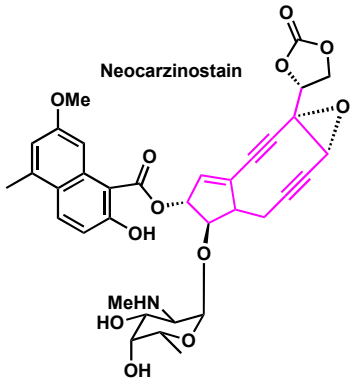
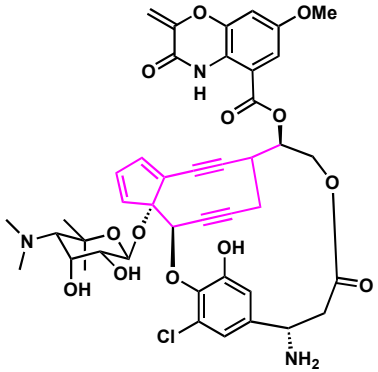
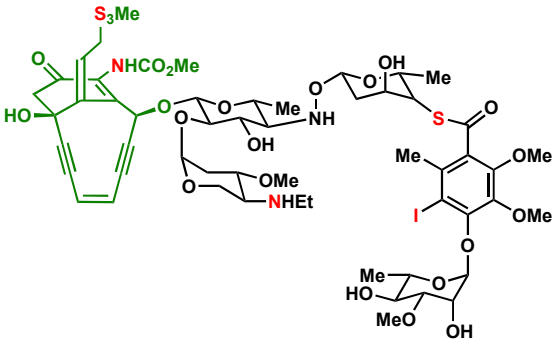
## Structures of representative enediyne natural products

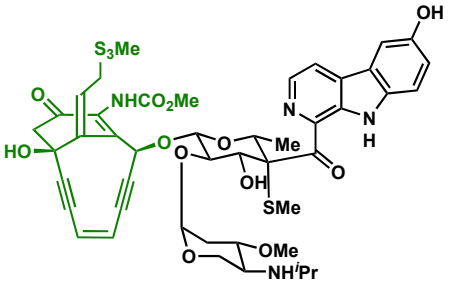


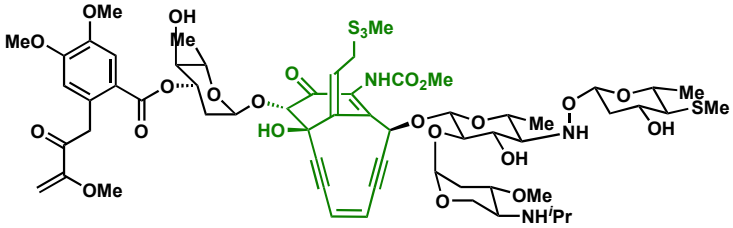
C-1027



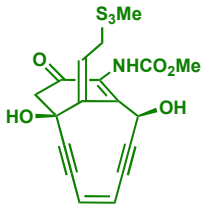
Calicheamicin $\gamma_1^I$



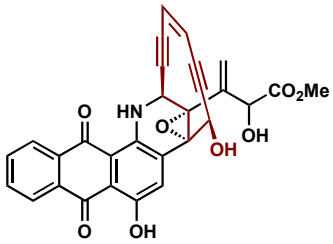
Shishijimicin A



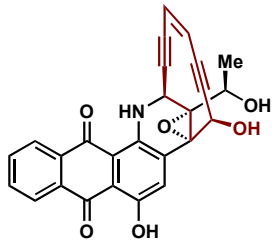
Esperamicin $A_1$



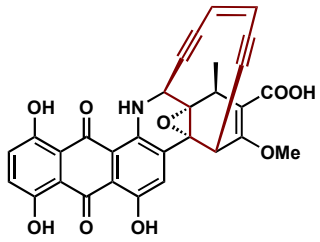
Calicheamicinone



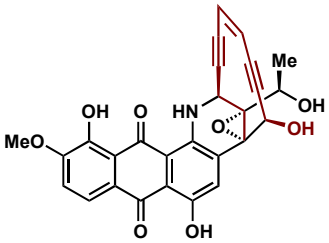
Sealutomicin A



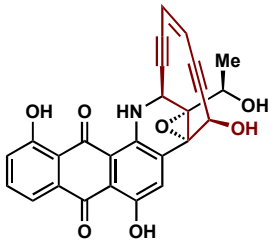
Uncialamycin



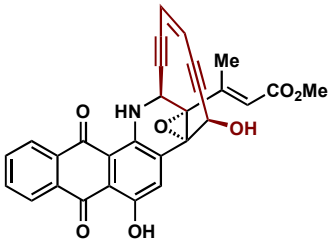
Dynemicin A



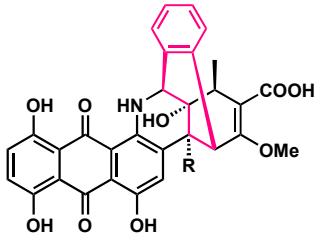
Tiancimycin A



Yangpumicin A



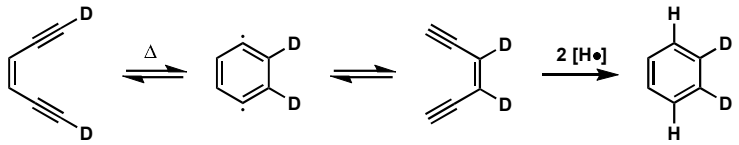
Tiancimycin B



Dynemicin L: R = Cl
Dynemicin N: R = OH

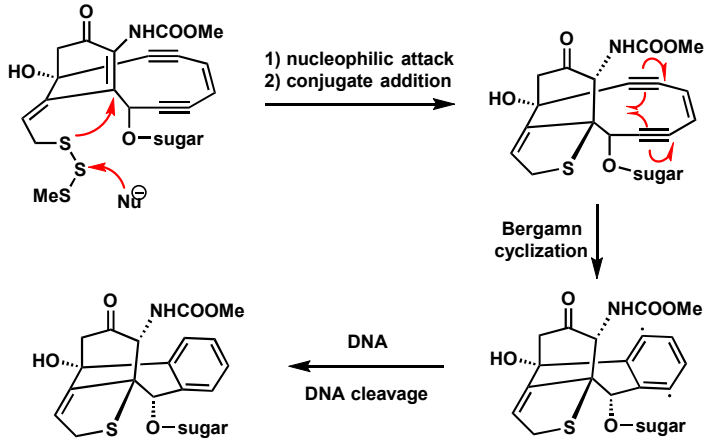
X-H Yan. Nat. Prod. Rep. 2022, 39, 703.

## Bergman cyclization

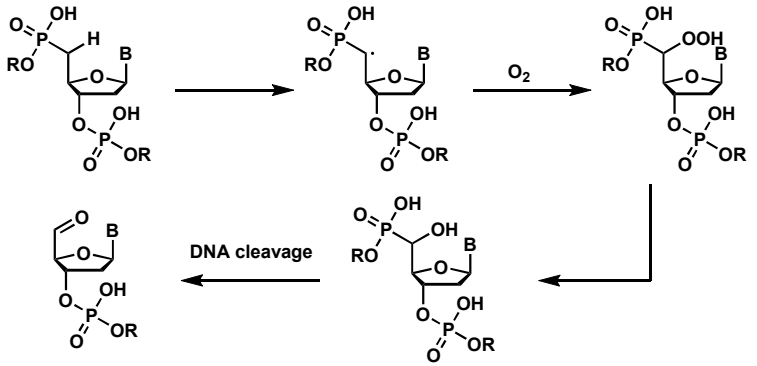


Bergman, JACS 1972, 94, 660.

## Calicheamicin type action mechanism

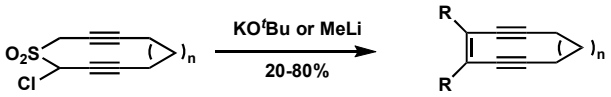



## DNA cleavage main mechanism

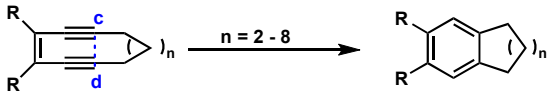



Nicolaou, Angew. Chem. Int. Ed. Engl. 1991, 30, 1387.

## Synthesis of enediynes

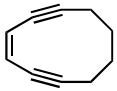
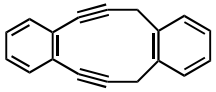
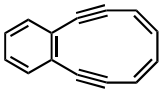
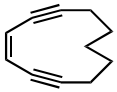
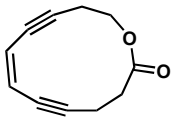
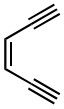



## Nicolaou's proposal

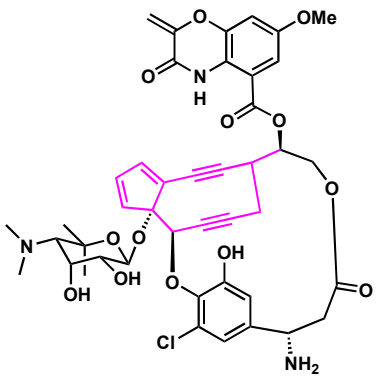



At least in monocyclic systems, the distance between the remote acetylenic carbons correlated with the stability of enediyne.

Nicolaou, JACS 1988, 110, 4866.

