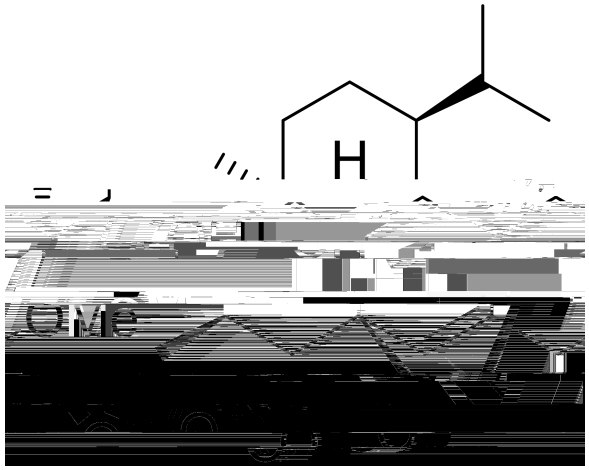
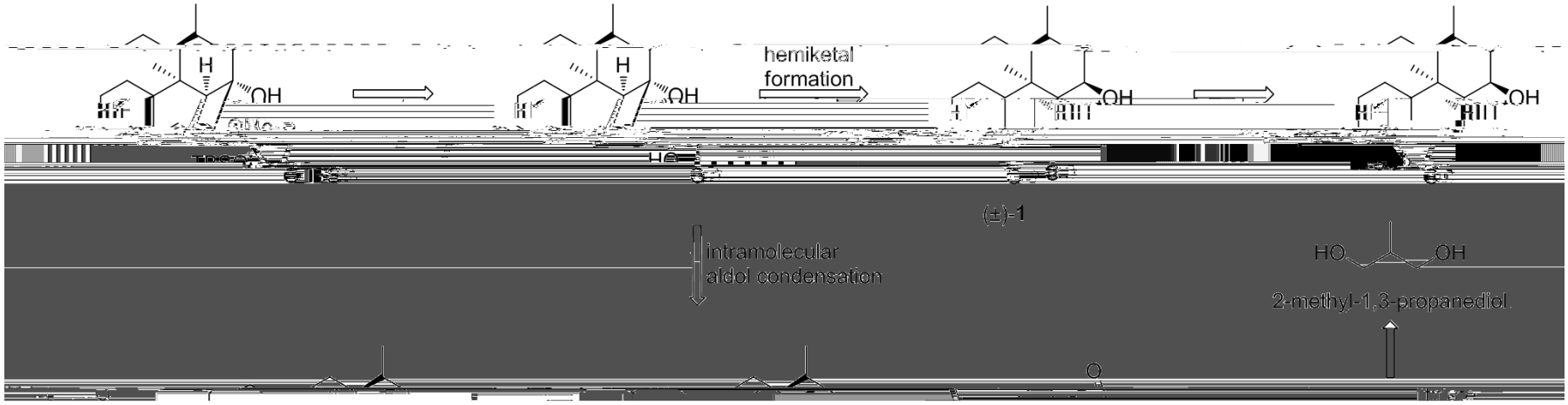
!"#$%&'&"( )*+*,"(-*$. "'+$ /&" *)()$ 0$1 '"'&,(&
2 ' #$345 647$6 '(8 &*#$.4$94$*Angew. Chem. Int. Ed.* 2015, *54,* :;;<=:;;>4



2', '!/$?4$@(A)"!'
B(A$@! AC
9'&A'!/$:#$;D:>

E!*-(A)$ /&" *)*)



R Racemic synthesis reported by GTssinger in 1998.

R 33 steps longest linear sequence from thymoquinone.

J(, U*!I*!#$V4$W47$J(I&*!#$947$@T))(&I*!#$%47$@!AU*!#$M47$6*&X#$@4$*Monatsh. Chem.* 1994, *125,* YY:=:D:D4$Z@*!8'&$ <
$$$$$+'&IA'I*[
J(I&*!#947@T))(&I*!#$%47$M\ +(I#$O47$6*&X#$@47$E0+AI)*G*!#M4$*Angew. Chem. Int. Ed.* 1998, *37,* ;;;>=;;;Q4

