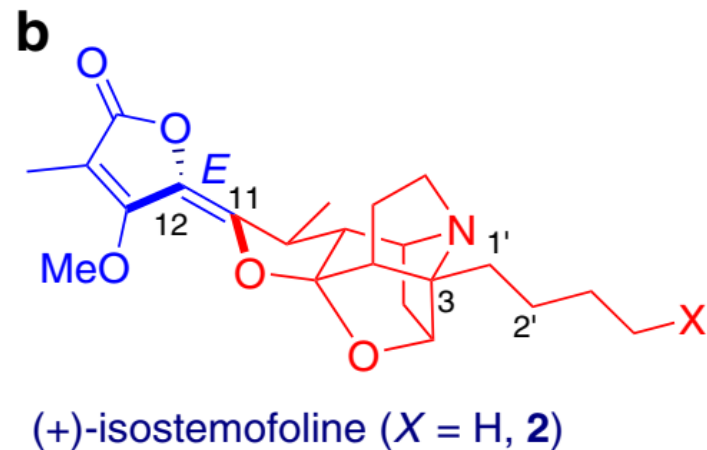
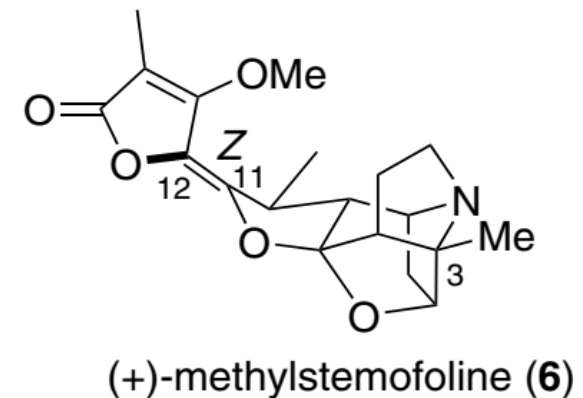
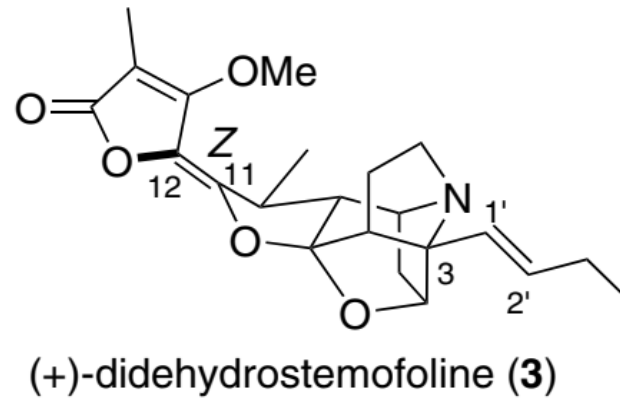
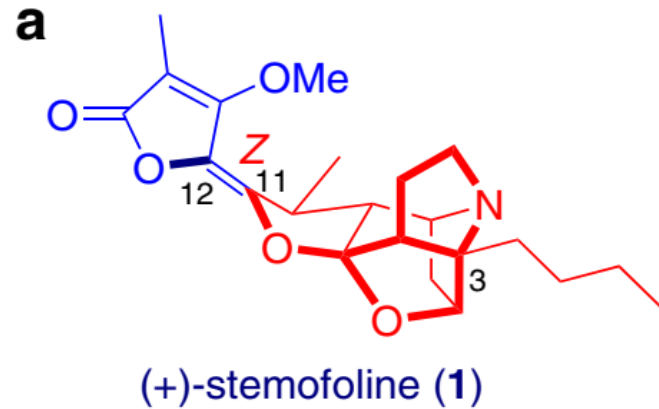


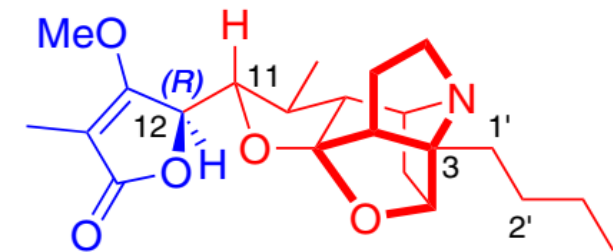
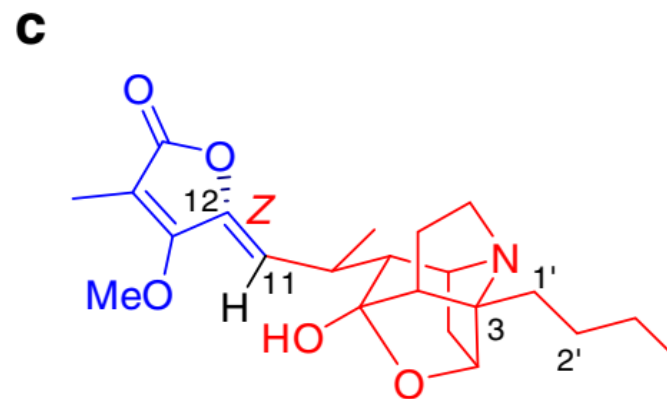
Enantioselective total syntheses of (+)-stemofoline and three congeners based on a biogenetic hypothesis

Xiong-Zhi Huang¹, Long-Hui Gao¹ & Pei-Qiang Huang¹✉

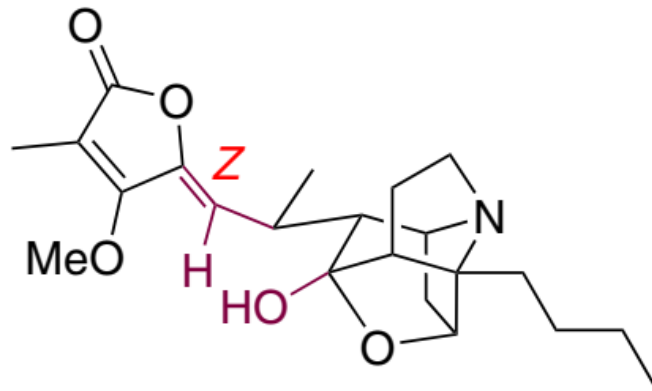


(+)-isodidehydrostemofoline ($X = \text{H}$, $\Delta^{1',2'}$, **4**)

(+)-methoxystemofoline ($X = \text{OMe}$, **5**) (revised structure)



