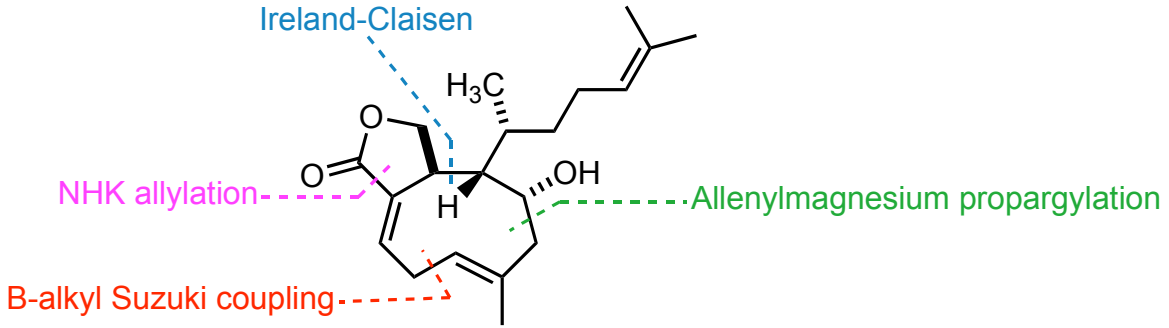
A Stereocontrolled Total Synthesis of 4-Hydroxydictyolactone



4-Hydroxydictyolactone

David R. Williams, Martin J. Walsh, and Nathan A. Miller
J. Am. Chem. Soc, **2009**, ASAP

Wipf Group Current Literature
Tingting Mo
June, 20, 2009

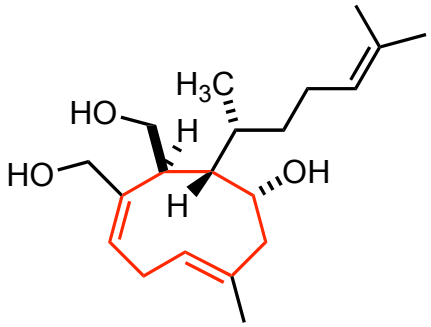
Isolation and Biological Activity of the Xenicane family

Isolated from brown algae, sea hare, soft coral and seaweed, etc

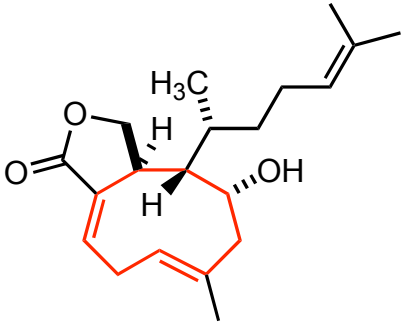
contain a rare nonconjugated (E), (Z)-cyclononadiene motif

Individual compounds exhibit antibacterial and antifungal properties, ichthyotoxicity, and the inhibition of HIV-1 reverse transcriptase

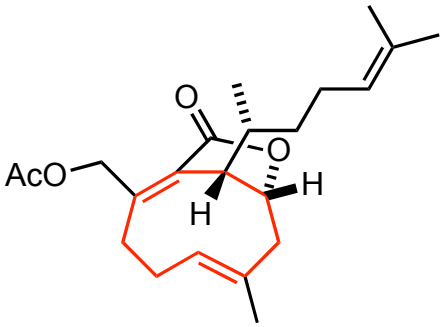
7 is an unusual member bearing a nitrogen atom



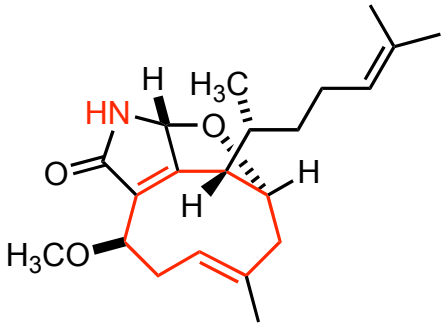
1 Dictyodiol
1979, from *Dictyota crenulata*



