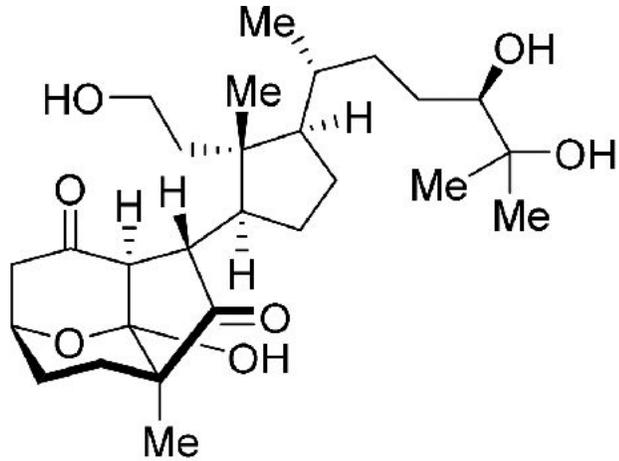
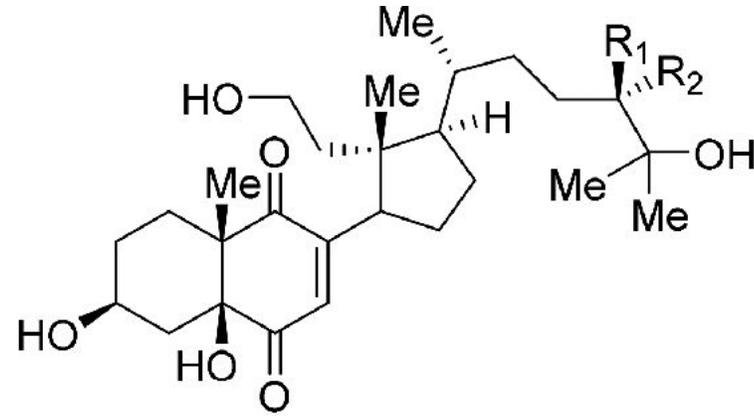


Total Synthesis of Aplysiasecosterol A

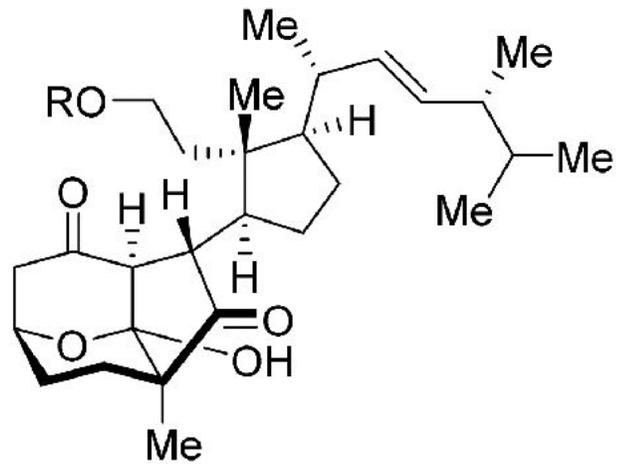


1: aplysiasecosterol A



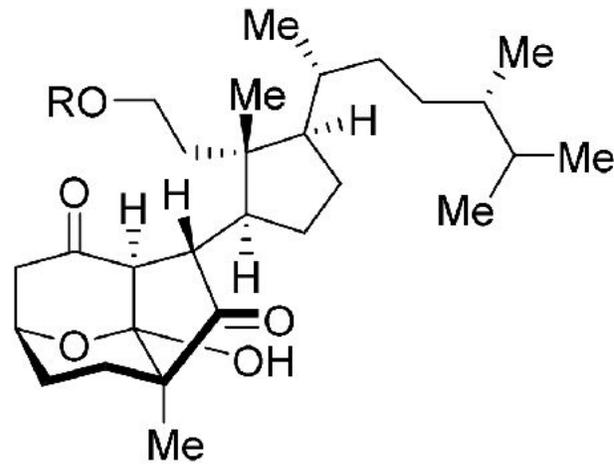
2: $R_1 = \text{OH}$, $R_2 = \text{H}$; aplysiasecosterol B

