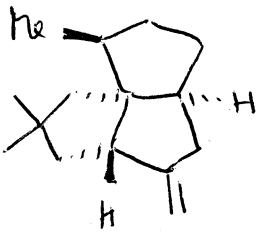
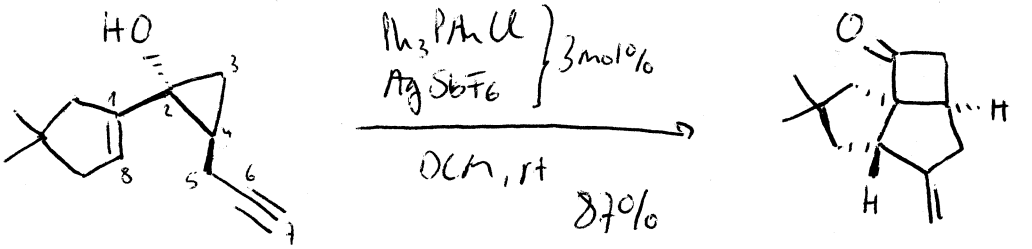
Naturstoffsynthese

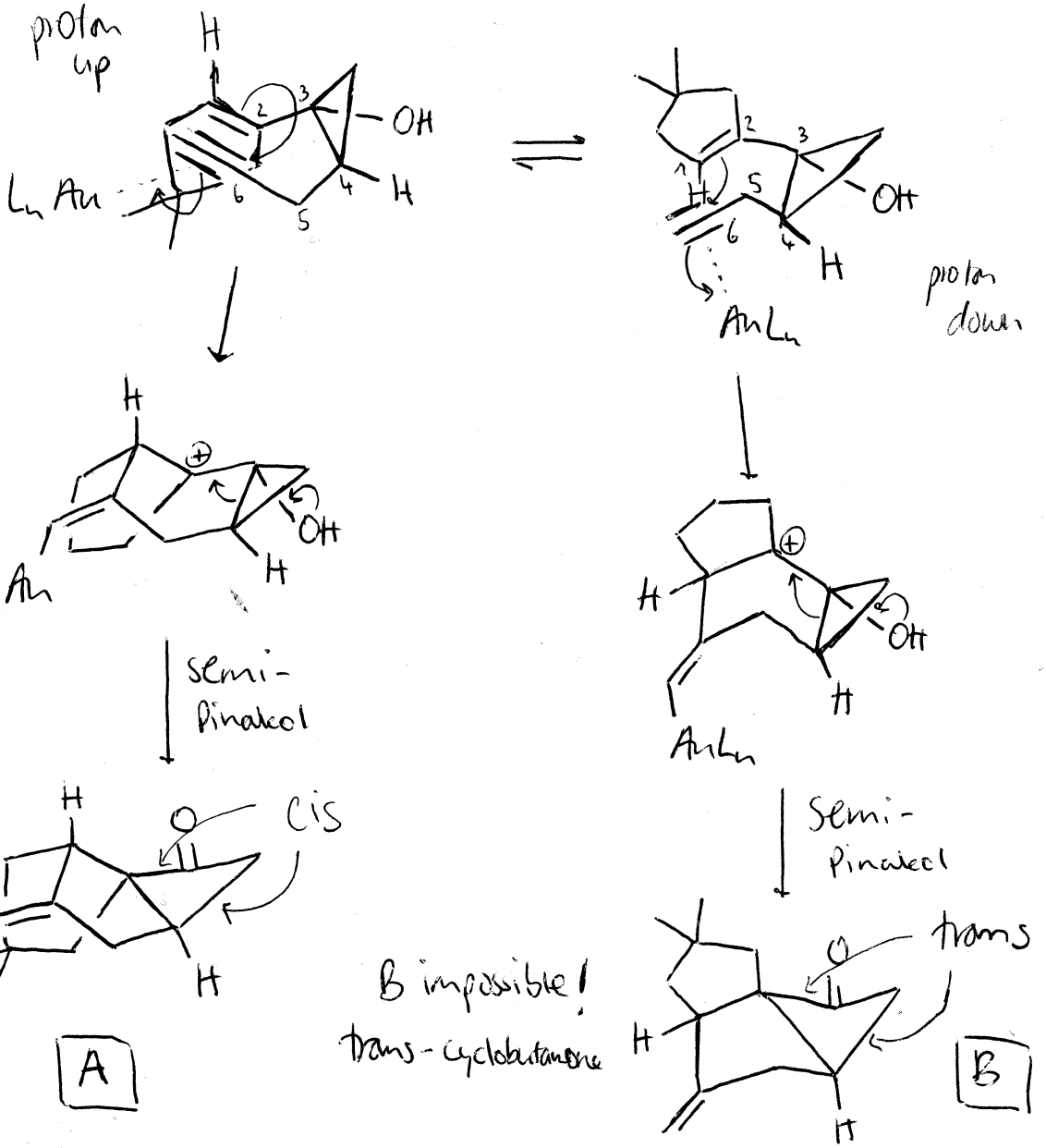
Dean Toste et al., Org. Lett. 2008, 4315

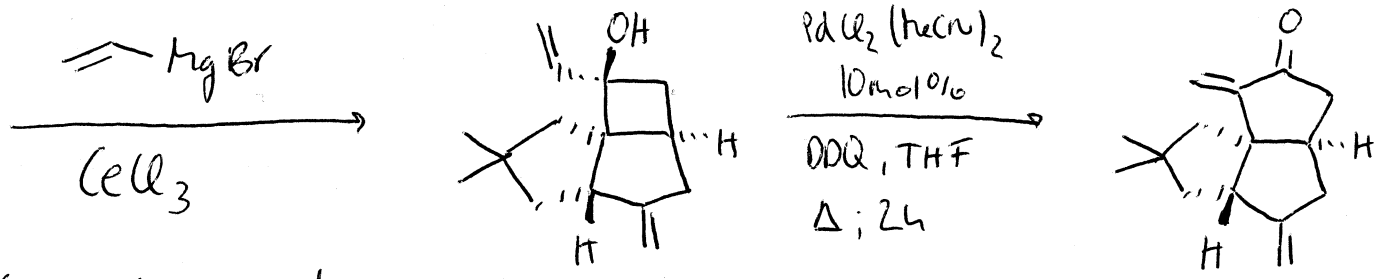


Venticosene



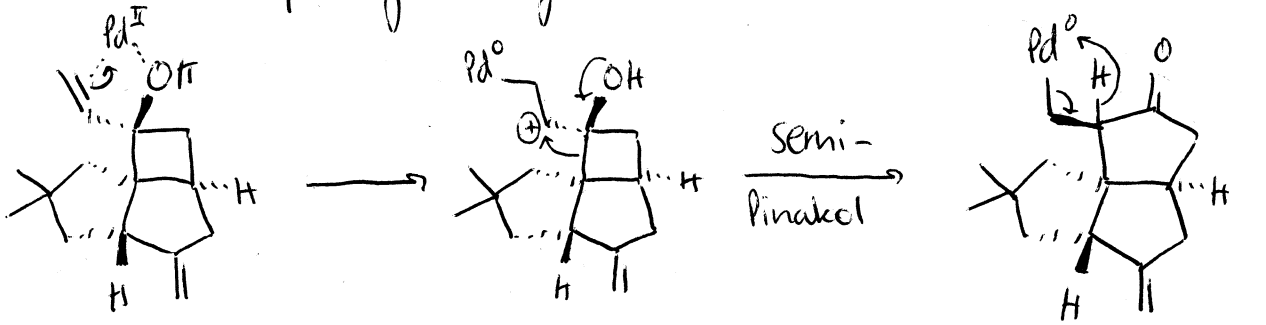
Stereochemistry of the gold-catalysis:

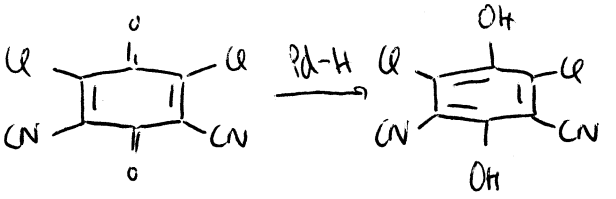




Ce-species are not basic, grignard would enolize ketone!

Mechanism of ring-enlargement:

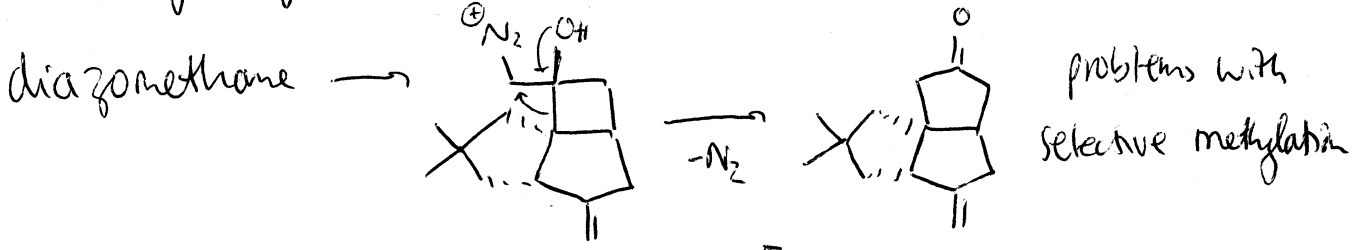


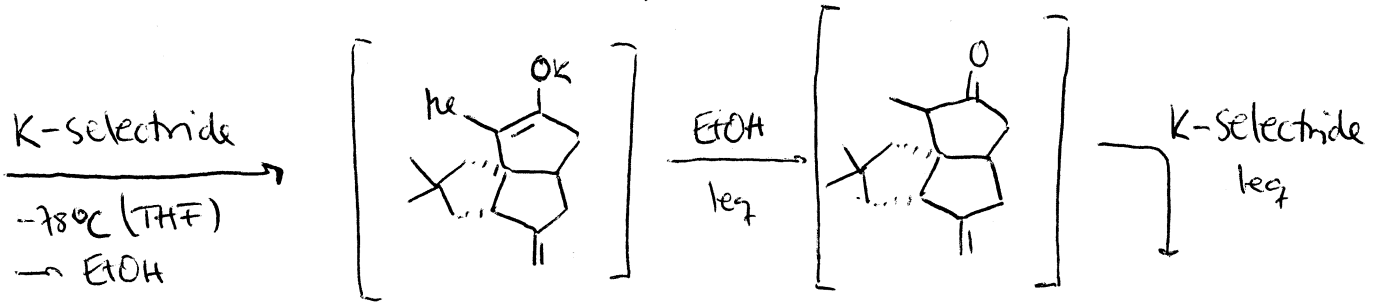


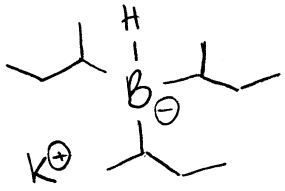
red. Elimination

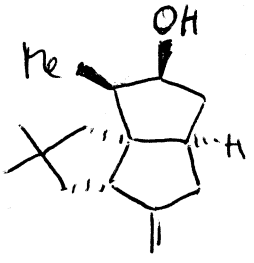
Pd^{II} ← DDQ ← Pd^0

Usual ringentargement:



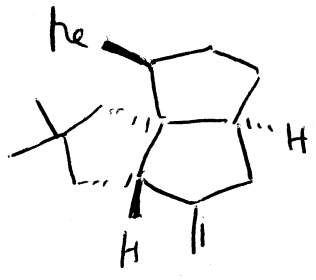




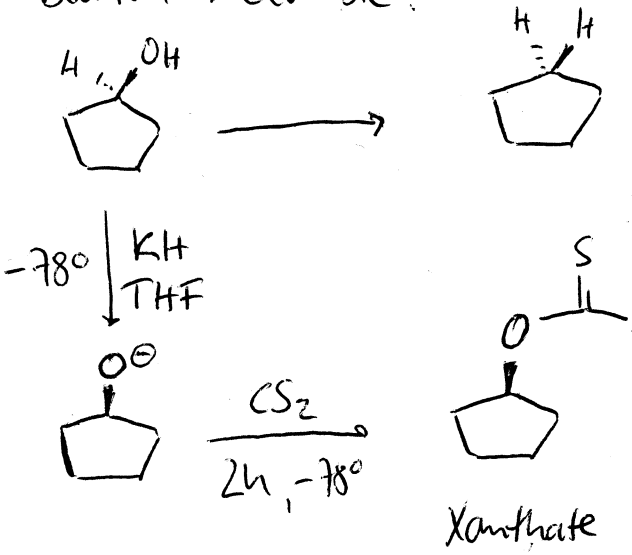


reduces α,β-unsat. ketone/aldehyde/amide

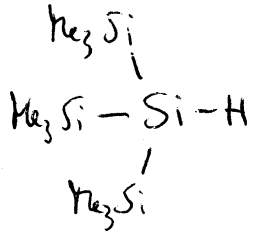
Barton
McCombie



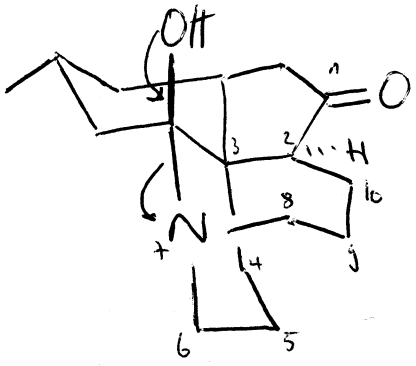
Barton McCombie:



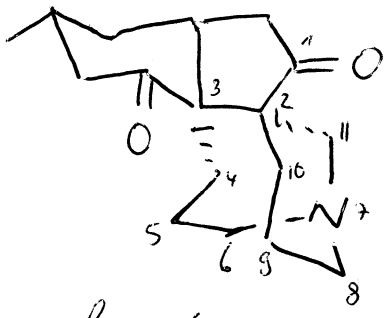
Alternative to Stannane: TTMSS



Fawcettimine: lycopodium alkaloide



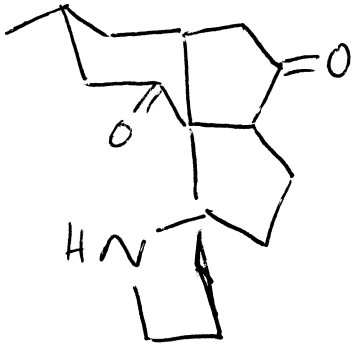
fawcettimine

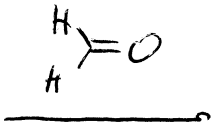


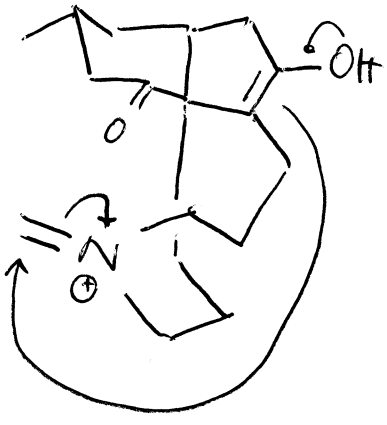
lycoflexin

one carbon more

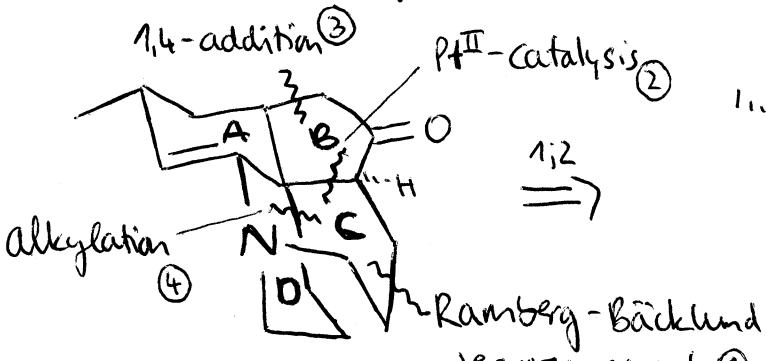
?

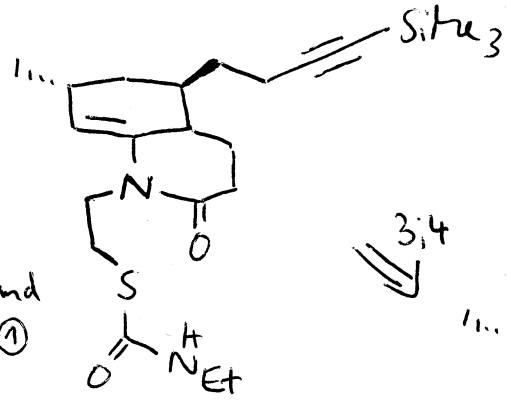




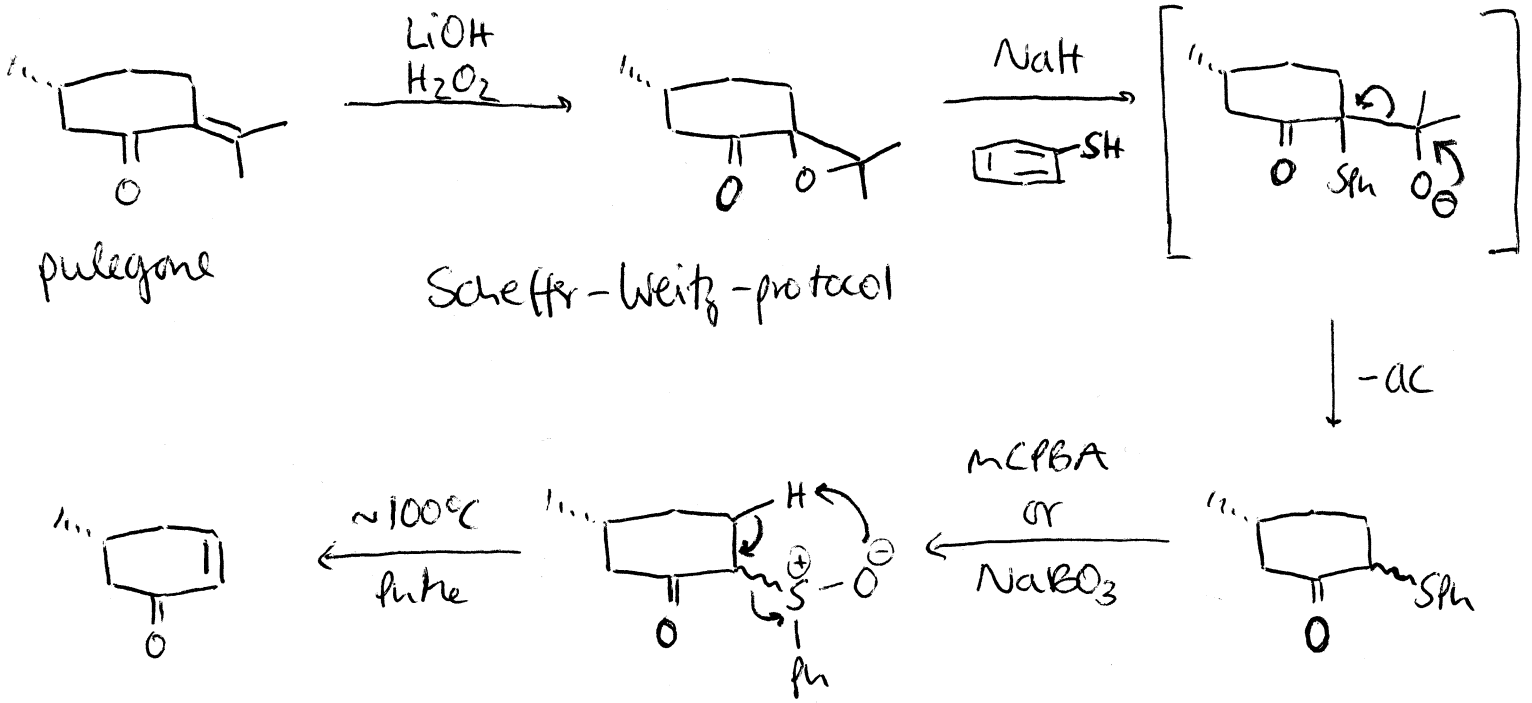


(+)-fawcettidine: G.R. Dake et.al. ACIE, 2008, 4221

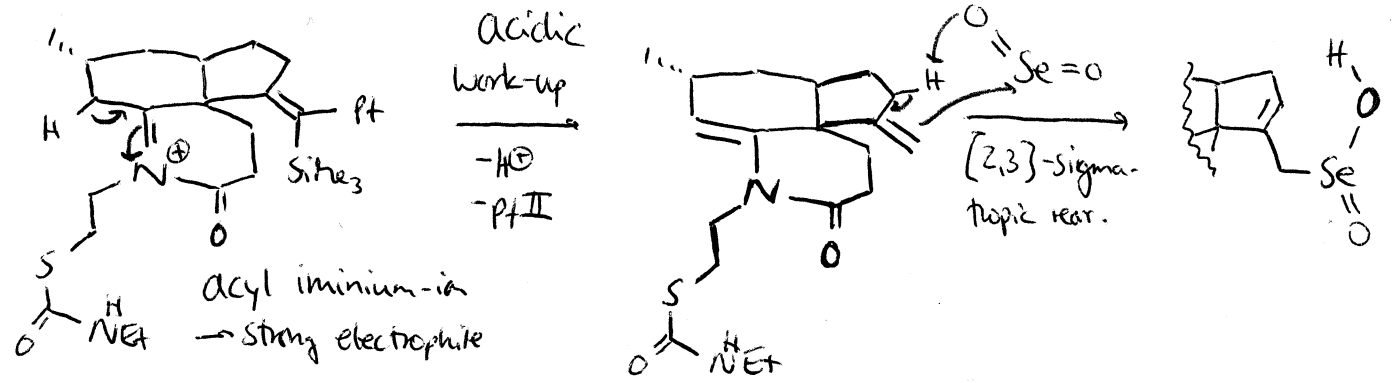


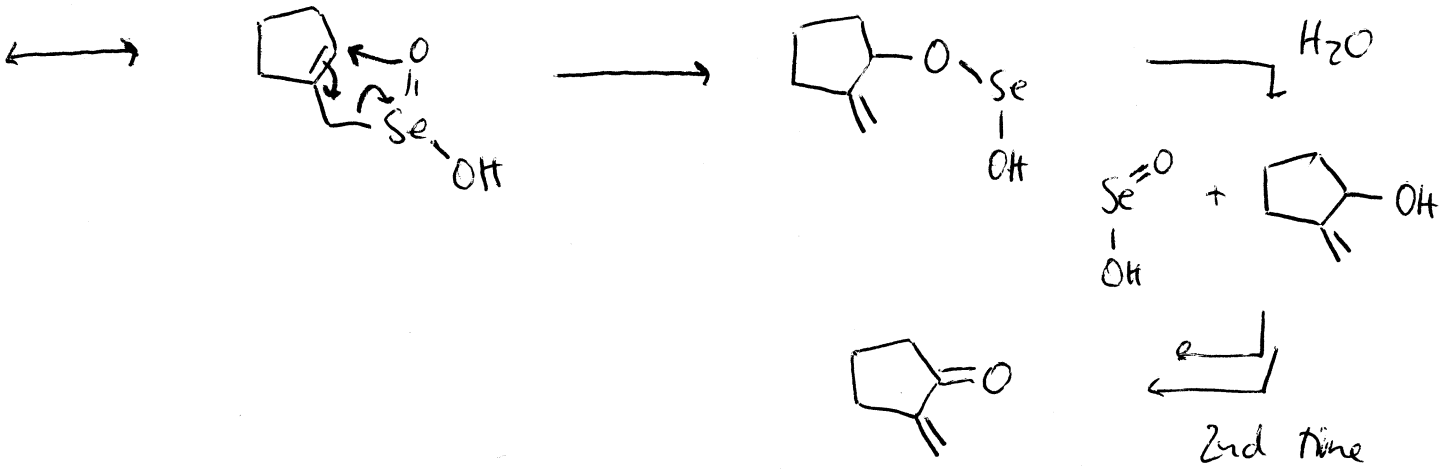


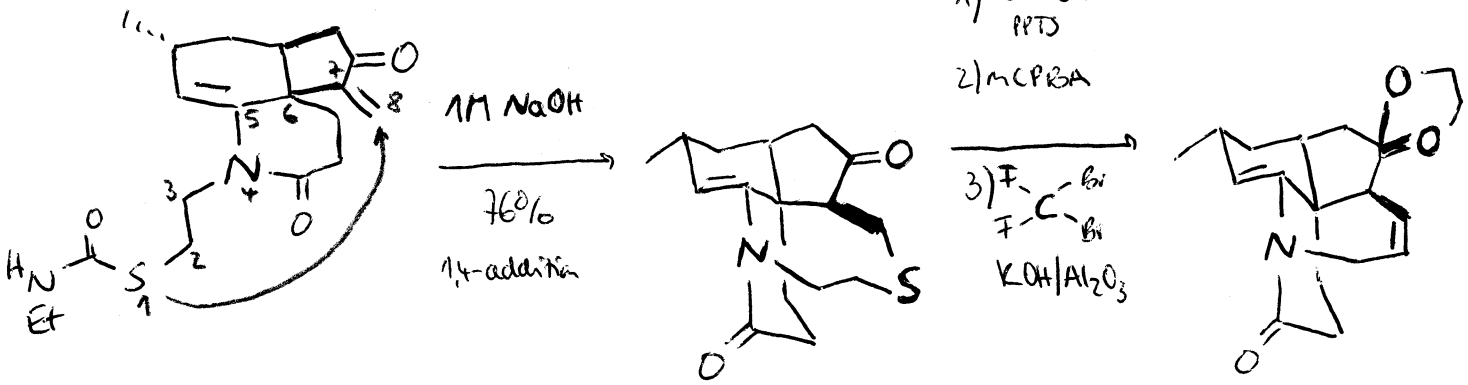
Synthesis:



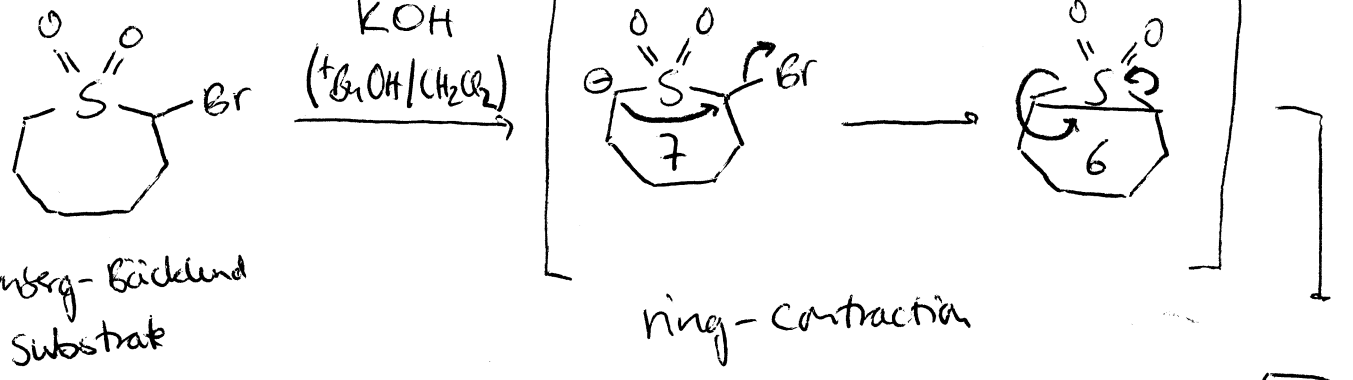
Mechanism:

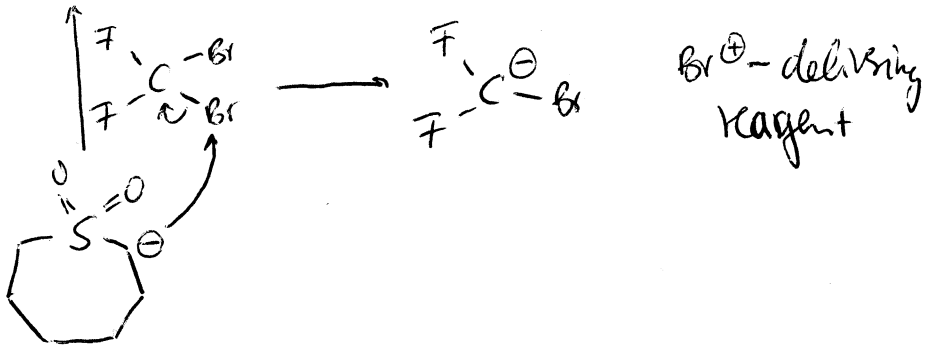


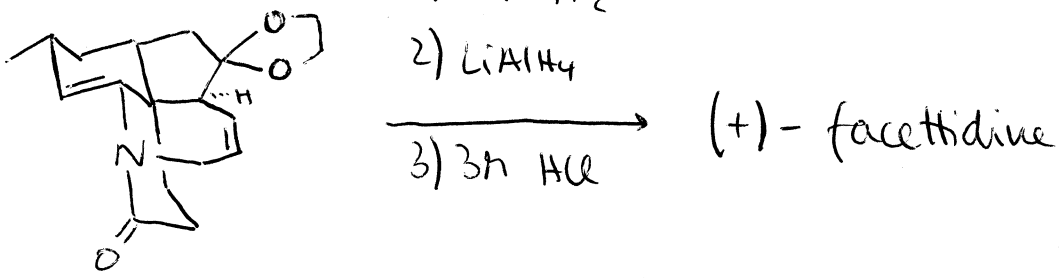

H2O
2nd time


1M NaOH
76%
1,4-addition
1) PPTS
2) mCPBA
3) KOH/Al2O3

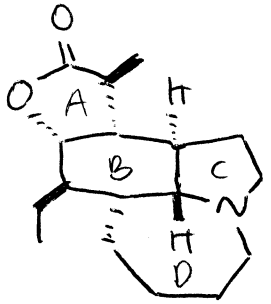
Mechanism:


KOH
(tBuOH/CH2Cl2)
Ramberg-Bäcklund
substrat
ring-contraction

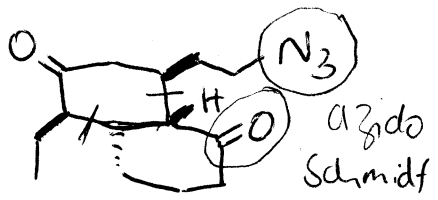

Br⊕-delivering
reagent

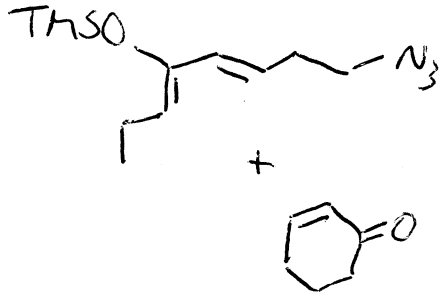

1) Pd/C; H2
2) LiAlH4
3) 3M HCl
(+)-Lacettidine

Stenine: J. Aube et al., JACS 2005, 127, 15712

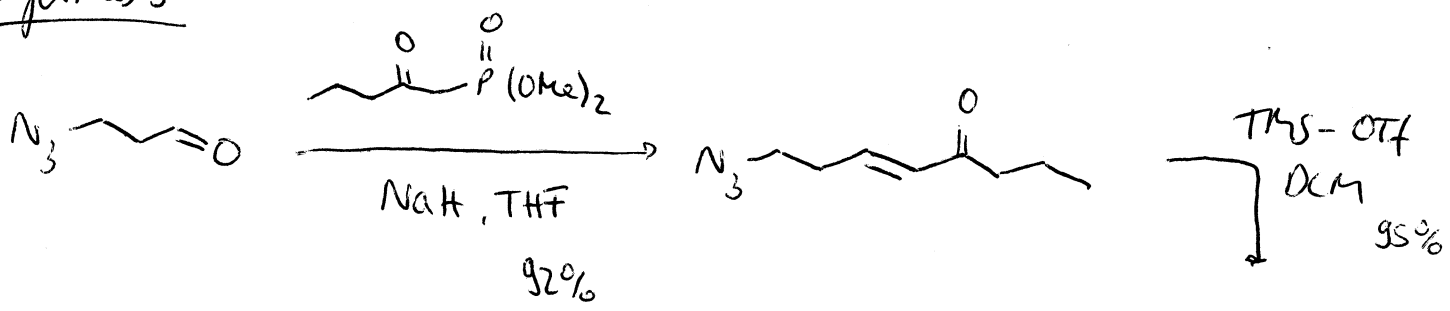


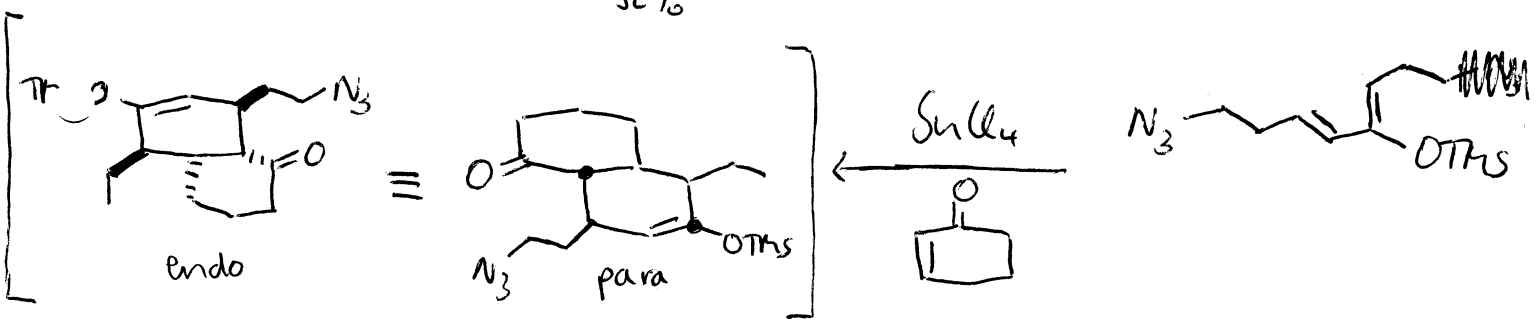
- C-O ring formed by azido-Schmidt
→ ring contraction/enlargement reaction



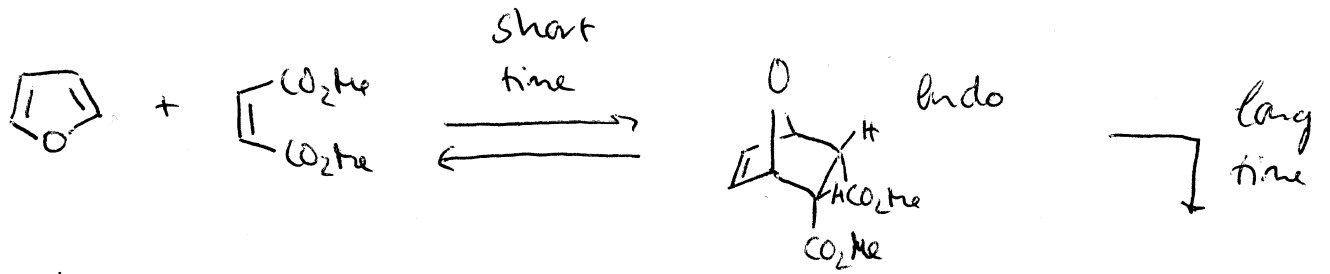


Synthesis:





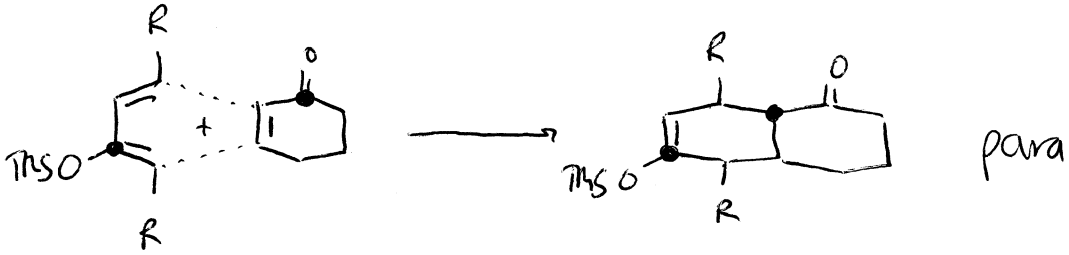
Diels-Alder reactions: stereoselectivity



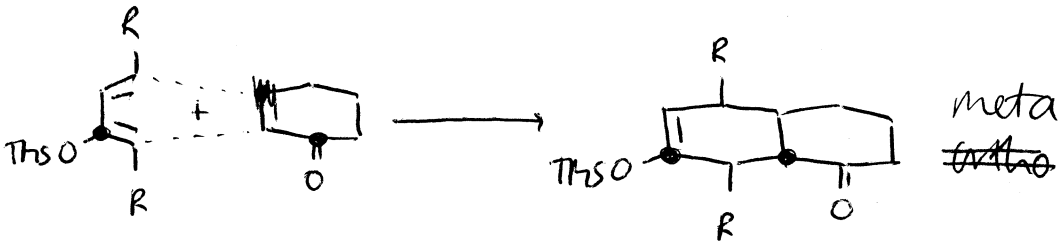
→ kinetic product: endo

→ thermodynamic product: exo

Regioselectivity:



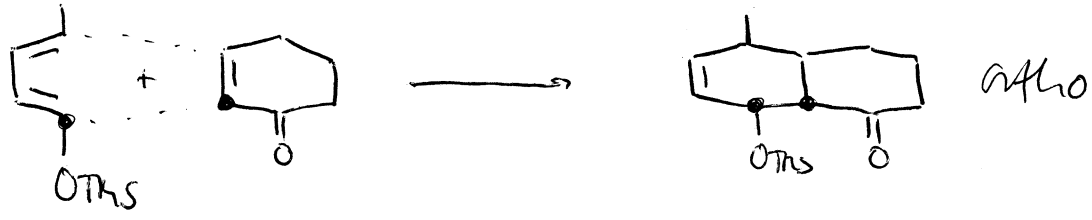
para



meta

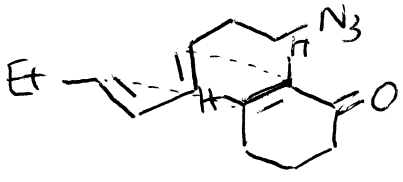
~~ortho~~

→ ortho/para-rule: always get ortho/para-positions of electron-rich & poor center

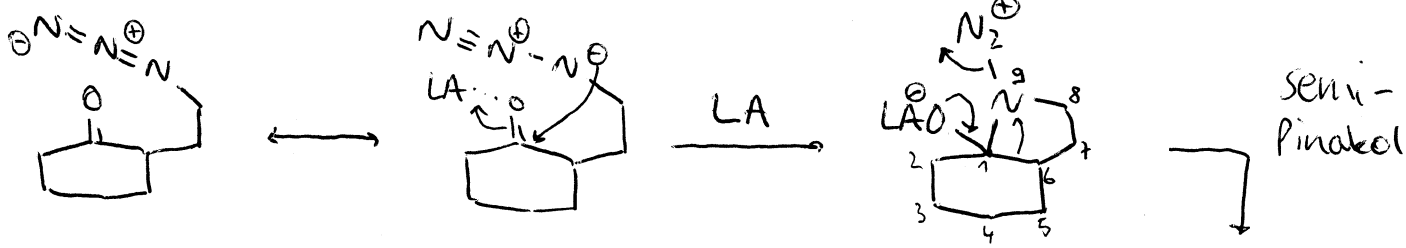


ortho

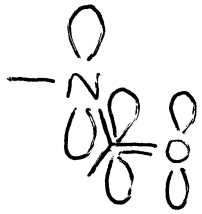
Endo-product: transition state



Azido-Schmidt reaction:

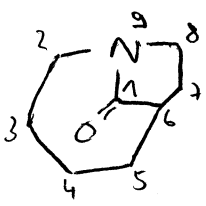


here is no Overlap possible

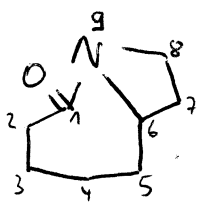


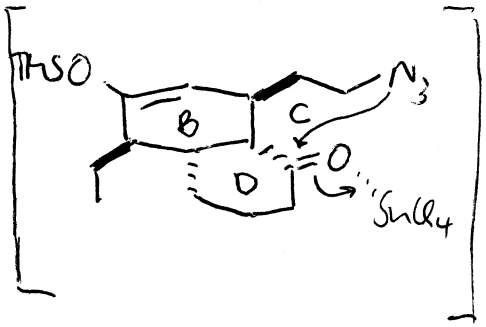
Orbital Overlap

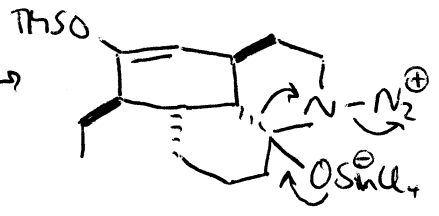
2nd possible migration

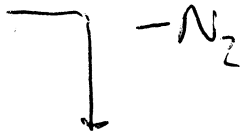


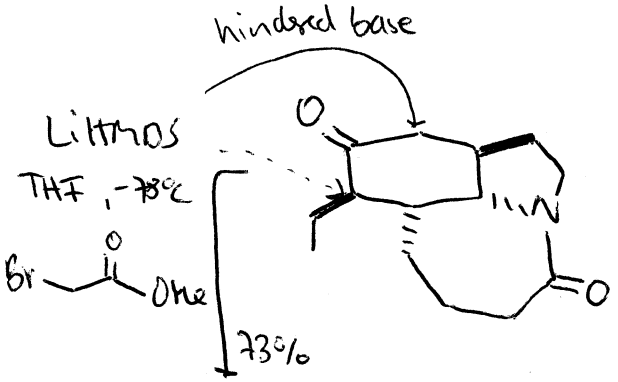
bridge head lactame



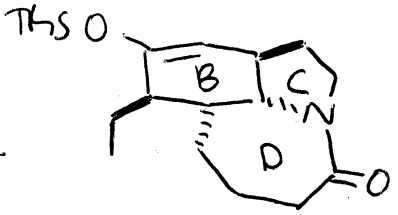




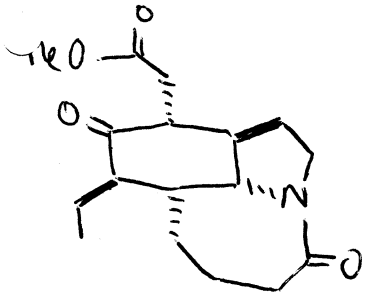




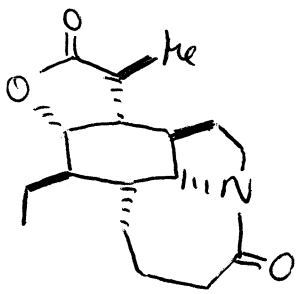
hydrolysis



70% for Cascade reaction



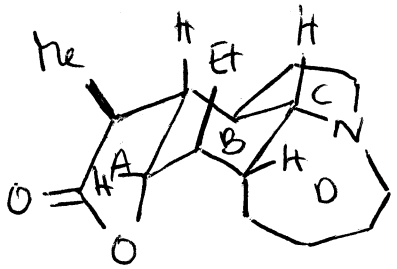
1) $NaBH_4$, MeOH, 0°C
2) LiHMDS, MeI



1) Lawesson reagent
6) Ra-Ni

Stemmine

Stereoselectivity:

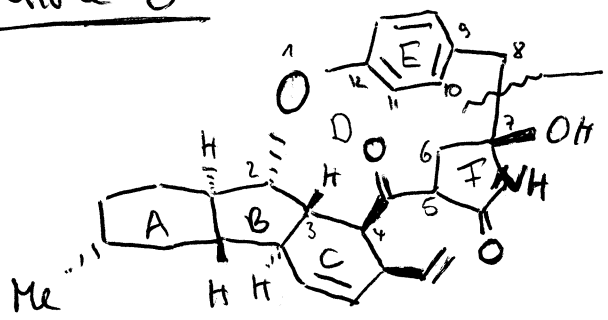


~~→ Me group equatorial, axial is shielded by Ethyl group~~

8 steps synthesis : 19% overall yield

Hirsutellone B

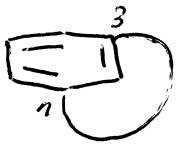
K.C. Nicolaou, ACIE 2009, 48, 6870



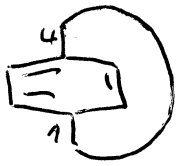
Ramberg Bäcklund

Cyclophane Structure

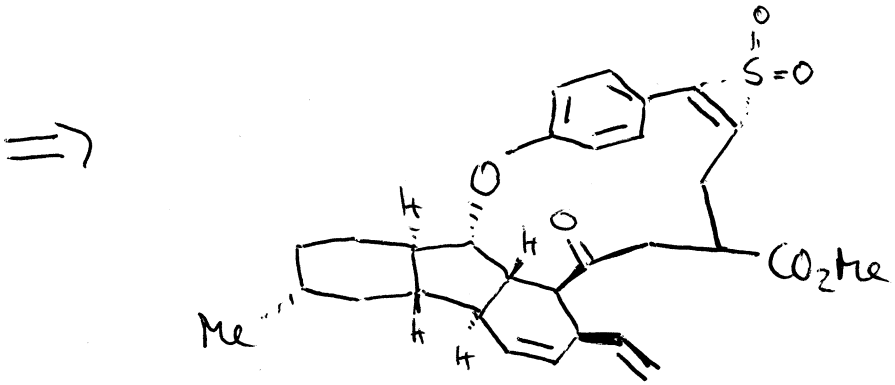
Annelation

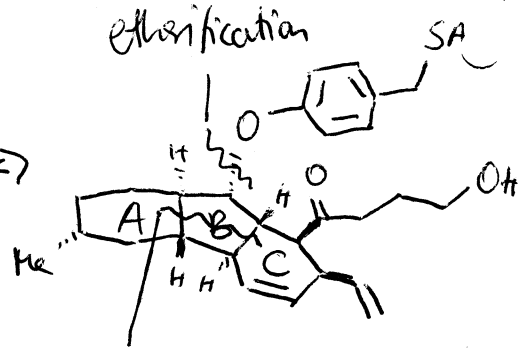


1,3-Cyclophane



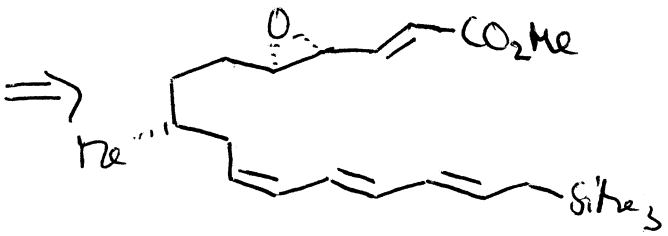
1,4-cyclophane



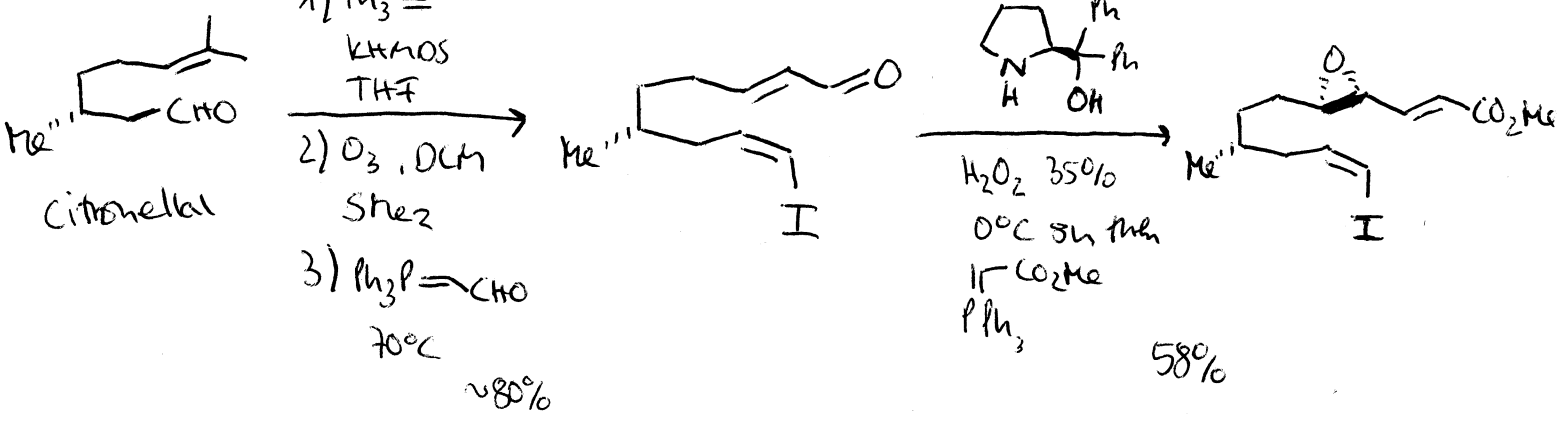


etherification

Cyclisation cascade: epoxide opening & Diels Alder



Synthesis:

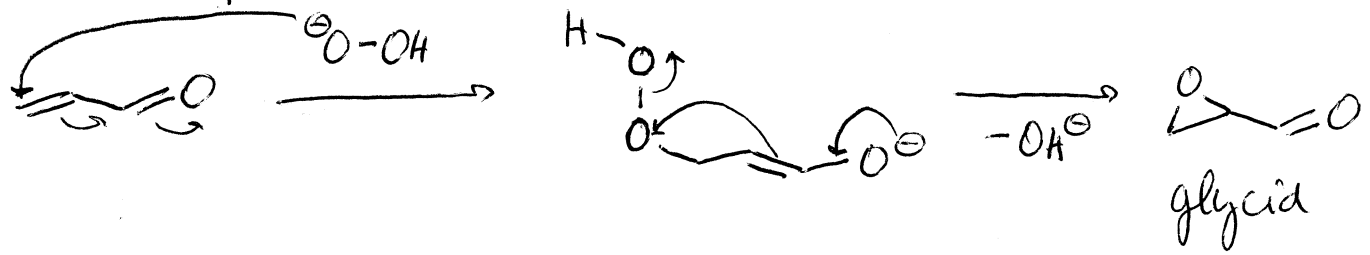


Citronellal

Stheffr-Weitz:

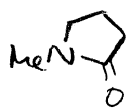
epoxidation of electron-poor double bonds

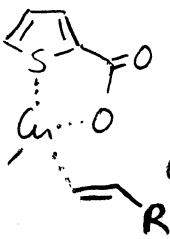
Michael acceptor



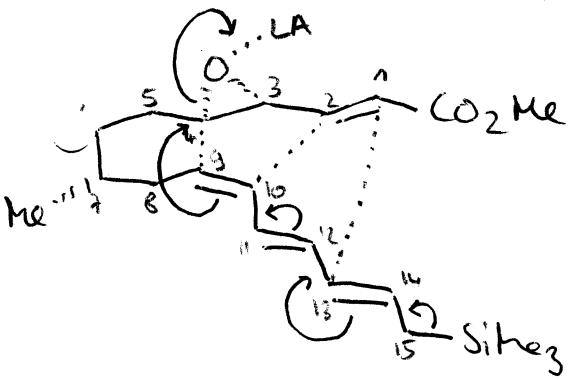
CuTC, NMP

25%, 6h → 70%

NMP=  solvent like DMF

CuTC=  stabalizes the transition compound during cross coupling

} very useful reagent, if cross-coupling makes problems because of to unstable intermediates

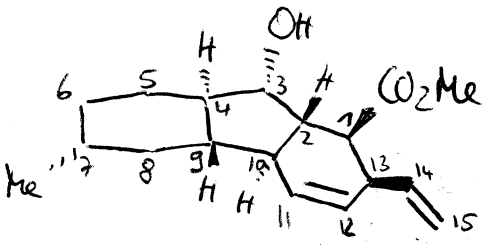


Et_2AlCl

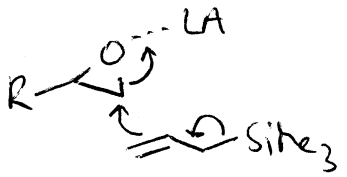
$-78° \rightarrow 25°C$

CH_2Cl_2

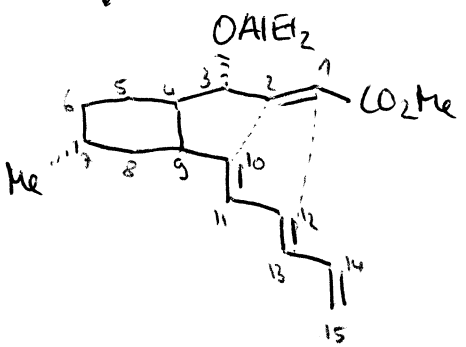
50%



analoge to:



$-ClSiMe_3$

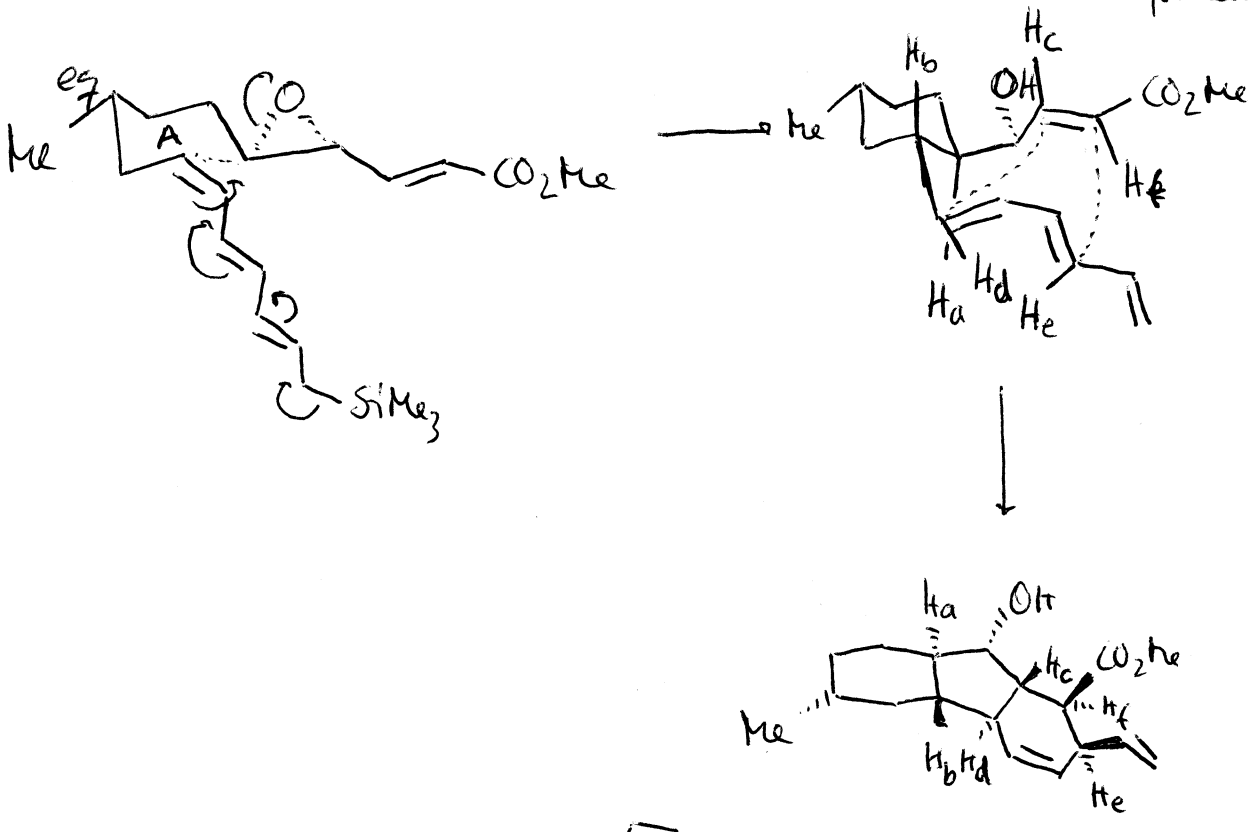


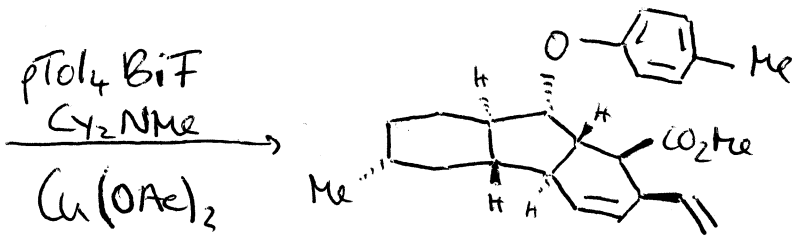
Diels-Alder

Stereochemistry:

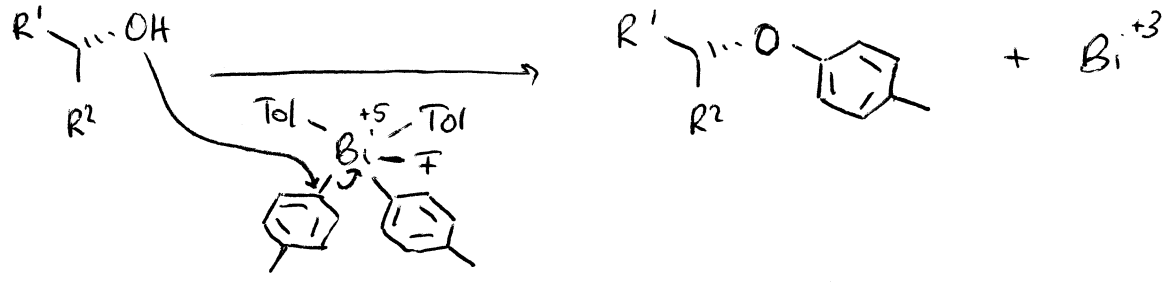
−78 °C → endo-selective

2nd order effect of carbonyl & newly formed double bond



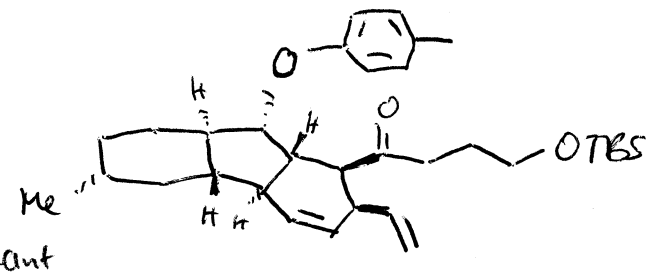


Organobismuth-reagent:

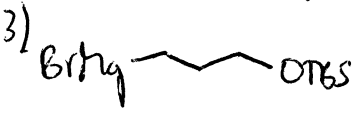


performs a S_NAr-reaction on an aryl ring!

