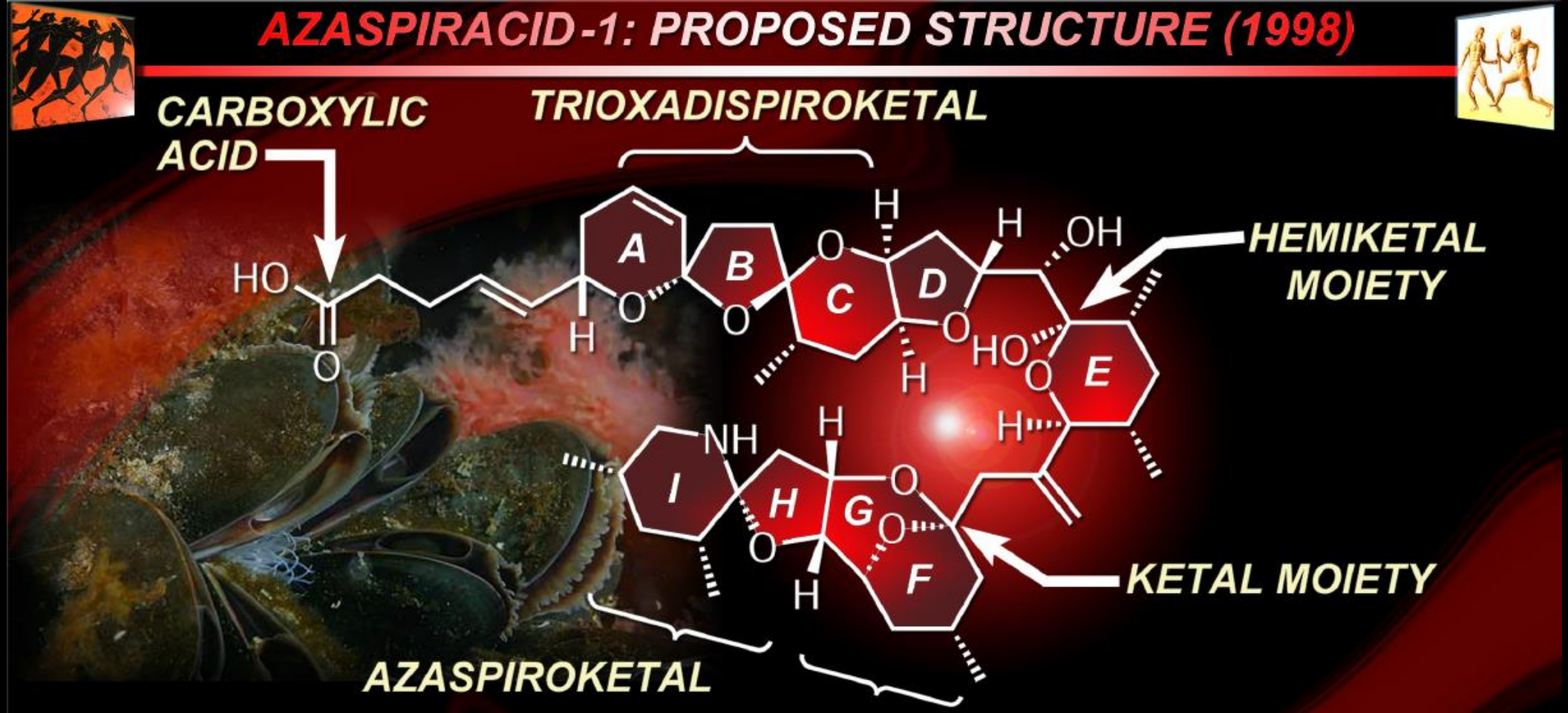
必须穿防护服
Must wear
protective clothes
必须戴防护手套
Must wear protective gloves
必须戴防护眼镜
Must wear
protective goggles
离开实验室前请洗手
WASH HANDS
BEFORE LEAVING
LABORATORY

AZASPIRACID-1: PROPOSED STRUCTURE (1998)

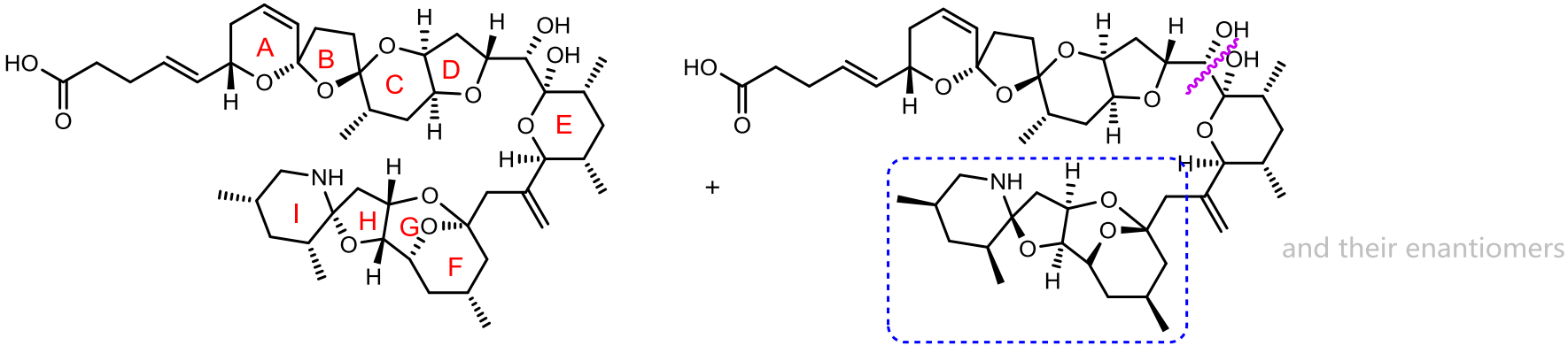


- Architecturally complex marine neurotoxin.
- Azaspiracid syndrome declared in 1998.
- Isolated from mussels Mytilus edulis cultivated in Killary Harbour, Ireland.
- People in Netherlands became ill after ingestion, symptoms included vomiting, severe diarrhea.
- Unprecedented molecular framework with nine rings and twenty stereocenters.
- The absolute stereochemistry and relative stereochemistry between the ABCDE and FGHI domains remain unknown.

Reporter: Yuejun Ma
Supervisor: Saiyong Pan
Date: 2024.06.05

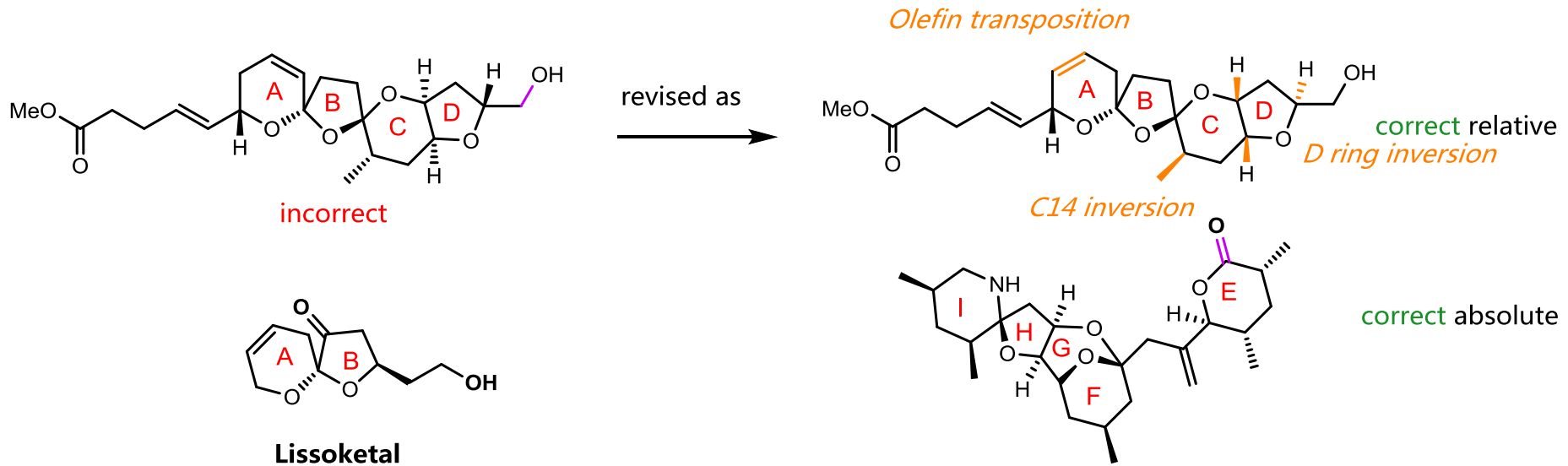
Satake, M.; Ofuji, K.; Naoki, H.; James, K.J.; Furey, A.; McMahon, T.; Silke, J.; Yasumoto, T. J. Am. Chem. Soc. 1998. 120. 9967.

Azasapiracid 1: four originally proposed structures



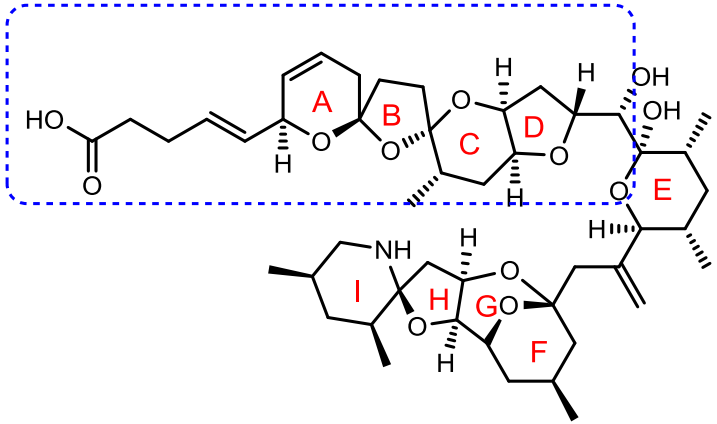
Satake, K. Ofuji, et al., *J. Am. Chem. Soc.* **1998**, 120, 9967

Their total syntheses by Nicolaou et al. and degradation exeriments indicated wrong assignments.

