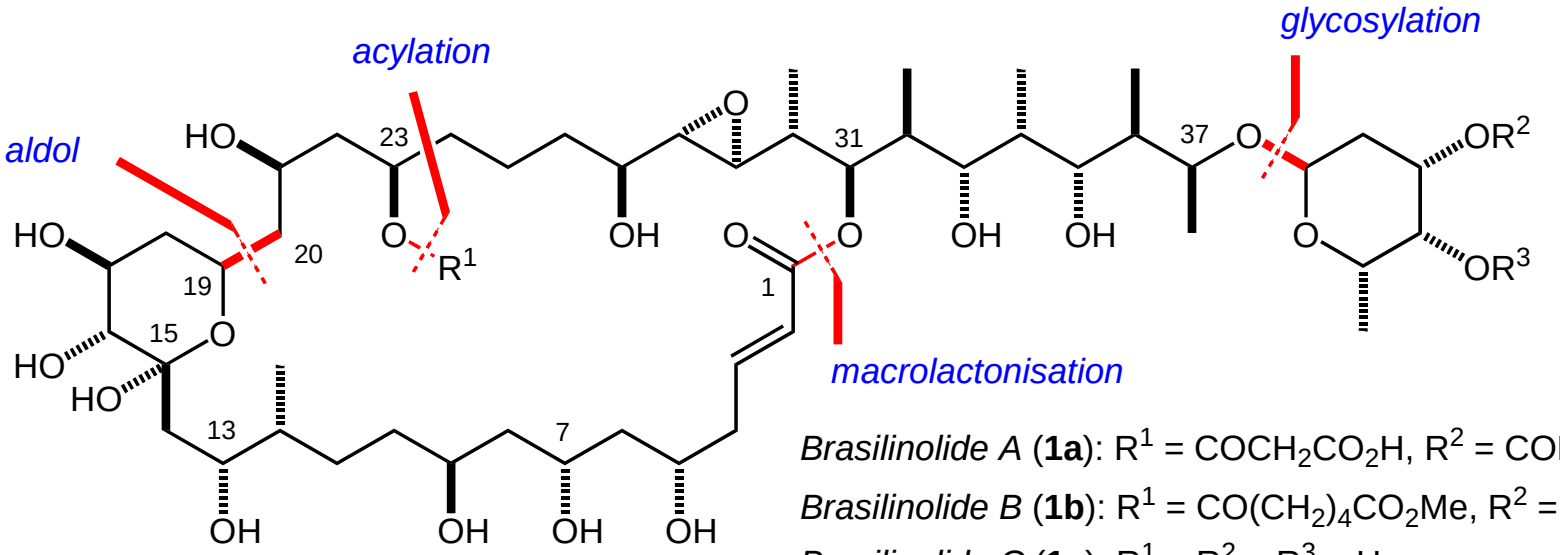
Literature Report 2009-9-8

王躲生　　检查: 陈庆安

Toward the Total Synthesis of the Brasilinolides: Stereocontrolled Assembly of a C1-C19 Polyol Segment

Paterson, I.*, *et al*
Org. Lett. **2009**, *11*, 353-356.

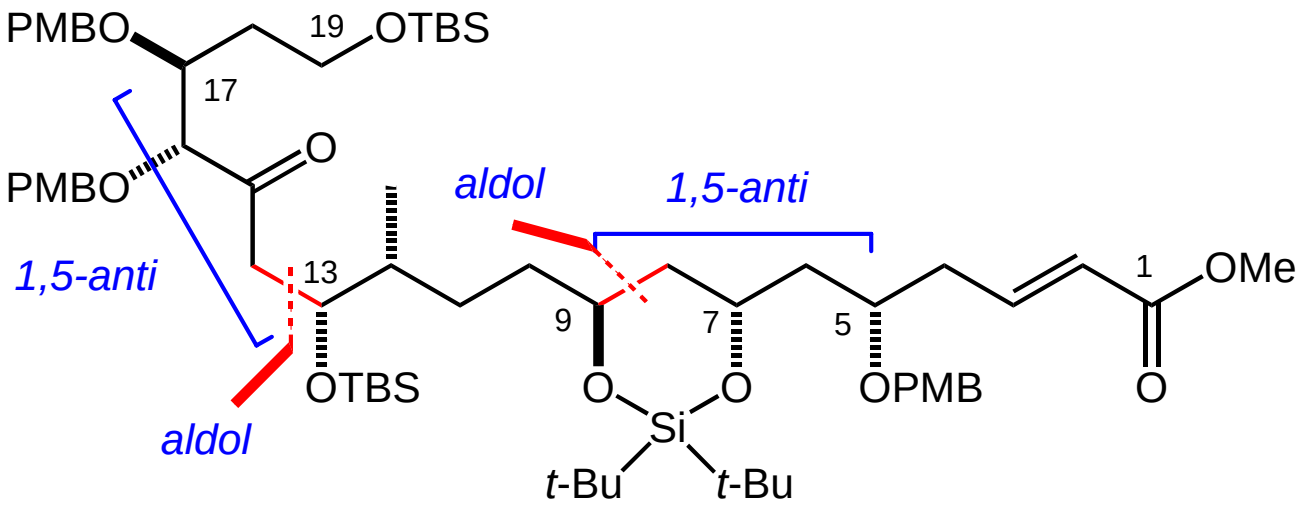
Retrosynthesis Analysis of the Brasilinolides



Brasilinolide A (**1a**): $R^1 = COCH_2CO_2H$, $R^2 = COBu$, $R^3 = H$

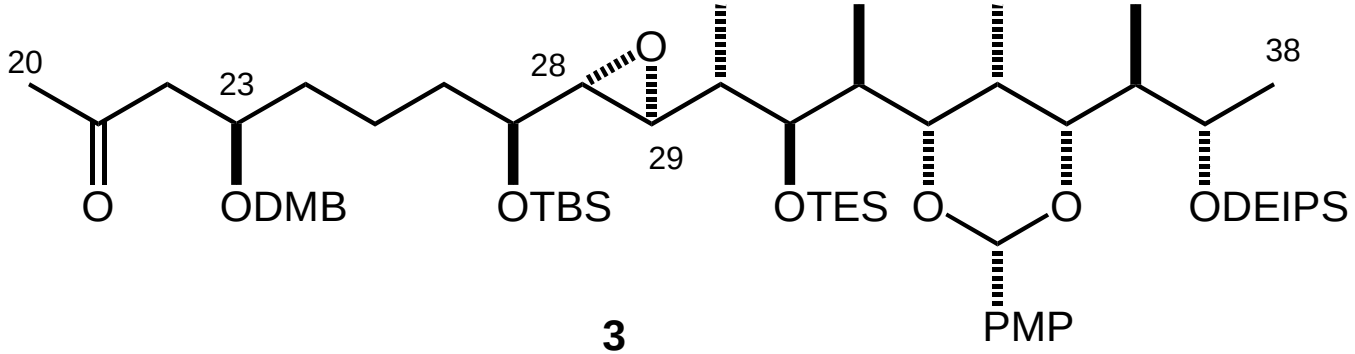
Brasilinolide B (**1b**): $R^1 = CO(CH_2)_4CO_2Me$, $R^2 = R^3 = Me$

Brasilinolide C (**1c**): $R^1 = R^2 = R^3 = H$

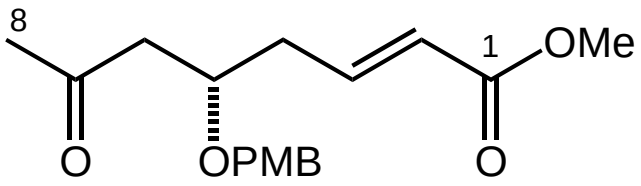

PMBO
19
OTBS
17
O
PMBO
aldol
1,5-anti
1,5-anti
13
1
OMe
9
7
5
OTBS
O
O
OPMB
O
Si
aldol
t-Bu
t-Bu

