Stereoselective Total Synthesis of (±)-Pleurospiroketals A and B

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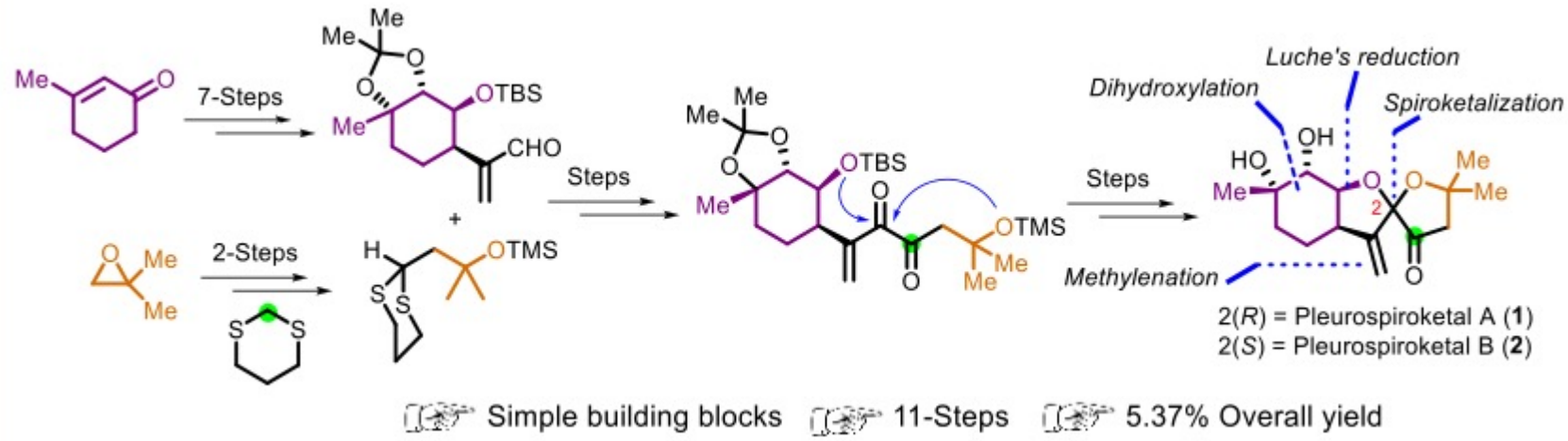

Danylo Hatych
Liu Research Group
Total Synthesis Presentation
11/10/2021

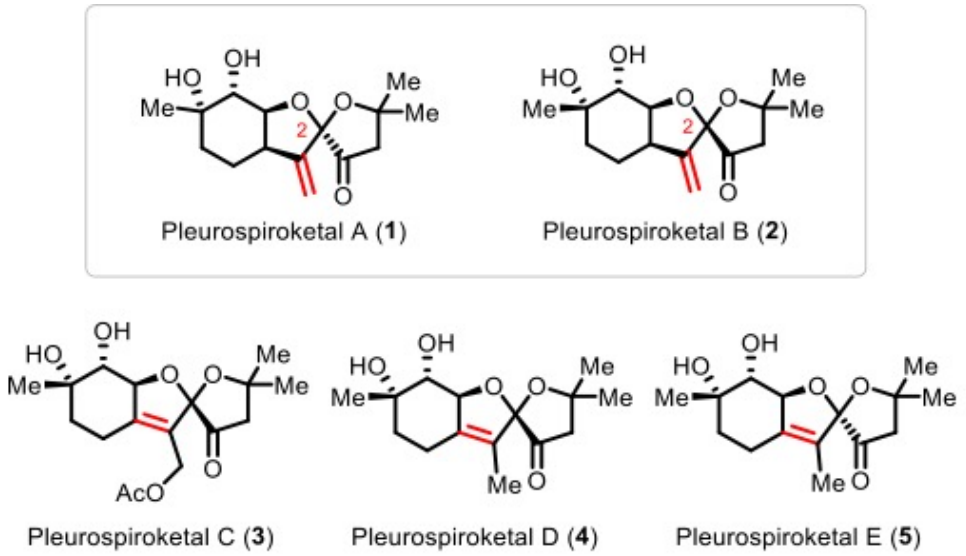

Figure 1. Structures of Pleurospiroketals A–E (**1**–**5**).

- Sesquiterpenes are the largest subgroup of terpenoids
- Pleurospiroketals A-E isolated in 2013 from the culture of the edible mushroom *Pleurotus cornucopiae.*
- **1** and **2** displayed cytotoxic activity against the HeLa cell line (IC50 = 20.6, and 32.8 µM)
- **1** and **2** are C2-epimers(at spiro-center)
- 6/5/5-tricyclic ring system
- perhydrobenzannulated [5,5]-spiroketal framework
- four contiguous stereocenters.

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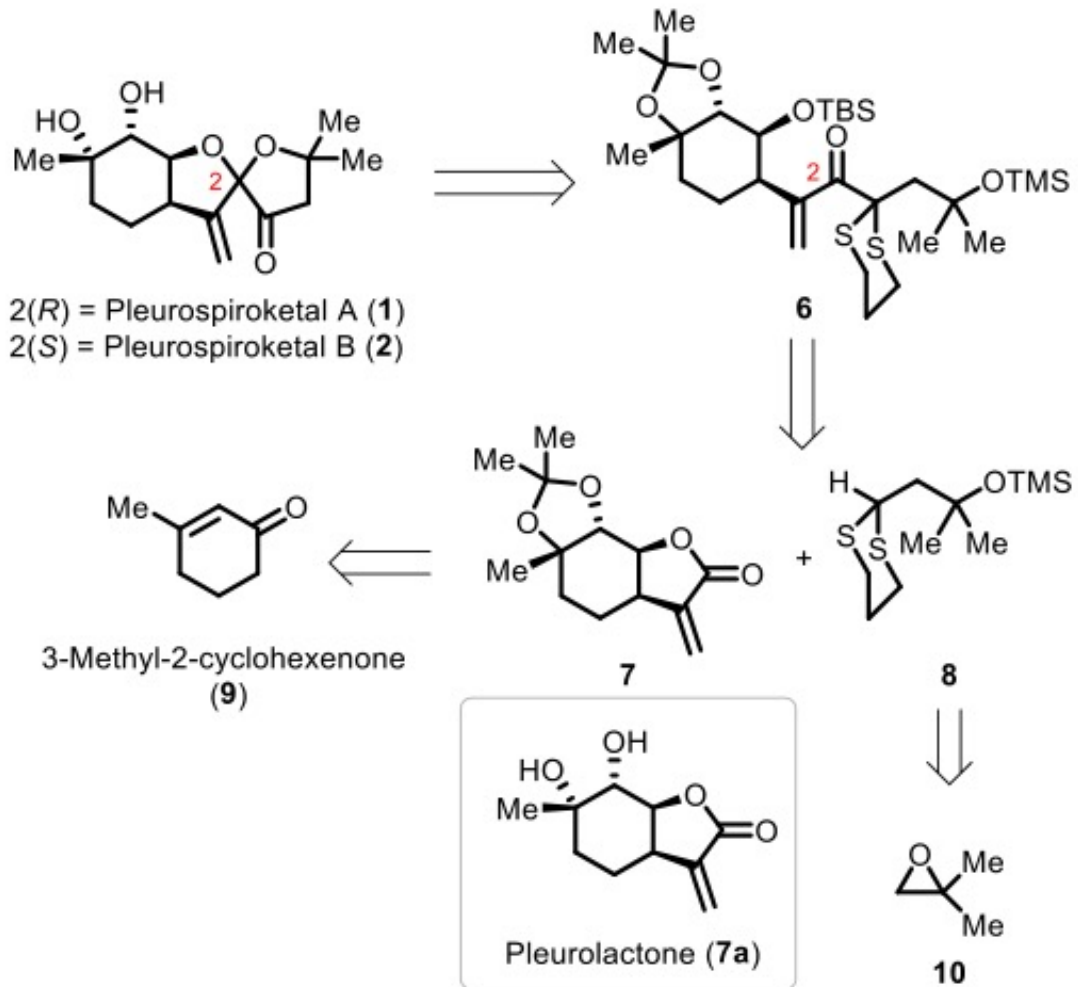
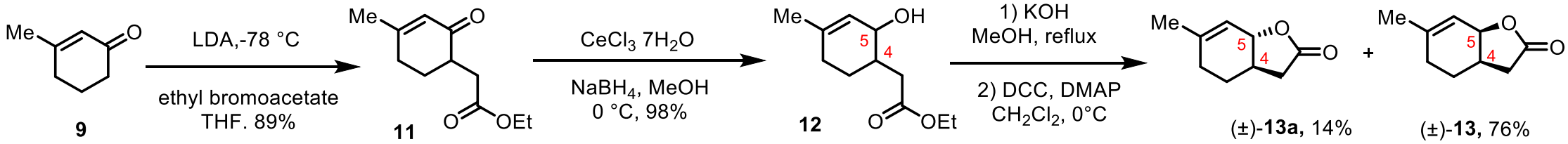
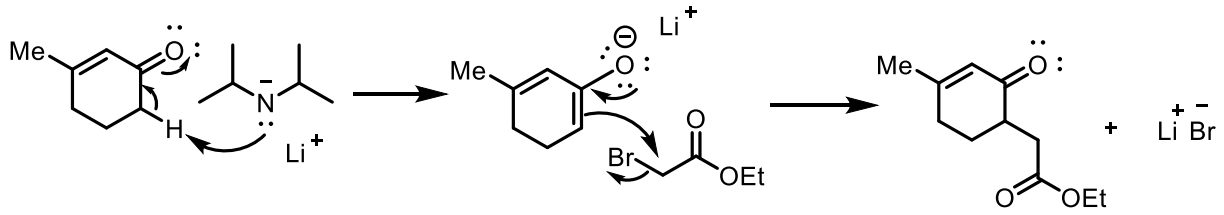
Initial Retrosynthetic Analysis of Pleurospiroketals A (1) and B (2)