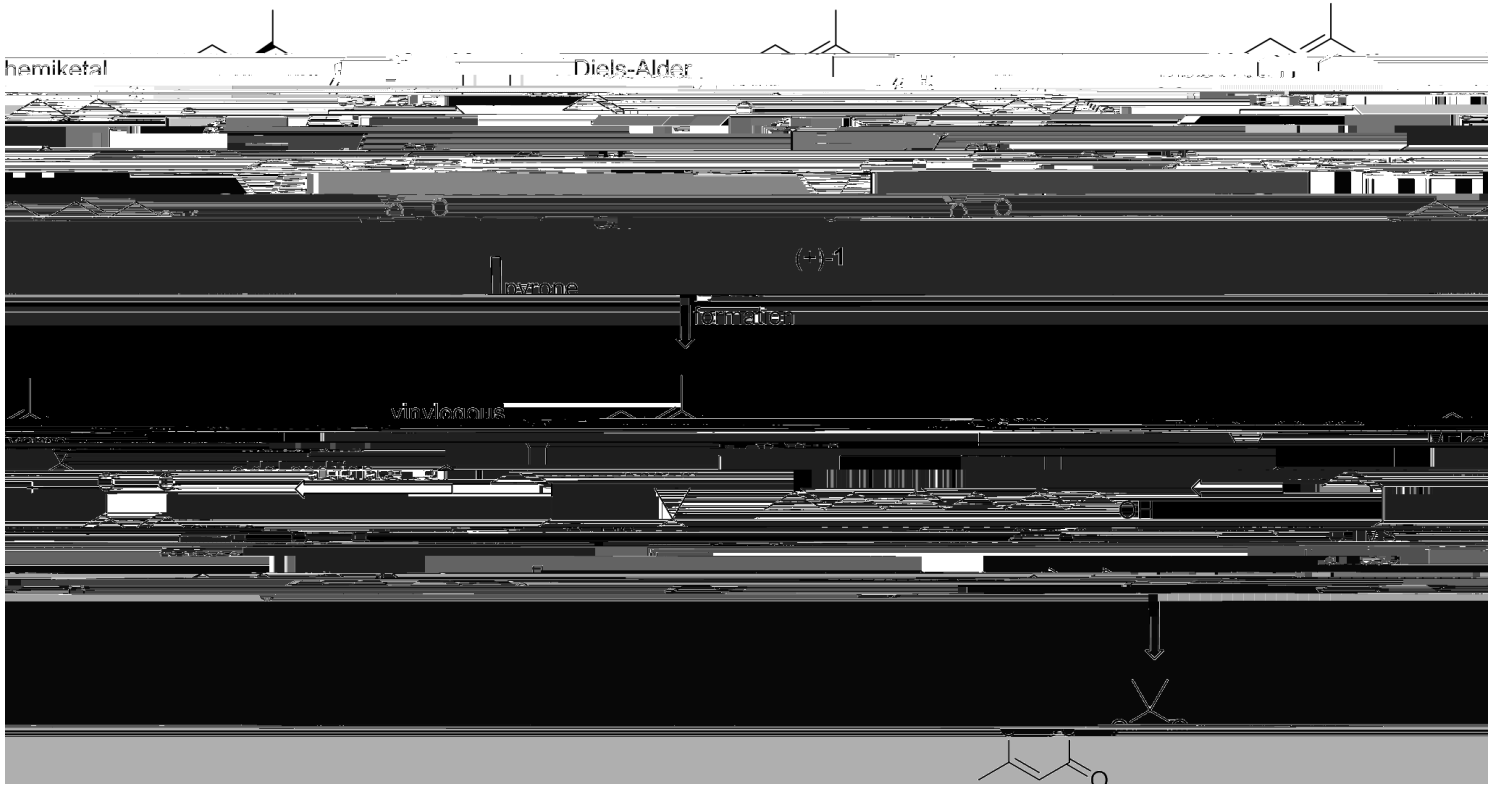
E!*-(A)$ /&" *)*)

R Enantioselective synthesis achieved by Deslongchamps in 2003.

R

]

Zb[51$c*"!)/&" *)()



R Exceedingly acid-sensitive hemiketal moiety formed in the penultimate step.

R Intramolecular Diels-Alder cyclization with pyrone diene to set four of the final product's seven stereocenters.

R Vinylogous Mukaiyama aldol addition to combine two fragments containing all necessary carbon atoms.

