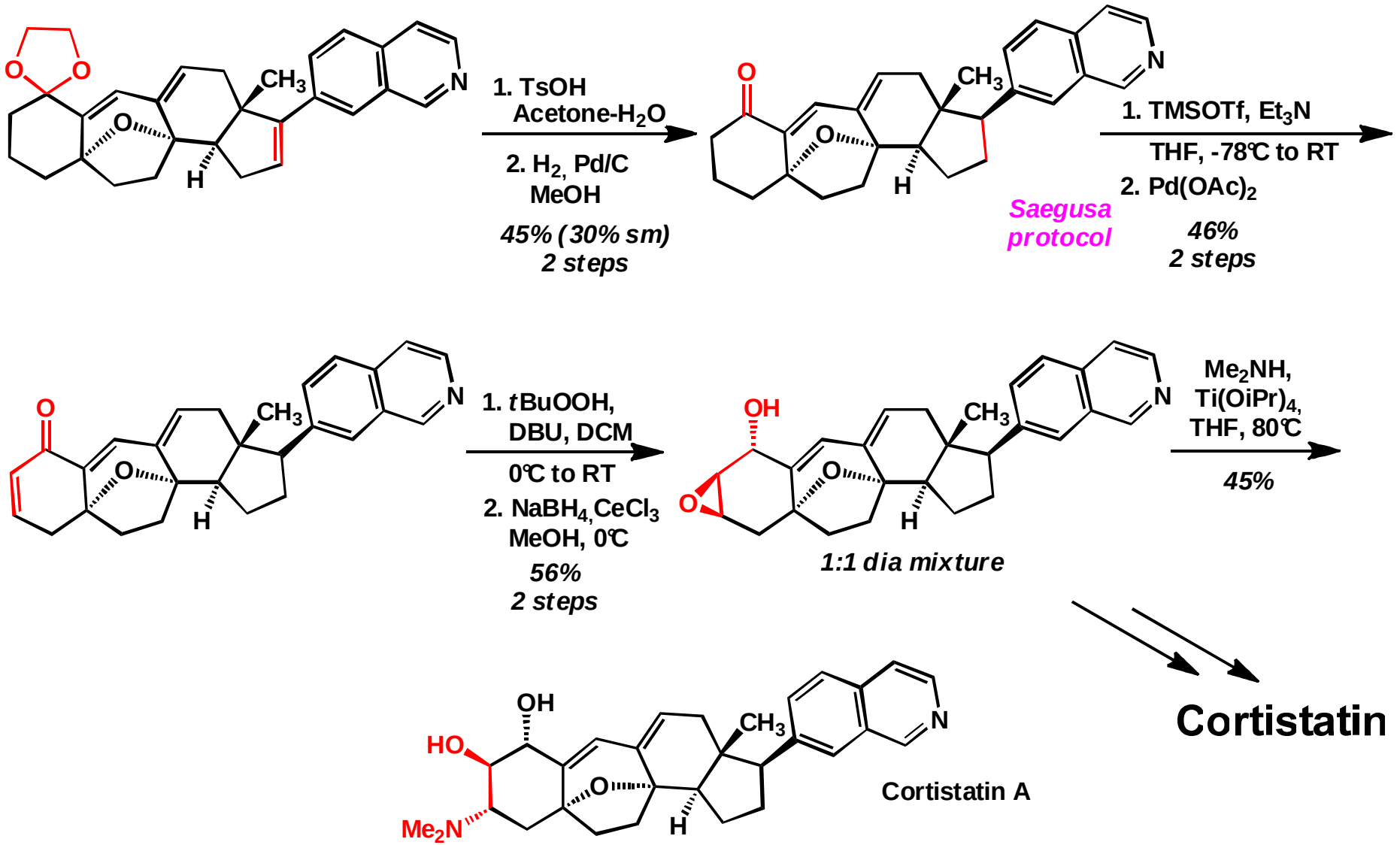
Cortistatin A : Nicolaou-Chen's synthesis

