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Total syntheses of Tetrodotoxin and 9-*epi*Tetrodotoxin

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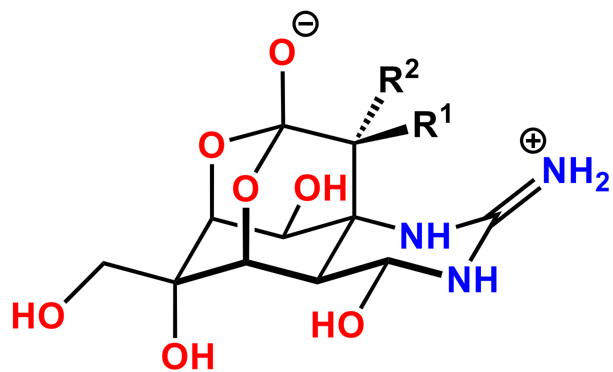
First isolation of TTX in 1909

Structure solved in 1964

First synthesis in 1972

One of the most potent neurotoxins



R^1 = OH, R^2 = H **Tetrodotoxin (1)**

R^1 = H, R^2 = OH **9-*epi*Tetrodotoxin (1a)**

Rigid Dioxa-adamantane Cage

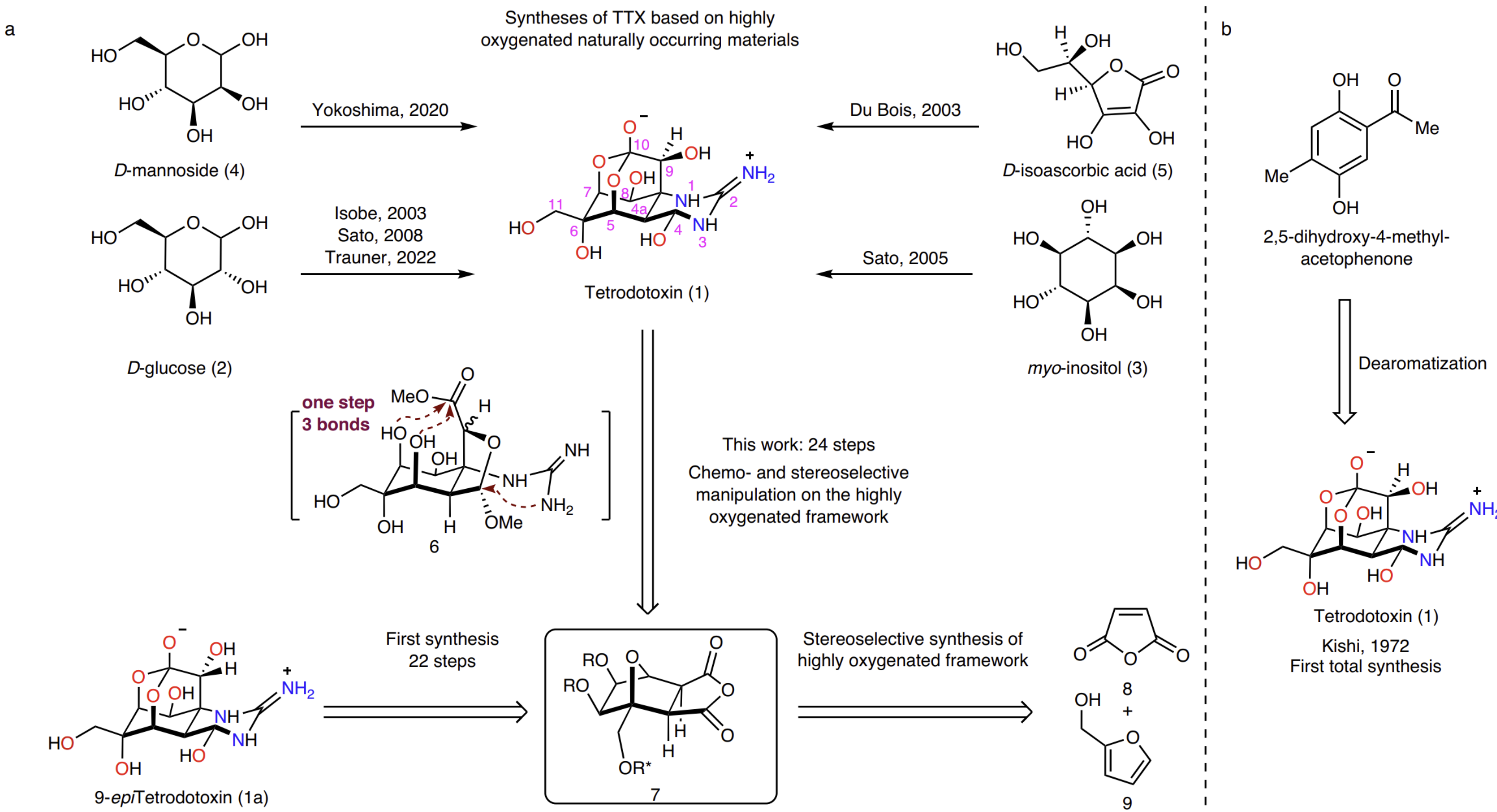
Cyclic Guanidinium

9 Consecutive Stereocenters

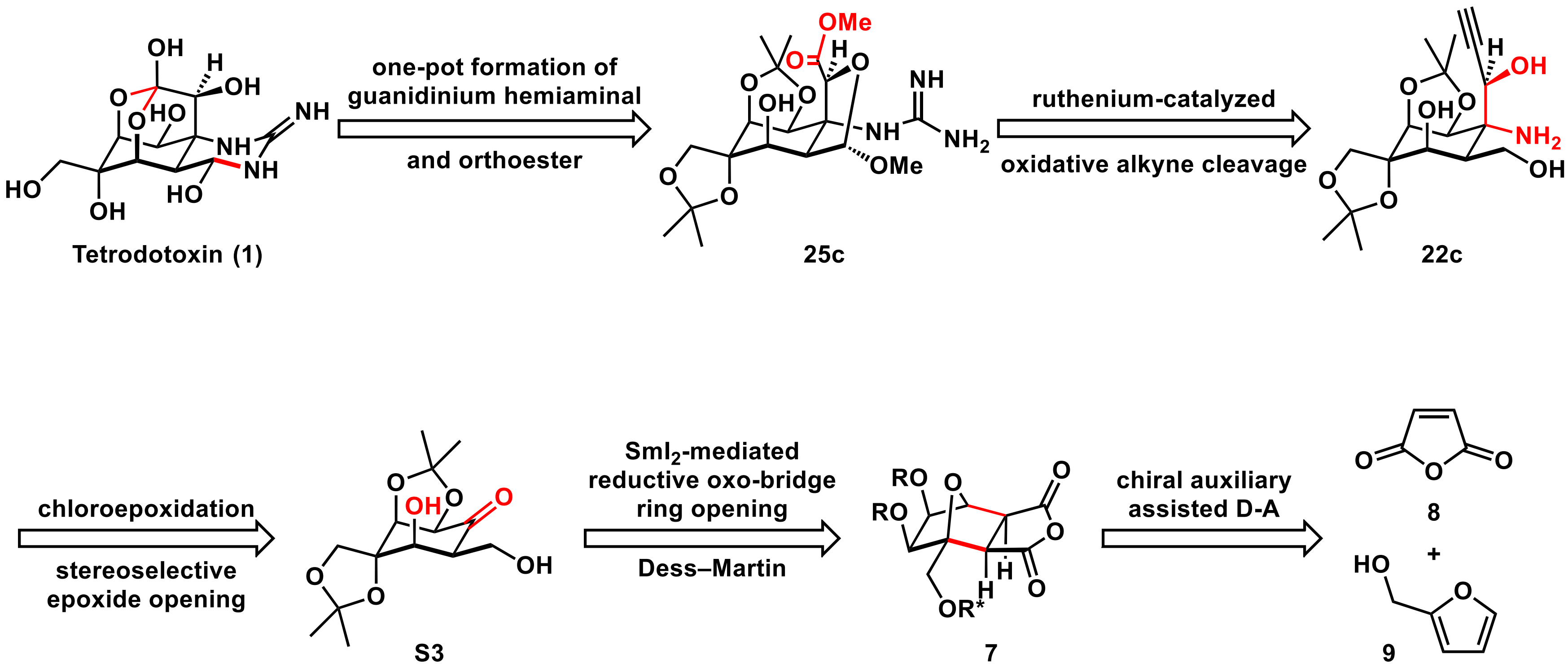
Bridgehead N-containing Quaternary Center