Biogenetic hypothesis

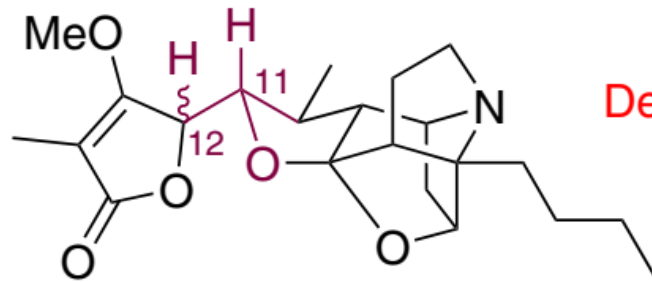


Stemoburkilline (7)

Oxidative cyclization

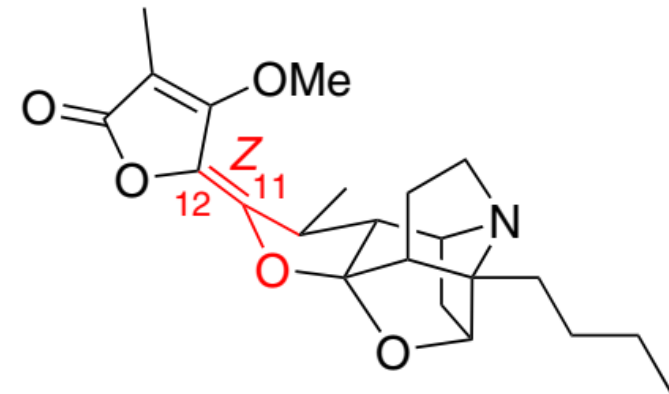


or
Dehydrogenative oxidation

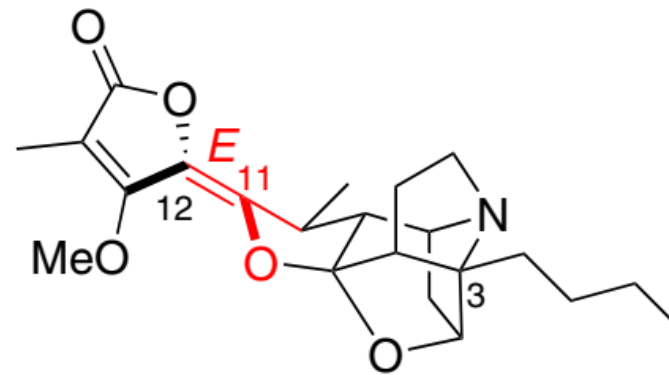


(11S,12R)-dihydrostemofoline (8)

(11S,12S)-dihydrostemofoline (9)

