

Total Synthesis of (-)-Nakadomarin A

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Structural Features of the Target

- 15-membered ring with Z-olefin
- Many fused heterocycles

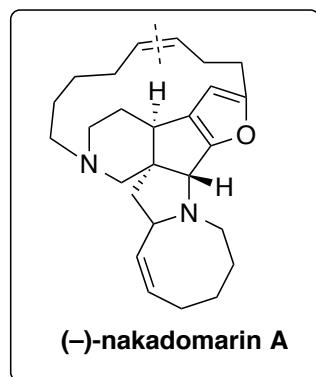
Previous Syntheses Include:

Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632.

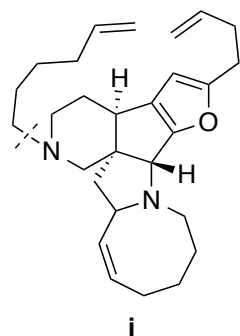
Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88.

Evans, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 9338.

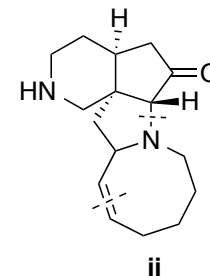
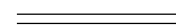
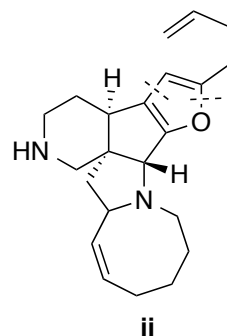
Retrosynthesis



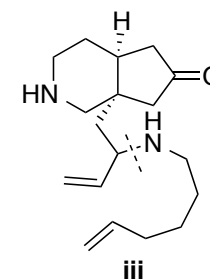
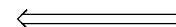
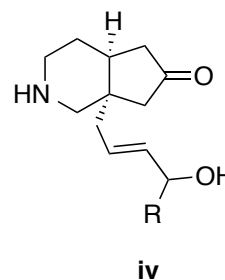
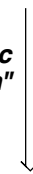
Ring-Closing
Metathesis



Acylation/
Reduction

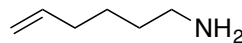


"Electrophilic
Amination" and Ring-
Closing
Metathesis

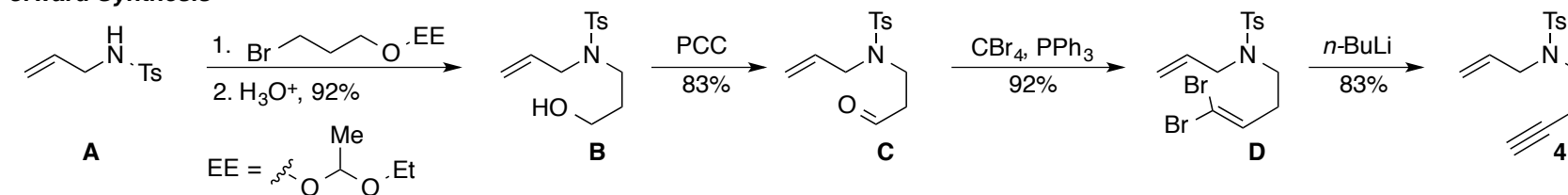


Key Steps:

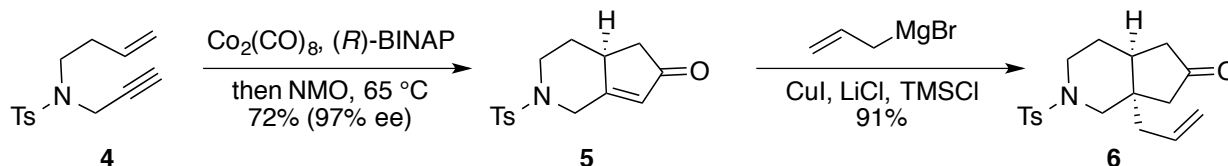
- Heavy use of olefin metathesis (3x)
- Overman rearrangement for C–N formation
- Pauson-Khand reaction for efficient bicycle synthesis



