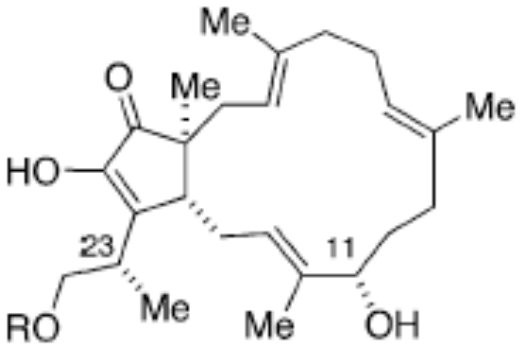
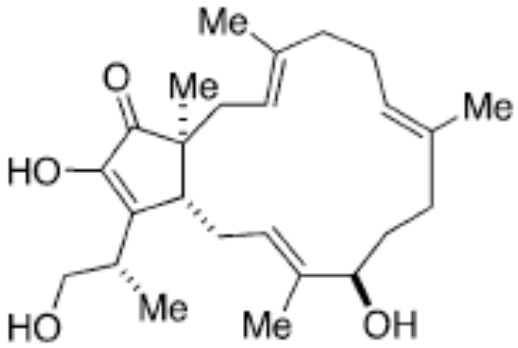
Enantioselective Synthesis of (−)-Terpestacin and Structural Revision of Siccanol Using Catalytic Stereoselective Fragment Couplings and Macrocyclizations

Massachusetts Institute of Technology, Department of Chemistry

1. Johann Chan and Timothy F. Jamison; *JACS*, **2004**, ASAP
2. Johann Chan and Timothy F. Jamison; *JACS*, **2003**, *125*, 11514-11515
3. Elizabeth A. Colby and Tomothy F. Jamison; *JOC*, **2003**, *68*, 156-166



1 (R = OH; terpestacin)
3 (R = Ac; fusaproliferin)



2
11-*epi*-terpestacin ("siccanol")

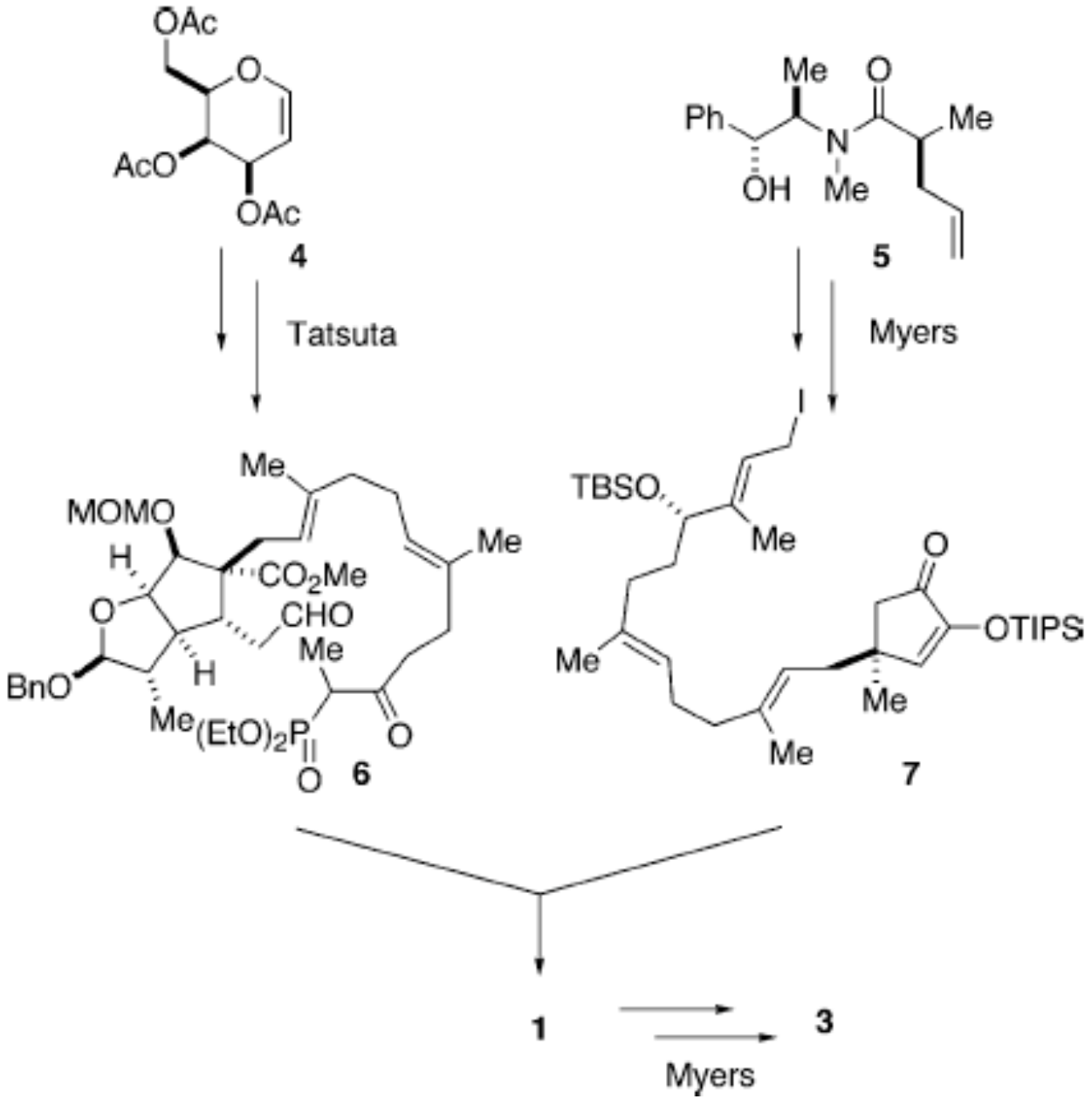
*Bioactivities of terpestacin **1***

- Inhibits the formation of syncytia, giant-multinucleated cell related to HIV infection
- Inhibits angiogenesis

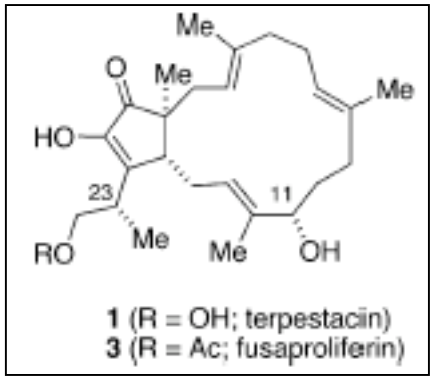
*History of terpestacin **1** and siccanol **2**:*

• **1993** Isolation of **1** (*Arthrinium sp.*)	Oka	$[\alpha]_D$= +26° ($CHCl_3$, 22 °C)
• **1998** Enantiospecific synthesis of **1**	Tatsuta	$[\alpha]_D$= +27° ($CHCl_3$)
• **2001** Isolation of "enantiomer of **1**" *(Ulocladium sp.)*	Gräfe	$[\alpha]_D$= -16.5° ($CDCl_3$, 25 °C)
		$[\alpha]_D$= -21.5° (MeOH, 25 °C)
• **2002** Enantioselective syntheses of **1** & **3**	Myers	$[\alpha]_D$= -17° ($CHCl_3$, 28 °C)
		$[\alpha]_D$= -18° (MeOH, 25 °C)
		Gräfe's discovery is **1** itself
• **2002** Isolation of "siccanol **2**" *(Bipolaris sorokiniana)*	Miyagawa	
• **2003** Enantioselective syntheses of **1** & **2**	Jamison	siccanol **2** is actually terpestacin **1**

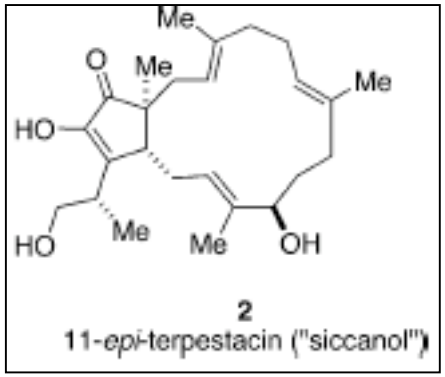
Scheme 1. Previous Enantioselective Syntheses of Terpestacin (**1**) and Fusaproliferin (**3**)



