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# VL\_Naturstoffsynthese

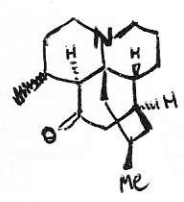
## SS 2011

### Lecture notes

from  
**Erik Stempel**

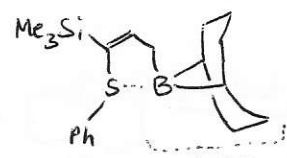
Besucheradresse:  
Callinstrasse 24  
30167 Hannover  
[www.oci.uni-hannover.de](http://www.oci.uni-hannover.de)

Tel. +49 511 762 8973  
Fax +49 511 762 3456  
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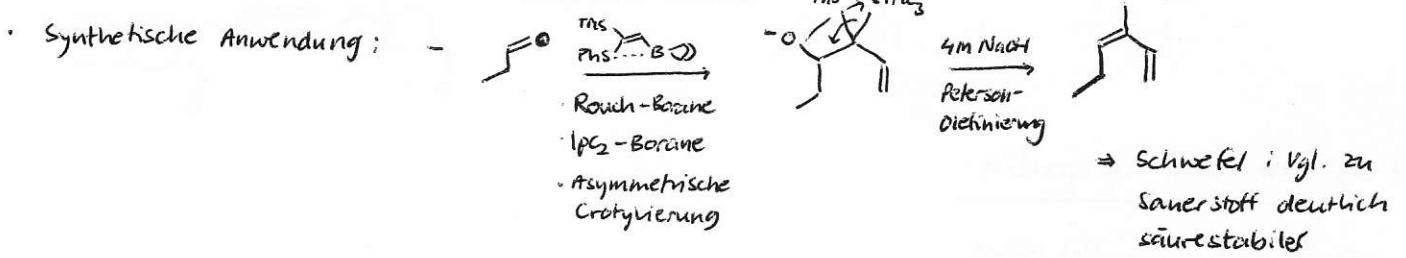
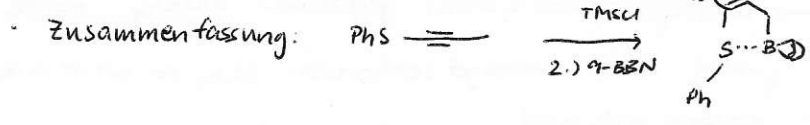
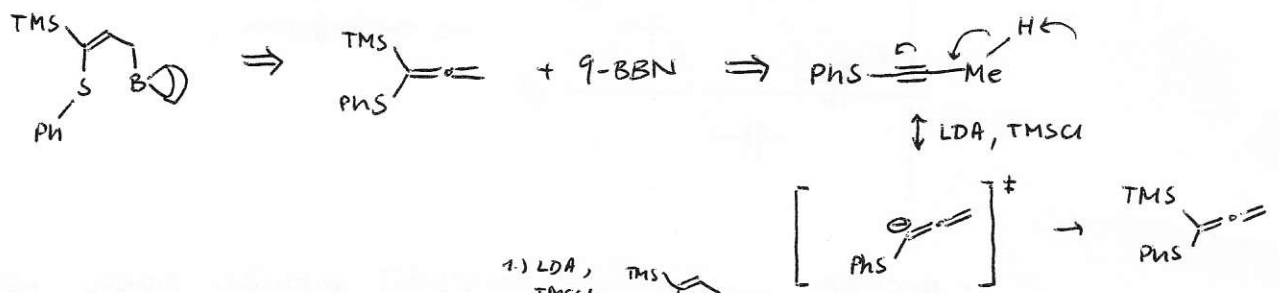


(Lycopodin)

- Besonderheit: 5 Stereozentren nebeneinander
- Strukturelement: drei Ringe mit Überbrückung
- Lit.: P.A. Grieco, JACS, 1998, 120, 5128-5129

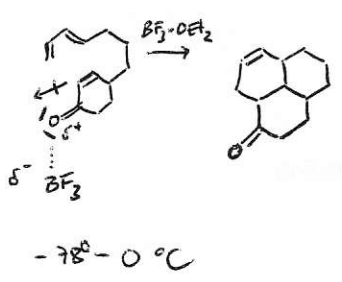
- für Synthese benötigt:
  - Ringkontraktion / Ringerweiterung (Stieglitz-Umlagerung)
  - Beckman-Umlagerung
  - Pearson's Reagenz: 
  - kationischer Diels-Alder
  - Starteinheit
    - ↳ Birch-Reduktion (unterer 6-Ring)

• Herstellung vom Pearson Reagenz:

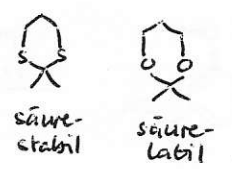
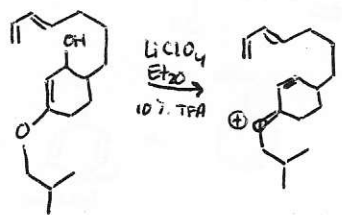


• Diels-Alder:

Lewis-Säure katalysiert

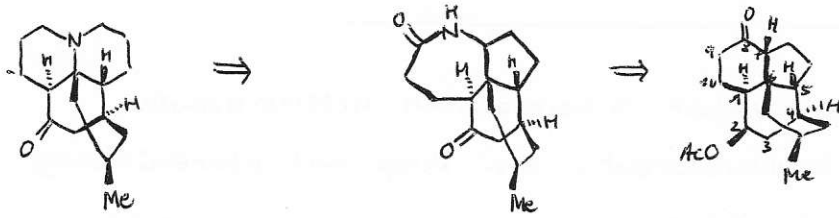


kationischer Diels-Alder



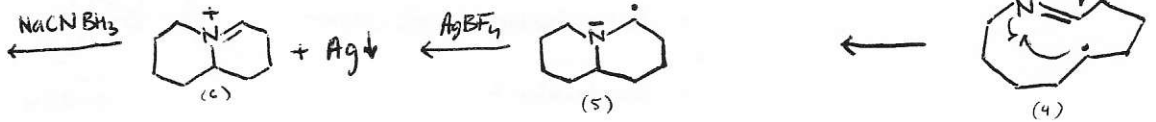
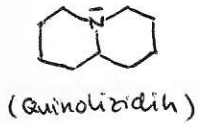
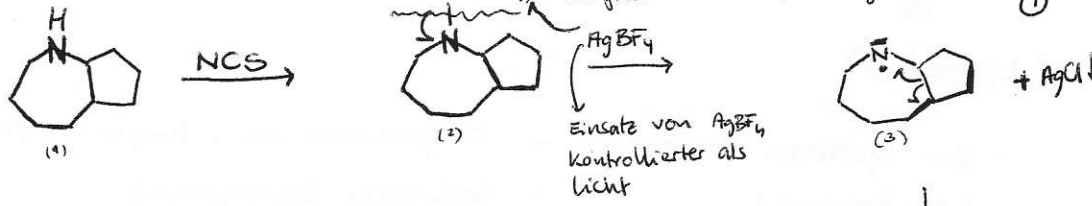
• LiClO<sub>4</sub>: erhöht im Alq. die Ionenstärke

Retrosynthese:

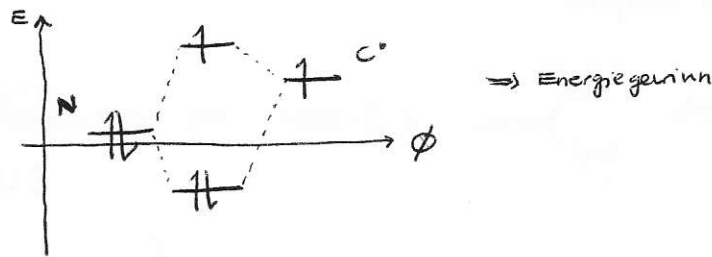


12-04-11  
①

Stieglitz-Umlagerung:



Warum (5) stabiler als (3) → WW zwischen N-Lone-Pair und Elektron

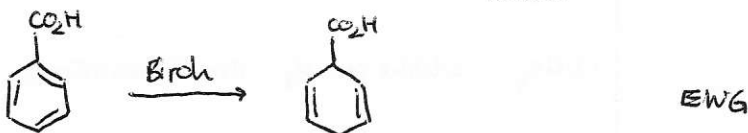
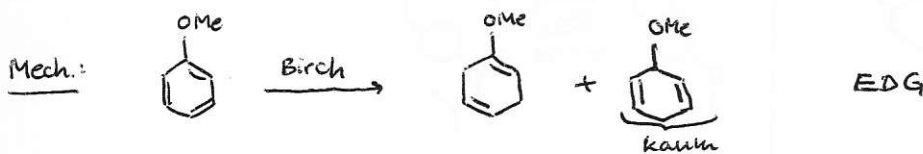
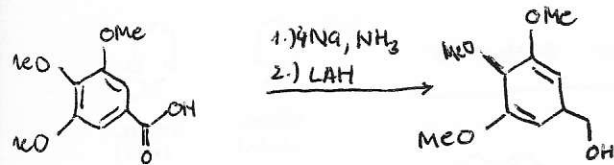


•  $\text{NaCNBH}_3$  → verringerte Reaktivität gegenüber  $\text{NaBH}_4$ , sollte  $\text{N}^+$  und Aldehyd vorhanden sein, so wird nur ersteres reduziert.

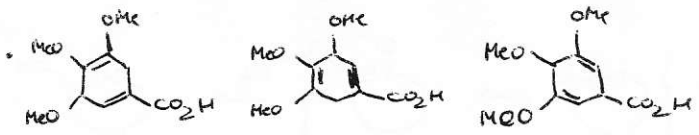


Synthese von Lycopodin:

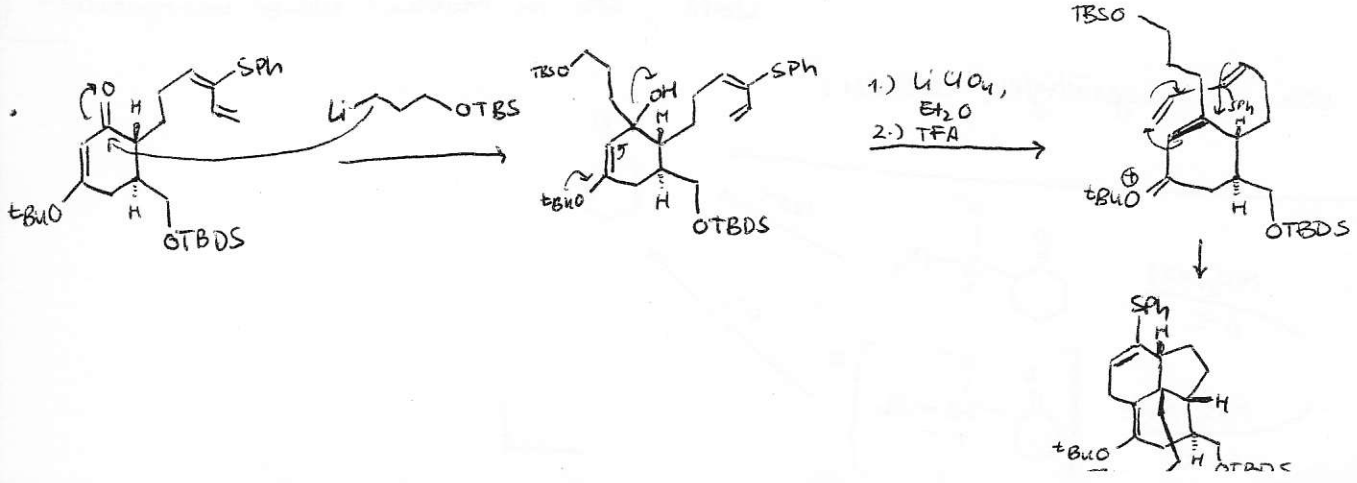
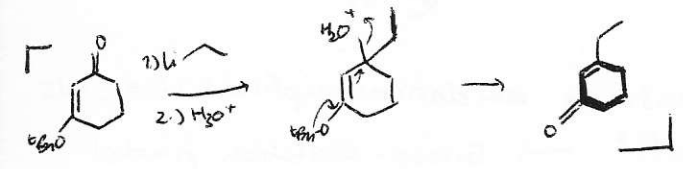
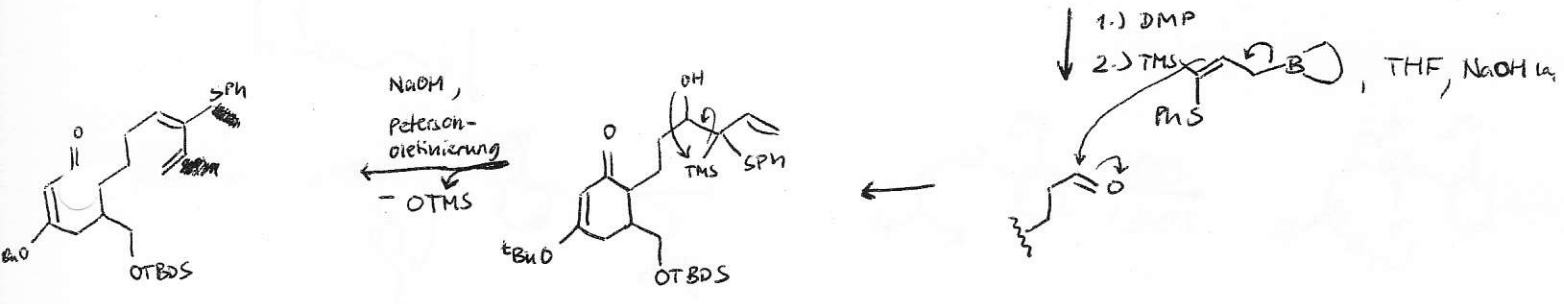
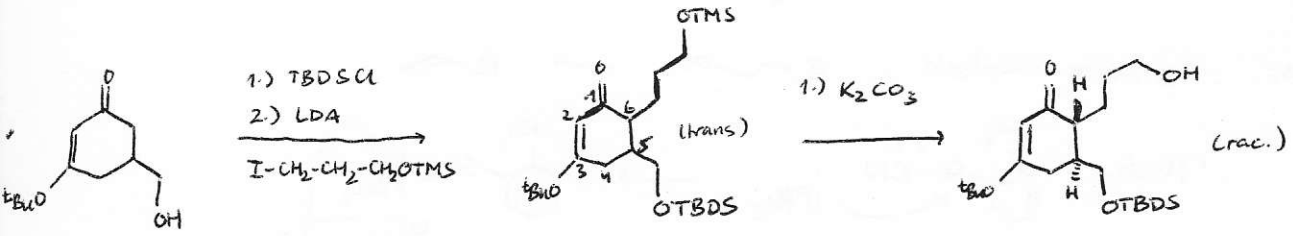
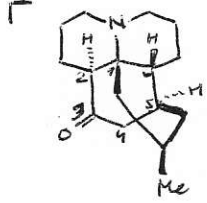
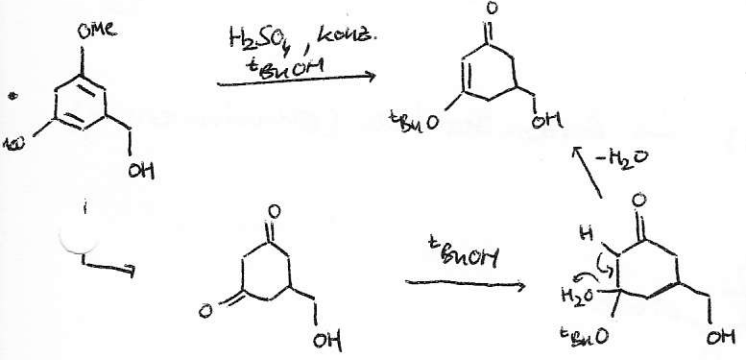
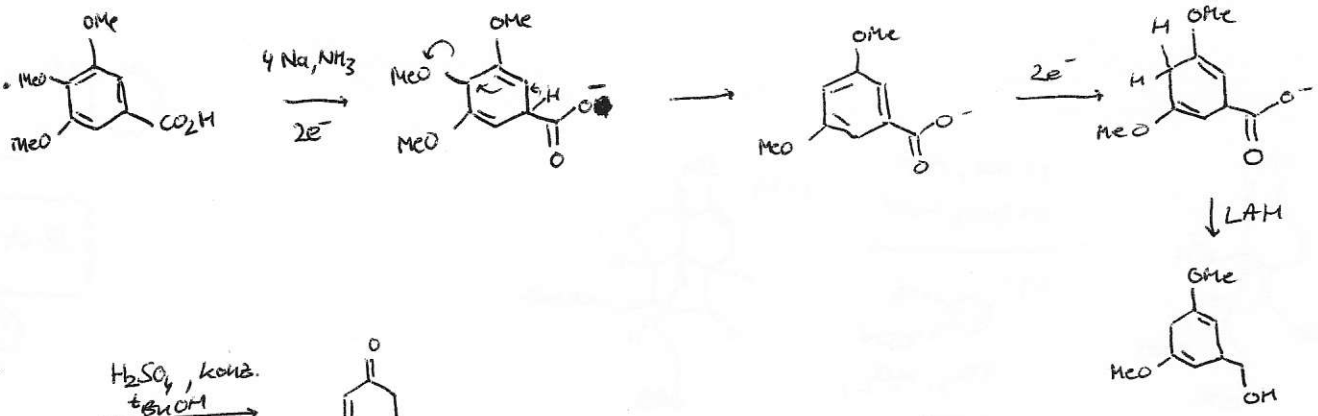
- Start mit Pyragallol säure

