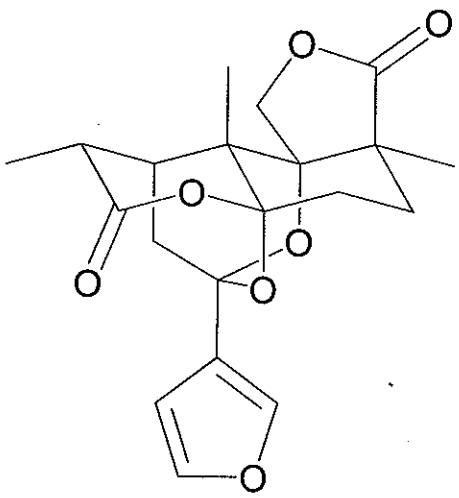
Literature Seminar 2007.4.18 Tatsuya Nitabaru (as B4)

Total Synthesis of Saudin



Saudin (**1**)

Isolation

Cluytia richaradiana (Euphorbiaceae)

Structural Elucidation

A. G. Schultz, et. al. *J. Org. Chem.* **1985**, *50*, 916

Bioactivity

Hypoglycemic activity (mice) 血糖降下作用

Total Synthesis

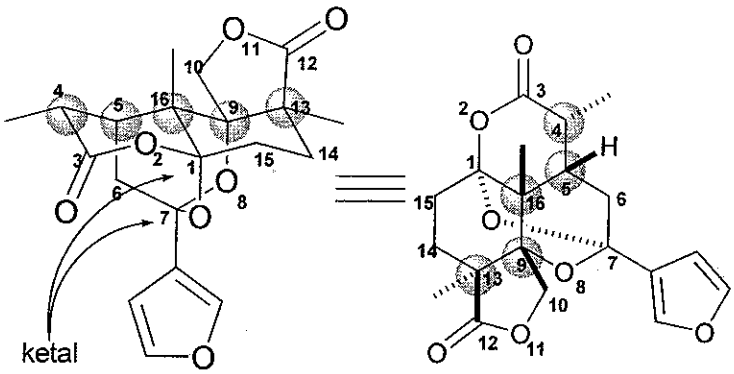
J. D. Winkler, et. al. *J. Am. Chem. Soc.* **1999**, *121*, 7425

R. K. Boeckman, Jr., et. al. *J. Am. Chem. Soc.* **2002**, *124*, 190

Contents

1. Strategy for Total Synthesis

1-1. Stractural Features



Saudin (**1**)

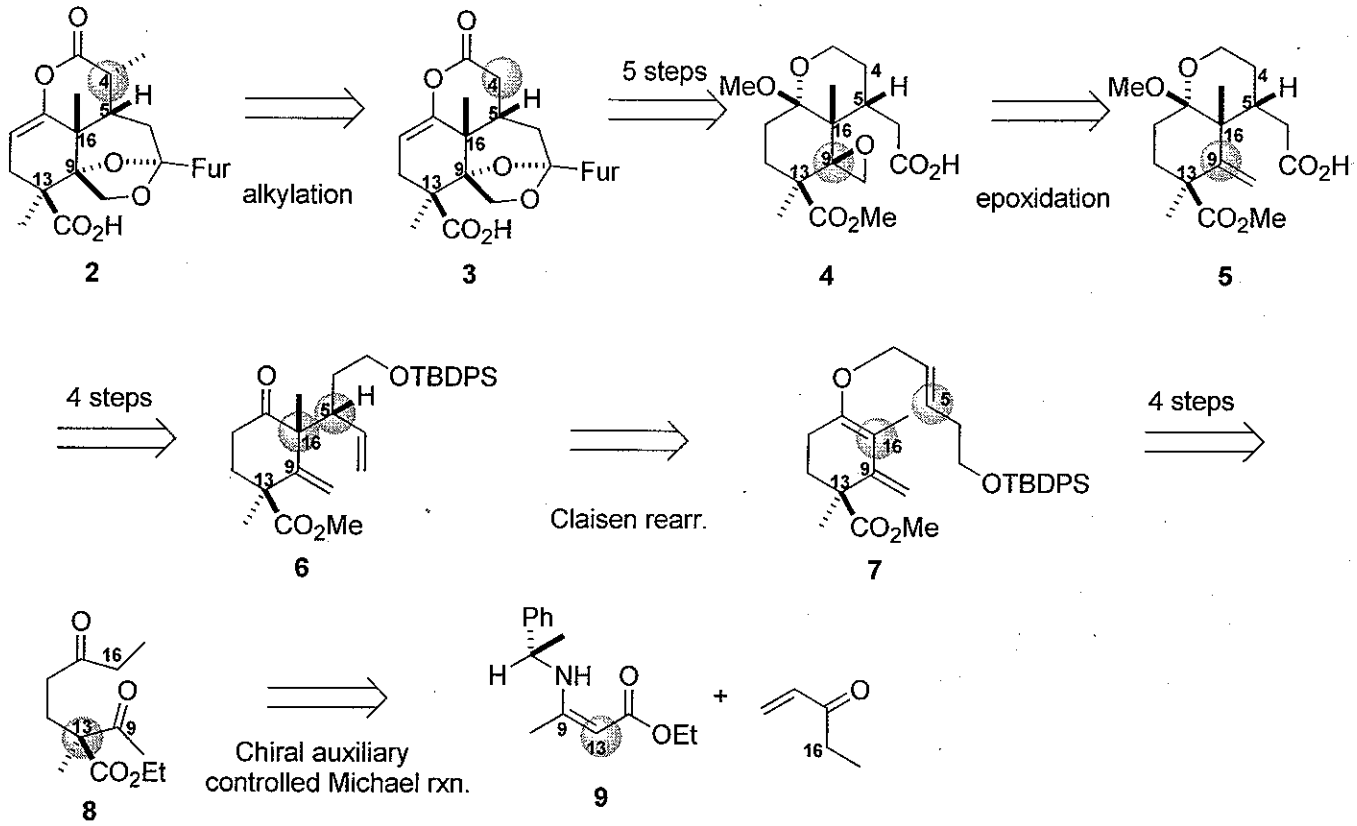
Fig. 1

- highly oxygenated caged structure
- bisketal backbone
- 5 contiguous stereogenic carboncenters at C_{13}, C_9, C_{16}, C_5, C_4
- reactive furan ring contain

