文献汇报

潘赛勇课题组

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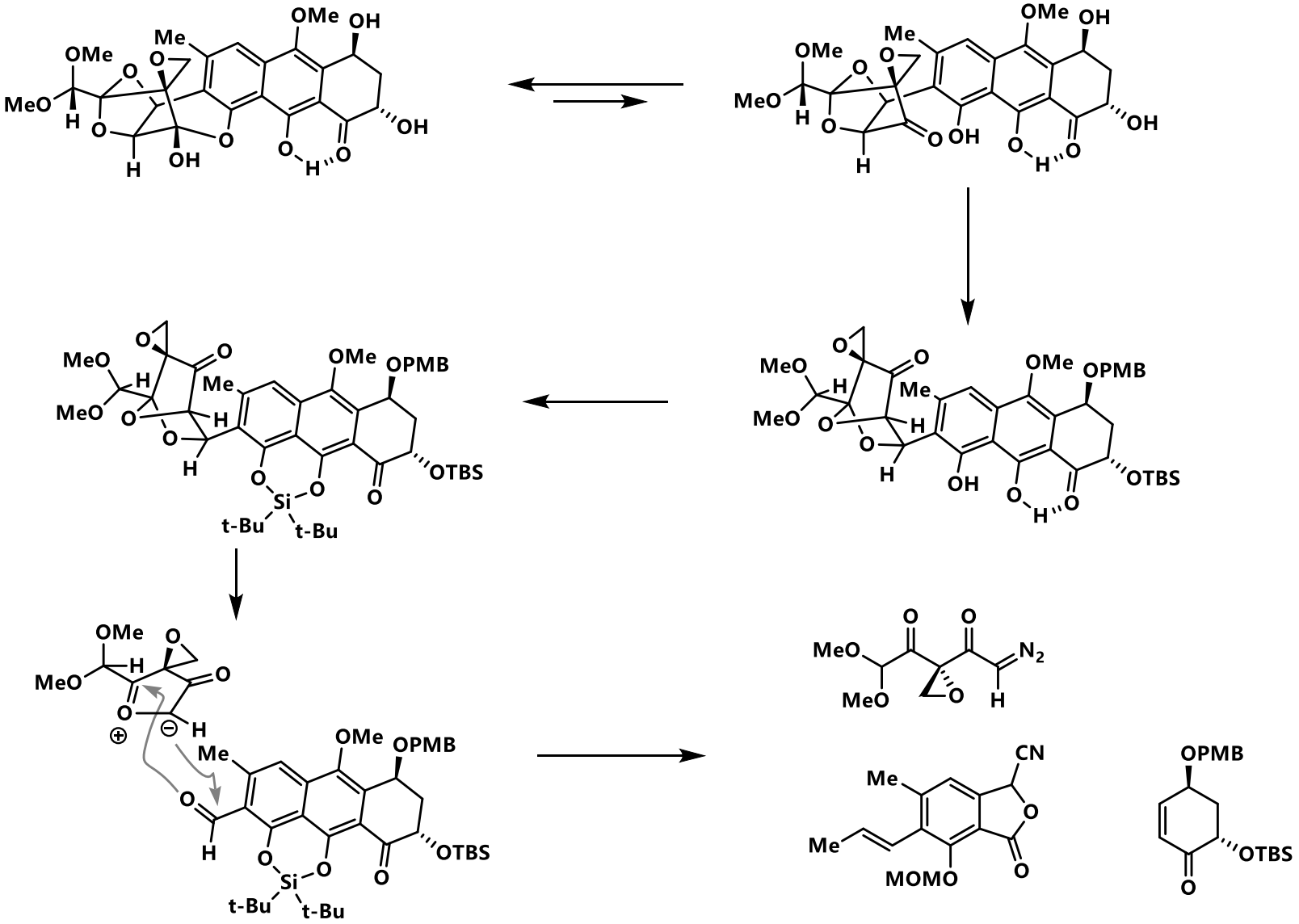
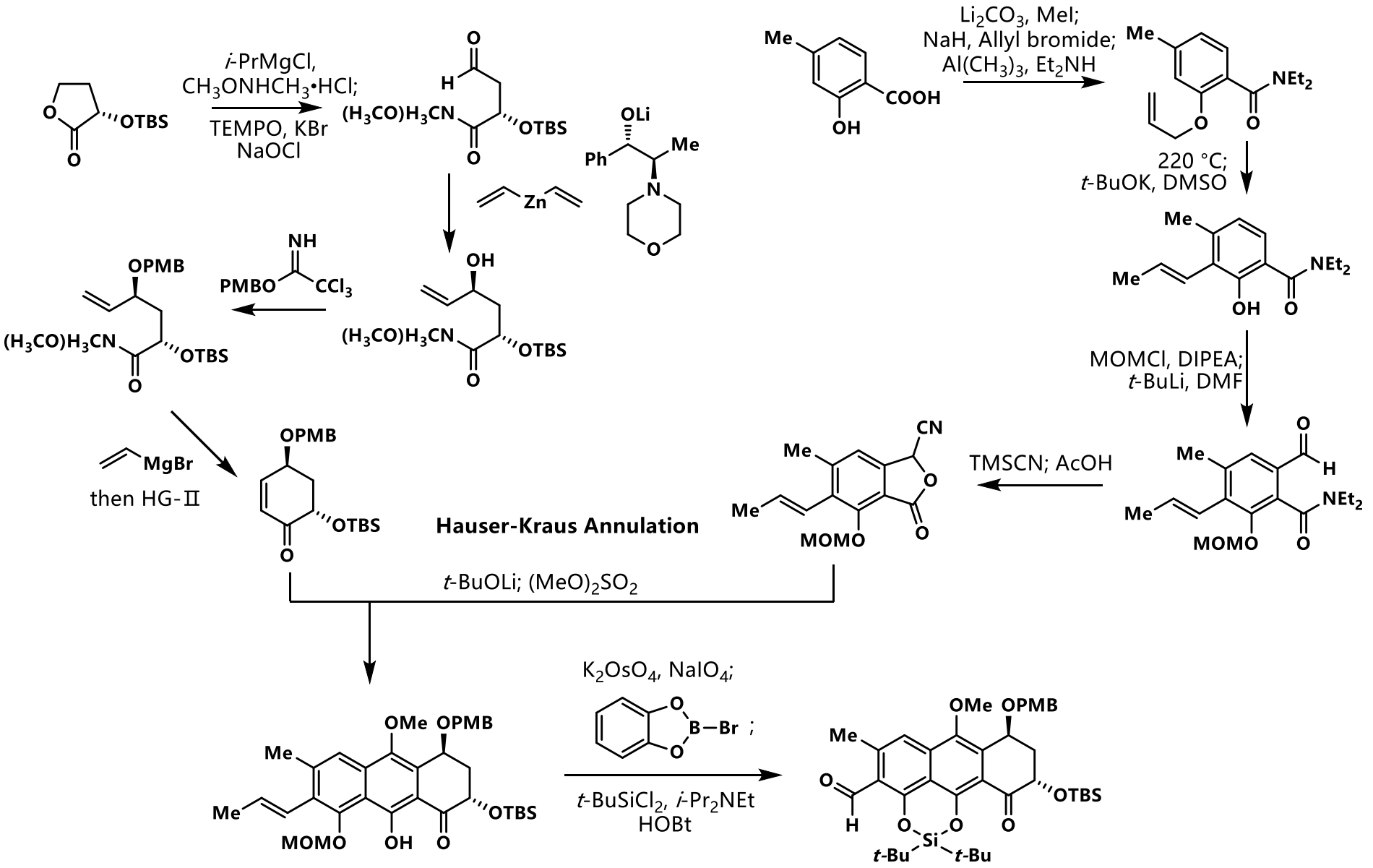
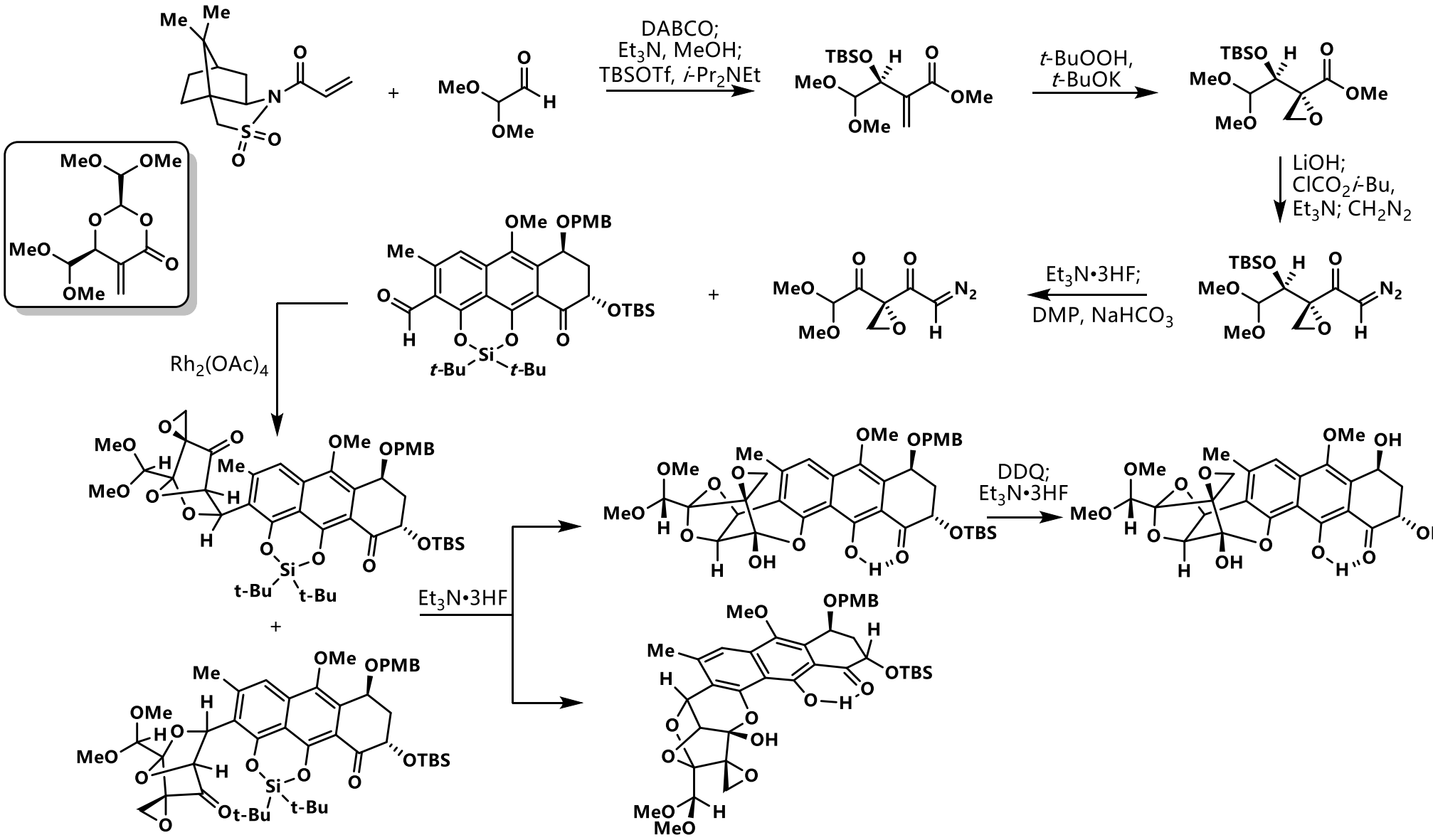
2024.04.13

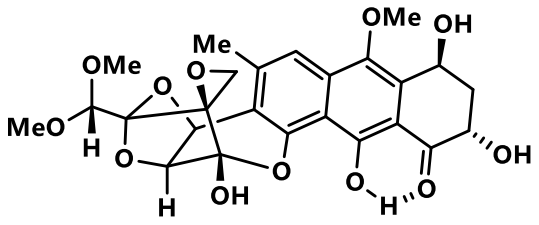
♦**Andrew G. Myers课题组的工作**（Proc. Natl Acad. Sci. USA, **2011**, *108*, 6709–6714）

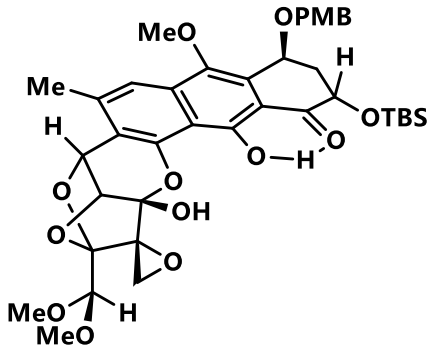
♦**A multiply convergent platform for the synthesis of trioxacarcins**