3: $R_1 = \text{H}$, $R_2 = \text{OH}$; aplysiasecosterol C



4: $R = \text{H}$; pinnigorgiol A

6: $R = \text{Ac}$; pinnigorgiol D



5: $R = \text{H}$; pinnigorgiol B

7: $R = \text{Ac}$; pinnigorgiol E

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

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

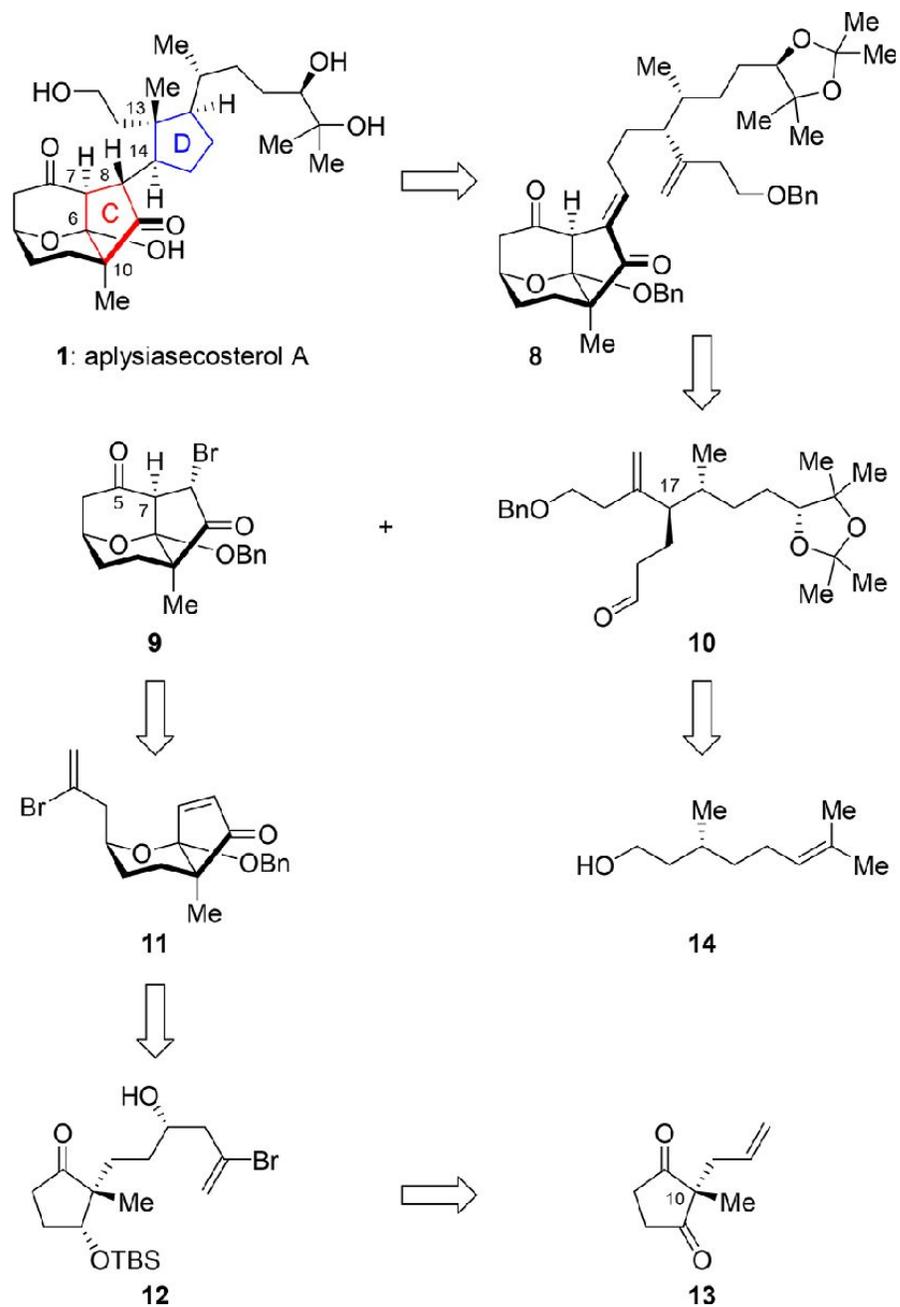
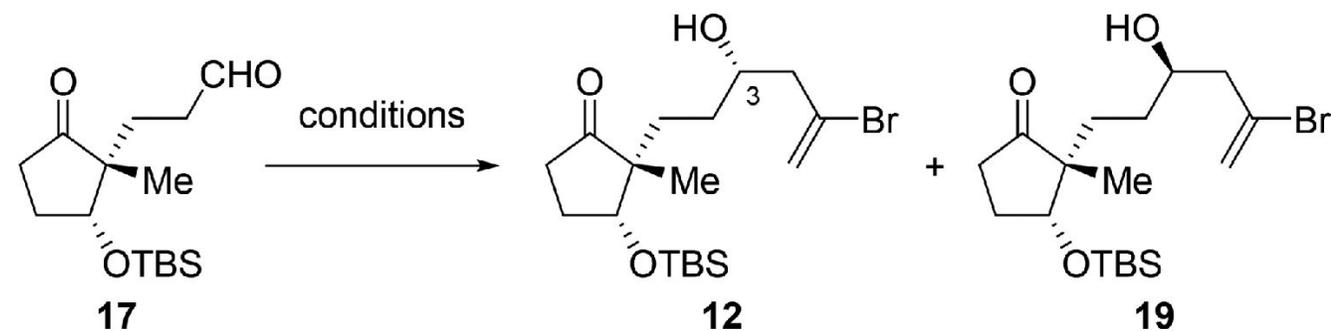