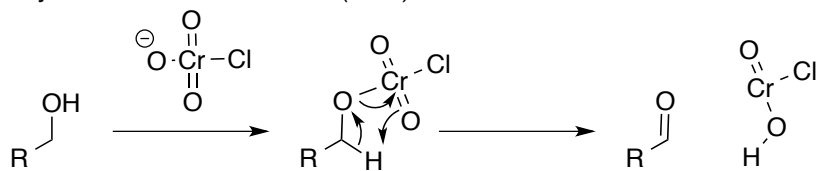
Forward Synthesis



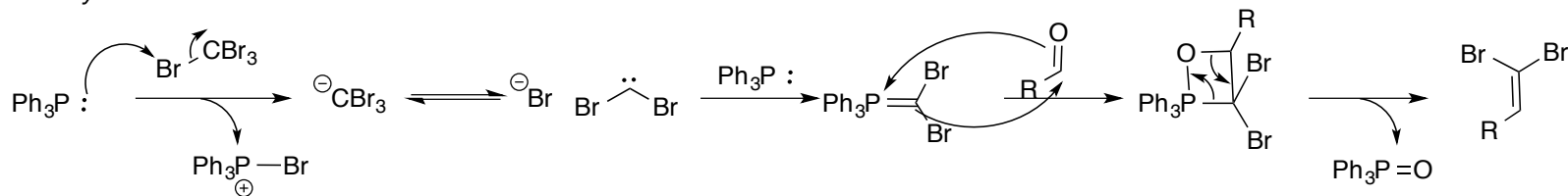
Mori, M.; Watanuki, S. *Heterocycles* **1993**, *35*, 679.



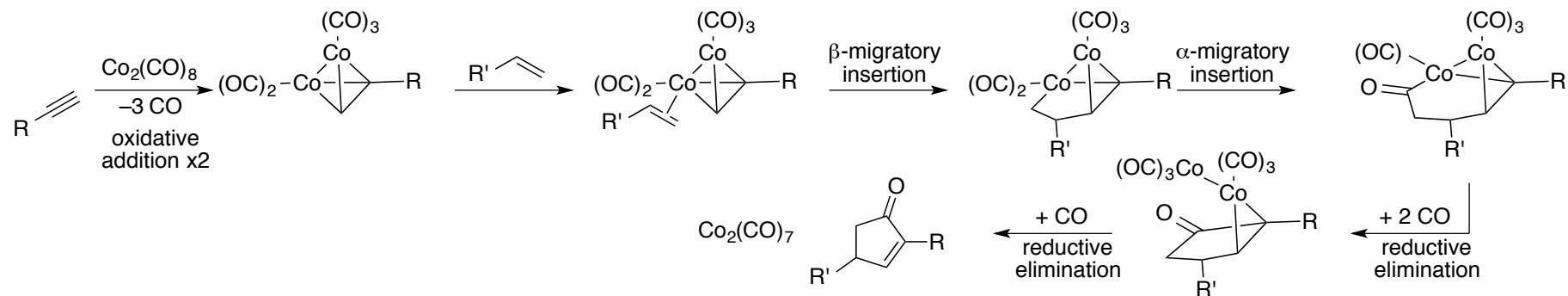
B to C: Pyridinium Chlorochromate (PCC) oxidation