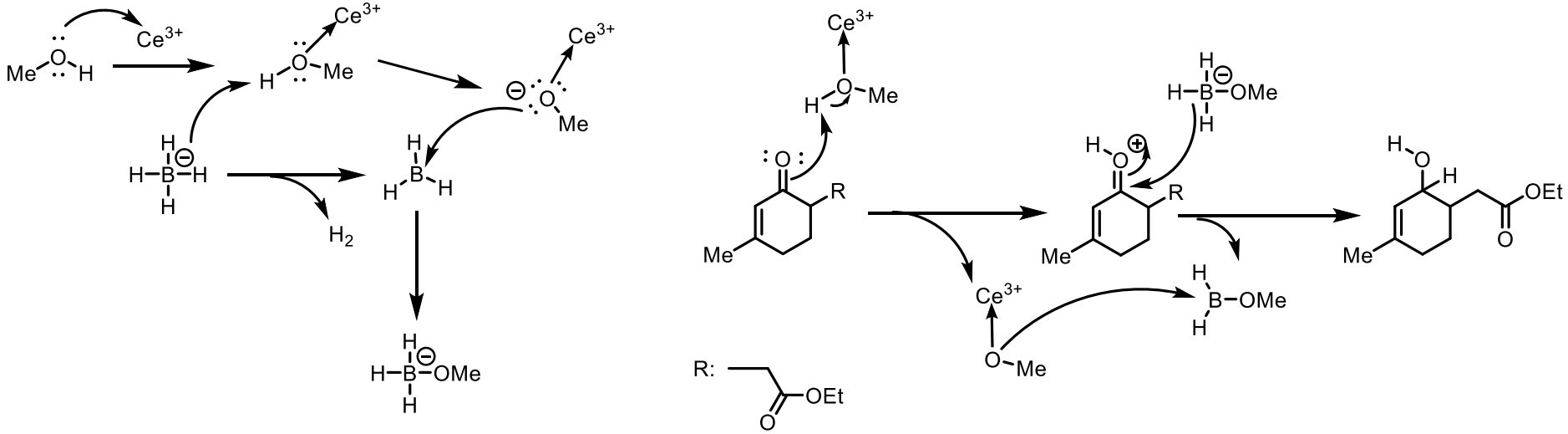
From **9** to **11**:

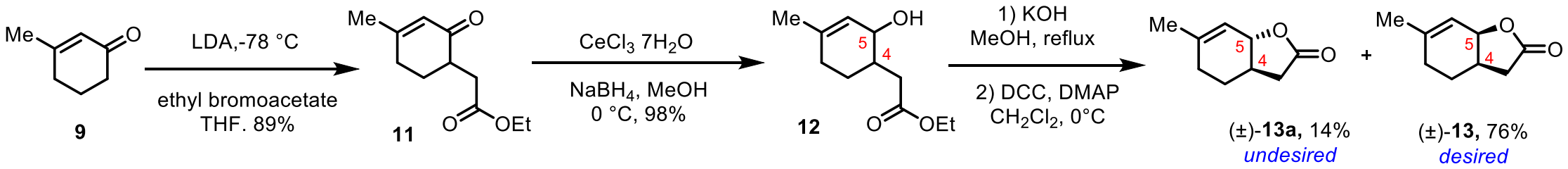
Alkylation of enolate



From **11** to **12**:

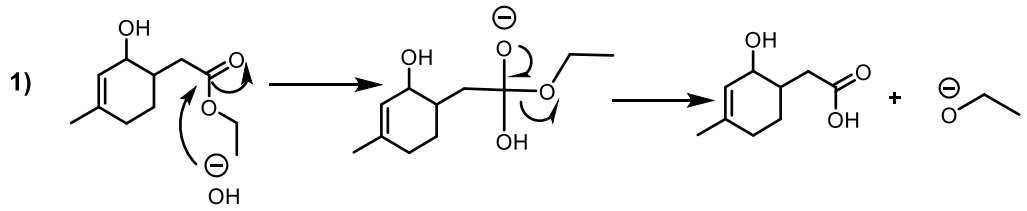
Luche reduction

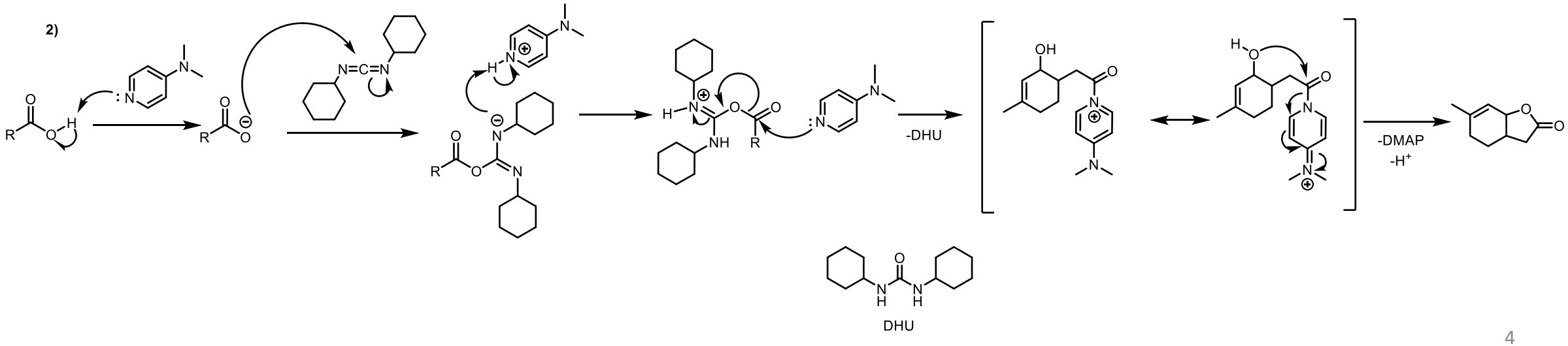


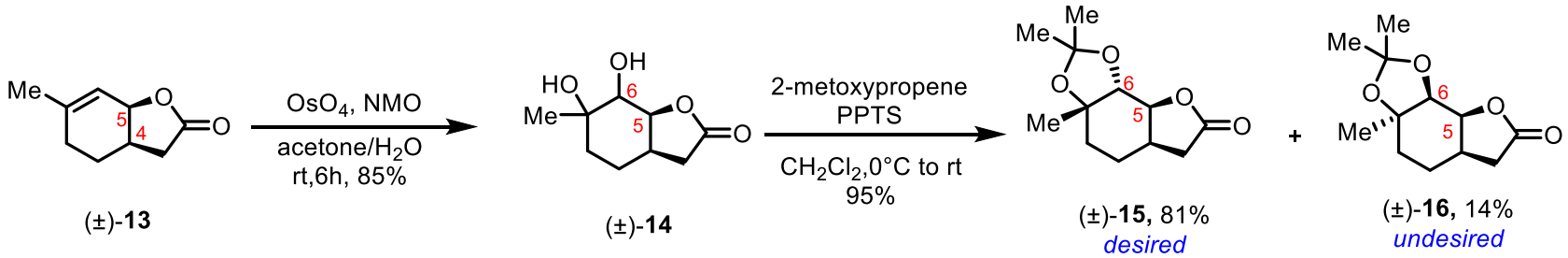


From **12** to **13**:

1) Saponification;
2) Steglich type esterification



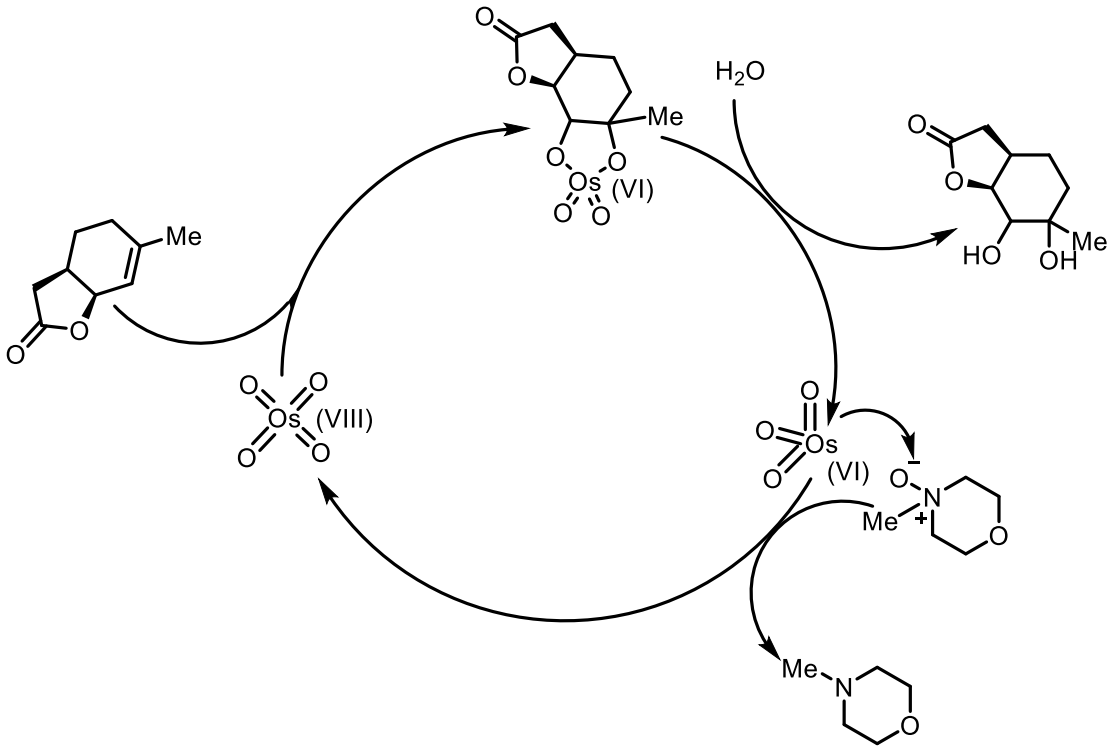




(±)-**13** (±)-**14** (±)-**15,** 81% *desired* (±)-**16,** 14% *undesired*

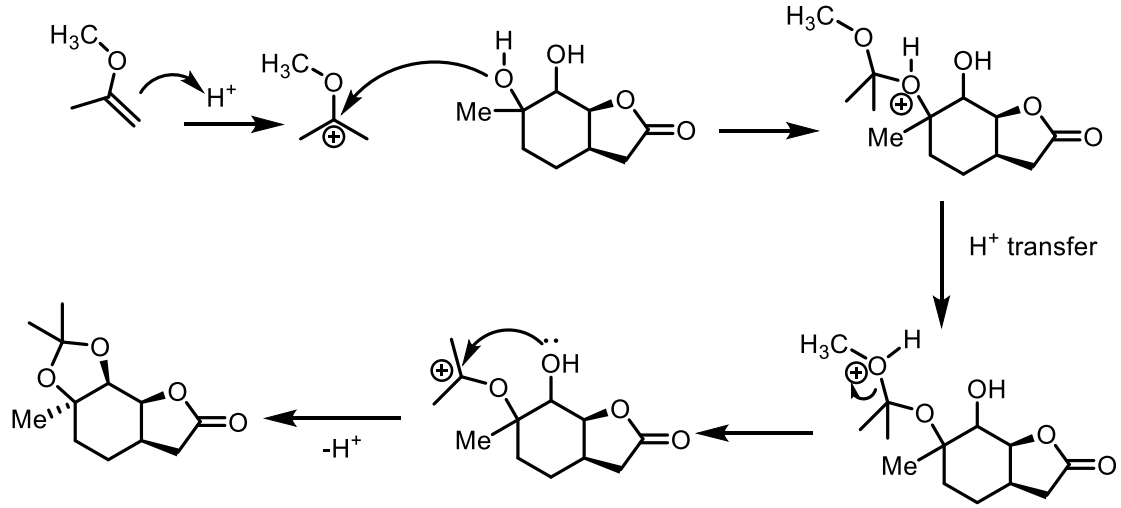
From **13** to **14:**

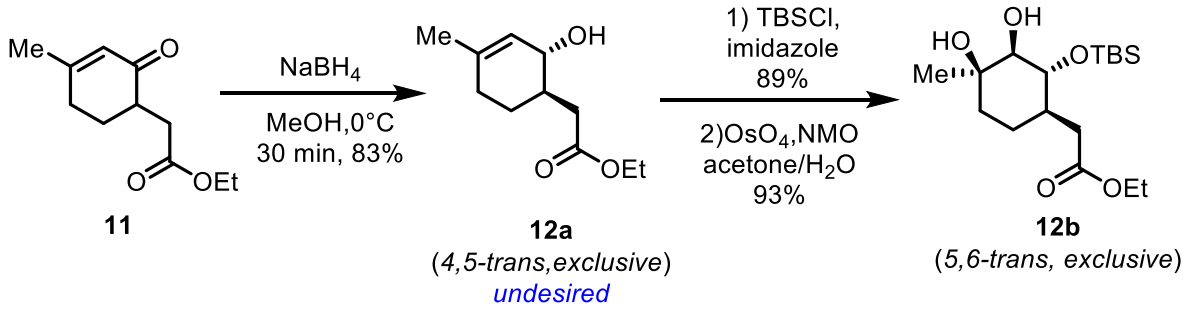
Upjohn Dihydroxylation



From **14** to **15:**

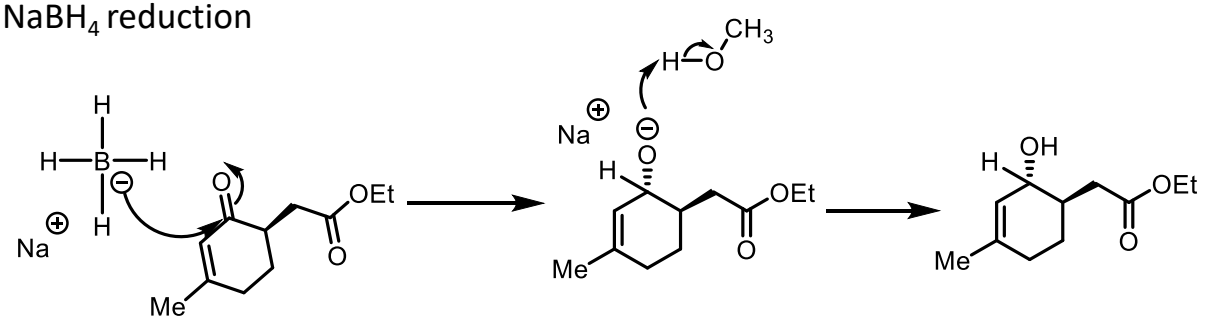
2-methoxypropene protection





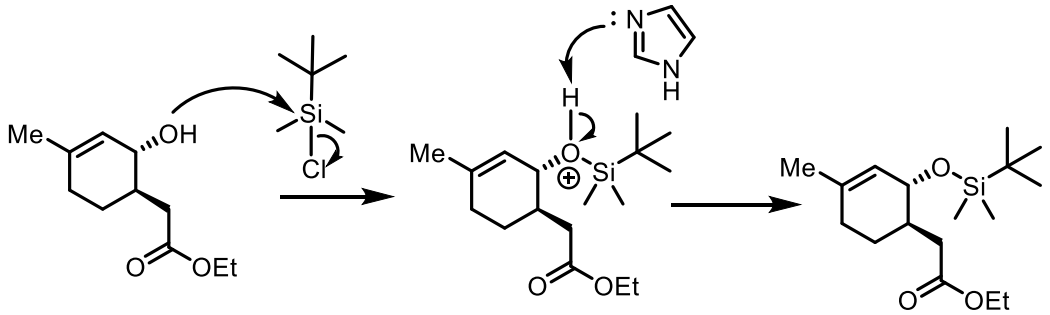
From **11** to **12:**

$NaBH_4$ reduction

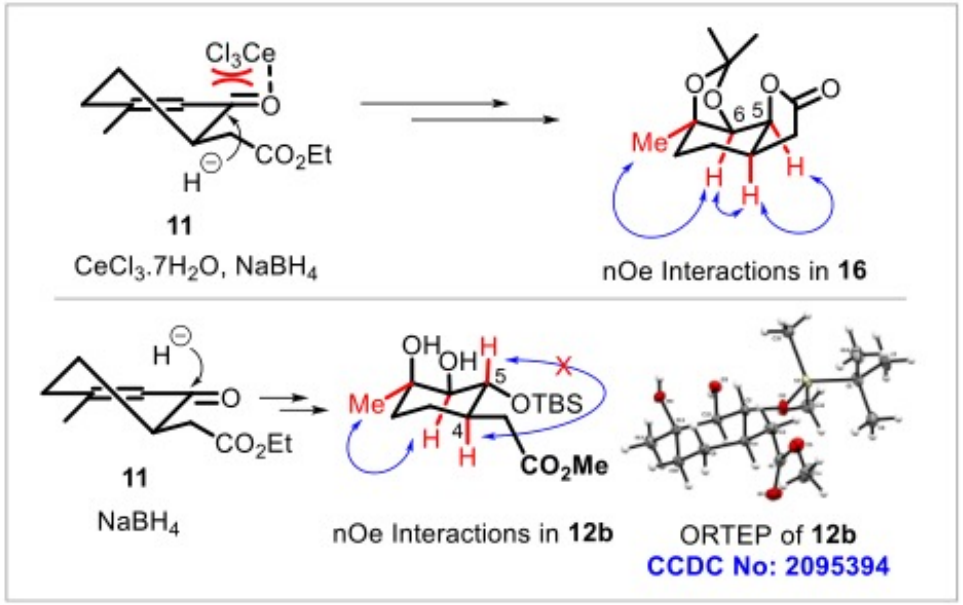


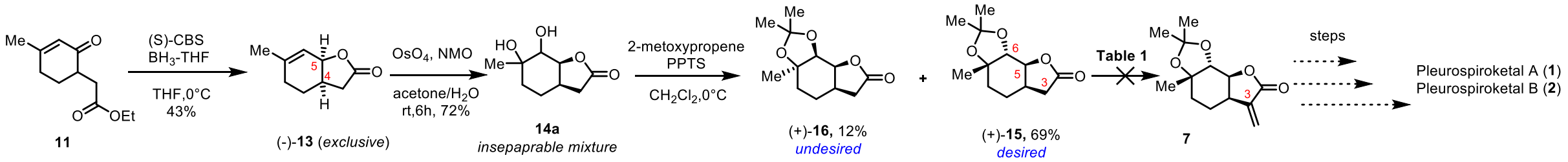
From **12a** to **12b:**

TBS protection of alcohol



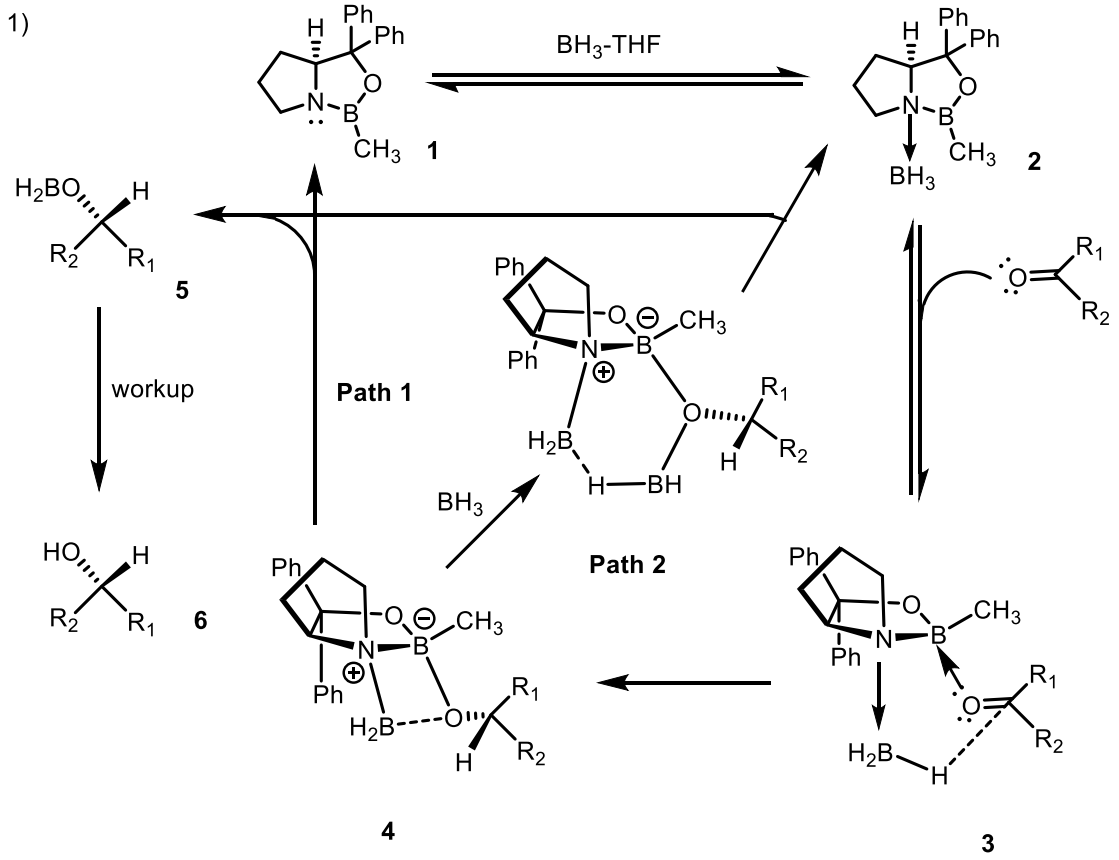
c. Analysis of stereochemical outcome in reduction of 11:





From **11** to **13:**

1) Corey-Bakshi-Shibata reaction
2) Formation of lactone



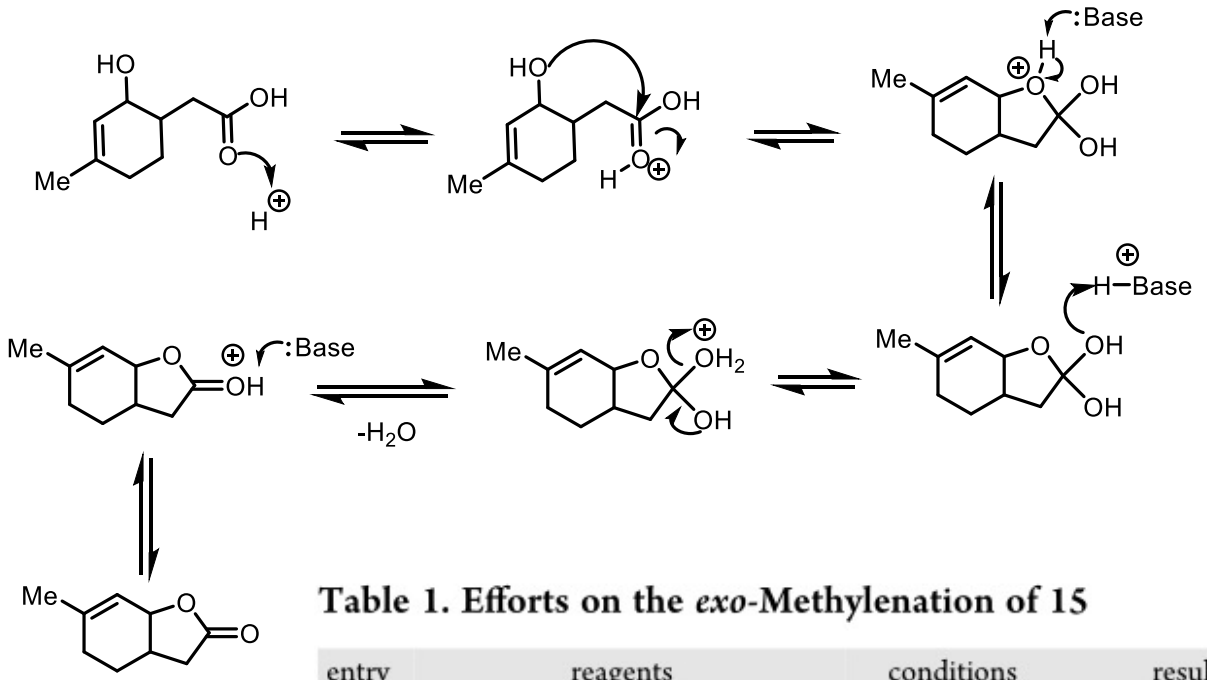
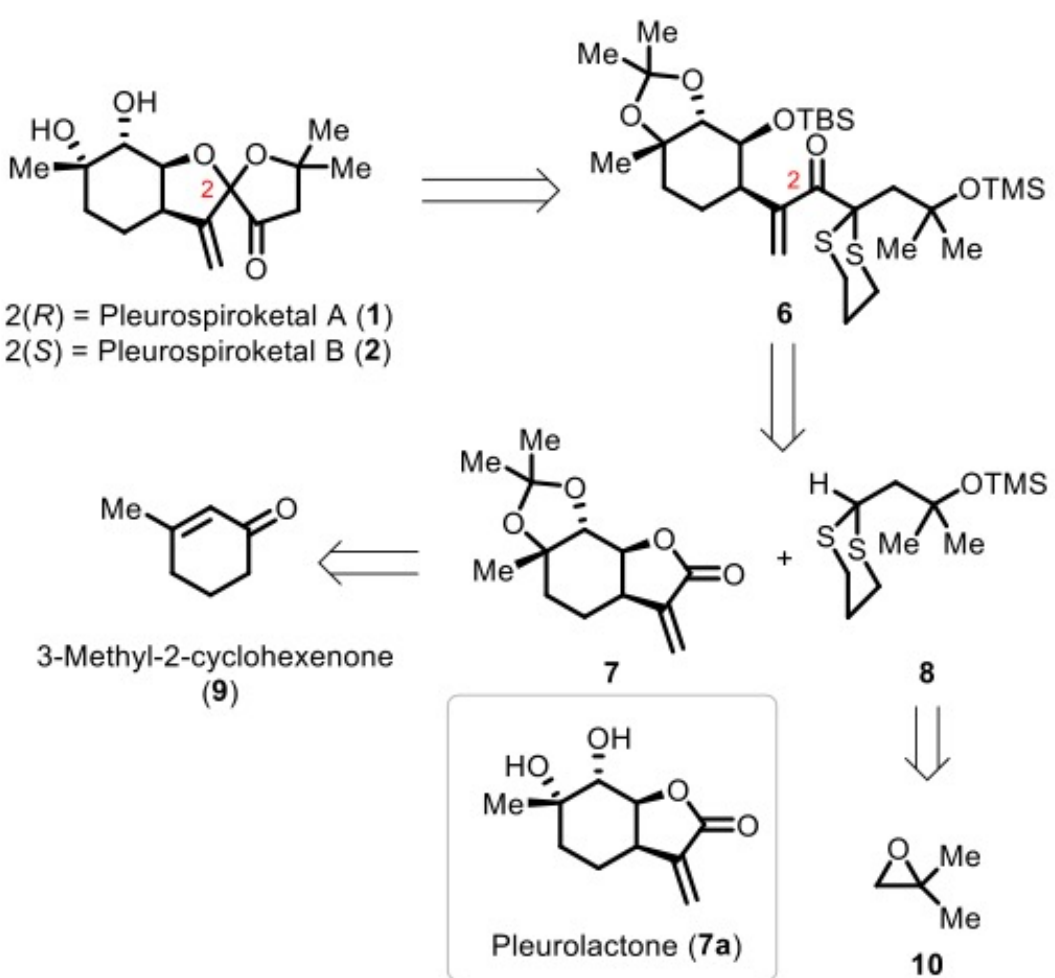
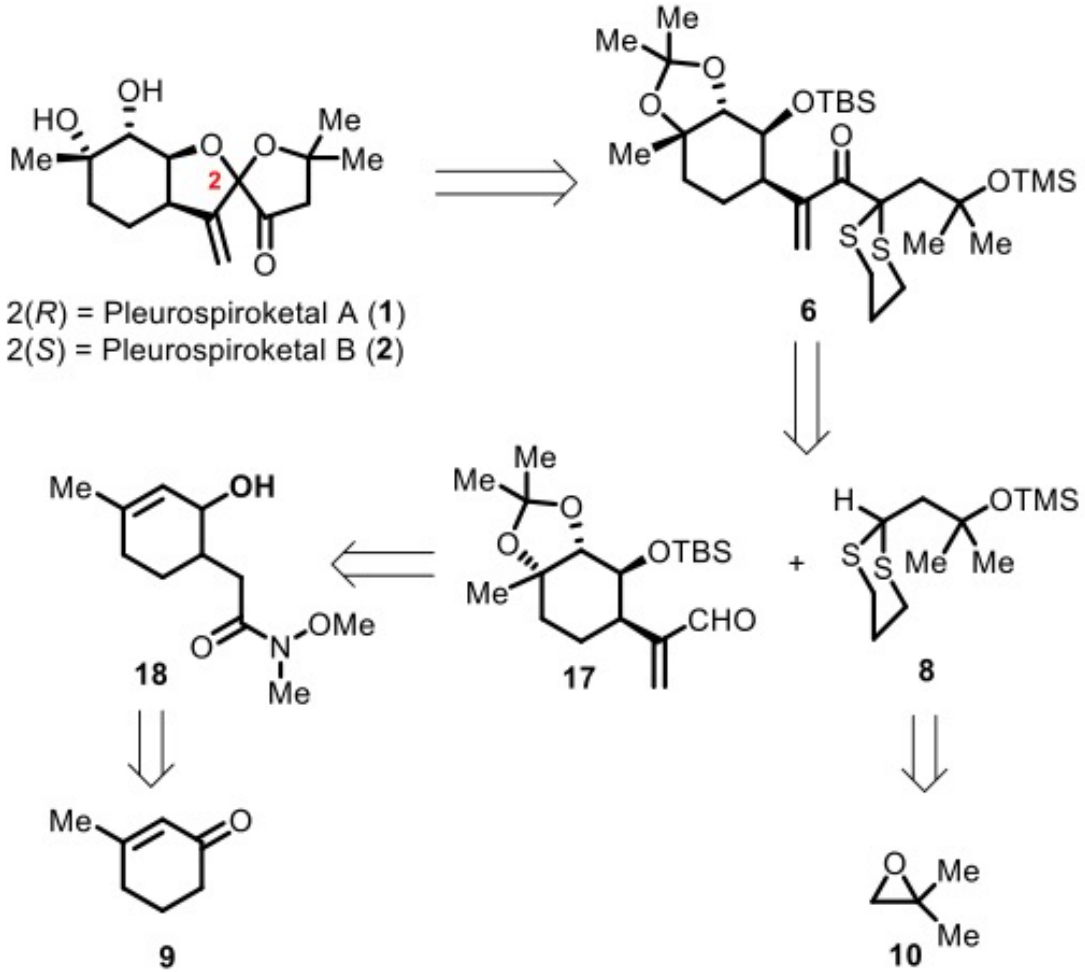


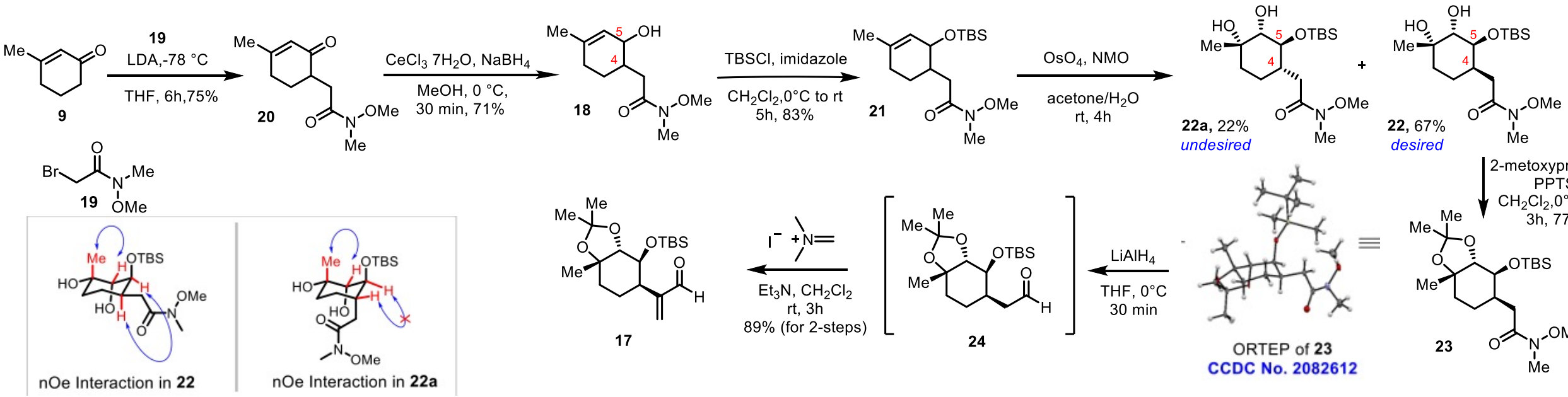
Table 1. Efforts on the *exo*-Methylenation of 15

entry	reagents	conditions	result
1	Eschenmoser's salt, Et_3N	CH_2Cl_2, rt	**15** recovered
2	Eschenmoser's salt, LDA	THF, −78 °C	**15** recovered
3	LDA, $(CH_2O)_n$	THF, −78 °C	**15** recovered
4	LDA, hydroxymethyl phthalimide	THF, −78 °C	**15** recovered
5	PhNHMe·TFA, $(CH_2O)_n$	THF, 70 °C	**15** recovered
6	(1) LDA, PhSeCl	THF, −78 °C	decomposition
	(2) LDA, MeI, then H_2O_2, $NaHCO_3$		

Initial and Revised Retrosynthetic Analysis of (±)Pleurospiroketals A (1) and B (2)

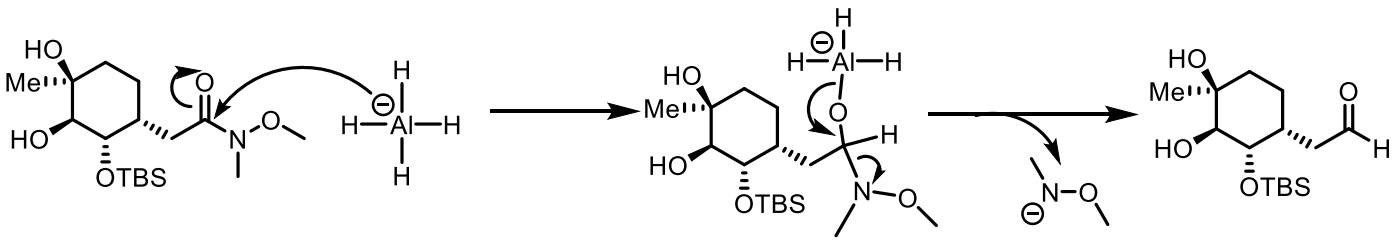




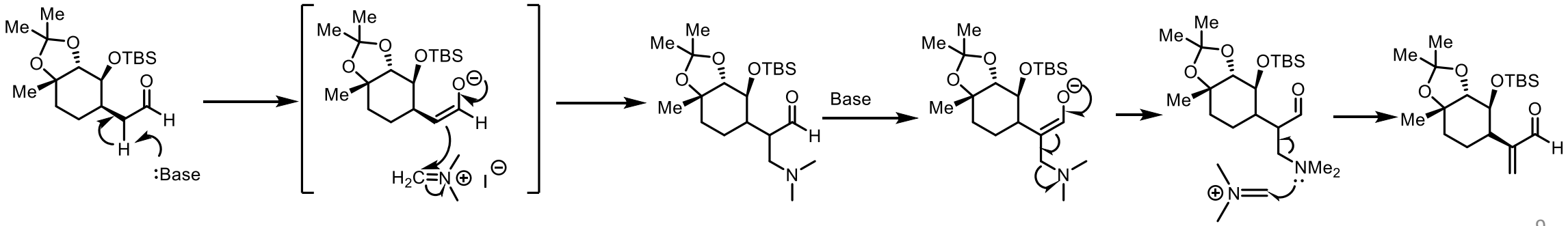


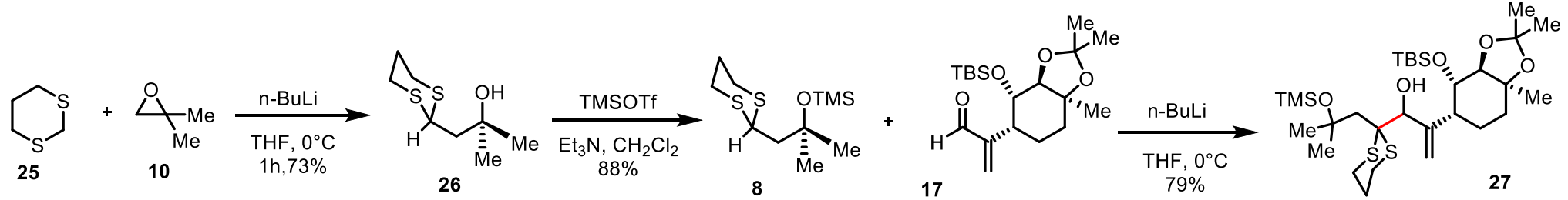
From **23** to **17:**

1) Reduction of Weinreb amide



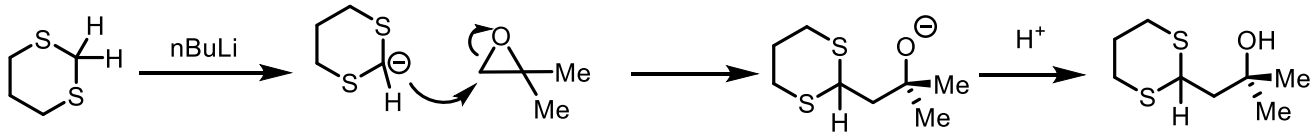
2) methylenation with Eschenmoser`s salt





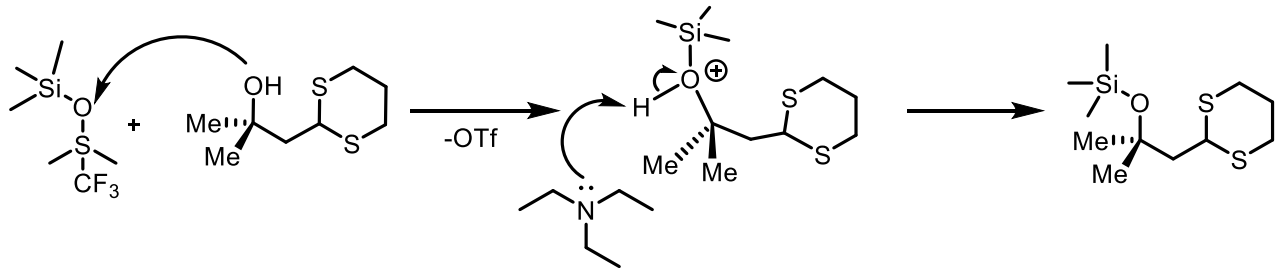
From **25** to **26:**

Corey-Seebach Reaction

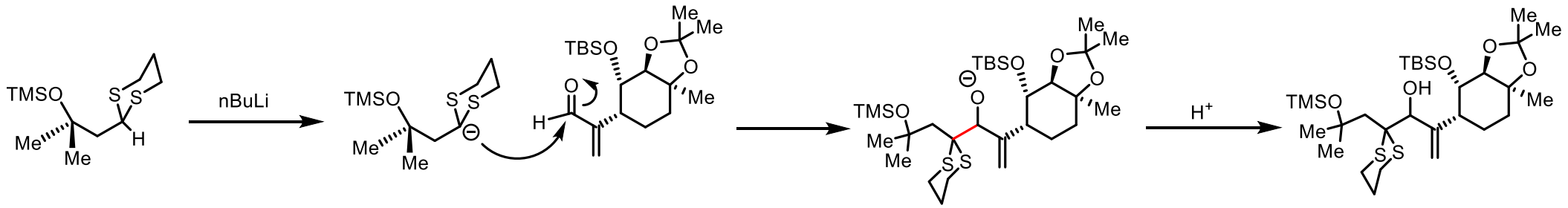


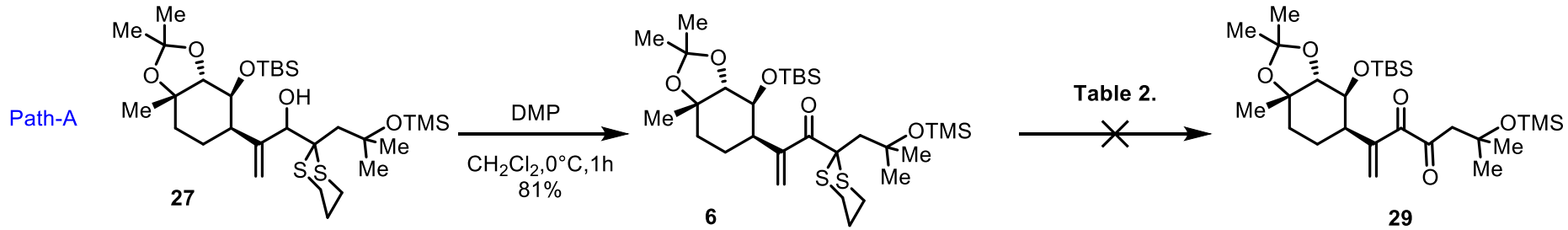
From **26** to **8:**

TMS protection of alcohol



From **17** to **27:**





From **27** to **6:**

Dess-Martin Oxidation

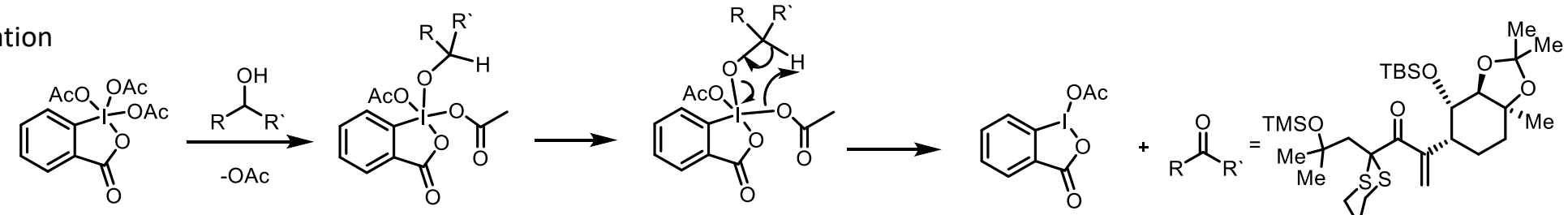
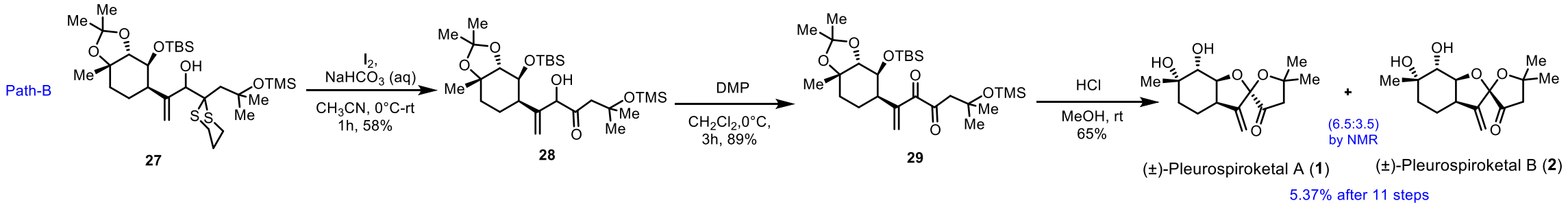
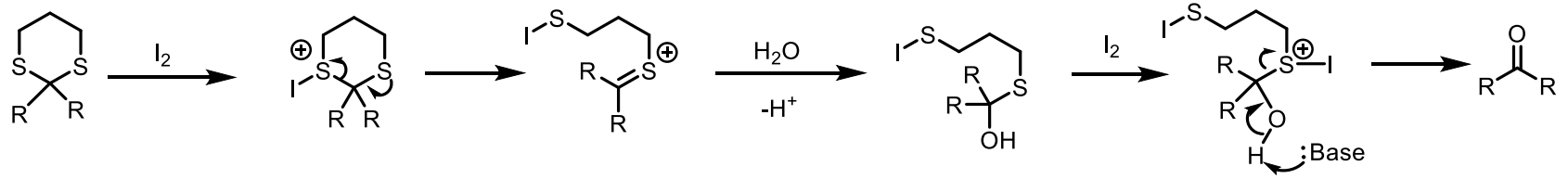


Table 2. Efforts on the Dithiane Deprotection of 6

entry	reagents	conditions	result
1	I_2, sat. aq. $NaHCO_3$	CH_3CN	**6** recovered
2	NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene	MeOH:H_2O (2:1)	complex mixture
3	H_5IO_6	Et_2O, THF, 0 °C	complex mixture
4	$HgCl_2$, $CaCO_3$	THF/CH_3CN/H_2O (1:8:1)	complex mixture
5	$CuCl_2$, CuO	acetone:H_2O	complex mixture
6	$ZnBr_2$	CH_2Cl_2, MeOH, rt, 4 h	decomposed
7	MeI, K_2CO_3	CH_3CN/H_2O (10:1), 45 °C, 5 h	complex mixture
8	Eosin Y, 45 W, CFL	CH_3CN/H_2O, rt, open-air	complex mixture

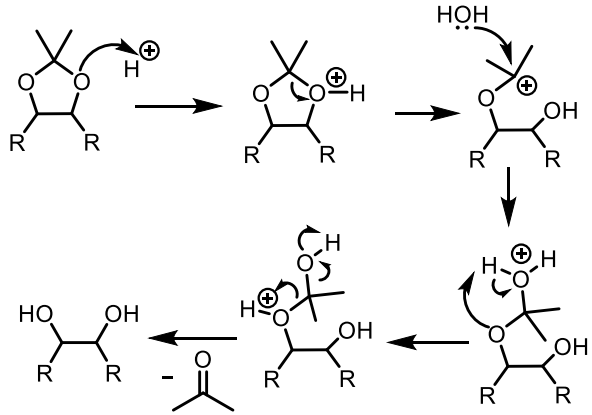


From **27** to **28:** 1,3 -dithiane deprotection

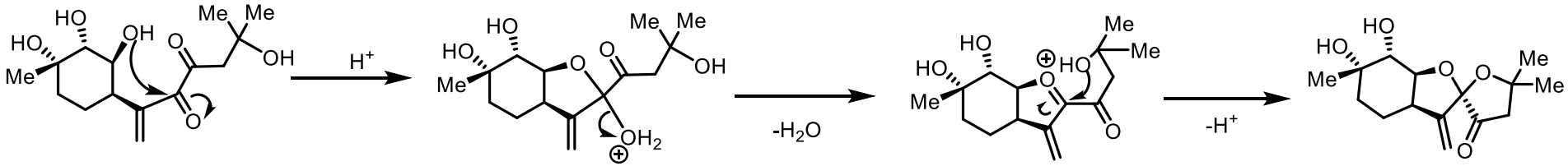


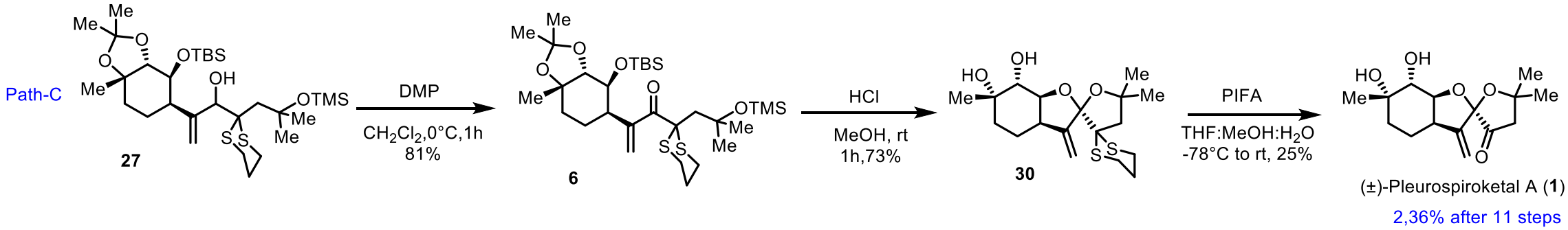
From **29** to **1** and **2:**

Hydrolysis of the protecting groups



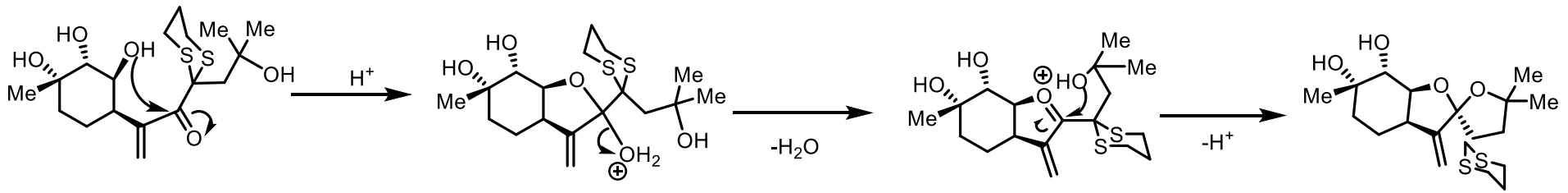
Acid-induced spiroketalization

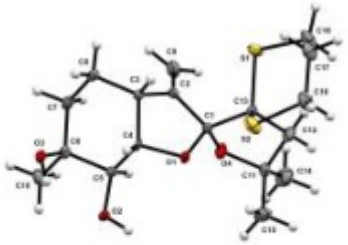




From **6** to **30:**

Acid-induced spiroketalization



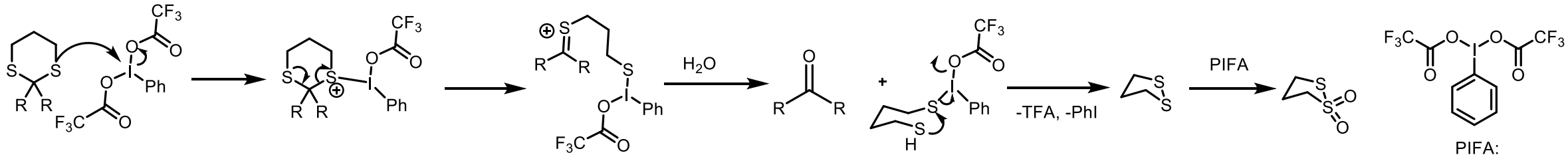


ORTEP of **30**

CCDC No. 2086259

From **30** to **1:**

Oxidative 1,3-dithiane deprotection



PIFA:
Phenyliodine(III) bis(trifluoroacetate)