Solanoeclepin A: Remarkable Chemistry to Protect the Potato Plant

Lecture at the
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by

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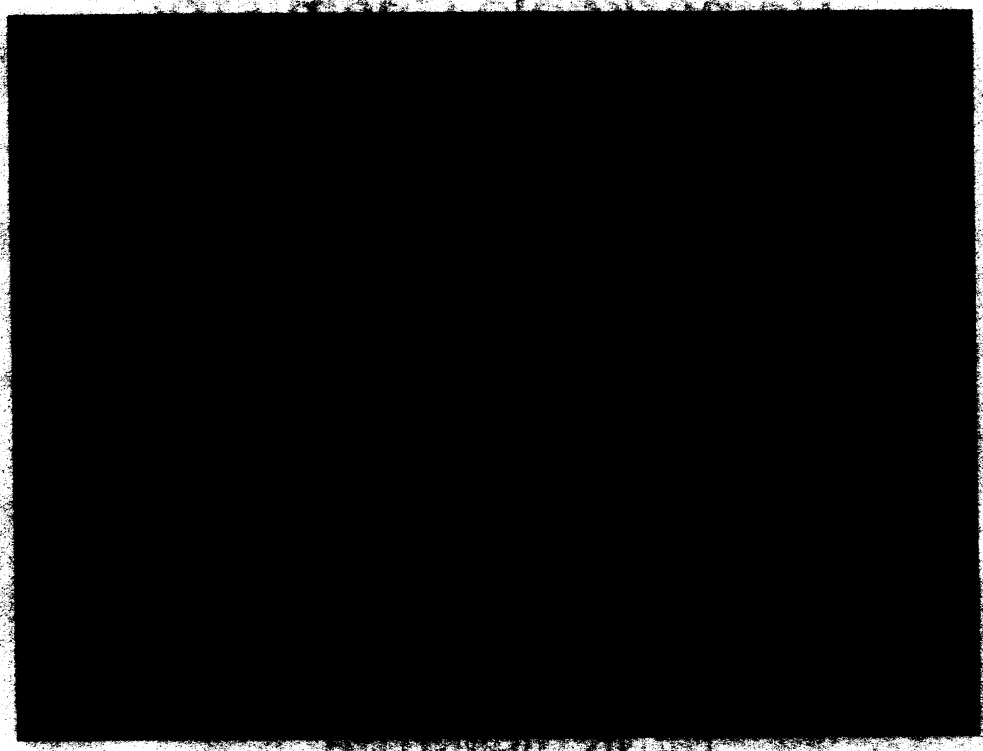
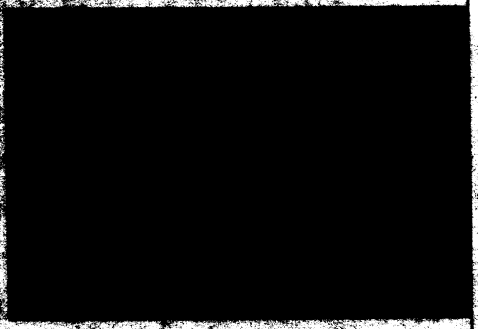
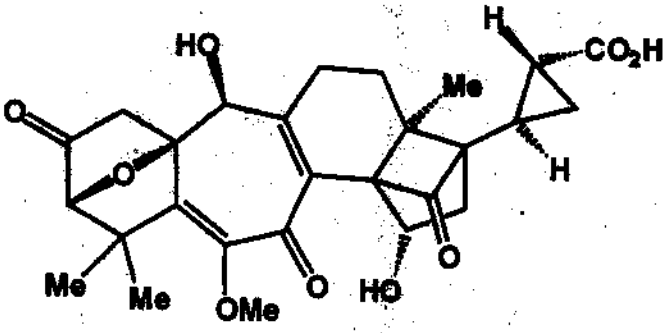


POTATO CYST NEMATODES (PCN)



- PCN are parasites feeding solely on roots of the potato plant
- PCN have one life cycle per year
- PCN hibernate as eggs in very robust cysts in the ground
- eggs hatch only in the presence of growing potato roots in spring
- roots produce a hatching agent which acts in minute amounts
- structure of the hatching agent was elucidated after 40 years of research

SOLANOECLEPIN A



$C_{27}H_{38}O_9$

Mol. Wt.: 498.59

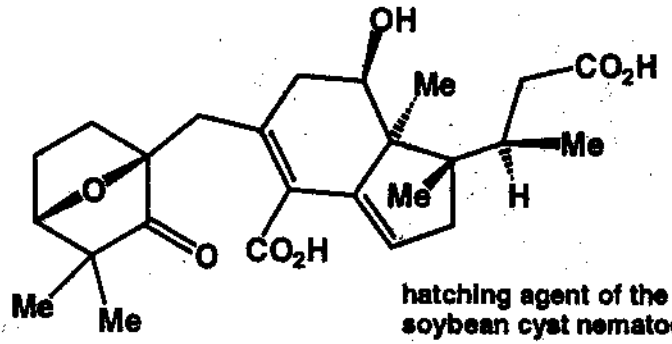
7 rings

9 stereocentra

Mulder, J.G.; Diepenhorst, P.; Plieger, P.; Brüggemann-Rotgans, I.E.M. PCT Int. Appl. WO 93/02,063; *Chem. Abstr.* 1993, *118*, 185844z.

Schenk, H.; Driessen, R.A.J.; De Gelder, R.; Goubitz, K.; Nieboer, H.; Brüggemann-Rotgans, I.E.M.; Diepenhorst, P. *Croat. Chem. Acta* 1999, *72*, 593

GLYCINOECLEPIN A



hatching agent of the soybean cyst nematode

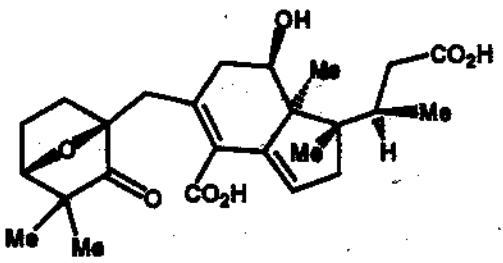
structure elucidation:

- Fukuzawa, A.; Furusaki, A.; Mitsuhiko, I.; Masamune, T. *J. Chem. Soc., Chem. Commun.* 1985, 222

synthesis:

- Murai, A.; Tanimoto, N.; Sakamoto, N.; Masamune, T. *J. Am. Chem. Soc.* 1988, *110*, 1985
- Watanabe, H.; Mori, K. *J. Chem Soc., Perkin Trans. 1* 1991, 2919
- Corey, E.J.; Houpis, I.N. *J. Am. Chem. Soc.* 1990, *112*, 8997
- Corey, E.J.; Hong, B. *J. Am. Chem. Soc.* 1994, *116*, 3149

COMPARISON OF THE HATCHING AGENTS

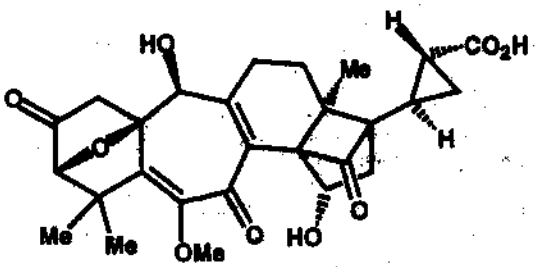


glycinoeclepin A

hatching agent of the soybean cyst nematode

$C_{25}H_{34}O_7$, MW 446.53

4 rings, 6 stereocentra



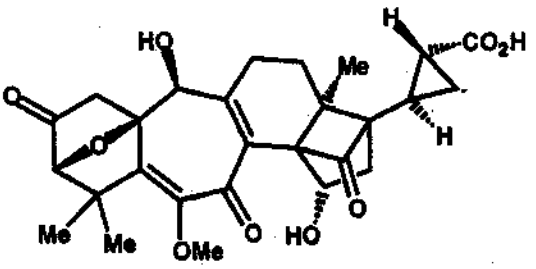
solanoeclepin A

hatching agent of the potato cyst nematode

$C_{27}H_{30}O_9$, MW 498.52

7 rings, 9 stereocentra

WHY SYNTHESIZE SOLANOECLEPIN A?



solanoeclepin A

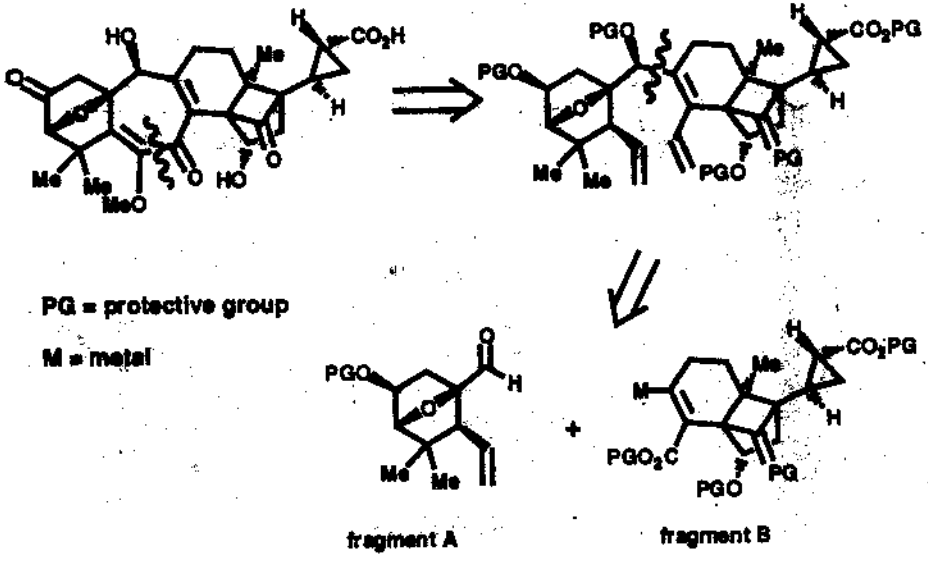
hatching agent of the potato cyst nematode