1-2. Retrosynthetic Analysis

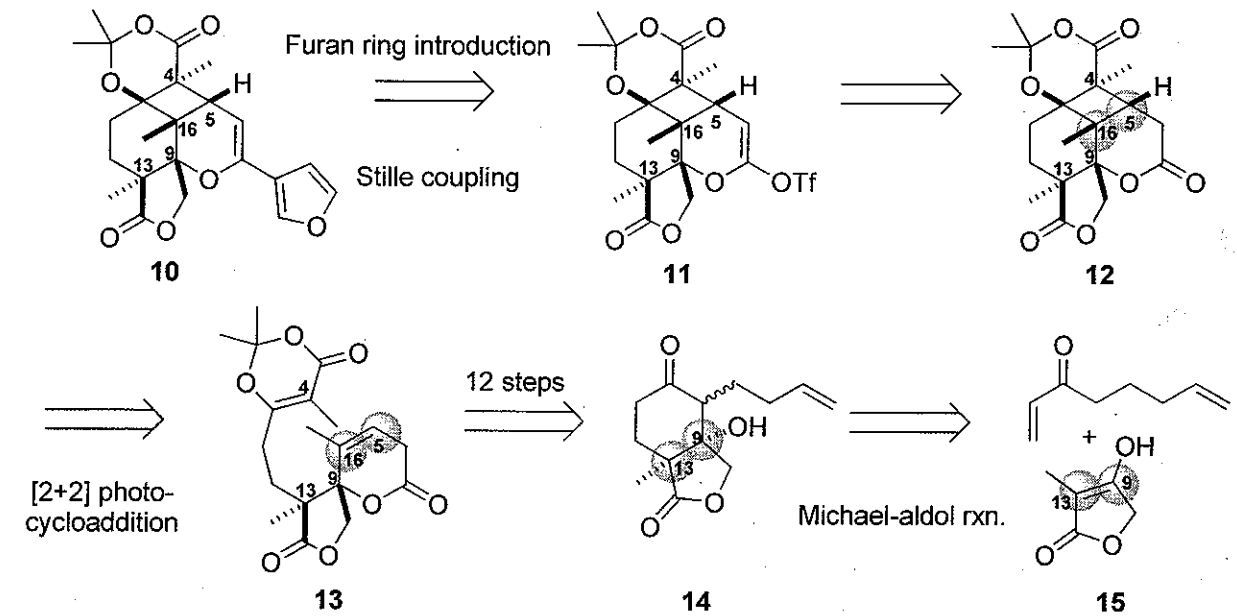
Boeckman's Synthesis

Scheme 1



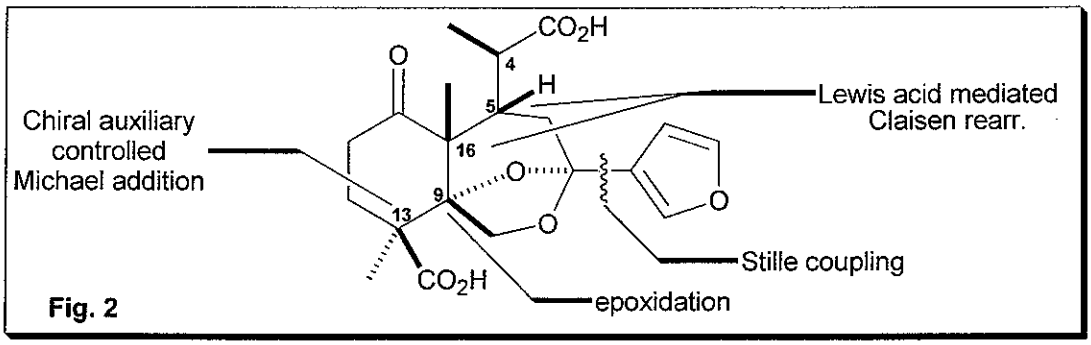
Winkler's Synthesis

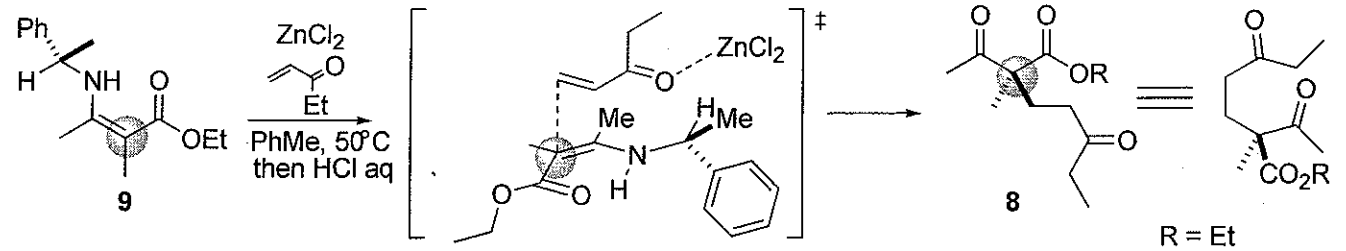
Scheme 2

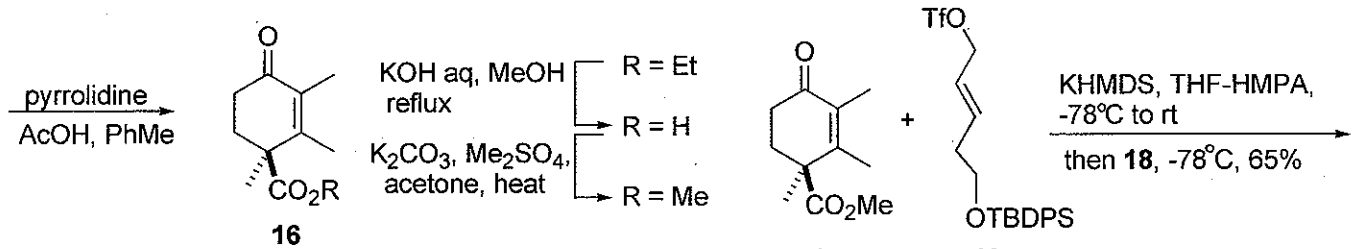


3. Total Synthesis of Saudin

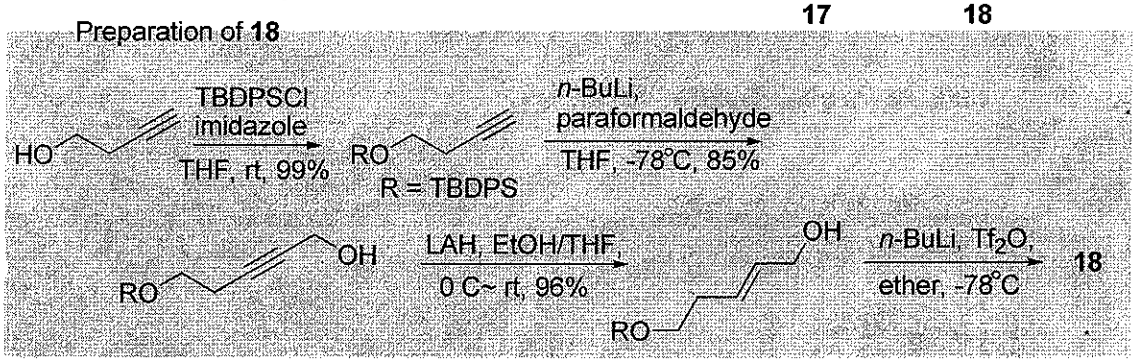