P

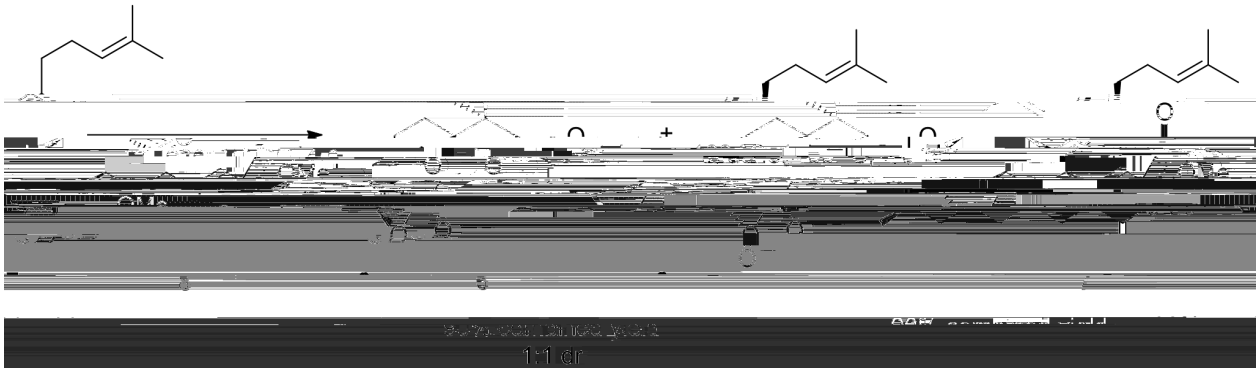
d !N'!G$ /&" *)()

W 6 EeW*))5 6 '!"(&$C*!(G(&'&*
2 ' #$345 6 47$ 6 '(8 &*#$. 4$94$*Angew. Chem. Int. Ed.* 2015, *54,* : ; ; <=: ; ; >4
%)"f -*X#$c4$%47$9A)"(,('#$947$H'XG(#$H47$dA*&"*)#$g47$E'!'G')#$ 6 47$1 hA*)(++ 5B'XE# ¨O 3 >

d !N'!G$ /&" *)()

BWJe+(" (A8$G(() C! C/+'8(G*7$W6EeW*))56'!"(&$C*!(G(&'&*7$WFE%Je*N*#N*-G(() C! C/+5*N*5*" /+'8(&* a
2 ' #$345647$6'(8 &*#$.4$94$*Angew. Chem. Int. Ed.* 2015, *54,* :;;<=:;;>4
d*""*)#$J7$1'!!*(!'#$%4$64$*J. Org. Chem.* 2003, *68,* Y;a]=Y;Q<4

d !N'!G$ /&" *)()

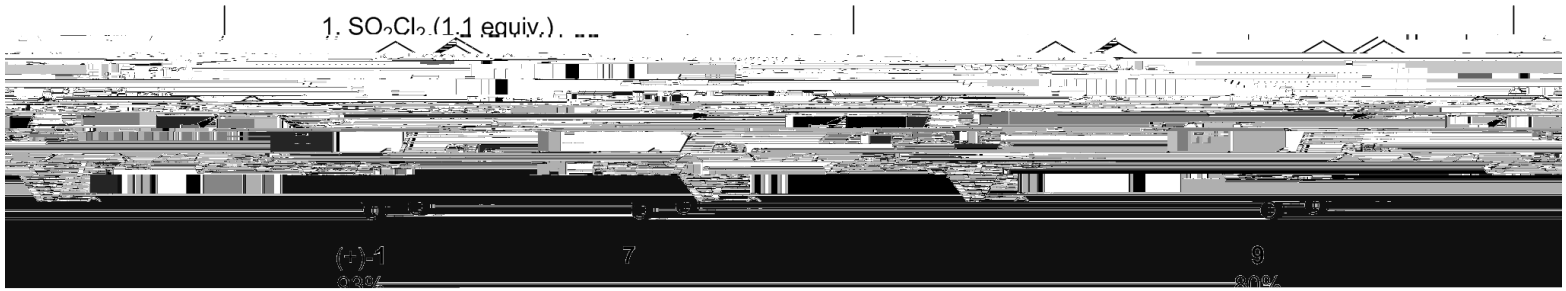


R Diastereomers 7 and 8 separable by column chromatography.

R Only decarboxylated products obtained when attempted with triflate 5.

R Significant decarboxylation also observed in more polar solvents (DMF, acetonitrile), and at higher temperatures (120 jC).