$C_{27}H_{30}O_9$, MW 498.52

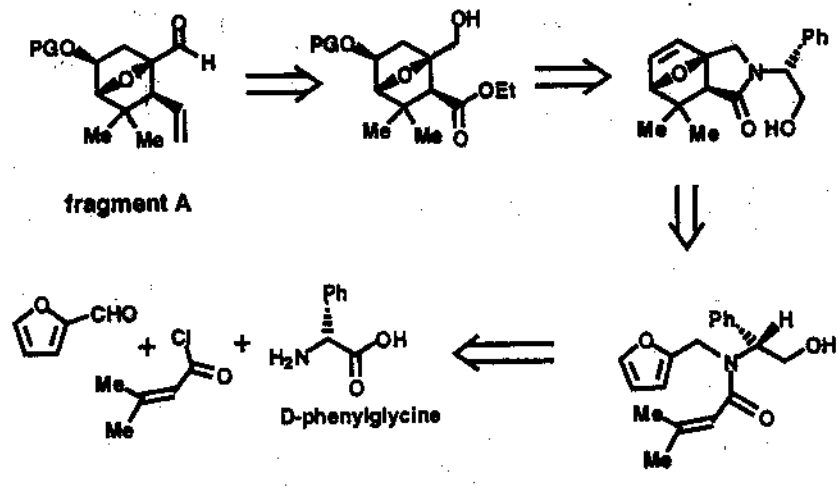
7 rings, 9 stereocentra

- highly challenging, unique architecture: 3, 4, 5, 6 and 7-membered rings
- unavailable in useful amounts from natural sources
- why is it stable only at $2 < pH < 7$ and at temperatures < 35 °C?
- can it play a role as a natural, environmentally benign nematocide as an alternative to crop rotation, soil fumigation and other chemical treatments?
- which parts of the molecule are responsible for biological activity?
- are there simpler analogues with useful hatching activity?

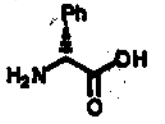
RETROSYNTHETIC ANALYSIS



RETROSYNTHESIS OF FRAGMENT A

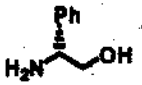


SYNTHESIS DIELS-ALDER PRECURSOR

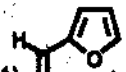


D-phenylglycine
(gift from DSM)

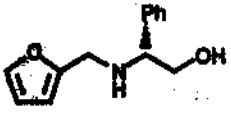
$NaBH_4$, THF
then add slowly
H_2SO_4 in Et_2O



91%

1) 
toluene, Δ

2) $NaBH_4$, *i*-PrOH

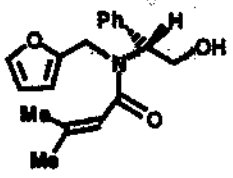


91%

1) TMSCl, pyridine, THF

2) 
, pyridine, THF

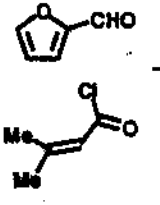
3) aq. HCl

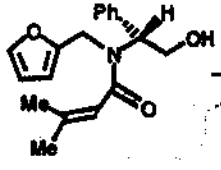


87%

carried out on 200 g scale

DIELS-ALDER REACTION

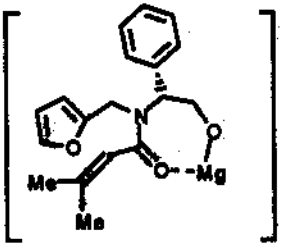




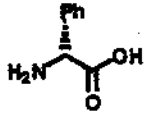
6 steps

(overall 72%
on 200 g scale)

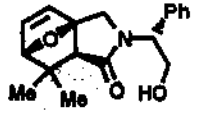
n-BuMgCl
Et_2O
-60 °C



toluene
16 h, reflux



D-phenylglycine
(gift from DSM)

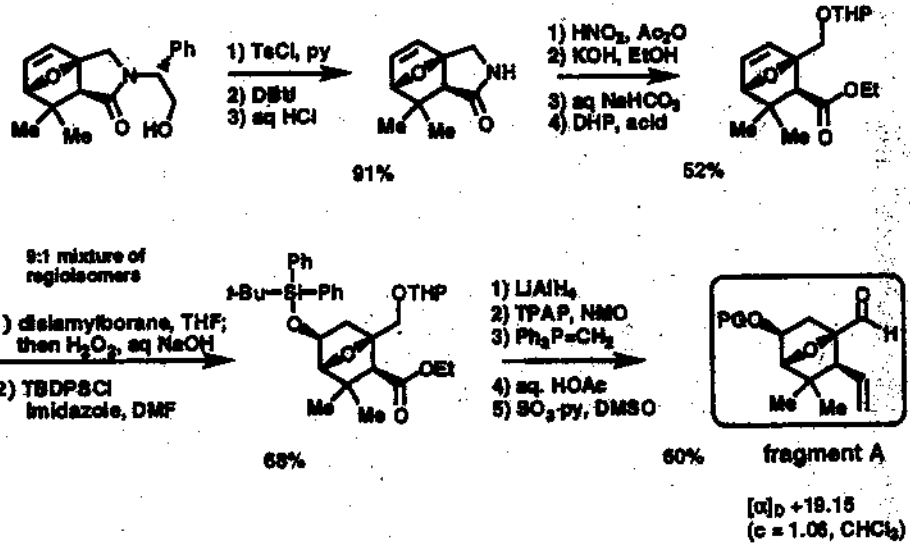


69% (26% s.m.) on 50 g scale

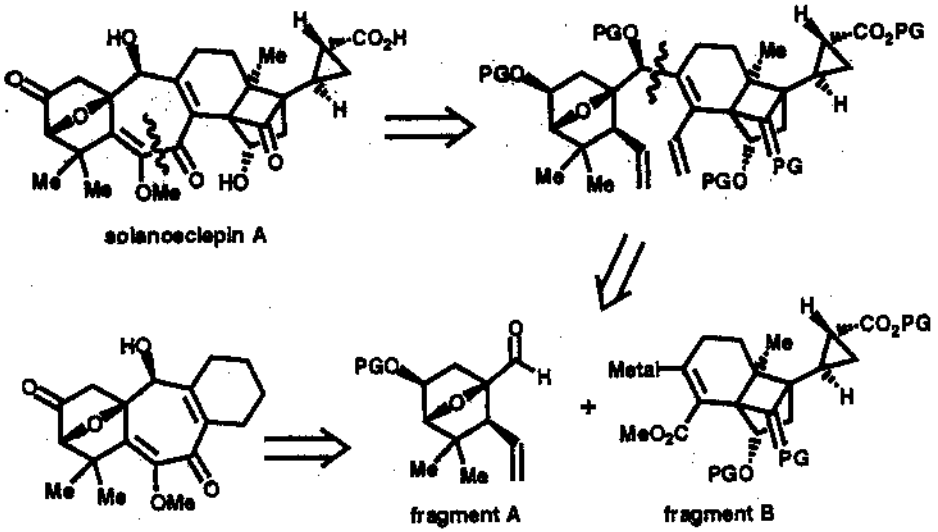
90:10 ratio of
diastereomers

cf T. Mukaiyama, N. Iwasawa, *Chem. Lett.* 1981, 29
M.R. Gmünder, C.H. Eugster, *Helv. Chim. Acta* 1990, *73*, 2190