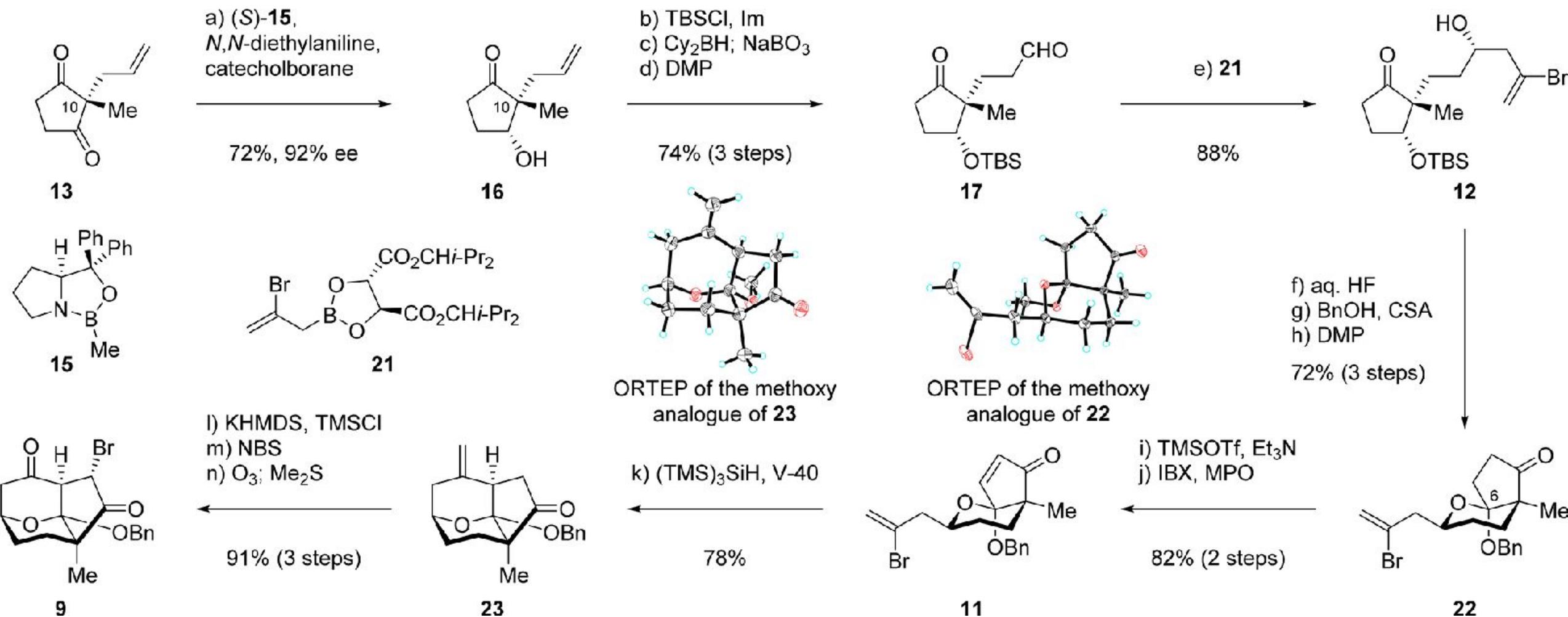
Table 1. Studies of 2-Bromoallylation of Aldehyde 17



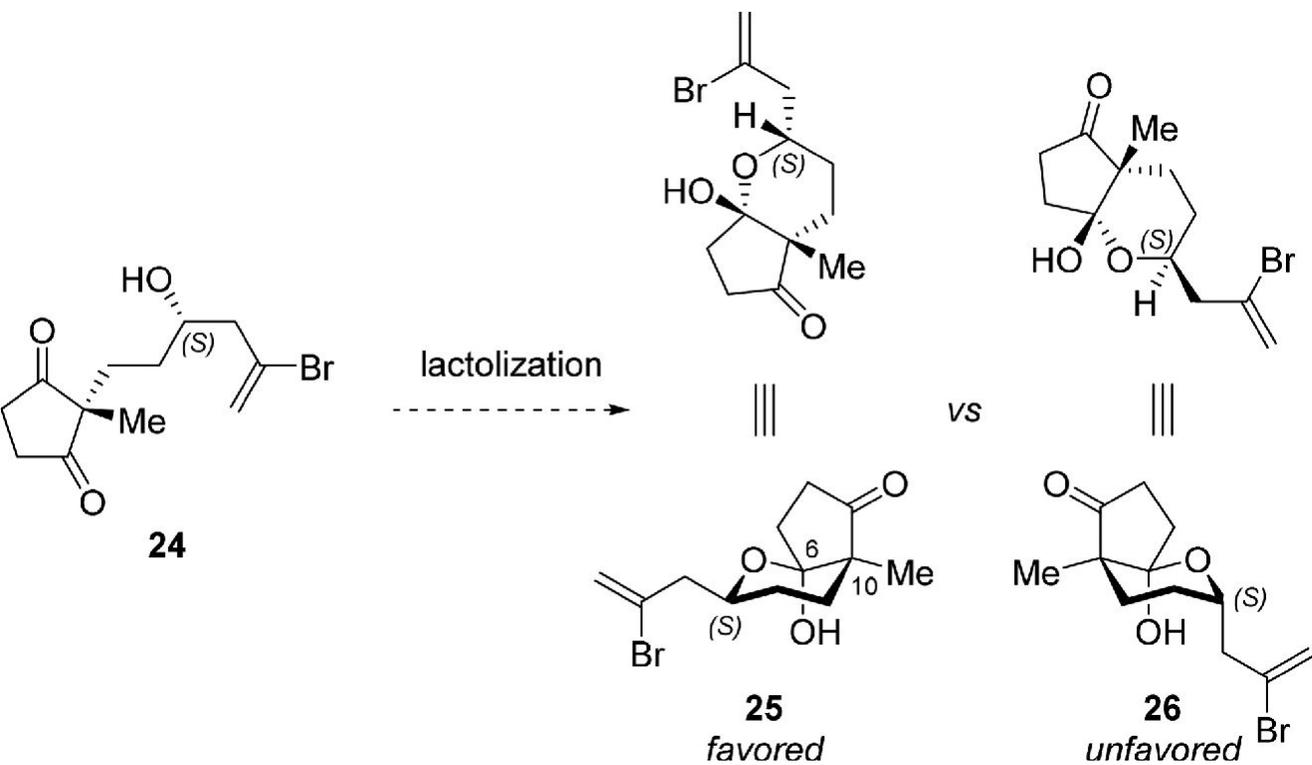
entry	conditions	yield of 12	yield of 19
1	TiCl ₄ , 18, CH ₂ Cl ₂ , -78 to 22 °C, 3 h	13%	14%
2 ^a	CrCl ₂ , Lil, 20, THF, 22 °C, 2.5 h	16%	18%
3 ^b	In, La(OTf) ₃ , 20, aq. NH ₄ Cl, 22 °C, 5 h	18%	18%
4	Sn, 20, TBAI, aq. HCl, Et ₂ O, 22 °C, 3 h	31%	33%
5 ^a	21, toluene/pentane, -95 °C, 2 h	88%	9%