4 4-Hydroxydictyolactone
1993, from *Dictyota ciliolata*



6 Dictyolide B
2007, from *Xenia elongata*

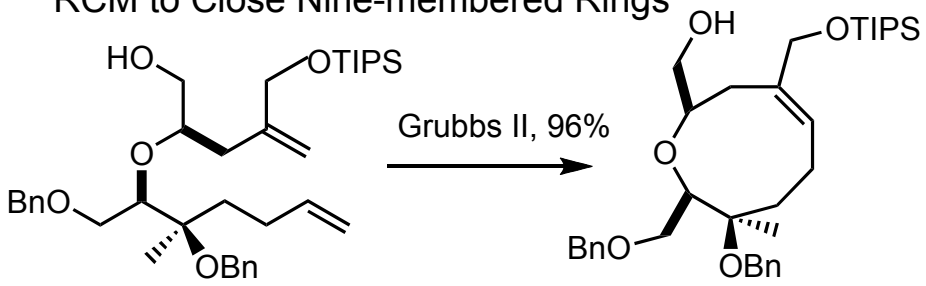


7 Joalin
1993, from *Dictyotales*

Moore, R. E. *et. al. JOC* **1979**, *44*, 2044
Higa, T. *et. al. Chem. Lett* **1984**, *13*, 231
Kakisawa, H. *et. al. JOC* **1988**, *53*, 5010
Guella, G. *et. al. J. Chem. Soc., Perkin Trans. 1* **1993** *14*, 1545

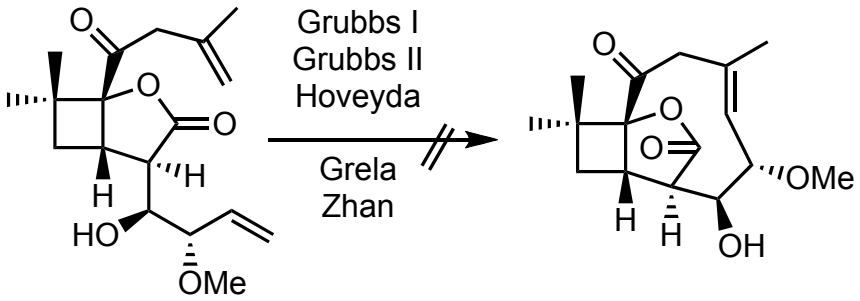
General Methods for the Direct Closure of Cyclononene

RCM to Close Nine-membered Rings



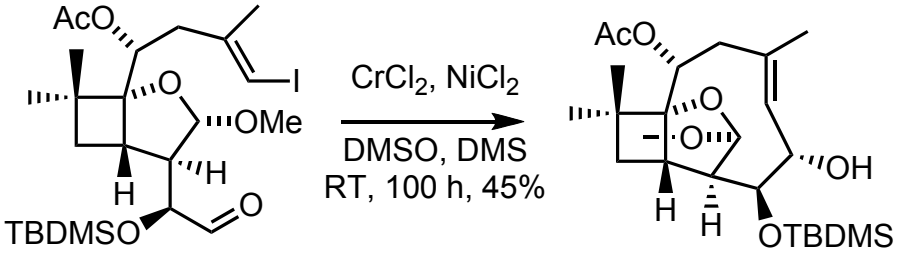
Crimmins, M. T. *et. al. JACS* **2006**, *128*, 1371

RCM Failed to Close Cyclononene



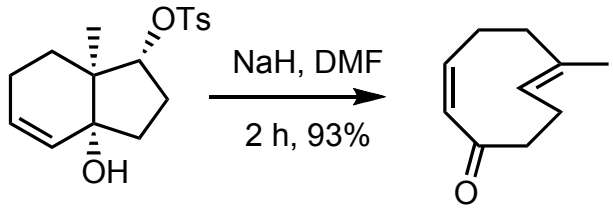
Paquette, L. A. *et. al. JOC* **2007**, *72*, 7135

NHK Reaction



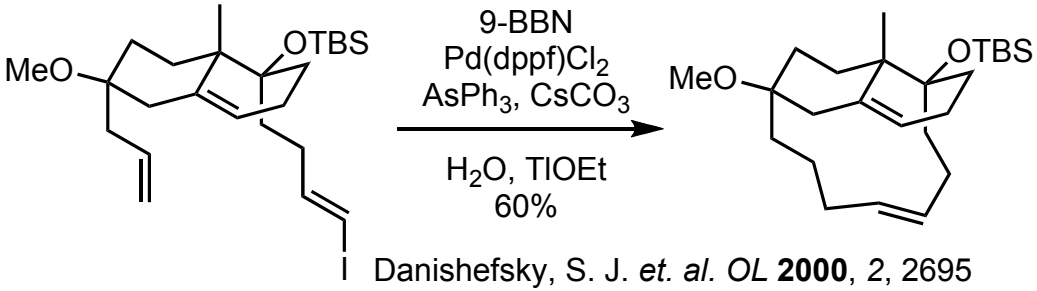
Procter, D. J. *et. al. ACIE* **2008**, *47*, 5631

