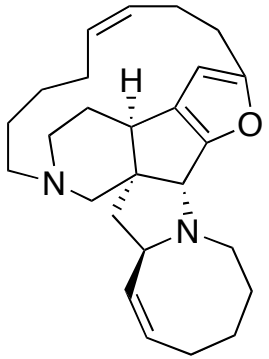
Total synthesis of (-)-Nakadomarin A



(-)-Nakadomarin A

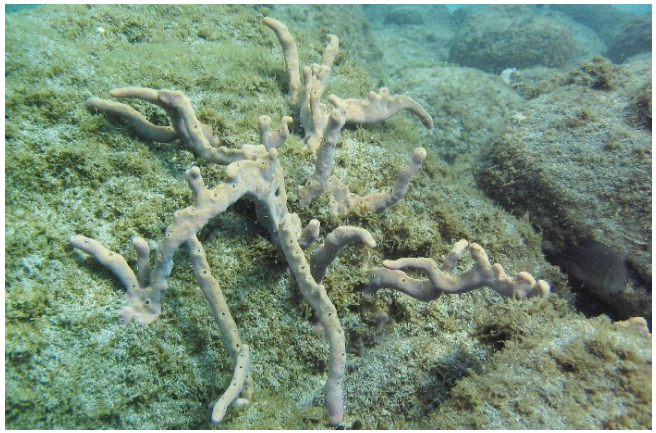
Jakubec, P.; Cockfield, D. M.; Dixon, D. J.

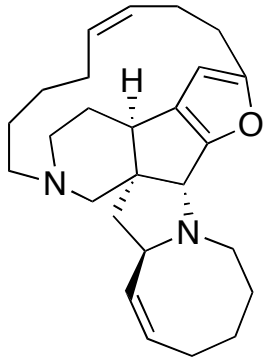
J. Am. Soc. Chem. ASAP.

Outline

- Biological activity
- Previous synthesis
- Synthesis from the paper
- Retrosynthesis
- Forward synthesis

Biological activity





(-)-Nakadomarin A
1

Isolated in 1997 from a sea sponge *Amphimedo*
by Kobayashi off the coast of the Kerama Islands, Okinawa

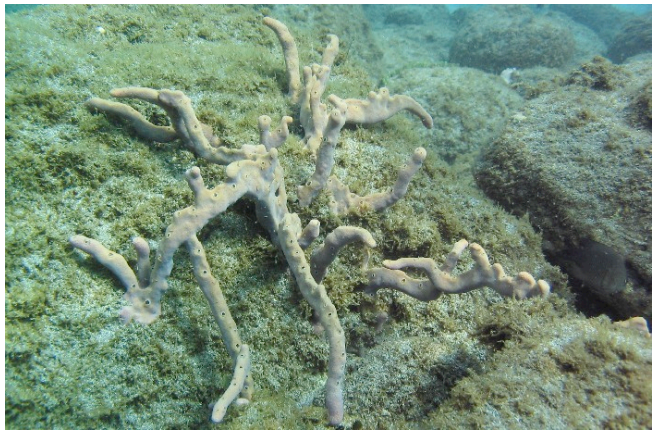
only known member of the manzamine family to contain a furan ring

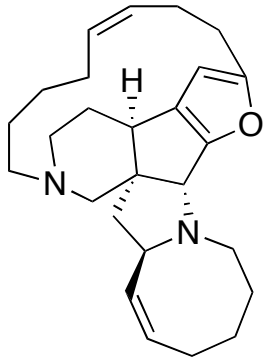
Limited availability from nature:
6 mg isolated from 1 kg of wet sponge

Bioactivity includes anticancer, antifungal and antibacterial

Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* ***1997, 62, 9236-9239.***

Structure





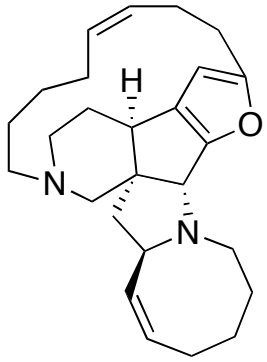
(-)-Nakadomarin A
1

Structural features:

- Ring system: 8/5/5/5//15/6
- 4 stereogenic centers, 1 quaternary
- Z alkene

Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* ***1997, 62, 9236-9239.***

Previous Synthesis



(-)-Nakadomarin A
1

Completed Syntheses:

(+)-Nakadomarin A:
Nagata, Nakagawa and Nishida, JACS, *2003, 125, 7484*
Young and Kerr, JACS, *2007, 129, 1465*

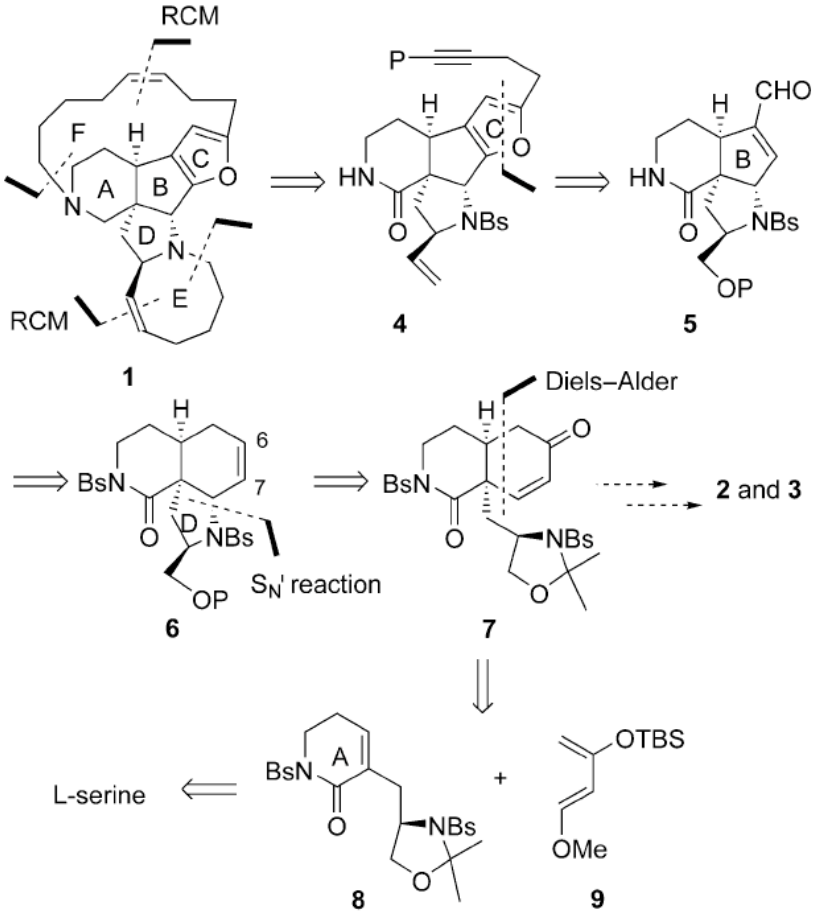
(-)-Nakadomarin A: Ono, Nakagawa and Nishida, ACIE, *2004, 43, 2020*

Published Approaches:

Furstner, JACS, *1999, 121, 11108*
Magnus, TL, *2002, 43, 947*
Tius, OL, *2003, 5, 1171*
Williams, OL, *2004, 6, 4539*
Funk, OL, *2006, 8, 3833.*

Nakagawa's synthesis

(-)-Nakadomarin A



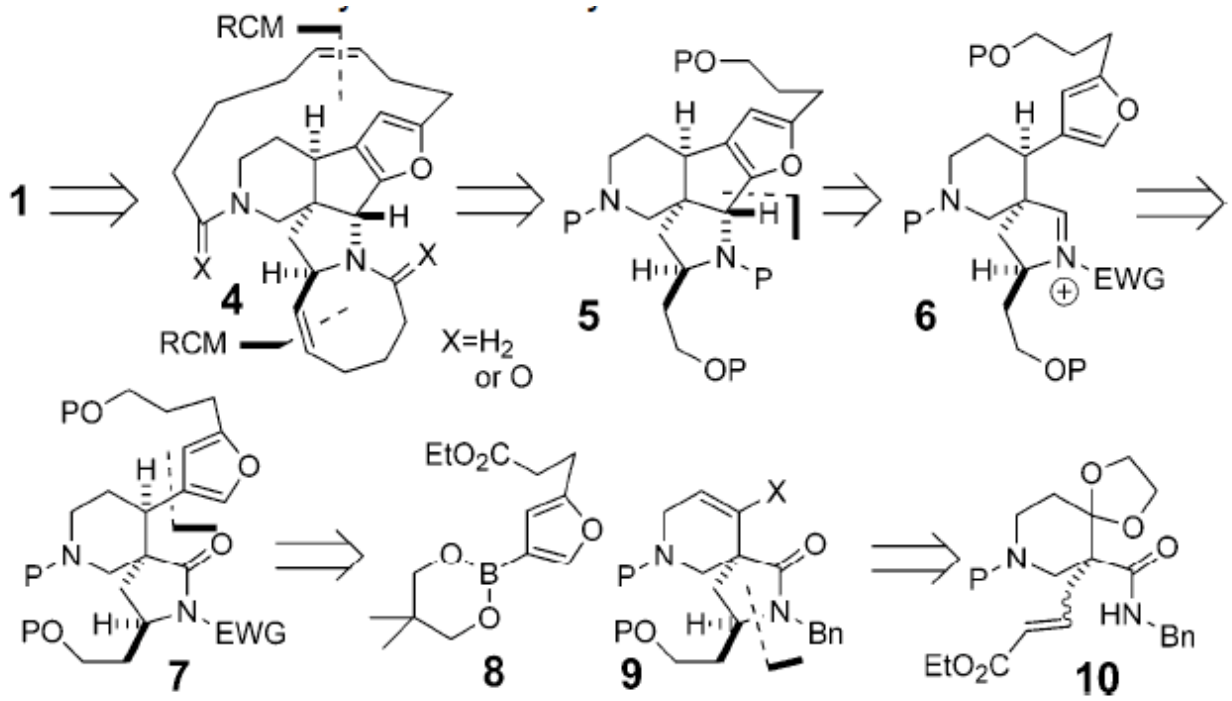
Forward Synthesis:

36 longest linear steps

2.5 mg of the target product.