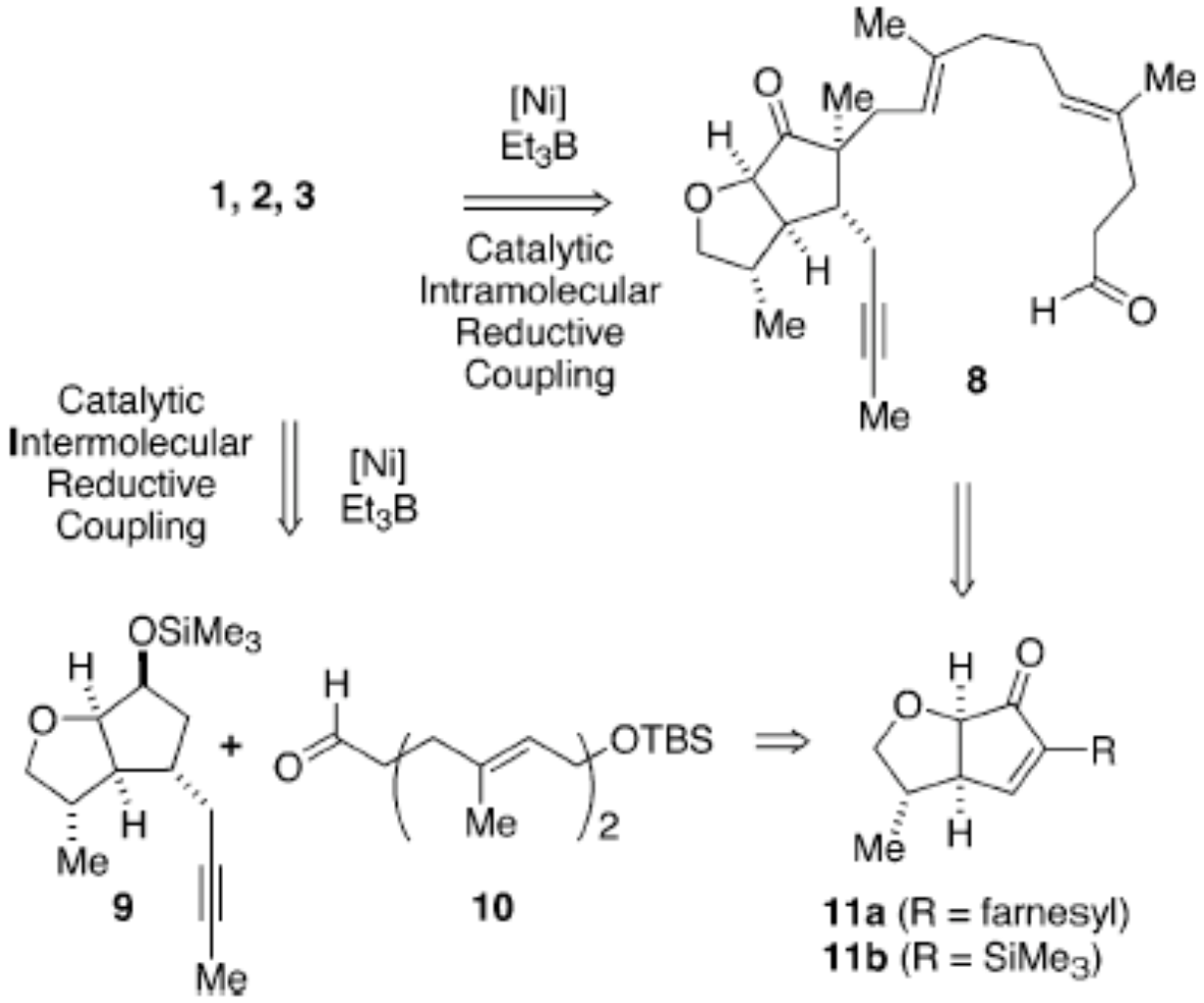
Scheme 3. Nickel-Catalyzed Alkyne–Aldehyde Coupling Strategies



1 (R = OH; terpestacin)
3 (R = Ac; fusaproliferin)

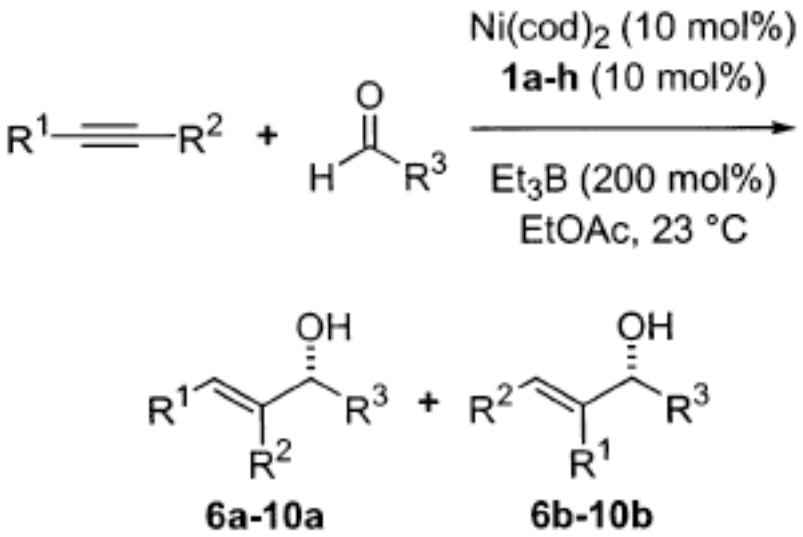


2
11-*epi*-terpestacin ("siccanol")



Johann Chan and Timothy F. Jamison; *JACS*, **2004**, ASAP

Ni-catalyzed Asymmetric Reductive Coupling



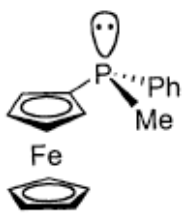
6a,b: $R^1 = c\text{–}C_6H_{11}$, R^2 = Me, $R^3 = i$–Pr

7: $R^1 = R^2 = n$–Pr, R^3 = Ph

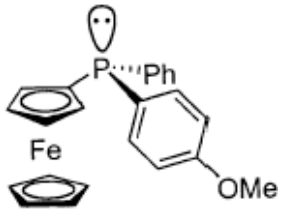
8: $R^1 = R^2 = R^3 = n$–Pr

9: $R^1 = R^2 = n$–Pr, $R^3 = i$–Pr

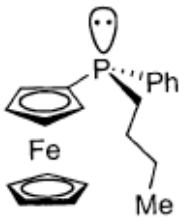
10a,b: $R^1 = c\text{–}C_6H_{11}$, R^2 = Me, $R^3 = n$-Pr



