Development of New Methods for the Preparation of Hindered Cyclohexene Systems

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Thursday, September 23, 2004

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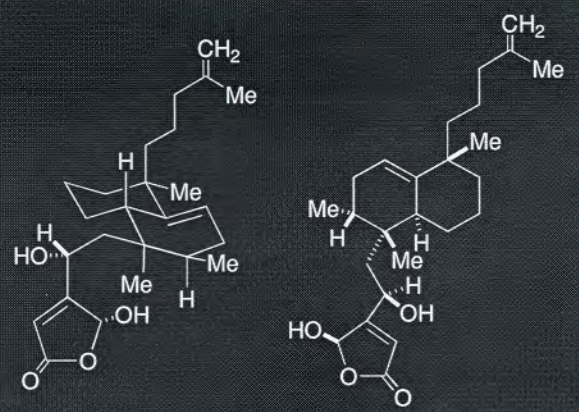


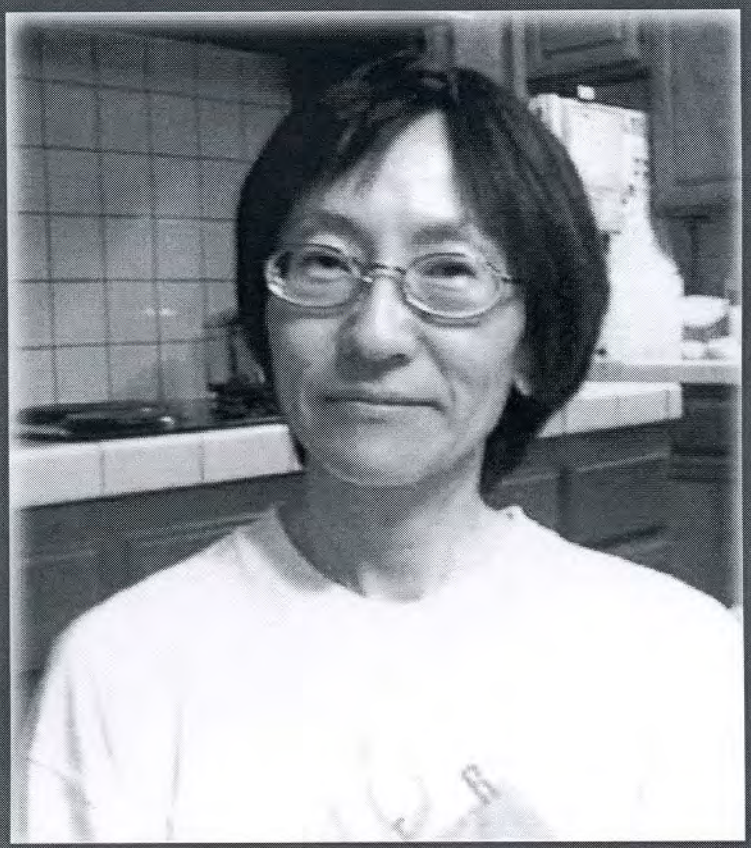
Dysidiolide 1

Claimed to be an inhibitor of protein phosphatase cdc25A with an IC_{50} of 9.4 μM and also inhibited the growth of the A-549 human lung carcinoma and P388 leukemia cell lines, with IC_{50} values of 4.7 and 1.5 μM respectively.

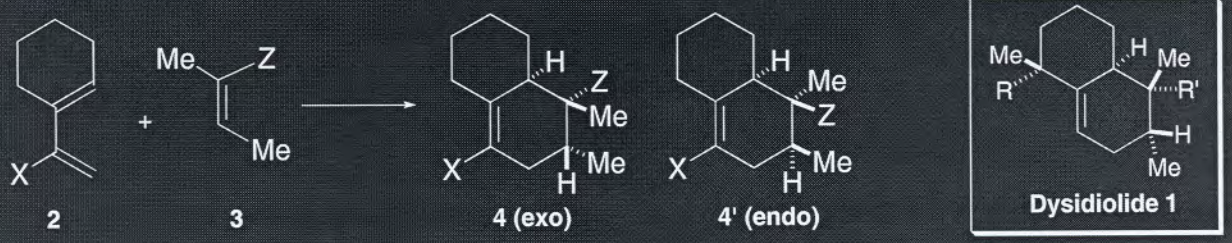
Isolation: Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1996**, *118*, 8759. Biology: Blanchard, J. L.; Epstein, D. M.; Boisclair, M. D.; Rudolph, J.; Pal, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2537. b) Takahashi, M.; Dodo, K.; Sugimoto, Y.; Aoyagi, Y.; Yamada, Y.; Hashimoto, Y.; Shirai, R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2571.

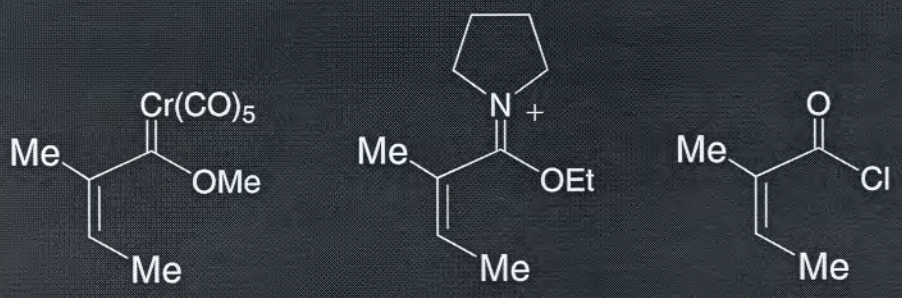
Syntheses: a) Corey, E. J; Roberts, B. E. *J. Am. Chem. Soc.* **1997**, *119*, 12425. b) Boukouvalas, J.; Cheng, Y. X.; Robichaud, J. *J. Org. Chem.* **1998**, *63*, 228. c) Magnuson, S. R.; Sepp-Lorenzino, L.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 1615. d) Brohm, D.; Waldmann, H. *Tetrahedron Lett.* **1998**, *39*, 3998. e) Piers, E.; Caillé, S.; Chen, G. *Org. Lett.* **2000**, *2*, 2483. f) Demeke, D.; Forsyth, C. J. *Org. Lett.* **2000**, *2*, 3177. g) Miyaoka, H.; Kajiwara, Y.; Yamada, Y. *Tetrahedron Lett.* **2000**, *41*, 911. h) Takahashi, M.; Dodo, K.; Hashimoto, Y.; Shirai, R. *Tetrahedron Lett.* **2000**, *41*, 2111. i) Paczkowski, R.; Maichle-Mossmer, C.; Maier, M. E. *Org. Lett.* **2000**, *2*, 3967. j) Miyaoka, H.; Kajiwara, Y.; Hara, Y.; Yamada, Y. *J. Org. Chem.* **2001**, *66*, 1429.

Jung, M. E.; Nishimura, N. *Org. Lett* **2001**, *3*, 2113; *J. Am. Chem. Soc.* **1999**, *121*, 3529. .



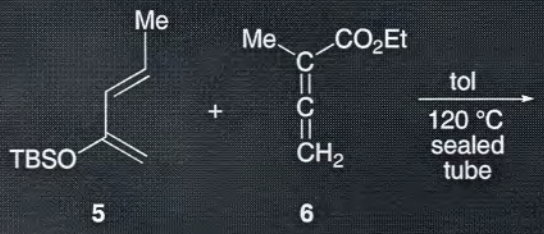
Synthetic Strategy



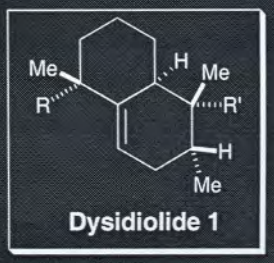


None of the highly activated dienophiles gave any adducts, presumably due to steric hindrance!

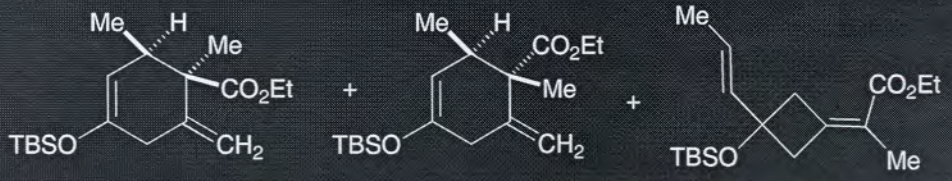
New Synthetic Strategy



5 6



Dysidiolide 1

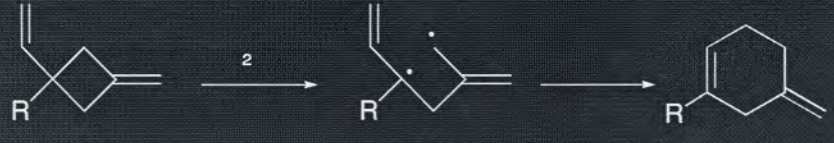


7n **7x** **8**

14h	15%	28%	tol/² /4d	22%
			90%	
4d	14%	58%		0%

[2+2] Cycloadducts in reactions of allenes with dienes: a) Jung, M. E.; Node, M.; Pfluger, R.; Lyster, M. A.; Lowe, J. A., III *J. Org. Chem.* **1982**, *47*, 1150. b) Jung, M. E.; Lowe, J. A., III; Lyster, M. A.; Node, M.; Pfluger, R.; Brown, R. W. *Tetrahedron* **1984**, *40*, 4751. c) Spitzner, D.; Klein, I. *Liebigs Ann. Chem.* **1990**, 63. d) *Angew. Chem.* **1982**, *94*, 639. These authors report that their [2 + 2] cycloadduct does not rearrange to the [4 + 2] cycloadduct on heating.

