Transition-Metal Catalysis

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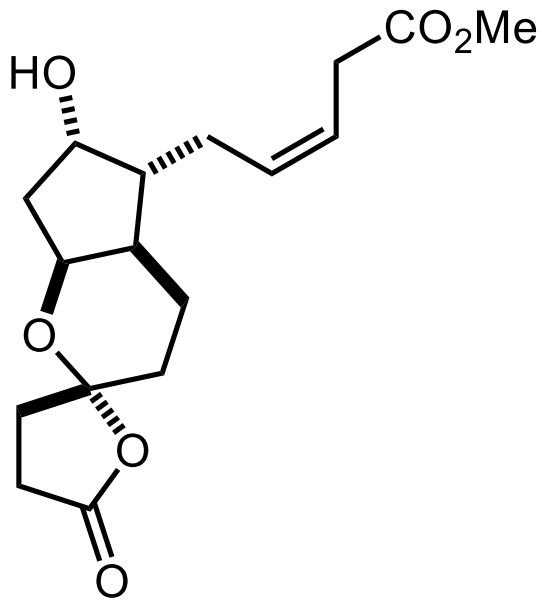
Catalysis-Enabled Concise and Stereoselective Total Synthesis of the Tricyclic Prostaglandin D_2 Metabolite Methyl Ester

*Hunter S. Sims, Pedro de Andrade Horn, Ryota Isshiki, Melissa Lim, Yan Xu, Robert H. Grubbs, and Mingji Dai**



tricycle-PDGM methyl ester (**3**)

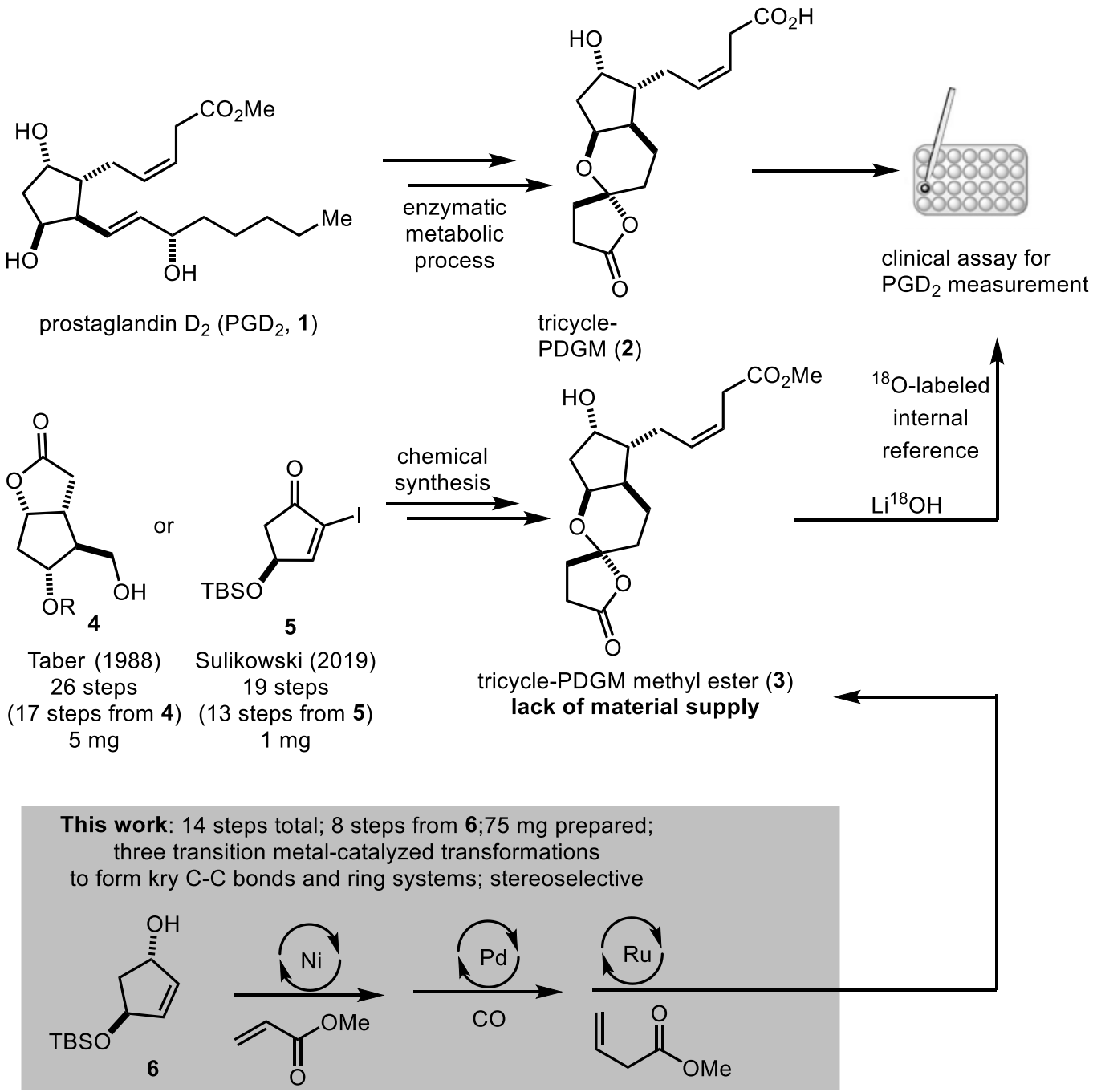
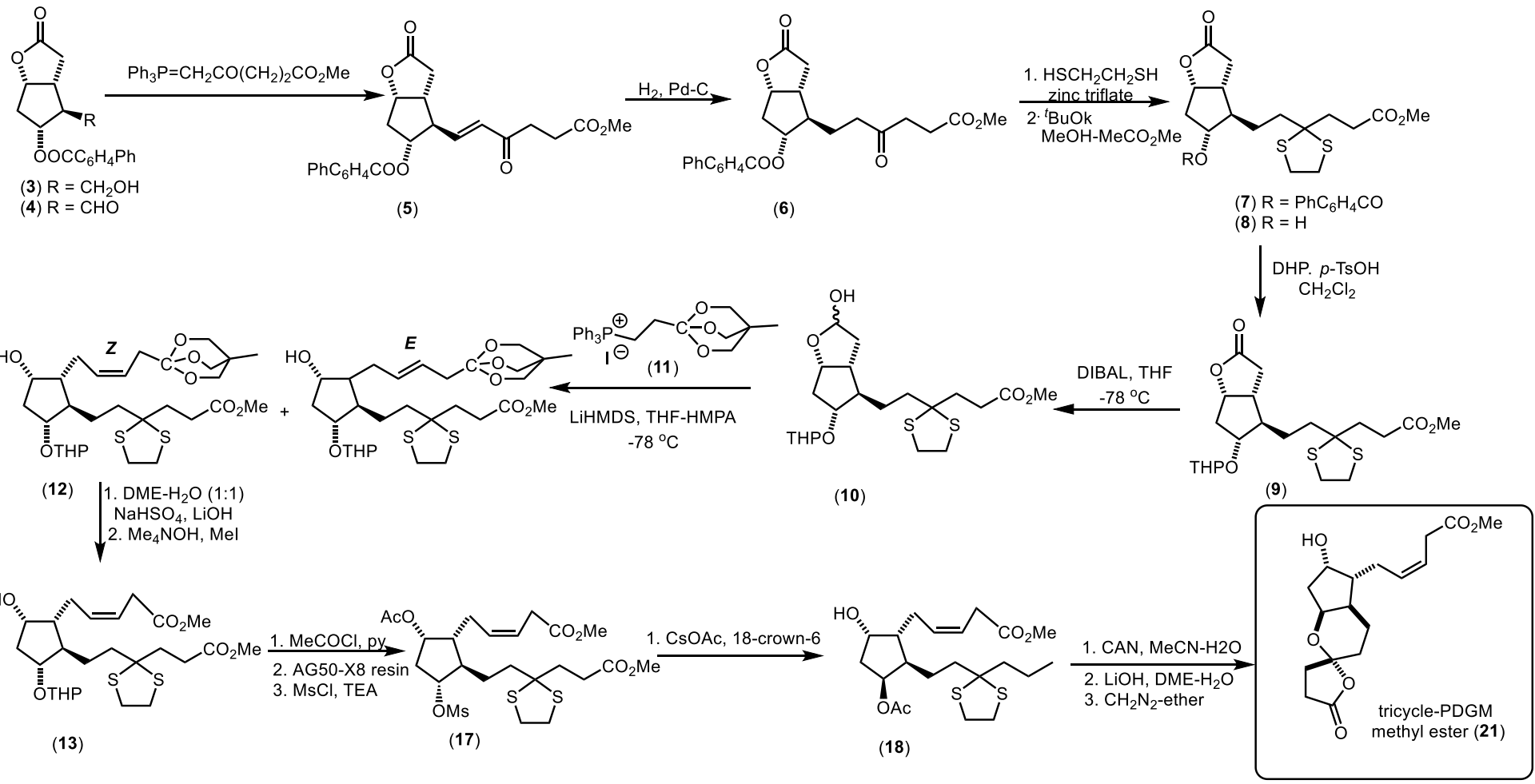
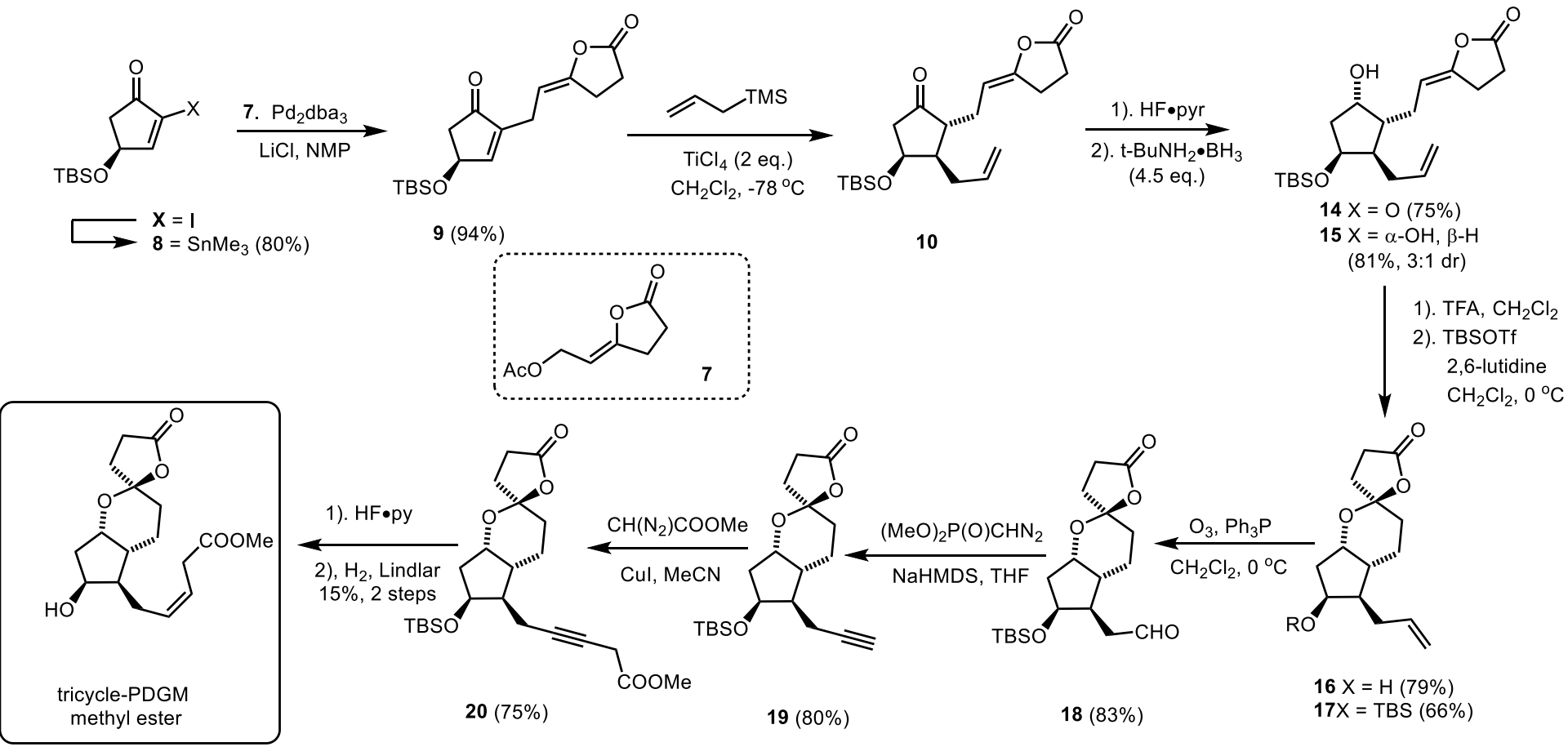


Figure 1. Clinical use of tricycle-PDGM methyl ester and its synthesis

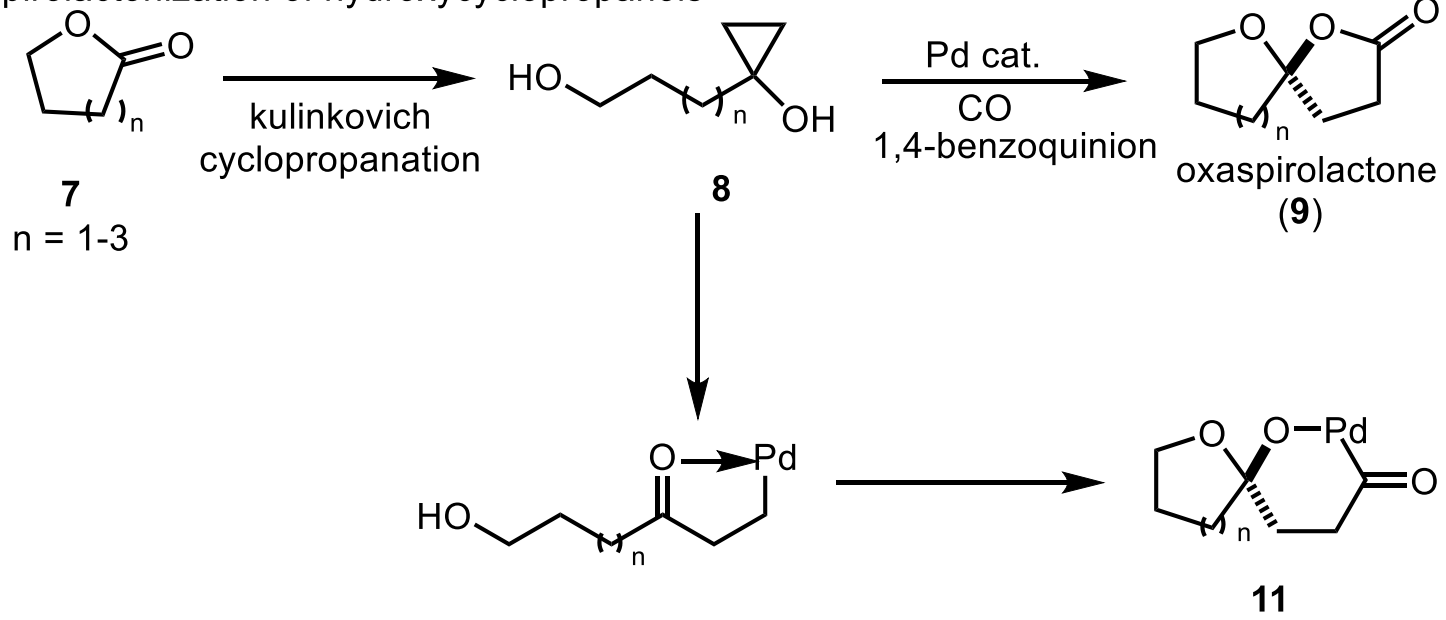


J.Chem. Soc. Perkin Trans. **1988**, 2821.



Org. Lett. **2019**, *21*, 10048.

A. Pd-catalyzed carbonylative spirolactonization of hydroxycyclopropanols



7
n = 1-3

8

oxaspirolactone (**9**)

11

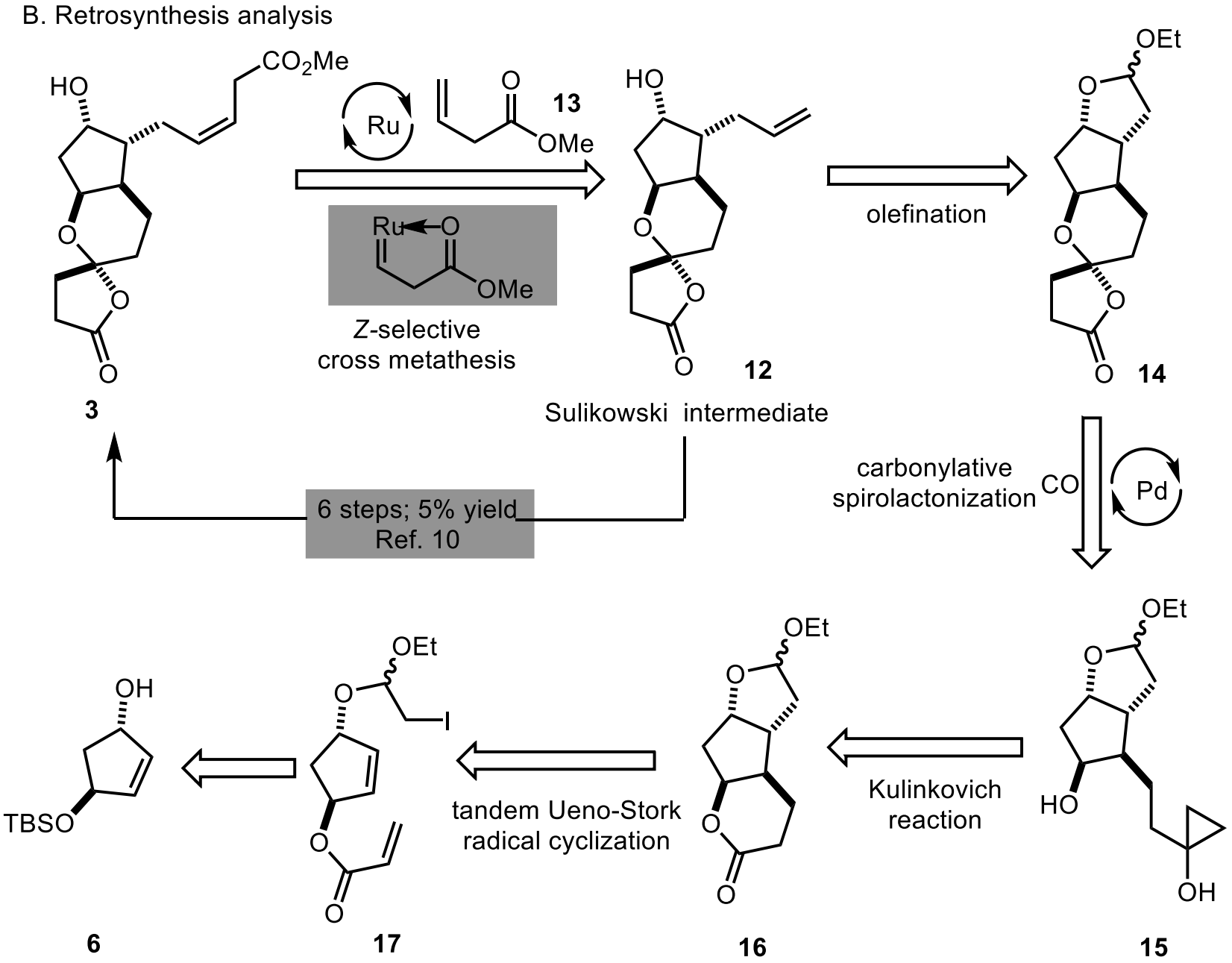
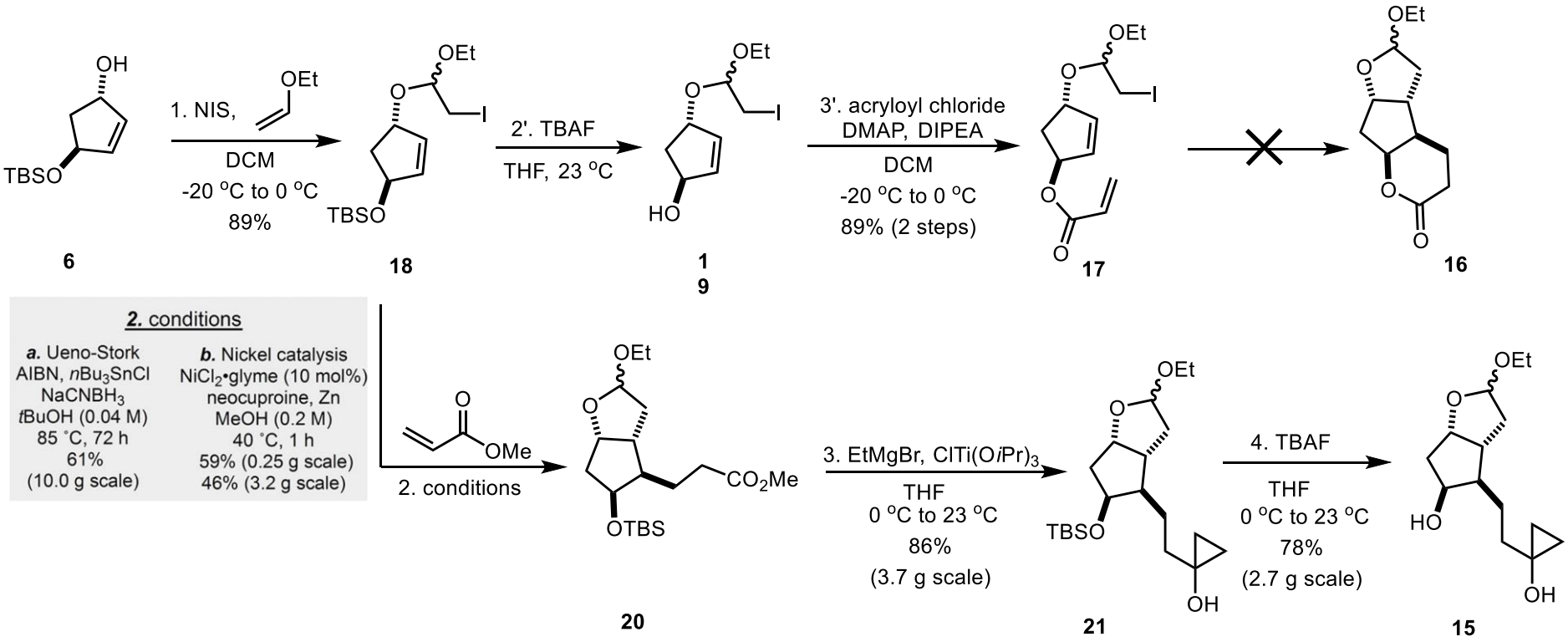
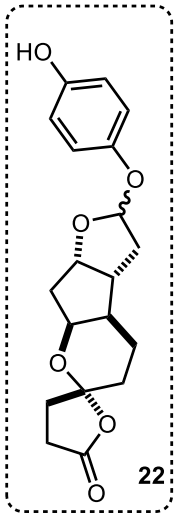
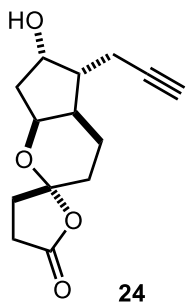


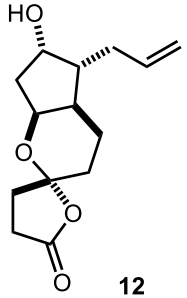
Figure 2. Carbonylative spirolactonization and retrosynthetic analysis.

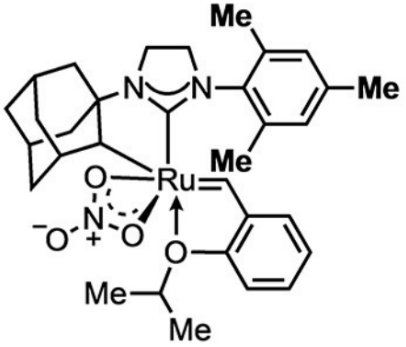


8. conditions	
Entry 1: Ru-Z-DIPP (15 mol%), **13** (8 equiv), DCE, 40 ˚C, 2 h	52% (>95% *Z*; 35% sm)
Entry 2: Ru-Z-DIPP (5 mol%), **13** (5 equiv), DCE, 30 ˚C, 12 h (100 mg scale)	38% (>95% *Z*)
Entry 3: Ru-Z-Mes (Sigma-repurified, 20 mol%), **13** (8 equiv), DCE, 53 ˚C, 2 h	35% (90% *Z*; 40% sm)
Entry 4: Ru-Z-Mes (Sigma, 20 mol%), **13** (10 equiv), DCE, 53 ˚C, 2 h	10-15% (90% *Z*)
Entry 5: Ru-Z-DIPP (20 mol%), **13** (8 equiv), THF, 40 ˚C, 2 h	7% (95% *Z*; 65% sm)
Entry 6: Ru-Z-DIPP (20 mol%), **13** (8 equiv), DCE, 53 ˚C, 2 h	42% (94% *Z*; 45% sm)
Entry 7: Ru-Z-DIPP (20 mol%), **13** (2 equiv), DCE, 40 ˚C, 2 h	35% (94% *Z*; 45% sm)

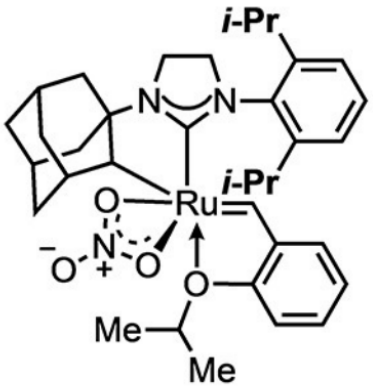




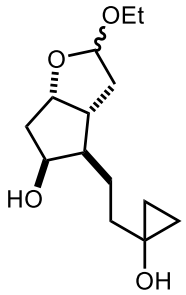




Ru-*Z*-Mes

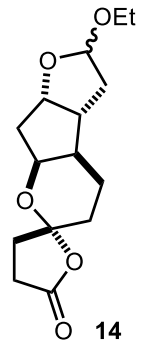


Ru-*Z*-DIPP



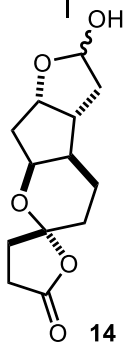
15

5' $[Pd(neoc)(OAc)_2]_2(OTf)_2$
1,4-benzoquinone, CO
DCE, 50 °C
40-50% (**14** + **22**)
or $Pd(OAc)_2$, DDQ, CO
PhH, 23 °C
67%(**14** only)



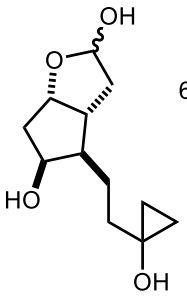
14

6'. HCl (0.5 M)
THF, 23 °C
90%



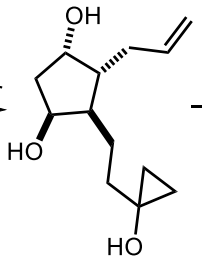
14

5. HCl (0.5 M)
THF, 23 °C
90%



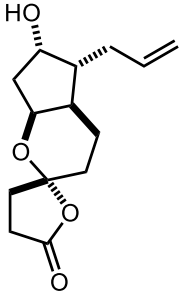
25

6. KHMDS, CH_3PPh_3Br
THF, 0 °C
55%
(2 steps;0.5 g scale)



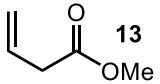
26

7, $Pd(OAc)_2$
DDQ, CO
PhH, 23 °C
53%
200 mg scale

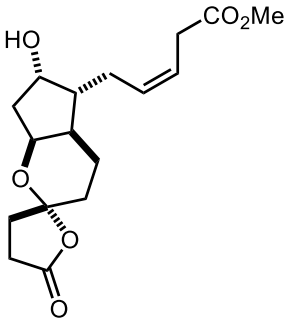


12

8. conditions



13



tricycle-PDGM
methyl ester (**3**)

KULINKOVICH REACTION

Mechanism:

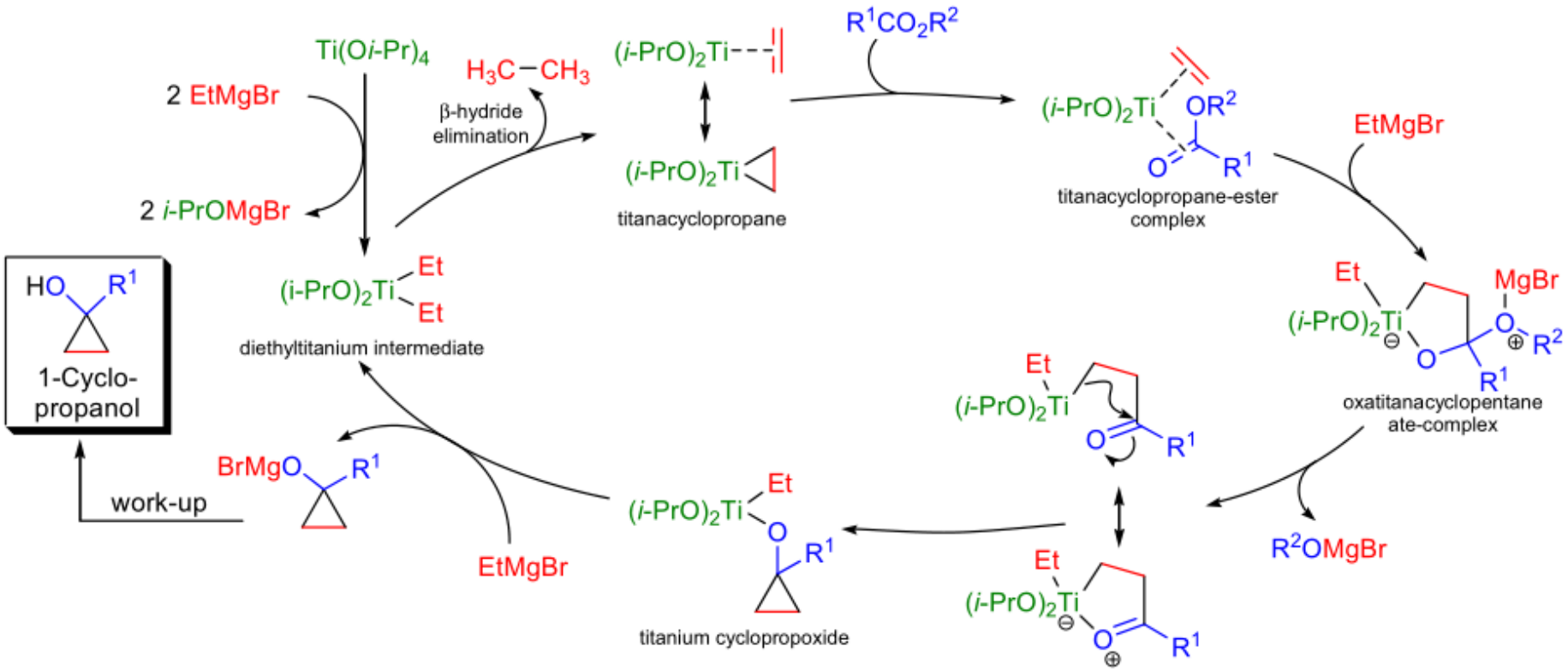
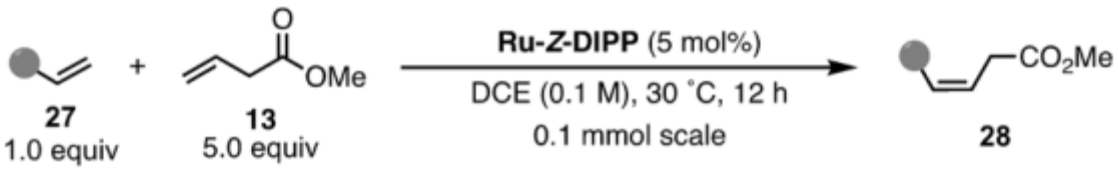


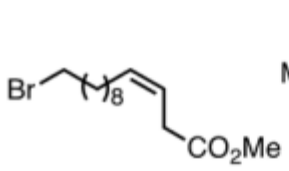
Table 1: Substrate scope for the *Z*-selective cross-metathesis with **13**.



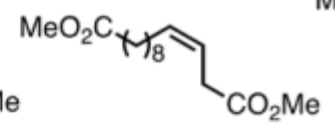
27 1.0 equiv

13 5.0 equiv

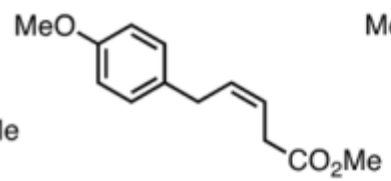
28



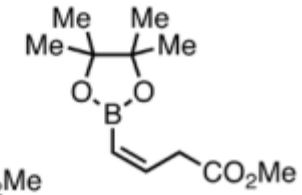
28a
54% (95% *Z*)



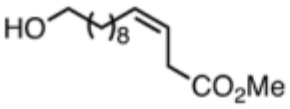
28b
60%, (>95% *Z*)



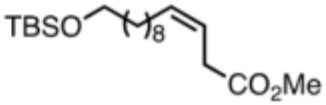
28c
59% (>95% *Z*)



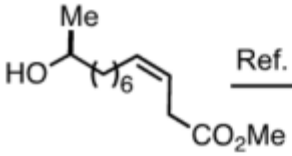
28d
35% (>95% *Z*)



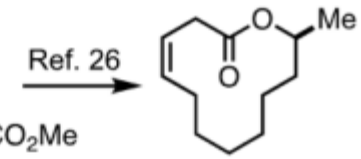
28e
68% (>95% *Z*)



28f
57% (>95% *Z*)



28g
69% (>95% *Z*)



Ferrulactone II