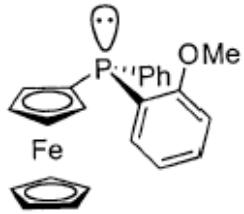
1a



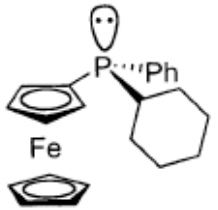
1e



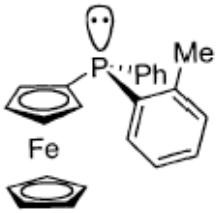
1b



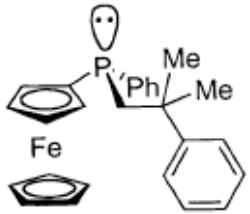
1f



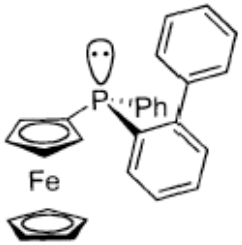
1c



1g

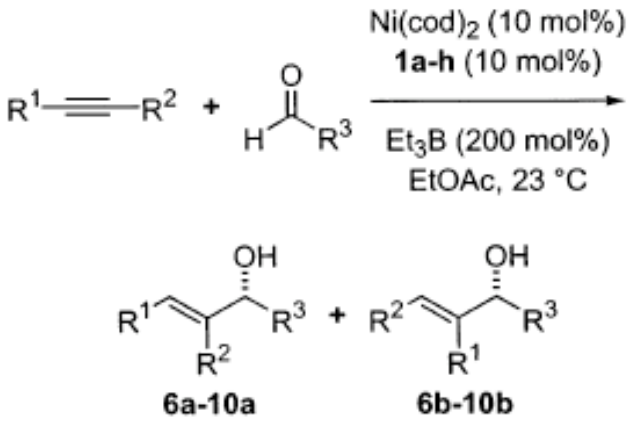


1d



1h

Elizabeth A. Colby and Tomothy F. Jamison; *JOC*, **2003**, *68*, 156-166



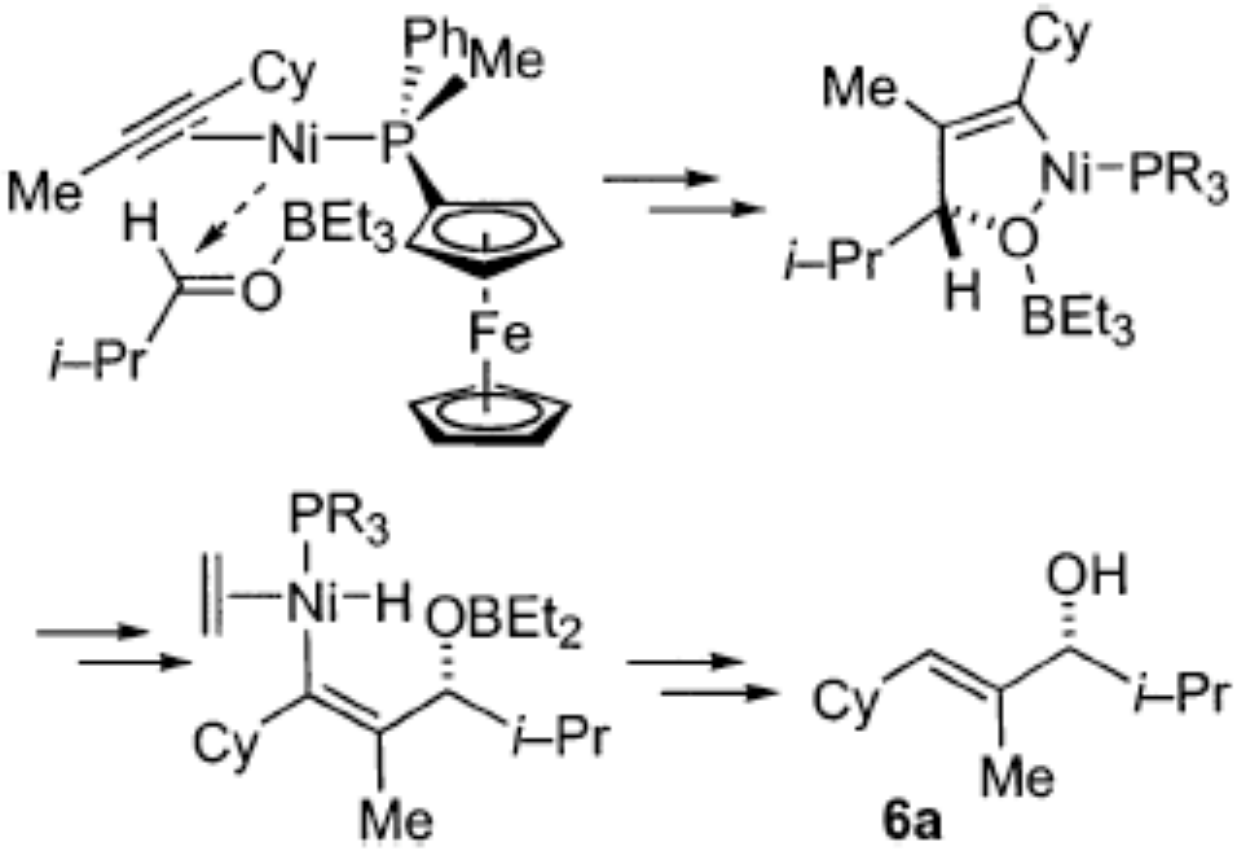
6a,b: $R^1 = c\text{–}C_6H_{11}$, R^2 = Me, $R^3 = i$–Pr
7: $R^1 = R^2 = n$–Pr, R^3 = Ph
8: $R^1 = R^2 = R^3 = n$–Pr
9: $R^1 = R^2 = n$–Pr, $R^3 = i$–Pr
10a,b: $R^1 = c\text{–}C_6H_{11}$, R^2 = Me, $R^3 = n$-Pr

TABLE 2[a]

entry	ligand	product[b]	R^1	R^2	R^3	yield (%)[c]	**a**:**b**[d]	ee **a** (%)[e]	ee **b** (%)[f]
1	Bu_3P	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	55	2.0:1	na	na
2	Ph_2P(*n*-Bu)	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	56	1.9:1	na	na
3	Ph_2P(Cy)	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	62	2.0:1	na	na
4	$FcPPh_2$	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	60	3.0:1	na	na
5	**1a**	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	65	2.2:1	46	45
6	**1b**	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	27	1.8:1	8	12
7	**1c**	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	53	1.6:1	−34	−28
8	**1d**	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	33	1:1	−44	−10
9	**1e**	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	60	2.4:1	2	4
10	**1f**	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	60	3.8:1	−28	−17
11	**1g**	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	46	5.7:1	−55	−19
12	**1h**	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	33	1:1	−52	−37
13	**11**	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	50	2.0:1	−35	−38
14	**12**	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	40	1:1	−20	−17
15	**13**	**6a**, **6b**	*c*-C_6H_{11}	Me	*i*-Pr	22	1.2:1	−35	−39
16	**1a**	**7**	*n*-Pr	*n*-Pr	Ph	85	na	49	na
17	**1c**	**7**	*n*-Pr	*n*-Pr	Ph	80	na	−4	na
18	**1f**	**7**	*n*-Pr	*n*-Pr	Ph	81	na	12	na
19	**1g**	**7**	*n*-Pr	*n*-Pr	Ph	79	na	−28	na
20	**1h**	**7**	*n*-Pr	*n*-Pr	Ph	87	na	−36	na
21	**1a**	**8**	*n*-Pr	*n*-Pr	*n*-Pr	80	na	55	na
22	**1a**	**9**	*n*-Pr	*n*-Pr	i-Pr	80	na	55	na
23	**1a**	**10a**, **10b**	*c*-C_6H_{11}	Me	*n*-Pr	30	2.2:1	67	68

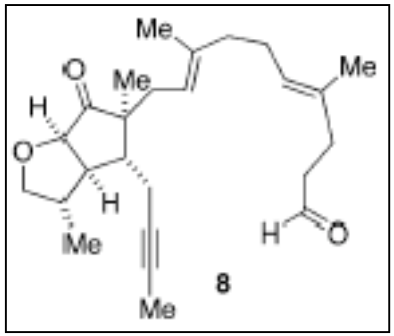
Elizabeth A. Colby and Tomothy F. Jamison; *JOC*, **2003**, *68*, 156-166