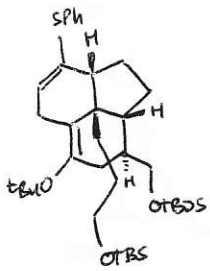
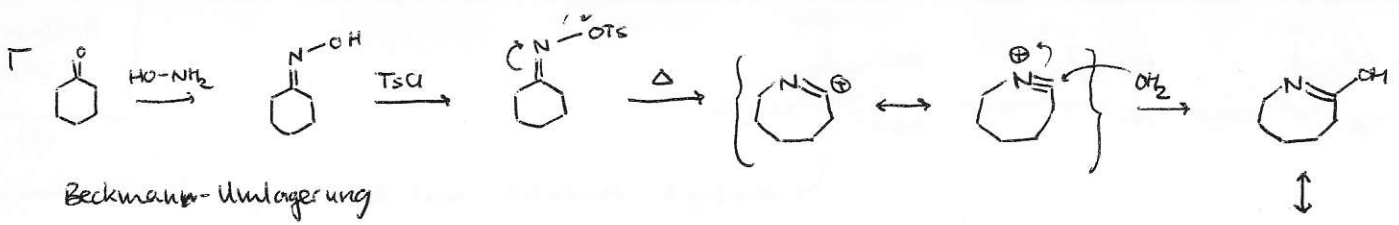


②



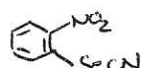
↳ einziges Produkt mit bevorzugter DB-Anordnung

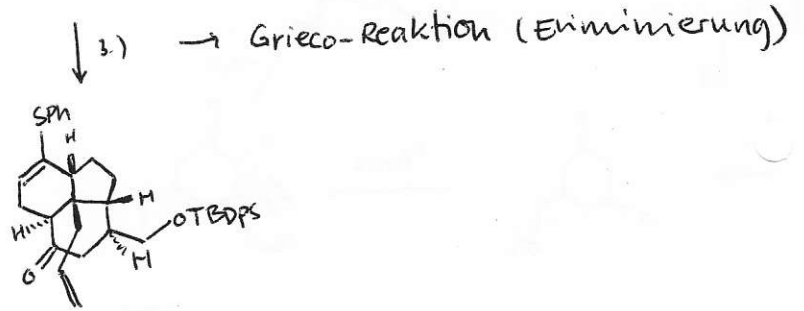
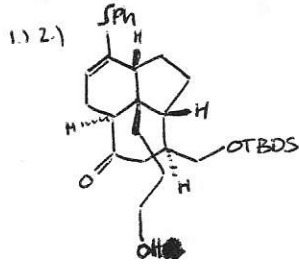




1.) HCl, THF

2.) K<sub>2</sub>CO<sub>3</sub>, MeOH

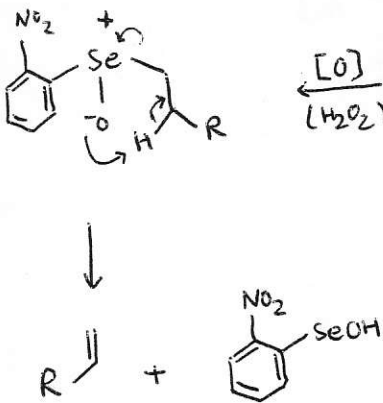
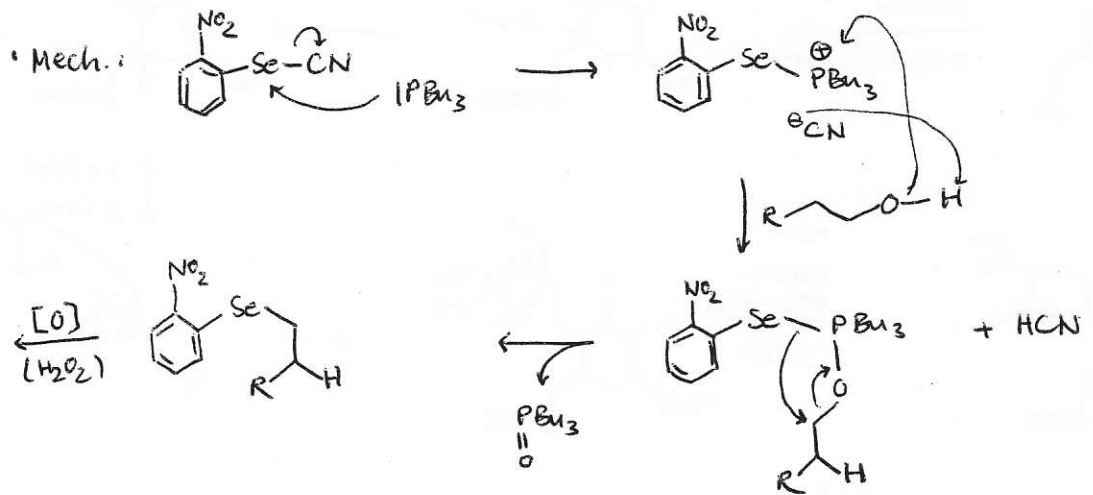
3.)   
 PBu<sub>3</sub>, H<sub>2</sub>O<sub>2</sub>,  
 THF



18.04.

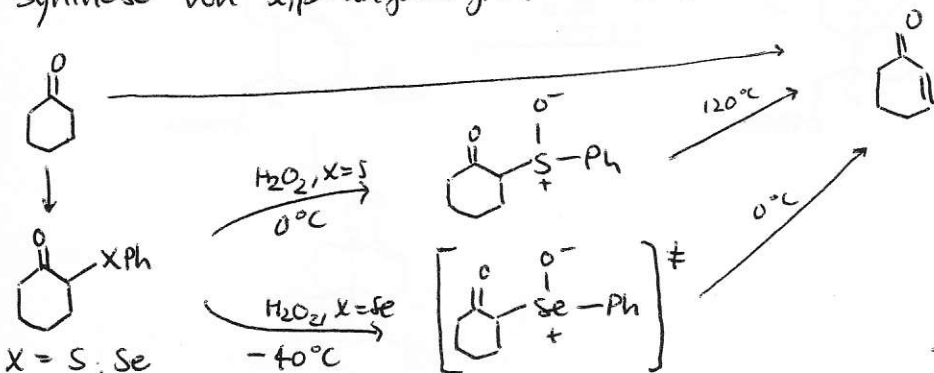
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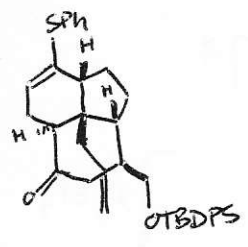
Grieco-Reaktion: • primäre Alkohole:  $R-CH_2OH \rightarrow R-CH=CH_2$



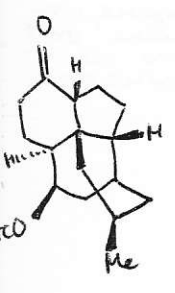
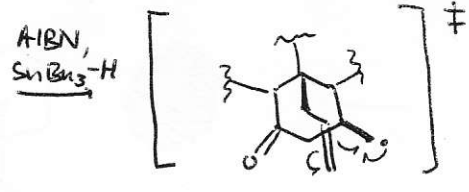
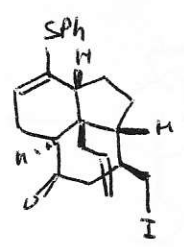
Anmerkung: Se deutlich oxidationsempfindlicher, als Schwefel → Grieco-Reaktion findet statt, SPH in Molekül bleibt unangetastet!

Synthese von  $\alpha,\beta$ -ungesättigten Ketonen:

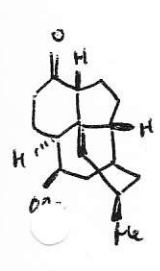
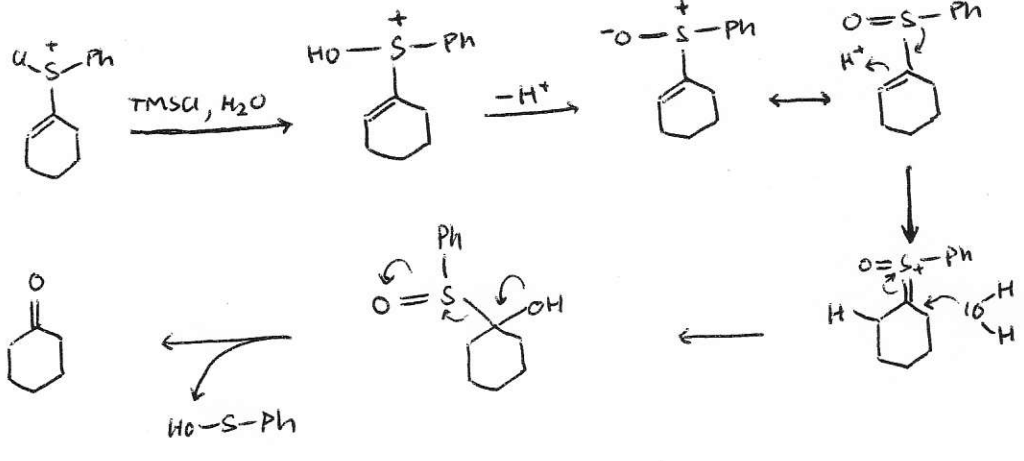
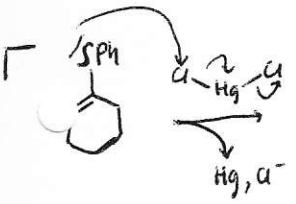
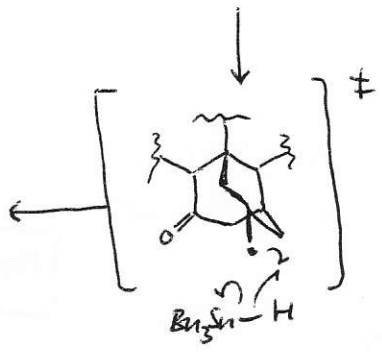
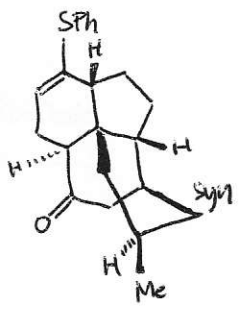




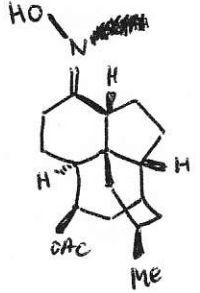
- 1.) TBAF
- 2.) MsCl, TEA, DCM
- 3.) NaI,



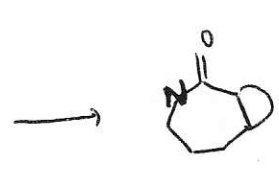
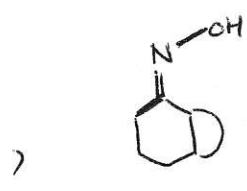
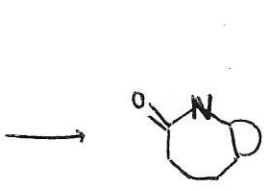
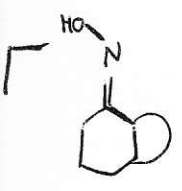
- 1.)  $\text{LiAl}(\text{O}^t\text{Bu})_3\text{H}$
- 2.)  $\text{As}_2\text{O}_3$ , Pyridin
- 3.)  $\text{HgCl}_2$ , NaI, TMSCl,  $\text{H}_2\text{O}$ ,  $\text{CH}_3\text{CN}$



- $\text{NH}_2\text{-OH}$ , EtOH



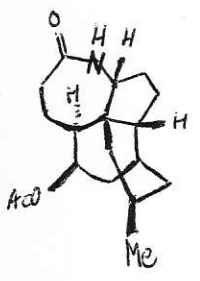
Beckmann



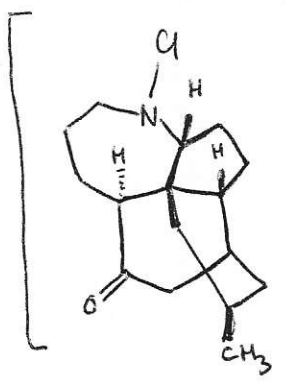
Beckmann  $\Rightarrow$  anti benötigt

02.05.2011

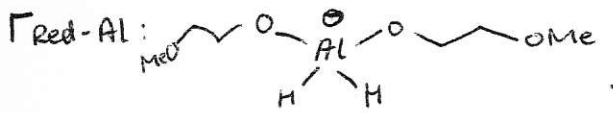
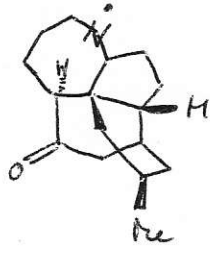
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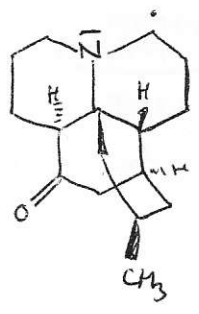
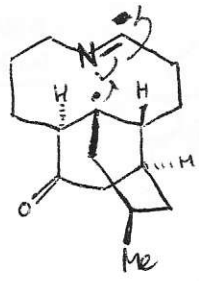
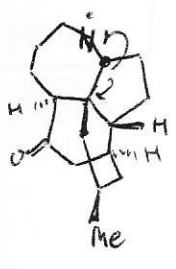


- (Red. von Amid)
- 1.) Red-Al, THF, 80%
  - 2.) NCS, TPAP
- $\downarrow$  NH, 4N-U       $\downarrow$  Ox. von OAc

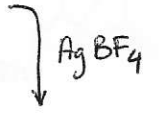


$\text{AgBF}_4$

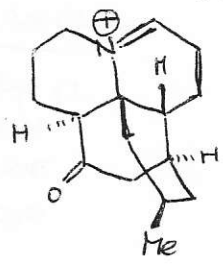
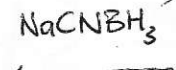




7#



Standardreagenz um selektiv 'imine' statt Keton zu reduzieren



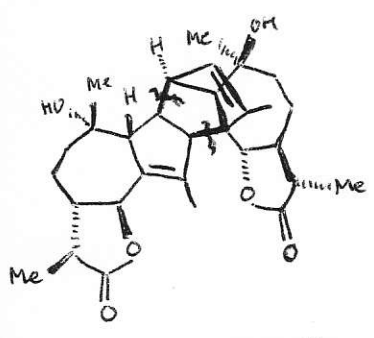
Produkt

(+)-ABSINTHIN

[ JACS, 2005, 127, p. 18-19; Hongbin zhan ]

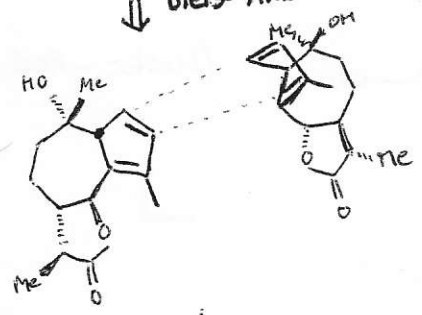
02.05.11  
②

- 1953 : Isolierung
- 1980 : Struktur durch X-Ray
- Struktur:

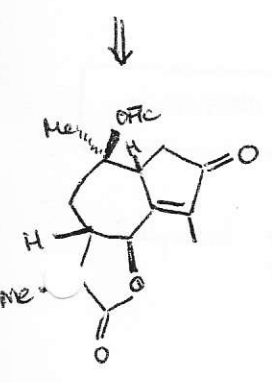


- Terpen
- DMAP: PPO — CC(=C)C
- C30-Terpenoid (2 x C15)

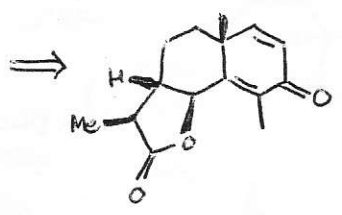
Diels-Alder



zu produzierender Baustein



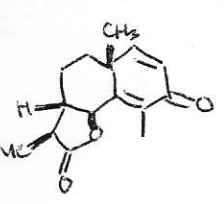
Santonin-Umlagerung



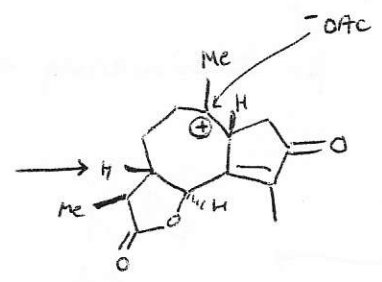
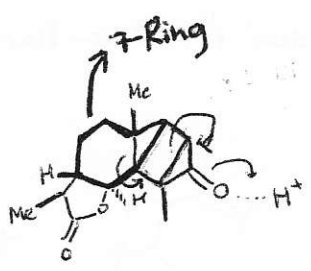
(-)-α-Santonin (15 ≡ 19)