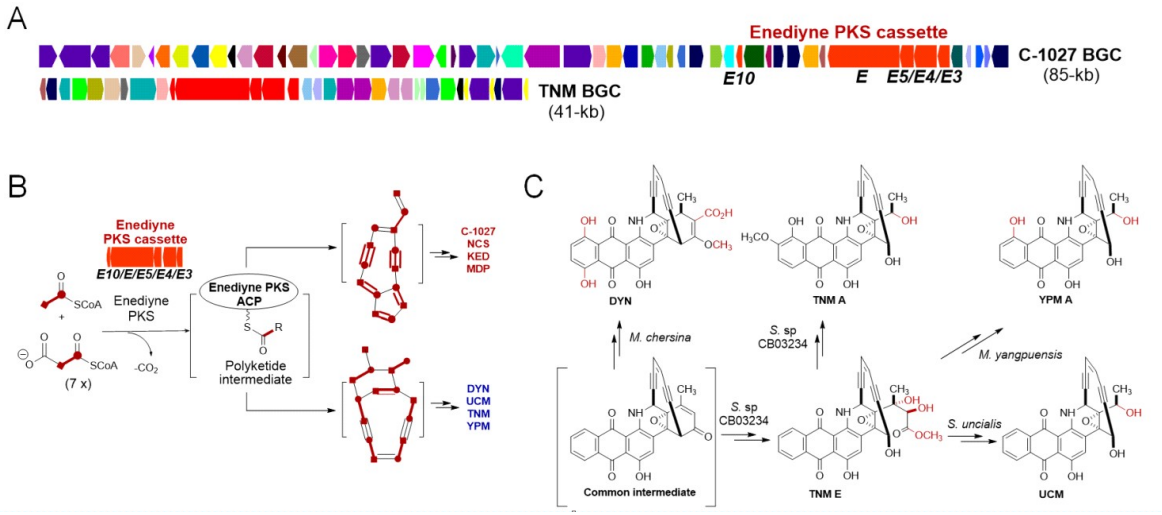
| entry | compound | ring size | d [A] | stability |
|---|---|---|---|---|
| 1 |  | 10 | 3.25 | $t_{1/2}$ = 18 h at 37°C |
| 2 |  | 10 | 3.03 | cyclized at 25 "C |
| 3 |  | 10 | 3.01 | cyclized < 25°C |
| 4 |  | 11 | 3.61 | stable at 25°C |
| 5 |  | 12 | 3.77 | stable at 25°C |
| 6 |  | | 4.12 | stable at 25°C<br>$t_{1/2}$ = 30 s at 200°C |

**Using C-1027 as a model system for the 9-membered enediyne NPs and TNM as a model system for the 10-membered enediyne NPs**




C-1027

Ben Shen, Science 2002, 297, 1170.




Picture taken from Prof. Ben Shen's website. https://shen.scripps.ufl.edu/sample-page/enediyne-family-of-natural-products/

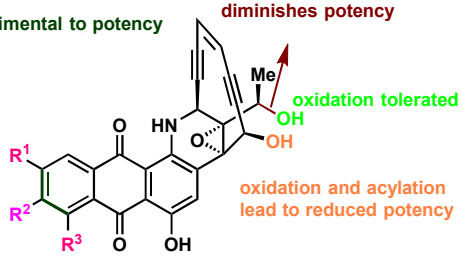
**Summary of derived structure–activity relationships (SARs)**

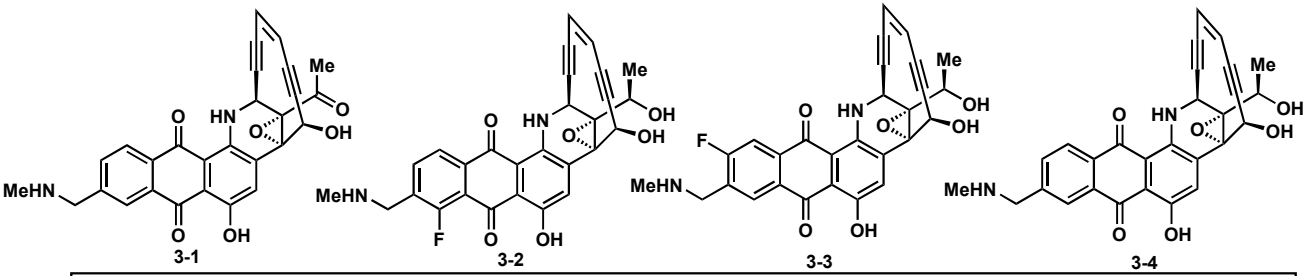
$R^1$ & $R^3$: installation of fluorine residue enhances potency

$R^2$: free or protected amine detrimental; methylamino methyl side chain enhances potency

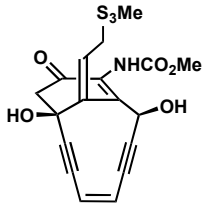
incorporation of $\alpha,\beta$-unsaturated carboxylic acid, estes and amide diminishes potency

annulation detrimental to potency

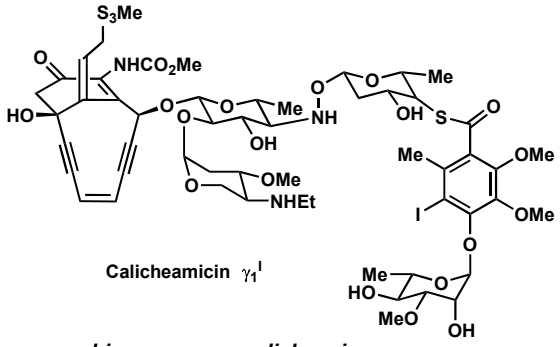



| | cell line | | | | | |
|---|---|---|---|---|---|---|
| | HEK 293T $IC_{50}$ (nM) | MES SA/DX $IC_{50}$ (nM) | MES SA/DXE $IC_{50}$ (nM) | SKBR3 $IC_{50}$ (nM) | SKOV3 $IC_{50}$ (nM) | HeLa $IC_{50}$ (nM) |
| N-Acetyl calicheamicin $\gamma_1^I$ | 0.016 | >100 | 0.024 | 0.078 | 0.012 | 33.070 |
| 3-1 | 0.005 | 0.003 | 0.003 | 0.009 | 0.002 | 0.092 |
| 3-2 | 0.002 | 0.003 | 0.001 | 0.007 | 0.002 | 0.052 |
| 3-3 | 0.001 | 0.002 | 0.001 | 0.004 | 0.001 | 0.042 |
| 3-4 | 0.006 | 0.015 | 0.004 | 0.025 | 0.010 | 1.204 |



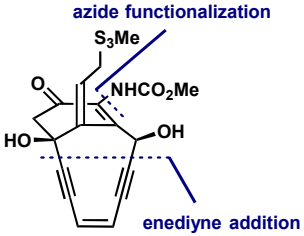
Calicheamicinone



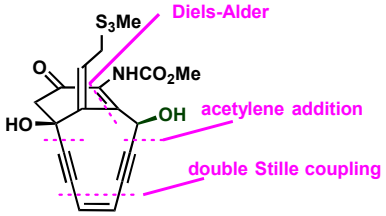
Calicheamicin $\gamma_1^I$

**Isolated**
bacterial strain *Micromonospora echinospora ssp calichensis*
(JACS 1987, 109, 3464.)

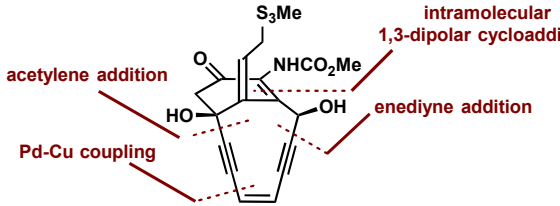
## Total synthesis of calicheamicinone



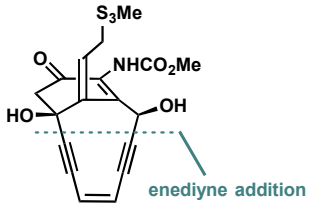

Danishefsky (1990, racemic)




Clive (1996, racemic)

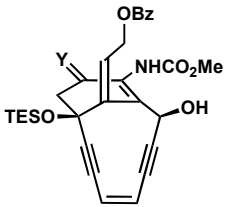


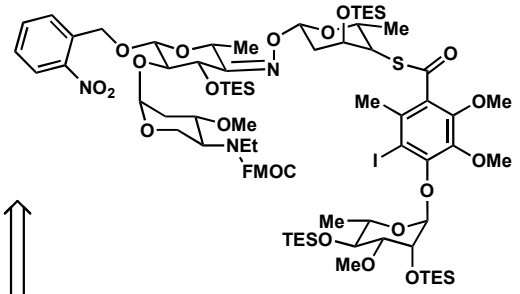

Nicolaou (1993, enantiomeric)



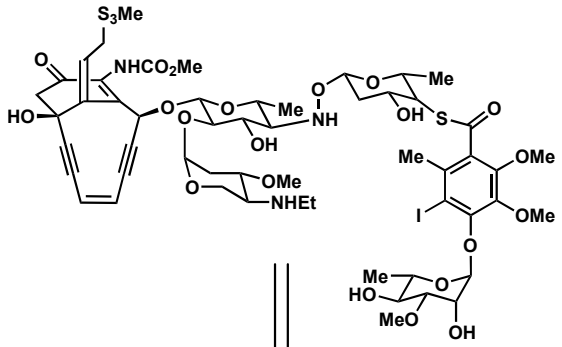

Magnus (1998, racemic)

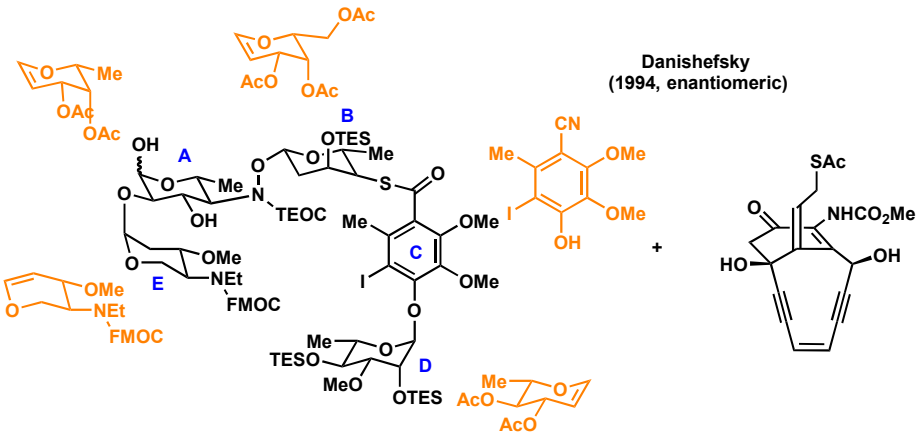
## Total synthesis of calicheamicin $\gamma_1^I$