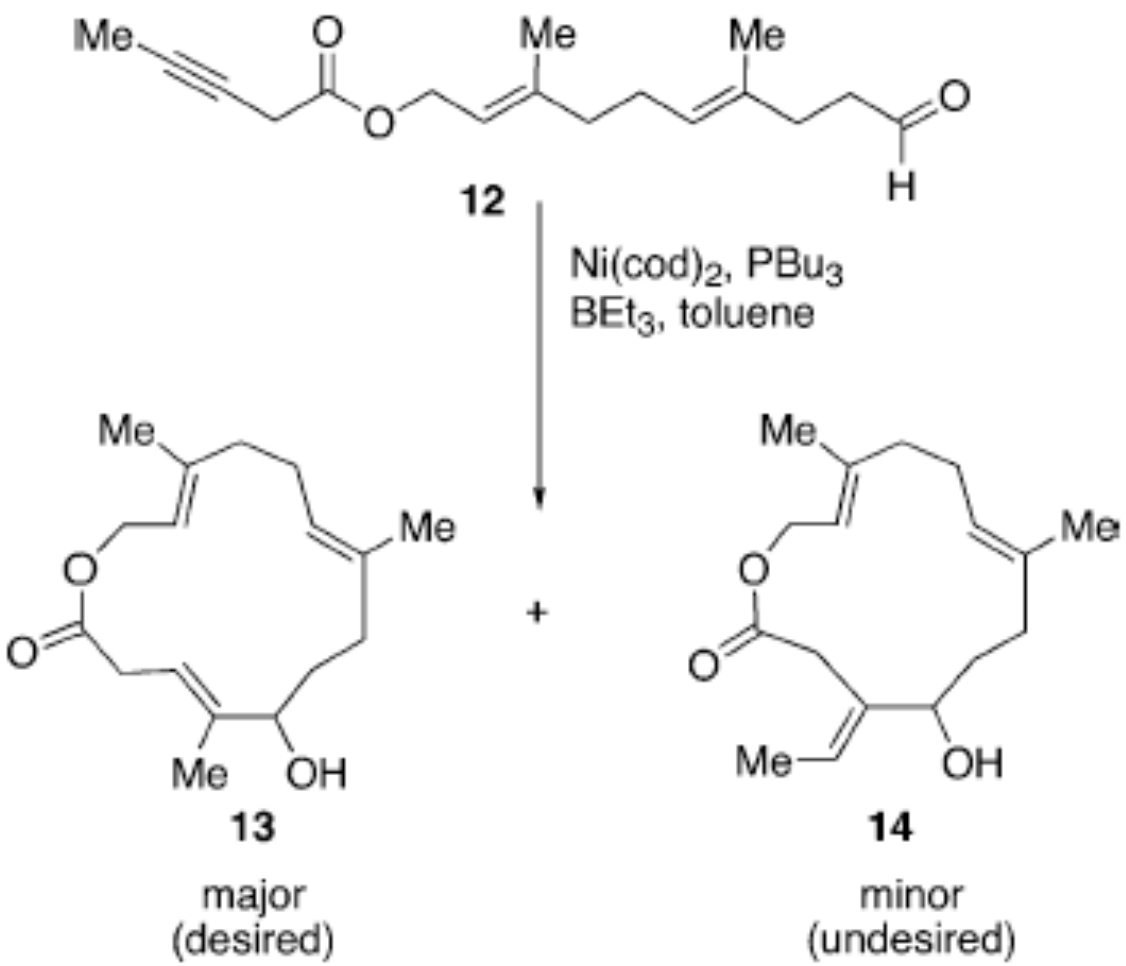
Proposed Mechanism



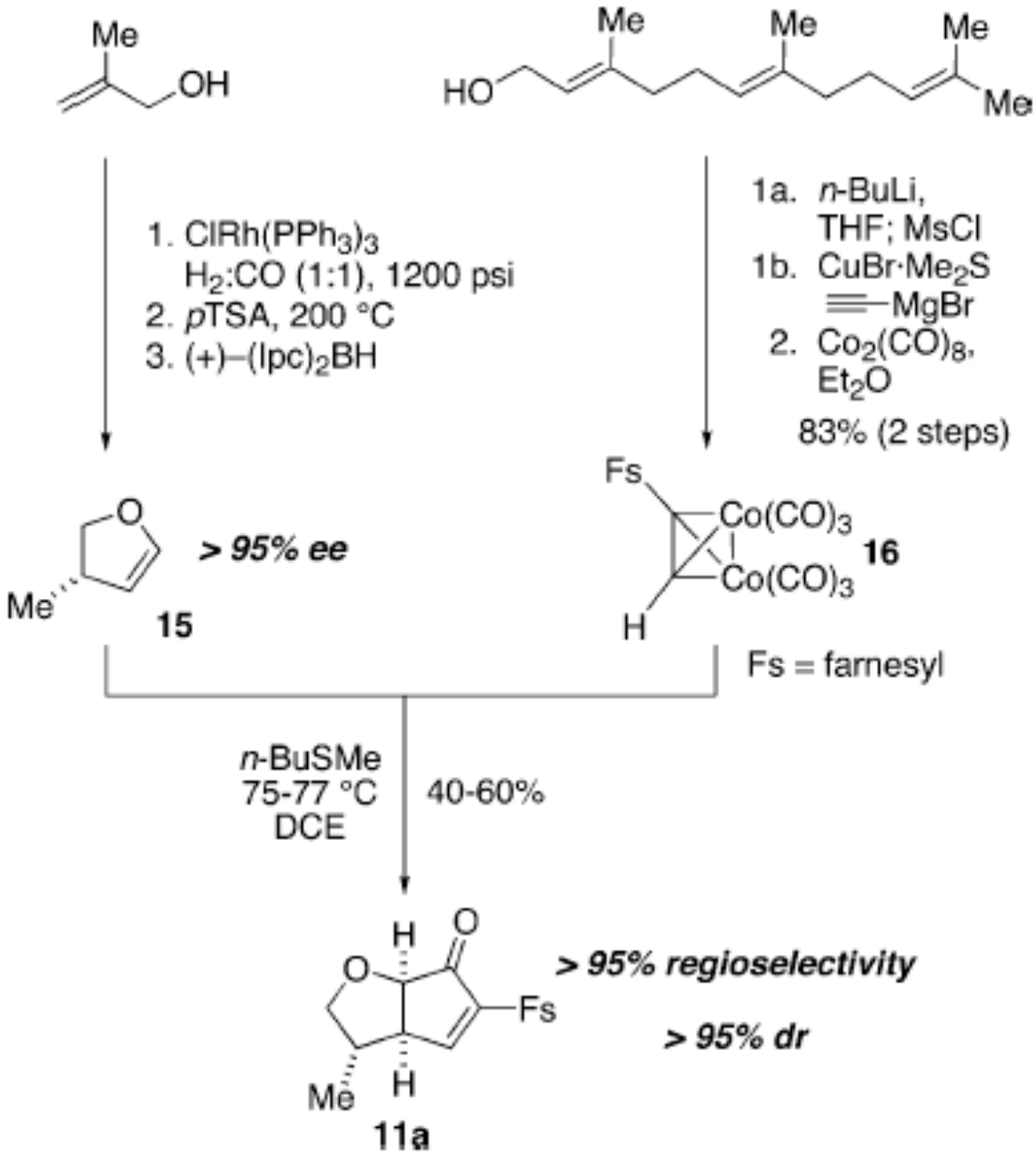
Elizabeth A. Colby and Tomothy F. Jamison; *JOC*, **2003**, *68*, 156-166