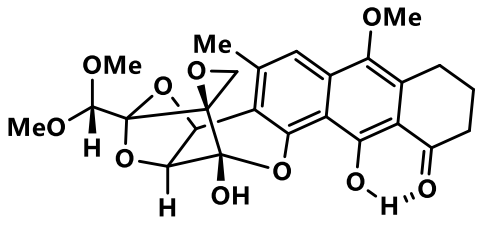



i-PrMgCl,
CH3ONHCH3•HCl;
TEMPO, KBr
NaOCl
Li2CO3, MeI;
NaH, Allyl bromide;
Al(CH3)3, Et2NH
220 °C;
t-BuOK, DMSO
MOMCl, DIPEA;
t-BuLi, DMF
TMSCN; AcOH
then HG-Ⅱ
Hauser-Kraus Annulation
t-BuOLi; (MeO)2SO2
K2OsO4, NaIO4;
t-BuSiCl2, i-Pr2NEt
HOBt


DABCO;
Et3N, MeOH;
TBSOTf, i-Pr2NEt
t-BuOOH,
t-BuOK
LiOH;
ClCO2i-Bu,
Et3N; CH2N2
Et3N•3HF;
DMP, NaHCO3
Rh2(OAc)4
Et3N•3HF
DDQ;
Et3N•3HF



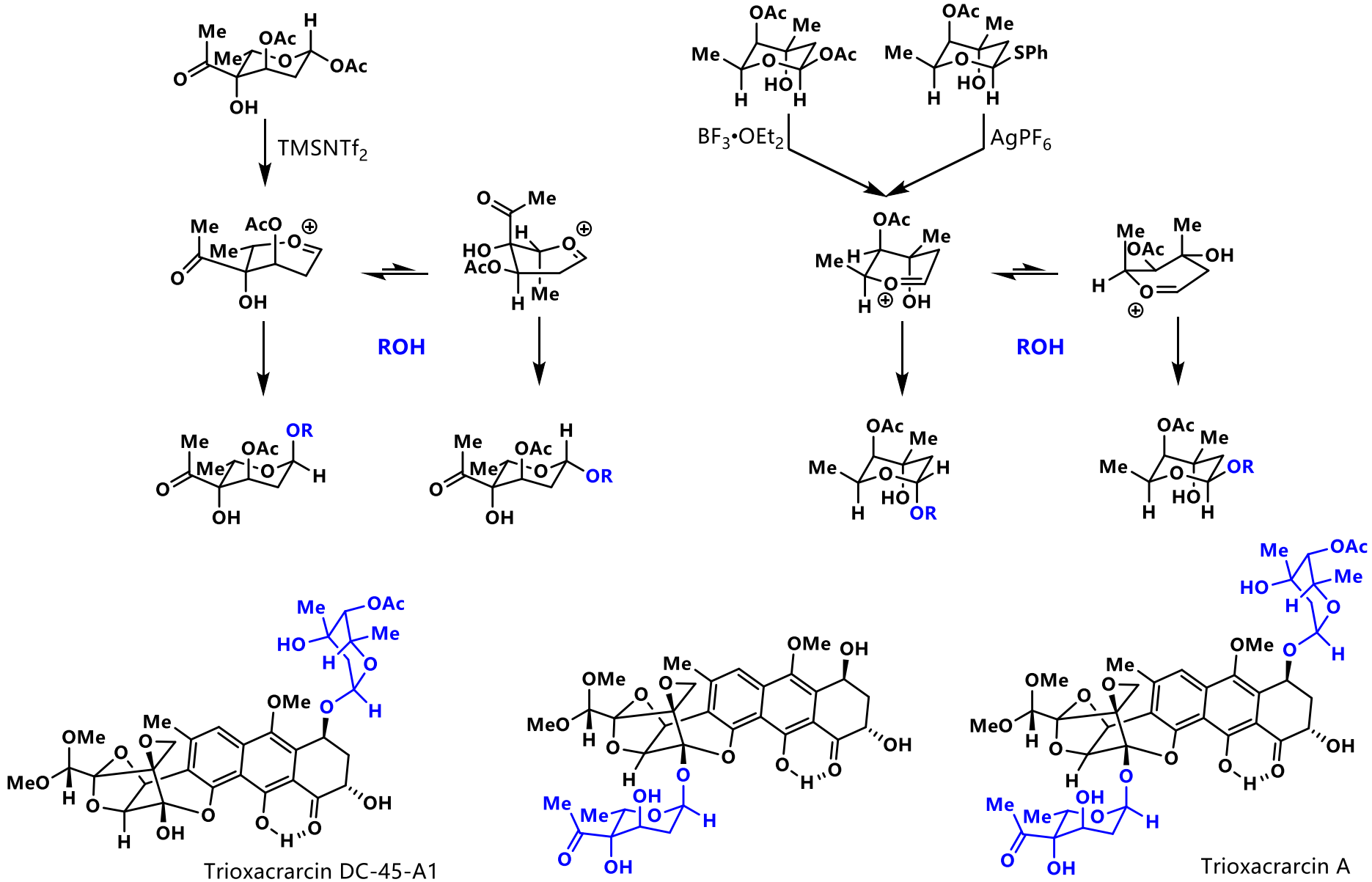


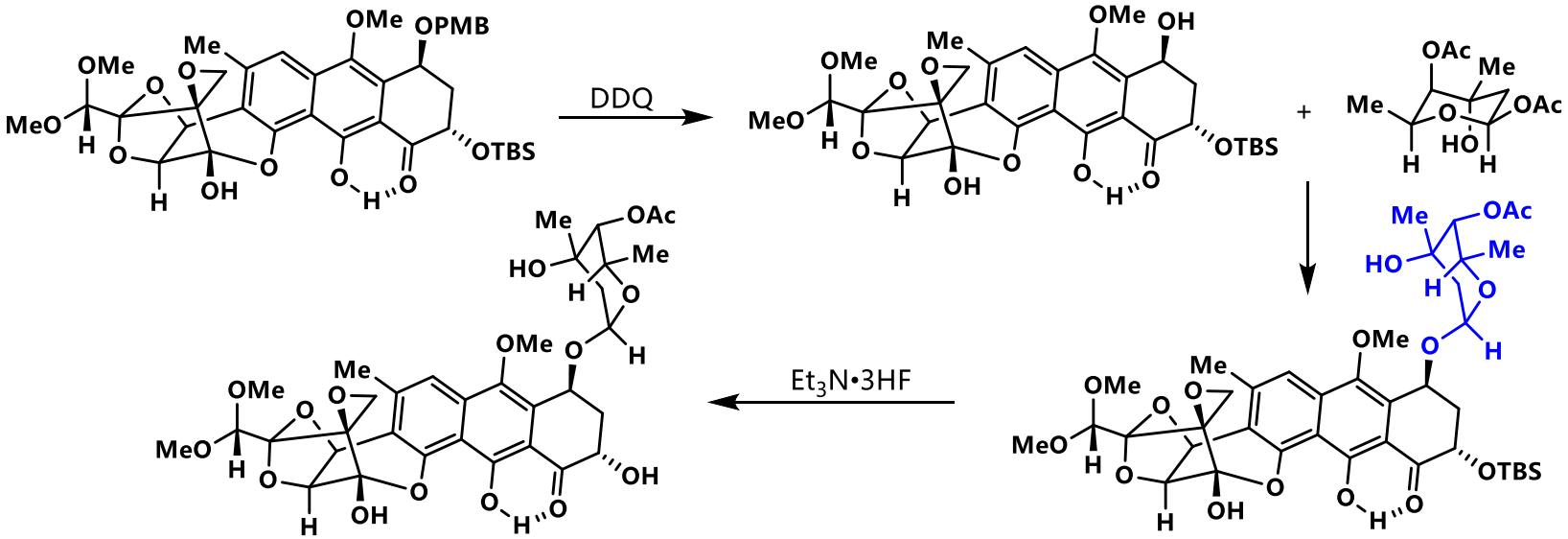


	DC-45-A2	**iso-DC-45-A2**	**dideoxy-DC-45-A2**
IC_{50} (HeLa)	5.6 ± 1.3 μM	> 83 μM	0.12 ± 0.04 μM
IC_{50} (H460)	5.1 ± 0.4 μM	> 83 μM	0.15 ± 0.03 μM

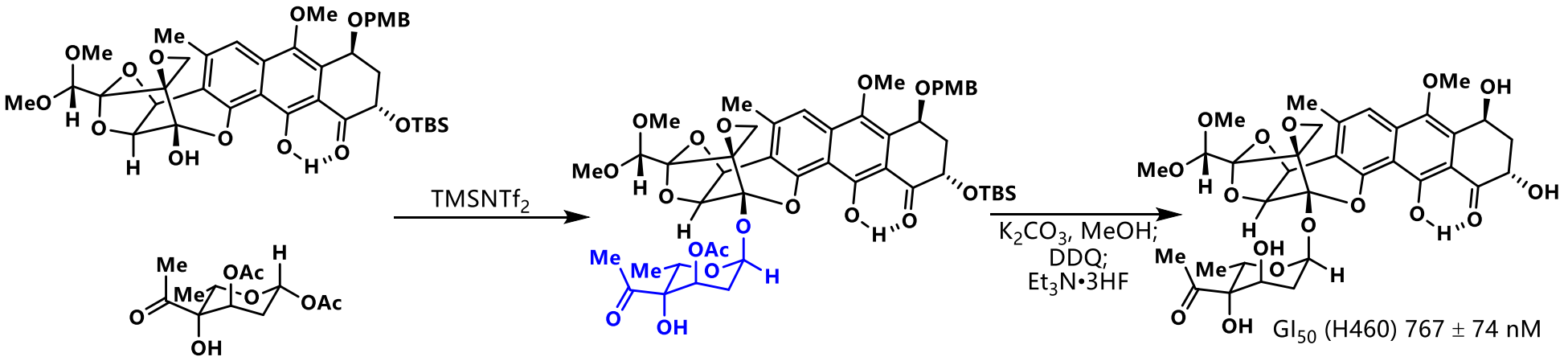
♦**Andrew G. Myers课题组的工作**（Nat. Chem. **2013**, *5*, 886 – 893.）