Grob Fragmentation



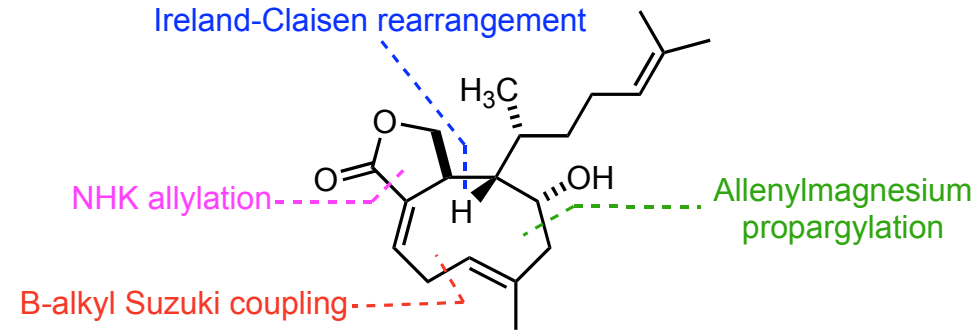
Corey, E. J. *et. al. JACS* **2008**, *130*, 2954

B-Alkyl Suzuki Reaction

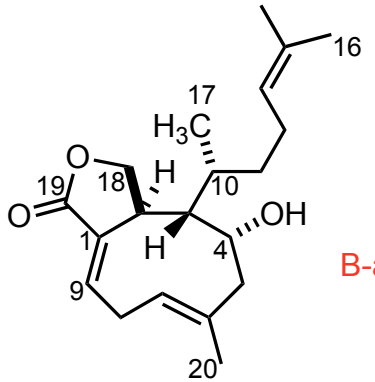


Danishefsky, S. J. *et. al. OL* **2000**, *2*, 2695

Retrosynthetic Analysis of **4**

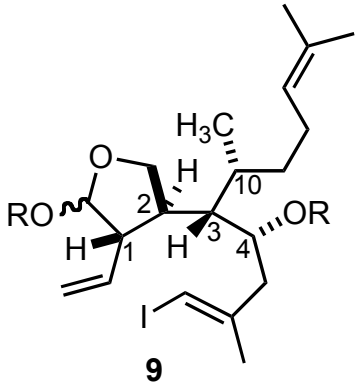


4-Hydroxydictyolactone



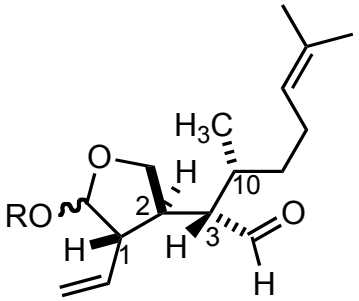
4

B-alkyl Suzuki coupling



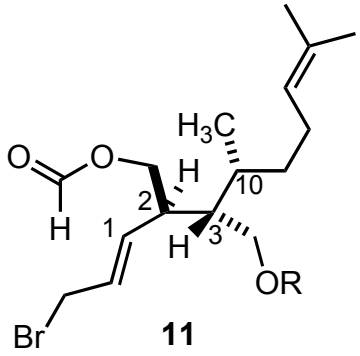
9

Allenylmagnesium propargylation



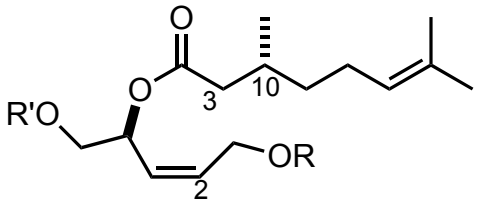
10

NHK allylation



11

Ireland-Claisen rearrangement



15

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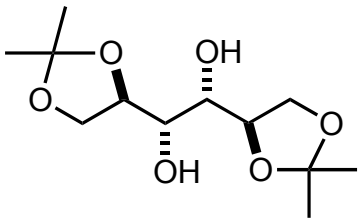
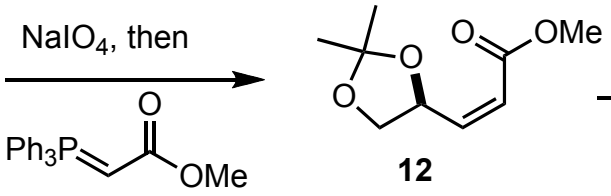
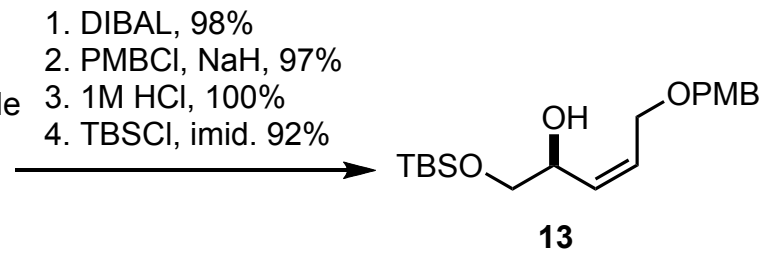
Ireland-Claisen Reaction to Set C_2, C_3 and C_{10} Stereocenters