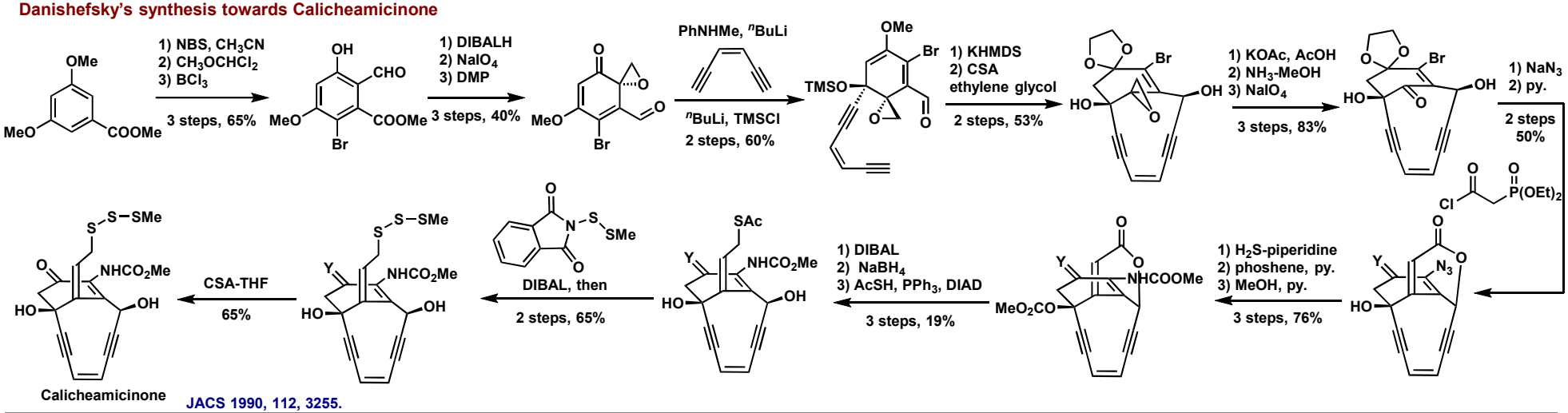


Nicolaou
(1992, enantiomeric)



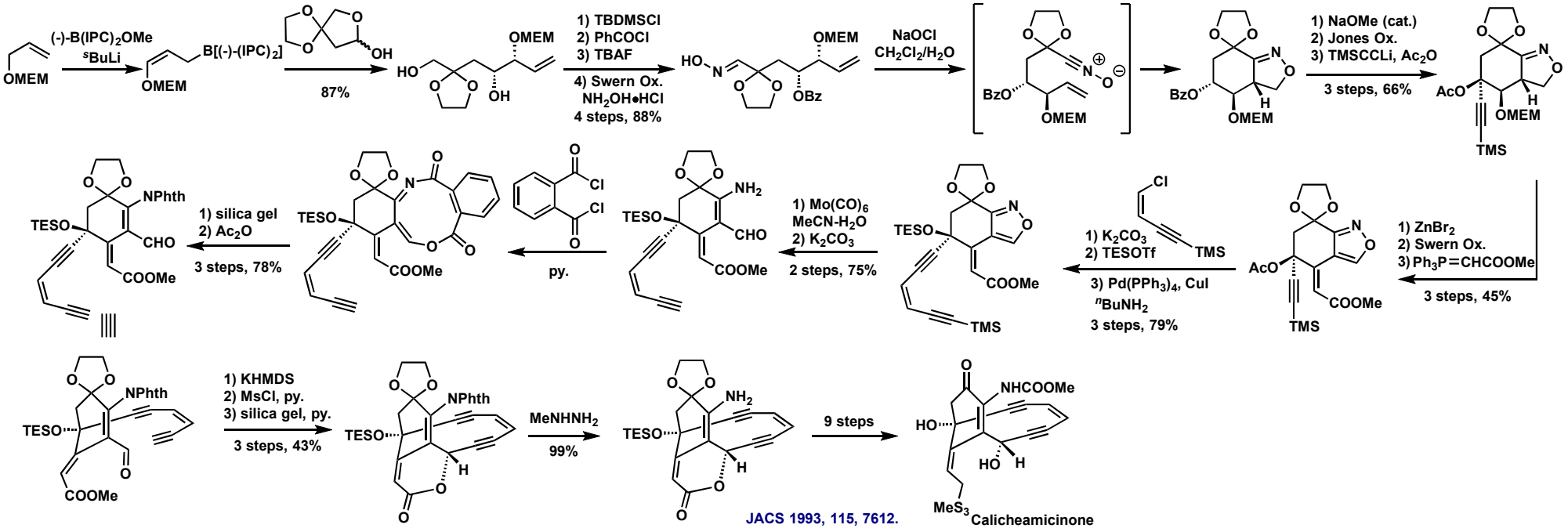


## Danishefsky's synthesis towards Calicheamicinone



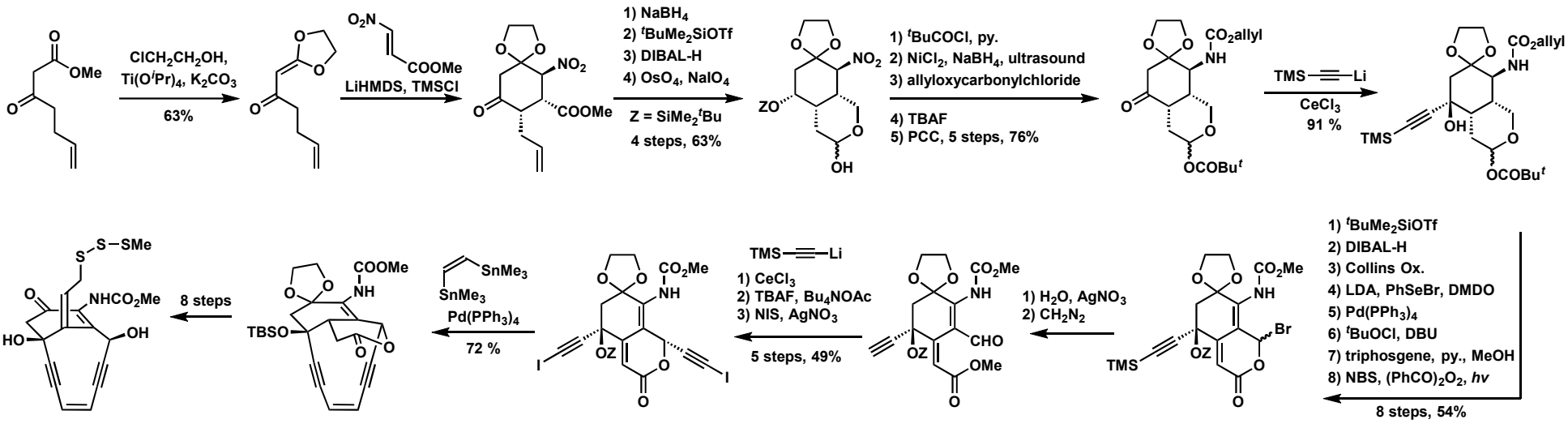

JACS 1990, 112, 3255.

## Nicolaou's synthesis towards Calicheamicinone



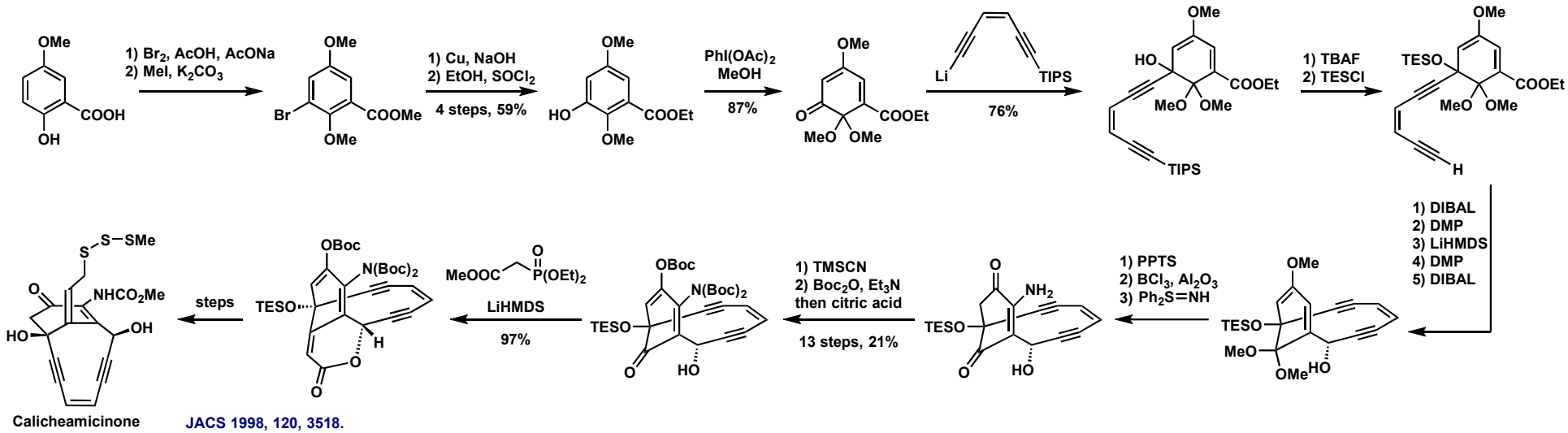

JACS 1993, 115, 7612.

