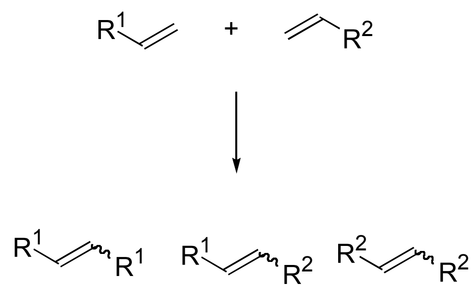
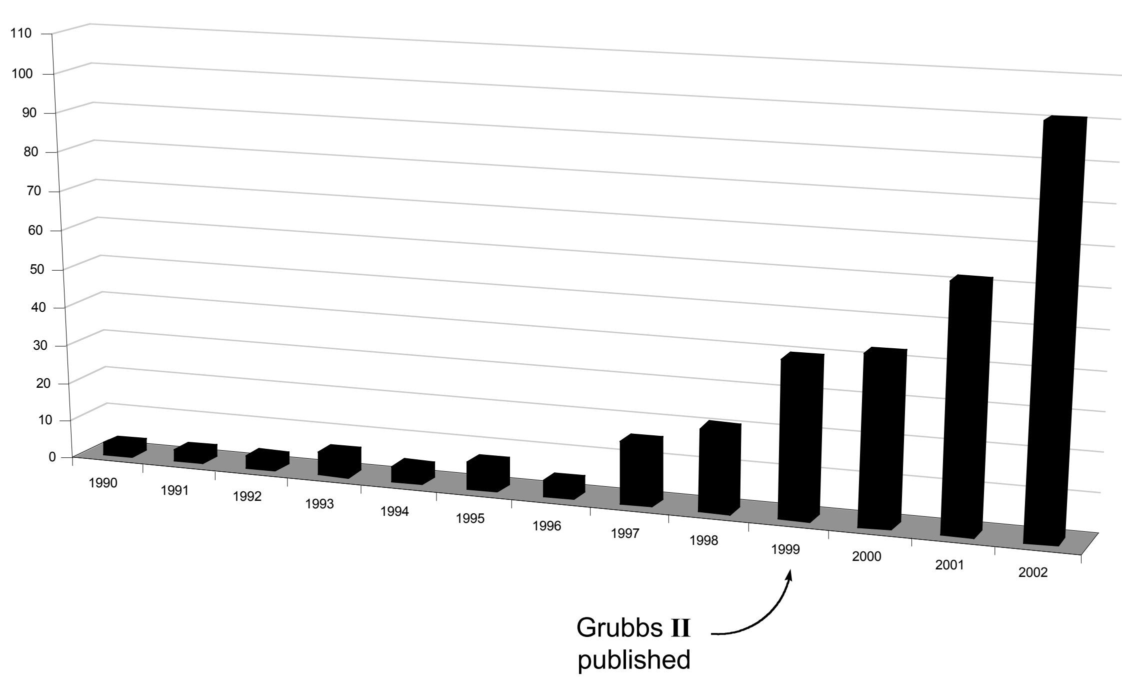
Frontier of Chemistry: Cross Metathesis
Chris Kendall
Saturday, December 27, 2003

Review covering 1998-2002:
"Recent Developments in Olefin Cross Metathesis"
Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900

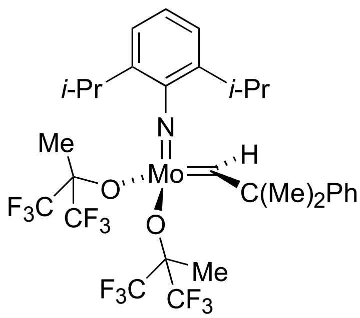
Key Reference (Methodology):
"A General Model for Selectivity in Olefin Cross Metathesis"
Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360



R^1:R^2	CM (%)
1:1	50
1:2	67
1:3	75
1:4	80
1:5	83
1:10	91
1:20	95
1:50	98
1:100	99

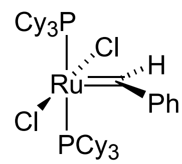


The Catalysts



Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Reagan, M.
J. Am. Chem. Soc. **1990**, *112*, 3875

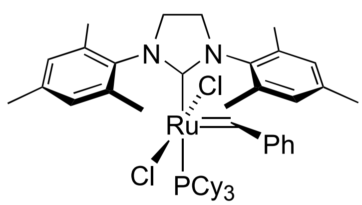
Schrock **I**



$Cl_2(PCy_3)_2Ru{=}CHPh$

Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H.
Angew. Chem. Int. Ed. Engl. **1995**, *34*, 2039

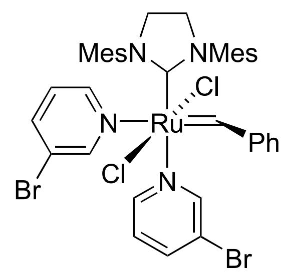
Grubbs **I**



$(H_2IMes)(PCy_3)Cl_2Ru{=}CHPh$

Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H.
Org. Lett. **1999**, *1*, 953

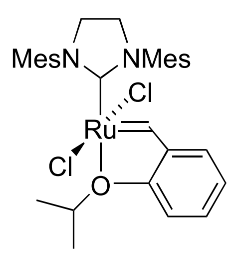
Grubbs **II**



$(H_2IMes)(3\text{-}Br\text{-}py)_2Cl_2Ru{=}CHPh$

Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H.
Angew. Chem. Int. Ed. **2002**, *41*, 4035

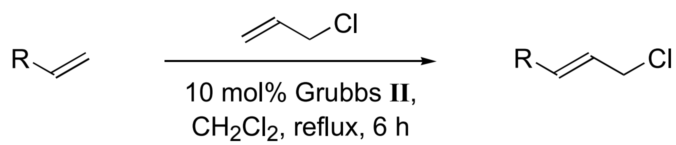
Grubbs **III**



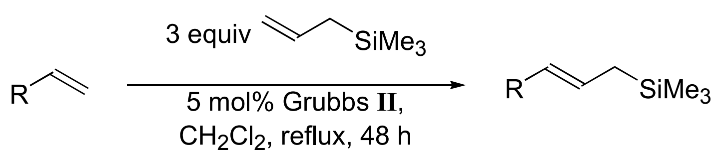
Kingsbury, J. S.; Harrity, J. P. A.; Hoveyda, A. H.
J. Am. Chem. Soc. **1999**, *121*, 791

Green Grubbs

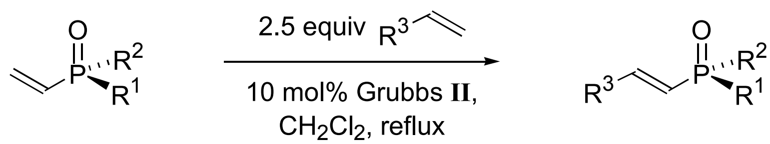
Selective Functionalization of Terminal Olefins



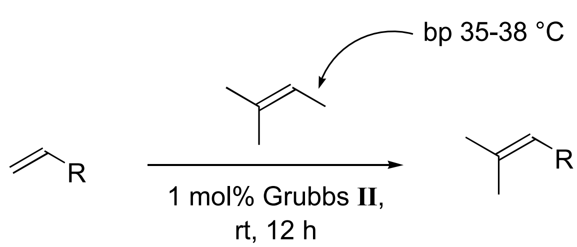
Liu, B.; Das, S. K.; Roy, R. *Org. Lett.* **2002**, *4*, 2723



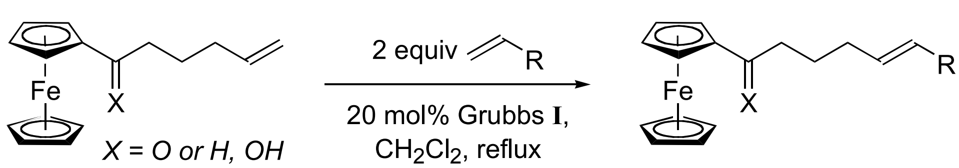
Thibaudeau, S.; Gouverneur, V. *Org. Lett.* **2003**, *5*, 4891



Demchuk, O. M.; Pietrusiewicz, K. M.; Michrowska, A.; Grela, K. *Org. Lett.* **2003**, *5*, 3217

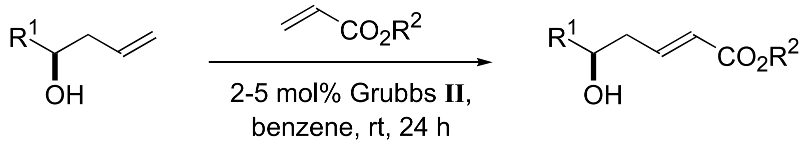


Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939

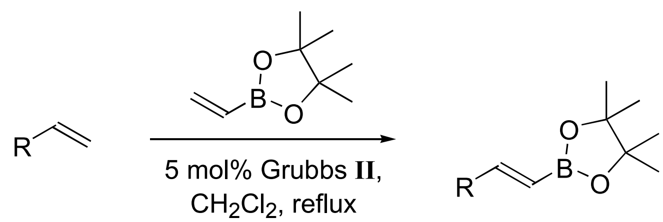


Seshadri, H.; Lovely, C. J. *Org. Lett.* **2000**, *2*, 327

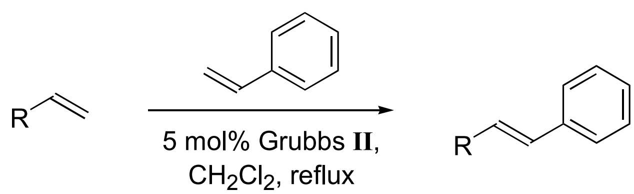
Selective Functionalization of Terminal Olefins



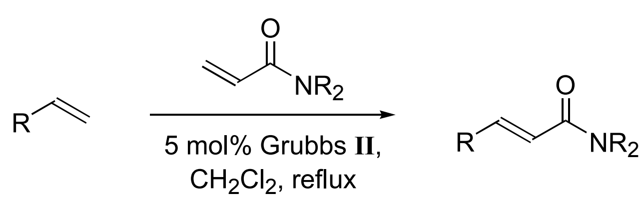
Smith, C. M.; O'Doherty, G. A. *Org. Lett.* **2003**, *5*, 1959



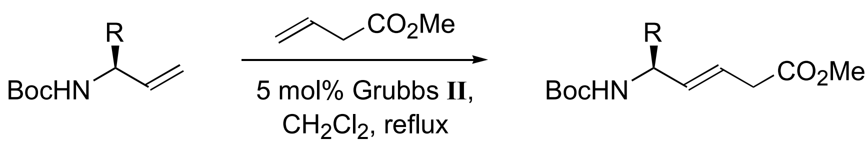
Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031



Chatterjee, A. K.; Toste, F. D.; Choi, T.-L.; Grubbs, R. H. *Adv. Synth. Catal.* **2002**, *344*, 634



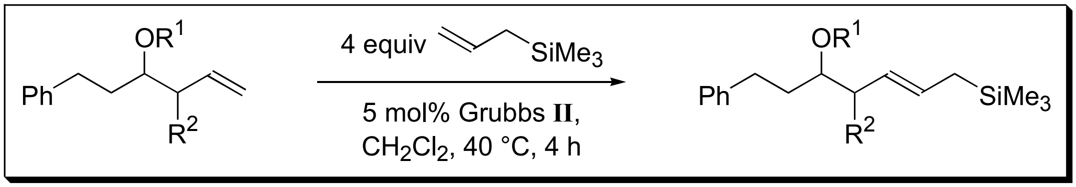
Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1277

