Water as a solvent in organic synthesis. WHY?

- The most abundant liquid and the only inorganic liquid that occurs naturally on earth ; very cheap (not free)
- Non toxic, odorless, non flammable, incombustible.
- Highly structured liquid with a three-dimensional molecular network with the highest cohesive energy density, **source of hydrophobic effects**
- Very high dielectric constant ; highest E_T parameter

⇒ Influence on chemical reactivity

- rate enhancement
  - Lower temperature
  - No promotors
  - Less catalysts
- different selectivities compared with organic solvents
- allows reactions otherwise impossible

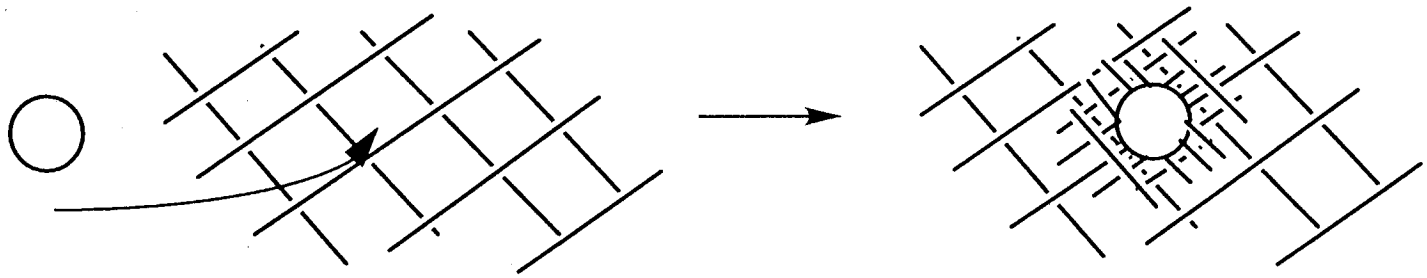
Water has

- the highest cohesive energy density
  550 cal.mL^{-1} = **22000 atm**.
- A very large surface tension
- A very large heat capacity, which is reduced to half its value upon boiling or freezing

These Three points are coherent with a structured - liquid which is the source of special effects called

HYDROPHOBIC EFFECTS

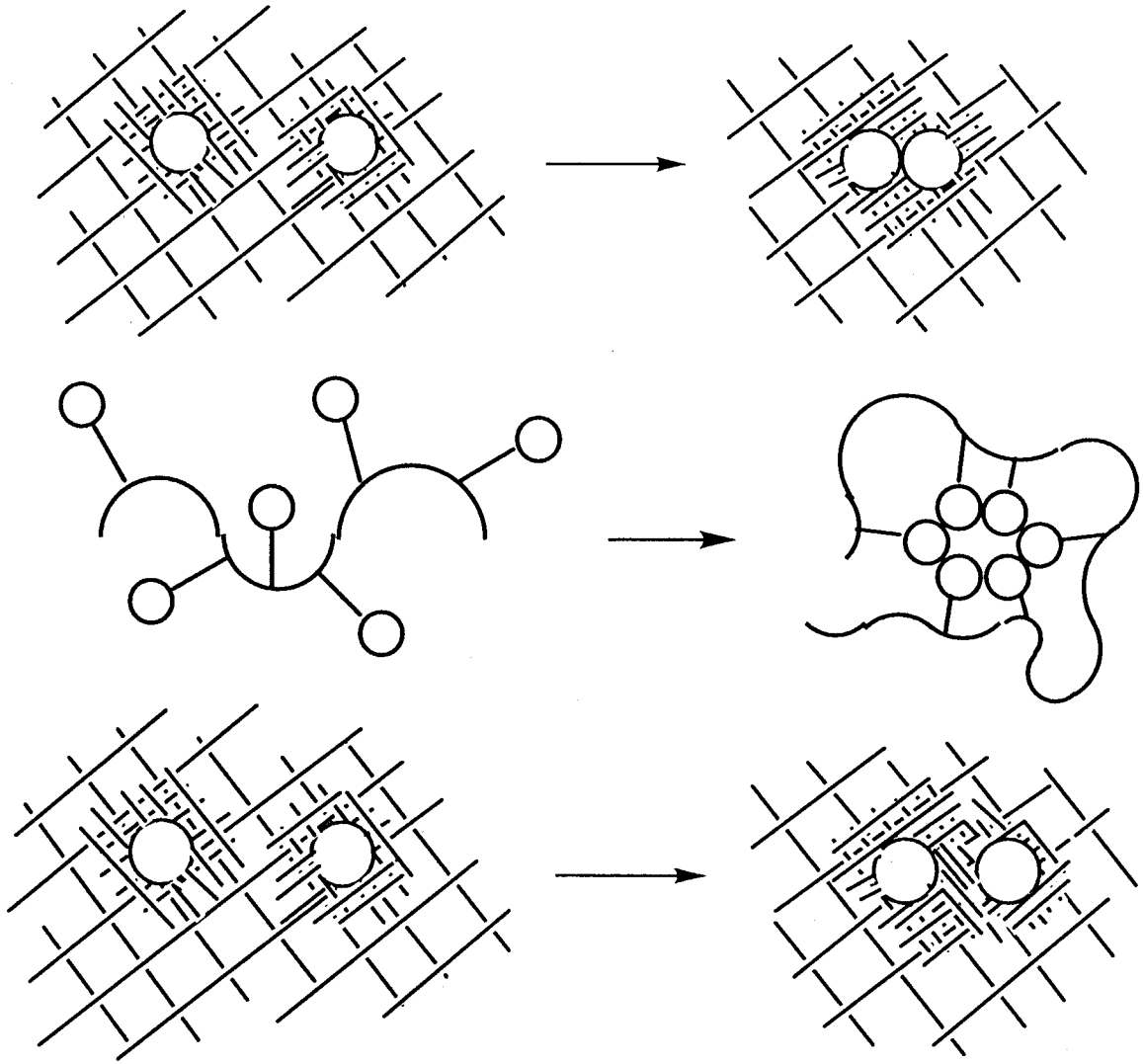
Hydrophobic hydration



	Hydrophobic	Hydrophilic
ΔG_2^E (cal. mol^{-1})	≥ 5000	$\approx \pm 600$
ΔH_2^E (cal. mol^{-1})	$\approx \pm 1000$	$\approx \pm 1000$
ΔS_2^E	$T\lvert\Delta S_2^E\rvert >> \lvert\Delta H_2^E\rvert$	$T\lvert\Delta H_2^E\rvert > \lvert\Delta S_2^E\rvert$
ΔC_{p2}^E (cal. mol^{-1}.deg^{-1})	≥ 50	≈ 3
ΔV_2^E (cm^3. mol^{-1})	≤ -15	$\approx \pm 1$