2

+

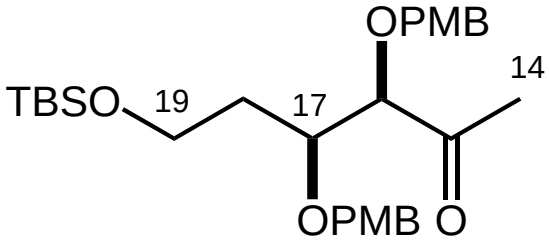

20
23
28
O
38
29
O
ODMB
OTBS
OTES
O
O
ODEIPS
PMP

3



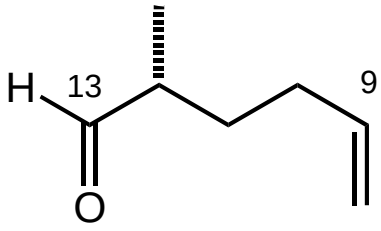
4

+



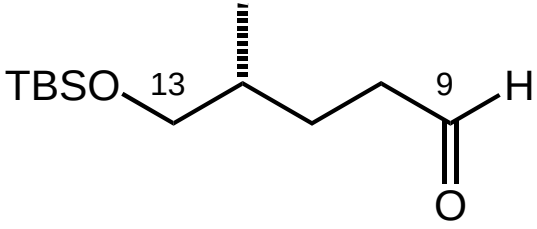
5

+



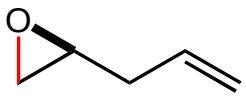
6

or



7

Synthesis of **4** and **5**

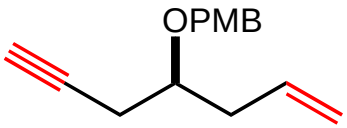


8

1.  Li·EDA, DMSO

2. PMBBr, NaH, THF

69%, 2 steps

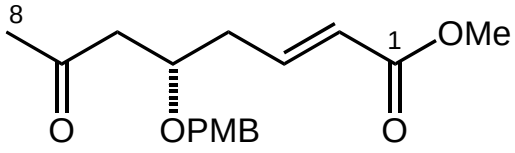


9

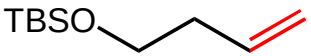
1. PPTS, $Hg(OAc)_2$, H_2O, acetone

2. methyl acrylate, Grubbs II, CH_2Cl_2

75%, 2 steps

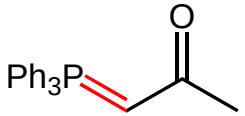


4

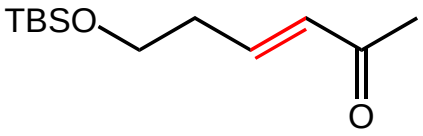


10

a. O_3, CH_2Cl_2

b. 

76%

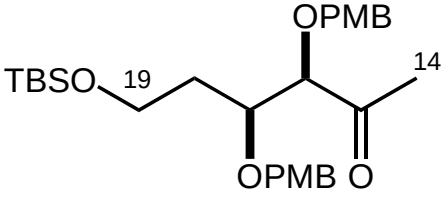


(*E:Z* > *95:5*) **11**

1. Sharpless dihydroxylation

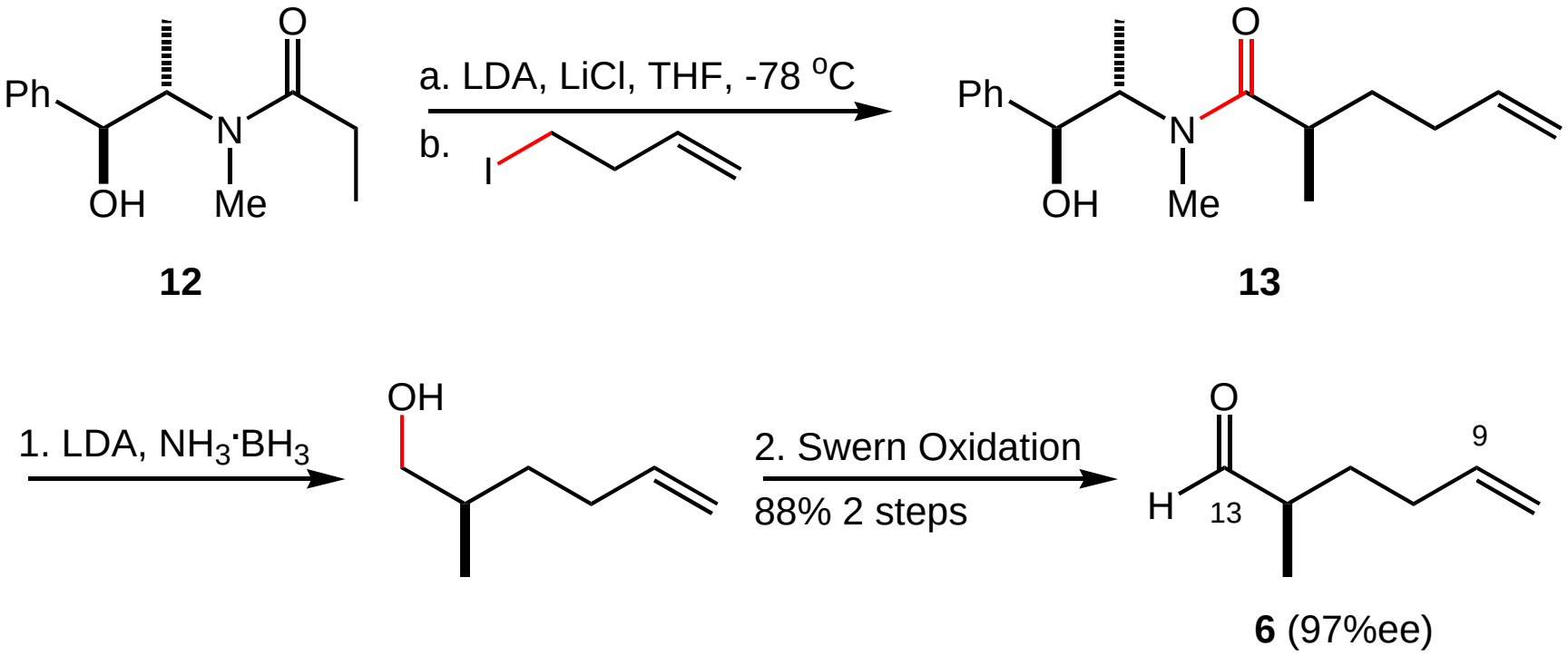
2. PMBTCA, $Ph_3C^+BF_4^-$, THF

68%, 2 steps



5 (97%ee)