♦Component-based syntheses of trioxacarcin A, DC-45-A1 and structural analogues

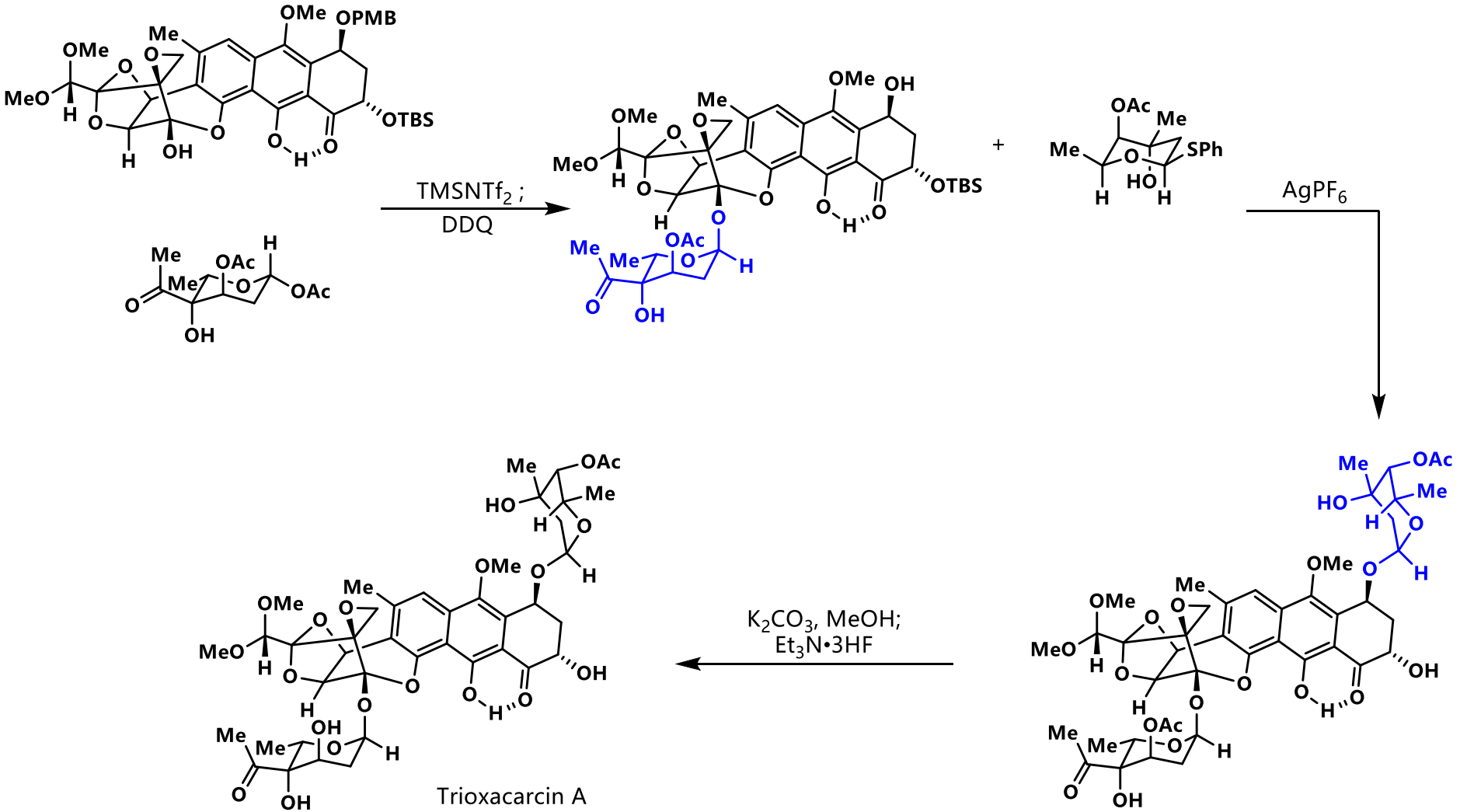




GI_{50} (H460) 37 ± 7 nM

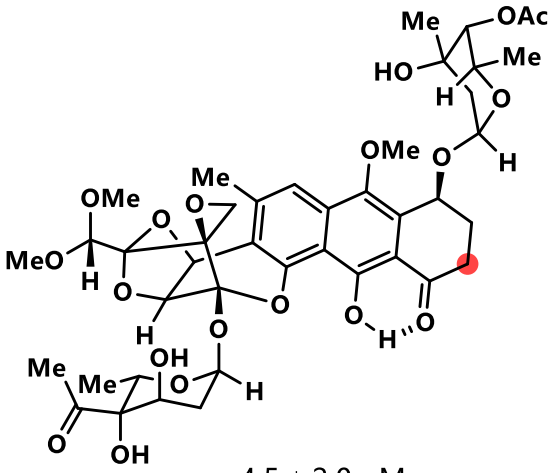


GI_{50} (H460) 767 ± 74 nM

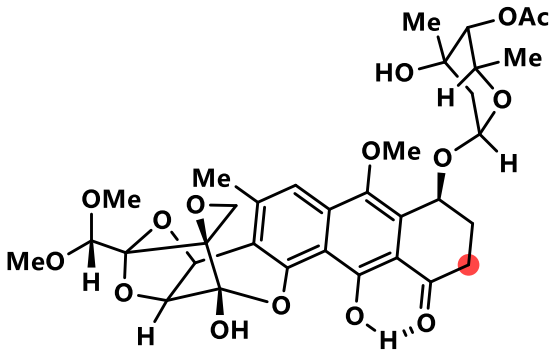


Trioxacarcin A

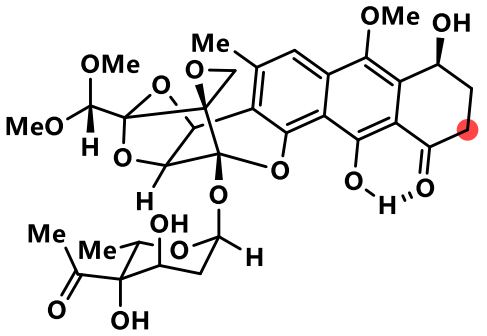
GI_{50} (H460) 0.85 ± 0.36 nM



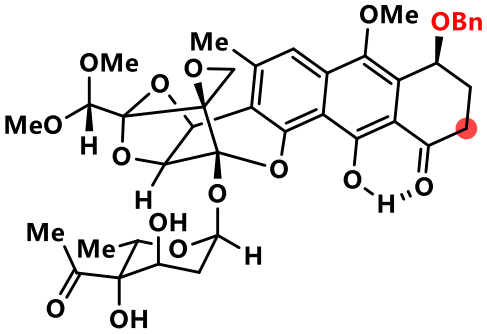
4.5 ± 2.0 nM



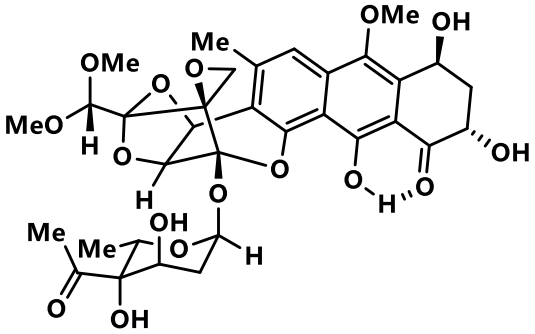
17 ± 2 nM



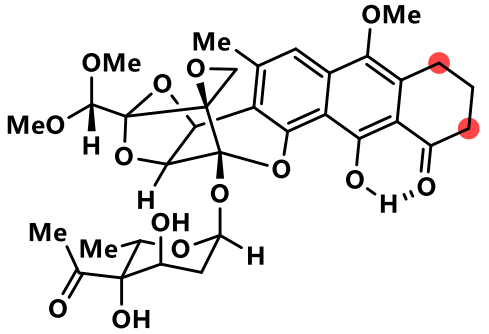
206 ± 70 nM



315 ± 58 nM

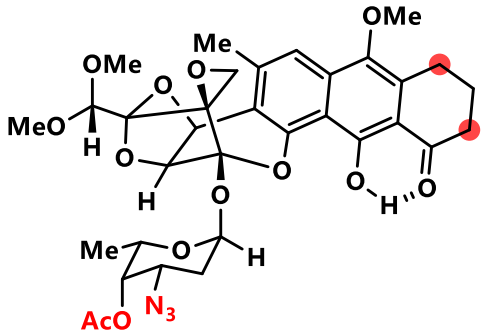


767 ± 74 nM

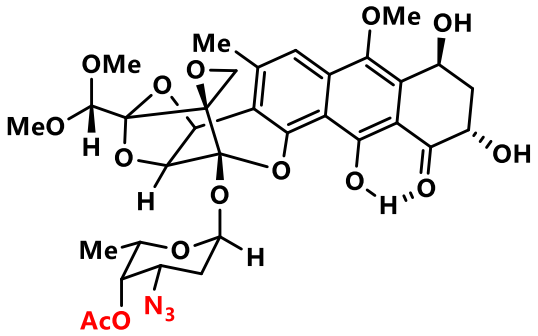


19 ± 7 nM

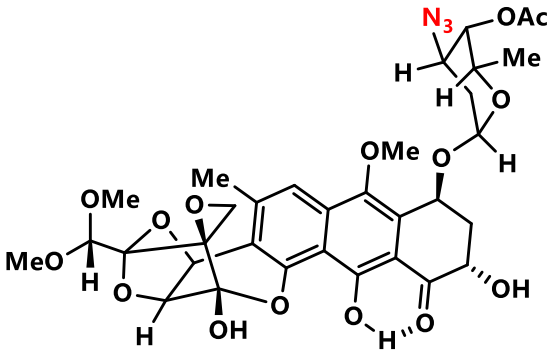
GI_{50} (H460)



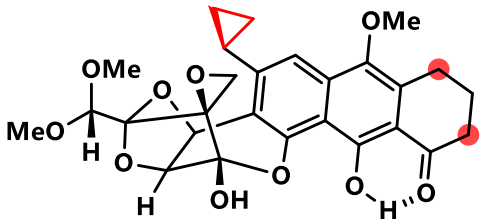
102 ± 3 nM



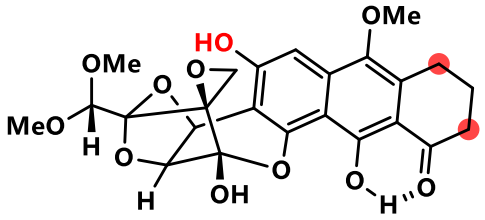
397 ± 82 nM



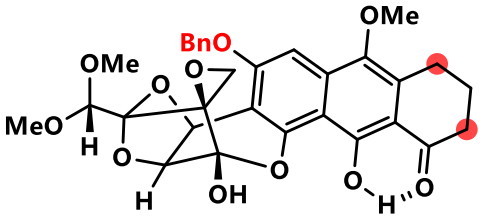
225 ± 26 nM



374 ± 87 nM



>2500 nM

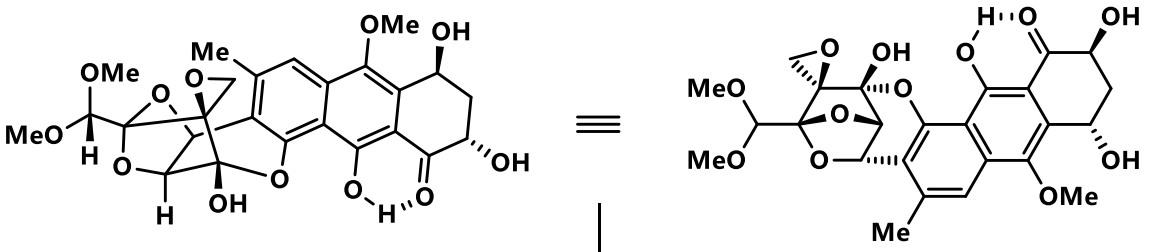


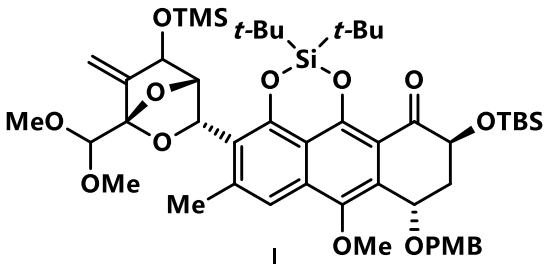
>2500 nM

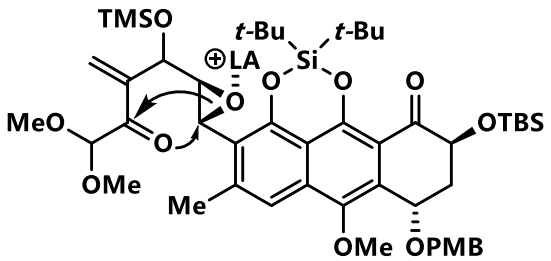
GI_{50} (H460)

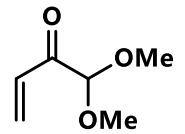
♦**K. C. Nicolaou课题组的工作**（Angew. Chem. Int. Ed. **2015**, *54*, 3074 – 3078）

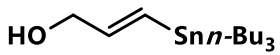
♦**Total Synthesis of Trioxacarcin DC-45-A2**