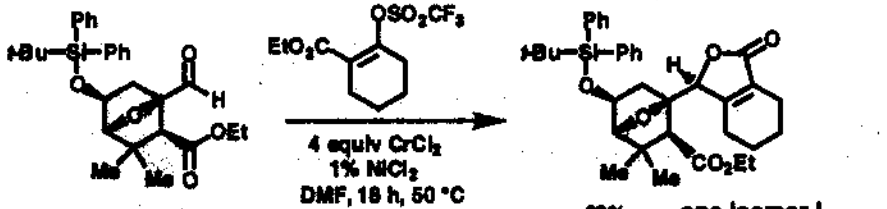
SYNTHESIS OF FRAGMENT A

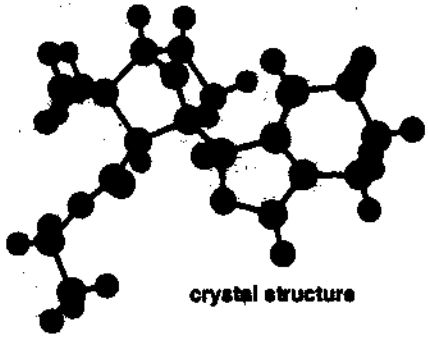


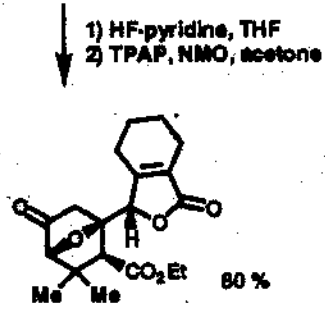
RETROSYNTHETIC ANALYSIS



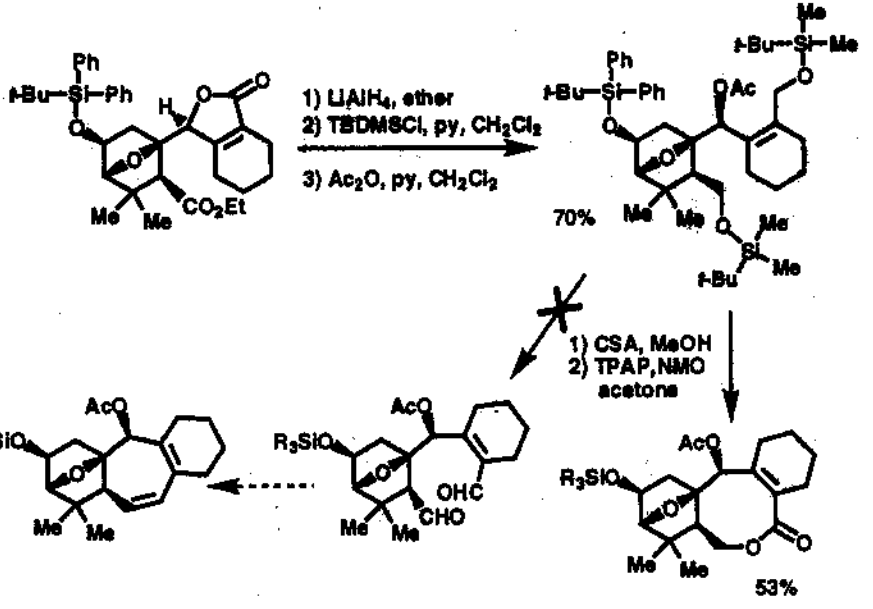
NOZAKI-HIYAMA COUPLING ESTER



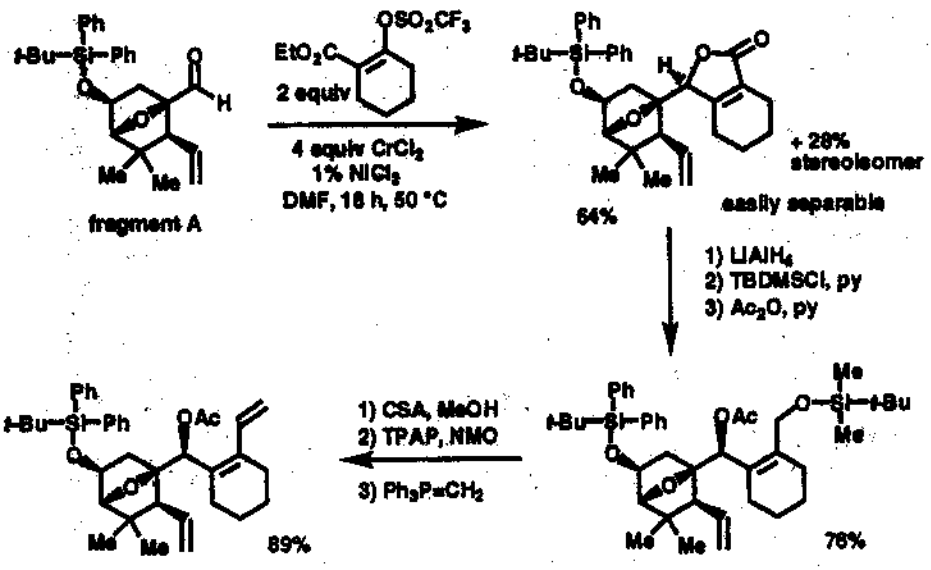




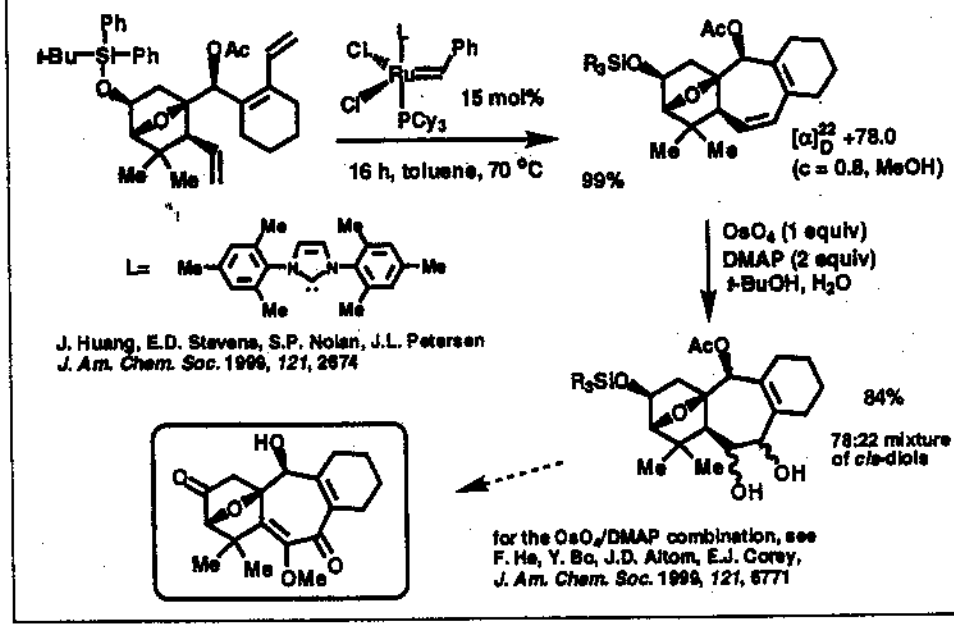
8-MEMBERED LACTONE



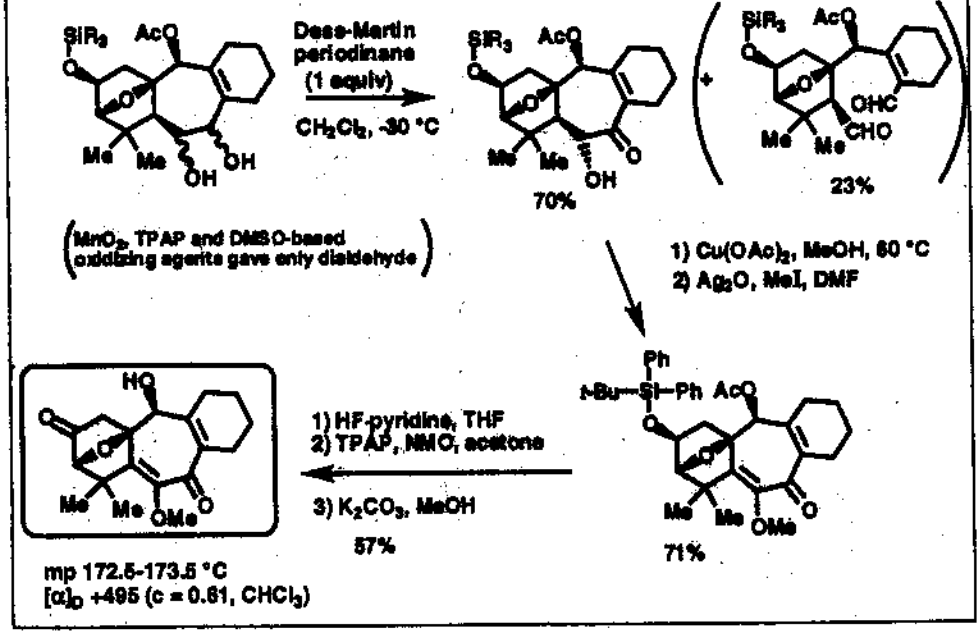
NOZAKI-HIYAMA COUPLING ALKENE



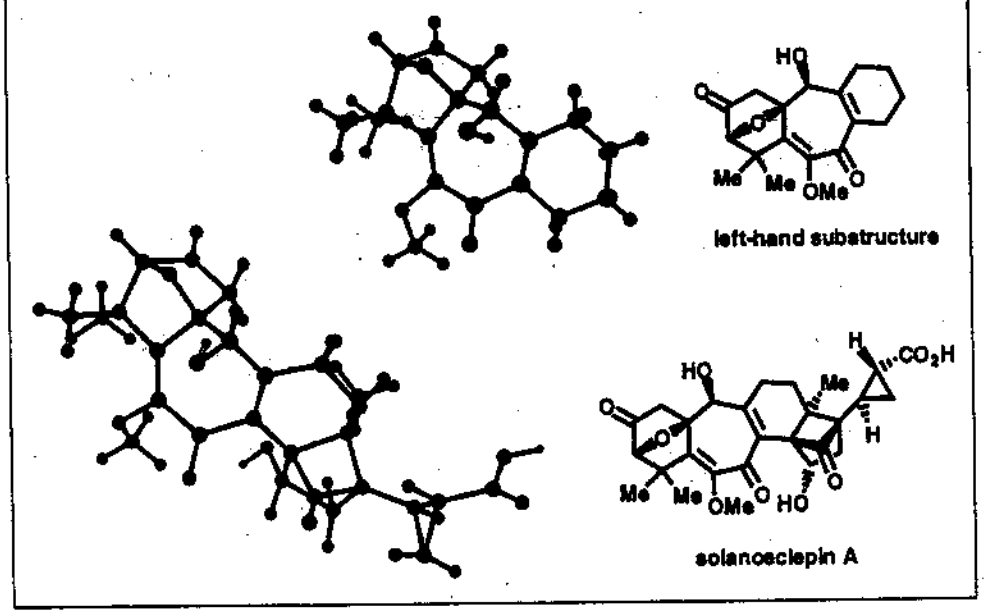
RING CLOSING METATHESIS



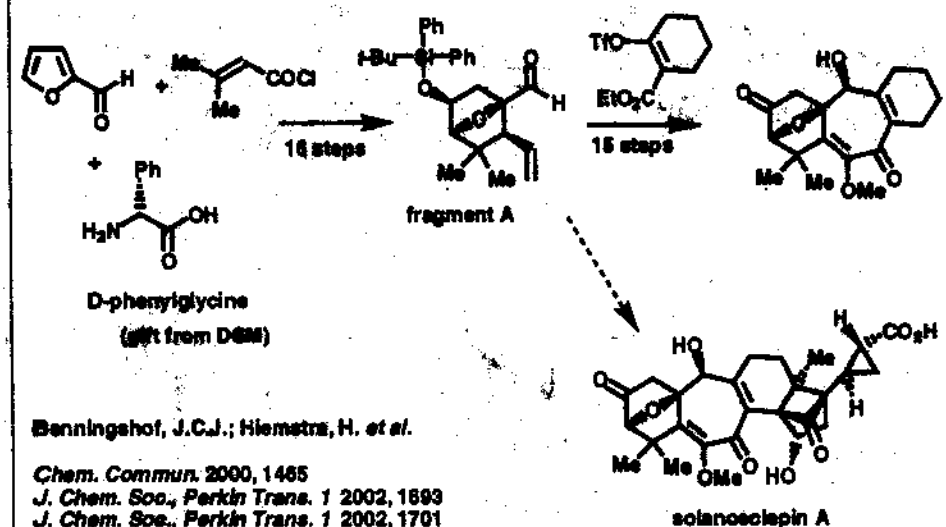
COMPLETION OF THE LEFT-HAND SUBSTRUCTURE



