Literature report

Enantioselective Formal Total Syntheses of Didehydrostemofoline and Isodidehydrostemofoline through a Catalytic Dipolar Cycloaddition Cascade

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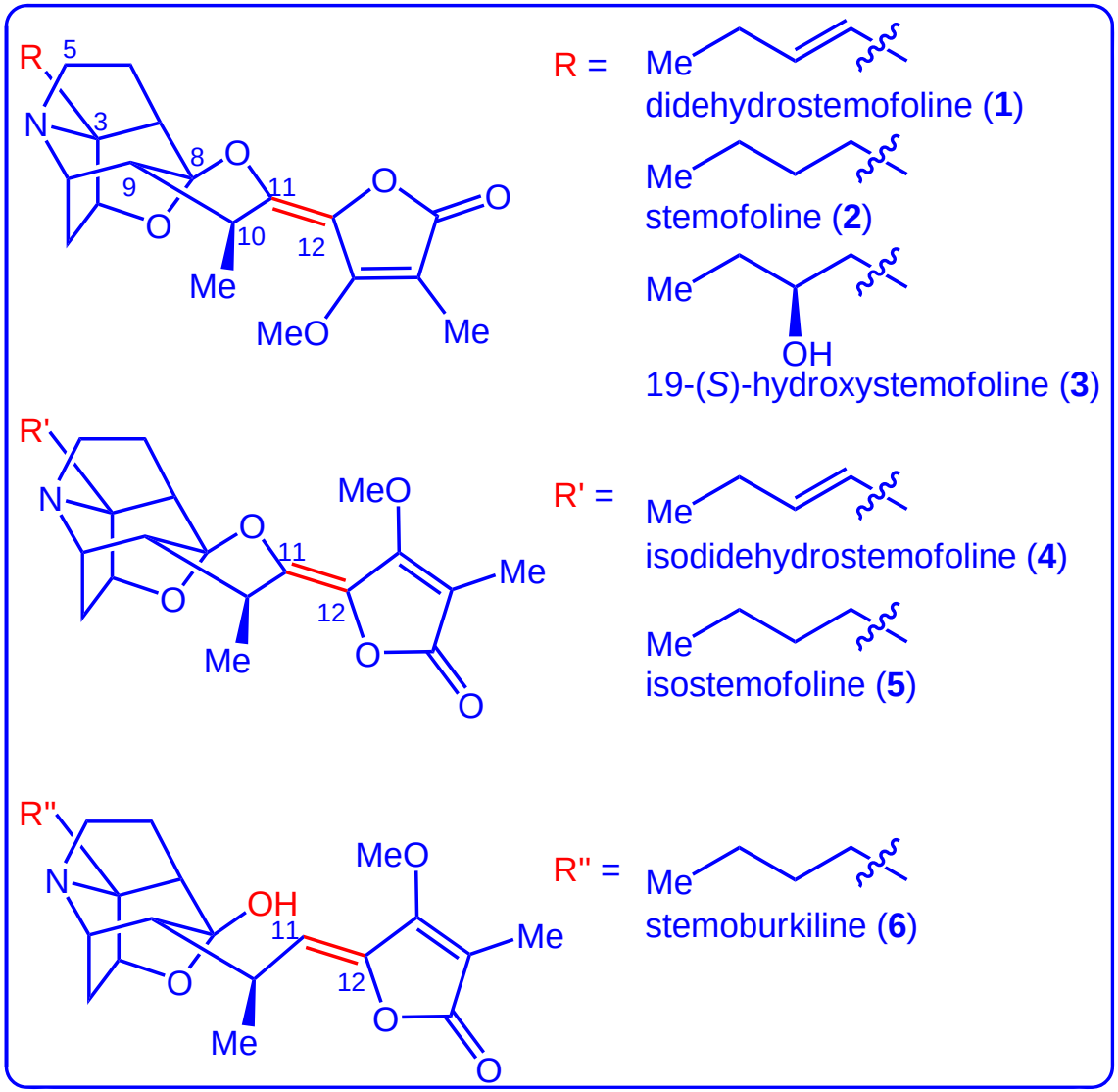
Checker : Chang-Bin Yu

Date: 2012/10/24

Martin, S. F. *et al.*
Angew. Chem. Int. Ed. **2012**, *51*, 10596-10599.