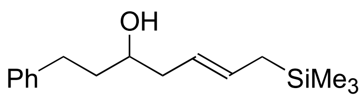


Vasbinder, M. M.; Miller, S. J. *J. Org. Chem.* **2002**, *67*, 6240

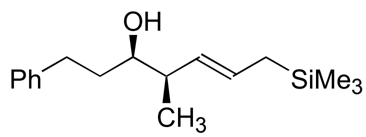
Heteroatom Effect on Cross Metathesis *E/Z* Selectivity

Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. E.
Org. Lett. **2001**, *3*, 2209

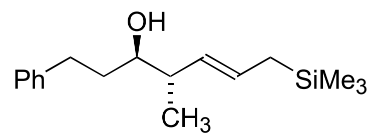




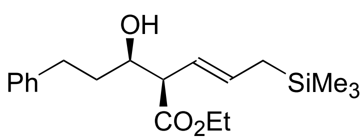
84%, E/Z = 2.3:1



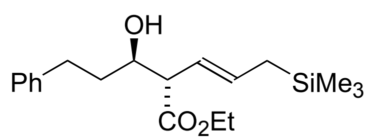
81%, E/Z = 4:1



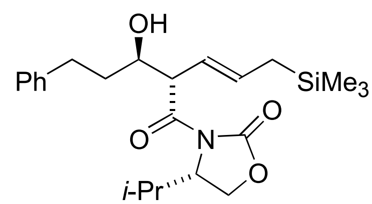
86%, E/Z = 11.5:1



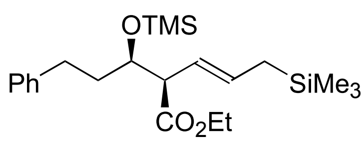
74%, E/Z = 4:1



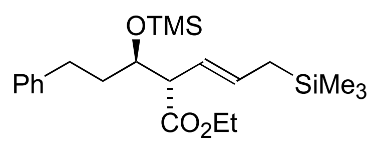
67%, E/Z = 11.5:1



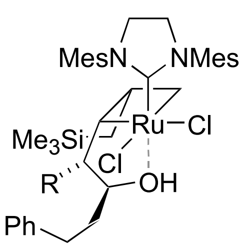
75%, E/Z > 20:1



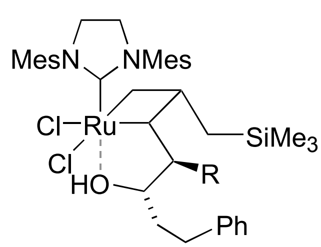
E/Z = 11.5:1



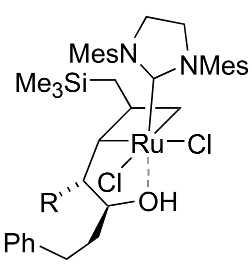
E/Z = 8.1:1



anti □ *Z*

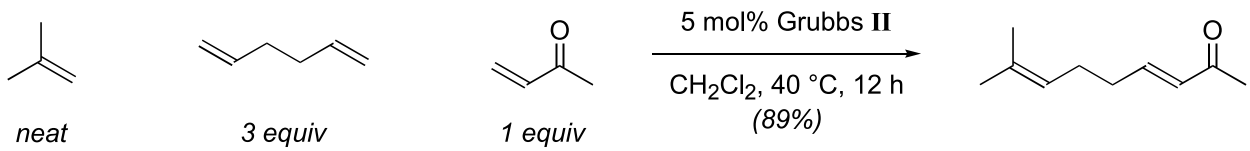


anti □ *Z*

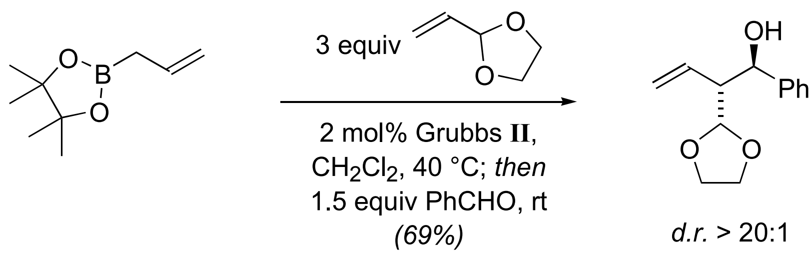


anti □ *E*

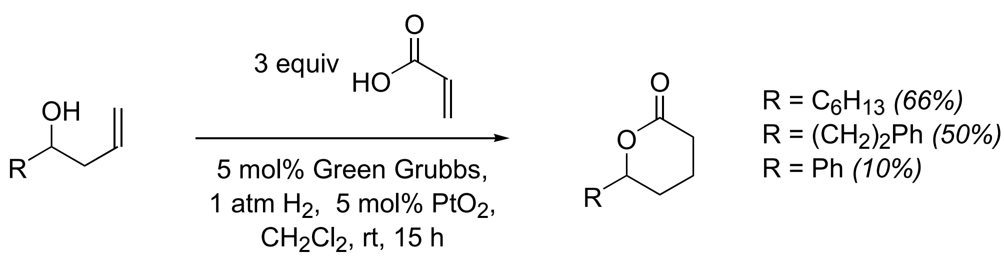
Tandem Cross Metathesis Reactions



Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360



Goldberg, S. D.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 807



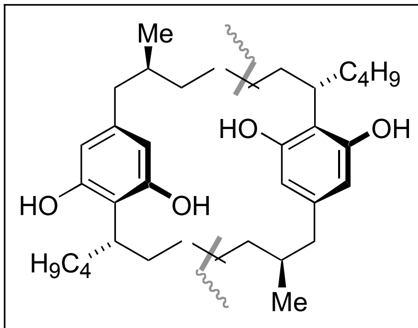
Cossy, J.; Bargiggia, F.; BouzBouz, S. *Org. Lett.* **2003**, *5*, 459

Cross Metathesis in Natural Product Total Synthesis

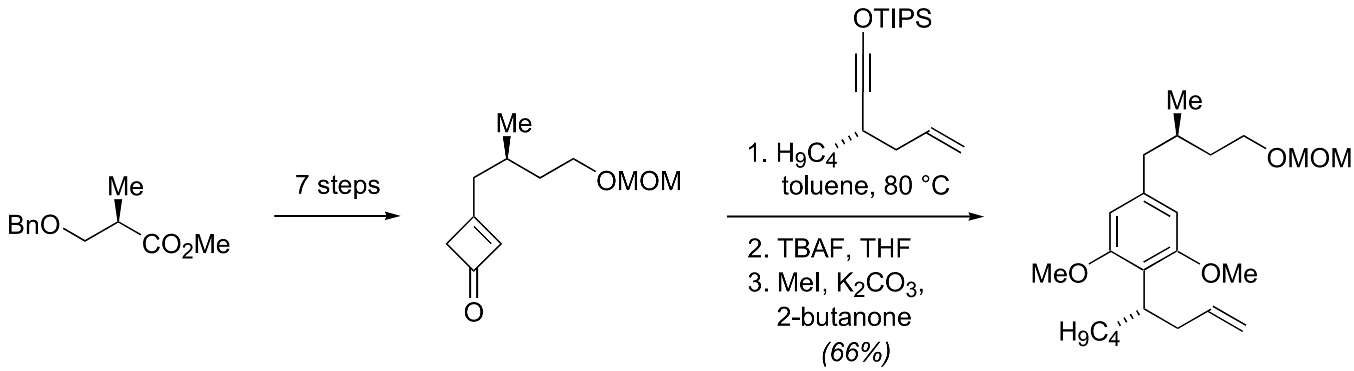
Smith, A. B., III; Kozmin, S. A.; Paone, D. V.
J. Am. Chem. Soc. **1999**, *121*, 7423

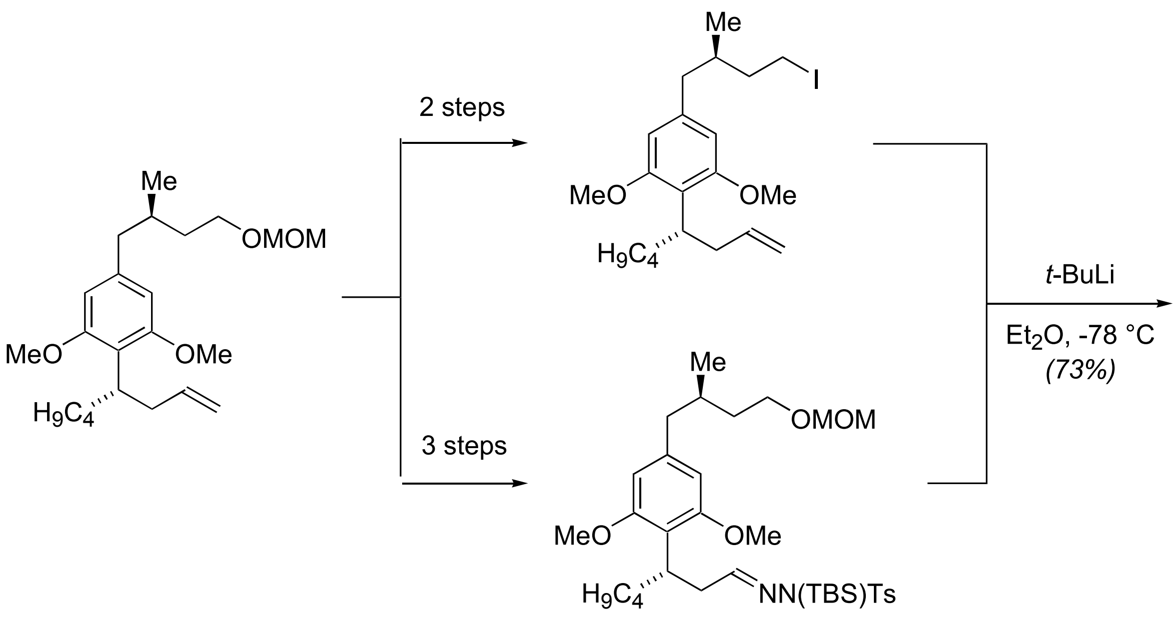
Smith, A. B., III; Adams, C. M.; Kozmin, S. A.; Paone, D. V.
J. Am. Chem. Soc. **2001**, *123*, 5925

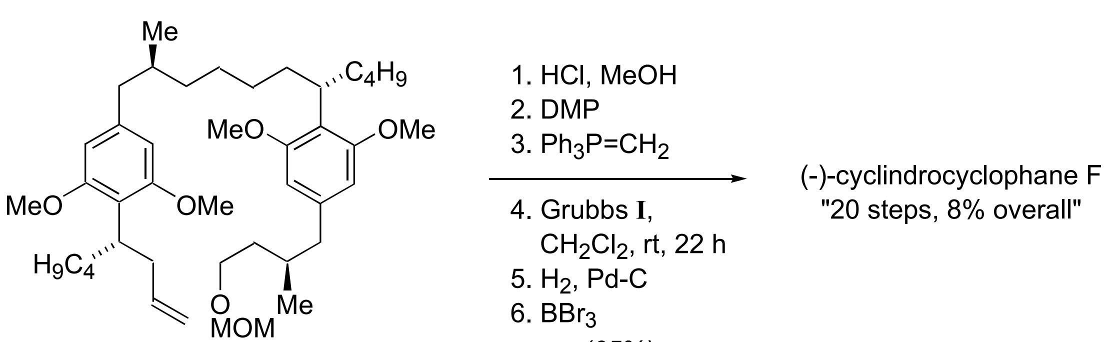
- strategy 1: thiolate alkylation, sulfur extrusion (dimerization)
- strategy 2: sulfone alkylation, elimination (dimerization)
- strategy 3 ("low-risk"): alkylation, macrocyclization (stepwise)