X-RAY COMPARISON



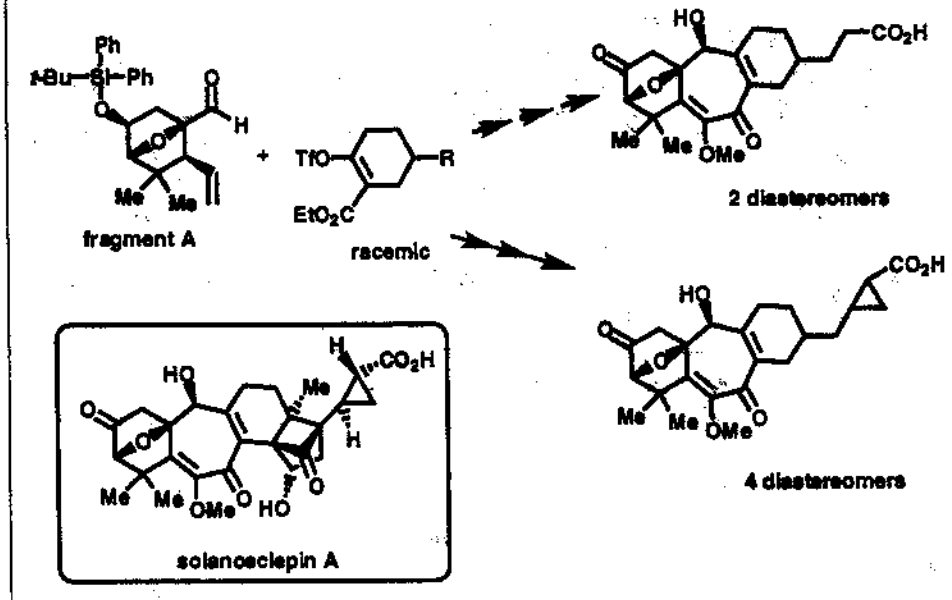
SUMMARY ON THE LEFT-HAND SIDE



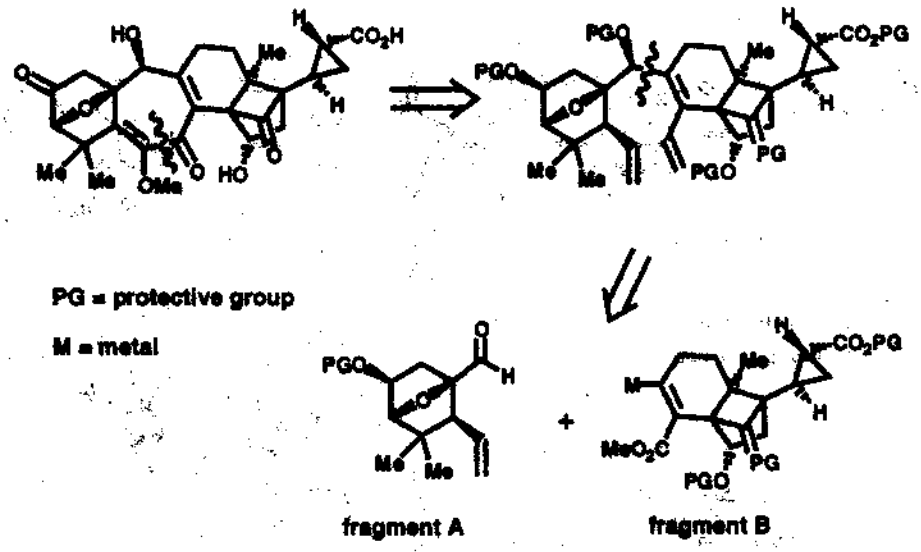
Benningshof, J.C.J.; Hiemstra, H. *et al.*

Chem. Commun. 2000, 1465
J. Chem. Soc., Perkin Trans. 1 2002, 1693
J. Chem. Soc., Perkin Trans. 1 2002, 1701

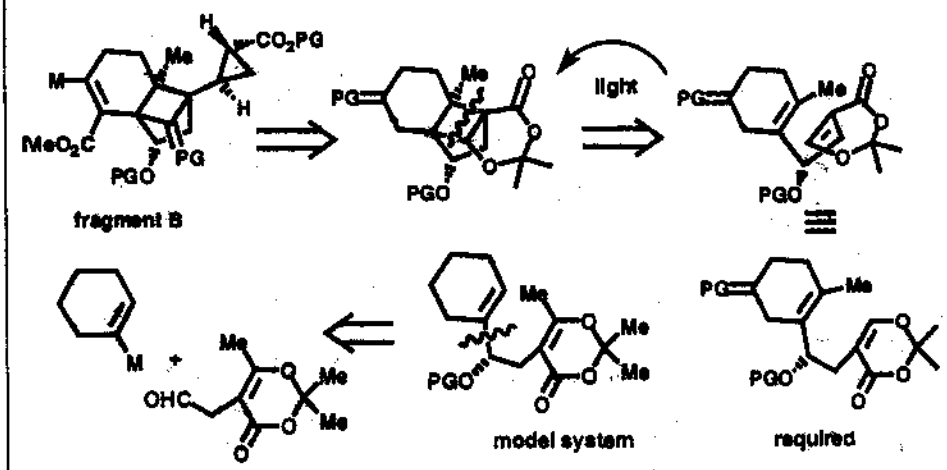
MORE ELABORATE ANALOGUES



RETROSYNTHETIC ANALYSIS

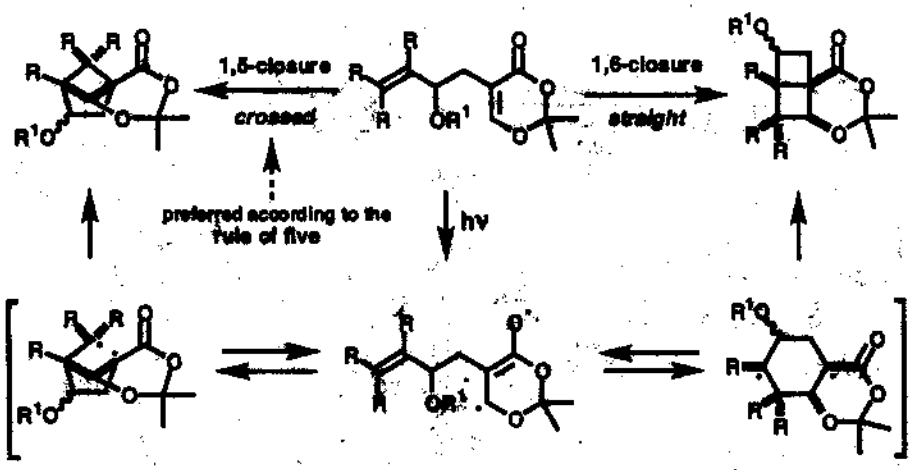


RETROSYNTHESIS OF FRAGMENT B



for intramolecular dioxenone photocycloaddition, see
Sato, M.; Abe, Y.; Takayama, K.; Sekiguchi, K.; Kaneko, C. *J. Heterocycl. Chem.* 1991, *28*, 241
Winkler, J.D.; Mazur Bowen, C.; Liotta, F. *Chem. Rev.* 1995, *95*, 2003