The stemofoline family of natural products

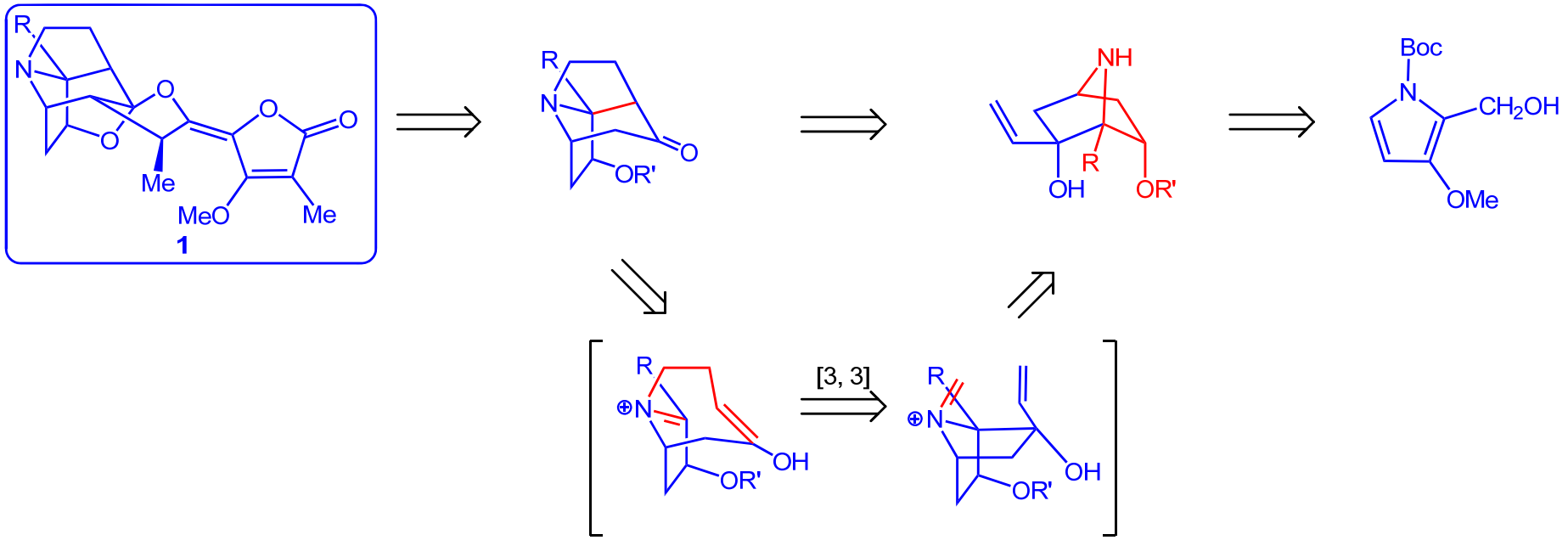


◆ **Polycyclic structures:**
densely functionalized
caged hexacyclic architecture

◆ **Biological activities:**
insecticidal activity
antitumor activity

◆ **First reported in 1970; Limited syntheses success:**
Kende (1999, **(±)-5**); Overman (2003, **(±)-1** and **(±)-4**)

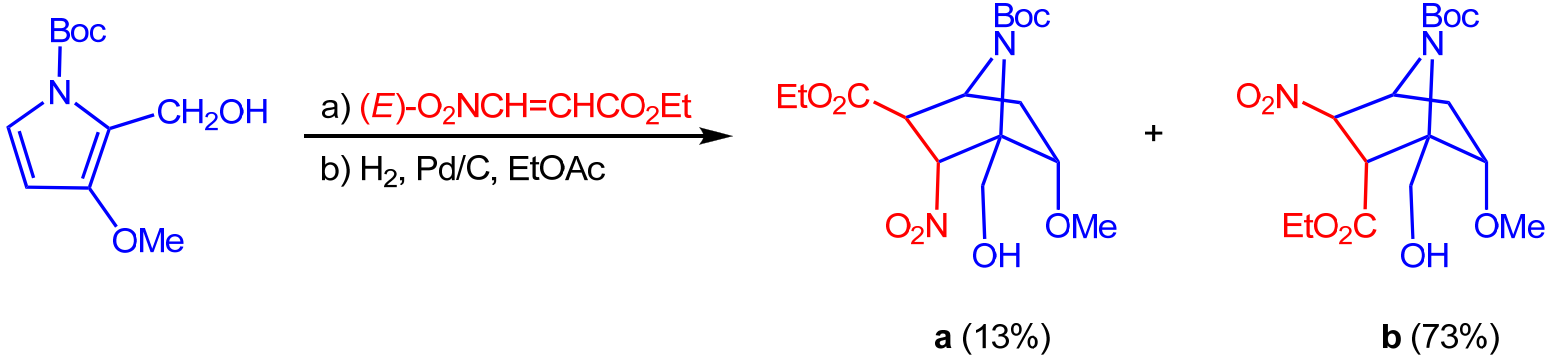
Overman's strategy



Aza-Cope-Mannich Reaction

Overman, L. E. *et al. J. Am. Chem. Soc.* **2003**, *125*, 15284-15285.

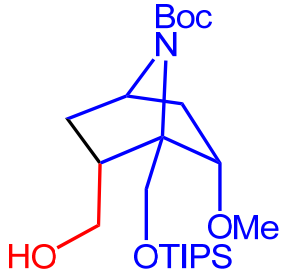
Overman's work



a (13%) **b** (73%)

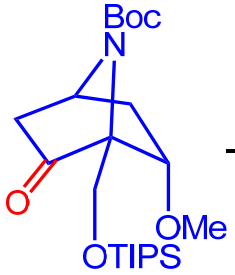
b

a) DBU, CH_2Cl_2
b) H_2, Pd/C, EtOAc
c) TIPSOTf, 2,6-lutidine
d) DIBALH, PhMe



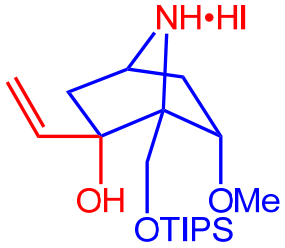
(51%)

a) DMP, CH_2Cl_2
b) TIPSOTf, Et_3N, CH_2Cl_2
c) O_3, MeOH-CH_2Cl_2



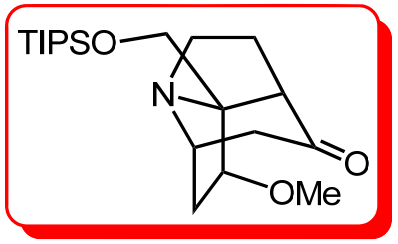
(72%)