Ⓐ

Santonin-Umlagerung:

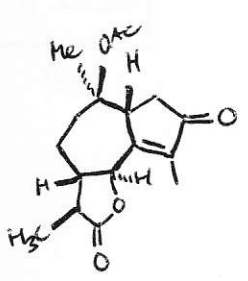


AcOH, hv (250 nm)

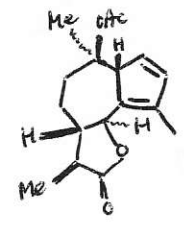


~ 40%  
Ⓐ



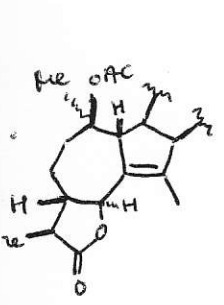
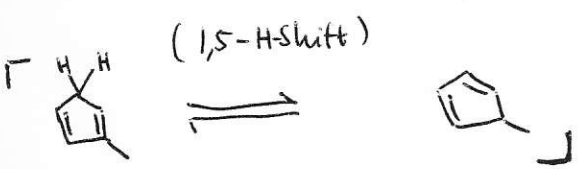
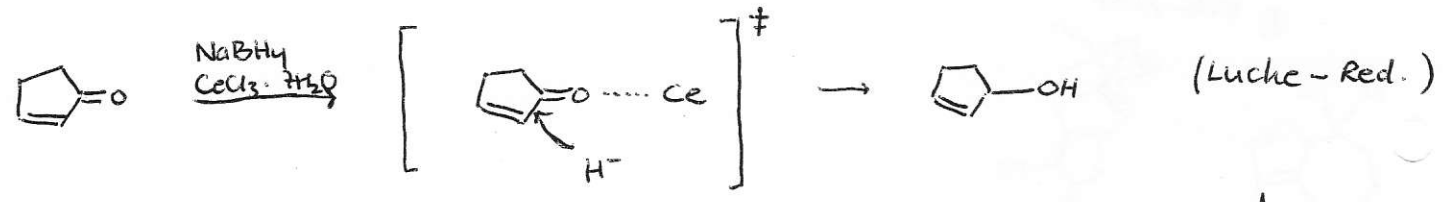
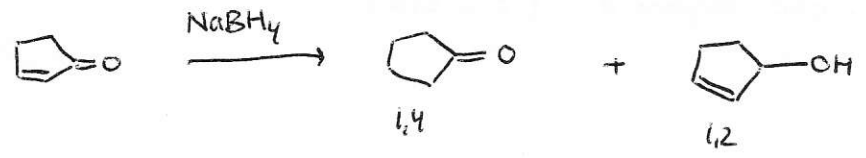


- 1.)  $\text{NaBH}_4, \text{MeOH} \rightarrow 1,2$
- 2.)  $\text{ArSeCN}, \rightarrow \text{ArSe-R}$   
 $\text{PbEt}_2, \text{THF}$
- 3.)  $\text{NaIO}_4, \text{MeOH}$

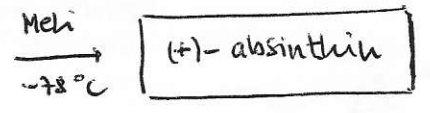
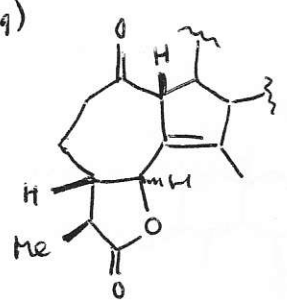


10 Tage stehen lassen  
→  
[Diels-Alder]

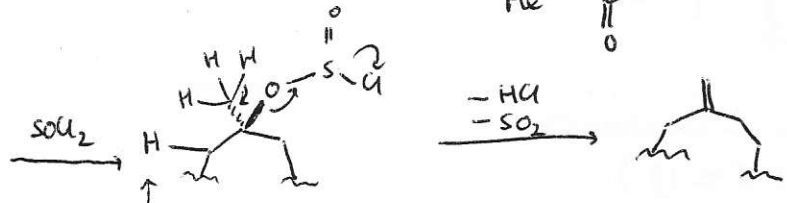
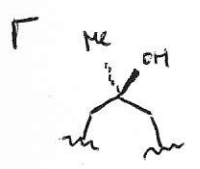
Reduktion mit  $\text{NaBH}_4$  - Mischbedingungen bei Michael-Systemen



- 1.)  $\text{KOH}, \text{MeOH}$  (Ac-Entfernung)
- 2.)  $\text{SOCl}_2, \text{NEt}_3$
- 3.)  $\text{OsO}_4$
- 4.)  $\text{NaIO}_4$

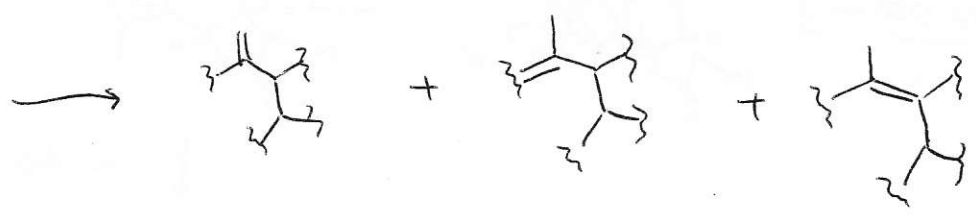
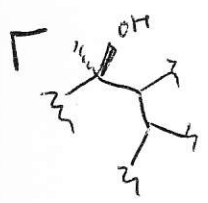
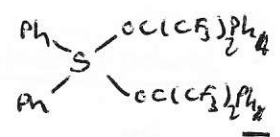


↳ eine Seite komplett geblockt!  
↑ abgeschirmt



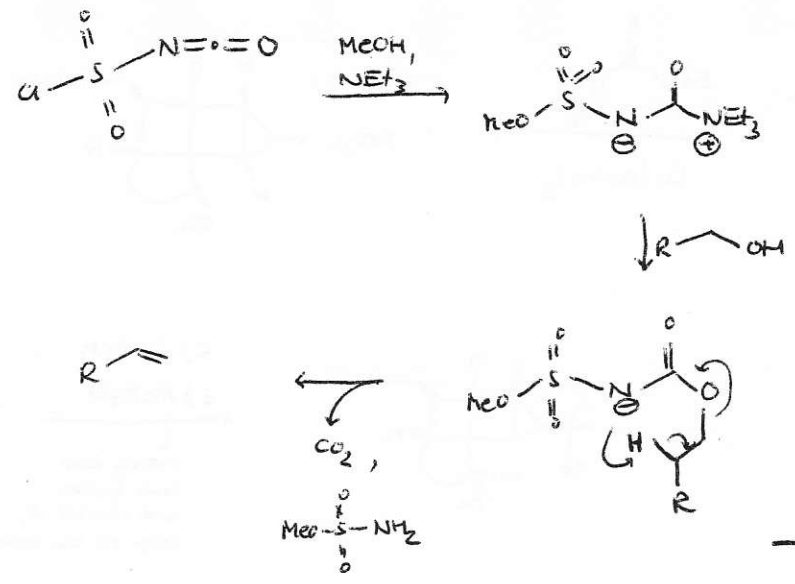
↳ mit  $\text{SOCl}_2$  wird am wenigsten substituiertes CH eliminiert

für Eliminierung von dem H: Dess-Martin-Sulfuran



- $\text{SOCl}_2$
- Burgess-Reagent
- Dess-Martin-Sulfuran

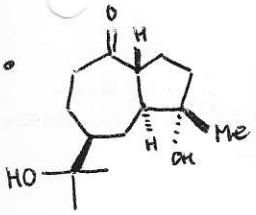
Burgess-Reagenz:



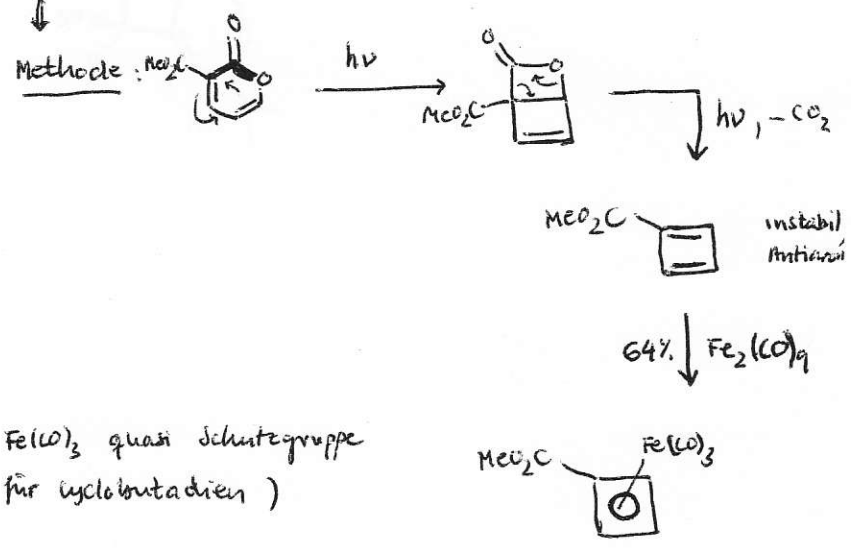
Nat Syn  
03-05-11  
②

PLEOCARPENON

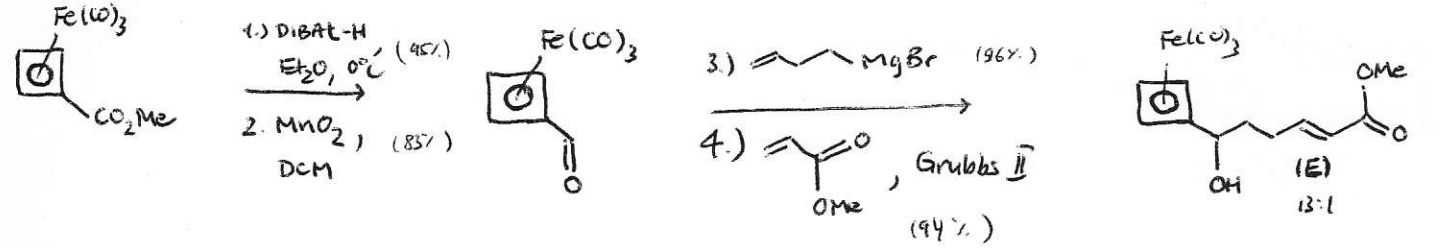
Marc L. Snapper, JACS, 2007, 129, 486



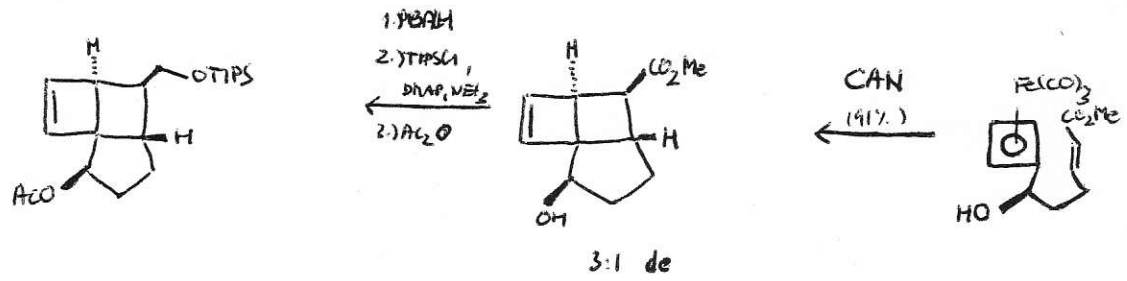
Key Feature: - Eisen-tricarbonyl-cyclobutadiene-chemistry

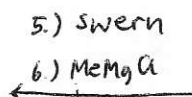
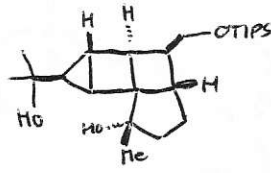
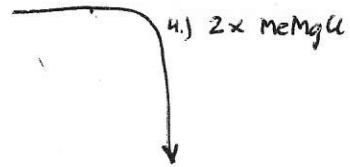
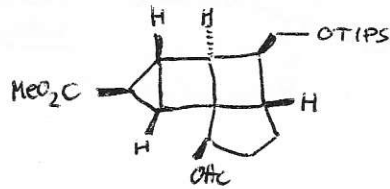
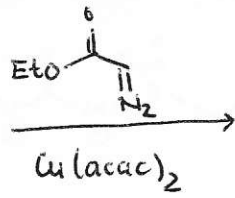
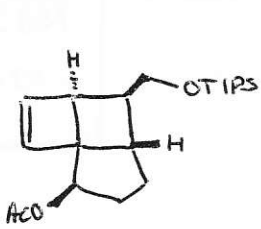


Aufbau des 7-Rings:

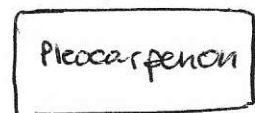
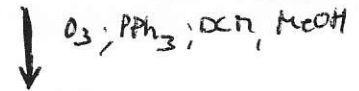
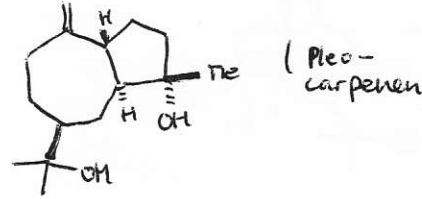
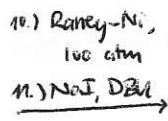
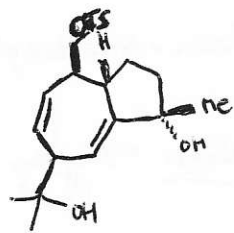
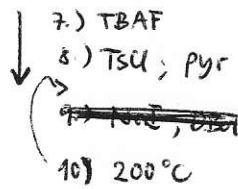
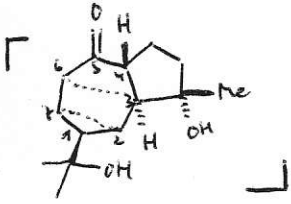
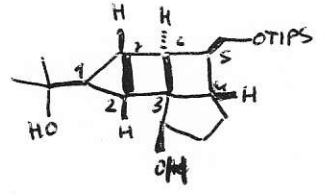


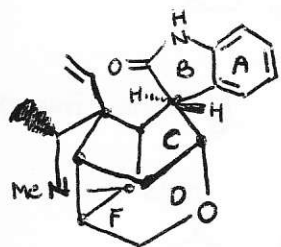
1.) MnO<sub>2</sub>  
2.) CBS





s-Ring steht nach hinten und schimmt ab, daher Me von vorne

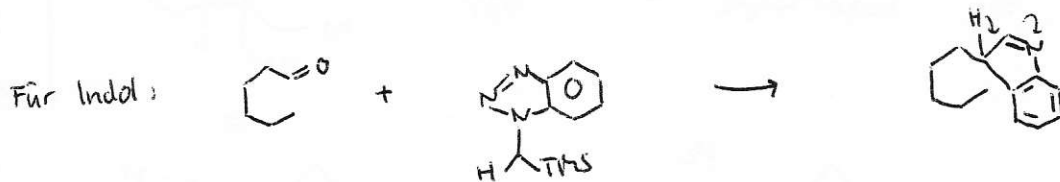
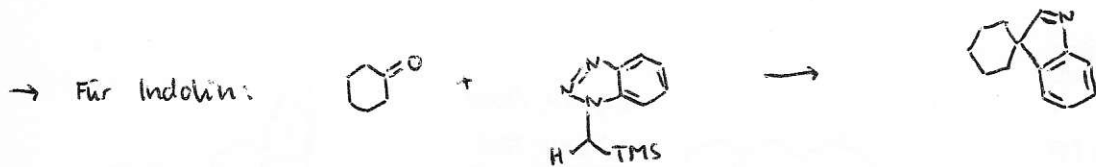
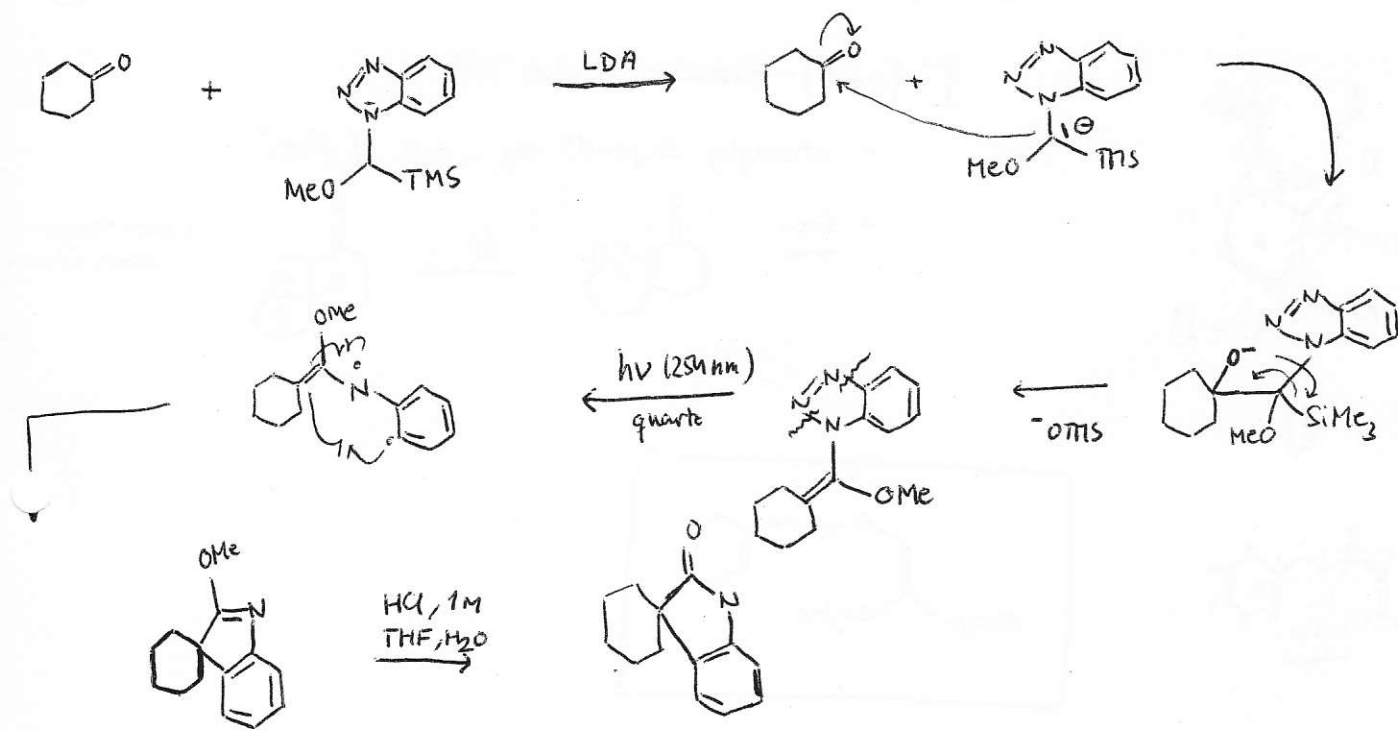