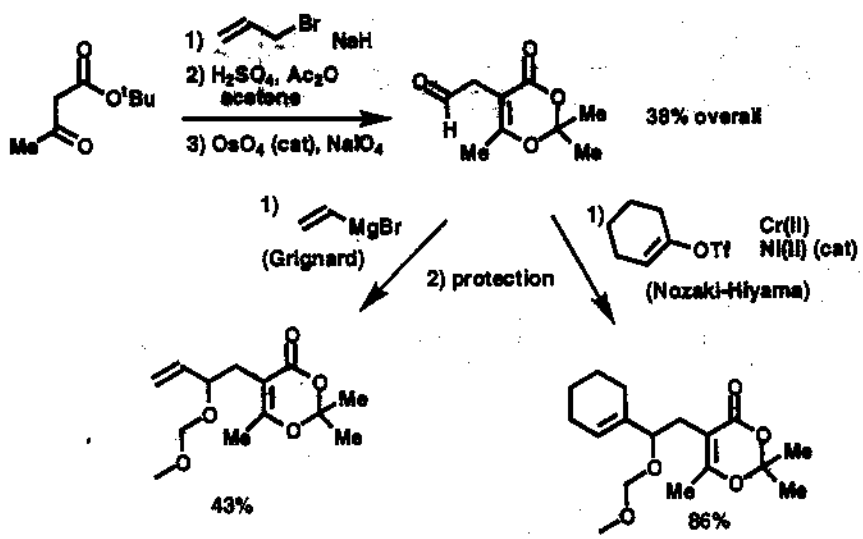
PHOTOCHEMISTRY: MECHANISM

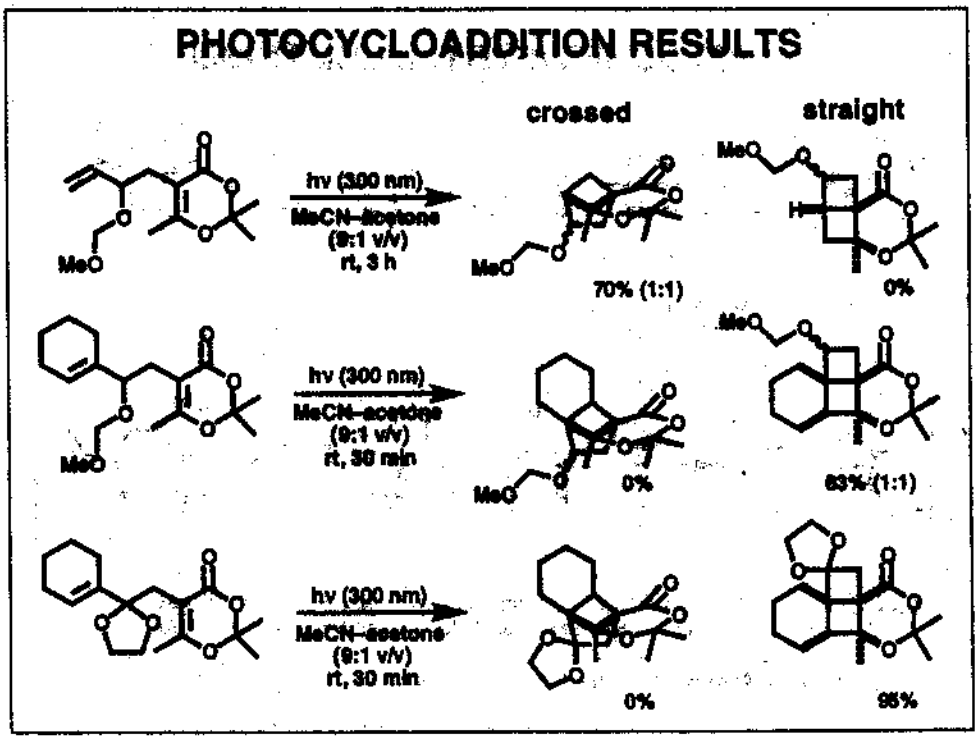


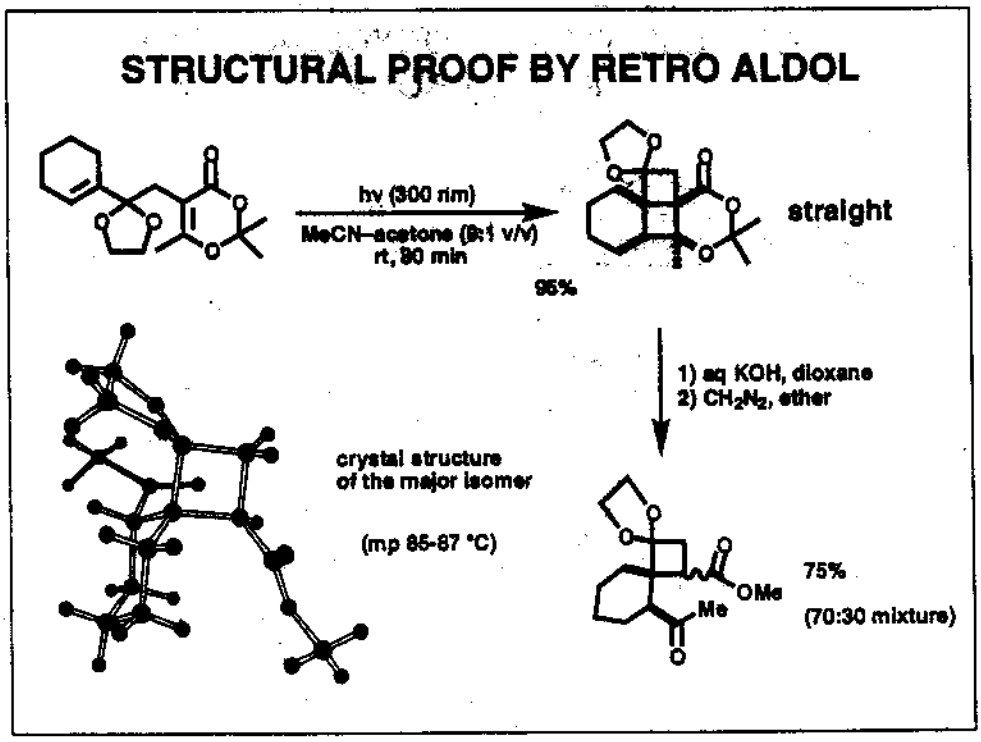
rule of five: R. Srinivasan, K.H. Carlough, *J. Am. Chem. Soc.* 1967, *89*, 4932
R.S.H. Liu, G.S. Hammond, *J. Am. Chem. Soc.* 1967, *89*, 4936

see also: D. Andrew, A.C. Weedon, *J. Am. Chem. Soc.* 1995, *117*, 5647

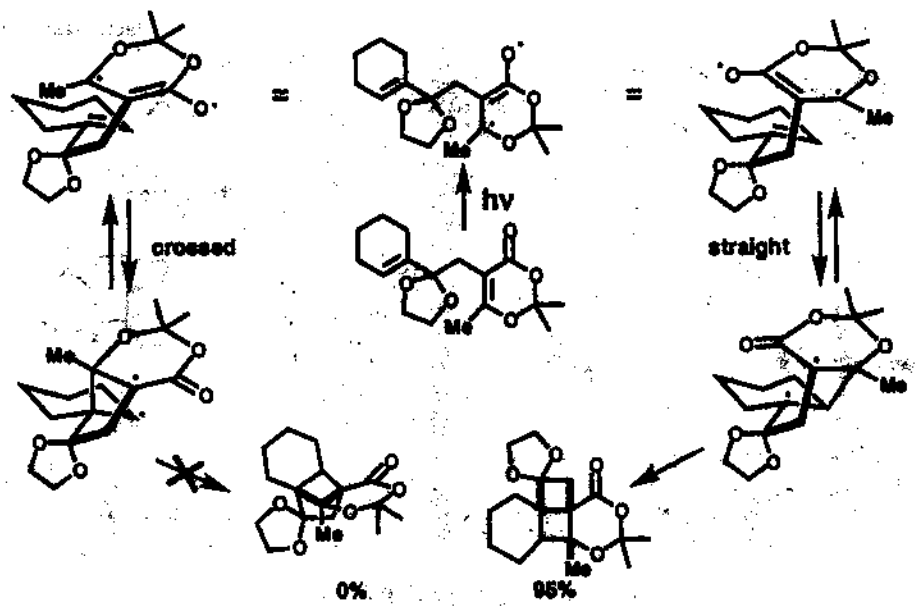
SYNTHESIS OF PHOTOCYCLOADDITION PRECURSORS



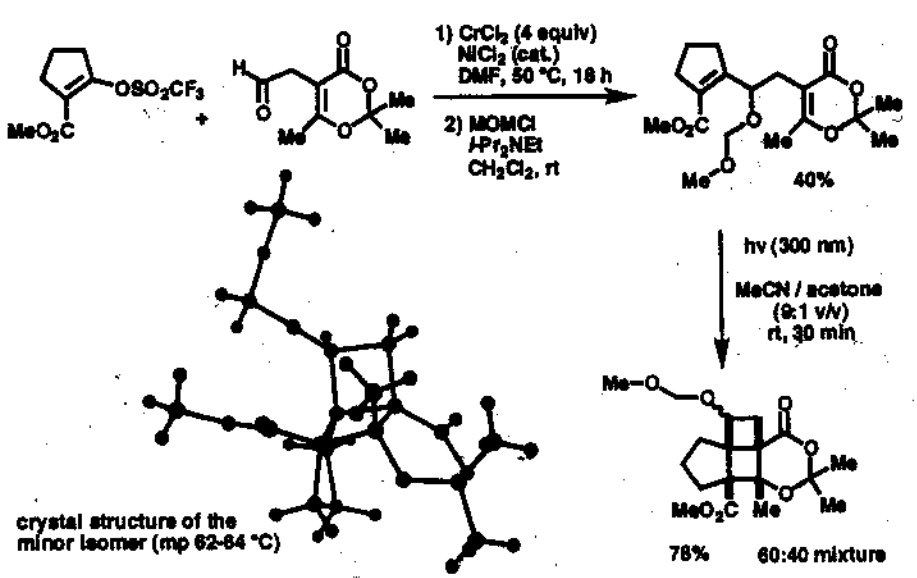

PHOTOCYCLOADDITION RESULTS
crossed
straight
hv (300 nm)
MeCN–acetone
(9:1 v/v)
rt, 3 h
MeO
70% (1:1)
0%
hv (300 nm)
MeCN–acetone
(9:1 v/v)
rt, 30 min
0%
83% (1:1)
hv (300 nm)
MeCN–acetone
(9:1 v/v)
rt, 30 min
0%
95%

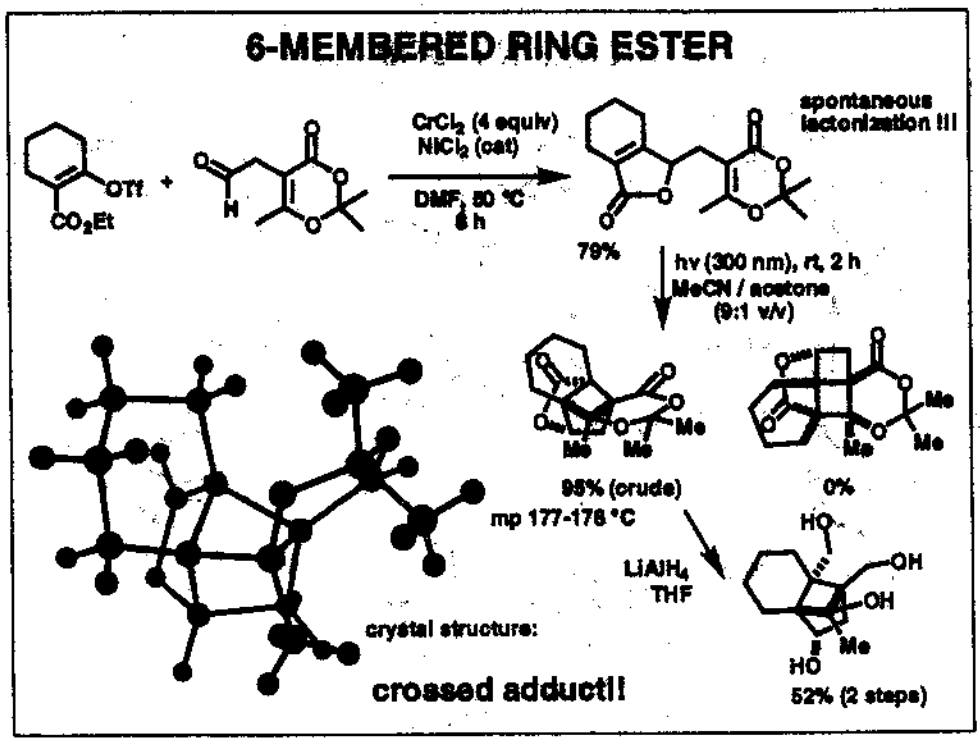

STRUCTURAL PROOF BY RETRO ALDOL
hv (300 nm)
MeCN–acetone (9:1 v/v)
rt, 30 min
95%
straight
1) aq KOH, dioxane
2) CH2N2, ether
crystal structure
of the major isomer
(mp 85-87 °C)
OMe
Me
75%
(70:30 mixture)