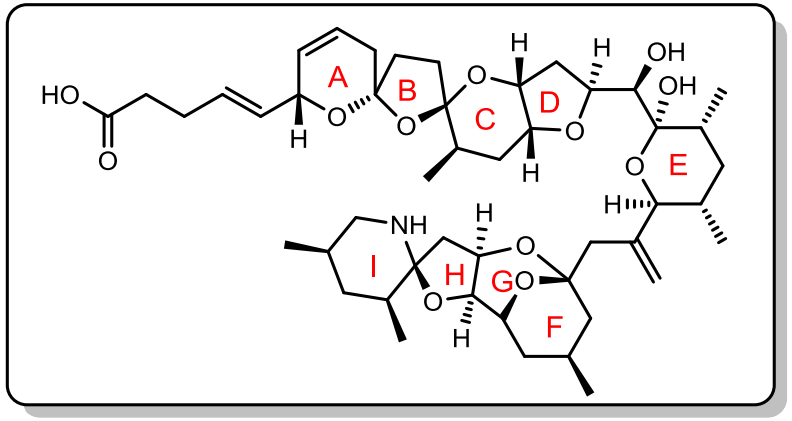


Lissoketal
(discovered in 1997)

Azasapiracid-1: revised structures



or



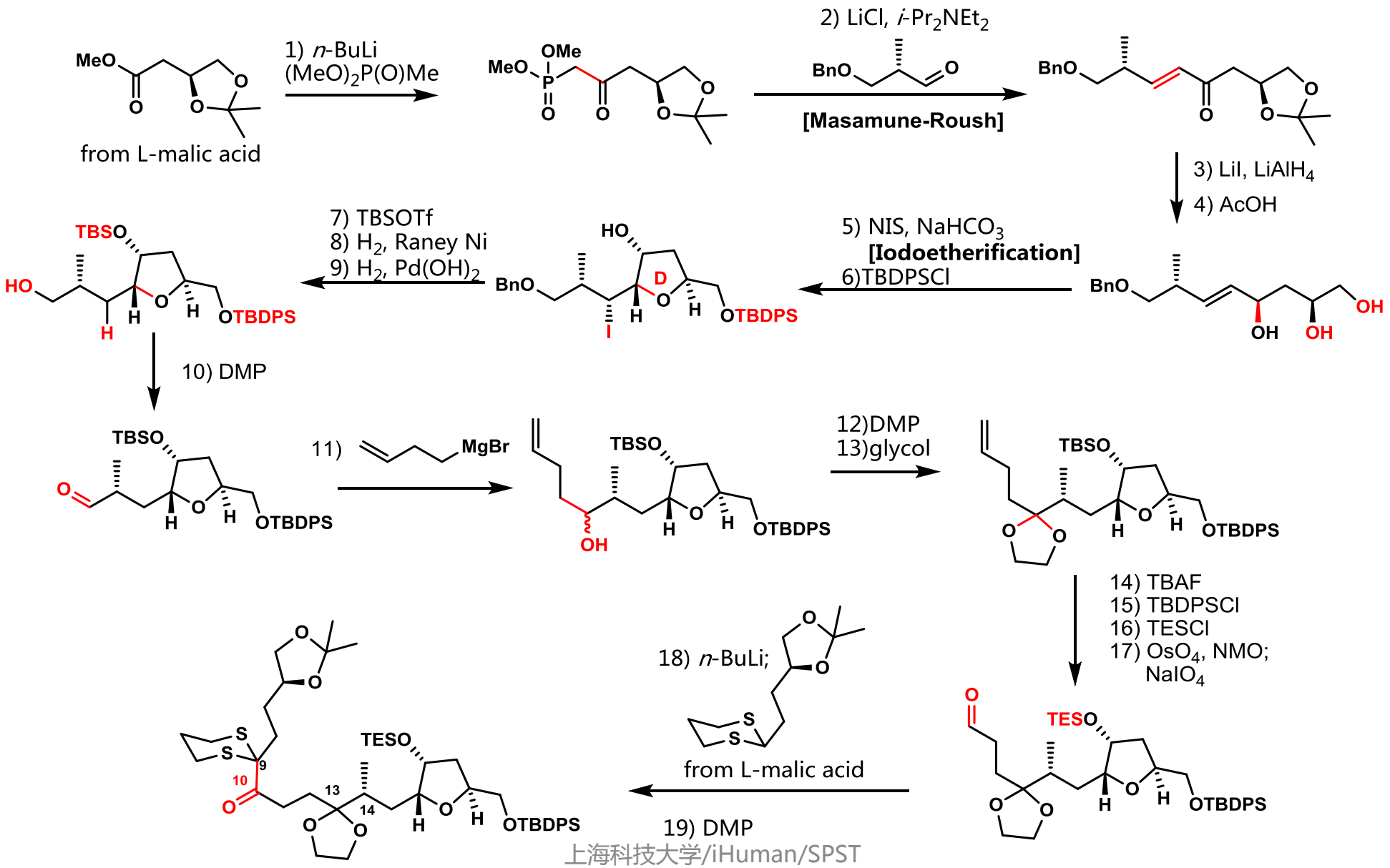
***First total syntheses* and structural revision by Nicholaou et al. (2004)**

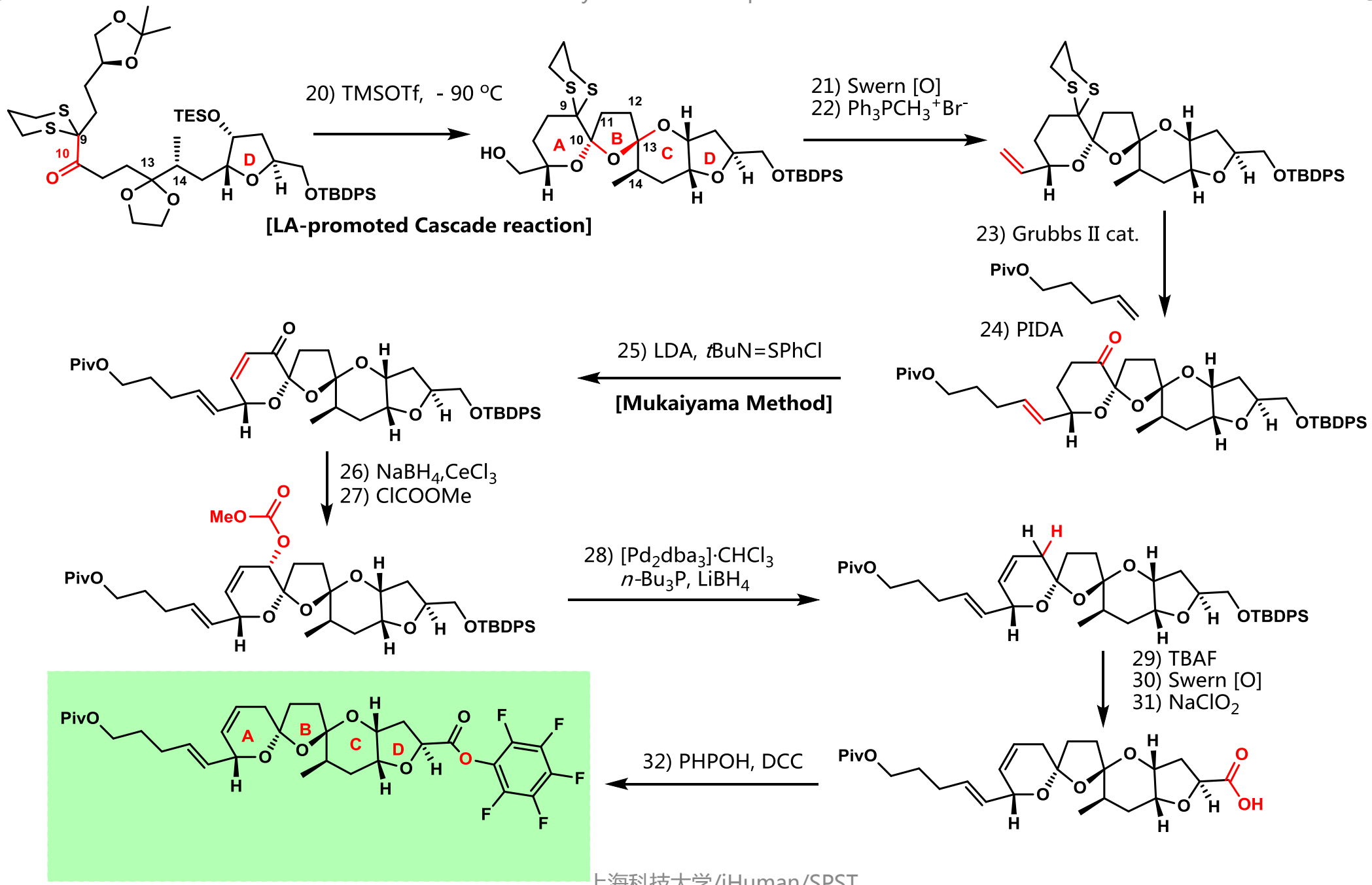
K. C. Nicolaou et al.
Angew. Chem. Int. Ed. **2004**, 43, 4312 –4318
Angew. Chem. Int. Ed. **2004**, 43, 4318 –4324
J. Am. Chem. Soc. **2006**, 128, 2859-2872

♦**K.C. Nicolaou课题组的工作** (*J. Am. Chem. Soc.* **2006**, 128, 2859-2872)

♦Total Synthesis and Structural Elucidation of Azaspiracid-1. Final Assignment and Total Synthesis of the Correct Structure of Azaspiracid-1