a) H_2C=CHMgBr, $CeCl_3$
b) TMSI, 2,6-lutidine, MeOH



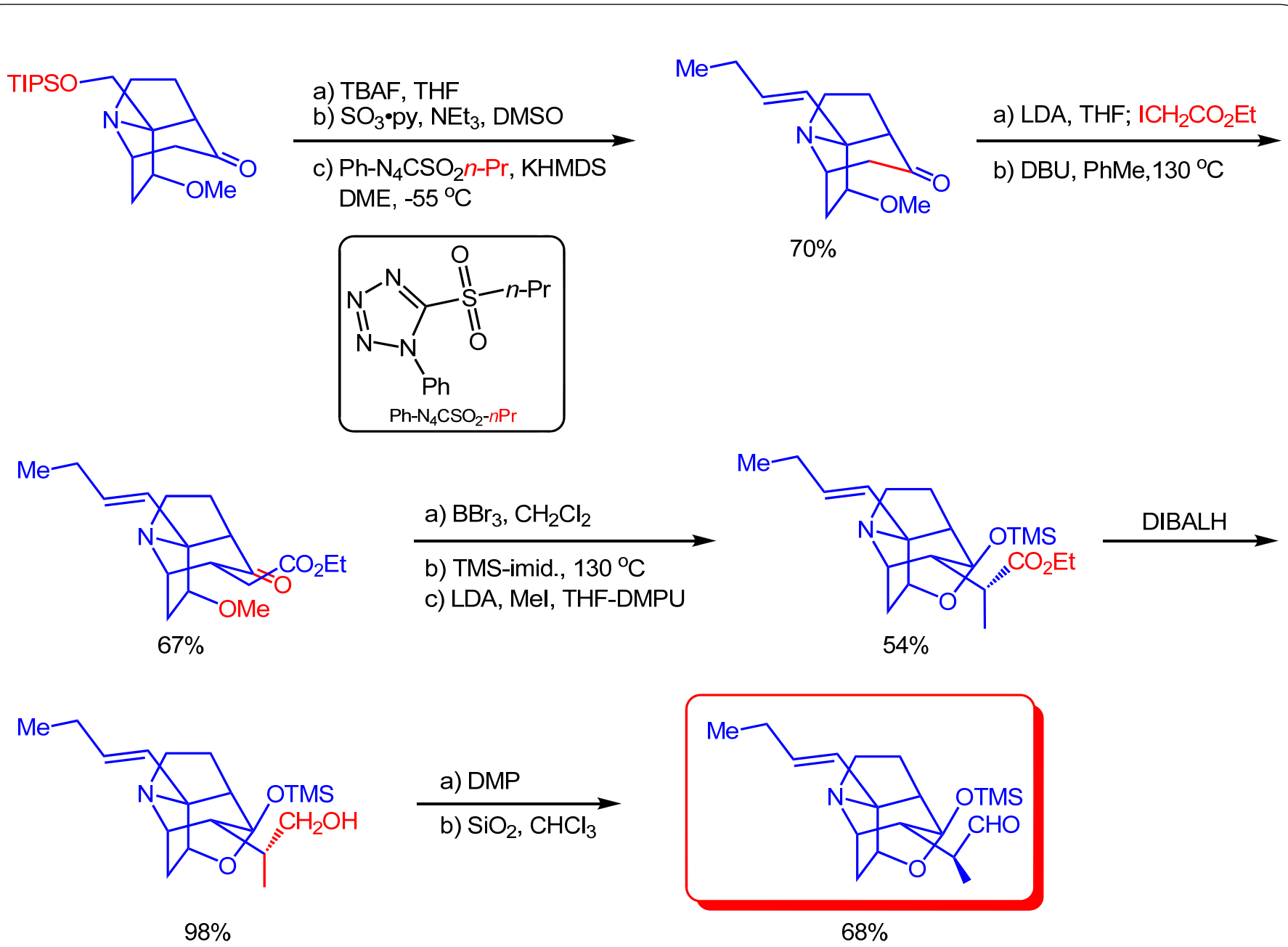
(85%)