Ono, K.; Nakagawa, M.; Nishida, A. Angew. Chem. Int. Ed. 2004, 43, 2020.

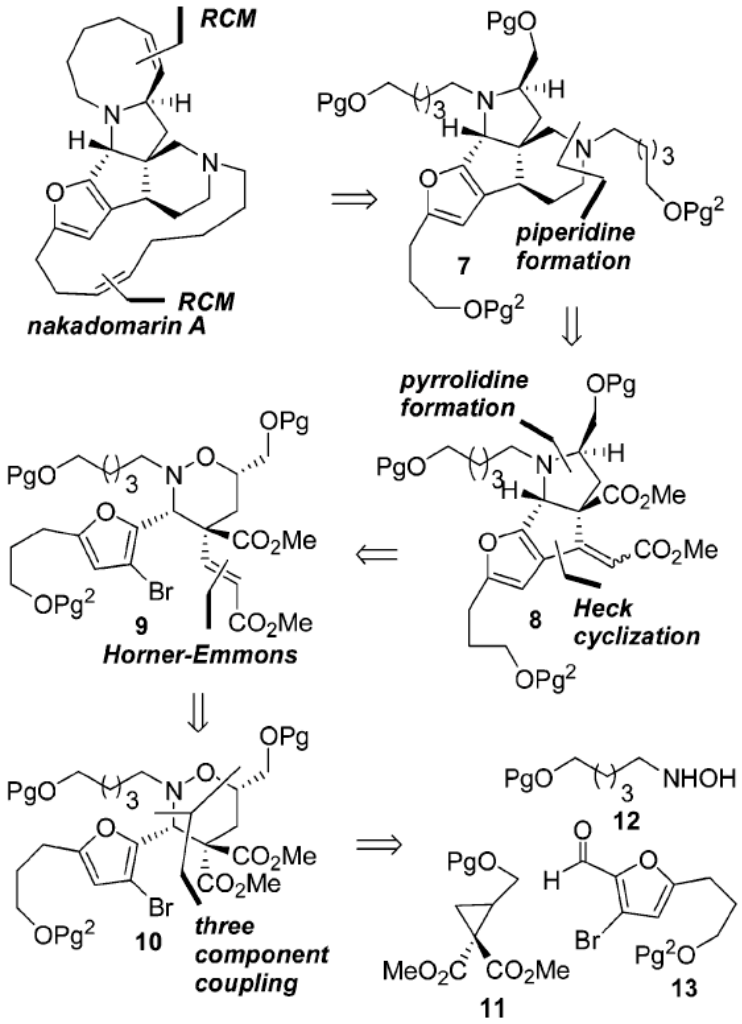
Nakagawa's synthesis
(+)-Nakadomarin A



Forward synthesis: 37 longest linear steps

Nagata, T.; Nakawaga, M.; Nishida, A. J. Am. Chem. Soc. 2003, 125, 7484.

Kerr's synthesis
(+)-Nakadomarin A

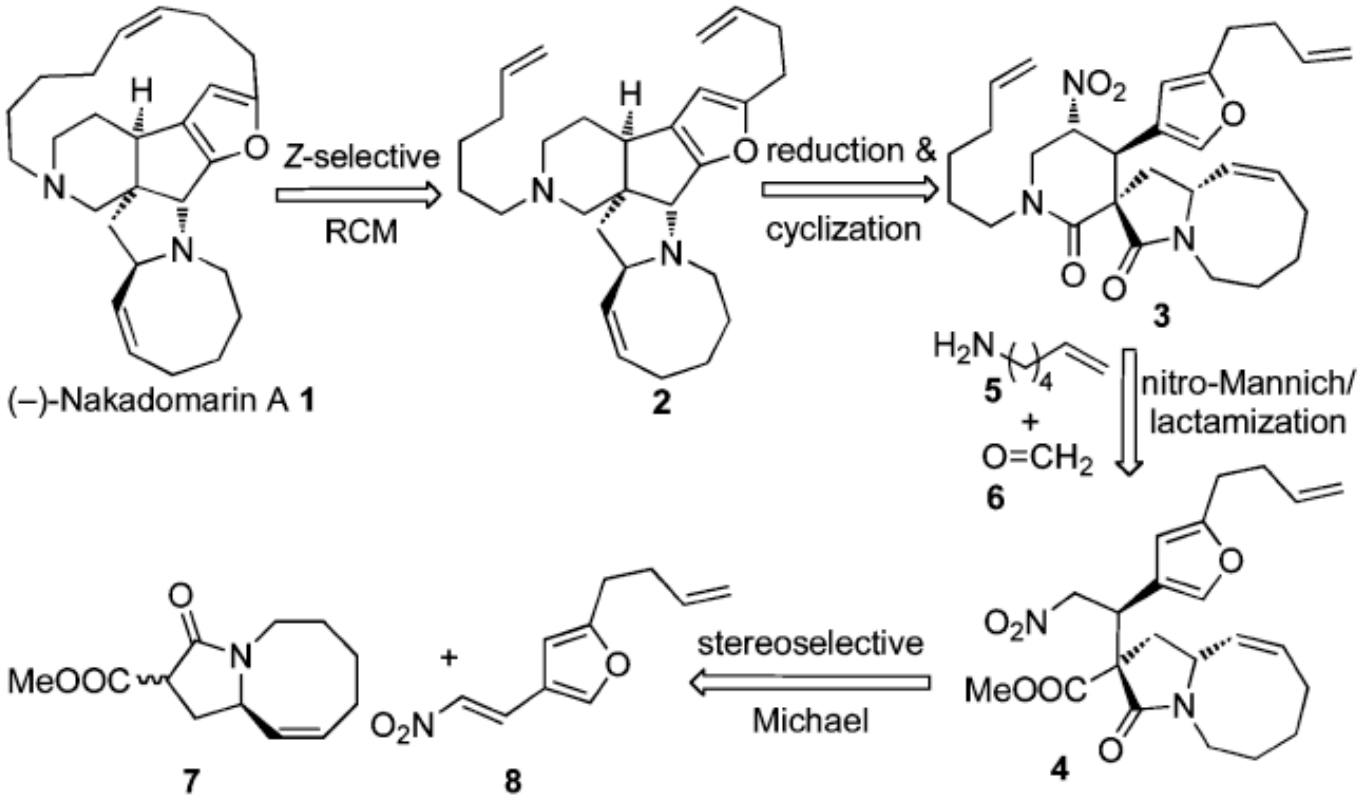


Forward synthesis:

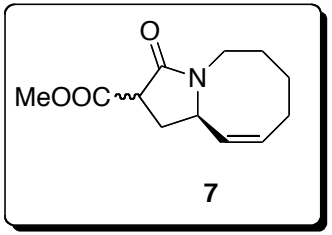
29 longest linear steps

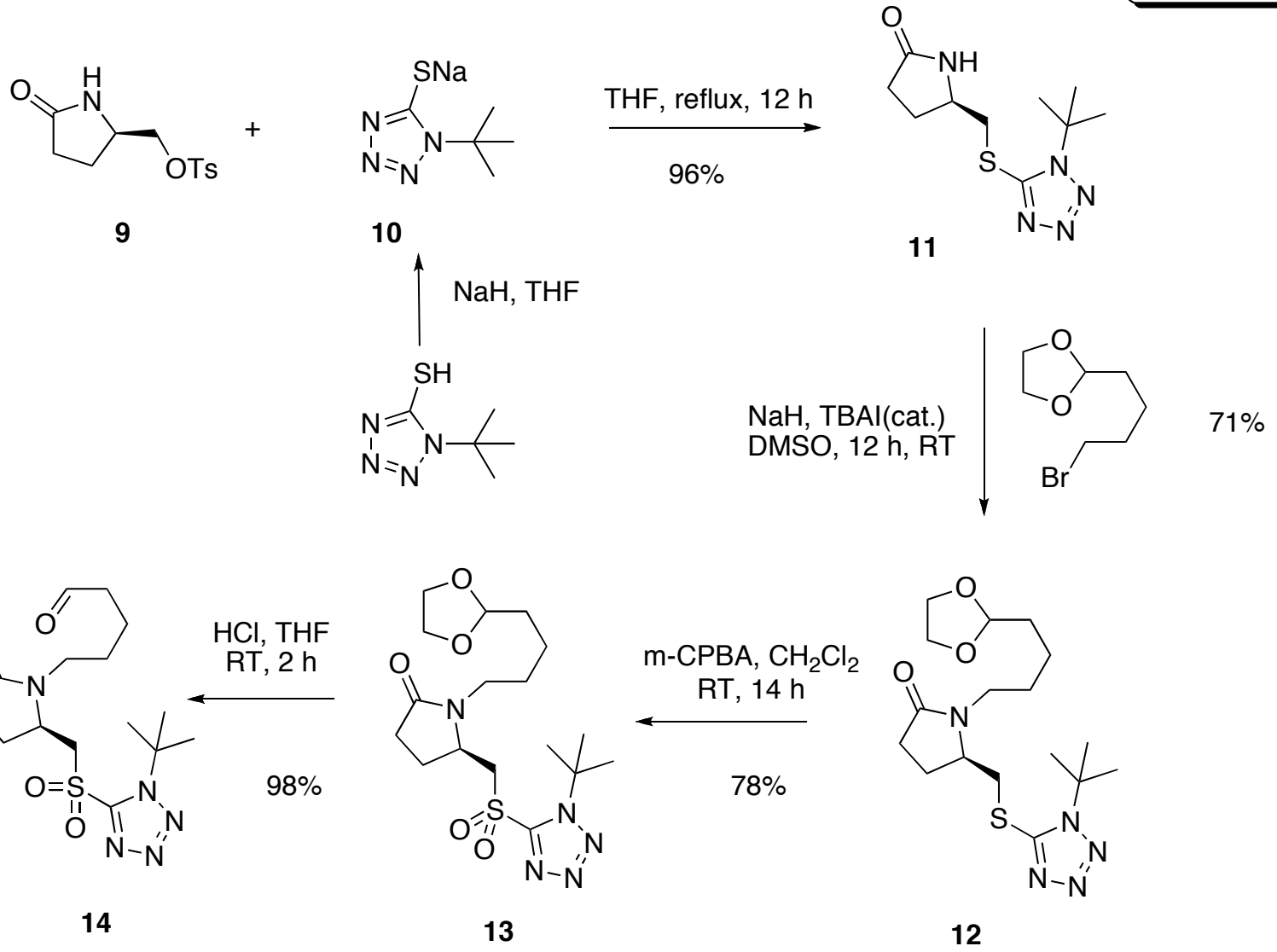
Young, I. S.; Kerr, M. A. J. Am. Soc. Chem. 2007, 129, 1465.