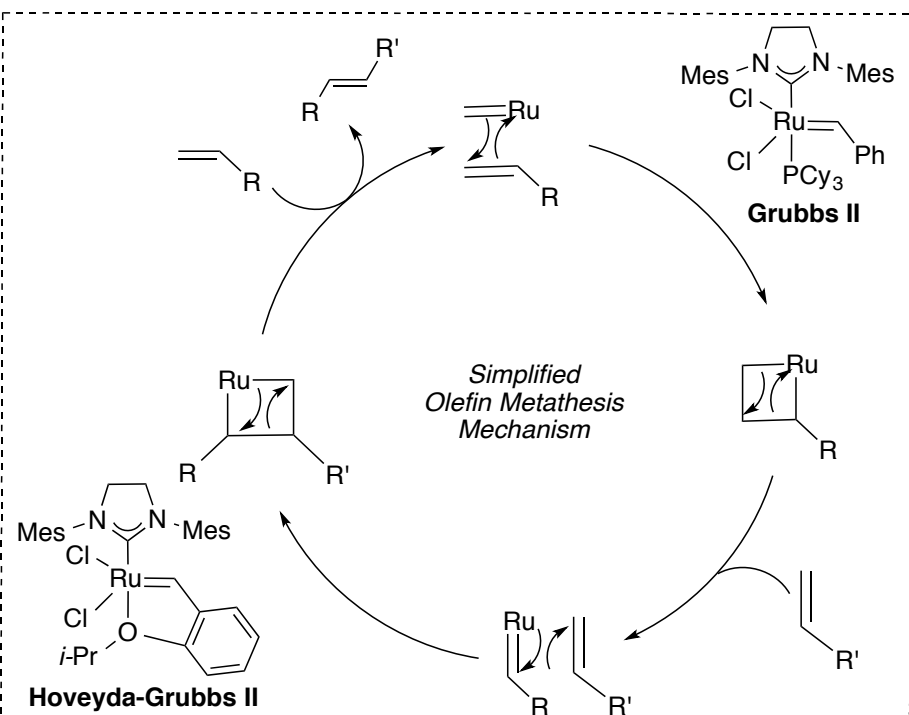
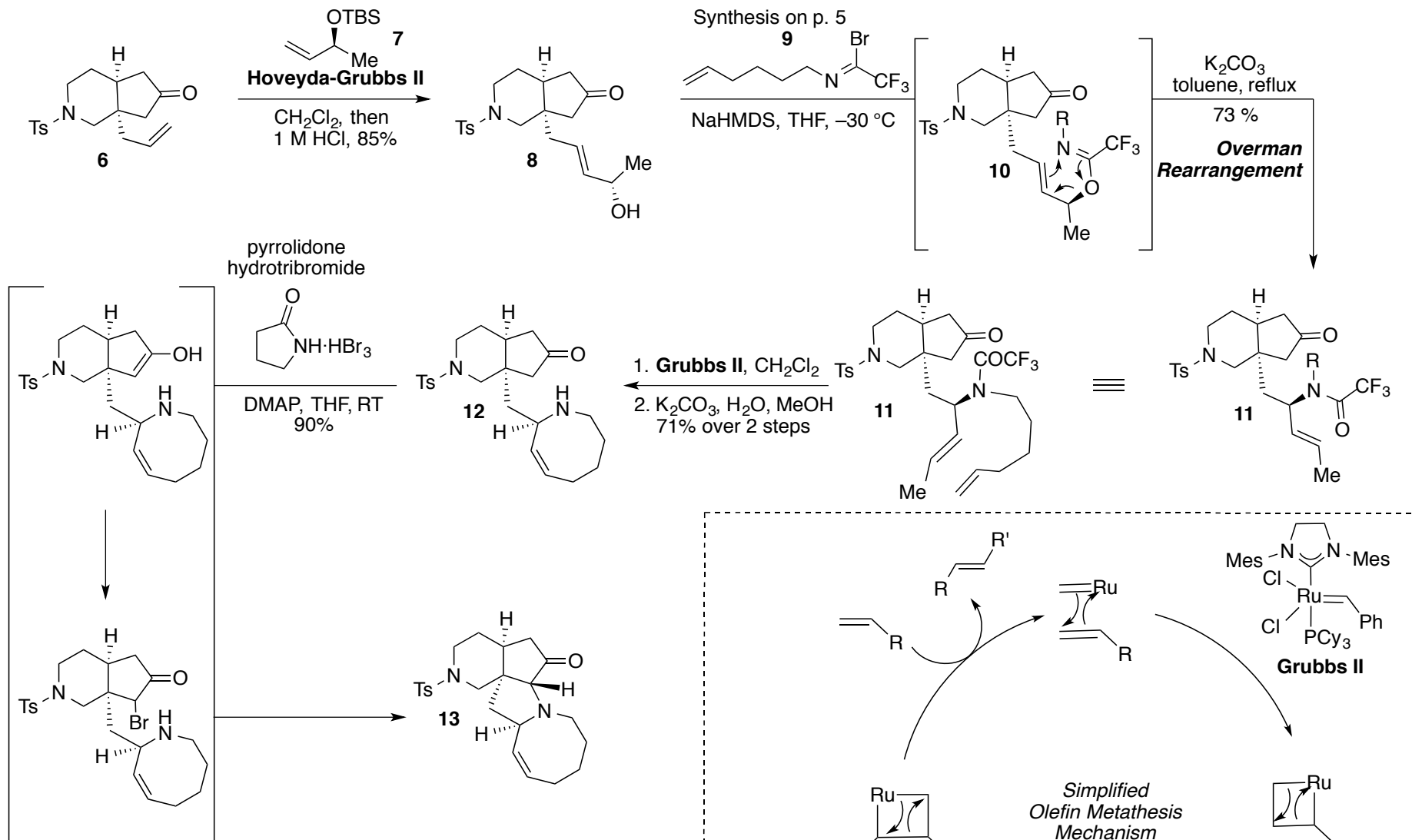