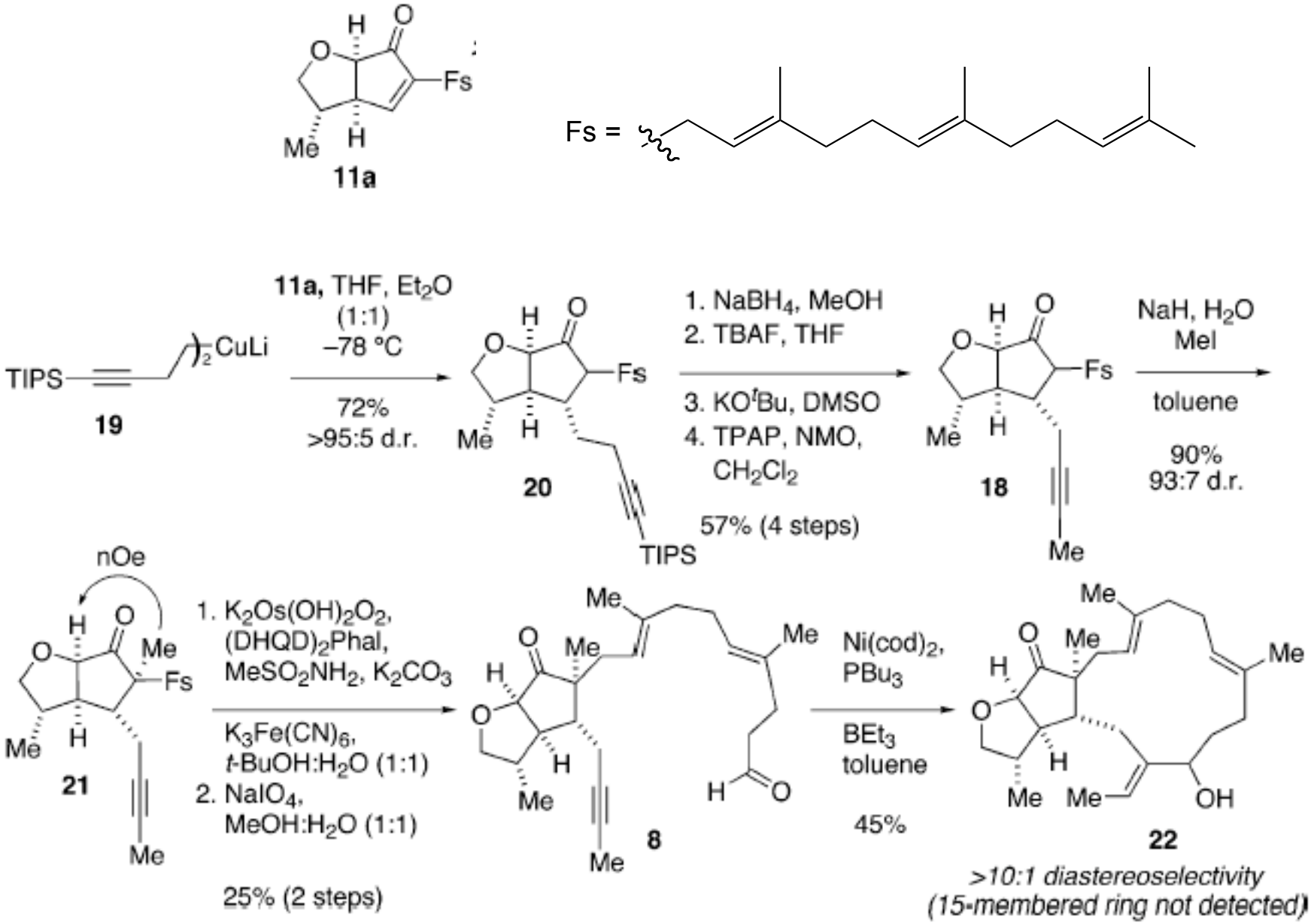
Macrocyclization of Model Substrate 12



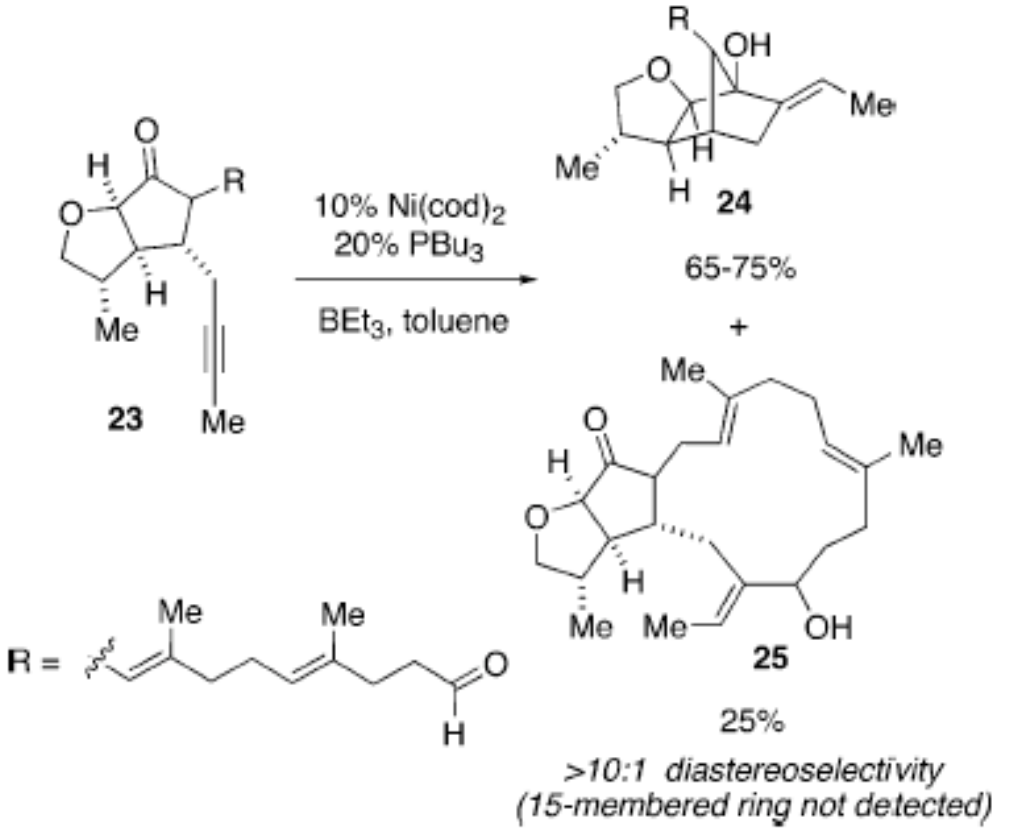


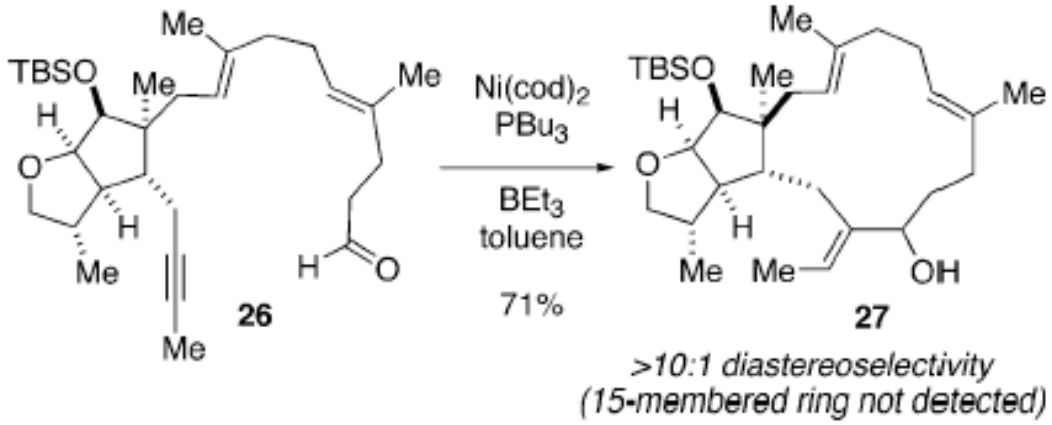
Synthesis of the *cis*-fused 5,5-ring System



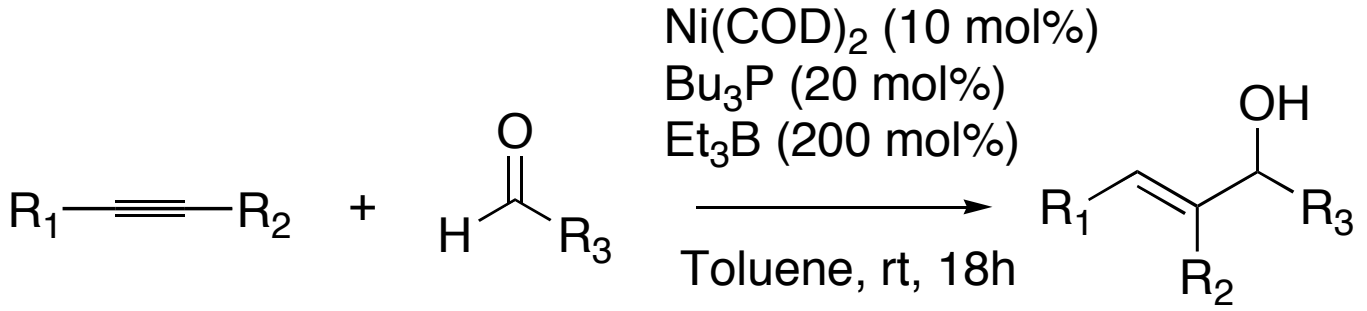

11a
Fs =
11a, THF, Et2O
(1:1)
–78 °C
72%
>95:5 d.r.
19
20
1. NaBH4, MeOH
2. TBAF, THF
3. KOtBu, DMSO
4. TPAP, NMO,
CH2Cl2
57% (4 steps)
18
NaH, H2O
MeI
toluene
90%
93:7 d.r.
nOe
21
1. K2Os(OH)2O2,
(DHQD)2Phal,
MeSO2NH2, K2CO3
K3Fe(CN)6,
t-BuOH:H2O (1:1)
2. NaIO4,
MeOH:H2O (1:1)
25% (2 steps)
8
Ni(cod)2,
PBu3
BEt3
toluene
45%
22
>10:1 diastereoselectivity
(15-membered ring not detected)