COM

Hydrophobic interaction



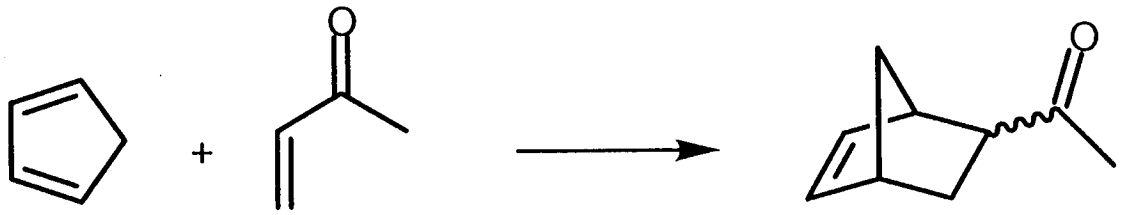
	ced (cal cm^{-3})	E_T (kcal.mol^{-1})	ε
water	550.2	63.1	78.5
formamide	376.4	56.6	109.5
ethyleneglycol	213.2	56.3	37.7
methanol	208.8	55.5	32.6
dimethylsulfoxide	168.6	45.0	48.9
ethanol	161.3	51.9	24.3
nitromethane	158.8	46.3	38.6
1-propanol	144	50.7	20.1
acetonitrile	139.2	46.0	37.5
dimethylformamide	139.2	43.8	36.7
2-propanol	132.3	48.6	18.3
1-butanol	114.5	50.2	17.1
t-butanol	110.3	43.9	12.2
dioxan	94.7	36.0	2.2
aceton	94.3	42.2	20.7
tetrahydrofuran	86.9	37.4	7.4
chloroform	85.4	39.1	4.7
toluene	79.4	33.9	2.4
diethyl ether	59.9	34.6	4.2
hexane	52.4	30.9	1.9

Organic synthesis in water

- **(4+2) CYCLOADDITIONS (DIELS ET ALDER)**
- (4+6) CYCLOADDITIONS
- **(4+3) CYCLOADDITIONS (THROUGH OXYALLYL CATIONS)**
- (3+2) CYCLOADDITIONS (AZOMETHINE YLIDS CYCLOADDITIONS)
- COPE, CLAISEN REARRANGMENTS
- **ALDOLISATION**
- **MICHAEL ADDITIONS**
- PROCHIRAL KETONES REDUCTIONS
- α, β - UNSATURATED KETONES REDUCTIONS
- AROMATIC ELECTROPHILIC SUBSTITUTIONS
- **HETERO DIELS - ALDER (C=O)**
- **BAYLIS HILLMAN REACTIONS**
- **OXIDATION**

COM

Origine of the rate enhancements



K_{H_2O} $4400\ 10^{-5}\ M^{-1}\ s^{-1}$

K_{MeOH} $75\ 10^{-5}\ M^{-1}\ s^{-1}$

	$\Delta H^{\ddagger}$ (cal)	$\Delta S^{\ddagger}$ (u.e.)
H_2O	9125 ± 400	-33.79 ± 1.5
MeOH	9090 ± 270	-41.77 ± 0.9

COM

HYPOTHESIS

The cohesive energy of water acts as an external pressure

An organic reaction, under kinetic control, between two small hydrophobic organic molecules(at least partially soluble in water) must be accelerated in water if its activation volume is negative

If two transition states are possible, the more compact will be favored

	$\Delta V^{\ddagger}$ ($cm^3\ M^{-1}$)
Bond formation	-10 to -15
Charges concentration	-5 to -10
Ionisation	-20

Ex : for the Diels-Alder reaction, $\Delta V^{\ddagger} = -30\ cm^3\ M^{-1}$.

$$\Delta V^{\ddagger}_{endo} < \Delta V^{\ddagger}_{exo}$$

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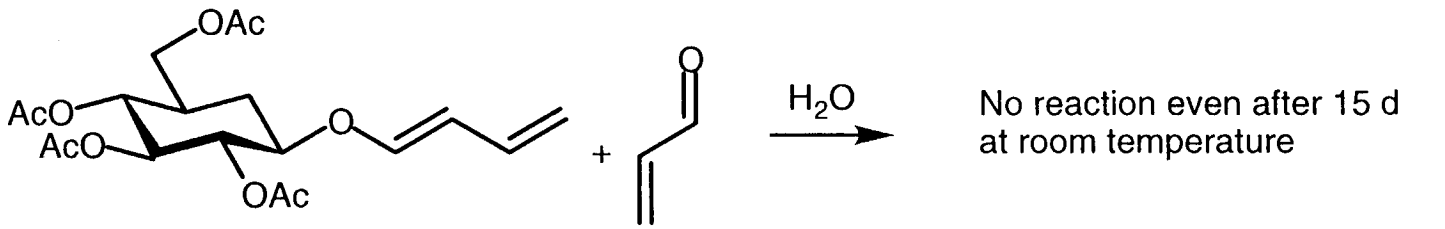
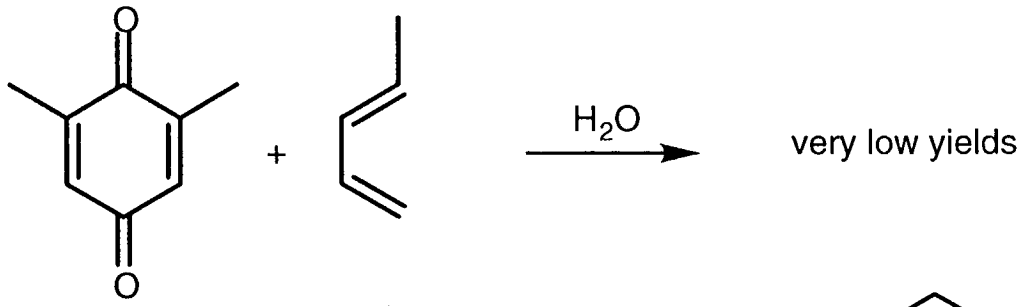
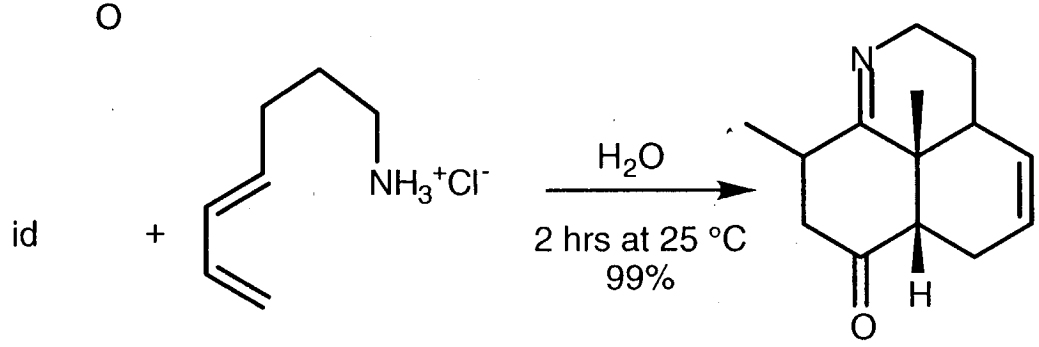
IT IS NECESSARY TO USE A WATER SOLUBLE COMPOUND