^a4 Å molecular sieves. ^bSonication.

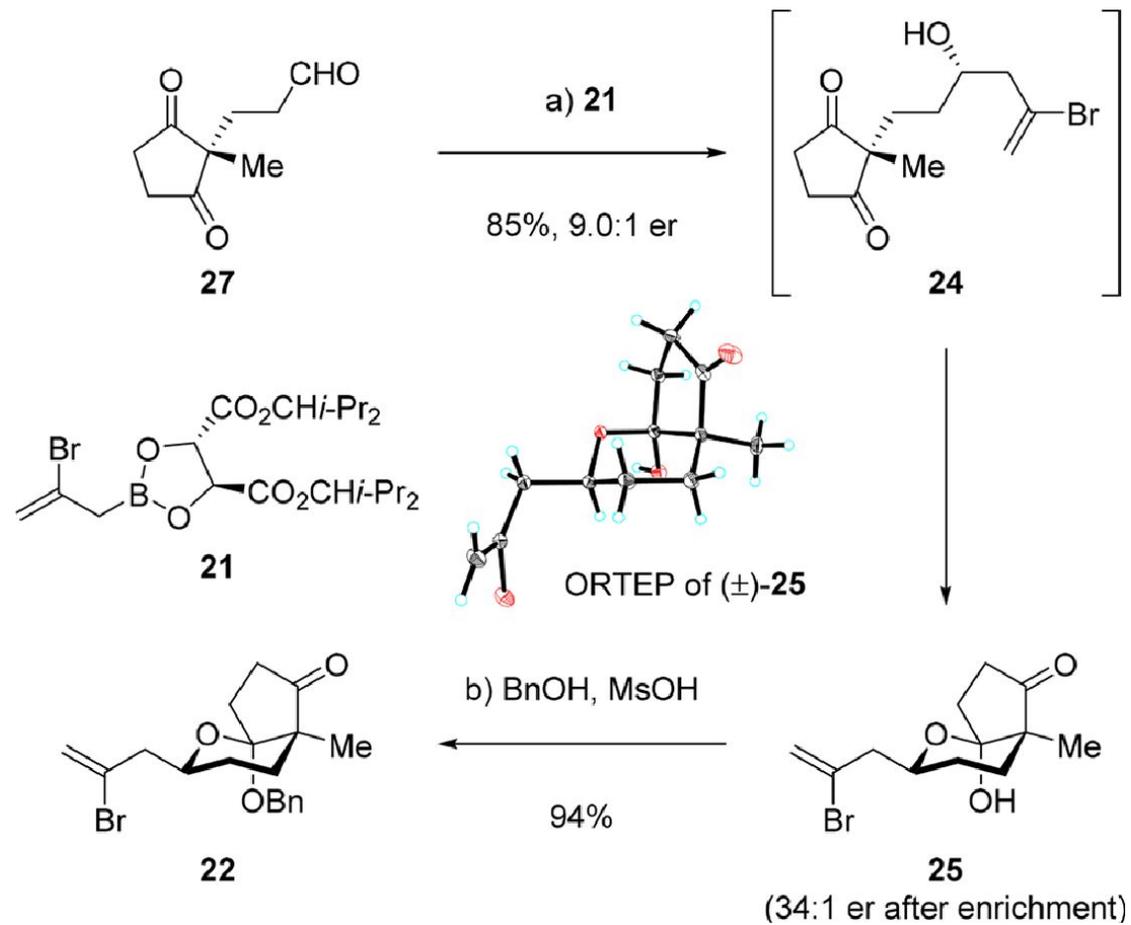
Scheme 1. Preparation of the Left-Hand Segment 9



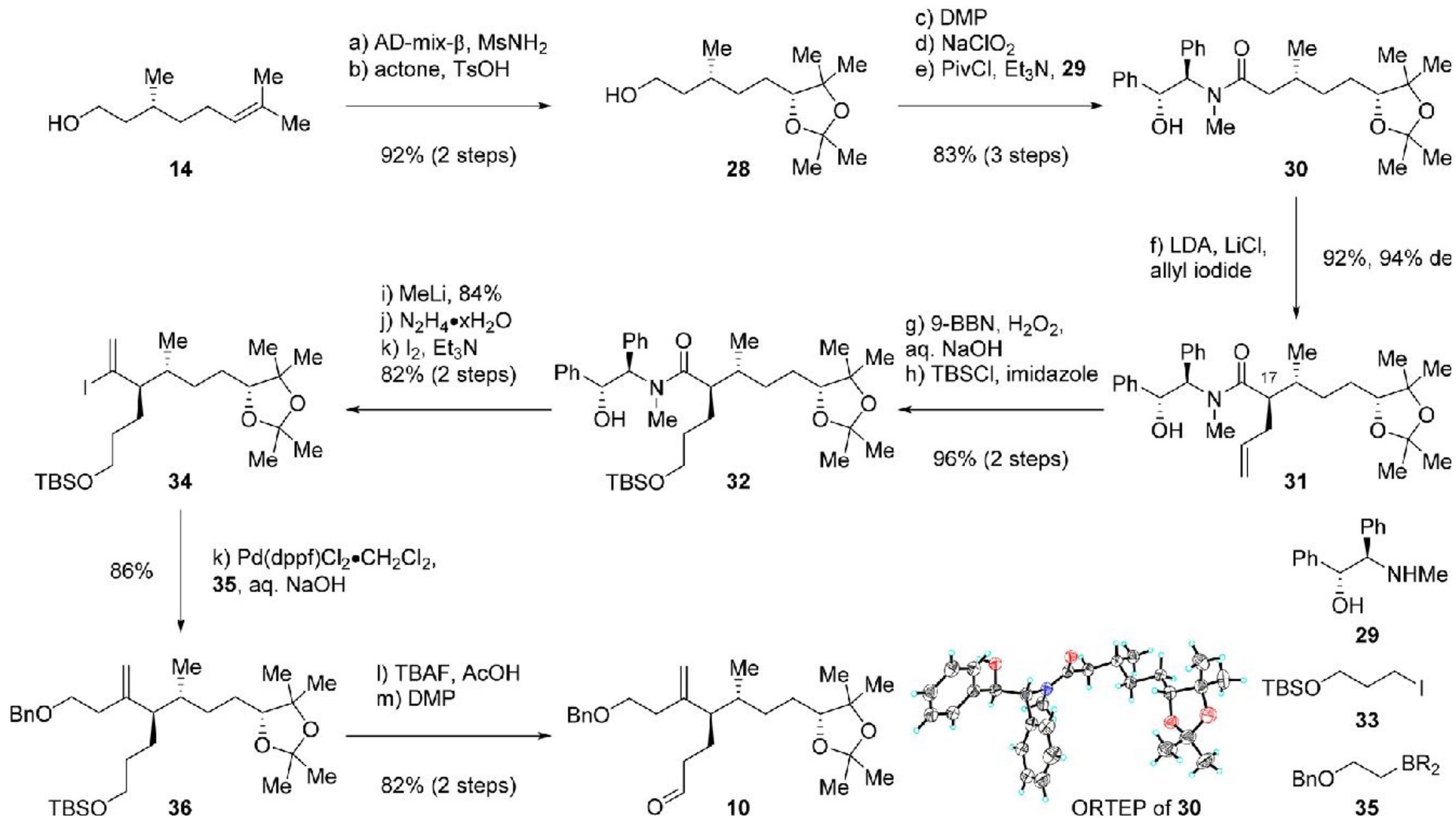
Scheme 2. Devised Desymmetrizing Lactolization Process



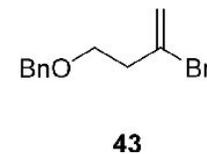
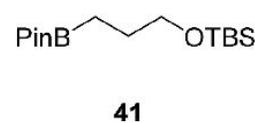
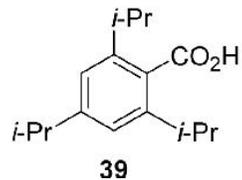
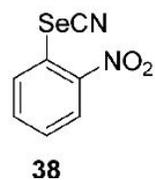
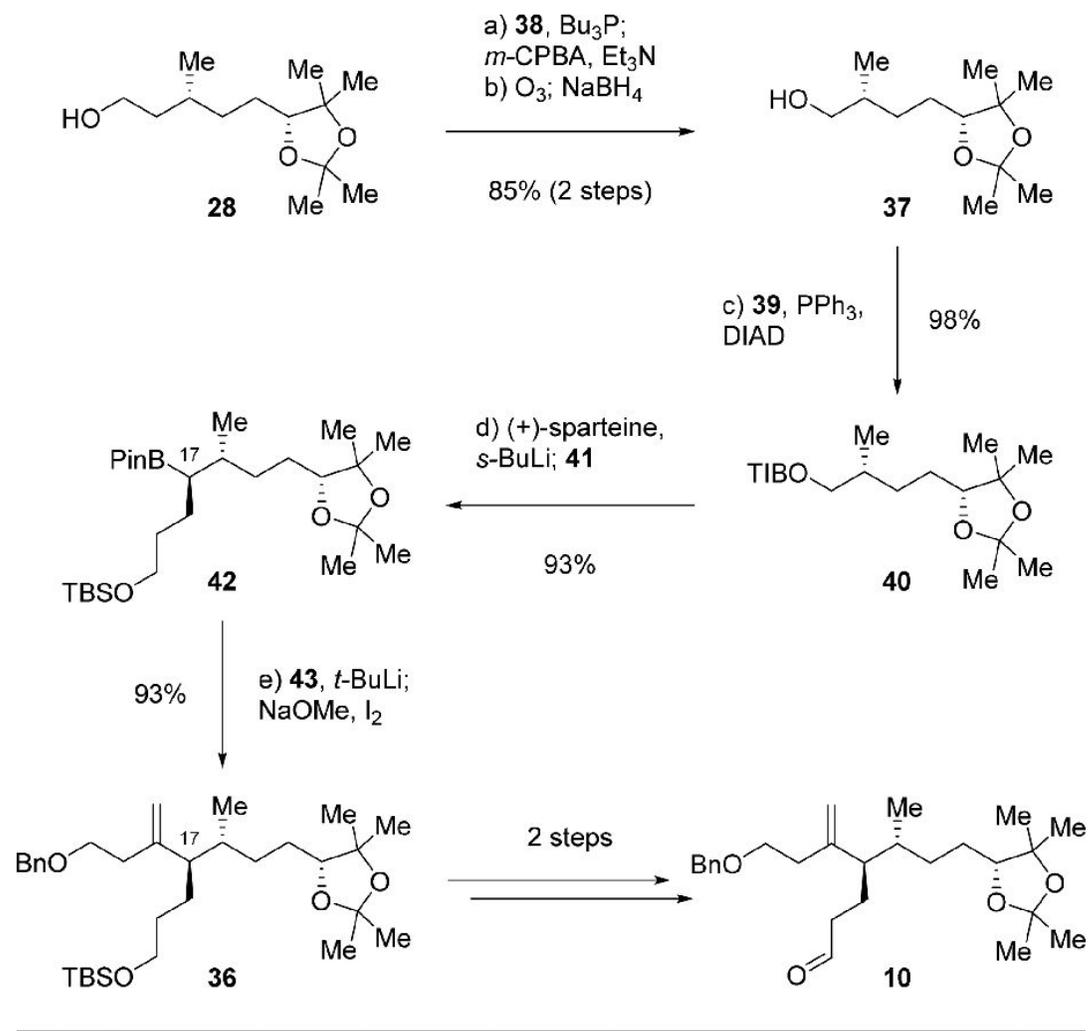
Scheme 3. Two-Step Synthesis of 22



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)

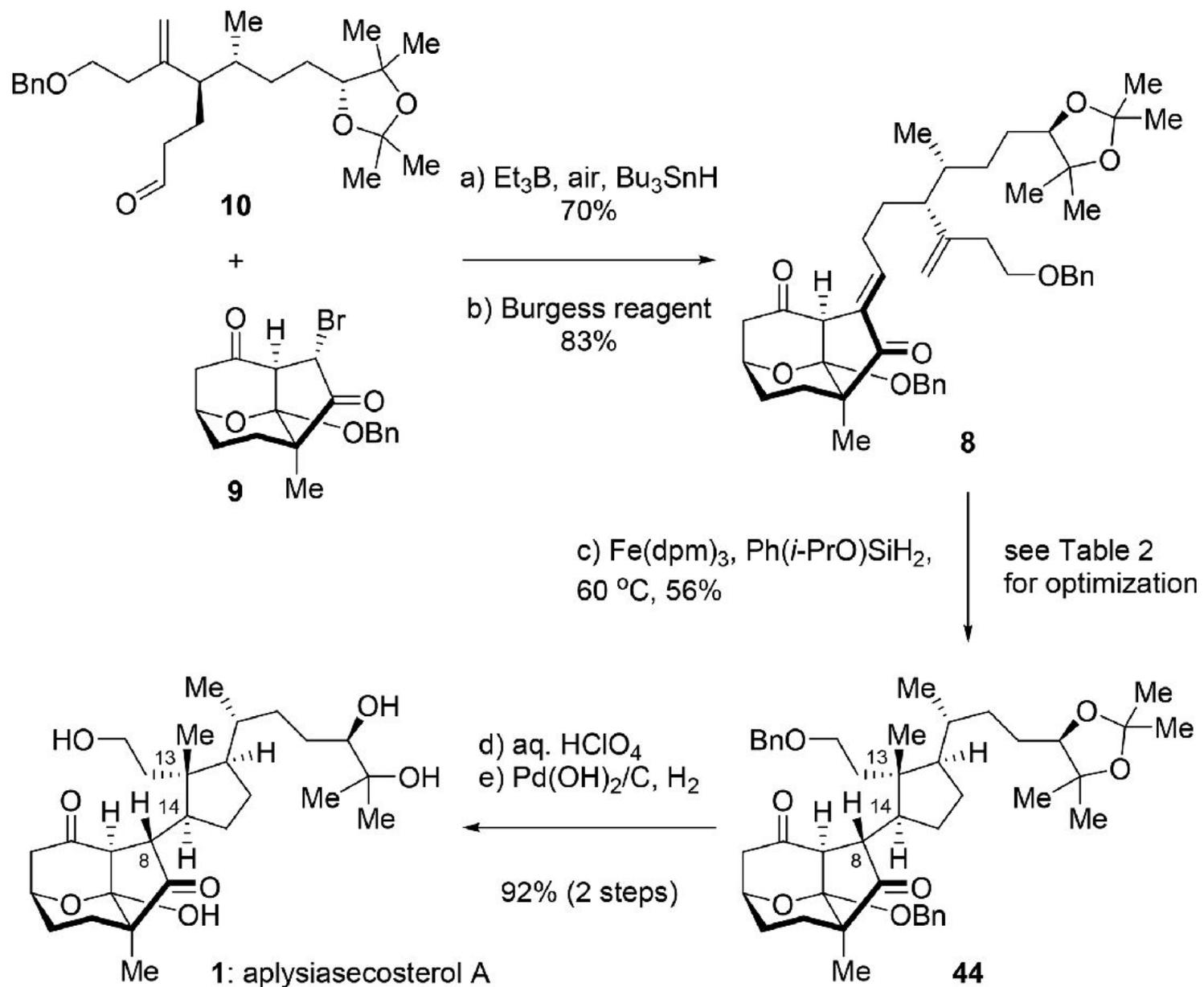
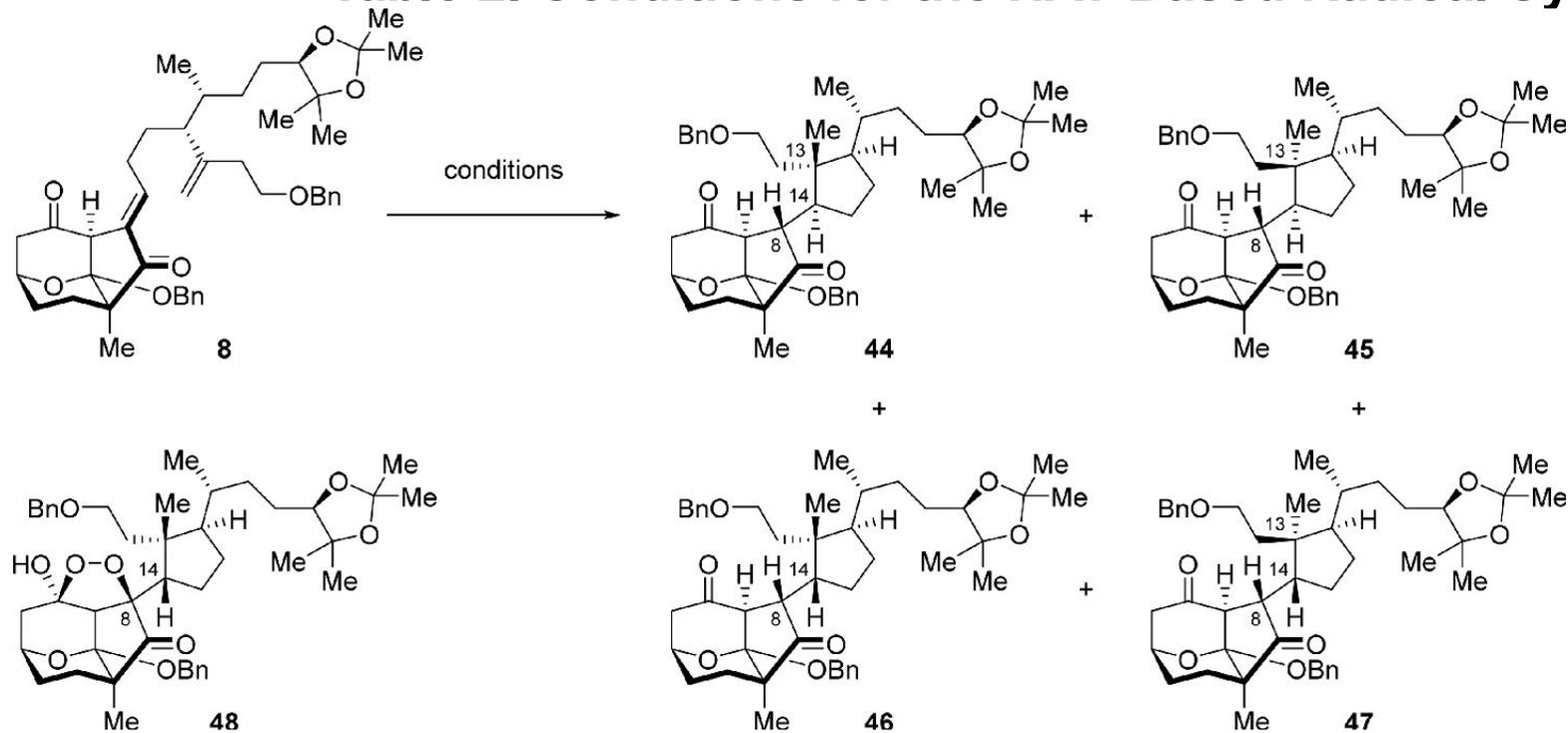


Table 2. Conditions for the HAT Based Radical Cyclization of 8



entry	conditions ^a	yield of mixture	yield of 44	ratio ^b (44:45:46:47)
1 ^c	Fe(acac) ₃ , PhSiH ₃ , EtOH/(CH ₂ OH) ₂ , 60 °C	60%	25%	1:0.33:0.47:0.58
2 ^c	Fe(acac) ₃ , PhSiH ₃ , EtOH/(CH ₂ OH) ₂ , 60 °C	70%	30%	1:0.33:0.46:0.59
3 ^d	Fe(acac) ₃ , Ph(i-PrO)SiH ₂ , EtOH/(CH ₂ OH) ₂ , 22 °C	41%	21%	1:0.33:0.21:0.39
4 ^d	Fe(acac) ₃ , Ph(i-PrO)SiH ₂ , EtOH/(CH ₂ OH) ₂ , 50 °C	60%	27%	1:0.35:0.38:0.51
5 ^d	Fe(acac) ₃ , Ph(i-PrO)SiH ₂ , EtOH/(CH ₂ OH) ₂ , 60 °C	84%	44%	1:0.29:0.29:0.32
6 ^d	Fe(acac) ₃ , Ph(i-PrO)SiH ₂ , EtOH/(CH ₂ OH) ₂ , 70 °C	90%	36%	1:0.34:0.55:0.57
7 ^d	Fe ₂ (ox) ₃ ·6H ₂ O, Ph(i-PrO)SiH ₂ , EtOH/(CH ₂ OH) ₂ , 60 °C	22%	17%	1:0.18:0:0.09
8 ^e	Fe(dibm) ₃ , Ph(i-PrO)SiH ₂ , EtOH/(CH ₂ OH) 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 ₂ OH) ₂ , 60 °C	77%	56%	1:0.22:0.04:0.14

^aThe solvents were subjected to freeze-pump-thaw cycling except for entry 1. $V_{\text{EtOH}}:V_{(\text{CH}_2\text{OH})_2} = 4:1$, unless otherwise noted. All reactions were complete in 1 h.

^bDetermined by ¹H NMR analysis of the mixture.

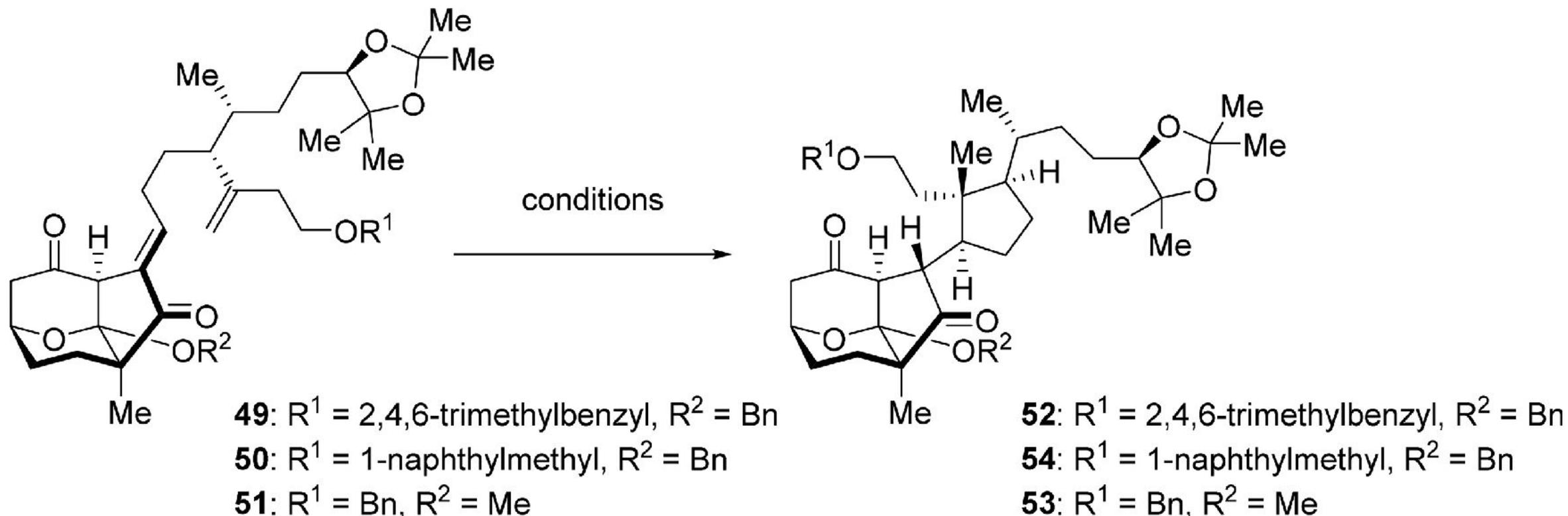
^c1.0 equiv. [Fe], 2.5 equiv. [Si].

^d0.50 equiv. [Fe], 2.5 equiv. [Si].

^e0.50 equiv. [Fe], 5.0 equiv. [Si].

^f $V_{\text{EtOH}}:V_{\text{DCE}}:V_{(\text{CH}_2\text{OH})_2} = 3:1:1$.

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



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

^aThe 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.

^bThe ratio of the desired product and the other three isomers. Determined by ¹H NMR analysis of the mixture.