C to D: Corey-Fuchs reaction

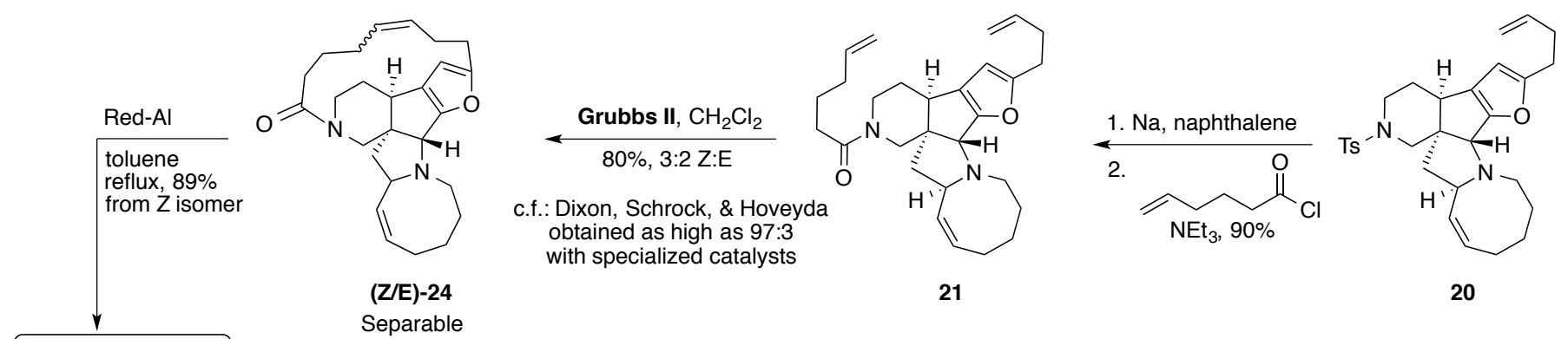
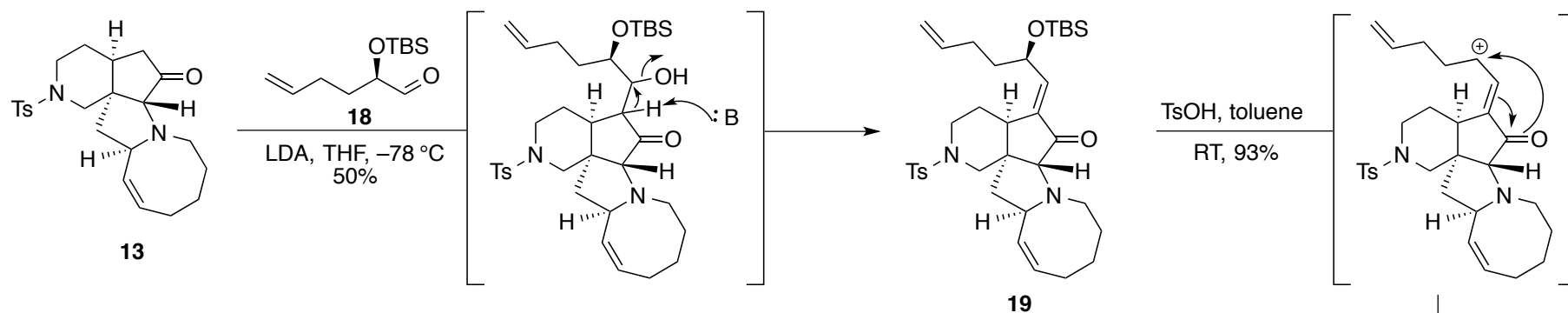