Retrosynthetic analysis

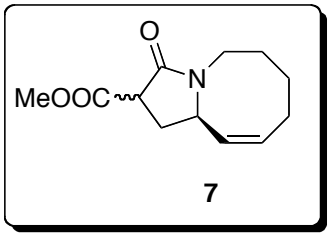


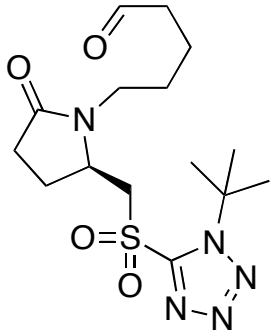
Synthesis of fragment **7**





Synthesis of fragment **7**



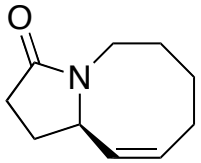


14

Cs_2CO_3, DMF, THF, H_2O

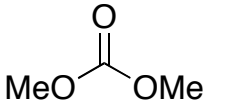
70 °C, 10 h

56%



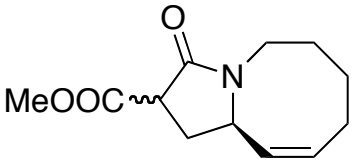
15

LHMDS, THF



-78 °C to 0 °C, 2.5 h

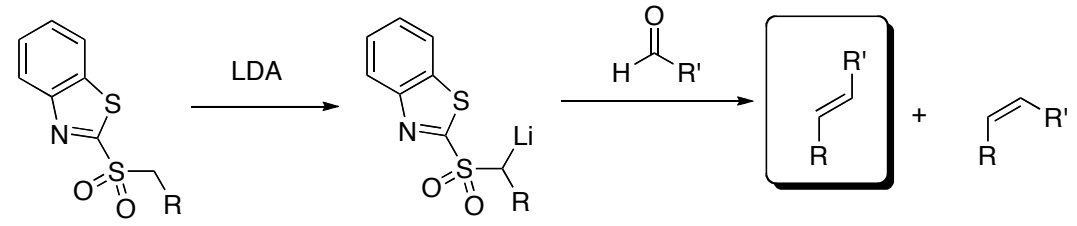
82%

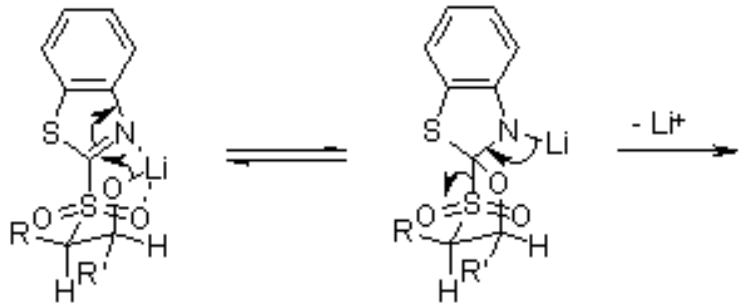


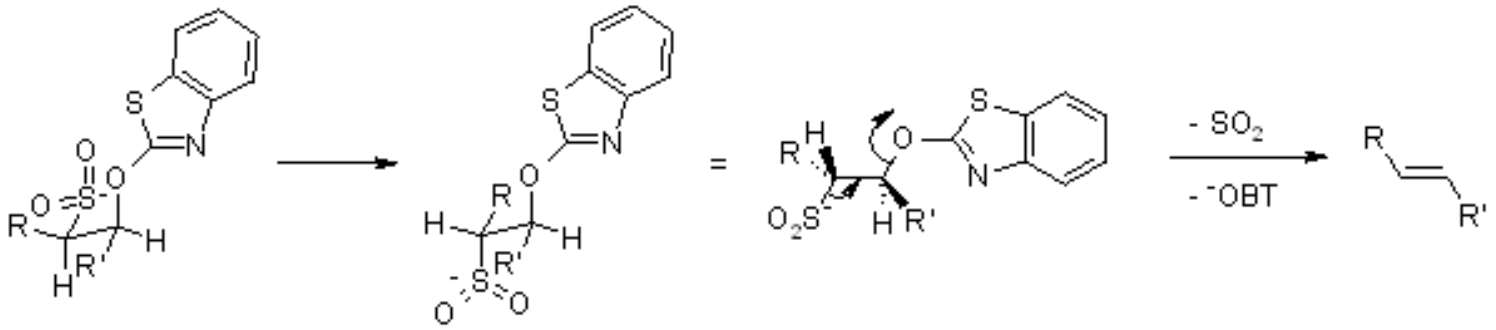
7

Intramolecular Julia-Kocienski

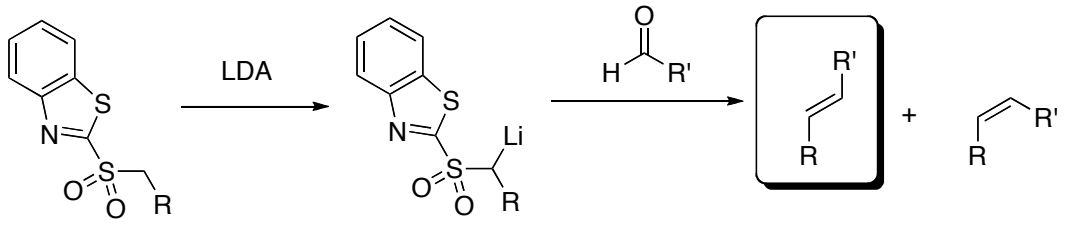
Modified Julia olefination

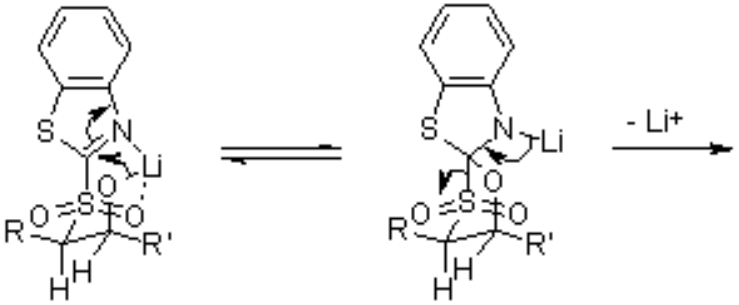


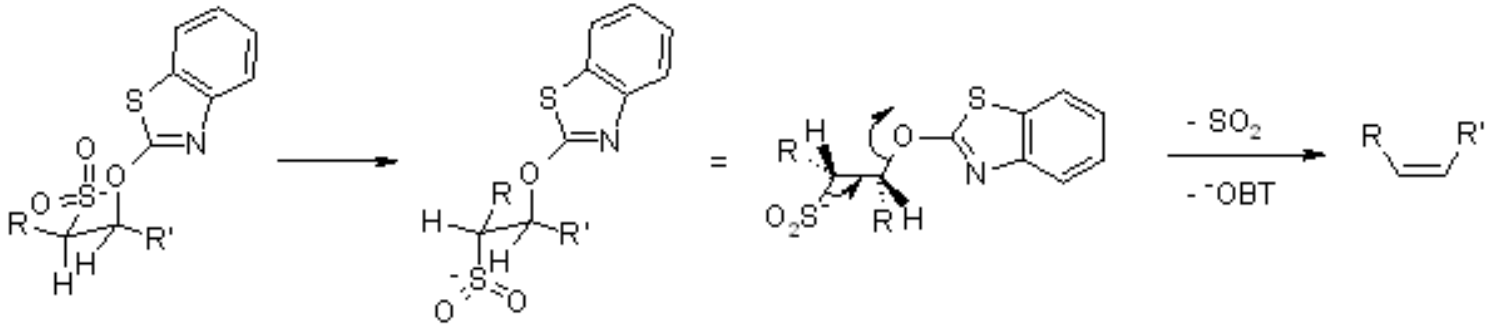




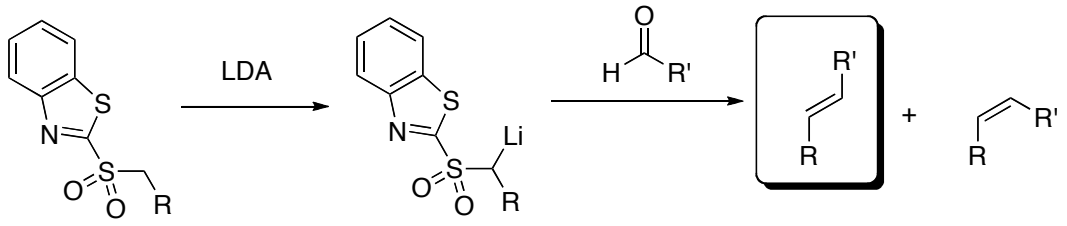
Modified Julia olefination

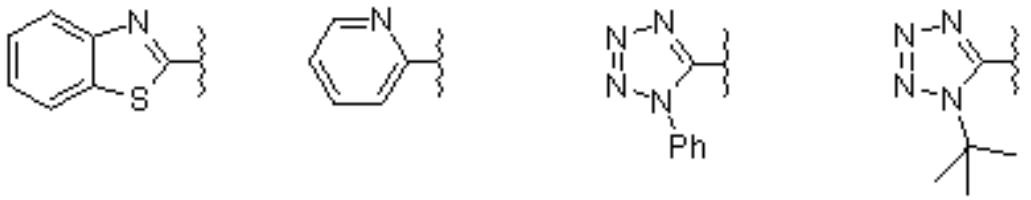






Modified Julia olefination

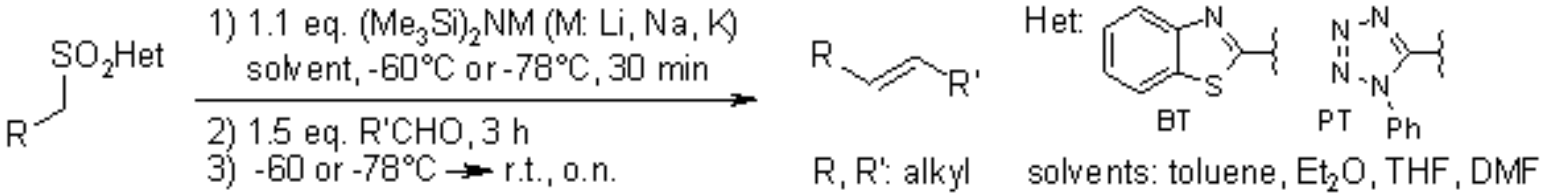


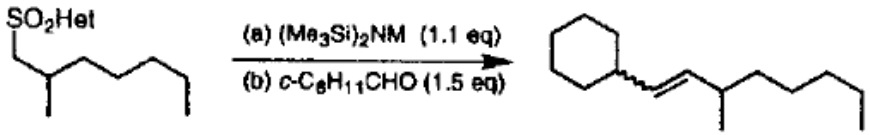


BT **Py** **PT** **TBT**

Py, PT, TBT provides even higher E selectivity than BT in intermolecular reactions.

Julia-Kocienski olefination

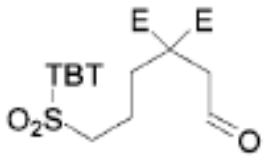
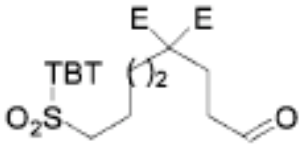
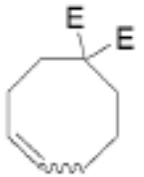
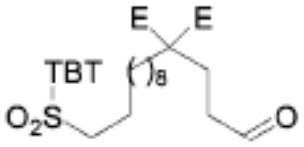
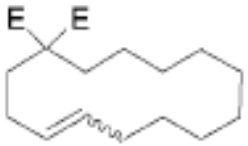




Entry	Solvent	M	Benzothiazole (BT) % Yield **13**	E:Z	Phenyltetrazole (PT) % Yield **13**	E:Z
1	PhMe	Li	88	70:30	85	39:61
2		Na	66	86:14	83	67:33
3		K	48	76:24	68	98:2
4	Et_2O	Li	70	67:33	74	41:59
5		Na	75	87:13	98	53:47
6		K	68	78:22	28	92:8
7	THF	Li	87	72:28	90	53:47
8		Na	84	67:33	71	48:52
9		K	85	40:60	58	97:3
10	DME	Li	83	58:42	100	40:60
11		Na	96	55:45	100	84:16
12		K	100	36:64	59	99:1

Blakemore, P. R.; Cole, W. J. Kocienski, P. J. Synlett, 2008, 26.

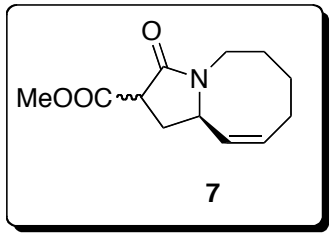
Intramolecular Julia-Kocienski olefination

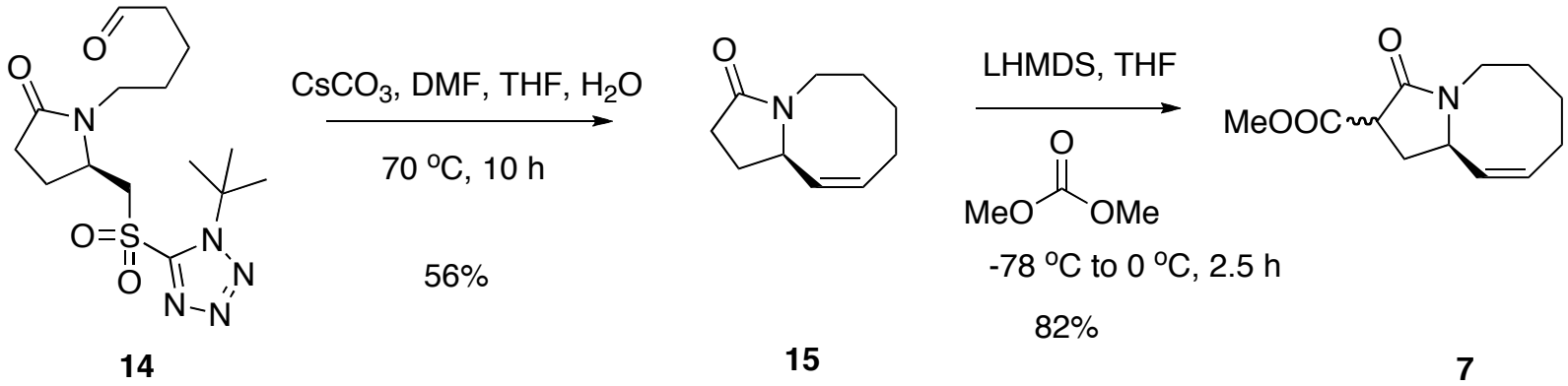
Precursor	Cycloalkene	Yield%(*E*/*Z*)
 **52**	 **55**	91
 **53**	 **56**	32 (1/1)[a,b]
 **54**	 **57**	56 (2/1)[a,b]

[a] THF was replaced by dioxane. [b] *E*/*Z* ratio was determined by NMR.