Lubineau 1985

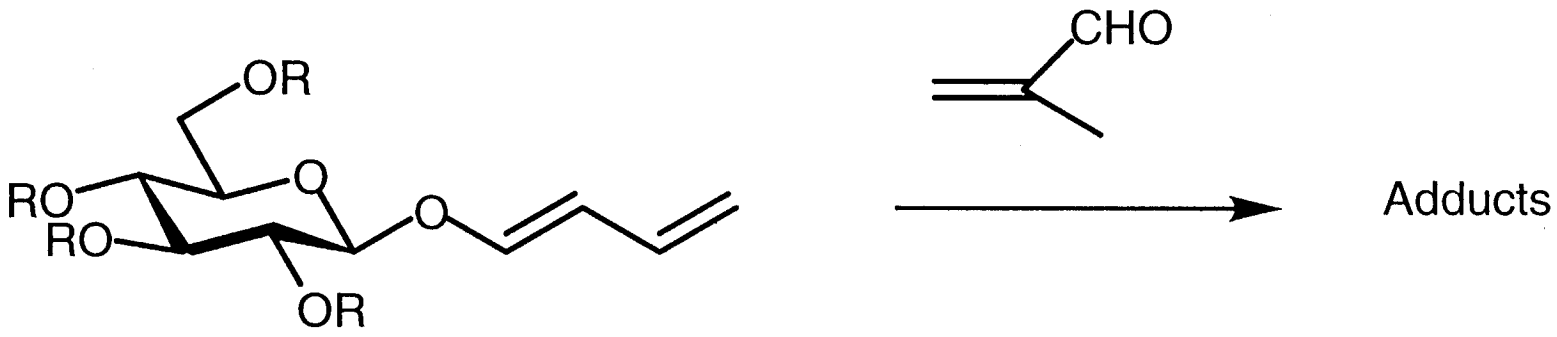




Grieco 1986

COM

Glyco-organic compound



R	Solvent	t(hrs)	T (°C)	yields	endo / exo	re / si
Ac	toluene	168	80	80	87 : 13	62 : 38
H	water	3.5	20	90	>98 : 2	60 : 40

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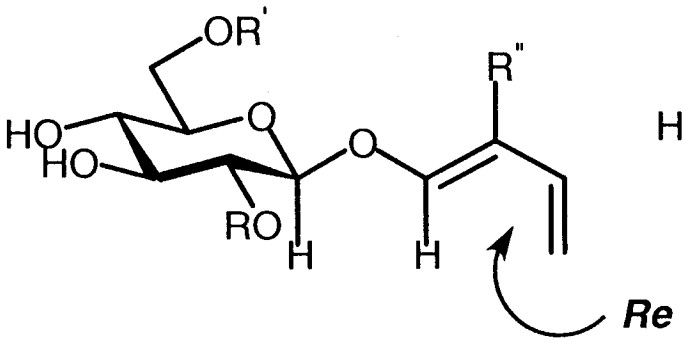
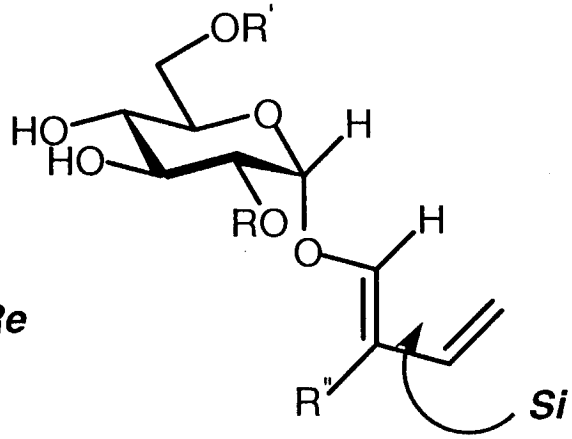
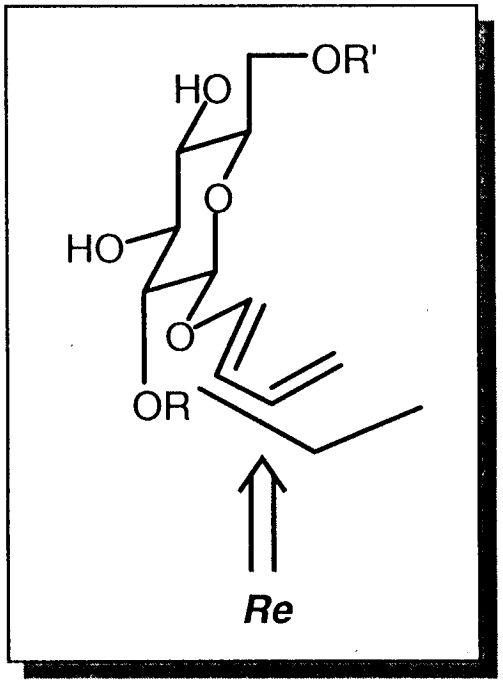
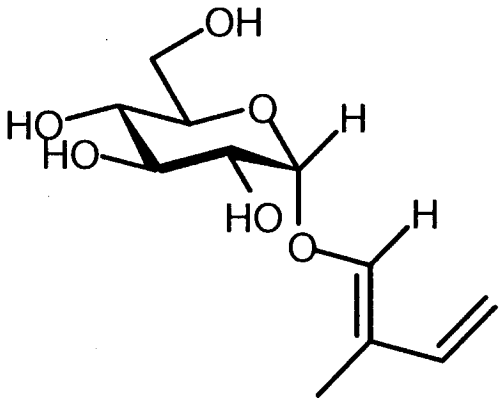
Using carbohydrate chemical versatility









78% isolated yields of one out of the four possible diastereoisomers (*endo Si*)

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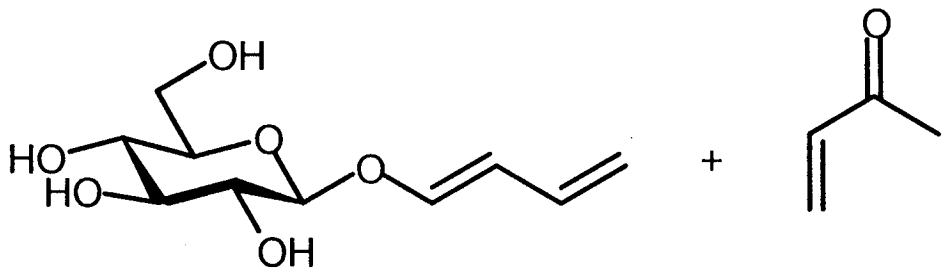
Is it possible to enhance even more the reaction rate ?



Additives	10^5 k (M^{-1} s^{-1})	Re : Si
-	28.2	60 : 40
MeOH 50%	7.5	
β-cyclodextrine (saturated)	41.6	
Glucose 1M	34.8	
2M	44.6	
3M	61.3	

Neat on glucose (after co-crystallization)	70 : 30
Neat on saccharose (after co-crystallization)	88 :12

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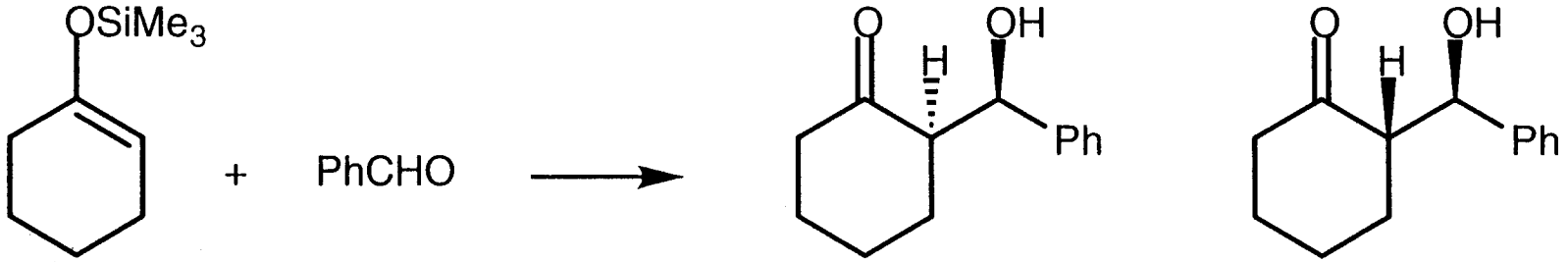

syn anti

Solvent	Temp, Time	Conditions	Yields	Syn / Anti
CH_2Cl_2	20°C, 2 h	$TiCl_4$, 1eq	82%	25/75
CH_2Cl_2	60°C, 9 d	10000atm	90%	75/25
H_2O	20°C, 5 d	ST	23%	85/15
H_2O - THF (1:1)	20°C, 5 d	ST	45%	74/26
id	55°C, 2 d	US	76%	74/26