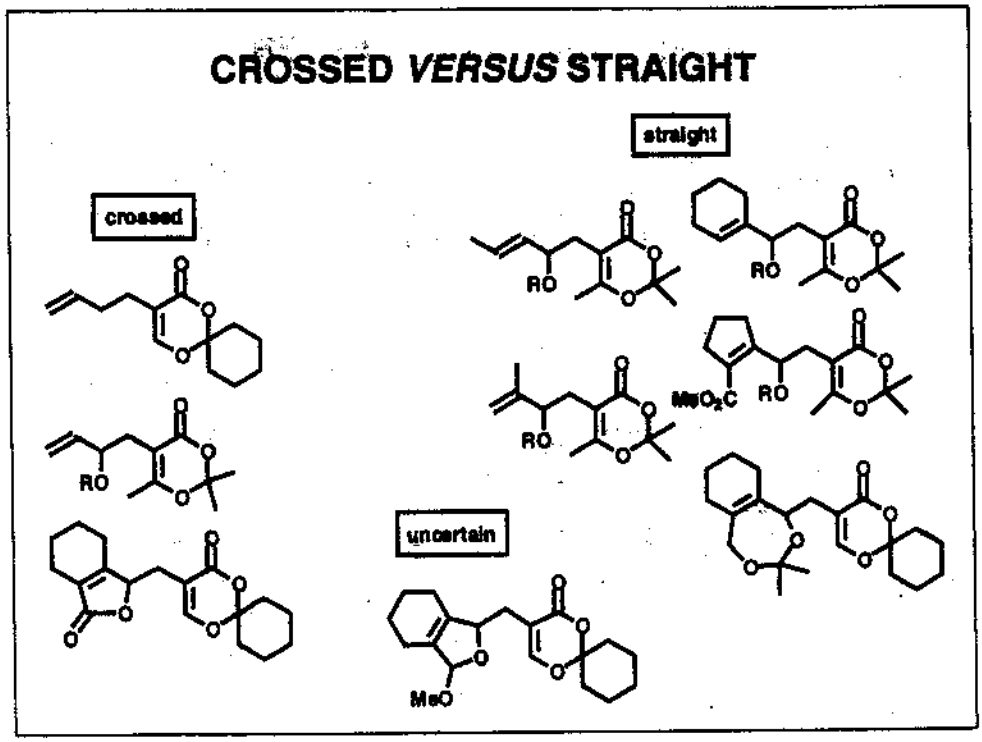
MECHANISM IN MORE DETAIL



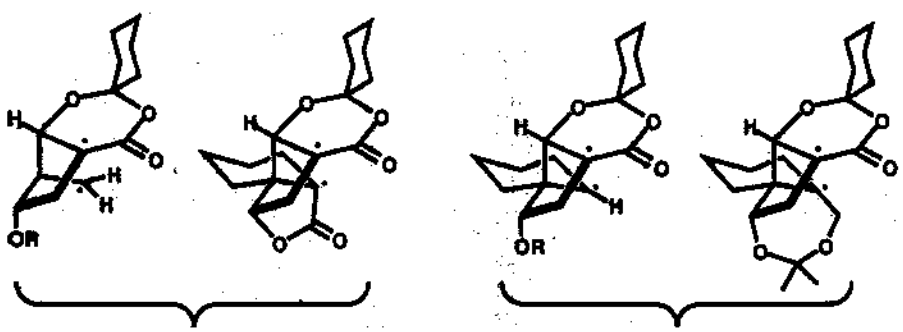
5-MEMBERED RING ESTER




6-MEMBERED RING ESTER
OTf
CO2Et
CrCl2 (4 equiv)
NiCl2 (cat)
DMF, 60 °C
6 h
spontaneous lactonization !!!
79%
hv (300 nm), rt, 2 h
MeCN / acetone
(9:1 v/v)
95% (crude)
mp 177-178 °C
0%
LiAlH4
THF
52% (2 steps)
crystal structure:
crossed adduct!!


CROSSED VERSUS STRAIGHT
crossed
straight
uncertain
RO
MeO2C
MeO

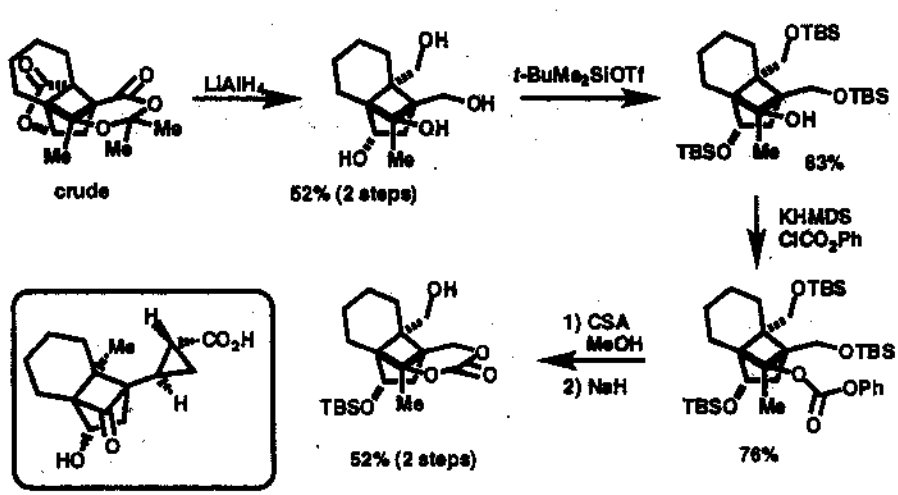
CROSSED *VS* STRAIGHT MECHANISM



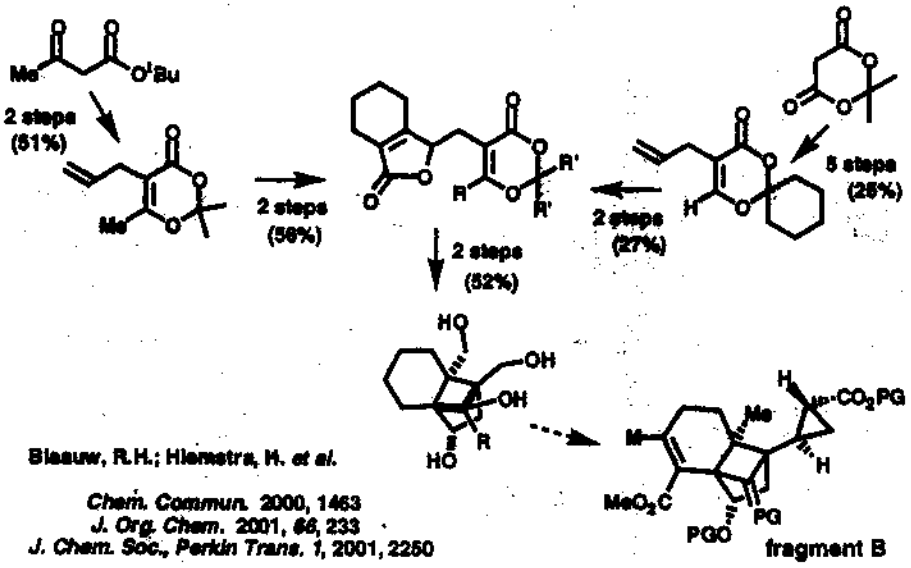
cyclize directly to crossed products

do not cyclize, but instead return to starting materials and then cyclize to straight products

HOW TO DISTINGUISH HYDROXYL GROUPS?



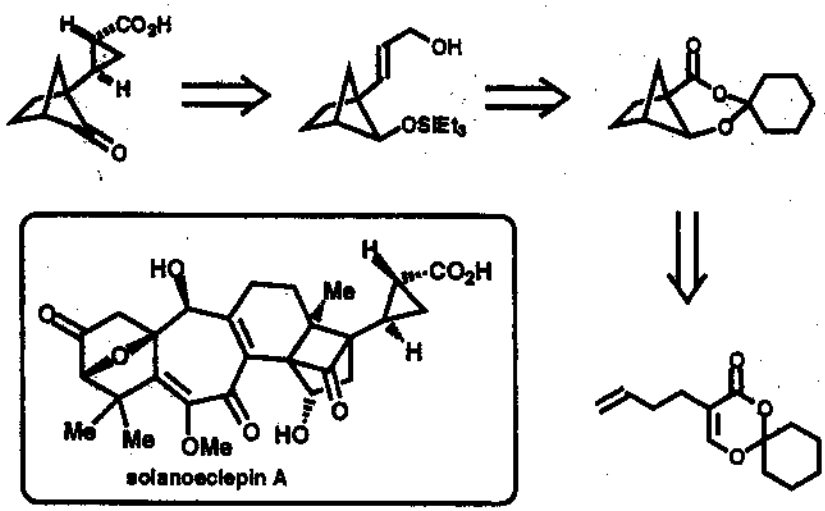
HOW TO APPROACH FRAGMENT B?