Synthesis of **6**

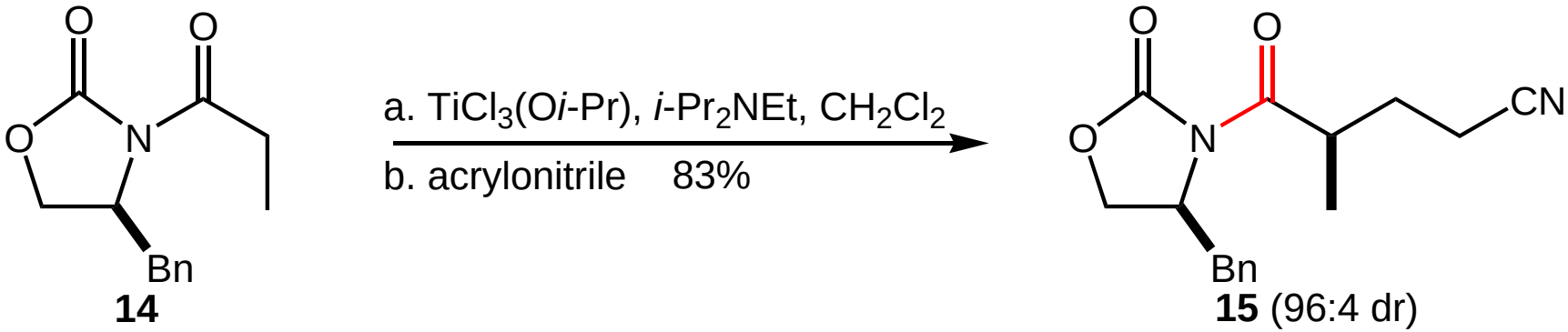


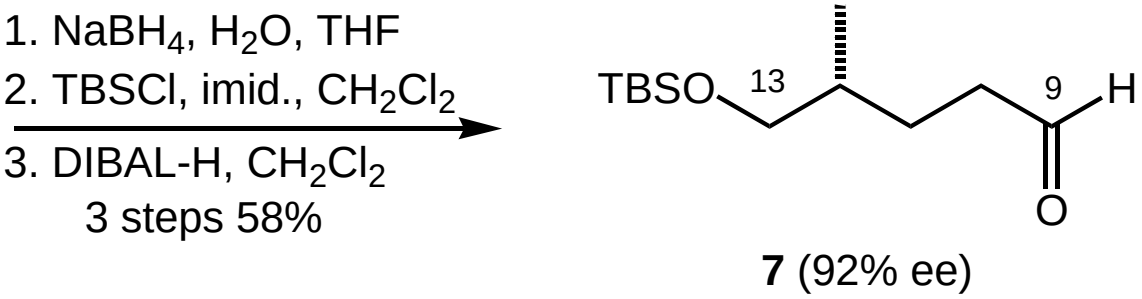
12

13

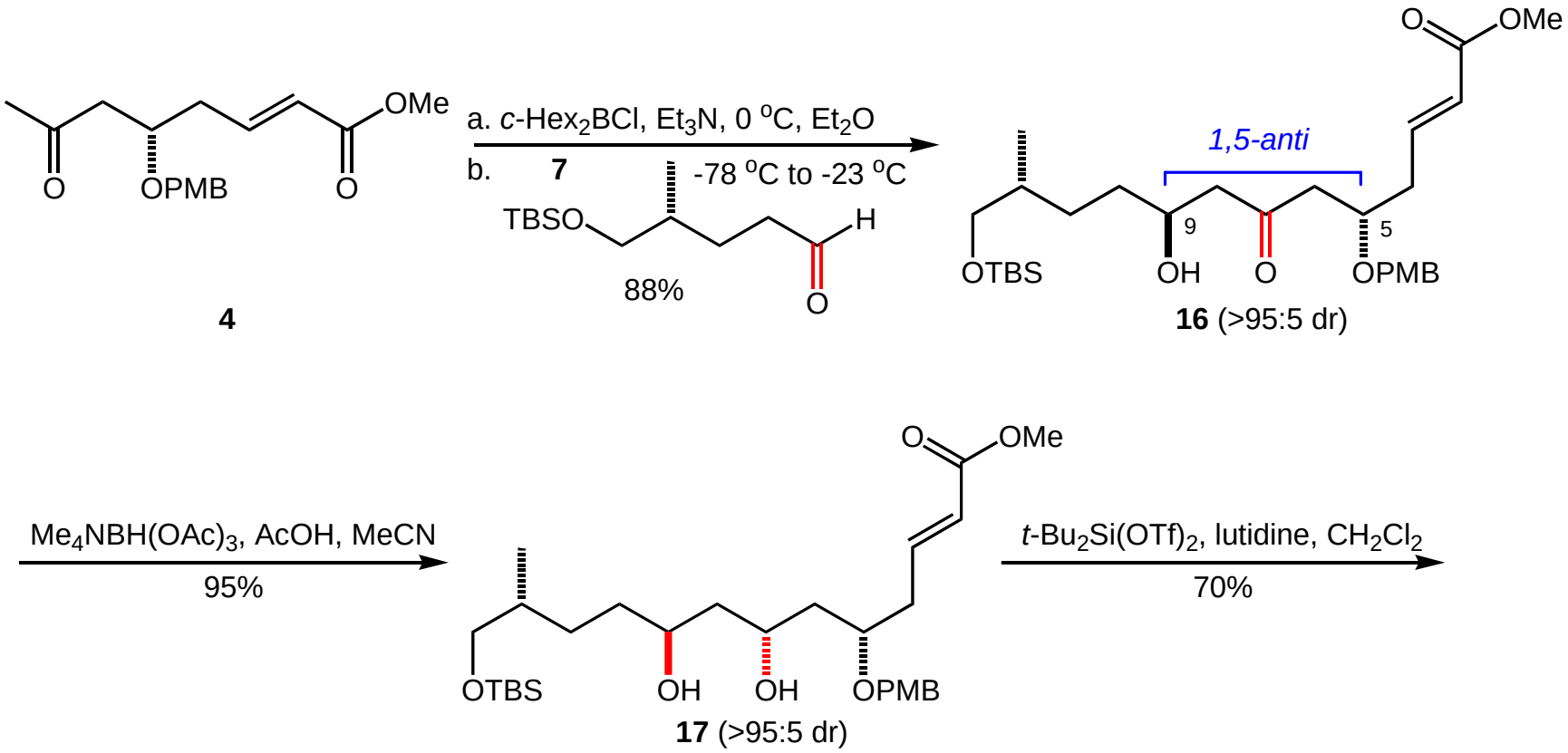
6 (97%ee)