Mukaiyama et al, 1974
Yamamoto et al, 1983

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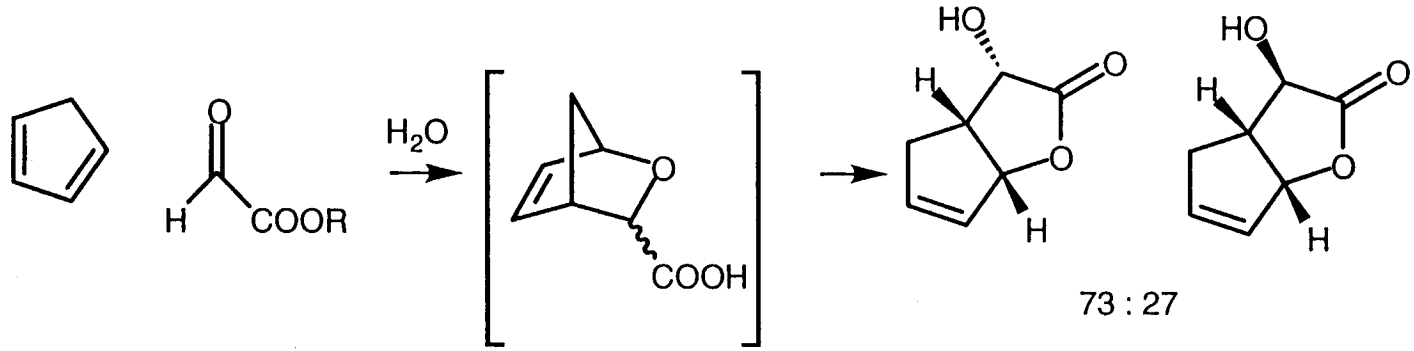
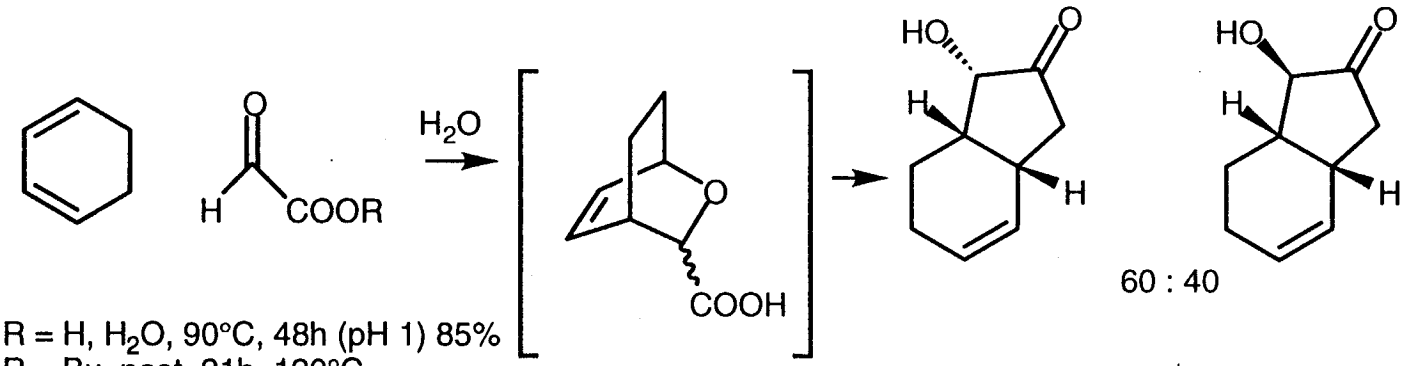


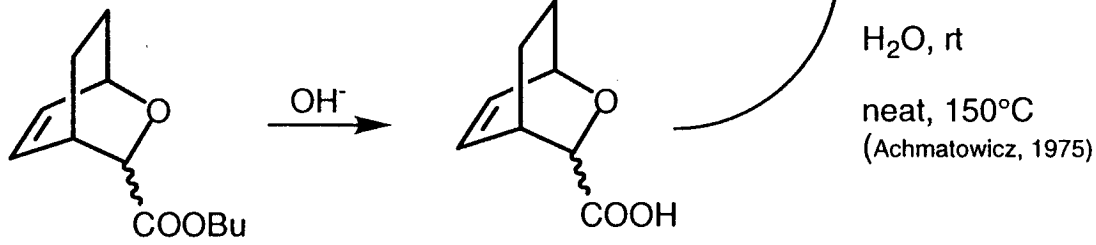
73 : 27

R - Bu, neat or organic solvent, no reaction
R =H, H_2O, 83%, 1.5h, 40°C (pH 0.9)