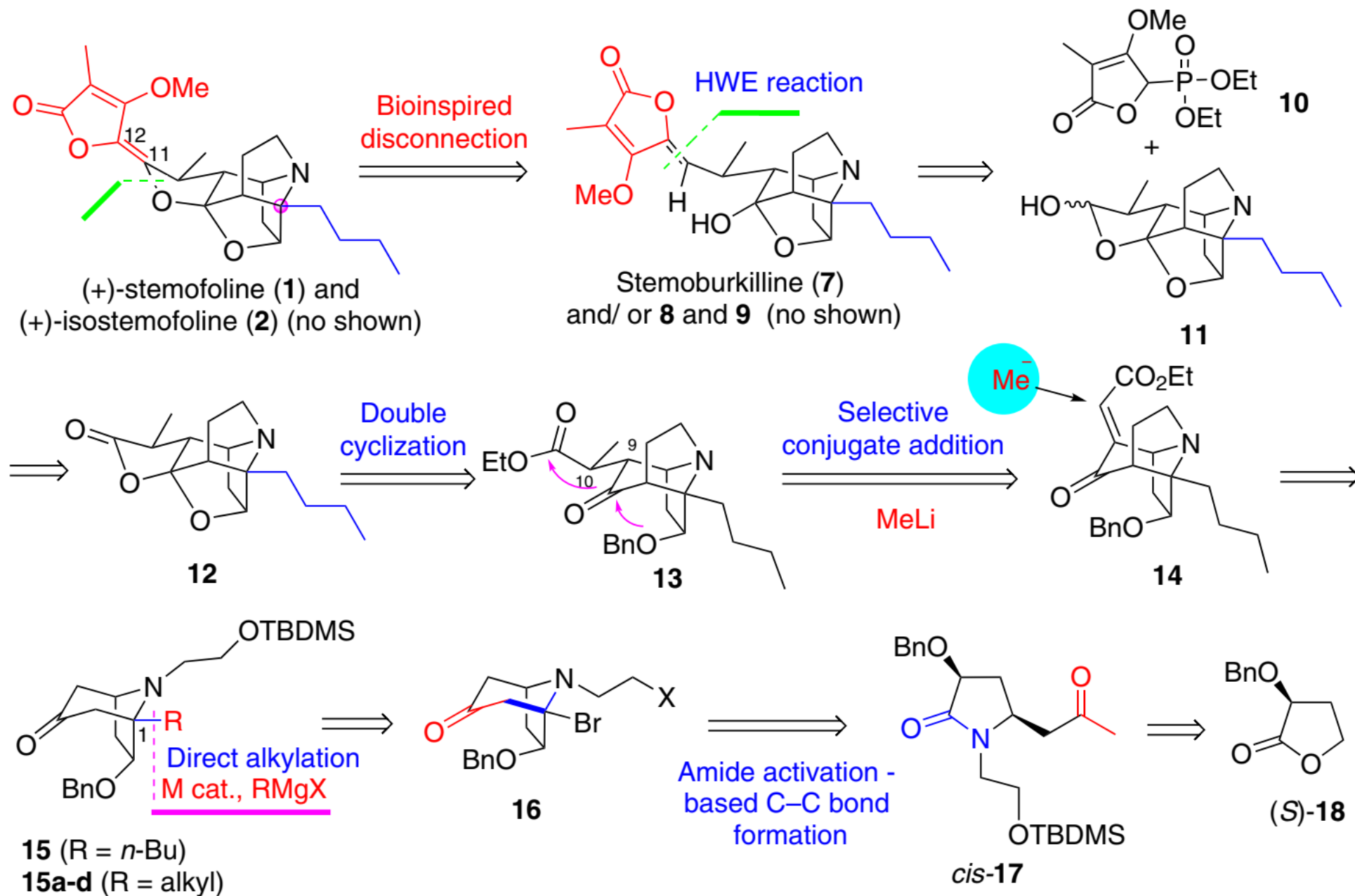


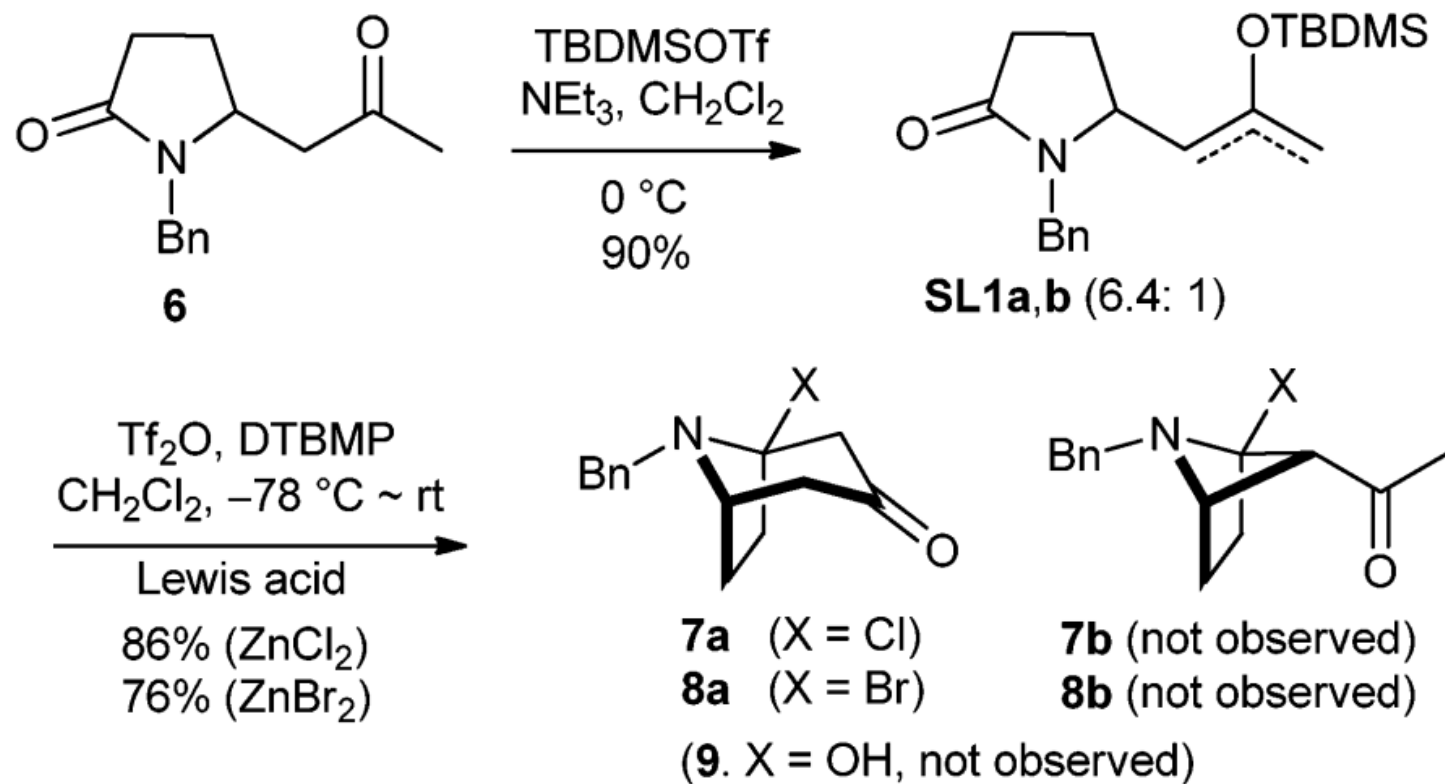
Stemofoline (1)



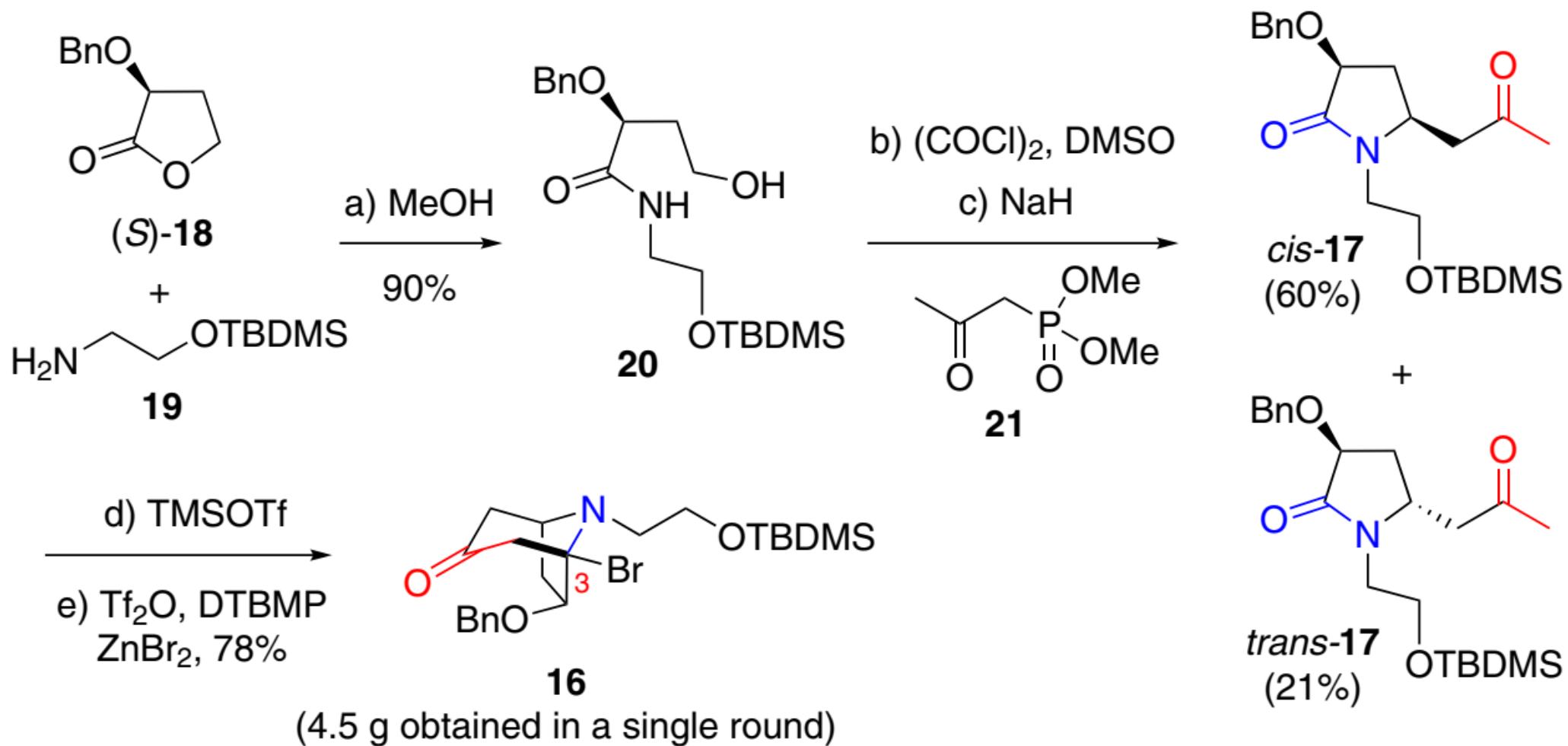
Isostemofoline (2)