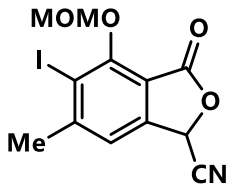


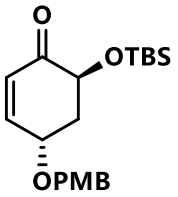


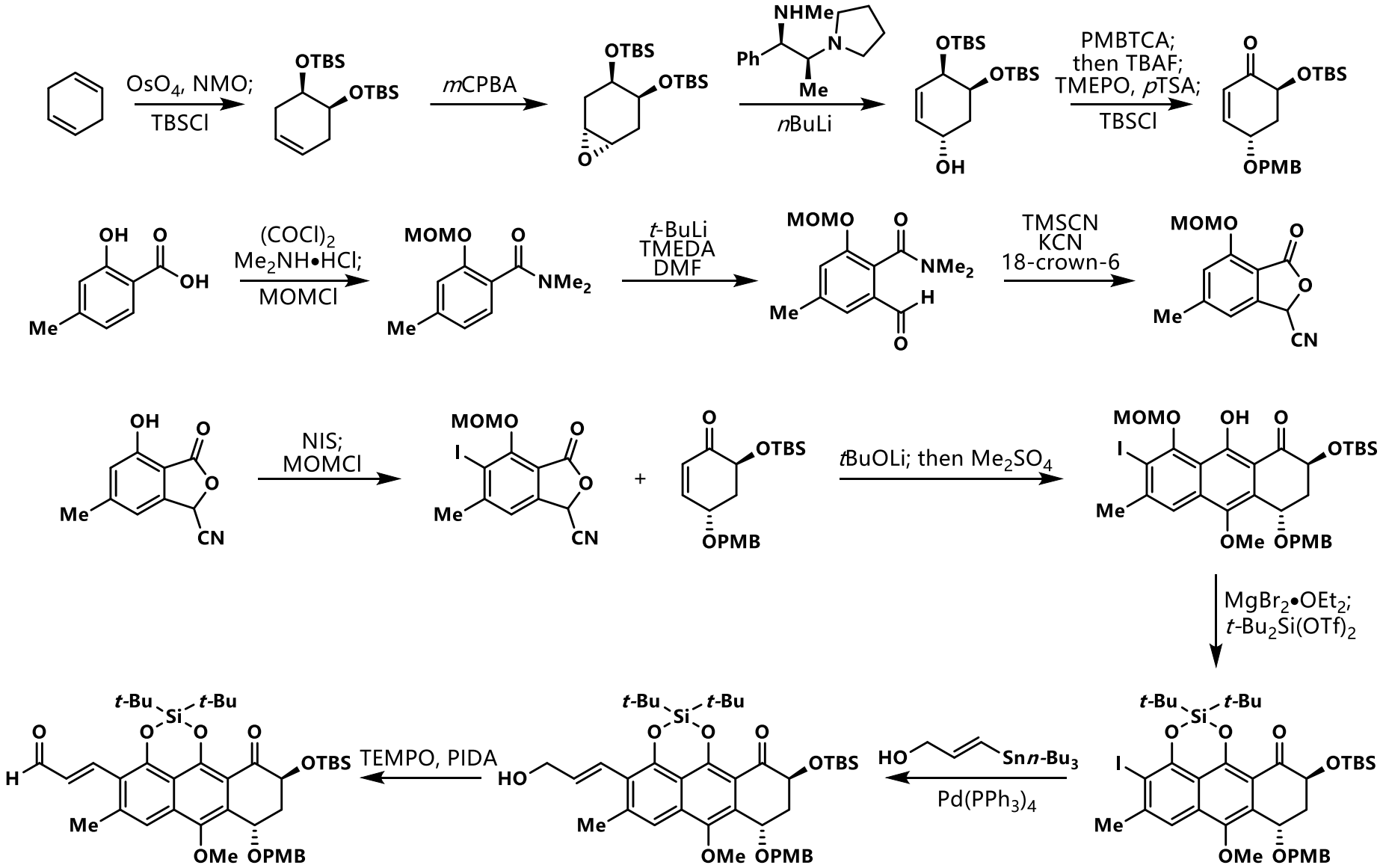


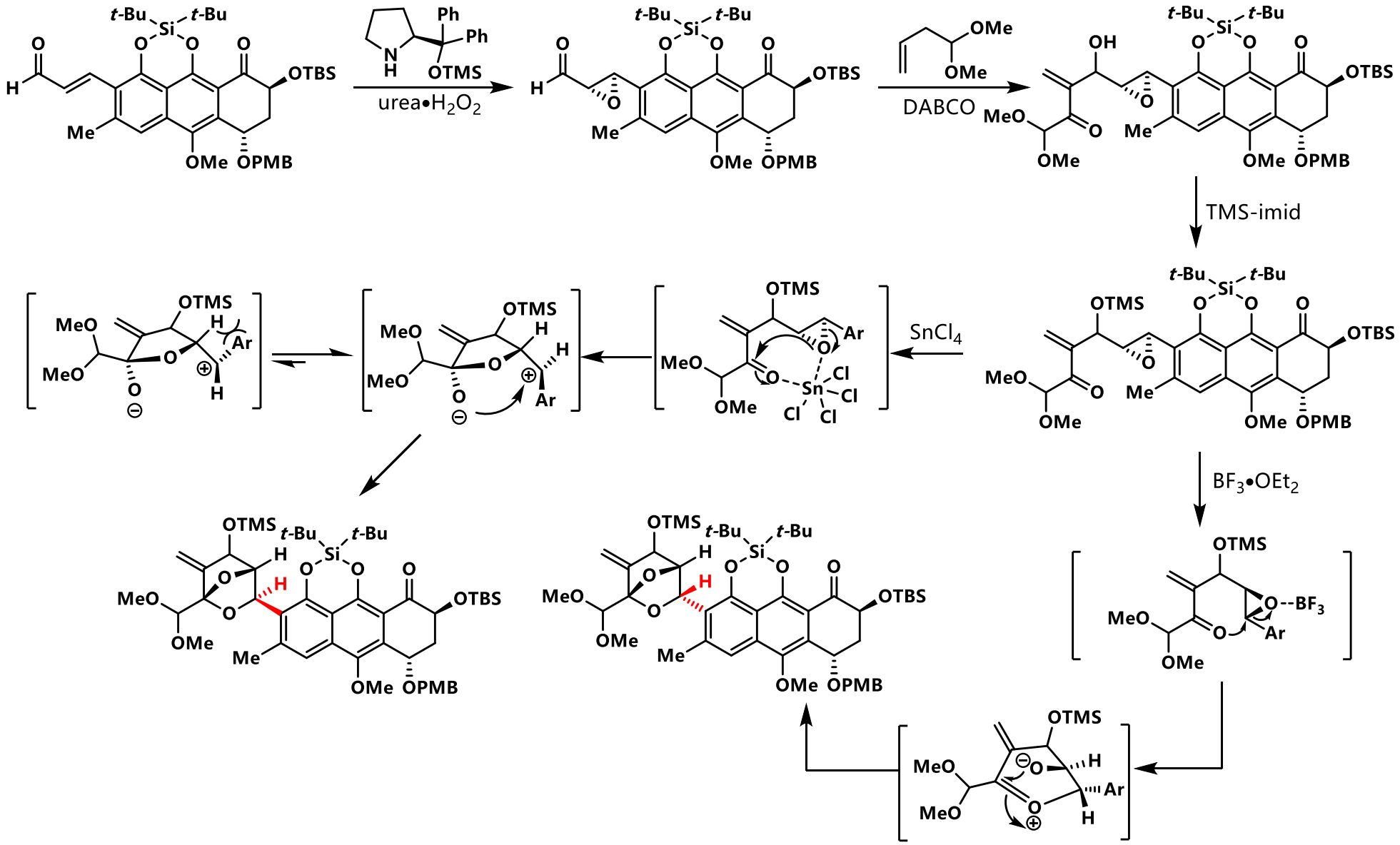


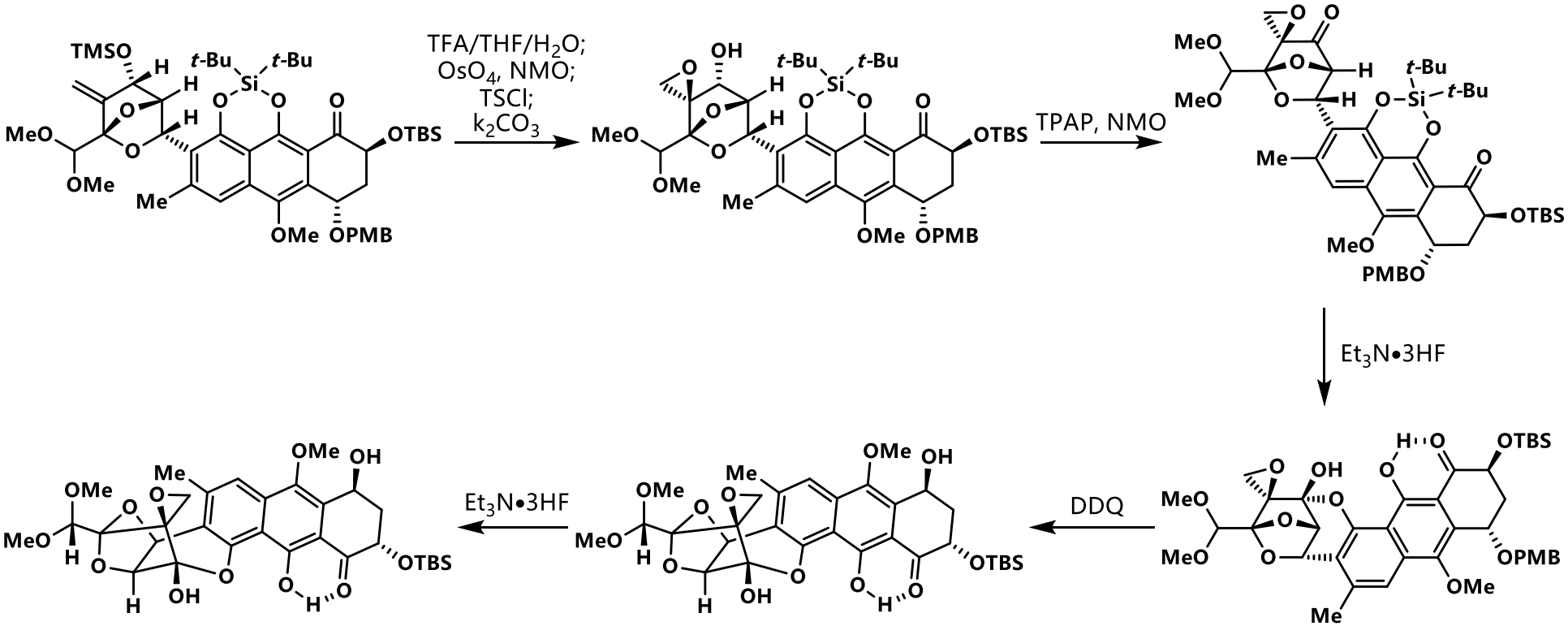






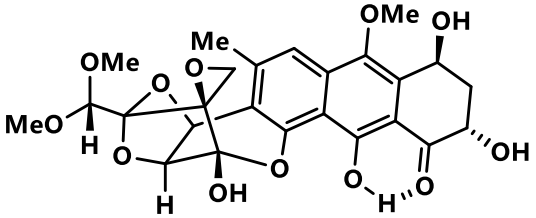

OsO4, NMO;
TBSCl
OTBS
OTBS
mCPBA
OTBS
OTBS
NHMe
Ph
N
Me
nBuLi
OTBS
OTBS
OH
PMBTCA;
then TBAF;
TMEPO, pTSA;
TBSCl
O
OTBS
OPMB
OH
O
OH
Me
(COCl)2
Me2NH•HCl;
MOMCl
MOMO
O
NMe2
Me
t-BuLi
TMEDA
DMF
MOMO
O
NMe2
Me
H
O
TMSCN
KCN
18-crown-6
MOMO
O
O
Me
CN
OH
O
Me
CN
NIS;
MOMCl
MOMO
I
O
Me
CN
+
O
OTBS
OPMB
tBuOLi; then Me2SO4
MOMO
OH
O
I
OTBS
Me
OMe
OPMB
MgBr2•OEt2;
t-Bu2Si(OTf)2
t-Bu
Si
t-Bu
O
O
O
O
OTBS
Me
OMe
OPMB
HO
Snn-Bu3
Pd(PPh3)4
t-Bu
Si
t-Bu
O
O
O
O
OTBS
HO
Me
OMe
OPMB
TEMPO, PIDA
t-Bu
Si
t-Bu
O
O
O
O
OTBS
H
Me
OMe
OPMB


urea•H2O2
DABCO
TMS-imid
SnCl4
BF3•OEt2

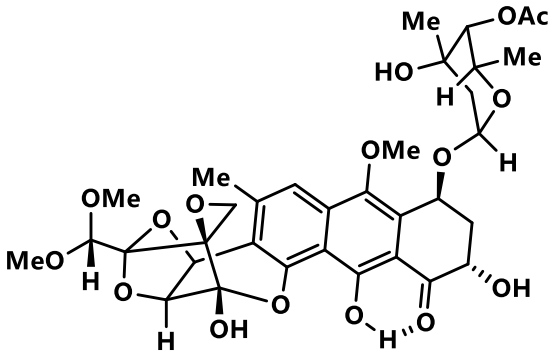

TMSO
t-Bu
t-Bu
Si
MeO
OMe
Me
OMe
OPMB
OTBS
TFA/THF/H2O;
OsO4, NMO;
TSCl;
k2CO3
OH
TPAP, NMO
PMBO
Et3N•3HF
DDQ

♦**K. C. Nicolaou课题组的工作** (J. Am. Chem. Soc. **2016**, *138*, 3118−3124)

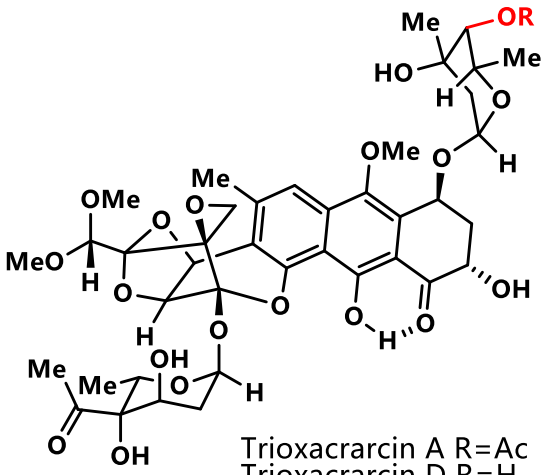
♦**Total Synthesis of Trioxacarcins DC-45-A1, A, D, C, and C7″-epi-C and Full Structural Assignment of Trioxacarcin C**



