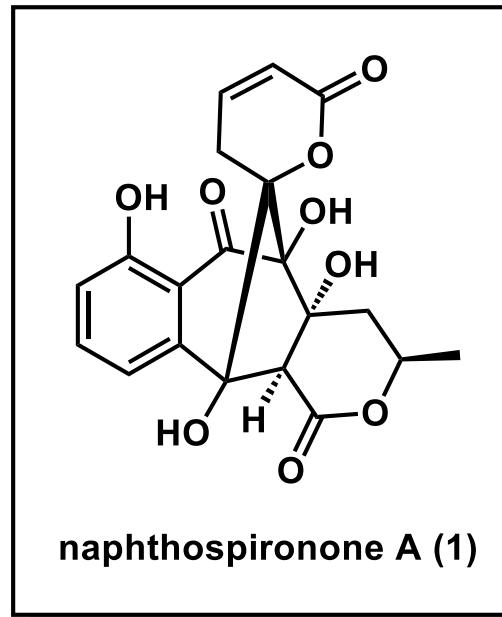
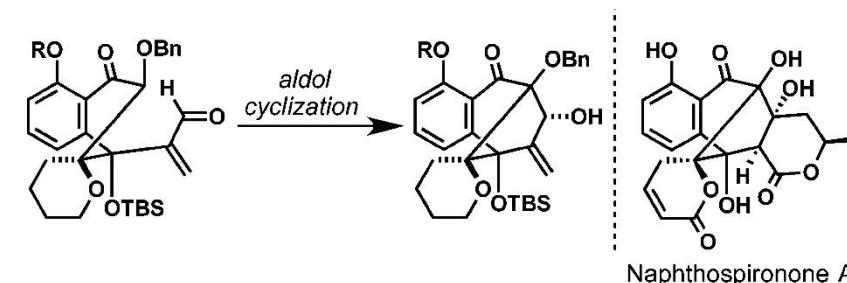


Asymmetric Total Synthesis of Naphthospironone A

Jia-Xuan Liu[†], Shi-Peng Zhang[†], Feng-Sen Sun, Hui Li, Ya-Ling Gong,* Shi-Chao Lu,* and Shu Xu*

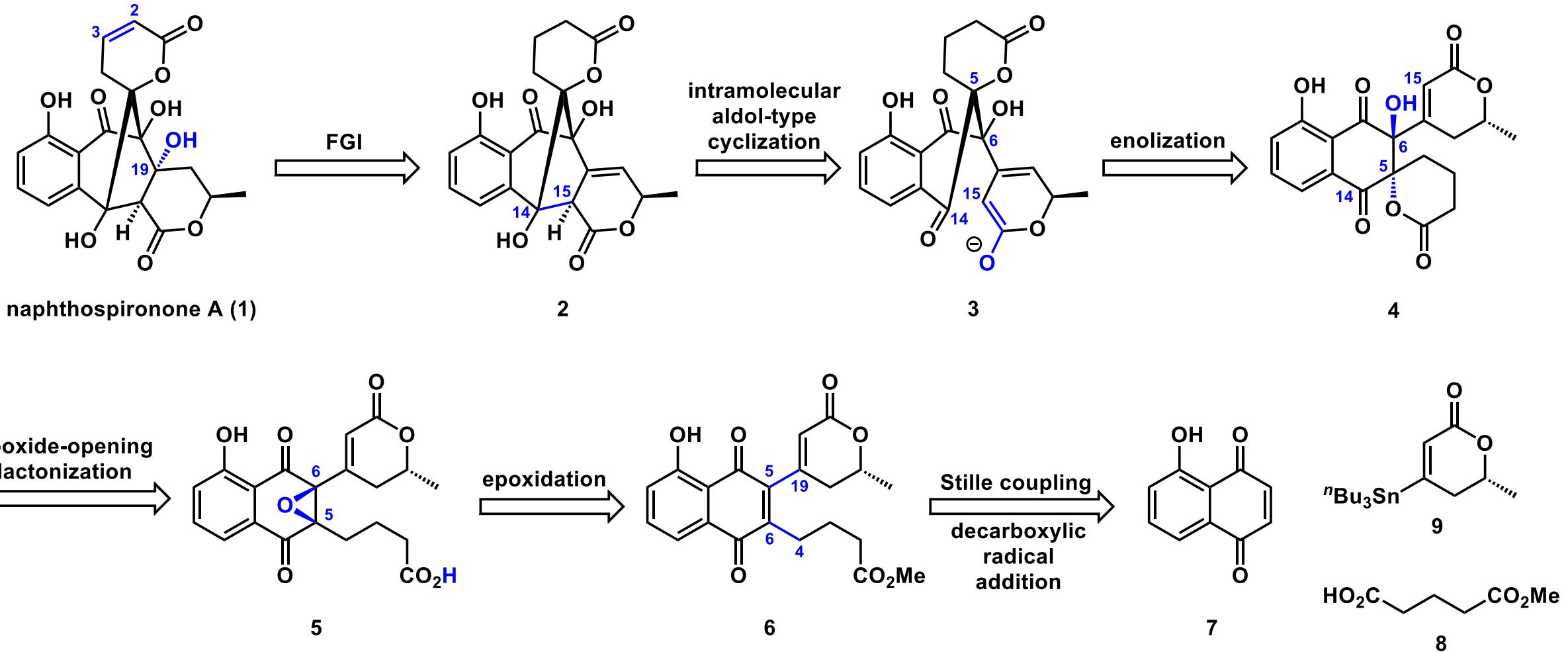


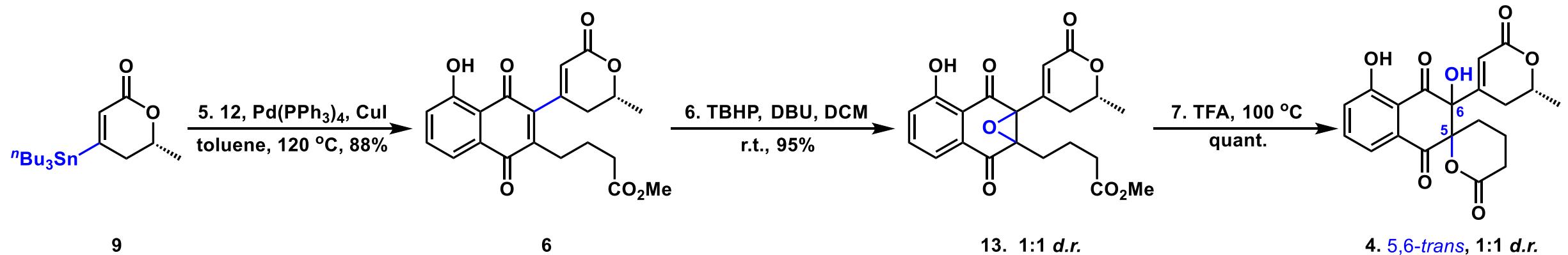
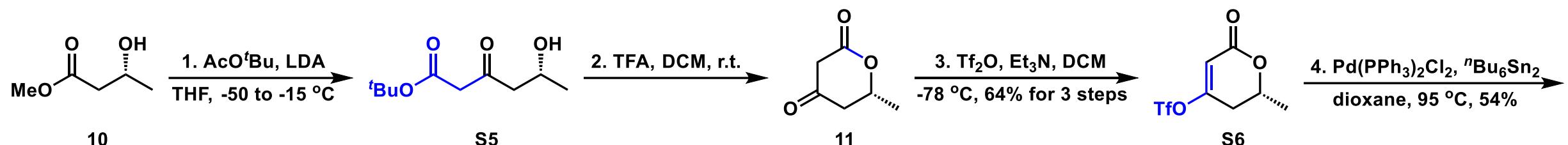
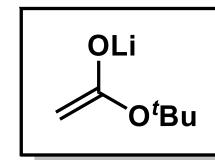
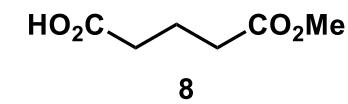
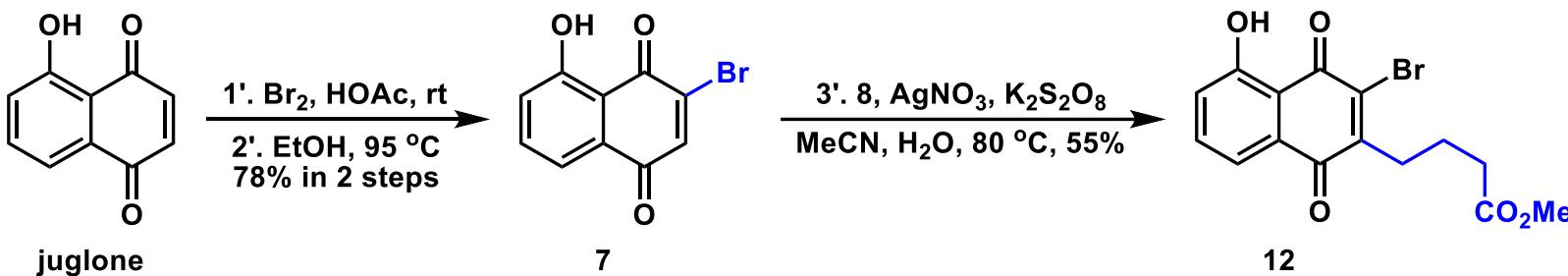
- Isolated from alkaliphiles thriving optimally at or above pH
Displayed cell cytotoxicity and antibiotic activity.
- Highly oxidised cage-like structure
Congested bicyclo[3.2.1]octane rings
- 5 contiguous chiral carbons, 4 tertiary oxygenated centres