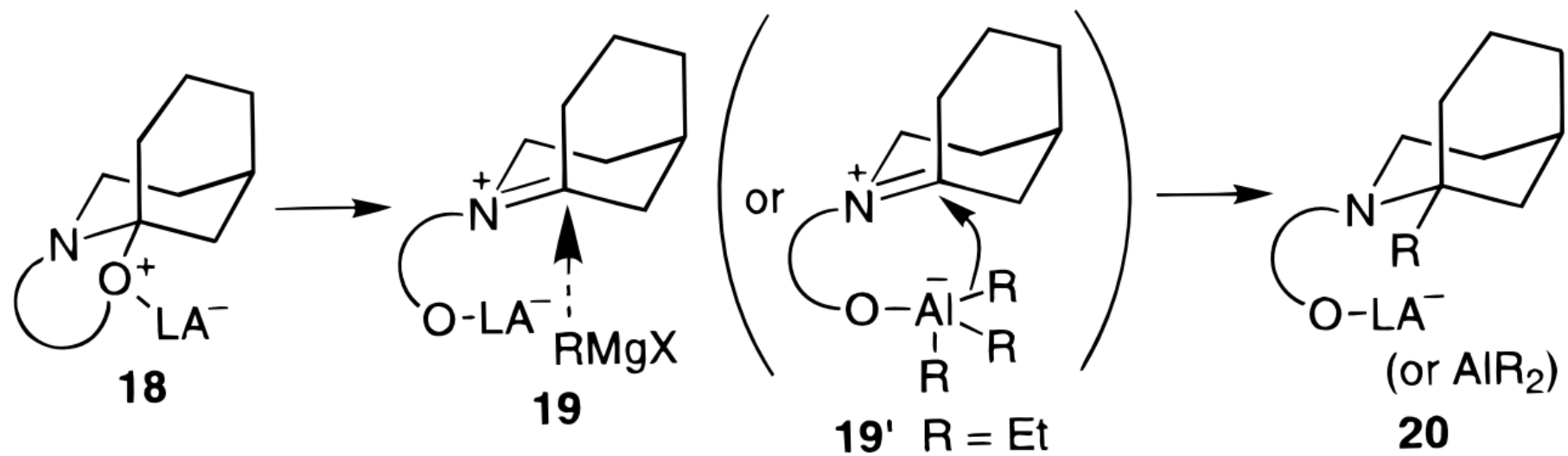
The retrosynthetic analysis of Stemofoline alkaloids





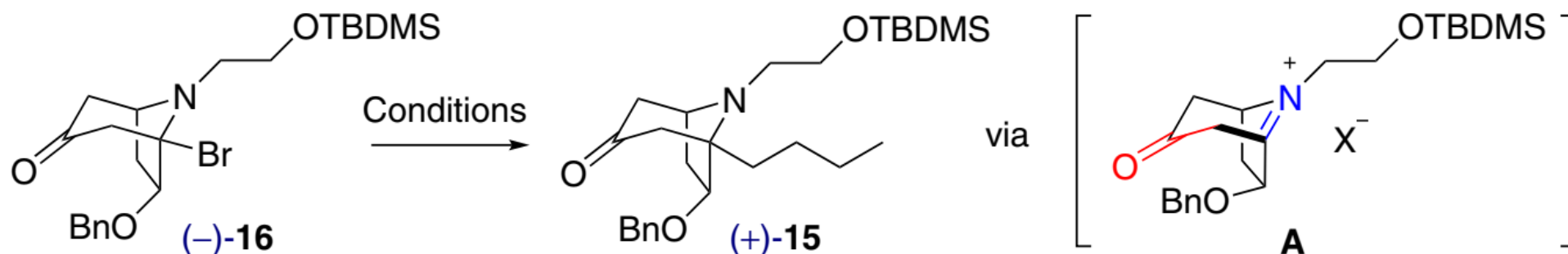
Enantioselective synthesis of the tropinone building block 16





J. Org. Chem. **1997**, 62, 8280.

Screening of reaction conditions for the butylation of 16 with *n*-BuM



Entry	Conditions	Yield of 15 ^a (%)
1	Fe(acac) ₃ , L1 , <i>n</i> -BuMgBr, THF, 0 °C	24 (41) ^b
2	FeCl ₃ , L1 , <i>n</i> -BuMgBr, THF, 0 °C	Trace
3	Fe(OAc) ₂ , L2 , <i>n</i> -BuMgBr, THF, 0 °C	Trace
4	Fe(acac) ₃ ^c , L1 , <i>n</i> -BuMgBr, THF, 0 °C	21 (40) ^b
5	Ni(cod) ₂ , L3 , <i>n</i> -BuZnBr, DMA, rt	ND ^d
6	NiCl ₂ •glyme, L4 , <i>n</i> -Bu ₂ Zn, DMF, rt	ND
7	CuI, L1 , LiOMe, <i>n</i> -BuMgBr, THF, 0 °C	28 (42) ^b
8	CuOAc, L1 , LiOMe, <i>n</i> -BuMgBr, THF, 0 °C	40 (60) ^b
9	Cu(OTf) ₂ , L1 , LiOMe, <i>n</i> -BuMgBr, THF, 0 °C	26 (36) ^b
10	CuBr ₂ , L1 , LiOMe, <i>n</i> -BuMgBr, THF, 0 °C	41 (57) ^b
11	CuCl ₂ , L1 , LiOMe, <i>n</i> -BuMgBr, THF, 0 °C	52 (68) ^b
12	CuCl ₂ , L1 , LiOMe, <i>n</i> -BuMgBr, THF, rt	81 ^e

L1: TMEDA; L2: IMes•HCl; L3: *s*-Bu-Pybox; L4: 4,4'-di-*tert*-butyl-bipyridine.

^aIsolated yield.