D-mannitol



12



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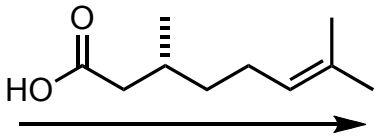
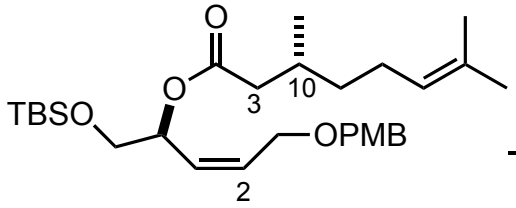


EDCI, DMAP, 97%



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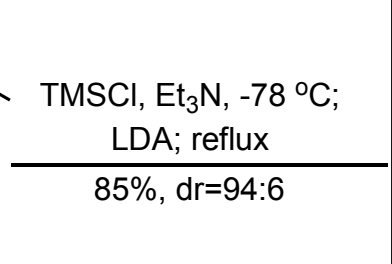
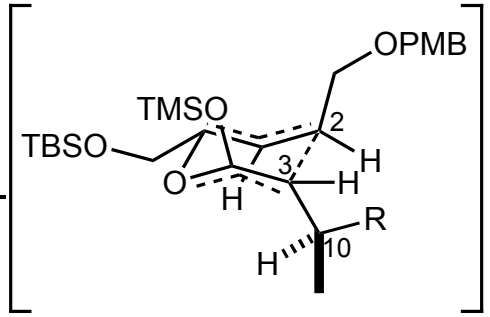
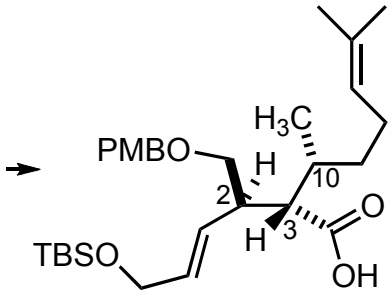
Ireland-Claisen Rearrangement





17 R=C_6H_{11}



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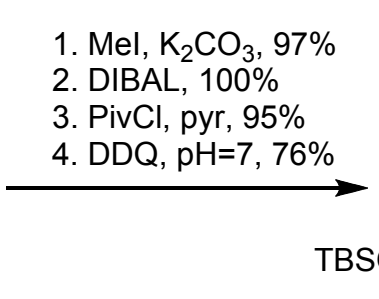

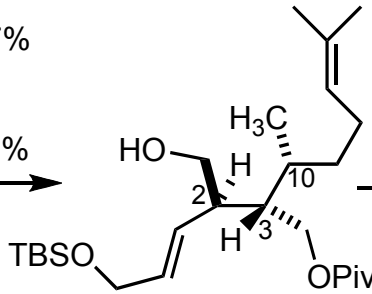

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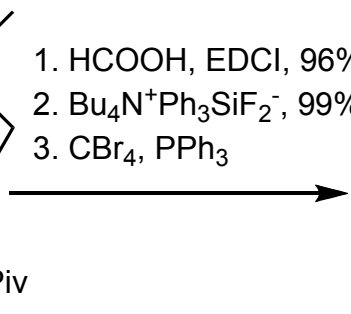