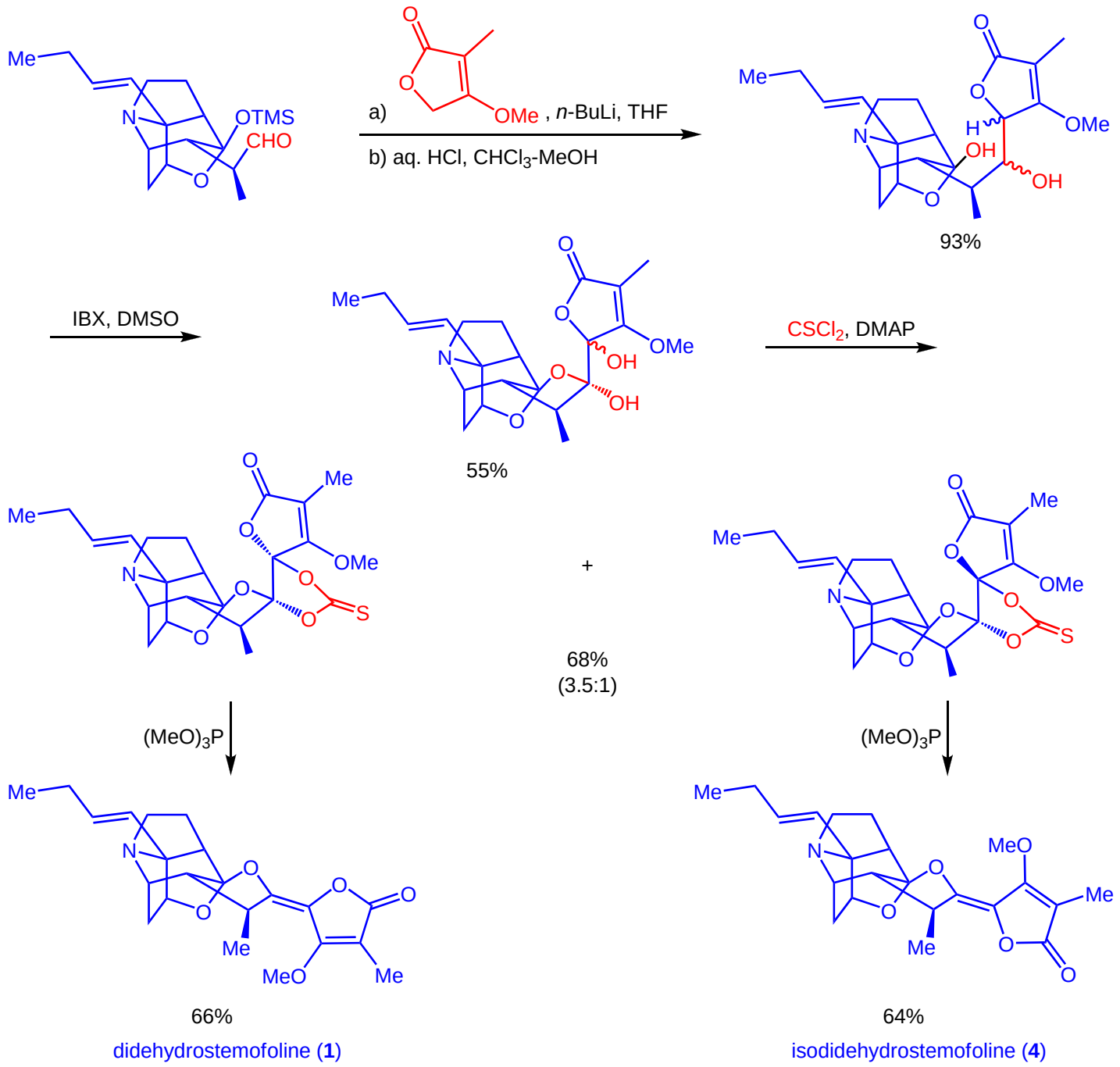
$(CH_2O)_n$



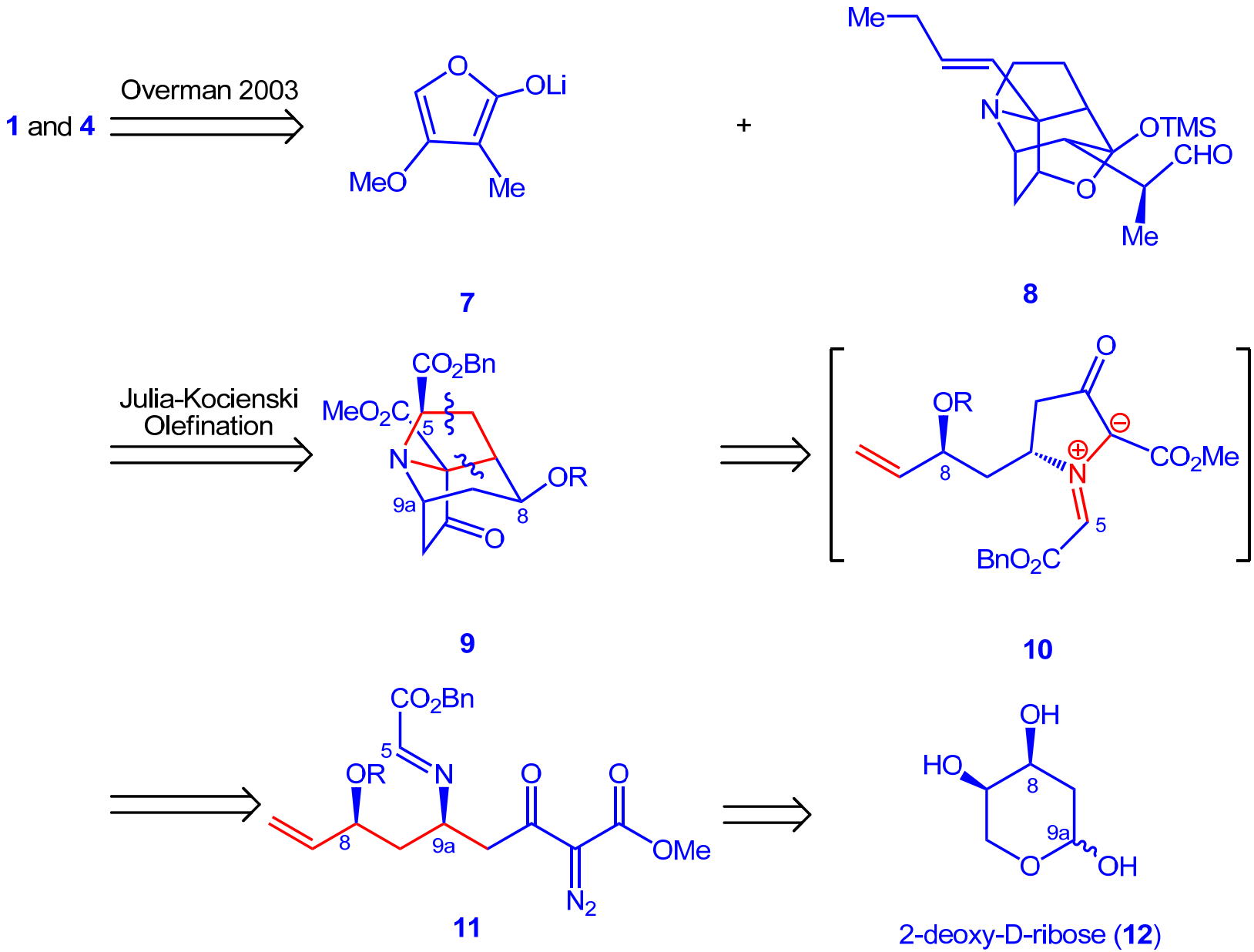
(94%)