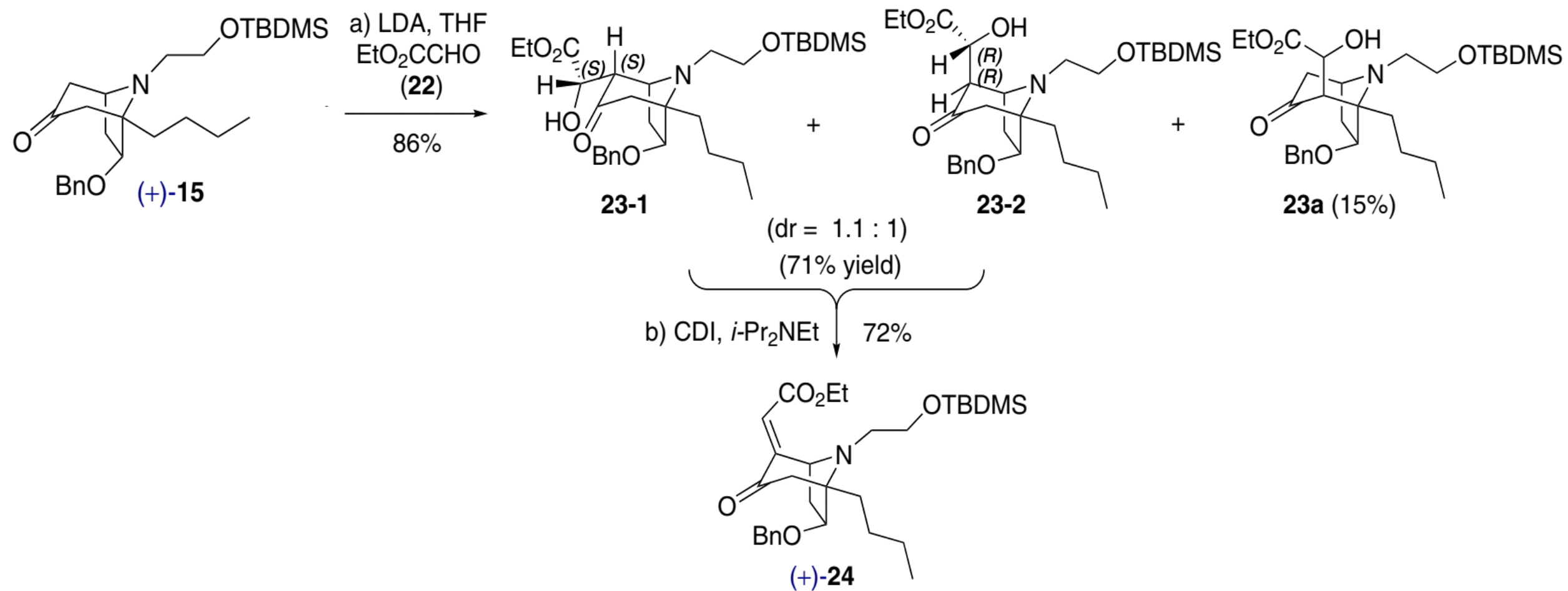
^bBased on the recovered starting material.

^c1.2 equiv.

^dNot detected.

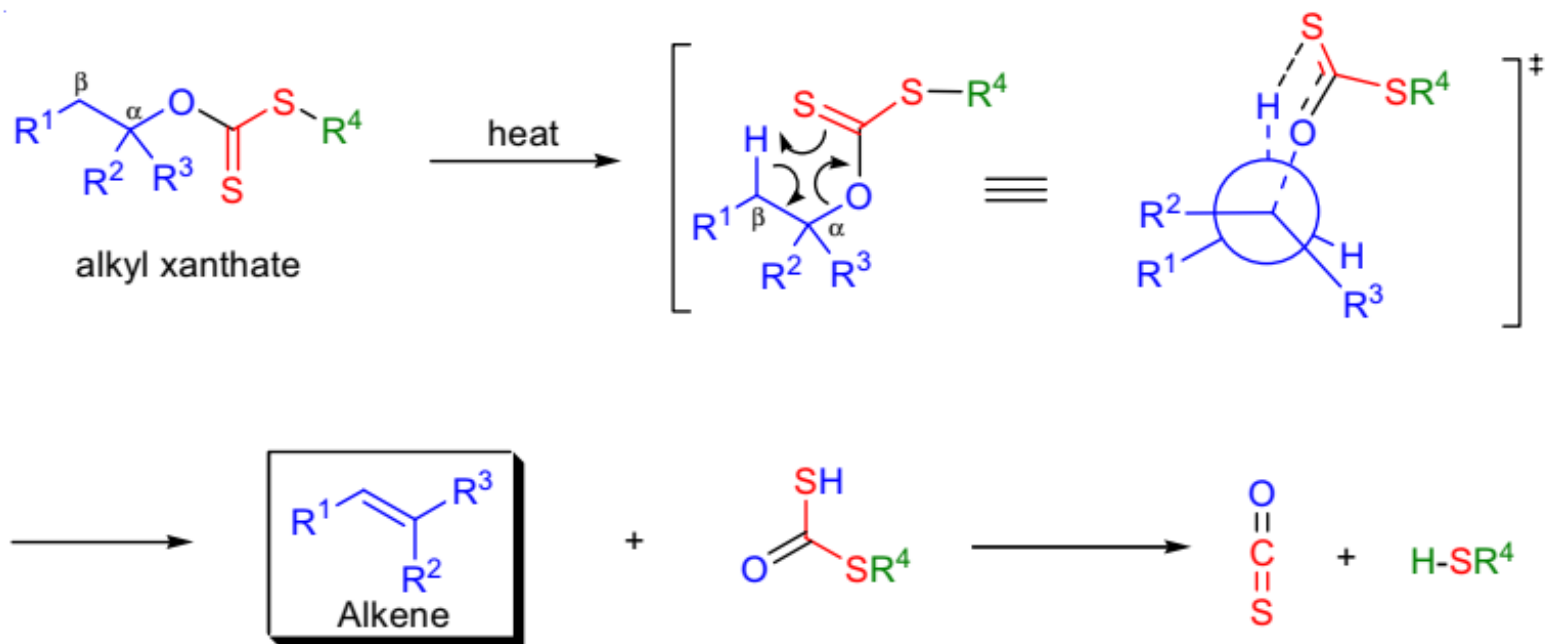
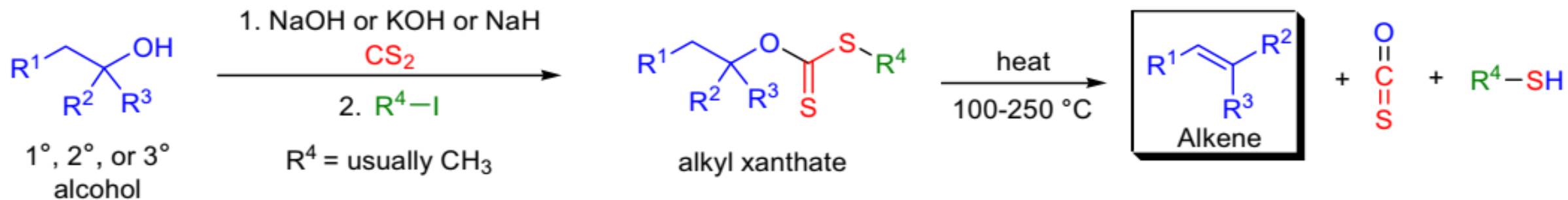
^eGram scale.