## Clive's synthesis towards Calicheamicinone



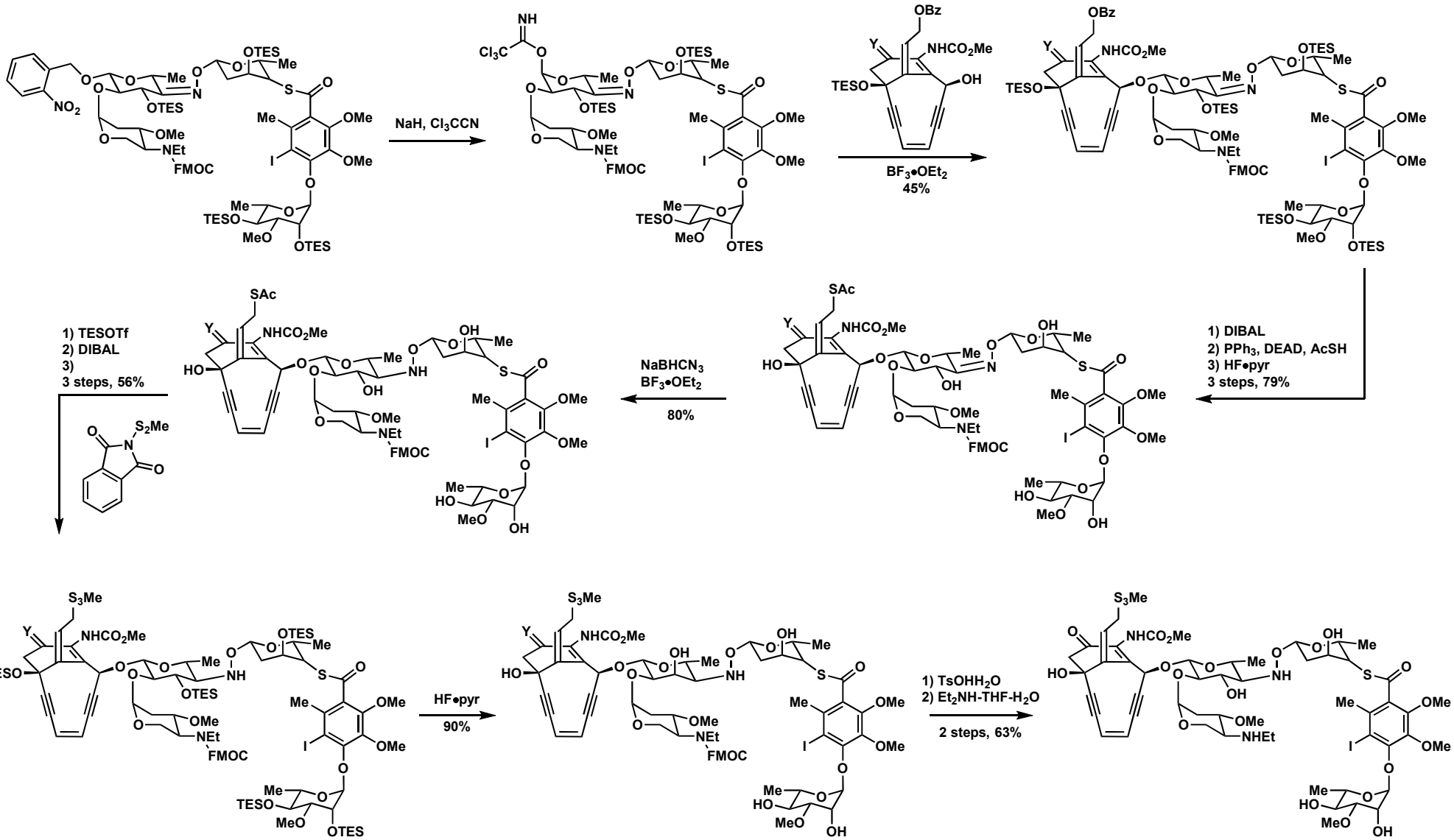

JACS 1996, 118, 4904.

## Magnus' synthesis towards Calicheamicinone



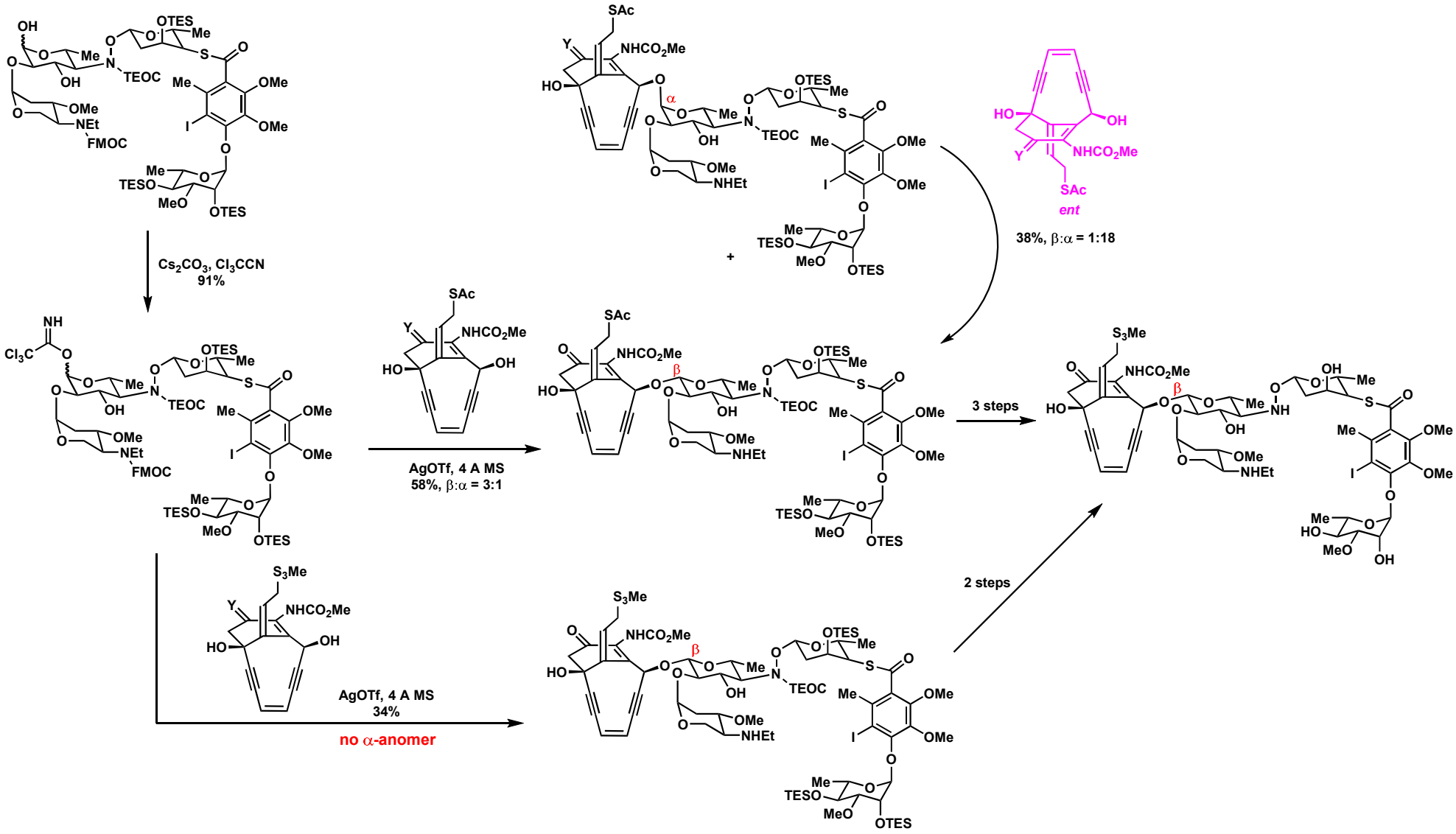

JACS 1998, 120, 3518.

Nicolaou's synthesis towards Calicheamicin $\gamma_1^I$

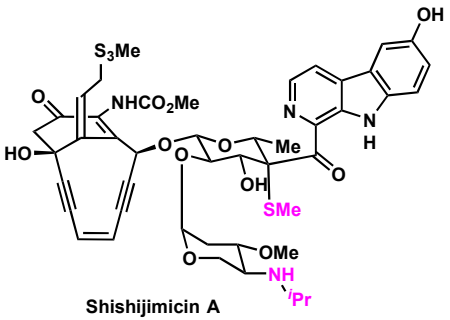


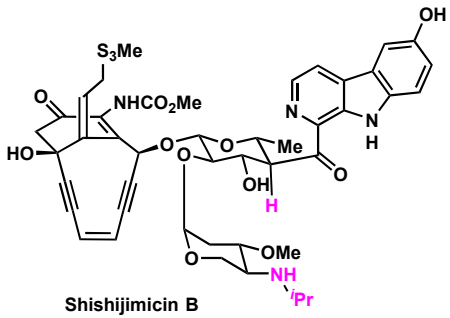

JACS 1992, 114, 10084.

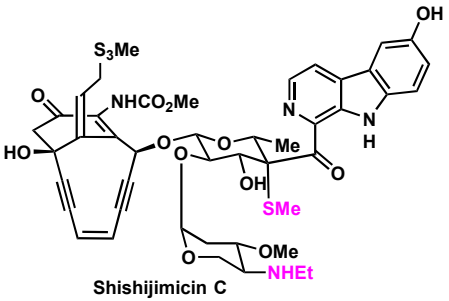
**Danishefsky's synthesis towards Calicheamicin $\gamma_1^I$**




Angew. Chem. Int. Ed. Engl. 1994, 33, 858.