(-)-cyclindrocyclophane F



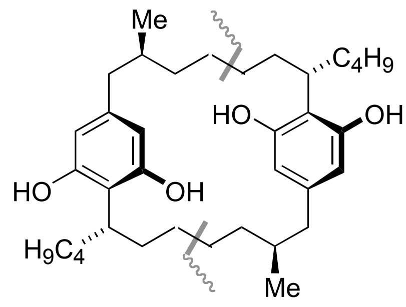




Cross Metathesis in Natural Product Total Synthesis

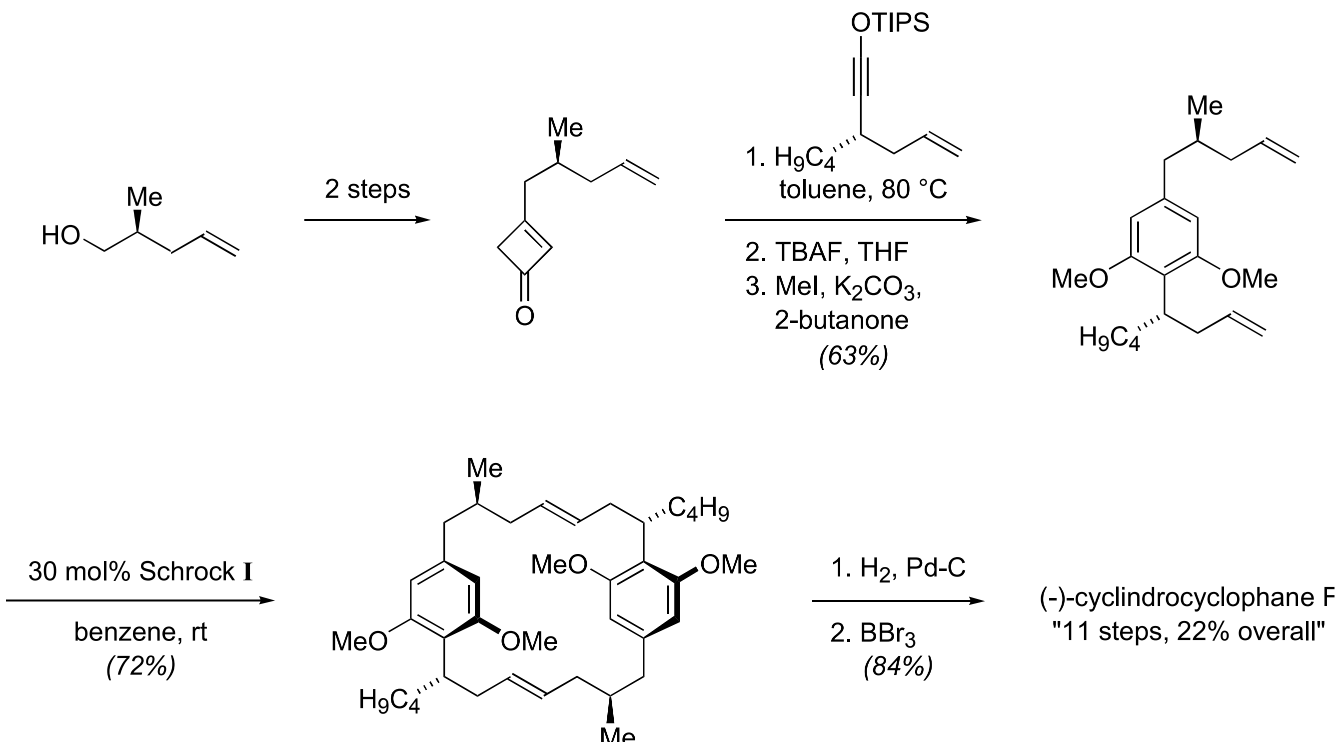
Smith, A. B., III; Kozmin, S. A.; Adams, C. M.; Paone, D. V.
J. Am. Chem. Soc. **2000**, *122*, 4984

Smith, A. B., III; Adams, C. M.; Kozmin, S. A., Paone, D. V.
J. Am. Chem. Soc. **2001**, *123*, 5925



(-)-cyclindrocyclophane F

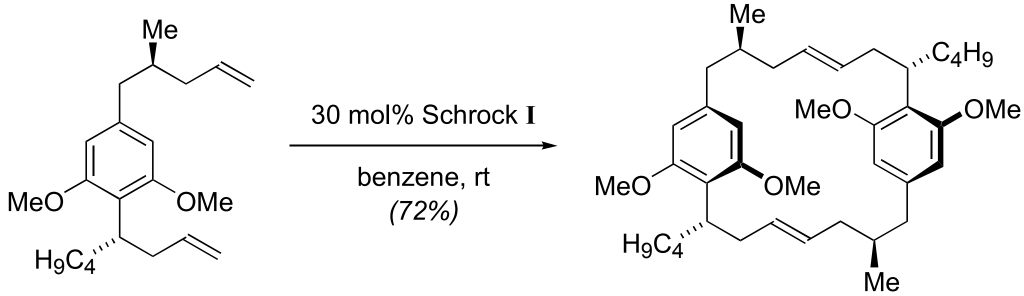
- strategy 1: thiolate alkylation, sulfur extrusion (dimerization)
- strategy 2: sulfone alkylation, elimination (dimerization)
- strategy 3 ("low-risk"): alkylation, macrocyclization (stepwise)
- strategy 4: cross metathesis (dimerization) ☆

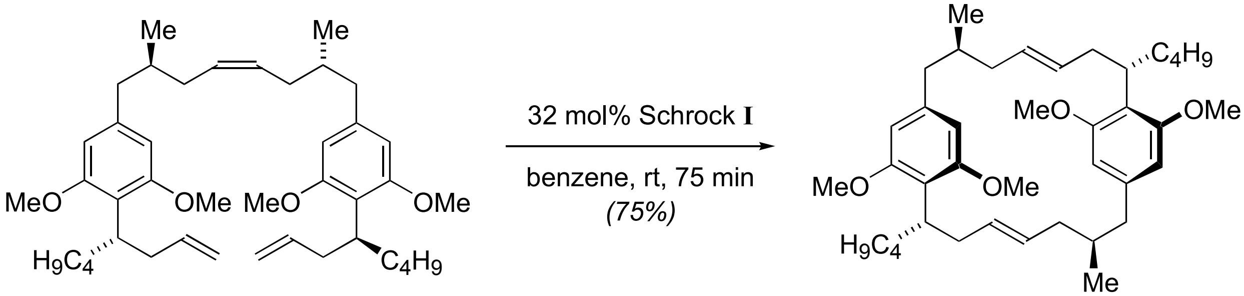


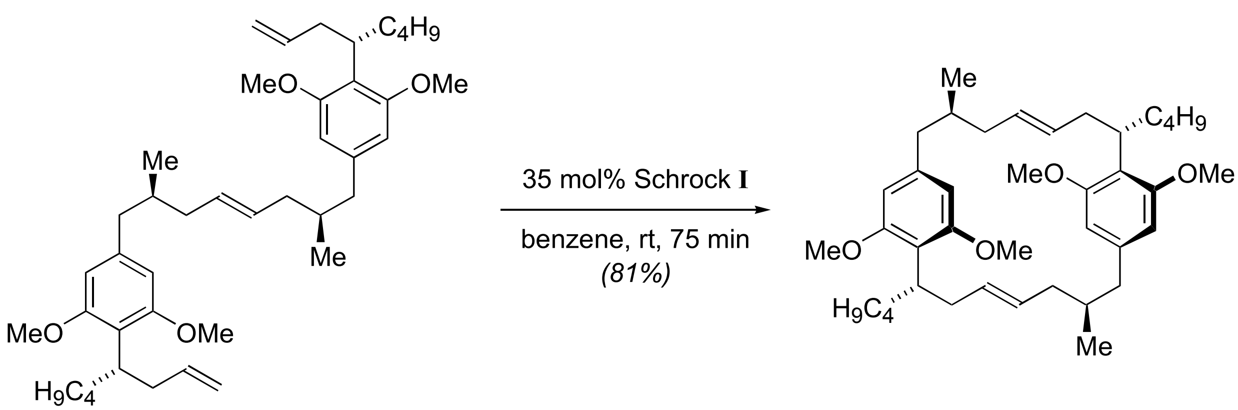
Cross Metathesis in Natural Product Total Synthesis

Smith, A. B., III; Adams, C. M.; Kozmin, S. A.
J. Am. Chem. Soc. **2001**, *123*, 990

Smith, A. B., III; Adams, C. M.; Kozmin, S. A.; Paone, D. V.
J. Am. Chem. Soc. **2001**, *123*, 5925

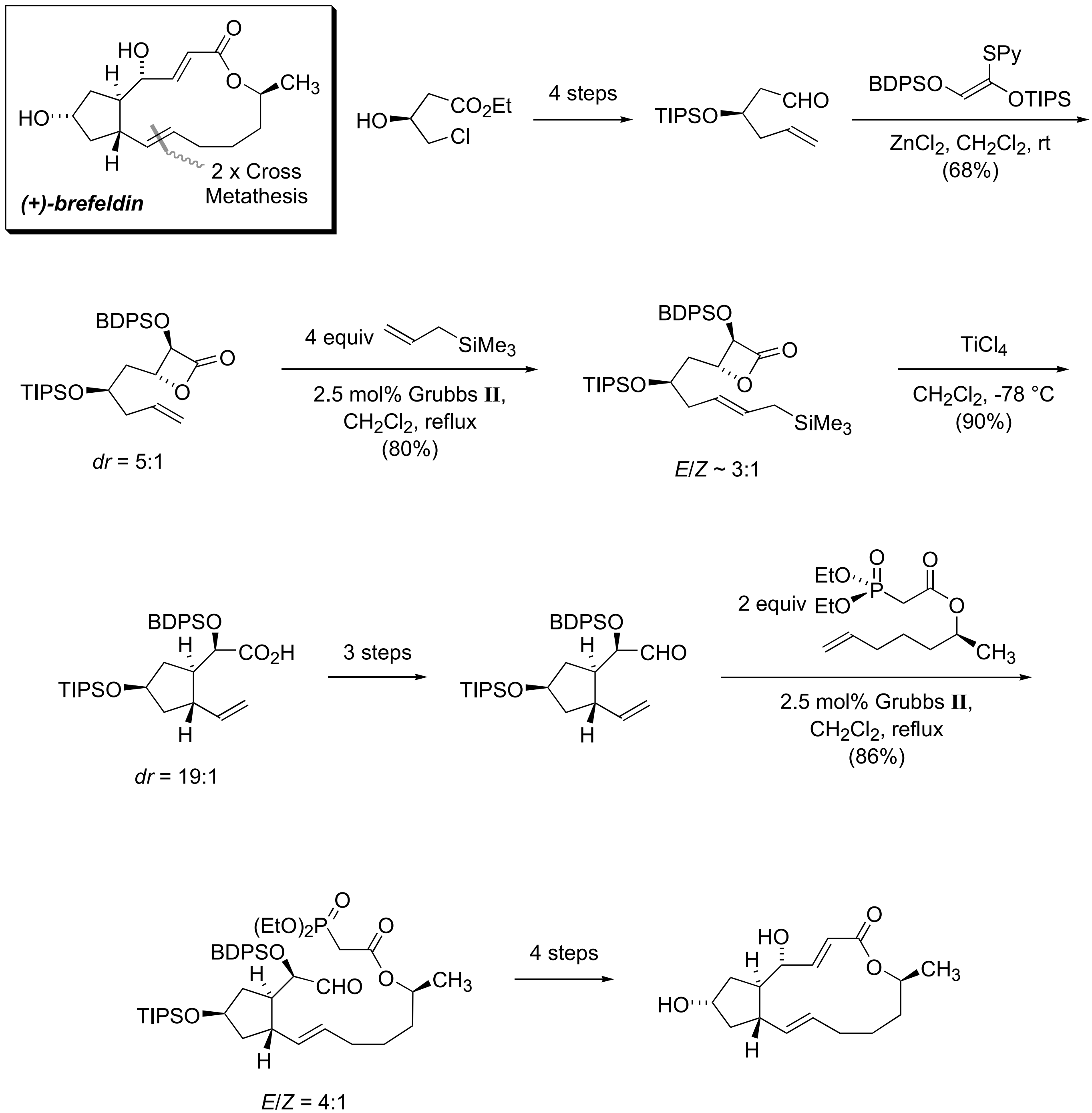






Cross Metathesis in Natural Product Total Synthesis

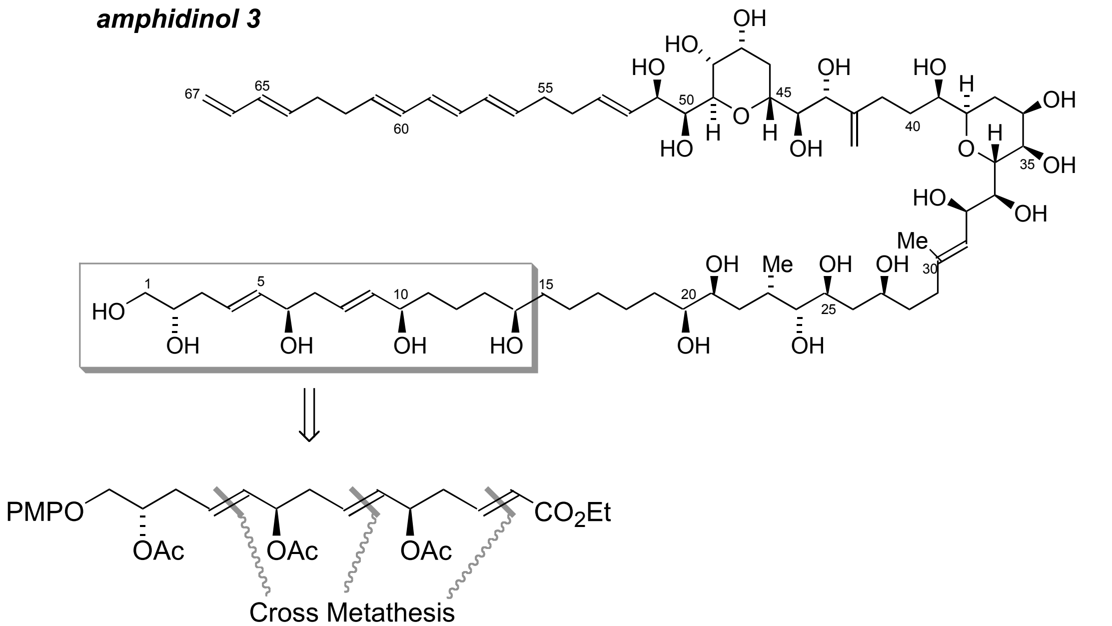
Wang, Y.; Romo, D.
Org. Lett. **2002**, *4*, 3231

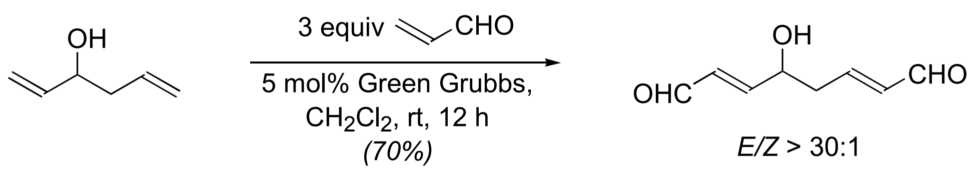


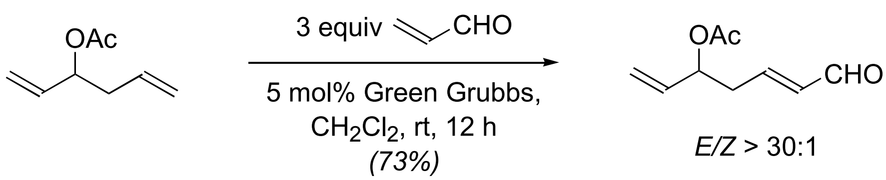
Cross Metathesis in Natural Product Total Synthesis

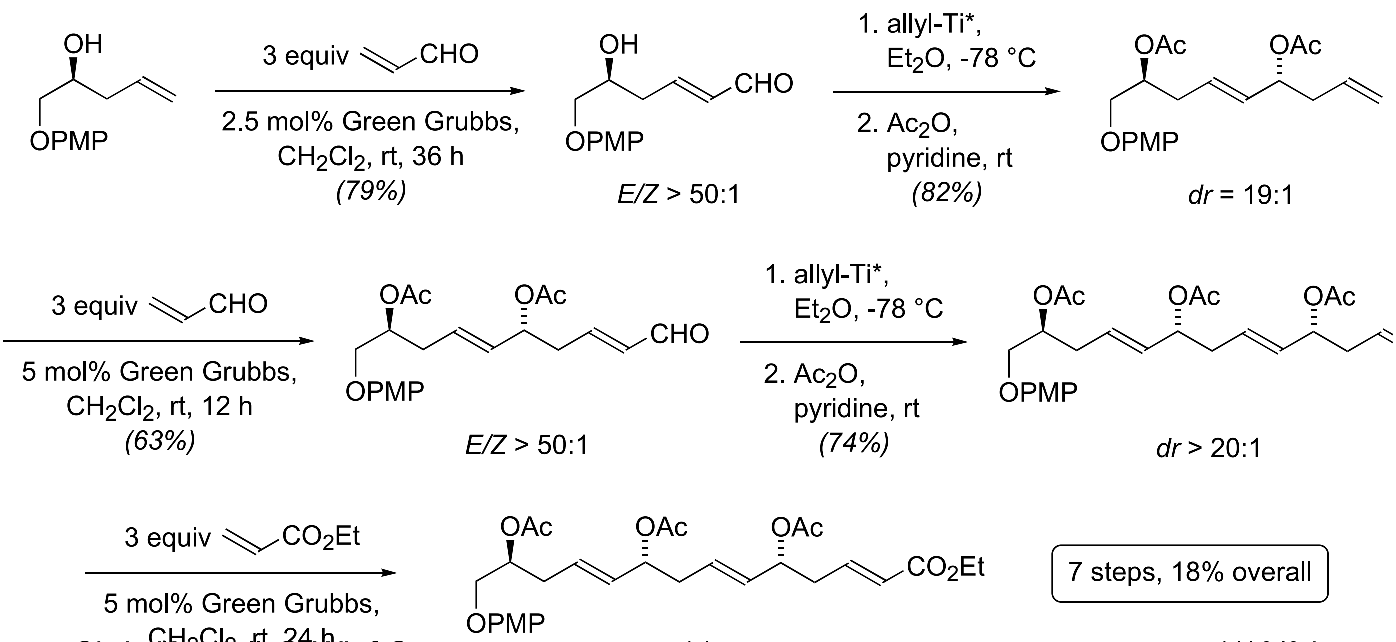
BouzBouz, S.; Cossy, J.
Org. Lett. **2001**, *3*, 1451

amphidinol 3



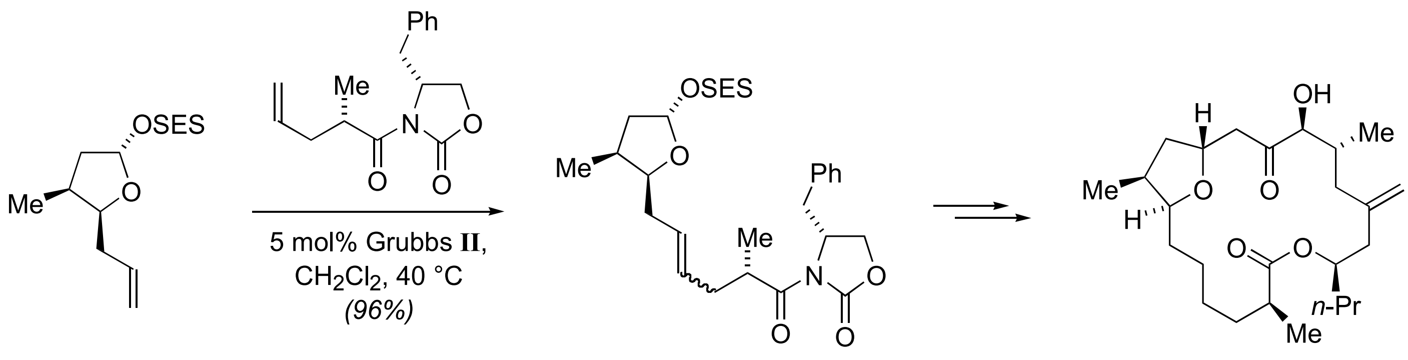






Cross Metathesis in Natural Product Total Synthesis

Ghosh, A. K.; Liu, C.
J. Am. Chem. Soc. **2003**, *125*, 2374

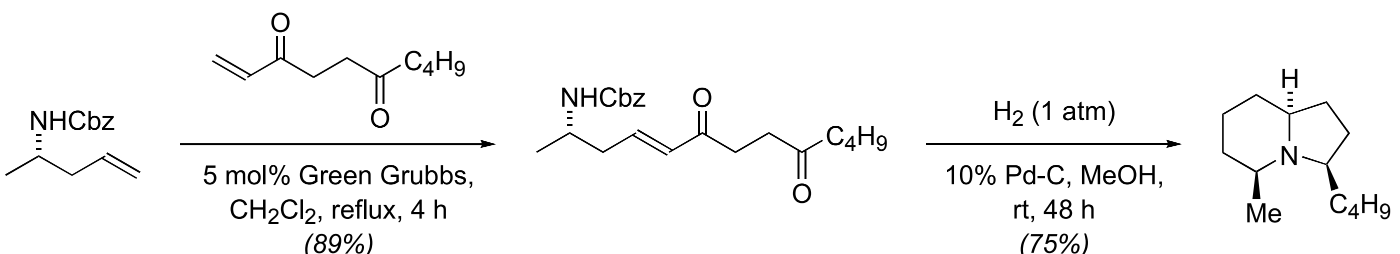


E/Z = 1:1

amphidinolide T1

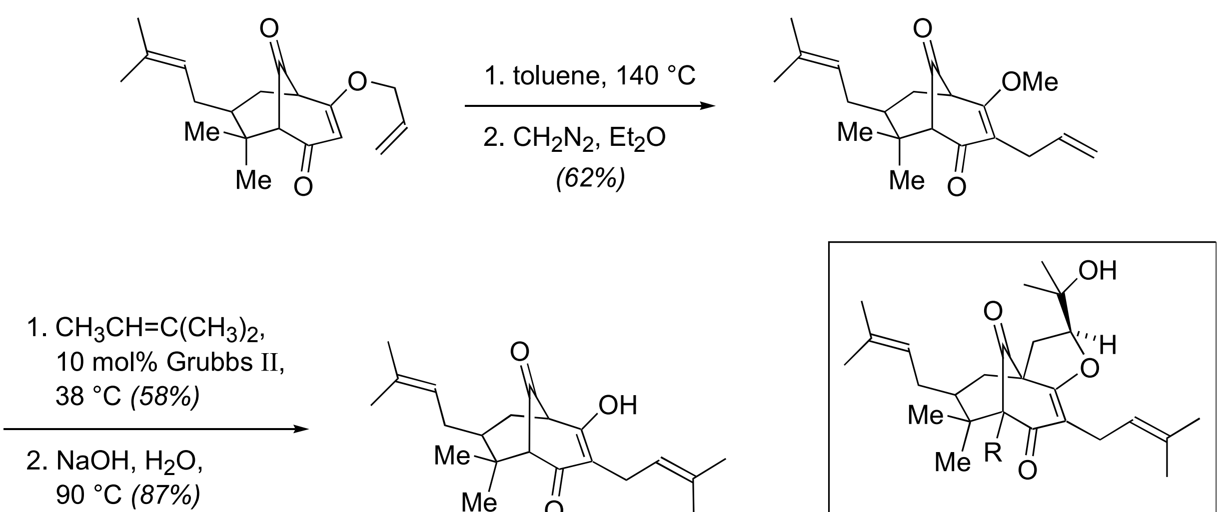
- first cycle: 60% yield + (separable) dimers
- separate dimers and re-subject
- second cycle: 36% yield

Randl, S.; Blecert, S.
J. Org. Chem. **2003**, *68*, 8879



(+)-monomorine I

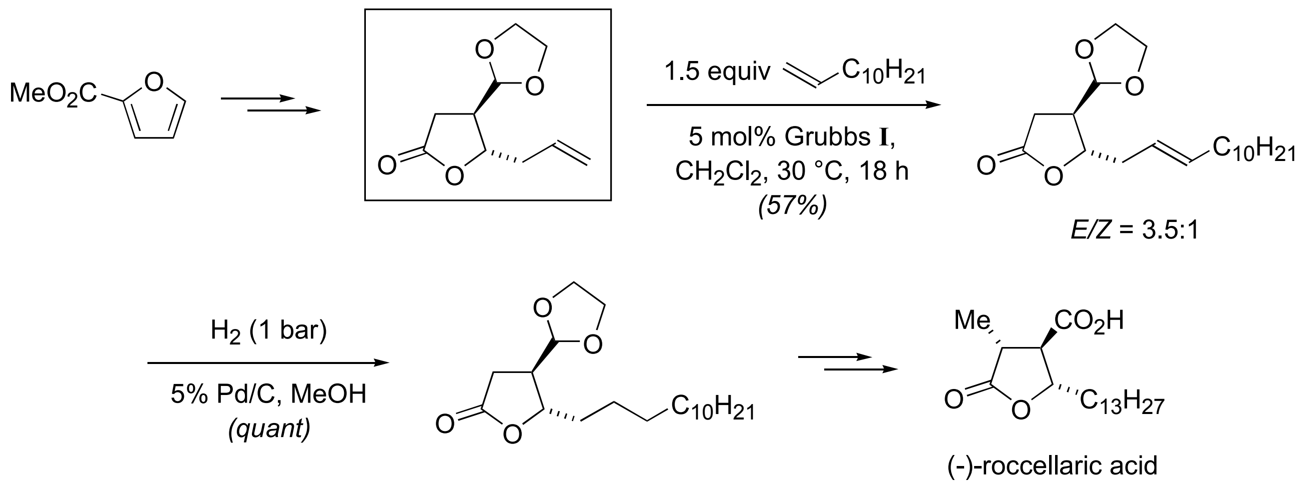
Spessard, S. J.; Stoltz, B. M.
Org. Lett. **2002**, *4*, 1943

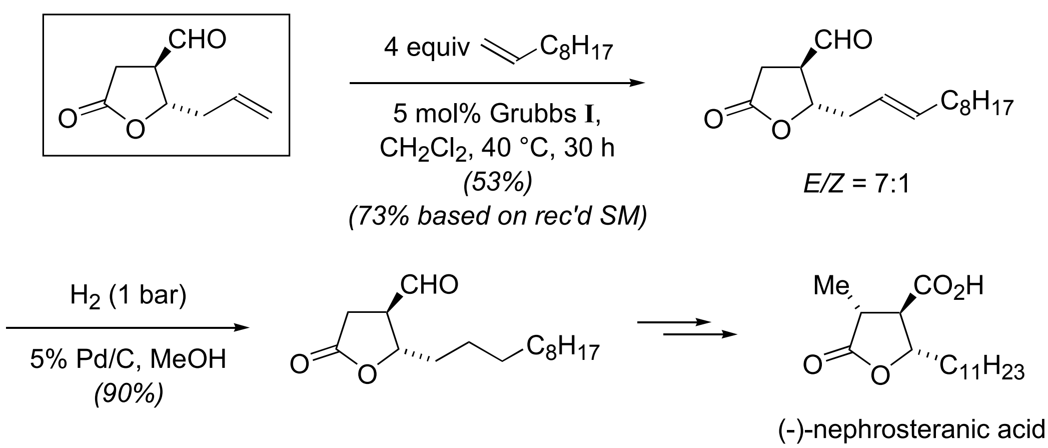


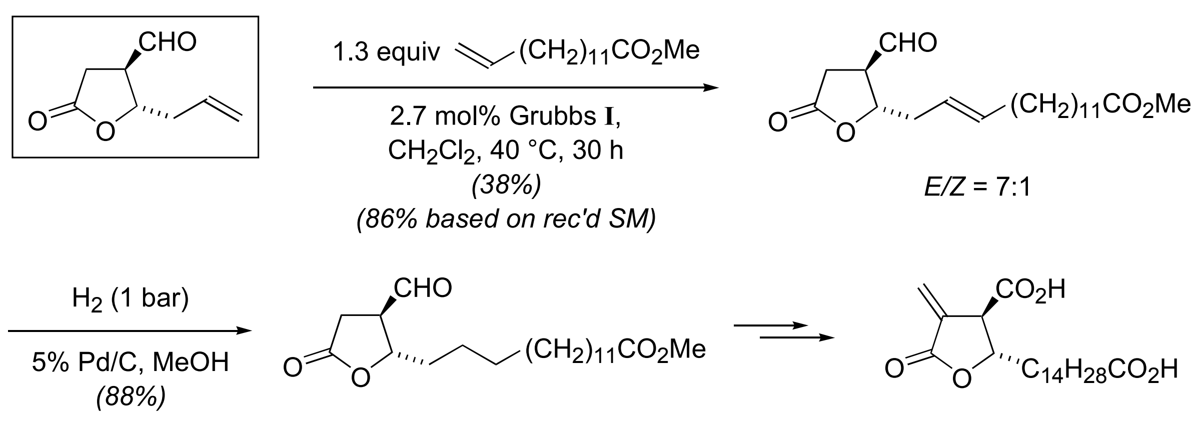
garsubellin A
(R = CO*i*-Pr)

Cross Metathesis in Natural Product Total Synthesis

Chlor, R. B.; Nosse, B.; Sörgel, S.; Böhm, C.; Seitz, M.; Reiser, O.
Chem. Eur. J. **2003**, *9*, 260

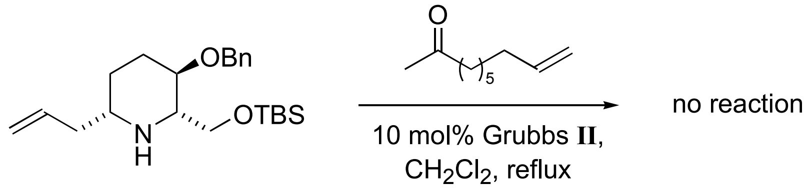


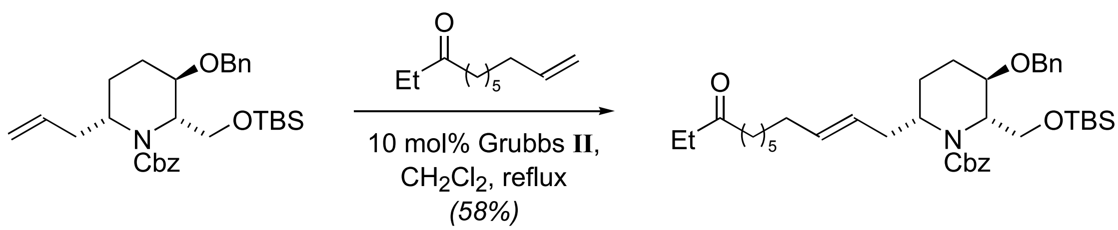


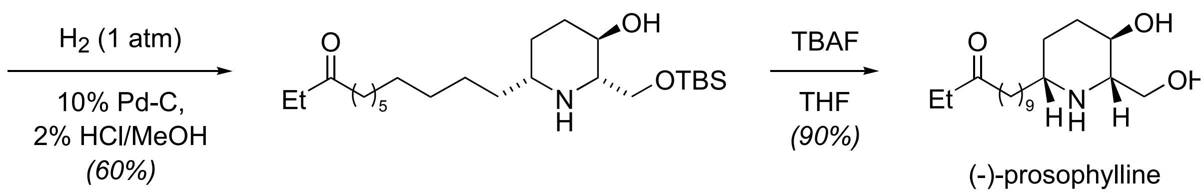


Heteroatom Effect on Cross Metathesis Reactivity

Cossy, J.; Willis, C.; Bellosta, V.; BouzBouz, S.
J. Org. Chem. **2002**, *67*, 1982