3-1. Boeckman's Synthesis



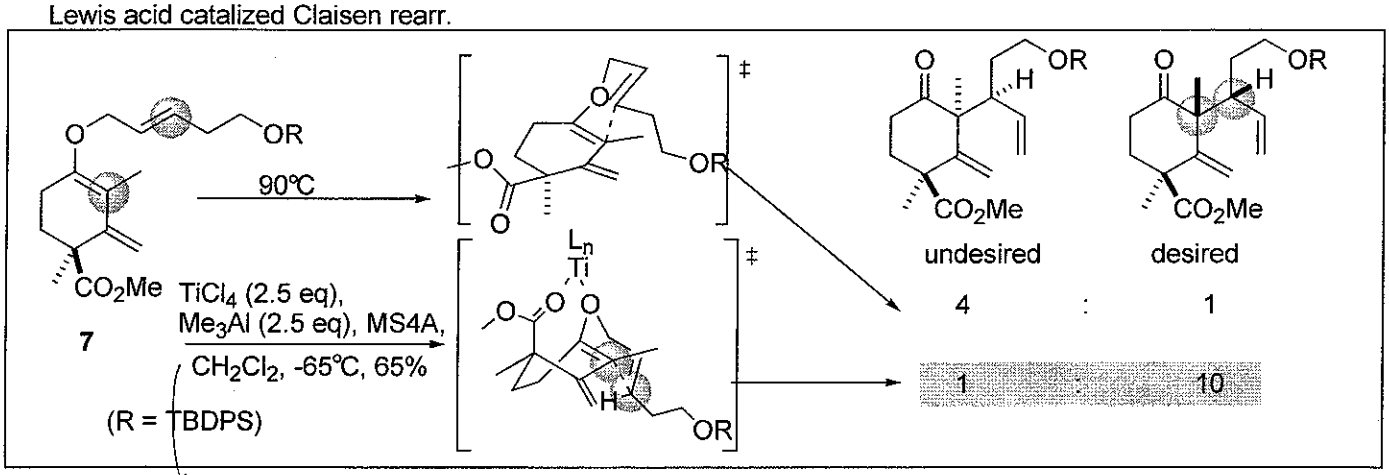




Preparation of **18**

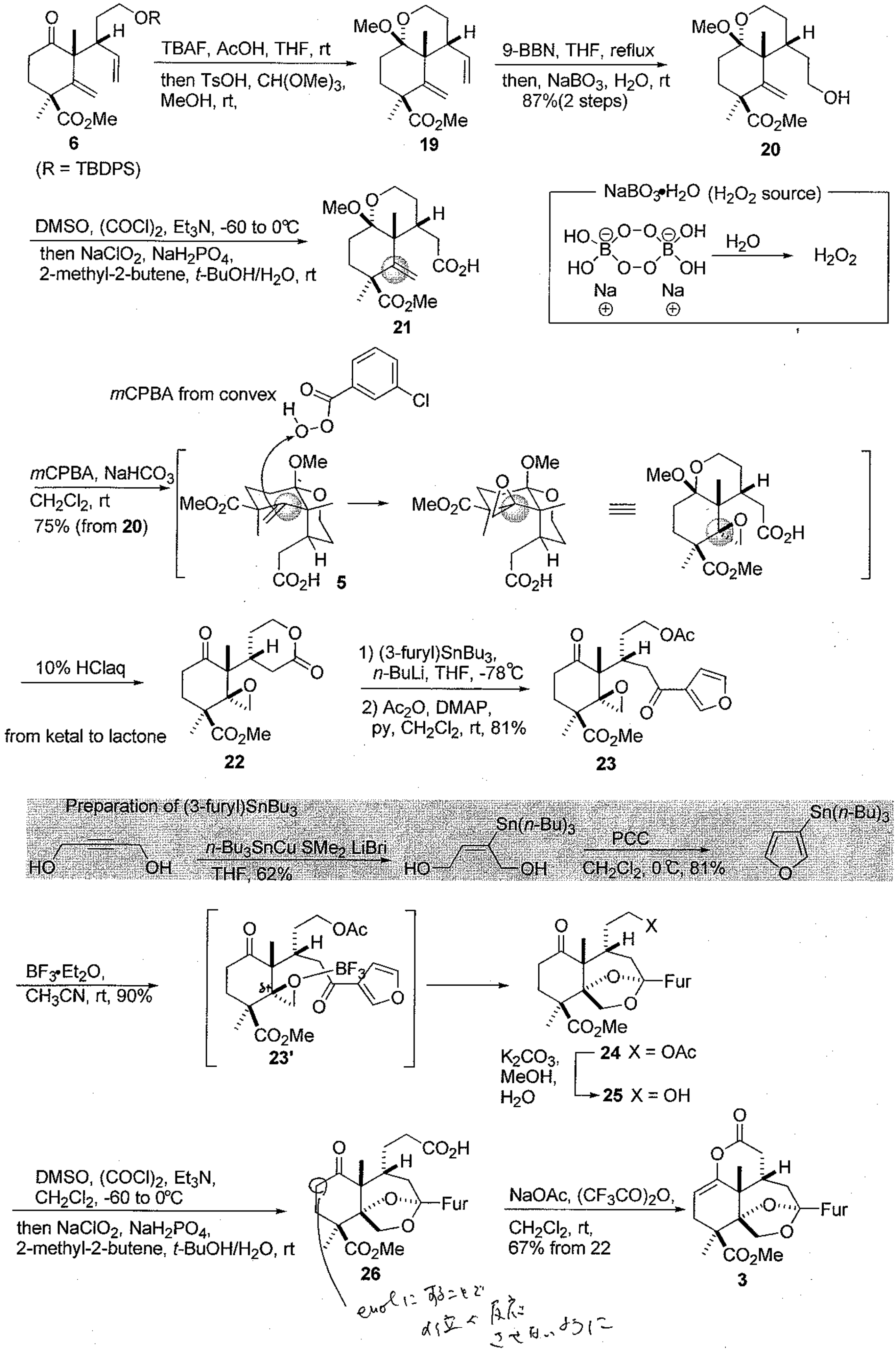


Lewis acid catalized Claisen rearr.

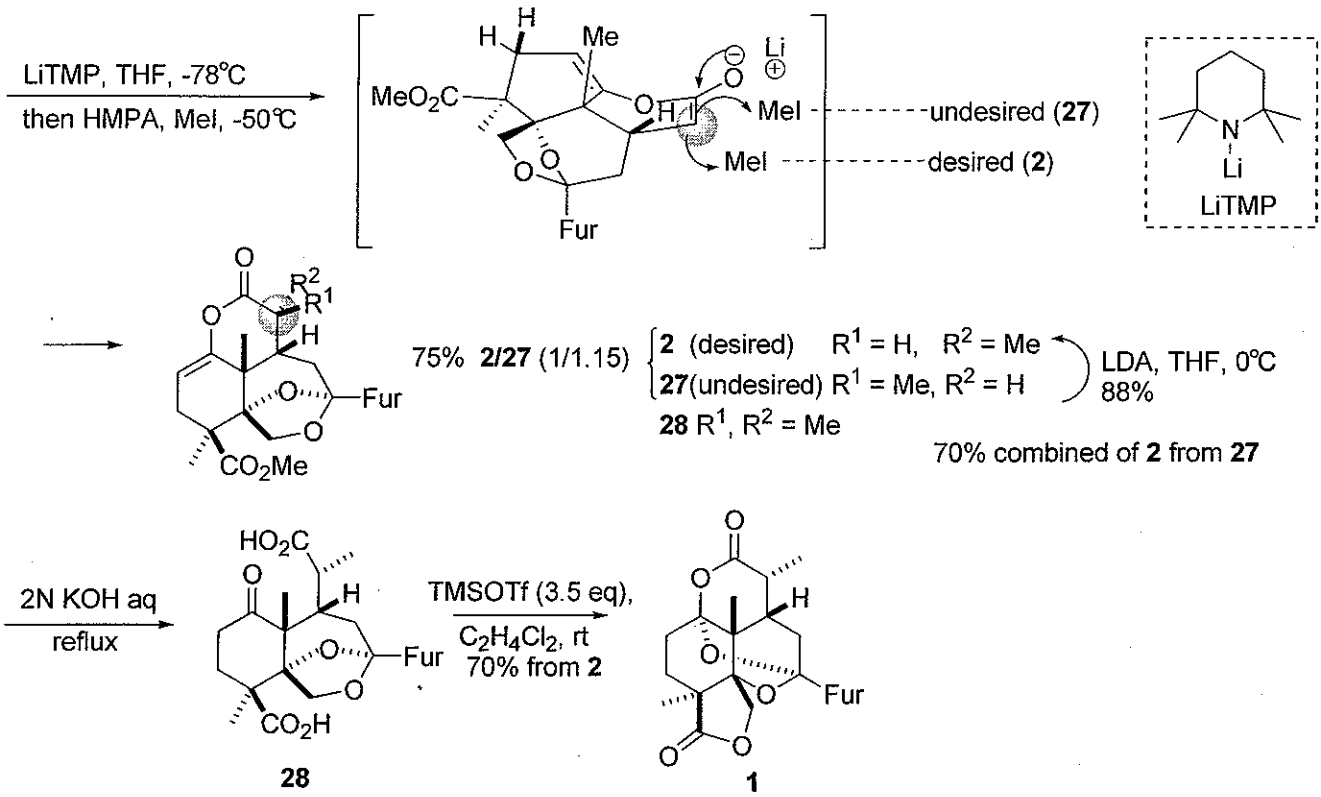


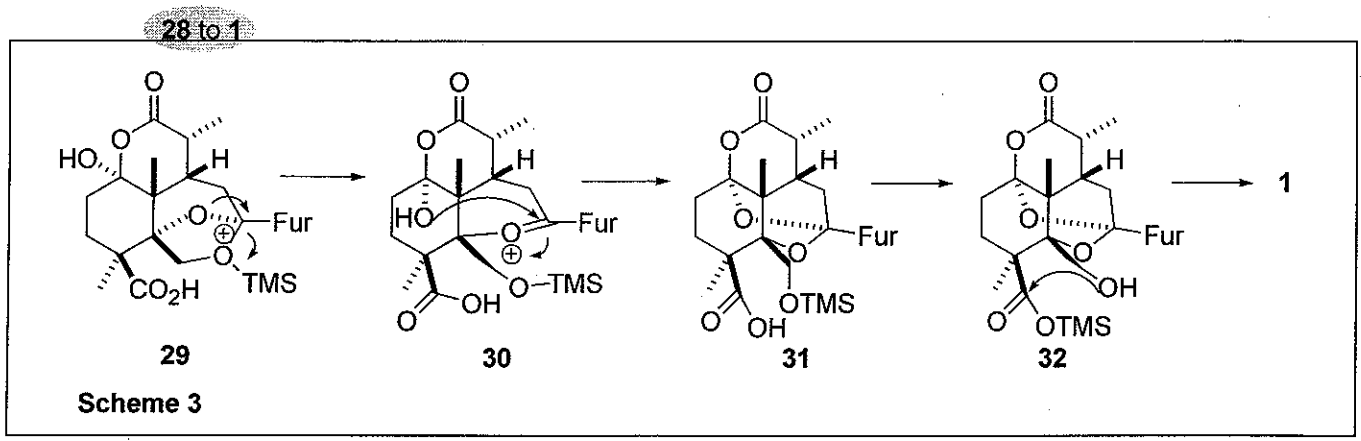
HCl トラップに使うことが多いらしい.

$Me_3Al + HCl \rightarrow MeH + Me_2AlCl$.