Previous Work: *Org. Lett.*, **2015**, 17, 3746.

Retrosynthetic Analysis

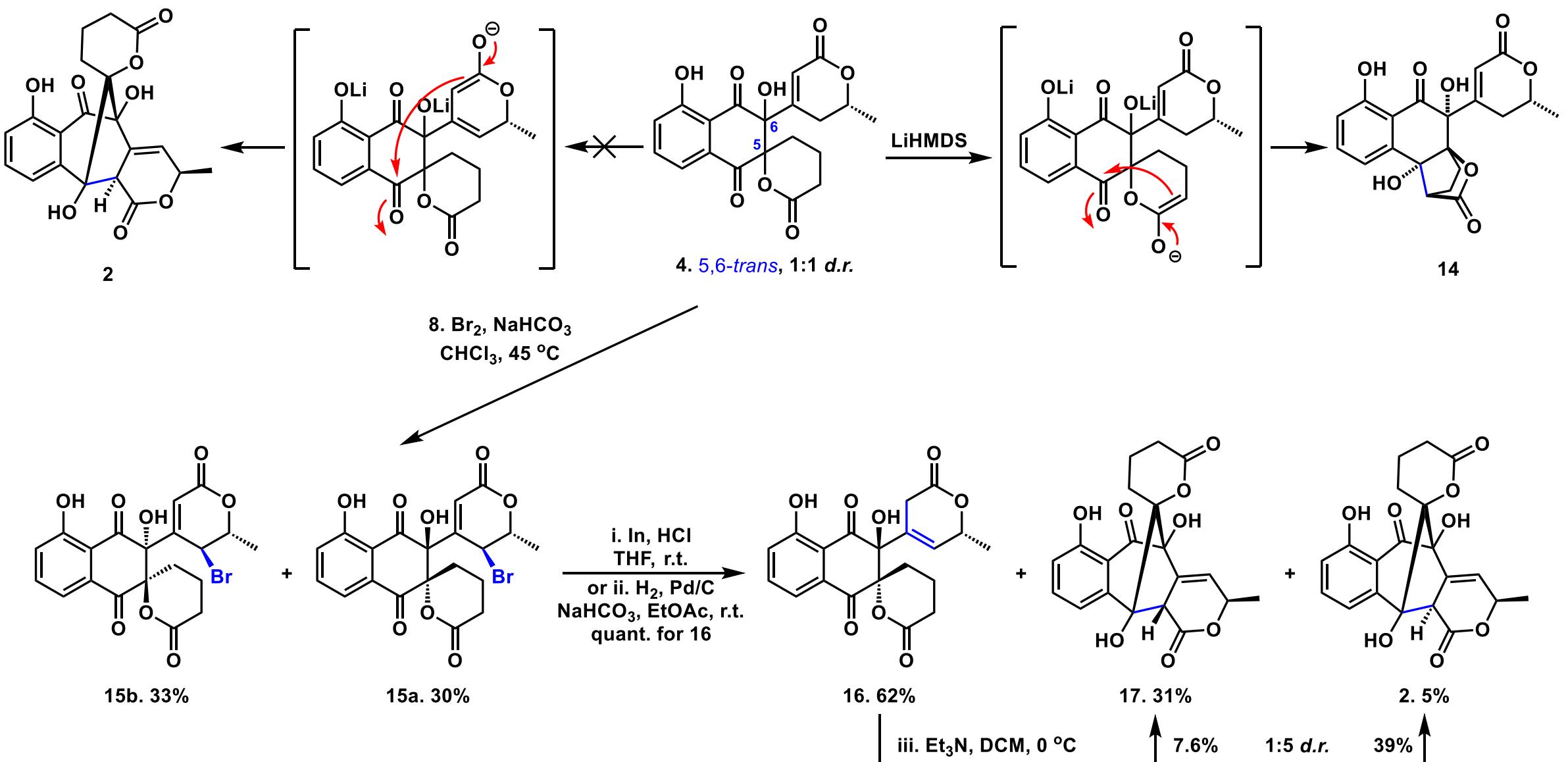


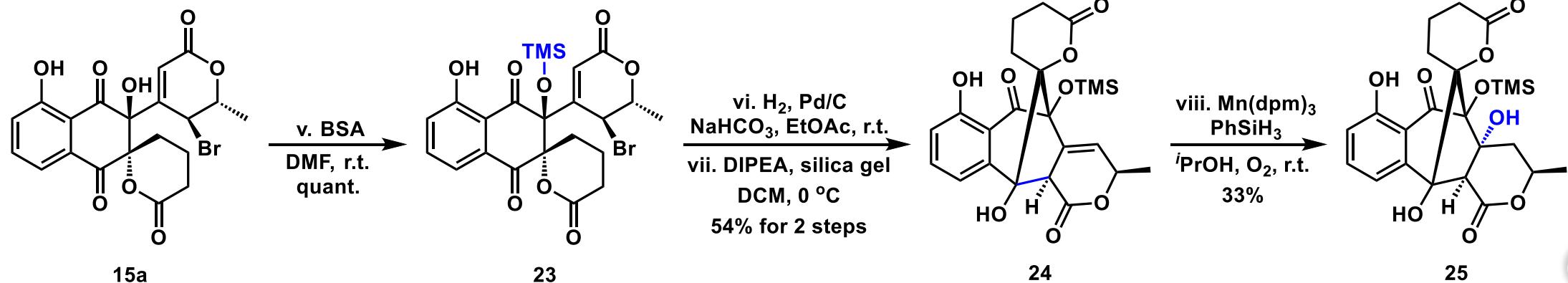
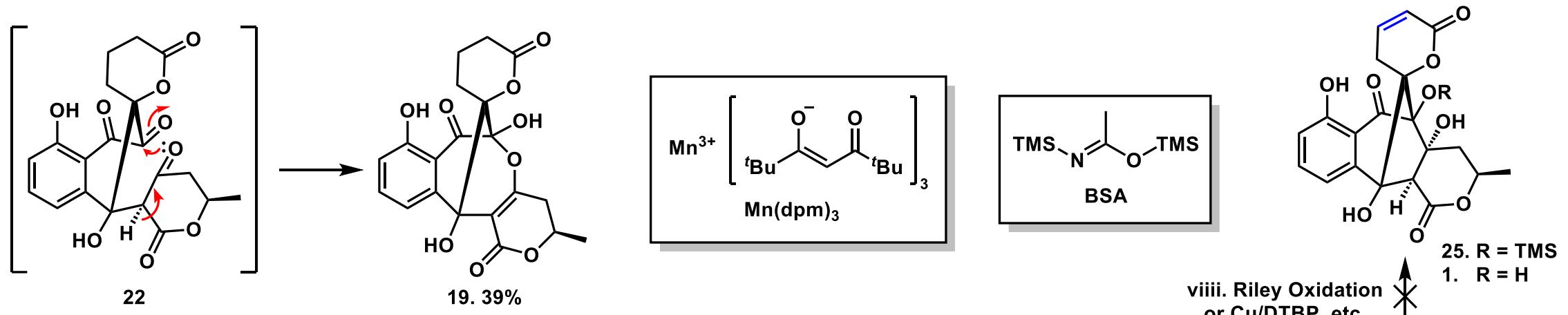
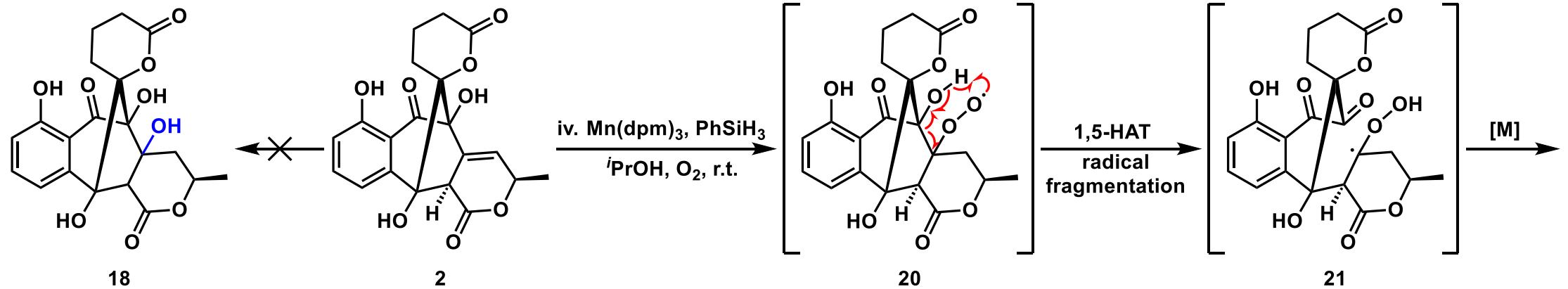