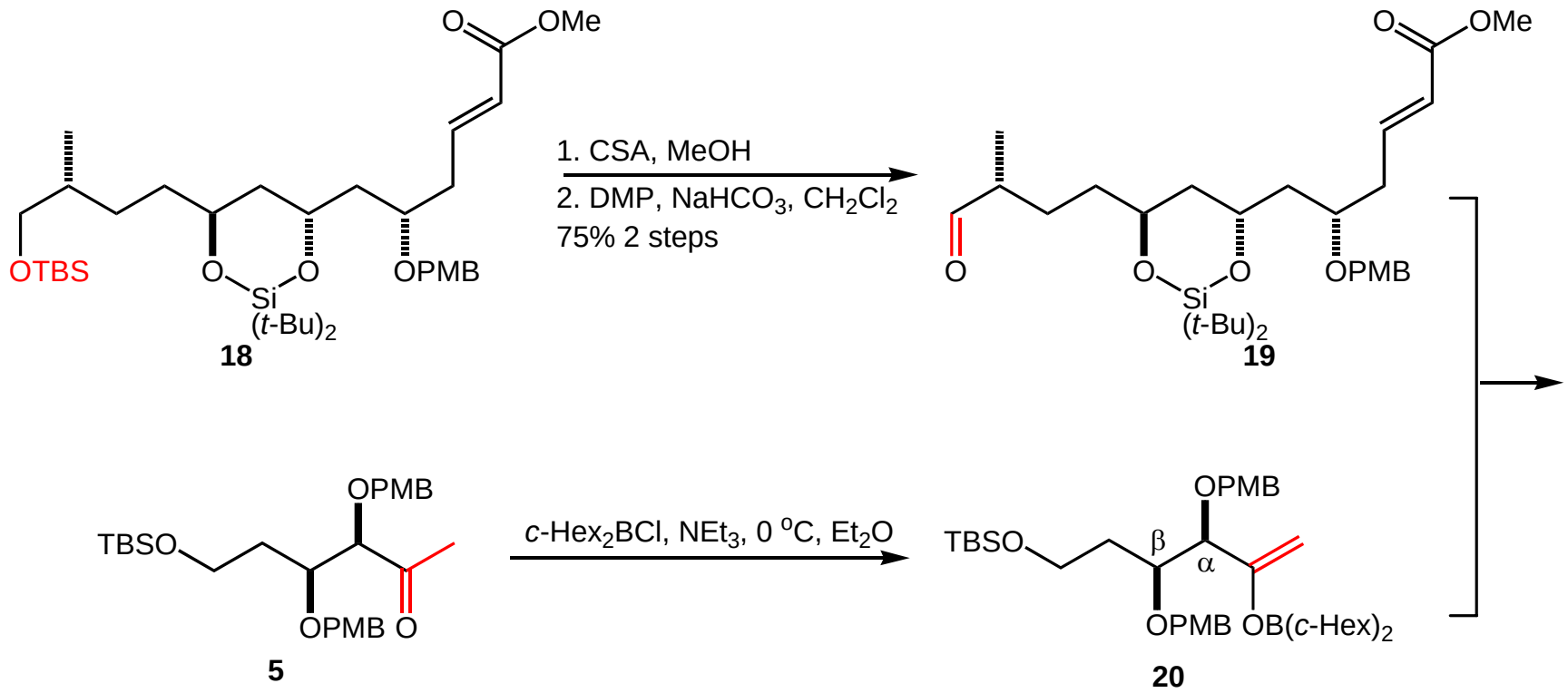
Synthesis of **7**

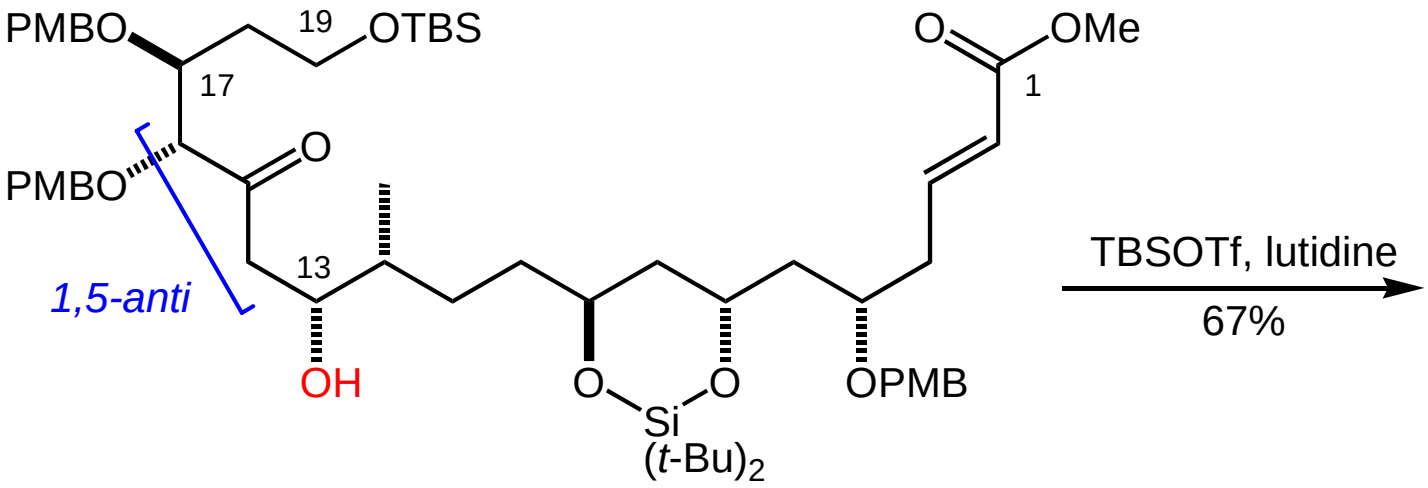




Synthesis of **2**



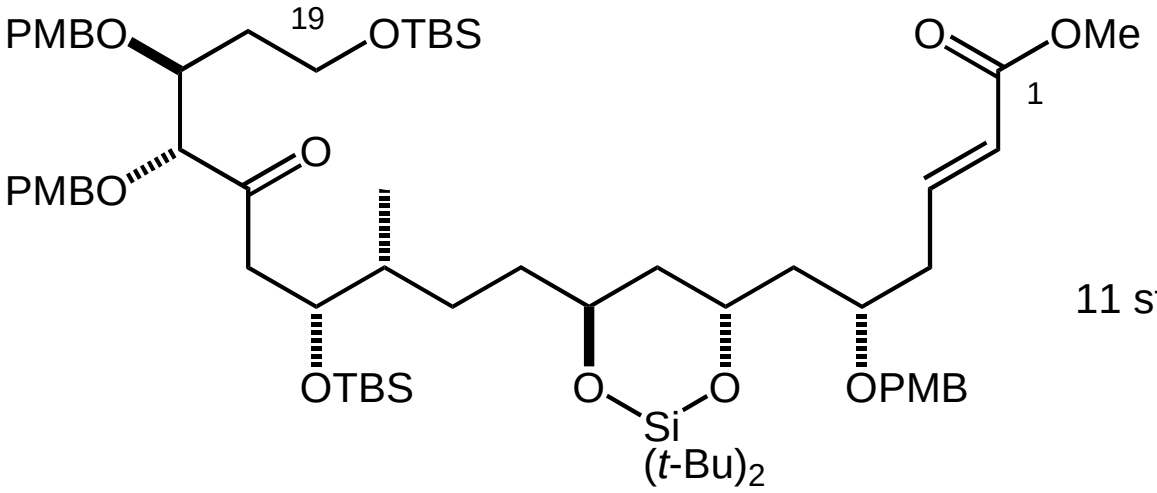

O
OMe
OTBS
O
Si
O
OPMB
(t-Bu)2
18
1. CSA, MeOH
2. DMP, NaHCO3, CH2Cl2
75% 2 steps
O
OMe
O
O
Si
O
OPMB
(t-Bu)2
19
OPMB
TBSO
OPMB
O
5
c-Hex2BCl, NEt3, 0 °C, Et2O
OPMB
TBSO
β
α
OPMB
OB(c-Hex)2
20



TBSOTf, lutidine

67%

23 (87:13 dr)