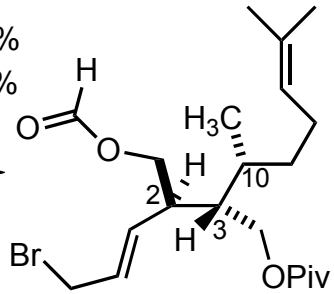

20

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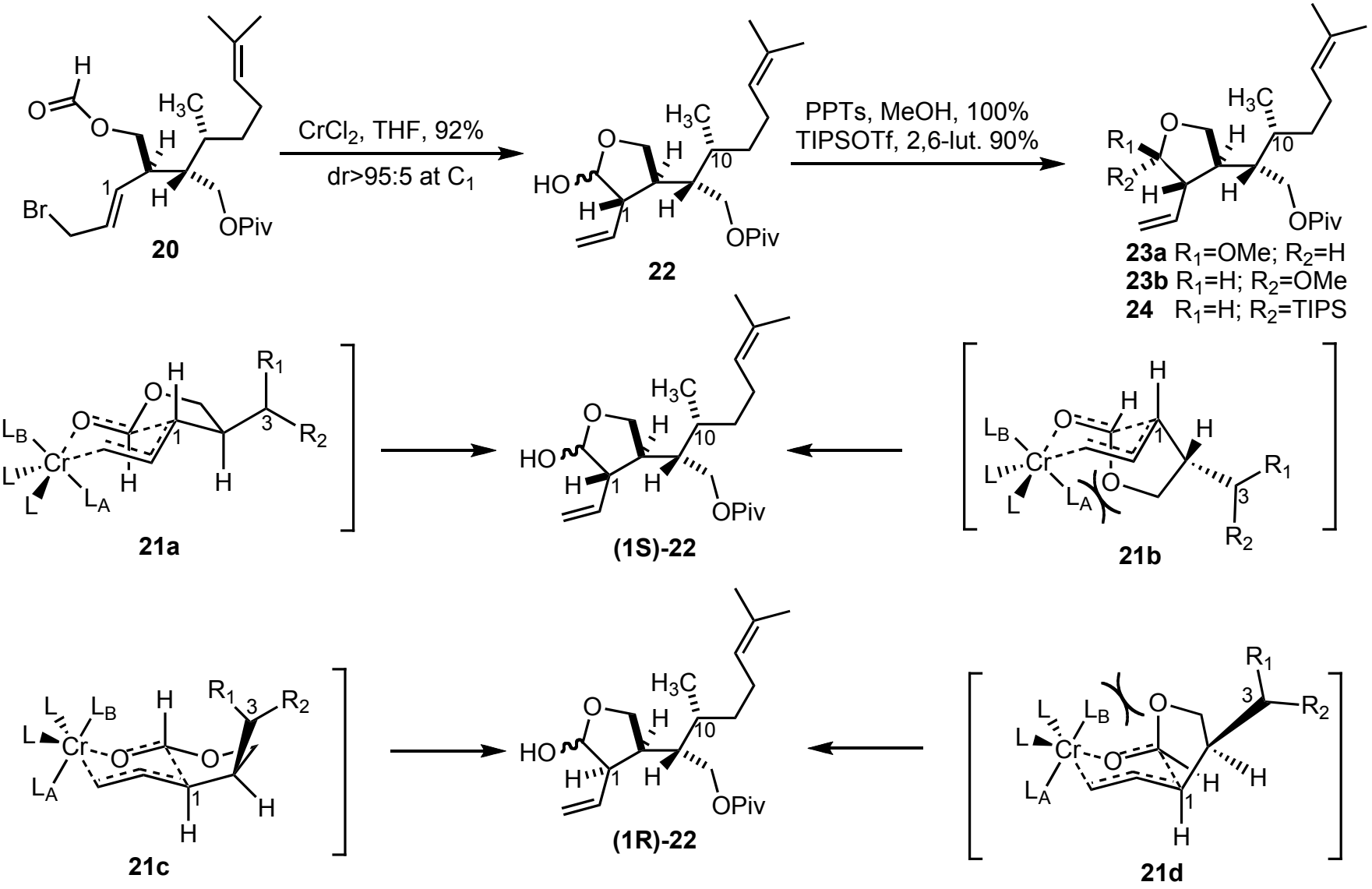
Nozaki-Hiyama-Kishi Intramolecular Cyclization