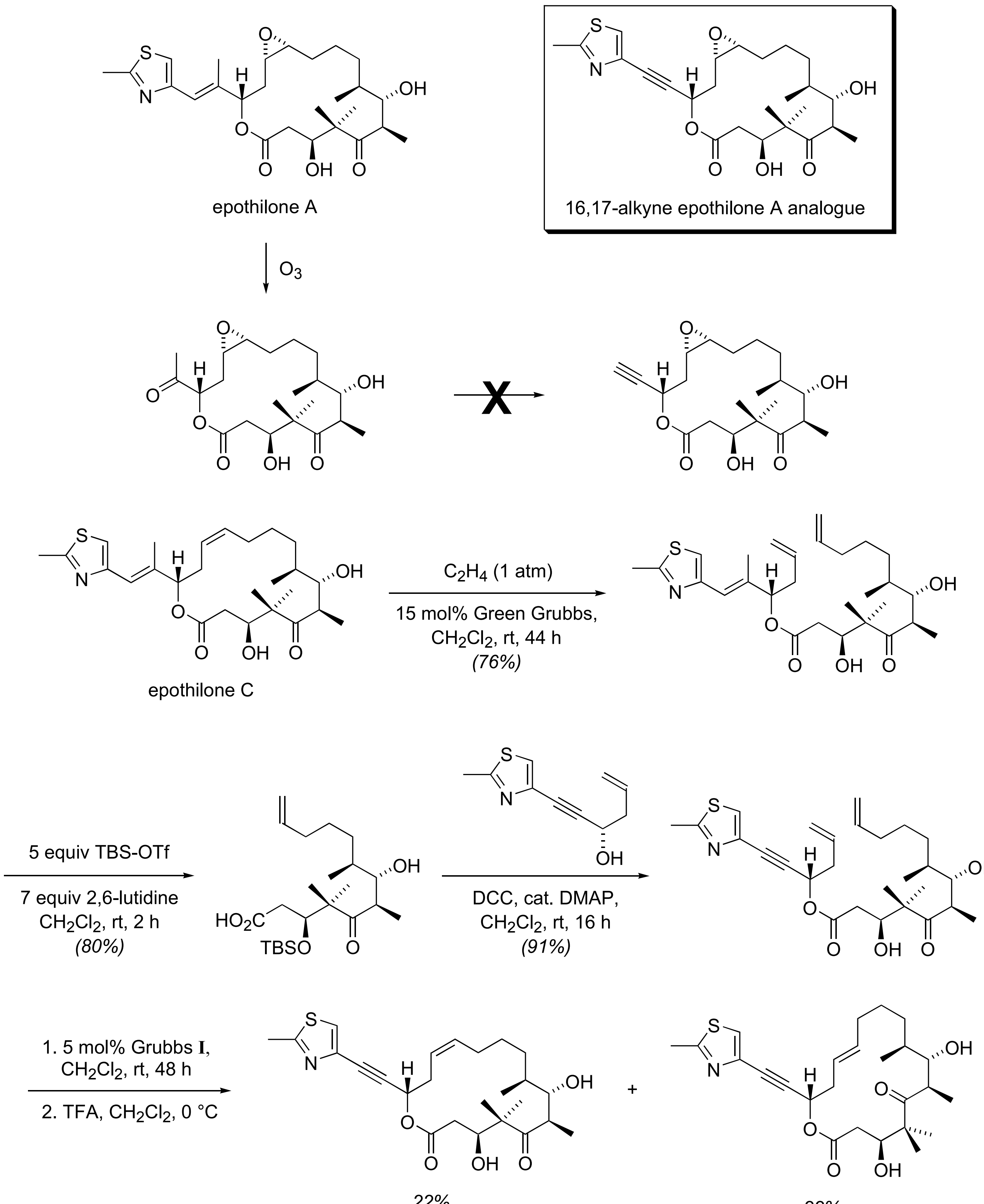






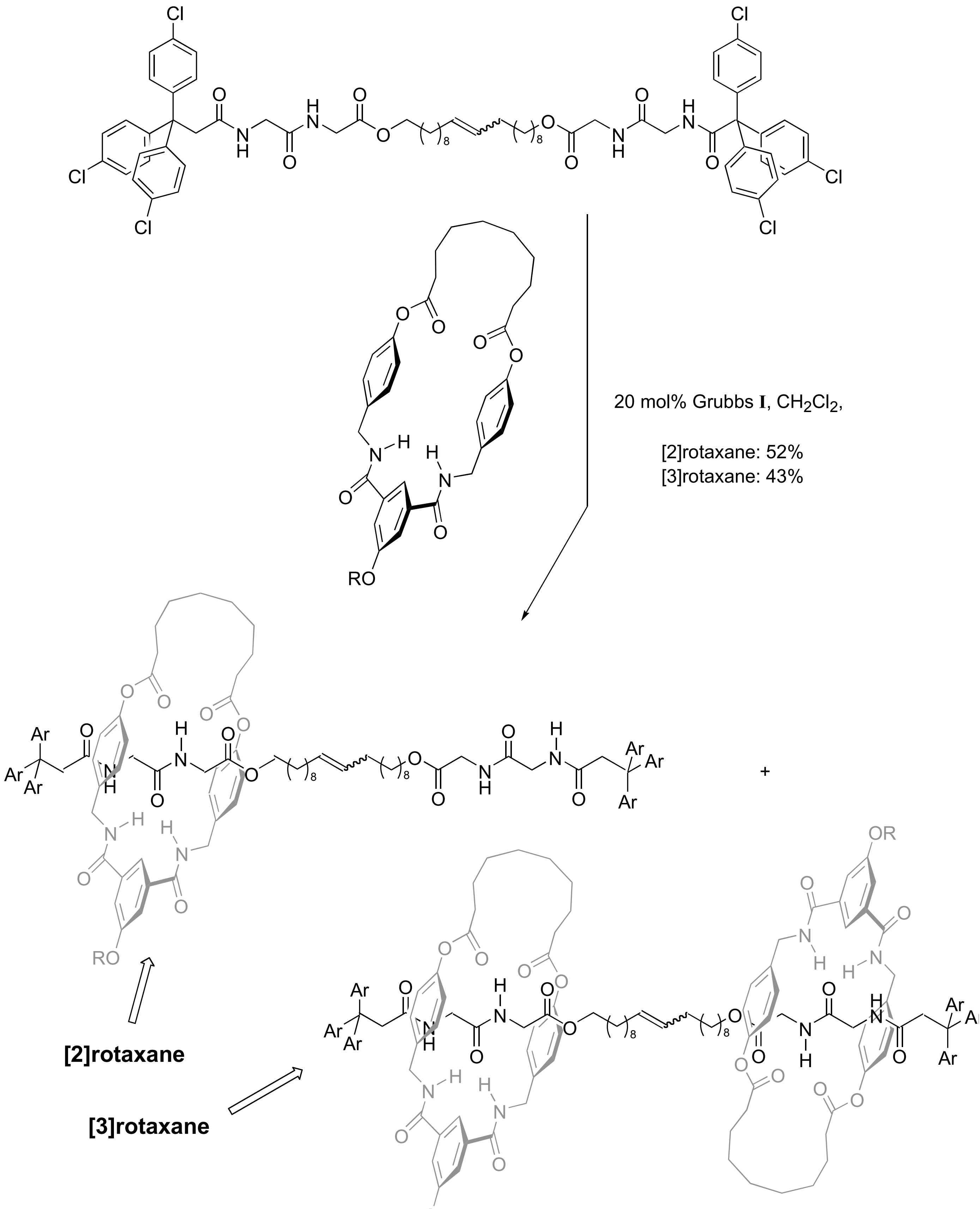
Cross Metathesis in Natural Product Modification

Karama, U.; Höfle, G.
Eur. J. Org. Chem. **2003**, 1042



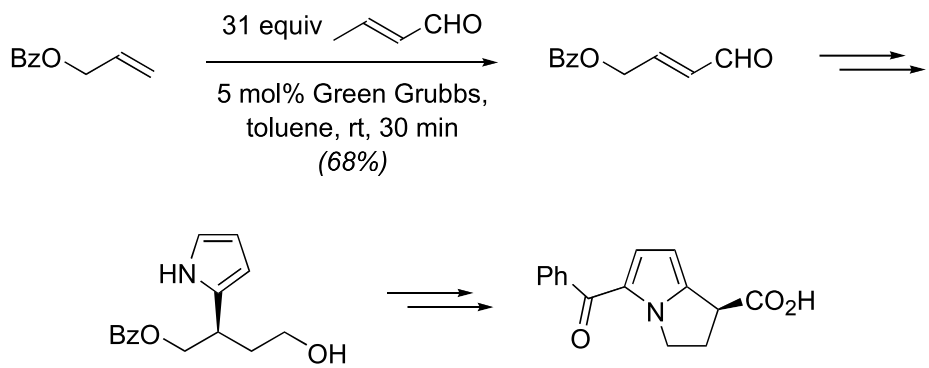
Cross Metathesis for "Rotaxane" Synthesis

Hannam, J. S.; Kidd, T. J.; Leigh, D. A.; Wilson, A. J.
Org. Lett. **2003**, *5*, 1907

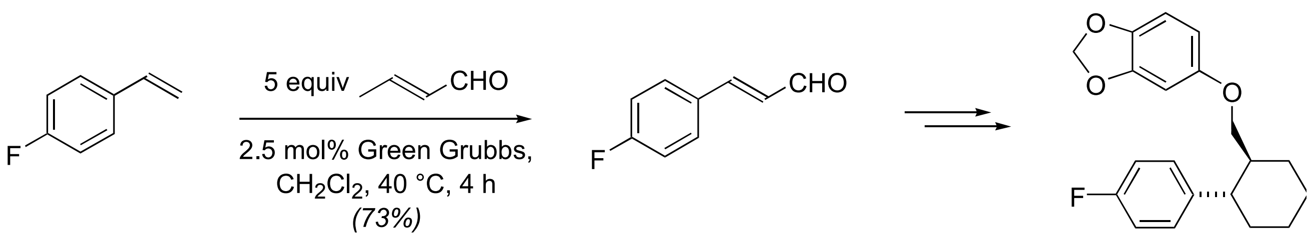


Cross Metathesis in Pharmaceutical Synthesis

Pederson, R. L.; Fellows, I. M.; Ung, T. A.; Ishihara, H.; Hajela, S. P.
Adv. Synth. Cat. **2002**, *344*, 728



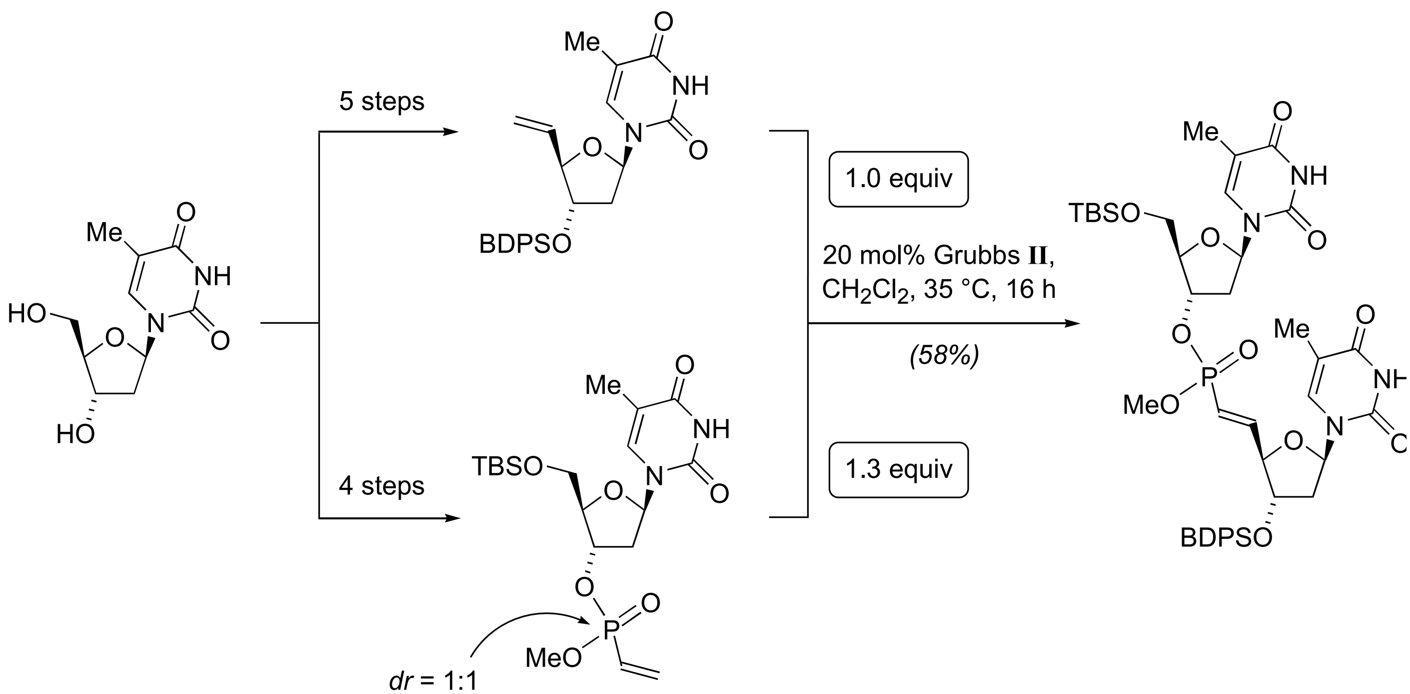
(-)-ketorolac (NSAID)
Acular™ -or- *Toradol IM™*



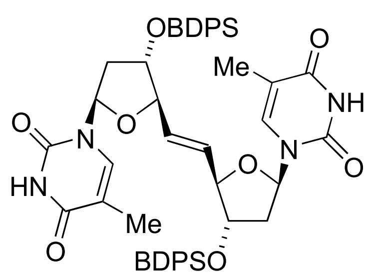
paxil (5-HT inhibitor)
Seroxat™

Cross Metathesis in Complex Molecule Synthesis

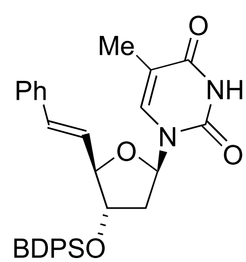
Lera, M.; Hayes, C. J.
Org. Lett. **2001**, *3*, 2765



Also Formed:



(10%)