1. Imine Formation
2. Aza-Cope-Mannich Reaction

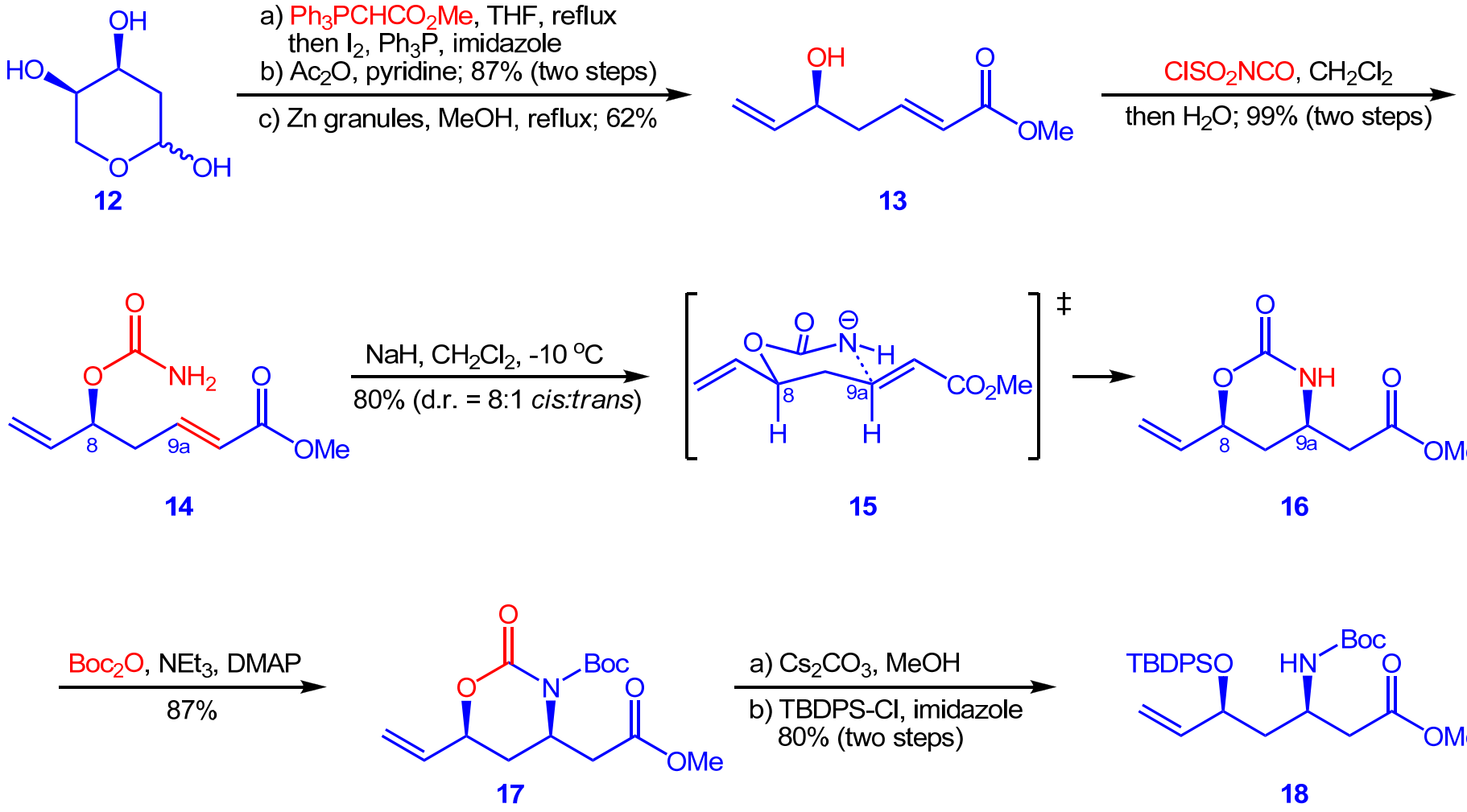

TIPSO
N
O
OMe
a) TBAF, THF
b) SO3•py, NEt3, DMSO
c) Ph-N4CSO2n-Pr, KHMDS
DME, -55 °C
Me
N
O
OMe
70%
a) LDA, THF; ICH2CO2Et
b) DBU, PhMe,130 °C
N
N
N
N
O
S
n-Pr
O
Ph
Ph-N4CSO2-nPr
Me
N
CO2Et
O
OMe
67%
a) BBr3, CH2Cl2
b) TMS-imid., 130 °C
c) LDA, MeI, THF-DMPU
Me
N
OTMS
CO2Et
O
54%
DIBALH
Me
N
OTMS
CH2OH
O
98%
a) DMP
b) SiO2, CHCl3
Me
N
OTMS
CHO
O
68%