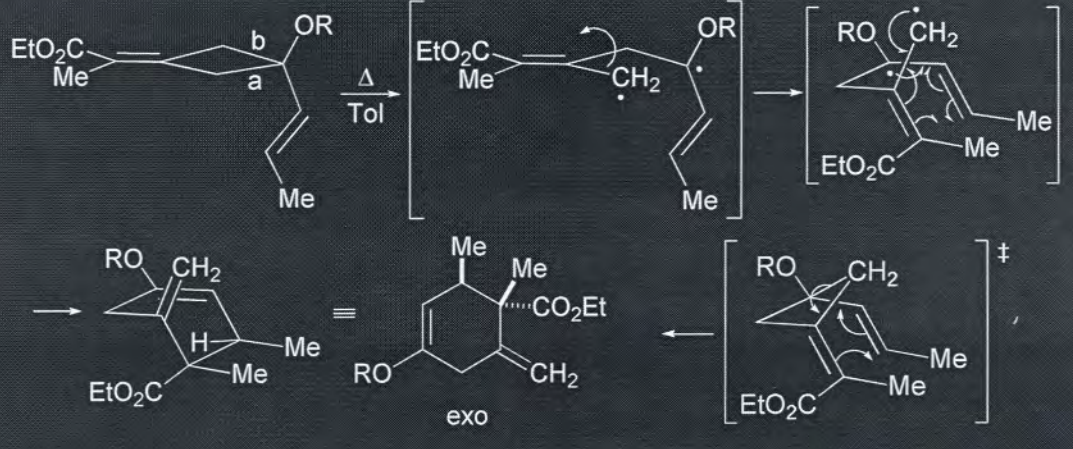
Formal [3,3]-Sigmatropic Rearrangement



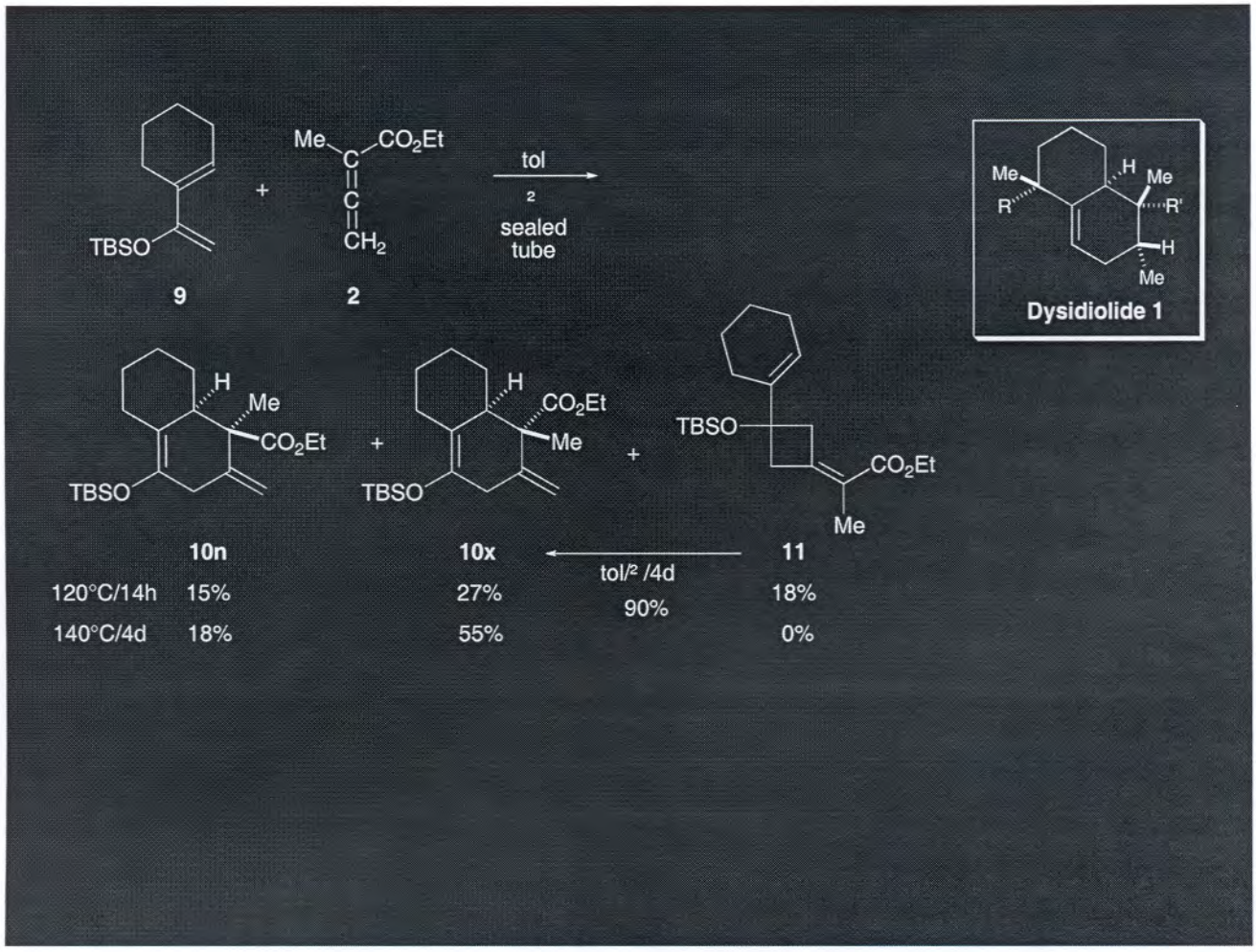
I II III

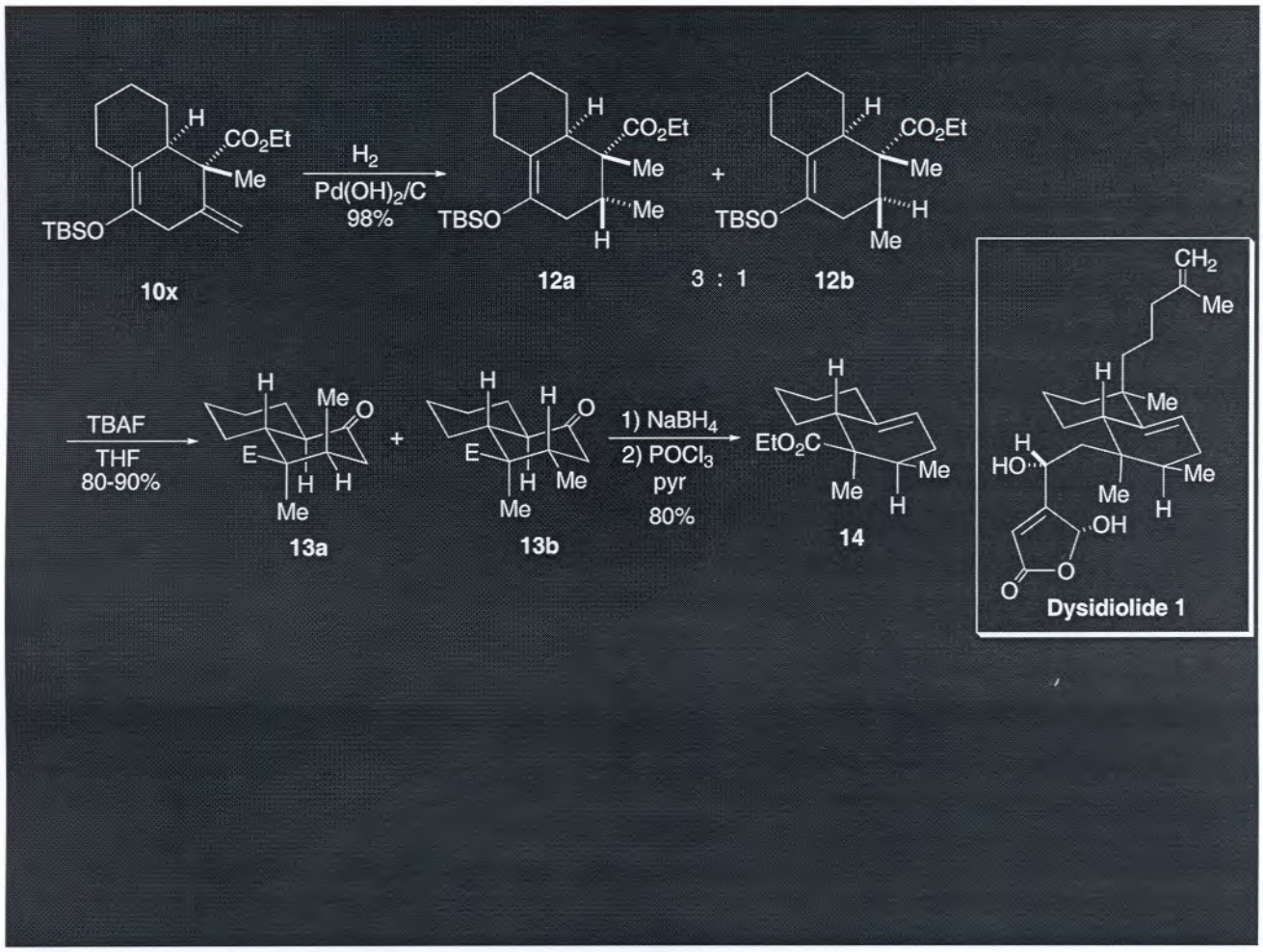
Dolbier, W. R., Jr.; *et al. Tetrahedron Lett.* **1975**, 2141. *ibid.* **1979**, 2957.

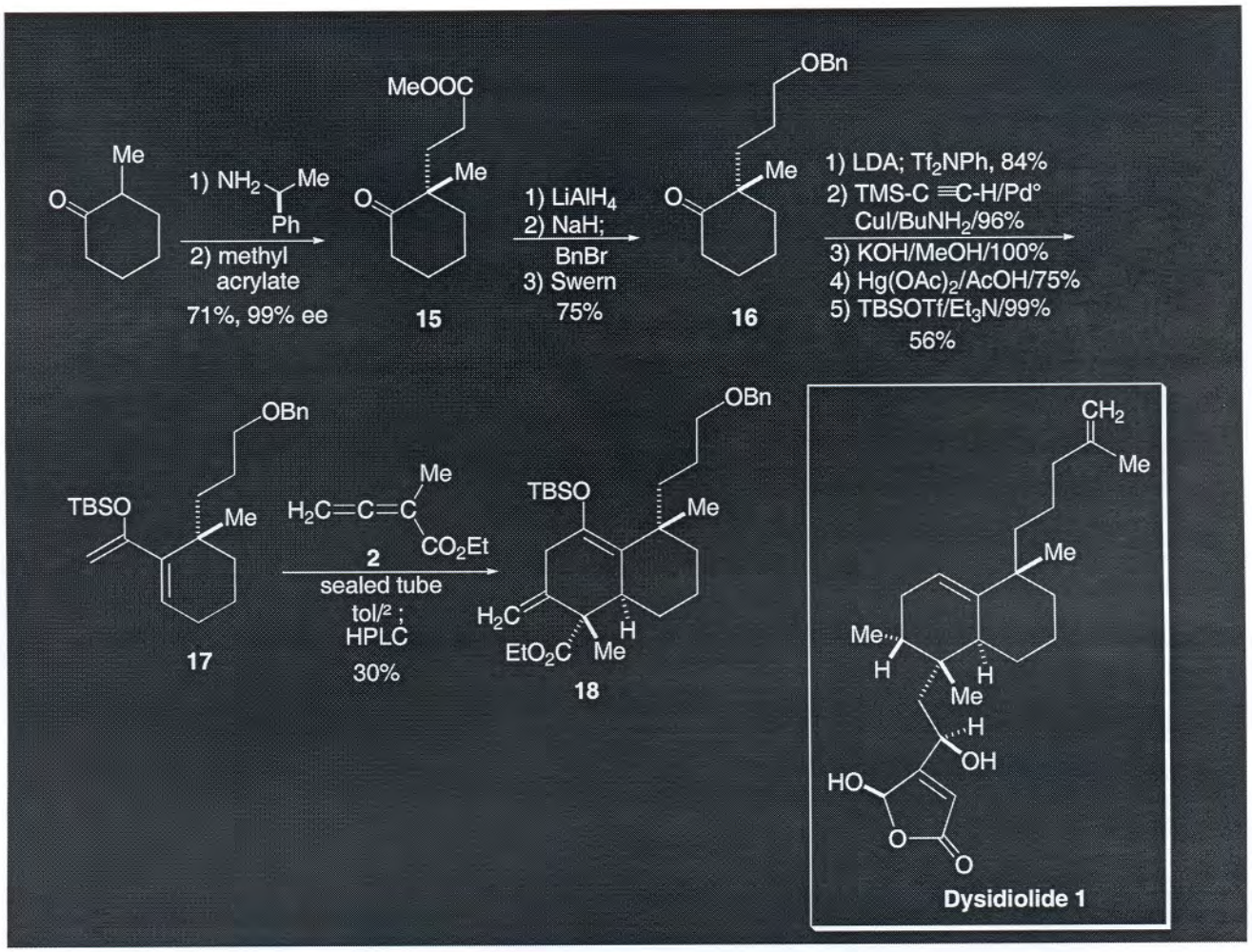
Possible Mechanism of Rearrangement

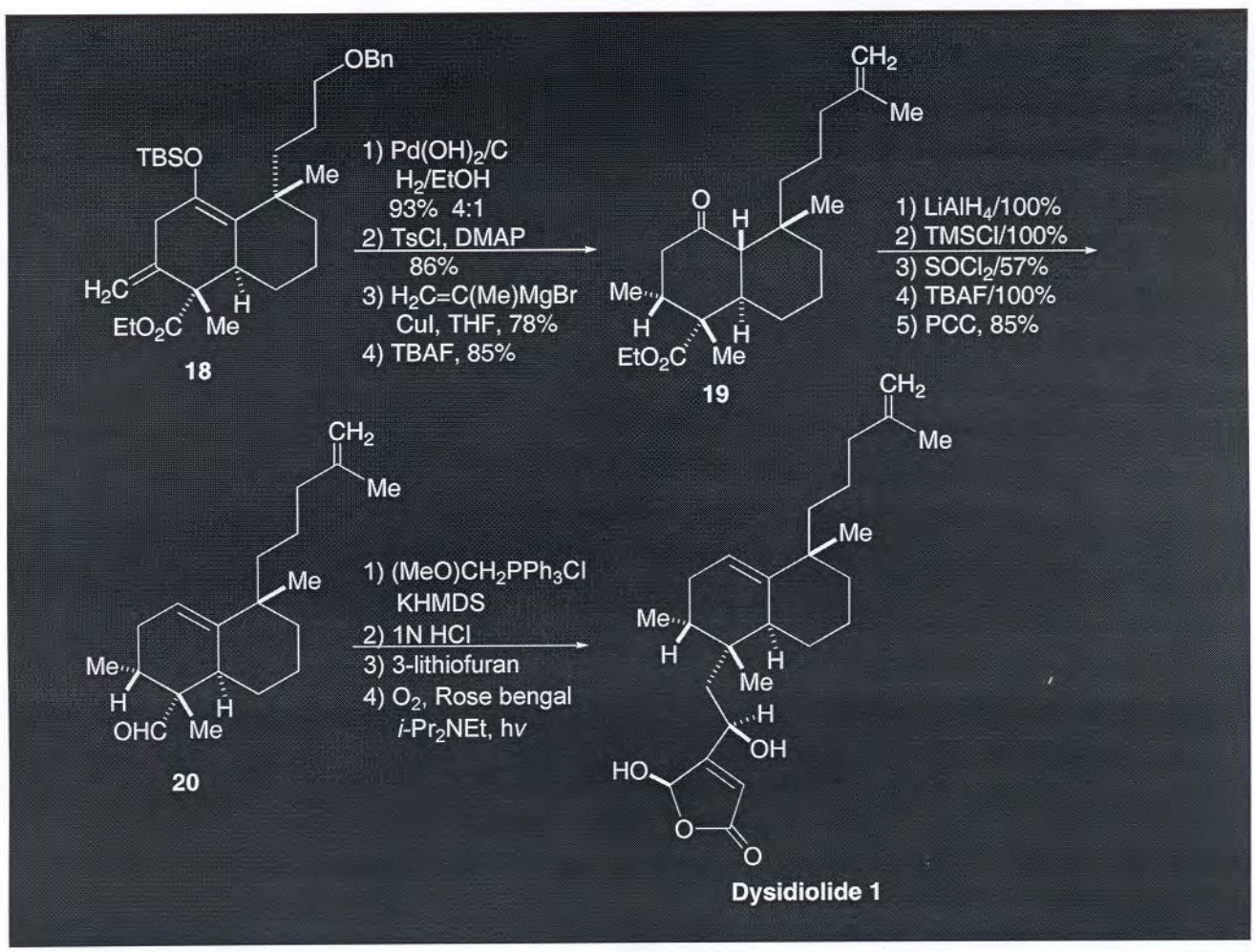


But No Effect of Radical Inhibitors so Likely it is a Concerted [3,3] Rearrangement Which Resembles a Diradical Pathway, e.g., Breaking the Bond that Gives the Best Diradical

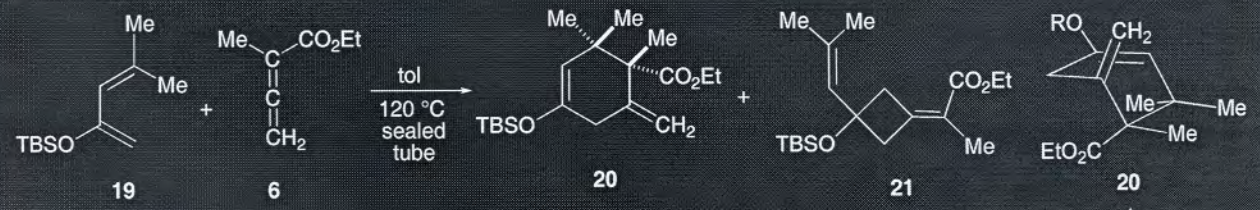

TBSO
9
Me
CO2Et
C
C
CH2
2
tol
2
sealed
tube
Dysidiolide 1
10n
10x
11
120°C/14h 15%
140°C/4d 18%
27%
55%
tol/2 /4d
90%
18%
0%


10x
H2
Pd(OH)2/C
98%
12a
3 : 1
12b
TBAF
THF
80-90%
13a
13b
1) NaBH4
2) POCl3
pyr
80%
14
Dysidiolide 1


1) NH2 Me Ph
2) methyl acrylate
71%, 99% ee
15
1) LiAlH4
2) NaH; BnBr
3) Swern
75%
16
1) LDA; Tf2NPh, 84%
2) TMS-C ≡C-H/Pd° CuI/BuNH2/96%
3) KOH/MeOH/100%
4) Hg(OAc)2/AcOH/75%
5) TBSOTf/Et3N/99%
56%
17
2
sealed tube
tol/² ; HPLC
30%
18
Dysidiolide 1