(R = TBDPS)
TBAF, AcOH, THF, rt
then TsOH, CH(OMe)3, MeOH, rt,
9-BBN, THF, reflux
then, NaBO3, H2O, rt
87%(2 steps)
DMSO, (COCl)2, Et3N, -60 to 0℃
then NaClO2, NaH2PO4,
2-methyl-2-butene, t-BuOH/H2O, rt
NaBO3•H2O (H2O2 source)
H2O
mCPBA from convex
mCPBA, NaHCO3
CH2Cl2, rt
75% (from 20)
10% HClaq
from ketal to lactone
1) (3-furyl)SnBu3,
n-BuLi, THF, -78℃
2) Ac2O, DMAP,
py, CH2Cl2, rt, 81%
Preparation of (3-furyl)SnBu3
n-Bu3SnCu SMe2 LiBr
THF, 62%
PCC
CH2Cl2, 0℃, 81%
BF3•Et2O,
CH3CN, rt, 90%
K2CO3,
MeOH,
H2O
24 X = OAc
25 X = OH
DMSO, (COCl)2, Et3N,
CH2Cl2, -60 to 0℃
then NaClO2, NaH2PO4,
2-methyl-2-butene, t-BuOH/H2O, rt
NaOAc, (CF3CO)2O,
CH2Cl2, rt,
67% from 22
enolにすることで


LiTMP, THF, -78℃
then HMPA, MeI, -50℃
MeO2C
Me
H
O
Li
MeI
undesired (27)
desired (2)
Fur
N
Li
LiTMP
75% 2/27 (1/1.15)
2 (desired) R1 = H, R2 = Me
27(undesired) R1 = Me, R2 = H
LDA, THF, 0℃
88%
28 R1, R2 = Me
70% combined of 2 from 27
CO2Me
2N KOH aq
reflux
HO2C
CO2H
TMSOTf (3.5 eq),
C2H4Cl2, rt
70% from 2
28
1


28 to 1
HO
Fur
CO2H
TMS
OH
OTMS
29
30
31
32
1
Scheme 3

3-2. Winkler's Synthesis

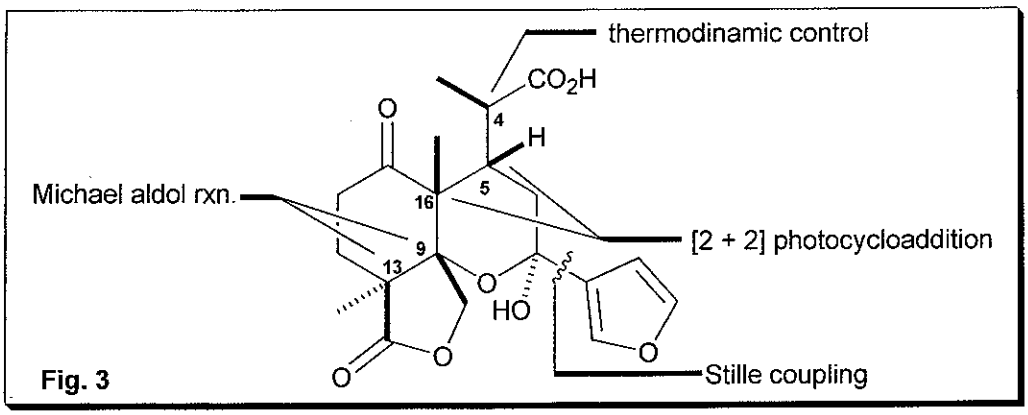
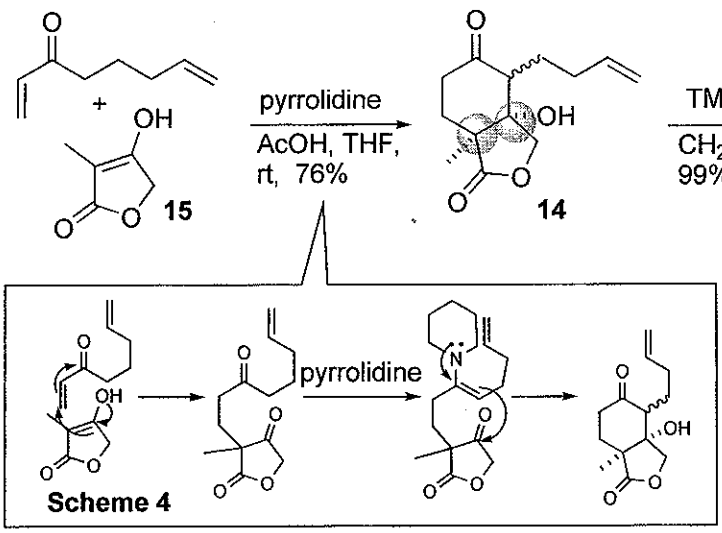
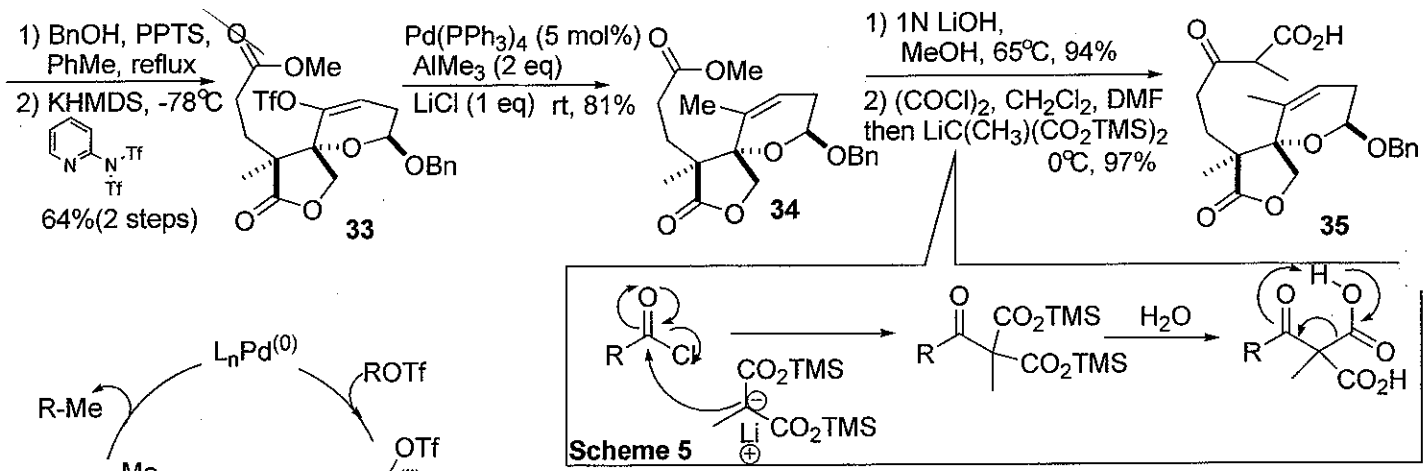


Fig. 3





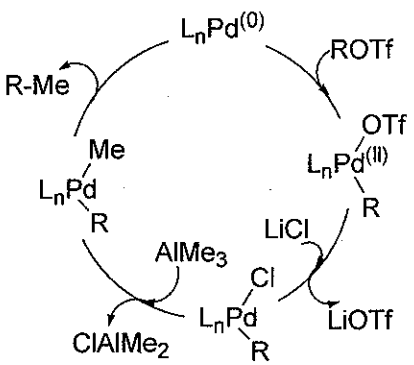
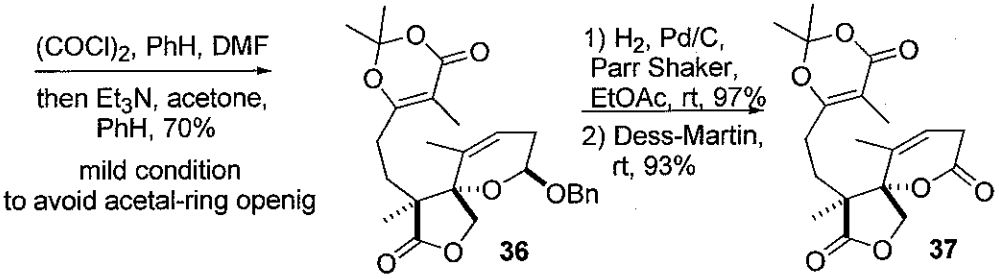
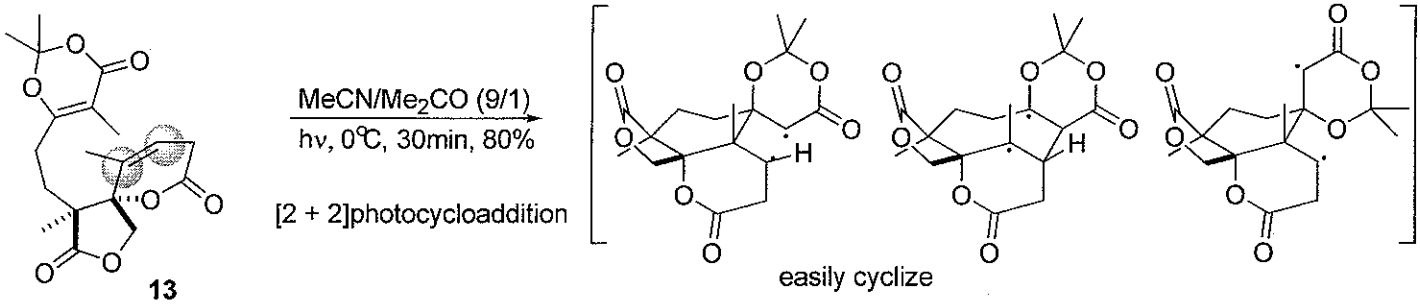
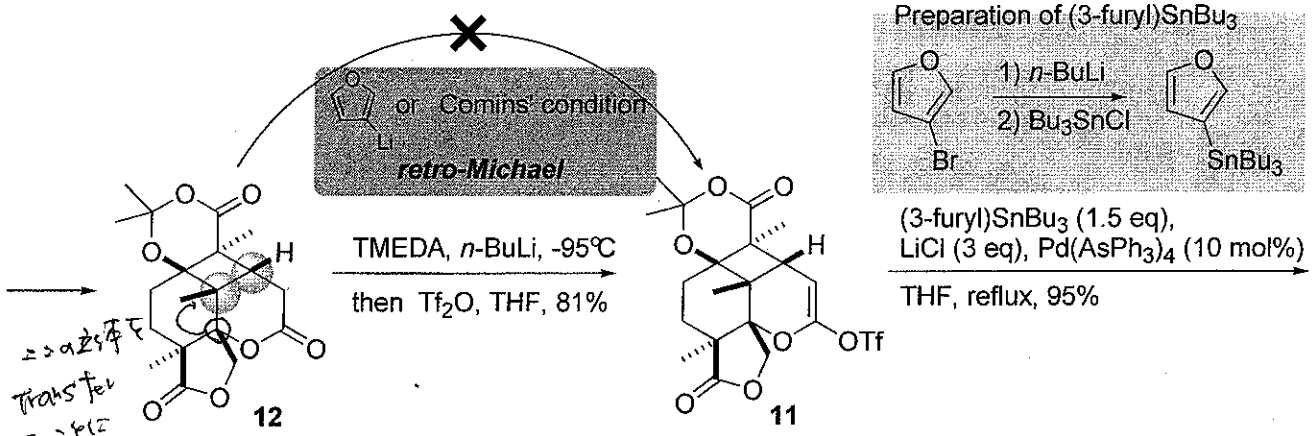