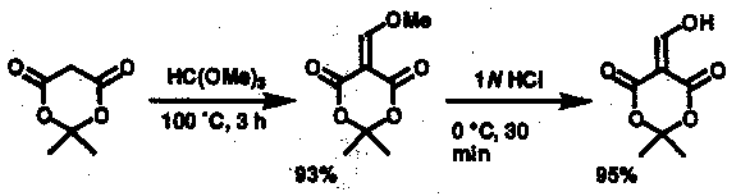
Biesuw, R.H.; Hiemstra, H. *et al.*

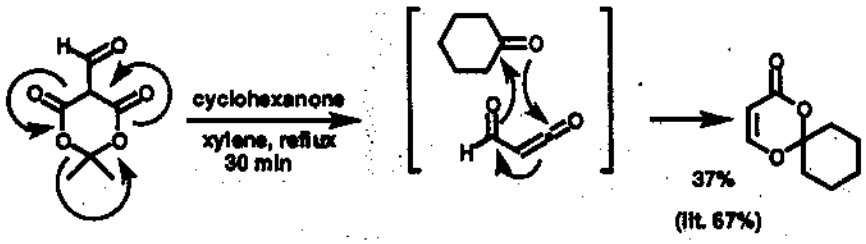
Chem. Commun. 2000, 1463
J. Org. Chem. 2001, *66*, 233
J. Chem. Soc., Perkin Trans. 1, 2001, 2250

SYNTHESIS OF THE RIGHT-HAND SIDE



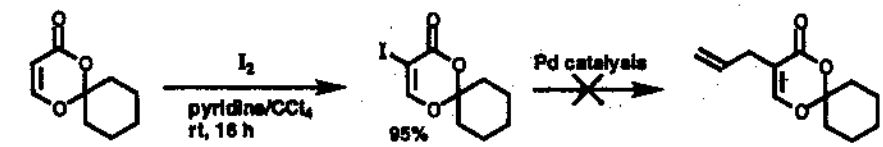
6-UNSUBSTITUTED DIOXENONE

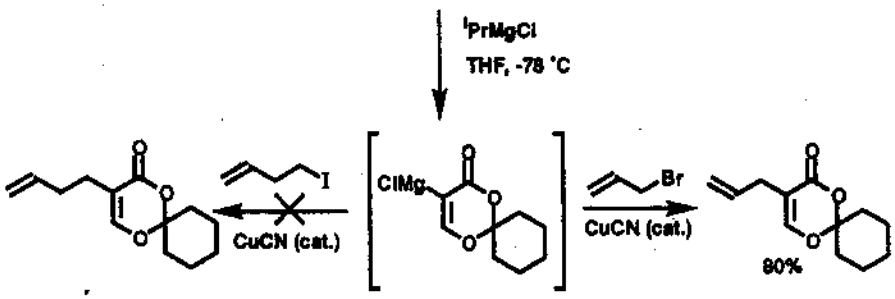




M. Sato, K. Sekiguchi, H. Ogasawara, C. Kaneko, *Synthesis* 1985, 224

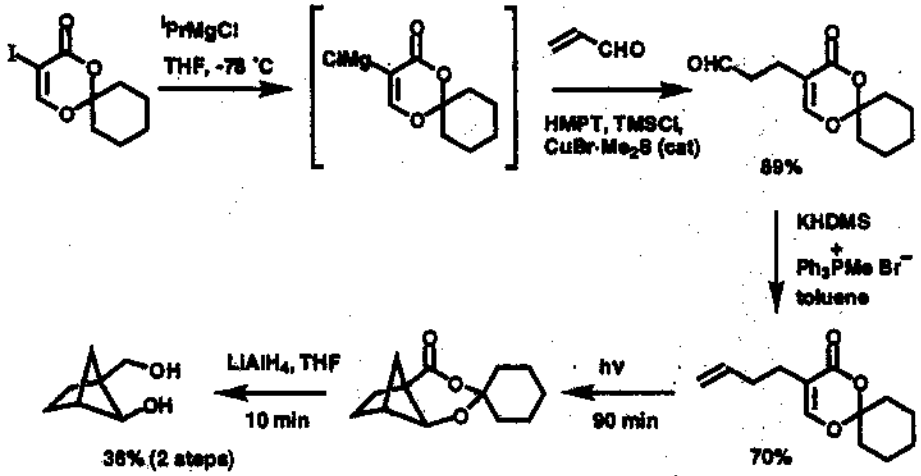
DIOXENONE FUNCTIONALIZATION



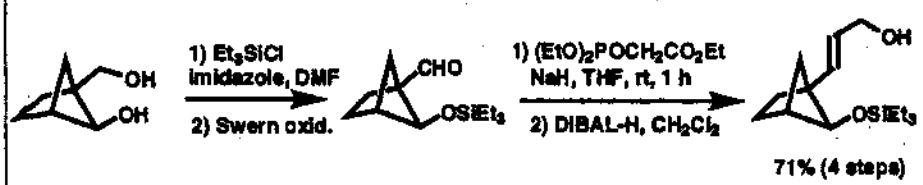


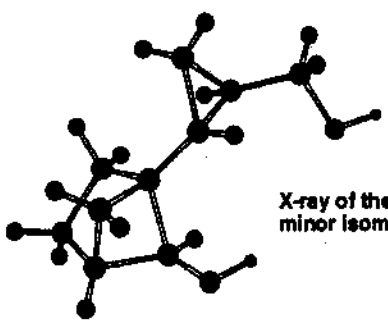
For the iodine-magnesium exchange, cf. M. Abrardi, P. Knochel, *Synlett* 1999, 1577

SYNTHESIS OF THE BICYCLO[2.1.1]HEXANE

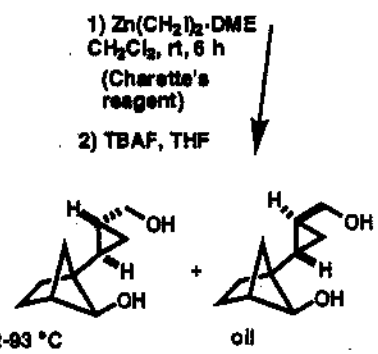


CYCLOPROPANE SYNTHESIS

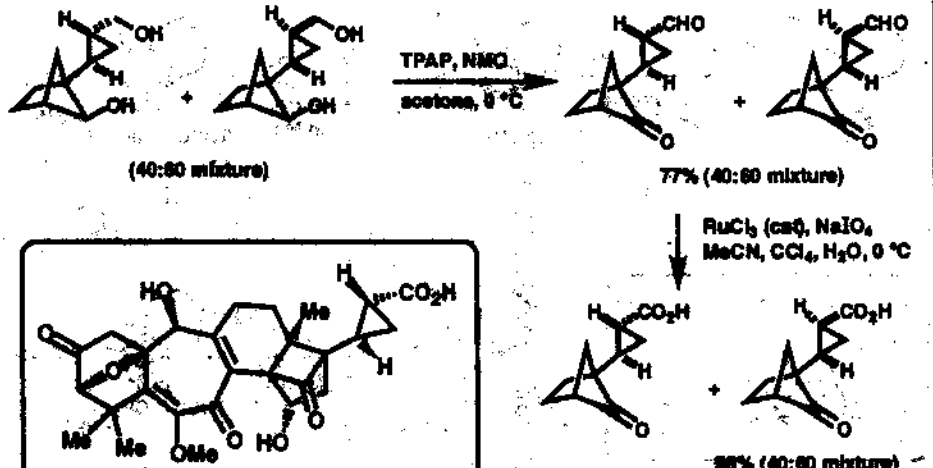




X-ray of the minor isomer

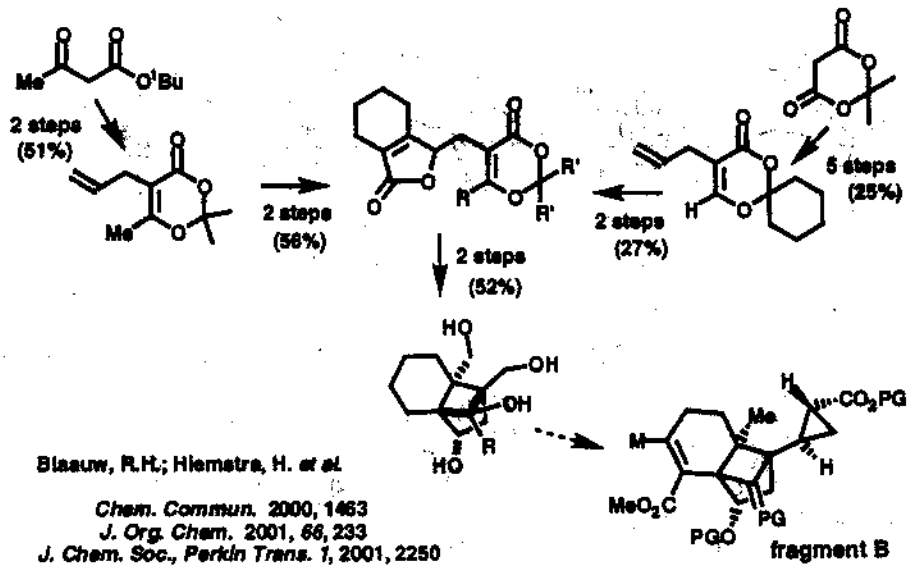


CYCLOPROPANECARBOXYLIC ACID



Brière, J.-F.; Hiemstra, H. *et al.*
Eur. J. Org. Chem. 2001, 2371

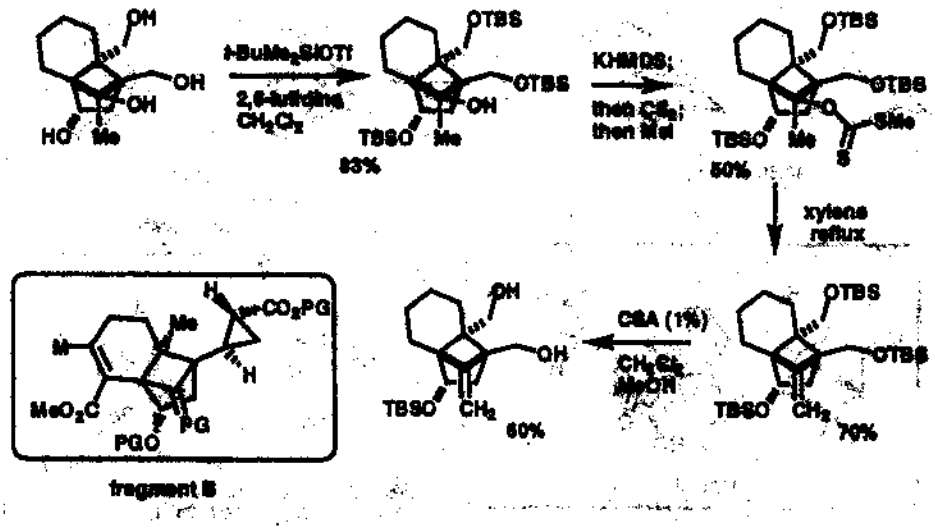
HOW TO APPROACH FRAGMENT B?