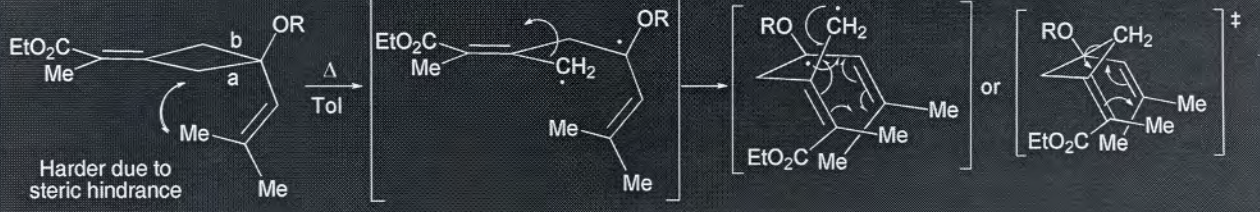

18
1) Pd(OH)2/C H2/EtOH 93% 4:1
2) TsCl, DMAP 86%
3) H2C=C(Me)MgBr CuI, THF, 78%
4) TBAF, 85%
19
1) LiAlH4/100%
2) TMSCl/100%
3) SOCl2/57%
4) TBAF/100%
5) PCC, 85%
20
1) (MeO)CH2PPh3Cl KHMDS
2) 1N HCl
3) 3-lithiofuran
4) O2, Rose bengal i-Pr2NEt, hv
Dysidiolide 1

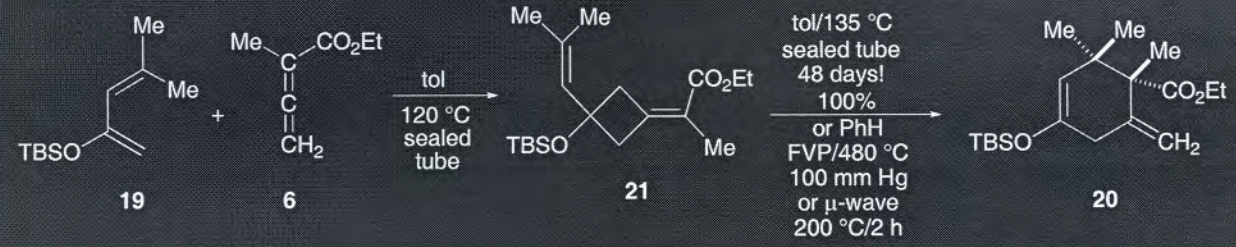
Possible Formation of Contiguous Quaternary Centers in Cyclohexenes via Cycloaddition



19 6 20 21 20

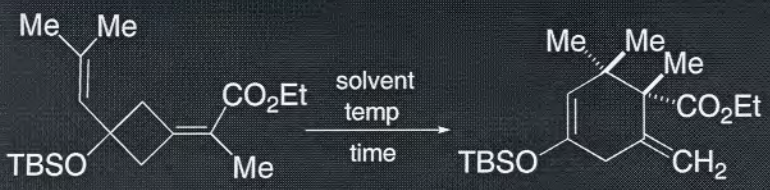
Via this Possible Mechanism



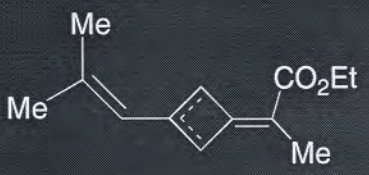


19 6 21 20

Solvent Effect on Rearrangement

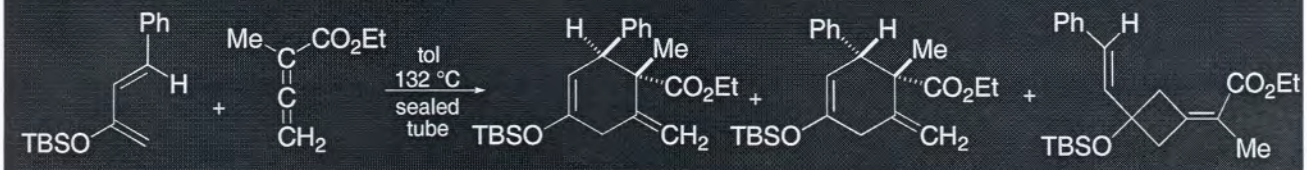


Toluene-d_8	135 °C	48 days	quant.
Acetonitrile	131 °C	27 days	not observed
DMSO	131 °C	7 days	elimination
DMF	131 °C	9 days	elimination
Chlorobenzene	133 °C	10 days	quant.
m-Dichlorobenzene	133 °C	10 days	quant.
THF	133 °C	10 days	quant.



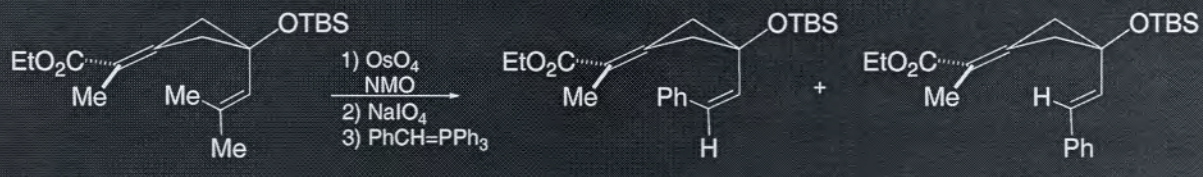
Thus, Polar Solvents Accelerate the Rate but only Slightly, e.g., by a Factor of 5 or so!
This Lends Evidence to the Mechanism Not being Zwitterionic but Rather Concerted.

A Phenyl Substitutent on the Diene Speeds up the Rearrangement

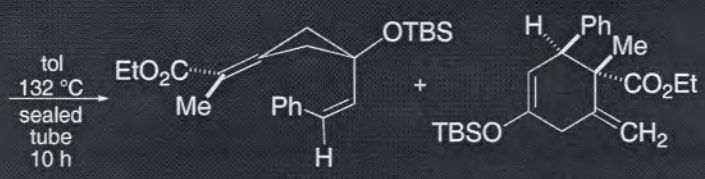


22 **6** **23x** **23n** **24**

5 h	15%	5%	56%
18 h	55%	18%	0%

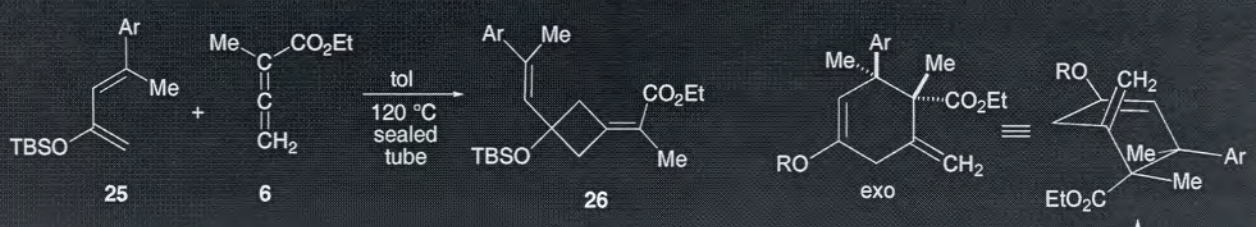


21 **24*Z*** 4 : 1 **24*E***



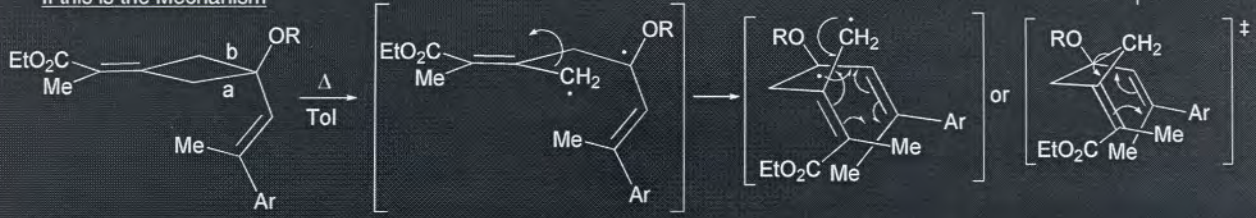
24*Z* 4 : 1 **23x**

Could one Achieve Useful Diastereoselectivity in Making 2 Contiguous Quaternary Centers?

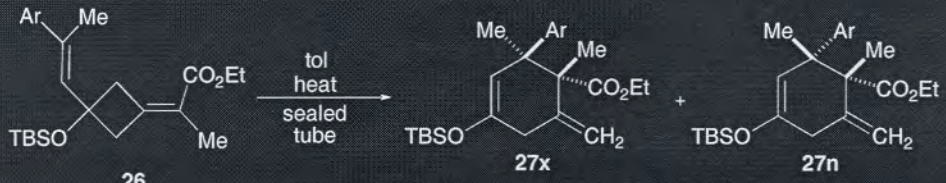


25 **6** **26**

If this is the Mechanism



Result!

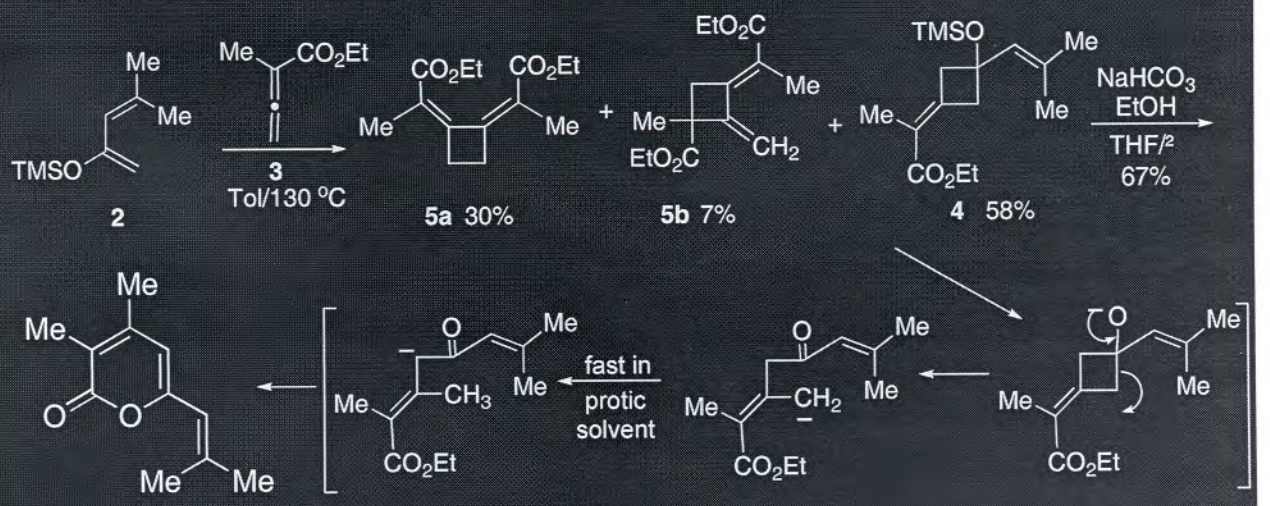


26 **27x** **27n**

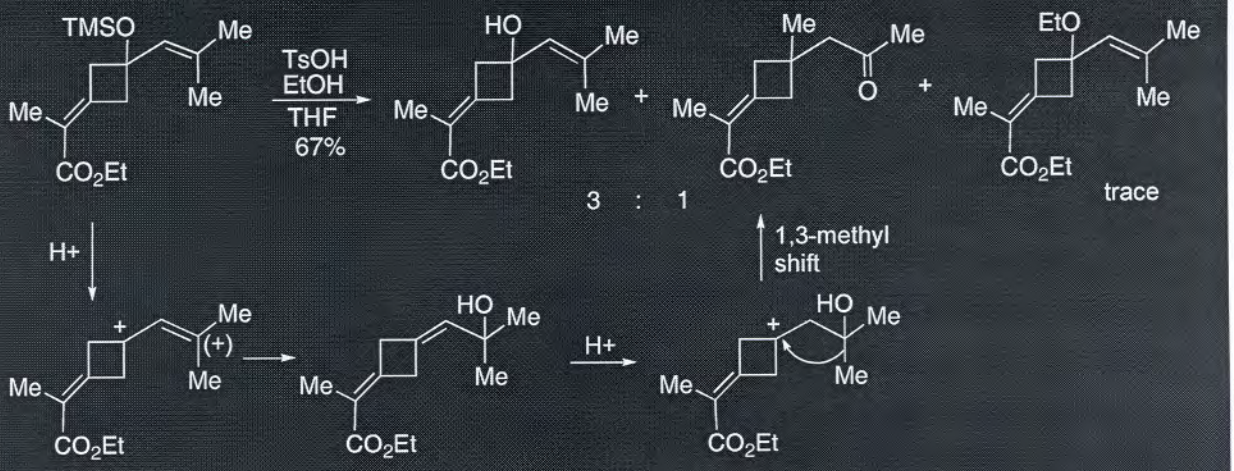
12 days/135-8 °C	Ar = Ph	1 : 1
17 days/127-9 °C	Ar = p-OMePh	1.9 : 1
17 days/120-8 °C	Ar = p-NO_2Ph	2 : 1

This May Imply that Both Bonds a and b Break at Similar Rates, Giving Rise to Both Exo and Endo Products, or that the Allylic-benzylic Radical can Undergo Some Scrambling!

Try to Accelerate Reaction by Using a Strongly Electron-Donating Group, e.g., OH

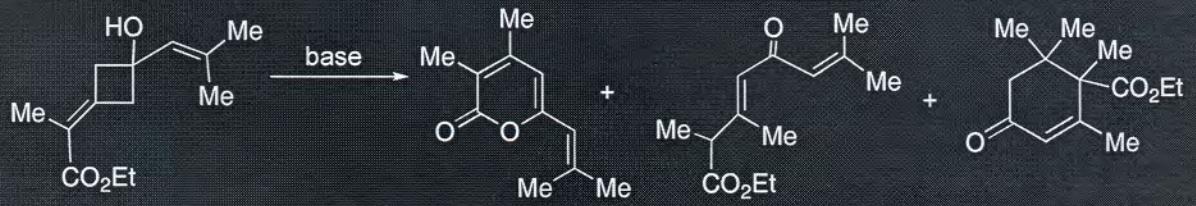


Unusual Result when Trying to Use Acidic Conditions to Generate the OH

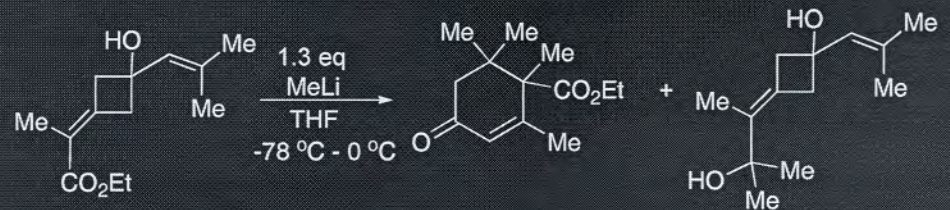


This is One of Only Two Reported Examples of a 1,3-Methyl Shift in a Carbocationic Rearrangement, the Other Being Due to Gault, et al., *J. Am. Chem. Soc.* **1976**, *98*, 7690.