Construction of ABCD ring system

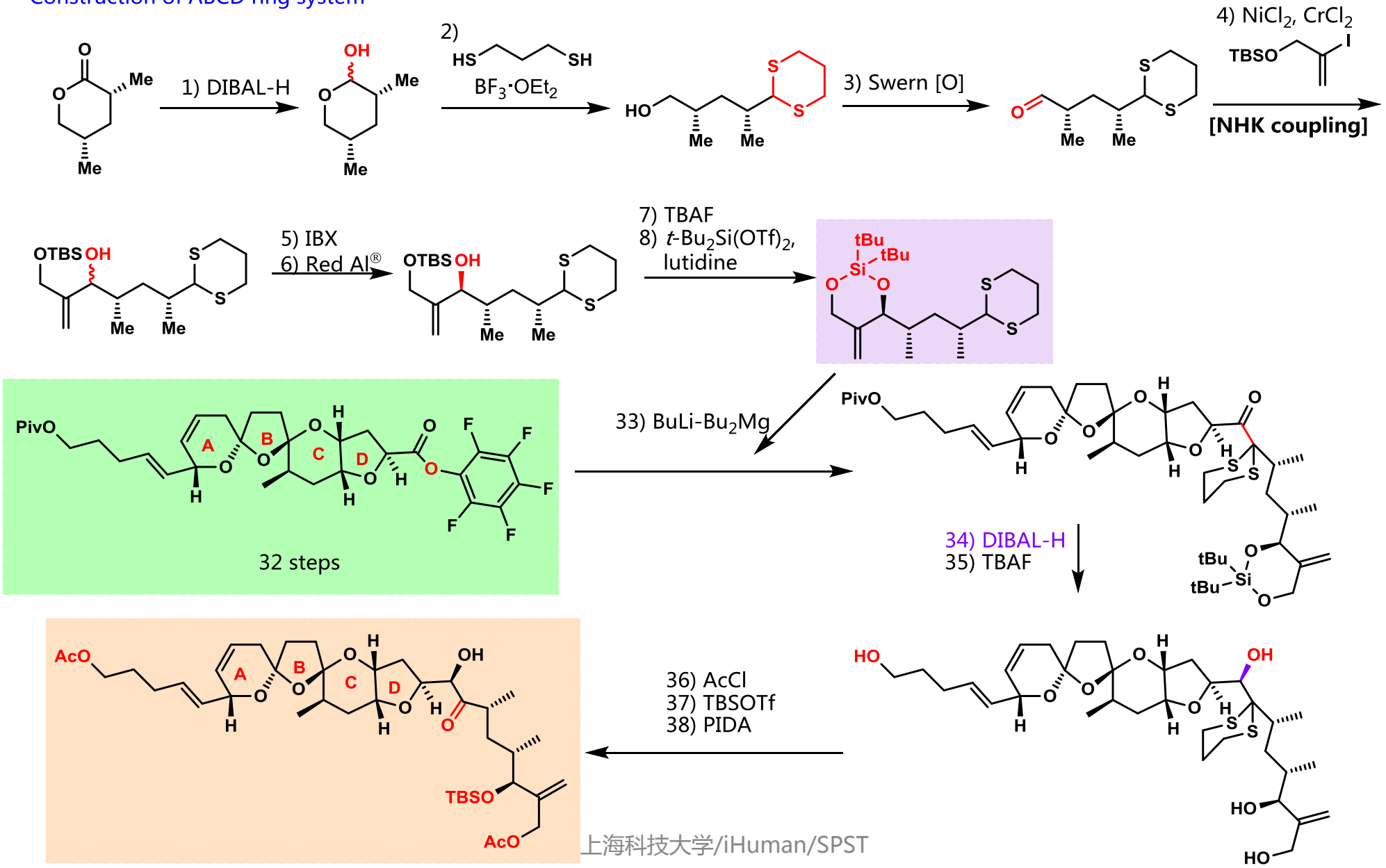



20) TMSOTf, - 90 °C
[LA-promoted Cascade reaction]
21) Swern [O]
22) Ph3PCH3+Br-
23) Grubbs II cat.
24) PIDA
25) LDA, tBuN=SPhCl
[Mukaiyama Method]
26) NaBH4,CeCl3
27) ClCOOMe
28) [Pd2dba3]·CHCl3
n-Bu3P, LiBH4
29) TBAF
30) Swern [O]
31) NaClO2
32) PHPOH, DCC
TESO
HO
PivO
MeO
OTBDPS
OH

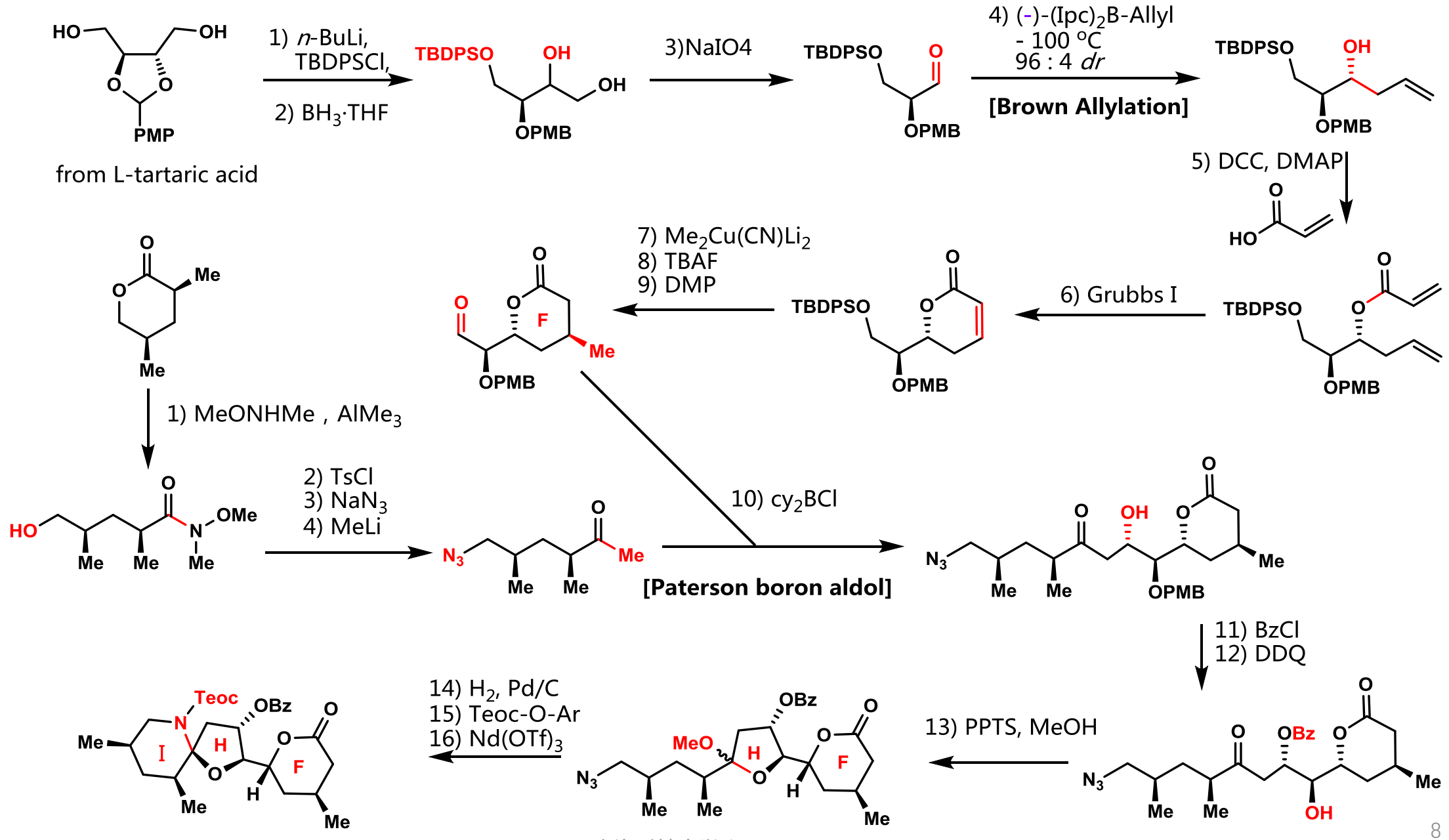
♦**K.C. Nicolaou课题组的工作** (*J. Am. Chem. Soc.* **2006**, 128, 2859-2872)

♦Total Synthesis and Structural Elucidation of Azaspiracid-1. Final Assignment and Total Synthesis of the Correct Structure of Azaspiracid-1