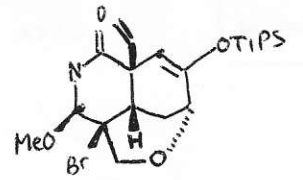
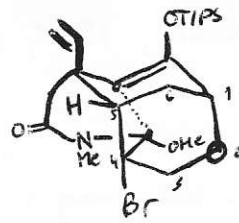
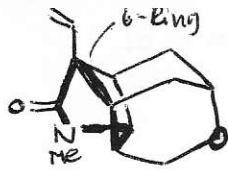
- Isolierung: 1883 (Gerrard)
- Strukturklärung 1959 (Wilson) mit X-Ray
- Features:
  - spiro-Indol
  - Hexazyklus, Käfigstruktur
  - 7 benachbarte Stereozentren
- 7 Totalsynthesen (eine enantioselectiv von Fukuyama)

- Key Features:
  - 1.) spiro-Cyclisierung zum Indolinon (Benzotriazol, photochem.)
  - 2.) [2+2]-Cycloaddition + Grob-Fragmentierung

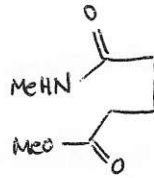
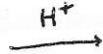
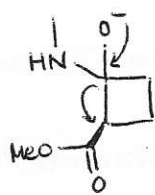
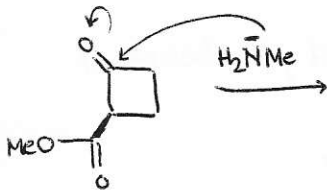
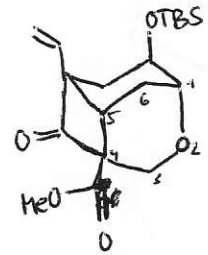
• Photochemische Indol-Synthese



Gelsemin  $\Rightarrow$



$\Downarrow$  Grds. Fragment.



begünstigt, da stabiles Anion gebildet und Ringspannung aufgegeben wird

Natsyn  
10-05-11

①

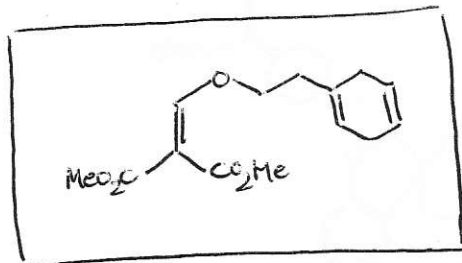
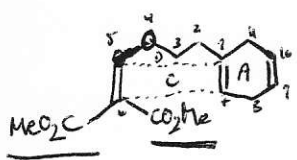
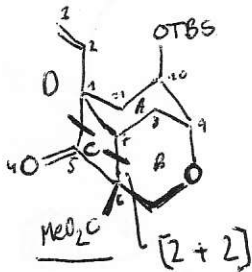
[2+2]-photochemische CA:

- strongly depends on „rule of fives“

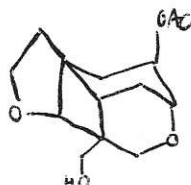
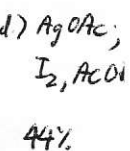
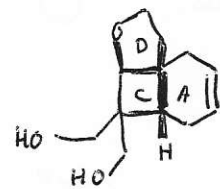
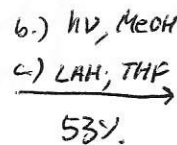
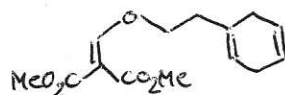
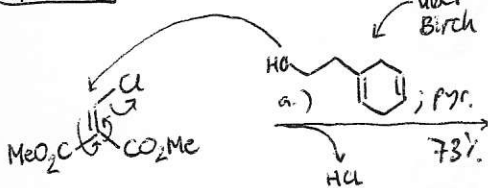
- Ex.:

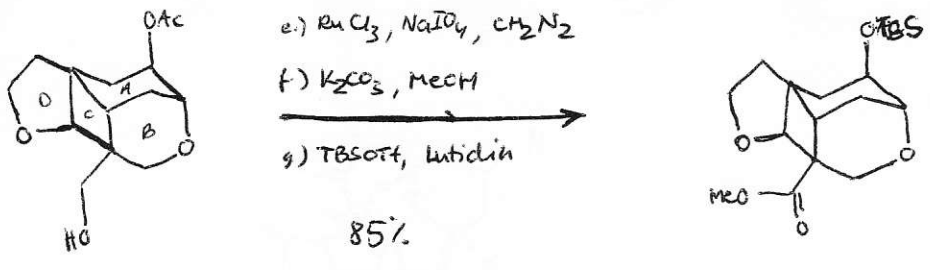


(Diels-Alder-Reaktion)



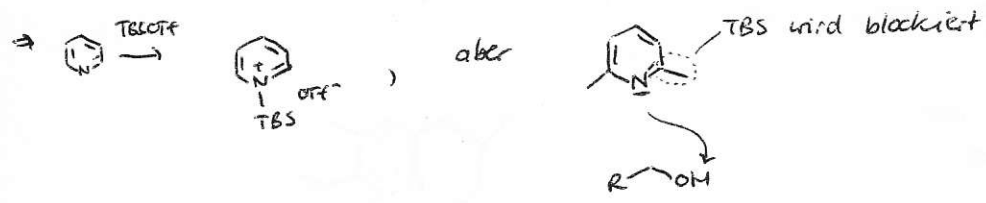
Synthese:



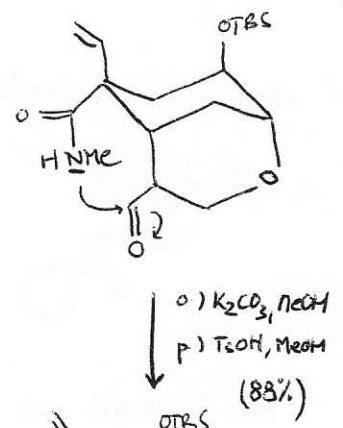
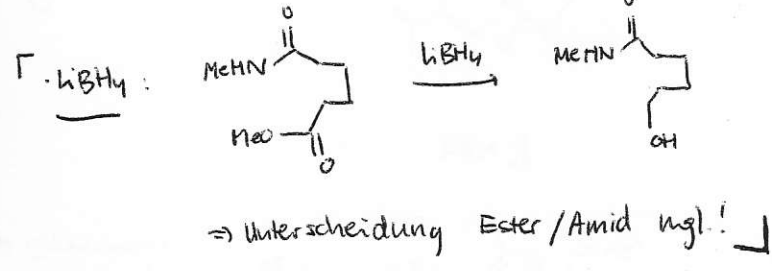
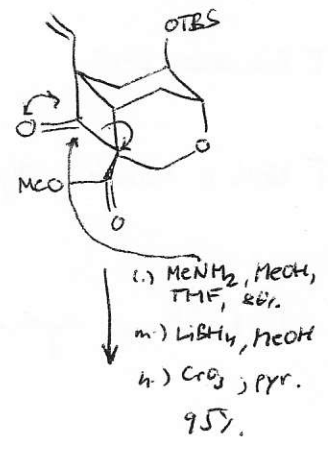
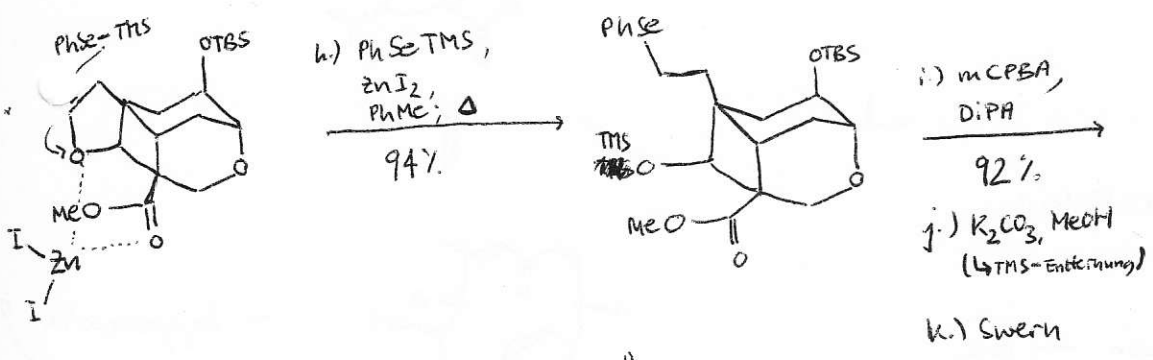


Γ. 2,6-Lutidin:

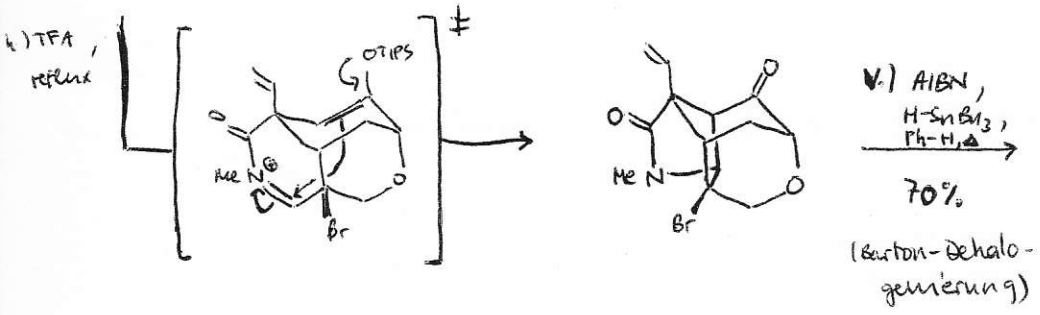
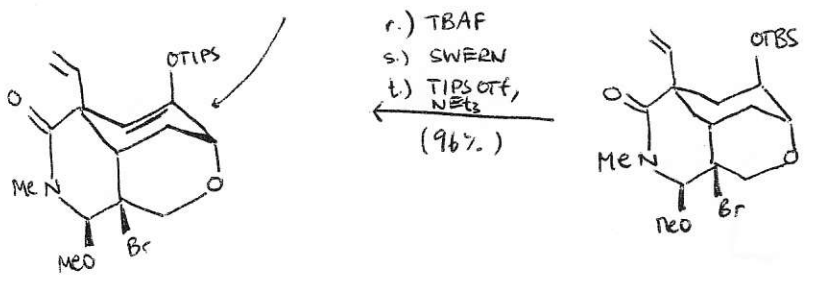
• Warum Lutidin statt Pyridin?

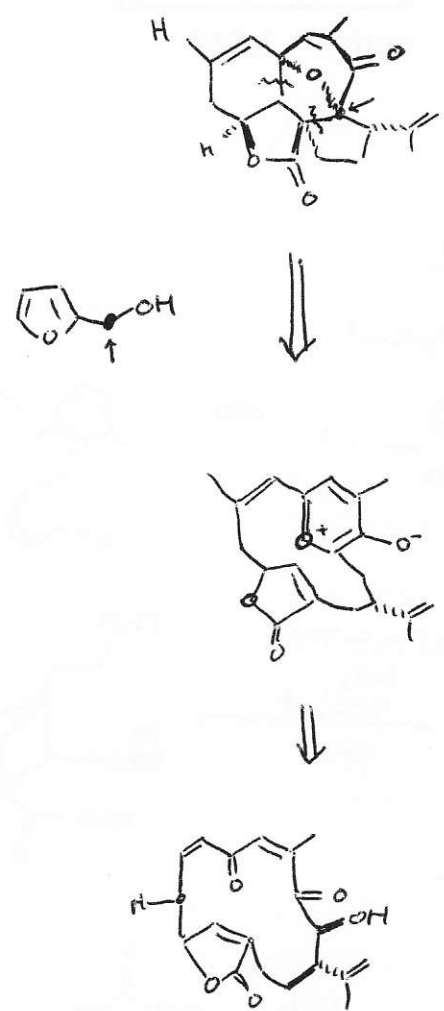
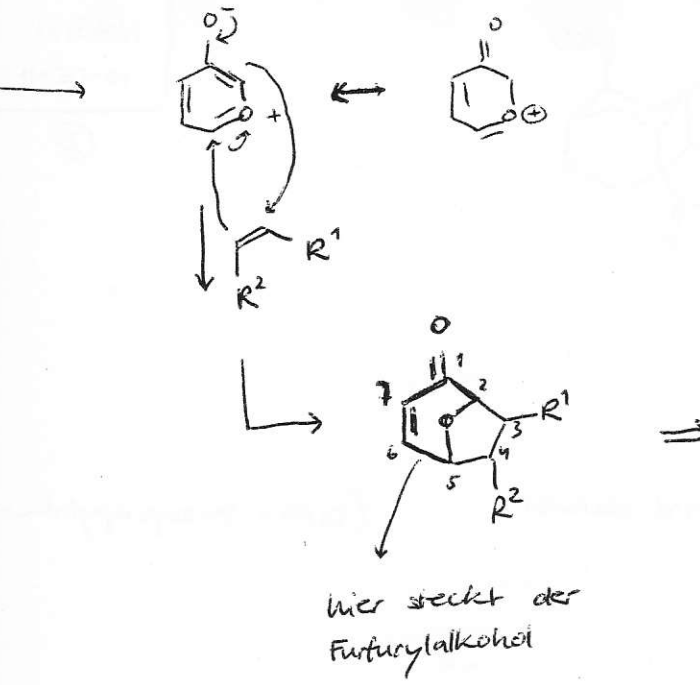


(DiPA = Diisopropylamin)



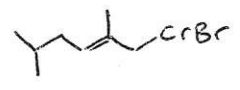
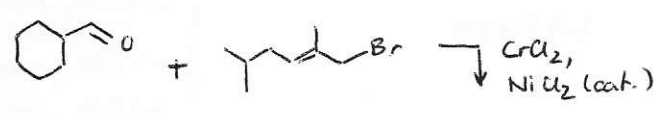
ob nicht hier ⇒ Bredt'sche Regel



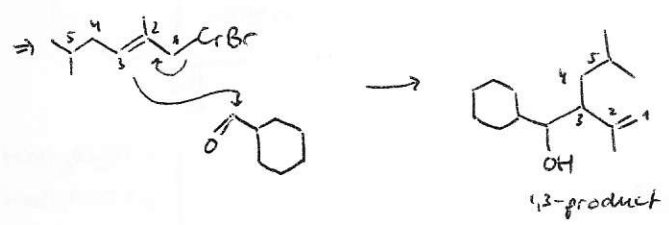


T Traumer et al.,

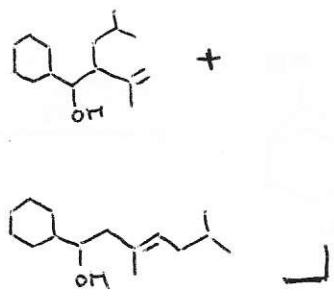
T NHK = Nozaki-Hiyama-Kishi:



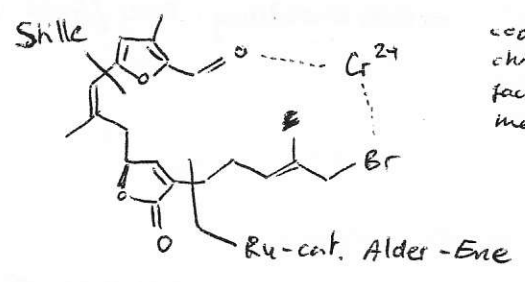
• Cr-species reacts also 1,3!