4 to 5: Pauson-Khand reaction

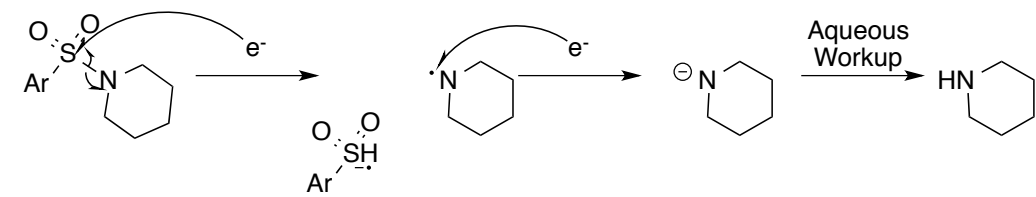




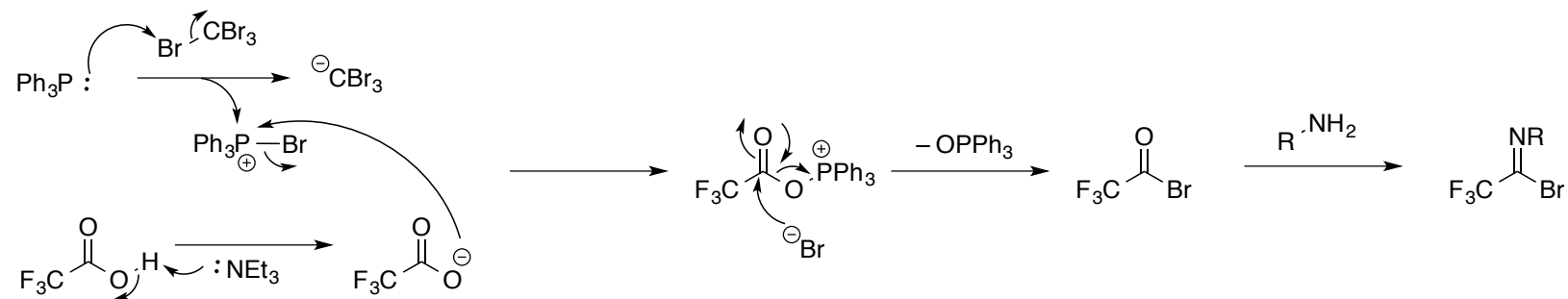
Pyrrolidone hydrotribromide brominates ketones at the alpha carbon selectively
 Awang, D. V. C.; Wolfe, S. *Can. J. Chem.* **1969**, *47*, 706.



20 to 21 step 1: reductive deprotection of N-Ts

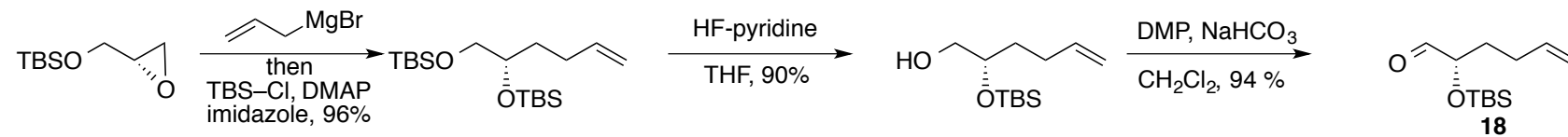


Synthesis of imidoyl bromide **9**



Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32.

Synthesis of **18**



Dess-Martin Oxidation