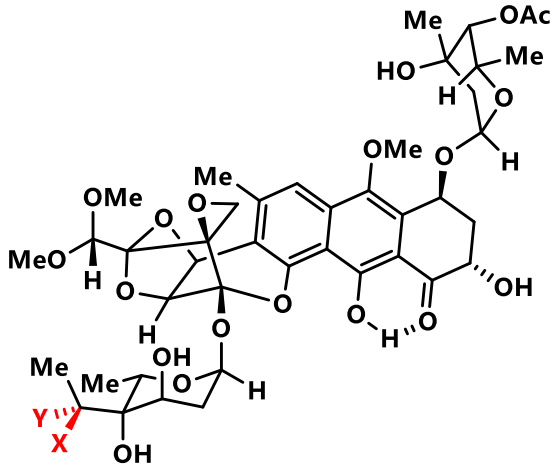
Trioxacrarcin DC-45-A2



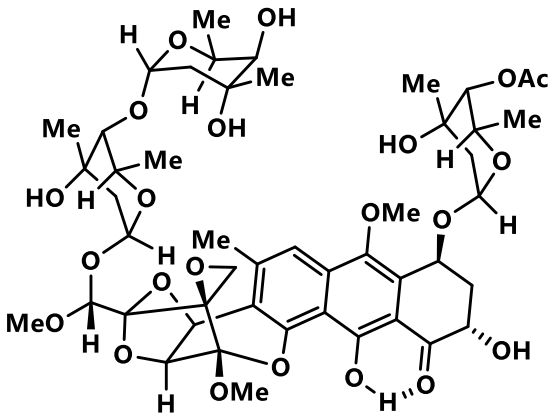
Trioxacrarcin DC-45-A1



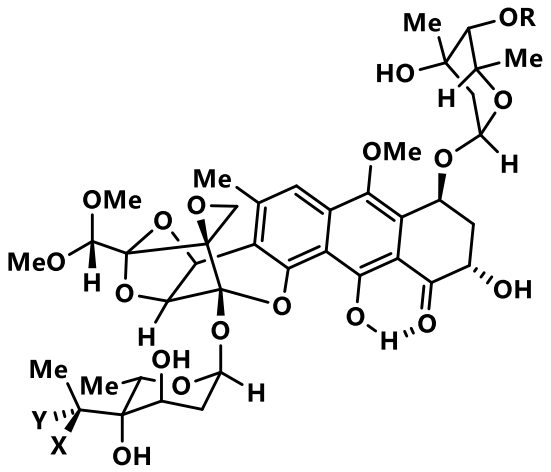
Trioxacrarcin A R=Ac
Trioxacrarcin D R=H