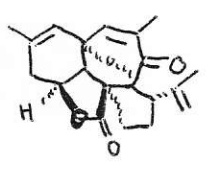
Mit Grignard →



↓ NHK

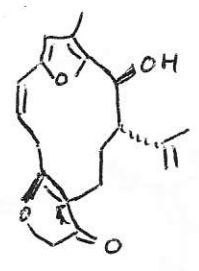


Total Synthesis as a tool for investigating biosynthetic relationships between Natural Products.

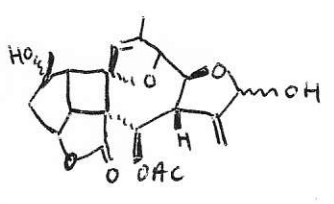


**(+)-inticarene**

family of furano cembranoides



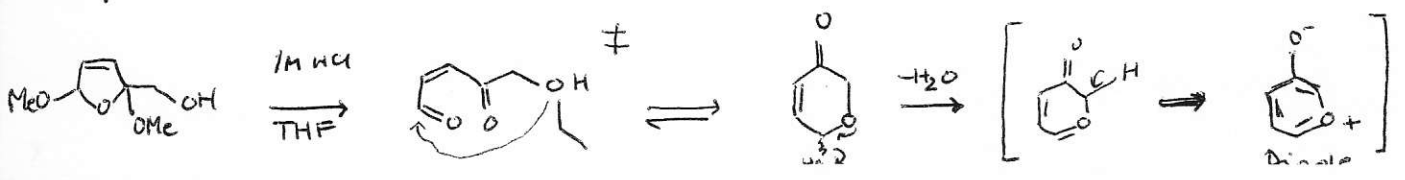
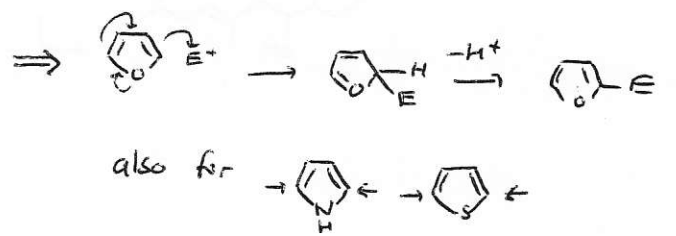
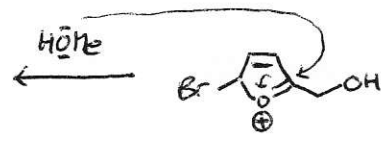
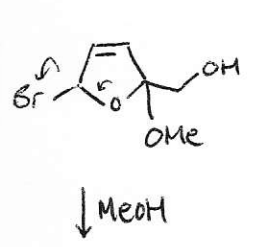
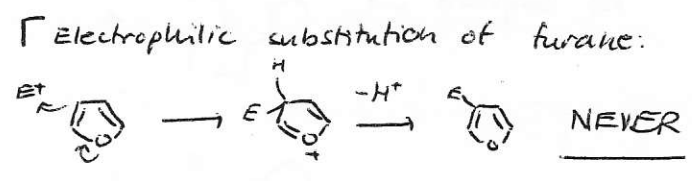
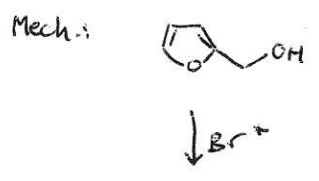
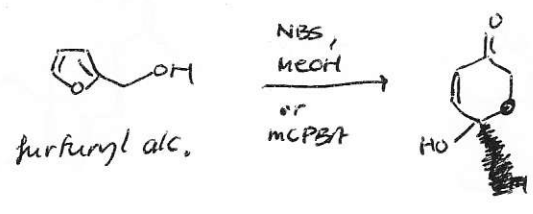
bispiannatin J



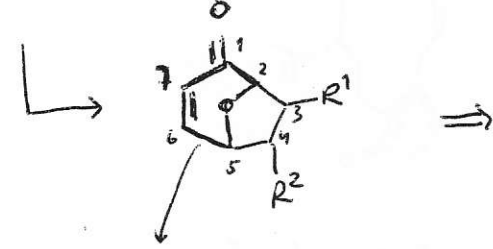
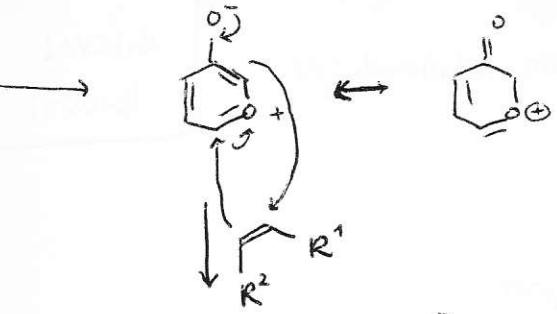
bielschowskyin

- Key features:
  - Achmatowicz reaction
  - stereoselective reductions (alpine borane)
  - Ru-catalyzed Alder-Ene-Reaction

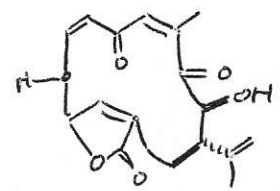
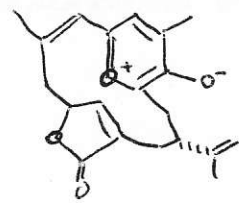
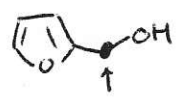
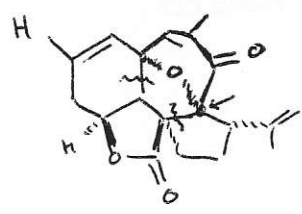
Achmatowicz reaction:





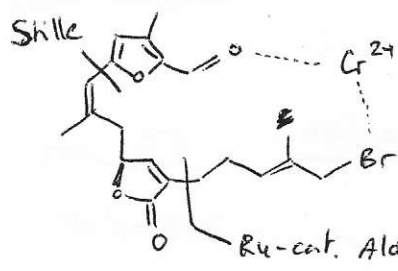


Wier steckt der Furfurylalkohol



→ bippanahin

↓ NHK

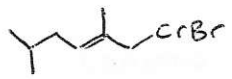
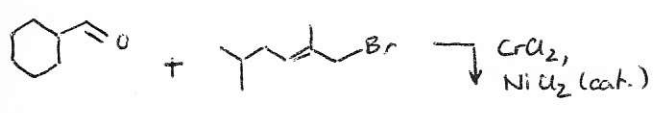


coordination of chromium facilitates macrocycl.

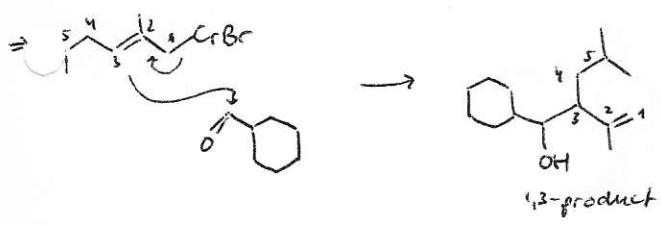
Ru-cat. Alder-Ene

T. Lamer et al.,

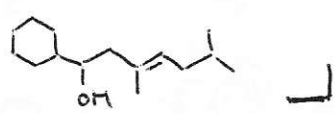
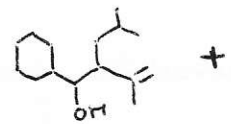
Γ NHK = Nozaki-Hiyama-Kishi:

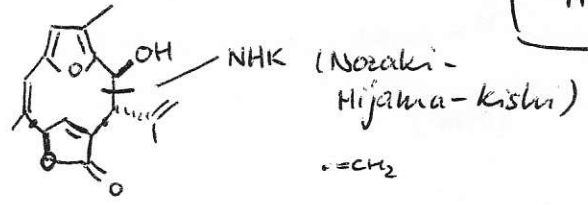
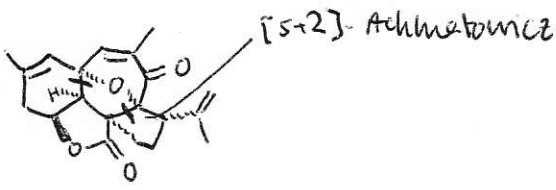


• Cr-species reacts also 1,3!

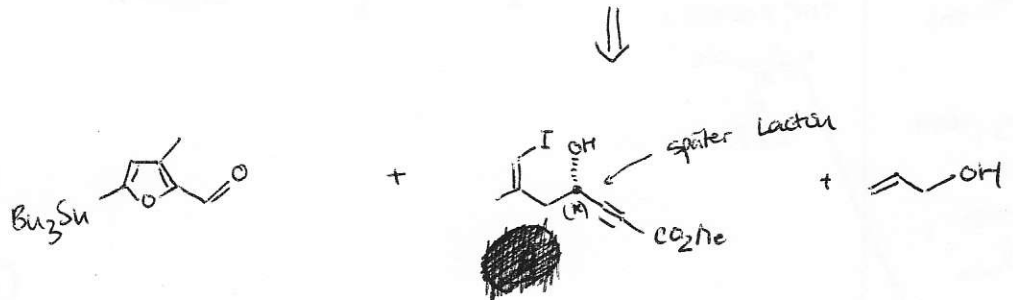
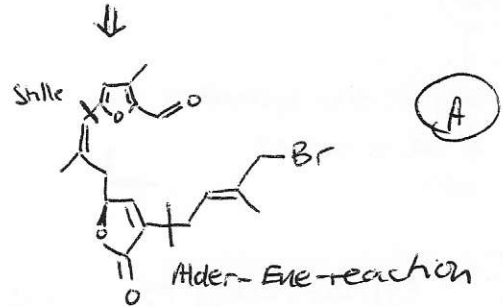
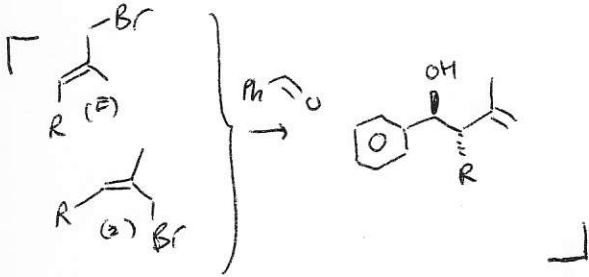


Mit Grignard →

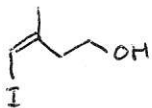




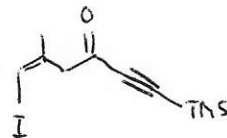
bipinnatin ]



Reactions ;

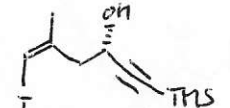


- 1.) DMP
- 2.) Li-C≡C-TMS
- 3.) DMP



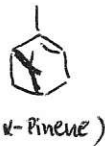
4.) (s)-Alpine-borane

55% (4 steps)



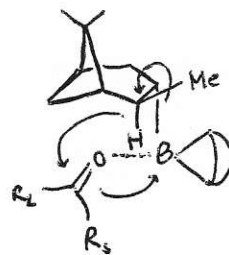
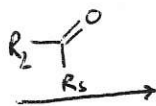
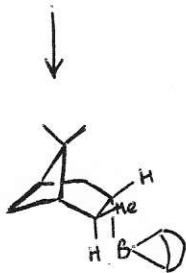
Alpine-Borane-Reduction:

9-BBN +



others

CBS, Brown's ((Ipc)<sub>2</sub>BH),  
BINAL-H (and other Noyori-typ  
reaction)

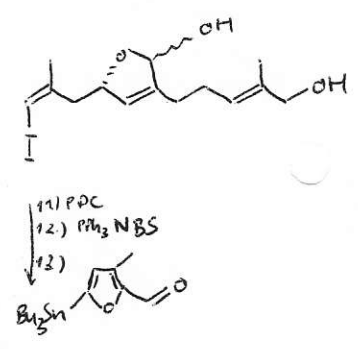
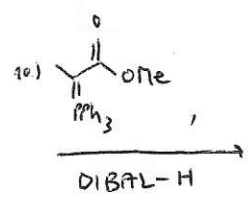
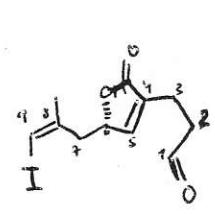
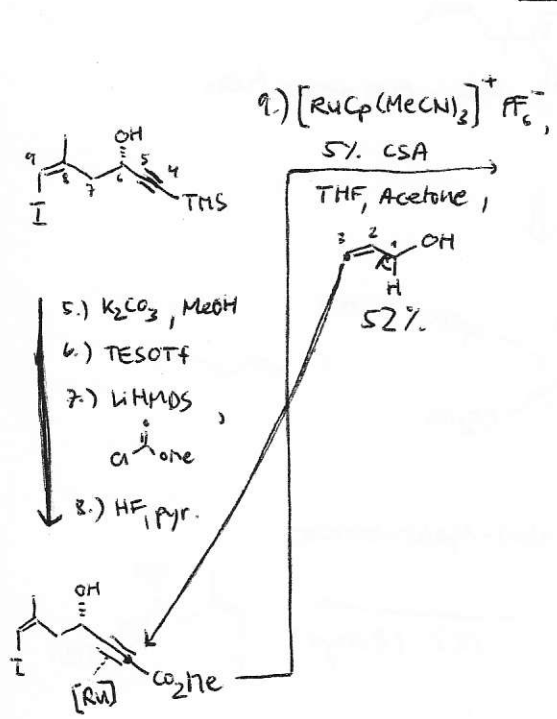
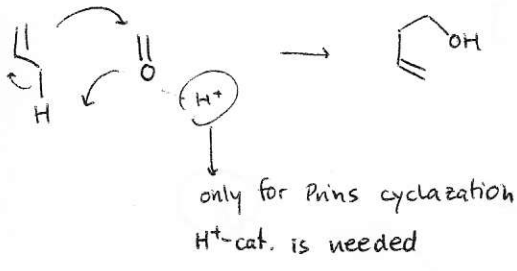
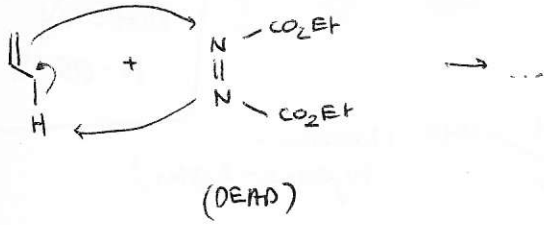


hier der kleine Substituent,  
um NW zu minimieren

Alder-Ene-Reaktion:



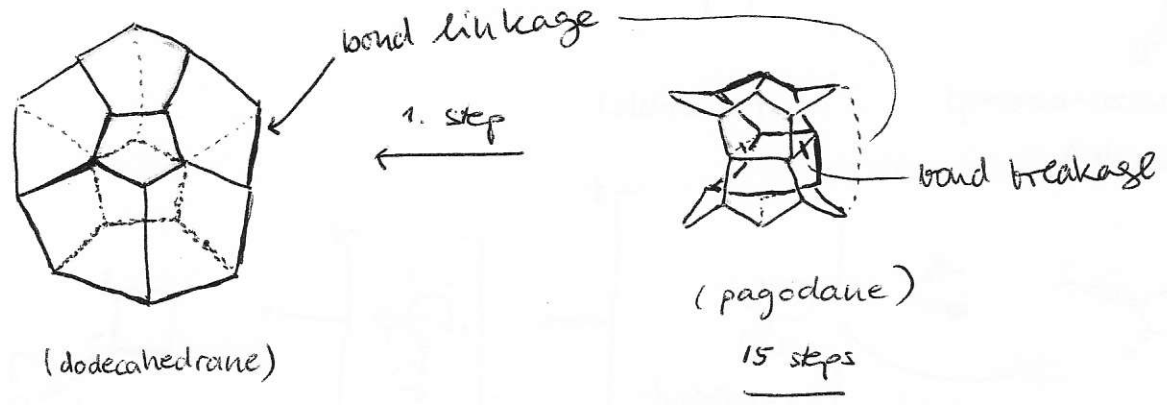
Triebkraft: Ausbildung einer  $\sigma$ -Bindung unter Aufgabe einer  $\pi$ -Bindung



(A)

Total Synthesis of dodecahedrane

- L.A. Paquette
- H. Prinzbach



Platonic solids:

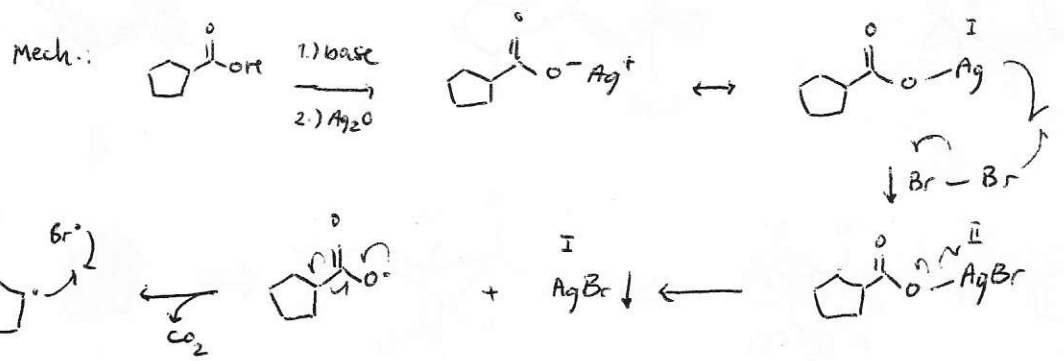
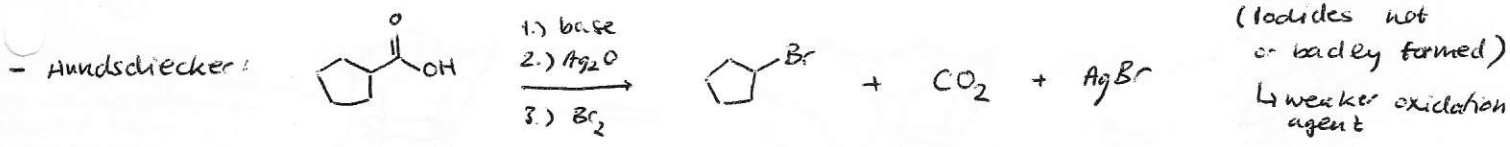


↳ characteristic: 1 NMR-signal

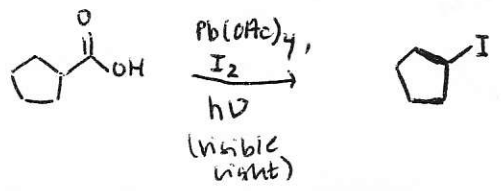
Features of the synthesis (Prinzbach):

- 15 steps (for pagodane)
- Kochi-reaction
- Wolff-rearrangement

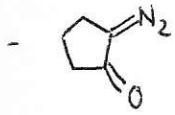
Kochi-reaction (variant of the Hunsdiecker reaction)



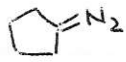
- Kochi conditions: (alkyl halides from carboxylates)



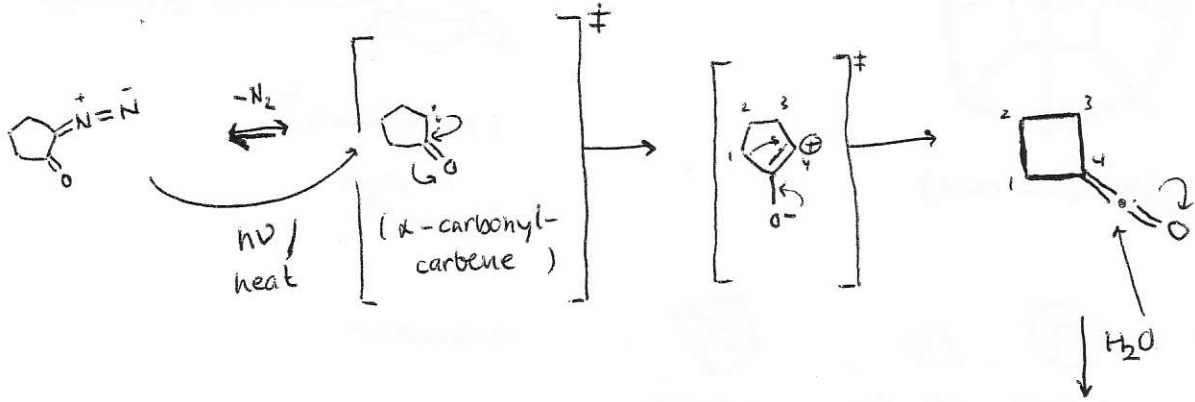
Wolff rearrangement



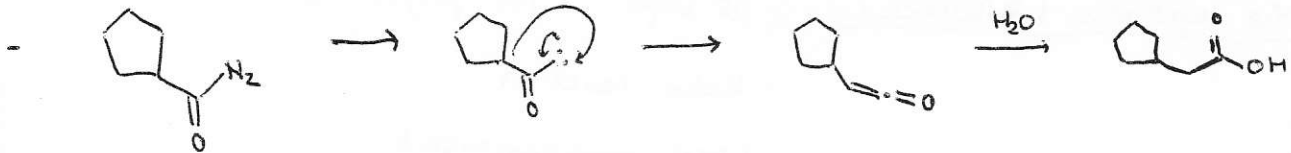
$\alpha$ -Diazo-carbonyl  
(stable)



(unstable)



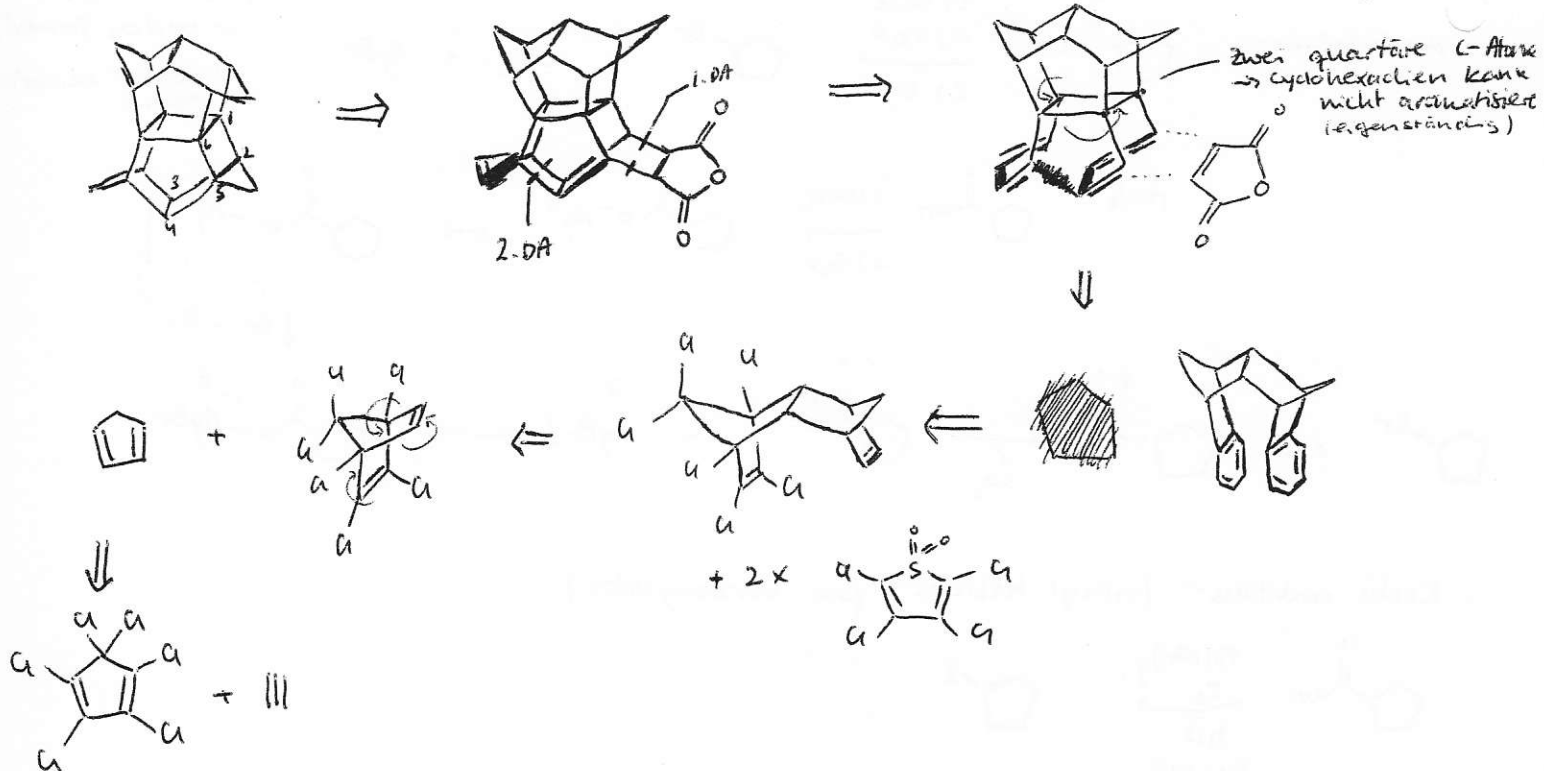
Arndt-Eistert-Homologation

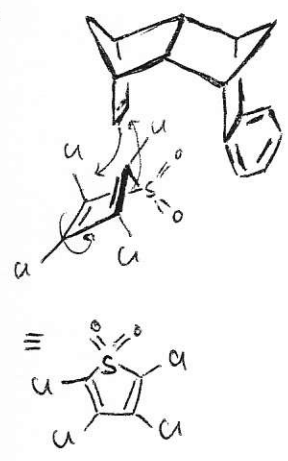


Retrosynthese Pagoda:

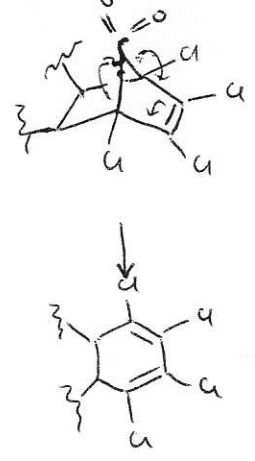
Natsyn  
24-05-11

①

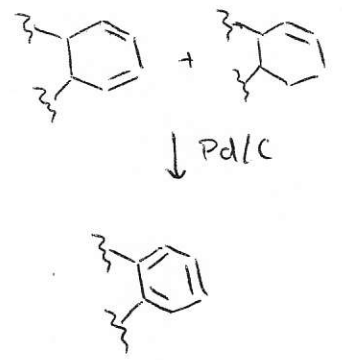




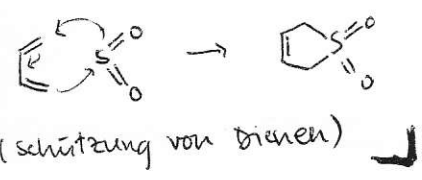
Toluol  
120°C



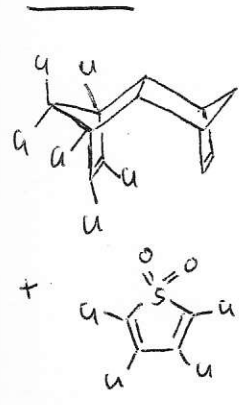
"Birch"



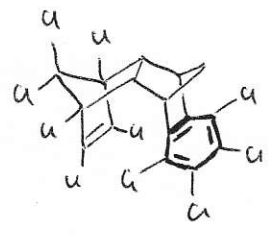
Chelotrope Reaktion:



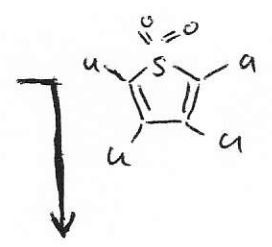
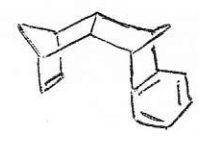
Reaktion:

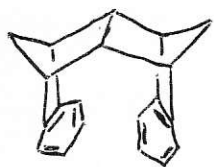


CCl<sub>4</sub>,  
Zn, reflux  
100%

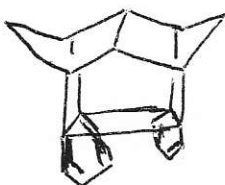


Li, THF,  
+ BuOH  
reflux

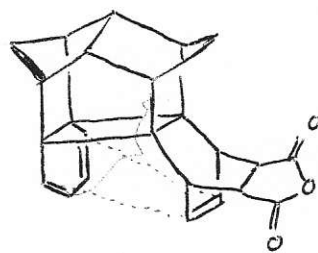




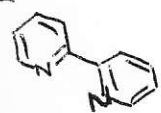
99%  
D.A.  
hv,  
2,2,4-Trimethyl-  
pentan



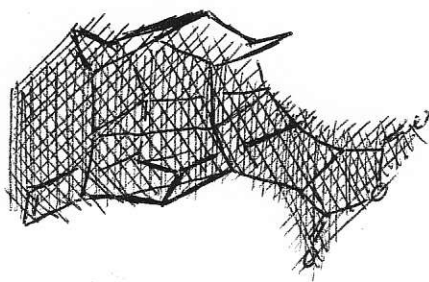
98%  
PhH, 80°C



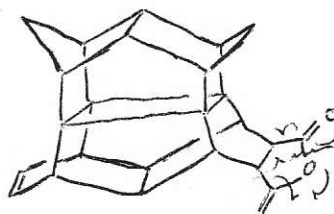
≠



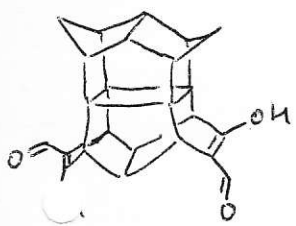
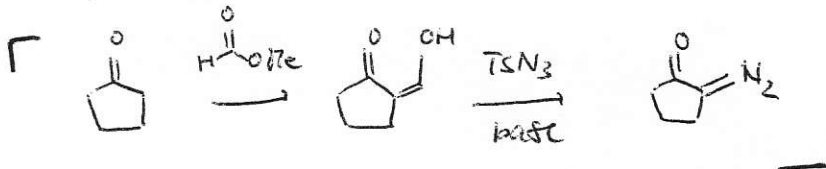
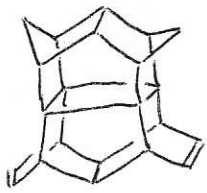
2,2'-bipyridine



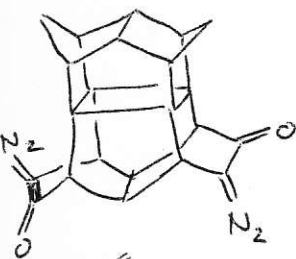
$Cu_2O$ ,  
2,2'-bipyridin  
= "e"  
-  $CO_2$ ,  
- CO  
78%



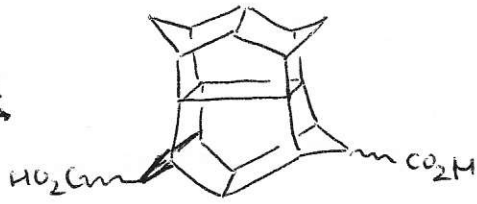
(90%)  
1.)  $BH_3 \cdot THF$ ,  
 $H_2O_2$ , NaOH  
2.)  $CrO_3$ ,  
Acetone  
(92%)  
3.)  $HCO_2Me$ ,  
NaH



TSN<sub>3</sub>

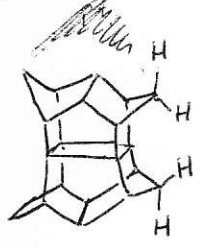


hv,  
NaHCO<sub>3</sub>

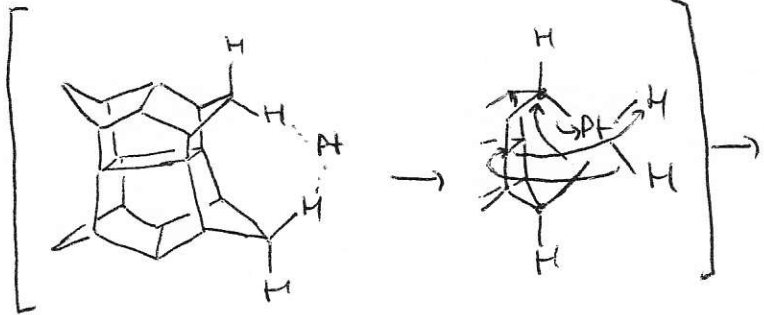


1.)  $Pb(OAc)_4$ ,  
 $F_2$   
2.) Na-K,  
THF,  
Et-OH

Pagodan



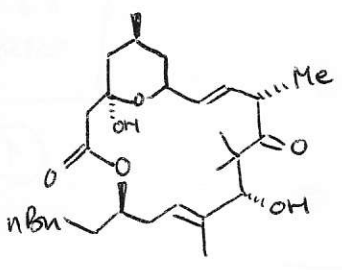
$Pt / Al_2O_3$   
350°C  
(8%)



Dodecahedrane

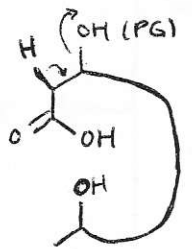
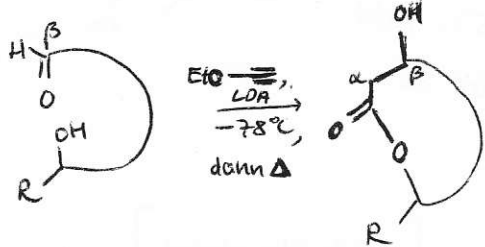
• Key features:

- i) Macrolactonisierung (mit  $EtO \equiv$ )
- ii) Allenchemie (zentrale Chiralität  $\leftrightarrow$  axiale Chiralität)
- iii) Hydrozirkonierung



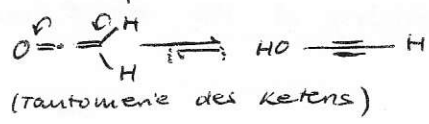
(+)-acutiphycin

• Macrolactonisierung:

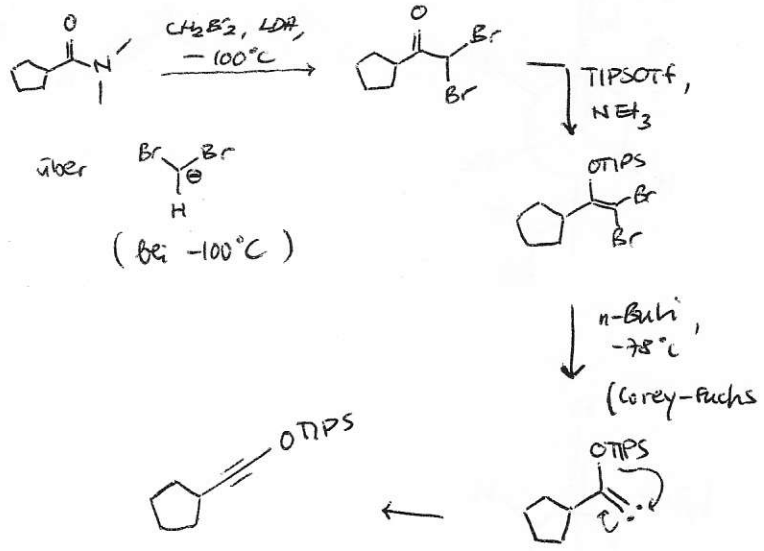


bei „Standardverfahren“ (Cory-Nicolau, Yamaguchi, Keck, Ortega-Kat.)

