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11-Step Total Synthesis of Pallambins C and D

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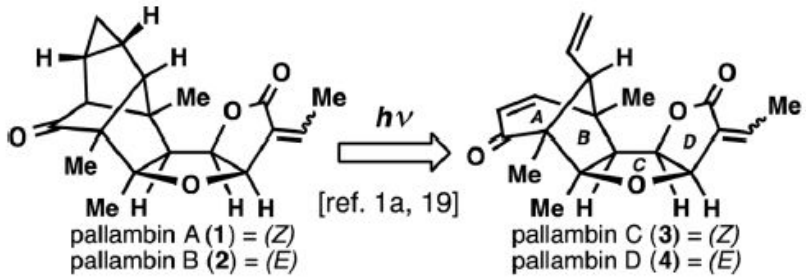
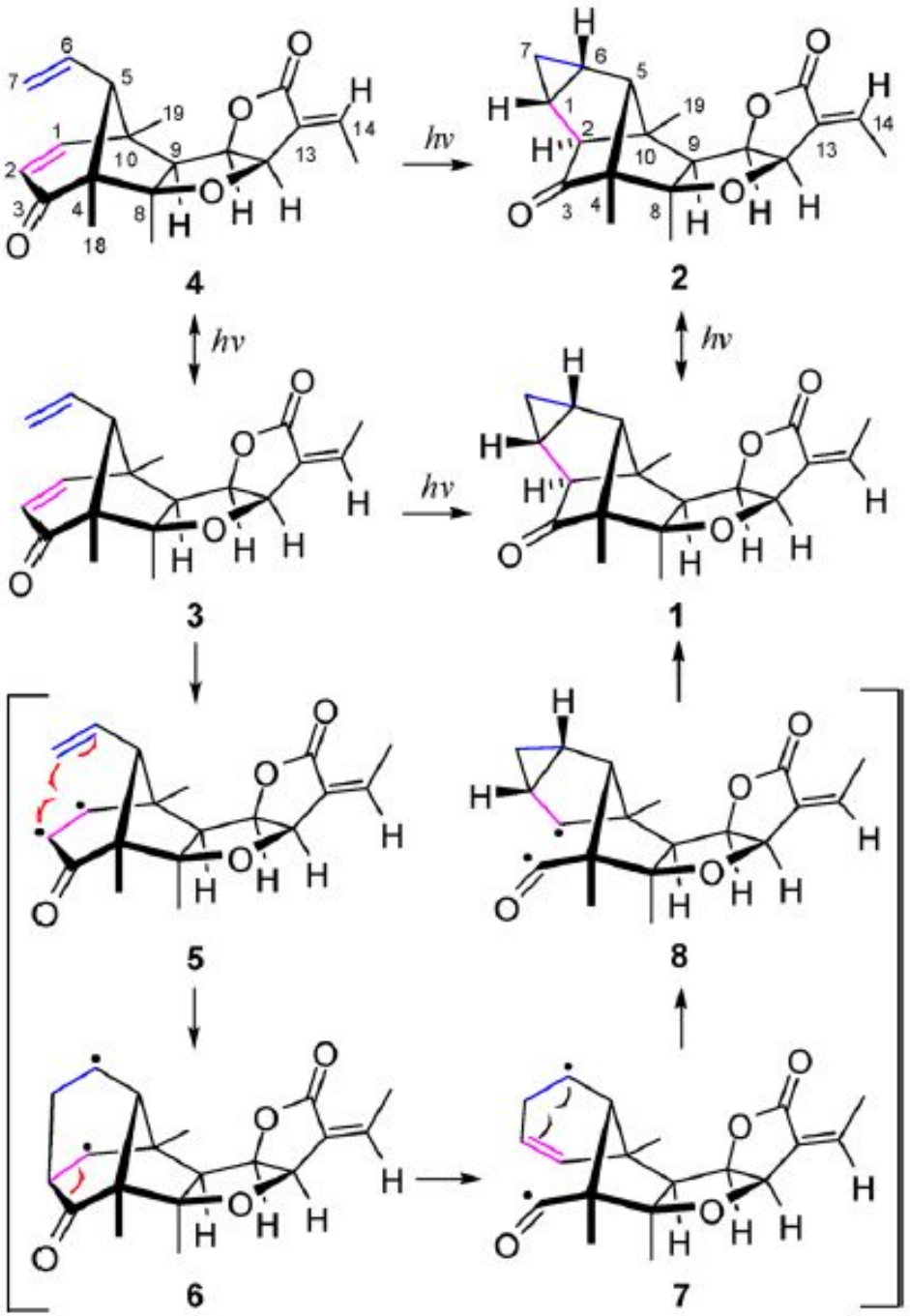
Supporting Information

ABSTRACT: The structurally intriguing terpenes pallambins C and D have been assembled in only 11 steps from a cheap commodity chemical: furfuryl alcohol. This synthesis, which features a redox-economic approach free of protecting-group manipulations, assembles all four-ring systems via a sequential cyclization strategy. Of these four-ring constructing operations, two are classical (Robinson annulation and Mukaiyama aldol) and two are newly devised. During the course of this work a method for the difunctionalization of enol ethers was developed, and the scope of this transformation was explored.



In fact, of the 11 discrete steps of this synthesis, only two are nonstrategic (steps 7 and 9), making it 81% ideal


hv
hv
hv
hv
4
2
3
1
5
8
6
7

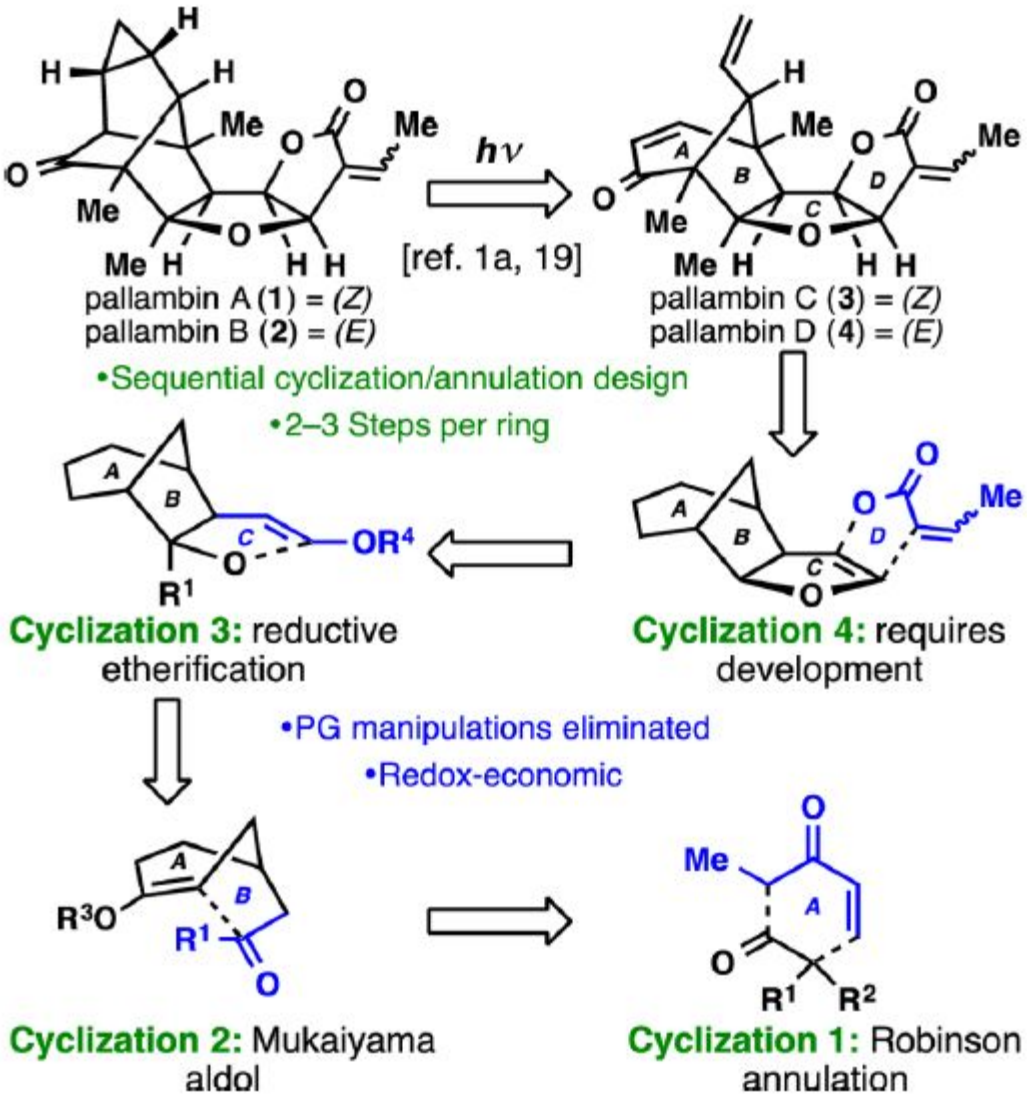
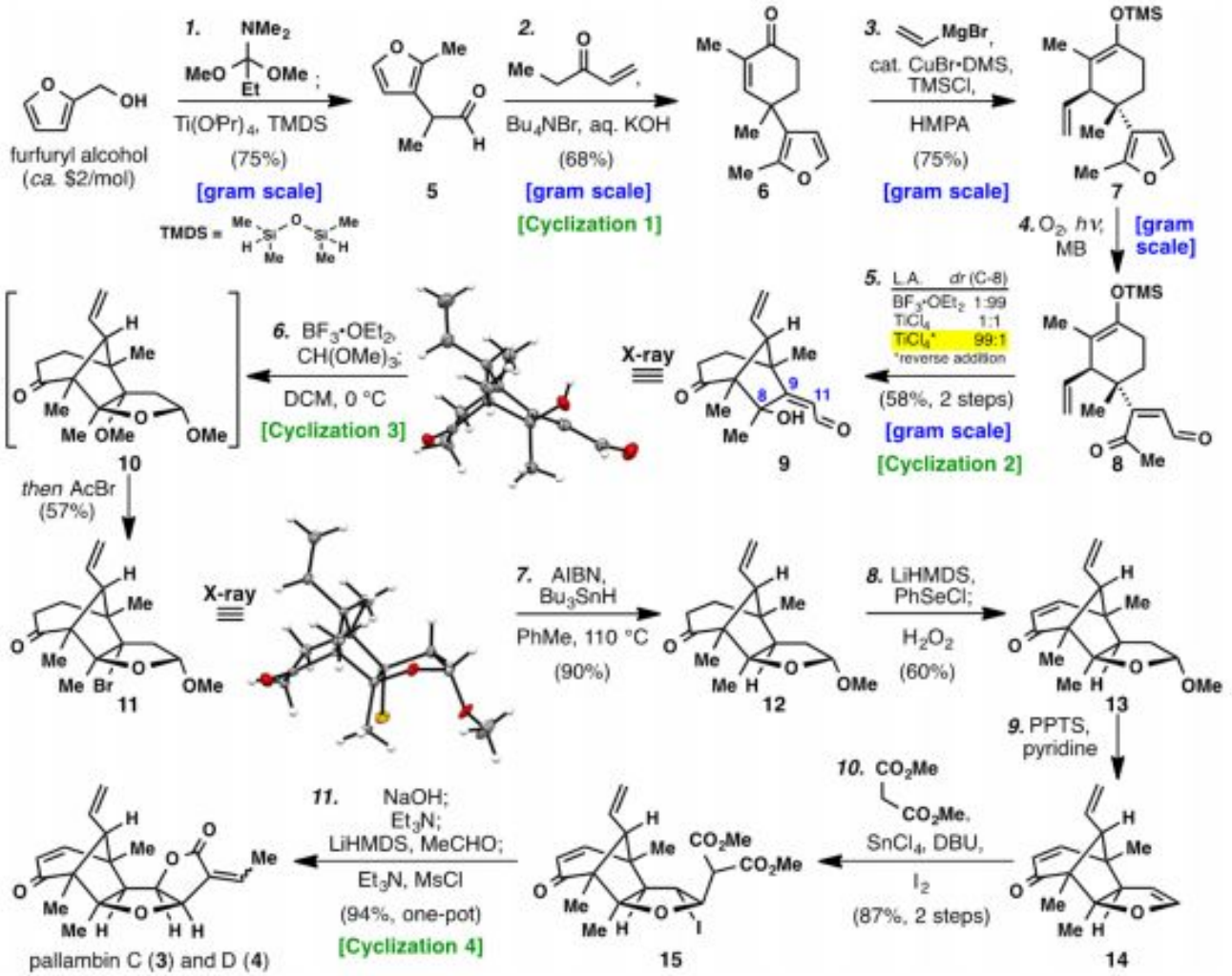
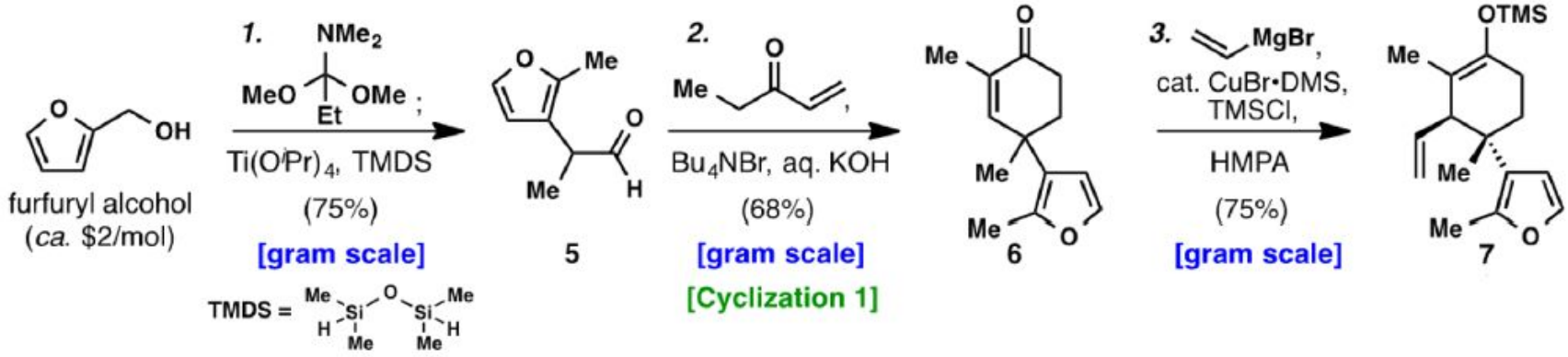


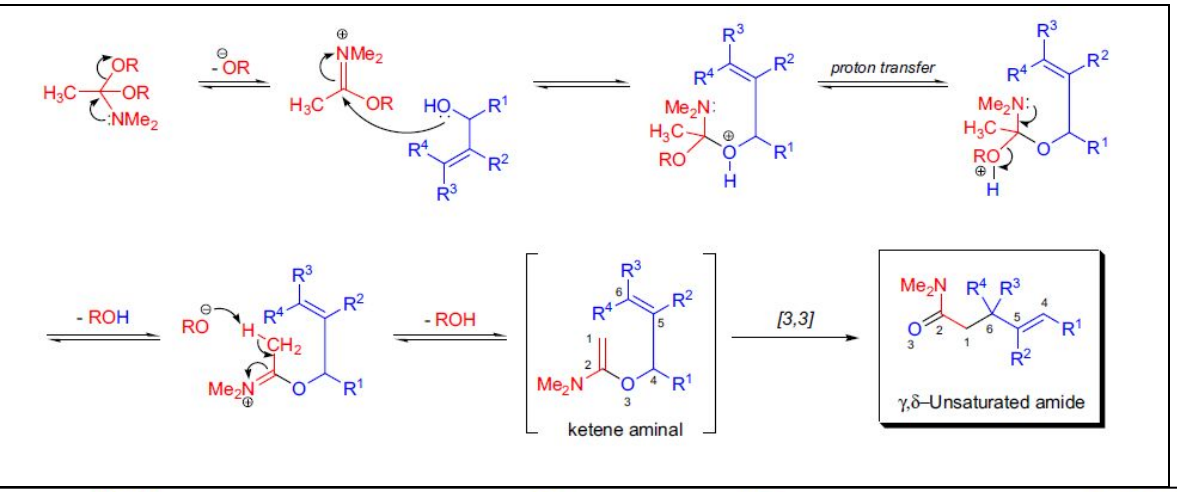
Figure 1. A sequential cyclization strategy enables an exceptionally concise pathway to pallambins C and D.

Scheme 1. Total Synthesis of Pallambins C (3) and D (4)[a]



[a]Reagents and conditions: (1) furfuryl alcohol (1 equiv), 1,1-dimethoxy-*N*,*N*-dimethylpropan-1-amine (1.5 equiv), PhMe, 110 °C then TMDS (2 equiv), $Ti(O^iPr)_4$ (1.5 equiv), 50 °C (75%, one-pot); (2) ethyl vinyl ketone (1.5 equiv), Bu_4NBr (10 mol %), 60% aq. KOH, PhMe, 23 °C (68%); (3) vinyl magnesium bromide (3.5 equiv), CuBr-DMS (20 mol %), HMPA (4 equiv), TMSCl (1.1 equiv), THF, −78 °C (75%); (4) O_2, methylene blue, *hν*, DCM, −10 °C, then thiourea (1.5 equiv), 23 °C; (5) $TiCl_4$ (1.5 equiv), Et_2O, −78 °C (58%, 2 steps); (6) $CH(OMe)_3$ (1.5 equiv), BF_3·OEt_2 (1.1 equiv), $MgSO_4$ (25 equiv), DCM, 0 °C then AcBr (1 equiv) (57%); (7) Bu_3SnH (1.5 equiv), AIBN (1 equiv), PhMe, 110 °C (90%); (8) LiHMDS (2 equiv), PhSeCl (2 equiv), THF, −78 °C then H_2O_2 (5.0 equiv), 0 °C (60%, one-pot); (9) PPTS (4 equiv), pyridine (4 equiv), PhCl, 130 °C; (10) dimethyl malonate (5 equiv), $SnCl_4$ (5 equiv), DBU (5 equiv), I_2 (1 equiv), DCM, 23 °C (87%, 2 steps); (11) 2 M NaOH, MeOH, 23 °C then Et_3N (10.0 equiv), MeCN, 60 °C then LiHMDS (2.5 equiv), MeCHO (5 equiv), THF, −78 °C then Et_3N (30 equiv), MsCl (5.0 equiv), DMAP, DCM, 23 °C (94%, one-pot); TMDS = 1,1,3,3-tetramethyldisiloxane, EVK = ethyl vinyl ketone, DMS = dimethyl sulfide, HMPA = hexamethylphosphoramide, MB = methylene blue, DCM = dichloromethane, AIBN = 2,2′-azobis(2-methylpropionitrile), DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, LiHMDS = lithium bis(trimethylsilyl)amide, PPTS = pyridinium *p*-toluenesulfonate, DMAP = 4-(dimethylamino)-pyridine

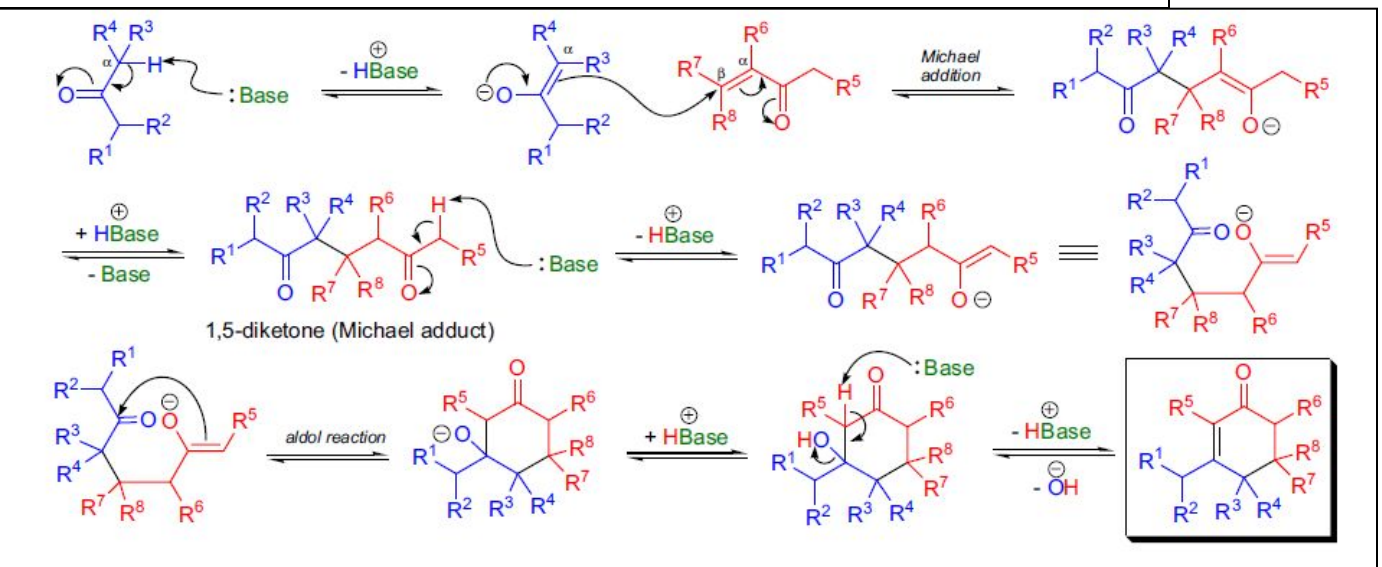


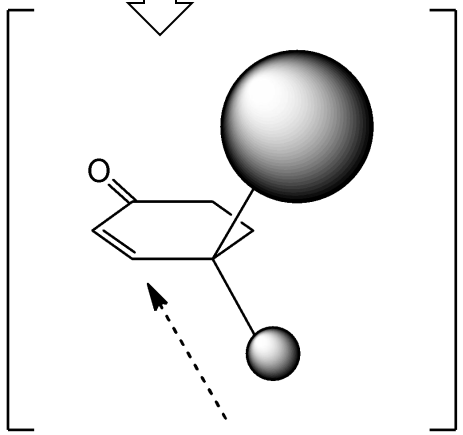


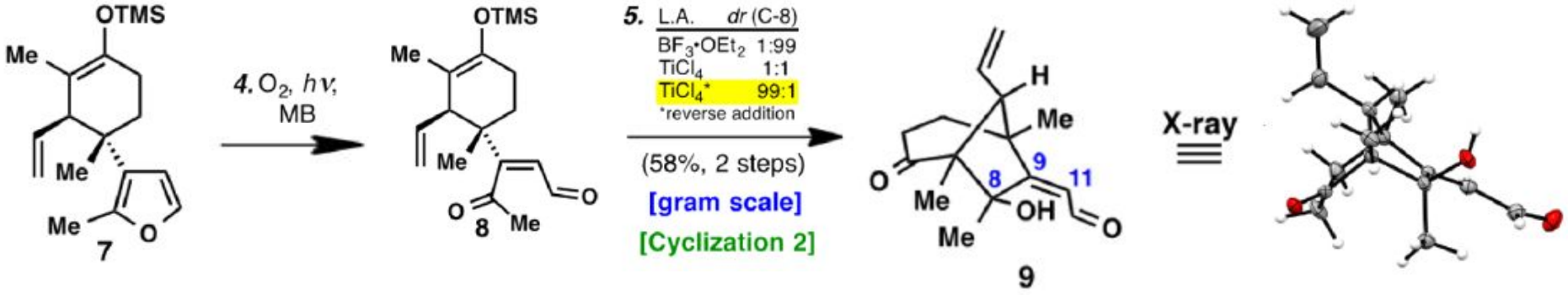
Eschenmoser-Claisen Rearrangement

Robinson annulation

Stereoselectivity







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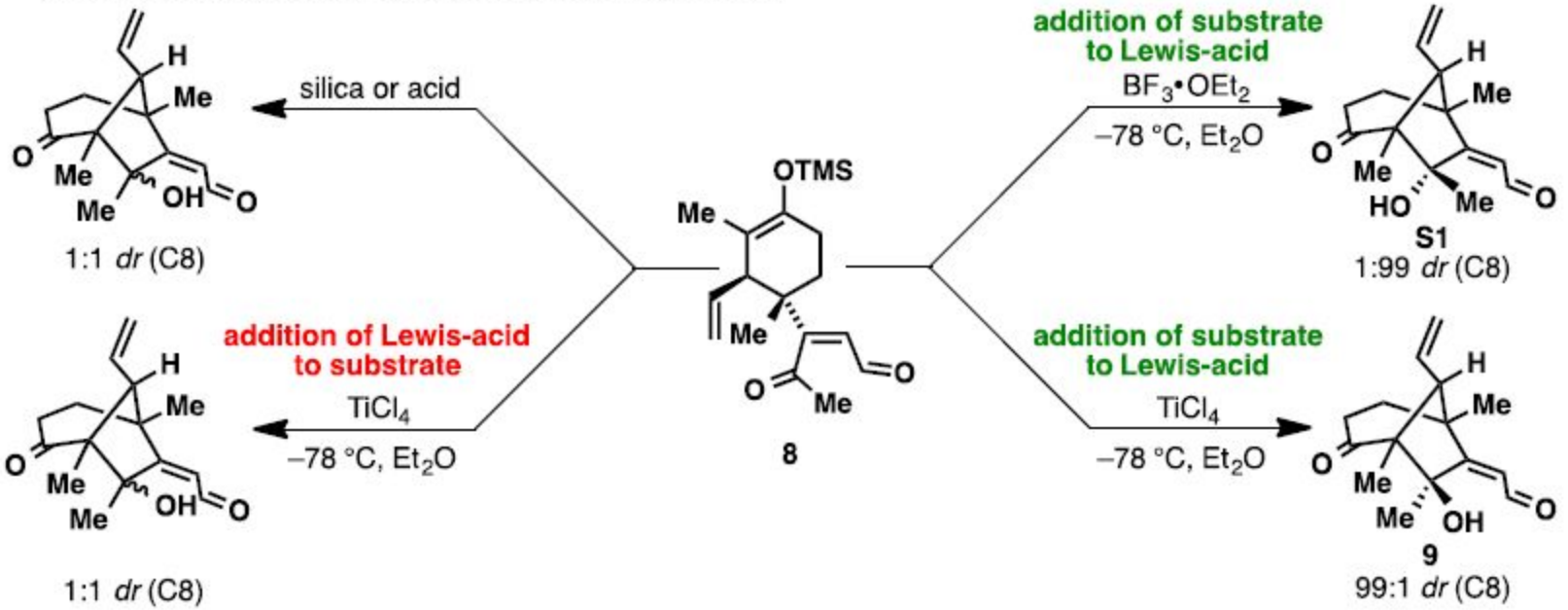
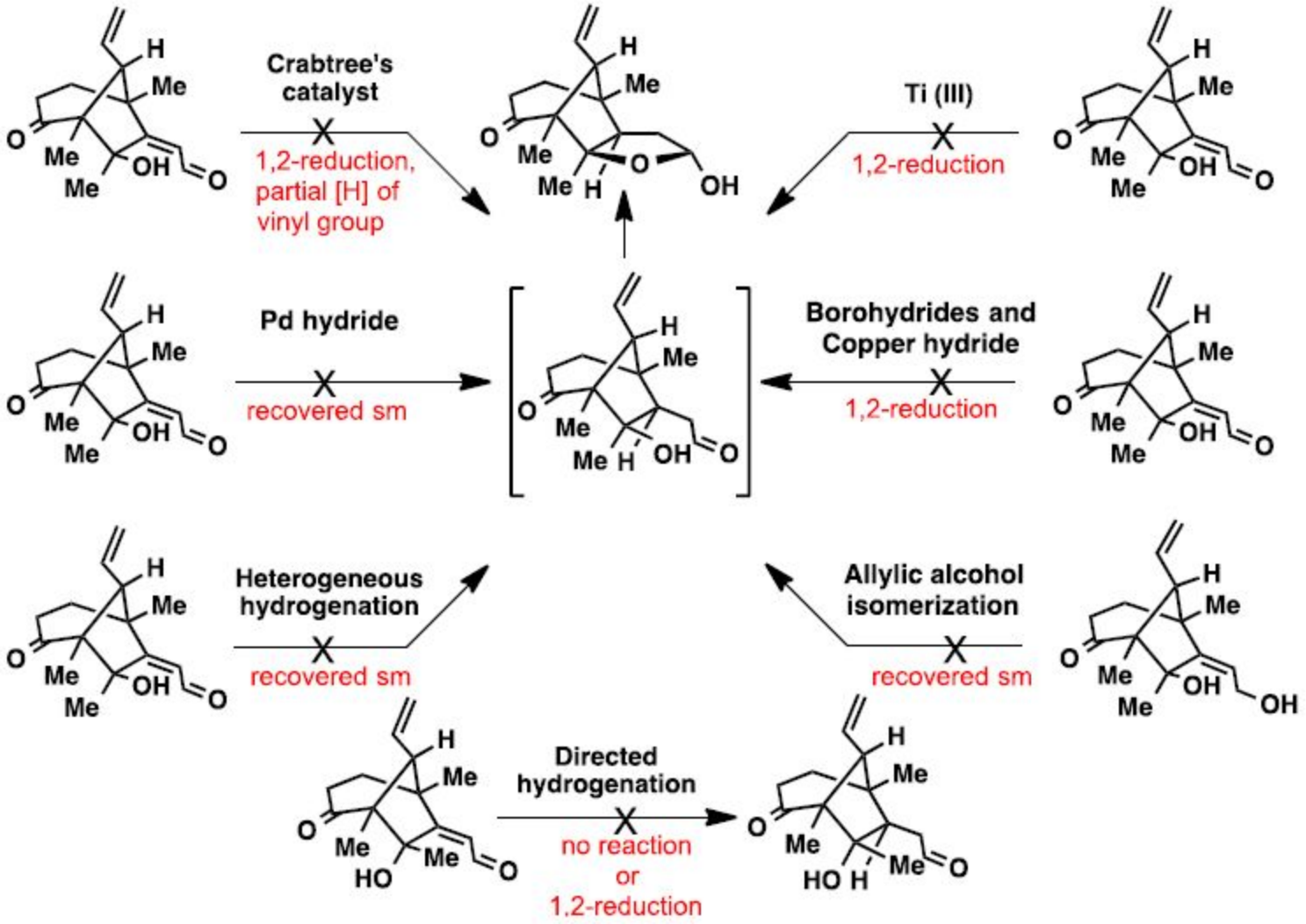
4) Order of addition and effect on diastereoselectivity

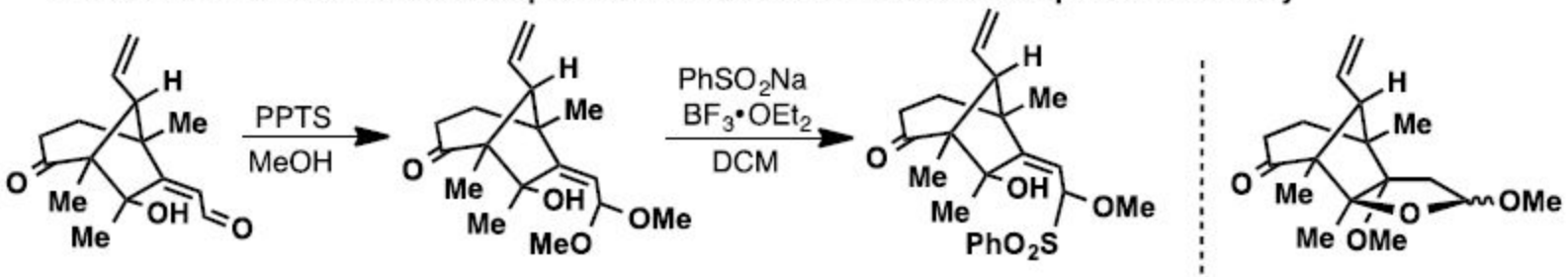


Evolution of C9–C11 reduction

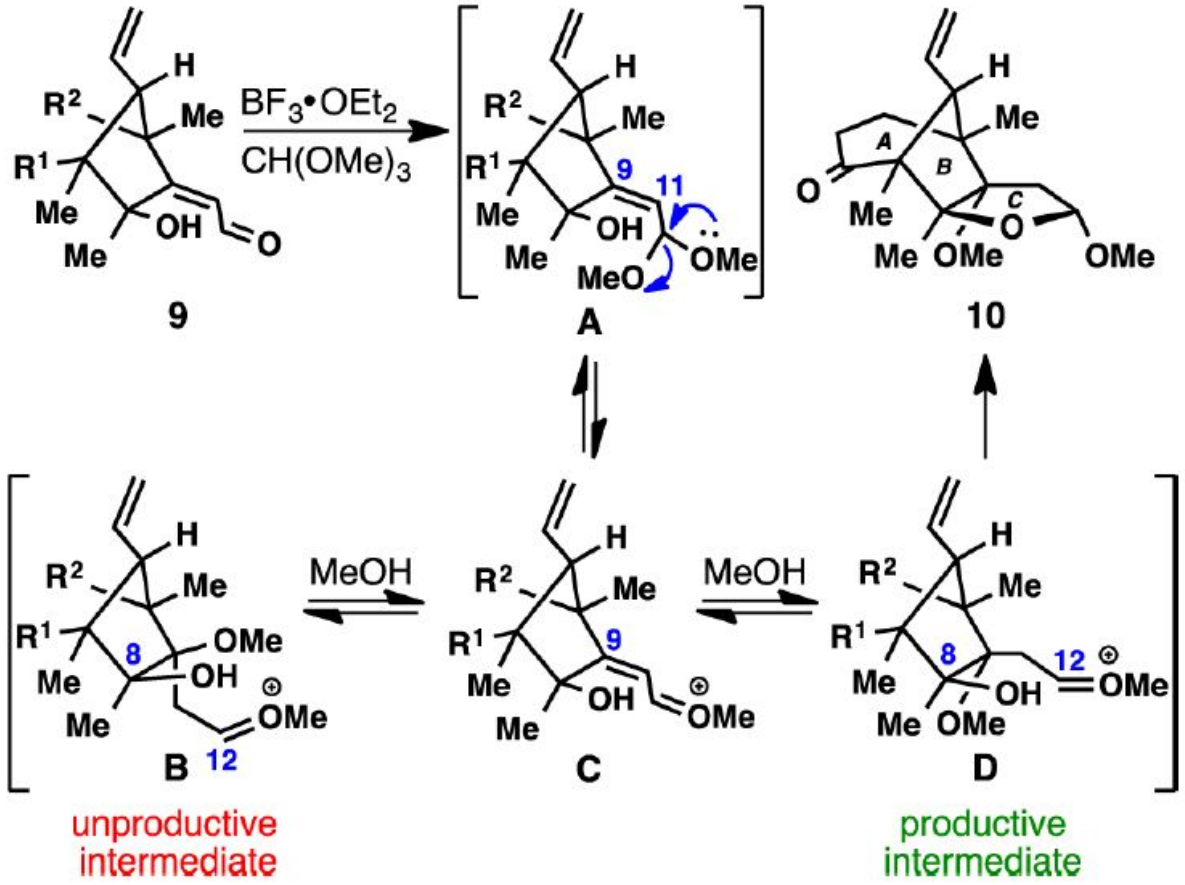
1) Failed attempts at C9–C11 reduction

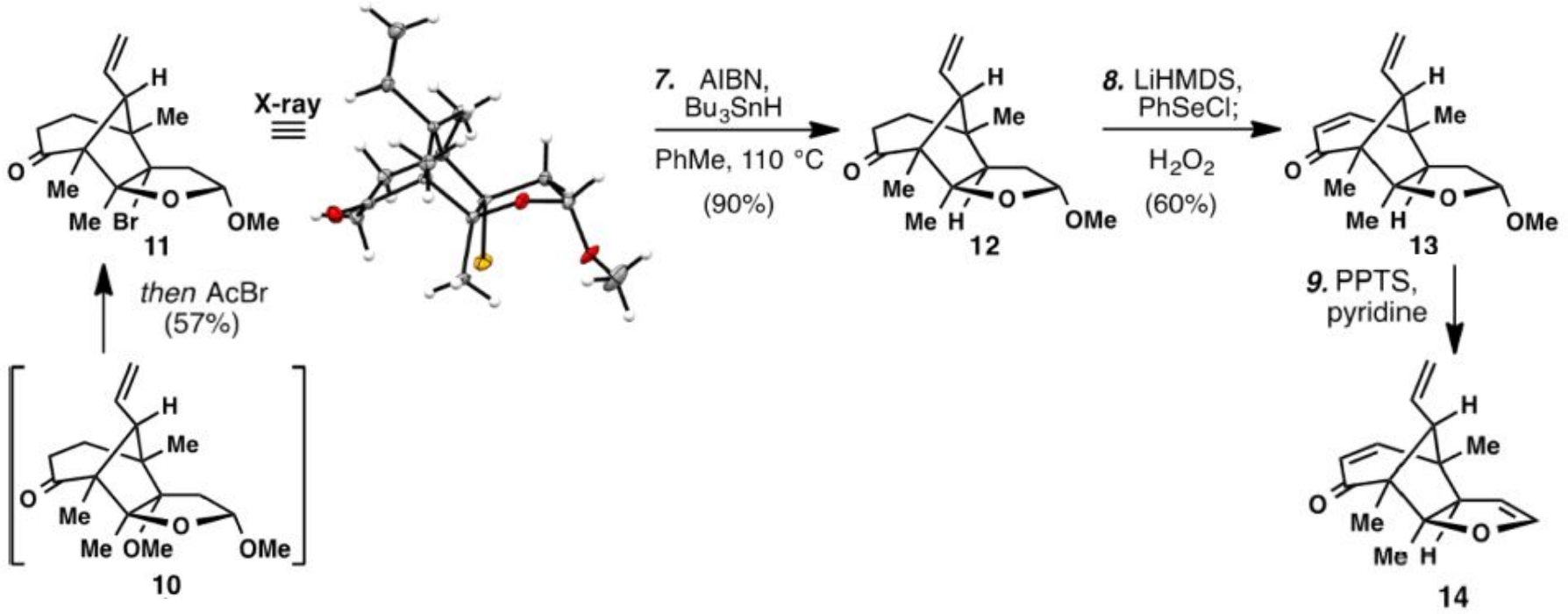


Derivatization of enal to further explore C9–C11 reduction leads to unexpected discovery

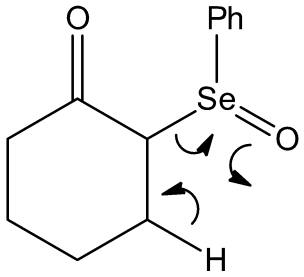


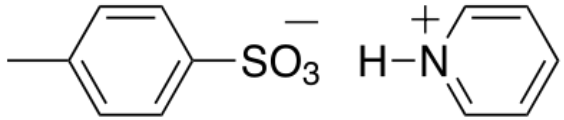
The enal was converted to an acetal in an effort to examine selectivity with an electronically different olefin. To our surprise this resulted in spontaneous cyclization forming ring C.




X-ray
7. AIBN, Bu_3SnH
PhMe, 110 °C
(90%)
8. LiHMDS, PhSeCl;
H_2O_2
(60%)
9. PPTS, pyridine
then AcBr
(57%)
11
12
13
14
10

PPTS


O
Ph
Se
O
H


SO_3^-
$H-N^+$

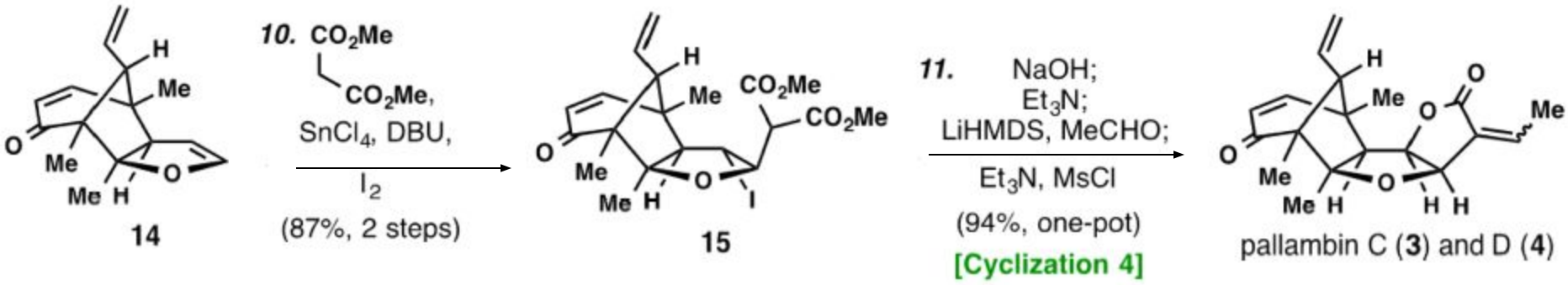
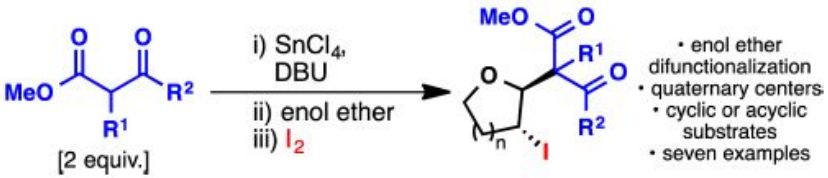
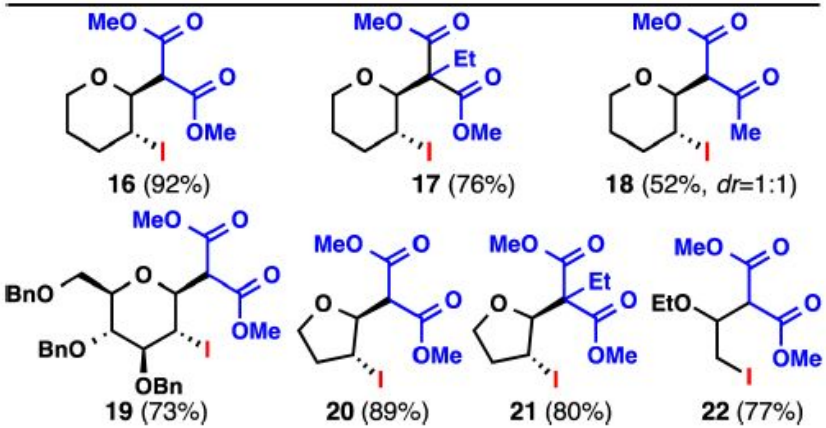
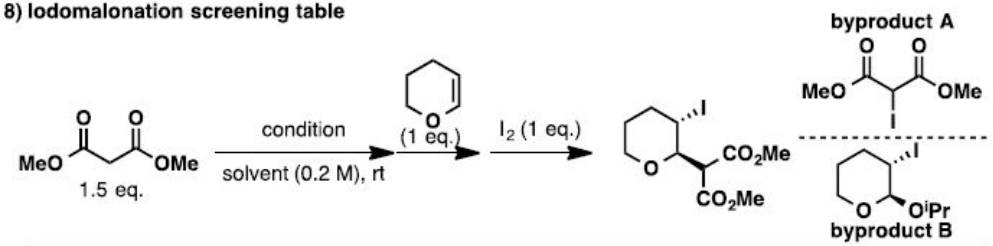


Table 1. Scope of the Enol-Ether Difunctionalization Reaction





8) Iodomalonation screening table



Entry	Solvent	Condition	Yield / %	Comment
1	THF	NaH	0	byproduct A was obtained.
2	THF	NaH, 15-crown-5	0	byproduct A was obtained.
3	THF	DBU	0	byproduct A was obtained.
4	THF	Et_3N	0	byproduct A was obtained.
5	DCM	$Ti(^iPrO)_4$	0	byproduct B was obtained.
6	DCM	$TiCl_4$, Et_3N	complex	
7	DCM	$TiCl_4$, DBU	complex	
8	DCM	$Zn(OTf)_2$, DBU	complex	
9	DCM	$SnCl_4$, DBU	60	vinyl ether (3 eq.), malonate (1 eq.)
10	DCM	$SnCl_4$, DBU	78	
11	THF	$SnCl_4$, DBU	complex	
12	MeCN	$SnCl_4$, DBU	complex	
13	PhMe	$SnCl_4$, DBU	33	
14	**DCM**	**$SnCl_4$, DBU**	**92**	**vinyl ether (1 eq.), malonate (2 eq.)**
15	DCM	$CeCl_3$, DBU	complex	
16	DCM	$InCl_3$, DBU	complex	
17	DCM	AgOAc	complex	