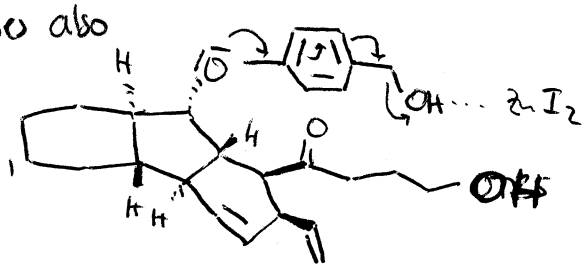
1) $LiAlH_4$, Et_2O
0°C
2) TEMPO, $PhI(OAc)_2$
CH_2Cl_2
78%
(Oxidant for TEMPO)



1) CAN
$MeCN/H_2O$
20:1
2) $Na(OAc)_3BH$

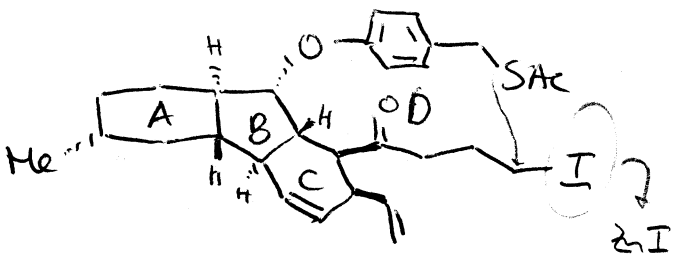
3) 
4) DMP
91%

TBS-group goo also off with CAN
↓
acidity of ammonium nitrate



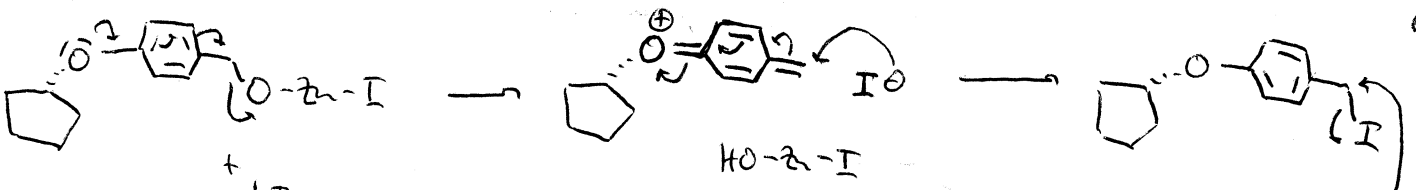
problem of CAN oxidations or other e⁻ transfer oxidations like DDQ
→ can't stop it at the position of the alcohol → aldehyde

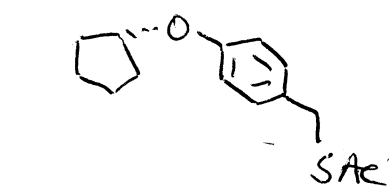
68%
ZnI_2, AcSH
25°C, 2.5h



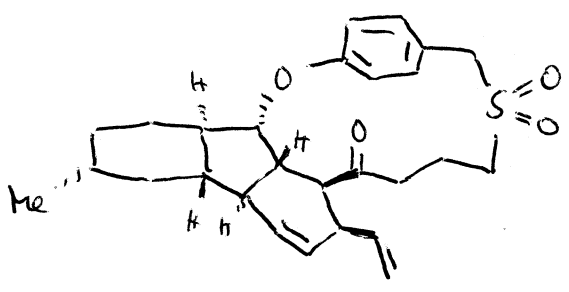
ZnI_2 attacks alcohol as well

Mechanism:





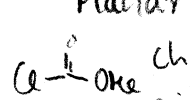
1) NaOMe
MeOH, THF
2) H_2O_2
Na_2WO_4



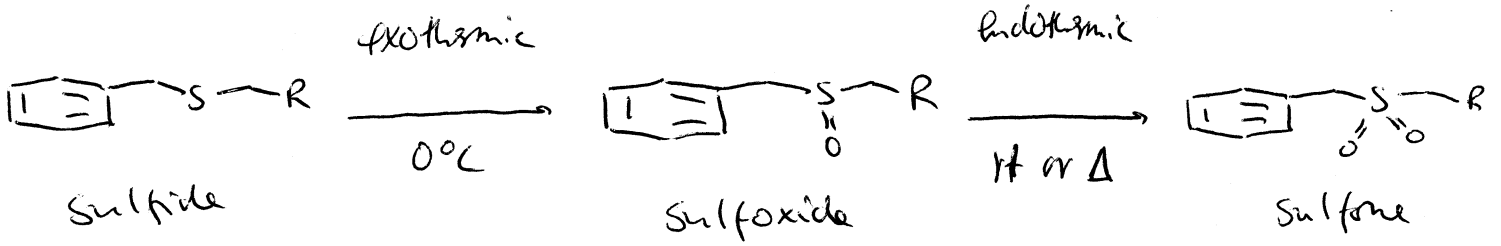
CF_2Br_2
KOH/Al_2O_3
DCM/^tBuOH
0°C
79%

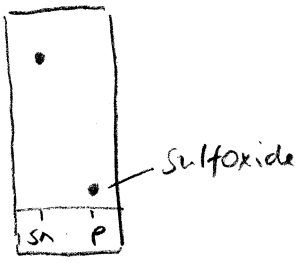
$LiHMDS$

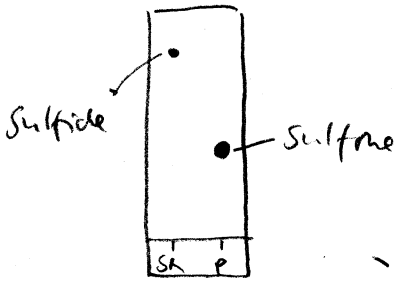
Hauser's reagent
Chloride sometimes gives O-alkylation



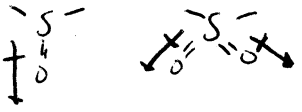
Sulfide - Oxidations

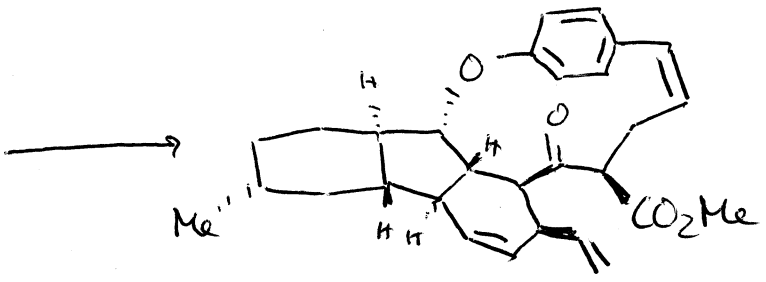




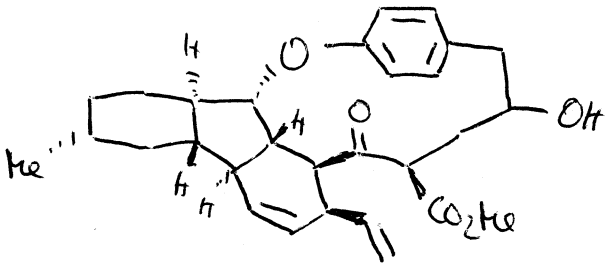


not that polar because of dipol moment

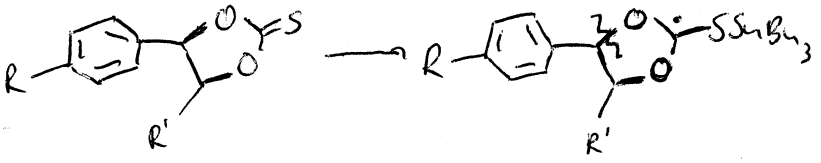


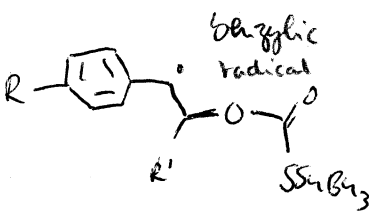


1) AD-mix β
2) S=CCl2
65% 3) AIBN, nBu3SnH, PhMe, 110°C



Mechanism:

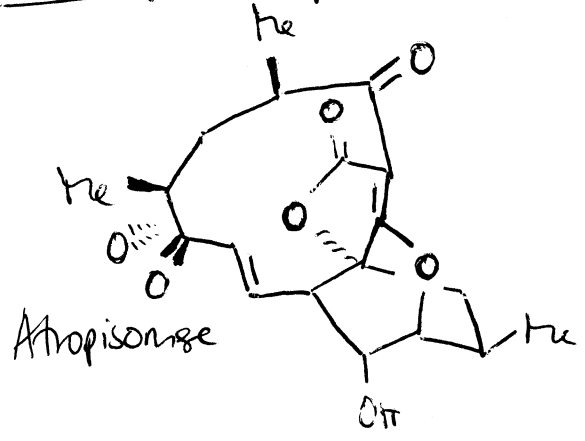




92% 1) DMP
50% 2) NH3, EtOH, 120°C

Hirsutellone B

Abyssomycin C



Atropisomere

Inhibierung d. Shikimisäure pathways

PABA (para-Aminobenzoesäure)

⇒ Antibiotikum: wirkt selektiv im Stoffwechsel v. Mikroorganismen

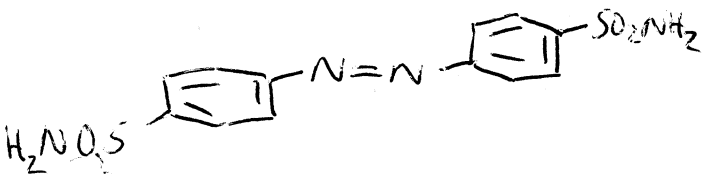
PABA-Inhibierung ⟷ Block der Folat-Biosynthese

↳ Vitamin B_9

biologische Verwendung Vit. B_9: DNA/RNA Biosynthese (stöchiometrisch)

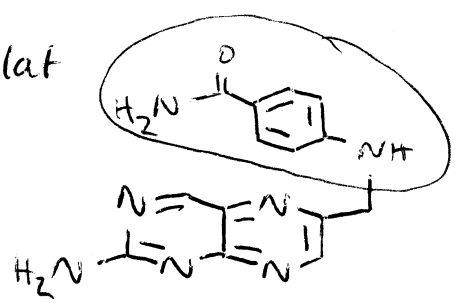
→ Vit. B_9 wird von Mikroorganismen de-novo synthesisiert

erstes Antibiotikum von Bayer: Prontosil von Domagk



Analog PABA — inhibiert Enzym

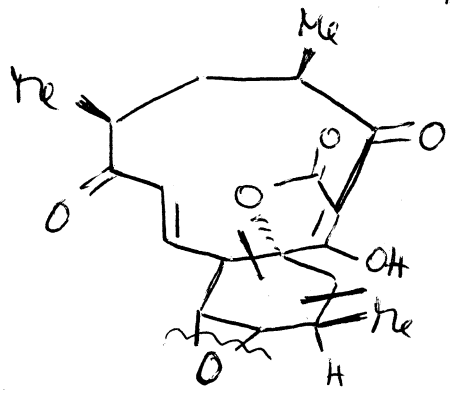
Vitamin B_9: Folat



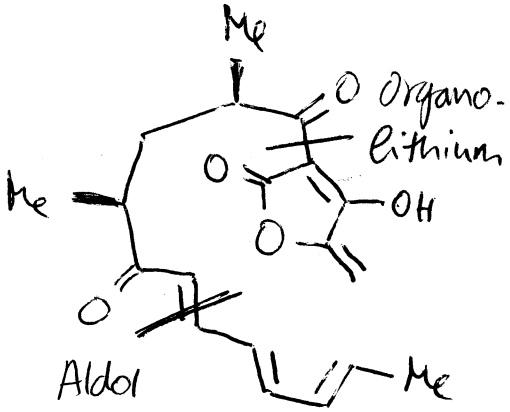
PABA-Element

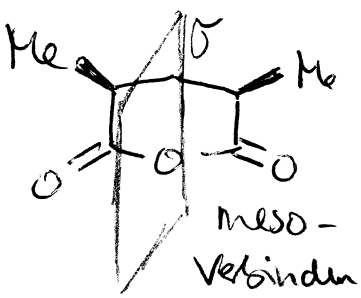
Total Synthesis E. Sorensen et al., ACIE 2005, 6533

Epoxide Opening ⟹

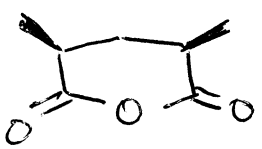


⟹ DA ⟹

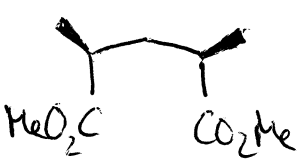




Synthese:

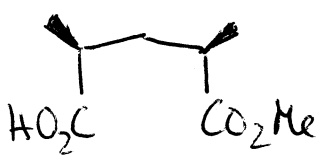


1) MeOH, 24h, 65°C
2) MeOH, H_2SO_4, PhH, 80°C/18h



87%

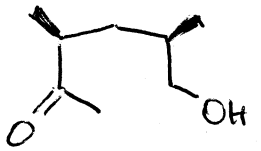
X-chymotrypsin, pH = 7.8, 4d

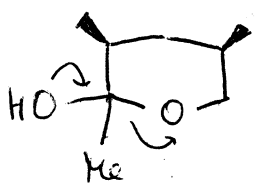


96%
93% ee

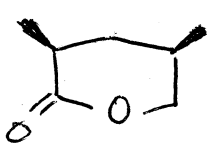
$LiBH_4$ reduziert selektiv Ester, auch in Anwesenheit von Amiden / Nitrilen

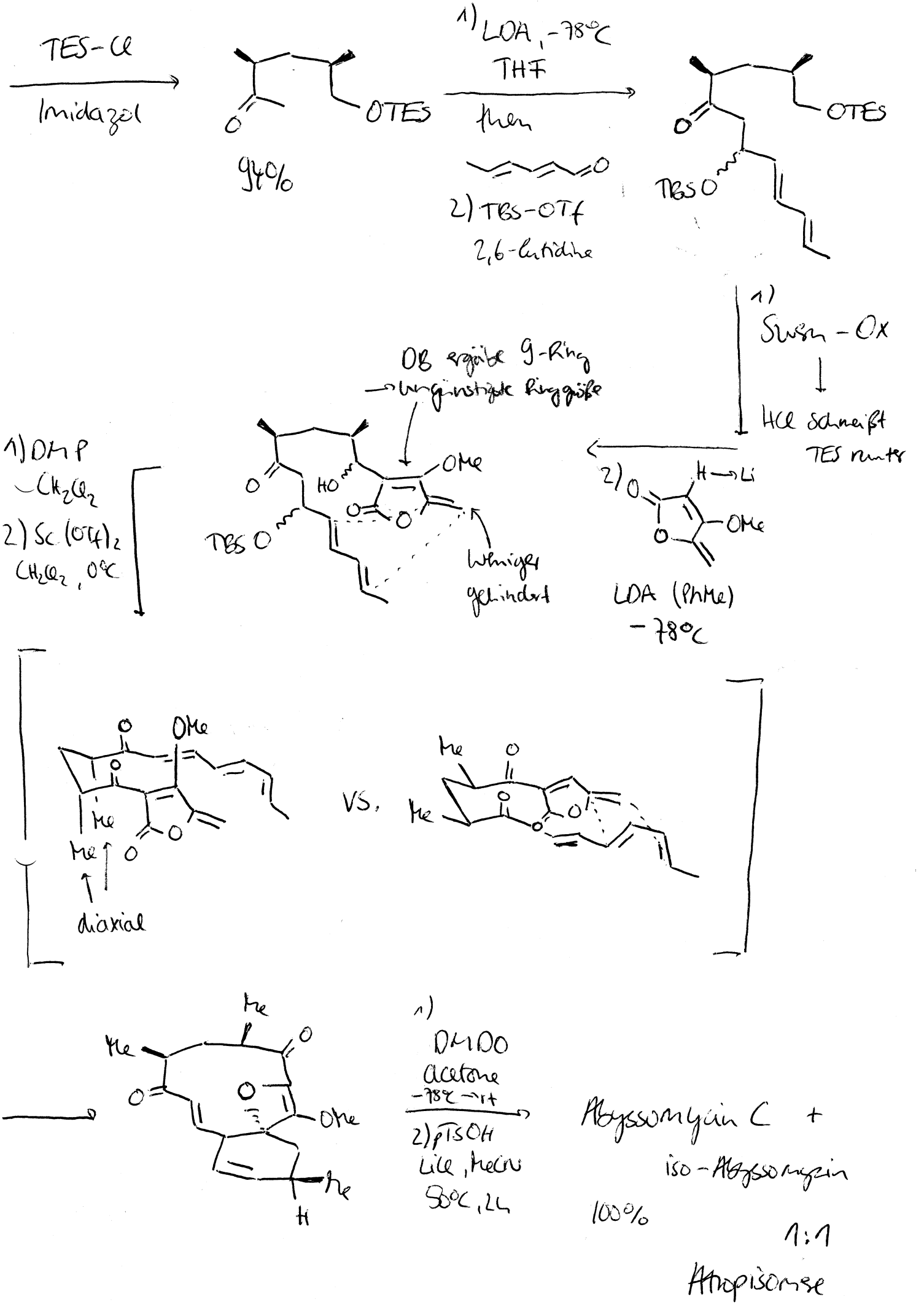
$LiBH_4$, THF, 50°C, $H^{\oplus}$



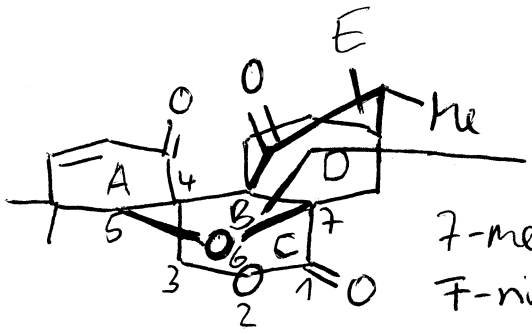


MeLi, Et_2O, -78°C ←




TES-Cl
Imidazol
OTES
94%
1) LDA, -78°C
THF
then
2) TBS-OTf
2,6-Lutidine
TBSO
1) Swern-Ox
HCl schneidet TES runter
2) H→Li
OMe
LDA (PhMe)
-78°C
OH ergibt 9-Ring
→ ungünstige Ringgröße
HO
Weniger gehindert
1) DMP
CH2Cl2
2) Sc(OTf)2
CH2Cl2, 0°C
diaxial
vs.
Me
1) DMDO
Aceton
-78°C → rt
2) pTSOH
LiCl, MeCN
50°C, 2h
Abyssomycin C +
iso-Abyssomycin
100%
1:1
Atropisomere

Maoecrystal V Zang Y. et al; JACS 2010, 16745



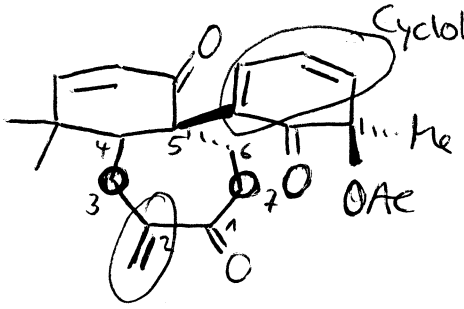
Diels-Alder

7-membered F-ring

- Nor-diterpenoid (C19)

→ lost one carbon-atom

→ also synthetically a big challenge

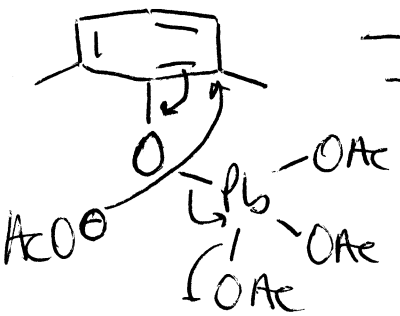


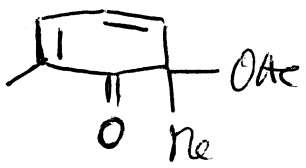
Diene: 2,4-Cyclohexadienone

dienophile

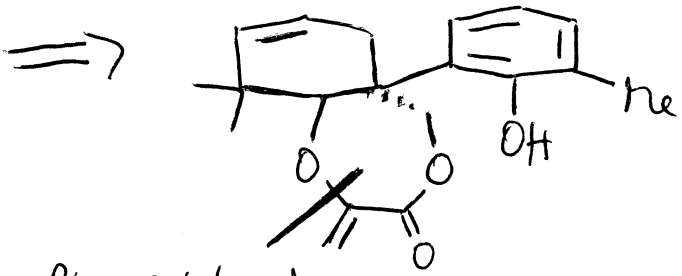
- Wessely oxidation

Oxidative dearomatization

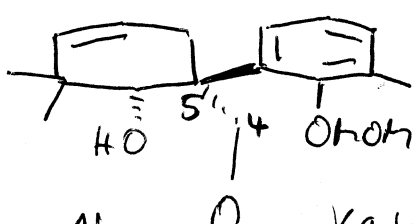


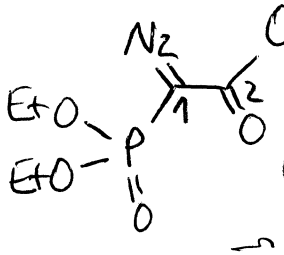


Very unstable, HOMO-dimerization (DA)



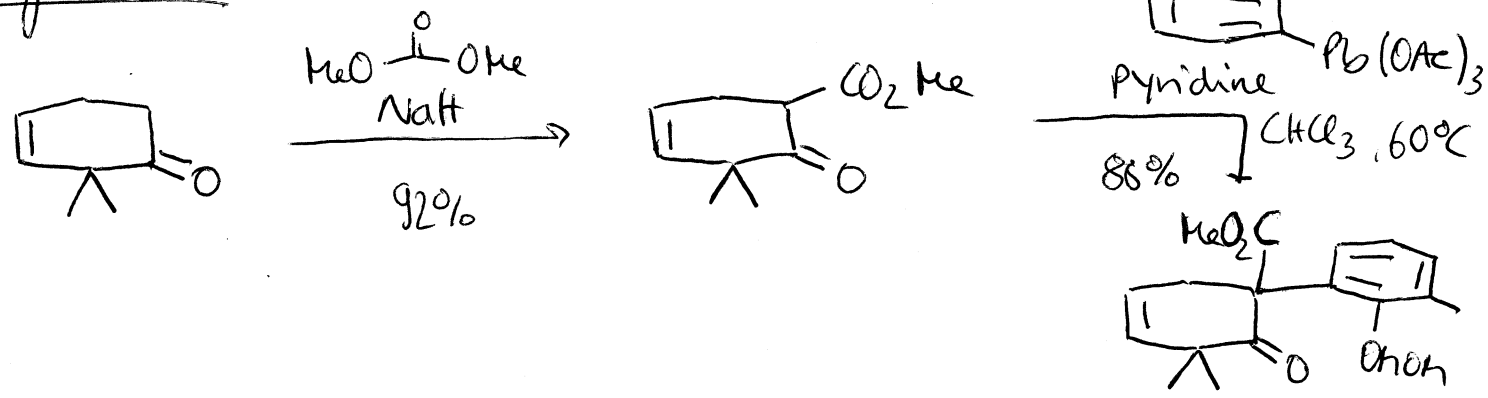
Rh-catalyzed OH-bond insertion



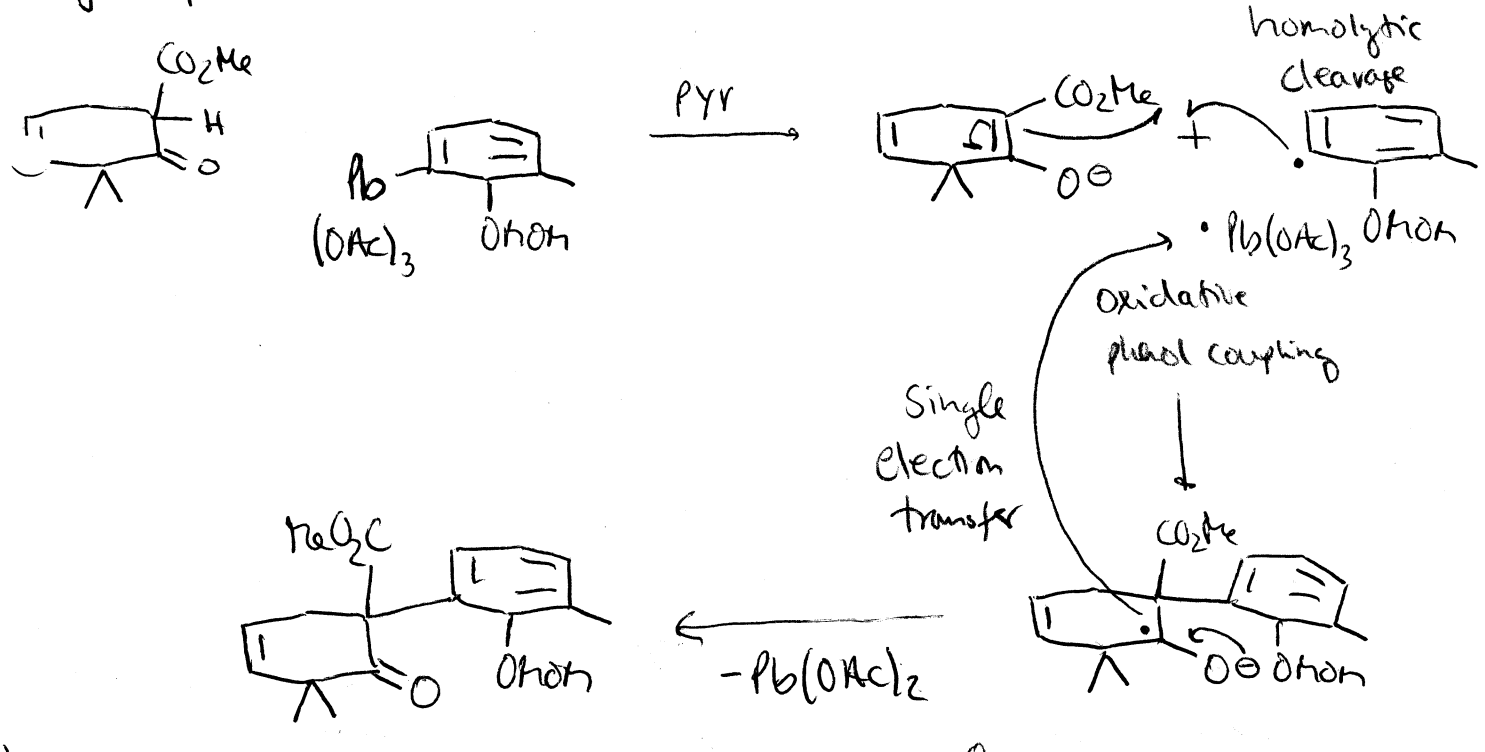


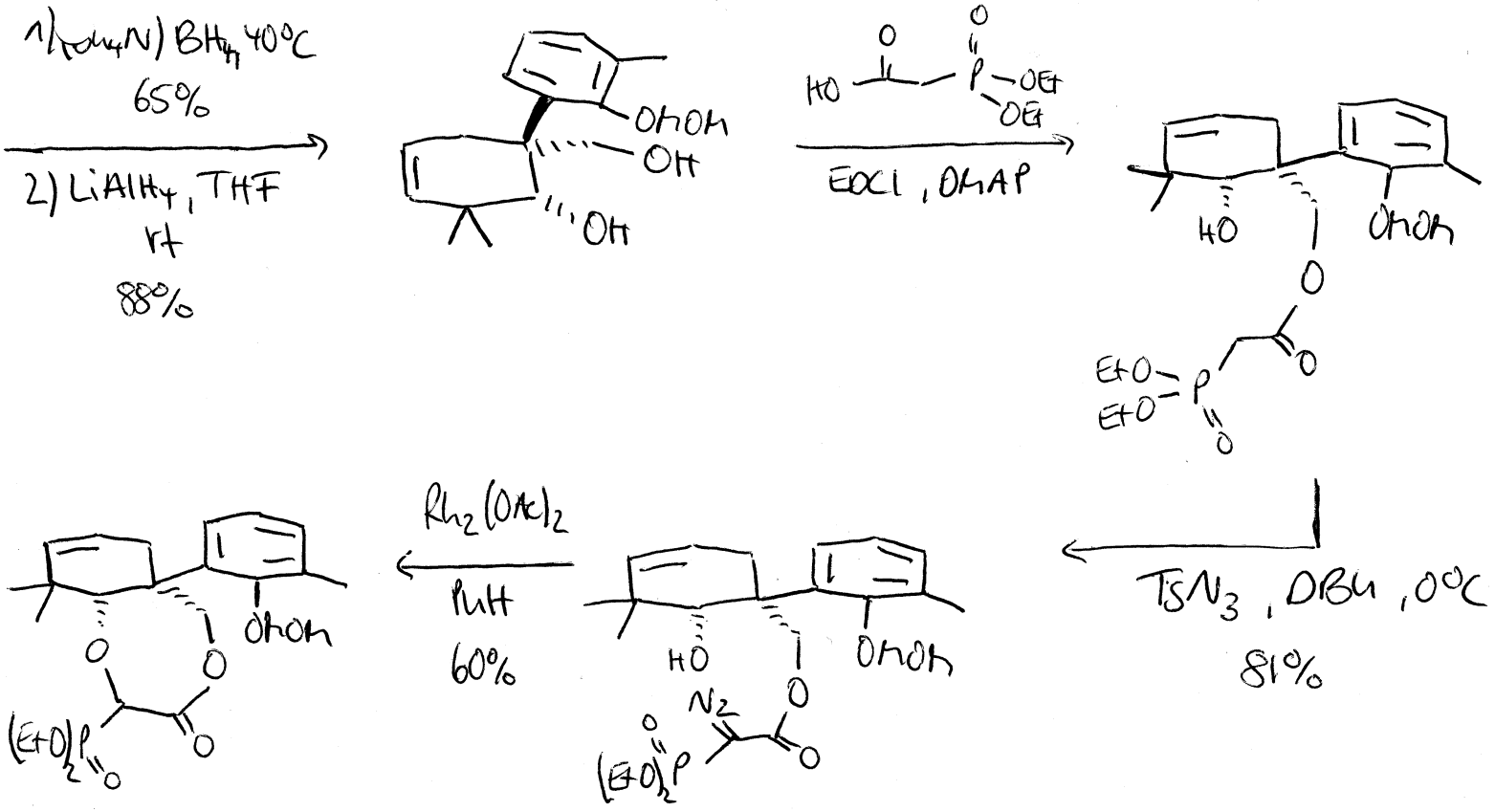
Konkurenz: CH-insertion macht bevorzugt 5-Ringe → quartnärer Kohlenstoff hier