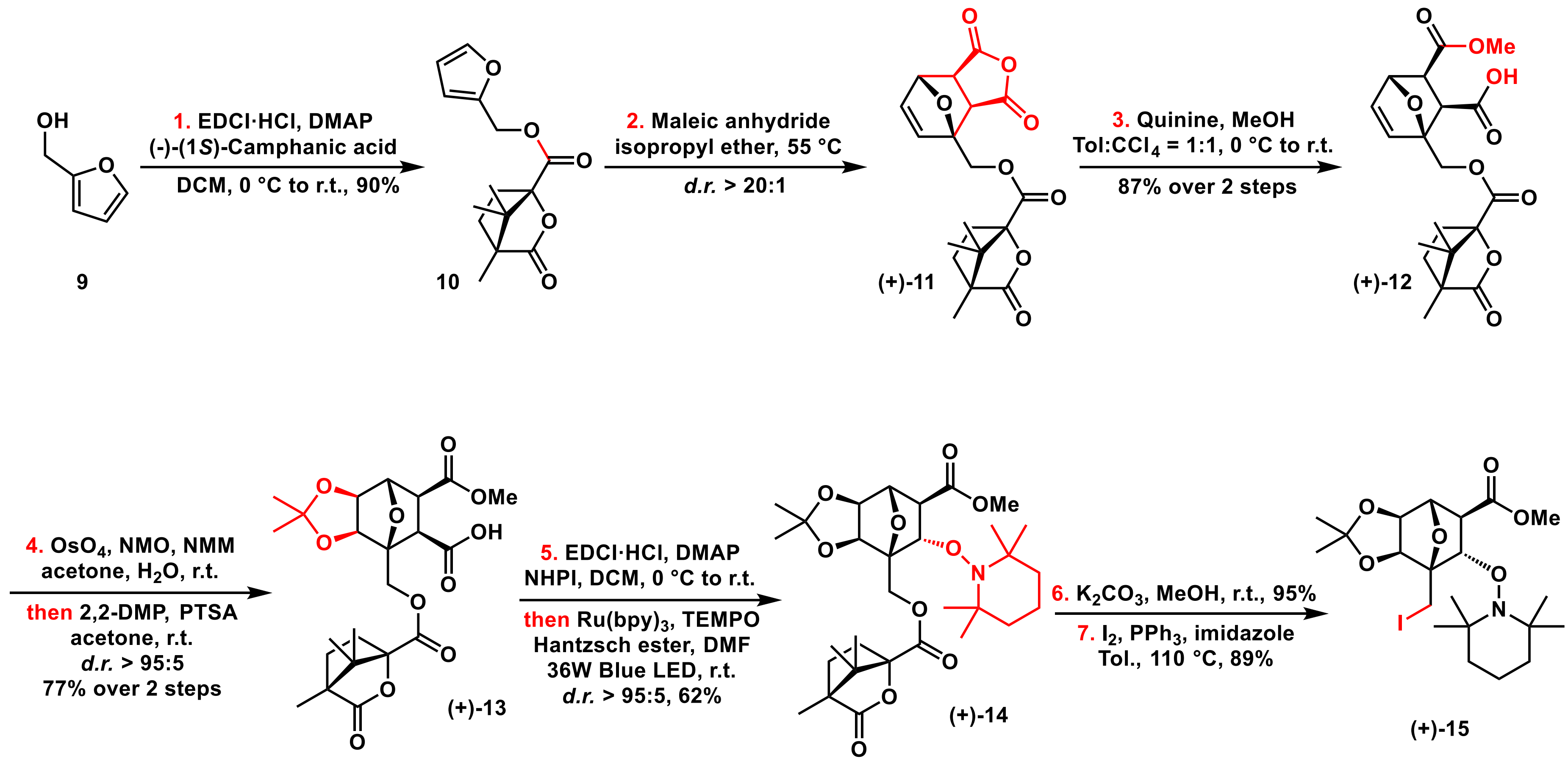
Nat. Commun., **2024**, *15*, 679.