After Some Problems, Finally Success

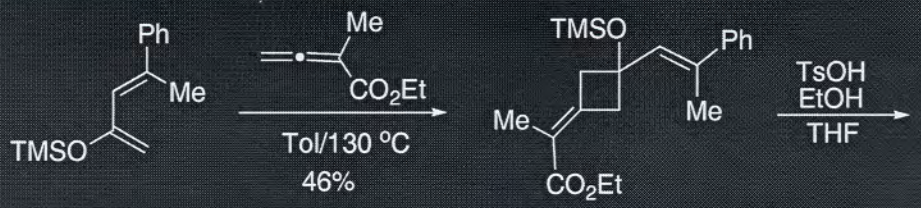


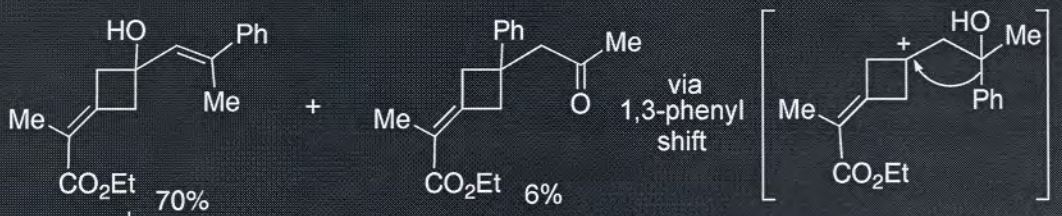
NaH/THF			
$NaH/ZnCl_2$ or $NaH/MgCl_2$	5-8	1	
tBuLi	1	1	1
LDA	1	3	2

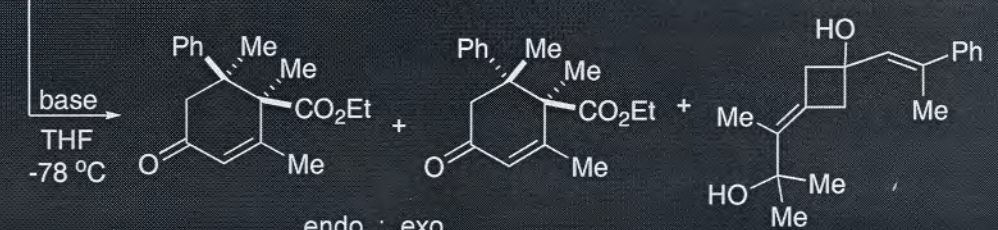


5 : 1

But Different Diastereoselectivity!

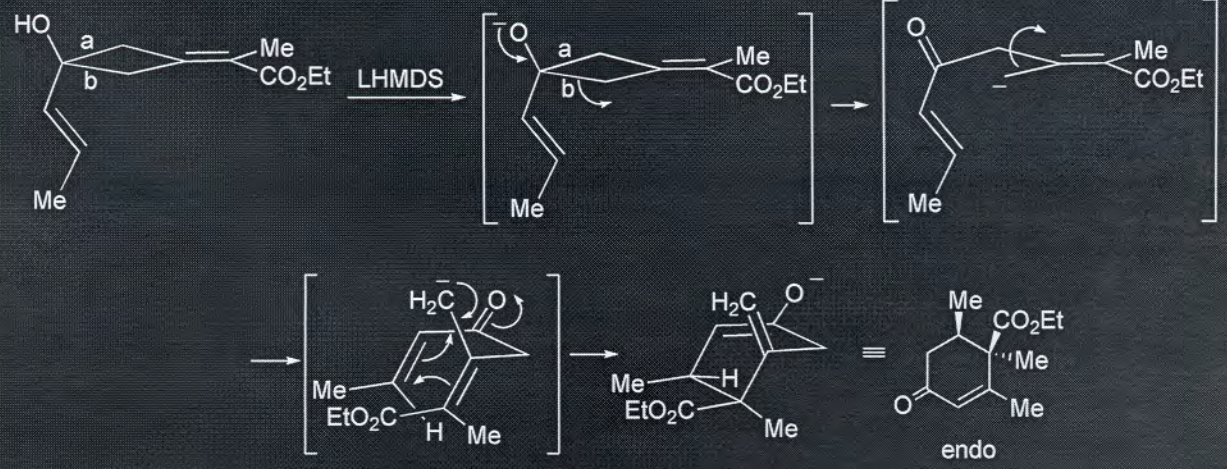


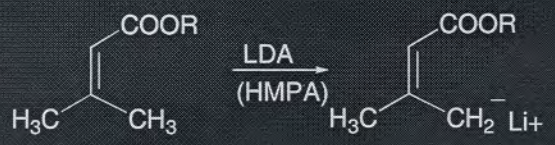




	endo : exo
1.3 eq MeLi	8 : 1
1.5 eq MeLi	15 : 1
LiHMDS	>25 : 1

Possible Mechanism for Anionic Rearrangement



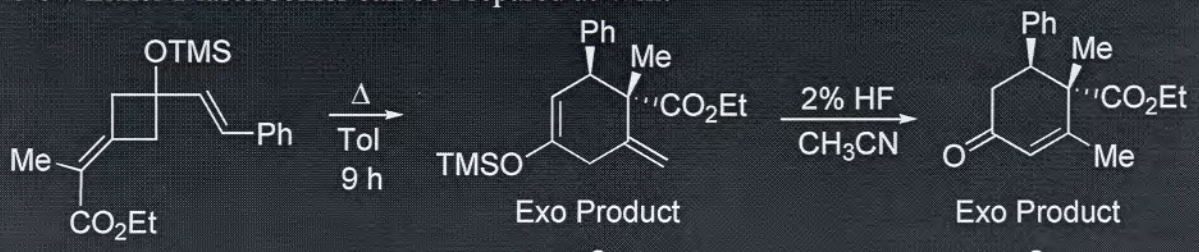


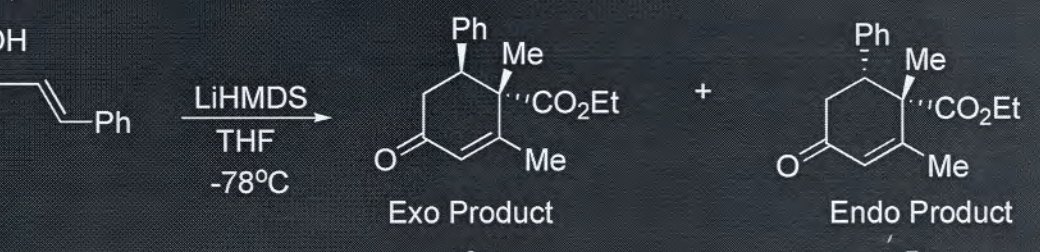
R = Me, anion

proved by deuterium labelling

Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1985**, *26*, 1939; **1984**, *25*, 1333.

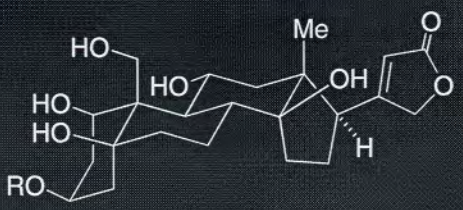
Now Either Diastereomer can be Prepared at Will!





Ratio 1 : 4

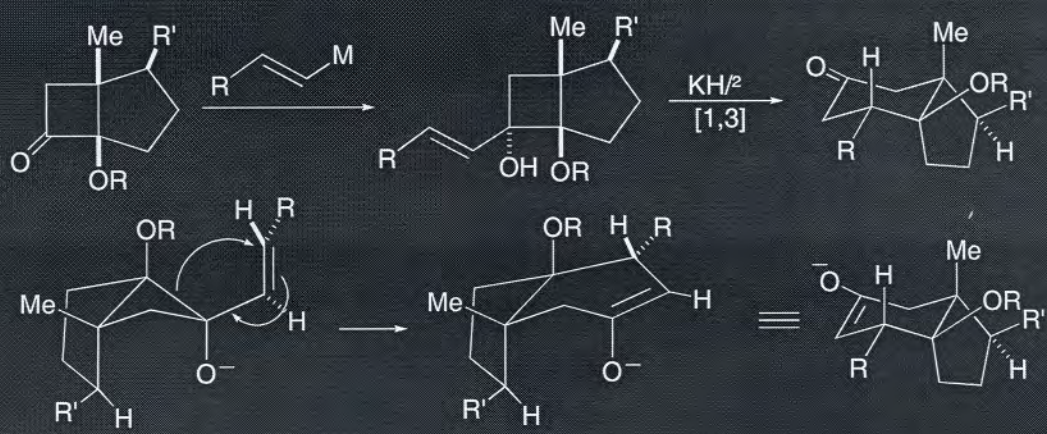
Aaron Novack, unpublished results

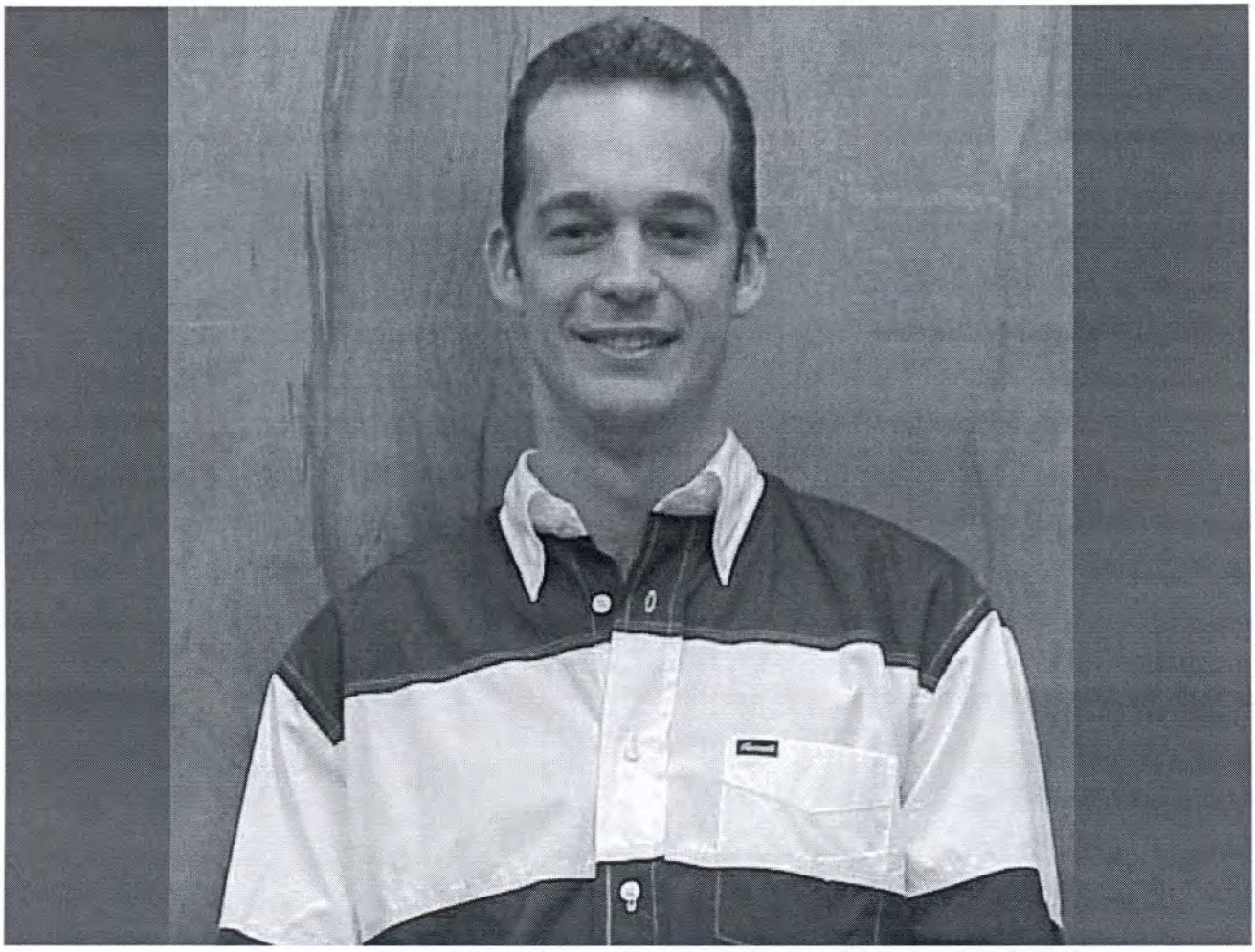


Ouabain 1 (R = Rhamnose)
Ouabagenin (R = H)