Construction of ABCD ring system

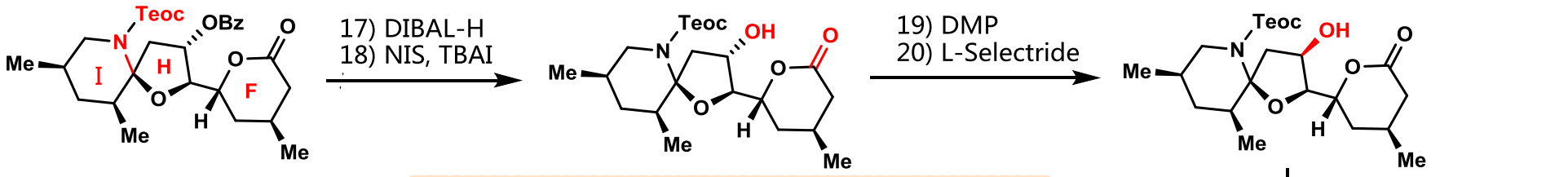


Construction of FHI ring system

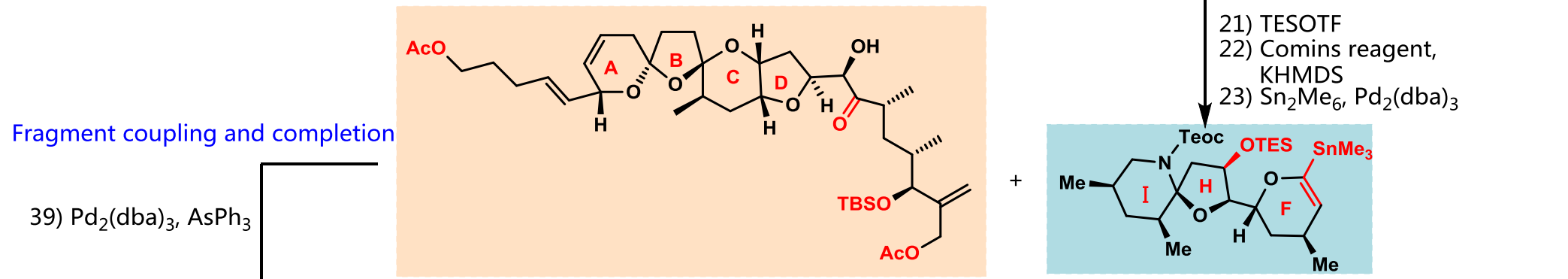


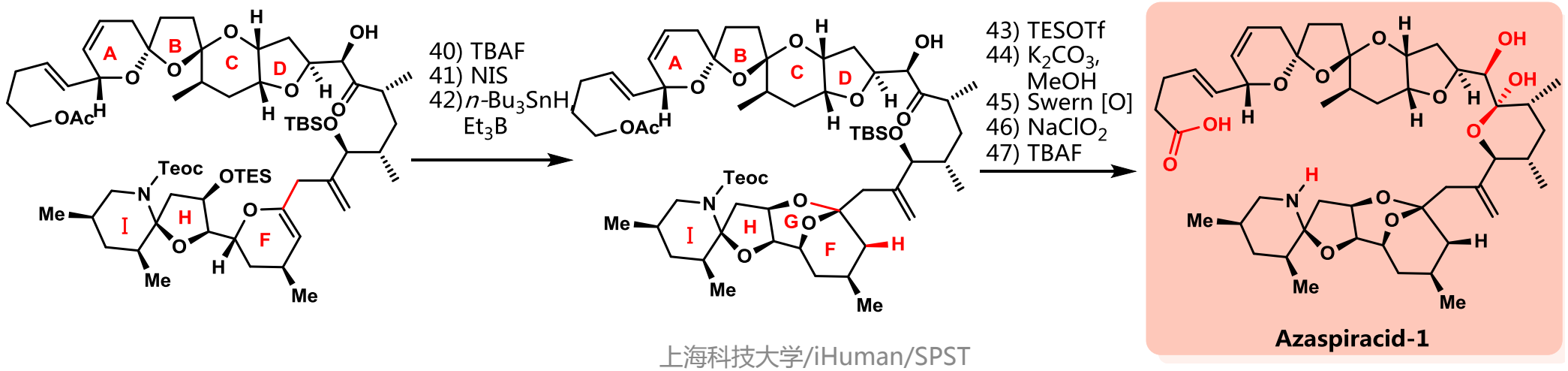
♦**K.C. Nicolaou课题组的工作** (*J. Am. Chem. Soc.* **2006**, 128, 2859-2872)
♦Total Synthesis and Structural Elucidation of Azaspiracid-1. Final Assignment and Total Synthesis of the Correct Structure of Azaspiracid-1

Construction of FHI ring system



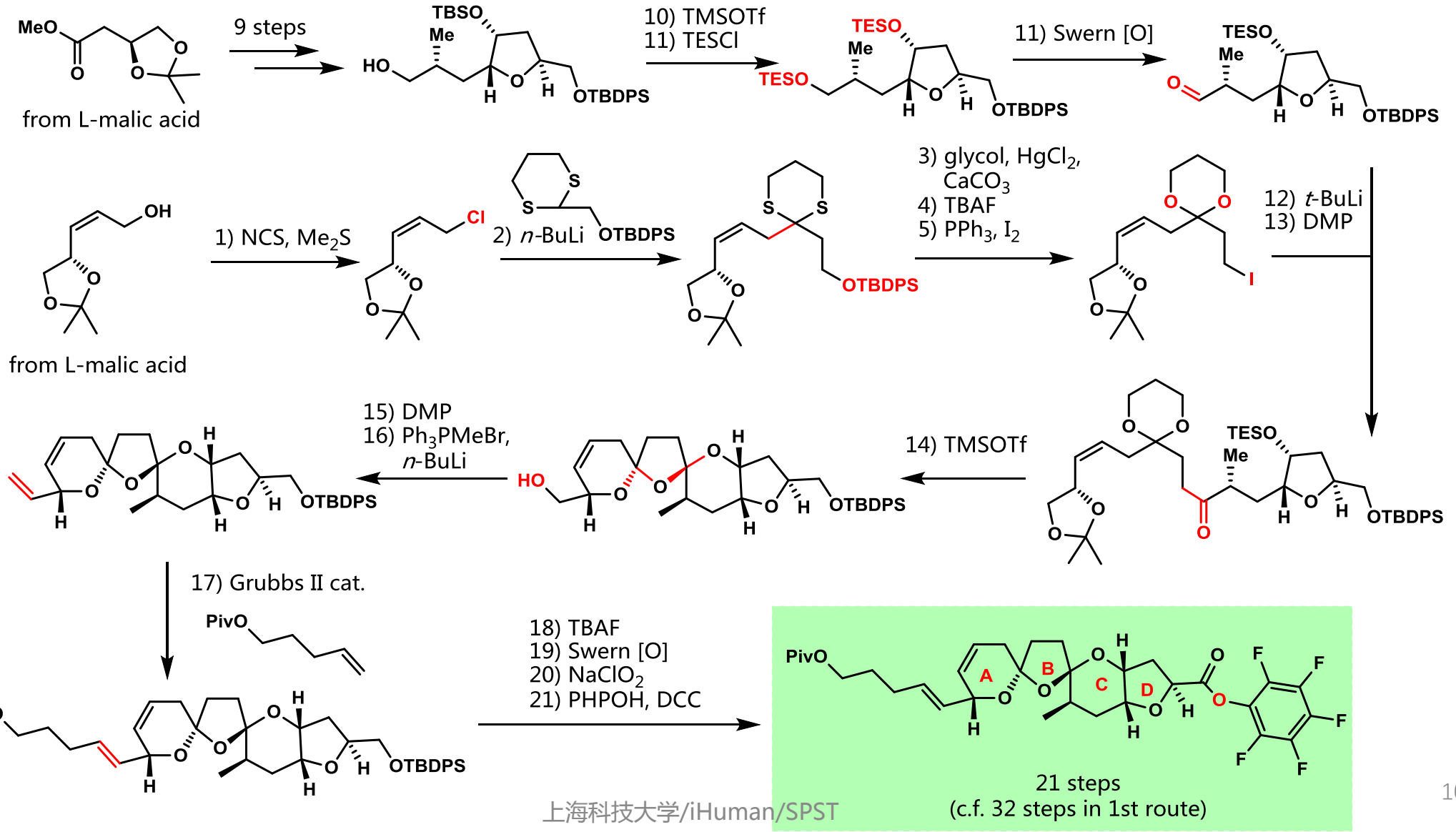
Fragment coupling and completion



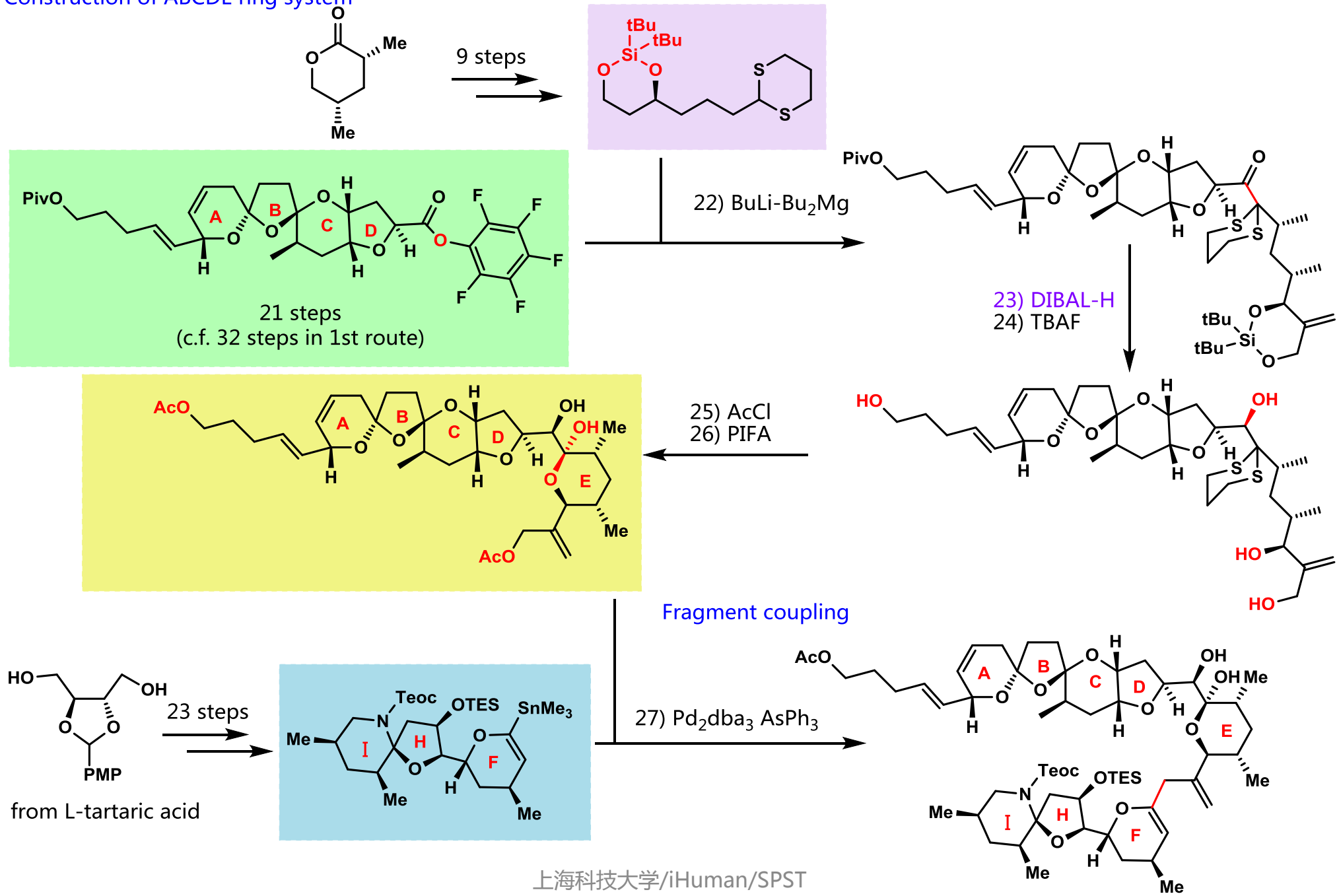


♦**K.C. Nicolaou课题组的工作**（*Chem. Asian. J.* **2006**, 245, 1–2.）
♦Second-Generation Total Synthesis of Azaspiracids-1, -2, and -3