Synthesis

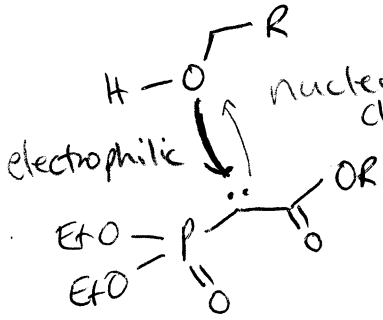


Organoplumbates: mechanism





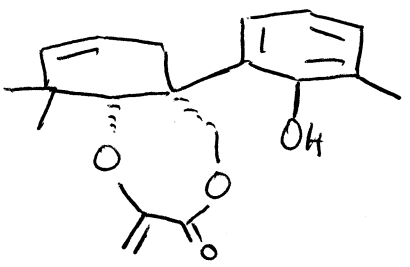
Carbenes : electrophilic carbene



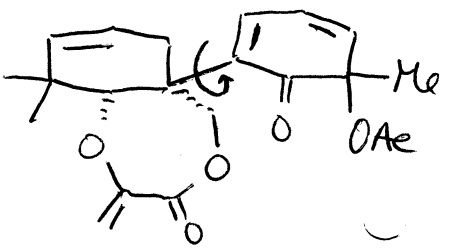
nucleophilic would mean a positive charge is build between both carbons

→ electrophilic : negative charge

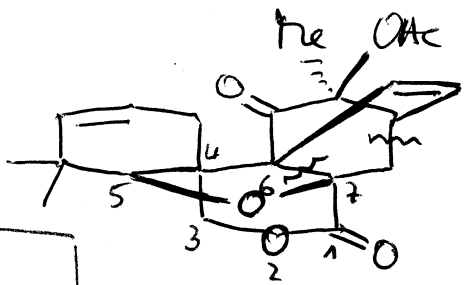
1) ^{t}BuOK
$(CHO)_4$, THF, 0°C
2) TFA, CH_2Cl_2
90%



$Pb(OAc)_4$
AcOH
0°C

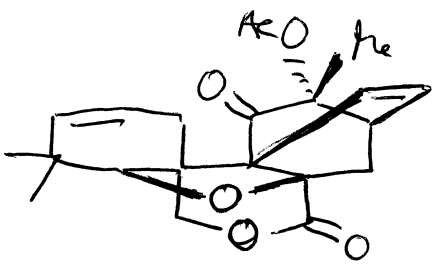


145°C
24h



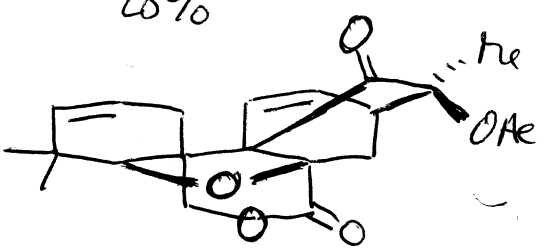
12%

+



28%

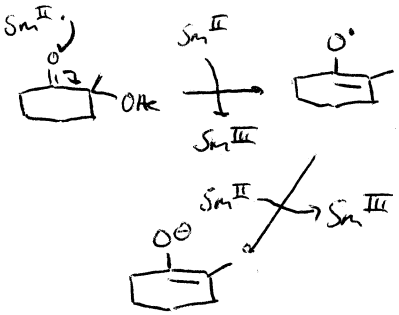
all allylic oxidations failed here!



36%

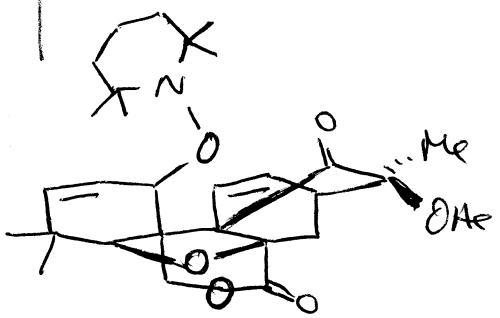
1) NBS, CCl_4
$h\nu$, reflux
[BPO]
90%

2) TEMPO, $SnBu_3H$, PhH
reflux, 2h
75%

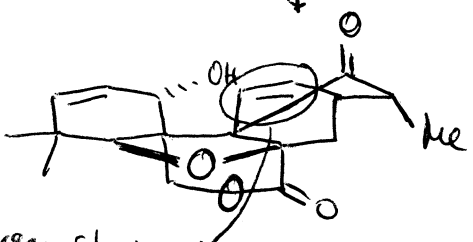


Samarium-reduction

1) AcOH, Zn, 2h
70°C; 85%
2) SmI_2, THF
MeOH, rt, 10min



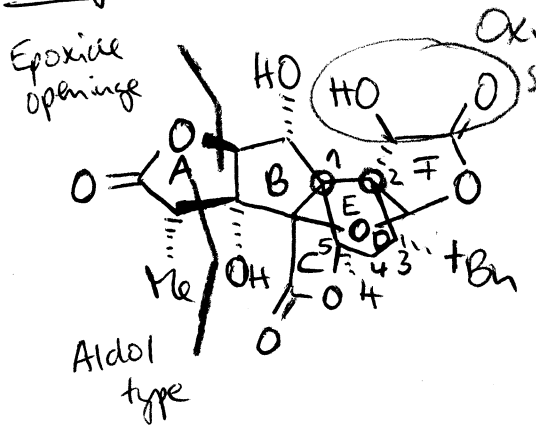
1) Lindlar, MeOH, H_2
92%
2) DMP, CH_2Cl_2; 88%



very strained double bond → Lindlar cat reduces this DB, normally only triple bonds

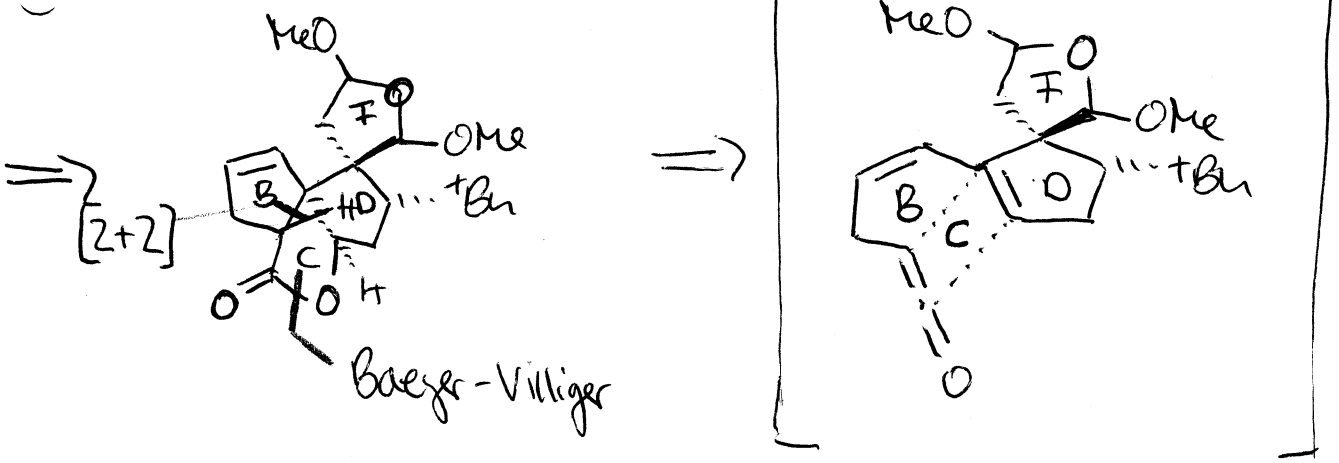
→ Maoecrystal V

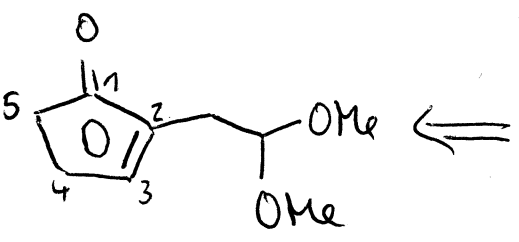
Ginkolide B : E.J. Corey et al. JACS 1988, 649-651

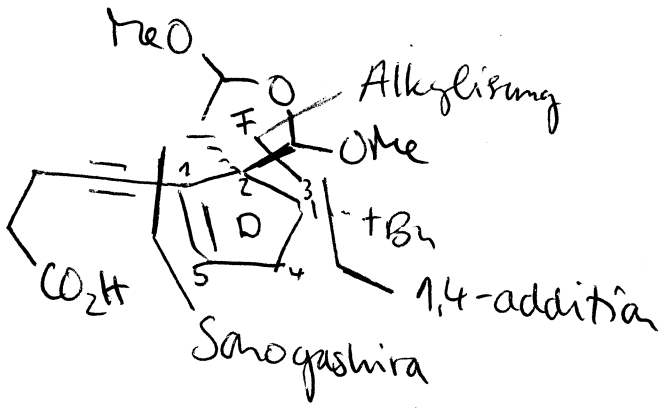


- 11 Stereozentren, davon 2 quat.
- ausschließlich 5-Ringe
- 2 Carbocycles spiro
- ^{t}Butyl-group am Stereozentrum

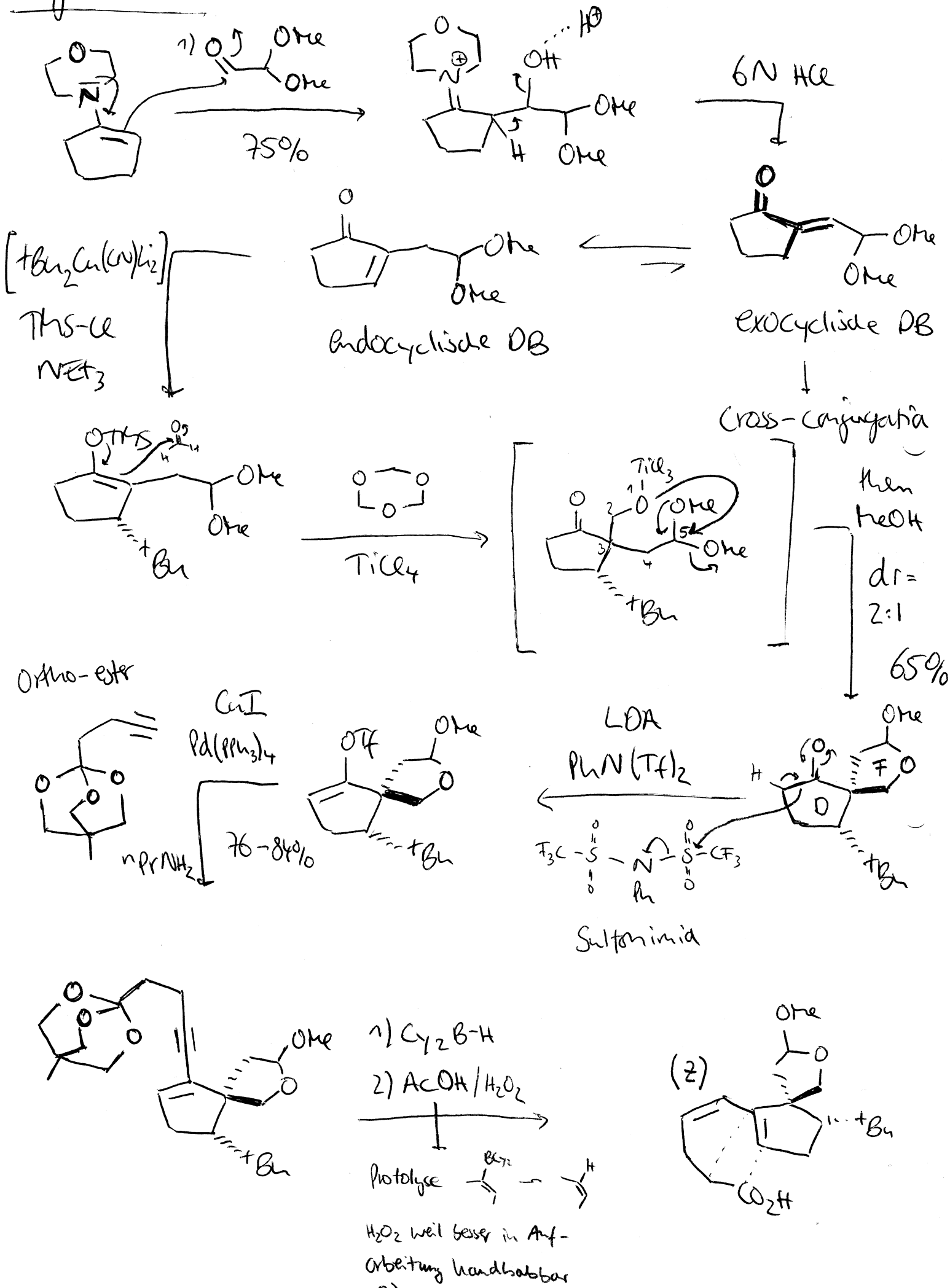
→ 1967 Isolation (Nakanishi)



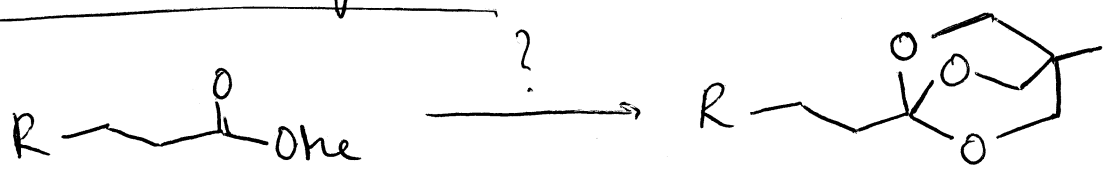




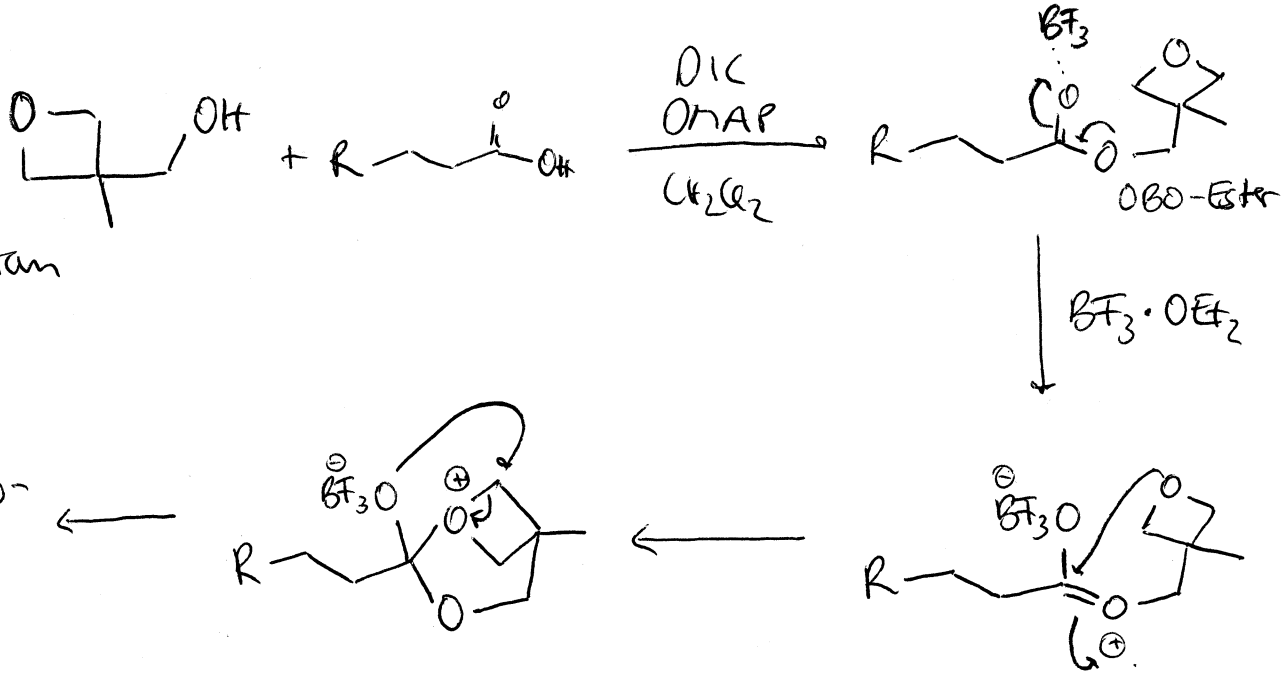
Synthese:


75%
6N HCl
Endocyclische DB
exocyclische DB
Cross-Conjugation
TMS-Cl
NEt3
TiCl4
dr = 2:1
65%
Ortho-ester
CuI
Pd(PPh3)4
nPrNH2
76-84%
LDA
PhN(Tf)2
Sulfonimid
1) Cy2B-H
2) AcOH/H2O2
Protolyse
H2O2 weil besser in Aufarbeitung handhabbar
3) pH=3
(Z)

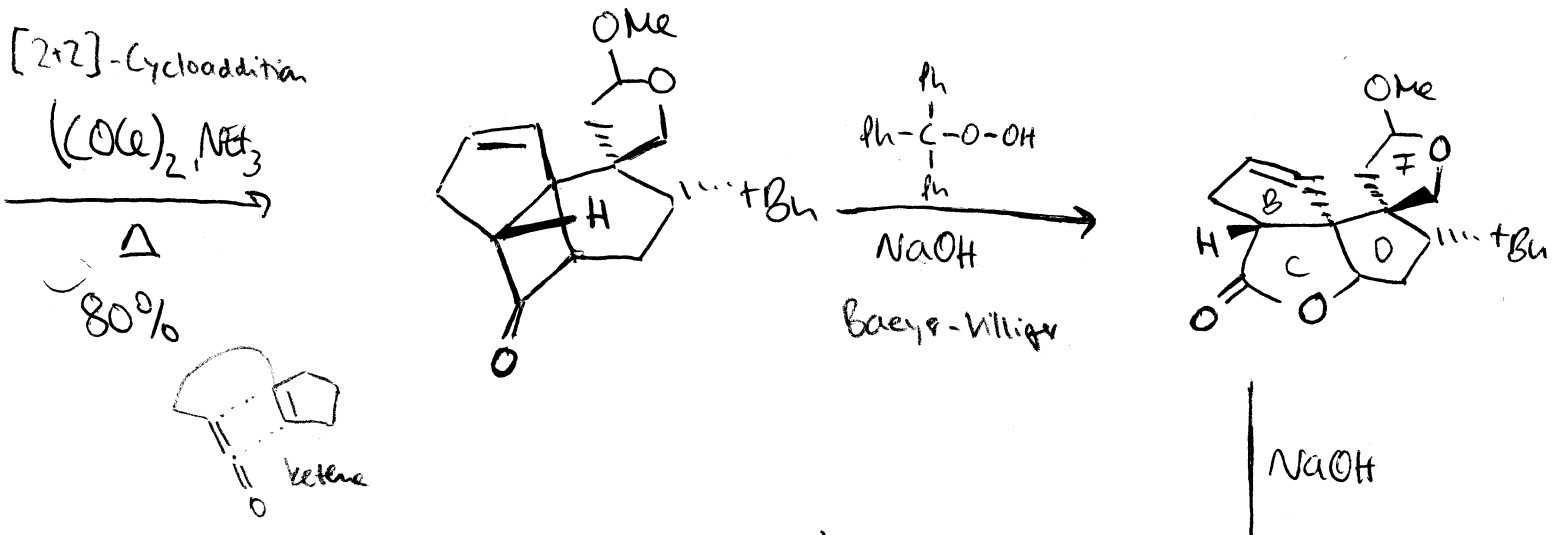
Ortho-Ester Synthesis

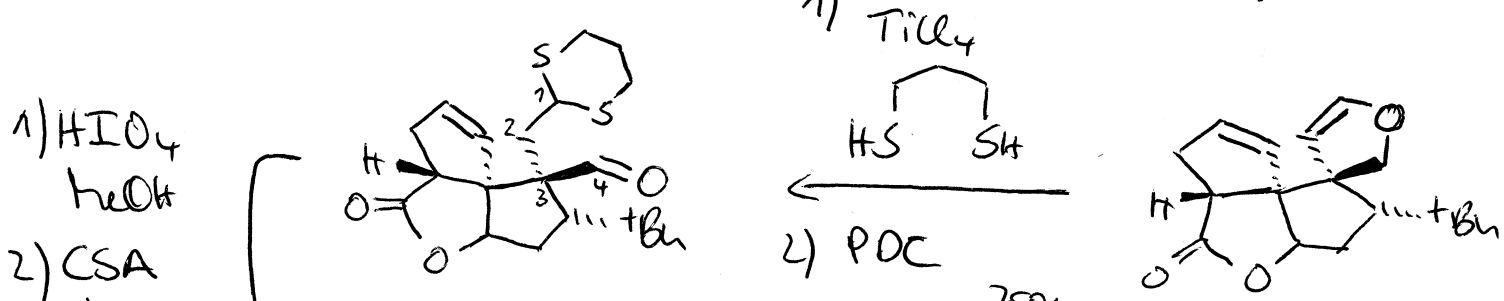


OBO-Ester:

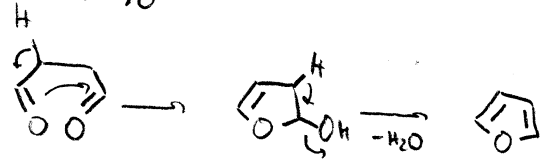


[2+2]-Cycloaddition

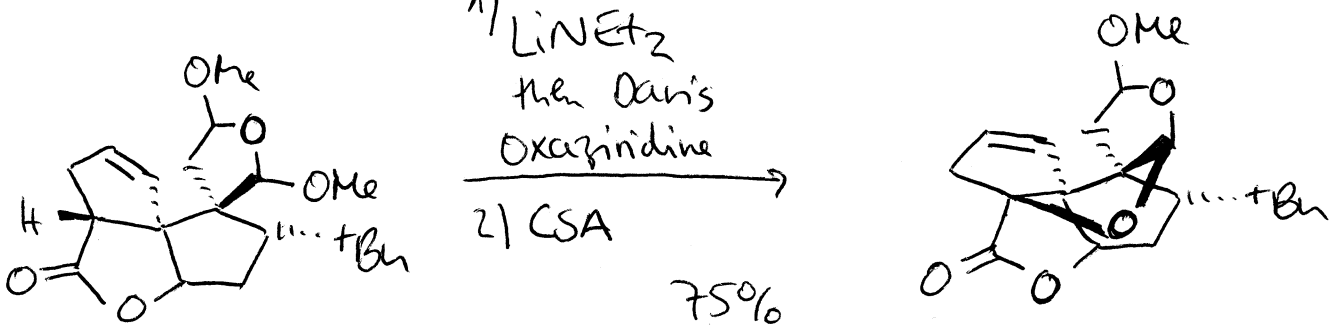




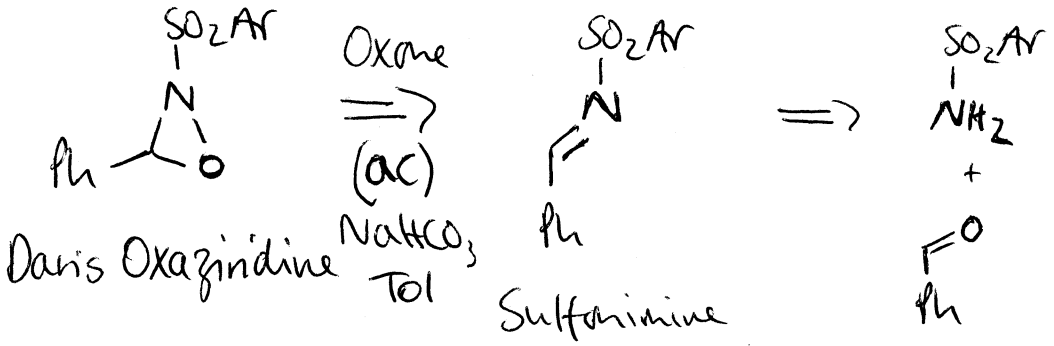
→ forms normally furanes:



→ but here: quartenary carbon!