Aissa, C. J. Org. Chem. 2006, 71, 360.

Synthesis of fragment **7**

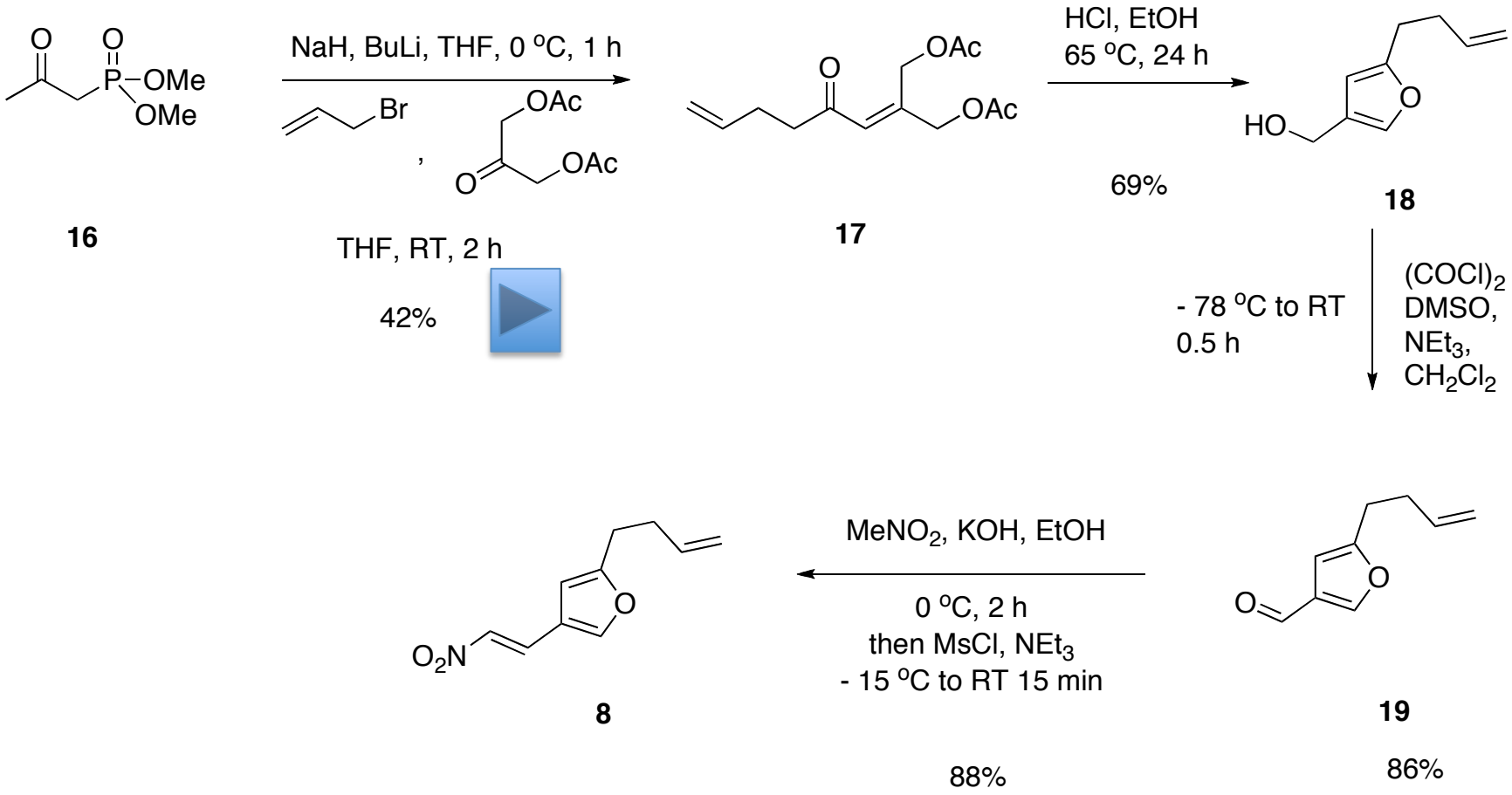




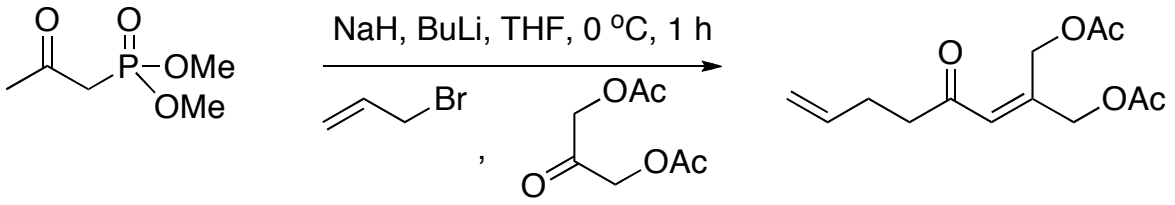
Intramolecular Julia-Kocienski

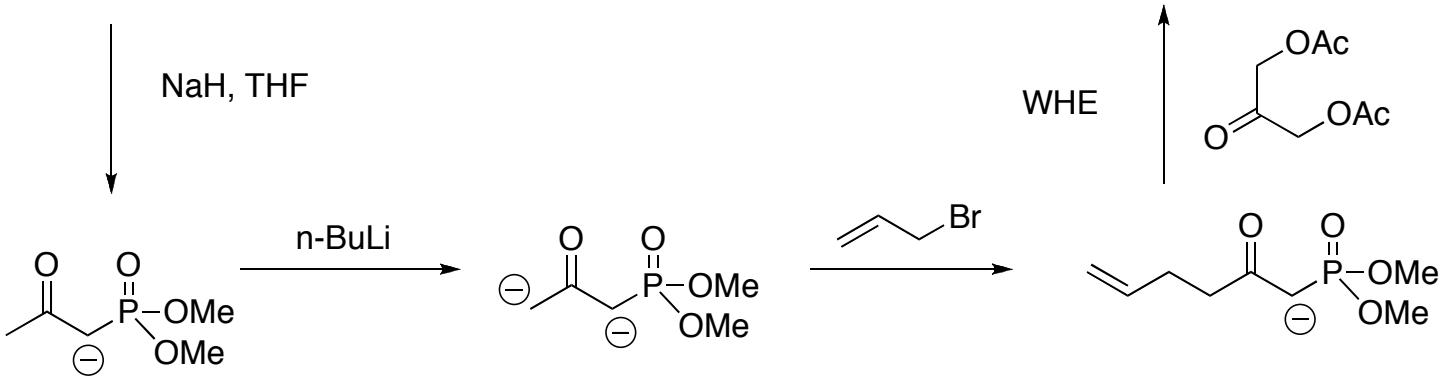
First example of Intramolecular Julia-Kocienski in complex natural product synthesis