R Cyclization reaction was markedly sluggish at 80 jC.

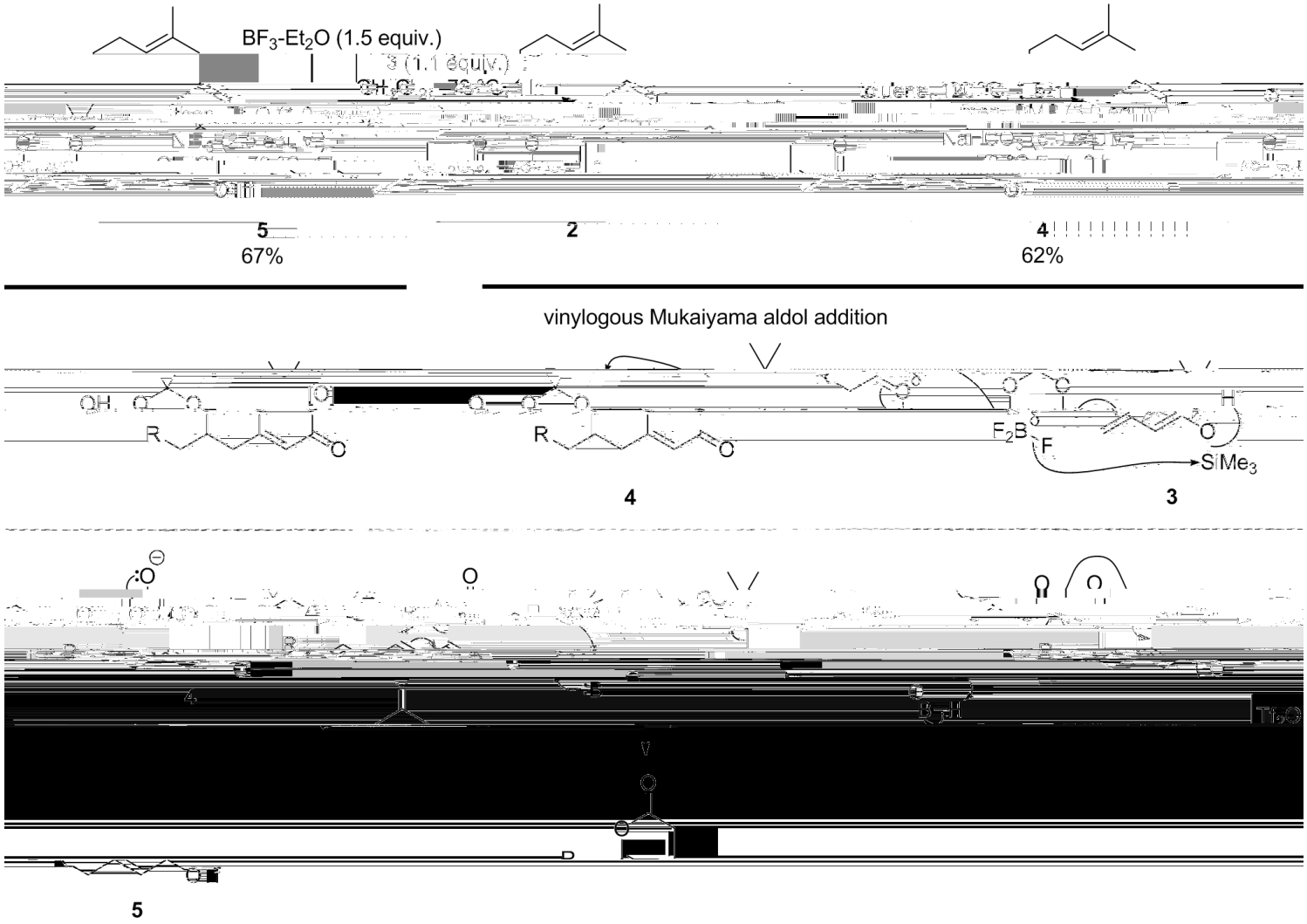


Y

%)"f-*X#$c4$%47$9A)"(,('#$947$H'XG(#$H47$dA*&"*)#$g47$E'!'G')#$647$1 hA*)(++ 5B'X'!"*#$W47$@'!,i'#$94$647$c U+*)#$c47
$$$$$@'&)\A*!#$J47$1A*!-'#$94$647$L+"!'#$94$%4$*Chem. Eur. J.* 2009, *15,* ;;a]=;aY:4