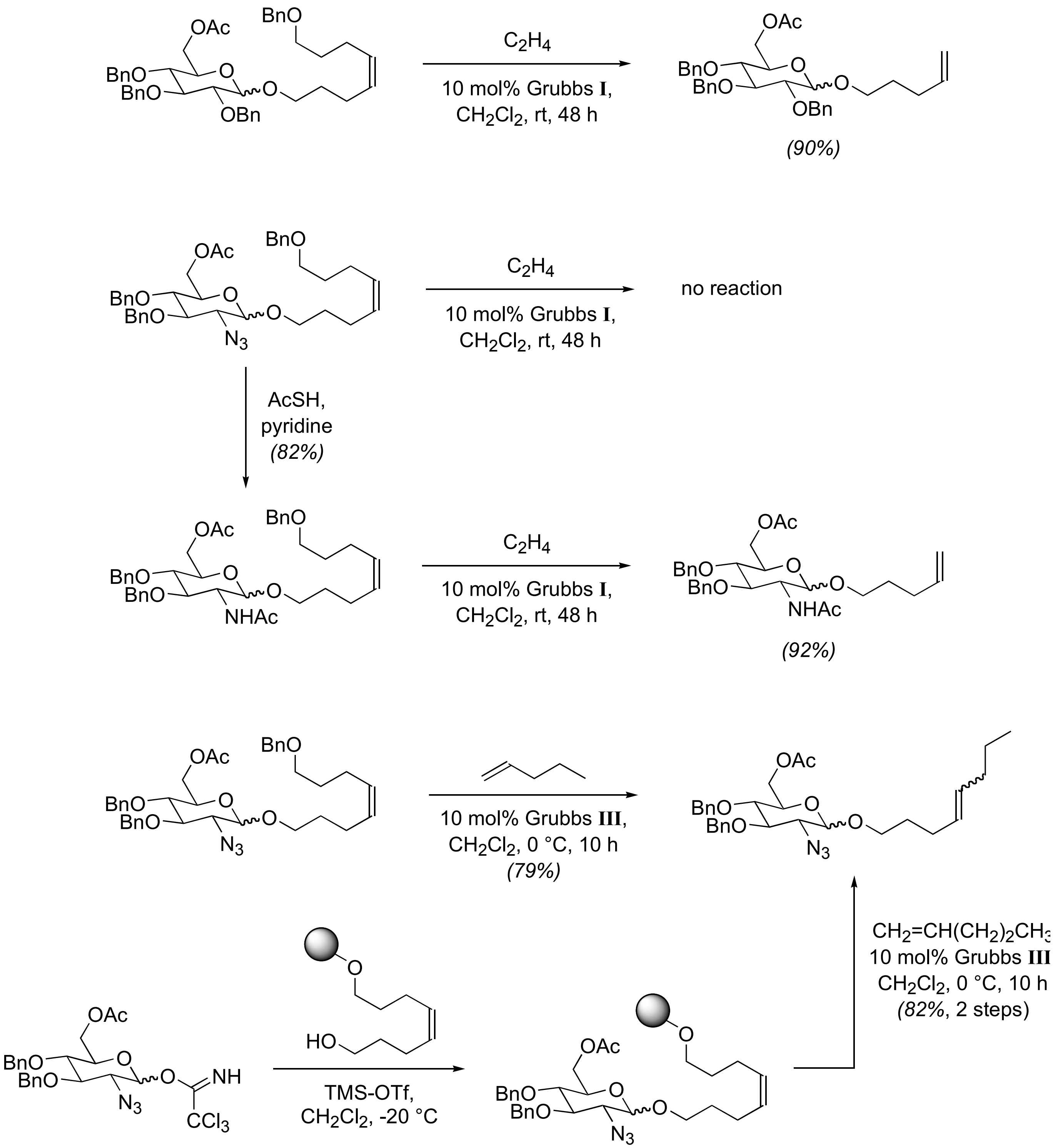


(20%)

- 5 mol% Grubbs **II**: sluggish reaction of low conversion
- excess metathesis partner: impractical

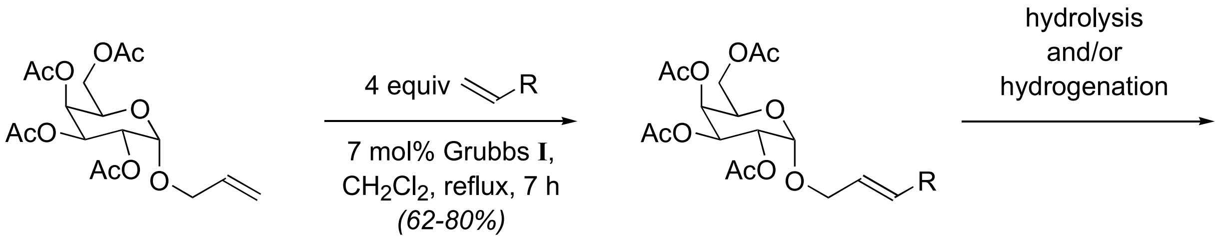
Cross Metathesis in Automated Synthesis

Kanemitsu, T.; Seeberger, P. H.
Org. Lett. **2003**, *5*, 4541



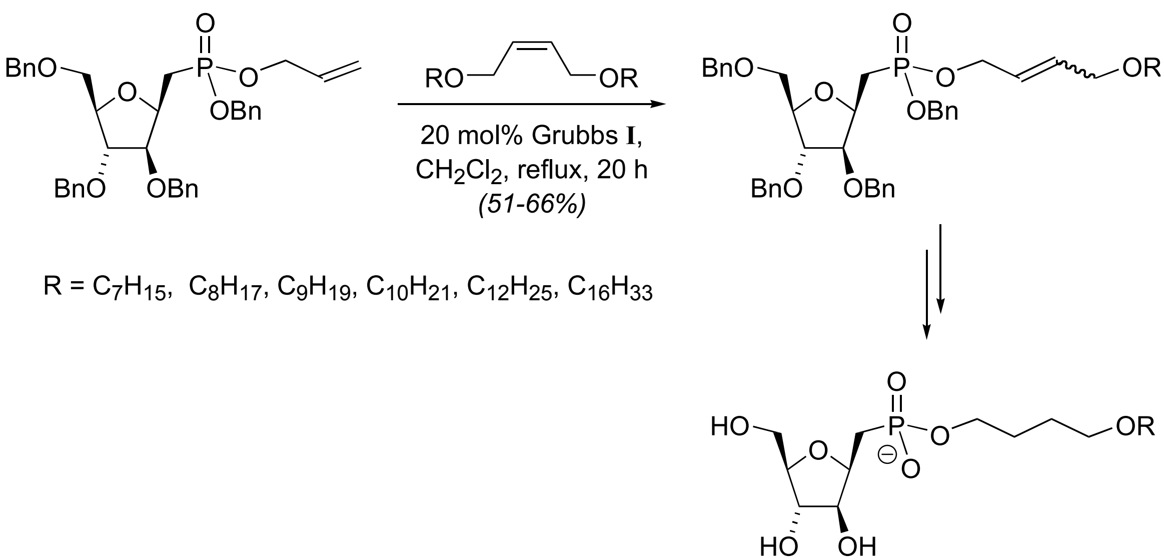
Cross Metathesis for Library Synthesis

Plettenburg, O.; Mui, C.; Bodmer-Narkevitch, V.; Wong, C.-H.
Adv. Synth. Catal. **2002**, *344*, 622



R = C_6H_{13}, C_8H_{17}, $C_{10}H_{21}$, $C_{12}H_{25}$, $C_{14}H_{27}$, $C_{16}H_{31}$,
CH_2Ph, $(CH_2)_2Ph$, CH_2OPh, CH_2OBn

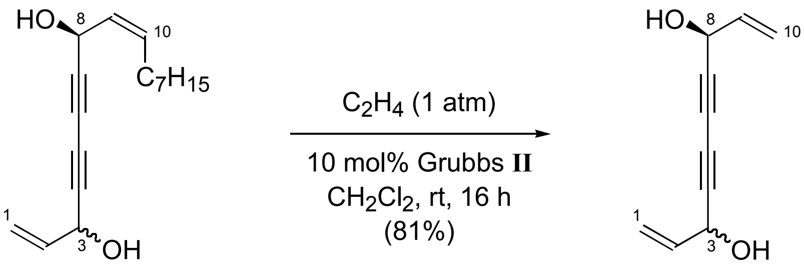
Centrone, C. A.; Lowary, T.
J. Org. Chem. **2002**, *67*, 8862



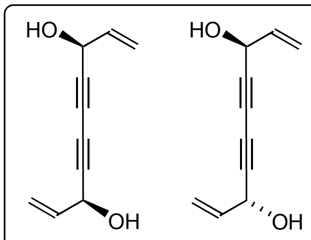
R = C_7H_{15}, C_8H_{17}, C_9H_{19}, $C_{10}H_{21}$, $C_{12}H_{25}$, $C_{16}H_{33}$

Cross Metathesis in Natural Product Structure Determination

Ratnayake, A. S.; Hemscheidt, T.
Org. Lett. **2002**, *4*, 4667



(+)-falcarindiol



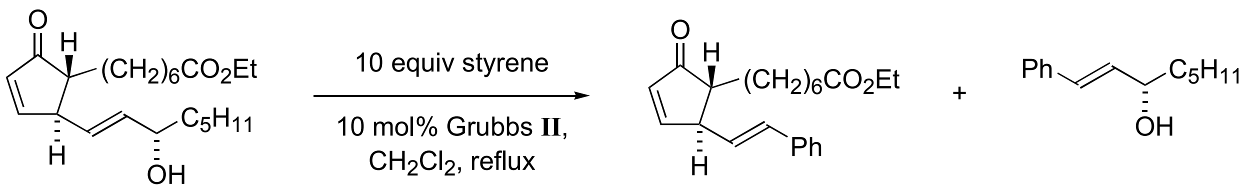
(3*S*): chiral (3*R*): meso

Year	$[\alpha]_D$	assigned configuration	sample (assignment)
1981	+ 284 (*c* 1.0, Et_2O)	3*R*	isolated from *Peucedanum oreoselinum* (chemical correlation)
1996	+ 300 (*c* 0.14, Et_2O)	3*S*	isolated from *Dendropanax arboreus* (Mosher analysis)
1999	+ 219 (*c* 4.6, $CHCl_3$)	3*R*	(total synthesis)
2002	+ 302 (*c* 1.0, Et_2O) + 276 (*c* 0.14, Et_2O) + 250 (*c* 4.6, $CHCl_3$)	3*R*	isolated from *Tetraplasandra hawaiiensis* (chemical degradation)

Cross Metathesis in Natural Product Structure Determination

Tanaka, K.; Nakanishi, K.; Berova, N.
J. Am. Chem. Soc. **2003**, *125*, 10802

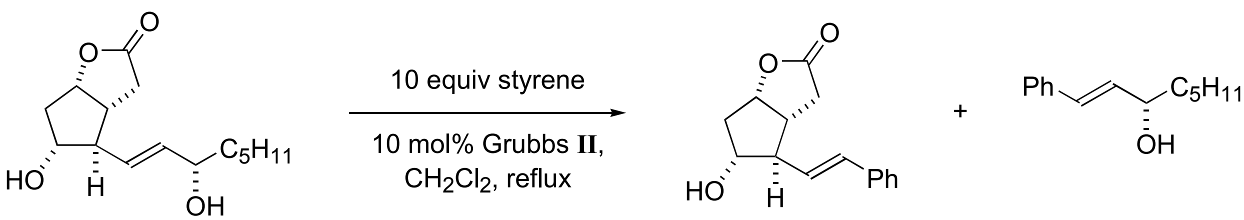
- absolute configuration of allylic alcohols commonly determined by circular dichroism of corresponding benzoate
- can be complicated by other chromophores



PGA$_1$ ethyl ester

(85%) *(89%)*

- PGA$_1$ enone λ_{MAX} 231 nm, allylic benzoate λ_{MAX} ~230 nm
- reaction easily run on 0.1 mg scale