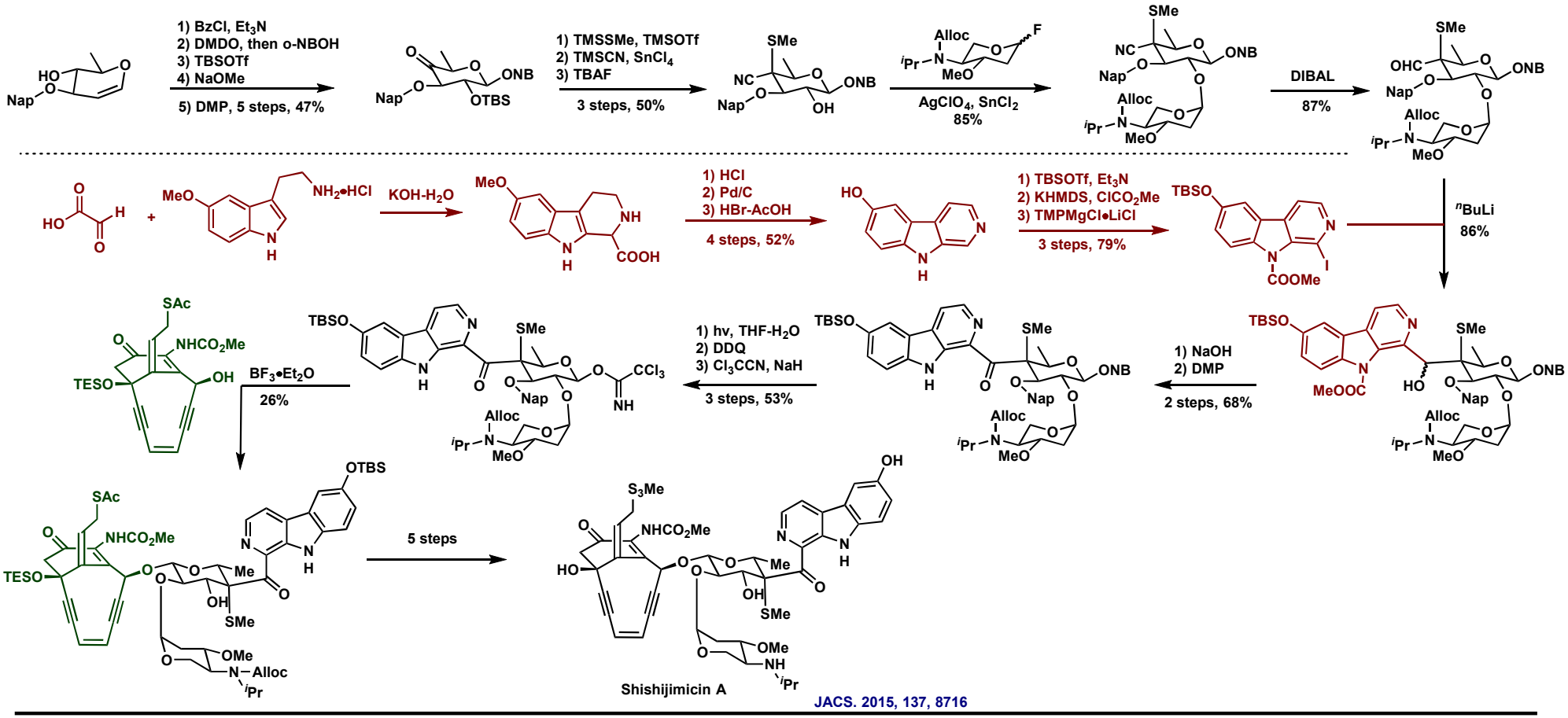



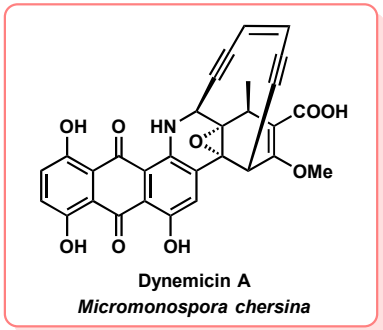




**Isolation**
lipophilic extract of the thin encrusting orange *ascidian Didemnum proliferum* (JACS 2003, 125, 2044.)

**Biological activity**
P388 leukemia cells ($IC_{50}$ = 0.47 nM )

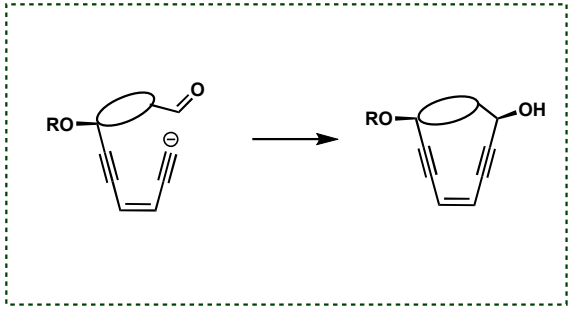
**Total synthesis of shishijimicin A**
Nicolaou (2015, enantiomeric)