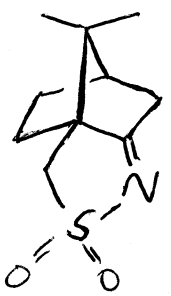


α-hydroxylation of lactones:

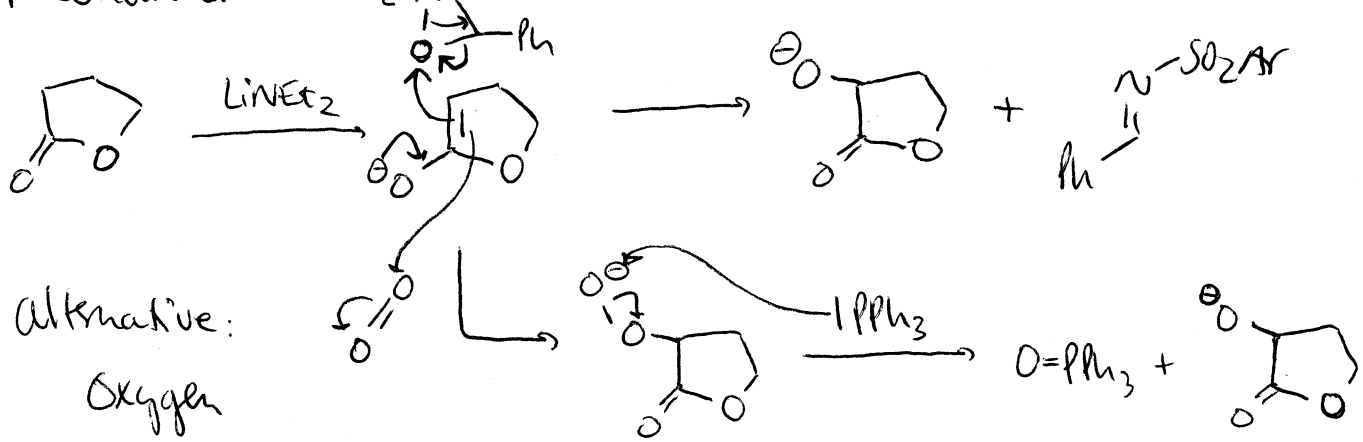


Oxone + acetone →  DMDO = dimethyldioxirane

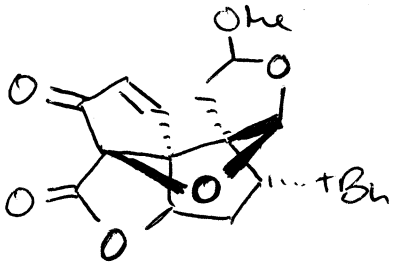
→ also in asymmetric variants available:



Mechanism: ArO_2SN

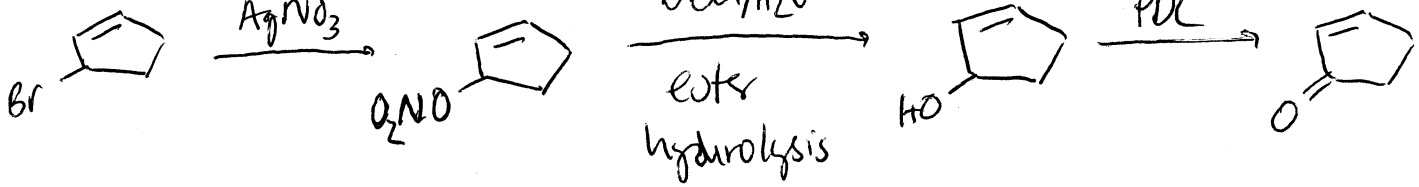


1) NBS, hν
$AgNO_3$/OBn
H_2O then
PDC, MeOH

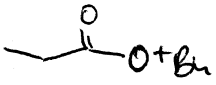


40%

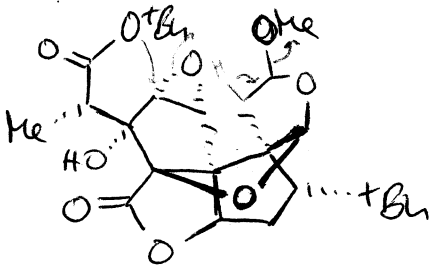
Mechanism:



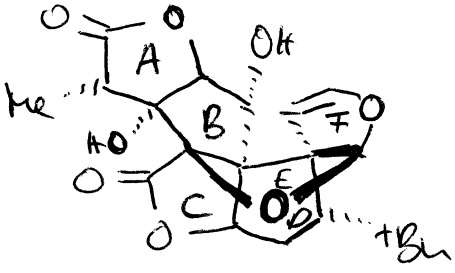
1) Ph_3COOH
$BnMe_3N$-OH
Schafer Weitz
2) LDA, HMPA



68%



CSA
CH_2Cl_2
92%

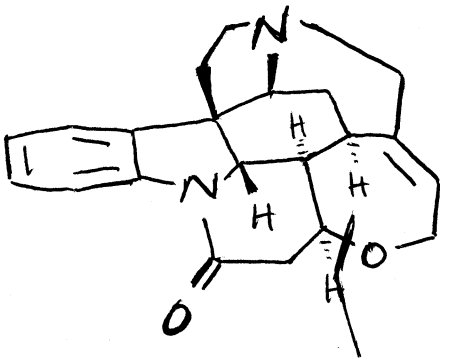


1) TBS-OTf, 2-6-Lutidine
2) OsO_4, Pyr
65%

1) I_2, $CaCO_3$
2) $BF_3 \cdot OEt_2$
89%

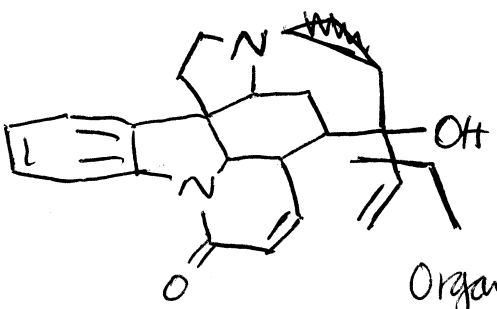
Gilvocidin B

Strychnine : R.B. Woodward et. al, JACS 1954, 4749

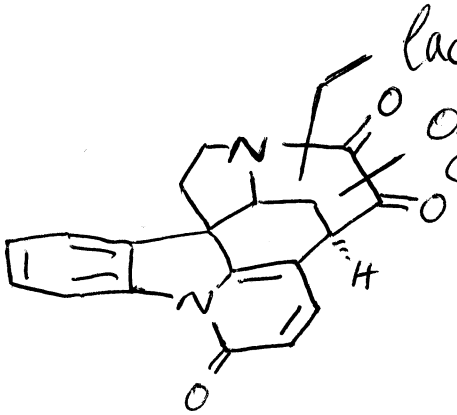


- isolated in 1818
- Structure elucidation 1947 (40 years)
  R. Robinson & H. Leuchs
  → ~250 communications required

allylic rearrangement & oxa-Michael addition

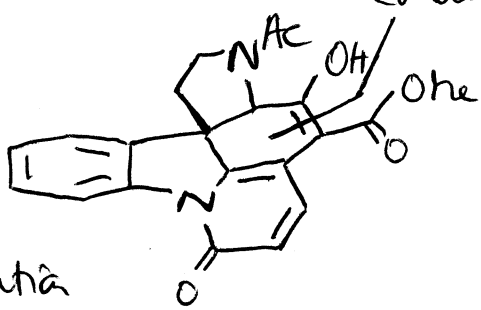


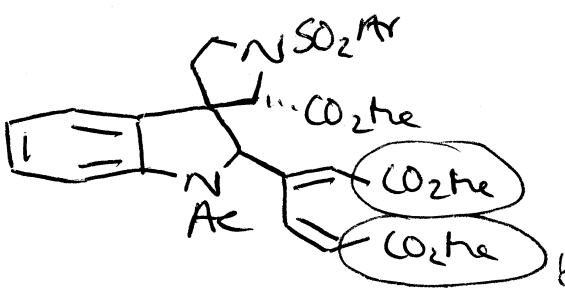
Organometal addition



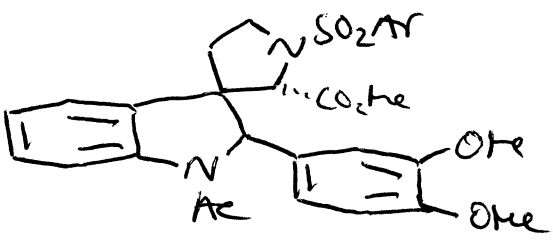
lactamization
oxidative carboxyl.

Dieckmann condensation

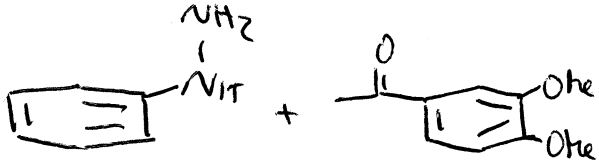




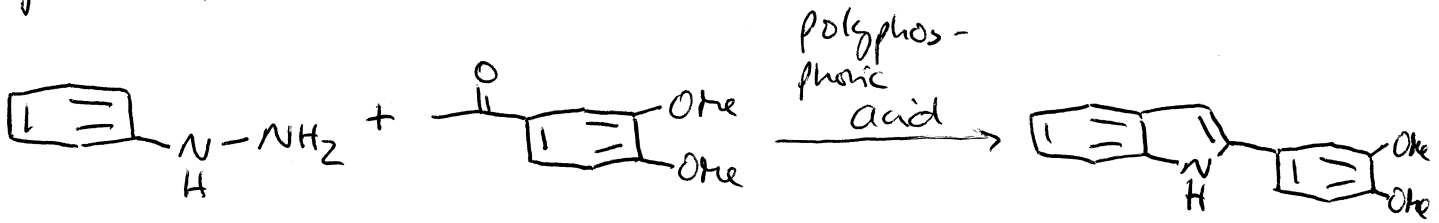
ester differentiation by double bond geometry
E/Z → only (Z) brings 6-ring lactame

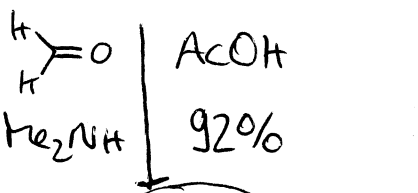


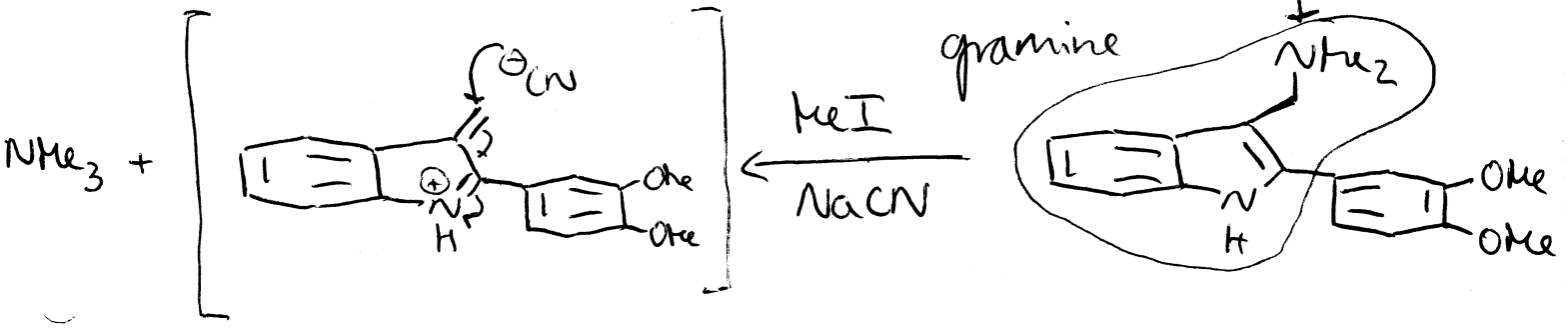
Fischer Indole

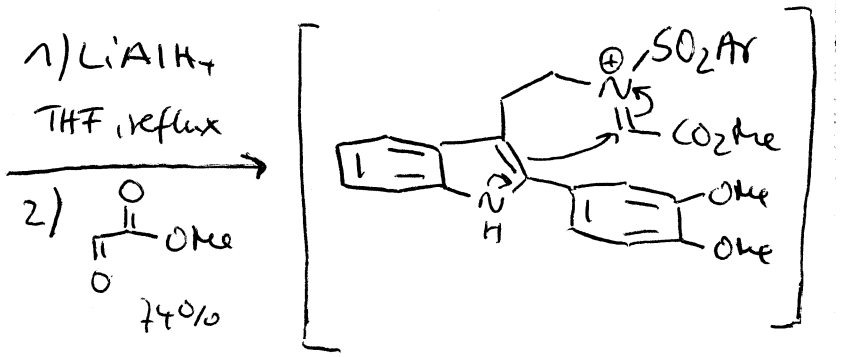


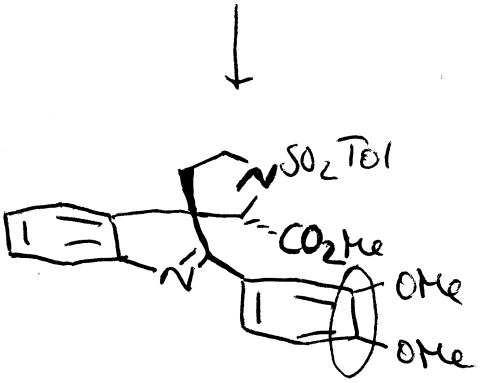
Synthesis:

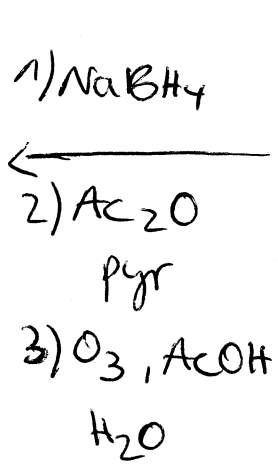


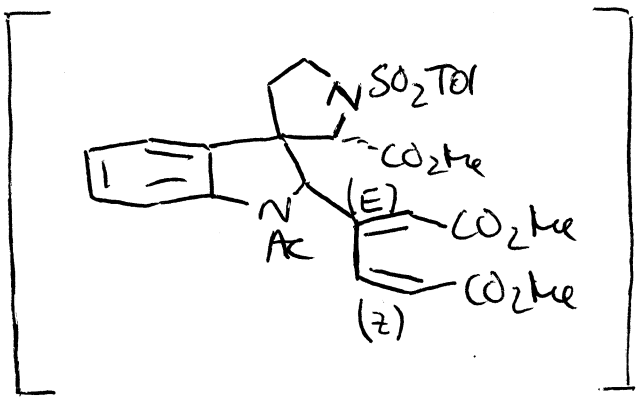








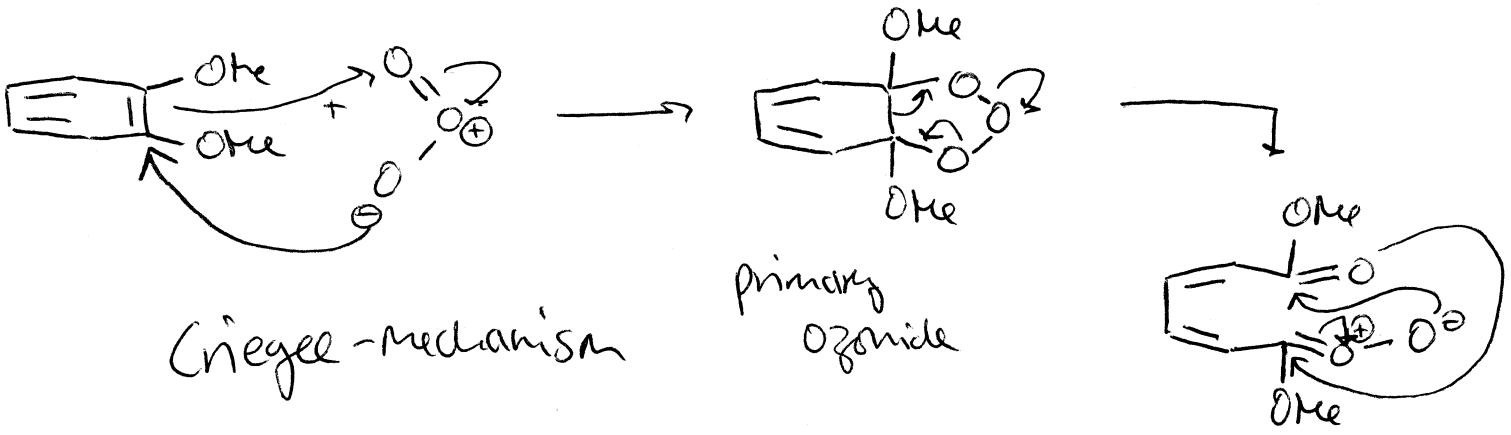




double Michael-acceptor

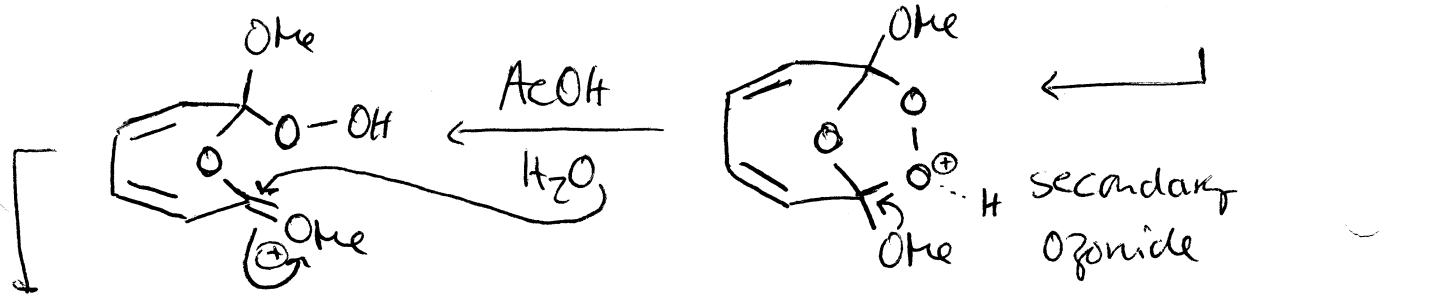
→ doesn't isolate this

mechanism:

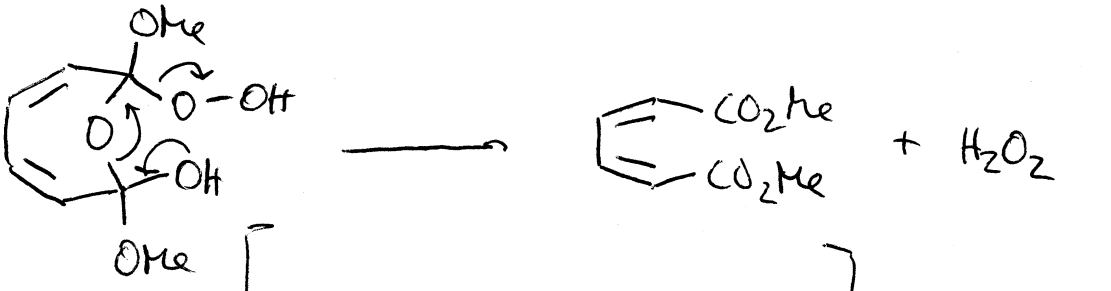


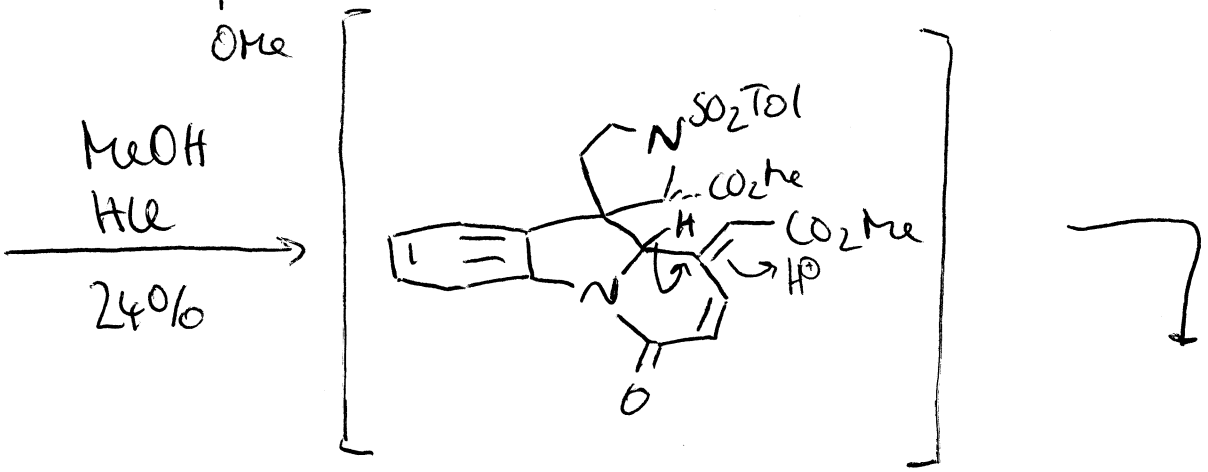
Criegee-mechanism

primary ozonide



secondary ozonide



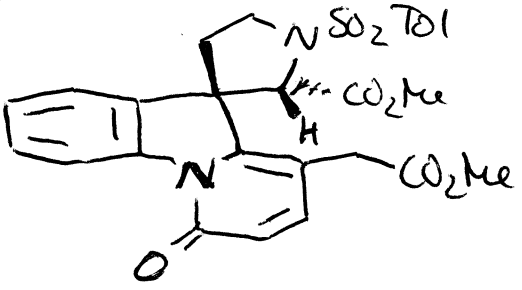


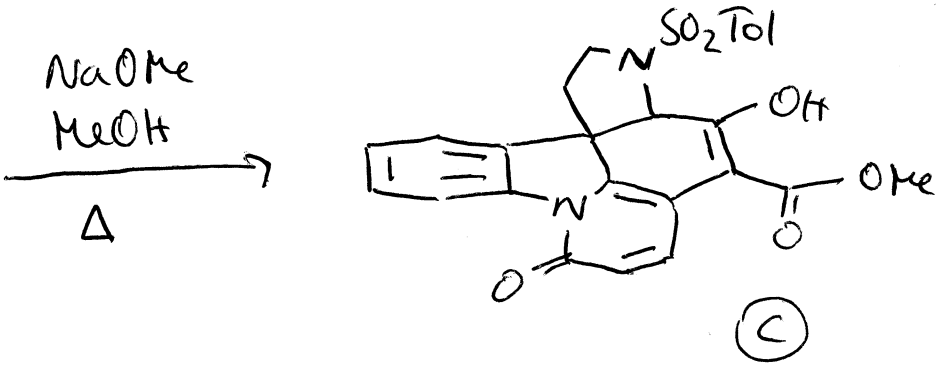
problem: ester looks to wrong side for Dieckmann-condensation

→ equilibrate by deprotonation

→ reprotonation brings right stereochemistry

→ Dieckmann-condensation can take place and drives equilibrium





Ⓒ

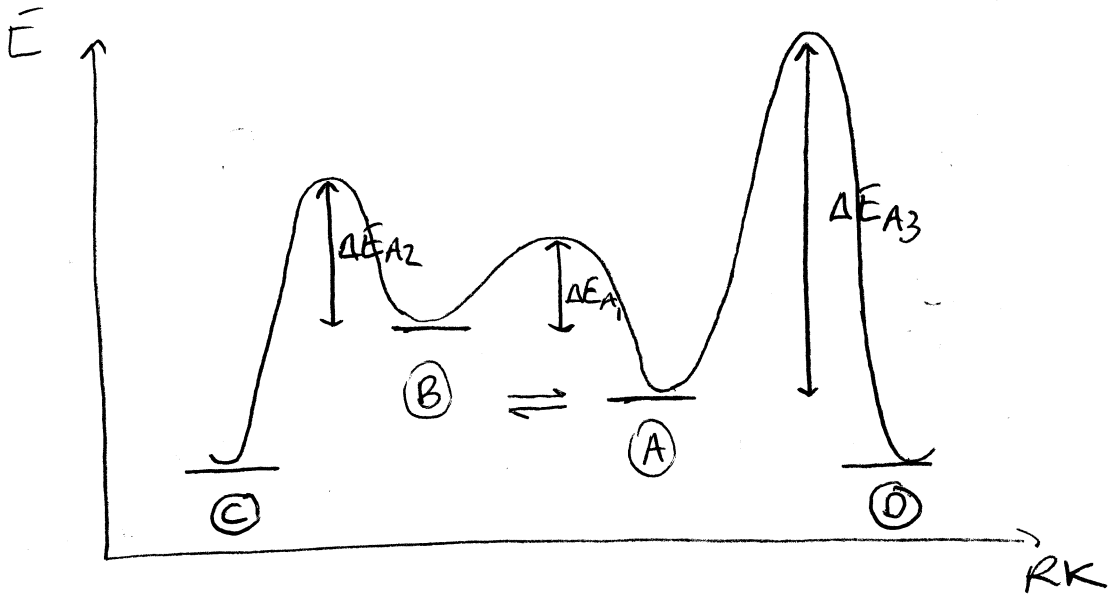
before condensation protecting group change from NSO_2Tol to NAc:

1) HI, red phosphor
2) CH_2N_2 → carboxylic acid back to ester
3) Ac_2O, Pyr

Curtin-Hammett-principle:

→ 2 compounds, one more stable, in equilibrium

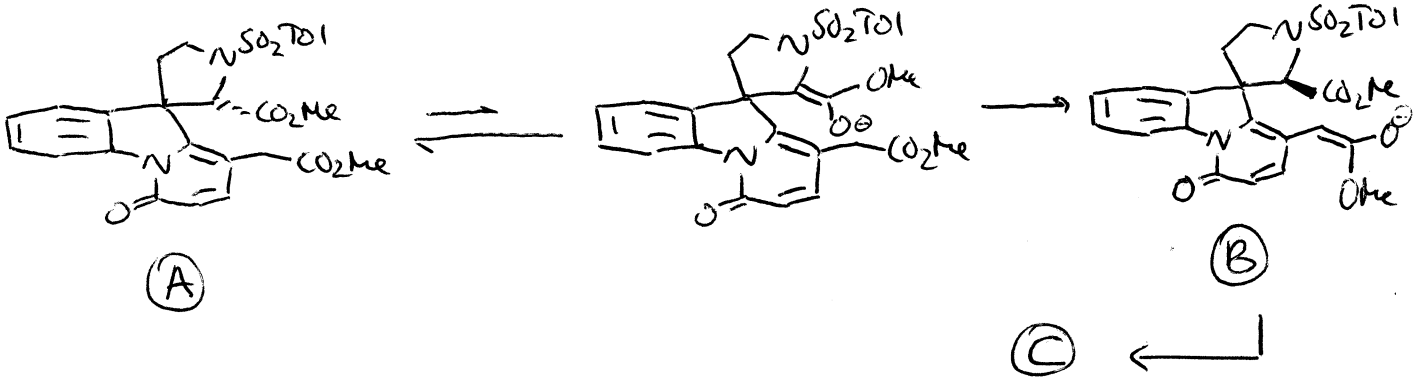
→ less stable compound is more reactive and influences in this way the equilibrium

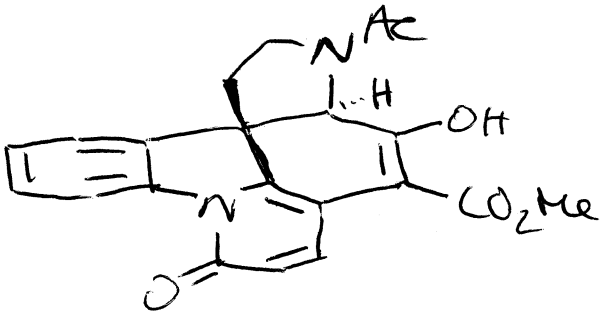


Ⓐ is more stable than Ⓑ ; Ⓐ ⟷ Ⓑ

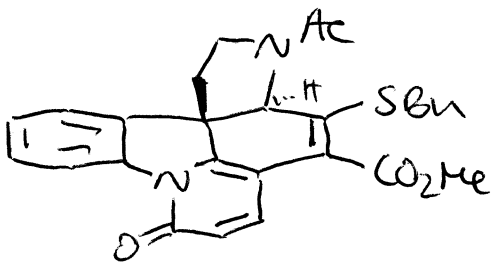
$\Delta E_{A2} < \Delta E_{A3}$ ⇒ product Ⓒ is formed

Kinetic control with pre-existing equilibrium

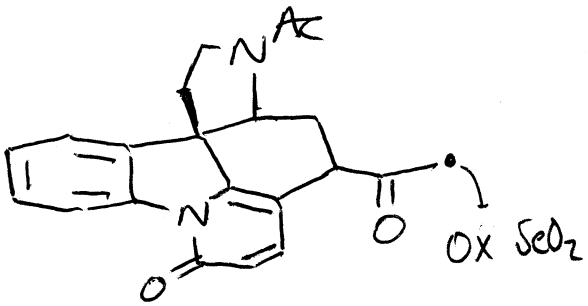




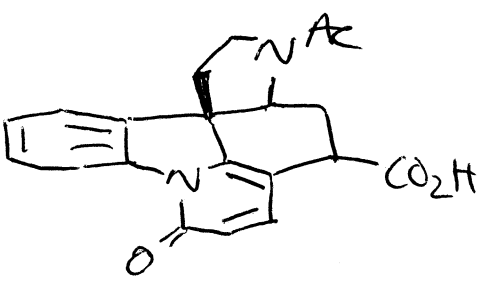
1) TsCl, Pyr.
2) NaS- 



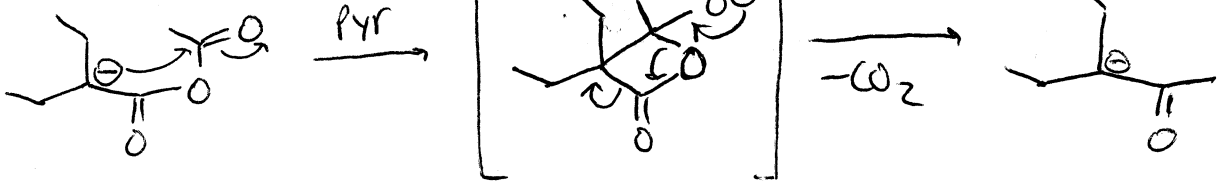
1) Ra-Ni
2) H_2 / Pd-C
3) KOH, MeOH/H_2O