Synthesis of the pentacyclic lactone 12



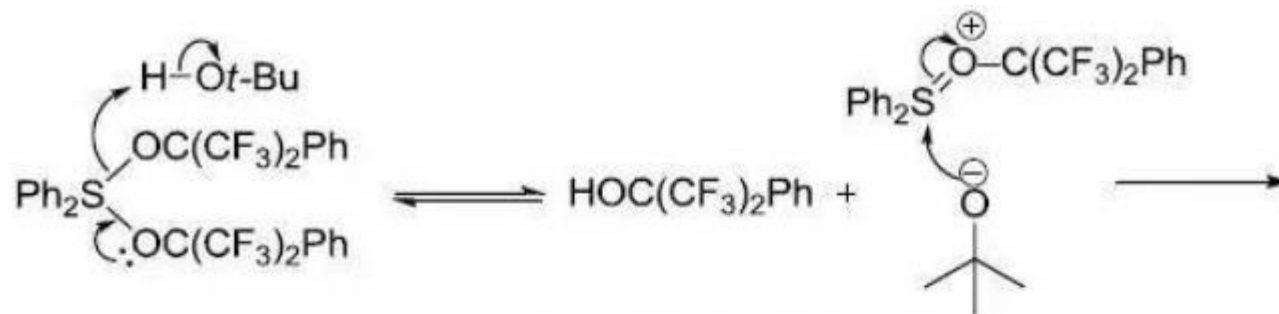
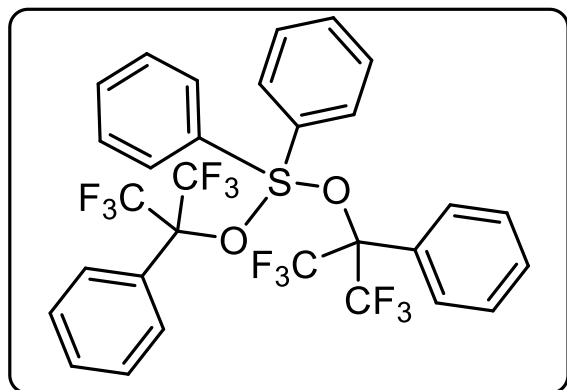
The dehydration reaction

1. Chugave elimination reaction

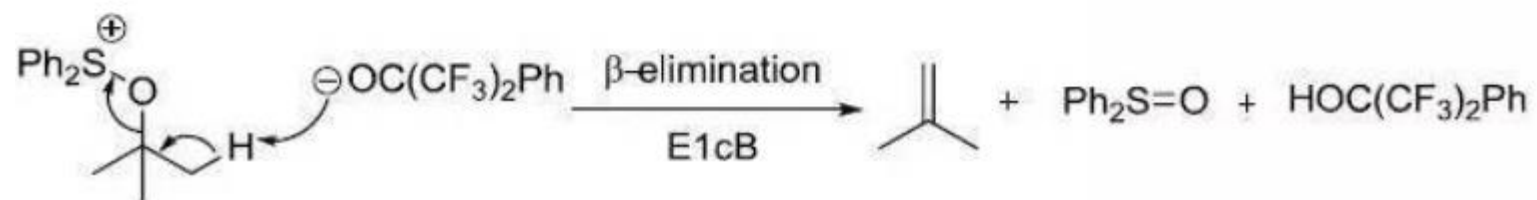
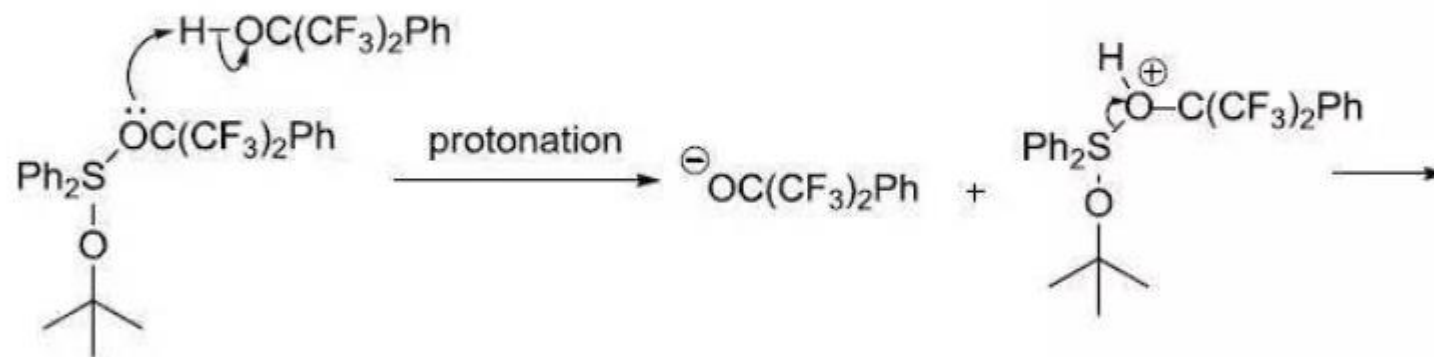


The dehydration reaction

2. The Martin sulfurane reagent

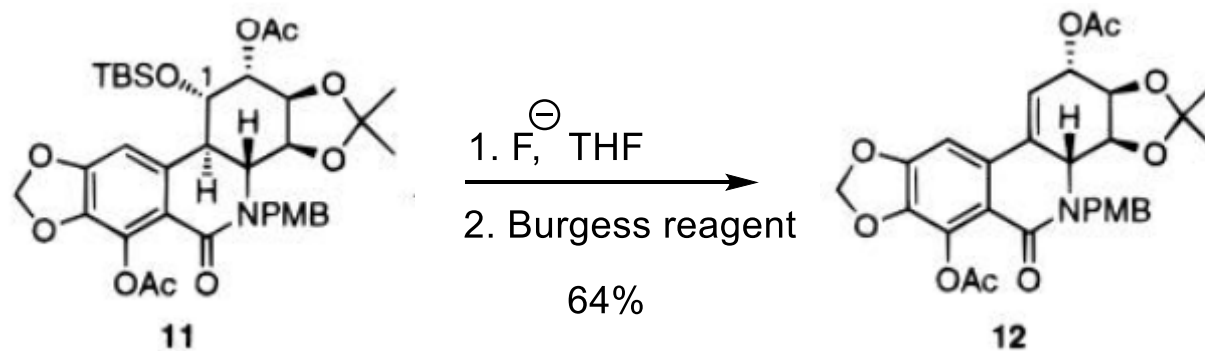
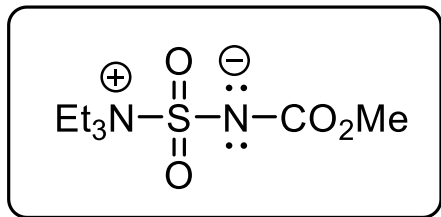