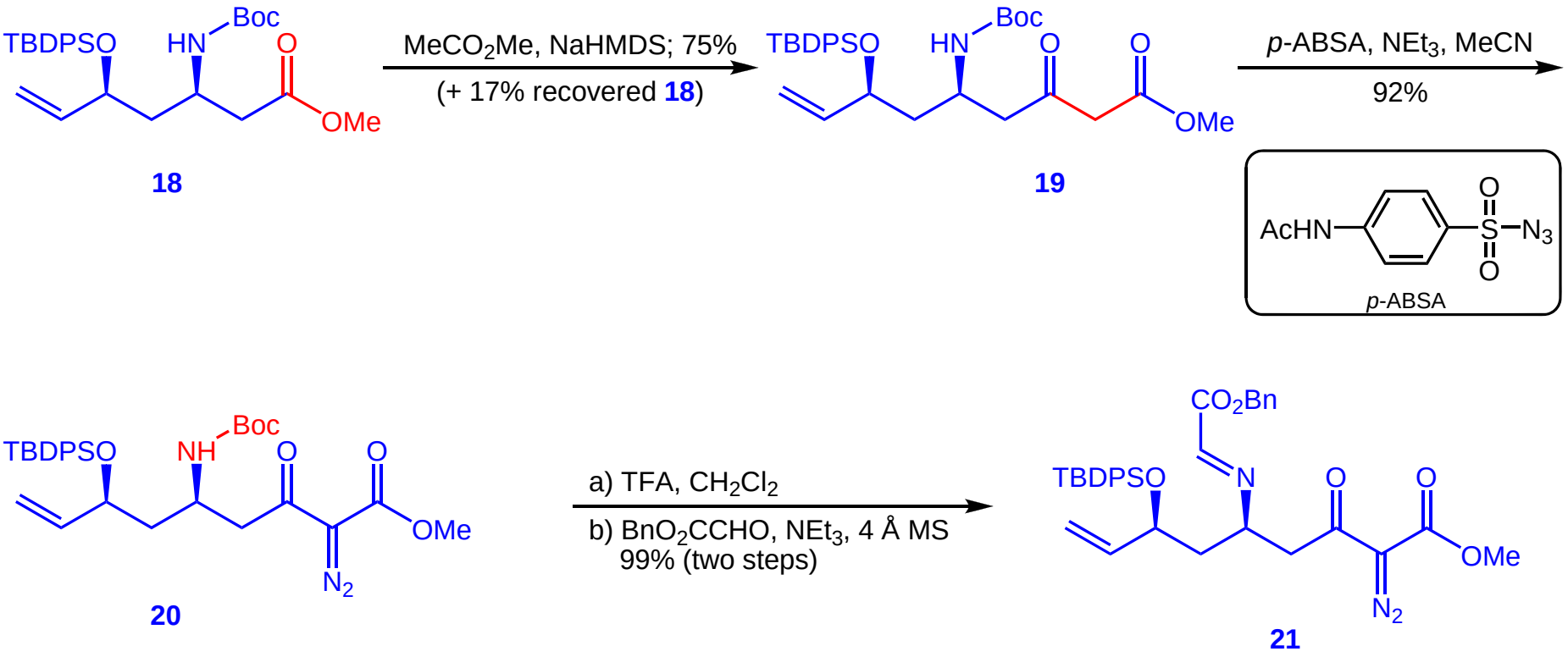

a)
OMe , n-BuLi, THF
b) aq. HCl, CHCl3-MeOH
93%
IBX, DMSO
55%
CSCl2, DMAP
+
68%
(3.5:1)
(MeO)3P
(MeO)3P
66%
didehydrostemofoline (1)
64%
isodidehydrostemofoline (4)