60 : 40

R = H, H_2O, 90°C, 48h (pH 1) 85%
R = Bu, neat, 21h, 120°C



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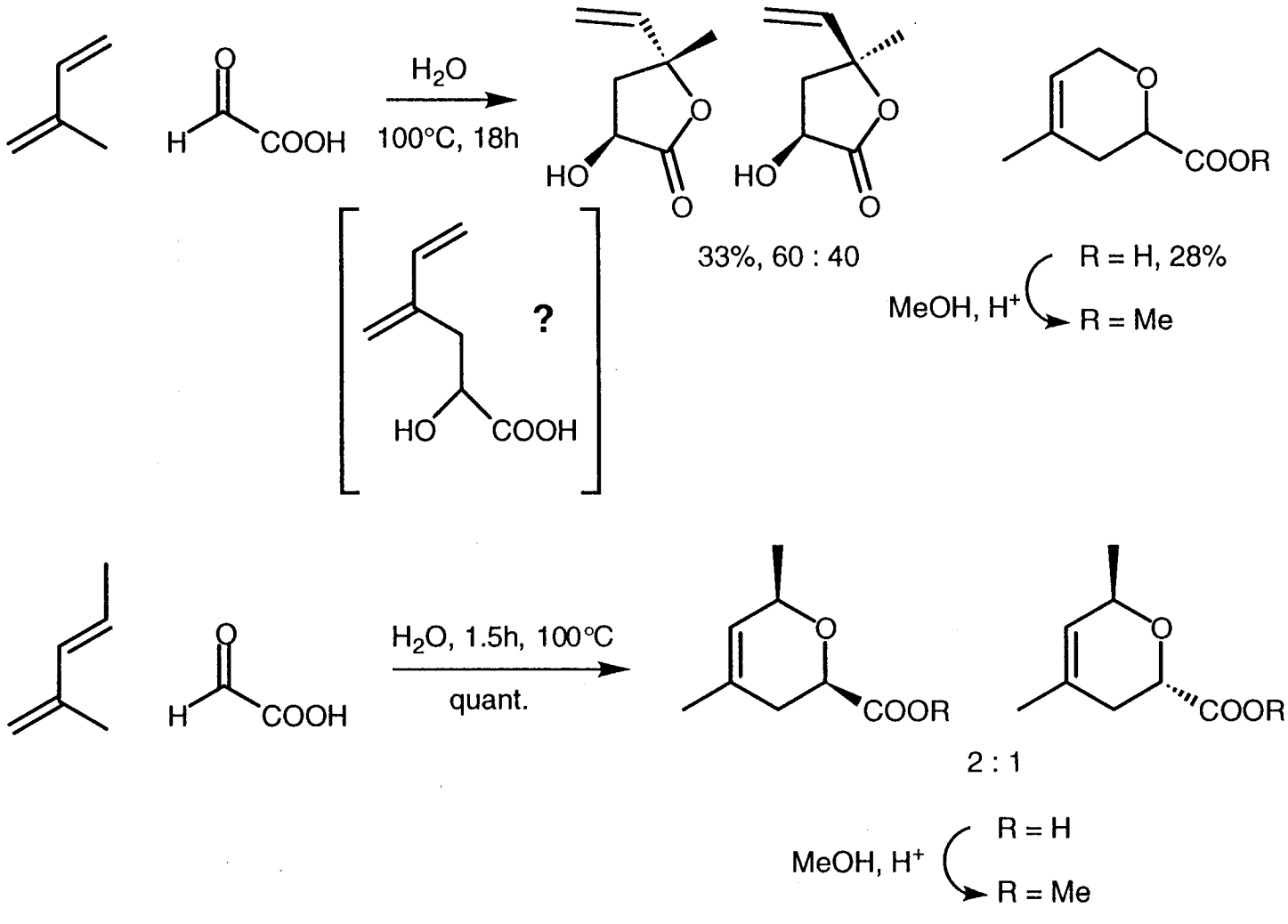
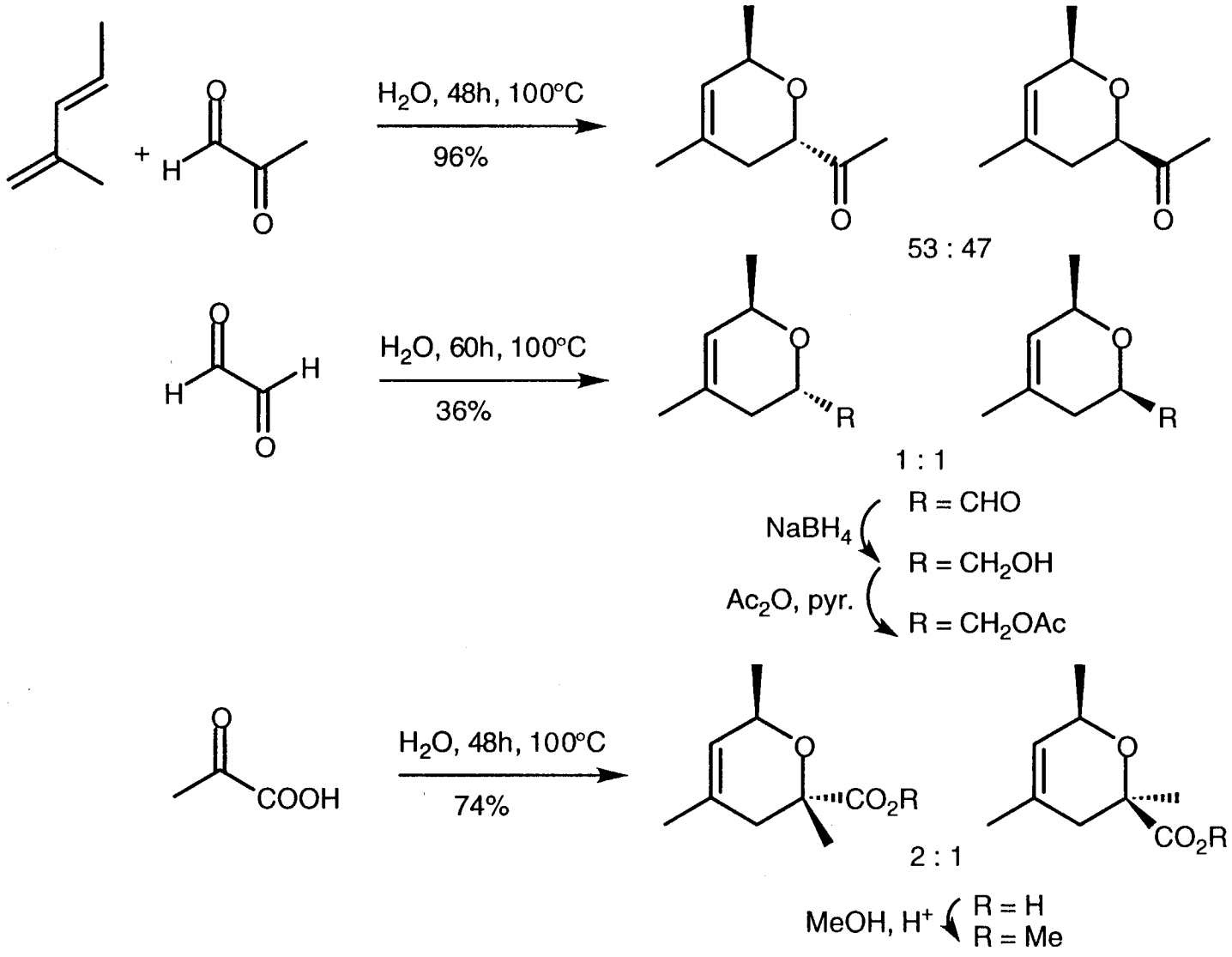
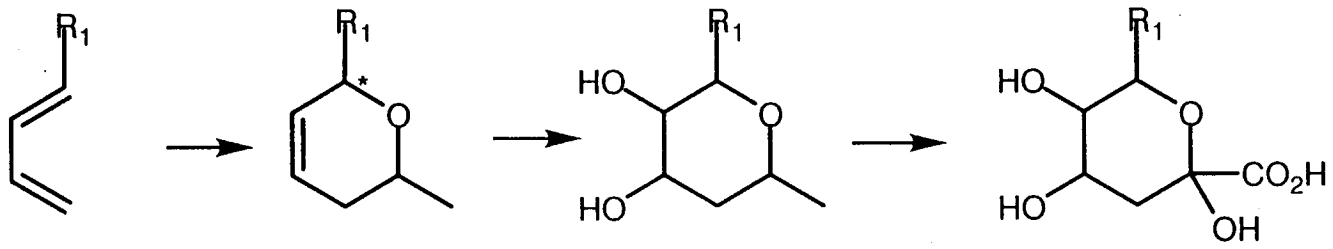

H2O
100°C, 18h
HO
O
COOR
33%, 60 : 40
MeOH, H+
R = H, 28%
R = Me
?
HO
COOH
H2O, 1.5h, 100°C
quant.
2 : 1
MeOH, H+
R = H
R = Me


H2O, 48h, 100°C
96%
53 : 47
H2O, 60h, 100°C
36%
1 : 1
R = CHO
NaBH4
R = CH2OH
Ac2O, pyr.
R = CH2OAc
COOH
H2O, 48h, 100°C
74%
CO2R
2 : 1
MeOH, H+
R = H
R = Me