The alcohol is acidic

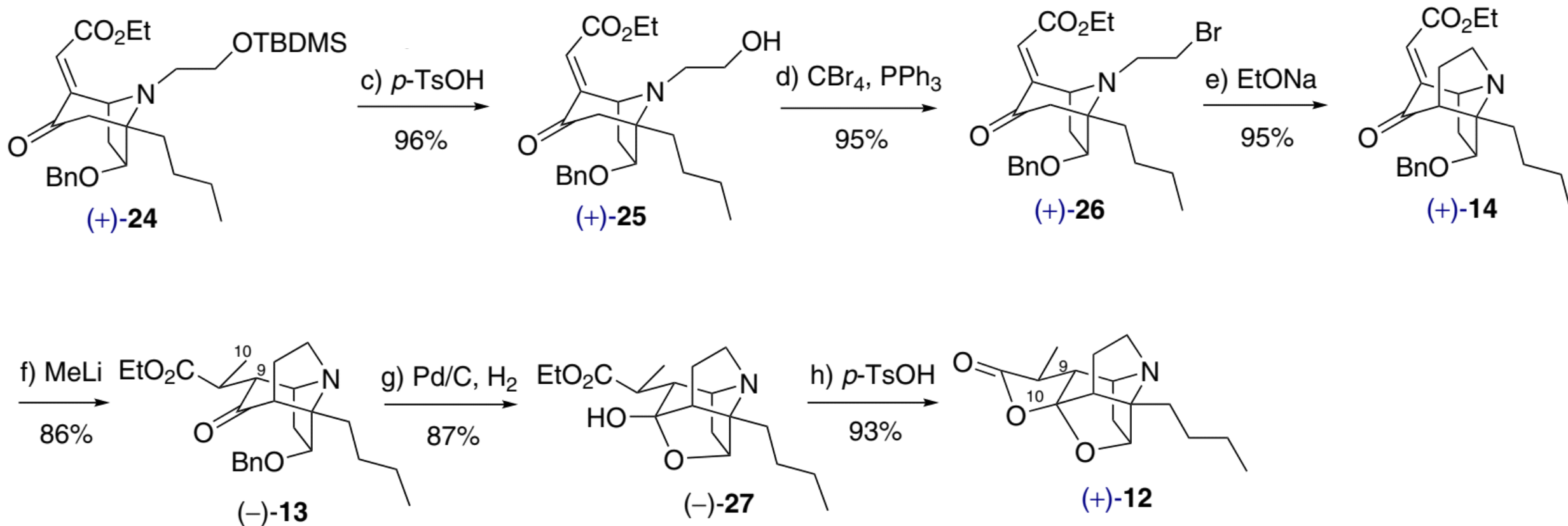


The dehydration reaction

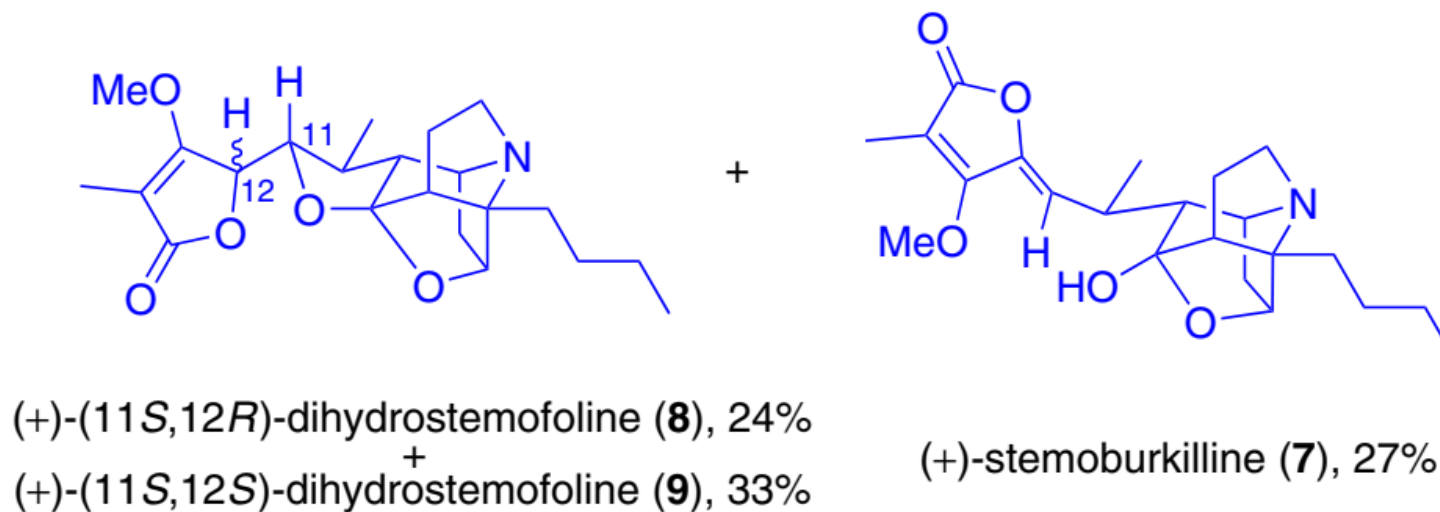
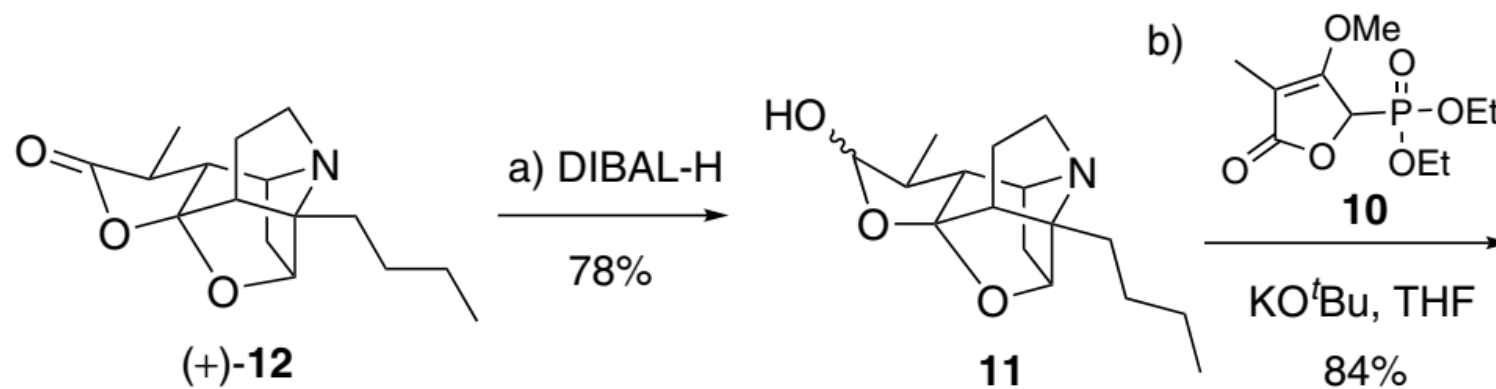
3. The Burgess reagent