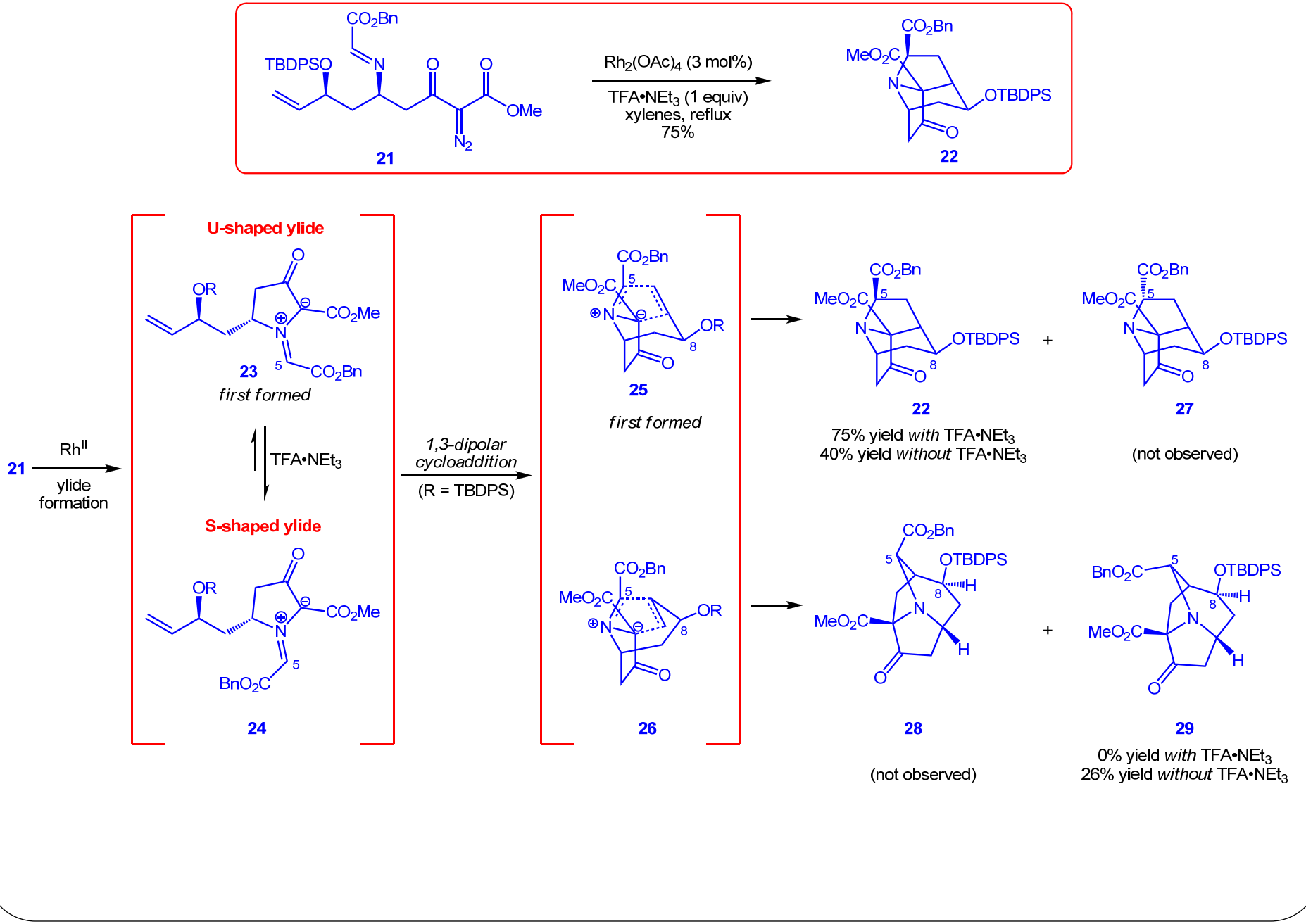
Martin's strategy

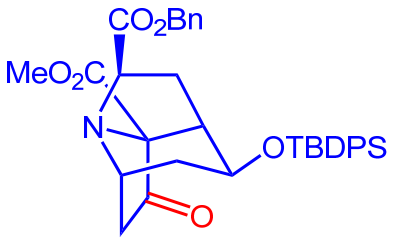


Martin's work




TBDPSO
HN
Boc
O
OMe
18
MeCO2Me, NaHMDS; 75%
(+ 17% recovered 18)
19
p-ABSA, NEt3, MeCN
92%
AcHN
S
N3
p-ABSA
NH
N2
20
a) TFA, CH2Cl2
b) BnO2CCHO, NEt3, 4 Å MS
99% (two steps)
CO2Bn
N
21

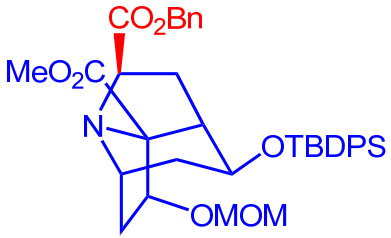

CO2Bn
TBDPSO
N
O
O
OMe
N2
21
Rh2(OAc)4 (3 mol%)
TFA•NEt3 (1 equiv)
xylenes, reflux
75%
CO2Bn
MeO2C
N
OTBDPS
O
22
U-shaped ylide
OR
O
CO2Me
N
5
CO2Bn
23
first formed
TFA•NEt3
S-shaped ylide
BnO2C
24
21
RhII
ylide
formation
1,3-dipolar
cycloaddition
(R = TBDPS)
MeO2C
5
8
25
first formed
26
22
75% yield with TFA•NEt3
40% yield without TFA•NEt3
27
(not observed)
28
(not observed)
29
0% yield with TFA•NEt3
26% yield without TFA•NEt3
+



22

a) $NaBH_4$, MeOH

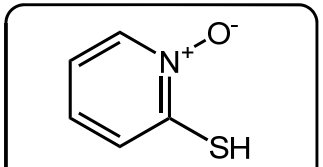
b) MOM-Cl, *i*-Pr_2NEt, DMF
75% (two steps)



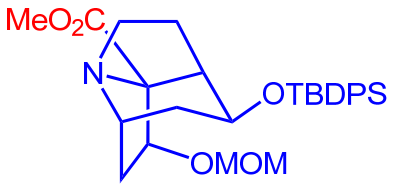
30

a) Pd/C, H_2, EtOH

b) 2-mercaptopyridine-*N*-oxide
DCC, DMAP, *t*-BuSH, $CHCl_3$, hv
63% (two steps)