Synthesis of fragment **8**



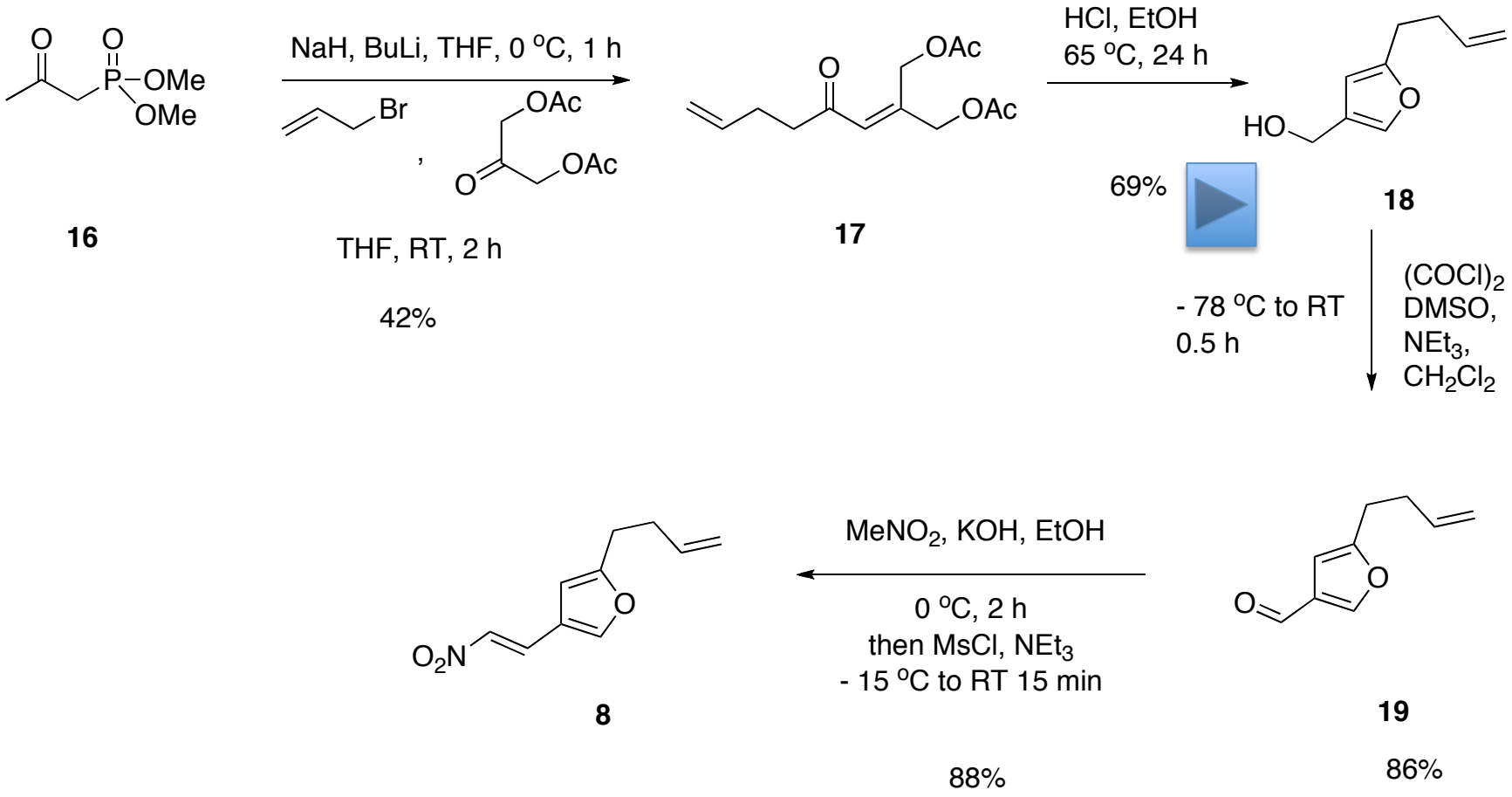
Synthesis of fragment **8**



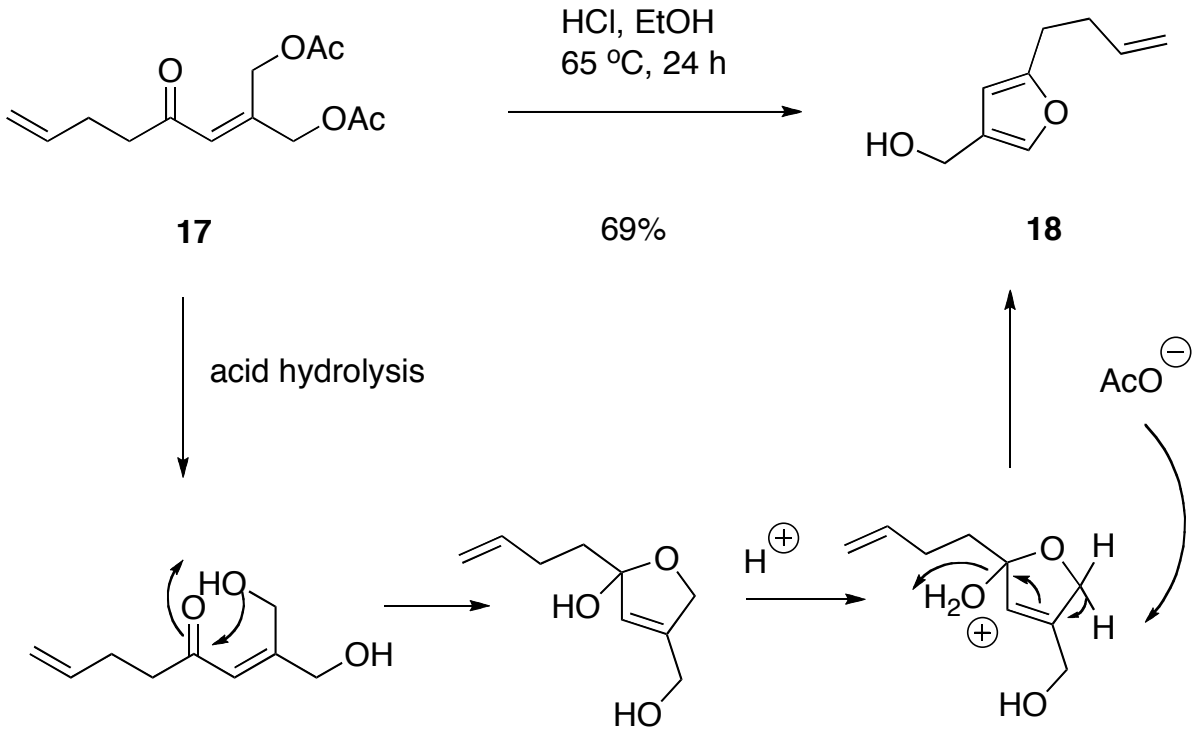


Grieco, P. A.; pogonowski, C. S. *J. Am. Chem. Soc.* 1973, 95, 3071.