- Introduction of the isoquinoline :



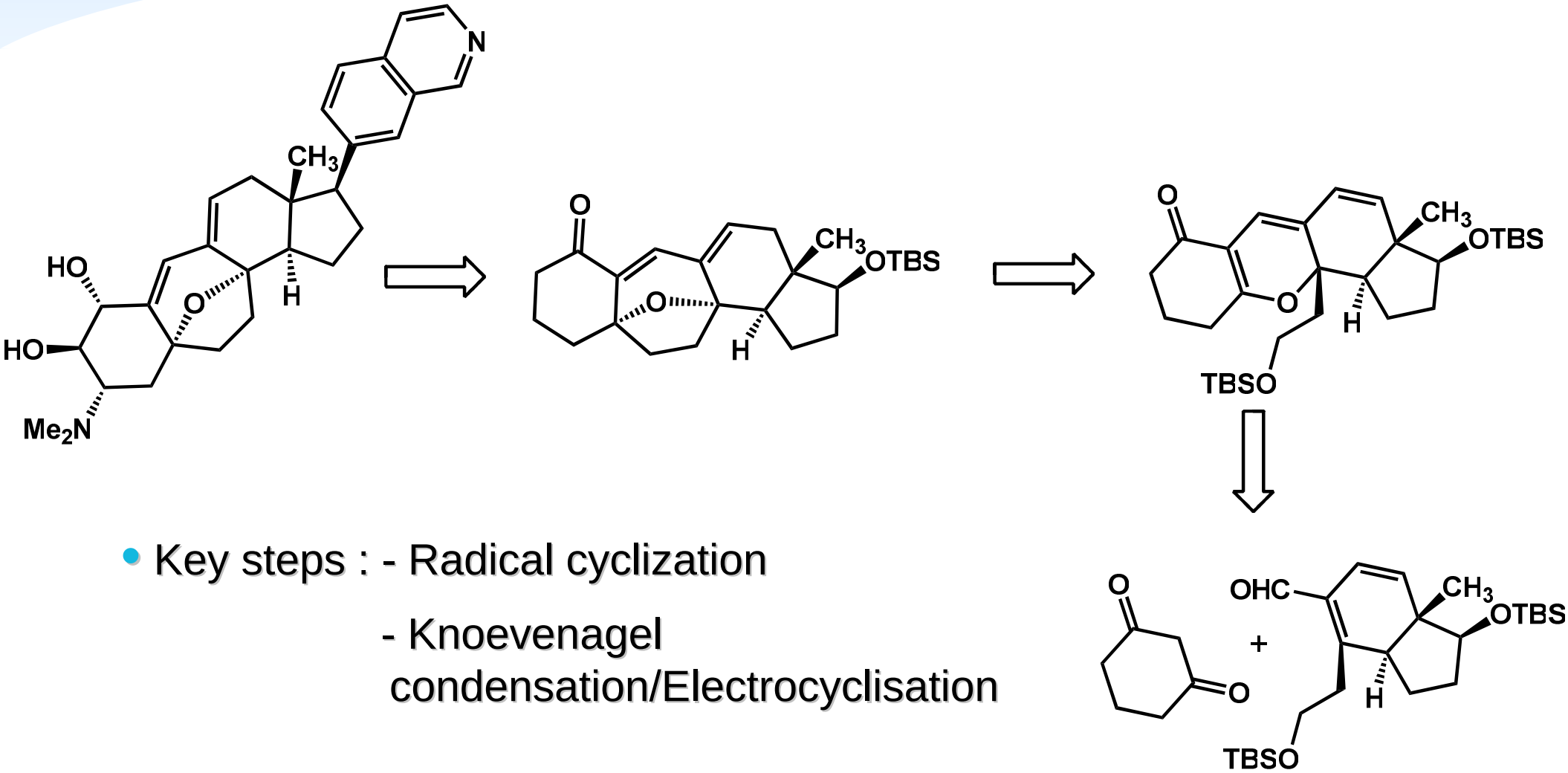
Cortistatin A : Nicolaou-Chen's synthesis