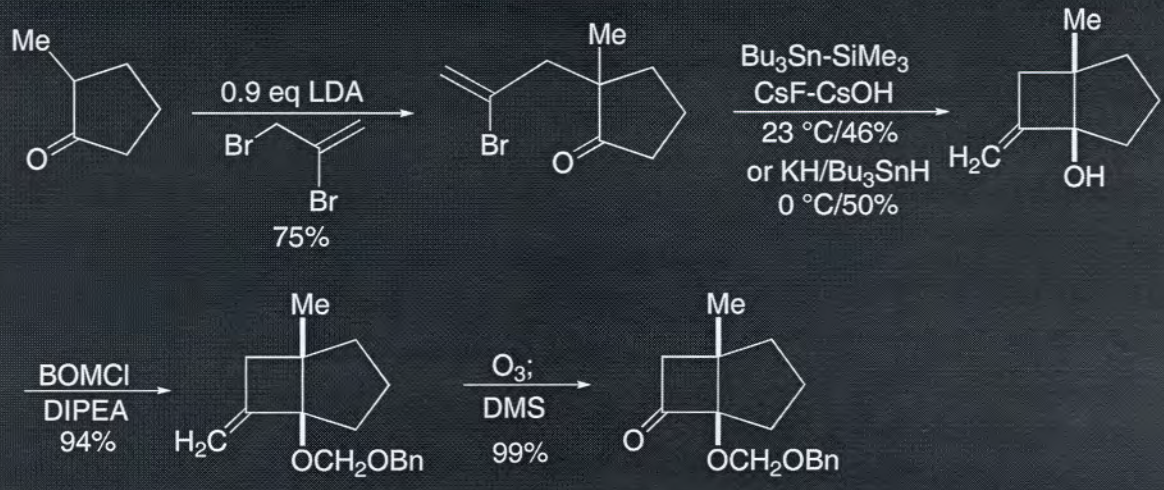
Cardiotonic Steroids Used in Treatment of Congestive Heart Failure (CHF)

Possible Synthetic Strategy for CD Rings

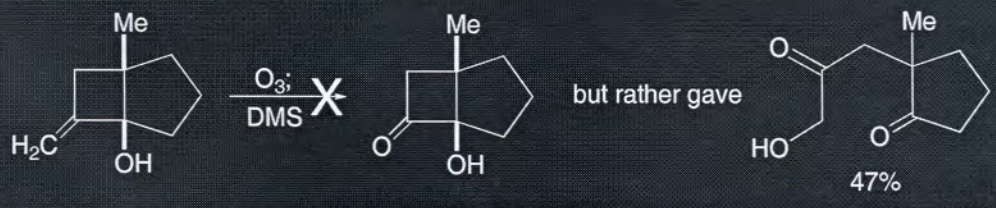




Preparation of 5-Alkoxybicyclo[3.2.0]heptan-6-one

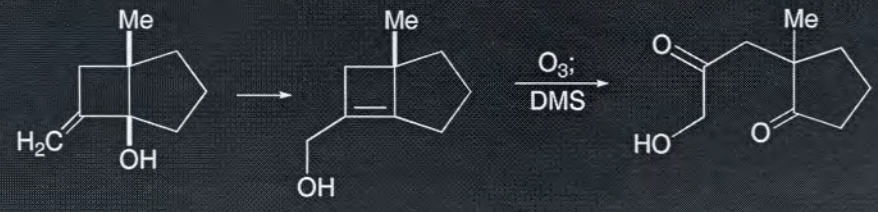


Ozonolysis of the Alcohol Led to a Novel Result!

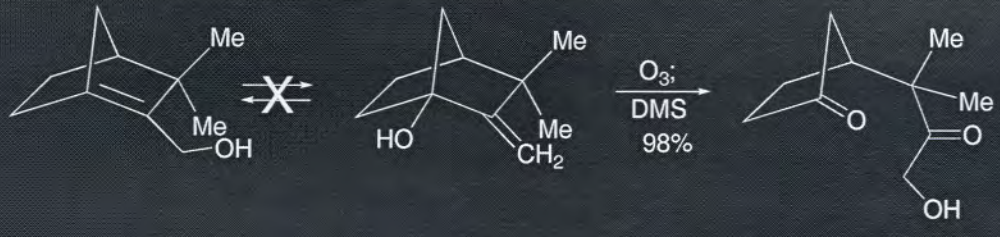


What is the Mechanism of this Unusual Transformation?

Perhaps an Allylic Rearrangement, although Unlikely, had Occurred Prior to Ozonolysis

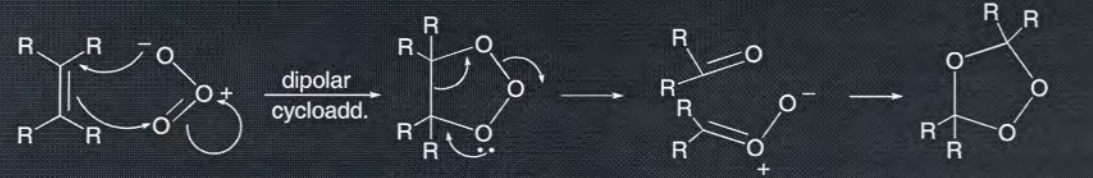


But this Pathway is Ruled Out since the Camphor Derivative Also Gave a Similar Diketone



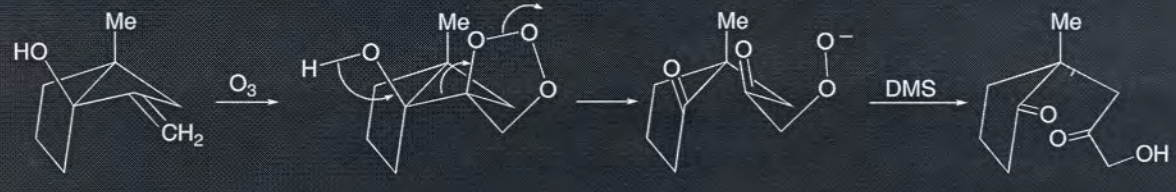
We Believe that This Result is the First Example of the Trapping of a Primary Ozonide (a 'Molozonide') During an Ozonolysis

Mechanism of Ozonolysis

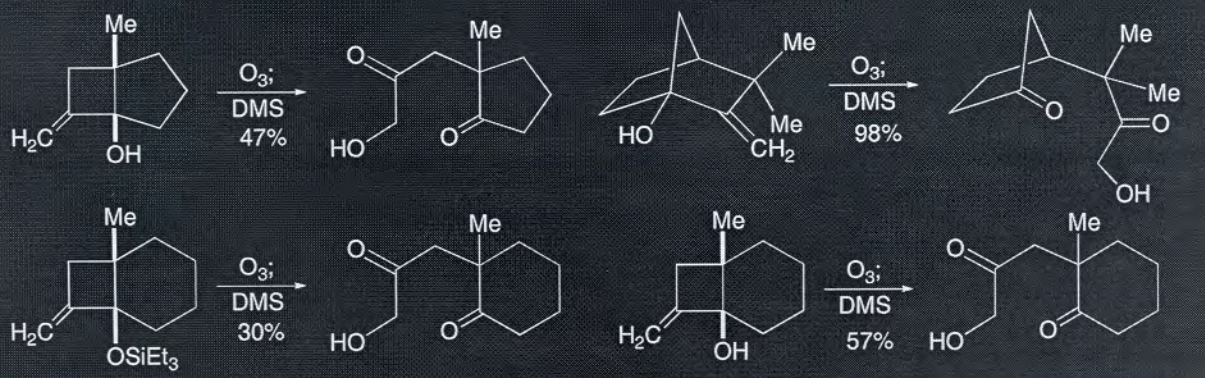


There are many examples of trapping the carbonyl oxide intermediate but none, to our knowledge, of trapping the molozonide

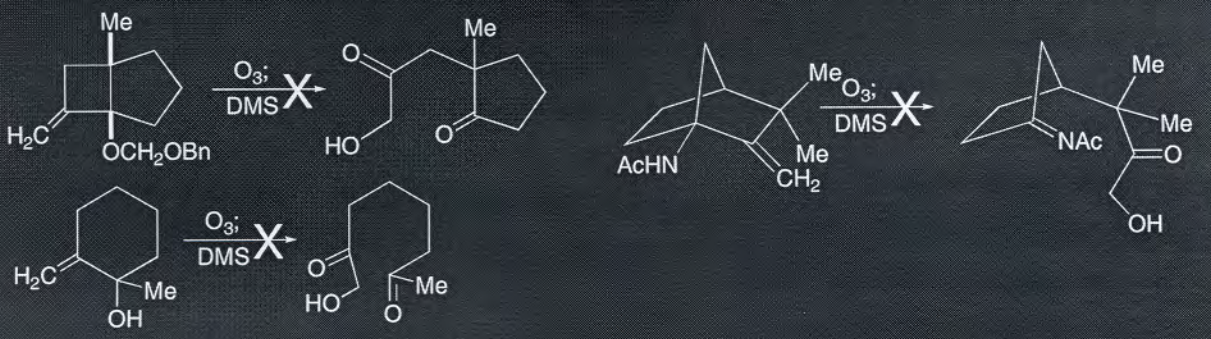
We Believe that A Grob-Type Fragmentation Occurs to Open the Strained Cyclobutane Ring with the Assitance of the Hydroxyl Group, as Shown