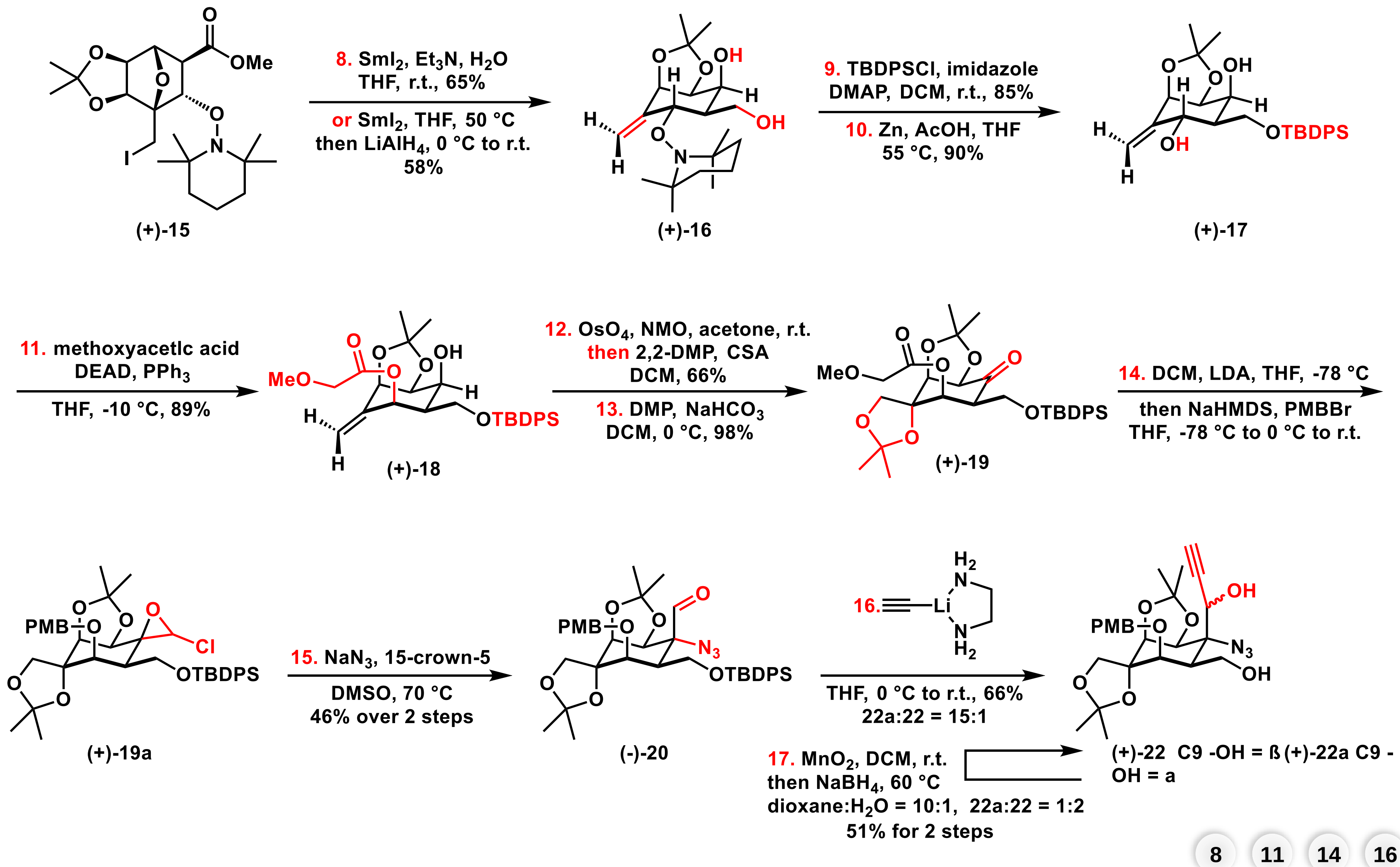
Previous Synthesis of Tetrodotoxin and Retrosynthetic Analysis

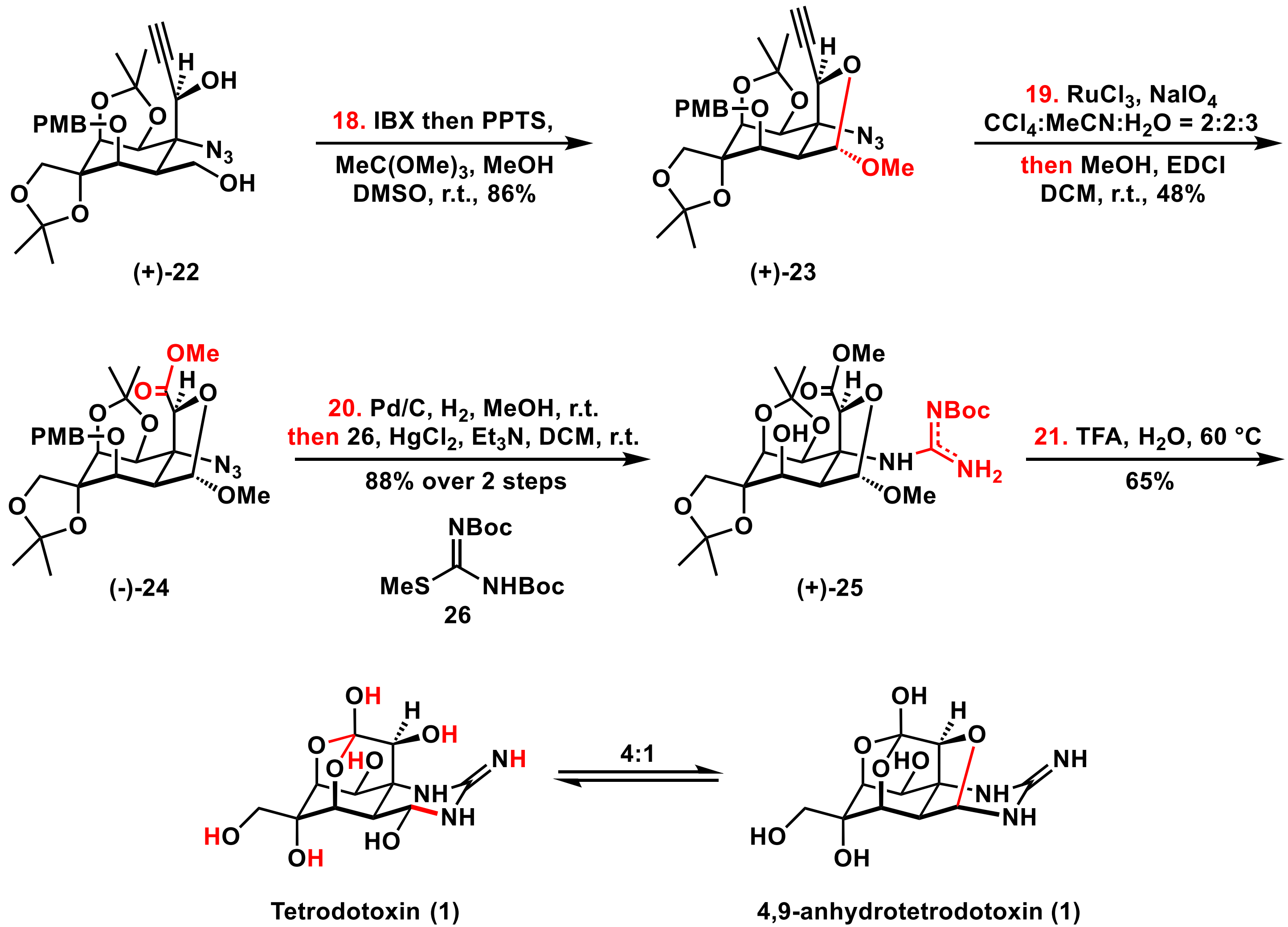


Retrosynthetic Analysis

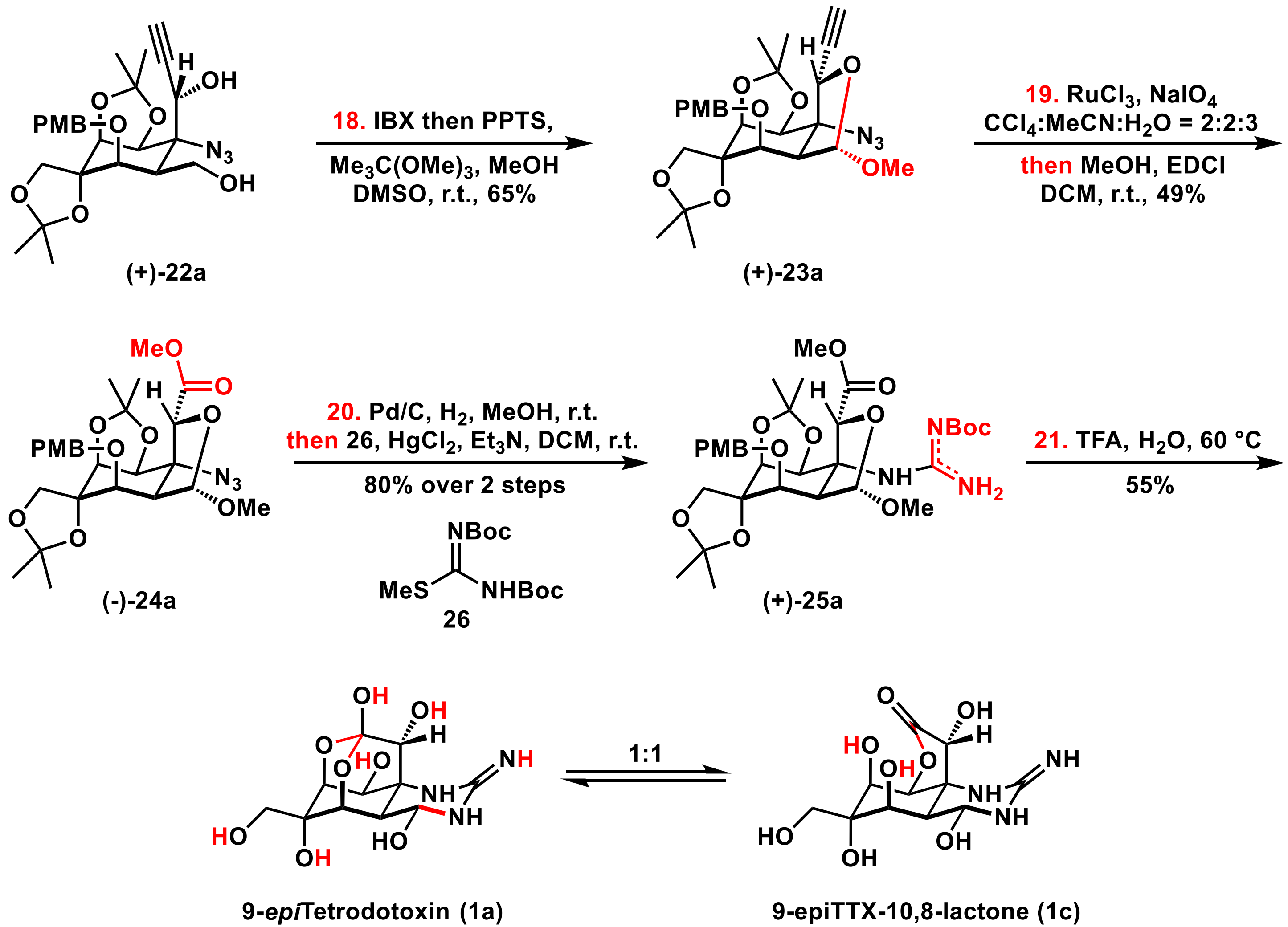



9
1. EDCI·HCl, DMAP
(-)-(1S)-Camphanic acid
DCM, 0 °C to r.t., 90%
10
2. Maleic anhydride
isopropyl ether, 55 °C
d.r. > 20:1
(+)-11
3. Quinine, MeOH
Tol:CCl_4 = 1:1, 0 °C to r.t.
87% over 2 steps
(+)-12
4. OsO_4, NMO, NMM
acetone, H_2O, r.t.
then 2,2-DMP, PTSA
acetone, r.t.
d.r. > 95:5
77% over 2 steps
(+)-13
5. EDCI·HCl, DMAP
NHPI, DCM, 0 °C to r.t.
then Ru(bpy)$_3$, TEMPO
Hantzsch ester, DMF
36W Blue LED, r.t.
d.r. > 95:5, 62%
(+)-14
6. K_2CO_3, MeOH, r.t., 95%
7. I_2, PPh_3, imidazole
Tol., 110 °C, 89%
(+)-15


(+)-15
8. SmI2, Et3N, H2O
THF, r.t., 65%
or SmI2, THF, 50 °C
then LiAlH4, 0 °C to r.t.
58%
(+)-16
9. TBDPSCl, imidazole
DMAP, DCM, r.t., 85%
10. Zn, AcOH, THF
55 °C, 90%
(+)-17
11. methoxyacetlc acid
DEAD, PPh3
THF, -10 °C, 89%
(+)-18
12. OsO4, NMO, acetone, r.t.
then 2,2-DMP, CSA
DCM, 66%
13. DMP, NaHCO3
DCM, 0 °C, 98%
(+)-19
14. DCM, LDA, THF, -78 °C
then NaHMDS, PMBBr
THF, -78 °C to 0 °C to r.t.
(+)-19a
15. NaN3, 15-crown-5
DMSO, 70 °C
46% over 2 steps
(-)-20
16.
THF, 0 °C to r.t., 66%
22a:22 = 15:1
17. MnO2, DCM, r.t.
then NaBH4, 60 °C
dioxane:H2O = 10:1, 22a:22 = 1:2
51% for 2 steps
(+)-22 C9 -OH = ß (+)-22a C9 - OH = a
8
11
14
16

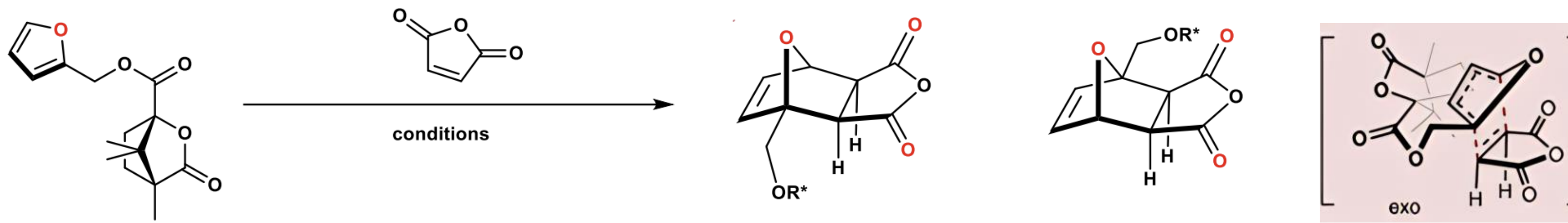


(+)-22
18. IBX then PPTS,
MeC(OMe)3, MeOH
DMSO, r.t., 86%
(+)-23
19. RuCl3, NaIO4
CCl4:MeCN:H2O = 2:2:3
then MeOH, EDCI
DCM, r.t., 48%
(-)-24
20. Pd/C, H2, MeOH, r.t.
then 26, HgCl2, Et3N, DCM, r.t.
88% over 2 steps
26
(+)-25
21. TFA, H2O, 60 °C
65%
4:1
Tetrodotoxin (1)
4,9-anhydrotetrodotoxin (1)



PMB
(+)-22a
18. IBX then PPTS,
Me3C(OMe)3, MeOH
DMSO, r.t., 65%
(+)-23a
19. RuCl3, NaIO4
CCl4:MeCN:H2O = 2:2:3
then MeOH, EDCI
DCM, r.t., 49%
(-)-24a
20. Pd/C, H2, MeOH, r.t.
then 26, HgCl2, Et3N, DCM, r.t.
80% over 2 steps
26
(+)-25a
21. TFA, H2O, 60 °C
55%
1:1
9-epiTetrodotoxin (1a)
9-epiTTX-10,8-lactone (1c)

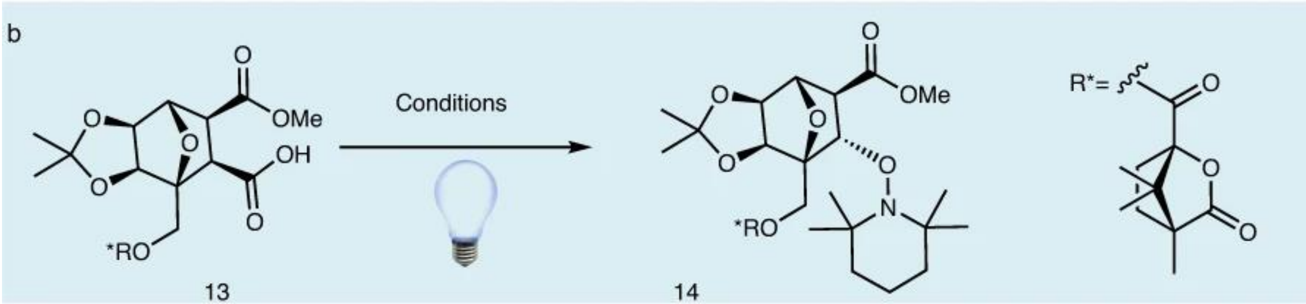
Step 2 Chiral Auxiliary Assisted Diels–Alder



(-)-10 (+)-11 11a

Entry	Maleic anhydride (eq.)	Temperature(ºC)	Solvent	Time(h)	(+)-11 [a] [%]	11:11a
1	1.0	55	Neat	24	36.5	5:4
2	1.0	55	Toluene	24	16.8	1:1
3	1.0	55	MTBE	24	38.9	10:1
4	1.0	55	Isopropyl Ether	24	65.5	10:1
5	1.0	55	THF	24	13.8	1:1
6	1.0	55	CHCl3	24	11.4	1:1
7	1.0	55	CH3CN	24	17.1	5:6
8	1.0x2[b]	55	Neat	48	68.5	5:1
9	2.0x2[b]	55	Neat	48	71.1	10:3
10	4.0x2[b]	55	Neat	48	39.7	5:6
11	1.0x2[b]	55	Isopropyl Ether	48	86.8	>20:1
12	1.0x2[b]	55	Isopropyl Ether	48	91.3[c]	>20:1

Step 5 Optimization of Decarboxylative Hydroxylation

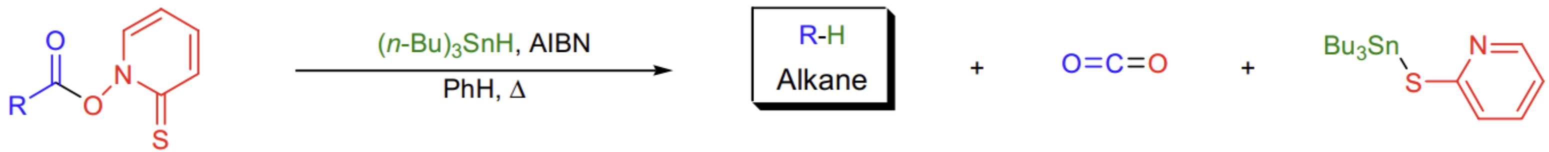


Entry	Conditions	Yield [%]	d.r.
1	Mes-AcrClO$_4$/K$_2$HPO$_4$/O$_2$/blue LEDs then NaBH$_4$	<5	-
2	EDCI/DMAP/1-Hydroxy-pyridinethione then ^{t}BuSH/O$_2$/Hg lamp then P(OEt$_3$)	<5	-
3	EDCI/DMAP/NHPI then Ru(bpy)$_3$Cl$_2$/TEMPO/Hantzsch ester/blue LEDs	62[a]	> 95:5
4	EDCI/DMAP/NHPI then Ru(bpy)$_3$Cl$_2$/TEMPO/Hantzsch ester/blue LEDs	66[b]	> 95:5

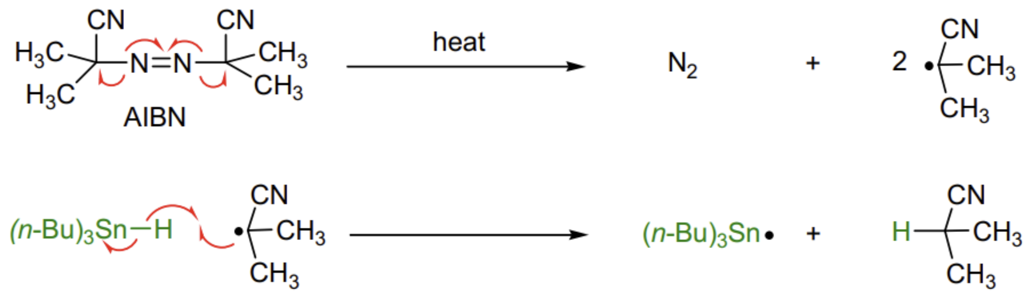
[a] d.r. > 95:5, 30 g scale.

[b] Isolated yield on 1 g scale using a circulating flow system.

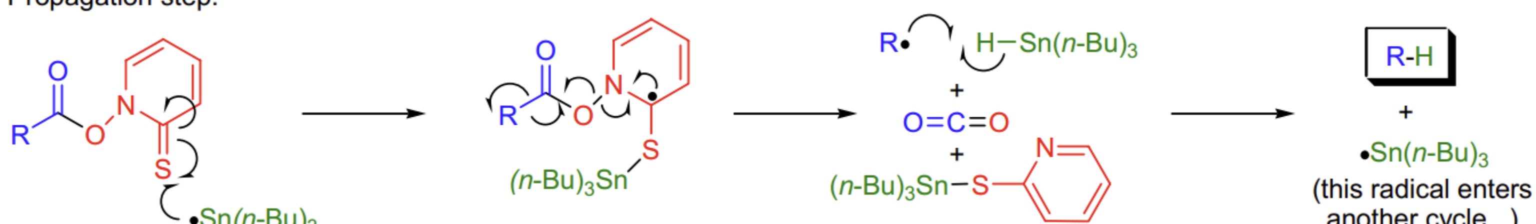
Step 5 Barton Decarboxylation Reaction



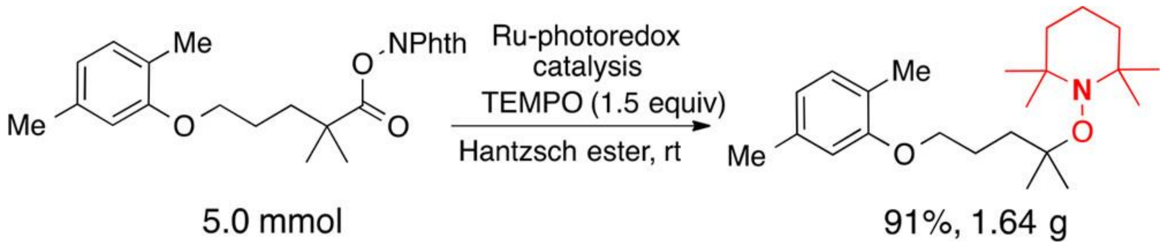
Initiation step:

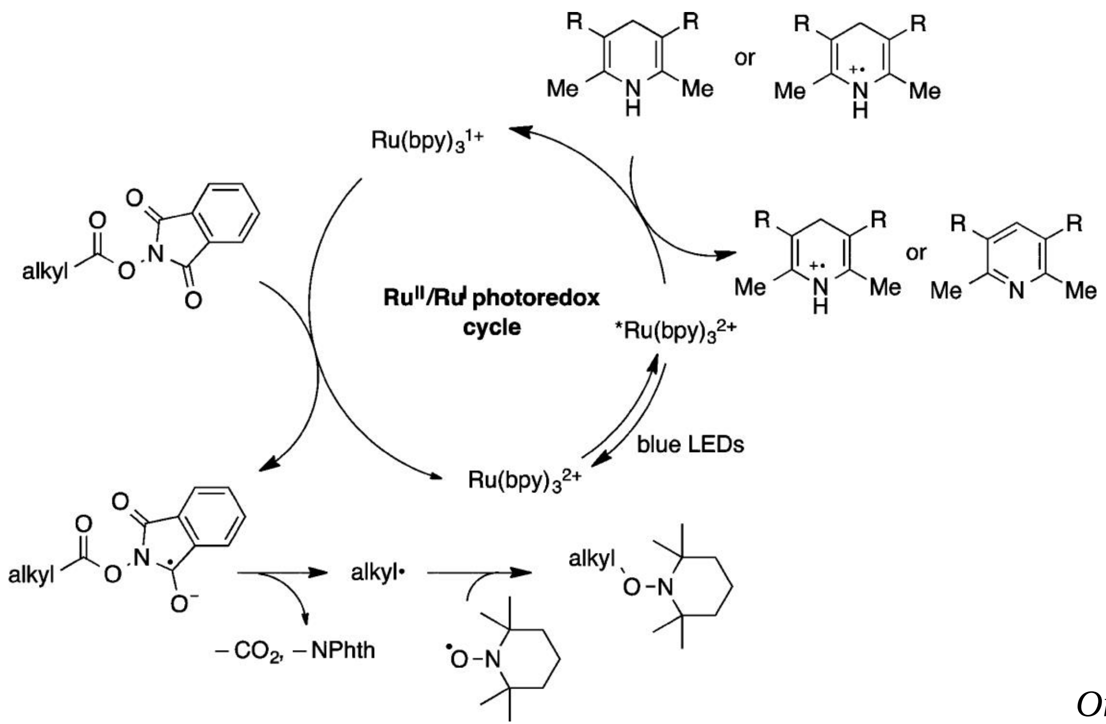


Propagation step:



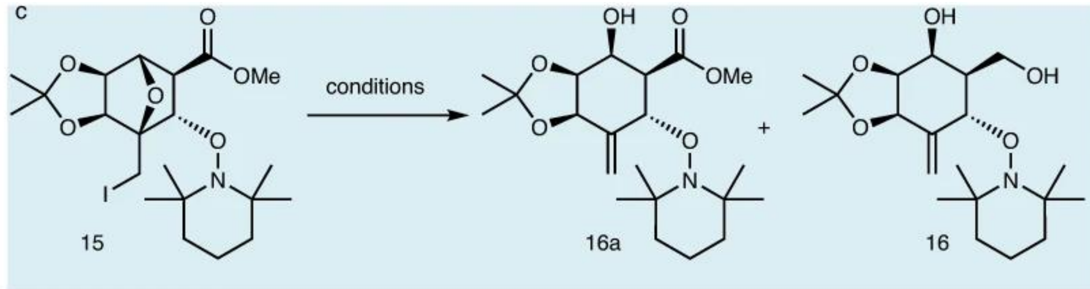
Step 5 Ru-Catalyzed Photoredox Decarboxylative Hydroxylation





Org. Lett., **2018**, *20*, 4824.

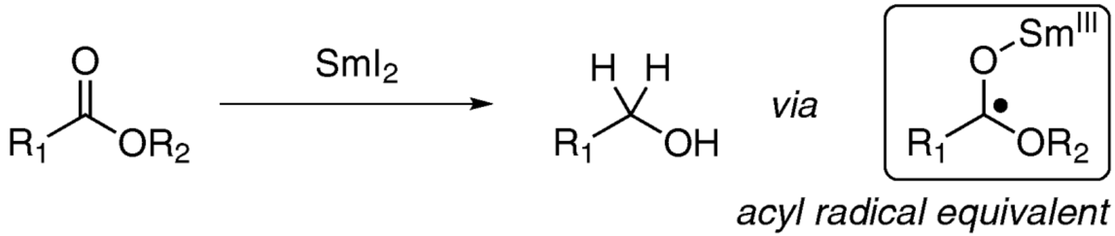
Step 8 SmI_2/H_2O/Amine-Mediated Fragmentation



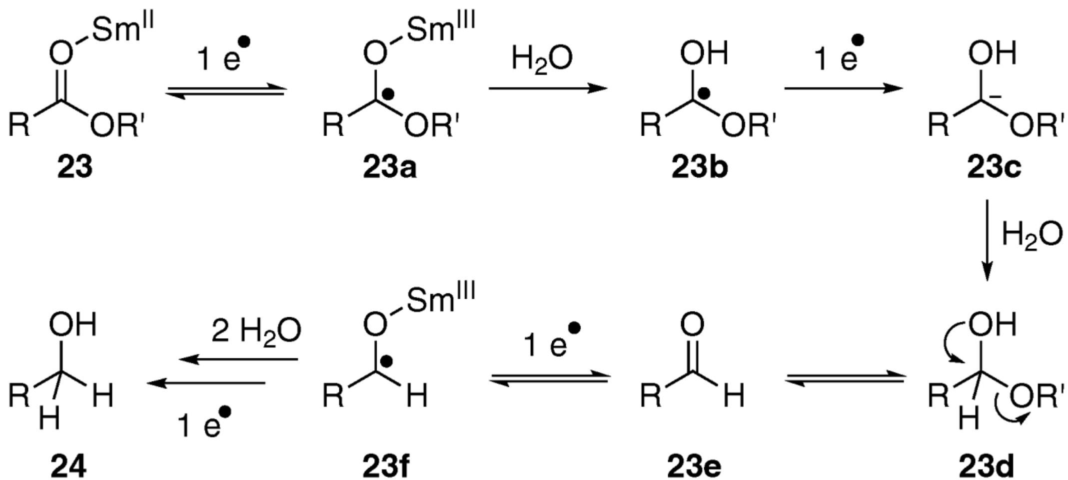
Entry	SmI_2 (equiv.)	Additives	16a [%]	16 [%]
1	8	HMPA[a]	88	-
2	12	Et_3N/H_2O[b]	<5	77(65%)
3	12	Et_3N/H_2O[c]	<5	55
4	20	pyrrolidine/H_2O[d]	20	18
5	3	-	-	58[e]

[a] HMPA (10 eq). [b] Et_3N (24 eq)/H_2O (24 eq). The yield in the bracket is an isolated yield. [c] Et_3N (36 eq)/H_2O (36 eq). [d] pyrrolidine (60 eq)/H_2O (60 eq). [e] SmI_2 (3 eq), 55 °C, without purification followed by reduction using $LiAlH_4$. The yield is isolated yields for the two steps on decagram scale.

Step 8 Reduction of Esters Using $SmI_2–H_2O$

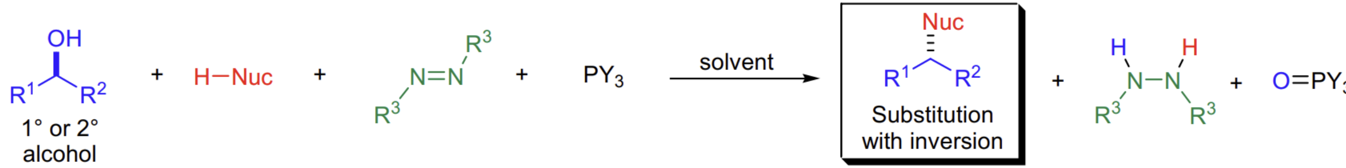


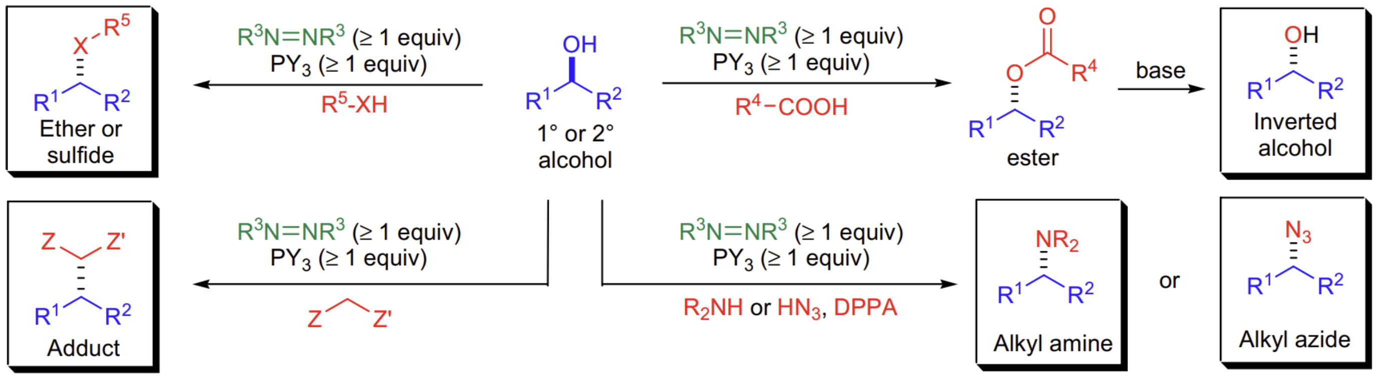
- Unique role of water as an additive for use with SmI_2
- Triethylamine could be replaced by a variety of amines, e.g. pyrrolidine

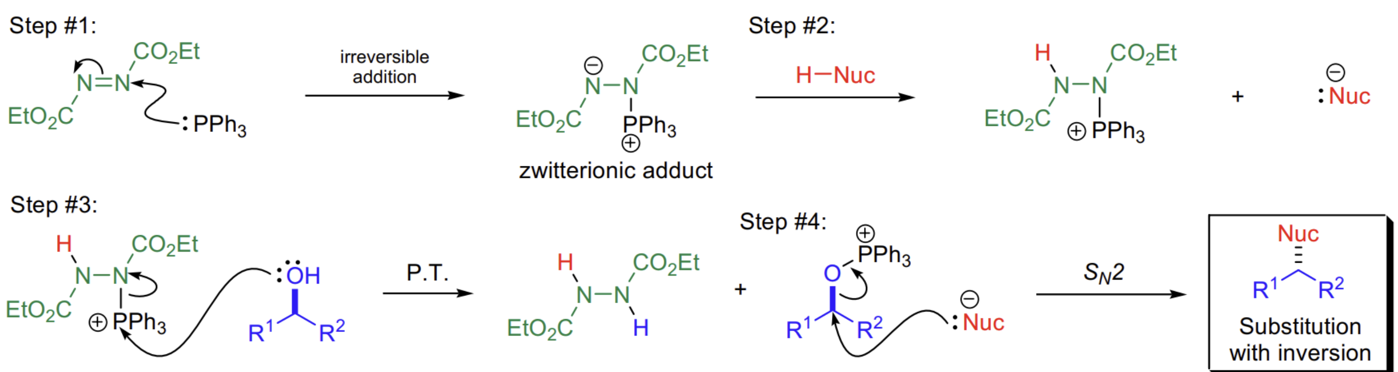


Chem. Commun., **2011**, *47*, 10254.

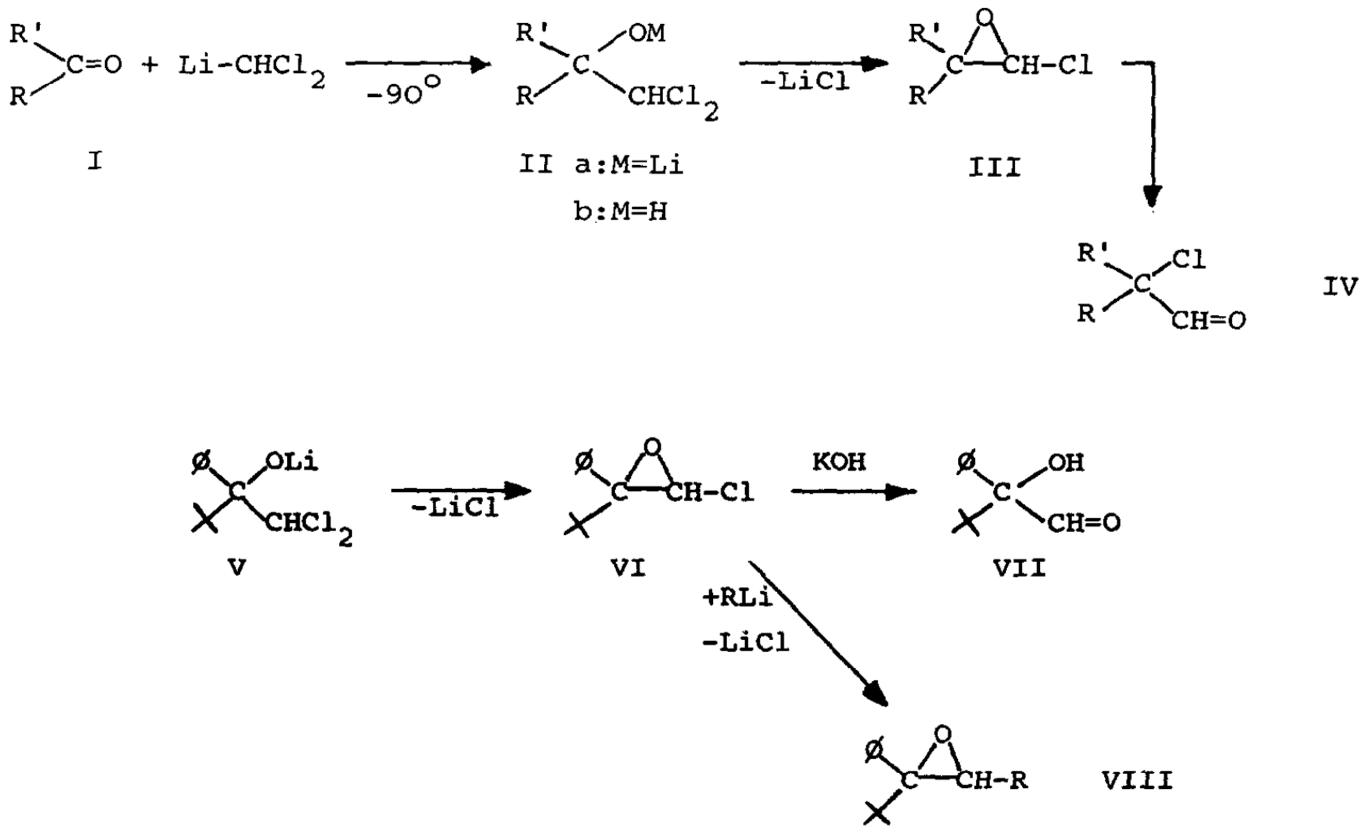
Step 11 Mitsunobu Reaction





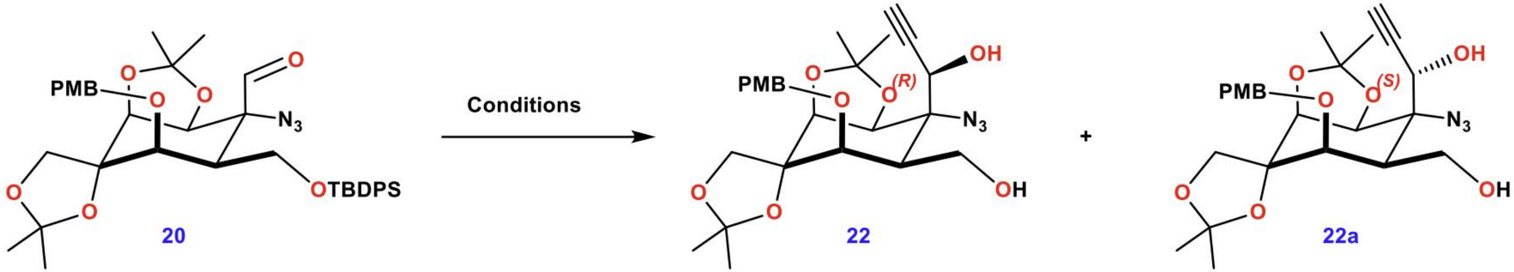


Step 14 Construction of Spiro α-Chloroepoxide with $LiCHCl_2$



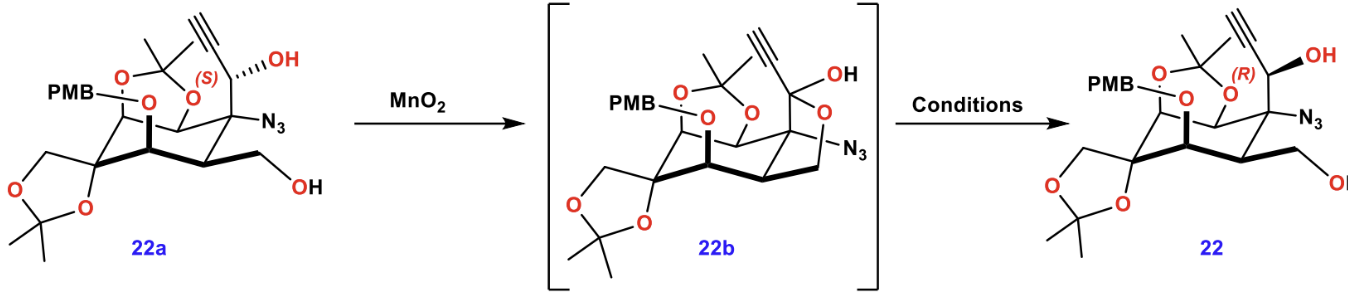
Tetrahedron Lett., **1969**, *10*, 2181.

Step 16 Optimization of 1,2-Addition of Acetylide Anion to 20



Entry	[b]Conditions	Solvent, temperature (°C)	Time (h)	22a:22[a]	Combined yields[a]
1	TMS—≡—Li	THF, -78 °C	2	>20:1	80%
2	TMS—≡—Li/ HMPA	THF, -78 °C	2	-	<10%
3	TMS—≡—Li/ $ZnBr_2$	THF, 0 °C to r.t.	16	-	<10%
4	TMS—≡—Li	Et_2O, -78 °C	2	>20:1	53%
5	TMS—≡—Li/ $ZnBr_2$	Et_2O, 0 °C to r.t.	16	-	<10%
6	TMS—≡—MgBr	THF, -78 °C to r.t	2	N.D.	N.D.
7	CaC_2	THF, -78 °C	2	-	N.R.
8	≡—Li $NH_2CH_2CH_2NH_2$	THF, -78 °C	2	15:1	70%(66%)
9	≡—MgBr	THF, -78 °C to r.t	2	N.D.	N.D.

Step 16 Optimization of the Epimerization Conditions



Entry	Conditions	Solvent, temperature (°C)	Time (h)	22a:22[a]	Combined yields[a]
1	$LiBH_4$	THF, r.t.	0.5h	1:1	87%
2	L-selectride	CH_2Cl_2, -78 °C to r.t.	16h	-	N.D.
3	L-selectride/$ZnCl_2$	CH_2Cl_2, -78 °C to r.t.	3h	-	N.D.
4	$LiAlH_4$	THF, 0 °C to r.t.	1h	-	N.D.
5	DIBAL-H	THF, -78 °C to r.t.	3h	1:2	25%
6	CBS cat./ BH_3•THF	THF, -15 °C	16h	-	N.D.
7	$NaBH_4$	Dioxane:H_2O(10:1), r.t.	1.5h	1:2	76%
8	$NaBH_4$	Dioxane:H_2O(10:1), 60°C	0.5h	1:2	85% (77%[b])