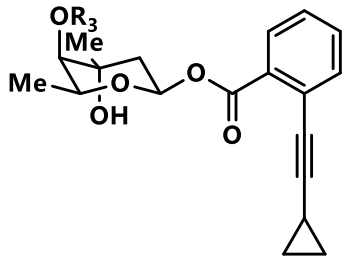


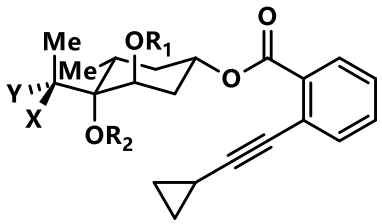
Trioxacrarcin C
X=H, Y=OH
X=OH, Y=H

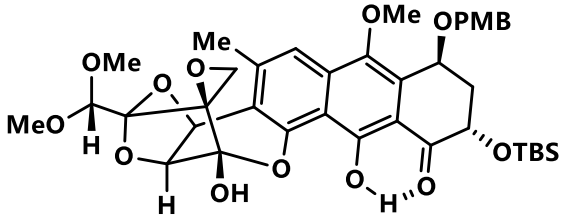


Trioxacrarcin LL-D49194α1



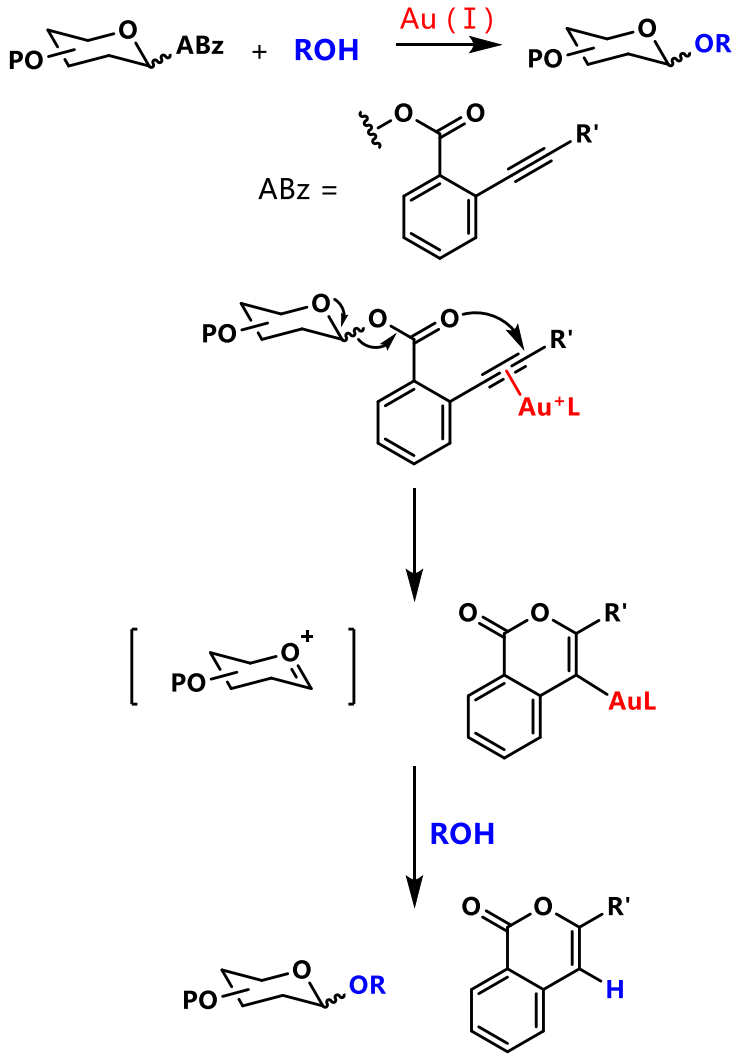


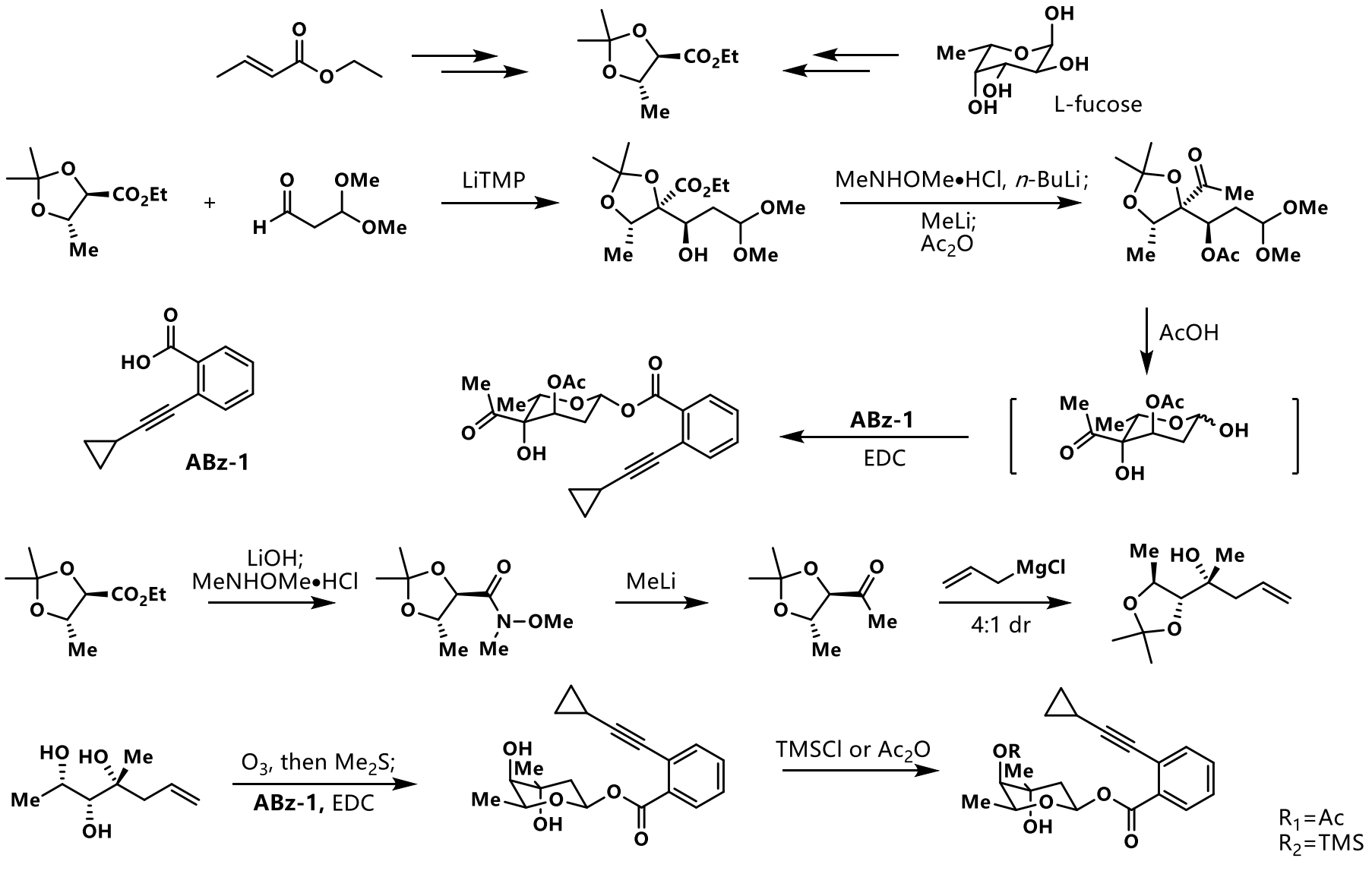


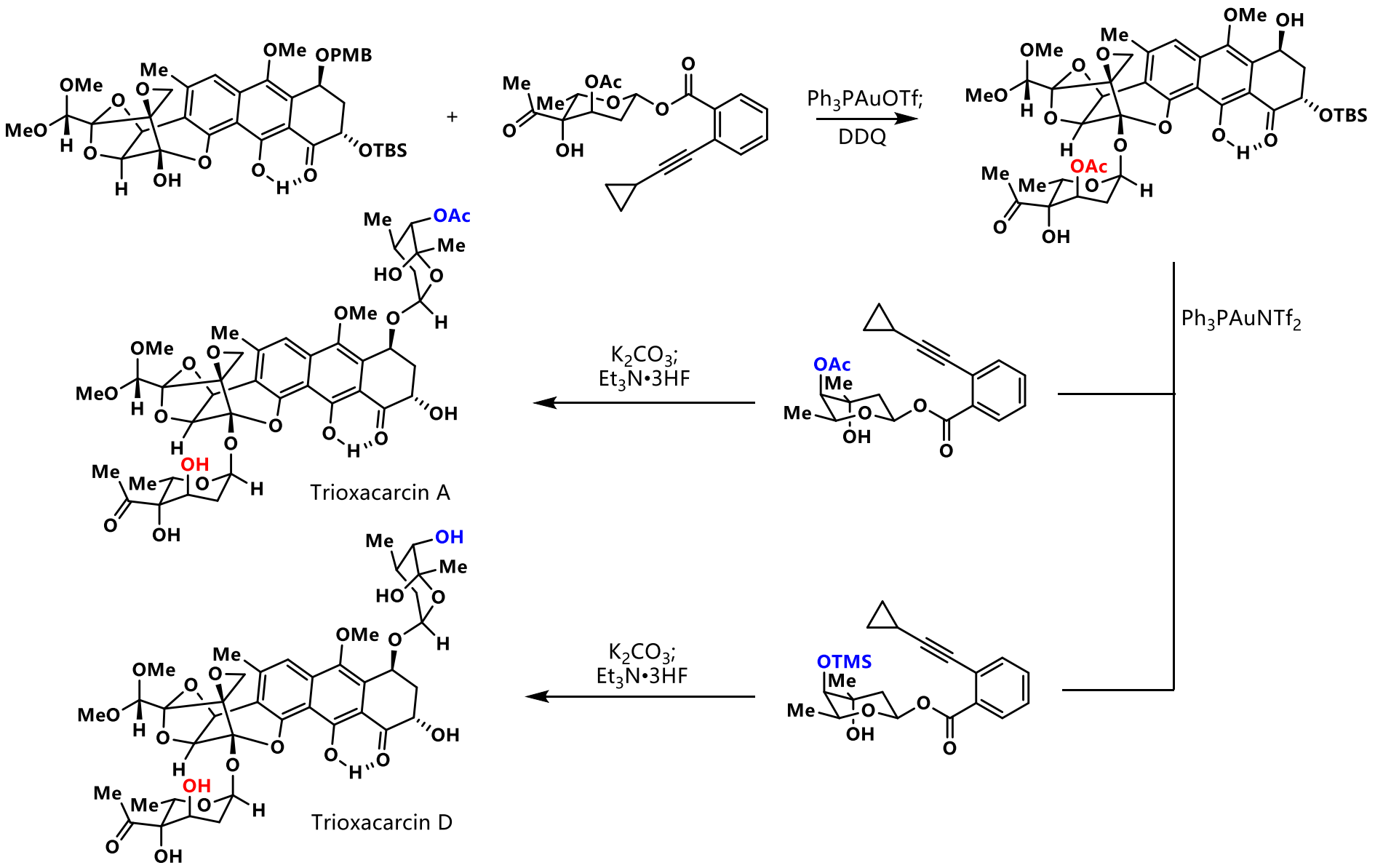


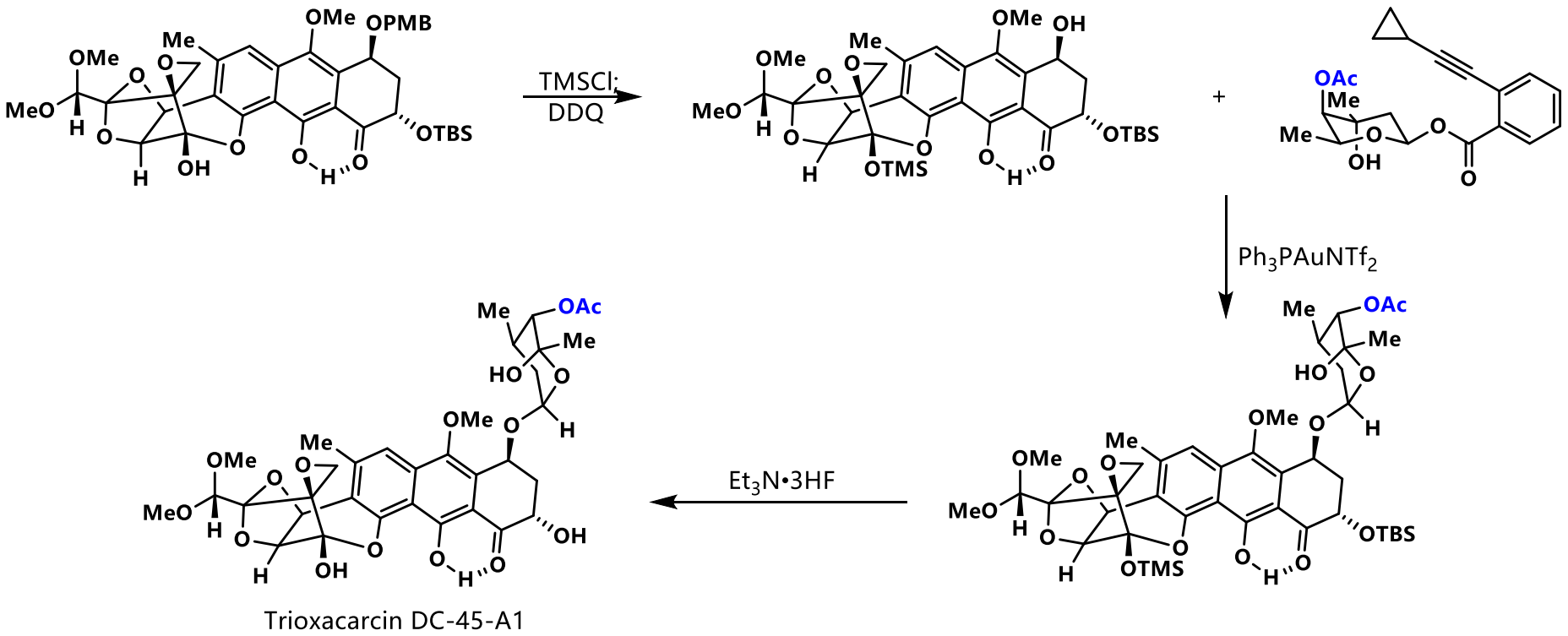
200 mg scale

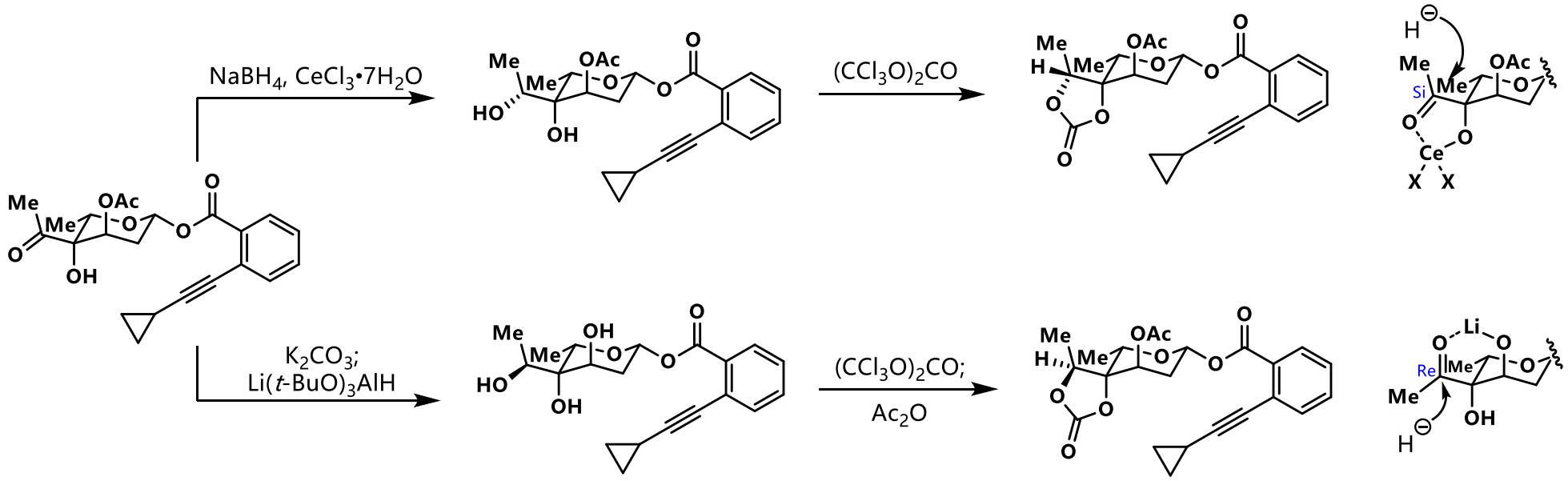
Yu Glycosylation

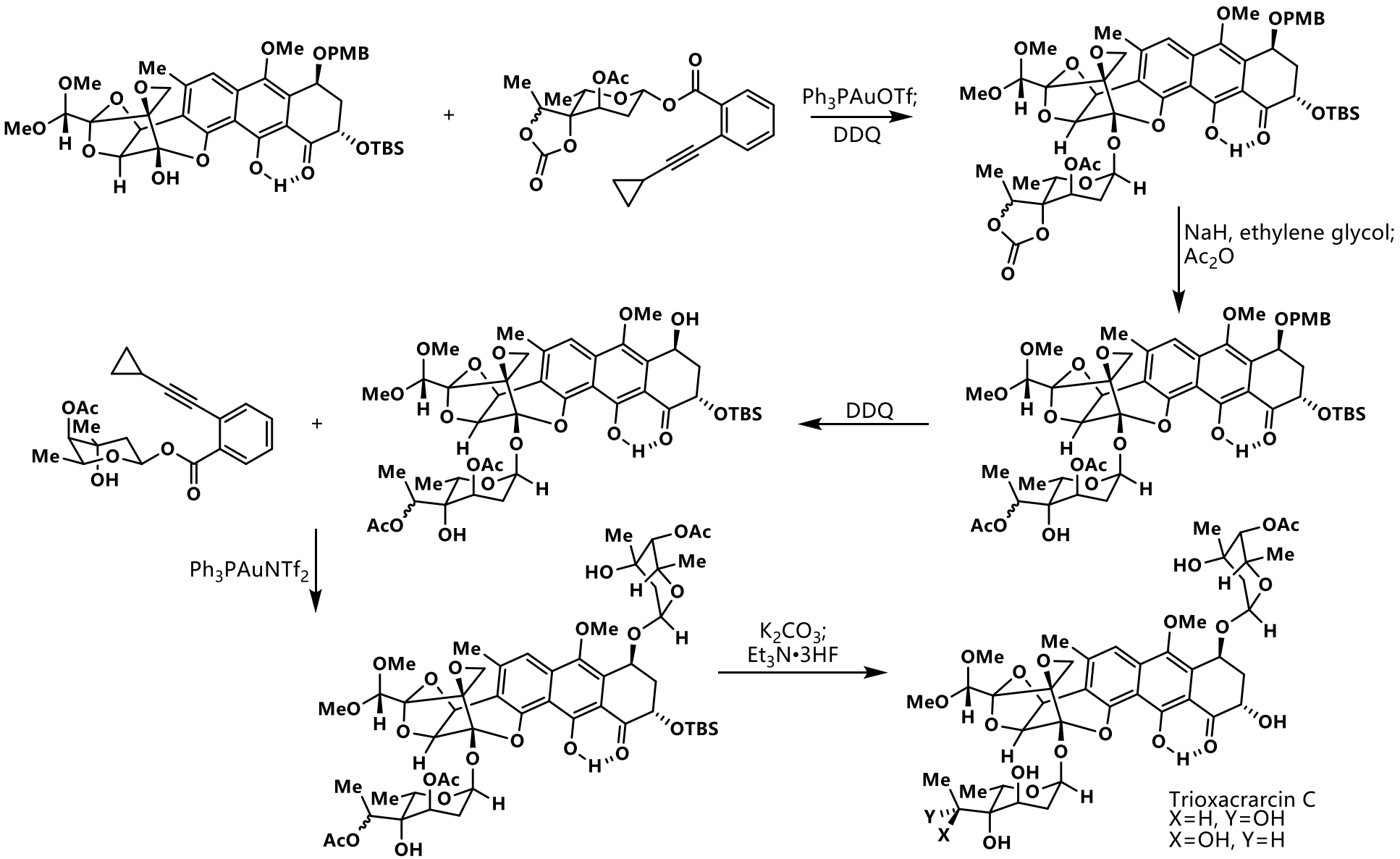



L-fucose
LiTMP
MeNHOMe•HCl, n-BuLi;
MeLi;
Ac2O
AcOH
ABz-1
EDC
LiOH;
MeNHOMe•HCl
MeLi
MgCl
4:1 dr
O3, then Me2S;
ABz-1, EDC
TMSCl or Ac2O
R1=Ac
R2=TMS


Ph3PAuOTf;
DDQ
Ph3PAuNTf2
K2CO3;
Et3N•3HF
K2CO3;
Et3N•3HF
Trioxacarcin A
Trioxacarcin D