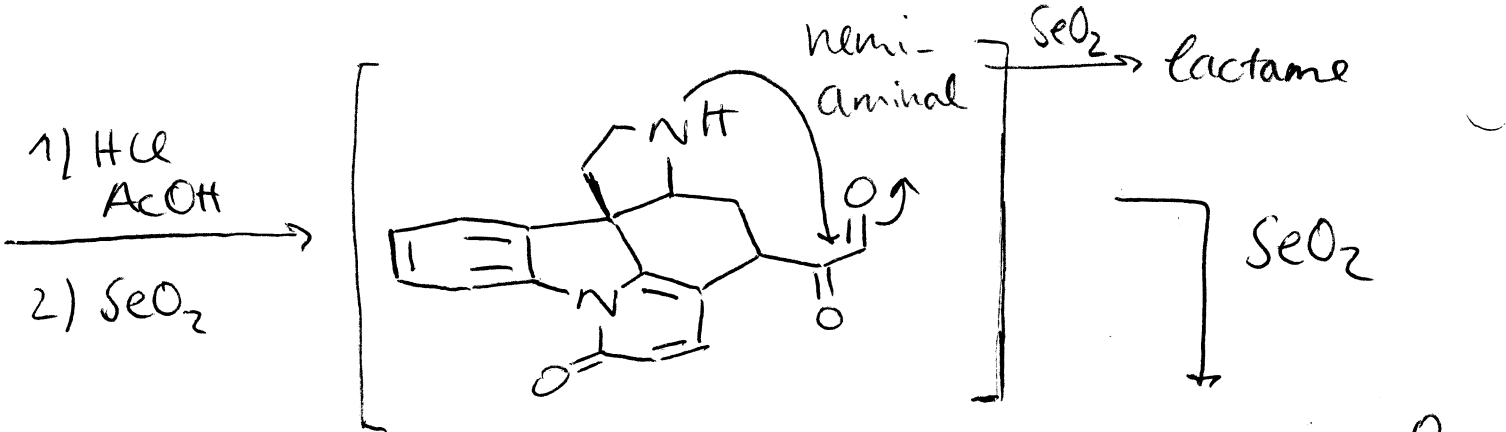


Ac_2O, Pyr, 42%



Mechanism:



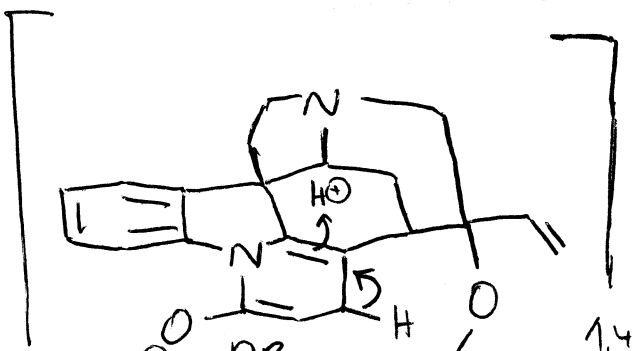


1) HCl, AcOH
2) SeO_2

hemi-aminal

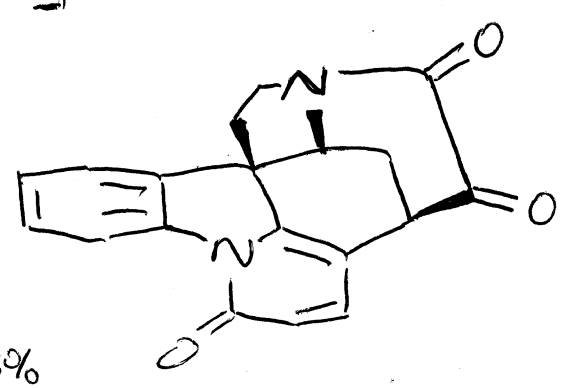
SeO_2 → lactame

SeO_2



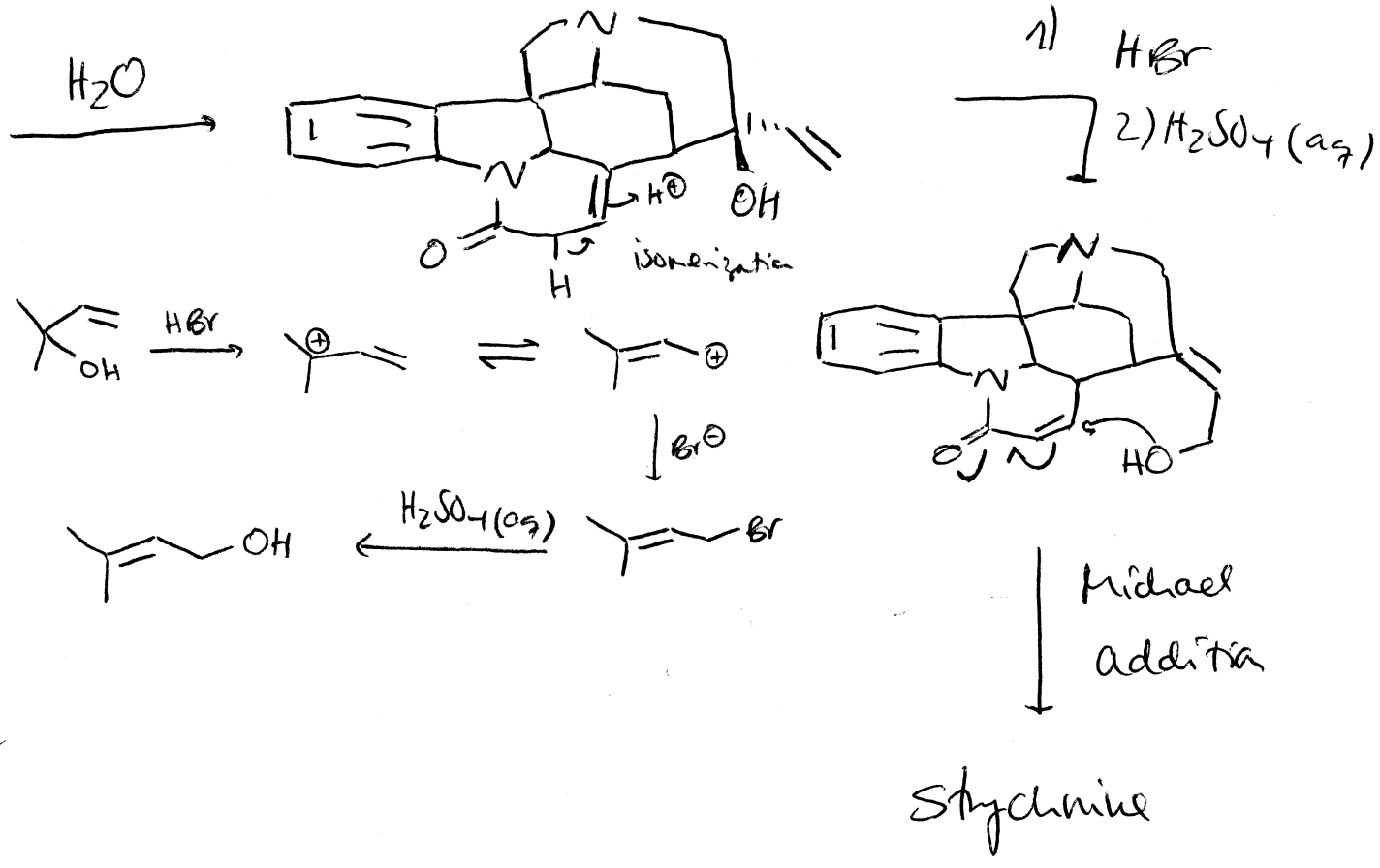
Shifts in conjugation

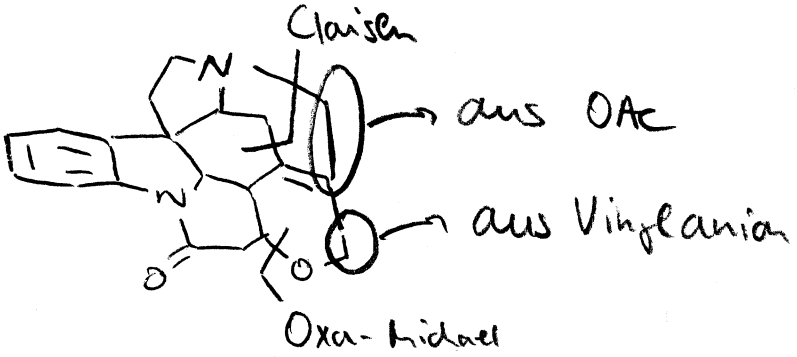
1) Na-≡
2) Lindlar
3) $LiAlH_4$

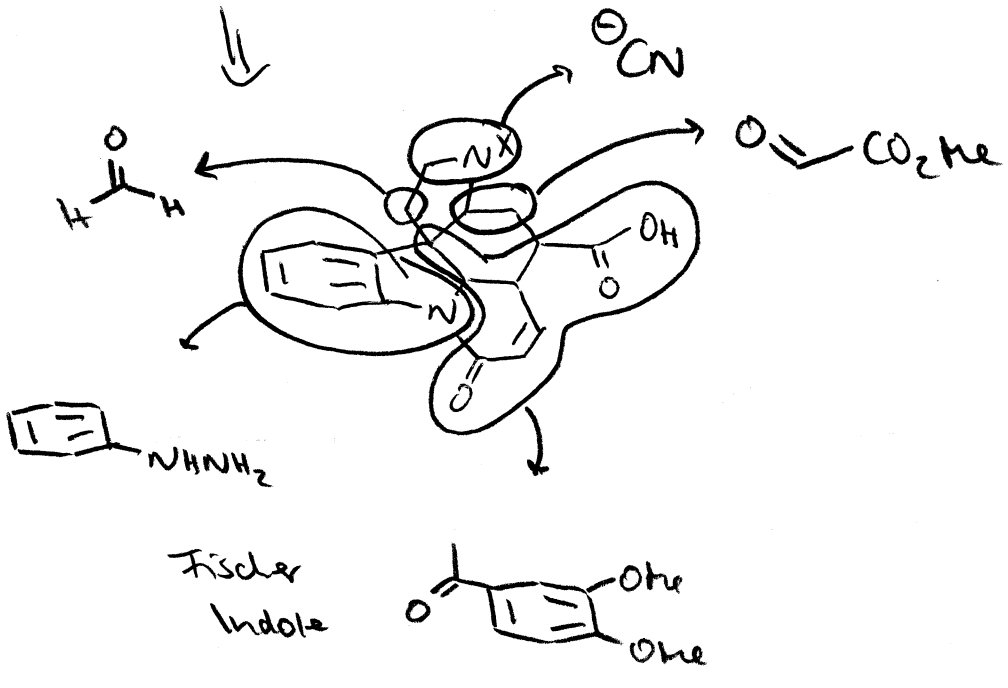


13%

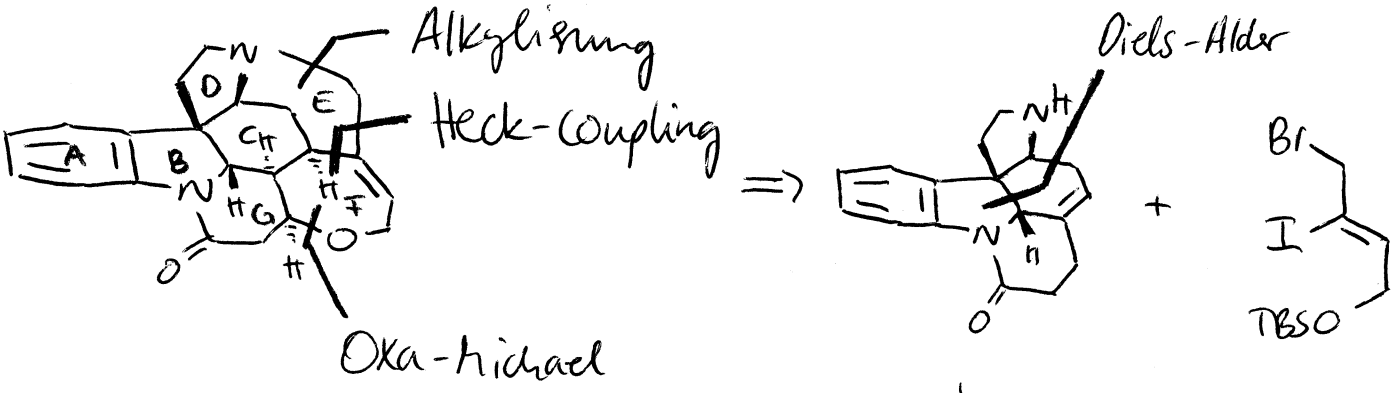
1,4-reduction by coordination of $LiAlH_4$ by alcohol → enolate forming → differentiation between 2 lactames

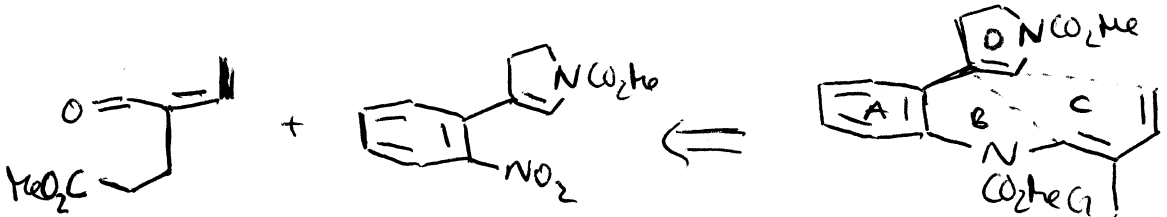

H2O
1) HBr
2) H2SO4 (aq)
HBr
isomerization
Br⊖
H2SO4 (aq)
OH
Br
Michael addition
Strychnine

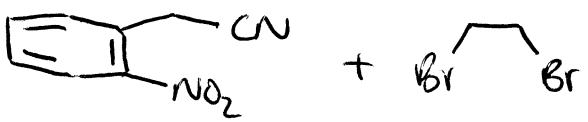

Claisen
aus OAc
aus Vinylanion
Oxa-Michael


⊖CN
CO2Me
OH
NHNH2
Fischer Indole
OMe
OMe

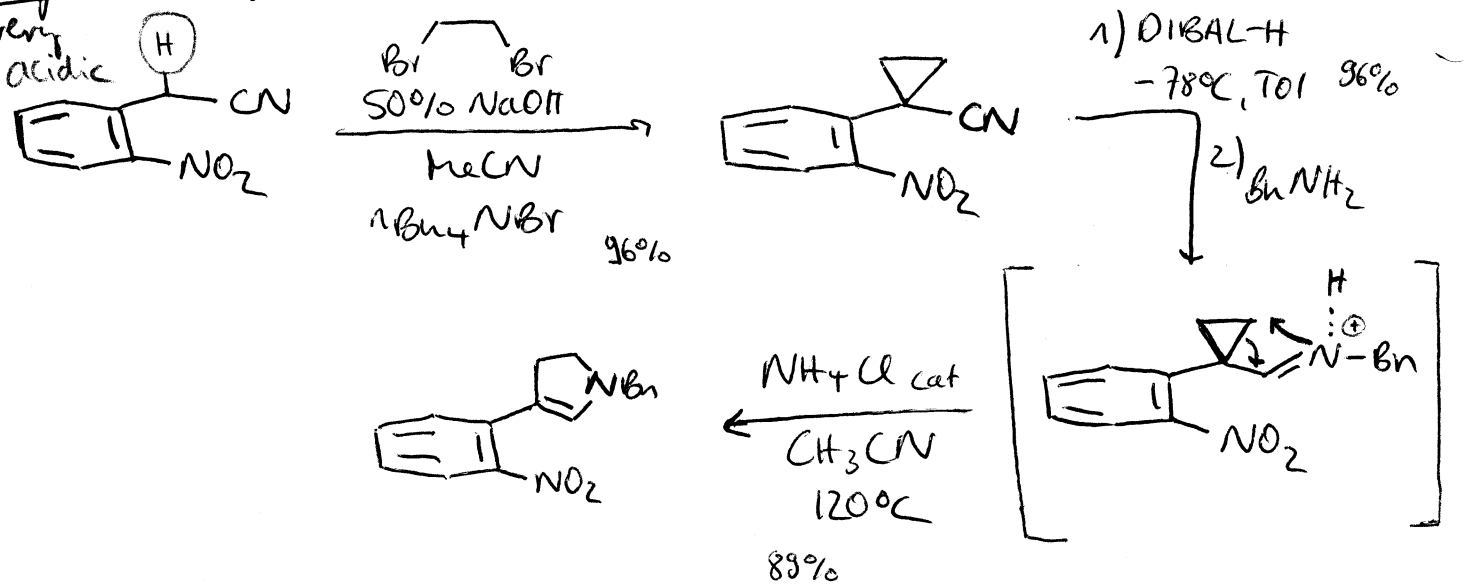
Retrosynthese von V. H. Rawal

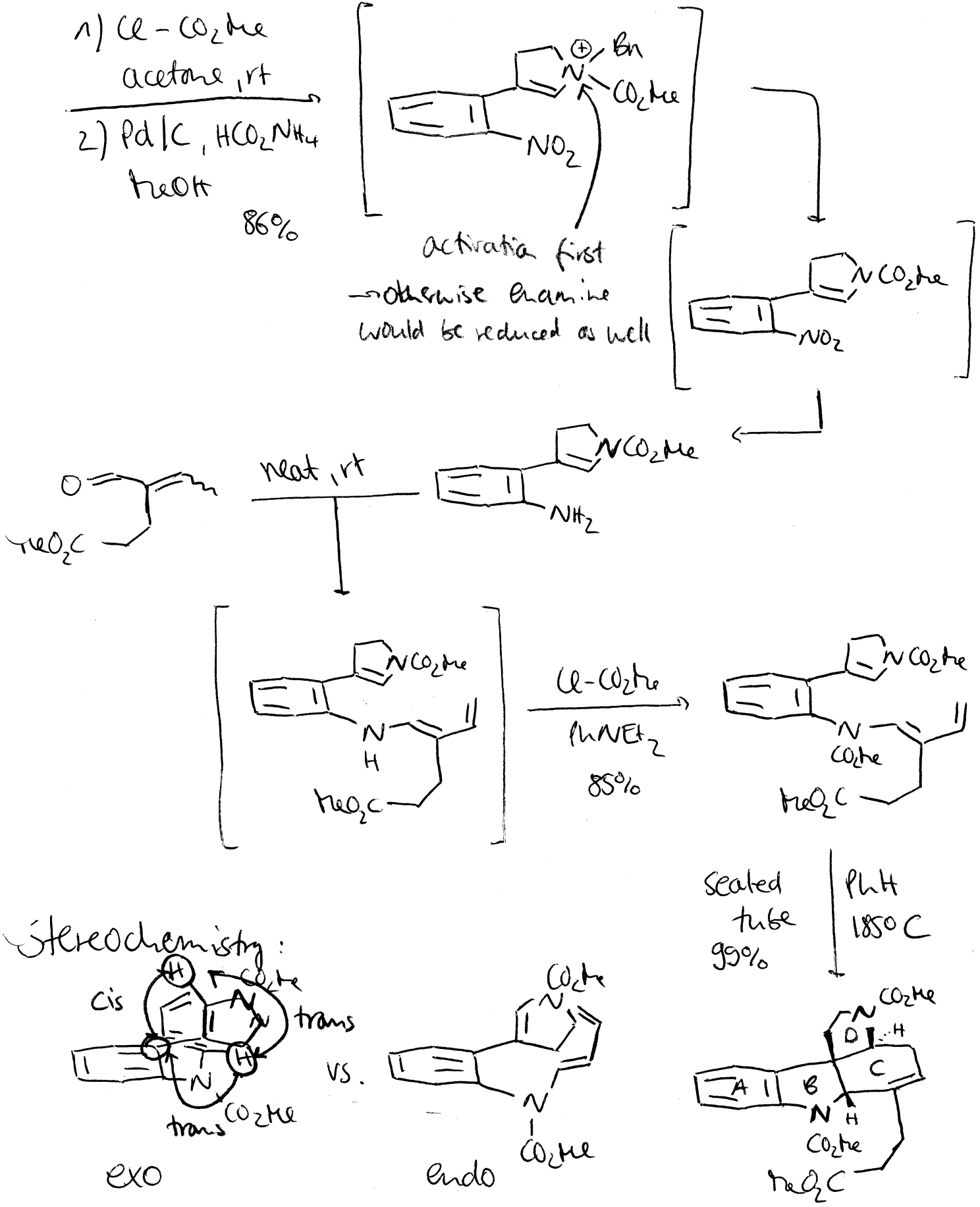


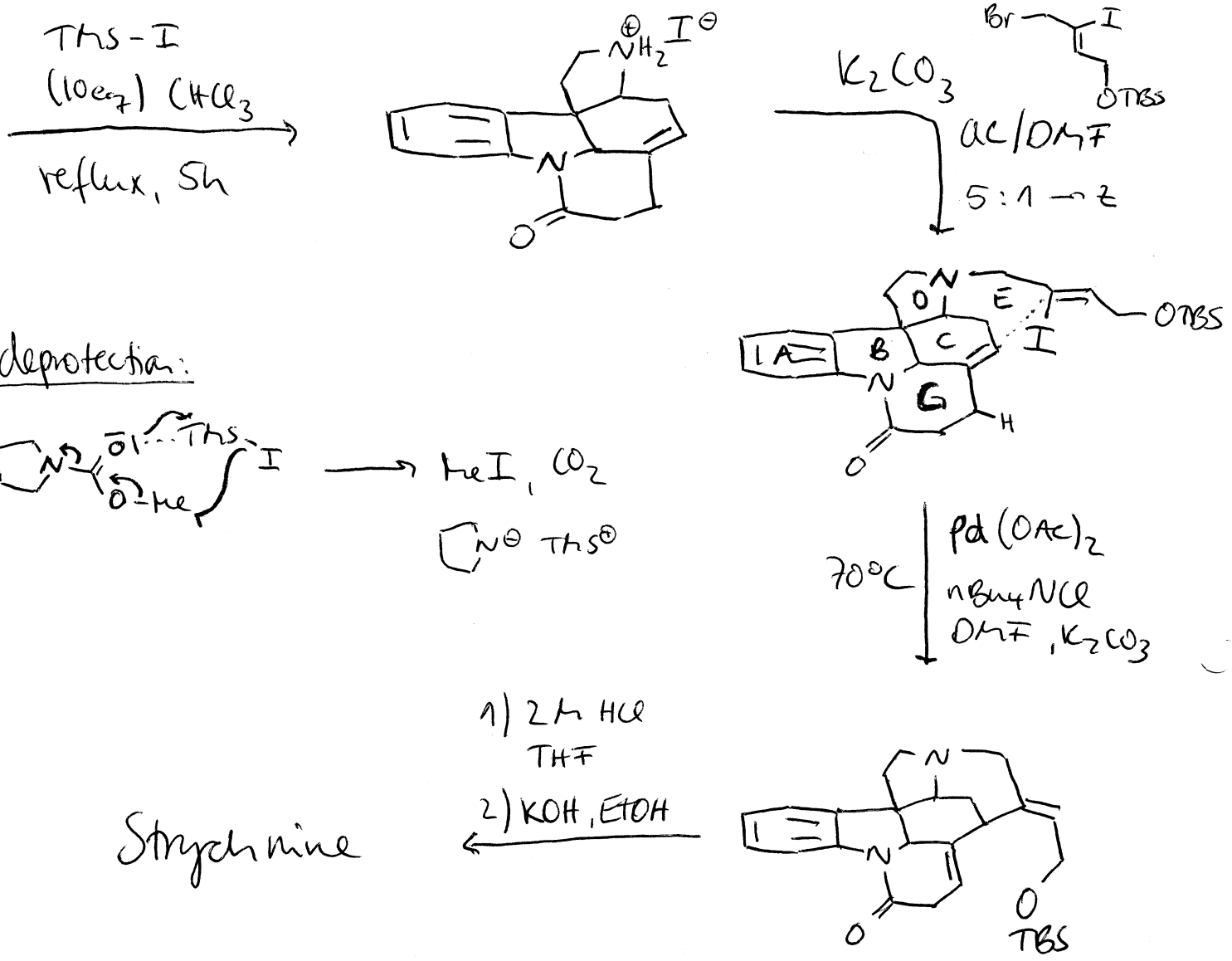




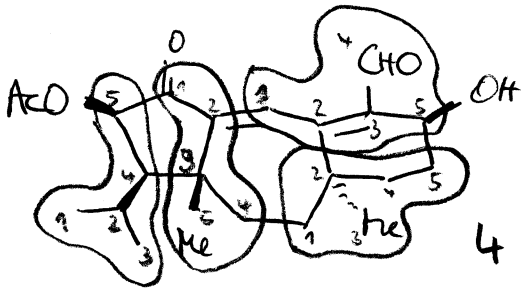
Synthese: JACS 1993, 115, 3030 & JOC 1994, 59, 2685




1) Cl-CO2Me
acetone, rt
2) Pd/C, HCO2NH4
MeOH
86%
activate first
→ otherwise enamine would be reduced as well
neat, rt
Cl-CO2Me
PhNEt2
85%
sealed tube
99%
PhH
185°C
Stereochemistry:
cis
trans
trans
vs.
exo
endo
normally preferred end:
secondary orbital interactions
→ between newly formed double bond & carbonyl
→ here: no secondary orbital interactions take place
→ exo-product


TMS-I
(10 eq.) CH_2Cl_2
reflux, 5h
K_2CO_3
Ac/DMF
5:1 → t
OTBS
deprotection:
MeI, CO_2
70°C
$Pd(OAc)_2$
nBu_4NCl
DMF, K_2CO_3
1) 2M HCl
THF
2) KOH, EtOH
Strychnine
TBS