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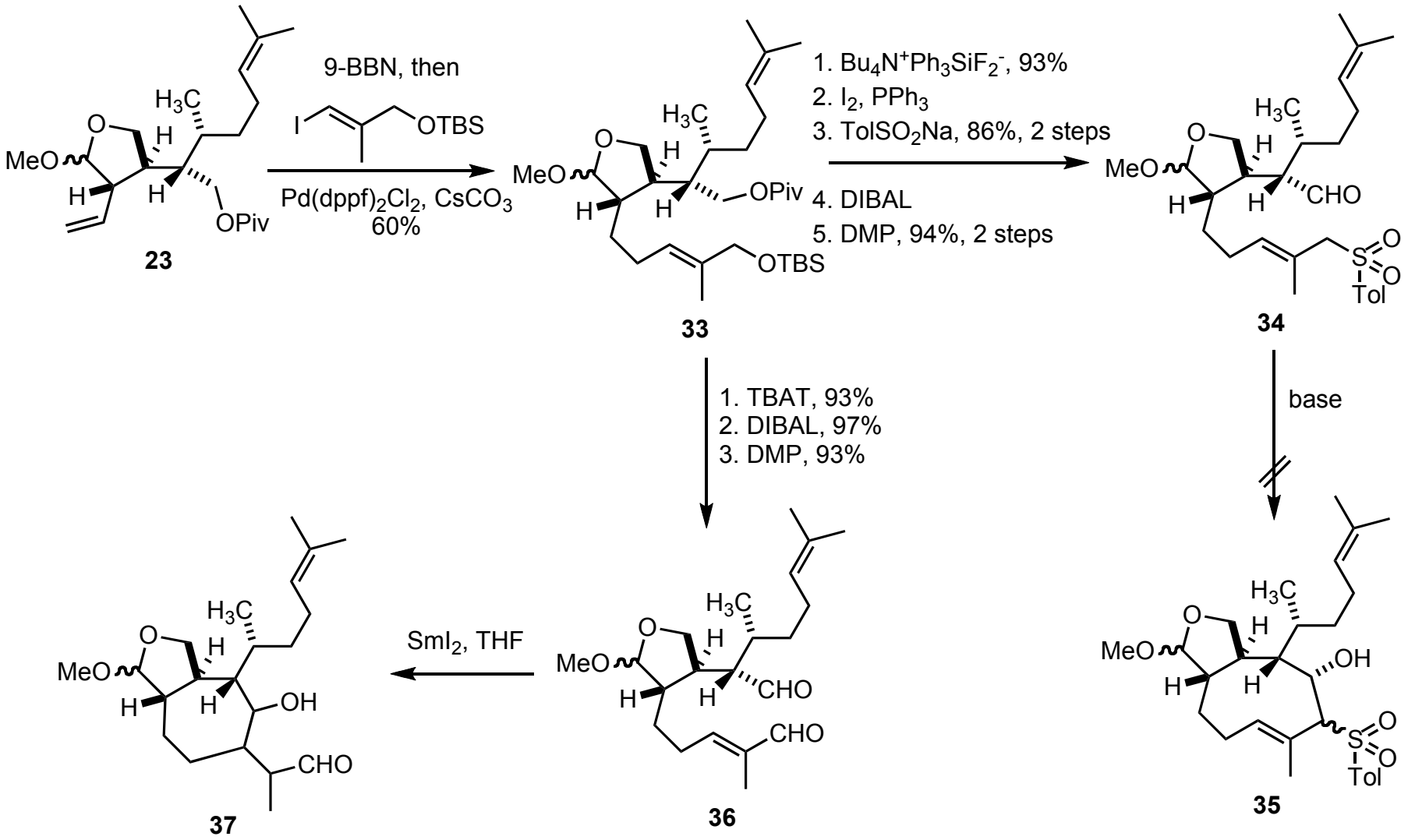
Attempted Cylication via C_4-C_5 Bond Formation



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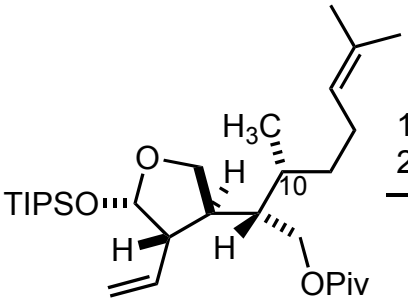
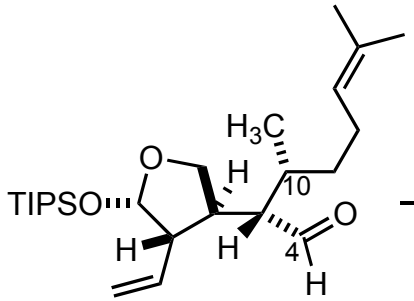
Diastereoselective Propargylation to Set C_4 Stereocenter



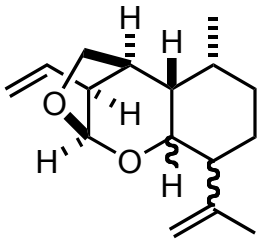
24

1. DIBAL, 96%
2. TPAP, NMO, 99%



25

$SnCl_4$, -78 °C



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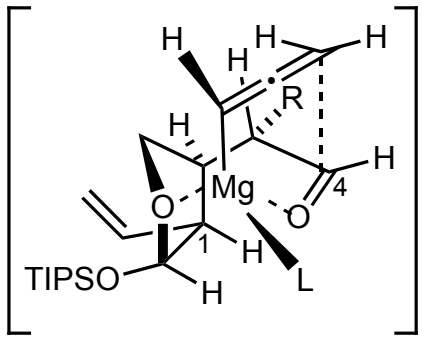
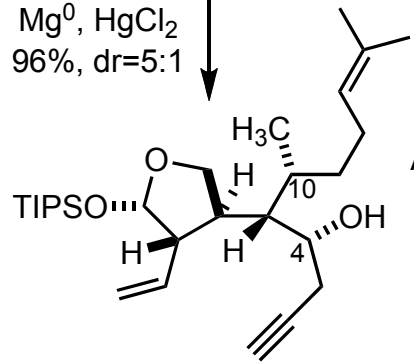