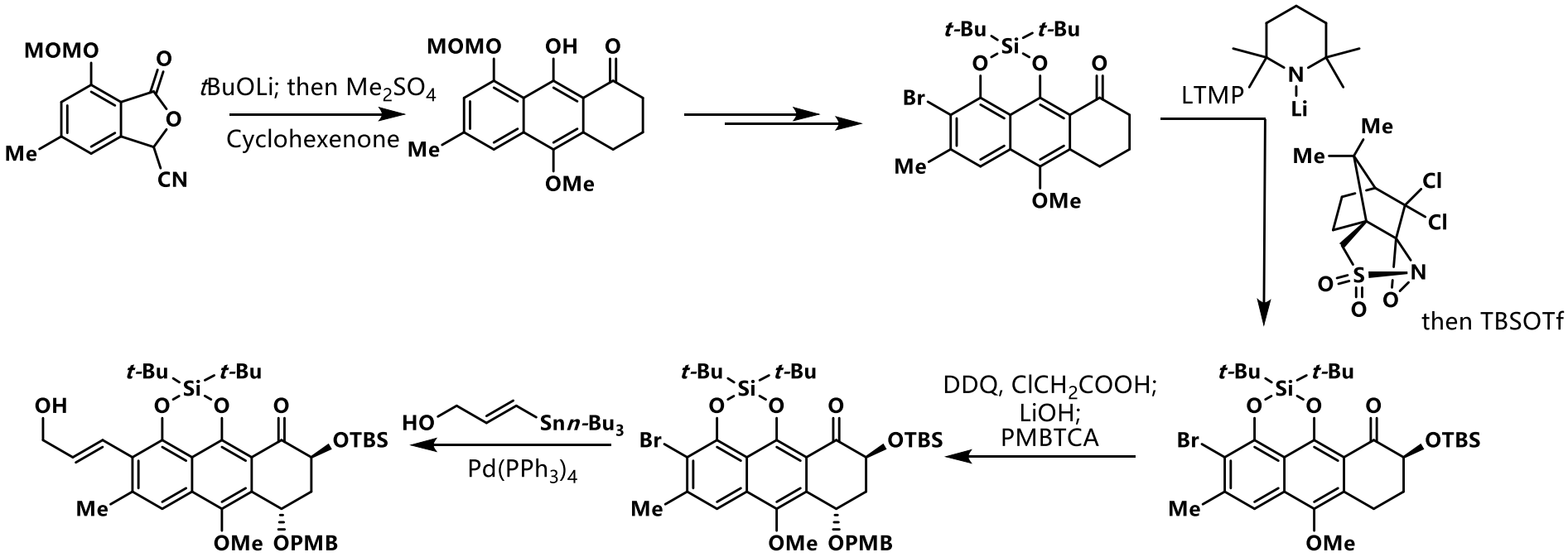

TMSCl;
DDQ
+
Ph3PAuNTf2
Et3N•3HF
Trioxacarcin DC-45-A1

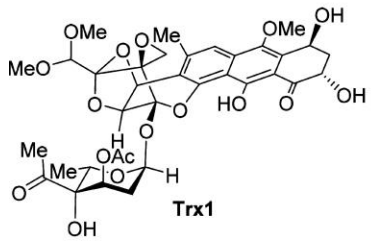

NaBH4, CeCl3•7H2O
K2CO3;
Li(t-BuO)3AlH
(CCl3O)2CO
(CCl3O)2CO;
Ac2O
Me
OAc
OH
HO
H
Si
Ce
X
Li
Re


Ph3PAuOTf;
DDQ
NaH, ethylene glycol;
Ac2O
DDQ
Ph3PAuNTf2
K2CO3;
Et3N•3HF
Trioxacrarcin C
X=H, Y=OH
X=OH, Y=H

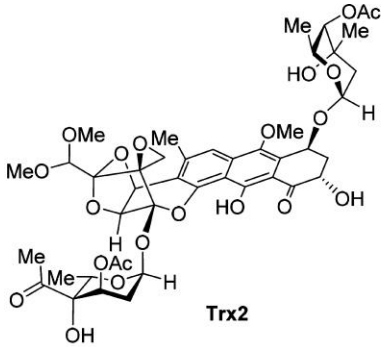
♦**K. C. Nicolaou课题组的工作**（J. Am. Chem. Soc. **2017**, *139*, 15467-15478）

♦Streamlined Total Synthesis of Trioxacarcins and Its Application to the Design, Synthesis, and Biological Evaluation of Analogues Thereof. Discovery of Simpler Designed and Potent Trioxacarcin Analogues

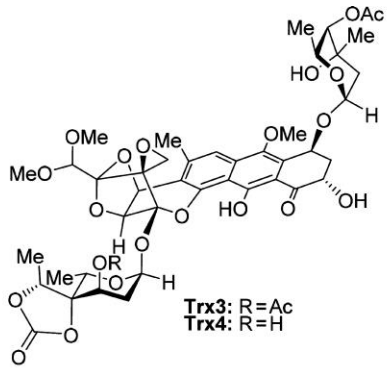




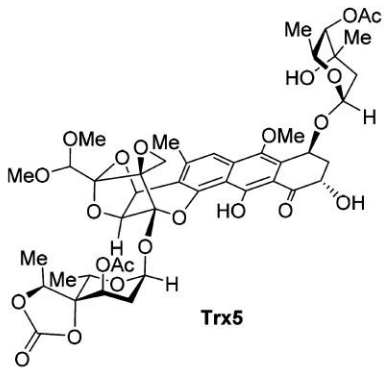
Trx1



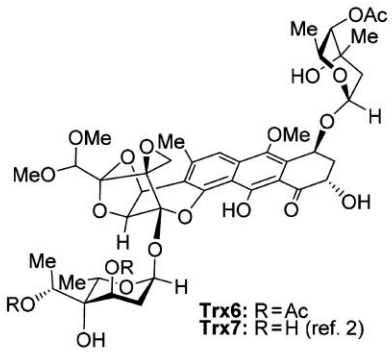
Trx2



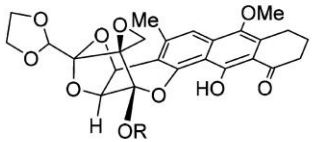
Trx3: R = Ac
Trx4: R = H



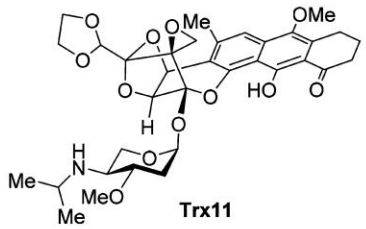
Trx5



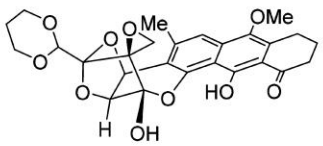
Trx6: R = Ac
Trx7: R = H (ref. 2)



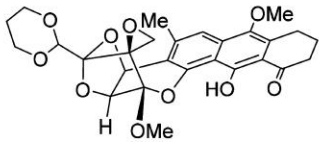
Trx8: R = H
Trx9: R = Me
Trx10: R = MOM



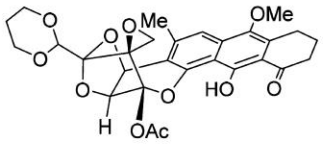
Trx11



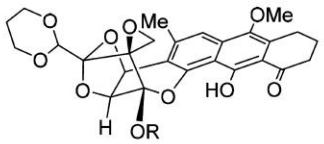
Trx12



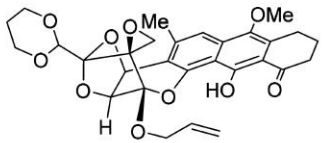
Trx13



Trx14

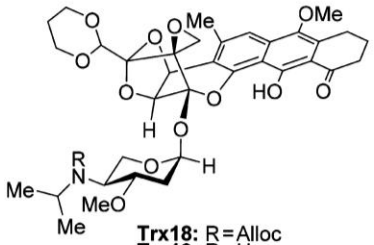


Trx15: R = MOM
Trx16: R = MEM

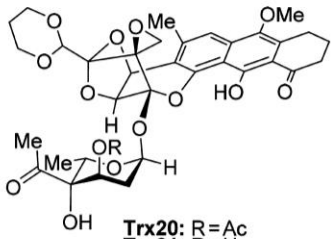


Trx17

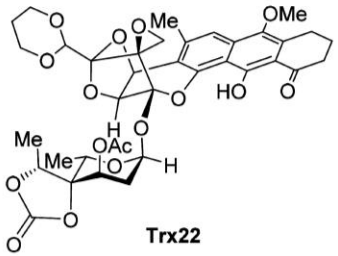
Compound	MES SA	MES SA DX	HEK 293T
MMAE[c]	0.06	>70	0.08
DC-45-A2 (**1**)	>2500	>2500	>2500
DC-45-A1 (**2**) [KCN-Triox 12]	18.08	>1000	14.89
Trioxacarcin A (**3**) [KCN-Triox 13]	0.74	203.5	0.702
Trioxacarcin D (**4**) [KCN-Triox 14]	11.06	>1000	8.02
Trioxacarcin C (**5**) [KCN-Triox 22]	6.09	>500	5.25
Trx1 [KCN-Triox 15]	157.4	>1000	95.4
Trx2 [KCN-Triox 16]	2.02	>1000	2.82
Trx3 [KCN-Triox 17]	7.22	>500	10.14
Trx4 [KCN-Triox 18]	8.8	>500	7.92
Trx5 [KCN-Triox 21]	22.18	>500	24.13
Trx6 [KCN-Triox 19]	8.8	>500	11.4
Trx7 [KCN-Triox 20]	10.73	>500	7.72
Trx8 [KCN-Triox 30]	51.87	49.33	30.71
Trx9 [KCN-Triox 31]	4.67	2.63	2.04
Trx10 [KCN-Triox 32]	3.88	2.18	1.51
Trx11 [KCN-Triox 29]	1.07	3.03	0.92
Trx12 [KCN-Triox 7]	3.72	5.72	2.46
Trx13 [KCN-Triox 8]	0.56	0.42	0.40
Trx14 [KCN-Triox 9]	6.11	17.42	6.89
Trx15 [KCN-Triox 10]	1.82	2.2	1.34
Trx16 [KCN-Triox 11]	1.56	4.1	1.09
Trx17 [KCN-Triox 34]	4.91	3.48	2.77



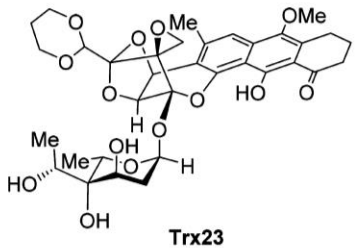
Trx18: R=Alloc
Trx19: R=H



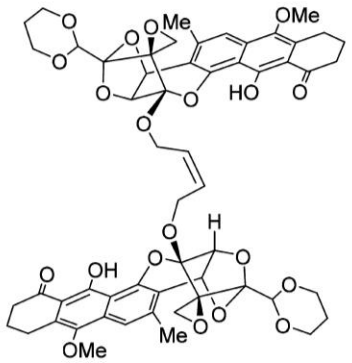
Trx20: R=Ac
Trx21: R=H



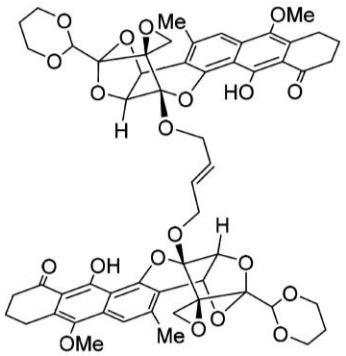
Trx22



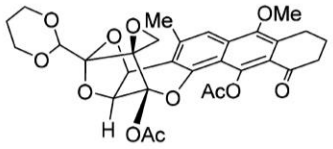
Trx23



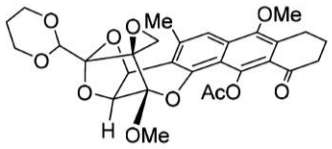
Trx24 (*Z*)



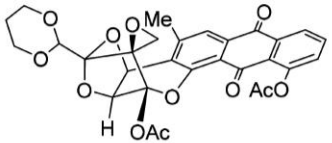
Trx25 (*E*)