Rapid synthesis of ulosonic acids

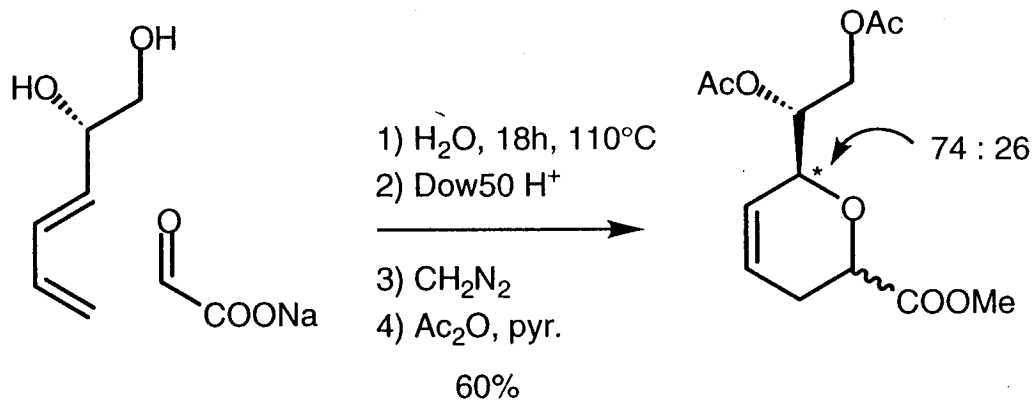


$R_1 = CH_2OH$ KDH

$R_1 = CHOHCH_2OH$ KDO

$R_1 = CHOHCHOHCH_2OH$ KDN

Ex : KDO



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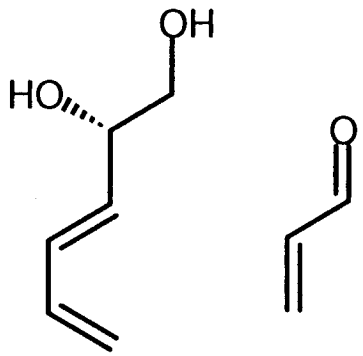
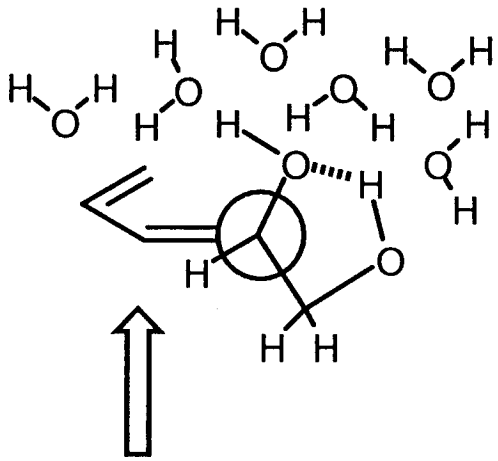


adducts

toluene	4 d, 60 °C	90%	1.1 : 1
Water	2 h, 60 °C	85%	2 : 1
	7 d, 0 °C	95%	2 : 1



Hydrophobic face

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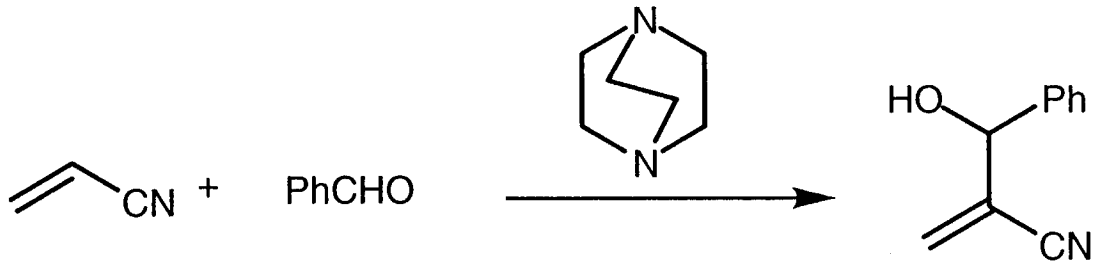
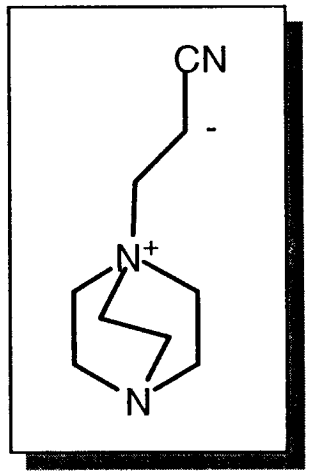
Baylis-Hillman reaction



Activation volume : -70 mL. Mol^{-1}

H_2O : 7 h, 98%

MeOH : 34 h
N-methylacetamide : 48 h
DMSO, DMF or neat, 3-5 days
THF, Toluene, after one week, only 15-30%



Benzaldehyde, acetaldehyde, butyraldehyde or furaldehyde

Furaldehyde : 98% in 2 hrs at 0 °C in water !

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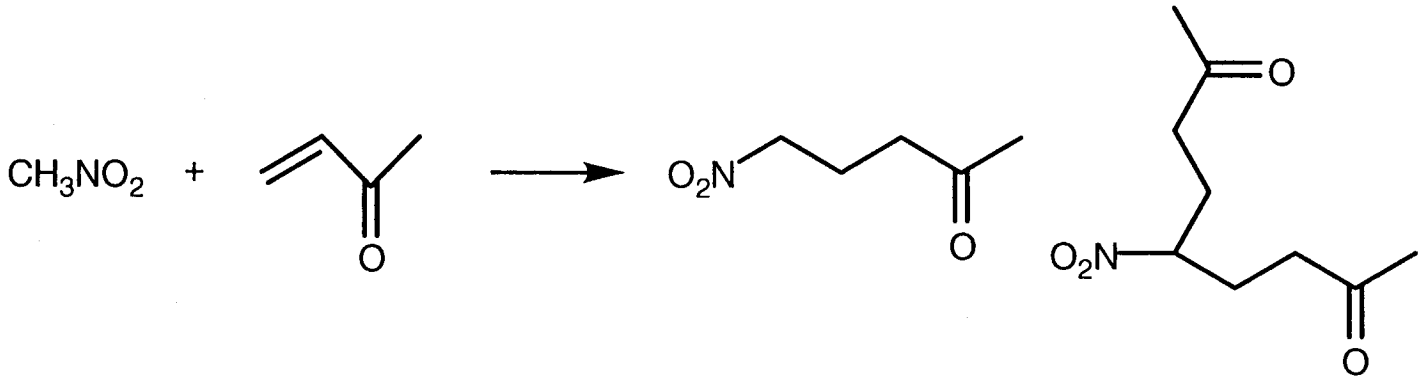
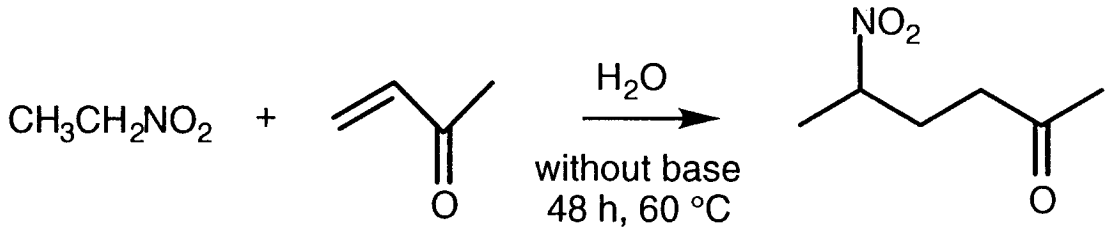
Michael addition



In presence of NaOH, CH_3NO_2 (2eq), 20 h at 20°C	MeOH	46	54	65%
	H_2O	91	9	90%
Without base, CH_3NO_2 (2eq), 24 h at 60 °C	THF			0%
	CH_2Cl_2			0%
	Toluene			0%
38 h at 40 °C	**H_2O**	**72**	**28**	**100%**