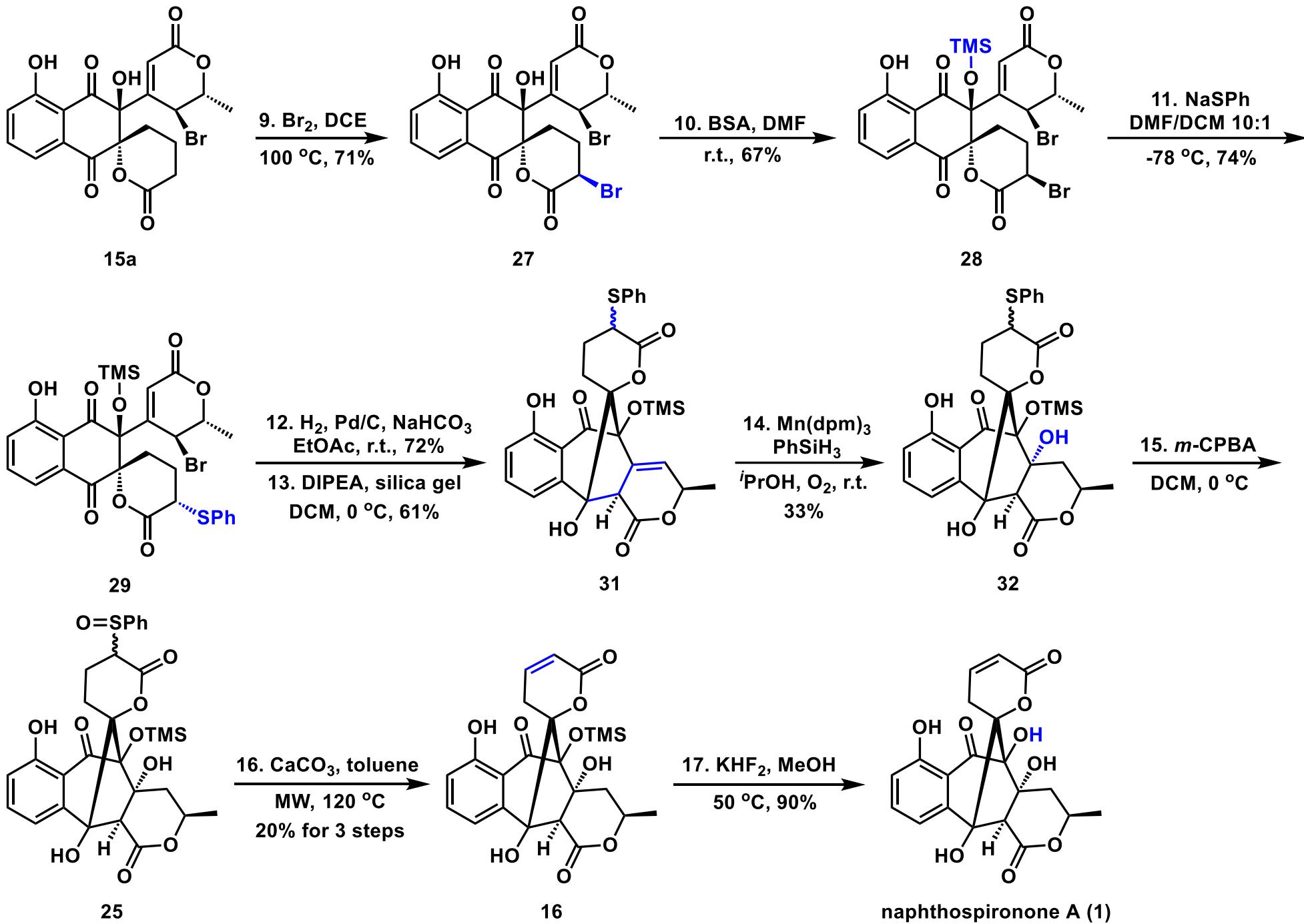
3'

5

6



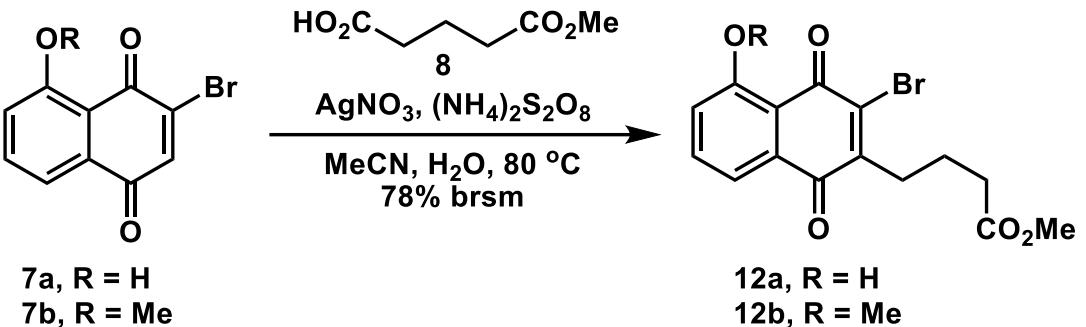




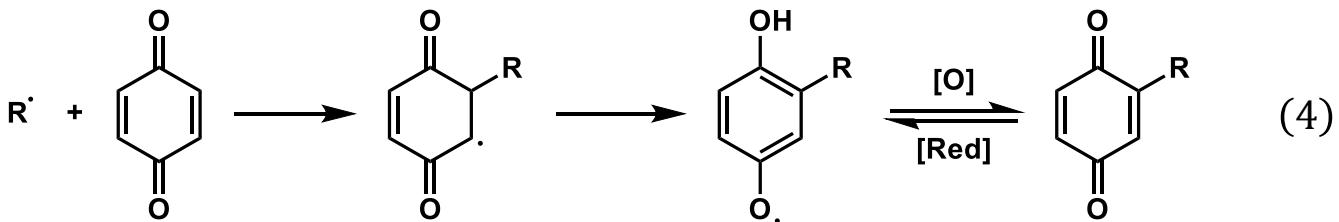
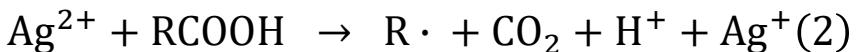
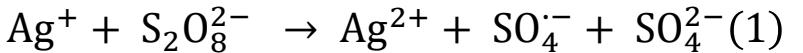