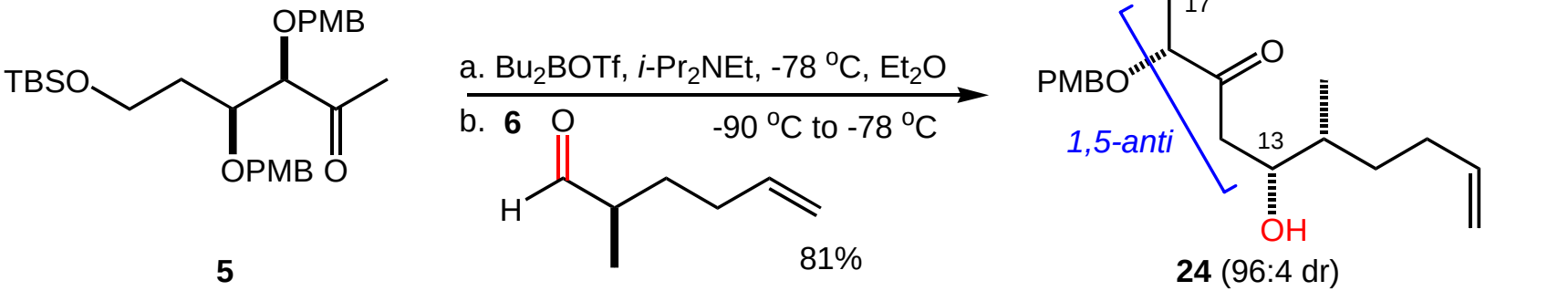


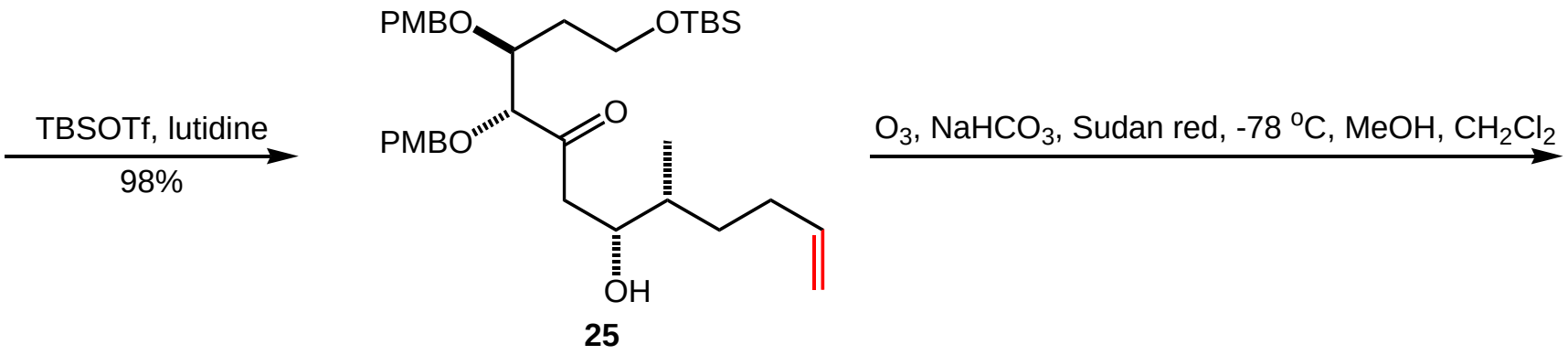
2

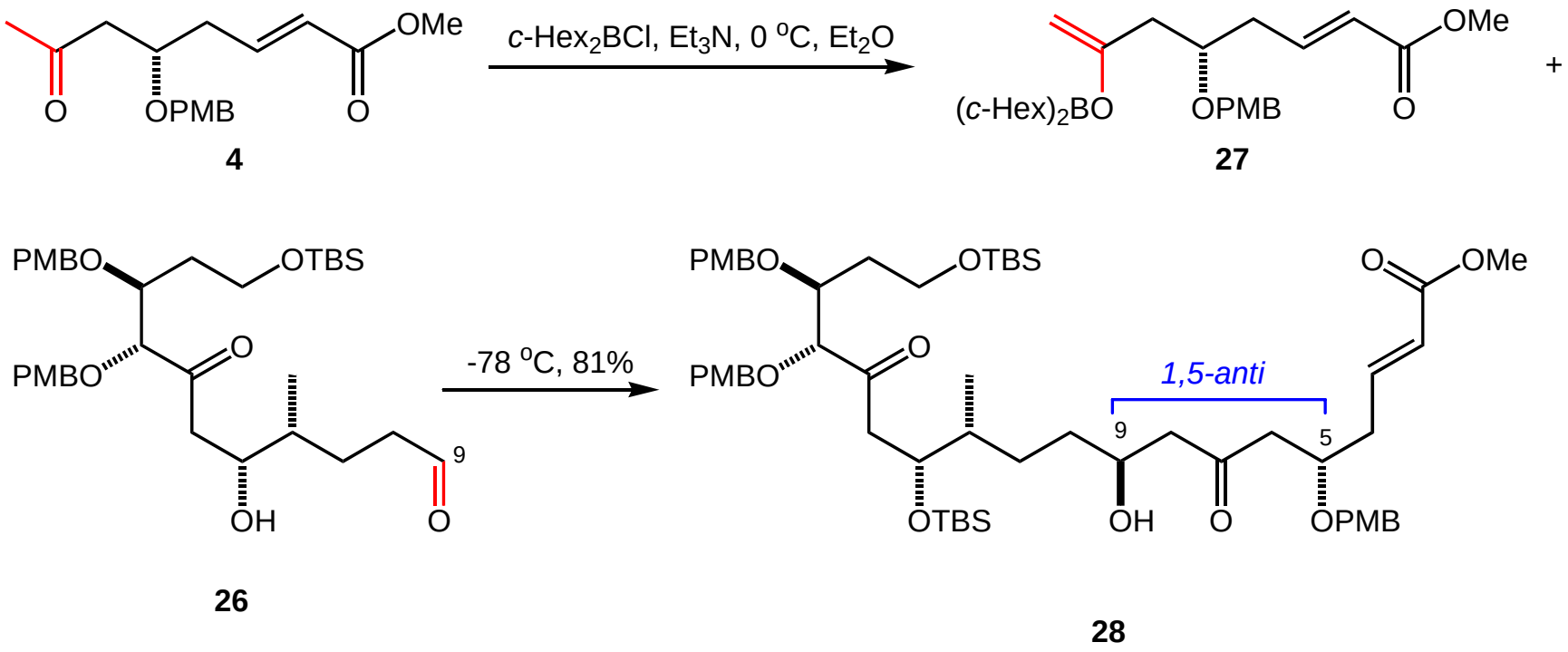
11.5% overall yield

11 steps longest linear sequence from **8**

Alternative route of synthesis of **2**

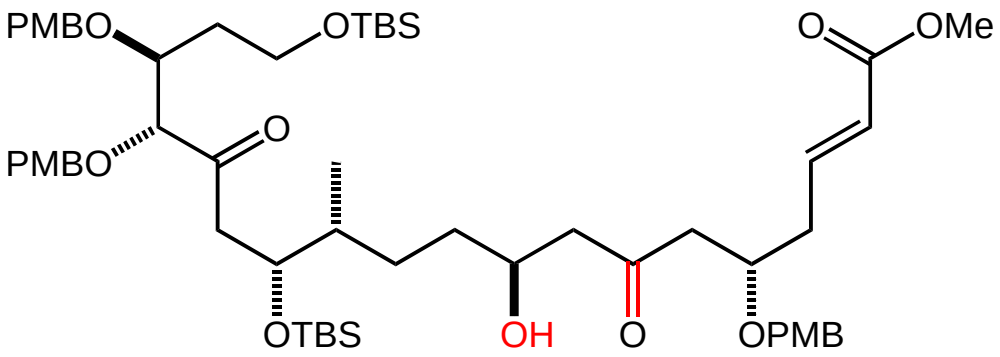





OMe
O
OPMB
O
c-Hex2BCl, Et3N, 0 °C, Et2O
OMe
(c-Hex)2BO
OPMB
O
+
PMBO
OTBS
PMBO
O
OH
O
9
-78 °C, 81%
PMBO
OTBS
PMBO
O
O
OMe
1,5-anti
9
5
OTBS
OH
O
OPMB