Other Attempts on Intramolecular Cyclization





Intermolecular Coupling of Alkynylsilanes

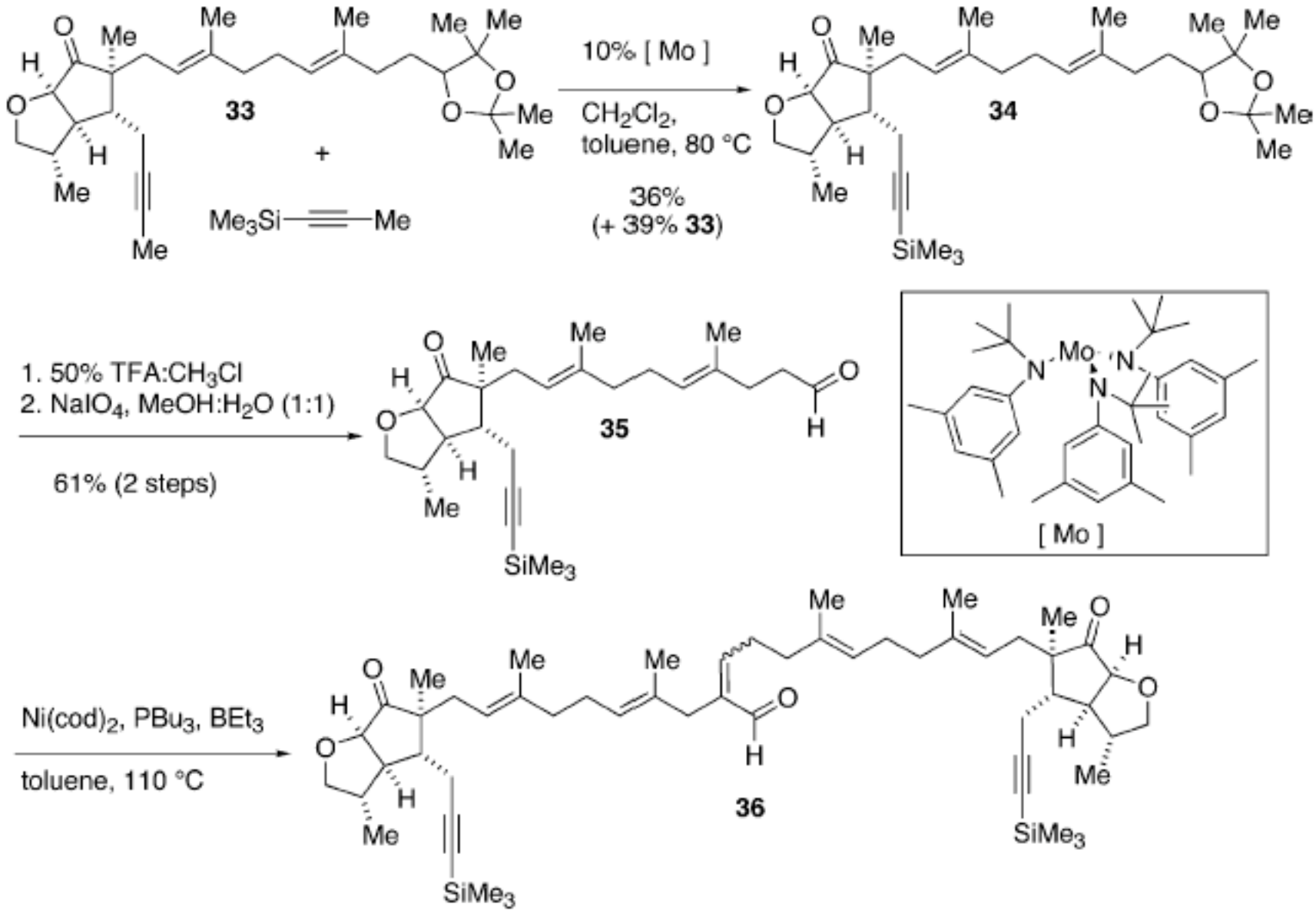


R_1 = Ph, R_2 = $SiMe_3$, R_3 = n-Hept — 89% (> 98:2)

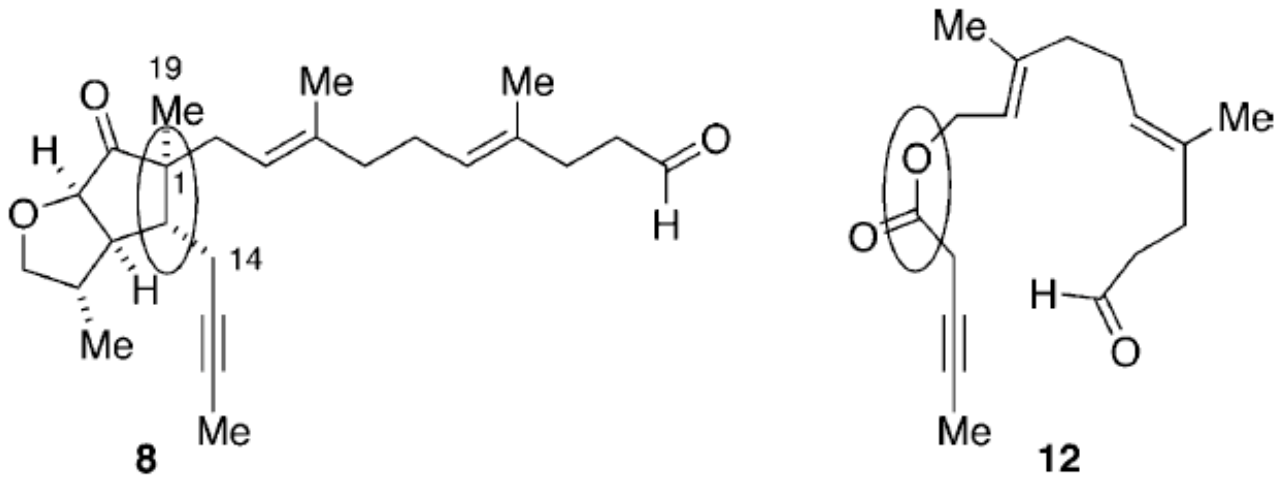
R_1 = n-Bu, R_2 = $SiMe_3$, R_3 = n-Hept — 58% (> 98:2)