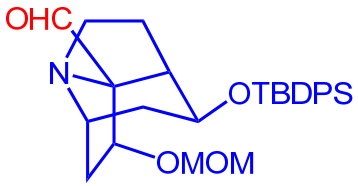


2-mercaptopyridine-*N*-oxide



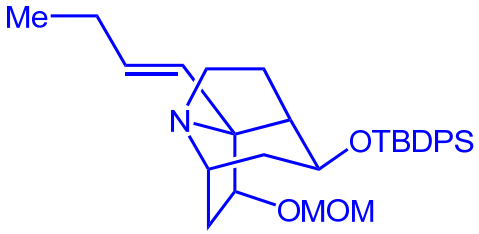
31

DIBALH, CH_2Cl_2, -78 °C; 90%

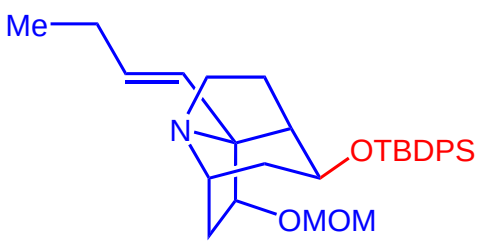


32

Ph-N_4CSO_2*n*-Pr, KHMDS
89%



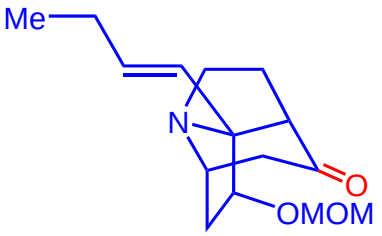
33



33

a) TBAF, THF, 50 °C; 95%

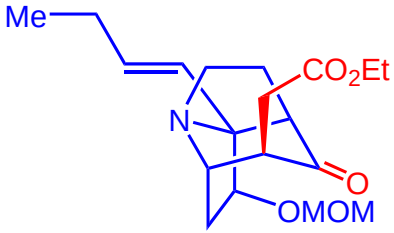
b) SO_3•py, NEt_3, DMSO; 77%



34

LDA, ICH_2CO_2Et, THF, -10 °C

62%

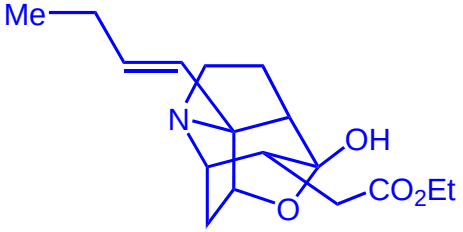


35

a) DBU, PhMe, 130 °C

b) TFA, CH_2Cl_2

81% (two steps)



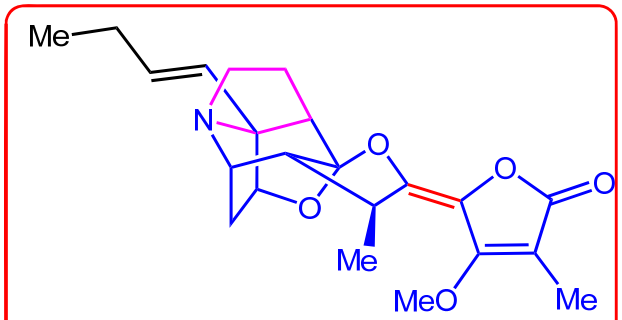
36

Stemofoline alkaloids

Summary

Overman's work

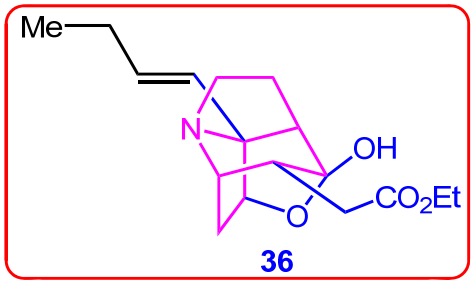
- ◆Total synthesis of **(±)-1** and **(±)-4**
- ◆Key reactions:
  - ➢Aza-Cope-Mannich Rearrangement
  - ➢Julia-Kocienski Olefination
  - ➢Corey-Winter Olefination



didehydrostemofoline (**1**)

Martin's work

- ◆Prepared the key intermediate **36** in enantiomerically pure form and formal total synthesis of **1, 2, 4, 6**
- ◆Key reactions:
  - ➢Catalytic Dipolar Cycloaddition Cascade
  - ➢Julia-Kocienski Olefination



36

Plants of the *Stemonacea* family, which are indigenous to a number of areas in Southeast Asia, have long been used in traditional oriental medicine for treating a variety of ailments. Extraction of the roots and leaves of these plants have yielded a number of biologically active alkaloids that have been targets of many synthetic investigations. Arguably the most complex members of the *Stemona* alkaloids are those belonging to the stemofoline family, which are characterized by a densely functionalized, caged hexacyclic architecture and differ in the geometry of the C11-C12 double bond and the oxidation state of the butyl side chain at C3. These alkaloids, which were first reported by Irie and co-workers in 1970 and later isolated from other *Stemona* species, exhibit strong insecticidal activity because they act as insect acetylcholine receptor antagonists. Didehydrostemofoline is not only the most potent acetylcholine receptor antagonist, but it also exhibits in vivo anti-oxytocin activity as well as antitumor activity against gastric carcinoma. A recent study has shown that stemofoline (**2**) increases the sensitivity of anticancer drugs such as vinblastine, paclitaxel, and doxorubicin by reversal of P-glycoprotein mediated multi-drug resistance. A number of semisynthetic analogs of these alkaloids have been prepared and found to exhibit acetylcholinesterase inhibitory activity.

In summary, the tricyclic compound **36**, a key intermediate in Overman's elegant synthesis of didehydrostemofoline (**1**) and isodidehydrostemofoline (**4**), has been prepared in enantiomerically pure form, thereby completing the first enantioselective approach to these alkaloids. Inasmuch as **1** has also been transformed into other stemofoline alkaloids, this accomplishment also constitutes a formal synthesis of many other members of the stemofoline family of natural products. The synthesis begins with commercially available 2-deoxy-D-ribose and features a novel cascade of reactions that culminates in the intramolecular dipolar cycloaddition of an acyclic diazo imine intermediate to form the cage-like, tricyclic core of the stemofoline alkaloids. Further applications of similar cascade reactions to complex molecule synthesis are in progress as is the use of **22** as an intermediate in even shorter routes to the stemofoline alkaloids. The results of these investigations will be reported in due course.