4 **27**

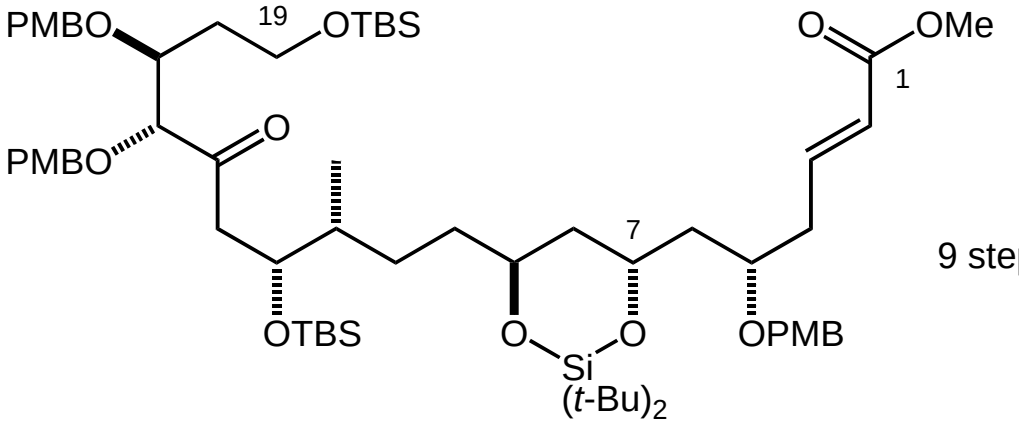
26 **28**



28

1. $Me_4NBH(OAc)_3$, -30 °C, AcOH, MeCN
2. *t*-$Bu_2Si(OTf)_2$, lutidine

54% 2 steps

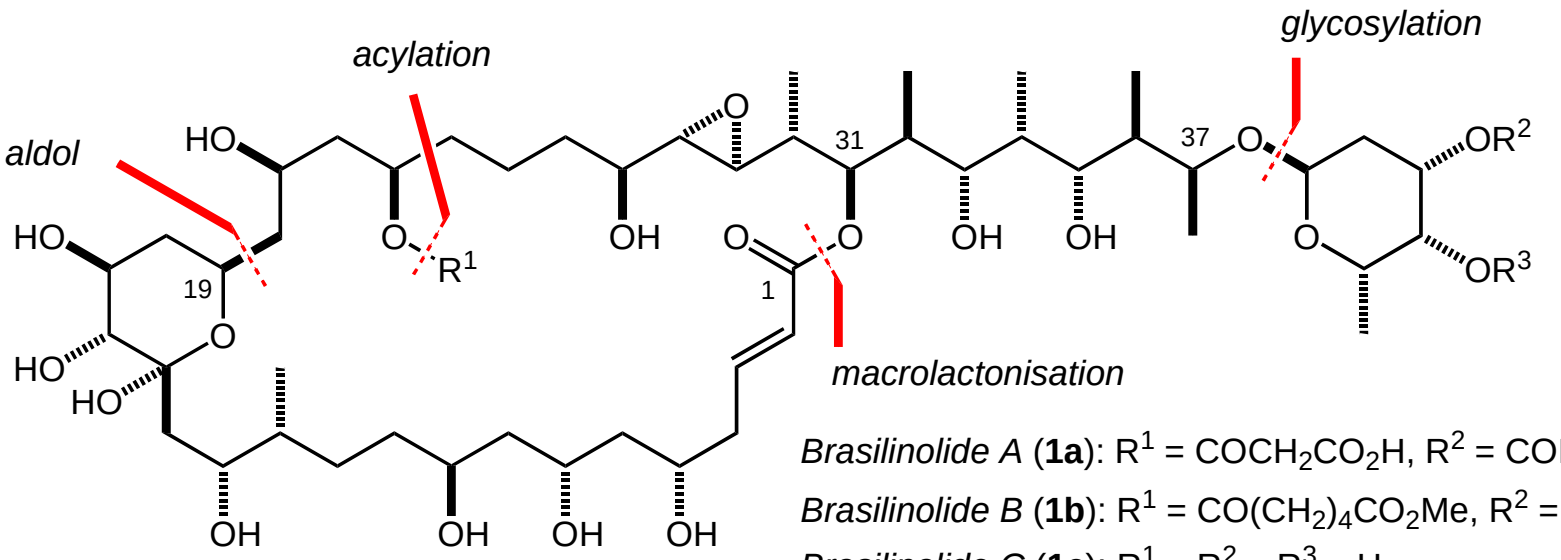


2

17.4% overall yield

9 steps longest linear sequence from **10**

Retrosynthesis Analysis of the Brasilinolides

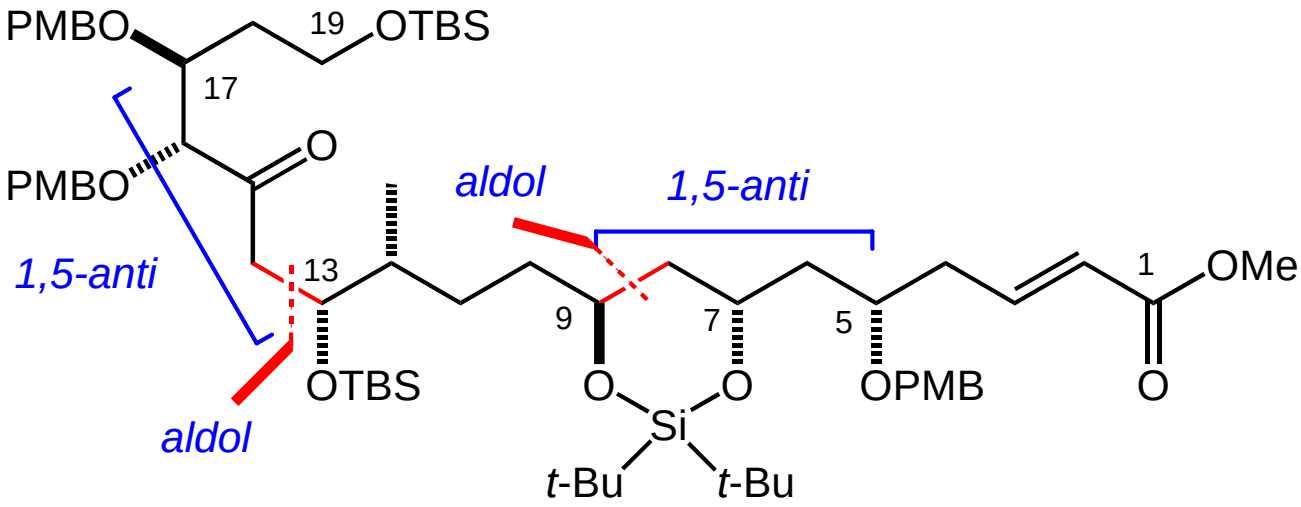


Brasilinolide A (**1a**): $R^1 = COCH_2CO_2H$, $R^2 = COBu$, $R^3 = H$

Brasilinolide B (**1b**): $R^1 = CO(CH_2)_4CO_2Me$, $R^2 = R^3 = Me$

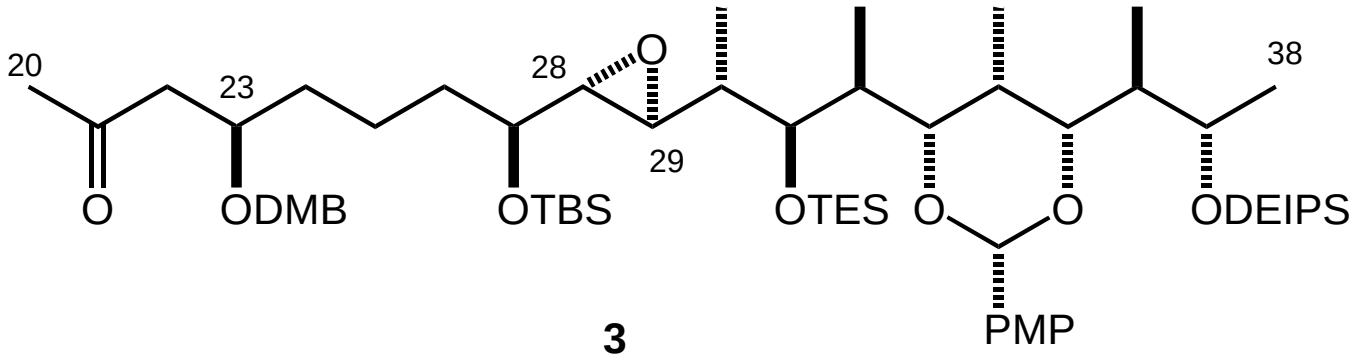
Brasilinolide C (**1c**): $R^1 = R^2 = R^3 = H$

Paterson, I.*, *et al Org. Lett.* **2009**, *11*, 693-696.

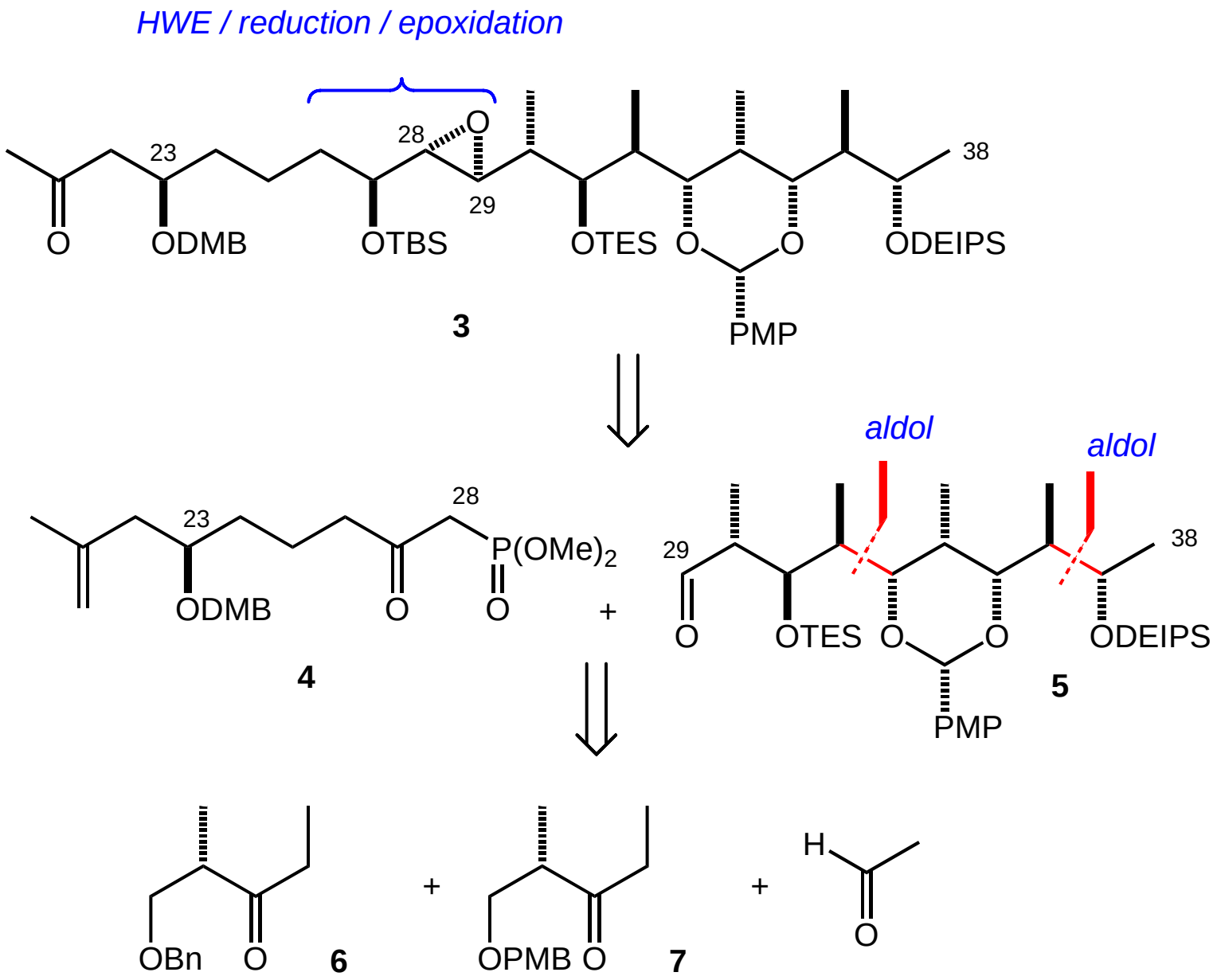

PMBO
19
OTBS
17
O
PMBO
aldol
1,5-anti
1,5-anti
13
1
OMe
9
7
5
aldol
OTBS
O
O
OPMB
O
Si
t-Bu
t-Bu

2

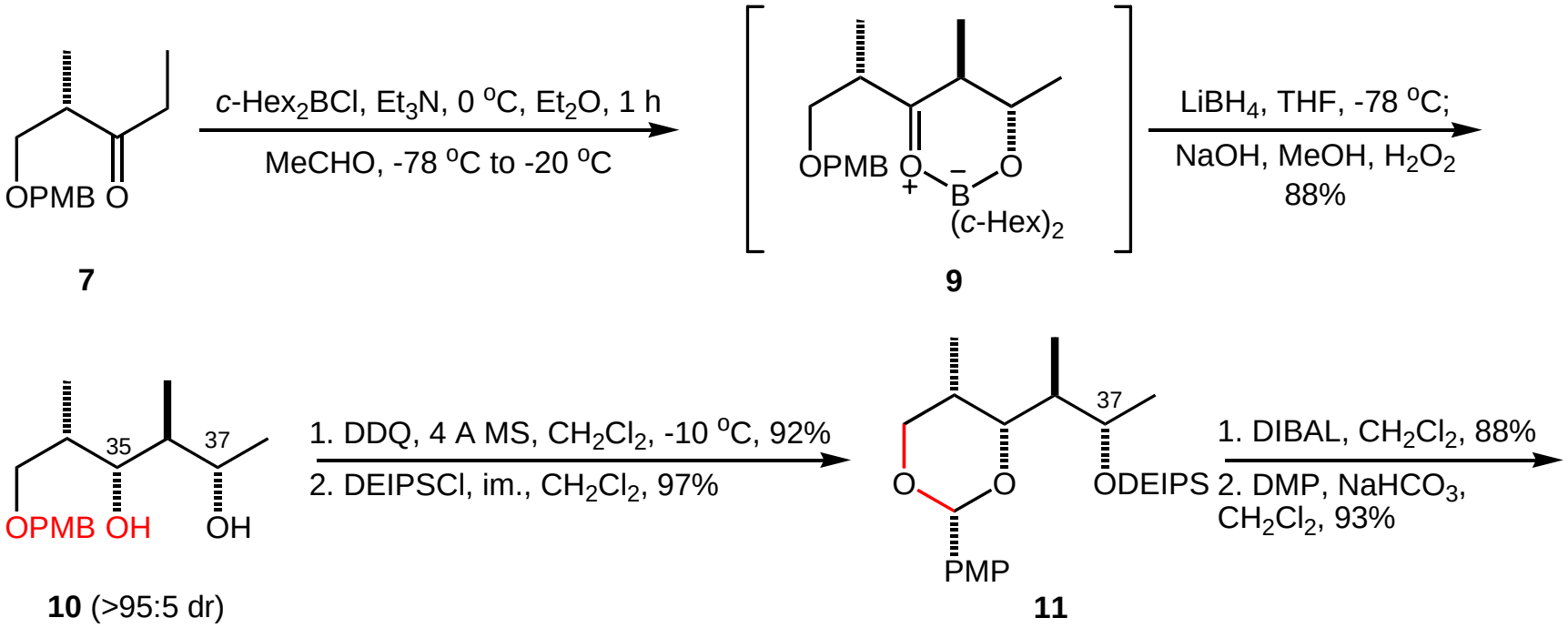
+


20
23
28
O
38
29
O
ODMB
OTBS
OTES
O
O
ODEIPS
PMP

3



Paterson, I.*, *et al Org. Lett.* **2009**, *11*, 693-696.