Weisheng Huang, Johann Chan and Timothy F. Jamison, *OL*, **2000**, 4221-4223

Intramolecular Cyclization of an Alkynylsilane



Possible Reason for the Failure

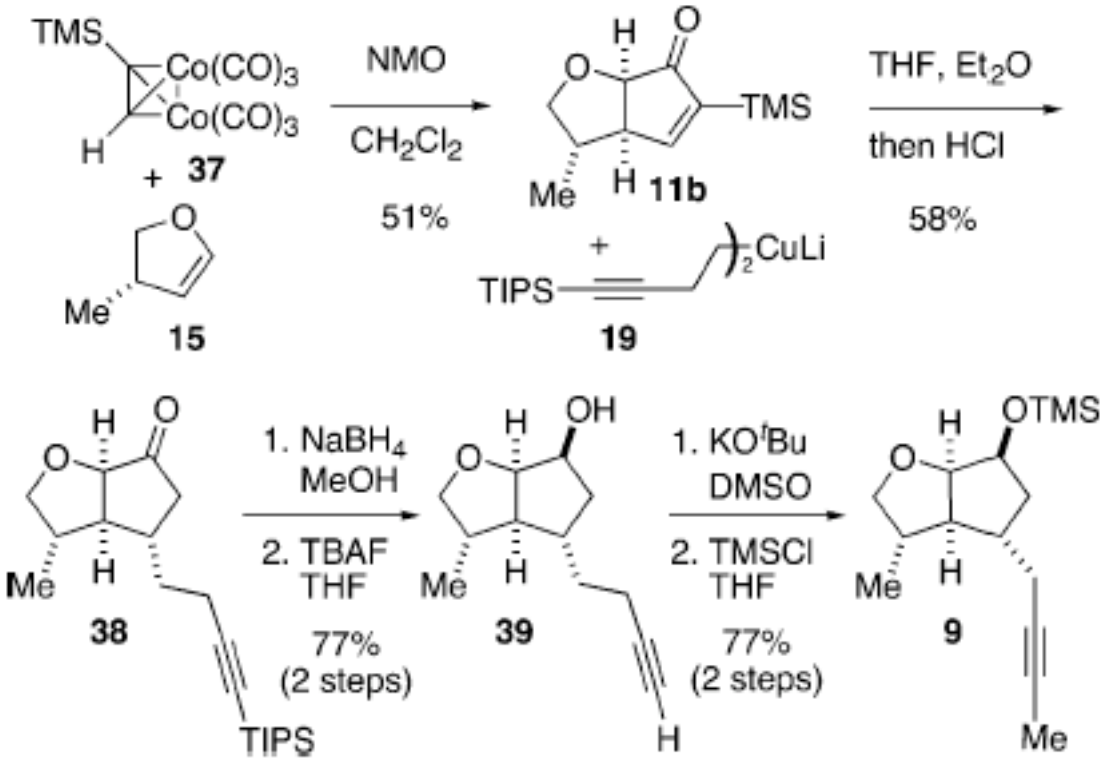


8 12

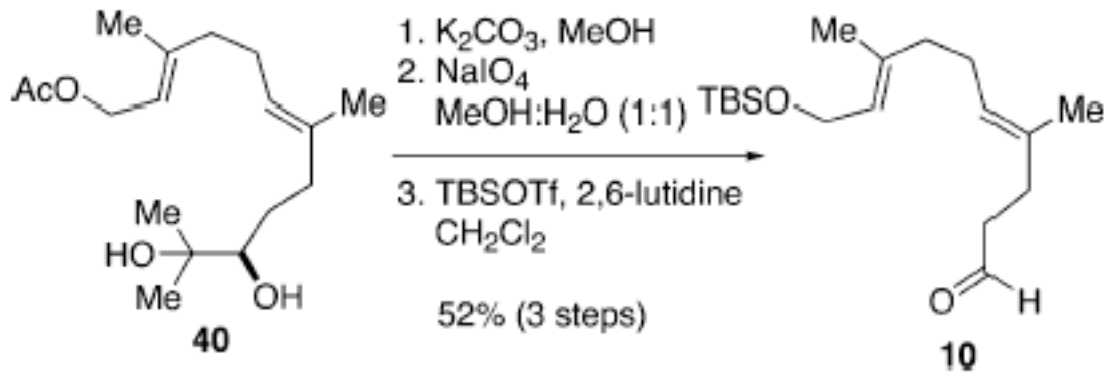
Figure 3. Comparison of **8** to a cyclization model compound (**12**); (*E*)-ester conformer shown for clarity.

Intermolecular Strategy: Synthesis of Fragment 9 and 10

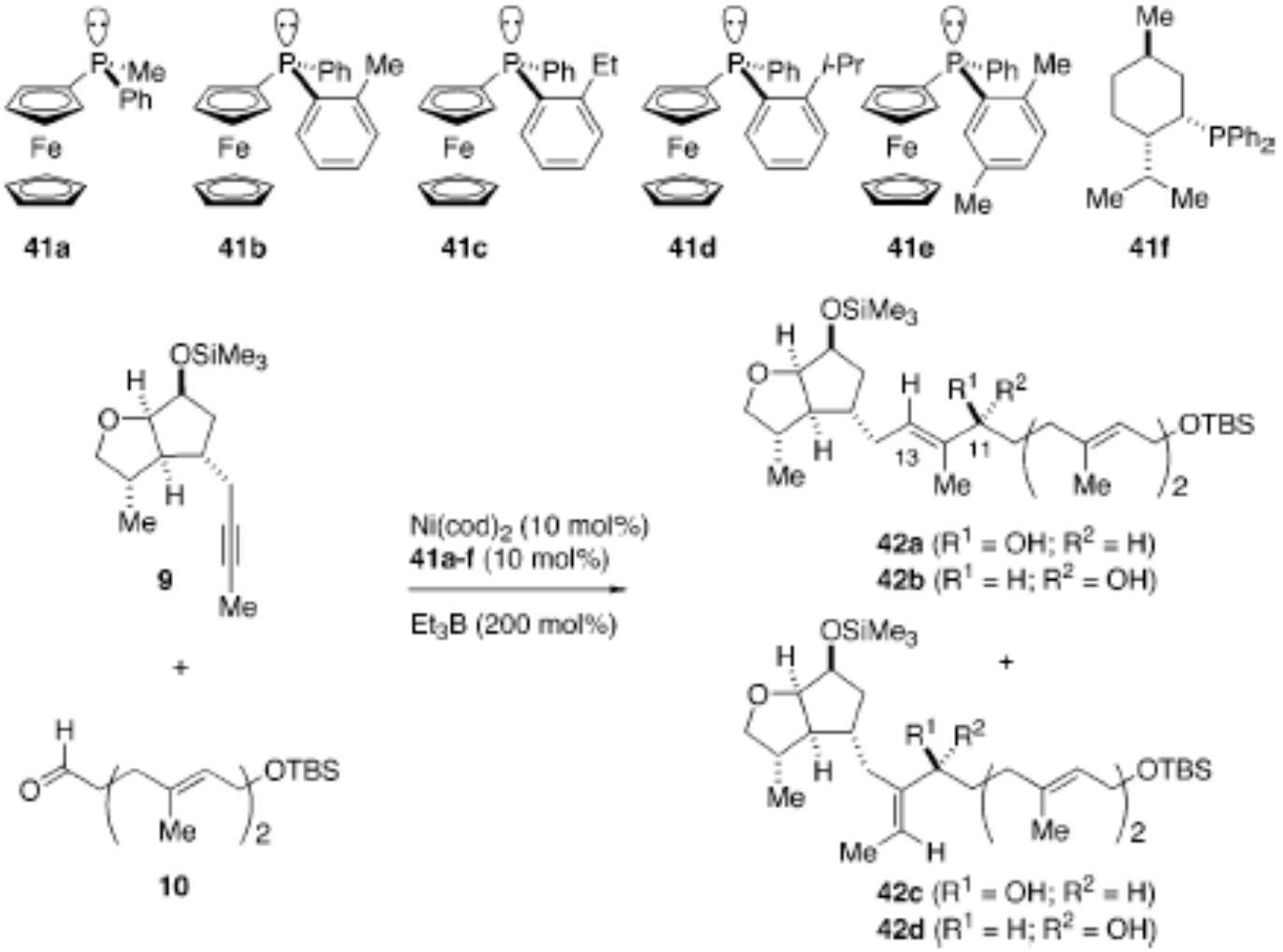
Scheme 12



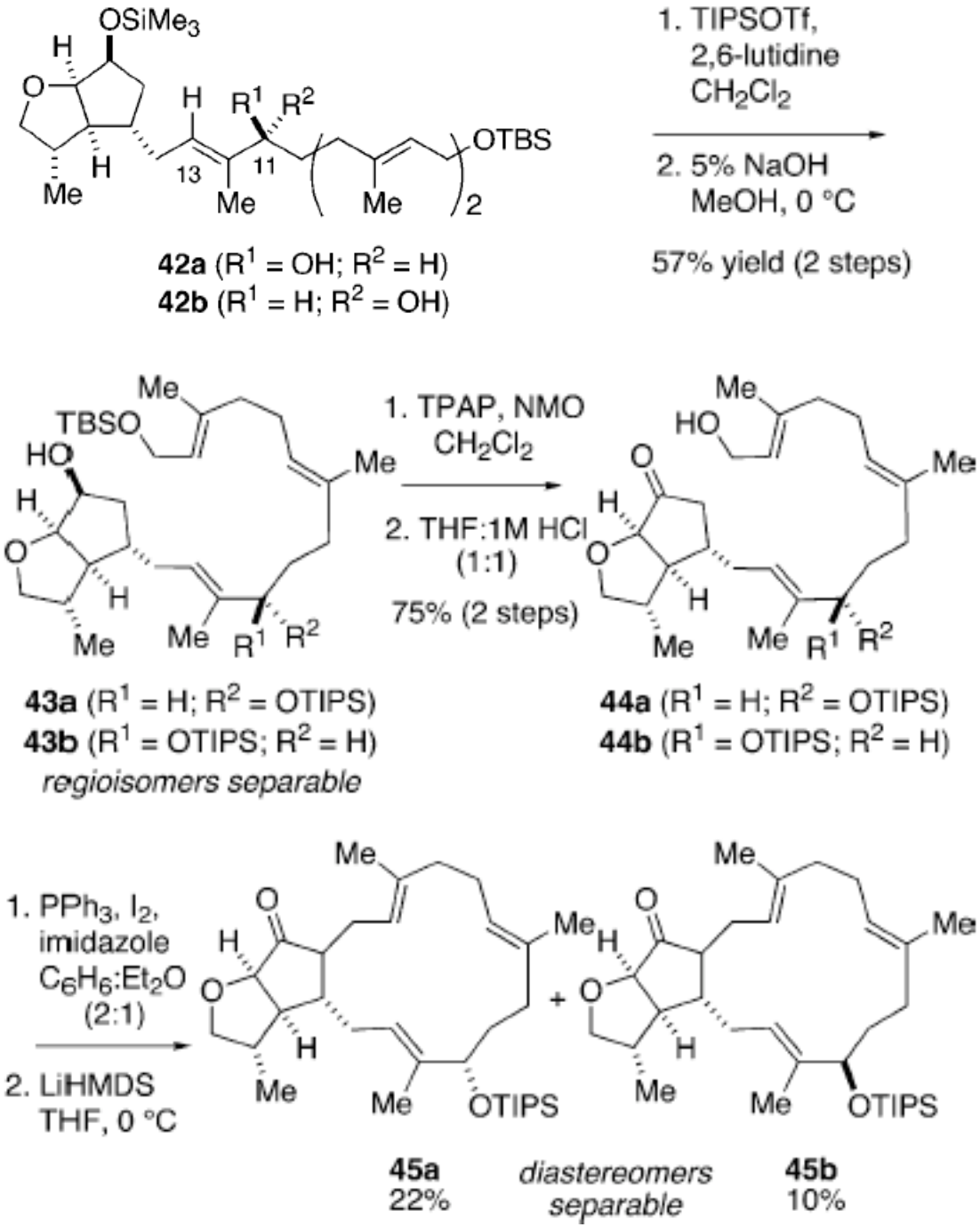
Scheme 13



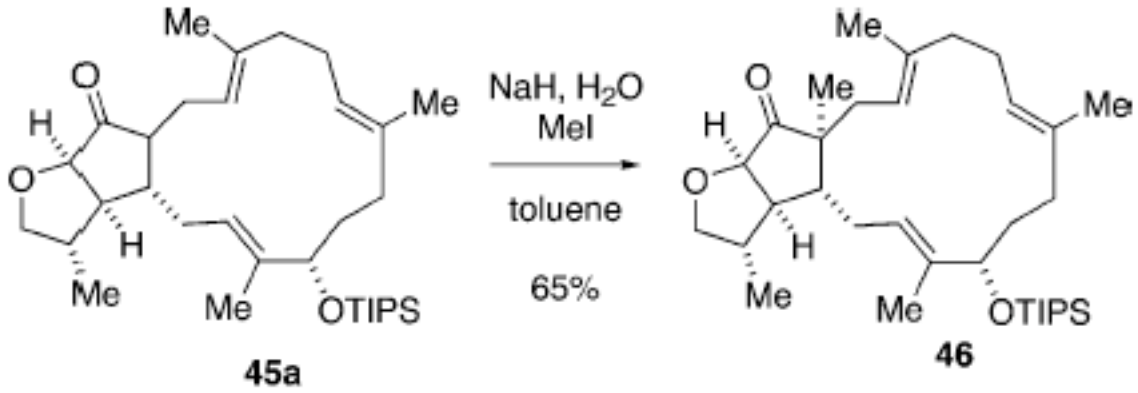
Intermolecular Ni-catalyzed Reductive Coupling



	Diastereoselectivity (**42a**+**42c**/**42b**+**42d**)	Regioselectivity (**42a**+**42b**/**42c**+**42d**)	overall yield
PBu_3	1 : 1	1.5 : 1	
41e	2 : 1	2.6 : 1	85%

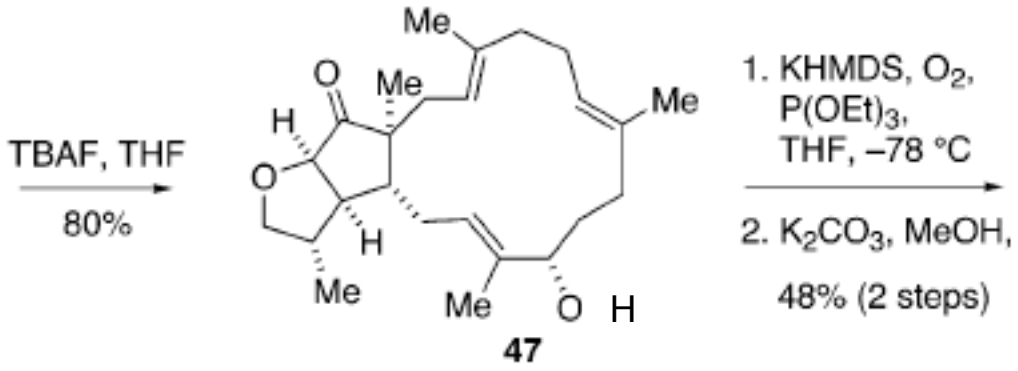

OSiMe3
H
O
H
H
Me
13
11
Me
Me
2
OTBS
1. TIPSOTf,
2,6-lutidine
CH2Cl2
2. 5% NaOH
MeOH, 0 °C
57% yield (2 steps)
42a (R1 = OH; R2 = H)
42b (R1 = H; R2 = OH)
TBSO
HO
1. TPAP, NMO
CH2Cl2
2. THF:1M HCl
(1:1)
75% (2 steps)
HO
43a (R1 = H; R2 = OTIPS)
43b (R1 = OTIPS; R2 = H)
regioisomers separable
44a (R1 = H; R2 = OTIPS)
44b (R1 = OTIPS; R2 = H)
1. PPh3, I2,
imidazole
C6H6:Et2O
(2:1)
2. LiHMDS
THF, 0 °C
45a
22%
diastereomers
separable
45b
10%

Scheme 15

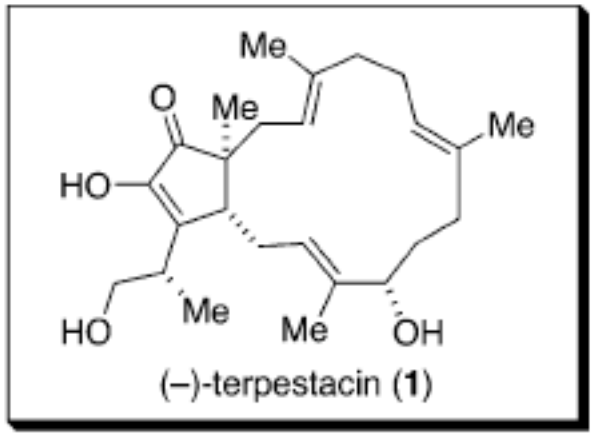


45a **46**

>95:5 diastereoselectivity

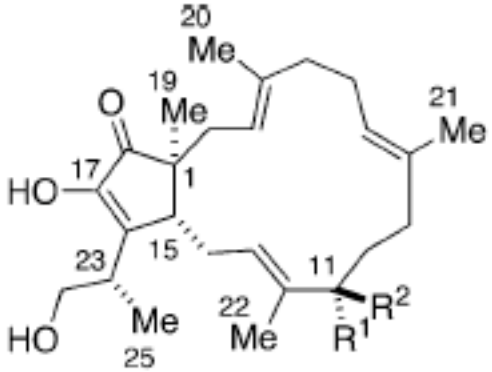


47



(–)-terpestacin (**1**)

h



1 (R^1 = OH; R^2 = H; terpestacin)
2 (R^1 = H; R^2 = OH; 11-*epi*-terpestacin)

carbon	terpestacin (Oka, Myers, Jamison)	11-*epi*-terpestacin (Jamison)	siccanol (Miyagawa)
2	1.68−1.80, 2.40	2.05−2.27	1.75, 2.36
3	***5.25***	***5.34***	***5.25***
5	1.90−2.04, 2.22−2.30	1.98, 2.05−2.27	2.01, 2.24
6	2.09−2.12, 2.22−2.30	2.05−2.27	2.11, 2.26
7	5.14	5.13	5.13
9	1.68−1.80, 2.09−2.12	1.70−1.88, 2.05−2.27	1.78, 2.18
10	1.68−1.80	1.70−1.88	1.70, 1.75
11	4.06	4.06	4.07
13	***5.41***	***5.50***	***5.38***
14	1.90−2.04, 2.45	1.70−1.88, 2.50	1.92, 2.44
15	***2.72***	***2.57***	***2.72***
19	***1.01***	***1.13***	***0.99***
23	2.68	2.7	2.66
24	3.83, 3.90	3.83, 3.89	3.80, 3.85
25	1.29	1.30	1.29