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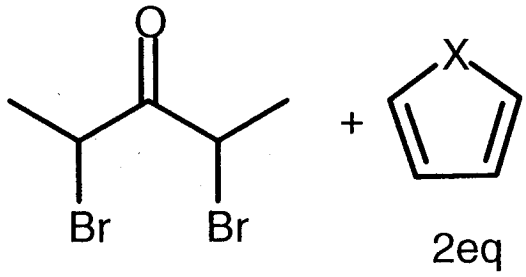


+

2eq

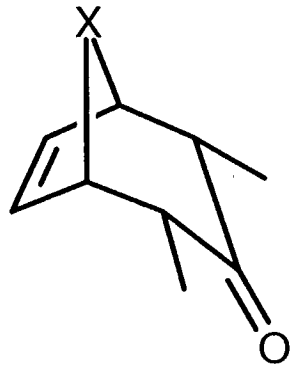
Fe (commercial powder) (3eq)

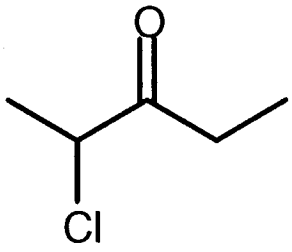
H_2O

X = O, rt, 34h, 82%, αα:ββ, 89:11
X = C, rt, 24h, 66%, αα:ββ, 68:32

Cu (3eq), NaI (6eq)

X = O, H_2O, rt, 48h, 88%, αα:ββ, 84:76





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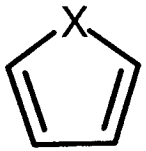

NEt_3 (1.04eq), H_2O, 8h, rt

X = O, 88%, αα:ββ, 90:10
X = C, 76%, αα:ββ, 70:30

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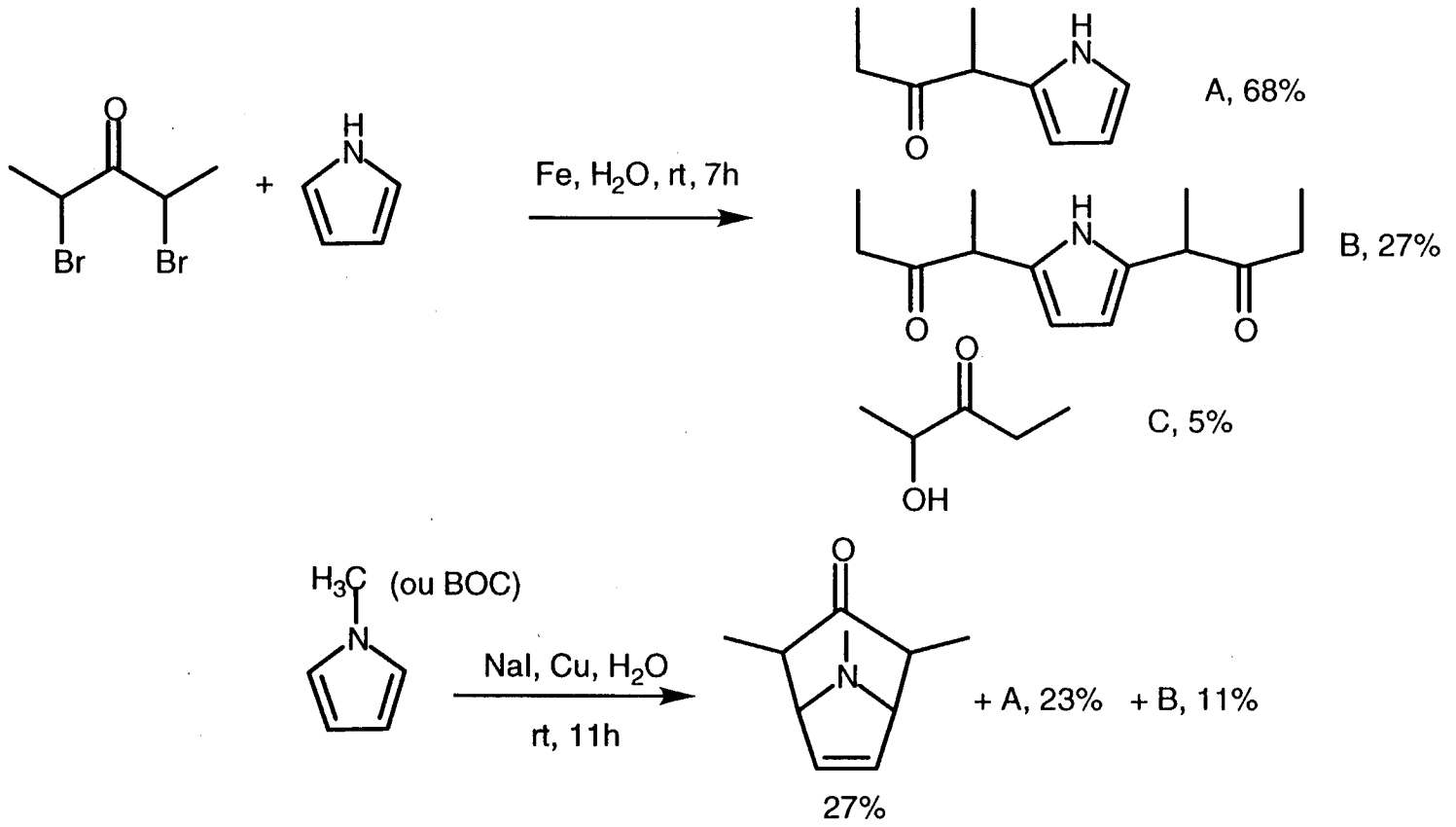
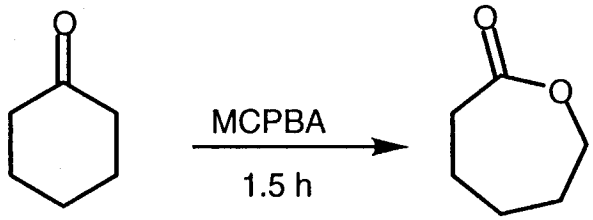

Br
Br
+
Fe, H_2O, rt, 7h
A, 68%
B, 27%
C, 5%
OH
H_3C (ou BOC)
NaI, Cu, H_2O
rt, 11h
27%
+ A, 23% + B, 11%
Cl
+
NEt_3, H_2O
rt, 11h
25%
+ A, 25% + B, 44%

Oxidations

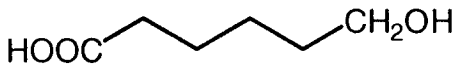
The Baeyer-Villiger reaction



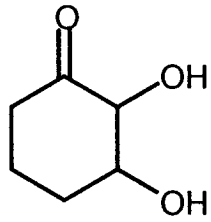
MCPBA

1.5 h

+

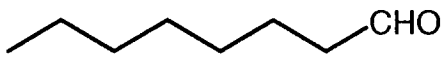


				Total
Water	20 °C	80	6	86
	40 °C	83	12	95
	80 °C	16	83	99
CH_2Cl_2	20 °C	82	0	82
	40 °C	94	0	94