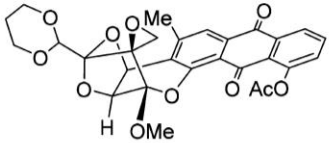
Trx26



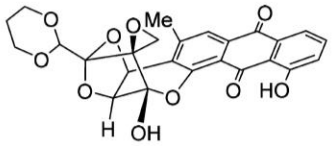
Trx27



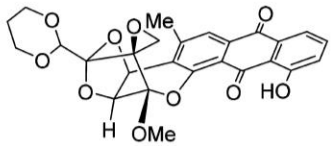
Trx28



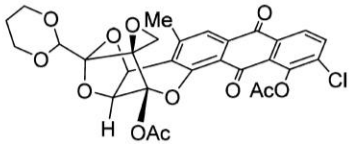
Trx29



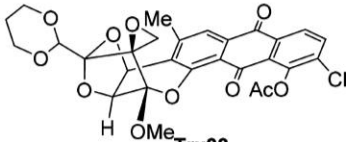
Trx30



Trx31

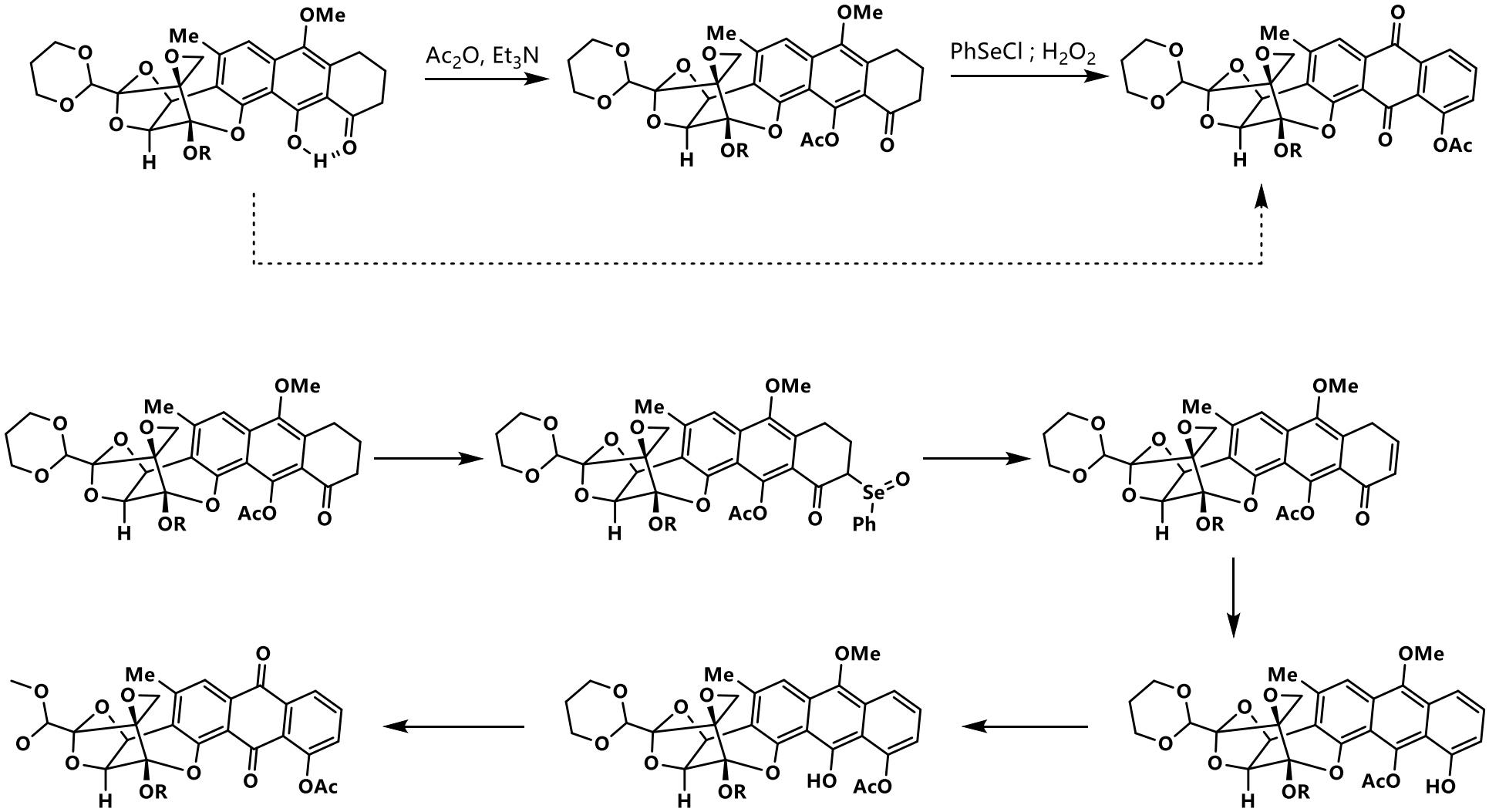


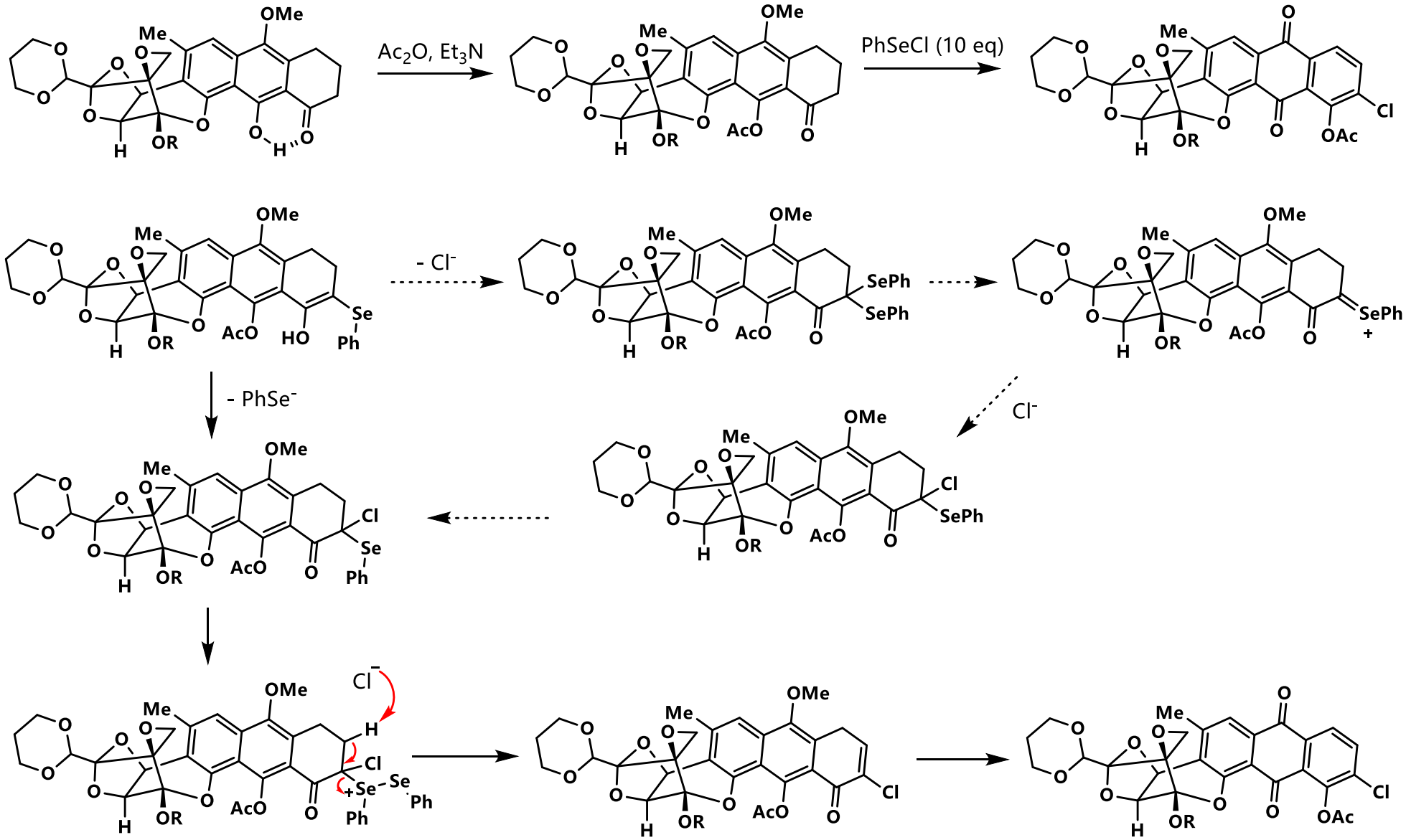
Trx32

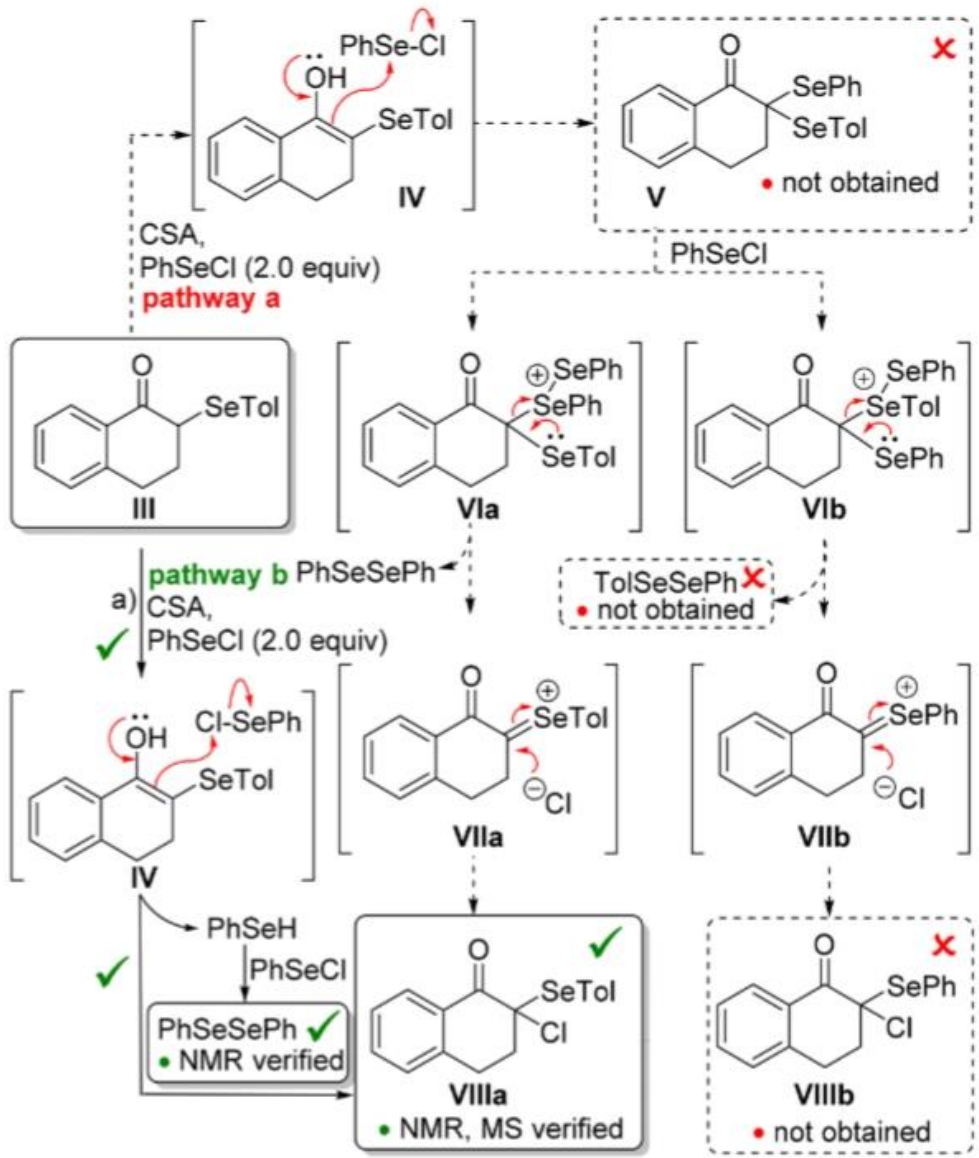


Trx33

Compound	MES SA	MES SA DX	HEK 293T
Trx18 [KCN-Triox 27]	>1000	>1000	40.24
Trx19 [KCN-Triox 28]	0.96	70.65	0.77
Trx20 [KCN-Triox 24]	5.14	52.4	4.31
Trx21 [KCN-Triox 23]	1.47	4.67	1.26
Trx22 [KCN-Triox 25]	5.74	56.94	4.2
Trx23 [KCN-Triox 26]	5.85	33.7	2.74
Trx24 [KCN-Triox 35]	>1000	>1000	115.3
Trx25 [KCN-Triox 36]	235	429	105
Trx26 [KCN-Triox 39]	67.44	60.29	11.62
Trx27 [KCN-Triox 33]	2.15	1.43	1.24
Trx28 [KCN-Triox 40]	11.08	11.86	11.21
Trx29 [KCN-Triox 37]	1.44	1.05	1.87
Trx30 [KCN-Triox 41]	42.01	37.81	50.52
Trx31 [KCN-Triox 38]	1.09	0.65	1.44
Trx32 [KCN-Triox 42]	5.96	4.41	6.73
Trx33 [KCN-Triox 43]	54.27	33.16	38.77


OMe
Me
O
OR
H
Ac2O, Et3N
AcO
PhSeCl ; H2O2
OAc
Se
Ph
HO


Ac2O, Et3N
PhSeCl (10 eq)
- Cl-
- PhSe-
Cl-
Cl-


PhSe-Cl
OH
SeTol
IV
SePh
SeTol
V
not obtained
CSA,
PhSeCl (2.0 equiv)
pathway a
PhSeCl
SeTol
III
SePh
SePh
SeTol
VIa
SePh
SeTol
SePh
VIb
pathway b PhSeSePh
a)
CSA,
PhSeCl (2.0 equiv)
TolSeSePh
not obtained
OH
Cl-SePh
SeTol
IV
SeTol
Cl
VIIa
SePh
Cl
VIIb
PhSeH
PhSeCl
PhSeSePh
NMR verified
SeTol
Cl
VIIIa
NMR, MS verified
SePh
Cl
VIIIb
not obtained

感谢聆听