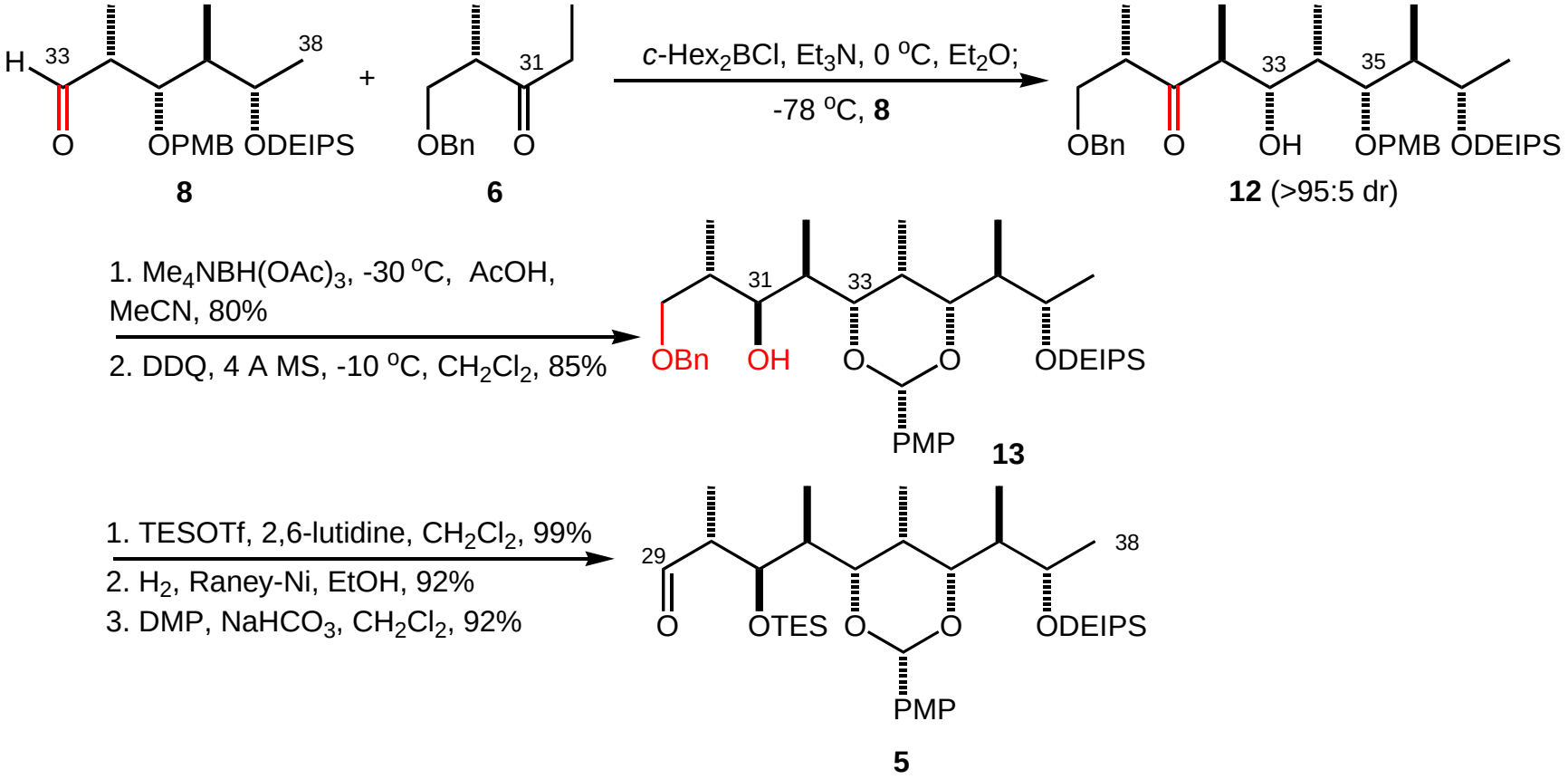


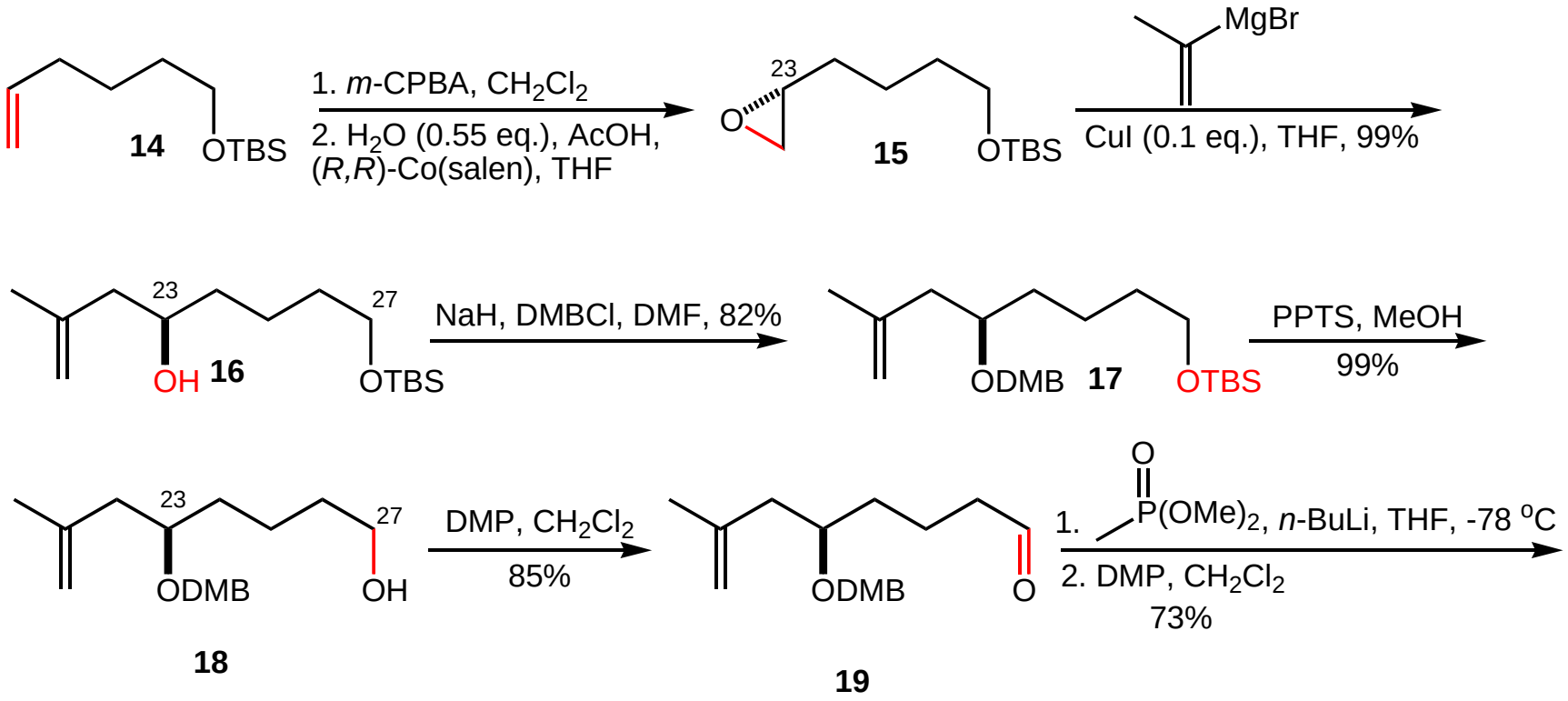
7

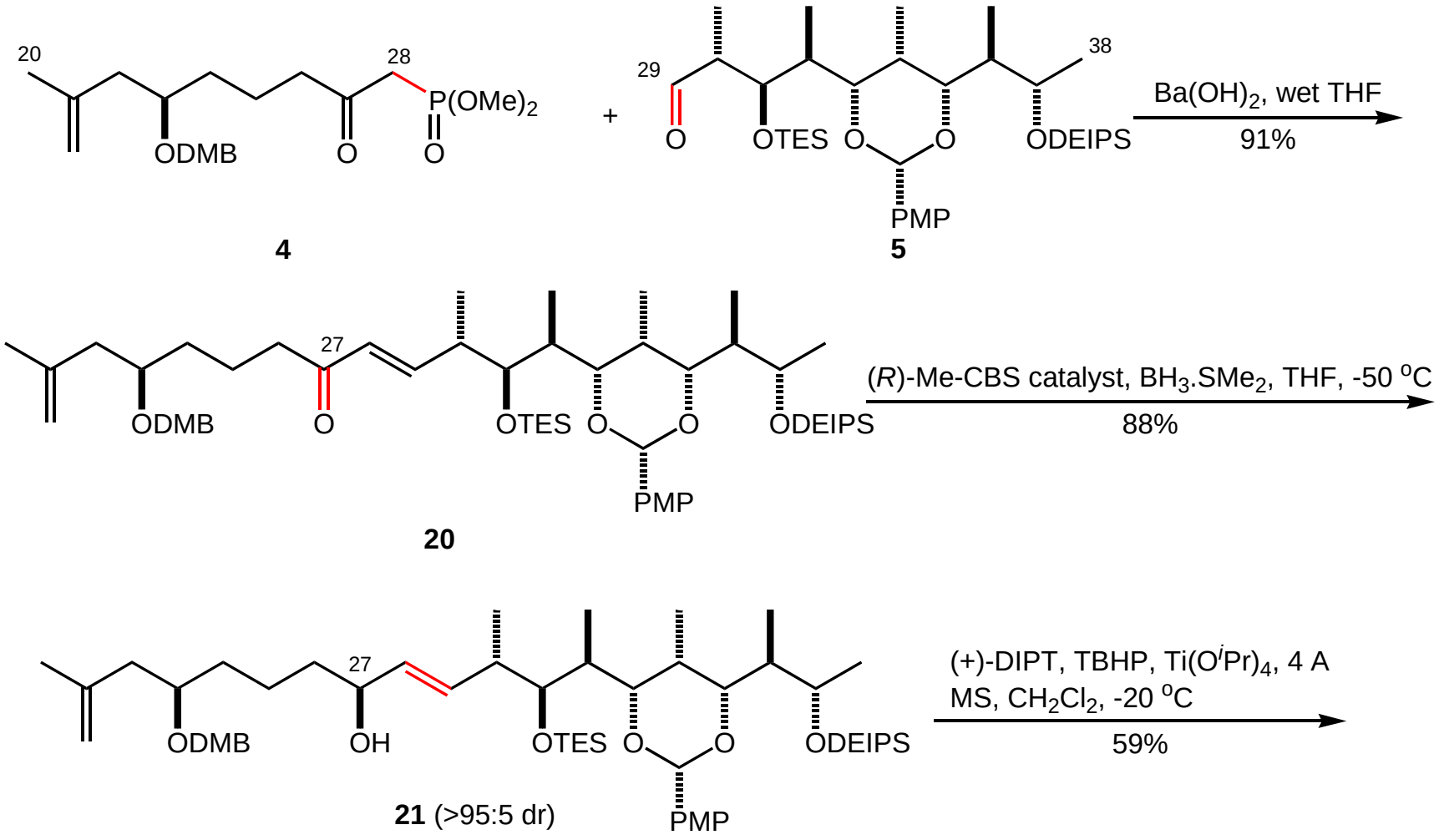
9

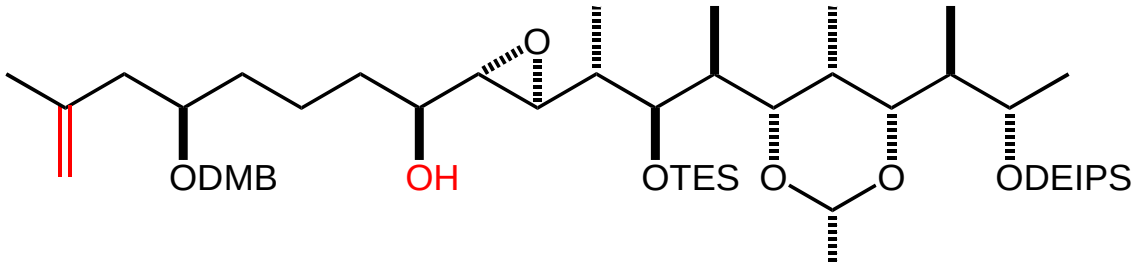
10 (>95:5 dr)

11


H
33
38
O
OPMB
ODEIPS
8
+
31
OBn
O
6
c-Hex2BCl, Et3N, 0 °C, Et2O;
-78 °C, 8
33
35
OBn
O
OH
OPMB
ODEIPS
12 (>95:5 dr)
1. Me4NBH(OAc)3, -30 °C, AcOH, MeCN, 80%
2. DDQ, 4 A MS, -10 °C, CH2Cl2, 85%
31
33
OBn
OH
O
O
ODEIPS
PMP
13
1. TESOTf, 2,6-lutidine, CH2Cl2, 99%
2. H2, Raney-Ni, EtOH, 92%
3. DMP, NaHCO3, CH2Cl2, 92%
29
38
O
OTES
O
O
ODEIPS
PMP
5


14
OTBS
1. m-CPBA, CH2Cl2
2. H2O (0.55 eq.), AcOH,
(R,R)-Co(salen), THF
23
O
15
OTBS
MgBr
CuI (0.1 eq.), THF, 99%
23
27
OH
16
OTBS
NaH, DMBCl, DMF, 82%
ODMB
17
OTBS
PPTS, MeOH
99%
23
27
ODMB
OH
18
DMP, CH2Cl2
85%
ODMB
O
19
O
1.
P(OMe)2, n-BuLi, THF, -78 °C
2. DMP, CH2Cl2
73%


20
28
P(OMe)2
ODMB
O
O
4
+
29
38
O
OTES
O
O
ODEIPS
PMP
5
Ba(OH)2, wet THF
91%
27
ODMB
O
OTES
O
O
ODEIPS
PMP
20
(R)-Me-CBS catalyst, BH3.SMe2, THF, -50 °C
88%
27
ODMB
OH
OTES
O
O
ODEIPS
PMP
21 (>95:5 dr)
(+)-DIPT, TBHP, Ti(OiPr)4, 4 A MS, CH2Cl2, -20 °C
59%