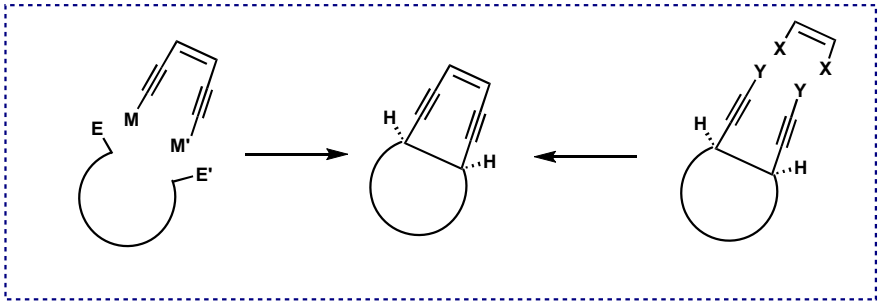




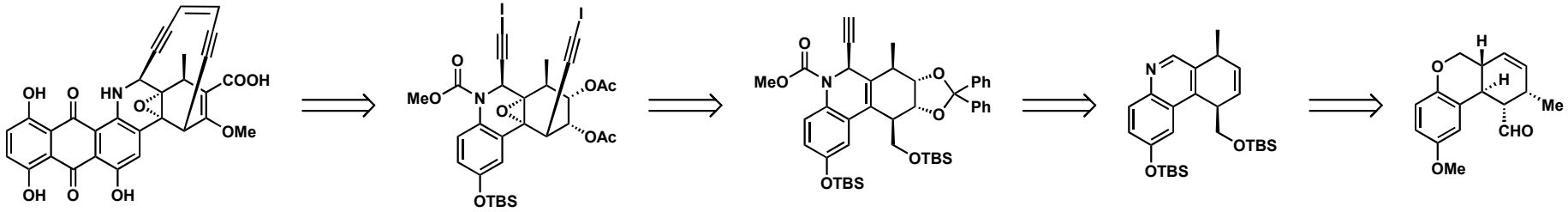

Dynemicin A

*Micromonospora chersina*

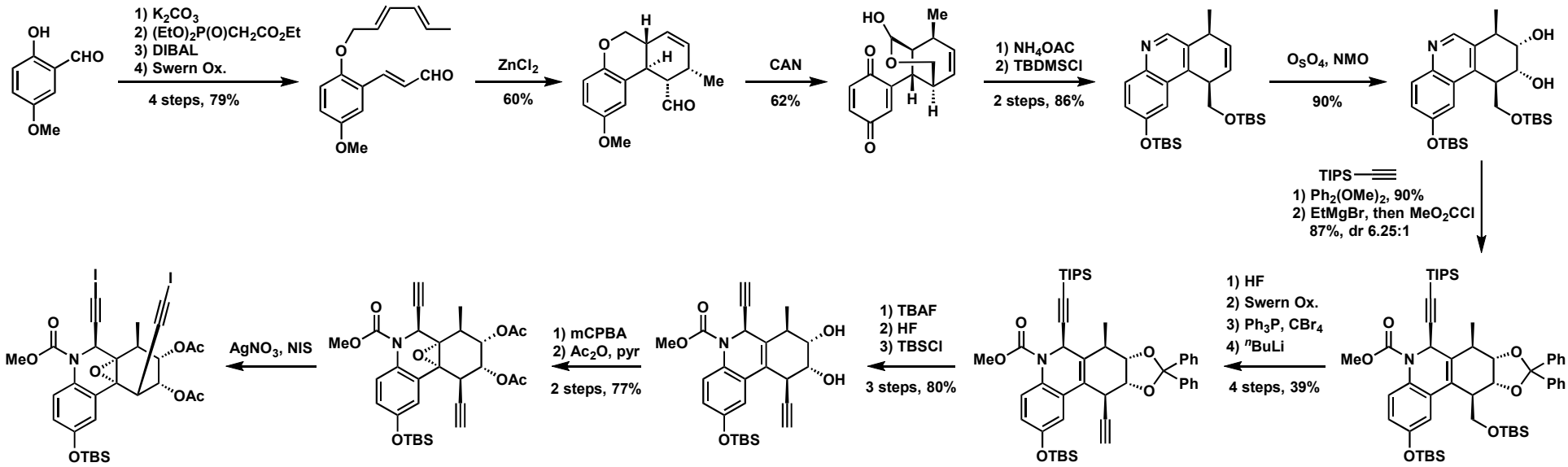



Total synthesis of Dynemicin A

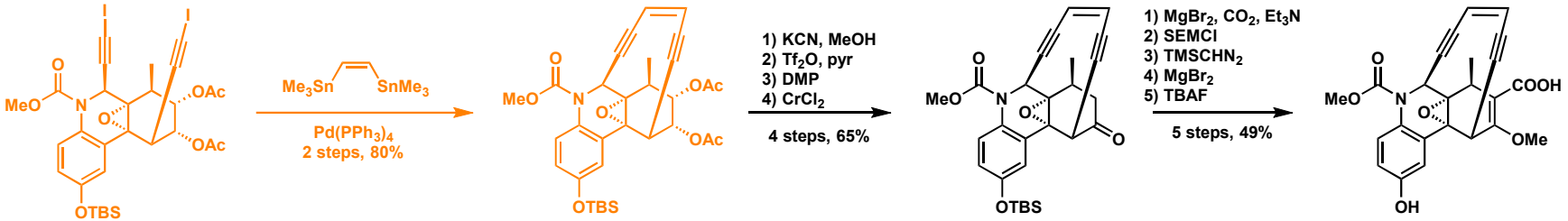



Dynemicin A

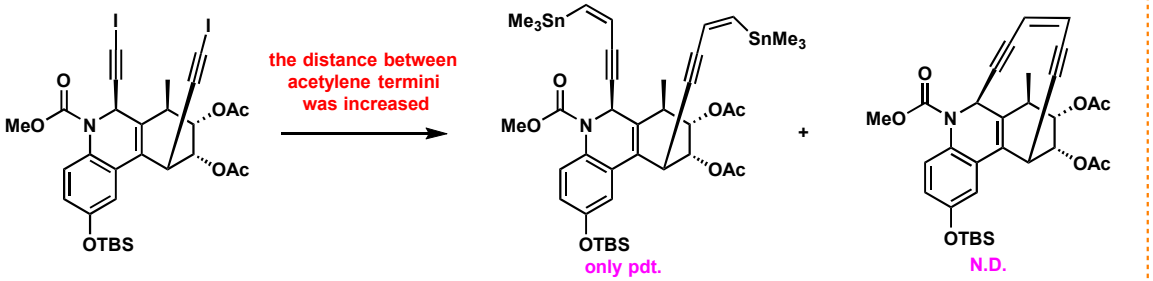


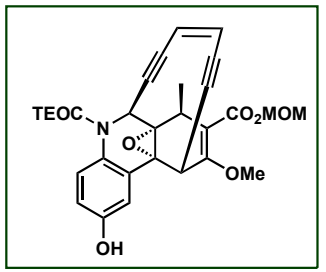

JOC 1994, 59, 3752.

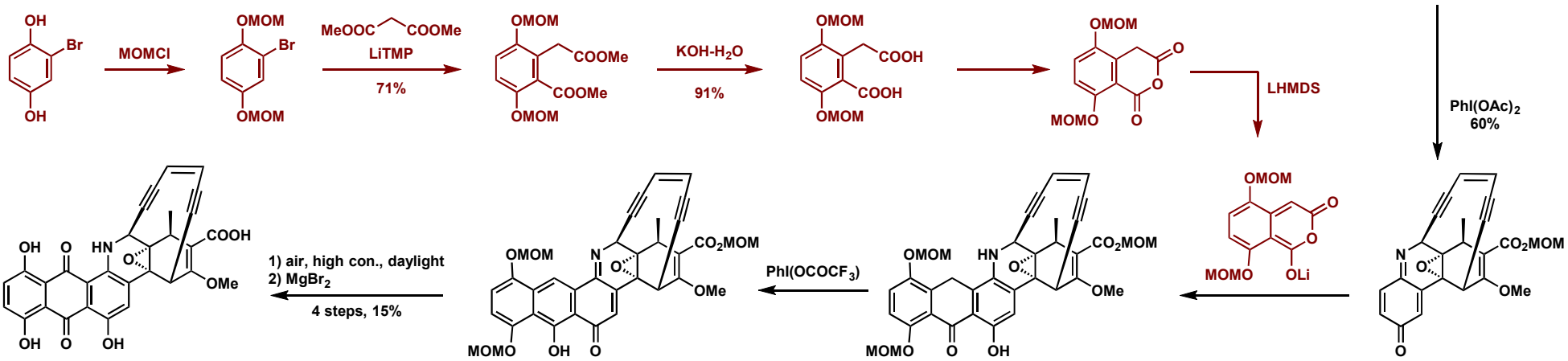
Total synthesis of Dynemicin A




JOC 1994, 59, 3755.

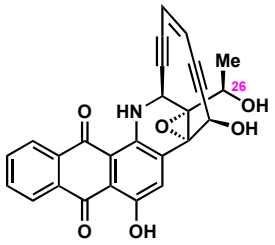


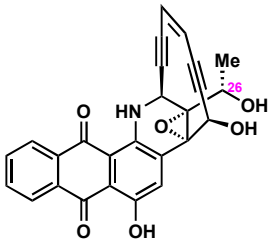



Dynemicin A

ACIE 1995, 34, 1721.




Uncialamycin



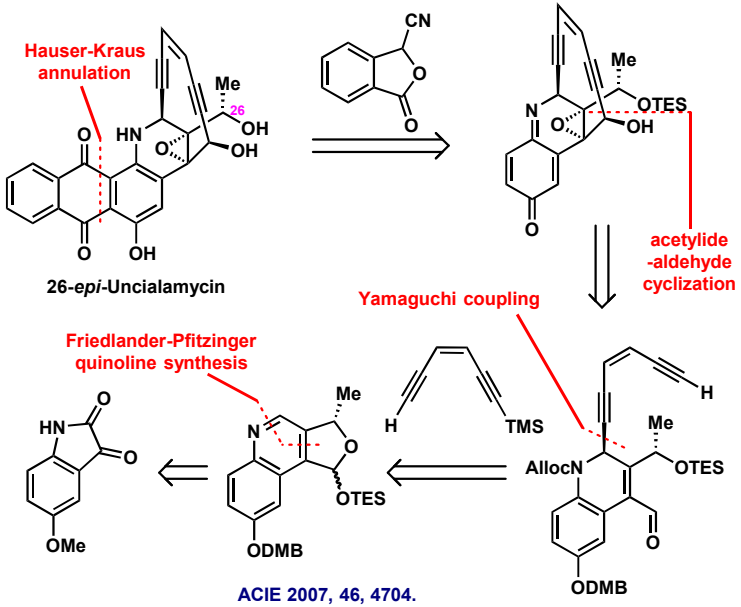

26-*epi*-Uncialamycin

**Isolation**
an unreported strain of streptomycete
related to *Streptomyces cyanogenus (*OL 2005, 7, 5233.)

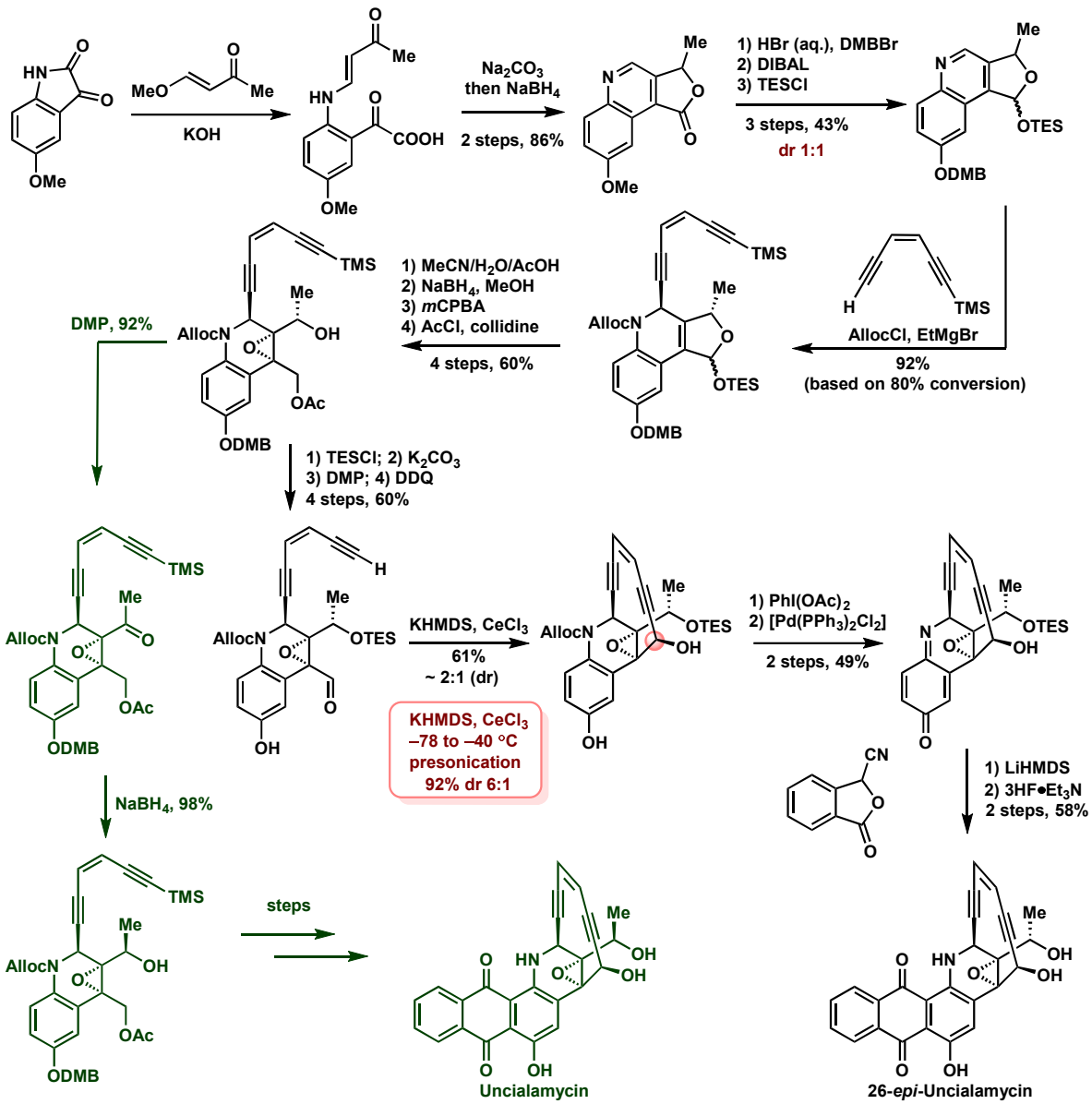
**Biological activity**
*Staphylococcus aureus* (MIC = 0.000 0064 μg/mL) against
*Escherichia coli* (MIC = 0.002 μg/mL)
*Burkholderia cepacia* (MIC= 0.001 μg/mL)