Fig. 4

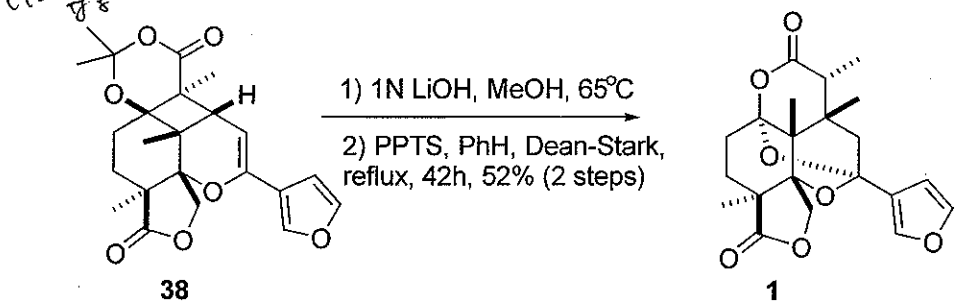




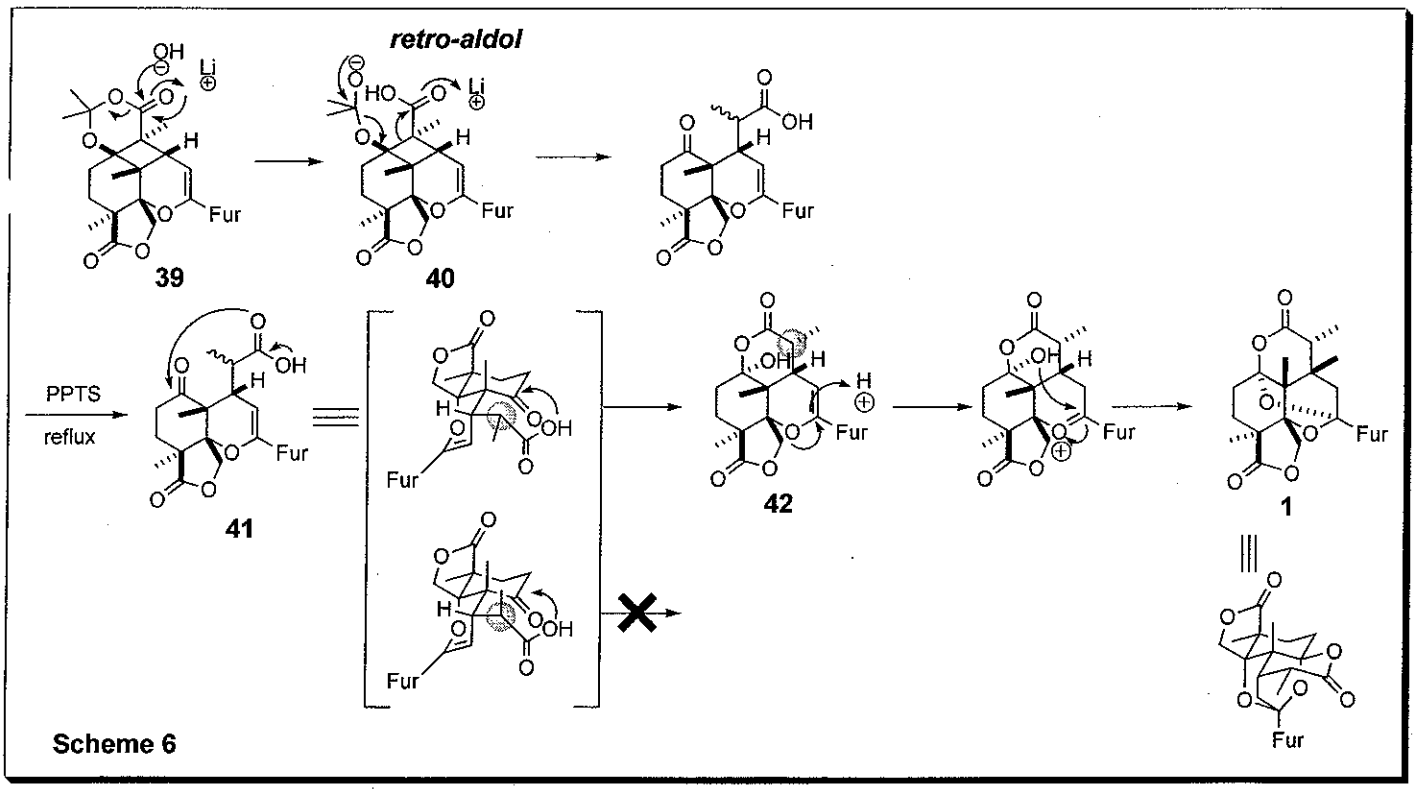
13



12 11



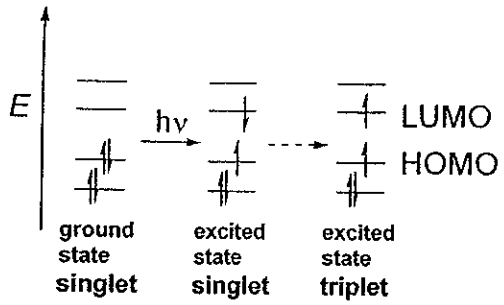
38 1

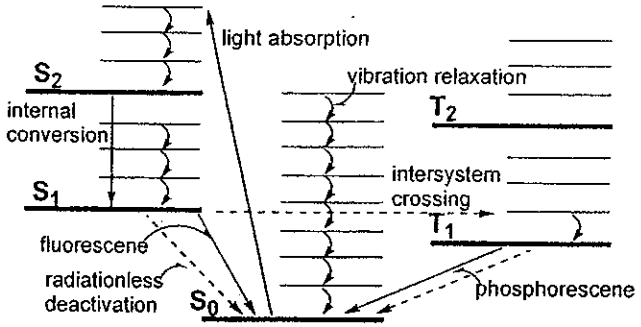


39 40 41 42 1

Scheme 6

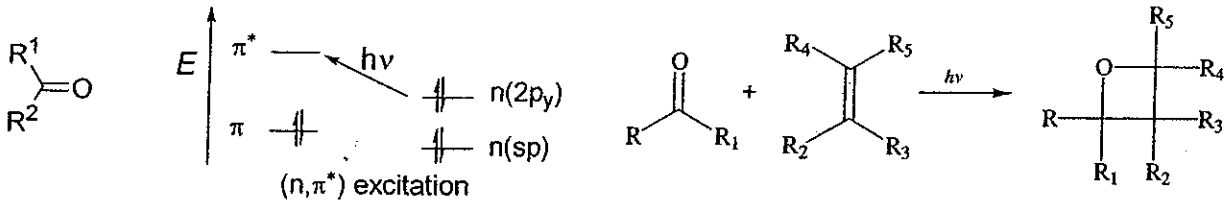
Key Reaction ~ [2+2] photocycloaddition ~





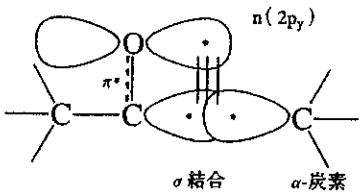
Carbonyl compounds

Paterno - Büchi rxn.