MCPBA

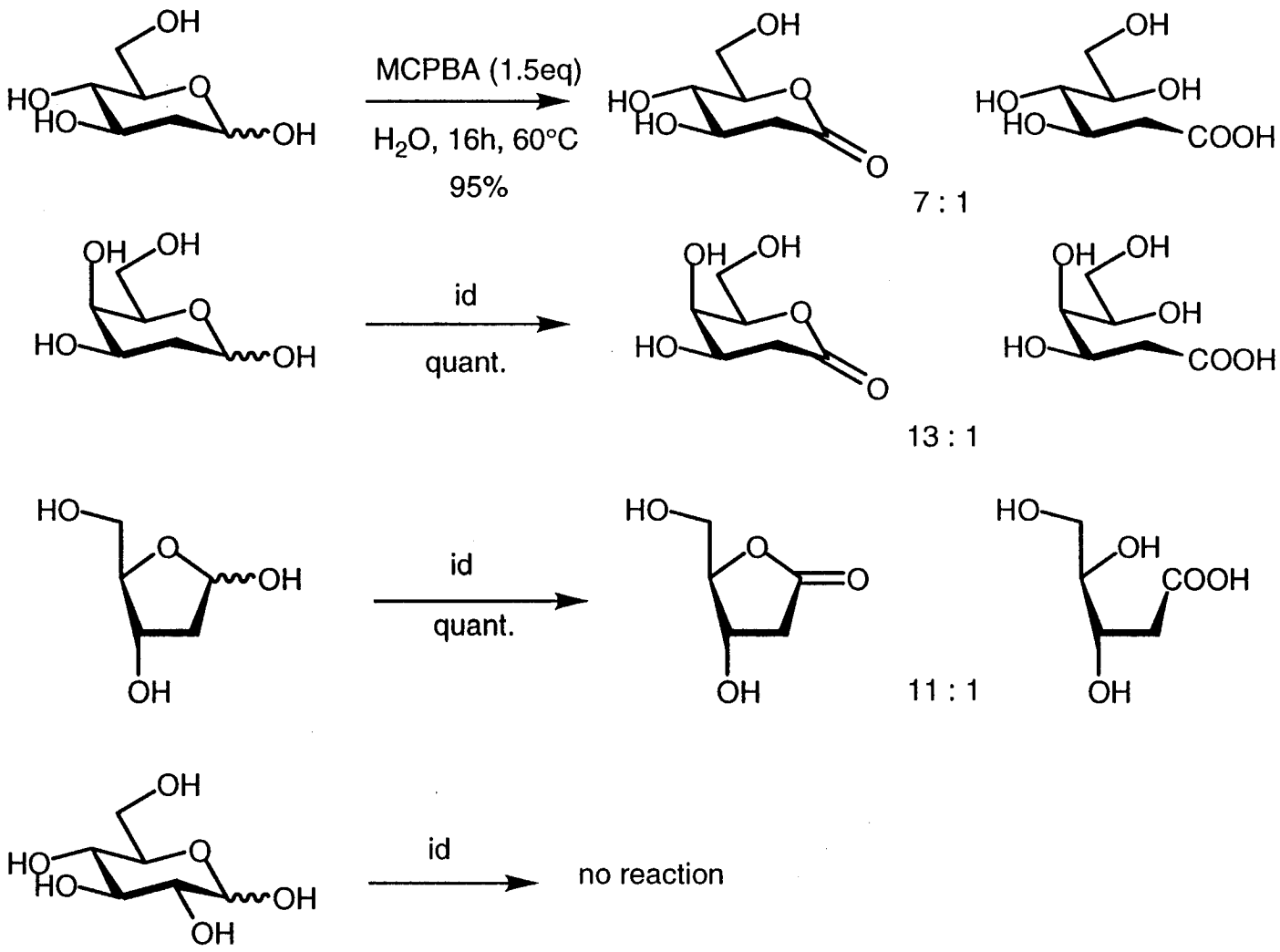
H_2O, 24 h, rt, quant.

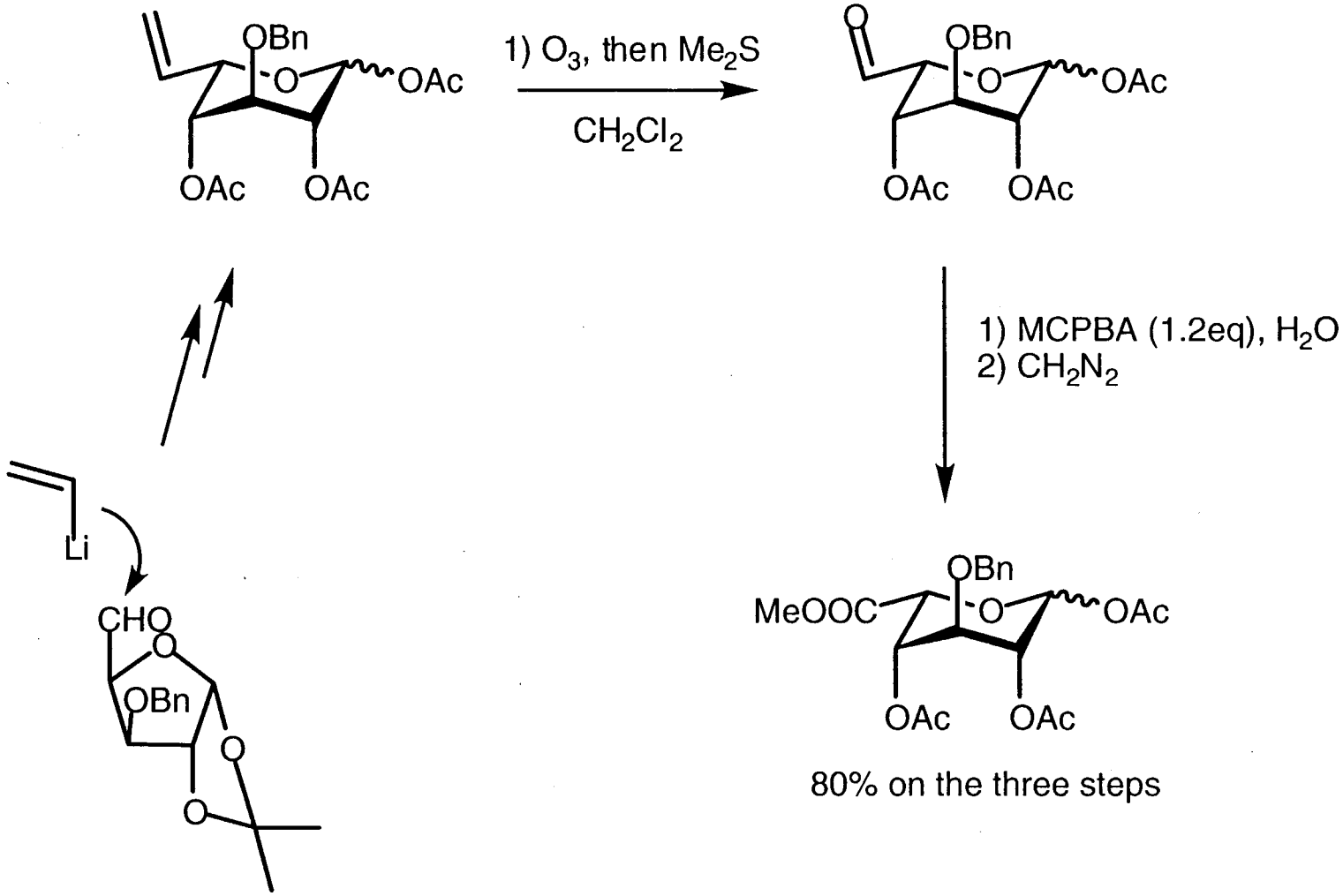


MCPBA (1.5 eq)

H_2O, 10 mn, rt, quant.

or CH_3CO_2H, H_2O_2, (9eq), rt, 2.5 H, quant.


MCPBA (1.5eq)
H2O, 16h, 60°C
95%
7 : 1
id
quant.
13 : 1
id
quant.
11 : 1
id
no reaction



80% on the three steps

COM