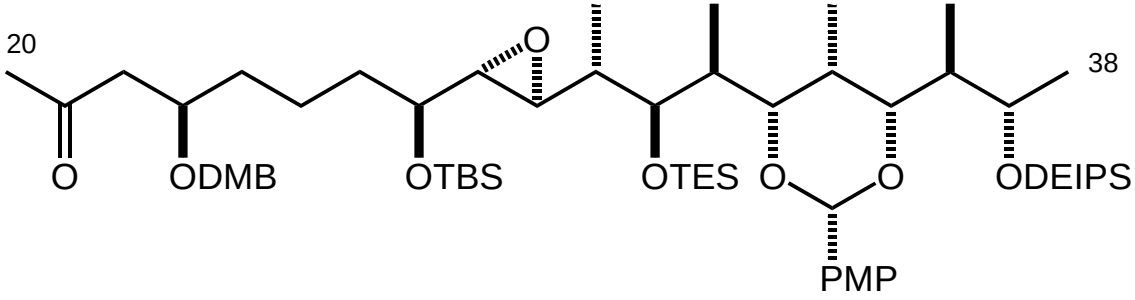


22 (7:1 dr)

1. TBSOTf, 2,6-lutidine

2. OsO_4, NMO, THF, H_2O; $NaIO_4/SiO_2$, CH_2Cl_2

86%



3

13% overall yield

16 steps longest linear sequence from (*S*)-**7**

The brasilinolides (**1a**-**c**, Scheme 1), first isolated in 1996 by Kobayashi and co-workers from the pathogenic actinomycete *Nocardia brasiliensis* IFM-0406, constitute a structurally unique family of bioactive 32-membered macrolides. Recently, the relative and absolute configuration was determined inter alia by controlled chemical degradation of brasilinolide C (**1c**) and detailed spectroscopic studies of the resulting fragments.

In summary, we have completed the stereocontrolled synthesis of the fully protected C1-C19 polyol segment **2** of the brasilinolides using two highly convergent routes. Efficient fragment couplings were achieved using boronmediated 1,5-*anti* aldol reactions. Ongoing work into the assembly of the northern hemisphere **3** (Scheme 1) should further advance the total synthesis of this novel family of immunosuppressive macrolides.