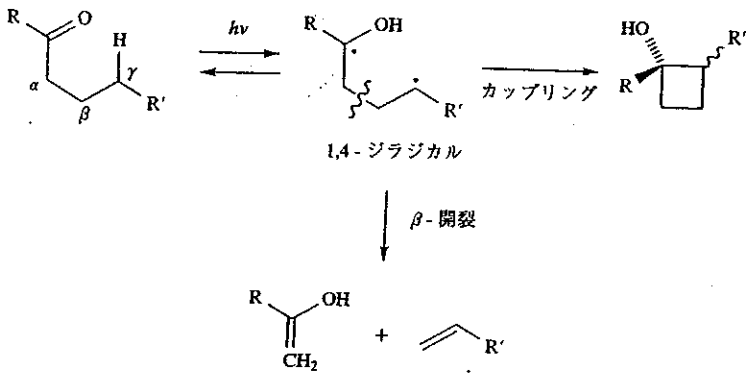


Norrish type 1 rxn.

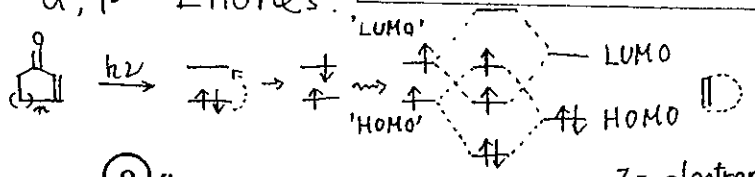
α -開裂反応（α - cleavage reaction）



Norrish type 2 rxn.

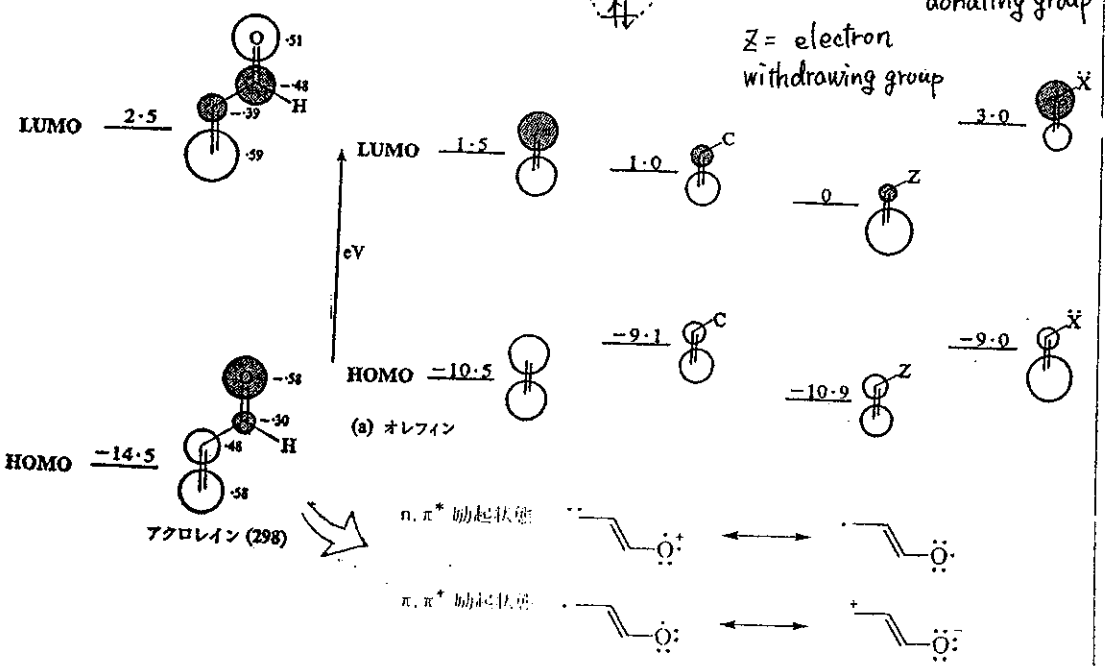


α, β - Enones.

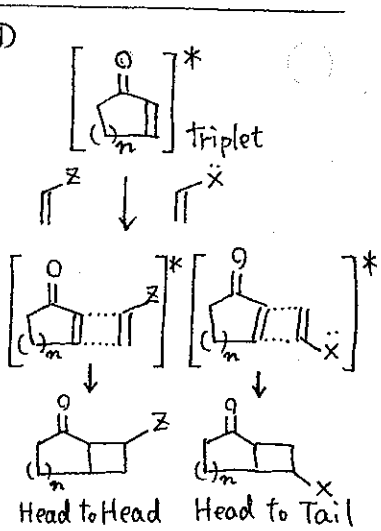


X = electron donating group

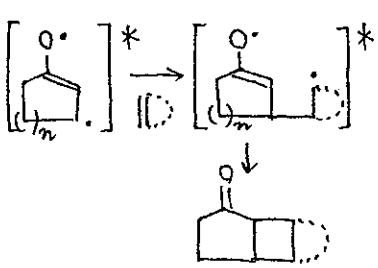
Z = electron withdrawing group



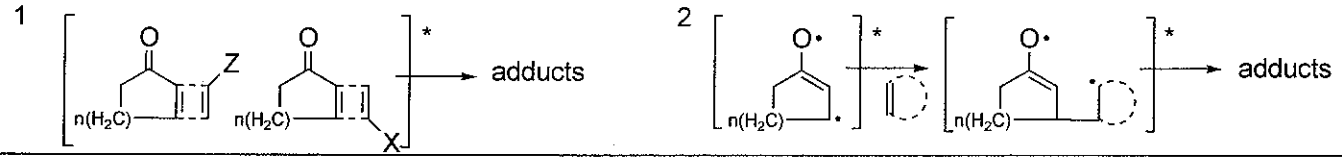
①

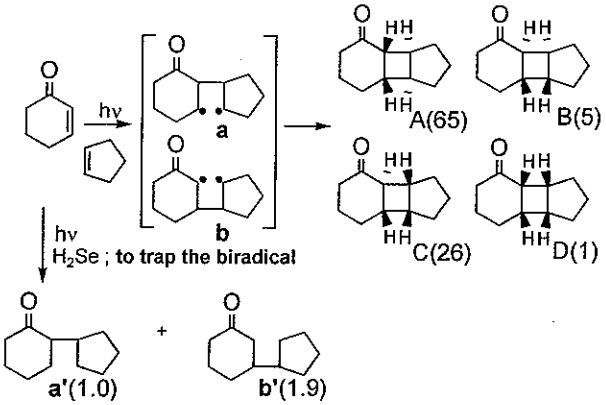


②

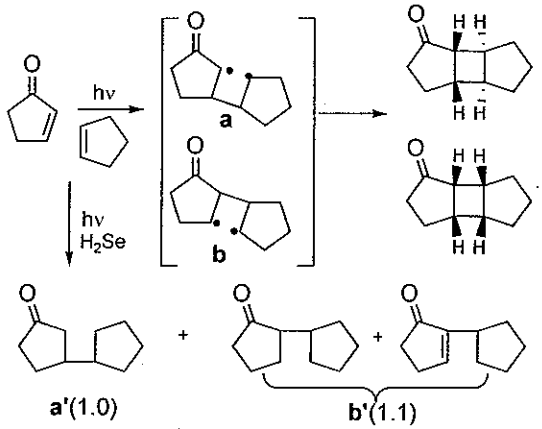


α,β - Enones ~ via lowest excited state (π,π^*) ~



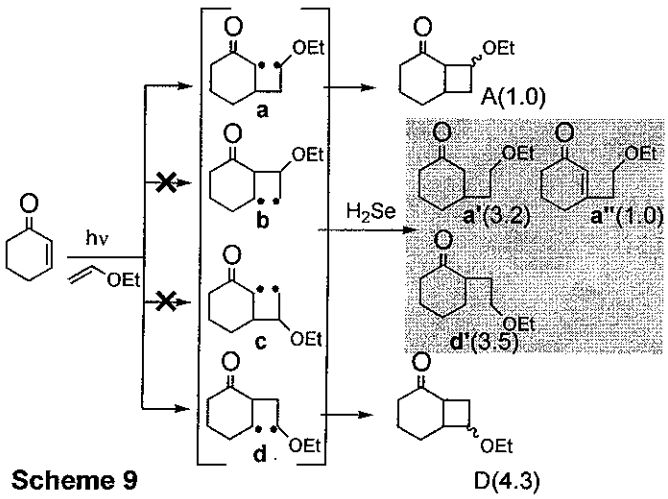


Scheme 7

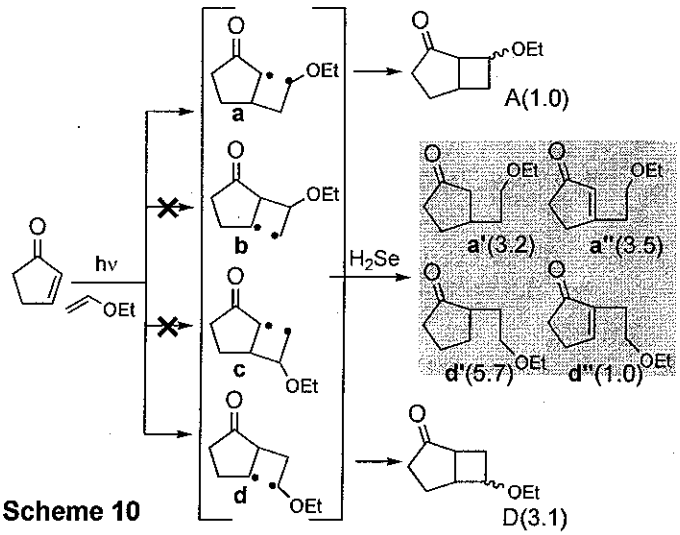


Scheme 8

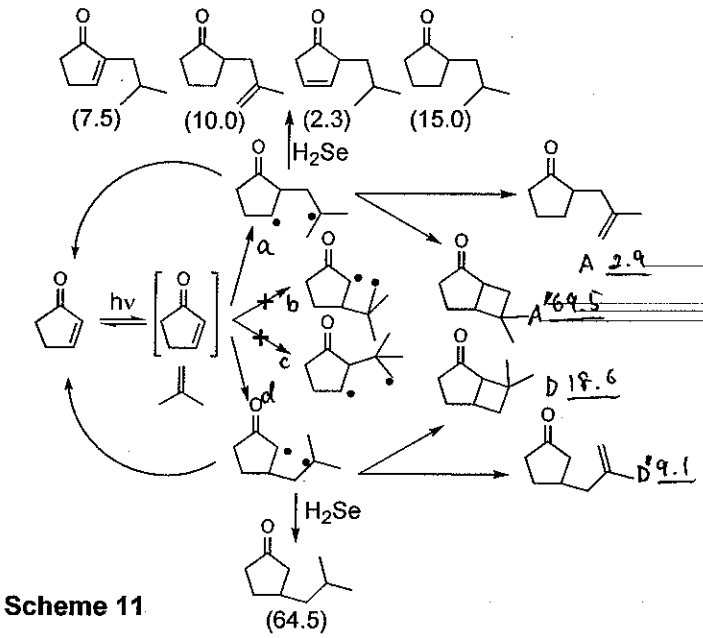
In the presence of H_2Se, cycloadducts are completely depressed.



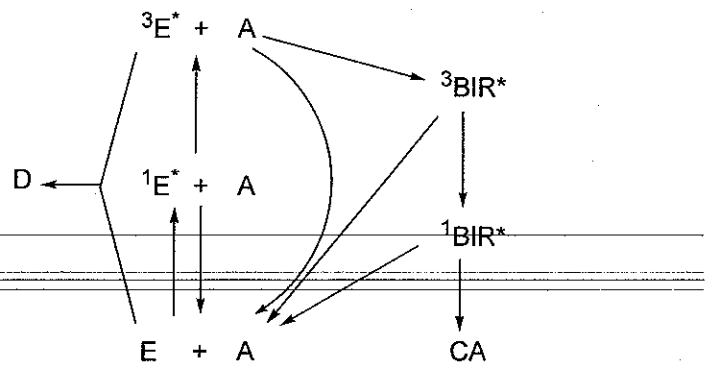
Scheme 9



Scheme 10



Scheme 11



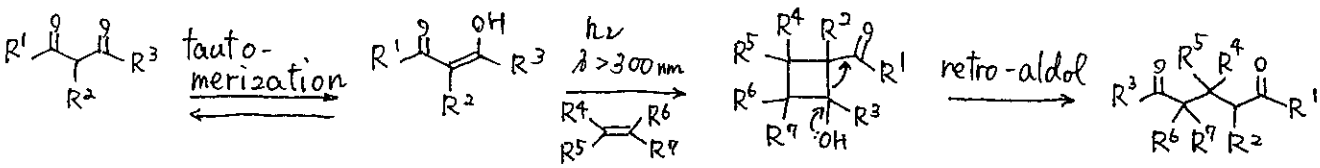
E = enone, A = alkene, BIR = biradical,
CA = cycloadducts, D = dimer

Fig. 5

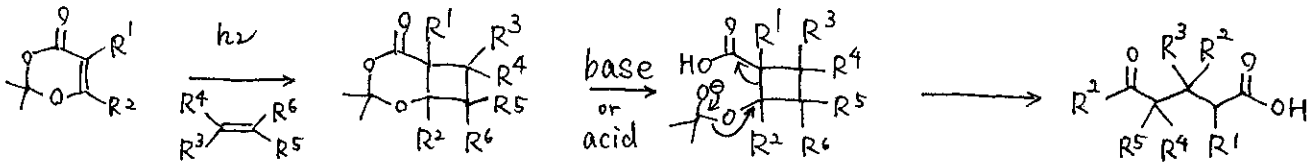
Schuster et al. *Chem. Rev.* 1993, *93,* 3
Weedon et al. *J. Am. Chem. Soc.* 1991, *113,* 3
Weedon et al. *Tetahedron Lett.* 1991, *35,* 8107
Sonoda et al. *Chem. Lett.* 1987, 8107

Application of [2+2] photocycloaddition.

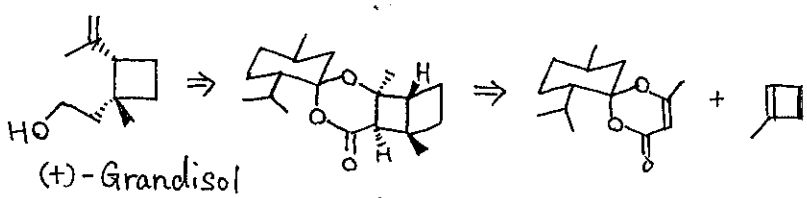
- de Mayo cycloaddition.



- modification.

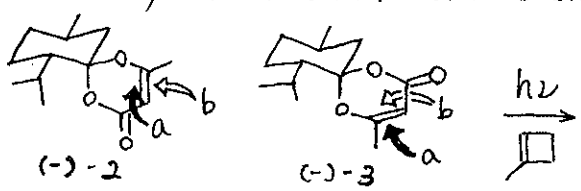


1. Cyclobutane construction ~ Synthesis of (±)-Grandisol ~



(+)-Grandisol

Cyclobutene attacks from b side?



(-)-2 (-)-3

Table 1. Photocycloadditions of the dioxacyclohexenones (−)-2 and (−)- with olefins [a]. The spectroscopic data of the products (+)-5 and (+)-8 a given in Table 3.

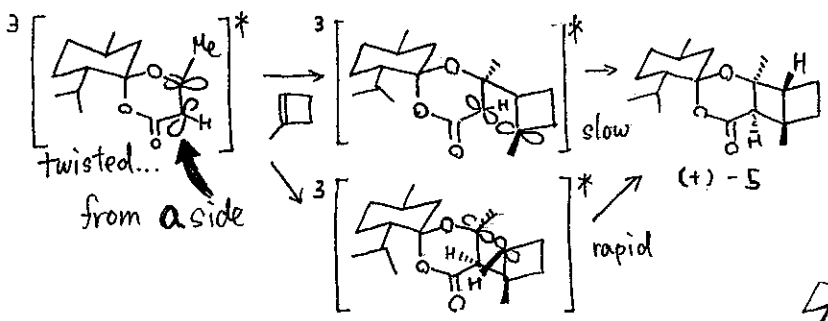
Expt.	Dioxa-cyclohexenone	Olefin	Photoproducts [b, c] [9] P	P'
1	(−)-2		(+)-5	
2	(−)-2			
3	(−)-2			
4	(−)-3		(+)-8	

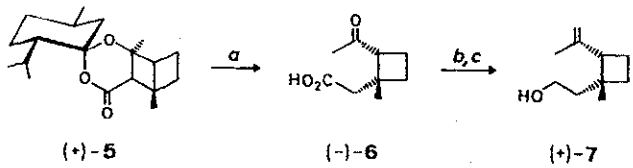
[a] Molar ratio dioxacyclohexenone : olefin = 1 : 4; $c((-)\text{-}2) \approx c((-)\text{-}3) \approx 0.$ mol/L; experiments 1, 2, 4 in *n*-hexane, experiment 3 in acetonitrile. [b] Besides the regioisomers P and P', small amounts of stereoisomers with complementary four-membered ring configurations are formed (cf. *a* : *b* values in Table 2). [c] Pure products after column-chromatographic separation.

Table 2. Results of the reactions listed in Table 1.

Expt.	*T* [°C]	Yield [%] [a] P + P'	Regio-selectivity P : P'	Stereo-selectivity [b] *a* : *b*
1	−78	55 (70)	7 : 1	5 : 1
	+20	[c]	1 : 1	1 : 1
2	−78	33 (48)	3 : 1	8 : 1
	+20	[c]	1 : 1	2.5 : 1
3	−40	70 (82)	—	10 : 1
	+ 5	64 (81)	—	9 : 1
4	−78	56 (72)	7 : 1	5 : 1
	+20	[c]	1 : 1	1 : 1

[a] Purity of P and P' > 96%; crude yields of all cycloadducts in brackets. [b] Corresponds to the facial selectivity (see Fig. 1); cf. also footnote [b] of Table 1. [c] Preparatively uninteresting yields.