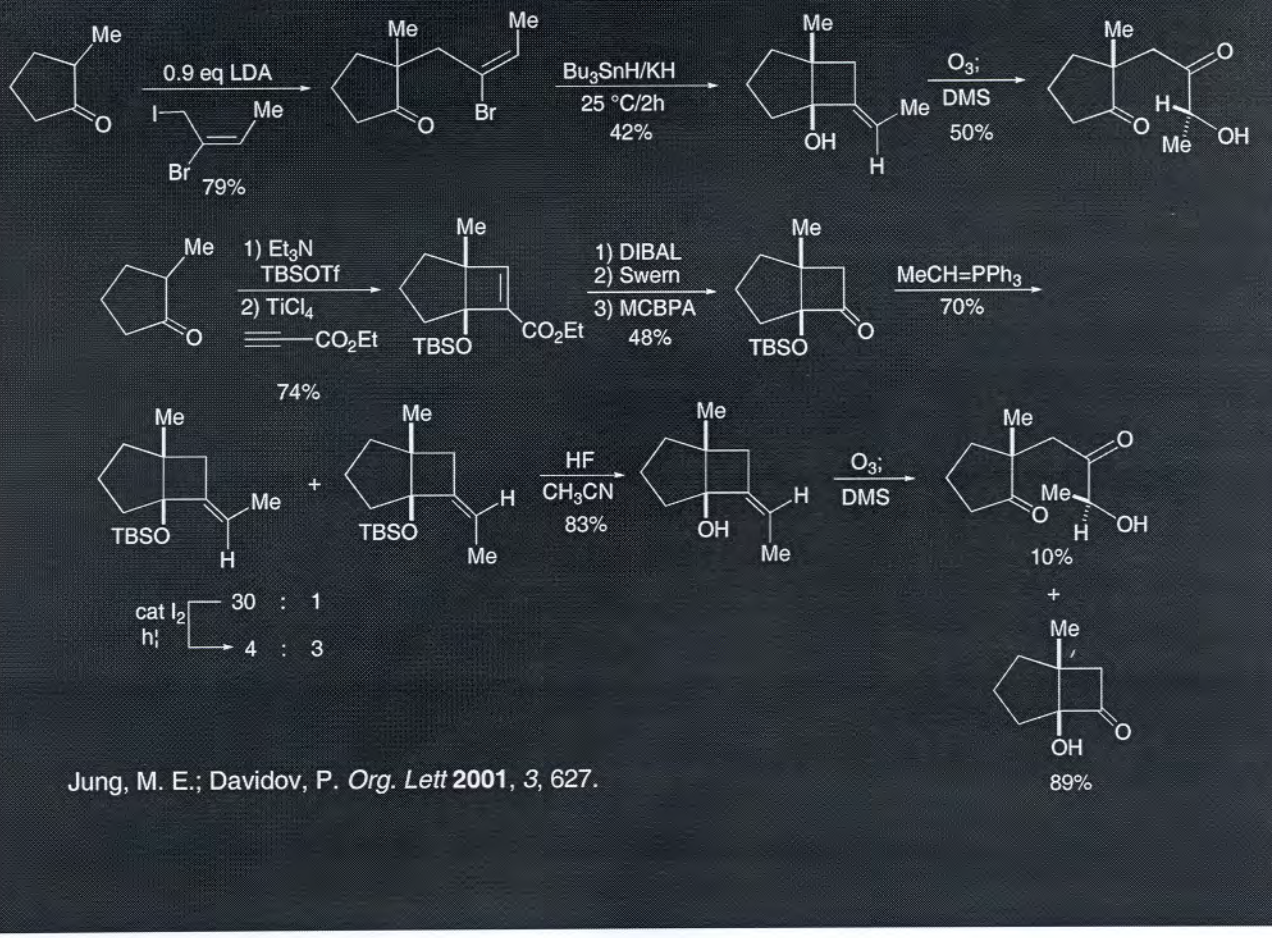


Successful Examples

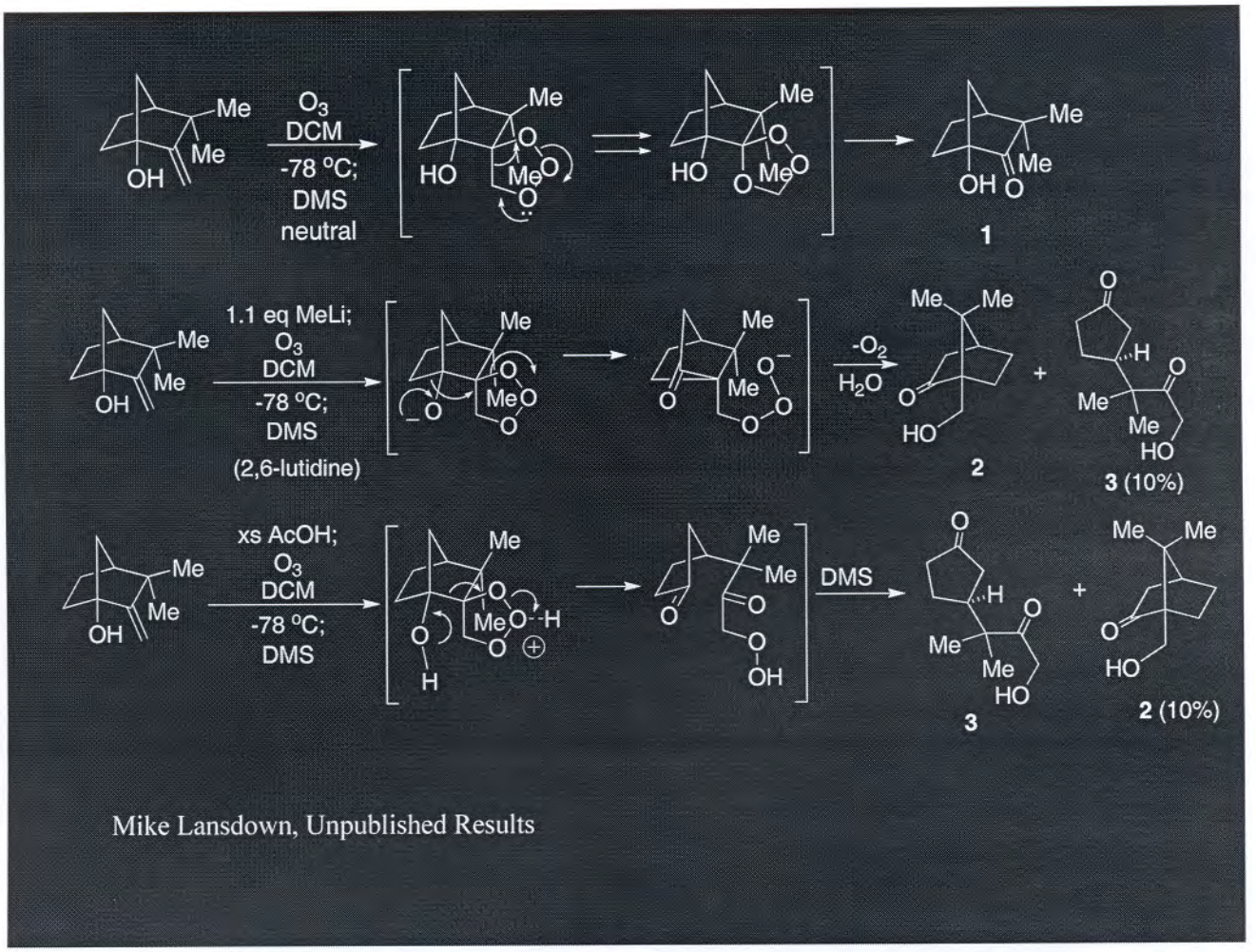


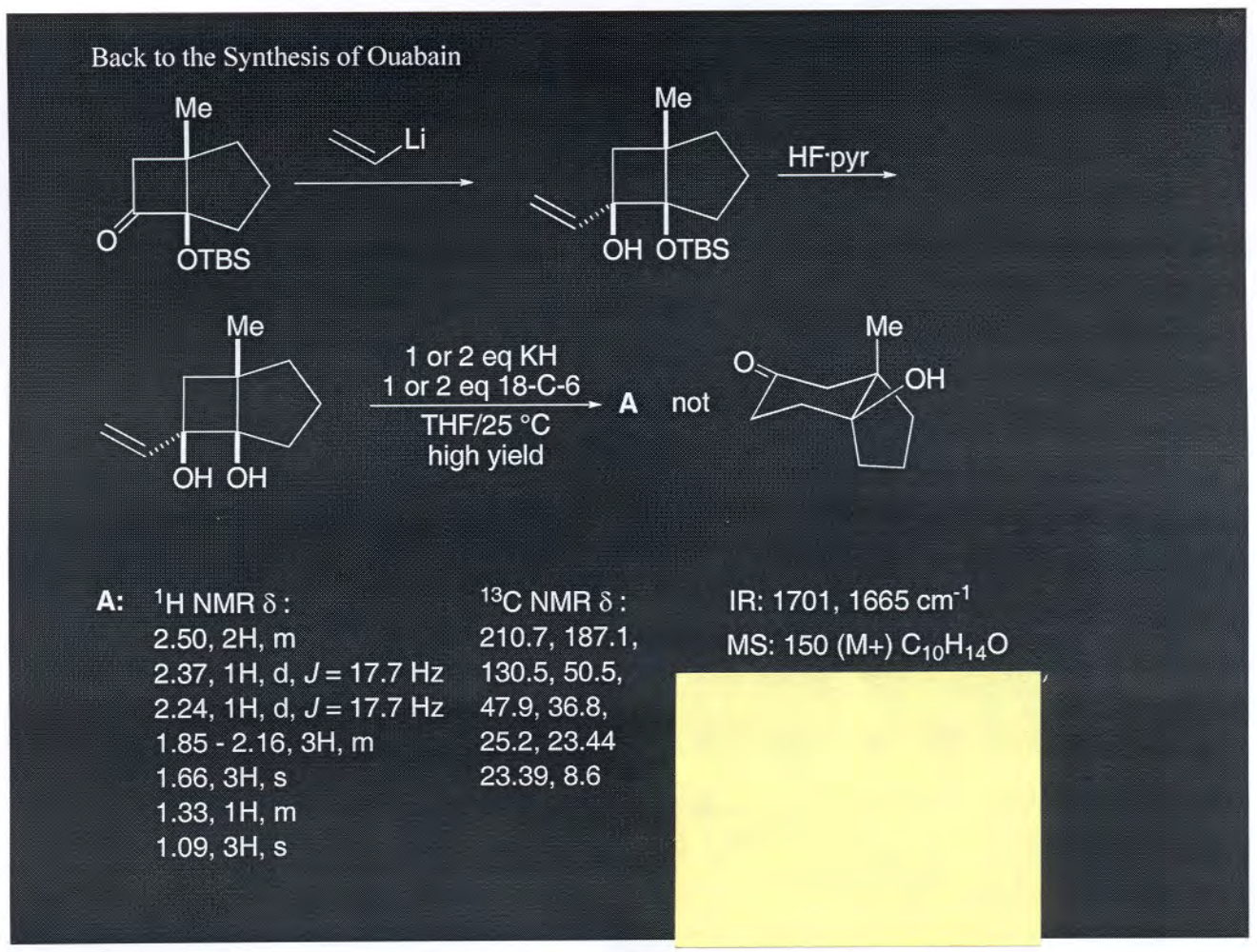
Unsuccessful Examples - One Needs A Strained Ring and Either an OH or O-Silyl for Rearrangement to Occur





Jung, M. E.; Davidov, P. *Org. Lett* **2001**, *3*, 627.



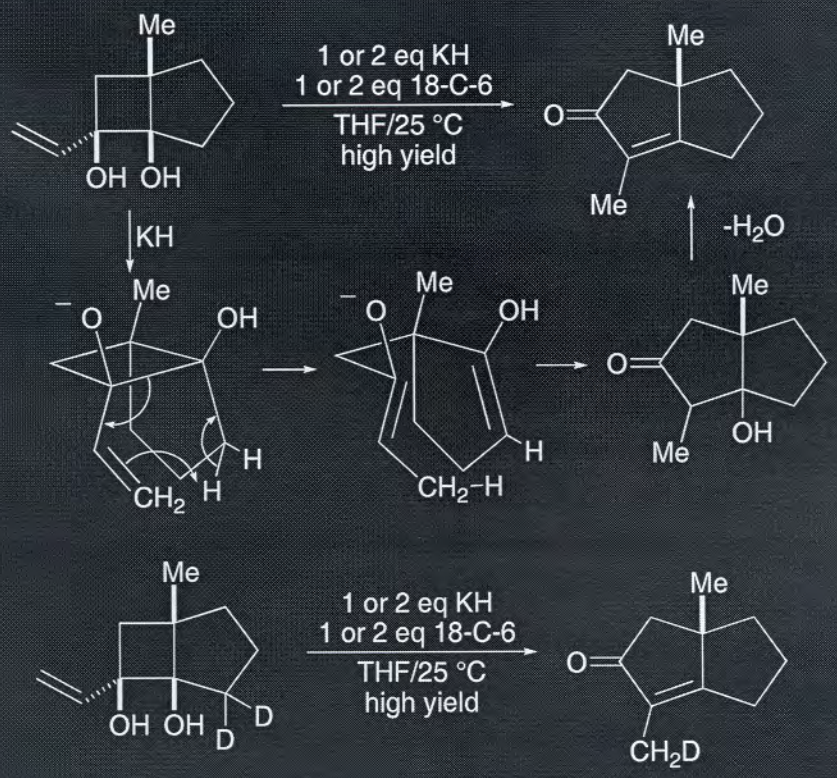


A: ^{1}H NMR δ :
2.50, 2H, m
2.37, 1H, d, *J* = 17.7 Hz
2.24, 1H, d, *J* = 17.7 Hz
1.85 - 2.16, 3H, m
1.66, 3H, s
1.33, 1H, m
1.09, 3H, s

^{13}C NMR δ :
210.7, 187.1,
130.5, 50.5,
47.9, 36.8,
25.2, 23.44
23.39, 8.6

IR: 1701, 1665 cm^{-1}
MS: 150 (M+) $C_{10}H_{14}O$

First Example of an Anion-Accelerated Retro-Ene Reaction



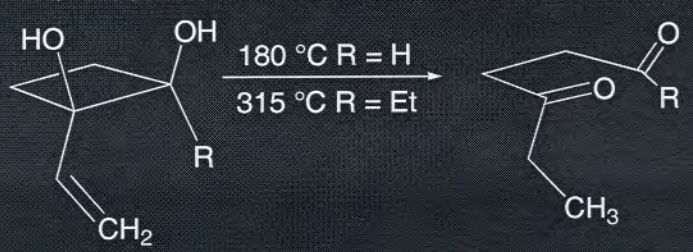
Jung, M. E.; Davidov, P. *Org. Lett* **2001**, *3*, 3025.

Retro-Ene Reactions

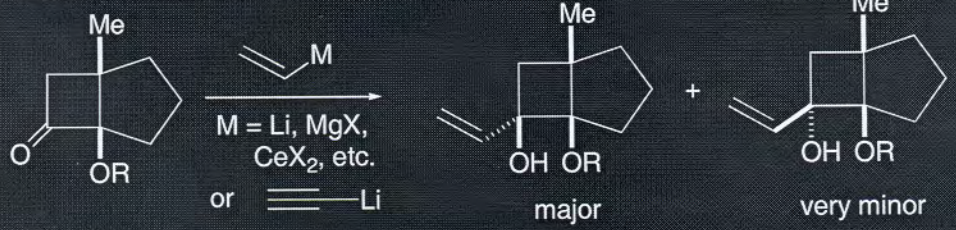
Reviews: Hoffman, H. M. R. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 556;
Paderes, G. D.; Jorgensen, W. L. *J. Org. Chem.* **1992**, *57*, 1904.

Roth, W. R.; König, J. *Liebigs Ann. Chem.* **1965**, *688*, 28.

Conia, J. M.; Barnier, J. P. *Tetrahedron Lett.* **1971**, 4981. (R = H)
Barnier, J. P.; Ollivier, J.; Salaun, J. *Tetrahedron Lett.* **1989**, *30*, 2525 (R = Et)

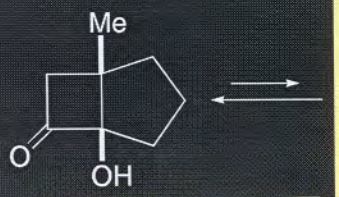


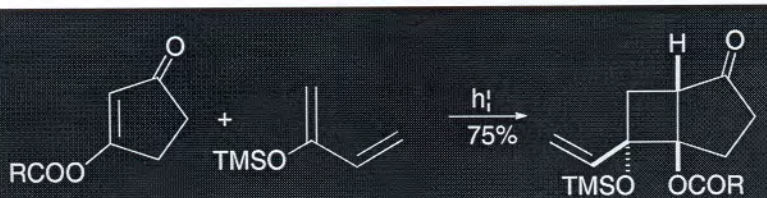
Back to the Synthesis of Ouabain



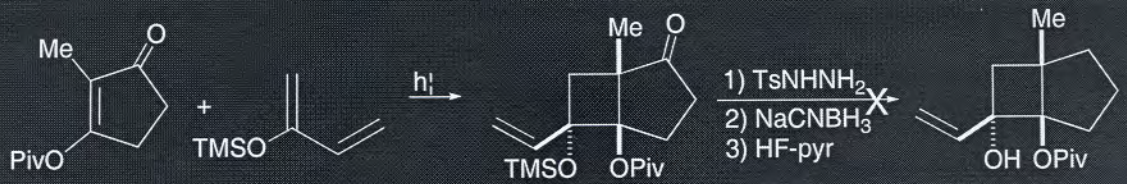
R = TBS, Piv, BOM

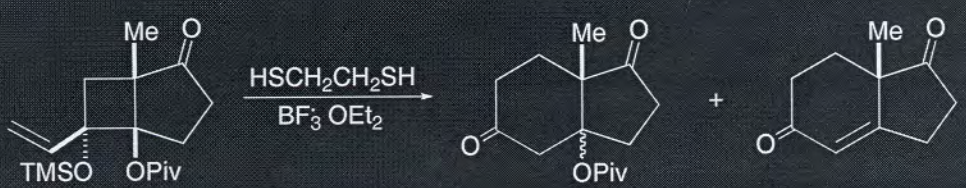
R = TBS
TBAF





Demuth, M.; et al., *Helv. Chim. Acta* **1988**, *71*, 1392

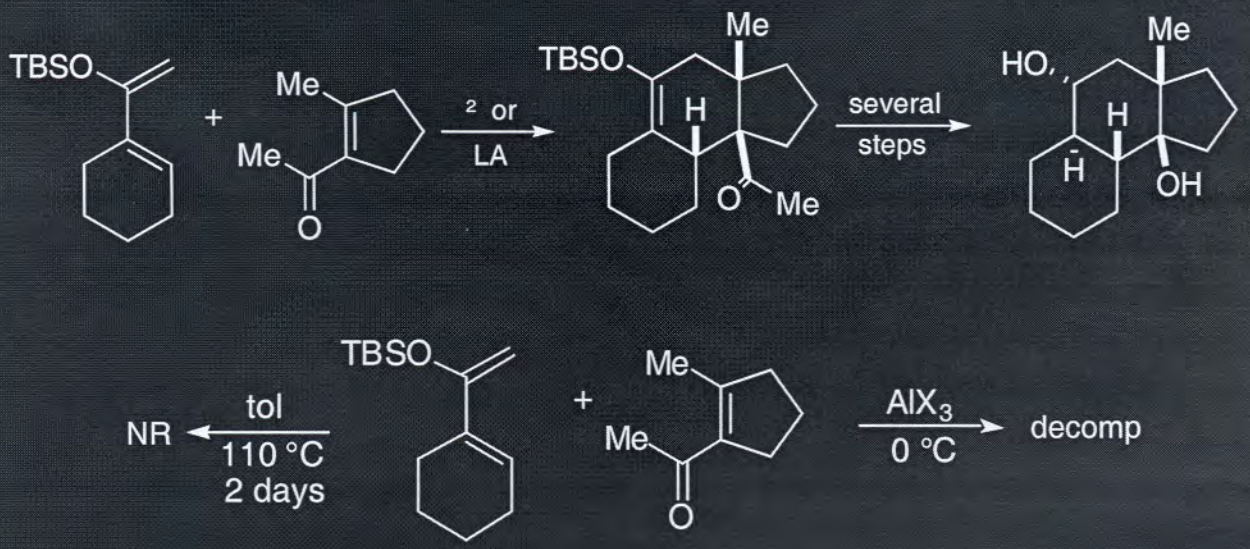




37% (3 : 2 b : a)