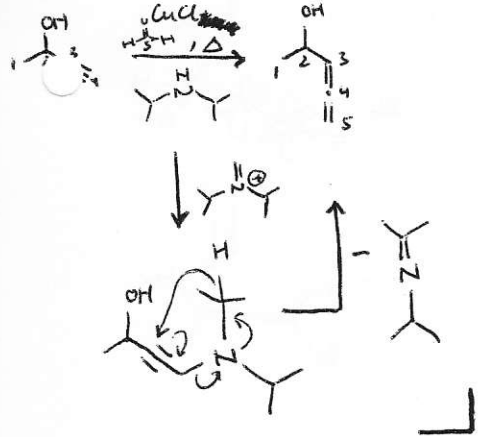
• Ethoxyacetylen: - Keten-Äquivalent



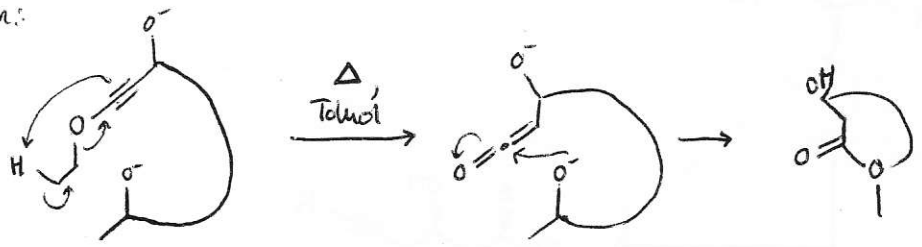
• Kowalski-Protokoll:



Seacless-Graibé:

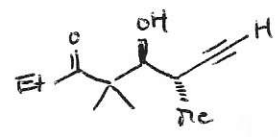
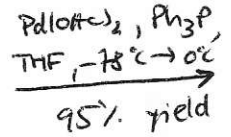
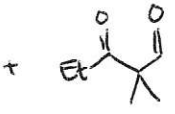
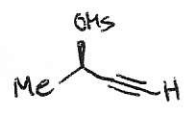
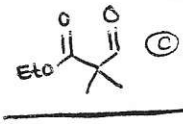
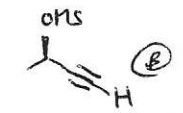
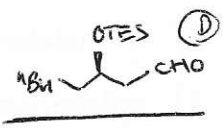
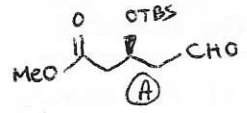
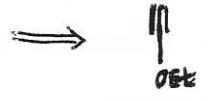
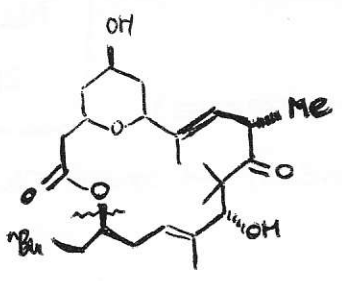


• Mech:



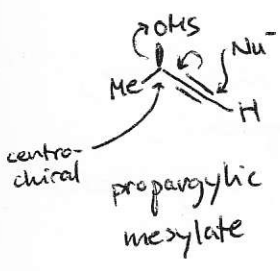


(1)

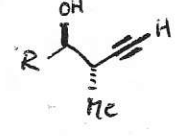
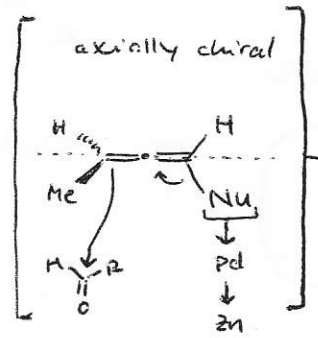


90% ee

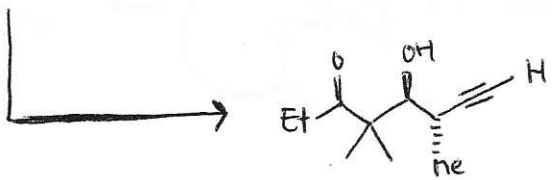
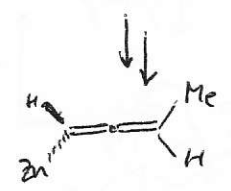
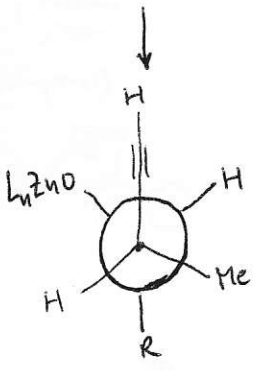
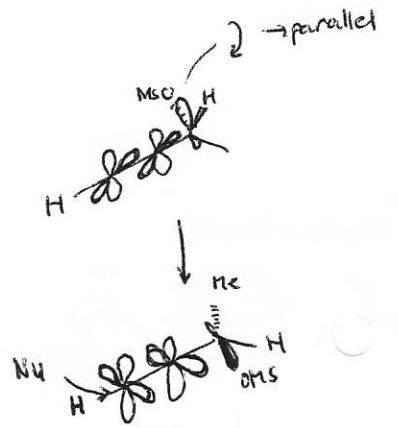
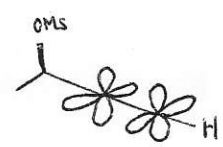
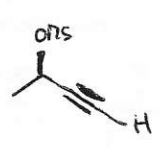
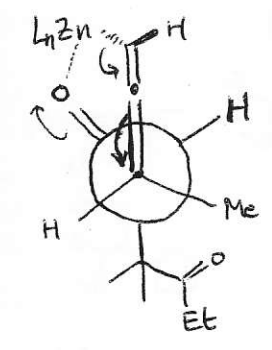
Marshall chemistry:



"Reagent"  
Nucleophile  
 $S_N2'$ -mechanism

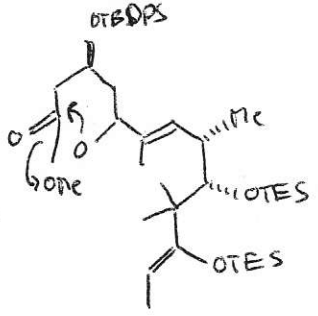
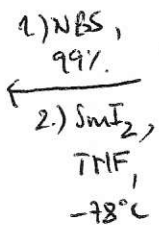
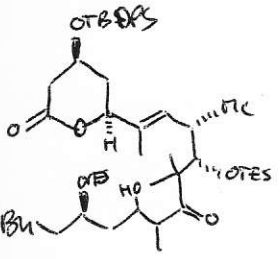
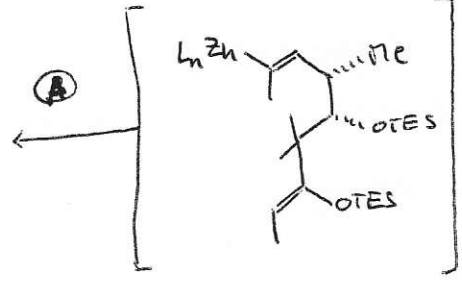
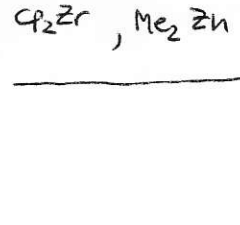
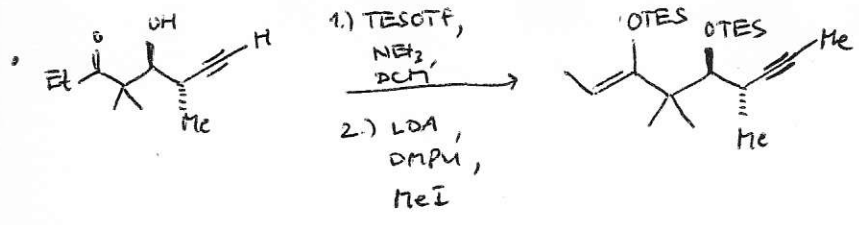


Stereo chemistry of the allene/reaction:



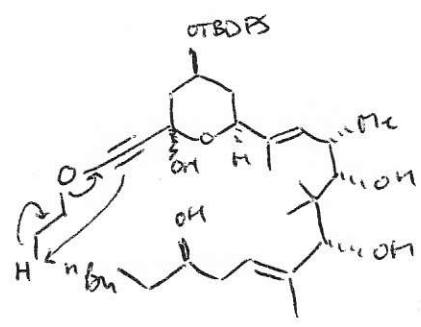
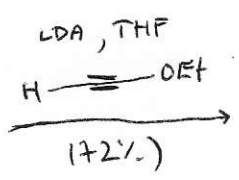
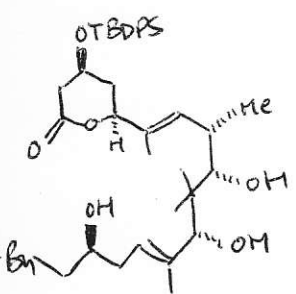
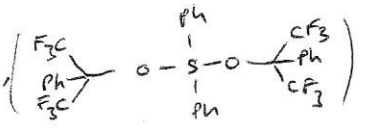
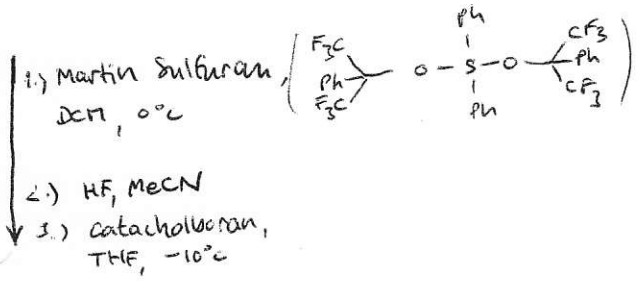
NatSYN  
06.06.11

②



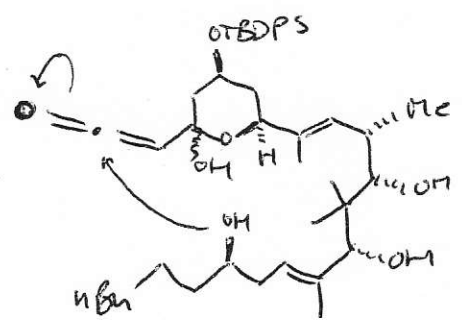
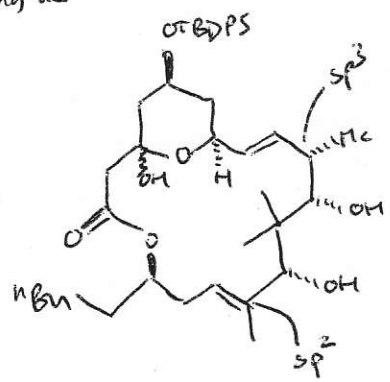
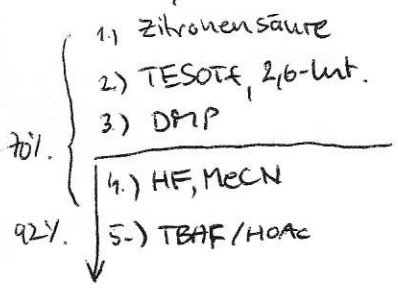
NatSYN  
07.06.11

①



Xylen, 130°C  
NEt<sub>3</sub>

Equilibrierung der OH-Gruppe

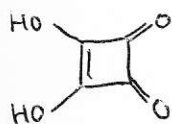


(+) - acutiptycin

# Building Block: Squaric Acid

Natsyn  
07.06.11

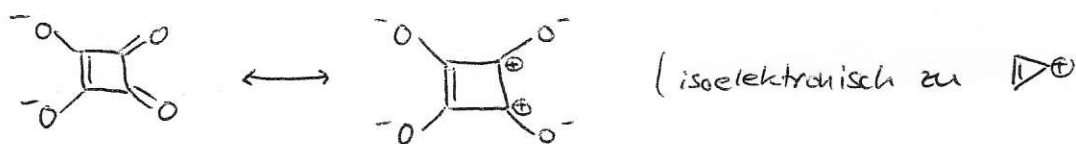
②



(1g / 311€)

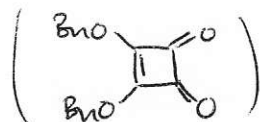
physical properties:  $pK_{a1} = 1.5$ ,  $mp = 293^\circ C$ ,  
 $pK_{a2} = 3.4$ , white solid

- Synthesis from Uranium carbonyl complexes
- dianion (squarate) = aromatic compound



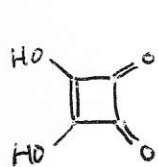
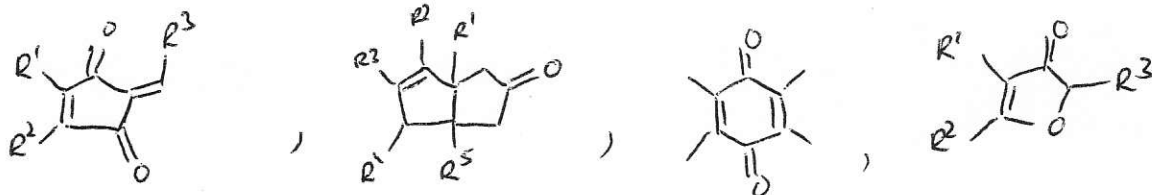
Hückel sense  $\rightarrow n = 0$

- usage:
  - photochemistry ( $\rightarrow$  solar cells)
  - material science ( $\rightarrow$  polymere chemistry)
  - biology: warts-treatment, tumor therapy

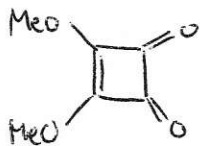


- OS: ring expansion

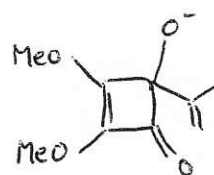
Expansions:



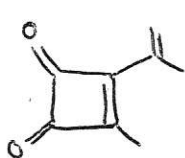
MeOH,  
Benzene  
 $H^+$  (cat.)