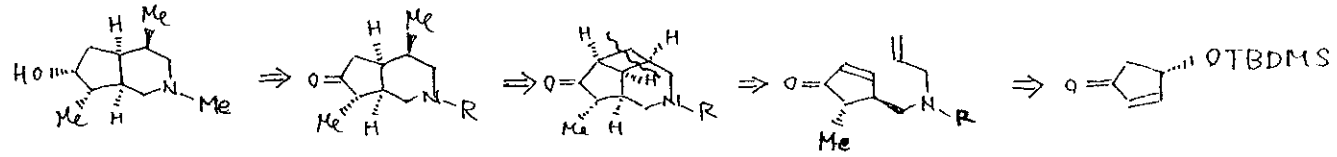




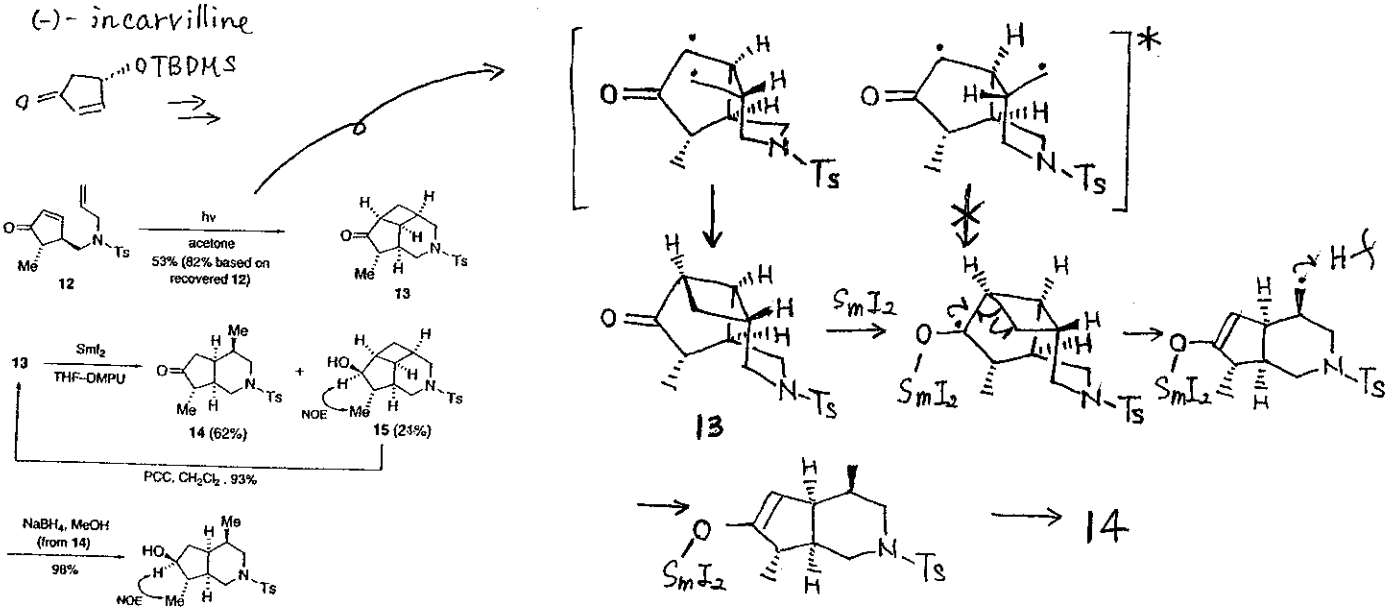
Scheme 2. Shortest synthesis of (+)-grandisol, (+)-7, reported so far. a) HCOOH, H_2O/Me_2CO, 40°C, 20 h. b) Me_3SiCH_2MgCl, tetrahydrofuran, reflux, $SOCl_2$, room temperature; analogously as in [13d]. c) $LiAlH_4$, Et_2O, room temperature; analogously as in [13d].

Demuth et al. Angew. Chem, Int. Ed. Engl 1986, 25, 1117

2 Stereocontrol ~ Total Synthesis of (-)-Incarvilline ~

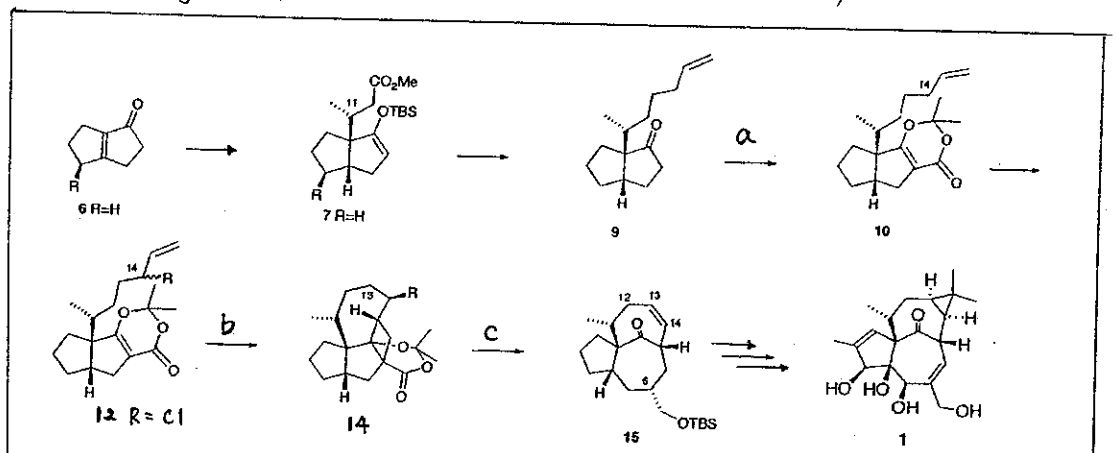


(-)-incarvilline



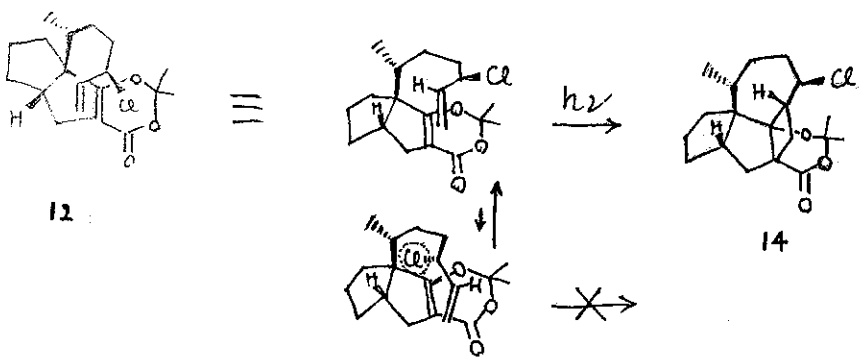
Kibayashi et al. Tetrahedron Lett, 2005, 46, 2327

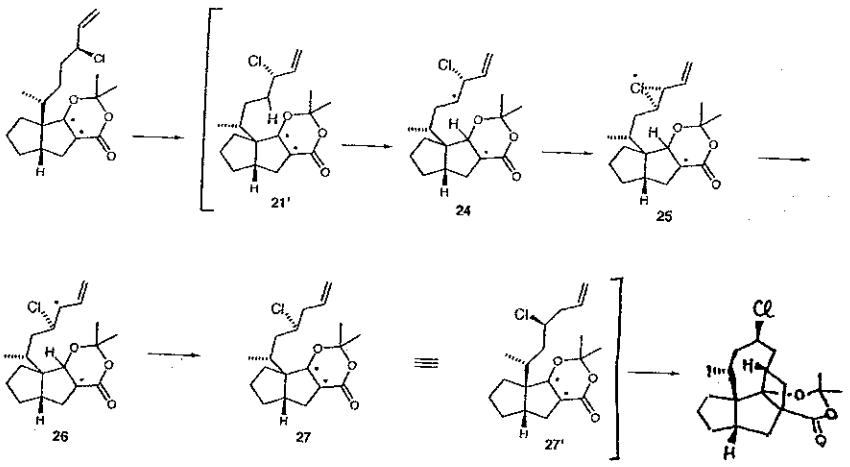
3. Ring Expansion ~ Total Synthesis of (±)-Ingenol ~



(C_{14}-β chloro : C_{13}-β chloro = 5 : 1) Winkler et al. J. Am. Chem. Soc. 2002, 124, 9726

(b)





Scheme 6

Summary of [2+2] photocycloaddition.

- Ring strain of cyclobutyl ketone photoadducts can be used to drive designed secondary fragmentation and rearrangemen
- Polycyclic structures can be constructed under mild conditions.
- Intramolecular [2+2] photocycloaddition controls stereo- and regiochemistry when synthesizing natural products.