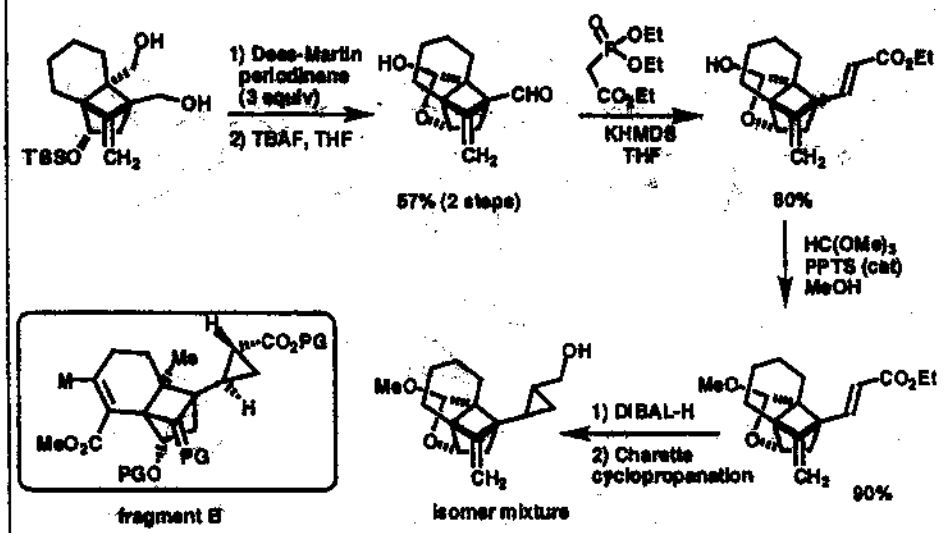
Blaauw, R.H.; Hiemstra, H. *et al.*

Chem. Commun. 2000, 1463
J. Org. Chem. 2001, *66*, 233
J. Chem. Soc., Perkin Trans. 1, 2001, 2250

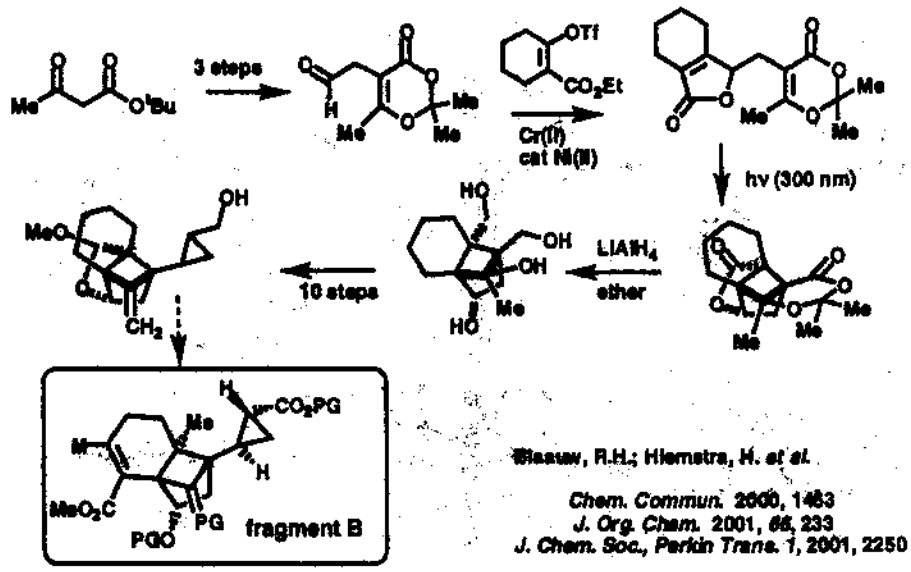
SYNTHESIS OF THE METHYLENECYCLOBUTANE



REDUCTION TO THE ANGULAR METHYL



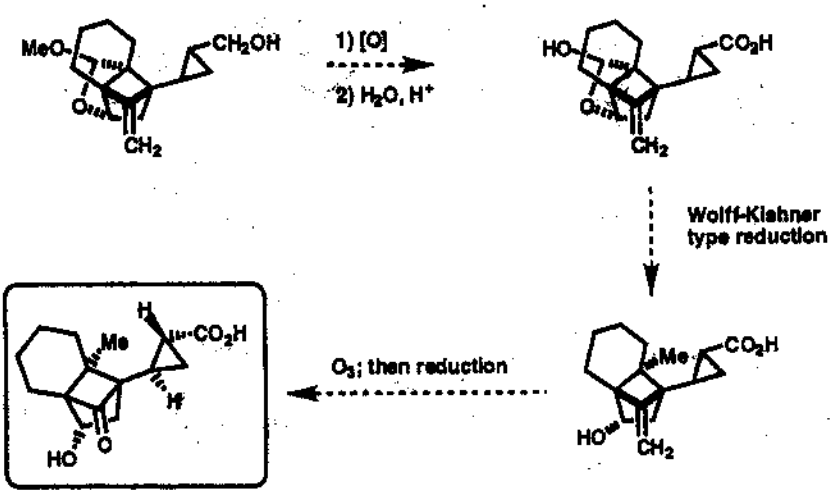
SUMMARY ON THE APPROACH TO FRAGMENT B



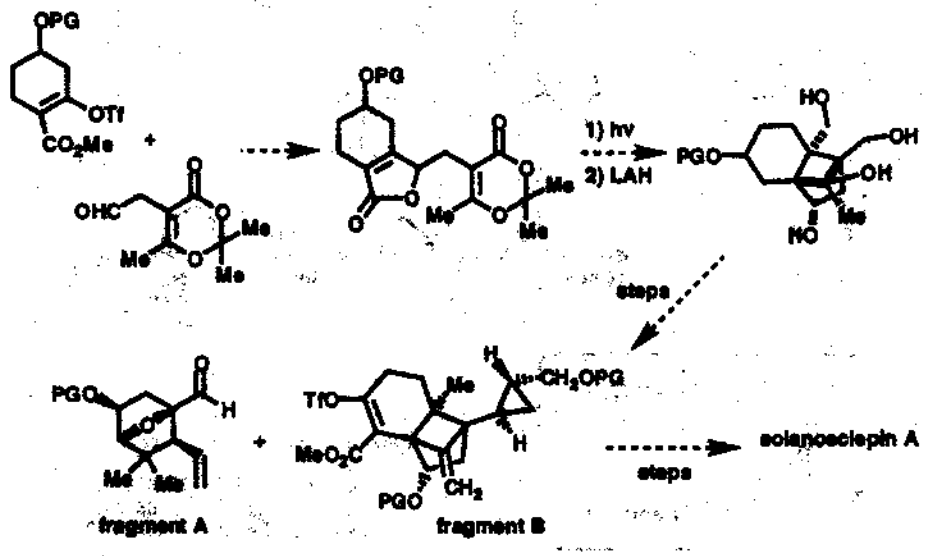
Blaauw, R.H.; Hiemstra, H. *et al.*

Chem. Commun. 2000, 1483
J. Org. Chem. 2001, *66*, 233
J. Chem. Soc., Perkin Trans. 1, 2001, 2250

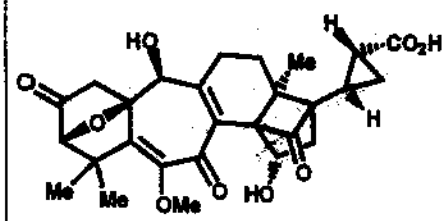
FURTHER PLANS I



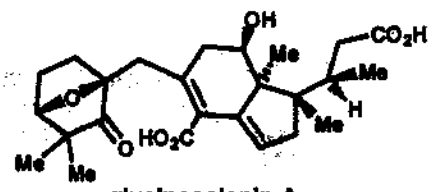
FURTHER PLANS II



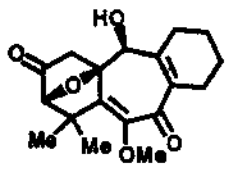
PCN HATCHING ACTIVITY TESTS



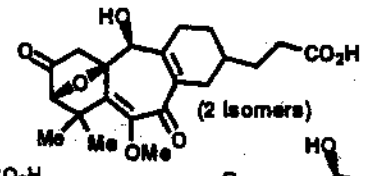
solanoeclepin A,
PCN natural hatching agent



glycinoeclepin A,
SCN natural hatching agent;
no activity to PCN

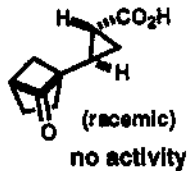


no activity



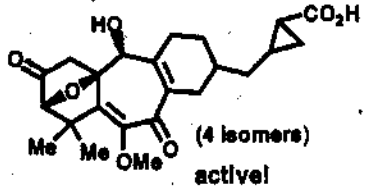
(2 isomers)

active!



(racemic)

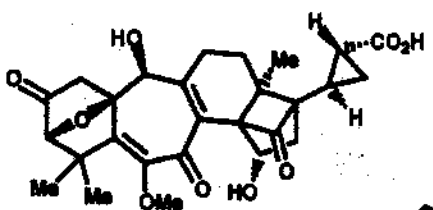
no activity



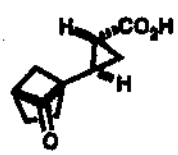
(4 isomers)

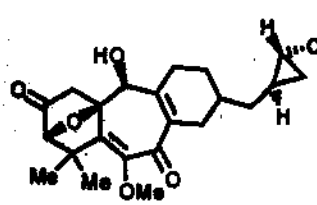
active!

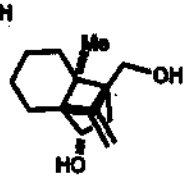
ACKNOWLEDGEMENTS



solanoeclepin A







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