Guanacasterpene



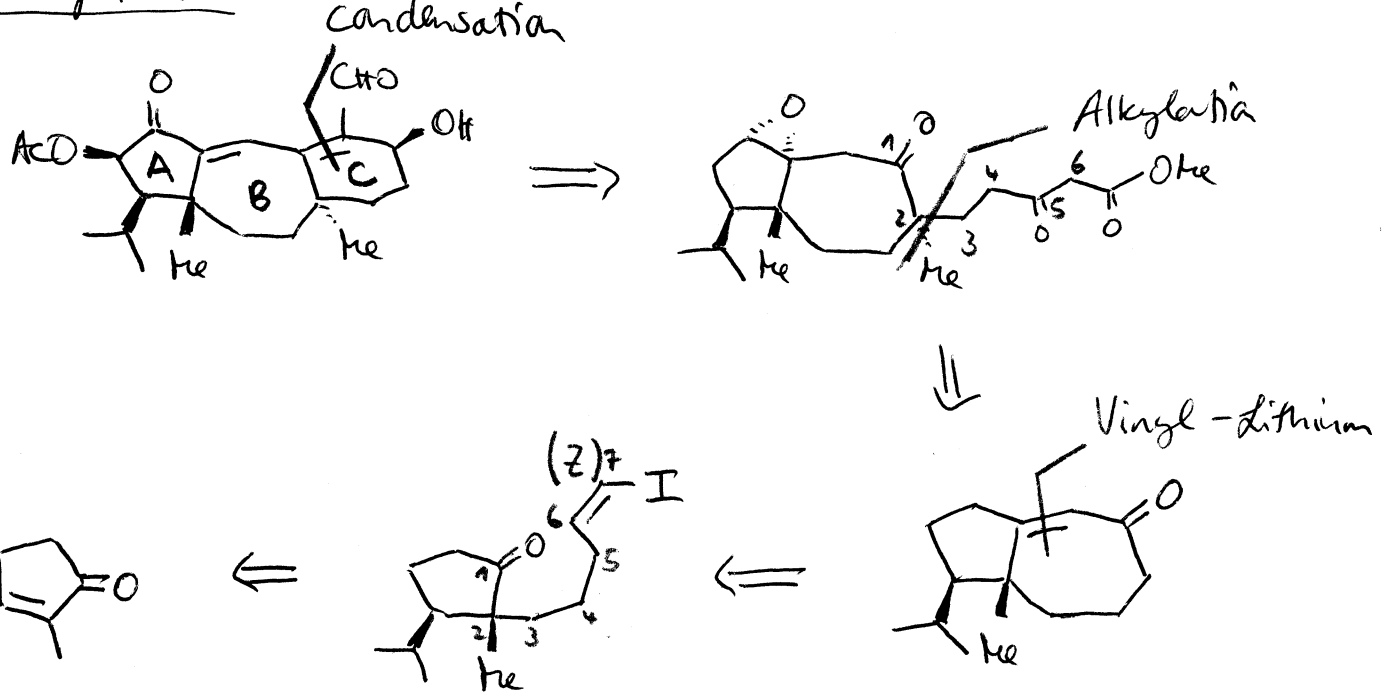
4 C_5-Einheiten

Guanacasterpene A

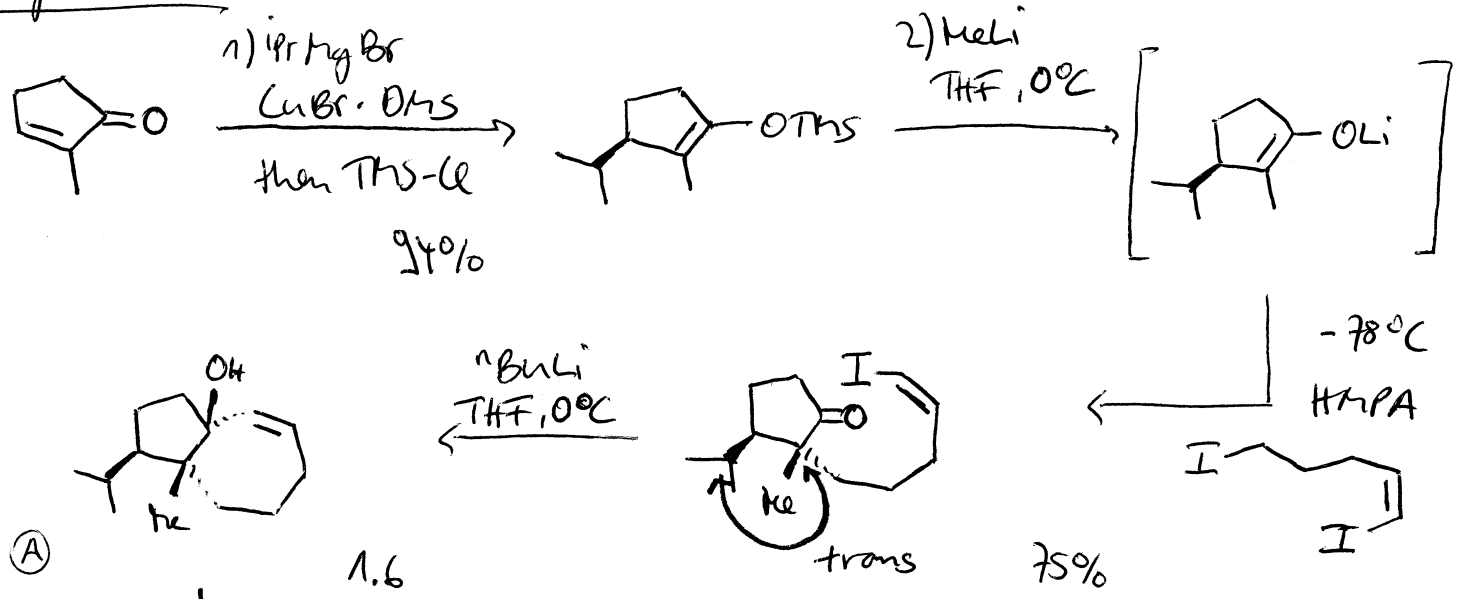
S. Danishefsky, ACIE 2002, 2185 & 2188

- Diterpen (C_{20})
- Isolation J. Clardy et al. (2000) Costa Rica "Area" aus Endophytic fungus
- antibiotische Wirkung gegen S. aureus & E. faecalis
- Nordteil: funktionalisiert, Südteil: unfunktionalisiert

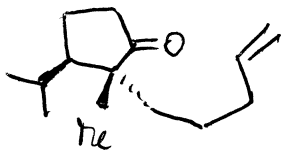
Retrosynthese:



Synthesis:



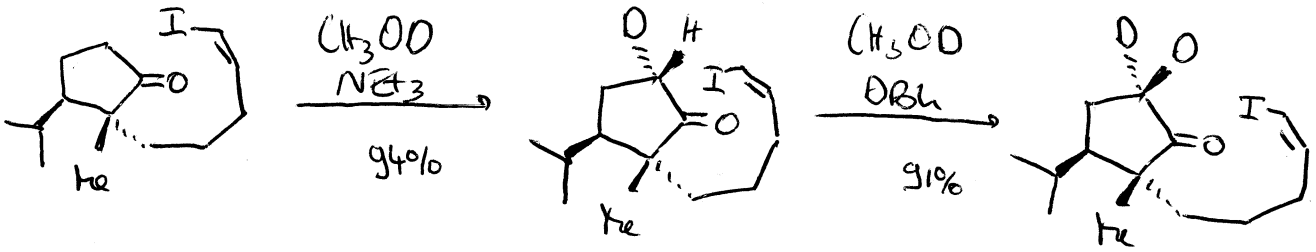
Ⓐ + 1.6 zu 1

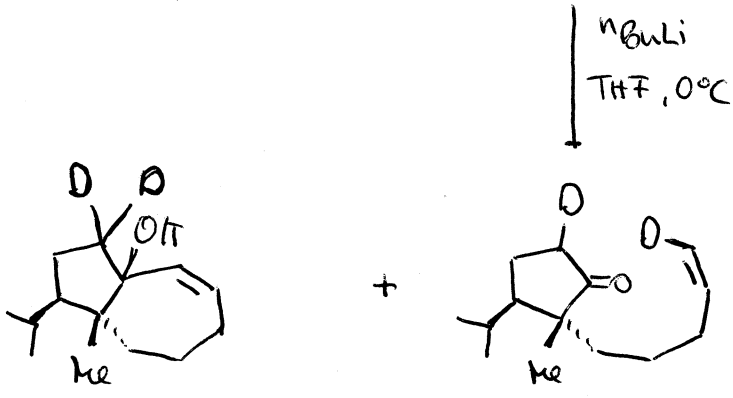


Ⓑ via Li-Enolat

Ⓑ

Studie:



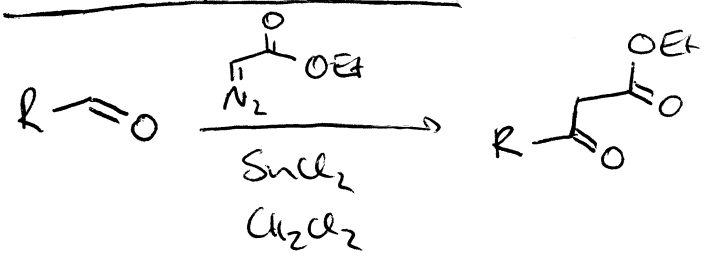


Deuterium wandert

9 zu 91

→ kinetischer Isotopeneffekt und über hohe Verdünnung intermolekulare Reaktion vermindert

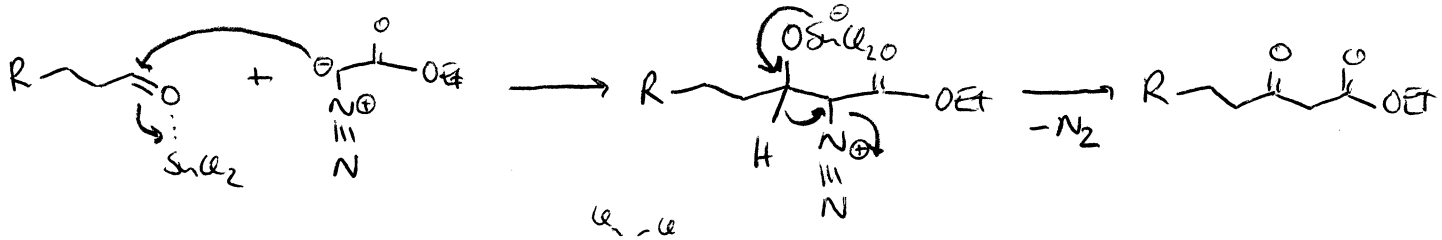
Roskamp Reaktion

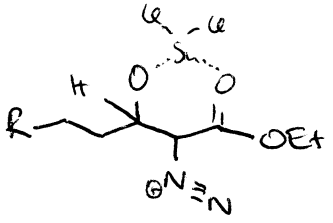


β-ketoester

→ gelt am besten mit unverzweigten Aldehyden

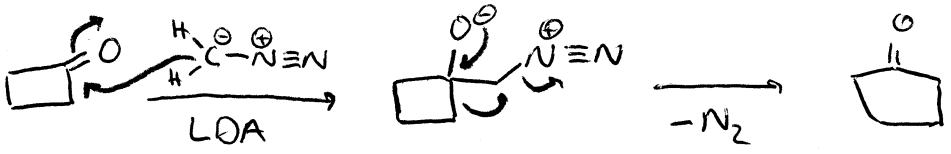
Mechanismus:



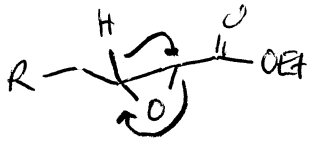


geringer Elektronensog über Koordination des Esters verursacht Wanderung des H's im Gegensatz zum Alkylrest wie bei T.-O.

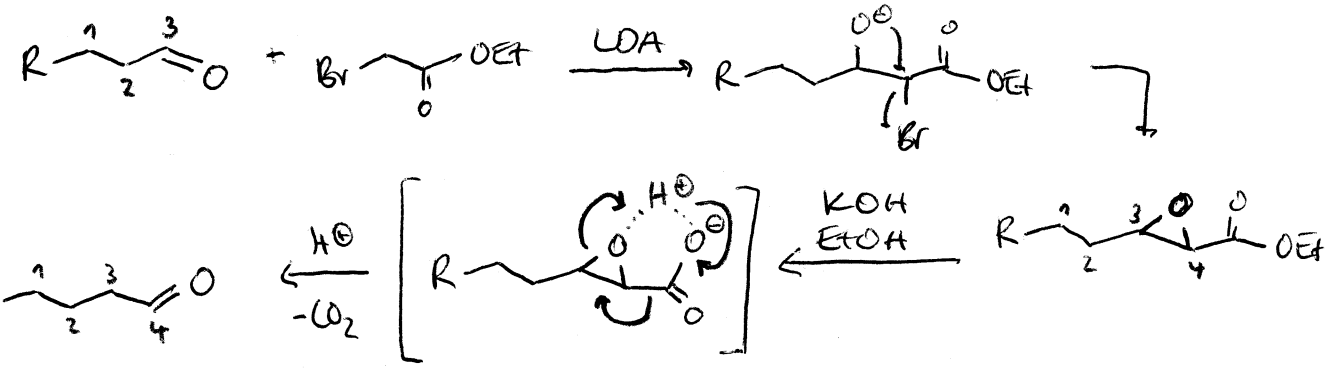
Tiffeneau - Demjanow:



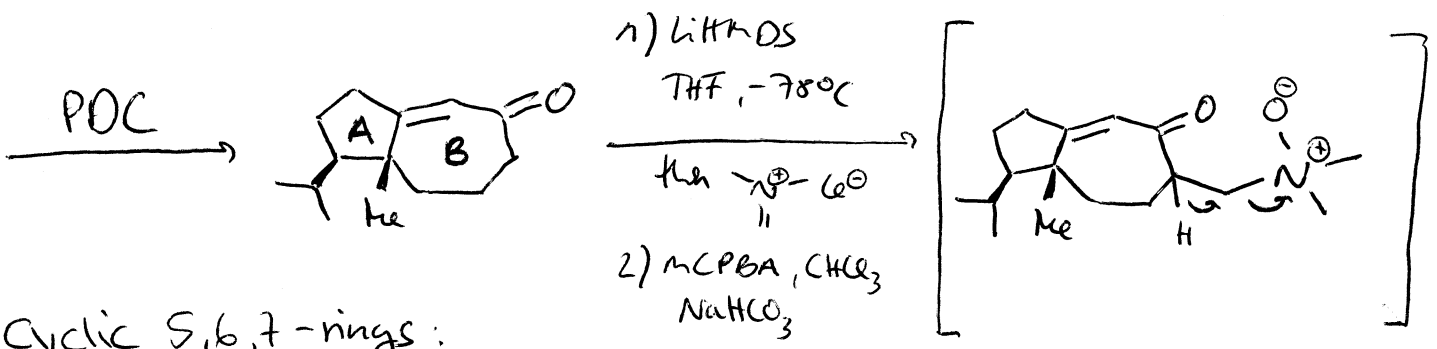
Alternativer Mechanismus via Glycidester:



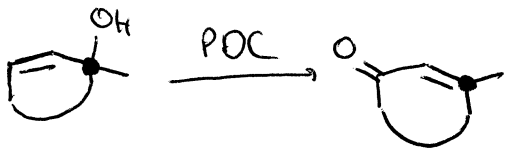
→ Darzens Glycidester-Synthese:



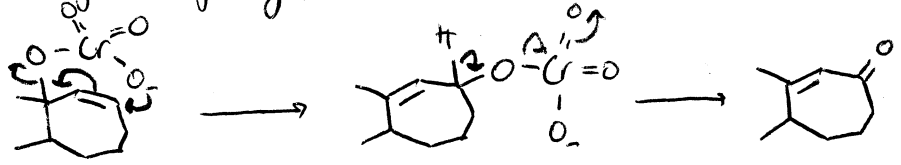
→ C1-Verlängerter Aldehyd



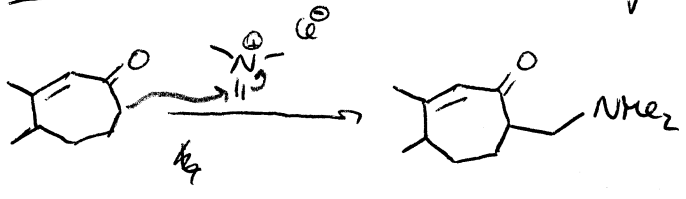
Cyclic 5,6,7-rings:

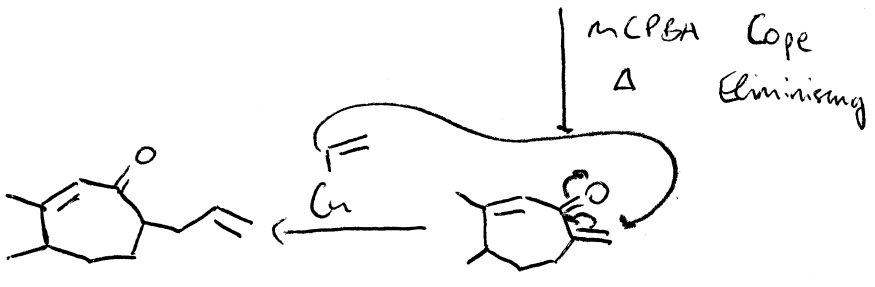


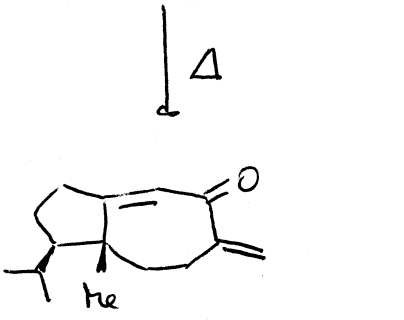
Allylumlagerung:

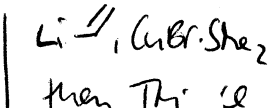


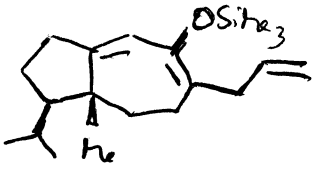
Ersatz für direkte Allylierung:

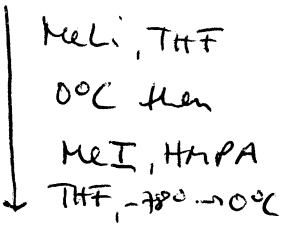


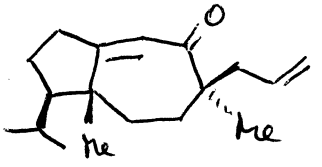




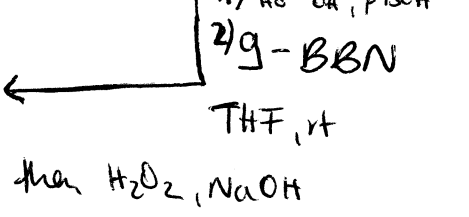


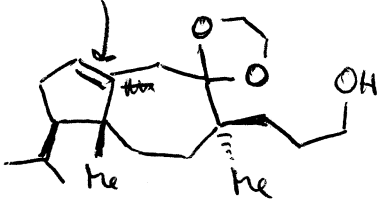


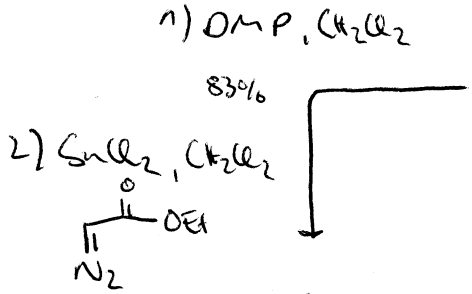


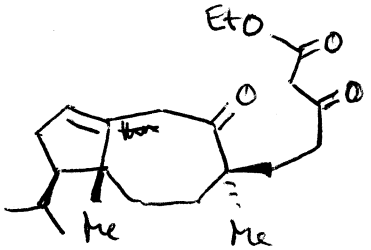


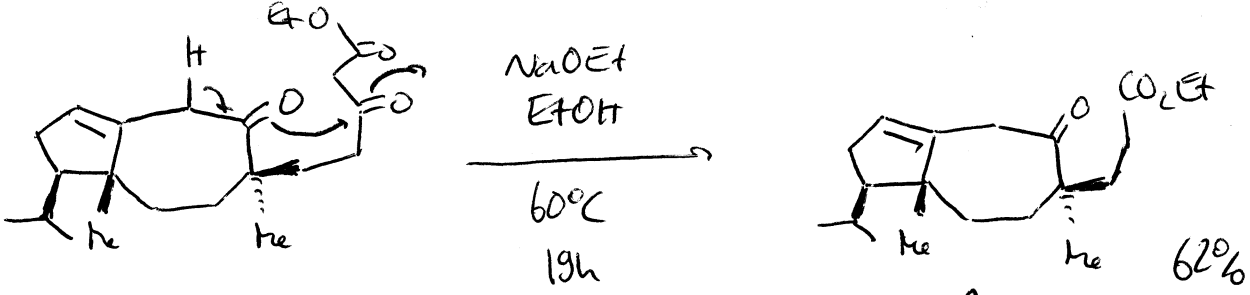
Doppelbindung shiftet beim Schritten

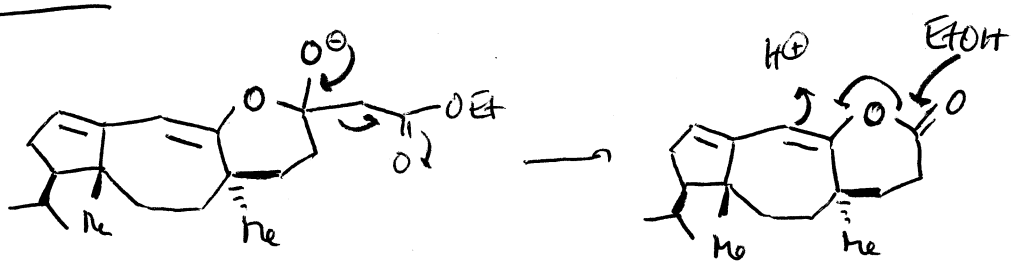








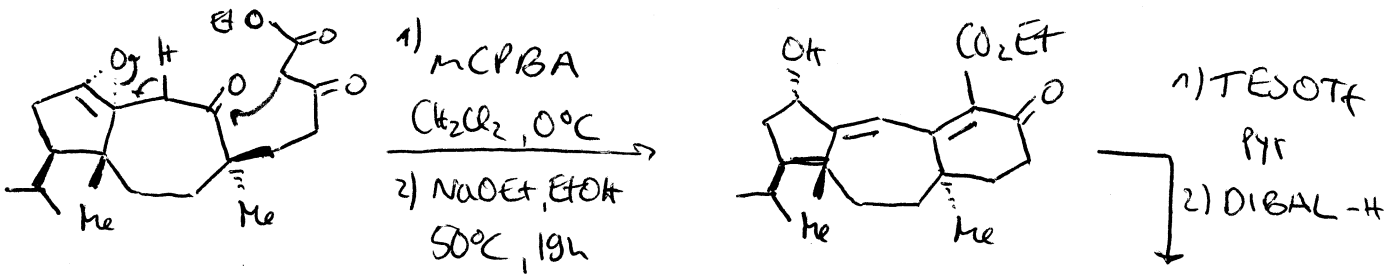


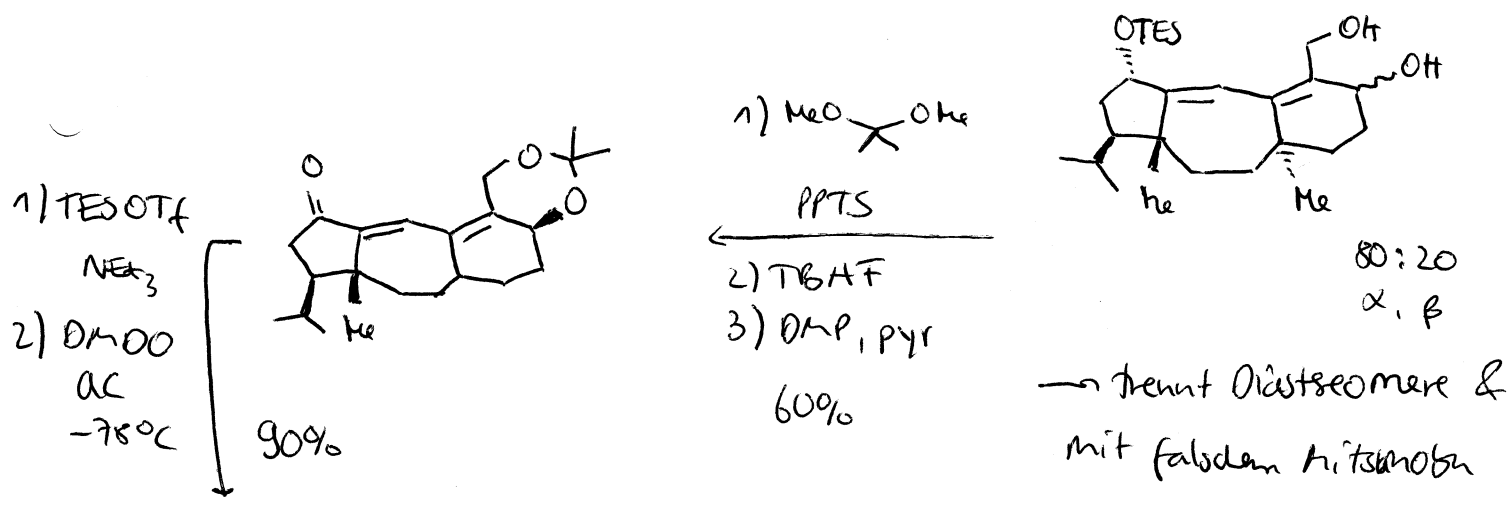


Via:

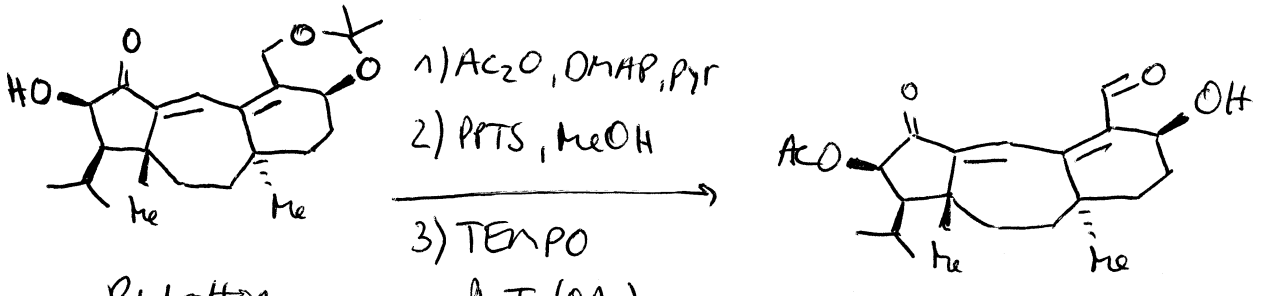
→ anderes Proton zu acide, weil allylisch & α zum Carbonyl

⇒ Ausweg:





→ trennt Diastereomere & mit falschem Mitsunobu

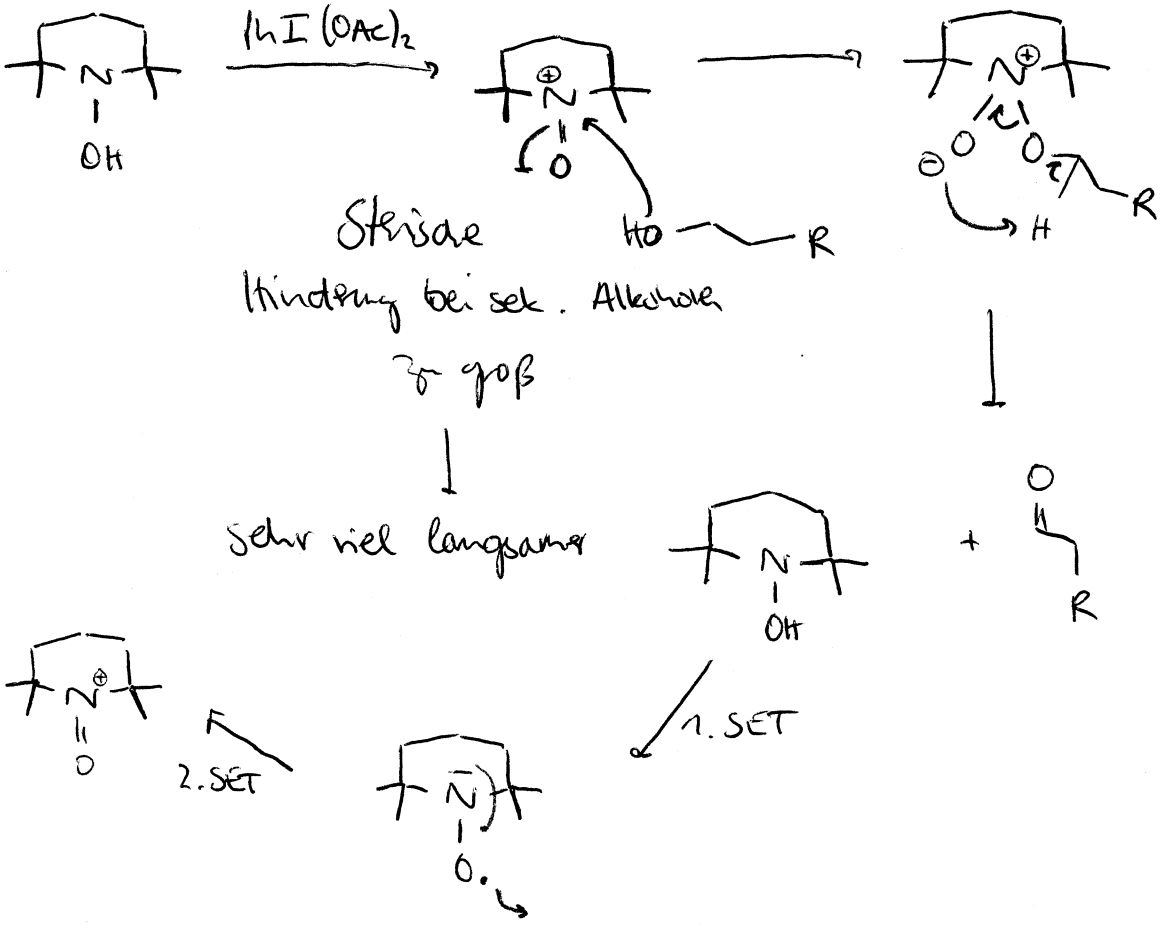


Rubottom Oxidation

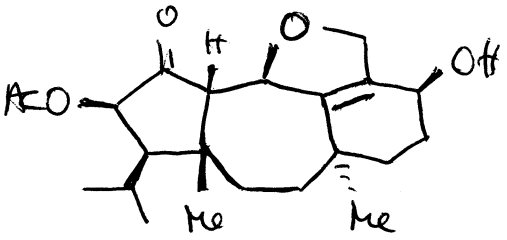
Guanacastepene A

TEMPO-Ox.:

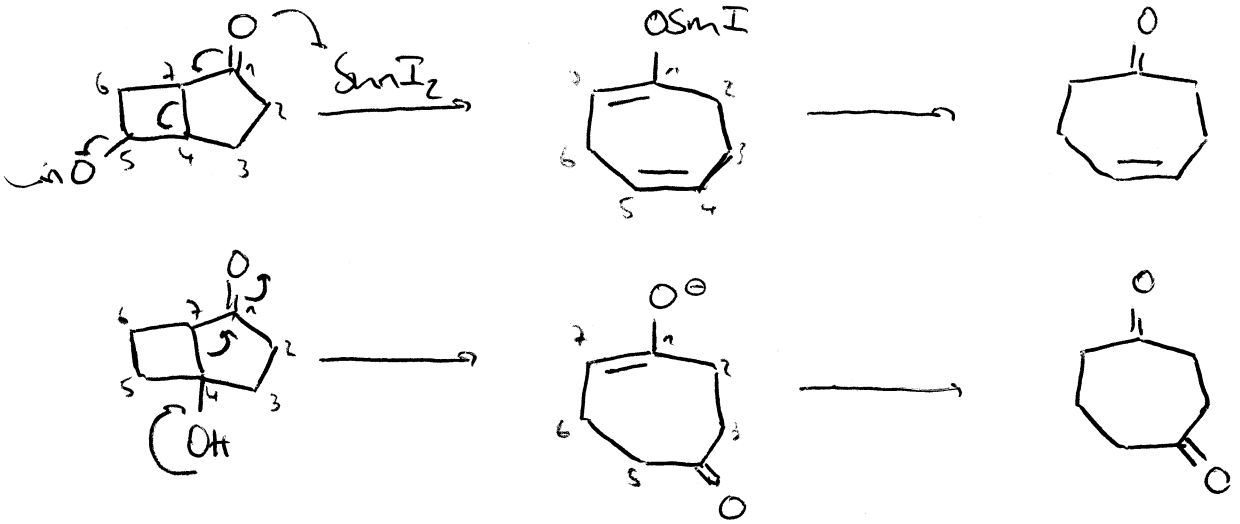
Oxidiert selektiv primären Alkohol in Anwesenheit eines Sekundären



Guanacastepene E Sorensen et. al JACS 2006, 128, 7025



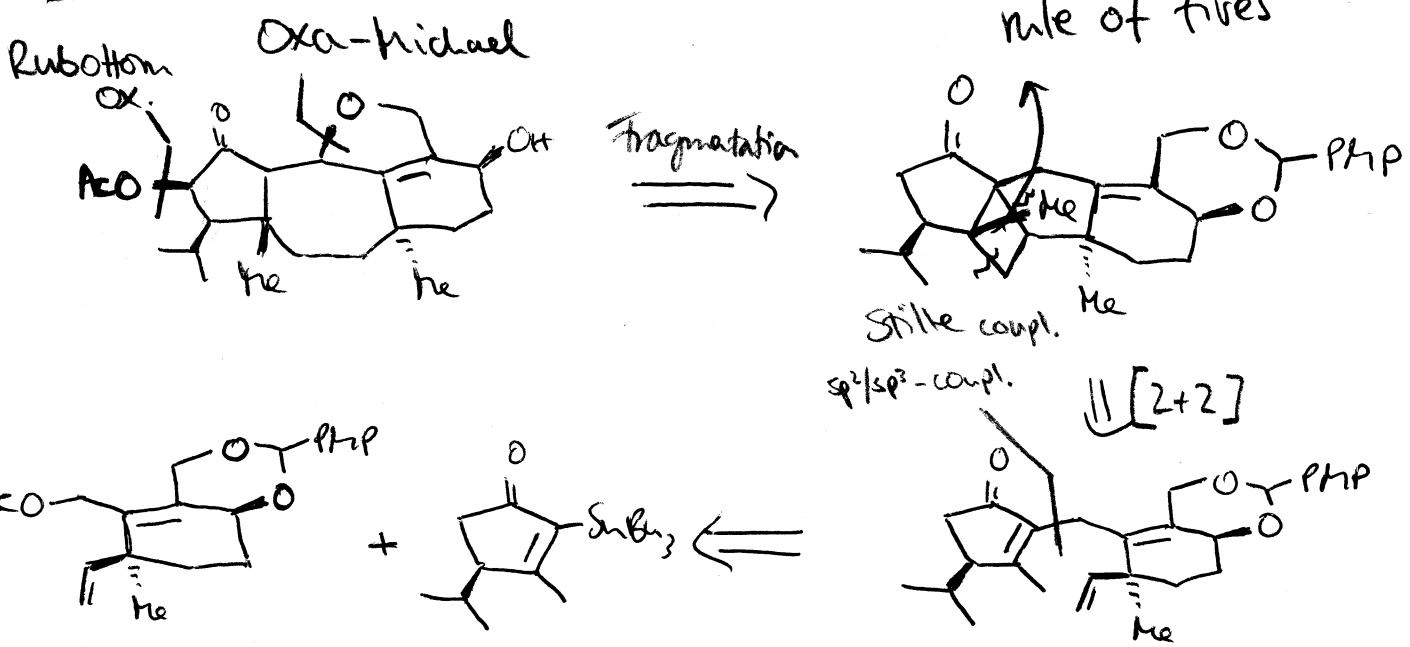
7-Ring Synthese via [2+2] / Fragmentation



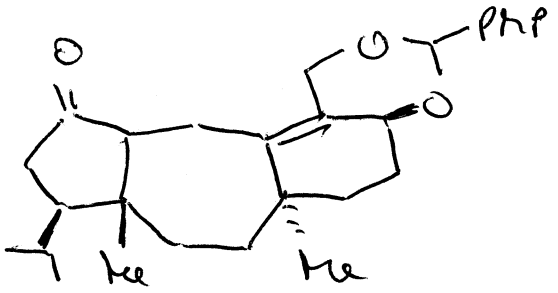
⇒ Ringspannung von 4-Ring erlaubt Fragmentierung

⇒ 5-Ring Anellierung muss während Synthese günstig sein für SM

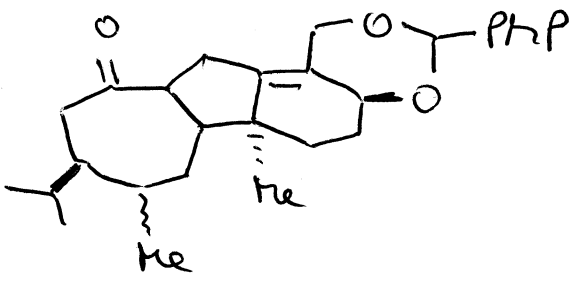
Retrosynthese:



Fragmentation: 2 Siebringe möglich

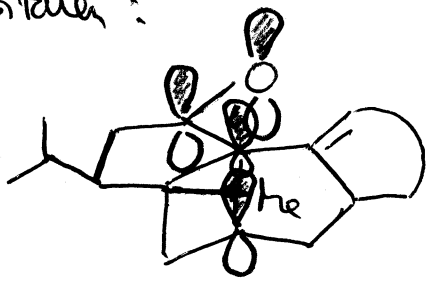


vs.



not formed!

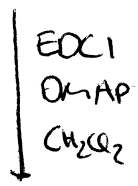
⇒ parallele Anordnung der Orbital von brechender Bindung mit C=O π-Orbitalen:



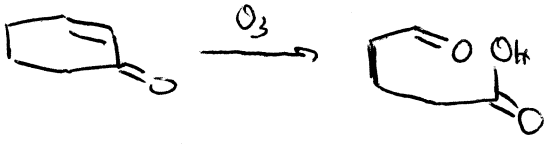
⇒ iso-Propylgruppe diregiert Stereochemie der [2+2]

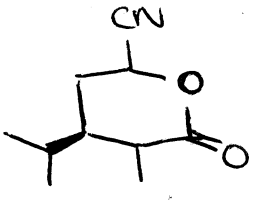
Synthese:

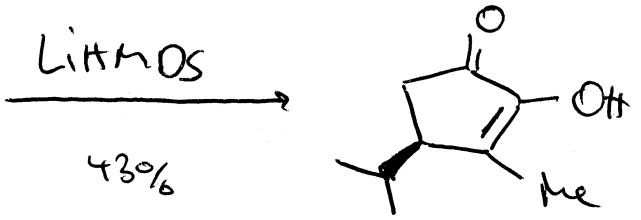
(S)-Carvone



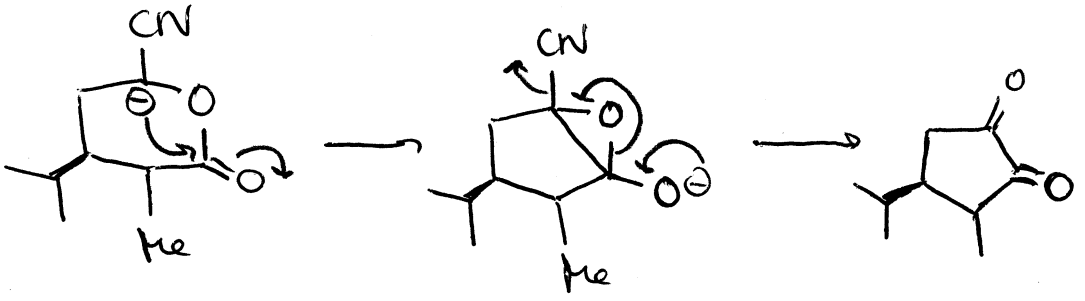
Ozonolyse von α,β-unges. Keton:





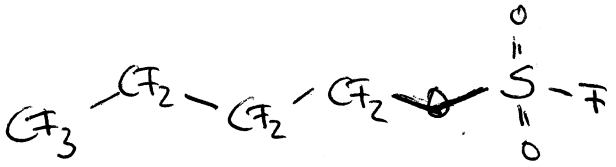


via:



→ Kupplung via Triflat hat nicht funktioniert

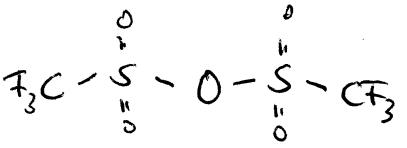
→ Nonaflat: eingeführt via

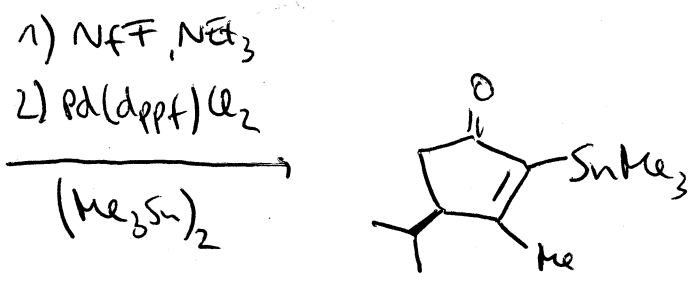


Säurefluorid

→ milder als Anhydrid

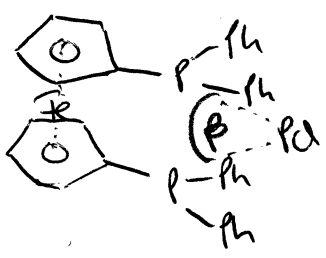
abgekürzt NfF





dppf wird gerne als Ligand

bei schwierigen Kupplungen verwendet

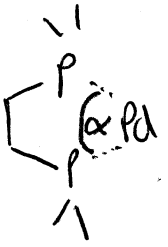


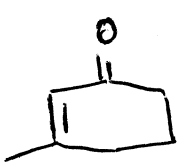
binding angle

vg. Ferrocen

wesentlich geringer

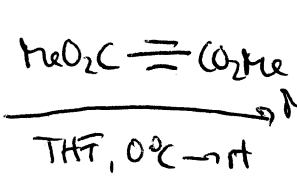
$\alpha > \beta$



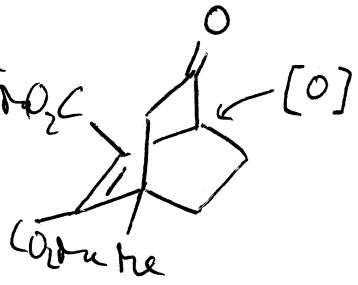


LDA, TMS-Cl
−15°C → 0°C
12 h 98%

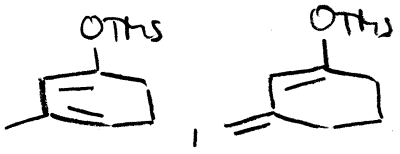
kinetisches Produkt



THF, 0°C → rt
then 1M HCl
12 h 99%

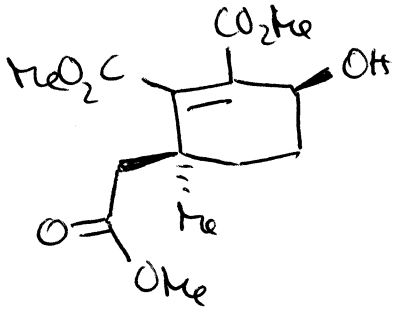


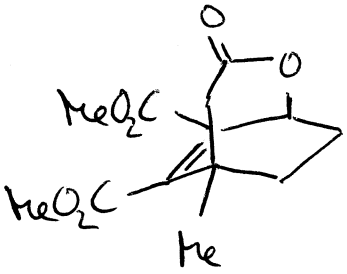
therm. Produkte:



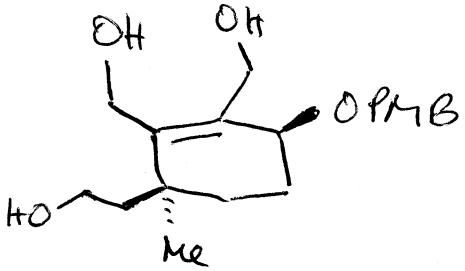
mCPBA
$NaHCO_3$
16 h 96%

[CSA]
MeOH, Δ
12 h 100%



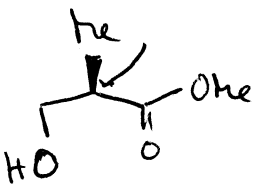


1) [CSA], CH_2Cl_2
Bundles reagent
2) LiAlH, Et_2O; 0°C → rt

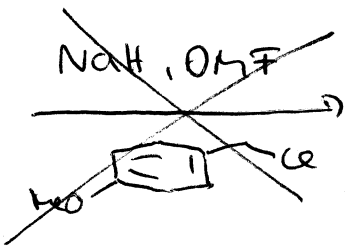


87%

Bundles reagent:

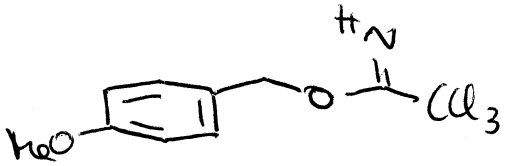


NaH, OMF



→ racemisation

→ komplementäre Methode unter schwach sauren Bedingungen



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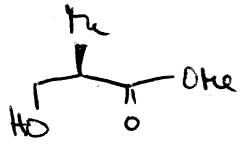
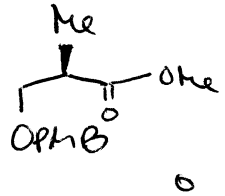
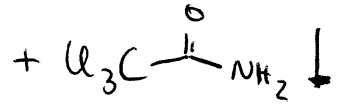


5-10 mol% CSA
CH_2Cl_2, rt

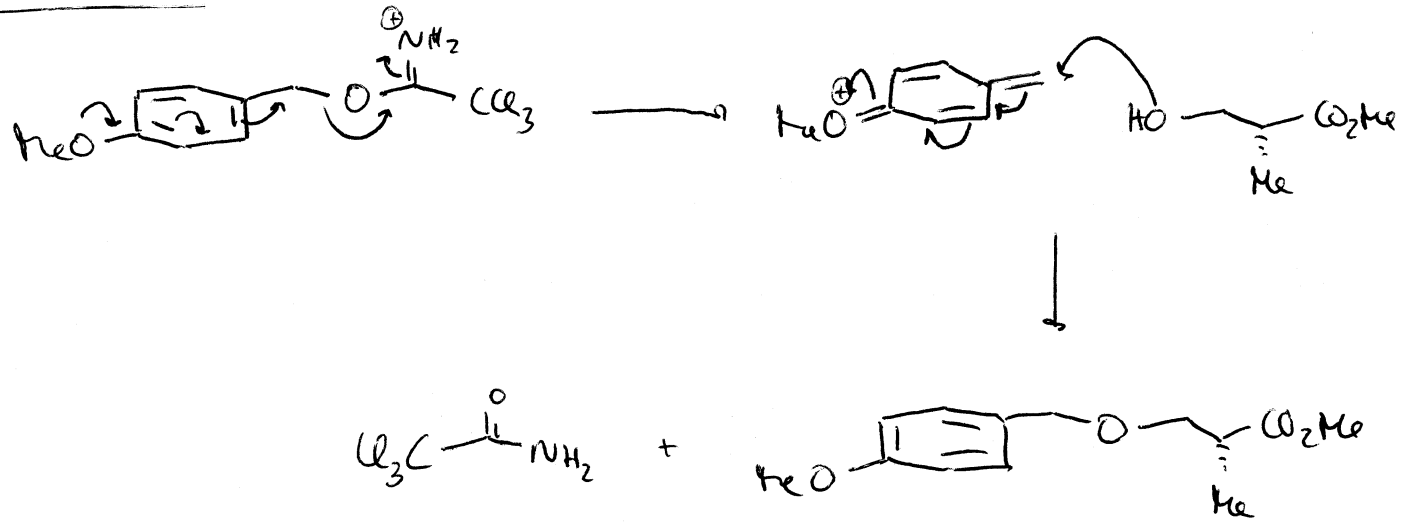




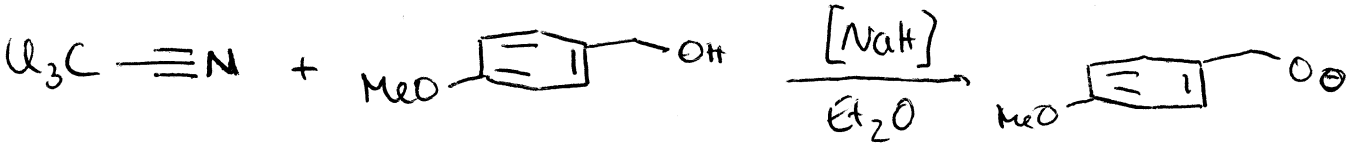
Trichloracetimidat

Sehr feuchtigkeits-empfindlich

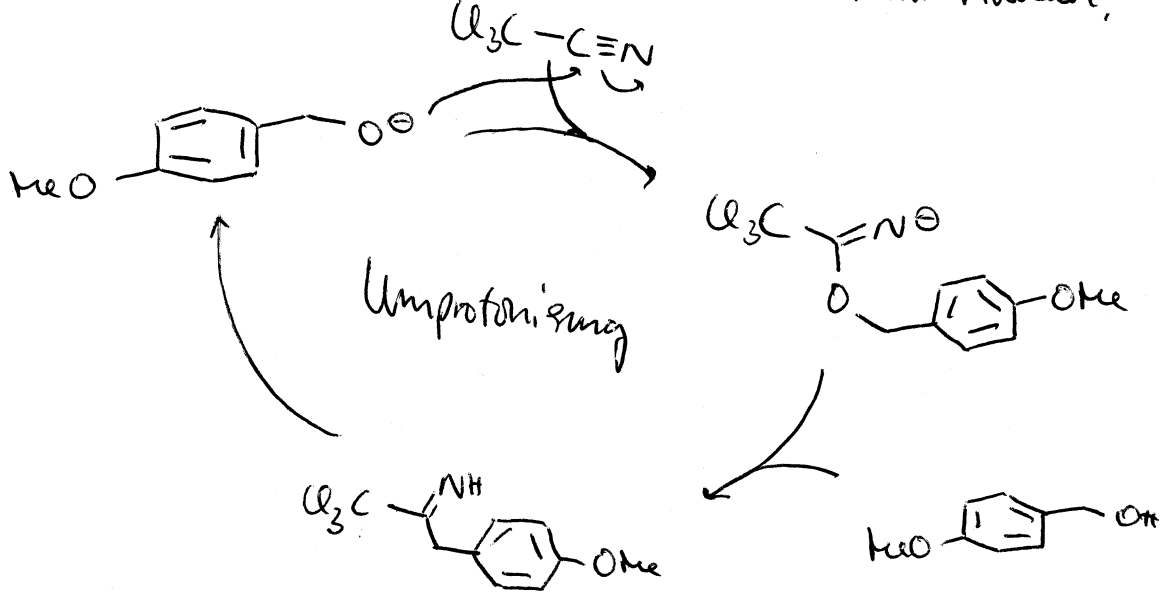
Mechanism:



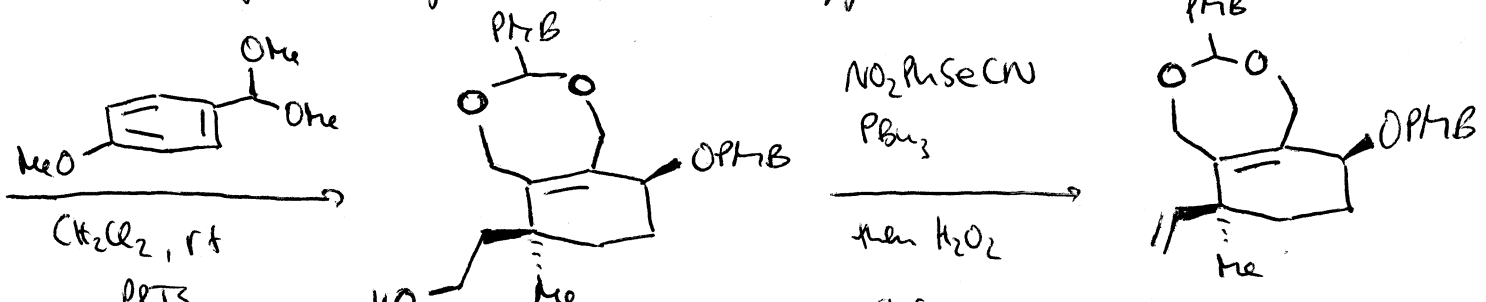
Darstellung:



nur katalytische Mengen NaH verwenden!

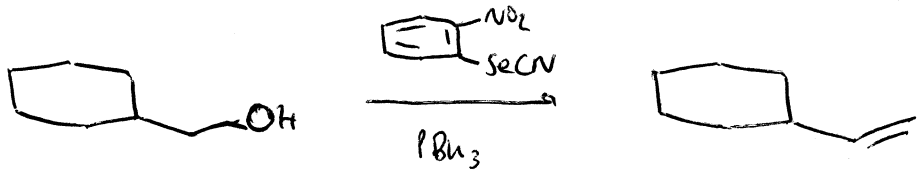


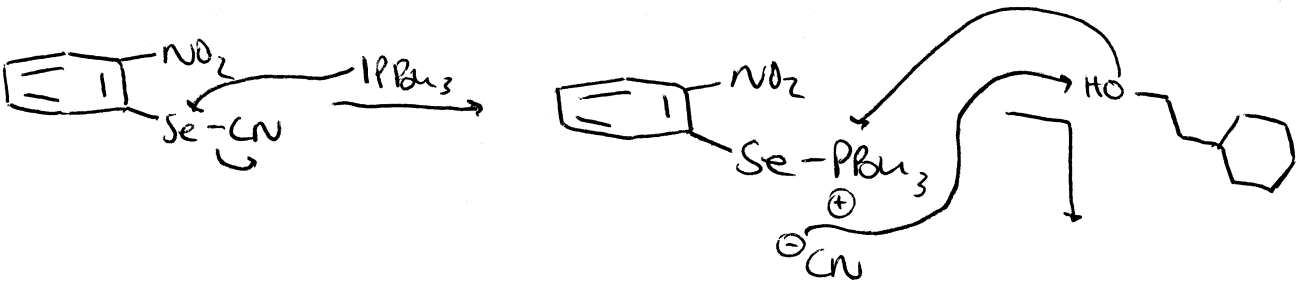
→ Hydrolyse nicht möglich mit H_2O, daher Umprotonierung und nur katalytische Mengen NaH, sonst ist Zyklus tot!

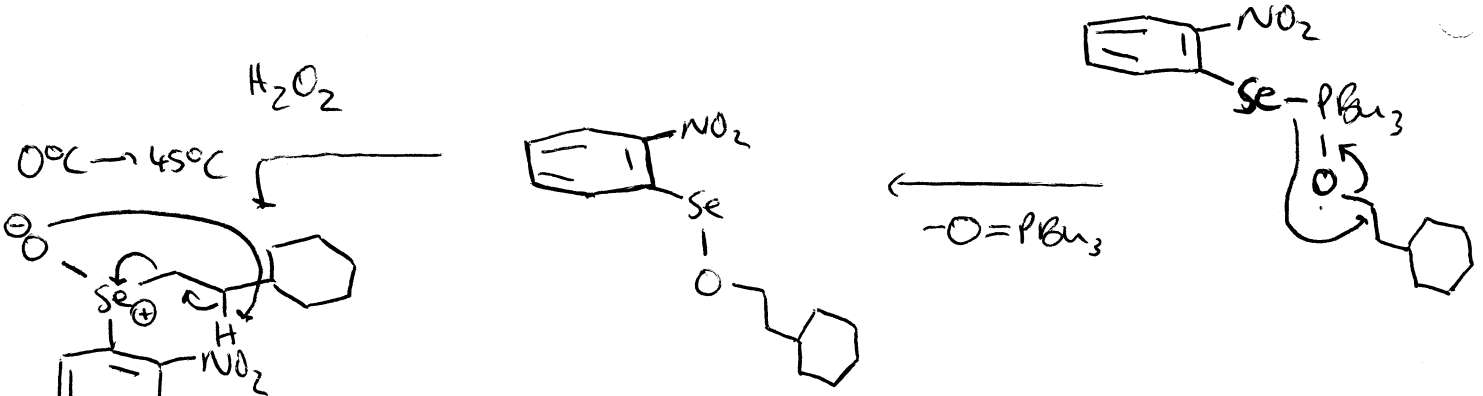


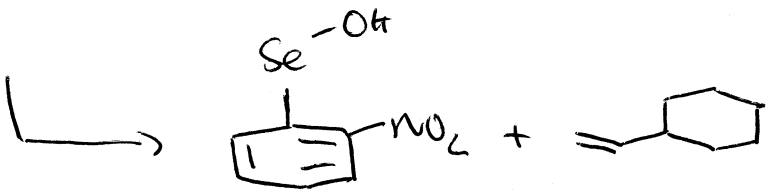
Grieco-Protokoll:

Selektiv primäre Alkohole eliminieren

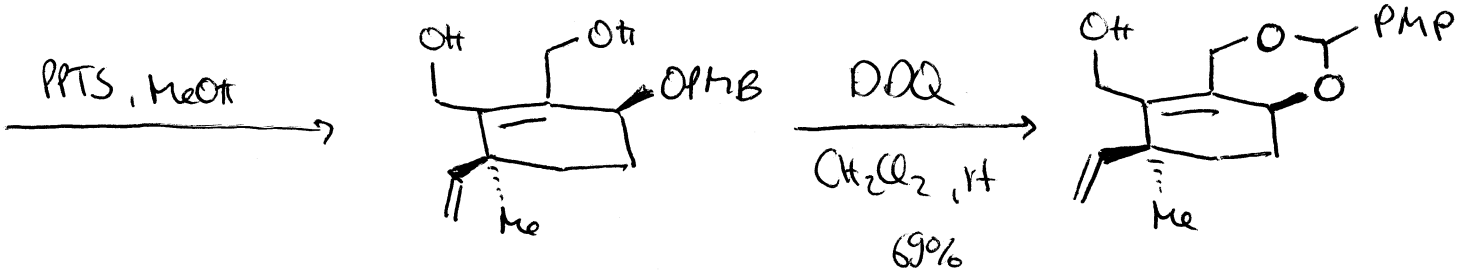


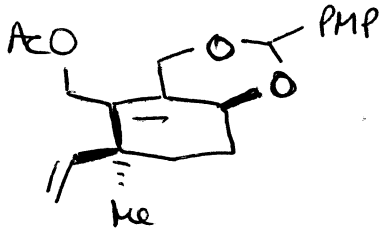






selenige Säure





Mechanism: