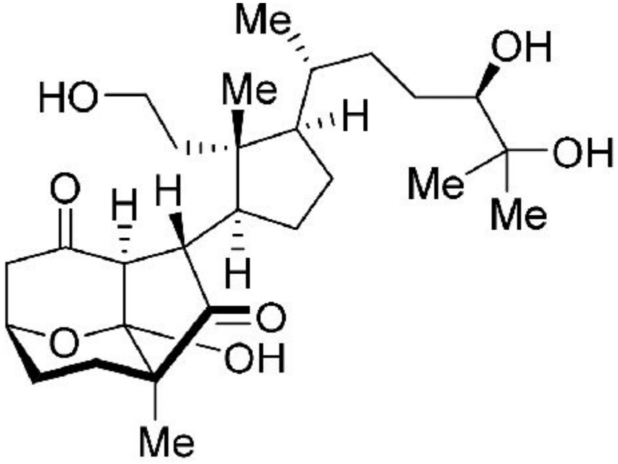
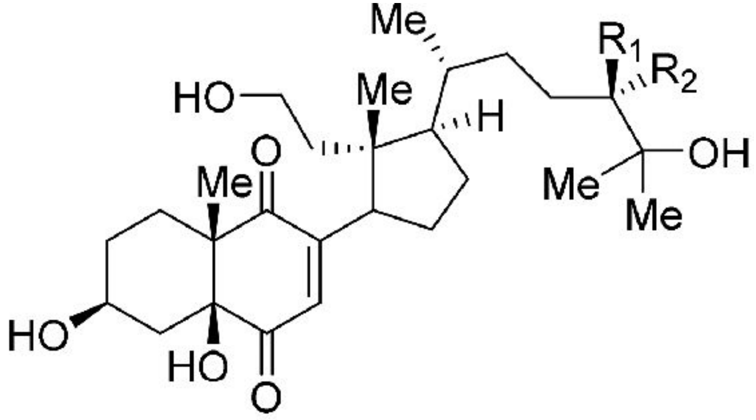
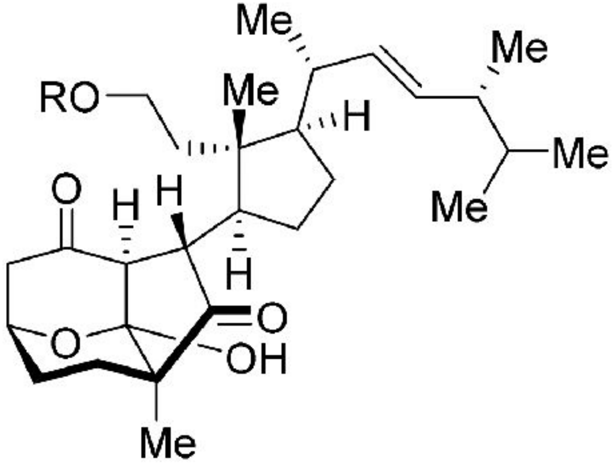
Total Synthesis of Aplysiasecosterol A



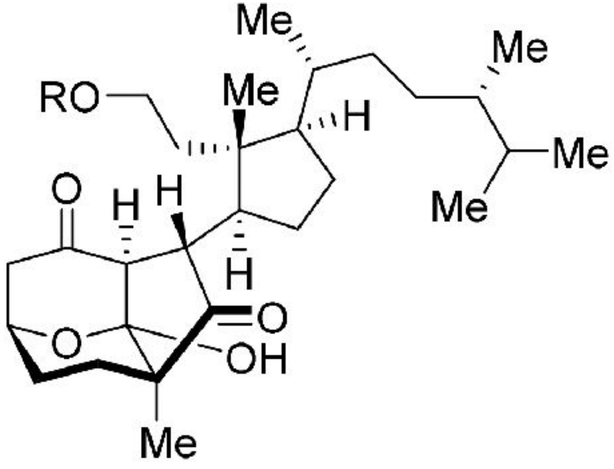
1: aplysiasecosterol A



2: R_1 = OH, R_2 = H; aplysiasecosterol B
3: R_1 = H, R_2 = OH; aplysiasecosterol C



4: R = H; pinnigorgiol A
6: R = Ac; pinnigorgiol D



5: R = H; pinnigorgiol B
7: R = Ac; pinnigorgiol E

Figure 1. Aplysiasecosterol A (1) and related secosteroids.

Figure 2. Retrosynthetic analysis of aplysiasecosterol A (1).

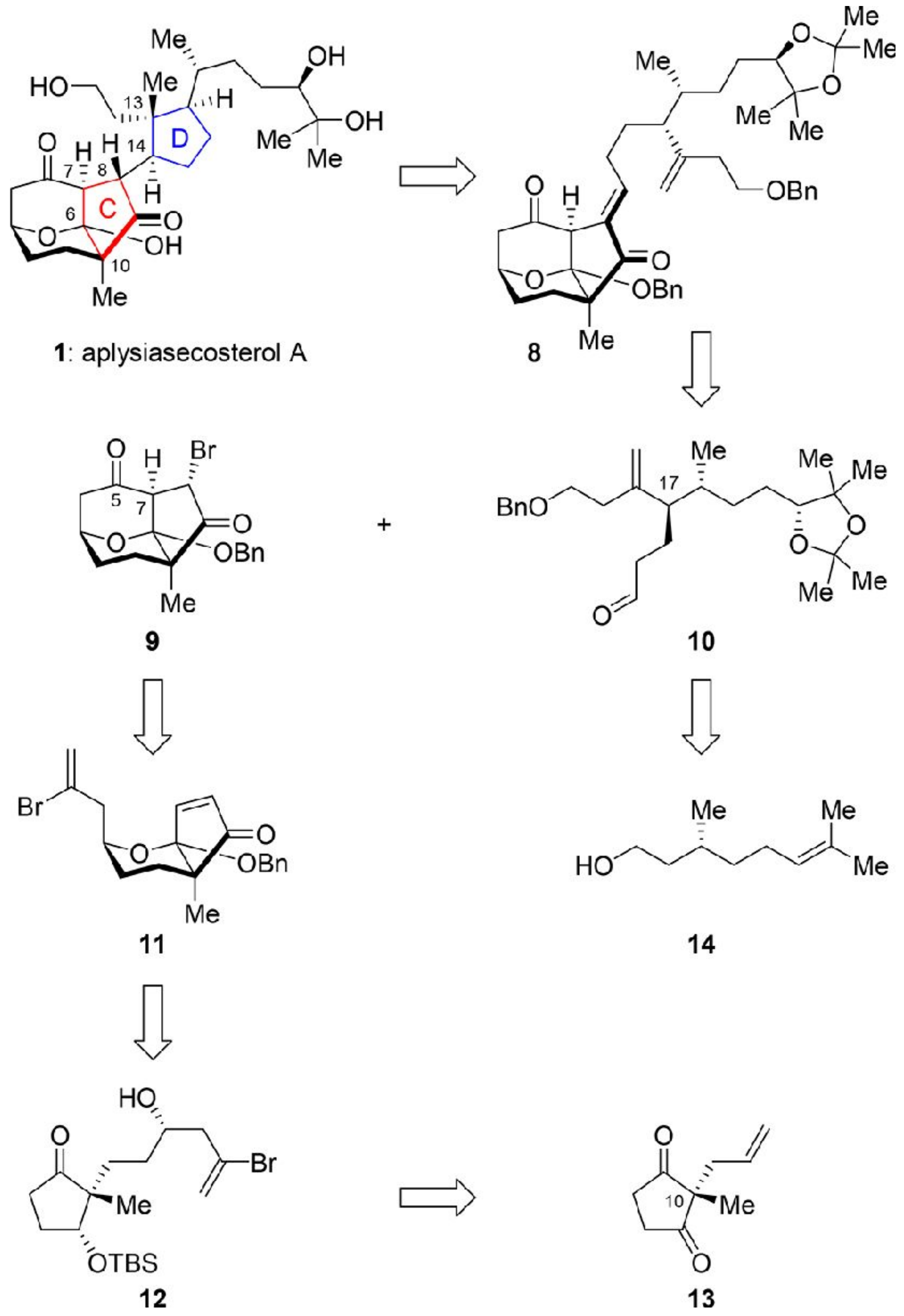
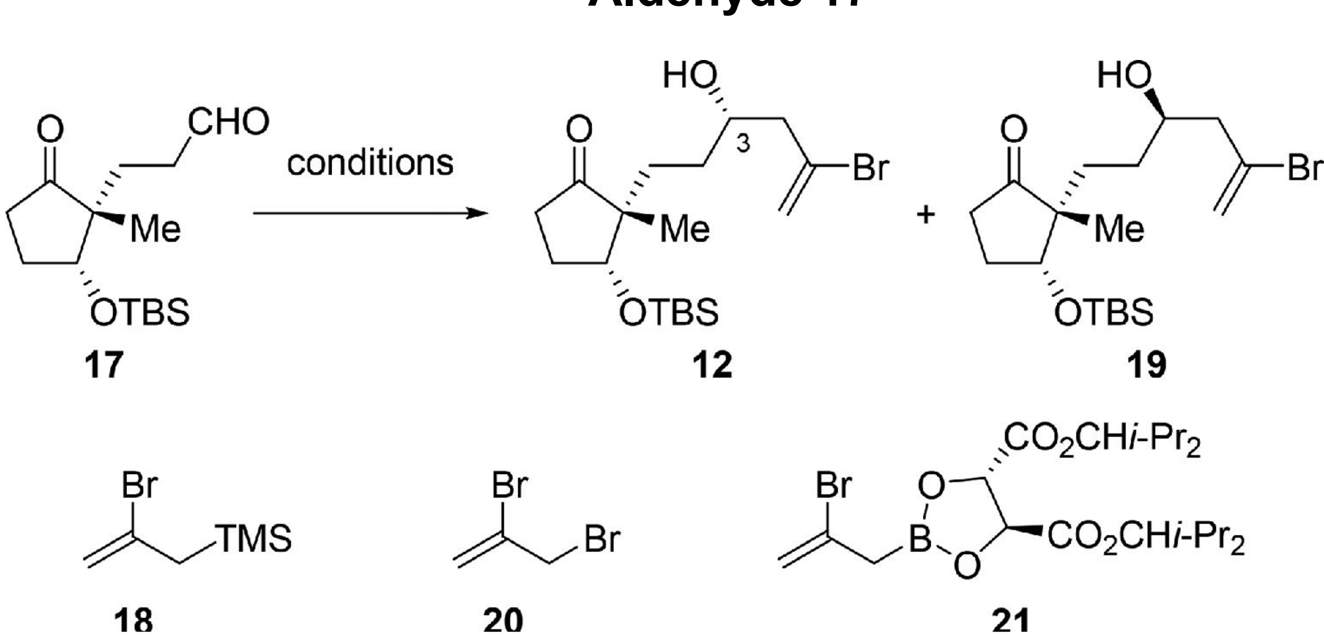


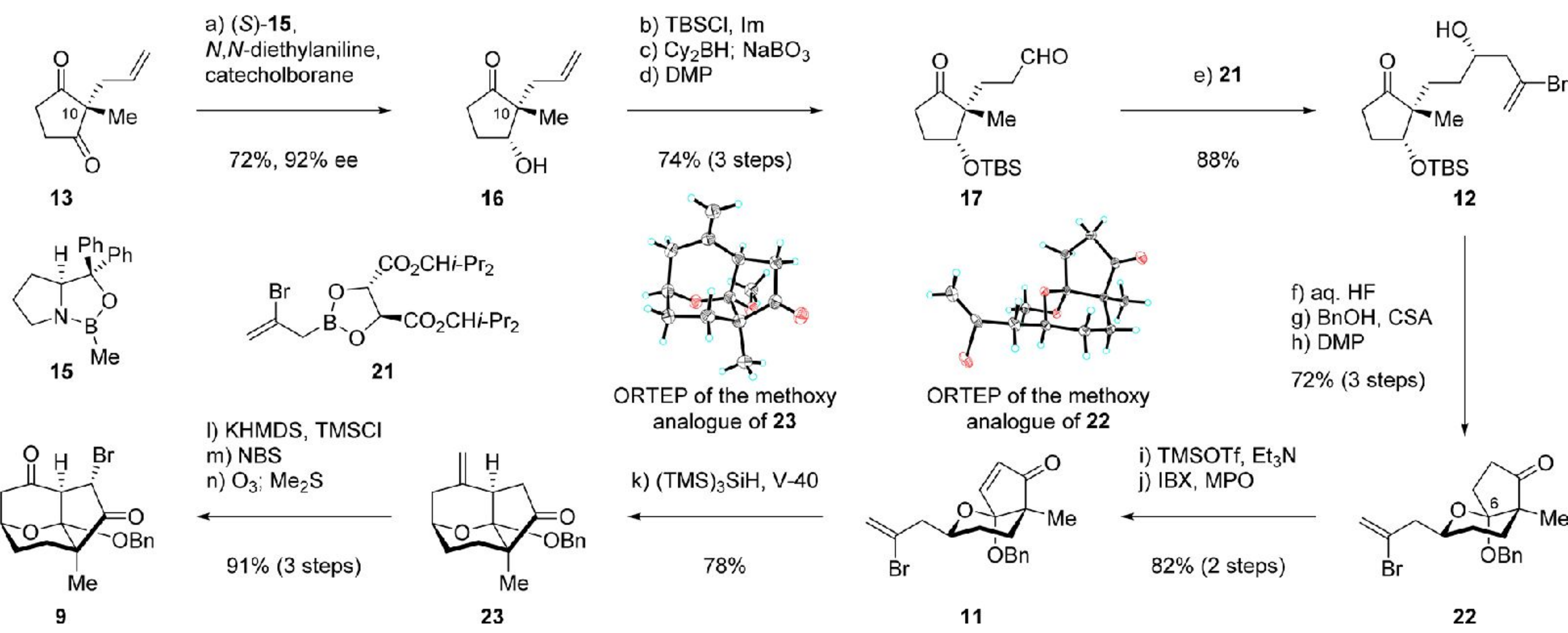
Table 1. Studies of 2-Bromoallylation of Aldehyde 17



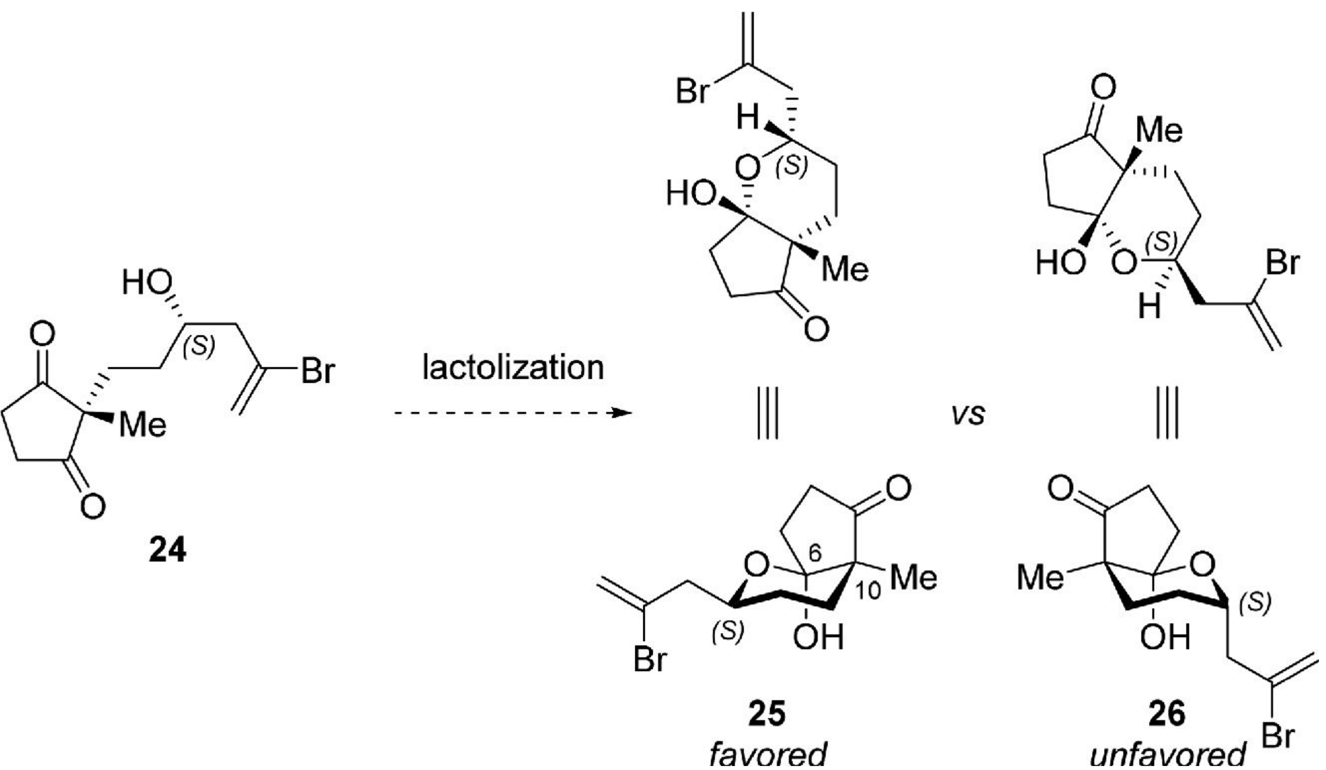
entry	conditions	yield of 12	yield of 19
1	$TiCl_4$, 18, CH_2Cl_2, −78 to 22 °C, 3 h	13%	14%
2[a]	$CrCl_2$, LiI, 20, THF, 22 °C, 2.5 h	16%	18%
3[b]	In, $La(OTf)_3$, 20, aq. NH4Cl, 22 °C, 5 h	18%	18%
4	Sn, 20, TBAI, aq. HCl, Et_2O, 22 °C, 3 h	31%	33%
5[a]	21, toluene/pentane, −95 °C, 2 h	88%	9%

[a]4 Å molecular sieves. [b]Sonication.

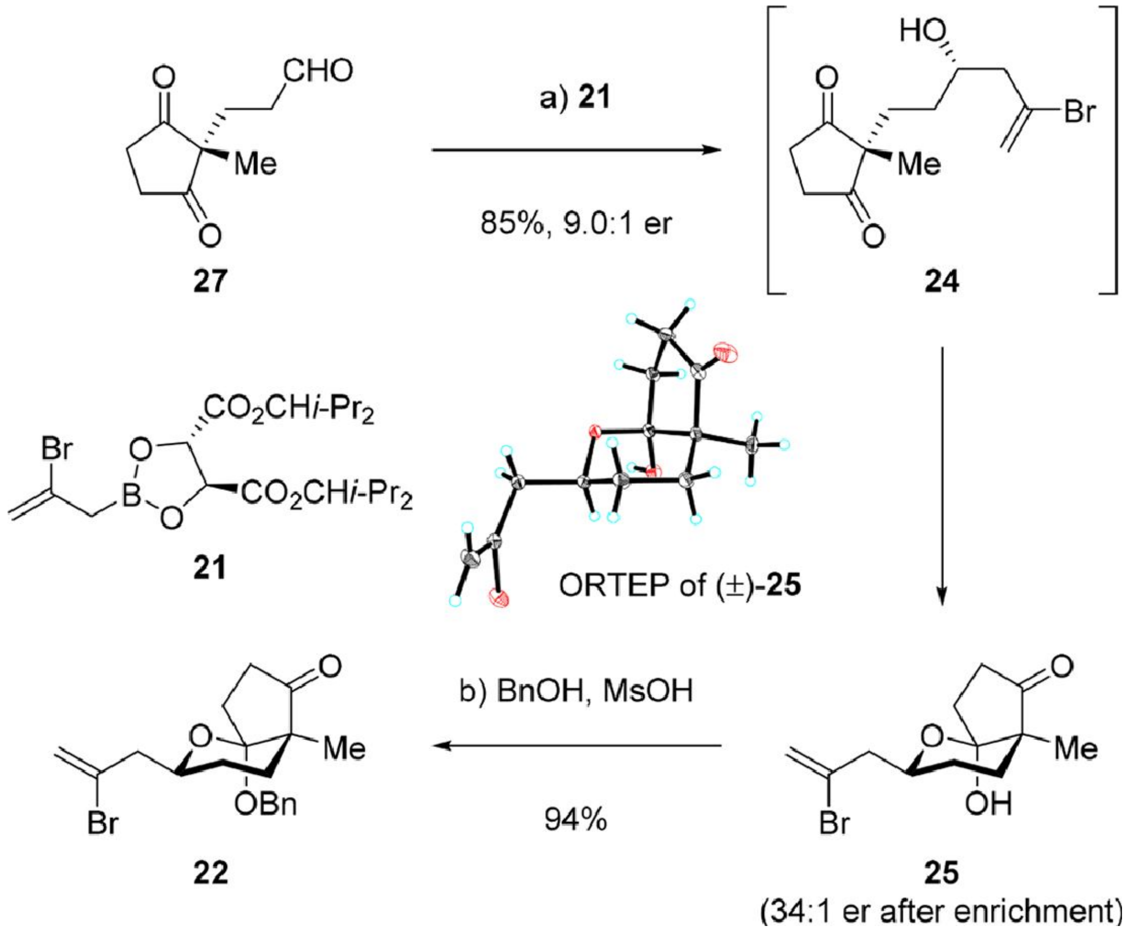
Scheme 1. Preparation of the Left-Hand Segment 9



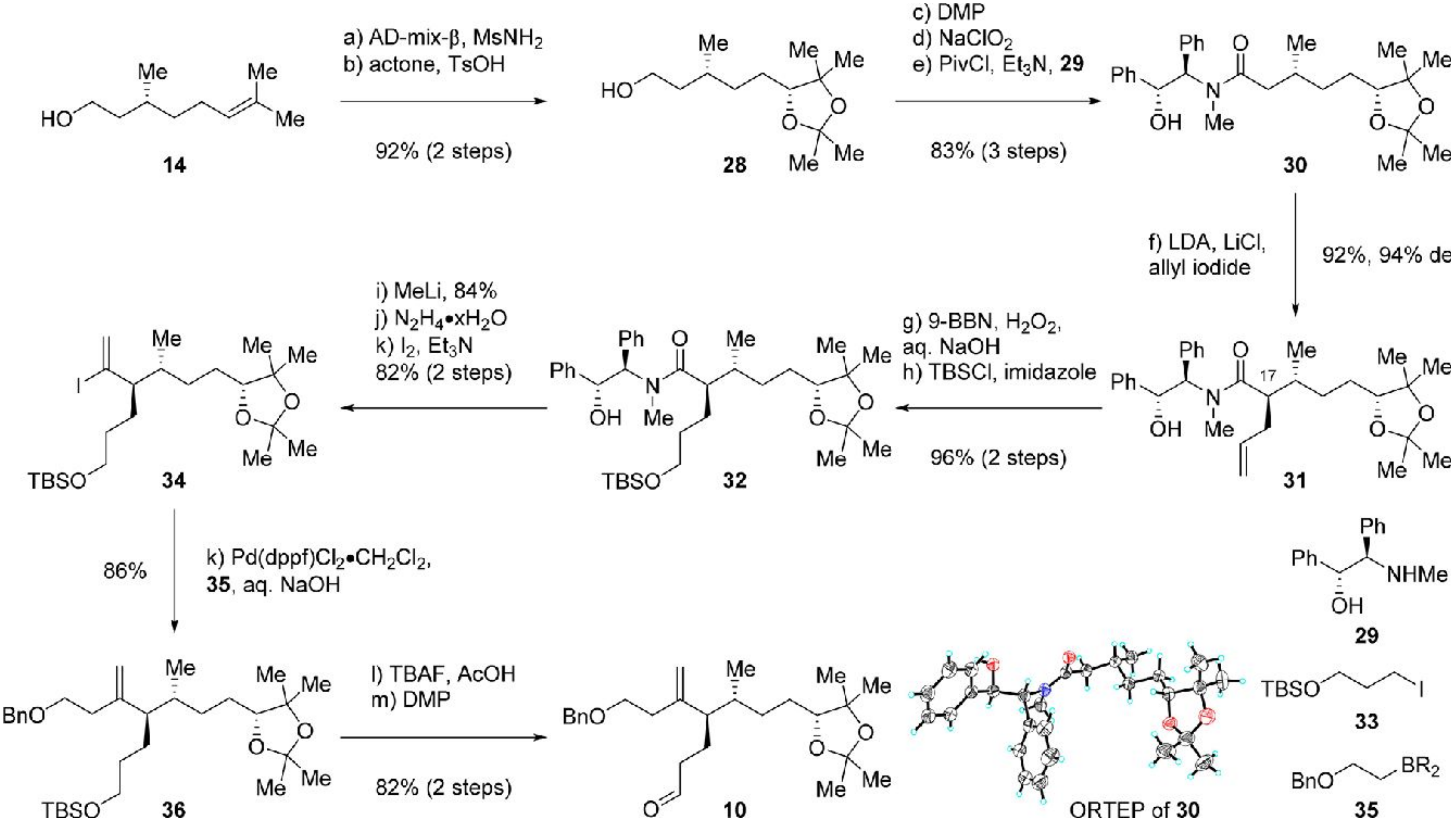
Scheme 2. Devised Desymmetrizing Lactolization Process



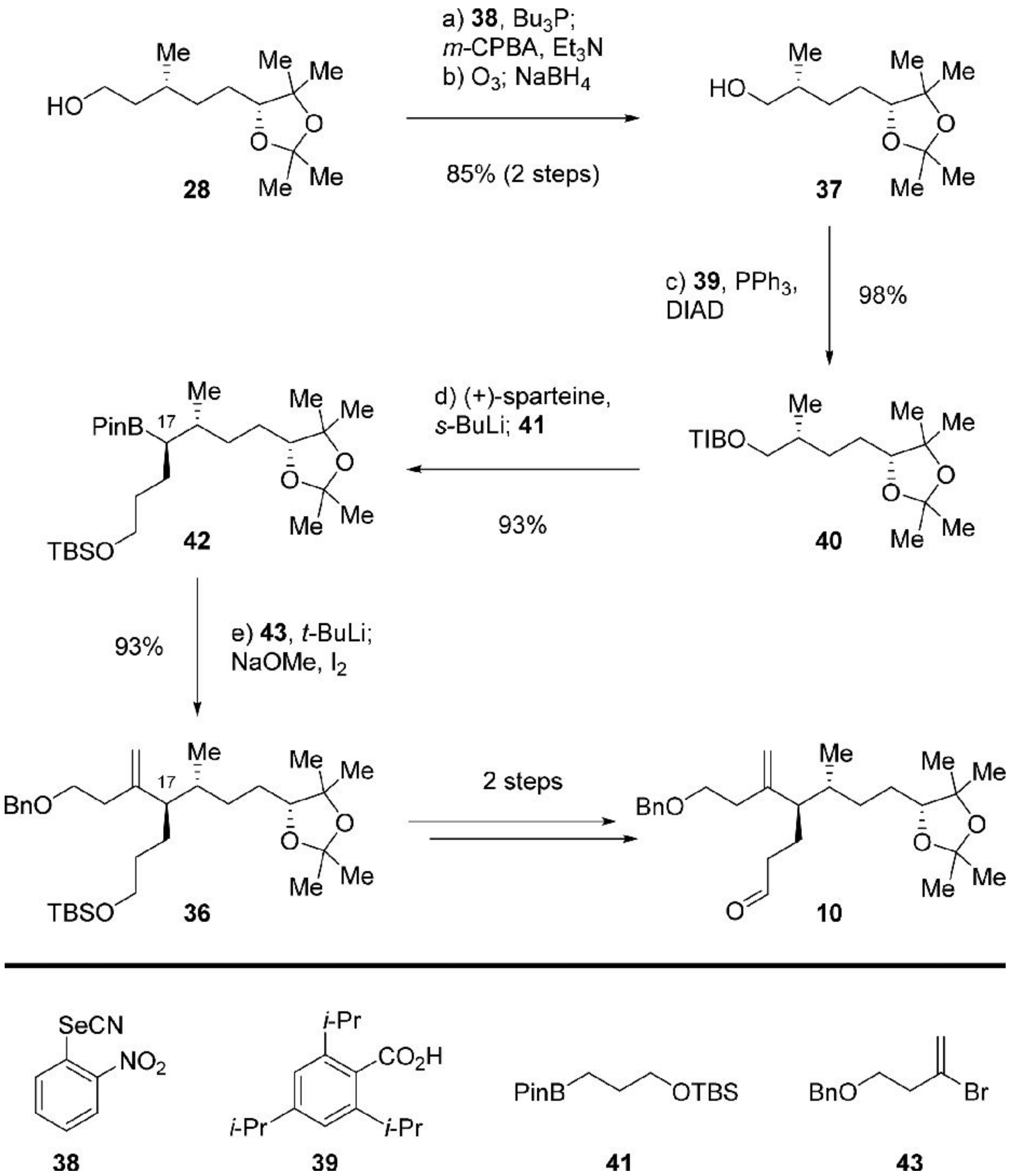
Scheme 3. Two-Step Synthesis of 22



Scheme 4. First Route to the Right-Hand Segment 10



Scheme 5. Second Route to the Right-Hand Segment 10



Scheme 6. Completion of the Synthesis of Aplysiasecosterol A (1)

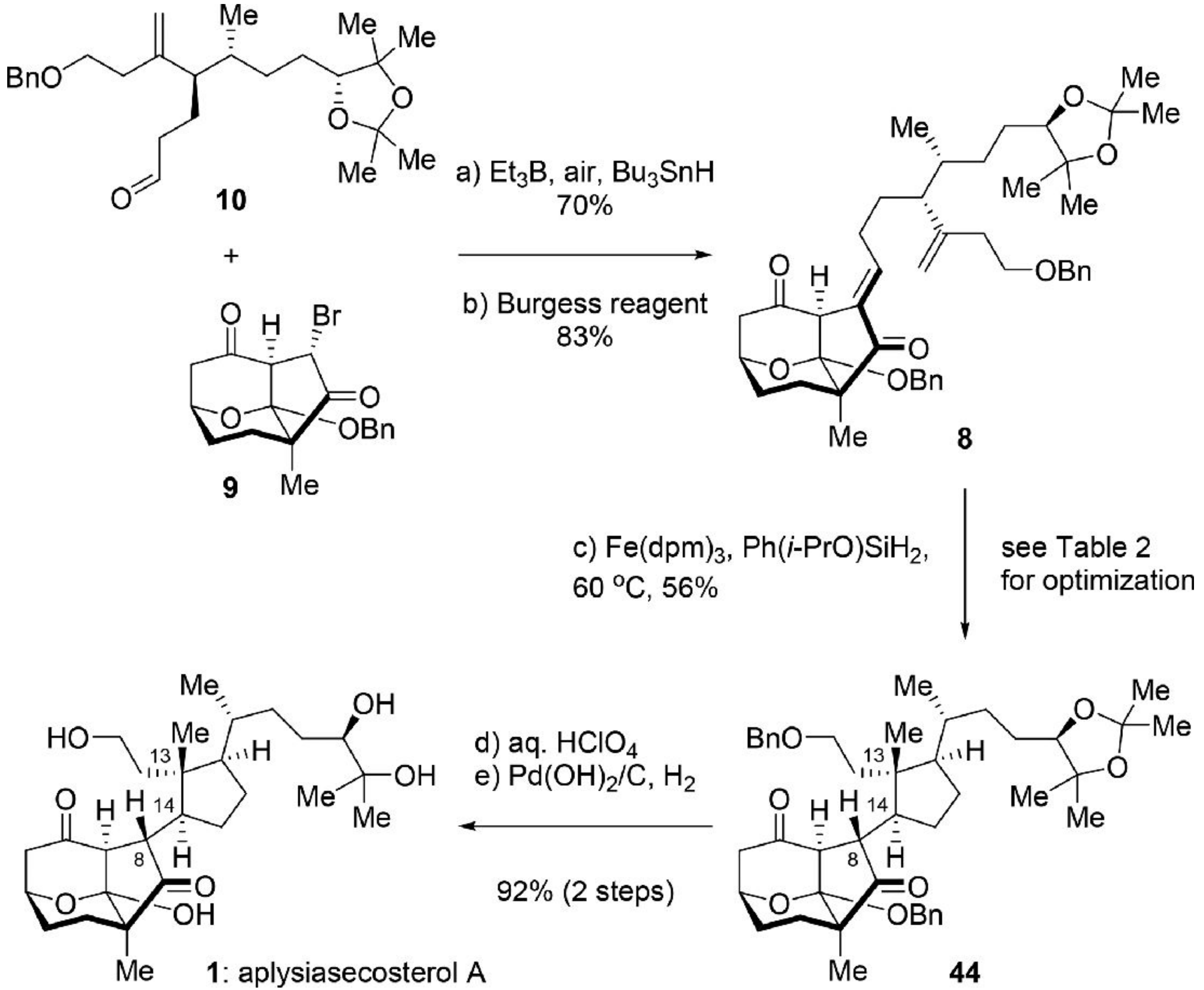
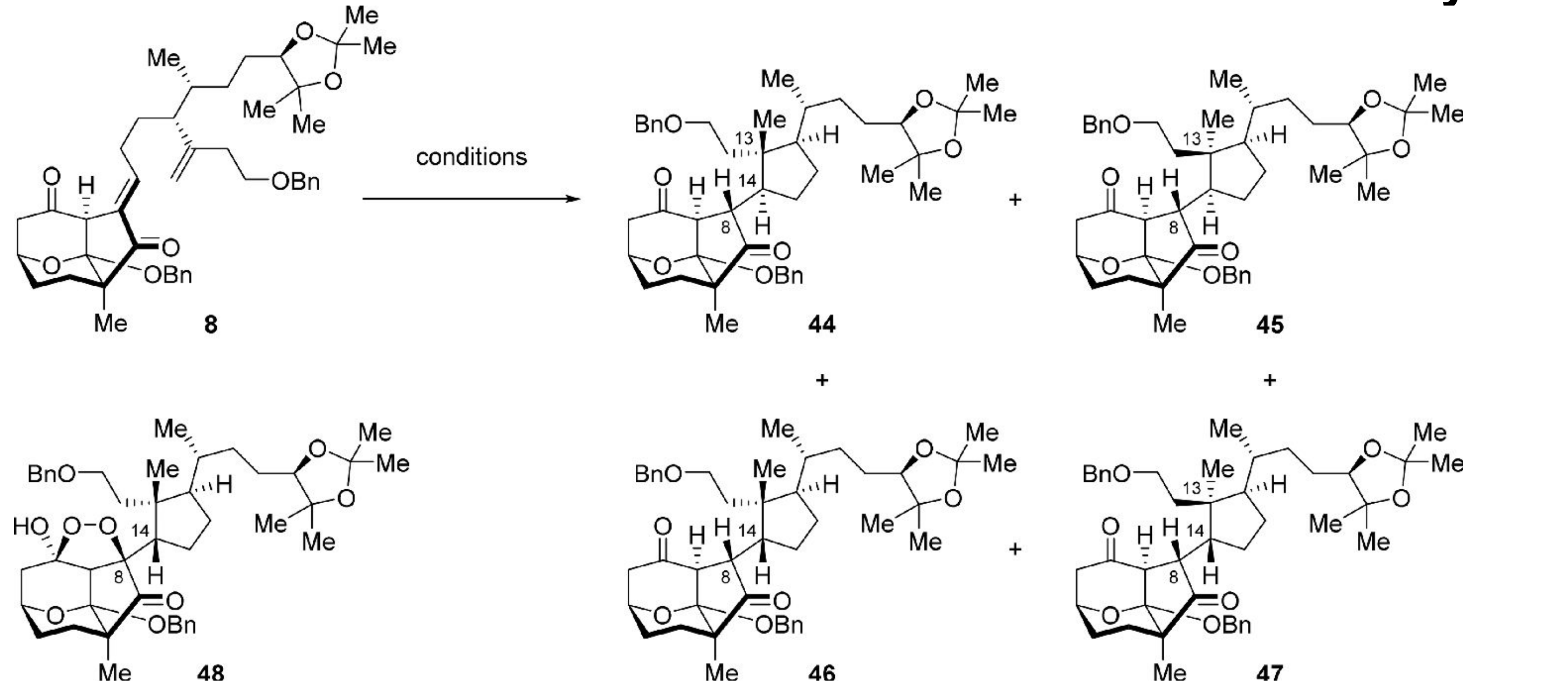


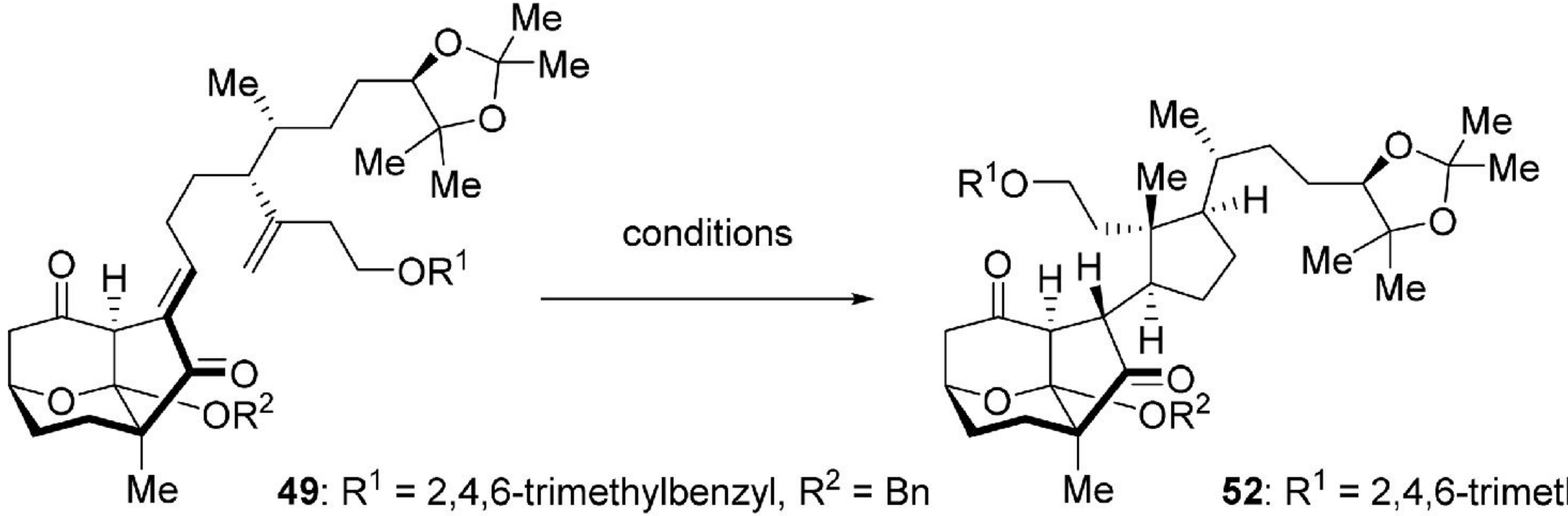
Table 2. Conditions for the HAT Based Radical Cyclization of 8



entry	conditions[a]	yield of mixture	yield of 44	ratio[b] (44:45:46:47)
1[c]	$Fe(acac)_3$, $PhSiH_3$, $EtOH/(CH_2OH)_2$, 60 °C	60%	25%	1:0.33:0.47:0.58
2[c]	$Fe(acac)_3$, $PhSiH_3$, $EtOH/(CH_2OH)_2$, 60 °C	70%	30%	1:0.33:0.46:0.59
3[d]	$Fe(acac)_3$, Ph(i-PrO)SiH_2, $EtOH/(CH_2OH)_2$, 22 °C	41%	21%	1:0.33:0.21:0.39
4[d]	$Fe(acac)_3$, Ph(i-PrO)SiH_2, $EtOH/(CH_2OH)_2$, 50 °C	60%	27%	1:0.35:0.38:0.51
5[d]	$Fe(acac)_3$, Ph(i-PrO)SiH_2, $EtOH/(CH_2OH)_2$, 60 °C	84%	44%	1:0.29:0.29:0.32
6[d]	$Fe(acac)_3$, Ph(i-PrO)SiH_2, $EtOH/(CH_2OH)_2$, 70 °C	90%	36%	1:0.34:0.55:0.57
7[d]	Fe2$(ox)_3$·6H2O, Ph(i-PrO)SiH_2, $EtOH/(CH_2OH)_2$, 60 °C	22%	17%	1:0.18:0:0.09
8[e]	$Fe(dibm)_3$, Ph(i-PrO)SiH_2, $EtOH/(CH_2OH)_2$, 60 °C	75%	47%	1:0.25:0.14:0.19
9[e,f]	$Fe(dpm)_3$, Ph(i-PrO)SiH_2, $EtOH/DCE/(CH_2OH)_2$, 60 °C	77%	56%	1:0.22:0.04:0.14

[a] The solvents were subjected to freeze−pump−thaw cycling except for entry 1. $V_{EtOH}:V_{(CH2OH)2}$ = 4:1, unless otherwise noted. All reactions were complete in 1 h. [b] Determined by ^{1}H NMR analysis of the mixture. [c] 1.0 equiv. [Fe], 2.5 equiv. [Si]. [d] 0.50 equiv. [Fe], 2.5 equiv. [Si]. [e] 0.50 equiv. [Fe], 5.0 equiv. [Si]. [f] $V_{EtOH}:V_{DCE}:V_{(CH2OH)2}$ = 3:1:1.

Table 3. Cyclization of the Analogues of 8 under the Optimal Conditions[a]



49: R^1 = 2,4,6-trimethylbenzyl, R^2 = Bn
50: R^1 = 1-naphthylmethyl, R^2 = Bn
51: R^1 = Bn, R^2 = Me

52: R^1 = 2,4,6-trimethylbenzyl, R^2 = Bn
54: R^1 = 1-naphthylmethyl, R^2 = Bn
53: R^1 = Bn, R^2 = Me

entry	substrate	desired product	yield of mixture	yield of the desired product	ratio[b]
1	49	52	75%	55%	2.8:1
2	50	53	59%	45%	3.2:1
3	51	54	77%	56%	2.8:1

[a]The solvents were subjected to freeze−pump−thaw cycling. 0.50 equiv. [Fe], 5.0 equiv. [Si]. $V_{EtOH}:V_{DCE}:V_{(CH2OH)2}$ = 3:1:1, 60 °C. All reactions were complete in 1 h.

[b]The ratio of the desired product and the other three isomers. Determined by ^1H NMR analysis of the mixture.