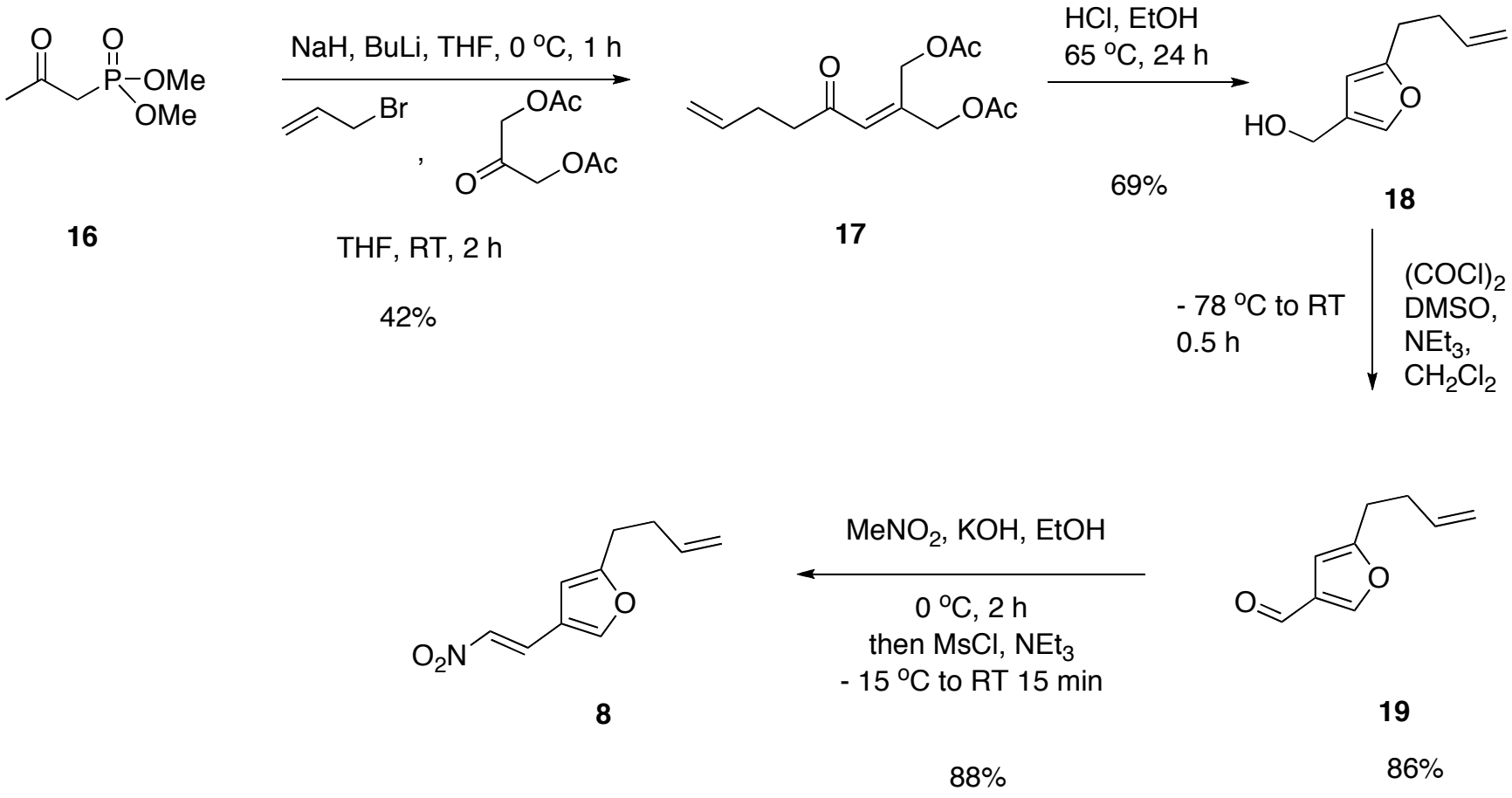
Synthesis of fragment **8**



Synthesis of fragment **8**

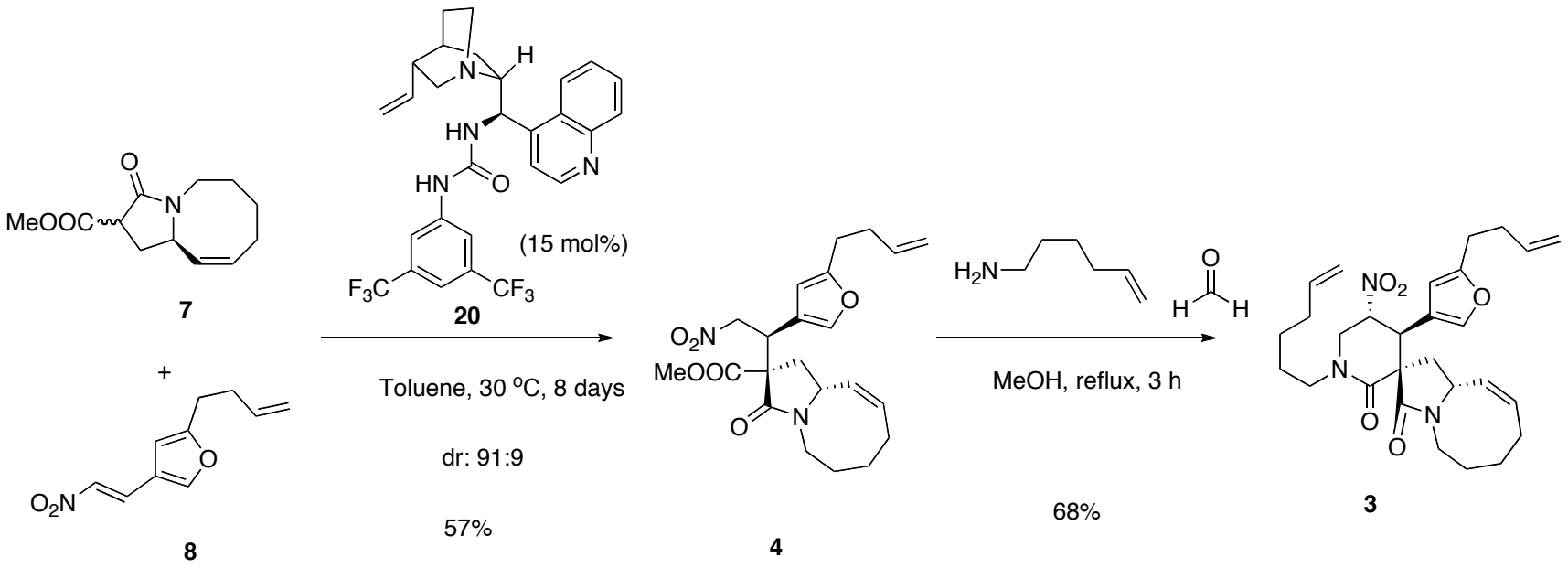


Synthesis of fragment **8**



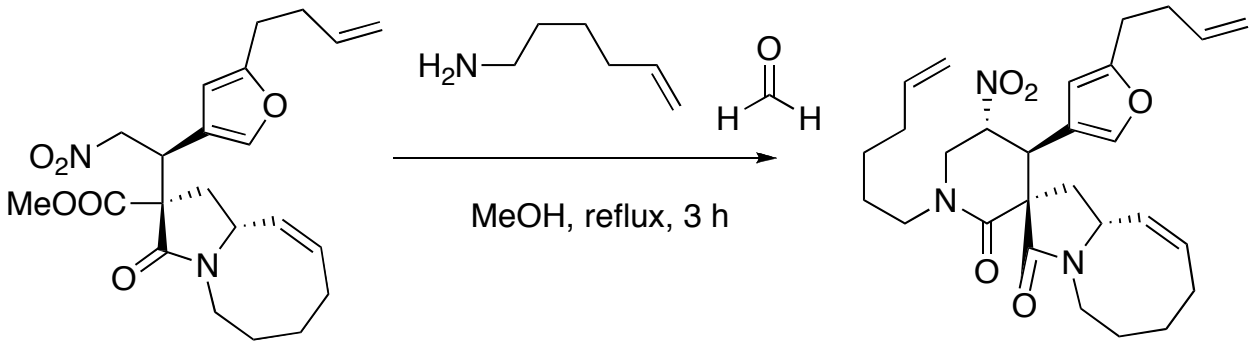
16 **17** **18** **19** **8**

Forward synthesis



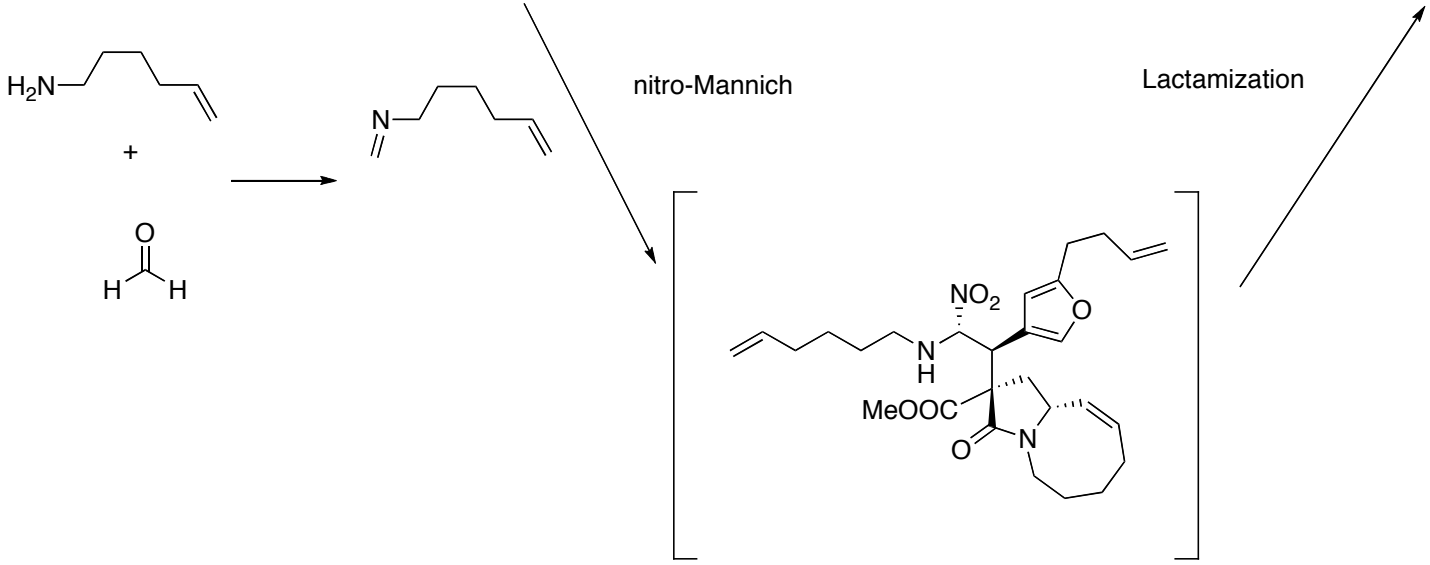
Nitro-Mannich/Lactamization cascade

Nitro-Mannich/Lactamization cascade

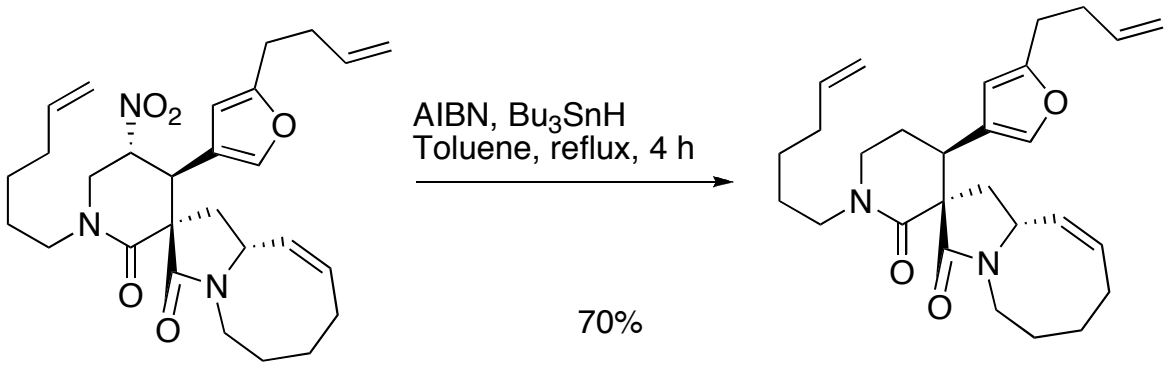


68%

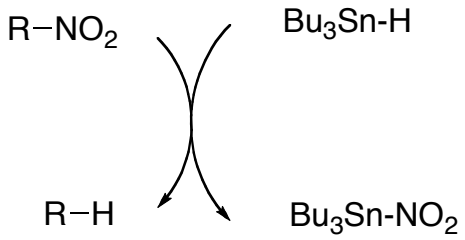
4 **3**



Forward synthesis

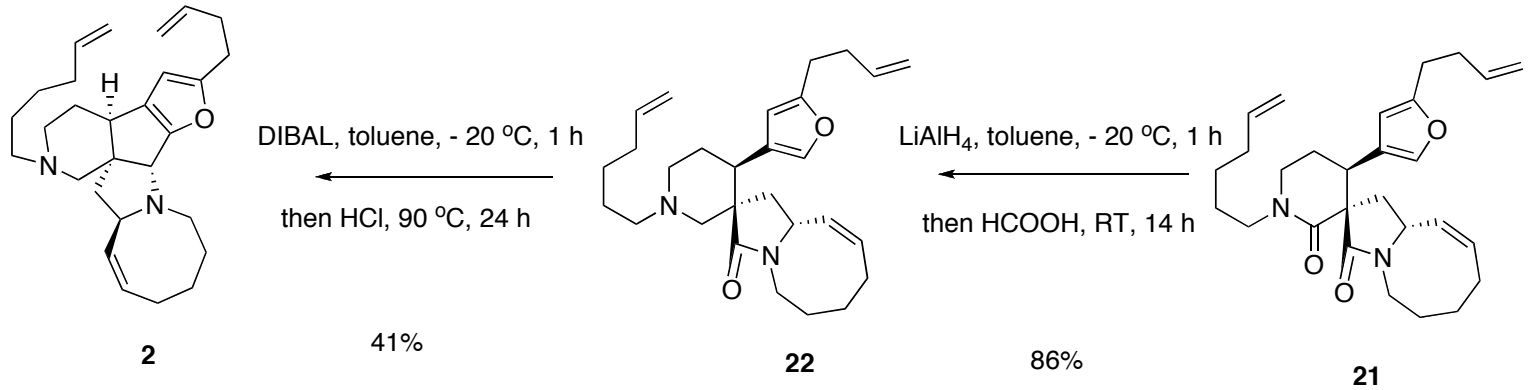


3 **21**



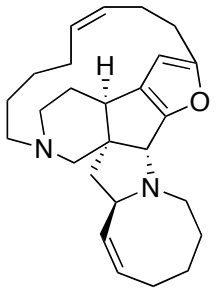
Forward synthesis

Selective reduction of lactam