Step 3'

Decarboxylic Radical Addition



J. Chem. Soc. Perkin Trans., **1981**, 2091.

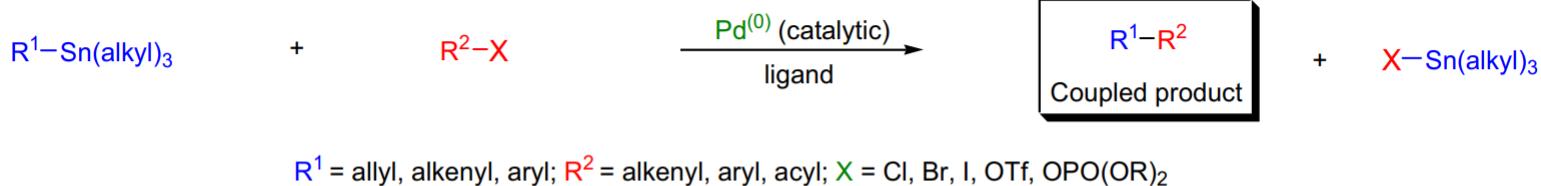


Liebigs Ann. Chem., **1972**, 763, 135.
Acta Chem. Scand., **1973**, 27, 3211.

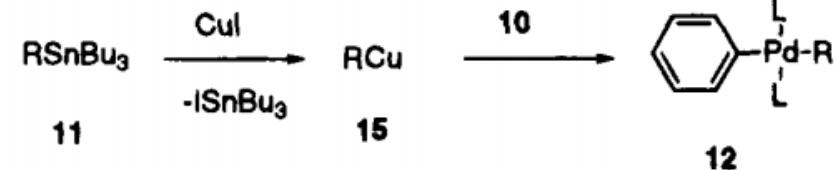
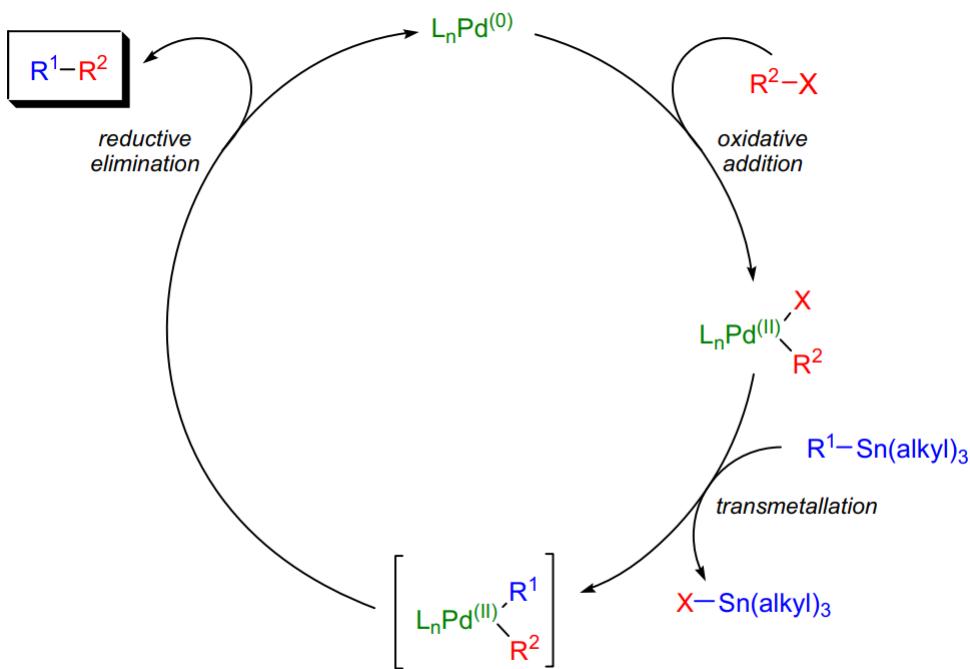


Step 5

Stille Cross-Coupling



Mechanism: ^{6,7,41,43-46,12,47-53,27,54}

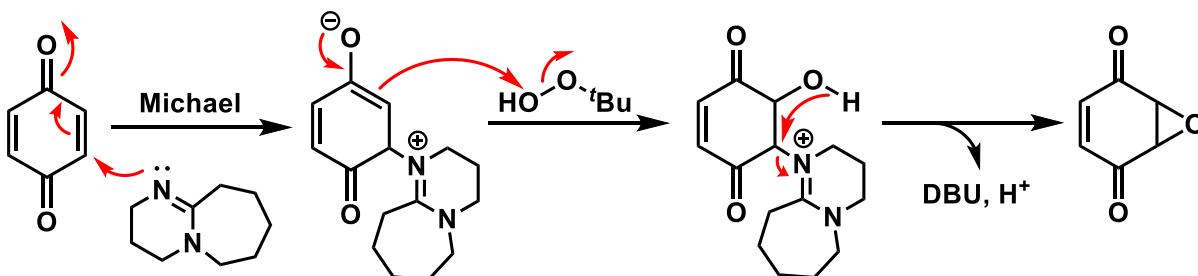


“Copper Effect”

J. Org. Chem., **1994**, *59*, 5905.

Step 6**DBU-Promoted Epoxidation of Electron Deficient Alkenes**

- α,β -Unsaturated- δ -lactones and enones
- Suitable for easily-ring-opening lactones, acetoxy group tolerant
- Sensitive to steric effects
- No aldol byproducts observed
- High regioselectivity with 2,4-dienones



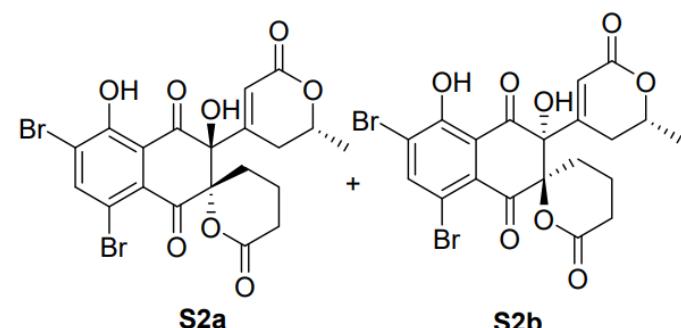
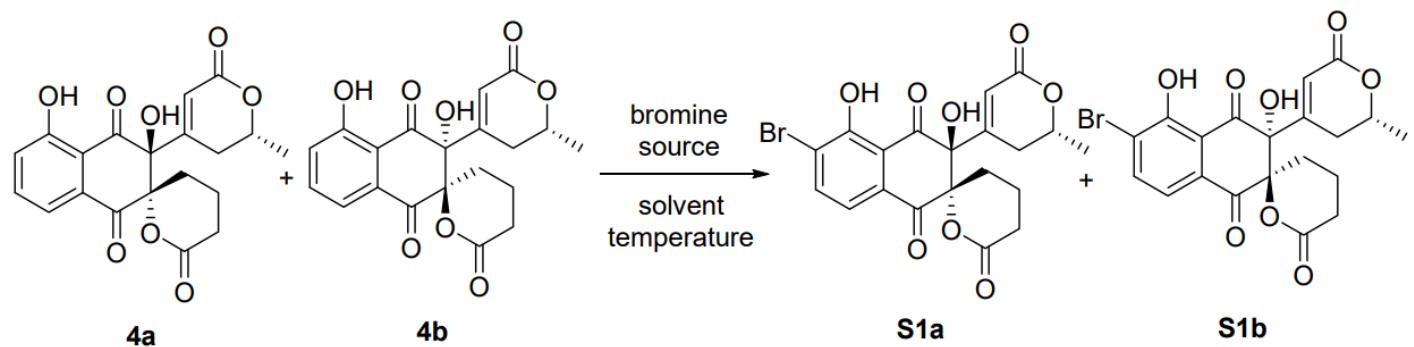
TABLE

Entry	Substrate	Product	Time/h	Yield ^a	Entry	Substrate	Product	Time/h	Yield ^a
1.			12	75	8.			10	100 ^d
2.			18	35 ^b	9.			12	90
3.			10	92	10.			10	70 ^e
4.			24	65 ^c	11.			96	35 ^h
5.			10	80 ^d	12.			30	100
6.			10	100 ^e	13.			1/2	100
7.			28	100 ^f	14.			2	100 ⁱ
8.		NO REACTION	32		15.				
9.									