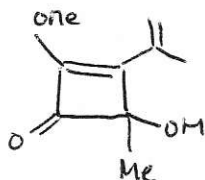
1 eq.  $CH_2=C(Me)MgBr$ ,  
THF  
 $-78^\circ C$



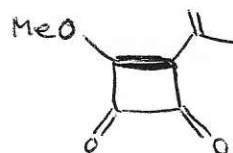
to rt,  
hydrolyse



$H^+$ ,  
 $H_2O$



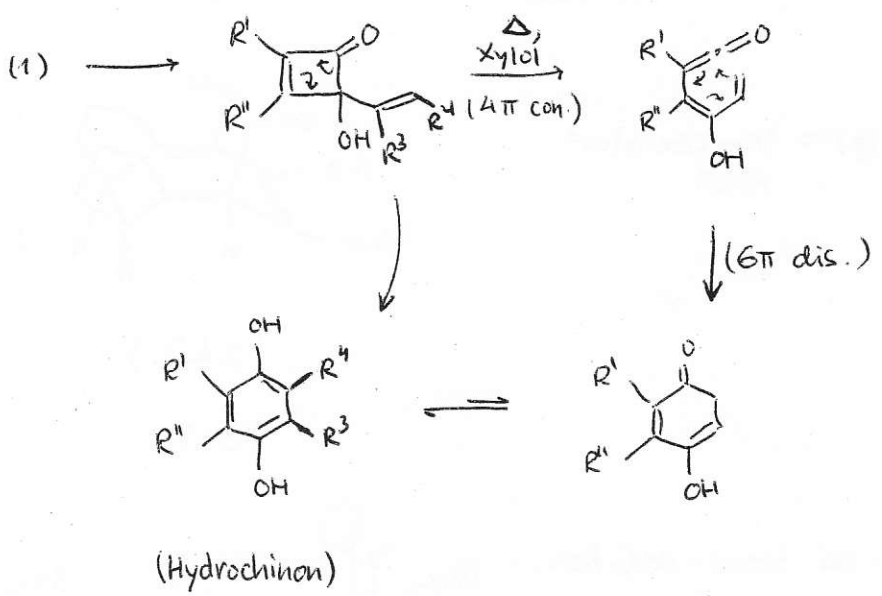
MeLi,  
THF  
 $-78^\circ C$



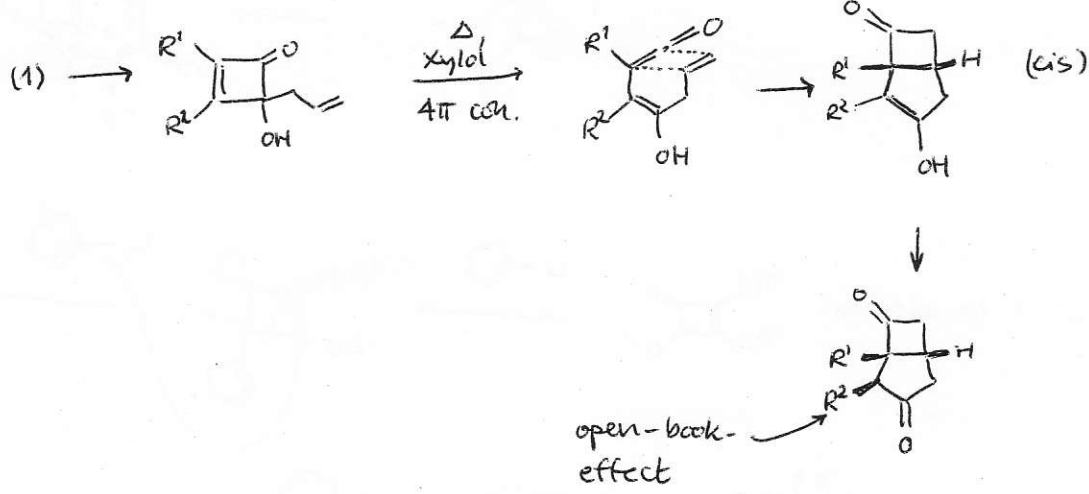


Cyclobutadienone,  $R^1, R^2 = \text{Alkyl}$

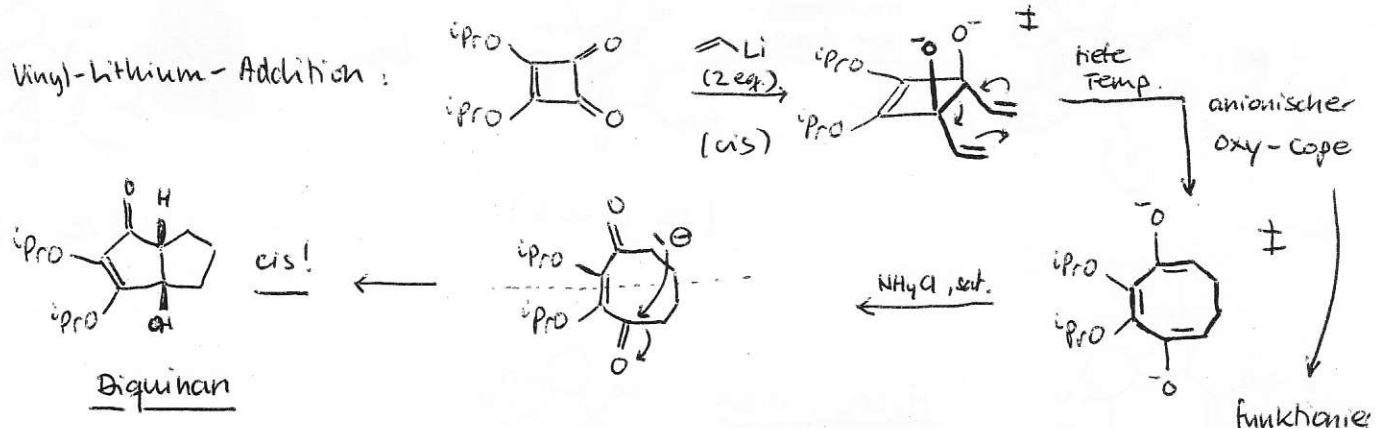
1.) Vinyl-lithium-Addition:



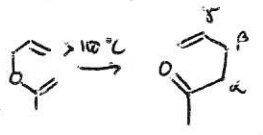
2.) Allyl-lithium-Addition:



3.) Doppelte Vinyl-lithium-Addition:

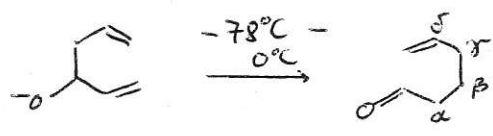


oxy-Cope



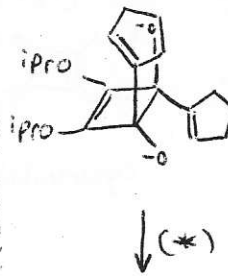
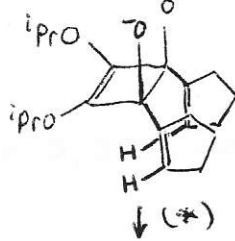
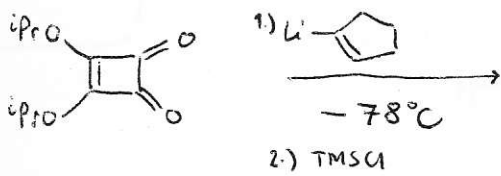
vs.

Anionischer oxy-Cope



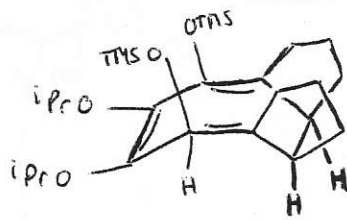
Funktioniere nur bei cis-Addition trotz dem entsteht Biquinan bei trans-Addition

• Synthese von Paquet



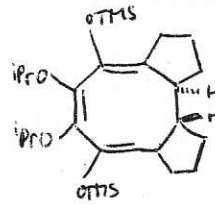
l.u.  
↓ (\*)

(\*) = transannulare Aldol



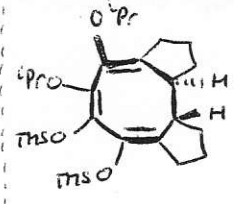
(24%)

(cis)



(43%)

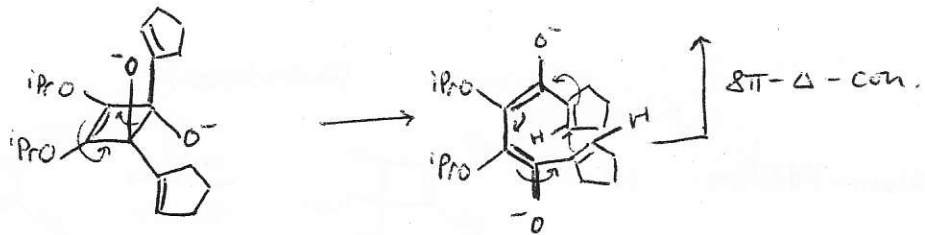
(trans)



(57%)

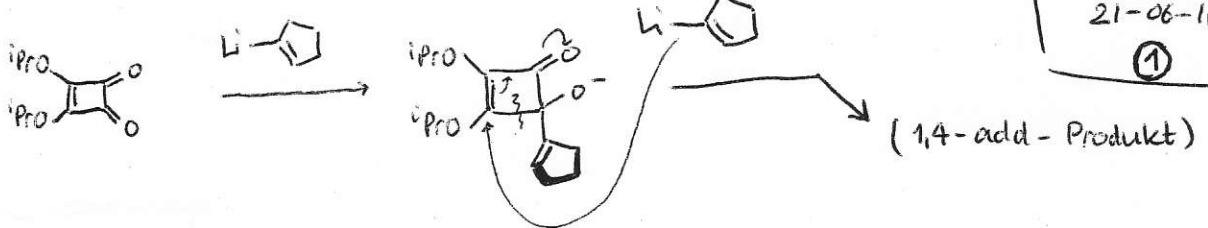
(1,4-add)

• bei trans-Addition:



$\delta\pi$ - $\Delta$ -con.

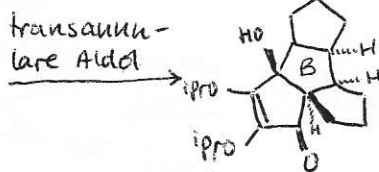
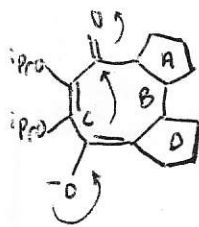
• 1,4-addition:



NatSYN  
21-06-11  
①

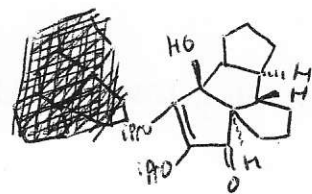
(1,4-add-Produkt)

• (\*):

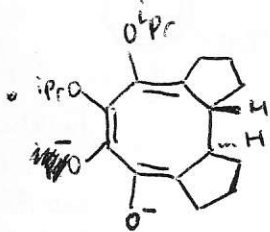


(bei 1,2-cis)

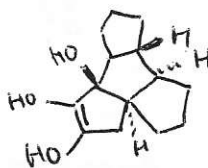
bzw.



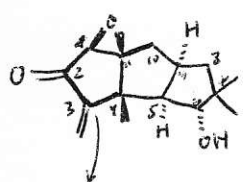
(bei 1,2-trans)



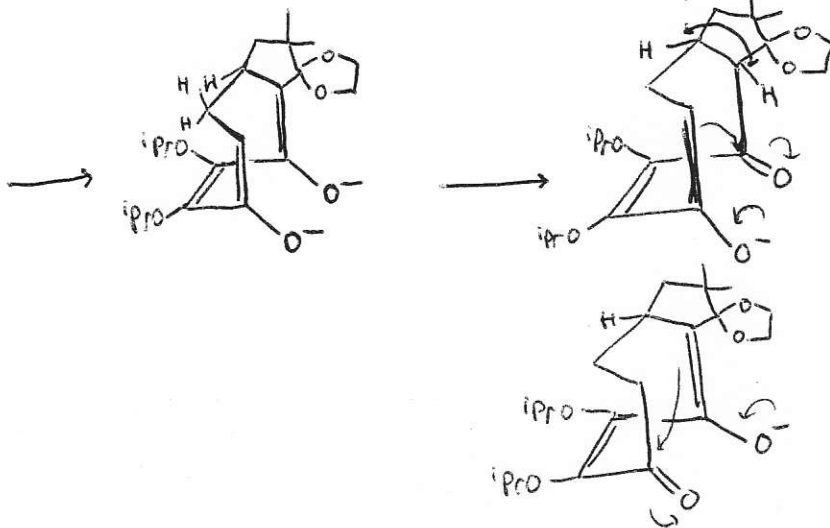
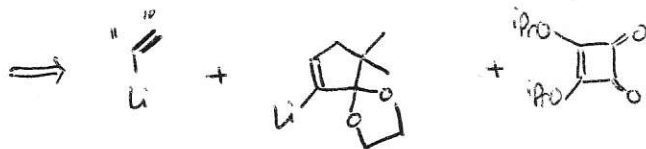
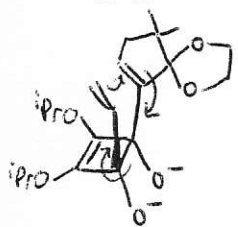
$\text{H}_2\text{SO}_4, 10-20\%$



(2)

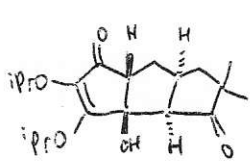


von Quadrat-  
säure

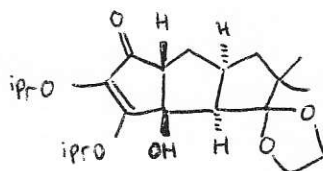


(A) → bevorzugt

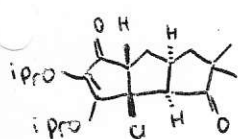
(B) (Endat hat mehr Substituenten)



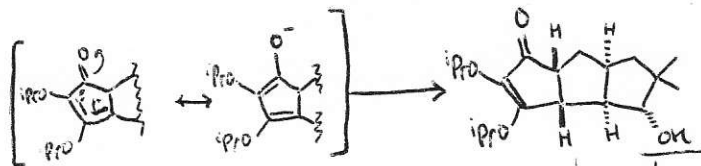
H<sub>2</sub>SO<sub>4</sub>, 110°



SOCl<sub>2</sub>,  
NEt<sub>3</sub>



Li, NH<sub>3</sub>

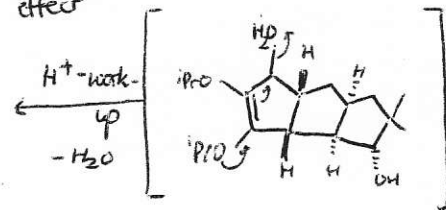
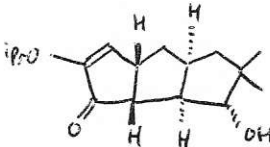


open-back-  
effect

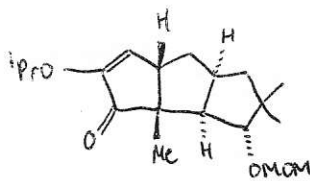
LAH, Et<sub>2</sub>O

1.) MOMCl, Hünig-  
base

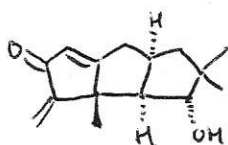
2.) LDA,  
MELi



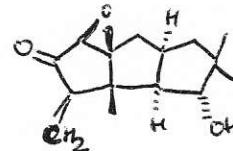
MELi  
2 H<sub>2</sub>SO<sub>4</sub>  
(30%)



1.) LDA, DMPU,  
TMSCl, Pd(OAc)<sub>2</sub>

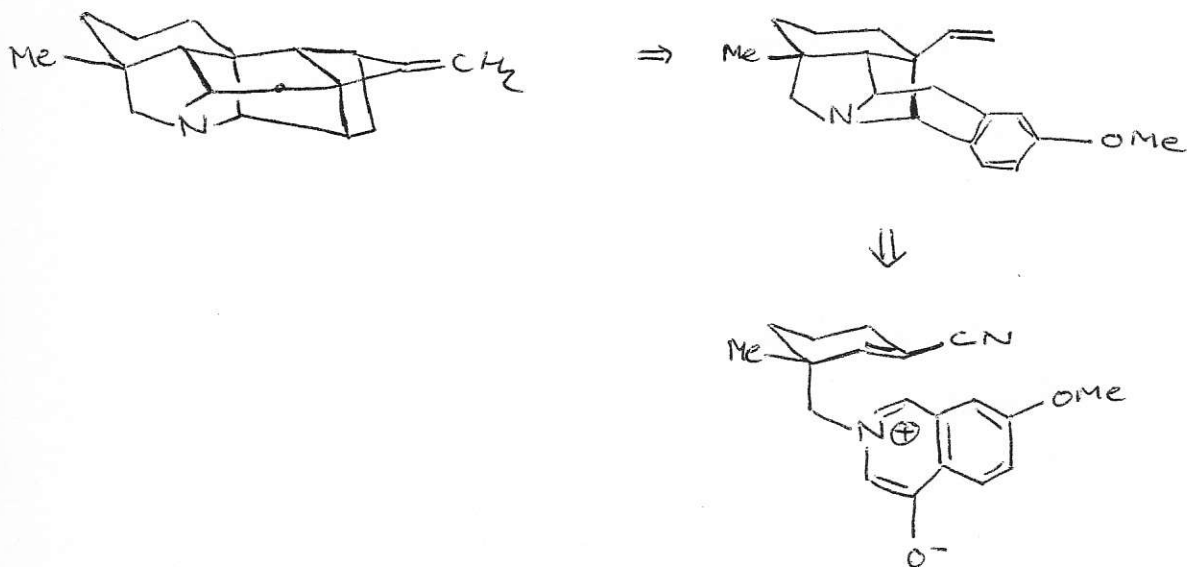


K<sub>2</sub>CO<sub>3</sub>,  
H<sub>2</sub>O<sub>2</sub>



Nominine

David Y. Gin et al., JACS, 128, 8734



• Achmatowicz-Intermediat



→ analog mit Stickstoff