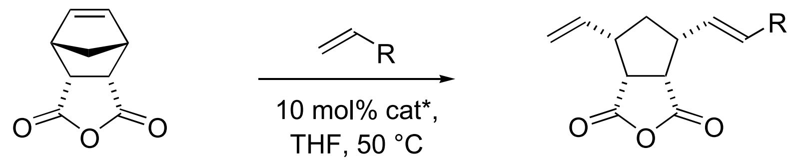


"Corey lactone"

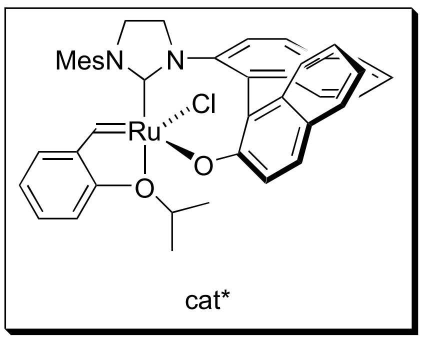
(66%) *(63%)*

Asymmetric Cross Metathesis

Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H.
J. Am. Chem. Soc. **2002**, *124*, 4954



R	yield (%)	*ee* (%)
Ph	71	80
C_5H_{11}	57	> 98
c-C_6H_{11}	60	> 98

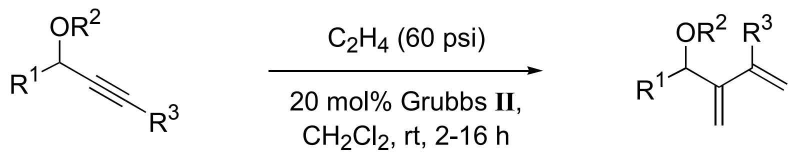


full story:

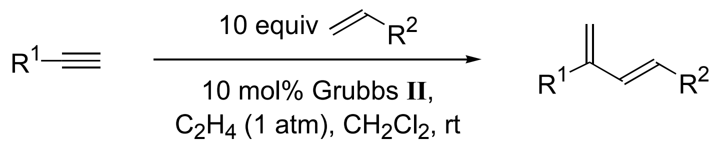
"Molybdenum and Tungsten Imido Alkylidene Complexes as Efficient Olefin-Metathesis Catalysts'

Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592

Ene-Yne Cross Metathesis



Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271

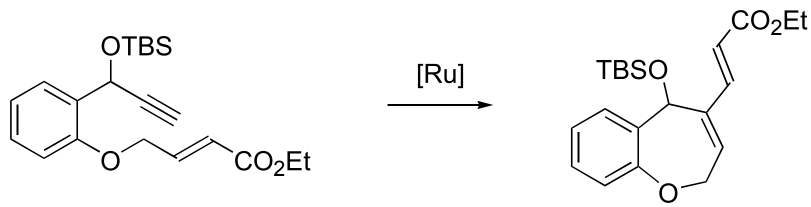


Lee, H.-Y.; Kim, B. G.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 1855

Tandem Ene-Yne Metathesis / Cross Metathesis

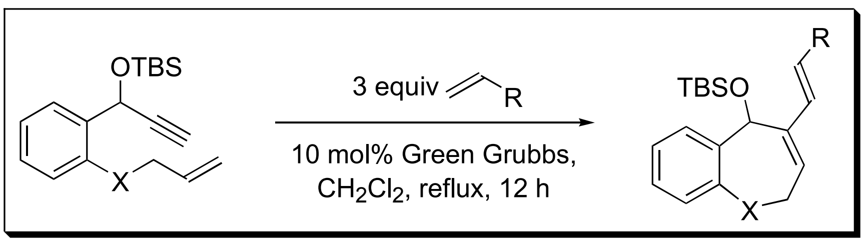
Royer, F.; Vilain, C.; Elkaïm, L.; Grimaud, L.
Org. Lett. **2003**, *5*, 2007

Desired Reaction: ring closing ene-yne metathesis



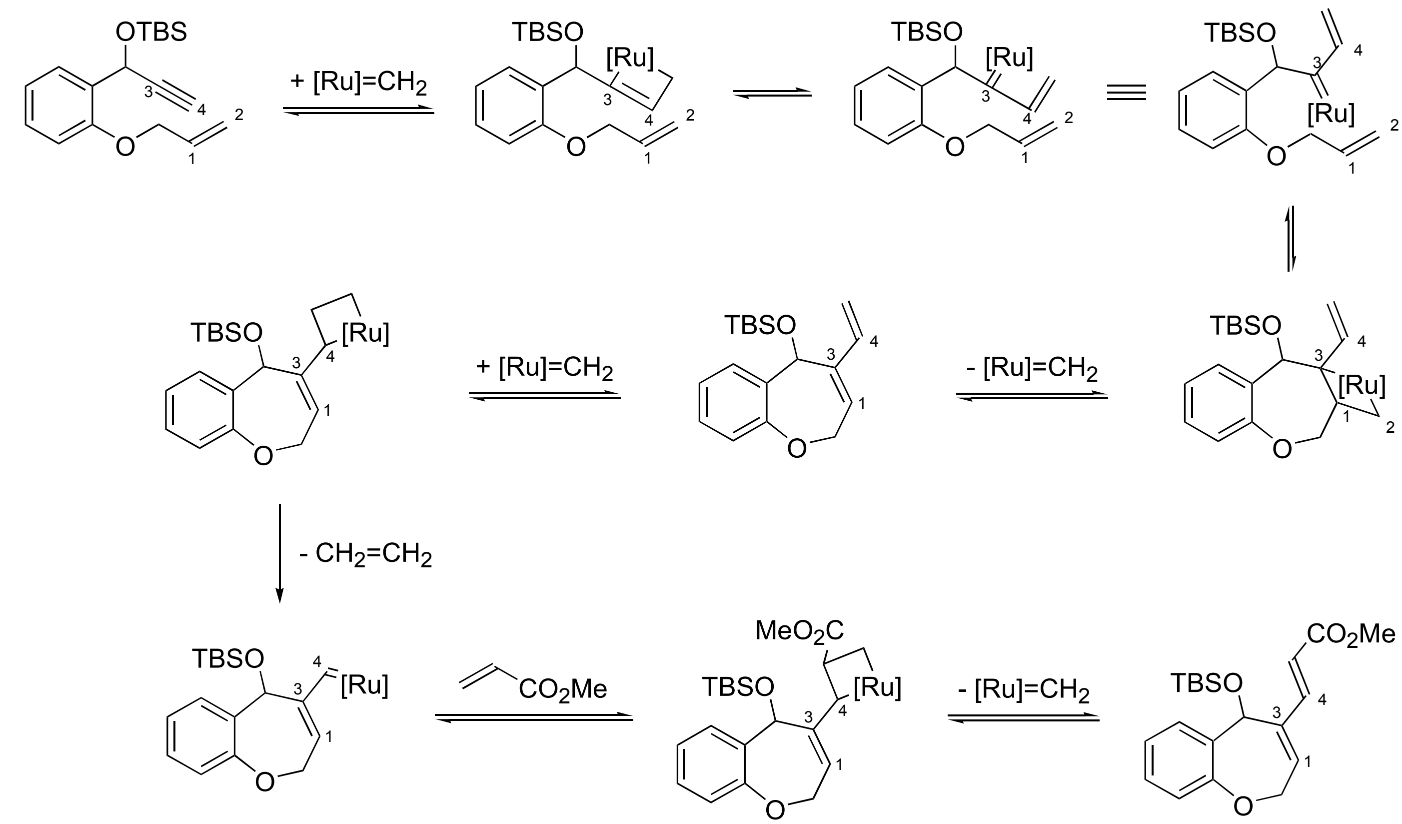
Result: failure

Modification: tandem ring closing ene-yne / cross metathesis



R	X	Yield (%)
CO_2Me	O	67
	CH_2	88
COMe	O	68
	CH_2	73
CHO	O	65
	CH_2	61

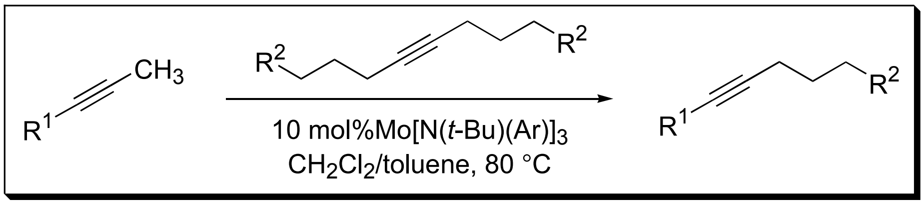
1 possible mechanism

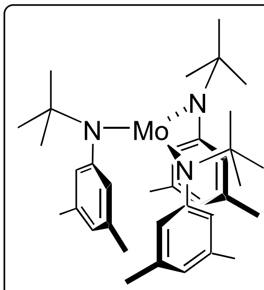


Alkyne Cross Metathesis

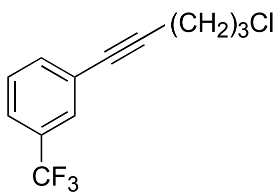
Fürstner, A.; Grela, K.; Mathes, C.; Lehmann, C. W.
J. Am. Chem. Soc. **2000**, *122*, 11799

Fürstner, A.; Mathes, C.
Org. Lett. **2001**, *3*, 221

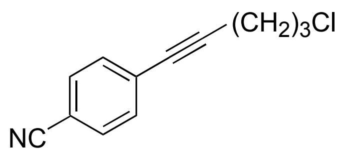




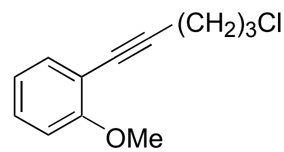
Mo[N(*t*-Bu)(Ar)]$_3$



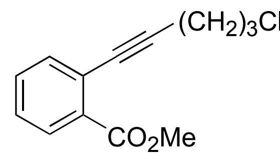
70%



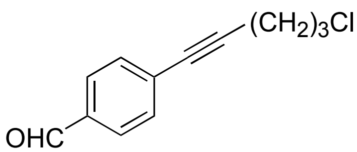
70%



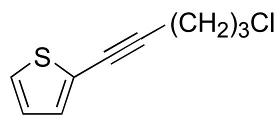
67%



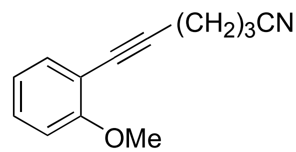
62%



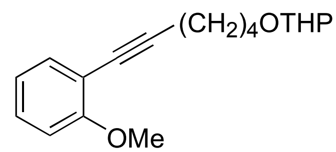
47%



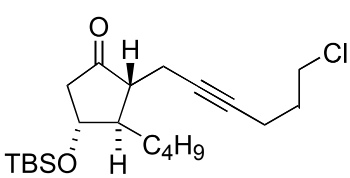
55%



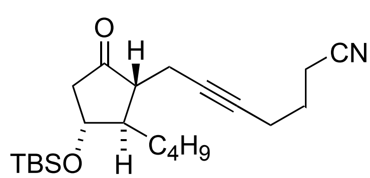
82%



68%



46%



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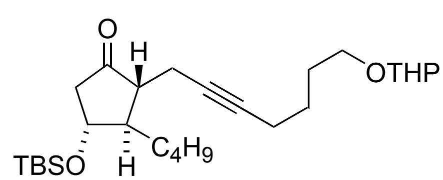
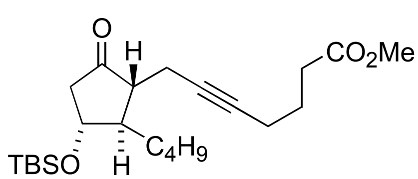
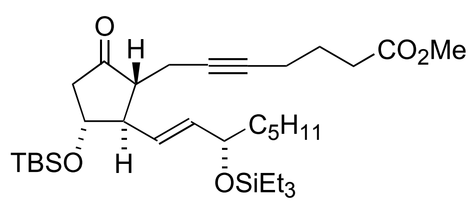


53%



43%



51%