**Total synthesis**
K. C. Nicolaou
(*ACIE* 2007, 46, 4704.; *ACIE* 2008, 47, 185.; JACS 2016, 138, 8235.)

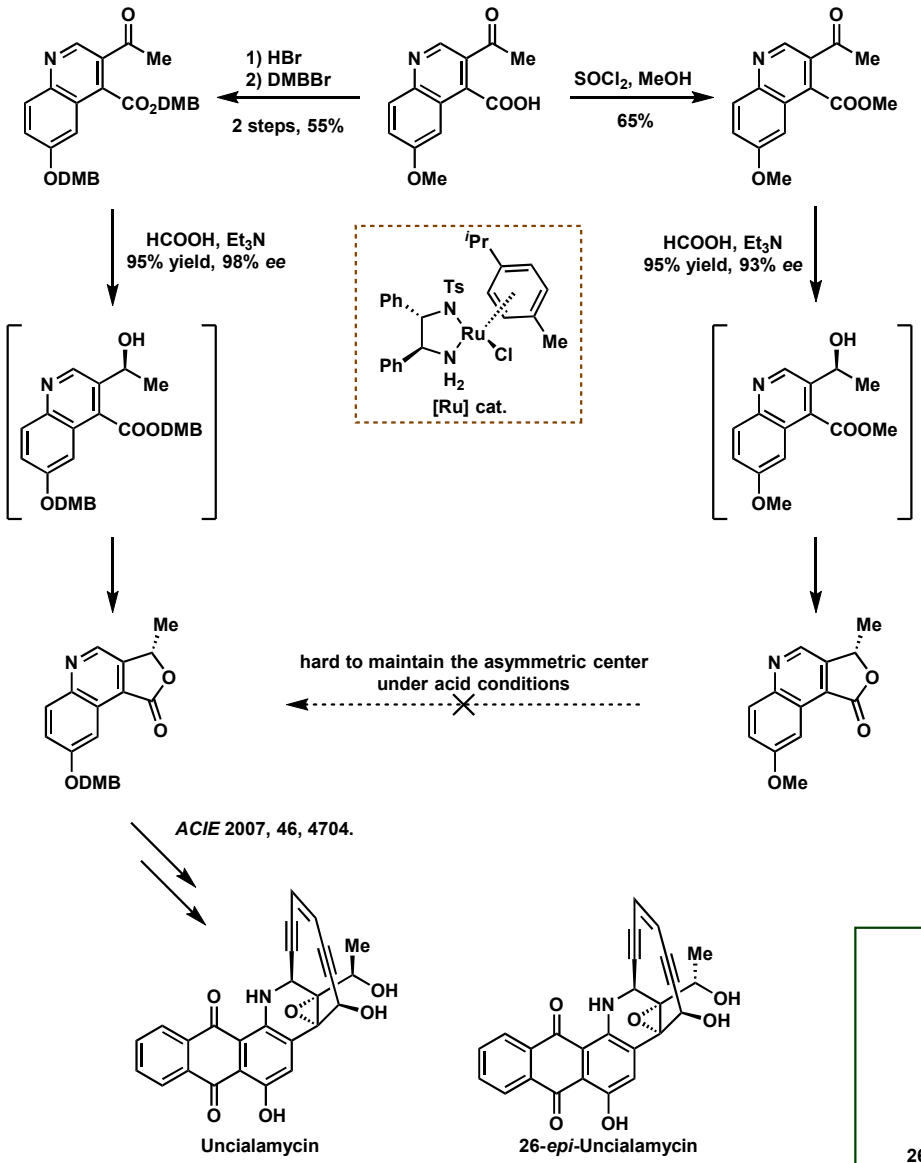
**First Generation Retrosynthetic Analysis**




ACIE 2007, 46, 4704.

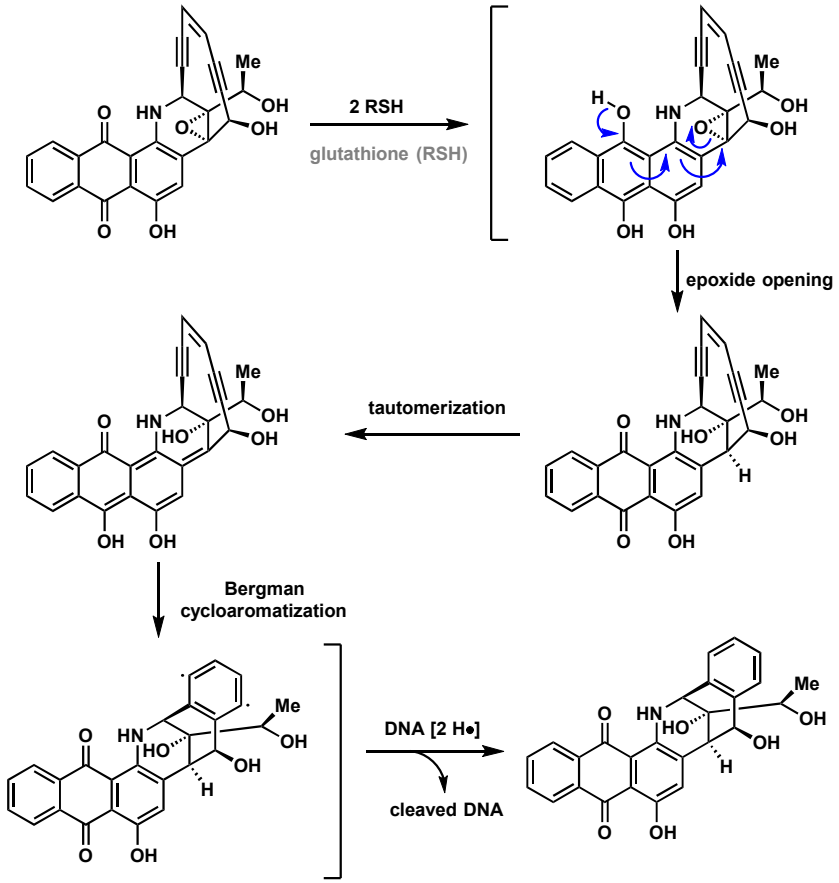


## Catalytic asymmetric synthesis of Uncialamycin and 26-*epi*-Uncialamycin



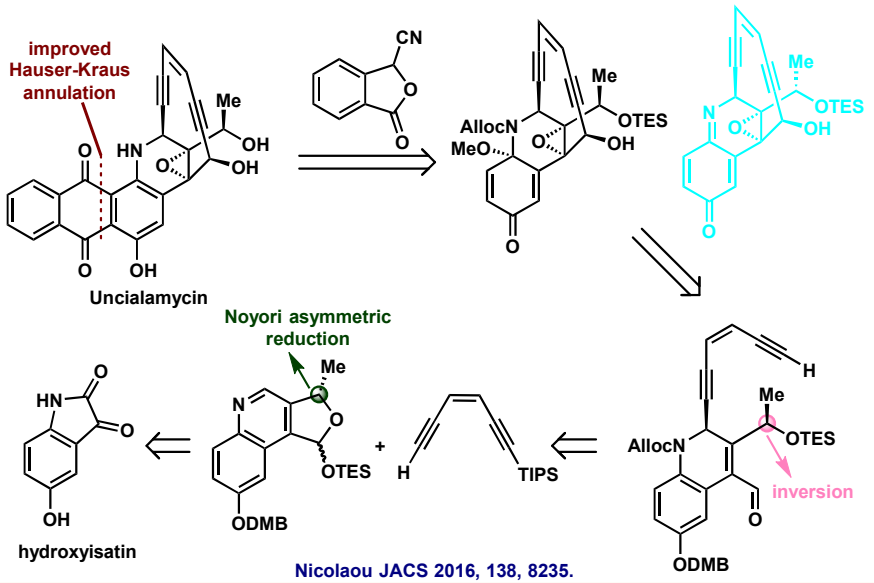

ACIE 2008, 47, 185

## Presumed mechanism of DNA cleavage by Uncialamycin and 26-*epi*-Uncialamycin

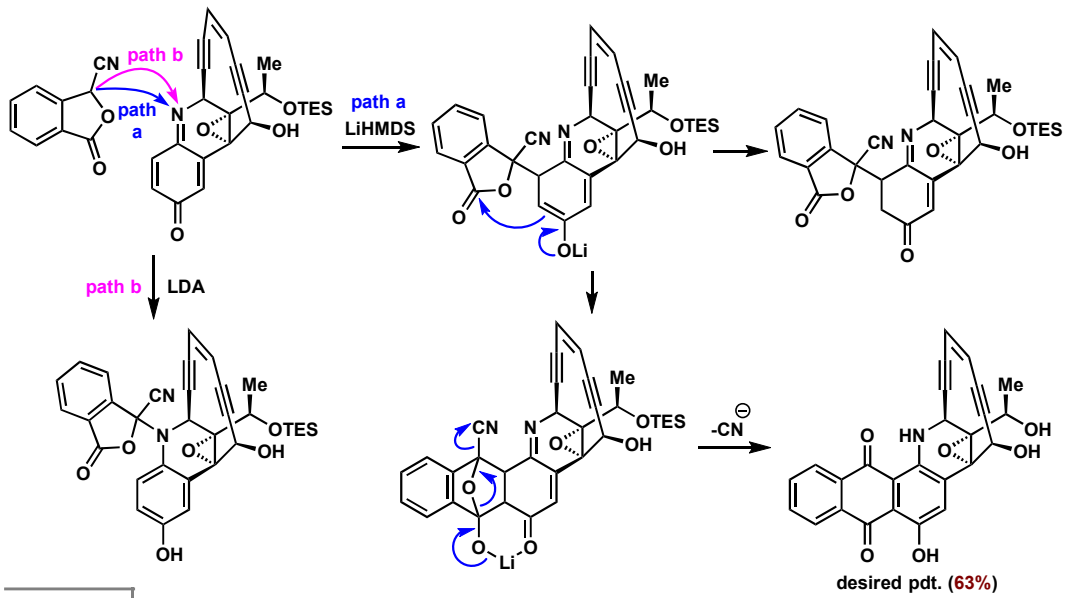



| | Bacterial strain | | |
|---|---|---|---|
| | *MRSA* MIC (mg/mL) | *Staphylococcus epidermidis* MIC (mg/mL) | *Bacillus cereus* MIC (mg/mL) |
| vancomycin | 1 | 2 | 2 |
| Uncialamycin | 0.0002 | 0.00009 | 0.0003 |
| 26-*epi*-Uncialamycin | 0.001 | 0.0003 | 0.002 |

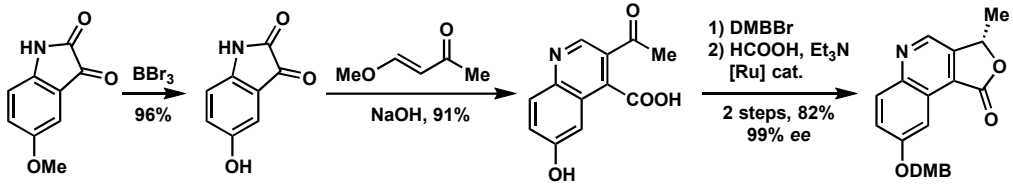
## Streamlined Retrosynthetic Analysis



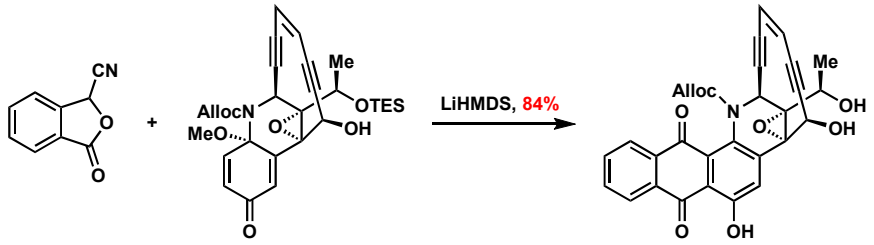

## Conventional Hauser-Lraus annulation



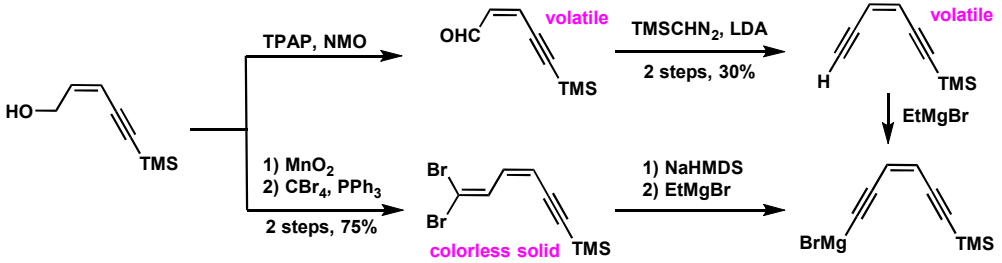

## Streamlined process for the preparation of quinoline derivative



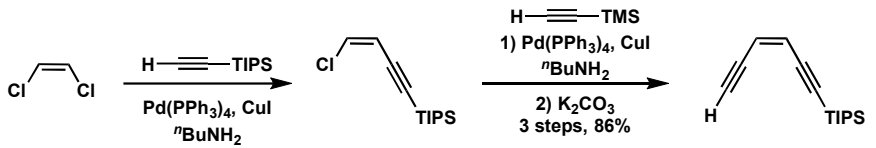

## Improved Hauser-Lraus annulation



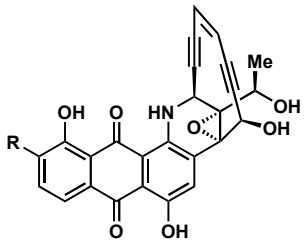

## Original process for the preparation of enediyne fragment



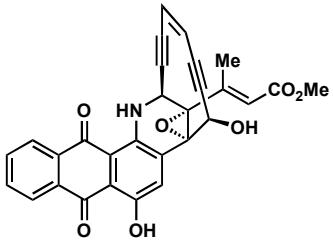

## Streamlined synthesis of enediyne




The yield of Yamaguchi coupling was improved.



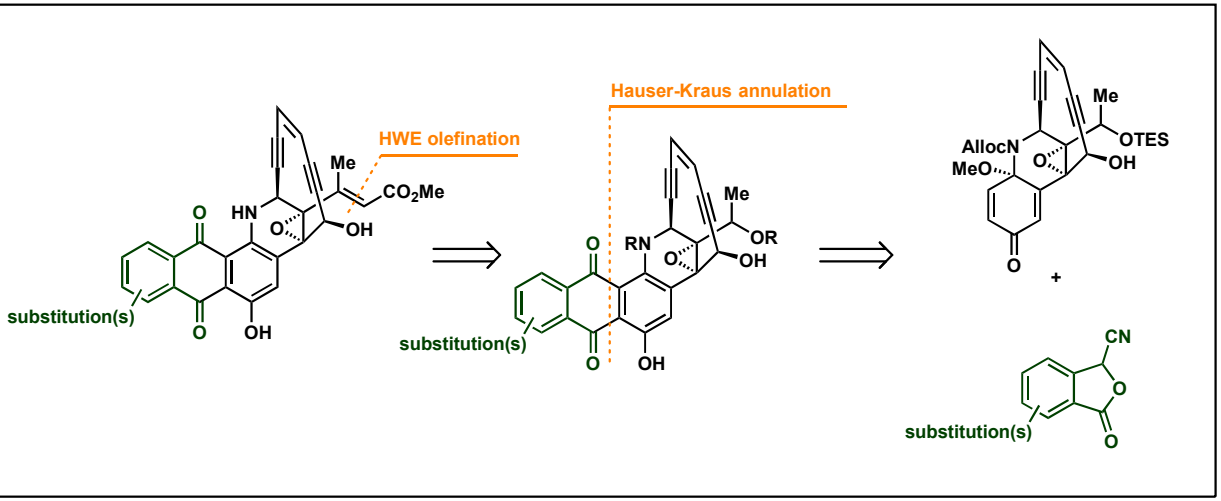
Tiancimycin A (R = OMe)
Yangpumicin A (R = H)

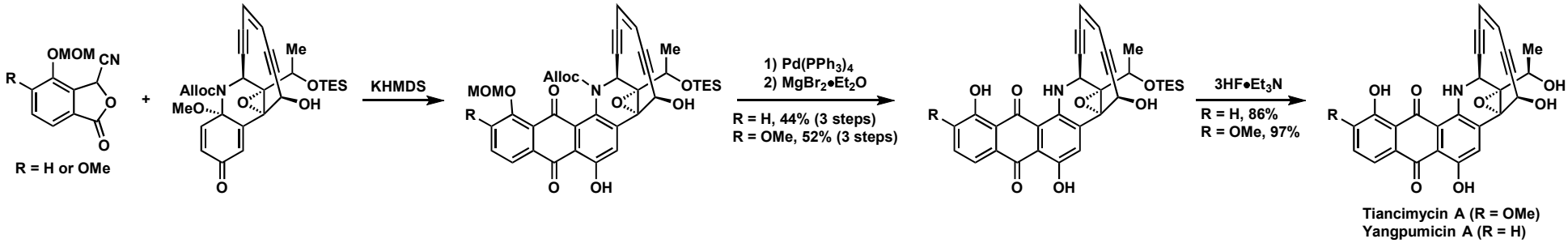


Tiancimycin B

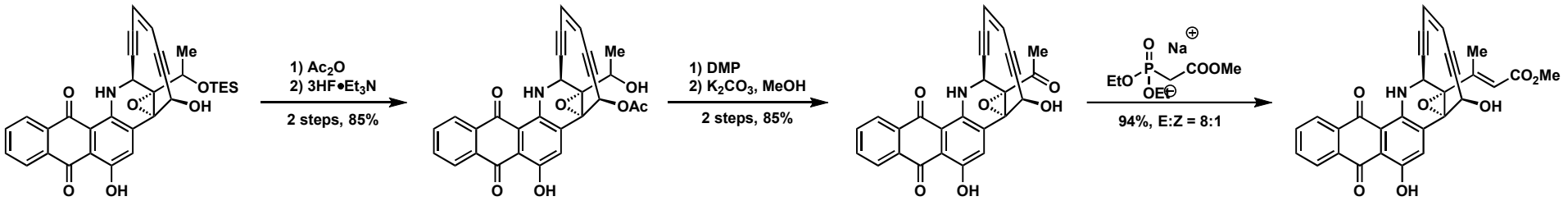
**Isolation**
*Micromonospora yangpuensis* DSM 45577,
*Streptomyces* sp. CB03234

**Total synthesis**
K. C. Nicolaou (*JACS* 2020, 142, 2549)




Tiancimycin A (R = OMe)
Yangpumicin A (R = H)




Tiancimycin B