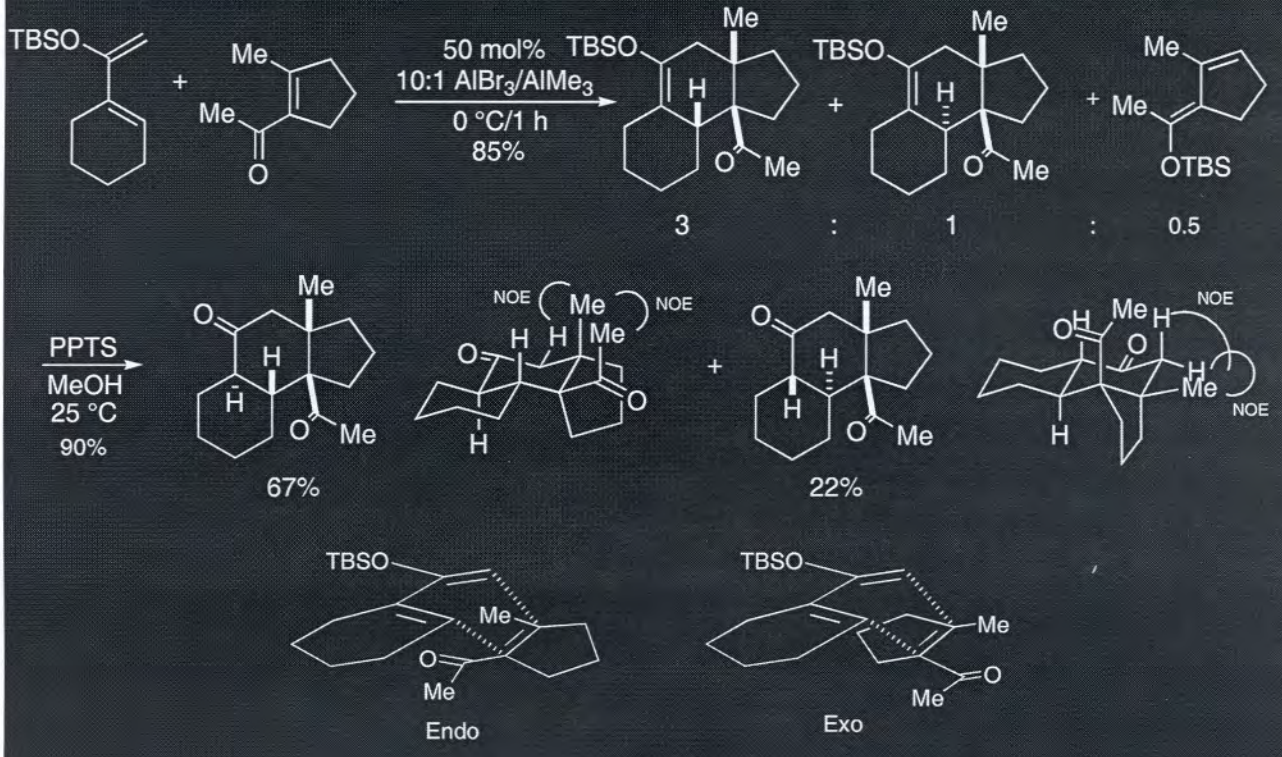
46%

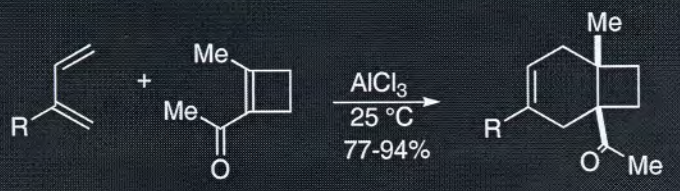
Back to the Synthesis of Ouabain



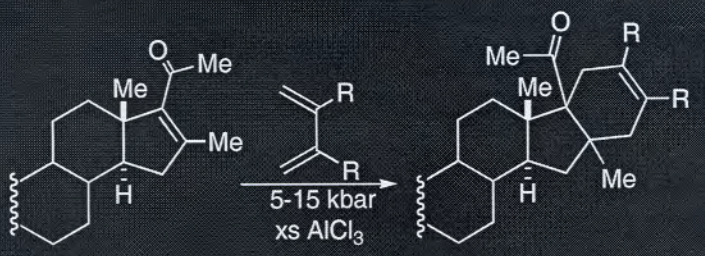
What we needed was an extremely strong Lewis acid without a trace of HX!

We decided to use a mixed Lewis acid system to guarantee the absence of HX! And it works!!!

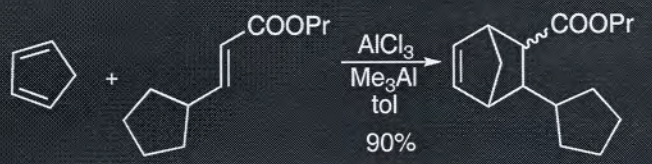




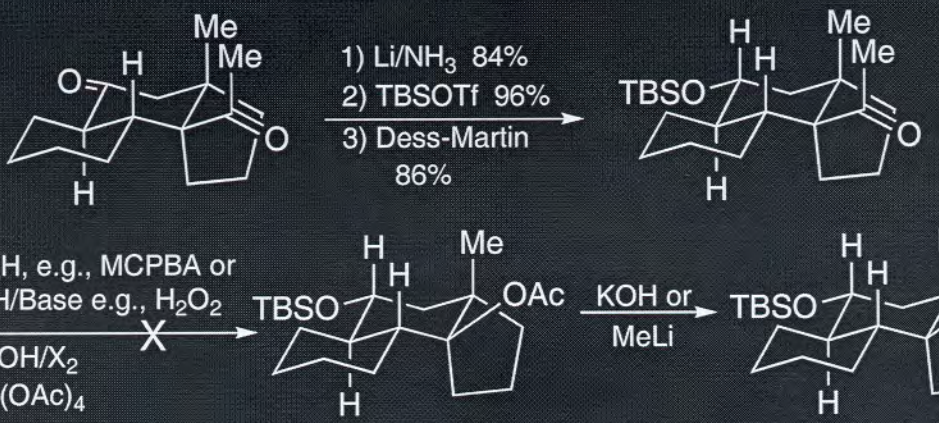
Fujiwara, T.; Ohsaka, T.; Inoue, T.; Takeda, T. *Tetrahedron Lett.* **1988**, *29*, 6283.



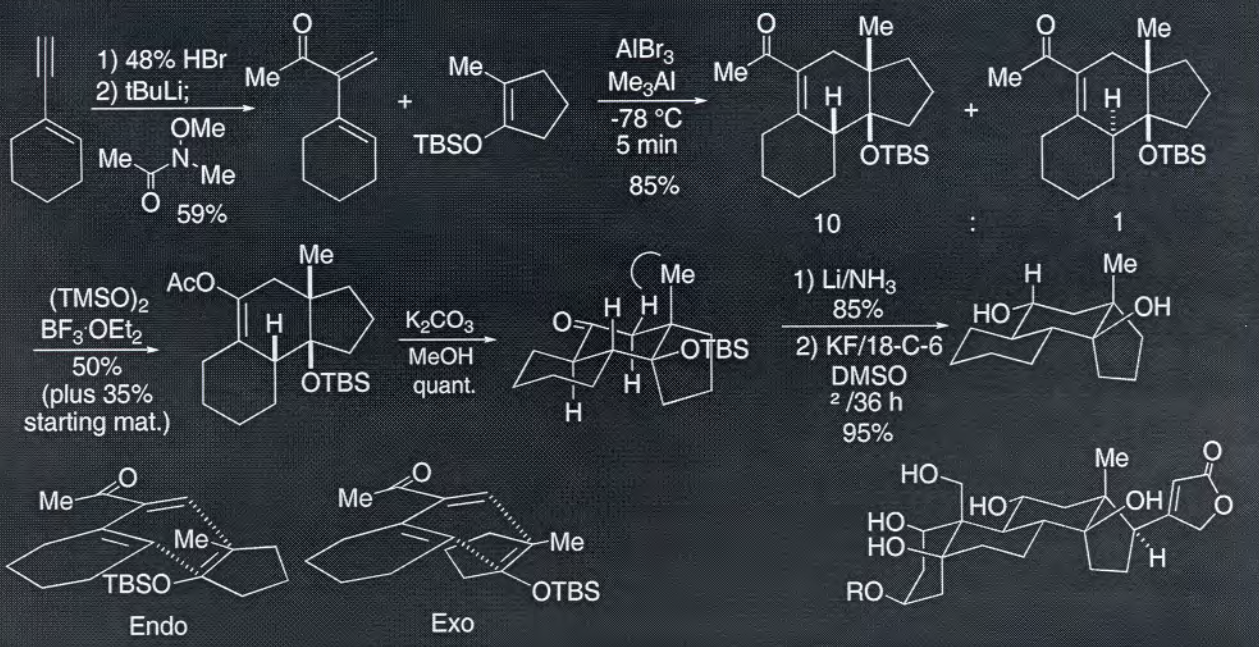
Levina, I. S.; Kulikova, L. E.; Kamernitskii, A. V.; El'yanov, B. S.; Gonikberg, E. M. *Izv. Akad. Nauk, Ser. Khim.* **1992**, 1622.



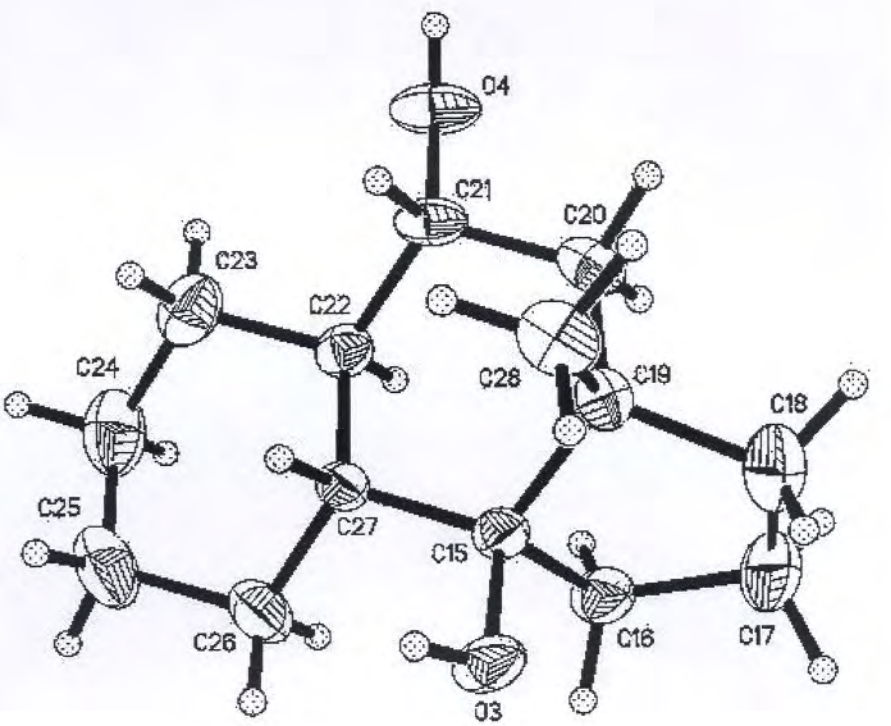
Hubbard, R. D.; Miller, B. J. *J. Org. Chem.* **1998**, *63*, 4143.



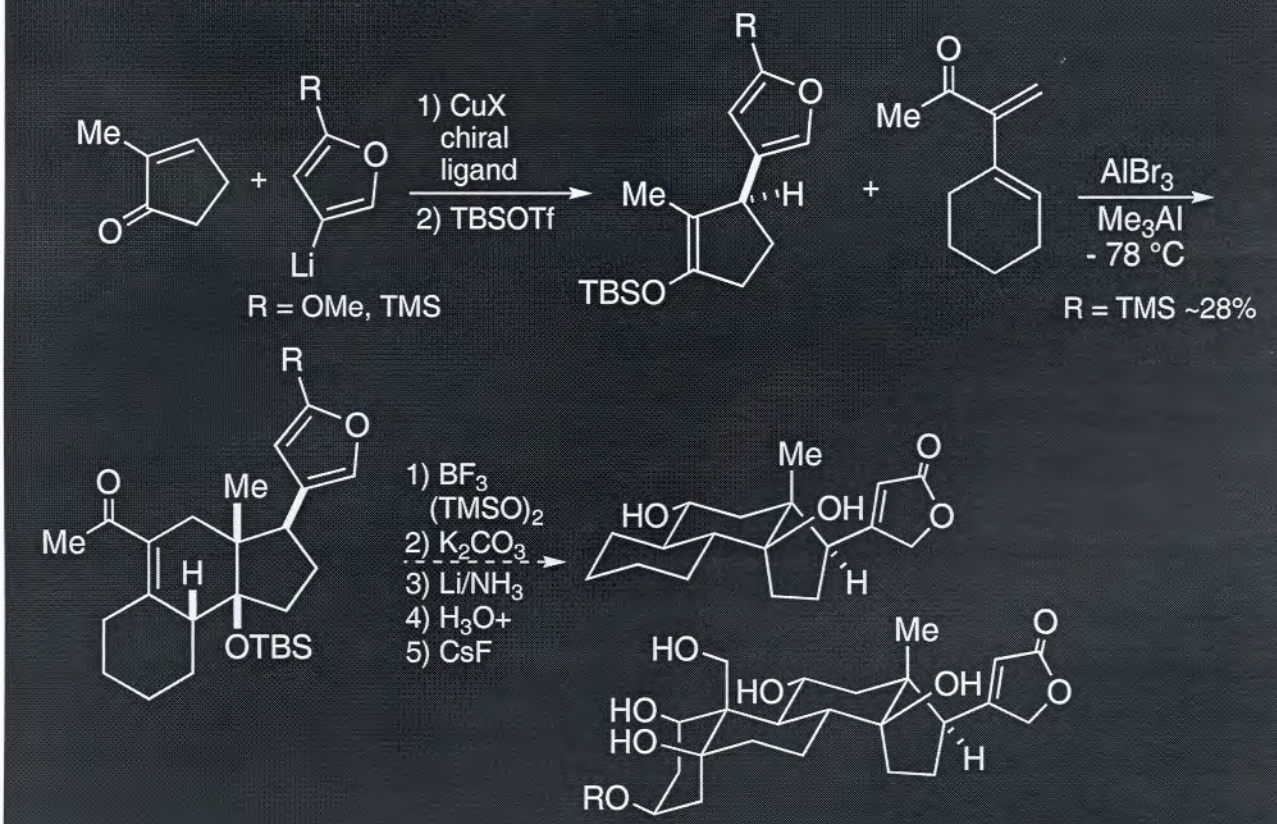
Change the substituents on the diene and dienophile, namely inverse-electron-demand Diels-Alder!



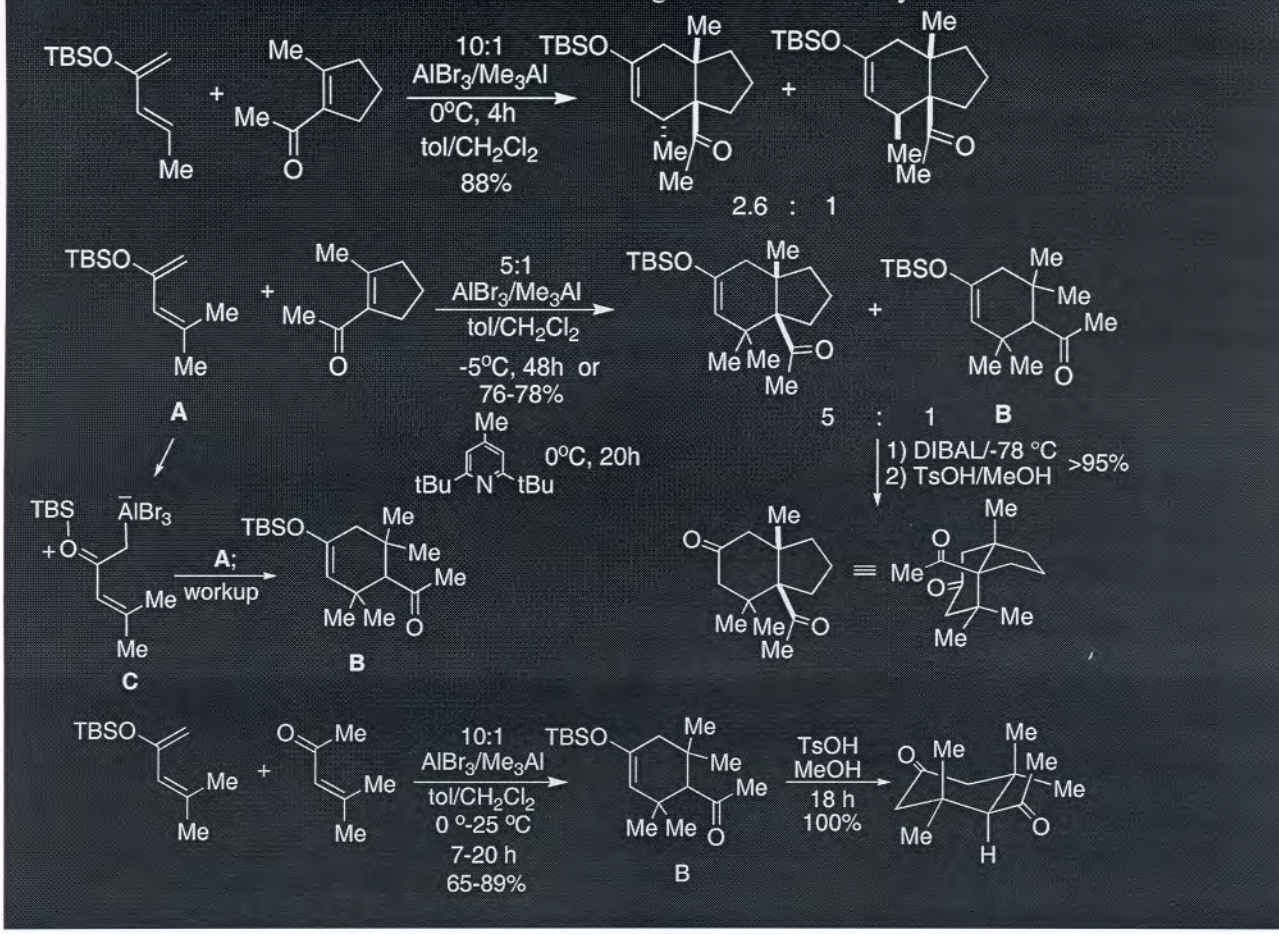
Jung, M. E.; Davidov, P. *Angew. Chem.* **2002**, *41*, 4125.

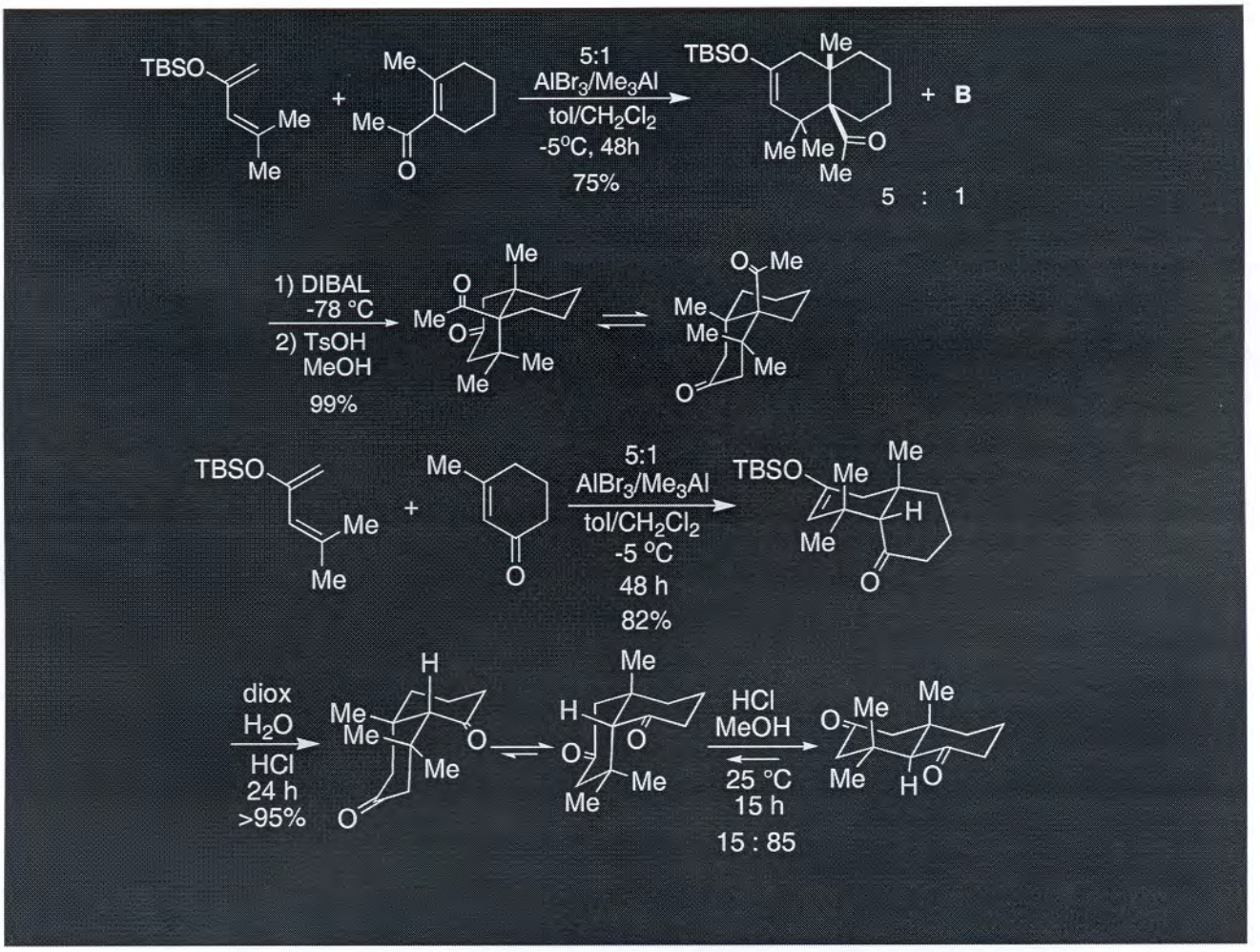


Method for introduction of the C-17 side chain butenolide

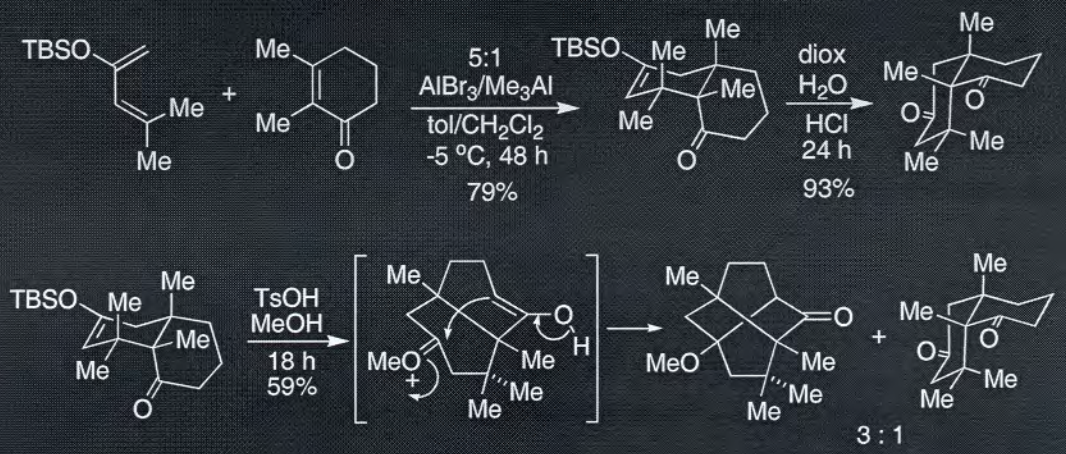


Extensions of hindered Diels-Alder reaction using mixed Lewis acid system



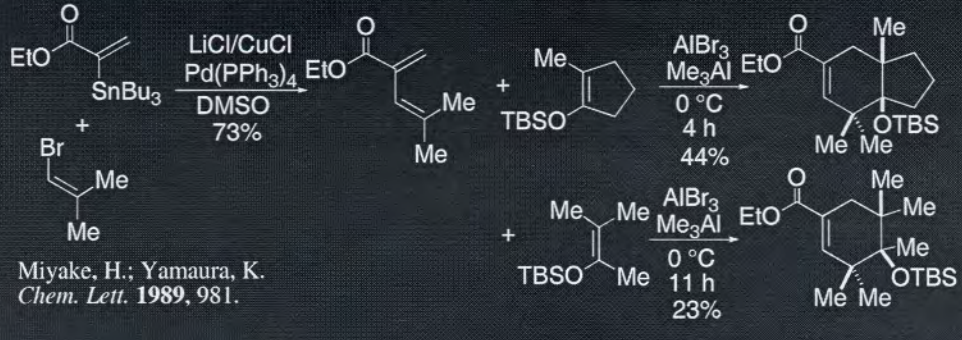


And finally the most hindered system yet!

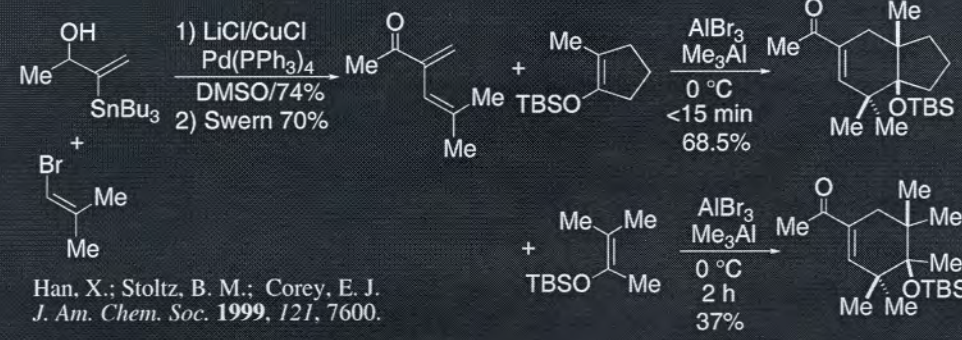


David Ho, unpublished results

Inverse-Electron-Demand Diels-Alder Reactions



Miyake, H.; Yamaura, K.
Chem. Lett. **1989**, 981.



Han, X.; Stoltz, B. M.; Corey, E. J.
J. Am. Chem. Soc. **1999**, *121*, 7600.

Hiufung Chu, unpublished results

ACKNOWLEDGEMENTS

Hands and Minds

Current Coworkers

Robert Tinder
Hisham Eissa
Sun-Joon Min
Brian Duclos
Aaron Novack
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Jamie Im
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Samedy Ouk
Andreas Maderna
Wan-Joong Kim
Yuichi Fukuda
Dawei Yue
Jeremy Clemens
Mike Lansdown
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Satoshi Kobayashi
Kentoku Gotanda
Franck Slowinski
Jean-Marie Contreras
Mehrak Kiankarimi
Ted Johnson

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Rudy Marquez
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Grazia Piizzi
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Erich Wohlhieter
Masayoshi Fukuoka
Nobuko Nishimura
Adrian Huang
Joseph Pontillo
Tsvetelina Lazarova
Daqing Sun
Woo Song Lee

Dollars and Cents

National Institutes of Health
National Science Foundation
University of California AIDS Research Program
UCLA Gold Shield Faculty Prize
Susan Komen Breast Cancer Fund
Prostate Cancer Foundation (CaP CURE) and SPORE Program

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Rohm & Haas
Sankyo
Boehringer Ingelheim
Neurocrine Biosciences