Construction of ABCDE ring system

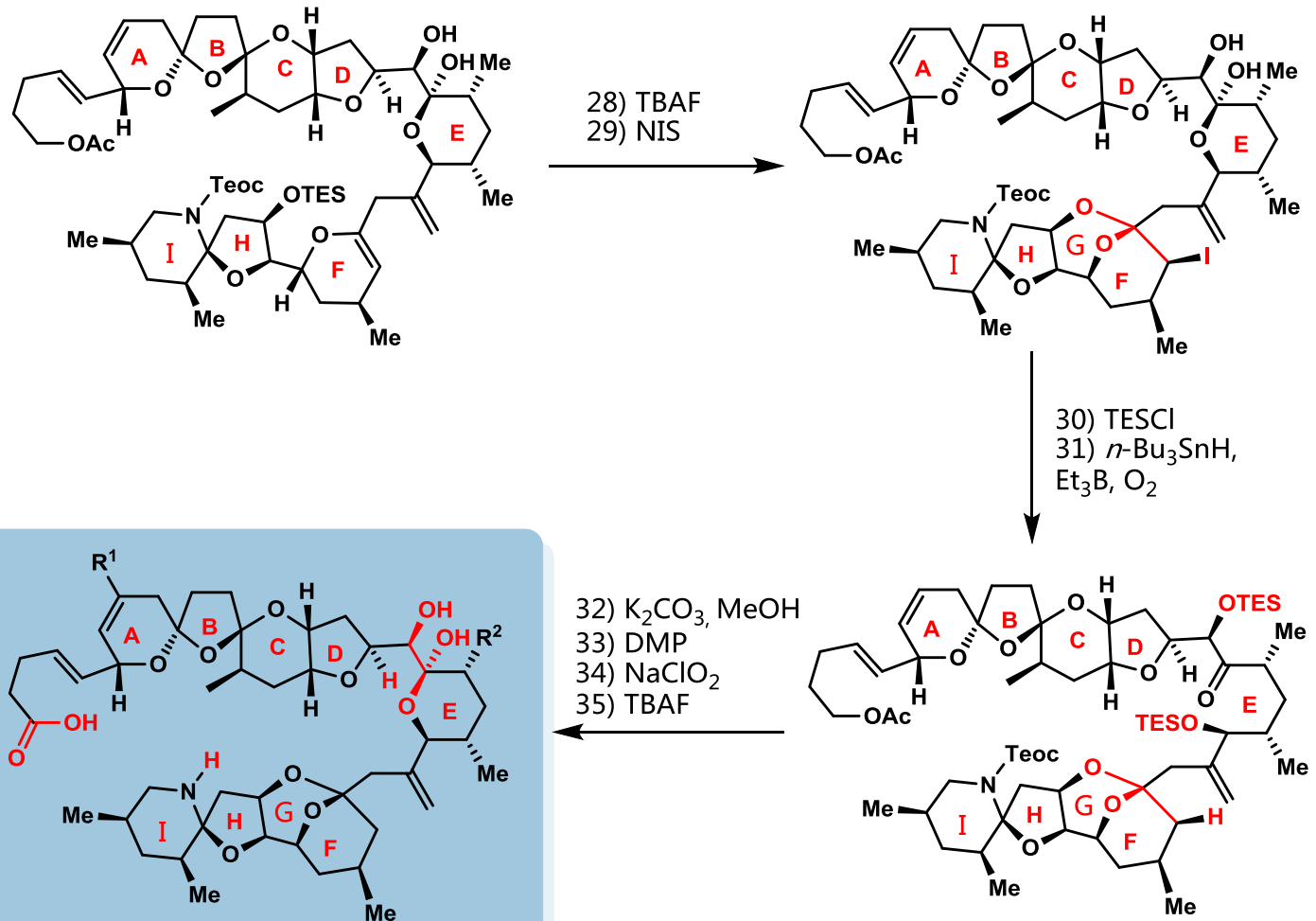


Construction of ABCDE ring system



♦**K.C. Nicolaou课题组的工作**（*Chem. Asian. J.* **2006**, 245, 1–2.）
♦Second-Generation Total Synthesis of Azaspiracids-1, -2, and -3

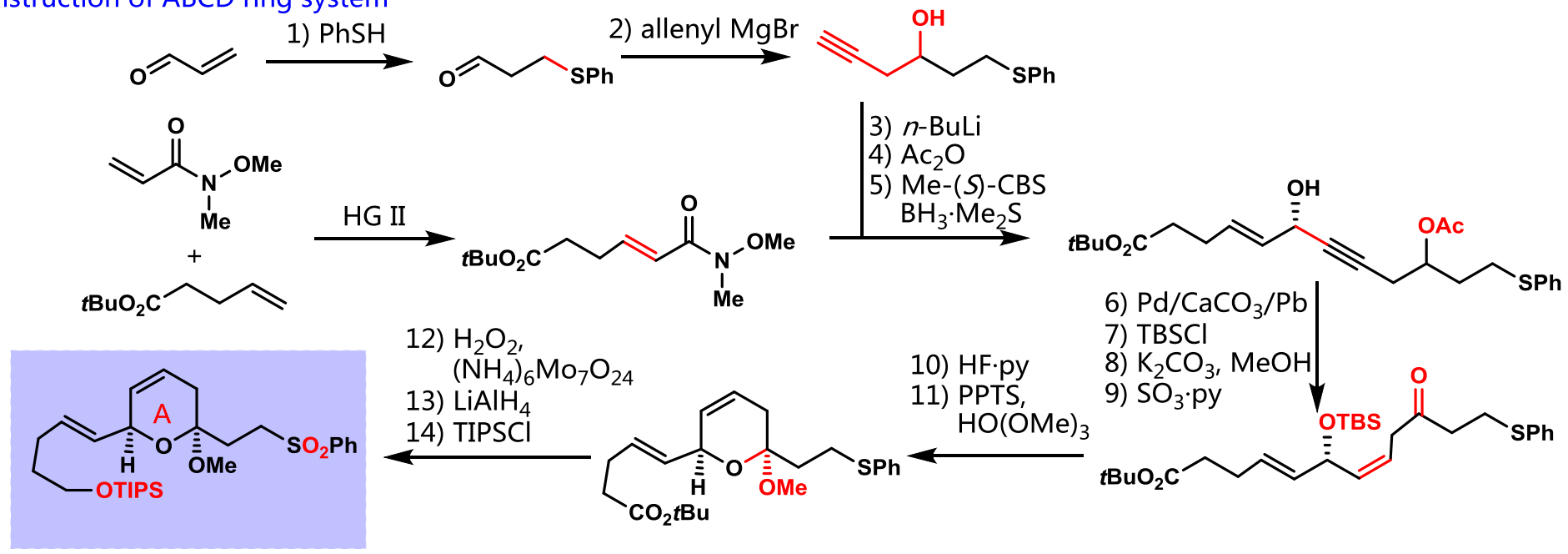
Completion of synthesis

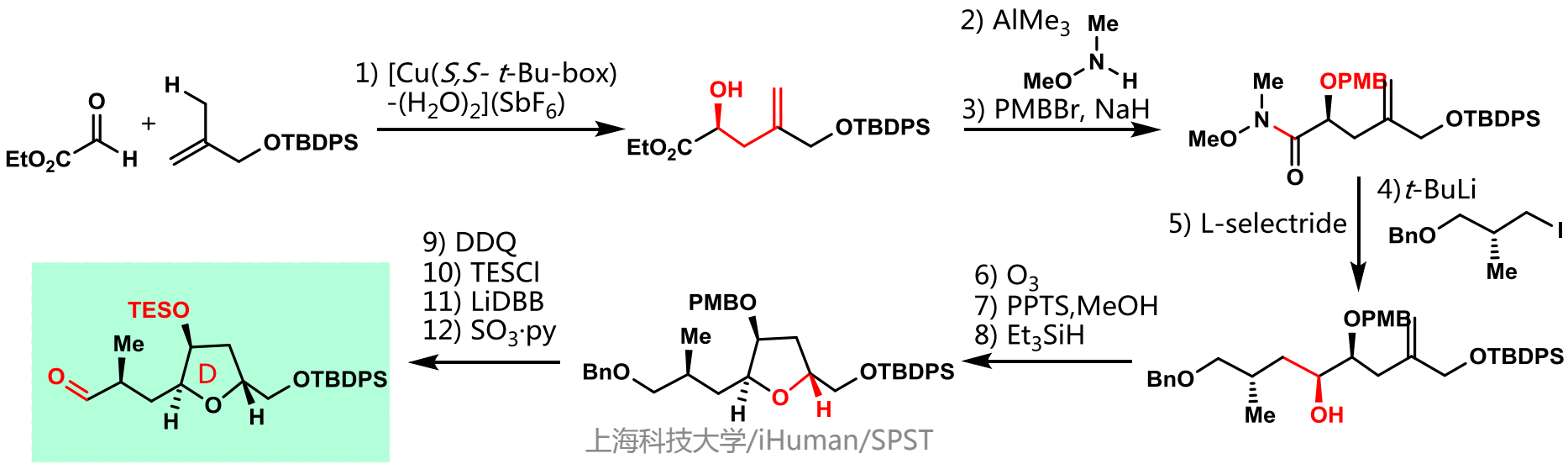


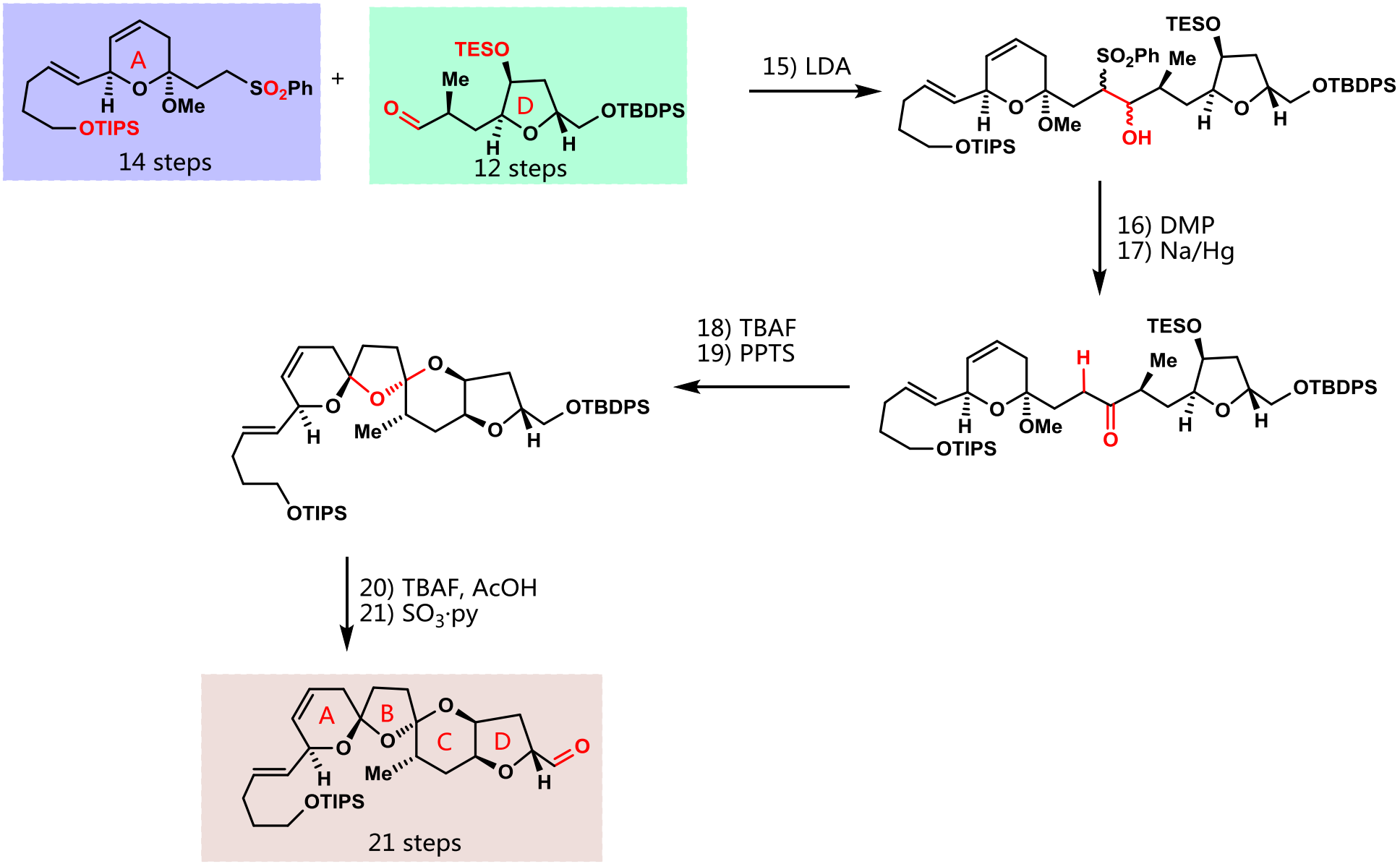
♦**D.A.Evans课题组的工作** (*J. Am. Chem. Soc.* **2008**, *130*, 16295–16309)

♦Total Synthesis of (+)-Azaspiracid-1. An Exhibition of the Intricacies of Complex Molecule Synthesis

Construction of ABCD ring system



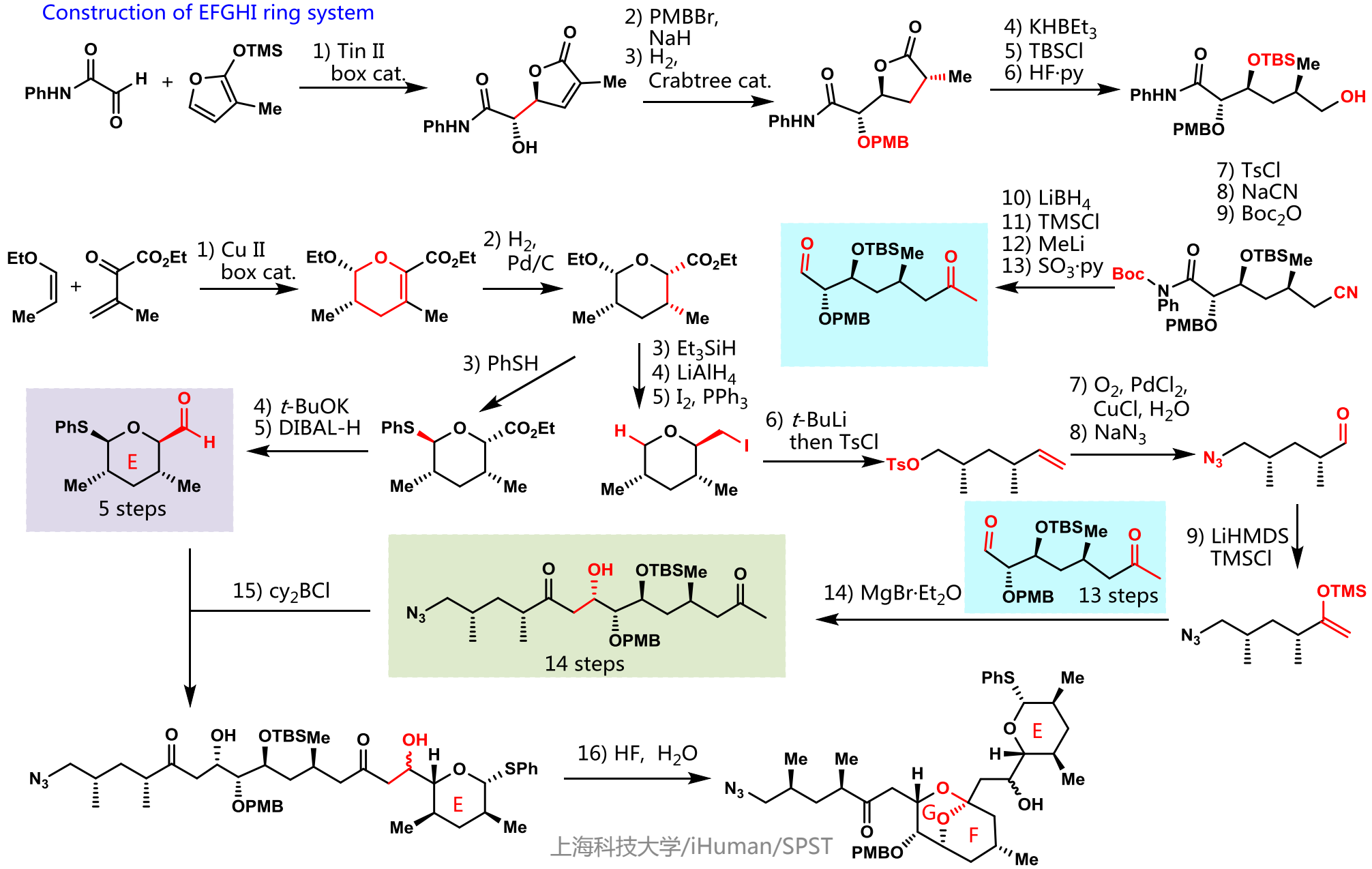


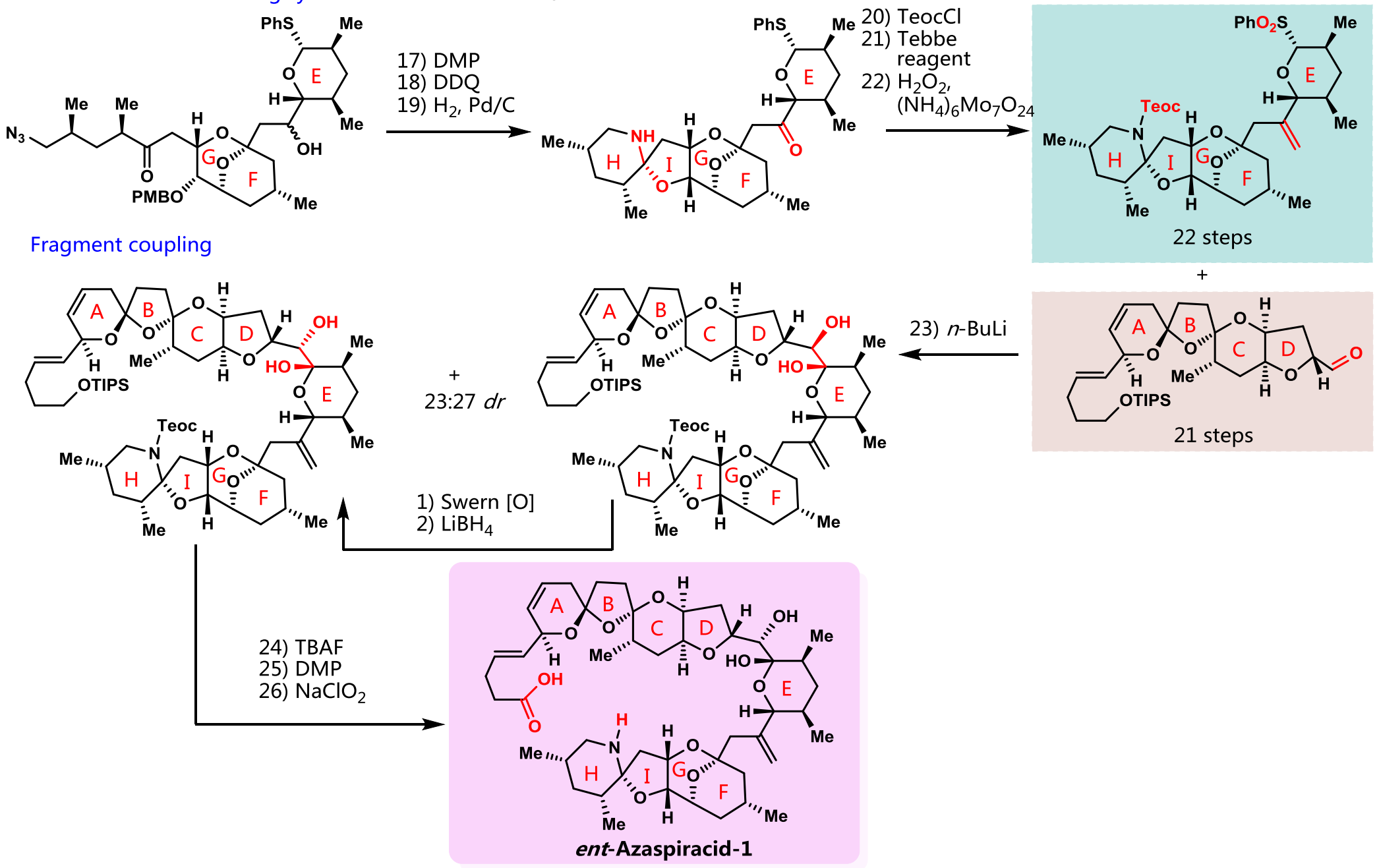

A
H
O
OMe
SO2Ph
OTIPS
14 steps
+
TESO
Me
O
D
H
O
H
OTBDPS
12 steps
15) LDA
TESO
SO2Ph
Me
OTBDPS
H
O
OMe
H
O
H
OTIPS
OH
16) DMP
17) Na/Hg
TESO
H
Me
OTBDPS
H
O
OMe
H
O
H
OTIPS
O
18) TBAF
19) PPTS
O
O
O
OTBDPS
H
Me
O
H
OTIPS
20) TBAF, AcOH
21) SO3·py
A
B
O
O
C
D
O
O
H
Me
O
H
OTIPS
21 steps

♦**D.A.Evans课题组的工作** (*J. Am. Chem. Soc.* **2008**, *130*, 16295–16309)

♦Total Synthesis of (+)-Azaspiracid-1. An Exhibition of the Intricacies of Complex Molecule Synthesis

Construction of EFGHI ring system

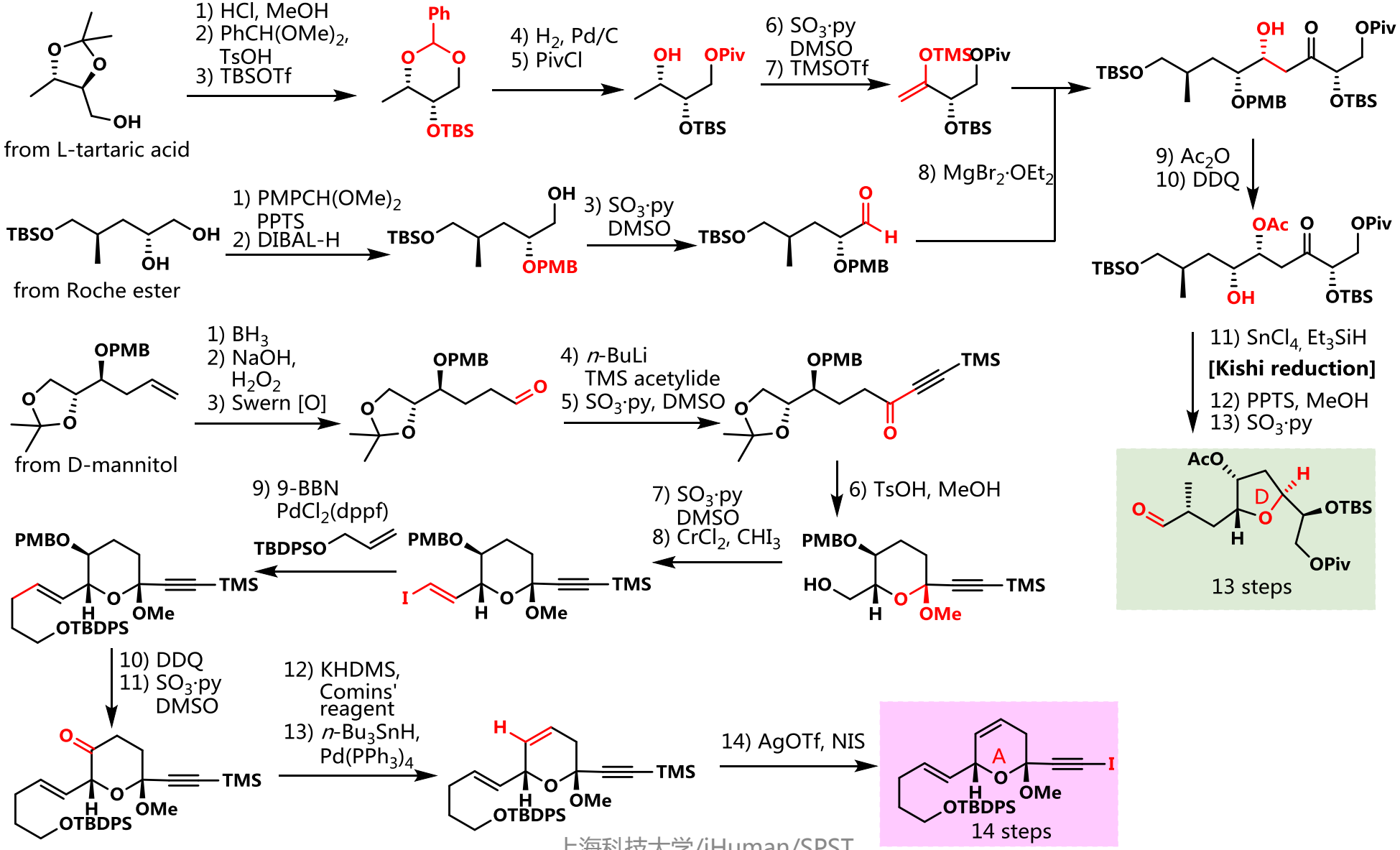


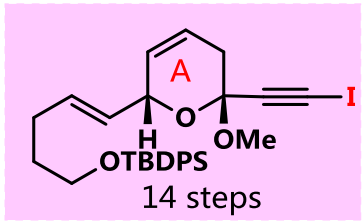

17) DMP
18) DDQ
19) H2, Pd/C
20) TeocCl
21) Tebbe reagent
22) H2O2, (NH4)6Mo7O24
22 steps
Fragment coupling
+
23:27 dr
23) n-BuLi
21 steps
1) Swern [O]
2) LiBH4
24) TBAF
25) DMP
26) NaClO2
ent-Azaspiracid-1

♦**C.J.Forsyth课题组的工作**（*Angew. Chem.* **2018,** *130*, 818 –821）

♦Stereochemical Definition of the Natural Product (6R,10R,13R, 14R, 16R,17R,19S,20S,21R,24S,25S,28S,30S,32R,33R,34R,36S,37S,39R)-Azaspiracid-3 by Total Synthesis and Comparative Analyses

Construction of ABCD





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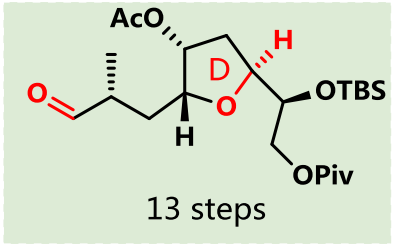
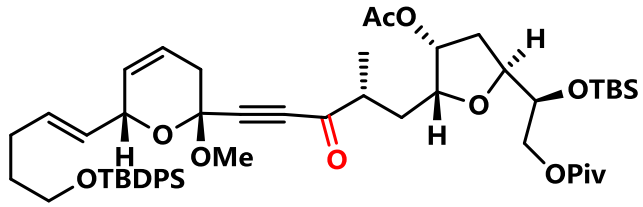
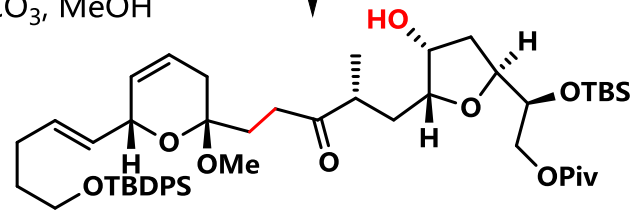


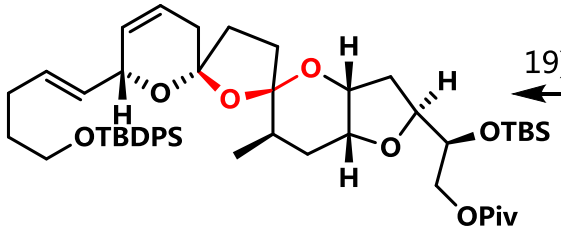
15) $CrCl_2$, $NiCl_2$
[NHK reaction]
16) MnO_2



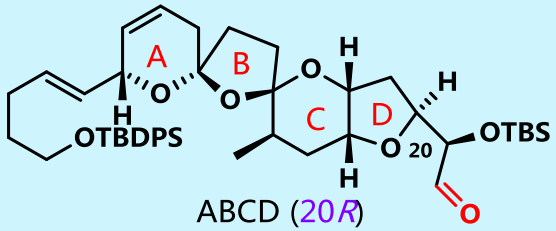
17) $(CuHPPh_3)_6$, $PhSiH_3$, H_2O
[Stryker reduction]
18) K_2CO_3, MeOH



19) PPTS

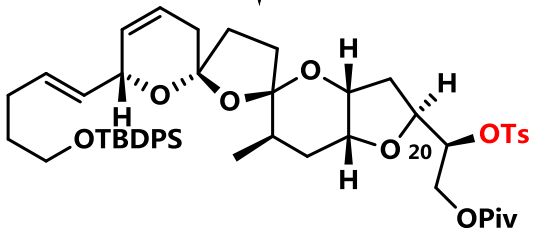


20) DIBAL-H
21) DMP

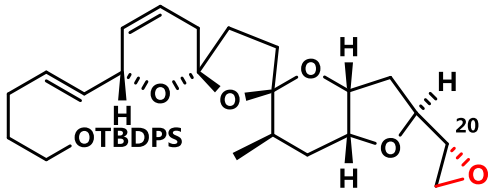


ABCD (20*R*)
21 steps

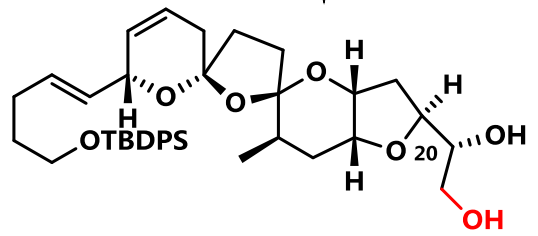
20) TBAF
21) TBDPSCl
22) TsCl



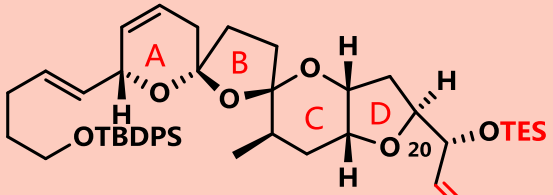
23) TBAOH



24) H_2O,(*R*,*R*)-(-) salen cat.



25) TESOTf
26) Swern [O]

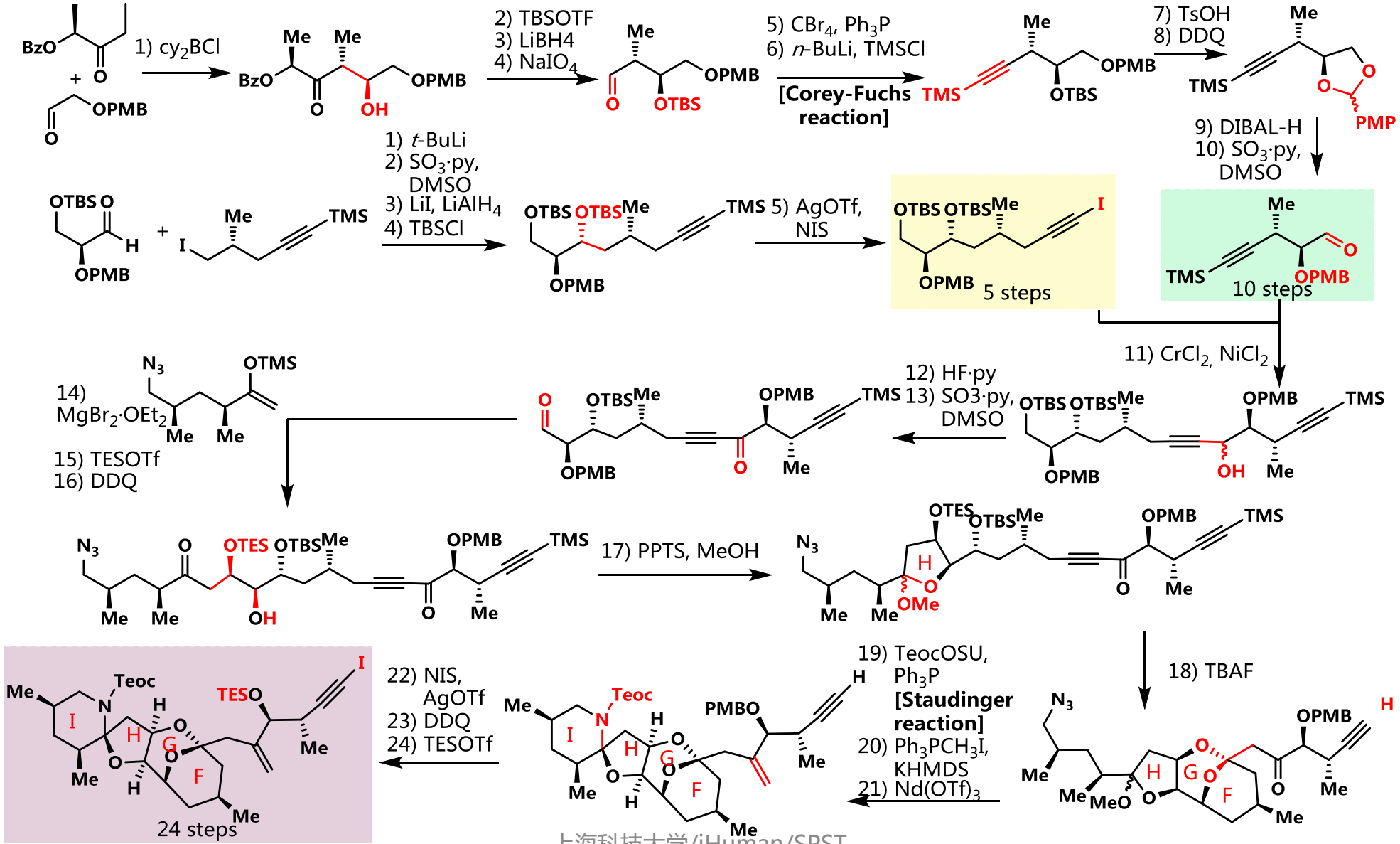


ABCD (20*S*)
26 steps

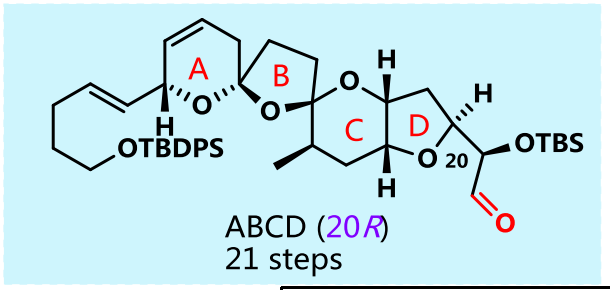
♦**C.J.Forsyth课题组的工作**（*Angew. Chem.* **2018,** *130*, 818 –821）

♦Stereochemical Definition of the Natural Product (6R,10R,13R, 14R, 16R,17R,19S,20S,21R,24S,25S,28S,30S,32R,33R,34R,36S,37S,39R)-Azaspiracid-3 by Total Synthesis and Comparative Analyses

Construction of FGHI

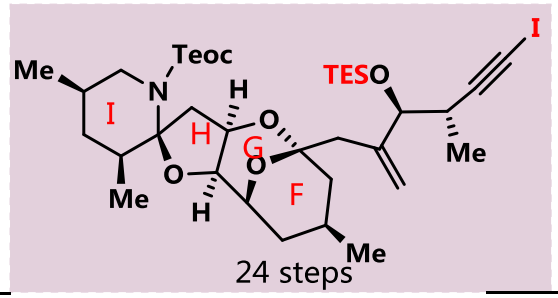


Fragment coupling



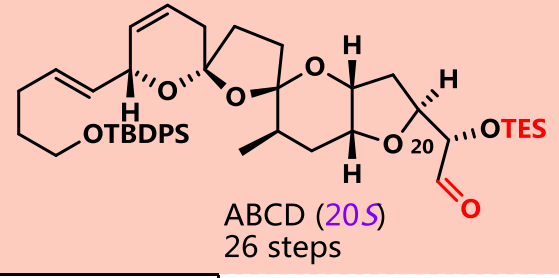
ABCD (20*R*)
21 steps

+



24 steps

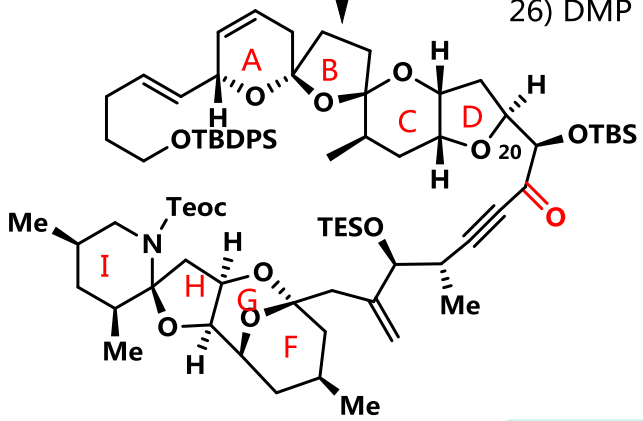
+

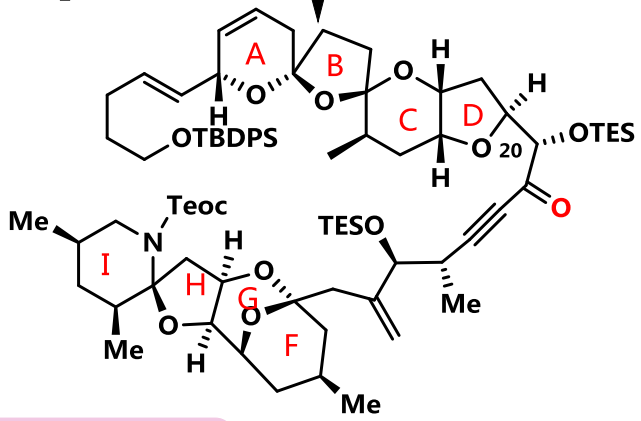


ABCD (20*S*)
26 steps

25) $CrCl_2$, $NiCl_2$
26) DMP

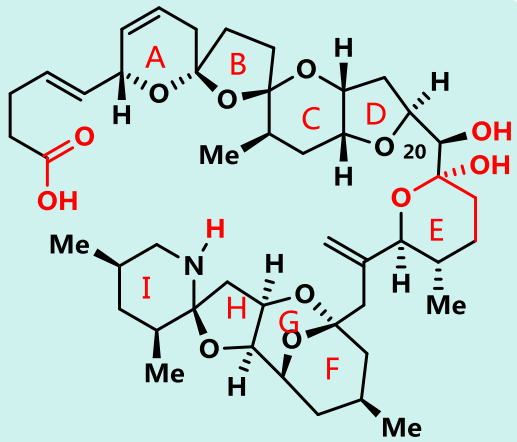
27) $CrCl_2$, $NiCl_2$
28) DMP



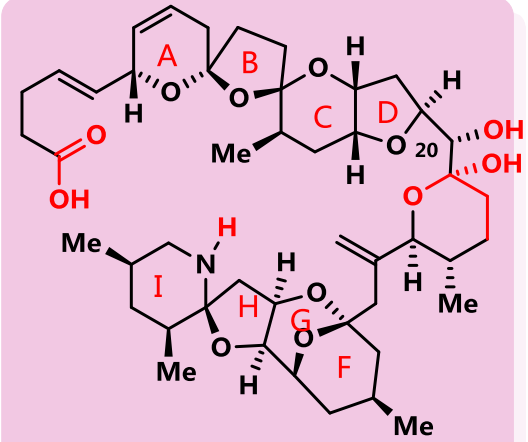


Structural revision by total synthesis

27) $(CuHPPh_3)_6$
BDP, PhSiH,
H_2O
28) TBAF
29) DMP
30) $NaClO_2$



(20*R*)-AZP-3
30 steps



(20*S*)-AZP-3
32 ateps

29) $(CuHPPh_3)_6$
BDP, PhSiH,
H_2O
30) TBAF
31) DMP
32) $NaClO_2$

Previously assigned structure
not matching natural AZP-3

Reassigned structure
matching natural AZP-3

THANKS