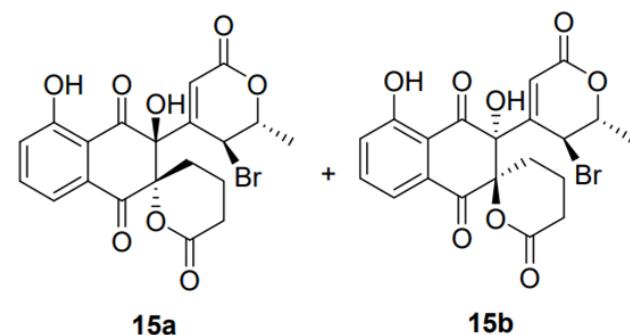
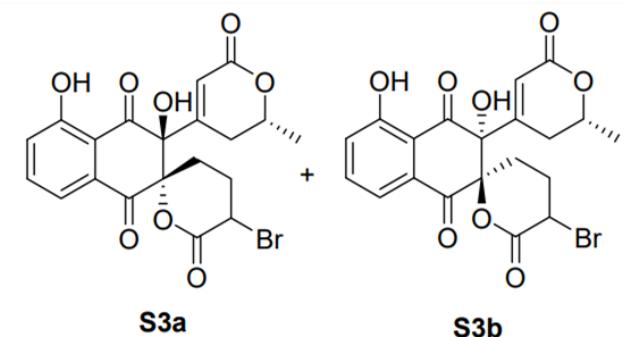
Step 8

Conditions tested on bromination of compound **4**^[a]



Entry	Conditions	Results (%) ^[b]
1	NBS (1.0 equiv.), AIBN (0.05 equiv.), CCl ₄ -DCE, 80°C, 16 h	S1ab (15) + S2ab (10) ^[c]
2	NBS (1.0 equiv.), AIBN (0.05 equiv.), DCE, 80°C, 2 h	S1ab (40) + S2ab (40) ^[c]
3	Br ₂ (0.9 equiv.), DCM, rt, 12 h	NR
4	Br ₂ (4.0 equiv.), DCE, 70°C, 21 h	S3ab (64) ^[d] + 4ab (24)
5	Br ₂ (12.5 equiv.), CHCl ₃ , 50°C, 72 h	15ab (63)
6	Br ₂ (5.0 equiv.), NaHCO ₃ (1 equiv.), CHCl ₃ , 45°C, 32 h	15ab (63) ^[e] + 4ab (12)

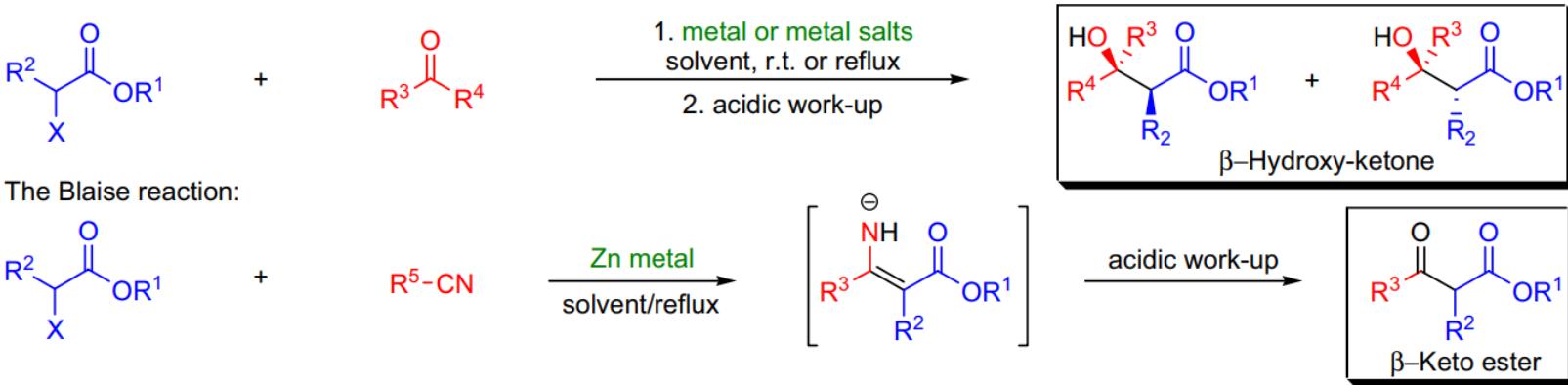
[a] All starting material were 1:1 diastereomer mixture. [b] Isolated yield. [c] **S1** and **S2** were inseparable mixture. The yields were calculated according to the ¹H NMR ratio of the crude mixture. [d] 83% based on recovered starting material. [e] 73% based on recovered starting material. NBS = *N*-bromosuccinimide, equiv. = equivalent, AIBN = azobisisobutyronitrile, NR = no reaction.





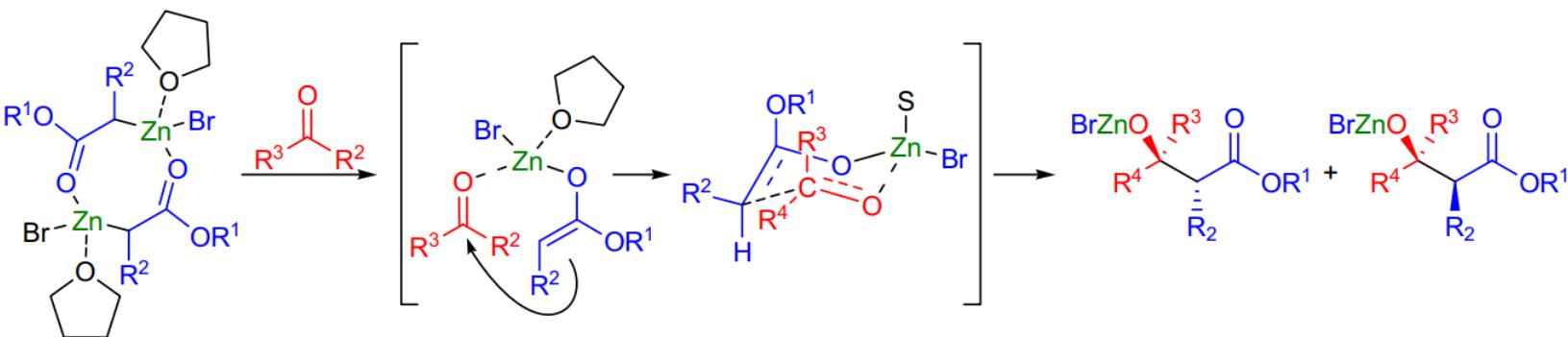
Step i

Reformatsky Reaction



$X = \text{Cl, Br, I}$; $R^1 = \text{alkyl}$; $R^2 = \text{H, alkyl, aryl}$; $R^3, R^4 = \text{H, alkyl, aryl}$; $R^5 = \text{alkyl, aryl}$; solvent: Et_2O , THF, 1,4-dioxane, DME, benzene, toluene, MeCN, DMF, DMSO; metal: Zn, Mg, Cd, Ba, In, Ge, Co, Ni, Ce; metal salt: Sml_2 , CrCl_2 , TiCl_2 , CeX_3 , Na_2Te , R_3SnLi , $\text{R}_3\text{Sb}/\text{I}_2$, Et_2AlCl ;

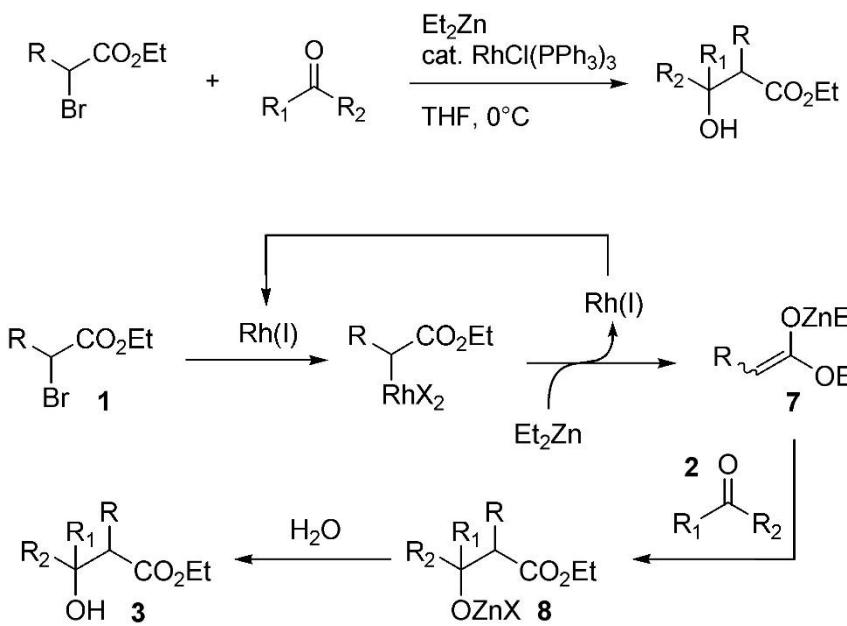
Mechanism:⁵³⁻⁵⁷





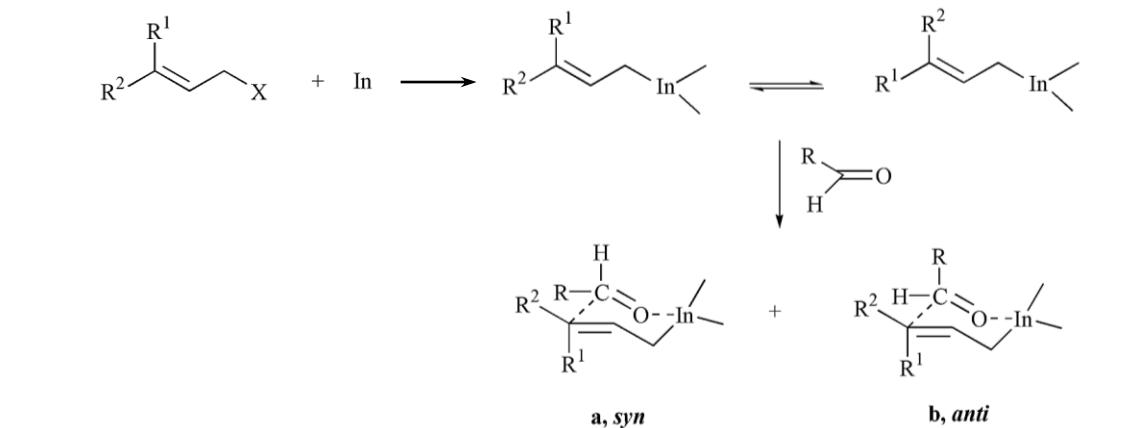
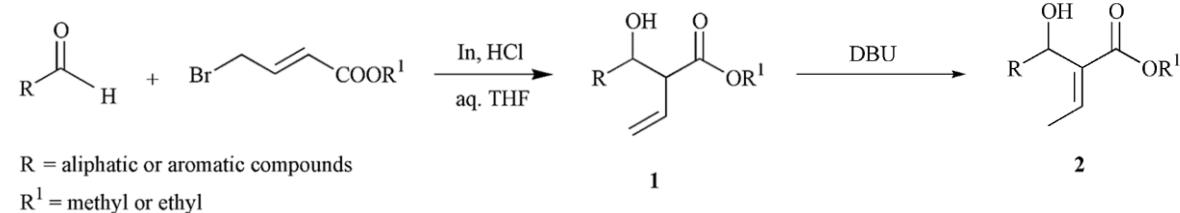
Step i

Reformatsky-Type Reaction



Rhodium-Catalyzed
Reformatsky-Type Reaction

Org. Lett., **2000**, *2*, 2549.



- HCl accelerates the reaction

Indium-Mediated Allylation of Aldehydes

J. Chem. Soc. Perkin Trans., **2001**, 2079.

←

Step i

Conditions screened on Reformatsky-type cyclization of 15a

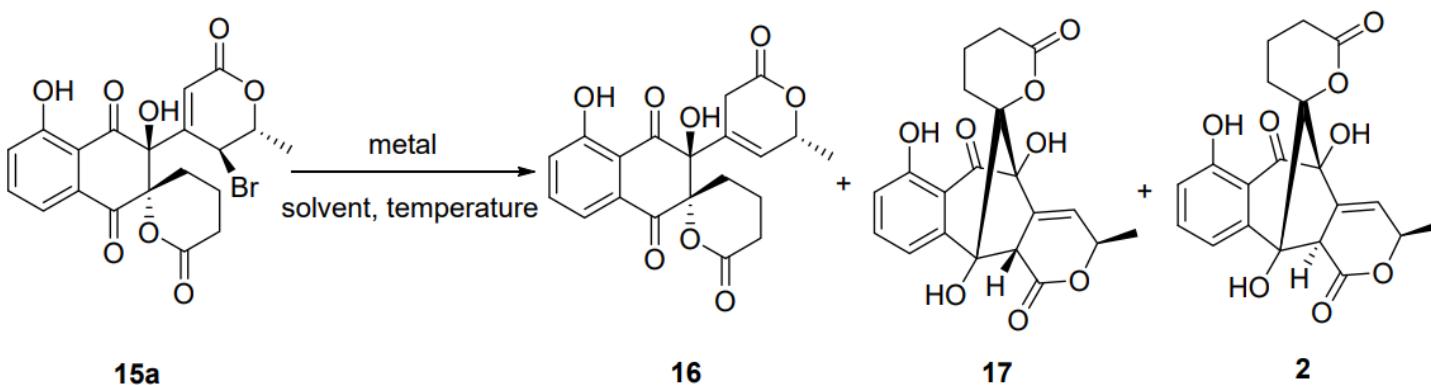


Table S2. Conditions screened on Reformatsky-type cyclization of **15a**

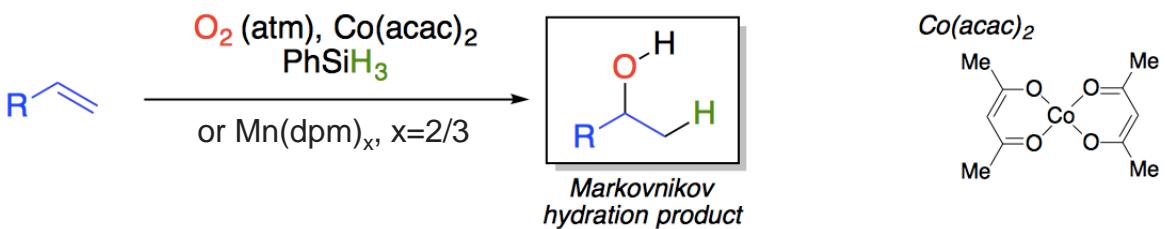
Entry	Conditions	Results
1	Zn (10 equiv.), THF, rt, 1 h ; then ultrasonication, rt, 30 min	NR
2	Zn (10 equiv.), TMSCl (excess), THF, rt, 1 h	16 (14% ^[a]), 17 (8% ^[a])
3	Et ₂ Zn (3 equiv.), RhCl(PPh ₃) ₃ (0.1 equiv.), THF, rt to 70°C, 19 h	Decomposed
4	In (3 equiv.), THF, rt, 2 h; then ultrasonication, rt, 30 min	NR
5	In (3 equiv.), aq. HCl (1 M, 1 equiv.), THF, rt, 15 min	16 (62% ^[b]), 17 (31% ^[b]), 2 (5% ^[b])
6	In (2 equiv.), InBr (2.0 equiv.), THF, rt, 18 h	16 (25% ^[c]), 17 (16% ^[c]), 2 (13% ^[c])
7	H ₂ , Pd-C (0.22 equiv.), EtOAc, rt, 1 h	only 16 (quant. ^[b])

[a] Calculated yield according to the ratio of isomers in the ^1H NMR of the isolated mixture. [b] Isolated yield. [c] Calculated yield according to the ratio of isomers in the ^1H NMR of the crude mixture.

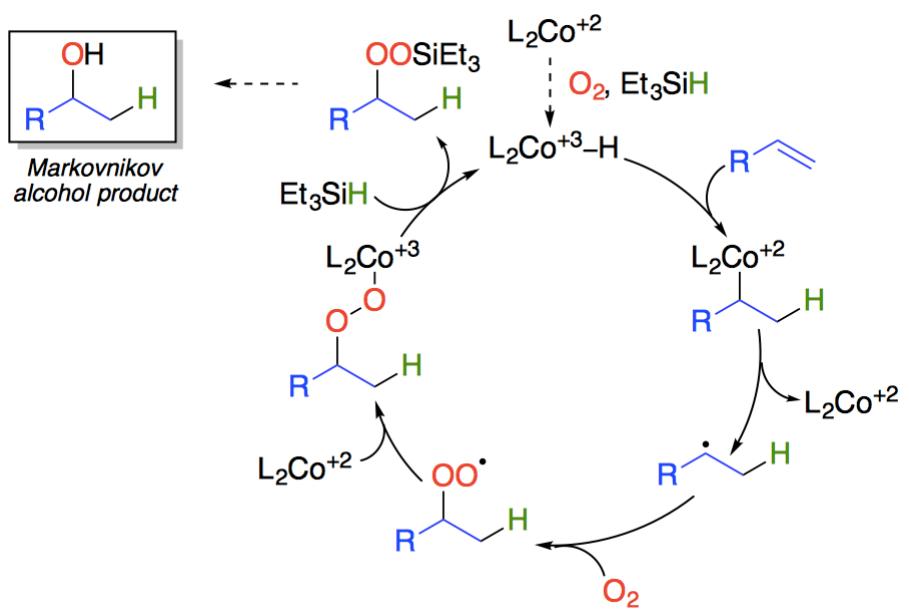


Step iv

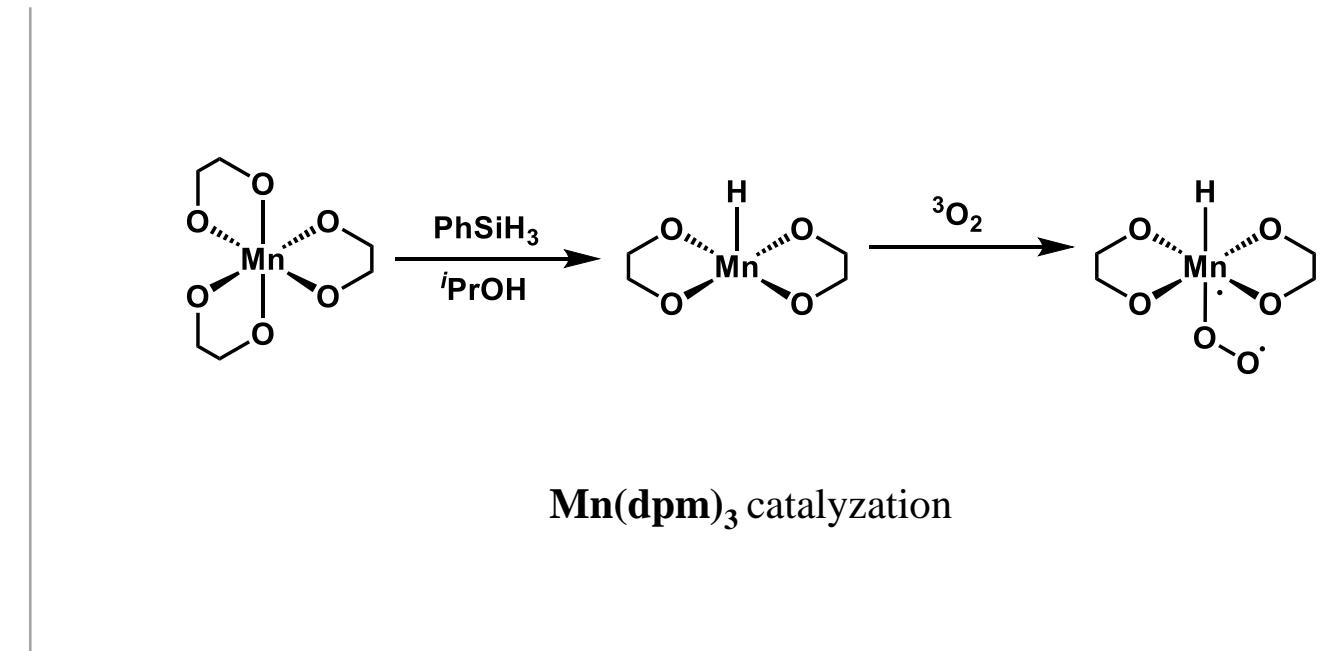
Mukaiyama Hydration



Mechanism:



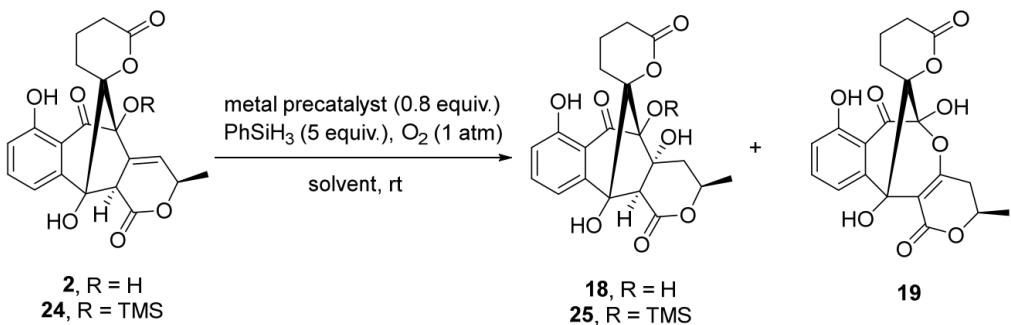
Org. Lett., **2002**, *4*, 3595.



Tetrahedron Letters, **2000**, *41*, 9725.

Step iv

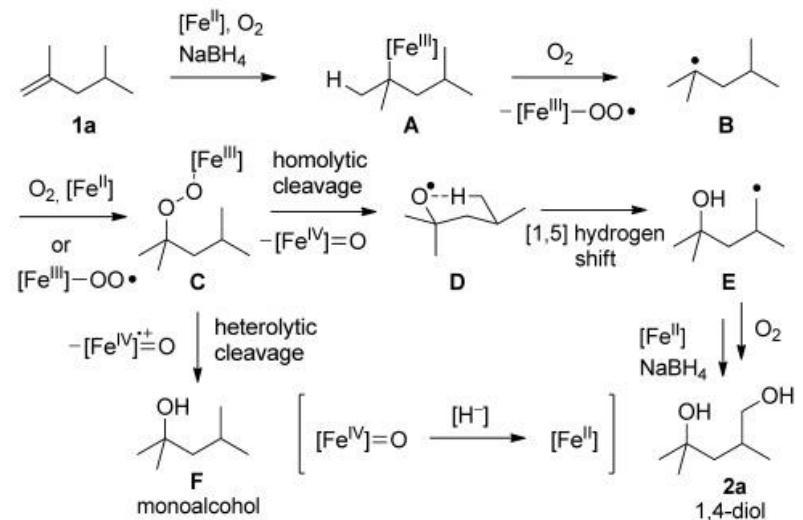
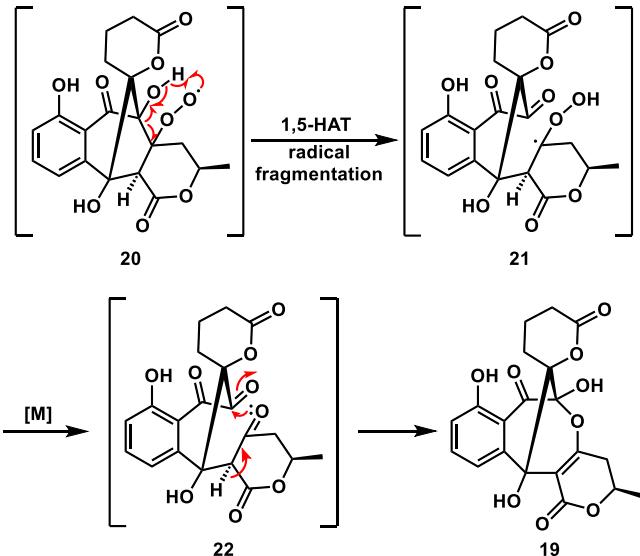
Mukaiyama Hydration

**Table S3.** Conditions screened on Mukaiyama hydration^[a]

Entry	R	Metal precatalyst	Solvent	Additive	Time (h)	Yield of 18/25 (%) ^[b]	Yield of 19 (%) ^[b]
1	H	Mn(dpm) ₃	iPrOH	-	3	-	39
2	H	Mn(dpm) ₃	iPrOH	PPh ₃	2.5	-	42
3 ^[c]	H	Fe(acac) ₃	iPrOH	NaHCO ₃	17	-	-

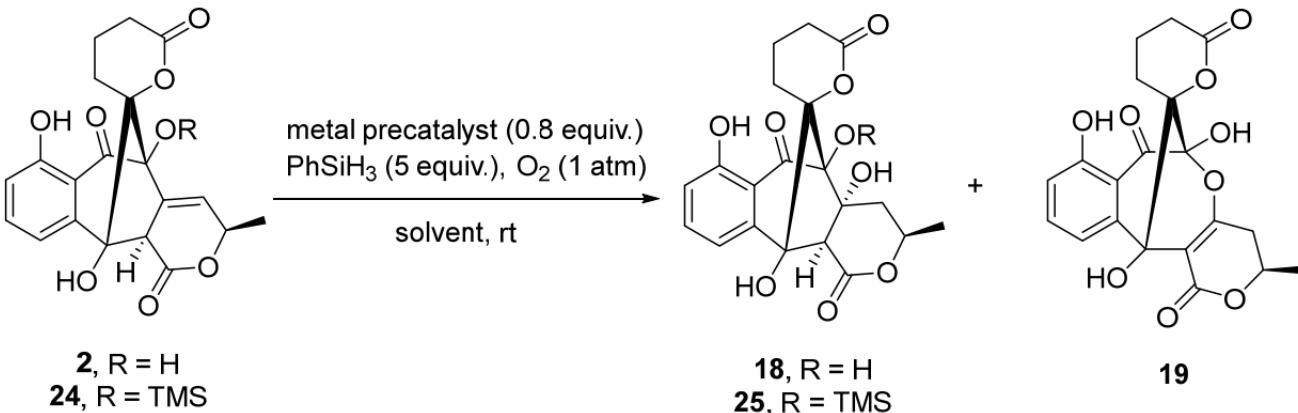
[a] Reaction conditions: **2/24** (0.022 mmol), metal precatalyst (0.8 equiv.), PhSiH₃ (5.0 equiv.) and O₂ (1 atm, balloon) at room temperature. [b] Isolated yield. [c] Methyl 4-nitrobenzenesulfonate (1.3 equiv.) was used instead of O₂.^[1] [d] Using cobalt as a precatalyst resulted in complex products in which the phenol hydroxyl group of each product chelated with cobalt (II). Attempts to dissociate cobalt (II) from the products were not successful. [e] Et₃SiH (2.0 equiv.) was used as hydride source instead.^[2] [f] Mn(dpm)₃ (0.2 equiv.). [g] Mn(dpm)₃ (1.6 equiv.). dpm = dipivaloylmethanate, acac = acetylacetone.

- PPh₃: prevent intermediate peroxide adduct from generating by-product

Nature **2016**, *532*, 90.**1,5-HAT***Angew. Chem. Int. Ed.*, **2014**, *53*, 2730.

Step iv

Mukaiyama Hydration

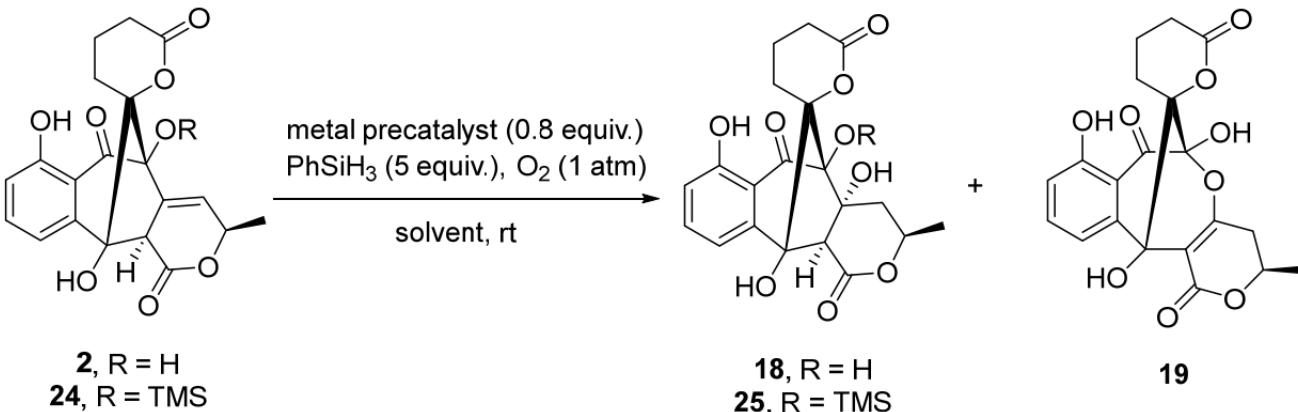
**Table S3.** Conditions screened on Mukaiyama hydration^[a]

Entry	R	Metal precatalyst	Solvent	Additive	Time (h)	Yield of 18/25 (%) ^[b]	Yield of 19 (%) ^[b]
4	TMS	Fe(acac) ₃	EtOH	-	3.5	-	30
5 ^[d]	TMS	Co(acac) ₂	iPrOH	-	3.5	-	-
6 ^[d,e]	TMS	Co(acac) ₂	iPrOH	TBHP	2	-	-
7	TMS	Mn(acac) ₃	iPrOH	PPh ₃	7	9	22
8	TMS	Mn(dpm) ₃	iPrOH	PPh ₃	6	16	31

[a] Reaction conditions: **2/24** (0.022 mmol), metal precatalyst (0.8 equiv.), PhSiH₃ (5.0 equiv.) and O₂ (1 atm, balloon) at room temperature. [b] Isolated yield. [c] Methyl 4-nitrobenzenesulfonate (1.3 equiv.) was used instead of O₂.^[1] [d] Using cobalt as a precatalyst resulted in complex products in which the phenol hydroxyl group of each product chelated with cobalt (II). Attempts to dissociate cobalt (II) from the products were not successful. [e] Et₃SiH (2.0 equiv.) was used as hydride source instead.^[2] [f] Mn(dpm)₃ (0.2 equiv.). [g] Mn(dpm)₃ (1.6 equiv.). dpm = dipivaloylmethanate, acac = acetylacetone.

Step iv

Mukaiyama Hydration

**Table S3.** Conditions screened on Mukaiyama hydration^[a]

Entry	R	Metal precatalyst	Solvent	Additive	Time (h)	Yield of 18/25 (%) ^[b]	Yield of 19 (%) ^[b]
9	TMS	Mn(dpm) ₃	DCM- <i>i</i> PrOH	-	7	14	22
10 ^[f]	TMS	Mn(dpm) ₃	<i>i</i> PrOH	-	19	19	19
11 ^[g]	TMS	Mn(dpm) ₃	<i>i</i> PrOH	-	3	20	20
12	TMS	Mn(dpm) ₃	<i>i</i> PrOH	-	6	33	26

[a] Reaction conditions: **2/24** (0.022 mmol), metal precatalyst (0.8 equiv.), PhSiH₃ (5.0 equiv.) and O₂ (1 atm, balloon) at room temperature. [b] Isolated yield. [c] Methyl 4-nitrobenzenesulfonate (1.3 equiv.) was used instead of O₂.^[1] [d] Using cobalt as a precatalyst resulted in complex products in which the phenol hydroxyl group of each product chelated with cobalt (II). Attempts to dissociate cobalt (II) from the products were not successful. [e] Et₃SiH (2.0 equiv.) was used as hydride source instead.^[2] [f] Mn(dpm)₃ (0.2 equiv.). [g] Mn(dpm)₃ (1.6 equiv.). dpm = dipivaloylmethanate, acac = acetylacetone.



Step viii

α,β -Dehydrogenation of Ketones: Cu/DTBP