28

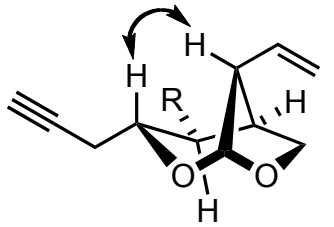
Mg^0, $HgCl_2$
96%, dr=5:1



27

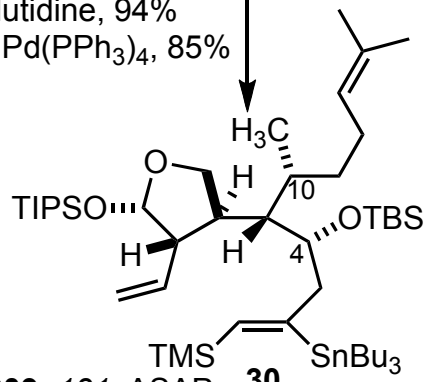
$AlMe_3$, Cp_2ZrCl_2

62%



29 NOESY

1. TBSOTf, 2,6-lutidine, 94%
2. $Me_3SiSnBu_3$, $Pd(PPh_3)_4$, 85%



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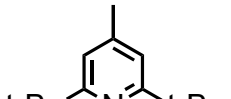
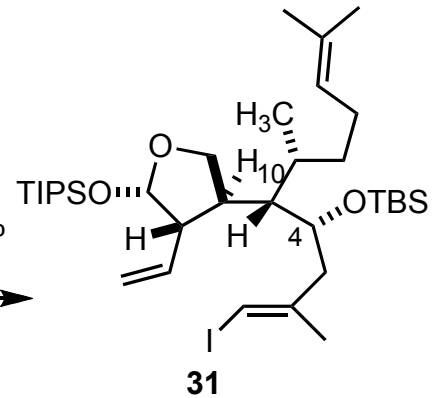


1. I_2, 93%
2. MeLi, CuI, 98%
3. NIS, 82%



31

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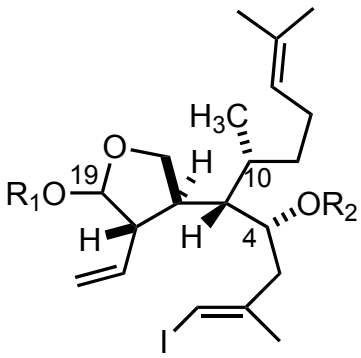
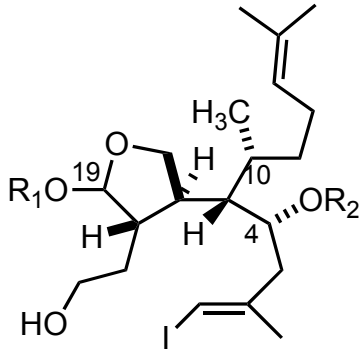
Hydroboration of Compounds with Different Protecting Groups

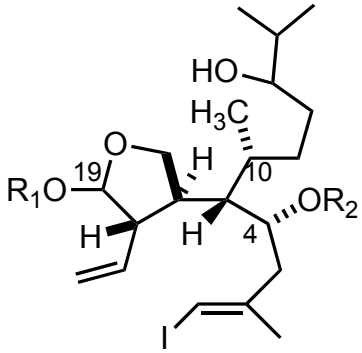


31 R_1=TIPS, R_2=TBS
39 R_1=Me, R_2=TBS
40 R_1=Me, R_2=H

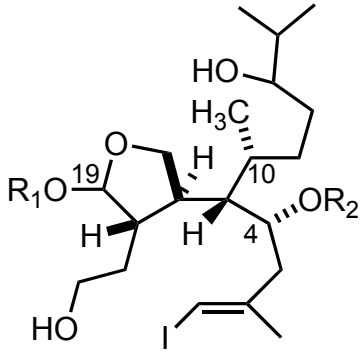
9-BBN then
H_2O_2, NaOH



A



B



C

Entry	R_1	R_2	conditions	product ration (A:B:C)
1	TIPS	TBS	9-BBN (5 eq), 80 ^oC, 72 h	1:1:4
2	Me	TBS	9-BBN (1.5 eq), rt, 12 h	>19:1:1
3	Me	H	9-BBN (1.2 eq), 0 ^oC, 1 h	>19:1:1

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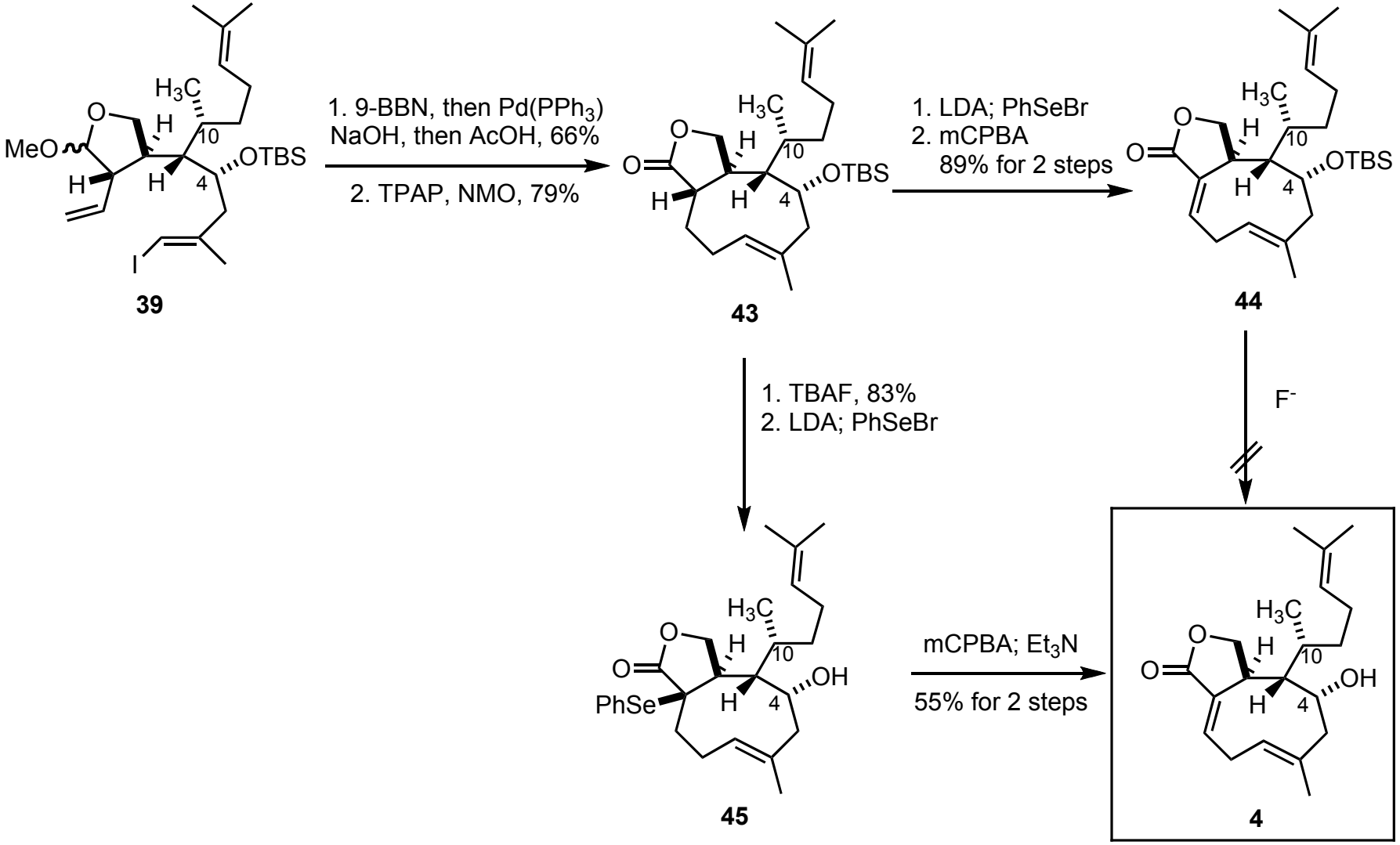
Optimization of B-Alkyl Suzuki Macrocylization



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Conclusions

An efficient, enantiocontrolled total synthesis of 4-Hydroxydictyolactone was completed

Ireland-Claisen rearrangement set the consecutive tertiary stereocenters

An intramolecular NHK SE' allylation of a formate ester stereoselectively synthezied the five-membered lactol

Internally directed SE' propargylation using allenylmagnesium bromide installed the desired stereocenter

Complex (*E*)-Cyclononene was formed from B-alkyl Suzuki cross-coupling reaction