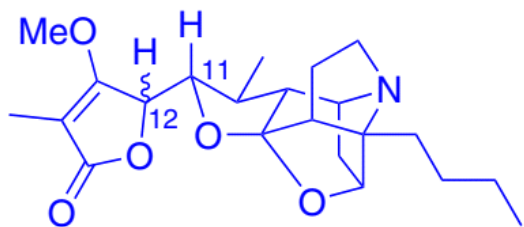
Synthesis of the pentacyclic lactone 12



Completion of the total syntheses of 7, 8, 9

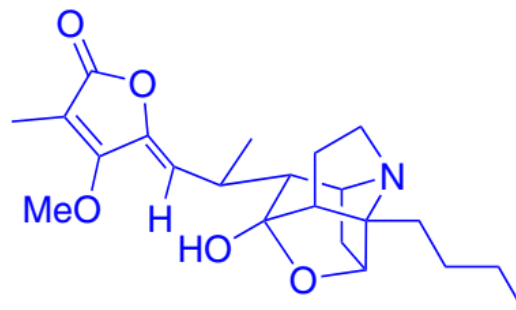


Attempted transformation of 7-9 into 1

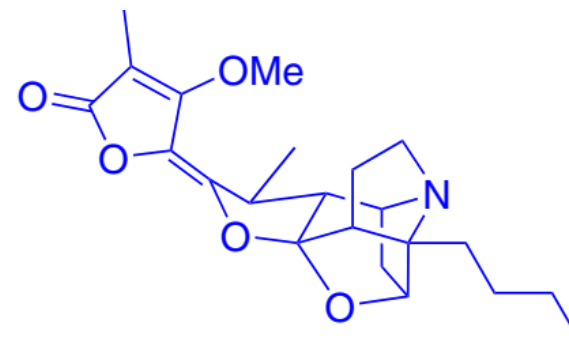


(+)-(11*S*,12*R*)-dihydrostemofoline (**8**)

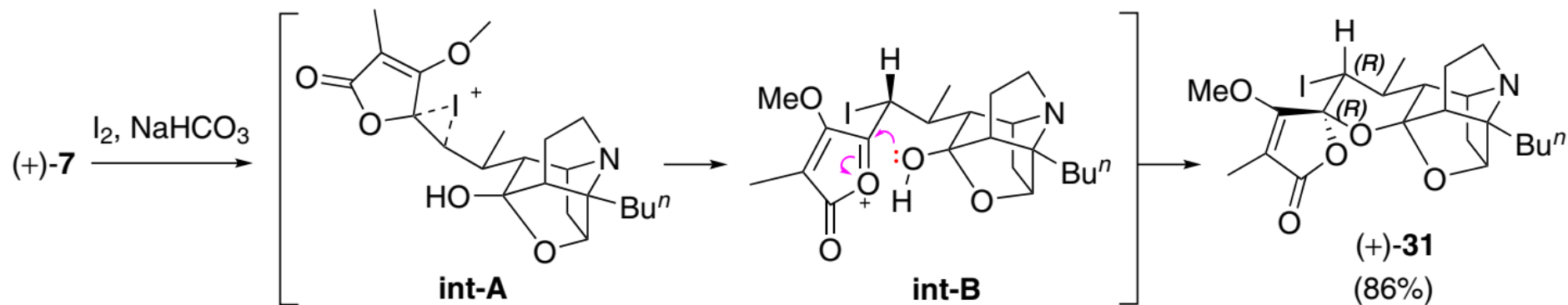
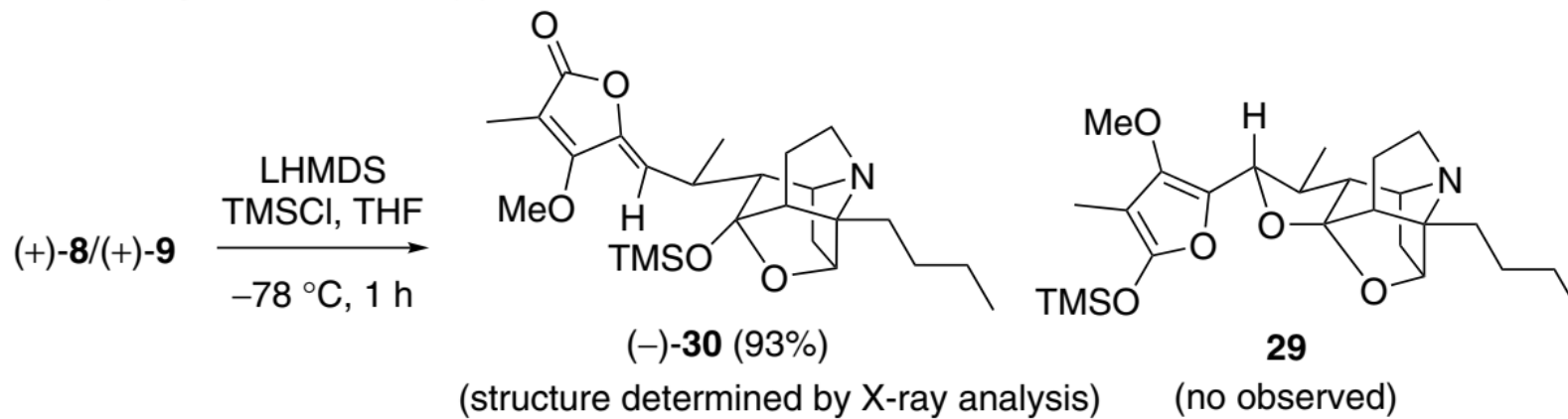
(+)-(11*S*,12*S*)-dihydrostemofoline (**9**)



(+)-stemoburkilline (**7**)



(+)-stemofoline (**1**)



Completion of the total syntheses of Stemofoline (1) and isostemofoline (2)