- A-ring functionalization and completion of the synthesis :



Cortistatin A : Hirama's synthesis

- Retrosynthesis :

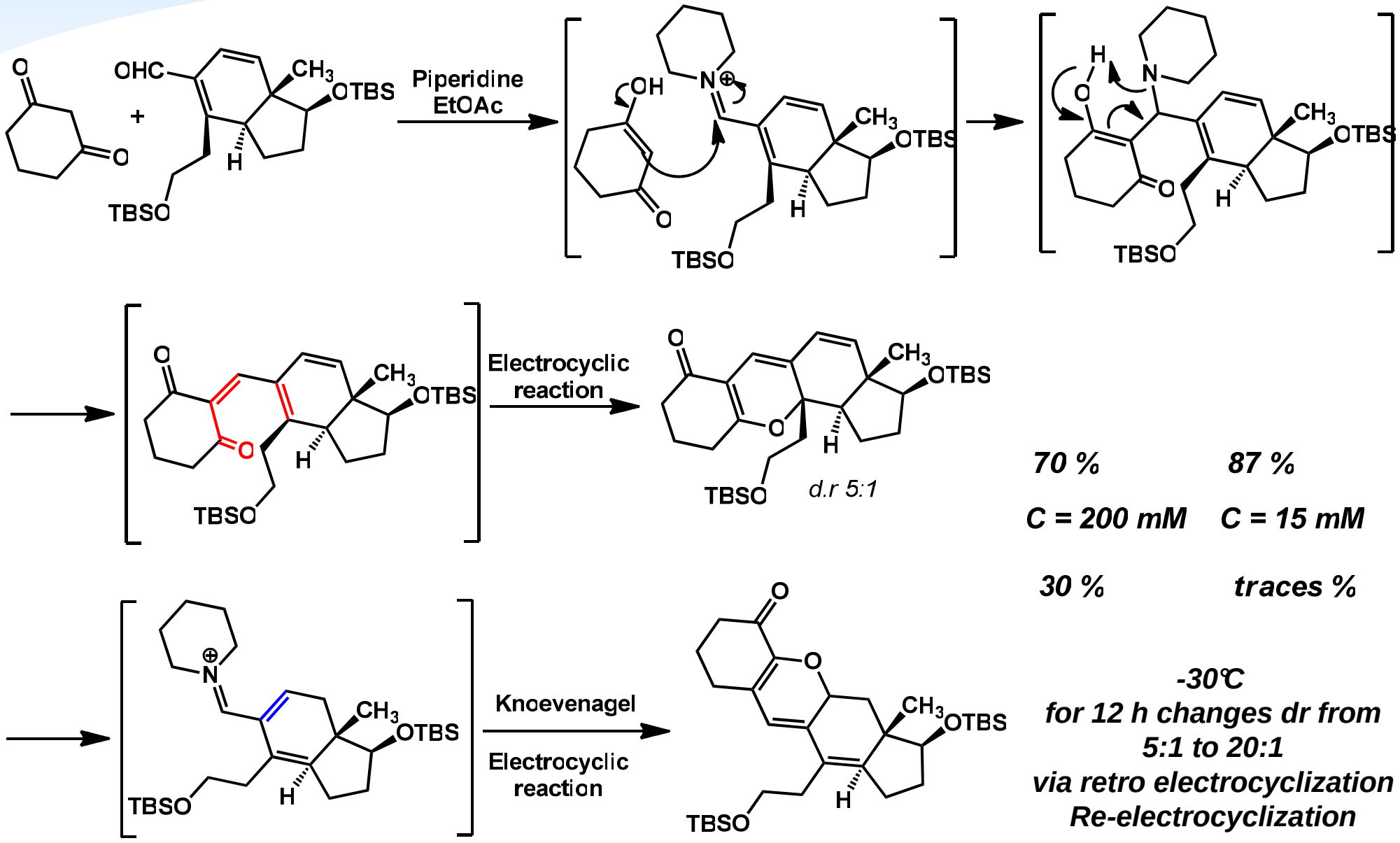


- Key steps : - Radical cyclization

  - Knoevenagel condensation/Electrocyclisation

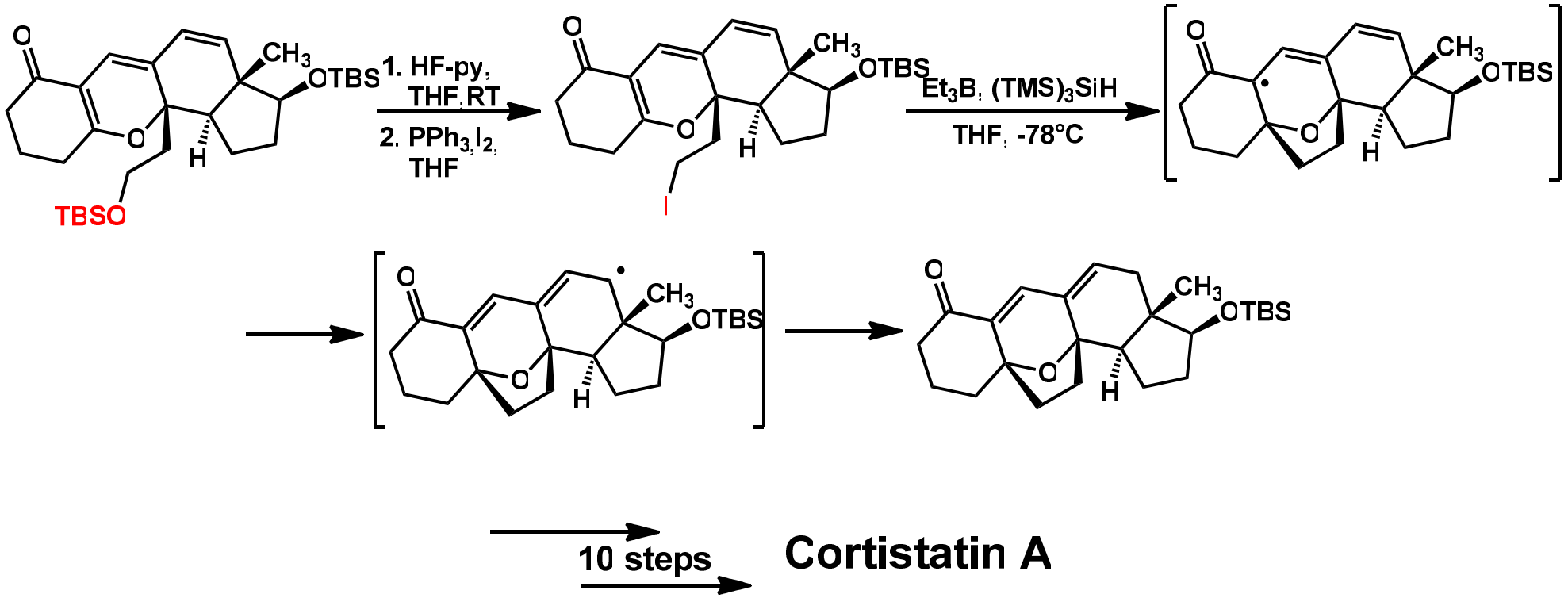
Cortistatin A : Hirama's synthesis

- B-ring set-up :



Cortistatin A : Hirama's synthesis

- B-ring completion by radical cyclization :



Completion by installation of the isoquinoline group before A-ring functionalization to obtain Cortistatin A and J