6*, '&()8)

6*, '&()8)


BF3-Et2O (1.5 equiv.)
67%
62%
vinylogous Mukaiyama aldol addition
F2B
SiMe3

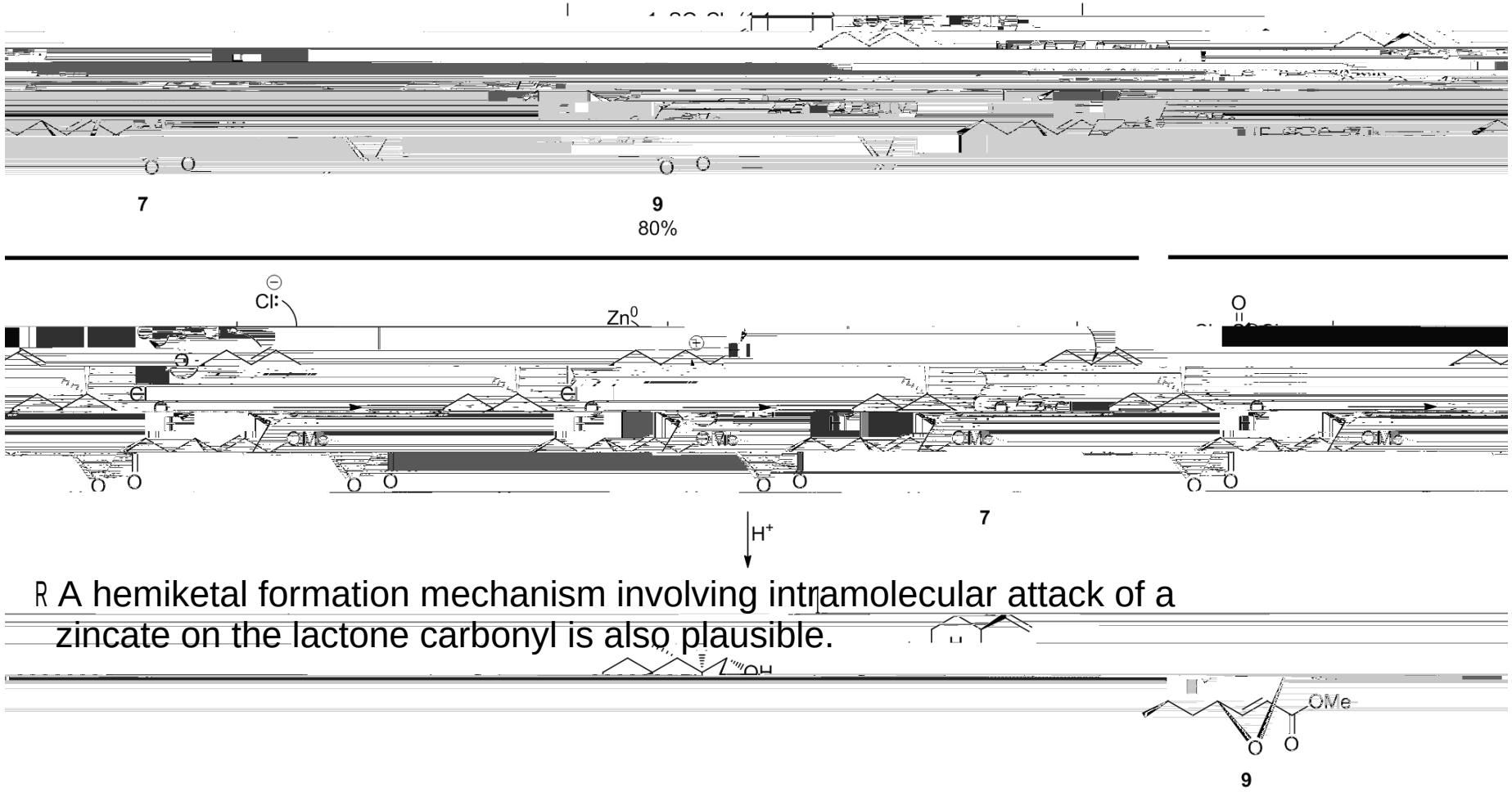
:<

6*, '&()8)

:]

6*, '&()8)

:P



R A hemiketal formation mechanism involving intramolecular attack of a zincate on the lactone carbonyl is also plausible.