RCM 62%

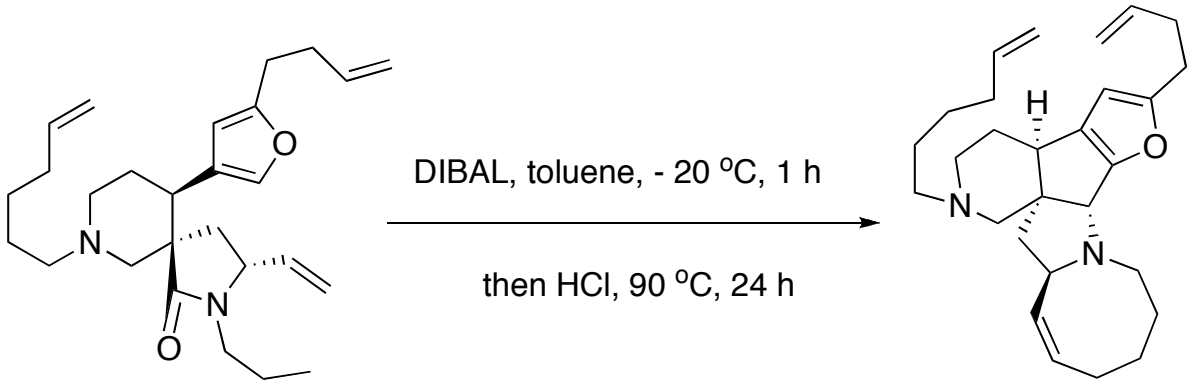
Grubb's 1st generation catalyst
(+)-CSA, CH2Cl2, reflux, 3.5 h



62:37 Z/E

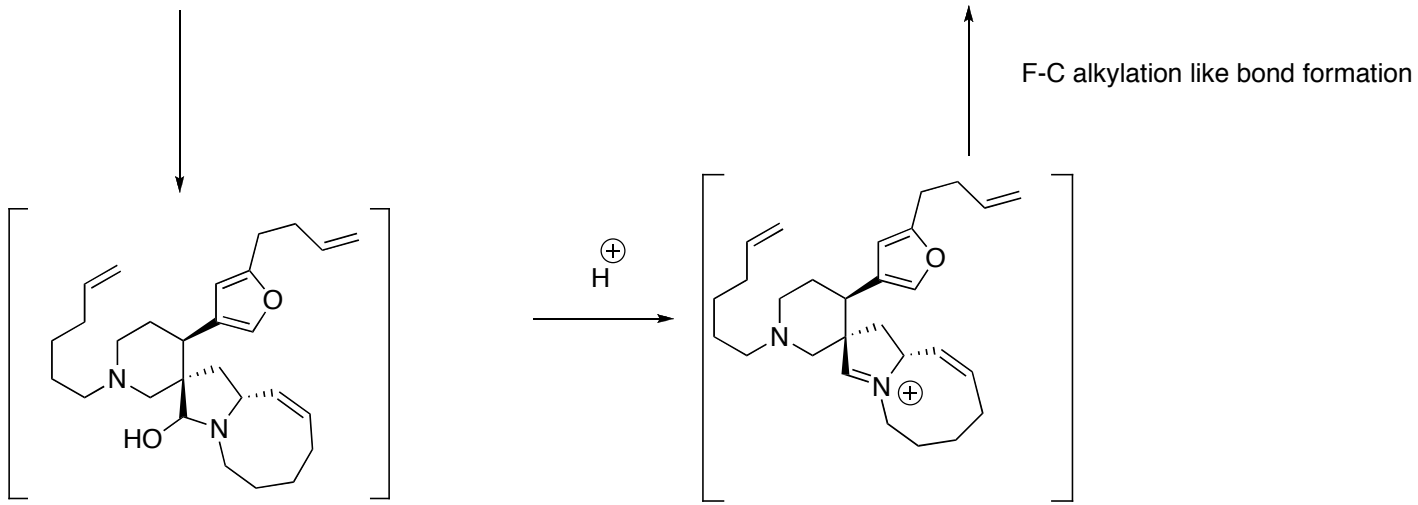
(-)-Nakadomarin A
1

Forward synthesis



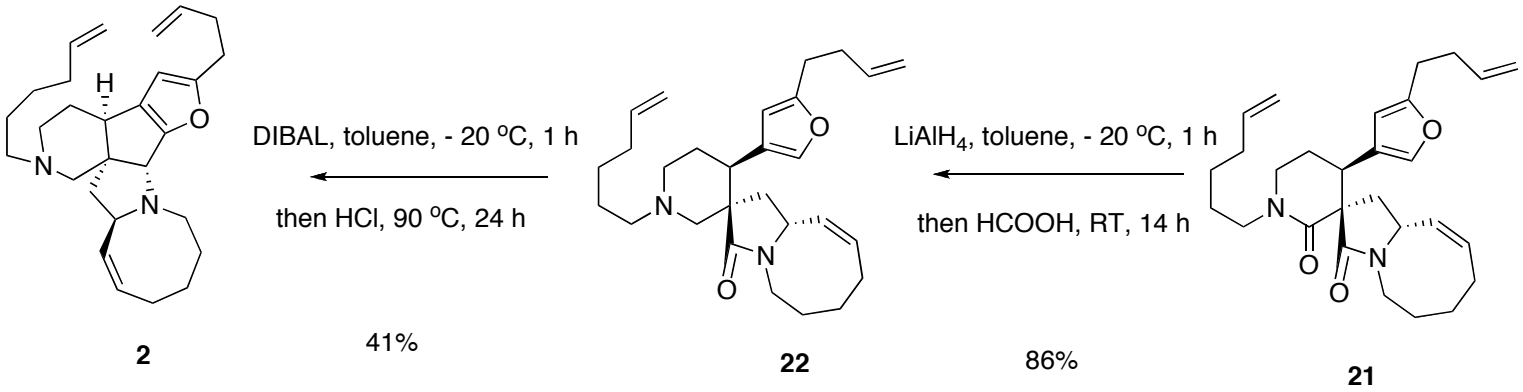
22 **2**

Reduction/iminium ion formation/diastereoselective C-C bond forming cyalization



Forward synthesis

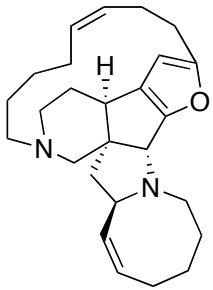
Selective reduction of lactam



2 **22** **21**

RCM 62%

Grubb's 1st generation catalyst
(+)-CSA, CH2Cl2, reflux, 3.5 h



62:37 Z/E

(-)-Nakadomarin A
1

The first example of E/Z selectivity being reversed with and without acid

Thank you!